New Continuous Flow Oxidation Methodology

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MCPAKE, CHRISTOPHER C. (2011) New Continuous Flow Oxidation Methodology. Doctoral thesis, Durham University.

Durham University

A Thesis Entitled

New Continuous Flow Oxidation Methodology

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A Candidate for the Degree of Doctor of Philosophy 2011

Declaration

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To date, part of this work has been the subject of the following:

- Christopher. B. McPake, Christopher. B. Murray, Graham. Sandford, *Tett. Letts.*, **2009**, 50, 1674
- Christopher. B. McPake, Christopher. B. Murray, Graham. Sandford, *Chim. Oggi.* **2010**, 28, 3

and has been presented at:

- 10th RSC Symposium for Fluorine Chemistry, Durham, 2010
- Organic Chemistry Seminar, Durham University, 2010

Statement of Copyright

Acknowledgements

The thirty nine months I have spent at Durham University studying towards my PhD has without a doubt been some of the most enjoyable times of my working career and, whilst many people at have contributed towards this, some of those deserve special mention.

First and foremost, I would like to especially thank my supervisor, Graham Sandford, for his fantastic support, guidance and encouragement throughout the course of my research and, also, for giving me the opportunity to work on such an exciting research project. For this, I will always be indebted to him.

With this in mind, I would also like to thank AnneMarieO'Donoghue, whom I have always felt was instrumental in bringing me to Durham University.

For technical support and guidance, I would like to thank Chris Murray of AWE, all the members of the Durham Fluorine Group and all of the analytical and support staff.

I have also made many friends over the past three years, all of which have made my time at Durham such an enjoyable one; whilst naming all of these is not possible, special mention must to go to Ian Wilson, Katharine Linton, Matt Cargill, Anita Lindsay, Peter Harrisson, Jessica Breen, Graham Sandfordand Harriet Teare.

Lastly, but by no means least, I would like to thank my girlfriend, Julie, and the rest of my family and friends for their continuous support throughout all of my studies.

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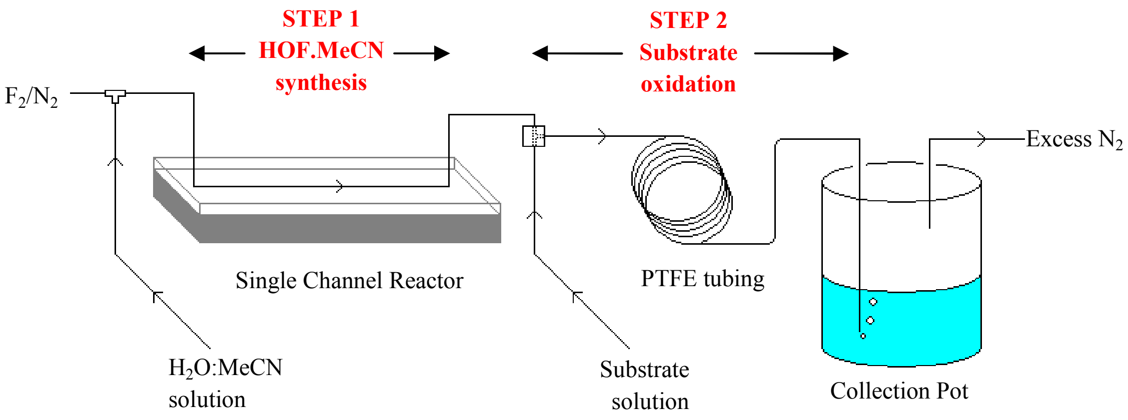
Abstract

The HOF.MeCN complex, formed from the reaction of elementary fluorine with aqueous acetonitrile, was discovered by Shlomo Rozen in 1987 and, in a series of publications, he demonstrated that the complex is a uniquely effective electrophilic oxygen transfer agent. However, it is estimated that the HOF.MeCN complex has a half life of a few hours at 0ºC and thus, must be produced and used immediately when required. In addition to this, highly exothermic, rapid oxidation processes can be problematic with reaction control and safety when reagents are added into an excess of a highly oxidizing medium. Consequently, scale-up of oxidations to a larger industrial level using the HOF.MeCN complex in batch processes would not be possible.

In recent years, continuous flow reactors using microchannels have been viewed as a viable method for avoiding many of the problems encountered when a laboratory process is scaled-up. The low chemical inventory of such reactors means that even highly reactive reactions can be performed safely and, with the application of multiple reaction channels in parallel, large quantities of product can be easily obtained.

In this thesis we present new continuous flow methodology for the *in situ* generation of HOF.MeCN and, without isolation, immediate substrate oxidation in a two-step process. The continuous process, therefore, provides a genuine method for oxidizing large quantities of material, without the problems associated with batch oxidations. Scale-up oxidations of various amines, alkenes, and anilines are also presented along with a safe and accurate method for calibrating HOF.MeCN amounts.



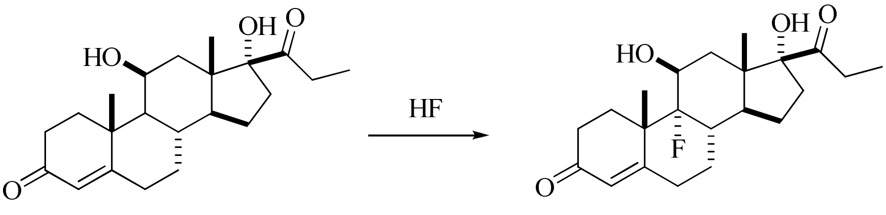
Chapter 1 - Introduction to Elemental Fluorine as a Reagent in Organic Synthesis

1.1 Introduction

The importance of selectively introducing fluorine atoms into organic molecules is exemplified by the sheer scale of commercial and industrial organofluorine compounds available. Pesticides, anaesthetics, pharmaceuticals(i), refrigerants, lubricants, surfactants, and many more consumables[1-3] all make use of organofluorine compounds but, since only a select few naturally occurring compounds contain fluorine[4](ii), all fluoroorganic compounds available today are ‘man made’.

The development of industrial organofluorine chemistry began in 1931[5](iii) with the availability of anhydrous hydrogen fluoride in commercial quantities and it was in this decade that fluoromethane systems were developed as refrigerants and PTFE was discovered.

It was not until 1954, when Fried and Sabo demonstrated the enhanced biological activity of fluorocortisone **(1)** (*scheme 1*) compared to its parent compound[6], that fluoroorganic chemistry began to flourish. The late 1950’s and early 1960’s then experienced a surge in civilian applications of fluoroorganic compounds[7].



(1)

Scheme 1

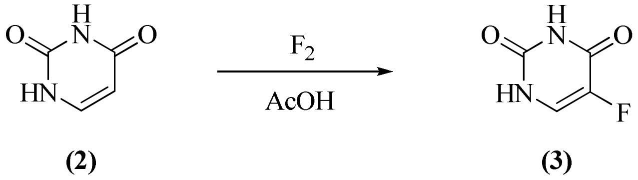
(i) It is estimated that 30 % of the leading blockbuster drugs and 20 % of prescribed pharmaceuticals contain fluorine[8]

(ii) It is noteworthy that fluorine is the 13th most abundant element in the earth’s crust, existing largely as the fluorite minerals calcium fluoride, CaF_2 (fluorspar) and Na_3AlF_6 (cryolith)[4]

(iii) Anhydrous hydrogen fluoride was first isolated in 1845 by Frémy, who heated KHF_2 (Frémy’s salt) to produce KF and HF; whilst this method is still used to produce ‘small’ quantities in the lab, quantities were not being produced on a large scale until 1931[5]

However, of the thousands of publications over this time covering the synthesis of fluoroorganic systems, elemental fluorine was rarely used as a fluorinating agent, with scientists opting to use sources such as HF or metal fluorides[9]. The underutilization of elemental fluorine is a result of years of the general opinion that the element is too reactive, and also, too dangerous to be controlled in reactions[9].

Over the past 40 years, a select few research groups have been working to overturn the negative view towards elemental fluorine, with some useful progress[10]. Although there are still only a small number of research institutions that have the facilities to work with F_2, the growing number of publications demonstrate that the viability of F_2 as a selective fluorinating reagent is undeniable[10]. Fluorouracil **(3)**, the popular chemotherapy agent and precursor, is synthesized from uracil **(2)** using elemental fluorine (*scheme 2*).



Scheme 2: Synthesis of Fluorouracil using F_2

Although the use of elemental fluorine for selective fluorinations is now more widely used, its use as a reagent for fluorine-free organic compounds is relatively un-researched[9]. Shlomo Rozen is a pioneer in this field, and sections 1.3 and 1.4 are devoted to reviewing his research progress in this area.

Before these reactions are discussed, the next section will review some important aspects about elemental fluorine.

1.2 Elemental Fluorine

1.2.1 Brief History

The synthesis and isolation of elemental fluorine in 1886 by Henri Moissan is a feat not to be taken lightly. Its closest counterpart, chlorine, was isolated more than 100 years earlier by Scheele in 1774[11], and both other non-radioactive halogens were isolated within the next 50 years (iodine by Courtois, *ca*. 1811, and bromine by Balard, *ca*. 1824)[11]. However, given the extreme reactivity of fluorine, the highly toxic nature of the reactants involved, and the apparatus available at the time, the isolation of fluorine was by far the most prestigious and also the most tragic.

Initial attempts to isolate fluorine date back some 72 years prior to Moissan taking up the challenge, when, in 1812, Humphrey Davy investigated the action of chlorine on red hot metal fluorides and also the electrolysis of hydrogen fluoride[11]. Apart from experiencing the toxic effects of concentrated hydrogen fluoride, in which he reported 'prolonged and excruciating pain to the fingers and eyes', his efforts were not successful[11].

More unfortunate than Davey's encounters with hydrofluoric acid were some whom followed his attempts. In the 1930's, G. Knox permanently lost his voice due to inhalation of the toxic gas and worse still, are the reported fatalities of P. Louyet and F. Nicklés[11].

Even though many scientists were discouraged by these reports, there were still those who attempted to synthesize and isolate fluorine(iv), with, according to British fluorine chemist H. J. Emeléus, 'often partial success in actually generating fluorine, but only failing in its isolation'[11].

It was not until 1884 that Moissan took up the challenge, and, on the 28th June 1886, using the apparatus shown in *figure 1*, he successfully declared the isolation of fluorine *via* electrolysis of anhydrous hydrogen fluoride containing small amounts of potassium fluoride[12] (v).

Not only was this an astonishing accomplishment for its time, and one which gained him the Nobel Prize in 1906, but it is also considered by many to be 'one of the most important discoveries of the last centuries'[13].

(iv) Published efforts were made by: G. Aimé (1833), M. Faraday (1834), E. Frémy (1854, 1856), T. L. Phipson (1861), H. Kammerer (1862), J. P. Prat (1867), P. Cillis (1868), G. Gore (1869, 1870, 1871), L. Varenne (1880), O. Loew (1881), B. Brauner (1881), and H. B. Dixon (1883)

(v) Similar attempts of electrolysis were made by Davy, the Knox brothers and Gore and Frémy, but were either carried out at temperatures too high or using hydrated substances[11]

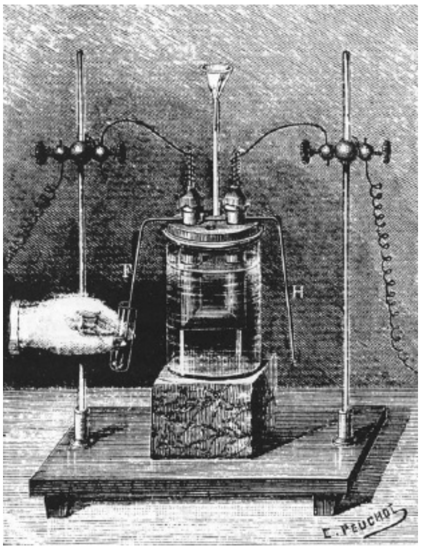


Figure 1: Drawing of Henri Moissan's apparatus used for the isolation of fluorine in 1886[12]

1.2.2 Preparation

1.2.2.1 Electrochemical preparation

With credit to Moissan, industrial generation of F_2 still uses a variation of his original procedure, namely the electrolysis of KF.*x*HF, in which the fluoride ion is oxidised at the anode to liberate fluorine gas. However, over the course of time, the materials used, along with the electrolyte composition and the equipment, have all been modified to increase product efficiency and prolong equipment life[14].

Although many slight modifications have been made to the cells, for the purpose of this review, these modifications can be broadly classed into three types; the 'low', 'medium' and 'high' temperature cells[14].

Moissan's cell was classed as a low temperature cell (15-50°C) and used KF.*x*HF as the electrolyte and, with only minor adjustments, this was successfully used to create F_2 for more than 30 years[14].

The next major change came in 1919 when Argo, Mathers, Humiston and Anderson introduced the high temperature cell (239-310°C), which used KF.HF as the electrolyte. In 1925, Lebeau and Damiens then introduced the medium temperature cell (70-130°C), which used KF.2HF as the electrolyte[14].

Intensive studies carried out on all three types concluded that the medium temperature cell was the most practical source of F_2. This type has the advantage of lower corrosion of components, combined with a low vapour pressure of HF over the electrolyte. Higher variations of electrolyte composition can also be tolerated[15].

Due to these benefits, the medium temperature cell was the main choice of cell to be scaled up for industrial manufacture from the pre 1940's laboratory production[15].

Today, large scale fluorine cells are used to produce the majority of industrial and commercially available fluorine and fluorine products. A cross-section view of the cell currently used by F2 Chemicals Ltd. is shown in *figure 2*, which is operated using an electrolyte temperature of 80-90°C and a current of 5 kA to produce 3.3 kg h^{-1} of fluorine[15]. The fluorine cell room at F2 Chemicals Ltd.[15] is shown in *figure 3*.

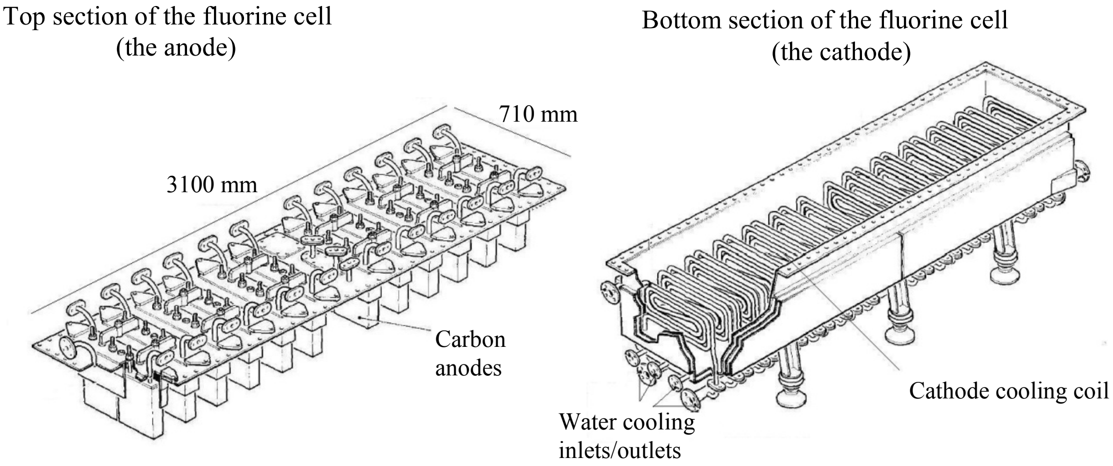


Figure 2: Fluorine cells used for large scale production of F_2

Figure 3: Fluorine cell room at F2 Chemicals Ltd., Preston

1.2.2.1.1 Anhydrous Hydrofluoric Acid

Anhydrous hydrogen fluoride (AHF) is the main precursor for the production of fluorine and, its large scale availability was a major attributing factor to the production of fluorine on an industrial scale(vi). Whilst AHF is still produced in the laboratory using Frémy's salt (KHF_2), commercially it is produced by the treatment of calcium fluoride, CaF_2, with concentrated sulfuric acid (*scheme 3*)[5]:

$$CaF_2 + H_2SO_4 \rightarrow 2HF + CaSO_4$$

Scheme 3: Production of AHF

1.2.2.2 Chemical preparation(vii)

Many early pioneers including Davey, Frémy, Moissan and Ruff, attempted the chemical synthesis and isolation of elemental fluorine but all to no avail[16-20]. The difficulty in obtaining elemental fluorine purely by chemical means, although sound in theory, is that the decomposition of fluorine compounds to liberate F_2 is thermodynamically very unfavourable.

Although trace amounts of fluorine were generated in several attempts, including those by Steel in 1959[21], the first practical synthesis was reported by Christie in 1986[22]. This approach was based on the anionic stabilization of high oxidation state transition metal (M) fluorides (*scheme 4* [1]), and the subsequent displacement of a weak Lewis acid (MF_4), from a stronger Lewis acid (SbF_5) (*scheme 4* [2]). The liberated MF_4 is thermodynamically unstable so spontaneously decomposes with the evolution of F_2 (*scheme 3* [3]).

$$MF_4 \text{ (unstable)} \rightarrow MF_6^{2-} \text{ (stable)} \qquad [1]$$

$$K_2MF_6 + 2SbF_5 \rightarrow 2KSbF_6 + MF_4 \qquad [2]$$

$$MF_4 \rightarrow MF_3 + F_2 \qquad [3]$$

Scheme 4: Chemical production of F_2

(vi) The F2 Chemicals Ltd. design (*figure 2*) typically uses 39-42 % w/w HF concentration, which is also quite typical of other operating cells[15]

(vii) Chemical preparation refers to means excluding electrolysis or photolysis discharge or without the use of elemental fluorine to synthesise starting materials

Christie successfully demonstrated this using manganese as the metal (*scheme 5*)[22]

$$K_2MnF_6 + 2SbF_5 \rightarrow 2KSbF_6 + MnF_3 + \tfrac{1}{2} F_2$$

Scheme 5

1.2.3 Properties

1.2.3.1 Physical properties

Only one isotope, ^{19}F, is found in nature, although the ^{18}F isotope, which has a half-life of 109.7 mins, can be synthesized and is often used as a radio tracer. An overview of the physical properties of fluorine (both diatomic and atomic), along with those of the other non-radioactive halogens for comparison, are summarized in *Table 1*[7,23-26].

Table 1 – Physical properties of atomic and diatomic halides

Property	**Fluorine**	**Chlorine**	**Bromine**	**Iodine**
Molecular properties (X_2)				
Melting point (°C)	-218.6	-101.0	-7.3	114.0
Boiling point (°C)	-188.1	-34.0	59.5	185.0
Density of solid (g cm^{-3})	1.3	1.9	3.4	4.9
Heat of vaporisation (kJ mol^{-1})	6.5	20.4	29.6	41.6
Heat of dissociation (kJ mol^{-1})	158.8	242.6	192.8	151.1
Atomic properties (X)				
Covalent radius (Å)	0.71	0.99	1.14	1.33
Ionisation potential (kJ mol^{-1})	1681	1250	1139	1007
Electron affinity (kJ mol^{-1})	-328.0	-348.8	-324.6	-295.3
Electronegativity (Pauling)	4.0	3.0	2.8	2.5

1.2.3.2 Chemical properties

Fluorine, which is strictly univalent, is the most reactive element of the Periodic Table[7]. This is not surprising given the weak diatomic bond of F_2 in comparison to its bonding strength with other elements (particularly carbon and hydrogen). *Table 2* shows some of the bond energies of fluorine with other common elements.

Table 2 – Bond energies of fluorine

Bond	**Bond dissociation energy (kJ mol^{-1})**
H-F	565
Si-F	565
C-F	485
P-F	490
N-F	283
O-F	188
F-F	155

The weak bond in F_2 is due to its small covalent radius combined with its relatively high nuclear charge which causes a decrease in overlap between bonding orbitals. The increased repulsion between the non-bonding orbitals reduces the bond strength of diatomic fluorine even further[7,25].

Fluorine, therefore, reacts with all the other elements (except nitrogen and some of the lighter noble gasses), often quite energetically (see section 1.3.1.1). It reacts with hydrogen with extreme violence to produce HF and also produces HF when reacted with water (along with oxygen and oxygen difluoride). Inter-halogen compounds are formed upon reaction with other halogens and all metals are corroded at room temperature upon exposure to high concentrations of fluorine[7,25].

1.3 Elemental Fluorine and Organic Synthesis

Although elemental fluorine can play an important role in direct fluorination of organic molecules, the main purpose of this review is to cover its use as a general synthetic organic tool. However, whilst the reader is directed to the references cited herein for a more comprehensive review[27-30], it is still important to briefly discuss the role that elemental fluorine has to play as a fluorinating reagent.

Moissan was the first to carry out fluorinations using neat fluorine on compounds such as CH_4, $CHCl_3$ and CCl_4, although he had little success and only observed a 'burning of the substrate with frequent explosions'[31].

Carbon tetrafluoride was the first perfluorocarbon to be made with fluorine and was isolated and characterised in 1926 by Lebeau and Damiens[32], and also in the same year by Ruff and Keim[33].

The first selective fluorination came in 1933, when Bockemeuller discovered that high dilution and low temperatures were the key to unlock the selective potential of elemental fluorine and proceeded to demonstrate this with the selective fluorination of aliphatic carboxylic acids[34].

Yet at the end of the 1960's, only a very limited literature of selective fluorinations using F_2 existed, upholding the current view that 'it cannot be considered a useful method'[35]. This however, is not accurate and by taking certain steps to avoid perfluorination, selective fluorination using elemental fluorine can be achieved. Before selective fluorination methods are discussed, perfluorination methods will be briefly discussed.

1.3.1 Direct Fluorinations using F_2

Direct fluorination of organic molecules proceeds *via* two routes, either a free radical or an electrophilic process[36]. In general, radical reactions are more rapid, less controlled, and usually unselective. In comparison, electrophilic reactions are slower, more controlled, and are directed by charge interactions[36]. Promotion of the electrophilic route will therefore increase control and selectivity.

1.3.1.1 Perfluorination (Radical Process)

Forming strong C-F and C-H bonds from weak F-F bonds is a highly exothermic process, which has led to the belief that fluorination generally proceeds *via* a free radical process (*scheme 6*)[27].

		ΔH (kJ mol^{-1})
Step 1	Initiation	$F_2 \rightarrow 2F^{\bullet}$	+159
Step 2	Propagation	$R\text{-}H + F^{\bullet} \rightarrow R^{\bullet} + H\text{-}F$	-131
		$R^{\bullet} + F_2 \rightarrow R\text{-}F + F^{\bullet}$	-314
Step 3	Termination	$R^{\bullet} + F^{\bullet} \rightarrow R\text{-}F$	-472
Overall		$R\text{-}H + F_2 \rightarrow R\text{-}F + H\text{-}F$	-430

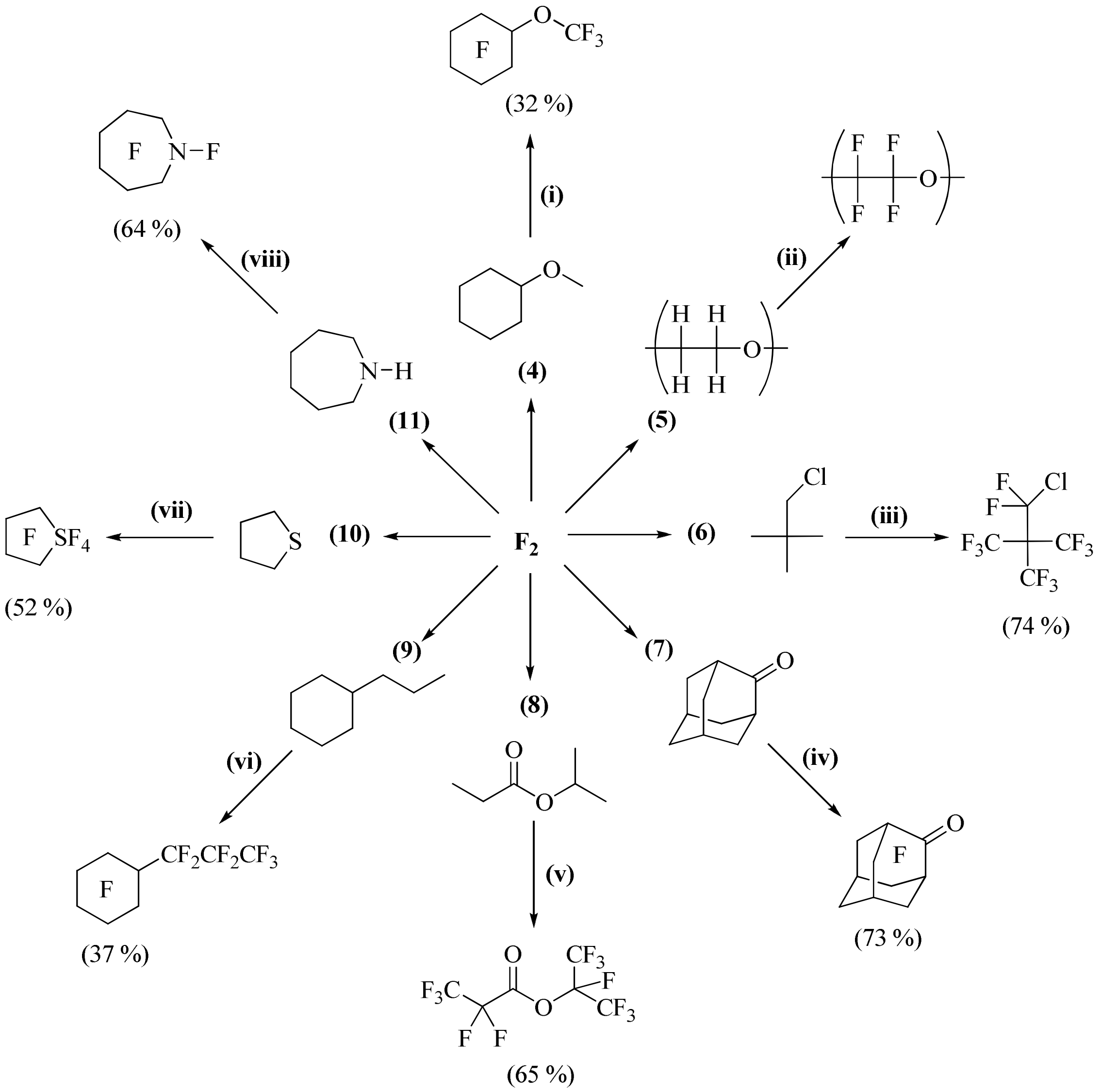
Scheme 6: Free radical fluorination process

The highly exothermic propagation and termination steps are said to offset the endothermic F_2 bond cleavage in the initiation step[27]. However, the dissociation of F_2 requires quite high temperatures (only ~1 % of fluorine is dissociated at room temperature), and this has led to the suggestion of an alternative initiation mechanism (*scheme 7)*, in which the radical species is generated by the reaction of fluorine with a C-H bond[27].

		ΔH (kJ mol^{-1})
Initiation	$RH + F_2 \rightarrow R^{\bullet} + F^{\bullet} + HF$	+28

Scheme 7: Alternative initiation process for free radical fluorinations

The uncontrolled nature of radical fluorination processes on organic molecules makes them much more suited to perfluorination reactions, an overview of which can be seen in *scheme 8*[27]. These include perfluorinations of ethers **(4)**, polyethers **(5)**, haloalkanes **(6)**, ketones **(7)**, esters **(8)**, alkanes **(9)**, and sulfur **(10)** and nitrogen containing **(11)** compounds.



Conditions: (i)-(v) F_2/N_2, aerosol process[(viii)]; (vi)-(viii) F_2/N_2, -78°C-rt, LaMar process[(ix)]

Scheme 8: Radical Perfluorinations performed using F_2

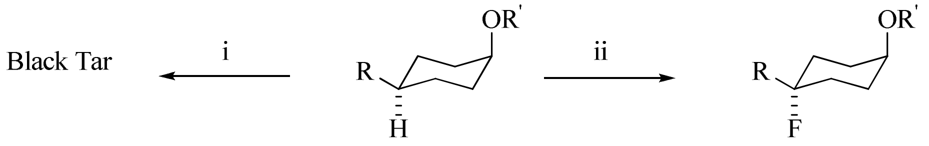
[(viii)] The 'aerosol' fluorination process, developed by Adcock in 1982, works by absorbing the substrate as an aerosol onto the surface of airborne sodium fluoride particles in the fluorination apparatus[28].

[(ix)] The 'LaMar' fluorination process developed by Lagow and Margrave in 1979, works by condensing the substrates at low temperatures into a tube packed with copper turnings. Diluted fluorine is initially passed through the tube followed by higher concentrations of fluorine and an increase of temperature. This process is carried out over several days[28].

1.3.1.2 Selective Fluorination (Electrophilic Process)

Selectivity can be increased in fluorinations but, in order to do this, certain measures have to be taken to inhibit the ‘unselective’ radical process. This can be partially achieved by effective cooling of the reaction, use of diluted substrates and diluted fluorine, and by carrying out reactions without the presence of light[29].

However, as was discovered by Rozen when F_2 was bubbled through a solution of protected 4-methyl cyclohexanol **(12)**, these steps alone are not enough. A fast radical reaction took place resulting in the formation of a black tar (*scheme 9 i*)[29]. On changing the solvent however, from the non-polar trichlorofluoromethane to the more polar mixture of trichlorofluoromethane and chloroform, Rozen discovered that selective substitution of the tertiary hydrogen at the C-4 position occurred **(13)** (*scheme 9ii*). Selective substitution at the C-4 position was also found to occur in other polar solvents[29].

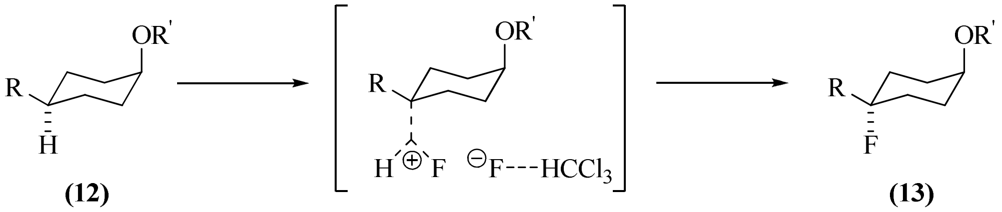


(12) **(13)** (60 %)

Conditions: R=Me, R’= pCOC$_6$H$_4$NO$_2$ (i) F_2/N_2, -78°C, $CFCl_3$; (ii) F_2/N_2, -78°C, $CFCl_3$:$CHCl_3$,

Scheme 9: Selective fluorination of methyl cyclohexanol

Due to retention of configuration of the substituted fluorine compound **(13)**, Rozen suggested that this was an electrophilic substitution at the C-H σ bond, with a mechanism similar to that previously suggested by Olah[30], involving a non-classical three centre, 2-electron transition state (*scheme 10*)[29].



(12) **(13)**

Scheme 10: Transition state suggested for the fluorination of methyl cyclohexanol

Ab initio calculations on the fluorination of methane supported the theory of an electrophilic substitution, along with the fact that neither products of elimination, nor products of rearrangement, were observed[29]. Further evidence of an electrophilic route was the observation that the reactions exhibited a very close parallel to electrophilic fluorination reactions using Selectfluor® [(x)].

It was proposed that the polar solvent not only encourages polarization of the fluorine molecule, therefore making it more susceptible to nucleophilic attack, but also, acts as an acceptor for the development of a F^- counterion through H bonding (*scheme 11*)[29]. It is also thought to serve as a good radical scavenger[29].

$$\mathrm{F{-}F} \rightarrow \overset{\delta+}{\mathrm{F}}{-}\overset{\delta-}{\mathrm{F}}\cdots\mathrm{X} \qquad \mathrm{X} = \text{polar solvent}$$

$$\mathrm{F{-}F} \rightarrow \overset{\delta+}{\mathrm{F}}{-}\overset{\delta-}{\mathrm{F}}\cdots\mathrm{H{-}Y} \qquad \mathrm{H{-}Y} = \text{acid}$$

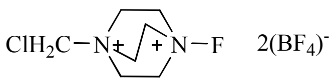
Scheme 11

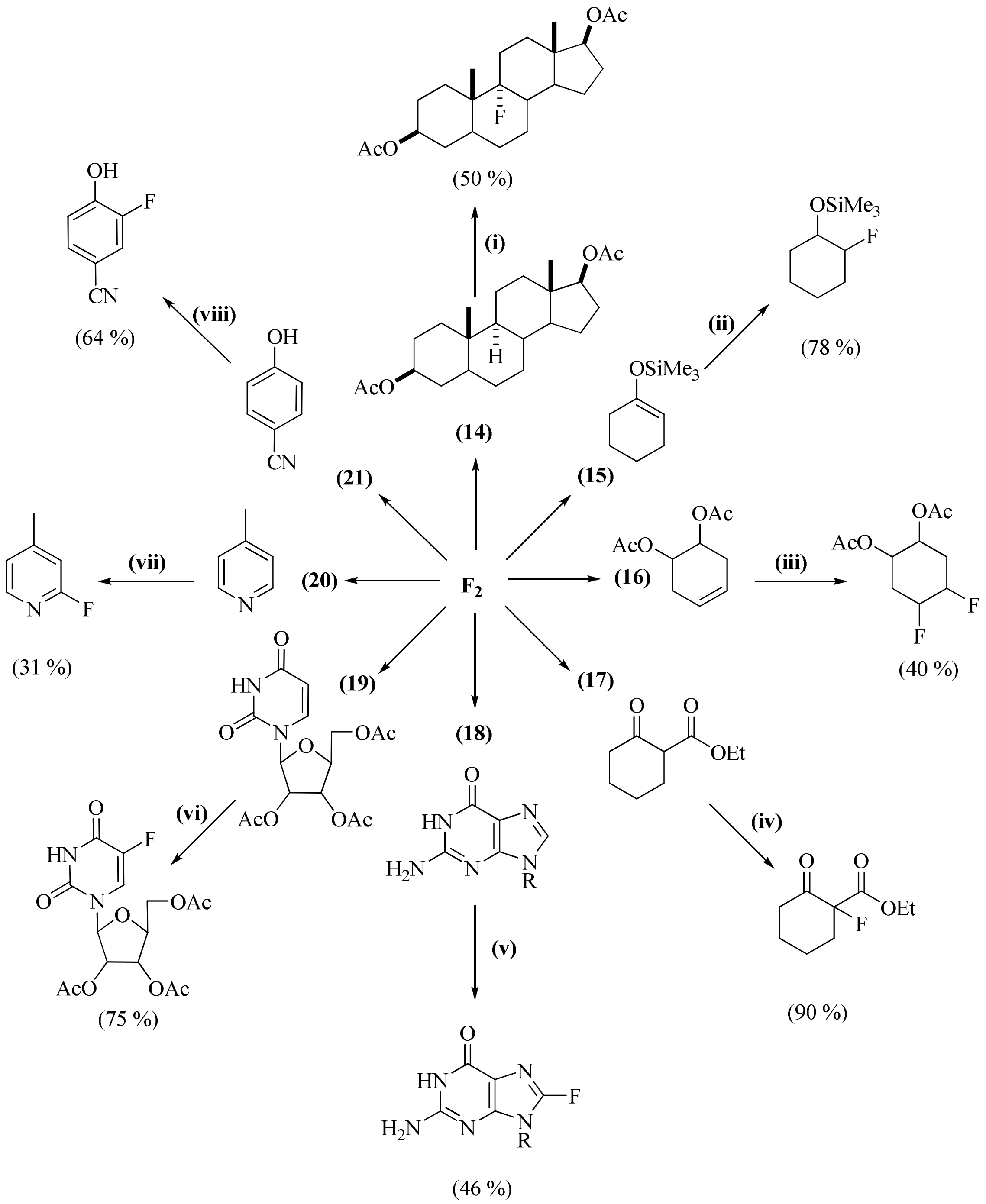
Selective electrophilic fluorinations have since been successfully carried out on a number of different compounds, *scheme 13* overleaf[27], which have included steroids **(14)**, alkenes **(15)** and **(16)** [addition across the double bond], 1,3-dicarbonyl systems, **(17)** nitrogen containing compounds including, nucleosides **(18)**, guanines **(19)**, and other pyridine derivatives **(20)**, and also benzenoid compounds **(21)**.

Evidence suggests that electrophilic fluorinations at unsaturated carbon proceed *via* nucleophilic attack on the fluorine, *scheme 12*[27].

Scheme 12: Nucleophilic attack on fluorine

[(x)] Selectfluor® is a common electrophilic fluorinating reagent and has the structure:





Conditions: (i) F_2, -78°C, $CFCl_3$, $CHCl_3$ (ii) F_2, -78°C, $CFCl_3$ (iii) F_2, -78ºC (iv) F_2, 10°C, HCOOH (v) F_2, rt, EtOH, $Et_4^+OH^-$ (vi) F_2, -78°C, $CHCl_3$, $CFCl_3$, EtOH (vii) F_2, -25°C, CF_2Cl-$CFCl_2$ (viii) F_2, 10°C, HCOOH

Scheme 13: Selective Electrophilic fluorination reactions performed using elemental fluorine

1.3.2 F_2 as a Reagent for Non-Fluorinated Compounds

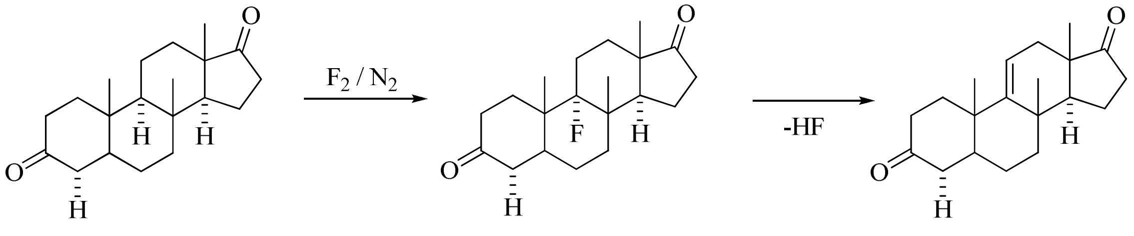
1.3.2.1 Introduction

Shlomo Rozen, a pioneer in this field, suggested that there are two driving forces for elemental fluorine to be utilized as a reagent for non-fluorine containing organic molecules[37]. The first is the generation of fluorine-containing intermediates which can easily eliminate H-F. The second is based on the *in-situ* generation of fluorine reagents which utilize the electronegative fluorine in some way. As this 'secondary fluorinated' reagent is made *in situ*, its isolation is not required and these reactions, which start and finish as fluorine free products, can be classed as 'one pot' reactions.

Section 1.3.2.2 describes the use of the HF elimination procedure, whilst the remaining sections all concern the *in situ* generation of fluorine reagents. The *in situ* fluorine reagents discussed are BrF or IF (section 1.3.2.3), acetyl, methyl, and *t*-butoxylhypofluorite (section 1.3.2.4) and hypofluorous acid (section 1.3.2.5). The hypofluorous acid reagent forms the basis of our research and will be covered in detail in section 1.4.

1.3.2.2 Creating alkenes at un-reactive sites

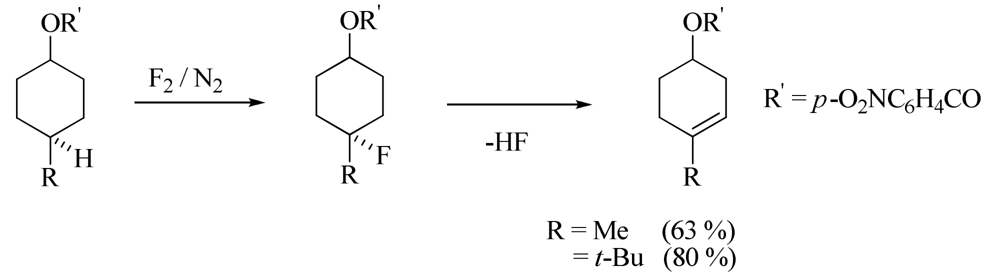
Steroids are good examples of compounds which have saturated carbons remote from any activating groups, and fluorine has been shown to be able to generate an alkene at tertiary C-H bond by fluorination followed by elimination[38]. Thus, the fluorination of 3,17-androstandione **(22)** (*scheme 14*) gave the 9α-fluoro derivative **(23)**, which eliminates H-F to give the alkene derivative **(24)**[38].



(22) **(23)** **(24)**

Scheme 14: Use of F_2 to create alkenes at un-reactive sites in steroids

Similarly, this process has been used to create a double bond at the difficult 4 position of 4-alkyl-cyclohexanol systems **(25)** (*scheme 15*)[39]. Fluorine substitutes the tertiary hydrogen at the 4 position **(26)**, and is eliminated along with hydrogen to give the alkene **(27)**.

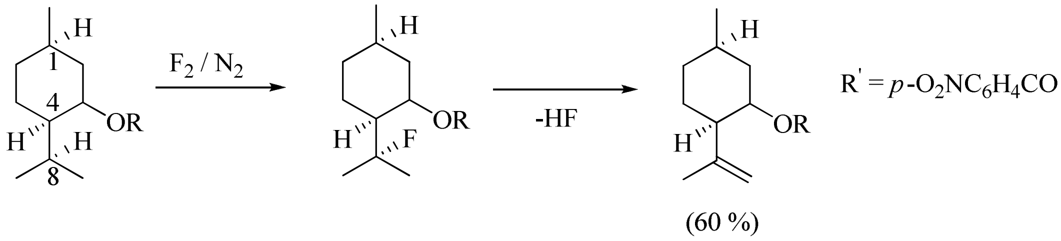


(25) **(26)** **(27)**

Conditions: **(26)** generated using 5% F_2, **(27)** generated at 10°C from a solution of **(26)** in benzene

Scheme 15: Use of F_2 to create alkenes at un-reactive sites in 4-alkyl-cyclohexanol derivatives

The high degree of selectivity of these fluorination reactions has also been demonstrated using the menthol derivative **(28)** (*scheme 16*). The selectivity of the fluorine was sensitive enough to differentiate between the three tertiary hydrogen atoms, which, according to calculations, the hybridization of each lies in the order of C1-H $sp^{2.7}$, C4-H $sp^{2.8}$ and C8-H $sp^{2.9}$. This was experimentally proven to be the case with fluorination of the 8 position **(29)** being predominant, and only 10 % of the fluorinated 4 position molecule being isolated[39].



(28) **(29)**

Conditions: **(29)** generated using 5% F_2, alkene product generated at 10°C from a soln. of **(29)** in dry benzene

Scheme 16: Use of F_2 to create olefins at un-reactive sites in menthol derivatives

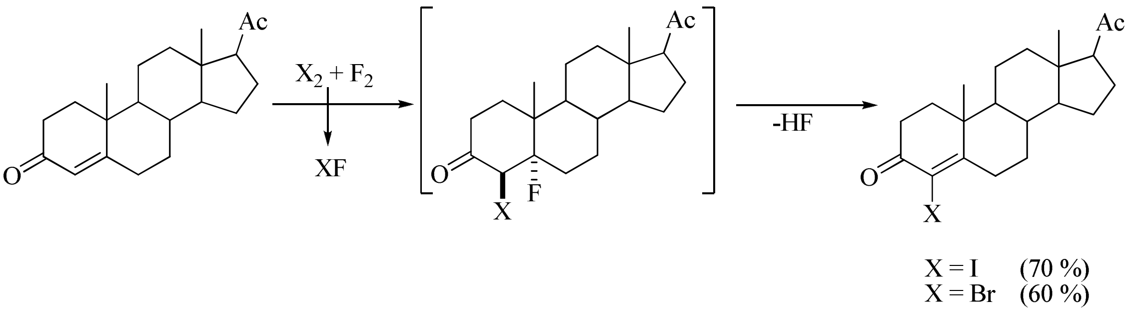
Acidic ($BF_3{\cdot}OEt_2$ or AHF) and basic (NaOH) dehydrofluorinating reagents can be used in the above two schemes, although, by using basic reagents the E2 mechanism is encouraged, therefore, avoiding carbocationic rearrangements encountered if acidic reagents are used.

1.3.2.3 Bromination and Iodination of π-Centers

1.3.2.3.1 Halogenation of Deactivated Alkenes

The reagents BrF and IF, in which the bromine and iodine are strong electrophiles, were prepared *in situ* by Rozen by reacting F_2 with Br_2 or I_2 at -78°C. Initially they were used to convert carbonyl groups to CF_2 moieties[40-41] and to carry out halofluorinations of deactivated double bonds[45] and, in both applications, they presented a particular benefit over other methods.

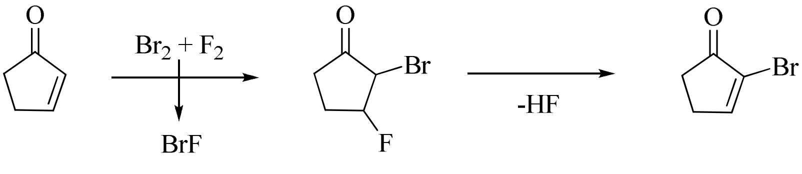
More applicable though is when the halogen is attached to a position with an acidic hydrogen, such as the reaction of XF with progesterone **(30)** to form the addition product -CX-CF- **(31)**[42]. Gentle heating removes the fluorine *via* elimination of HF to give the non-fluorinated product **(32)** (*scheme 17*)[42]. BrF was also applied to other electron poor alkenes (*scheme 18*)[42] which gave the brominated product *via* elimination of HF.



(30) **(31)** **(32)**

Conditions: XF generated using a suspension of the halogen and F_2 (10 %) at -78°C in $CFCl_3$ for 10 h; **(41)** generated with XF at -78°C for 10 h (not isolated)

Scheme 17: Halogenation of deactivated alkenes



(33) (90 %)

Conditions: XF generated using a suspension of the halogen and F_2 (10 %) at -78°C in $CFCl_3$ for 10 h; fluoro-bromo compound generated with XF at -78°C for 10 h (not isolated)

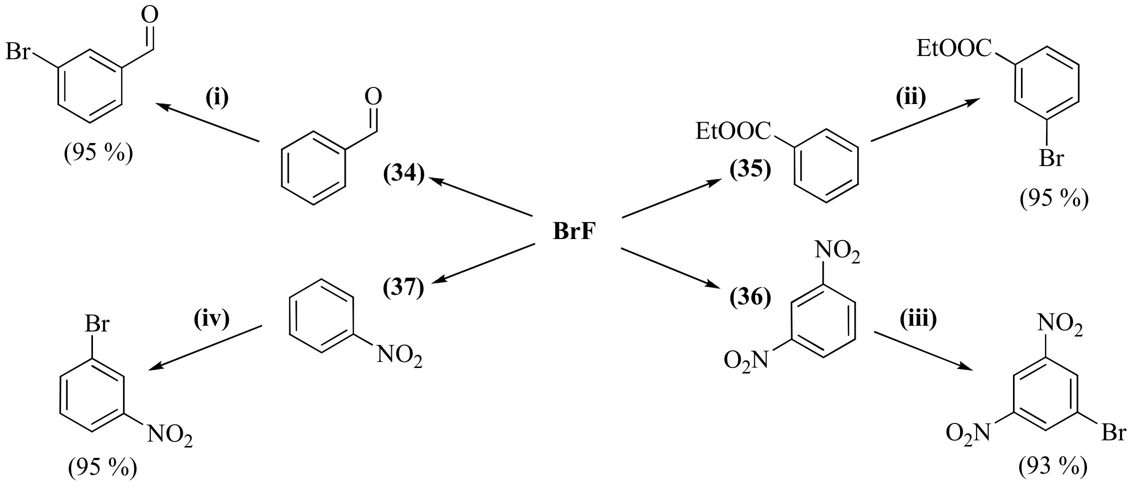
Scheme 18: Bromination of deactivated alkenes

1.3.2.3.2 Bromination of Aromatic compounds

Although activated aromatic compounds are easily brominated in certain solvents with just the halogen present, bromination of deactivated aromatic systems requires a strong Lewis acid catalyst such as $AlCl_3$, usually in stoichiometric amounts. This creates environmental and cost issues and also their use requires anhydrous conditions. Generally the processes are also quite lengthy, require high temperatures, produce relatively low yields and due to the generation of HBr, have a lowered atom efficiency[43].

Alternative routes either employ the use of NaOBr, which has the required electrophilic bromine but is not very soluble in organic solvents, or the use of an aniline derivative for bromo-diazotisation, which requires lengthy reaction times[43].

However, Rozen's use of BrF for electrophilic bromination and dibromination offers much shorter reaction times, mild conditions, improved yields and no metal catalyst. *Scheme 19* summarizes some of the deactivated aromatic compounds **(34-37)** that have been brominated[44].

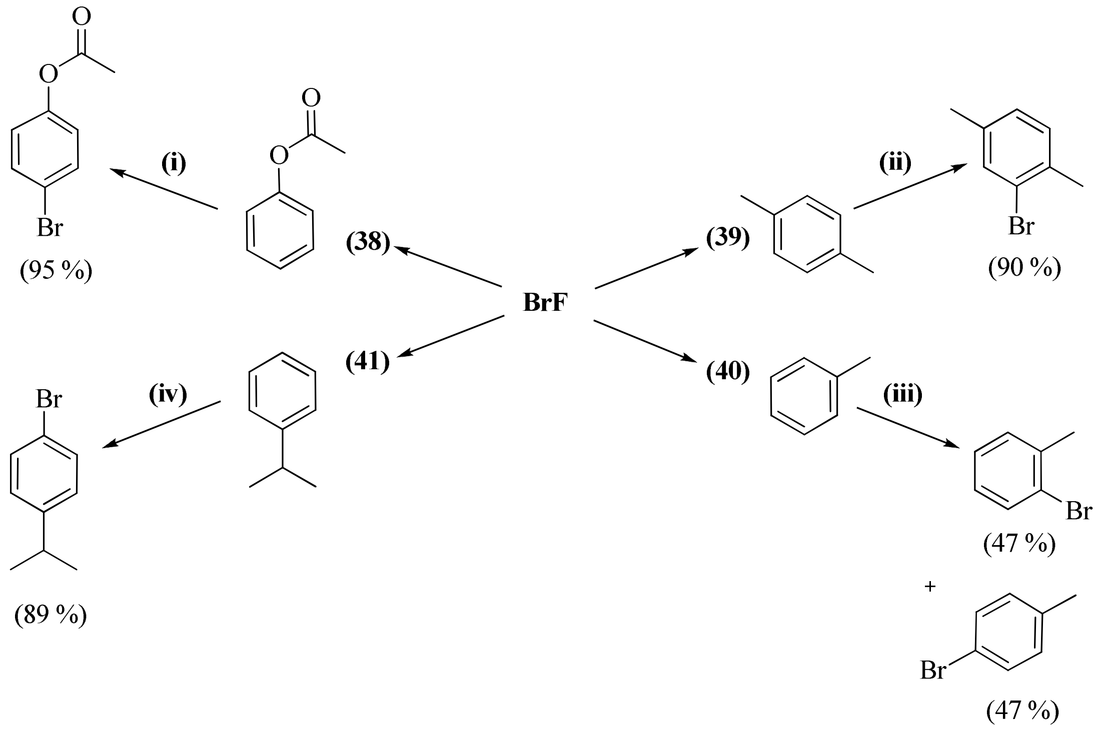


Conditions: BrF generated at -78°C in $CFCl_3$ using 10 % F_2; reactions carried out at -40°C in $CFCl_3$:$CHCl_3$(i) 1.45 mol. equiv. BrF, 15 mins; (ii) 1.5 mol. equiv. BrF, 120 mins; (iii) 7 mol. equiv. BrF, 45 mins; (iv) 1.7 mol. equiv. BrF, 120 mins

Scheme 19: Bromination of deactivated aromatics

A further advantage of the BrF reagent was that it is not a strong oxidising agent, therefore making it suitable for brominating compounds such as benzaldehyde **(34)** (*scheme 19*) without affecting the aldehyde moiety[44].

Activated aromatics such as **(38-41)** (*scheme 20)* were brominated within 15 mins[44].



Conditions: BrF generated at -78°C in $CFCl_3$; reactions carried out at -40°C in $CFCl_3$:$CHCl_3$ (i) 1.1 mol. equiv. BrF, 15 mins; (ii) 1.1 mol. equiv. BrF, 5 mins; (iii) 1.1 mol. equiv. BrF, 10 mins; (iv) 1.1 mol. equiv. BrF, 5 mins

Scheme 20: Bromination of activated aromatics

1.3.2.3.3 Iodination of Aromatic Compounds

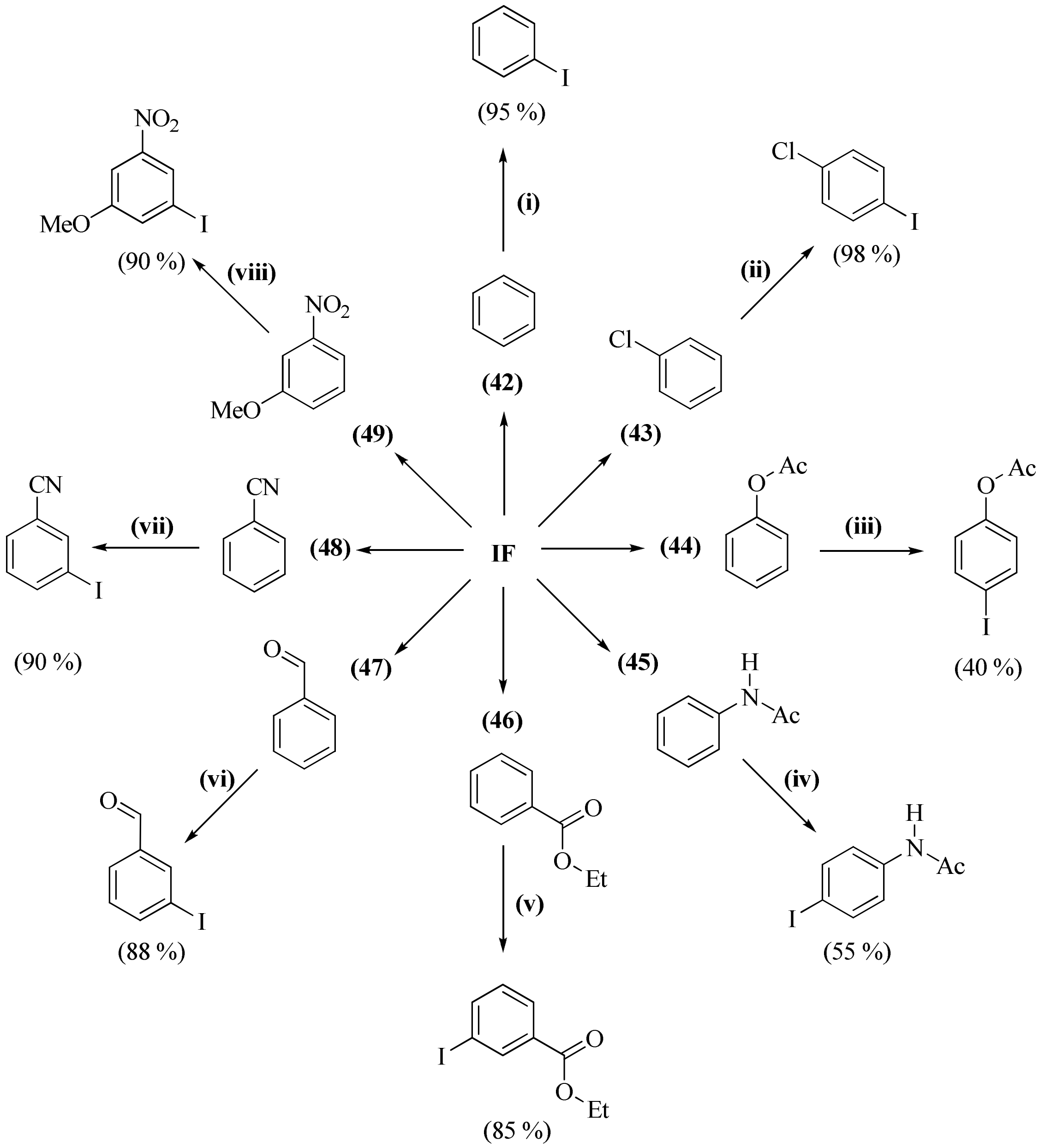
Of all the aromatic halogenations, iodinations pose the greatest challenge. The versatility in methodology is much less than exists for both bromination and chlorination[45].

Due to the low electrophilic strength of iodine, direct aromatic iodination requires a strong oxidising agent such as HNO_3 or liquid SO_3 and can only be carried out on strongly activated aromatic rings[46]. The indirect method converts an appropriate aniline derivative to the corresponding diazonium salt, which is then quenched with iodine or KI. Use of a Friedel Crafts catalyst is also not generally efficient as these cannot sufficiently increase the electrophilicity of iodine enough to halogentate deactivated aromatic rings[45]. Suitable polarization of iodine is still not obtained using the usual iodinating agents such as the *N*-iodo compound, silver salts of iodine or mercury derivatives[46].

However, even though the IF molecule is much less reactive than its BrF counterpart, it is still sufficiently polarized to accomplish aromatic iodinations, even with mildly deactivated rings[46]. *Scheme 21* summarizes some of the aromatic iodinations carried out by Rozen using IF.

Due to the decreased reactivity of IF, only mono-iodinations were achieved on the more deactivated rings and in comparison to the brominations, all required extended reaction times and increases in temperature[46].

As with the BrF reagent, IF was not sufficiently strong enough to oxidise the sensitive aldehyde group in benzaldehyde and also, no signs of iodination were observed on the ester or acetyl moieties[46].



Conditions:IF generated at -78°C in $CFCl_3$, reactions carried out in $CFCl_3$:$CHCl_3$; (i) -78°C, 24 h; (ii) -20°C, 3 h; (iii) 25°C, 1 h; (iv) -20°C, 0.5 h; (v) 25°C, 16 h; (vi) 25°C, 3 h; (vii) 25°C, 16 h; (viii) -78°C, 4 h

Scheme 21: Iodination of activated and de-activated aromatics

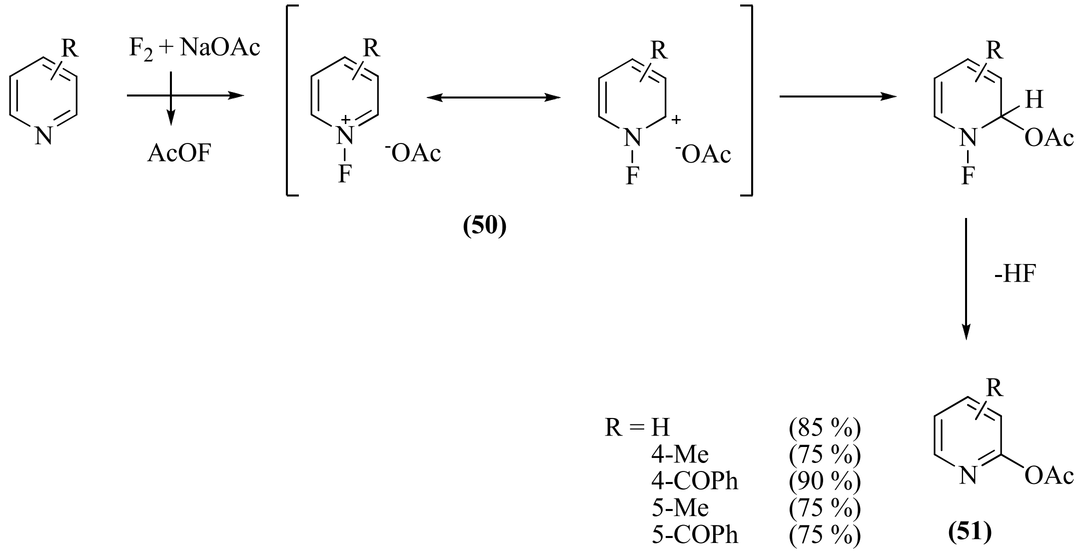
1.3.2.4 Hypofluorites

1.3.2.4.1 Acetyl Hypofluorite

In 1981 Rozen synthesized acetyl hypofluorite by passing fluorine through a suspension of sodium acetate[46] and applied it extensively to fluorinations of various compounds[47].

More appropriate to this review is when the AcOF was applied to pyridine systems. Apart from the Chichibabin reaction, nucleophilic substitution of the pyridine ring is very difficult, generally requiring harsh conditions and producing poor yields[48-49]. The most practical method for introducing an oxygen atom at the 2-position was to prepare the *N*-oxide and carry out a rearrangement by prolonged heating with acetic anhydride[50] or $SbCl_5$[51].

The fluorine in AcOF is attacked by the pyridine's nitrogen creating a positively charged *N*-fluoropyridinium intermediate **(50)** (*scheme 22*)[52-53] which, in the absence of other nucleophiles, reacts with the acetate ion. HF elimination and restoration of aromaticity then take place to give the 2-acetoxypyridine **(51)**



Conditions: **(31)** generated at -78°C using 15% F_2

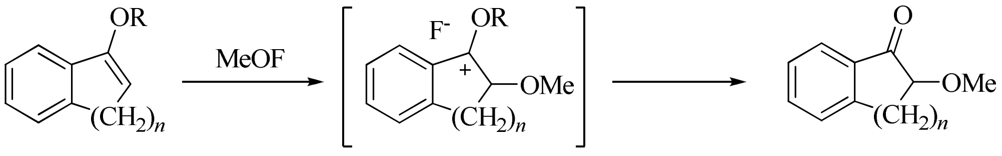
Scheme 22: Activation of pyridines using AcOF

1.3.2.4.2 Alkyl Hypofluorites

Until 1991 it was thought that compounds possessing a fluoroxy group bonded to an alkyl group were too un-stable to be synthesized. This is because the hydrogen and fluorine atoms are too close to prevent the spontaneous elimination of HF. However, in an analogous reaction to his synthesis of hypofluorous acid (section 1.3.2.5), Rozen was able to synthesize and isolate methyl hypofluorite (MeOF) by passing fluorine through a mixture of methanol and acetonitrile[55].

Due to its bonding with the more electronegative fluorine atom, the oxygen molecule is unique in that is possess a methoxylium species (MeO^+) therefore leaving the fluorine bound to the oxygen nucleophilic.

Like the acetyl hypofluorite, MeOF can be used as an electrophilic fluorinating reagent, adding across many types of double bonds to give fluorinated methoxy adducts[56]. Of more relevance to this review however, are its reactions with electron rich alkene centres such as enol derivatives[57]. Enol acetates, silylenol ethers and methyl enol ethers of tetralone **(52)**, 1-indanone **(53)** and acetophenone **(54)** all reacted with methyl hypofluorite to give the corresponding α-methoxy carbonyl **(55)** in reasonable to good yield (*scheme 23*).

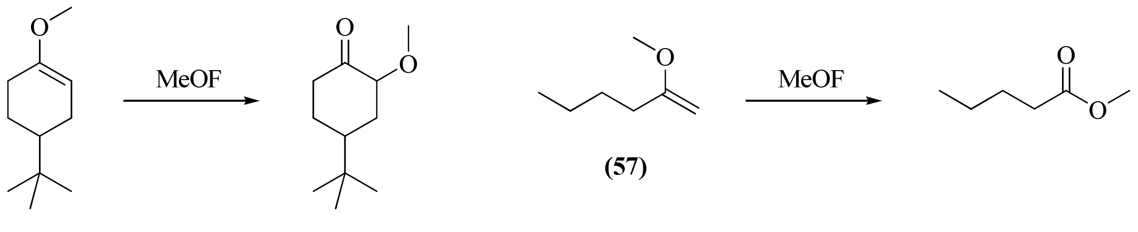


R = Ac, Me or $SiMe_3$
(52) $n = 2$
(53) $n = 1$
(54) $n = 0$

(55)

Scheme 23: Electophilic Methoxylation of Enol Ethers

Aliphatic methyl enol ethers **(56)-(57)** were also successfully methoxylated using methyl hypofluorite (*scheme 24*)[57].

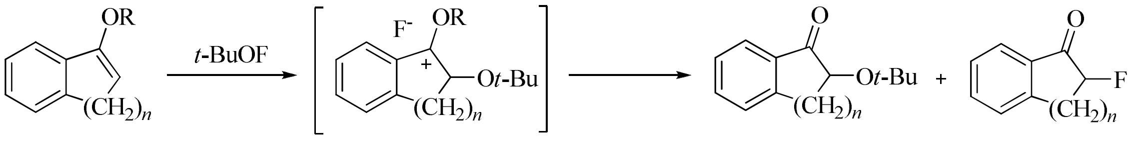


(57)

(56)

Scheme 24: Electrophilic Methoxylation of the Aliphatic Methyl Enol ethers

t-Butyl Hypofluorite (*t*BuOF) was synthesised by Rozen two years later[58] using *tert*-butyl alcohol in acetonitrile and undergoes similar reactions to methyl hypofluorite, adding across many types of double bonds to give fluorinated butoxy adducts[58] and creating the α-*t*-butoxy ketones **(58)** (*scheme 25*)[58-59] of silyl, acetetyl and methyl enol ethers, without the use of the usually required heavy metal catalysts[60-61].



R = Ac, Me and $SiMe_3$
n = 1
n = 2

(58) **(59)**

Scheme 25: Electrophilic Butoxylation

A major difference between the *t*BuOF reactions and the analogous MeOF reactions are the difference in size of the electrophilic substrate. The bulky *t*-butyl group requires longer reaction times, which, results in some radical decomposition of the reagent whose half-life is about 1 hour at room temperature. Therefore, not only are the yields of the *t*-butoxy analogues lower for all reactions, but small amounts of side products **(59)** were also obtained[58].

1.3.2.5 Hypofluorous Acid as an Oxygen Transfer Agent

Hypofluorous Acid (HOF) was first prepared by Nobel and Pimentalin 1967, by photolysis of F_2 and water in a solid nitrogen matrix; however, the highly unstable nature of the acid means it decomposes at temperatures above -100°C[62]. Owing to its instability and the complex apparatus required for its synthesis, HOF was thought to have little practical use in organic synthesis[62].

However, in 1986, Rozen and co-workers discovered a way to stabilize HOF; by passing F_2 through an aqueous solution of acetonitrile, at 0°C, the fluorine and water react to form HOF which complexes with the acetonitrile. The HOF.MeCN complex is much more stable than HOF itself and has a reported half life of up to two hours at room temperature[62].

HOF is unique as it possesses an oxygen which, because it is attached to the only element which is more electronegative, possesses a permanent positive dipole which therefore makes it the ideal candidate as an electrophilic oxygen transfer agent.

Rozen subsequently investigated the oxidising capabilities of the complex on a wide variety of substrates and discovered that HOF.MeCN is a very powerful oxidising agent, capable of oxidising a wide variety of functional groups, some of which were previously un-oxidizable, in very short reaction times and at ambient conditions.

As the main scope of this thesis is based upon the generation and use of hypofluorous acid, the following section will be devoted to discuss in detail the functional groups that, to date, HOF.MeCN complex has been used to oxidise.

1.4 The HOF.MeCN Complex as a Powerful Oxidant

1.4.1 Introduction to Oxidations in Organic Chemistry

1.4.1.1 Definition

Oxidation in organic chemistry is regarded as ‘the loss of electron density at a carbon centre’, which is achieved by increasing the bonding of a carbon atom to a more electronegative heteroatom, such as oxygen, nitrogen or a halogen. With this in mind, a functional group is said to be oxidised if the carbon atom carrying the functional group increases the number of bonds it has to a heteroatom, with the compound that has donated the heteroatom being the oxidant. For the purpose of this review, oxidation will always infer that the heteroatom is ‘oxygen’, and that the oxidising agent is therefore an ‘oxygen transfer agent’.

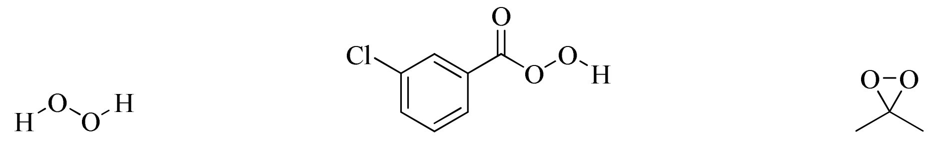
As oxygen is the second most electronegative element, its addition to any element (other than fluorine) will decrease the electron density around that element and, therefore, nitrogen and sulfur are both oxidised by the addition of oxygen.

1.4.1.2 Conventional Oxidants

The purpose of this section is to briefly outline some of the current oxidants used in organic chemistry and the hazards associated with using them. Mechanistic detail will not be covered as a vast literature already exists.

The majority of oxidations in organic chemistry are either carried out using substances bearing the peroxy moiety (R-O-O-R) or metal oxides and, for the purposes of this review, these will be referred to as ‘conventional oxidants’[63].

Peroxy oxidising agents, examples of which are shown in *figure 4*, make use of the electronegativity of oxygen to induce a small positive dipole on the adjacent oxygen, thus making it sufficiently electrophilic for nucleophilic attack. This is made more favourable by the resonance stabilisation of a leaving carboxylic group such as a peroxy acid, as in *m*CPBA, or relief of strain of a small dioxirane ring, as in DMDO[64].

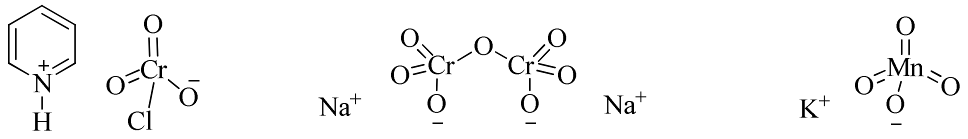


Hydrogen Peroxide *meta*-chloroperoxybenzoic acid (*m*CPBA) Dimethyldioxirane (DMDO)

Figure 4: Common peroxy oxidising agents

Peroxides, however, are usually quite dangerous. One of the strongest and most common peroxy oxidising agents, hydrogen peroxide, is, depending on concentration, highly flammable, explosive, corrosive, and toxic (particularly if ingested). Their highly reactive nature also means particular care must also be taken for safe disposal[64].

The oxides of metals are also commonly used as oxidising agents, examples of which are given in *figure 5*.



pyridinium chlorochromate PCC sodium dichromate potassium permanganate

Figure 5: Common metal oxidising agents

Metal oxidising agents, however, are particularly harmful to the environment and their disposal requires more specialist and costly methods. They are also generally quite toxic and carcinogenic. For the purposes of this review, comparisons, when available, will be made with conventional oxidants to exhibit the benefits of HOF.MeCN.

1.4.2 Generation of HOF.MeCN and General Reaction Procedure

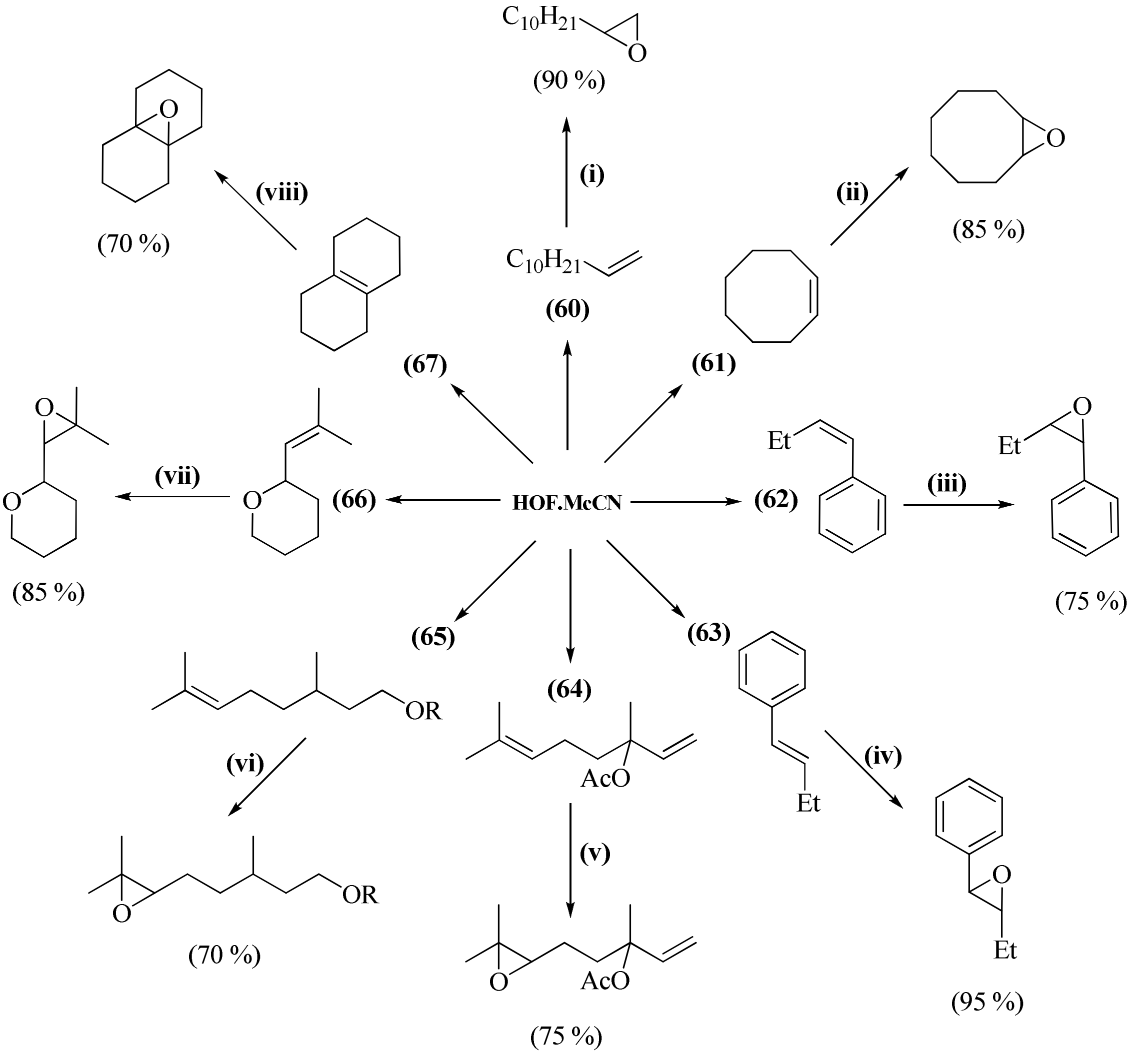
Conditions for all of Rozen's reactions (F_2 amounts, reaction times and temperatures) when available are shown in each reaction scheme. However, the general procedure for each reaction reported by Rozen was as follows: the required concentration of HOF.MeCN was generated in a glass vessel by passing F_2 (diluted to 10-15 % in nitrogen) at 400 mL min^{-1} through a 9:1 mixture of acetonitrile:water (-10°C). The oxidant was then added to a temperature controlled solution of the substrate (4-10 mmol) in CH_2Cl_2 (20-50 mL) and mechanically mixed. After an appropriate time the reaction was quenched using a saturated $NaHCO_3$ solution and then worked up using standard extraction procedures. Variations, if any, of this general procedure will be stated in the appropriate section.

1.4.3 HOF.MeCN Oxidations

1.4.3.1 Epoxidation of Alkenes

Of all the functional group oxidations using HOF.MeCN that Rozen has carried out, epoxidation of alkenes has received the most attention.

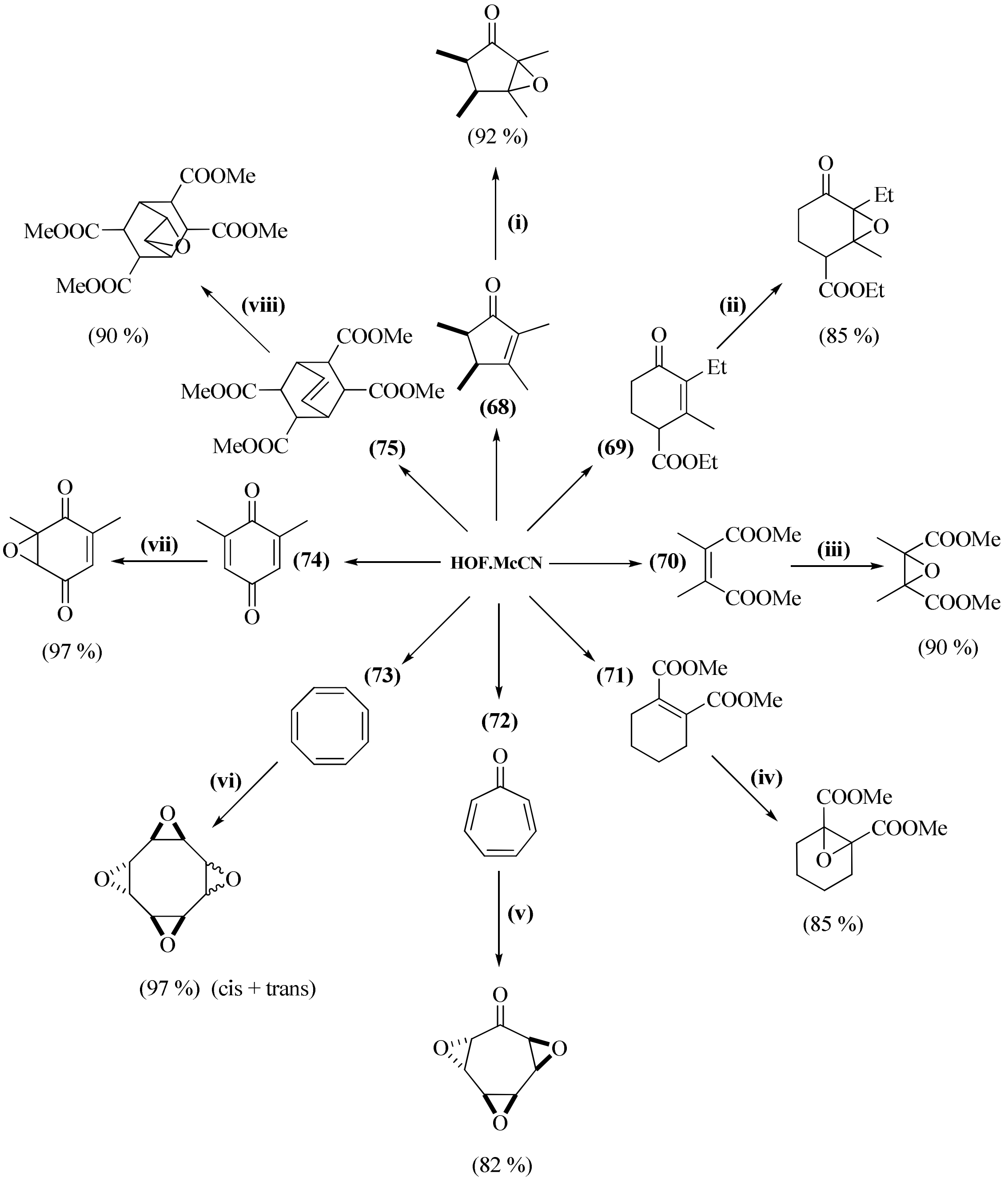
Some activated alkenes epoxidized by Rozen are shown in *scheme 26*, which includes di- **(60-63)**, tri- **(64-66)** and the more crowded tetra-substituted **(67)** alkenes. All were easily oxidised to their corresponding epoxide, usually within minutes, and in very good yields[65-66].



Conditions: (i)-(vii) 1 min, 0°C, mol. equiv. HOF.MeCN; (xiii) 5 sec, -35°C, mol. equiv. HOF.MeCN

Scheme 26: Oxidation of activated alkenes using HOF.MeCN

However, due to the powerful oxidizing capabilities of the HOF.MeCN complex, even strongly deactivated alkenes, such as those in *scheme 27*[67], are easily epoxidized.



Conditions: All molar equivalents refer to HOF.MeCN (i) 1 min, 0°C, 1.1 mol. equiv. (ii) 15 mins, rt, 15 mol. equiv. (iii) 10 mins, 0°C, 5 mol. equiv. (iv) 5 mins, rt, 3 mol. equiv. (v) 15 mins, 0°C, 2 mol. equiv. (vi) 30 sec, 0°C (vii) 5 mins, 0°C, 2 mol. equiv. (viii) 30 sec, 0°C

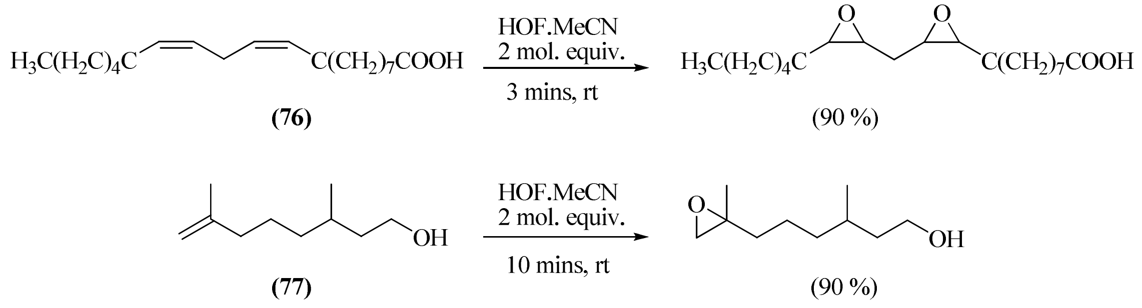
Scheme 27: Oxidation of deactivated alkenes using HOF.MeCN

Epoxidation of the deactivated and sterically hindered enones **(68)** and **(69)**, have never been reported and treatment by Rozen with H_2O_2, *m*CPBA and DMDO, in all cases, gave less than a 10% yield[67]. Treatment with HOF.MeCN gave the corresponding epoxides in less than a minute, and in yields of 92% and 85% respectively[67].

The very stable aromatic ketone tropone **(72)**, had never been directly epoxidized and the only existing method for the preparation of its tri-epoxide requires five steps, over 94 hours, and using a number of different oxidising agents. Tri-epoxidation of tropone **(72)** using HOF.MeCN took only 15 minutes[67]. Similarly, the four double bonds of cyclooctatetraene **(73)** were all epoxidized on treatment with HOF.MeCN, this time in just 30 seconds. To carry this out using DMDO requires 17 days[67].

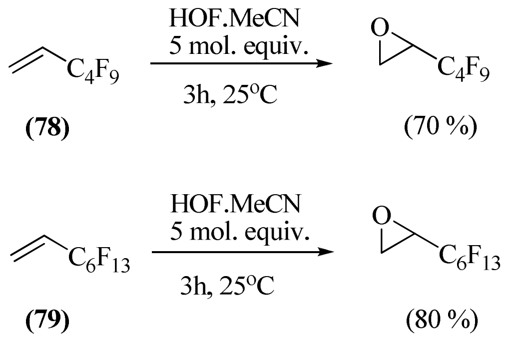
Treatment of the weakly nucleophilic bond in the very oxygen rich tetramethylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylate **(75)** with *m*CPBA and DMDO resulted in zero epoxide formation. However, using HOF.MeCN, the corresponding epoxide was obtained in just 1 minute[67].

The HOF.MeCN complex also exhibits greater chemoselectivity than conventional oxidants of the alkene in unsaturated acids or alcohols, which react with the sensitive carboxy and hydroxyl functional groups to produce the peroxide[68]. Thus, previous attempts to epoxidize linoleic acid **(76)** (*scheme 28*) gave a yield of just 35%[68], whereas HOF.MeCN successfully epoxidized **(76)** in just 3 minutes with a 90 % yield[68]. Citronellol **(77)** (*scheme* 28) was used to demonstrate the HOF.MeCN complexes ability to cope with unsaturated alcohols and the corresponding epoxide was obtained in 90% yield[68].



Scheme 28: Oxidations of alkenes in the presence of acids and alcohols

Polyfluorinated alkenes are also too deactivated for direct electrophilic epoxidation, which is therefore carried out *via* indirect methods. Attempts by Rozen to epoxidize the electron deficient double bond in polyfluorohexene **(78)** using *m*CPBA or trifluoroperacetic acid were un-successful, even with extended reaction times[69]. Although reaction times of 2 hours were required, along with an increased temperature of 25°C, the action of HOF.MeCN on polyfluorohexene **(78)** and polyfluorooctene **(79)** (*scheme 29*) was successful in epoxidizing the alkene[69].



(78) (70 %)

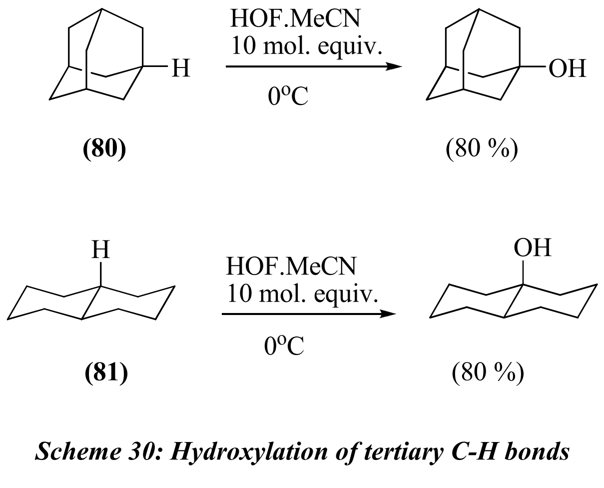
(79) (80 %)

Scheme 29: Oxidation of polyfluorinated hexene

1.4.3.2 Tertiary Hydroxylation of C-H Bonds

In molecules that do not possess double bonds, the bonds most susceptible to electrophilic attack are those with the highest *p*-orbital contribution and usually, these are the tertiary C-H bonds situated far away from any electron withdrawing groups[70].

Rozen discovered that tertiary C-H bonds of compounds **(80)** and **(81)** could be hydroxylated using HOF.MeCN in good yields (*scheme 30*)[70].

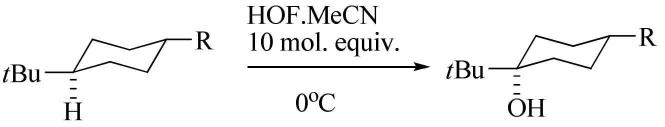


(80) (80 %)

(81) (80 %)

Scheme 30: Hydroxylation of tertiary C-H bonds

If heteroatoms are present in the starting material, the tertiary C-H bond is practically immune to hydroxylation using peroxy reagents[70], but, with HOF.MeCN, the previously inaccessible hydroxylated compounds **(82)** and **(83)** (*scheme 31*) were obtained, albeit in quite low yields[70].



(82) R = OAc (50 %)

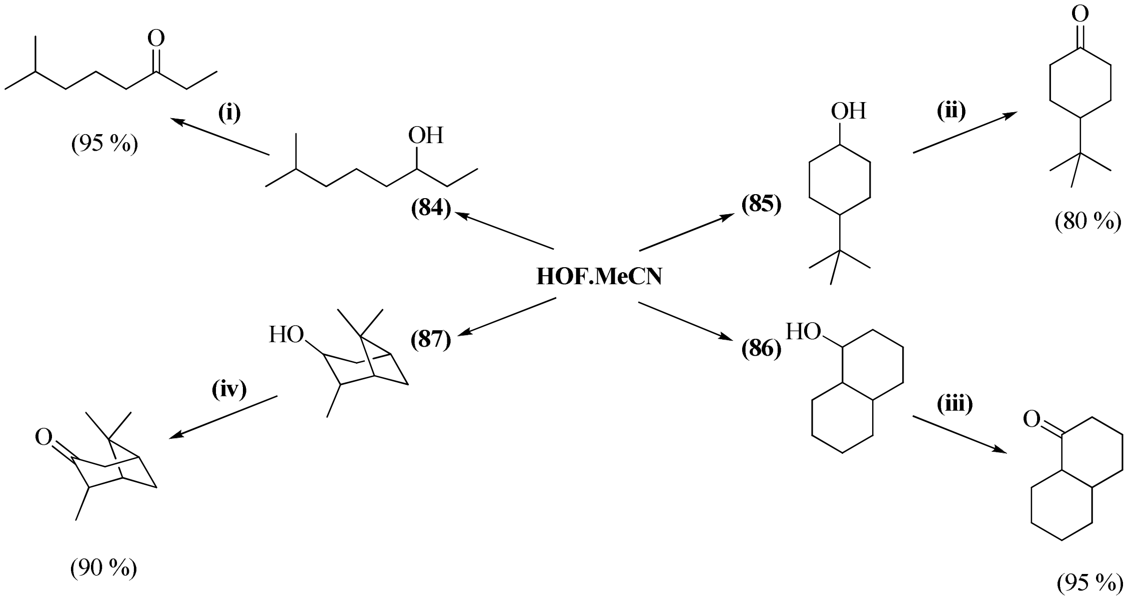
(83) R = Cl (30 %)

Scheme 31: Hydroxylation of tertiary C-H bonds in the presence of electron withdrawing groups

1.4.3.3 Oxidation of Secondary Alcohols to Ketones

Chemoselective oxidation of secondary alcohols to ketones is usually carried out using a solution of chromium trioxide[71] (i.e. from sodium or potassium dichromate) which raises disposal and environmental issues. This procedure also requires dilute H_2SO_4, which can reduce yields of acid sensitive systems[71].

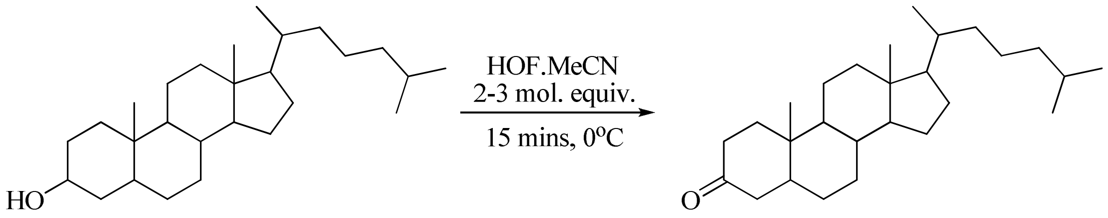
HOF.MeCN is able to oxidise a wide variety of secondary alcohols **(84-87)** (*scheme 32*) to their corresponding ketones, in very high yields and short reaction times[72].



Conditions: All reactions were carried out at 0°C using 2-3 mol. equiv. HOF.MeCN (i) 30 mins, (ii) 2 mins, (iii) 5 mins, (iv) 30mins

Scheme 32: Oxidation of secondary alcohols

The oxidation of the steroid **(88)** (*scheme 33*) was also achieved in good yield[72].

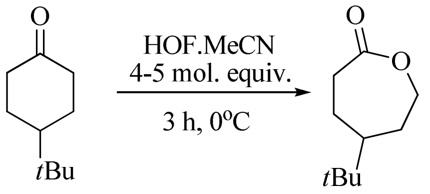


(88) (80%)

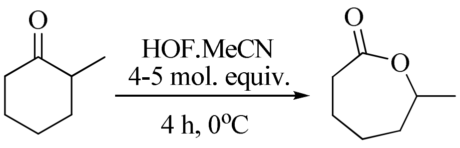
Scheme 33: Oxidation of secondary alcohols in steroids

1.4.3.4 Baeyer-Villiger Oxidations

Classical Baeyer-Villiger reactions with peracids usually require high temperatures and extended reaction times (i.e. >24 hours)[72]. However, these reaction conditions can be greatly improved by using HOF.MeCN, as was demonstrated using ketones **(89)** and **(90)** (*scheme 34*), which were both oxidised at 0°C in 3 and 4 hours respectively[72].



(89) (85 %)



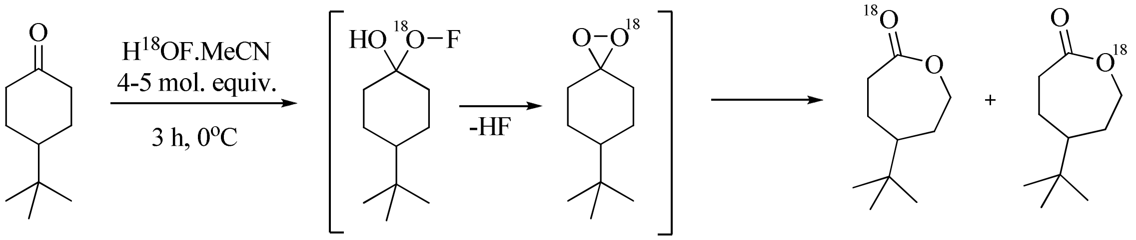
(90) (85 %)

Scheme 34: Baeyer-Villiger Oxidations using HOF.MeCN

Rozen proposed that the reduced reaction time required by HOF.MeCN to complete the Baeyer-Villiger oxidations is due to the difference in reaction mechanisms between the two reagents[72].

The peracid mechanism was deduced by Doering[73] using ketones labelled with the ^{18}O isotope. Doering showed that the original ketone provided the carbonyl oxygen of the product and that the peracid provides the etheric oxygen atom.

The mechanism of the HOF.MeCN oxidation is proposed to be similar to that postulated by Baeyer and Villiger themselves[74], which is that *via* a dioxirane ring formation **(92)** (*scheme 35*). The dioxirane mechanism would lead to scrambling of the oxygen atoms and Rozen proved this to be the case by using radio labelled $H^{18}OF.MeCN$ and *t*-butylcyclohexanone **(91)**[72]. The resulting carbonyl and etheric oxygen of the lactone were composed of both the ^{18}O and ^{16}O in equimolar amounts.



(91) **(92)** 1 : 1 (90 %)

Scheme 35: Baeyer-Villiger Oxidations using radio labelled HOF.MeCN to determine reaction mechanism

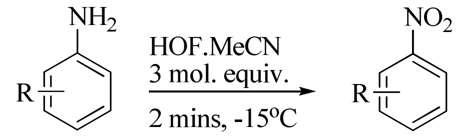
1.4.3.5 Amine Oxidations

1.4.3.5.1 Anilines

Oxidation of anilines to the corresponding nitro group, whilst generally more efficient than aliphatic amines, still requires quite harsh conditions, particularly for electron poor anilines. Electron rich anilines are usually oxidised using peracetic acid, DMDO or sodium perborate, whilst electron poor anilines require stronger oxidants such as peroxytrifluoroacetic acid or peroxydisulphuric acid[75].

HOF.MeCN is capable of oxidising electron poor anilines such as 4-aminoacetophenone **(93)** and 4-nitroaniline **(94)**, and electron rich anilines such as 2-methoxyaniline **(95)** and 4-aminoacetanilide **(96)** (*scheme 36*), all in very high yields and very short reaction times[75].

The use of HOF.MeCN also allows oxidations to be carried out in the presence of a hydroxy group without affecting the hydroxyl moiety. Thus, 4-aminobenzoic acid **(97)** and 3-aminophenol **(98)** (*scheme 36*) were converted to their corresponding nitro derivatives without formation of the respective perbenzoic acid or quinine compound[75].



(93)	R = 2-CO_2Me	(100 %)
(94)	R = 4-NO_2	(95 %)
(95)	R = 2-OMe	(82 %)
(96)	R = 4-NHAc	(80 %)
(97)	R = 4-CO_2H	(80 %)
(98)	R = 3-OH	(71 %)

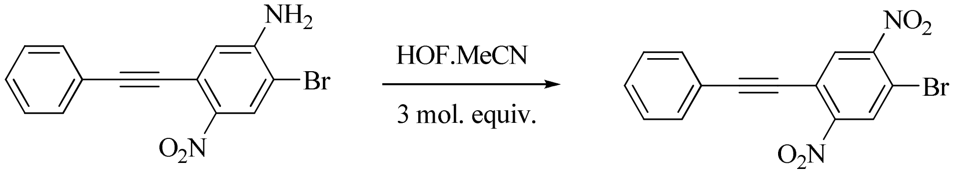
Scheme 36: Aniline oxidations using HOF.MeCN

Rozen discovered that an excess of 3 molar equivalents of HOF.MeCN were required to oxidize each amine, which led him to postulate the following reaction sequence (*figure 6*)[76].

$$R-NH_2 \xrightarrow[-HF]{HOF.MeCN} \left[R-NHOH\right] \xrightarrow[-HF,\ -H_2O]{HOF.MeCN} \left[R-NO\right] \xrightarrow[-HF]{HOF.MeCN} R-NO_2$$

Figure 6: Amine oxidation sequence using HOF.MeCN

Electron deficient anilines were also successfully oxidized using HOF.MeCN by Tour *et al.*, who, after failed attempts to oxidize the amine group of compound **(99)** using sodium perborate and DMDO, used HOF.MeCN to selectively oxidize the amine without affecting the alkyne moiety (*scheme 37*)[77].

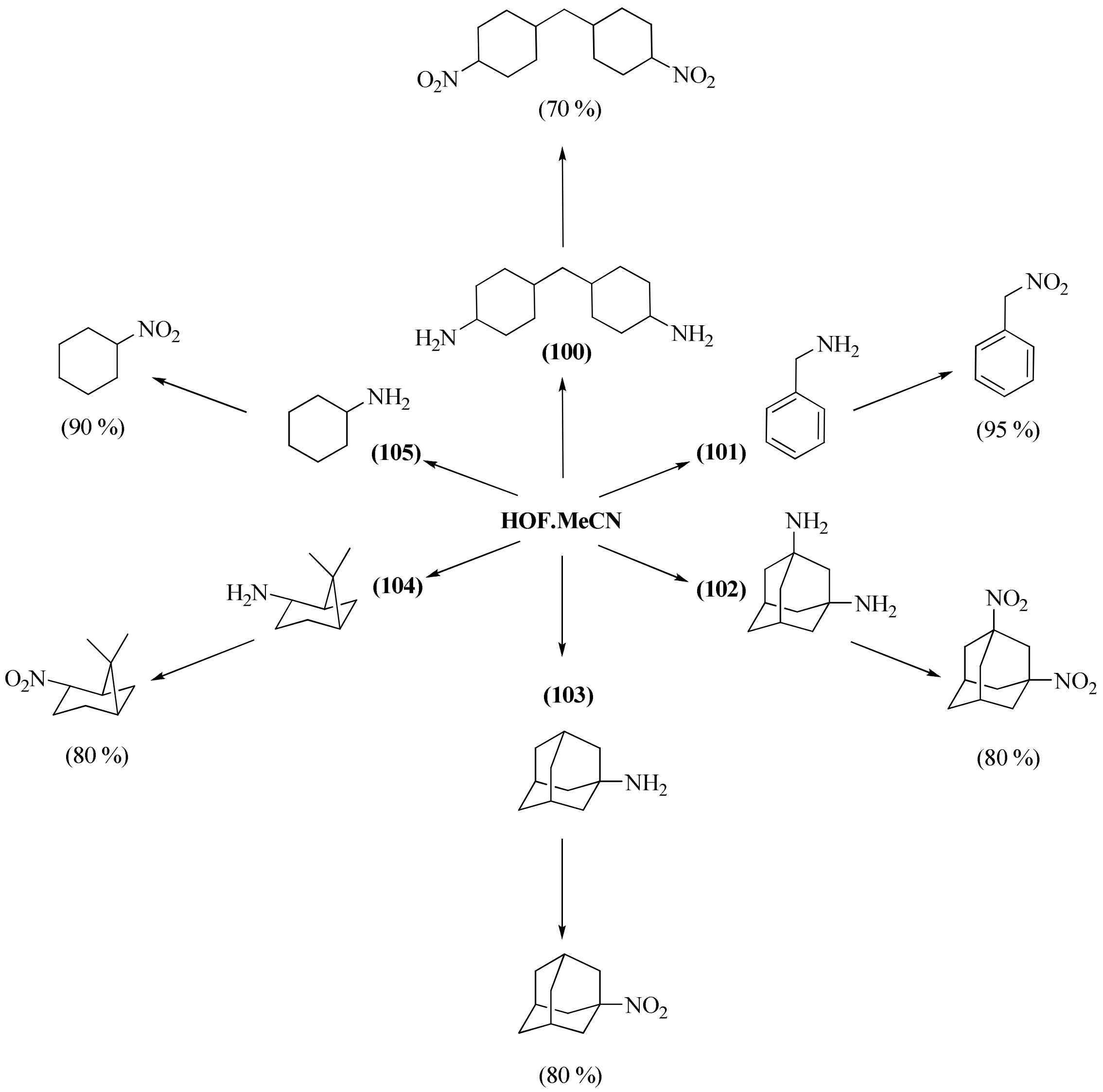


(99) (60 %)

Scheme 37: Oxidations performed by Tour et al. using HOF.MeCN

1.4.3.5.2 Aliphatic Amines

Oxidations of aliphatic amines generally pose a greater challenge than aromatic amines and many methods require multistep reactions or metal containing catalysts. HOF.MeCN was able to oxidise amines **(100-105)** in *scheme 38* within 15 mins, all in excellent yields[76].



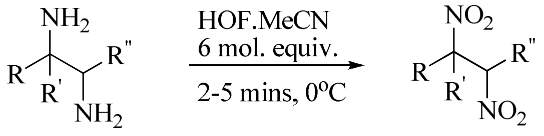
Conditions: All reactions carried out at -15°C for 15 mins using 3 mol. equiv. HOF.MeCN (per NH_2) containing 5g NaF (added to minimise the effect of HF on the amines)

Scheme 38: Aliphatic amine oxidations using HOF.MeCN

Aliphatic amines are stronger bases than aniline by about 6-7 pKa units and Rozen discovered that the HF which is formed as a by-product of HOF.MeCN, would react with the amines and therefore suppress the reaction. To counteract this, NaF was added to the HOF.MeCN mixture and allowed to stir for 10 minutes. Whilst this had very little effect on the HOF.MeCN complex, it did bound most of the HF as $NaHF_2$, allowing efficient oxidation of the amine[76].

1.4.3.5.3 Vicinal Di-Amino Compounds

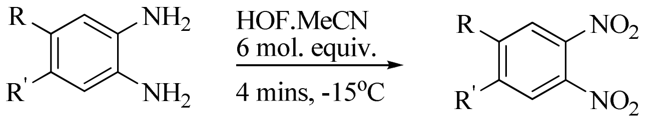
Oxidations of aliphatic vicinal di-amino compounds usually requires the use of the very toxic N_2O_4, because the use of peroxy oxidation reagents results in C-C bond cleavage. Fragmentation also occurs due to the high temperatures and prolonged reaction times that are required[78], and previous oxidation of 1,2-diaminopropane **(106)** using propene and N_2O_4 afforded a yield of only 20% of the vicinal di-nitro compound[79]. HOF.MeCN was capable of nitrating both of the amine groups of vicinal di-amino compounds **(106-108)** (*scheme 39*) to give the corresponding vicinal di-nitro compounds in excellent yields and, the mild conditions required to oxidize these compounds meant that no fragmentation of the carbon-carbon bond occurred. The reactions also proceeded with retention of stereochemistry.



(106) R = R' = H; R'' = Me (82 %)
(107) R = H; R' = R'' = Me (90 %)
(108) R = R'' = Ph; R' = H (1*S*, 2*S*) (95 %)

Scheme 39: Oxidation of aliphatic vicinal amines

The oxidation also proceeded well with aromatic diamines to produce the vicinal dinitro compounds **(109-111)** (*scheme 40*) in very good yields[78]. The electron withdrawing group on the aromatic ring of compound **(111)** did reduce the nucleophilicity of the amine groups and therefore gave a lower yield of the di-nitro compound.

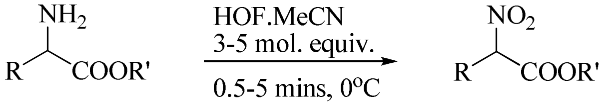


(109)	$R = R' = H$	(85 %)
(110)	$R = R' = CH_3$	(87 %)
(111)	$R = H; R' = PhCO$	(55 %)

Scheme 40: Aromatic diamine oxidations using HOF.MeCN

1.4.3.5.4 Amino Acids

As the presence of a carboxylic acid group does not interfere with the oxidative capability of HOF.MeCN (see section 4.3.1 *scheme 28*) to form the acid, the amine group of amino acids could also be selectively oxidised. Hence, a number amino acids **(112-120)** *scheme 41*, were oxidised to their corresponding α-nitro derivatives, in very short reaction times and at room temperature[80]. Also, by minimizing reaction times, the aromatic ring of **(118)** and **(119)**, and the hydroxyl moiety in **(120)** were all unaffected[80].



(112)	$R = H; R' = Et$	(100 %)
(113)	$R = CH_3; R' = CH_2Ph$	(95 %)
(114)	$R = i\text{-}Pr; R' = Me$	(85 %)
(115)	$R = i\text{-}PrCH_2; R' = Me$	(80 %)
(116)	$R = MeOOCCH_2; R' = Me$	(80 %)
(117)	$R = MeOOC(CH_2)_2; R' = Me$	(80 %)
(118)	$R = PhCH_2; R' = Me$	(85 %)
(119)	$R = p\text{-}HOC_6H_4CH_2; R' = Me$	(95 %)
(120)	$R = HOCH_2; R' = Et$	(70 %)

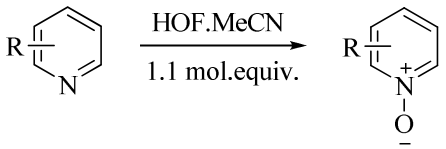
Scheme 41: Amino acid oxidations to the corresponding α-nitro compounds

1.4.3.5.4 Tertiary Nitrogen Atoms

Tertiary *N*-oxides are very important compounds with a wide variety of applications such as fibre preparation, hair products, pharmaceuticals and solvents[81]. They are also of great interest to the energetic materials industry[82].

Rozen showed that the *N*-oxides of various pyridines **(121-125)** could be easily obtained using HOF.MeCN, again under very mild conditions and short reaction times (*scheme 42*). Even those with electron withdrawing groups attached to the pyridine ring **(123)** gave excellent yields[83].

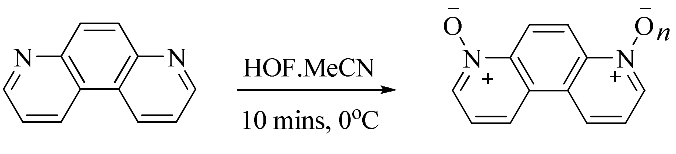
Of particular interest were those which contained functional groups that would compete for oxidation. Thus, oxidation of 4-vinylpyridine **(124)** gave none of the epoxide and only the ring nitrogen was oxidized in 4-(dimethylamino)pyridine **(125)**[83].



(121)	R = H	(95 %)
(122)	R = 4-OMe	(70 %)
(123)	R = 2-CN	(98 %)
(124)	R = 4-CH=CH_2	(70 %)
(125)	R = 4-NMe_2	(70 %)

Scheme 42: Pyridine oxidations

Using varying amounts of HOF.MeCN Rozen was also able to obtain the mono- and di-*N*-oxide of 4,7-phenanthroline **(126)** (*scheme 43*)[83].

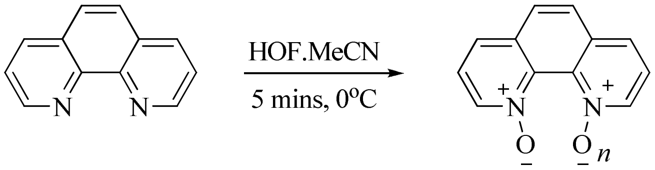


(126)	1.1 mol.equiv.	*n* = 0	(80 %)
	2.2 mol.equiv.	*n* = 1	(73 %)

Scheme 43: Mono- and di- N-oxidations

Repeated attempts to synthesize 1,10-phenanthroline *N*,*N'*-dioxide **(129)** by conventional methods had been unsuccessful for over 50 years, with chemists only able to prepare the mono-

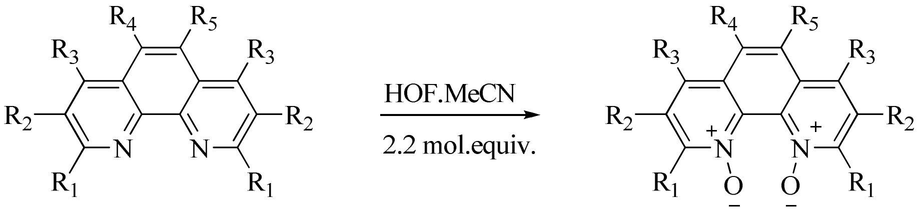
N-oxide **(128)**[84-85]. The difficulty of di-oxidation is due to the aromatic planar structure of 1,10-phenanthroline **(127)**, which does not have the space to accommodate two oxygen atoms without forcing the rings out of planarity. However, Rozen showed that HOF.MeCN was powerful enough to oxidize both nitrogen atoms to give the *N*,*N'*-dioxide **(129)** (*scheme 44*)[86].



(127) 1.1 mol/equiv. **(128)** $n = 0$ (80 %)
2.2 mol/equiv. **(129)** $n = 1$ (60 %)

Scheme 44: Synthesis of 1,10-phenanthroline N,N'-dioxide

Rozen then followed this work up by making the *N*,*N'*-dioxides from a number of 1,10-phenanthroline derivatives **(130-134)** (*scheme 45*)[87].

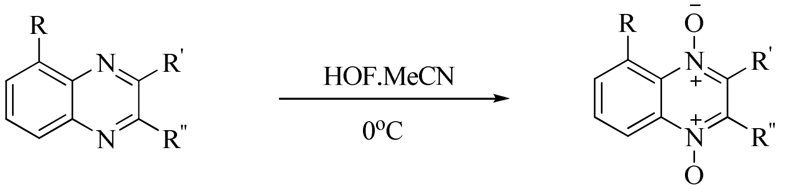


(130) $R_1 = R_2 = R_3 = R_4 = H; R_5 = Cl$ (67 %)
(131) $R_1 = R_2 = R_4 = R_5 = H; R_3 = Ph$ (74 %)
(132) $R_1 = R_4 = H\ R_5 = H; R_2 = R_3 = Me$ (67 %)
(133) $R_2 = R_4 = H\ R_5 = H; R_1 = Me; R_3 = Ph$ (66 %)
(134) $R_1 = R_2 = R_3 = R_4 = H; R_5 = NO_2$ (47 %)

Scheme 45: Synthesis of 1,10-phenanthroline N,N'-dioxide derivatives

Quinoxoline *N*,*N'*-dioxides are not reported in the literature because oxidation of one of the nitrogen atoms makes the diazine less reactive towards electrophilic substitutions. This effect is even more profound if electron withdrawing groups are introduced on to the diazine ring. Consequently, whilst the synthesis of haloquinoxoline *N*-oxides is difficult, haloquinoxoline *N*,*N'*-dioxides were thought to be impossible using conventional oxygen transfer agents[88].

Rozen showed that not only were the *N,N'*-dioxides available from the corresponding quinoxolines **(135-140)** (*scheme 46*) using HOF.MeCN, the *N,N'*-dioxides could also be synthesized form the electron poor halo derivatives **(141-142)**[88].



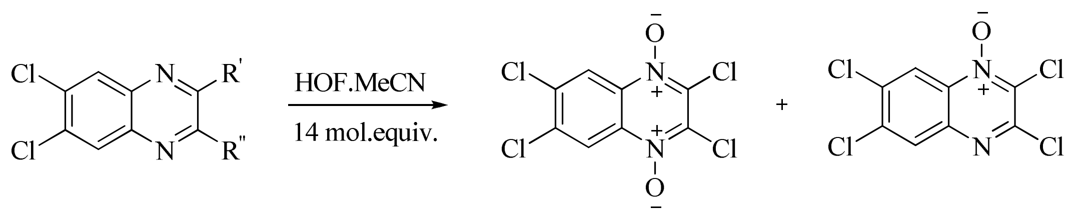
(135) $R = R' = R'' = H$	(95 %)
(136) $R = R' = H$; $R'' = Me$	(90 %)
(137) $R = H$; $R' = R'' = Me$	(95 %)
(138) $R = Me$; $R' = R'' = H$	(40 %)
(139) $R = H$; $R' = R'' = Ph$	(65 %)
(140) $R = H$; $R' = R'' = CH_2Br$	(90 %)
(141) $R = H$; $R' = Cl$; $R'' = H$	(60 %)
(142) $R = H$; $R' = R'' = Cl$	(45 %)

Conditions: All reactions carried out at 0°C; **(135-137)** 2-3 mol/equiv. HOF.MeCN, 2-3 mins; **(138)** 2.5mol/equiv. HOF.MeCN, 30 mins; **(139-140)** 4 mol/equiv. HOF.MeCN, 60 secs; **(141)** 2.0 mol/equiv. HOF.MeCN, 60 secs; **(142)** 3.0 mol/equiv.HOF.MeCN, 60 secs

Scheme 46: Synthesis of quinoxoline N,N'-dioxides using HOF.MeCN

In comparison to conventional oxidants, treatment of **(141)** and **(142)** with $K_2S_2O_8$ with H_2SO_4 gave only the mono-*N*-oxide in low yields, and with 30 % H_2O_2 with HOAc, only starting material was recovered from **(142)** and 6 % of the mono-*N*-oxide from **(141)**. *m*CPBA could also only achieve the mono-*N*-oxide of **(141)** with a 63 % yield over 72 hours[89-90].

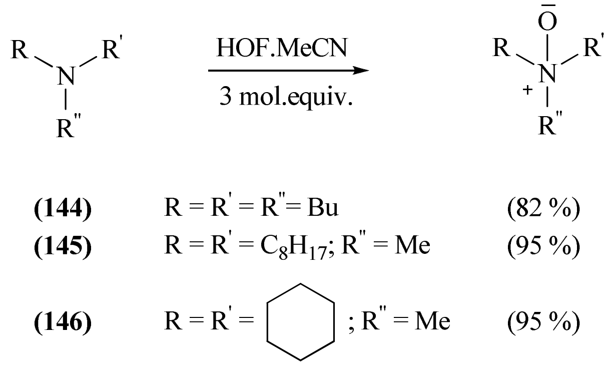
Exceptionally strong oxidants such as peroxydichloromaleic acid[91] and 90 % H_2O_2[92] were also only able to produce the mono-*N*-oxide of the perhalogenated 2,3,6,7-tetrachloroquinoxoline **(143)**. Whilst oxidation with the HOF.MeCN complex required a large excess of oxidant and 40 minutes, the *N,N'*-dioxide was obtained in 40 % yield (*scheme 47*)[88].



(143) (40 %) (55 %)

Scheme 47: Oxidation of 2,3,6,7-tetrachloroquinoxoline using HOF.MeCN

HOF.MeCN has also been successfully applied to the oxidation of tertiary aliphatic amines **(144-146)** (*scheme 48*)[83].



(144) R = R' = R'' = Bu (82 %)
(145) R = R' = C_8H_{17}; R'' = Me (95 %)
(146) R = R' = ; R'' = Me (95 %)

Scheme 48: Tertiary aliphatic N-oxidations using HOF.MeCN

1.4.3.6 Azide oxidations

1.4.3.6.1 Aliphatic azides

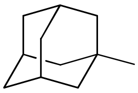
With the exception of Corey's multistep method, the oxidation of azides to the corresponding nitro compound is practically unknown[93]. Corey converts the azide to the phosphine amine ($RN{=}PR_3$) which has to be isolated and then oxidized using ozone. The nitro derivatives obtained (40-70 % yield) were also accompanied by the corresponding phosphine oxide along with the aldehyde.

HOF.MeCN was able to oxidize a range of aliphatic azides **(147-158)** (*scheme 49*), which were made from the corresponding alkyl bromide, in excellent yields and in just a few seconds[93].

The HOF.MeCN complex again exhibits good selectivity in oxidation of the azide over other functional groups. Thus, the three tertiary hydrogen atoms of 1-azidoadamantane **(150)** were not oxidized, nor was the primary alcohol moiety of 11-azidoundecanol **(154)**, the aromatic ring of benzyl azide **(155)** or the ester moiety of 5-azidopentyl acetate **(151)**.

$$R{-}Br \xrightarrow{NaN_3} R{-}N_3 \xrightarrow[0^{o}C,\ 5\ secs]{HOF.MeCN\ 3\ mol/equiv.} R{-}NO_2 \quad + \quad N_2$$

(147) R = $C_{10}H_{21}$ (98 %)
(148) R = cyclo-C_6H_{11} (95 %)
(149) R = cyclo-C_5H_9 (90 %)
(150) R = (95 %)



(151) R = $AcO(CH_2)_5$ (90 %)
(152) R = CH_2COOEt (75 %)
(153) R = $CH_3(CH_2)_3CHCOOEt$ (70 %)
(154) R = $(CH_2)_{11}OH$ (65 %)
(155) R = $PhCH_2$ (96 %)
(156) R = $PhCOCH_2$ (90 %)
(157) R = $(CH_2)_6Cl$ (87 %)
(158) R = $(CH_2)_6CN$ (80 %)

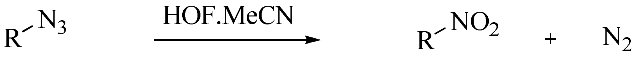
Scheme 49: Aliphatic azide oxidations using HOF.MeCN

α-Nitro acids have great synthetic value, but their synthesis is characterized by long reaction times and low yields. Thus, Rozen was able to selectively oxidize the α-azido esters **(152)** and **(153)** to the corresponding α-nitro ester, which could then be easily converted to the α-nitro acid[93].

The speed of these oxidations led Rozen to attempt them with conventional oxidants. Thus, methylene chloride solutions of 1-azidodecane **(147)** were treated with 8 mol equivalents of *m*CPBA for six hours and 14 mol equivalents of DMDO for three hours, but in both cases only starting material was recovered[93].

1.4.3.6.2 Aromatic azides

Oxidation of aromatic azides to the corresponding nitro compound was also successful with HOF.MeCN[94], but as the carbon bound nitrogen of the aromatic azides is not as nucleophilic as in the aliphatic substrates, the reactions are much slower. Thus it took 60 minutes to oxidize azidobenzene **(159)**, and only starting material was obtained from the oxidation of 4-nitro azidobenzene **(161)**. However, the reaction times could be shortened by increasing electron density on the ring and 4-methyl azidobenzene **(160)** was oxidized in 10 minutes (*scheme 50*)[94].



(159)	R = Ph	(68 %)
(160)	R = 4-MeOC$_6$H$_4$	(65 %)
(161)	R = 4-O$_2$NC$_6$H$_4$	no reaction

Conditions: All reactions carried out in CHCl$_3$; **(159)**10 mol.equiv. HOF.MeCN at rt; **(160)** 10 mol.equiv. HOF.MeCN at 0°C; **(161)**10 mol.equiv.HOF.MeCN at rt;

Scheme 50: Aromatic azide oxidations using HOF.MeCN

During the aromatic oxidations Rozen observed the blue/green colour of the nitroso compound appeared and quickly faded away just before the reaction came to completion. This led him to suggest a two-step reaction mechanism (*figure7*)[94], with the first step, formation of the nitroso compound, being the rate limiting step.

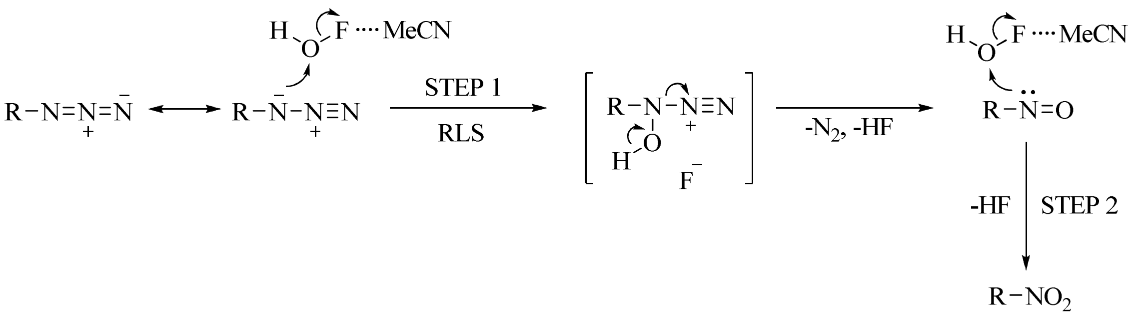
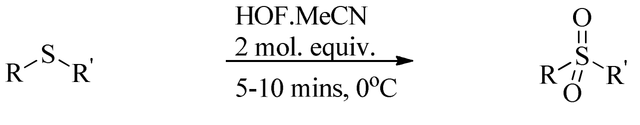


Figure 7: Two Step Reaction Mechanism for Azide Oxidation with HOF.MeCN

1.4.3.7 Sulfur Oxidations

1.4.3.7.1 Di-alkyl Sulfide Oxidations

Although quite a few methods exist for oxidising sulfides to sulfones, these usually involve lengthy treatment with peroxy oxidants or polluting heavy metals at high temperatures. HOF.MeCN was able to carry out the oxidation of a range of di-alkyl sulphides **(162-167)** *scheme 51*, in very high yields and short reaction times[95], including sterically hindered sulphides **(167)** and those attached to strongly electron withdrawing groups **(164)**. Di-oxidation of 2-methyl-1,3-dithiane **(168)** was also achieved with 4 molar equivalents of HOF.



(162) R = 4-$CH_3C_6H_4$; R' = CH_3 (100 %)

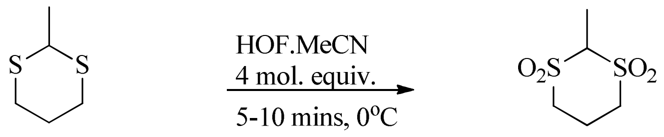
(163) R = 4-$CH_3C_6H_4$; R' = $CH_2CH_2(CF_2)_5CF_3$ (100 %)

(164) R = 4-$NO_2C_6H_4$; R' = CH_3 (90 %)

(165) R = R' = Bu (75 %)

(166) R = *t*Bu; R' = CH_3 (75 %)

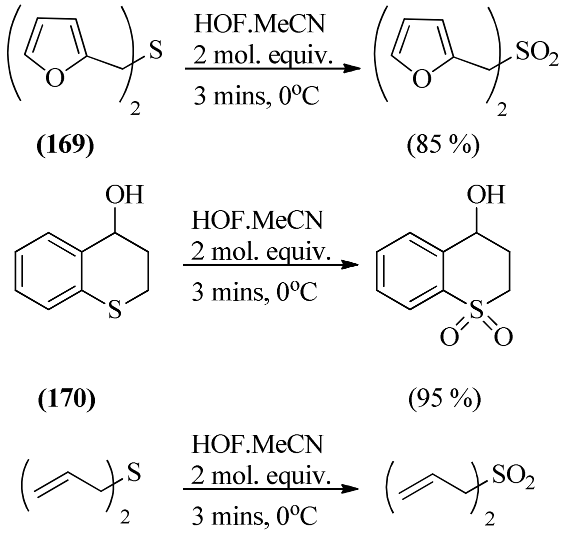
(167) R = R' = *t*Bu (95 %)



(168) (95 %)

Scheme 51: Dialkyl sulphide oxidations

HOF.MeCN also showed good chemoselectivity of sulfides over other functional groups known to be oxidized by the complex. Thus, the weakly aromatic double bonds of furfurylsulfide **(169)** (*scheme 52*), the hydroxyl group of thiochroman-4-ol **(170)** and the alkenes of di-allylsulfide **(171)**, were all selectively oxidised at the sulfur atom without an excess of HOF.MeCN[95].



(169) (85 %)

(170) (95 %)

(171) (86 %)

Scheme 52: Sulfide oxidations in the presence of other oxidizable groups

The sulfoxide can be obtained by using one mole of the HOF.MeCN complex, although protic solvents such as methanol and water must be added[95]. When the reaction is carried out in aprotic solvents, the sulfoxide forms clusters with the HOF *via* H-bonding (*figure8*), which, due to their close proximity, favour the formation of the sulfone (*scheme 53i*).

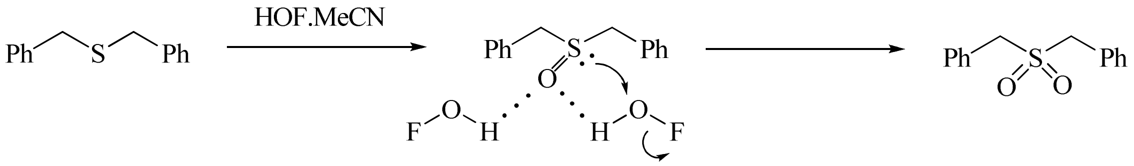
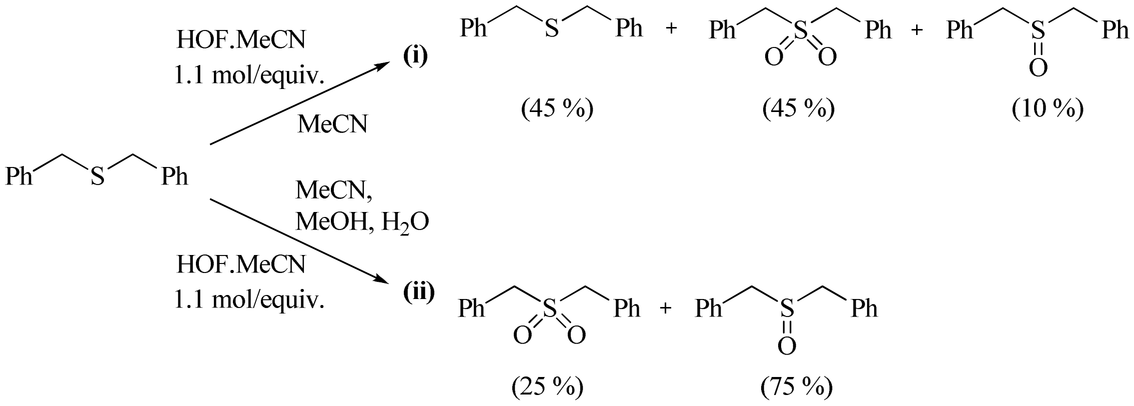


Fig 8: HOF cage formed around a sulfoxide molecue

The addition of the protic solvent provides additional centres for the HOF to hydrogen bond to, reducing the sulfoxide-HOF clusters and therefore allowing more of the HOF to react with the sulfide starting material (*scheme 53ii*)[95].



Scheme 53: Oxidation of dibenzyl sulfide with HOF.MeCN in different solvents

1.4.2.7.2 Electron Deficient Sulfide Oxidations

Many reagents exist for the oxidation of sulfides, however, there are practically none for the efficient oxidation of electron deficient ones. Even potent oxidants such as chromic anhydride or H_2O_2 in trifluoroacetic anhydride are not very efficient[96-97].

Even though a large excess of HOF.MeCN was required along with longer reaction times, a number of electron depleted sulphides **(172-176)** were successfully oxidized to the corresponding sulfones in good yields (*scheme 54*). Rozen attempted to oxidize the highly electron deficient sulphides **(175-176)** with *m*CPBA for 18 hours at room temperature and with 30 % H_2O_2 in boiling acetic acid, but in each case, only traces of the sulfoxide and near quantitative amounts of the starting material were obtained.

(172) Ar = p-$CH_3C_6H_4$; R = n-C_4F_9 (95 %)
(173) Ar = p-$CH_3C_6H_4$; R = n-C_8F_{17} (85 %)
(174) Ar = 4-BrC_6H_4; R = n-C_4F_9 (95 %)
(175) Ar = 3,4-$Cl_2C_6H_3$; R = n-C_4F_9 (95 %)
(176) Ar = R = C_6F_5 (95 %)

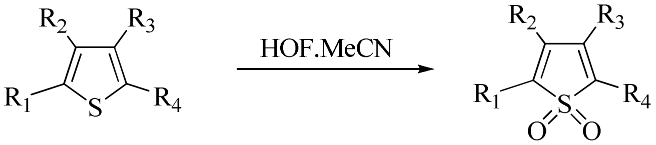
Conditions: All reaction carried out at room temp. **(172-175)** 4.5 mol. equiv. HOF.MeCN for 20 mins; **(176)** 7.0 mol. equiv. HOF.MeCN for 30 mins

Scheme 54: Oxidation of electron deficient sulphides using HOF.MeCN

1.4.3.7.3 Thiophene Oxidations

Thiophene dioxide compounds are somewhat undeveloped because of the opposing factors involved in their oxidation. The high temperatures and prolonged reaction times that are required to overcome the aromatic stabilization, result in the non-aromatic *S,S*-dioxide being sensitive to Diels-Alder and other ene and diene reactions[95].

The high reactivity of the HOF.MeCN complex, even under very mild conditions, meant that thiophenes could be readily oxidized without further reactions taking place (*scheme 55*)[95]. Attempted oxidations by Rozen using peracids or DMDO on the highly electron depleted thiophenes **(179)** and **(182)** were un-successful[95].

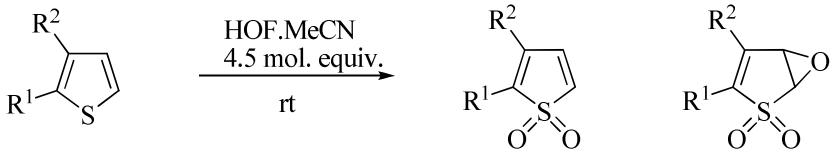


(177) R_1 = Me; R_2 = R_3 = H; R_4 = Me (95 %)
(178) R_1 = Br; R_2 = R_3 = H; R_4 = Br (95 %)
(179) R_1 = Cl; R_2 = H; R_3 = H; R_4 = Cl (70 %)
(180) R_1 = COOEt; R_2 = R_3 = H; R_4 = Me (90 %)
(181) R_1 = R_4 = Me; R_2 = $COCH_3$; R_3 = Br (80 %)
(182) R_1 = R_2 = R_3 = R_4 = Br (70 %)

Conditions: All reactions carried out at room temp. using 4.5 mol/equiv. HOF.MeCN; **(177)** 20 mins; **(178-182)** 30 mins

Scheme 55: Formation of S,S-dioxides from thiophenes using HOF.MeCN

However, for efficient oxidation of thiophenes using HOF.MeCN, substituents on both sides of the ring are required[95]. This is to prevent the unsubstituted double bond taking part in a Diels-Alder reaction or being epoxidized. Thus, oxidation of 2-cyanothiophene **(183)** and 3-bromothiophene **(184)** gave only unidentifiable dimeric products, whilst 2,3-dibromo thiophene **(185)** produced a mixture of the *S,S*-dioxide along with the undesired epoxythiophene *S,S*-dioxide **(186)** (*scheme 56*).



(183) R^1= CN; R^2= H	no clean reaction	
(184) R^1= H; R^2= Br	no clean reaction	
(185) R^1= R^2= Br	(40 %)	**(186)** (45 %)

Scheme 56

1.4.4 Concluding Remarks

Rozen's work has shown that the HOF.MeCN complex offers a very convenient way for organic oxidations to be carried out. Its extreme versatility and the exceptional ease in which a range of functional groups can be oxidised, undoubtedly make this a very appealing reagent and could well offset a prejudice retained by many of using elemental fluorine.

However, whilst the complex has proven to offer many benefits for small scale laboratory batch oxidations, its relatively short half-life would be a major inhibiting factor should it be required for batch scale-up.

Therefore, for the complex to be considered useful on an industrial scale, a process would be required in which the complex is used as it is generated and the use of continuous flow reactors offers a potential solution to this problem.

Chapter 2 - Introduction to Continuous Flow Reactors

2.1 Introduction

Mass scale up of a laboratory designed chemical process is often the major stumbling block in successful commercialisation of potentially marketable products. Although there are a number of important issues to be taken into account, including throughput capabilities, waste and energy minimisation, cost, and environmental issues, two of the most problematic issues are often process control and safety[98-99].

Increasing the scale of a reaction often decreases the control over the process and amongst other factors, this is largely due to the increased difficulty of mass and heat transfer of the reactants over larger volumes[98-99]. Consequently, a reaction may proceed perfectly well on a laboratory scale, but problems can be encountered if the reaction vessel and reactants are proportionally increased in size or 'scaled-up'.

Further scale-up problems are often encountered due to the vast differences between conventional laboratory equipment(xi) and industrial equipment and bridging this gap to gain control of a reaction, is something that is often very costly and time consuming.

There are also a number of safety issues that can arise during scale-up of a reaction. Safe working exposure limits of toxic reagents are often exceeded during scale-up and for highly exothermic process such as rapid oxidations, the scaled-up process may be highly energetic and unstable.

However, continuous flow 'micro-channel' reactors, which have excellent mass and heat transfer capabilities and a very low chemical inventory, offer a genuine solution to improving the control and safety issues faced during reaction scale up. Flow reactors can also be used for both laboratory research and mass scale production, therefore providing a solution to the differences between laboratory and large scale industrial equipment. The work in this thesis concerns the use of continuous flow equipment for HOF.MeCN oxidation processes and so a brief overview of flow systems for gas-liquid processes will be presented here.

(xi) For the purpose of this review, conventional laboratory equipment will refer to reaction vessels such as beakers and round bottomed flasks and stirring devices such a magnetic stirrer bars

2.1.1 Terminology

Although there are many types of 'continuous flow reactors' such as packed column, spinning disk/tube and hex reactors, the ones used for our research and therefore those that will be reviewed, are microchannel reactors. These are reactors that are used to carry out chemical reactions in a continuous process on a sub-millimetre level. Although many of these systems are often sub-categorized to macro (mm), micro (μm) and nano (nm) channels, for the purpose of this review, the term will refer to all reaction channels typically less than 1000 μm.

2.1.2 Microchannel Reactor Classification

Of the hundreds of variations of flow reactors that have been invented, they can be broadly classified into four different types; 'liquid phase', 'gas phase', 'gas-liquid phase', and 'liquid/gas-solid phase'[100].

Liquid phase and gas phase reactors are by far the most investigated systems[100-105] and although the interest in continuous flow technology is still relatively in its infancy, a vast literature covering numerous designs and hundreds of reactions exist for each[100-105].

Solid phase reactors refer to those in which the solid (usually a catalyst) is embedded onto the surface of the reaction channel[100]. Insoluble solid reagents often cause blockage of the microchannel and likewise, solid by-products formed during a reaction can cause similar problems, so, in general, reaction involving these types of reagents are usually avoided in continuous flow reactors.

Gas-liquid continuous flow type reactions are the least investigated and relatively few practical designs exist for such processes[100]. However, before these are discussed, the benefits of using continuous flow systems will be outlined.

2.2 Benefits

Continuous flow chemistry in microchannels is ideally suited to overcoming problematic issues faced during scale up, because they provide an excellent means of both process control and safe operation.

2.2.1 Control

To control the selectivity of a reaction and hence obtain high yields of the desired product, the mass and heat transfer of the reaction must be carefully controlled. The main feature of continuous flow microchannel reactors, in comparison to conventional chemical reactors, is their high surface area to volume ratio[100,105]. Whereas traditional chemical reactors generally have specific surface areas of about 100 m^2 m^{-3}, those of the micro reaction channel typically lie between 10,000 and 50,000 m^2 m^{-3}, which allows for improved heat and mass transfer[100,105].

2.2.1.1 Mass Transfer

Conventional stirring in classical reactors is severely limited to the laminar flow fields that can be created by the stirring device. Flow fields are more concentrated in the reaction mixture that is close to the stirring device, but are severely dampened as the distance from the stirrer is increased[105]. Visual studies using the mixing of dyes have shown that these inhomogeneities produce convective 'dead zones', which, depending upon the concentration and viscosity of the reactants, can persist for hours[105].

Fluid behaviour in micro channel systems is dominated by non-convective laminar flow and, therefore, mixing is primarily dependent upon diffusion between reagents. However, due to the low surface area-volume ratio, diffusion in micro channels is often generally reported to be much more rapid than in conventional batch reactors[100,105], which means that only small reaction path lengths of the channel are often required.

It should be noted that the absence of turbulence in plug or laminar flow often means that sufficient mixing in the microchannel is not generated by diffusion alone and, in such cases, micromixing must be achieved *via* other methods[106]. Many methods have been devised to improve mixing in microchannels, which are categorized into two groups; passive micromixing, where no external forces are applied other than pumping, and active micromixing, where external forces are applied[106]. Passive micromxing includes methods such as pre-mixing devices (ranging from Y-type addition pieces to various multi-lamellae micro channel arrangements), segmented flow and chaotic advection, and active micromixing includes methods such as periodic flow switching and microimpellars.

To aid investigation into the mixing in microchannels, two dimentionaless quantities are often used to provide an insight into the expected performance of a particular mixing design[106]. The Reynolds number (Re) and the Peclét number (Pe) are commonly used to characterise mixing in microfluidic systems[106]. Reynolds number (Re) represents the ratio of convective to viscous forces and is given as:

$$Re = \frac{Ud}{v}$$

where U is the average velocity, d the hydraulic diameter of the microchannel and v the kinematic velocity. Reynolds number gives an estimate of whether or not flow is laminar (<2100 for cylindrical systems). The Peclét number (Pe) represents the ratio of mass transport due to convection and that of diffusion and is expressed as

$$Re = \frac{Ud}{D}$$

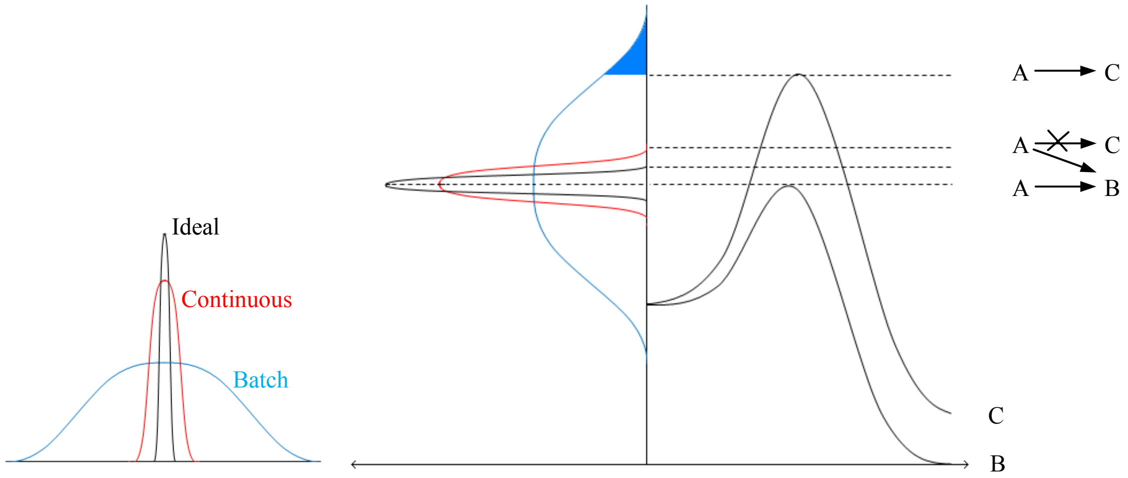
where D is the diffusion coefficient.

2.2.1.2 Heat Transfer

Uncontrolled heating and cooling in a reaction can lead to very slow reactions (requiring heat), or runaway reactions (requiring cooling). Control of heating over larger batches is much more difficult, which leads to a much broader temperature profile for the reaction, thus allowing multiple reaction pathways and reducing yields of the desired product[105]. Poor heat transfer also leads to the formation of 'hot-spots' in the reaction mixture, which is another attributing factor to the formation of by-products[105].

Since the heat transfer coefficient is inversely proportional to the channel diameter, values in the order of 10 $kWm^{-2} K^{-1}$ are obtained in microchannels, resulting in a much narrower temperature distribution. This is reported to be up to 10 times higher than that of conventional reaction vessels[105], resulting in the formation of fewer by-products and increased yields of the desired product.

Figure 9 compares the temperature distributions in batch and microchannel reactions to the kinetic energy needed to access a by-product forming pathway[107].



Left - Temperature distributions for a hypothetical ideal reaction (black), an actual batch reaction (blue) and a continuous flow microchannel reaction (red). **Right** - Comparison of the temperature distributions to two product forming pathways; the broad distribution of the batch reaction allows formation of the undesired product C, whereas the narrow temperature distribution of the microchemical system restricts the reaction to formation of the desired product B.

Figure 9: Temperature distributions of continuous and batch reactions[107]

2.2.2 Safety

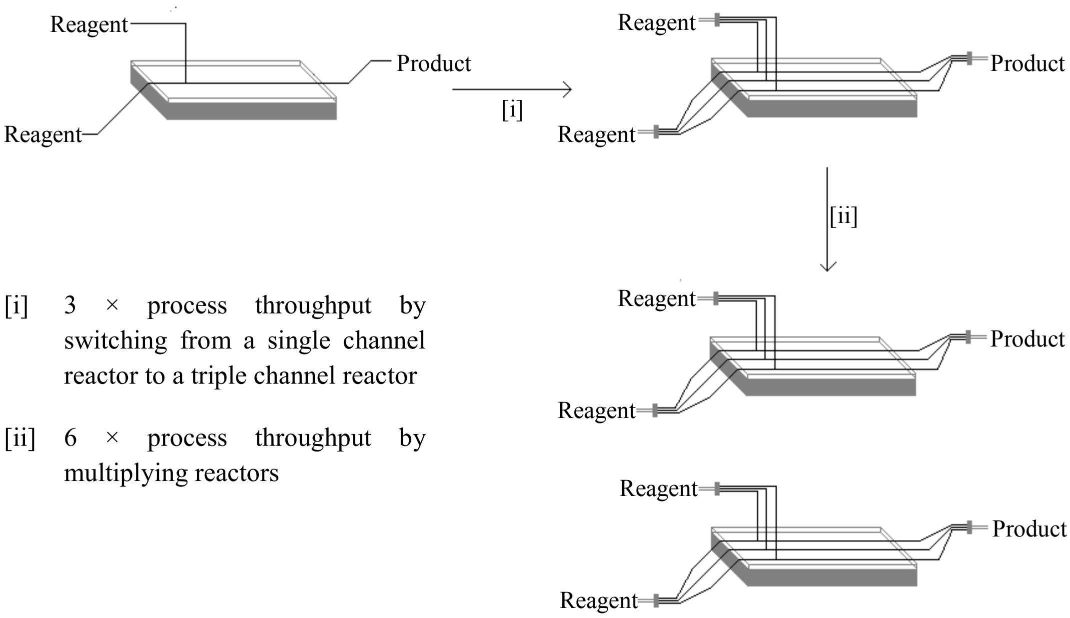
Due to the nature of continuous processes in microchannels, the reagent inventory of a reaction at any one time is very low, therefore minimizing the potential risks associated with mixing larger amounts of reactive chemicals. This makes continuous flow processes ideally suited to highly exothermic reactions such as oxidations, where increasing the volume of powerful oxidants in a batch reaction vessel could potentially be dangerous.

Continuous flow processes also require reactants to be added mechanically, using devices such as mechanical pumps for liquids and gas cylinders for gasses, which greatly reduces user exposure limits.

2.2.3 Scale-out for Mass Production

The benefits offered by continuous flow reactors would not appeal to industry if they could not be applied to the mass production of chemicals. However, by simple arithmetic ‘scale-out’ (also referred to as ‘numbering up’)[108], continuous flow reactors can be very easily used for mass scale production, therefore avoiding the problems associated with simply scaling up the size of a batch vessel[100].

Switching from a single channel reactor to multichannel reactor (a triple channel reactor will be used to exemplify this) the out-put is tripled (*figure 10* [i]); but the optimised conditions for the reaction are unaffected and the operator simply has to add three times more reagent. Further scale-out can then be achieved by running numerous reactors in parallel to each other (*figure10* [ii]), once again without affecting the optimised conditions of the reaction.



[i] 3 × process throughput by switching from a single channel reactor to a triple channel reactor

[ii] 6 × process throughput by multiplying reactors

Figure 10: 'Scale-out' of Continuous Flow Reactors

2.2.4 Batch vs. Flow

Whilst it is widely accepted that many of the cited advantages of performing chemical reactions in microchannels are true, claims of microreactor systems routinely accelerating organic reactions (via better mass diffusion) and increasing desired yields (via improved heat transfer properties), are often thought to be overzealous. In a recent publication by Blacker and co-workers[109], a critical analysis of 'flask vs flow' was undertaken on single-phase homogeneous reactions to investigate such claims.

Note that the work described in this thesis use reactions involving multiphase (gas-liquid) processes and so this analysis may need to be adapted to be fully relevant.

2.2.4.1 Molecular Diffusion

The claims of improved molecular diffusion are often based upon mathematical calculations and compare diffusion in microfluidic channels to those in reaction flasks. Such calcualtions reveal that a molecule in the centre of a microfluidic device can take micro seconds to reach the wall of the channel (due to the large surface area-volume ratio) compared to hours in a flask[109].

The argument against this is that the time it actually takes for a molecule to move to the reactor wall is irrelevant if the wall does not participate in the reaction (as it would do if immobilized reagents or catalysts were used) and that in a homogenous solution, where solvent molecules make up greater than 90 % of the reactor contents, the driving force of molecular diffusion actually displaces a molecule the same distance, in the same time, regardless of the type of container it is in[109].

However, for a gas-liquid process, a much higher gas-liquid interface in microchannels aids molecular diffusion.

2.2.4.2 Heat Transfer

It is claimed that in a homogenous solution, where reactants encounter each other solely by molecular diffusion, heat produced in a exothermic reaction can be dissipated more efficiently in a microchannel, due to the greater surface area-volume ratio. Therefore, the improved heat dissipation of reactions performed in microchannels allows them to be conducted at higher temperatures than in flasks, because a better thermal profile can be maintained[109]. However, Blacker and co-workers used theoretical calculations of an organocatalyzed aldol reaction performed at 60°C in a microchannel and showed that carrying out the same reaction in a flask would give, at maximum, a 1.3°C rise in temperature. Experimentally this was also shown to be the case and organocatalyzed aldol reactions performed in both 'flask and flow' were shown to give similar reaction rates at 60°C[109].

2.3 Miniaturized Total Analysis Systems (µ-TAS)

The benefits of micro-chemical processing have been exploited for both process intensification and improved safety, however, two potential drawbacks to using such devices as stand-alone systems are 'offline analysis' for quantification and 'off-line' purification. Halting the continuous process to perform either of these tasks will undoubtedly slow down the process. To avoid these potential timely procedures, various methods have been devised to include 'in-line analysis' for accurate quantification[110-116] and 'in-line' purification, so that the continuous process can be performed without isolation of intermediates[117-119]. Such continuous systems that include analysis and purification of products are known as 'miniaturized total analysis systems' or μ-TAS.

Although it is important to mention the importance and benefits of such developments, the focus of this section is briefly outline the benefits of continuous flow reactions in microchannels and, therefore, specific details of each technique will not be explained.

2.3.1 In-line Analysis

Continuous flow processes allow for rapid optimization of reactions by investigation of parameters such as time, flow rates and stoichiometry and thus, large numbers of samples can be generated per day. With such a large number of samples, time consuming off-line analysis for quantification is often the bottle neck during the optimization procedure and, therefore, in-line analysis techniques offer the advantage of immediate qualitative information.

In-line analysis is most often achieved using optical sensors, which are integrated into the flow system to monitor reactions. Techniques such as UV[110], IR [111] and Raman[112] spectroscopy have all been utilized as well as in-line NMR[113], mass spectroscopy[114], laser induced fluorescence[115] and HPLC[116] analysis.

In-line monitoring of continuous flow reactions is also very desirable if kinetic information about a flow process is required.

2.3.2 Continuous Product Separation

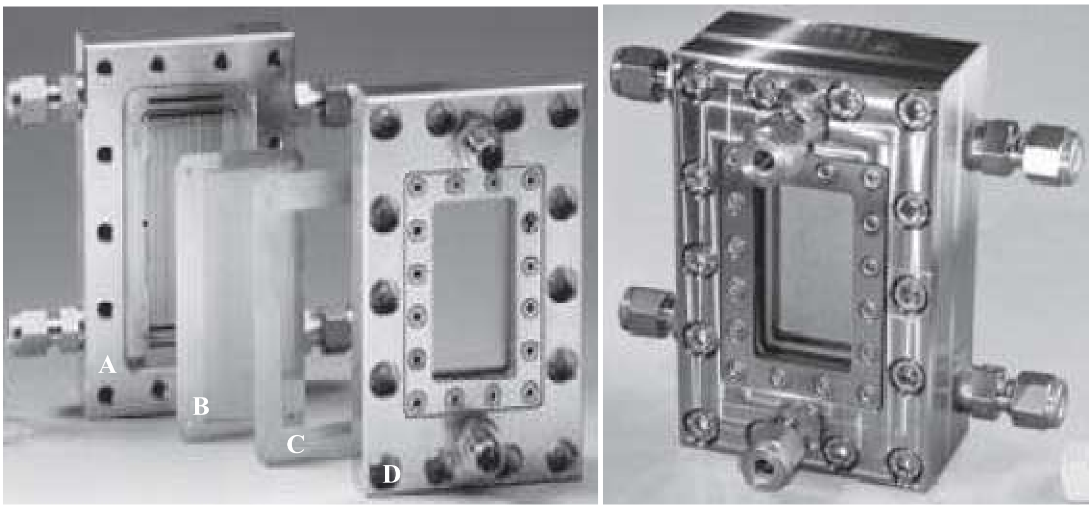
Separations are central to synthetic chemistry and therefore another potential bottle neck to a continuous flow process, particularly for a multi-step synthesis, would be the need for off-line purification. Although continuous flow multi-step reactions have been performed without intermediate separation[117], this is often not feasible and therefore it is much more desirable if intermediates can be separated in flow, without isolation.

Continuous distillation[118] and continuous extraction[119] methods are two of the most widely exploited separation techniques to be incorporated in μ-TAS.

2.4 Gas-Liquid Reactors

2.4.1 Falling Film Reactor

The falling film reactor is one of the most widely recognized gas-liquid reaction devices and was developed at the Institut für Mikrotechnik (IMM) in Germany. The reactor consists of four components (*figure11*); the bottom plate [A], which houses the liquid inlet/outlet valves and integrated heat exchanger, the reaction plate [B], a contact zone mask [C] and the top plate [D], which is the gas chamber and houses the gas inlet/outlet valves.



Left - disassembled Falling Film Reactor [A] bottom plate (with heat exchanger and liquid inlet/outlet slits) [B] reaction plate [C] contact zone mask and [D] top plate (with window and gas inlet/outlet valves); **Right** - assembled Falling Film Reactor

Figure 11: The Falling Film Reactor

The main component is the reaction plate [B] which is a stainless steel plate with multiple micro channels fabricated onto the surface. Depending on the plate, these range from widths of 100-1200 μm and depths of 100-600 μm. Each channel has an inlet hole at the top, which aligns to the liquid inlet slit of the bottom plate [A]. Therefore when the liquid is injected through the slit, it is evenly distributed into each reaction channel and flows down the channels *via* gravity. The end of the reaction channels are aligned to the liquid outlet slit of the bottom plate.

The top (gas chamber) plate [D] is placed over the reaction channels and the gas is injected through a diffuser at the bottom of the chamber, which ensures the gas is distributed throughout the chamber homogeneously. The gas flows in an upward motion over the falling liquid film where a reaction takes place and excess gas is released through the outlet gas valve at the top of the reactor (*figure 12*).

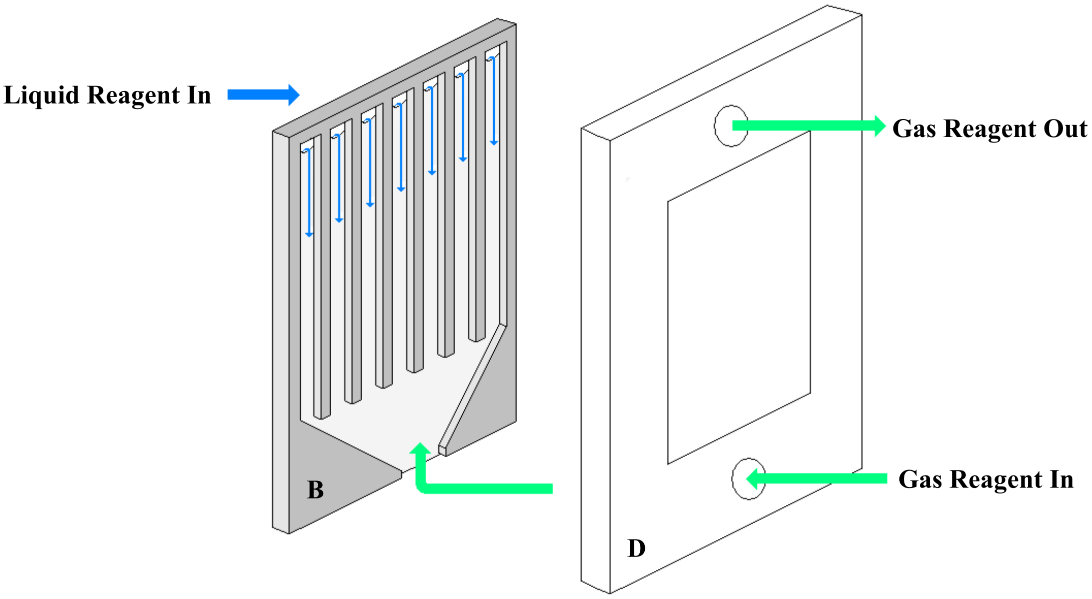
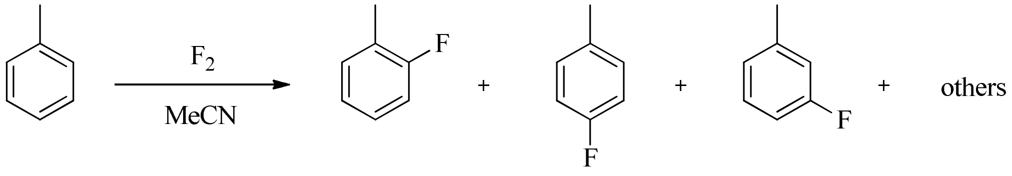


Figure 12: Drawing of the Falling Film Reactor

The falling film reactor is capable of producing liquid films with a depth of just 15 µm, which corresponds to a specific phase interface of 20,000 m^2 m^{-3}. This is approximately ten times that of other commercial gas-liquid systems such as the jet reactor and the laboratory bubble column[120].

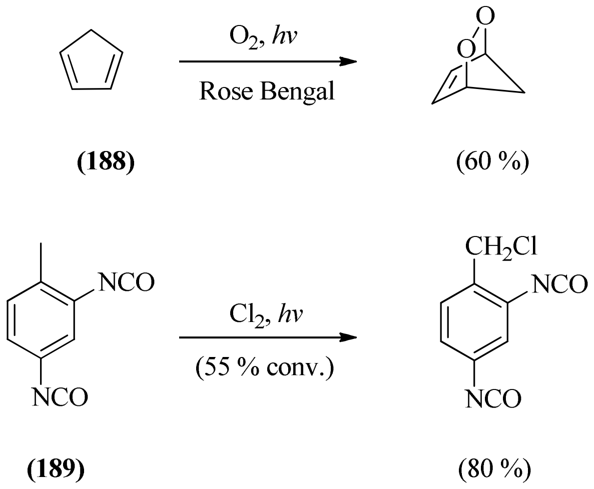
Initial experiments using this flow reactor were carried out in separate research institutions by Jähnisch, Hessel and Gruber, who demonstrated that toluene **(187)** could be selectively mono-fluorinated with elemental fluorine in the *ortho*, *meta* and *para* positions (*scheme 57*) with yields up to 28 %[121]. These were benchmarked against the laboratory bubble column, which gave, at best, yields of 8 % mono-fluorination.



(187) Ratio: 5 3 1

***Scheme 57: Direct fluorination of toluene using the falling film reactor*[12]**

By fabricating a quartz window into the device, photochemical reactions can also be performed using this reactor. Jähnisch reported the photooxidation of cyclopentadiene **(188)**[122] and the selective chlorination of toluene-2,4-diisocyanate **(189)** (*scheme 58*)[123], both of which gave improved selectivity of the desired product over the batch process.



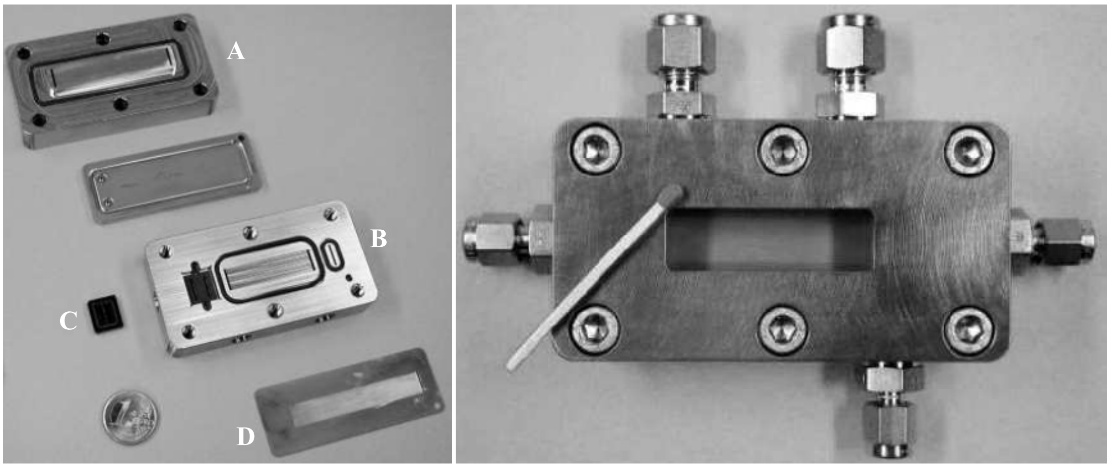
(188) (60 %)

(189) (80 %)

Scheme 58: Photochemical reactions performed using the falling film reactor[122-123]

2.4.2 The Microbubble Reactor

The microbubble reactor was also developed by IMM and their collaborators, although unlike the falling film reactor, the microbubble reactor is operated horizontally. It consists of four components (*figure 13*), the top and bottom plates [A and B] which have integrated heat exchangers, the microdispersion gas/liquid inlet unit [C] and the reaction plate [D].



Left - disassembled Microbubble Reactor [A] top housing plate [B]microdispersion unit [C] bottom housing plate [D] reaction channel plate; **Right** - assembled Microbubble Reactor

Figure 13: The Microbubble Reactor

The central components of this reactor are the static microdisperser unit [C] and the reaction channel plate [D]. The microdisperser unit is made of a nickel/copper alloy through which the gas and liquid are added at opposing ends of the unit. Uniform distribution of the reactants is achieved by the small size of the inlet micro dispersion channels, which are no larger than 5 µm for the gas and 20 µm for the liquid.

The microdispersion unit [C] sits vertically in the reactor and attached, perpendicular to this, is the stainless steel reaction channel plate [D] with 64 reaction channels of 20 × 600 µm fabricated onto it. The gas and liquid reactants are fed into the reaction channels *via* the microdispersion unit (*figure 14*).

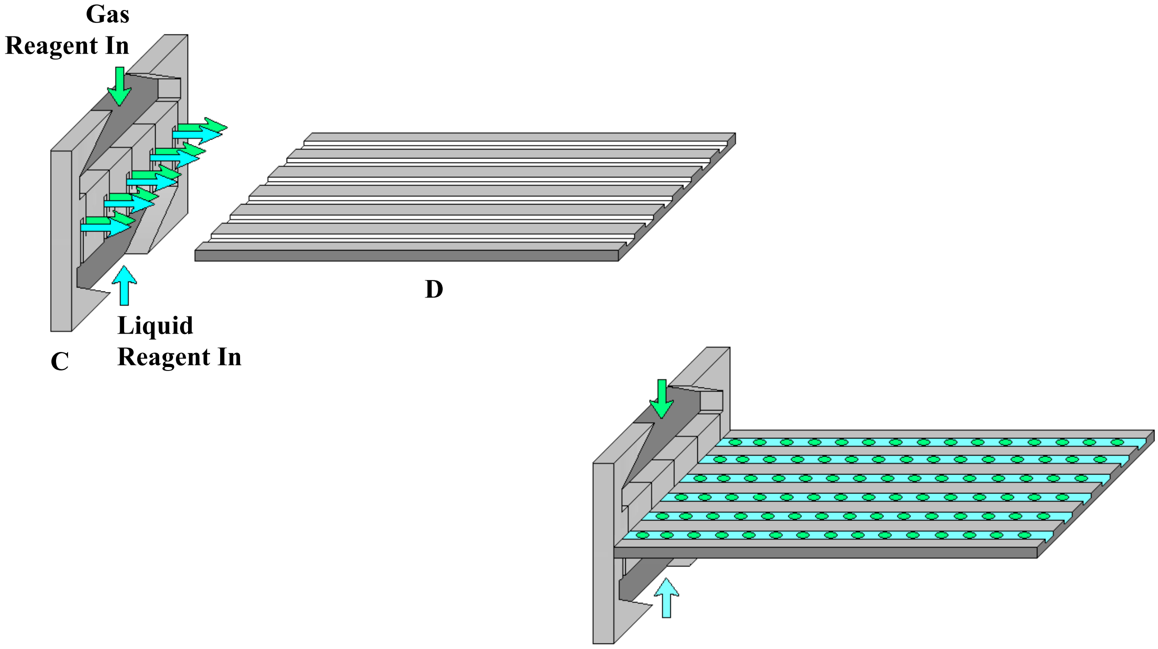


Figure 14: Drawing of the Microbubble Reactor

The reaction plate and microdispersion unit are locked between the top and bottom housing plates [A] and [B], which are also the heat exchangers. The bottom plate also houses the reactant outlet slit to collect the reactants.

This reactor is designed for rapid reactions (in the order of 1 second and below) and by varying the gas and liquid superficial velocities, other flow regimes such as slug, annular and spray flow can be obtained.

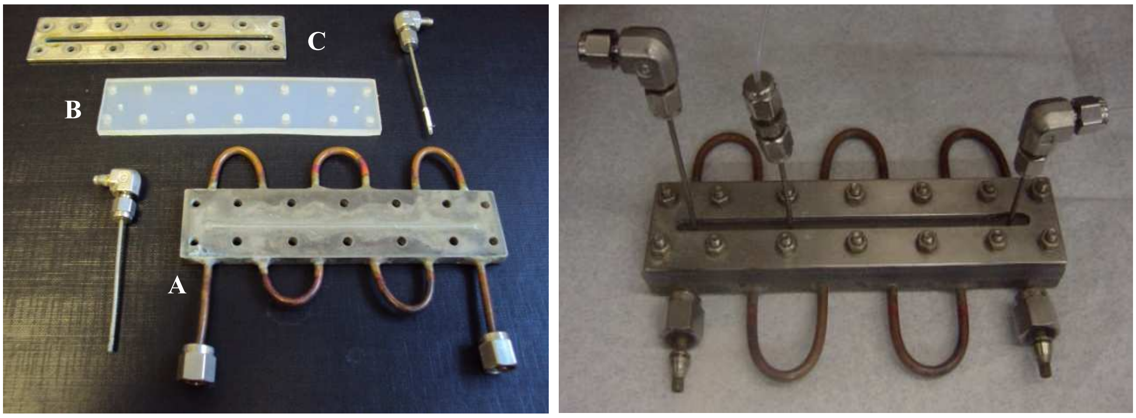
Direct fluorinations of toluene experiments were also carried out using this microreactor and although the conversion and yields was not as good as the falling film reactor, they still gave an improvement over the standard liquid bubble column[121].

2.4.3 Durham Continuous Flow Reactors

2.4.3.1 Horizontal Rectors

In 1999, the Durham Fluorine Group published the design of a reactor specifically constructed for the manipulation of elemental fluorine[124].

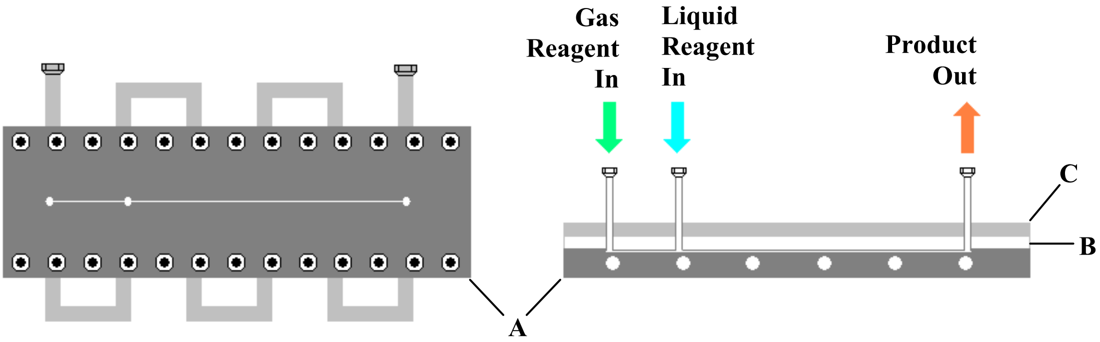
The reactor consists of three parts (*figure 15*); a solid block of nickel metal (120 mm × 27 mm × 5 mm) with a 100 mm long, 500 µm diameter reaction channel etched onto its surface [A]. Attached to the surface of the nickel channel is a transparent solid polychlorotrifluoroethylene (PCTFE) block (120 mm × 27 mm × 5 mm) [B] which is held in place *via* a bolted stainless steel block (120 mm × 27 mm × 2 mm) [C]. The PCTFE block has 3 holes (1000 µm diameter) drilled into it which align to the reaction channel and allow stainless steel tubing (1000 µm external diameter and 800 µm internal diameter) to be inserted into the PCTFE block, which sit just above the reaction channel. This allows the gas and liquid reactants to be added and the product to be collected. Temperature of the reaction block is controlled *via* a copper channel which is threaded through the nickel block and attached to a cryostat.



Left - disassembled horizontal single channel reactor [A] nickel block with reaction channel and copper cooling pipe [B]PCTFE block [C] top housing plate; **Right** - assembled flow reactor

Figure 15: The Durham Single Channel Flow Reactor[124]

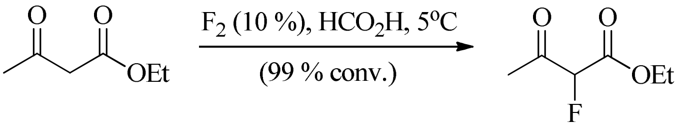
Elemental fluorine is added to the first inlet and is mixed with the liquid reagent which is added to the second inlet. Products and excess reagents are then collected in a catch pot *via* the outlet tube (*figure 16*). Mixing in the reactor proceeds by the preferred annular or ‘pipe’ flow (as appose to intermittent or ‘slug’ flow) (see section 3.4.4) which also ensures increased heat transport from the reaction zone to the nickel block.



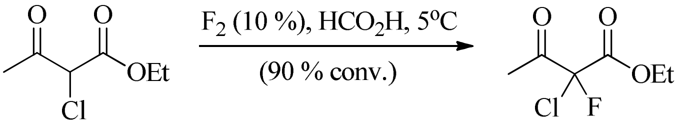
Left - top view **Right** - side view

Figure 16: The Durham Single Channel Flow Reactor[124]

To demonstrate the reactors capabilities, it was initially used to selectively fluorinate ethyl acetoacetate **(190)** and chloro-ethyl acetoacetate **(191)** (*scheme 59*)[124], giving excellent conversions and yields in each case. A range of 1,3-dicarbonyl compounds were also selectively fluorinated, also in excellent yields[125], and always providing the same, if not better conversion and yields compared to the same reactions using conventional batch techniques(xii)[126].



(190) (73 %)



(191) (62 %)

Scheme 59: Selective fluorinations of 1,3-dicarbonyl compounds using the single channel reactor

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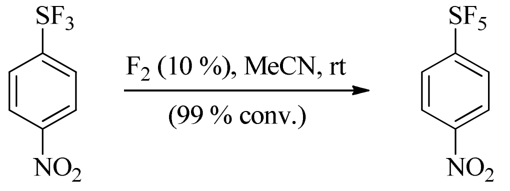
(xii) Conventionally, fluorinations in batch are performed in a sealed glass reaction vessel which allows fluorine to be passed through the reaction and safely vented. Mixing is carried out using an overhead paddle stirrer.

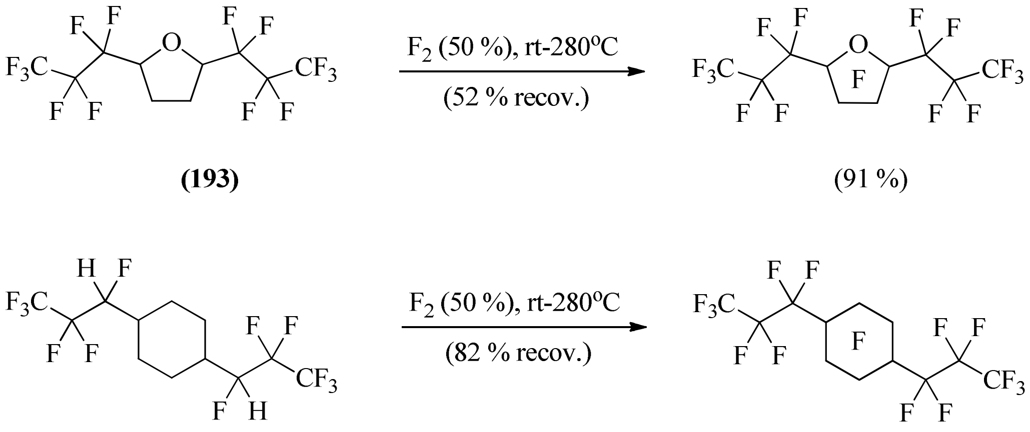
The single channel reactor was also used to synthesize sulfur pentafluoride derivates from sulfur trifluorides **(192)** (*scheme 60*)[124].



(192) (44 %)

Scheme 60: Synthesis of a sulfur pentafluoride using the single channel reactor

By fitting an additional heating device to the outlet of the reaction channel, perfluorination reactions could also be performed on substrates such as **(193-194)** (*scheme 61*)[124,126].

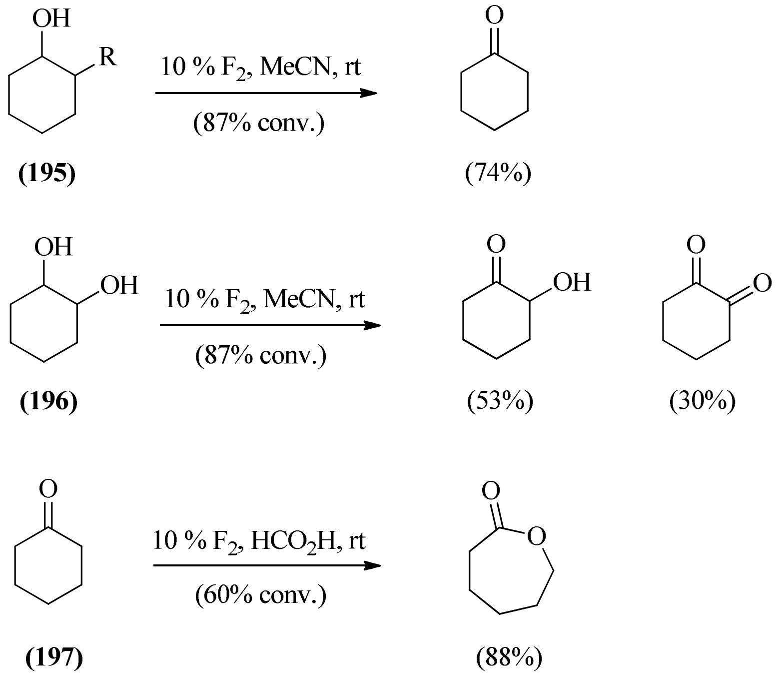


(193) (91 %)

(194) (70 %)

Scheme 61: Perfluorinations using the single channel reactor

In 2003, the Durham Fluorine Group, continuing their oxidation work using F_2 and anhydrous acetonitrile[127], demonstrated that their flow reactor could also be used to perform these oxidations[128]. Thus, secondary alcohols **(195-196)** and Baeyer-Villiger oxidations previously carried out in batch[127], were mirrored in the single channel reactor (*scheme 62*).



Scheme 62: Continuous flow oxidation of secondary alcohols and cyclic ketones

Scale out of the horizontal flow reactor was then demonstrated by constructing a triple channel reactor (*figure 17*). The principle of this reactor is much the same as the single channel reactor, although reservoirs are required at the gas and liquid inlets to provide equal distribution of reagents to each channel.

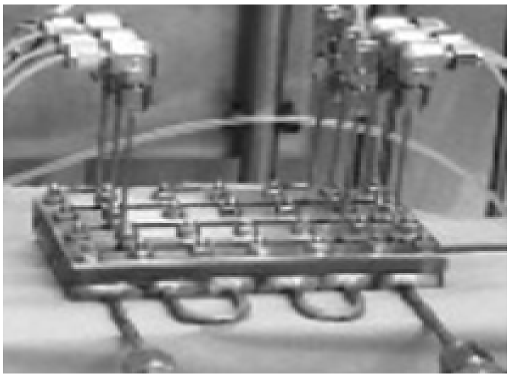
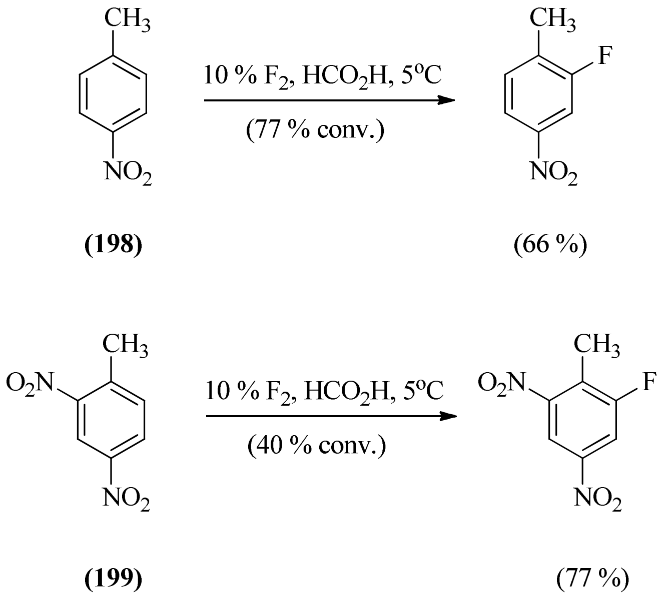


Figure 17: The Triple Channel Reactor

The triple channel reactor was successfully used to repeat the 1,3-dicarbonyl fluorinations shown in *scheme 59*[125] and was also used to perform selective fluorinations of deactivated aromatic compounds **(198-199)** (*scheme 63*)[125].



Scheme 63: Selective fluorination of deactivated aromatics in the triple channel reactor

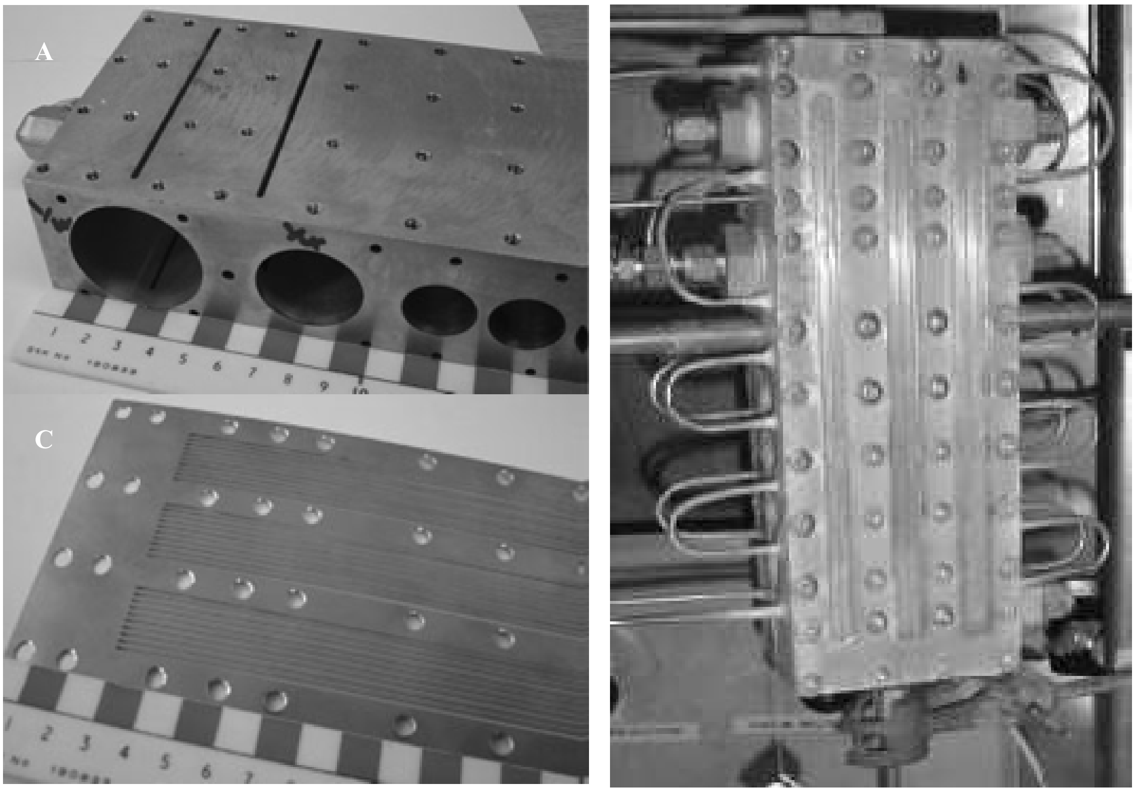
2.5.3.2 Vertical Reactor

To perform further scale-out of continuous reactions, the Durham Fluorine Group designed and manufactured a gas-liquid vertical flow modular reactor system which allows many reaction channels to be supplied from single reservoir sources[129].

The reactor consists of 5 parts (*figure 18*), which are place together in the following order:

[A]	A steel reservoir block	(250 mm × 96 mm × 50 mm)
[B]	Nickel base plate	(250 mm × 96 mm × 0.5 mm)
[C]	Stainless steel channel plate	(250 mm × 96 mm × 0.5 mm)
[D]	PTCFE sealing block	(250 mm × 96 mm × 6 mm)
[E]	Top window plate	(250 mm × 96 mm × 2 mm)

The steel block [A] has two substrate reservoirs (40 mm and 30 mm diameter for the gas and liquid respectively) cut through the width of the top end of the block, and a collection reservoir (20 mm diameter) at the bottom of the block. These have slits cut along their width which emerge at the surface of the block. The nickel base plate [B] also has slits cut into it which exactly align to the steel block slits and provides the base of the reaction channel.



Top left: The steel reservoir block [A] **Bottom left**: Reaction channel plate [C] **Right**: Assembled vertical reactor

Figure 18: The Vertical Continuous Flow Reactor

The actual channels themselves, typically 500 µm wide, are cut into a stainless steel plate. The depth of the channels are therefore, dictated by the thickness of the plate, which is also typically 500 µm. Channel plates have 9, 18 or 30 channels cut into them.

A transparent PTCFE block is then placed onto the reaction plate which completes the reaction channel, and a top window plate is bolted onto the base plate which keeps the whole unit together. The window allows the flow of the reaction channels to be viewed.

The reactants are added to the reservoirs of the nickel block [A], which once filled, flow through the slits to the surface of the block and down the channels (*figure 19*). The volume of the reservoirs is substantially greater than the sum of the volumes of the channel paths, therefore ensuring equal fluid distribution into each individual channel. Upon entry to the channels, the gas and liquid flow down the reactor and the reaction takes place and at the end of each channel, the product flows into the product reservoir slit, which can then be collected through an exit tube.

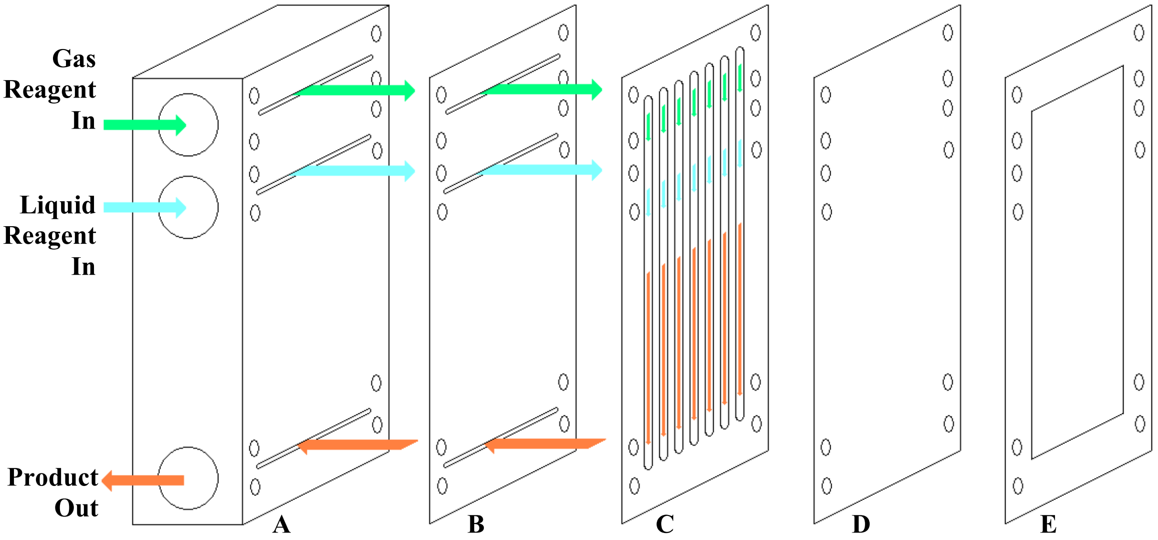
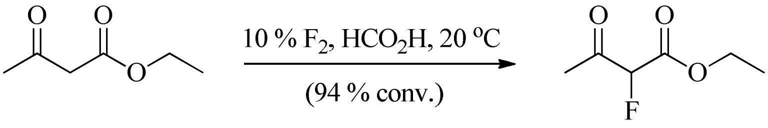


Figure 19: 5 separate parts of the vertical flow reactor

As with the horizontal reactors, piping threaded through the reaction block can be connected to a cryostat to allow for thermal control of the reaction.

Fluorination experiments performed on ethyl acetoacetate **(200)** demonstrated that with optimized conditions, excellent conversions and yields could be obtained of the mono-fluorinated product using a 9-channel reactor (*scheme 64*)[130]. Continuous operation over an extended time period of 150 hours has been performed with no loss of yield or conversion[130] and with each channel able to synthesize *ca.*0.3 g of product per hour, approximately 220 g of product can be synthesized per day using the 30-channel reaction plate.

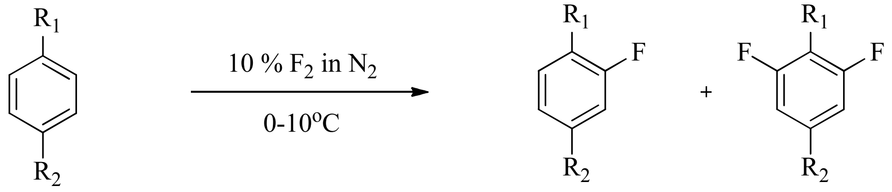


(200)

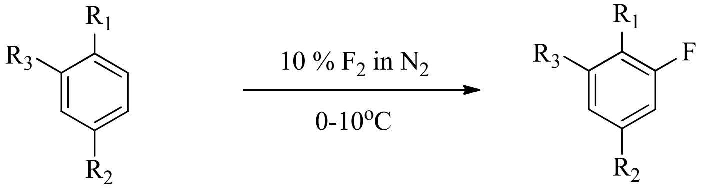
(79 %)

Scheme 64: Selective fluorination of ethyl acetoacetate in the vertical flow reactor

A number of 1,3-ketoesters and 1,3-diketones were then selectively mono-fluorinated using the 9-channel vertical reactor, often with near quantitative yields[131], and the selective mono fluorination of the deactivated aromatic compounds **(201-208)** was also performed using the 9-channel reactor (*scheme 65*)[132].



	R_1	R_2	Conversion		
(201)	OCH_3	NO_2	(87 %)	(77 %)	(11 %)
(202)	OH	NO_2	(67 %)	(71 %)	(18 %)
(203)	CH_3	CN	(78 %)	(75 %)	(7 %)
(204)	OCH_3	CHO	(91 %)	(82 %)	(9 %)



	R_1	R_2	R_3	Conversion	
(205)	CH_3	NO_2	NO_2	(38 %)	(98 %)
(206)	OCH_3	NO_2	NO_2	(86 %)	(79 %)
(207)	F	NO_2	NO_2	(34 %)	(94 %)
(208)	Cl	NO_2	NO_2	(53 %)	(97 %)

Scheme 65: Selective fluorinations of deactivated aromatic compounds in the vertical flow reactor

The following chapter describes how gas-liquid continuous flow techniques developed at Durham University, were utilized to overcome the limitations of Rozen's powerful oxygen transfer agent that arise when it is used in batch oxidation reactions.

Chapter 3 - New Continuous Flow Oxidation Methodology

3.1 Aims

Two important points made in the introduction were that:

A) The labile and highly reactive nature of Rozen's HOF.MeCN complex prevents it being used for the scale-up of batch oxidation reactions

B) The continuous means of operation of flow reactors provides easy access to scale-up of reactions and their low chemical inventory offers safe operation of highly exothermic reactions

Therefore, if Rozen's HOF.MeCN complex could be synthesized in a continuous fashion and, without isolation, be used to oxidize a substrate in a continuous flow device, the instability of the complex would not be an issue, nor would the safety implications that would arise from batch scale-up. The high oxidative power of the HOF.MeCN reagent would not be limited to small scale laboratory batch oxidations and could be applied to industrial scale processes.

The initial aims of the project were:

1. To utilize the gas-liquid continuous flow techniques developed at Durham University and apply them to the continuous synthesis of HOF.MeCN and subsequent reagent oxidation reactions in a two step process
2. Optimization of the process to ensure that no fluorine remains in the reaction channel when the substrate is added, therefore, avoiding competing substrate fluorination
3. Develop a means of accurately measuring the HOF.MeCN concentration, therefore avoiding the necessity for using iodimetric titrations
4. Demonstrate the practicality of the process by oxidation of a range of substrates
5. Demonstrate scale-up of reactions *via* increased reaction run-times and the use of higher concentrations of HOF.MeCN

Before the specific details of our flow processes are discussed, the hazards associated with the use of elemental fluorine and the apparatus and techniques involved in its safe handling will be described. As one mole of hydrogen fluoride is generated with each mole of HOF.MeCN, the hazards associated with HF will also be outlined.

3.2 Handling of Elemental Fluorine and Hydrogen Fluoride

3.2.1 Associated Hazards

The highly reactive nature of elemental fluorine means that at a sufficiently high concentration, it will corrode all exposed tissues. Due to its reactive nature, an emergency exposure limit of 150 ppm over 10 mins has been suggested and comprehensive studies have determined the lethal concentration limit (LC_{50}) in rats to be 3500 ppm over a 5 min exposure[133].

One of the keys to successfully applying elemental fluorine to organic reactions is dilution, which also makes working with the gas much safer. The fluorine gas used throughout this work is supplied as 20 % F_2 (diluted in nitrogen) and for all experiments this was further diluted to 10 % in nitrogen. Whilst dilution of the element reduces its reactivity and therefore its toxicity, it is still very easily detectable at levels as low as 20 ppb[133].

Anhydrous hydrogen fluoride (AHF) is also very corrosive and causes severe irritation upon exposure. AHF has a threshold limit value of 3 ppm (over 8 hours), but like fluorine, it is also detectable at concentrations as low as 20 ppb[134].

Hydrofluoric acid (aqueous hydrogen fluoride) can easily migrate through the lipid layers of skin cells and is, therefore, capable of extremely deep burns and even permanent bone damage. In small quantities, this can occur without surface tissue damage or even irritation, so any detrimental effects may be delayed. Reaction with the body’s calcium inside cells can also cause a cardiac arrest. Spills of over just 2.5% of the body’s surface area have been reported to be fatal[134], therefore the Durham University HF safety course is compulsory and calcium gluconate (HF antidote gel) is available in all labs.

3.2.2 Fluorine Handling Apparatus

Based on a previous design, the apparatus (or ‘rig’) used for the safe handling of fluorine, which was purposely built for this research project, is shown in *figure 20.*

The apparatus consists of a permanent fluorine storage cylinder [A] which connects to the 20 % fluorine cylinder(xiii) and also a nitrogen cylinder and is filled from these two cylinders using the operating board [B].

(xiii) The 20 % fluorine cylinder is housed in its own extracted fume hood and is fitted with its own safety cut off valve, regulator and exhaust valve.

A second operating board [C] then controls the safe passage of fluorine from the storage cylinder [A] through our desired reaction setup [D], the flow of which is controlled by a calibrated gas mass flow controller (MFC) [E]. The flow valve of the gas MFC is operated by the control unit [F] which has a maximum flow capacity of 100 mL min^{-1}.

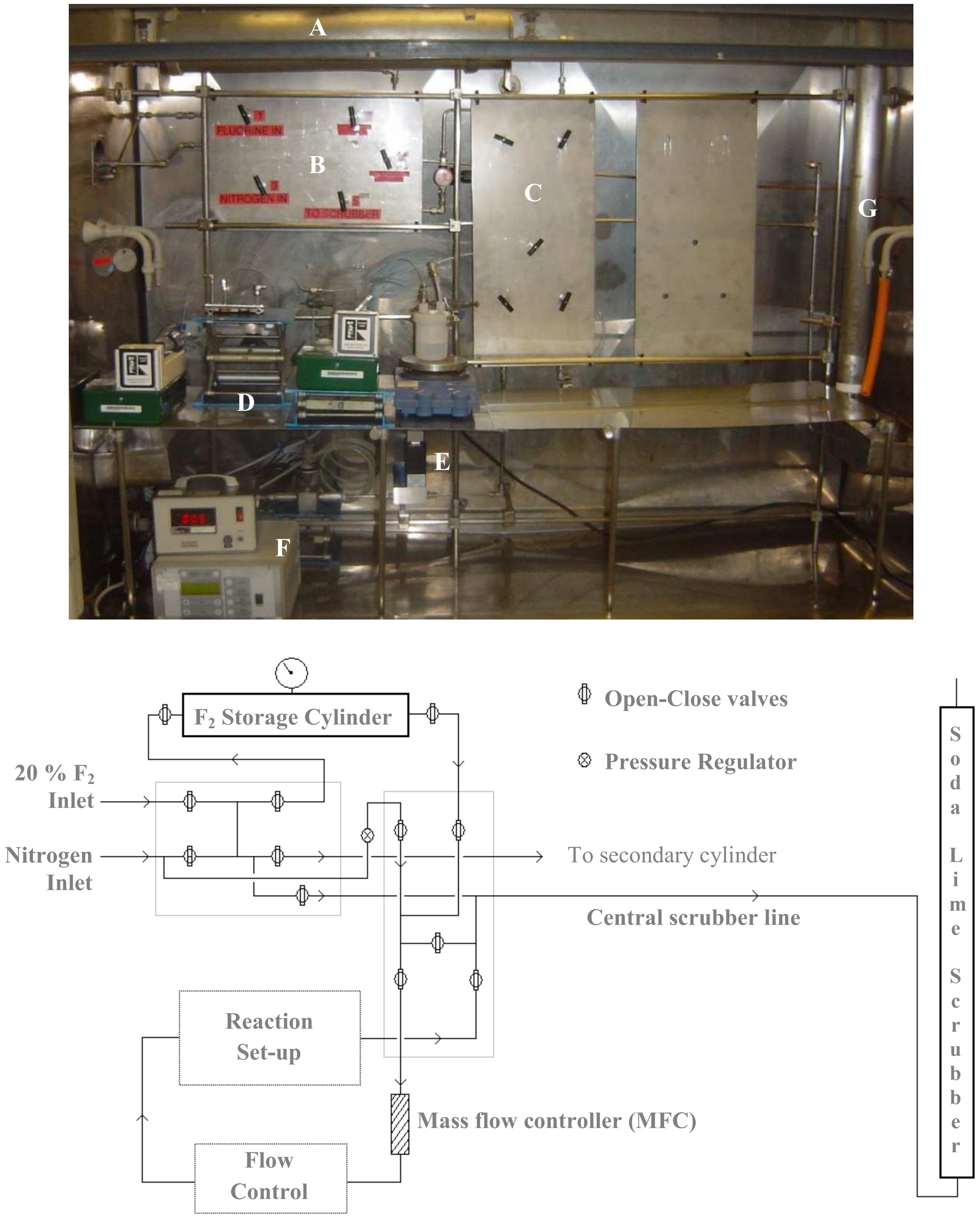


Figure 20: Fluorine handling apparatus used at Durham University

The outlet of the reaction set-up is attached to a 'soda lime scrubber'. This is a metal cylinder [G] filled with 75% calcium hydroxide which reacts with any excess elemental fluorine or HF gas from the reaction, thus preventing both atmospheric and fume hood emissions. All of the operating boards can also be opened to the soda lime scrubber *via* a central 'scrubber line', so excess fluorine in all parts of the rig can be safely discharged.

The valves and connections of the rig are made from stainless steel, as is the majority of tubing. Teflon tubing is used in parts of the rig that are frequently moved or adjusted (i.e. those attached to the reaction vessel), and the reaction vessel itself is also made of Teflon. All tubing is connected by Swagelok® fittings.

3.2.2.1 Passivation

Although fluorine reacts with all metals, its reaction with some alloys forms a protective metal-fluoride coating on the surface of the alloy, which prevents further corrosion. This forms the basis of a technique called 'passivation', and allows fluorine to be handled without severe deterioration of the rig. Therefore, all parts of the rig, including mass flow controllers and flow reactors, are passivated before being used. Passivation is performed by slowly passing fluorine through the metal at different concentrations, starting with the lowest, to allow a fluoride coating to gradually form on the surface of the metal, thus creating the protective barrier.

3.3 Continuous HOF.MeCN Synthesis and Batch Oxidation

Successful completion of our aims not only relied upon the ability to synthesize the HOF in a flow reactor, but also that the HOF would complex to acetonitrile so it would be sufficiently long lived to carry out oxidations. To investigate this, the reaction set-up shown in *figure 21* was used.

Fluorine, supplied at a known rate, was added into the flow reactor *via* inlet 1 and the water and acetonitrile were added together at a known flow rate to inlet 2. Any HOF.MeCN complex formed could then be collected in the 'catch pot' and tested with known concentrations of a suitable reagent.

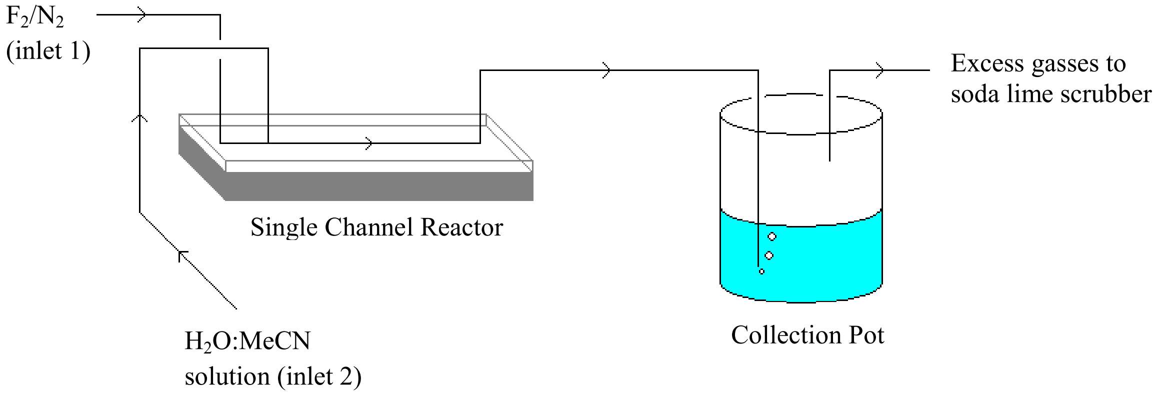


Figure 21: Initial setup devised for the synthesis and collection of HOF.MeCN

3.3.1 Variables

A number of variables need to be considered to optimize the generation of the HOF complex using this system:

1. Flow rates of the fluorine and aqueous acetonitrile
2. Ratio of the acetonitrile:water (v/v) mixture
3. Temperature and reaction path length of the reactor
4. Catch-pot contents and temperature
5. Substrate concentration

The flow rate of the elemental fluorine is obviously a major variable and one which, due to the nature of the gas MFC, changes with time. MFC's use the thermal properties of the gas to directly measure its flow rate and are calibrated to the required gas concentration. The thermal properties are measured using a sensor which is attached to the gas flow range *via* a small capillary by-pass. However, due to the gradual build up of fluorides to the inner surface of the MRC over time, the diameter of the passivated capillary becomes smaller, which in turn affects the sensor reading and therefore the flow rate. Therefore, once optimized HOF.MeCN synthesis conditions have been established, an accurate calibration procedure is also required so that any variation of the flow control units could be detected.

3.3.2 Initial Tests

As no real time method was available to analyze reactions, work-up of each reaction would be required to show if oxidation had occurred. Therefore the substrate chosen for initial testing and optimization must fulfil the following criteria:

1. It should be very easily to oxidize using one molar equivalent of HOF.MeCN
2. It should also react rapidly with fluorine, thus allowing excess of fluorine to be monitored (only applicable for continuous substrate oxidation)
3. It should produce no unstable intermediates during its oxidation, thus limiting the possibility of side products
4. The proton NMR shifts of the oxidized and un-oxidized peaks should be easily identifiable, enabling quick and quantitative identification of starting material and product
5. It should have a reasonably high molecular weight so manageable quantities could be used at low concentrations
6. The starting reagent and product must be insoluble in water and have a low vapour pressure, enabling easy work up *via* aqueous extraction
7. The product must be stable to base, thus allowing HF or excess HOF.MeCN to be quenched with $NaHCO_3$

1-Dodecene and *trans*-stilbene and their corresponding epoxides fulfil all of these criteria.

Initial tests carried out by Chris Murray (AWE secondment to Durham University, Oct-Dec. 2006) demonstrated that HOF.MeCN could be synthesized and collected using this apparatus and then be used to oxidize 1-dodecene. Murray showed that a ratio of 1:4 water:acetonitrile gave higher quantities of HOF.MeCN than the 1:9 ratio used by Rozen and that a cooled reaction channel was not required.

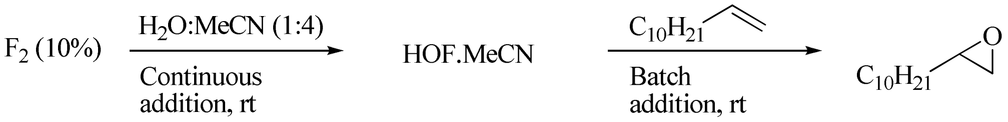
Following on from Murray's work, our next aim was to optimize the amount of HOF.MeCN generated so that higher yields of the epoxide could be obtained. All subsequent tests, unless otherwise stated, were performed using the 1:4 ratio of water: acetonitrile and a reaction channel at room temperature.

It was also initially established that an acetonitrile collection pot was required to keep the HOF.MeCN complex stable long enough to carry out the batch oxidations and that if the HOF.MeCN was collected in water it was too labile. So in all of the batch oxidation reactions, 20 mL of acetonitrile was used to collect the HOF.MeCN complex.

3.3.3 HOF Optimization

To optimize the HOF.MeCN amounts, a number of experiments were performed using the flow apparatus in *figure 21* with increasing amounts of fluorine, whilst keeping the water:acetonitrile flow rate constant at 5.0 mL h^{-1} (*results table 1*). For all experiments, only starting material and epoxide were obtained.

Results table 1:



Expt.	F$_2$ flow rate (mL min^{-1})	H$_2$O:MeCN flow rate (mL h^{-1})	1-dodecene		NMR Yields (%)	
			mmol	mixing (mins)	Alkene	Epoxide
1	6.0	5.0	2.0	2.0	16	84
2	6.5	5.0	2.0	2.0	13	87
3	7.0	5.0	2.0	2.0	9	91
4	7.5	5.0	2.0	2.0	5	95
5	8.0	5.0	2.0	2.0	5	95

The fact that there was no increase in epoxide yield in experiment 5 indicates that the optimal fluorine flow rate is 7.5 mL min^{-1}, however, the presence of starting material is also an indication that insufficient water is being added to the reaction for full conversion of fluorine to HOF. Therefore the tests were repeated but with increased levels of 10.0 mL h^{-1} of water and acetonitrile (*results table 2*). Proton NMR for these experiments are included in *figure 22* with the alkene peaks highlighted red and epoxide peaks blue.

Results table 2:

Expt.	F$_2$ flow rate (mL min^{-1})	H$_2$O:MeCN flow rate (mL h^{-1})	Alkene		NMR Yields (%)	
			mmol	mixing (mins)	Alkene	Epoxide
6	6.0	10.0	2.0	2.0	15	85
7	6.5	10.0	2.0	2.0	10	90
8	7.0	10.0	2.0	2.0	6	94
9	7.5	10.0	2.0	2.0	0	100
10	8.0	10.0	2.0	2.0	0	100

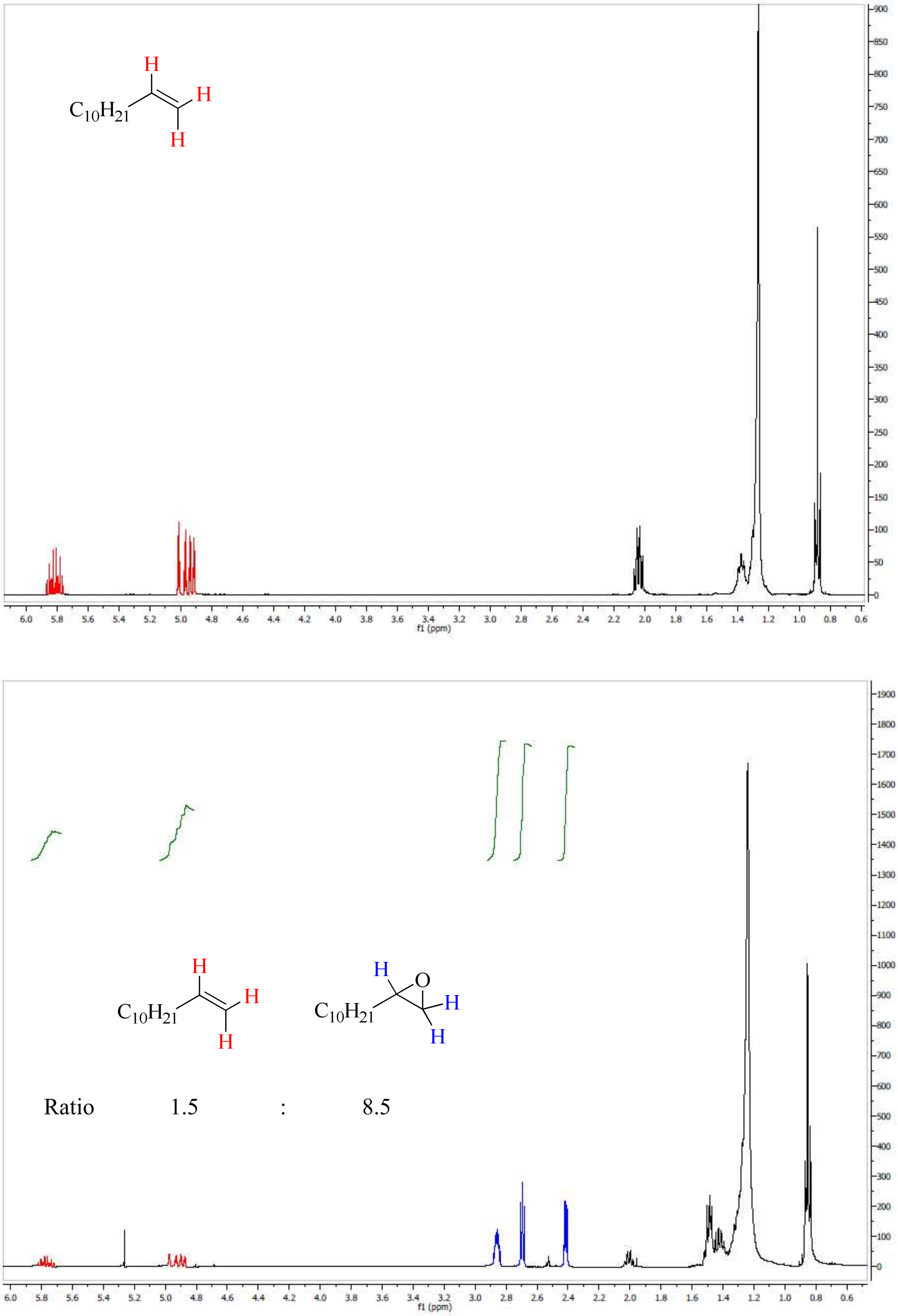


Figure 22: Proton NMR used to optimize the HOF.MeCN synthesis conditions

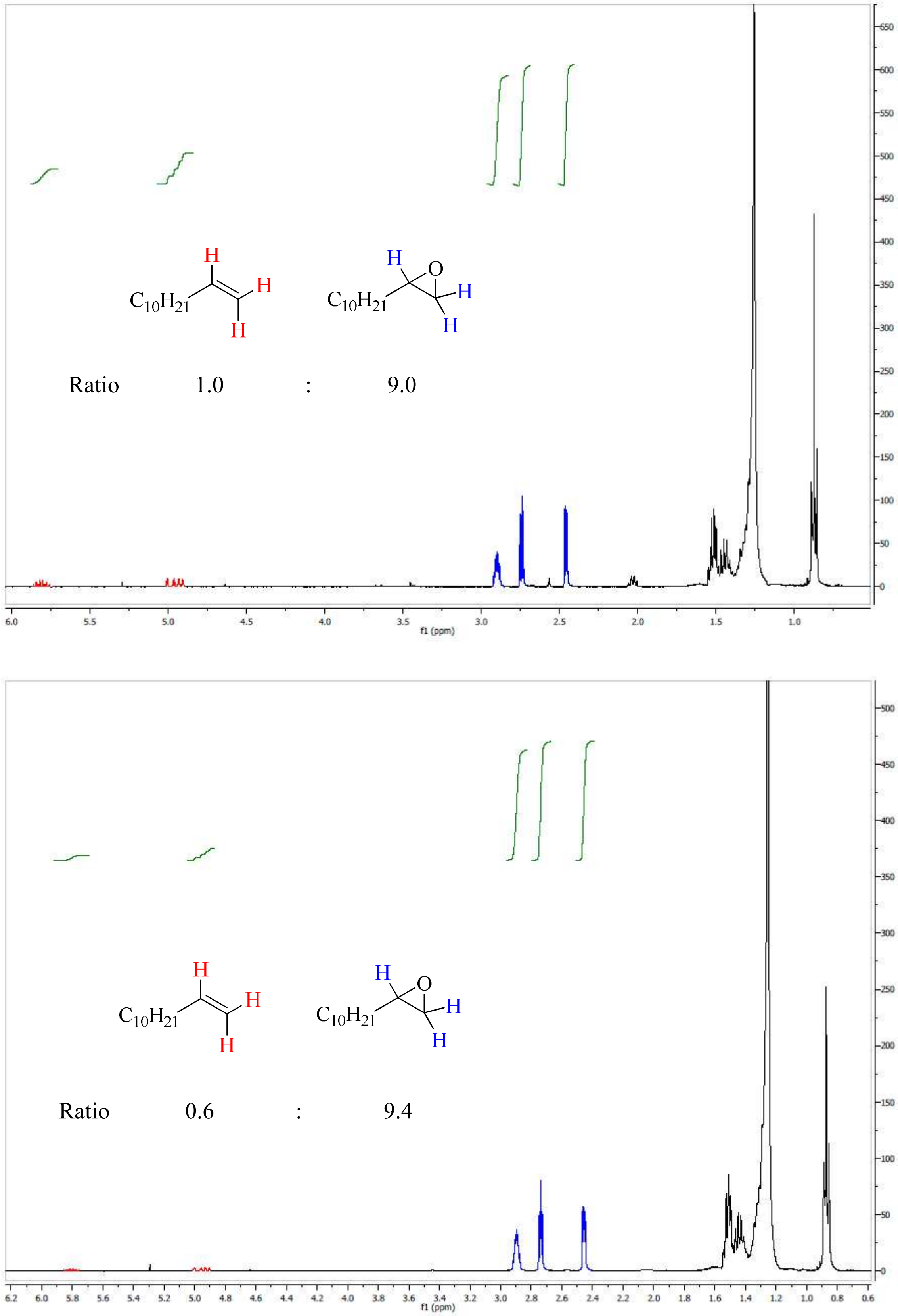


Figure 22 (cont): Proton NMR used to optimize the HOF.MeCN synthesis conditions

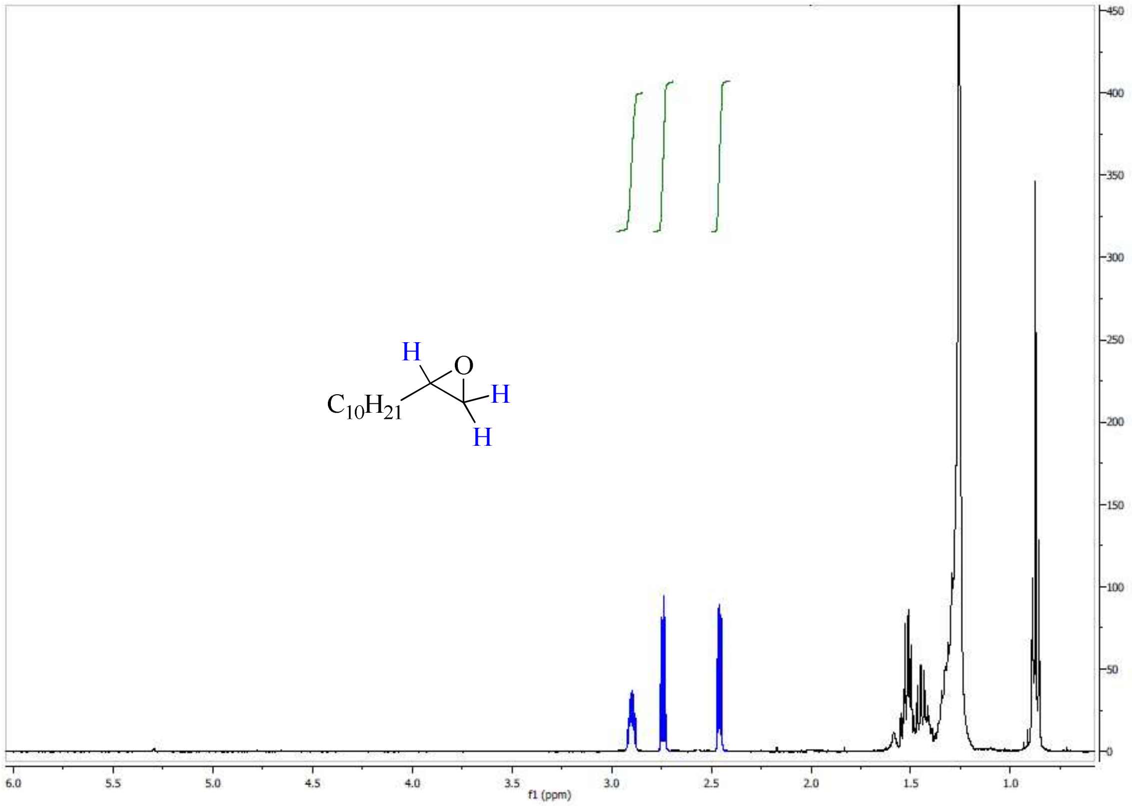


Figure 22 (cont): Proton NMR used to optimize the HOF.MeCN synthesis conditions

The results showed that with the increased water level of 10.0 mL h^{-1} and 7.5 mL min^{-1} of fluorine, at least 2.0 mmol of HOF.MeCN can be generated so that 2.0 mmol of 1-dodecene can be quantitatively converted to its epoxide.

Once it was established that the HOF.MeCN could be generated in the flow reactor, the next step towards completing our aims was to determine if the substrate could be oxidized using continuous flow methodology.

Continuous addition of the substrate will also allow the substrate to react with excess fluorine (if any) therefore providing information as to whether all of the fluorine is being used to form HOF in the reactor or if an excess of fluorine is being generated. By a means of back calculation, this will also provide a method of accurately calibrating the actual fluorine flow rates.

3.3.4 Variations on Setup

During the initial testing and optimization stage, frequent blockages were occurring in the reactor at the fluorine:aqueous acetonitrile interphase of the reactor (*figure 23*). There also seemed to be slight corrosion of the channel close to this inlet.

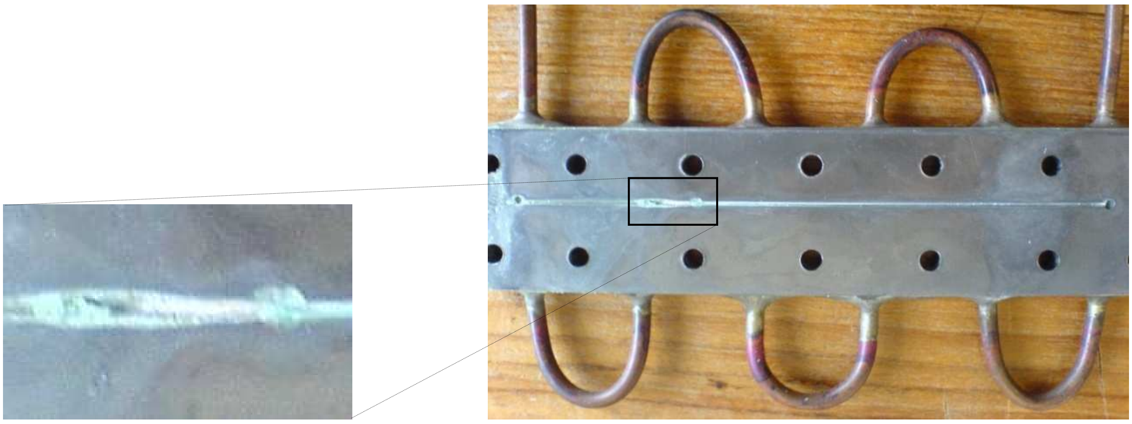


Fig 23: Blockage of the flow reactor at the fluorine:aqueous acetonitrile interface

To prevent blockages and possible channel corrosion, the reactor design was modified slightly so that the H_2O:MeCN solution was added to a Swagelok® T-piece attached to the fluorine inlet (*figure 24*), therefore, any corrosion would occur in the replaceable T-piece and not the nickel block. Calibration tests using the slightly modified design showed that the revised set-up gave the same results as those in results table 2.

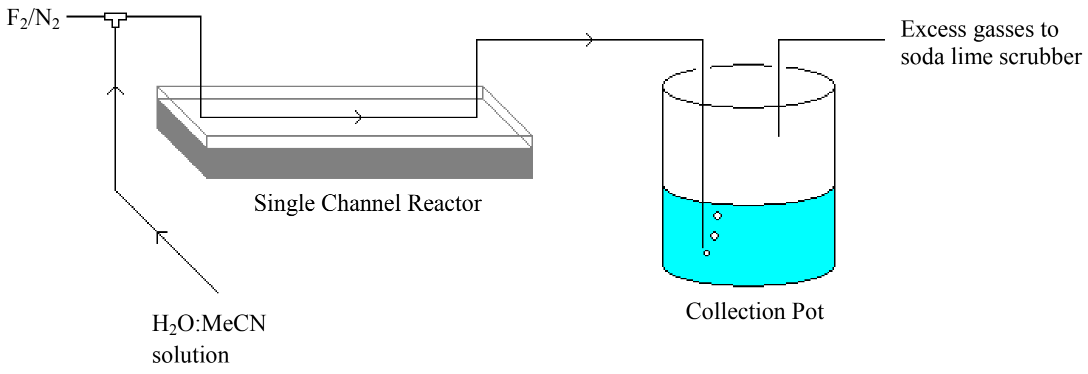


Figure 24: Revised HOF.MeCN continuous synthesis and collection set-up

3.4 Continuous HOF.MeCN Synthesis and Continuous Oxidation

Continuous addition of the substrate was performed by using a PCTFE mixing T-piece attached to the outlet of our HOF.MeCN flow reactor, which has a length of PTFE attached through which the reagent could be continuously added (using a mechanical syringe pump) at a known concentration per hour (*figure 25*).

The substrate:HOF.MeCN T-piece used was specifically designed and constructed from PCTFE so that the internal diameter of the actual mixing channel was as small as possible (800 µm), thus hopefully providing more efficient mixing than that of a Swagelok® T-piece.

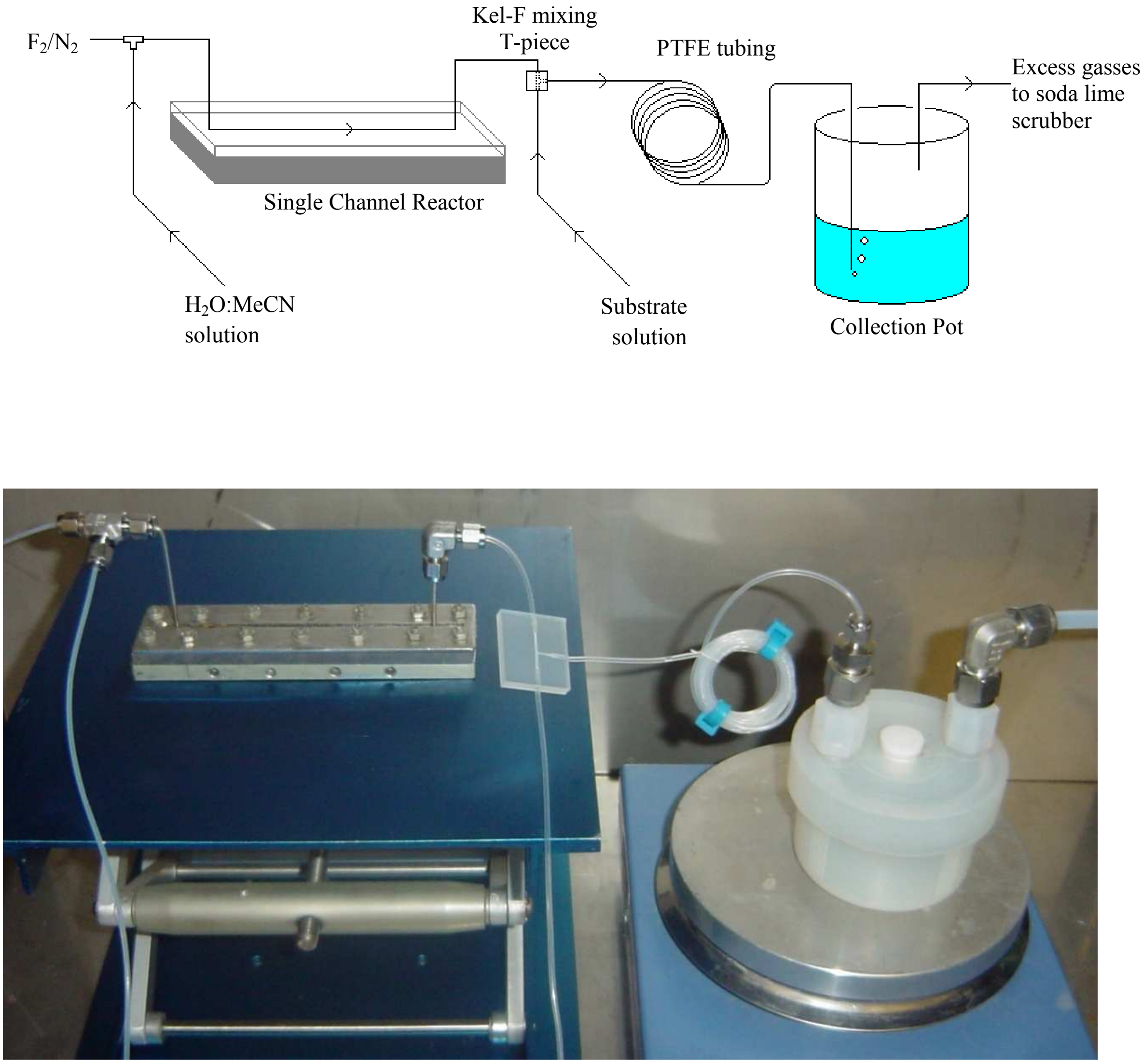
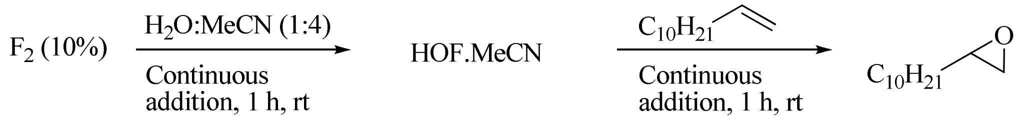


Figure 25: Apparatus for the continuous HOF.MeCN synthesis and substrate oxidation

3.4.1 Initial tests and Calibration

It has already been determined that 10.0 mL h^{-1} of the aqueous acetonitrile is required for 2.0 mmol h^{-1} of HOF.MeCN to be generated, so the optimized experimental flow rates from the batch oxidation process were applied directly to the new full continuous flow process (*results table 3*). As previously stated, the alkene can now react with any excess fluorine in the reaction, thus allowing the detection of excess fluorine in the reaction.

Results table 3:



Expt.	F_2 flow rate (mL min^{-1})	H_2O:MeCN flow rate (mL h^{-1})	1-dodcene (mmol h^{-1})	NMR Yields (%)		
				Alkene	Epoxide	Fluorinated alkene
15	6.0	10.0	2.0	17	83	0
16	6.5	10.0	2.0	10	90	0
17	7.0	10.0	2.0	5	95	0
18	7.5	10.0	2.0	0	100	0
19	8.0	10.0	2.0	0	>99	trace

The results obtained (in results table 3) demonstrated that 1-dodecene can be continuously oxidized in an extremely efficient reaction. The traces of alkene that remained in experiment 17 show that 7.0 mL min^{-1} of fluorine is not quite enough to generate 2.0 mmol h^{-1} of HOF.MeCN, whilst the trace of fluorinated alkene obtained from experiment 19 (the NMR of which is shown in *figure 26*) meant that the flow of fluorine is slightly higher than 2.0 mmol h^{-1}. The quantitative epoxide yields obtained from experiment 18 indicates that 7.5 ml min^{-1} of fluorine is enough to generate 2.0 mmol h^{-1} of HOF.MeCN and that all of the fluorine is being quantitatively used for this. We can therefore say with some accuracy that at the present time, a MFC flow rate read-out of 7.5 mL min^{-1} of 10 % fluorine, equates to 2.0 mmol h^{-1} of fluorine(xiv). This provided us with a method of accurately calibrating both the amount of HOF.MeCN generated per hour and the flow rate of fluorine.

(xiv) This is based on the assumption that all excess fluorine reacts with the alkene. However, slight mixing in-efficiencies will result in a very small amount of un-reacted fluorine passing through the flow setup.

Due to the possible deterioration of the mass flow controller, these calibrations were performed at regular intervals throughout the course of the three year research period.

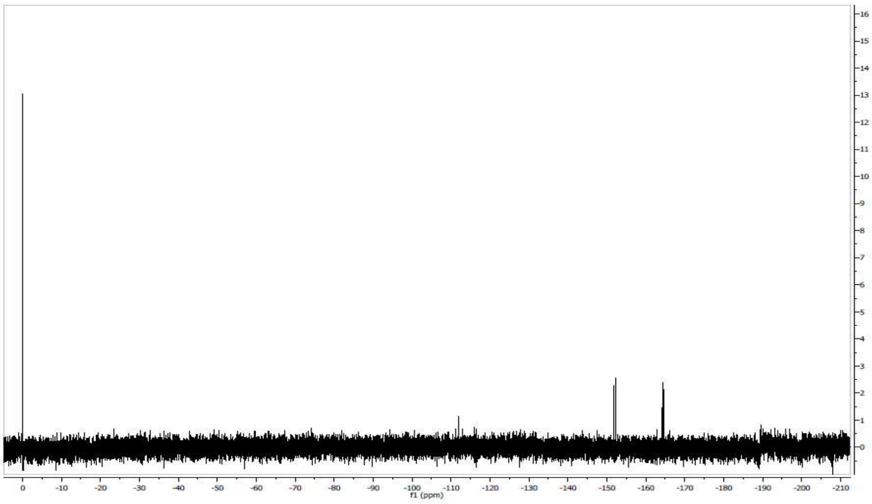
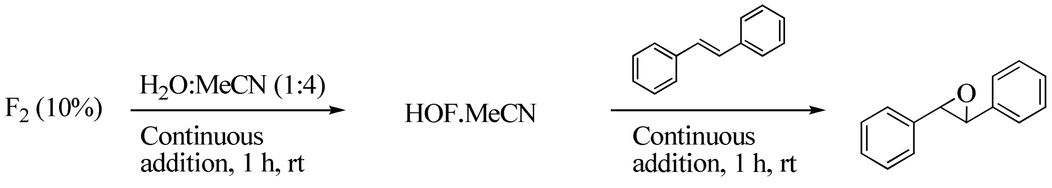


Figure 26: Fluorine NMR for Expt. 19 showing trace amounts of fluorinated starting material

To test the repeatability of our process, the optimization and calibration tests were performed on *trans*-stilbene (*results table 4*). Proton NMR spectra for these reaction have been included with alkene and epoxide peaks highlighted red and blue respectively (*figure 27*).

Results table 4:



Expt.	F_2 flow rate (mL min^{-1})	H_2O:MeCN flow rate (mL h^{-1})	Stilbene (mmol h^{-1})	NMR Yields (%)		
				Alkene	Epoxide	Fluorinated alkene
20	6.0	10.0	2.0	15	85	0
21	6.5	10.0	2.0	10	90	0
22	7.0	10.0	2.0	5	95	0
23	7.5	10.0	2.0	0	100	0
24	8.0	10.0	2.0	0	>99	trace

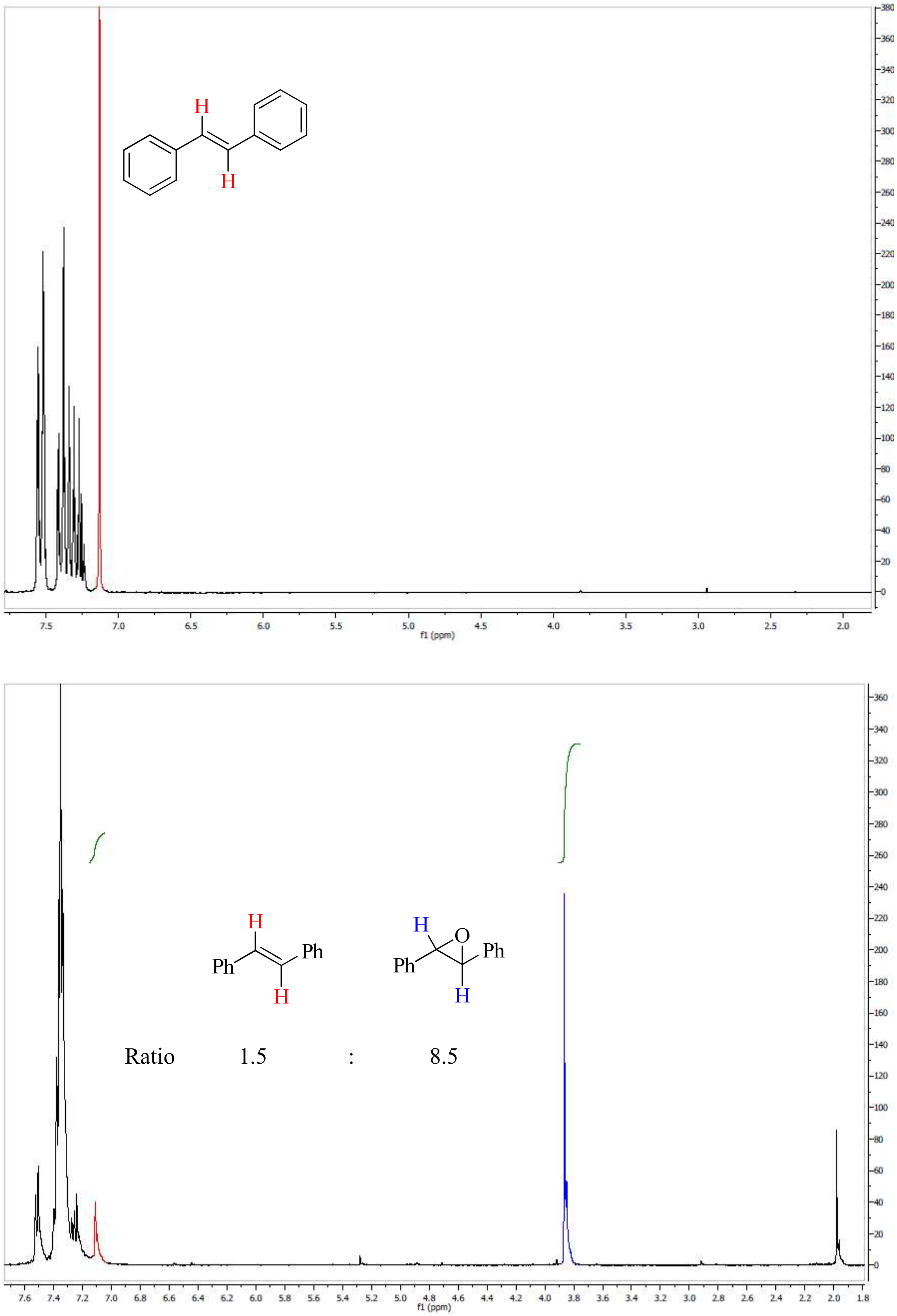


Figure 27: Proton NMR used to optimize the full continuous HOF.MeCN synthesis and substrate oxidation conditions

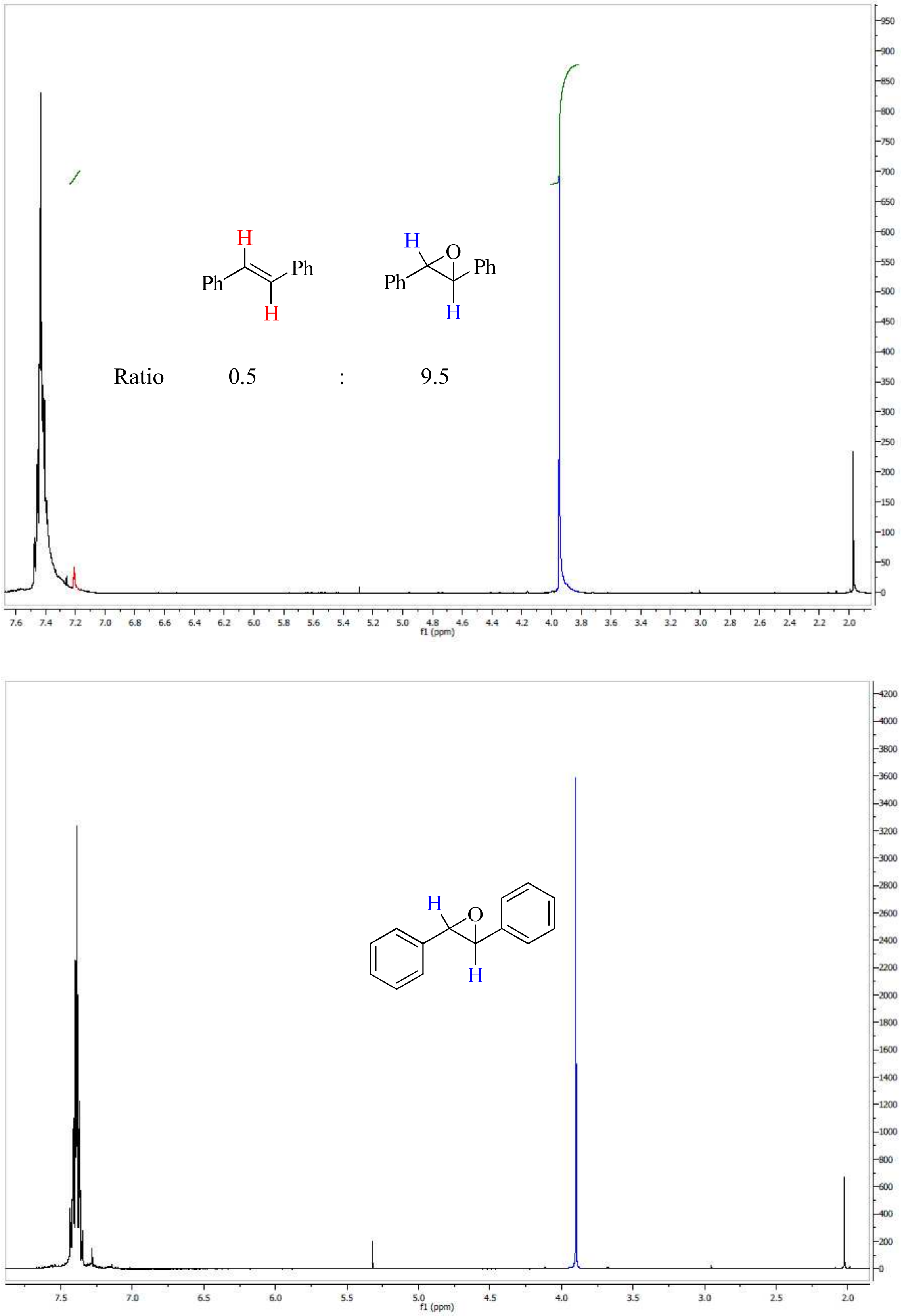


Figure 27 (cont): Proton NMR used to optimize the full continuous HOF.MeCN synthesis and substrate oxidation conditions

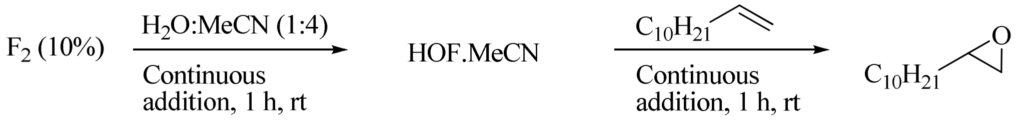
Results from the proton and fluorine NMR spectra show that very similar results to that obtained for 1-dodecene, were obtained using *trans*-stilbene, thus confirming the accuracy of our calibration process. Due to the fact that the flow rate of the control unit [F] (figure 20 page 73) is subject to variation, the calibrated fluorine flow rate will be quoted for the remainder of this thesis as oppose to the control unit read-out.

3.4.2 Scale-up of the Continuous Process

Using the calibrated fluorine flow rates and optimized conditions required for the synthesis of 2.0 mmol h^{-1} of HOF.MeCN, these were applied to maximize the amount of HOF.MeCN that could be generated and continuously used to epoxidize 1-dodecene.

The fluorine flow rate was increased to 8.0 mmol h^{-1} and using 10.0 mL h^{-1} of the H_2O:MeCN mixture, equimolar amounts of the alkene were added continuously per hour. However, 10.0 mL h^{-1} of the aqueous acetonitrile mixture was not high enough to produce 8.0 mmol h^{-1} of HOF.MeCN and therefore, only 71 % of the epoxide was obtained (*results table 5*); the remainder was either starting material or fluoroalkane by-products. An increased flow rate of 20.0 mL h^{-1} of the H_2O:MeCN mixture was required to provide enough water to synthesize 8.0 mmol h^{-1} of HOF.MeCN and, therefore, give quantitative yields of the epoxide.

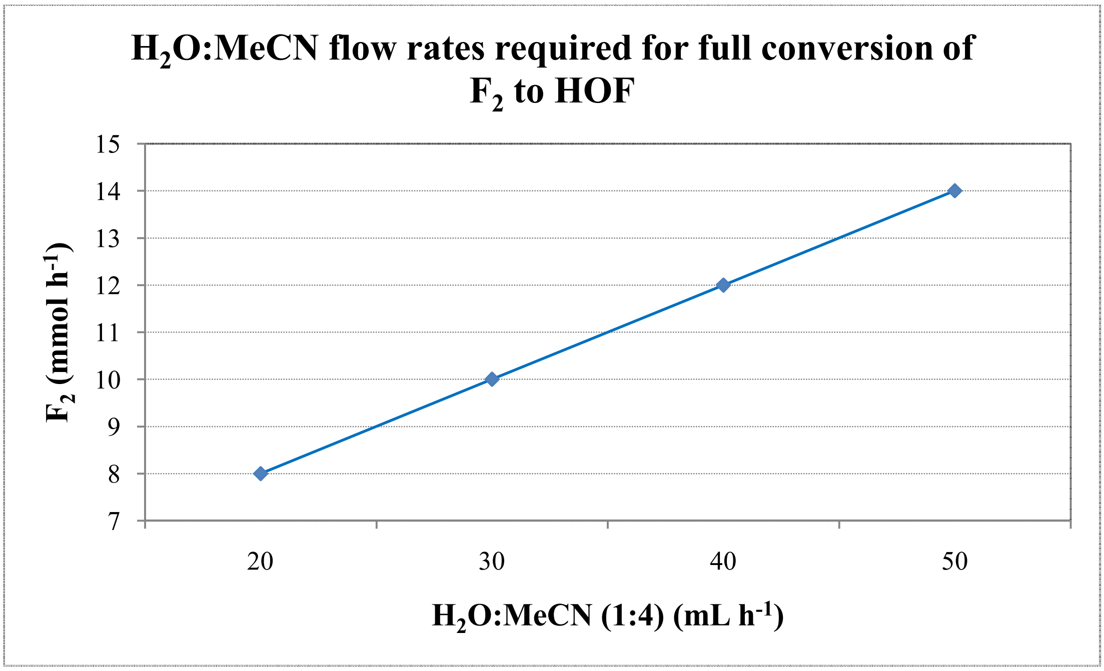
Results table 5:



Fluorine (mmol h^{-1})	**8.0 mmol h^{-1}**		
H_2O:MeCN (1:4) (mL h^{-1})	10.0	15.0	20.0
^{1}H NMR results (epoxide:SM/fluoroalkanes) (%)	71:29	92:8	100

A similar situation arose when the fluorine flow rates were increased to 10.0, 12.0 and 14.0 mmol h^{-1} to give the equimolar amounts of HOF.MeCN. Quantitative amounts of alkene could be continuously oxidized, but in each case, the water flow rate had to be increased to accommodate the extra fluorine and therefore, give quantitative amounts of HOF.MeCN.

The following graph shows how much water is required to quantitatively transform fluorine to HOF.MeCN.

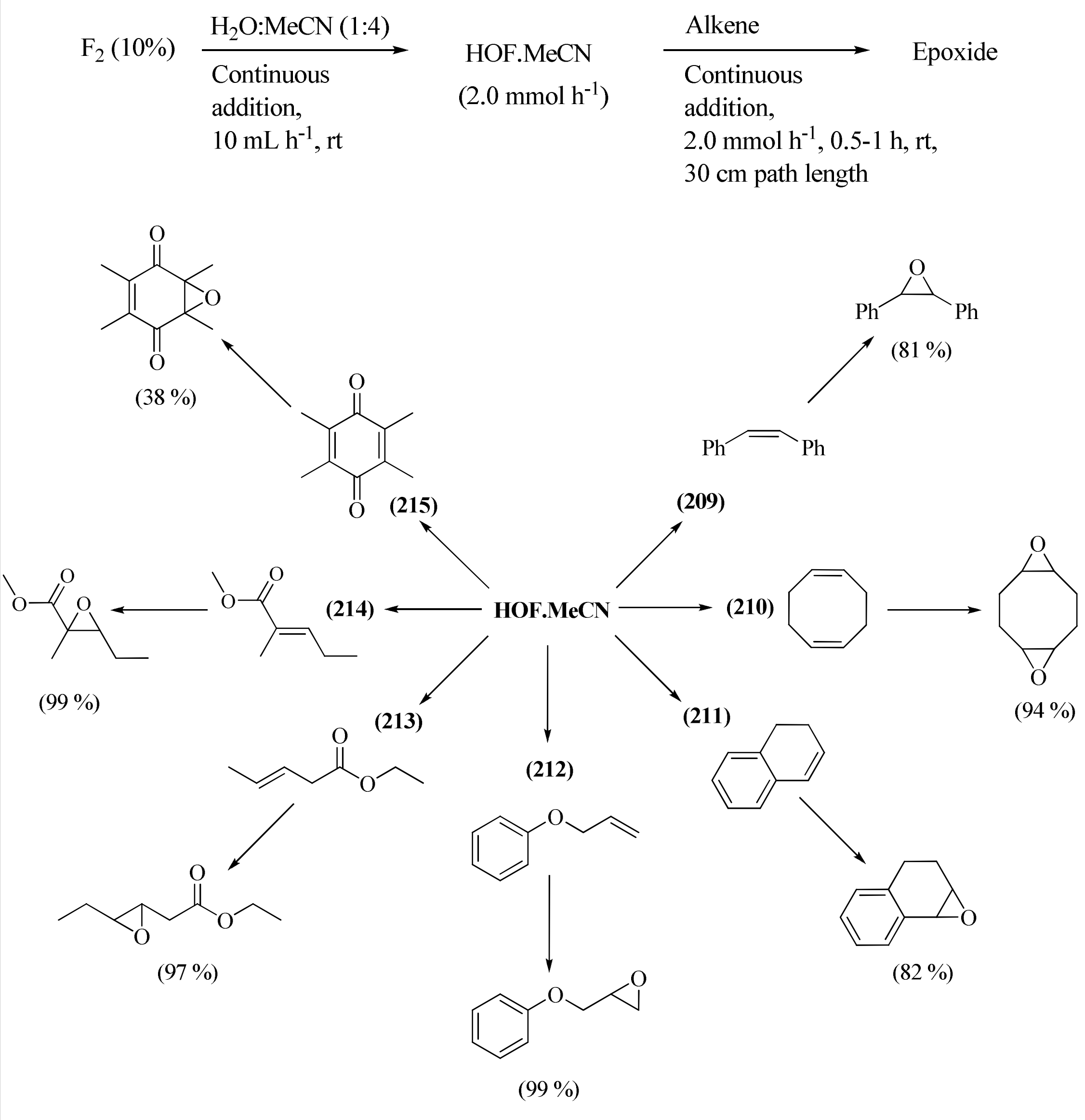


To put the increased HOF.MeCN amounts into perspective, oxidation of 14.0 mmol h^{-1} of dodecene equates to the production of 2.4 g of the epoxide per hour. Continuous operation of the single channel reactor over one day would equate to 57.6 g, and scale-out using the 9-channel dual reactor would give over 1 Kg of epoxide per day.

Once the optimized water flow rates for the higher levels of fluorine were established, our calibration procedure was also applied to each HOF.MeCN level (8, 10, 12 and 14 mmol h^{-1}) to investigate if there was a significant difference of epoxide yields at higher flow rates. Very little variation was experienced which confirmed that our calibration procedure is also accurate at higher HOF.MeCN levels.

3.4.3 Continuous Flow Oxidations

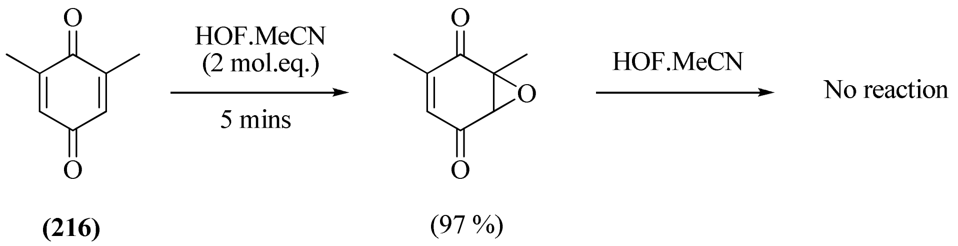
Our two-step continuous flow epoxidation methodology was applied to a range of different alkenes **(209-215)** (*scheme 66*)[135], including those which were both deactivated and hindered. All epoxidation reactions shown were very efficient and produced no un-wanted side products.



All yields taken from proton NMR spectra

Scheme 66: Alkene epoxidations performed using the continuous flow apparatus shown in figure 25

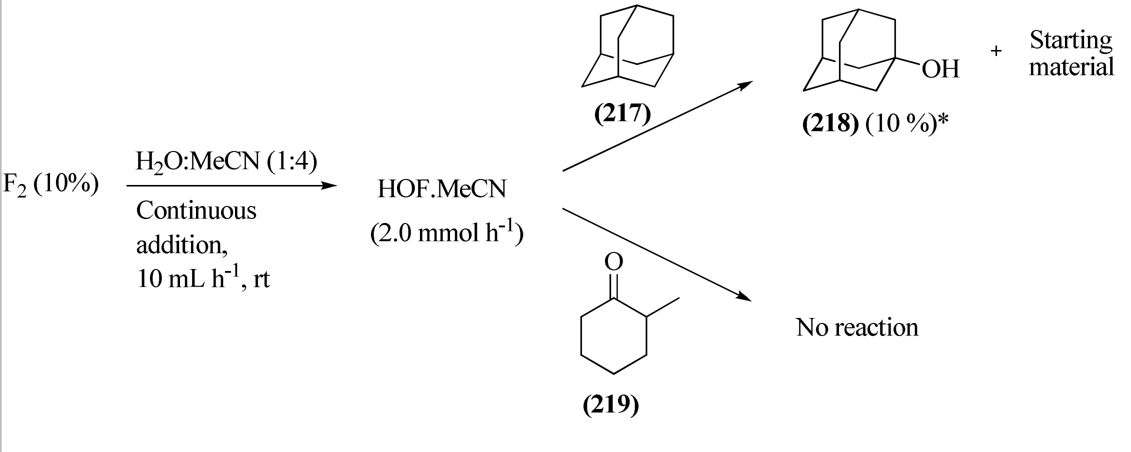
Similar to Rozen's batch oxidation of the quinone **(216)** (*scheme 67*)[67], only one of the deactivated double bonds of duroquinone **(215)** were epoxidized, however, a yield of just 38 % was obtained. An attempt to improve this yield was carried out by increasing the oxidation reaction path length from 30 cm to 60 cm, which increased the epoxide yield to 48 %.



Scheme 67: Rozen's batch oxidation of a quinone

The poor yield obtained for the oxidation of duroquinone was an early indication that oxidation path length could be an issue for substrates that require longer reaction times for complete oxidation with HOF.MeCN. To investigate this, oxidation of these types of substrates was attempted in our continuous process.

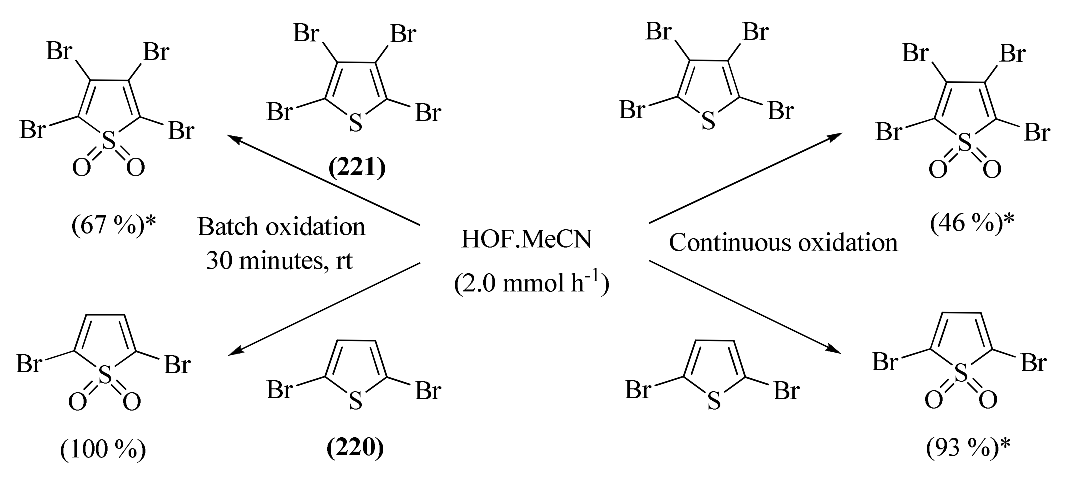
Rozen reported a reaction time of 30 mins for the oxidation of adamantane **(217)** to adamantanol **(218)** (80 %)[72] and 4 hours for the Bayer-Villiger oxidation of 2-methylcyclohexanone **(219)**[72]. In our hands, similar times were required to obtain yields of 80 % of adamantanol using our continuous-batch oxidation of adamantane and 4 molar equivalents of HOF.MeCN. However, attempts to oxidize each of these compounds in a full continuous fashion were less successful, giving only starting material upon oxidation of 2-methylcyclohexanone and low yields of 1-adamantanol **(218)** (*scheme 68*). Increasing the reaction path length from 100 cm to 300 cm did not improve either reaction, nor did using increased amounts of HOF.MeCN.



Conditions: 2.0 mmol of substrate added continuously over 1 h at rt; 100 cm oxidation path length used; *Product was not isolated and the yield is taken from proton NMR spectra

Scheme 68: Continuous oxidation of adamantane and 2-methylcyclohexanone

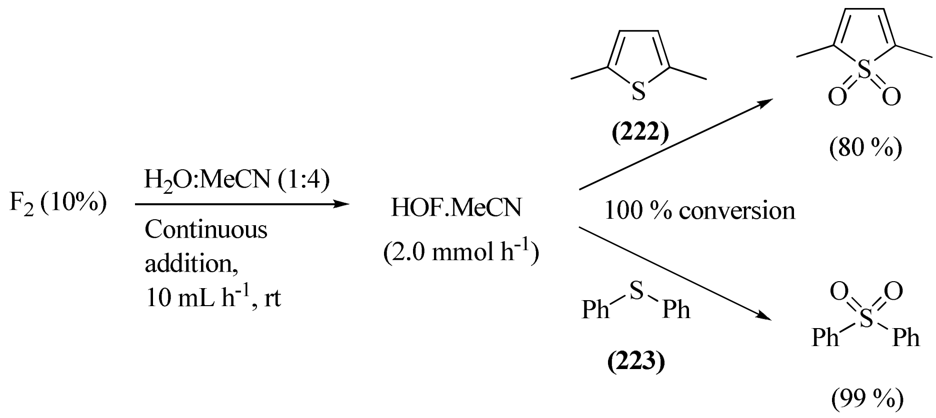
Similar results were obtained with other compounds that required longer reaction times to be oxidized. Rozen reported that thiophenes which contained electron withdrawing groups such as 2,5-dibromothiophene **(220)** and 2,3,4,5-tetrabromothiophene **(221)** both required mixing times of 30 minutes (*scheme 55*, section 1.4.3.7.3) to give the corresponding sulfone. In our hands 30 minutes was sufficient to give comparative yields of both sulfone products. However, continuous oxidation of these compounds using a 3 m path length gave lower yields of the corresponding sulfone (*scheme 69*), although the reactions were still very efficient and other than the sulfone, only starting material was obtained. Using a 100 cm oxidation path length gave lower yields of each sulfone.



Continuous oxidation conditions: 2.0 mmol of substrate added continuously over 1 h at rt; 300 cm oxidation path length used; *Products were not isolated and yields are taken from quantitative carbon NMR spectra

Scheme 69: Batch and continuous oxidation of electron deficient thiophenes

The more electron rich sulfur atoms of 2,5-dimethyl thiophene **(222)** and diphenyl sulphide **(223)** were both easily oxidized to the corresponding sulfone using the continuous flow apparatus in excellent yields (*scheme 70*).



Conditions: 2.0 mmol of substrate added continuously over 1 h, at rt, using 100 cm oxidation path length
Both yields are isolated

Scheme 70: Other sulfur continuous oxidations

3.4.4 Variation of Setup

We revised our current continuous process so that the oxidations were carried out in a second reactor instead of PTFE tubing (*figure 28*) which more accurately replicates scale-out for the oxidation reactions in the vertical reactor shown in section 2.4.3.

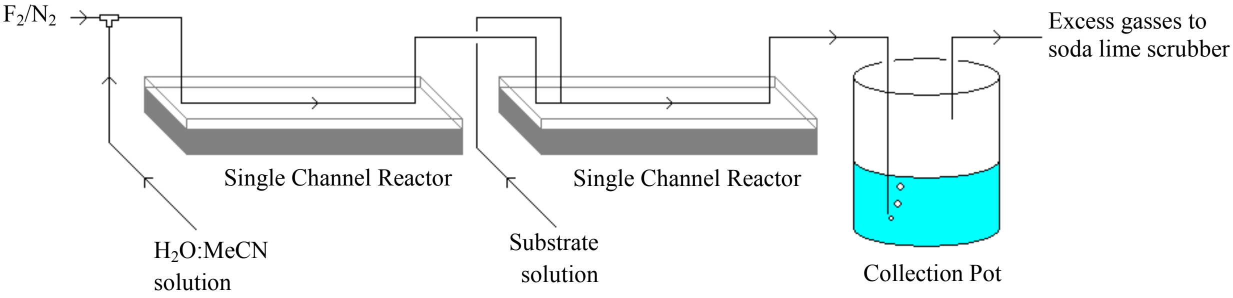


Figure 28: Dual flow reaction set-up to perform oxidations in a nickel reaction channel

Performing reactions in a second reactor would allow oxidation reactions to be cooled if necessary and the nickel block also provides improved heat transfer capabilities over PTFE. However, unlike the PTFE tubing, the reaction path length is fixed in the flow reactor.

Calibration tests using 1-dodecene and *trans*-stilbene were performed using the dual reactor device, which gave similar results to those obtained in the PTFE tubing device. The substrate range was then extended to include thiophenes and later on (see chapter 4) aliphatic and aromatic amines, all of which gave results that were comparable to those obtained in the PTFE oxidation channel.

However, no significant improvement was gained by oxidation of the substrates in a second reactor, even for reactions in which cooling of the oxidation channel may reduce decomposition products (see chapter 4).

The following set-up (*figure 29*) was assembled to investigate if the HOF.MeCN complex be synthesized in PTFE tubing as appose to the flow reactor, and a number of oxidations were performed on various substrates.

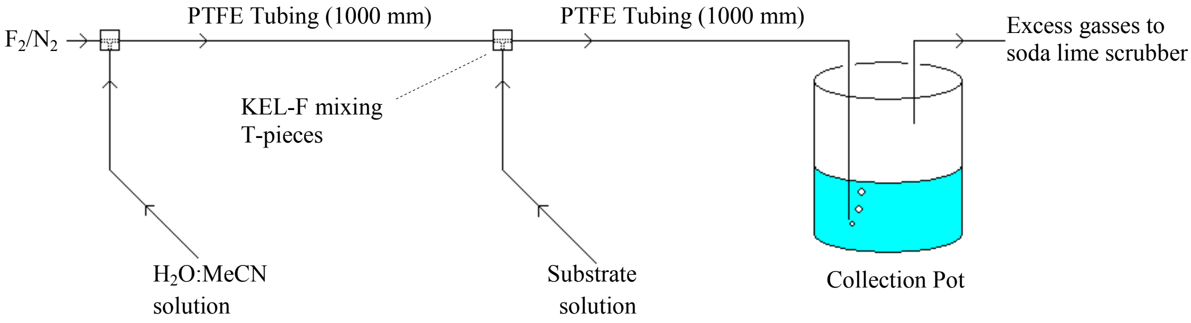
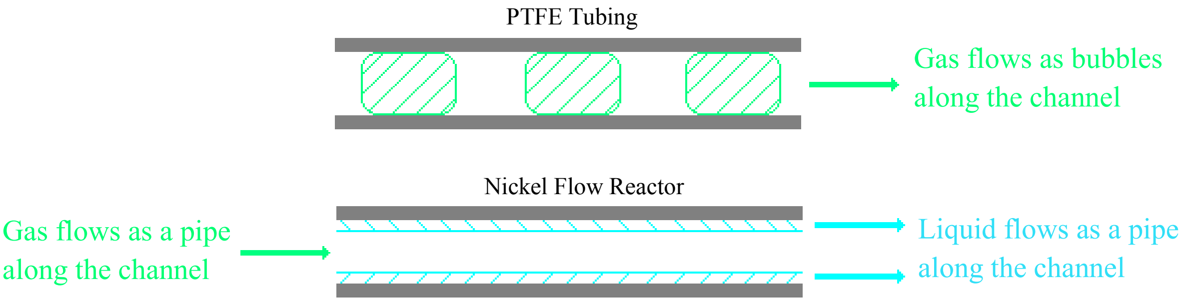


Figure 29: Flow apparatus designed to synthesize HOF.MeCN in PTFE tubing

Oxidation reactions performed using a device entirely fabricated from PTFE tubing, however, were much less efficient and resulted in high amounts of either starting material, or fluorinated material. The poor results obtained using this set-up are attributed to the different flow regimes observed for the gas-liquid reactions in the different reaction channels(xv). Mixing of the gas-liquid reagents in the PTFE tubing proceeds by an intermittent 'slug' flow (*figure 30*), which is a much less efficient method of mixing than the preferred annular 'pipe' flow (*figure 30*) observed when the fluorine and water are mixed in the flow reactor.

(xv) The transparency of both reaction channels allows the flow patterns to be observed



Top: Intermittent flow in PTFE tubing; **Bottom:** Annular flow in nickel flow reactor

Figure 30: Gas-Liquid flow regimes

The flow mixing regimes of the liquid-liquid (second step) oxidations proceeded by an intermittent flow in both the flow reactor and PTFE tubing, which explains why similar yields of products are obtained when the oxidation reactions are carried out in either the nickel reactor and PTFE tubing.

3.4.4.1 Thermodynamics

Calculation of the enthalpy of the reaction of water and fluorine also reveals that the reaction is not very exothermic which indicates that the reaction would not really benefit from cooling of the microchannel.

F-F + H-O-H → H-O-F + H-F

	ΔH (kJ mol^{-1})
Breaking of F-F bond	+159
Breaking of O-H bond	+493
Formation of H-F bond	-569
Formation of O-F bond (approximate)	-180
Enthalpy of reaction	-97

To investigate whether the synthesis of HOF.MeCN depended upon the ability of the PTFE microchannel to dissipate heat from the reaction (PTFE is a good heat insulator where as nickel is known to readily dissipate heat) experiments involving cooling of the PTFE channel were performed. However, we found that cooling of the PTFE channel gave no performance increase and the reactions were equally inefficient.

It should be noted that no kinetic data for the formation of HOF is recorded in the literature, so it is unsure if the process is so rapid that it is an adiabatic one(xvi). However, the differences in data we obtained between the nickel microchannel and the PTFE microchannel suggest that HOF synthesis does not occur rapidly in the T-piece.

3.4.5 Freezing of HOF.MeCN

Not all research institutions have the facilities to work with elemental fluorine and many researchers still hold a prejudice towards working with the gas. Therefore, if the HOF.MeCN complex could be frozen and still retain its activity, this would allow the frozen HOF.MeCN complex to be transported at low temperature and, therefore, be made available to other research institutions.

Frozen HOF.MeCN would limit the complex to small scale oxidations as it could only be used in batch process, but this could be a valuable tool for trial oxidations of certain compounds before deciding upon acquiring the facilities for continuous scale-out oxidations.

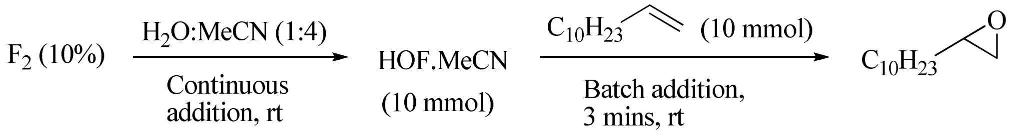
To test the feasibility of freezing HOF.MeCN, the continuous-batch process was used to generate 10.0 mmol h^{-1} of HOF.MeCN and collected in acetonitrile in the usual way (see section 3.3). The HOF.MeCN solution was then divided into two equal portions, and its activity tested using equimolar amounts of 1-dodecene (*results table 6*):

Portion 1 - Stored at room temperature for a set period of time

Portion 2 - Stored at -78ºC for the same period of time as portion 1

(xvi) An adiabatic process is a thermodynamic process in which the net heat transfer to or from the working fluid is zero. Such a process can occur if the process happens in an extremely short time, so that there is no opportunity for significant heat exchange.

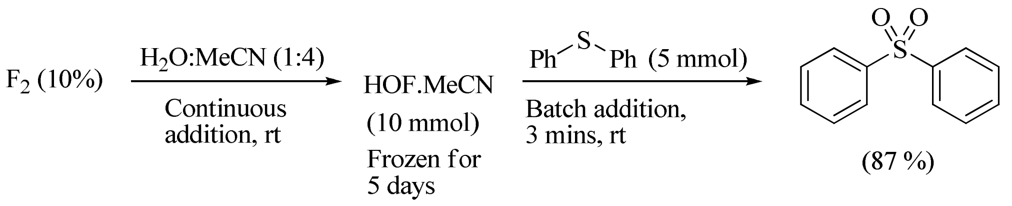
Results Table 6:



	1 hour	1 day	2 days	5 days
	^{1}H NMR yields (epoxide : alkene)			
Portion 1 - Un-frozen	50 : 50	0 : 100	0 : 100	0 : 100
Portion 2 - Frozen	95 : 5	94 : 6	93 : 7	89 : 11

The results show that the un-frozen sample lost half of its reactivity over a period of one hour, but when frozen for one hour and then used, the frozen sample retained 95 % of its activity. The frozen HOF.MeCN complex retained 89 % of its activity after 5 days, demonstrating that the complex could be frozen and transported at low temperature (-78°C).

The oxidation capabilities of the HOF.MeCN complex after it had been frozen were also tested on diphenyl sulphide, and after 5 days it was shown to have retained 87 % of its activity (*scheme 71*).



Scheme 71: Activity of HOF.MeCN after being frozen for five days

3.5 Summary

To summarize the chapter, we have successfully devised a continuous flow system for the synthesis of HOF.MeCN and subsequent substrate oxidation in a continuous flow process. Up to 14.0 mmol h^{-1} of substrate has been oxidized continuously over a period of five hours with no loss of performance, therefore providing a genuine method to scale-up the use of HOF.MeCN without encountering any stability or safety issues.

An accurate and safe method for the calibration of F_2 flow rates and HOF.MeCN concentration has also been devised, so any problems associated with the fluctuation of mass flow controllers can easily be avoided and accurate experiments can be carried out without having to use iodimetric titrations.

The flow process has been successfully demonstrated to oxidize a variety of different compounds, most of which proceed with excellent efficiency and yields. The HOF.MeCN complex does exhibit similar properties in flow as it does in batch, so compounds which were not efficiently oxidized in batch were also poor in our flow system. Also, compounds which required extended batch reaction times such as hydroxylations, were only partially oxidized because of low residence times in the flow system.

We have also shown that the HOF.MeCN complex can be frozen for up to 5 days without major loss of its oxidative capabilities, therefore proving a means of transporting the complex.

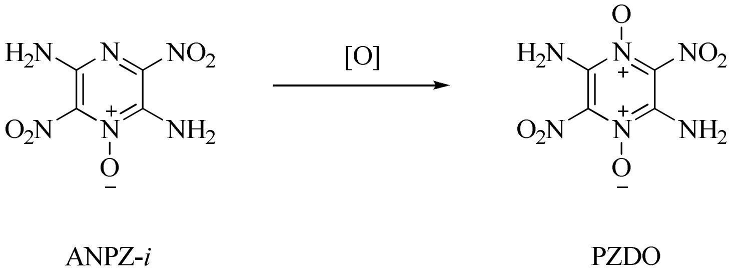
The apparatus built for our research has been used without problems or leaks, and thus fluorine is rarely detected. The oxidation step has been shown to proceed in an equally efficient manner when performed using a flow reactor, and a proposed variation of our vertical flow scale-out reactor which could be used for our two-step processes shown in chapter 6.0.

Chapter 4 - Oxidations at Nitrogen

4.1 Introduction and Aims

Polynitro aromatic systems are particularly important to the energetic materials industry, but, because of their electron deficient nature, techniques such as electrophilic aromatic substitution or direct amine oxidationcan be un-suitable for synthesizing such compounds[136].

Nitroheteroaromatic compounds are also of increasing importance to the energetic materials industryand over the past two decades they have received a great amount of interest, because, in general, they have higher heats of formation, density and oxygen balance over their carbocyclic counterparts[136]. Oxidation of the tertiary ring nitrogen also offers another method to increase the density and oxygen balance of the system. However, electrophilic aromatic substitution of electron deficient heteroaromatic systems can also be problematic and although there are many reagents that exist for the synthesis of *N*-oxides, they are not suited to electron deficient heterocycles[136]. Thus, potentially energetic materials such as PZDO (*scheme 72*) are currently inaccessible[137].



Scheme 72: Oxidation of ANPZ-i to give PZDO is currently not possible

The HOF.MeCN complex could offer apotential solution to the problem of forming polynitro and *N*-oxide heteroaromatic derivatives and our continuous flow systemwould also provide a safe and scalable process.Following on from the development and application of the oxidation flow methodology[135]described in the previous chapter, our aims were therefore to investigate the feasibility of using our flow oxidation process for the synthesis of these types of systems, in particular:

1. The synthesis of nitro aliphatic derivatives from the corresponding amine and azide compounds
2. The synthesis of electron deficient nitro benzene compounds from their corresponding anilines
3. The oxidation of a range of electron deficient nitrogen heterocycles, including:

a) Those without an amine moiety attached to the ring so ring nitrogen oxidation can be investigated without competing reactions
b) Those with an amine moiety attached to the ring so that the selectivity of theHOF.MeCN reagentcan be examined

4.2 Aliphatic Nitro Compounds

4.2.1 From Aliphatic Amines

Aliphatic nitro compounds are another class of compounds with potential value to the energetic materials community, but, very few methods exist for the efficientsynthesis ofsuch compounds, in particular those withan alkane chain greater than 6 carbon atoms. Murrayreported the oxidation of primary aliphatic amines using DMDO and showed thatshort chain amino alkanes **(224-226)** and aliphatic cage/cyclic amino compounds **(227-230)**could be oxidized in very good yields, butthose with slightly longer chains **(231)** gave very poor yields (*scheme 73*)[138-139]. Oxidationof aliphatic amines with DMDOalso requires reactions times in excess of 24 hours.

$$R{-}NH_2 \xrightarrow[\text{acetone, rt, >24h}]{\text{DMDO}} R{-}NO_2$$

(224) *n*-butylamine	84 %
(225) sec-butylamine	87 %
(226) *tert*-butylamine	90 %
(227) Cyclohexylamine	95 %
(228) 1-Aminoadamantane	95 %
(229) 1,4-diaminocubane	81 %
(230) 1,3,5,7-tetraamino-adamantane	91 %
(231) 1,6-diaminohexane	20 %

Scheme 73: DMDO oxidation of aliphatic amines

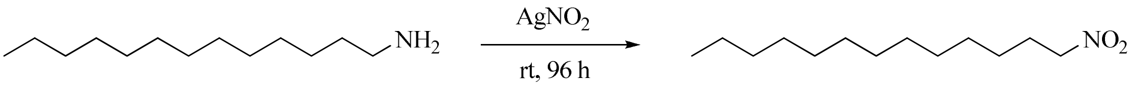
Later Crandall reported the oxidation of longer chain aliphatic amines**(232-233)**(*scheme 74*) with DMDO, but still only moderate yields of the nitrated systems were obtained[140].

$$R{-}NH_2 \xrightarrow[\text{acetone, 5}^{\circ}\text{C, 17h}]{\text{DMDO}} R{-}NO_2$$

(232) $R = C_7H_{15}$	60 %
(233) $R = C_{10}H_{23}$	51 %

Scheme 74: Oxidation of longer chain aliphatic amines using DMDO

Improved yields of longer chain aliphatic nitro compounds such as nitrododecane**(234)** could be synthesized from the corresponding amine using silver nitrate (*scheme 75*), but these reactions required reaction times of up 96 hours and also disposal of the expensive metal by-products[141].



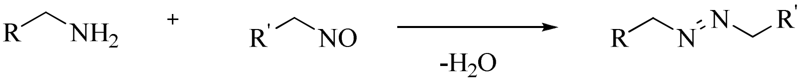
(234) 76 %

Scheme 75

We expected that oxidation of aliphatic amine compounds using HOF.MeCN in our continuous flow set-up to be more problematic than the alkene oxidations because, unlike the epoxidation of alkenes, the oxidation of amines proceeds *via* reactive intermediates (*scheme 76*), which could giverise to the possibility ofside reactions and un-wanted by-products. In particular, the nitroso group is very nucleophilic and, therefore,available for reaction with both the hydroxylamine and the starting material to give the corresponding diazo compound (*scheme 77*).

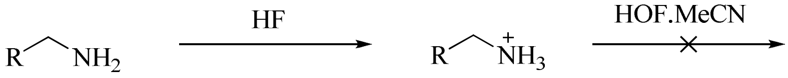
$$R{-}NH_2 \xrightarrow{\text{HOF.MeCN}} \left[\, R{-}NHOH \,\right] \xrightarrow[\text{-HF, -}H_2O]{\text{HOF.MeCN}} \left[\, R{-}NO \,\right] \xrightarrow[\text{-HF}]{\text{HOF.MeCN}} R{-}NO_2$$

Scheme76: Intermediates involved during the oxidation of amines using HOF.MeCN



Scheme 77: Possible formation of a diazo side product

Also, as was explained in section 1.4.3.5.2, the basicity of the starting material means that it is vulnerable to protonation from hydrogen fluoride, rendering it un-reactive to HOF.MeCN (*scheme 78*).To counteract this in batch oxidations, Rozen mixed a base (NaF) into thesolution of HOF.MeCN to neutralize the HF, but this would not be possible in our continuous flow process.



Scheme 78: Protonation of the amine renders the compound un-reactive towards HOF.MeCN

The amine group is also very reactive towards fluorine in polar solvents such as acetonitrile, so strict calibration of our flow process was required to ensure no excess fluorine was available to react with the amine in a competing process (*scheme 79*).

Scheme 79:Fluoramine formation

4.2.1.1 Continuous Flow Synthesis

Despite the more intrinsic nature of these reactions, we were able to apply our continuous flow oxidation methodology, the apparatus of this is shown again in *figure 31*, to synthesize a range of aliphatic nitro derivatives, including short chain, long chain, cyclic and cage structures, from the corresponding amines (*scheme 80*)[142]. These were very efficient reactions and in most cases,near quantitative weights of the nitro compound were obtained.Proton NMR spectrafor some of the crude aliphatic nitro products have been included (*figure 32*) to show how clean these reactions were.Also, unlike batch oxidations of aliphatic amines using HOF.MeCN, no base was required to achieve high yields of the nitro compounds.

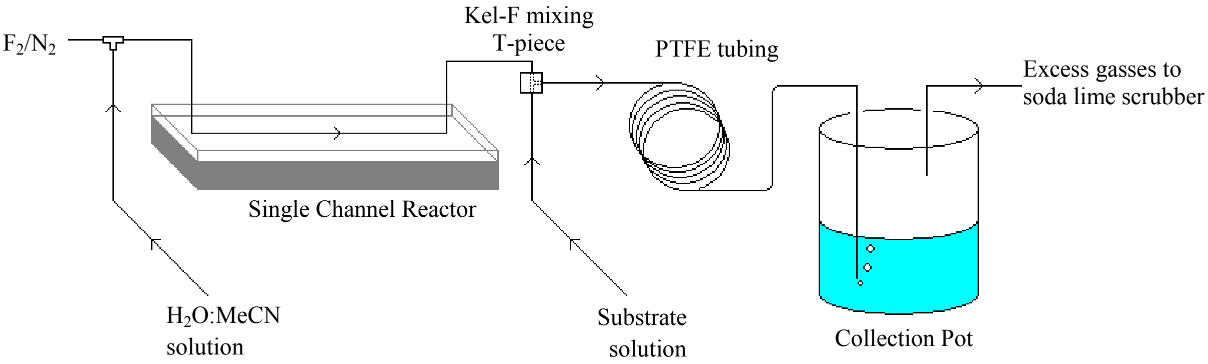
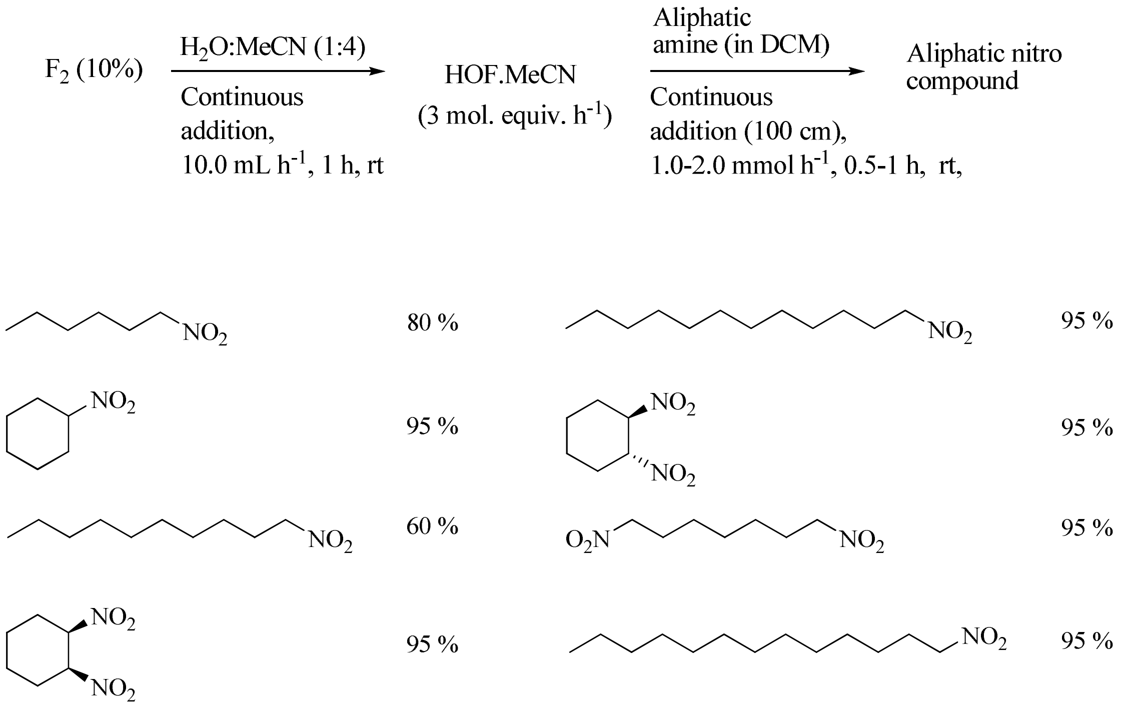


Figure 31:Apparatus for the continuous HOF.MeCN synthesis and substrate oxidation



Conditions: 100 cm oxidation reaction path length, 30-60 mins run time, water collection pot; all yields isolated

Scheme 80: Continuous synthesis of aliphatic nitro compounds from the corresponding amines

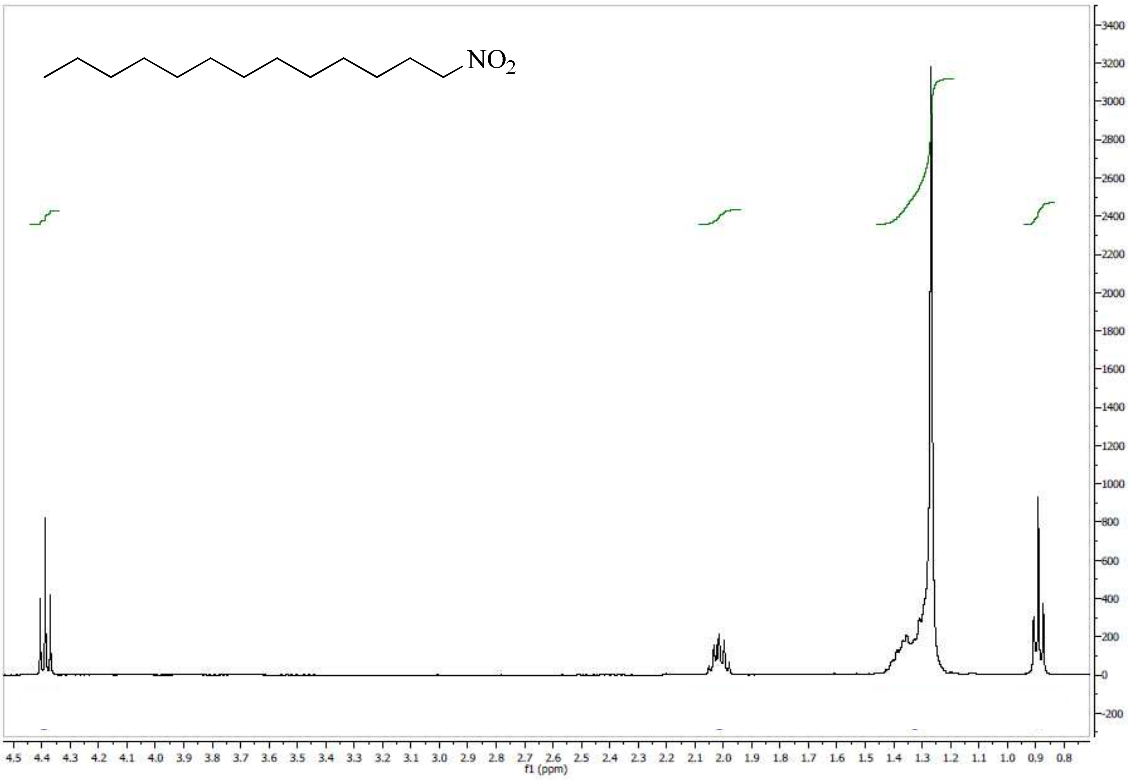


Figure 32: Crude ^{1}H NMR spectra of 1-nitrotridecane obtained from the oxidation of the corresponding amine

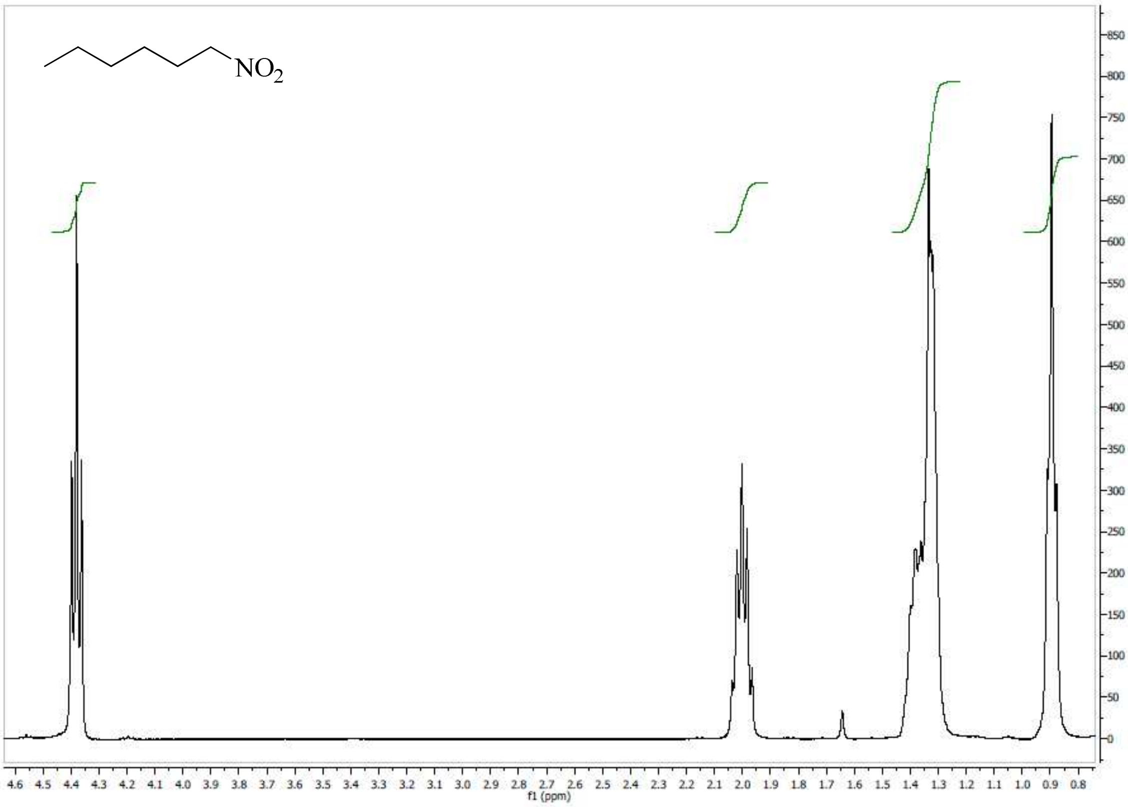


Figure 32(cont):Crude ^{1}H NMR spectra of 1-nitrohexane obtained from the oxidation of the corresponding amine

Initially the oxidation of the aliphatic amine compoundsgave un-identifiable side products, particularly for reactions involving the shorter chain amines such as aminohexane and the cyclic amines. It was difficult to explain why these reactions were less efficient than their longer chain counterparts, and numerous experiments were performed, varying conditions such as flow rates and channel temperature, none of which gave any improvements on the initial optimized conditions.Proton NMR spectra for one such reaction performed on aminohexane is shown in *figure 33*, and GC confirmed the presence of multiple products.It was later discovered that the aq. $NaHCO_2$ in thecollection-pot was reacting with the aliphatic nitro compounds as they were collected, thus giving the un-wanted by-products.The aq. $NaHCO_2$ in the collection-pot was replacedwith water which prevented the problem of side reactions.

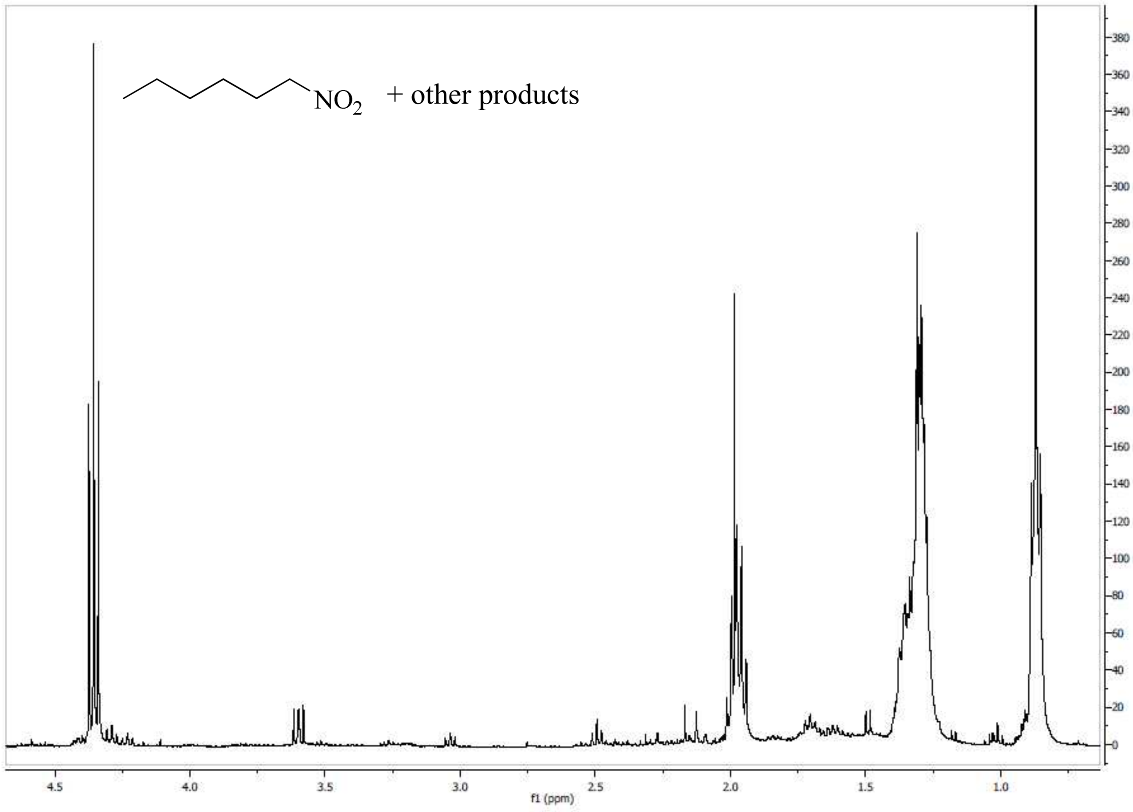
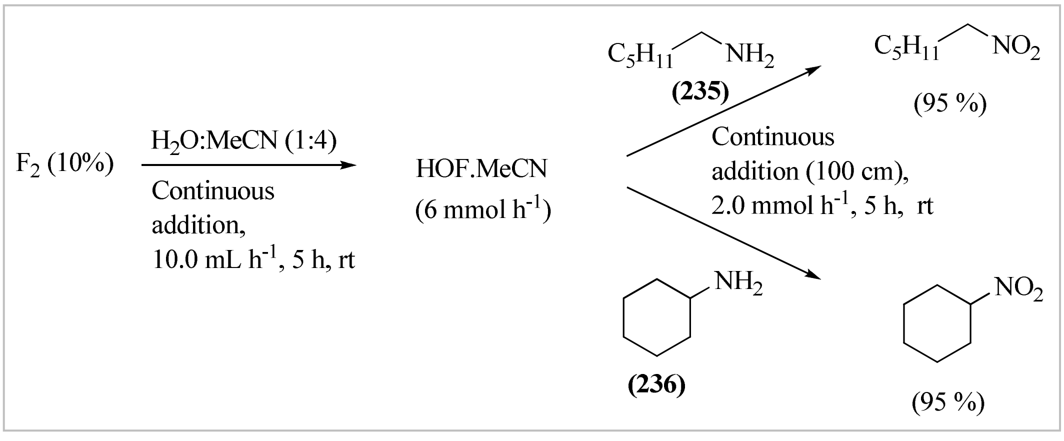


Figure 33: Crude ^{1}H NMR spectra of 1-nitrohexane to show impurities when collected in a basic catch pot

Scale-up was demonstrated usingaminohexane**(235)** and cycloaminohexane**(236)**as substrates by increasing the reaction flow times to 5 hours. These extended reaction flow times provided no problems to either reactionand near quantitative weights of the corresponding aliphatic nitro compound were obtained for each (*scheme 81*).



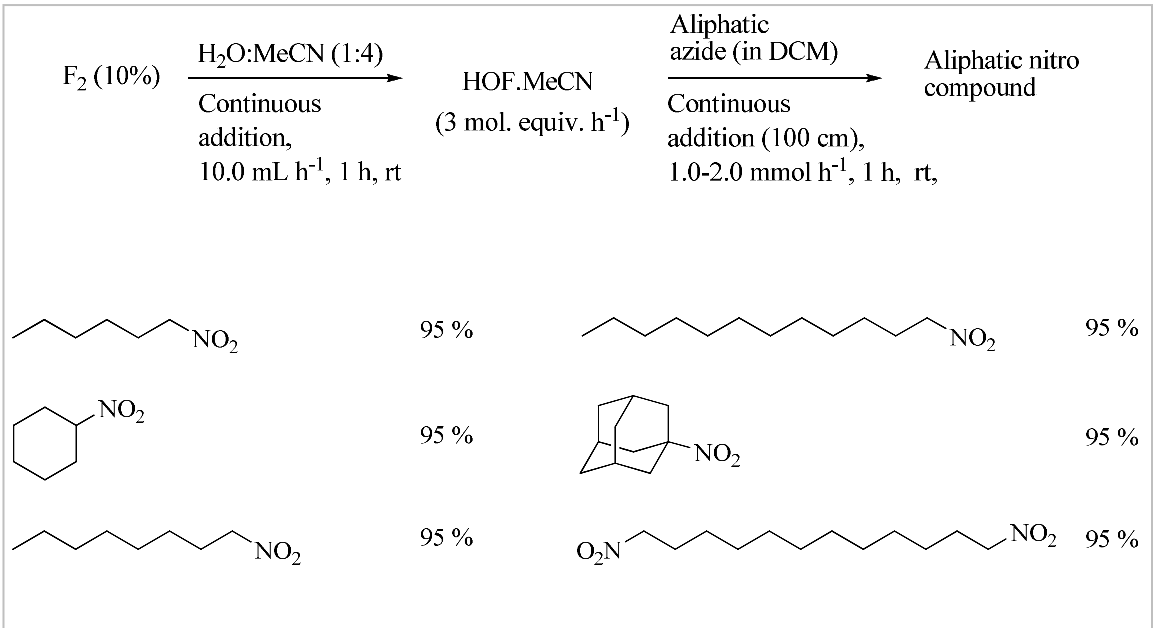
Scheme 81: Scale-up continuous flow oxidations of aliphatic amines

4.2.2 From Aliphatic Azides

Prior to Rozen demonstrating that the HOF.MeCN complex could be used to oxidize an azide group to a nitro group in one step[93], the only other method to directly perform this functional group interconversion was Corey's multistep synthesis[93]. Due to the synthetic value of this process, particularly to the energetic material industry, we also attempted to oxidizealiphatic azidesusing HOF.MeCNin our continuous flow process.

4.2.2.1 Continuous Flow Synthesis

Thealiphatic azides tested were again chosen to includeshort chain, long chain, cyclic and cage structures, and were either commercially available or synthesized from a standard literature procedure[143].Although the oxidation of azides also proceeds *via* reactive intermediates, we were able to apply our continuous flow process to oxidize a range of aliphatic azides to their corresponding nitro compounds (*scheme 82*). Similar to the oxidation of aliphatic amines, the oxidation reactions of aliphatic azides were very efficient and for all of the reactions near quantitative weights of the aliphatic nitro compound were obtained.



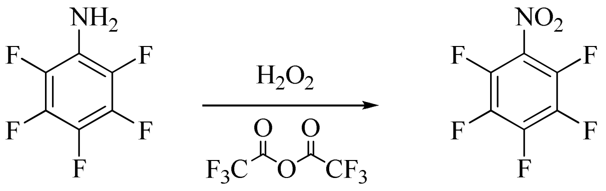
Conditions: 100 cm oxidation reaction path length, 60 mins run time, water collection pot; *all yields isolated*

Scheme 82:Continuous synthesis of aliphatic nitro compounds from the corresponding azides

4.3 Aromatic Nitro Compounds

Our next aim was to investigate the feasibility of using our flow methodology to oxidize a variety of aniline derivatives. However, due to the potentially explosive materials that could be obtained by oxidizing nitroanilines, for example, oxidation of 3,5-dintroaniline to give the explosive 1,3,5-trinitrobenzene, these types of compounds could not be treated with HOF.MeCN. Instead, fluorinated anilines were used to provide us with suitable electron withdrawing analogues in which to mimic the electron deficient aromatic ring of polynitro aromatic derivatives, but which would be safe to handle upon oxidation. The fluorinated aniline compounds are also easily synthesized*via*nucleophilic aromatic substitution of fluorinated benzenes (see chapter 5 for synthesis of starting materials).

Direct oxidation of compounds such as pentafluoroaniline**(237)** has been attempted using dihydrogen peroxide andtrifluoroacetic anhydride, but the reactions required heating under reflux and gave poor yields of the nitro compound (*scheme 83*)[144]. They are also not suitable for scale-up.



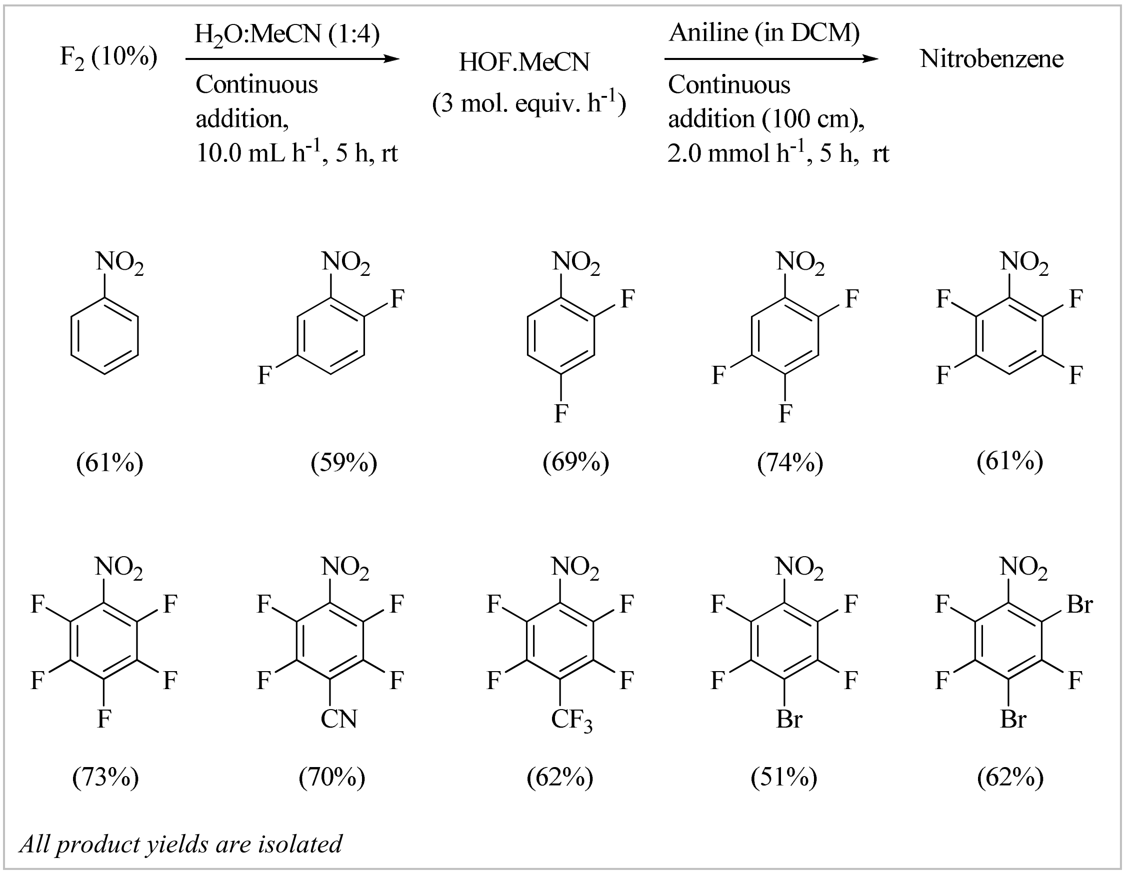
(237)

(50 %)

Scheme 83: Peroxide oxidation of pentafluoroaniline

4.3.1 Continuous Flow Synthesis

To provide a comprehensive overviewof the oxidation capabilities of the HOF.MeCN complex on electron deficient anilines, a number offluoroanilines, each with differentelectron environments, were oxidized using our flow process. The oxidation of all the anilines proceeded reasonably efficiently and, thus, the following range of nitro benzene derivatives were obtained in moderate to good yields (*scheme 84*)[142].



All product yields are isolated

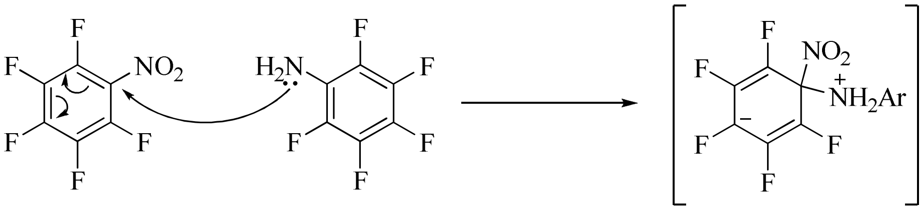
Scheme 84: Nitrobenzenes synthesized using HOF.MeCN in our continuous flow process

100 % conversion of the aniline was observed in all reactions and the NMR of the crude product showed near quantitative yields of the nitrobenzene. The lower isolated yields of the nitrobenzene derivatives indicate that product decomposition occurred in each reaction, which was probably caused by side reactions of the reactive intermediates.

The morenucleophilic electron rich anilines are more reactive and, therefore, give more decomposition products whichlead to lower yields of the desired nitrobenzene compounds.

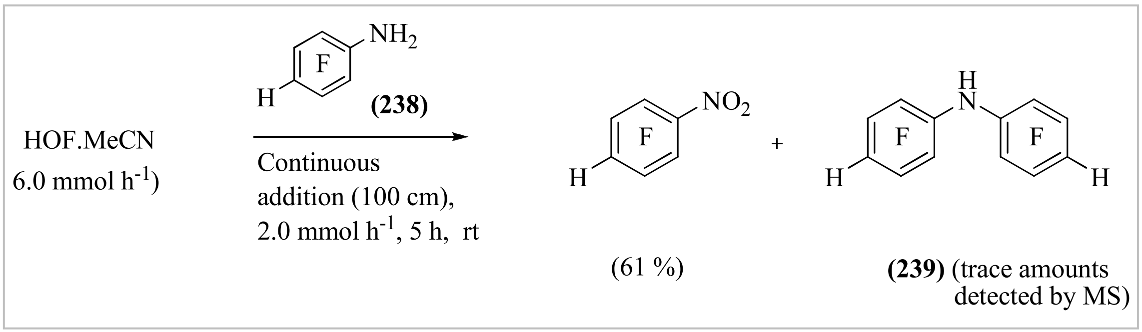
The position of the ring fluorine atoms also affects the yields of nitrobenzene, which is possibly due to substitution of the nitro group once it is formed. In the presence of nucleophiles,polyfluoronitrobenzene systemscan undergo nucleophilic substitution at the nitro position, but kinetic studies have shown thatdue to the un-favourable Meisenheimer complex,the site of nucleophilic attack is deactivated by a fluorine *para* to this position[xvii](*scheme 85*).The reasons for this effectare explained in Chapter 5.

[xvii] Fluorine atoms *ortho* and *meta* to the nucleophilic position actually activate the fluorobenzene to nucleophilic attack. This effect is explained in detail in Chapter 5.0.



Scheme 85: The un-favourable Meisenheimer intermediate formed by para fluorine

Therefore, it is postulated that the slightlylower yields of the nitrobenzene that were obtained in all compounds which do not possess a fluorine atom*para* to the nitro group are possibly due to substitution of the nitro group of these compounds. Evidence to suggest this was obtained by GC-MS, in which small amounts of the coupled product **(239)**was detected after the oxidation of 2,3,5,6-tetrafluoroaniline**(238)**, but could not be isolated.



Scheme 86

4.4 Nitrogen Heteroaromatic Derivatives

Once we had established that the HOF.MeCN complex could oxidize the amine group of an electron deficient ring system in a continuous flow process, our next aims were to establish:

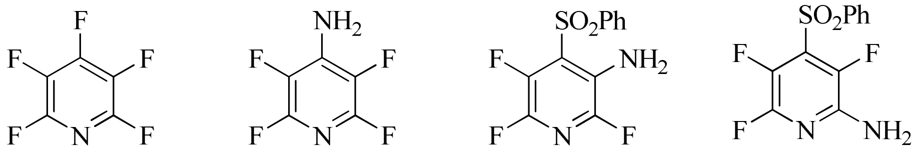
a) If oxidation of the ring nitrogen of electron deficient nitrogen heteroaromatic compounds was possible
b) If theHOF.MeCN complex exhibited any selectivity towards either the ring nitrogen or the amine group of amino nitrogen heteroaromatic compounds

The batch process described in section 3.3 was initially used for all oxidations. Reactions that did not produce high amounts of tar and were considered of practical use, were then scaled-up using the full continuous flow oxidation process (*figure 31*).

The water soluble nature of *N*-oxide compounds also posed a problem in accurately assessing the products of the crude material. Using the standard aqueous work-up procedures that had previously been used for the work in this thesis was not possible, because the water soluble*N*-oxide would remain dissolved in the water layer and thus make the quantitative comparison of products very difficult. To overcome this problem and quantitatively measure the products of each reaction, the crude product of all batch reactions was extracted from the acetonitrile catch pot by removing the acetonitrile under vacuum and the residue wasquantitatively assessed using NMR and ASAP-MS.

4.4.1 Pyridines

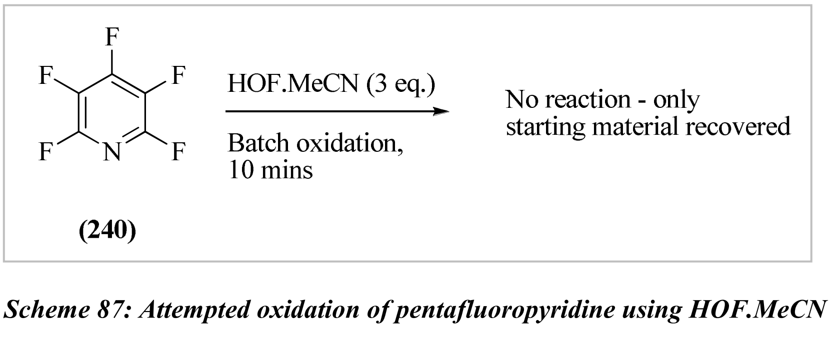
Pyridine analogues, as appose to diazines, were chosen to begin our investigations so thatoxidation of the ring nitrogen atom could be assessed without a competing reaction with a second ring nitrogen atom. Once again, fluorinated analogues were used to provide a suitable electron deficient environment (*figure 34*).



(240) **(241)** **(242)** **(243)**

Figure 34

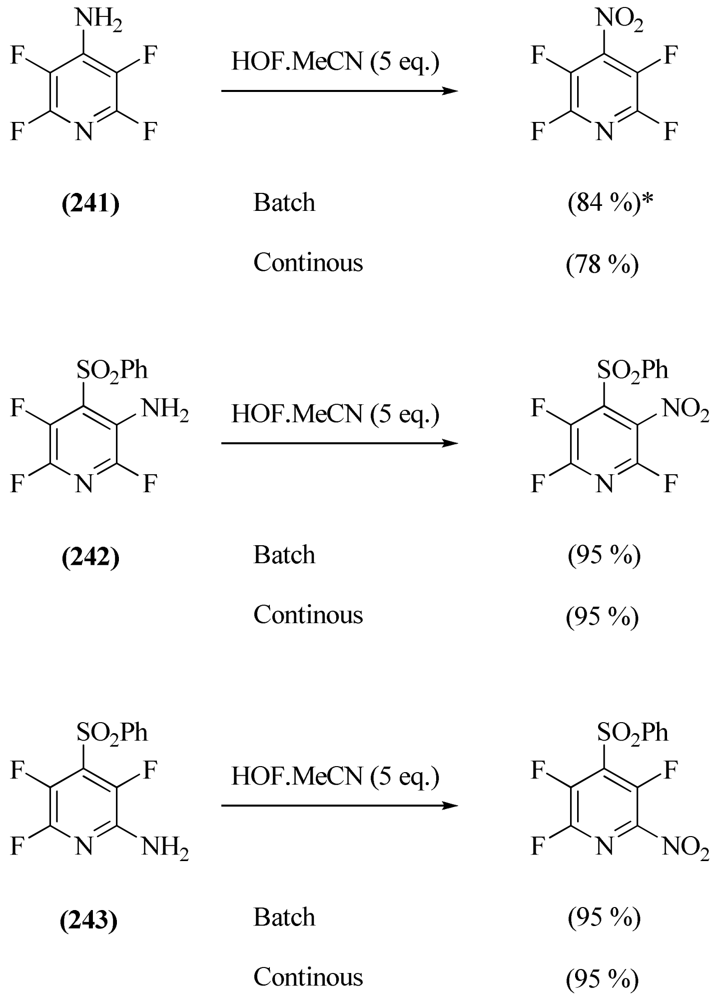
Oxidation of the ring nitrogen of pentafluoropyridine **(240)**to give pentafluoropyridine-*N*-oxide, has previously been impossible due to the fluorine atoms in the 2- and 6- positions, which renders the ring nitrogen almost non-nucleophilic. Although the HOF.MeCN complex has been shown to be able to oxidize compounds that previous oxidants could not, the complex was unable to oxidize pentafluoropyridine and thus,quantitative amounts of stating material were obtained upon work-up (*scheme 87*).



Scheme 87: Attempted oxidation of pentafluoropyridine using HOF.MeCN

Oxidation of the amine group of the three perfluoropyridine systems**(241-243)** was possible using HOF.MeCN, although only the nitro pyridine was obtained (*scheme 88*) and no oxidation of the ring nitrogen was observed. These reactions were very efficient and gave excellent yields of the corresponding nitro compound so they were scaled-up in our oxidation flow process.

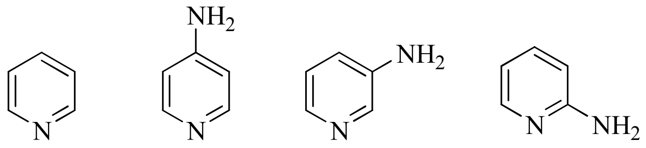
The lower yields of the 4-nitropyridine are caused by slight product decomposition which isthought to be caused by nucleophilic substitution of the nitro group. This is due to the fact that the nitro group at the 4-position ismuch more susceptible to nucleophilicattack caused by the activating effect of the*para* ring nitrogen. The position γ to the ring nitrogen is also activated towards nucleophilic substitutionby the *ortho* and *para* fluorine atoms (see chapter 5).



Conditions: Batch reactions - 2.0 mmol of substrate (in DCM) mixed for 10 minutes at rt; Continuous reactions- 2.0 mmol h^{-1} of substrate (in DCM) added over a time period of 5h at rt using an oxidation path length of 100 cm. **Product was not isolated and yield was obtained from ^{19}F NMR; all other yields isolated*

Scheme 88: Batch and continuous oxidations of electron deficient aminopyridines using HOF.MeCN

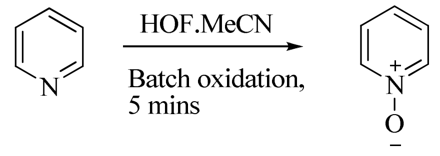
So that a comparison could be made with thecorresponding electron rich pyridines, those shown in *figure 35* were alsotreated with HOF.MeCN.To provide an accurate assessment of selectivity of the HOF.MeCN complex, the amino pyridines were tested with just one molar equivalent of HOF.MeCN and also 5 molar equivalents.



(244) **(245)** **(246)** **(247)**

Figure 35

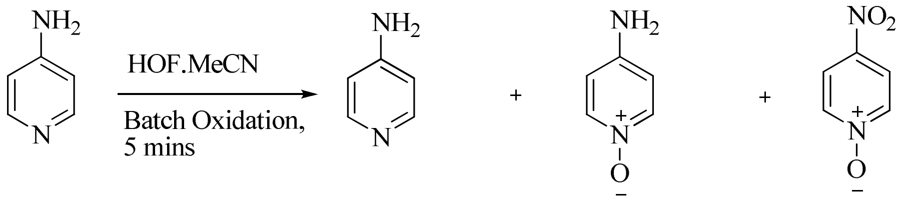
Pyridine**(244)** was oxidized to give the corresponding *N*-oxide in near quantitative amounts (*scheme 89*).



(244) 1 eq. HOF (95%)

Scheme 89: Oxidation of pyridine using HOF.MeCN

4-Amino pyridine**(245)** also gave an excellent yield of the amine-*N*-oxide with one molar equivalent of HOF.MeCN, indicating high selectivity of the ring nitrogen over the amine (*scheme 90*).



(245)	1 eq. HOF*	(8%)	(91%)	(0.8%)
	5 eq. HOF*	(5%)	(82%)	(10%)

**Products not isolated and yields obtained from ^{1}H NMR*

Scheme 90: Oxidation of 4-aminopyridine using HOF.MeCN

However, even with 5 molar equivalents of HOF.MeCN, only low yields of the nitro-*N*-oxide were obtained. The difficultly in oxidizing the amine group of 4-aminopyridine **(245)**is possibly due to the stabilizing effect that the positive charge of the *N*-oxide has on the amine when it is delocalized at the 4-position (*figure 36*).

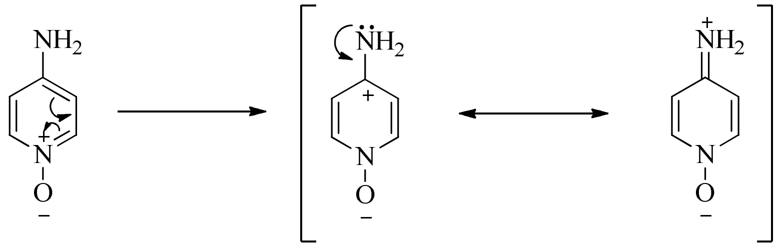
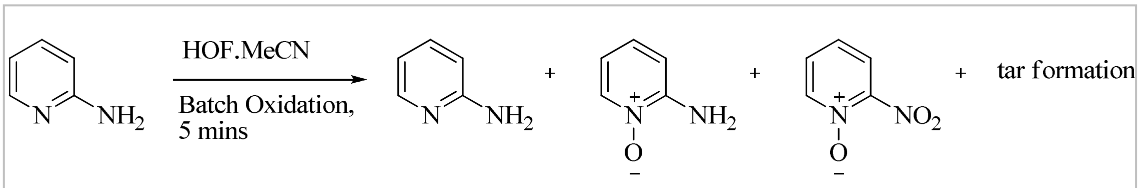


Figure 36: Positive charge delocalized onto the amine which makes it less nucleophilic

The amine group of 2-amino pyridine**(247)** is also stabilized by the carbocation intermediate, however, higher yields of the nitro-*N*-oxide were obtained than with the oxidation of 4-aminopyridine (*scheme 91*). It appears that the *N*-oxide adjacent to the carbocation intermediate inductively reduces the contribution of the positive charge in the 2-position and therefore the amine group is less stabilized by the carbocation and more available for oxidation (*figure 37*). Treatment of **(247)** with HOF.MeCN also gave high amounts of tar, so the reaction was not considered to bepreparatively useful.



(247)	1 eq. HOF*	(11%)	(41%)	(6%)
	5 eq. HOF*	(4%)	(28%)	(25%)

**Products not isolated and yields obtained from ^{1}H NMR with referenced to an internal standard*

Scheme 91: Oxidation of 2-aminopyridine using HOF.MeCN

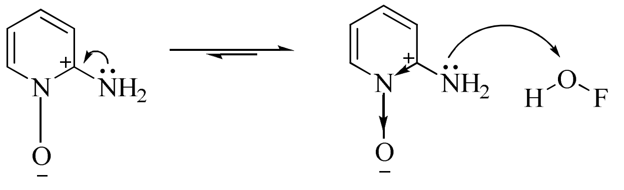
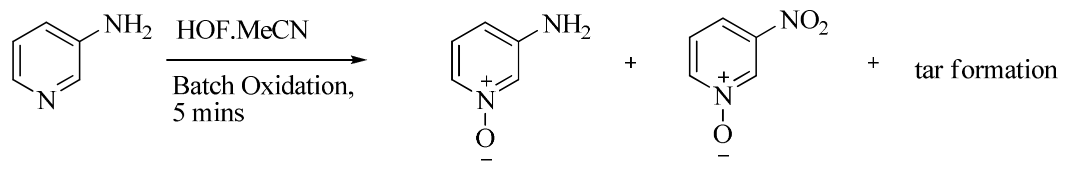


Figure 37: Less contribution of the carbocation intermediate at the 2-position reduces amine stabilization so more of the nitro compound is formed

The amine of 3-amino pyridine-*N*-oxide**(246)** is not stabilized by an adjacent positive charge and therefore the ring nitrogen readily undergoes oxidation, giving much higher yields of the nitro-*N*-oxide with both equimolar amounts of HOF.MeCN and a fivefold excess (*scheme 92*). This reaction however, also gave high amounts of decomposition products and is not considered preparatively useful.



(246)	1 eq. HOF*	(19%)	(30%)
	5 eq. HOF*	(12%)	(36%)

**Products not isolated and yields obtained from ^{1}H NMR with referenced to an internal standard*

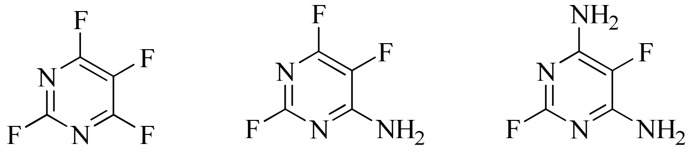
Scheme 92: Oxidation of 3-aminopyridine using HOF.MeCN

Attempts were made to reduce the amount of tar formation upon treatment of 2-amino pyridine **(247)** and 3-amino pyridine **(246)**with HOF.MeCNby varying reactions conditions such as flow rates and channel temperature, including performing the oxidations in a cooled nickel flow reactor, but these reactions gave similar yields of decomposition products.

4.4.2 Diazines

The basicity of diazines is reduced, relative to pyridine, because the second electronegative heteroatom reduces the capacity of the diazine to tolerate the positive charge[145].Diazines are also correspondingly more reactive towards nucleophilic substitution than pyridine systems, due to the additional electron withdrawing effect of the second ring nitrogen[146]. Both of these factors are accentuated by the addition of electron withdrawing groups such as fluorine.

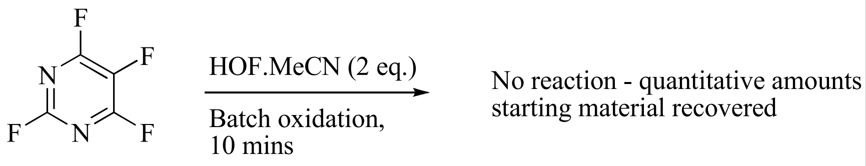
So that we could extend our investigations to the study of oxidation reactions of electron deficient diazines, theperfluoropyrimidine derivativesshown in *figure 38* were synthesized (see chapter 5)and treated with various concentrations ofHOF.MeCN in our batch oxidation process.



(248) **(249)** **(250)**

Figure 38

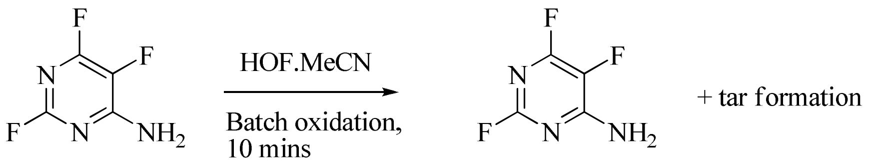
However, much like pentafluoropyridine**(240)**, the fluorine atoms of tetrafluoropyrimidine**(248)** render the ring nitrogen atoms non-basic so that synthesis of the *N*-oxide was not possible using HOF.MeCN (*scheme 93*). Extended mixing of 30 minutes and a six fold excess of HOF.MeCN were not able to oxidizethe ring nitrogen atoms.



(248)

Scheme93: Attempted oxidation of tetrafluoropyrimidine using HOF.MeCN

The amine group of 4-aminotrifluoropyrimidine **(249)** is less nucleophilic in nature, compared to perfluoropyridine compounds, because of the extra electronegative ring nitrogen and, therefore, treatment of compound **(249)** with HOF.MeCN gaverelatively high amounts of the starting material (*scheme 94*). The reaction also produced high amounts of tar, which arelikelyto be caused by substitution of the of the nitro group once it is oxidized. This is because sites α- and γ- to the ring nitrogens are very activated towards nucleophilic attack, so the nitro group iseasily substituted by either starting material or water and, therefore,subject to further oxidations.



(249)

2 eq. HOF* (76%)

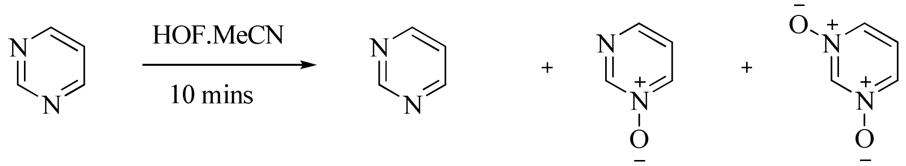
6 eq. HOF* (36%)

**Products not isolated and yields obtained from ^1H NMR with referenced to an internal standard*

Scheme 94: Oxidation of 4-aminotrifluoropyrimidine using HOF.MeCN

Similar results were obtained upon treatment of2,5-difluoropyrimidine-4,6-diamine**(250)** with HOF.MeCN. Only starting material and tar products were recovered and neither reaction is considered practically useful.

So that a comparison could be made with electron rich systems, pyrimidine**(251)** was treated with the HOF.MeCN complex. Treatment with one equivalent of HOF.MeCN gave the pyrimidine 1-oxide, however, this seems to render the second tertiary ring nitrogen almost non-basic because treatment with two equivalents of HOF.MeCN gave only 3 % of the 1,3-dioxide (*scheme 95*). Extended mixing of 30 minutes only slightly improved the 1,3-dioxide yield to 5 %, and an excess of HOF.MeCN gave only 6 %.



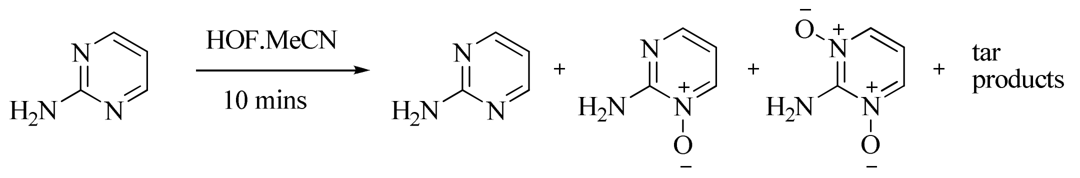
(251)	1 eq. HOF*	(1.3 %)	(80 %)	-
	2 eq. HOF*	-	(90 %)	(3 %)
	5 eq. HOF*	-	(87 %)	(6 %)

**Products not isolated and yields obtained from ^{1}H NMR*

Scheme 95: Oxidation of pyrimidine using HOF.MeCN

Slightly higher amounts of the 1,3-dioxide were obtained from the oxidation of 2-aminopyrimidine**(252)** (*scheme 96*) and this is possibly due to the electron donating influence of the attached amine group.

However, upon treatment of 2-aminopyrimidine with HOF.MeCN, none of the nitro pyrimidine derivatives were detected, either by NMR or ASAP-MS, and these reactions also produced high amounts of tar. It is therefore likely that the tar products formed in these reactions are caused by oxidation of the amine group to the corresponding nitro compound(s) and that these undergo further reactions to give the decomposition products.



(252)	1 eq. HOF*	(34%)	(48%)	-
	2 eq. HOF*	(23%)	(56%)	(6%)
	6 eq. HOF*	(12%)	(42%)	(10%)

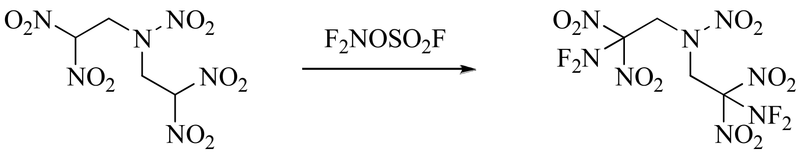
**Products not isolated and yields obtained from ^{1}H NMR with referenced to an internal standard*

Scheme 96: Oxidation of 2-aminopyrimidine using HOF.MeCN

2.5 Difluoramines

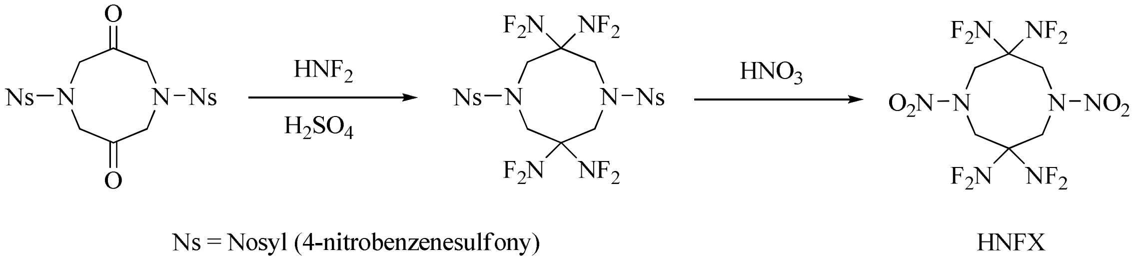
Due to its decomposition to form HF,the difluoramino group (-NF_2) is quite energetic and interest in this functional group has been predominantly due to their potential as energetic materials[147].

Two of the most widely used approaches to the synthesis of difluoramines are the electrophilic difluoroamination using *N*,*N*-difluorohydroxylamine-*O*-sulfonyl fluoride (F_2NOSO_2F) (*scheme 97*)[147] and the formation of geminaldifluoramino groups by reacting ketones with difluoramine in fuming sulfuric acid (*scheme 98*)[147] and these two methods have been used to synthesize two interesting energetic materials DFAP and HNFX.



DFAP

Scheme 97



Scheme 98

Although elemental fluorine has been reported for the synthesis of difluoramines, very few examples appear in the literature[147] and only one refers to the synthesis of difluoramino benzenes[148].

However, an accidental increase in fluorine flow rates when we first attempted to oxidize 4-amino-2,3,5,6-tetrafluorobenzonitrile**(253)** led us to a serendipitous discovery. The fluorine NMR not only gave the two expected aromatic fluorine peaks corresponding to thedesired nitrobenzene (*figure 39*blue), but also showed three more peaks, of equal but lower intensity (*figure 39*red). Two of these were in the aromatic region and the third peak was at 63.8 ppm, which corresponds to fluorine bonded to nitrogen. This indicated to us that some of the difluoramine compound had been formed.

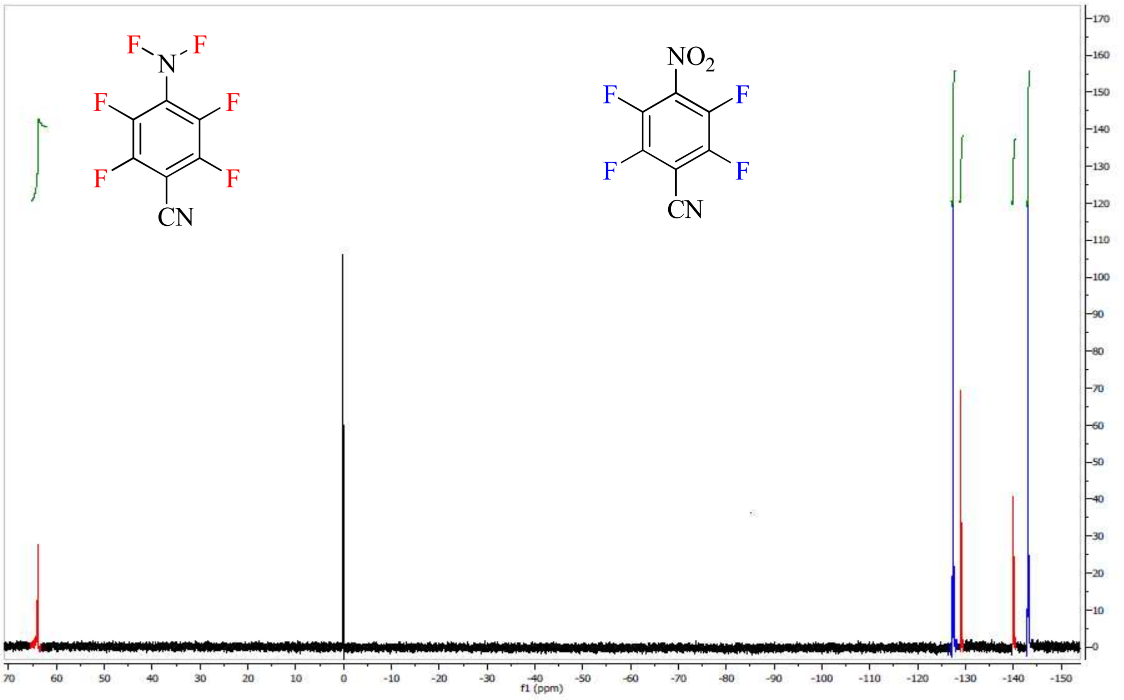
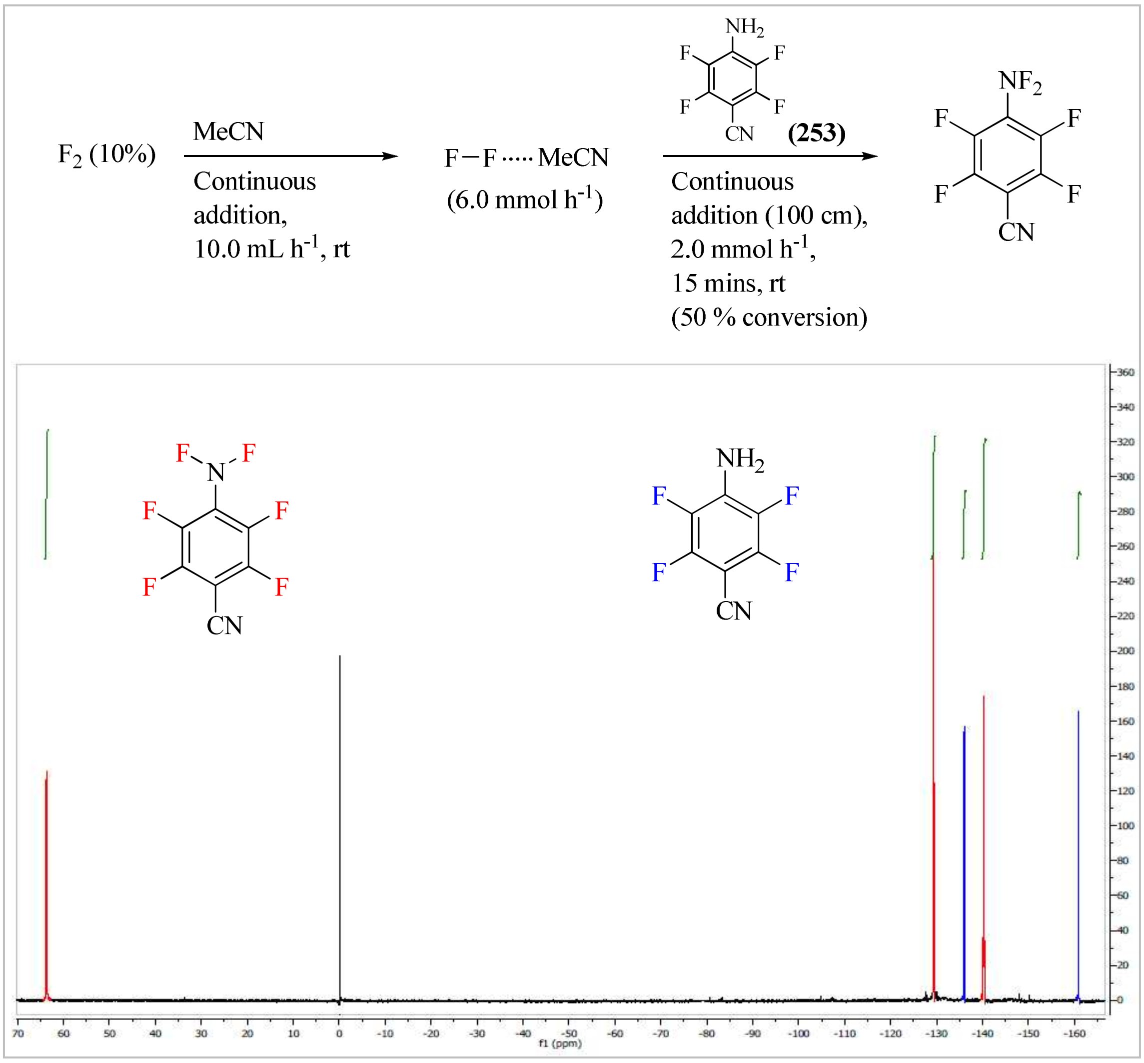


Figure 39: NMR obtained from the oxidation of 4-cycanotetrafluoroaniline with accidental increased fluorine flow rate

The two compounds were separated *via* silica column chromatography, and the molecular ion of the difluoramine was characterized by ASAP-MS.

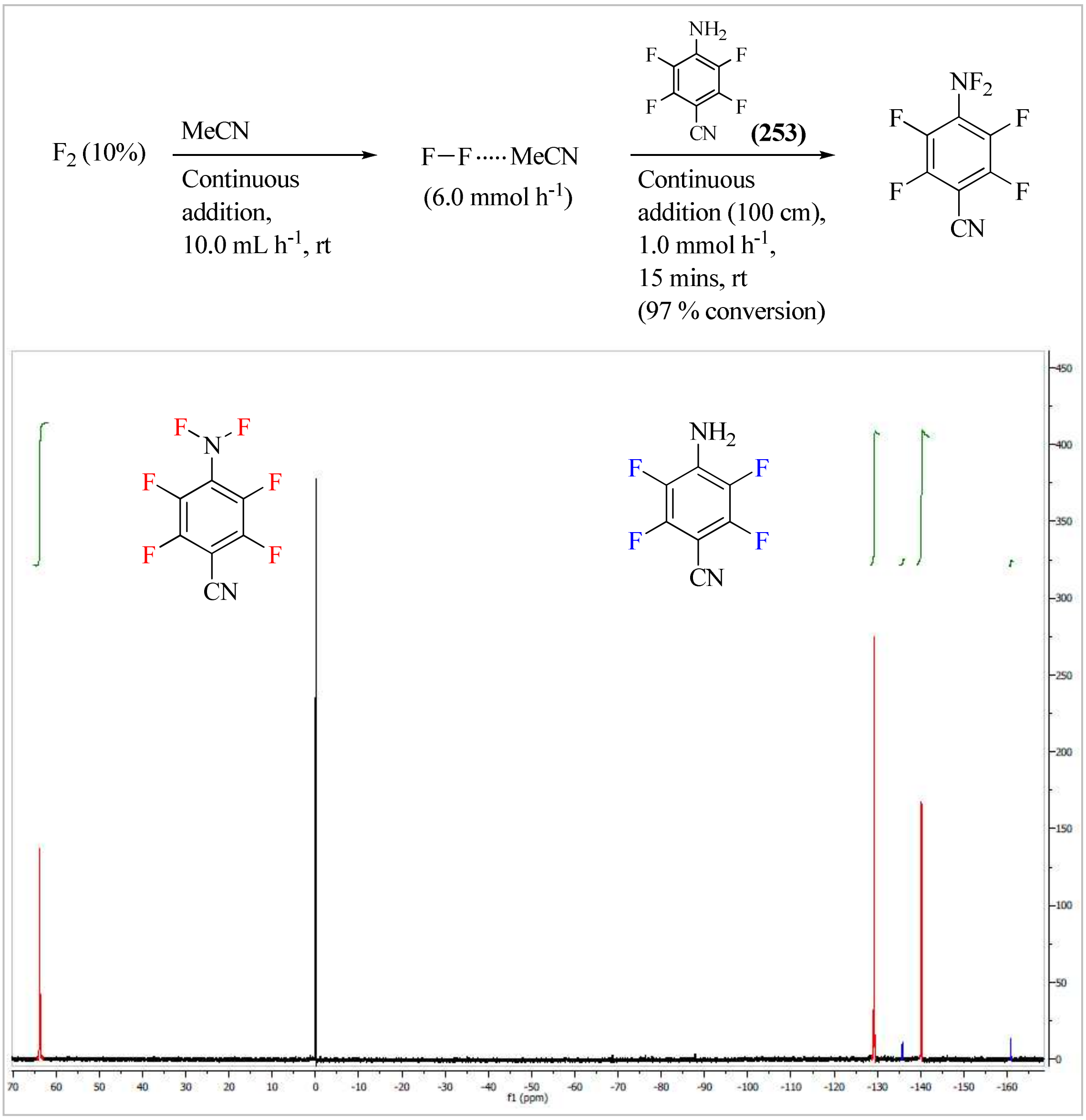
Following successful characterization of the difluoramine,direct synthesis of these compounds was attemptedin our continuous flow setup using elemental fluorine. To accomplish this, the water was omitted from the water:acetonitrile mixture so that no HOF.MeCN was formed for the amine to react with.

Our initial investigation of 4-amino-2,3,5,6-tetrafluorobenzonitrile**(253)** with 3.0 molar equivalents of 10 % fluorine did give the corresponding difluoramine, but,the ^{19}FNMR spectra of the crude product also showed significant amounts of starting material (*scheme99*).



Scheme99:Difluoramine synthesis with NMR

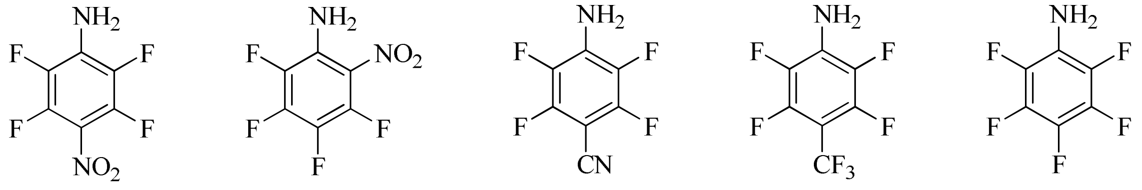
Decreasing the flow of **(253)** to a sixth of the molar fluorine rate (*scheme 100*) gave much higher conversion to the difluoramine and only traces of starting material were obtained.



Scheme100: Difluoramine synthesis with NMR

Purification was carried out using a silica column to give the difluoramine in good yield, and identification was carried out using ^{19}F NMR spectral data and ASAP-MS.

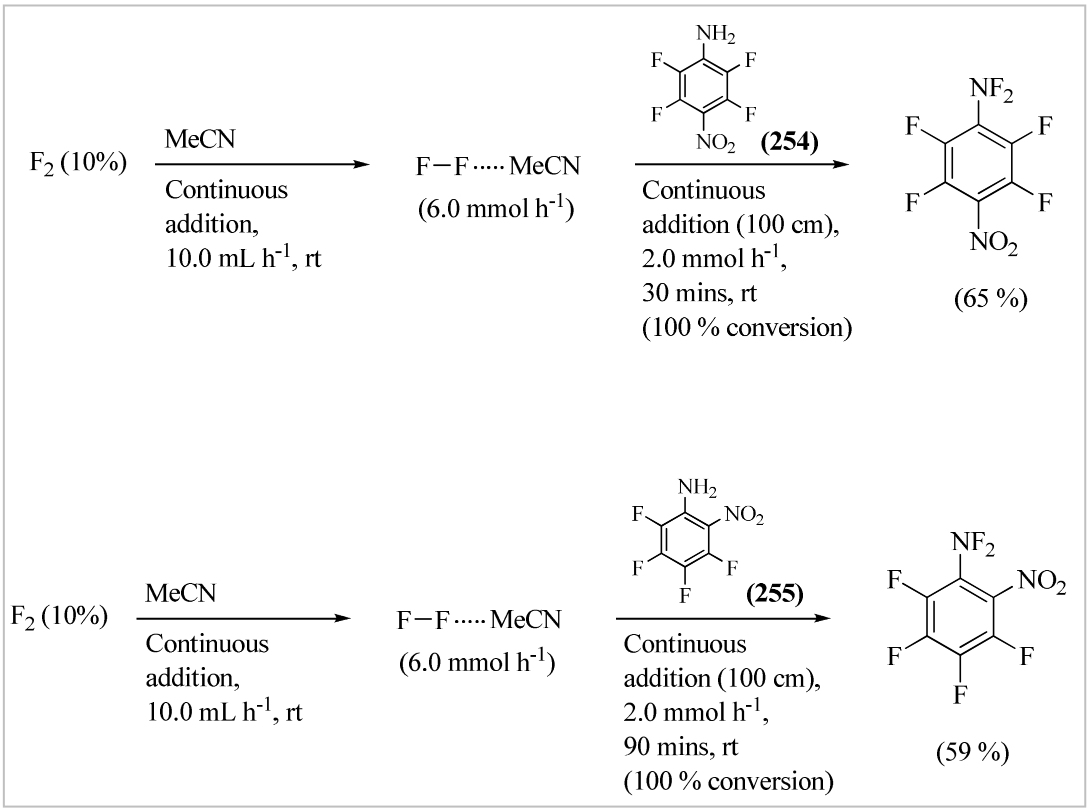
Upon applying the reaction to other variousfluoroanilines wediscovered that only those with electron withdrawing groups other than fluorine were sufficiently reactive enough to react with elemental fluorine. Therefore, anilines **(253-256)**(*figure 40*) all gave the difluoramine when treated with fluorine in our flow system, whilst pentafluoroaniline**(237)**did not react and gave only starting material upon work-up.



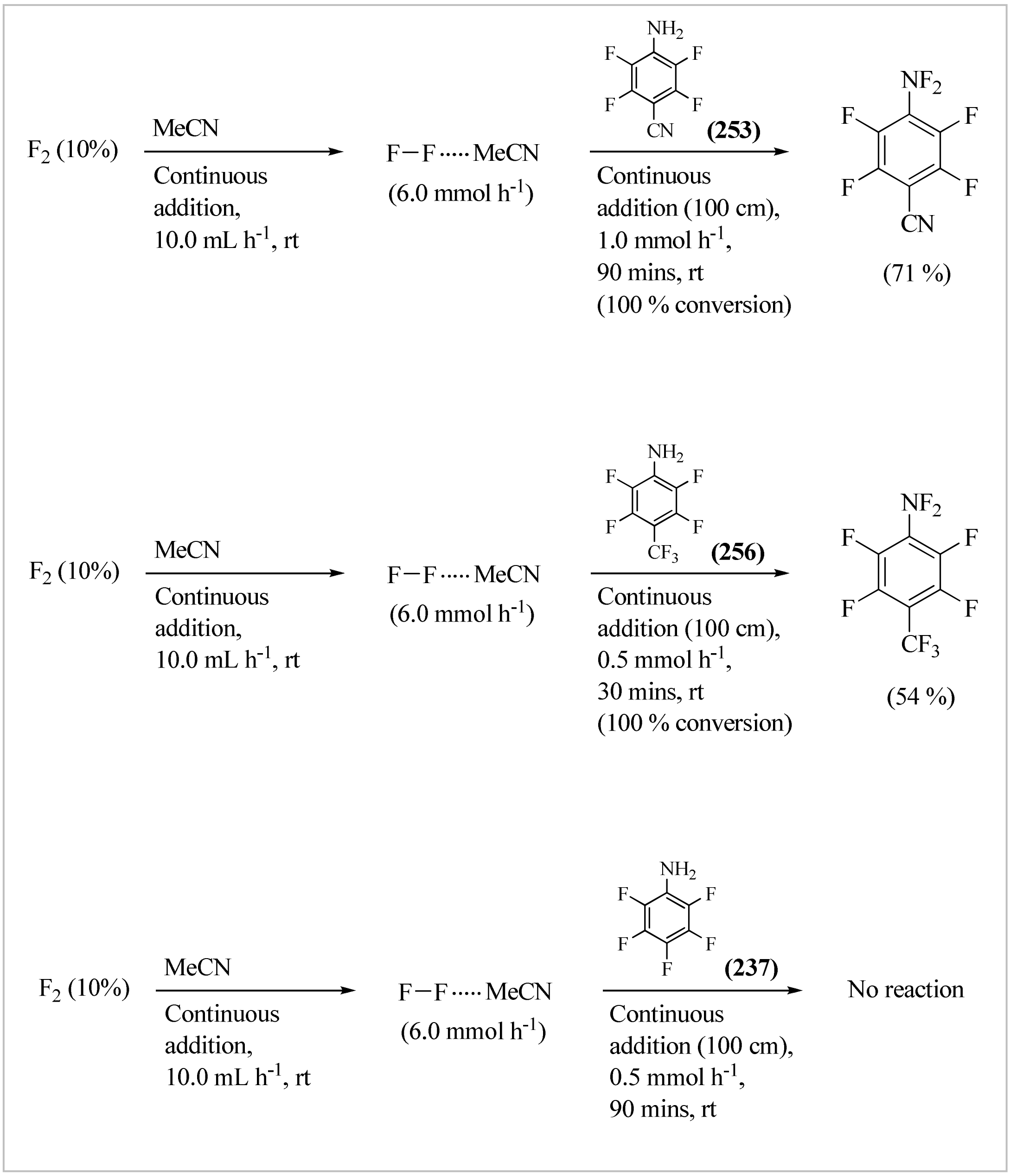
(254) **(255)** **(253)** **(256)** **(237)**

Figure 40

Of the perfluoroanilines that would react with fluorine to give the corresponding difluoramine, the reactivity of each differed greatly and those with stronger electron withdrawing groups attached to the ring, were much more reactive towards fluorine. Thus, although full conversion of each substrate was possible, 2,3,5,6-tetrafluoro-4-nitroaniline **(254)** and 2,3,4,5-tetrafluoro-6-nitroaniline **(255)** required only 3.0 molar equivalents of fluorine for full conversion, whereas2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline**(256)** required 12 equivalents of fluorine (*scheme 101*).

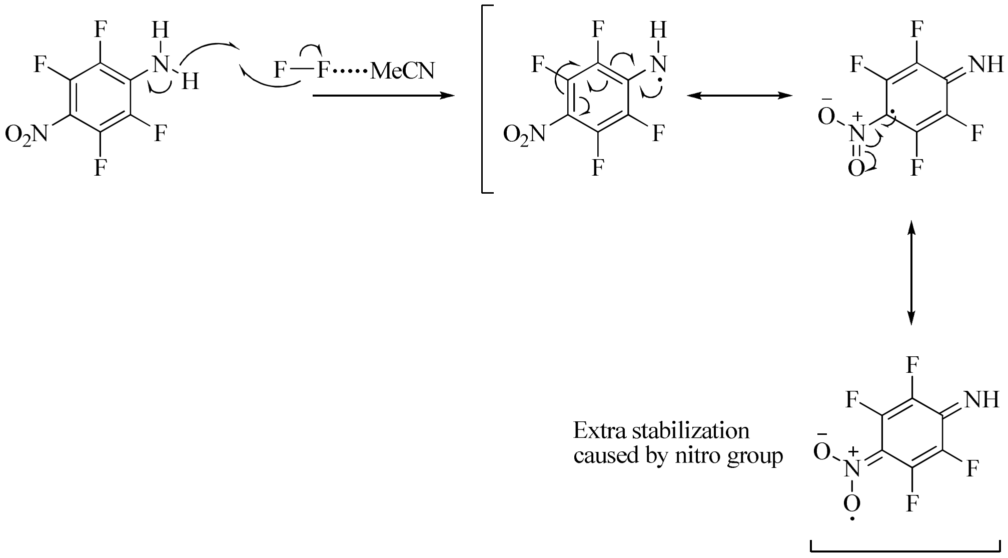


Scheme 101:Difluoramine synthesis using the continuous flow apparatus



Scheme 101 (cont): Difluoramine synthesis using the continuous flow apparatus

This supports a radical mechanistic theory proposed by Coon *et. al.*[148] as opposed to an electrophilic one,becausethe radical intermediate would be stabilized by the stronger EWG's (*scheme 102*). If the mechanism was electrophilic in nature, electron withdrawing groups would reduce the reactivity of the amine group towards electrophiles and the reactivity of the five fluoroanilineswould be reversed.



Scheme 102: Stabilization of the radical intermediate by the EWG

In order to compare the physical properties of the difluoramine compounds with their amine analogues, differential scanning calorimetry (DSC) experiments were attempted on both sets of compounds. However, the labile nature of the difluoramine compounds meant that no suitable DSC data could be obtained.

4.6 Summary

To summarize, our new continuous flow oxidation methodology has been applied to successfully oxidize a range of aliphatic amine and aliphatic azide compounds to their corresponding nitro compounds in near quantitative yields.

We have also demonstrated that our HOF.MeCNflow system can be used to oxidize amines of electron deficient and electron rich aniline compounds.

The amine of electron deficient nitrogen heteroaromatic compounds was easily oxidized to give excellent yields of the corresponding nitro compounds, although the oxidation of the ring nitrogen of such systems was not possible.

Oxidation was possible on the more electron rich nitrogen heterаromatic compounds; however, the HOF.MeCN complex is not suitable for complete oxidation of electron rich nitrogen heteroaromatic compounds with an amine group attached because in general, treatment of these types of compounds gave high amounts of tar products.

We have also demonstrated that our flow system can be applied to the synthesis of difluoraminebenzenoid compounds.

Chapter 5 - Synthesis of Perfluoroaromatic Amine Derivatives and Palladium Catalyzed C-F Bond Activation Processes

5.1 Introduction

The object of this chapter is to discuss some of the more general synthetic work that has been carried out throughout the course of this thesis. The first section (5.2) discusses the synthesis of polyfluoroaminobenzene, pyridine and pyrimidine systems, which were used as starting materials for the continuous flow oxidation process reported in chapter 4.0. As these were all made using nucleophilic aromatic substitution processes of perfluoro systems, an explanation of this chemistry is briefly introduced.

The second section (5.3) relates to research into the palladium catalysed C-F bond activation of polyfluorinated nitrobenzene systems for Suzuki cross coupling reactions. The Durham Fluorine group has recently published the first examples of such reactions and demonstrated that the nitro group has an *ortho* directing influence of the haloaryl coupling partner. The work included in this section relates to extending the functionality of the polyfluorinated nitrobenzene systems using this methodology.

5.2 Synthesis of Perfluoroaromatic Amine Derivatives

5.2.1 Nucleophilic Substitution of Polyfluorinated Aromatics

Due to the high electronegativity of fluorine, highly fluorinated aromatic compounds are particularly electron deficient and are, therefore, susceptible to nucleophilic attack[149-151]. As the majority of starting materials that were used as precursors for our oxidation reactions were synthesized using nucleophilic aromatic substitution, it is important to explain some the features that govern this type of chemistry.

Nucleophilic aromatic substitution of a fluorine atom in fluorinated systems proceeds *via* a two stage mechanism (*figure 41*) in which the first stage, attack by the nucleophile, is the rate limiting step[149, 152-154].

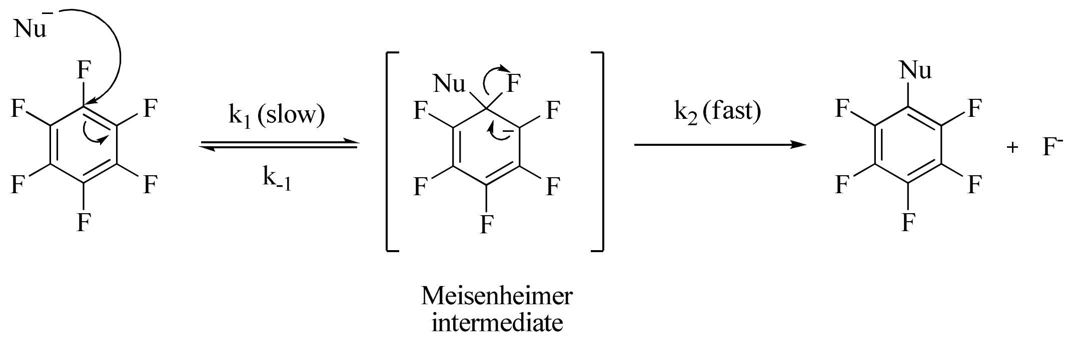


Figure 41

The positions of the fluorine atoms play an important role with regards to the site of nucleophilic attack. Kinetic studies on poly-fluoroaromatic systems have determined that a fluorine atom *para* to the site of attack is slightly deactivating, whereas those *ortho* and *meta* to the site of attack are activating, with respect to a hydrogen atom of the same position (*table 3*)[152,154].

Table 3: Comparison of k_F/k_H using CH_3O^-

	Ortho	Meta	Para
Benzene Derivatives	57	106	0.43
Pyridine Derivatives	79	30	0.33

The electron distribution of the Meisenheimer complex can explain the observed substitution patterns in fluorinated aromatic species, of which there are two situations to consider:

- fluorine attached adjacent to the carbanion centre $^{\ominus}C—C—F$
- fluorine attached directly to the carbanion centre $^{\ominus}C—F$

In the first situation, the carbanion is highly stabilized due to the Iσ electron withdrawing effect[149,155-156].

$$^{\ominus}C \rightarrowtail C \rightarrowtail F$$

Therefore, the activating effect of a fluorine atom *meta* to the site of attack can be explained by examining the Meisenheimer intermediate, in which the negative charge is delocalised adjacent to the carbon-fluorine bond (*figure 42*).

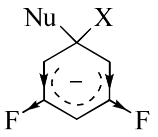


Figure 42: Fluorine atoms meta to the site of substitution stabilize the adjacent carbanion

In the second situation there are two opposing factors to consider: the electron withdrawing effect (Iσ) and electron pair repulsion (Iπ) and the dominant factor determines the effect of a fluorine atom upon the carbanion. The electron withdrawing (Iσ) effect (*figure 43*) is strongly carbanion stabilizing[149,155-156], however, the electron pair repulsion that arises due to interaction of the carbanion lone pair and the lone pairs of electrons of the fluorine atom (*figure 44*) is strongly destabilizing[149,155-156](xviii). The latter effect dominates, resulting in an overall destabilization of the carbanion.

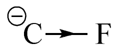


Figure 43: Electron withdrawing effect of the fluorine stabilizes the carbanion

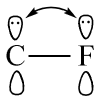


Figure 44: Electron pair repulsion of the fluorine lone pairdestabilizes the carbanion

Therefore, by considering the stability of the Meisenheimer intermediates, a fluorine atom *para* to the site of attack gives an intermediate that is destabilized. The same effect would be expected for a fluorine atoms *ortho* to the site of attack, however, the activating effect of an *ortho* fluorine atom is caused by the polar influence (Iσ) on the initial state, which enhances the electrophilic character of the carbon atom under attack[149,155-156]. This inductive effect (*figure 45*) activates the initial state such that it effectively compensates for the deactivating influence of the adjacent negative charge of the Meisenheimer complex.

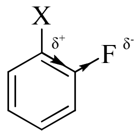


Figure 45: Inductive effect of the fluorine atom ortho to the site of substitution activates the initial state

Replacing a fluorine atom with an electron withdrawing group that is not capable of *pi* donation (Y), for example, in hexafluorobenzene, would therefore activate the position *para* to itself towards nucleophilic aromatic substitution (*figure 46*) because this group would no longer destabilize the carbanion intermediate.

(xviii) This only includes fluorine atoms adjacent to sp^2 carbanions; in sp^3carbanions, the angle of the p orbital bearing the negative charge and the fluorine atom is greater, so these systems have a stabilizing effect

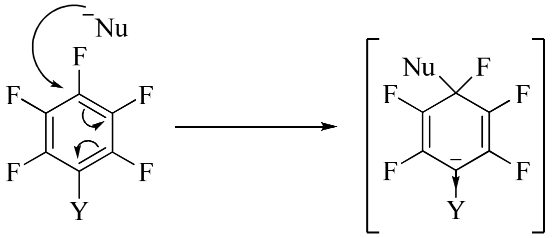
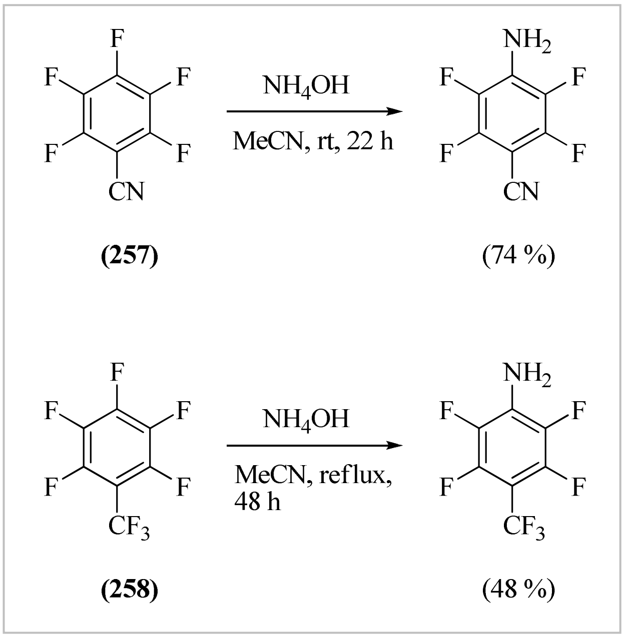


Figure 46: EWG stabilizes the carbanion by either an Iσ or Iπ effect and thus, activates the para position

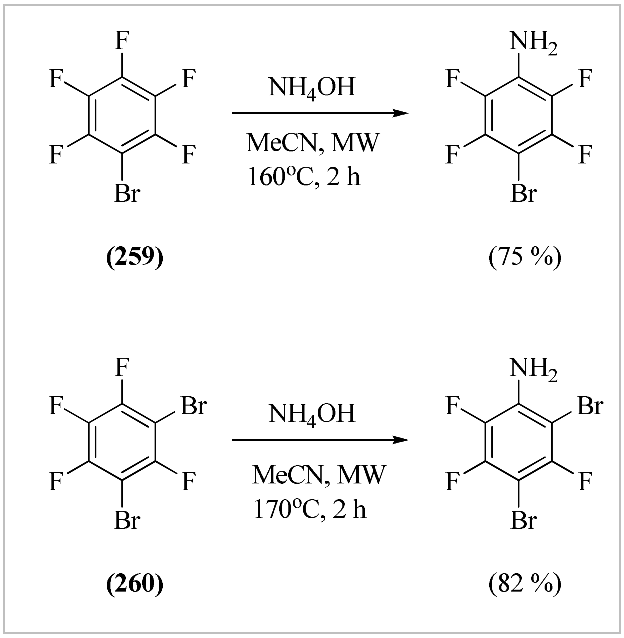
5.2.2 Synthesis of polyfluoroamino benzene, pyridine and pyrimidine systems

A range of amino benzene and heterocycles were required for the oxidation studies discussed in chapter 4.0 and so S_NAr reactions using ammonia and a range of polyfluoroaromatic derivatives was carried out.

Due to the directing effects discussed above, when compounds **(257-260)** were treated with ammonia (*scheme 103*), nucleophilic substitution of the amine occurred solely at the position *para* to the non-fluorine substituents, because this position is activated by the α-, β- and γ-positions. Although bromine is capable of *pi* donation, the lone pairs of bromine are in a higher energy orbital and, therefore, *pi* donation is less effective and the inductive effect of bromine dominates.



Scheme 103: Synthesis of polyfluoroaniline derivatives

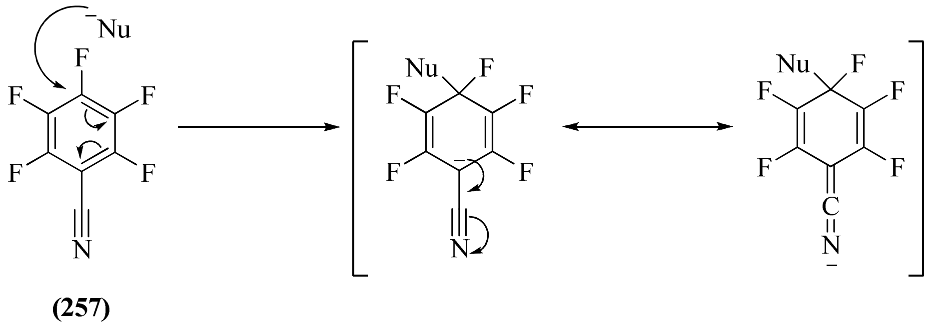


(259)

(260)

Scheme 103 (cont): Synthesis of polyfluoroaniline derivatives

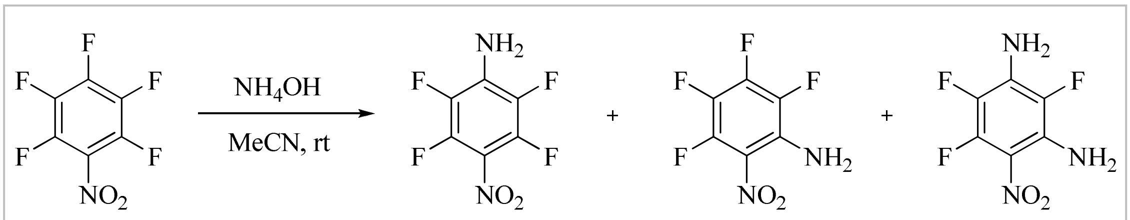
The nitrile group stabilizes the carbanion intermediate by a mesomeric electron withdrawing effect (*figure 47*) which is much more stabilizing than the inductive effect of the CF_3 group or the bromine atom. The position *para* to the nitrile group of compound **(257)** is, therefore, more activated towards nucleophilic substitution than the position *para* to the bromine and CF_3 group of compounds **(258-260)**. This reactivity is reflected in the lower temperature that was required to synthesize the aminobenzene from compound **(257)**.



(257)

Figure 47: Mesomeric stabilization of the carbanion

A carbanion intermediate with a nitro group attached is also strongly stabilized by a mesomeric withdrawing effect, so it was expected that nucleophilic substitution of ammonia on pentafluoronitro benzene **(252)** to also occur solely at the *para* position. However, experimentally, this was not the case and substitution of the amine occurred at the *ortho* and *para* positions to the nitro group (*scheme 104*), resulting in three products **(261-263)**. These were separated and isolated by column chromatography.



(252) **(261)** (15 %) **(262)** (37 %) **(263)** (19 %)

Scheme 104

The reason ammonia also attacks the carbon *ortho* to the nitro group, even though this position is deactivated by a *para* fluorine atom, is due to interaction of the nitro group with the ammonia by hydrogen bonding, which directs the amine into the *ortho* position (*figure 48*).

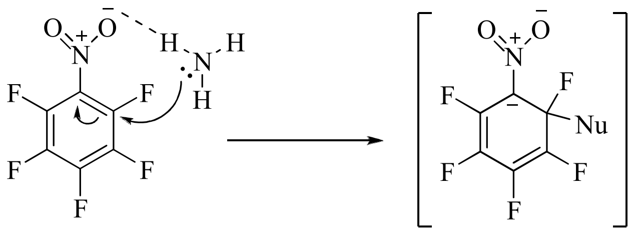


Figure 48: Ortho directing effect of the nitro group

Polyfluoro-nitrogen-heteroaromatic systems are all activated, relative to the corresponding benzenoid compounds, towards nucleophilic substitution and this is due to the activating effect of the ring nitrogen (*figure 49*)[147].

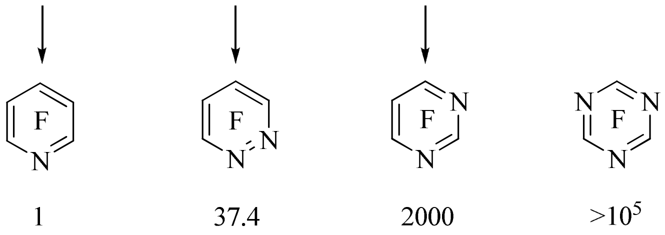
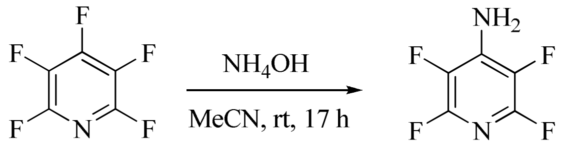


Figure 49: Relative rate constants for nucleophilic attack by NH_3/aq. dioxane

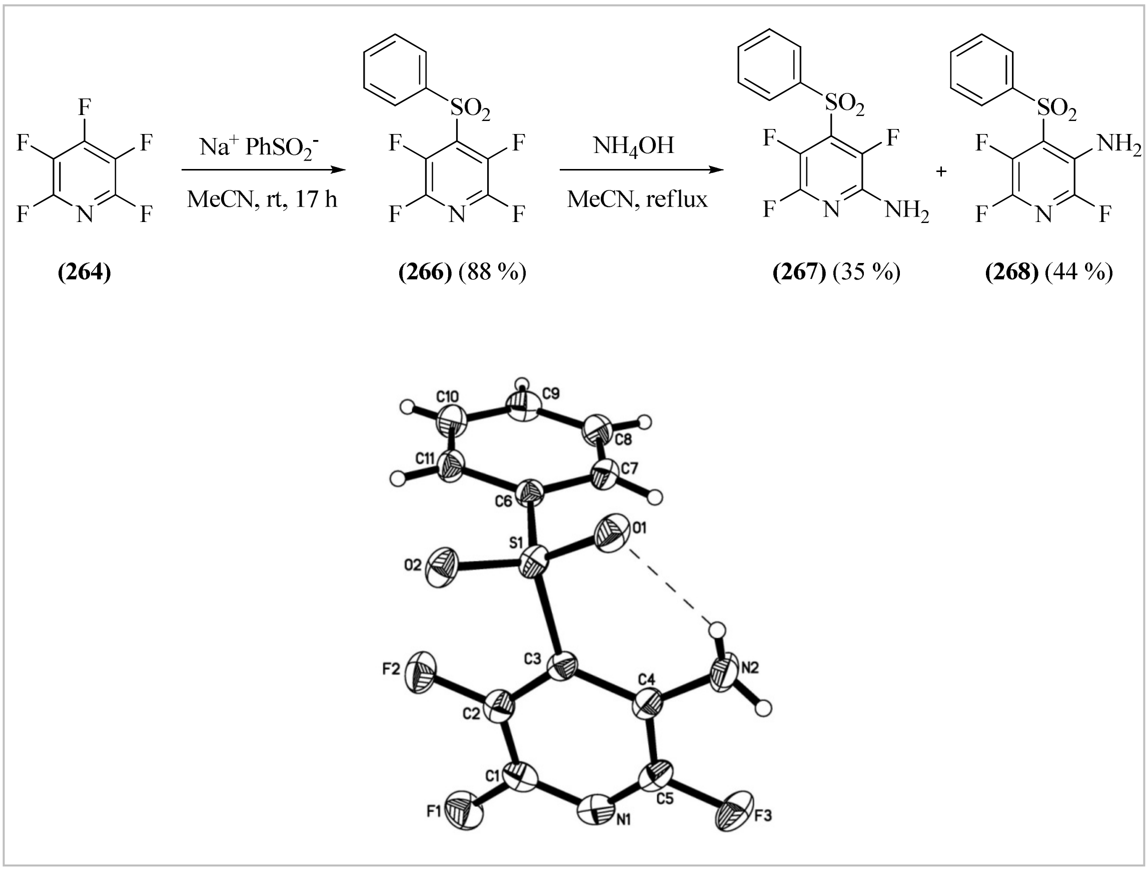
The site of nucleophilic attack is, therefore, governed by a combination of directing effects of the ring nitrogen and the activating/deactivating effects of the fluorine atoms[151-152]. So in the case of pentafluoropyridine, the ring nitrogen would be expected to direct a nucleophile *ortho* and *para* to itself, but due to the fluorine atoms in the 3 and 5 positions, the position *para* to the ring nitrogen is most activated and substitution occurs exclusively at the 4 position. Reaction of ammonia with pentafluoropyridine **(264)** gave only 4-aminotetrafluoropyridine **(265)** in excellent yield (*scheme 105*).



(264) **(265)** (85 %)

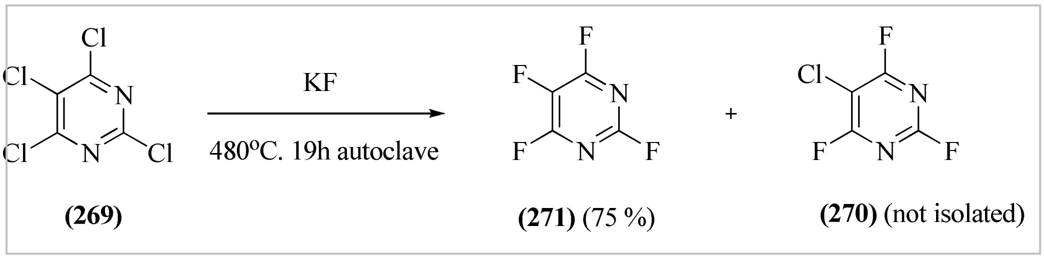
Scheme 105

To synthesize a perfluoropyridine compound with an amine in the 2- and 3- position, pentafluoropyridine would initially have to be reacted with a nucleophile to block the 4-position. A suitable nucleophile must not be electron donating because this would deactivate the ring and the nucleophile must also not react with the HOF.MeCN in the subsequent oxidation process. Consequently, sodium benzenesulfinate was used to synthesize 2,3,5,6-tetrafluoro-4-(phenylthio)pyridine **(266)**, which was reacted with ammonia to give a mixture of 3,5,6-trifluoro-4-(phenylthio)pyridin-2-amine **(267)** and 2,5,6-trifluoro-4-(phenylthio)pyridin-3-amine **(268)** (*scheme 106*), which were separated and isolated. X-ray crystallography was used to verify the position of the amine group.



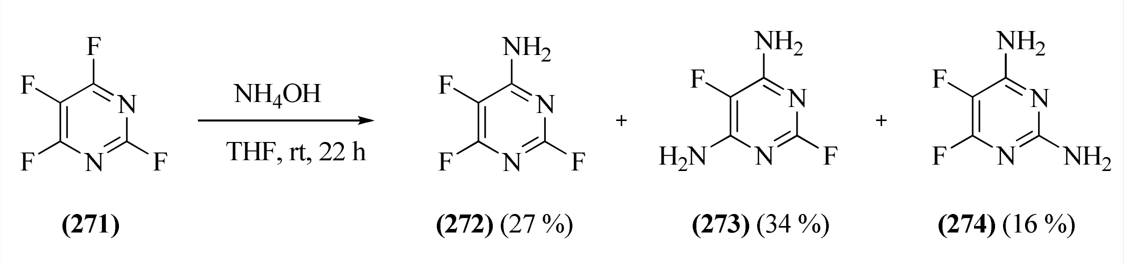
Scheme 106

Synthesis of tetrafluoropyrimidine **(271)** was achieved *via* the fluorination of the commercially available tetrachloropyrimidine **(269)** using potassium fluoride at high temperatures in an autoclave reaction vessel (*scheme 107*). Initially a temperature of 360°C was used, however, this produced only small amounts of **(271)** and gave large amounts of 5-chloro-trifluoropyrimidine **(270)**; increasing the temperature of the autoclave to 480°C resulted in higher amounts of the desired tetrafluoropyrimidine **(271)**, which was isolated *via* distillation.



Scheme 107

The positions γ to the ring nitrogen atoms of tetrafluoropyrimidine **(271)** are the most activated towards nucleophilic substitution because these positions are activated by an *ortho* and *meta* fluorine atom and also, *ortho* and *para* ring nitrogen atoms. Substitution was therefore expected to occur solely in these positions when **(271)** was reacted with ammonia (*scheme 108*), because the other two positions (2- and 5-) are deactivated by *para* fluorine atoms. Experimentally this was not the case, and the reaction also yielded 5,6-difluoropyrimidine-2,4-diamine **(274)**. All three compounds were separated and characterized.



Scheme 108

5.2 Palladium Catalyzed C-F Bond Activation

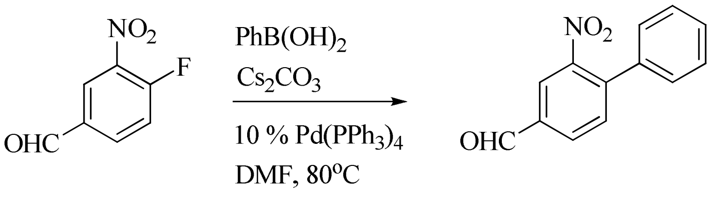
5.2.1 Introduction

Metal catalyzed cross coupling reactions are very important because of the wide variety of synthetically useful carbon-carbon bond forming reactions that may be achieved.

The oxidative addition step of the catalytic cycle is believed to be the rate limiting step for many cross coupling reactions and the rate of this step depends on both the nucleophilicity of the metal centre, and the reactivity of the electrophilic aryl halide species[157]. Generally the order of reactivity of the aryl halide is dependent upon the strength of the carbon-halogen bond and, therefore, the haloaromatic species of many metal catalyzed processes is most frequently an aryl iodide and bromide[158]. In contrast, the higher bond strength of the carbon-chlorine bond means chlorides are much less reactive and are subsequently used much less often as electrophilic coupling partners. For the same reason, analogous reactions involving metal catalyzed C-F activation are rarer still[158].

Although there are reported examples of palladium being used as the catalyst for cross coupling reactions using aryl fluorides, the majority of literature reports related to these processes make use of nickel(0) based catalysts. However, nickel catalysts are very air sensitive and generally difficult to use for organic synthesis, so the development of this type of chemistry using commercially available and robust catalysts such as palladium systems would be advantageous.

Kim and Yu reported the palladium catalyzed C-F activation of monofluorinated nitrobenzene derivatives **(275)** under standard Suzuki-Miyaura conditions using conventional palladium catalysts (*scheme 109*)[159] and it was suggested that the nitro group, in addition to its activating electron withdrawing properties, directs the palladium catalyst towards the adjacent *ortho* C-F bond (*figure 50*), thereby lowering the activation energy for the oxidative addition step[159].



(275)

(80 %)

Scheme 109

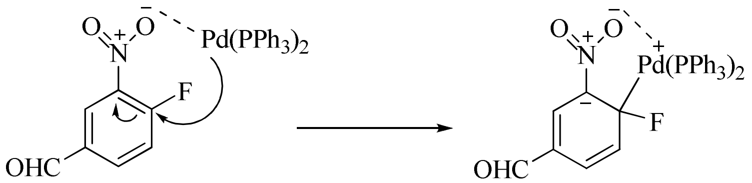
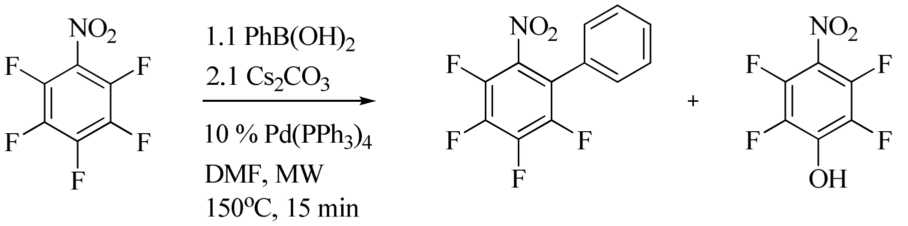


Figure 50: Ortho directing effect of the nitro group on the palladium catalyst

The Durham Fluorine group found that highly fluorinated nitrobenzene derivatives, such as pentafluoronitrobenzene, could be sufficiently activated towards nucleophilic oxidative addition by a palladium catalyst and the presence of a nitro group on the aromatic ring, directs the aryl group to the adjacent *ortho* position to provide new positions of functionality[158].

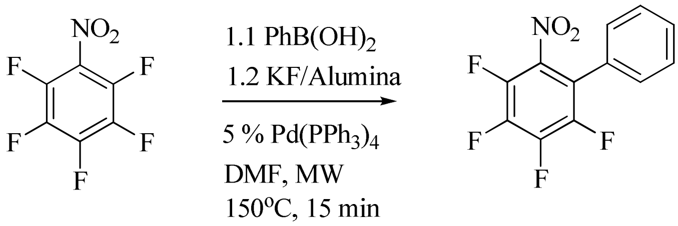
Initial studies on the direct arylation of pentafluoronitrobenzene employed similar reaction conditions that were used by Kim and Yu with **tetrakis**(triphenylphosphine)palladium(0) as the catalyst, cesium carbonate as the base and DMF as the solvent. Although the reaction gave a high yield of the desired biaryl compound **(276)** (*scheme 110*), 11 % of 2,3,5,6-tetrafluoro-4-nitrophenol **(277)** was also isolated from the reaction. It was suggested that the phenol by-product was formed from nucleophilic attack of water (present in small quantities in the hygroscopic base) or direct attack of the Cs_2CO_3 and its subsequent decarboxylation[158].



(252) **(276)** (84 %) **(277)** (11 %)

Scheme 110

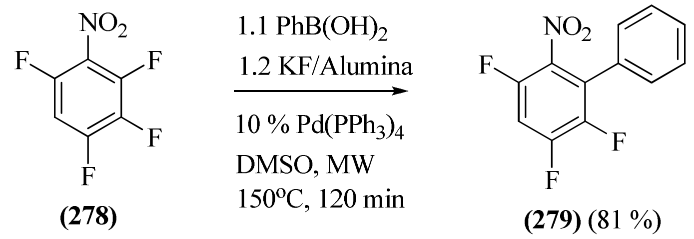
To avoid formation of the un-wanted phenol, the cesium base was replaced with potassium fluoride, therefore, any reaction of the base with **(252)** would not affect the starting material. KF on alumina was used and the biaryl coupled product was obtained in high yields (*scheme 111*) and without the phenol derivative. This represented the first example of a palladium catalyzed Suzuki cross coupling reaction of polyfluorinated aromatic substrates[158].



(252) **(276)** (80 %)

Scheme 111

Tetrafluoronitrobenzene and trifluorobenzene derivatives are significantly less reactive towards palladium catalyzed arylation than **(252)** which reflects the lower number of activating fluorine atoms present in these substrates. Although more forcing conditions were required, such substrates (1,2,3,5-tetrafluoro-6-nitrobenzene **(278)** is shown as an example) were also shown to be sufficiently activated towards arylation using a palladium catalyst (*scheme 112*)[158].

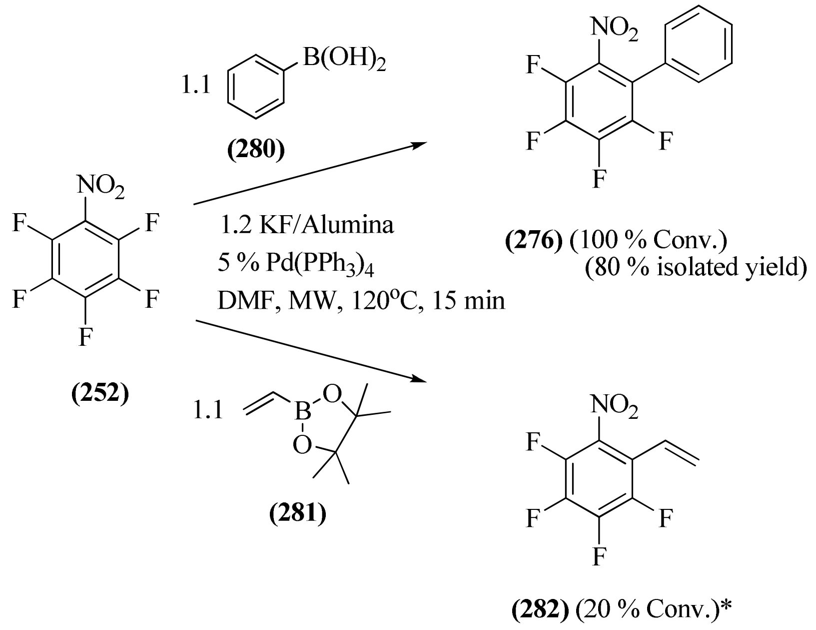


Scheme 112

5.3.1 Palladium catalyzed vinyl coupling reactions

Our aim was to extend the functionality of the palladium catalyzed Suzuki coupling reactions of polyfluoronitrobenzene derivatives by using vinylation process.

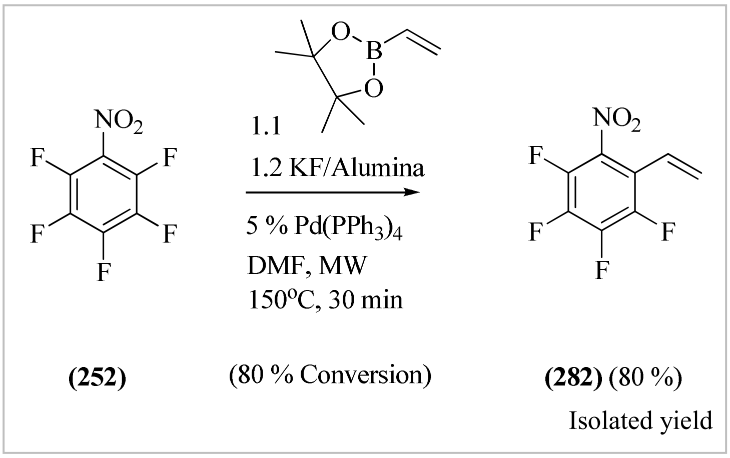
The highly fluorinated nitrobenzene systems that were synthesized using our oxidation processes were used to investigate the vinylation processes and the optimized conditions determined for the aryl coupling reactions were initially applied. However, the vinyl pinacol ester **(281)** was found to be less reactive than phenyl boronic acid **(280)** and much lower yields of the vinyl benzene **(282)** were obtained (*scheme 113*).



* **(282)** was not isolated and ^{19}F NMR spectra was used to obtain conversions

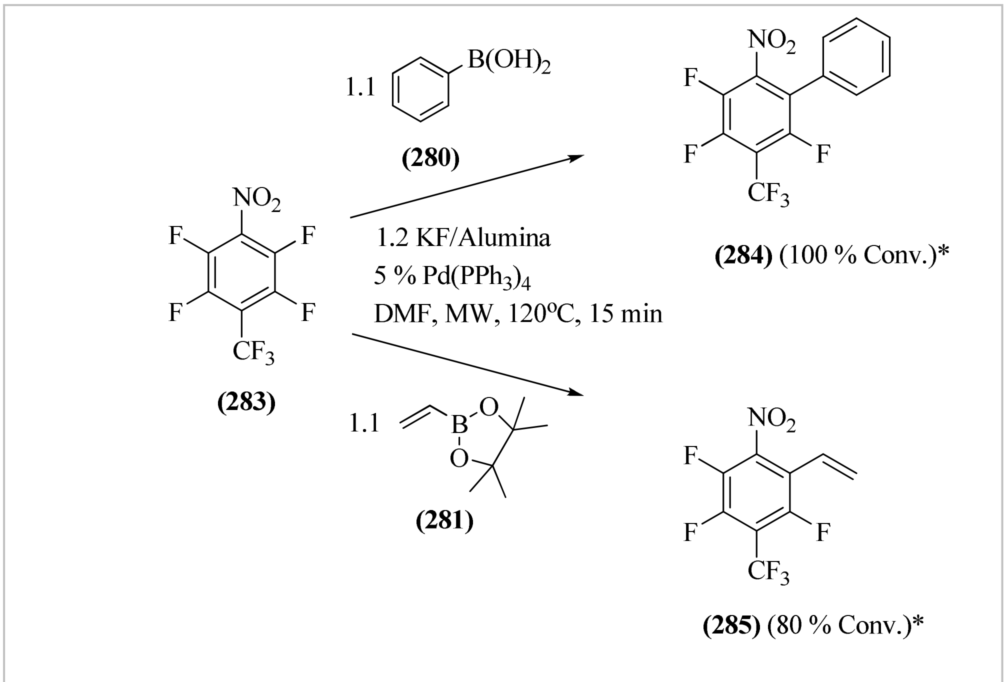
Scheme 113

To increase the yield of **(282)**, an increase in reaction time and temperature was required (*scheme 114*). The regioselectivity of the vinyl group was determined using ^{19}F NMR spectra resonance and coupling values and corresponds to the ^{19}F NMR data obtained for **(276)**.



Scheme 114

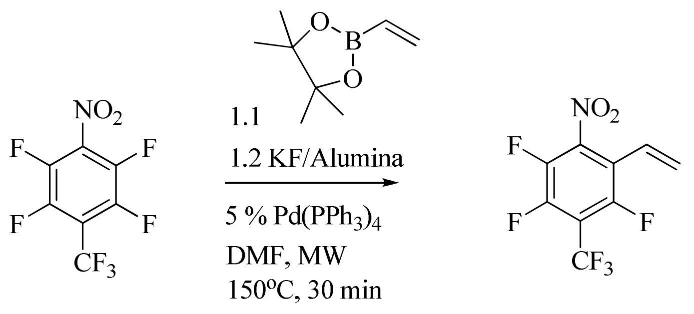
A similar pattern of reactivity between the two boron coupling reagents **(280)** and **(281)**, was observed when they were reacted with 1,2,4,5-tetrafluoro-3-nitro-6-(trifluoromethyl)benzene **(283)** in the Suzuki reaction. Using the same conditions as those in *scheme 113*, the vinyl benzene **(285)** was formed in lower yields than the biaryl compound **(284)** (*scheme 115*).



* These compounds were not isolated and ^{19}F NMR spectra was used to obtain conversions

Scheme 115

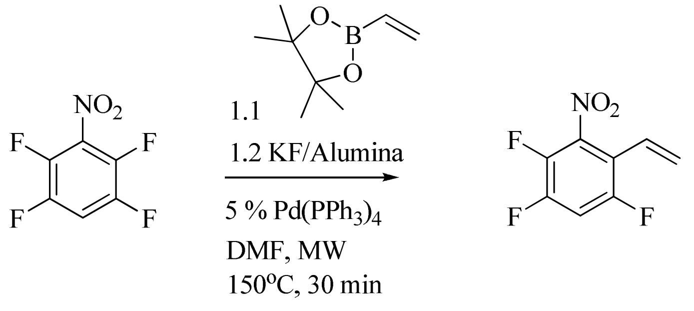
Similar to the reaction of pentafluoronitrobenzene **(252)** (*scheme 114*), increasing the reaction time and reaction temperature for the Suzuki reaction of **(283)** with **(281)** improved the conversion of the reaction (*scheme 116*).



(283) (100 % Conversion) **(285)** (80 %) Isolated yield

Scheme 116

The lower reactivity of 2,3,5,6-tetrafluoronitrobenzene **(286)** towards palladium catalyzed cross coupling reactions meant that, even with the increased reaction temperature and time, only 50 % of starting material was converted to the vinyl benzene **(287)** (*scheme 117*) which was isolated in an 80 % yield. Once again, the regioselectivity of the vinyl group was determined using ^{19}F NMR spectra resonance and coupling values and corresponds to the ^{19}F NMR data obtained for the corresponding biaryl compound.

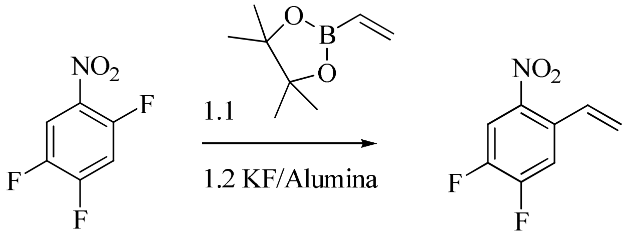


(286) (50 % Conversion) **(287)** (80 %) Isolated yield

Scheme 117

The reactivity of 2,4,5-trifluoronitrobenzene **(288)** towards palladium catalyzed cross coupling reactions is lower still, compared to tetrafluoronitrobenzene derivatives, so the reaction of **(288)** with the vinyl boronic ester **(281)** under the same conditions as those in *scheme 117*, gave only starting material. To obtain a suitable conversion of starting material to the coupled product **(289)**, an increase in reaction time and catalyst amount were required along with a more polar solvent. The Suzuki cross coupling reactions performed on **(288)**, along with the NMR ratios of starting material and product, are summarized in *results table 7*.

***Results Table** 7*

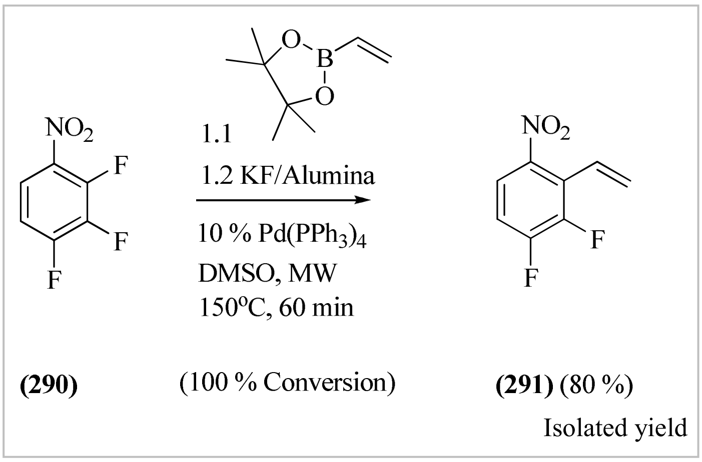


(288) **(289)**

Expt	Temperature (°C)	Time (mins)	Catalyst loading (%)	Solvent	Ratio (%)	
					(288)	**(289)**
1	150	30	5	DMF	100	0
2	150	60	10	DMF	78	22
3	150	60	10	DMSO	44	56

All ratios determined using ^{19}F NMR. Only **(289)** of experiment 3 was isolated and regioselectivity of the vinyl group was determined using ^{19}F NMR spectra resonance and coupling values and, corresponds to the ^{19}F NMR data obtained for the analogous biaryl compound.

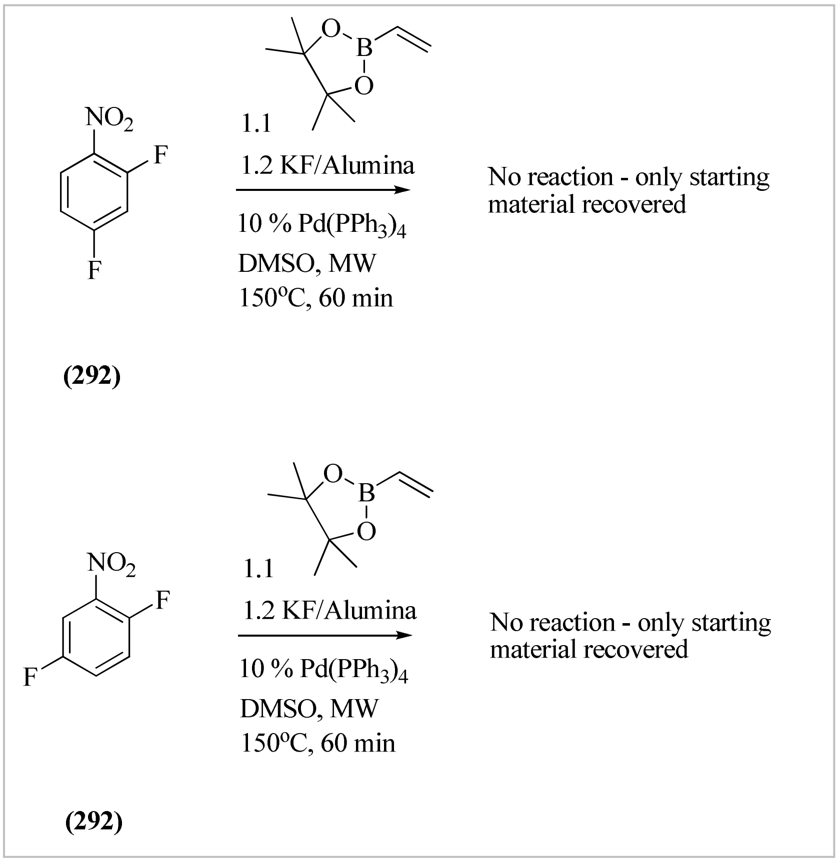
Although trifluoronitrobenzene derivatives are much less reactive towards palladium catalyzed cross coupling reactions, the position of the fluorine atoms are very important in determining the reactivity of the nitrobenzene system. The activating/deactivation effects of the ring fluorine atoms that are described in section 5.2.1, also apply to the electrophile in palladium catalyzed Suzuki cross coupling reactions. In the reaction of **(288)** (*results table 7*), the fluorine in the 5 position deactivates the C-F bond α to the nitro group, so only low yields of the vinyl benzene **(289)** were obtained. However, the C-F bond α to the nitro group of 2,3,4-trifluoro-1-nitrobenzene **(290)** is not deactivated by a *para* fluorine atom, so the reaction of **(290)** under the same reaction conditions in experiment 3 (*results table 7*), gave 100 % conversion of starting material and a high isolated yield of the vinyl benzene **(291)** was obtained (*scheme 118*).



(290) (100 % Conversion) **(291)** (80 %) Isolated yield

Scheme 118

Difluoronitrobenzenes are not electrophilic enough for the palladium catalayzed Suzuki reactions and therefore when 2,4-difluoro-1-nitrobenzene **(292)** and 2,5-difluoro-1-nitrobenzene **(293)** were reacted under forcing conditions with the vinyl boronic ester, only starting material was retrieved for each reaction (*scheme 119*).



(292)

(292)

Scheme 119

5.4 Summary

To summarize, S_NAr reactions have been successfully utilized for the synthesis of various polyfluoro amino aromatic compounds using procedures similar to those documented in the literature.

We have also demonstrated that highly fluorinated nitro aromatic systems are suitable substrates for the palladium catalyzed C-F bond vinylation reactions. Similar to the arylation reaction performed by Sandford *et al*[158], vinylation occurs *ortho* to the nitro group which is a result of the directing influence of the nitro group.

Chapter 6 - Conclusions and Next Steps

6.1 Conclusions and Next Steps

The main aim of this project was to develop new methodology to incorporate Rozen's highly versatile and powerful oxygen transfer reagent, HOF.MeCN, into a continuous process, so that the reagents limitations could be avoided and it could be used on an industrial scale. To accomplish this, we have successfully devised a two-step continuous process, in which the HOF.MeCN is generated in the first step (using wet acetonitrile and elemental fluorine) and, without isolation, the oxidant is used to continuously oxidize the chosen substrate (*figure 51*).

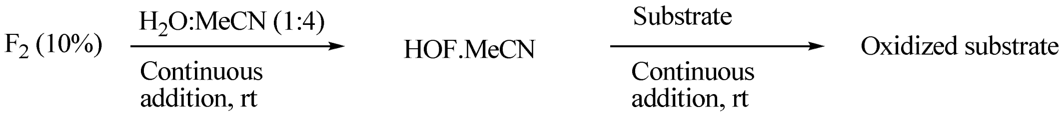


Figure 51

Due to the highly reactive nature of elemental fluorine, the process required careful optimization of reagent flow rates in order to prevent excess fluorine from reacting with the substrate. Safe and effective HOF.MeCN calibration methods have also been devised for our process, which, using simple calculations, can be used to accurately calibrate fluorine flow rates.

Scale-up of the process has been demonstrated by carrying out the reactions for extended time periods and, by scaling up the amounts of HOF.MeCN generated. The next steps with regards to scale-up would be to 'scale-out' the process, by transferring it into the Durham multichannel vertical reactor. To accomplish this, slight modification to the Durham vertical reactor design would be required, so that a second reagent could also be added to the reactor. A proposed variation of the vertical flow reactor is shown in *figure 52* (page 140).

Our continuous flow process has been successfully used to perform a variety of oxidations for the synthesis of compounds such as epoxides[135], thiophene *S,S*-dioxides, aliphatic and aromatic nitro compounds[142], *N*-oxides and alcohols. However, one drawback to our process is the limited scope for oxidizing compounds which require longer reaction times. For example, Beayer-Villiger oxidations performed by Rozen using HOF.MeCN in batch required reaction times of up to four hours, however, the reaction path length in our continuous process is too short for these types of oxidations to be performed.

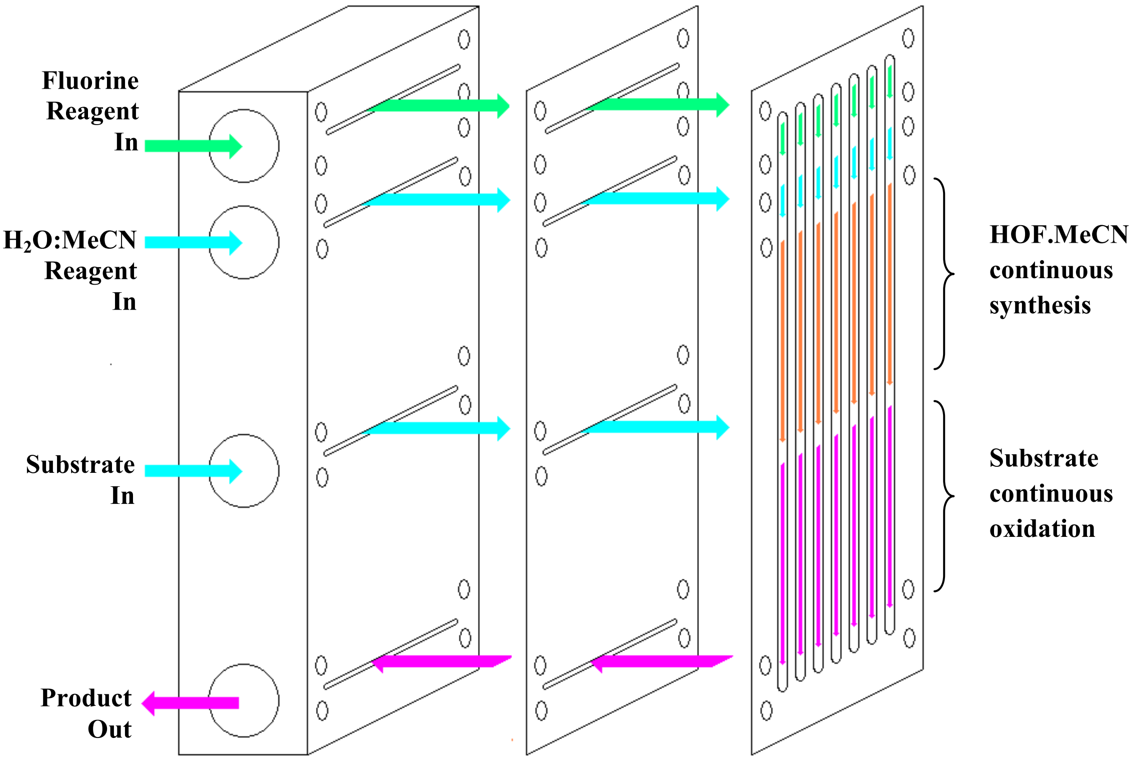
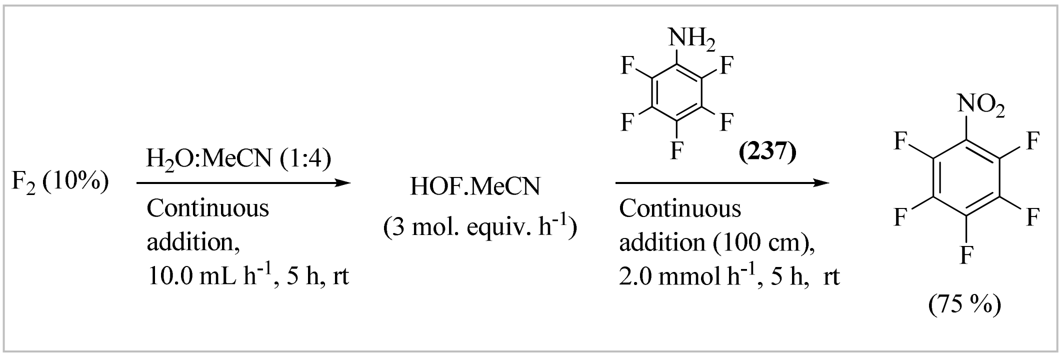


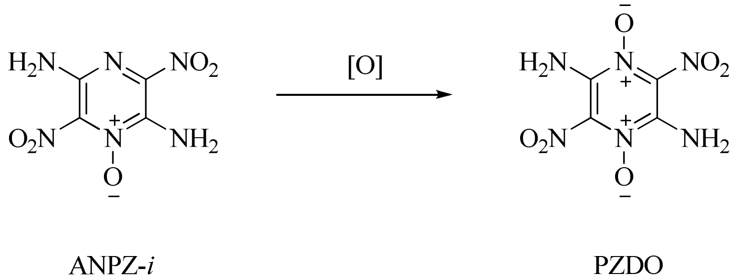
Figure 52: Proposed variation of the vertical flow reactor to allow HOF.MeCN synthesis and substrate oxidation in a two-step continuous process

Oxidations performed on nitrogen compounds were geared around those which may be of benefit to the energetic materials industry, such as the synthesis of aliphatic and aromatic nitro compounds. Highly fluorinated compounds were used to mimic the electron deficiency that many energetic compounds possess, which did not affect the HOF.MeCN complexes ability to oxidize the amine moiety of such systems (*scheme 120*).



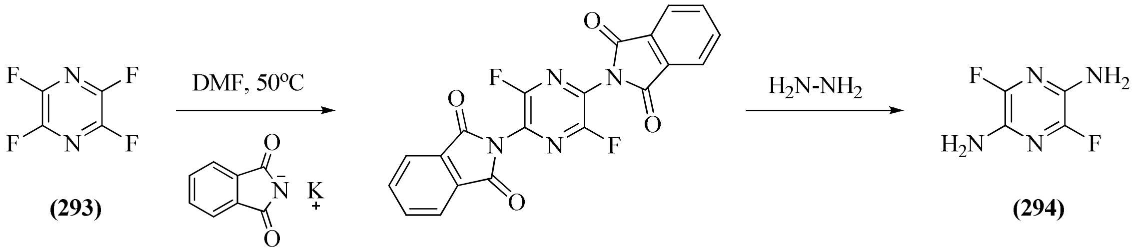
Scheme 120

However, ring nitrogen oxidation of electron deficient heterocyclic compounds such as pentafluoropyridine and tetrafluoropyrimidine was not possible using HOF.MeCN. Therefore, whilst it was thought that the complex would be a strong enough oxidant to synthesize previously un-accessible heterocyclic *N*-oxide derivatives, such as PZDO (*scheme 121*), our data suggests that this would not be the case.



Scheme 121: Our current data suggests synthesis of PZDO would not be possible using HOF.MeCN

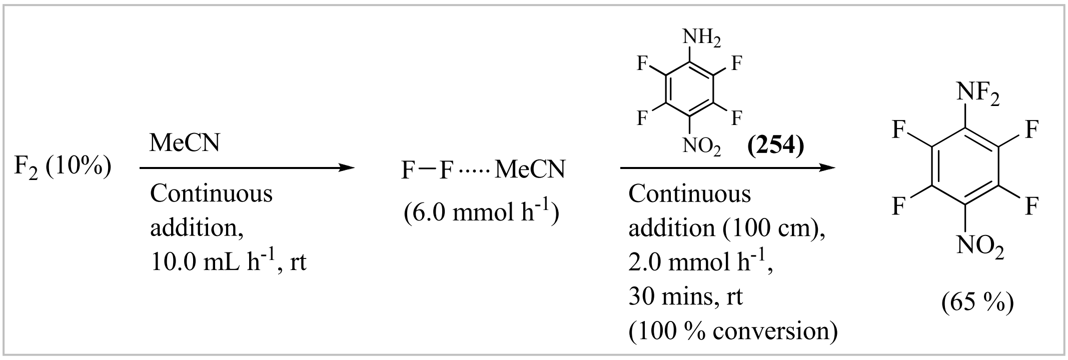
To further investigate the possibility of synthesizing PZDO using HOF.MeCN, as suitable analogue of this would be to use the currently unknown 3,6-difluoropyrazine-2,5-diamine **(294)**, a proposed synthetic route of which is shown in *scheme 122*.



Scheme 122: Proposed synthesis of 3,6-difluoropyrazine-2,5-diamine

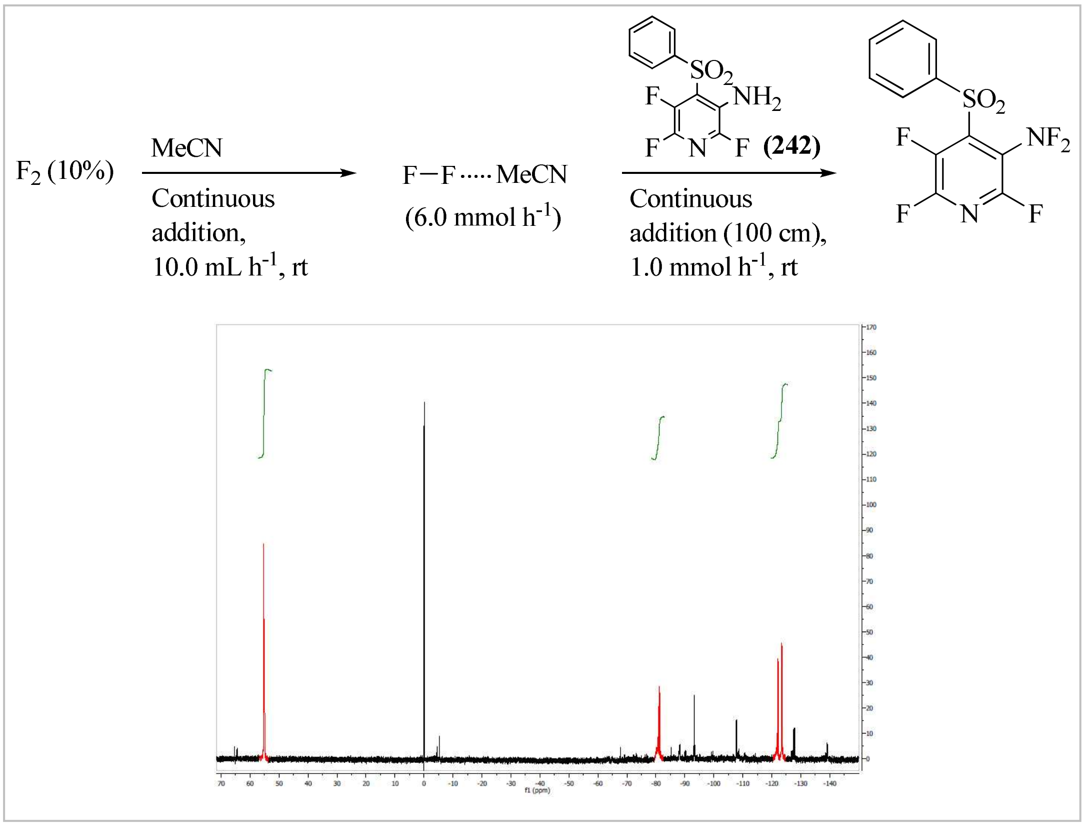
(294) cannot by synthesized using direct ammonolysis of tetrafluoropyrazine **(293)**, because di-substitution of **(293)** tends to give either the 2,6- or 2,3- isomers. However, in a process described by Barclay et al., the Gabriel synthesis is employed to give 2,5- diamino substitution of tetrachloropyrazine[160], which should be a viable option for the synthesis of **(294)**.

We have also demonstrated that our continuous flow process can be applied to the synthesis of novel difluoramino benzene derivatives (*scheme 123*).



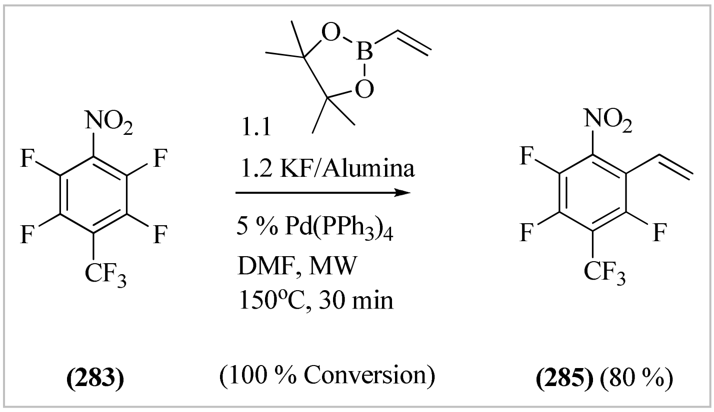
Scheme 123

To extend this area of research, the synthesis of pyridinium difluoramine compounds was attempted, with, what appears to be some initial success. Results indicated that our attempts to synthesize difluoramine compounds from aminopyridine derivatives such as 2,5,6-trifluoro-4-(phenylsulfonyl)pyridin-3-amine **(242)**, were successful (*scheme 124*), although these compounds were not isolated and characterized. Further investigation into these types of reactions would be very interesting and could give access to some interesting energetic materials.



Scheme 124: Pyridine difluoramine synthesis with NMR (proposed difluoramine peaks shown in red)

And finally, continuing on from the palladium catalyzed Suzuki arylation of highly fluorinated nitrobenzene compounds[158] described in chapter 5.0, the functionality of such systems has been extended to include palladium catalyzed Suzuki vinylation processes, such as those shown in *scheme 125*.



Scheme 125: Palladium catalyzed Suzuki vinylation process

Whilst the boronic ester **(281)** was shown to be less reactive than phenyl boronic acid **(280)** and, therefore, required slightly more forcing conditions for suitable conversion of starting material to the coupled product, the reactivity of the polyfluoronitrobenzene derivatives did mirror those reported by Sandford *et al*.

In terms of extending this work, this should include extending the substrate scope to include more tetra- and tri- fluoro nitrobenzene isomers.

Chapter 7 - Experimental Section

7.1 General

NMR: Proton, carbon and florine nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{17}F NMR) were recorded on either a Varian Mercury 400, Bruker Advance 400 or a Bruker 400 Ultrashield (^{1}H NMR, 400 MHz; ^{13}C NMR, 126 MHz; ^{19}F NMR 376 MHz) or a Varian Inova 500 (^{13}C NMR, 126 MHz) or a Varian VNMRS-700 (^{13}C NMR, 126 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.36 ppm; ^{19}F NMR, $CFCl_3$ at 0.00 ppm). ^{1}H, ^{13}C and ^{19}F spectroscopic data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (Hz) and assignment.

Mass Spectrometry: GC-MS analysis was performed on a Trace GC-MS device (Thermo-Finnigan Corporation) operating in electron impact ionization (EI) mode or chemical ionization (CI) mode. Accurate mass analysis was achieved with a Xevo QtoF mass spectrometer (Waters Ltd, UK) equipped with an accurate solids analysis probe (ASAP).

Elemental Analysis: C, H, and N analysis was collected with an Exeter Analytical CE-440 Elemental Analyser.

Infra Red Analysis: Infra-red (IR) spectra were recorded on a Perkin Elmer 1600 Series FTIR fitted with an ATR attachment.

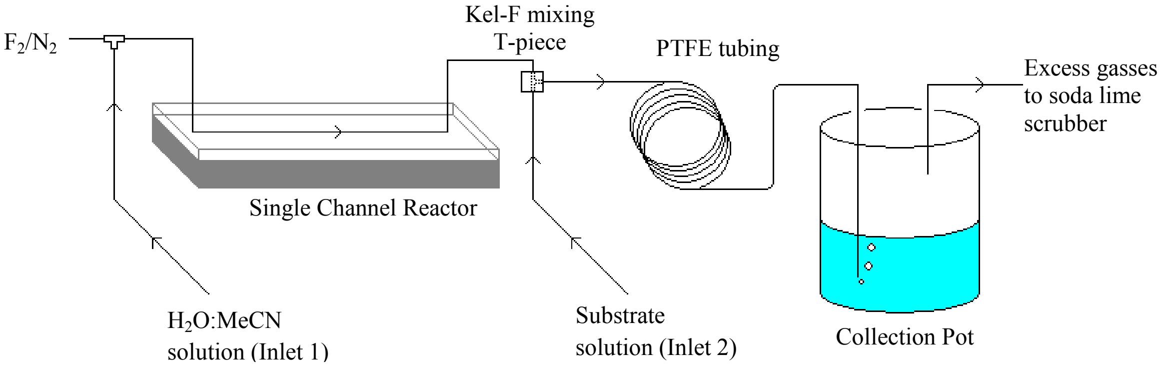
X-Ray Analysis: Crystallographic data was recorded with a Rigaku R-Axis SPIDER IP diffractometer equipped with a Cryostream (Oxford Cryosystems) low temperature device at 120 K.

Melting Point Analysis: Melting points (mp) were measured with a Gallenkamp apparatus at atmospheric pressure and are uncorrected.

Microwave reactions: All microwave irradiated reactions (MW) were heated in a Biotage Initiator Sixty Microwave.

Chemicals and Solvents: Unless otherwise stated, commercially available reagents were used without purification. An Innovative Technology Inc. Solvent Purification System was used for all dry solvents other than DMSO, which was purchased from Sigma Aldrich. All flash column chromatography was carried out using Silicagel LC60A (40–63 micron) purchased from Fluorochem.

Diagram of Flow Apparatus



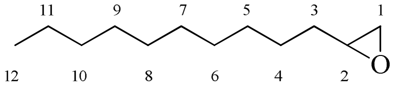
7.2 Experimental for Chapter 3.0

7.2.1 Experimental for the Epoxidation of Alkenes

General Procedure

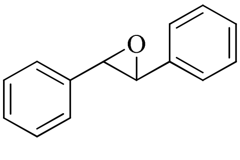
Under a flow of F_2 (10 % in N_2) of 2.0 mmol h^{-1}, MeCN : H_2O (4:1) was added to inlet 1 at a rate of 10.0 ml h^{-1} (110.0 mmol h^{-1} water) to give HOF.MeCN at a calibrated rate of 2.0 mmol h^{-1}. The alkene (in a 1:1 mixture of DCM :MeCN) was added to inlet 2 at a rate of 2.0 mmol h^{-1}, and the reaction was allowed to run for continuously for either 30 mins or 60 mins, over an oxidation path length of 30 cm. All reaction fluids were collected in a stirring pot of sodium bicarbonate solution (50 mL), whilst excess gasses were vented through a soda lime scrubber. The reaction mixture was then added to another 25 mL of sodium bicarbonate solution, washed with DCM (3 × 75 mL), dried over $MgSO_4$ and filtered. The organic solvent was removed under reduced pressure to yield the epoxide

2-decyloxirane



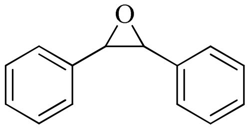
Using dodec-1-ene (0.18 g, 1.07 mmol) as the alkene, this was added continuously over a period of 30 mins, after which time the reaction yielded **2-decyloxirane** (0.195 g, 99 %) as a pale yellow oil, with no further purification required; ν_{max} (cm^{-1}) 2954, 2823 (sp^3 C-H), 916, 833 (C-

O-C); δ_H (400 MHz, $CDCl_3$)0.86 (3H, t, $^3J_{HH}$ 6.4, -CH_2CH_3),1.17–1.36 (16H, m, 8 × -CH_2-), 1.36–1.55 (4H, m, 2 × -CH_2-), 2.44 (1H, dd, $^2J_{HH}$ 5.1, $^3J_{HH}$ 2.7 H1)(xix), 2.72 (1H, dd, $^2J_{HH}$ 5.0, $^3J_{HH}$ 4.0 H1), 2.81-2.96 (1H, m, H2); δ_C (100 MHz, $CDCl_3$) 14.0 (1C, s, C12), 22.6 (1C, s, C11), 25.9 (1C, s, C4), 29.3, 29.4, 29.5, 29.6, 31.9 (5C, s, C5-9), 32.4 (1C, s, C10), 32.5 (1C, s, C3), 47.0 (1C, s, C1), 52.3 (1C, s, C2); *m/z* (EI) 184 (M^+, 2 %), 169 (M^+ -CH_3, 100 %), and as compared to literature data[162]



***trans*-2,3-diphenyloxirane**

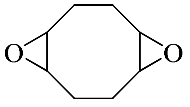
Using *trans*-stilbene (0.36 g, 2.0 mmol) as the alkene, this was added continuously over a period of 60 mins, after which time the reaction yielded ***trans*-2,3-diphenyloxirane** (0.39 g, 99 %) as a yellow solid, mp 65–66 ºC (lit. 65–66 ºC)[163], with no purification required; ν_{max} (cm^{-1}) 2989 (sp^3 C-H), 1493 (Ar-*H*), 846 (C-O-C); δ_H (400 MHz, $CDCl_3$) 3.95 (2H, s, OC*H*), 7.27–7.54 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 61.1 (2C, s, C2), 123.8 (4C, s, C2′), 126.6 (2C, s, C4′), 126.9 (4C, s, C3′), 135.4 (2C, s, C1′); *m/z* (EI) 196 (M^+, 38 %), 195 (M^+ -H, 52 %), and as compared to literature data[164]



***cis*-2,3-diphenyloxirane**

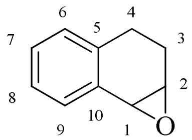
Using *cis*-stilbene (0.18 g, 1.00 mmol) as the alkene, this was added continuously over a period of 30 mins, after which time the reaction yielded a mixture of 3 products (confirmed by GC) (0.19 g) as a red oil, which included starting material and ***cis*-2,3-diphenyloxirane** (0.16 g, 81 %); ν_{max} (cm^{-1}) 2984 (sp^3 C-H), 1497, (Ar-H), 848 (C-O-C); δ_H (400 MHz, $CDCl_3$) 4.38 (2H, s, OC*H*), 7.15–7.25 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 59.8 (2C, s, C2), 126.9 (2C, s, C2′), 127.5 (2C, s, C4′), 127.8 (4C, s, C3′), 134.4 (2C, s, C1′); *m/z* (EI) 196 (M^+, 44 %), 195 (M^+ -H, 64 %), and as compared to literature data[165]

(xix) The coupling constant for geminal protons of an oxirane ring are reported to be in the region of 5-6.5[161]



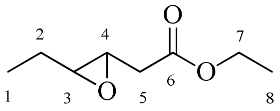
1,5-dioxatricyclodecane

Using 1,5-cyclooctadiene (0.11 g, 1.02 mmol) as the alkene, this was added continuously over a period of 30 mins, after which time the reaction yielded **1,5-dioxatricyclodecane** (0.13 g, 94 %) as a clear oil with no purification required; ν_{max} (cm^{-1}) 2926 (sp^3 C-H), 925, 838 (C-O-C); δ_H (400 MHz, CDCl$_3$) 1.73–2.05 (8H, m, 4 × -C*H*$_2$-), 2.92–2.97 (4H, m, OC*H*); δ_C (100 MHz, CDCl$_3$) 21.9 (4C, s, C2), 56.0 (4C, s, C1); *m/z* (EI) 141 (MH$^+$, 26 %) 140 (M$^+$, 34 %), and as compared to literature data[166]



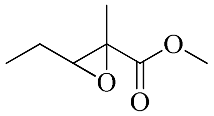
1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene

Using 1,2-dihydronaphthalene (0.13 g, 1.00 mmol) as the alkene, this was added continuously over a period of 30 mins, after which time the reaction yielded a mixture of mixture of 6 products (confirmed by GC) (0.15 g) as a dark red oil, which included starting material and **1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene** (0.12 g, 82 %); ν_{max} (cm^{-1}) 2950, 2926 (sp^3 C-H), 1491 (Ar-H), 1246, 784 (C-O-C); δ_H (400 MHz, CDCl$_3$) 1.79 (1H, td, $^3J_{HH}$ 14.0, $^3J_{HH}$ 5.6, H3), 2.43 (1H, dd, $^3J_{HH}$ 15.5, $^3J_{HH}$ 5.5, H4), 2.82 (1H, td, $^3J_{HH}$ 14.8, $^3J_{HH}$ 6.4, H3), 3.76 (1H, t, $^3J_{HH}$ 3.2, H2), 2.44 (1H, dm, $^3J_{HH}$ 14.4, H4), 3.88 (1H, d, $^3J_{HH}$ 4.2, H1), 7.13 (1H, d, $^3J_{HH}$ 7.3, H6),7.19–7.33 (2H, m, H7,8), 7.42 (1H, dd, $^3J_{HH}$ 7.2, $^4J_{HH}$ 1.3, H9); δ_C (100 MHz, CDCl$_3$) 21.8 (1C, s, C3), 24.4 (1C, s, C4), 52.8 (1C, s, C2), 55.1 (1C, s, C1), 126.1 (1C, s, C9), 128.4 (1C, s, C8), 128.5 (1C, s, C7), 129.6 (1C, s, C6), 132.6 (1C, s, C10), 136.7 (1C, s, C5); *m/z* (EI) 148 (MH^{2+}, 1 %) 147 (MH$^+$, 10 %), 146 (M$^+$, 77 %), 131 (MH$^+$ -O, 10 %), 115 (M$^+$ -CH$_3$O, 33 %), 104 (100 %), 91 (M$^+$ -C$_3$H$_4$O, 16 %), and as compared to literature data[167]



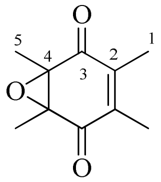
ethyl 2-(3-ethyloxiran-2-yl)acetate

Using ethyl *trans*-3-hexenoate (0.14 g, 0.98 mmol) as the alkene, this was added continuously over a period of 30 mins, after which time the reaction yielded **ethyl-2-(3-ethyloxiran-2-yl)acetate** (0.15 g, 97 %) as a clear oil, with no further purification required; ν_{max} (cm^{-1}) 2973 (sp^3 C-H), 1734 (C=O), 1462 (Ar-H), 1180, 1027 (C-O), 1253, 887 (C-O-C); δ_H (400 MHz, CDCl$_3$) 1.00 (3H, t, $^3J_{HH}$ 7.5, H1), 1.28 (3H, t, $^3J_{HH}$ 7.1, H8), 1.60 (2H, q, d, $^3J_{HH}$ 7.5, $^4J_{HH}$ 5.6, H2), 2.55 (2H, q,d, $^3J_{HH}$ 16.2, $^3J_{HH}$ 5.9, H5), 2.74 (1H, t,d, $^3J_{HH}$ 5.5, $^3J_{HH}$ 2.2, H3), 3.05 (1H, t,d, $^3J_{HH}$ 5.9, $^3J_{HH}$ 2.2, H4) 4.18 (2H, q,d, $^3J_{HH}$ 7.1, $^5J_{HH}$ 0.9, H7); δ_C (100 MHz, CDCl$_3$) 9.7 (1C. s, C1), 14.1 (1C, s, C8), 24.8 (1C, s, C2), 37.8 (1C, s, C5), 53.7 (1C, s, C4), 59.6 (1C, s, C3), 60.8 (1C, s, C7), 170.4 (1C, s, C6); *m/z* (EI) 159 (MH$^+$, 2 %), and as compared to literature data[168]



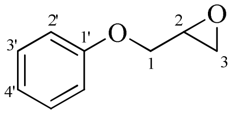
Methyl 3-ethyl-2-methyloxirane-2-carboxylate

Using methyl *trans*-2-methyl pentenoate (0.14 g, 1.09 mmol) as the alkene, this was added continuously over a period of 30 mins, after which time the reaction yielded **methyl 3-ethyl-2-methyloxirane-2-carboxylate** (0.16 g, 99 %) as a clear oil, with no further purification required; ν_{max}(cm^{-1}) 2974 (sp^3 C-H), 1729 (C=O), 1179, 1022 (C-O), 1252, 881 (C-O-C); δ_H (400 MHz, CDCl$_3$) 1.04 (3H, t, $^3J_{HH}$ 7.6, -CH$_2$CH_3), 1.49 (3H, s, CCH_3), 1.56 (2H, m, CH$_3$CH_2-), 3.11 (1H, t, $^3J_{HH}$ 6.3, -CH$_2$CH), 3.72 (3H, s, OCH_3) ; δ_C (100 MHz, CDCl$_3$) 10.2 (1C, s, C1), 13.3 (1C, s, C4), 21.4 (1C, s, C2), 52.5 (1C, s, C7), 57.6 (1C, s, C5), 63.4 (1C, s, C3), 172.0 (1C, s, C6); *m/z* (EI) 144 (M$^+$, 14 %), and as compare to literature data[169]



1,3,4,6-tetramethyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione

Using duroquinone (0.32 g, 1.95 mmol) as the alkene, this was added continuously over a period of 60 mins, after which time the reaction yielded a mixture of 2 products (0.34 g) (confirmed by GC) as yellow crystals which contained starting material and **1,3,4,6-tetramethyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione** (0.13 g, 38 %); δ_H (400 MHz, $CDCl_3$) 1.6 (6H, s, -OCC*H*$_3$), 1.97 (6H, s, -C=CC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 11.7 (2C, s, C1), 13.5 (2C, s, C5), 63.3 (2C, s, C4), 141.1 (2C, s, C2), 194.5 (2C, s, C3); *m/z* (EI) 165 (M^+-CH_3, 8 %), and as compared to literature data[170]



2-(phenoxymethyl)oxirane

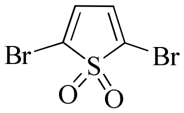
Using allyloxybenzene (0.13 g, 1.00 mmol) as the alkene, this was added continuously over a period of 30 mins, after which time the reaction yielded a mixture of products (confirmed by GC) (0.15 g) as a clear oil, which included starting material and **2-(phenoxymethyl)oxirane** (0.12 g, 84 %); δ_H (400 MHz, $CDCl_3$) 2.79 (1H, dd, $^2J_{HH}$ 4.9, $^3J_{HH}$ 2.7, H3), 2.91–2.95 (1H, m, H3), 3.38 (1H, ddt, $^3J_{HH}$ 5.6, $^3J_{HH}$ 4.1, $^3J_{HH}$ 3.0, H2), 3.99 (1H, dd, $^2J_{HH}$ 11.0, $^3J_{HH}$ 5.6, H1), 4.24 (1H, dd, $^2J_{HH}$ 11.0, $^3J_{HH}$ 3.0, H1), 6.95 (2H, d, $^3J_{HH}$ 8.0, H2'), 7.0 (1H, tt, $^3J_{HH}$ 7.3, $^4J_{HH}$ 0.9. H4'), 7.32 (2H, t, $^3J_{HH}$ 8.6, H3'); 44.7 (1C, s, C3), 50.1 (1C, s, C2), 68.6 (1C, s, C1), 114.6 (2C, s, C2'), 121.2 (1C, s, C4'), 129.5 (2C, s, C3'), 158.4 (1C, s, C1'); MS (ASAP) 151 (MH^+, 14 %), 150 (M^+, 56 %) and as compared to literature data[171]

7.2.2 Experimental for the Oxidation of Sulfur Compounds

General Procedure

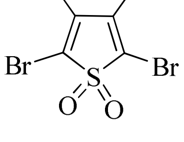
Under a flow of F_2 (10 % in N_2) of 4.0 mmol h^{-1}, MeCN : H_2O (4:1, 10.0 mL) was added to inlet 1 at a rate of 10.0 ml h^{-1} (110.0 mmol h^{-1} water) to give HOF.MeCN at a calibrated rate of 4.0 mmol h^{-1}. The thiophene or sulfide (in DCM, 10.0 mL) was added to inlet 2 at a rate of 2.0 mmol h^{-1}, and the reaction was allowed to run for continuously for 60 mins, over an oxidation path length of either 100 cm or 300 cm. All reaction fluids were collected in a stirring pot of sodium bicarbonate solution (50 mL), whilst excess gasses were vented through a soda lime scrubber. The reaction mixture was then added to another 25 mL of sodium bicarbonate solution, washed with DCM (3 × 75 mL), dried over $MgSO_4$ and filtered. The organic solvent was removed under reduced pressure to yield the crude product.

2,5-dibromothiophene-1,1-dioxide



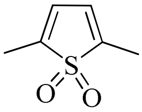
Using 2,5-dibromothiphene (0.48 g, 2.0 mmol) as the thiophene and 4.0 mmol h^{-1} HOF.MeCN, workup yielded a mixture of 2 products (0.54 g) which were identified by ^1H NMR as **starting material** (7 %) and **2,5-dibromothiophene-1,1-dioxide** (0.51 g, 93 %); δ_H (400 MHz, $CDCl_3$) 6.84 (2H, s, H3); δ_C (100 MHz, $CDCl_3$) 119.57 (2C, s, C3), 128.36 (2C, s, C2); *m/z* (EI) 276 (M^+, 1 × ^{79}Br, 1 × ^{81}Br, 100 %) and as compared to literature data[172]

2,3,4,5-tetrabromothiophene-1,1-dioxide



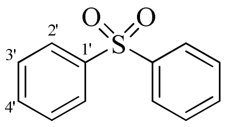
Using 2,3,4,5-tetrabromothiophene (0.80 g, 2.0 mmol) as the thiophene and 4.0 mmol h^{-1} HOF.MeCN, workup yielded a mixture of 2 products (0.83 g) which were identified by ^1H NMR as **starting material** (54 %) and **2,3,4,5-tetrabromothiophene-1,1-dioxide** (0.40 g, 46

%); δ_C (100 MHz, $CDCl_3$) 119.93 (2C, s, C3), 127.97 (2C, s, C2); *m/z* (EI) 432 (M^+, 1 × ^{79}Br, 1 ^{81}Br, 62 %) and as compared to literature data[173]



2, 5-dimethylthiophene-1,1-dioxide

Using 2,5-dimethylthiophene (0.22 g, 2.0 mmol) as the thiophene and 4.0 mmol h^{-1} HOF.MeCN, workup yielded **2, 5-dimethylthiophene-1,1-dioxide** (0.23 g, 80 %) with no purification required; δ_H (400 MHz, $CDCl_3$)2.04 (6H, s, 2 × CH_3), 6.27 (2H, s, H3); δ_C (100 MHz, $CDCl_3$) 9.47 (2C, s, -CH_3), 123.13 (2C, s, C3), 139.47 (2C, s, C2); *m/z* (EI) 144 (M^+, 57 %) and as compared to literature data[174]



Sulfonyldibenzene

Using diphenylsulfane (0.37 g, 2.0 mmol) as the sulfide and 4.0 mmol h^{-1} HOF.MeCN, workup yielded **sulfonyldibenzene** (0.41 g, 95 %) with no purification required; δ_H (400 MHz, $CDCl_3$) 7.51 (2H, t, $^3J_{HH}$ 7.7, H3'), 7.57 (1H, t, $^3J_{HH}$ 7.3, H4'), 7.95 (2H, d, $^3J_{HH}$ 7.4, H2'); δ_C (100 MHz, $CDCl_3$) 127.9 (4C, s, C2'), 129.5 (4C, s, C3'), 133.4 (2C, s, C4'), 141.4 (2C, s, C1'); and as compared to literature data[175]

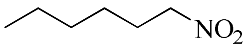
7.3 Experimental for Chapter 4.0

7.3.1 Experimental for the Oxidation of Aliphatic Amines

General procedure

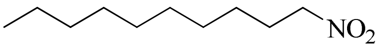
Under a calibrated flow of F_2 (10% in N_2) of 6.0 mmol h^{-1}, MeCN:H_2O (4:1) was added *via* inlet 1 at a rate of 15.0 mL h^{-1} (165.5 mmol h^{-1} water) to generate the HOF.MeCN complex at a calibrated rate of rate of 6.0 mmol h^{-1}. The aliphatic amine (dissolved in either MeCN or DCM) was added *via* inlet 2 at a rate of 10.0 mL h^{-1} (1.0-2.0 mmol h^{-1}) and the reactants were allowed to run continuously for a fixed period of time over a reaction path length of 100 cm. All liquid products were collected in a vessel containing distilled water, whilst excess gasses were vented through a soda lime scrubber. The reactants were extracted from the aqueous layer using DCM, which was then dried over $MgSO_4$, filtered, and evaporated *in vacuo* to yield the crude product.

1-nitrohexane



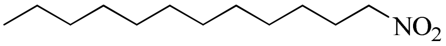
Using 1-aminohexane (0.20 g, 2.0 mmol, in 10 mL of MeCN) as the aliphatic amine and 15 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 60 minutes and all liquid products were collected in distilled water (25 mL). Work-up yielded **1-nitrohexane** (0.21 g, 80 %) as a pale yellow oil; ν_{max} (cm^{-1}) 2929 (sp^3 C-H), 1549 and 1380 (NO_2); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, $^3J_{HH}$ 6.6, $CH_2C\mathit{H_3}$), 1.24–1.45 (6H, m, 3 × $C\mathit{H_2}$), 2.00 (2H, qn, $^3J_{HH}$ 6.8, $CH_3C\mathit{H_2}$), 4.38 (2H, t, $^3J_{HH}$ 7.0, $C\mathit{H_2}NO_2$); δ_C (100 MHz, $CDCl_3$) 13.8 (C6), 22.3 (C5), 25.9 (C2), 27.3 (C3), 31.0 (C4), 75.7 (C1); *m/z* (EI) 132 (MH^+, 8%), 102 (MH^+ - NO, 54 %), 88 (100 %), 84 (MH^+ - NO_2, 59 %); and as compared to literature data[176]

1-nitrodecane



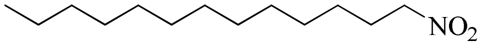
Using 1-aminodecane (0.16 g, 1.0 mmol, in 5 mL of DCM) as the aliphatic amine and 7.5 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 30 minutes and all liquid products were collected in distilled water (25 mL). Work-up yielded **1-nitrodecane** (0.11 g, 60 %) as clear oil with no further purification required: ν_{max} (cm^{-1}) 2922 (sp^3 C-H), 2850 (sp^3 C-H), 1550 and 1382 (NO_2); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, $^3J_{HH}$ 6.9, $CH_2C\mathit{H_3}$), 1.08–1.43 (14H, m, 7 × $C\mathit{H_2}$), 2.01 (2H, qn, $^3J_{HH}$7.2, $C\mathit{H_2}CH_2NO_2$), 4.39 (2H, t, $^3J_{HH}$ 7.1, $C\mathit{H_2}NO_2$); δ_C (100 MHz, $CDCl_3$) 14.3 (C10), 22.9 (C9), 26.4 (C2), 27.6 (C3), 29.0 (C4), 29.4 (C7), 29.5 (C6), 29.6 (C5), 32.1 (C8), 75.9 (C1); *m/z* (EI) 188 (MH^+, 1%), 170 (MH^+ -H_2O, 26%), 152 (100%), 140 (MH^+ - NO_2, 42 %) and as compared to literature data[177]

1-Nitrododecane

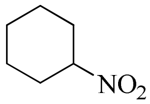


Using 1-aminododecane (0.19 g, 1.0 mmol, in 5 mL of DCM) as the aliphatic amine and 7.5 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 30 minutes and all liquid products were collected in distilled water (25 mL). Work-up yielded **1-nitrododecane** (0.19 g, 95 %) as a clear oil with no further purification required: ν_{max} (cm^{-1}) 2924 (sp^3 C-H), 2854 (sp^3 C-H), 1552 and 1381 (NO_2); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, $^3J_{HH}$ 6.9, CH_2CH_3), 1.20–1.43 (18H, m, 8 × CH_2), 2.01 (2H, qn,$^3J_{HH}$ 6.8, $CH_2CH_2NO_2$), 4.39 (2H, t, $^3J_{HH}$ 7.1, CH_2NO_2); δ_C (100 MHz, $CDCl_3$) 14.3 (C12), 22.9 (C11), 26.4 (C2), 27.6 (C3), 29.1, 29.4, 29.5, 29.7, 29.8, 29.8 (C4-C9), 32.1 (C10), 76.0 (C1); *m/z* (EI) 198 (MH$^+$ -H_2O, 3%), 180 (MH$^+$ -H_2O, 8 %); and as compared to literature data[178]

1-nitrotridecane

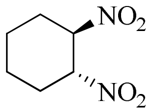


Using 1-aminotridecane (0.20 g, 1.0 mmol, in 5 mL of DCM) as the aliphatic amine and 7.5 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 30 minutes and all liquid products were collected in distilled water (25 mL). Work-up yielded **1-nitrotridecane** (0.21 g, 95 %) as a clear oil with no further purification required: ν_{max} (cm^{-1}) 2923 (sp^3 C-H), 2854 (sp^3 C-H), 1552 and 1380 (NO_2); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, $^3J_{HH}$ 6.9, CH_2CH_3), 1.20–1.45 (20H, m, 10 × CH_2), 2.01 (2H, qn, $^3J_{HH}$ 7.2, $CH_2CH_2NO_2$), 4.39 (2H, t, $^3J_{HH}$ 7.1, CH_2NO_2); δ_C (100 MHz, $CDCl_3$) 14.3 (C13), 22.9 (C12), 26.4 (C2), 27.6 (C3), 29.1, 29.5, 29.6, 29.7, 29.79, 29.84, 29.9 (C4-10), 32.1 (C11), 75.9 (C1); *m/z* (CI) 213 (M - H_2O, 7 %), 200 (MH$^+$ - NO, 100 %), 198 (50 %); and as compared to literature data[179]



1-nitrocyclohexane

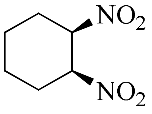
Using aminocyclohexane (0.2 g, 2.0 mmol, in 10 mL of MeCN) as the aliphatic amine and 15.0 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 60 minutes and all liquid products were collected in distilled water (25 mL). Work-up yielded **1-nitrocyclohexane** (0.25 g, 95 %) as a pale yellow oil with no further purification required: ν_{max} (cm^{-1}) 2940 (sp^3 C-H), 1538 and 1377 (NO_2); δ_H (400 MHz, $CDCl_3$) 1.17–1.46 (3H, m, 1 × C*H*$_2$, 1 × C*H*), 1.60–1.73 (1H, m, 1 × C*H*), 1.76–1.96 (4H, m, 2 × C*H*$_2$), 2.10–2.31 (2H, m, 2 × C*H*), 4.37 (1H, tt, $^3J_{HH}$ 10.7, $^3J_{HH}$ 4.0, C*H*NO$_2$); δ_C (100 MHz, $CDCl_3$) 24.3 (C4), 25.0 (C3), 31.1 (C2), 84.9 (C1); *m/z* (EI) 83 (M^+ -NO_2 98%), 55 (100 %), 41 (78 %); and as compared to literature data[180]



***trans*-1,2-dinitrocyclohexane**

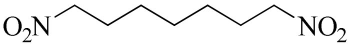
Using *trans-1*,2-diaminocyclohexane (0.11 g, 1.0 mmol, in 10 mL DCM) as the aliphatic amine and 15.0 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 60 minutes and all liquid products were collected in distilled water (25 mL). Work-up yielded ***trans*-1,2-dinitrocyclohexane** (0.16 g , 95 %) as a white solid; mp 45–46°C (purified product value 45.5–46.5°C); ν_{max} (cm^{-1}) 2955 (sp^3 C-H), 1542 and 1390 (NO_2); δ_H (400 MHz, $CDCl_3$) 1.44–1.52 (2H, m, 2 × C*H*), 1.71–1.87 (2H, m, 2 × C*H*) 1.93–2.07 (2H, m, 2 × C*H*), 2.59–2.72 (2H, m, 2 × C*H*), 4.94–5.10 (2H, m, C*H*NO$_2$); δ_C (100 MHz, $CDCl_3$) 23.9 (C4), 30.9 (C3), 84.2 (C1); *m/z* (EI) 127 (MH^+ -NO_2, 8 %), 97 (MH^+ -NO, 18 %), 81 (MH^+ - 2 × NO_2, 100 %); and as compared to product data which was purified *via* silica flash column chromatography (using dichloromethane : hexane 7:3 as the eluent): Found: C 41.41, H 5.74, N 16.05; $C_6H_{13}NO_2$ Requires: C 41.38, H 5.79, N 16.09 %

cis-1,2-dinitrocyclohexane



Using *cis*-1,2-diaminocyclohexane (0.061 g, 0.54 mmol, in 5.0 mL DCM) as the aliphatic amine and 7.5 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 30 minutes and all liquid products were collected in distilled water (25 mL). Work-up yielded ***cis*-1,2-dinitrocyclohexane** (0.09 g, 95 %) as a clear oil with no further purification required: ν_{max} (cm^{-1}) 2955 (sp^3 C-H), 1547 and 1390 (NO_2); δ_H (400 MHz, $CDCl_3$) 1.48–1.75 (4H, m, 2 × C*H*$_2$), 2.20–2.27 (2H, m, 2 × C*H,* H4 and H3) 2.54–2.62 (2H, m, 2 × C*H,* H4 and H3), 4.94–4.96 (2H, m, C*H*NO_2); δ_C (100 MHz, $CDCl_3$) 23.9 (C4), 30.7 (C3), 84.2 (C1); *m/z* (EI) 127 (MH$^+$ -NO_2, 8 %), 97 (MH$^+$ -NO, 18 %), 81 (MH$^+$ - 2 × NO_2, 100 %); and as compared to product data which was purified *via* silica flash column chromatography (using dichloromethane : hexane 3:1 as the eluent): Found: C 41.38, H 5.79, N 16.13; $C_6H_{13}NO_2$ Requires: C 41.38, H 5.79, N 16.09 %

1,7-dinitroheptane



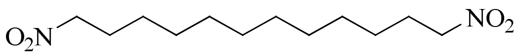
Using 1,7-dinitroheptane (0.08 g, 0.6 mmol, in 5 mL DCM) as the aliphatic amine and 7.5 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 30 minutes and all liquid products were collected in distilled water (25 mL). Work-up yielded **1,7-dinitrohexane** (0.11 g, 95 %) as a clear oil with no further purification required: ν_{max} (cm^{-1}) 2933 (sp^3 C-H), 1545 and 1383 (NO_2); δ_H (400 MHz, $CDCl_3$) 1.41 (6H, m, 3 × C*H*$_2$, H1 and H2), 2.03 (4H, qn,$^3J_{HH}$ 6.8, 2 × C*H*$_2$, C*H*$_2$$CH_2NO_2$) 4.40 (4H, t, $^3J_{HH}$7.0, C*H*$_2$$NO_2$); δ_C (100 MHz, $CDCl_3$) 26.2 (C4), 27.4 (C3), 28.3 (C2), 75.7 (C1); *m/z* (CI) 192 (MH^{2+}, 2%), 174 (MH^{2+} -H_2O, 36 %), 127 (MH^{2+} -H_2O -NO_2, 100%), 125 (70%), 112 (18%) and as compared to literature data[181]

7.3.2 Experimental for Aliphatic Azide Oxidation

General procedure

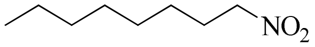
As per the oxidation of aliphatic amines except a reaction path length of 100 cm was used.

1,12-dinitrododecane



Using 1,12-diazidododecane (0.25 g, 1.0 mmol, in 10 mL of DCM) as the aliphatic azide and 15.0 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 60 minutes and all liquid products were collected in distilled water (25 mL). Work-up yielded **1,12-dinitrododecane** (0.26 g, 99 %) as clear oil with no further purification required: ν_{max} (cm^{-1}) 2931 (sp^3 C-H), 1542 and 1380 (NO_2); δ_H (400 MHz, $CDCl_3$) 1.18-1.45 (16H, m, 8 × C*H*$_2$, H3-H10), 1.98 (4H, qn, $^3J_{HH}$ 7.1, 2 × C*H*$_2$CH$_3$, H2 and H11), 4.36 (4H, t,$^3J_{HH}$7.1, 2 × CH$_2$C*H*$_3$, H1 and H12); δ_C (100 MHz, $CDCl_3$) 26.1 (C2), 27.3 (C3), 28.7 (C4), 29.1 (C5), 29.2 (C6), 75.7 (C1); *m/z* (EI) 244 (MH^{2+} -H_2O, 19 %), 152 (100%); 216 (MH^{2+} - NO_2, 31 %) and as compared to literature data[181]

1-nitrooctane



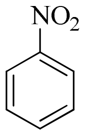
Using 1-azidooctane (0.31 g, 2.0 mmol, in 10 mL of DCM) as the aliphatic azide and 15.0 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 60 minutes and all liquid products were collected in distilled water (25 mL). Work-up yielded **1-nitrooctane** (0.31 g, 99 %) as clear oil with no further purification required: ν_{max} (cm^{-1}) 2920 (sp^3 C-H), 1550 and 1384 (NO_2); δ_H (400 MHz, $CDCl_3$) 0.84 (3H, t, $^3J_{HH}$ 6.9, CH$_2$C*H$_3$*), 1.18–1.38 (10H, m, 5 × C*H$_2$*), 1.96 (2H, qn,$^3J_{HH}$ 7.2, C*H*$_2$CH$_2$NO$_2$), 4.35 (2H, t, $^3J_{HH}$ 7.1, C*H*$_2$NO$_2$); δ_C (100 MHz, $CDCl_3$) 14.1 (C8), 22.7 (C7), 26.5 (C2), 27.2 (C3), 28.3 (C4), 29.3 (C5), 31.9 (C6), 75.5 (C1); *m/z* (EI) 161 (MH^+, 3%), 143 (MH^+ -H_2O, 32%), 115 (MH^+ - NO_2, 47 %); and as compared to literature data[182]

7.3.3 Experimental for Aromatic Amine Oxidations

General procedure

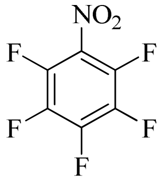
Under a calibrated flow of F_2 (10 % in N_2) of 6.0 mmol h^{-1}, MeCN:H_2O (4:1) was added *via* inlet 1 at a rate of 15.0 mL h^{-1} (165.5 mmol h^{-1}) to generate the HOF.MeCN complex at a calibrated rate of rate of 6.0 mmol h^{-1}. The amino benzene or amino pyridine (dissolved in MeCN) was added *via* inlet 2 at a rate of 10.0 mL h^{-1} (2.0 mmol h^{-1}) and the reactants were allowed to run continuously over a fixed period of time. All liquid products were collected in a vessel containing distilled water (50 mL), whilst excess gasses were vented through a soda lime scrubber. The reactants were extracted from the aqueous layer using DCM, which was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude product.

1-nitrobenzene



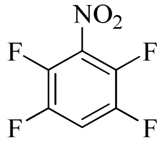
Using aniline (0.93 g, 10.0 mmol, in 50 mL MeCN) as the amino benzene and 75 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 300 minutes. The crude product was purified *via* distillation to yield **nitrobenzene** (0.75 g, 61 %) as a pale yellow oil; bp 209–210°C (lit. value 209–210°C)[183]; ν_{max} (cm^{-1}) 3076 (sp^2 C-H), 1518 and 1343 (NO_2), 1478 (Ar C-C); δ_H (400 MHz, $CDCl_3$) 7.55 (2H, tm, ${}^3J_{HH}$ 7.4, H3), 7.70 (1H, tt, ${}^3J_{HH}$ 7.4, ${}^4J_{HH}$ 1.2, H4), 8.23 (2H, dd, ${}^3J_{HH}$ 8.8, ${}^4J_{HH}$ 1.2, H2); δ_C (126 MHz, $CDCl_3$) 123.7 (1C, s, C4), 129.5 (2C, s, C3), 134.9 (2C, s, C2), 148.4 (1C, s, C1); *m/z* (EI) 123 (MH^+, 74 %), 77 (MH^+ -NO_2, 96 %), 51 (100 %); and as compared to literature data[184-185]

1,2,3,4,5-pentafluoro-6-nitro-benzene

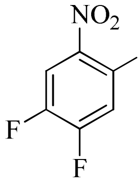


Using 2,3,4,5,6-pentafluoroaniline (1.83 g, 10.0 mmol, in 50 mL MeCN) as the amino benzene and 75 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 300 minutes. The crude product was purified *via* distillation to yield **1,2,3,4,5-pentafluoro-6-nitro-benzene** (1.55 g, 73 %) as pale yellow oil; bp 160–162°C, (lit. value 160–161°C)[186]; ν_{max} (cm^{-1}) 1557 and 1353 (NO_2), 1506 (Ar C-C); δ_C (126 MHz, $CDCl_3$) 126.5–127.2 (1C, m, C6), 137.9 (2C, dm, $^1J_{CF}$ 263.2, C1/2), 141.3 (2C, dm, $^1J_{CF}$ 267.1, C2/1), 144.1 (1C, dtt, $^1J_{CF}$ 263.5, $^2J_{CF}$ 13.3, $^3J_{CF}$ 4.1, C3); δ_F (376 MHz, $CDCl_3$) -145.5 (2F, d, $^3J_{FF}$ 16.6, F1), -146.2 (1F, t, $^3J_{FF}$ 21.4, F3), -158.0 (2F, t, $^3J_{FF}$ 19.8, F2); *m/z* (EI) 214 (MH^{2+}, 2 %), 213 (MH^+, 34%), 183 (MH^+ -NO, 18 %), 167 (MH^+ -NO_2, 24 %), 117 (90 %); and as compared to literature data[187]

1,2,4,5-tetrafluoro-3-nitrobenzene

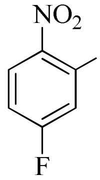


Using 2,3,5,6-tetrafluoroaniline (1.65 g, 10.0 mmol, in 50 mL MeCN) as the amino benzene and 75 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 300 minutes. The crude product was purified *via* silica flash column chromatography (using a mixture of hexane : dichloromethane 4:1 as the eluent) to yield **1,2,4,5-tetrafluoro-3-nitrobenzene** (1.19 g, 61 %) as a yellow oil; ν_{max} (cm^{-1}) 3055 (sp^2 C-H), 1557 and 1352 (NO_2), 1511 (Ar C-C); δ_H (400 MHz, $CDCl_3$) 7.35 (1H, tt, $^3J_{HF}$ 9.4, $^4J_{HF}$ 7.0, H6); δ_C (126 MHz, $CDCl_3$) 109.7 (1C, t, $^2J_{CF}$ 22.5, C6), 131.5 (1C, t, $^2J_{CF}$ 12.9, C3), 140.31 (2C, ddd, $^1J_{CF}$ 263.1, $^2J_{CF}$ 17.0, $^3J_{CF}$ 4.8, C2), 146.3 (2C, ddd, $^1J_{CF}$ 254.2, $^2J_{CF}$ 11.6, $^3J_{CF}$ 5.8, C1); δ_F (376 MHz, $CDCl_3$) -134.8—135.0 (2F, m, F1), -146.6—146.8 (2F, m, F2); *m/z* (EI) 195 (M^+, 70 %), 165 (M^+ -NO, 52 %), 149 (M^+ -NO_2, 77 %), 99 (100 %); and as compared to literature data[187]



1,2,4-trifluoro-5-nitrobenzene

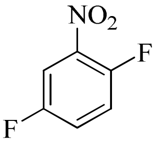
Using 2,4,5-trifluoroaniline (1.49 g, 10.0 mmol, in 50 mL MeCN) as the amino benzene and 75 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 300 minutes. The crude product was purified *via* vacuum distillation to yield **1,2,4-trifluoro-5-nitrobenzene** (1.31 g, 74 %) as pale yellow oil; bp 78–79°C, 15 mbar (lit. value 80–81°C 15 mbar)[188]; ν_{max} (cm^{-1}) 3081 (sp^2 C-H), 1508 (Ar C-C), 1538 and 1346 (NO$_2$); δ_H (400 MHz, CDCl$_3$) 7.21 (1H, td, $^3J_{HF}$ 9.7, $^4J_{HF}$ 6.3, H3), 8.01 (1H, dd, $^3J_{HF}$ 16.5 $^4J_{HF}$ 7.7, H6); δ_C (126 MHz, CDCl$_3$) 108.2 (1C, dd, $^2J_{CF}$ 26.3, $^2J_{CF}$ 22.1, C3), 115.1 (1C, dt, $^2J_{CF}$ 23.1, $^3J_{CF}$ 2.3, C6), 133.0 (1C, s, C5), 145.9 (1C, ddd, $^1J_{CF}$ 252.0, $^3J_{CF}$ 13.5, $^4J_{CF}$ 4.0, C4), 152.1 (1C, ddd, $^1J_{CF}$ 265.9, $^2J_{CF}$ 16.5, $^4J_{CF}$ 3.2, C1), 153.8 (1C, ddd, $^1J_{CF}$ 263.2, $^2J_{CF}$ 14.1, $^3J_{CF}$ 11.0, C2); δ_F (376 MHz, CDCl$_3$) -116.1–-116.4 (1F, m, F4), -120.6–-120.9 (1F, m, F1), -137.2–-137.4 (1F, m, F2); *m/z* (EI) 178 (MH$^+$, 4 %), 177 (M$^+$, 50 %), 146 (M$^+$ -NO, 20 %), 131 (M$^+$ -NO$_2$, 48 %), 119 (38 %), 81 (100 %); and as compared to literature data[188]



2,4-difluoro-1-nitrobenzene

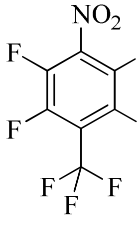
Using 2,4-difluoroaniline (1.29 g, 10.0 mmol, in 50 mL MeCN) as the amino benzene and 75 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 300 minutes. The crude product was purified *via* vacuum distillation to yield **2,4,-difluoro-1-nitrobenzene** (1.10 g, 69 %) as a yellow oil; bp 73–74°C, 15 mbar (lit. value 85–86°C)[189]; ν_{max} (cm^{-1}) 3092 (sp^2 C-H), 1530 and 1345 (NO$_2$), 1493 (Ar C-C); δ_H (400 MHz, CDCl$_3$) 7.00–7.12 (2H, m, H3 and H5), 8.12–8.24 (1H, m, H6); δ_C (126 MHz, CDCl$_3$) 106.5 (1C, dd, $^2J_{CF}$ 26.6, $^2J_{CF}$ 24.3, C3), 112.2 (1C dd, $^2J_{CF}$ 23.1, $^4J_{CF}$ 4.1, C5), 128.2 (1C dd, $^3J_{CF}$ 11.0, $^3J_{CF}$ 1.9, C6), 134.1 (1C s, C1), 156.7 (1C, dd, $^1J_{CF}$ 267.8, $^3J_{CF}$ 13.2, C4), 165.7 (1C, dd, $^1J_{CF}$ 260.2, $^3J_{CF}$ 11.2, C2); δ_F (376 MHz, CDCl$_3$) -97.4–-97.7 (1F, m, F2), -110.8–-111.0 (1F, m, F4); *m/z* (EI) 159 (M$^+$, 54 %), 129 (M$^+$ -NO, 42 %), 113 (M$^+$ -NO$_2$, 61 %), 101 (45 %), 63 (100 %); and as compare to literature data[190]

1,4-difluoro-2-nitrobenzene

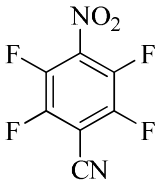


Using 2,5-difluoroaniline (1.29 g, 10.0 mmol, in 50 mL MeCN) as the amino benzene and 75 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 300 minutes. The crude product was purified *via* vacuum distillation to yield **1,4-difluoro-2-nitrobenzene** (0.94 g, 59 %) as a yellow oil; bp 74–75°C, 10 mbar (lit. value 74–75°C)[191]; ν_{max}(cm^{-1}) 3088 (sp^2 C-H), 1534 and 1347 (NO$_2$), 1496 (Ar C-C); δ_H (400 MHz, CDCl$_3$) 7.27–7.42 (2H, m, H5 and H6), 7.79 (1H, dd, $^4J_{HH}$ 7.6, $^5J_{HH}$ 3.1, H3); δ_C (126 MHz, CDCl$_3$) 113.0 (1C, dd, $^2J_{CF}$ 28.3, $^3J_{CF}$ 2.5, C5), 119.8 (1C, dd, $^2J_{CF}$ 23.5, $^3J_{CF}$ 8.2, C6), 122.8 (1C, dd, $^2J_{CF}$ 23.9, $^3J_{CF}$ 8.5, C3), 137.2 (1C, s, C2), 151.9 (1C, dd, $^1J_{CF}$ 263.3, $^4J_{CF}$ 3.2, C4), 157.4 (1C, dd, $^1J_{CF}$ 248.2, $^4J_{CF}$ 3.1, C1); δ_F (376 MHz, CDCl$_3$) -114.3–-14.4 (1F, m, F1), -122.4–-122.6 (1F, m, F4); *m/z* (EI) 159 (M$^+$,75 %), 129 (M$^+$ -NO, 24 %), 113 (M$^+$ -NO$_2$, 92 %), 101 (71 %), 63 (100 %); and as compared to literature data[192-193]

1,2,4,5-tetrafluoro-3-nitro-6-(trifluoromethyl)benzene

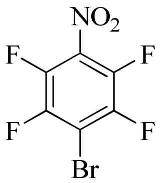


Using 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline (1.42 g, 6.0 mmol, in 30 mL MeCN) as the amino benzene and 45 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 180 minutes. The crude product was purified *via* vacuum distillation to yield **1,2,4,5-tetrafluoro-3-nitro-6-(trifluoromethyl)benzene** (0.98 g, 62 %) as yellow oil; bp 68–69°C, 5.0 mbar (lit. value 74–75°C)[187]; ν_{max} (cm^{-1}) 1560 and 1358 (NO$_2$), 1500 (Ar C-C); δ_C (126 MHz, CDCl$_3$) 113.5 (1C, qt, $^2J_{CF}$ 35.9, $^2J_{CF}$ 12.8, C6), 120.2 (1C, qm, $^1J_{CF}$ 277.2, *C*F$_3$), 133.0 (1C, tm, $^2J_{CF}$ 13.7, C3), 140.5 (2C, ddd, $^1J_{CF}$ 265.2, $^2J_{CF}$ 16.3, $^3J_{CF}$ 6.2, C1), 144.8 (2C, dd, $^1J_{CF}$ 267.8, $^2J_{CF}$ 12.7, C2); δ_F (376 MHz, CDCl$_3$) -57.0 (3F, t, $^2J_{FF}$ 22.2, C*F*$_3$), -135.6 (2F, dq, $^2J_{FF}$ 22.1, $^3J_{FF}$ 10.0, F1), -144.1–-144.3 (2F, m, F2); *m/z* (EI) 263 (M$^+$, 76 %), 233 (M$^+$ -NO, 4 %), 217 (M$^+$ -NO$_2$, 74 %), 167 (46 %); and as compared to literature data[187]



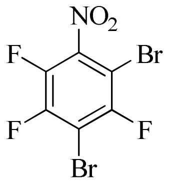
2,3,5,6-tetrafluoro-4-nitrobenzonitrile

Using 4-amino-2,3,5,6-tetrafluorobenzonitrile (2.11 g, 10.0 mmol, in 50 mL MeCN) as the amino benzene and 75 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 300 minutes. The crude product was purified *via* silica flash column chromatography (using a mixture of hexane : ethyl acetate 9:1 as the eluent) to yield **2,3,5,6-tetrafluoro-4-nitrobenzonitrile** (1.54 g, 70 %) as colourless crystals; mp 76–77°C (lit. value 79–81°C)[193]; ν_{max} (cm^{-1}) 1553 and 1346 (NO_2), 1493 (Ar C-C); δ_C (126 MHz, $CDCl_3$) 98.2 (1C, tt, $^2J_{CF}$ 17.0, $^3J_{CF}$ 1.9, C1), 105.9 (1C, t, $^3J_{CF}$ 3.4, -*C*N), 134.1 (1C, t, $^2J_{CF}$ 13.4, C4), 140.3 (2C, ddd, $^1J_{CF}$ 266.9, $^2J_{CF}$ 14.9, $^3J_{CF}$ 5.9, C2), 147.8 (2C, ddm, $^1J_{CF}$ 266.8, $^2J_{CF}$ 11.7, C3); δ_F (376 MHz, $CDCl_3$) -126.9–-127.0 (2F, m, F3), -142.6–-142.7 (2F, m, F2); *m/z* (EI) 220 (M^+, 4 %), 190 (M^+ -NO, 2 %), 174 (M^+ -NO_2, 14 %), 124 (44 %); and as compared to literature data[193]



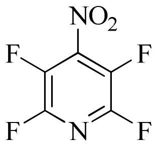
1-bromo-2,3,5,6-tetrafluoro-4-nitrobenzene

Using 4-bromo-2,3,5,6-tetrafluoroaniline (2.44 g, 10.0 mmol, in 50 mL of MeCN) as the amino benzene and 75 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 300 minutes. The crude product was purified *via* silica flash column chromatography (using hexane : ethyl acetate 4:1 as the eluent) to yield **1-bromo-2,3,5,6-tetrafluoro-4-nitrobenzene** (1.40 g, 51%) as yellow crystals; mp 53–54°C (lit. value 50–51°C)[195]; ν_{max} (cm^{-1}) 1548 and 1349 (NO_2), 1489 (Ar C-C); δ_C (126 MHz, $CDCl_3$) 105.8 (1C, t, $^2J_{CF}$ 22.3, C1), 130.0 (1C, t, $^2J_{CF}$ 14.0, C4), 140.6 (2C, ddd, $^1J_{CF}$ 270.8, $^2J_{CF}$ 21.5, $^3J_{CF}$ 2.2, C2), 145.4 (2C, ddm, $^1J_{CF}$ 255.6, $^2J_{CF}$ 13.8, C3); δ_F (376 MHz, $CDCl_3$) -128.0–-128.2 (2F, m, F3), -144.9–-145.0 (2F, m, F2); *m/z* (EI) 275 (MH^+, 1 × ^{79}Br, 1 × ^{81}Br, 32 %), 245 (MH^+ -NO, 1 × ^{79}Br, 1 × ^{81}Br, 24 %), 228 (M^+ -NO_2, 1 × ^{79}Br, 1 × ^{81}Br, 18 %), 148 (100 %); and as compared to literature data[195]



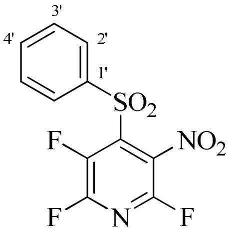
1,3-dibromo-2,4,5-trifluoro-6-nitrobenzene

Using 1,3-dibromo-2,4,5,6-tetrafluorobenzene (3.1 g, 10.0 mmol, in 50 mL of MeCN) as the amino benzene and 75 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 300 minutes. The crude product was purified *via* vacuum distillation to yield **1-1,3-dibromo-2,4,5-trifluoro-6-nitrobenzene** (2.08 g, 62 %) as a yellow oil; bp 84–85°C, 0 mbar; Found: C 20.83, H 0.0, N 4.0 $C_6Br_2F_3NO_2$ Requires: C 21.52, H 0.0, N 4.18 %; ν_{max} (cm^{-1}) 1368 and 1550 (NO_2), 699, 773, 897, 1468; δ_C (126 MHz, $CDCl_3$) 98.3 (1C, dd, $^2J_{CF}$ 29.1, $^3J_{CF}$ 5.5, C1), 103.8 (1C, dd, $^2J_{CF}$ 27.7, $^2J_{CF}$ 21.8, C3), 140.7 (1C, ddd, $^1J_{CF}$ 264.2, $^2J_{CF}$ 17.6, $^3J_{CF}$ 5.2, C4), 140.0–140.5 (1C, m, C6), 148.4 (1C, ddd, $^1J_{CF}$ 256.4, $^2J_{CF}$ 13.8, $^4J_{CF}$ 3.6, C6), 153.3 (1C, dm, $^1J_{CF}$ 249.6, C2); δ_F (376 MHz, $CDCl_3$) -96.7 (1F, d, $^4J_{FF}$ 10.3 F2), -121.7 (1F, d, $^3J_{FF}$ 22.0, F6), -145.4 (1F, dd, $^3J_{FF}$ 22.0, $^4J_{FF}$ 10.3, F4); *m/z* (EI) 335 (M^+, 33 %), 305 (M^+ - NO, 32 %), 289 (M^+ - NO_2, 22 %), 129 (100 %)



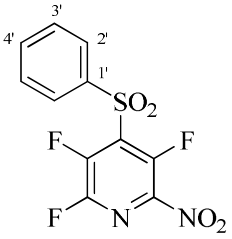
2,3,5,6-tetrafluoro-4-nitropyridine

Using 2,3,5,6-tetrafluoropyridin-4-amine (1.66 g, 10.0 mmol, in 50 mL MeCN) as the amino pyridine and 75 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 300 minutes. The crude product was purified *via* distillation to yield **2,3,5,6-tetrafluoro-4-nitropyridine** (1.53g, 78 %) as yellow oil; bp 152–154°C (lit. value 152–153°C)[196]; δ_C (126 MHz, $CDCl_3$) 135.1 (2C, dddd, $^1J_{CF}$ 275.7, $^2J_{CF}$ 34.5, $^3J_{CF}$ 14.0, $^4J_{CF}$ 4.2, C2), 138.4–139.2 (1C, m, C4), 143.9 (2F, dm, $^1J_{CF}$ 251.7, C3); δ_F (376 MHz, $CDCl_3$) -83.1 (2F, t, $^3J_{FF}$ 15.8, F2), -146.5 (2F, quintet, $^3J_{FF}$ 15.8, F3); *m/z* (EI) 196 (M^+, 78 %), 150 (M^+ -NO_2, 36 %) and as compared to literature data[196]



2,3,6-trifluoro-5-nitro-4-(phenylsulfonyl)pyridine

Using 2,5,6-trifluoro-4-(phenylsulfonyl)pyridin-3-amine (2.88 g, 10.0 mmol, in 50 mL MeCN) as the amino pyridine and 75 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 300 minutes. Work-up yielded **2,3,6-trifluoro-5-nitro-4-(phenylsulfonyl)pyridine** (3.00 g, 95 %) as a yellow solid with no purification required; mp 130–131°C; (Found: C40.40, H 1.72, N 8.31; $C_{11}H_5F_3N_2O_4$ Requires: C 41.52, H 1.58, F 17.91, N 8.80, O 20.11 %); ν_{max} (cm^{-1}) 1356 and 1557 (NO_2), 1164, 1450; δ_H (400 MHz, $CDCl_3$) 7.70 (2H, t, $^3J_{HH}$ 7.8, H3’), 7.83 (1H, t, $^3J_{HH}$ 7.8, H4’), 8.13 (2H, d, $^3J_{HH}$ 8.4, H2’); δ_C (126 MHz, $CDCl_3$) 127.8–128.2 (1C, m, C5), 129.16 (2C, s, C2’), 130.1 (2C, s, C3’), 136.3 (1C, s, C4’), 137.3 (1C, s, C1’ or C4), 137.4 (1C, s, C4 or C1’), 139.5 (1C, ddd, $^1J_{CF}$ 272.6, $^2J_{CF}$ 27.7, $^4J_{CF}$ 6.9, C2), 146.8 (1C, ddd, $^1J_{CF}$ 254.9, $^3J_{CF}$ 12.2, $^4J_{CF}$ 3.8, C6), 149.4 (1C, ddd, $^1J_{CF}$ 259.8, $^2J_{CF}$ 18.3, $^3J_{CF}$ 12.6, C1); δ_F (376 MHz, $CDCl_3$) -73.23 (1F, dd, $^4J_{FF}$ 22.7, $^5J_{FF}$ 10.7, F6), -76.85 (1F, dd, $^3J_{FF}$ 28.8, $^5J_{FF}$ 10.7, F3), -134.17 (1F, dd, $^3J_{FF}$ 28.8, $^4J_{FF}$ 23.1, F2), *m/z* (ASAP) 319 (MH^+, 100 %), 242 (MH^+ -Ph, 18 %)

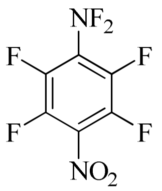


2,3,5-trifluoro-6-nitro-4-(phenylsulfonyl)pyridine

Using 3,5,6-trifluoro-4-(phenylsulfonyl)pyridin-2-amine (2.88 g, 10.0 mmol, in 50 mL MeCN) as the amino pyridine and 75 mL of the aqueous acetonitrile mixture, the reaction was allowed to run continuously for 300 minutes. Work-up yielded **2,3,5-trifluoro-6-nitro-4-(phenylsulfonyl)pyridine** (3.00 g, 95 %) as a yellow solid with no purification required; mp 112–114°C; (Found: C 40.96, H 1.74, N, 8.38; $C_{11}H_5F_3N_2O_4$ Requires: C 41.52, H 1.58, F 17.91, N 8.80, O 20.11 %); ν_{max} (cm^{-1}) 1355 and 1557 (NO_2), 1164, 1230, 1459; δ_H (400 MHz, $CDCl_3$) 7.69 (2H, t, $^3J_{HH}$ 7.9, H3’), 7.81 (1H, t, $^3J_{HH}$ 7.4, H4’), 8.13 (2H, d, $^3J_{HH}$ 7.9, H2’); δ_C (126 MHz, $CDCl_3$) 128.7 (2C, s, C2’), 130.1 (2C, s, C3’), 133.9 (1C, dd, $^2J_{CF}$, 17.1, $^2J_{CF}$, 11.7, C3), 136.1

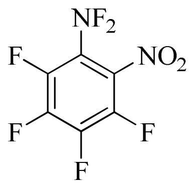
(1C, s, C4'), 136.6–137.4 (1C, m, C6), 138.6 (1C, s, C1'), 145.3 (1C, dm, $^1J_{CF}$ 256.6, C2 or C3 or C5), 145.4 (1C, dm, $^1J_{CF}$ 255.2, C2 or C3 or C5), 145.9 (1C, dm, $^1J_{CF}$ 285.2, C2 or C3 or C5); δ_F (376 MHz, CDCl$_3$) -80.18 (1F, dd, $^4J_{FF}$ 31.2, $^5J_{FF}$ 24.0, F3), -118.7 (1F, dd, $^3J_{FF}$ 23.9, $^5J_{FF}$ 4.7, F5), -119.1 (1F, dd, $^3J_{FF}$ 31.2, $^4J_{FF}$ 4.6, F2), *m/z* (ASAP) 319 (MH$^+$, 100 %)

7.3.4 Experimental for Difluoramine Compounds



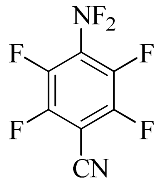
2,3,5,6-tetrafluoro-4-nitro-1-difluoramine

Under a calibrated flow of F_2 (10 % in N_2) of 6.0 mmol h^{-1}, MeCN was added *via* inlet 1 at a rate of 10.0 mL h^{-1}, and 2,3,5,6-tetrafluoro-4-nitroaniline (0.21 g, 1.0 mmol, in 5.0 mL DCM) was added *via* inlet 2 at a rate of 10.0 mL h^{-1} (2.0 mmol h^{-1}), and the reactants were allowed to run continuously over a period of 30 minutes. All liquid products were collected in a vessel containing distilled water (25 mL), whilst excess gasses were vented through a soda lime scrubber. The reactants were extracted from the aqueous layer using 3 × 25 mL DCM, and the organic extract was then dried over MgSO$_4$, filtered, and concentrated under reduced pressure to yield the crude product as an orange oil. TLC and fluorine NMR indicated no starting material remained. Purification *via* flash column chromatography (using a mixture of hexane : DCM 4:1 as the eluent) yielded **2,3,5,6-tetrafluoro-4-nitro-1-difluoramine** as a yellow oil (0.16 g, 65 %); δ_C (126 MHz, CDCl$_3$) 128.3 (1C, t, $^2J_{CF}$ 9.7, C4), 133.0–133.4 (1C, m, C1), 140.4 (2C, ddd, $^1J_{CF}$ 266.0, $^2J_{CF}$ 14.8, $^3J_{CF}$ 6.1, C3), 142.9 (2C, ddd, $^1J_{CF}$ 270.0, $^2J_{CF}$ 12.9, $^3J_{CF}$ 6.8, C2); δ_F (376 MHz, CDCl$_3$) 64.2 (2F, t, $^4J_{FF}$ 10.0, NF$_2$), -138.8–-139.3 (2F, m, F2), -143.8–-144.1 (2F, m, F3); *m/z* (ASAP) 247 (MH$^+$, 25 %), 217 (100 %), 194 (M$^+$ -NF$_2$, 33 %), 84.0 (81 %)



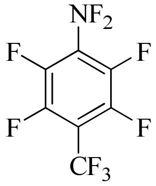
2,3,4,5-tetrafluoro-6-nitro-1-difluoramine

Under a calibrated flow of F_2 (10 % in N_2) of 6.0 mmol h^{-1}, MeCN was added *via* inlet 1 at a rate of 10.0 mL h^{-1}, and 2,3,4,5-tetrafluoro-6-nitroaniline (0.63 g, 3.0 mmol, in 15.0 mL DCM) was added *via* inlet 2 at a rate of 10.0 mL h^{-1} (2.0 mmol h^{-1}), and the reactants were allowed to run continuously over a period of 90 minutes. All liquid products were collected in a vessel containing H_2O (40 mL), whilst excess gasses were vented through a soda lime scrubber. The reactants were extracted from the aqueous layer using 5 × 40 mL DCM. The organic extract was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude product as an orange oil. TLC and fluorine NMR indicated no starting material remained. Purification *via* flash column chromatography (using a mixture of hexane : DCM 2:1 as the eluent) yielded **2,3,4,5-tetrafluoro-6-nitro-1-difluoramine** as a pale yellow oil (0.44 g, 59 %); δ_C (126 MHz, $CDCl_3$) 124.2–124.5 (1C, m, C6), 132.1–132.9 (1C, m, C1), 140.3 (1C, ddd, $^1J_{CF}$ 264.5, $^2J_{CF}$ 13.8, $^3J_{CF}$ 5.7, C2/5), 143.4 (1C, dt, $^1J_{CF}$ 265.0, C 3/4), 143.7 (1C, dm, 270.0, C2/5), 144.4 (1C, dt, $^1J_{CF}$ 268.5, C 3/4); δ_F (376 MHz, $CDCl_3$) 64.2 (2F, t, $^4J_{FF}$ 10.0, NF_2), -136.1–-136.9 (1F, m, F2/5), -141.6 (1F, tm, $^3J_{FF}$ 20.6, F3/4) -145.2 (1F, ddd, $^3J_{FF}$ 21.7, $^4J_{FF}$ 9.2, $^5J_{FF}$ 5.4, F5/2), -145.6 (1F, td, $^3J_{FF}$ 20.5, $^4J_{FF}$ 5.3, C4/3); *m/z* (ASAP) 247 (MH^+, 27 %), 217 (M^+ - NO, 100 %), 194 (M^+ -NF_2, 44 %), 84.0 (70 %)



4-(difluoroamino)-2,3,5,6-tetrafluorobenzonitrile

Under a calibrated flow of F_2 (10 % in N_2) of 6.0 mmol h^{-1}, MeCN was added *via* inlet 1 at a rate of 10.0 mL h^{-1}, and 4-amino-2,3,5,6-tetrafluorobenzonitrile (0.283 g, 1.50 mmol, in 15.0 mL DCM) was added *via* inlet 2 at a rate of 10.0 mL h^{-1} (1.0 mmol h^{-1}), and the reactants were allowed to run continuously over a period of 90 minutes. All liquid products were collected in a vessel containing H_2O (40 mL), whilst excess gasses were vented through a soda lime scrubber. The reactants were extracted from the aqueous layer using 3 × 40 mL DCM. The organic extract was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude product as an orange oil. TLC and fluorine NMR indicated no starting material remained. Purification *via* flash column chromatography (using a mixture of hexane : DCM 2:1 as the eluent) yielded **4-(difluoroamino)-2,3,5,6-tetrafluorobenzonitrile** as a clear oil (0.24 g, 71 %); δ_C (126 MHz, $CDCl_3$) 98.9 (1C, tt, $^2J_{CF}$ 17.1, $^3J_{CF}$ 2.1, C1), 106.1 (1C, s, CN), 130.1 (1C, t, $^2J_{CF}$ 8.9, C4), 142.5 (2C, dddd, $^1J_{CF}$ 267.9, $^2J_{CF}$21.5, $^3J_{CF}$ 14.3, $^4J_{CF}$ 8.1 C2), 147.7 (2C, ddm, $^1J_{CF}$ 268.0, $^2J_{CF}$ 12.6, C3); δ_F (376 MHz, $CDCl_3$) 63.8 (2F, t, $^4J_{FF}$ 10.3, NF_2), -129.3 (2F, ddm, $^3J_{FF}$ 20.8, $^4J_{FF}$ 10.4, F3), -140.2 (2F, ddm, $^3J_{FF}$ 20.3, $^4J_{FF}$ 10.3, F2); *m/z* (ASAP) 227 (MH^+, 5 %), 207 (100 %), 191 (40 %), 160, (17 %)



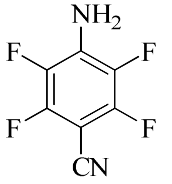
2,3,5,6-tetrafluoro-4-(trifluoromethyl)difluoramine

Under a calibrated flow of F_2 (10 % in N_2) of 6.0 mmol h^{-1}, MeCN was added *via* inlet 1 at a rate of 10.0 mL h^{-1}, and 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline (0.06 g, 0.25 mmol, in 2.5 mL DCM) was added *via* inlet 2 at a rate of 5.0 mL h^{-1} (0.5 mmol h^{-1}), and the reactants were allowed to run continuously over a period of 30 minutes. All liquid products were collected in a vessel containing H_2O (25 mL), whilst excess gasses were vented through a soda lime scrubber. The reactants were extracted from the aqueous layer using 3 × 25 mL DCM. The organic extract was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude product as an orange oil. TLC and fluorine NMR indicated no starting material remained. Purification *via* flash column chromatography (using a mixture of hexane : DCM 2:1 as the eluent) yielded **2,3,5,6-tetrafluoro-4-(trifluoromethyl)difluoramine** as a clear oil (0.04 g, 54 %); δ_C (126 MHz, $CDCl_3$) 95.1 (1C, tt, $^2J_{CF}$ 17.0, $^3J_{CF}$ 3.8, C1), 103.1 (1C, m, CF_3), 129.0 (1C, t, $^2J_{CF}$ 9.4, C4), 143.8 (2C, ddd, $^1J_{CF}$ 262.0, $^2J_{CF}$20.5, $^3J_{CF}$ 14.0, C2), 147.7 (2C, ddm, $^1J_{CF}$ 268.0, $^2J_{CF}$ 12.3, C3); δ_F (376 MHz, $CDCl_3$) 64.0 (2F, t, $^4J_{FF}$ 10.2, NF_2), -57.1 (3F, t, $^2J_{FF}$ 22.3, CF_3), -137.7 (2F, ddm, $^3J_{FF}$ 22.1, $^4J_{FF}$ 9.4, F2), -141.8 (2F, ddm, $^3J_{FF}$ 19.3, $^4J_{FF}$ 9.7, F3); *m/z* (ASAP) 270 (MH^+, 18 %), 217 (M^+ -NF_2, 53 %)

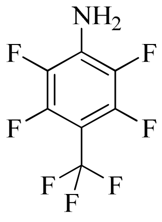
7.4 Experimental for Chapter 5.0

7.4.1 Aniline Synthesis

4-amino-2,3,5,6-tetrafluorobenzonitrile

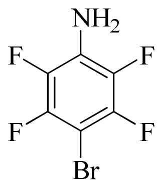


2,3,4,5,6-pentafluorobenzonitrile (6.0 g, 31.0 mmol) was added to a clean, dry Radleys Flask (100 mL), which was then sealed and purged with argon. To the flask, ammonium hydroxide (7.0 mL, 40 mmol) and MeCN (40 mL) were added, and the reaction mixture was mixed at room temperature for 22 hours. After this time, both TLC and fluorine NMR indicated that only traces of starting material remained and the reaction had gone to completion. The reaction mixture was quenched with 40 mL water and extracted with 3 × 50 mL DCM. The organic extract was then washed with 150 mL water and 150 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. This was purified *via* silica flash column chromatography (using a mixture of hexane : ethyl acetate 4:1 as the eluent) and then a re-crystallization (from chloroform) to yield **4-amino-2,3,5,6-tetrafluorobenzonitrile** (4.41 g, 74 %) as white crystals; mp 95–96 ºC (lit. value 95–96ºC)[197]; ν_{max} (cm^{-1}) 3228, 3358 and 3476 (NH_2), 2236 (CN), 1168, 1315, 1506 and 1640; δ_H (400 MHz, $CDCl_3$) 4.64 (2H, b, N*H*$_2$); δ_C (176 MHz, $CDCl_3$) 80.4 (1C, tm, $^2J_{CF}$ 17.6, C4), 109.0 (1C, t, $^3J_{CF}$ 3.6, -*C*N); 132.6 (1C, tt, $^2J_{CF}$ 13.4, $^3J_{CF}$ 4.6, C1), 135.6 (2C, dddd, $^1J_{CF}$ 242.0, $^2J_{CF}$ 14.4, $^3J_{CF}$ 6.0, $^4J_{CF}$ 3.9, C3), 147.9 (2C, dddd, $^1J_{CF}$ 256.4, $^2J_{CF}$ 10.0, $^3J_{CF}$ 5.8, $^4J_{CF}$ 3.7, C2); δ_F (376 MHz, $CDCl_3$) -135.5–-135.6 (2F, m, F2), -160.7—160.9 (2F, m, F3); *m/z* (EI) 190 (MH^+, 100 %), 162 (M - CN, 20 %), 143 (24 %), 124 (18 %); and as compared to literature data[198]



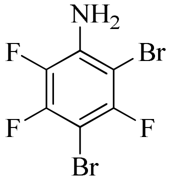
2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline

Octaflorotoluene (3.0 g, 12.72 mmol) was weighed into a Radleys Flask (100 mL), which was then sealed and purged with argon. To the flask, ammonium hydroxide (4.0 mL, 40 mmol) and MeCN (10 mL) were added, and the solution was refluxed for 17 hours. After this time, fluorine NMR indicated that approximately 75 % of the starting material still remained, so a further 8.0 mL of ammonium hydroxide was added (in increments of 2.0 mL) and refluxed for a further 48 hours until both fluorine NMR, and TLC indicated that no stating material remained. The reaction mixture was quenched with 40 mL water and extracted with 3 × 40 mL DCM. The organic extract was then washed with 120 mL water and 120 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification *via* silica flash column chromatography (using a mixture of hexane : ethyl acetate 4:1 as the eluent) yielded **2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline** (1.43 g, 48 %) as a clear orange oil; ν_{max} (cm^{-1}) 3600 and 3428 (NH_2), 1127, 1330, 1506 and 1654; δ_H (400 MHz, $CDCl_3$) 4.38 (2H, b, $N\mathit{H}_2$); δ_C (176 MHz, $CDCl_3$) 97.0 (1C, qt, $^2J_{CF}$ 34.8, $^2J_{CF}$ 21.6, C4), 121.8 (1C, qm, $^1J_{CF}$ 272.7, *C*F_3), 130.2 (1C, tt, $^2J_{CF}$ 13.9, $^3J_{CF}$ 4.4, C1), 136.3 (2C, ddm, $^1J_{CF}$ 240.0, $^2J_{CF}$ 16.0, C3), 144.9, (2C, dm, $^1J_{CF}$ 255.3, C2); δ_F (376 MHz, $CDCl_3$) -55.3 (3F, t, $^4J_{FF}$ 21.1, $C\mathit{F}_3$); -144.0–-144.3 (2F, m, F3), -162.0–-162.2 (2F, m, F2); *m/z* (EI) 234 (MH^+, 4 %), 233 (M^+, 42 %), 214 (82 %), 183 (64 %), 117 (34 %), 69 (100 %); and as compared to literature data[199]



4-bromo-2,3,5,6-tetrafluoroaniline

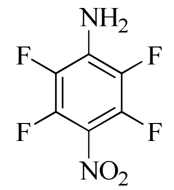
1-bromo-2,3,4,5,6-pentafluorobenzene (3.0 g, 12.0 mmol) was weighed into a clean, dry microwave vial (10-20 mL), which was then sealed and purged with argon. NH_4OH (3.6 mL, 36 mmol) and then MeCN (10 mL) were then added and the vial irradiated at 160ºC for 2 hours. After this time fluorine NMR indicated a 100 % conversion of starting material. The reaction mixture was quenched with 40 mL water and extracted with 3 × 40 mL DCM. The organic extract was then washed with 120 mL water and 120 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification *via* silica flash column chromatography (using a mixture of hexane : DCM 3:1 as the eluent) yielded **4-bromo-2,3,5,6-tetrafluoroaniline** (2.2 g, 75 %) as a white solid; mp 59–61ºC (lit. value 59–61ºC)[200]; ν_{max} (cm^{-1}) 3381 and 3471 (NH_2), 835, 922, 1100, 1172, 1493, 1648; δ_H (400 MHz, $CDCl_3$) 4.08 (2H, b, N*H*$_2$); δ_C (176 MHz, $CDCl_3$) 85.5 (1C, t, $^2J_{CF}$ 23.0, C1), 125.9 (1C, tt, $^2J_{CF}$ 14.2, $^3J_{CF}$ 3.4, C4), 136.8 (2C, dm, $^1J_{CF}$ 241.3, C2), 144.9 (2C, ddt, $^1J_{CF}$ 243.7, $^2J_{CF}$ 13.1, $^3J_{CF}$ 4.5, C3); δ_F (376 MHz, $CDCl_3$) -136.2–-136.4 (2F, m, F3), -160.0–-160.2 (2F, m, F2); *m/z* (EI) 245 (MH^+, 100 %), 164 (MH^+ - Br, 83 %), 144 (66 %), 138 (100%); and as compared to literature data[200]



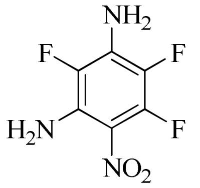
2,4-dibromo-3,5,6-trifluoroaniline

1,3-dibromo-2,4,5,6-tetrafluorobenzene (3.0 g, 10.0 mmol) was weighed into a clean, dry microwave vial (10-20 mL), which was then sealed and purged with argon. NH_4OH (3.0 mL, 30 mmol) and then MeCN (10 mL) were then added and the vial irradiated at 170ºC for 2 hours. After this time fluorine NMR indicated a 95 % conversion of starting material. The reaction mixture was quenched with 40 mL water and extracted with 3 × 40 mL DCM. The organic extract was then washed with 120 mL water and 120 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification *via* silica flash column chromatography (using a mixture of hexane : DCM 2.5:1.5 as the eluent) yielded **2,4-dibromo-3,5,6-trifluoroaniline** as white crystals (2.50 g, 82 %) mp 36–38ºC; (Found: C 23.85, H 0.61, N 4.49 ; $C_6Br_2F_3NH_2$ Requires: C 23.64, H 0.66, Br 52.41, F 18.69, N 4.59 %); ν_{max} (cm^{-1}) 3494 and 3389 (NH_2), 868, 1454, 1482 and 1626; δ_H (400 MHz, $CDCl_3$) 4.46 (2H, b, N*H*$_2$); δ_C (176 MHz, $CDCl_3$) 85.3 (1C, dd, $^2J_{CF}$ 27.9, $^2J_{CF}$ 22.4, C4), 91.6 (1C, ddd, $^2J_{CF}$ 26.9, $^3J_{CF}$ 3.8, $^3J_{CF}$ 2.8, C1), 134.7 (1C, dt, $^2J_{CF}$ 12.4, $^3J_{CF}$ 4.1, C4), 136.2 (1C, ddd, $^1J_{CF}$ 242.7, $^2J_{CF}$ 16.4, $^4J_{CF}$ 4.1, C6), 147.5 (1C, ddd, $^1J_{CF}$ 246.3, $^2J_{CF}$ 13.1, $^3J_{CF}$ 5.8, C5), 152.7 (1C, dd, $^1J_{CF}$ 241.2, $^3J_{CF}$ 4.2, C3); δ_F (376 MHz, $CDCl_3$) -103.9 (1F, d, $^4J_{FF}$ 8.3, F3); -130.6 (1F, d, $^3J_{FF}$ 21.1, F6); -158.7 (1F, dd, $^3J_{FF}$ 21.1, $^4J_{FF}$ 8.3, F5); *m/z* (EI) 305 (M^+, 1 × ^{79}Br, 1 × ^{81}Br, 100 %), 226 (M^+ - ^{79}Br, 20 %), 224 (M^+ - ^{81}Br, 26 %), 145 (M^+ - 2Br [1 × ^{79}Br, 1 × ^{81}Br], 37 %)

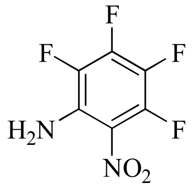
2,3,5,6-tetrafluoro-4-nitroaniline



and **2,4,5-trifluoro-6-nitrobenzene-1,3-diamine**



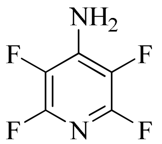
and **2,3,4,5-tetrafluoro-6-nitroaniline**



1,2,3,4,5-pentafluoro-6-nitrobenzene (2.3 g, 10.8 mmol) was added to a clean, dry Radleys Flask (100 mL), which was then sealed and purged with argon. To the flask, ammonium hydroxide (1.1 mL, 11 mmol) and THF (20 mL) were added, and the reaction mixture was mixed at room temperature for 20 hours. After this time, fluorine NMR indicated that approximately 72 % of the starting material still remained, so a further 1.0 mL of ammonium hydroxide was added and mixed at room temperaure for a further 8 hours until both fluorine NMR, and TLC indicated that no stating material remained. The reaction mixture was quenched with 40 mL water and extracted with 3 × 40 mL DCM. The organic extract was then washed with 150 mL water and 150 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a dark red oil. This was purified *via* silica flash column chromatography (using a mixture of hexane : ethyl acetate 2:1 as the eluent) to yield **2,3,5,6-tetrafluoro-4-nitroaniline** (0.37 g, 15 %) as yellow crystals; mp 105–106 ºC (lit. value 106–108ºC)[201]; δ_H (400 MHz, $CDCl_3$) 4.62 (2H, b, N*H*$_2$); δ_C (176 MHz, $CDCl_3$) 119.6–120.2 (1C, m, C1), 131.2 (1C, tt, $^2J_{CF}$ 13.9, $^3J_{CF}$ 4.1, C4), 135.3 (2C, ddm, $^1J_{CF}$ 243.6, $^2J_{CF}$ 14.2, C3), 142.1 (2C, dddd, $^1J_{CF}$ 260.6, $^2J_{CF}$ 13.4, $^3J_{CF}$ 4.0, $^4J_{CF}$ 2.6, C2); δ_F (376 MHz, $CDCl_3$) -147.6–-147.8 (2F, m, F2); -161.6–-161.8 (2F, m, F3); *m/z* (EI) 211 (MH^+, 4 %), 210 (M^+, 80 %), 180 (M^+ - NO, 67 %), 164 (M^+ - NO_2, 57 %), 144 (42 %), 137 (100 %); and **2,3,4,5-tetrafluoro-6-nitroaniline** (0.85 g, 37 %) as red crystals; mp 45–46 ºC (lit. value 43–44ºC)[202]; δ_H (400 MHz, $CDCl_3$) 5.87 (2H, b, N*H*$_2$); δ_C (176 MHz, $CDCl_3$) 120.7–121.1 (1C, m, C6), 132.12 (1C, dddd, $^1J_{CF}$ 245.6, $^2J_{CF}$ 16.5, $^3J_{CF}$ 13.7, $^4J_{CF}$ 2.9, C2), 132.3 (1C, ddd, $^2J_{CF}$ 13.2, $^3J_{CF}$ 3.8, $^4J_{CF}$ 1.9, C1), 136.2 (1C, dddd, $^1J_{CF}$ 243.2, $^2J_{CF}$ 12.5, $^3J_{CF}$ 5.5, $^4J_{CF}$ 2.3, C5), 143.7 (1C, ddt, $^1J_{CF}$ 262.4, $^2J_{CF}$ 12.8, $^3J_{CF}$ 4.7,

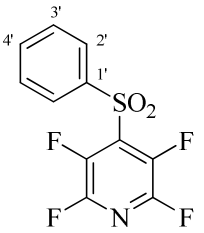
C3 or C4), 144.2 (1C, dtd, $^{1}J_{CF}$ 260.2, $^{2}J_{CF}$ 13.9, $^{3}J_{CF}$ 4.6, C4 or C3); δ_F (376 MHz, $CDCl_3$) -145.5 (1F, dt, $^{3}J_{FF}$ 22.6, $^{4}J_{FF}$ 8.9, F3 or F4), -147.5 (1F, td, $^{3}J_{FF}$ 21.4, $^{4}J_{FF}$ 8.9, F3 or F4), 160.5 (1F, ddd, $^{3}J_{FF}$ 20.6, $^{4}J_{FF}$ 8.9, $^{5}J_{FF}$ 5.9, F2 or F5), (1F, td, $^{3}J_{FF}$ 22.4, $^{4}J_{FF}$ 5.8, F2 or F5); *m/z* (EI) 208 (MH^+, 5 %), 207 (M^+, 81 %), 177 (M^+ - NO, 50 %), 161 (M^+ - NO_2, 58 %), 134 (100 %);
and **2,4,5-trifluoro-6-nitrobenzene-1,3-diamine** (0.42 g, 19 %) as yellow crystals; mp 145–147 ºC (lit. value 147–148ºC)[201]; δ_H (400 MHz, $CDCl_3$) 4.48 (2H, b, C3-N*H*$_2$), 5.86 (2H, b, C1-N*H*$_2$); δ_C (176 MHz, $CDCl_3$) 113.6–113.9 (1C, m, C3), 131.8 (1C, ddd, $^{1}J_{CF}$ 234.5, $^{2}J_{CF}$ 16.4, $^{3}J_{CF}$ 7.9, C4), 133.0 (1C, dm, $^{1}J_{CF}$ 226.2, C2), 133.0 (1C, td, $^{2}J_{CF}$ 15.0, $^{3}J_{CF}$ 4.5, C3), 143.6 (1C, ddd, $^{1}J_{CF}$ 254.8, $^{2}J_{CF}$ 12.9, $^{4}J_{CF}$ 3.2, C5); δ_F (376 MHz, $CDCl_3$) -147.9 (1F, dd, $^{3}J_{FF}$ 21.5, $^{4}J_{FF}$ 8.9 F4), -163.4 (1F, dd, $^{4}J_{FF}$ 8.9, $^{5}J_{FF}$ 2.0 F2), -172.2 (1F, dd, $^{3}J_{FF}$ 21.5, $^{5}J_{FF}$ 2.0 F5); *m/z* (EI) 208 (MH^+, 5 %), 207 (M^+, 81 %), 177 (M^+ - NO, 50 %), 161 (M^+ - NO_2, 58 %), 134 (100 %) and all as compared to literature data[203]

7.4.2 Amino Pyridine Synthesis



2,3,5,6-tetrafluoropyridin-4-amine

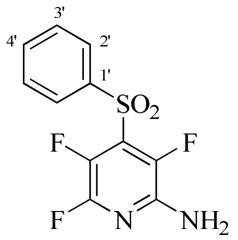
Pentafluoropyridine (4.0 g, 23.7 mmol) was added to a 100 mL Radleys flask, which was then sealed and purged with argon. Ammonium hydroxide (2.3 mL, 23.0 mmol) and MeCN (20 mL) were added, and the solution was stirred at room temperature for 17 hours. After this time, TLC and fluorine NMR indicated that no more starting material remained. The reaction mixture was quenched with 40 mL of distilled water, and extracted with 3 × 40 mL DCM. The organic extracts were added together and washed with 120 mL distilled water and then again with 120 mL brine, then dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as white crystals. Purification *via* re-crystallization from DCM yielded **2,3,5,6-tetrafluoropyridin-4-amine** as white crystals (3.34 g, 85 %); mp 83.0–83.5ºC (lit. value 83–84ºC)[204]; δ_H (400 MHz, $CDCl_3$) 4.72 (2H, b, N*H*$_2$); δ_C (176 MHz, $CDCl_3$) 131.9 (2C, dd, $^{1}J_{CF}$ 242.3, $^{2}J_{CF}$ 34.8, C3), 137.6 (1C, m, C4), 144.0 (2C, dt, $^{1}J_{CF}$ 235.3, $^{2}J_{CF}$ 14.0, C2); δ_F (376 MHz, $CDCl_3$) -93.81 (2F, s, F2), -164.6–-164.9 (2F, m, F3); *m/z* (EI) 166 (M^+, 100) and as compared to literature data[204]



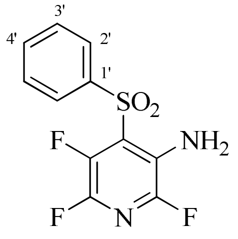
2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine

Sodium phenylsulfinic acid (7.6 g, 45.0 mmol) was weighed into a 100 mL Radleys flask, which was then sealed and purged with argon. To the flask, pentafluoropyridine (2.6 mL, 47.4 mmol) and DMF (40 mL) were added, and the solution was refluxed for 17 hours. After this time, TLC and fluorine NMR indicated that no more starting material remained. The reaction mixture was cooled to room temperature, poured onto cold water (250 mL) and the precipitated solid was filtered off to give the crude product as an off white solid. Purification *via* re-crystallization from ethyl acetate gave **2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine** as white crystals (11.5g, 88 %); mp 148–149ºC (lit. value 148–149ºC)[204]; δ_H (400 MHz, $CDCl_3$) 7.67 (2H, tm, $^3J_{HH}$ 7.8, C3′), 7.79 (1H, tt, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.8, C4′), 8.13 (2H, d, $^3J_{HH}$ 7.4, C2′); δ_C (176 MHz, $CDCl_3$) 128.7 (2C, s, C3′), 130.2 (2C, s, C2′), 133.3 (1C, t, $^2J_{CF}$ 12.7, C4), 135.9 (1C, s, C4′), 138.7 (2C, dm, $^1J_{CF}$ 272.4, C2), 139.4 (1C, s, C1′), 144.2 (2C, dm, $^1J_{CF}$ 251.6, C3); δ_F (376 MHz, $CDCl_3$) -86.1–-86.4 (2F, m, C2), -137.4–-137.6 (2F, m, C3); *m/z* (EI) 291 (M^+, 71 %), 141 (M^+ -C_5F_4N, 84 %), 77 (M^+ - $C_5F_4NSO_2$, 100 %); and as compared to literature data[204]

3,5,6-trifluoro-4-(phenylsulfonyl)pyridin-2-amine



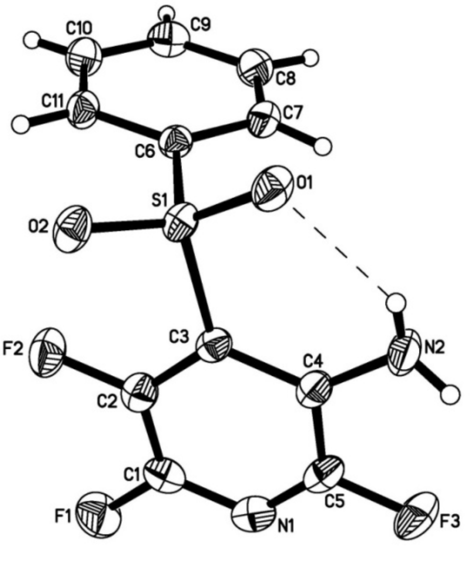
and **2,5,6-trifluoro-4-(phenylsulfonyl)pyridin-3-amine**



2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine (3.0 g, 10.3 mmol) was weighed into a 100 mL Radleys flask, which was then sealed and purged with argon. Ammonium hydroxide (2.5 mL, 25.0 mmol) and MeCN (20 mL) were added, and the solution was refluxed for 24 hours. After this time, TLC and fluorine NMR indicated that no more starting material remained. The reaction mixture was quenched with 40 mL of distilled water, and extracted with 3 × 40 mL DCM. The organic extracts were added together and washed with 120 mL distilled water and then again with 120 mL brine, then dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as yellow crystals. Purification *via* silica flash column chromatography (using a mixture of hexane : ethyl acetate 2:1 as the eluent) yielded **3,5,6-trifluoro-4-(phenylsulfonyl)pyridin-3-amine** as a yellow solid (1.26 g, 44 %); mp 102–104ºC; ν_{max} (cm^{-1}) 3327 and 3476 (NH_2), 1160, 1248, 1498; δ_H (400 MHz, $CDCl_3$) 5.65 (2H, b, NH_2) 7.60 (2H, tm, $^3J_{HH}$ 7.8, C3′), 7.73 (1H, tt, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.8, C4′), 8.05 (2H, d, $^3J_{HH}$ 8.5, C2′); δ_C (176 MHz, $CDCl_3$) 121.1 (1C, dd, $^2J_{CF}$ 13.6, $^3J_{CF}$ 5.0, C3 or C4), 127.3 (2C, s, C2’), 129.6 (2C, s, C3′), 130.8 (1C, dd, $^2J_{CF}$ 31.1, $^3J_{CF}$ 4.9, C4 or C5), 134.9 (1C, s, C4′), 136.3 (1C, ddd, $^1J_{CF}$ 238.8, $^2J_{CF}$ 18.7, $^3J_{CF}$ 12.4, C6), 139.2 (1C, ddd, $^1J_{CF}$ 258.4, $^2J_{CF}$ 28.1, $^4J_{CF}$ 6.4, C6), 140.9 (1C, s, C1’), 143.3 (1C, ddd, $^1J_{CF}$ 243.9, $^3J_{CF}$ 10.6, $^4J_{CF}$ 3.0, C2); δ_F (376 MHz, $CDCl_3$) -85.2 (1F, dd, $^3J_{FF}$ 30.8, $^5J_{FF}$ 14.8, F5), -105.9 (1F, dd, $^3J_{FF}$ 21.9, $^5J_{FF}$ 14.8, F2), -141.5 (1F, dd, $^3J_{FF}$ 30.8, $^4J_{FF}$ 21.9, F6); *m/z* (EI) 290 (MH^{2+}, 3 %), 289 (MH^+, 7 %), 288 (M^+, 50 %), 223 (88 %), 77 (100 %) 51 (72 %) and as compared to product data which was purified *via* silica flash column chromatography (using hexane : ethyl acetate 2:1 as the eluent): Found: C 45.73, H 2.47, N 9.73; $C_{11}H_7F_3N_2O_2S$ Requires: C 45.84, H 2.45, N 9.72 %; and **3,5,6-trifluoro-4-(phenylsulfonyl)pyridin-2-amine** as a yellow solid (1.0 g, 35%); mp 160–162ºC; ν_{max} (cm^{-1}) 3328 and 3476 (NH_2), 1160, 1249, 1450; δ_H (400 MHz, $CDCl_3$) 4.75 (2H, b, NH_2) 7.61 (2H, tm,

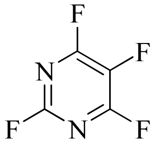
${}^3J_{HH}$ 7.8, C3′), 7.73 (1H, tt, ${}^3J_{HH}$ 7.5, ${}^4J_{HH}$ 1.8, C4′), 8.10 (2H, d, ${}^3J_{HH}$ 7.8, C2′); δ_C (176 MHz, $CDCl_3$) 128.2 (2C, s, C2’), 129.1-129.4 (1C, m, C2 or C4), 129.6 (2C, s, C3’), 131.8 (1C, dd, ${}^1J_{CF}$ 261.1, ${}^2J_{CF}$ 31.7, C5), 135.0 (1C, s, C4’), 137.8 (1C, ddd, ${}^1J_{CF}$ 263.2, ${}^3J_{CF}$ 5.0, ${}^4J_{CF}$ 2.1, C3), 1401 (1C, s, C1’), 142.1–142.4 (1C, m, C4 or C2), 146.1 (ddd, ${}^1J_{CF}$ 239.3, ${}^2J_{CF}$ 16.6, ${}^4J_{CF}$ 3.3, C6); δ_F (376 MHz, $CDCl_3$) -89.6 (1F, dd, ${}^3J_{FF}$ 32.3, ${}^4J_{FF}$ 24.6, F5), -139.4 (1F, dd, ${}^3J_{FF}$ 32.3, ${}^5J_{FF}$ 11.1, F6), -153.8 (1F, dd, ${}^4J_{FF}$ 24.6, ${}^5J_{FF}$ 11.1, F3); *m/z* (EI) 290 (MH^{2+}, 6 %), 289 (MH^+, 12 %), 288 (M^+, 72 %), 223 (8 %), 77 (100 %) 51 (77 %) and as compared to product data which was purified *via* silica flash column chromatography (using hexane : ethyl acetate 2:1 as the eluent): Found: C 45.22, H 2.43, N 9.62; $C_{11}H_7F_3N_2O_2S$ Requires: C 45.84, H 2.45, N 9.72 %;

To confirm connectivity, a small amount of **3,5,6-trifluoro-4-(phenylsulfonyl)pyridin-3-amine** was re-crystallized from hexane to afford light yellow crystals to obtain a crystal structure:



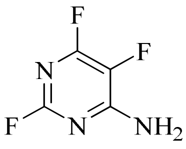
7.4.3 Amino Pyrimidine Synthesis

Tetrafluoropyrimidine

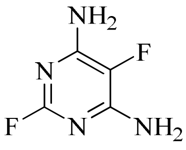


A stainless steel, oven dried autoclave (0.5 dm^3) was charged with flame dried potassium fluoride (this was also put under vacuum for 1 h) (200 g, 3.4 mol) and tetrachloropyrimidine (50 g, 0.23 mol). The air was evacuated from the autoclave using a high pressure pump, and then it was heated to 480ºC for 19 hours. After this time, the autoclave was allowed to cool to 200ºC and the gaseous fluorinated products were removed under reduced pressure and condensed into a Young's tap-equipped vessel. The crude product (yellow oil) was purified *via* distillation to yield **tetrafluoropyrimidine** (25.8 g, 75 %) as a colourless oil; pb 80–81ºC (lit. value 80–81ºC)[205]; δ_C (176 MHz, $CDCl_3$) 132.6 (1C, dtd, $^1J_{CF}$ 249.0, $^2J_{CF}$ 24.0, $^4J_{CF}$ 10.2, C5), 154.1 (1C, dtd, $^1J_{CF}$ 222.0, $^3J_{CF}$ 21.2, $^4J_{CF}$ 5.0, C2), 162.3 (2C, dm, $^1J_{CF}$ 256.0, C4); δ_F (376 MHz, $CDCl_3$) -47.15 (1F, m, F2), -73.6 (2F, m, F4), -171.4 (1F, m, C5); *m/z* 152 (M^+, 100 %), 133 (28 %); and as compared to literature data[205]

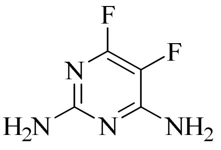
2,5,6-trifluoropyrimidin-4-amine



2,5-difluoropyrimidine-4,6-diamine

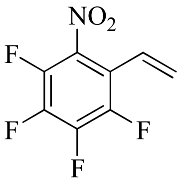


5,6-difluoropyrimidine-2,4-diamine



Tetrafluoropyrimidine (2.0 g, 13.2 mmol) was weighed into a 100 mL round bottomed flask, which was then sealed and purged with argon. Ammonium hydroxide (6.0 mL, 60.0 mmol) and THF (20 mL) were added, and the solution was mixed at room temperature for 22 hours. After this time, ^{19}F NMR indicated starting material was still present. The reaction mixture was refluxed for 2 hours, after which time ^{19}F NMR indicated no starting material remained. The reaction mixture was quenched with 20 mL of distilled water, and extracted with 3 × 20 mL DCM. The organic extracts were then dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as yellow solid. Purification *via* silica flash column chromatography (using a mixture of hexane : ethyl acetate 1:1 as the eluent) yielded **2,5,6-trifluoropyrimidin-4-amine** (0.52 g, 27 %) as a white solid; mp 182–184ºC (lit. value 156–157ºC)[206]; ν_{max} (cm^{-1}) 3205 and 3382 (NH_2); δ_H (400 MHz, CD_3OD) 4.81 (2H, b, N*H*$_2$); δ_C (176 MHz, CD_3OD) 127.26 (1C, ddd, $^1J_{CF}$ 249.3, $^2J_{CF}$ 22.5, $^4J_{CF}$ 8.5, C5), 154.9 (1C, ddd, $^1J_{CF}$ 214.5, $^3J_{CF}$ 21.6, $^4J_{CF}$ 3.1, C2), 156.4 (1C, ddd, $^1J_{CF}$ 243.9, $^2J_{CF}$ 20.0, $^4J_{CF}$ 10.2, C4), 158.4–158.8 (1C, m, C6); δ_F (376 MHz, CD_3OD) -51.6 (1F, d, $^3J_{FF}$ 24.9, F5), -90.8 (1F, $^4J_{FF}$ 16.5, F1), -182.3 (1F, dd, $^3J_{FF}$ 24.9, $^4J_{FF}$ 16.5, F4); *m/z* (EI) 150 (MH^+, 14 %), 149 (M^+, 100 %); and **2,5-difluoropyrimidine-4,6-diamine** (0.65 g, 34 %) as a white solid; mp 225–227ºC (lit. value 232-233ºC)[205]; ν_{max} (cm^{-1}) 3145 and 3303 and 3485 (N*H*$_2$); δ_H (400 MHz, CD_3OD) 4.92 (2H, b, N*H*$_2$); δ_C (176 MHz, CD_3OD) 127.5 (1C, dd, $^1J_{CF}$ 232.7, $^4J_{CF}$ 6.9, C5), 153.1 (2C, dd, $^2J_{CF}$ 19.6, $^3J_{CF}$ 12.5, C4), 156.4 (1C, dd, $^1J_{CF}$ 207.5, $^4J_{CF}$ 2.3, C2); δ_F (376 MHz, CD_3OD) -54.7 (1F, d, $^5J_{FF}$ 12.0, F1), -185.2 (1F, d, $^5J_{FF}$ 12.0, F5); *m/z* (EI) 147 (MH^+, 15 %), 146 (M^+, 53 %), 119 (100 %); and **5,6-difluoropyrimidine-2,4-diamine** (0.31 g, 16 %) as a white solid; mp 142–144ºC; 3184 and 3341 and 3422 and 3528 (NH_2); δ_H (400 MHz, CD_3OD) 4.85 (2H, b, N*H*$_2$), 5.41 (2H, b, N*H*$_2$); δ_C (176 MHz, CD_3OD) 125.2 (1C, dd, $^1J_{CF}$ 239.8, $^2J_{CF}$ 24.4, C5/6), 158.2 (1C, dd, $^1J_{CF}$ 237.5, $^2J_{CF}$ 10.5, C5/6), 159.1 (1C, dd, $^3J_{CF}$ 10.3, $^4J_{CF}$ 6.8, C1), 159.7 (1C, dd, $^2J_{CF}$ 21.3, $^3J_{CF}$ 5.5, C4); δ_F (376 MHz, CD_3OD) -92.8 (1F, d, $^3J_{FF}$ 22.4, F5/6), -192.8 (1F, dd, $^3J_{FF}$ 22.4, F5/6); *m/z* (EI) 147 (MH^+, 9 %), 146 (M^+, 64 %), 119 (100 %) and all as compared to literature data[206]

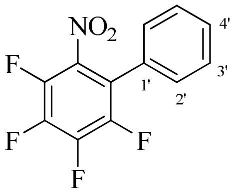
7.4.4 C-F Bond Activation



1,2,3,4-tetrafluoro-5-nitro-6-vinylbenzene

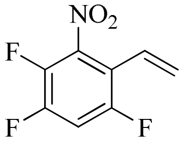
1,2,3,4,5-pentafluoro-6-nitrobenzene (0.1 g, 0.47 mmol), KF alumina (0.08 g, 1.30 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.03 g, 0.024 mmol) were all weighed into a clean, dry microwave vial (2–5 mL), which was then sealed and purged with argon. Degassed, dry DMF (2.0 mL) and then 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.09 mL, 0.52 mmol) were then added and the vial irradiated at 150ºC for 30 minutes. After this time fluorine NMR indicated a 100 % conversion of starting material. The reaction mixture was place through a silica plug using acetone as the eluent, and the organic extract was then concentrated under reduced pressure to give the crude product as a yellow liquid (still with DMF). Purification *via* silica flash column chromatography (using a mixture of hexane : dichloromethane 4:1 as the eluent) to give **1,2,3,4-tetrafluoro-5-nitro-6-vinylbenzene** as a pale yellow oil (0.071 g, 68 %); (Found: MH$^+$ 222.0171, $C_8H_3F_4NO_2$, Requires: MH$^+$ 222.0133); δ_H (400 MHz, $CDCl_3$) 5.80 (1H, d, $^3J_{HH}$ 11.7, H8), 5.95 (1H, d, $^3J_{HH}$ 17.8, H8), 6.44 (1H, dd, $^3J_{HH}$ 17.8, $^3J_{HH}$ 11.7, H7); δ_C (176 MHz, $CDCl_3$) 116.8 (1C, ddd, $^2J_{CF}$ 15.1, $^3J_{CF}$ 4.5, $^4J_{CF}$ 1.0, C6) 122.0 (1C, d, $^4J_{CF}$ 2.1, C8), 126.3 (1C, dd, $^3J_{CF}$ 8.9, $^4J_{CF}$ 1.3, C7), 134.3–134.7 (1C, m, C5), 139.5 (1C, dm, $^1J_{CF}$ 259.5, C-F), 140.7 (1C, dddd, $^1J_{CF}$ 259.5, $^2J_{CF}$ 13.4, $^3J_{CF}$ 4.7, $^4J_{CF}$ 2.8, C-F), 142.5 (1C, dddd, $^1J_{CF}$ 260.2, $^2J_{CF}$ 17.1, $^2J_{CF}$ 12.3, $^3J_{CF}$ 3.2, C-F), 145.2 (1C, dddm, $^1J_{CF}$ 255.5, $^2J_{CF}$ 11.6, $^3J_{CF}$ 4.7, C-F); δ_F (376 MHz, $CDCl_3$) -139.0 (1F, ddd, $^3J_{FF}$ 21.7, $^4J_{FF}$ 3.9, $^5J_{FF}$ 11.3, F1 or F4), -148.2 (1F, ddd, $^3J_{FF}$ 21.7, $^4J_{FF}$ 5.3, $^5J_{FF}$ 10.8, F4 or F1), -150.4 (1F, td, $^3J_{FF}$ 20.6, $^4J_{FF}$ 5.3, F2 or F3), -153.2 (1F, td, $^3J_{FF}$ 21.0, $^4J_{FF}$ 4.6, F3 or F2); *m/z* (EI) 222 (MH$^+$, 1 %), 221 (M$^+$, 8 %), 204 (M$^+$ - H_2O, 60 %), 191 (M$^+$ - NO, 100 %), 176 (M$^+$ - NO_2, 44 %)

2,3,4,5-tetrafluoro-6-nitrobiphenyl



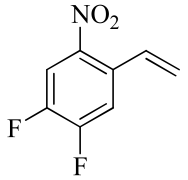
1,2,3,4,5-pentafluoro-6-nitrobenzene (0.1 g, 0.47 mmol), KF alumina (0.09 g, 1.3 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.034 g, 0.024 mmol) were all weighed into a clean, dry microwave vial (2–5 mL), which was then sealed and purged with argon. Degassed, dry DMF (2.0 mL) and then phenyl boronic acid (0.061 mL, 0.52 mmol) were then added and the vial irradiated at 120ºC for 15 minutes. After this time fluorine NMR indicated a 100 % conversion of starting material. The reaction mixture was place through a silica plug using acetone as the eluent, and the organic extract was then concentrated under reduced pressure to give the crude product as a dark oil (still with DMF). Purification *via* silica flash column chromatography (using a mixture of hexan:DCM 4:1 as the eluent) to give **2,3,4,5-tetrafluoro-6-nitrobiphenyl** as an off white solid (0.10 g, 80 %); δ_H (400 MHz, $CDCl_3$) 7.32 (2H, d, $^3J_{HH}$ 7.3, H2'), 7.46–7.51 (3H, m, H3' and H4'); δ_F (376 MHz, $CDCl_3$) -138.2 (1F, ddd, $^3J_{FF}$ 22.4, $^4J_{FF}$ 3.4, $^5J_{FF}$ 10.7, F2 or F5), -147.8 (1F, ddd, $^3J_{FF}$ 21.5, $^4J_{FF}$ 5.1, $^5J_{FF}$ 10.8, F5 or F2), -149.9 (1F, ddd, $^3J_{FF}$ 22.3, $^3J_{FF}$ 20.5, $^4J_{FF}$ 5.1, F3 or F4), -152.9 (1F, td, $^3J_{FF}$ 21.0, $^4J_{FF}$ 3.6, F4 or F3); *m/z* (EI) 272 (MH^+, 2 %), 271 (M^+, 10 %), 243 (64 %), 224 (70 %), 187 (100 %); and as compared to literature data[146]

1,2,5-trifluoro-3-nitro-4-vinylbenzene



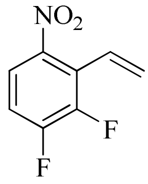
1,2,4,5-tetrafluoro-3-nitrobenzene (0.1 g, 0.51 mmol) KF alumina (0.08 g, 1.40 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.03 g, 0.026 mmol) were all weighed into a clean, dry microwave vial (2–5 mL), which was then sealed and purged with argon. Degassed, dry DMF (2.0 mL) and then 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.09 mL, 0.56 mmol) were then added and the vial irradiated at 150ºC for 30 minutes. After this time fluorine NMR indicated a ration of 1:1 product : starting material. The reaction was then irradiated for another 30 minutes at 150ºC, which did not give any more conversion of starting material. The reaction mixture was place through a silica plug using acetone as the eluent, which was then concentrated under reduced pressure to give the crude product as a yellow liquid (still with DMF). Purification *via* silica flash column chromatography (using a mixture of hexane : dichloromethane 4:1 as the eluent) to give **1,2,5-trifluoro-3-nitro-4-vinylbenzene** as a pale yellow oil (0.05 g, 49 %); (Found: M^+ 203.0183, $C_8H_4F_3NO_2$, Requires: M^+ 203.0194); δ_H (400 MHz, $CDCl_3$) 5.72 (1H, d, $^3J_{HH}$ 11.7, H8), 5.90 (1H, d, $^3J_{HH}$ 17.8, H8), 6.42 (1H, dd, $^3J_{HH}$ 17.8, $^3J_{HH}$ 11.7, H7), 7.15 (1H, td, $^3J_{HF}$ 9.7, $^4J_{HF}$ 6.5, H6); δ_C (176 MHz, $CDCl_3$) 108.0 (1C, dd, $^2J_{CF}$ 28.8, $^2J_{CF}$ 20.8, C6), 116.2 (1C, ddd, $^2J_{CF}$ 18.7, $^3J_{CF}$ 4.8, $^4J_{CF}$ 1.9, C4), 122.5 (1C, s, C8), 125.0 (1C, dd, $^3J_{CF}$ 9.0, $^4J_{CF}$ 1.8, C7), 139.6 (1C, m, C3), 139.8 (1C, ddd, $^1J_{CF}$ 257.2, $^2J_{CF}$ 16.2, $^4J_{CF}$ 4.8, C2), 148.8 (1C, dm, $^1J_{CF}$ 256.5, C1), 155.1 (1C, ddd, $^1J_{CF}$ 253.7, $^3J_{CF}$ 9.7, $^4J_{CF}$ 3.5, C5); δ_F (376 MHz, $CDCl_3$) -113.5 (1F, ddd, $^3J_{FH}$ 14.0, $^4J_{FF}$ 4.4, $^5J_{FF}$ 9.9, F5), -131.0 (1F, ddd, $^3J_{FF}$ 14.0, $^3J_{FH}$ 9.9, $^4J_{FF}$ 4.4, F1), -151.7 (1F, ddd, $^3J_{FF}$ 14.0, $^3J_{FH}$ 4.4, $^4J_{FF}$ 9.9, F2); *m/z* (EI) 203 (M^+, 17 %), 186 (M^+ - H_2O, 42 %), 174 (M^+ - NO, 72 %), 158 (M^+ - NO_2, 36 %), 145 (100 %)

1,2-difluoro-4-nitro-5-vinylbenzene



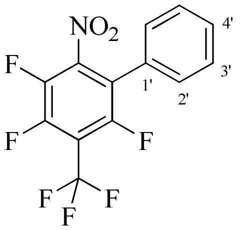
1,2,4-trifluoro-5-nitrobenzene (0.1 g, 0.56 mmol), KF alumina (0.09 g, 1.54 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.03 g, 0.028 mmol) were all weighed into a clean, dry microwave vial (2–5 mL), which was then sealed and purged with argon. Degassed, dry DMSO (2.0 mL) and then 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.09 mL, 0.56 mmol) were then added and the vial irradiated at 150ºC for 60 minutes. After this time fluorine NMR indicated a ratio of 1.0 : 0.8 (product : stating material). The reaction mixture was place through a silica plug using acetone as the eluent, and the organic extract was then concentrated under reduced pressure to give the crude product as a yellow oil. Purification *via* silica flash column chromatography (using a mixture of hexane : dichloromethane 4:1 as the eluent) gave **1,2-difluoro-4-nitro-5-vinylbenzene** as a pale yellow oil (0.054 g, 52 %); (Found: M^+ 185.0251, $C_8H_5F_2NO_2$, Requires: M^+ 185.0288); δ_H (400 MHz, $CDCl_3$) 5.55 (1H, d, $^3J_{HH}$ 10.9, H8), 5.70 (1H, d, $^3J_{HH}$ 17.3, H8), 7.18 (1H, ddm, $^3J_{HH}$ 17.3, $^3J_{HH}$ 10.9, H7), 7.42 (1H, dd, $^3J_{HF}$ 10.6, $^4J_{HF}$ 7.6, H3/6), 7.90 (1H, dd, $^3J_{HF}$ 9.7, $^4J_{HF}$ 7.2, H6/3); δ_C (176 MHz, $CDCl_3$) 115.1 (1C, dd, $^2J_{CF}$ 21.8, $^3J_{CF}$ 2.2, C3/6), 117.3 (1C, d, $^3J_{CF}$ 9.6, C5), 120.5 (1C, s, C8), 131.5 (1C, s, C7), 132.2 (1C, dd, $^2J_{CF}$ 21.8, $^3J_{CF}$ 2.2, C6/3), 142.8–143.2 (1C, m, C4), 149.1 (1C, dd, $^1J_{CF}$ 254.8, $^2J_{CF}$

14.0, C1/2), 153.4 (1C, dd, $^1J_{CF}$ 258.8, $^2J_{CF}$ 12.7, C2/1); δ_F (376 MHz, $CDCl_3$) -127.9 (1F, ddd, $^3J_{FF}$ 21.3, $^3J_{FH}$ 10.4, $^4J_{FH}$ 7.4, F1/2), -134.5–-134.5 (1F, m, F2/1); *m/z* (EI) 185 (M^+, 5 %), 168 (M^+ - H_2O, 78 %), 156 (M^+ - NO, 86 %), 140 (M^+ - NO_2, 38 %), 127 (88 %), 101 (100 %), 63 (94 %)



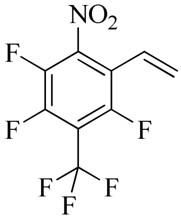
1,2-difluoro-4-nitro-3-vinylbenzene

1,2,3-trifluoro-4-nitrobenzene (0.1 g, 0.56 mmol), KF alumina (0.09 g, 1.54 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.03 g, 0.028 mmol) were all weighed into a clean, dry microwave vial (2–5 mL), which was then sealed and purged with argon. Degassed, dry DMSO (2.0 mL) and then 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.09 mL, 0.56 mmol) were then added and the vial irradiated at 150ºC for 30 minutes. After this time fluorine NMR indicated a 100 % conversion of starting material. The reaction mixture was place through a silica plug using acetone as the eluent, and the organic extract was then concentrated under reduced pressure to give the crude product as a dark red oil. Purification *via* silica flash column chromatography (using a mixture of hexane : dichloromethane 4:1 as the eluent) gave **1,2-difluoro-4-nitro-3-vinylbenzene** as a pale red oil (0.077 g, 74 %); (Found: M^+ 185.0239, $C_8H_5F_2NO_2$, Requires: M^+ 185.0288); δ_H (400 MHz, $CDCl_3$) 5.80 (1H, dm, $^3J_{HH}$ 11.7, H8), 5.86 (1H, ddt, $^3J_{HH}$ 17.8, $^5J_{HF}$ 2.2, $^6J_{HF}$ 0.8, H8), 6.77 (1H, dd, $^3J_{HH}$ 17.8, $^3J_{HH}$ 11.7, H7), 7.20 (1H, dd, $^3J_{HF}$ 16.4, $^3J_{HH}$ 8.9, H6), 7.77 (1H, ddd, $^3J_{HH}$ 9.2, $^4J_{HF}$ 4.5, $^5J_{HF}$ 2.1, H5); δ_C (176 MHz, $CDCl_3$) 115.4 (1C, d, $^2J_{CF}$ 19.0, C3), 120.3 (1C, s, C8), 121.4 (1C, dd, $^3J_{CF}$ 7.9, $^4J_{CF}$ 4.4, C5), 127.5 (1C, d, $^2J_{CF}$ 18.0, C6), 133.7 (1C, s, C7), 140.1–141.0 (1C, m, C4), 147.2 (1C, ddm, $^1J_{CF}$ 252, $^2J_{CF}$ 13.8, C-F), 152.0 (1C, ddm, $^1J_{CF}$ 258, $^2J_{CF}$ 14.0, C-F); δ_F (376 MHz, $CDCl_3$) -127.5 (1F, ddd, $^3J_{FF}$ 20.0, $^3J_{FH}$ 8.5, $^4J_{FH}$ 4.5, F1), -136.2 (1F, dd, $^3J_{FF}$ 20.0, $^4J_{FH}$ 4.5, F2); *m/z* (EI) 185 (M^+, 5 %), 168 (M^+ - H_2O, 64 %), 156 (M^+ - NO, 80 %), 140 (M^+ - NO_2, 46 %), 127 (74 %), 63 (100 %)



2,4,5-trifluoro-6-nitro-3-(trifluoromethyl)biphenyl

1,2,4,5-tetrafluoro-3-nitro-6-(trifluoromethyl)benzene (0.25 g, 0.95 mmol), KF alumina (0.15 g, 2.62 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.055 g, 0.048 mmol) were all weighed into a clean, dry microwave vial (2–5 mL), which was then sealed and purged with argon. Degassed, dry DMF (2.0 mL) and then phenyl boronic acid (0.09 mL, 0.56 mmol) were then added and the vial irradiated at 120ºC for 30 minutes. After this time fluorine NMR indicated a 100 % conversion of starting material. The reaction mixture was place through a silica plug using acetone as the eluent, and the organic extract was then concentrated under reduced pressure at 100ºC to give the crude product as a dark red oil. Purification *via* silica flash column chromatography (using a mixture of hexane : dichloromethane 4:1 as the eluent) gave **2,4,5-trifluoro-6-nitro-3-(trifluoromethyl)biphenyl** as yellow crystals (0.21 g, 70 %) (Found: C 48.94, H 1.88, F 35.14, N 4.29, O 9.72); $C_{13}H_5F_6NO_2$ Requires: C 48.62, H 1.57, F 35.49, N 4.36, O 9.96 %); δ_H (400 MHz, $CDCl_3$) 7.37 (1H, tt, $^3J_{HH}$ 7.3, $^4H_{HH}$ 1.2, H4′), 7.47 (2H, t, $^3J_{HH}$ 7.6, H3′), 7.62 (2H, dd, $^3J_{HH}$ 8.3, $^4H_{HH}$ 1.2, H2′); δ_C (176 MHz, $CDCl_3$) 111.4–112.5 (1C, m, C3), 120.7 (1C, dm, $^1J_{CF}$ 277.2, *C*F$_3$), 121.5 (1C, ddd, $^2J_{CF}$ 23.4, $^3J_{CF}$ 5.1, $^4J_{CF}$ 1.8, C1), 126.4 (1C, s, C1′), 129.3 (1C, s, ArC), 129.4 (1C, s, ArC), 130.6 (1C, s, ArC), 140.1 (1C, ddd, $^1J_{CF}$ 260.6, $^2J_{CF}$ 16.0, $^3J_{CF}$ 5.3, C4/5), 141.9–142.6 (1C, m, C6) 147.9 (1C, ddm, $^1J_{CF}$ 273.7, $^2J_{CF}$ 16.0, C4/5), 152.4 (1C, dm, $^1J_{CF}$ 260.2, C2); δ_F (376 MHz, $CDCl_3$) -57.2 (3F, t, $^4J_{FF}$ 23.1, C*F*$_3$), -113.4 (1F, qd, $^4J_{FF}$ 14.1, $^3J_{FF}$ 22.2, F4/2), -130.8 (1F, p, $^4J_{FF}$ 23.4, F2/4), -148.7 (1F, dd, $^3J_{FF}$ 21.5, $^5J_{FF}$ 14.1, F5); *m/z* (EI) 322 (MH^+, 3 %), 321 (M^+, 25 %), 304 (M^+ -H_2O, 22 %), 292 (100 %), 276 (M^+ -NO_2, 28 %), 265 (64 %), 206 (84 %)



1,2,4-trifluoro-6-nitro-3-(trifluoromethyl)-5-vinylbenzene

1,2,4,5-tetrafluoro-3-nitro-6-(trifluoromethyl)benzene (0.10 g, 0.38 mmol), KF alumina (0.06 g, 1.05 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.044 g, 0.038 mmol) were all weighed into a clean, dry microwave vial (2–5 mL), which was then sealed and purged with argon. Degassed, dry DMSO (2.0 mL) and then 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.06 g, 0.42 mmol) were then added and the vial irradiated at 150ºC for 30 minutes. The reaction mixture was place through a silica plug using acetone as the eluent, and the organic extract was then concentrated under reduced pressure to give the crude product as a dark red oil. Purification *via* silica flash column chromatography (using a mixture of hexane : dichloromethane 19:1 as the eluent) gave **1,2,4-trifluoro-6-nitro-3-(trifluoromethyl)-5-vinylbenzene** as a pale yellow oil (0.057 g, 54 %); (Found: M^+ 271.1301, $C_9H_3F_6NO_2$, Requires: M^+ 271.0068); δ_H (400 MHz, $CDCl_3$) 5.81 (1H, d, $^3J_{HH}$ 11.8, H8), 5.94 95 (1H, d, $^3J_{HH}$ 17.8, H8), 6.44 (1H, dd, $^3J_{HH}$ 17.8, $^3J_{HH}$ 11.8, H7); δ_C (176 MHz, $CDCl_3$) 109.4–111.0 (1C, m, C3), 119.4 (1C, dm, $^1J_{CF}$ 270.8, *C*F$_3$), 120.9 (1C, ddm, $^2J_{CF}$ 22.7, $^3J_{CF}$ 4.9, C1), 125.3 (1C, s, C1′), 129.7 (1C, s, ArC), 130.8 (1C, s, ArC), 131.3 (1C, s, ArC), 141.0 (1C, ddm, $^1J_{CF}$ 270.1, $^2J_{CF}$ 16.0, C2/4/5), 141.5–142.0 (1C, m, C6), 145.3 (1C, dm, $^1J_{CF}$ 264.4, C2/4/5), 150.9 (1C, dm, $^1J_{CF}$ 263.2, C2); δ_F (376 MHz, $CDCl_3$) -57.3 (3F, t, $^4J_{FF}$ 22.3, C*F*$_3$), -114.0 (1F, qd, $^4J_{FF}$ 13.8, $^3J_{FF}$ 22.4, F2), -131.2–-131.5 (1F, m, F1 or F4), -149.1 (1F, dd, $^4J_{FF}$ 13.8, $^3J_{FF}$ 21.4, F1), *m/z* (EI) 271 (M^+, 2 %), 154 (MH^+ - H_2O, 44 %), 242 (MH^+ - NO, 86 %), 140 (MH^+ - NO_2, 38 %)

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