The development of new applications for pentafluoropyridine in organic chemistry.

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A thesis entitled

The development of new applications for pentafluoropyridine in organic chemistry

Submitted by

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Declaration

This work was conducted in the Department of Chemistry of Durham University between October 2021 and September 2022. The work has not been submitted for a degree in this or any other university. Unless otherwise indicated, this is my own work.

Abstract

Esters are a class of organic compounds, that have uses in a wide variety of industries including, fragrances, lubrication, and medicine. One of the most common ways to approach ester synthesis is through a reactive acyl chloride moiety which is accessed by employing reagents such as thionyl chloride. Acyl fluorides are of similar reactivity to their chloride counterparts but have largely remained unexplored for ester preparation as the synthetic methods required to access them can require toxic conditions. This work primarily describes the utilisation of pentafluoropyridine (PFP) to prepare acyl fluorides which were subsequently used to produce esters and thioesters. Recent studies by Brittain *et al*. have shown that PFP can be used in a carboxylic acid deoxyfluorination process for the *in-situ* preparation of acyl fluorides.[1] Herein, this methodology is expanded to one-pot esterification and thioesterification reactions. High yields were readily obtained in the esterification (92%) and thioesterification (89%) processes. The methods reported are mild and easily adaptable for any lab, requiring no specialist handling equipment such as plastic reaction vessels which can often be required for reactions utilising fluorine.

Following this successful esterification work, one of the proposed intermediates of the reaction process was explored and tetrafluoropyridyl esters were successful synthesised. A novel sulfonyl reagent was prepared and successfully shown to be able to access tetrafluoropyridyl esters directly from carboxylic acids which negates the need for acid anhydrides or acid chlorides.

In-situ preparations of acyl fluorides were then used to successfully demonstrate *in-situ* Suzuki-Miyaura cross-couplings which prepared ketones from acyl fluorides and boronic acids in less-than-optimal yields.

Acknowledgments

Firstly, I would like to thank Professor Steven Cobb for accepting me into his group to undertake this study. Throughout the year he has provided an immense amount of support, guidance and ideas whilst also giving me a great deal of freedom in conducting this research.

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A massive thankyou goes to all members of the Cobb Group. I was lucky to start at the same time as another MRes student, Lewis, without him this would have been a very different experience and I am thankful that I had someone to bounce ideas off, share a laugh with and go on a night out with. Thank you to all the other members of the Cobb group; Carissa, Izzy, Diana, Hirunhika, Yazmin, Katie and Eleanor for all their help over the last year.

Katherine (Brittain Group) also deserves an honourable mention for all the discounted cakes she supplied us with over the summer and chemistry humour.

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Publications and Conferences

This work has been presented in part in the following -

- As a publication: **L. N. D. Beardmore**, S. L. Cobb and W. D. G. Brittain, *Org. Biomol. Chem.*, 2022, **20**, 8059-8064
- As a poster: The Annual RSC Fluorine Interest Group Meeting 2022 (held virtually)
- As a talk: The Durham Postgraduate Research Symposium 2022 (Durham University)
- As CCDC deposits
    - **Beardmore, Liam**, Cobb, Steven L., Brittain, William D.G., Yufit, Dmitry S. CCDC 2206304: Experimental Crystal Structure Determination, 2022, DOI: 10.5517/ccdc.csd.cc2d1v3f
    - **Beardmore, Liam**, Cobb, Steven L., Yufit, Dmitry S. CCDC 2206305: Experimental Crystal Structure Determination, 2022, DOI: 10.5517/ccdc.csd.cc2d1v4g

Abbreviations

ASAP	Atmospheric Solids Analysis Probe
Boc-Ser-OH	Boc-L-Serine
CBz	Benzylozycarbonyl
CCDC	Cambridge Crystallography Data Centre
CD_3CN	Deuterated Acetonitrile
$CDCl_3$	Deuterated Chloroform
CFC	Chlorofluorocarbon
DAST	Diethylaminosulfur Trifluoride
DCC	*N*,*N*′-Dicyclohexylmethanediimine
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EDC	3-(((ethylimino)methylene)amino)-*N*,*N*-dimethylpropan-1-amine
EDT	Ethane-1,2-dithiol
ESI	Electrospray Ionisation
Fmoc	Fluorphenylmethyloxycarbonyl
GCMS	Gas Chromatography Mass Spectrometry
GWP	Global Warming Potential
HBTU	Hexafluorophosphate Benzotriazole Tetramethyl Uronium
HF	Hydrogen Fluoride
HFO	Hydrofluoroolefin
HOBt	Hydroxybenzotriazole

HOMO	Highest Occupied Molecular Orbital
LCMS	Liquid Chromatography Mass Spectrometry
LUMO	Lowest Unoccupied Molecular Orbital
m/z	Mass/charge ratio
MHz	Mega Hertz
NCS	*N*-Chlorosuccinimide
NMR	Nuclear Magnetic Resonance
PFB	Perfluorobenzene
PFHA	Perfluoroheteroaromatic
PFP	Pentafluoropyridine
Ppm	Parts Per Million
PTSA	*para*-toluenesulfonic acid
PTFE	Polytetrafluoroethylene
S_EAr	Nucleophilic Electrophilic Aromatic Substitution
S_N2	Nucleophilic Substitution
S_NAr	Nucleophilic Aromatic Substitution
SPhos	Dicyclohexyl(2′,6′-dimethoxy[1,1′-biphenyl]-2-yl)phosphane
TFPO	Tetrafluoropyridyl-4-ol
TMS	Trimethylsilyl
UV	Ultraviolet

Contents

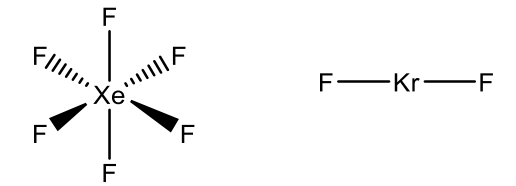
1 Introduction

1.1 Organofluorine Chemistry

1.1.1 History and background of Fluorine

Fluorine is the most electronegative element on the periodic table. Despite being held in large reserves in the ground in the form of minerals such as fluorspar, there are only a handful of fluorinated natural organic products. Fluorine, in the form of elemental F_2 was first isolated in 1886 by Henri Moissan but remained unused for synthetic applications for around the next 50 years. The growth of fluorine chemistry started during the 1930's with the introduction of refrigeration freons.[2] The popularity of fluorine chemistry continued to increase in the 1940's after its use in refining uranium as UF_6 for the atomic weapons of the Manhattan Project. The ^{19}F isotope is 100% abundant, so the weight of UF_6 is dependent completely on which isotope of uranium is present which in turn can be used to separate U-235 from U-238 in a centrifuge.

Fluorine possesses unusual reactivity properties due to its extreme electronegativity. For example, an unusual property uncharacteristic of other elements is the ability of fluorine to react with noble gases such as xenon and krypton which are interesting molecules to study because of their geometries (**Figure 1.1**).



hexafluoroxenon
1

difluorokrypton
2

Figure 1.1: Fluorine containing group 18 molecules.

1.1.2 General Chemistry of Fluorine

Fluorine has the electronic configuration $1s^2$ $2s^2$ $2p^5$ and in common with other group 17 elements desires an electron to completely satisfy the octet rule. Given the extreme electronegativity of fluorine it can often be found as the fluoride anion. The addition of fluorine atoms to molecules, especially organic molecules, can have a huge impact on the properties of these molecules. The strength of the C-F bond, the strongest single covalent bond that can be made in organic molecules, has a bond dissociation energy of 536 kJ mol^{-1}. For comparison the C-H bond is 413 kJ mol^{-1}. This strength is due to the electronegativity of fluorine which highly polarises the bond giving this covalent bond some ionic character.

Industrially HF (hydrofluoric acid) and F_2 are the most commonly employed sources of fluorine atoms. F_2 or fluorine gas is particularly reactive and has a much lower bond energy of 157.0 kJ/mol compared to Cl_2 (242.6 kJ/mol) and Br_2 (193.9 kJ/mol) group 7 counterparts due to repulsive effects. Given the extreme reactivity of F_2 gas and the associated difficulties with handling, HF is often preferred. This still carries extreme safety risks requiring careful handling and specialised apparatus such as PTFE reaction vessels and personal protective equipment. Unlike it's halide acid counterparts HI, HBr and HCl, HF is considered a weak acid with a p*K*a of ~3. The extreme electronegativity of fluorine means the hydrogen is more tightly bound and less likely to dissociate.

The ^{19}F isotope is NMR active with a spin ½. Fluorine in the form of ^{19}F is 100% abundant and has magnetogyric ratio which gives high sensitivity that's around 83% that of the ^{1}H nucelus.[3, 4] By using ^{19}F NMR spectroscopy reactions or compounds containing fluorine are easily monitored due to a wide ppm range and the effects of even minor conformation changes in the environment surrounding a fluorine atom are usually distinguishable.[3] Fluorine NMR spectroscopy is a popular choice of technique in biological imaging, such as in proteins and peptidomimetics as there is a significant lack of background fluorine signals. In addition, there are an abundance of fluorinated labels and tags available and the process is non-invasive.[3-5]

1.1.3 Applications of Fluorinated Products

The carbon fluorine bond is one of the strongest bonds known (485 kJ/mol) and is widely accepted as the strongest single covalent bond in organic chemistry. This gives fluorinated

organic molecules characteristic properties like high hydrophobicity which has led to widespread “non-stick” applications such as cooking pans. Teflon™ is a product name for a brand of popular non-stick pans. The C-F bond in Teflon™ is not readily broken down by the high temperatures of cooking. Due to the hydrophobic nature of the bond water and foods slide off surfaces coating the Teflon™ material, making it the ideal material for cookware. Fluorinated products are of great importance to day-to-day life and some common examples are listed below (**Figure 1.2**). Fluorinated compounds have huge market values, for example perfluoro and polyfluoro alkyl care products had a $100 billion market value in North America in 2019, of which approximately $20 billion was accounted for by the cosmetic industry.[6]

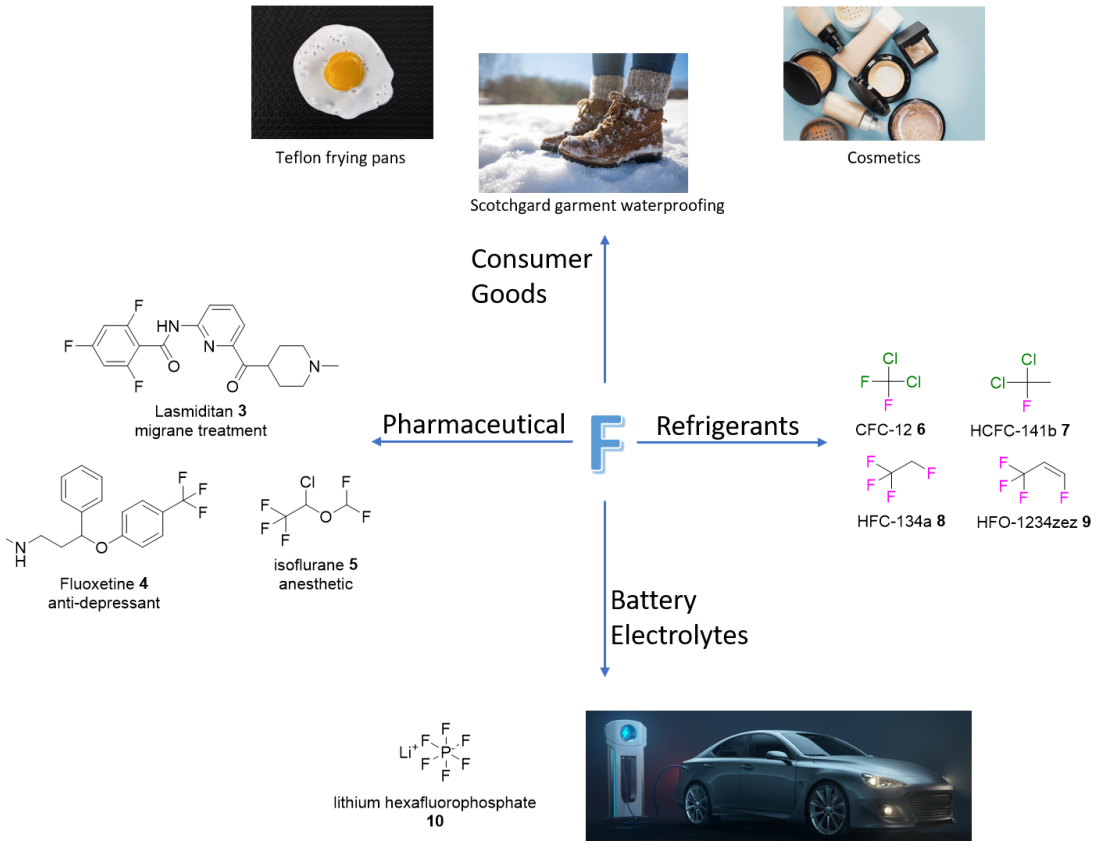


Figure 1.2: Some everyday applications of fluorinated compounds.

Perfluorinated compounds are highly biopersistent and have become known as forever chemicals. These forever chemicals were recently highlighted in the 2019 film Dark Waters which centred around the dumping of perfluorooctanoic acid into the local environment by Dupont.[7] These dumped chemicals were by-products in the manufacturing of non-stick pans. Chemicals such as perfluorooctanoic acid are known as forever chemicals due to major

concerns they accumulate in the body with no mechanism for clearance.. These forever chemicals are receiving increased media attention due to these potential carcinogenic effects along with their prevalence in the environment and goods, such as in North American school uniforms. [8, 9]

Fluorine atoms are present in over 20% of all commercial drugs.[10] The application of fluorine in medicinal chemistry has grown rapidly, just 2% of drugs on the market in 1970 contained fluorine, but by 2014 that number had risen to around 25% and three of the top 5 bestselling pharmaceuticals of 2014 contain at least one fluorine atom.[11] By 2022 the figure has exceeded 25% of all pharmaceuticals containing fluorine.[12] Fluorine is a suitable replacement for a hydrogen atom given their similar atomic radii and as such this substitution creates little steric impact, meaning that drug molecules can still access and interact with their biological targets. Fluorine is incorporated primarily to affect physiological properties, metabolic stability, or binding affinity.[13] There are numerous fluorine containing blockbuster drugs, with one example being the HIV-integrase inhibitor Dolutegravir which had a 2019 market value of $6.1 bn.[14] Defluorination reactions of drugs can occur spontaneously and the wider implications these have on health are still relatively unexplored.[15] Away from pharmaceutical products, fluorine is also a useful tool for medical imaging. The ^{18}F isotope can be artificially synthesised and is commonly employed in radioactive imaging of biological pathways which has led it to become an important tool in drug discovery.[16]

Fluorine is very important in battery production as it forms non-aqueous electrolytes that are crucial to ionic exchange. An example of such is the electrolyte salt $LiPF_6$, which is one of the most common electrolyte salts due to its well-balanced range of properties such as wide window of stability and excellent solubility.[17] Additives are an important aspect of batteries as they influence factors such as solid electrolyte interphase (SEI) formation. Fluorinated battery additives, such as fluoroethylene carbonate are important compounds that can increase columbic efficiency.[18] Recently, the UK government has committed to zero emissions at the exhaust for new cars and vans by 2035.[19] Electric cars are seen as one of the ways to achieve this goal. These electric cars require lithium-ion batteries so fluorine will continue to play a huge role in the advancement of these technologies.

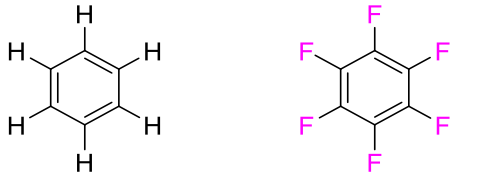
Despite all the fluorinated compounds discussed so far, the most well-known class of fluorinated molecules are probably the chlorofluorocarbons (CFC's) (**Figure 1.2**). CFC's were primarily used as refrigerants and propellants and were banned under the Montreal Protocol

due to the adverse effect these chemicals had on the ozone layer.[20] These CFC's are also extremely potent greenhouse gases with small concentrations having a much larger effect than comparable concentrations of CO_2.[21] CFC's provided such a vital function in foam blowing, refrigeration and propellants that comparable replacements have had to be found. The ideal substitutes are "drop-in" replacements which means existing systems require little to no modification. Work is now focussing on their replacement with hydrofluoroolefins (HFO's) which have a greenhouse effect in line with that of carbon dioxide, the HFO 1234yf (2,3,3,3-Tetrafluoropropene) for example has a global warming potential GWP of 4, by comparison CO_2 as the reference gas has a GWP of 1.[22]

1.2 Perfluoroaromatics

1.2.1 Introduction and Examples of Perfluoroaromatics (PFA) and Perfluoroheteroaromatics (PFHA)

Perfluoroaromatics are a class of organofluorine compounds with fluorine atoms saturating the molecule. An illustrative example is benzene (**11**) and its perfluorinated equiv. hexafluorobenzene (**12**) which was first synthesised in 1947.[23] The inclusion of fluorine atoms on the aromatic ring dramatically influences the reactivity of the molecule.

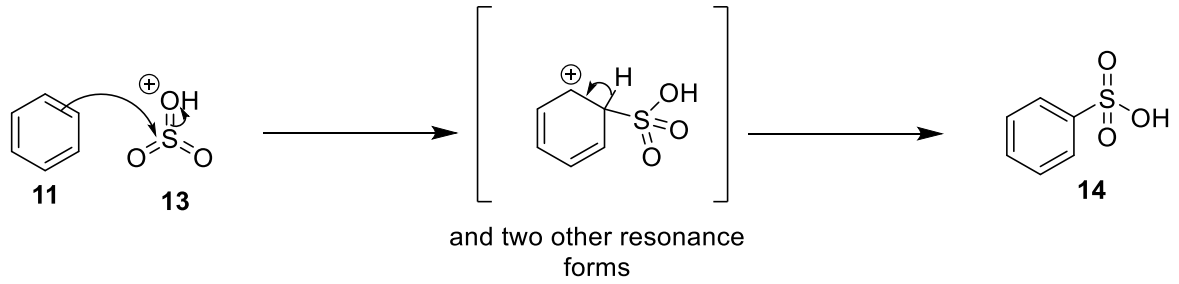


Benzene **11** Hexafluorobenzene **12**

Figure 1.4: Chemical structures of benzene (**11**) and perfluorobenzene (**12**).

Aromatic compounds such as benzene (**11**) are expected to undergo electrophilic aromatic substitution reactions (S_EAr) through a Wheland intermediate where a positive charge is stabilised round the ring (**Scheme 1.1, Figure 1.5**). The sulfonation of benzene is an example

of S_EAr where the delocalised electrons of the benzene ring attack the electron poor sulfur atom in an electrophilic process.



Scheme 1.1: Electrophilic aromatic substitution of benzene (sulfonation reaction).

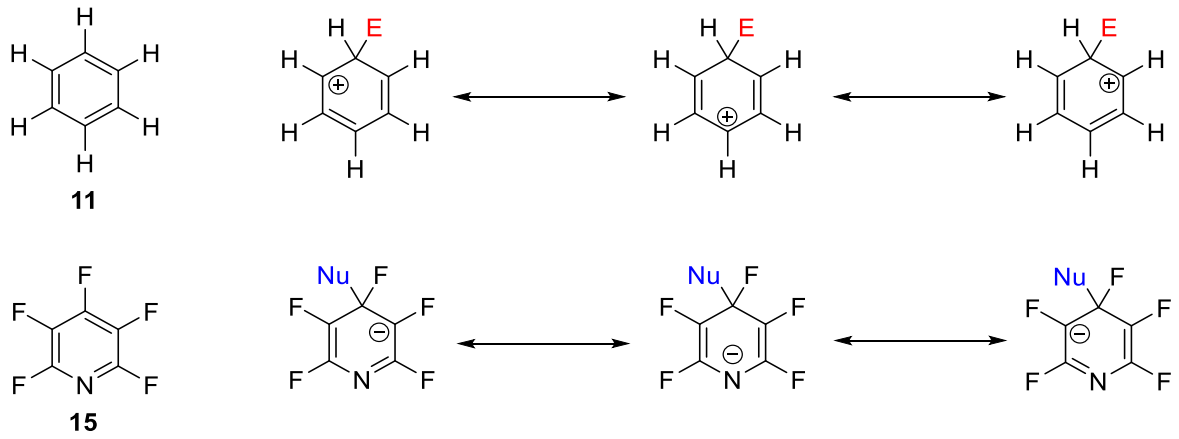


Figure 1.5: Depictions of stabilisation of charge on benzene (**11**) and pentafluoropyridine (PFP,**15**) showing the difference between a Meisenheimer and Wheland intermediate.

Perfluoroaromatics by contrast are susceptible to nucleophilic aromatic substitution reactions (S_NAr) commonly through a Meisenheimer intermediate (**Figure 1.5**).[24] The reason for this shift in reactivity is explained by the extreme electron withdrawing nature of the fluorine atom which draws electron density away from the aromatic ring. In a nucleophilic aromatic substitution, an electron rich nucleophile attacks upon an electron deficient position on the ring, which is then followed by the departure of a leaving group and overall substitution of the leaving group by the nucleophile. This is a two-step process and examples are discussed in **Section 1.2.3**, which covers the reactivity of pentafluoropyridine **15** (PFP).

Alongside PFP (**15**) other perfluoroheteroaromatics exhibit similar susceptibility to nucleophilic substitutions, a few examples are shown in **Figure 1.6**. Hexafluorobenzene (**12**) is an illustrative example and will undergo S_NAr reactions under mild conditions in a regioselective

process after the first substitution occurs (**Scheme 1.2**). Cystine peptide stapling of hexafluorobenzene under mild conditions with thiols as the nucleophiles showed exclusive 1,4-substitution.[25]

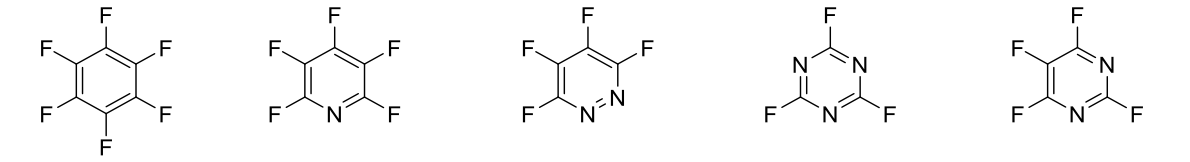
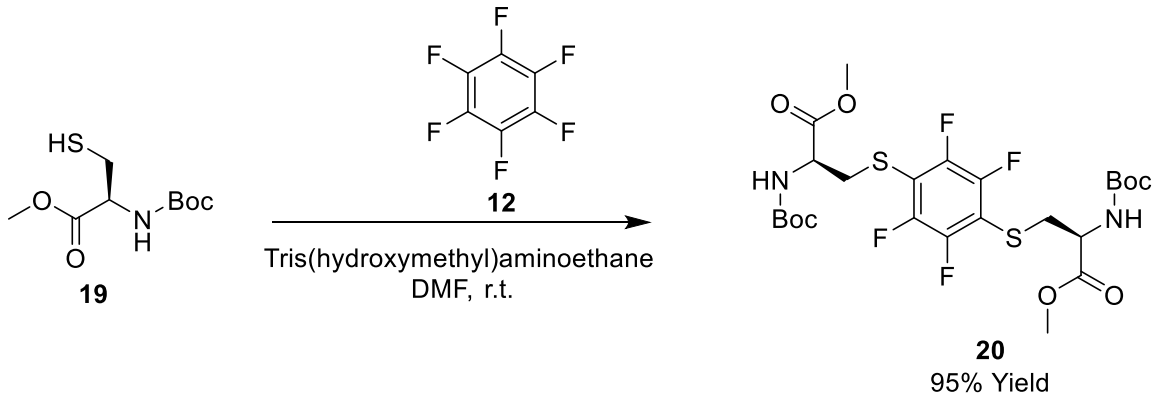


Figure 1.6: Examples of some perfluoroaromatic compounds.



Scheme 1.2: Cystiene stapling reported by Pentelute and co-workers.[25]

The extreme electron deficiency of perfluoroaromatics is also evident from their behaviours in stacking with benzene. Perfluoroaromatics will stack in an alternating arrangement with regular aromatic compounds. An example is a 1:1 mixture of **11** and **12** which forms an alternating stacked arrangement which can be exploited for self-assembly reactions.[26, 27] This stacking ability can have detrimental effects for separation however and some problems regarding this are discussed later in the experimental of **Chapter 2**. Evidence of this stacking is also apparent in some of the crystal structures obtained for tetrafluoropyridyl esters (**Figure 1.7**) which will be discussed later in **Chapter 3, Section 3.1**.

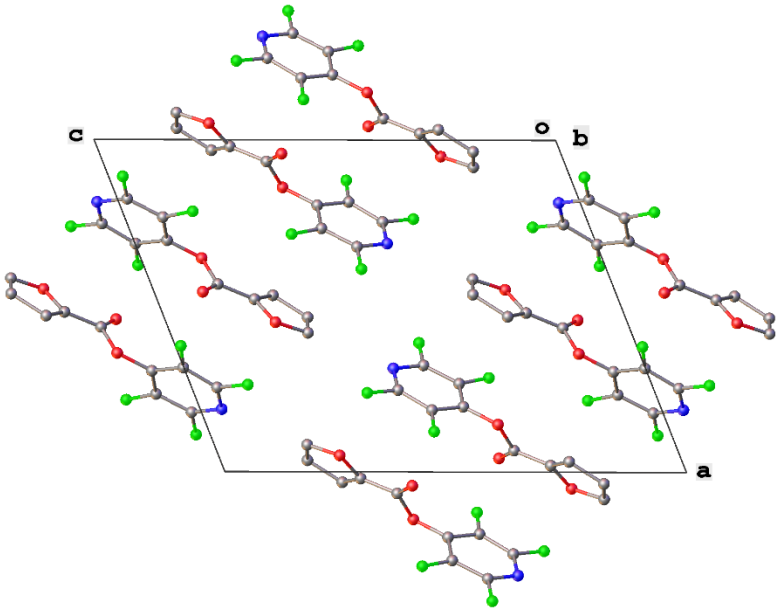
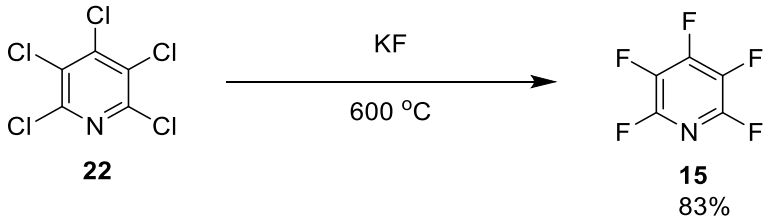


Figure 1.7: Alternating stacking arrangement example from the work within this thesis. This is the stacking of perfluoropyridin-4-yl cyclopenta-1,3-diene-1-carboxylate (**21**).

1.2.2 Introduction to Pentafluoropyridine

Pentafluoropyridine **15** (PFP) is a cheap, bench stable and commercially available perfluoroaromatic compound. In terms of safety PFP possesses flammable and harmful hazard codes which are compatible with most organic synthesis labs. PFP is an odourless and colourless compound with a boiling point of approximately 83 °C. This is useful as it can comfortably be heated to 50 °C to increase kinetics but is still compatible with removal via distillation at reduced pressure which makes reaction mixtures easier to purify. PFP is extremely non basic with an estimated p*Ka* of -11 which was determined by attempted protonation's with FSO_3H.[28] This is in a stark contrast to pyridine which has a p*Ka* of 5.25 and is often utilised as a base in organic synthesis. PFP has a low pK_{HB} of -0.49 which was the lowest in a table of 65 measured related pyridines.[29]

Methods of manufacturing PFP have been known since the 1960's.[30] The synthesis requires simple industrial conditions to prepare PFP from the pentachloropyridine **22** using potassium fluoride at high temperatures in a tube furnace (**Scheme 1.3**).[31]



Scheme 1.3: Synthesis of PFP (**15**) from pentachloropyridine (**22**).[31]

1.2.3 Reactivity of Pentafluoropyrdine

Pentafluoropyridine (**15**) undergoes S_NAr reactions which exclusively direct at the ring position which is *para* to the nitrogen first. This can be explained by the dominating effect of stabilising the Meisenhiemer intermediate (**Figure 1.5**) coupled with the activating and deactivating effects of the fluorine atoms on the ring.

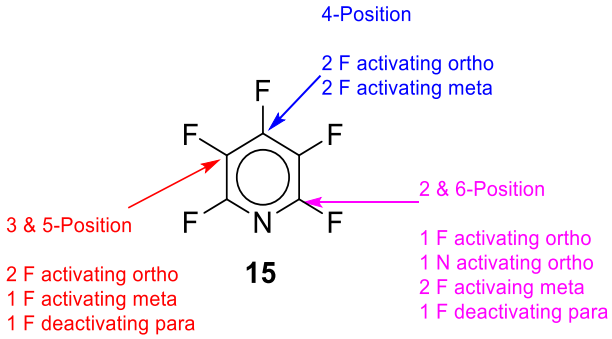


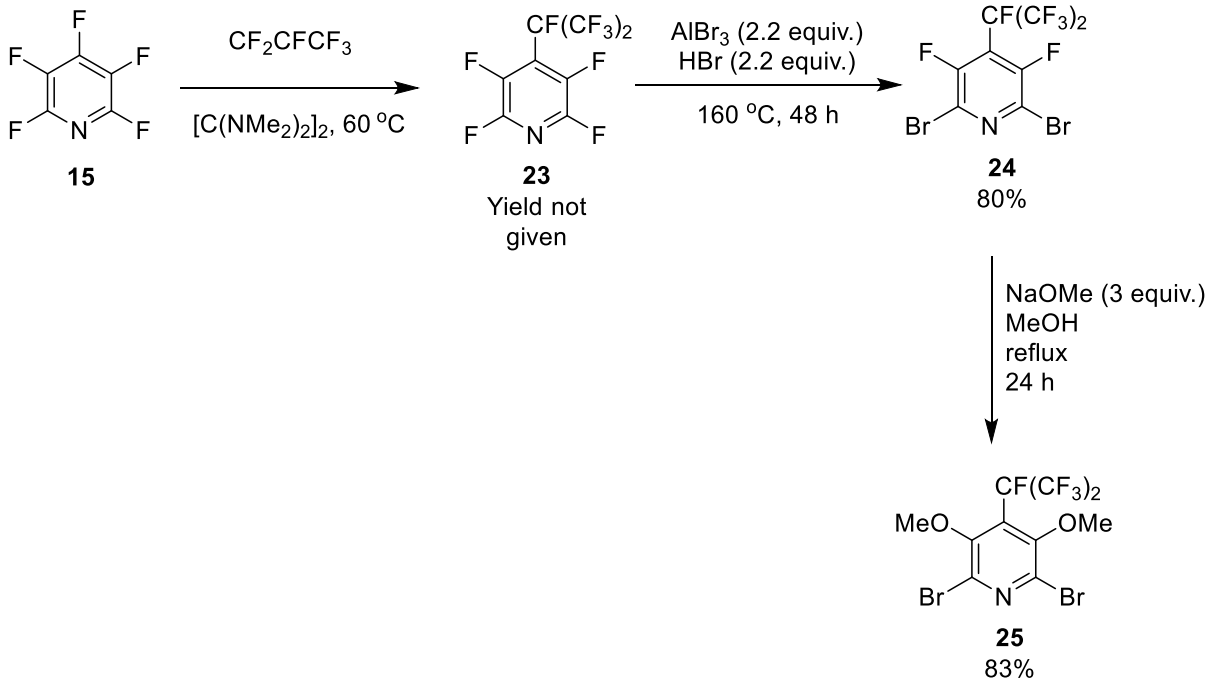
Figure 1.8: Highlighting the effects exerted on the different positions of the pentafluoropyridine ring

If we start by considering a molecule of PFP **15** highlighted in **Figure 1.8**, the nitrogen occupies position one of this ring. The 4-positon is *para* to this ring nitrogen and is a position which allows for the stabilisation of charge within the Meisenhiemer intermediate (**Figure 1.5)**. Chambers *et al.* discovered this stabilisation to be the major influence surrounding activity, although this argument can also be made for the ring 2- and 6-positions (**Figure 1.5**).[24] The preference for the 4-position over the 2 or 6 positions then comes down to the effect of the other fluorine atoms on the ring. The 4-position has no *para* fluorine deactivating it, rather there is a nitrogen occupying that position (i.e., position 1 as shown in **Figure 1.8**). The lone

pair of a *para* orientated fluorine destabilise the Meisenheimer intermediate because of unfavourable orbital overlap. Furthermore the 4-position also has two activating *ortho* substituted fluorine's relative to it (in this case at positions 3 and 5 on the generic ring) as well as two *meta* fluorine's which are also slightly activating (positions 2 and 6).

By contrast the 2 and 6 positions on the ring, which are also capable of using the nitrogen to stabilise the Meisenheimer intermediate both have a fluorine substituent on the carbon that is relatively *para* to them which destabilises the position. The preference for the 4-position over all the others is thus then driven by the lack of deactivating *para* fluorine combined with the Meisenheimer stabilisation factors.

There are many examples of preferential nucleophilic substitution onto the 4-position of PFP (**15**), for example reactions with nucleophiles such as amines, isocyanides, carboxylates and sulfurs.[32] When the 4-position is occupied, the next preferential substitution is at the 2-position of PFP. This observation is explained by the effects described previously. Despite there being a *para* located deactivating fluorine, the 2 and 6 positions can push the negative charge of the Meisenheimer intermediate onto the stabilising ring nitrogen. If the 2 and the 4 positions are occupied substitution will direct to the 6-position for this reason. The effects are well illustrated in work by Chambers *et al.* in 2001 (**Scheme 1.4**).[33] In this work PFP was used to modify scaffolds to access therapeutics, by starting with PFP a succession of 5 nucleophilic steps could be performed using PFP as the heart of the molecule [33]

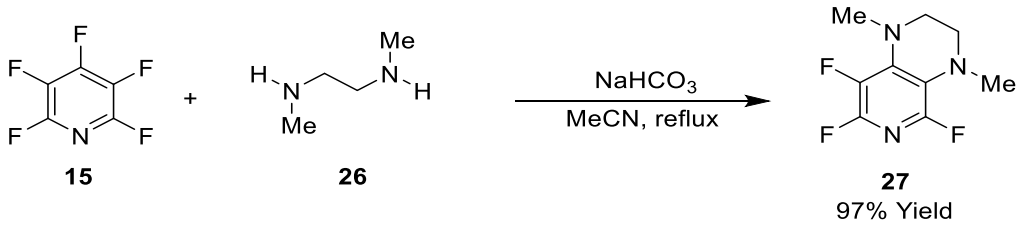


Scheme 1.4: Chambers *et al*. synthesis of multi-substituted pyridine derivative.[33]

As reported above (**Scheme 1.4**) the five fluorine atoms in PFP (**15**) can be sequentially substituted by nucleophiles.[33] Attack by CF_2CFCF_3 in step 1 leads to substitution solely on the 4-position. In the first step the double bond is lost as initially the perfluoroalkene reacts with TDAE to produce a fluoride ion, in turn this fluoride ion attacks another molecule of perfluoroalkene to form a carbanion (this attack occurs because of how electron withdrawn the carbon centres are).[34] The generated carbanion then attacks onto the 4-position of **15**.

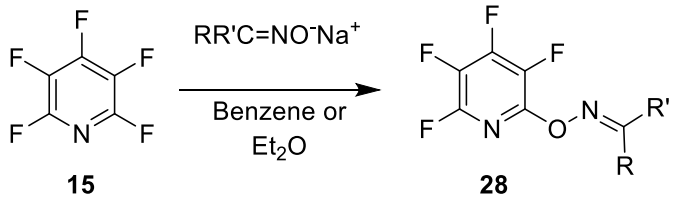
After this step, more forcing conditions are used to encourage attack onto the 2 and 6 positions which is possible with HBr in step 2 to produce **24**. Finally, in step 3, the 3 and 5 positions can be substituted when the other 2, 4 and 6 are all occupied to produce compound **25**. With each substitution, and subsequent removal of a fluorine on the ring, the electron density increases. As the ring becomes less electrophilic further substitutions require more forcing conditions, as seen in **Scheme 1.4**, first 60 °C was used, then 160 °C then reflux. The less electrophilic the ring, the less susceptible it is to nucleophiles. Substitution on the *meta* (3 and 5) positions is much less favourable due to the loss of both nearby activating fluorine atoms and an inability to push negative charge onto the nitrogen in the Meisenhiemer intermediate but as shown in **Scheme 1.4 and 1.5**, substitution on these positions is possible.

Ring formation driven from initial substitution at the 4-position can also drive substitution onto the 3-position rather than the 2-position.[35, 36] This “out of order” substitution is possible as it is driven by steric effects, allowing for the energetically favourable formation of a 6-membered ring (**Scheme 1.5**).



Scheme 1.5: Substitution onto the 4-position followed by the 3-position described by Cartwright *et al*.[36]

In addition there are also some very limited instances where substitution can be directed solely to the two-position; this was observed when certain sodium or potassium ketoximates were employed. It is believed the lone pair on the PFP ring nitrogen has an interaction effect that favours substitution at the *ortho* position (**Scheme 1.6**).[37]



Scheme 1.6: Substitution directed to the two-position described by Banks *et al*.[37]

Finally, despite PFP (**15**) already being extremely susceptible to nucleophilic substitution, if a *meta* ring position is substituted with a nitrogen equating to tetrafluoropyrimidine the reaction would direct *ortho*, though not between the ring nitrogen’s (**Figure 1.**9, pink circle) with a greatly increased rate compared to that of regular PFP (rates increase ~10^2 for each introduction of a ring nitrogen) (**Figure 1.9**).[38] The reasoning for not attacking between the ring nitrogens in the case of 18 is that there is still the deactivating effect of a *para* fluiorine substituent to consider.Two of these substitutions would result in the structurally similar cyanuric fluoride **17** that was pioneered by Olah which reacts 10^5 times faster than PFP (**15**).[39]

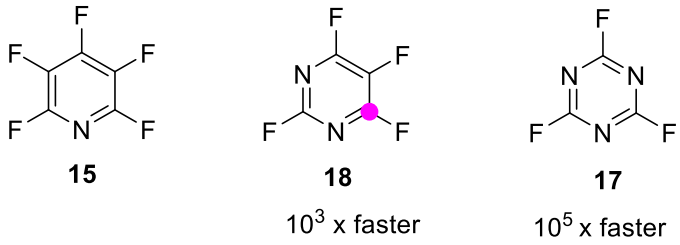
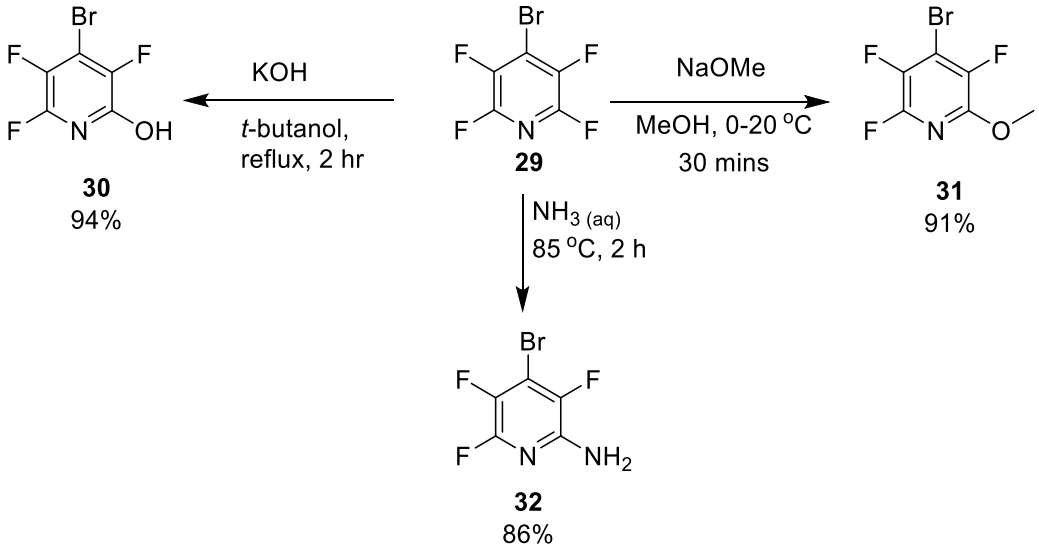


Figure 1.9: Comparing the relative rates between different levels of nitrogen substituted perfluorinated rings.

1.2.4 Pentafluoropyridine in Organic Chemistry

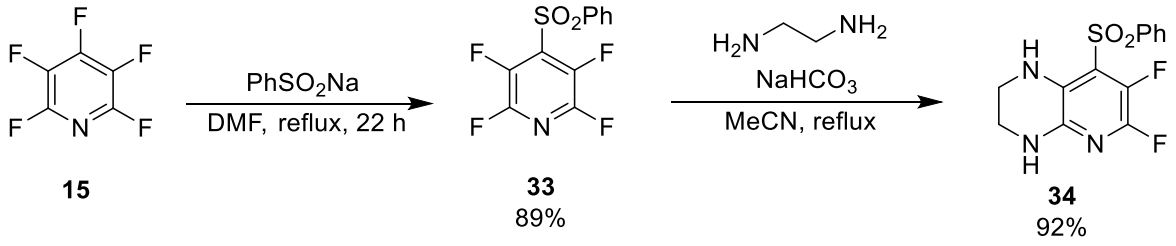
PFP (**15**) has been researched in organic chemistry for over 60 years. By the late 1950's and early 1960's perfluoroaromatics were beginning to receive increasing amounts of attention. Reactions such as carbanions and 1,4-polymerisations of hexafluorobenzene (**12**) were reported in 1961.[40]

Some earlier examples are the series of reactions of PFP which were described from around 1964 at Durham University (Part III Chambers, Hutchinson and Musgrave). One of the earlier, readily accessible examples of this series was the 1965 work of Chambers *et al*. where after substituting an amine group onto PFP, they were able to form the 4-nitrotetrafluoropyridine by oxidation.[41] Further experimentation showed that 4-aminotetrafluoropyridine was also susceptible to bromination. By occupying this 4-position with a bromine they were then able to easily access substitution at the 2-position of the ring (**Scheme 1.7**), which at this point in time was uncommon.[41]



Scheme 1.7: Modifications of PFP by firstly occupying the 4-position with a bromine.[41]

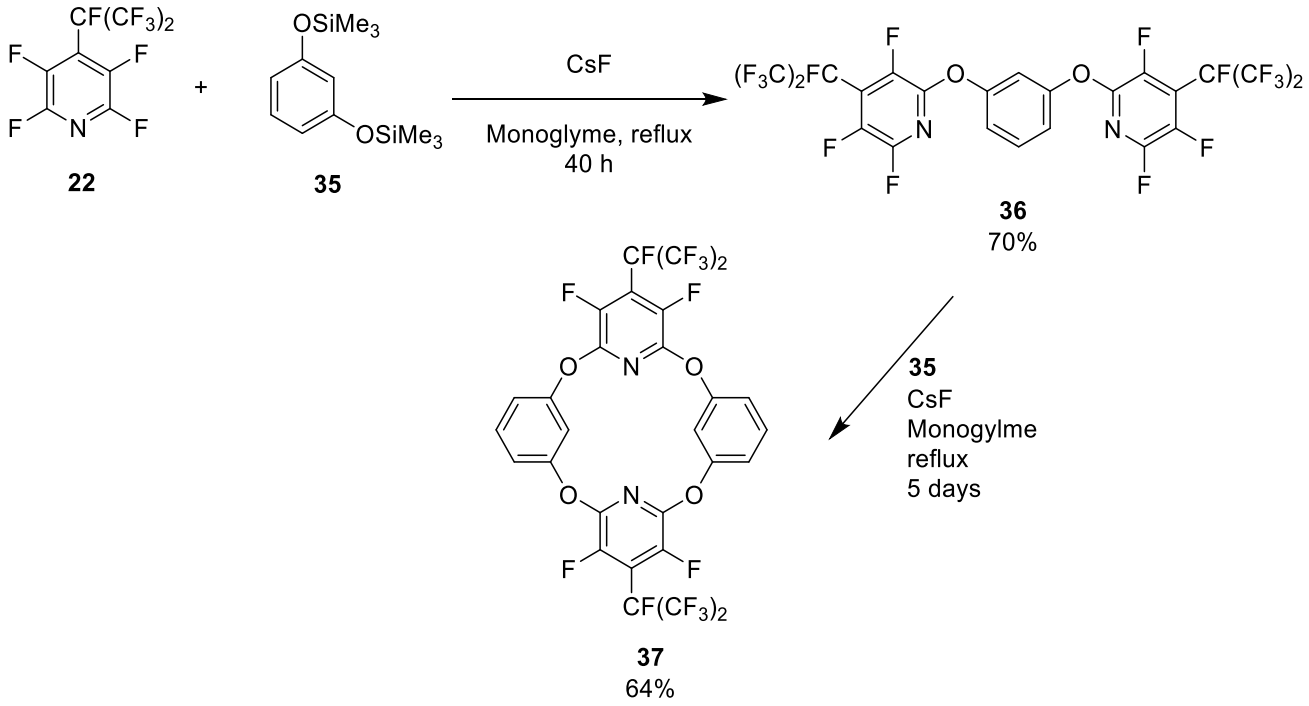
More recently, PFP (**15**) was used to access 6,6-ring systems, which were formed by blocking substituting the 4-position with a nucleophile first followed by further addition of a bifunctional nucleophile which would attack at the 2-position before being forced to attack onto the usually unreactive 3-position (**Scheme 1.8**).[42]



Scheme 1.8: 6,6-ring formations from a PFP core described by Baron *et al*.[42]

This work was a continuation of studies previously discussed which generated these rings from the 4 and 3-positions (**Scheme 1.5**) and was highlighted in a review which discussed the reactivity advantages of PFP over chlorinated analouges.[35, 43] Similar scaffold building reactions are also possible with structurally similar perfluoroheteroaromatics PFHA's, such as tetrafluoropyrazine or tetrafluoropyridazine. These are further examples of fluorinated molecules where in theory all the fluorine atoms can eventually be displaced.[44] Chambers *et al.* reported that by blocking the 4-position with a nucleophilic substitution and then reacting at the 2 and 6 positions with bifunctional nucleophiles allowed for the synthesis of large macrocycles. Here the susceptibility of nucleophilic substitution was exploited to form the

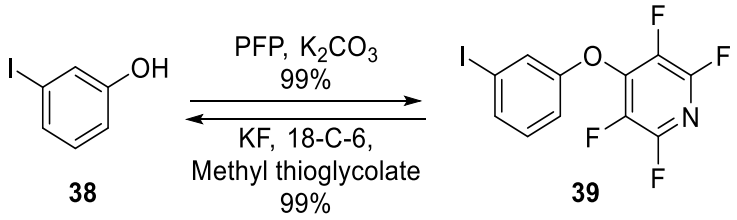
macrocycle, the synthesis of which is reportedly an uncommon way to access these compounds (**Scheme 1.9**).[45]



Scheme 1.9: Preparation of PFP based macrocycles by Chambers *et al*.[45]

Furthermore, substitution of PFP has allowed for the preparation of heterocyclic therapeutics. By using PFP as a scaffold, modified heterocycles can easily be accessed by reacting at the 4 position first, followed by modification of the 2 and 6 positions, such as a class of p38 MAP Kinase inhibitors reported by Revesz *et al.*[46]

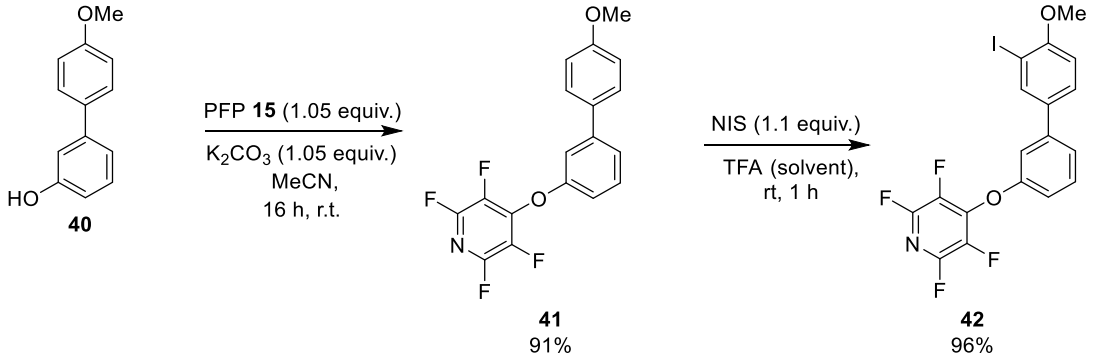
In the past few years, Brittain and Cobb have applied pentafluoropyridine in several ways. By mixing PFP (**15**) and a base together under mild conditions phenols were shown to be easily protected (**Scheme 1.10**).[47] The nucleophilic phenoxide ion attacked the 4-posiiton of pentafluoropyridine forming a tetrafluoropyridyl ether.



Scheme 1.10: Utilisation of PFP (**15**) as a protecting group described by Brittain and Cobb.[47]

The tetrafluoropyridyl-4-ol (TFPO) protecting group could then be removed upon adding potassium fluoride, 18-crown-6 and methyl thioglycolate.[47] Using this method is seen as advantageous as it removes the need for harsh deprotection conditions while also providing a mild method of installation providing overall yields of up to 99%.

In a further publication, Brittain *et al.* were able to use PFP (**15**) to control remote electrophilic substitution, where by adding PFP to one side of a bisphenol system, iodine or bromine could be selectively added to the non-protected side of the system exclusively (**Scheme 1.11**).[48] This served as a dual protecting and directing group. Without the TFPO protecting group electrophilic halogenation of **39** would result in a reaction occurring unselectively on either of the aromatic rings.



Scheme 1.11: Regioselective S_EAr halogenation reactions reported by Brittain*et al.*.[48]

This regioselectivity of substitution is explained by the extreme electronegativity of the tetrafluoropyridyl group deactivating the protected of the aromatic ring in the bi-aryl ring system. The relatively deactivated ring does not undergo S_EAr reactions under the mild conditions employed and exclusive reaction to the ring without the protecting group is observed. The reported isolated yields from the TFP protected **41** was up to 96%.

In 2021 PFP was utilised by Brittain *et al.* for the *in-situ* preparation of acyl fluorides which were then used to prepare amides following a nucleophilic addition elimination reaction. The work of Brittain *et al.* forms part of the basis for this thesis and is continued within **Chapter 2**. The publication of deoxyfluorination reactions of carboxylic acids is discussed in more detail in the introduction to that **Chapter 2**.[1]

In 2022 Brittain and Coxon performed a systematic review into perfluoroaromatics in peptides and proteins. This provided a positive and exciting outlook for the use of PFP and other perfluoroaromatics for the modification of biologically relevant molecules.[49] Within this review pentafluoropyridine was discussed pertaining to its ability to act as a molecular building block and its capacity as a way of performing S_NAr arylations of peptides.

1.3 Acyl Fluorides

1.3.1 Applications of Acyl fluorides

Acyl fluorides are a class of fluorinated compounds, and their reactivity towards nucleophiles is somewhat similar to that of acyl chlorides, although acyl fluorides are less prone to hydrolysis.[50, 51] Acyl fluorides can be made from the corresponding acyl chloride via a halogen exchange reaction in excellent yields but this often requires high temperatures and is not appropriate for molecules which contain multiple sensitive functional groups.[52,53] Much like acyl chlorides, acyl fluorides can have applications in the synthesis of amides, esters, thioesters and peptide synthesis but are more useful substitutes when strong acid incompatible functional groups are present.[1, 54, 5556]

In recent years acyl fluorides have seen a resurgence as focus has shifted towards developing more expansive methods of synthesis (**Figure 1.10**). The developments of acyl fluorides are driven by the preferable properties. They are less prone to hydrolysis and solvolysis than acyl chlorides and achieve a good balance between stability and reactivity under nucleophilic conditions.[50, 57] The increased stability towards solvolysis is attributed to an increase in ground state stabilization energy.[57]

Recent examples of utilising acyl fluorides has included acyl Suzuki cross-couplings which are modified to an *in-situ* process later within **Section 4**.[58] The use of acyl fluorides in organometallic chemistry is becoming increasingly common, such as in a three component coupling reaction with palladium acetate used with an acyl fluoride.[59] Another report described a decarbonylative Suzuki-Miyaura coupling which proceeded using a nickel catalyst without the use of a base.[60] Furthermore, decarbonylative trifluoromethylation using a palladium catalyst, this is an interesting method to install the CF_3 substituent on aromatic ring systems.[61]

Acyl fluorides are useful tools for amide bond formation. They are more reactive to amines than the equiv. acyl chlorides and show better compatibility with protecting groups such as Fmoc or Cbz.[56] Sterically hindered and electron deficient amines that have traditionally resisted coupling by standard methods have been shown to be accessible by using an *in-situ* acyl fluoride.[62] Another example of accessing amides from the corresponding carboxylic acids through acyl fluorides is a one pot synthesis using the commercially available, but relatively expensive Deoxo-Fluor **43**.[63]

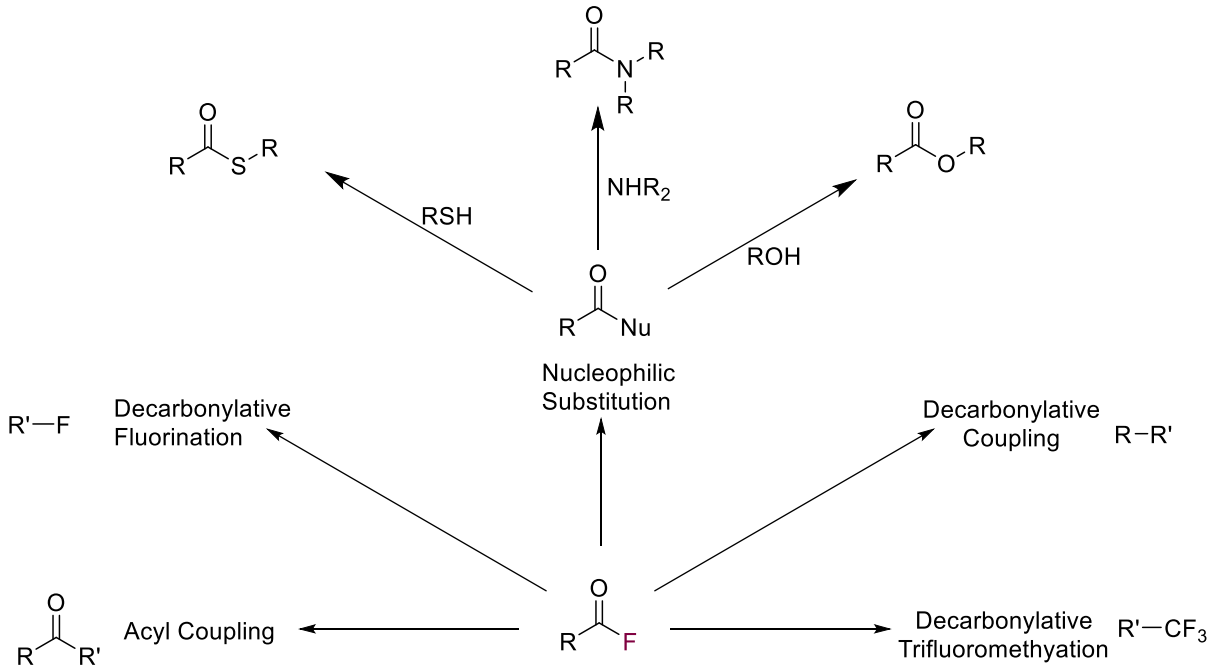


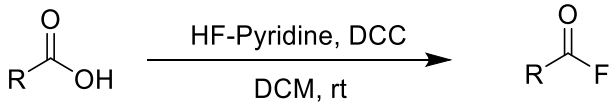
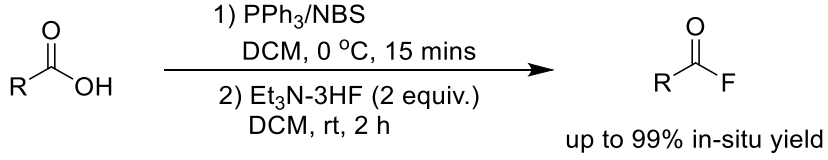
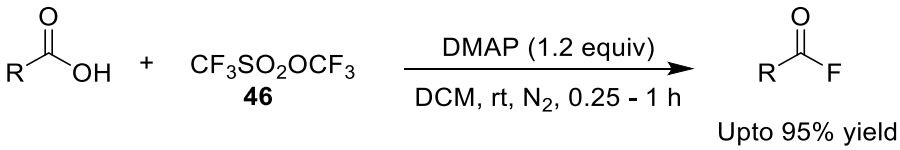
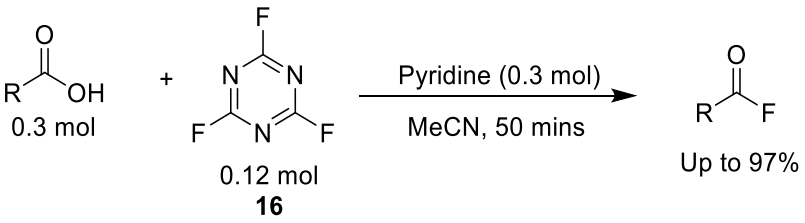
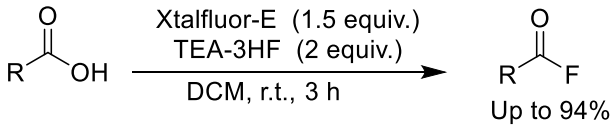
Figure 1.10: Summary of some common reactions that utilise acyl fluorides.

1.3.2 Common Approaches to Acyl Fluoride Synthesis from Carboxylic Acids

There are a range of reagents that can be used to access acyl fluorides directly from a carboxylic acid. One of the classic examples is cyanuric fluoride **16**, pioneered by the laboratory of Olah in 1971. This reagent shares similar structural properties to PFP (**15**) but it is extremely corrosive and harmful to handle.[39] Hydrogen fluoride-pyridine; **44**; another reagent pioneered by Olah is commonly referred to as Olah's reagent. This reagent is extremely toxic but will give acyl fluorides from carboxylic acids in good to excellent yields.[52]

HF:Pyridine **44** does require specialised handling facilities and is not amenable to procedures in glassware. Some established approaches to deoxyfluorination are discussed in **Table 1.1**.

Table 1.1: Some common approaches to acyl fluoride synthesis directly from carboxylic acids.

Entry	Generic Scheme	Comment	Ref
1		HF-Pyridine **44** is extremely toxic	52
2		Et_3N-3HF **45** is acutely toxic	64
3		$CF_3SO_2OCF_3$ **46** Stored frozen	65
4		Cyanuric fluoride **16** is extremely toxic.	39
5		Requires acutely toxic HF additive.	.66

Sulfur containing reagents are a popular class of deoxyfluorination reagents (**Figure 1.11**). These reagents included branded reagents such as DAST, Deoxo-fluor (**Table 1.1, Entry 5**) or other fluoroformamidinium salts.[67] These reagents have advantages over cyanuric fluoride **16** as this suffers from difficult reaction control and poor functional group tolerance.[68]

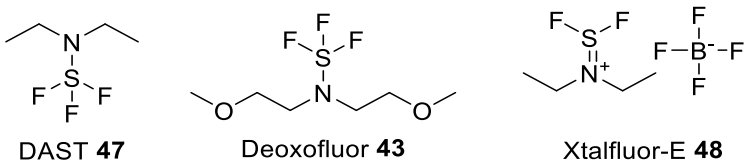
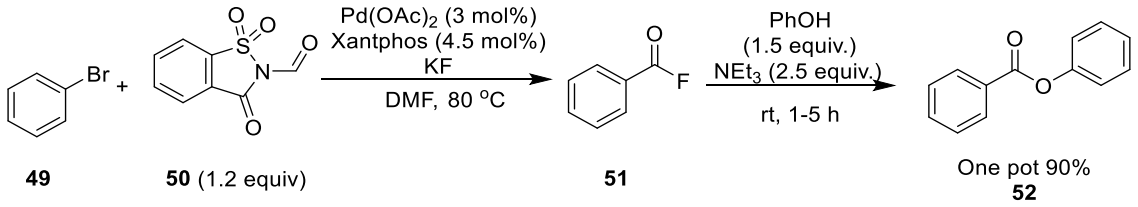


Figure 1.11: Examples of sulfur containing deoxyfluorination reagents.

Sulfur-containing deoxyfluorination reagents also have their associated drawbacks. For example, **47** and **43** release toxic, free, HF as a by-product which is extremely corrosive and etches glassware, there are also risks of fires due to thermal instability.[66] The safer replacements for these compounds, such as **48** are costly and this hinders their applicability to general synthetic approaches, such as esterifications. XtalFluor-E for example is more favourable than Deoxo-fluor due to increased thermal stability but this reagent costs over £2.75 per gram making it uneconomical for larger scale applications.[69] At the time of writing, this equates to 4.4 mmol for the cost of £2.75, by contrast PFP (**15**) is £0.82 (fluorochem) for 5.91 mmol.

A one pot esterification from aryl halides using palladium catalysts has been described which used *N*-formylsaccharin as the CO source and was able to offer in-situ acyl fluorides in excellent yields (**Scheme 1.12**).[54] This methodology was then used to facilitate *in-situ* production of esters (e.g. **52**) when alcohols were used. By using amines or thiols the synthesis of amides and thioesters respectively was also possible in excellent yields. In this report however limited examples were synthesised.

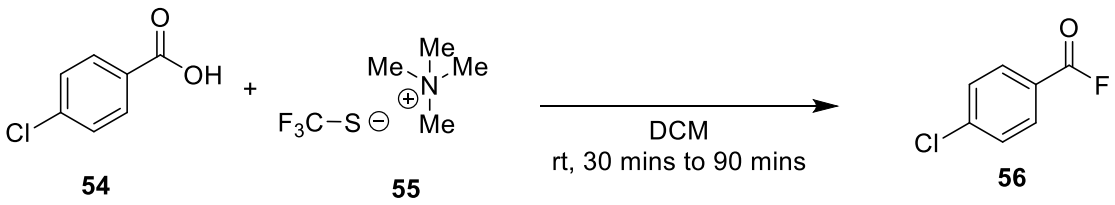


Scheme 1.12: Exemplar esterification using acyl fluorides to yield esters in a one pot method.[54]

Another very recent example of a reagent capable of generating acyl fluorides was the use of SOF_2 **53** which is discussed in **Chapter 2**. While the yields for acyl fluoride formation utilising **53** were generally excellent, this is a very toxic reagent to handle, carrying significant hazards. Furthermore, the handling is also complicated by the gaseous nature of this reagent and

therefore requires much more complicated experimental set-ups than the alternative liquid or solid reagents.[70]

Synthesis of acyl fluorides directly from carboxylic acids using bench stable, solid reagents has also been investigated. One method disclosed by Scattolin *et al.* is highly desirable as purification is easy and there are no organic by products to deal with, however, the reagent described is not available commercially and needs to be synthesised from an uneconomical starting reagent (Tetramethylammonium fluoride) (**Scheme 1.13**).[68]



Scheme 1.13: Solid acyl fluoride preparation reagent described by Scattolin *et al.*[68]

Although the synthesis of the solid reagent is straightforward with minimal purification required synthesising the fluorinating reagent beforehand is time consuming .[71]

1.4 Esters

As briefly mentioned in **Section 1.3,** acyl fluorides can be used to synthesise esters. The ester group is an organic functional group characterised by containing a carbonyl group and an ether linkage (**Figure 1.12**).

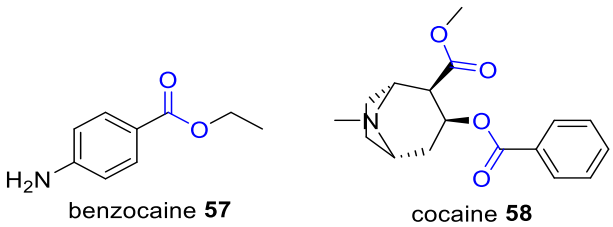


Figure 1.12: Naturally occuring esters with ester functionality highlighted in blue.

Esters are often formed from a carboxylic acid and an alcohol through a condensation reaction where the equiv. of a molecule of water is lost. Laboratory approaches to synthesising esters often suffer because they rely on harsh conditions and can also lack substrate selectivity.[72]

Fischer esterification's are some of the most well established conditions known and involve refluxing a carboxylic acid with an alcohol in the presence of an acid catalyst. While this approach is generally well tolerated for many substrates it is disadvantaged by the need to use large excesses of alcohol to drive the equilibrium. Issues are also present if functional groups are acid sensitive.

The fragrance industry is a big market for esters, both natural and synthetic. Esters are often very pleasantly smelling, giving aromas such as that of pear drops (**Figure 1.13**). There is estimated to be 6400 natural volatile fragrance/aroma esters and 10,000 synthetic fragrances. Esters also make useful bio lubricants as they are more environmentally friendly than those derived from crude oil.[74]

Butyl butyrate **59**
pineapple

Methyl salicylate **60**
wintergreen

methyl cinnamate **61**
strawberry

ethyl cinnamate **62**
cinnamon

Figure 1.13: Examples of esters commonly used in the fragrance industry.

Some illustrated examples of where esters are found in day-to-day life are plastics and polymers such as polyethylene terephthalate (PET) **63** which feature repeating ester linkages (**Figure 1.14**). Ester linkages have medical applications, the topical local anaesthetic benzocaine is an ester that features in many over the counter products. Prodrugs such as aspirin (pain relief), enalapril (high blood pressure treatment) and fluorescein diacetate (cell staining) all contain ester bonds.[75] In nature, cocaine is a biosynthetic molecule that contains two ester linkages. Esters feature in many organic molecules and accessing them in new ways is of significant scientific interest.

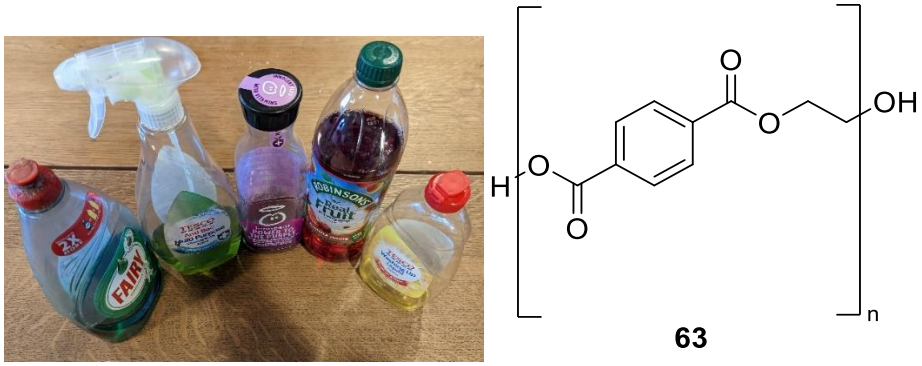
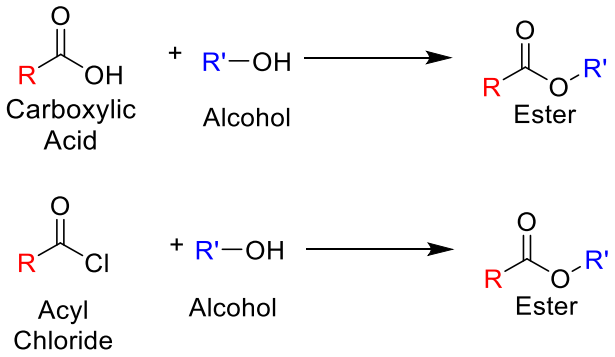


Figure 1.14: Collection of PET bottles (left) and the structure of PET **63** (right)

To avoid the use of water as a solvent, and to greatly increase reactivity, acyl chlorides are widely employed as carboxylic substitutes in organic synthesis. The chloride ion acts as a much better leaving group than the comparable hydroxide ion (**Scheme 1.14**). Acyl chlorides are activated carboxylic acids and are readily produced from a carboxylic acid and chlorination reagent such as thionyl chloride, oxalyl chloride, phosphorus trichloride, phosphorous oxychloride or phosphorus pentachloride.[56] Alternatively acid anhydrides also act as activated versions of carboxylic acids, these however are often synthesised from acyl chlorides.

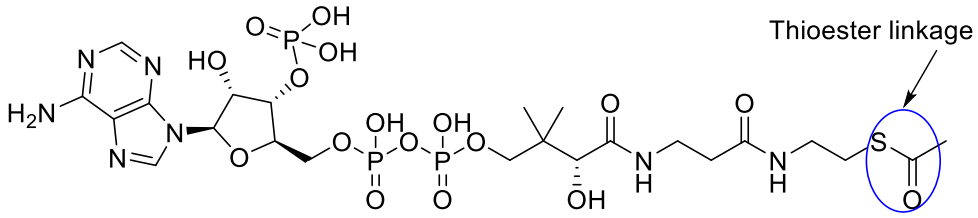


Scheme 1.14: General processes for ester synthesis.

Discussed earlier were some approaches for the production of acyl fluorides. The work discussed later in this thesis (**Chapter 2**) will use an *in-situ* approach for the preparation of a range of esters and thioesters directly from carboxylic acids.

1.5 Thioesters

Thioesters are very similar to esters but contain a sufhur atom rather than oxygen (**Figure 1.15**). While esters are stabilised by resonance, thioesters do not benefit from this effect. Unlike the 2p/2p orbital overlap present in an ester, the 2p/3p overlap in thioesters is very poor which reduces stabilisation, therefore thioesters are more susceptible to nucleophilic attack.[76] Thioesters are of interest because they play important roles in biology such as leaving groups in the sense of coenzyme A (CoA) **64**, this uses the earlier mentioned property of being more susceptible to nucleophilic attack.



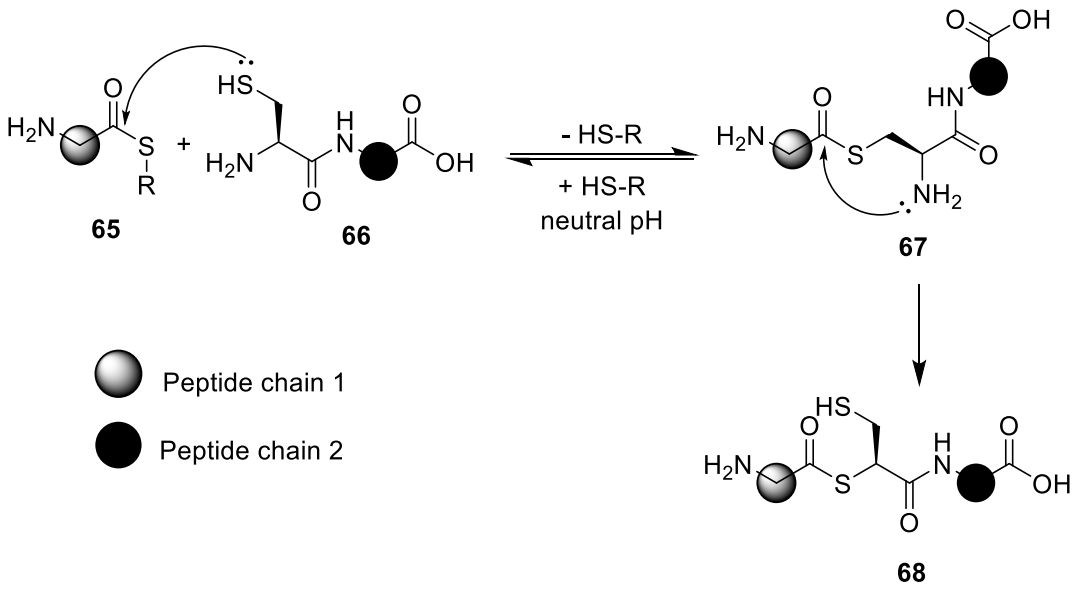
acetyl coenzyme A
64

Figure 1.15: The thioester group, a target functional group highlighted in acetyl coenzyme-A.

Thioesters have otherwise shown to be useful substrates for cross-couplings and peptide synthesis.[77-79] Thioesters are a natural way of activating carboxylic acids and can allow for the formation of C-C bonds, amides or esters.[80] The reactivity of thioesters can be compared to that of acyl chlorides or acid anhydrides, and they remain stable for long periods of time.[81] An excellent review by Fleischer and co-workers summarises some of the many applications for thioesters such as cross-coupling reactions, decarbonylative processes and photo-redox catalysis to name a few.[82] Thioesters are also useful reagents for the functionalisation of polymers due to the ease at which they are added to polymer chains and the specificity to which they can be added.[76]

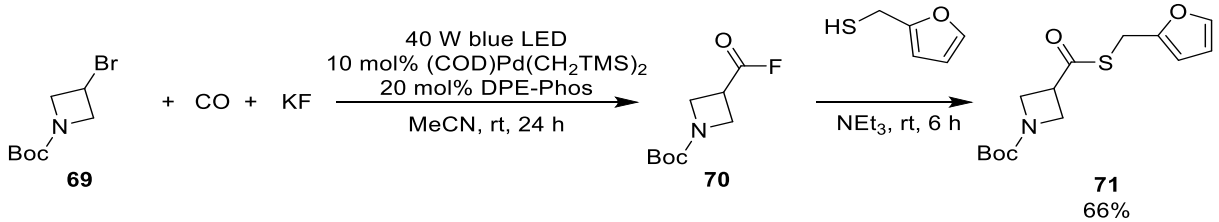
Thioesters are very important in native chemical ligation (NCL) which is a capture/rearrangement process. By using this methodology native proteins are readily synthesised. In the process a reversible thioester/thiol exchange occurs producing a thioester, after this an irreversible nucleophilic substitution occurs giving a single product linked by a peptide bond.[83] The process is used to modify proteins, total protein synthesis or for

conjugation. The benefits of NCL are discussed in depth in a 2008 review by Hackenberger and Schwarzer which also provides an easy-to-follow mechanism (**Scheme 1.15**).[84]



Scheme 1.15 Native chemical ligation mechanism adapted from Hackenberger *et al*.[84]

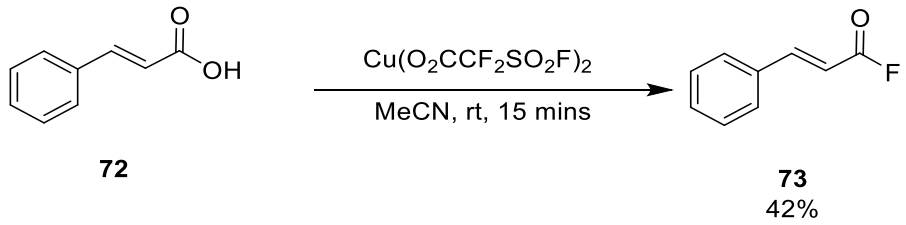
While the synthesis of thioesters from acyl chlorides and acid anhydrides is well demonstrated, literature on the synthesis of thioesters from acyl fluorides is much more sparse.[53, 85] One recently reported approach used visible light and palladium catalysis to prepare acyl fluorides in very good yields, three thioesters were exemplified, offering thioesters in moderate to good yields (**Scheme 1.16**).[55] This method does however require the use of Schlenk lines and the toxic and flammable reagent carbon monoxide.



Scheme 1.16 Preparation of an acyl fluoride and subsequent nucleophilic substitution described by Arndtsen and co-workers.[55]

Another recent approach to synthesising esters and thioesters from acyl fluorides prepared from carboxylic acids was a copper based reagent although this offered somewhat low

conversions of acyl fluorides and required preparation of the fluorinating reagent (**Scheme 1.17**).[53]



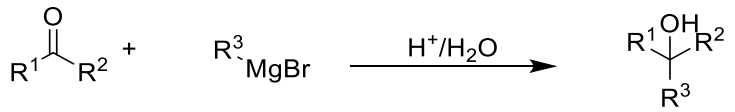
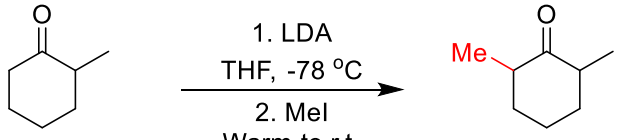
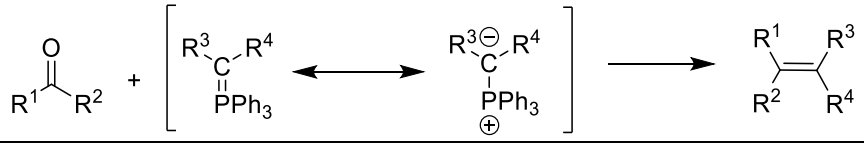
72 **73** 42%

Scheme 1.17: Acyl fluorides prepared from carboxylic acid deoxyfluorination by Le *et al*.[53]

1.6 Carbon-Carbon Cross-coupling Reactions

Historically, the formation of carbon-carbon bonds has presented a synthetic challenge. Some common approaches to this challenge are the backbone of undergraduate chemistry courses. Problems occur regarding the type of reagents used or the requirement for specific functional groups, such as carbonyls. Some example reactions are included in **Table 1.2**. They all produce a new carbon-carbon bond but are reliant on carbonyls or the associated enols.

Table 1.2: Text-book approaches to carbon-carbon bond formation

Entry	Approach to C-C bond Formation	C-C bond formation scheme
1	Grignard Reaction	
2	Lithium Alkylation	 **74** **75**
3	Wittig Reaction	

Pioneered in the 1970's organometallic cross-couplings have come a long way to remove these limitations and are now a core reaction of organic chemistry in the laboratory and on an industrial scale. Cross-couplings represent one of the simplest, efficient, and most elegant ways of accessing new carbon-carbon bonds. Cross-couplings can be successful at room temperature and typically use safe coupling partners. These reactions require a metal catalyst and two reaction partners. Often cross-couplings are mediated by palladium and some common cross-coupling reactions are shown in **Table 1.3**.

Table 1.3: Common cross-coupling reactions using palladium catalysts.

Entry	Cross-Coupling	Generic Scheme
1	Sonogashira Coupling	R_1—X (aryl/vinyl halide) + H—≡—R_2 (alkyne) → Pd (cat.), Cu (cat.), Base, r.t. → R_1—≡—R_2
2	Heck Coupling	R_1—X (X = halide OTf) + R_2 (Alkene) → Pd (cat.), Base → R_2 R_1
3	Stille Coupling	R^1-Sn(alkyl)$_3$ + R^2-X → Pd (cat.), ligand → R^1-R^2 + X-Sn(alkyl)$_3$
4	Suzuki Coupling	R^1-X + R^2-BY_2 → Pd (cat.), Base → R^1-R^2

The Suzuki coupling, also commonly referred to as the Suzuki-Miyaura coupling is one of particular interest.[86] This reaction couples boronic acids/esters with halides. These boronic acids are usually non-toxic, bench stable solids which are beneficial over the comparable Stille coupling (**Table 1.3, Entry 3**) as organotin compounds are toxic and require careful handling.[87]

A sub-category of the Suzuki coupling reaction allows the cross-coupling of acyl halides with boronic acids to form a new carbon-carbon bond featuring a ketone functional group.[86] The catalytic cycle follows the cycle of oxidative addition, transmetallation and finally a reductive elimination.

With these processes being catalytic, they have huge application in industry, especially in the manufacture of pharmaceuticals where they can greatly reduce the costs of making complex

molecules. Some of key advantages listed are the high functional group tolerance, stability and commercial availability of boronic acids and the ease of separating reaction mixtures.[88]

As mentioned previously, acyl fluorides have been able to give excellent yields in cross-coupling reactions.[50, 58] Sakai and co-workers have continued their research into this reaction and have been able to determine the exact catalytic cycles being followed by these cross-coupling reactions.[89] Further applications of these methodologies are discussed in **Chapter 4**.

1.7 Project Aims

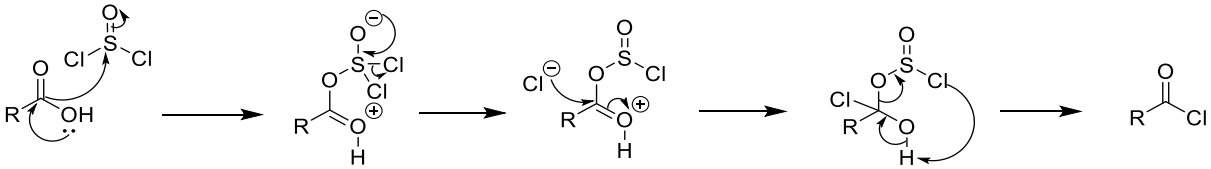
Acyl fluorides are a valuable class of synthetic compounds. They have applications in nucleophilic addition elimination reactions, allowing for the preparations of amides, esters, and thioesters. Previously Brittain and Cobb,[1] have shown that these acyl fluorides are readily accessed from the perfluoroaromatic compound pentafluoropyridine (PFP, **15**). This project will continue research into the preparation of acyl fluorides by deoxyfluorination of carboxylic acids. Firstly, the methodology will be used to prepare a range of esters using both aromatic and aliphatic acids and alcohols. The reaction partners are to focus on demonstrating different capabilities of the reaction such as the use of electron withdrawn acids and alcohols. Long chain aliphatic compounds will also be explored. Alongside esters the methodology will also be explored to possibly allow an *in-situ* one pot method for the preparation of thioesters.

A suspected intermediate of acyl fluoride generation using pentafluoropyridine was a tetrafluoropyridin-4-yl ester. This moiety should be extremely susceptible to nucleophilic substitution at the carbonyl centre, much like pentafluorophenyl counterparts. The second aim of this project is therefore to investigate the difference in reactivity towards nucleophilic substitution between pentafluorophenyl benzoates and tetrafluoropyridin-4-yl benzoates. This aim also lends itself to exploring the synthesis of tetrafluoropyridin-4-yl esters, as so few of them have been described in literature.

Finally, examples of non-nucleophilic substitution reactions on acyl fluorides will be examined. Recent work in the use of acyl fluorides by Sakai and co-workers for use in Suzuki-Miyaura couplings was deemed appropriate to replicate but using an *in-situ* acyl fluoride generation approach.[58]

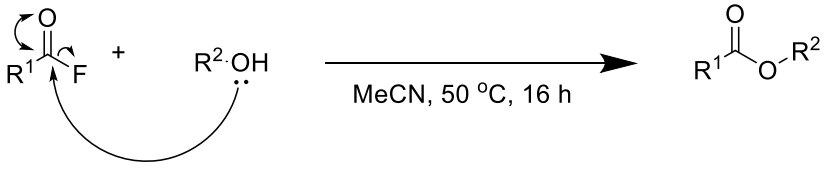
2 Chapter 2: One-pot Esterification and Thioesterification

There are a myriad of esters utilised across a variety of applications, for example, they are widely employed in pharmaceuticals, fragrances, and lubricants as was discussed in **Chapter one**. The synthesis of esters from carboxylic acids can be difficult and in some cases requires activation of the carboxylic acid component. Common approaches towards activation are to use acyl chlorides or acid anhydrides with acyl chlorides being the most common approach. Acyl chloride generation often requires reagents such as $SOCl_2$ (**Scheme 2.1**), PCl_3 or PCl_5 which that can be detrimental to other acid sensitive functional groups within a molecule.[56]



Scheme 2.1: Typical mechanism for preparation of acyl chlorides from carboxylic acids using thionyl chloride.

Being able to perform esterifications under mild conditions would circumvent current limitations of these types of reaction, such as functional group tolerance, and may allow for a greater range of compatible substrates. Acyl fluorides can undergo similar nucleophilic addition elimination reactions with alcohols to displace a fluoride leaving group and allow for esterification, amidation and thioesterification (**Scheme 1.9 and 2.2**). Acyl fluorides offer advantages over their acyl chloride counterparts such as increased hydrolytic stability and increased compatibility with protecting groups such as Fmoc, CBz and acid labile ester groups.[56]

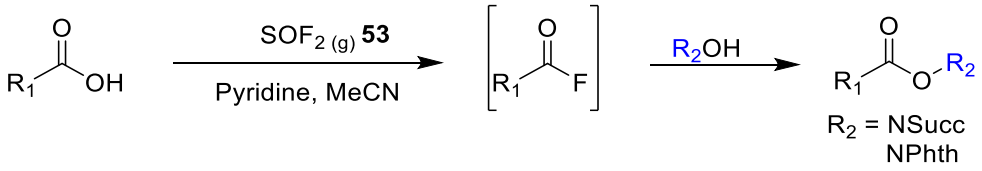


Scheme 2.2: General scheme of esterification from acyl fluorides.

As previously discussed, **Table 1.1** highlighted some of the common, longstanding approaches to the synthesis of acyl fluorides. Additional developments in the field are discussed here. Fundamentally the synthesis of these valuable acyl fluoride substrates remains challenging due to the associated hazards with the fluorination reagents. In the recent

method disclosed by Qin *et al.* over 110 examples were reported with yields which were between 41-99% (**Scheme 2.3**).[90] Although the study by Qin *et al.* reported a highly efficient amidation, SO_2F_2 (**76**) is a corrosive gaseous reagent that also acts as a fumigant. This makes handling difficult and requires extra special controls which are often time consuming to deal with. Furthermore, this methodology is not environmentally friendly with sulfuryl fluoride acting as a potent greenhouse gas.

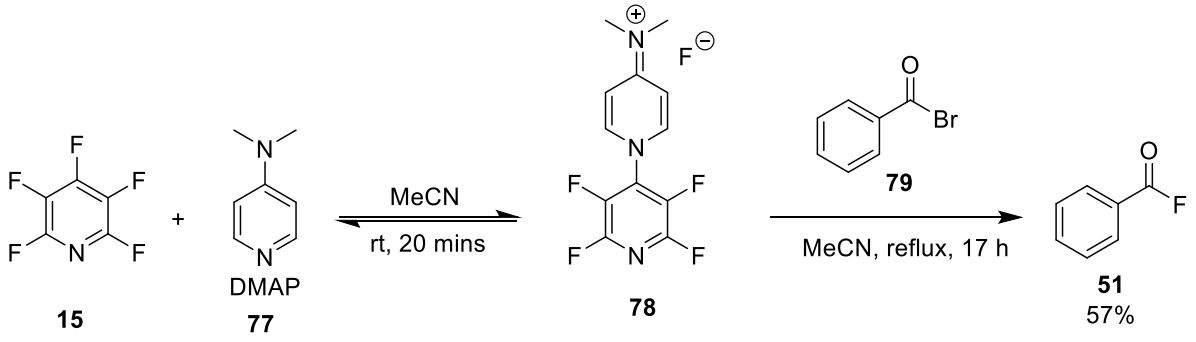
Scheme 2.3: Amidation reaction of carboxylic acids reported by Qin and co-workers.[90]



Scheme 2.4: Esterification using acyl fluorides reported by Sammis and co-workers.[91]

Sammis and co-workers reported using an acyl fluoride in an *in-situ* method (**Scheme 2.4**) to generate amides, esters and thioesters.[91] The scope of the reported esterification was somewhat limited in terms of variation of the oxygen nucleophiles but excellent yields of between 64% and 99% were reported for 24 different examples. Despite these high yields, the methodology still required the handling of the gaseous, highly poisonous reagent thionyl fluoride which is less than ideal from an ease-of-use standpoint.

An, acyl fluorides (**51**) has previously been accessed from an acyl bromide (**79**) by using PFP **15** as an fluoride source in combination with DMAP **77**.[92] Although **15** is used as the fluorine source in this work, to access these compounds, they were not accessed directly from the carboxylic acids, which are often cheaper, safer and more commercially available. (**Scheme 2.5**) In addition, the yield was only a satisfactory 57%, and a 17-hour reflux was required. Furthermore, no acyl nucleophilic substitution reactions were reported thus making it difficult to judge if these reaction conditions would be conducive to esterification.



Scheme 2.5: Preparation of acyl fluorides from an acyl bromide using a fluoride ion released from PFP.[92]

Recently, Brittain and Cobb have shown that using PFP **15** as a fluorine source allows for the *in-situ* generation of acyl fluorides directly from the parent carboxylic acid at room temperature in a deoxyfluorination process. The mechanistic details for this reaction are discussed in detail later within this **Chapter 2** (**Section 2.3**). Use of PFP is seen as advantageous over the recently described approaches such as those of Qin (**Scheme 2.3**) or Sammis (**Scheme 2.4**) as it overcomes many of the dangers usually associated with the access of acyl fluorides directly from carboxylic acids.[90, 91, 93] The approach using PFP forgoes the need to use gaseous reagents which require enhanced safety considerations.

As part of the report by Brittain and Cobb they probed the ability for PFP to generate acyl fluorides which could be isolated, and it was found that a range of substrates were compatible (**Figure 2.1**). Also, within the study the ability to use PFP for an *in-situ* reaction with amines or alcohols to prepare the corresponding amide or esters in moderate to excellent yields was also developed. There were only a limited number of esters reported by Brittain *et al.* (4 in total – see **Figure 2.2**) with an open desire to continue the ester scope expressed. To that end the focus of the research presented here involves the expansion of this previous work to further explore scope of esterification and to expand to other nucleophiles (e.g. thiols).

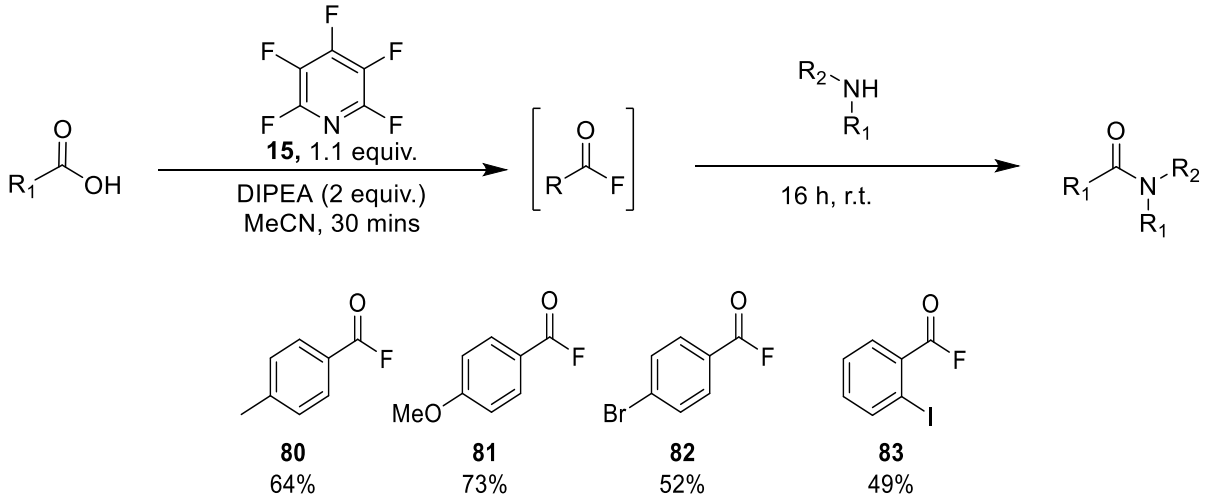


Figure 2.1: Representative examples of acyl fluorides isolated from PFP deoxyfluorination methodology by Brittain and Cobb.[1]

2.1 Esterification Reactions Using Literature Conditions

Brittain *et al*. reported the synthesis of four esters in the initial explorations of deoxyfluorination reactions with PFP.[1] This was the basis of the beginning of the work described here as it allowed repetition of known reactions to gain practice of the required experimental techniques that this chapter would be built around. Therefore, to start with the esterification reactions previously reported were repeated with no modification. A solution of carboxylic acid in MeCN was stirred with PFP and DIPEA at room temperature for 30 mins followed by the addition of an alcohol (**Figure 2.2**).

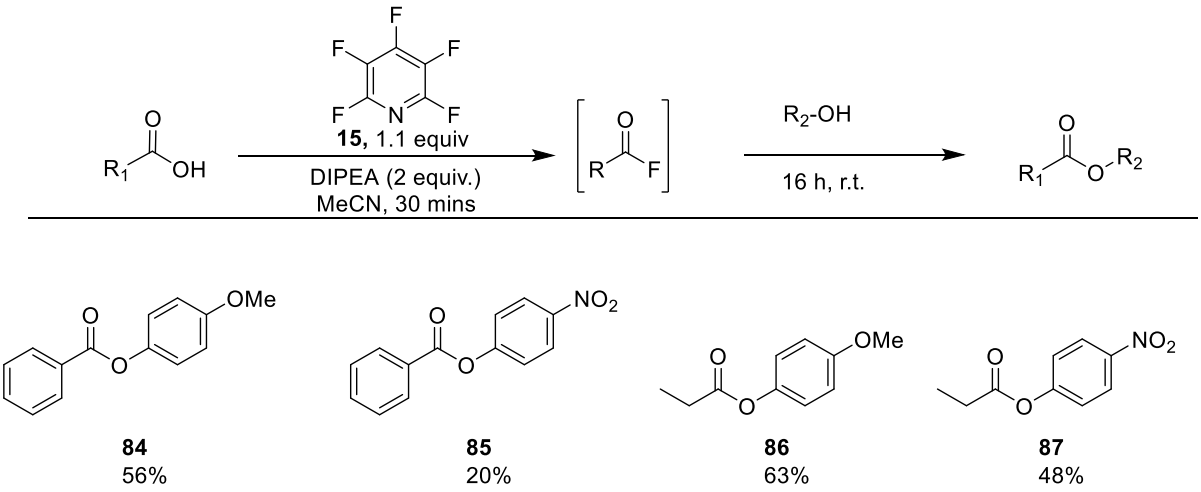


Figure 2.2: Compounds initially synthesised using the literature conditions of Brittain *et al*.[1]

Yields for the esterification's utilising benzoic acid, **84** and **83** were consistent with those reported previously.[1] The yields of the propionic acids **86** and **87** were significantly higher than those previously reported. Brittain reported a yield of 23% for compound **86** and 24% for **87**.[1] By changing to bromobenzoic acid there was a significant drop off in yield (22%, **88**) in comparison to the electron neutral benzoic acid **84** which gave a yield of 56%(**Figure 2.3**). The observed effect is attributed to the electronic effects of the 4-bromobenzoic acid (**89**) which withdraws electron density from the aromatic ring. In turn this has withdrawn electron density away from the carbonyl group, reducing the ability to act as a nucleophile in the production of the acyl fluoride. No product was observed when 6-bromo-2-picolinc acid was used for esterification (**90**) which is attributed to the electron withdrawn nature of the aryl unit.

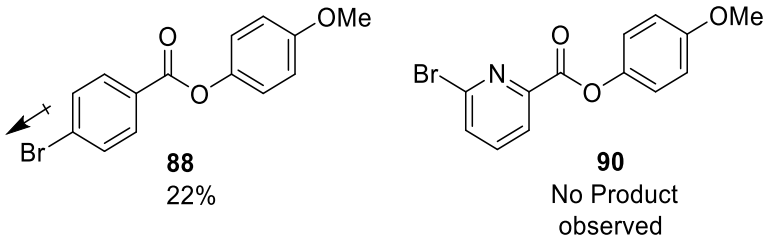
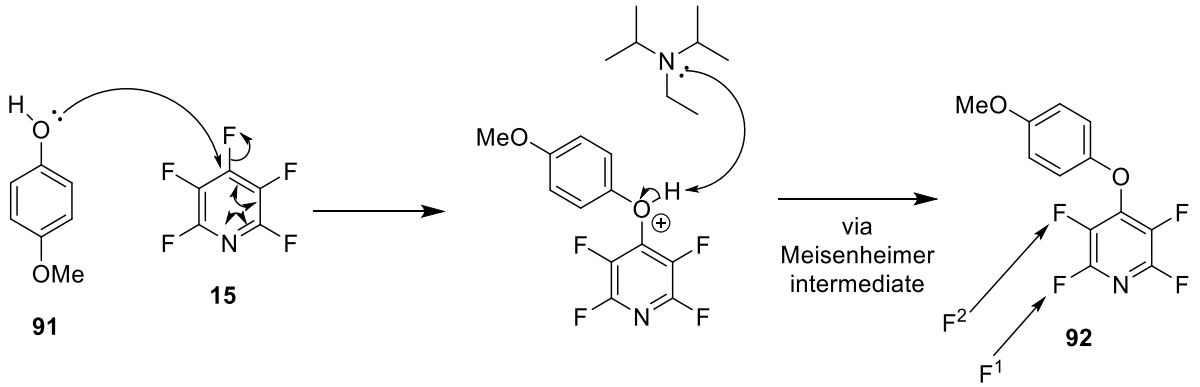


Figure 2.3: Early trials at preparing esters using un-refined acyl fluroide preparation conditions.

Electron withdrawing groups are known to be better at stabilising benzoate anions.[94] Stabilisation of charge decreases nucleophilicity as the electron density is more spread out. Electron donating groups on the other hand put more electron density into the system,

increasing the nucleophilicity and increasing the rate of reaction with pentafluoropyridine (PFP, **15**).

During purification, it was noted that aromatic acid examples (**84, 85, 88 and 90**) led to a fluorine containing by-product in the fractions that had eluted just before the product during column chromatography. It is believed that this fluorine contaminant is a tetrafluoropyridyl ether (**92**), which arises due to the aromatic alcohol reacting with left over PFP **15** in an S_NAr process (**Scheme 2.6**), The formation of the tetrafluoropyridyl ethers were confirmed by comparison of the ^{19}F NMR spectroscopy shifts previously published by Brittain *et al.* during the work surrounding tetrafluoropyridyl ethers as protecting groups (**Table 2.1**).[47]



Scheme 2.6: A likely possible mechanism for tetrafluoropyridyl ether (**78**) formation through S_NAr reaction on PFP.

Table 2.1: Identification of observed fluorinated product compared to literature.

Fluorine atom	Reference Value δ[47]	Observed δ
92 F^1	-88.92 to -89.19 (m)	-89.15 to -89.31 (m)
92 F^2	-154.98 to -155.19 (m)	-155.00 to -155.18 (m)

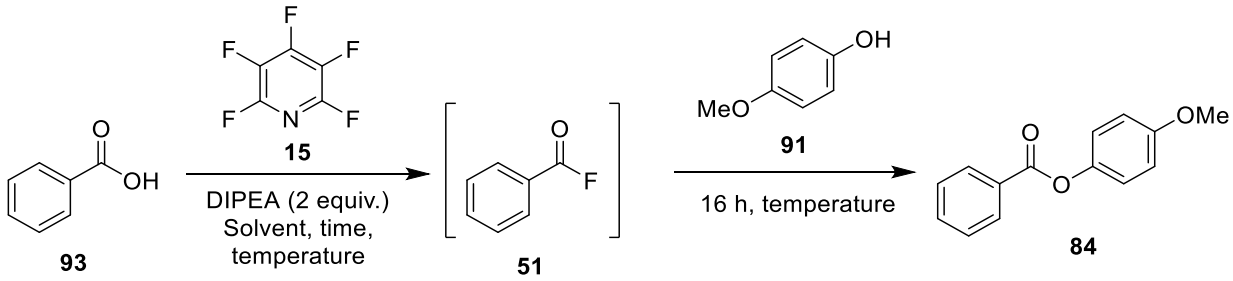
The formation of the ether **92** is detrimental to the reaction in two ways. Firstly, it is both capable of consuming the PFP (**15**) which in turn decreased acyl fluoride **51** conversion and subsequently ester output. It is also plausible that the decrease in concentration of **91** could decrease ester output as the alcohol is being sequestered into the ether.

2.2 Optimisation of Esterification Conditions

Given the identification of an ether by-product, it indicated that there was still an amount of PFP remaining after the 30-minute acyl fluoride activation period. By increasing the equiv. of the aromatic alcohol (**91**) it was hypothesised there would be a resulting drop in yield because

of the increased equiv. of alcohol outcompeting the benzoic acid for PFP. With this in mind, screening of the isolated yields when increasing the equiv.of the aromatic alcohol, in this case **91** was carried out to test the hypothesis that increased concentrations of aromatic alcohols would compete with **93** for PFP (**15**).

Table 2.2: Optimisations of esterification reactions using 4-methoxyphenol (**91**).

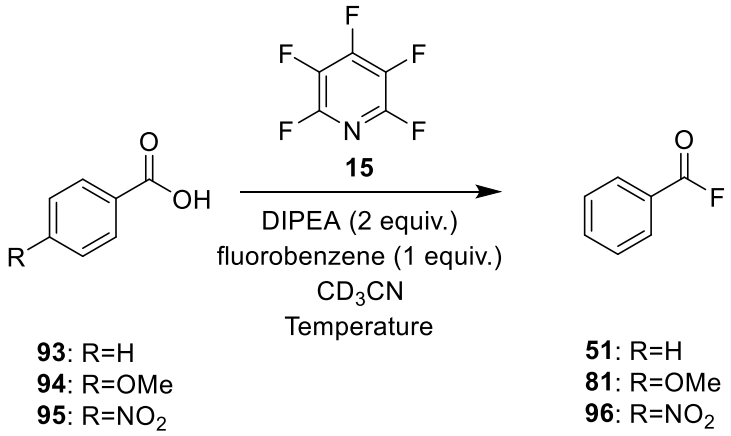


Entry[a]	Temp	Time (h)	4-methoxyphenol (equiv.)	DIPEA (equiv.)	PFP (equiv.)	Solvent	Yield (%)
1	rt	0.5	1	2.0	1.1	MeCN	56
2	rt	0.5	1.5	2.0	1.1	MeCN	36
3	rt	0.5	3.75	2.0	1.1	MeCN	27
4	50 °C	4	1	2.0	1.1	MeCN	71
5	50 °C	4	-	1.0	1.1	Toluene	-[b]

[a] standard condition. [b] No conversion to acyl fluoride observed by ^{19}F NMR spectroscopic monitoring.

When 1 equiv. of **91** was used a respectable 56% yield of ester (**84**) was observed (**Table 2.2, Entry 1**). By further increasing the equiv. of **91** to 1.5 and 3.75 equiv. the isolated yield of the product decreased to 36% and 27% respectively (**Table 2.2, Entry 2 & 3**). Upon taking these observations into consideration it was suspected that even after the 30 minute activation period it was likely the case that acyl fluoride generation was not occurring fast enough leading to unreacted PFP being present. This was therefore hypothesised to be the main reason that the ester yield was not higher. This conclusion had similarly been described by Brittain *et al.* during their studied on amidation when they noted increased activation times could have a positive effect on amide yield.[1]

Informed by these observations and those previously reported a four-hour activation window at elevated temperature was attempted which afforded a 15% increase of the isolated yield of **84** on the previous best examples (**Table 2.2, Entry 4**). Finally, some variation to the reaction solvent was performed using toluene rather than acetonitrile but it was confirmed it was an incompatible solvent for the formation of acyl fluorides (**Table 2.2, Entry 5**). Further solvent effects were not investigated as this work had previously been performed by Brittain *et al.*[1] With regard to the 15% increase in yield **Table 2.2, Entry 4** it was decided that the rate of acyl fluoride formation would be investigated by ^{19}F NMR spectroscopy to try and gain a further insight into the reaction rate. A custom ^{19}F NMR spectroscopy experiment was set up for this data collection as the stock programmes available all used a sweep width optimization. Small acyl fluoride peaks observed in some of the earliest readings were being consistently ignored by the software automation. Without this custom programme it was found to be extremely challenging to acquire the data required for reaction monitoring over the entire timeframe that would give the most information on acyl fluoride formation rate.



Scheme 2.7: Substrate scope for the acyl fluoride optimisation reactions.

To test rates of acyl fluoride formation, three distinctly different aromatic carboxylic acids were chosen (**Scheme 2.7**). Substituents on aromatic rings are well known to influence electron density. It was hypothesised that the methoxy group, with its electron donating properties would increase the ability of the carboxylate to act as a nucleophile upon addition of PFP (**Figure 2.5**). This should in turn increase the rate of acyl fluoride formation. Benzoic acid, in this case is relatively electron neutral, and holds a middle in the series. The nitro group is electron withdrawing, somewhat decreasing the nucleophilic ability of the carboxylate group and thus it was speculated that a slower rate of acyl fluoride generation would be observed.

Fluorobenzene (**97**) was used as the ^{19}F NMR spectroscopic internal standard as it offers a characteristic peak and would not interfere with the reaction. Experimentation was performed by adding the carboxylic acid, DIPEA, fluorobenzene and CD_3CN to an NMR tube. Afterwards PFP (**15**) was added, and the timing started. For room temperature experiments the NMR tubes were left in the sample holder, for elevated temperature they were taken from a thermostated water bath for analysis and then returned to the water bath afterwards. The measurements were made by comparing the integrals of acyl fluoride with fluorobenzene. Due to the relaxation times associated with ^{19}F NMR spectroscopy the integrals did go higher than the expected 1:1 ratio.

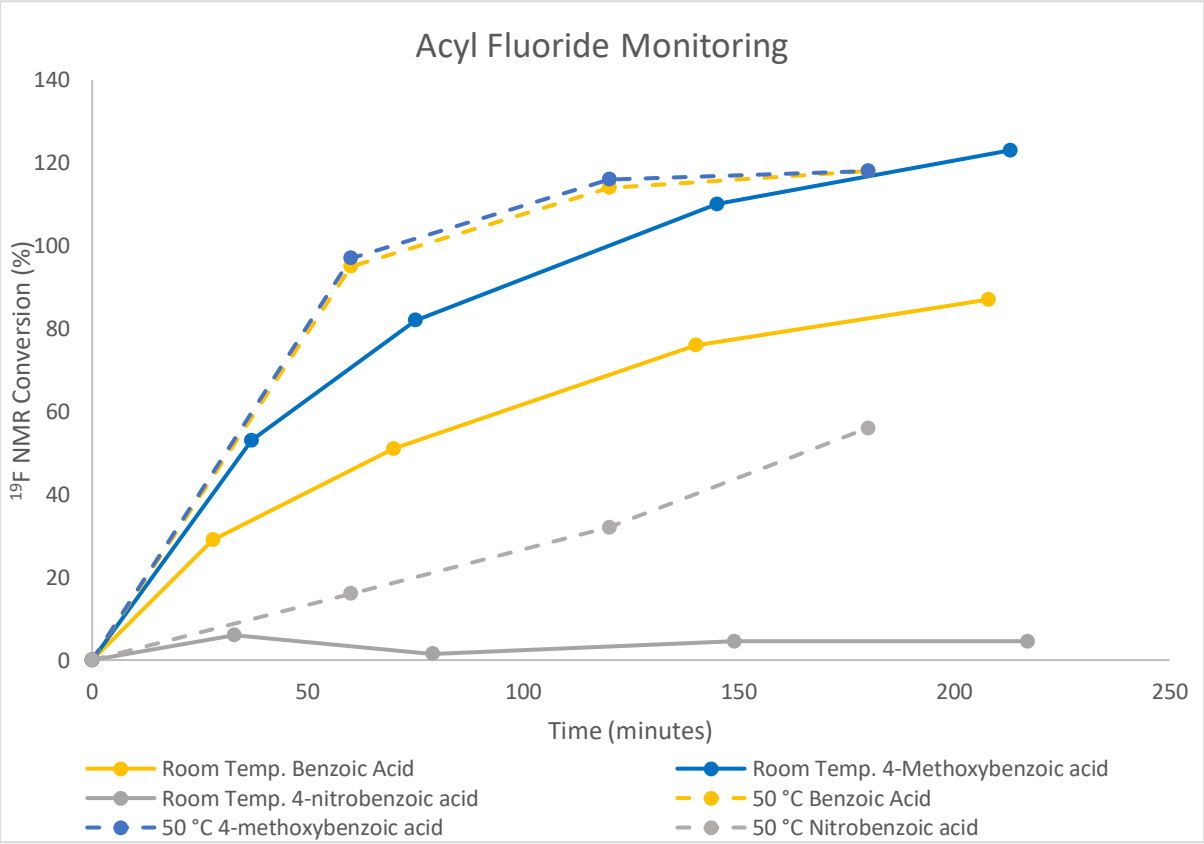
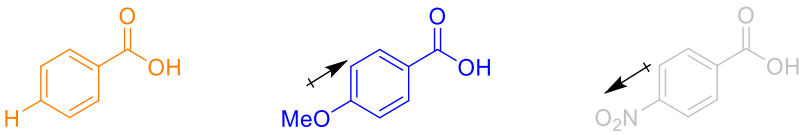


Figure 2.4: Conversion to acyl fluoride vs internal standard of varied benzoic acids. Colour coded molecule representation below in **Figure 2.5**. Please note T_1 was not optimised so the data cannot be quantified. The graph is intended to give an indication of the relative values between each of the points between the two temperatures used.

As seen in **Figure 2.4** (solid lines), when the reaction was left at room temperature, the rate of acyl fluoride formation was relatively slower for benzoic acid (**93**) and nitrobenzoic acid (**95**)

compared to the much quicker rate of 4-methoxybenzoic acid (**94**). The observed trend followed the expectations due to the earlier described electronic effects.



93 **94** **95**

Figure 2.5: Representations of the aromatic substituent electronic effects within the different aromatic acids.

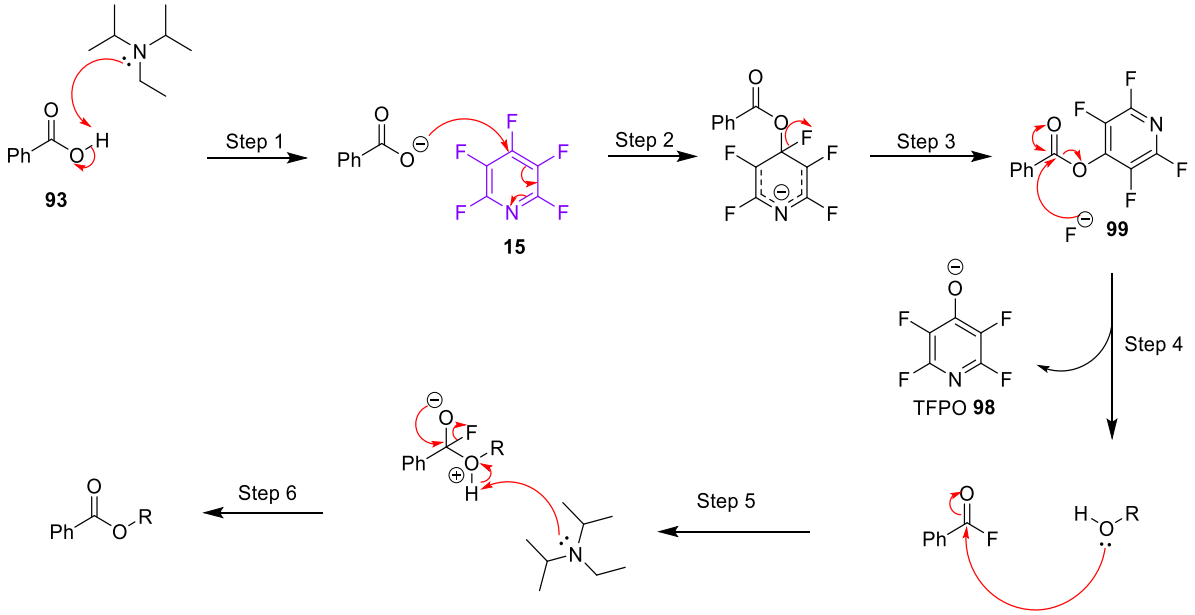
The room temperature reaction monitoring concluded that while electron rich acids (**94**) are suitable substrates for good conversion to acyl fluorides at room temperature, electron neutral (**93**) and electron deficient (**95**) examples may require a longer activation time or increased temperature to achieve full conversion.

Informed by these observations at room temperature further ^{19}F NMR spectroscopic reaction monitoring was undertaken at 50 °C. By increasing the reaction temperature, it was hoped the reaction kinetics would be improved allowing for better conversion over the same period of time. Formation of benzoyl fluoride (**51**) was now nearly in line with the rate of formation of 4-methoxybenzoyl fluoride (**81**) (**Figure 2.4,** blue and yellow hashed lines). Within 3 hours it was apparent both had gone to full conversion. The rate of formation of the 4-nitrobenzoyl fluoride (**96,** grey hashed lines) was also greatly increased when compared to the room temperature monitoring.

With these results considered, a general four-hour activation window was chosen at 50 °C. These conditions which allowed for full conversion of electron rich and neutral examples (**51 and 81**) would also allow for better conversion of electron deficient examples (**96**) while remaining practical for the laboratory-based chemist. Further increasing the temperature was not explored given the increase in conversion observed at 50 °C and factoring in the boiling points of the reagents employed. The slower formation of **96** and the desire to apply a general method led to the decision to continue the use of 1.1 equiv. of PFP as it was hoped increasing the concentration would allow for greater conversion of acyl fluoride, with minimum by product formation.

2.3 Mechanistic description of PFP mediated Esterification

The mechanism for a similar nucleophilic addition elimination process with amines to form amides was proposed by Brittain *et al.* in 2021.[1] Before detailing the scope of the reaction it seemed logical to first attempted to understand the mechanistic process and role of each reagent. Given the prior work on amidation an initial mechanism for esterification was proposed (**Scheme 2.8**).

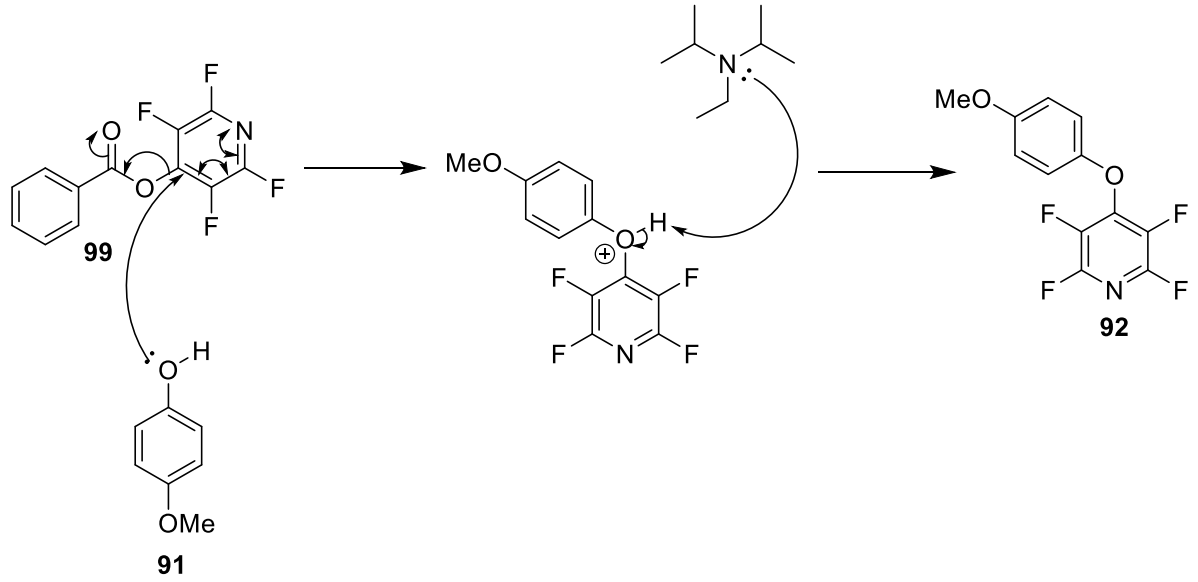


Scheme 2.8: Proposed mechanism for deoxyfluorination of benzoic acid and subsequent addition-elimination reaction with alcohols.

With reference to **Scheme 2.8**, a base, in this case diisopropylethylamine (DIPEA) is used to deprotonate the carboxylic acid, represented by benzoic acid here (**step 1**). The carboxylate acts as a nucleophile which attacks the 4-position of the PFP, forming the Meisenheimer intermediate which was discussed in **Chapter 1** (**step 2**). PFP is well established to preferentially react with the nucleophiles through the 4-position, as was discussed extensively in **Chapter 1**.

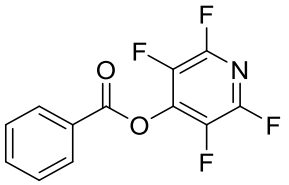
In **step 3** the reintroduction of aromaticity kicks out a fluoride ion which goes into the acetonitrile solution. The resulting tetrafluoropyridyl ester is very susceptible to attack by nucleophiles and acts as a good leaving group this is further discussed in **Chapter 3** (**step 4**). The fluoride ion attacks the carbonyl carbon of the tetrafluoropyridin-4-yl ester, to form the acyl

fluoride in a nucleophilic addition-elimination process (**step 4**). It should be noted that there has been suspected ^{19}F NMR spectroscopic evidence for the tetrafluoropyridyl ester as a reaction intermediate. As discussed in earlier (**Scheme 2.6**) it was hypothesised that S_NAr attack of *p*-methoxyphenol (**91**) onto the slight excess of PFP (**15**) led to the tetrafluoropyridyl ether **92** which was believed to be lowering the yield. An alternative explanation for this may be attack of **91** on to **99**, the carboxylic acid is then the leaving group and ether **92** is formed. Longer activation times would also circumvent this as the fluoride ion would have no competition, as soon as the alcohol is added this gives a competing nucleophile which decreases the yield of acyl fluoride as the PFP **15** is consumed (**Scheme 2.9**).



Scheme 2.9: An alternative mechanism to **Scheme 2.6** that explains to formation of a tetrafluoropyridyl ether

Upon introduction of an alcohol to the mixture, nucleophilic attack occurs at the carbonyl centre of the acyl fluoride. This kicks out the fluoride ion which yields the desired product after deprotonation (**step 5 & 6**).



perfluoropyridin-4-yl benzoate
99

Figure 2.6: Suspected reaction intermediate **99** which has been isolated in the past and later in this thesis.[95]

While acyl fluorides are certainly the predominant method of reaction, which is supported by ^{19}F NMR spectroscopy analysis showing a large conversion to the acyl fluoride, it could be plausible that the activated ester itself contributes somewhat to the formation of the product. This ester (**99**) which is discussed later in **Chapter 3** is shown to be susceptible to nucleophilic attack.

2.4 Ester Synthesis Mediated by PFP

The methodology was applied to make a library of esters from carboxylic acids and alcohols in a deoxyfluorination process. Benzoic acid (**93**) was chosen as the partner acid for alcohol substrate testing, **93** allowed for ease of purification because of the UV activity of generated aromatic containing esters. Further reasoning was influenced by the electron neutrality of the acid and the information about rate monitoring which demonstrated that **93** is fully converted to benzoyl fluoride (**51**) within the four-hour activation time frame.

For this methodology to find synthetic utility, a broad range of acids and alcohols should be tolerated. To that end, a range of acids and alcohols were investigated, and the results of these reactions are discussed below. Although acyl fluorides are known for their greater tolerance to hydrolysis compared with acyl chlorides, to limit any potential degradation acetonitrile was dried over molecular sieves and all reaction glassware and stirrer bars were pre-dried in an oven to limit any unnecessary exposure to water.

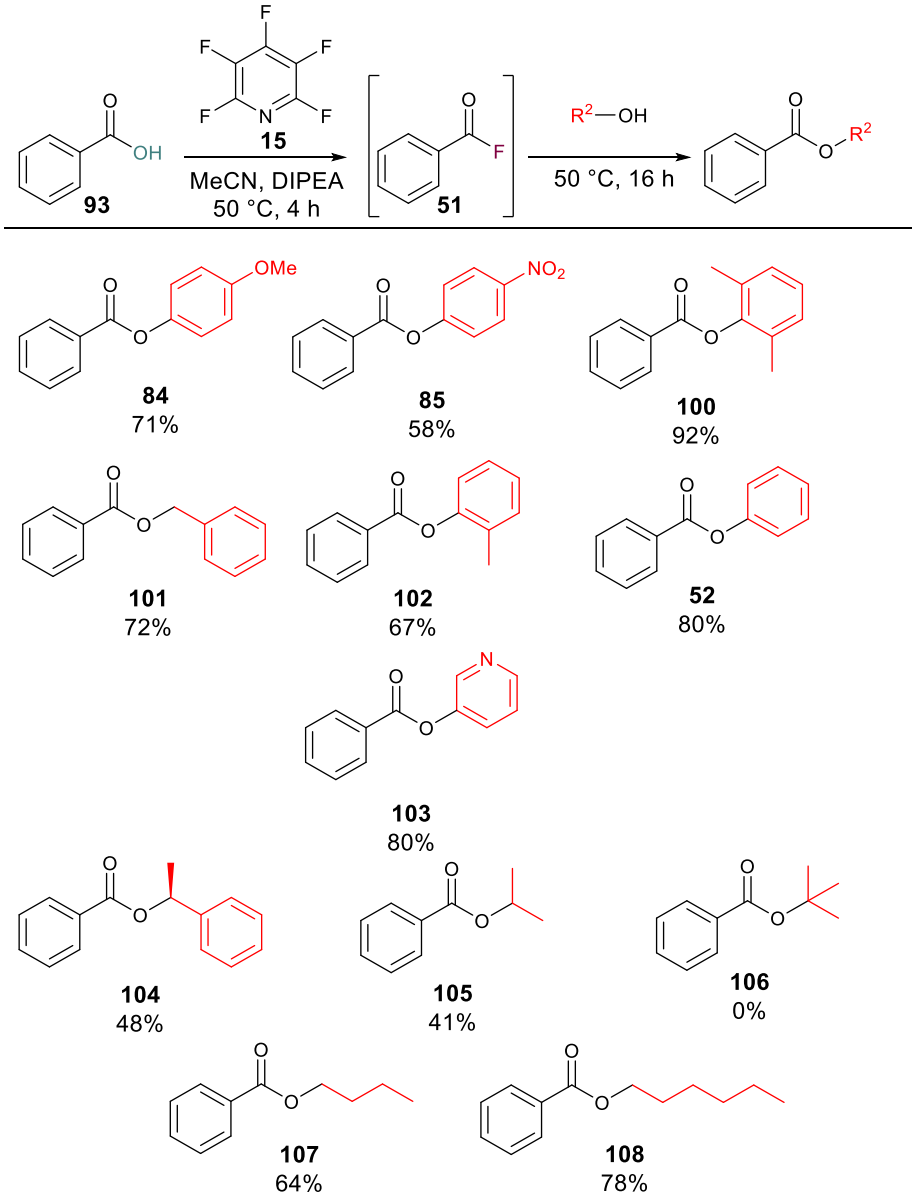


Figure 2.7: Testing the alcohols scope for esterification reactions using the optimised methodology.

In the developed one pot esterification reaction, alcohols were well tolerated generally with yields of up to 92% observed (**100**) (**Figure 2.7**). Esters prepared from aromatic alcohols bearing electron donating substituents 4-methoxyphenol (**84**) and 2-methylphenol (**102**) gave 71% and 67% yield respectively. The electronically withdrawn 4-nitrophenol gave a satisfactory 58% yield of ester **85**. Upon using a heteroaromatic example, 2-picolinic acid gave 80% of **103** a coincidental matching yield with the non-heteroaromatic benzoic acid equiv. (**52**)

was observed, this was a good demonstration that the method is applicable to heteroaromatics.

Aliphatic primary alcohols were also very amenable to the *in-situ* process. **93** coupled with benzyl alcohol and *n*-hexanol gave good yields of 72% (**101**) and 78% (**108**) respectively. When the shorter chain *n*-butanol was used the yield decreased to a still acceptable 64% (**107**). The reasoning for this is not clear but could possibly be due to contamination with water as the alcohols were not dried over molecular sieves.

Upon using secondary alcohols, a noticeable drop in yield was observed which is attributed to an increase in steric crowding. Upon using isopropanol (**105**) a moderate yield of 41% was obtained and similarly another secondary alcohol (**104**) also gave a comparatively low yield of 48%. This near 30-40% drop compared to primary alcohols is attributed to the steric bulk associated with these molecules and further study to try to further the scope of secondary alcohols under more forcing conditions, such as a heated pressure tube would be a valuable research avenue.

When expansion to tertiary alcohols was attempted, *tert*-butanol was unable to afford the desired *tert*-butyl ester (**106**). This is expected as literature work on the synthesis of tertiary esters from acyl fluorides or acyl chlorides is sparse. The observed effect is attributed to the increasing steric bulk around the oxygen, this increasing steric hinderance decreases nucleophilicity. This effect was expected as *tert*-butoxides are commonly employed as non-nucleophilic bases. Potassium *tert*-butoxide was also trialled as a source of a *tert*-butoxide group as this had been successful with acyl fluorides in the past .[96] Problems with homogeneity were observed and no product was observed by crude NMR spectroscopy or mass-spectrometry.

Despite the lower yields observed with increasing steric bulk, the results were promising and showed that this *in-situ* methodology was tolerant to aromatic, primary and secondary alcohols. Work then shifted to examining the scope of varying the acids, with some variation in the alcohol.

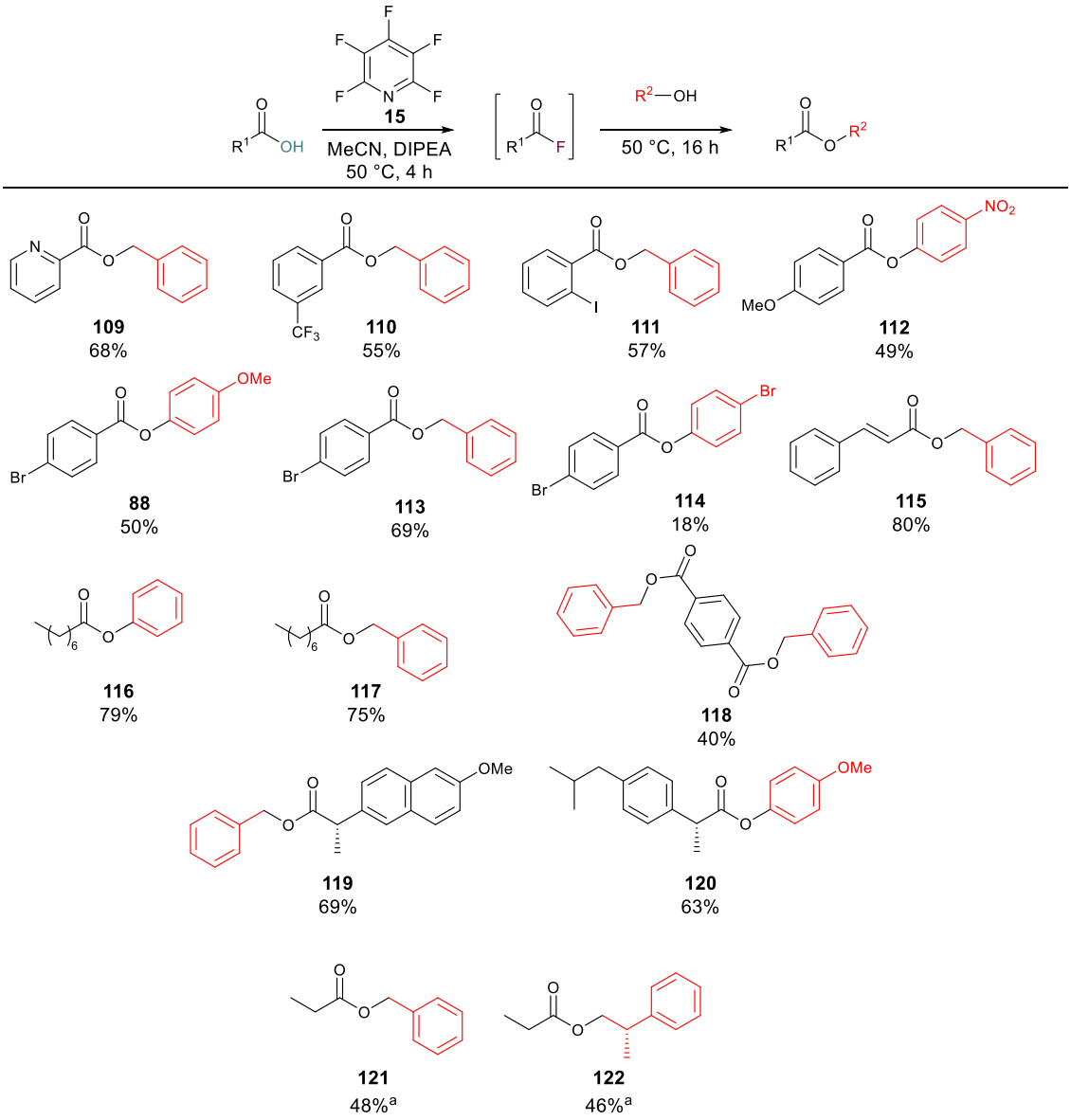
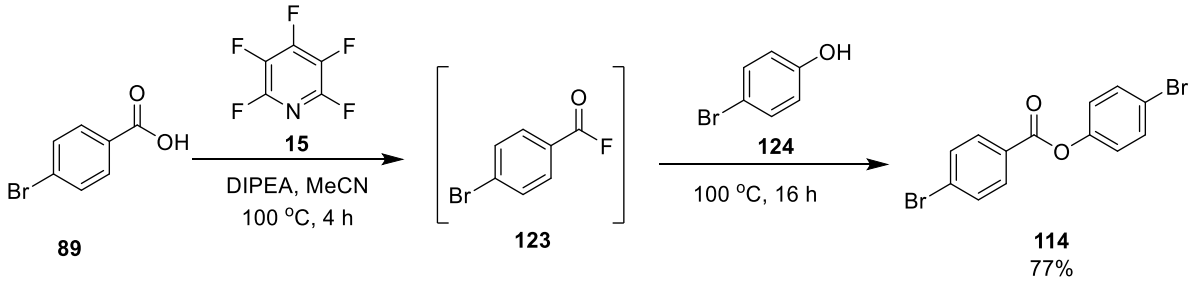


Figure 2.8: Expansion of *in-situ* methodology to various carboxylic acids. [a]Reaction run at 35 °C.

Firstly, the scope of aromatic acids was investigated as the couplings with benzoic acids had shown good yields. The electron rich 4-methoxybenzoic acid (**112**) gave a 49% yield which was expected given the electron deficient nature of the partner alcohol 4-nitrophenol, which had typically given lower yields in the previous substate investigations (**85**). The lower yield of **112** vs **85** was unexpected but could be explained by the increased electron density on the carbonyl carbon somewhat disfavouring substitution of 4-nitrophenol upon the formed acyl fluoride.

Investigations into electron deficient acids showed an acceptable tolerance to esterification. 4-Bromobenzoic acid offered the best yield when partnered with benzyl alcohol of 69% (**113**). Lower, but still acceptable yields were observed with other electron deficient acids with **110, 111** and **88** being isolated in 55%, 57% and 50% respectively. The PFP (**15**) mediated esterification of **114** initially proved to be difficult and only afforded a 18% yield. This low yield was anticipated as 4-bromophenol (**124**) is an electron deficient system, decreasing the hydroxyl groups ability to act as a nucleophile. This 18% yield was unsatisfactory and as a result the preparation of **114** was repeated in a sealed pressure tube at elevated temperature for both the activation and coupling stage (**Scheme 2.10**).



Scheme 2.10: Synthesis of **115** at elevated temperature in a sealed pressure tube.

These more forceful conditions were highly beneficial and an increase in the yield to 77% was observed. This was a positive result and highlights that some of the other moderate yields could potentially be improved by increasing reaction temperature in the activation or esterification step. It is probable that increased temperatures could also increase the yield of other electron poor examples like **110** or **111.**

Esterification using the heteroaromatic 2-picolinic acid was well tolerated and gave a good yield of 68% (**109**) which further demonstrates the potential range of compatible candidates for this reaction. This yield was directly comparable to that of the structurally similar benzoic acid (**100**) which had previously offered a yield of 72%.

Advancement to aliphatic acid compounds also showed good tolerance and the best yield of 80% was observed when the unsaturated cinnamic acid (**115**) was used. This was an important example as it demonstrated that the methodology was also compatible with non-aromatic alkene containing compounds. By variation to the long chain saturated aliphatic octanoic acid this gave very good yields both with an aromatic (**117**) and an aliphatic alcohol (**116**), giving 75% and 79% respectively.

The yields for shorter chain carboxylic acids, such as propionic acid were lower than expected, when reactions were conducted under standard conditions a yield of 30% was obtained for **121** and **122**. This is attributed to the propionyl fluoride having a boiling point of 42-43 °C.[97] It is therefore likely some propionyl fluoride was lost to the gas phase and wasn't available for reaction leading to a lower overall yield of the corresponding ester.

To compensate for this, these problematic reactions were repeated at a lower temperature and when doing so, increased yields up to 48% (**121** and **122**) were obtained. This represented a decent increase, but the low yield can still probably be directly attributed to volatility of the acyl fluoride which could be lost to the environment from a Radleys carousel tube. These results contrast well with the initial experimental work of this report which when propanoic acid was used at room temperature, much better yields with aromatic alcohols were observed.

Expansion to the more complex aliphatic examples of ibuprofen and naproxen were well tolerated. The reaction of ibuprofen with 4-methoxyphenol (**120**) gave an acceptable 63% yield. Naproxen and benzyl alcohol as the coupling partners saw an isolated yield of 68% (**119**). These results were extremely promising as they showed that the methodology could be applied to more complex, biologically relevant molecules.

When the di-carboxylic acid, terephthalic acid was employed as the substrate, **118** was synthesised in less-than-optimal yield (40%). The reason for this low yield however is unclear. It is unlikely this is a result of competitive formation of the ether as the ether was not observed when aliphatic alcohols, such as benzyl alcohol were used. Further investigations into di-acids could be an interesting further work objective, especially as molecules like these can allow for the rapid building of molecular complexity. Expanding this work to substrates with protecting groups would also deal with the problem of symmetrical synthesis.

From here it was decided to explore if the methodology could be employed with multi-functional nucleophiles to generate multiple esters in one step. To this end, and to further demonstrate the synthetic utility of the methodology, some exploratory work was performed to target diesters from their corresponding diols.

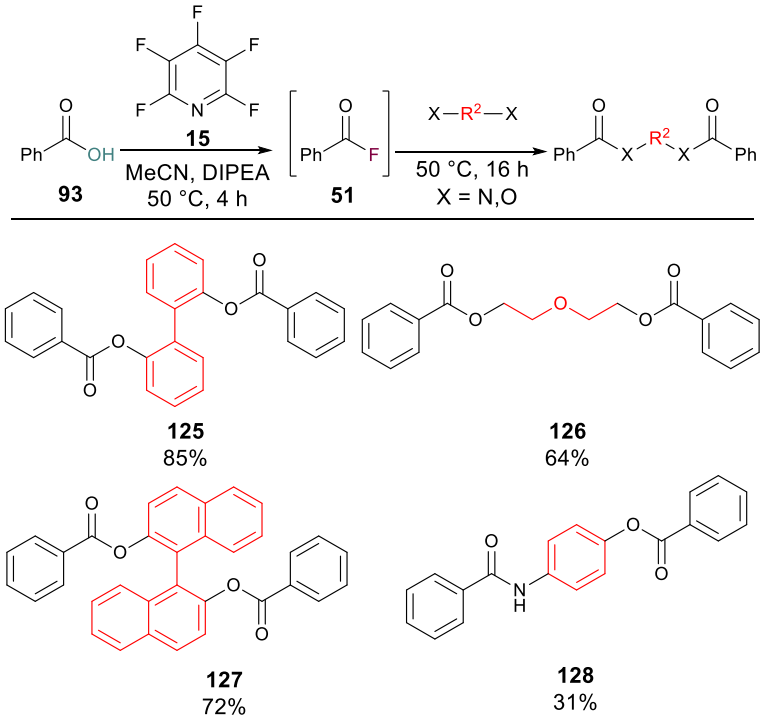
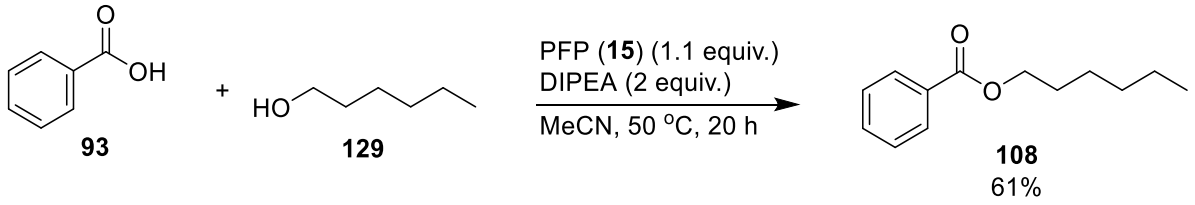


Figure 2.9: Examples of synthesised di-esters.

Employment of 2,2-biphenol with benzoic acid (**93**) as the substrate gave excellent conversion, affording **125** in 85% yield. When racemic 2,2-binaphthol was the alcohol partner, esterification gave an excellent yield of **127** (72%). These results were encouraging, and it was pleasing to see high yields obtained when aromatic alcohols were used. Variation of the diol to diethylene glycol saw a small drop in yield, with 64% of **126** obtained representing a good yield. To round off the study into di-nucleophilic substrates an amide and ester containing duality was synthesised from 4-aminophenol. Noticeably different from the other experiments described **128** was found to be insoluble in MeCN, although all the initial reagents solubilised well; within one hour a white solid had precipitated from the reaction mixture. This precipitation likely explains the low yield of **128** which was 31%, the precipitated product **128** was of such consistency to prevent further mixing of the substrates together. The insolubility of **128** also required adaptation to the purification which rinsing and removing the solid from the filter paper. Despite the problems encountered during the synthesis of **128** it was especially interesting because aside from sparse mass spectrometry and melting point data, the analysis included herein is the first time that this compound has been properly characterised by NMR and mass spectrometry to the best of our knowledge.

With the ester scope established it seemed prudent to apply the reaction conditions to a larger scale reaction (**Scheme 2.11**). The ability to scale synthetic processes is very important and critical for any industrial applications.

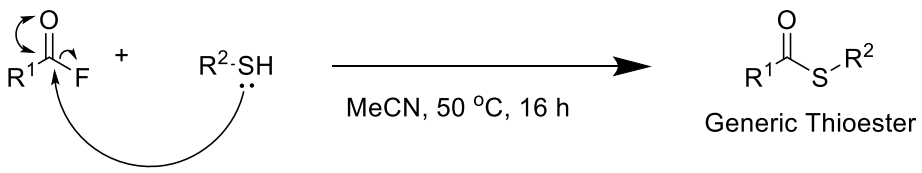


Scheme 2.11: Gram scale synthesis using pentafluoropyridine mediated methodology.

The target molecule for the gram scale synthesis was **108** which was chosen because of the ready availability of *n*-hexanol (**129**) factored in with the excellent yield **108** (78%) had afforded previously on the small-scale reaction. The standard reaction conditions were successfully applied to gram scale methodology when **93** (1.00 g) was activated to the acyl fluoride under the usual 4-hour activation conditions. Addition of **129** then yielded the desired product in an acceptable 61% yield. The yield of this gram scale synthesis was slightly lower than expected but this may be due to the purification process.

2.5 Thioesterification

With a well optimised esterification reaction in hand, it was decided to attempt to apply the same reaction conditions to thiols (which are also known as mercaptans) to generate thioesters. Sulfur sits below oxygen in group 6 and thiols are softer nucleophiles than their alcohol counterparts and are more reactive. The mechanism of thioesterification is the same as esterification but in this case yields a compound known as a thioester (**Scheme 2.12**). The lone pair on the sulfur atom attacks into the carbonyl carbon, displacing the fluorine (which acts as a leaving group) in an addition-elimination process resulting in the formation of the thioester.



Scheme 2.12: Depiction of a general addition-elimination thio-esterification mechanism.

Due to thiols being softer nucleophiles than both alcohols and amines, it is well understood that they will substitute well onto the 4-position of PFP (**15**) so maximum consumption of **15** is desirable in a thioesterification process. In the reactions described however 1.1 equiv. was still utilised as it was concluded that driving the maximum possible conversion of carboxylic acid to acyl fluoride was critical for high yielding reactions. Thiol equiv. were maintained at 1 equiv. throughout.

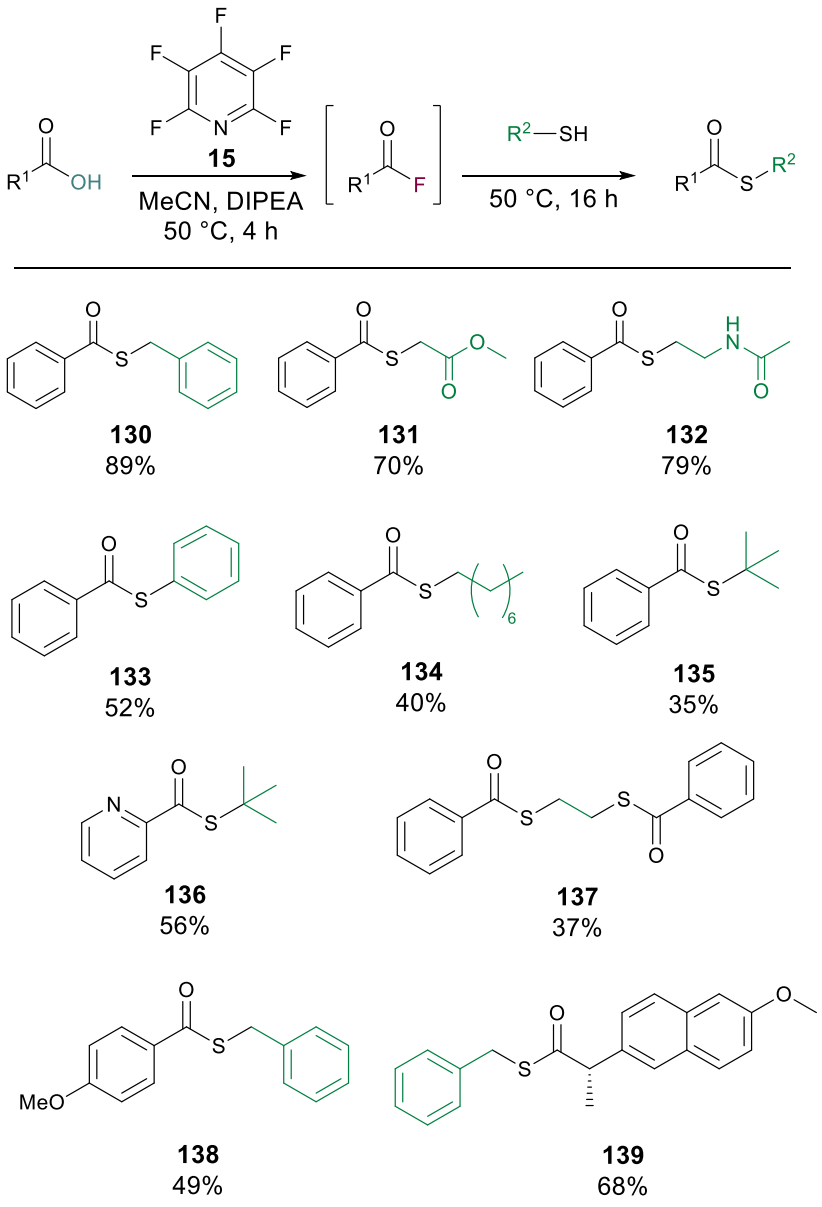


Figure 2.11: Thioesters synthesised from *in-situ* acyl fluoride generation.

In this methodology a range of thiols were found to be compatible substrates. The maximum observed yield was 89% (**130**) with acceptable final isolated yields throughout. Purification was straightforward but unfortunately thioether by-products were observed with both aliphatic and aromatic thiols. Unfortunately, the ether did lower the yield of thioesters as it would contaminate column fractions during purification, likely through pi-stacking interactions. For these examples it may pay dividends to leave the acyl fluoride generation for much longer which would allow maximum consumption of the PFP. Although 1.1 equiv.worked well for esters, allowing for a maximum yield of 92%, it could be helpful to reduce the PFP (**15**) equiv. used for thioester formation to reduce any formation of unwanted thioethers.

Aliphatic thiols were very acceptable substrates under the reaction conditions used. Benzyl mercaptan worked well and gave a yield of 89% **130** when coupled with **93**. Aliphatic thiols which contained ester (**131**) and amide functional groups (**132**) were well tolerated giving 70% and 79% respectively. Unlike the observations made in the esterification studies, the use of a tertiary thiol successfully gave the desired product (**135** and **136**). This successful reaction was surprising, and the observation highlights the differences in the nucleophilicity between thiols and alcohols as discussed previously. The aromatic thiol, benzenethiol, produced the corresponding thioester (**133**) in an acceptable 52% yield.

When *tert*-butyl thiol was used for the preparation of thioesters with 2-picolinic acid (**136**) (**Figure 2.12**), the yield was an acceptable 56%. This is good evidence that tertiary thiols are acceptable reaction partners thus confirming heteroaromatic acyl fluorides are also acceptable partners for thioesterifications. It is believed this to be the first reported characterisation of this molecule.

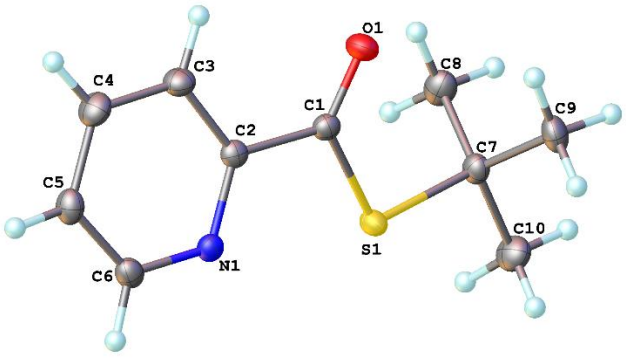


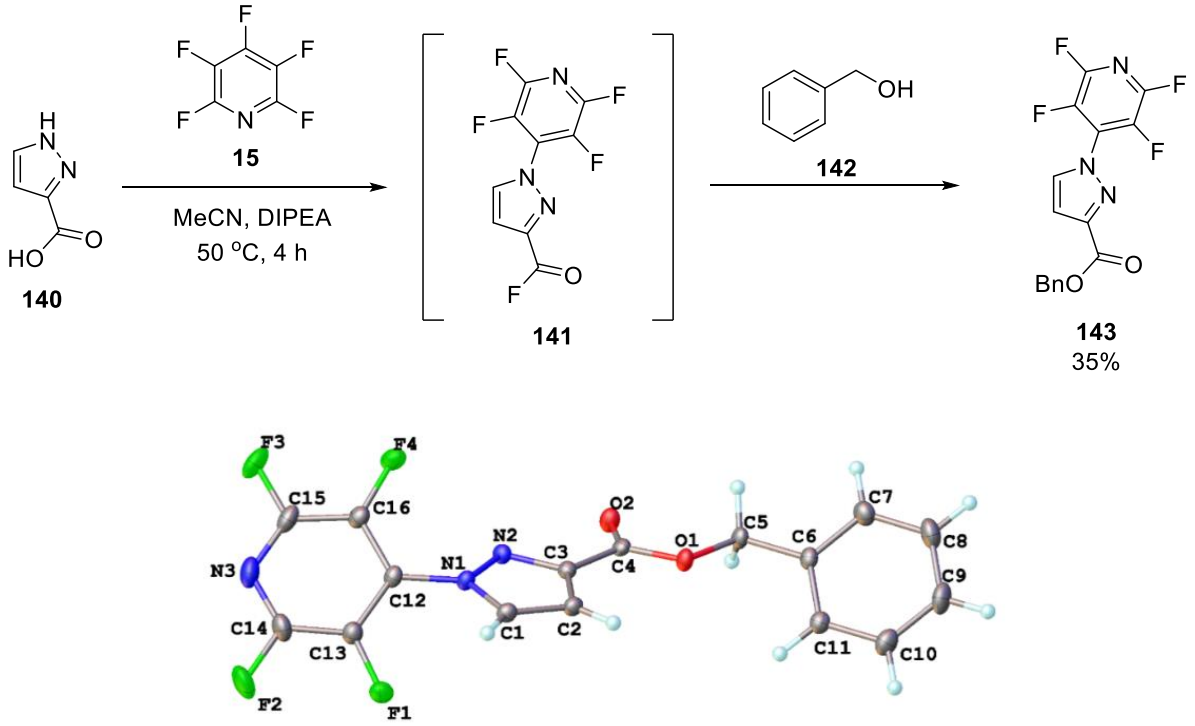
Figure 2.12: Crystal structure of **136** which was previously unreported. Crystal structure data are reported with a 50% thermal ellipsoid probability. This structure was deposited in the CCDC.

Expansion to biologically relevant naproxen showed a good conversion with the aliphatic benzyl mercaptan which gave a 68% yield of the corresponding thioester (**139**). Coincidentally this was also the first time this compound had been characterised. Variation to long chain aliphatic thiols were somewhat difficult to deal with but did allow for isolation of the corresponding thioester (**134**) in 40% yield. Despite the use of a lower particle diameter silica during purification of **134** the separation remained difficult with significant loss with co-elution of with the undesirable tetrafluoropyridyl ether occurring. Long chain aliphatic thiols such as **134** are quite "greasy" and during the purification the fractions with a tetrafluoropyridyl-thioether eluted very close together in pure hexane which resulted in a significantly lower yield.

To finalise the investigations into the thioester scope, the process was attempted to form a di-thioester using 1,2-ethanedithiol (EDT). This gave the di-thioester **137** in a low, but acceptable yield of 37%. During this purification the formation of some mono- and di-thioether was evident from TLC. The thioethers eluted first and after some careful column chromatography the later eluting pure fractions were able to give the desired product.

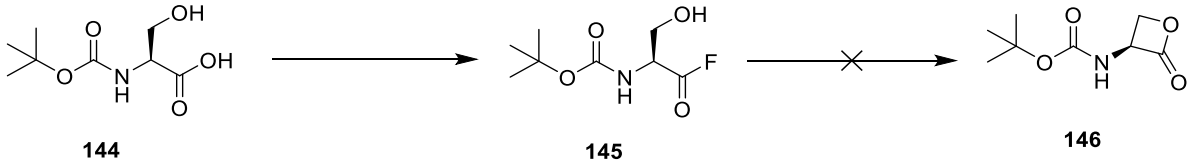
2.6 Difficult and Unsuccessful Substrates

PFP mediated ester and thioester couplings were typically functional group tolerant but there were some compounds which caused issues. For example, pyrazoles which contain a nucleophilic nitrogen. While there did appear to be traces of the desired ester, the major observed product contained the *N*-substituted tetrafluoropyridyl group (**Scheme 2.13**). Attempts to Boc-protect this pyrazole were unsuccessful which was not unexpected as there are no previous examples of this **140** being Boc-protected.



Scheme 2.13: Observed product when an unprotected pyrazole was used **143**. Crystal structures are reported with a 50% thermal ellipsoid probability. This crystal structure was deposited into the CCDC.

The possibility of using the *in-situ* methodology to access cyclic products was briefly investigated. Boc-Ser-OH (**144**) was used as a substrate, but it did not show any lactone formation (**Scheme 2.14**). Whilst the acyl fluoride (**145**) was readily formed, as evidenced by the production of TFPO, which was observed by ^{19}F NMR spectroscopy, no cyclisation was observed. There were a few attempts made at this reaction, but it is likely the acyl fluoride was not reactive enough to generate the often difficult and kinetically disfavoured 4-membered ring. Instead, mass spectrometry evidence suggested that dimerization was the likely product as evidenced by the observation of expected the $[M+H]^+$ 393.4 dimer peak.



Scheme 2.14: Attempted cyclisation of Boc-Ser-OH (**144**) to a 4-membered lactone ring.

When using 6-bromopyridine-2-carboxylic acid **147** there was no sign of the product after purification of the reaction mixture. This could be due to the electron withdrawn nature of this compound leading to very slow formation for the acyl fluoride. Boc-Alanine **149** was another

carboxylic acid substrate that appeared to be unsuccessful (**Figure 2.12**). The hypothesis for this example is there could have been a missed lack of UV-activity which meant the desired compound was being missed during purification, during this work benzyl groups were found to not always be strongly UV active. This would be another ideal substrate for further study as it remains unclear why the product was not isolated. Brittain *et al.* have successfully prepared an amide from the corresponding Boc-Alanine and alanine methyl ester, so the methodology is known for the preparation of acyl fluorides which means that purification is the likely issue.[1]

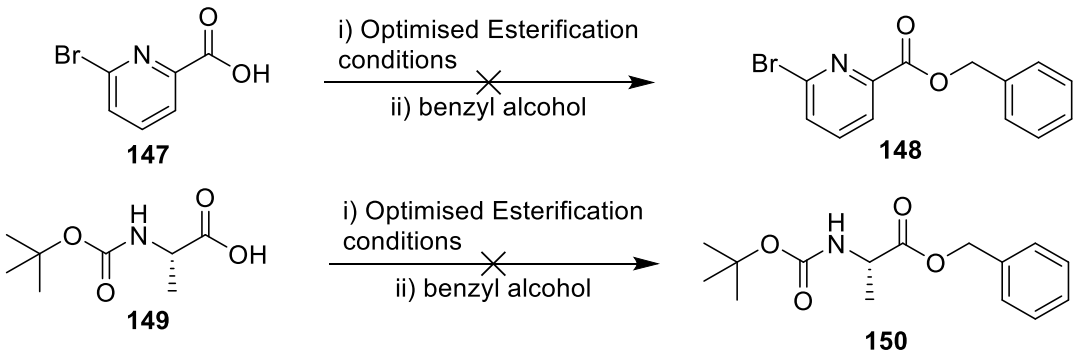


Figure 2.12: Examples of acids which didn't show any conversion to esters under optimised conditions.

The esterification of naproxen with 4-methoxybenzoate **151** was attempted and deemed successful as observed by NMR spectroscopy. Significant conversion was observed but the purification was hampered by a non-negligible amount of the PFP ether that coeluted with the product, this is likely due to pi-stacking. Similar difficulties were observed with the thiol example **152** which is unsurprising given the lipophilicity of the associated reaction constituents. It may be appropriate to decrease the equivalence of PFP in examples where purification is difficult to limit the amount of fluorpyridyl ethers/thioethers present.

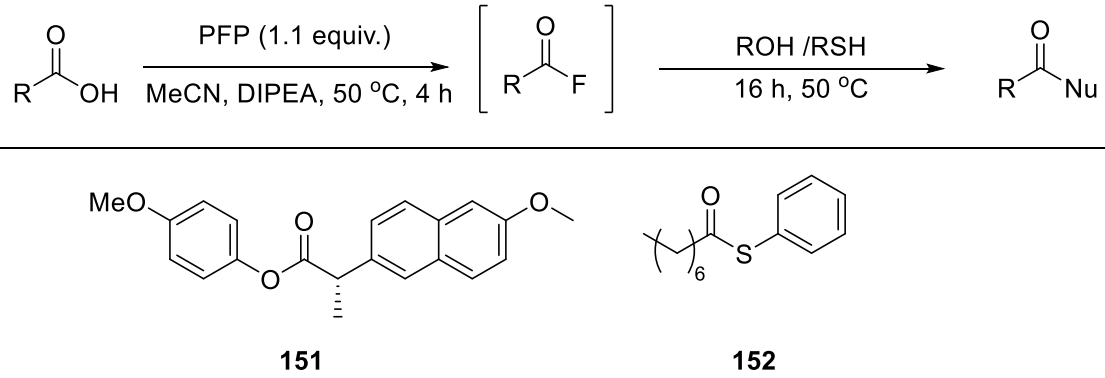


Figure 2.13: Synthesised products that were difficult to isolate.

Other examples of unsuccessful thioesterifications were 4-bromobenzoic acid coupled with benzyl mercaptan which did not yield the desired benzyl 4-bromobenzylthioate (**153**). This was surprising as preparation of **153** from acyl fluorides has been described previously in the literature.[98] This reaction could be more suited to heating in a pressure tube, as was the case with compound **114** which saw a large increase in yield under pressure tube conditions. Column chromatography of terephtalic acid and benzyl mercaptan **154** did yield a very low amount of product but this was a disappointing result. While this compound has been isolated once in 1959 from the corresponding acyl chloride, there are no reports regarding preparation from the corresponding acyl fluoride (**Figure 2.14**).[99]

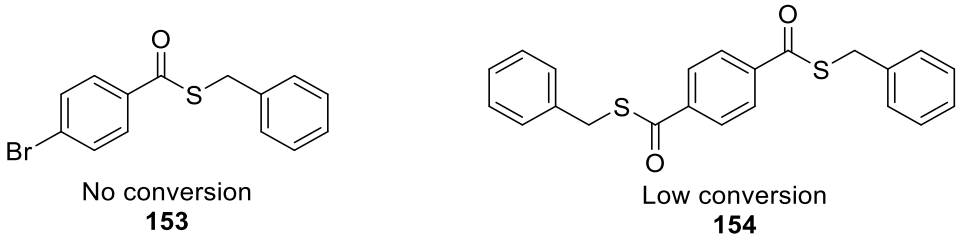
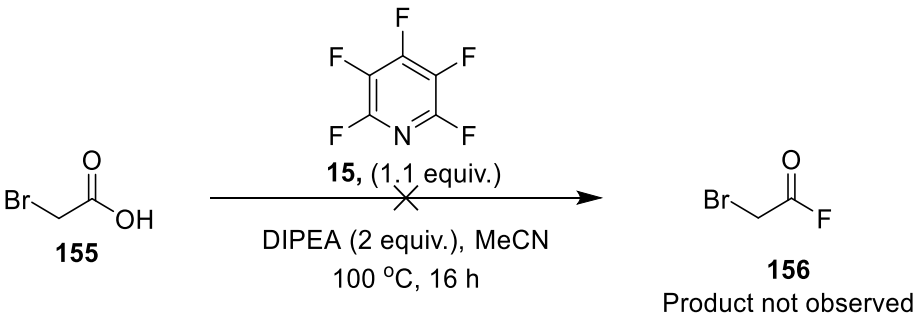


Figure 2.14: Attempted thioesterifications that yield no (e.g., **153**) or low yields of product (e.g., **154**).

Bromoacetic acid is a popular reagent for peptoid couplings. An attempt was made to replace the carboxylic acid group with an acyl fluoride. Despite the elevated temperature and overnight timeframe there was no formation of the acyl fluoride observed and the pentafluoropyridine remained unconsumed as evidenced by the lack of TFPO (**Scheme 2.15**). The lack of conversion to the acyl fluoride (**156**) is attributed to the electron withdrawing effect of the bromine on the carboxylate, removing the ability of this substrate to act as a nucleophile. Bromoacetic acid has a p*Ka* of 2.86 which suggests the carboxylate should form and the lack of reactivity must be due to an inability to substitute onto the molecule of PFP. The boiling

point of **156** is 104 °C so volatility is not thought to be an issue, unlike the similar chain length propionyl fluoride discussed earlier.[100]



Scheme 2.15: Attempted synthesis of bromoacetyl fluoride (**161**).

2.7 Fluorinated Isoquinolines as PFP Substitutes

Another class of perfluorinated compounds capable of undergoing S_NAr reactions are the heteroaromatics heptafluoroquinoline **157** and heptafluoroisoquinoline **158** (**Figure 2.15**). These heterocycles bear similar S_NAr reactivities to PFP (**15**) and thus react in similar ways in the presence of nucleophiles.

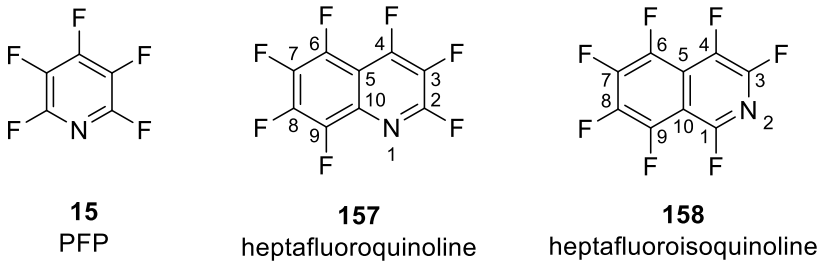
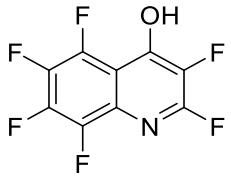


Figure 2.15: Examples of perfluoroheteroaromatics susceptible to S_NAr.

Aromatic nucleophilic substitution using hard nucleophiles such as nitrogen is known to occur at both the 4-position and 2-position of heptafluoroquinoline (**157**).[101] In contrast heptafluoroisoquinoline (**158**) is known to react at the 1-position with oxygen and nitrogen nucleophiles.[101]

Due to the structural similarities that the perfluoroheteroaromatic compounds **15**, **157** and **158** possess it was hypothesised that they might also be able to generate acyl fluorides in a similar

manner to PFP as described earlier in this chapter. Acyl fluoride generation from benzoic acid was attempted with heptafluoroquinoline (**157**) and monitored by ^{19}F NMR spectroscopy (**Figure 2.17**). Pleasingly the characteristic resonance for benzoyl fluoride **51** at 17.1 ppm was observed confirming that **157** can act as deoxyfluorination reagent. Only 6 other major peaks were visible in the *in-situ* ^{19}F NMR spectroscopic monitoring which indicated production of 2,3,5,6,7,8-hexafluoroquinolin-4-ol **159.** This was further supported by mass spectrometry which showed the $[M-H]^-$ peak of 252.3.



2,3,5,6,7,8-hexafluoroquinolin-4-ol
159

Figure 2.16: Structure of the hexafluoroquinoline, the proposed by-product of the deoxyfluorination reaction.

In **157** the ^{19}F NMR resonance of the 2-position is approximately -72.9 ppm and the 4-position is -124.6 ppm as was described by Fox *et al*.[101] In the *in-situ* reaction monitoring here, after 24 hours resonances were observed at -89.1, 150.6, 156.1, 161.4, 170.4 and 179.2 ppm (splitting observed but numbers rounded). These resonances suggest that substitution was directed to the 4-position of **159**. This is supported by 6 resonances of equal integration, including one of the peaks observed of -89.1 ppm which likely correlates to the 2-posiiton, like the -72.9 reported by Fox *et al*. There was also no visible peak in the -124 to -140 ppm region (**Figure 2.17**). A Reaxys search did not turn up any previously reported data for **159** so a direct comparison was not possible.

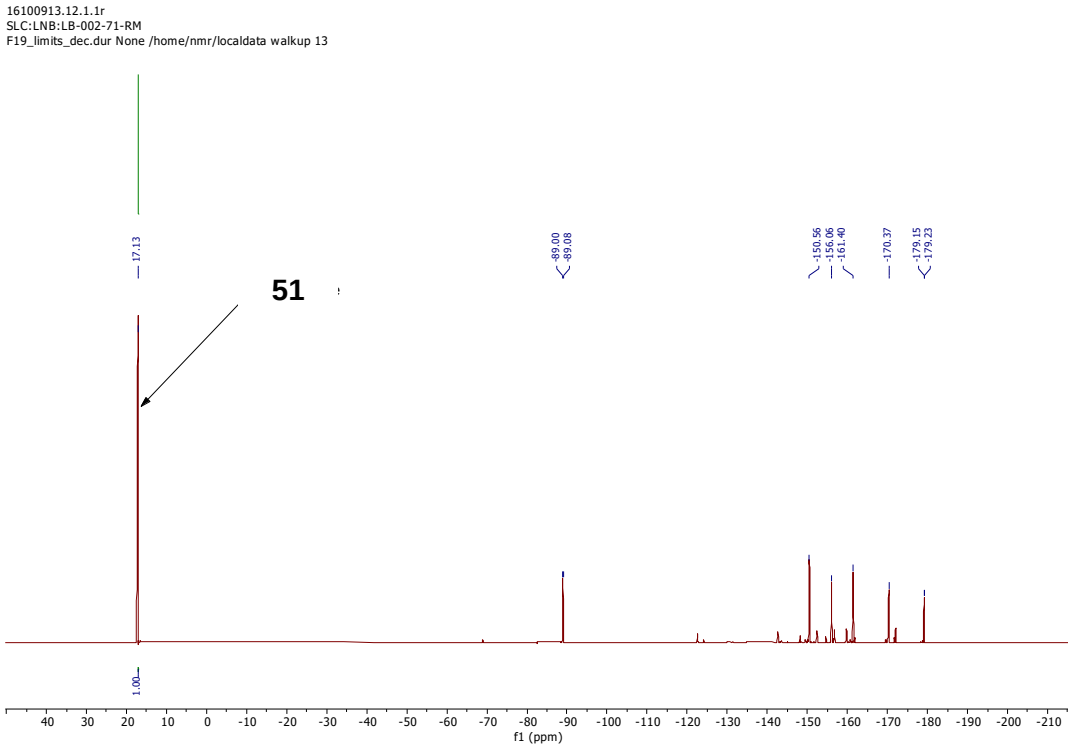
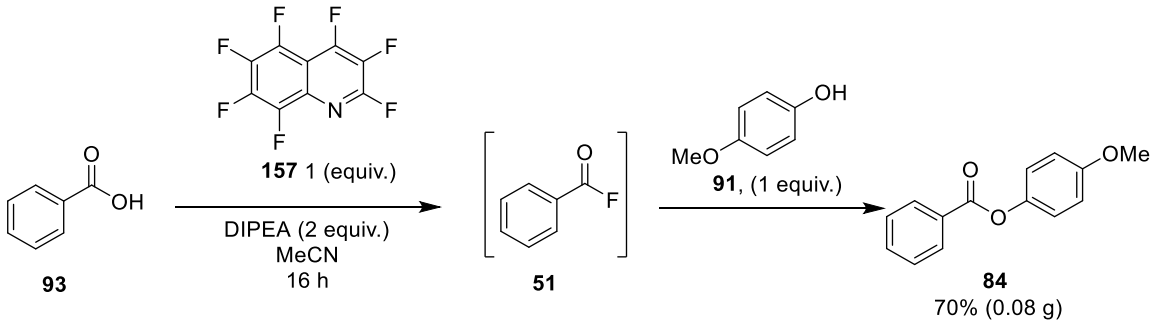


Figure 2.17: *In-situ* ^{19}F NMR monitoring of acyl fluoride generation using heptafluoroquinoline (**157**).

An esterification using the acyl fluoride generated from benzoic acid using heptafluoroquinoline (**157**) was performed. In contrast with the PFP mediated esterification's, in this procedure 1 equiv. of **157** was used and the acyl fluoride was allowed to activate for 16 hours (overnight) before the 4-methoxyphenol was added (**Scheme 2.16**). Ideally these would have been repeated with 4-hour intervals but a lack of availability of **157** prevented this. This reaction was successful with **84** being isolated in 70% yield, which is a yield directly comparable to when PFP was previously employed which had given a yield of 71%.



Scheme 2.16: Heptafluoroquinoline (**157**) mediated preparation of acyl fluorides and subsequent esterification.

Although the results of this exploratory reaction are promising, heptafluoroquinolines are expensive and have limited commercial availability. These drawbacks mean that whilst **157** can be used as a deoxyfluorination reagent, PFP (**15**) would still be the preferred option in terms of cost and commercial availability.

2.8 Chapter 2 Summary

The *in-situ* deoxyfluorination of carboxylic acids to yield acyl fluorides from pentafluoropyridine has been further probed and optimised. By conducting NMR spectroscopy which monitored the formation of acyl fluorides, modifications to the experimental procedure, namely increased reaction times, have been made compared to that of the original publication by Brittain and Cobb.[1] The scope of a one-pot synthesis of esters and thioesters using an easy to conduct reaction manifold has been described and published including the preparation of some compounds which previously lacked literature data, such as **136** and **139**.[102] Generally, substrates were well tolerated and aromatic alcohols and aliphatic alcohols were successfully coupled with a range of aromatic and aliphatic carboxylic acids, including the modification of biologically relevant compounds. Pleasingly, the methodology was also applicable to an exemplar gram scale reaction which resulted in good yield of ester **108**. Some difficulties arose when testing some more electron deficient acids, tertiary alcohols, and amino acids. Interestingly, tertiary thiols were able to offer thioesters whereas the alcohol counterparts could not offer esters. This observation is believed to be a result of the increased nucleophilicity of the softer sulfur nucleophile. In some cases, such as **151** and **152** the desired product was synthesised, but purification was hampered by the formation of tetrafluoropyridyl ethers. This indicates a longer reaction time or less equiv. of PFP may be required to allow for a more straightforward purification.

For examples that were found to be completely unamenable to the process it is recommended that an in-situ monitoring is performed to probe the rate of formation and consumption of acyl fluorides for compounds such as **147, 149, 151, 152** and **154**. By performing this analysis, the problem of either difficulties in acyl fluoride generation or of nucleophilicity of the nucleophile can be identified and overcome.

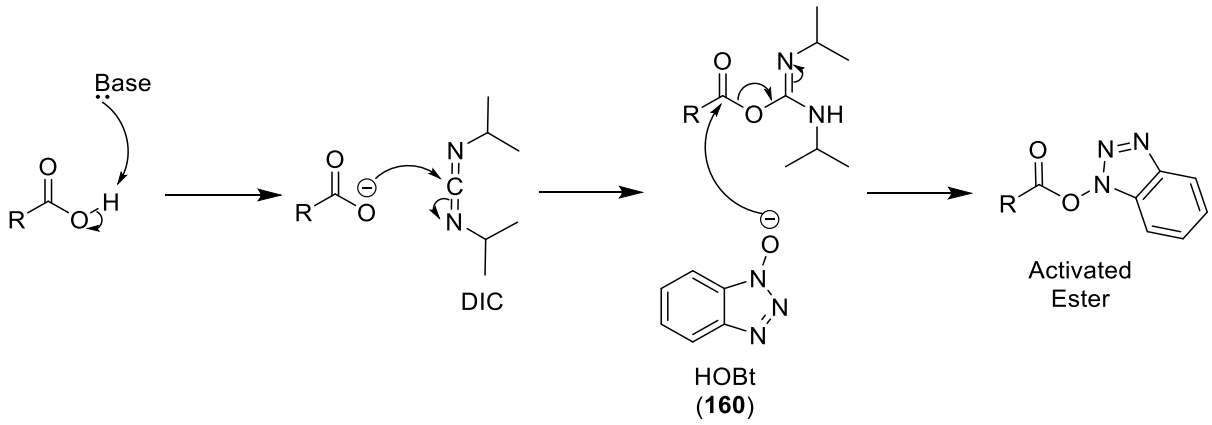
Variation of the deoxyfluorination source to heptafluoroquinoline was a good success which saw excellent conversion to the acyl fluoride and the desired ester product in similar yield as the one observed during when PFP was used. Rate comparisons between PFP and heptafluoroquinoline (**157**) would be an interesting avenue of further exploration but currently that is hampered by lack of commercial availability and high cost of the heptafluoroquinolines.

3 Tetrafluoropyridin-4-yl Esters

Carboxylic acids are well known to have low reactivity in nucleophilic addition elimination reactions. To activate carboxylic acids and make them reactive enough for such processes, a range of different approaches have been developed. One such approach is to generate an activated acid directly from a parent carboxylic acid. Examples of activated esters include compounds like acyl fluorides and acyl chlorides, in which the carbonyl centre has been activated to be extremely susceptible to attack by a nucleophile. Activation of carboxylic acids is an important reactivity concept; this was demonstrated in the activation of carboxylic acids to acyl fluorides mediated by PFP (**15**) in the earlier discussions of esterification in **Chapter 2**.

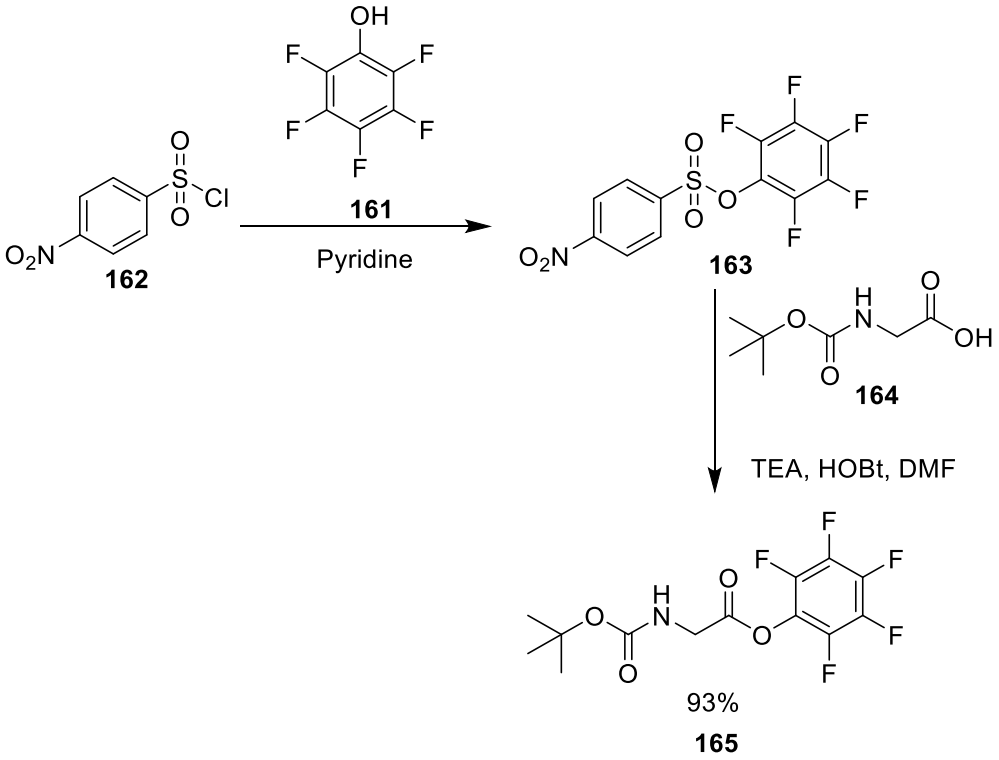
Peptide synthesis is a discipline that relies on the activation of carboxylic acids to generate amide bonds. Coupling reagents play an important role in peptide modification, 1*H*-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), *N*,*N*′-dicyclohexylmethanediimine (DCC) and hexafluorophosphate benzotriazole tetramethyl uronium (HBTU) are all reagents known for their coupling ability in this field.[103] These coupling reagents are required to mitigate against potential side products as peptides can be large and complex with specific amino acid sequences featuring many side chains. Simply adding $SOCl_2$ to generate the acyl chloride from an amino acid may seem a straightforward solution but such harsh conditions are not usually compatible with the rest of the peptide chain. The generation of HCl that this approach would entail is especially detrimental to acid sensitive groups.[56] The application of acyl chlorides in peptide synthesis can also have unwanted issues with the scrambling of the stereochemistry of the alpha carbon. Coupling reagents can help suppress racemisation and release by-products that do not have a detrimental effect on the other functional groups within the peptide.

Activated esters can be regarded as their own class of coupling reagents. These activated esters are synthesised using alcohols with electron withdrawing properties, for example HOBt (**160**) or pentafluorophenol (**161**) (**Scheme 3.1**) are often chosen because of their ability to increase electrophilicity at the carbonyl centres.[56] Cyanuric fluoride has also been shown to be useful as an activated ester in a one-step synthesis of beta-lactams.[104]



Scheme 3.1: Synthesis of an example HOBt activated ester using DIC.

Pentafluorophenyl esters, include the electron withdrawing perfluorophenyl functionality as highly reactive activated esters. Their reactivity is useful as not only carboxylic acid activators but also cross-coupling partners in Suzuki-Miyaura couplings and palladium catalysed intramolecular alkene formation.[105-107] A range of methods and reagents are available to enable the production of pentafluorophenyl esters, and include the application of acyl chlorides or coupling reagents such as EDC in combination with pentafluorophenol.[107, 108] While these are all synthetically useful methods of accessing these compounds, one example that stood out in particular was that of using a sulfonyl ester to synthesise pentafluorophenyl esters (**165**) from amino acids (**Scheme 3.2**).[109] This method was used to prepare a variety of activated esters of amino acids in excellent yield.



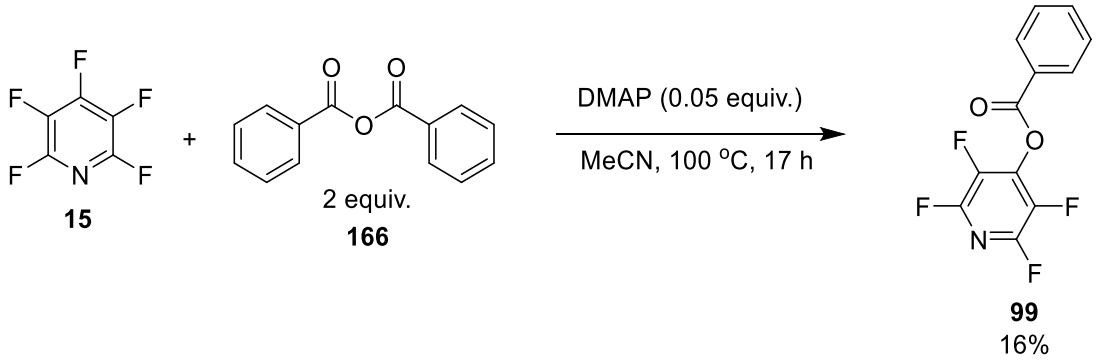
Scheme 3.2: Synthesis of activated esters of amino acids using disclosed by Pudhom *et al*.[109]

3.1 Investigations into Tetrafluoropyridin-4-yl Esters

Despite there being many examples of pentafluorophenyl esters in the literature, there is limited information available on the structurally related tetrafluoropyridyl esters when conducting a Reaxys search. It was hypothesised that the reactivity of tetrafluoropyridyl esters may be like pentafluorophenyl esters and preliminary investigations into the synthesis and utility of this class of compounds was carried out here. Based on previous observation of the typical properties of fluoropyridyl containing compounds, it was suspected that this class of molecules could be used as a bench stable, solid acyl fluoride substitute. The fluoropyridine esters may act as better leaving groups than the fluorophenyl counterparts due to the increased electron withdrawal of the fluoropyridyl ring, allowing for better stabilisation of the negative charge.

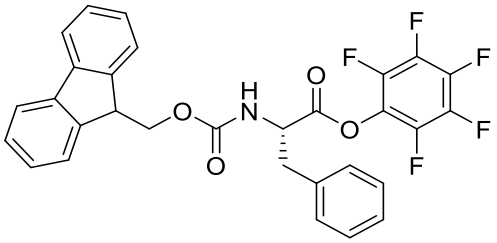
One of the suspected mechanistic intermediates of the pentafluoropyridine (PFP) mediated acyl fluoride preparation, (**Scheme 2.5**) is actually a tetrafluoropyridyl ester. Previously **99** has

been prepared by Crimmin and co-workers from an acid anhydride (**166**). To begin probing susceptibility to nucleophilic attack this work was replicated, and a small amount of **99** was prepared in 16% yield (**Scheme 3.3**). This was substantially lower than the 56% yield isolated by Crimmin and co-workers but this could be due to differences in reaction setup, such as lack of glovebox and Schlenk line in this probing work.[95]



Scheme 3.3: Replication of tetrafluoropyridin-4-yl benzoate (**99**) synthesis from the literature.[95]

It was suspected that **99** would react very quickly in the presence of a nucleophile, due to the obvious structural similarities with pentafluorophenyl esters (**Scheme 2.5**). Although these tetrafluoropyridyl esters must readily form, as was seen in the acyl fluoride preparations, there are very few examples of them being isolated in the literature. By contrast there are many examples of pentafluorophenyl esters described in the literature, some of these activated esters such as Fmoc-Phe-OPfp **167** are even commercially available (**Figure 3.1**).



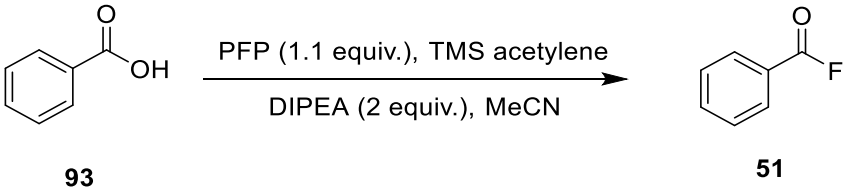
167

Figure 3.1: Commercially available activated ester Fmoc-Phe-Opfp (**167**).

Given that there are so few examples of tetrafluoropyridin-4-yl esters described in the literature it seemed prudent to try and isolate some examples for further investigation as activated acids.

At the very least the scope of this work was to probe the synthesis of this type of compound and isolate new examples to deposit into the crystal database.

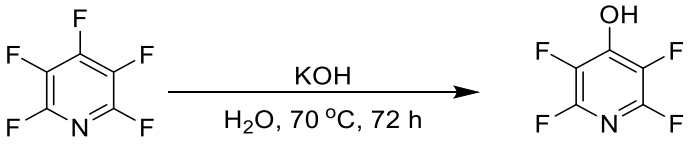
It was initially hypothesised that tetrafluoropyridin-4-yl esters could be isolated using the usual *in-situ* methodology using pentafluoropyridine with addition of TMS-acetylene to potentially trap the fluoride ion eliminated during the first S_NAr substitution; thus in turn preventing acyl fluoride formation. Unfortunately, significant conversion towards the acyl fluoride was still observed (for example see **Scheme 3.4**).



93 **51**

Scheme 3.4: Unsuccessful attempt to isolate a tetrafluoropyridyl ester.

Attention then turned to alternative ways which these activated esters could be synthesised. From a search of the literature a straight forward and quick synthesis of these esters has previously been disclosed for the synthesis of tetrafluoropyridyl containing methacrylates.[110] This procedure uses an acyl chloride in combination with 4-hydroxytetrafluoropyridine (TFPO)(**98**) in a standard esterification process. TFPO was therefore firstly synthesised by exposure of PFP to KOH in water with a maximum yield of 87% obtained on the multigram scale (**Scheme 3.5**). Gram scale attempts to synthesise **97** using NaOH instead of KOH were much less successful with a maximum yield of only 25% (1.0 g) being observed.



15
5.0 g

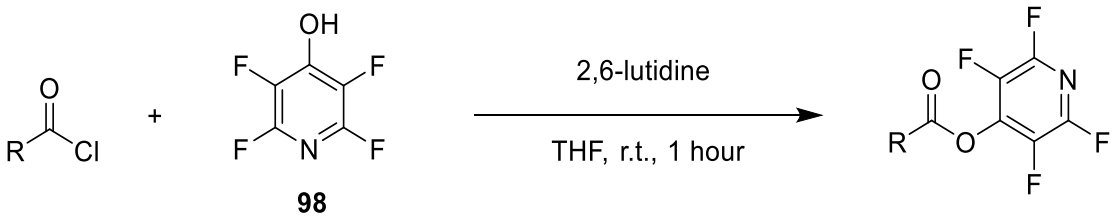
98
80%
4.3 g

Scheme 3.5: Synthesis of 4-hydroxytetrafluoropyridine (TFPO) **98**.

With TFPO (**98**) synthesised some representative tetrafluoropyridyl esters could then be prepared. As literature analytical data was readily available, the benzoate ester was synthesised to test the feasibility of the method.[95] Benzoyl chloride and TFPO (**98**) were able to yield the tetrafluoropyridyl benzoate (**99**) in an excellent 97% yield (**Table 3.1, Entry 1)**.

Automated column chromatography was employed to aid in the purification. The resulting tetrafluoropyridyl ester was found to be a highly crystalline bench stable solid and thus was suitable for single crystal determination.

Table 3.1: Tetrafluoropyrid-4-yl esters synthesised from corresponding acyl chlorides. Crystal structures are reported with a 50% thermal ellipsoid probability.



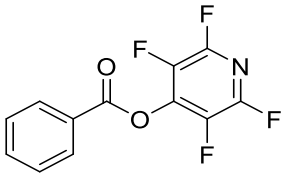
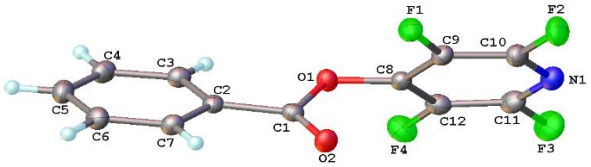
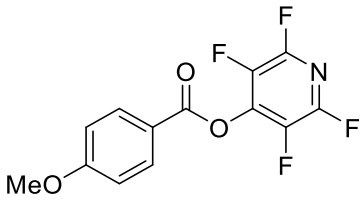
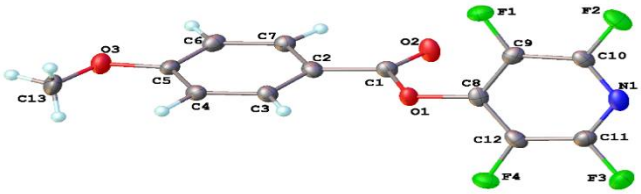
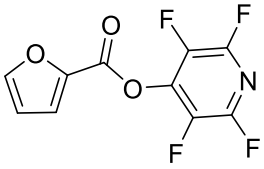
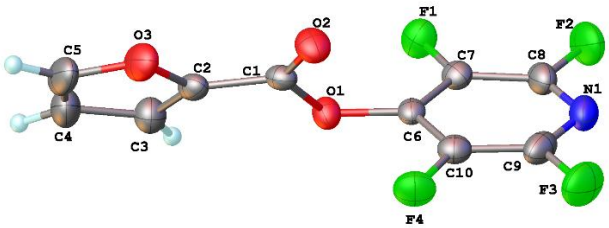
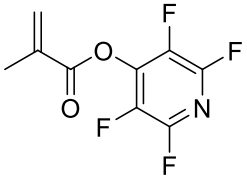
Entry	Structure	Crystal Structure	Yield
1	 **99**		97%
2	 **168**		71%
3	 **21**		67%
4[a]	 **169**	No Crystal Structure (liquid)	14%

Table 3.1, Entry 2 with a methoxy functional group in the 4-position of the benzoyl chloride afforded 71% of a crystalline solid **168** (**Table 3.1, Entry 3**). π-π stacking interactions within the crystal packing were observed. Two virtually identical molecules form the unit cell, and these are held together by the π-π interactions. (**Table 3.1, Entry 2**) (**Figure 3.2**).

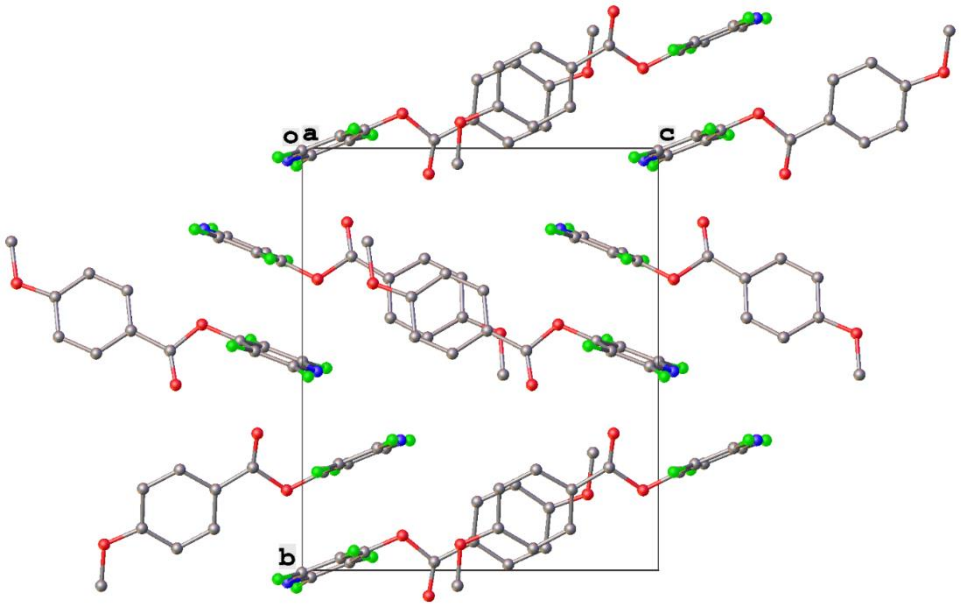


Figure 3.2: Unit cell of **168** (**Table 3.1, Entry 2**), which shows the two identical composites of the unit cell.

Upon using heteroaromatic 2-oxalyl chloride, the corresponding ester **21** was isolated in a good yield of 67% (**Table 3.1, Entry 3**). Again, **21** was found to be a highly crystalline solid and crystals suitable for single crystal determination were successfully grown from hexane/EtOAc vapour diffusion.

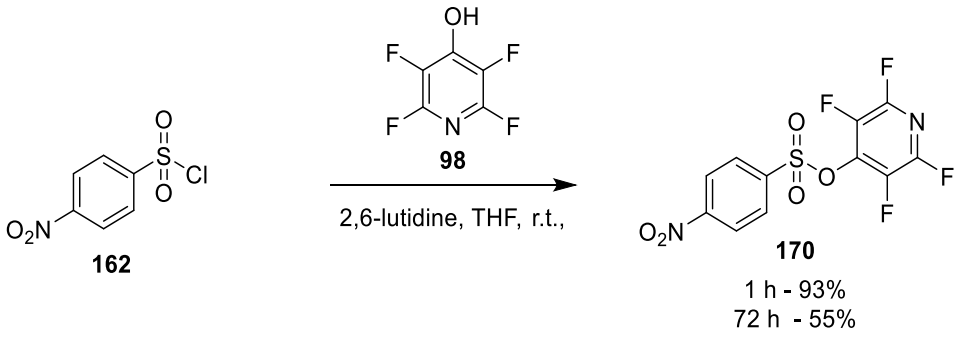
An acrylate ester of PFP has previously been reported in literature.[110] This process was applied to a methacrylate which afforded a 14% yield of the desired methacrylate monomer **169** (**Table 3.1, Entry 4**). This product was not crystalline at room temperature.

3.2 PFP Derived Sulfonyl Esters

With example PFP derived esters synthesised from acyl chlorides (**Table 3.1**) it was decided to explore avenues to directly access the tetrafluoropyridinyl esters from the parent carboxylic

acids. This would allow for the synthesis of an activated ester without requiring the use of the intermediatory acyl chloride. This approach would circumvent the acidic conditions that can be detrimental to other functional groups, such as acid sensitive peptide groups. A pentafluorophenol sulfonyl reagent has been previously described which was useful for adding the activating pentafluorophenol group to the carboxylic acids of amino acids to yield the corresponding pentafluorophenylester (**Scheme 3.2**).[109]

Replicating the literature conditions using pyridine as the solvent/base with TFPO (**98**) proved difficult and no product was observed after working up the reaction. Modification to the literature procedure was deemed to be necessary.[109] As a result, pyridine was substituted for THF and 2,6-lutidine was added as the base followed by direct column purification. These conditions had been shown to work well for the synthesis of the tetrafluoropyridinyl esters from acyl chlorides and it seemed sensible to try and apply them to a sulfonyl chloride (**Scheme 3.6**).



Scheme 3.6: Preparation of a novel tetrafluoropyridin-4-yl sulfonate **170.**

Using the aforementioned conditions formation of **170** occurred very rapidly, and the reaction was found to favour shorter reaction times. When a one-hour reaction time was used a yield of 93% of **170** was obtained. Under the same conditions but adjusting the reaction time to 72 hours the isolated yield of **170** significantly decreased to 55%. The reduction in yield can most likely be attributed to the reformation of **162** through a nucleophilic addition-elimination of the generated chloride ion(**98**). Despite the use of dry MeCN, the reaction was not performed under inert conditions. This assumption is supported by ^{19}F NMR spectroscopy of the isolated product which had shown an increase in the relative integrals between **98** and the product after several days. The increase was from integral 2:0.16 product:TFPO, 3 days later the relative integrals had changed to 2:0.52 product/TFPO. It was found that storing the final product under an inert gas in the fridge could slow down this unwanted hydrolysis. Given the

ease of synthesis and simplicity of automated purification it is recommended that sulfonyl esters are synthesised as and when required. **170** was found to be a highly crystalline substance which allowed for the collection of X-ray crystallography data. The crystal structure of **170** was successfully determined (**Figure 3.3**).

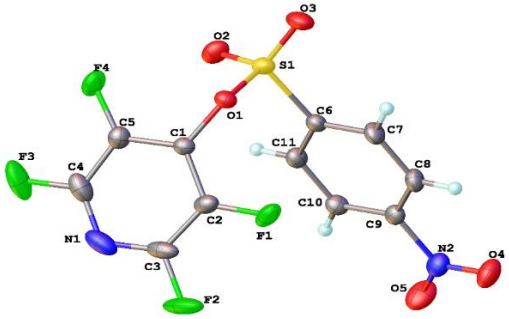
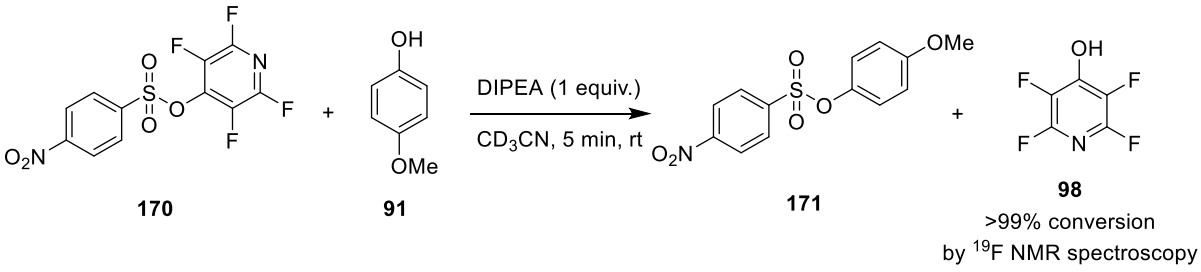


Figure 3.3: Crystal structure of tetrafluoropyrid-4-yl sulfonate **170**. Crystal structure reported with a 50% thermal ellipsoid probability.

3.3 Explorations into the synthetic utility of perfluoropyridin-4-yl 4-nitrobenzenesulfonate

Tetrafluoropyridyl-4-nitrosulfonate (**170**) was expected to be susceptible to nucleophilic attack. This was confirmed by subjecting **170** to reaction with 4-methoxyphenol (**91**) and DIPEA (**Scheme 3.7**). The reaction occurred on such a timescale that complete conversion to the expected product TFPO (**98**) could be seen in the time it took to perform the standard three ^{19}F NMR spectroscopy sweep width optimisation experiments (<5 mins).

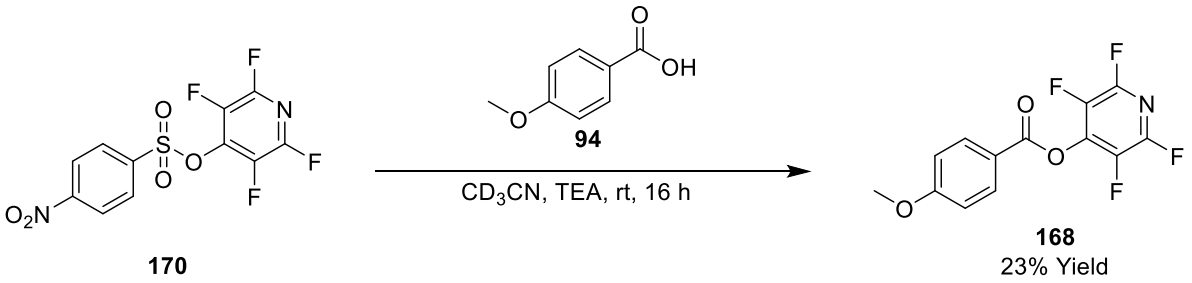


Scheme 3.7: *In-situ* nucleophilic substitution of perfluoropyridin-4-yl 4-nitrobenzenesulfonate (**183**).

Within 5 minutes, all of compound **170** had been consumed and there was only **98** visible by ^{19}F NMR spectroscopy.

Following the successful synthesis of **170** and demonstrating susceptibility to nucleophilic substitution, adding the tetrafluoropyridin-4-yl to a carboxylic acid became the next target. This was initially probed using DMF and benzoic acid **93**. When DMF was used it was found that purification was troublesome and DMF was contaminating the product post purification. Reassuringly however there was evidence of the formation of the desired product **99** by ^{19}F NMR spectroscopy, doping with a sample of **99** that was known to be pure saw growth in the already present peaks at (-88.20 and -151.80 ppm).

The reaction solvent was then changed from DMF to MeCN (which is easier to remove in the work up) and to aid in conversion monitoring, the acid was changed to 4-methoxybenzoic acid **94** which offers a useful methyl handle in ^{1}H NMR spectroscopy (**Scheme 3.8**). Previously in the pentafluorophenyl literature methodology, the coupling reagent HOBt was used in catalytic amounts.[109] Reactions performed during this work showed very similar ^{1}H and ^{19}F NMR spectroscopy patterns with or without addition of HOBt. As HOBt is shipped as a hydrate its use was dropped for future reactions here due to concerns about the potential hydrolysis of tetrafluoropyridin-4-yl ester that the HOBt hydrate may induce.



Scheme 3.8: Transferal of tetrafluoropyridyl group using the synthesised reagent **170**.

Analysis of the reaction mixture by ^{19}F NMR spectroscopy monitoring showed the immediate formation of a new set of shifted peaks which corresponded to that of the previous observed tetrafluoropyridyl 4-methoxybenzoate **168** (**Figure 3.4**).

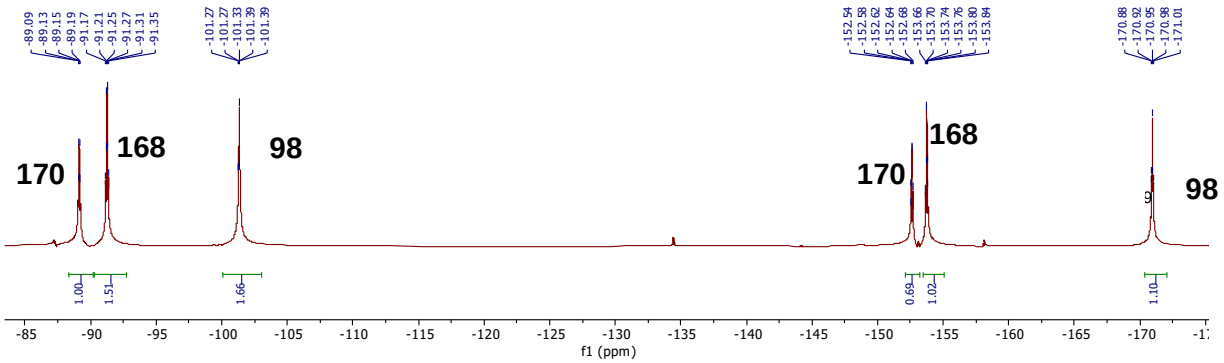
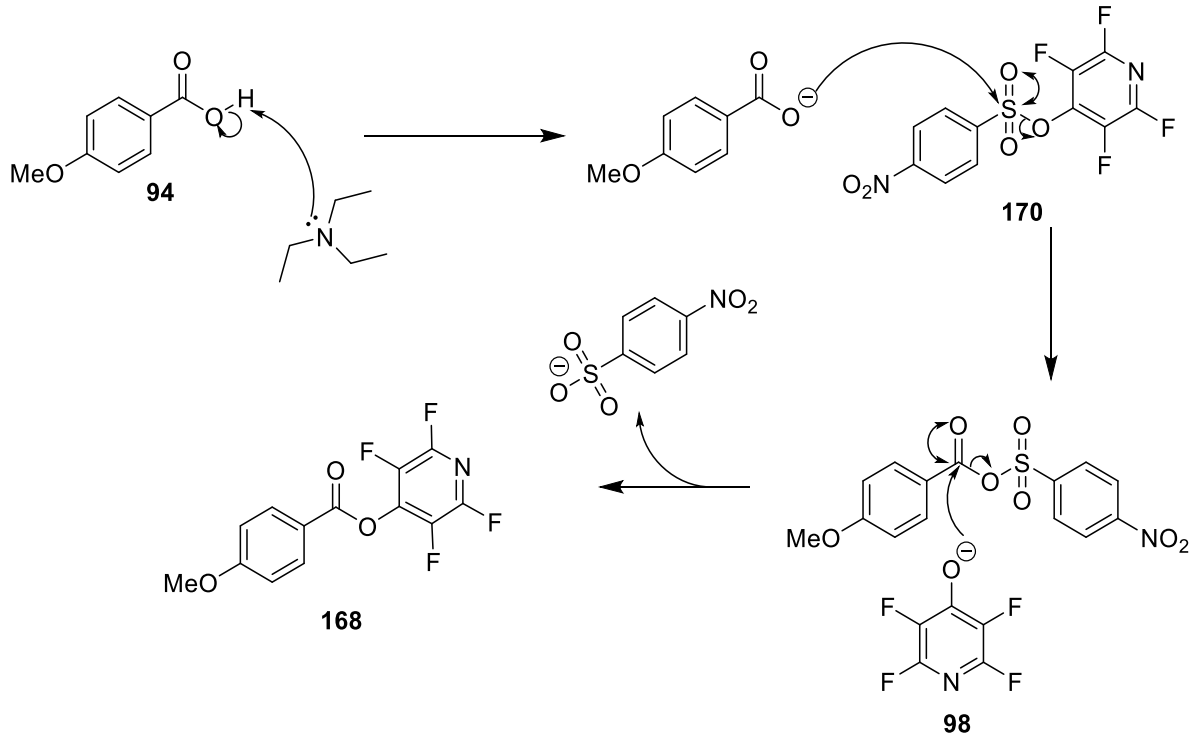


Figure 3.4 *In-situ* ^{19}F NMR monitoring of **Scheme 3.9** taken at 5 minutes.

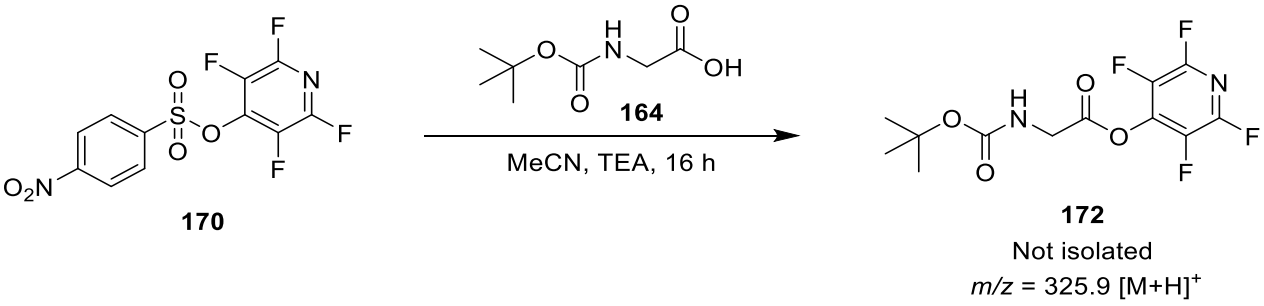


Scheme 3.9: Proposed mechanism for the formation of tetrafluoropyridin-4-yl ester (**180**) using a novel coupling compound.

Given the rapid formation of TFPO it is proposed that following deprotonation of **94**, the benzoate anion attacks into the electrophilic sulfur eliminating the TFPO (**98**). The sulfonyl ester (**170**) was found to be susceptible to nucleophilic substitution as was shown in **Scheme 3.7**. Following this attack, it is then proposed that **98** acts as a nucleophile, in a similar mechanism that generating tetrafluoropyridyl esters from acyl chlorides follows. The sulfonate

anion acts as a leaving group, which is expected as sulfonate anions are well known to be good leaving groups as they can delocalise electron charge across three oxygen atoms. This then yields the desired tetrafluoropyridyl ester **168**. The yield of **168** was only 23% (0.011 g) but this was achieved using a set of unoptimized conditions. Importantly, the isolation of **168** provides evidence that this is an approach which can be used to access this type of ester directly from carboxylic acids under mild conditions.

Attempts were made to then add the tetrafluoropyridyl group to an amino acid. Both Boc-glycine **171** and Boc-phenylalanine **164** were used as acid substrates. *In-situ* ^{19}F NMR monitoring showed the rapid formation of a new set of peaks which are believed to correspond to the desired ester **172**, unfortunately despite multiple attempts at separation using column chromatography the desired product could not be isolated.



Scheme 3.10: Attempted expansion to incorporate tetrafluoropyridyl group to an amino acid. There was NMR and mass spectrometry evidence of the desired product, but the activated ester could not be isolated.

The ^{19}F NMR spectroscopy evidence fully supports partial conversion to the product **172** as *in-situ* monitoring showed new peaks, however, there were two sets of new peaks very close together which may demonstrate a possibly competing reaction (-88.52, -90.03, -152.01 and -152.53 ppm). Alternatively, these peaks may represent different rotamers as different conformations of the ester or carbamate are possible.

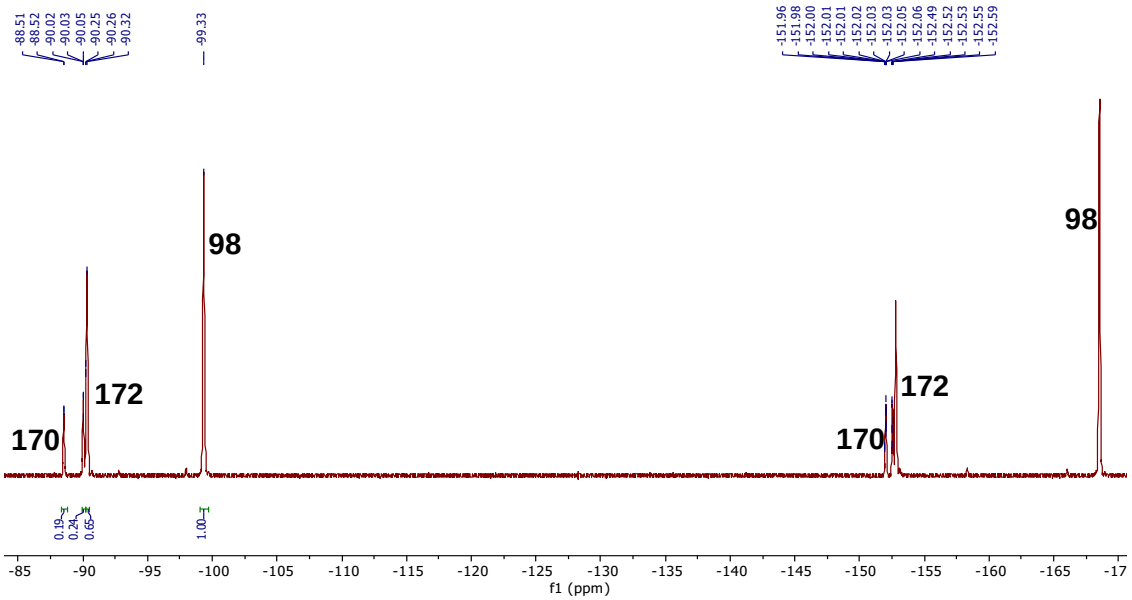
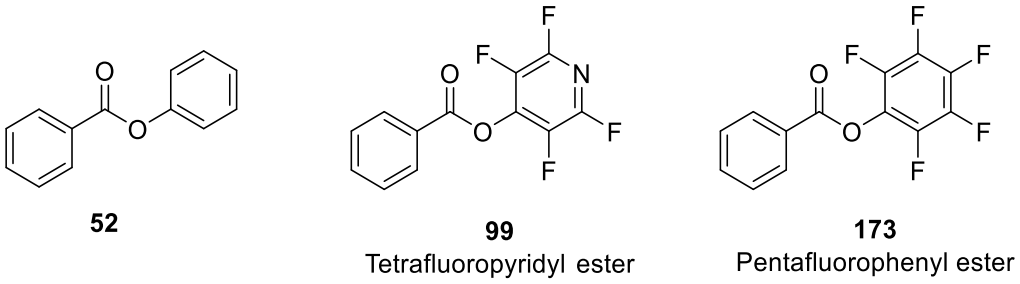


Figure 3.5: *In situ* monitoring when using Boc-glycine as the acid substrate.

Significant formation of **98** was also evident, which is expected given the proposed mechanism (-99.33 and -168.60 ppm). Mass spectrometry analysis also supported the formation of **172**, and it is unclear why the amino acid esters themselves could not be isolated. It is hypothesised that this problem could be due to the instability of the ester when subjected to chromatography on acidic silica media.

3.4 Computational Calculations

To further understand the reactivity of tetrafluoropyridin-4-yl esters a series of substitution reactions were trialled. It was decided that probing the reactivity of tetrafluoropyridyl esters would shed light on their overall activity.



52

99
Tetrafluoropyridyl ester

173
Pentafluorophenyl ester

Figure 3.6: Series of esters subject to computation calculations.

It was hypothesised that tetrafluoropyridyl esters may be more reactive than the pentafluorophenyl esters due to the increased electron withdrawal properties of the tetrafluoropyridin-4-yl group caused by the introduction of the ring nitrogen. To lend more evidence to this, computation calculations were conducted (kindly performed by Mr Matthew Smith, Durham University). Firstly, Mulliken charge distribution calculations were conducted to probe the differences in charge on each compound's carbonyl carbon (**99, 52 and 173**) which were relatively small. These calculations did suggest that the pyridyl ester **99** should be more susceptible to nucleophilic attack, albeit only by a very small margin. In addition to charge distribution, further computational work to better understand the potential effects of the leaving group showed that the LUMO energy for the pyridyl ester **99** (**Table 3.2, Entry 3**) was much lower than phenyl benzoate **52** (**Table 3.2, Entry 1**) and pentafluorophenyl benzoate **173** (**Table 3.2, Entry 2**). This effect appeared to be much more significant than the differences in charge distribution due to the magnitude of difference in LUMO energy across the series of compounds described (**Figure 3.7** and **Figure 3.8)**

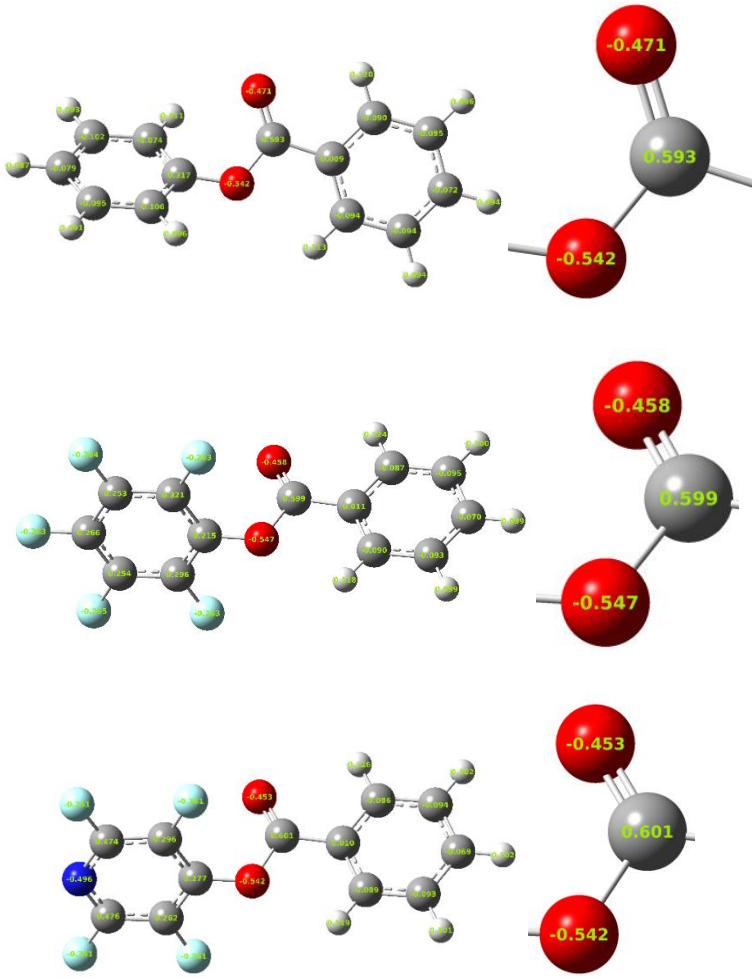


Figure 3.7: Calculations by Mr. Matthew Smith, Durham University. Optimised geometry charge calculation. Phenyl benzoate (**52**) = 0.593, pentafluorophenyl benzoate (**173**) = 0.599 and tetrafluoropyridin-4-yl benzoate (**99**) = 0.601.

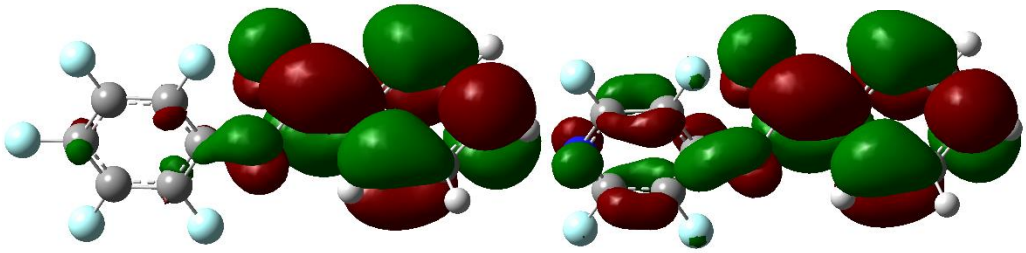


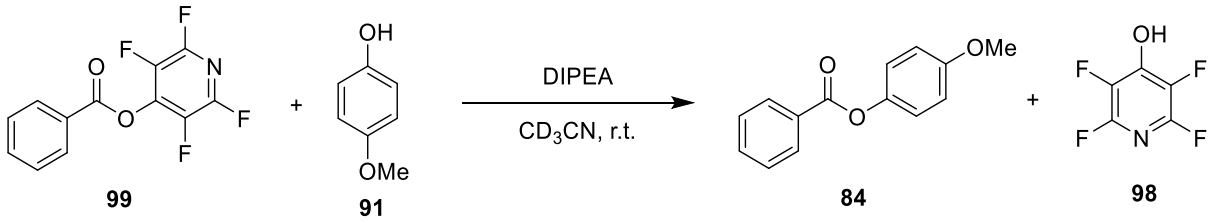
Figure 3.8: Visual representation of pentafluorophenyl benzoate **173** (left) and tetrafluoropyrid4-yl benzoate **99** (right) LUMO's. (Images produced by Mr. Matthew Smith, Durham University.)

Table 3.2: Molecular orbital energy calculation for the LUMO and HOMO of related esters.

Entry	Molecule	LUMO Energy	HOMO Energy
1	Phenyl Benzoate **52**	-0.05152	-0.23948
2	Pentafluorophenyl benzoate **173**	-0.06339	-0.26021
3	Tetrafluoropyrid-4-yl benzoate **99**	-0.07060	-0.26167

3.5 Competition Experiments

Informed by the results of the computational calculations, it was considered desirable to lend experimental evidence to the theoretical values. Firstly, the susceptibility of **99** to nucleophiles was tested. To allow for easy reaction monitoring, *in-situ* ^{1}H and ^{19}F NMR spectroscopy was performed. To an NMR tube was added **99** (1 equiv.) and CD_3CN (0.6 mL) and an initial ^{1}H and ^{19}F NMR spectrum taken. After this 4-methoxyphenol **91** (1 equiv.) and DIPEA (1 equiv.) were added and repeated ^{1}H and ^{19}F NMR spectrums were acquired. As was mentioned earlier in this chapter, the methoxy group offers a useful proton NMR handle (**Figure 3.9**) and hence **91** was selected as the nucleophile here (**Scheme 3.11**).



Scheme 3.11: Nucleophilic susceptibility testing reaction of tetrafluoropyridyl ester **98** with a phenoxide anion.

^{1}H NMR spectroscopy afforded a good description of the reaction process (**Figure 3.8**). Two different O-$\underline{CH_3}$ environments were observed. One at 3.7 ppm which shrunk as **91** was consumed and one the peak at 3.8 ppm which grew as the 4-methoxyphenyl benzoate was formed. This change in environments of the methoxy-groups was caused by esterification and the peaks correspond to **91** and **84**. The aromatic region also saw significant change. As **91** was consumed the peaks at 6.8 ppm disappeared, accompanied by growth of new peaks at 7.0 and 7.2 ppm which belonged to the aromatic groups in **84**. Significant shift in the benzoic

acid protons was also evident with the expected growth of peaks belonging to **84** and decrease in **99** peaks.

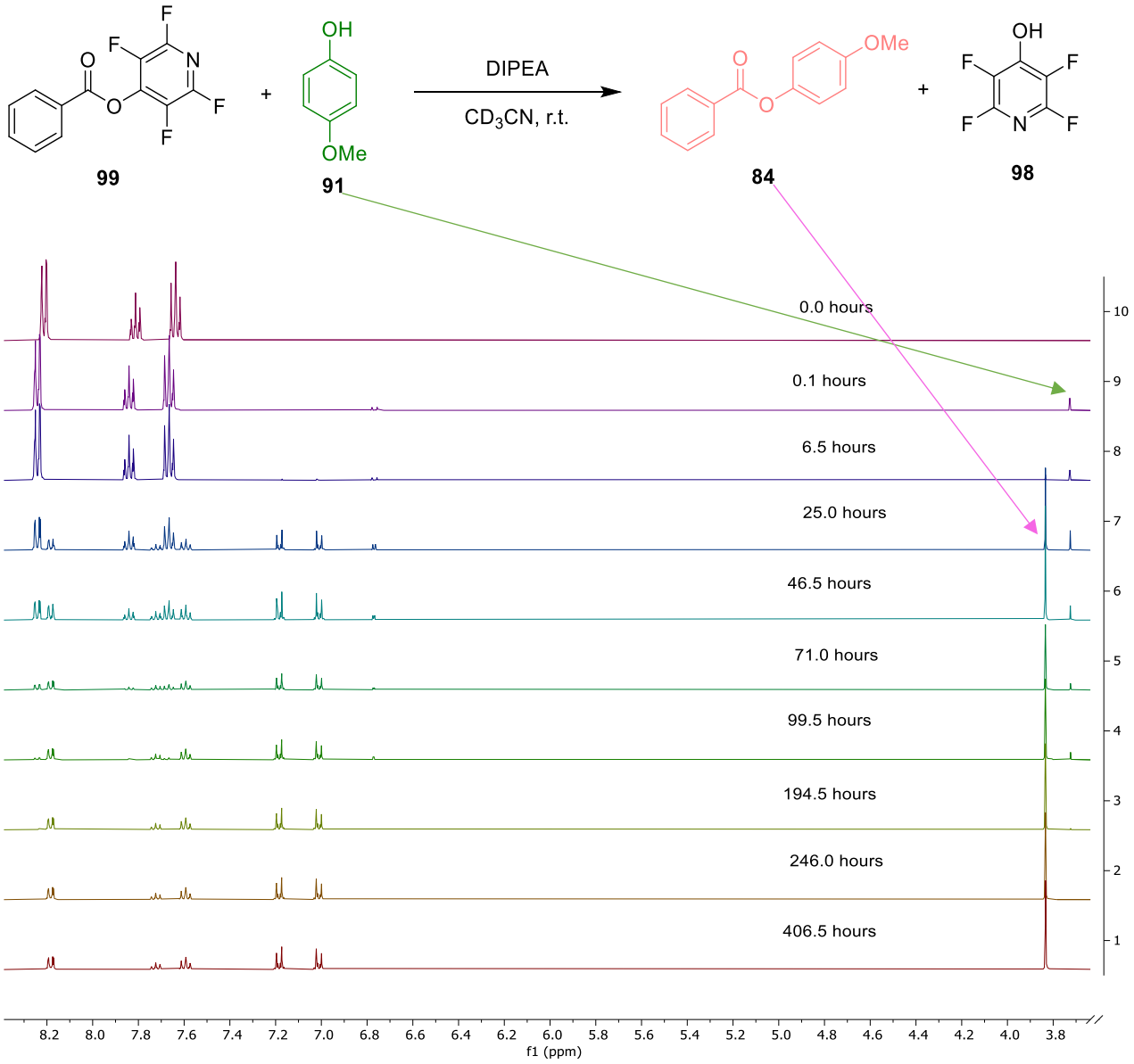


Figure 3.9: ^{1}H NMR spectroscopy reaction monitoring experiment of **Scheme 3.11.**

The observations discussed regarding **Figure 3.9** are also supported by *in-situ* ^{19}F NMR spectroscopy monitoring (**Figure 3.10**). Formation of TFPO (**98**) was evident at 25 hours which coincides with the change in the **91** environments in the ^{1}H NMR spectrum. The production of **98** as a by-product was expected as transesterification occurs.

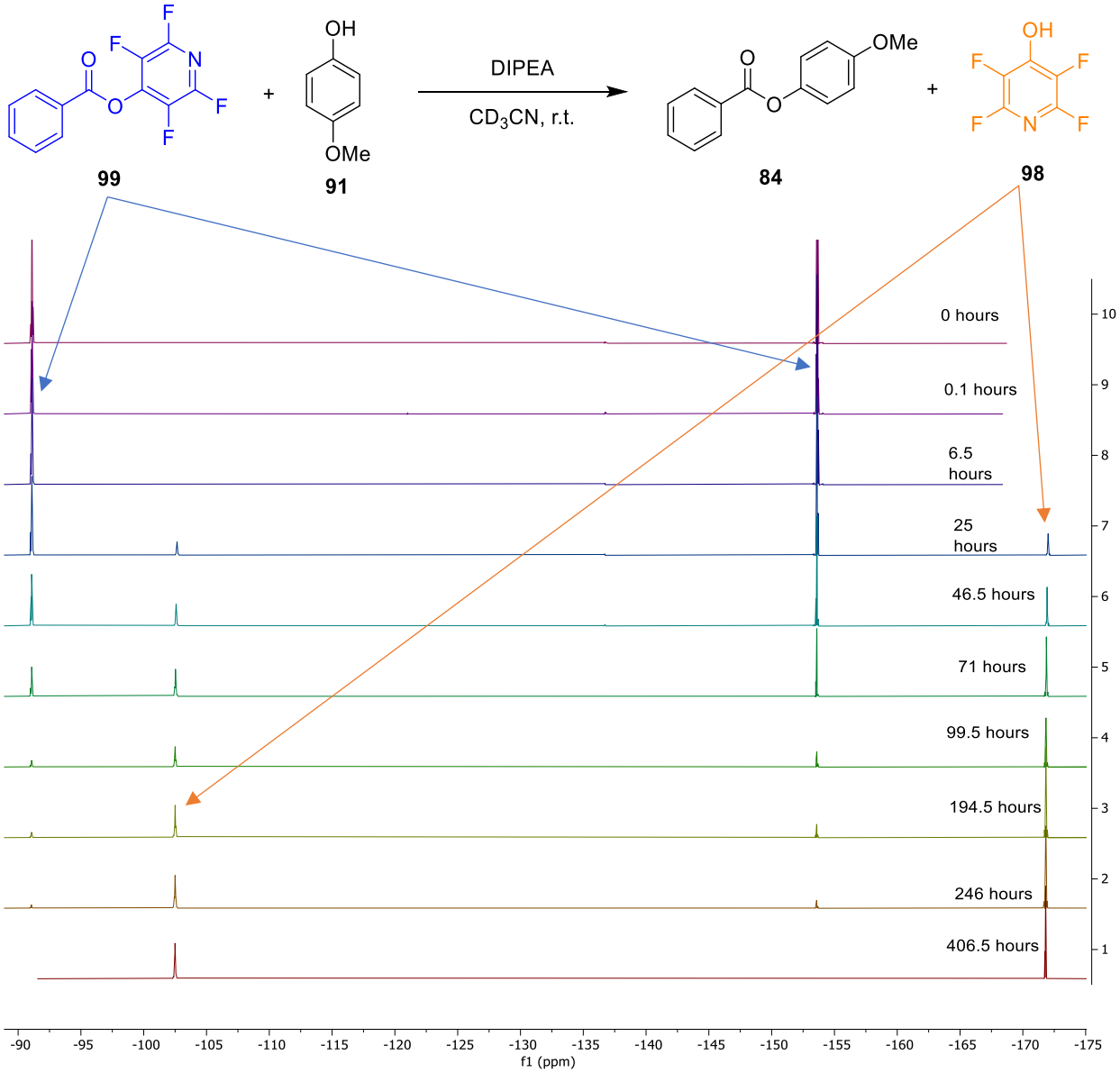


Figure 3.10: ^{19}F NMR spectroscopy reaction monitoring experiment of **Scheme 3.11**.

Significant conversion to the ester product **84** was observed by the 99.5-hour mark. From the ^{19}F NMR analysis if could be seen that there was still a small amount of **99** visible after 246 hours. The final consumption of **99** appears to have occurred sometime before the 406.5-hour interval. It should be noted that the time taken for complete conversion may not be completely indicative of the kinetics of the reaction as the competition reactions were performed at room temperature, in an NMR tube with no stirring.

After demonstrating that **99** was indeed susceptible to nucleophilic attack it was decided to perform a competition experiment between **99** and a structurally similar perfluorinated ester

(**173**) (**Figure 11**). This competition experiment was carried out to study the relative reactivities. To conduct this study **99** was mixed with **173** in a 1:1 ratio which was followed by the addition of 1 equiv. of **91**.

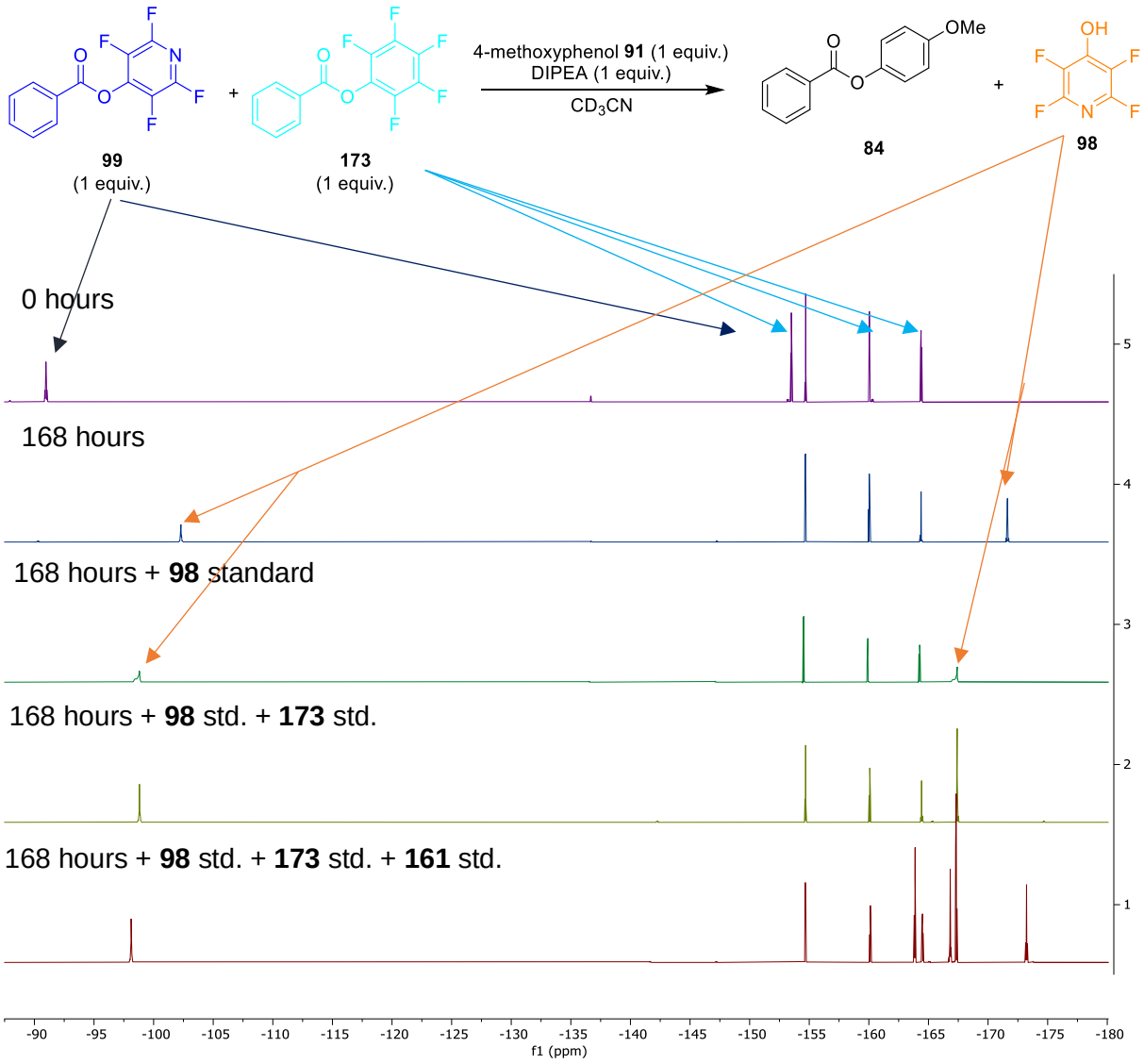


Figure 3.11: ^{19}F NMR spectroscopic tracking of the competition experiment from **Scheme 3.12.**

Similarly, to the previous reaction monitoring, a ^{19}F NMR spectrum of **99 and 173** (1 equiv.) in CD_3CN (0.6 mL) was first obtained as a reference. The peak patterns when **99 and 173** were as expected (**Figure 3.11**, Spectra 5). Five distinct peaks corresponding to the five different fluorine environments present in the solution were observed (^{19}F NMR spectroscopy shifts given in **Figure 11**). The ^{19}F NMR spectroscopy peaks were chosen as their unique splitting patterns assigning their identity easy and straightforward.

Following this DIPEA (1 equiv.) and **91** (1 equiv.) were added and further spectra collected at various time points. The NMR tube was then left for one week at room temperature. Upon analysing the reaction after seven days there was a significant change in some of the ^{19}F NMR environments (**Figure 3.11**, spectra 4) the pattern being visibly different. Observing the shifts in two of the peaks indicated a change in the environment of the fluoropyridyl ester **99.** To check whether the formation of TFPO (**98**) by-product had been the result of nucleophilic attack or potential hydrolysis of **99**, ^{1}H NMR spectroscopy was performed which confirmed only one methyl peak belonging to the methoxy group of **84** was present. Mass spectrometry confirmed the expected products, **98** (*m/z* = 166.2 in negative mode) and for **84**, the expected product (*m/z* = 229.4).

Unfortunately, there was operator error in running this analysis and $CDCl_3$ was selected as the solvent rather than the actual reaction solvent CD_3CN. This had the undesirable effect of shifting the NMR signals in the spectra. To allow for spectrum alignment, the peaks of the pentafluorophenyl (**161**) ester were referenced instead (**Figure 3.11**) as during the doping experiments discussed later in this section, it was confirmed that **173** was not consumed during this reaction monitoring.

To confirm with more evidence that TFPO (**98**) had been generated a spiking experiment was conducted. Doping with a pure sample of **98** saw significant growth in the outer most peaks, indicating that in agreement with mass spectrometry analysis **98** was being generated (**Figure 3.11**, Spectra 3). This somewhat shifted the TFPO peaks however and this is suspected to be down to over concentrating the NMR sample as the peaks also became broader.

An aliquot of the TFPO doped sample was then doped with pure **173** which saw the relative integrals change but no observable new peaks (**Figure 3.11**, Spectra 2), confirming that the remaining peaks must belong to the pentafluorophenyl ester **173**. Had **173** been consumed, the expected by-product would be pentafluorophenol **161**. The aliquot also confirmed that the TFPO peak has shifted, as confirmed by comparing it's unique splitting pattern.

Upon doping the NMR sample with **161** three new fluorine environments were observed at -163, -167 and -174 ppm confirming that no **161** had been generated during this experimentation (**Figure 3.11,** Spectra 1). Doping the sample with **161** slightly shifted the TFPO (**98**) peak to -166 ppm which is likely due to interaction with the newly introduced **161**. The results of the competitions experiment were promising although there was the desire to

repeat them due to errors in solvent assigning, it was considered more pressing to explore the susceptibility of these esters to amine nucleophiles (**Figure 3.12**).

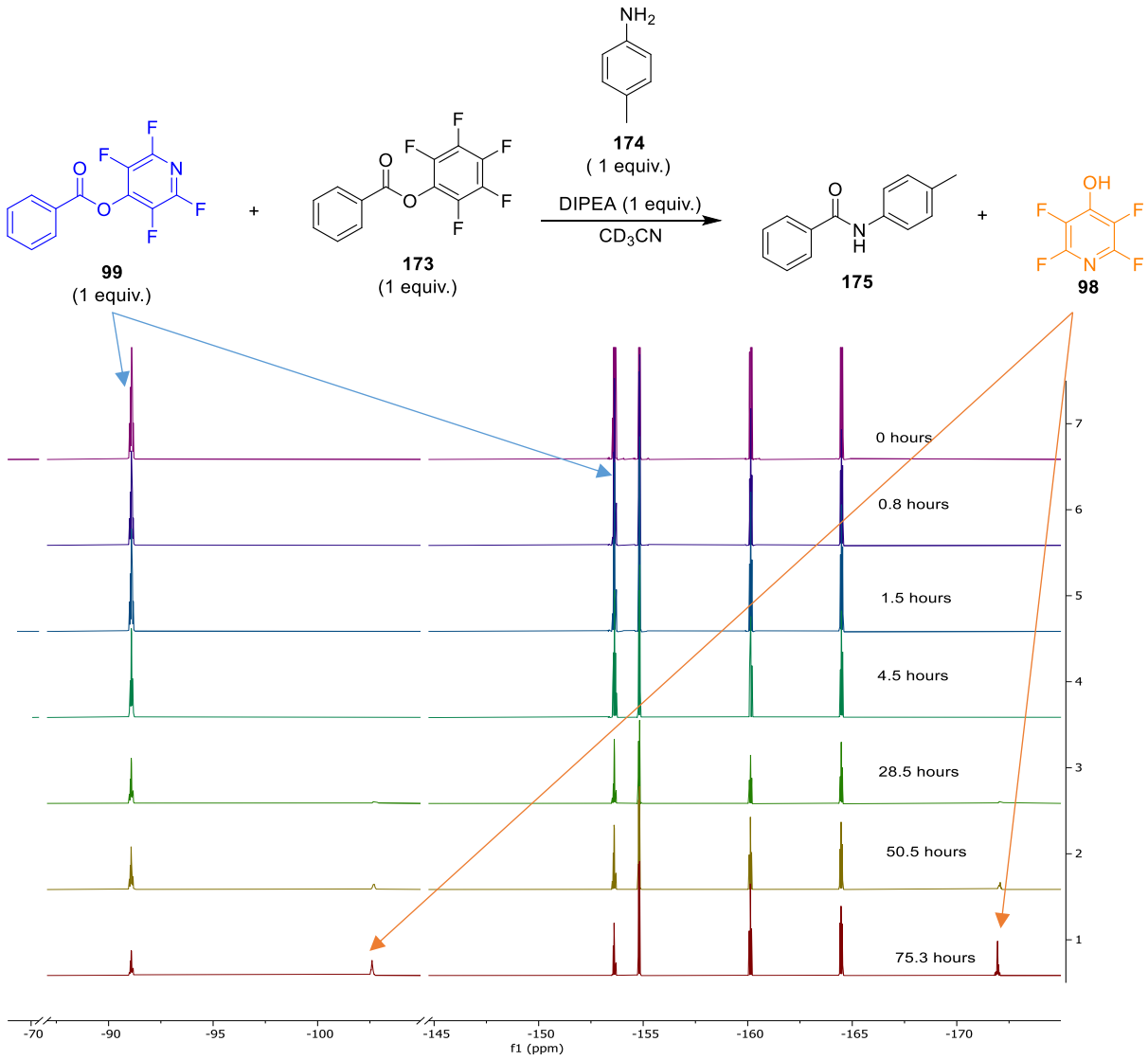


Figure 3.12 Competition experiment between tetarfluoropyridin-4yl benzoate and pentafluorophenyl benzoate with an amine nucelophile (**Scheme 3.13**).

Following the same procedure as the previous competition experiment, ^{19}F NMR spectrums were obtained (**Figure 3.12**). Although the reaction was slow the results looked promising and over the course of several days the reaction was further monitored with ^{19}F NMR spectroscopy. Within 50.5 hours, evidence of formation of TFPO **98** was visible (**Figure 3.12,** Spectra 3). Encouragingly there was no evidence of **161** which supports the hypothesis that the reaction with **99** is more favourable with **174** to produce **175**. By 72 reaction hours, a solid had precipitated in the NMR tube (**Figure 3.12,** Spectra 1). This precipitate was suspected to

be related to the amide product of this reaction **175**, as it had not been observed in the earlier days of reaction monitoring or in previous monitoring experiments. The presence of this precipitate was detrimental to further reaction monitoring as NMR samples only have a tolerance to a small amount of precipitate. Attempts to redissolve the precipitate that had formed with extra $CDCl_3$ failed. It is encouraged that in future work to re-attempt a competition by changing the type of amine nucleophile or the NMR solvent.

3.6 Chapter Summary

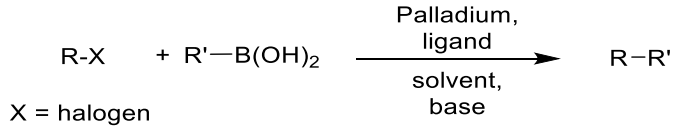
Within this chapter the successful preparation of some novel compounds (**168, 21 and 169**) directly from acyl chlorides has been reported and successfully characterised. Investigations were then undertaken into directly preparing tetrafluoropyridyl esters from carboxylic acids. To that end, a sulfonyl TFPO transfer reagent **165** based upon a corresponding literature example for pentafluorophenol was prepared, which was successfully shown to be capable of preparing a tetrafluoropyridin-4-yl ester **168** directly from the corresponding carboxylic acid. This process was not optimised, and it would be beneficial to explore the reaction conditions used in this route further in the future.

To better understand the possible application of tetrafluoropyridyl esters some reactivity theoretical computational calculations were performed followed by reaction monitoring to determine the differences in reactivity of tetrafluoropyridyl ester **99** and pentafluorophenyl ester **173**. Reactions with an oxygen nucleophile appeared to demonstrate a favourability of attack upon the tetrafluoropyridin-4-yl ester (**Figure 3,11**). Following on from this, the monitoring was then performed using an amine-based nucleophile (**Figure 3.12**). Although this reaction monitoring of susceptibility to amines was unable to produce conclusive results due to the formation of a precipitate hampering the reliability of the data, it still looks very promising that tetrafluoropyridyl ester **99** is more susceptible to nucleophilic substitution than their pentafluorophenyl counterparts **173**. This was evidenced by the formation of TFPO **98** and not pentafluorophenol **161**. This preferential selectivity could be used in several ways, such as building molecules with varying activated ester functionality and selectively substituting at different sites.

4 *In-situ* Acyl Fluoride Suzuki Cross-Couplings

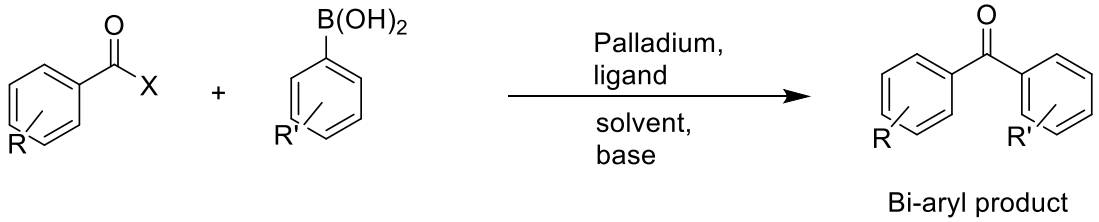
After the completion of **Chapter 2** and informed by the knowledge that the protocol described was a feasible method for the *in-situ* preparation of acyl fluorides, the focus turned to potential areas in which this methodology could be exploited.

Cross-coupling reactions have undoubtedly been one of the biggest breakthroughs in modern organic chemistry. One of the most well-known examples of this class of reactions is the Suzuki-Miyaura coupling first described in the 1970's.[86] This Nobel Prize winning reaction generally involves employing an aryl halide and boronic acid in the presence of a palladium catalyst to generate a new carbon-carbon bond. Perhaps most commonly the reaction is used to access bi-aryl compounds in high yields (**Scheme 4.1**).



Scheme 4.1: Generic Suzuki cross-coupling between organohalide and a boronic acid.

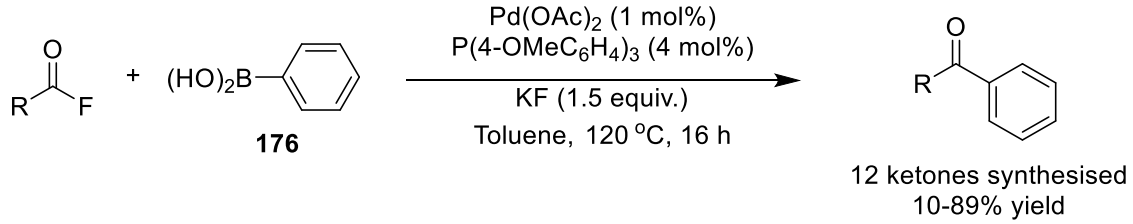
Although not thought of as a classical Suzuki reaction, ketones are one example of compounds readily accessed by applying this cross-coupling reaction (**Scheme 4.2**). Commonly when accessing ketones, acyl chlorides are a popular halide containing coupling partner.



Scheme 4.2: Suzuki-Miyaura coupling accessing ketones from acyl halides and a boronic acid.

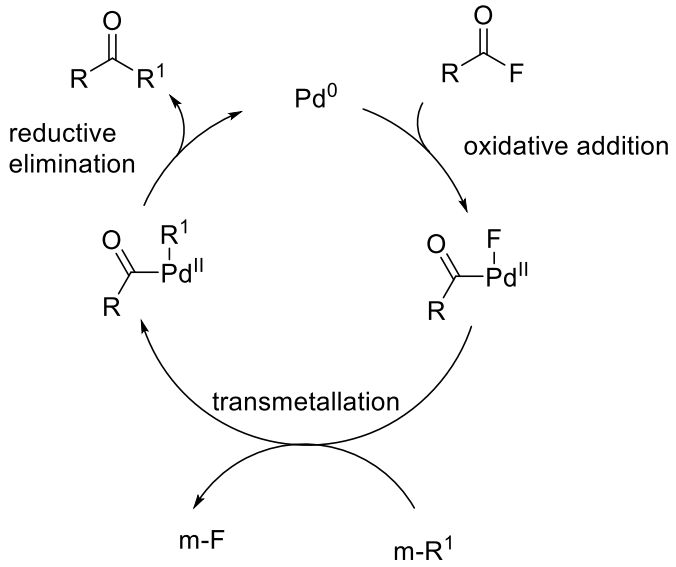
The favourability of Suzuki-Miyaura cross-coupling reaction is highlighted by the over 10,000 citations of the 1996 review into palladium catalysed organoboron couplings published by Miyaura and Suzuki.[86]

Recently the application of acyl fluorides as reagents in cross-couplings have been receiving attention. In 2017 Sakai and co-workers reported the Suzuki cross-coupling reaction between a range of isolated acyl fluorides and boronic acids to generate ketones in good to excellent yields (**Scheme 4.2**).[58]



Scheme 4.2: Scheme depicting of the work of Sakai and co-workers.[58]

The developed reactions allowed for preparation of ketones in good to excellent yields with the best reported isolated yield being 89%. The catalytic cycle proposed by Sakai and co-workers is given in **Scheme 4.3**.



Scheme 4.3: Catalytic cycle for acyl fluoride palladium cross-coupling which was later proposed by Sakai and co-workers.[89]

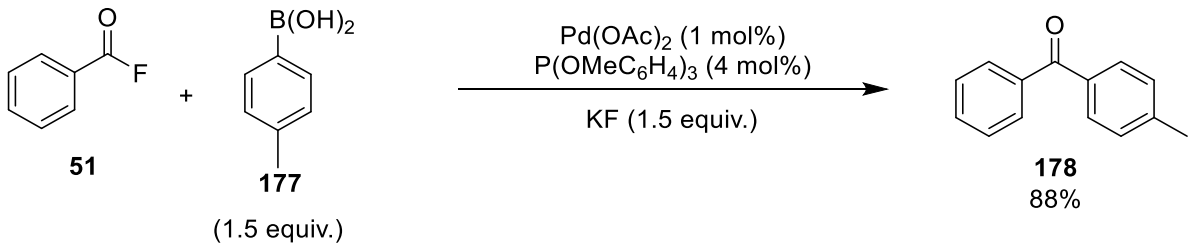
Whilst this reaction manifold is useful, it relies on using isolated acyl fluorides as coupling partners. While some examples, such as benzoyl fluoride are commercially available, most must be synthesised prior to their use in cross-coupling reactions. Isolating acyl fluorides can be complicated due to their inherent reactivity meaning that purification by column chromatography can be difficult. In addition, due to potential hydrolysis it is often the case the

acyl fluorides are not compatible with long term “on the shelf” storage. One way that these limitations could be addressed is to generate the acyl fluoride for cross-coupling *in-situ* thus removing the need for any isolation and storage.

In addition to Suzuki-Miyaura couplings, there are other examples of cross-coupling reactions compatible with acyl fluorides. Nishihara and co-workers in 2022 demonstrated a three-component cross-couplings of alkynes with silanes and acyl fluorides to yield alkenes.[59] Acyl fluorides have also demonstrated good synthetic utility in decarbonylative cyanation which was described by Sakai *et al.* where they achieved excellent yields of cyanide products up to 95%.[111] The acyl fluorides in this case were synthesised from a literature method, again utilising the expensive reagent DAST.

4.1 Preliminary Experimentation and Optimisation

To test the hypothesis that using pentafluoropyridine for *in-situ* generation of acyl fluorides could be compatible with Suzuki cross-coupling reactions it was deemed necessary to repeat a previously reported reaction by Sakai and co-workers. This would allow for benchmarking of *in-situ* acyl fluoride generation in comparison to using an isolated acyl fluoride. Cross-coupling of commercial benzoyl fluoride **51** with the 4-tolylbenzeneboronic acid (**177**) using palladium acetate (1 mol%), $P(OMeC_6H_4)_3$ (4 mol%) and KF successfully generated compound **183** in 88% yield which was in agreement with the literature yield of 89% (**Scheme 4.4**).[58] PPh_3 was also found to be a suitable ligand, offering an isolated yield of 67% (**Table 4.1, Entry 10**).



Scheme 4.4: Repetition of literature conditions described by Sakai and co-workers, offering excellent yields.[58]

With it confirmed that the literature method could be replicated, in the absence of a glovebox, attention turned trying to combine the work of Sakai and co-workers with *in-situ* preparation of acyl fluorides reported by Brittain and Cobb.[1] It was noted that Sakai and co-workers had run

their cross-coupling reactions in toluene. This led to a dilemma as it had been previously found (**Chapter 2**) that toluene was not compatible with PFP *in-situ* acyl fluoride generation. Due to the generation of acyl fluorides requiring MeCN an initial cross-coupling was attempted in this MeCN (**Table 4.1, Entry 1**). This reaction gave rise to the formation of the desired product **178** in a yield of 28%. Although unremarkable compared to the literature, this was encouraging as it was the first demonstration that acyl fluorides prepared from pentafluoropyridine *in situ*, thus using carboxylic acids as viable cross-coupling partners.

Cross-coupling optimisation was then performed. Changing ligands from PPh_3 to SPhos (**Table 4.1 Entry 2**) or tris(2,4,6-trimethoxyphenyl)phosphine (**Table 4.1, Entry 3**) led to no conversion to **178**. Further ligands could have been investigated here, but given the low yield using PPh_3 (**Table 4.1, Entry 1**) which had previously shown good conversion with isolated acyl fluorides,[58] solvent effects were explored instead. It was hypothesised that a mixed solvent system could allow for both *in situ* acyl fluoride generation followed by cross-coupling. To test this acyl fluoride generation was conducted in 2 mL of MeCN, after four hours this was followed the by direct addition of 9 mL of toluene at the same time the other cross-coupling components were added to the reaction mixture (**Table 4.1, Entry 4**). This greatly improved the yield of **178** to 48%. By changing the order again to generating the acyl fluoride separately in a vial and then adding this to an already prepared round bottomed flask of cross-coupling partners the yield increased to 62% (**Table 4.2, Entry 5**).

Table 4.1: Optimisation reactions for palladium cross-couplings

Entry	Acyl Fluoride Solvent MeCN (mL)	Cross-Coupling Solvent Toluene (mL)	Pd Loading (mol%)	Phosphine Ligand	Ligand Loading (mol%)	Yield (%)
1[a]	-	10	5	PPh_3	16	28
2[a]	-	10	5	SPhos	16	-
3[a]	-	10	5	Tris(2,4,6-trimethoxyphenyl)phosphine	16	-
4	2	9	5	PPh_3	16	48
5	2	9	5	PPh_3	16	62
6	0.5	12	5	PPh_3	16	52
7	0.25	20	5	PPh_3	16	38
8	2	9	5	PCy_3	16	60
9[b]	2	9	5	PPh_3	16	49
10[C]	0	11	1	PPh_3	4	67
11[C]	0	11	1	$P(OMeC_6H_4)_3$	4	88
12	2	9	2.7	$P(OMeC_6H_4)_3$	4.5	69
13	2	9	5	$P(OMeC_6H_4)_3$	20	53
14[d]	2	9	5	$P(OMeC_6H_4)_3$	20	50
15	2	9	2.5	$P(OMeC_6H_4)_3$	4	52
16	2	9	1	$P(OMeC_6H_4)_3$	4	49

General conditions using benzoic acid (1 mmol), 4-tolylbenzenboronic acid (1.5 mmol) and KF (1.5 toluene was used as the general cross-coupling solvent except in 1, 2 and 3. Four hours was allowed for activation of acyl fluoride and cross-couplings were left for 16 hours overnight. [a] Acyl fluoride generated first and all reactants successively added to activated mixture. [b] K_2CO_3 used as the base (1.5 mmol). [c] Performed using purchased benzoyl fluoride. [d] Using 3 equiv. of KF.

Further ratios of MeCN to toluene were tested however none showed significant improvement in reaction yield (**Table 4.1, Entries 5-7**). Changing base to K_2CO_3 also did not offer any appreciable improvement in yield giving 49% of the ketone **178** (**Table 4.1, Entry 9**). Several additional ligands had subsequently become available for screening therefore PCy_3 and $P(OMeC_6H_4)$, which were the ligands previously reported in the literature were tested giving 60% and 53% yields respectively (**Table 4.1, Entries 8 and 13**).[58] The results of this ligand variation were unexpected, when $P(OMeC_6H_4)_3$ was used with commercial benzoyl fluoride **51**, 88% yield was observed (**Table 4.1, Entry 11**). Conversely, PPh_3 with commercial **51** had only offered 69% yield (**Table 4.1**, **Entry 10**), a near 20% decrease. The results of the

optimisations led to another dilemma as, $P(OMeC_6H_4)_3$ has offered excellent yields with isolated benzoyl fluorides, but lower than expected during the *in-situ* process. Finally, palladium to ligand ratio was investigated, and an initially promising yield of 69% being obtained using 1:1.6 palladium:ligand loading (**Table 4.1, Entry 12**). Further variation of the ligand loading to palladium (5 mol%) and $P(OMeC_6H_4)_3$ (20 mol%) also did not offer an increase in yield (**Table 4.1, Entry 13**)

With these exploratory works completed and with confirmation that the three literature ligands all offered conversion to **178** the scope of the cross-couplings was investigated. To keep the cross-coupling process as similar as possible to that of the literature which had been demonstrated to work well, $P(OMeC_6H_4)_3$ was chosen as the reaction ligand.[58] The 1:4 ratio of this ligand and pure acyl fluoride has offered the product in an excellent yield (88%, **Table 4.1, Entry 11**) and although the factors for the anomalous result are still poorly understood, the best in-situ yield had also been obtained with this ligand.

4.2 Scope of Cross-couplings

4.2.1 Variation of carboxylic acids

Acyl fluorides can be difficult substrates to handle. For example, not commonly isolated due to their volatility are some furoic acid-based acyl fluorides. The boiling points of these acyl fluorides are particularly low meaning removing solvents in vacuo is challenging. If an *in-situ* generation using PFP could be used, these volatile acyl fluorides would be ideal substrates to give the method a general synthetic utility. Such a method would allow access to generally unused carboxylic acid coupling partners. With these aims in mind, the scope of carboxylic acids was probed.

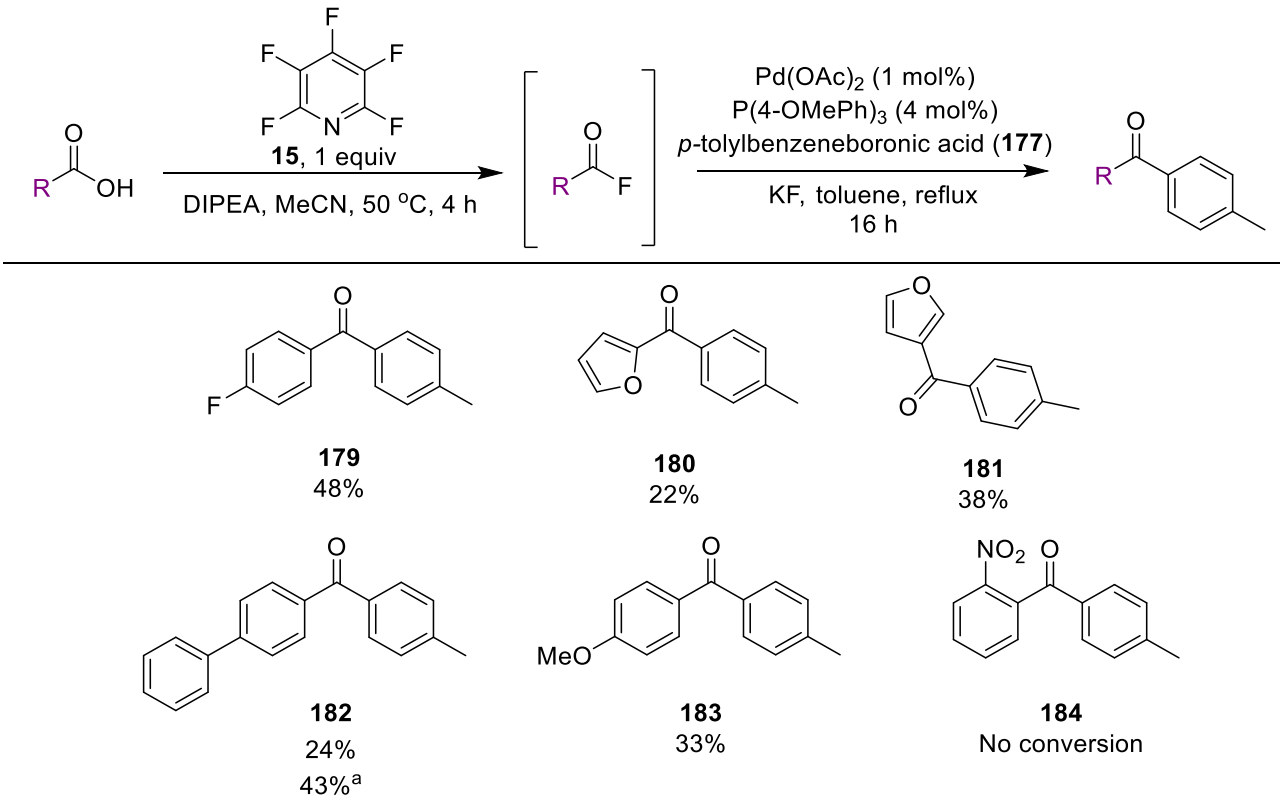


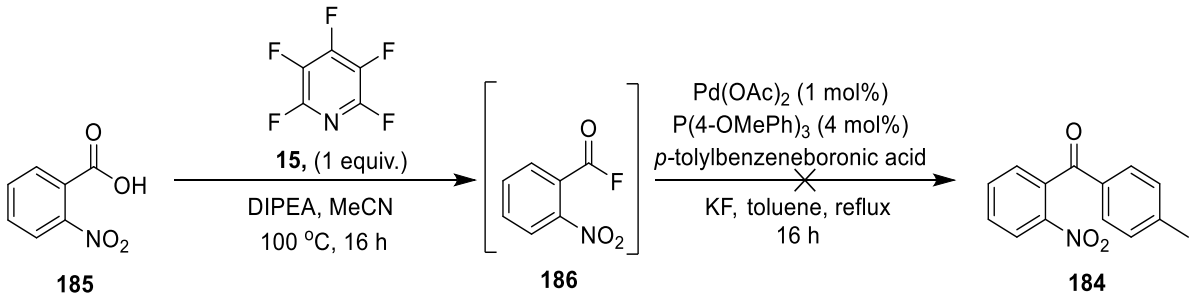
Figure 4.1: *In-situ* palladium cross-couplings with variation of the acid partner. [a] PCy_3 used as the ligand.

Cross coupling with an electron withdrawn carboxylic acid partner (**179**) gave an acceptable yield of 48%, this was promising as previously in the lab the isolation of 4-fluorobenzoyl fluoride was found to be difficult as the compound degraded upon interaction with silica. By using the *in-situ* method the need for re-crystallisation or distillation of the acyl fluoride is avoided. Heteroaromatic carboxylic acids gave low but encouraging yields with 22% and 38% observed for **180** and **181** respectively. In this case it may be a wise choice to revert to lower reaction temperature for the preparation of these acyl fluorides, to prevent possible loss to the gaseous phase before addition to the mixture. The acyl fluoride partner **181**, furan-3-carbonyl fluoride has seen very little use in literature due to this volatility and is usually not isolated with yields typically reported by NMR only.[70, 93] By employing the developed one pot methodology problems associated with the volatility of acyl fluoride can be overcome as there is no necessity for purification of the acyl fluoride intermediate.

Using 4-methoxybenzoic acid, which was known to rapidly convert to the acyl fluoride under PFP conditions only yield 33% of the corresponding ketone **183** which points towards issues with the cross-coupling conditions, rather than acyl fluoride generation. The bi-aryl 4-

phenylbenzoic acid gave a low yield of only of 24% (**182**) when P(OMeC$_6$H$_4$) was used as the ligand. A change of ligand to PCy$_3$ was attempted which offered an increase to 43% yield of **182**. With this considered it would be appropriate for greater ligand screening across all reaction partners to be conducted.

The extremely electron poor 2-nitrobenzoic acid did not give rise to any product following attempted purification **184**. A low yield for **184** was expected but to see no conversion was disappointing. The expected low yield was attributed to the activation time required for acyl fluoride generation. During the optimisation work for *in-situ* formation of acyl fluorides it was noted that the structurally similar 4-nitrobenzoic acid (**96**) did not reach full conversion after 4-hours. This is likely to also be the case for 2-nitrobenzoic acid. This however did not appear to be the influencing factor. Repetition of the reaction where the 2-nitrobenzoyl fluoride was allowed to activate for 24 hours in a sealed pressure tube at 100 °C also did not afford the cross-coupling product. Thus, pointing towards the electron poor nature of the acyl fluoride being the limiting factor in this reaction (**Scheme 4.5**).



Scheme 4.5: 2-nitrobenzoic cross-coupling attempted under elevated pressure tube conditions.

4.2.2 Variation of Boronic acids

Next it was decided to test the scope of boronic acid coupling partners for this reaction (**Figure 4.2**). The electron rich 3-methoxybenzoic acid (**187**) and 2,6-methoxybenzoic acids partners (**188**) giving 34% and 33% respectively. Modification of the boronic acid to 4-biphenylboronic acid saw conversion to the expected ketone product (**190**), albeit only in 23% yield. The bicyclic 1-napthylboronic acid (**191**) saw the best conversions at 48%. Acetophenone (**192**) had a very low yield of 10%.

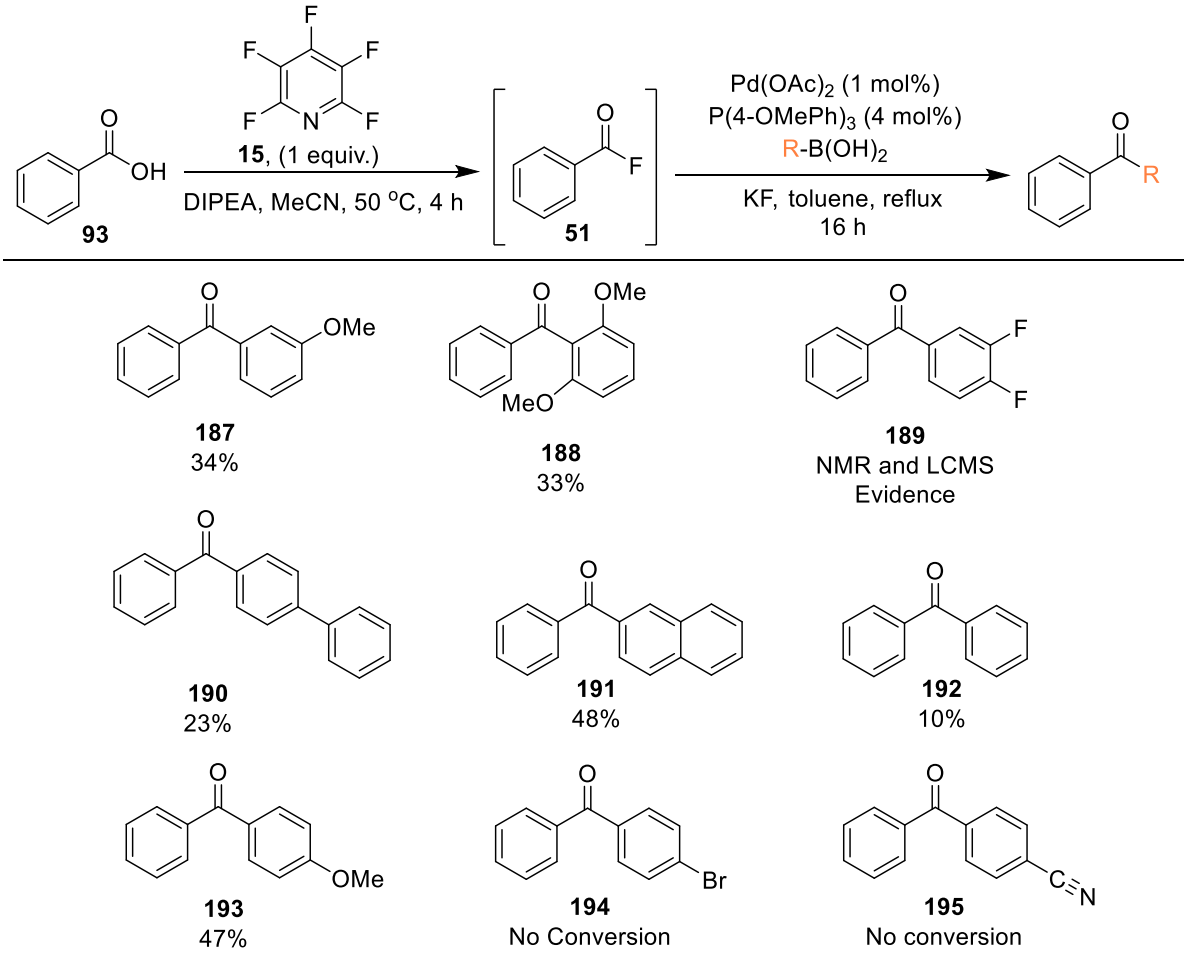
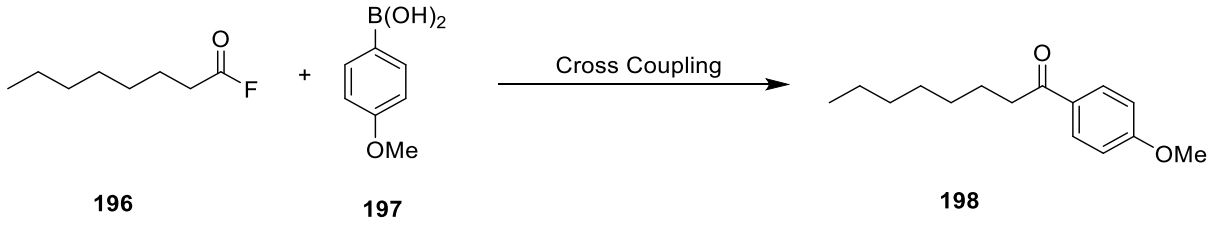


Figure 4.2: *In-situ* palladium cross-couplings with variation of the boronic acid.

The introduction of electron deficient boronic acids were poorly tolerated. It appears the *in-situ* generated cross-coupling methodology is not very tolerant of electron deficient boronic acid partners. The reaction of both 4-cyanophenyl boronic acid (**195**) and 4-bromophenyl boronic acid (**194**) did not give rise to any product. There was a small amount of observable product for **194** which was confirmed by mass spectrometry analysis. These results do follow the general trend reported by Sakai and co-workers.[58] They also experienced a significant drop in yield when electron deficient boronic acids, such as 4-fluoro (44%) and 4-chloro (33%) were used which was down from the previously observed maximum of 90% that they isolated.[58]

4.3 Aliphatic Benzoic Acid Partners

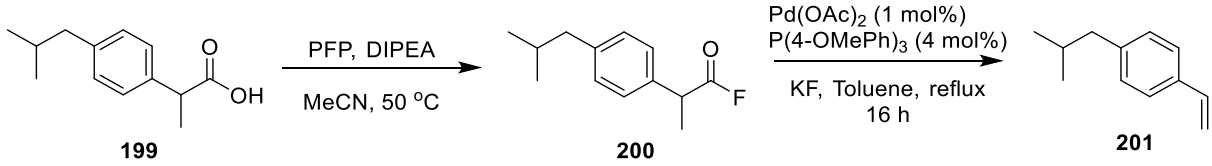
By using an octanoic acid to form octanoyl fluoride it was hoped compatibility with aliphatic acids could be demonstrated. There was evidence which supported successful cross-coupling with 4-methoxybenzene boronic acid, although the product was not isolated due to the complications caused by the lipophilicity of **198**. There was evidence of the product in crude mass spectrometry with the expected $[M+H]^+$ peak of *m/z* =225.6 peak being observed (**Scheme 4.6**).



196 **197** **198**

Scheme 4.6: Cross-coupling of octanoyl fluoride (**196**) with 4-methoxy benzene boronic acid **197**.

Attempting to use ibuprofen (**199**) as an aliphatic acid saw an unexpected result (**Scheme 4.7**). The product of this reaction appeared to contain a double bond by ^{1}H NMR spectroscopy analysis. This was determined to be 1-isobutyl-4-vinylbenzene (**201**) by matching to recorded spectroscopic data with the literature data.[112] There have been no reported preparations of **201** from acyl fluorides in the past but reactions of the aldehyde, potassium carbonate and methyltriphenylphosphonium bromide have yielded this product, this however was a Wittig-type process which probably was not happening here.[112] Instead this is probably a decarboxyltion/decarbonylation but further attempts to elucididate the mechanism were not undertaken during this work.



199 **200** **201**

Scheme 4.7: Styrene (**201**) production from ibuprofen (**199**) under cross-coupling conditions.

4.4 Chapter Summary

Following the work conducted in **Chapter 2** on the *in-situ* generation of acyl fluorides for ester and thioester synthesis it was hypothesised that a similar approach could be used for *in situ* generation of acyl fluorides for Suzuki cross-coupling reactions. If the previously developed approach could be employed this would allow for a wider variety of substrates to be amenable to cross-coupling, as all problems with acyl fluoride generation, such as volatility of **181** could be circumvented.

The initial work of Ogiwara and Sakai was replicated which was able to afford yields in agreement with literature values yielding 88% of **178**.[58] Attempts were then made to optimise an in-situ process utilising a pentafluoropyridine mediated preparation of acyl fluorides. Using just MeCN across the whole process including cross coupling was able to give a yield of 23%. By altering the ratio of solvent and order of addition to performing the acyl fluoride preparation in MeCN then adding to a cross-coupling mix a maximum yield of 69% was obtained during the optimisation process. Yields of 50% of **178** could also be consistently achieved (**Table 4.1**).

Further investigations were then made into carboxylic acid and boronic acid scope (**Figure 4.1** and **4.2**). It was found that electron rich **183** and neutral carboxylic acids **182** were amenable to the process.

Further investigations into electron deficient boronic acids such as **194** and **195** will be required. During these reaction scope explorations, a maximum yield of 48% was observed (**179** and **191**) and this leaves a good scope for further optimisation to the *in-situ* process.

5 Conclusions and Future Work

This thesis centred around reactions associated with pentafluoropyridine. By expanding on previous work within the group, PFP has continued to be explored as an easy route to access *insitu* acyl fluorides. In turn these acyl fluorides have now been successfully coupled with alcohols and thiols to produce esters and thioesters respectively. Optimisation was required which built in an activation window for the preparation of the acyl fluoride, which had an advantageous effect on the yield (**Figure 2.4**). The methodology was found to be tolerant to a wide range of substrates including various aromatic and heteroaromatic compounds. 35 ester examples and 10 thioesters were successfully isolated. Yields of up to 92% (**100**) were obtained for esters and 89% for thioesters (**130**). Generally acceptable yields for a process readily amenable to laboratory synthesis were obtained throughout. Tert-butyl alcohol **106** was not an acceptable coupling partner offering no esterification with in-situ generated acyl fluoride or commercial benzoyl fluoride. Reactions with secondary aliphatic alcohols suffered from a drop in yield such as **121 and 122** but acceptable yields were still obtained of 48% and 46% respectively. The pentafluoropyridine route to esters and thioesters through acyl fluorides overcomes not only some of the common problems with acyl fluoride preparation, such as toxicity of reagents but also the need for acyl chlorides which can require harsh conditions or incompatible reagents. Some of the reported work of **Chapter 2** was also successfully published.[102] Two previously unreported crystal structures were uploaded to the CCDC **136** and **143**.

In the future investigations into esterifications of amino acids should be probed, as it remained unclear why Boc-Alanine, **149** which gave excellent yield in the previous synthesis of amides from acyl fluorides by Brittain *et al.* was not amenable to the esterification here.[1] Furthermore, as described during the *in-situ* amidation work of Brittain *et al*.,[1] throughout these investigations 1.1 equiv. of PFP were used. It was decided this offered the best approach to ensuring the maximum generation of acyl fluorides, as including an excess of fluorinating reagent allows for a small amount of potential hydrolysis to occur, as the slight excess can regenerate a hydrolysed acyl fluoride. Occasionally though tetrafluoropyridyl ethers (**Scheme 2.6**) posed somewhat of a problem; further investigations into different equiv. of pentafluoropyridine may be able to drive the yields even higher, though the yields obtained during this work were still satisfactory.

Finally, the fate of the fluoride ion leaving group has thus far not been clear. It is not believed to be due to the formation of free HF. There was no evidence of etching of glassware throughout the reaction. It is possible the fate is as a HF-DIPEA complex but no peaks

corresponding to this complex were ever observed in ^{19}F NMR spectroscopy. Similar peaks, such as those of HF-triethylamine in $CDCl_3$ have been reported in the literature.[113] The suspected fate of the fluoride is complexation in the acetonitrile solvent and it could be of further interesting study to probe the fate of the fluoride ion. Overall, the main aim of the project discussed in **Chapter 2** was achieved and a wide scope of esters and thioesters were successfully synthesised using the in-situ pentafluoropyridine approach.

In **Chapter 3,** one of the suspected intermediates of this reaction, an "activated ester" was then probed in depth to try and understand if these tetrafluoropyridyl esters could be useful as possible acyl fluoride substitutes. During this probing some novel teatrafluoropyridin-4-yl esters (**168, 21 and 169**) were synthesised and characterised accordingly. The aromatic examples were found to be highly crystalline substances that were stable solids. The tetrafluoropyridine-4-yl esters were readily synthesised from commercially available acyl chlorides and TFPO which itself is readily prepared from pentafluoropyridine and hydroxide base. It would be useful to prepare a library of these compounds as this would allow for the exploration of the effects of different functional groups while simultaneously allowing for the characterisation of a relatively unexplored class of compounds in tandem.

Informed by externally conducted theoretical calculations the reactivity of benzoic acid esters partnered with fluoroaromatic alcohols was assessed by competition experiments. It was found that tetrafluoropyridin-4-yl benzoate (**99**) were more susceptible to oxygen nucleophiles (**Scheme 3.11**) than their corresponding pentafluorophenyl benzoate counterparts (**173**). Following on from this testing it seems appropriate that retesting amine nucleophiles is performed and that sulfur nucleophiles are the subject of future testing. The aim during this work was to prepare some examples of tetrafluoropyridyl esters and attempt to assess comparative reactivity, this was achieved with 4-methoxyphenol. The experimentation then further developed into preparing a novel tetrafluoropyridyl transfer reagent (**170**)**.** While the method from acyl chlorides is useful, a direct method that accessed tetrafluoropyridin-4-yl esters directly from carboxylic acids would be more beneficial, as this would allow access to a greater range of potential esters without the need of first preparing the acyl chloride. As discussed in **Chapter 3**, a sulfonyl reagent (**170**) was prepared in 93% yield in just 30 minutes. This reagent could transfer the tetrafluoropyridyl group directly to carboxylic acids (**Scheme 3.8**). Indeed, **168** was successfully prepared from **170** and 4-methoxybenzoic acid in 23% yield using an unoptimized process.

Unfortunately, there was not time to develop this methodology further but applications of using this reagent on amino acids should be explored. Pentafluorophenyl esters are commercially available as an activating group on amino acids. By employing the developed direct transfer

methodology, the rate comparison of many different pentafluorophenyl and tetrafluoropyridin-4-yl esters could be undertaken, including those not readily available as commercial acyl chlorides. If the reactivity was found to be selective of one over the other this may offer benefits in peptide synthesis, such as increasing reaction rates.

In **Chapter 4**, a non-nucleophilic acyl fluoride process was examined, and the in-situ preparations of acyl fluorides were utilised in Suzuki-Miyaura cross-couplings. This process was based on a previously reported literature example that utilised isolated acyl fluorides.[58] By expanding the in-situ acyl fluoride preparations away from solely nucleophilic processes the uses of the in-situ methodology could be greatly increased. The potential benefit of the PFP mediated process here is the removal of the need to prepare acyl fluorides separately, which eliminates lengthy purifications and removes the associated problems with volatility, hydrolysis, and stability.

Herein 12 in-situ cross-coupling reactions were successfully conducted in less-than-optimal yield ranging between 10 and 48% were observed. While this somewhat achieved the aim of this work there is much more optimisation required. Although 4-fluorobenzoic acid was an acceptable reaction partner **179**, other examined electron deficient carboxylic acids, and hence the corresponding acyl fluorides as well as electron deficient boronic acids appear to be incompatible with the methodology (**184**, **194** and **195**). This observation should be further tested to determine the reaction partner scope of in-situ cross-couplings. This observation maybe down to the inherent reduced activity of electron withdrawn substrates.

For some substrates different ligands offered different isolated yields. The optimisation work could be repeated and investigations into ligand loading ratios and various other ligands is recommended. The effects of solvent and possible interactions of TFPO should also be the subject of future work as by following the literature conditions using isolated acyl fluorides a yield of 88% (**178**) was observed (**Scheme 4.4)**. Cross-couplings with aliphatic acids was not fully assessed. Octanoic acid as the acid basis appeared to give conversion **198**, but the mixture could not be separated in the hexane/ethyl acetate solvent conditions employed (**Scheme 4.6**). Unexpectedly, the acyl fluoride of ibuprofen saw an elimination type reaction and the formation of a new double bond which could also make for interesting future explorations (**Scheme 4.7**). Erroneously a yield was not reported for this reaction.

All the aims of this project were met, pentafluoropyridine has been shown to be an acceptable basis for different organic processes. Explored here was the usefulness of this substrate as an acyl fluoride generation reagent for esterification and thioesterification. Development was made into exploring tetrafluoropyridyl esters which allowed the comparison of susceptibility to nucleophilic attack versus pentafluorophenyl esters. This also led to the preparation of a novel

tetrafluoropyridyl transfer reagent which was a crystalline solid. Finally, an approach which used in-situ acyl fluorides for Suzuki couplings was examined and found to be somewhat feasible. Further optimisation of this process will be required which could hopefully expand the process to the poorly tolerated benzoic acids and boronic acids that were described.

6 Experimental

6.1 General Experimental

General

All starting materials and reagents were purchased from commercial sources and used as received. Acetonitrile and toluene was dried over 4 Å molecular sieves which had been dried under vacuum at 150 °C for 3 h. Column chromatography was carried out on silica purchased from Fluorochem using hexane/ethyl acetate solvent systems or using a Combiflash Nextgen 100 equipped with a silca 4 g silver redisep column using hexane/ethyl acetate solvent systems. Reactions were conducted in air unless otherwise specified.

^{1}H NMR spectra were recorded at 400, 600 MHz or 700 MHz using Bruker Avance III, Varian VNMRS-600 or Varian VNMRS-700 spectrometers respectively. ^{13}C NMR spectra were recorded at 100, 151 and 176 MHz using a Bruker Avance III, Varian VNMRS-600 or Varian VNMRS-700 respectively. ^{19}F NMR spectra were recorded at 376 MHz using a Bruker Avance III spectrometer. All coupling constants are reported in Hertz (Hz). In cases where it was required 2D NMR techniques were used to confirm compound identity. Chemical shifts are reported in ppm and are referenced to residual solvent peaks; $CHCl_3$ (^{1}H 7.26 ppm, ^{13}C 77.0 ppm), CH_3CN (^{1}H 1.94 ppm, ^{13}C ppm) or DMSO (^{1}H 2.50 ppm, ^{13}C 39.5 ppm).

Mass spectra were collected either using ESI-LC, GCMS or ASAP. ESI-LC in MeCN were collected using a Waters TQD mass spectrometer with a Acquity UPLC BEH C18 1.7 µm (2.1 mm x 50 mm). ESI-LC was collected using water containing formic acid (0.1% v/v) and MeCN mixture in a 95:5 to 5:95 gradient over 5 min with a 0.6 mL/min flow rate. GCMS experiments were carried out on a Shimadzu QP2010-Ultra with a Rxi-5Sil MS (0.15 µm x 10 m x 0.15 mm). Helium was employed as the carrier gas (0.41 mL/min). EI is carried at 70ev and the working mass range is 35 – 650 u for all GCMS experiments. ASAP samples were run isothermally at 350 °C vaporising the sample to enable atmospheric pressure chemical ionisation. Accurate mass measurements were processed using Elemental Composition 4.0 embedded within MassLynx 4.1 (Waters Ltd, UK)

6.2 Chapter 2 Experimental

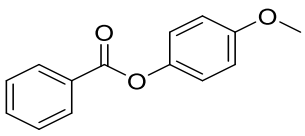
General procedure for the synthesis of esters

To an oven dried glass vial or Radley's carousel tube equipped with a stirrer bar was added carboxylic acid (1.0 equiv.), acetonitrile dried over 4 Å molecular sieves (3 mL), diisopropylethylamine (DIPEA) (2.0 equiv.) and pentafluoropyridine (PFP) (1.1 equiv.). This mixture was allowed to stir at 50 °C for 4 h, at which point the desired alcohol (1.0 equiv.) was added. The mixture was then stirred at 50 °C for 16 h. Following this time, the mixture was concentrated under reduced pressure, the resulting residue was dissolved in a minimum amount of DCM (dichloromethane) and the recovered crude material was purified directly by flash column chromatography which yielded the desired compounds.

General procedure for the synthesis of thioesters

To an oven dried glass vial or Radley's carousel tube equipped with a stirrer bar was added carboxylic acid (1.0 equiv.), acetonitrile dried over 4 Å molecular sieves (3 mL), diisopropylethylamine (DIPEA) (2.0 equiv.) and pentafluoropyridine (1.1 equiv.). This mixture was allowed to stir for a period of 4 h, after which thiol (1.0 equiv.) was added. The mixture was then allowed to stir at 50 °C for 16 h after this time, the mixture was allowed to cool, was concentrated under reduced pressure, and the resulting residue was dissolved in a minimum amount of (DCM) and purified directly by flash column chromatography which yielded the desired compounds**.**

Synthesis of 4-methoxyphenyl benzoate (84)



Synthesised according to the general method for esterification from benzoic acid **93** (0.102 g, 0.84 mmol) and 4-methoxyphenol (0.105 g, 0.86 mmol). The crude material was purified by flash column chromatography (100% hexane to 2.5% EtOAc 97.5% hexane) to give the desired product **84** as a white solid in 71% yield (0.135 g).

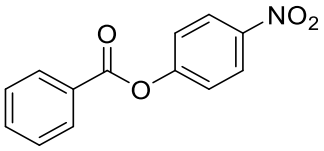
Characterisation data was consistent with previously reported literature values.[114]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.22 (m, 2H), 7.64 (t, *J* = 7.5, 1H), 7.52 (t, *J* = 7.5, 2H), 7.17 (d, *J* = 9.1, 2H), 6.97 (d, *J* = 9.1 , 2H), 3.83 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 157.3, 144.4, 133.5, 130.1, 129.6, 128.6, 122.5, 114.5, 55.6.

LCMS (ESI^+) rt = 2.7 mins, *m/z* = 229.2 $[M+H]^+$

Synthesis of 4-nitrophenyl benzoate (85)



Synthesised according to the general method for esterification from benzoic acid **93** (0.101 g, 0.83 mmol) and 4-nitrophenol (0.112 g, 0.81 mmol). The crude material was purified by flash column chromatography (100% hexane to 2.5% EtOAc 97.5% hexane) to give the desired product **85** as a white solid in 58% yield (0.115 g).

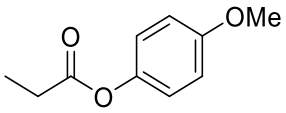
Characterisation data were consistent with previously reported literature values.[115]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.28 (m, 2H), 8.24 – 8.18 (m, 2H), 7.71-7.64 (m, 1H), 7.58 – 7.51 (m, 2H), 7.46 – 7.39 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 155.8, 145.5, 134.4, 130.4, 128.9, 128.6, 125.4, 122.8.

LCMS (ESI^-)- r.t. = 3.8 mins, *m/z* =242.1 $[M]^-$

Synthesis of 4-methoxyphenyl propionate (86)



Synthesised using literature conditions from propionic acid (0.113 g, 1.52 mmol) and 4-methoxyphenol (0.189 g, 1.52 mmol).[1] Purified using column chromatography (100% hexane to 97.5% hexane/2.5% EtOAc). To yield the desired product **86** as a colourless oil in 63% yield (0.173 g).

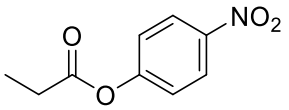
Characterisation data was consistent with previously reported literature values.[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 – 6.96 (m, 2H), 6.93 – 6.85 (m, 2H), 3.80 – 3.73 (m, 3H), 2.56 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 157.2, 144.3, 122.0, 114.4, 55.5, 27.6, 9.1

LCMS (ESI^+) r.t. = 3.0 mins, *m/z* = 181.4 $[M+H]^+$

Synthesis of 4-nitrophenyl propionate (87)



Synthesised using literature conditions from propionic acid (0.111 g, 1.50 mmol) and 4-nitrophenol (0.197 g, 1.42 mmol).[1] Purified using column chromatography (100% hexane to 80% hexane/20% EtOAc). To yield the desired product **87** as a colourless oil in 45% yield (0.124 g).

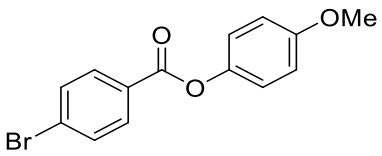
Characterisation data was consistent with previously reported literature values.[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (m, 2H), 7.28 (m, 2H), 2.64 (q, *J* = 7.4 Hz, 2H), 1.28 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 155.6, 145.2, 125.2, 122.5, 27.8, 8.9.

LCMS (ESI^-) r.t. = 3.1 mins, *m/z* = 194.4 $[M+H]^-$

Synthesis of 4-methoxyphenyl 4-bromobenzoate (88)



Synthesised using modified literature conditions from 4-bromobenzoic acid (0.100 g, 0.50 mmol) and 4-methoxyphenol (0.062 g, 0.50 mmol).[1] Purified using manual column chromatography (100% hexane to 97.5% hexane/2.5% EtOAc). To yield the desired product **88** as a colourless oil in 22% yield (0.033 g).

Optimised synthesis of 4-methoxyphenyl 4-bromobenzoate (88)

Synthesised according to the general method for esterification from 4-bromobenzoic acid (0.100 g, 0.50 mmol) and 4-methoxyphenol (0.061 g, 0.50 mmol). The crude material was purified by flash column chromatography (eluted in 100% hexanes) to give the desired product **88** as a white solid in 50% yield (0.075 g).

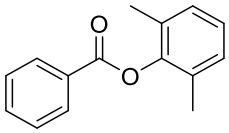
Characterisation data were consistent with previously reported literature values.[116]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.04 (m, 2H), 7.66 – 7.63 (m, 2H), 7.15 – 7.1 (m, 2H), 6.96 – 6.92 (m, 2H), 3.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 157.5, 144.3, 132.0, 131.7, 128.8, 128.6, 122.4, 114.6, 55.7.

LCMS (ESI^+) r.t. = 3.1 mins, *m/z* = 307.12 $[M+H]^+$

Synthesis of 2,6-dimethylphenyl benzoate (100)



Synthesised according to the general method for esterification from benzoic acid **93** (0.099 g, 0.81 mmol) and 2,6-dimethylphenol (0.103 g, 0.84 mmol). The crude material was purified using automated flash column chromatography combiflash (eluted in 100% hexanes) to give the desired product **100** as a clear oil in 92% yield (0.172 g).

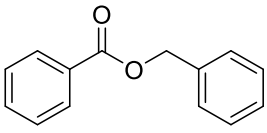
Characterisation data was consistent with previously reported literature values.[115]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.28 (m, 2H), 7.70 – 7.66 (m, 1H), 7.58 – 7.54 (m, 2H), 7.16 – 7.11 (m, 3H), 2.24 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 148.4, 133.7, 130.5, 130.3, 129.4, 128.8, 128.7, 126.0, 16.5.

LCMS (ESI^+) r.t. = 3.1 mins, *m/z* = 227.2 $[M+H]^+$

Synthesis of benzyl benzoate (101)



Synthesised according to the general method for esterification from benzoic acid **93** (0.101 g, 0.83 mmol) and benzyl alcohol (0.090 g, 0.83 mmol). The crude material was purified by flash column chromatography (100% hexane to 2.5% EtOAc 97.5% hexane) to give the desired product **101** as a colourless oil in 72% yield (0.122 g).

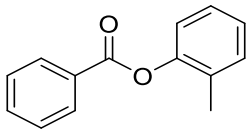
Characterisation data were consistent with previously reported literature values.[117]

^{1}H NMR (599 MHz, $CDCl_3$) δ 8.15-8.12 (m, 2H), 7.60-7.56 (m, 1H), 7.51 – 7.38 (m, 7H), 5.41 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.7, 136.4, 133.3, 130.5, 130.0, 128.9, 128.7, 128.5, 128.5, 67.0.

GCMS (EI^+) r.t. = 4.8 mins, *m/z*= 212.1 $[M]^+$

Synthesis of *o*-tolyl benzoate (102)



Synthesised according to the general method for esterification from benzoic acid **93** (0.101, 0.83 mmol) and *o*-cresol (0.092 g, 0.85 mmol). The crude material was purified using automated flash column chromatography combiflash (100% Hexane for 4 mins to 40% EtOAc 60% Hexane for 10 mins) to give the desired product **102** as a clear oil in 67% yield (0.116 g).

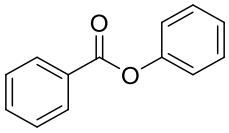
Characterisation data were consistent with previously reported literature values.[118]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.27 (m, 2H), 7.68 – 7.66 (m, 1H), 7.58 – 7.54 (m, 2H), 7.33 – 7.18 (m, 4H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 149.6, 133.7, 131.3, 130.4, 130.2, 129.6, 128.7, 127.1, 126.2, 122.1, 16.3.

LCMS (ESI^+) r.t. = 2.9 mins, *m/z* =213.3 $[M+H]^+$

Synthesis of phenyl benzoate (52)



Synthesised according to the general method for esterification from benzoic acid **93** (0.100 g, 0.82 mmol) and phenol (0.082 g, 0.87 mmol). The crude material was purified by flash column chromatography (100% hexane to 5% EtOAc 95% hexane) to give the desired product **52** as a white solid 80% yield (0.130 g).

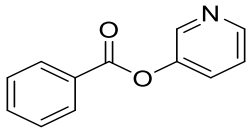
Characterisation data were consistent with previously reported literature values.[117]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.26 (m, 2H), 7.71 – 7.66 (m, 1H), 7.59-7.54 (m, 2H), 7.51 – 7.46 (m, 2H), 7.35 – 7.26 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 151.1, 133.7, 130.3, 130.2, 130.1, 129.7, 129.6, 128.7, 126.0, 121.8.

LCMS (ESI^+) r.t. = 2.8 mins, *m/z* = 199.2 $[M+H]^+$

Synthesis of pyridine-3-yl-benzoate (103)



Synthesised according to the general method for esterification from benzoic acid **93** (0.100 g, 0.82 mmol) and 3-hydroxypyridine (0.081 g, 0.85 mmol). The crude material was purified by flash column chromatography (100% hexane to 5% EtOAc 95% hexane) to give the desired product **103** as an orange solid in 80% yield (0.130 g).

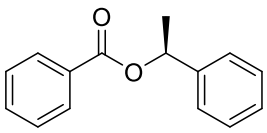
Characterisation data was consistent with previously reported literature.[119]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56-8.55 (m, 1H), 8.54 (dd, *J* = 4.8, 1.4, 1H), 8.24 – 8.18 (m, 2H), 7.69 – 7.64 (m, 1H), 7.62 (ddd, *J* = 8.3, 2.7, 1.4, 1H), 7.53 – 7.48 (m, 2H), 7.36 (ddd, *J* = 8.3, 4.8, 0.7, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 147.6, 147.0, 143.6, 134.0, 130.3, 129.4, 128.8, 128.7, 124.0.

LCMS (ESI^+) r.t. = 2.5 mins, *m/z* = 200.1 $[M+H]^+$

Synthesis of (S)-1-phenylethyl benzoate (104)



Synthesised according to the general method for esterification from benzoic acid **93** (0.103 g, 0.84 mmol) and (*S*)-(-)-1-phenylethanol (0.102 g, 0.83 mmol). Purified using automated

column chromatography combiflash (eluted in 100% hexanes) to give the desired product **104** as a clear oil in 48% yield (0.091 g).

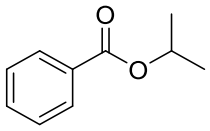
Characterisation data were consistent with previously reported literature values.[120]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.10 (m, 2H), 7.69 – 7.55 (m, 1H), 7.49 – 7.43 (m, 4H), 7.42 – 7.37 (m, 2H), 7.35 – 7.30 (m, 1H), 6.16 (q, *J* = 6.6, 1H), 1.70 (d, *J* = 6.6, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 141.8, 133.0, 130.6, 129.7, 128.6, 128.4, 127.9, 126.1, 73.0, 22.5.

GCMS (EI^+) r.t. = 4.8 mins, *m/z* =226.2 $[M]^+$

Synthesis of isopropyl benzoate (105)



Synthesised according to the general method for esterification from benzoic acid **93** (0.105 g, 0.86 mmol) and isopropanol (0.057 g, 0.095 mmol). The crude material was purified by automated flash column chromatography combiflash (eluted in 100% hexanes) to give the desired product **105** as a colourless oil in 41% yield (0.055 g).

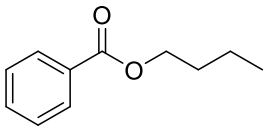
Characterisation data was consistent with previously reported literature values.[121]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.03 (m, 2H), 7.56 – 7.52 (m, 1H), 7.43 (m, 2H), 5.26 (hept, *J* = 6.3, 1H), 1.37 (d, *J* = 6.3, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 132.8, 131.0, 129.6, 128.4, 68.4, 22.0.

GCMS (EI^+) r.t = 3.3 mins, *m/z* = 164.1 $[M]^+$

Synthesis of butyl benzoate (107)



Synthesised according to the general method for esterification from benzoic acid **93** (0.100 g, 0.82 mmol) and butan-1-ol (0.067 g, 0.90 mmol). The crude material was purified by flash

column chromatography (100% hexane to 5% EtOAc 95% hexane) to give the desired product **107** as a clear oil in 64% yield (0.093 g).

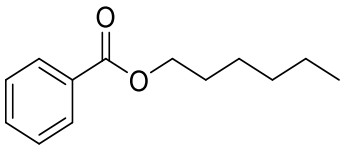
Characterisation data was consistent with previously reported literature values.[122]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.03 (m, 2H), 7.56 – 7.52 (m, 1H), 7.45 – 7.40 (m, 2H), 4.32 (t, *J* = 6.6, 2H), 1.79 – 1.71 (m, 2H), 1.53 – 1.43 (m, 2H), 0.98 (t, *J* = 7.4, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 132.8, 130.5, 129.5, 128.3, 64.8, 30.8, 19.3, 13.8.

LCMS (ESI^+) r.t. = 2.9 mins, *m/z* = 179.2 $[M+H]^+$

Synthesis of hexyl benzoate (108)



0.1 g scale: Synthesised according to the general method for esterification from benzoic acid **93** (0.100 g, 0.82 mmol) and hexan-1-ol (0.089 g, 0.87 mmol). The crude material was purified by automated flash column chromatography (100% hexanes) to give the desired product **108** as a clear oil in 78% yield (0.131 g).

1 g scale (**Scheme 2.10**): Synthesised according to the general method for esterification from benzoic acid **93** (1.001 g, 8.19 mmol) and hexan-1-ol (0.871 g, 8.52 mmol). The crude material was purified by automated flash column chromatography (100% hexanes) to give the desired product **108** as a clear oil in 61% yield (1.031 g).

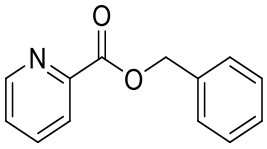
Characterisation data was consistent with reported literature.[122]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.01 (m, 2H), 7.58 – 7.49 (m, 1H), 7.48 – 7.36 (m, 2H), 4.31 (t, *J* = 6.7, 2H), 1.76 (dq, *J* = 8.0, 6.7, 2H), 1.53 – 1.37 (m, 2H), 1.40 – 1.29 (m, 4H), 0.97 – 0.85 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 132.8, 130.6, 129.6, 128.4, 65.2, 31.5, 28.8, 25.8, 22.6, 14.1.

LCMS (ESI^+) r.t. = 3.4 mins, *m/z* = 207.3 $[M+H]^+$

Synthesis of Benzyl picolinate (109)



Synthesised according to the general method for esterification from picolinic acid (0.105 g, 0.85 mmol) and benzyl alcohol (0.88 g, 0.81 mmol). Purified using automated column chromatography combiflash (100% Hexane to 60% Hexane 40% EtOAc gradient) to give the desired product **109** as a red coloured oil in 68% yield (0.118 g)

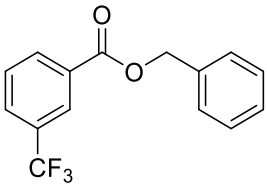
Characterisation data were consistent with previously reported literature values.[120]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (ddd, *J* = 4.8, 1.8, 0.9, 1H), 8.10 (dt, *J* = 7.9, 1.1, 1H), 7.78 (td, *J* = 7.8, 1.8, 1H), 7.50 – 7.26 (m, 6H), 5.44 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 149.9, 147.9, 137.0, 135.6, 128.6, 128.5, 128.4, 126.9, 125.2, 67.4.

GCMS (EI^+) r.t. = 4.9 mins, *m/z* 213.1 $[M]^+$

Synthesis of benzyl 3-(trifluoromethyl)benzoate (110)



Synthesised according to the general method for esterification from 3-(trifluoromethyl)benzoic acid (0.105 g, 0.55 mmol) and benzyl alcohol (0.064 g, 0.59 mmol). Purified using automated flash column chromatography combiflash (eluted in 100% Hexane) to give the desired product **110** as a colourless oil in 55% yield (0.085 g).

Characterisation data were consistent with previously reported literature values.[123]

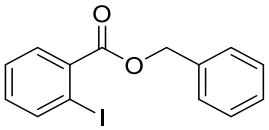
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (app s, 1H), 8.31 – 8.24 (m, 1H), 7.82 (m, 1H), 7.59 (tt, *J* = 7.8, 0.8, 1H), 7.54 – 7.33 (m, 5H), 5.42 (s, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.75 (s, 3F).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 135.7, 133.0 (m), 131.2 (q, *J* = 33.0), 129.7 (q, *J* = 3.8), 129.2, 128.8, 128.6, 128.5, 126.7 (q, *J* = 3.8), 125.1, 122.4, 67.4.

GCMS (EI^+) r.t = 4.6 mins, *m/z* = 280.12 $[M]^+$

Synthesis of benzyl 2-iodobenzoate (111)



Synthesised according to the general method for esterification from 2-iodobenzoic acid (0.100 g, 0.40 mmol) and benzyl alcohol (0.052 g, 0.48 mmol). Purified using automated flash column chromatography combiflash (eluted in 100% hexanes) to give the desired product **111** as a colourless oil in 57% yield (0.077 g).

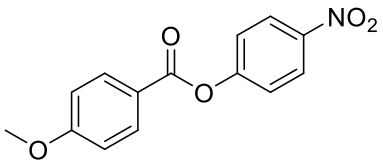
Characterisation data were consistent with previously reported literature values.[124]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.9, 1.2, 1H), 7.82 (dt, *J* = 7.9, 1.5, 1H), 7.50 – 7.48 (m, 2H), 7.43 – 7.36 (m, 4H), 7.14 (td, *J* = 7.7, 1.7, 1H), 5.39 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 141.4, 135.5, 135.0, 132.8, 131.1, 128.7, 128.6, 128.5, 128.0, 94.3, 67.5.

GCMS (EI^+) r.t. = 5.5 mins, *m/z* = 338.1 $[M]^+$

Synthesis of 4-nitrophenyl 4-methoxybenzoate (112)



Synthesised according to the general method for esterification from 4-methoxybenzoic acid (0.100 g, 0.66 mmol) and 4-nitrophenol (0.096 g, 0.66 mmol). Purified using automated flash column chromatography combiflash (100% Hexane for 6 mins to 50% Hexane 50% EtOAc for 12 mins) to give the desired product **112** as a cream solid in 49% yield (0.089 g).

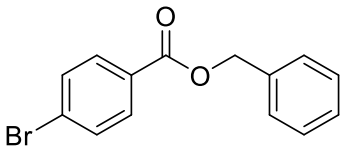
Characterisation data were consistent with previously reported literature values.[125]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (m, 2H), 8.19 – 8.11 (m, 2H), 7.44 – 7.36 (m, 2H), 7.04 – 6.96 (m, 2H), 3.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 164.0, 156.1, 145.4, 132.7, 125.3, 122.8, 120.8, 114.2, 55.7.

GCMS (EI^+) r.t. = 6.0 mins, *m/z* = 135.2 $[M]^+$

Synthesis of benzyl 4-bromobenzoate (113)



Synthesised according to the general method for esterification from 4-bromobenzoic acid **89** (0.104 g, 0.52 mmol) and benzyl alcohol (0.061 g, 0.50 mmol). The crude material was purified by flash column chromatography (100% hexane to 5% EtOAc 95% hexane) to give the desired product **113** as a clear oil in 69% yield (0.100 g).

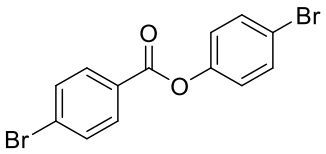
Characterisation data were consistent with previously reported literature values.[126]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 2H), 7.60 – 7.57 (m, 2H), 7.47 – 7.36 (m, 5H), 5.37 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 135.8, 131.8, 131.3, 129.1, 128.7, 128.5, 128.3, 128.3, 67.1.

GCMS (EI^+) r.t. = 5.3 mins, *m/z* = 290.1 $[M]^+$

Synthesis of 4-bromophenyl 4-bromobenzoate (114)



Synthesised according to the general method for esterification from 4-bromobenzoic acid **89** (0.099 g, 0.49 mmol) and 4-bromophenol (0.087 g. 0.50 mmol). Purified using automated flash column chromatography combiflash (eluted in 100% hexanes) to give the product **114** as a white solid in 18% yield (0.031 g).

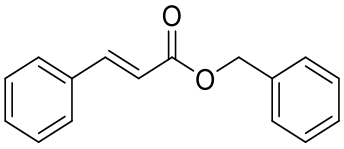
Characterisation data was consistent with previously reported literature values.[127]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.01 (m, 2H), 7.70 – 7.62 (m, 2H), 7.59 – 7.50 (m, 2H), 7.14 – 7.07 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 149.8, 132.6, 132.1, 131.7, 129.1, 128.1, 123.5, 119.2.

GCMS (EI$^+$) r.t.= 5.7 mins, *m/z* = 353.9 [M]$^+$ (2 ×^{79}Br), 355.9 [M]$^+$, 357.9 [M]$^+$ (2 × ^{81}Br)

Synthesis of benzyl cinnamate (115)



Synthesised according to the general method for esterification from cinnamic acid (0.103 g, 0.070 mmol) and benzyl alcohol (0.084 g, 0.77 mmol). Purified using automated flash column chromatography combiflash (eluted in step gradient hexane 100% to hexane 99.2% EtOAc 0.8%) to give the desired product **115** as a colourless oil in 80% yield (0.132 g).

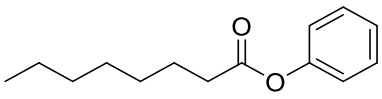
Characterisation data were consistent with previously reported literature values.[128]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 16.0, 1H), 7.55 – 7.53 (m, 2H), 7.46 – 7.38 (m, 8H), 6.52 (d, *J* = 16.0, 1H), 5.28 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 145.3, 136.2, 134.4, 130.4, 129.0, 128.7, 128.4, 128.3, 128.2, 118.0, 66.4.

LCMS (ESI$^+$) r.t. = 3.1 mins, *m/z* = 239.2 [M+H]$^+$

Synthesis of Phenyl Octanoate (116)



Synthesised according to the general method for esterification from octanoic acid (0.099 g, 0.69 mmol) and phenol (0.065 g, 0.69 mmol). The crude material was purified by flash column chromatography (100% hexane to 10% EtOAc 90% hexane) to give the desired product **116** as a clear oil in 79% yield (0.120 g).

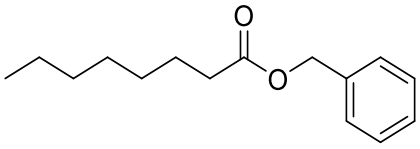
Characterisation data was consistent with previously reported literature values.[129]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H), 7.28 – 7.23 (m, 1H), 7.14 – 7.10 (m, 2H), 2.60 (t, *J* = 7.5, 2H), 1.80 (p, *J* = 7.5, 2H), 1.5 – 1.31 (m, 8H), 0.97 – 0.93 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 150.9, 129.5, 125.8, 121.7, 34.5, 31.8, 29.2, 29.0, 25.0, 22.7, 14.2.

LCMS (ESI^+) r.t. = 3.6 mins, *m/z* = 221.3 $[M+H]^+$

Synthesis of Benzyl Octanoate (117)



Synthesised according to the general method for esterification from octanoic acid (0.099 g, 0.69 mmol) and benzyl alcohol (0.079 g, 0.73 mmol). The crude material was purified by flash column chromatography (100% hexane to 10% EtOAc 90% hexane) to give the desired product **117** as a clear oil in 75% yield (0.129 g).

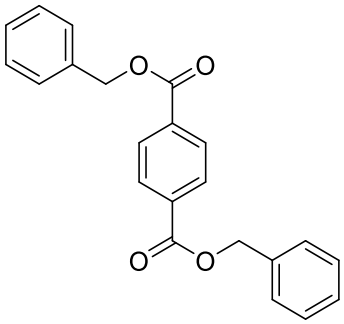
Characterisation data were consistent with previously reported literature values.[130]

^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 5H), 5.13 (s, 2H), 2.37 (t, *J* = 7.5, 2H), 1.72 – 1.62 (m, 2H), 1.37 – 1.23 (m, 8H), 0.91 – 0.87 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 136.2, 128.6, 128.3, 128.2, 66.1, 34.4, 31.8, 29.2, 29.0, 25.1, 22.7, 14.2.

GCMS (EI^+) r.t.= 4.7, *m/z* = 234.2 $[M]^+$

Synthesis of dibenzyl terephthalate (118)



Synthesised according to the general method for esterification from terephtalic acid (0.100 g, 0.60 mmol) and benzyl alcohol (0.130 g, 1.20 mmol). The crude material was purified by automated flash column chromatography combiflash (100% hexanes 4 mins to 20% EtOAc 80% hexanes using a step gradient 9 mins) to give the desired product **118** as a white solid in 40% yield (0.082 g).

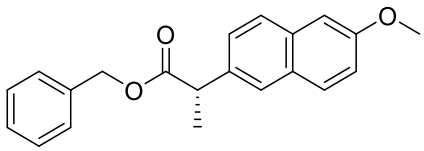
Characterisation data were consistent with previously reported literature value.[131]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 4H), 7.49 – 7.37 (m, 10H), 5.40 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 135.7, 134.1, 129.8, 128.7, 128.5, 128.4, 67.2.

GCMS (EI^+) r.t. = 6.9 mins, *m/z* 346.5 $[M]^+$

Synthesis of benzyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate (119)



Synthesised according to the general method for esterification from naproxen (0.101 g, 0.44 mmol) and benzyl alcohol (0.053 g, 0.49 mmol). Purified using automated flash column chromatography combiflash (step gradient; 100% hexane for 4 mins, 90% Hexane to EtOAc for 4 mins) to yield the product **119** as a colourless oil in 69% yield (0.095 g).

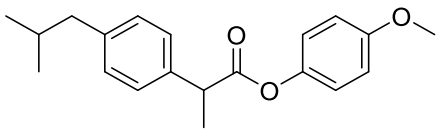
Characterisation data was consistent with previously reported literature values.[132]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 3H), 7.46 (dd, *J* = 8.5, 1.8, 1H), 7.35 – 7.28 (m, 5H), 7.21 – 7.16 (m, 2H), 5.19 (m, 2H), 3.95 (m, 4H), 1.65 (d, *J* = 7.1, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 157.7, 136.1, 135.6, 133.8, 129.4, 129.0, 128.6, 128.2, 128.0, 127.2, 126.4, 126.1, 119.1, 105.6, 66.6, 55.4, 45.5, 18.7.

GCMS (EI^+) r.t. = 6.4 mins, *m/z* = 320 $[M+H]^+$

Synthesis of 4-methoxyphenyl 2-(4-isobutylphenyl)propanoate (120)



Synthesised according to the general method for esterification from ibuprofen (0.100 g, 0.48 mmol) and 4-methoxyphenol (0.061 g, 0.49 mmol). Purified using automated flash column chromatography combiflash (eluted in 100% hexanes) to give the desired product **120** as a clear oil in 63% yield (0.094 g).

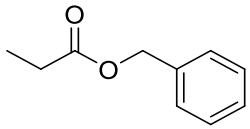
Characterisation data were consistent with previously reported literature values.[133]

^{1}H NMR (400 MHz, CDCl3) δ 7.34 – 7.31 (m, 2H), 7.18 – 7.15 (m, 2H), 6.98 – 6.90 (m, 2H), 6.89 – 6.83 (m, 2H), 3.94 (q, *J* = 7.1, 1H), 3.78 (s, 3H), 2.50 (d, *J* = 7.2, 2H), 1.97 – 1.82 (m, 1H), 1.62 (d, *J* = 7.1, 3H), 0.94 (d, *J* = 6.6, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 157.2, 144.5, 140.8, 137.5, 129.6, 127.3, 122.2, 114.4, 55.6, 45.3, 45.1, 30.3, 22.5, 18.7.

LCMS (ESI^+) r.t = 3.6 mins, *m/z* = 313.4 [M+H]

Synthesis of Benzyl Propionate (121)



Synthesised according to the general method* of esterification from propionic acid (0.100 g, 1.35 mmol) and benzyl alcohol (0.152 g, 1.41 mmol). The crude material was purified using automated flash column chromatography combiflash (eluted in 100% hexanes) to give the desired product **121** as a colourless oil in 48% yield (0.107 g)

Characterisation data was consistent with previously reported literature values. [134]

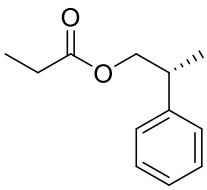
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 5H), 5.13 (s, 2H), 2.40 (q, *J* = 7.6, 2H), 1.18 (t, *J* = 7.6, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 136.2, 128.6, 128.3 (2 × C), 66.2, 27.7, 9.2.

GCMS (EI^+) r.t. = 3.4 mins, *m/z* = 164.1 $[M]^+$

*Performed at 35 °C

Synthesis of 2-phenylpropyl propionate (122)



Synthesised according to the general method* for esterification from propionic acid (0.101 g, 1.36 mmol) and 2-phenylpropanol (0.187 g, 1.37 mmol). The crude material was purified by

flash column chromatography (hexane to 10% EtOAc 90% hexane) to give the desired product **122** as a clear oil in 46% yield (0.120 g).

Characterisation data were consistent with previously reported literature values.[135]

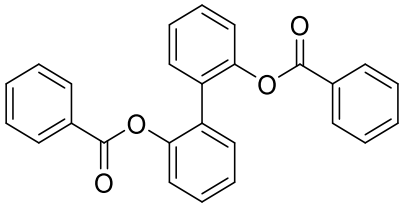
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.9, 6.9, 2H), 7.30 – 7.22 (m, 3H), 4.30 – 4.13 (m, 2H), 3.15 (m, 1H), 2.33 (q, *J* = 7.6, 2H), 1.35 (d, *J* = 7.0, 3H), 1.14 (t, *J* = 7.6, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 143.3, 128.5, 127.4, 126.7, 69.3, 39.0, 27.6, 18.1, 9.2.

GCMS (EI^+) r.t. = 3.8 mins, *m/z* 193.1 $[M]^+$

*Performed at 35°C

Synthesis of [1,1'-biphenyl]-2,2'-diyl dibenzoate (125)



Synthesised according to the general method for esterification from benzoic acid **93** (0.106 g. 0.87 mmol) and 2,2'-biphenol (0.076 g, 0.41 mmol, 0.82 mmol OH equiv.). The crude material was purified by flash column chromatography (100% hexane to 7.5% EtOAc 92.5% hexane) to give the desired product **125** as a viscous clear oil in 85% yield (0.138 g).

^{1}H NMR (599 MHz, $CDCl_3$) δ 8.00-7.98 (m, 2H), 7.57-7.54 (m, 1H), 7.43 – 7.36 (m, 4H), 7.30–7.26 (m, 2H).

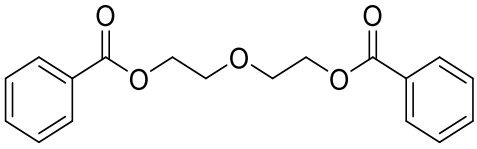
^{13}C NMR (151 MHz, $CDCl_3$) δ 165.0, 148.5, 133.5, 131.3, 130.7, 130.1, 129.5, 129.1, 128.5, 126.0, 122.6.

LCMS (ESI^+) r.t. = 3.3 mins, *m/z* = 395.3 $[M+H]^+$

HRMS – Calculated for $[M+H]^+$ $[C_{26}H_{19}O_4]$ 395.1283, found $[C_{26}H_{19}O_4]$ 395.1281, difference = -0.5 ppm

IR vmax (ATR)/cm^{-1} 3069, 1732, 1601, 1474, 1449, 1248, 1192, 1059, 700

Synthesis of oxybis(ethane-2,1-diyl) dibenzoate (126)



Synthesised according to the general method for esterification from benzoic acid **93** (0.097 g, 0.79 mmol) and diethylene glycol (0.044 g, 0.41 mmol, 0.82 mmol OH equiv.). The crude material was purified by flash column chromatography (100% hexane to 20% EtOAc 80% hexane) to give the desired product **126** as a viscous clear oil in 64% yield (0.082 g).

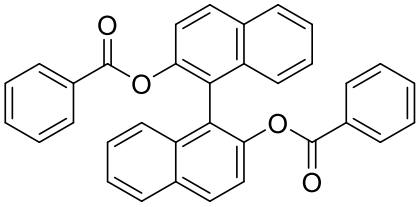
Characterisation data was consistent with previously reported literature values.[136]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.02 (m, 4H), 7.56 – 7.51 (m, 2H), 7.42 – 7.37 (m, 4H), 4.51 – 4.49 (m, 4H), 3.89 – 3.87 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 133.1, 130.1, 129.7, 128.4, 69.3, 64.1.

LCMS (ESI^+): r.t.= 2.7 mins, *m/z* = 315.2 $[M+H]^+$

Synthesis of [1,1'-binaphthalene]-2,2'-diyl dibenzoate (127)



Synthesised according to the general method for esterification from benzoic acid **93** (0.106 g, 0.87 mmol) and [1,1′-binaphthalene]-2,2′-diol (0.120 g, 0.42 mmol, 0.84 OH equiv.). The crude material was purified by flash column chromatography (100% hexane to 7.5% EtOAc 92.5% hexane) to give the desired product **127** as a white solid in 72% yield (0.149 g).

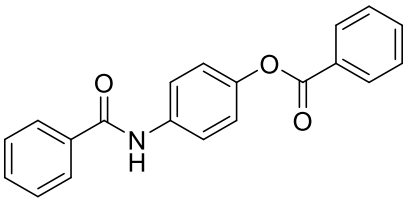
Characterisation data was consistent with previously reported literature values.[137]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.98 (d, *J* = 8.4, 2H), 7.92 (dt, *J* = 8.2, 0.9, 2H), 7.75 – 7.67 (m, 4H), 7.61 (d, *J* = 8.9, 2H), 7.51 – 7.41 (m, 6H), 7.36 (ddd, *J* = 8.7, 6.6, 1.3, 2H), 7.32 – 7.22 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 147.1, 133.5, 133.3, 131.6, 129.9, 129.7, 129.3, 128.3, 128.1, 126.9, 126.2, 125.8, 123.7, 121.9.

LCMS (ESI^+) r.t.= 3.7 mins, *m/z* = 495.3 $[M+H]^+$

Synthesis of 4-benzamidophenyl benzoate (128)



Synthesised according to the general method for esterification from benzoic acid **93** (0.100 g, 0.82 mmol) and 4-aminophenol (0.048 g, 0.44 mmol (0.88 mol equiv.)). During the course of the reaction a white solid precipitated from the reaction mixture. The solid was filtered and then triturated with MeCN (25 mL), hexane (25 mL), ethyl acetate (50 mL) and DCM (50 mL). The solid was allowed to dry and removed from the filter paper to yield **128** as a flaky white solid in 31% yield (0.040 g)

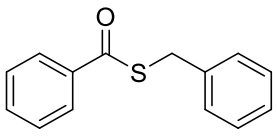
^{1}H NMR (599 MHz, d_6-DMSO) δ 10.38 (s, 1H), 8.16 – 8.14 (m, 2H), 7.99 – 7.97 (m, 2H), 7.88 – 7.86 (m, 2H), 7.76 – 7.74 (m, 1H), 7.63 – 7.59 (m, 3H), 7.54-7.51 (m, 2H), 7.29 – 7.28 (m, 2H).

^{13}C NMR (101 MHz, d_6-DMSO) δ 165.7, 164.8, 146.3, 137.1, 134.9, 134.1, 131.7, 129.8, 129.1, 129.0, 128.5, 127.7, 122.1, 121.4.

ASAP HRMS (ESI$^+$) Calculated for $[M+H]^+$ $C_{20}H_{16}NO_3$ = 318.1130, Found = 318.1108

IR vmax (ATR)/cm^{-1} 3333, 1726, 1653, 1510, 1410, 1314, 1272, 1194, 1065, 703

Synthesis of S-benzyl benzothioate (129)



Synthesised according to the general method for thioesterification from benzoic acid **93** (0.103 g, 0.84 mmol) and benzyl mercaptan (0.107 g, 0.86 mmol). The crude material was purified by flash column chromatography (100% hexane to 2.5% EtOAc 97.5% Hexane) to give the desired product **129** as a clear oil in 89% yield (0.166 g)

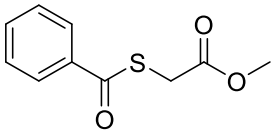
Characterisation data was consistent with previously reported literature values.[138]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.98 (m, 2H), 7.58 (m, 1H), 7.51 – 7.40 (m, 4H), 7.39 – 7.24 (m, app 4H, 3H), 4.37 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 137.6, 136.8, 135.3, 129.1, 129.0, , 128.7, 128.6, 128.3, 127.4, 33.4.

LCMS (ESI^+) r.t. = 3.1 mins, *m/z* = 229.2 $[M+H]^+$

Synthesis of methyl 2-(benzoylthio)acetate (130)



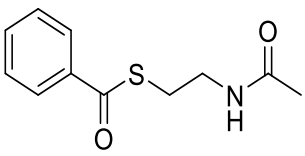
Synthesised according to the general method for thioesterification from benzoic acid **93** (0.107 g, 0.88 mmol) and methyl 2-mercaptoacetate (0.092 g, 0.86 mmol). The crude material was purified by flash column chromatography (100% hexanes to 5% EtOAc 95% hexanes) to give the desired product **130** as a clear oil in 70% yield (0.126 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 2H), 7.58 – 7.54 (m, 1H), 7.45 – 7.41 (m, 2H), 3.87 (s, 2H), 3.74 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1, 169.3, 136.1, 133.9, 128.8, 127.4, 52.9, 31.1.

LCMS (ESI^+) r.t. = 2.6 mins, *m/z* = 211.2 $[M+H]^+$
HRMS Calc $[C_{10}H_{11}O_3S]$ 211.0429, Obtained – $[C_{10}H_{11}O_3S]$ 211.0437 $[M+H]^+$, difference = 5.7 ppm

Synthesis of S-(2-acetamidoethyl) benzothioate (131)



Synthesised according to the general method for esterification from benzoic acid **93** (0.098 g, 0.80 mmol) and *N*-(2-mercaptoethyl)acetamide (0.142 g, 1.20 mmol). The crude material was purified by flash column chromatography (100% hexane to 85% EtOAc 15% hexane) to give the desired product **131** as white solid in 79% yield (0.141 g).

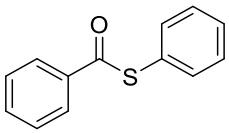
Characterisation data were consistent with previously reported literature values.[139]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 2H), 7.58 – 7.52 (m, 1H), 7.45 – 7.40 (m, 2H), 6.36 (broad s, 1H), 3.49 (q, *J* = 6.3, 2H), 3.19 (t, *J* = 6.5, 2H), 1.94 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 170.6, 136.7, 133.7, 128.7, 127.3, 39.6, 28.6, 23.2.

LCMS (ESI^+) r.t. = 1.7 mins, *m/z* = 246.2 $[M+Na]^+$

Synthesis of S-Phenyl benzothioate (132)



Synthesised according to the general method for thioesterification from benzoic acid **93** (0.100 g, 0.082 mmol) and thiophenol (0.090 g, 0.082 mmol). The crude material was purified using automated column chromatography combiflash (eluted in 100% hexanes) to yield the desired product **132** as cream solid in 52% yield (0.091 g).

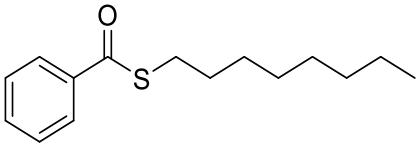
Characterisation data were consistent with previously reported literature.[140]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.04 (m, 2H), 7.64 – 7.60 (m, 1H), 7.57 – 7.45 (m, 7H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 136.7, 135.2, 133.8, 129.6, 129.4, 128.9, 127.6, 127.5.

LCMS (ESI^+) r.t. = 3.2 mins, *m/z* = 215.4 $[M+H]^+$

Synthesis of Octyl Benzothioate (133)



Synthesised according to the general method for thioesterification from benzoic acid **93** (0.100 g, 0.82 mmol) and octanthiol (0.140g, 0.96 mmol). The crude material was purified by flash column chromatography (100% hexane to 5% EtOAc 95% hexane) to give the desired product **133** as a colourless oil in 40% yield (0.081g).

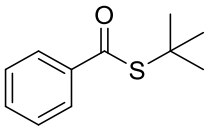
Characterisation data was consistent with previously reported literature.[140]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.96 (m, 2H), 7.55 – 7.53 (m, 1H), 7.45 – 7.41 (m, 2H), 3.09 – 3.05 (m, 2H), 1.69 – 1.63 (m, 2H), 1.44 – 1.27 (m, 9H), 0.90 – 0.87 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 137.4, 133.3, 128.6, 127.3, 31.9, 29.7, 29.3, 29.2, 29.2, 29.1, 22.8, 14.2.

LCMS (ESI$^+$) r.t. = 4.2 mins, *m/z* = 251.3 $[M+H]^+$

Synthesis of *S*-(*tert*-butyl) benzothioate (134)



Synthesised according to the general method for thioesterification from benzoic acid **93** (0.099 g, 0.81 mmol) and 2-methylpropane-2-thiol (0.074 g, 0.82 mmol). The crude material was purified using automated column chromatography (eluted in 100% hexane). The fractions were contaminated with an ether side product, so the fractions were re-purified using manual column chromatography (100% hexane to 90% hexane and 10% EtOAc) to yield the desired product **134** as a colourless oil in 35% yield (0.052 g).

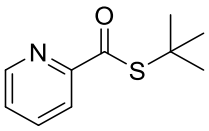
Characterisation data were consistent with previously reported literature values.[141]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.89 (m, 2H), 7.56 – 7.48 (m, 1H), 7.45 – 7.37 (m, 2H), 1.58 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 138.3, 132.9, 128.5, 127.0, 48.2, 30.0.

LCMS (ESI$^+$) r.t = 3.2 mins, *m/z* 195.2 $[M+H]^+$

Synthesis of S-(tert-butyl) pyridine-2-carbothioate (135)



Synthesised according to the general method for thioesterification from 2-picolinic acid (0.100 g, 0.81 mmol) and 2-methylpropane-2-thiol (0.074 g, 0.82 mmol). The crude material was purified using automated column chromatography (product eluted in 100% hexane) to yield the desired product **135** as a white solid in 59% yield (0.093 g)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 4.8, 1.7, 0.9, 1H), 7.94 – 7.88 (m, 1H), 7.83 (td, *J* = 7.7, 1.7, 1H), 7.47 (ddd, *J* = 7.5, 4.8, 1.3, 1H), 1.57 (s, 9H).

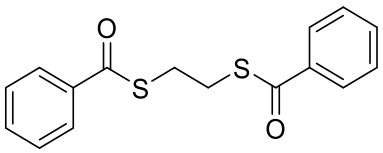
^{13}C NMR (151 MHz, $CDCl_3$) δ 193.8, 153.3, 149.0, 137.4, 127.6, 120.1, 47.1, , 29.9.

LCMS (ESI$^+$) r.t = 2.5 mins, *m/z* 196.2 $[M+H]^+$

HRMS (ESI$^+$) Calculated [$C_{10}H_{14}NOS$] 196.0796, Found [$C_{10}H_{14}NOS$] 196.0794 $[M+H]^+$

IR (cm^{-1}) 2963, 1662, 1453, 1221, 1159, 921, 802, 713, 650, 617

Synthesis of *S,S'*-(ethane-1,2-diyl) dibenzothioate (136)



Synthesised according to the general method for thioesterification from benzoic acid **93** (0.100 g, 0.82 mmol) and ethanedithiol (0.35 mL, 0.41 mmol, 0.82 SH equiv.). The crude material was purified using automated column chromatography (product eluted in 100% hexane) to give the desired product **136** as a cream solid in 37% yield (0.046 g).

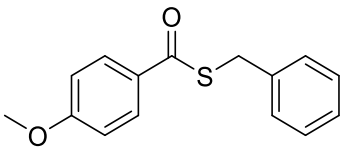
Characterisation data were consistent with previously reported literature values.[142]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 4H), 7.62 – 7.55 (m, 2H), 7.50 – 7.41 (m, 4H), 3.36 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 136.8, 133.7, 128.8, 127.4, 29.0.

LCMS (ESI$^+$) r.t = 3.6 mins, *m/z* = 303.2 $[M+H]^+$

Synthesis of *S*-benzyl 4-methoxybenzothioate (137)



Synthesised according to the general method for thioesterification from 4-methoxybenzoic acid (0.099 g, 0.65 mmol) and benzyl mercaptan (0.089 g, 0.72 mmol). The crude material was purified using automated flash column chromatography combiflash (product eluted in 100% hexanes) to yield the desired product **137** as a white solid in 49% (0.083 g).

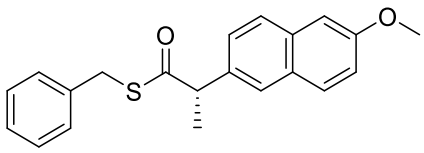
Characterisation data were consistent with previously reported literature values.[143]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.97 (m, 2H), 7.43 – 7.40 (m, 2H), 7.37 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 6.97 – 6.93 (m, 2H), 4.34 (s, 2H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8, 163.9, 137.8, 129.7, 129.6, 129.1, 128.7, 127.3, 113.9, 55.6, 33.3.

GCMS (EI^+) r.t = 5.8 mins, *m/z* =258.2 $[M]^+$

Synthesis of *S*-benzyl 2-(6-methoxynaphthalen-2-yl)propanethioate (138)



Synthesised according to the general method for thioesterification from Naproxen (0.100 g, 0.43 mmol) and benzyl mercaptan (0.054 g, 0.43 mmol). The crude material was purified using automated column chromatography (100% hexanes 5.5 mins, gradient to 10% EtOAc 90% hexanes 0.5 mins, 10% EtOAc 90% hexanes 2 mins followed by gradient to 50/50 EtOAc/hexane) to yield the desired product **138** as a colourless oil in 68% yield (0.100 g)

^{1}H NMR (599 MHz, $CDCl_3$) δ 7.77 – 7.72 (m, 3H), 7.46 (dd, *J* = 8.5, 1.9, 1H), 7.32 – 7.25 (m, 5H), 7.21-7.16 (m, 2H), 4.19 – 4.05 (m, 3H), 3.95 (s, 3H), 1.68 (d, *J* = 7.1, 3H).

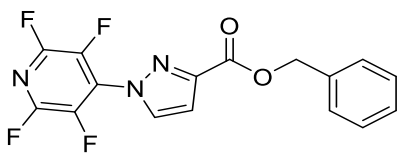
^{13}C NMR (151 MHz, $CDCl_3$) δ 200.8, 157.9, 137.5, 134.9, 134.0, 129.5, 129.0, 128.9, 128.7, 127.3, 127.3, 126.8, 126.5, 119.2, 105.7, 55.4, 54.1, 33.6, 18.5.

LCMS (ESI^+) r.t = 3.5 mins, *m/z* = 337.3

HRMS (ESI^+) – Calculated $[C_{21}H_{21}O_2S]$ 337.1262, Found $[C_{21}H_{21}O_2S]$ 337.1272 $[M+H]^+$, difference = 3.0 ppm

IR vmax (ATR)/cm $^{-1}$ 3029, 2938, 1677, 1601, 1268, 1229, 1029, 944, 854, 818, 750, 698

Benzyl 1-(perfluoropyridin-4-yl)-1*H*-pyrazole-3-carboxylate (143)



Synthesised according to the general method for esterification from 1*H*-pyazole-3-carboxylic acid (0.101 g) and benzyl alcohol (0.103 g). Purified by automated column chromatography (100% hexane to 100% EtOAc) to yield the identified product **143** as a white crystalline solid in 35% yield (0.113 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dt, *J* = 2.7, 1.7 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.44 – 7.32 (m, 3H), 7.12 (d, *J* = 2.7, 1H), 5.44 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 147.3, 145.3 -145.0 (m), 144.9, 142.8 - 142.5 (m), 137.5 - 137.1 (m), 135.1, 134.9 - 134.5 (m), 133.4 - 133.4, 129.6 - 129.4 (m), 128.4, 128.3, 128.2, 128.2, 110.9, 67.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -86.52 – -86.88 (m, 2F), -147.55 – -147.79 (m, 2F).

LCMS (ESI^+) r.t.= 2.9 mins, *m/z* = 352.5 $[M+H]^+$

HRMS (ESI^+) Calc $[C_{16}H_{10}F_4N_3O_2]$ 352.0709, found $[C_{16}H_{10}F_4N_3O_2]$ 352.0710 $[M+H]^+$, difference =0.3 ppm

Acyl Fluoride Reaction Monitoring

To an oven dried vial was added carboxylic acid (1 equiv.), DIPEA (2 equiv.), PFP **15** (1 equiv.), fluorobenzene (1 equiv.) and CD_3CN (0.6 mL). The contents were then transferred from the vial to a clean, dry NMR tube stoppered with a lid.

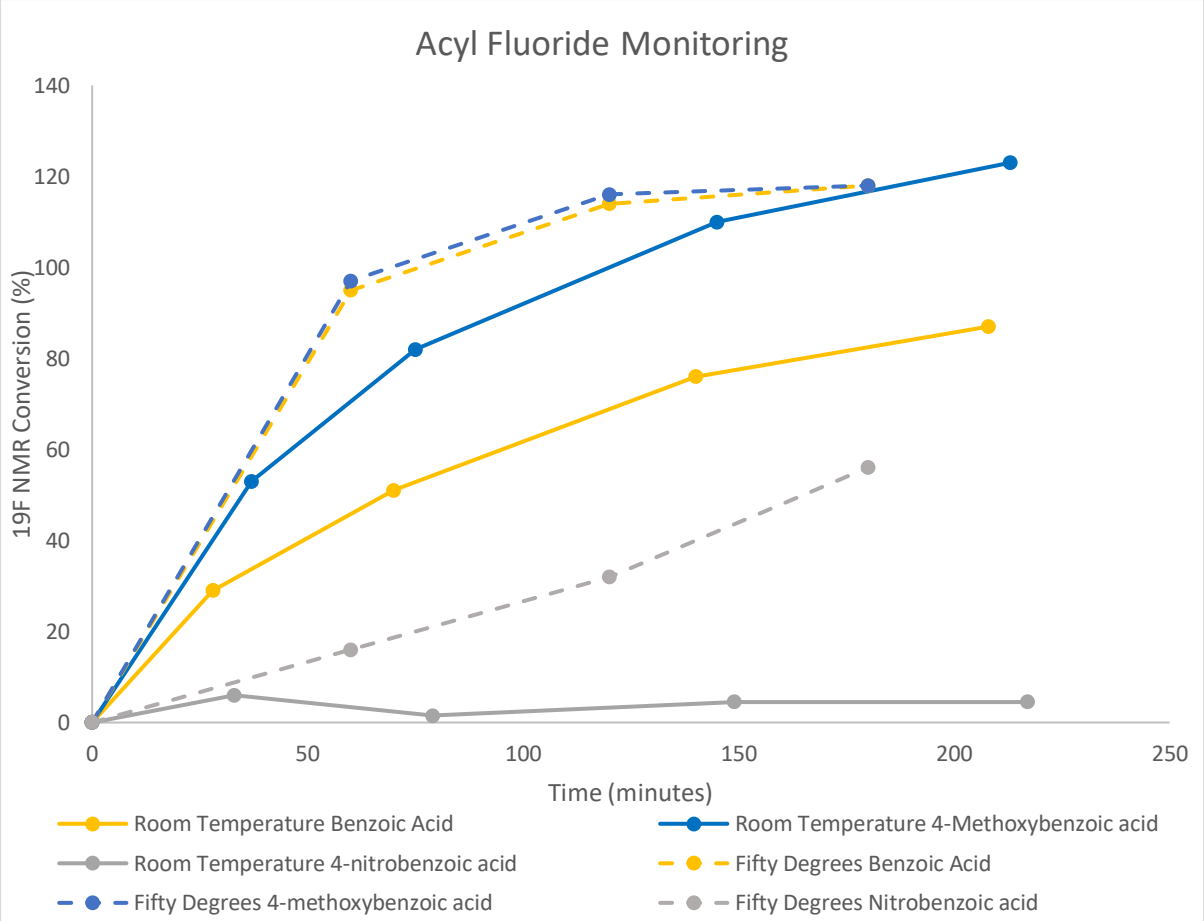
For room temperature analysis the NMR tubes were placed into the NMR instrument autosampler and left there for the duration of the experiment.

For reactions conducted above rt the NMR tubes were transferred to a thermostatically controlled water bath set at 50 °C, the tubes were removed after an hour and an NMR taken. When the acquisition was complete the tube was retrieved and placed back into the water bath.

The time points recorded equates to the amount of time the sample was held in the water bath.

After NMR spectral acquisition spectra were analysed by direct integration to the resonance corresponding to the acyl fluoride compared to the integration value of the internal standard.

Please note values recorded were to determine when a constant integration ratio between acyl fluoride and internal standard was reached.



Raw data for acyl fluoride monitoring at room temperature

Benzoic acid			**4-methoxybenzoic acid**			**4-nitrobenzoic acid**	
mins	Area AF		mins	Area AF		mins	Area AF
0	0		0	0		0	0
28	0.29		37	0.53		33	0.06
70	0.51		75	0.82		79	0.015
140	0.76		145	1.1		149	0.045
208	0.87		213	1.23		217	0.045

*A 1.5 equiv. of fluorobenzene was added, areas of acyl fluorides were multiplied by 1.5 to accommodate.

Raw data for acyl fluoride monitoring 50°C

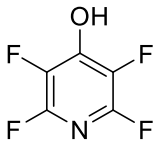
Benzoic Acid			**4-methoxybenzoic acid**			**4-nitrobenzoic acid**	
Mins**	Area AF		Mins**	Area AF		Mins**	Area AF
0	0		0	0		0	0
60	0.95		60	0.97		60	0.16
120	1.14		120	1.16		120	0.32
180	1.18		180	1.18		180	0.56

**Minutes spent in the water bath

The areas in excess of the expected 1:1 ratio is attributed to different relaxation times. It was not feasible to employ a longer relaxation time on the NMR spectrometers used for this analysis. The relaxation time used was 2.77 seconds.

6.3 Chapter 3 Experimental

Synthesis of Tetrafluoropyridinyl hydroxide TFPO (98)



TFPO (**98**) was synthesised according to modified literature methods.[144] To 10 mL of de-ionised water in a pressure tube was added pentafluoropyridine **15** (5.00 g, 29.6 mmol) and potassium hydroxide (4.00 g, 71.3 mmol). The pressure tube was heated to 70 °C and the mixture stirred for 72 hours. After cooling the aqueous mixture was washed with dichloromethane (20 mL). The reaction mixture was then acidified with concentrated hydrochloric acid to pH ~1 followed by extraction with diethyl ether (30 mL x 3). Upon concentration of the ether layer the desired product **98** was obtained as a white solid in 87% yield (4.30 g).

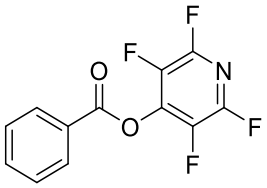
Characterisation data were consistent with previously published literature values.[144]

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7 (tt, *J* = 12.6, 6.1 Hz), 146.0 – 141.7 (m), 135.4 – 131.3 (m).

^{19}F NMR (376 MHz, $CDCl_3$) δ -92.33 – -92.88 (m, 2F), -162.92 – -163.31 (m, 2F).

LCMS (ESI^-) r.t. = 1.0 mins, *m/z* = 166.1 $[M-H]^-$

Synthesis of perfluoropyridin-4-yl benzoate from literature method (99)



Synthesised according to literature procedure.[95] To an oven dried microwave vial equipped with a stirrer was added PFP **15** (0.240 g, 1.2 mmol), benzoic anhydride **166** (3.327 g, 14.7 mmol), DMAP **77** (0.02 g) and MeCN (5 mL). The vial was sealed, and the mixture heated to

100 °C with stirring for 16 hours. Afterwards the mixture was allowed to cool, and the volatiles removed under reduced pressure. The resulting crude material was redissolved in a minimum amount of DCM and purified by flash column chromatography (hexane/DCM 7:3) to give the desired product **99** as a white solid in 16% yield (0.052 g).

Characterisation data were consistent with previously reported literature values.[95]

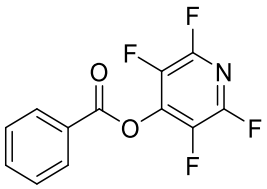
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.16 (m, 2H), 7.79 – 7.69 (m, 1H), 7.58 (t, *J* = 7.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 135.3, 131.1, 129.2, 126.4.
(Pyridyl carbons were not observed due to sample concentration and fast relaxation times).

^{19}F NMR (376 MHz, $CDCl_3$) δ -88.37 – -88.70 (m, 2F), -151.85 – -152.14 (m, 2F).

LCMS (ESI^+) r.t. = 1.9 mins, *m/z* = 272.3 $[M+H]^+$

Synthesis of perfluoropyridin-4-yl benzoate from benzoyl chloride (99)



To a round bottomed flask equipped with a stirrer bar was added THF (50 mL), TFPO **98** (0.169 g, 1.01 mmol) and 2,6-lutidine (0.109 g, 1.02 mmol). Upon dissolution of the TFPO **98**, benzoyl chloride (0.147 g, 1.05 mmol) was added. Some minutes later the 2,6-lutidiene hydrochloride salt was visible indicating conversion. Purified by automated column chromatography (100% hexane) to yield the desired product **99** as a white crystalline solid in 97% yield (0.264 g).

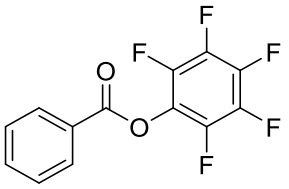
^{1}H NMR (400 MHz, CD_3CN) δ 8.25 – 8.19 (m, 2H), 7.87 – 7.78 (m, 1H), 7.69 – 7.60 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 145.1 - 144.8 (m), 142.7 - 142.4 (m), 140.0 - 139.8 (m), 138.1 - 137.8 (m), 135.5 - 135.1 (m), 135.3, 131.0, 129.2, 126.4.

^{19}F NMR (376 MHz, CD_3CN) δ -90.90 – -91.25 (m, 2F), -153.50 – -153.78 (m, 2F).

Compound identity was also confirmed by single crystal X-ray crystallography.

Synthesis of perfluorophenyl benzoate (173)



To a round bottomed flask equipped with a stirrer bar was added THF (50 mL), pentafluorophenol **161** (0.325 g, 1.77 mmol) and 2,6-lutidine (0.219 g, 2.04 mmol). Upon dissolution of the TFPO, benzoyl chloride (0.249 g, 1.77 mmol) was added. Purified using automated column chromatography to yield the desired product **173** as a white solid in 68% yield (0.345 g).

Characterisation data were consistent with previously reported literature values.[145]

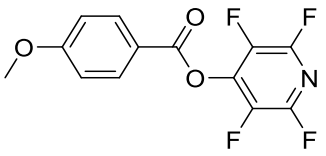
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.19 (m, 2H), 7.76 – 7.65 (m, 1H), 7.61 – 7.47 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 143.0-142.7 (m), 141.1 - 140.2 (m), 139.6 - 139.2 (m), 138.6 - 138.3 (m), 137.1 - 136.7 (m), 134.8, 130.8, 129.0, 127.1, 125.7 - 125.4 (m).

^{19}F NMR (376 MHz, $CDCl_3$) δ -152.53 – -153.28 (m, 2F), -158.38 (t, *J* = 21.5 Hz, 1F), -162.05 – -163.56 (m, 2F).

ASAP (AI+) *m/z* = 289.1 $[M+H]^+$

Synthesis of perfluoropyridin-4-yl 4-methoxybenzoate (168)



To a round bottomed flask equipped with a stirrer bar was added THF (50 mL), 2,6-lutidine (0.107 g, 1.00 mmol) and TFPO **98** (0.172 g, 1.03 mmol). After the complete dissolution of the TFPO, 4-methoxybenzoyl chloride was added (0.172 g, 1.01 mmol) and the mixture was stirred at room temperature. The reaction mixture was allowed to stir for a half an hour. The mixture was then filtered, and the filtrate washed with a further 100 mL of THF. Volatiles were removed by rotary evaporation. Purified by automated column chromatography (100% hexane) to yield the desired product which was re-crystallised by vapour diffusion

(hexane/EtOAc) to yield the desired **168** product as colourless crystals in71% yield (0.215 g).

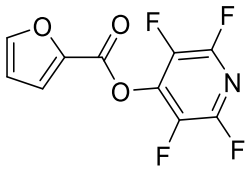
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.31 – 7.92 (m, 1H), 7.24 – 6.67 (m, 1H), 3.92 (s, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 165.3, 161.1, 144.4 - 143.0 (m), 140.1 (m), 137.6 - 135.8 (m), 133.3, 118.4, 114.5, 55.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -88.72 – -88.96 (m, 2F), -151.98 – -152.28 (m, 2F).

ASAP (AI^+) HRMS Calc 302.0440 [$C_{13}H_8NO_3F_4$], Found 302.0422[$C_{13}H_8NO_3F_4$] $[M+H]^+$, difference = -6.0 ppm

Synthesis of perfluoropyridin-4-yl furan-2-carboxylate (21)



To a round bottomed flask equipped with a stirrer bar was added THF (50 mL), 2,6-lutidine (0.112 g, 1.04 mmol) and TFPO **98** (0.170 g, 1.02 mmol). After complete dissolution of the TFPO **98**, oxalyl chloride was added (0.131 g, 1.03 mmol) and the mixture was stirred at room temperature. The reaction mixture was allowed to stir for a further half an hour and then the mixture was filtered, and the filtrate washed with a further 100 mL of THF. Volatiles were removed by rotary evaporation and the crude mixture was purified by automated column chromatography (100% hexane) to yield the desired product as an orange solid in 67% yield. The solid was re-crystallised by vapour diffusion (hexane and EtOAc) to give the desired product **21** as orange crystals.

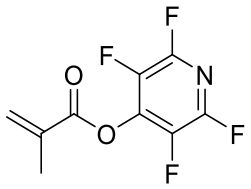
^{1}H NMR (599 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.54 (dd, *J* = 3.7, 0.8 Hz, 1H), 6.68 (dd, *J* = 3.7, 1.8 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.6, 149.2, 144.7 - 144.4 (m), 143.0 - 142.8 (m), 141.1, 139.1 - 138.9 (m), 137.6 -137.4 (m), 135.9 - 135.6 (m), 122.8, 113.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -87.98 – -88.29 (m, 2F), -151.55 – -151.79 (m, 2F).

ASAP (AI^+) HRMS Calc 262.0127 [$C_{10}H_4NO_3F_4$], Found 262.0120 [$C_{10}H_4NO_3F_4$] $[M+H]^+$, difference = -2.7 ppm.

Synthesis of perfluoropyridin-4-yl methacrylate (169)



To a round bottomed flask equipped with a stirrer bar was added TFPO **98** (0.495 g) and methacroyl chloride (0.31 mL) for two hours. Purified by manual column chromatography (9:1 hexane:DCM isocratic) which yielded the desired product **169** as a colourless oil in 14% yield (0.100 g).

No literature data available.

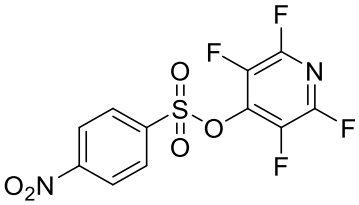
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 – 6.45 (m, 1H), 6.01 – 5.94 (m, 1H), 2.09 (dd, *J* = 1.6, 1.0, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 145.1 -142.3 (m), 139.9 (m), 138.0 135.0 (m), 133.4, 131.1, 18.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -88.44 – -89.22 (m, 2F), -152.07 – -153.10 (m, 2F).

LCMS (ESI^+) r.t. = 3.3 mins, *m/z* – not detected

Synthesis of perfluoropyridin-4-yl 4-nitrobenzenesulfonate (170)



To a round bottomed flask equipped with a stirrer bar was added TFPO **98** (0.332 g, 1.99 mmol) and 2,6-lutidene (0.218 g, 2.03 mmol) and THF (10 mL). Upon dissolution of the TFPO **98**, 4-nitrobenzenesulfonyl chloride **162** was added (0.450 g, 2.03 mmol) and the mixture was allowed to stir for one hour. After one hour the mixture was filtered and concentrated onto silica under reduced pressure. Purification using automated column chromatography (100%

hexane to 100% EtOAc) gave the desired product **170** as a yellow crystalline solid in 93% yield (0.650 g).

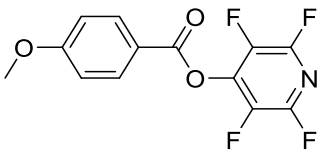
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 – 8.49 (m, 2H), 8.32 – 8.20 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9, 145.2 - 142.4 (m), 140.1, 138.5 - 135.5 (m), 137.4 - 137.1 (m), 130.1, 125.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -85.95 – -86.19 (m, 2F), -150.65 – -150.85 (m, 2F).

ASAP (AI^+) HRMS Calc $[M+H]^+$ 352.9855 [$C_{11}H_5F_4N_2O_5S$], found 352.9842 [$C_{11}H_5F_4N_2O_5S$], -3.7 ppm.

Synthesis of perfluoropyridin-4-yl 4-methoxybenzoate directly (168, Scheme 3.8)



To an oven dried round bottomed flask equipped with a stirrer bar was added CD_3CN (0.7 mL) 4-methoxybenzoic acid **94** (0.024 g) and perfluoropyridin-4-yl 4-nitrobenzenesulfonate **170** (0.052 g). Upon dissolution, TEA was added (0.015 g) and the mixture was allowed to stir at room temperature for 16 hours. Then the mixture was concentrated onto silica under reduced pressure and purified by automated column chromatography (product eluted in 100% hexane) to yield the desired product **168** as a white solid in 23% yield (0.011 g)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.0 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 1H), 3.93 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 161.1, 133.4, 118.5, 114.5, 55.9.

(pyridyl carbons were not observed due to sample concentration and fast relaxation times).

^{19}F NMR (376 MHz, $CDCl_3$) δ -88.37 – -88.70 (m, 2F), -151.85 – -152.14 (m, 2F).

ASAP (AI^+) 302.0 $[M+H]^+$

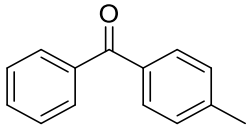
NMR Competition Monitoring Experiments General Figure 3.11/3.12

To a vial was added tetrafluoropyrid-4-yl benzoate (1 equiv.) and CD_3CN (0.6 mL). Following subsequent transfer to an NMR tube an initial analysis was taken. Then to the NMR tube

pentafluorophenyl benzoate (1 equiv.) was added and a second analysis taken so that the peaks corresponding to each substrate could be identified. After this analysis, to a vial was added 4-methoxyphenol or *p*-toluidine (1 equiv.), DIPEA (1 equiv.) and CD_3CN (0.2 mL). This vial mixture was added to the NMR tube and recordings taken. The NMR tube was left in the NMR autosampler on a 400 MHz Bruker Avance III spectrometer as the instrument room is a constant temperature.

6.4 Chapter 4 Experimental

Synthesis of phenyl(p-tolyl)methanone from an isolated acyl fluoride 178



Synthesised according to adapted literature methods.[58] To a round bottomed flask equipped with a condensor was added toluene (11 mL), KF (0.089 g), *p*-tolylbenzeneboronic acid **177** (0.207 g), $Pd(OAc)_2$ (2.2 mg) and $P(C_6H_4OMe)_3$ (0.014 g) or PPh_3 (0.011 g). Upon re-sealing the system, through a septum was added benzoyl fluoride **51** (0.123 g). The mixture was then heated to reflux and left to stir for 16 hours. After 16 hours the mixture was diluted with deionised water (15 mL) and seperated with EtOAc (3 x 15 mL). The volatiles were concentrated onto silica under reduced pressure and purified by automated column chromatography (100% hexane) to yield the desired product **178** as a clear oil in 88% yield (0.172 g) for $P(C_6H_4OMe)_3$ and 69% yield (0.131 g) for PPh_3.

Characterisation data were consistent with previously reported literature values.[58]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.78 (m, 2H), 7.76 – 7.72 (m, 2H), 7.63 – 7.53 (m, 1H), 7.53 – 7.41 (m, 2H), 7.33 – 7.23 (m, 2H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 143.2, 137.9, 134.8, 132.1, 130.3, 129.9, 128.9, 128.2, 21.6.

LCMS (ESI^+) r.t. = 3.0 mins, *m/z* = 197.7 $[M+H]^+$

General procedure for Suzkui-Miyaura cross-coupling of acyl fluorides

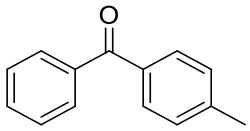
To an oven dried screw cap vial equipped with a stirrer bar was added carboxylic acid (1 mmol, 1 equiv.), MeCN (2 mL), DIPEA (1 mmol, 1 equiv.) and PFP (1 mmol, 1 equiv.). The vial was then sealed, and the acyl fluoride was allowed to generate for 4 hours.

In a separate 2-neck round bottomed flask equipped with a condenser, rubber septum and stirrer bar were purged with nitrogen for one hour. At which point, while still under a positive

atmosphere was added potassium fluoride (0.087 g, 1.5 mmol), boronic acid (1.5 mmol, 1.5 equiv.), $P(OMeC_6H_4)_3$ (4%) and $Pd(OAc)_2$ (1%). Once the flask was charged, the septum was replaced, and toluene (9 mL) was added quickly followed by the acyl fluoride that had been generated in a vial for the previous 4 hours.

The reaction was heated to reflux, and the mixture was allowed to stir for 16 hours. After which the mixture was cooled to room temperature and deionised water (15 mL) was added. The contents were extracted with ethyl acetate and dried over sodium sulfate followed by rotary evaporation with silica to allow for compounds to be dry loaded for automated column chromatography.

Optimisation of phenyl(p-tolyl)methanone (178) synthesis



This is the generic optimisation reaction for the formation of **178**. Purified by automated column chromatography (100% hexane) to yield the desired product as a white solid or oil. Individual yields are given in the optimisation table of **chapter 4**.

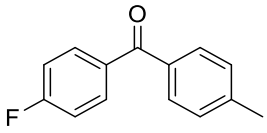
Results were consistent with product synthesised from literature preparations.

Table 4.1: Optimisation reactions for palladium cross-couplings

Entry	Acyl Fluoride Solvent MeCN (mL)	Cross-Coupling Solvent Toluene (mL)	Palladium Loading (mol%)	Phosphine Ligand	Ligand Loading (mol%)	Yield (%)
1[a]	-	10	5	PPh_3	16	28
2[a]	-	10	5	SPhos	16	-
3[a]	-	10	5	Tris(2,4,6-trimethoxyphenyl)phosphine	16	-
4	2	9	5	PPh_3	16	48
5	2	9	5	PPh_3	16	62
6	0.5	12	5	PPh_3	16	52
7	0.25	20	5	PPh_3	16	38
8	2	9	5	PCy_3	16	60
9[b]	2	9	5	PPh_3	16	49
10[C]	0	11	1	PPh_3	4	67
11[C]	0	11	1	$P(OMeC_6H_4)_3$	4	88
12	2	9	2.7	$P(OMeC_6H_4)_3$	4.5	69
13	2	9	5	$P(OMeC_6H_4)_3$	20	53
14[d]	2	9	5	$P(OMeC_6H_4)_3$	20	50
15	2	9	2.5	$P(OMeC_6H_4)_3$	4	52
16	2	9	1	$P(OMeC_6H_4)_3$	4	49

General conditions using benzoic acid (1 mmol), 4-tolylbenzenboronic acid (1.5 mmol) and KF (1.5 mmol). Toluene was used as the general cross-coupling solvent except in 1, 2 and 3. Four hours was allowed for activation of acyl fluoride and cross-couplings were left for 16 hours overnight. [a] Acyl fluoride generated first and all reactants successively added to activated mixture. [b] K_2CO_3 used as the base (1.5 mmol). [c]Performed using purchased benzoyl fluoride. [d] Using 3 equiv. of KF.

Synthesis of (4-fluorophenyl)(p-tolyl)methanone (179)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from 4-fluorobenzoic acid (0.139 g, 0.99 mmol) and *p*-tolylbeznene boronic acid **177** (0.210 g, 1.54 mmol). Purified by automated column chromatography (100% hexane) to give the desired product **179** as a colourless oil in 48% yield (0.104 g).

Characterisation data was consistent with previously reported literature values.[89]

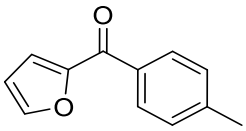
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.78 (m, 2H), 7.76 – 7.63 (m, 2H), 7.36 – 7.25 (m, 2H), 7.23 – 7.09 (m, 2H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1, 165.2 (d, *J* = 253.8), 143.4, 134.8, 134.2 (d, J = 8.9), 132.6, 132.6, 130.2, 129.1, 115.4 (d, *J* = 21.9), 21.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -106.39 (ttd, *J* = 8.5, 5.5, 0.6 Hz, 1F).

LCMS (ESI^+) r.t. = 3.1, *m/z* = 215.2 $[M+H]^+$

Synthesis of furan-2-yl(p-tolyl)methanone (180)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from 2-furoic acid (0.115 g, 1.02 mmol) and *p*-tolybenzene boronic acid **177** (0.209 g, 1.54 mmol). Purified by automated column chromatography (100% hexane 5 mins to 100% EtOAc 6 mins). Obtained the desired product **180** as a clear oil in 22% yield.

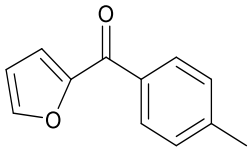
Characterisation data were consistent with previously reported literature values.[145]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.86 (m, 2H), 7.73 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.36 – 7.22 (m, 3H), 6.63 (dd, *J* = 3.6, 1.7 Hz, 1H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 183.3, 152.2, 147.6, 144.0, 134.3, 129.7, 129.3, 121.5, 112.5, 21.8.

LCMS – LCMS data for this compound was lost.

Synthesis of furan-3-yl(p-tolyl)methanone (181)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from 3-furoic acid (0.113 g, 1.0 mmol) and 4-tolylbenzene boronic acid **177** (0.204 g, 1.5 equiv.) Purified by automated column chromatography (100% hexane 5 mins to 100% EtOAc 6 mins) to yield the desired product **181** as an oil in 38% yield (0.071 g)

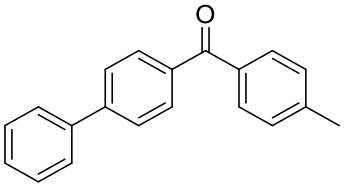
Characterisation data was consistent with previously reported literature values.[146]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 1.5, 0.8 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.50 (dd, *J* = 1.9, 1.4 Hz, 1H), 7.32 – 7.27 (m, 2H), 6.90 (dd, *J* = 1.9, 0.8 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.3, 148.4, 144.0, 143.4, 136.2, 129.4, 129.2, 126.7, 110.4, 21.8.

LCMS (ESI^+) r.t. = 2.8 mins, *m/z* =187.2 $[M+H]^+$

Synthesis of [1,1'-biphenyl]-4-yl(*p*-tolyl)methanone (182)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from bi-phenyl carboxylic acid (0.199g, 1.00 mmol) and 4-tolylbenzeneboronic acid **177** (0.209 g, 1.50 mmol). Purified by automated column chromatography (eluted in 100% hexane) to yield the desired product **182** as a white solid in 24% yield (0.066 g).

Alternatively, synthesised according to the general procedure for cross-couplings using PCy_3 as the ligand from bi-phenyl carboxylic acid (0.198 g, 1.00 mmol) and 4-tolylbenzeneboronic

acid (0.209 g, 1.50 mmol). Purified by automated column chromatography (gradient 100% hexane to 100% EtOAc) to yield the desired product as a cream solid in 43% yield (0.116 g).

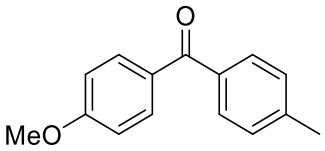
Characterisation data were consistent with previously reported literature values.[145]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.86 (m, 2H), 7.79 – 7.75 (m, 2H), 7.73 – 7.68 (m, 2H), 7.68 – 7.63 (m, 2H), 7.52 – 7.46 (m, 2H), 7.44 – 7.38 (m, 1H), 7.34 – 7.28 (m, 2H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.3, 145.1, 143.3, 140.2, 136.7, 135.1, 130.7, 130.4, 129.1, 129.1, 128.3, 127.4, 127.0, 21.8.

LCMS (ESI^+) r.t. = 3.4 mins, *m/z* = 273.3 $[M+H]^+$

Synthesis of (4-methoxyphenyl)(*p*-tolyl)methanone (183)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from 4-methoxybenzoic acid (0.152 g, 1.00 mmol) and 4-tolylbenzene boronic acid **177** (0.205 g, 1.50 mmol). Purified by automated column chromatography (100% hexane) to yield the desired **188** product as a colourless oil in 33% yield.

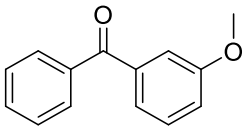
Characterisation data were consistent with previously reported literature values.[147]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.70 – 7.64 (m, 2H), 7.31 – 7.26 (m, 2H), 7.01 – 6.93 (m, 2H), 3.89 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0, 163.6, 143.3, 135.2, 132.9, 130.3, 130.1, 129.1, 113.7, 55.7, 21.8.

LCMS (ESI^+) r.t. = 3.1 mins, *m/z* = 227.6 $[M+H]^+$

Synthesis of (3-methoxyphenyl)(phenyl)methanone (187)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from benzoic acid **93** (0.121 g, 0.99 mmol) and 3-methoxybenzene boronic acid (0.226 g, 1.49 mmol). Purified by automated column chromatography (100% hexane 5 mins to 50/50 hexane/EtOAc) to yield the product **187** as a clear oil in 34% yield (0.073 g).

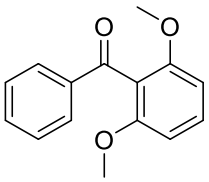
Characterisation data were consistent with previously reported literature values.[148]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.77 (m, 2H), 7.62 – 7.56 (m, 1H), 7.51 – 7.43 (m, 2H), 7.42 – 7.31 (m, 3H), 7.14 (ddd, *J* = 7.8, 2.7, 1.4 Hz, 1H), 3.92 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7, 159.7, 139.0, 137.7, 132.6, 130.7, 130.2, 129.4, 129.0, 128.4, 123.0, 119.0, 114.4, 55.6.

LCMS (ESI^+) r.t. 2.6 mins, *m/z* = 213.2 $[M+H]^+$

Synthesis of (2,6-dimethoxyphenyl)(phenyl)methanone (188)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from benzoic acid **93** (0.123 g, 1.01 mmol) 2,6-dimethoxybenzene boronic acid (0.280 g, 1.53 mmol). Purified by automated column chromatography (100% hexane 5 mins to 50/50 hexane/EtOAc) to yield the desired product **188** as a white solid which was approx. 33% yield (0.080 g). There was some contamination.

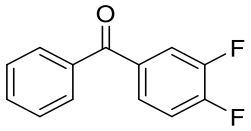
Characterisation data were consistent with previously reported literature values.[149]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.84 (m, 2H), 7.67 – 7.62 (m, 1H), 7.58 (ddt, *J* = 7.9, 6.9, 1.3 Hz, 1H), 7.54 – 7.43 (m, 1H, app 4H), 7.37 (t, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 2H), 3.72 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 157.7, 137.6, 133.5, 131.0, 128.6, 128.5, 117.7, 104.1, 55.9.

LCMS (ESI^+) r.t 2.4 mins, *m/z* = 243.2 $[M+H]^+$

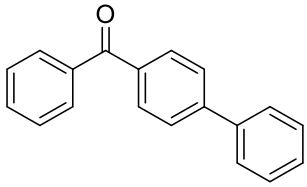
Synthesis of (3,4-difluorophenyl)(phenyl)methanone (189)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from benzoic acid **93** (0.122 g, 1.00 mmol) and 3,4-difluorophenyl boronic acid (0.237 g, 1.50 mmol). Purified by automated column chromatography (100% hexane 5 mins to 100% EtOAc 6 mins). Unfortunately, sufficiently clean material could not be recovered for full characterisation. The presence of the desired product **189** was supported by mass spectrometry analysis and ^{19}F NMR spectroscopy.

LCMS (ESI^+) r.t. = 2.7 mins, *m/z* = 219.2 $[M+H]^+$

Synthesis of [1,1'-biphenyl]-4-yl(phenyl)methanone (190)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from benzoic acid **93** (0.122 g, 1.00 mmol) and 4-biphenylboronic acid (0.307 g, 1.55 mmol). Purified twice by automated column chromatography (100% hexane) to yield the desired product **190** as a white solid in 23% yield (0.060 g).

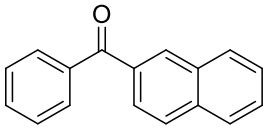
Characterisation data were consistent with previously reported literature values.[147]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.89 (m, 2H), 7.88 – 7.83 (m, 2H), 7.76 – 7.70 (m, 2H), 7.69 – 7.64 (m, 2H), 7.64 – 7.58 (m, 1H), 7.55 – 7.46 (m, 4H), 7.45 – 7.39 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 145.3, 140.0, 137.8, 136.3, 132.5, 130.8, 130.1, 129.1, 128.4, 128.3, 127.4, 127.1.

LCMS (ESI^+) r.t. = 3.2 mins, m/z = 259.3 $[M+H]^+$

Synthesis of naphthalen-2-yl(phenyl)methanone (191)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from benzoic acid **93** (0.124 g, 1.02 mmol) and 1-napthaleneboronic acid (0.190 g, 1.10 mmol). Purified by automated column chromatography (100% hexane) to give the desired product **191** as a white solid in 48% yield (0.111 g).

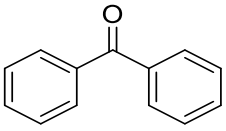
Characterisation data were consistent with previously reported literature values.[145]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.11 (m, 1H), 8.01 (dt, *J* = 8.2, 1.2 Hz, 1H), 7.96 – 7.92 (m, 1H), 7.92 – 7.87 (m, 2H), 7.63 – 7.44 (m, 7H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1, 138.4, 136.4, 133.8, 133.3, 131.3, 131.0, 130.5, 128.5, 128.5, 127.8, 127.3, 126.5, 125.7, 124.4.

LCMS (ESI^+) r.t. = 3.0 mins, m/z = 233.3 $[M+H]^+$

Synthesis of benzophenone (192)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from benzoic acid **93** (0.124 g, 1.02 mmol) and phenylboronic acid (0.187 g, 1.53 mmol). Purified by automated column chromatography (100% hexane) to yield the expected product **192** as an oil in 10% yield (0.019 g).

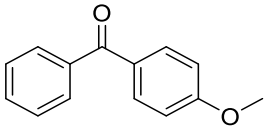
Characterisation data were consistent with previously reported literature values.[145]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 4H), 7.64 – 7.55 (m, 2H), 7.49 (ddt, *J* = 8.2, 6.5, 1.2 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.9, 137.7, 132.5, 130.2, 128.4.

LCMS (ESI^+) r.t. = 2.6 mins, m/z = 183.2 $[M+H]^+$

Synthesis of (4-methoxyphenyl)(phenyl)methanone (193)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from benzoic acid **93** (0.122 g, 1.00 mmol) and 4-methoxybenzeneboronic acid (0.228 g, 1.50 mmol). Purified by automated column chromatography (100% hexane 5 mins to 100% EtOAc 6 mins) to give the desired product **193** as a yellow oil in 47% yield.

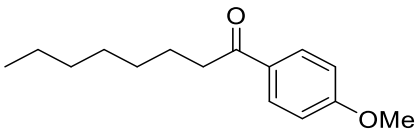
Characterisation data were consistent with previously reported literature values.[145]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 2H), 7.82 – 7.74 (m, 2H), 7.62 – 7.56 (m, 1H), 7.53 – 7.43 (m, 2H), 7.07 – 6.87 (m, 2H), 3.90 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 163.6, 138.1, , 132.8, 132.2,, 129.9, , 128.3, 113.7, 55.6.

LCMS (ESI^+) r.t.= 2.9 mins, *m/z* =213.5 $[M+H]^+$

Synthesis of 1-(4-methoxyphenyl)octan-1-one (198)

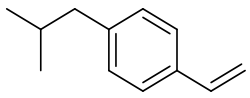


Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from octanoic acid (0.149 g, 1.05 mmol) and 4-methoxybenzeneboronic acid (0.227 g, 1.50 mmol). Attempted purification by automated column chromatography (100% hexanes).

Unfortunately, sufficiently clean material of **198** could not be recovered for full characterisation. Product evidenced by LCMS.

LCMS (ESI^+) r.t.= 3.4 mins, *m/z* =235.6 $[M+H]^+$

Synthesis of 1-isobutyl-4-vinylbenzene (201)



Synthesised according to the general procedure for Suzkui-Miyaura cross-coupling of acyl fluorides from ibuprofen (0.212 g). There was a 5% $Pd(OAc)_2$ loading (0.011 g) and 20% PPh_3 loading (0.046 g). 4-tolylbenzene boronic acid (0.203 g) was also present in the mixture. Yield of **201** not recorded.

Characterisation data were consistent with previously reported literature values.[112]

^1H NMR (599 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 2H app 3H), 7.18 – 7.08 (m, 2H), 6.73 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.74 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.22 (dd, *J* = 10.8, 1.0 Hz, 1H), 2.50 (d, *J* = 7.2 Hz, 2H), 1.89 (m, , 1H), 0.94 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 141.6, 136.9, , 129.4, , 126.1, 112.9, 45.3, 30.4, 22.5.

LCMS (ESI^+) r.t. = 3.4 mins, *m/z* not detected

Structure confirmed by 2D NMR spectroscopy including a DOSEY which estimated the molecular weight to be approximately 170-180. There was a small amount of contamination present which was believed to be overpowering the peak in mass spectrometry.

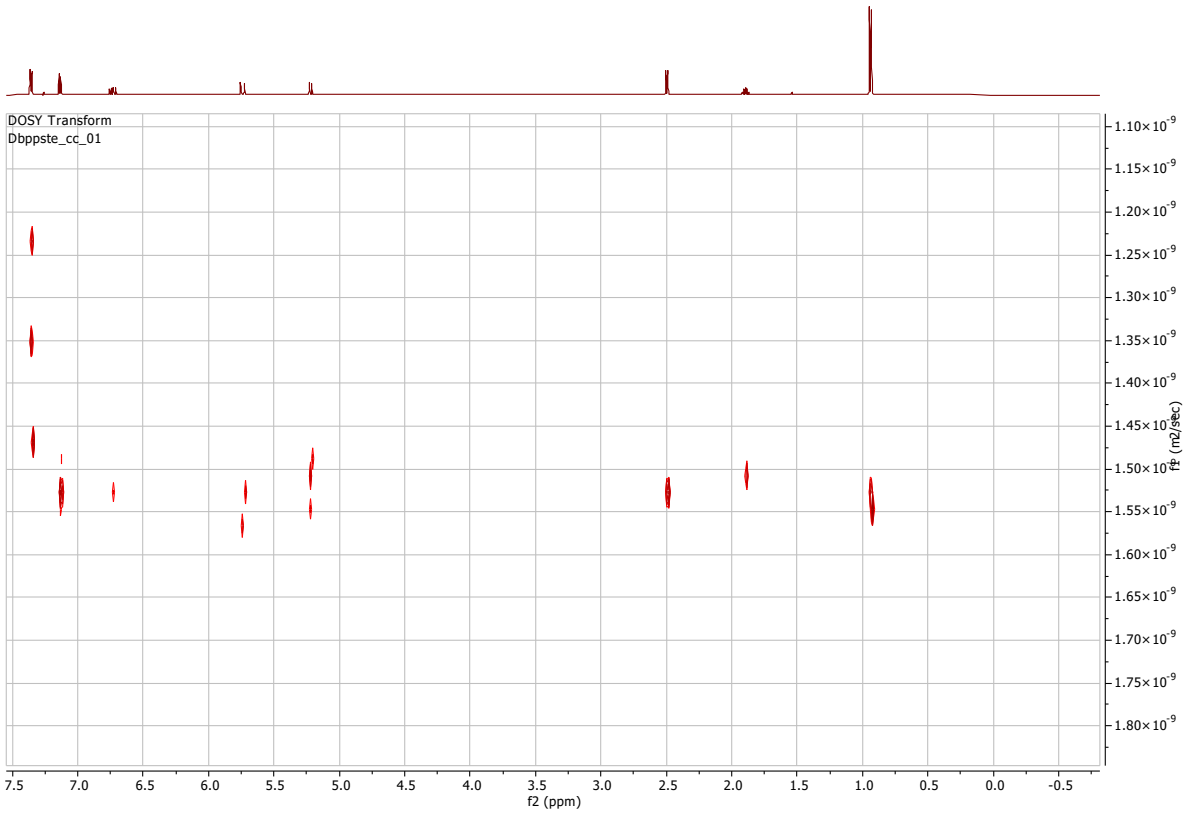
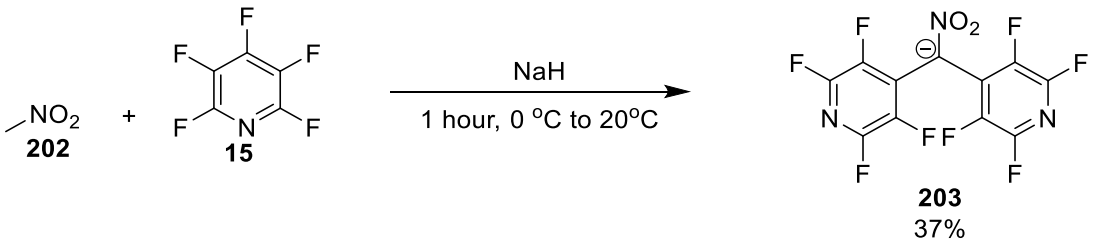


Figure 6.2: DOSY NMR Experiment to estimate molecular weight.

7 Appendix 1: Sodium nitrobis(perfluoropyridin-4-yl)methanide

Previously the Cobb group have described the preparation of a stable fluoropyridyl carbanion (**203**).[150] They found that **203** was found to be remarkably stable surviving purification by column chromatography. Furthermore, within their research protonation of the carbanion by HCl occurred very rapidly. Due to the focus on PFP (**15**) so far, this work seemed like as good opportunity to explore potential applications of this molecule further and some of the molecule was synthesised (**Scheme 8.1**)



Scheme 8.1: Preparation of a PFP derived carbanion **203**.

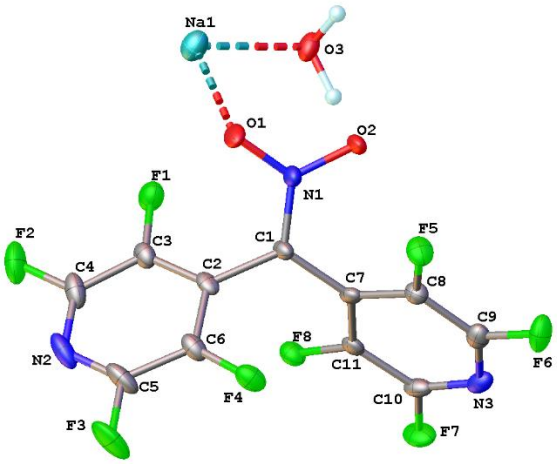
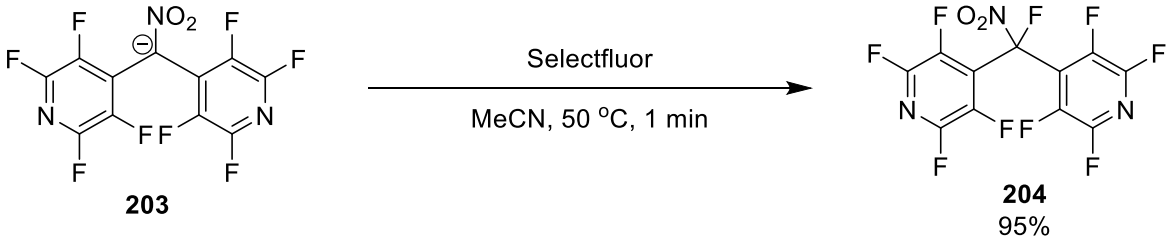


Figure 8.1: Monohydrate of desired product **203**. Crystal structures are reported with a 50% thermal ellipsoid probability.

7.1 Fluorination of the Anion

As pentafluoropyridine has been used as an F- source in the decarbonylative fluorination process, it was hypothesized that by fluorinating this molecule it may be possible to use the fluorinated species as a F+ source given the stability of this anion and the electron withdrawing effects of the PFP molecules substituted upon it.

By using selectfluor it was found to be possible to fluorinate the anion in approximately one minute. Work up of this compound yielded a crystalline solid which X-Ray crystallography data was obtained for (**Scheme 8.2 and Figure 8.2**).



Scheme 8.2: Synthesis of 4,4'-(fluoro(nitro)methylene)bis(2,3,5,6-tetrafluoropyridine) (**204**).

Compound **204** was characterised by NMR spectroscopy and X-ray crystallography to determine the structure. ^{13}C NMR spectroscopy showed the splitting of the non-aromatic carbon, as is expected when fluorine coupled experiments are run. Mass spectrometry however was unable to identify the product and further work could be undertaken to understand this. It may be the case that this compound is too easily dissociated for mass spectrometry analysis.

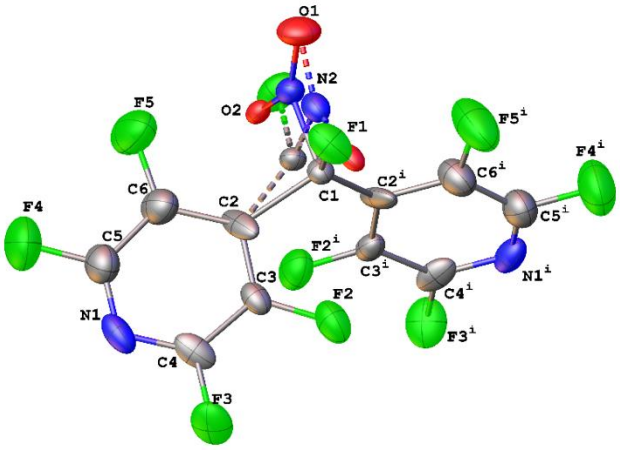
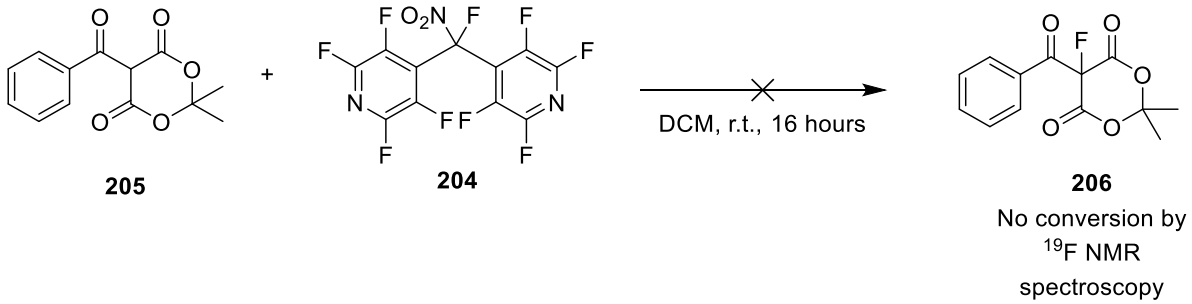


Figure 8.2: Crystal structure of **204** crystal structures are reported with a 50% thermal ellipsoid probability

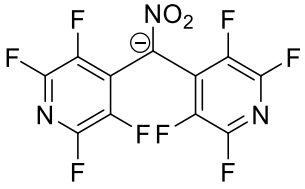
Attempts to utilise this potential dissociation as a F^+ source proved unsuccessful. A tri-cabronyl system that was shown by Sandford and co-workers to be very susceptible to electrophilic fluorination by selectfluor was attempted but no conversion was observed (**Scheme 8.3**).[151] Photochemical conditions were also unable to afford conversion and these were monitored by in-situ ^{19}F NMR spectroscopy.



Scheme 8.3: Attempted electrophilic fluorination using **204**.

Finally, with the ease and rapidness at which selectfluor added an "F+" to **203**, the focus then turned to could any other electrophiles be added to anion. Umemoto reagent (CF_3^+) did not react with the anion. More forceful heating conditions may have been useful here. NCS (Cl^+) was another unsuccessful substrate. The likely reason for this is due to size. The fluoride ion is similar in size to that of a proton, whereas chlorine and the trifluoromethyl group are much bigger, there are likely steric effects at play which are preventing this reaction.

Synthesis of sodium nitrobis(perfluoropyridin-4-yl)methanide (203)



Prepared in accordance to literature methods from nitromethane (0.630 g, 10.3 mmol), sodium hydride 60% dispersion (0.512 g, 0.410 g of NaH, 17.0 mmol) and pentafluoropyridine **15** (3.402 g, 20.1 mmol) in DMF (10 mL).[150] Purified by manual column chromatography (100% hexane to 50:50 hexane: EtOAc) to yield the desired product **203** as an orange flaky solid in 36% yield (1.300 g).

Characterisation data were consistent with previously reported literature values.[150]

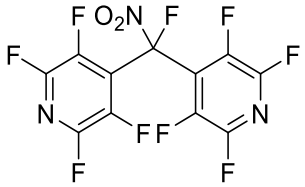
^{1}H NMR (700 MHz, CD_3CN) – No protons detected.

^{13}C NMR (176 MHz, CD_3CN) δ 144.35 (d, *J* = 240.2 Hz), 140.17 (dd, *J* = 256.2, 33.2 Hz), 130.40, 93.19.

^{19}F NMR (658 MHz, CD_3CN) δ -95.69 – -95.79 (4F, m), -139.63 – -139.73 (4F, m).

LCMS (ESI^-) r.t = 3.8 mins, *m/z* = 358.3 [M]

Synthesis of 4,4'-(fluoro(nitro)methylene)bis(2,3,5,6-tetrafluoropyridine) (204)



To an oven dried vial equipped with a stirrer bar was added MeCN 2 mL, sodium nitrobis(perfluoropyridin-4-yl)methanide **203** (0.068 g) and selectfluor (0.161 g). After one minute the reaction mixture went much paler in colour, the mixture was allowed to stir for a further two hours. After two hours the MeCN was removed under reduced pressure and diethyl ether added to the crude mixture. The insolubilised selectfluor was then removed by filtration and rotary evaporation afforded a crystalline material of **204** in 95% yield. The structure was confirmed by X-ray crystallography.

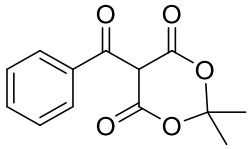
^{1}H NMR (400 MHz CD_3CN) - No protons detected.

^{13}C NMR (151 MHz, CD_3CN) δ 146.5 – 145.7 (m), 144.7 – 144.0 (m), 142.2 – 141.5 (m), 140.4 – 139.8 (m), 123.6 – 123.1 (m), 109.7 (d, *J* = 251.7 Hz).

^{19}F NMR (376 MHz, CD_3CN) δ -88.85 – -89.34 (m, 4F), -113.57 (p, *J* = 24.6 Hz, 1F), -139.54 – -139.95 (m, 4F).

Mass spectrometry was unable to match the product.

Synthesis of 5-benzoyl-2,2-dimethyl-1,3-dioxane-4,6-dione (205)



To a round bottomed flask cooled in ice water was added MeCN (2.5 mL), Meldrum's acid (1.448 g) and DMAP (2.440 g). Upon complete dissolution of these reagents, benzoyl chloride dissolved in MeCN (0.5 mL) was added over 40 minutes. The mixture was allowed to stir for 16 hours and allowed to warm to room temperature. Afterwards 1M HCl (2 mL) was added, and the mixture stirred for a further 5 minutes. The volatiles were removed under reduced pressure, the mixture was filtered, and the filtrate washed with water which yielded the desired product **205** as a cream solid in 60% yield (1.508 g).

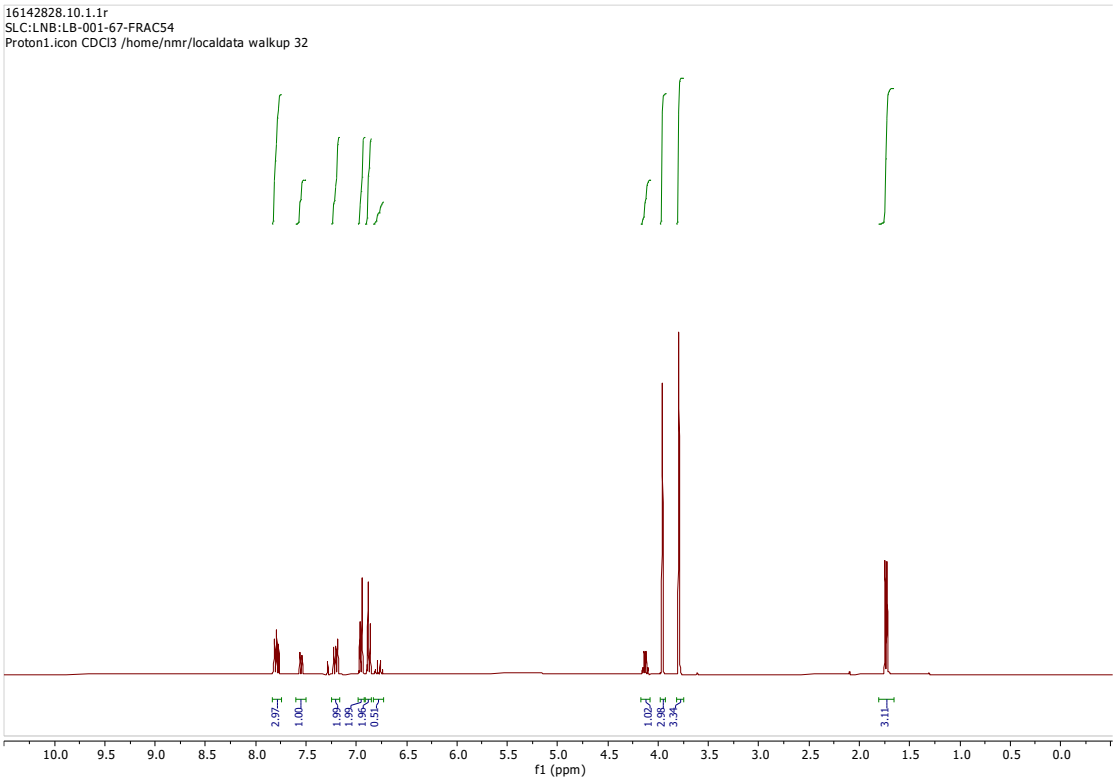
^{1}H NMR (400 MHz, $CDCl_3$) δ 15.47 (s, 1H), 7.72 – 7.64 (m, 2H), 7.63 – 7.56 (m, 1H), 7.52 – 7.41 (m, 2H), 1.84 (s, 6H).

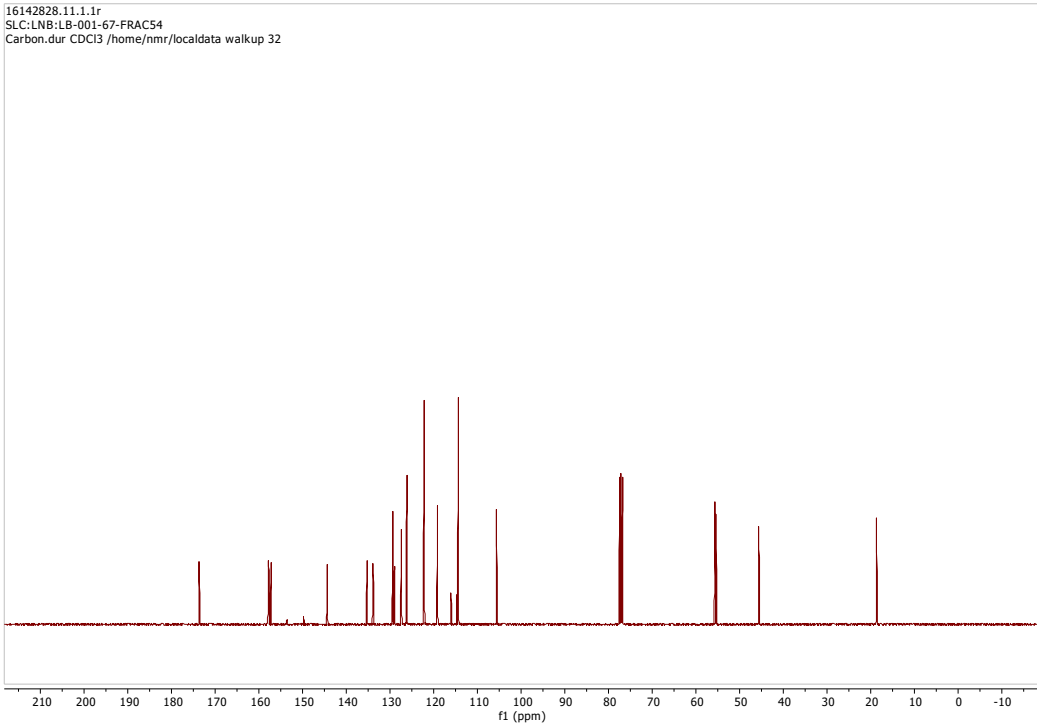
^{13}C NMR (101 MHz, $CDCl_3$) δ 189.4, 171.1, 159.9, 133.5, 132.8, 129.6, 128.2, 105.1, 91.0, 26.9.

LCMS (ESI^+) r.t. = 1.5 mins, *m/z* = 249.3 $[M+H]^+$

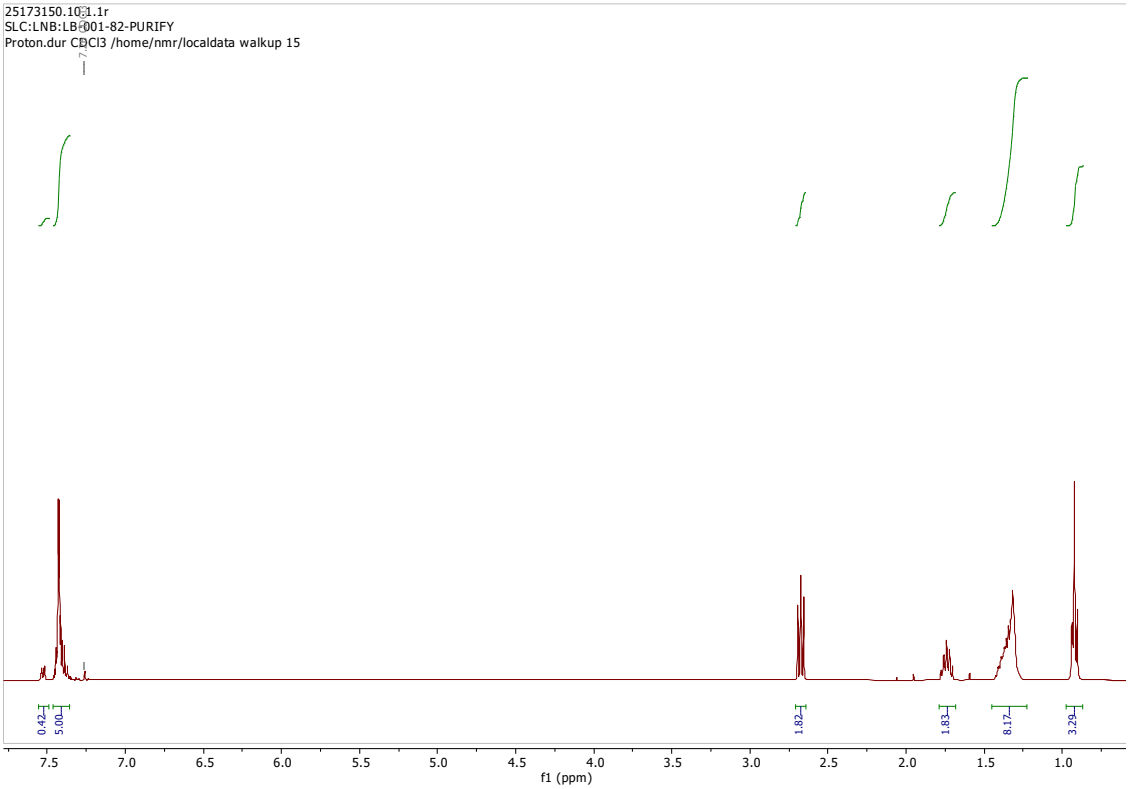
8 NMR data for 151 and 152

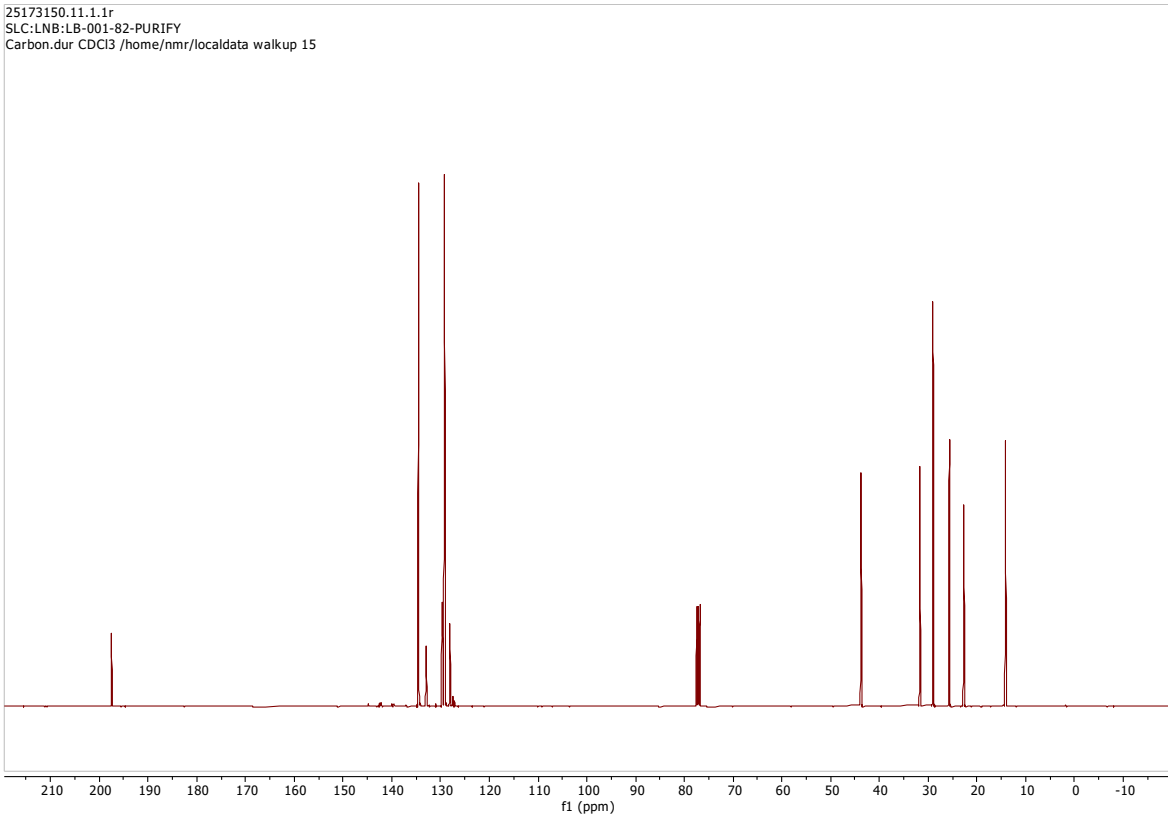
8.1 NMR Data evidencing preparation of 151





8.2 NMR Data evidencing preparation of 152





9 Appendix: Crystal Structure Data

9.1 Sample Analysis

For X-Ray crystallography, single crystals were taken and analysed at 120 K, except for **21** which was collected at 250 K. Samples were collected using a Bruker D8 Venture, the radiation source was Mo Kα (λ = 0.71073). Structures were solved by direct method and refined by full-matrix least squares on F^2 using Olex2, the refinement program was SHELXL 2017/1 (Sheldrick 2015) and the solution program was XS (Sheldrick 2008).

All sample analysis and refinement was performed by Dr Dmitry Yufit, Durham University who is kindly thanked for the help in obtaining theses samples.

9.2 Crystal Structure Determination of 98

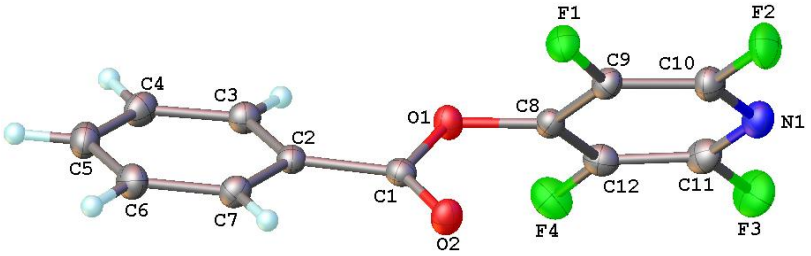


Figure 9.1: Crystal structure of **99**. Crystal structures are reported with a 50% thermal ellipsoid probability.

Table 9.1: Crystal structure data for **99**.

Identification code	22srv181
Empirical formula	$C_{12}H_5F_4NO_2$
Formula weight	271.17
Temperature/K	120.00
Crystal system	orthorhombic
Space group	Pbcn
a/Å	14.9414(5)
b/Å	5.9311(2)
c/Å	24.0754(8)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2133.54(12)
Z	8
ρ_{calc}g/cm^3	1.688
μ/mm^{-1}	0.162
F(000)	1088.0
Crystal size/mm^3	0.19 × 0.08 × 0.03
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.346 to 59.992
Index ranges	-21 ≤ h ≤ 20, -8 ≤ k ≤ 8, -33 ≤ l ≤ 33
Reflections collected	59656
Independent reflections	3110 [R_{int} = 0.0562, R_{sigma} = 0.0197]
Data/restraints/parameters	3110/0/192
Goodness-of-fit on F^2	1.105
Final R indexes [I>=2σ (I)]	R_1 = 0.0524, wR_2 = 0.1159
Final R indexes [all data]	R_1 = 0.0615, wR_2 = 0.1200
Largest diff. peak/hole / e Å^{-3}	0.39/-0.25

Sample **99** was crystallised by removal of column chromatography solvent under reduced pressure.

9.3 Crystal Structure Determination of 135

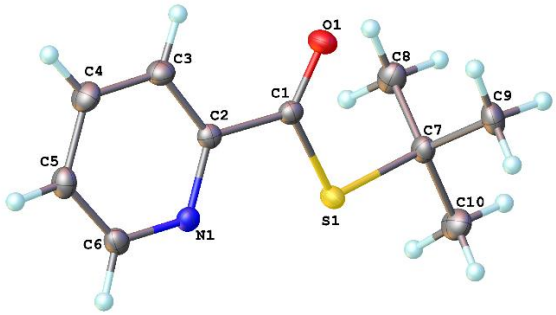


Figure 9.2: Crystal structure of compound **135**. Crystal structures are reported with a 50% thermal ellipsoid probability.

Table 9.2: Crystal data and refinement properties of compound **135**.

Identification code	22srv226
Empirical formula	$C_{10}H_{13}NOS$
Formula weight	195.27
Temperature/K	120.00
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.3548(2)
b/Å	9.7389(2)
c/Å	11.1668(3)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1017.36(4)
Z	4
ρ_{calc}g/cm^3	1.275
μ/mm^{-1}	0.278
F(000)	416.0
Crystal size/mm^3	0.26 × 0.06 × 0.04
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.55 to 59.988
Index ranges	-13 ≤ h ≤ 13, -13 ≤ k ≤ 13, -15 ≤ l ≤ 15
Reflections collected	30767
Independent reflections	2963 [R_{int} = 0.0437, R_{sigma} = 0.0216]
Data/restraints/parameters	2963/42/170
Goodness-of-fit on F^2	1.089
Final R indexes [I>=2σ (I)]	R_1 = 0.0262, wR_2 = 0.0615
Final R indexes [all data]	R_1 = 0.0276, wR_2 = 0.0621
Largest diff. peak/hole / e Å^{-3}	0.29/-0.19
Flack parameter	0.02(2)

Sample **135** was crystallised by slow evaporation of column chromatography solvents. This structure was published in the CCDC database.

9.4 Crystal Structure Determination of 143

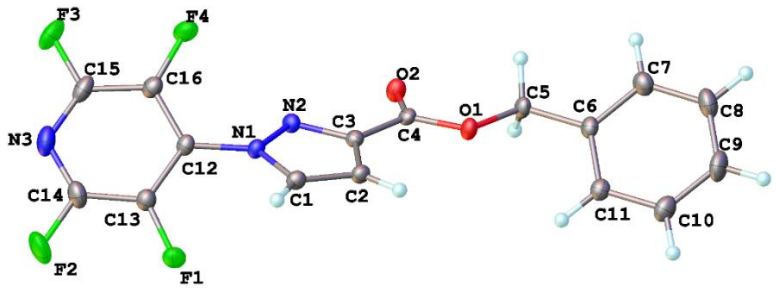


Figure 9.3: Crystal structure of compound **143**. Crystal structures are reported with a 50% thermal ellipsoid probability.

Table 9.3: Crystal data and refinement properties of compound **143**.

Identification code	22srv228
Empirical formula	$C_{16}H_9F_4N_3O_2$
Formula weight	351.26
Temperature/K	120.00
Crystal system	triclinic
Space group	P-1
a/Å	7.4235(3)
b/Å	7.7365(3)
c/Å	14.5301(5)
α/°	84.0800(13)
β/°	87.0755(13)
γ/°	61.6321(12)
Volume/Å^3	730.36(5)
Z	2
ρ_{calc}g/cm^3	1.597
μ/mm^{-1}	0.142
F(000)	356.0
Crystal size/mm^3	0.31 × 0.11 × 0.02
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.638 to 59.998
Index ranges	$-10 \leq h \leq 10$, $-10 \leq k \leq 10$, $-20 \leq l \leq 20$
Reflections collected	24350
Independent reflections	4250 [R_{int} = 0.0564, R_{sigma} = 0.0376]
Data/restraints/parameters	4250/0/262
Goodness-of-fit on F^2	1.061
Final R indexes [I>=2σ (I)]	R_1 = 0.0447, wR_2 = 0.1058

Final R indexes [all data]	R_1 = 0.0533, wR_2 = 0.1104
Largest diff. peak/hole / e Å^{-3}	0.41/-0.23

Sample **143** was crystallised by slow evaporation of EtOAc.

9.5 Crystal Structure Determination of 170

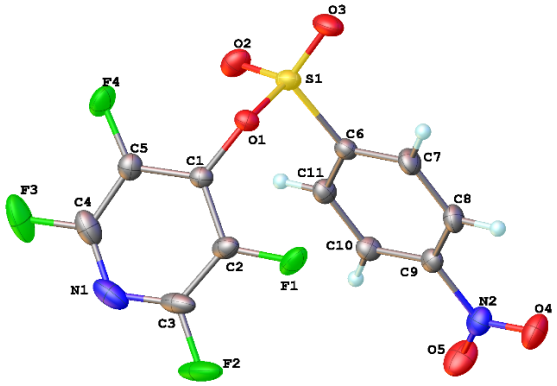


Figure 9.4: Crystal structure of compound **170**. Crystal structures are reported with a 50% thermal ellipsoid probability.

Table 9.4: Crystal data and refinement properties of compound **170**.

Identification code	22srv194
Empirical formula	$C_{11}H_4F_4N_2O_5S$
Formula weight	352.22
Temperature/K	120.00
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.0768(2)
b/Å	11.1268(3)
c/Å	16.2657(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1280.80(6)
Z	4
ρ_{calc}g/cm^3	1.827
μ/mm^{-1}	0.334
F(000)	704.0
Crystal size/mm^3	0.21 × 0.18 × 0.05
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.436 to 59.982
Index ranges	-9 ≤ h ≤ 9, -15 ≤ k ≤ 15, -22 ≤ l ≤ 22
Reflections collected	38493
Independent reflections	3717 [R_{int} = 0.0413, R_{sigma} = 0.0208]

Data/restraints/parameters	3717/0/208
Goodness-of-fit on F^2	1.052
Final R indexes [I>=2σ (I)]	R_1 = 0.0280, wR_2 = 0.0688
Final R indexes [all data]	R_1 = 0.0298, wR_2 = 0.0696
Largest diff. peak/hole / e $Å^{-3}$	0.24/-0.25
Flack parameter	0.03(2)

Sample **170** was crystallised by removal of column chromatography solvent under reduced pressure.

9.6 Crystal Structure Determination of 168

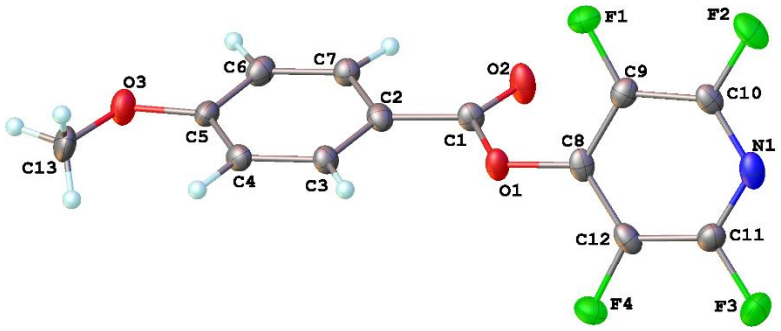


Figure 9.5: Crystal structure of **168**. Crystal structures are reported with a 50% thermal ellipsoid probability.

Table 9.5: Crystal structure data for **168.**

Identification code	22srv193
Empirical formula	$C_{13}H_7F_4NO_3$
Formula weight	301.20
Temperature/K	120.00
Crystal system	monoclinic
Space group	$P2_1$
a/Å	7.3541(5)
b/Å	13.9976(8)
c/Å	11.8164(8)
α/°	90
β/°	90.754(2)
γ/°	90
Volume/$Å^3$	1216.27(14)
Z	4
$\rho_{calc}g/cm^3$	1.645
μ/mm^{-1}	0.157
F(000)	608.0
Crystal size/mm^3	0.13 × 0.11 × 0.06
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.512 to 59.99

Index ranges	-10 ≤ h ≤ 10, -19 ≤ k ≤ 19, -16 ≤ l ≤ 16
Reflections collected	27320
Independent reflections	7090 [R_{int} = 0.0498, R_{sigma} = 0.0508]
Data/restraints/parameters	7090/1/382
Goodness-of-fit on F^2	1.025
Final R indexes [I>=2σ (I)]	R_1 = 0.0586, wR_2 = 0.1349
Final R indexes [all data]	R_1 = 0.0710, wR_2 = 0.1417
Largest diff. peak/hole / e $Å^{-3}$	0.43/-0.28
Flack parameter	-0.1(3)

Sample **168** was crystallised by hexane/EtOAc vapour diffusion.

9.7 Crystal Structure Determination of 21

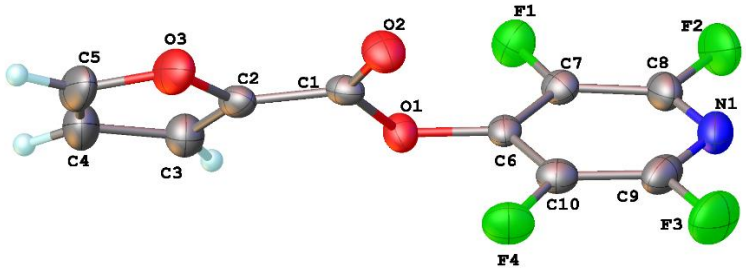


Figure 9.6: Crystal structure of **21**. Crystal structures are reported with a 50% thermal ellipsoid probability.

Table 9.6: Crystal structure data for **21**.

Identification code	22srv192
Empirical formula	$C_{10}H_3F_4NO_3$
Formula weight	261.13
Temperature/K	250.00
Crystal system	monoclinic
Space group	P2/n
a/Å	12.1379(7)
b/Å	5.6504(3)
c/Å	15.6992(10)
α/°	90
β/°	111.639(2)
γ/°	90
Volume/$Å^3$	1000.83(10)
Z	4
ρ_{calc}g/cm^3	1.733
μ/mm^{-1}	0.176
F(000)	520.0
Crystal size/mm^3	0.26 × 0.22 × 0.07
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.316 to 54.998

Index ranges	-15 ≤ h ≤ 15, -7 ≤ k ≤ 7, -20 ≤ l ≤ 20
Reflections collected	24079
Independent reflections	2305 [R_{int} = 0.0532, R_{sigma} = 0.0284]
Data/restraints/parameters	2305/0/163
Goodness-of-fit on F^2	1.167
Final R indexes [I>=2σ (I)]	R_1 = 0.0757, wR_2 = 0.1356
Final R indexes [all data]	R_1 = 0.0941, wR_2 = 0.1430
Largest diff. peak/hole / e $Å^{-3}$	0.24/-0.22

Sample was crystallised by hexane/EtOAc vapour diffusion.

Note: Compound undergoes a phase transition at 150 - 160 K and this data was collected at 250 K to accommodate. There are also weak CH…N bonds present.

9.8 Crystal Structure Determination of 203

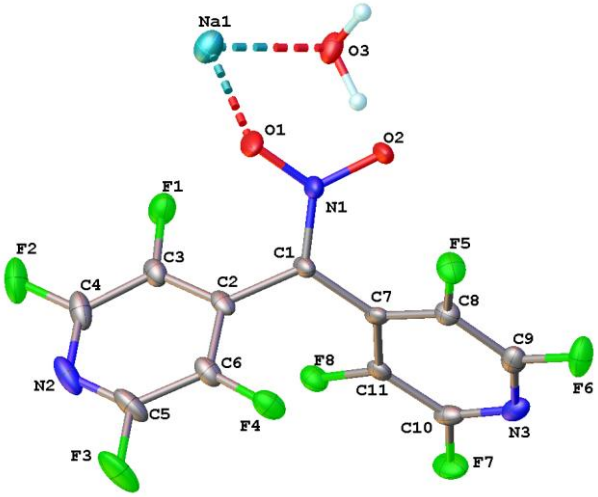


Figure 9.7: Crystal structure of **203**. Crystal structures are reported with a 50% thermal ellipsoid probability.

Table 9.7: Crystal structure data for **203.**

Identification code	22srv176
Empirical formula	$C_{11}H_2F_8N_3NaO_3$
Formula weight	399.15
Temperature/K	120.00
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	5.6625(2)
b/Å	25.8630(10)
c/Å	9.6369(4)
α/°	90
β/°	106.1621(15)
γ/°	90
Volume/$Å^3$	1355.54(9)
Z	4

ρ_{calc}g/cm^3	1.956
μ/mm^{-1}	0.240
F(000)	784.0
Crystal size/mm^3	0.16 × 0.04 × 0.01
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.674 to 53.988
Index ranges	-7 ≤ h ≤ 7, -33 ≤ k ≤ 33, -12 ≤ l ≤ 12
Reflections collected	32972
Independent reflections	2961 [R_{int} = 0.0519, R_{sigma} = 0.0253]
Data/restraints/parameters	2961/2/243
Goodness-of-fit on F^2	1.134
Final R indexes [I>=2σ (I)]	R_1 = 0.0684, wR_2 = 0.1567
Final R indexes [all data]	R_1 = 0.0792, wR_2 = 0.1627
Largest diff. peak/hole / e Å^{-3}	0.70/-0.84

Sample **203** was crystallised by using hexane/EtoAc vapour diffusion.

9.9 Crystal Structure Determination of 204

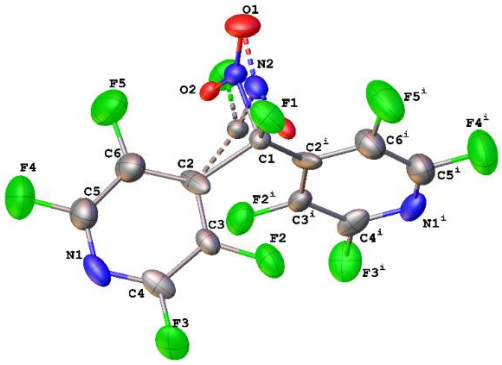


Figure 9.8: Crystal structure of **204**. Crystal structures are reported with a 50% thermal ellipsoid probability.

Table 9.8: Crystal structure data for **204**

Identification code	21srv483
Empirical formula	$C_{11}F_9N_3O_2$
Formula weight	377.14
Temperature/K	120.0
Crystal system	orthorhombic
Space group	Fdd2
a/Å	28.897(3)
b/Å	7.7609(8)
c/Å	11.1083(12)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2491.3(5)
Z	8
ρ_{calc}g/cm^3	2.011

μ/mm^{-1}	0.229
F(000)	1472.0
Crystal size/mm^3	0.22 × 0.14 × 0.02
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.64 to 51.972
Index ranges	-35 ≤ h ≤ 35, -9 ≤ k ≤ 9, -13 ≤ l ≤ 13
Reflections collected	9421
Independent reflections	1225 [R_{int} = 0.0478, R_{sigma} = 0.0322]
Data/restraints/parameters	1225/8/132
Goodness-of-fit on F^2	1.114
Final R indexes [I>=2σ (I)]	R_1 = 0.0702, wR_2 = 0.1594
Final R indexes [all data]	R_1 = 0.0876, wR_2 = 0.1708
Largest diff. peak/hole / e Å^{-3}	0.28/-0.24
Flack parameter	0.2(6)

Sample **204** was crystallised by rapid removal of Et_2O under reduced pressure. Note: Compound was severely disordered and can only be used as conformation of chemical identity. Attempts to recrystallise in a more ordered fashion were unsuccessful.

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