Synthesis of aryl-CHFCF3 systems.

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A thesis entitled

Synthesis of aryl-$CHFCF_3$ systems.

Submitted by

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Declaration

This work presented within this thesis was carried out at Durham University between October 2017 and August 2018. This thesis is the work of the author, except where acknowledged by reference and has not been submitted for any other degree.

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Contents

Chapter 1: Organofluorine chemistry and trifluoromethyl-containing aromatic systems 1

1.1 Organofluorine chemistry 1

1.1.1 Effect of fluorine on molecular properties 1

1.2 Organofluorine systems in pharmaceuticals 5

1.3 Trifluoromethyl derivatives in organic chemistry 8

1.3.1 Synthesis of CF_3 groups by C-F bond formation 8

1.3.2 CF_3 nucleophilic insertion 10

1.3.3 CF_3 radical insertion 14

1.4 Trifluoromethoxy derivatives in organic chemistry 14

1.5 Pentafluoroethyl derivatives in organic chemistry 17

1.6 Synthesis of Ar-$CFHCF_3$ functional group 20

1.7 Synthesis of Ar-$CFHCF_2CF_3$ functional group 22

1.8 Conclusions 23

Chapter 2 Synthesis and Properties of $ArCHFCF_3$ systems 24

2.1 Aims and Approach: 24

2.2 Results and Discussion 25

2.2.1 Reaction of benzaldehyde with $TMSCF_3$ 25

2.2.3 Conformation of $–CFHCF_3$ units 35

2.2.5 Synthesis of $ArCHOHCF_2CF_3$ derivatives 43

2.2.7 Formation of $ArCFC=CFCF_3$ derivatives 50

2.3 Conclusions 53

Chapter 3: Experimental 54

3.1 General 54

3.2 Synthesis of 1-phenyl-1,2,2,2-trifluoroethanol derivatives: 55

3.3 Synthesis of 1-phenyl-1,2,2,2-tetrafluoroethane derivatives (3a-j, l): 61

3.4 Reaction of fluorinated aromatics with nitronium tetrafluoroborate: 67

3.5 Synthesis of 2,2,3,3,3-pentafluoroaryl derivatives: 69

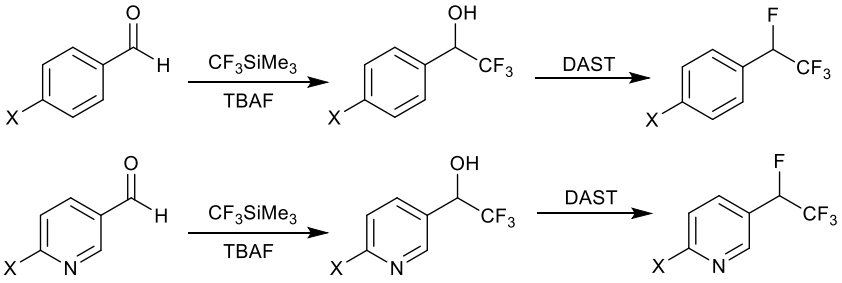
3.6 Synthesis of 1-aryl-1,2,2,3,3,3-hexafluoropropane derivates (3k&m): 70

3.7 Dehydrofluorination reactions (4a&m): 71

Chapter 4: Overall References 81

Abstract

The fluorine-containing functional group Ar-CFHCF$_3$ is potentially useful within the pharmaceutical, agrochemical and polymer industries if synthetic methodology is available for the synthesis of these systems. Here, a new general synthetic pathway for the synthesis of 1-aryl-1,2,2,2-tetrafluoroethanes starting from either benzaldehyde or 3-pyridinecarboxaldehyde derivatives is presented.



Reactions of aldehydes with CF_3SiMe_3 and a catalyst of TBAF (tetrabutylammonium fluoride) and then DAST (diethylaminosuphur trifluoride) were generally very efficient for a range of substrates bearing electron donating/ withdrawing substituents on the aromatic ring.

Chapter 1: Organofluorine chemistry and trifluoromethyl-containing aromatic systems

1.1 Organofluorine chemistry

Organofluorine chemistry is focussed on organic molecules that contain at least one single bond between a carbon and a fluorine atom. The addition of fluorine to an organic molecule to replace a hydrogen atom does not have a major steric effect because the van der Waals radius of a fluorine atom (1.47 Å) is between the sizes of a hydrogen atom (1.09 Å) and an oxygen atom (1.52 Å). Additionally, the C-F bond length (1.35 Å) is between that of the C-H (1.09 Å) and C-O (1.43 Å) bond lengths. On the other hand, there is a large electrostatic effect on a molecule following replacement of H and F because fluorine is the most electronegative element (on the Pauling scale of electronegativities F = 4.0, H = 2.1 and O = 3.5). This effect would be greatest when the addition of a fluorine atom is to a non-polar molecule or the non-polar region in a larger system[1]. The changes in molecular properties caused by the presence of C-F bonds compared to their C-H analogues can significantly change chemical, biological and physical properties, giving rise to unusual and valuable systems. Consequently, next we will discuss further the effect of fluorine atoms on molecular properties and the use of fluorinated systems in pharmaceutical applications.

1.1.1 Effect of fluorine on molecular properties

1.1.1.1 Effect of fluorine on inter- and intra-molecular interactions

Adding fluorine to organic molecules can influence intramolecular or intermolecular interactions. For intramolecular interactions, fluorine causes a decrease in polarity of nearby polar covalent bonds between two bonded atoms that have a difference in electronegativities between 0.5 - 1.9, so that the electron density between those two atoms is shifted towards the more polar atom of that covalent bond (fig. 1).

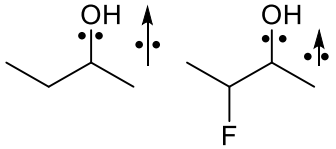


Figure 1-the effect of fluorine on nearby polar groups within a molecule[2-3]

Alongside this, fluorine can increase intramolecular forces (between other bonded atoms) due to high fluorine electronegativity, which slightly changes the polarity of some nonpolar covalent bonds and makes them slightly polar (fig. 2).

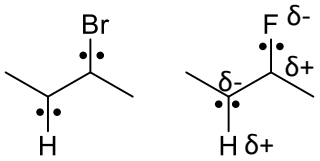


Figure 2- the effect of fluorine on nearby non-polar covalent bonds[4-5]

In terms of intermolecular bonding, it is possible for fluorine to be involved in hydrogen bonding (C-F···H) due to the difference of electronegativities between H and F. However, fluorine can only be involved in weak hydrogen bonding as, unlike oxygen and nitrogen, its high electronegativity means it has poor polarizability. Thus, organofluorine moieties are hydrogen acceptors and bad donors. Furthermore, fluorine will reduce the maximum potential energy of intermolecular London dispersion forces as there is a smaller chance and smaller potential energy of a temporary induced dipole because fluorine is the least polarizable element.

It is possible for fluorine to both increase and decrease dipole-dipole interactions of a molecule. Addition of fluorine to a non-polar molecule can induce such dipole-dipole interactions as the C-F bond contains a large dipole. Fluorine can increase a pre-existing dipole-dipole interaction when it is added to a molecule already containing a polar group (e.g. OH, NH or Cl). Furthermore, fluorine can increase such interactions, and even make a molecule appear more polar, when fluorine is added at the opposite end of a molecule containing an electropositive element such as silicon or phosphorus. However, when fluorine is attached to the same or adjacent carbon to an element with a lower electronegativity than carbon, then the dipole-dipole will be reduced and may even be lost completely. These effects show that a C-F bond can bring about large charge-dipole interactions even when hydrogen bonding is not likely.[1]

1.1.1.2 Carbon-Fluorine bonds

The high electronegativity of fluorine affects the bonding interactions of a molecule and has direct influence on the reactivity of a C-F bond. The C-F bond is highly polarized

leading to a low lying σ* orbital and fluorine is a poor π donor so the formation of a $C=F^+$ system is highly unlikely (fig. 3).

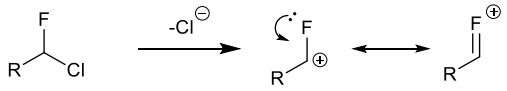


Figure 3- Unlikely formation of the $C=F^+$ system

The C-F bond has the highest bond dissociation energy (105.4 kcal mol^{-1}) of all single covalent bonds to carbon and, this effect is primarily seen in the high stability of many fluoropolymers.[1]

Since the C-F bond is very strong, F^- is a poor leaving group in S_N2 reactions. F^- is not formed in this type of reaction because of the almost ionic-like C-F bond. However, there is one type of substitution reaction that is possible and that is aromatic nucleophilic substitution (fig. 4). Fluorine stabilises the carbanionic intermediate and leaves as fluoride to allow the aromatic ring to reform. Also, one consistently possible way for F^- to be a leaving group is via an $E1_{CB}$ process to form an alkene. A base must cleave the beta-hydrogen atom to form the carbanionic intermediate which is stabilised by fluorine. This will eventually lead to the irreversible loss of the fluoride ion.[1,6]

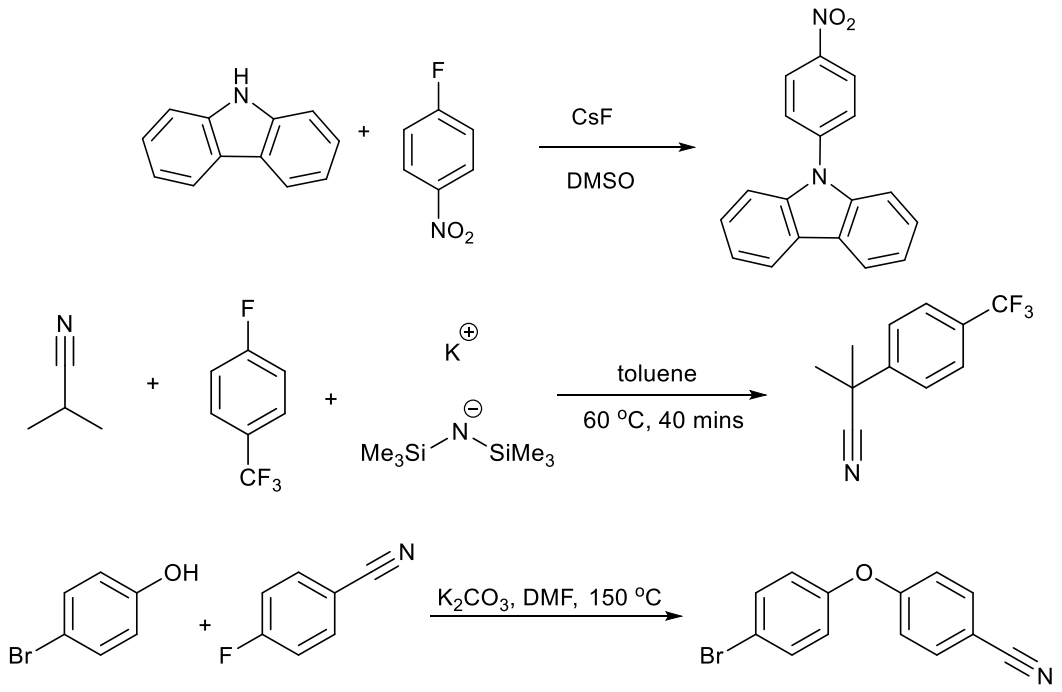


Figure 4- Examples of aromatic nucleophilic substitution with fluoride as the leaving group[7,8,9]

1.1.1.3 The effects of fluorine on lipophilicity

Lipophilicity is the relative solubility of an unionized compound between organic and aqueous phases (i.e. octanol and water) at equilibrium. This is expressed as the partition coefficient (log *P*) between octanol and water. Lipophilicity can be affected by pH especially when a molecule contains ionizable groups (i.e. OH, NH_2) and this can be quantified by the distribution coefficient (log *D*) which measures log *P* at differing pH values.[10] Pharmaceutical molecules need to pass through cell membranes into the lipid core and then not become trapped in it. This is part of the passive transport for orally-administrated drugs which are absorbed and distributed throughout the body. For effective drugs, molecules cannot have a log *P* > 5 otherwise there would probably be poor absorption. This comes from the Lipinski "rule of 5"[10]. The poor absorption would mean that the molecule is not effective at getting through the cell membrane because it is too soluble in water. Fluorination generally leads to an increase in lipophilicity, but not always. Fluorination on an aromatic ring or adjacent to a π-system will increase the lipophilicity because of the low polarizability of the C-F bond. In saturated alkyl groups, a decreased lipophilicity is observed when it undergoes monofluorination or trifluoromethylation.[10,11,12]

A problem for many drugs is their metabolic oxidation by cytochrome P450 enzymes, thus decreasing lipophilicity. This means that molecules can, therefore, be easily excreted before it reaches its target and have its desired effect. To prevent this, the metabolically-liable sites can be blocked by fluorine substitution. Replacing a methyl or methoxy group with a fluorinated group can prevent this reaction. An example of this in practice is the antidepressant drug Rolipram, which was optimised by replacing methoxy and cyclopentoxide substituents with difluoromethoxy groups as well as protecting the para position on the phenyl ring with by a di(trifluoromethyl)methoxy group (fig. 5).

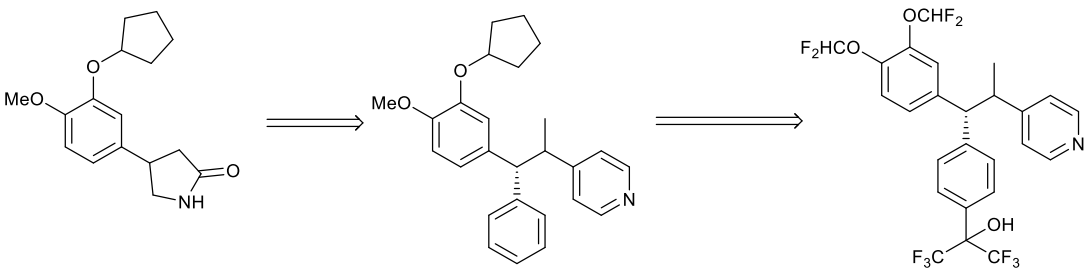


Figure 5- Lead optimisation of Rolipram, in part by fluorinations[11]

1.2 Organofluorine systems in pharmaceuticals

Fluorine has several uses in pharmaceuticals. Firstly, fluorine-containing groups can stabilise biologically active systems so they have a longer lifetime in the body. This improved bioavailability is caused by the strong C-F bond that allows a greater permeability throughout the body owing to a lower metabolic clearance rate.[11] Ezetimib, a plasma cholesterol lowering drug (fig. 6), had to be doubly fluorinated to prevent oxidation of both the pendant phenyl position and the methoxy group to increase its metabolic clearance.[11]

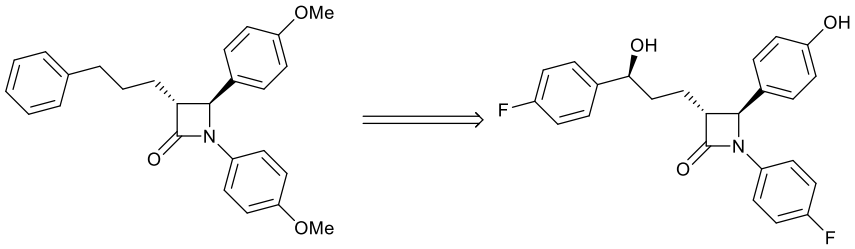


Figure 6- Lead optimisation of Ezetimib, in part by fluorination[11]

Thalidomide has both the useful *R*-enantiomer, which is used as a treatment of morning sickness, and the unwanted *S*-enantiomer which is a potent teratogen. However, the enantiomers can interconvert *in vivo*. This can be prevented by replacing the acidic hydrogen on the chiral centre with a fluorine which prevents epimerisation and so allows the useful *R*-enantiomer to be used as a treatment of morning sickness (fig. 7).

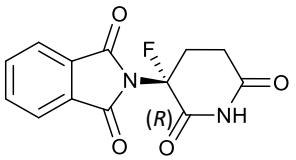


Figure 7- Structure of (3R)-fluorothalidomide[11]

Another use of fluorine is that ^{18}F can be used to track a drug's passage through the body via positron emission topography (PET) to assess the lifetime of the drug to help decide an appropriate dosage. ^{18}F glucose is a radiopharmaceutical (fig. 8) that is used in medical imaging and positron emission and is used to measure the uptake of glucose in tissues. This makes it a good compound for cancer detection because ^{18}F glucose accumulates in tumours.[11]

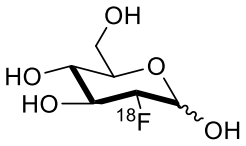


Figure 8- Structure of 2-Deoxy-2-[^{18}F]fluoro-D-glucose[11]

Aprepitant is an antiemetic compound that blocks the neurokinin 1 receptor. [^{18}F]SPA-RQC is used to track the passage of Aprepitant throughout the body (fig. 9).[11]

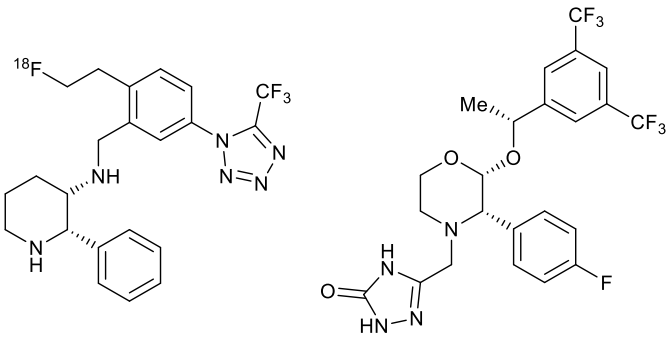


Figure 9- Structure of [^{18}F]SPA-RQC and Aprepitant[11]

The addition of the fluorine(s) can reduce the pKa of a drug which will make it more stable to acids within the body[13]. When 3-piperidinylindole, an antipsychotic, is fluorinated on its piperidine ring its pKa decreased from 10.4 to 8.5 which improved its bioavailability (fig. 10).

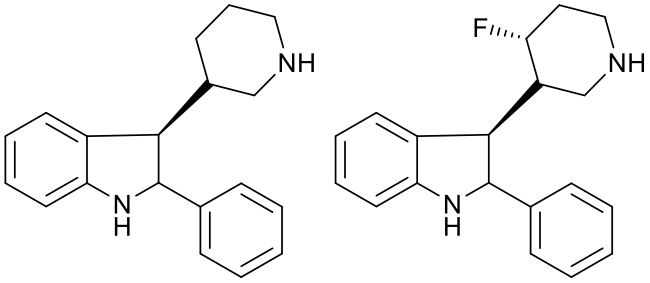


Figure 10- Reduced pKa on the fluorination of 3-piperidinylindole antipsychotic drugs[11]

Some examples of fluorine being used in drugs are shown in fig. 11: fludrocortisone,[14] which increases the bioactivity by an order of magnitude; lipitor[14-15] (atorvastatin), which is used as a cholesterol inhibitor by blocking the *in vivo* cholesterol biosynthesis; prevacid[16] (Lansoprazole) that is used for stomach acid/ ulcers via undergoing an acid catalysed rearrangement to produce a sulfenamide which reduces gastric acid secretion; and Efavirenz[16] is an anti-HIV agent that stops the reverse transcriptase enzyme which

prevents the HIV's genetic code. As well as molecules containing one C-F bond, many valuable pharmaceuticals contain CF_3 groups (CF_3, OCF_3, SCF_3).

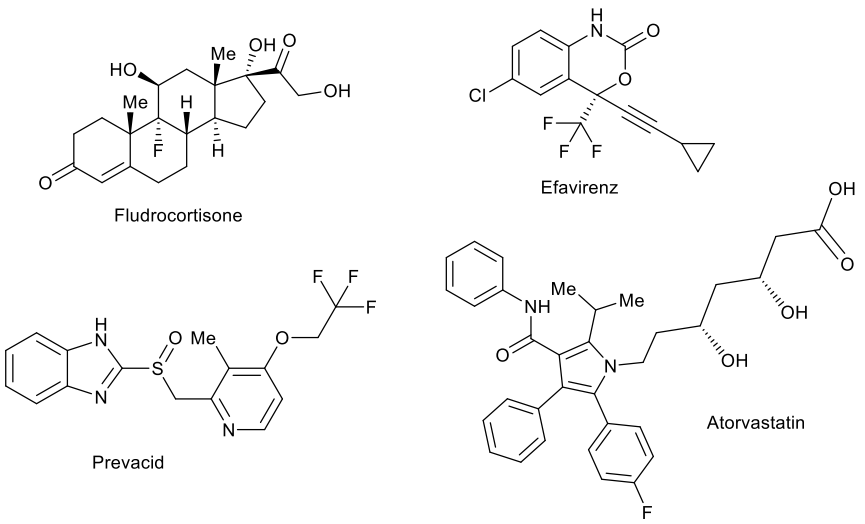


Figure 11- Examples of drugs containing at least one fluorine atom[14-16]

Trifluoromethyl groups are attached to many drug systems. When CF_3 is directly attached to an aromatic ring it is meta-directing in electrophilic substitution processes and has a long-range electron withdrawing effect because of the three fluorine atoms. Some important CF_3-containing pharmaceuticals are listed in figure 11.

The trifluoromethoxy group can lower molecular dielectric constant and surface tension properties.[17] Furthermore, it can promote *in vivo* uptake and transport in biological systems as well as promoting binding affinities because OCF_3 has an excellent lipophilicity. This is shown from the Hansch-Leo parameter π_x (OCF_3) = +1.04 and is further highlighted by having a better parameter than for CF_3 (π_x (CF_3) = +0.88).[17] Therefore, adding an OCF_3 group to a molecule will not decrease lipophilicity as much as a CF_3 group. Just like with the CF_3 group, the trifluoromethoxy group could be added to increase the metabolic stability of the pharmaceutical compound. Trifluoromethoxy has an even further long-range electron withdrawing effect then a trifluoromethyl group because of the additional oxygen. This group is present in the pharmaceutical compound Riluzole, which is used in the treatment of amyotrophic lateral sclerosis (fig. 12). A further example of a pharmaceutical molecule containing a trifluoromethoxy group is Sonidegib which is an anticancer agent (fig. 12).

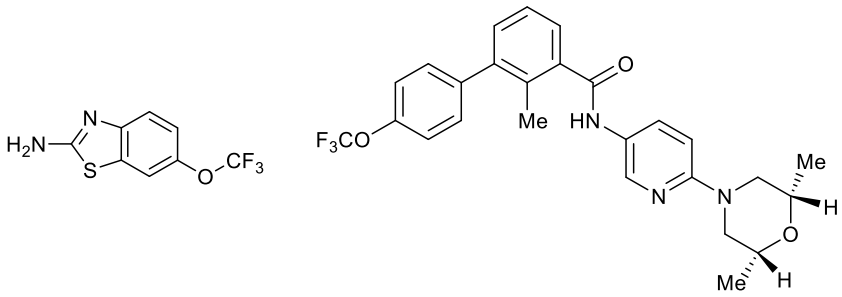


Figure 12- Structures of Riluzole and Sonidegib[17-18]

CF_2H groups can also make molecules more lipophilic as it is a hydrogen-bond donor and can act as a bioisostere for both alcohols and thiols.[19] The group has also been known to improve metabolic stability, solubility and oral bioavailability for many systems.[20]

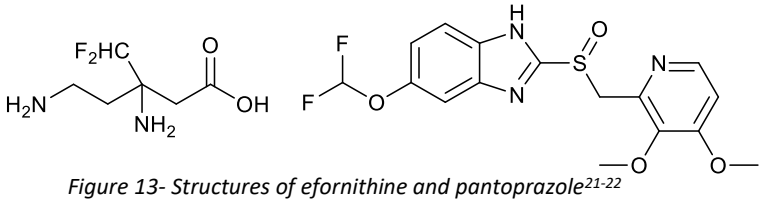


Figure 13- Structures of efornithine and pantoprazole[21-22]

Eflornithine Hydrochloride is used to treat African trypanosomiasis (sleeping sickness) as well as excessive hair growth (fig. 13). Pantoprazole is used as a proton pump inhibitor to treat certain stomach and esophagus problems (fig. 13). The synthesis of some of these fluorinated functional groups (CF_3, OCF_3) will be discussed in more detail in the following section.

1.3 Trifluoromethyl derivatives in organic chemistry

To synthesis a molecule containing a CF_3 group can be done via C-F bond formation or a trifluoromethylating agent. There are three types of trifluoromethylating agents which are electrophilic, nucleophilic, and free radical.[23,24,35]

1.3.1 Synthesis of CF_3 groups by C-F bond formation

To form trifluoromethyl compounds via C-F bond-forming reaction, synthesis generally starts with either an α,α,α-trihalide (i.e. Cl or Br) or a carboxylic acid containing-compound. The transfer of α,α,α-trihalides to trifluoromethyl compounds can be done on both aryl and alkyl systems using Swarts[23-24] reactions (SbF_3 + $SbCl_5$) or anhydrous hydrofluoric acid (HF). The Swarts reaction on α,α,α-trihalides is problematic because after each successive halogen exchange the ability of chlorine to act as a donor to the catalyst diminishes. To accommodate for this, high temperatures and pressures

are used. The alternative to a Swarts reaction is the use of HF, but this reagent is even more hazardous. Below are some examples of the applications of both these reagents, figure 14.

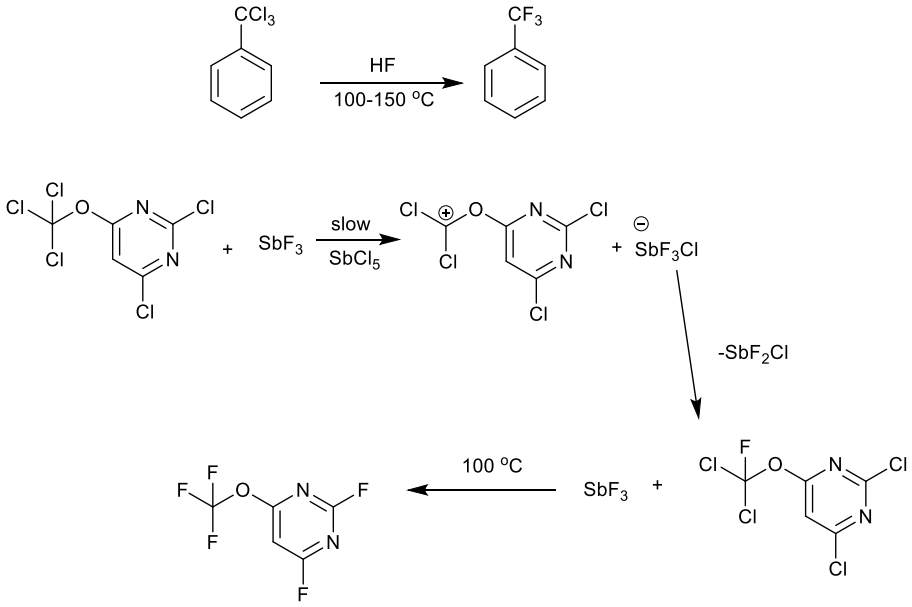


Figure 14- Examples of syntheses to form the -CF_3 functional group via C-F bond formaton[25-26]

Another CF_3-forming reagent is SF_4 (fig. 15). It is a deoxyfluorinating agent for carboxylic acids with a catalytic amount of HF. Initially the reaction forms the acid fluoride before being heated to complete the conversion of the carbonyl group.[27]

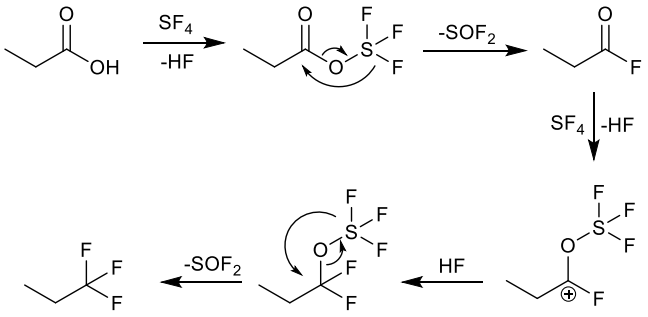


Figure 15- SF_4 mechanism and example synthesis for forming the -CF_3 functional group[27-28]

Again, SF_4 and HF are both hazardous and, therefore, can be unsafe for laboratory use or late-stage pharmaceutical molecule synthesis. A milder form of the SF_4 reagent is DAST (diethylamino sulfur trifluoride). However, DAST would only form the acid fluoride (figure 15) as it is quite unreactive in comparison to SF_4. DAST is a nucleophilic fluorinating agent which fluorinates by a S_N2 type pathway. The general uses of DAST are to replace a hydroxy group with a fluoride ion, to change an aldehyde to a geminal

difluoride group or to convert ketones to a difluoride functional group. When going from R-OH to R-F there is an inversion in the stereochemistry.

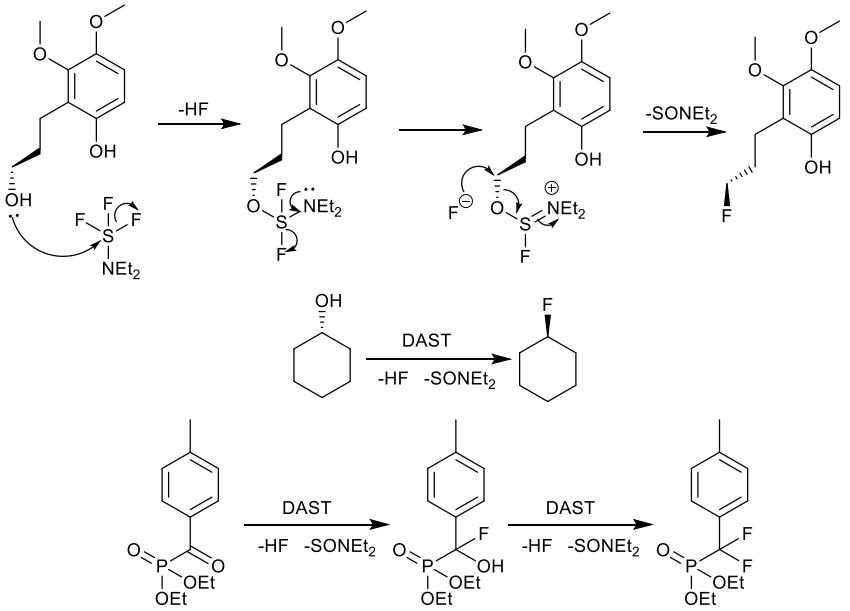


Figure 16- Example synthesises using the nucleophilic fluorinating agent DAST[29-31]

A few examples of where DAST has been used in synthesis are shown in figure 16: cyclohexanol,[29] diethyl (4-methylbenzoyl) phosphonate[30] and 3-(3,4-dimethoxyphenol)-1-propanol (a primary alcohol).[31] These reactions were carried out in DCM (Dichloromethane) and at temperatures starting from 0 °C to room temperature. This temperature range is used because DAST decomposes at 90 °C to give sulfur tetrafluoride and bis(dimethylamino)sulphur difluoride with the latter being explosive.[32-35]

1.3.2 CF_3 nucleophilic insertion

Trifluoromethylating agents are generally quite useful for laboratory use as well as late-stage functionalisation of complex pharmaceuticals, because they are not as hazardous and do not require harsh reaction conditions. Three useful trifluoromethylating agents are trifluoromethyl iodide,[36] trifluoroacetonitrile,[37] and sodium acetate.[38] Trifluoromethyl iodide requires a solvent of DMF (dimethyl formamide) and a light source to initiate the catalyst tetrakis(diethylamino) ethylene to form the trifluoromethyl anion *in situ* which can then attack the carbonyl group (fig. 17).

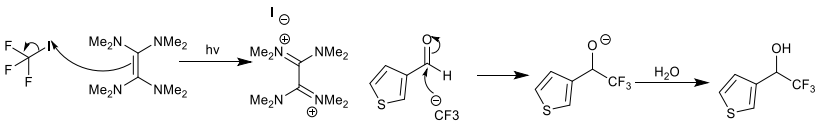


Figure 17- Mechanism for CF_3 addition from trifluoromethyl iodide[36]

Trifluoroacetonitrile requires a solvent of dry THF with a catalyst of DBU (1,8-diazabicyclo(5.4.0)undec-7-ene) on polystyrene (PS)). This reagent adds 1-diazo-2,2,2-trifluoroethane to a carbonyl group (fig. 18).

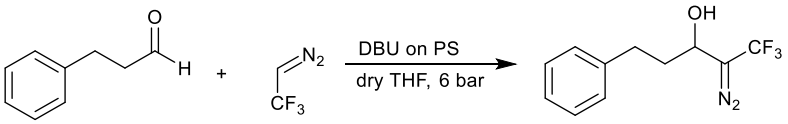


Figure 18- Reaction using trifluoroacetonitrile[37]

Sodium trifluoroacetate can be used to replace halides with a CF_3 group (fig. 20). It is made initially from electrofluorination of acetyl chloride to give trifluoroacetyl fluoride, which is then followed by a hydrolysis to give trifluoroacetic acid. Next, sodium sulfate is dissolved in trifluoroacetic acid to give sodium trifluoroacetate.[39] The nucleophilic CF_3 agent was then dissolved in DMF before being heated enabling a decarboxylation reaction to give sodium trifluoromethanide, which could then react with a carbonyl group (fig. 19).

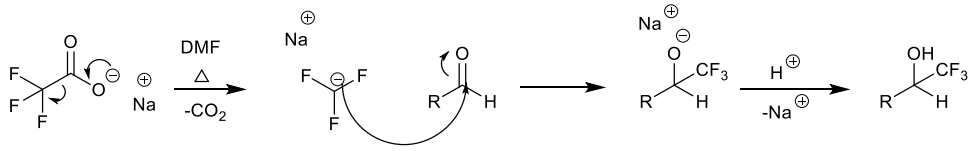


Figure 19- Mechanism for CF_3 addition from sodium trifluoroacetate[38]

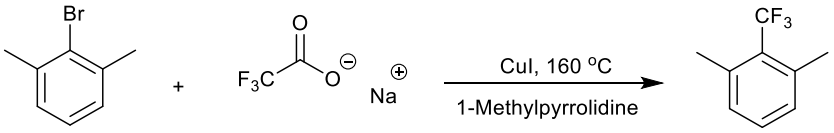


Figure 20- Copper-catalysed sodium trifluoroacetate reaction[40]

A more effective nucleophilic trifluoromethylating agent, $TMSCF_3$, can be used and many reviews have described the use of this Ruppert-Prakash reagent. The reagent can be used in a variety of reactions and, for all the reactions with this reagent, there needs to be an initiator (catalyst). The CF_3^- nucleophile has a good working range where it can be effective at low and high temperatures depending upon the number of available electrophilic sites, type of initiator used and/ or the steric and electronic effects of a substrate.

$TMSCF_3$ can react with a variety of electrophilic functional groups such as halides, imines, ketones and aldehydes. Halides react with $TMSCF_3$ and for this reaction there needs to a catalyst of copper(I) thiophene-2-carboxylate and a potassium fluoride initiator (fig. 21&22).

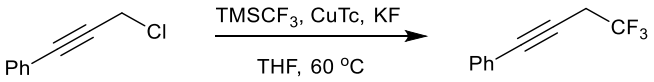


Figure 21- Copper-catalysed $TMSCF_3$ reaction with halide 1[41]

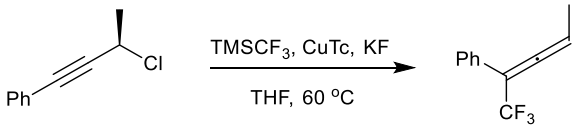


Figure 22- Copper-catalysed $TMSCF_3$ reaction with halide 2[41]

Cyclic imines, azirines and aldimines as well as cyano and amide functional groups can react with $TMSCF_3$ and these reactions generally have an initiator of tetrabutylammonium fluoride (TBAF), tetramethylammonium fluoride (TMAF), caesium fluoride (CsF), HF or KF. The reaction is done below 0 °C and up to room temperature (fig. 23&24).

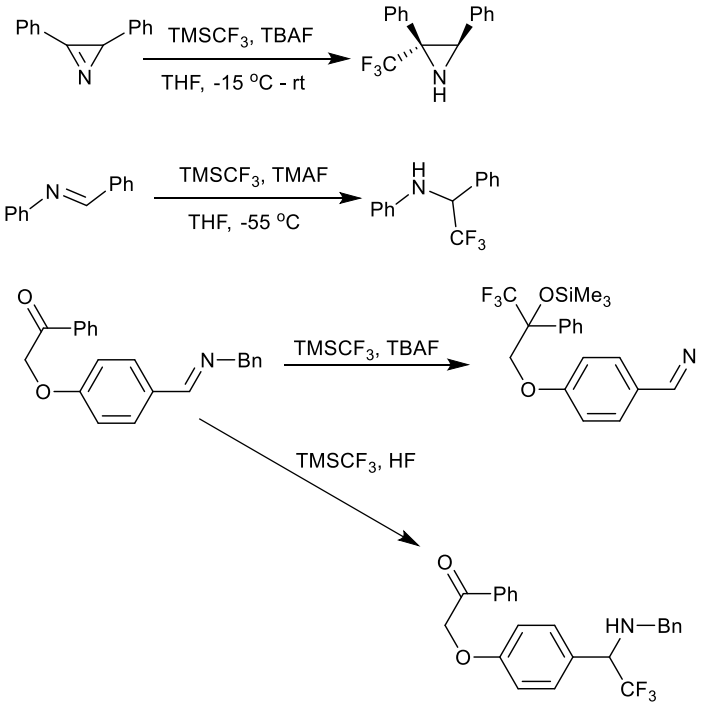


Figure 23- $TMSCF_3$ reaction with imides[41]

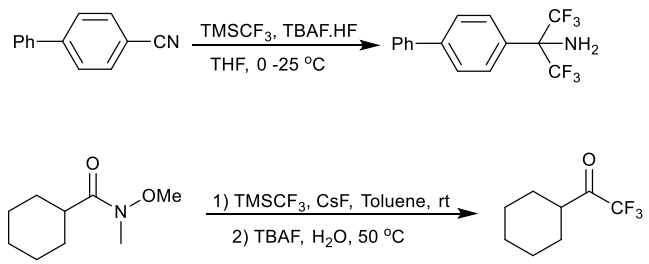


Figure 24- $TMSCF_3$ reaction with cyano and amide groups[41]

The most important electrophilic groups that react with $TMSCF_3$ are carbonyl groups (i.e. ketones and aldehydes). They also require an initiator such as sodium acetate (NaOAc), TMAF, TBAF, HF, CsF or potassium hydroxide (KOH) to enable their reaction. Generally, dry tetrahydrofuran (THF) or N,N-dimethyl-formamide (DMF) are used as solvents; some examples of $TMSCF_3$ reacting with ketones are in figure 25.

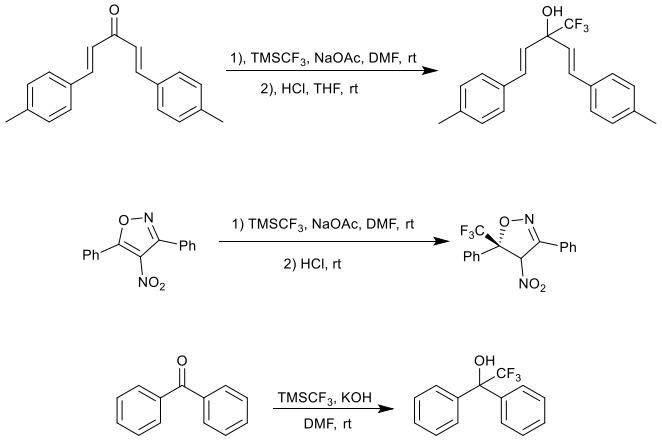


Figure 25- $TMSCF_3$ reactions with ketones[41,42]

The ketone will normally react more slowly than an aldehyde. So, for aldehyde reactions there needs to be less heating or less catalyst for reactions to go to completion. Benzaldehyde reacts to form the trifluoromethyl alcohol[43] and some examples of $TMSCF_3$ reacting with aldehydes are in figure 26.

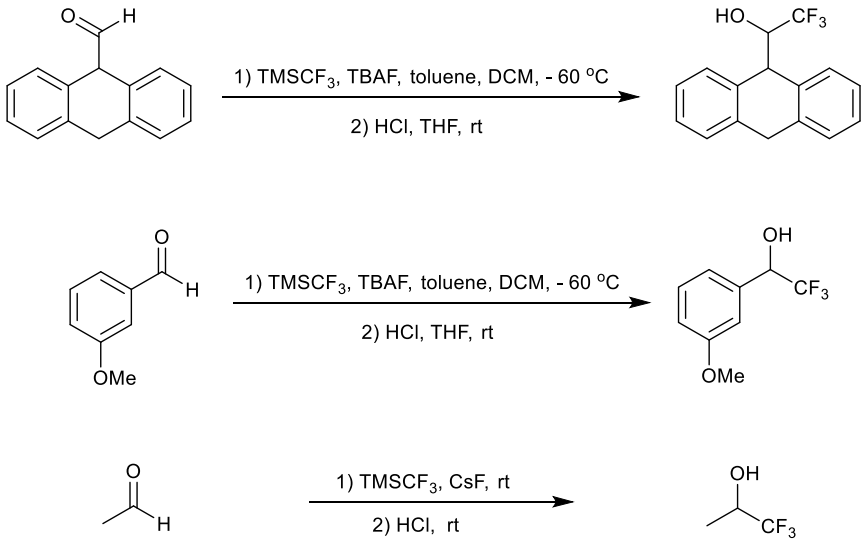


Figure 26- $TMSCF_3$ reactions with aldehydes[41,44]

1.3.3 CF_3 radical insertion

A third way a CF_3 group can be added to a molecule is via radical insertion. This is where the connecting bond to the CF_3 is cleaved via a photo-induced homolytic fission. Alternatively, a precursor reaction could make a hypervalent copper species which could then decompose to form $\cdot CF_3$. The reaction below is an example of the later (fig. 27).[24]

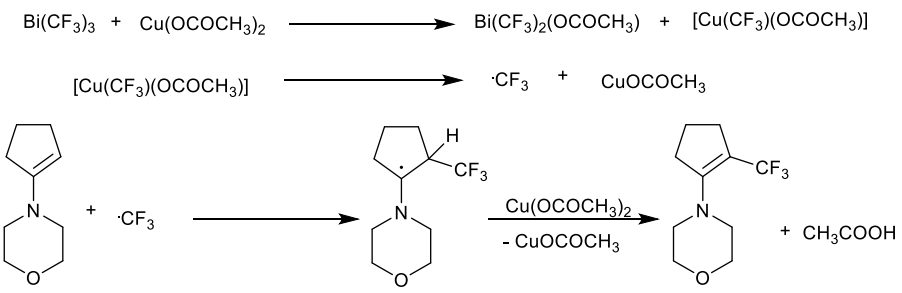


Figure 27- Hypervalent copper CF_3 radical insertion reactions[24]

1.4 Trifluoromethoxy derivatives in organic chemistry

There are two mains ways to add the OCF_3 functional group to a molecule and they are by C-F bond formation or via OCF_3 insertion using both CF_3O^+ and CF_3O^- reagents. The first way to form the OCF_3 moiety is by C-F bond forming reactions which is similar to when forming the CF_3 functional group. This can be done by S_N2 reactions with carbonyl fluoride, thiophosgene, carbon tetrachloride or iodomethane. Next are reactions of methoxy groups with a mix of PCl_5 (phosphorus pentachloride) and Cl_2 (elemental chlorine) to form the OCl_3 functional group which is easier to convert to the OCF_3 functional group. As above in section 1.3.1, SF_4, HF, SbF_3/ $SbCl_5$ and BrF_3 are used to form the C-F bonds. Below are examples of forming the OCF_3 functional group by C-F bond formation (fig. 28-32).

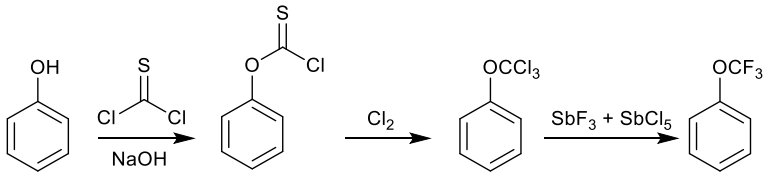


Figure 28- Reaction showing the formation of the trifluoromethoxy group via thiophosgene[45]

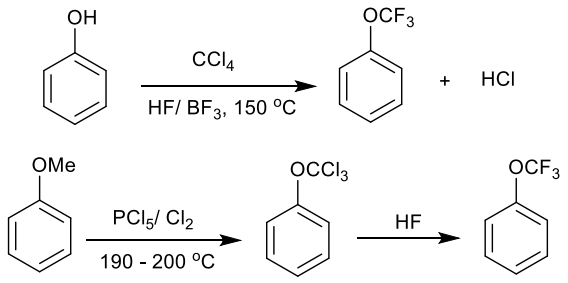


Figure 29- Synthesis of trifluoromethoxy benzene via HF[46]

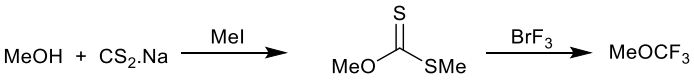


Figure 30- Synthesis of methyltrifluoromethyl ether via BrF_3[46,47]

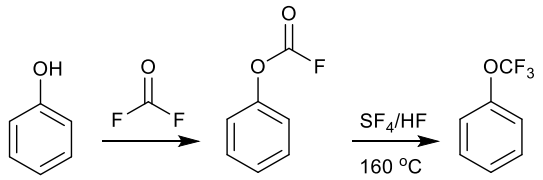


Figure 31- Reaction for the formation of the trifluoromethoxy group via carbonyl fluoride[45]

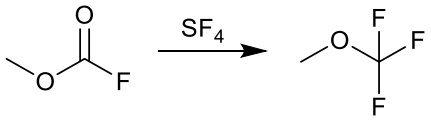


Figure 32-Synthesis of methyltrifluoromethyl ether via SF_4[48]

Another way to add OCF_3 to a molecule is via trifluoromethoxy insertion. First this can be done as CF_3O^+ reagents such as CF_3O-F (trifluoromethyl hypofluorite) or CF_3O-Cl (trifluoromethyl hypochlorite),[47] which must be made *in situ*. These reagents are kinetically stable, but not thermodynamically stable so their concentration must be carefully controlled. These can react with alkenes, or phenyl rings (fig. 33-35). Trifluoromethyl hypofluorite is very explosive so has to be used at low temperatures and/or diluted in nitrogen.

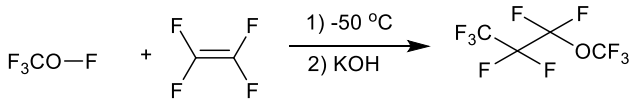


Figure 33- Trifluoromethyl hypofluorite reacting with an alkene[49]

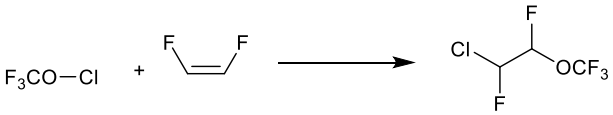


Figure 34- Trifluoromethyl hypochlorite reacting with an alkene[50]

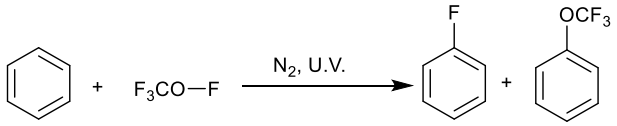


Figure 35- U.V. promoted reaction between benzene and trifluoromethyl hypofluorite[51]

A further method for forming OCF_3 compounds is via the use of silver trifluoromethoxide (CF_3O^-), which can be used in reactions with both aromatic and alkyl alcohols, haloalkanes and acid chlorides (fig. 36&37).

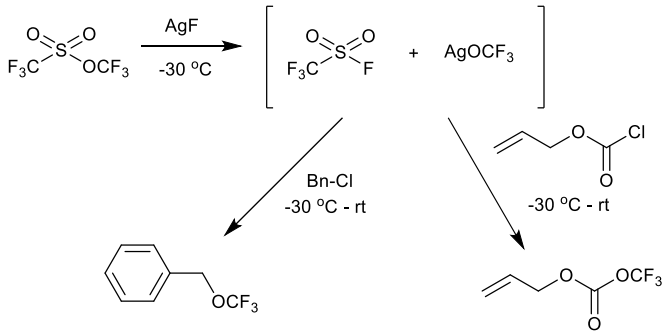


Figure 36- Example reaction of the silver trifluoromethoxide nucleophile[52]

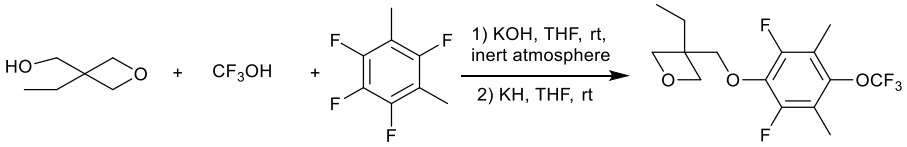


Figure 37- Example reaction for trifluoromethanol[53]

The final way to add a CF_3 group to a molecule is by 'radical' insertion where $TMSCF_3$ is used with silver triflate. When reacted with an alcohol forms a hypervalent silver complex which decomposes to give the trifluoromethoxy functional group (fig. 38).

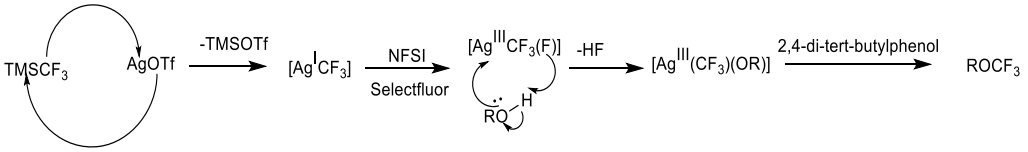


Figure 38- Mechanism for the formation of the trifluoromethoxy group via silver trifluoromethoxide[54]

The following example (fig. 39) is a photo-induced radical insertion, which cannot go via a S_N2 pathway because the three fluorine atoms all have partial negative charges, which prevent the oxygen anion from attacking the weak C-I bond.

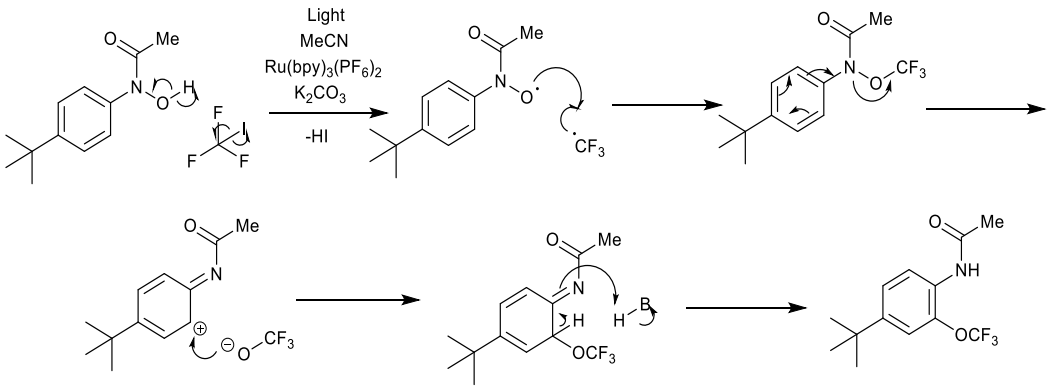


Figure 39- Aromatic trifluoromethoxy formation via trifluoromethyl iodide[55]

1.5 Pentafluoroethyl derivatives in organic chemistry

The pentafluoroethyl group has a lower electronegativity than for a CF_3 group (3.4 < 3.46)[56] because there are less fluorines bonded to the primary carbon. The CF_2CF_3 functional can be added to a molecule by C-F bond forming reactions or by nucleophilic $^-CF_2CF_3$ insertion. For C-F bond formation this can be done on nitriles, carboxylic acids, perchloro alkenes and perchloro alkanes. They are generally carried with either HF or germanium tetrafluoride (GeF_4). The reactions below all show the formation of pentafluoroethane (fig. 40).

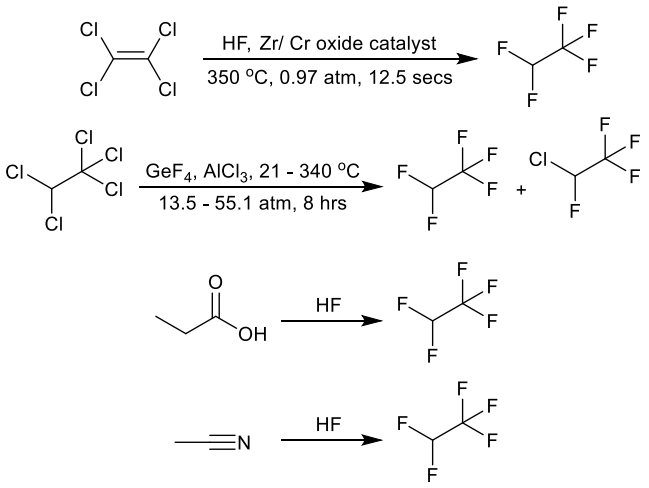


Figure 40- Ways of forming the –CF_2F_3 functional group[57-59]

A more general method to add CF_2CF_3 to a molecule is via pentafluoroethyl insertion. This is generally done via nucleophilic reagents such as $TMSCF_2CF_3$, CF_3CF_2I, CF_3CF_2Li and CF_3CF_2Cu, normally react with carbonyls and halides. These reagents are formed from pentafluoroethane as synthesized above. The first nucleophile is CF_3CF_2I, which is formed from either from pentafluoroethane, tetrafluoroethylene (TFE) or perfluoropropanoyl fluoride. Shown below are the different ways of forming pentafluoroethyl iodide (fig. 41).

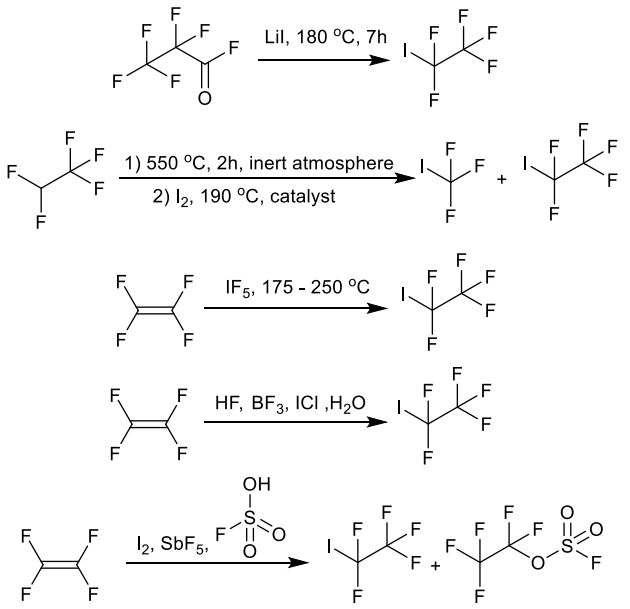


Figure 41- Synthetic pathways to form pentafluoroethyl iodide[60-64]

The figure below shows a couple of examples for the use of CF_3CF_2I. The first example is of a radical substitution on an alkene (fig. 42) and the second example is of a nucleophilic attack on a ketone (fig. 43).

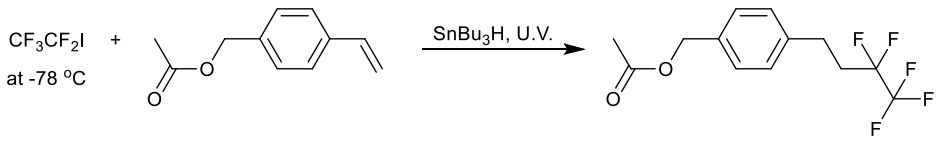


Figure 42- Radical CF_3CF_2 insertion[65]

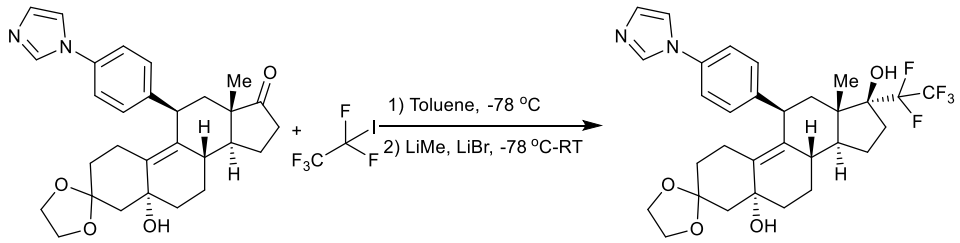


Figure 43- Nucleophilic CF_3CF_2 insertion from ICF_2CF_3[66]

The remaining three nucleophiles $TMSCF_2CF_3$, CF_3CF_2Li and CF_3CF_2Cu are all formed via a very similar pathway. $TMSCF_2CF_3$ is made via a reaction between pentafluoroethane and trimethylsilyl chloride (TMSCl); examples of some conditions used to make this reagent are given in fig. 44.

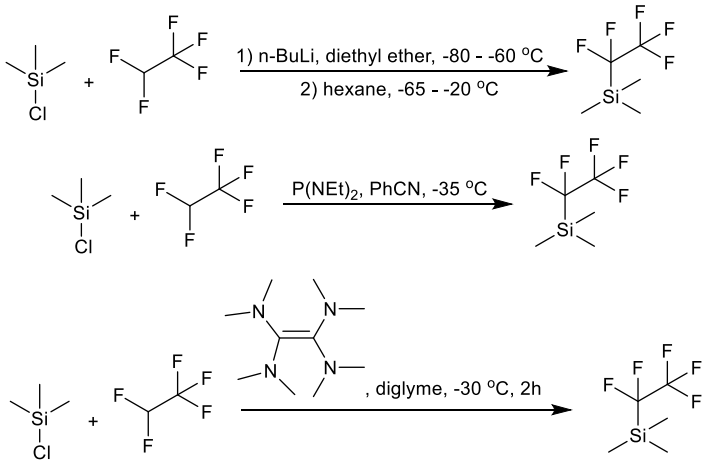


Figure 44- Current synthetic pathways to form $TMSCF_2CF_3$[67-69]

A third $CF_3CF_2^-$ nucleophile is $LiCF_2CF_3$, which is generally made *in situ* because it is not very stable above –70 °C. The nucleophile can be trapped by TMSCl to give $TMCF_2CF_3$ as shown in figure 45.

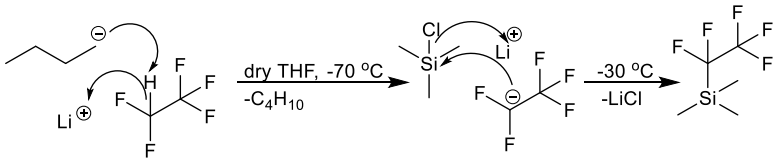


Figure 45- Mechanism for transforming pentafluoroethane to $TMSCF_2CF_3$[67]

CF_3CF_2I is a better reagent because it is safer to transfer and handle and below is an example reaction (fig. 46).

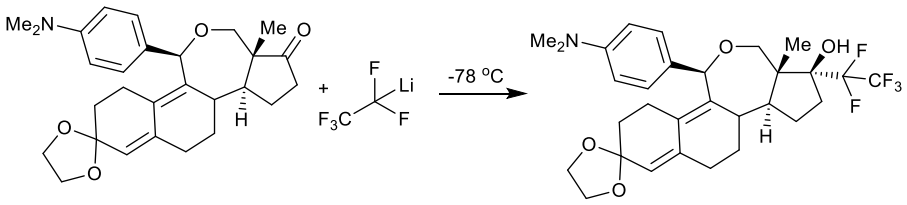


Figure 46- Nucleophilic CF_3CF_2 insertion from $LiCF_2CF_3$[70]

CF_3CF_2Cu is formed via a reaction between the lithium nucleophile and a copper halide and the copper nucleophile can attack soft electrophilic sites (fig. 47).

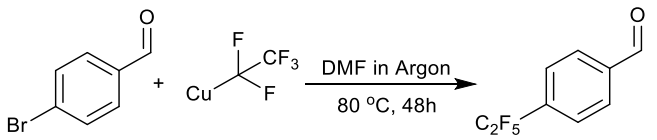


Figure 47- Nucleophile CF_3CF_2 insertion from $CuCF_2CF_3$ [71]

Of the compounds listed above $TMSCF_2CF_3$ is the best nucleophile for synthetic use because it is usable at room temperature and is bench stable. As with CF_3TMS it would require a fluoride source, such as TBAF, to act as an initiator.

$TMSCF_2CF_3$ can be used in the same reactions as $TMSCF_3$, but it is a weaker nucleophile and significantly bulkier. For $^-CF_2CF_3$ reactions, this means that more TBAF and $TMSCF_2CF_3$ are needed (relative to the substrate) to ensure sufficient conversions. Shown below (fig. 48-50) are examples of $TMSCF_2CF_3$ reactions.

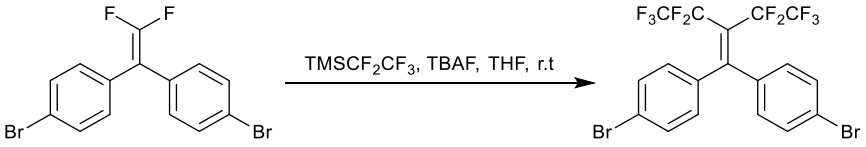


Figure 48- $TMSCF_2CF_3$ reacting with a difluoroalkene[72]

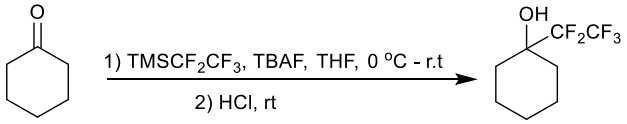


Figure 49- $TMSCF_2CF_3$ reacting with a ketone[73]

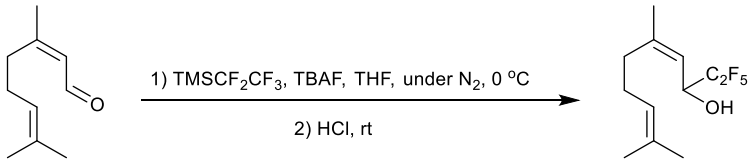


Figure 50-$TMSCF_2CF_3$ reacting with an aldehyde[74]

1.6 Synthesis of Ar-$CFHCF_3$ functional group

In this thesis, we develop methods for forming Ar-$CHFCF_3$ systems. Consequently, we discuss methods in the literature for synthesis of $ArCFHCF_3$ derivatives. This functional group has not been studied to any great extent in the pharmaceutical, agricultural and polymer industries.

The first method reported to form the $–CFHCF_3$ group started with a benzylic diazo group which reacted with HF pyridine in DCM, under an inert atmosphere, in a sealed tube and at 0 °C[35] (fig. 51). This method it has been done for methyl, nitro, methoxy and bromo phenyl derivatives.

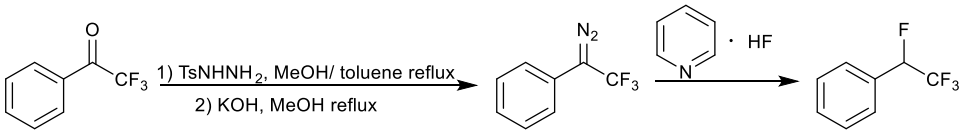


Figure 51- Formation of the Ar-$CHFCF_3$ from a diazo group[35]

This method is not very good for laboratory use because the diazo functional group is very unstable at room temperature.

The second method reported to form the $ArCFHCF_3$ group was by a reaction between 1-phenyl-2,2,2-trifluoroethanol and diphenylsulphur (VI) oxide difluoride in DCM at 25 ^oC. This dehydroxy-fluorinating agent is made by reaction between 1,1'-sulfinylbisbenzene and xenon difluoride in DCM with a catalyst of tetraethylammonium chloride.[75] The fluorinating agent must then be stored at low temperature and under an inert atmosphere. This is because it will readily react with water to produce HF. Below is the mechanism for reaction of this dehydroxy-fluorinating agent (fig. 52).

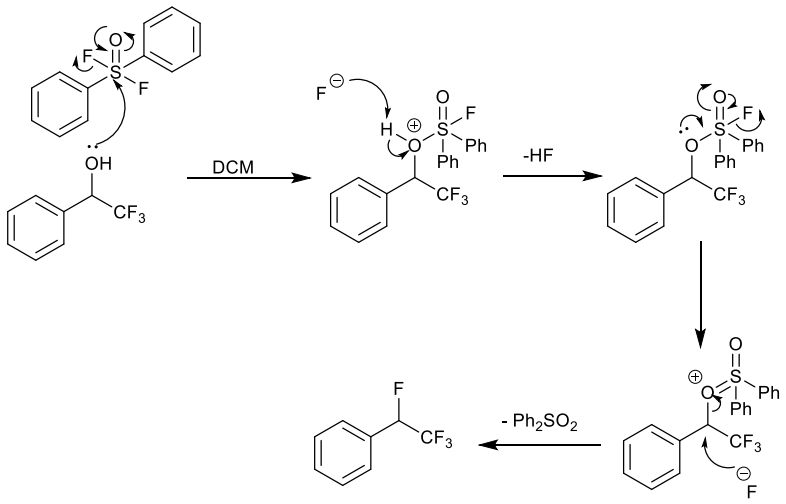


Figure 52- Mechanism of fluorination from diphenylsulfur (VI) oxide difluoride[75,76]

Once the attack by the alcohol has occurred, the fluoride ion is released to form HF making the first step irreversible. The slow step is the S_N1 release of the second fluoride ion and then the final fluoride attack is fast.

The final method to turn the trifluoromethyl alcohol into the desired functional group uses DAST. It is dehydroxy-fluorinating agent that must be dissolved in DCM before it is added to the reaction mixture at -70 ^oC before a reaction is allowed to warm to 20 ^oC during the reaction[31] (fig. 53).

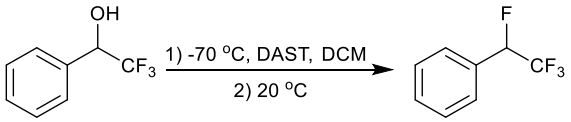


Figure 53- Reaction scheme for DAST[32,33]

This reaction scheme was very similar to the processes carried out in this thesis. However, in the published paper only 3 examples of the $ArCFHCF_3$ systems (Ar = Ph,

CH_3Ar, CH_3OAr) were prepared and then used to make fluoro-substituted styrene monomers.

1.7 Synthesis of Ar-$CFHCF_2CF_3$ functional group

In this thesis, we also develop methods for forming Ar-$CFHCF_2CF_3$ systems. Consequently, we discuss here methods in the literature for synthesis of $ArCFHCF_2CF_3$ derivatives.

$ArCFHCF_2CF_3$ derivatives can be made via a variety of different methods that have been published and they all either start from benzaldehyde or benzoyl chloride/ ethyl benzoate. The hydroxy group can be converted to a fluorine atom via two different one step pathways.

The first pathway reported to form the pentafluoroethyl-substituted alcohol is to first convert benzoyl chloride or ethyl benzoate to pentafluoroethyl phenyl ketone. This can be done either by reacting benzoyl chloride with pentafluoroethyl iodide with hexaethylphosphoric triamide in DCM (fig. 54) or by reacting ethyl benzoate and pentafluoroethyl iodide with a mixture of methyl lithium and lithium bromide in dry diethyl ether at -110 ^oC under a nitrogen atmosphere (fig 54).

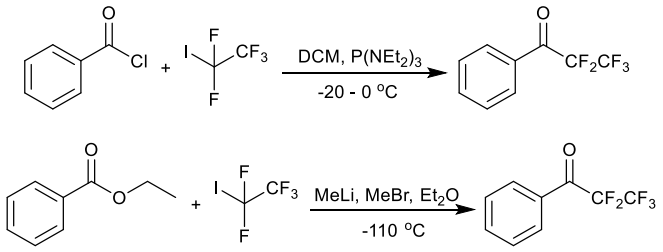


Figure 54- Different methods for making pentafluoroethyl phenyl ketone[77-78]

Next the ketone is reduced to the alcohol by reacting with a suitable hydride source. Two of the better options are to react with sodium borohydrate in methanol or lithium aluminium hydrate in dry diethyl ethyl (fig. 55).[34,79]

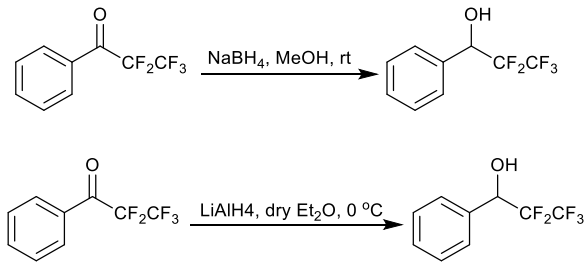


Figure 55- Two methods to make 1-phenyl-2,2,3,3,3-pentafluoropropanol[34,79]

An alternative to making the pentafluoro-substituted alcohol is to start with benzaldehyde then react it with $TMSCF_2CF_3$ in dry THF or with pentafluoroethyl iodide with a mix of methyl lithium and lithium bromide in dry diethyl ether at -78 °C under a nitrogen atmosphere (fig. 56).

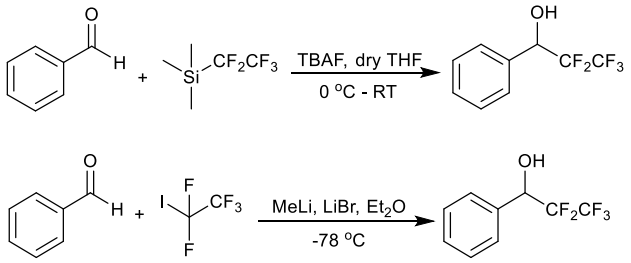


Figure 56- A further two methods to form 1-phenyl-2,2,3,3,3-pentafluoropropanol[68,80]

When the pentafluoroethyl-substituted alcohol had been formed it can be converted to the hexafluoro compound either using DAST in DCM or by FAR (the Ishikawa reagent, which is a hexafluoropropene-diethylamine mix)[47] also in DCM (fig. 57).

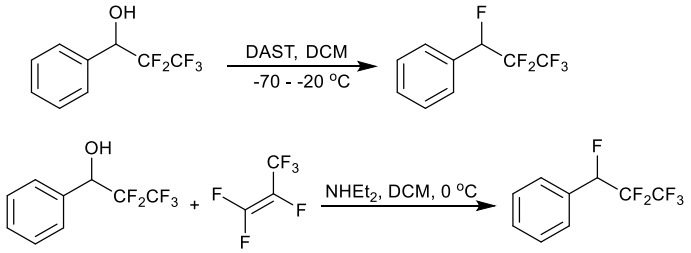


Figure 57- Different methods for making 1-phenyl-1,2,2,3,3,3-hexafluoropropane[34,81]

1.8 Conclusions

Organic molecules containing fluorine atoms, CF_3 or OCF_3 groups can be very valuable pharmaceuticals because of the change in physical, chemical and biological properties caused by fluorine atoms.

There are many synthetic methods available for C-F bond formation as well as approaches to introduce CF_3, and OCF_3 groups into organic synthesis.

In this thesis, we aim to develop methodology for the formation of aryl–$CFHCF_3$ derivates to compare properties with corresponding CF_3 and OCF_3 systems.

Chapter 2 Synthesis and Properties of $ArCHFCF_3$ systems

2.1 Aims and Approach:

The main aim of this research is to develop a general synthetic pathway to synthesise $ArCHFCF_3$ systems (fig. 58) and compare properties of $ArCFHCF_3$ and $ArCFHCF_2CF_3$ systems with corresponding $ArCF_3$ and $ArOCF_3$ derivatives. Further functionalization to alkenes from $ArCFHCF_2CF_3$ to generate useful fluorinated building blocks is a further goal (fig. 58).

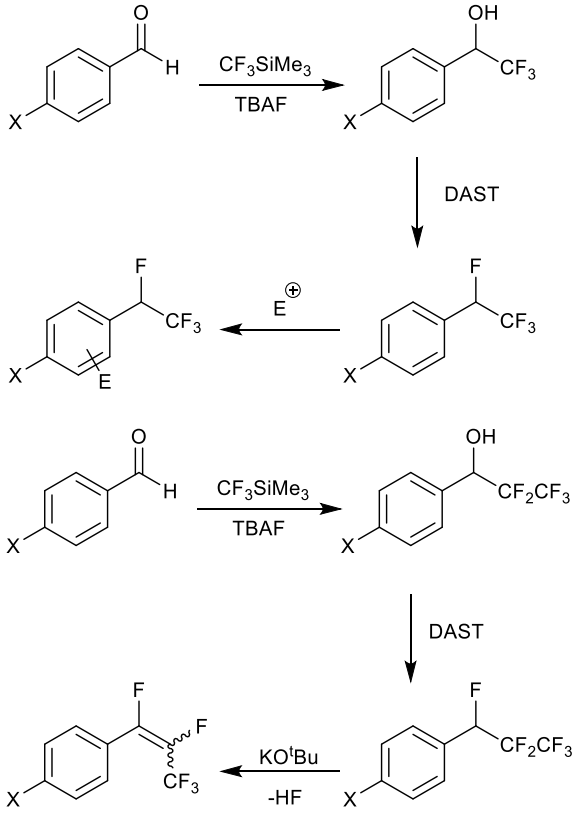


Figure 58- Proposed overall experimental aims of this thesis

The first target molecules were 1-phenyl-1,2,2,2-tetrafluoroethane derivatives and our strategy was a reaction between benzaldehydes and $TMSCF_3$ with TBAF catalyst, before reacting the resulting trifluoromethyl-substituted alcohol with DAST (fig. 59).

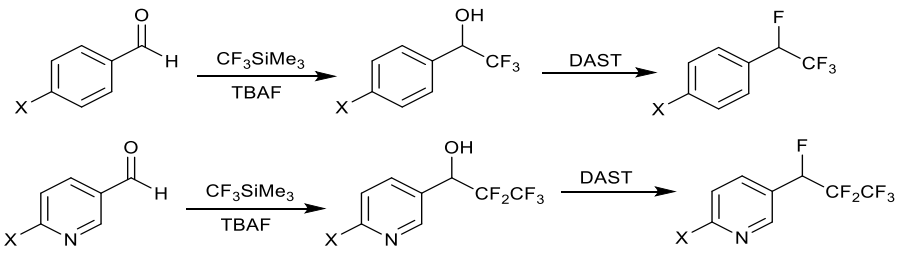


Figure 59- Proposed synthetic approach to make $ArCHFCF_3$ derivatives

A variety of compounds containing the Ar-$CHFCF_3$ functional group were to be synthesized with different functionalities. These analogues have different substituents in the *para* position of the phenyl ring, which were either electron donating or electron withdrawing groups.

The initial target molecule, 1-phenyl-1,2,2,2-tetrafluoroethane, could then be reacted with electrophiles to see how susceptible the molecule is to electrophilic substitution processes (fig. 60). The kinetics of the electrophilic reaction would be studied via a kinetic comparison with two other aromatic systems, which contain different fluorine containing substituents (e.g. $ArOCF_3$, $ArCF_3$).

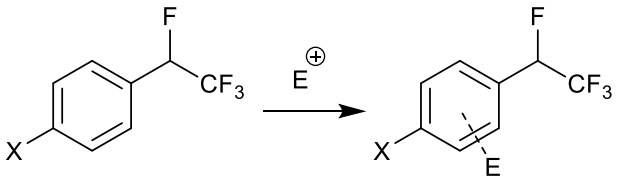


Figure 60- $ArCHFCF_3$ electrophilic substitution pathway

Another aim of this project was to synthesise 1-(3-pyridyl)-1,2,3,3,3-pentafluoroprop-1-ene using similar methodology to that developed above. The starting material would be 3-pyridinecarboxaldehyde, which would be reacted with $TMSCF_2CF_3$ and a catalyst of TBAF before reacting the resulting trifluoromethyl substituted alcohol with DAST to form the hexafluoro compound. The hexafluoro compound could be reacted with potassium tert-butoxide to form the target molecule (fig. 61).

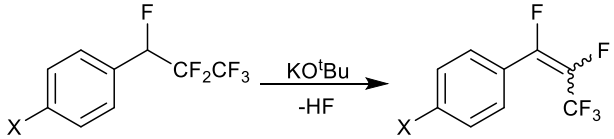


Figure 61- Proposed synthetic pathway to form

2.2 Results and Discussion

2.2.1 Reaction of benzaldehyde with $TMSCF_3$

The first target was the synthesis of unsubstituted $ArCFHCF_3$ following the strategy discussed above. First, benzaldehyde and $TMSCF_3$ were dissolved in dry THF at 0 ^oC before the addition of a catalytic amount of tetra-n-butylammonium fluoride (TBAF). The reaction was stirred continually, while it was warmed to room temperature. After 3 hours the resulting benzyl-trimethylsilyl ether was hydrolysed by the addition of 6 M

hydrochloric acid and allowed to stir for 48 hours to give 1-phenyl-2,2,2-trifluoro-ethanol, **2a** (fig. 62). This procedure was adapted from literature procedures.[82,83]

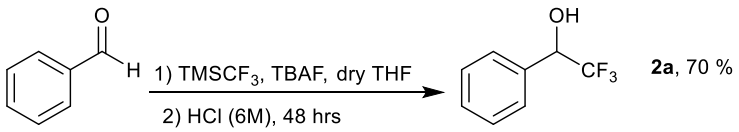


Figure 62- Reaction of benzaldehyde with $TMSCF_3$

It was necessary for the reaction to be carried out in a dry solvent (i.e. dry THF) and under an atmosphere of argon to remove the presence of water in the reaction mixture from solvent and atmosphere until the hydrolysis stage. These steps were undertaken as TBAF reacts with water to form hydrofluoric acid (HF).

To separate out the product and starting materials, in this case, we added a saturated solution of sodium hydrogen sulfite dissolved in water. This causes the aldehyde starting material to hydrolyse and move it into the aqueous phase while leaving only the product in the organic phase. The reaction of benzaldehyde gave a yield of 70 % when the reaction was carried out in dry conditions and scaled up from 30 mmol to 60 mmol.

The reaction proceeds via an F^- attack on $TMSCF_3$ to form the CF_3 anion before it can attack the electron-deficient carbon in the aldehyde. Next the resulting oxide is thought to propagate the reaction via reacting with $TMSCF_3$, which will then attack another benzaldehyde molecule. This reaction occurs via a concerted S_N2 pathway (fig. 63).

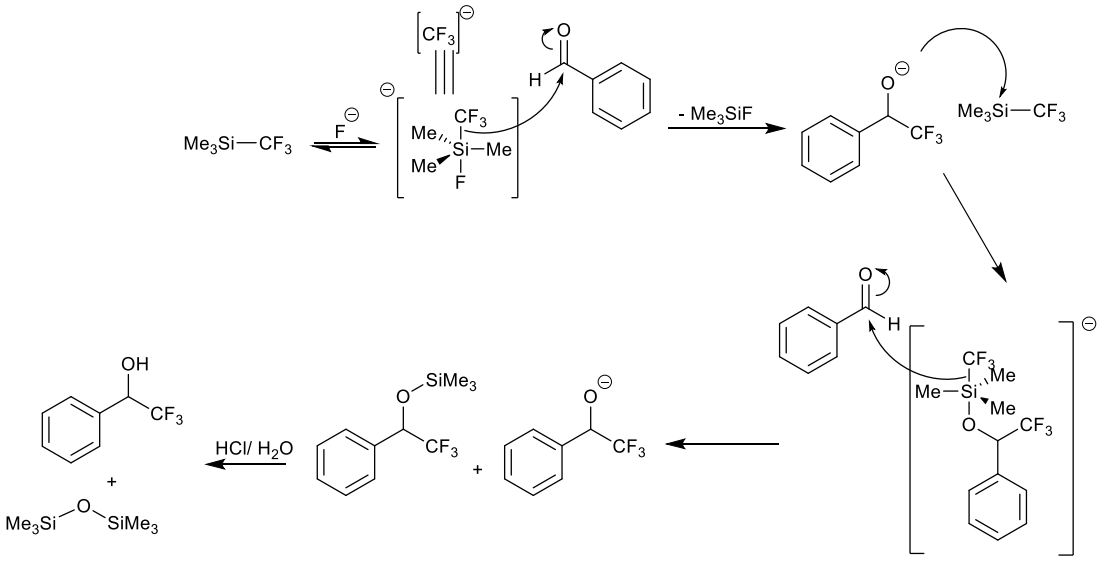


Figure 63- Mechanism for the addition of CF_3 to a carbonyl via $TMSCF_3$[41]

With our general process for synthesis of trifluoromethyl alcohols established (fig. 64), the reaction was expanded to a range of substituents bearing different electron donating and electron withdrawing groups as listed in Table 1. It would be expected that an increased yield would be observed for an electron withdrawing group because it causes the aldehyde to be become more activated towards nucleophilic reagents. However, there was not much difference observed between the yields of electron withdrawing groups compared to electron donating groups shown below.

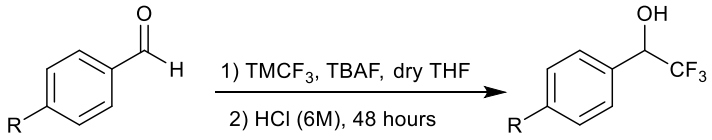
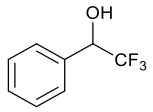
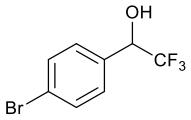
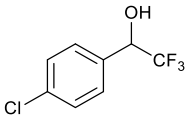
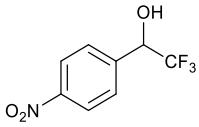
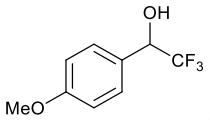
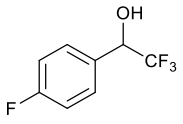


Figure 64- Trifluoromethylation of benzaldehyde derivatives

Product	% yield	Reference
 **2a**	70	82
 **2b**	36	89
 **2c**	85	83
 **2d**	36	83
 **2e**	74	82
 **2f**	51	83

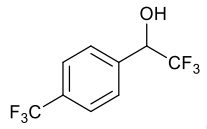
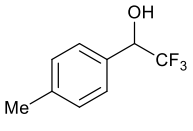
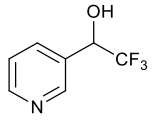
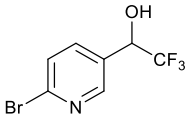
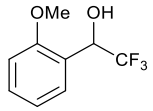
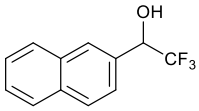
 **2g**	67	82
 **2h**	37	83
 **2i**	51	57
 **2j**	72	-
 **2l**	59	54
 **2n**	46	90

Table 1- Yields from reactions between benzaldehyde derivatives and $TMSCF_3$

Compounds **2** were characterized by NMR spectroscopy and GC-MS analysis. The obtained data was consistent with literature data. NMR spectroscopic data for **2a** are discussed here and all other data for **2** followed similar patterns.

All the $ArCHOHCF_3$ compounds gave only one peak in the ^{19}F NMR spectrum (fig. 65). This chemical shift was a unique doublet ($^3J_{FH}$ 6.6 Hz) for each compound dependent on the side group, δ_F = -78.4 ppm for **2a**. An upfield chemical shift between 0.05-0.65 ppm is observed for the different substituents.

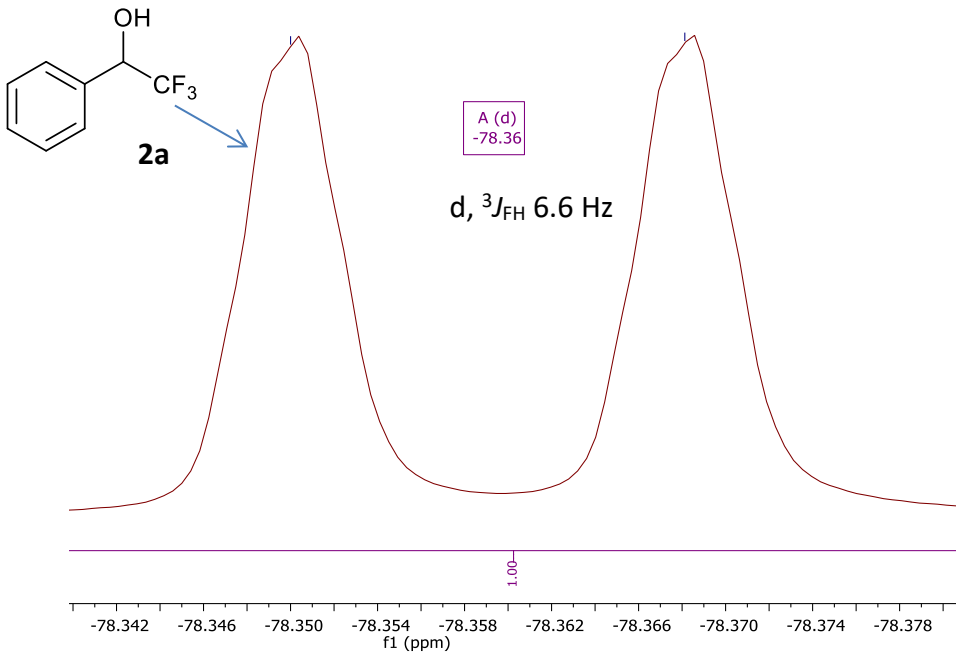


*Figure 65- ^{19}F NMR spectrum of compound **2a** in $CDCl_3$ on a 376 MHz spectrometer*

In the ^{1}H NMR spectrum of **2a** the most important peak is for C***H***(OH) which is a quartet ($^{3}J_{HF}$ 6.6 Hz) at 5.02 ppm because it has been split by the adjacent CF_3 group (fig. 66). This was backed up by the appearance of a broad singlet at 2.74 ppm for the alcohol proton. In the ^{13}C NMR spectrum of **2a** the two non-aromatic carbon peaks are quartets and, to differentiate between them, the CF_3 carbon at 124.4 ppm has a $^{1}J_{CF}$ coupling value of 282 Hz while the **C**HOH resonance has $^{2}J_{CF}$ 32 Hz coupling at 73.0 ppm (fig. 67).

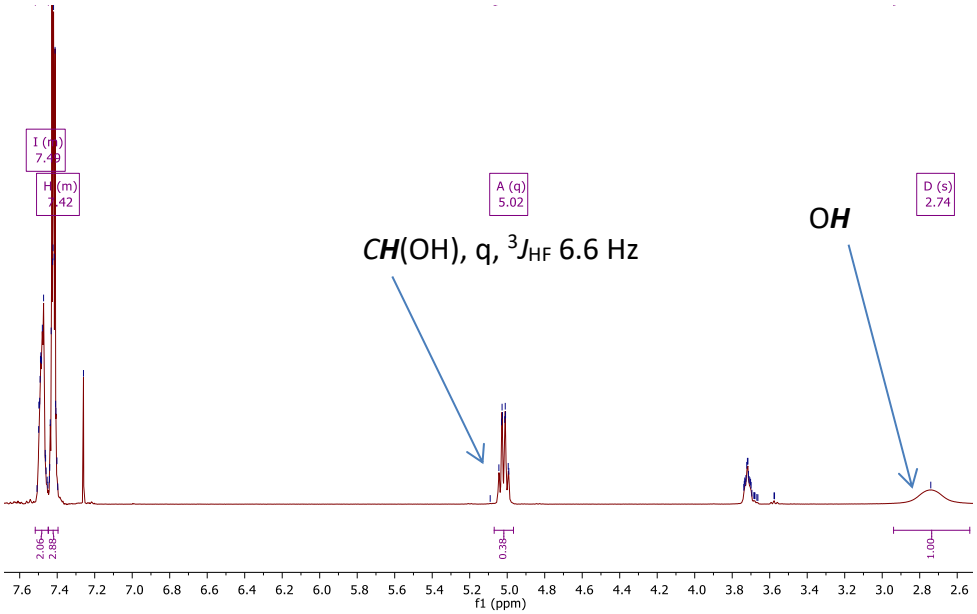


*Figure 66- ^{1}H NMR spectrum for compound **2a** in $CDCl_3$ on a 400 MHz spectrometer*

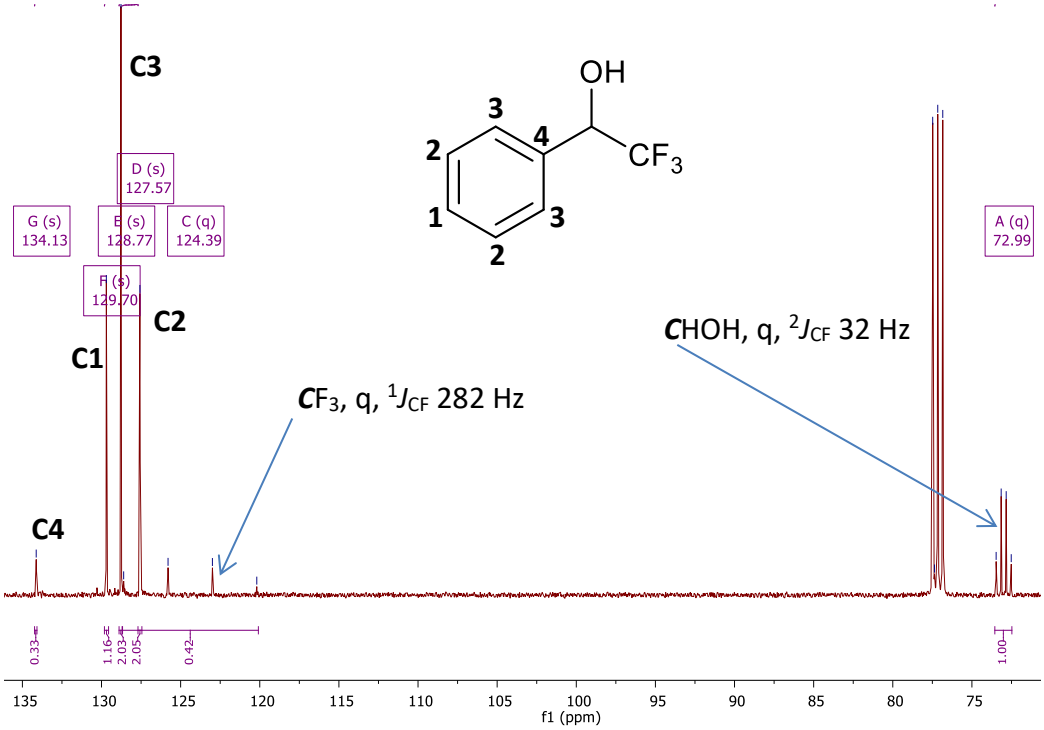


*Figure 67- ^{13}C NMR spectrum for compound **2a** in $CDCl_3$ on a 101 MHz spectrometer*

Gas chromatography-mass spectrometry was also used, alongside these NMR spectral analysis to prove that all compounds mentioned above were formed. The molecular ion for compound **2a** at m/z = 176.1 was observed for the component at a retention time of 3 mins. The main fragment ion for compounds **2** was $[M\text{-}CF_3]^+$.

Crystals of **2d** were formed via recrystallization from chloroform followed by slow evaporation in a solution of acetone. Compound **2d** then had its structure determined by X-ray crystallography (fig. 68&69). We thank Dr. Dimitry Yufit for carrying out the X-ray crystallography.

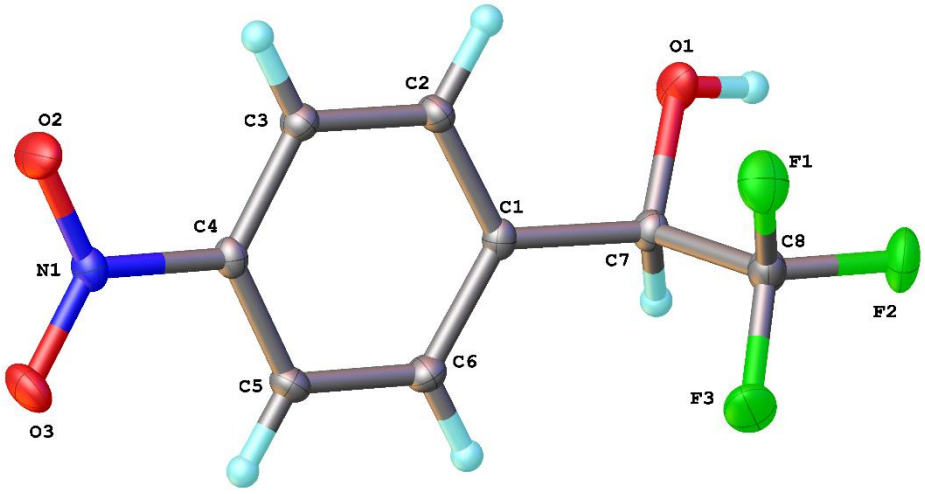


*Figure 68- Molecular structure of compound **2d***

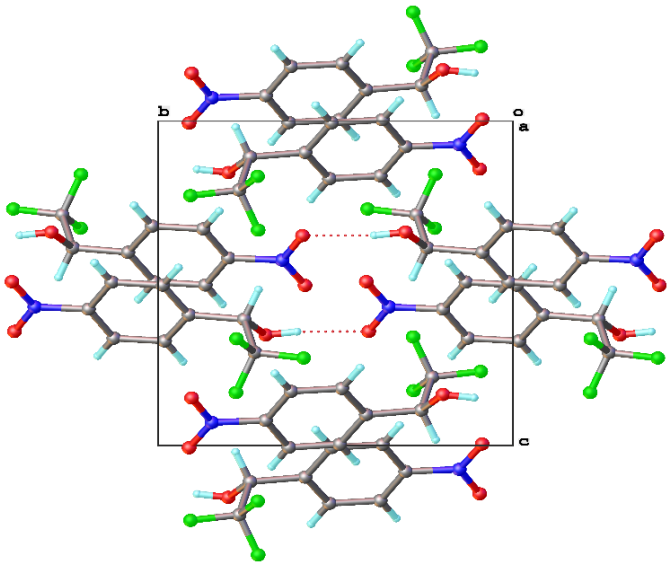


*Figure 69- Compound **2d** unit cell*

Compound **2d** has a monoclinic crystal structure in space group $P2_1/c$. The crystal structure is constructed of hydrogen bonding between O-H…O-N and π-π interactions into double chains. Alongside this, π-π aromatic stacking is observed.

This crystal structure is consistent with the structure of **2d**. We also measured the crystal structures for compounds **2j** (2-bromopyridyl) and **2n** (napthyl) where the only major difference was for the hydrogen bonding sites. So, for the side groups that do not contain oxygen or nitrogen, the hydrogen bonding would be between O-H…O. This means that the space group changes to P-1 and the crystal of **2n** is now triclinic in structure. It can be concluded from the crystal of **2j** that the pyridyl equivalents have hydrogen bonding between OH…N. Just like with crystal **2d**, the space group was $P2_1/c$ and the crystal was monoclinic. The experimental data from this X-ray crystallography is shown appendix 1.

2.2.2 Synthesis of $ArCFHCF_3$ derivatives from $ArCHOHCF_3$

Once the trifluoromethyl-substituted alcohol **2** had been formed, the hydroxy group was replaced by a fluorine atom via reaction with DAST. To this end compound **2a** was dissolved in DCM at 0 °C before the slow addition of DAST to the reaction mixture, which was then warmed to room temperature and stirred for 48 hours to give 1-phenyl-1,2,2,2-tetrafluoroethane, **3a** after work up (fig. 70).

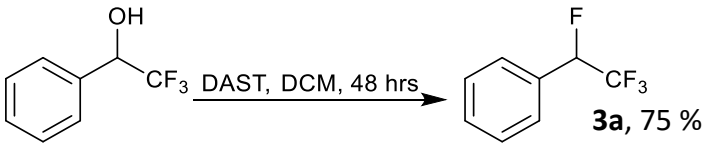


*Figure 70- Reaction scheme for compounds **2a-l** with DAST*

DAST is a potentially dangerous reagent so it must be added when the reaction mixture has been cooled by an ice bath. If we carried out reactions at 90 ^{o}C, DAST can react itself to form bis(dimethylamino)sulphur difluoride which is quite explosive. To further increase safe use, DAST was dissolved in 10 mL of DCM (over a spill tray) so that it was diluted if it got spilled.

The reaction between an alcohol group and DAST starts via the oxygen attacking the sulfur and producing a fluoride ion which can attack the carbon to remove the oxygen and form the tetrafluoro product (fig. 71). It is reported that there is an inversion of the stereochemistry as the rate determining step goes via an S_N2 pathway.[84]

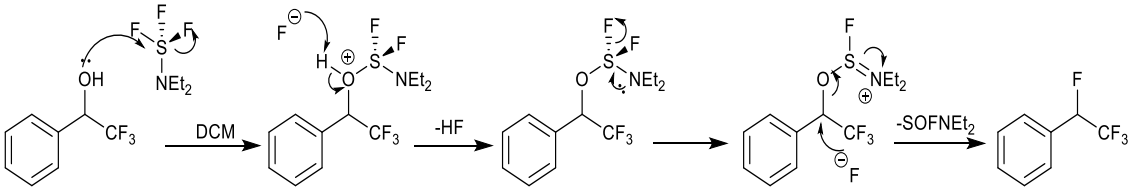
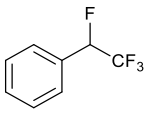
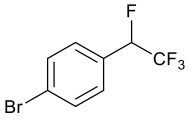
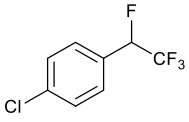


Figure 71- Mechanism for DAST reacting with an alcohol[84]

With conditions for the formation of **3a** established, DAST reactions with **2a-k, l & n** were carried out to form a family of $ArCFHCF_3$ derivatives as shown below in table 2.

Product	% yield
 **3a**	42
 **3b**	49
 **3c**	49

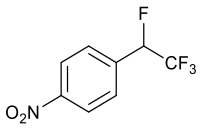
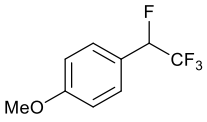
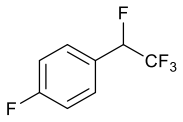
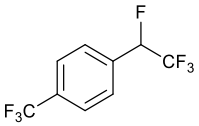
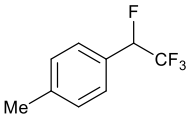
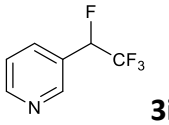
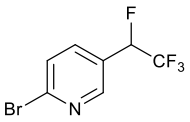
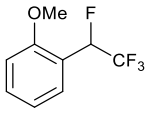
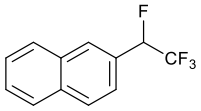
 **3d**	94
 **3e**	65
 **3f**	81
 **3g**	12
 **3h**	21
 **3i**	58
 **3j**	85
 **3l**	43
 **3n**	74

Table 2- Synthesis of $ArCFHCF_3$ derivatives

Compounds **3** were characterized by NMR spectroscopy and GC-MS analysis could be assigned. NMR spectral data for **3a** are discussed here and all other data for **3** followed similar patterns. It was expected that an electron donating group would have an

increased yield because the alcohol would have been slightly activated for nucleophilic attack, but not much difference was observed in the yield.

All compounds **3** gave two characteristic peaks in their ^{19}F NMR spectra. For compound **3a**, there was a doublet of doublets for CF_3 ($^3J_{FF}$ 12.9 Hz, $^3J_{FH}$ 6.2 Hz) at δ = -78.8 and a doublet of quartets for C***F***H ($^2J_{FH}$ 44.1 Hz, $^3J_{FF}$ 12.9 Hz) at δ = -194.6 (fig. 72). These shifts were unique for each side group derivative, with a shift range of 0.2 ppm and 0.1 ppm for the doublet of doublets, and a shift range of 3.5 ppm and 4 ppm for the quartet of doublets.

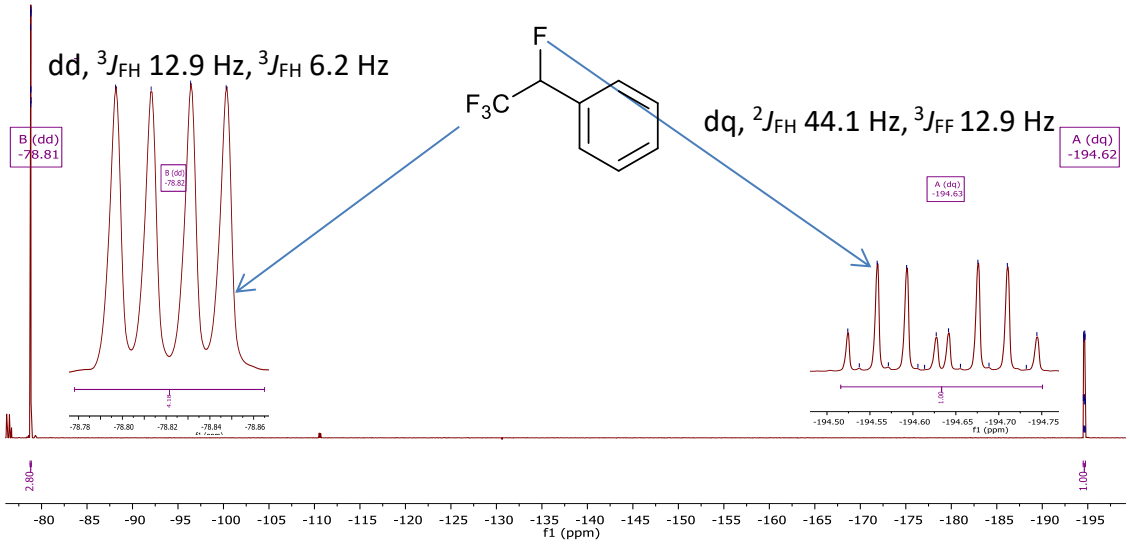


*Figure 72- ^{19}F NMR spectrum of compound **3a** in $CDCl_3$ on 400 MHz spectrometer*

The ^1H and ^{13}C NMR spectra were consistent with the formation of **3a**. In the ^1H spectrum the most important peak was for the C***H***F moiety which is now a doublet of quartets ($^2J_{HF}$ 44.1 Hz, $^3J_{HF}$ 6.2 Hz) at 5.60 ppm (fig. 73). In the ^{13}C spectrum of **3a** the two non-aromatic carbon peaks are in similar positions as they were previously in the alcohol (fig. 74). However, the ***C***FH carbon at 89.1 ppm is now a doublet of quartets ($^1J_{CF}$ 186 Hz, $^2J_{CF}$ 35 Hz) whereas the CF_3 carbon at 122.4 is now a quartet of doublets ($^1J_{CF}$ 281 Hz, $^2J_{CF}$ 29 Hz). The aromatic carbons can be differentiated by ^{13}C DEPT and by their splitting.

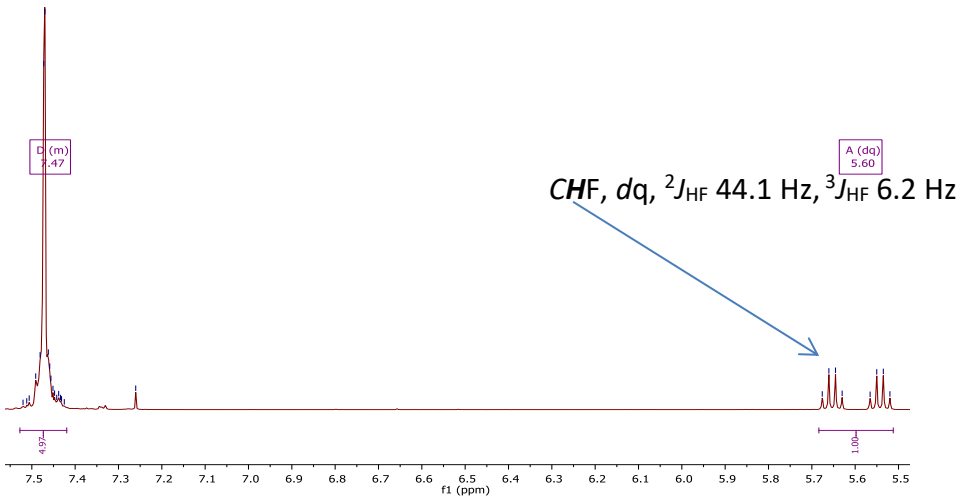


*Figure 73- ^{1}H NMR spectrum of compound **3a** in $CDCl_3$ on a 400 MHz spectrometer*

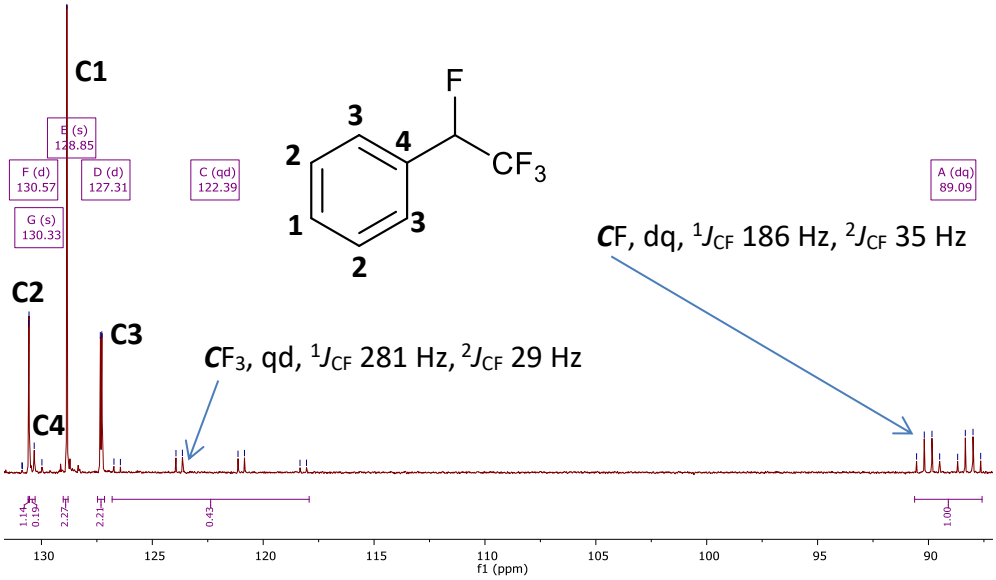


*Figure 74- ^{13}C NMR spectrum of compound **3a** in $CDCl_3$ on a 101 MHz spectrometer*

For compounds **3d**, **3i** and **3j,** high-resolution mass spectrometry was used to confirm their composition. The molecular ion for compound **3a** at m/z = 178.0 at a retention time of 2.01 mins and the main fragment ion for compounds **3** was $[M\text{-}CF_3]^+$.

2.2.3 Conformation of –CFHCF$_3$ units

In the following section, the conformation of the Ar-CHFCF$_3$ unit will be discussed and in particular, if the functional group lies in or out of the aromatic ring plane. The dihedral angle between the aromatic ring and the benzylic CF bond was required to find out the preferred conformation of the functional group via a rotational energy profile. This is important because it can give an indication of the intra- and intermolecular forces within a molecule.

The purpose of the first set of calculations was to see how the benzylic CF sits in relation to the aromatic ring for the –C***F***HCF_3 functional group. The $CFHCF_3$ functional group was to be compared to three other related functional groups (-OCF_3, OCH_3 and –$CFHCH_3$) all of which have known conformations when directly bonded to an aromatic ring. The rotational energy profiles of the four functional groups were calculated respectively from the dihedral angle shown below (fig. 80).

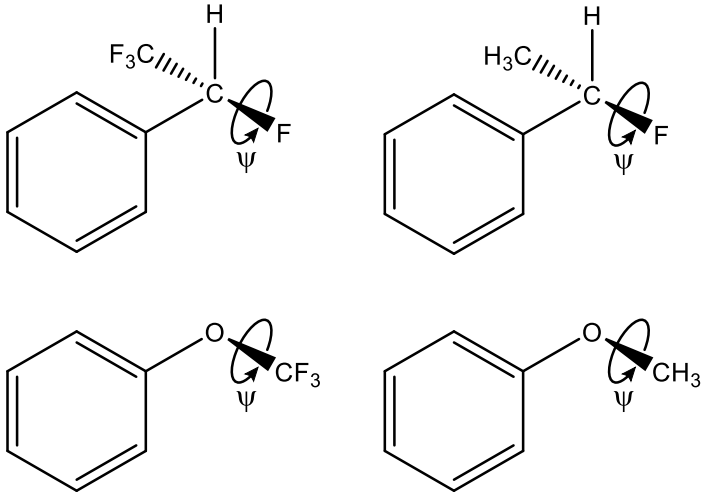


Figure 80- Dihedral angle used to determine relative conformation preferences

We thank Dr. Mark Fox, Durham University, for carrying out these calculations. Through these calculations it was found that the optimum conformation of the (H)C-F bond is perpendicular to the ring plane. The following graph shows the difference between carbon and oxygen being the connecting atom between the phenyl ring and the functional group (fig. 81). The other comparison is between a methyl and a trifluoromethyl functional groups.

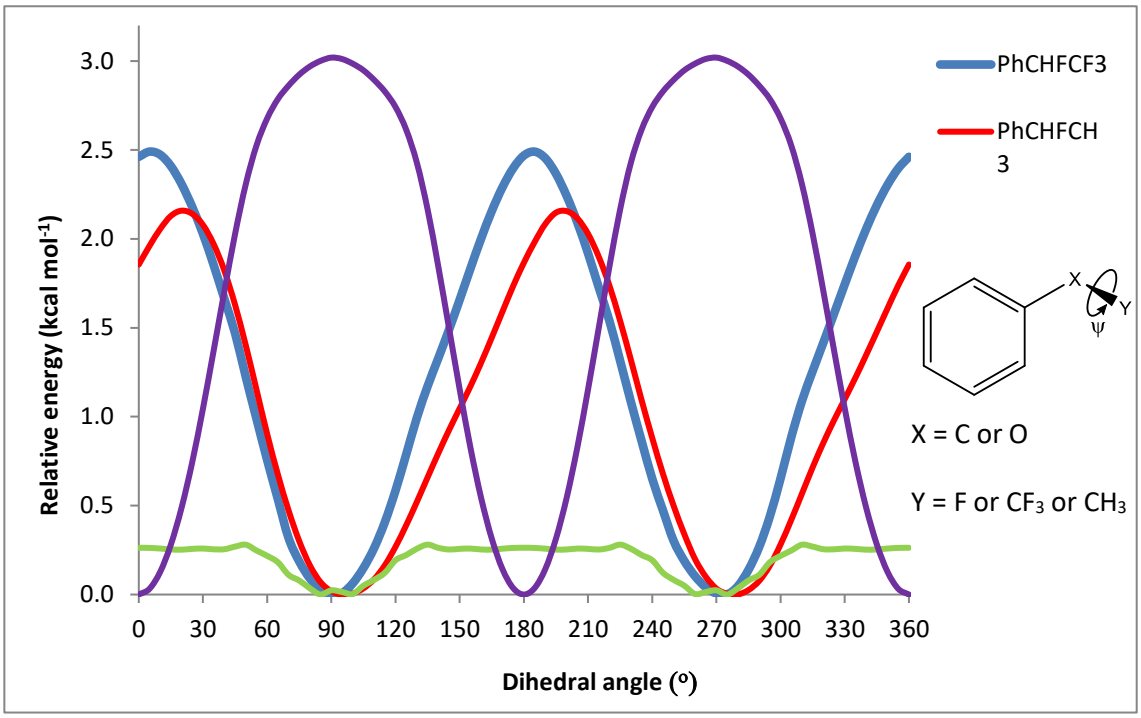


Figure 81- Varying dihedral angle to find optimal conformations of ArX-Y

The $-OCH_3$ side group is unusual because, unlike $-CHFCF_3$, $-CHFCH_3$ and $-OCF_3$, the methyl group of OCH_3 prefers to be in the same plane as the aromatic ring. This is shown by the graph above, where the energy maxima are at 90 ° and 270 ° for $-OCH_3$ whereas these angles are the relative energy minima (optimal conformation) for the other three side groups including $-CHFCF_3$. This is because one the lone pairs on the oxygen will be perpendicular to the ring plane to participate in resonance structures. The most interesting side group is $-OCF_3$ because there are small maxima at 90 ° and 270 ° so the CF_3 group cannot be fully perpendicular to the ring plane. This is to limit electronic repulsions between the oxygen pairs and the aromatic nucleus. Hence, the non-bonding oxygen lone pairs and the aromatic nucleus are not conjugated.[53] Further to this the $-OCF_3$ side group, surprisingly, has a very small rotational energy barrier. This means there are relatively small energy maxima compared to the other side groups preventing the lone pairs from being perpendicular to the ring plane. Thus, the fluorine atoms in the trifluoromethyl group are further away from the delocalised π electrons to minimise electrostatic repulsions. There is little difference between the relative energy/ dihedral angle of $CHFCF_3$ and $CHFCH_3$. The CF_3 group causes a small decrease in rotational energy barrier and a small change in optimal dihedral angle (relative to CH_3) because of a minor repulsion of the fluorine lone pairs and the aromatic nucleus.

The second set of calculations was done to test the rotational energy of the ArC-CF_3 bond. for $-CH_2CH_3$, CH_2CF_3 and $-CF_2CF_3$ functional groups bonded to an aromatic ring and to assess whether the CF_3/ CH_3 group would prefer to be in or out of the aromatic ring plane. The calculation was also done on the dihedral angle between the functional group and the aromatic ring, but this time based the alkyl chain rather than the benzylic CF (fig. 82).

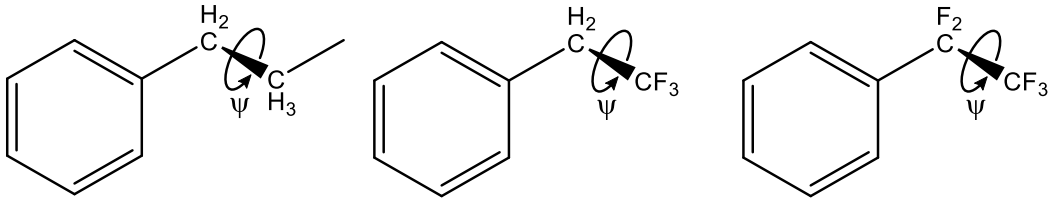


Figure 82- Dihedral angle used to determine relative conformation preferences

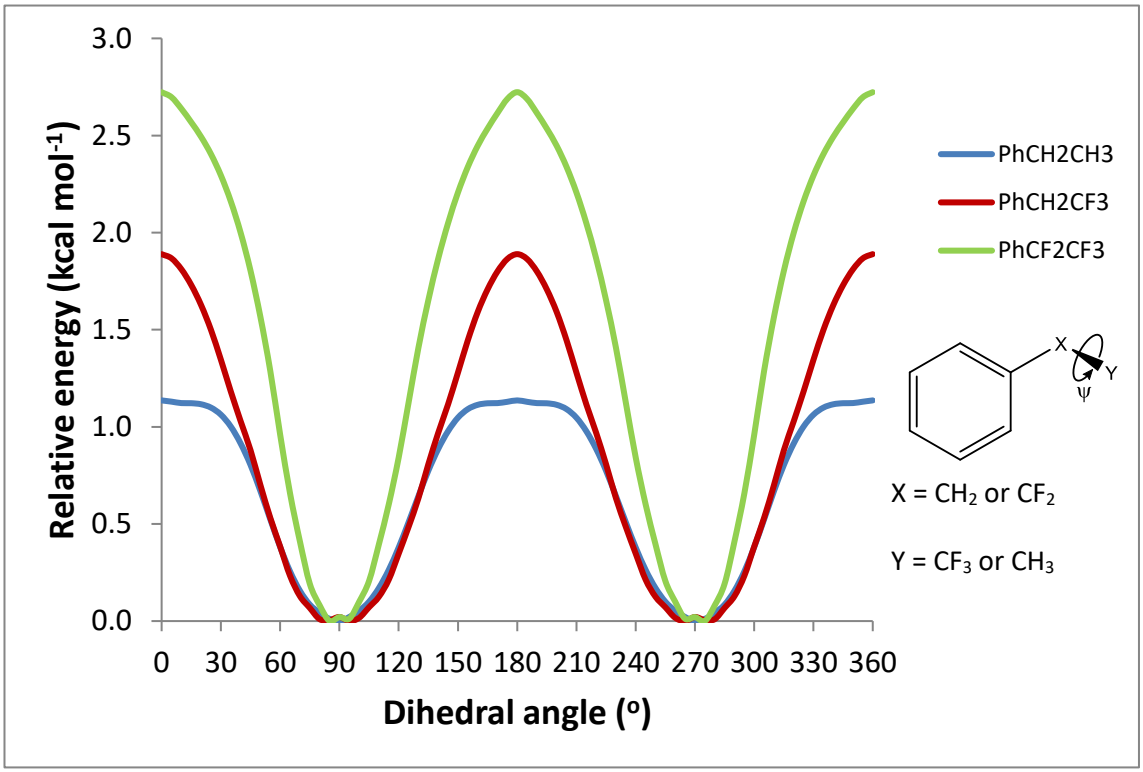


Figure 83- Varying the dihedral angle to see how Ar-CCF_3/ CH_3 is affected

The graph above indicates that both the CF_3 and CH_3 groups prefer to be orthogonal to the aromatic ring plane. The CH_3 containing functional group had the smallest rotational energy barrier preventing it from rotating into the aromatic ring plane. This is due to the CF_3 being a larger group than CH_3 (increased steric repulsion) and an increase in electronic repulsion between the CF_3 group and the aromatic ring. It was also observed that the benzylic CH_2 group caused a lower rotational energy barrier compared to the benzylic CF_2 group. This was because the benzylic CF_2 group would cause more

electronic and steric repulsion (same reasons as for CF_3 group) when in the plane of the aromatic ring. This means that the CH_2 containing functional groups would have more freedom to rotate, as there would be hardly any electronic repulsion in comparison.

2.2.4.1 Nitration of Ar-$CHFCF_3$ (3a) by NO_2BF_4

We next studied how $CFHCF_3$ substituents affected electrophilic substitution processes in comparison with CF_3 and OCF_3 derivatives. There are several ways to add a nitro group to an aromatic ring such as a mix of concentrated nitric and sulfuric acids,[85] nitryl chloride with a catalyst of titanium tetrachloride[86]/ boron trifluoride[86] or silver nitrate with boron trifluoride as a catalyst.[87] For mono substitution reactions carried out on phenyl rings the simplest reagent to use is nitronium tetrafluoroborate.[88] This is because under standard laboratory conditions (room temperature and pressure) nitration reactions are relatively selective.

First nitronium tetrafluoroborate was dissolved in nitromethane at 0 ^oC under an atmosphere of argon. Next, compound **3a** was dissolved in nitromethane before being added dropwise to the nitronium tetrafluoroborate. The reaction was then stirred continually at room temperature for 4 days to give 1-(3-nitrophenyl)-1,2,2,2-tetrafluoroethane, **5a** in a good yield. Both CF_3 and OCF_3 derivatives substitute at the meta position because they are both electron withdrawing functional groups (fig. 83).

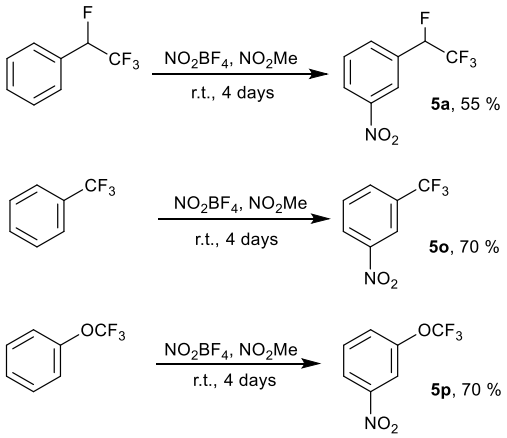


Figure 83- Reactions of CF_3 substituted phenyl derivates with NO_2BF_4

From previous research,[88] the most suitable solvents for NO_2BF_4 nitration are nitromethane or sulfolane. However, the main problem with sulfolane is that its melting point (25 ^oC) is near room temperature so it would have required vigorous stirring to constantly keep it in a liquid state before either of the reagents could be added. So, nitromethane is the more convenient solvent.

The ^{1}H, ^{13}C and ^{19}F NMR spectra of compound **5a** all indicated that the compound **3a** had been nitrated. Gas chromatography-mass spectroscopy showed that the reaction had only proceeded to mono substitution. The molecular ion for compound **5a** at m/z = 223.1 was at a retention time of 3.27 mins. The main fragment ion for compound **5a** was $[M\text{-}CF_3]^+$.

The most useful spectrum for determining the position of substitution of the nitro group on compound **5a** was the ^{1}H NMR spectrum. In the ^{1}H spectrum, there was a double of quartets ($^{2}J_{HF}$ 44.1 Hz, $^{3}J_{HF}$ 5.9 Hz) at 5.74 ppm for the CF***H*** resonance (fig. 84). The remaining four peaks were in the aromatic region indicating that substitution was either in the *ortho* or *meta* position because the previous synthesized *para* nitro equivalent (**3d**) only had two aromatic proton resonances. For *ortho* substitution, it was expected that the splitting of the four peaks would be three doublet of doublet of doublets and one doublet of doublets. For *meta* substitution, it was expected that there would be one doublet, two doublet of doublets and one doublet of doublet of doublets. The splitting pattern of **5a** was consistent with *meta* substitution. The C***H***CCFH (H_c) resonance was a doublet of doublet of doublets ($^{4}J_{HF}$ 8.8 Hz, $^{3}J_{HH}$ 7.7 Hz, $^{4}J_{HH}$ 1.4 Hz) at 7.69 ppm. The next peak was doublet of doublet ($^{3}J_{HH}$ 7.7, $^{3}J_{HH}$ 2.0 Hz) at 7.82 ppm for the C***H***CHCCFH (H_b). The following peak was a doublet ($^{4}J_{HF}$ 8.1 Hz) at 8.33 ppm for the O_2NC***H***CCFH (H_d). The final aromatic proton was the C***H***CNO_2 (H_a) resonance at 8.36 ppm which was a doublet of doublets ($^{3}J_{HH}$ 3.5 Hz, $^{4}J_{HH}$ 1.4 Hz).

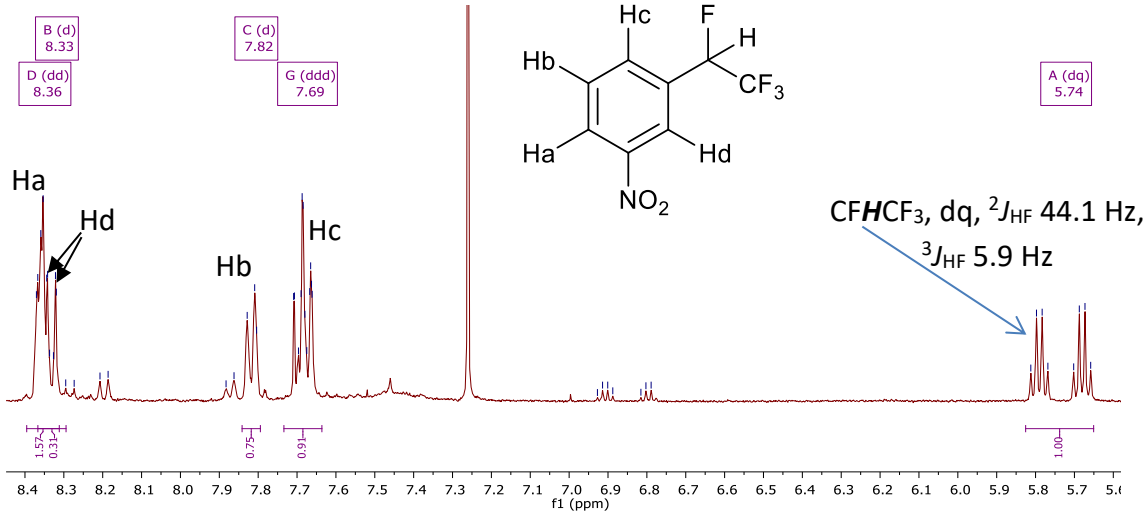


*Figure 84- ^{1}H NMR for compound **5a** in $CDCl_3$ on a 400 MHz spectrometer*

The ^{19}F and ^{13}C NMR spectra from a reaction between compound **3a** and nitronium tetrafluoroborate were consistent with the formation of **5a**. In the ^{19}F NMR spectrum

there were two peaks (fig. 85). The first peak was a doublet of doublets ($^{3}J_{FF}$ 12.8 Hz, $^{3}J_{FH}$ 5.9 Hz) at -78.7 ppm for the CF_3 group. The final peak was a doublet of quartets ($^{2}J_{FH}$ 44.1 Hz, $^{3}J_{FF}$ 12.8 Hz) at -196.5 ppm for the C***F***H resonance. In the ^{13}C NMR, the two non-aromatic carbons are a doublet of quartets ($^{1}J_{CF}$ 189 Hz, $^{2}J_{CF}$ 36 Hz) at 87.9 ppm for the CFH carbon and a quartet of doublets ($^{1}J_{CF}$ 282 Hz, $^{2}J_{CF}$ 28 Hz) at 121.8 ppm for the CF_3 carbon (fig. 86). ^{13}C DEPT was used first alongside their *J* coupling values to determine the ***C***NO_2 carbon (C2) and ***C***CFH carbon (C6). The ***C***CFH resonance was a doublet ($^{2}J_{CF}$ 8 Hz) at 122.3 ppm. Then the ***C***NO_2 resonance is a doublet ($^{4}J_{CF}$ 1 Hz) at 125.4 ppm. Next the ***C***HCCFH carbon (C5) and the O_2N***C***HCCFH carbon (C1) can be assigned because they are both doublets and that C1 was further de-shielded as it is closer to the nitro group. The C5 resonance was a doublet ($^{3}J_{CF}$ 7 Hz) at 128.2 ppm. Then the C1 resonance was a doublet ($^{3}J_{CF}$ 7 Hz) at 132.9 ppm. The final two aromatic carbons were both singlets and were assigned as the ***C***$HCNO_2$ carbon (C3) was closer to the nitro group so was further de-shielded. The ***C***$HC(H)CNO_2$ carbon (C4) resonance was a singlet at 124.0 ppm. Finally, the C3 resonance was a singlet at 130.2 ppm.

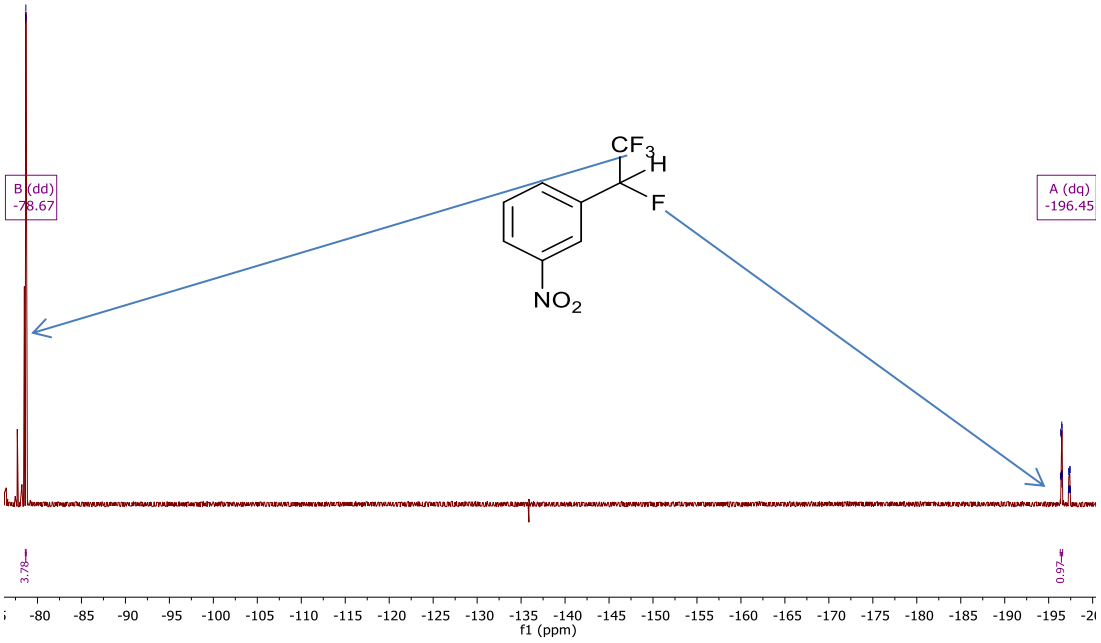


*Figure 85- ^{19}F NMR for compound **5a** in $CDCl_3$ on a 376 MHz spectrometer*

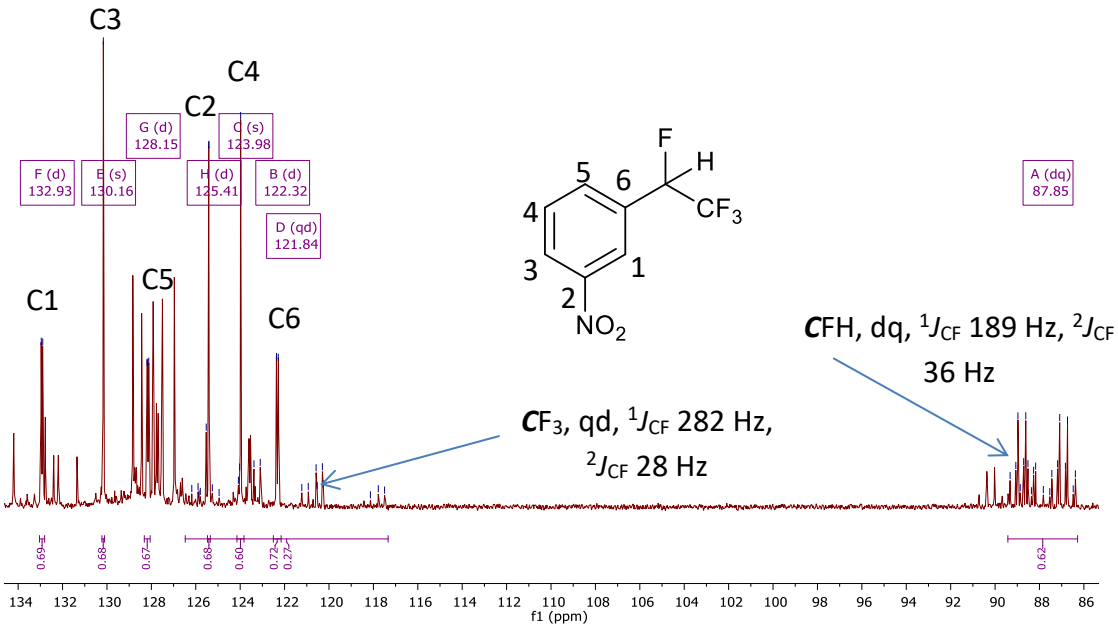


*Figure 86- ^{13}C NMR for compound **5a** in $CDCL_3$ on a 101 MHz spectrometer*

This electrophilic nitration mainly occurs at the meta site on the phenyl ring because the functional group ($CFHCF_3$) is electron withdrawing (fig. 87). However, as seen above in figure 86, the reaction was left too long so a small amount of dinitro substituted compound was produced meaning that the ^{13}C CMR spectrum was not pure.

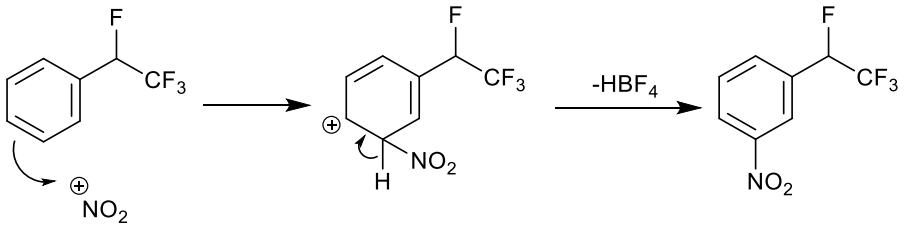


Figure 87- Mechanism for reactions between NO_2BF_4 and alkoxy/ alkyl fluoride substituted aromatics

Nitration of **3a** as the substrate was used to assess the effect of the $CFHCF_3$ functional group on the S_EAr process. **5o** and **5p** were synthesised to see how the nitrating agent reacted with on similar aromatic compounds with fluorine-containing side groups. Compounds **5o** and **5p** were formed in high yield. Similarly, compound **5o** was assigned as meta substitution from the ^1H NMR which matched the literature data[91] for the formation of 3-nitro-α,α,α-trifluorotoluene. Compound **5p** was also assigned as meta substitution by comparison to literature data.[92]

2.2.4.2 Competitive nitration kinetics between $ArCFHCF_3$, $ArOCF_3$ and $ArCF_3$

In the previous section we proved that the $ArCFHCF_3$ functional group is electron withdrawing by its meta substitution just like $ArOCF_3$ and $ArCF_3$. To study the $ArCFHCF_3$ functional group's relative rate of reactivity we carried out a competitive kinetic nitration reaction. To do this 0.055 mmol of nitronium tetrafluoroborate was dissolved

in 0.65 ml of nitromethane. Then the resulting solution was transferred to an NMR tube along with a D_2O lock tube. Next 0.056 mmol of each of the substrates (1-phenyl-1,2,2,2-tetrafluoroethane **3a**, trifluoromethoxy benzene **3p** and α,α,α-trifluorotoluene **3o**) was added to the NMR tube as a liquid. The reaction was then monitored by ^{19}F NMR at fairly regular intervals.

The reaction was monitored over a 24-hour period. Monitoring was possible by ^{19}F NMR spectroscopy because the addition of a nitro group caused a change in the shift for the CF_3 group in the range 0.1 – 0.15 ppm for each molecule. This change was observable in the NMR spectrum. The $ArOCF_3$ functional group reacted fastest and showed the greatest conversion. This means that it was the least electron withdrawing functional group and hence had the most activated phenyl ring. The next fastest functional group was $ArCF_3$ which was indicated from NMR spectra. From the data collected, it was about 0.9 times less reactive than $ArOCF_3$. The slowest reacting was the $ArCFHCF_3$ which was roughly 0.5 times less reactive than the $ArCF_3$ system.

2.2.5 Synthesis of $ArCHOHCF_2CF_3$ derivatives

Addition of a CF_2CF_3 functional group to organic molecules can be done via compounds such as $LiCF_2CF_3$, ICF_2CF_3 or $CuCF_2CF_3$ as mentioned in section 1.5. For the reactions carried out on aryl aldehydes the best reagent to use is $TMSCF_2CF_3$. First benzaldehyde and $TMSCF_2CF_3$ were dissolved in dry THF at 0 ^oC under an atmosphere of argon before the addition of the catalytic tetra-n-butylammonium fluoride (TBAF). The reaction was stirred continually while it was warmed to room temperature over the following 3 hours. The resulting benzyl-trimethylsilyl ether was hydrolysed by the addition of 6M hydrochloric acid and then the reaction mixture was allowed to stir for 48 hours to give 2,2,3,3,3-pentafluoro-1-phenyl-propan-1-ol, **2k**, after work up (fig. 88).

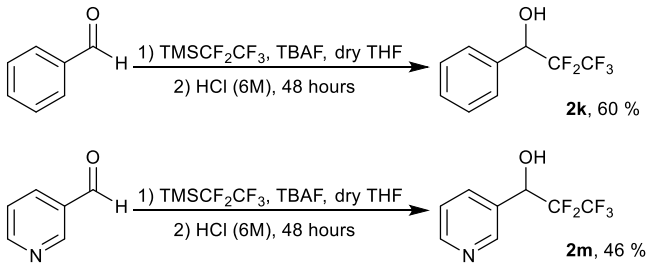


Figure 88- Reaction of aryl aldehydes derivatives and $TMSCF_2CF_3$

When switching substrates from phenyl to pyridine derivatives, it seems that the aldehyde became less susceptible to nucleophilic attack. The pyridine substrate under similar conditions (only 1.5 equivalents TBAF) to the $TMSCF_3$ reaction gave less than half of the $TMSCF_3$ reaction yield (51 %) since $TMSCF_2CF_3$ is a weaker nucleophile compared to $TMSCF_3$.

For compound **2k** three peaks in the ^{19}F NMR spectrum were observed (fig. 89). First a singlet at δ = -81.3 for the CF_3 group. The final two peaks were a doublet of doublets at δ = -121.9 ($^2J_{FF}$ 275.8 Hz, $^3J_{FH}$ 7.3 Hz) and -129.4 ($^2J_{FF}$ 275.8 Hz, $^2J_{FH}$ 16.7 Hz) for the CF_2 fluorine atoms because they are diasterotopic. The two fluorines are differentiated by their *J* coupling value to the proton on the adjacent carbon atom. The fluorine which closer in space to that proton will have a higher splitting value.

Pyridine derivatives were identified by having similar shifts. The first doublet of doublets was shifted upfield by about 1.4 ppm because of the deshielding caused by the pyridine ring whereas the second doublet of doublets showed little change when going to a pyridine ring for **2m**.

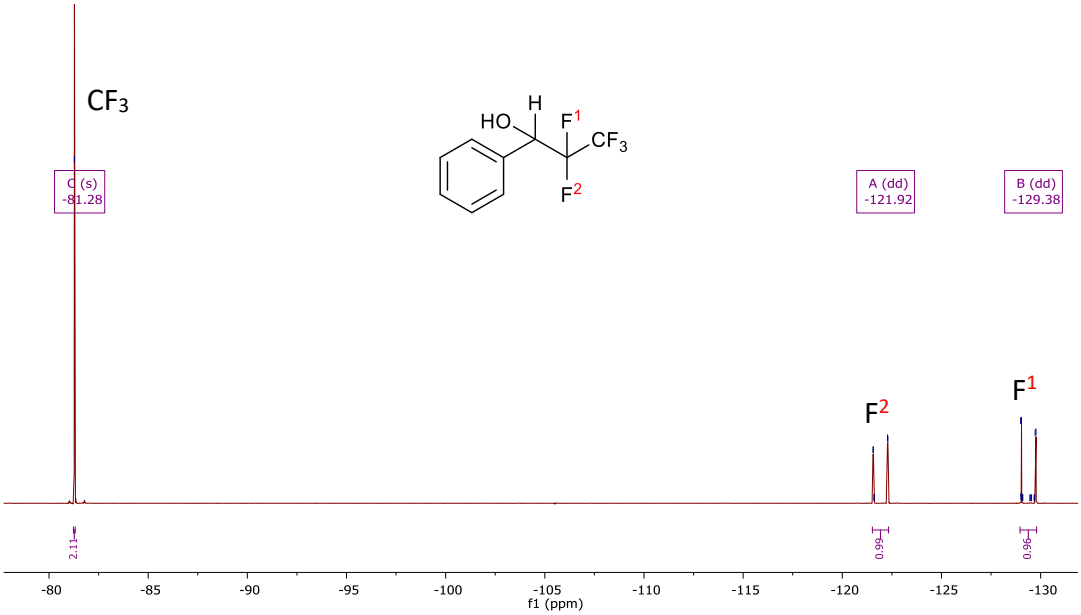


*Figure 89- ^{19}F NMR for compound **2k*** in $CDCl_3$ on a 376 MHz spectrometer

The ^1H and ^{13}C NMR spectra were consistent with the formation of **2k**. In the ^1H spectrum the most diagnostic peak is for C***H***(OH) which is a doublet of doublets ($^3J_{HF}$ 16.7 Hz, $^3J_{HF}$ 7.3 Hz) at 5.12 ppm because it has been split by the CF_2 group showing that the product had been formed (fig. 90). The formation of **2k** was backed up by the appearance of a broad singlet at 2.61 ppm for the alcohol proton. In the ^{13}C NMR

spectrum, the three non-aromatic carbon peaks are doublet of doublets, doublet of doublet of quartets and quartet of triplets (fig. 91). The CF_3 carbon is a quartet of triplets ($^1J_{CF}$ 287 Hz, $^2J_{CF}$ 36 Hz) at 119.3 ppm, the CF_2 carbon is a doublet of doublet of quartets ($^1J_{CF}$ 261 Hz, $^1J_{CF}$ 255 Hz, $^2J_{CF}$ 36 Hz) at 113.2 ppm and the ***C***HOH resonance is a doublet of doublets ($^2J_{CF}$ 28 Hz, $^2J_{CF}$ 22 Hz) at 72.1 ppm. ^{13}C DEPT was used to determine the singlet aromatic *ipso* carbon at 134.2 ppm because it was the only aromatic carbon not bonded to a hydrogen atom. Next the singlet *para* carbon was determined to be at 129.7 ppm as it is the smallest of three remaining peaks. The remaining two peaks are assigned as a broad singlet at 128.0 ppm for the *ortho* carbons (peak is broad because of a small long-range splitting with the CF_2 group) and narrow singlet at 128.7 ppm for *meta* carbons.

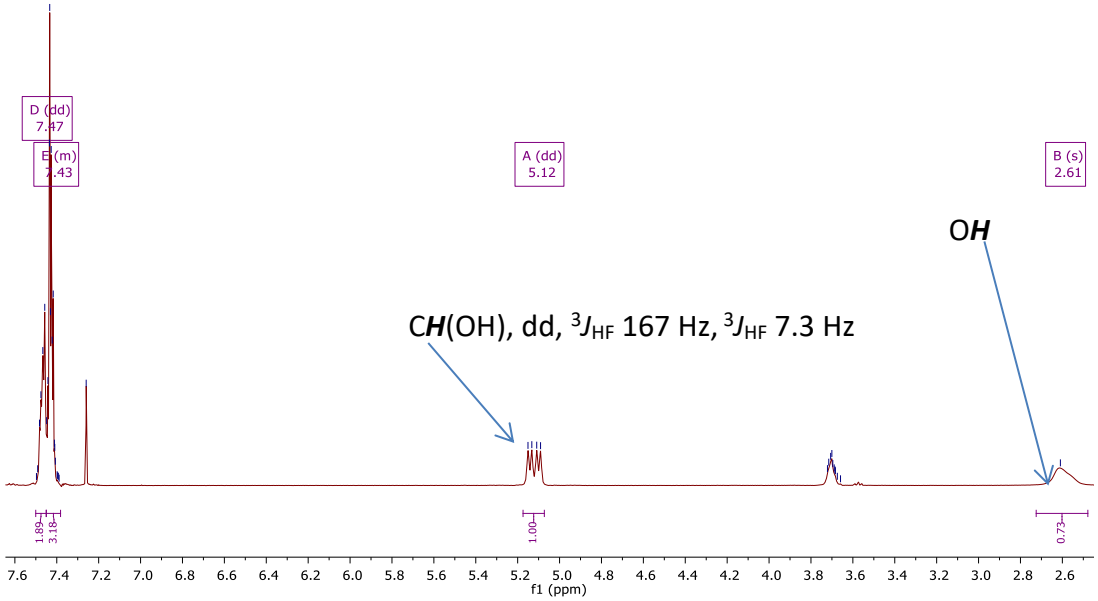


*Figure 90- ^1H NMR for compound **2k*** in $CDCl_3$ on a 400 MHz spectrometer

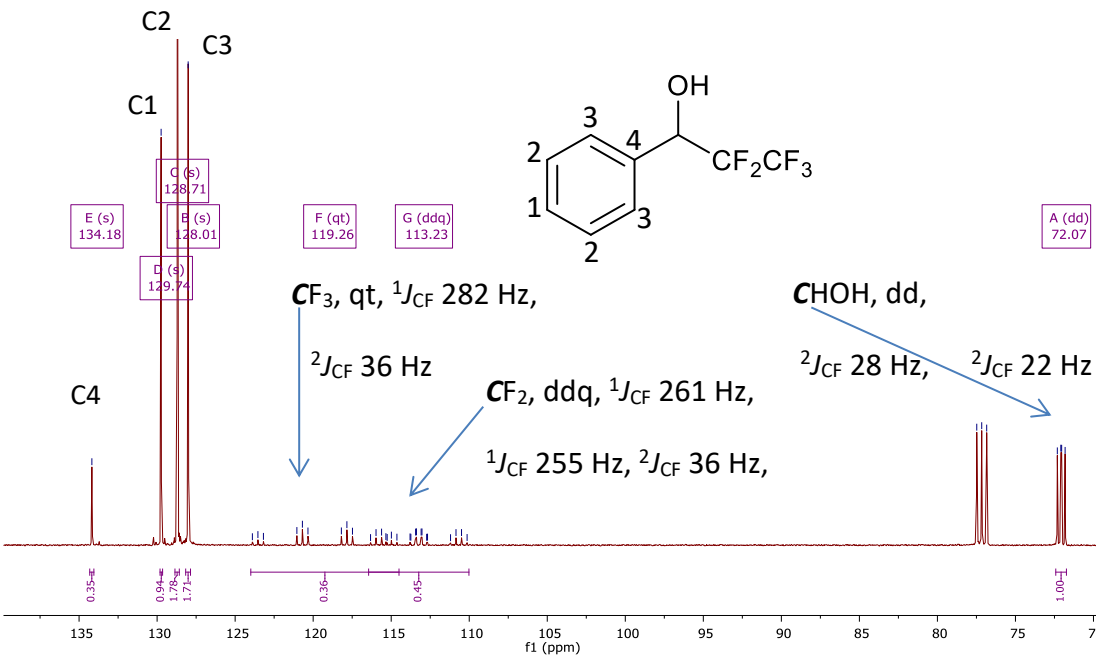


*Figure 91- ^{13}C NMR for compound **2k*** in $CDCl_3$ on a 101 MHz spectrometer

Gas chromatography-mass spectrometry was also used, alongside these NMR spectra, to prove that all compounds mentioned above were formed. The molecular ion for compound **2m** at m/z = 226.1 at a retention time of 2.91 mins. The main fragment ion for compounds **2** was $[M\text{-}CF_2CF_3]^+$.

Crystals of **2m** were formed via recrystallization in a mixture of hexane/ acetone followed by a slow evaporation in a mixture of hexane/ DCM. Compound **2m** then had its structure determined by x-ray crystallography (fig. 92&93). Again, we thank Dr. Dimitri Yufit for carrying out this X-ray crystallography.

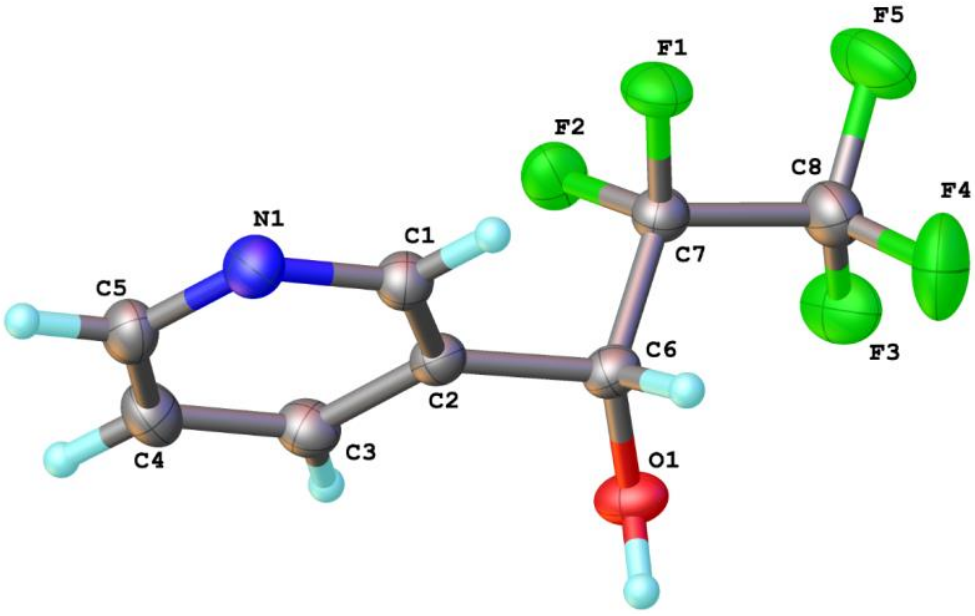


*Figure 92- Molecular structure for compound **2m***

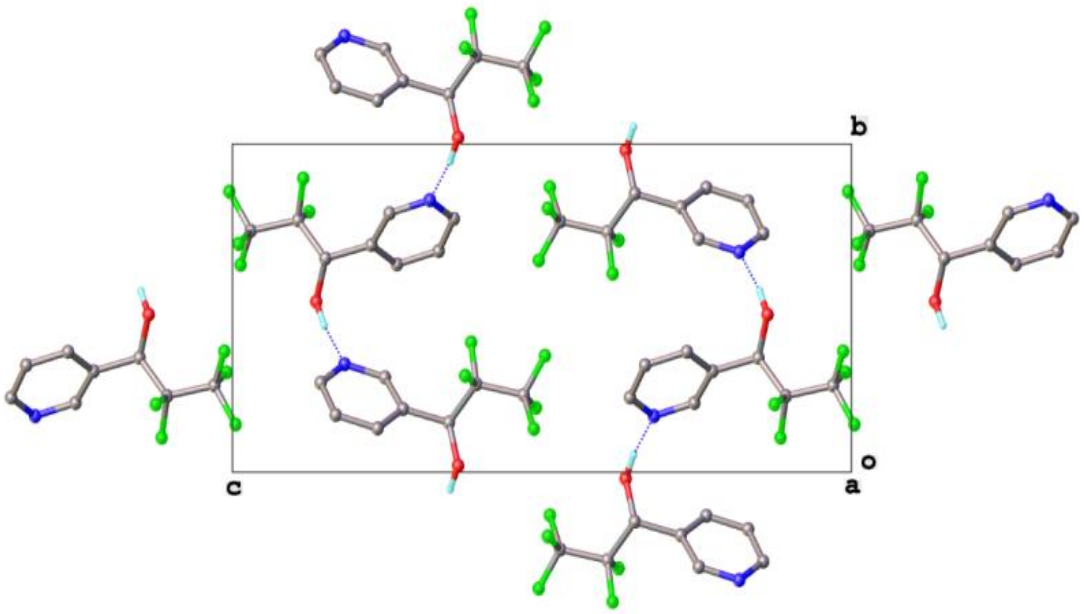


*Figure 93- Compound **2m** unit cell*

2m has a monoclinic crystal in the space group $P2_1/n$. and is constructed of hydrogen bonding between O-H…N and π-π interactions into double chains. Alongside this, π-π aromatic stacking is observed. The experimental data from this X-ray crystallography is shown in appendix 2.

2.2.6 Synthesis of $ArCFHCF_2CF_3$ derivatives

Once the pentafluoroethyl substituted alcohol is formed, the hydroxy group can be replaced by a fluorine atom via a reaction with DAST using methodology described in section 2.2.2. Compound **2k** was dissolved in DCM at 0 °C before the slow addition of DAST to the reaction mixture after which the reaction warmed to room temperature and stirred for 48 hours to give 1,2,2,3,3,3-hexafluoro-1-phenylpropane, **3k**, after work up (fig.94).

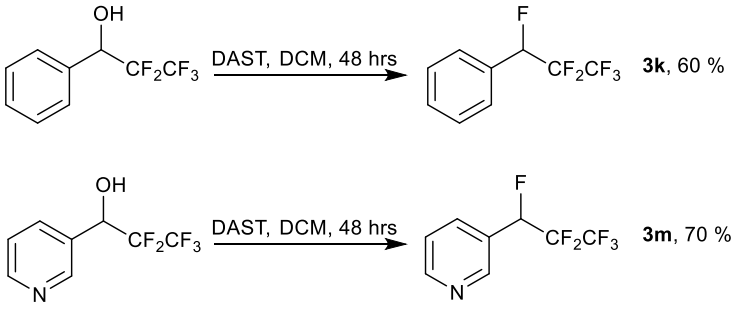


*Figure 94- Reaction scheme for compounds **3k&m** with DAST*

For compound **3k** four peaks were observed in the ^{19}F NMR (fig. 95). The first peak was a doublet of doublets ($^3J_{FF}$ 11.1 Hz, $^3J_{FH}$ 2.2 Hz) at -82.2 ppm for the CF_3 group. Then

the next two peaks are a doublet of doublet of doublets at -122.9 ppm ($^2J_{FF}$ 283.9 Hz, $^3J_{FF}$ 11.1 Hz, $^3J_{FH}$ 4.3 Hz) and -131.6 ppm ($^2J_{FF}$ 283.9 Hz, $^3J_{FH}$ 17.5 Hz, $^3J_{FF}$ 15.1 Hz) for the CF_2 fluorine atoms because they are diasterotopic. As with the alcohol precursor, the two fluorines are differentiated by their *J* coupling values with either the fluorine or the proton on the adjacent carbon atom. The fluorine which is closer in space to both the fluorine and the proton will have a higher splitting value from both. The final peak was a doublet of doublet of pentuplets ($^2J_{FH}$ 43.8 Hz, $^3J_{FF}$ 15.1 Hz, $^{3/4}J_{FF}$ 11.1 Hz) at -195.7 ppm for the C***F***H resonance. For **3m**, we observed a similar spectrum, but the CF_2 and CF_3 resonances were slightly shifted upfield (0.1 – 0.25 ppm) whereas the C***F***H resonance was shifted downfield by 2.8 ppm.

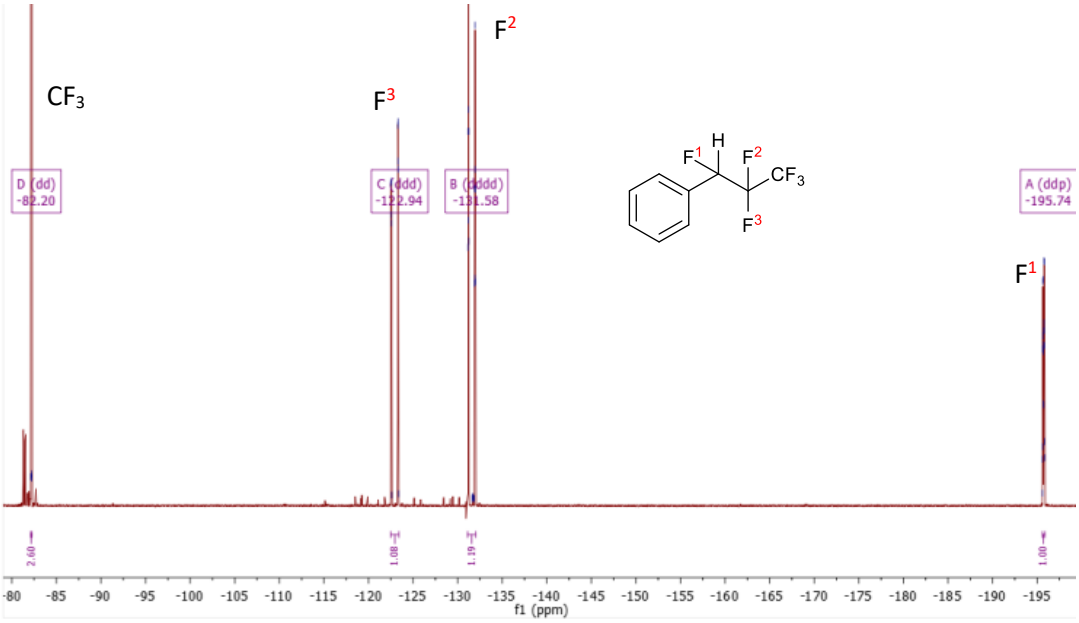


*Figure 95- ^{19}F NMR of compound **3k*** in $CDCl_3$ on a 400 MHz spectrometer

The ^1H and ^{13}C NMR spectra were consistent with the formation of **3k**. In the ^1H spectrum the most important peak is for C***H***F which is a doublet of doublet of doublets ($^2J_{HF}$ 43.8 Hz, $^3J_{HF}$ 17.5 Hz, $^3J_{HF}$ 4.3 Hz) at 5.73 ppm because it is split by the CF_2 group and now by the CFH fluorine atom (fig. 96). In the ^{13}C spectrum, the three non-aromatic carbon peaks are in similar positions as they were previously in the alcohol **2k** (fig. 97). The CF_3 carbon is now a quartet of triplet of doublets ($^1J_{CF}$ 288 Hz, $^2J_{CF}$ 36 Hz, $^3J_{CF}$ 2 Hz) at 119.2 ppm. Next the CF_2 carbon is now a doublet of doublet of doublet of quartets ($^1J_{CF}$ 263 Hz, $^1J_{CF}$ 254 Hz, $^2J_{CF}$ 37 Hz, $^2J_{CF}$ 29 Hz) at 111.5 ppm. The ***C***FH resonance was a doublet of doublet of doublets ($^1J_{CF}$ 186 Hz, $^2J_{CF}$ 32 Hz, $^2J_{CF}$ 24 Hz) at 88.4 ppm. ^{13}C DEPT was used assign the doublet ($^2J_{CF}$ 20 Hz) *ipso* aromatic carbon at 129.8 ppm because it was the only aromatic carbon not bonded to a proton. Both the *ortho* and *meta* aromatic

carbons are determined to be doublets and assigned based on their *J* coupling value. The *ortho* carbons were a doublet ($^3J_{CF}$ 7 Hz) at 127.7 ppm and the *meta* carbons were a doublet ($^4J_{CF}$ 2 Hz) at 130.7 ppm. Then the remaining unassigned peak was a singlet for the *para* carbon at 128.8 ppm.

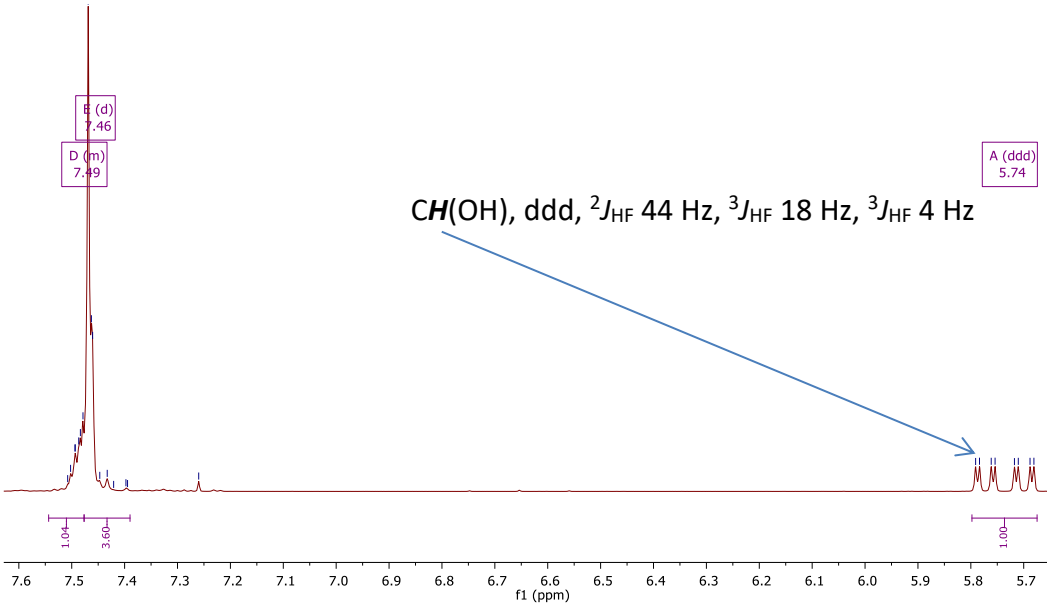


*Figure 96 ^1H NMR of compound **3k*** in $CDCl_3$ on a 400 MHz spectrometer

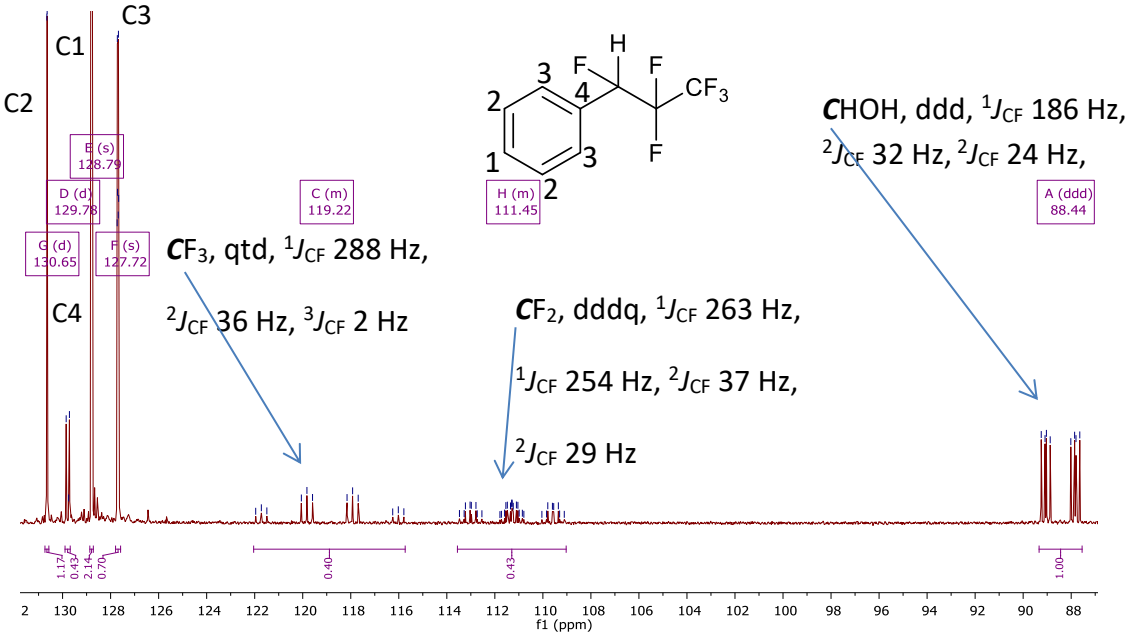


*Figure 97- ^{13}C NMR of compound **3k*** in $CDCl_3$ on a 101 MHz spectrometer

The molecular ion for compound **3k** at m/z = 228.0 was at a retention time of 2.15 mins in GC/ MS. The main fragment ion for compounds **3** was $[M\text{-}CF_2CF_3]^+$.

2.2.7 Formation of ArCFC=CFCF$_3$ derivatives

An alkene substituted with both an aromatic group and trifluoromethyl functional group can be made by reacting the hexafluoro aromatic compound **3k** with a strong base, such as KO^{t}Bu. First 1,2,2,3,3,3-hexafluoro-1-phenylpropane was dissolved in dry THF at 0 ^{o}C and under an atmosphere of argon before the addition of KO^{t}Bu. The reaction was then stirred continually while warmed to room temperature for t two hours to give 1-phenyl-1,2,3,3,3-pentafluoro-1-propene, **4k** after work up (fig. 98).

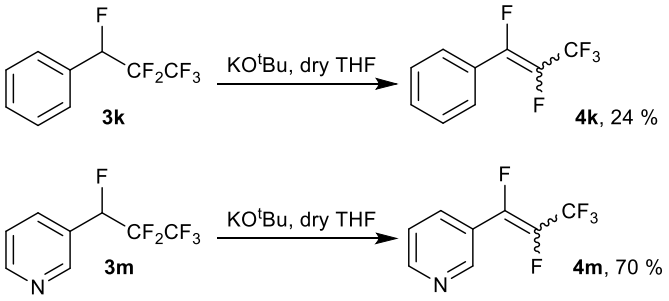


*Figure 98 Reaction of potassium butoxide and -CFHCF$_2$CF$_3$ compounds **3k** and **3m***

It was necessary for the reaction to be done in a dry solvent (i.e. dry THF) and under an atmosphere of argon to remove the presence of water in the reaction mixture from solvent and atmosphere.

The elimination reaction of **3k** and **3m** occurs either as an E_{1CB} or a concerted E_2 elimination, but at this stage it is not possible to determine which mechanism is followed (fig. 99&100).

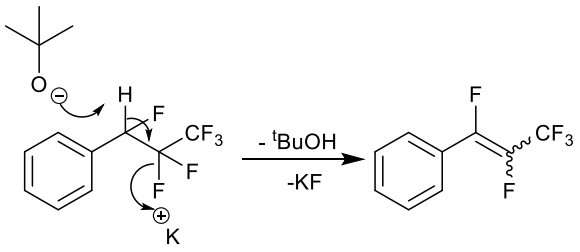


Figure 99- E_2 elimination pathway

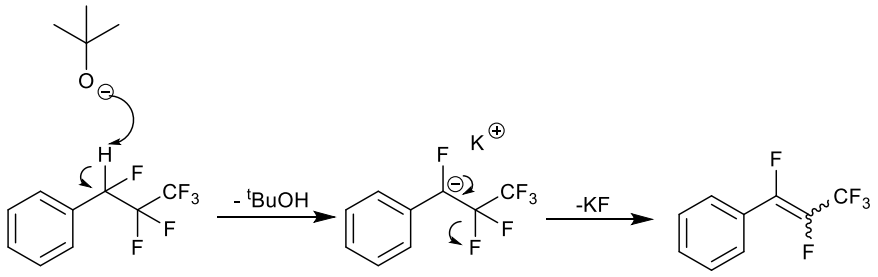


Figure 100- E_{1CB} elimination pathway

Both of compounds **4k** and **4m** showed three peaks in their ^{19}F NMR. For compound **4k**, there was a doublet of doublets ($^{3}J_{FF}$ 22.0 Hz, $^{4}J_{FF}$ 10.6 Hz) at –67.0 ppm for the CF_3 group. Both of the fluorines directly bonded to the double bond showed a splitting pattern of a doublet of quartets and could be differentiated by their J coupling values. The C***F***CF_3 resonance was a doublet of quartets ($^{3}J_{FF}$ 131.7 Hz, $^{4}J_{FF}$ 22.0 Hz) at -146.3 ppm. Then the C***F***Ph resonance was a doublet of quartets ($^{3}J_{FF}$ 131.7 Hz, $^{4}J_{FF}$ 10.6 Hz) at -169.5 ppm (fig. 101).

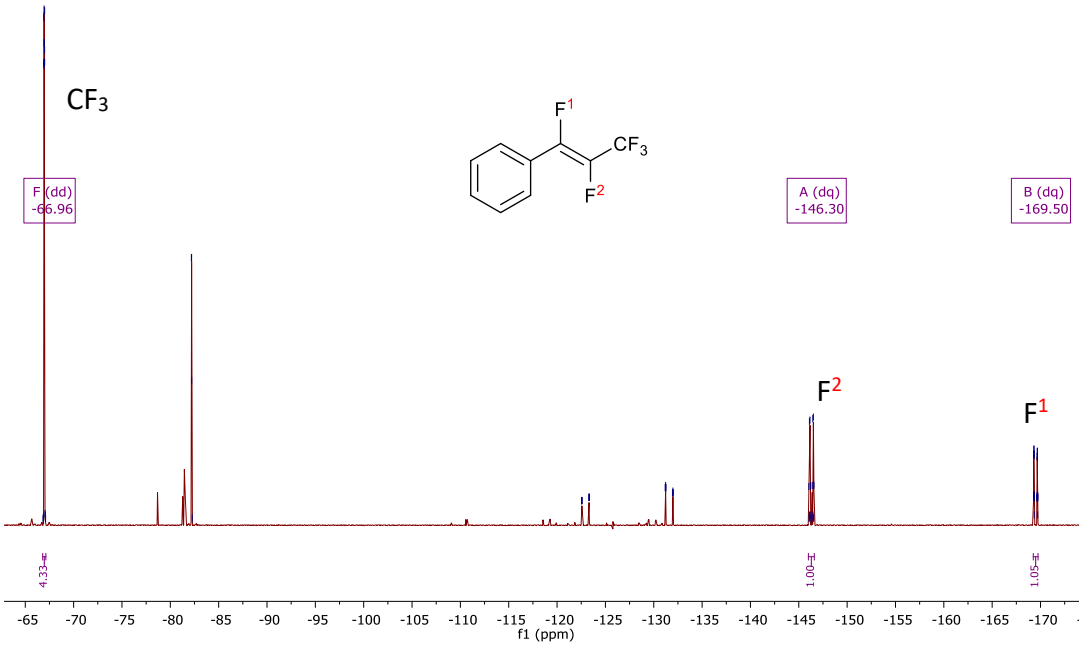


*Figure 101- ^{19}F NMR for compound **4k*** in $CDCl_3$ on a 376 MHz spectrometer

The ^{1}H and ^{13}C NMR spectra were consistent with the formation of **4k**. The only peaks observed on the ^{1}H NMR spectrum were for the aromatic protons indicating that the CFH proton was lost in the reaction and the reaction went to completion (fig. 102). For the ^{13}C NMR spectrum, the three non-aromatic carbons have characteristic shifts (fig. 103). The CF_3 carbon is now a quartet of doublet of doublets ($^{1}J_{CF}$ 272 Hz, $^{2}J_{CF}$ 36 Hz, $^{3}J_{CF}$ 4 Hz) at 119.5 ppm. Next the ***C***FCF_3 carbon is a doublet of doublet of quartets ($^{1}J_{CF}$ 249 Hz, $^{2}J_{CF}$ 51 Hz, $^{2}J_{CF}$ 40 Hz) at 138.4 ppm. Finally, the ***C***FPh resonance is a doublet of doublet of quartets ($^{1}J_{CF}$ 250 Hz, $^{2}J_{CF}$ 36 Hz, $^{3}J_{CF}$ 3 Hz) at 151.4 ppm. The alkene carbon resonances could be differentiated by their *J* coupling values. The *ipso* carbon is a doublet of doublets ($^{2}J_{CF}$ 24 Hz, $^{3}J_{CF}$ 6 Hz) at 127.2 ppm. Next the *ortho* carbons were a doublet ($^{3}J_{CF}$ 8 Hz) at 126.6 ppm. The *meta* carbons are also a doublet ($^{4}J_{CF}$ 2 Hz) at 128.9 ppm. Finally, the *para* carbon resonance appears as a doublet ($^{4}J_{CF}$ 2 Hz) at 131.3 ppm.

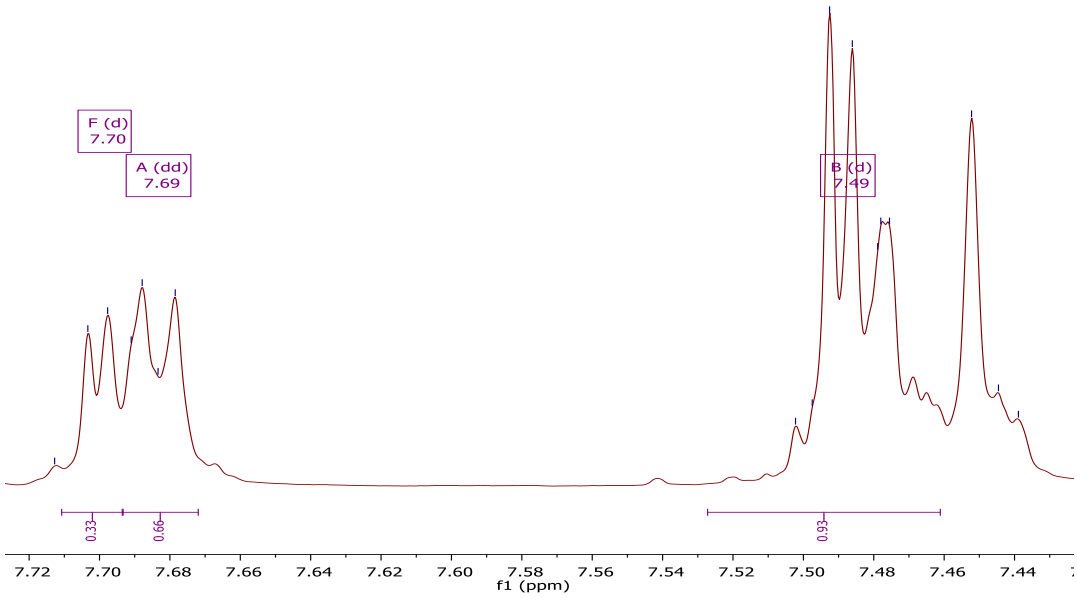


*Figure 102 ^{1}H NMR for compound **4k*** in $CDCl_3$ on a 400 MHz spectrometer

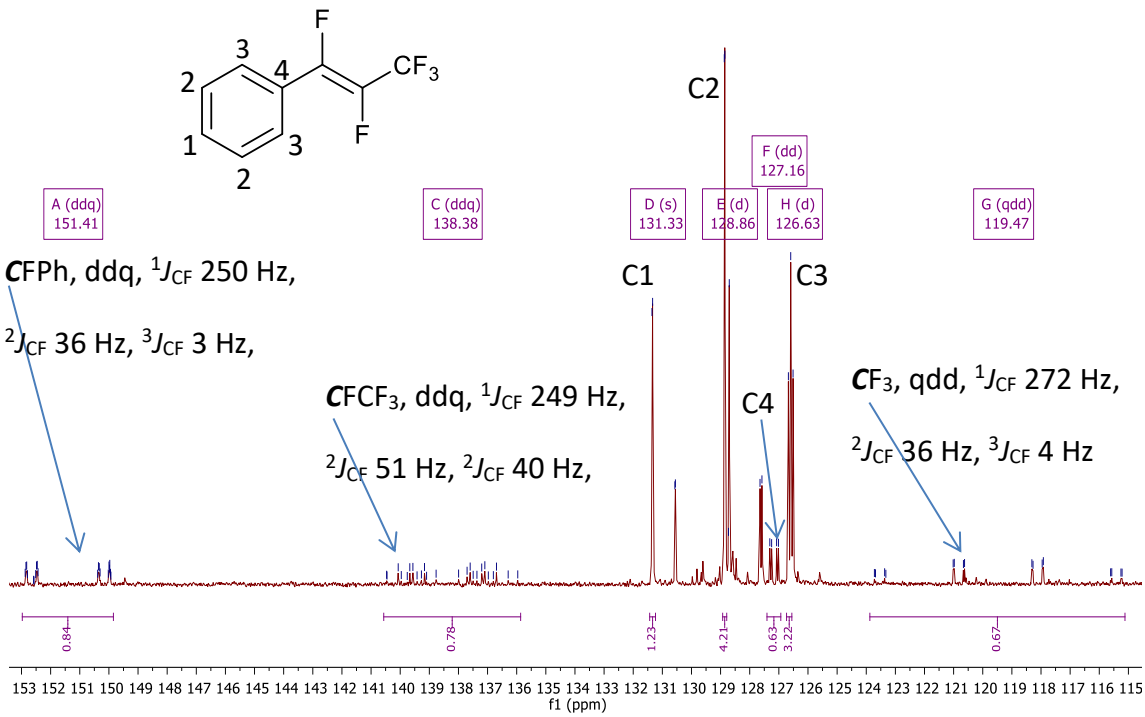


*Figure 103- ^{13}C NMR for compound **4k*** in $CDCl_3$ on a 101 MHz spectrometer

Gas chromatography-mass spectrometry was also used, alongside these NMR spectra, to prove that all compounds mentioned above were formed. The molecular ion for compound **4k** at m/z = 208.0 at a retention time of 2.34 mins. The main fragment ion for compounds **4** was $[M\text{-}CF_3+F]^+$.

2.3 Conclusions

We have developed methodology for the synthesis of $ArCHFCF_3$ derivatives by a two-step process for benzaldehyde derivates (fig. 104).

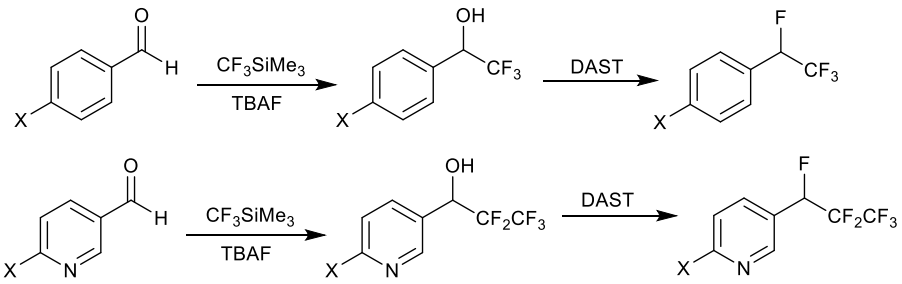


Figure 104- Two step reaction scheme for the formation of the $ArCHFCF_3$ functional group

A ray of systems bearing substituents have been prepared for the first time and characterized by NMR, mass spec. and x-ray crystallography.

Overall all compounds have been made in good yield and confirmed by assigning the data from GC-MS, crystal structures and ^{1}H, ^{13}C and ^{19}F NMR spectra. Within this thesis we have shown that the $ArCFHCF_3$ functional group can be synthesized by the pathway set out in section **2.1**. The first part of the pathway ($TMSCF_3$ and TBAF) worked in a good yield for all alcohols irrelevant of the substituent on the aromatic ring.

The DAST stage (Fig. 104) on average gave slightly lower yields than the first stage. Nevertheless, the $ArCFHCF_3$ analogues were produced in good yield and only formed the desired product. An unforeseen problem was that compounds **3a**, **3f** and **3k** decomposed upon heating on the high vacuum line. We have shown that the most likely decomposition pathway gives an ether. Furthermore, we have shown how to avoid this unexpected decomposition occurring upon workup.

We next studied the reaction of $ArCFHCF_3$ derivatives with an electrophile such as nitronium tetrafluoroborate. As expected the $ArCFHCF_3$ functional group was electron withdrawing and, hence, activating the aromatic ring to electrophilic substitution in the meta position. Competition reactions of $ArCFHCF_3$ with trifluoromethoxy benzene and α,α,α-trifluorotoluene. A competitive NMR experiment was carried out to see which of the functional groups was most reactive and the $-CFHCF_3$ functional group was less reactive than CF_3 and OCF_3.

1-(3-Pyridyl)-1,2,3,3,3-pentafluoroprop-1-ene was synthesized by a reaction between the prior hexafluoro compound and a base, KO^tBu.

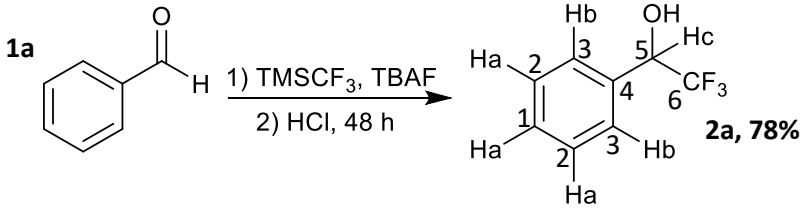
Chapter 3: Experimental

3.1 General

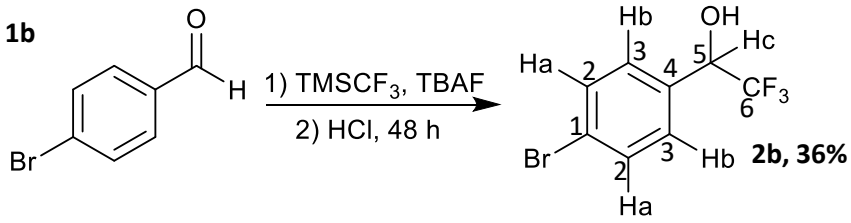
Anhydrous solvents were purchased from Acros Organics and stored over 3Å molecular sieves under an argon atmosphere. Unless otherwise stated, all other chemicals were purchased from Fisher Scientific, Fluorochem or Sigma Aldrich and were used without any further purification. Thin layer chromatography was carried out using Macherey-Nagel™ standard SIL G silica layers (5-17 µm with fluorescence indicator UV_{254}, compounds visualised under UV light) on Polygram™ polyester sheets purchased from Fisher Scientific and column chromatography using silica gel LC401 (40-63 µm) purchased from Fluorochem. Proton, carbon and fluorine nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 Ultrashield (^{1}H NMR at 400 MHz; ^{13}C NMR at 101 MHz; ^{19}F NMR at 376 MHz) spectrometer with residual solvent peaks as the internal standard (^{1}H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.16 ppm) or relative to an external standard (^{19}F NMR, $CFCl_3$ at 0.00 ppm). NMR spectroscopic data are reported as follows: chemical shift (ppm), integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, m=multiplet), coupling constant(s) (Hz), assignment. NMR assignments were made using COSY, DEPT-135, HSQC and HMBC experiments. Low resolution LC-MS data was recorded on a Waters Ltd TQD mass spectrometer equipped with Acquity UPLC. GC-MS data was recorded on a Shimadzu QP2010-Ultra. Accurate mass analysis was achieved with a Waters Ltd QtoF Premier mass spectrometer equipped with an accurate solids analysis probe (ASAP) or a Waters Ltd LCT Premier XE mass spectrometer equipped with Acquity UPLC and ASAP. Infra-red (IR) spectra were recorded on a Perkin Elmer FTIR Spectrum Two fitted with an ATR probe and selected absorption maxima are reported in wavenumbers. Melting points were measured with a manually operated Gallenkamp apparatus in open capillary tubes at atmospheric pressure and are uncorrected.

3.2 Synthesis of 1-phenyl-1,2,2,2-trifluoroethanol derivatives:

General Procedure – Trifluoromethylation using Ruppert's reagent (2a-j, l). Aldehyde derivative **1** (30 mmol) and CF_3SiMe_3 (5.1 g, 5.4 mL, 36 mmol) were dissolved in THF (30 mL) at 0°C under an atmosphere of argon. TBAF (0.1 g) was added and the reaction was allowed to warm to RT and stirred for 2 h. 6 M HCl (6 mL) was added and the mixture stirred for 48 h. The reaction mixture was extracted with ether (3 x 30 mL), washed with water (2 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent evaporated to yield the alcohol product without any further purification required.

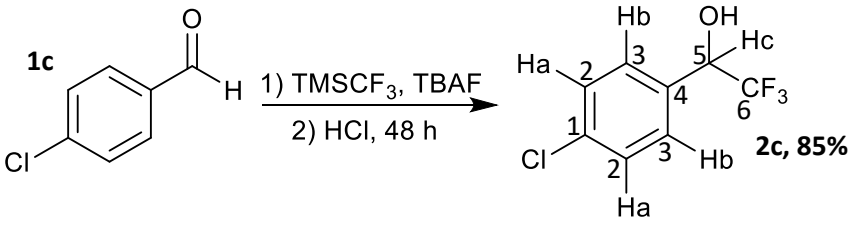


1-Phenyl-2,2,2-trifluoroethanol (2a). Benzaldehyde, **1a**, (3.2 g, 30 mmol) and $TMSCF_3$ (5.1 g, 36 mmol) gave 1-phenyl-2,2,2-trifluoroethanol, **2a**, (4.12 g, 78 %) as clear, yellow liquid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.51 – 7.45 (2H, m, Ar-H_b), 7.44 – 7.40 (3H, m, Ar-H_a), 5.02 (1H, q, $^3J_{HF}$ 6.6, H_c), 2.74 (1H, s, OH). ^{19}F NMR (376 MHz, Chloroform-d) δ -78.4 (d, $^3J_{FH}$ 6.6, CF_3). ^{13}C NMR (101 MHz, Chloroform-d) δ 134.1 (s, Ar-C4), 129.7 (s, Ar-C1), 128.8 (s, Ar-C3), 127.6 (s, Ar-C2), 124.4 (q, $^1J_{CF}$ 282, C6), 73.0 (q, $^2J_{CF}$ 32, C5). GC-MS: 3.0 mins, m/z = 176.1 (65 %, $[M]^{+\bullet}$), 159.1 (1, $[M\text{-}F]^+$), 107.1 (100, $[M - CF_3]^+$), 79.1 (96, $[C_2F_2HO]^+$, 77.1 (86, $[Ph]^+$); as compared to literature data.[82]

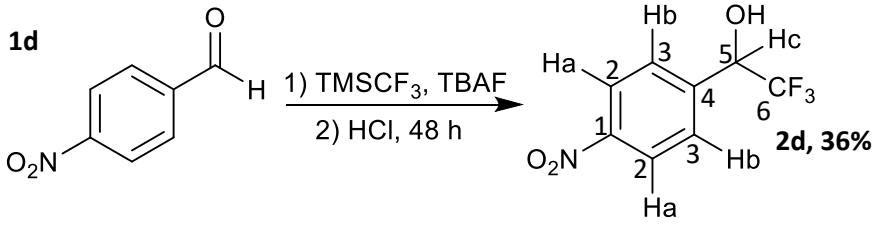


1-(4-Bromophenyl)-2,2,2-trifluoroethanol (2a). 4-Bromobenzaldehyde, **1b**, (4.28 g, 30.6 mmol) and CF_3SiMe_3 (5.1 g, 36 mmol) gave 1-(4-bromophenyl)-2,2,2-trifluorethanol, **2b**, (2.10 g, 36 %) as a clear, pale orange liquid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.54 (2H, d, $^3J_{HH}$ 8.1, Ar-H_a), 7.35 (2H, d, $^3J_{HH}$ 8.1, Ar-H_b), 5.00 (1H, q, $^3J_{HF}$ 6.6, H_c) 2.87 (1H, s, OH). ^{19}F NMR (376 MHz, Chloroform-d) δ -78.5 (d, $^3J_{FH}$ 6.6, CF_3). ^{13}C NMR (101 MHz, Chloroform-d) δ 132.0 (s, Ar-C4), 131.9 (s, Ar-C2), 129.2 (s, Ar-C3), 124.1 (q, $^1J_{CF}$ 282, C6), 123.9 (s, Ar-C1), 72.3 (q, $^2J_{CF}$ 32, C5). GC-MS: 3.84 mins, m/z = 254.0 (37

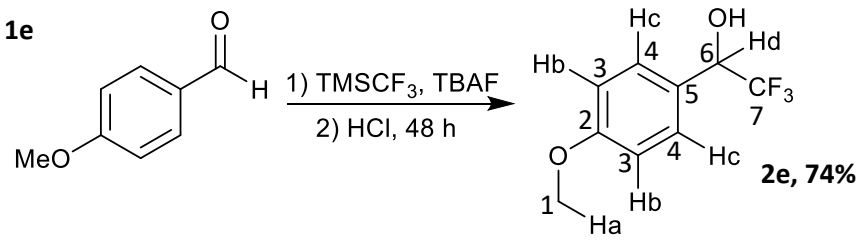
%, $[M]^{+\bullet}$), 185.0 (100, $[M\text{-}CF_3]^+$), 157.0 (22, $[PhBr]^+$), 77.1 (100, $[Ph]^+$); as compared to literature data.[89]



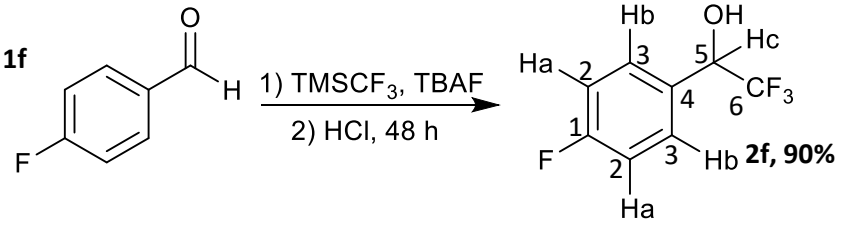
1-(4-Chlorophenyl)-2,2,2-trifluoroethanol (**2c**). 4-Chlorobenzaldehyde, **1c**, (4.21 g, 29.9 mmol) and CF_3SiMe_3 (5.1 g, 36 mmol) gave 1-(4-chlorophenyl)-2,2,2-trifluoroethanol, **2c**, (5.36 g, 85 %) as an opaque, light orange liquid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.44 – 7.40 (2H, m, Ar-H_a), 7.40 – 7.36 (2H, m, Ar-H_b), 4.99 (1H, q, $^3J_{HF}$ 6.6, H_c) 3.20 (1H, s, OH). ^{19}F NMR (376 MHz, Chloroform-d) δ -78.5 (d, $^3J_{FH}$ 6.6, CF_3). ^{13}C NMR (101 MHz, Chloroform-d) δ 135.6 (s, Ar-C1), 132.6 (s, Ar-C4), 129.0 (s, C2), 128.9 (s, C3), 124.2 (q, $^1J_{CF}$ 282, Ar-C6), 72.2 (q, $^2J_{CF}$ 32, C5). GC-MS: 3.57 mins, m/z = 210.0 (55 %, $[M]^{+\bullet}$), 141.2 (100, $[M\text{-}CF_3]^+$), 113.1 (46.2, $[PhCl]^+$), 77.1 (99.3, $[Ph]^+$); as compared to literature data.[83]



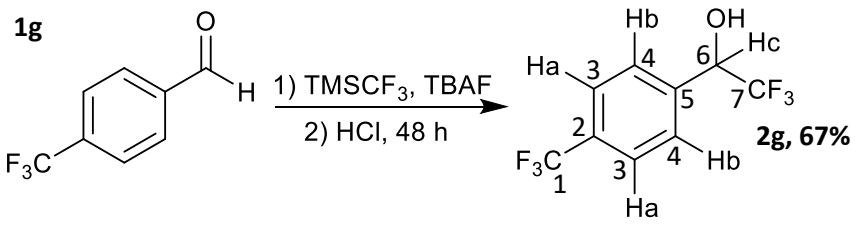
1-(4-Nitrophenyl)-2,2,2-trifluoroethanol (2d). 4-Nitrobenzaldehyde, **1d**, (4.60 g, 30.5 mmol) and CF_3SiMe_3 (5.1 g, 36 mmol) gave 1-(4-nitrophenyl)-2,2,2-trifluoroethanol, **2d**, (2.10 g, 36 %) as a pale orange solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.19 (2H, d, $^3J_{HH}$ 8.7, Ar-H_a), 7.66 (2H, d, $^3J_{HH}$ 8.7, Ar-H_b), 5.47 (1 H, s, OH), 5.12 (1H, q, $^3J_{HF}$ 6.5, H_c). ^{19}F NMR (376 MHz, Chloroform-d) δ -78.1 (d, $^3J_{FH}$ 6.5, CF_3). ^{13}C NMR (101 MHz, Chloroform-d) δ 148.4 (s, Ar-C1), 141.84 (s, Ar-C4), 128.6 (s, Ar-C_2), 124.1 (q, $^1J_{CF}$ 283.0, Ar-C_6), 123.5 (s, Ar-C_3), 71.4 (q, $^2J_{CF}$ 32, Ar-C_5). GC-MS: 4.27 mins, m/z = 221.0 (12 %, $[M]^{+\bullet}$), 152.1 (100, $[M\text{-}CF_3]^+$), 127.1 (22, $[PhCH_2CF_2H]^+$), 77.0 (100, $[Ph]^+$); as compared to literature data.[83]



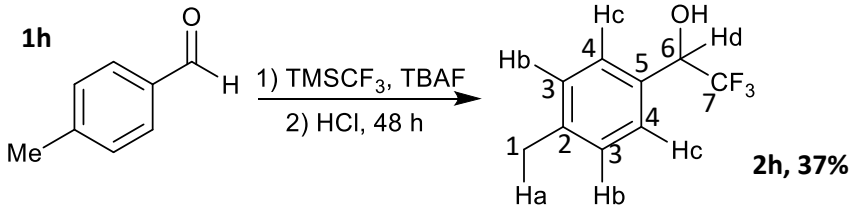
1-(4-Methoxyphenyl)-2,2,2-trifluoroethanol (2e). 4-Methoxybenzaldehyde, **1e**, (4.11 g, 30.2 mmol) and CF_3SiMe_3 (5.1 g, 36 mmol) gave 1-(4-methoxyphenyl)-2,2,2-trifluoroethanol, **2e**, (5.20 g, 74 %) as a clear, dark orange liquid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.38 (2H, d, $^3J_{HH}$ 9.0, Ar-H_b), 6.91 (2H, d, $^3J_{HH}$ 9.0, Ar-H_c), 4.91 (1H, q, $^3J_{HF}$ 6.9, H_d), 4.07 (1H, s, OH), 3.80 (3H, s, H_a). ^{19}F NMR (376 MHz, Chloroform-d) δ -78.6 (d, $^3J_{FH}$ 6.9, CF_3). ^{13}C NMR (101 MHz, Chloroform-d) δ 160.6 (s, Ar-C2), 128.9 (s, Ar-C3), 126.4 (s, Ar-C5), 124.5 (q, $^1J_{CF}$ 282, C7), 114.2 (s, Ar-C4), 72.6 (q, $^2J_{CF}$ 32, C6), 55.44 (s, C1). GC-MS: 3.70 mins, m/z = 206.1 (83 %, $[M]^{+\bullet}$), 137.3 (100, $[M\text{-}CF_3]^+$), 109.1 (22, $[PhO(H)Me]^+$), 94.1 (59, $[PhOH]^+$), 77.1 (49, $[Ph]^+$) ; as compared to literature data.[82]



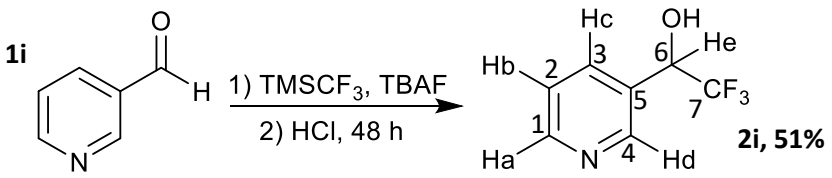
4-(Fluorophenyl)-2,2,2-trifluoroethanol (2f). 4-Fluorobenzaldehyde, **1f**, (3.82 g, 30.8 mmol) and $TMSCF_3$ (5.1 g, 36 mmol) gave 1-(4-fluorophenyl)-2,2,2-trifluoroethanol, **2f**, (5.39 g, 90 %) as a translucent, yellow liquid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.47 (2H, dd, $^3J_{HH}$ 8.9, $^4J_{HF}$ 5.2, Ar-H_b), 7.10 (2H, dd, $^3J_{HH}$ 8.9, $^3J_{HF}$ 8.7, Ar-H_a), 5.02 (1H, q, $^3J_{HF}$ 6.6, H_c), 2.51 (1H, s, OH). ^{19}F NMR (376 MHz, chloroform-d) δ -78.66 (3F, d, $^3J_{FH}$ 6.6, CF_3), -111.81 (1F, tt, $^3J_{FH}$ 8.7, $^4J_{FH}$ 5.2, Ar-F). ^{13}C NMR (101 MHz, chloroform-d) δ 163.5 (d, $^1J_{CF}$ 284, Ar-C1), 129.9 (s, Ar-C4), 129.4 (d, $^3J_{CF}$ 9, Ar-C3), 124.3 (q, $^1J_{CF}$ 282, C6), 123.4 (d, $^2J_{CF}$ 22.0, Ar-C2), 72.3 (q, $^2J_{CF}$ 32, C5). GC-MS: 3.84 mins, m/z = 194.0 (29 %, $[M]^{+\bullet}$), 125.0 (100, $[M\text{-}CF_3]^+$), 97.1 (22, $[PhF+H]^+$), 77.0 (36, $[Ph]^+$); as compared to literature data.[83]



1-(4-Trifluoromethylphenyl)-2,2,2-trifluoroethanol (2g). 4-Trifluoromethyl-benzaldehyde, **1g**, (5.23 g, 30.1 mmol) and $TMSCF_3$ (5.1 g, 36 mmol) gave 1-(4-trifluoromethylphenyl)-2,2,2-trifluoroethanol, **2g**, (4.93 g, 67 %) as a translucent, white liquid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.69 (2H, d, $^3J_{HH}$ 8.2, Ar-H_a), 7.63 (2H, d, $^3J_{HH}$ 8.2, Ar-H_b), 5.07 (1H, q, $^3J_{HF}$ 6.5, H_c), 3.82 (1H, s, OH). ^{19}F NMR (376 MHz, chloroform-d) δ -62.8 (3F, s, Ar-CF_3), -78.4 (3F, d, $^3J_{FH}$ 6.5, CF_3). ^{13}C NMR (101 MHz, chloroform-d) δ 138.1 (s, Ar-C5), 131.8 (q, $^2J_{CF}$ 32, Ar-C2), 128.0 (s, Ar-C4), 125.6 (q, $^3J_{CF}$ 4, Ar-C3), 124.2 (q, $^1J_{CF}$ 284, C7), 124.0 (q, $^1J_{CF}$ 272, C1), 72.3 (q, $^2J_{CF}$ 32, C6). GC-MS: 3.05 mins, m/z = 244.0 (15 %, $[M]^{+\bullet}$), 175.0 (100, $[M\text{-}CF_3]^+$), 145.1 (21, $[PhCF_3\text{-}H]^+$), 127.1 (100, $[PhCF_2]^+$); as compared to literature data.[82]

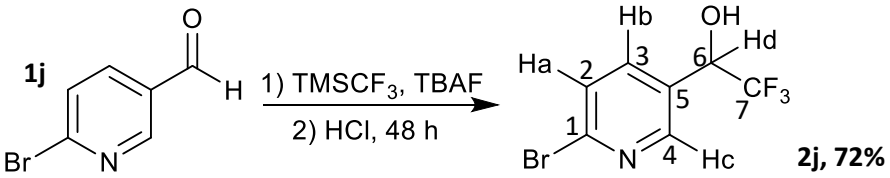


1-(4-Methylphenyl)-2,2,2-trifluoroethanol (2h). 4-Methylbenzaldehyde, **1h**, (3.66 g, 30.5 mmol) and $TMSCF_3$ (5.2 g, 36.7 mmol) gave 1-(4-methylphenyl)-2,2,2-trifluoroethanol, **2h**, (2.14 g, 37 %) as a very pale, clear yellow liquid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.36 (2H, d, $^3J_{HH}$ 7.8, Ar-H_b), 7.22 (2H, d, $^3J_{HH}$ 7.8, Ar-H_c), 4.99 (1H, q, $^3J_{HF}$ 6.9, H_d), 2.57 (1H, s, OH), 2.38 (3H, s, H_a). ^{19}F NMR (376 MHz, chloroform-d) δ -78.4 (d, $^3J_{FH}$ 6.9, CF_3). ^{13}C NMR (101 MHz, chloroform-d) δ 139.7 (s, Ar-C5), 131.2 (s, Ar-C2), 129.5 (s, Ar-C3), 127.5 (s, Ar-C4), 124.5 (q, $^1J_{CF}$ 282, C7), 72.9 (q, $^2J_{CF}$ 32, Ar-C6), 21.4 (s, C1). GC-MS: 3.27 mins, m/z = 190.0 (50 %, $[M]^{+\bullet}$), 121.1 (100, $[M\text{-}CF_3]^+$), 93.1 (77, $[PhMe+H]^+$), 91.1 (71, $[PhCH_2]^+$), 77 (39, $[Ph]^+$); as compared to literature data.[83]

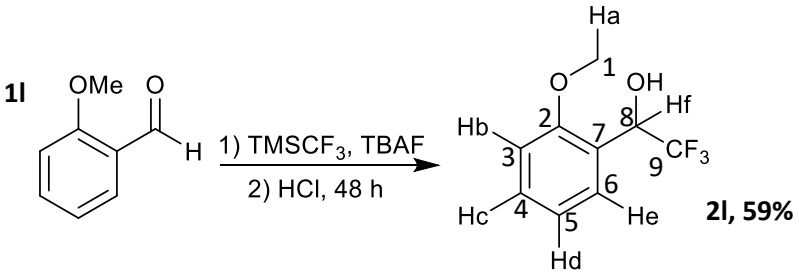


1-(3-pyridyl)-2,2,2-trifluoroethanol (2i). 3-Pyridinecarboxaldehyde, **1i**, (3.19 g, 29.8 mmol) and $TMSCF_3$ (5.1 g, 36 mmol) gave 1-(3-pyridyl)-2,2,2-trifluoroethanol, **2i**, (2.67 g, 51 %) as a clear, yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.60 (1H, s, H_d),

8.55 (1H, dd, $^{3}J_{HH}$ 4.7, $^{4}J_{HH}$ 2.2, H_a), 7.96 (1H, dd, $^{3}J_{HH}$ 8.0, $^{4}J_{HH}$ 2.2, H_c), 7.41 (1H, ddd, $^{3}J_{HH}$ 8.0, $^{3}J_{HH}$ 4.7, $^{5}J_{HH}$ 0.8, H_b), 5.1 (1H, q, $^{3}J_{HF}$ 6.7, H_e). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -78.4 (d, $^{3}J_{FH}$ 6.7, CF_3). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.8 (s, Ar-C4), 148.4 (s, Ar-C1), 136.1 (s, Ar-C2), 131.5 (s, Ar-C3), 124.4 (q, $^{1}J_{CF}$ 283, C7), 124.0 (s, Ar-C5), 70.5 (q, $^{2}J_{CF}$ 32, C6). GC-MS: 3.46 mins, m/z = 177.1 (77 %, $[M]^{+\bullet}$), 108.2 (100, $[M\text{-}CF_3]^{+}$), 80.1 (22, $[C_5H_5N+H)$; as compared to literature data.[57]

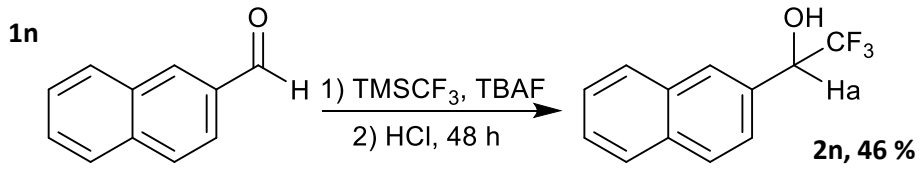


1-(6-bromo-3-pyridinyl)-2,2,2-trifluoroethanol (2j). 6-Bromonicotinaldehyde, **1j**, (5.57 g, 30.1 mmol) and $TMSCF_3$ (5.1 g, 36 mmol) gave 1-(6-bromo-3-pyridinyl)-2,2,2-trifluoroethanol, **2j**, (2.40 g, 31 %) as a very dark orange, translucent liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.39 (1H, d, $^{4}J_{HH}$ 2.5, Hc), 7.76 (1H, dd, $^{3}J_{HH}$ 8.4, $^{4}J_{HH}$ 2.5, Hb), 7.52 (1H, dd, $^{3}J_{HH}$ 8.4, $^{5}J_{HH}$ 0.7, Ha), 5.97 (1H, s, OH), 5.10 (1H, q, $^{3}J_{HF}$ 6.2, Hd). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -78.4 (d, $^{3}J_{FH}$ 6.2, CF_3). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.1 (s, Ar-C4), 142.6 (s, Ar-C1), 138.3 (s, Ar-C2), 130.5 (s, Ar-C5), 128.4 (s, Ar-C5), 123.9 (q, $^{1}J_{CF}$ 282.4, C7), 69.7 (q, $^{2}J_{CF}$ 33, C6). GC-MS: 3.84 mins, m/z = 255.0 (41 %, $[M]^{+\bullet}$), 186.0 (100, $[M\text{-}CF_3]^{+}$), 77.1 (97, $[C5H5N]^{+}$). HRMS (ASAP, ES+) m/z calculated for $C_7H_6NOF_3Br$ $[M+H]^{+}$, 255.9585, found 255.9588.



1-(2-Methoxyphenyl)-2,2,2-trifluoroethanol (2l). 2-Methoxybenzaldehyde, **1l**, (4.23 g) and $TMSCF_3$ (5.1 g, 36 mmol) gave 1-(2-methoxyphenyl)-2,2,2-trifluoroethanol, **2l**, (3.80 g, 59 %) as a clear, orange liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 (1H, d, $^{3}J_{HH}$ 8.1, H_b), 7.37 (1H, ddd, $^{3}J_{HH}$ 8.1, $^{3}J_{HH}$ 7.8, $^{4}J_{HH}$ 1.7, H_c), 7.02 (1H, td, $^{3}J_{HH}$ 7.8, $^{4}J_{HH}$ 1.1, $H_{d)}$, 6.96 (1H, d, $^{3}J_{HH}$ 7.8, H_e), 5.29 (q, $^{3}J_{HF}$ 7.1, H_f), 3.88 (3H, s, H_a), 3.78 (1H, s, OH). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -78.1 (d, $^{3}J_{FH}$ 7.1, CF_3). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.7 (s, Ar-C2), 130.7 (s, Ar-C3), 129.4 (s, Ar-C6), 124.8 (q, $^{1}J_{CF}$ 283, C9), 122.3 (s, Ar-C7), 121.2 (s, Ar-C4), 111.4 (s, Ar-C5), 69.9 (q, $^{2}J_{CF}$ 33, C8), 55.90 (s, C1). GC-MS: 3.53 mins,

m/z = 206.0 (83 %, $[M]^{+\bullet}$), 137.3 (100, $[M - CF_3]^+$), 121.1 (28, $[C_6H_5CHOCH_3]^+$), 107.1 (96, $[C_6H_4OMe]^+$, 94.1 (24, $[PhOH]^+$), 77 (41, $[Ph]^+$); as compared to literature data.[54]

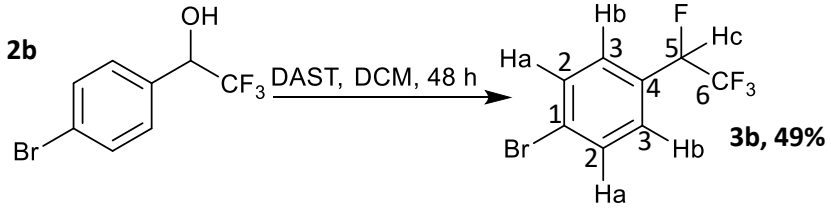


1-(2-Napthyl)-2,2,2-trifluoroethanol (2n). 2-Napthaldehyde, **1n**, (4.72 g, 30.2 mmol) and $TMSCF_3$ (5.1 g, 36 mmol) reacts to give 1-(2-napthyl)-2,2,2-trifluoroethanol, **2n**, (4.16 g, 61 %) as a pale, yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 (1H, s, Ar-H), 7.88 (2H, t, *J* 8.7, Ar-H), 7.87 (1H, d, *J* 2.9, Ar-H), 7.57 (1H, d, *J* 9.4, Ar-H), 7.54 (1H, t, *J* 5.9, Ar-H), 7.54 (1H, d, *J* 7.3, Ar-H), 5.17 (1H, q, $^3J_{HF}$ 6.7, Ha), 2.90 (1H, s, OH). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -78.0 (d, $^3J_{FH}$ 6.7, CF_3). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 133.9 (s, Ar-C6), 133.0 (s, Ar-C1), 131.4 (s, Ar-C10), 128.7 (s, Ar-C7), 128.4 (s, C9), 127.9 (s, C8), 127.5 (s, C5), 127.0(s, C2), 126.7 (s, C4), 124.5 (q, $^1J_{CF}$ 282, C12), 124.4 (s, C3), 73.1 (q, $^2J_{CF}$ 32, C11). GC-MS: 4.34 mins, m/z = 226.1 (70 %, $[M]^{+\bullet}$), 157.1 (75, $[M\text{-}H\text{-}CF_3]^+$), 129.2 (100, $[M–CHOHCF_3+2H]^+$), 128.1 (55, $[M\text{-}CHOHCF_3+H]^+$), 127.1 (40, $[M\text{-}CHOHCF_3]^+$), 78.5 (14, $[Ph+H]^+$); as compared to literature data.[90]

3.3 Synthesis of 1-phenyl-1,2,2,2-tetrafluoroethane derivatives (3a-j, l):

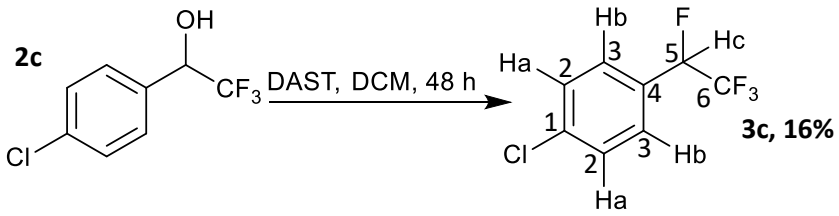
General procedure – 1-Aryl-2,2,2-trifluoroethanol **2** (10 mmol) was dissolved in DCM (40 mL) and stirred at 0 °C. Diethylaminosulfur trifluoride, DAST, (3.54 g, 22 mmol) dissolved in DCM (10 mL) was added to the reaction mixture. The reaction was allowed to warm to RT and stirred for 48 hours. Water (50 mL) and DCM (50 mL) were added to the reaction mixture, followed by neutralisation with $NaHCO_3$. The organic layer was washed with water (2 x 50 mL) and the solvent evaporated to yield product **3**, which did not require any further purification.

1-Phenyl-1,2,2,2-tetrafluoroethane (3a). 1-Phenyl-2,2,2-trifluoroethanol, **2a**, (1.76 g, 10 mmol) and DAST (3.54 g, 22 mmol) gave 1-phenyl-1,2,2,2-tetrafluoroethane, **3a**, (1.34 g, 75 %) as a clear, orange liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 – 7.42 (5H, m, Ar-H), 5.60 (1H, dq, $^{2}J_{HF}$ 44.1, $^{3}J_{HF}$ 6.2, Ha). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -78.8 (3F, dd, $^{3}J_{FF}$ 12.9, $^{3}J_{FH}$ 6.2, CF_3), -194.6 (1F, dq, $^{2}J_{FH}$ 44.1, $^{3}J_{FF}$ 12.9, C**F**H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 130.6 (d, $^{4}J_{CF}$ 2, Ar-C2), 130.4 (d, $^{2}J_{CF}$ 20, Ar-C4), 128.9 (s, Ar-C1), 127.3 (d, $^{3}J_{CF}$ 7, Ar-C3), 122.4 (qd, $^{1}J_{CF}$ 281, $^{2}J_{CF}$ 29, C6), 89.1 (dq, $^{1}J_{CF}$ 186, $^{2}J_{CF}$ 35, C5). GC-MS: 2.01 mins m/z = 178.0 (82 %, $[M]^{+\bullet}$), 159.1 (8, $[M\text{-}F]^{+}$), 109.2 (100 %, $[M\text{-}CF_3]^{+}$), 83.0 (35 %, $[CH_2CF_3]^{+}$); as compared to literature data.[34]

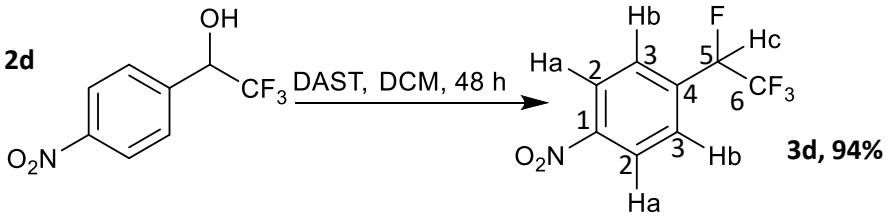


1-(4-Bromophenyl)-1,2,2,2-tetrafluoroethane (3b). 1-(4-Bromophenyl)-2,2,2-trifluoroethanol, **2b**, (1.77 g, 6.97 mmol) and DAST (3.54 g, 22 mmol) gave 1-(4-bromophenyl)-1,2,2,2-tetrafluoroethane, **3b** (0.88 g, 49 %) as an opaque, dark orange liquid. ^{1}H NMR (700 MHz, Chloroform-d) δ 7.59 (2H, d, $^{3}J_{HH}$ 8.3, H_a), 7.33 (2H, m, $^{3}J_{HH}$ 8.3, H_b), 5.56 (1H, dq, $^{2}J_{HF}$ 44.2, $^{3}J_{HF}$ 5.9, H_c). ^{19}F NMR (376 MHz, Chloroform-d) δ -78.87 (3F, dd, $^{3}J_{FF}$ 13.0, $^{3}J_{FH}$ 5.9, CF_3), -195.12 (1F, dq, $^{2}J_{FH}$ 44.2, $^{3}J_{FF}$ 13.0, C**F**H). ^{13}C NMR (176 MHz, Chloroform-d) δ 132.2 (s, Ar-C2), 129.4 (dq, $^{2}J_{CF}$ 21, $^{3}J_{CF}$ 1, Ar-C4), 128.9 (dq, $^{3}J_{CF}$ 7, $^{4}J_{CF}$ 1, Ar-C3), 125.06 (s, Ar-C1(^{81}Br)), 125.15 (s, Ar-C1(^{79}Br)), 122.1 (qd, $^{1}J_{CF}$ 281.6, $^{2}J_{CF}$ 29, C6),

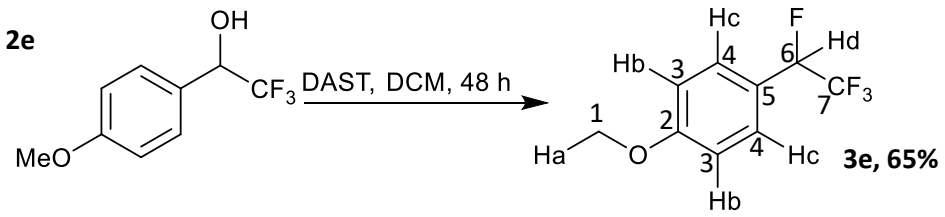
88.5 (dq, $^{1}J_{CF}$ 187, $^{2}J_{CF}$ 35, C5). GC-MS: 3.0 mins m/z = 256.0 (54 %, $[M]^{+\bullet}$), 187.0 (100 %, $[M\text{-}CF_3]^{+}$), 108.1 (58 %, $[M\text{-}CF_3\text{-}Br]^{+}$); as compared to literature data.[35]



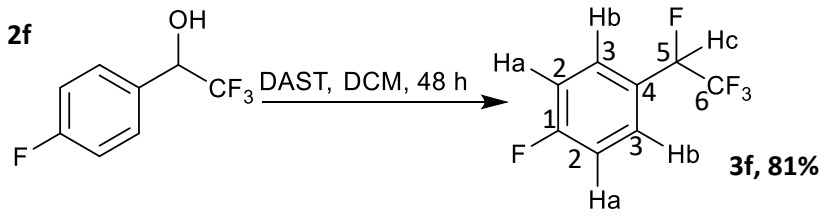
1-(4-Chlorophenyl)-1,2,2,2-tetrafluoroethane (3c). 1-(4-Chlorophenyl)-2,2,2-trifluoroethanol, **2c**, (1.77 g, 8.39 mmol) and DAST (3.25 g, 20.17 mmol) gave 1-(4-chlorophenyl)-1,2,2,2-tetrafluoroethane, **3c**, (0.88 g, 40 %) a translucent, orange liquid. ^{1}H NMR (700 MHz, Chloroform-d) δ 7.44 (2H, d, $^{3}J_{HH}$ 8.7, H_a), 7.40 (2H, d, $^{3}J_{HH}$ 8.7, H_b), 5.58 (1H, dq, $^{2}J_{HF}$ 44.1, $^{3}J_{HF}$ 6.0, H_c). ^{19}F NMR (376 MHz, Chloroform-d) δ -78.9 (3F, dd, $^{3}J_{FF}$ 13.0, $^{3}J_{FH}$ 6.0, CF_3), -194.8 (1F, dq, $^{2}J_{FH}$ 44.1, $^{3}J_{FF}$ 13.0, C**F**H). ^{13}C NMR (176 MHz, Chloroform-d) δ 136.8 (s, Ar-C1(^{35}Cl)), 129.2 (s, Ar-C2), 128.8 (d, $^{2}J_{CF}$ 20, Ar-C4), 128.65 (d, $^{3}J_{CF}$ 7, Ar-C3), 122.1 (qd, $^{1}J_{CF}$ 282, $^{2}J_{CF}$ 29, C6), 88.5 (dq, $^{1}J_{CF}$ 187, $^{2}J_{CF}$ 35, C5). GC-MS: 2.7 mins m/z = 211.95 (70 %, $M^{+\bullet}$), 143.2 (100 %, $[M\text{-}CF_3]^{+}$), 107.1 (58 %, $[M\text{-}CF_3\text{-}HCl]^{+}$/ $[C_7H_4F]^{+}$); as compared to literature data.[34]



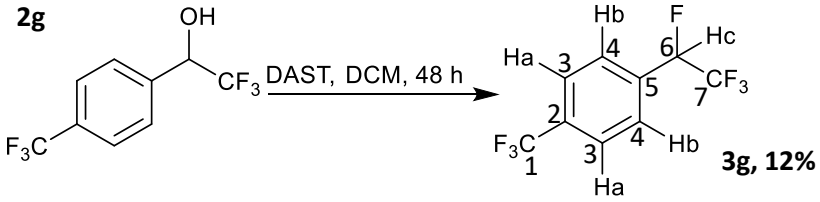
1-(4-Nitrophenyl)-1,2,2,2-tetrafluoroethane (3d). 1-(4-Nitrophenyl)-2,2,2-trifluoroethanol, **2d**, (1.68 g, 7.6 mmol) and DAST (3.54 g, 22 mmol) gave 1-(4-nitrophenyl)-1,2,2,2-tetrafluoroethane, **3d**, (1.81 g, 94 %) as an opaque, dark brown liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 (1H, d, $^{3}J_{HH}$ 8.5, H_a), 7.67 (1H, d, $^{3}J_{HH}$ 8.5, H_b), 5.75 (1H, dq, $^{2}J_{HF}$ 44.0, $^{3}J_{HF}$ 5.8, H_c). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -78.5 (3F, dd, $^{3}J_{FF}$ 12.7, $^{3}J_{FH}$ 5.9, CF_3), -197.4 (1F, dq, $^{2}J_{FH}$ 44.0, $^{3}J_{FF}$ 12.7, C**F**H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.3 (s, Ar-C1), 136.8 (d, $^{2}J_{CF}$ 20, Ar-C4), 128.2 (d, $^{3}J_{CF}$ 7, Ar-C3), 124.0 (s, Ar-C2), 121.8 (qd, $^{1}J_{CF}$ 282, $^{2}J_{CF}$ 28, C6), 88.0 (dq, $^{1}J_{CF}$ 189, $^{2}J_{CF}$ 35, C5). GC-MS: 3.93 mins m/z = 223.0 (61 %, $M^{+\bullet}$), 177.0 (24, $[M\text{-H-}NO_2]^{+}$), 154.1 (50, $[M\text{-}CF_3]^{+}$), 127.1 (100, $[CHFPhOH+2H]^{+}$), 107.1 $(CHPhOH]^{+}$). HRMS (LC-MS, ES-) m/z calculated for $C_8H_4F_4NO_2$ $[M\text{-}H]^{-}$, 222.0178, found 222.0181.



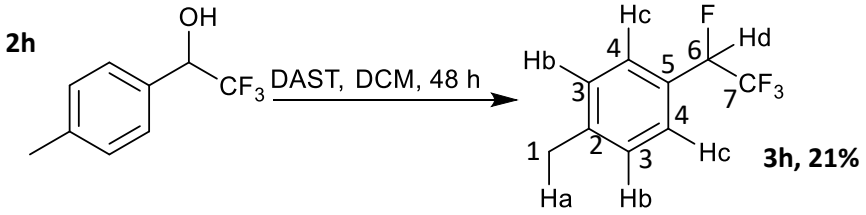
1-(4-Methoxyphenyl)-1,2,2,2-tetrafluoroethane (3e). 1-(4-Methoxyphenyl)-2,2,2-trifluoroethanol, **2e**, (2.11 g, 10.14 mmol) and DAST (3.54 g, 22 mmol) gave 1-(4-methoxyphenyl)-1,2,2,2-tetrafluoroethane, **3e**, (1.09 g, 52 %) as a clear, pale orange liquid. ^{1}H NMR (700 MHz, Chloroform-d) δ 7.39 (2H, d, $^{3}J_{HH}$ 8.5, Ar-H_b), 6.96 (2H, d, $^{3}J_{HH}$ 8.5, Ar-H_c), 5.52 (1H, dq, $^{2}J_{HF}$ 43.9, $^{3}J_{HF}$ 6.2, H_d), 3.84 (3H, s, H_a). ^{19}F NMR (376 MHz, Chloroform-d) δ -78.9 (3F, dd, $^{3}J_{FF}$ 13.5, $^{3}J_{FH}$ 6.2, CF_3), -190.8 (1F, dq, $^{2}J_{FH}$ 43.9, $^{3}J_{FF}$ 13.5, C**F**H). ^{13}C NMR (176 MHz, Chloroform-d) δ 161.4 (d, *J* 2, Ar-C2), 129.0 (d, $^{3}J_{CF}$ 6, Ar-C4), 122.5 (qd, $^{1}J_{CF}$ 281, $^{2}J_{CF}$ 30, C7), 122.4 (d, $^{2}J_{CF}$ 21, Ar-C5), 114.3 (s, C3), 88.9 (dq, $^{1}J_{CF}$ 185, $^{2}J_{CF}$ 35, C6), 55.50 (s, C1). GC-MS: 3.0 mins m/z = 208.1 (74 %, $M^{+\bullet}$), 139.3 (100 %, [M-CF3]+), 109.1 (15, [PhO(H)Me]+), 96.1 (26, $[PhOH+2H]^{+}$); as compared to literature data.[34]



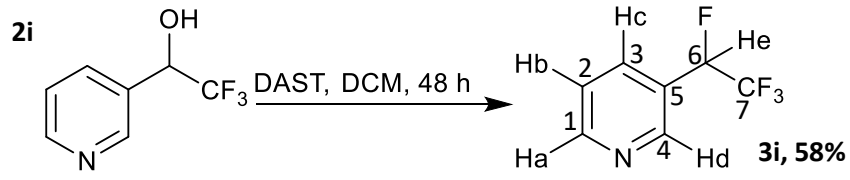
1-(4-Fluorophenyl)-1,2,2,2-tetrafluoroethane (3f). 1-(4-Fluorophenyl)-2,2,2-trifluoroethanol, **2f**, (1.79 g, 9.2 mmol) and DAST (3.54 g, 22 mmol) gave 1-(4-fluorophenyl)-1,2,2,2-tetrafluoroethane, **3f**, (2.28 g, 81 %) as a translucent, light orange liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (2H, dd, $^{3}J_{HH}$ 8.1, $^{3}J_{HF}$ 5.2, H_b), 7.14 (2H, dd, $^{3}J_{HF}$ 8.5, $^{3}J_{HH}$ 8.1, H_a), 5.58 (1H, dq, $^{2}J_{HF}$ 44.0, $^{3}J_{HF}$ 6.0, H_c). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -79.0 (3F, dd, $^{3}J_{FF}$ 13.0, $^{3}J_{FH}$ 6.0, CF_3), -110.1 (1F, tt, $^{3}J_{FH}$ 8.5, $^{4}J_{FH}$ 5.2, Ar-F), -193.1 (1F, dq, $^{2}J_{FH}$ 44.0, $^{3}J_{FF}$ 13.0, C**F**H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.1 (d, $^{1}J_{CF}$ 250, Ar-C1), 129.4 (dd, $^{3}J_{CF}$ 9, $^{3}J_{CF}$ 7, Ar-C3), 126.3 (d, $^{2}J_{CF}$ 21, Ar-C4), 122.2 (qd, $^{1}J_{CF}$ 282, $^{2}J_{CF}$ 29, C6), 116.1 (d, $^{2}J_{CF}$ 22, Ar-C2), 88.5 (dq, $^{1}J_{CF}$ 187, $^{2}J_{CF}$ 35, C5). GC-MS: 2.04 mins m/z = 196.0 (91 %, $M^{+\bullet}$), 128.1 (82, $[M-CF_3+H]^{+}$), 127.2 (100, $[M-CF_3]^{+}$), 101.0 (24, $[CF_3CFH]^{+}$), 77.1 (12, $[Ph]^{+}$).



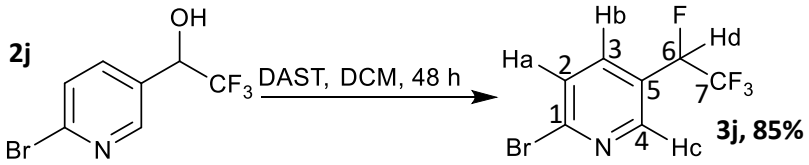
1-(4-Trifluoromethylphenyl)-1,2,2,2-tetrafluoroethane (3g). 1-(4-Trifluoromethyl-phenyl)-2,2,2-trifluoroethanol, **2g**, (2.49 g, 10.1 mmol) and DAST (3.30 g, 20.5 mmol) gave 1-(4-trifluoromethylphenyl)-1,2,2,2-tetrafluoroethane, **3g**, (0.32 g, 12 %) as a translucent, dark orange liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (2H, dq, $^{3}J_{HH}$ 8.2, $^{4}J_{HF}$ 0.9, H_a), 7.60 (2H, dq, $^{3}J_{HH}$ 8.2, $^{5}J_{HF}$ 0.7, H_b), 5.67 (1H, dq, $^{2}J_{HF}$ 44.4, $^{3}J_{HF}$ 6.0, H_c). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -63.0 (3F, s, Ar-CF_3), -78.7 (3F, dd, $^{3}J_{FF}$ 12.8, $^{3}J_{FH}$ 6.0, CF_3), -196.9 (1F, dq, $^{2}J_{FH}$ 44.4, $^{3}J_{FF}$ 12.8, C**F**H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 134.1 (q, $^{2}J_{CF}$ 20, Ar-C2), 132.8 (qd, *J* 33, 2, Ar-C5), 127.6 (dq, $^{3}J_{CF}$ 7, $^{4}J_{CF}$ 1, Ar-C4), 125.9 (q, $^{3}J_{CF}$ 4, Ar-C3), 123.8 (q, $^{1}J_{CF}$ 273, C1), 122.0 (qd, $^{1}J_{CF}$ 282, $^{2}J_{CF}$ 28, C7), 88.3 (dq, $^{1}J_{CF}$ 188, $^{2}J_{CF}$ 35, C6). GC-MS: 2.1 mins m/z = 246.0 (41 %, $M^{+\bullet}$), 227 (18 %, $[M-F]^{+}$), 177.0 (100 %, $[M-CF_3]^{+}$), 127.0 (47, $[PhCF_2]^{+}$).



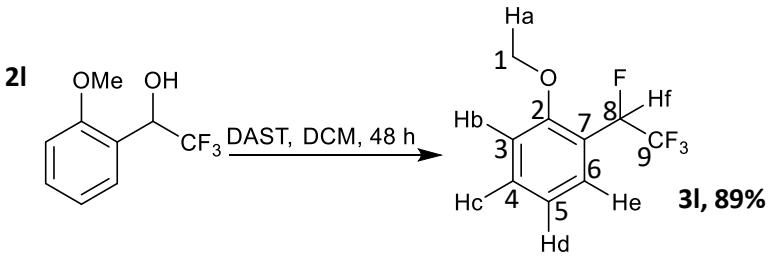
1-(4-Methylphenyl)-1,2,2,2-tetrafluoroethane (3h). 1-(4-Methylphenyl)-2,2,2-trifluoroethanol, **2h**, (1.74 g, 9.2 mmol) and DAST (3.54 g, 22 mmol) gave 1-(4-methylphenyl)-1,2,2,2-tetrafluoroethane, **3h**, (0.36 g, 21 %) as a viscous, translucent, dark orange liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 (2H, d, $^{3}J_{HH}$ 7.9, H_b), 7.25 (2H, dd, $^{3}J_{HH}$ 7.9, H_c), 5.55 (1H, dq, $^{2}J_{HF}$ 44.1, $^{3}J_{HF}$ 6.1, H_d), 2.39 (3H, s, H_a). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -78.8 (3F, dd, $^{3}J_{FF}$ 13.1, $^{3}J_{FH}$ 6.1, CF_3), -193.3 (1F, dq, $^{2}J_{FH}$ 44.1, $^{3}J_{FF}$ 13.1, C**F**H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 140.8 (d, $^{2}J_{CF}$ 2, Ar-C2), 129.5 (s, Ar-C3), 127.5 (d, $^{2}J_{CF}$ 19, Ar-C5), 127.3 (d, $^{3}J_{CF}$ 6, Ar-C4), 122.4 (qd, $^{1}J_{CF}$ 281, $^{2}J_{CF}$ 30, C6), 89.1 (dq, $^{1}J_{CF}$ 186, $^{2}J_{CF}$ 35, C7), 21.5 (s, C1). GC-MS: 2.44 mins m/z = 192.1 (58 %, $M^{+\bullet}$), 173.1 (6, $[M-F]^{+}$), 123.2 (100, $[M-CF_3]^{+}$), 103.1 (20, $[M-CF_3-HF/\ C_8H_7]^{+}$), 77.0 (18, $[Ph]^{+}$); as compared to literature data.[34]



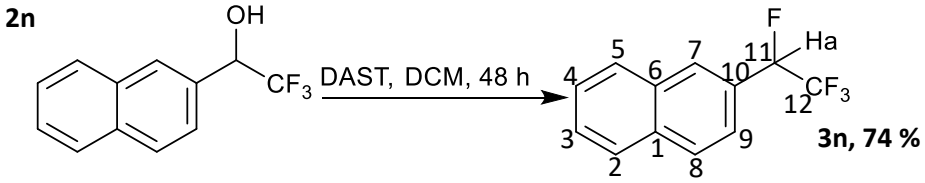
3-(1,2,2,2-Tetrafluoro-ethyl)-pyridine (3i). 1-(3-Pyridyl)-2,2,2-trifluoroethanol, **2i**, (1.77 g, 10.0 mmol) and DAST (3.54 g, 22 mmol) gave 3-(1,2,2,2-tetrafluoro-ethyl)-pyridine, **3i**, (1.04 g, 58 %) as a translucent, dark orange liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.73 (1H, dd, $^{3}J_{HH}$ 4.7, $^{4}J_{HH}$ 1.4, Ar-H_a), 8.69 (1H, s, Ar-H_d), 7.83 (1H, dd, $^{3}J_{HH}$ 8.0, $^{4}J_{HH}$ 1.4, Ar-H_c), 7.39 (1H, dd, $^{3}J_{HH}$ 8.0, $^{3}J_{HH}$ 4.7, Ar-H_b), 5.66 (1H, dq, $^{2}J_{HF}$ 44.1, $^{3}J_{HF}$ 6.0, Ar-H_e). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -78.82 (3F, dd, $^{3}J_{FF}$ 13.1, $^{3}J_{FH}$ 6.0, CF_3), -197.37 (1F, dq, $^{2}J_{FH}$ 44.1, $^{3}J_{FF}$ 13.1, C**F**H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.8 (d, $^{4}J_{CF}$ 2, Ar-C2), 148.5 (d, $^{3}J_{CF}$ 7, Ar-C3), 134.9 (d, $^{4}J_{CF}$ 6, Ar-C4), 126.4 (d, $^{2}J_{CF}$ 20, Ar-C5), 123.7 (s, Ar-C1), 122.0 (qd, $^{1}J_{CF}$ 282, $^{2}J_{CF}$ 29, C7), 87.2 (dq, $^{1}J_{CF}$ 188, $^{2}J_{CF}$ 36, C6). GC-MS: 2.24 mins m/z = 179.1 (100 %, $M^{+\bullet}$), 160.1 (13, $[M-F]^{+}$), 110.1 (100, $[M-CF_3]^{+}$), 83.1 (53, $[CF_3CH_2]^{+}$). HRMS (ASAP, ES+) m/z calculated for $C_7H_6NF_4$ $[M+H]^{+}$, 180.0436, found 180.0442.



2-Bromo-5-(1,2,2,2-tetrafluoro-ethyl)-pyridine (3j). 1-(6-Bromo-3-pyridinyl)-2,2,2-trifluoroethanol, **2j**, **(**1.95 g, 7.6 mmol) and DAST (3.54 g, 22 mmol) gave 2-bromo-5-(1,2,2,2-tetrafluoro-ethyl)-pyridine, **3j**, (1.21 g, 62 %) as a translucent, dark brown liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.41 (1H, s, H_c), 7.65 (1H, dd, $^{3}J_{HH}$ 8.3, $^{4}J_{HH}$ 2.7, H_b), 7.57 (d, $^{3}J_{HH}$ 8.3, H_a), 5.64 (1H, dq, $^{2}J_{HF}$ 43.7, $^{3}J_{HF}$ 5.9, H_d). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -79.0 (3F, dd, $^{3}J_{FF}$ 13.2, $^{3}J_{FH}$ 5.9, CF_3), -198.0 (1F, dq, $^{2}J_{FH}$ 43.7, $^{3}J_{FF}$ 13.2, C**F**H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.9 (d, $^{3}J_{CF}$ 7, Ar-C4), 144.7 (s, Ar-C1), 137.0 (d, $^{3}J_{CF}$ 6, Ar-C3), 128.5 (s, Ar-C2), 125.7 (d, $^{2}J_{CF}$ 22, Ar-C5), 121.7 (qd, $^{1}J_{CF}$ 282, $^{2}J_{CF}$ 29, C7), 86.7 (dq, $^{1}J_{CF}$ 188, $^{2}J_{CF}$ 36, C6). GC-MS: 3.16 mins m/z = 257.0 (100 %, $M^{+\bullet}$), 188.0 (97, $[M-CF_3]^{+}$), 178.1 (59, $[M-Br]^{+}$), 109.1 (54, $[M-Br-CF_3]^{+}$). HRMS (ASAP, ES+) m/z calculated for $C_7H_5BrF_4N$ $[M+H]^{+}$, 257.9547, found 257.9541.



1-(2-Methoxyphenyl)-1,2,2,2-tetrafluoroethane (3l). 1-(2-Methoxyphenyl)-2,2,2-trifluoroethanol, **2l**, (2.07 g, 10.05 mmol) and DAST (3.66 g, 22.7 mmol) gave 1-(2-methoxyphenyl)-1,2,2,2-tetrafluoroethane, **3l**, (0.89 g, 43 %) as a translucent, dark orange liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 (1H, dd, $^{3}J_{HH}$ 7.6, $^{4}J_{HH}$ 1.9, H_b), 7.42 (1H, dddd, $^{3}J_{HH}$ 8.4, $^{3}J_{HH}$ 7.6, $^{4}J_{HH}$ 1.9, $^{5}J_{HF}$ 1.0, H_d), 7.05 (1H, td, $^{3}J_{HH}$ 7.6, $^{4}J_{HH}$ 1.2, H_c), 6.94 (1H, dt, $^{3}J_{HH}$ 8.4, $^{4}J_{HH}$ 1.2, $^{4}J_{HF}$ 1.2, H_e), 6.18 (1H, dq, $^{2}J_{HF}$ 43.8, $^{3}J_{HF}$ 6.1, H_f), 3.85 (3H, s, H_a). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -78.8 (3F, dd, $^{3}J_{FF}$ 13.0, $^{3}J_{FH}$ 6.1, CF_3), -198.1 (1F, dq, $^{2}J_{FH}$ 43.8, $^{3}J_{FF}$ 13.0, C**F**H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.3 (d, $^{3}J_{CF}$ 5, Ar-C2), 131.7 (d, $^{4}J_{CF}$ 2.1, Ar-C3), 128.1 (d, $^{3}J_{CF}$ 7, Ar-C6), 122.74 (qd, $^{1}J_{CF}$ 282, $^{2}J_{CF}$ 30, C9), 120.9 (s, Ar-C4), 119.0 (d, $^{2}J_{CF}$ 21, Ar-C7), 110.9 (s, Ar-C5), 83.2 (dq, $^{1}J_{CF}$ 182, $^{2}J_{CF}$ 36, C8), 55.8 (s, C1). GC-MS: 2.84 mins m/z = 208.1 (91 %, $M^{+\bullet}$), 189.1 (1, $[M-F]^+$), 139.1 (93, $[M-CF_3]^+$), 109.1 (43, $[PhO(H)Me]^+$), 91.2 (100, $[M-CFHCF_3\text{-}Me\text{-}2H]^+$), 83.1 (15, $[CHCF_3]^+$). HRMS (ESI, ES+) m/z calculated for $C_9H_8F_4O$ $[M-F]^+$ 189.0527, found 189.0539.

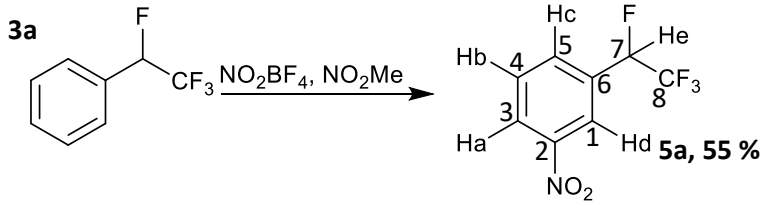


1-(2-napthyl)-1,2,2,2-tetrafluoroethane (3n). 1-(2-napthyl)-2,2,2-trifluoroethanol, **2n**, (2.29 g, 10.1 mmol) and DAST (3.54 g, 22 mmol) gave 1-(2-napthyl-1,2,2,2-tetrafluoroethane, **3n**, (1.70 g, 74 %) as an orange solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.96 (1H, s, Ar-H), 7.93 (1H, d, $^{3}J_{HF}$ 8.8, Ar-H), 7.93 – 7.86 (1H, m, Ar-H), 7.81 (1H, dd, *J* 9.3, *J* 3.2, Ar-H), 7.60 – 7.52 (2H, m, Ar-H), 7.48 (1H, ddd, *J* 10.9, *J* 7.2, *J* 2.4, Ar-H), 5.77 (1H, dq, $^{2}J_{HF}$ 44.2, $^{3}J_{HF}$ 6.1, H_a). ^{19}F NMR (376 MHz, Chloroform-d) δ -78.4 (3F, dd, $^{3}J_{FF}$ 13.1, $^{3}J_{FH}$ 6.1, CF_3), -193.8 (1F, dq, $^{2}J_{FH}$ 44.2, $^{3}J_{FF}$ 13.1, C**F**H). ^{13}C NMR (101 MHz, Chloroform-d) δ 134.2 (d, $^{5}J_{CF}$ 1.4, Ar-C1), 132.8 (s, Ar-C6), 128.9 (s, Ar-C3), 128.5 (s, Ar-C4), 128.0 (s, Ar-C2), 127.7 (d, $^{2}J_{CF}$ 20, Ar-C10), 127.5 (s, Ar-C5), 127.0 (s, Ar-C8), 126.7 (d, $^{3}J_{CF}$ 8, Ar-C9), 123.6 (d, $^{2}J_{CF}$ 8 Ar-C7), 122.49 (qd, $^{1}J_{CF}$ 282, $^{2}J_{CF}$ 29, C11), 89.31 (dq, $^{1}J_{CF}$ 186, $^{2}J_{CF}$ 35, C12). GC-MS: 2.0 mins m/z = 228.1 (94 %, $M^{+\bullet}$), 209.1 (5, $[M-F]^+$), 177.1 (7,

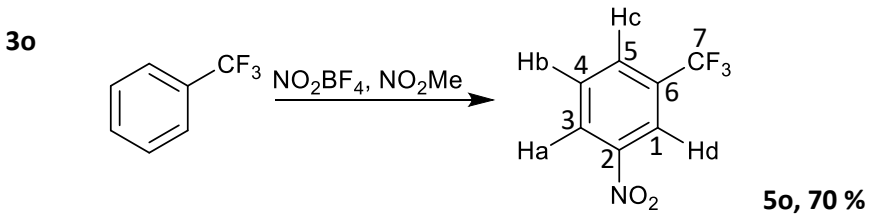
[M-C_4H_3]$^+$), 159.2 (100 %, [M-CF_3]$^+$), 79.6 (21 %, [PhH+H]$^+$); as compared to literature data.[34]

3.4 Reaction of fluorinated aromatics with nitronium tetrafluoroborate:

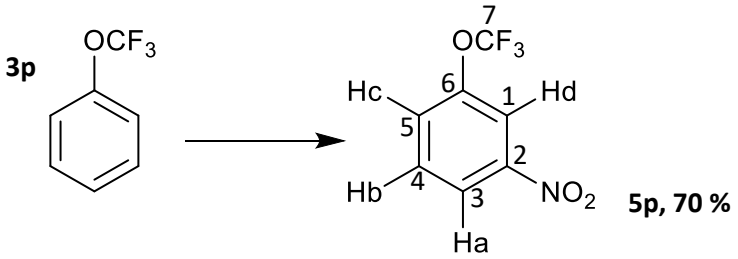
General procedure – Nitration (5a, n-o). Nitronium tetrafluoroborate, NO_2BF_4, (0.28 g, 2.1 mmol) was dissolved in nitromethane (10 mL) while being stirred at 0 °C under argon. 1-Phenyl-1,2,2,2-tetrafluoroethane (2 mmol) in nitromethane (10 mL) and then was added to the reaction mixture. The reaction was allowed to warm to RT and stirred for 4 d. The reaction was quenched by the addition of water (20 mL) and washed by 5 % $NaHCO_3$ solution (3x 25 mL) before the product was extracted in DCM (3x 25 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield the product mixture.



1-(3-nitrophenyl)-1,2,2,2-tetrafluoroethane (5a). 1-Phenyl-1,2,2,2-tetrafluoroethane, **3a**, (0.36 g, 2.1 mmol) and nitronium tetrafluoroborate (0.29 g, 2.2 mmol) gave 1-(3-nitrophenyl)-1,2,2,2-tetrafluoroethane, **5a**, (0.25 g, 55 %) as a clear, pale orange liquid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.36 (1H, dd, $^3J_{HH}$ 3.5, $^4J_{HH}$ 1.4, Ar-H_a), 8.33 (1H, d, $^4J_{HF}$ 8.1, Ar-H_d), 7.82 (1H, dd, $^3J_{HH}$ 7.7, $^3J_{HH}$ 3.5, Ar-H_b), 7.69 (1H, ddd, $^4J_{HF}$ 8.8, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.4, Ar-H_c), 5.74 (1H, dq, $^2J_{HF}$ 44.1, $^3J_{HF}$ 5.9, H_e). ^{19}F NMR (376 MHz, chloroform-d) δ -78.7 (3F, dd, $^3J_{FF}$ 12.8, $^3J_{FH}$ 5.9, CF_3), -196.5 (1F, dq, $^2J_{FH}$ 44.1, $^3J_{FF}$ 12.8, C**F**H). ^{13}C NMR (101 MHz, chloroform-d) δ 132.9 (d, $^3J_{CF}$ 7, Ar-C1), 130.2 (s, Ar-C3), 128.2 (d, $^3J_{CF}$ 7, Ar-C5), 125.4 (d, $^4J_{CF}$ 1, Ar-C2), 124.0 (s, Ar-C4), 122.3 (d, $^2J_{CF}$ 8, Ar-C6), 121.8 (qd, $^1J_{CF}$ 282, $^2J_{CF}$ 28, C8), 87.9 (dq, $^1J_{CF}$ 189, $^2J_{CF}$ 36, C7). GC-MS: 3.27 mins, m/z = 223.1 (54 %, $M^{+\bullet}$), 204.0 (7, [M-F]$^+$), 127.1 (100, [FC_6H_4NHOH]$^+$), 177.1 (25, [M-NO_2]$^+$), 154.1 (65, [M-CF_3]$^+$), 108.1 (21, [M-NO_2-CF_3]), 101.1 (5, [M-$C_6H_4NO_2$]$^+$); as compared to literature data.[34]



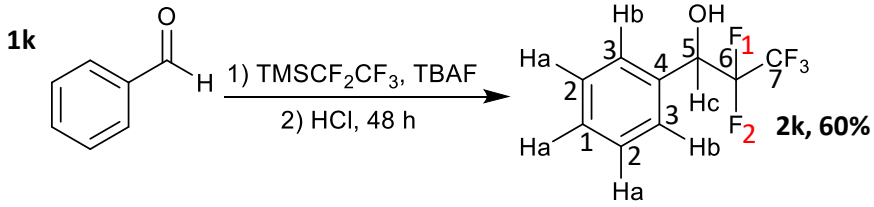
3-Nitro-α,α,α-trifluorotoluene (5o). α,α,α-Trifluorotoluene **3o** (0.72 g, 4.92 mmol) and nitronium tetrafluoroborate (0.7 g, 5.3 mmol) gave 3-nitro-α,α,α-trifluorotoluene, **5o**, (0.67 g, 71 %) as a clear, light orange liquid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.51 (1H, s, Ar-Hd), 8.44 (1H, dd, $^{3}J_{HH}$ 8.1, $^{4}J_{HH}$ 2.0, Ar-Hc), 7.98 (1H, dd, $^{3}J_{HH}$ 8.1, $^{4}J_{HH}$ 2.0, Ar-Ha), 7.74 (1H, t, $^{3}J_{HH}$ 8.1, Ar-Hb). ^{19}F NMR (376 MHz, chloroform-d) δ -63.0 (s, CF_3). ^{13}C NMR (101 MHz, chloroform-d) δ 148.4 (s, Ar-C2), 132.5 (q, $^{2}J_{CF}$ 34, Ar-C6), 131.3 (q, $^{3}J_{CF}$ 4, Ar-C1), 130.5 (s, Ar-C3), 126.8 (s, Ar-C4), 123.0 (q, $^{1}J_{CF}$ 273, C7), 121.0 (q, $^{3}J_{CF}$ 4, Ar-C5). GC-MS: 2.96 mins, m/z = 191.0 (82 %, $M^{+\bullet}$), 145.2 (100, $[M\text{-}NO_2]^+$), 125.1 (30, $[M\text{-}CF_3\text{+}3H]^+$), 95.1 (49, $[Ph\text{-}OH\text{+}H]^+$), 75.0 (28, $[Ph\text{-}2H]^+$); as compared to literature data.[91]



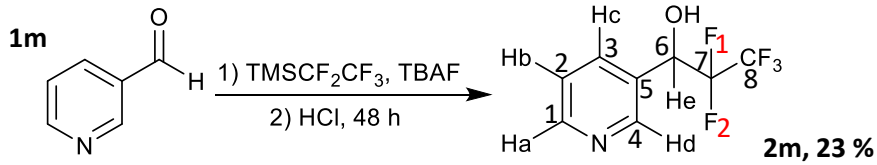
1-Nitro-3-(trifluoromethoxy) benzene (5p). (Trifluoromethoxy) benzene, **3p**, (0.80 g, 4.92 mmol) and nitronium tetrafluoroborate (0.7 g, 5.3 mmol) gave 1-nitro-3-(trifluoromethoxy) benzene, **5o**, (0.70 g, 69 %) as a clear, dark yellow liquid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.31 (1H, t, $^{3}J_{HH}$ 9.3, Ar-H_b), 8.31 (1H, q, $^{5}J_{HF}$ 5.5, Ar-H_d), 7.37 (2H, dd, $^{3}J_{HH}$ 9.3, $^{4}J_{HH}$ 1.1, Ar-H_a), 7.37 (2H, dd, $^{3}J_{HH}$ 9.3, $^{4}J_{HH}$ 1.1, Ar-H_c). ^{19}F NMR (376 MHz, chloroform-d) δ -57.8 (s, CF_3). ^{13}C NMR (101 MHz, chloroform-d) δ 153.7 (q, $^{4}J_{CF}$ 2, Ar-C1), 146.0 (s, Ar-C2), 134.4 (s, Ar-C3), 126.9 (q, $^{3}J_{CF}$ 167.0, Ar-C6), 125.9 (s, Ar-C4), 121.0 (q, $^{4}J_{CF}$ 2, Ar-C5), 120.3 (q, $^{1}J_{CF}$ 260, C7). GC-MS: 2.99 mins, m/z = 207.0 (95 %, $M^{+\bullet}$), 191.0 (4, $[M\text{-}O]^+$), 177.0 (34, $[M\text{-}HF]^+$), 161.1 (15, $[M\text{-}NO_2]^+$), 122.1 (14, $[M\text{-}OCF_3)$, 95.1 (100, $[Ph\text{-}OH\text{+}H]^+$), 69.0 (34, $[CF_3]^+$); as compared to literature data.[92]

3.5 Synthesis of 2,2,3,3,3-pentafluoroaryl derivatives:

General Procedure – Pentafluoroethylation reactions (2k&m). Aldehyde (30 mmol) and $CF_3CF_2SiMe_3$ (6.9 g, 6.3 mL, 36 mmol) were dissolved in THF (30 mL) at 0°C under an atmosphere of argon. TBAF (0.1 g) was added and the reaction was allowed to warm to RT and stirred for 3 h. 6 M HCl (6 mL) solution was added and the reaction stirred for 48 h. The mixture was extracted with ether (3 x 30 mL), washed with water (2 x 50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and solvent evaporated to give the pentafluoro- alcohol product.



1-Phenyl-2,2,3,3,3-pentafluoropropan-1-ol (2k). Benzaldehyde, **1k**, (3.22 g, 30.4 mmol) and $TMSCF_2CF_3$ (6.9 g, 36 mmol) gave 1-phenyl-2,2,3,3,3-pentafluoropropan-1-ol, **2k**, (4.12 g, 60 %) as a clear, pale yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (2H, dd, $^3J_{HH}$ 6.8, $^3J_{HH}$ 3.2, Ar-Hb), 7.45 -7.38 (3H, m, Ar-Ha), 5.12 (1H, dd, $^3J_{HF}$ 16.7, $^3J_{HF}$ 7.3, Hc), 2.61 (1H, s, OH). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.3 (3F, s, CF_3), -121.9 (1F, dd, $^2J_{FF}$ 275.8, $^3J_{FH}$ 7.3, F_2), -129.4 (1F, dd, $^2J_{FF}$ 275.8, $^3J_{FH}$ 16.7, F_1). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 134.2 (s, Ar-C4), 129.7 (s, Ar-C1), 128.7 (s, Ar-C2), 128.0 (s, Ar-C3), 119.3 (qt, $^1J_{CF}$ 287, $^2J_{CF}$ 36, C7), 113.2 (ddq, $^1J_{CF}$ 261, $^1J_{CF}$ 255, $^2J_{CF}$ 36, C6), 72.1 (dd, $^2J_{CF}$ 28, $^2J_{CF}$ 22, C5). GC-MS: 2.91 mins, m/z = 226.1 (12 %, $M^{+\bullet}$), 159.1 (4, $[M\text{-}CF_3]^+$), 107.1 (100, $[M–CF_2CF_3]^+$), 79.1 (85, $[Ph+2H]^+$), 77.1 (55, $[Ph]^+$); as compared to literature data.[68]



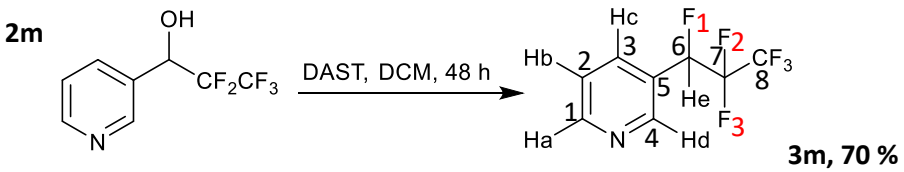
1-(3-pyridyl)-2,2,3,3,3-pentafluoropropan-1-ol (2m). 3-pyridinecarboxaldehyde, **1m**, (3.20 g, 29.9 mmol) and $TMSCF_2CF_3$ (11.6 g, 60.52 mmol) gave 1-(3-pyridyl)-2,2,3,3,3-pentafluoropropan-1-ol, **2m**, (3.74 g, 46 %) as pale white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) 8.45 (1H, s, H_d), δ 8.38 (1H, dd, $^3J_{HH}$ 5.0, $^4J_{HH}$ 1.9, H_a), 7.90 (1H, dd, $^3J_{HH}$ 8.0, $^4J_{HH}$ 1.9, H_c), 7.33 (1H, dd, $^3J_{HH}$ 8.0, $^3J_{HH}$ 5.0, H_b), 7.00 (1H, s, OH), 5.14 (1H, dd, $^3J_{HF}$ 17.4, $^3J_{HF}$ 6.7, H_e). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.1 (3F, s, CF_3), -120.4 (1F, dd, $^2J_{FF}$ 276.4, $^3J_{FH}$ 6.7, F_1), -129.4 (1F, dd, $^2J_{FF}$ 276.4, $^3J_{HH}$ 17.4, F_2). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.2 (s, C4), 148.2 (s, C1), 137.0 (s, C2), 132.2 (s, C5), 124.1 (s, C3),

119.2 (qt, $^{1}J_{CF}$ 287, $^{2}J_{CF}$ 36, C8), 113.3 (ddq, $^{1}J_{CF}$ 262, $^{1}J_{CF}$ 255, $^{2}J_{CF}$ 36, C7), 69.4 (dd, $^{2}J_{CF}$ 28, $^{2}J_{CF}$ 23, C6). GC-MS: 3.40 mins, m/z = 227.0 (31 %, $M^{+\bullet}$), 160.1 (3, $[M\text{-}CF_3+2H]^+$), 108.2 (100, $[M–CF_2CF_3]^+$), 80.1 (61, $[M\text{-}CHOHCF_2CF_3]^+$). HRMS (ASAP, ES+) m/z calculated for $C_7H_6NOF_3Br$ $[M+H]^+$, 228.0448, found 228.0456.

3.6 Synthesis of 1-aryl-1,2,2,3,3,3-hexafluoropropane derivates (3k&m):

General procedure – 1-Aryl-2,2,3,3,3-pentafluoropropan-1-ol **2** (10 mmol) was dissolved in DCM (40 mL) and stirred at 0 °C. Diethylaminosulfur trifluoride, DAST, (3.54 g, 22 mmol) dissolved in DCM (10 mL) was added to the reaction mixture. The reaction was allowed to warm to RT and stirred for 48 h. Water (50 mL) and DCM (50 mL) were added to the reaction mixture, followed by a neutralisation with $NaHCO_3$. The organic layer was washed with water (2 x 50 mL) and the solvent evaporated to yield product **3**.

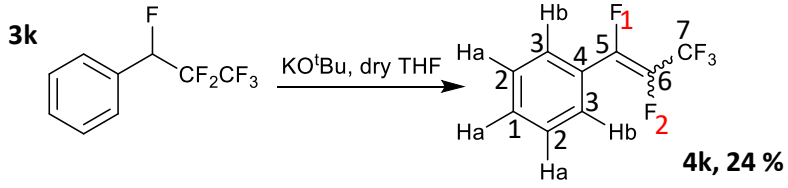
1-phenyl-1,2,2,3,3,3-hexafluoropropane (3k). 1-phenyl-2,2,3,3,3-pentafluoropropan-1-ol, **2k**, (2.28 g, 10.1 mmol) and DAST (3.54 g, 22 mmol) gave 1-phenyl-1,2,2,3,3,3-hexafluoropropane, **3k**, (2.33 g, 99 %) as a translucent, dark orange liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.39 (5H, m, Ar-H), 5.73 (1H, ddd, $^{2}J_{HF}$ 43.8, $^{3}J_{HF}$ 17.5, $^{3}J_{HF}$ 4.3, H_a). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -82.2 (3F, dd, $^{4}J_{FF}$ 11.1, $^{4}J_{FH}$ 2.2, CF_3), -122.9 (1F, ddd, $^{2}J_{FF}$ 283.9, $^{3}J_{FF}$ 11.1, $^{3}J_{FH}$ 4.3, F_3), -131.6 (1F, ddd, $^{2}J_{FF}$ 283.9, $^{3}J_{FH}$ 17.5, $^{3}J_{FF}$ 15.1, F_2), -195.7 (1F, ddp, $^{2}J_{FH}$ 43.8, $^{3}J_{FF}$ 15.1, $^{3/4}J_{FF}$ 11.1, F_1). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 130.7 (d, $^{4}J_{CF}$ 2, Ar-C2), 129.8 (d, $^{2}J_{CF}$ 20, Ar-C4), 128.8 (s, Ar-C1), 127.7 (d, $^{3}J_{CF}$ 7, Ar-C3), 119.2 (qtd, $^{1}J_{CF}$ 288, $^{2}J_{CF}$ 36, $^{3}J_{CF}$ 2, C7), 115.9 (dddq, $^{1}J_{CF}$ 263, $^{1}J_{CF}$ 254, $^{2}J_{CF}$ 37, $^{3}J_{CF}$ 29, C6), 88.3 (ddd, $^{1}J_{CF}$ 186, $^{2}J_{CF}$ 32, $^{2}J_{CF}$ 24, C5). GC-MS: 2.15 mins m/z = 228.0 (88 %, $M^{+\bullet}$), 189.0 (9, $[M\text{-}HF\text{-}F]^+$), 159.1 (4, $[M\text{-}CF_3]^+$), 109.2 (100, $[M\text{-}CF_2CF_3]^+$), 83.1 (40, $[CF_3CH_2]^+$); as compared to literature data.[34]



1-(3-Pyridyl)-1,2,2,3,3,3-hexafluoropropane (3m). 1-(3-Pyridyl)-2,2,3,3,3-pentafluoropropan-1-ol, **2m**, (2.17 g, 12.3 mmol) and DAST (3.54 g, 22 mmol) gave 1-(3-pyridyl)-1,2,23,3,3-hexafluoropropane, **3m**, (4.69 g, 70 %) as a dark orange, viscous liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (1H, dd, $^{3}J_{HH}$ 4.9, $^{4}J_{HH}$ 0.9, H_a), 8.54 (1H, s, H_d), 7.71 (1H, dd, $^{3}J_{HH}$ 8.0, $^{4}J_{HH}$ 0.9, H_c), 7.30 (1H, dd, $^{3}J_{HH}$ 8.0, $^{3}J_{HH}$ 4.9, H_b), 5.78 (1H, ddd, $^{2}J_{HF}$ 43.7, $^{3}J_{HF}$ 17.9, $^{3}J_{HF}$ 3.9, H_e). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -82.06 (3F, dd, $^{4}J_{FF}$ 11.0, $^{4}J_{FH}$ 1.1, CF_3), -122.72 (1F, ddd, $^{2}J_{FF}$ 285.5, $^{3}J_{FF}$ 11.0, $^{3}J_{FH}$ 3.9, F_2), -131.52 (1F, ddd, $^{2}J_{FF}$ 285.5, $^{3}J_{FH}$ 17.9, $^{3}J_{FF}$ 15.0, F_3), -198.58 (1F, ddp, $^{2}J_{FH}$ 43.7, $^{3}J_{FF}$ 15.0, $^{3/4}J_{FF}$ 11.0, F_1). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.6 (d, $^{4}J_{CF}$ 2, Ar-C2), 148.5 (d, $^{3}J_{CF}$ 7, Ar-C3), 135.2 (d, $^{3}J_{CF}$ 7, Ar-C4), 125.7 (d, $^{2}J_{CF}$ 21, Ar-C5), 123.5 (s, Ar-C1), 120.4 – 116.3 (qtd, $^{1}J_{CF}$ 290, 37, 2, C8), 115.0 – 107.0 (m (qtd), C7), 86.4 (ddd, $^{1}J_{CF}$ 186, $^{2}J_{CF}$ 33, $^{2}J_{CF}$ 24, C6). GC-MS: 2.34 mins m/z = 229.0 (94 %, $M^{+\bullet}$), 190.0 (9, $[M\text{-}HF\text{-}F]^{+}$), 159.1 (4, $[M\text{-}CF_3]^{+}$), 110.25 (100, $[M\text{-}CF_2CF_3]^{+}$), 83.1 (40, $[CF_3CH_2]^{+}$). HRMS (ASAP, ES+) m/z calculated for $C_8H_6F_6N$ $[M+H]^{+}$ 230.0404, found 230.0410.

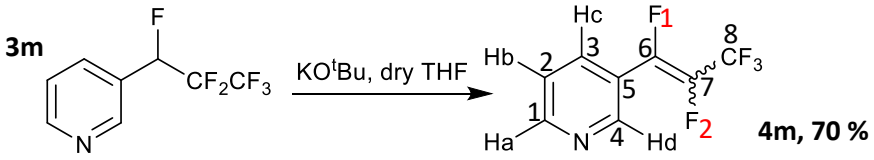
3.7 Dehydrofluorination reactions (4k&m):

General procedure – (4k&m). 1,2,2,3,3,3-Hexafluoropropane aryl derivatives (5.2 mmol) was dissolved in dry THF (30 mL) and stirred at 0 °C under argon. KO^{t}Bu (1.12 g, 10 mmol) was added to the reaction mixture, which was allowed to warm to RT and stirred overnight. The reaction was quenched by the addition of water (50 mL), followed by a neutralisation with $NaHCO_3$ and extracted with ether (3x 30 mL). The organic layer was washed with water (2 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated to yield the fluorinated product.



1-phenyl-1,2,3,3,3-pentafluoroprop-1-ene (4k). 1-Phenyl-1,2,2,3,3,3-hexafluoropropane, **3k**, (1.18 g, 5.17 mmol) and KO^{t}Bu (1.11 g, 9.91 mmol) gave 1-phenyl-1,2,3,3,3-pentafluoroprop-1-ene, **4k**, (0.43 g, 24 %) as an opaque orange liquid.

^{1}H NMR (400 MHz, Chloroform-d) δ 7.69 – 7.66 (3H, m, Ar-H_a), 7.48 – 7.44 (2H, m, Ar-H_b). ^{19}F NMR (376 MHz, Chloroform-d) δ -67.0 (3F, dd, $^{3}J_{FF}$ 22.0, $^{4}J_{FF}$ 10.6, CF_3), -146.3 (1F, dq, $^{3}J_{FF}$ 131.7, $^{4}J_{FF}$ 22.0, F_2), -169.5 (1F, dq, $^{3}J_{FF}$ 131.7, $^{4}J_{FF}$ 10.6, F_1). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.4 (ddq, $^{1}J_{CF}$ 250, $^{2}J_{CF}$ 36, $^{3}J_{CF}$ 3, Ar-C5), 138.4 (ddq, $^{1}J_{CF}$ 249, $^{2}J_{CF}$ 51, $^{2}J_{CF}$ 40, Ar-C6), 131.3 (d, *J* 2, Ar-C1), 128.9 (d, $^{4}J_{CF}$ 2, Ar-C2), 127.2 (dd, $^{2}J_{CF}$ 24, $^{3}J_{CF}$ 6, Ar-C4), 126.6 (d, $^{3}J_{CF}$ 8, Ar-C3), 119.5 (qdd, $^{1}J_{CF}$ 272, $^{2}J_{CF}$ 36, $^{3}J_{CF}$ 4, C7). GC-MS: 2.34 mins m/z = 208.0 (100 %, $M^{+\bullet}$), 189.0 (17, $[M\text{-}F]^+$), 169.1 (17, $[M\text{-}F\text{-}F\text{-}H]^+$), 158.1 (100, $[M\text{-}CF_3\text{+}F]^+$), 139.1 (22, $[M\text{-}CF_3]^+$), 99.0 (8, $[C_2F_4]^+$), 79.0 (7, $[Ph\text{+}2H]^+$); as compared to literature data.[34]



1-(3-Pyridyl)-1,2,3,3,3-pentafluoroprop-1-ene (4m). 1-(3-Pyridyl)-1,2,2,3,3,3-hexafluoropropane, **3m**, (0.94 g, 4.10 mmol) and KO^{t}Bu (0.9 g, 8.04 mmol) gave 1-(3-pyridiyl)-1,2,3,3,3-pentafluoroprop-1-ene, **4m**, (7.20 g, 89 %) as a dark red solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.95 (1H, d, $^{4}J_{HF}$ 2.3, Ar-H_d), 8.72 (1H, dd, $^{3}J_{HH}$ 4.9, $^{4}J_{HH}$ 1.9, Ar-H_a), 7.99 (1H, dt, $^{3}J_{HH}$ 8.2, $^{4}J_{HF}$ 2.0, $^{4}J_{HH}$ 1.9, Ar-H_c), 7.44 (1H, dd, $^{3}J_{HH}$ 8.2, $^{3}J_{HH}$ 4.9, Ar-H_b). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -67.2 (3F, dd, $^{3}J_{FF}$ 21.8, $^{4}J_{FF}$ 10.4, CF_3), -149.1 (1F, dq, $^{3}J_{FF}$ 131.9, $^{3}J_{FF}$ 21.8, F_2), -167.3 (1F, dq, $^{3}J_{FF}$ 131.9, $^{4}J_{FF}$ 10.4, F_1). GC-MS: 2.46 mins m/z = 208.0 (100 %, $M^{+\bullet}$), 190.0 (19, $[M\text{-}F]^+$), 170.0 (9, $[M\text{-}F\text{-}F\text{-}H]^+$), 159.1 (36, $[M\text{-}CF_3\text{+}F]^+$), 140.1 (16, $[M\text{-}CF_3]^+$), 112.1 (4, $[M\text{-}CFCF_3\text{+}H]^+$), 106.0 (19, $[M\text{-}CF_3\text{-}F\text{-}F\text{+}4H]^+$). HRMS (ASAP, ES+) m/z calculated for $C_8H_5F_5N$ $[M+H]^+$ 210.0342, found 210.0348.

Chapters 4: Appendices

Appendix 1- Crystallographic data for compound 2d

Table 1 Crystal data and structure refinement for 18srv145.	
Identification code	18srv145
Empirical formula	$C_8H_6F_3NO_3$
Formula weight	221.14
Temperature/K	120.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	9.2387(3)
b/Å	9.6082(3)
c/Å	10.3503(4)
α/°	90
β/°	109.1384(14)
γ/°	90
Volume/Å^3	867.99(5)
Z	4
ρ_{calc}g/cm^3	1.692
μ/mm^{-1}	0.169
F(000)	448.0
Crystal size/mm^3	0.21 × 0.2 × 0.19
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.666 to 59.996
Index ranges	-12 ≤ h ≤ 12, -13 ≤ k ≤ 13, -14 ≤ l ≤ 14
Reflections collected	18381
Independent reflections	2516 [R_{int} = 0.0282, R_{sigma} = 0.0175]
Data/restraints/parameters	2516/0/156
Goodness-of-fit on F^2	1.069
Final R indexes [I>=2σ (I)]	R_1 = 0.0331, wR_2 = 0.0938
Final R indexes [all data]	R_1 = 0.0407, wR_2 = 0.0978

Largest diff. peak/hole / e Å^{-3}	0.46/-0.25

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 18srv145. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
F1	9179.9(9)	7186.7(8)	3356.5(7)	26.34(18)
F2	9230.7(9)	9095.1(7)	2293.5(8)	26.94(19)
F3	10105.6(8)	7202.1(9)	1701.1(9)	30.5(2)
O1	6298.0(9)	8028.5(8)	1583.6(9)	20.86(19)
O2	6059.3(11)	935.2(8)	1475.1(10)	24.0(2)
O3	7179.2(10)	864.2(8)	-57.9(9)	21.86(19)
N1	6675.5(10)	1508.4(9)	720.9(9)	14.87(19)
C1	7155.0(11)	5861.2(10)	962(1)	12.44(19)
C2	6434.5(12)	5175.5(10)	1769.0(11)	14.1(2)
C3	6253.7(12)	3739.0(11)	1682.6(11)	14.1(2)
C4	6815.6(11)	3025.5(10)	786.3(10)	12.47(19)
C5	7516.7(12)	3677.8(11)	-44.4(11)	14.6(2)
C6	7679.9(12)	5113.6(11)	50.5(11)	15.1(2)
C7	7405.1(12)	7416(1)	1101.1(11)	14.4(2)
C8	8991.5(12)	7723.5(11)	2122.0(12)	17.9(2)

Table 3 Anisotropic Displacement Parameters (Å^2×10^3) for 18srv145. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F1	26.8(4)	27.0(4)	19.1(4)	0.2(3)	-0.8(3)	-1.5(3)
F2	25.1(4)	16.3(3)	35.5(4)	-5.5(3)	4.5(3)	-7.7(3)
F3	15.3(3)	35.7(4)	42.7(5)	-13.3(3)	12.7(3)	-3.2(3)
O1	18.9(4)	10.4(4)	35.3(5)	-0.7(3)	11.5(3)	1.4(3)
O2	34.4(5)	12.4(4)	31.7(5)	1.4(3)	19.9(4)	-1.5(3)
O3	31.2(5)	14.6(4)	21.7(4)	-4.1(3)	11.4(3)	3.5(3)
N1	16.3(4)	11.2(4)	15.6(4)	-0.9(3)	3.2(3)	1.1(3)
C1	11.4(4)	10.6(4)	13.6(4)	0.3(3)	1.8(3)	0.2(3)
C2	16.1(4)	11.7(4)	15.5(5)	-1.3(3)	6.8(4)	0.9(3)
C3	15.6(4)	13.0(4)	14.9(5)	0.6(3)	6.5(4)	-0.4(3)
C4	12.9(4)	9.4(4)	13.5(4)	-0.2(3)	2.3(3)	1.1(3)
C5	15.8(4)	14.7(5)	14.6(5)	-1.9(4)	6.7(4)	1.4(4)
C6	16.3(5)	15.0(5)	15.5(5)	0.8(4)	7.3(4)	-1.3(4)
C7	14.5(4)	11.3(4)	17.1(5)	0.2(4)	5.0(4)	-0.7(3)
C8	16.1(5)	15.2(5)	22.3(5)	-3.3(4)	6.3(4)	-1.5(4)

Table 4 Bond Lengths for 18srv145.						
Atom	**Atom**	**Length/Å**		**Atom**	**Atom**	**Length/Å**
F1	C8	1.3354(14)		C1	C6	1.3933(14)
F2	C8	1.3384(12)		C1	C7	1.5113(14)
F3	C8	1.3395(13)		C2	C3	1.3897(14)
O1	C7	1.4060(13)		C3	C4	1.3842(14)
O2	N1	1.2362(12)		C4	C5	1.3845(14)
O3	N1	1.2229(12)		C5	C6	1.3877(14)
N1	C4	1.4630(13)		C7	C8	1.5285(15)
C1	C2	1.3926(14)				

Table 5 Bond Angles for 18srv145.								
Atom	**Atom**	**Atom**	**Angle/˚**		**Atom**	**Atom**	**Atom**	**Angle/˚**
O2	N1	C4	117.82(9)		C4	C5	C6	117.92(9)
O3	N1	O2	122.98(9)		C5	C6	C1	120.44(9)
O3	N1	C4	119.20(9)		O1	C7	C1	109.96(8)
C2	C1	C6	120.21(9)		O1	C7	C8	108.53(9)
C2	C1	C7	119.92(9)		C1	C7	C8	109.81(8)
C6	C1	C7	119.86(9)		F1	C8	F2	106.82(9)
C3	C2	C1	120.15(9)		F1	C8	F3	107.08(9)
C4	C3	C2	118.13(9)		F1	C8	C7	112.42(9)
C3	C4	N1	118.53(9)		F2	C8	F3	107.48(9)
C3	C4	C5	123.14(9)		F2	C8	C7	111.18(9)
C5	C4	N1	118.33(9)		F3	C8	C7	111.58(9)

Table 6 Hydrogen Bonds for 18srv145.						
D	**H**	**A**	**d(D-H)/Å**	**d(H-A)/Å**	**d(D-A)/Å**	**D-H-A/°**
O1	H1	O2[1]	0.85(2)	1.96(2)	2.8008(11)	168.0(18)

[1]+X,1+Y,+Z

Table 7 Selected Torsion Angles for 18srv145.										
A	**B**	**C**	**D**	**Angle/˚**		**A**	**B**	**C**	**D**	**Angle/˚**
O1	C7	C8	F1	61.54(11)		C2	C1	C7	C8	93.26(11)
O1	C7	C8	F2	-58.16(11)		C3	C4	N1	O2	-0.06(14)
O1	C7	C8	F3	-178.14(9)		C3	C4	N1	O3	-179.37(9)
C1	C7	C8	F1	-58.68(12)		C5	C4	N1	O2	179.41(9)
C1	C7	C8	F2	-178.38(8)		C5	C4	N1	O3	0.10(14)
C1	C7	C8	F3	61.64(12)		C6	C1	C7	O1	155.47(9)
C2	C1	C7	O1	-26.10(13)		C6	C1	C7	C8	-85.17(11)

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 18srv145.				
Atom	***x***	***y***	***z***	**U(eq)**
H7	7325.16	7821.84	190.54	17
H1	6310(20)	8910(20)	1482(19)	39(5)
H2	6072(17)	5690(16)	2404(15)	19(3)
H3	5762(17)	3287(16)	2230(15)	20(4)
H5	7861(18)	3195(17)	-636(16)	23(4)
H6	8140(18)	5563(18)	-489(17)	27(4)

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups
2.a Ternary CH refined with riding coordinates:
 C7(H7)

Appendix 2- Crystallographic data from compound 2m

Table 1 Crystal data and structure refinement for 18srv350.	
Identification code	18srv350
Empirical formula	$C_8H_6F_5NO$
Formula weight	227.14
Temperature/K	120.0
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	5.0833(2)
b/Å	9.1799(4)
c/Å	19.7715(7)
α/°	90
β/°	90.861(4)
γ/°	90
Volume/Å^3	922.51(7)
Z	4
ρ_{calc}g/cm^3	1.635
μ/mm^{-1}	0.176
F(000)	456.0
Crystal size/mm^3	0.39 × 0.27 × 0.25
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.892 to 58.996
Index ranges	-6 ≤ h ≤ 7, -12 ≤ k ≤ 10, -27 ≤ l ≤ 27
Reflections collected	8980
Independent reflections	2560 [R_{int} = 0.0289, R_{sigma} = 0.0270]
Data/restraints/parameters	2560/0/140
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0404, wR_2 = 0.0914
Final R indexes [all data]	R_1 = 0.0539, wR_2 = 0.1002
Largest diff. peak/hole / e Å^{-3}	0.37/-0.26

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 18srv350. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.				
Atom	***x***	***y***	***z***	**U(eq)**
F1	10699.2(17)	6047.3(9)	3856.3(4)	33.7(2)
F2	6830.7(16)	7065.0(10)	3760.5(4)	33.2(2)
F3	7745(2)	8682.9(11)	4869.2(5)	42.4(3)
F4	11814(2)	8040.9(14)	4904.2(5)	55.3(3)
F5	8745(2)	6450.7(12)	5050.4(5)	53.6(3)
O1	9340(2)	9803.8(11)	3646.5(5)	29.5(2)
N1	11974(2)	6709.2(14)	1811.2(6)	28.6(3)
C1	12097(3)	7109.4(15)	2462.5(7)	25.5(3)
C2	10345(2)	8076.4(14)	2755.3(6)	22.4(3)
C3	8383(3)	8667.6(15)	2342.9(7)	27.4(3)
C4	8224(3)	8259.7(17)	1668.1(7)	31.1(3)
C5	10040(3)	7275.7(16)	1423.9(7)	29.6(3)
C6	10599(3)	8488.7(14)	3497.9(7)	23.2(3)
C7	9379(3)	7319.4(15)	3941.3(7)	24.7(3)
C8	9409(3)	7641.9(17)	4705.3(7)	33.8(3)

Table 3 Anisotropic Displacement Parameters (Å^2×10^3) for 18srv350. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.						
Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
F1	44.4(5)	21.6(4)	35.1(5)	1.9(3)	0.9(4)	6.2(4)
F2	28.0(4)	37.4(5)	34.3(5)	4.1(4)	-1.6(3)	-8.6(4)
F3	58.0(6)	37.8(5)	31.9(5)	-1.7(4)	16.6(4)	4.6(4)
F4	49.8(6)	82.1(9)	33.5(5)	-9.6(5)	-13.7(4)	-2.9(6)
F5	89.0(8)	40.0(6)	32.2(5)	12.8(4)	11.1(5)	5.3(6)
O1	35.3(5)	19.7(5)	33.8(6)	-2.3(4)	9.4(4)	1.3(4)
N1	32.1(6)	27.8(6)	25.9(6)	-3.1(5)	2.4(5)	2.5(5)
C1	25.8(6)	25.0(7)	25.6(7)	-0.8(5)	-0.4(5)	2.2(5)
C2	23.5(6)	20.4(6)	23.3(6)	-0.8(5)	1.0(5)	-1.2(5)
C3	27.7(7)	24.7(7)	29.7(7)	1.1(5)	1.9(5)	4.3(5)
C4	31.3(7)	33.2(8)	28.7(7)	5.2(6)	-3.8(5)	3.0(6)
C5	34.5(7)	32.0(8)	22.3(7)	0.0(5)	0.0(5)	-2.0(6)
C6	24.8(6)	20.2(6)	24.8(6)	-2.7(5)	1.7(5)	-0.1(5)
C7	25.9(6)	22.2(6)	25.8(7)	-0.2(5)	-1.2(5)	1.6(5)
C8	42.8(8)	33.4(8)	25.2(7)	2.0(6)	0.2(6)	0.3(7)

Table 4 Bond Lengths for 18srv350.						
Atom	**Atom**	**Length/Å**		**Atom**	**Atom**	**Length/Å**
F1	C7	1.3585(15)		C1	C2	1.3898(18)
F2	C7	1.3590(15)		C2	C3	1.3890(19)
F3	C8	1.3198(18)		C2	C6	1.5199(18)

F4	C8	1.3302(19)		C3	C4	1.387(2)
F5	C8	1.3349(18)		C4	C5	1.384(2)
O1	C6	1.3996(16)		C6	C7	1.5236(18)
N1	C1	1.3398(17)		C7	C8	1.539(2)
N1	C5	1.3419(18)				

Table 5 Bond Angles for 18srv350.								
Atom	**Atom**	**Atom**	**Angle/˚**		**Atom**	**Atom**	**Atom**	**Angle/˚**
C1	N1	C5	117.74(12)		F1	C7	C6	109.18(10)
N1	C1	C2	123.67(12)		F1	C7	C8	106.81(11)
C1	C2	C6	121.05(12)		F2	C7	C6	111.36(11)
C3	C2	C1	117.64(12)		F2	C7	C8	106.64(11)
C3	C2	C6	121.30(12)		C6	C7	C8	115.54(12)
C4	C3	C2	119.36(13)		F3	C8	F4	108.52(13)
C5	C4	C3	118.83(13)		F3	C8	F5	107.44(12)
N1	C5	C4	122.74(13)		F3	C8	C7	112.55(12)
O1	C6	C2	112.65(11)		F4	C8	F5	108.22(13)
O1	C6	C7	107.20(10)		F4	C8	C7	109.78(12)
C2	C6	C7	110.56(11)		F5	C8	C7	110.20(13)
F1	C7	F2	106.88(11)					

Table 6 Hydrogen Bonds for 18srv350.						
D	**H**	**A**	**d(D-H)/Å**	**d(H-A)/Å**	**d(D-A)/Å**	**D-H-A/°**
O1	H1	N1[1]	0.91(2)	1.83(2)	2.7278(16)	169.7(19)

[1]5/2-X,1/2+Y,1/2-Z

Table 7 Selected Torsion Angles for 18srv350.										
A	**B**	**C**	**D**	**Angle/˚**		**A**	**B**	**C**	**D**	**Angle/˚**
F1	C7	C8	F3	-167.00(11)		C2	C6	C7	F1	62.09(14)
F1	C7	C8	F4	72.02(15)		C2	C6	C7	F2	-55.69(14)
F1	C7	C8	F5	-47.09(16)		C2	C6	C7	C8	-177.55(12)
F2	C7	C8	F3	-52.99(16)		C3	C2	C6	O1	-20.13(18)
F2	C7	C8	F4	-173.97(12)		C3	C2	C6	C7	99.78(14)
F2	C7	C8	F5	66.92(15)		C6	C7	C8	F3	71.36(16)
O1	C6	C7	F1	-174.78(10)		C6	C7	C8	F4	-49.63(17)
O1	C6	C7	F2	67.45(13)		C6	C7	C8	F5	-168.74(12)
C1	C2	C6	O1	158.88(12)		C8	C7	C6	O1	-54.41(15)
C1	C2	C6	C7	-81.20(15)						

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 18srv350.				
Atom	***x***	***y***	***z***	**U(eq)**
H1A	13458.36	6709.86	2739.83	31
H3	7162.78	9344.83	2521.28	33
H4	6891.15	8648.99	1378.62	37
H5	9911.93	6989.3	962.87	36
H6	12507.67	8580.15	3619.97	28
H1	10450(40)	10520(20)	3519(10)	53(6)

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

1. Fixed Uiso
At 1.2 times of: All C(H) groups
2.a Ternary CH refined with riding coordinates:
C6(H6)
2.b Aromatic/amide H refined with riding coordinates:
C1(H1A), C3(H3), C4(H4), C5(H5)

Chapter 4: Overall References

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