Fluorinated Azaheterocycles

HEERAN, DARREN

Fluorinated Azaheterocycles

Darren Heeran

Department of Chemistry

University of Durham

This dissertation is submitted for the degree of

Doctor of Philosophy

St Aidan's College

2018

To Mam and Dad...

Declaration

The work described in this thesis was carried out at Durham University between October 2014 and October 2017. This thesis is the work of the author, except where acknowledged by reference, and has not been submitted for any other degree. The copyright of this thesis rests with the author. No quotation from it should be published without the prior written consent and information derived from it should be acknowledged.

Parts of this work have been the subject of the following publications:
1) D. Heeran, G. Sandford, *Tetrahedron*, 2016, **72**, 2456–2463, Fluorination of pyrrole derivatives by Selectfluor^{TM}.

This work has been presented, in part, at:
1) RSC Organic Division Meeting, 29th March 2017, Durham, UK, *poster presentation, prize for poster presentation.*
2) 18th Tetrahedron Symposium: Challenges in Organic Chemistry, 28th - 30th June 2017, Budapest, Hungary, *poster presentation*.
3) Department of Chemistry Annual Postgraduate Research Symposium, 15th June 2017, Durham, UK*, oral presentation, prize for oral presentation.*
4) European Symposium on Organic Reactivity, 3rd - 8th September 2017, Durham, UK, *poster presentation.*
5) 17th Annual RSC Fluorine Subject Group Meeting, 18th - 19th September 2017, Leicester, UK, *oral presentation, prize for oral presentation.*

Acknowledgements

Firstly, I would like to thank my supervisor, Professor Graham Sandford, for his invaluable support and many lessons, in chemistry and in life. Geezer.

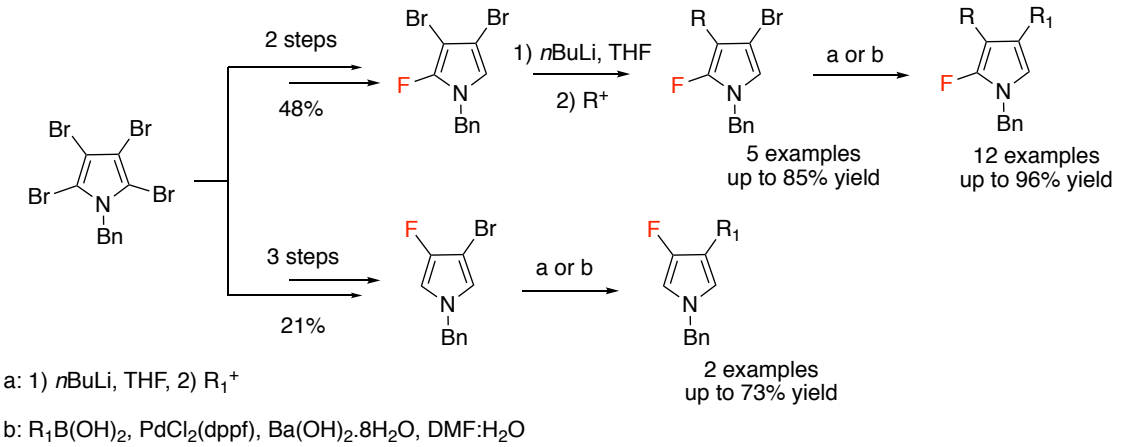
My research in Durham would not have been possible without the amazing help of the staff at Durham. Particular thanks go to Dr Alan Kenwright, Dr Juan Aguilar and Mrs Catherine Heffernan (NMR); Dr Jackie Mosely, Mr Peter Stokes and Dr Dave Parker (Mass Spectrometry); Mr Malcolm Richardson and Mr Aaron Brown (Glassblowing); Dr Dmitry Yufit (X-ray crystallography) and Dr Mark Fox (DFT). Thanks also go to EPSRC and the Royal Society for funding.

Thanks to all who have passed through CG115 during my time in Durham, particularly Tony, Craig, Etienne, Josh, Marcus, Alex H, Javi, Ben, Alex M, Hedi, Anne, and Zahide who made the failed reactions more bearable. A special mention to Tony and Craig for their help, support and enthusiasm when I first started in the lab, it was much appreciated. Finally, I would like to thank my family and friends for their love and support.

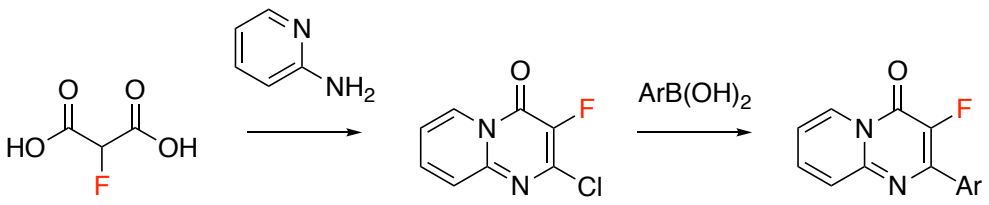
Abstract

Fluorinated heterocyclic motifs have found wide application across the life science industries. Therefore, there is profound interest in the development of new and efficient methodology for the incorporation of fluorine into heterocyclic structures. This thesis is concerned with the development of processes for the incorporation of fluorine into the biologically important azaheterocycles, pyrroles and pyrido[1,2-a]pyrimidines, for which current methods are limited.

Firstly, the fluorination of pyrroles with Selectfluor^{TM} was studied systematically. Pyrrole substrates bearing electron-withdrawing substituents were found to give fluorinated products but, in all cases, competing oxidation and subsequent polymerisation limited the attainable yields. From this, a tetrabromopyrrole was instead employed which, by lithiation and subsequent reaction with NFSI, gave access to polybrominated 2- and 3-fluoropyrroles. The bromine atoms could be used for subsequent derivatisation by debromolithiation and reaction with a range of electrophiles as well as palladium catalysed Suzuki cross-couplings to give access to a diverse library of highly functionalised fluoropyrrole products.



The synthesis of a fluorinated pyrido[1,2-a]pyrimidin-4-one scaffold was also investigated using a fluorinated building block approach. The cyclisation of 2-fluoromalonic acid with 2-aminopyridine in $POCl_3$ gave a fluorinated pyrido[1,2-*a*]pyrimidin-4-one substrate which was further derivatised by Suzuki cross-coupling reactions.



Contents

Nomenclature

Abbreviations

18-Crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane
Boc	*t*-Butyloxycarbonyl
DAST	Diethylaminosulphur trifluoride
DBMH	1,3-Dibromo-5,5-dimethylhydantoin
DBN	1,5-Diazobicyclo[4.3.0]non-5-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Diglyme	Diethylene glycol dimethyl ether
DMAD	Dimethyl acetylenedicarboxylate
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDG	Electron-donating group
EWG	Electron-withdrawing group
GC-MS	Gas chromatography-mass spectrometry
HFP	Hexafluoropropene

HMGC	Hexamethyl guanidinium chloride
LTMP	2,2,6,6-Tetramethylpiperidine
Mes	Mesityl
MTBE	Methyl *t*-butylether
MW	Microwave
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NFSI	*N*-Fluorobenzenesulfonimide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
OLED	Organic light emitting diode
OTFT	Organic thin film transistor
ppm	Parts per million
SAR	Structure-activity relationship
Selectfluor^{TM}	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TEA	Triethylamine
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
THF	Tetrahydrofuran

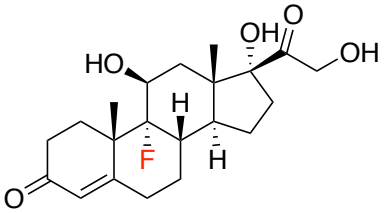
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl

Chapter 1

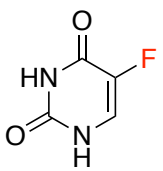
Synthesis of Fluorinated 5-Membered Azaheterocycles

1.1 Fluorine in Pharmaceuticals

The first reports of the introduction of fluorine into pharmaceutically relevant compounds were not made until the mid 1950s when seminal works by Fried and Sabo and Heidelberger *et al.*, reported the development of Fludrocortisone and 5-Fluorouracil respectively (Fig. 1.1).[1,2] These reports significantly altered current opinion at the time, which suggested that application of fluorinated molecules was limited to the industrial and military sectors. Fluorination has since became an important tool within drug design with over 150 fluorinated pharmaceuticals commercialised in the ensuing sixty years, revealing the ability of strategic fluorination to desirably modulate lipophilicity, metabolic stability and pH profiles of small molecules.



Fludrocortisone, **1**

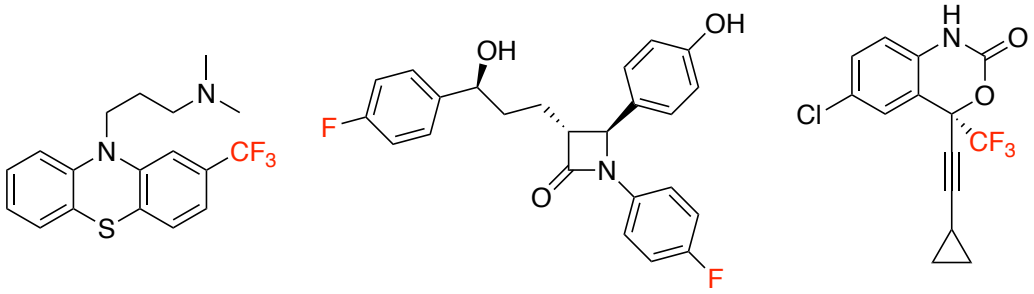


5-Fluorouracil, **2**

Figure 1.1: Structures of the first fluorine containing drugs.

The introduction of fluorinated moieties such as CF_3, SCF_3 or OCF_3, for example,

can significantly increase lipophilicity of an organic molecule and this effect can be exploited in drugs targeting the central nervous system, such as Triflupromazine (**3**), that require specific lipophilicities to efficiently pass the blood-brain barrier (Fig. 1.2).[3] Increased metabolic stability is also desirable for many pharmaceuticals to prevent rapid degradation *in vivo*, mainly via oxidative metabolism by the cyctochrome P450 enzyme family. Fluorine substitution of aromatic subunits has, therefore, been used to block metabolically labile sites and prolong the half-life of lead compounds, as exemplified by Ezetimibe (**4**). Modulation of pH has also been an effective strategy in improving drug potency, shown by Efavirenz (**5**), in which the trifluoromethyl group increases efficacy by lowering the p$K_a$of the cyclic carbamate enabling a key hydrogen bond with the target protein.[4]



Triflupromazine, **3**
Increased Lipophilicity

Ezetimibe, **4**
Enhanced Metabolic Stability

Efavirenz, **5**
pH Modulation

Figure 1.2: Examples of strategically fluorinated pharmaceuticals **3**, **4** and **5.**

The diversity of fluorinated moieties has also increased in recent years, coinciding with the development of new synthetic fluorination methodology, although the dominance of fluoro- and trifluoromethyl-aromatic subunits in FDA approved drugs is still clear to see (Fig. 1.3).

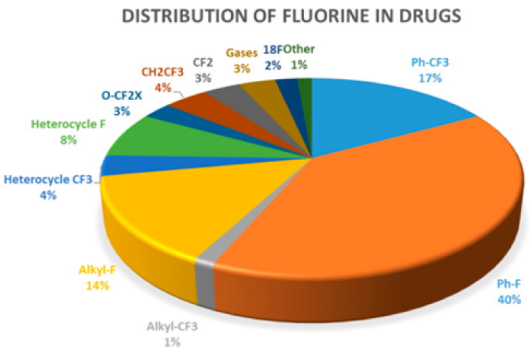


Figure 1.3: Distribution of fluorinated moieties in FDA approved drugs (1950-2014).[5]

These functionalities are made on large scale using well established Balz-Schiemann-, Halex- and Swarts-type chemistries and have allowed the successful discovery and optimisation of numerous drug molecules bearing ArF or $ArCF_3$ functional groups over many years (Fig. 1.4).[6] In contrast, fluoroheteroaromatic systems constitute a much smaller proportion of currently approved fluorinated drugs, and this is most likely a reflection of the availability of appropriate fluorinated heterocyclic building blocks and synthetic fluorination methodologies, which are often challenging, especially on the manufacturing scale.

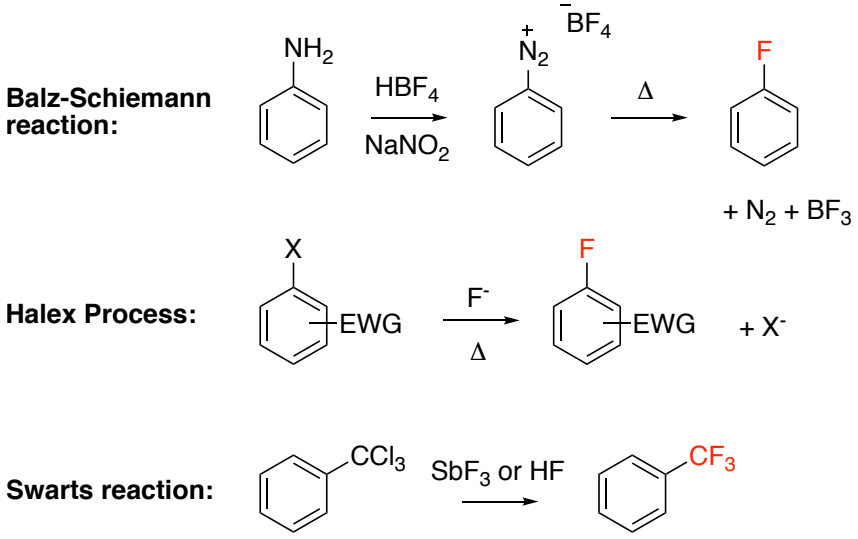


Figure 1.4: Traditional routes to fluoro- and trifluoromethyl-aromatic subunits of pharmaceuticals.

Of the fluoroheteroaromatic containing pharmaceuticals that have entered the market, fluorinated 6-membered azaheterocycles are found within a number of life science products. Voriconazole (antifungal, Pfizer), Capecitabine (anticancer, Roche), and Diclo-

sulam (herbicide, Dow) are well established pharmaceuticals (Fig. 1.5) with many others such as Abemaciclin (anticancer, Eli Lilly), Riociguat (heart failure, Bayer) and Verubecestat (Alzheimer's, Merck) in clinical trials.[7–9] Notably, these pharmaceuticals all contain a fluorinated six-membered azaheterocycle, such as a fluoro-pyridine or -pyrimidine structural subunit of which the synthesis at both discovery and manufacture scales is well established.[10–13]

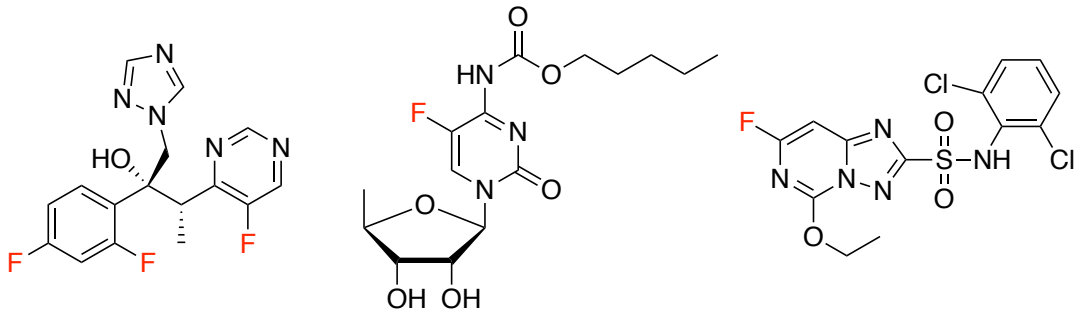


Figure 1.5: Commercialised life science products containing a fluorinated six-membered azaheterocycle.

For example, work in the late 1950s by Finger *et al.* demonstrated the efficient synthesis of 2-fluoropyridine and derivatives thereof, via a Halex process from the corresponding 2-chloropyridine derivative and KF. The synthesis of 3-fluoropyridines were later reported by Fukuhara *et al.* but, in this case, via a Balz-Schiemann type process from the corresponding 3-aminopyridine derivative (Fig. 1.6).[14–16]

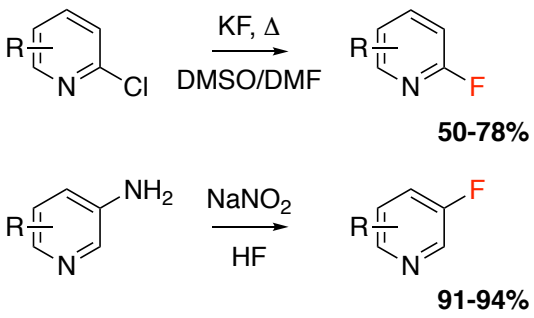


Figure 1.6: Synthesis of 2-fluoro and 3-fluoropyridine derivatives.

Similarly, 2-fluoropyrimidines have been synthesised in good yield via Halex processes from the corresponding 2-chloropyrimidine[17] whereas 5-fluoropyrimidines have been synthesised either by cyclisation of appropriate fluorinated precursors,[18–20] such as

fluoromalonate esters with amidine-based nucleophiles or via direct fluorination of a pyrimidine-based scaffold, such as uracil, which is used for the large scale synthesis of 5-fluorouracil (Fig. 1.7).[21]

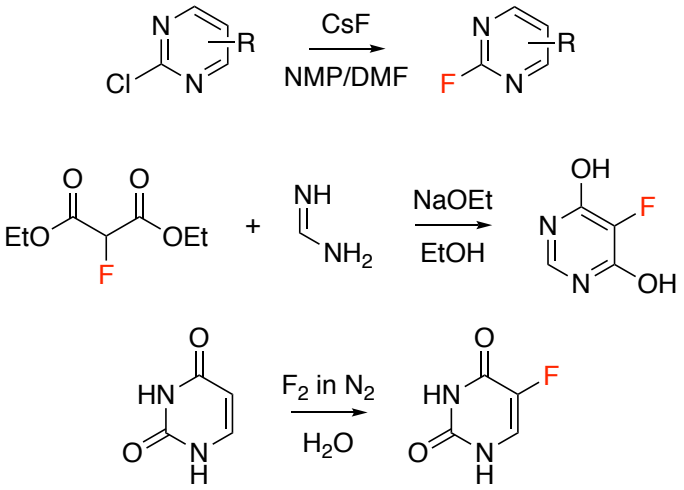
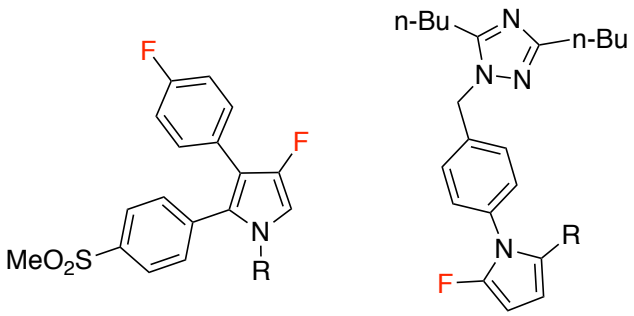


Figure 1.7: Synthesis of 2-fluoro and 5-fluoropyrimidines.

In contrast, corresponding five-membered azaheterocycles, such as fluoropyrrole derivatives, scarcely populate life science products, despite some biologically relevant fluorinated pyrroles coming to light recently (Fig. 1.8).[22,23] Therefore, the development of a general, efficient and regioselective process for the synthesis of a diverse library of functionalised fluoropyrrole derivatives would be hugely desirable and would facilitate the development of new, pharmaceutically relevant compounds. Hence, this chapter reviews the current state of the art for the synthesis of fluorinated pyrroles, as well as related imidazole and pyrazole derivatives, to provide background to the research described in this thesis.



9 **10**

Figure 1.8: Examples of biologically active fluoropyrrole derivatives.[22,23]

1.2 Synthesis of Fluoropyrroles

Controlled and selective monofluorination for regio- or stereo-selective incorporation of fluorine into organic substrates is a challenging task, especially in the context of five-membered heteroaromatic substrates such as fluoropyrroles. Current approaches utilise two main methods; i) cyclisation of fluorinated acyclic precursors, and ii) selective ring fluorination of a preformed pyrrole. There is also a limited number of examples in which fluorination of a non-aromatic precursor (such as pyrrolidine or pyrroline) followed by subsequent aromatisation yields the corresponding fluorinated pyrrole.

1.2.1 Fluorination of the Pyrrole Ring

Fluorination of pyrrole derivatives can be achieved using both electrophilic and nucleophilic sources of fluorine. Electrophilic fluorinating agents can exploit the innate reactivity of the electron-rich pyrrole core towards electrophiles without the need for prefunctionalisation, although some approaches do utilise a prefunctionalised substrate. Conversely, fluorination reactions of pyrroles with nucleophilic sources of fluorine require prefunctionalisation to give the desired umpolung reactivity of the pyrrole core.

1.2.1.1 Electrophilic Fluorination

The most direct method for the synthesis of fluoropyrroles is the transformation of C-H to C-F bonds by reaction of the parent pyrrole with an electrophilic fluorinating agent. Electrophilic bromination and chlorination reactions of pyrroles are very well established, where NBS, NCS, Br_2 or Cl_2, give simple access to a variety of halogenated pyrrole scaffolds.[24] However, the high reactivity of the electron rich aromatic system towards electrophiles has often proven to be problematic.

There have been a limited number of reactions of pyrrole derivatives and electrophilic fluorinating agents reported. An early study by Fornarini *et al.* attempted the selective fluorination of pyrrole with elemental fluorine, but recovered only tars, presumably resulting from oxidation/polymerisation pathways. In the same report, carefully controlled conditions (5% F_2 in He) were applied to *N*-methylpyrrole which yielded small

quantities of 2- and 3-fluoropyrroles alongside a small proportion of the fluoromethyl product. The conversion of the reaction was notably low (~ 6%) with higher conversions yielding tars, rendering this process synthetically impractical.[25]

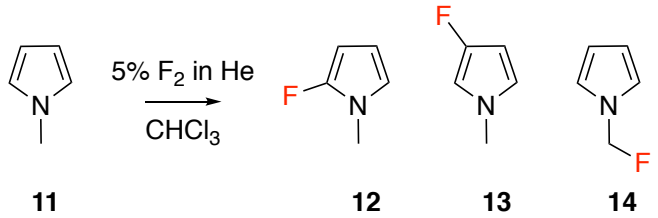
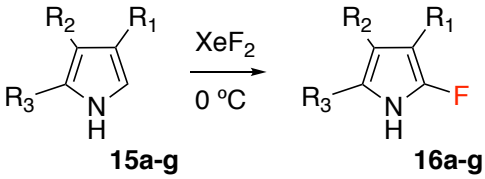


Figure 1.9: Fluorination reaction of *N*-methylpyrrole using F_2.

Following this early work, Wang and Scott later developed the first methodology for the synthesis of fluoropyrroles using XeF_2 without the requirement for *N*-protection.[26] Their findings show that pyrroles bearing EWGs, required to prevent oxidation of the substrate, could be fluorinated selectively at the 2-position even with substrates in which the 3-position was unsubstituted. (Table 1.1). Although, this methodology demonstrates good regioselectivity, the process is limited by yield, being constrained to substrates bearing EWGs and the economic restriction imposed by the use of XeF_2.

Table 1.1: Fluorination of pyrrole derivatives with XeF_2.



Entry	R_1	R_2	R_3	Solvent	Yield /%
a	H	H	CHO	MeCN	35
b	$CH_2CH_2CO_2Me$	CH_2CO_2Me	CHO	MeCN	32
c	H	H	CO_2Bn	MeCN	37
d	$CH_2CH_2CO_2Me$	CH_2CO_2Me	CO_2Bn	DCM	33
e	CH_2CO_2Me	$CH_2CH_2CO_2Me$	CO_2Bn	DCM	25
f	H	H	$COCl_3$	DCM	33
g	H	H	$CONMe_2$	DCM	54

Subsequent work by Gozzo *et al.* alleviated the need for EWGs in their synthesis of

2-fluoropyrrole (**18**) and *N*-methyl analogue (**12**) (Fig. 1.10).[27] Using SF_3^+, generated by electron ionisation of sulfur hexafluoride, F^+ is readily transferred in the gas phase to give the respective fluorinated cation which upon deprotonation using NMP rearomatises to give the desired monofluorinated compound. Despite this work demonstrating the first successful synthesis of 2-fluoropyrrole, the practical use of this methodology is unfeasible due to the nature of the fluorinating agent.

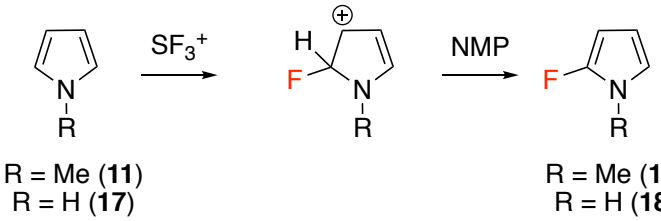


Figure 1.10: Fluorination of pyrrole and *N*-methylpyrrole using SF_3^+.

Soon after, however, Yamamoto *et al.* developed a much more convenient, solution phase methodology. Utilising a Lewis acid catalyst ($ZrCl_4$) and NFSI as the fluorinating agent, it was possible to regioselectively synthesise 2-fluoropyrrole in moderate yield (53%) under mild conditions (Fig. 1.11).[28] The success of this approach was attributed to the ability of $ZrCl_4$ to coordinate NFSI and consequently increase the electrophilicity of the fluorine atom. However, despite the reported success of this approach the substrate scope was not extended beyond this single example.

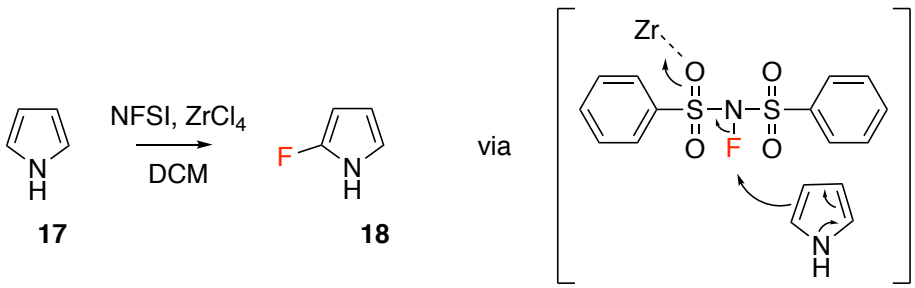


Figure 1.11: Lewis acid catalysed fluorination of pyrrole using NFSI.

An analogous approach using the more reactive Selectfuor^{TM} has also been demonstrated by Lindel *et al.* for a limited number of ester substituted pyrrole derivatives. Under microwave conditions, short reaction times were preferred to prevent by-product formation, which limited conversion to a maximum of approximately 50% in all instances. Despite

this, the desired 2-fluoropyrrole products could be isolated in low yields (18-44%) (Fig. 1.12).

Figure 1.12: Microwave assisted fluorination of substituted pyrrole derivatives using Selectfluor™.

More recent work by Tamamura *et al.*, using Selectfluor™, utilised a lipophilic anionic phase transfer catalyst in apolar solvents. Slow delivery of the insoluble Selectfluor™ into the apolar media tamed the reactivity towards electron rich pyrroles and provided access to some novel fluorinated pyrroles. However, in most cases, mixtures of fluorinated regiosomers were obtained, alongside appreciable quantities of recovered pyrrole starting material, which limited yields (Fig. 1.13).[29]

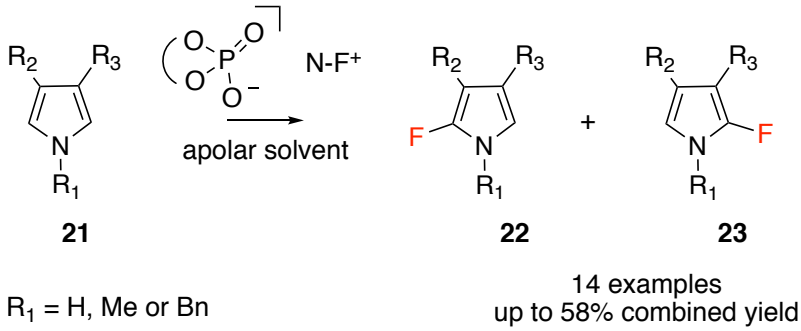
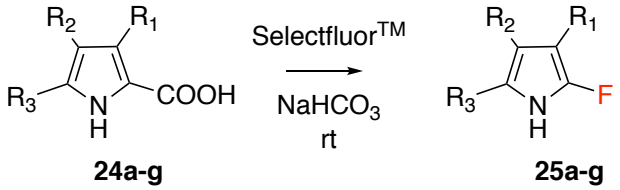


Figure 1.13: A phase transfer catalysis approach to substituted fluoropyrroles.

An alternative approach to fluorinated pyrroles, by formation of the corresponding anion prior to electrophilic fluorination has also been utilised. Using this approach, Wang and Scott developed a fluorodecarboxylation strategy in which the anion resulting from decarboxylation is subsequently fluorinated using Selectfluor™ (Table. 1.2). A range of highly substituted pyrrole-2-carboxylic acids, bearing both electron-withdrawing and electron-donating substituents, could be fluorinated in moderate yields.

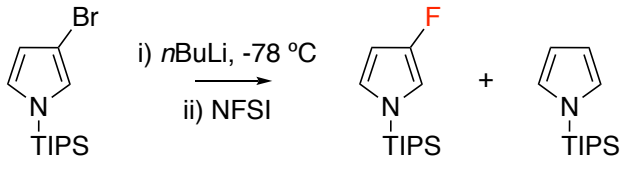
Table 1.2: Fluorodecarboxylation of pyrrole-2-carboxylic acids using Selectfluor™.



24a-g **25a-g**

Entry	R_1	R_2	R_3	Time /min	Yield /%
a	Me	Me	CO_2Bn	60	42
b	CH_2CO_2Me	CH_2CO_2Me	CHO	40	32
c	$CH_2CH_2CO_2Me$	CH_2CO_2Me	CO_2Bn	45	35
d	CH_2CO_2Me	$CH_2CH_2CO_2Me$	CO_2Bn	45	37
e	$CH_2CH_2CO_2Me$	CH_2CO_2Me	Me	20	47
f	Me	H	Me	20	34
g	Me	Me	Me	20	32

Similarly, alkyl lithium reagents can be used to form the corresponding anion that can be subsequently quenched with an electrophilic fluorinating agent. Early work in this area by Barnes *et al.* utilised a 3-bromopyrrole substrate (**26**) which, when treated with *n*BuLi followed by NFSI, gave the corresponding 3-fluoropyrrole (**27**) in 50% yield (Fig. 1.14).



26 **27** **28**

Figure 1.14: Synthesis of 3-fluoropyrrole derivative **27** via lithiation and quenching of brominated pyrroles.

The major observed by-product was hydrodebrominated starting material, attributed to a competing electron transfer reaction upon addition of NFSI.[30] Although no attempt was reported by Barnes *et al.* to remove the TIPS protecting group, later work by Leroy *et al.* showed that although deprotection and *in situ* use was possible for the synthesis of β-fluorinated porphyrins, isolation attempts yielded only sufficient quantities for char-

acterisation.[31,32] However, Barnes *et al.* did show the methodology to be applicable with alternative protecting groups with the synthesis of the highly functionalised 3-fluoropyrrole derivative **30** in 31% yield.

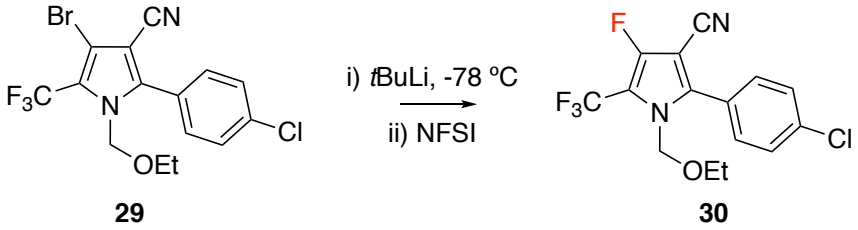


Figure 1.15: Synthesis of highly functionalised 3-fluoropyrrole derivative **30**.

A more recent modification of this methodology, offering the advantage of room temperature operation, involves the insertion of magnesium in the presence of LiCl to form the corresponding Grignard reagent (**31**). Treatment of **31** with NFSI in a 4:1 mixture of DCM/perfluorodecalin gives the desired fluoropyrrole product **27** in 43% yield (Fig. 1.16).[33] The fluorinated cosolvent is used in an attempt to minimise the formation of hydrodebrominated starting material **28**, with the authors suggesting the cosolvent provides a source from which the intermediate radical can abstract a fluorine atom.

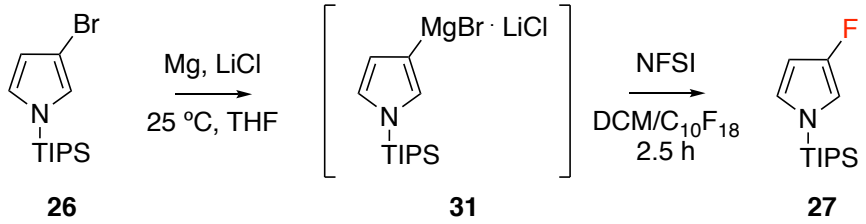
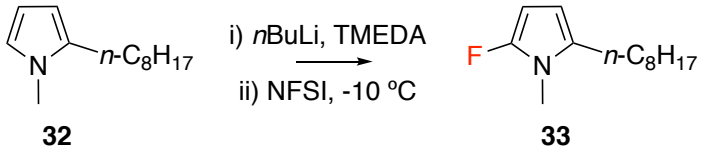


Figure 1.16: Grignard strategy for the synthesis of 3-fluoropyrrole derivative **27**.

A parallel approach was applied to provide access to 2-fluoropyrrole products without the need to prefunctionalise the pyrrole core with a halogen substituent. Dvornikova *et al.* successfully synthesised 2-fluoropyrrole derivative **33** in 40% yield by treatment of **32** with *n*BuLi and TMEDA at room temperature followed by quenching with NFSI (Fig. 1.17). Nonetheless, this methodology was not applied to any further pyrrole substrates.[34]

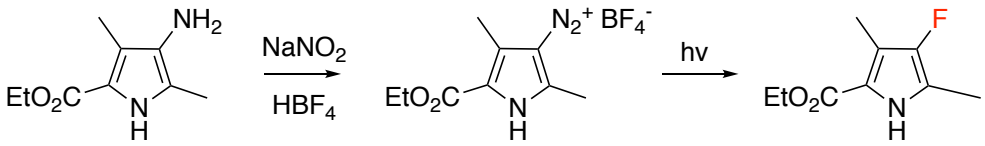


32 **33**

Figure 1.17: Synthesis of 2-fluoropyrrole derivative **33**.

1.2.1.2 Nucleophilic Fluorination

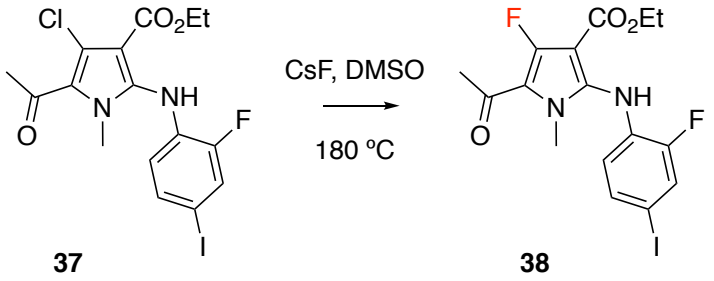
A limited number of reports that employ nucleophilic fluorinating agents to selectively fluorinate the pyrrole moiety have been reported. The first example of this approach was by Ogoshi *et al.* who developed a photochemical modification of the Balz-Schiemann reaction (See Fig. 1.4) as a route to 3-fluoropyrrole derivative **36** which was subsequently used for the synthesis of ring-fluorinated porphyrins (Fig. 1.18).[23] The process consisted of treatment of an aminopyrrole derivative with $NaNO_2$ in tetrafluoroboric acid to afford the diazonium tetrafluoroborate intermediate **35**. Subsequent irradiation of this intermediate gave the corresponding 3-fluoropyrrole product **36** in low yield (17%).



34 **35** **36**

Figure 1.18: Photochemical modification of the Balz-Schiemann reaction.

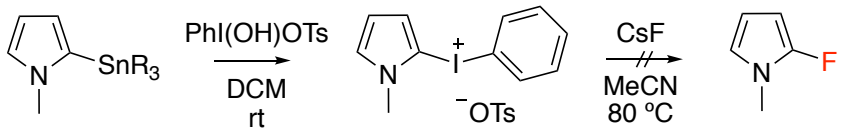
More recently, Wallace *et al.* showed showed that a suitably substituted chloropyrrole derivative, such as **37**, can undergo nucleophilic substitution using a fluoride source. The functionalisation of the pyrrole core with strongly electron-withdrawing substituents activates the chlorine atom towards substitution and, under forcing conditions, the corresponding 3-fluoropyrrole derivative **38** can be obtained (Fig. 1.19).[35] However, no yield was reported and the methodology was not expanded to encompass other analogues.



37 **38**

Figure 1.19: Nucleophilic substitution using CsF to produce 3-fluoropyrrole derivative **38**.

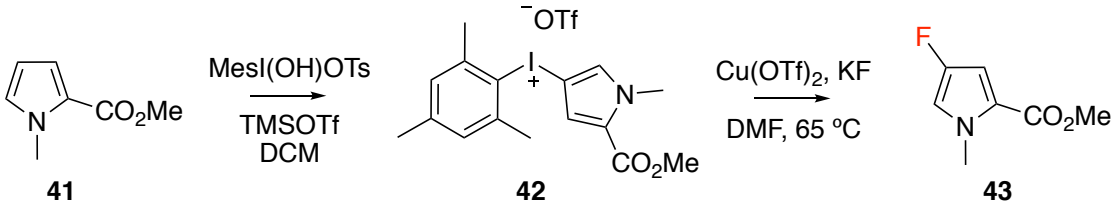
The nucleophilic fluorination of numerous aryl substrates was achieved by the reaction of an iodonium salt with a source of fluoride. Unfortunately, when this strategy was applied to the fluorination of arylheteroaryliodonium salt **40** using KF, prepared from the corresponding stannane derivative **39**, the reaction failed to give the corresponding fluoropyrrole derivative (Fig. 1.20).[36] In the case of pyrrole derivative **40**, the exclusive formation of fluorobenzene is observed, thought to be due to a combination of electronic and steric factors.



39 **40** **12**

Figure 1.20: Attempted synthesis of fluoropyrrole **12** via an intermediate iodonium salt.

However, more recently Sanford *et al.* have shown that Cu^{I} salts can promote the formation of fluorinated electron rich heterocycles via an intermediate iodonium salt. Mesityl substituted iodonium salts, such as **42**, are well known to undergo sterically controlled oxidative addition at Cu^{I}, with selective transfer of the smaller aryl group, allowing the synthesis of 3-fluoropyrrole derivative **43** in low yield (8%) (Fig. 1.21).[37] This methodology was used for the synthesis of the respective ^{18}F radiolabelled compound.



41 **42** **43**

Figure 1.21: Cu^{I} mediated fluorination of iodonium salt **42**.

1.2.2 Cyclisation Reactions

Early work using cyclisation processes for the synthesis of fluoropyrrole derivatives focused on the synthesis of 3,4-difluoropyrrole (**48**) due to its potential use as a precursor to fluorinated porphyrins. Leroy *et al.* first accessed **48** via a barium-promoted copper chromite decarboxylation of the corresponding 2-carboxylic acid **47**. This was obtained by thermal [3+2] cycloaddition of aziridine derivative **44** with chlorotrifluoroethene to give pyrrolidine **45**, which could be oxidised and deprotected to give **47** (Fig. 1.22).[38]

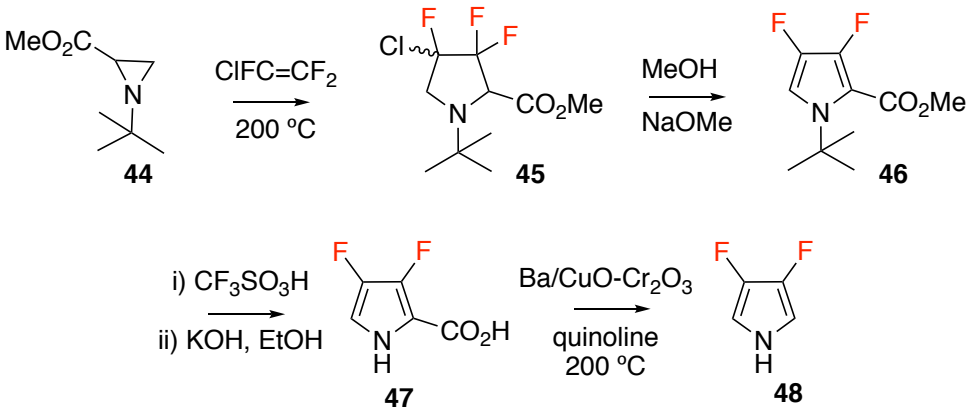


Figure 1.22: Synthesis of 3,4-difluoropyrrole (**48**) from *t*butyl aziridine derivative (**44**).

The limiting factor of this methodology, however, was the low yielding (21%), high temperature decarboxylation step that also proved difficult to scale up. Later work by DiMagno *et al.* developed an improved route that circumvented the decarboxylation step by elimination of HF from tetrafluoropyrrolidine (**49**) (Fig. 1.23).[39]

Figure 1.23: Improved synthesis of 3,4-difluoropyrrole (**48**).

Several cyclisation strategies towards monofluorinated pyrroles have also been reported. The first synthesis of 3-fluoropyrrole derivatives using this approach was reported by Buhr *et al.*, and involves the thermal or photochemically induced ring expansion of cyclobutane derivative **50**. This forms the highly strained azirine derivative **51** which readily

ring opens to the pyrroline carbene derivative **52**. The corresponding ylide of carbene **52** can then react with nucleophilic solvents, such as benzene, to give 5-aryl-3-fluoropyrrole derivatives in low yields (10-12%) (Fig. 1.24).[40]

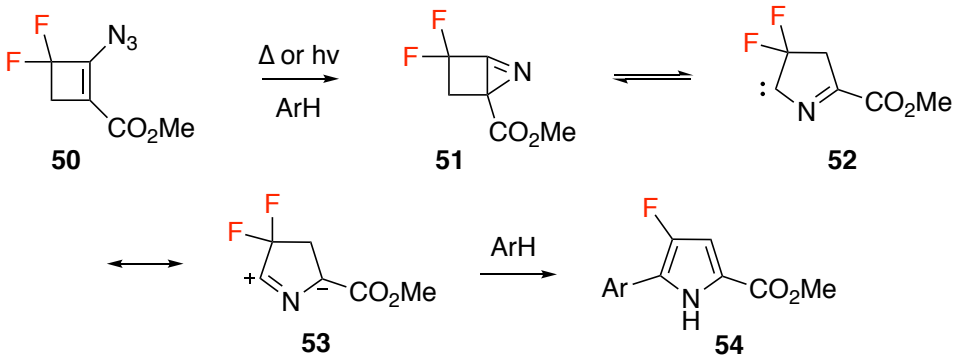
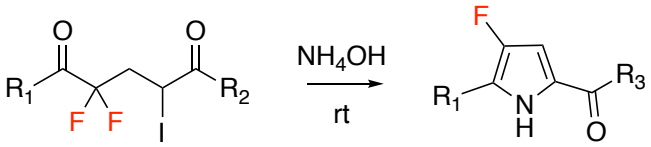


Figure 1.24: Buhr's synthesis of 5-aryl-3-fluoropyrrole derivatives **54**.

A much more convenient approach, developed by Burton *et al.*, showed that conversion of α,α-difluoro-γ-iodo-γ-(EWG)-substituted ketones in ammonium hydroxide to 3-fluoropyrrole derivatives (**56a-g**) proceeded smoothly at room temperature in good yields (Table 1.3).[41] The efficient synthesis of fluorinated precursors **55a-g**, via the photochemical addition of iododifluoromethyl ketones to electron deficient olefins, was also noted.

Table 1.3: Synthesis of 3-fluoropyrrole derivatives from α,α-difluoro-γ-iodo-γ-(EWG)-substituted ketones.

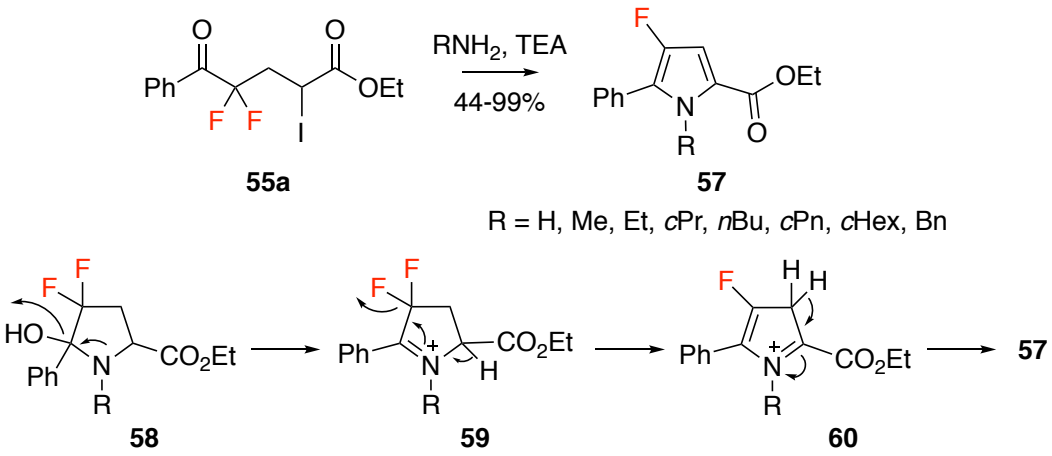


55a-g **56a-g**

Entry	R_1	R_2	R_3	Time /h	Yield /%
a	Ph	OEt	OEt	24	92
b	Ph	OMe	NH_2	24	95
c	Ph	NMe_2	NMe_2	24	79
d	nC_4H_9	OEt	NH_2	24	88
e	nC_4H_9	OMe	NH_2	24	90
f	nC_6H_{13}	OEt	NH_2	24	92
g	nC_6H_{13}	NMe_2	NMe_2	24	90[a]

[a]NaOH was added to complete conversion to **56g**

Moreover, the reaction of **55a** was extended by Kim *et al.* to incorporate various primary amines, producing a range of *N*-substituted 2-phenyl-3-fluoropyrrole derivatives in good yields (Fig. 1.25).[42] An ionic reaction mechanism involving deprotonation and dehydrofluorination was proposed on the basis of the isolation of hemiaminal intermediate **58**.



55a **57**

58 **59** **60**

Figure 1.25: Synthesis of *N*-substituted 3-fluoropyrrole derivatives from **55a** using primary amines.

Burton *et al.* also showed that it was possible to modify the starting substrate **55** to an analogous compound bearing a TMS substituent (**61**). After desilylation using KF, the synthesis of 3-fluoropyrrole derivatives without a substituent at the 2-position (**63**) was possible in excellent yield using these modified substrates (Fig. 1.26).[43]

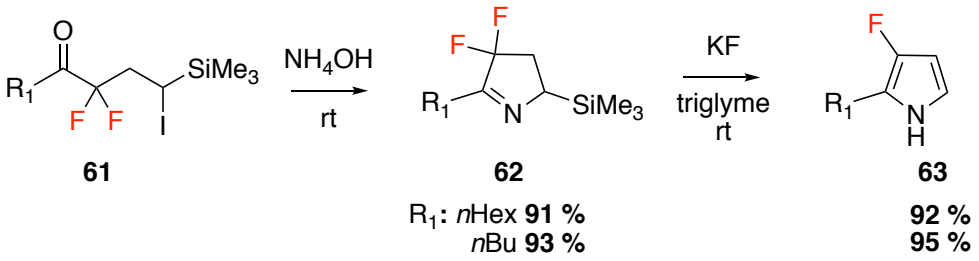


Figure 1.26: Synthesis of 2-alkyl-3-fluoropyrroles (**63**) from α,α-difluoro-γ-iodo-γ-TMS ketones.

The scope of this work was broadened further by Kim *et al.*, who employed an aldehydic analogue of **61** in combination with various primary amines to produce a range of *N*-substituted 3-fluoropyrrole derivatives. A notable result of this work was the synthesis of unprotected 3-fluoropyrrole in good yield (69% over two steps) (Fig. 1.27), which is not readily accessible by selective fluorination of pyrrole or its derivatives (See Section 1.2.1).[44]

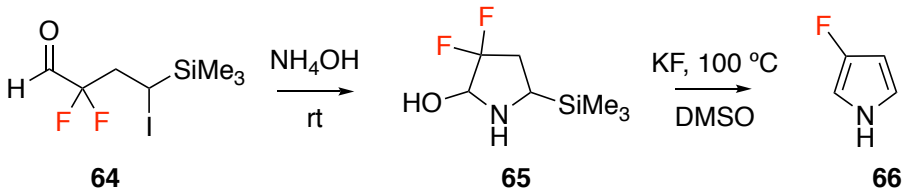


Figure 1.27: Synthesis of unprotected 3-fluoropyrrole **66**.

Isocyanide derivatives have also been applied as useful building blocks for the synthesis of pyrroles and analogous routes to fluoropyrrole derivatives have emerged. Uno *et al.* reported an early example of this approach, demonstrating the synthesis of 3-fluoropyrrole derivatives via the addition of isocyanomethylide anions to α-fluoroalkenyl sulfones and sulfoxides (Fig. 1.28).[45] However, the two isocyanide derivatives utilised (**68** and **70**) both proceeded to give low yields of the desired 3-fluoropyrrole derivatives.

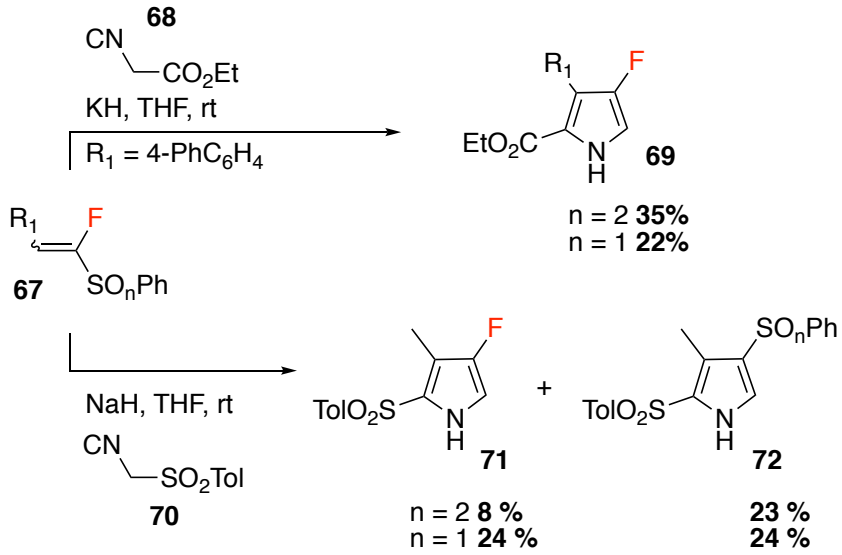


Figure 1.28: Synthesis of 3-fluoropyrrole derivatives **69** and **71** from isocyanide derivatives.

A recent elaboration of isocyanide application to fluoropyrrole synthesis was undertaken by Murahashi *et al.* by exploiting a rhodium catalysed reaction of ethyl isocyanoacetate (**68**) with 3-fluoro-2,4-pentanedione (**73**) to give 3-fluoropyrrole derivative **74** in 40% yield. (Fig. 1.29).[46] The success of this reaction was attributed to chemoselective α-C-H activation of **68**. The reaction is thought to proceed via a rhodium catalysed decarbonylation of the intermediate formamide (**75**), based on the exclusive formation of aniline from *N*-phenylformamide under analogous conditions.

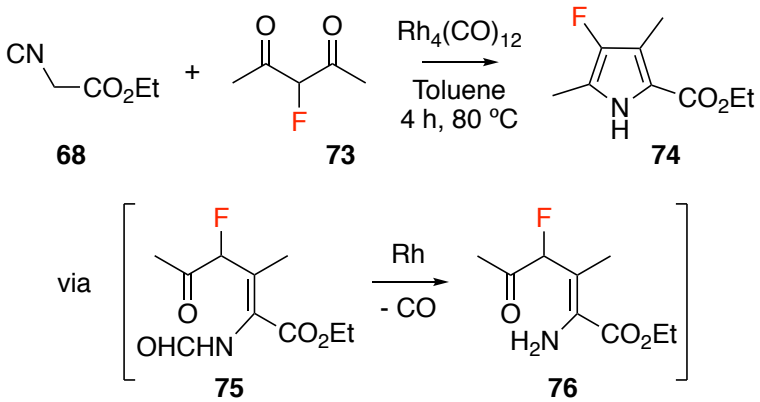
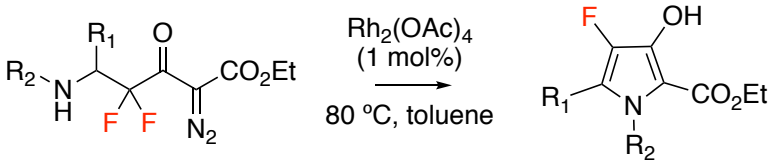


Figure 1.29: Rhodium catalysed synthesis of **74** from ethyl isocyanoacetate **68**.

A more successful application of rhodium catalysis for the synthesis of 3-fluoropyrroles was demonstrated by Zhu *et al.* who demonstrated the rhodium catalysed intramolecular

N-H insertion reaction of diazo-intermediates (**77a-h**) proceeded efficiently to give the corresponding 3-fluoropyrrole derivatives in excellent yields (Table 1.4).

Table 1.4: Rhodium catalysed intramolecular N-H insertion reactions to give 3-fluoropyrrole derivatives.



77a-h **78a-h**

Entry	R_1	R_2	Time /h	Yield /%
a	Ph	Ph	12	91
b	4-$MeOC_6H_4$	Ph	20	95
c	4-ClC_6H_4	Ph	10	93
d	Ph	4-ClC_6H_4	12	92
e	4-ClC_6H_4	4-$MeOC_6H_4$	9	90
f	2-naphthyl	Ph	10	93
g	2-furyl	Ph	10	91
h	Ph	Bn	10	93

Moreover, the synthesis of diazo intermediates **77a-h**, via Reformatsky-imine addition and subsequent diazo-transfer, were also high yielding processes (71-90%), providing a viable route to highly substituted 3-fluoropyrroles (Fig. 1.30).[47]

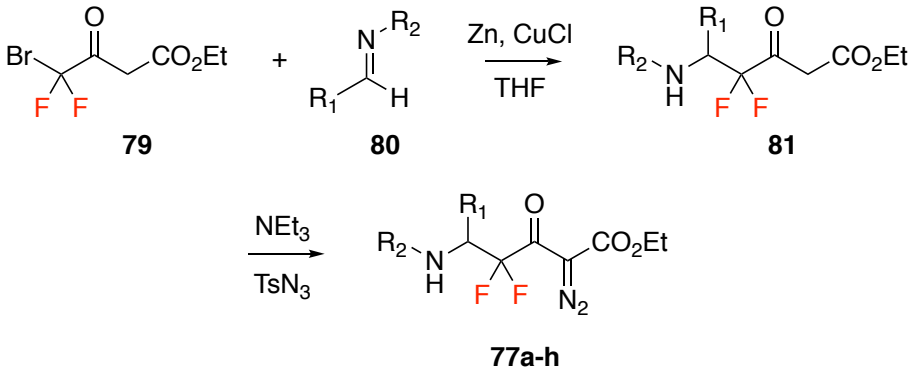


Figure 1.30: Synthesis of diazo-intermediates **77a-h**.

Another notable metal catalysed reaction leading to 3-fluoropyrrole derivatives, was re-

ported by Liu *et al.* more recently. After initially trialling palladium based catalytic systems in the presence of stoichiometric amounts of AgF and NFSI, it was shown that the yield of intermediate vinyl fluoride (**83**) increased by more than ten fold in the absence of $Pd(OAc)_2$. Hence, it was proposed that the aminofluorination was mediated by the AgF present in the reaction mixture with subsequent optimisation showing 20 mol% $AgNO_3$ to be optimal. The synthesis of the intermediate vinyl fluoride (**83**) proceeded in low to excellent yields (28-92%) with substrates bearing an electron-withdrawing substituent at R_2 performing most effectively, whilst the subsequent aromatisation proceeded smoothly to give the corresponding 3-fluoropyrrole **84** in good yields (69-89%) (Fig. 1.31).[48]

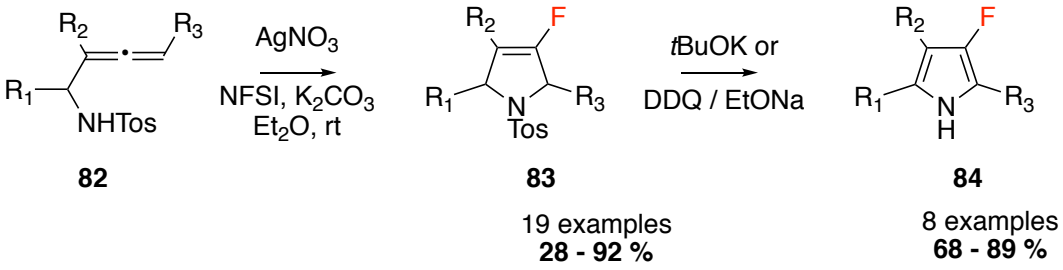


Figure 1.31: Silver catalysed aminofluorination of allenes and subsequent aromatisation to 3-fluoropyrrole derivatives.

An approach also forming an intermediate vinyl fluoride followed by aromatisation to the respective 3-fluoropyrrole product was developed by Cogswell *et al.* by application of a ring closing metathesis protocol. Using Grubbs 2nd generation catalyst, the synthesis of α-β-unsaturated lactam derivatives (**86**) was carried out in good to excellent yield (71-98%), which upon treatment with organometallic nucleophiles underwent efficient alkylation-aromatisation to give the corresponding 3-fluoropyrroles (**87**) also in high yields (73-93%) (Fig. 1.32).[49]

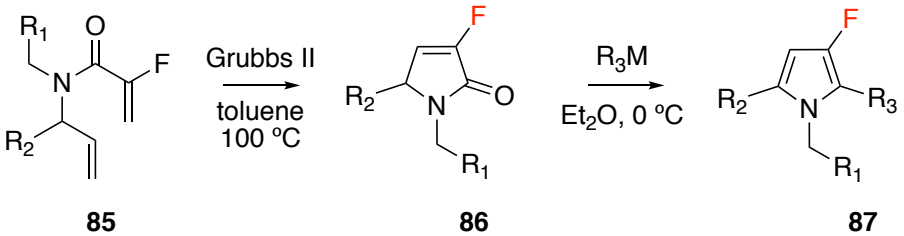


Figure 1.32: Ring closing metathesis and alkylation-aromatisation protocol for the synthesis of 3-fluoropyrrole derivatives (**87**).

A much more limited selection of reactions exists for the synthesis of 2-fluoropyrrole derivatives via a cyclisation approach with many protocols focusing on the use of difluorocarbene and its reaction with imine derivatives. Novikov *et al*. developed two similar approaches that fall into this category, the first of which involves reaction of an azadiene (**88**) with difluorocarbene to give the corresponding 2-fluoropyrrole derivative (**91**) in low yield (23%). The proposed reaction mechanism involves the formation of difluoroazomethine ylide (**89**) and 1,5-cyclisation followed by dehydrofluorination (Fig. 1.33). Despite demonstrating the applicability of this route towards 2-fluoropyrrole derivatives the isolated yield of the reaction was disappointingly low.

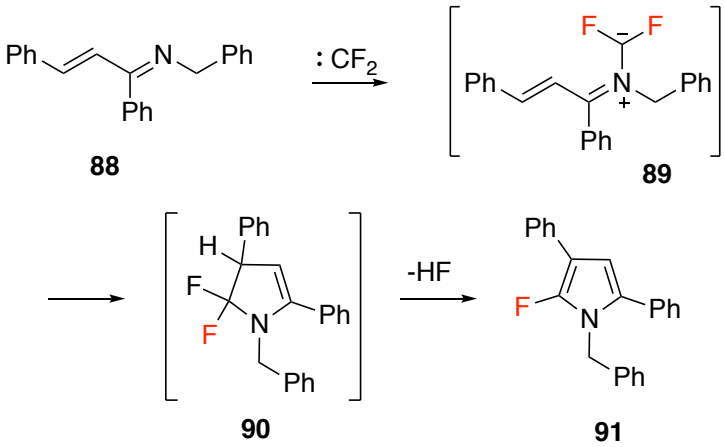
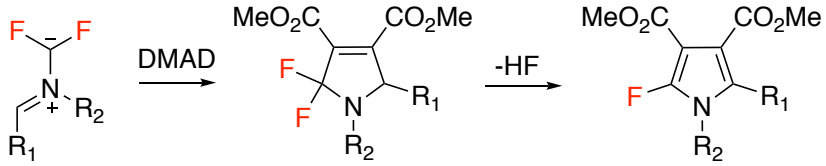


Figure 1.33: Synthesis of 2-fluoropyrrole derivative (**91**) from azadiene derivative (**88**).

However, using analogous azomethine ylides (**92a-k**), formed by reaction of the appropriate imine with difluorocarbene, it was possible to perform a 1,3-dipolar cycloaddition with DMAD, which after dehydrofluorination, gave access to 2-fluoropyrrole derivatives **94a–k** (Table 1.5).[50–52]

Table 1.5: Synthesis of 2-fluoropyrrole derivatives from azomethine ylides.



92a-k **93a-k** **94a-k**

Entry	R_1	R_2	Yield /%	
			Method A	Method B
a	Ph	Ph	58	-
b	Ph	4-$MeOC_6H_4$	30	70
c	Ph	4-ClC_6H_4	61	-
d	2,4-$Cl_2C_6H_3$	Ph	68	-
e	2-furyl	Ph	30	69
f	4-BrC_6H_4	Ph	-	78
g	4-$MeOC_6H_4$	Ph	-	57
h	3-$O_2NC_6H_4$	Ph	0	32
i	4-ClC_6H_4	4-ClC_6H_4	-	70
j	PhC≡C	Ph	11	42
k	PhCH=CH	Ph	-	41

Further improvements were observed upon modification of the procedure for the generation of difluorocarbene. The initial method (Method A) involved the reduction of dibromodifluoromethane with lead powder in the presence of TBAB, whilst the improved method utilised active lead obtained by reduction of aqueous lead(II) acetate with sodium borohydride (Method B). Method B, under otherwise unchanged conditions, provides shorter reaction times with improved yields for a range of functionalised imines.

A recent publication by Xiao *et al.* reveals a novel route to 2-fluoropyrrole derivatives by reaction of *gem*-difluorocyclopropyl ketones (**95**) with nitriles (Fig. 1.34).[53] Notably, the presence of TfOH was critical for the reaction and, in its absence or in the presence of various other acids, little to no desired product was observed. This was attributed to

the ability of TfOH to induce partial ring cleavage of the proximal bond of **95**, with the resulting carbocation stabilised by the neighbouring fluorine atoms.

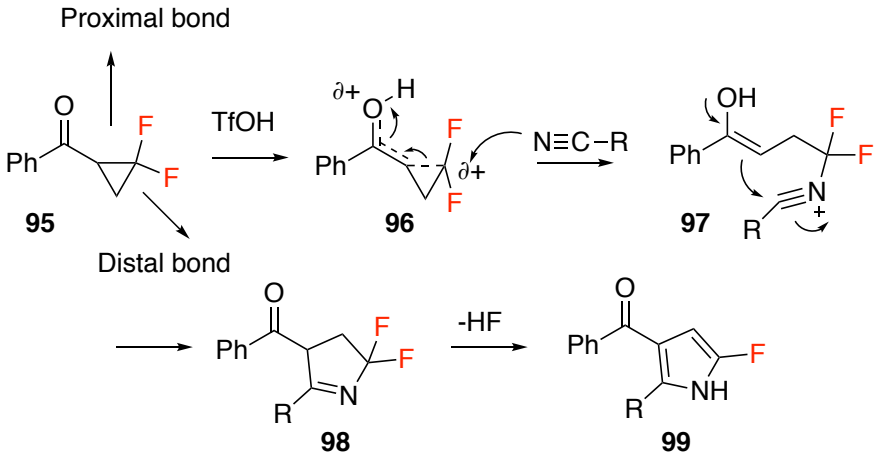


Figure 1.34: TfOH promoted synthesis of 2-fluoropyrrole derivatives from *gem*-difluorocyclopropyl ketones.

1.2.3 Fluorination of Non-Aromatic Precursors

Another possible route towards fluorinated pyrroles is the use of appropriate non-aromatic precursors. In contrast to cyclisation reactions (See section 1.2.2), fluorination of a preformed non-aromatic heterocycle, rather than fluorination and subsequent cyclisation of acyclic molecules, is involved. However, until recently, this strategy has scarcely been employed. Leroy *et al.* extended the synthetic strategy developed by Dugave *et al.*, who had demonstrated the synthesis of fluorinated proline derivative **101** by deoxygenative difluorination using DAST. Cleavage of the Boc protecting group followed by dehydrofluorination and dehydrogenation gave methyl 4-fluoropyrrole-2-carboxylate (**102**) in good yield (64%), but attempts to produce the decarboxylated product mostly resulted in decomposition (Fig. 1.35).[32,54]

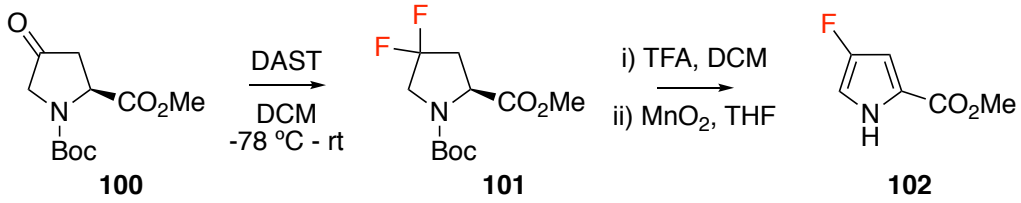
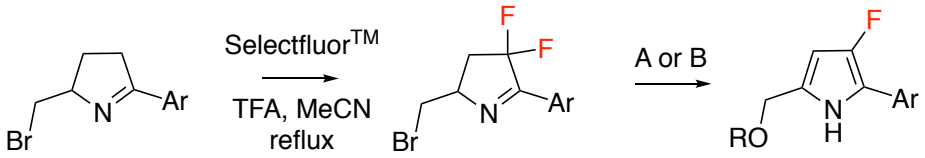


Figure 1.35: Synthesis of 3,3-difluoropyrrolidine (**101**) and subsequent aromatisation.

A more recent application of this strategy was shown by Surmont *et al.* who successfully

produced 3,3-difluoropyrrolines (**104**) by fluorination of the corresponding 1-pyrrolines (**103**) with Selectfluor^{TM}. Reaction of difluoropyrrolines with sodium alkoxides yields the desired 5-(alkoxymethyl)-3-fluoropyrroles (**105**) (Fig. 1.36).[55]



Ar = Ph, 4-FC_6H_4, R = Me, Et, *i*Pr

A = 2 M aq. NaOH, ROH, 1 h. B = 1 M aq. NaOR, ROH, 1h.

Figure 1.36: Synthesis of 3-fluoropyrroles bearing an alkoxymethyl substituent.

1.3 Synthesis of Fluoroimidazoles and Fluoropyrazoles

Selective incorporation of fluorine into 5-membered heterocycles containing two nitrogen atoms, such as imidazole or pyrazole scaffolds, has also proven to be a major challenge. Akin to that previously discussed for the synthesis of fluoropyrroles (See section 1.2), current approaches adopt two main strategies. Firstly, the cyclisation of fluorinated acyclic precursors and, secondly, selective fluorination of the preformed heterocyclic scaffold.

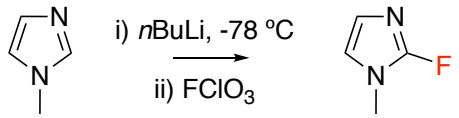
1.3.1 Fluorination of the Imidazole or Pyrazole Ring

Fluorination of both imidazole and pyrazole derivatives can be accomplished using electrophilic and nucleophilic sources of fluorine. Both, these electron rich heterocycles react in a similar fashion to pyrrole derivatives and, hence, are innately reactive towards electrophiles, whereas reactions with nucleophiles require prefunctionalisation to give the desired umpolung reactivity.

1.3.1.1 Electrophilic Fluorination

Early examples utilising electrophilic fluorinating agents were reported by the groups of Hay and Chambers for the synthesis of fluoroimidazole derivatives. Hay *et al.* demon-

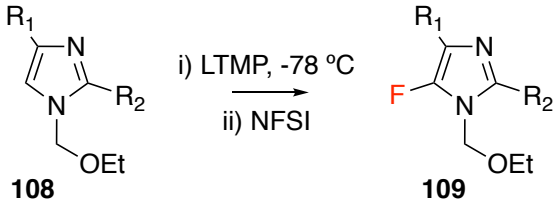
strated the synthesis of 2-fluoroimidazole derivative **107**, by treatment of the appropriate metalated intermediate with hazardous gaseous perchloryl fluoride, in 55% yield (Fig. 1.37), but the scope of this reaction was not extended further.[56]



106 **107**

Figure 1.37: Synthesis of 2-fluoroimidazole derivative using perchloryl fluoride.

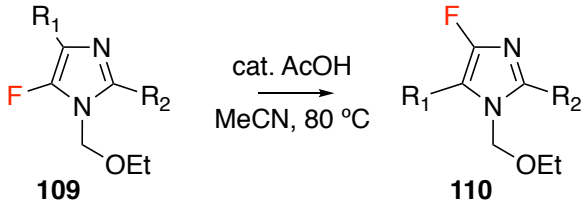
A modern elaboration of this work was recently reported by Albertshofer *et al.*, who synthesised a range of 5-fluoroimidazoles by fluorination of the corresponding metalated intermediate with NFSI in low to good yields (20-71%) (Fig. 1.38).[57] Notably, fluorination attempts using 2-fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide, *N*-fluoropyridinium salts and Selectfluor^{TM} gave no observable fluorinated product.



108 **109**

Figure 1.38: Synthesis of 5-fluoroimidazole derivatives using NFSI.

Interestingly, it was also possible to synthesise corresponding 4-fluoroimidazole derivatives in excellent yields (83-99%) by a controlled protecting group migration using catalytic acetic acid in MeCN (Fig. 1.39).

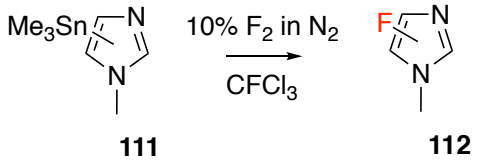


109 **110**

Figure 1.39: Controlled protecting group migration to produce 4-fluoroimidazoles from 5-fluoroimidazole derivatives.

In contrast, the work by Chambers *et al.* showed that 2- and 5-substituted organostannane derivatives could be reacted with fluorine gas at low temperatures to give crude

product mixtures containing the corresponding 2- and 5-fluoroimidazole derivatives as detected by ^{19}F NMR spectroscopy, but the products were not isolated (Fig. 1.40).[58]

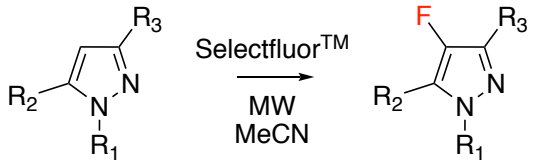


111 **112**

Figure 1.40: Synthesis of 2- and 5-fluoroimidazoles from organostannane derivatives.

More recently, Selectfluor^{TM} has been utilised for the synthesis of fluoro-imidazole and -pyrazole compounds. Work by Sloop *et al.* showed that reaction of highly substituted pyrazole derivatives with Selectfluor^{TM} gave the corresponding 4-fluoropyrazole derivatives **114a-j** in low to good yields (13-75%) with by-products formed by competing fluorination of the substituents R_1 and R_3 also observed (Table 1.6).[59]

Table 1.6: Synthesis of highly substituted 4-fluoropyrazole derivatives with Selectfluor™ under MW conditions.[a]



113a-j **114a-j**

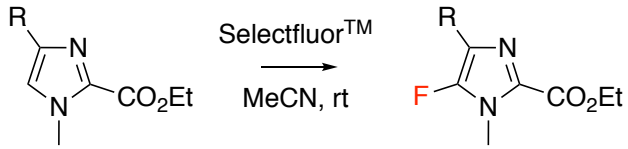
Entry	R_1	R_2	R_3	Yield /%
a	Ph	Me	Me	60
b	Ph	Me	4-$O_2NC_6H_4$	40
c	Ph	Me	CF_3	40
d	Ph	Ph	CF_3	0
e	4-$O_2NC_6H_4$	Me	Me	49
f	4-$O_2NC_6H_4$	Me	CF_3	13
g	2,4-$(O_2N)_2C_6H_4$	Me	Me	30
h	4-$MeOC_6H_4$	Me	Me	75[b]
i	4-$MeOC_6H_4$	Ph	Me	53
J	4-$MeOC_6H_4$	CF_3	4-$O_2NC_6H_4$	0

[a] Conditions: 6 x 5 min heating cycles in a standard 1450 W microwave at 10% power.

[b] Reaction performed at room temperature for 24 h.

Similarly, work by Jiang *et al.* has demonstrated the applicability of Selectfluor™ for the synthesis of both 4- and 5-fluoroimidazole-2-carboxylate derivatives. By strategically substituting the position at which fluorination was undesired it was possible to prevent regioisomeric products and, hence, obtain the desired fluorinated imidazole derivatives **116a-f** and **118a-e** in moderate yields (Tables 1.7 and 1.8).[60] Comparative reactions using NFSI as the fluorinating agent rather than Selectfluor™ were also performed and, although in both cases the desired 4- and 5-fluoroimidazoles could be obtained, the yields were lower than that obtained when using Selectfluor™.

Table 1.7: Synthesis of 5-fluoroimidazole-2-carboxylate derivatives by reaction with Selectfluor^{TM}.

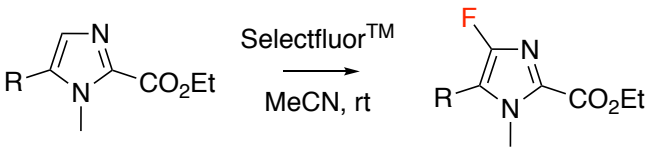


115a-f **116a-f**

Entry	R_1	Time /h	Yield /%
a	$NHCOCF_3$	1	67
b	NHAc	0.5	74
c	phthalimido	1	61
d	H	3	53
e	NO_2	24	–
f	$NHCOCF_3$	3	49[a]

[a] NFSI was used as the fluorinating agent.

Table 1.8: Synthesis of 4-fluoroimidazole-2-carboxylate derivatives by reaction with Selectfluor^{TM}.



117a-e **118a-e**

Entry	R_1	Time /h	Yield /%
a	$NHCOCF_3$	2	62
b	NHAc	1	68
c	phthalimido	2	65
d	NO_2	24	–
e	$NHCOCF_3$	6	43[a]

[a] NFSI was used as the fluorinating agent.

Selectfluor^{TM} has also been applied in fluorodecarboxylation reactions for the synthesis of 5-fluoropyrazole products that cannot be accessed via direct electrophilic substitution.

Yuan *et al.* showed that treatment of highly substituted pyrazole-5-carboxylic acids with Selectfluor™ in the presence of a weak base (KF or LiOAc) gave the corresponding fluorinated pyrazole derivatives in good yields (62-75%) (Fig. 1.41).[61]

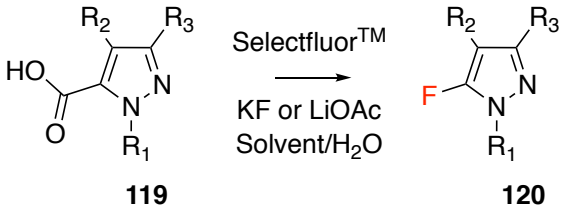
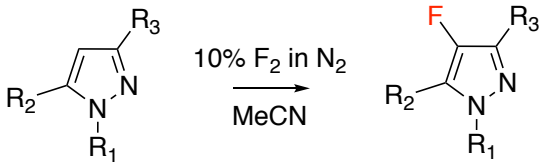


Figure 1.41: Synthesis of 5-fluoropyrzole derivatives by fluorodecarboxylation using Selectfluor™.

Also, under analogous conditions, various 3-substituted pyrazole-5-carboxylates without a substituent at the 4-position formed fluorinated dimer products with a 4,4'-linkage, via an oxidation process, as a single product in excellent yields (70-82%) (Fig. 1.42). It was noted that related fluorinating agents, NFSI and *N*-fluoropyridinium tetrafluoroborate, afforded none of the desired products for these transformations.

Figure 1.42: Synthesis of fluorinated pyrazole dimers with a 4,4'-linkage.

Fluorine gas has also been used for the direct fluorination of pyrazole derivatives. Work by Breen *et al.* showed that modest yields (40-45%) of 4-fluoropyrazole derivatives could be achieved but, it was noted the success of the reaction is very much dependant on the starting substrate employed (Fig. 1.43). For example, pyrazoles bearing two electron-withdrawing groups (CF_3, CO_2H, CO_2Me) gave only recovered starting material whereas, the fluorination of 3,5-dimethyl-1*H*-pyrazole gave extensive tar formation.[62]

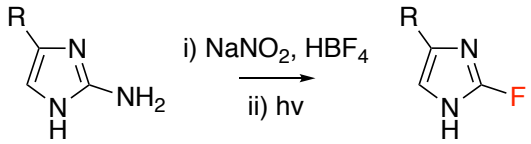


123 **124**

Figure 1.43: Synthesis of 4-fluoropyrazole derivatives using F_2 gas.

1.3.1.2 Nucleophilic Fluorination

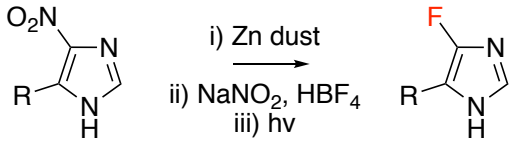
Of the available methodologies for the synthesis of fluoroimidazoles and fluoropyrazoles by far the most adopted is the Balz-Schiemann reaction, specifically a photochemical modification of this procedure, initially developed by Kirk *et al.* for the synthesis of 2-fluoroimidazoles after thermally activated conditions proved unsuccessful. The protocol involves the *in situ* generation of imidazole diazonium salts from 2-amino derivatives and subsequent irradiation in aqueous fluoroboric acid (Fig. 1.44).[63]



125 **126**

Figure 1.44: Photochemical Balz-Schiemann reaction for the synthesis of 2-fluoroimidazoles.

The procedure was also applied for the synthesis of 4-fluoroimidazole derivatives. However, due to the instability of 4-aminoimidazoles, the procedure utilised the appropriate 4-nitroanalogue which was reduced *in situ* and immediately used for diazotisation and subsequent photolysis in a one-pot process to give the desired 4-fluoroimidazole derivatives in low yields (10-37%) (Fig. 1.45).[64] The procedure has also been used for the synthesis of both 4,5-difluoro- and 2,4-difluoroimidazoles.[65,66]



127 **128**

Figure 1.45: Photochemical Balz-Schiemann reaction for the synthesis of 4-fluoroimidazoles.

The same methodology was applied to the synthesis of fluoropyrazoles by Fabra *et al.* to obtain 1-methyl 3-, 4- and 5-fluoropyrazole in low yields (Fig. 1.46)[67] and, in later work, 3,4-, 4,5- and 3,5-difluoropyrazoles.[68]

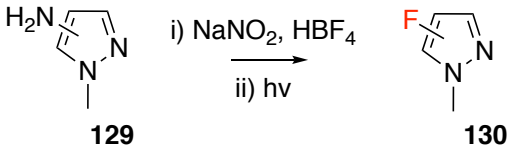


Figure 1.46: Photochemical Balz-Schiemann reaction for the synthesis of 3-, 4- and 5-fluoropyrazoles.

Interestingly, fluoropyrazole derivatives can be used for the synthesis of fluoroimidazole derivatives via a photoinduced 'nitrogen walk' procedure (Fig. 1.47). However, only low yields of the corresponding fluoropyrazoles could be obtained rendering this approach synthetically unappealing versus the previously discussed Balz-Schiemann processes.

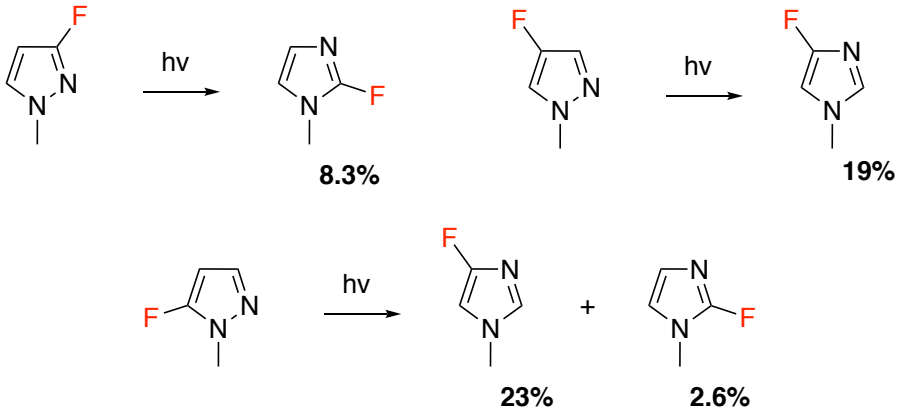


Figure 1.47: Photoinduced 'nitrogen walk' for the synthesis of fluoroimidazole derivatives.

Other than Balz-Schiemann type processes, Halex processes have also been developed for the synthesis of fluoroimidazoles. Initial attempts to displace activated halogens with fluoride by Kirk were unsuccessful[63] but, more recently, Coad *et al.* showed that with a sufficiently activated substrate (**131**) halide exchange can occur, using spray dried KF and 18-crown-6 catalyst, to give 2-fluoroimidazole derivative **132** in 89% yield (Fig. 1.48).[69] However, the scope of this strategy was not extended further.

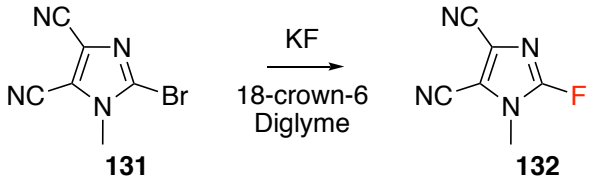


Figure 1.48: Halex process for the synthesis of 2-fluoroimidazole derivative **132**.

Sun and DiMagno later demonstrated the synthesis of fluorinated heteroaromatics including 5-fluoroimidazole derivative **134** from the corresponding chloride derivatives using "anhydrous" TBAF. The synthesis of this highly nucleophilic fluoride salt, via fluoride relay from KF, allows the nucleophilic substitution to occur rapidly, under notably mild conditions, in good yield (80%) (Fig. 1.49).[70]

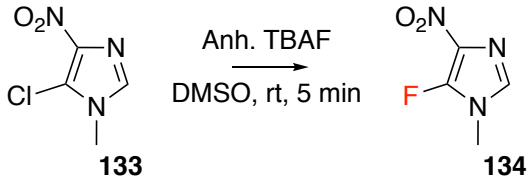


Figure 1.49: Synthesis of 5-fluoroimidazole derivative **134** using anhydrous TBAF.

A similar strategy for the large scale manufacture of 5-fluoropyrazole derivative **136** was applied by workers at Bayer Cropscience. From the corresponding chloride, using KF in chlorobenzene, fluoride exchange occurs at both the 5-position and acid chloride to give the desired fluorinated pyrazole in excellent yield (95%) (Fig. 1.50).[71]

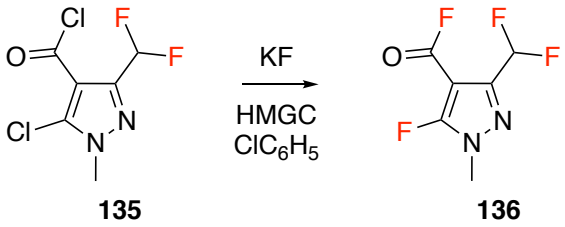


Figure 1.50: Synthesis of 5-fluoropyrrole derivative **136** using KF.

1.3.2 Cyclisation Reactions

Cyclisation reactions have scarcely been utilised for the synthesis of fluoroimidazoles with only one example of this strategy being reported. Burger *at al.* utilised $SnCl_2$ to

reduce Schiff bases, derived from amidines and hexafluoroacetone, resulting in the formation of 5-fluoroimidazole derivatives (**139**) in moderate yields (58-65%) (Fig. 1.51).[72]

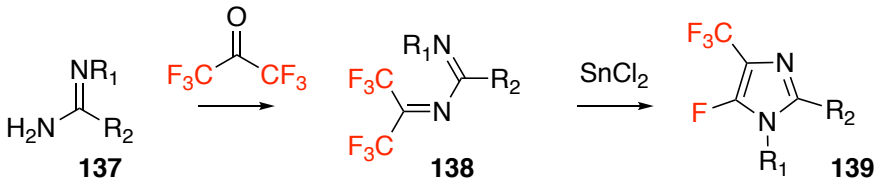


Figure 1.51: Synthesis of 5-fluoroimidazole derivatives from hexafluoroacetone and amidine precursors.

A fluorinated building block approach has been much more extensively utilised for the synthesis of related fluoropyrazoles. For example, the efficient, continuous flow fluorination of 1,3-diketones using dilute F_2 gas and subsequent cyclisation with hydrazines was demonstrated by Breen *et al.* for the synthesis of 4-fluoropyrazole derivatives in good yields (67-80%) (Fig. 1.52).[73]

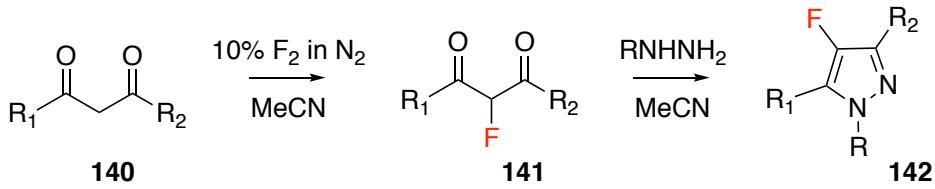


Figure 1.52: Continuous gas/liquid–liquid/liquid flow process for the synthesis of 4-fluoropyrazoles.

Surmont *et al.* also developed two routes to 4-fluoropyrazole derivatives by condensing mono- and di-fluorinated β-ketonitriles with hydrazine. For example, condensation of benzoylfluoroacetonitrile (**143**, X = H, R = Ph) gave the expected 3-amino-4-fluoropyrazole derivative (**144**) in good yield. In contrast, the corresponding difluorinated derivatives (**143**, X = F, R = aryl or alkyl), upon reaction with 2 eq. of hydrazine gave 4-fluoropyrazoles bearing no amino group at C-3. The mechanism is thought to proceed via initial condensation followed by hydrazine-mediated reduction (Fig. 1.53).[74]

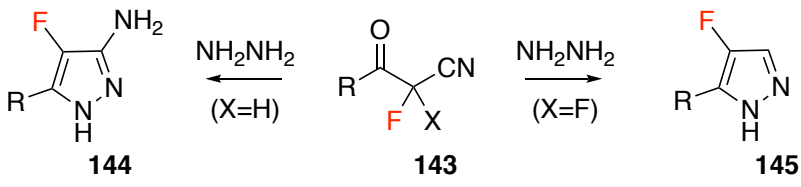
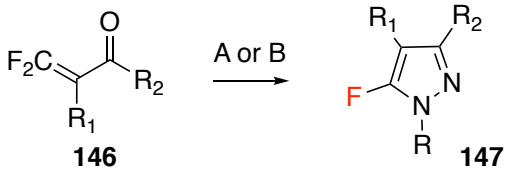


Figure 1.53: Synthesis of 4-fluoropyrazole derivatives from fluorinated β-ketonitriles.

The synthesis of both 3- and 5-fluoropyrazoles has also been demonstrated from a common fluorinated building block. Reaction of 2,2-difluorovinylketones with substituted alylhydrazines in EtOH, or arylhydrazines under basic conditions in THF, gives the corresponding 5-fluoropyrazole derivatives in good to excellent yields (76-95%) (Fig. 1.54). The regiochemistry was ascribed to initial 1,4-addition by *N*-1 of hydrazine, activated by the two vinyl fluorines, followed by cyclisation and dehydrofluorination.



A = $RNHNH_2$ (2 eq.), aq. EtOH.
B = $RNHNH_2$ (2 eq.), *n*BuLi (2 eq.), THF.

Figure 1.54: Synthesis of 5-fluoropyrazoles from 2,2-difluorovinylketones.

However, reaction of the same fluorinated building block with unsubstituted hydrazine, in the presence of TFA produces *N*-unsubstituted 3-fluoropyrazoles (exists as the 3-fluoro tautomer as evidenced by ^{13}C NMR). Subsequent reaction with alkyl-, allyl- and benzyl-bromides or substituted aryl-fluorides, in the presence of sodium hydride, leads to 3-fluoropyrazole derivatives (**149**) (Fig. 1.55).[75]

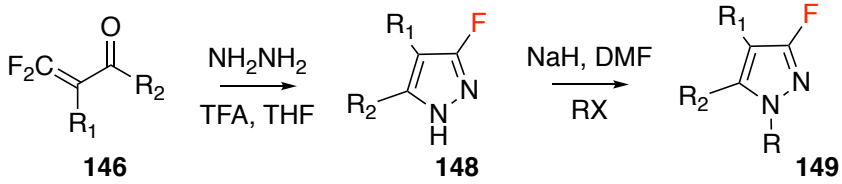


Figure 1.55: Synthesis of 3-fluoropyrazoles from 2,2-difluorovinylketones.

More recently, transition metal catalysts have been utilised in cyclisation reactions towards 4-fluoropyrazole derivatives. The first example of which, reported by Qian *et al*., utilised a gold catalyst for the tandem aminofluorination of alkynes in the presence of Selectfluor^{TM} to obtain the desired 4-fluoropyrazole derivatives (**151**) in moderate to excellent yields (43-90%). In some cases appreciable quantities of the corresponding non-fluorinated derivative was also produced under the reaction conditions limiting the isolated yields (Fig. 1.56).[76]

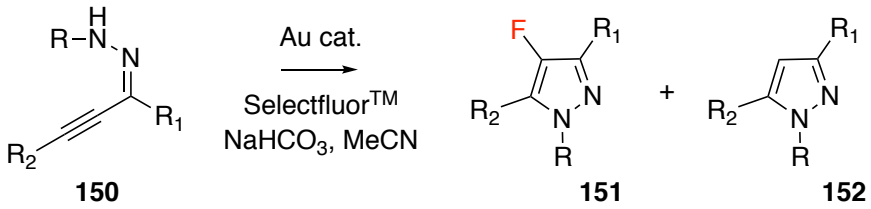


Figure 1.56: Gold catalysed synthesis of 4-fluoropyrazoles.

Prieto *et al.* applied a ruthenium based catalyst system in their approach towards 4-fluoropyrazoles utilising easily accessible aldehyde derived hydrazones (**153**) and tribromofluoromethane. The methodology allows the synthesis of a range of 4-fluoropyrazole derivatives in moderate to excellent yields (30-85%), via a proposed radical based mechanism, in which the concomitant fluorine incorporation and pyrazole formation ensures the associated non-fluorinated analogue is not formed (Fig. 1.57).[77]

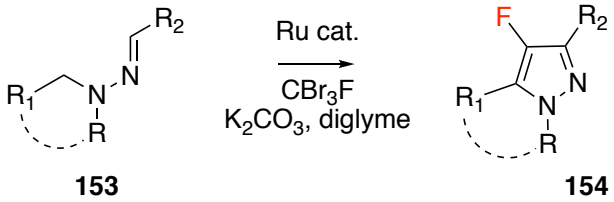


Figure 1.57: Ruthenium catalysed synthesis of 4-fluoropyrazoles.

1.4 Conclusions

The incorporation of fluorine into organic substrates, particularly heterocyclic scaffolds, is of clear importance for the discovery biologically active compounds. The significant effect fluorine incorporation can have on the physiological properties of life science products has triggered substantial research into fluorination methodologies. However, it is clear that no general method to synthesise diverse libraries of fluoropyrrole and related 5-membered fluorinated heterocyclic products, such as imidazoles or pyrazoles, for incorporation into screening libraries is readily available. Cyclisation reactions give only modest access to fluorinated derivatives, limited by the diversity that can be incorporated into the fluorinated building block. Equally, fluorination of the heterocyclic ring is often low yielding and utilises expensive or difficult to handle fluorinating agents which presents major obstacles to possible multi-gram scale up.

Therefore, in the remainder of this thesis, the development of methodologies for the expedient synthesis of biologically relevant fluorinated azaheterocycles is described. Chapters 2 and 3 cover approaches towards the synthesis of functional fluoropyrrole derivatives, whilst Chapter 4 examines the use of fluoromalonate esters for the synthesis of 3-fluorinated pyrido[1,2-*a*]pyrimidin-4-one derivatives.

Chapter 2 begins with a systematic study of the fluorination of a range of substituted pyrrole derivatives with Selectfluor^{TM}. The effect of electron-withdrawing and electron-donating substituents is examined and the regioselectivity of this class of fluorination processes is established. Access to some novel fluoropyrrole derivatives was achieved, however, due to competing oxidation/polymerisation pathways, we modified our approach. Therefore, Chapter 3 describes the use of tetrabrominated pyrrole derivatives for the synthesis of fluorinated pyrrole derivatives by lithiation and quenching with NFSI. Derivatisation via the remaining bromine handles using a combination of cross-coupling and lithiation/trapping chemistries and, by varying the order in which they are sequentially applied, gave access to a library of multifunctional fluoropyrrole products. This methodology circumvents many of the issues described above for current synthetic protocols, and therefore, would facilitate the development of life science products bearing the fluoropyrrole moiety in the first instance.

Chapter 4 outlines the use of fluoromalonate esters as versatile fluorinated building blocks. Specifially, condensation of fluoromalonic acid with 2-aminopyridine in $POCl_3$ gave access to a fluoronated pyrido[1,2-*a*]pyrimidin-4-one derivative which could be derivatised by Suzuki cross-coupling reactions. The development of this range of products has allowed their efficacy as β-catenin inhibitors to be screened using a ^{19}F NMR fragment-based drug discovery approach.

Chapter 2

Fluorination of Pyrrole Derivatives by Selectfluor^{TM}

2.1 Aims

As previously discussed, the most direct method for the synthesis of fluoropyrroles is the transformation of C-H to C-F bonds by reaction of the parent pyrrole with an electrophilic fluorinating agent. Despite this, as shown in Chapter 1, there have been only two reports in which electrophilic fluorinating agents XeF_2 [26] and Selectfluor^{TM} [78] have been employed in this manner.

In this chapter we describe our attempts to further develop this general selective fluorination strategy for the synthesis of functionalised fluoropyrrole derivatives for use in life science discovery laboratories. For this purpose, Selectfluor^{TM}, a shelf stable, commercially available fluorinating agent of the N-F class was used as the fluorinating agent.[79] We aimed to assess a model range of pyrrole substrates, bearing electron-donating and -withdrawing substituents as well as protecting groups attached to the pyrrole ring nitrogen, with a view to establishing the regioselectivity of electrophilic fluorination processes and providing access to a range of polyfunctional fluoropyrroles (Fig. 2.1).

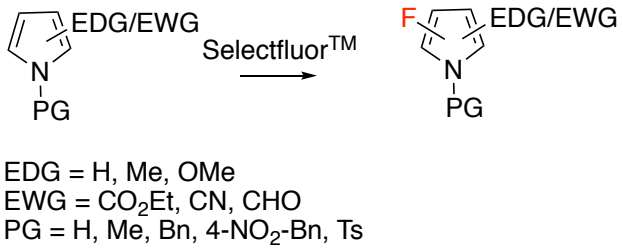


Figure 2.1: Proposed strategy for the synthesis of fluoropyrroles.

2.2 Initial experiments

We began our investigations by attempting the fluorination of pyrrole and *N*-methylpyrrole to assess the innate reactivity of the pyrrole core towards electrophilic fluorinating agents. However, reactions of these substrates with Selectfluor™ in MeCN, under various conditions, gave insoluble black solids which we attribute to the formation of appropriate poly(pyrrole) derivatives (Fig. 2.2).

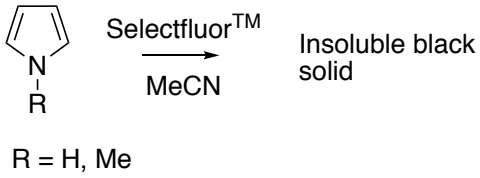


Figure 2.2: Polymerisation of pyrrole and *N*-methylpyrrole by Selectfluor™.

Pyrrole and related systems are readily polymerised by oxidising agents such as H_2O_2, *m*CPBA, O_3, $AgNO_3$ and $FeCl_3$,[80,81] and it appears that Selectfluor™ is a sufficiently strong oxidant to cause the formation of polymeric products to occur. Selectfluor™ has been reported to oxidise benzyl alcohols to the corresponding benzaldehydes, consistent with these observations (Fig. 2.3).[82]

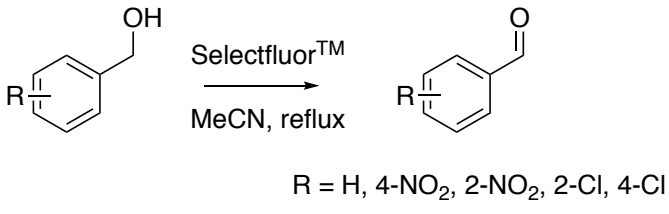


Figure 2.3: Oxidation of benzyl alcohols by Selectfluor™.[82]

2.3 Fluorination of Substituted Pyrroles

The high reactivity of pyrrolic units towards electrophiles, facilitated by the lone pair at nitrogen and consequent stability of the resulting Wheland intermediate (Fig. 2.4), can often be mediated by the use of a protecting group. *N*-protection, or substitution of the pyrrole ring with a suitable group can often provide the necessary balance to allow the exploitation of the the innate nucelophilicity of pyrroles, as well as to prevent polysubstitution and oxidation by-products.

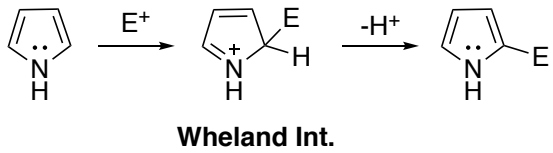


Figure 2.4: Electrophilic substitution of pyrrole via Wheland intermediate.

Electron-withdrawing groups can be used to reduce pyrrole nucleophilicity as well as block positions on the pyrrole core, whilst sterically bulky substituents can be utilised to prevent substitution at α-positions. We therefore applied this strategy to a range of pyrrole derivatives in the hope that we could sufficiently tune the reactivity of the substrate and, consequently, favour fluorination versus oxidation pathways.

2.3.1 Monosubstituted 1*H*-Pyrroles

Reaction of ethyl pyrrole-2-carboxylate (**155**) with 1 eq. of Selectfluor^{TM} was, therefore, first attempted at room temperaure and monitored by TLC until complete consumption of the starting material was observed. After a period of 72 h the reaction mixture was subjected to an aqueous work up, upon which ^{19}F NMR analysis of the crude product mixture revealed an array of fluorinated by-products. The reaction time was, therefore, decreased and the reaction monitored by NMR, as it was proposed that the fluorinated product could be potentially unstable under the reaction conditions. However, after a period of two hours (aliquots taken after 15, 30, 60 and 120 min) no significant quantity of the desired product was observed. Subsequent NMR analysis revealed a higher proportion of the desired product (by ^{19}F NMR), but this represented a small proportion of the total products formed and, hence, no purification was attempted.

In an attempt to increase the yield of the desired product, the reaction was performed using microwave irradiation, with the hope of providing greater conversions with shorter reaction times. Again, using 1 eq. of Selectfluor^{TM}, **155** was heated in a sealed vial using microwave irradiation at 70 ºC for 5 min. This resulted in a much greater proportion of the desired product by ^{19}F NMR, alongside some polymeric material and an appreciable amount of residual starting material. Purification of the crude product mixture by column chromatography gave the desired monofluorinated pyrrole derivative (**156**) in 23% yield (Fig. 2.5).

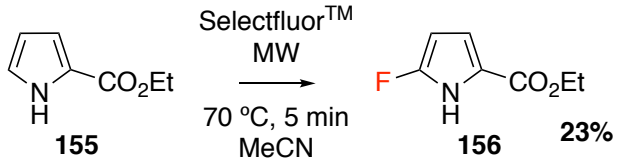


Figure 2.5: Synthesis of ethyl 5-fluoropyrrole-2-carboxylate (**156**) with Selectfluor^{TM} under MW conditions.

DFT computations were performed (Dr Mark Fox, Durham University) to predict the ^{19}F chemical shifts of the three possible fluorinated pyrrole isomers and, therefore, determine the regioselectivity of the fluorination reaction. The calculated values (Fig. 2.6), based on the known values of hexafluorobenzene (-162.8 ppm) and pentafluoropyridine (-162.8, -134.4 and -85.6 ppm), show that the predicted shift for fluorine attached to the carbon atom adjacent to the ring nitrogen (130.6 ppm) is in excellent agreement with the experimentally obtained value (**156** δ_F: -130.73 ppm).

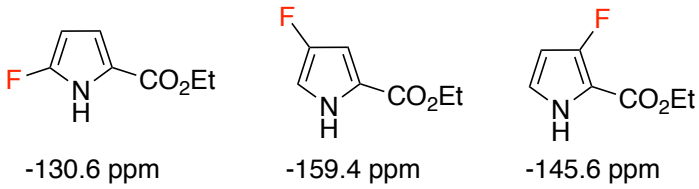


Figure 2.6: DFT predicted ^{19}F chemical shifts of monofluoropyrrole regioisomers.

In addition, the ^{19}F chemical shifts of the three possible difluorinated isomers were also calculated (Fig. 2.7), based on the observation of the correct mass for a difluorinated analogue by GC-MS.

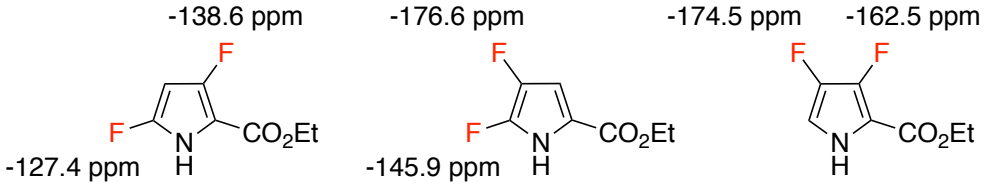


Figure 2.7: DFT predicted ^{19}F chemical shifts of difluoropyrrole regioisomers.

The results obtained show the shifts predicted for the 4,5-difluorinated derivative (-176.3 and -145.9 ppm) are again in good agreement with the experimentally obtained values of -177.09 and -145.25 ppm confirming the 4,5-difluorinated derivative is a major by-product from the reaction as shown by ^{19}F NMR analysis of the crude product mixture (Fig. 2.8).

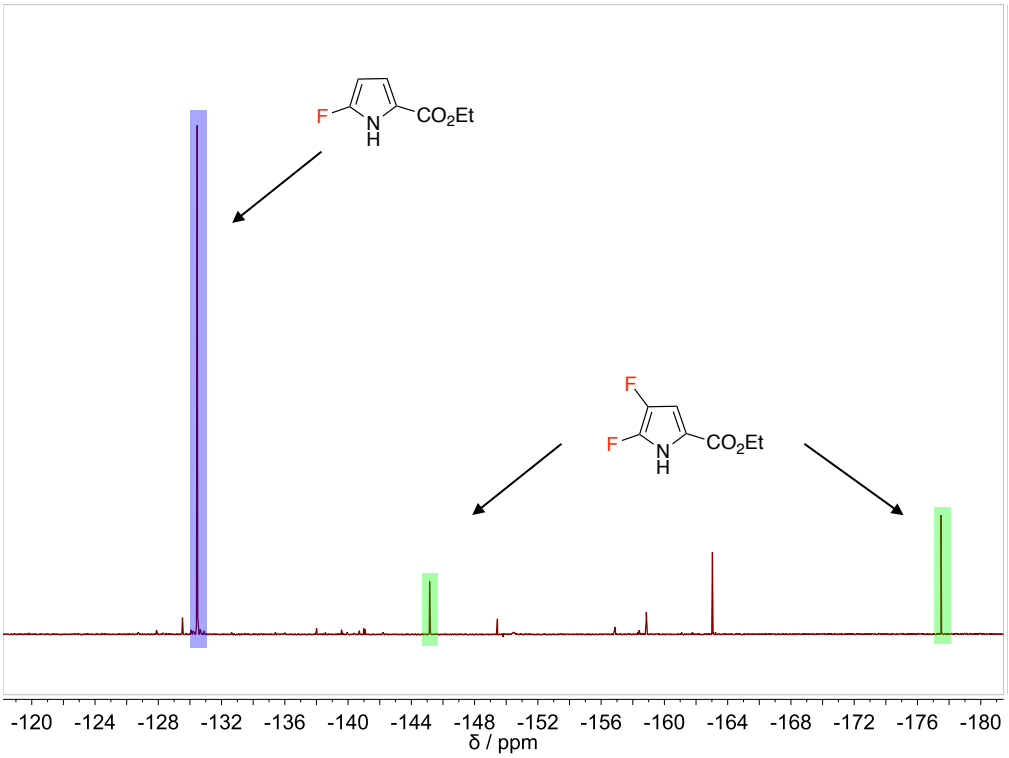
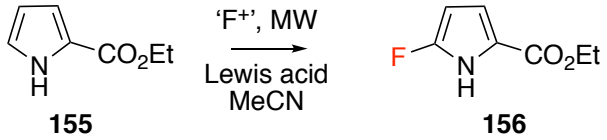


Figure 2.8: ^{19}F NMR of the crude product mixture from reaction of **155** with Selectfluor^{TM}, showing the 5-fluoro (blue) and 4,5-difluoropyrrole (green) products.

Lewis acids have been shown to positively influence reactions of pyrroles with electrophilic fluorinating agents.[28] Therefore, in an attempt to improve the regioselectivity of the process, fluorination of pyrrole (**155**) in the presence of various Lewis acids was screened. However, it was found that the addition of all Lewis acids lowered the observed yield of fluoropyrrole product, when either Selectfluor^{TM}, or related electrophilic

fluorinating agent NFSI were used (Table 2.1).

Table 2.1: Reaction of **155** with an electrophilic fluorinating agent in the presence of a Lewis acid under MW conditions.[a]



155 **156**

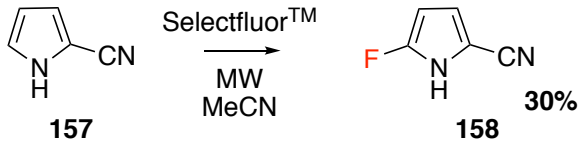
Entry	Fluorinating Agent	Lewis Acid	NMR Yield /%[b]
1	Selectfluor^{TM}	–	21
2	Selectfluor^{TM}	$ZrCl_4$	8
3	Selectfluor^{TM}	$AgNO_3$	2
4	Selectfluor^{TM}	$Ga(OTf)_3$	10
5	Selectfluor^{TM}	$BF_3.Et_2O$	6
6	Selectfluor^{TM}	$HfCl_4$	9
7	Selectfluor^{TM}	$InCl_3$	12
8	NFSI	–	4
9	NFSI	$ZrCl_4$	<1

[a] Conditions: **155** (1.5 mmol), 'F$^+$' reagent (1 eq.), Lewis acid (0.5 eq.), MeCN (15 mL), 70 ºC, 5 min.

[b] NMR yield determined using α-α-α-trifluorotoluene as reference.

We wanted to assess the effect of varying the substituent on the pyrrole ring. Pyrrole-2-carbonitrile (**157**) was chosen because the nitrile functional group is sufficiently electron-withdrawing to aid in preventing oxidation of the substrate, but also provides a lot of synthetic versatility for potential transformations post fluorination. The previously optimal conditions were first applied (Table 2.2, entry 1) and gave a much improved yield of 62% in comparison to the previously utilised ester substrate. However, variations in time and temperature in an attempt to increase conversion and yield, resulted only in a reduction in yield as assessed by NMR spectroscopy. The desired product (**158**) could be purified by column chromatography, but difficult separation of the fluoro- from the difluoro-isomers lowered the isolated yield significantly (30%) (Fig. 2.9).

Table 2.2: Reaction of **157** with Selectfluor™ under MW conditions.[a]

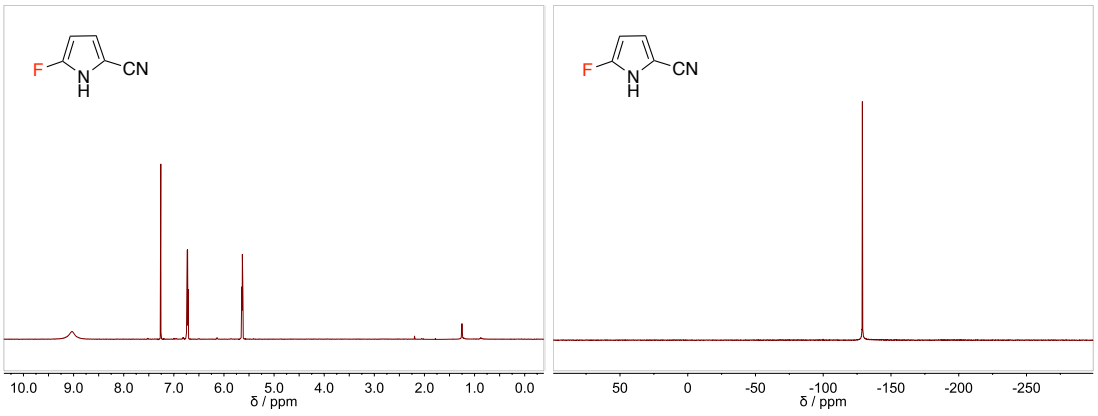


157 **158**

Entry	Temp / °C	Time /min	NMR Yield /%[b]
1	70	5	62 (30)
2	70	10	46
3	70	2	38
4	60	5	40
5	60	10	53
6	60	15	45
7	100	2	45
8	100	5	47

[a] Conditions: **157** (2-10 mmol), Selectfluor™ (1 eq.), MeCN (15-25 mL).

[b] NMR yield determined using α-α-α-trifluorotoluene as reference, isolated yield in parantheses.



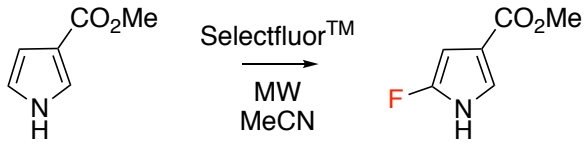
(a) (b)

Figure 2.9: ^{1}H (a) and ^{19}F (b) NMR spectra of isolated 5-fluoropyrrole-2-carbonitrile **158**.

The reactivity of 3-substituted pyrrole derivatives, such as methyl pyrrole-3-carboxylate (**159**), was also investigated. Based on steric and electronic arguments, the predicted major regioisomer was the 5-fluoropyrrole product, and the initial conditions that we

applied gave a promising yield of 10% as measured by ^{19}F NMR spectroscopy (Table 2.3). The major component obtained from this reaction was found to be unreacted starting material and, hence, the reaction time was increased, but this resulted in a larger quantity of insoluble polymeric material alongside a small decrease in yield. Therefore, a shorter reaction time was employed at both an unchanged temperature and an elevated temperature of 100 ºC but, in both cases, comparable yields were obtained. Finally, two equivalents of Selectfluor™ were used in an attempt to increase the conversion but, in this instance, a large amount of polymeric material was obtained and a negligible yield of 5-fluorinated product observed by NMR.

Table 2.3: Reaction of **159** with Selectfluor™ under MW conditions.[a]



159 **160**

Entry	Temp / ºC	Time /min	NMR Yield /%[b]
1	70	5	10
2	70	10	9
3	70	20	8
4	70	2	9
5	100	2	9
6[c]	70	5	–

[a] Conditions: **159** (2 mmol), Selectfluor™ (1 eq.), MeCN (15 mL).

[b] NMR yield determined using α-α-α-trifluorotoluene as reference.

[c] Selectfluor™ (2 eq.).

2.3.2 Disubstituted 1*H*-Pyrroles

Due to the issues of oxidation and formation of regioisomers encountered when employing monosubstituted pyrrole derivatives as substrates for fluorination with Selectfluor™, it was postulated that further substitution could aid in limiting these issues. We proposed that utilising a disubstituted pyrrole derivative would cause a further reduction in oxid-

ation potential, if another electron-withdrawing group is present, and would also block a possible site of fluorination and limit by-product formation. In addition, the added substituent could provide useful functionality for subsequent synthetic transformations.

We first chose to assess the fluorination of a 2,4-disubstituted pyrrole derivative to prevent the formation of a 4,5-difluorinated regioisomer, a major by-product observed for the fluorination of monosubstituted pyrrole derivatives employed previously. Therefore, the synthesis of **162** was performed and obtained in moderate yield (Fig. 2.10).[83]

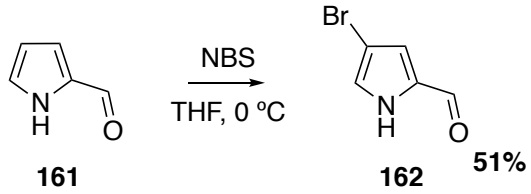
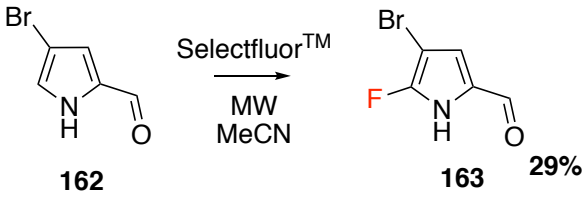


Figure 2.10: Bromination of pyrrole-2-carboxaldehyde using NBS.

A bromine substituent was chosen due to the ease of introduction and also because it is a versatile synthetic handle for further transformations, particularly via potential palladium catalysed cross-coupling chemistries. Optimisation of the fluorination of **162** was undertaken, and a slight increase in reaction time found to be optimal (Table 2.4) in comparison to the monosubstituted derivatives previously studied. Isolation by column chromatography could be achieved in 29% yield, with purification in this instance much more facile. Furthermore, it was also possible to grow a crystal suitable for x-ray crystallography by slow evaporation from acetone (Fig. 2.11). This confirmed the molecular structure of **163**, and the regiochemistry of the fluorination reaction was consistent with DFT predicted ^{19}F NMR data (See section 2.3.1).

Table 2.4: Reaction of **162** with Selectfluor^{TM} under MW conditions.[a]



162 **163**

Entry	Temp / ºC	Time /min	NMR Yield /%[b]
1	70	5	29
2	70	10	31
3	70	15	12
4	70	7.5	34 (29)

[a] Conditions: **162** (1-6 mmol), Selectfluor^{TM} (1 eq.), MeCN (15-25 mL).

[b] NMR yield determined using α-α-α-trifluorotoluene as reference, isolated yield in parantheses.

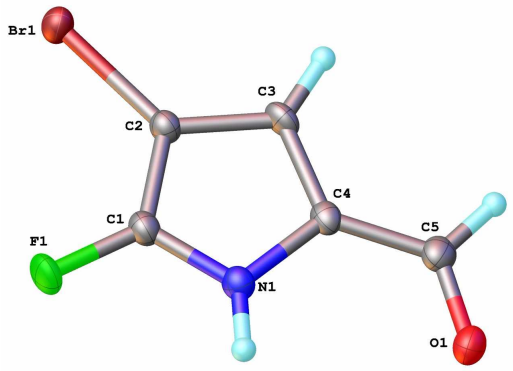
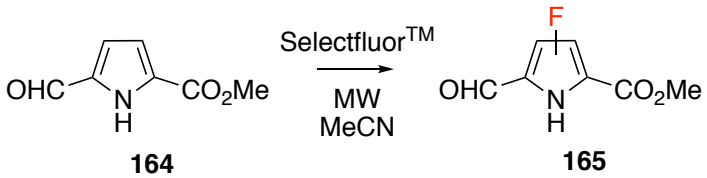


Figure 2.11: Molecular structure of **163** as determined by x-ray crystallography.

The reactivity of a representative 2,5-disubstituted pyrrole was also assessed as it was envisaged that two electron-withdrawing substituents at the reactive 2- and 5-positions would significantly aid in preventing competing oxidation/polymerisation pathways. Methyl 5-formylpyrrole-2-carboxylate (**164**) was employed and preliminary experiments at 70 ºC (Table 2.5) did not give rise to any polymeric products, consistent with a lower oxidation potential of the starting pyrrole substrate. However, even after a period of 2.5 h at this temperature (entry 3), the conversion and yield of fluorinated product was disappointingly low and so the reaction temperature was increased. The results obtained at a reaction temperature of 100 ºC were somewhat similar to that observed at 70 ºC,

with a comparable yield of 17% obtained after a reaction time of 2.5 h, although a large proportion of starting material still remained. Further increases in reaction temperature, however, offered no significant improvement in terms of observed yield, but appreciable amounts of polymer by-product began to form and purification was not possible.

Table 2.5: Reaction of **164** with Selectfluor™ under MW conditions.[a]



164 **165**

Entry	Temp / °C	Time /min	NMR Yield /%[b]
1	70	5	4
2	70	30	11
3	70	150	16
4	100	10	5
5	100	60	16
6	100	150	17
7	125	10	11
8	125	30	17
9	125	60	15
10	150	10	18

[a] Conditions: **164** (1 mmol), Selectfluor™ (1 eq.), MeCN (15 mL).

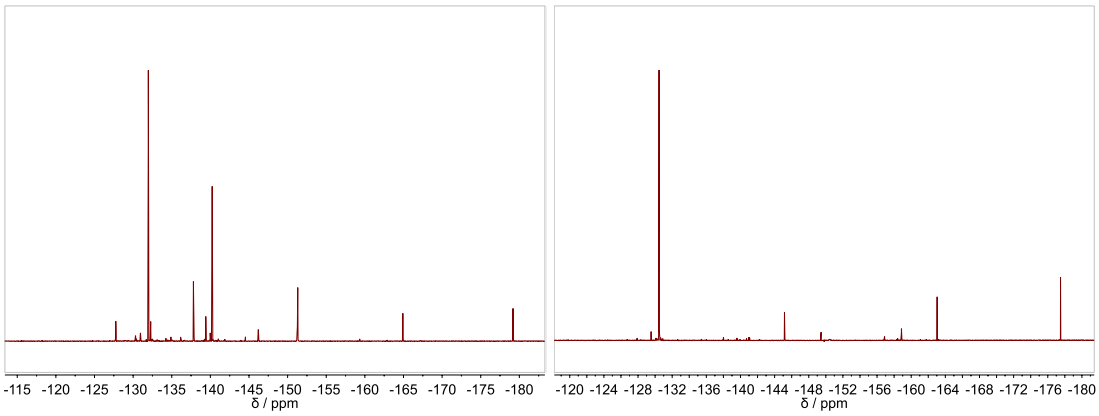
[b] NMR yield determined using α-α-α-trifluorotoluene as reference.

2.3.3 Fluorination of *N*-Protected Pyrroles

Due to the persistent competition between the desired fluorination and competing over substitution/oxidation side reactions when using 1*H*-pyrrole derivatives, we decided to employ *N*-protecting groups in combination with electron-withdrawing substituents on the pyrrole ring. Of course, for the protecting group to be successful it must be facile to introduce, be robust to the fluorination conditions and easily cleaved post-fluorination.

2.3.3.1 Fluorination of *N*-Methyl Protected Pyrroles

The first *N*-protected substrate trialled was the commercially available methyl *N*-methyl-pyrrole-2-carboxylate (**41**), as prior work by Fornarini *et al.* had shown *N*-methylpyrrole (**11**) to be superior to pyrrole in fluorination work using F_2 gas (See section 1.2.1). In addition, this would provide a direct comparison between the unprotected analogue (**155**) discussed previously in section 2.3.1. The reaction was performed under analogous conditions to that of **155**, but gave a complex mixture of fluorinated products (Fig. 2.12), which we attribute to the increased nucleophilicity of the pyrrole due to the electron-donating *N*-methyl substituent.



(a) (b)

Figure 2.12: Comparison of the ^{19}F NMR spectra of the crude reaction mixtures from fluorination of **41** (a) and **155** (b) with Selectfluor^{TM}.

The corresponding fluorinated product **166** could, however, be isolated, albeit in a reduced yield of 16% (Fig. 2.13) in comparison to the unprotected pyrrole analogue **156** (23%). This was attributed to a combination of two factors, firstly the greater proportion of by-products formed, but also due to the high volatility of the desired fluorinated compound during solvent removal. As a consequence, we considered the *N*-methyl protecting group unsuitable for our desired application and, hence, future work focussed on the use of electron-withdrawing protecting groups.

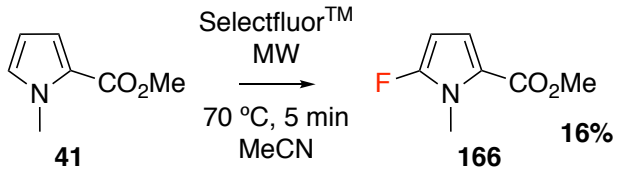


Figure 2.13: Synthesis of methyl *N*-methyl-5-fluoropyrrole-2-carboxylate (**166**) with Selectfluor™ under MW conditions.

2.3.3.2 Fluorination of *N*-(4-Nitrobenzyl) Protected Pyrroles

We then chose to assess the fluorination of a *N*-(4-nitrobenzyl) protected analogue (**168**) to compare the effect on the fluorination process with that observed for the unsubstituted (**155**) and *N*-methyl protected (**41**) analogues. The 4-nitrobenzyl variant was preferred to a simple benzyl group to prevent any competing fluorination of the aromatic ring of the protecting group. The synthesis of the *N*-(4-nitrobenzyl) derivative was carried out using sodium hydride in DMF and 4-nitrobenzyl bromide, which after purification by column chromtography, gave the desired protected pyrrole **168** in 51% yield (Fig. 2.14).

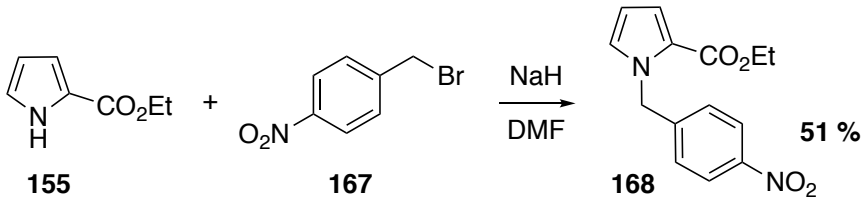
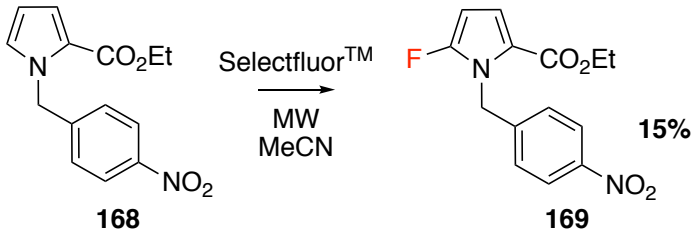


Figure 2.14: Synthesis of ethyl *N*-(4-nitrobenzyl)pyrrole-2-carboxylate (**168**).

Fluorination of pyrrole **168** was assessed and a range of reaction conditions were screened (Table 2.6). From the initial starting point (entry 1), the time of reaction was increased, but no improvement in yield was observed, despite significant quantities of starting material remaining. Hence, the reaction time was lowered (entry 4), but again, no improvement in yield was observed. The reaction temperature was varied, but neither an increase or decrease in temperature, over a range of reaction times, gave any increase in yield of the desired fluoropyrrole product and, in all cases, the yield remained low (~ 20%). Although the desired product (**169**) could be isolated by column chromatography in 15% yield (Fig. 2.15), this yield was lower than that attained for the unprotected analogue **156** (23%) which also does not require the additional steps for protecting group introduction and removal.

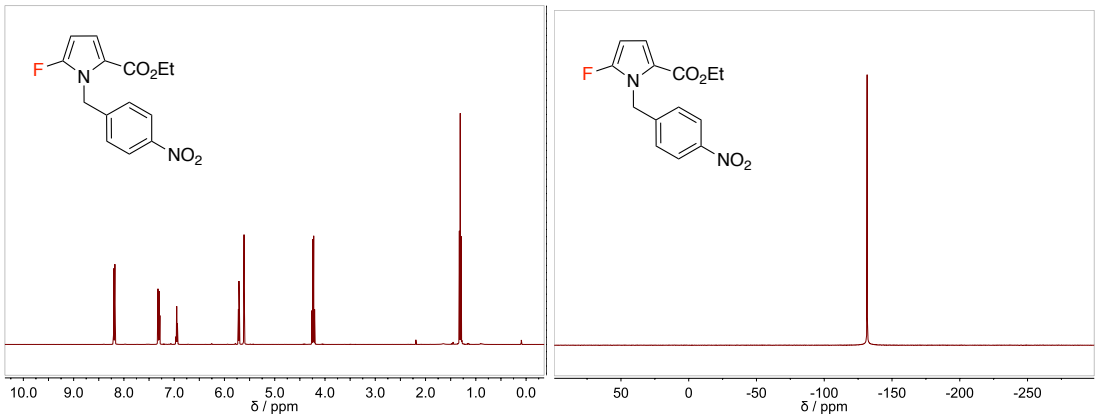
Table 2.6: Reaction of **168** with Selectfluor™ under MW conditions.[a]



Entry	Temp / °C	Time /min	NMR Yield /%[b]
1	70	5	27 (15)
2	70	10	21
3	70	15	20
4	70	2	23
5	100	5	22
6	100	10	20
7	100	15	20
8	60	5	20
9	60	10	25
10	60	15	25

[a] Conditions: **168** (0.5-0.6 mmol), Selectfluor™ (1 eq.), MeCN (15 mL).

[b] NMR yield determined using α-α-α-trifluorotoluene as reference, isolated yield in parantheses.



(a) (b)

Figure 2.15: ^{1}H (a) and ^{19}F (b) NMR spectra of isolated ethyl *N*-(4-nitrobenzyl)-5-fluoropyrrole-2-carboxylate **169**.

Similarly the *N*-(4-nitrobenzyl) protected analogue of **157** was also synthesised under the same conditions, but in this instance, could only be isolated in low yield (21%) (Fig. 2.16). Subsequent fluorination reactions again offered no distinct improvement in yield, which in combination with the low-yielding protection step meant that this route was inefficient and offered no advantage over the unprotected analogue. In both cases, when utilising the *N*-(4-nitrobenzyl) protecting group, we did not observe the desired reduction in nucleophilicity of the pyrrole substrates with over reaction and oxidation/ polymerisation pathways still significantly reducing the attainable yield of fluorinated pyrrole products.

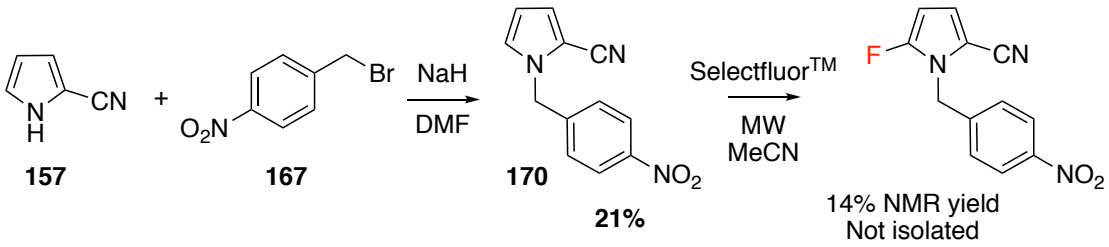


Figure 2.16: Synthesis of ethyl *N*-(4-nitrobenzyl)pyrrole-2-carbonitrile (**170**).

2.3.3.3 Fluorination of *N*-Tosyl Protected Pyrroles

Due to the lack of success when employing a 4-nitrobenzyl protecting group, we then moved our attention to the fluorination of *N*-tosyl protected pyrrole substrates. A sulfonyl-based protecting group was chosen based on the strong electron-withdrawing nature, which has previously been utilised in reducing the reactivity of pyrroles, to provide higher yields in regioselective alkenylation and acylation reactions.[84,85] Also of note was the facile, high-yielding introduction and cleavage of the group as well as stability towards oxidative conditions.

The synthesis of both *N*-tosyl protected pyrrole derivatives **171** and **172** was performed using sodium hydride in DMF and TsCl (Fig. 2.17). The reactions were monitored by ^{1}H NMR and, in both cases, full conversion was achieved after a period of 17 h. In the case of **171**, the crude product obtained after aqueous work up was a yellow oil which was purified by filtration through silica gel. This gave the desired product as a pale yellow solid in 88% yield. In contrast, the crude product **172** was obtained as a yellow solid,

which was purified by recrystallisation from hexane/EtOAc to give the desired product in 82% yield.

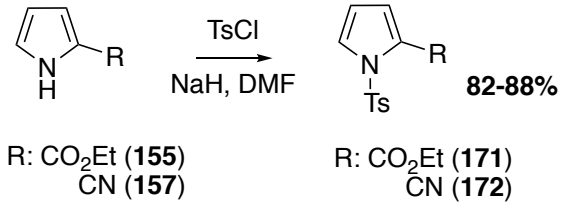
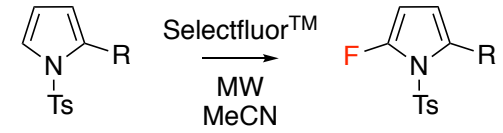


Figure 2.17: Synthesis of Ts protected pyrrole derivatives **171** and **172**.

Initially substrate **171** was subjected to the fluorination conditions previously found to be optimal for the analogous unprotected (**155**) and *N*-(4-nitrobenzyl) (**168**) protected substrates shown in entry 1 (Table 2.7). This clearly demonstrates the ability of the tosyl protecting group to deactivate the towards electrophiles as expected, with a negligible conversion to the fluorinated product and almost quantitative recovery of the starting material. As some conversion was achieved, initially the reaction temperature was held at 70 ºC and the reaction time was increased to 60 min. However, this had little effect on the yield of the desired product and, therefore, the reaction temperature was increased to 100 ºC. The result of this, shown in entry 3, again reveals no marked change in the yield of **173**, but did show the formation of a fluorinated by-product (appearing at ~ 66 ppm in ^{19}F NMR) in a comparable yield to the desired product (Fig 2.18).

Table 2.7: Reaction of **171** or **172** with Selectfluor™ under MW conditions.[a]



R: CO_2Et (**171**)
CN (**172**)

R: CO_2Et (**173**)
CN (**174**)

Entry	R	Temp / °C	Time /min	NMR Yield /%[b]
1	CO_2Et	70	5	<1
2	CO_2Et	70	60	2
3	CO_2Et	100	60	5
4	CN	70	5	0
5	CN	100	15	<1
6	CN	150	15	11
7	CN	100	60	6
8	CN	100	180	10

[a] Conditions: **171** or **172** (1 mmol), Selectfluor™ (1 eq.), MeCN (15 mL).

[b] NMR yield determined using α-α-α-trifluorotoluene as reference.

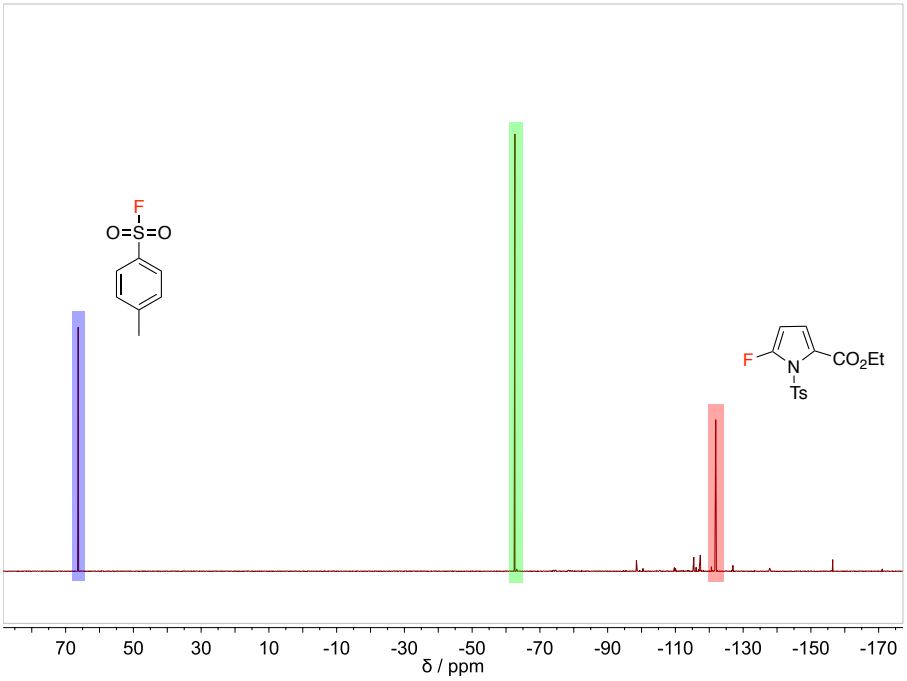


Figure 2.18: ^{19}F NMR of the crude product mixture showing the formation of fluorinated by-product (blue) and desired product (red) against the fluorinated reference (green).

Based on the observed ^{19}F NMR shift of this by-product, we postulated that it could be the resulting sulfonyl fluoride (**175**), via fluoride attack at the sulfur atom of the tosyl protecting group (Fig 2.19). We suspect that the fluoride ion originates from the tetrafluoroborate counterion of the Selectfluor^{TM} reagent due to prolonged exposure to high temperatures under microwave conditions. Subsequent GC-MS analysis of the crude reaction mixtures confirmed the presence of sulfonyl fluoride **175**, with the correct mass of 174 m/z was observed in all mixtures that showed the respective peak in ^{19}F NMR.

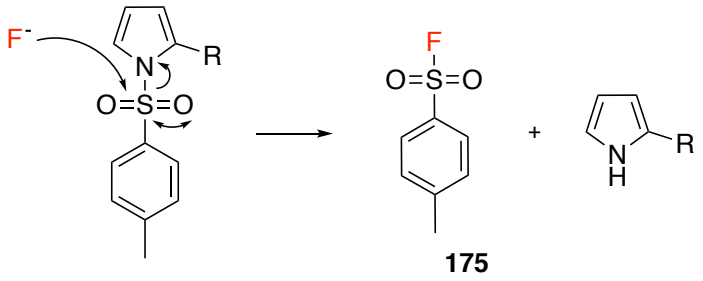


Figure 2.19: Possible reaction mechanism resulting in the formation of fluorinated by-product **175**.

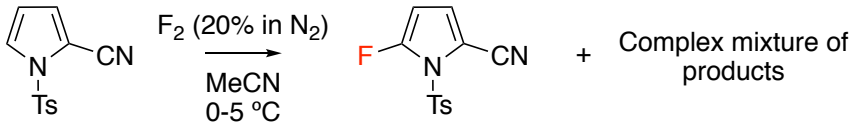
As a consequence of considerable by-product formation and the low yields attained for the desired fluorinated product (**173**), the *N*-tosylated substrate was considered too electron-deficient to achieve a good yield of the desired fluoropyrrole using Selectfluor^{TM}. Similar optimisation attempts were made using substrate **172**, which again, under the previously optimised conditions (entry 4), demonstrated the electron-withdrawing nature of the tosyl protecting group with no reaction observed and exclusive recovery of starting material. A range of reaction times (5-180 min) and temperatures (70-150 ºC) offered no distinct improvement in yield with formation of by-product **175**, again, a competing process.

2.4 Fluorination Using Fluorine Gas

We proposed the fluorination of tosyl substituted derivatives (**171** or **172**), that proved to be too unreactive to provide a synthetically useful reaction with Selectfluor^{TM}, may proceed more efficiently using F_2 gas. Historically, reactions using fluorine gas were

considered to be not of preparative significance owing to the extreme reactivity of F_2 towards nucleophiles. However, work at Durham has shown that many of the problems can be overcome and, with suitable substrates, the site selective fluorination of a range of aliphatic, dicarbonyl, aromatic, heteroaromatic, heterocyclic, steroid and carbohydrate derivatives has been achieved using F_2 gas.[86]

The reaction was conducted, by passing a dilute mixture of F_2 (20% in N_2 v/v) into a cooled (0-5 ºC) MeCN solution of substrate **172** at a rate of 20 mL/min for a period of 50 min, equating to 1.05 equivalents (Fig. 2.20).



172 **174**

Figure 2.20: Attempted fluorination of substrate **172** using F_2 gas.

The reaction was analysed by ^{19}F NMR, which revealed a very unselective reaction, with an array of fluorinated by-products being formed (Fig. 2.21). As a result, we ruled F_2 out as a possible fluorinating agent for pyrrolic systems, as it would seem even highly deactivated pyrrole substrates are still too electron rich to allow a regioselective fluorination to proceed under such conditions.

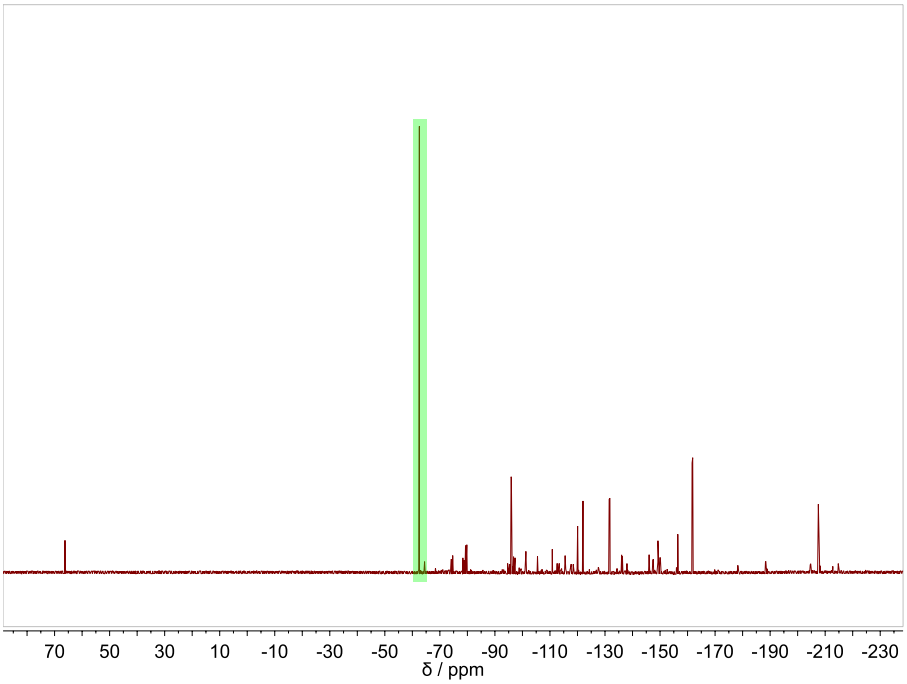


Figure 2.21: ^{19}F NMR spectrum of the crude reaction mixture following addition of 1.05 eq. F_2 (external reference highlighted in green).

2.5 Conclusions

In conclusion, the effect of various substituents on the fluorination of pyrrole substrates using Selectfluor^{TM} has been assessed. A systematic assessment of a range of pyrrole derivatives in electrophilic fluorination reactions was performed, but unfortunately, a general methodology for the facile synthesis of fluoropyrrole could not be achieved.

In general, competing oxidation and subsequent polymerisation of the pyrrole substrates by Selectfluor^{TM}, which is established as a reasonably strong oxidising agent as well as fluorinating agent, was a recurring problem for all substrates.

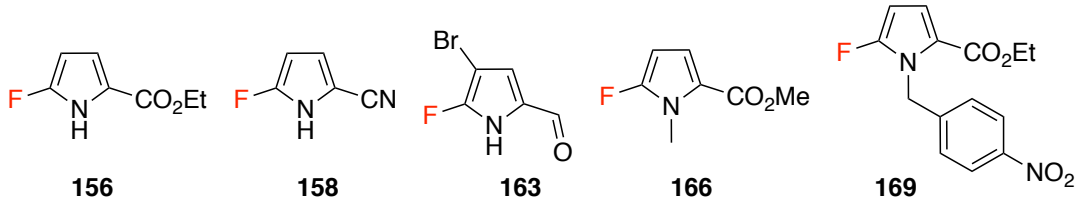


Figure 2.22: Fluorinated pyrrole derivatives synthesised by reaction with Selectfluor^{TM}.

However, the syntheses of fluorinated pyrrole derivatives bearing ester and cyano func-

tional groups (Fig. 2.22), which possess suitable functionality for further synthetic transformations to produce structures relevant for application in the life science industries, were achieved in synthetically useful reactions.

Chapter 3

Synthesis of Fluoropyrroles by Sequential Bromination-Derivatisation

3.1 Aims

In contrast to current methodologies for the synthesis of fluorinated pyrroles, corresponding procedures for the synthesis of brominated analogues are well established. The use of electrophilic brominating agents such as elemental bromine or NBS offers facile access to a variety of brominated pyrrole scaffolds.[24] In addition to the ease of introduction, bromine substituents on the pyrrole ring opens up the possibility for a range of metal-halogen exchange and cross-coupling reactions for further derivatisation.

Of interest to this study was the work by Barnes *et al.* who demonstrated the synthesis of a 3-fluoropyrrole derivative by sequential lithiation of 3-bromopyrrole derivative **26** and fluorination using NFSI (See Section 1.2.1).[30] Although, only applied to a single simple example, we envisioned that if we utilised a pyrrole starting material bearing multiple bromine handles we could perform fluorination reactions in conjunction with cross-coupling and lithiation/trapping chemistries and, by varying the order in which they are sequentially applied, access a diverse library of highly functionalised fluoropyrrole products which could then be incorporated into drug discovery screening libraries and parallel synthesis programmes (Fig. 3.1).

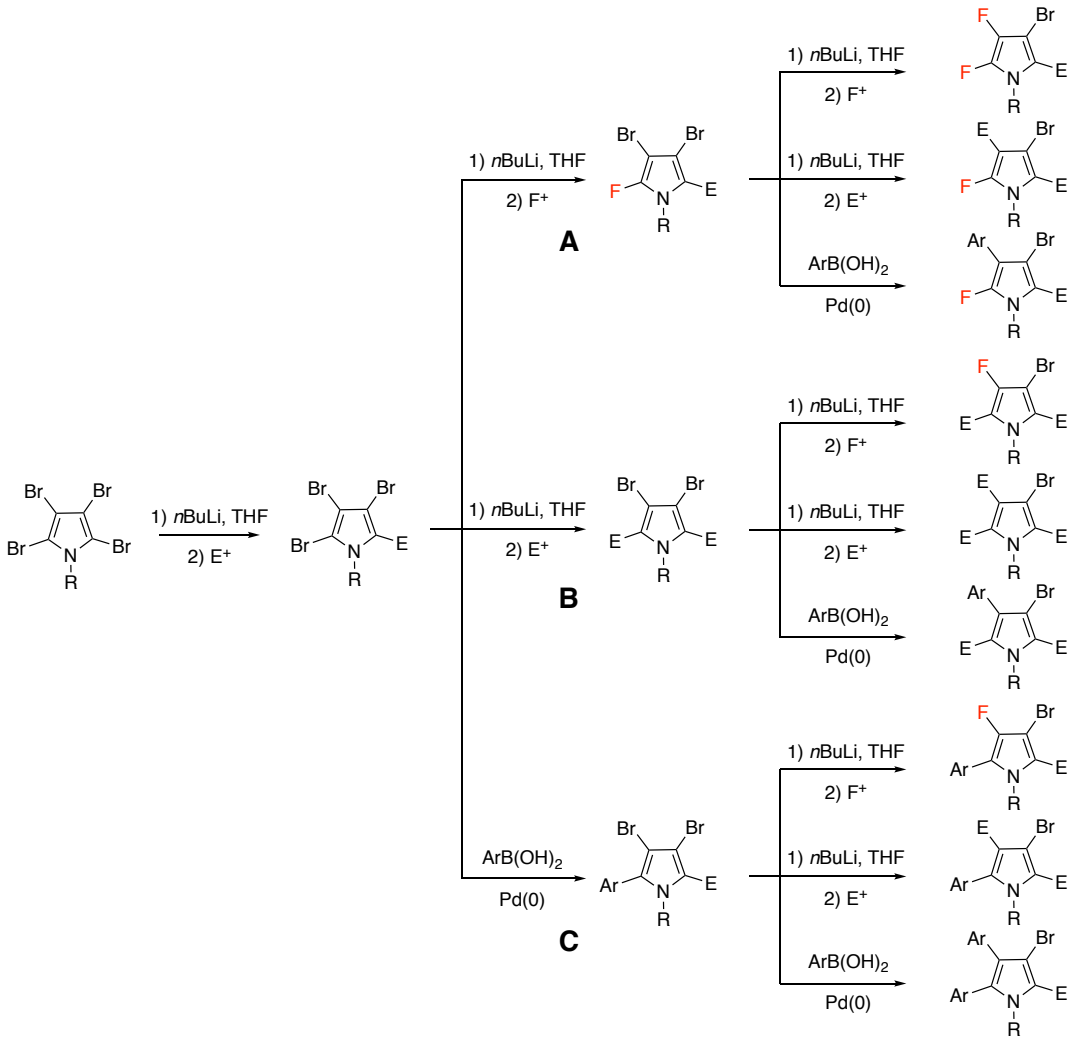


Figure 3.1: General bromination-derivatisation strategy to access a diverse library of functionalised pyrroles.

Consequently, we now review reactions of tetra- and tri-brominated pyrrole systems to provide background to the research undertaken using this strategy.

3.2 Chemistry of Polybrominated Pyrroles

Despite the potential utility of polybrominated pyrroles, tetra- and tri-brominated pyrroles have been scarcely utilised in synthesis, with only a limited number of reactions reported, focussing primarily on palladium-catalysed coupling chemistries with examples of Suzuki,[87–92] Sonogashira,[93] Heck,[94] and more recently, Stille[95] processes.

Based upon the predictions made by Zhang and Handy,[96] tetrabromopyrrole substrates

are expected to cross-couple at the 2- and 5-positions preferentially. Langer *et al.* verified this preference via Suzuki cross-coupling reactions to access symmetric 2,5-diaryl-3,4-dibromopyrroles that could be further functionalised to give tetraarylpyrroles. In addition to this it was also shown that, with careful optimisation of reaction conditions, synthesis of unsymmetric 2,5-diaryl-3,4-dibromopyrroles is possible (Fig. 3.2).[87]

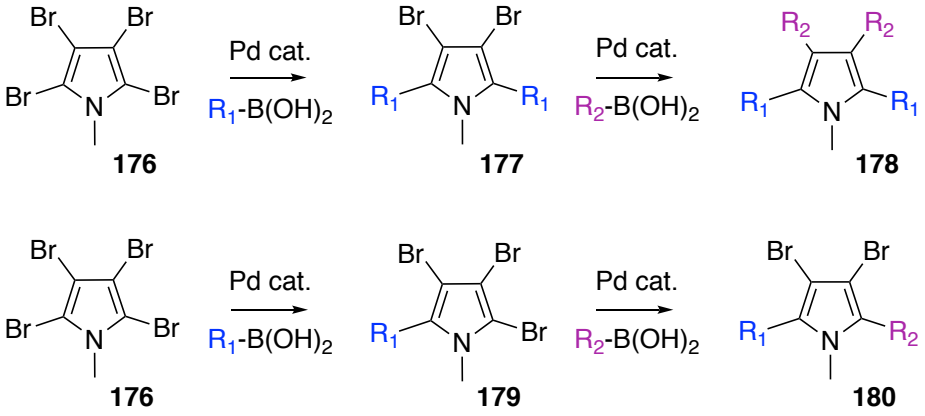


Figure 3.2: Regioselective Suzuki cross-coupling reactions of tetrabromopyrrole derivative **176**.

Similarly, work by the same group revealed that 2,3,5-tribromopyrroles also display good regioselectivity in cross-coupling reactions. Again, under Suzuki conditions, it was shown that the *N*-methyl derivative preferentially couples at the 5-position, likely due to less unfavourable steric interactions. This was followed by coupling at the 2- and 3-positions respectively, to give a range of mono-, di-, and tri-coupled products.[87]

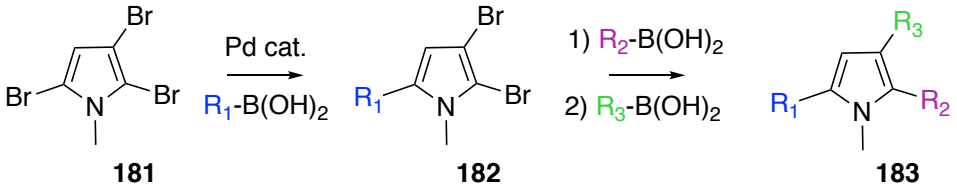


Figure 3.3: Regioselective Suzuki cross-coupling reactions of 2,3,5-tribromopyrrole derivative **181**.

Coupling reactions utilising 2,3,4-tribromopyrrole derivatives are less common. This is perhaps due to this regioisomer being thermodynamically disfavoured, and hence, synthesis requires functionalisation prior to bromination. TIPS protection of pyrrole, which is thought to sterically inhibit the formation of the 2,3,5-brominated isomer, followed by

treatment with NBS gives rise to *N*-TIPS-2,3,4-tribromopyrrole (**184**) in excellent yield (97% over two steps) (Fig. 3.4).[97]

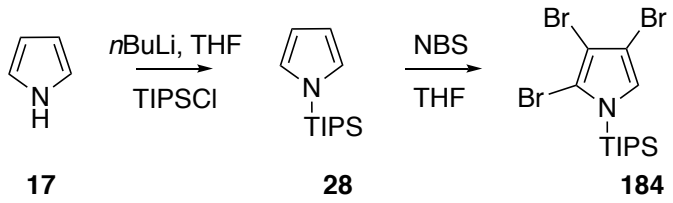


Figure 3.4: Synthesis of *N*-TIPS-2,3,4-tribromopyrrole (**184**).

Yamaguchi *et al.* used this protocol, and after switching to a Boc protecting group, were able to synthesise *N*-Boc-2,3,4-triphenylpyrrole (**186**) by three-fold Suzuki coupling in good yield (71%) (Fig. 3.5).[88]

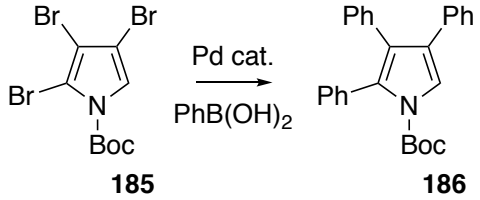


Figure 3.5: Synthesis of 2,3,4-triphenylpyrrole derivative **186**.

Bach *et al.* applied a different approach which utilised the readily available ethyl 2,3,4-tribromopyrrole-5-carboxylate (**187**). Although, initial attempts to perform Negishi and Sonogashira coupling reactions failed, Suzuki cross-coupling could be optimised to give a range of mono- and tricoupled products (Fig. 3.6). However, the authors noted no selectivity could be achieved between C-3 and C-4 following monoarylation.[91,92]

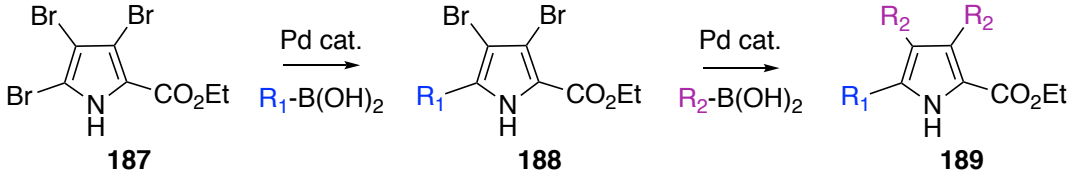


Figure 3.6: Regioselective Suzuki cross-coupling reactions of ethyl 2,3,4-tribromopyrrole-5-carboxylate (**187**).

In contrast, metal halogen exchange reactions of tetra- and tri-brominated pyrrole substrates have received less attention and, until very recently, metal-halogen exchange of a tetrabrominated pyrrole substrate had not been reported. In the only example,

Matravolgyi *et al*., showed that 1-phenyl-2,3,4,5-tetrabromopyrrole could be selectively lithiated at the 2-position before the addition of benzophenone and acidic work up to give the 5-diphenylmethylene substituted product **192** (Fig. 3.7).[98]

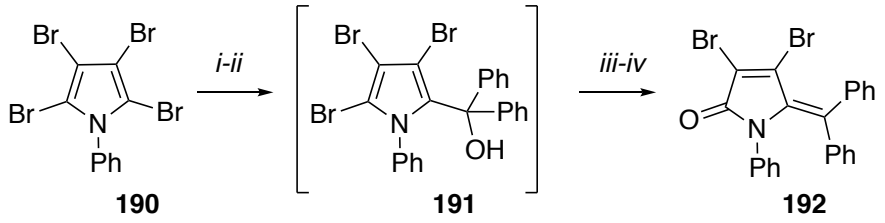


Figure 3.7: Metal-halogen exchange reaction of tetrabromopyrrole scaffold **190**.

Tribrominated pyrrole derivatives, such as *N*-TIPS-2,3,4-tribromopyrrole (**184**), have also been utilised in a limited number of metal halogen exchange reactions. Again, lithiation occurs selectivity at the 2-position, which can then be quenched by the addition of various electrophiles to yield 2-substituted-3,4-dibromopyrrole products (Fig. 3.8).[99,100]

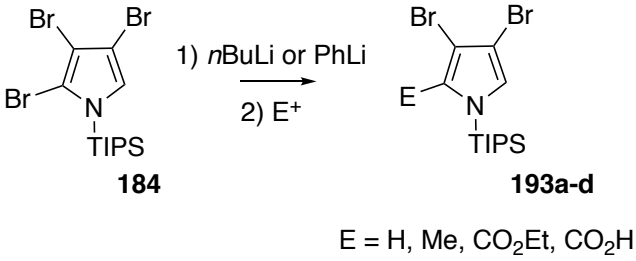
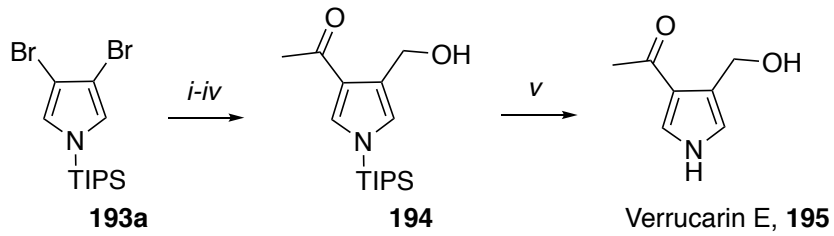


Figure 3.8: Metal-halogen exchange of tribromopyrrole derivative **184** and subsequent reactions with various electrophiles.

Further derivatisation of *N*-TIPS-3,4-dibromopyrrole (**193a**) was also demonstrated and, by applying two further sequential metal-halogen exchange reactions, gave access to the biologically relevant antibiotic verrucarin E (Fig. 3.9).[100]



i) *n*BuLi / THF / -78 ºC ii) *N*-Methoxy-*N*-methylacetamide
iii) *t*BuLi / THF / -78 ºC iv) HCHO v) F^-

Figure 3.9: Sequential metal-halogen exchange approach towards verrucarin E.

3.3 Synthesis of 2-Fluorinated Bromopyrrole Derivatives

Reactions of polybrominated pyrrole systems have been reported, but currently do not include fluorination reactions. Therefore, we initially proposed a synthetic strategy (strategy A, Figure 3.1) using polybrominated substrates for the synthesis of 2-fluoropyrrole derivatives.

3.3.1 Reactions of *N*-Methyl Protected Pyrroles

Due to reports of competing oxidation, which resulted in the formation of polymeric material, when unprotected pyrrole is reacted with 3 or more equivalents of NBS,[101] the bromination of a *N*-protected pyrrole substrate was first investigated. Based on the procedure reported by Langer *et al.*,[87] synthesis of 2,3,4,5-tetrabromo-*N*-methylpyrrole (**176**) was carried using NBS and gave the desired product **176** in a moderate yield (Fig. 3.10).

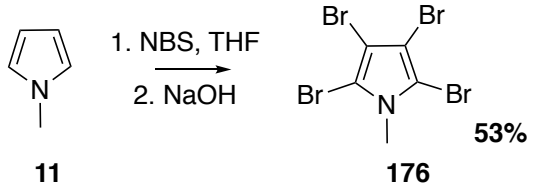


Figure 3.10: Bromination of *N*-methylpyrrole using NBS.

As cross-coupling reactions of this substrate have previously been reported[87] (See Section 3.2), the initial focus was placed upon developing an efficient protocol for metal-halogen exchange and subsequent reaction with a range of electrophiles. Thus,

hydrodebromination using 1 eq. *n*BuLi followed by the addition of dilute HCl, was performed in THF at -78 ºC which gave 2,3,4-tribromo-*N*-methylpyrrole (**196**) as a single product that could be isolated in good yield by column chromatography (Fig. 3.11).

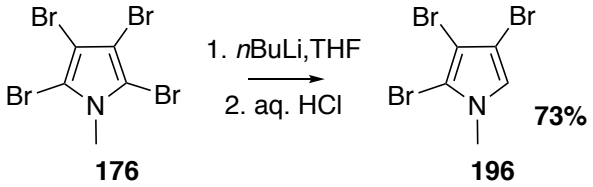


Figure 3.11: Hydrodebromination of 2,3,4,5-tetrabromo-*N*-methylpyrrole.

Encouraged by this result, fluorination was proposed via an analogous approach in which the metalated intermediate is quenched with an electrophilic source of fluorine, such as NFSI. However, despite the desired monofluorinated product being observed as the major product by GC-MS, purification attempts by column chromatography revealed the instability of the product on silica and, hence, isolation could not be achieved (Fig. 3.12).

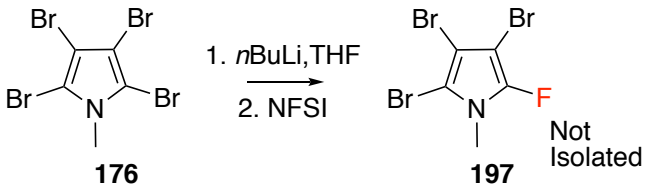


Figure 3.12: Attempted fluorination of 2,3,4,5-tetrabromo-*N*-methylpyrrole.

Fortunately, fluorination of 2,3,4-tribromo-*N*-methylpyrrole (**196**) gave the desired 2-fluoropyrrole **198** as the major product, but in this case, isolation via column chromatography was possible (Fig. 3.13). However, the high volatility of the resulting compound made removal of trace amounts of solvent very difficult leading to a reduced yield which was estimated by ^{1}H NMR, accounting for residual solvent. Kugelrohr distillation was also attempted as a means of purification, but the low thermal stability of the product proved to be an issue in this instance, giving polymeric tars upon heating.

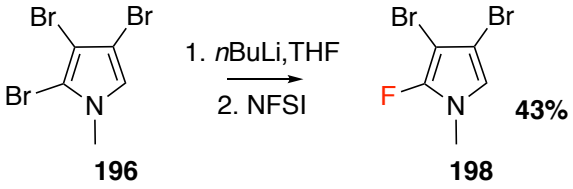


Figure 3.13: Synthesis of 2-fluoro-3,4-dibromopyrrole derivative **198**.

3.3.2 Reactions of *N*-Benzyl Protected Pyrroles

In an attempt to circumvent some of the issues encountered when using *N*-methyl pyrrole derivatives, we decided to modify the protecting group of the parent tetrabromopyrrole derivative to provide pyrrole scaffolds that are not too volatile or oxidatively unstable. A benzyl group was selected due to the ease of introduction and stability towards basic conditions. As such, the synthesis of 2,3,4,5-tetrabromo-*N*-benzylpyrrole (**200**) was carried out under the same conditions applied to the *N*-methyl analogue and was isolated in a much improved yield (Fig. 3.14).

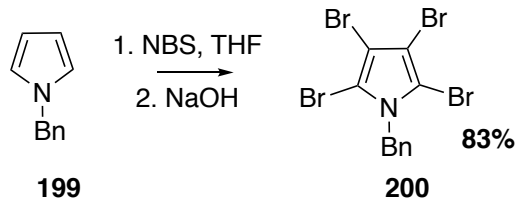


Figure 3.14: Bromination of *N*-benzylpyrrole using NBS.

The improved yield was attributed to a reduction in oxidation potential of the *N*-benzyl substrate versus the analogous *N*-methyl substrate, which aids to prevent competing oxidation reactions and the structure was confirmed by x-ray crystallography (Fig. 3.15).

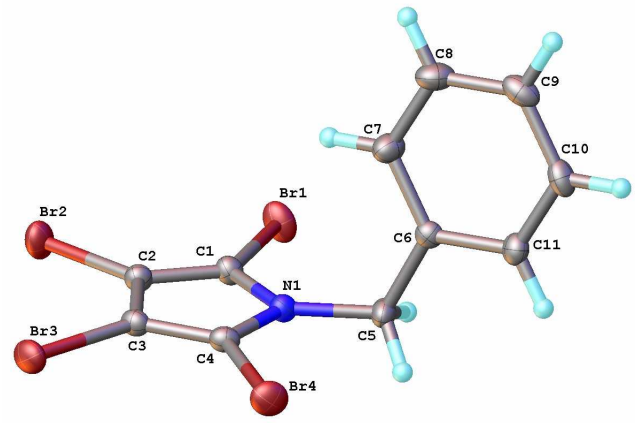


Figure 3.15: Molecular structure of **200** as confirmed by x-ray crystallography.

Using tetrabromo-*N*-benzylpyrrole (**200**) as the starting substrate we again observed excellent selectivity upon lithiation with *n*BuLi. The resulting intermediate was quenched with dilute HCl to give 2,3,4-tribromo-*N*-benzylpyrrole **201** as a single product in good yield (Fig. 3.16).

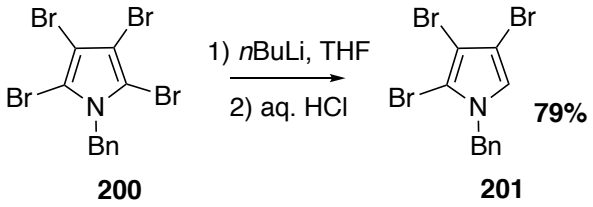


Figure 3.16: Hydrodebromination of 2,3,4,5-tetrabromo-*N*-benzylpyrrole.

We then attempted the analogous reaction quenching the metalated intermediate with a solution of NFSI in THF in order to give 2-fluoro-3,4,5-tribromopyrrole derivative **202** (Fig. 3.17).

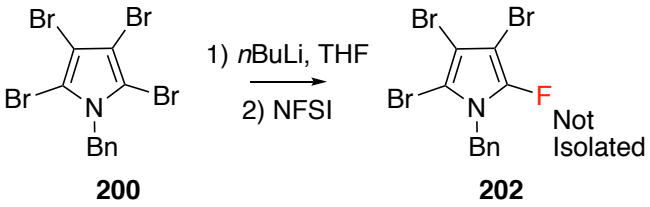


Figure 3.17: Attempted fluorination of 2,3,4,5-tetrabromo-*N*-benzylpyrrole.

However, under the reaction conditions a complex mixture of products was observed by GC-MS analysis, including appreciable quantities of difluorinated products as well as

recovered starting material, despite only using 1 eq. of *n*BuLi. We, therefore, postulate that these products are formed by 'halogen dance' type processes (Fig. 3.18), previously reported in similar halogenated heterocyclic systems by Schlosser *et al.*,[102] facilitated by a slow fluorination step.

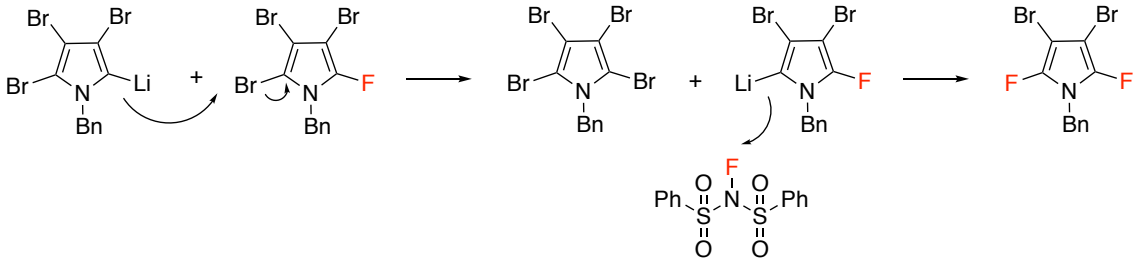


Figure 3.18: Proposed halogen dance type mechanism to account for the crude product composition.

Fortunately, fluorination of tribromo derivative **201**, under analogous conditions, gave the desired 2-fluoro-3,4-dibromopyrrole (**203**) as the major product. Initial isolation attempts by column chromatography using a gradient of ethyl acetate in hexane (0-10%) resulted in coelution of the desired product with an unknown fluorinated impurity. However, use of neat hexane as the eluent allowed the efficient isolation of fluoropyrrole **203** in good yield. (Fig. 3.19).

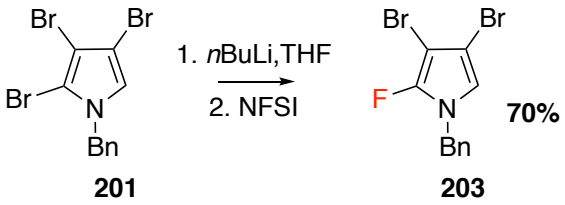


Figure 3.19: Synthesis of 2-fluoro-3,4-dibromopyrrole derivative **203**.

Storage of the isolated material at -18 ºC resulted in crystals of suitable quality for x-ray crystallography confirming the structure and, therefore, the regioselectivity of fluorination (Fig. 3.20).

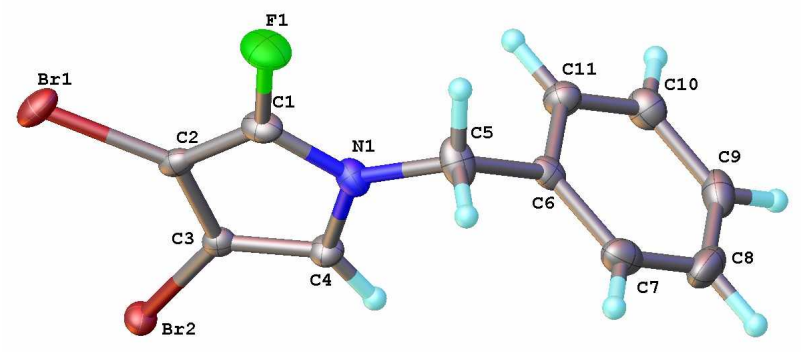


Figure 3.20: Molecular structure of **203** as confirmed by x-ray crystallography.

We then wanted to telescope the two reaction steps from tetrabromopyrrole **200** in an attempt to streamline the synthesis of 2-fluoropyrrole derivative **203**. In this case, the crude hydrodebrominated product **201**, prior to purification by column chromatography, was subjected to identical fluorination conditions. However, analysis of the resulting crude product mixture by ^{19}F NMR and GC-MS revealed a much more complex array of products and, hence, purification was not carried out and the telescoped synthesis was abandoned.

Due to the successful fluorination of tribrominated pyrrole derivative **201** we attempted to expand the scope of this protocol by varying the initial electrophile employed, followed by a fluorination step, to give access to a range of 2-fluoro-5-substituted pyrrole products (**205**) (Fig. 3.21).

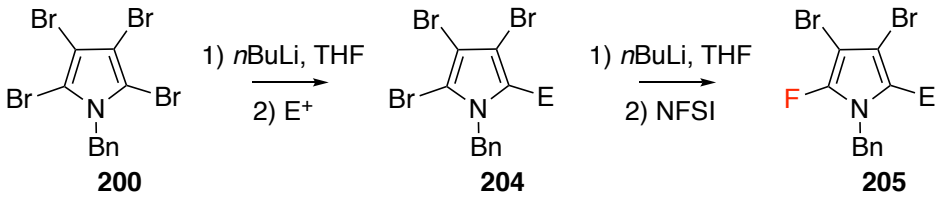


Figure 3.21: Proposed synthetic route to 2-fluoro-5-substituted-3,4-dibromopyrroles.

Unfortunately, under the same reaction conditions, using ethyl chloroformate or benzoyl chloride rather than aq. HCl as electrophiles only trace amounts of desired product could be observed, even when a large excess of electrophile was employed (5 eq.) (Fig. 3.22).

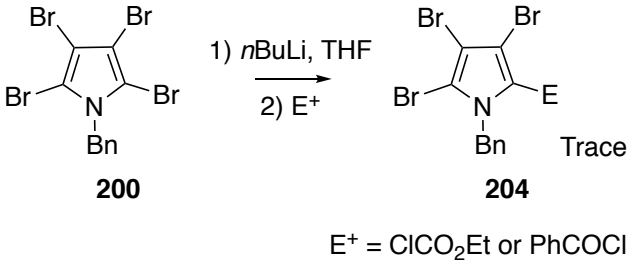


Figure 3.22: Attempted synthesis of substituted tribromopyrrole derivatives.

Due to the previous success observed when trapping with H^+, the poor yields attained in these instances were attributed to unfavorable steric interactions when bulkier electrophiles were used. Therefore, to test this hypothesis, we repeated the reaction using methyl iodide as the electrophile. In this case, we observed full conversion of the starting material by GC-MS, demonstrating that a less sterically demanding electrophile was preferred. Unfortunately, the resulting product (**206**) proved unstable upon purification attempts suggesting electron-withdrawing substituents are required to stabilise the substrate towards oxidative degradation (Fig. 3.23).

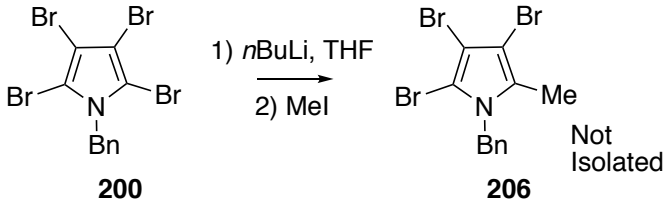


Figure 3.23: Attempted synthesis of 2-methyl substituted tribromopyrrole derivative **206**.

Although the efficient synthesis of 2-fluoro-3,4-dibromopyrrole derivative **203** was possible using a benzyl protected substrate, instability towards oxidative degradation limited the scope of substituents possible at the 5-position. Therefore, to allow a variety of substituents at this position, we decided to modify the protecting group used.

3.3.3 Reactions of *N*-(4-Nitrobenzyl) Protected Pyrroles

A 4-nitrobenzyl substituted tetrabromopyrrole was synthesised as it was proposed that addition of a nitro substituent could reduce the oxidation potential of the substrate. This would infer greater stability of the resulting compounds and potentially allow the

incorporation of a more diverse range of substituents.

Initial attempts to protect pyrrole with a 4-nitrobenzyl protecting group via deprotonation using sodium hydride and addition of 4-nitrobenzyl bromide gave only trace amounts of the desired product. However, an efficient redox reaction of 4-hydroxy-L-proline (**207**) with aldehydes to give the corresponding *N*-alkylpyrrole has been reported in the literature[103] and, under these conditions, it was possible to obtain the desired 4-nitrobenzyl derivative **209** in quantitative yield from 4-nitrobenzaldehyde (Fig. 3.24).

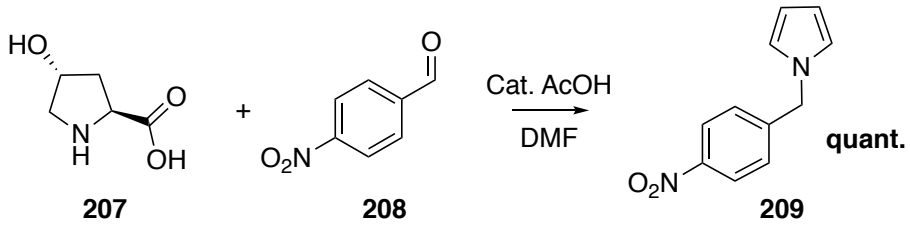


Figure 3.24: Synthesis of *N*-(4-nitrobenzyl)pyrrole via redox reaction of 4-hydroxy-L-proline.

Bromination of 4-nitrobenzyl protected pyrrole derivative **209** using NBS proceeded well and the desired tetrabrominated derivative **210** was isolated in moderate yield (Fig. 3.25).

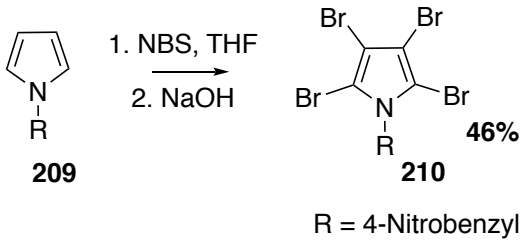


Figure 3.25: Bromination of *N*-(4-nitrobenzyl)pyrrole using NBS.

However, subsequent lithiation and trapping reactions were much less successful than those observed for the corresponding *N*-benzyl protected derivatives. Hydrodebromination by reaction with *n*BuLi followed by quenching with dilute HCl to give the corresponding 2,3,4-tribrominated pyrrole derivative **211** proceeded, but in a much reduced yield (Fig. 3.26). Initial isolation attempts by recrystallisation from hexane/DCM and $CHCl_3$/MeOH gave a mixture of the desired product and starting material, but isolation

could be achieved by column chromatography using a gradient of ethyl acetate in hexane (0-20%).

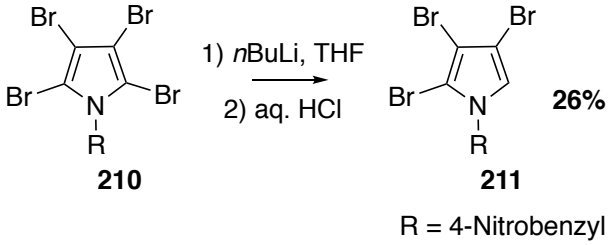


Figure 3.26: Hydrodebromination of 2,3,4,5-tetrabromo-*N*-(4-nitrobenzyl)pyrrole.

In addition, analysis of the crude reaction mixture from the attempted fluorination of **211** using NFSI, under conditions which allowed fluorination of the analogous *N*-benzyl derivative, showed no evidence of the formation of the desired product (Fig. 3.27). Due to the observed reactivity, we proposed that the nitro substituent could be potentially inducing side reactions either by activating the ortho protons on the aromatic ring, or by facilitating nucleophilic attack at oxygen of the nitro group, similar to that observed in the Bartoli indole synthesis.[104]

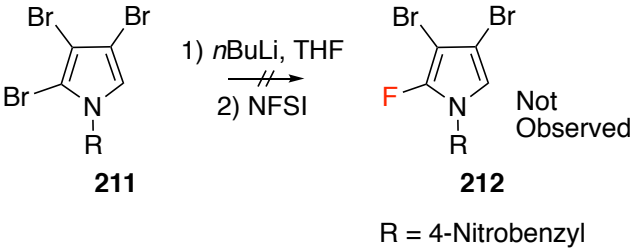


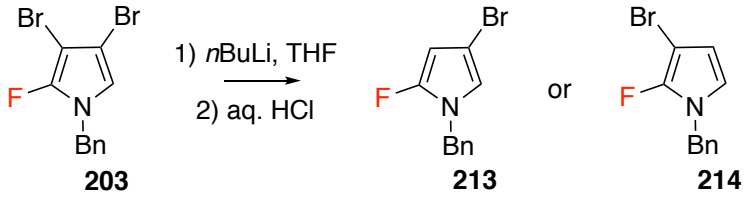
Figure 3.27: Attempted fluorination of 2,3,4-tribromo-*N*-(4-nitrobenzyl)pyrrole.

3.4 Reactions of *N*-Benzyl-2-Fluoro-3,4-Dibromopyrrole

As we had developed an efficient, high yielding process for the synthesis of *N*-benzyl-2-fluoro-3,4-dibromopyrrole (**203**), we decided to focus our attention on the diversification of this substrate by varying the substituents on the pyrrole ring by utilising the two remaining bromine handles for lithiation/trapping and cross-coupling chemistries.

3.4.1 Metal-Halogen Exchange Reactions

We first wanted to assess the regioselectivity of potential lithiation reactions with 2-fluoropyrrole derivative **203** and so, hydrodebromination using *n*BuLi followed by quenching with aq. HCl was performed (Fig. 3.28).



203 **213** **214**

Figure 3.28: Possible regioisomeric products formed by dehydrobromination of dibrominated pyrrole derivative **203**.

Lithiation proved to be very selective with both NMR and GC-MS inferring a single hydrodebrominated product was formed which could be isolated in good yield (78%). Analysis of the ^{1}H NMR of the resulting product is consistent with the formation of 2-fluoro-4-bromopyrrole derivative **213** with a mutual coupling of J=2.2 Hz observed. This value is much more indicative of a four-bond coupling as confirmed by comparison to the values reported by Iwao *et al.* for the related *N*-substituted 2,3- and 2,4-dibromopyrrole derivatives (Fig. 3.29).[105]

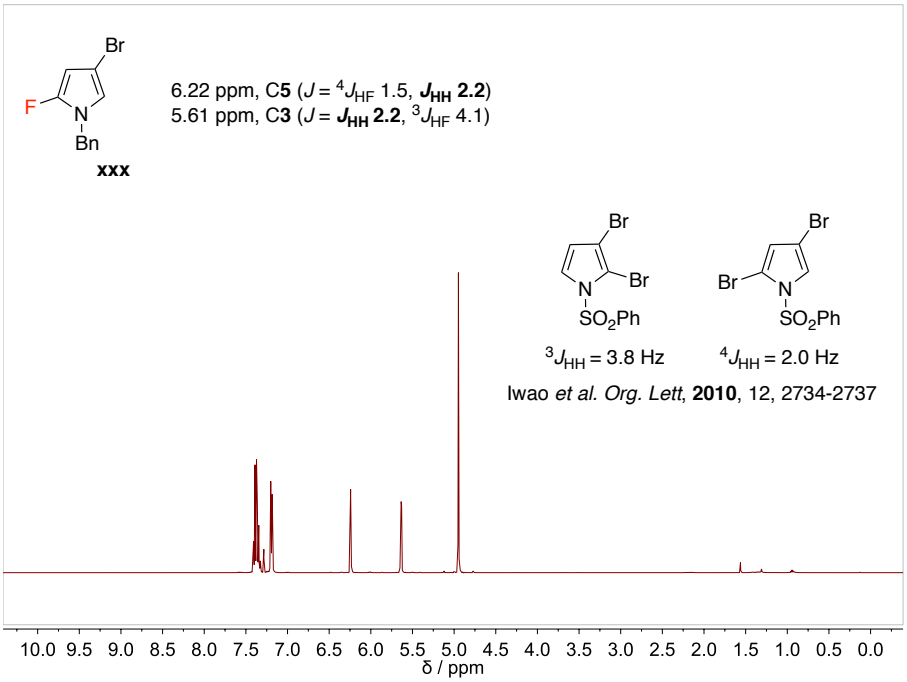


Figure 3.29: ^{1}H NMR spectrum of isolated hydrodebrominated product and related literature J values.[105]

We propose the observed regioselectivity is a result of the ability of the electron-withdrawing fluorine subsitutent to stabilise the intermediate anion and, hence, lithiation at the site adjacent to fluorine is favoured.

As well as providing evidence for the regioselectivity of subsequent lithiation reactions, this reaction also provided access to a fluorinated building block bearing a bromine substituent which could be utilised for further derivatisations. As a model reaction, hydrodebromination was first performed using *n*BuLi, followed by quenching with aq. HCl to give 2-fluoropyrrole derivative **215** (Fig. 3.30).

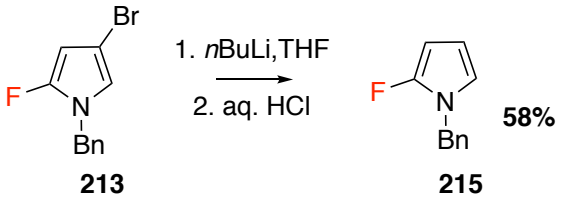


Figure 3.30: Synthesis of *N*-benzyl-2-fluoropyrrole.

The desired product could be isolated by column chromatography, however, in a similar manner to the observation for methyl protected substrate **198**, the high volatility of the

compound made removal of trace solvent difficult, reducing the isolated yield, which was estimated by ^{1}H NMR to account for residual solvent.

Fluorination was also attempted to give access to 2,4-difluoropyrrole derivative **216**, but when using NFSI in THF as the trapping electrophile, the major component of the crude reaction mixture was the hydrodebrominated product, alongside only trace amounts of the desired 2,4-difluoropyrrole derivative **216**. This is thought to be due to a competing electron transfer reaction between the intermediate lithiate and NFSI, in agreement with observations previously reported by Barnes *et al.* in their synthesis of 3-fluoro-*N*-TIPS-pyrrole **27** using NFSI[30] and by Differding *et al.* for reactions of a range of organometallic nucleophiles with N-F electrophilic fluorinating agents.[106,107]

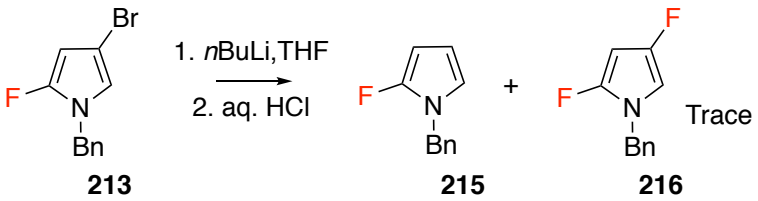


Figure 3.31: Attempted synthesis of 2,4-difluoropyrrole derivative **216**.

However, it was possible to synthesise a range of 2-fluorinated products from **213** bearing ester (**217**), aldehyde (**218**) and ketone (**219**) functional groups at the 4-position by lithiation and trapping with ethyl chloroformate, ethyl formate and benzoyl chloride respectively (Fig. 3.32). Initial conditions in which the reaction mixture was allowed to warm to room temperature after the addition of the electrophile were greatly improved by modification such that the reaction mixture was retained at -78 ºC for 1 h after the addition of the electrophile and quenched before being allowed to warm to room temperature. In addition, contamination of products with the corresponding acid derived from the acid chloride electrophile, even after column chromatography, could be prevented by washing the crude product with a saturated aqueous solution of $NaHCO_3$.

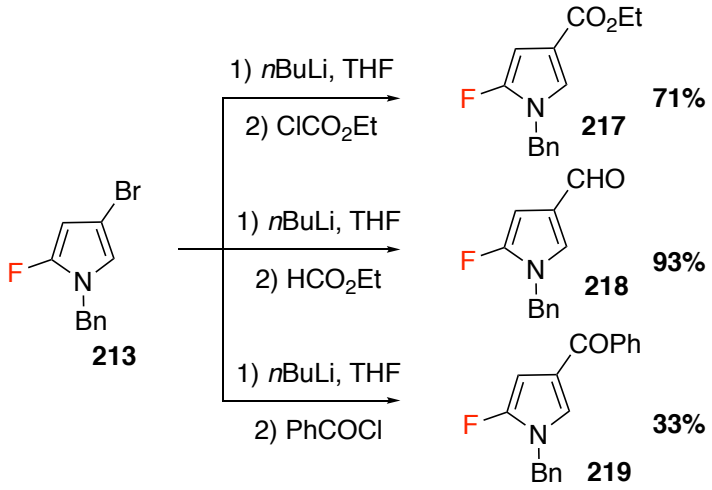
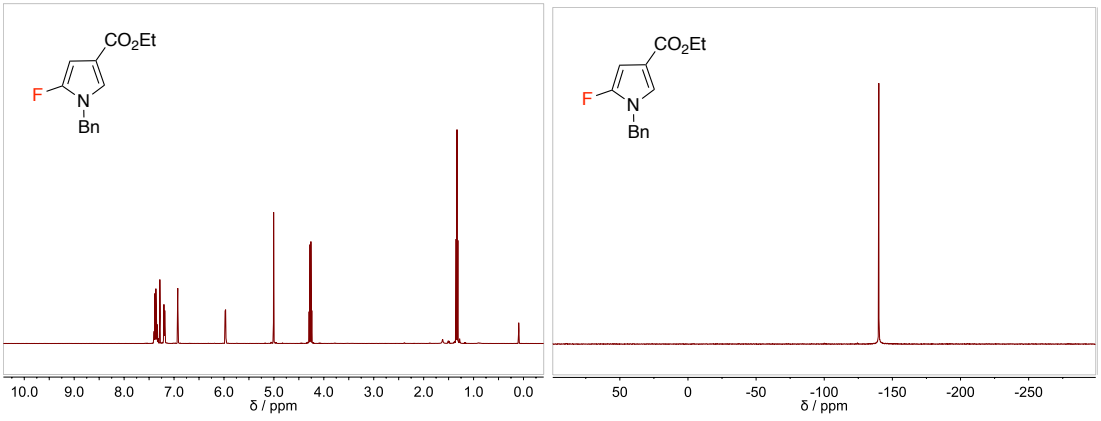


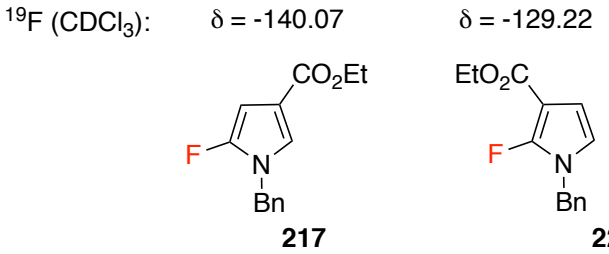
Figure 3.32: Synthesis of 2-fluoro-4-substituted pyrrole derivatives **218**, **218** and **219**.

Also, the spectroscopic data, including the ^{19}F NMR shift of 2-fluoropyrrole **217** (-140.04 ppm in $CDCl_3$) (Fig. 3.33), were in excellent agreement with that previously reported in the literature (-140.07 ppm) and very distinct from the expected chemical shift of the regioisomeric ethyl 2-fluoro-*N*-benzylpyrrole-3-carboxylate (**220**) (Fig. 3.34),[29] providing additional evidence that lithiation of 2-fluoro-3,4-dibromosubstrate **203** initially occurs at the 3-position, adjacent to the fluorine substituent.



(a) (b)

Figure 3.33: ^{1}H (a) and ^{19}F (b) NMR spectra of isolated ethyl 2-fluoro-*N*-benzylpyrrole-4-carboxylate (**217**).



Tamamura *et al.*, *Eur. J. Org. Chem.*, 2016**, 21**, 3491-3494

Figure 3.34: Reported ^{19}F chemical shifts of the 2-fluorinated 3- and 4-pyrrole ester regioisomers.[29]

These experiments opened up the possibility of expanding the range of fluoropyrrole products accessible from dibromofluoropyrrole **203** by varying the substituent at the 3-position. We hoped that the excellent regioselectivity previously observed upon lithiation would be retained even when using much more sterically demanding electrophiles as there is minimal steric change upon substituting a hydrogen atom for a fluorine atom. The same range of electrophiles was again applied, and gave the corresponding 3-substituted 2-fluoropyrroles with a remaining bromine handle in good to excellent yields (Fig. 3.35). Furthermore, it was also possible to grow a crystal of 2-fluoropyrrole **223** that was suitable for x-ray crystallography, allowing unequivocal assignment of structure and, hence, the regioselectivity of the debromolithiation process (Fig. 3.36).

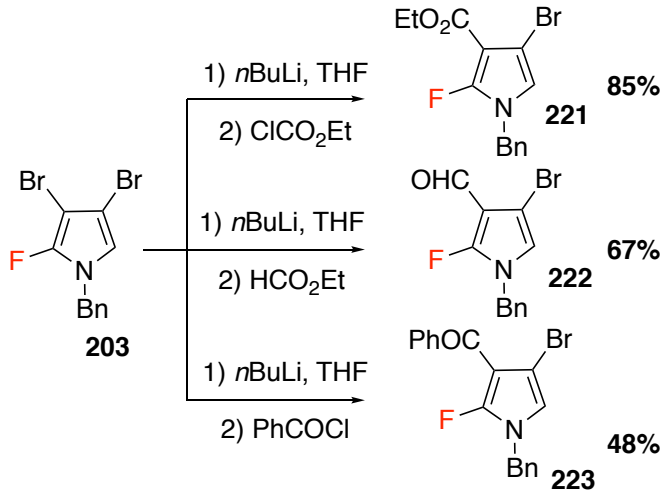


Figure 3.35: Synthesis of 2-fluoro-3-substituted-4-bromopyrrole derivatives **221**, **222** and **223**.

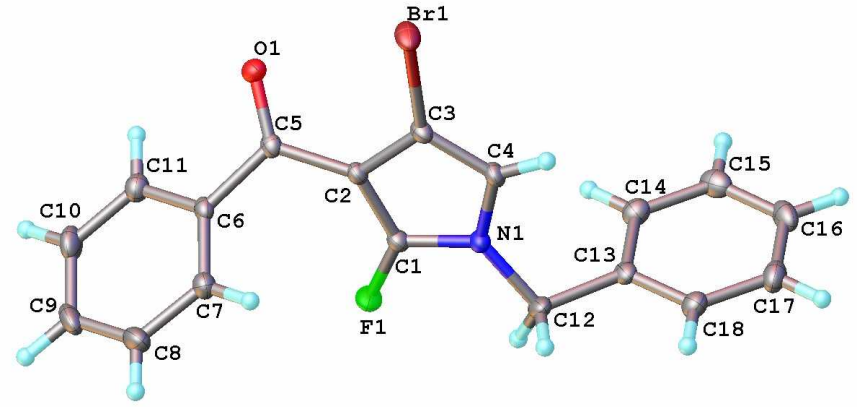


Figure 3.36: Molecular structure of **223** as confirmed by x-ray crystallography.

It was also desirable to expand the range of electrophiles employed to allow the synthesis of alkylated derivatives. Therefore, we employed the same set of reaction conditions as above with allyl bromide as the quenching electrophile (Fig. 3.37). However, ^{1}H and ^{19}F NMR analysis of the crude reaction mixture revealed the major product in this instance to be the previously synthesised hydrodebrominated product **213**. This is despite moderate yields being reported for the synthesis of the related 3-allylthiophene under comparable conditions.[108,109]

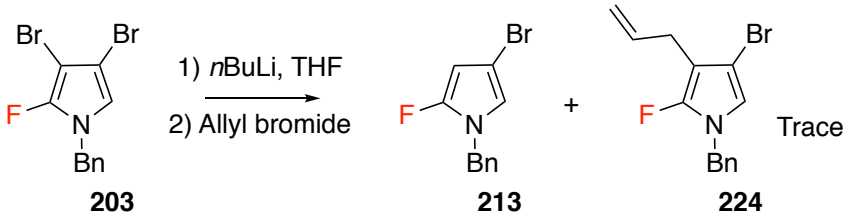


Figure 3.37: Attempted synthesis of 2-fluoro-3-allyl-4-bromo-*N*-benzylpyrrole.

We postulated that the resulting lithiated nucleophile is too hard[110] to efficiently react with allyl bromide. Therefore, we modified the procedure such that a Cu^{I} salt was added to the reaction mixture before the addition of the electrophile, in the hope that the resulting organocopper species, a much softer nucleophile, would favour the S_N2 reaction mechanism (Fig. 3.38).

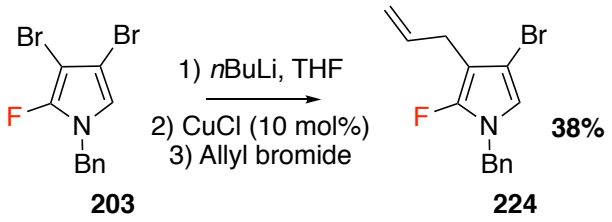
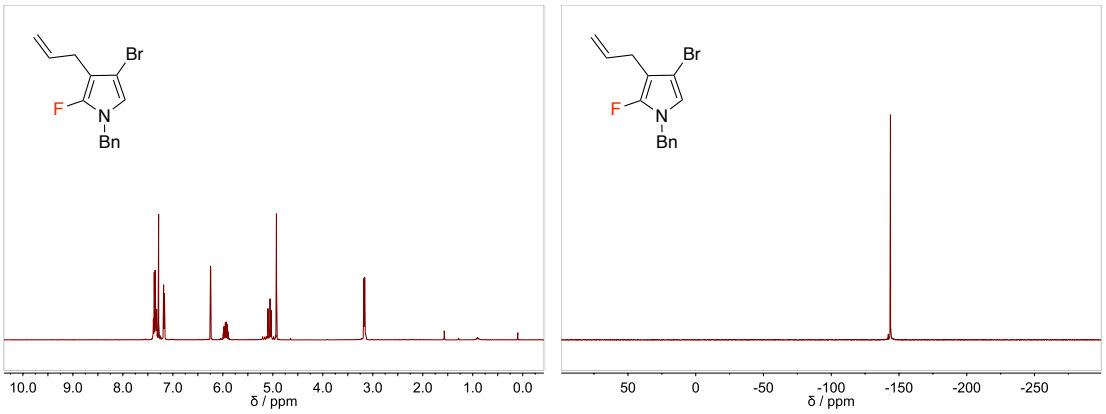


Figure 3.38: Allylation reaction by transmetallation with Cu^{I} salt.

Indeed, the resulting organocopper derivative reacted much more efficiently and the resulting allylated compound **224** could be isolated by column chromatography using 1% Et_2O in hexane. However, the isolated yield was disappointingly low (10%) using this means of isolation, likely due to a combination of volatility and stability on silica. As a result, the reaction was repeated and instead purified by Kugelrohr distillation resulting in a much improved isolated yield (38%) (Fig. 3.39).



(a) (b)

Figure 3.39: ^{1}H (a) and ^{19}F (b) NMR spectra of isolated 2-fluoro-3-allyl-4-bromo-*N*-benzylpyrrole (**224**).

Additionally, the series of 2-fluoro-3-substituted-4-bromopyrrole compounds (**221**, **222** and **223**) could also provide access to regioisomeric products of **217**, **218** and **219** respectively by performing hydrodebromination reactions. Using 2-fluoropyrrole **221** as an example, we showed this to be possible, under the same general conditions, using *n*BuLi followed by quenching with aq. HCl (Fig. 3.40).

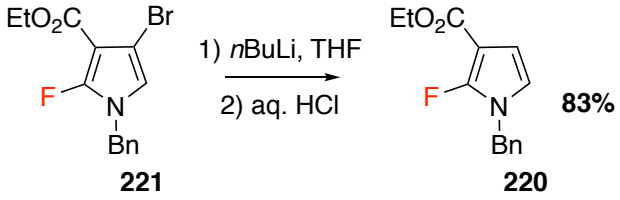


Figure 3.40: Synthesis of 2-fluoro-*N*-benzylpyrrole-3-carboxylate.

This demonstrates the ability of our general methodology to provide efficient access to regioisomeric products, controlled by the order in which we sequentially apply the same set of reaction conditions (Fig. 3.41). This is in contrast to the previously reported synthesis of compounds **217** and **220** in which a mixture of the two products was obtained.[29]

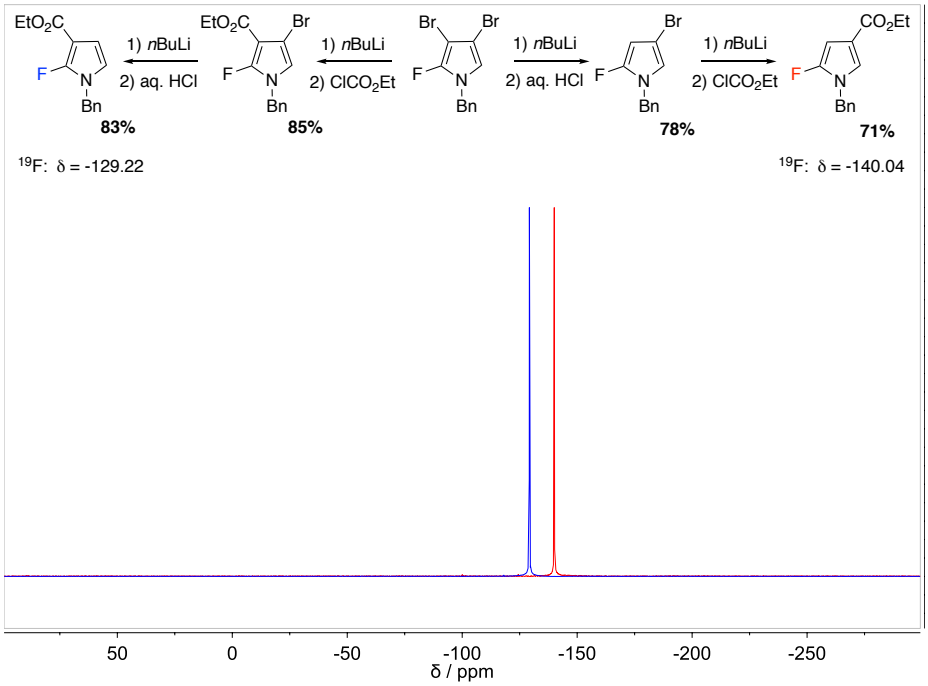


Figure 3.41: Overlayed ^{19}F NMR spectra of fluorinated regioisomers **217** and **220**.

Moreover, it was also possible to build complexity from fluoropyrrole derivatives **221**, **222** and **223** by varying the electrophile at the 4-position. Again, using 2-fluoropyrrole **221** as an example, we demonstrated the potential of this system as a starting material to synthesise a range of symmetric and asymmetric 3,4-disubstituted 2-fluoropyrrole products (**225**, **226** and **227**) in moderate yields by applying similar lithiation/quenching protocols (Fig. 3.42).

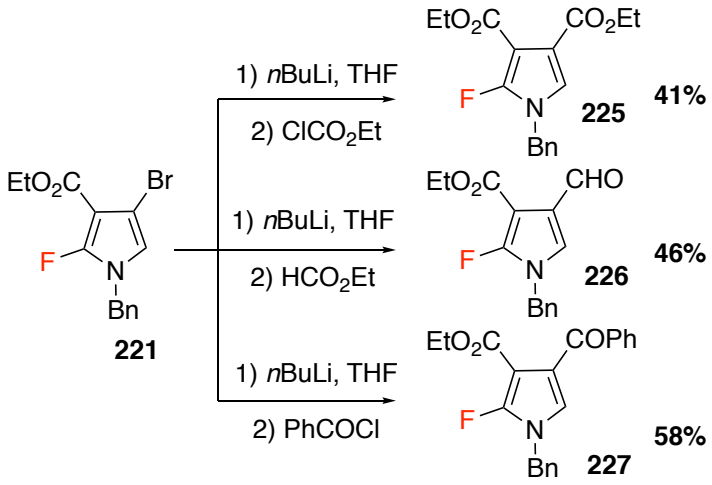
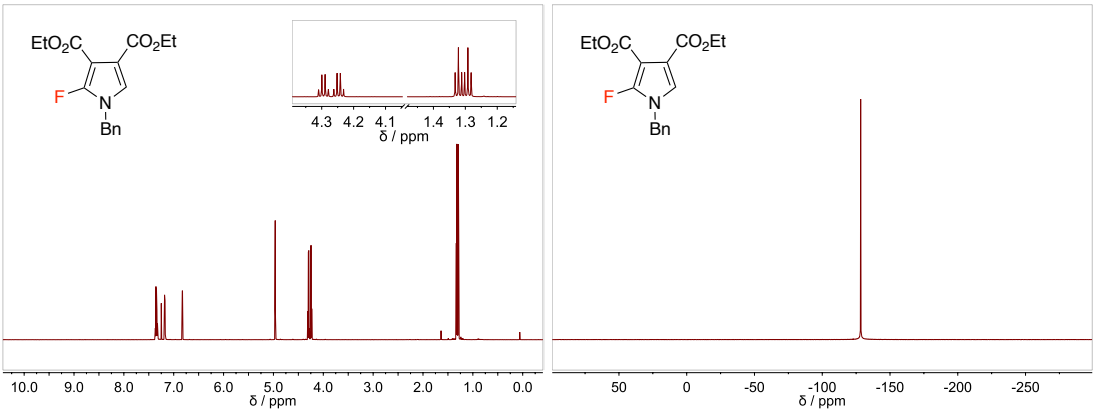


Figure 3.42: Synthesis of 2-fluoro-3,4-disubstituted pyrrole derivatives **225**, **226** and **227** by sequential lithiation and quenching.

The yields in this instance are unoptimised and analysis of the crude reaction mixtures by GC-MS and NMR revealed appreciable quantities of hydrodebrominated products, but no residual starting material. This suggests that lithiation is quantitative and the subsequent reaction with the corresponding electrophile is relatively slow, likely due to more unfavourable steric interactions. Therefore, an increase in reaction time and/or the number of equivalents of electrophile should result in an improved yield. Product structures were assigned based on ^{1}H and ^{19}F NMR spectra (Fig. 3.43) and, it was also possible to grow a crystal of **227** suitable for x-ray crystallography, with the structure confirming the assigned regiochemistry of the isolated products (Fig. 3.44).



(a) (b)

Figure 3.43: Illustrative ^{1}H (a) and ^{19}F (b) NMR spectra of isolated diethyl 2-fluoro-*N*-benzylpyrrole-3,4-dicarboxylate **225**.

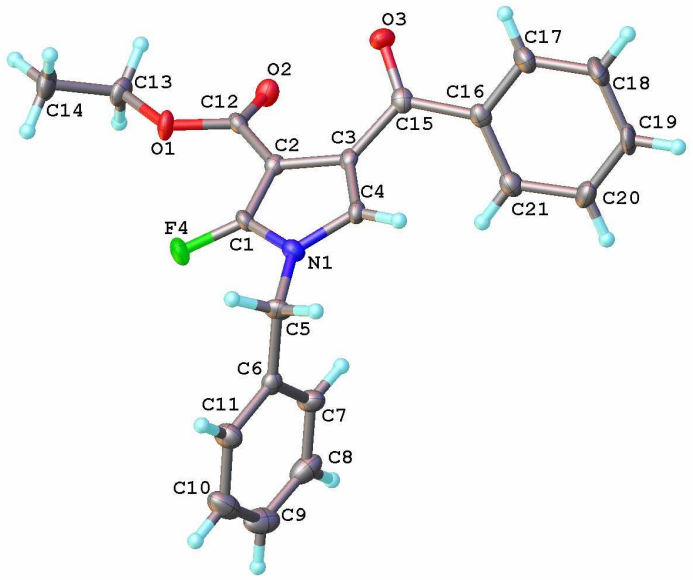
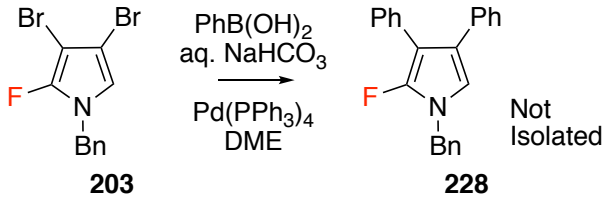


Figure 3.44: Molecular structure of **227** as determined by x-ray crystallography.

3.4.2 Suzuki Cross-Coupling Reactions

In addition to the previously demonstrated metal-halogen exchange reactions, we also wanted to utilise palladium catalysed cross-coupling chemistries, such as Suzuki reactions, to diversify the range of 2-fluoropyrrole products accessible using our general fluoropyrrole synthesis strategy.

Initially, using conditions reported by Fukuda *et al.*,[111] who demonstrated the efficient synthesis of a range of 3,4-diarylated pyrrole substrates from the corresponding dibrominated starting material, we attempted the Suzuki cross-coupling of 2-fluoro-3,4-dibromopyrrole derivative **203** with phenylboronic acid (Fig. 3.45).



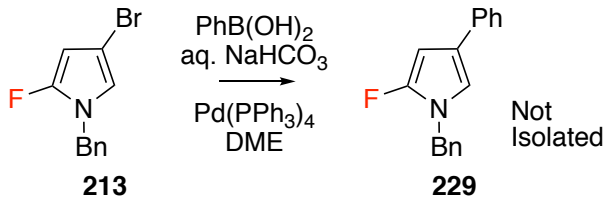
203 **228**

Figure 3.45: Attempted Suzuki cross-coupling of 2-fluoro-3,4-dibromopyrrole derivative **203**.

After a period of 20 h at reflux we observed good conversion by ^{19}F NMR but, this was accompanied by appreciable quantities of insoluble material, likely formed due

to instability of the starting material and/or products at reflux temperatures under the reaction conditions for prolonged periods. GC-MS analysis of the extractable material revealed formation of the desired diarylated product alongside small quantities of the corresponding monoarylated and hydrodebrominated products. Isolation, however, could not be achieved by column chromatography due to very similar R_f values on silica gel of the desired product and by-products.

Thus, we modified the starting substrate, instead using 2-fluoro-4-bromopyrrole **213** (Fig. 3.46), because a substrate bearing only one bromine substituent should limit the number of possible by-products.



213 **229**

Figure 3.46: Attempted Suzuki cross-coupling of 2-fluoro-4-bromopyrrole derivative **213**.

Under analogous conditions, after a period of 20 h at reflux we observed the formation insoluble material, again suggesting instability of the starting material and/or products at reflux under the reaction conditions. However, GC-MS analysis of the extractable material revealed the major product to be the desired monoarylated product **229** with no evidence of the corresponding hydrodebrominated product. Unfortunately, isolation attempts by column chromatography revealed the instability of the desired product on silica gel and, hence, isolation could not be achieved.

A survey of the literature, however, revealed a report from Ghosez *et al*. who demonstrated the efficient synthesis of a range 1,2-disubstituted-3-arylpyrroles from a range of electron-rich and electron-poor aryl and heteroaryl boronic acids.[112] The report shows that use of bidentate ligands (dppf) and polar solvent (DMF) significantly increases the rate of reaction as well as yield of the cross-coupled products. We proposed that an increased rate of reaction would allow a shorter reaction time for the Suzuki coupling and therefore aid in preventing degradation of the starting material and products

under the reaction conditions. In addition, we proposed a starting substrate bearing an electron-withdrawing group at the 3-position would provide greater stability of the resulting arylated products and also aid initial oxidative addition into the C-Br bond.

Indeed, under such conditions, we observed full conversion of starting material **223**, to a single new fluorinated product after a period of only 10 min at 80 ºC, for all boronic acids employed (as determined by ^{19}F NMR) (Fig. 3.47).

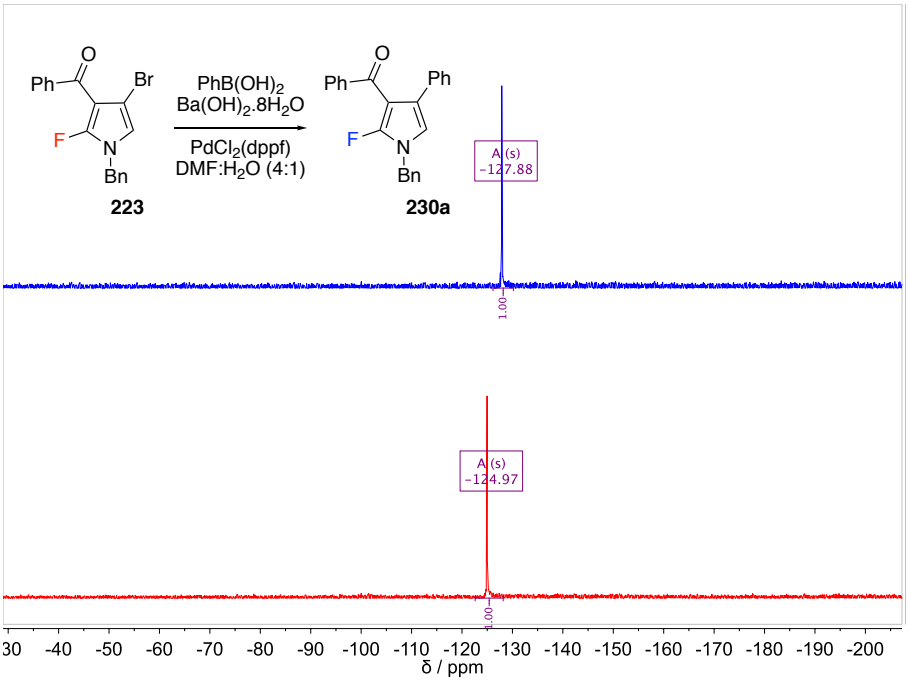


Figure 3.47: ^{19}F NMR spectra of the reaction mixture at time t=0 (red) and t=10min (blue) showing full conversion from the starting material.

A range of aryl substituted products (**230a-d**) was synthesised in good to excellent yields, with the conditions tolerating substituted arylboronic acids bearing both electron-donating and electron-withdrawing substituents, as well as heteroaromatic boronic acids (Fig. 3.48).

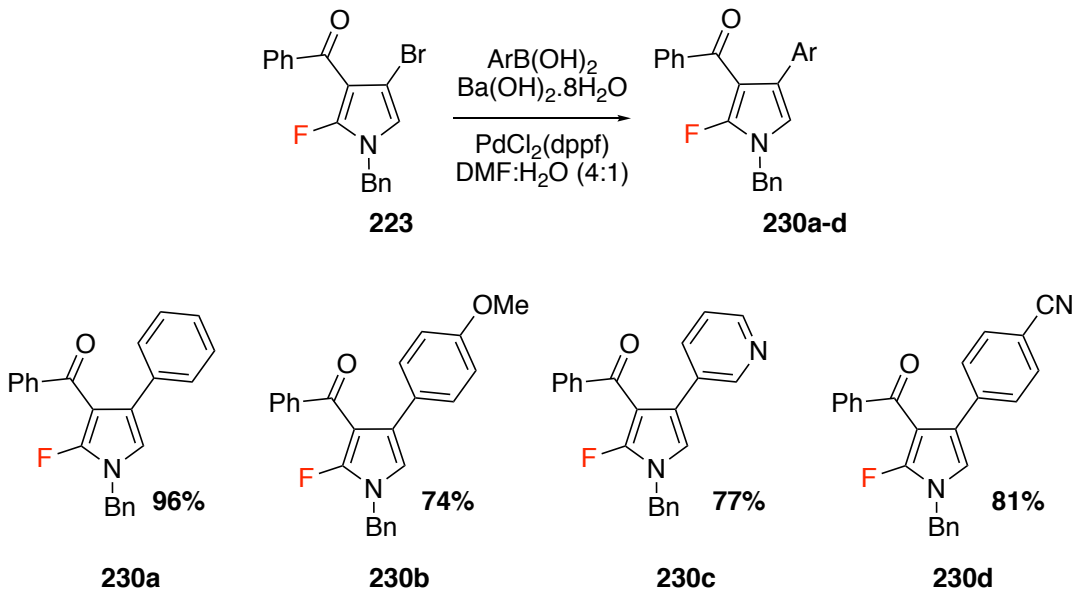
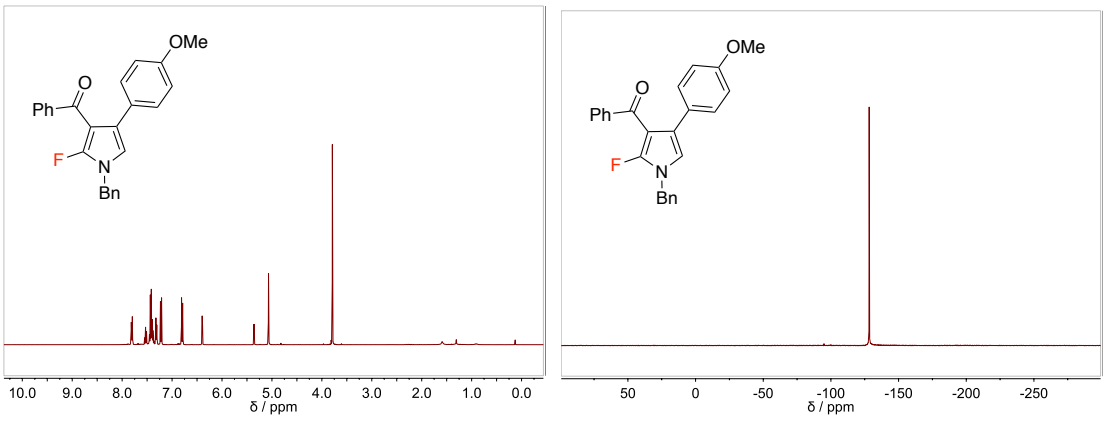


Figure 3.48: Suzuki cross-coupling reactions to give 2-fluoro-3-benzoyl-4-arylpyrrole derivatives **230a-d**.

Product structures were assigned based on ^{1}H and ^{19}F NMR spectra (Fig. 3.49) with the molecular structure of **230c** confirmed by x-ray crystallography (Fig. 3.50).



(a) (b)

Figure 3.49: Illustrative ^{1}H (a) and ^{19}F (b) NMR spectra of isolated 2-fluoro-3-benzoyl-4-(4-methoxyphenyl)-*N*-benzylpyrrole **230b**.

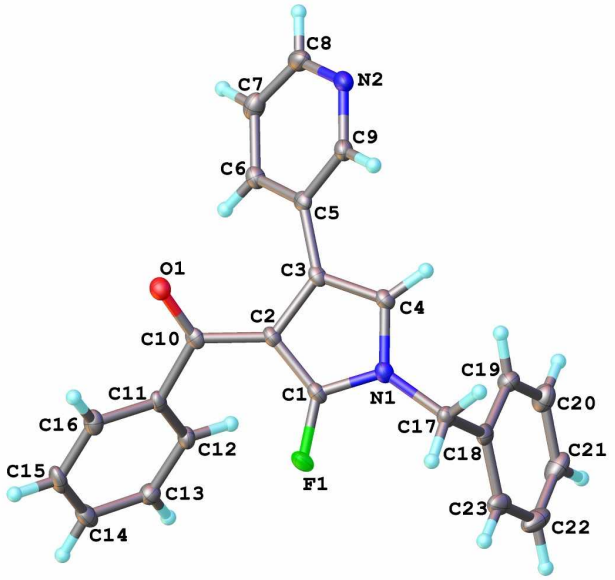


Figure 3.50: Molecular structure of **230c** as determined by x-ray crystallography.

3.5 Synthesis of 3-Fluorinated Bromopyrrole Derivatives

Having demonstrated the synthesis of a diverse range of 2-fluoro-*N*-benzylpyrrole derivatives, we wanted to expand the methodology to also provide access to 3-fluoropyrrole derivatives, as shown in strategy B outlined in Figure 3.1.

3.5.1 Reactions of *N*-Benzyl Protected Pyrroles

We envisioned this could be achieved utilising the previously synthesised 2,3,4-tribromopyrrole derivative **201**, by simply altering the sequence of the fluorination step in the reaction scheme, as shown in Figure 3.51.

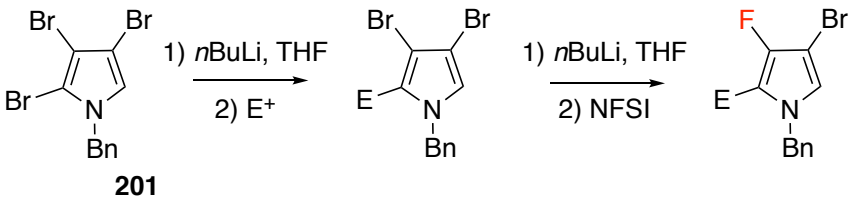


Figure 3.51: Synthetic strategy for the synthesis of 3-fluorinated pyrrole derivatives.

The simplest example of this would be the fluorination of 3,4-dibromopyrrole derivative **231**, which can be made in good yield by hydrodebromination of 2,3,4-tribromopyrrole

201 using *n*BuLi followed by quenching with aq. HCl (Fig. 3.52).

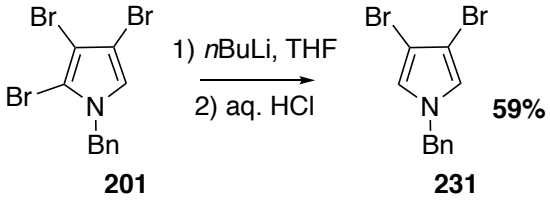


Figure 3.52: Synthesis of *N*-benzyl-3,4-dibromopyrrole **231**.

It was also possible to obtain a crystal of compound **231** suitable for x-ray diffraction confirming the remaining bromine handles are at the 3- and 4-positions of the pyrrole scaffold (Fig. 3.53).

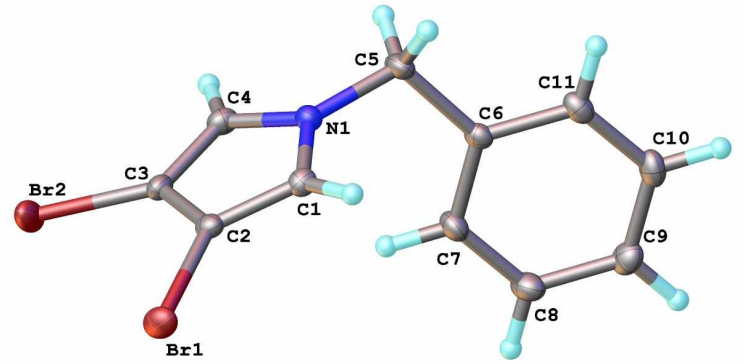


Figure 3.53: Molecular structure of **231** as determined by x-ray crystallography.

Fluorination of *N*-benzyl-3,4-dibromopyrrole (**231**) was performed, using the same lithiation protocol followed by quenching with NFSI, to give 3-fluoro-4-bromopyrrole derivative **232** in moderate yield (Fig. 3.54).

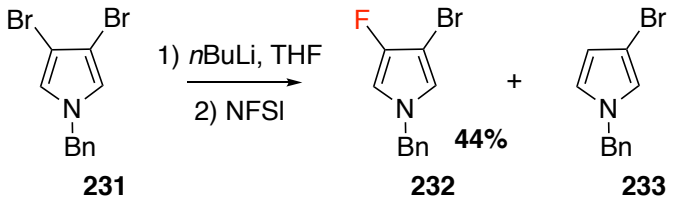


Figure 3.54: Synthesis of 3-fluoro-4-bromopyrrole derivative **232**.

The yield of this reaction was limited by formation of the corresponding hydrodebrominated product **233** which was difficult to separate and thought to be formed by a competing

electron transfer reaction between the intermediate lithiate and NFSI. Competing electron transfer was observed previously in the attempted synthesis of 2,4-difluoropyrrole **216** and also by the groups of Barnes[30] and Differding[106,107] for related systems as discussed previously. Optimisation attempts using excess or sub-stoichiometric amounts of NFSI had no desirable effect on yield, whilst the addition of Selectfluor™, a more powerful oxidant, in a THF/MeCN mixture gave exclusively hydrodebrominated product **233** (Fig. 3.55).

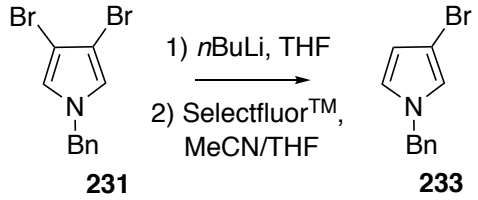


Figure 3.55: Attempted fluorination using Selectfluor™ resulting in exclusive hydrodebromination.

The ^{19}F NMR spectrum of the isolated 3-fluoro-4-bromopyrrole derivative **232**, however, corresponded well with that reported previously for 3-fluoropyrrole derivatives[30] and the regiochemistry was later confirmed by x-ray crystallography (Fig. 3.56).

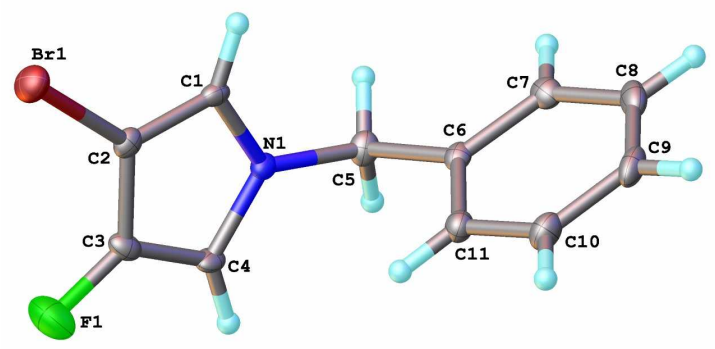


Figure 3.56: Molecular structure of **232** as determined by x-ray crystallography.

3.6 Reactions of *N*-Benzyl-3-Fluoro-4-Bromopyrrole

Using *N*-benzyl-3-fluoro-4-bromopyrrole (**232**), we wanted to validate the ability to synthesise a library of 3-fluoropyrrole derivatives by performing both a metal-halogen exchange reaction followed by quenching with an appropriate electrophile or a palladium catalysed cross-coupling reaction.

3.6.1 Metal-Halogen Exchange Reactions

To demonstrate the applicability of *N*-benzyl-3-fluoro-4-bromopyrrole (**232**) to metal-halogen exchange reactions we utilised the same lithiation protocol employed previously using *n*BuLi in THF, which was followed by the addition of ethyl chloroformate (Fig. 3.57).

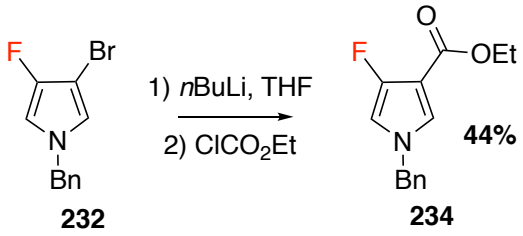


Figure 3.57: Synthesis of ethyl 3-fluoro-*N*-benzylpyrrole-4-carboxylate.

Under these unoptimised reaction conditions the desired product **234** was isolated in a moderate yield and this result thus highlights the potential suitability of this substrate for analogous reactions with various electrophiles to synthesise a range of 3-fluoro-4-substituted pyrrole derivatives.

3.6.2 Suzuki Cross-Coupling Reactions

Palladium catalysed cross-coupling chemistries, such as Suzuki reactions, previously performed using 2-fluorinated pyrrole substrate **223** were also applicable to 3-fluoro-pyrrole derivative **232**. Again, using the conditions utilised above, we observed full conversion of the starting material to a single new fluorinated product after 30 min at 80 ºC (Fig. 3.58).

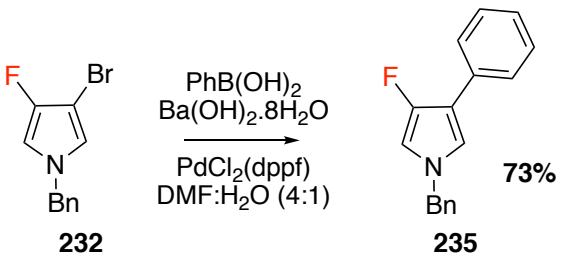


Figure 3.58: Synthesis of 3-fluoro-4-phenyl-*N*-benzylpyrrole.

The desired product was isolated in good yield by column chromatography, demonstrat-

ing the potential suitability of this substrate for the synthesis of a range of 3-fluoro-4-substituted pyrrole derivatives, via Suzuki as well as other palladium catalysed cross-coupling reactions.

3.7 Conclusions

We have developed an efficient bromination-derivatisation strategy for the synthesis of a diverse library of 2- and 3-fluoropyrrole by strategically varying the order in which sequential reactions are applied (Fig. 3.59).

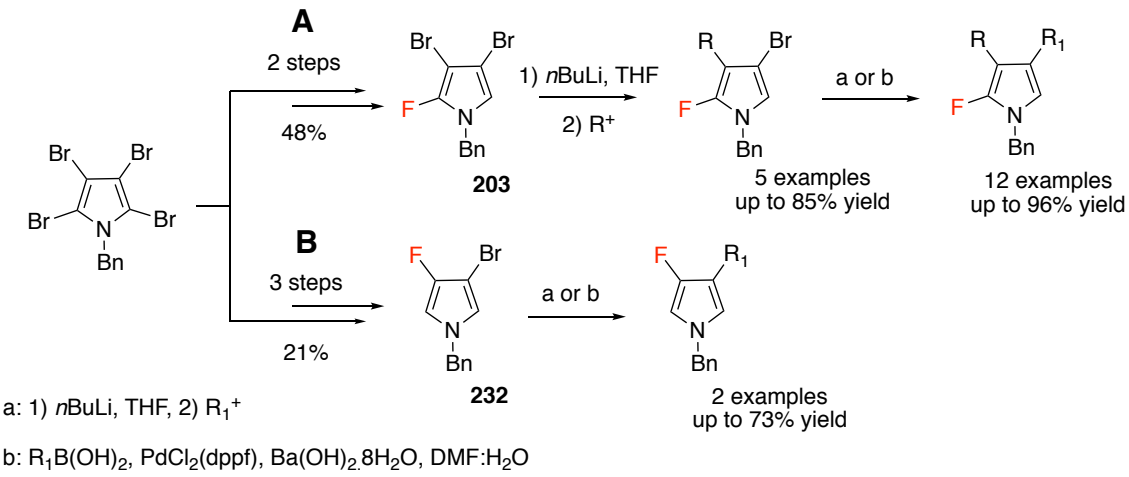


Figure 3.59: Summary of the library of 2-and 3-fluoropyrroles synthesised in this study.

Starting from a common protected tetrabromopyrrole, and by following strategies A and B outlined in Figure 3.1 we can efficiently access 2- and 3-fluorinated pyrrole building blocks with remaining bromine handles that can be utilised for further derivatisation reactions. Lithiation of 2-fluoro-3,4-dibromopyrrole **203** was shown to proceed efficiently and in a regioselective manner allowing the synthesis of a range of 2-fluoro-3-substituted-4-bromopyrroles upon trapping with a range of electrophiles. In addition, the series of 2-fluoro-4-bromopyrroles could be further derivatised by performing an additional lithiation/trapping reaction or a palladium catalysed cross-coupling to produce a diverse range of 2-fluoro-3,4-disubstituted pyrrole products. Similarly, we have also demonstrated the potential suitability of 3-fluoro-4-bromopyrrole derivative **232** for the synthesis of a range of 3-fluoro-4-substituted products by successfully performing a lithiation/trapping reaction as well as a palladium catalysed cross-coupling.

In conclusion, our methodology not only provides a useful method for the synthesis of the fluoropyrrole core but also supplies multiple reaction handles for further diversification and, therefore allows expedient access to a diverse array of polyfunctional fluoropyrrole products that potentially could be incorporated into life science screening libraries.

Chapter 4

Synthesis of 3-Fluorinated Pyrido[1,2-*a*]pyrimidin-4-ones

4.1 Introduction

Fluorinated heterocycles are prevalent structures within pharmaceutically relevant compounds (See Chapter 1), but the introduction of fluorine to heterocyclic structures, as previously discussed in the context of fluorinated pyrroles, can often be synthetically challenging. Alternatively, fluorinated building blocks, which can be made efficiently in high yields, have also been employed in the synthesis of fluorinated heterocycles to avoid potentially difficult fluorination steps. In this regard, work in Durham focussing on fluorination protocols using fluorine gas, has resulted in efficient and high yielding protocols for the synthesis 2-fluoromalonate esters[5] rendering them potentially valuable building blocks for the development of new methodology towards fluorinated heterocycles.

4.1.1 2-Fluoromalonate esters

4.1.1.1 Synthesis

2-Fluoromalonate esters were first synthesised in the late 1950s by reaction of gaseous perchloryl fluoride with various 2-substituted malonic esters (Fig. 4.1), but this methodology was not widely applied due to the hazardous nature of the fluorinating agent used.[113]

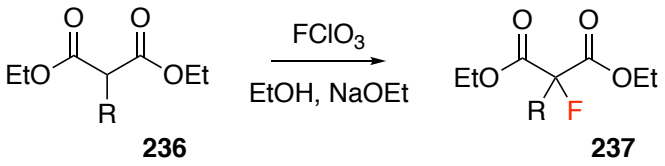


Figure 4.1: Synthesis of 2-fluoromalonate esters using $FClO_3$.

It was not until the 1980s, when the development of novel electrophilic fluorinating agents of the O-F and N-F classes, allowed access to a wider variety of 2-fluorinated malonate ester derivatives.[114–117] More recently, NFSI and Selectfluor™, the most widely adopted reagents of the N-F class, due to their stability, ease of use and commercial availability, have given access to a wider range of fluorinated dicarbonyl compounds. NFSI was used for the efficient asymmetric fluorination of prochiral malonates using a chiral auxiliary[118] (Fig. 4.2) whereas Selectfluor™ was used to synthesise 2-fluoromalonate derivatives (Fig. 4.3) for application in liquid crystals[119] and as potential pharmaceuticals.[120,121]

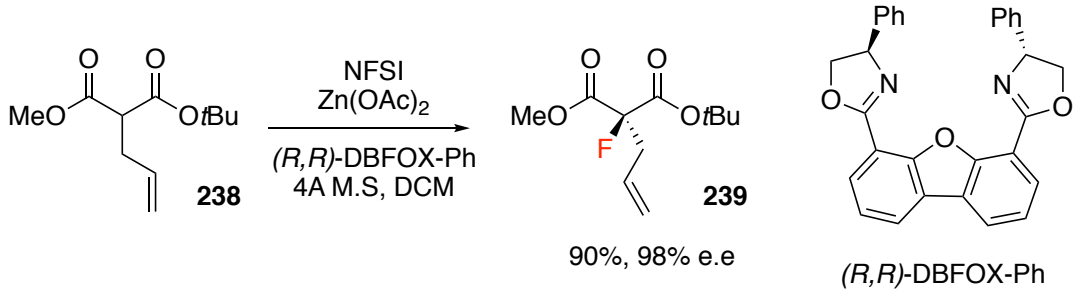


Figure 4.2: Assymetric fluorination of malonic ester derivative **238** with NFSI.

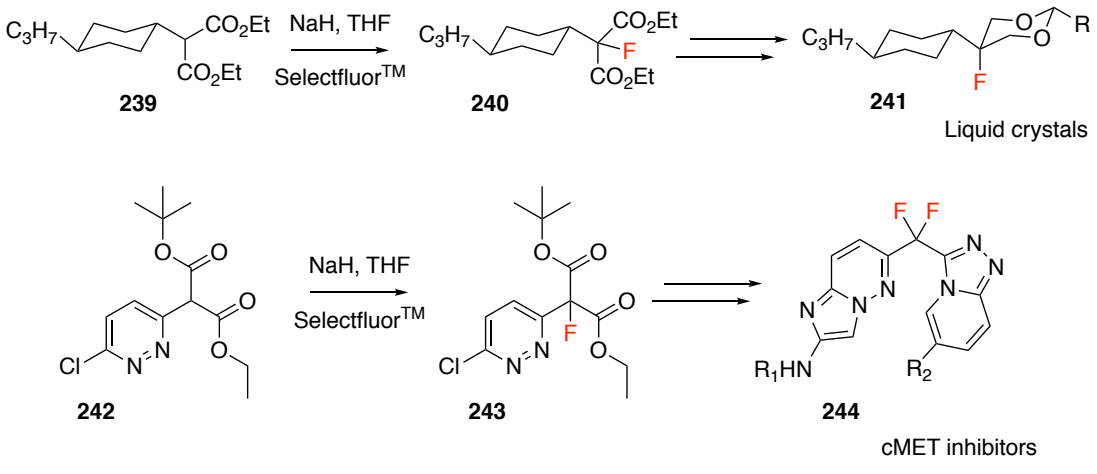


Figure 4.3: Fluorination of malonate esters using Selectfluor™.

Elemental fluorine was also used as an electrophilic fluorinating agent with malonate esters. Issues with selectivity, specifically competing difluorination in early works, were solved upon the addition of a catalytic amount of $Cu(NO_3).2.5H_2O$ which activated the malonate species towards fluorination. This resulted in a selective, high yielding process for the synthesis of a range of 2-fluoromalonate esters (Fig. 4.4).[20]

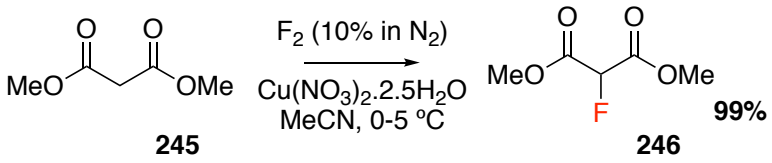


Figure 4.4: Elemental fluorine for the synthesis of 2-fluoromalonate ester **246**.

Halogen exchange of 2-chloromalonate esters using a suitable fluoride source as a route to 2-fluoromalonate esters was also demonstrated. Patents from Bayer[122,123] and Solvay[124] both detail protocols utilising HF, complexed with triethylamine or DBN respectively, as the fluoride source resulting in good conversions of chloromalonates to the desired fluoromalonate ester products on large scales (Fig. 4.5).

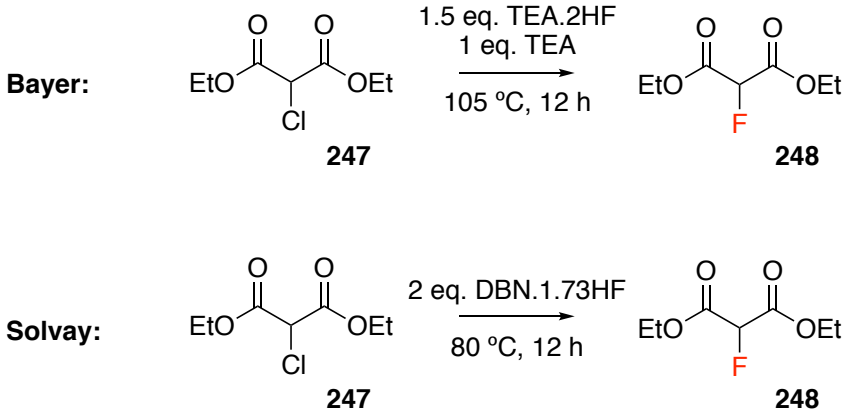


Figure 4.5: Halogen exchange protocols for the synthesis of 2-fluoromalonate **248**.

Step-wise basic alcoholysis of HFP is another possible route to 2-fluoromalonate esters. This route utilises the inexpensive hexafluoropropene (**249**), which is manufactured on large scale for the production of fluoropolymer products and gives dimethyl and diethyl 2-fluoromalonates in moderate yields (Fig. 4.6).[125,126]

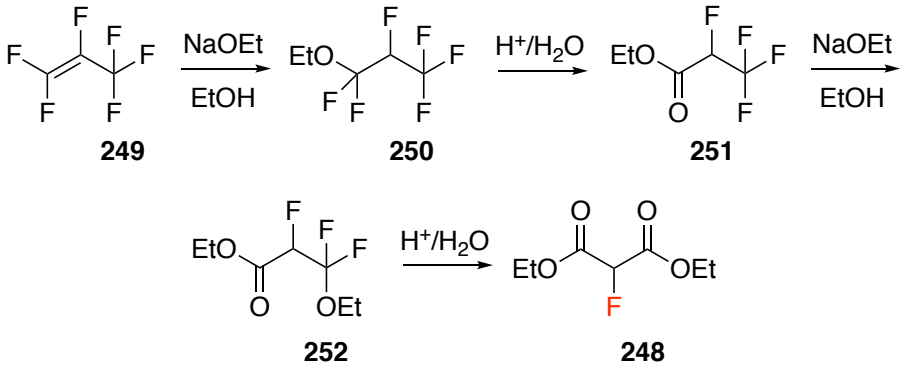


Figure 4.6: Synthesis of 2-fluoromalonate esters from HFP.

In summary, simple 2-fluoromalonate esters, such as diethyl 2-fluoromalonate **248**, can be synthesised on large scale by either halogen exchange, direct fluorination with elemental fluorine or solvolysis processes. In contrast, more complex systems can be accessed at discovery scale by reaction of the appropriate malonate derivative with NFSI or Selectfluor^{TM}.

Malonate esters are common building blocks within organic chemistry and their chemistry is well developed for a wide range of processes, such as, alkylation, acylation, Knoevenagal, aldol, reduction, Michael addition, nucleophilic substitution and annelation reactions.[127] However, the chemistry of related fluorinated analogues is not well developed, particularly for the synthesis of fluorinated heterocycles.

4.1.1.2 Synthesis of Fluorinated Heterocycles

The first fluoroheterocycle synthesis using diethyl fluoromalonate **248** was reported by Bergmann *et al.* for the preparation of 2-ethylthio-5-fluoro-4,6-dihydroxypyrimidine (**254**) by reaction with *S*-ethyl isothiouronium bromide (Fig. 4.7).[128]

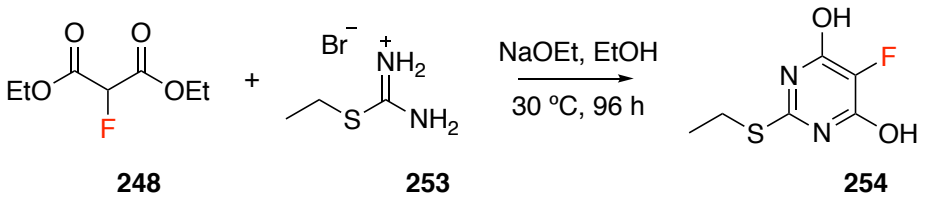


Figure 4.7: Synthesis of 5-fluoropyrimidine derivative **254** from diethyl 2-fluoromalonate **248**.

More recently, GSK patented the synthesis of a novel antibacterial drug family bearing a 5-fluoropyrimidine core. The synthesis is based in the condensation of diethyl 2-fluoromalonate with amidines and subsequent chlorination of the intermediate 4,6-dihydroxypyrimidine with PCl_5 and $POCl_3$ to give a 2-substituted 4,6-dichloro-5-fluoropyrimidine derivatives (**256**), which can be functionalised further by nucleophilic aromatic substitution using the newly installed chlorine handles (Fig. 4.8).[129]

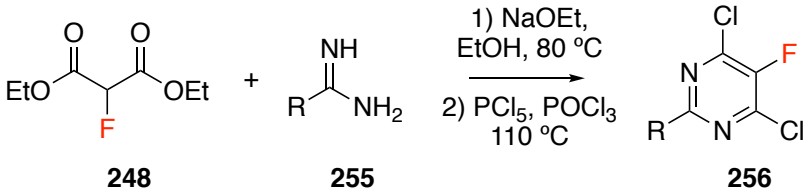


Figure 4.8: Synthesis of 2-substituted 4,6-dichloro-5-fluoropyrimidine derivatives (**256**).

This strategy is similar to that reported by Bayer CropScience, for the synthesis of the commercially available herbicide, Fluoxastrobin, which involves condensation of diethyl 2-fluoromalonate with formamide followed by chlorination using a mixture of Cl_2, PCl_3 and $POCl_3$ (Fig. 4.9).

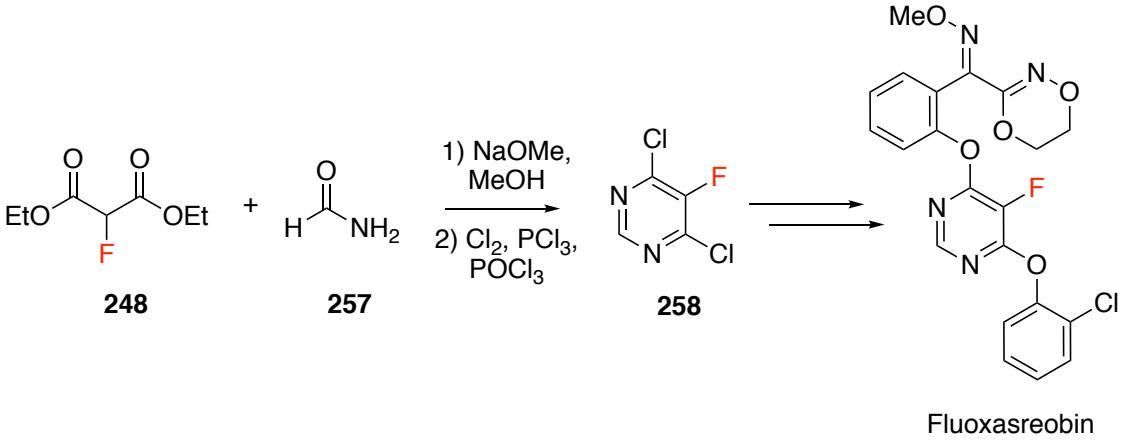


Figure 4.9: Synthesis of commercial herbicide Fluoxastrobin from diethyl 2-fluoromalonate.

Similar approaches have also been applied to more complex heterocycles, such as the synthesis of 6-fluoro-8-methylpyrido[2,3-*d*]pyrimidine-4,7-(3*H*,8*H*)-dione (**261**), recently published by Takeda Pharmaceuticals, for use in a range of medicinal applications (Fig. 4.10).[130]

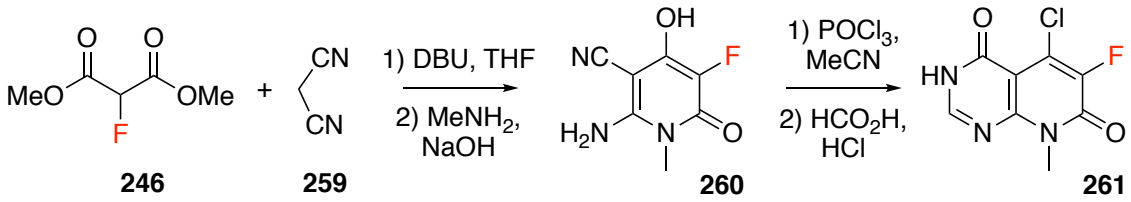


Figure 4.10: Synthesis of 6-fluoro-8-methylpyrido[2,3-*d*]pyrimidine-4,7-(3*H*,8*H*)-dione (**261**) from dimethyl 2-fluoromalonate.

In addition, work at Pfizer has shown that using 2-fluoromalonic acid **262**, formed by basic hydrolysis of diethyl 2-fluoromalonate **248**, it is possible to cyclise with aniline and chlorinate the intermediate dihydroxy compound in one step using $POCl_3$ as the solvent (Fig. 4.11).[131] In this process, $POCl_3$ performs two roles, firstly to form the more reactive acid chloride from 2-fluoromalonic acid and, secondly, to chlorinate the intermediate dihydroxy compound resulting from cyclisation.

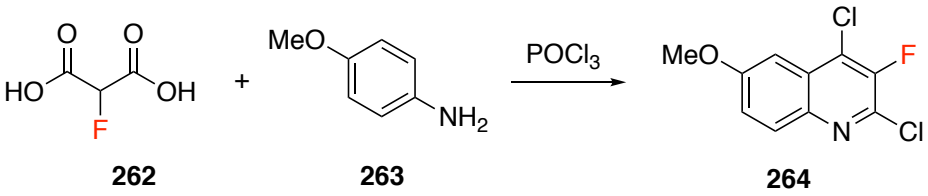


Figure 4.11: One step synthesis of 2,4-dichloro-3-fluoroquinoline derivative **264** from 2-fluoromalonic acid.

These examples demonstrate the use of 2-fluoromalonate esters as fluorinated building blocks for the synthesis of difficult to access fluorinated heterocycles and show the potential for future research utilising this substrate. In this context, we therefore employed fluoromalonate ester **248** for the synthesis of fluorinated pyrido[1,2-*a*]pyrimidin-4-ones.

4.1.2 Pyrido[1,2-*a*]pyrimidin-4-ones

Nitrogen heterocycles are important structures in drug discovery processes and numerous major prescription drugs comprise these scaffolds. The pyrimidinone motif, and particularly the related pyridine annulated analogues, pyrido[1,2-*a*]pyrimidin-4-ones, possess various biological activities[132] and examples include the tranquiliser Pirenperone,[133] analgesic Rimazolium,[134] antipsychotic Risperidone[135] and antiallergenic Pemirolast[136] (Fig. 4.12).

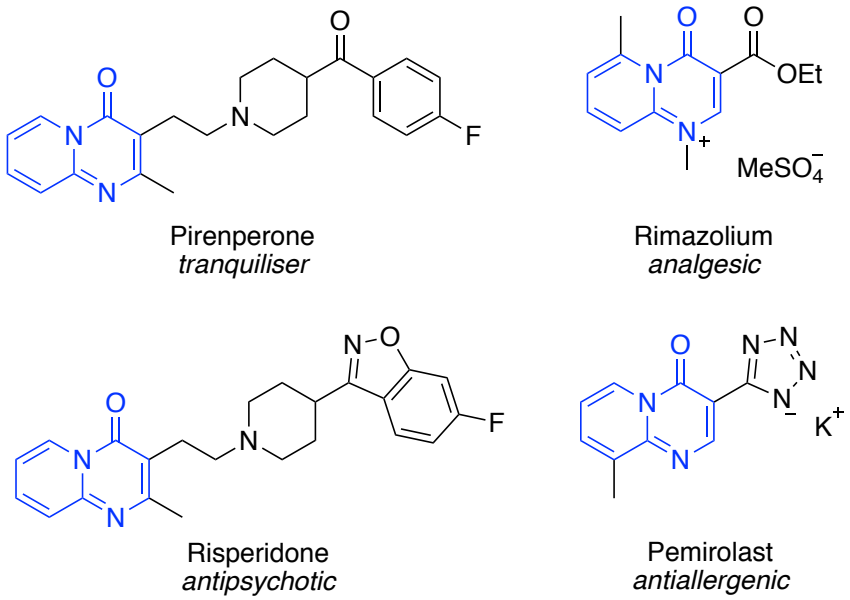


Figure 4.12: Notable pyrido[1,2-*a*]pyrimidin-4-one containing drugs.

In addition, some pyrido[1,2-*a*]pyrimidin-4-ones have been shown to possess antioxidant properties,[137] while others have shown potential for use against malaria,[138] hypertension[139] and tuberculosis[140] (Fig. 4.13).

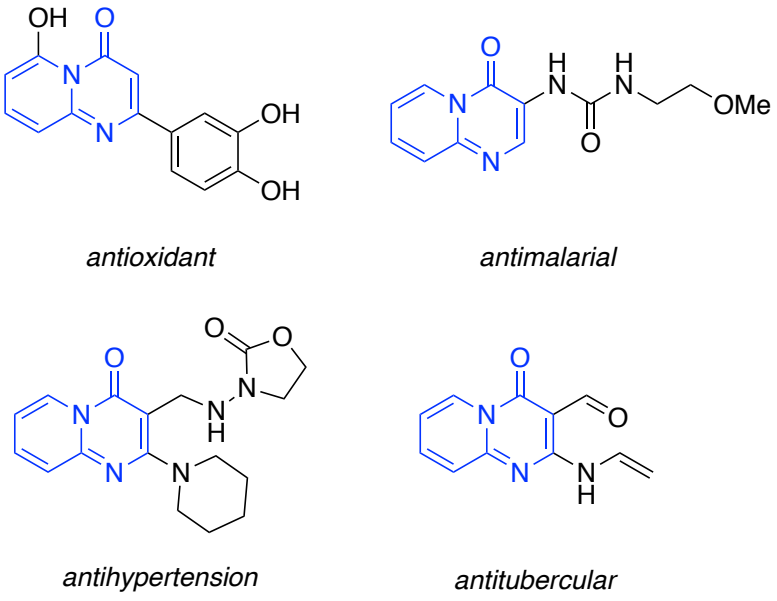


Figure 4.13: Examples of bioligically active pyrido[1,2-*a*]pyrimidin-4-ones.

Other than biological applications, pyrido[1,2-*a*]pyrimidin-4-ones have also found application as nylon and polyesters dyes, epoxy resin curing agents, photographic sensitisers and blue emitters for OLEDs.

4.1.2.1 Synthesis

The first reported synthesis of the pyrido[1,2-*a*]pyrimidin-4-one scaffold was reported in 1924 via the condensation of 2-aminopyridine with malonate esters.[141] However, the structure was not fully elucidated until 1962 when the previously named 'malonyl-α-aminopyridine' was determined to be a pyrido[1,2-*a*]pyrimidin-4-one derivative (Fig 4.14).

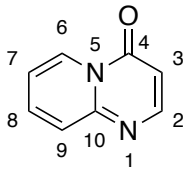


Figure 4.14: Labelled pyrido[1,2-*a*]pyrimidin-4-one structure.

Modern elaborations of this thermal condensation have since been reported. Abass *et al.* showed that the product distribution upon condensation of 2-aminopyridine and diethyl malonate was temperature dependant. Reaction at 100-110 ºC gave good yields of the desired 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**267**) whereas, at elevated reaction temperatures (180-200 ºC), the formation of by-product 1,8-naphthyridinone derivative **268** increased to around 40% of the converted 2-aminopyridine. Formation of by-product **268** was attributed to the thermal rearrangement of pyridopyrimidin-4-one **267** via a ketene intermediate (Fig. 4.15).[142]

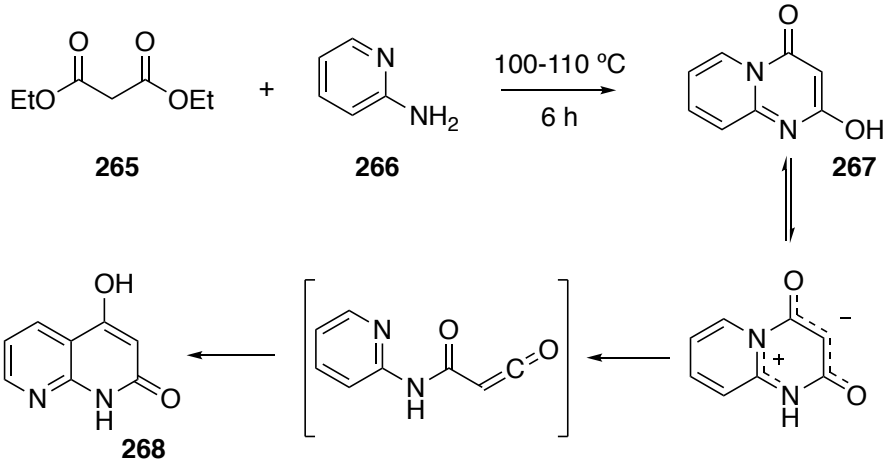


Figure 4.15: Thermal condensation of 2-aminopyridine and diethyl malonate.

An analogous two step process was later reported by Amgen, which involved isolation

of monoamide intermediate **269**, formed by thermal condensation of diethyl malonate and 2-aminopyridine (Fig. 4.16). Intermediate **269** was then heated to 210 ºC in diphenyl ether to give the desired annulated 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**267**).[143]

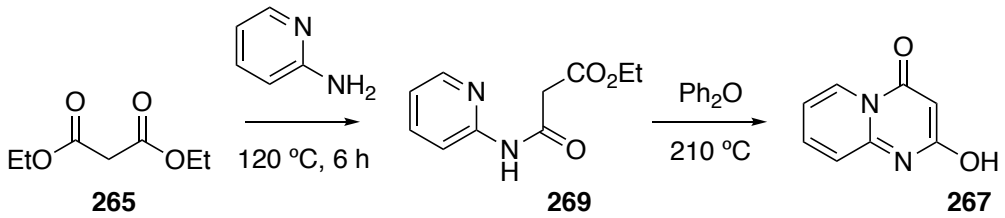


Figure 4.16: Two step process for the synthesis of 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**267**).

A related two step process, instead using Meldrum's acid and trimethyl orthoformate, which yields the corresponding pyrido[1,2-*a*]pyrimidin-4-one derivative **273** without a hydroxy group at C2 has also been reported (Fig. 4.17).[144]

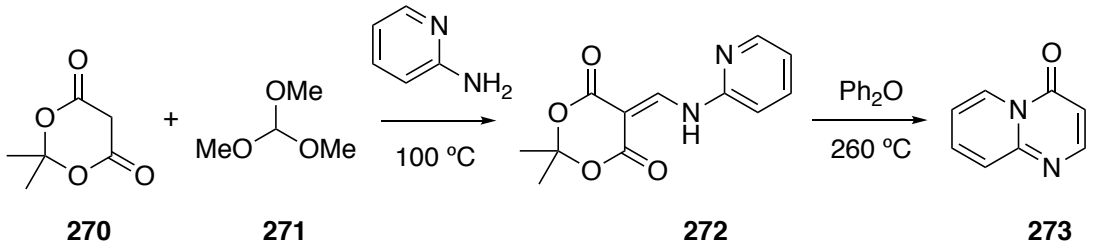


Figure 4.17: Synthesis of pyrido[1,2-*a*]pyrimidin-4-one (**273**) using Meldrum's acid.

More recently, a low temperature procedure was developed by Stepan *et al.* which utilised the activated ester bis(2,4,6-trichlorophenyl)malonate **274**. The reaction proceeded at much lower temperatures (66 ºC) than required when using simple alkyl malonates, and gave the desired 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**267**) in excellent yield (93%) (Fig. 4.18).[145]

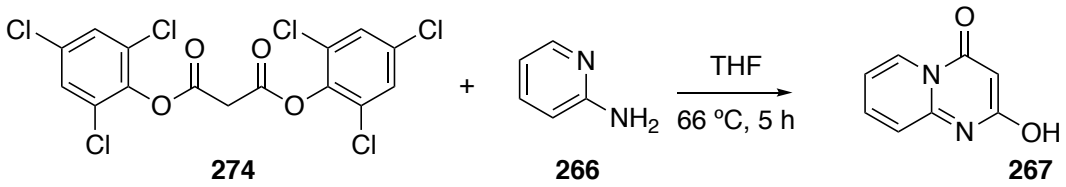


Figure 4.18: Low temperature condensation using activated ester **274**.

In addition, metal catalysts such as aluminium-exchanged tungstophosphoric acid salts ($Al_xH_{3-x}PW_{12}O_{40}$),[146] bismuth trichloride[147] and silver triflate[148] have also been used in combination with β-keto esters or alkynoates to give 2-substituted pyrido[1,2-*a*]pyrimidin-4-ones (Fig. 4.19).

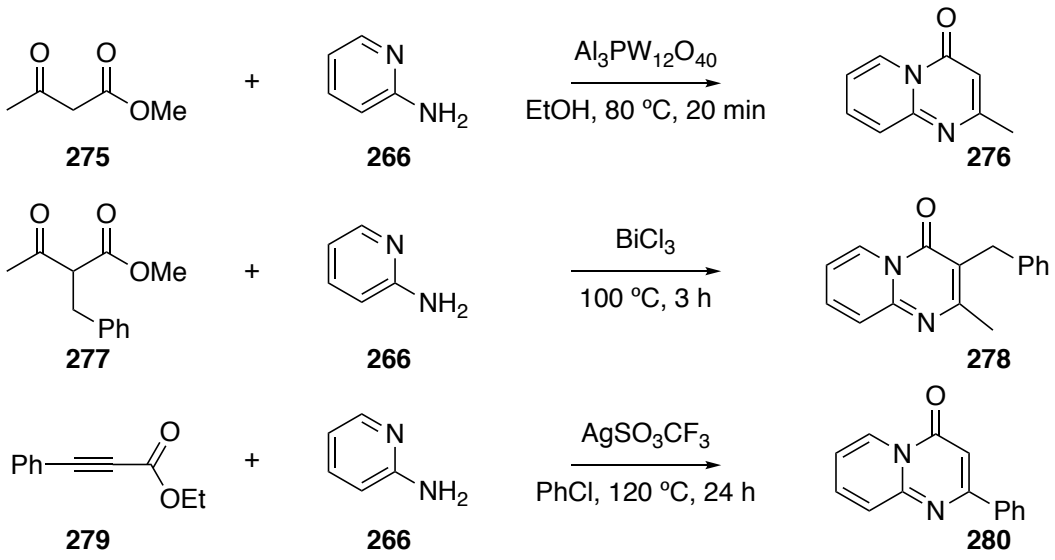


Figure 4.19: Metal catalysed synthesis of pyrido[1,2-*a*]pyrimidin-4-ones derivatives.

4.1.2.2 Fluorinated Pyrido[1,2-*a*]pyrimidin-4-ones

Examples of fluorinated pyrido[1,2-*a*]pyrimidin-4-ones have also been reported. However, in most cases, the fluorine substituent is incorporated into the pyridopyrimidin-4-one scaffold by utilising the corresponding fluorinated analogues of 2-aminopyridine as substrates (Fig. 4.20).[149,150]

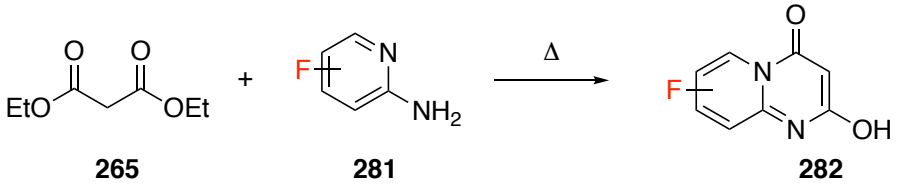


Figure 4.20: Synthesis of fluorinated pyrido[1,2-*a*]pyrimidin-4-ones using fluorinated 2-aminopyridines.

This methodology restricts the incorporation of fluorine to one half of the pyrido[1,2-*a*]pyrimidin-4-one skeleton (positions C6-9 in Figure 4.14), but it is also desirable to incorporate fluorine at C3. Currently, two patents detailing procedures to access 3-

fluorinated pyrido[1,2-*a*]pyrimidin-4-ones, which are used for treament of cancer and psychiatric conditions respectively, have been reported.[151,152] Both processes involve the formation of the pyrido[1,2-*a*]pyrimidin-4-one scaffold followed by low yielding electrophilic fluorination, using an N-F reagent such as Selectfluor™ (Fig. 4.21).

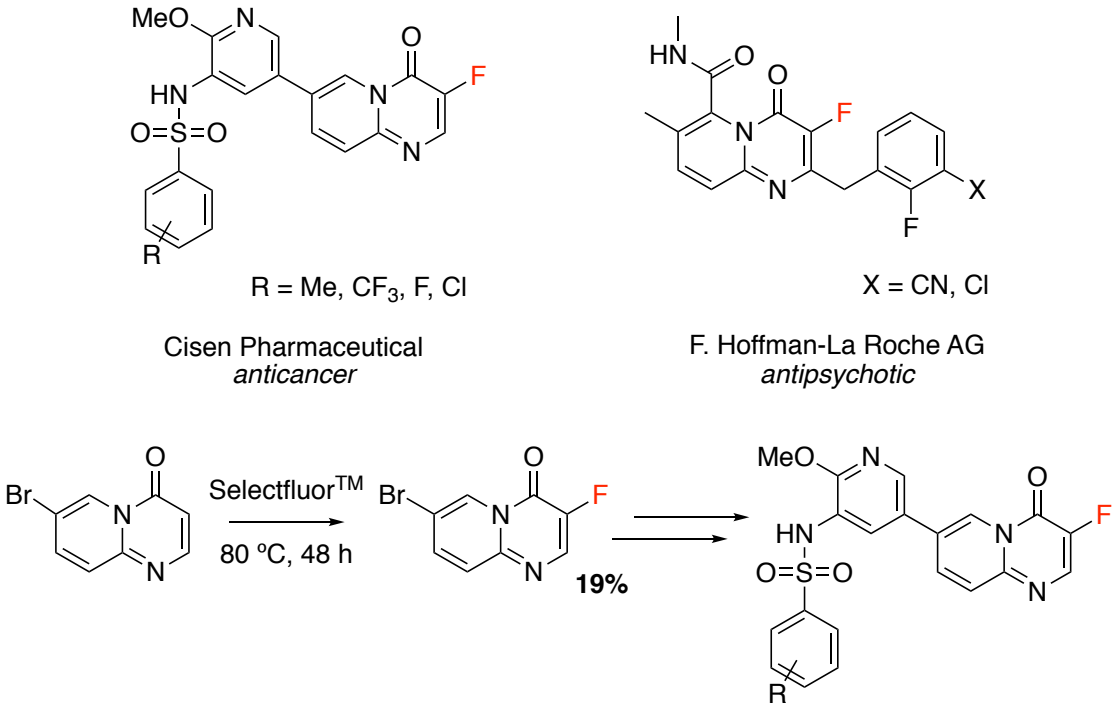


Figure 4.21: Patented 3-fluorinated pyrido[1,2-*a*]pyrimidin-4-ones.

4.2 Aims

The aim of this chapter is to utilise 2-fluoromalonate ester **248**, which can be made in excellent yield on large scale, for the synthesis of 3-fluorinated pyrido[1,2-*a*]pyrimidin-4-ones, avoiding the often difficult late stage fluorination of the preformed heterocycle (Fig. 4.22).

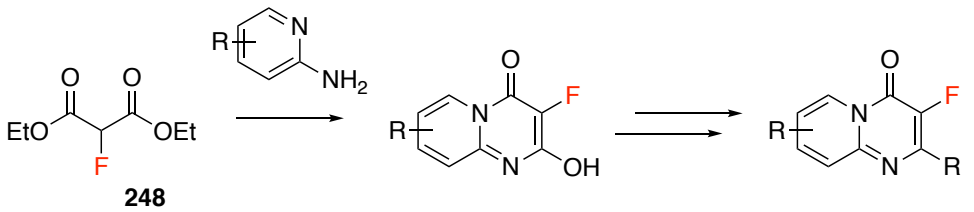
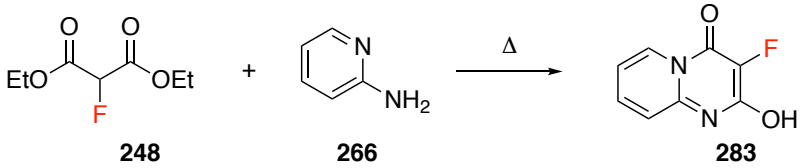


Figure 4.22: General strategy for the synthesis of fluorinated pyridopyrimidinones from 2-fluoromalonate ester **248**.

From this 3-fluorinated scaffold, we aimed to synthesise a library of 3-fluorinated pyrido[1,2-*a*]pyrimidin-4-ones to be screened for potential biological activity against β-catenin by our collaborators at the University of Vienna.

4.3 Synthesis of Pyrido[1,2-*a*]pyrimidin-4-one Core

We first attempted to repeat the thermal condensation reported by Abass *et al.* for the non-fluorinated analogue, using 2-fluoromalonate ester **248** (Fig. 4.23). However, after heating at 110 ºC for a period of 24 h we observed minimal conversion of 2-aminopyridine by GC-MS and NMR spectroscopy. As a result, we increased the reaction temperature to 175 ºC and after a period of 8 h could observe appreciable conversion of the starting material but ^{19}F NMR revealed the formation of fluoroacetate derivatives (characteristic triplets at ~ -220 – -230 ppm) likely due to thermally induced decarboxylation of 2-fluoromalonate **248**.



248 **266** **283**

Figure 4.23: Attempted thermal condensation of 2-fluoromalonate ester **248** and 2-aminopyridine.

Therefore, we proposed the use of an activated ester substrate that would allow the reaction to proceed at lower temperature and prevent the degradation of the starting materials to toxic fluoroacetate derivatives. We took inspiration from the synthesis of 3-fluoroquinoline derivative **264** (Fig. 4.11), which utilises 2-fluoromalonic acid and $POCl_3$ to form the much more reactive acid chloride *in situ*. In addition, utilising a $POCl_3$ based procedure also provides a chloro substituent at C3 in one step, possibly opening up a range of cross-coupling and S_NAr chemistries (Fig. 4.24).

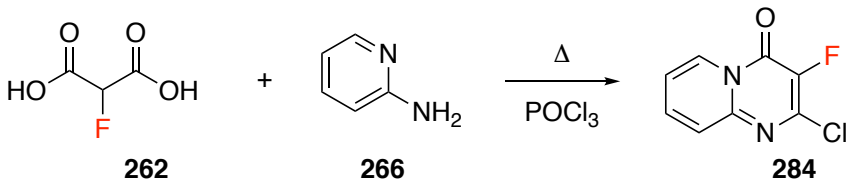


Figure 4.24: Proposed synthesis of 2-chloro-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **284**.

To access 2-fluoromalonic acid **262**, we performed the base catalysed hydrolysis of 2-fluoromalonate ester **248** using lithium hydroxide monohydrate.[153] After gentle heating at 60 ºC overnight, analysis by ^{19}F NMR spectroscopy showed a single new fluorinated product which, after acidic work up, gave 2-fluoromalonic acid in excellent yield on 30 g scale (Fig. 4.25).

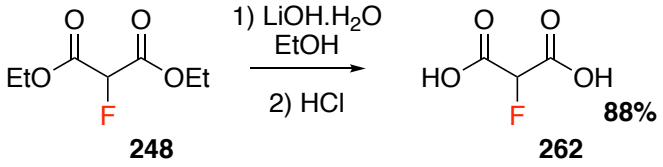
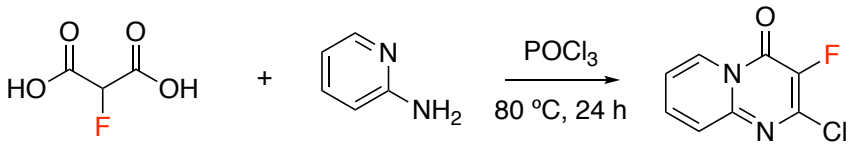


Figure 4.25: Hydrolysis of malonate ester to give 2-fluoromalonic acid (**262**).

We first employed 2-fluoromalonic acid (**262**) in neat $POCl_3$, followed by addition of 2-aminopyridine (Table 4.1, entry 1), conditions analogous to that previously reported for the corresponding cyclisation with aniline.

Table 4.1: Optimisation of conditions for the synthesis of 2-chloro-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**284**).[a]



262 **266** **284**

Entry	Cosolvent	Eq. $POCl_3$	Additive[b]	NMR Yield /%[c]
1	–	15	–	21(15)
2	Toluene	10	–	24
3	MeCN	10	–	27
4	MeCN	10	$BnEt_3NCl$	53 (51)
5	MeCN	15	$BnEt_3NCl$	37
6	MeCN	5	$BnEt_3NCl$	33

[a] Conditions: **262** (1.96 g, 16 mmol), 2-aminopyridine (1 eq.), $POCl_3$, cosolvent (30 mL), 80 °C, 24 h.

[b] $BnEt_3NCl$ (2 eq.)

[c] NMR yield determined using 1-fluoro-4-nitrobenzene as reference, isolated yield in parantheses.

The reaction was monitored by ^{19}F NMR and after a period of 24 h the mixture was allowed to cool and carefully quenched in ice-water. The resulting solid was filtered and dried to give the desired 2-chloro-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**284**), but in a disappointing yield.

Competing decomposition has often been reported for reactions involving $POCl_3$, particularly when used in large excesses as the reaction solvent.[154] Therefore, cosolvents such as toluene or MeCN (entries 2 and 3) were introduced and the number of equivalents of $POCl_3$ reduced. In both cases, this had a positive effect on the observed NMR yield, but significant decomposition was still evident.

A ^{31}P NMR study on chlorination using $POCl_3$ by Robins *et al.* also revealed that addition of an external chloride source can significantly enhance reaction yields.[155] Chlorination reactions were replicated in an NMR tube and analysis demonstrated evidence for the rapid formation of a phosphorylated intermediate which slowly reacted with

chloride to give the desired product (Fig. 4.26).

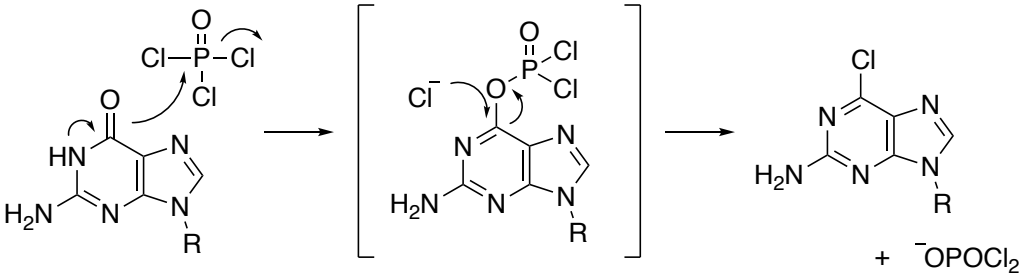


Figure 4.26: Chlorination reaction using $POCl_3$ studied by ^{31}P NMR spectroscopy.[155]

The authors, therefore, proposed that higher concentrations of chloride anion should favour the reaction with chloride prior to decomposition, and indeed, addition of an external chloride source significantly increased their isolated yield. Based on the proposed mechanism for the synthesis of 2-chloro-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**284**) (Fig. 4.27), we proposed that addition of an external chloride source, such as benzyltriethylammonium chloride, could also be beneficial to our process.

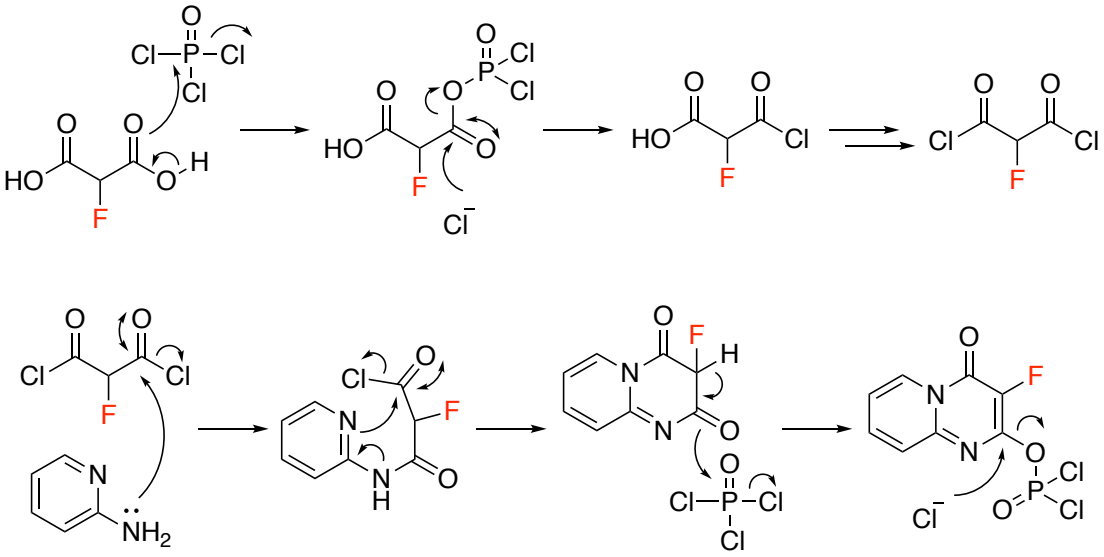


Figure 4.27: Proposed mechanism for the synthesis of 2-chloro-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

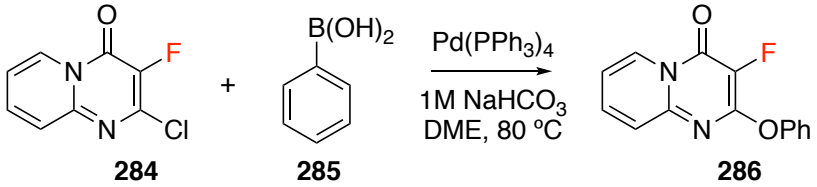
Indeed, addition of two equivalents of benzyltriethylammonium chloride to the reaction mixture resulted in a much improved NMR yield after 24 h, which allowed the material to be isolated after a slight modification of the work up procedure. In this instance, the acetonitrile cosolvent was removed *in vacuo* upon which the desired com-

pound began to crystallise and after trituration with water gave 2-chloro-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**284**) in a greatly improved 51% yield. Further variations in the number of equivalents of $POCl_3$ gave no further improvement in NMR yield, whilst addition of *N*,*N*-dimethylaniline, a common base used in chlorinations, appeared to significantly slow the reaction.

4.4 2-Substituted pyrido[1,2-*a*]pyrimidin-4-ones

With a robust route to 2-chloro-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**284**) in moderate yield with simple isolation, we aimed to utilise the 2-chloro substituent to synthesise a library of 2-substituted products for evaluation as β-catenin inhibitors. The first reaction proposed was the Suzuki cross-coupling with various aryl boronic acids to synthesise a range of 2-aryl-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones which have been shown to be of particular medicinal value.[156]

We investigated the conditions required for a Suzuki cross-coupling using phenyl boronic acid in the first instance. Using conditions reported by Molnar *et al.*,[157] we employed pyrido[1,2-*a*]pyrimidin-4-one **284**, phenyl boronic acid and $Pd(PPh_3)_4$ as catalyst (Fig. 4.28).



284 **285** **286**

Figure 4.28: Attempted Suzuki reaction of 2-chloro-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

After a period of 24 h we observed full conversion of the starting material by ^{19}F NMR spectroscopy, but, GC-MS revealed a single product with an unexpected mass. Isolation of this material by column chromatography, and analysis by NMR revealed the product to be the corresponding phenyl ether **286** which was later confirmed by x-ray crystallography (Fig. 4.29).

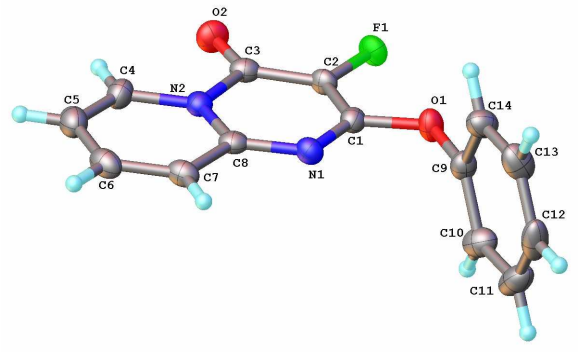


Figure 4.29: Molecular structure of **286** as determined by x-ray crystallography.

We proposed this occured via an S_NAr reaction of phenol formed by initial oxidation of phenylboronic acid, facilitated by insufficient degassing of the reaction solvents. Therefore, instead of degassing the solvents by passing argon through the reaction mixture, all solvents were throughly degassed via the freeze-pump-thaw method (3 cycles). Using solvents prepared in this manner, the reaction was repeated and, under otherwise unchanged conditions, after isolation by column chromatography, it gave the desired phenylated product **287** in excellent yield (Fig. 4.30), and the structure also confirmed by x-ray crystallography (Fig. 4.31).

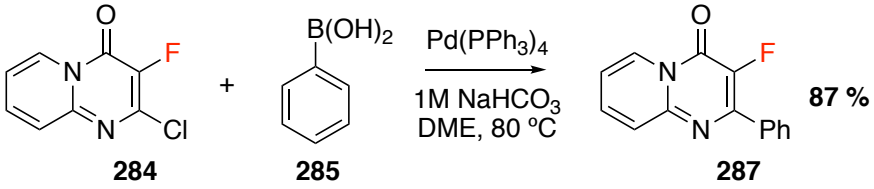


Figure 4.30: Synthesis of 2-phenyl-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**287**).

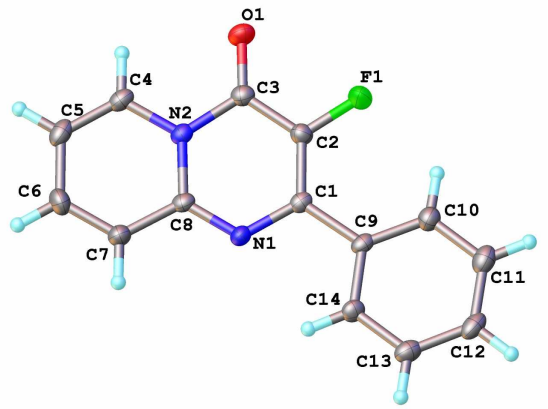
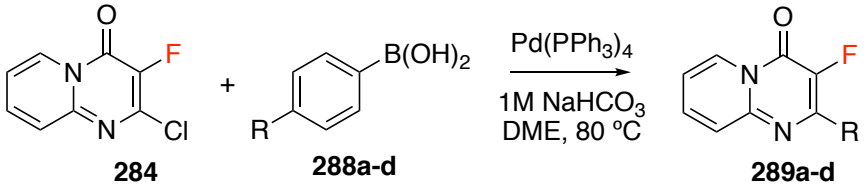


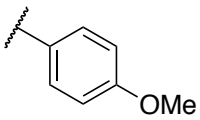
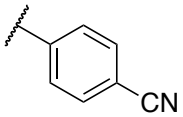
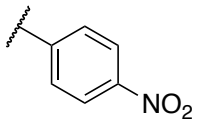
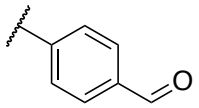
Figure 4.31: Molecular structure of **287** as determined by x-ray crystallography.

Having successfully demonstrated the suitability of 2-chloro-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**284**) for application in Suzuki and, somewhat serendipitously, S_NAr reactions, the substrate scope was expanded by Ben Murray (MChem student) as part of a 4th year MChem project and his results are included here for completeness. Using analogous conditions, the Suzuki cross-coupling for a range of 4-substituted arylboronic acids (Table 4.2) was performed to give a library of 2-substituted 3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

Table 4.2: Suzuki cross-coupling of 2-chloro-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**284**) with 4-substituted arylboronic acids.[a] [Reactions performed by B. Murray, 4th year MChem project]



284 **288a-d** **289a-d**

Entry	R	Time /h	Conversion[b]	Isolated Yield /%
a		18	98	63
b		18	100	63
c		24	87	76
d		20	100	85

[a] Conditions: **284** (1-2.5 mmol), Boronic acid (1.1 eq.), $Pd(PPh_3)_4$ (5 mol%), DME (20 mL), 80 °C.

[b] Conversion determined by ^{19}F NMR.

4.5 Conclusions

Starting from the easily accessible 2-fluoromalonate ester **248**, we have developed a simple synthetic strategy to access 2-chloro-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**284**), avoiding the often expensive and low yielding electrophilic fluorination of preformed pyrido[1,2-*a*]pyrimidin-4-one scaffolds (Fig. 4.32).

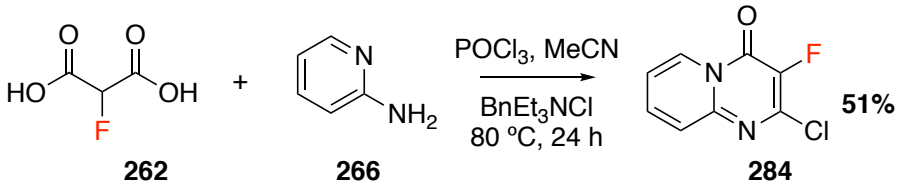


Figure 4.32: Synthesis of 2-chloro-3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**284**).

From this functional fluorinated building block we have demonstrated the synthesis of a range of 2-substituted 3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones via Suzuki cross-coupling reactions with substituted arylboronic acids (Fig. 4.33).

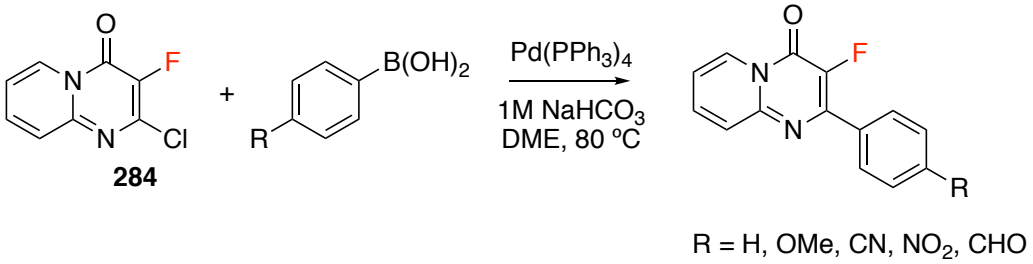


Figure 4.33: Synthetic routes to 2 substituted 3-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

These samples have now been sent to collaborators at the University of Vienna and University College Dublin for biological evaluation under the European ITN Fluor21 network provision and have shown promise as β-catenin inhibitors by a ^{19}F NMR fragment-based drug discovery approach.

Chapter 5

Fluoropyrene Derivatives

5.1 Pyrene Derivatives for Optoelectronics

OTFT technology employs organic semiconductors within electronic components. Such electronics have the advantage of low manufacturing costs and large area fabrication with potential applications ranging from sensors to flexible displays. However, current organic displays suffer from sluggish response times, limiting the ability of the display to render motion. This is a consequence of carrier mobility (the ability with which an atom shares electrons and holes with other atoms) of the organic compound and hence, much effort has been devoted to developing superior organic semiconductors with high charge carrier mobilities.

Pyrene, among many other polyaromatics, has been extensively studied due to its unique photophysical properties, including high charge carrier mobility. However, it is equally desirable to have a high fluorescence quantum yield, which has proven to be difficult to achieve as high mobility requires molecules which pack densely and periodically, while serious fluorescence quenching typically occurs when fluorescent materials begin to aggregate.[158]

5.2 Synthesis of Fluorinated Pyrene Derivatives

In collaboration with Prof. Deqing Gao (Nanjing Tech University), we proposed that incorporation of fluorinated pyrene moieties, could overcome some of the issues currently encountered and result in a device with superior performance. Fluorine atoms have been shown to lower both the HOMO and LUMO energy levels and, as a result, electron injection is made easier and the materials display a greater resistance to oxidative degradation. Moreover, the C–H···F interactions play an important role in the solid state, influencing π-stacking, which can enhance the charge carrier mobility.[159,160]

Following previous investigations into similar polyaromatic hydrocarbon systems by the Gao group in Nanjing,[161] pyrene derivatives bearing perfluoroaryl substituents were identified as target molecules. Work in Durham focussed solely on synthesis, whilst physical measurements and device testing were undertaken in Nanjing.

The proposed synthetic methodology to access perfluoroaryl substituted pyrene derivatives was based around initial bromination, which is well reported within the literature. Brominated pyrene derivatives can then be subjected to palladium catalysed cross coupling reactions or lithiation and quenching with appropriate electrophiles (Fig 5.1).

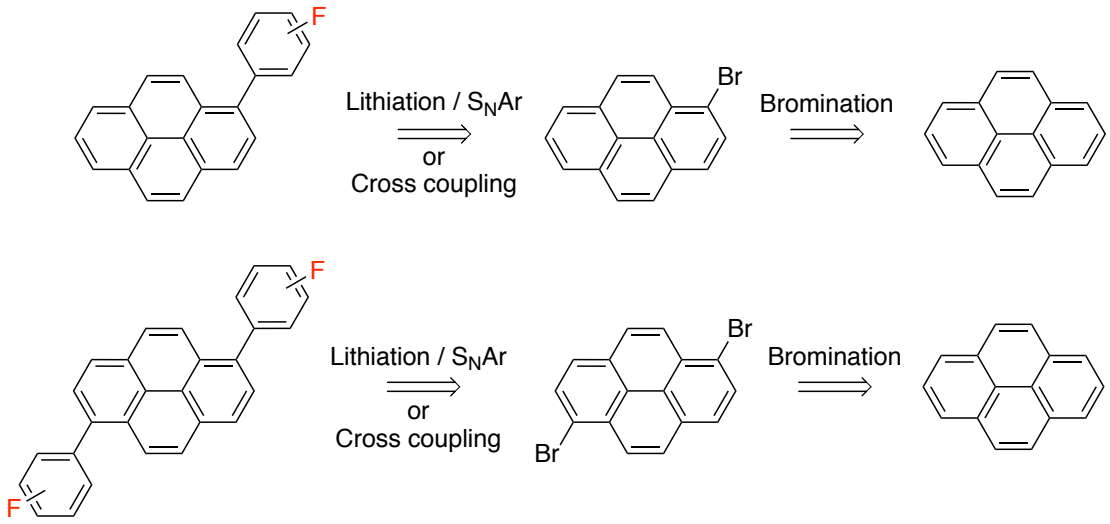


Figure 5.1: Proposed synthetic route to fluorinated pyrene derivatives.

5.2.1 Synthesis of Brominated Pyrene Derivatives

The first attempted synthesis was that of 1-bromopyrene from pyrene and involved the use of HBr with a peroxide initiator, shown in Figure 5.2.

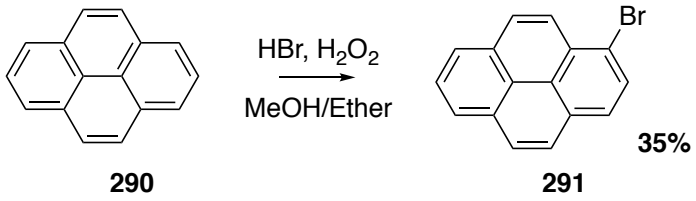


Figure 5.2: Synthesis of 1-bromopyrene (**291**) with HBr and H_2O_2.

The reaction was periodically sampled and analysed using GC-MS due to the complicated ^{1}H NMR spectra of pyrene derivatives. After a period of 15 h, GC-MS revealed the reaction mixture contained a 4:1 ratio of mono- and dibrominated products (Fig. 5.3).

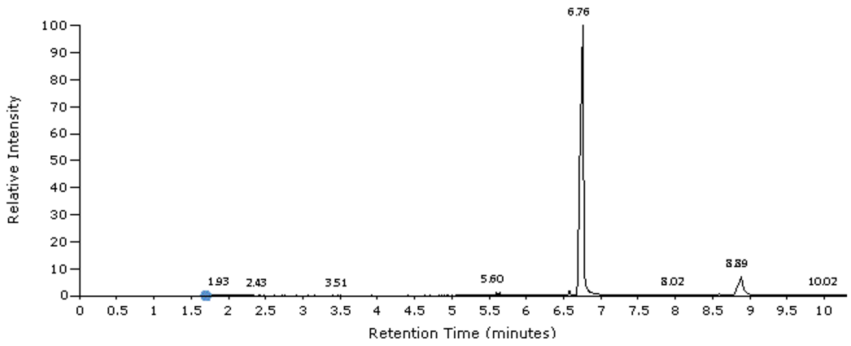


Figure 5.3: GC-MS trace showing the formation of mono- and dibromopyrene products.

The crude product obtained was first recrystallized from hexane/DCM and MeOH/DCM following literature procedures, but no separation of mono- and dibrominated pyrene was achieved. Separation, however, could be achieved by column chromatography using hexane as the eluent and the desired monobrominated product **291** was isolated in 35% yield.

In addition to 1-bromopyrene (**291**), we also wanted to synthesise 1,6-dibromopyrene (**292**) to provide access to a range of disubstituted pyrenes. For this we reacted pyrene with 1 equivalent of DBMH in dry DCM at room temperature (Fig. 5.4).

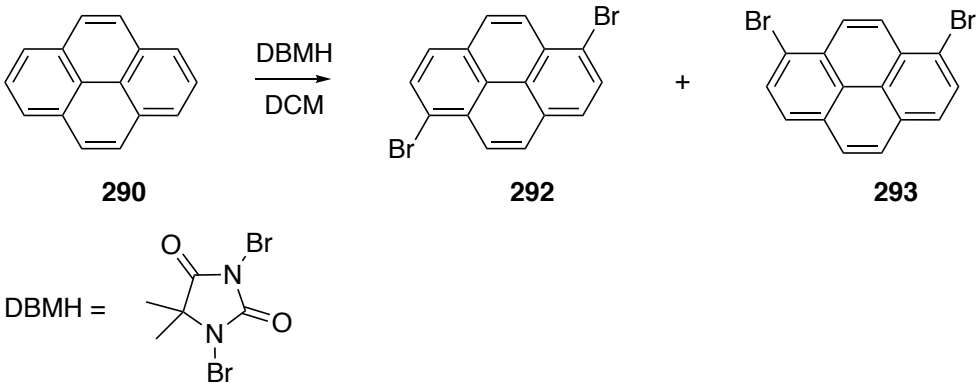


Figure 5.4: Synthesis of dibromopyrenes using DBMH.

After stirring for 48 h the resulting precipitate was filtered and analysed by ^{1}H NMR which revealed the formation of both 1,6-dibromopyrene (**292**) as well as 1,8-dibromopyrene (**293**), with the desired 1,6-isomer isolated by multiple recrystallisations from toluene, but in a disappointing 10% yield (Fig. 5.5).

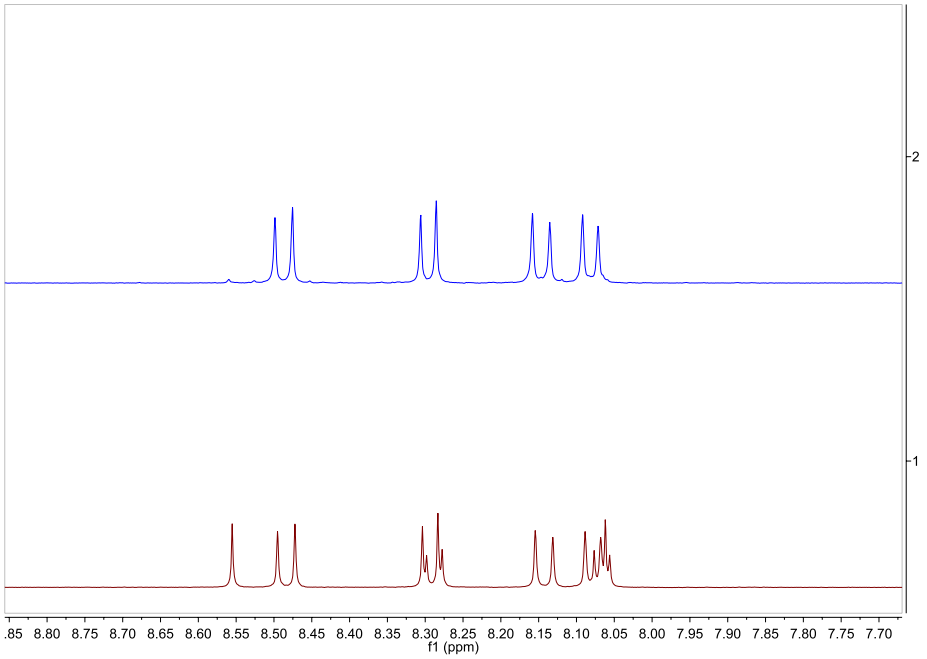


Figure 5.5: Aromatic region of the ^{1}H NMR spectra before (red) and after (blue) recrystallisations from toluene.

5.2.2 S_NAr Reactions with Highly Fluorinated Aromatics

First utilising 1-brompyrene (**291**) lithiation using *n*BuLi was carried out at -78 ºC in THF. Octafluorotoluene was then added in a large excess and the reaction mixture was

warmed to room temperature overnight before being quenched (Fig. 5.6).

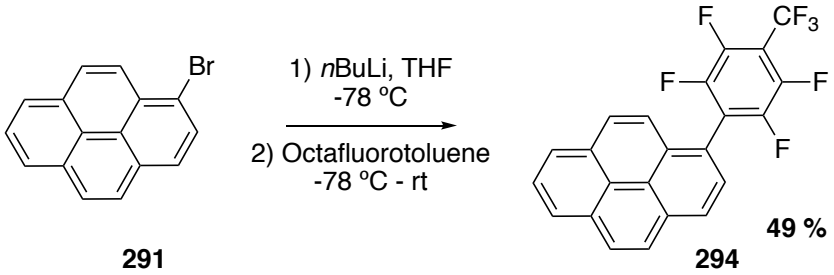


Figure 5.6: Synthesis of 1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pyrene (**294**).

Following work up, GC-MS analysis of the crude product showed two main peaks corresponding to the desired product and a small amount of pyrene. Subsequent recrystallization from hexane/DCM yielded the desired product in a 49% yield, with crystals suitable for x-ray crystallography (Fig. 5.7) confirming the structure.

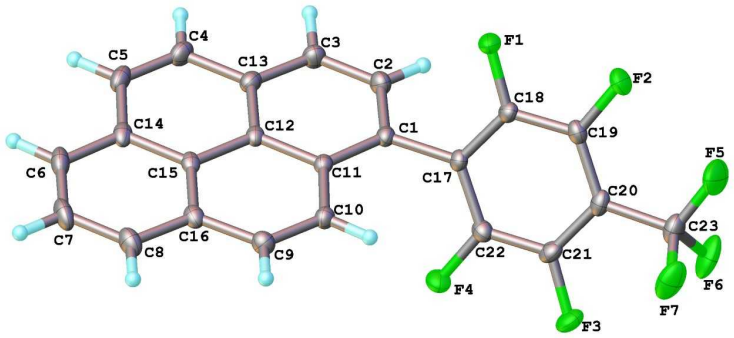


Figure 5.7: Molecular structure of **294** as determined by x-ray crystallography.

A similar strategy was employed for the synthesis of the disubstituted analogue arising from nucleophilic substitution of octafluorotoluene, starting from 1,6-dibromopyrene (**292**). A sequential approach was first attempted to avoid the potential formation of dianionic species but, the dibrominated starting material was only sparingly soluble in the THF solvent and mostly starting material was recovered following the addition of octafluorotoluene. Therefore, a one-step approach was employed utilising an excess of *n*BuLi (3 eq.), which was sufficient to form the corresponding dilithiated species which readily reacted with a large excess of octafluorotoluene (Fig. 5.8).

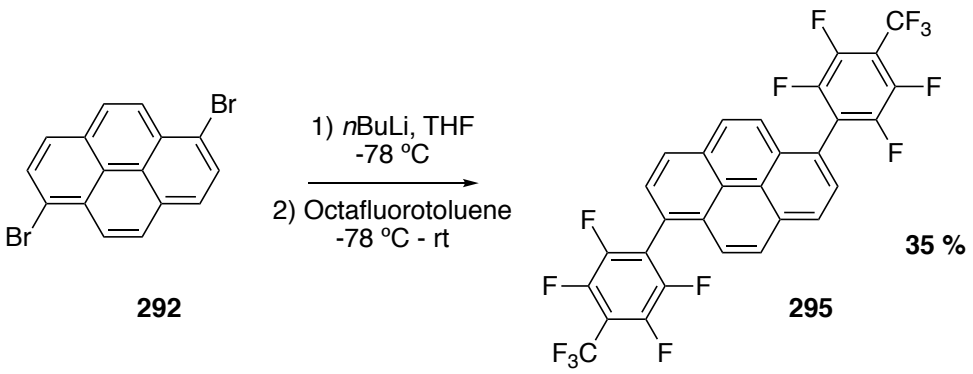


Figure 5.8: Synthesis of 1,6-di(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pyrene (**295**).

The crude reaction mixture showed the major component to be the desired disubstituted product **295** alongside some residual starting material and a small amount of debrominated products. Initial purification attempts via recrystallisation in various solvents proved difficult due to persistent contamination with starting material. Hence, the starting material was first removed by column chromatography and the resulting solid further purified by recrystallisation from hexane/DCM which gave the product in 35% yield, again with crystals of sufficient quality for x-ray crystallography (Fig. 5.9).

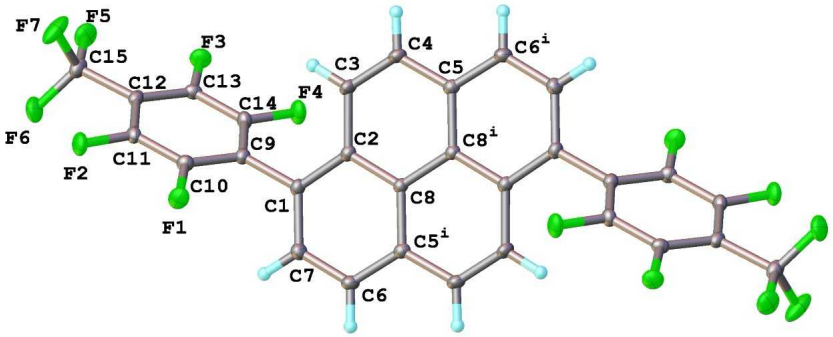


Figure 5.9: Molecular structure of **295** as determined by x-ray crystallography.

We then attempted to apply the same procedure to different fluorinated aromatics with the aim of building a library of compounds which have varying degrees of fluorination. Therefore, we next employed pentafluorobenzene in an attempt to access pyrene based molecules bearing tetrafluorinated substituents. However, under analogous conditions, reaction with pentafluorobenzene gave almost exclusively pyrene and only trace quantities of the desired product (Fig. 5.10).

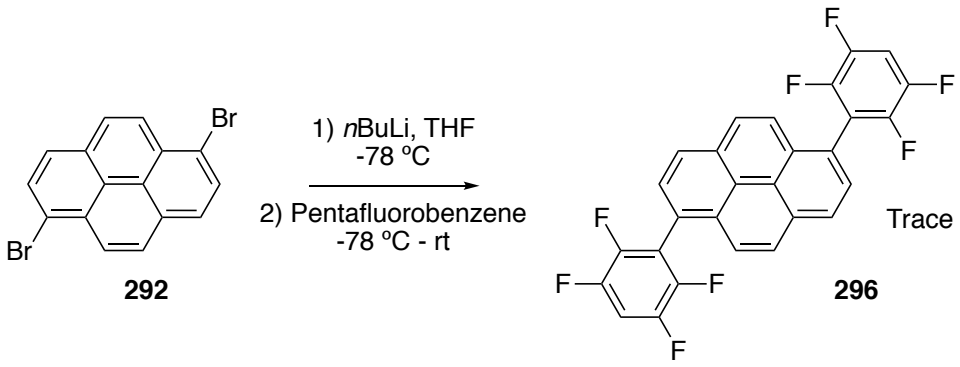


Figure 5.10: Attempted synthesis of tetrafluorobenzene substituted pyrene derivative **296**.

This suggests proton abstraction from pentafluorobenzene is preferred to nucleophilic substitution, likely due to the formation of a relatively stable perfluoroaryl anion.

Hence, we decided to use a fluorinated analogue, which does not possess an acidic proton, such as chloropentafluorobenzene. However, the use of this substrate gave rise to a complex mixture with GC-MS and ASAP analysis suggesting the formation of 1,6-dichloropyrene (Fig. 5.11) rather than the desired product.

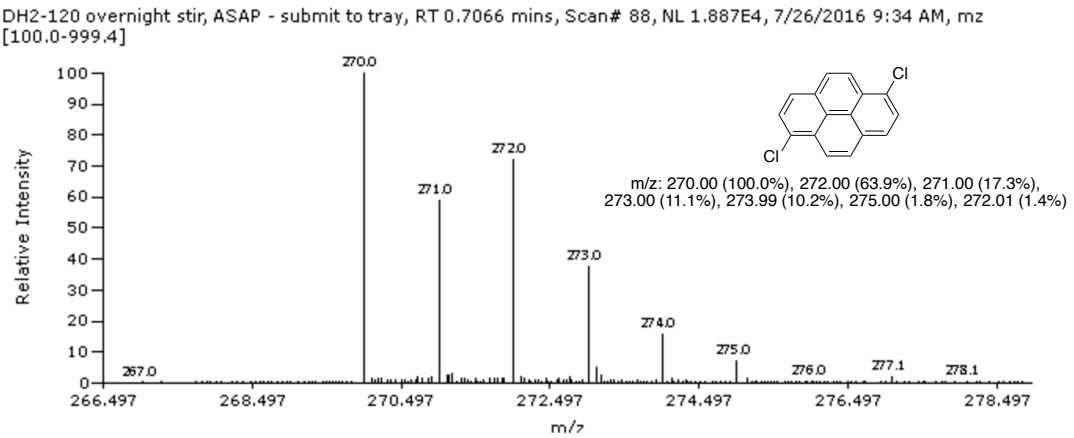


Figure 5.11: ASAP analysis showing the correct mass associated with 1,6-dichloropyrene.

We propose this occurs via chlorophilic attack of the anion, which is again facilitated by the strong electron withdrawing effect of the fluorine substituents making pentafluorobenzene a good leaving group.

Therefore, we again changed the substrate to pentafluorobenzonitrile as we hoped this

would be more robust in preventing the side reactions previously observed. Using pentafluorobenzonitrile, it was possible to synthesise 1-(2,3,5,6-tetrafluorobenzonitrile)pyrene (**297**) in 37% yield after recrystallisation from hexane/DCM (Fig. 5.12).

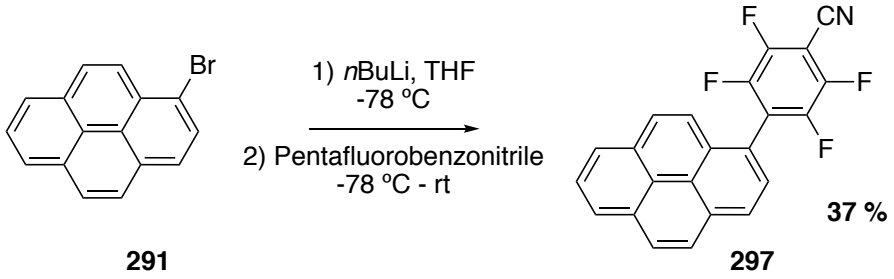


Figure 5.12: Synthesis of 1-(2,3,5,6-tetrafluorobenzonitrile)pyrene (**297**).

Synthesis of the corresponding disubstituted pyrene derivative was also undertaken, and although evidence of the desired product could be observed by NMR and GC-MS, purification by means of recrystallisation and/or column chromatography could not be achieved.

5.3 Conclusions

In conclusion, we have synthesised a series of highly fluorinated mono- and disubstituted pyrene derivatives by bromination and subsequent nucleophilic aromatic substitution with highly fluorinated aromatics. The photophysical properties of these compounds are currently being investigated in collaboration with Prof. Deqing Gao at Nanjing Tech University from which their suitability for application in organic electronics can be assessed.

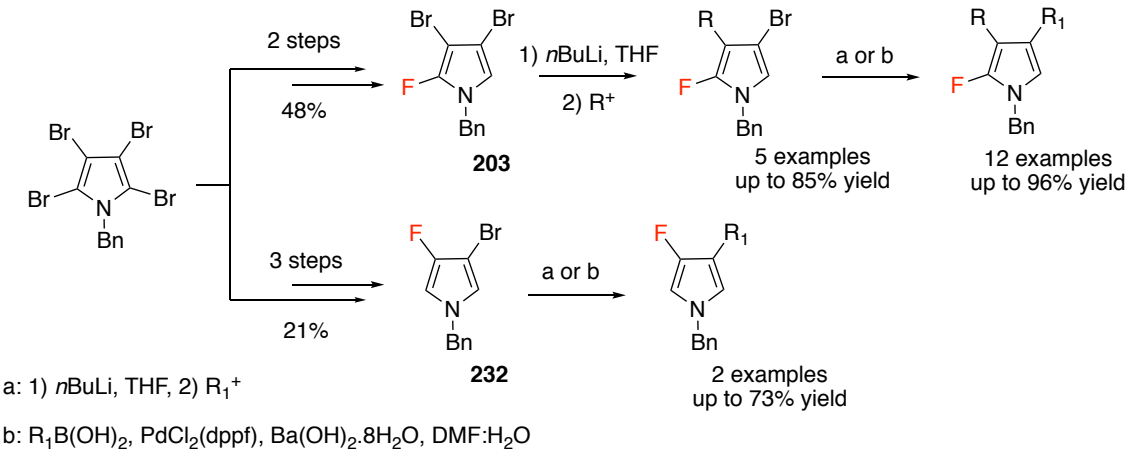
Chapter 6

Conclusions and Future Work

6.1 Conclusions

The direct C-H to C-F fluorination of various pyrrole derivatives using Selectfluor^{TM} has been systematically assessed and it was shown that, in general, competing oxidation and subsequent polymerisation limit yields of the desired fluorinated products even when highly electron-withdrawing substituents are incorporated into the pyrrole scaffold.

The synthesis of a range of highly functionalised 2- and 3-fluoropyrroles, however, was achieved from a common tetrabrominated pyrrole scaffold. Fluorination by means of lithiation and reaction with NFSI gave both 2- and 3-fluoropyrroles building blocks with remaining bromine substituents that were utilised for further derivatisation. Derivatisation by means of lithiation/quenching with electrophiles and Suzuki cross-coupling chemistries, in combination with variations in the order in which these reactions were sequentially applied, allowed the synthesis of an array of variously substituted fluoropyrrole products, including regioisomers.



This work demonstrates the applicability of our methodology for application in parallel synthesis programmes for the synthesis of libraries of highly functionalised fluorinated heterocycles with the diversity of accessible products easily expanded by varying:

1. The order of sequential reactions
2. The electrophiles used
3. The cross-coupling chemistry (Sonogashira, Stille, Buchwald-Hartwig etc.)
4. The heterocyclic scaffold (imidazole, pyrazole, thiophene etc.)

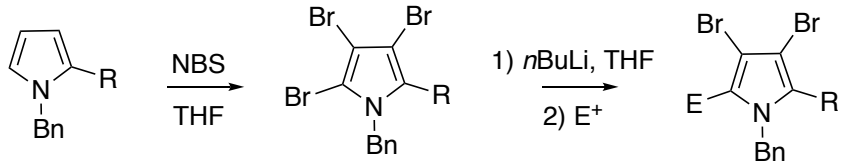
Further, a fluorinated building block approach using 2-fluoromalonate esters was used for the synthesis of a fluorinated pyrido[1,2-a]pyrimidin-4-one scaffold. This scaffold was derivatised by Suzuki cross-coupling reactions to give a library of 2-substituted 3-fluoro-4*H*-pyrido[1,2-a]pyrimidin-4-ones which have shown promise as β-catenin inhibitors by a ^{19}F NMR fragment-based drug discovery approach and SAR studies are ongoing.

Finally, a of a series of highly fluorinated pyrene derivatives was synthesised by nucleophilic aromatic substitution reactions of pyrene nucleophiles with highly fluorinated aromatics for potential application in organic electronics. Photophysical properties of these molecules are currently being assessed by collaborators at Nanjing Tech University.

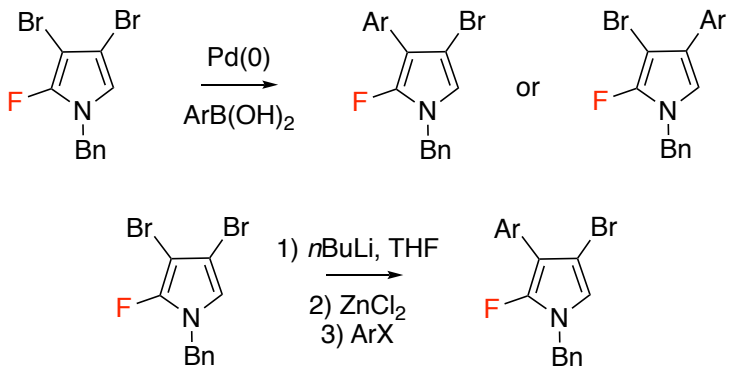
6.2 Future Work

6.2.1 Fluoropyrroles by Sequential Bromination-Derivatisation

Due to the observed difficulty in performing lithiation and trapping reactions when utilising a tetrabromopyrrole starting material, except when quenching with a proton source, further investigation into routes to access 2-substituted-3,4,5-tribromopyrrole derivatives is warranted to allow access to a wider variety of pyrrole derivatives using this approach. The combination of unfavourable sterics as well as competiting halogen dance processes could potentially be avoided by perbromination of pyrrole substrates prefunctionalised at the 2-position.



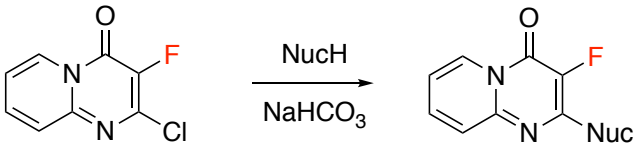
Also, assessment of the regioselectivity of Suzuki cross-coupling reactions of 2-fluoro-3,4-dibromo-*N*-benzylpyrrole would potentially allow cross-coupling reactions to be performed prior to lithiation and trapping protocols in the reaction sequence, to give access to, for example, regioisomeric products of compounds **230a-d**. Equally, if no selectivity can be achieved under Suzuki cross-coupling conditions, a potential alternative would be to utilise the already established regioselective lithitaion, followed by transmetallation to perform Negishi cross-coupling reactions. Expansion to encompass additional Pd catalysed cross-coupling chemistries (Buchwald-Hartwig, Stille, Sonogashira etc.) would also be desirable.



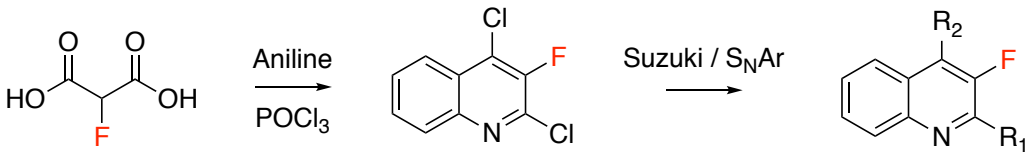
In addition, application of this methodology to alternative heterocycles such as imidazole- or pyrazole-based systems, could provide convenient access to multifunctional fluorinated derivatives, for which, current routes are limited.

6.2.2 3-Fluorinated Pyrido[1,2-*a*]pyrimidin-4-ones

As we have observed the S_NAr reaction of 2-chloro-3-fluoropyrido[1,2-*a*]pyrimidin-4-one with phenol (Fig. 4.28), formed by oxidation of phenylboronic acid due to insufficient degassing of solvents under Suzuki conditions, we propose that a range of 2-substituted products could be synthesised by S_NAr reactions with oxygen, nitrogen and sulfur nucleophiles in combination with a weak base. This range of products could then also be screened as potential β-catenin inhibitors using a ^{19}F NMR fragment-based drug discovery approach.



Equally, similar methodology could be used to synthesise related heterocyclic systems, such as 3-fluoroquinoline derivatives, which could also be derivatised using both Suzuki cross-coupling and S_NAr reactions.



Chapter 7

Experimental Section

7.1 General

NMR Spectroscopy: Proton, carbon and fluorine nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were recorded on a Bruker 400 Ultrashield (^{1}H NMR at 400 MHz; ^{13}C NMR at 101 MHz; ^{19}F NMR at 376 MHz) spectrometer or a Varian VNMRS-700 (^{1}H NMR at 700 MHz; ^{13}C NMR at 176 MHz) with residual solvent peaks as the internal standard. ^{1}H, ^{13}C and ^{19}F spectroscopic data are reported as follows: chemical shift (ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz). Assignments were made using the appropriate 2D techniques (HMBC and HSQC) where necessary.

Mass Spectrometry: GC-MS experiments were carried out on a QP2010-Ultra device (Shimadzu Corporation) operating in electron impact ionisation (EI^{+}) mode. Accurate mass analysis was achieved with a QtoF Premier mass spectrometer (Waters Ltd, UK) or an LCT Premier XE mass spectrometer (Waters Ltd, UK) equipped with an accurate solids analysis probe (ASAP).

IR: Infra-red (IR) spectra were recorded on a Perkin Elmer FTIR Spectrum Two^{TM} fitted with an ATR probe.

Melting Point Analysis: Melting points were measured with a Gallenkamp apparatus

at atmospheric pressure and are uncorrected.

Microwave Reactions: All microwave irradiated reactions were heated in a Biotage Initiator^{TM} Microwave using a 0.5–2 mL, 2–5 mL or 10–20 mL microwave vial fitted with a Biotage magnetic stirrer and sealed with a Reseal^{TM} Septum. The microwave was set to heat to a constant temperature, as specified in the relevant experimental procedure, and each reaction was timed from the point at which the target temperature had been reached. After the reaction time had expired, the microwave vial and its contents were cooled to 45 °C by an external flow of nitrogen gas.

Chemicals and Solvents: Unless otherwise stated, commercially available reagents were used without further purification. Dry solvents were obtained using an Innovative Technology Inc. Solvent Purification System. All column chromatography was carried out using Silicagel LC60A (40–63 micron) purchased from Fluorochem.

X-Ray Analysis: All crystallographic data were recorded with a Bruker D8 venture or Agilent XCalibur diffractometer equipped with Cryostream (Oxford Cryosystems) low temperature device at 120 K with graphite-monochromated MoKα-radiation (λ = 0.71073 Å).

DFT Calculations: All ab initio computations were carried out with the Gaussian09 package. Geometries were optimized at the B3LYP/6-31G* level of theory. Frequency calculations were computed on these optimized geometries at B3LYP/6-31G* and showed no imaginary frequencies. Calculated NMR shifts at GIAO-B3LYP/6-31G* were obtained from the optimized geometries, with ^{19}F chemical shifts converted to the $CFCl_3$ scale; δ (^{19}F) = 179.0 - 0.97σ (^{19}F).

7.2 Experimental to Chapter 2

7.2.1 Fluorination of Pyrroles. General Procedures

Reaction of ethyl pyrrole-2-carboxylate (155) with an electrophilic fluorinating agent in the presence of a Lewis acid under MW conditions (Table 2.1)

To a solution of **155** (0.21 g, 1.5 mmol) and Selectfluor^{TM} (0.53 g, 1.5 mmol) in dry MeCN (15 mL) was added Lewis Acid (50 mol%) before heating with microwave irradiation at 70 °C for 5 min. The reaction was quenched by the addition of H_2O (30 mL) and $CHCl_3$ (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with $CHCl_3$ (3 $\times$ 30 mL) before the solvent was removed *in vacuo*; analysis by ^{19}F NMR relative to an α,α,α-trifluorotoluene reference gave the yield of 5-fluorinated product.

Reaction of pyrrole-2-carbonitrile (157) with Selectfluor^{TM} under MW conditions (Table 2.2)

A solution of **157** (0.18 g, 2 mmol) and Selectfluor^{TM} (0.71 g, 2 mmol) in MeCN (15 mL) was heated with microwave irradiation. The reaction was quenched by the addition of H_2O (30 mL) and $CHCl_3$ (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with $CHCl_3$ (3 $\times$ 30 mL) before the solvent was removed *in vacuo*; analysis by ^{19}F NMR relative to an α,α,α-trifluorotoluene reference gave the yield of 5-fluorinated product.

Reaction of methyl pyrrole-3-carboxylate (159) with Selectfluor^{TM} under MW conditions (Table 2.3)

A solution of **159** (0.25 g, 2 mmol) and Selectfluor^{TM} (0.71 g, 2 mmol) in MeCN (15 mL) was heated with microwave irradiation. The reaction was quenched by the addition of H_2O (30 mL) and $CHCl_3$ (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with $CHCl_3$ (3 $\times$ 30 mL) before the solvent was removed *in vacuo*; analysis by ^{19}F NMR relative to an α,α,α-trifluorotoluene reference gave the yield of 5-fluorinated product.

Reaction of 4-bromopyrrole-2-carboxaldehyde (162) with Selectfluor™ under MW conditions (Table 2.4)

A solution of **162** (0.17 g, 1 mmol) and Selectfluor™ (0.35 g, 1 mmol) in MeCN (15 mL) was heated with microwave irradiation at 70 °C. The reaction was quenched by the addition of H_2O (30 mL) and $CHCl_3$ (30 mL) was subsequently added. he layers were separated and the aqueous phase extracted with $CHCl_3$ (3 × 30 mL) before the solvent was removed *in vacuo*; analysis by ^{19}F NMR relative to an α,α,α-trifluorotoluene reference gave the yield of 5-fluorinated product.

Reaction of methyl 5-formylpyrrole-2-carboxylate (164) with Selectfluor™ under MW conditions (Table 2.5)

A solution of **164** (0.15 g, 1 mmol) and Selectfluor™ (0.35 g, 1 mmol) in MeCN (15 mL) was heated with microwave irradiation. The reaction was quenched by the addition of H_2O (30 mL) and $CHCl_3$ (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with $CHCl_3$ (3 × 30 mL) before the solvent was removed *in vacuo*; analysis by ^{19}F NMR relative to an α,α,α-trifluorotoluene reference gave the yield of fluorinated product.

Reaction of ethyl *N*-(4-nitrobenzyl)-pyrrole-2-carboxylate (168) with Selectfluor™ under MW conditions (Table 2.6)

A solution of **168** (0.15 g, 0.55 mmol) and Selectfluor™ (0.20 g, 0.55 mmol) in MeCN (15 mL) was heated with microwave irradiation. The reaction was quenched by the addition of H_2O (30 mL) and $CHCl_3$ (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with $CHCl_3$ (3 × 30 mL) before the solvent was removed *in vacuo*; analysis by ^{19}F NMR relative to an α,α,α-trifluorotoluene reference gave the yield of 5-fluorinated product.

Reaction of *N*-tosylpyrroles (171 or 172) with Selectfluor^{TM} under MW conditions (Table 2.7)

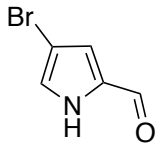
A solution **171** or **172** (1 mmol) and Selectfluor^{TM} (0.35 g, 1 mmol) in MeCN (15 mL) was heated with microwave irradiation. The reaction was quenched by the addition of H_2O (30 mL) and $CHCl_3$ (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with $CHCl_3$ (3 $\times$ 30 mL) before the solvent was removed *in vacuo*; analysis by ^{19}F NMR relative to an α,α,α-trifluorotoluene reference gave the yield of 5-fluorinated product. The presence of fluorinated by-product **175** was confirmed by a combination of ^{19}F NMR and GC-MS analysis. ^{19}F NMR (376 MHz, Chloroform-d) δ 66.31 (1 F, s, SF). GC-MS (EI) m/z 174.0.

Reaction of *N*-tosylpyrrole-2-carbonitrile (172) with fluorine gas

A solution of **172** (0.99 g, 4 mmol) in MeCN (20 mL) was cooled to 0-5 ºC and the system purged with N_2 for 5 min. After purging, fluorine gas (20% v/v in N_2, 20 mL min^{-1}, 4.2 mmol) was passed into the stirred mixture for 50 min. The reactor was purged with N_2 for 10 min and the solvent removed *in vacuo*; analysis was conducted by ^{19}F NMR relative to an α,α,α-trifluorotoluene reference.

7.2.2 Synthesis of Pyrrole Substrates

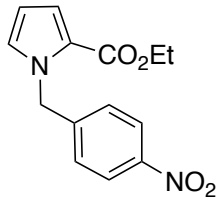
4-Bromopyrrole-2-carboxaldehyde (162)



A solution of pyrrole-2-carboxaldehyde (3.80 g, 40 mmol) in dry THF (40 mL) was cooled to 0 °C under Argon. NBS (7.12 g, 40 mmol) was added and the reaction mixture stirred for 15 min before the solvent was removed in vacuo. The crude product was dried under high vacuum for 30 min before the addition of distilled water (20 mL) and the suspension filtered. The resulting solid was dissolved in a minimum amount of hot ethanol/water solution (9:1) before the addition of activated charcoal and filtration

through a celite plug. Upon cooling, the product recrystallised to give 4-bromopyrrole-2-carboxaldehyde (3.54 g, 51%) as an off white solid; Mp 119-122 °C (lit. 120 °C).[83] IR (neat, cm^{-1}) 2861, 1653. ^{1}H NMR (400 MHz, Acetone-d_6) δ 11.39 (1H, s, N*H*), 9.52 (1 H, d, $^4J_{HH}$ 1.0, C*H*O), 7.34 – 7.31 (1H, m, C**5**H), 7.09 – 7.05 (1H, m, C**3**H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 179.4 (s, C=O), 134.3 (s, C**2**), 126.8 (s, C**5**), 121.5 (s, C**3**), 98.4 (s, C**4**). HRMS (ESI) m/z calculated for $[M+H]^+$ C_5H_4BrNO 173.9554; found 173.9553.

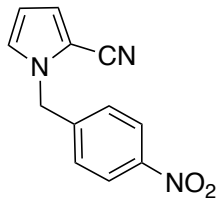
Ethyl *N*-(4-nitrobenzyl)pyrrole-2-carboxylate (168)



To a solution of ethyl pyrrole-2-carboxylate (2.09 g, 15 mmol) in dry DMF (25 mL) at 0 °C, sodium hydride (0.54 g, 23 mmol) was added. The reaction mixture was stirred for 20 min, before the dropwise addition of 4-nitrobenzyl bromide (4.80 g, 23 mmol) in dry DMF (10 mL). After a further 25 min, any excess hydride was decomposed by the addition of ethanol (15 mL) and the reaction mixture was poured into distilled water (50 mL). The aqueous solution was extracted with DCM (4 × 50 mL) and washed with distilled water (9 × 100 mL) and brine (100 mL) before being dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using a gradient of hexane/EtOAc (0-20% EtOAc) as the eluent to give *ethyl N-(4-nitrobenzyl)pyrrole-2-carboxylate* (2.10 g, 51%) as a yellow solid; Mp 92-94 °C. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.21 – 8.11 (2H, m, C**3'**H), 7.21 – 7.13 (2H, m, C**2'**H), 7.05 (1H, dd, $^3J_{HH}$ 4.0, $^4J_{HH}$ 1.8, C**5**H), 6.93 (1H, dd, $^3J_{HH}$ 2.6, $^4J_{HH}$ 1.8, C**3**H), 6.25 (1H, dd, $^3J_{HH}$ 4.0, $^3J_{HH}$ 2.6, C**4**H), 5.65 (2H, s, C**6**H), 4.19 (2H, q, $^3J_{HH}$ 7.1, CH_2CH$_3$), 1.28 (3H, t, $^3J_{HH}$ 7.1, CH$_2$CH_3). ^{13}C NMR (176 MHz, Chloroform-d) δ 161.1 (s, *C*=O), 147.4 (s, C**4'**), 146.1 (s, C**1'**), 129.2 (s, C**3**), 127.2 (s, C**2'**) , 124.0 (s, C**3'**), 122.4 (s, C**2**), 118.9 (s, C**5**), 109.2 (s, C**4**), 60.2 (s, *C*H$_2$CH$_3$), 51.8 (s, C**6**), 14.5 (s, CH$_2$*C*H$_3$). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{14}H_{15}N_2O_4$ 275.1032; found

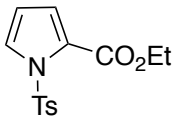
275.1043.

_N_-(4-Nitrobenzyl)pyrrole-2-carbonitrile (170)



The same procedure as for the synthesis of **168** was employed with pyrrole-2-carbonitrile (0.36 g, 4 mmol), sodium hydride (0.14 g, 6 mmol) and 4-nitrobenzyl bromide (1.28 g, 6 mmol). The crude product obtained was purified by column chromatography on silica gel using a gradient of hexane/EtOAc (0-10% EtOAc) as the eluent to yield *N-(4-Nitrobenzyl)pyrrole-2-carbonitrile* (0.22 g, 24%) as a yellow solid; Mp 97-99 °C. IR (neat, cm^{-1}) 2212, 1507, 1340. ^{1}H NMR (700 MHz, Chloroform-d) δ 8.22 – 8.19 (2H, m, C**3'**H), 7.30 – 7.27 (2H, m, C**2'**H), 6.91 (1H, dd, $^{3}J_{HH}$ 2.7, $^{4}J_{HH}$ 1.6, C**5**H), 6.88 (1H, dd, $^{3}J_{HH}$ 4.0, $^{4}J_{HH}$ 1.6, C**3**H), 6.28 (1H, dd, $^{3}J_{HH}$ 4.0, $^{3}J_{HH}$ 2.7, C**4**H), 5.33 (2H, s, C**6**H). ^{13}C NMR (176 MHz, Chloroform-d) δ 148.0 (s, C**1'**), 143.2 (s, C**4'**), 127.9 (s, C**2'**), 127.1 (s, C**5**), 124.4 (s, C**3'**), 121.1 (s, C**3**), 113.5 (s, *C*N), 110.8 (s, C**4**), 104.5 (s, C**2**), 51.7 (s, C**6**). HRMS (ASAP) m/z calculated for $[M]^{+}$ $C_{12}H_9N_3O_2$ 227.0693; found 227.0695.

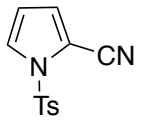
Ethyl _N_-tosylpyrrole-2-carboxylate (171)



Sodium hydride (0.43 g, 18 mmol) was suspended in anhydrous DMF (10 mL) and cooled to 0 °C before a solution of ethyl pyrrole-2-carboxylate (2.09 g, 15 mmol) in anhydrous DMF (15 mL) was added over a period of 20 min. The reaction mixture was then allowed to return to room temperature and stirred for 1 h before the addition of tosyl chloride (3.43 g, 18 mmol) in anhydrous DMF (10 mL). After 17 h the reaction mixture

was poured into distilled water (100 mL) and the aqueous solution extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with distilled water (4 × 100 mL) and brine (100 mL) before being dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was filtered through a silica plug using EtOAc as the eluent and the solvent removed *in vacuo* to yield *ethyl N-tosylpyrrole-2-carboxylate* (3.27 g, 88%) as a pale yellow solid; Mp 43-45 °C. IR (neat, cm^{-1}) 1681, 1359, 1171. ^{1}H NMR (700 MHz, Chloroform-d) δ 7.90 – 7.84 (2H, m, C**2'**H), 7.70 (1H, dd, $^3J_{HH}$ 3.2, $^4J_{HH}$ 1.9, C**5**H), 7.35 – 7.28 (2H, m, C**3'**H), 7.04 (1H, dd, $^3J_{HH}$ 3.7, $^4J_{HH}$ 1.9, C**3**H), 6.30 (1H, t, $^3J_{HH}$ 3.4, C**4**H), 4.19 (2H, q, $^3J_{HH}$ 7.1, CH_2CH$_3$), 2.42 (3H, s, ArCH_3), 1.26 (3H, t, $^3J_{HH}$ 7.1, CH$_2$CH_3). ^{13}C NMR (176 MHz, Chloroform-d) δ 158.9 (s, *C*=O), 145.0 (s, C**4'**), 136.1 (s, C**1'**), 129.6 (s, C**3'**), 129.2 (s, C**5**), 128.3 (s, C**2'**), 125.4 (s, C**2**), 123.2 (s, C**3**), 110.4 (s, C**4**), 60.9 (s, *C*H$_2$CH$_3$), 21.8 (s, Ar*C*H$_3$), 14.3 (s, CH$_2$*C*H$_3$). HRMS (ESI) m/z calculated for $[M-H]^-$ $C_{14}H_{14}NO_4S$ 292.0644; found 292.0640.

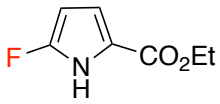
N-Tosylpyrrole-2-carbonitrile (172)



The same procedure as for the synthesis of **171** was employed with pyrrole-2-carbonitrile (1.38 g, 15 mmol), sodium hydride (0.43 g, 18 mmol) and tosyl chloride (3.43 g, 18 mmol). The crude product was recrystallized from hexane/EtOAc to give *N-tosyl-pyrrole-2-carbonitrile* (3.02 g, 82%) as a pale yellow solid; Mp 110-112 °C (lit 114-115 °C)[162]. IR (neat, cm^{-1}) 1354, 1134. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.01 – 7.85 (2H, m, C**2'**H), 7.47 (1H, dd, $^3J_{HH}$ 3.2, $^4J_{HH}$ 1.6, C**5**H), 7.40 – 7.34 (2H, m, C**3'**H), 6.95 (1H, dd, $^3J_{HH}$ 3.7, $^4J_{HH}$ 1.6, C**3**H), 6.32 (1H, t, $^3J_{HH}$ 3.5, C**4**H), 2.44 (3H, s, ArCH_3). ^{13}C NMR (176 MHz, Chloroform-d) δ 146.7 (s, C**4'**), 134.3 (s, C**1'**), 130.5 (s, C**3'**), 128.0 (s, C**2'**), 126.7 (s, C**5**), 126.7 (s, C**3**), 112.4 (s, C**4**), 111.8 (s, *C*N), 103.9 (s, C**2**), 21.9 (s, Ar*C*H$_3$). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{12}H_{11}N_2O_2S$ 247.0541; found 247.0547.

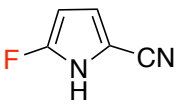
7.2.3 Preparative Scale Fluorination of Pyrrole Derivatives

Ethyl 5-fluoropyrrole-2-carboxylate (156)



A solution of ethyl pyrrole-2-carboxylate (0.56 g, 4 mmol) and Selectfluor™ (1.42 g, 4 mmol) in MeCN (25 mL) was heated by microwave irradiation at 70 °C for 5 min. The reaction was quenched by the addition of H_2O (50 mL) and $CHCl_3$ (50 mL) was subsequently added. The layers were separated and the aqueous phase extracted with $CHCl_3$ (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane/Et_2O (5:1) as the eluent to give *ethyl 5-fluoropyrrole-2-carboxylate* (0.15 g, 23%) as a yellow solid; IR (neat, cm^{-1}) 1676. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.85 (1 H, s, N*H*), 6.75 (1H, ddd, $^4J_{HF}$ 4.7, $^3J_{HH}$ 4.0, $^4J_{HH}$ 2.9, C**3**H), 5.58 (1H, app td, $^3J_{HF}$ 4.0, $^3J_{HH}$ 4.0, $^4J_{HH}$ 2.7, C**4**H), 4.31 (2H, q, $^3J_{HH}$ 7.1, CH_2CH$_3$), 1.34 (3H, t, $^3J_{HH}$ 7.2, CH$_2$CH_3). ^{19}F NMR (376 MHz, Chloroform-d) δ -130.64 (ddd, $^4J_{HF}$ 4.7, $^3J_{HF}$ 4.0, $^3J_{HF}$ 2.5). ^{13}C NMR (176 MHz, Chloroform-d) δ 161.0 (s, *C*=O), 149.4 (d, $^1J_{CF}$ 267.4, *C*F), 115.2 (s, C**3**), 114.2 (s, C**2**), 89.2 (d, $^2J_{CF}$ 11.4, C**4**), 60.6 (s, *C*H$_2$CH$_3$), 14.6 (s, CH$_2$*C*H$_3$). HRMS (ESI) m/z calculated for [M+H]$^+$ $C_7H_9FNO_2$ 158.0617; found 158.0598.

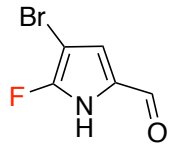
5-Fluoropyrrole-2-carbonitrile (158)



A solution of pyrrole-2-carbonitrile (0.90 g, 10 mmol) and Selectfluor™ (3.55 g, 10 mmol) in MeCN (25 mL) was heated with microwave irradiation at 70 °C for 5 min. The reaction was quenched by the addition of H_2O (50 mL) and $CHCl_3$ (50 mL) was subsequently added. The layers were separated and the aqueous phase extracted with

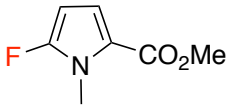
$CHCl_3$ (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using a gradient of hexane/Et_2O (0-10% Et_2O) as the eluent to give *5-fluoropyrrole-2-carbonitrile* (0.33 g, 30%) as a white solid; Mp 55-57 °C. IR (neat, cm^{-1}) 2227. ^1H NMR (400 MHz, Chloroform-d) δ 8.67 (1H, s, N*H*), 6.72 (1H, ddd, $^4J_{HF}$ 4.5, $^3J_{HH}$ 4.3, $^4J_{HH}$ 3.0, C**3**H), 5.64 (1H, ddd, $^3J_{HH}$ 4.1, $^3J_{HF}$ 3.6, $^4J_{HH}$ 2.7, C**4**H). ^{19}F NMR (376 MHz, Chloroform-d) δ -128.90 (ddd, $^4J_{HF}$ 4.5, $^3J_{HF}$ 3.6, $^3J_{HF}$ 2.5). ^{13}C NMR (176 MHz, Chloroform-d) δ 148.7 (d, $^1J_{CF}$ 268.1, *C*F), 120.7 (d, $^3J_{CF}$ 2.7, C**3**), 114.1 (s, *C*N), 92.8 (d, $^3J_{CF}$ 5.2, C**2**), 89.3 (d, $^2J_{CF}$ 11.0, C**4**). HRMS (ESI) m/z calculated for $[M-H]^-$ $C_5H_2FN_2$ 109.0202; found 109.0196.

4-Bromo-5-fluoropyrrole-2-carboxaldehyde (163)



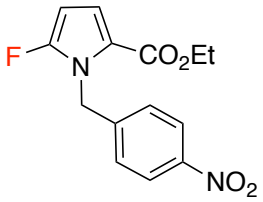
A solution of 4-bromopyrrole-2-carboxaldehyde (1.04 g, 6 mmol) and Selectfluor™ (2.13 g, 6 mmol) in MeCN (25 mL) was heated with microwave irradiation at 70 °C for 7.5 min. The reaction was quenched by the addition of H_2O (50 mL) and $CHCl_3$ (50 mL) was subsequently added. The layers were separated and the aqueous phase extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using a gradient of hexane/Et_2O (0-20% Et_2O) as the eluent to give *4-bromo-5-fluoropyrrole-2-carboxaldehyde* (0.33 g, 29%) as an off white solid; Mp 148-150 °C (with degradation). IR (neat, cm^{-1}) 2676, 1627. ^1H NMR (400 MHz, Acetone-d_6) δ 9.40 (1H, d, $^4J_{HH}$ 3.5, C*H*O), 7.05 (1H, d, $^4J_{HF}$ 4.5, C**3**H). ^{19}F NMR (376 MHz, Acetone-d_6) δ -132.70 – -132.75 (m). ^{13}C NMR (151 MHz, Acetone-d_6) δ 178.2 (d, $^4J_{CF}$ 2.7, *C*=O), 149.3 (d, $^1J_{CF}$ 268.0, *C*F), 124.3 (s, C**2**), 120.9 (s, C**3**), 76.1 (d, $^2J_{CF}$ 15.1, C**4**). HRMS (ESI) m/z calculated for $[M+H]^+$ C_5H_4BrNOF 191.9460; found 191.9463. Crystals suitable for x-ray diffraction were grown by slow evaporation from acetone.

Methyl *N*-methyl-5-fluoropyrrole-2-carboxylate (166)



A solution of methyl *N*-methyl-pyrrole-2-carboxylate (0.56 g, 4 mmol) and Select-fluor^{TM} (1.42 g, 4 mmol) in MeCN (25 mL) was heated by microwave irradiation at 70 °C for 5 min. The reaction was quenched by the addition of H_2O (50 mL) and $CHCl_3$ (50 mL) was subsequently added. The layers were separated and the aqueous phase extracted with $CHCl_3$ (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane/Et_2O (5:1) as the eluent to yield methyl *N-methyl-5-fluoropyrrole-2-carboxylate* (0.10 g, 16%) as a colourless oil; IR (neat, cm^{-1}) 1704. ^{1}H NMR (400 MHz, chloroform-d) δ 6.81 (1H, dd, $^4J_{HF}$ 6.3, $^3J_{HH}$ 4.3, C**3**H), 5.56 (1H, app t, $^3J_{HH}$ 4.3, $^3J_{HF}$ 4.3, C**4**H), 3.79 (3H, s, CO_2CH_3), 3.76 (3H, d, $^4J_{HF}$ 1.2, NCH_3). ^{19}F NMR (376 MHz, Chloroform-d) δ -131.89 (ddq, $^4J_{HF}$ 6.3, $^3J_{HF}$ 4.2, $^4J_{HF}$ 1.2). ^{13}C NMR (101 MHz, Chloroform-d) δ 161.4 (d, $^4J_{CF}$ 2.2, *C*=O), 150.5 (d, $^1J_{CF}$ 267.1, *C*F), 116.0 (d, $^3J_{CF}$ 4.3, C**3**), 114.5 (s, C**2**), 87.6 (d, $^2J_{CF}$ 12.2, C**4**), 51.1 (s, OCH_3), 30.6 (d, $^3J_{CF}$ 2.8, NCH_3). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_7H_9FNO_2$ 158.0617; found 158.0615.

Ethyl *N*-(4-nitrobenzyl)-5-fluoropyrrole-2-carboxylate (169)



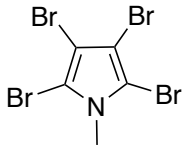
A solution of ethyl *N*-(4-nitrobenzyl)-pyrrole-2-carboxylate (0.15 g, 0.55 mmol) and Selectfluor^{TM} (0.20 g, 0.55 mmol) in MeCN (15 mL) was heated with microwave irradiation at 70 °C for 5 min. The reaction was quenched by the addition of H_2O (30 mL) and $CHCl_3$ (30 mL) was subsequently added. The layers were separated and the

aqueous phase extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using a gradient of hexane/Et_2O (0-10% Et_2O) as the eluent to give *ethyl N-(4-nitrobenzyl)-5-fluoropyrrole-2-carboxylate* (25 mg, 15%) as a pale yellow solid; Mp 52-54 °C. IR (neat, cm^{-1}) 1667, 1523, 1344. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.21 – 8.12 (2H, m, C**3'**H), 7.31 – 7.27 (2H, m, C**2'**H), 6.93 (1H, dd, $^4J_{HF}$ 6.2, $^3J_{HH}$ 4.2, C**3**H), 5.69 (1H, app t, $^3J_{HH}$ 4.2, $^3J_{HF}$ 4.2, C**4**H), 5.59 (2H, s, C**6**H), 4.21 (2H, q, $^3J_{HH}$ 7.1, CH_2CH$_3$), 1.29 (3H, t, $^3J_{HH}$ 7.1, CH$_2$CH_3). ^{19}F NMR (376 MHz, Chloroform-d) δ -131.65 (dd, $^4J_{HF}$ 6.2, $^4J_{HF}$ 4.2). ^{13}C NMR (176 MHz, Chloroform-d) δ 160.8 (d, $^4J_{CF}$ 2.1, *C*=O), 150.3 (d, $^1J_{CF}$ 268.7, *C*F), 147.5 (s, C**4'**), 144.7 (s, C**1'**), 127.7 (s, C**2'**), 124.1 (s, C**3'**), 117.0 (d, $^3J_{CF}$ 4.0, C**3**), 114.3 (s, C**2**), 88.3 (d, $^2J_{CF}$ 11.6, C**4**), 60.2 (s, *C*H$_2$CH$_3$), 46.2 (d, $^3J_{CF}$ 2.0, C**6**), 14.5 (s, CH$_2$*C*H$_3$). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{14}H_{14}FN_2O_4$ 293.0938; found 293.0944.

7.3 Experimental to Chapter 3

7.3.1 Synthesis of Brominated Pyrrole Substrates

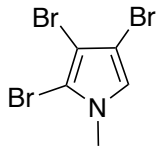
2,3,4,5-Tetrabromo-*N*-methylpyrrole (176)



To a solution of *N*-methylpyrrole (0.82 g, 10 mmol) in dry THF (20 mL) was cooled to 0 ℃ under an argon atmosphere. NBS (8.91 g, 50 mmol) was added and the solution stirred to room temperature overnight. To the mixture was added heptane (20 mL), THF removed *in vacuo* and the resultant succinimide precipitate filtered. To the filtrate was added saturated aq. NaOH (20 mL) and the solution heated to reflux for 2 h before being allowed to cool to room temperature. The aqueous layer was removed and the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallized from a solution of chloroform/methanol (1:1) and the resultant solid

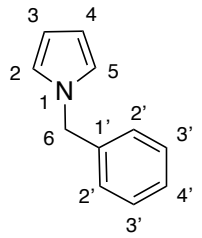
washed with cold EtOAc (5 mL) to give *2,3,4,5-tetrabromo-N-methylpyrrole* (2.10 g, 53%) as white needles; Mp 143-144 ºC (lit. 154-156 ºC).[87] ^{1}H NMR (Chloroform-d, 400 MHz) δ 3.68 (3H, s, NCH_3). ^{13}C NMR (Chloroform-d, 101 MHz) δ 103.7 (s, C**2**/C**5**) 101.1 (s, C**3**/C**4**), 37.1 (s, NCH$_3$). HRMS (ASAP) m/z calculated for $[M]^+$ $C_5H_3NBr_4$ 392.6999; found 392.7031.

2,3,4-Tribromo-*N*-methylpyrrole (196)



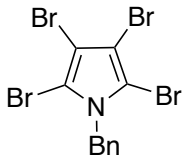
A solution of 2,3,4,5-tetrabromo-*N*-methylpyrrole (0.40 g, 1 mmol) in dry THF (20 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (0.40 mL, 2.5 M in hexanes, 1 mmol,) was added dropwise over 10 min and the resulting solution stirred at -78 ºC for 1 h. Aq. HCl (2 mL, 0.5 M) was then added and the solution stirred to room temperature over a period of 1.5 h. Water (30 mL) was added, the aqueous layer extracted with DCM (3 × 30 mL) and the combined organics dried ($MgSO_4$) before being concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel using hexane as the eluent to yield *2,3,4-tribromo-N-methylpyrrole* (0.23 g, 73%) as a white solid; Mp 67-68 ºC. ^{1}H NMR (Chloroform-d, 400 MHz) δ 6.80 (1H, s, C**5**H), 3.61 (3H, s, NCH_3). ^{13}C NMR (Chloroform-d, 101 MHz) δ 122.5 (s, C**5**), 104.1 (s, C**2**), 101.0 (s, C**4**), 98.0 (s, C**3**), 37.2 (s, NCH_3). HRMS (ASAP) m/z calculated for $[M]^+$ $C_5H_4NBr_3$ 314.7894; found 314.7889.

***N*-Benzylpyrrole (199)**



To *trans*-4-hydroxy-L-proline (15.8 g, 120 mmol) in 150 mL dry DMF was added acetic acid (0.48 mL, 8 mmol) and the solution heated to reflux under an argon atmosphere. Benzaldehyde (8.50 g, 80 mmol) in dry DMF (50 mL) was added dropwise over 50 min and stirred for a further 10 min before being allowed to cool to room temperature. Water (300 mL) was added and the aqueous layer extracted with EtOAc (3 × 200 mL). The combined organics were washed with water (3 × 200 mL) and brine (150 mL) before being dried ($MgSO_4$) and concentrated *in vacuo* to give *N-benzylpyrrole* (11.8 g, 94%) as a pale yellow oil; ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.49 – 7.34 (3H, m, C**3'**H/C**4'**H), 7.25 – 7.18 (2H, m, C**2'**H), 6.80 (2H, t, $^3J_{HH}$ 2.1, C**2**H/C**5**H), 6.33 (2H, t, $^3J_{HH}$ 2.1, C**3**H/C**4**H), 5.15 (2H, s, C**6**H). ^{13}C NMR (Chloroform-d, 101 MHz) δ 138.3, 128.8, 127.7, 127.0, 121.2, 108.6, 53.3. The data were consistent with those previously reported in the literature.[103]

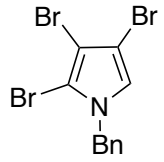
2,3,4,5-Tetrabromo-*N*-benzylpyrrole (200)



A solution of *N*-benzylpyrrole (1.57 g, 10 mmol) in dry THF (20 mL) was cooled to 0 ºC under an argon atmosphere. NBS (8.91 g, 50 mmol) was added portion wise and the solution stirred to room temperature overnight. Heptane (20 mL) was added to the mixture, the THF removed *in vacuo* and the resultant succinimide precipitate collected by filtration. To the filtrate was added saturated aq. NaOH (20 mL) and the solution heated to reflux for 2 h before being allowed to cool to room temperature. The aqueous layer was removed, extracted with DCM (20 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallized from a solution of chloroform/methanol (1:1) to give *2,3,4,5-tetrabromo-N-benzylpyrrole* (3.91 g, 83%) as white crystals; Mp 103-105 ºC. ^{1}H NMR (Chloroform-d, 700 MHz) δ 7.34 (2H, dd, $^3J_{HH}$ 8.2, $^3J_{HH}$ 6.7, C**3'**H), 7.32 – 7.29 (1H, m, C**4'**H), 7.12 – 7.06 (2H, m, C**2'**H), 5.30 (2H, s, C**6**H). ^{13}C NMR (Chloroform-d, 176 MHz) δ 135.5 (s, C**1'**), 129.0 (s, C**3'**), 128.1 (s, C**4'**), 126.6 (s, C**2'**), 103.8 (s, C**2**/C**5**), 102.1 (s, C**3**/C**4**), 53.1 (s, C**6**).

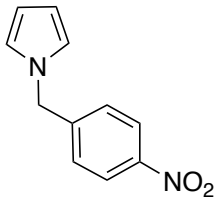
HRMS (ASAP) m/z calculated for $[M]^+$ $C_{11}H_7NBr_4$ 468.7312; found 468.7324.

2,3,4-Tribromo-*N*-benzylpyrrole (201)



A solution of 2,3,4,5-tetrabromo-*N*-benzylpyrrole (3.55 g, 7.5 mmol) in dry THF (50 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (3.0 mL, 2.5 M in hexanes, 7.5 mmol) was added dropwise over 10 min and the resulting solution stirred at -78 ºC for 1 h. Aq. HCl (15 mL, 0.5 M) was then added and the solution stirred to room temperature over a period of 1.5 h. Water (100 mL) was added, the aqueous layer extracted with DCM (3 × 75 mL) and the combined organics dried ($MgSO_4$) before being concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel using hexane as the eluent to yield *2,3,4-tribromo-N-benzylpyrrole* (2.32 g, 79%) as a white solid; Mp 44-46 ºC. IR (neat, cm^{-1}) 3132, 1454, 1304, 973, 720, 695, 609. ^{1}H NMR (Chloroform-d, 600 MHz) δ 7.40 – 7.29 (3H, m, C**3'**H/C**4'**H), 7.17 – 7.09 (2H, m, C**2'**H), 6.81 (1H, s, C**5**H), 5.09 (2H, s, C**6**H). ^{13}C NMR (Chloroform-d, 151 MHz) δ 135.8 (s, C**1'**), 129.1 (s, C**3'**), 128.4 (s, C**4'**), 127.4 (s, C**2'**), 122.1 (s, C**5**), 104.0 (s, C**2**), 101.7 (s, C**4**), 98.8 (s, C**3**), 53.6 (C**6**). HRMS (ASAP) m/z calculated for $[M]^+$ $C_{11}H_8NBr_3$ 390.8207; found 390.8185.

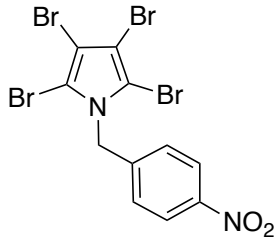
***N*-(4-Nitrobenzyl)pyrrole (209)**



To *trans*-4-hydroxy-L-proline (5.91 g, 45 mmol) in 50 mL dry DMF was added acetic acid (0.18 mL, 3 mmol) and the solution heated to reflux under an argon atmosphere. 4-Nitrobenzaldehyde in dry DMF (10 mL) was added dropwise over 50 min and stirred

for a further 10 min before being allowed to cool to room temperature. Water (200 mL) was added and the aqueous layer extracted with EtOAc (3 × 100 mL). The combined organics were washed with water (3 × 100 mL) and brine (100 mL) before being dried ($MgSO_4$) and concentrated *in vacuo* to give *N-(4-nitrobenzyl)pyrrole* (5.84 g, 98%) as a pale brown solid; ^{1}H NMR (Chloroform-d, 400 MHz) δ 8.18 (2H, d, $^3J_{HH}$ 8.7, C**3'**H), 7.20 (2H, d, $^3J_{HH}$ 8.7, C**2'**H), 6.69 (2H, t, $^3J_{HH}$ 2.1, C**2**H/C**5**H), 6.25 (2H, t, $^3J_{HH}$ 2.1, C**3**H/C**4**H), 5.19 (2H, s, C**6**H). ^{13}C NMR (Chloroform-d, 101 MHz) δ 147.6, 145.8, 127.5, 124.2, 121.4, 109.5, 52.7. HRMS (ASAP) m/z calculated for $[M+H]^+$ $C_{11}H_{11}N_2O_2$ 203.0821; found 203.0821. The data were consistent with those previously reported in the literature.[103]

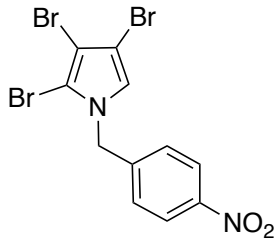
2,3,4,5-Tetrabromo-*N*-(4-nitrobenzyl)pyrrole (210)



A solution of N-(4-nitrobenzyl)pyrrole (2.02 g, 10 mmol) in dry THF (20 mL) was cooled to 0 ºC under an argon atmosphere. NBS (8.91 g, 50 mmol) was added portion wise and the solution stirred to room temperature overnight. The solvent was removed *in vacuo* and the resulting solid washed with water (100 mL) to remove succinimide. The remaining solid was taken up in DCM (20 mL), saturated aq. NaOH (20 mL) was added and the mixture was heated to reflux for 1 h before being allowed to cool to room temperature. The aqueous layer was removed, extracted with DCM (20 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallised from a solution of chloroform/methanol (2:1) to give *2,3,4,5-tetrabromo-N-(4-nitrobenzyl)pyrrole* (2.10 g, 46%) as yellow crystals; Mp 166-168 ºC. ^{1}H NMR (Chloroform-d, 400 MHz) δ 8.23 – 8.19 (2H, m, C**3'**H), 7.24 – 7.20 (2H, m, C**2'**H), 5.40 (2H, s, C**6**H). ^{13}C NMR (Chloroform-d, 101 MHz) δ 147.8 (s, C**4'**), 142.6 (s, C**1'**), 127.4 (s, C**2'**), 124.4 (s, C**3'**), 103.9 (s, C**2**/C**5**), 102.9 (s, C**3**/C**4**), 52.4 (s, C**6**).

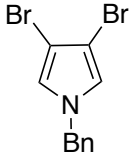
HRMS (ASAP) m/z calculated for $[M+H]^+$ $C_{11}H_7Br_4N_2O_2$ 514.7241; found 514.7249.

2,3,4-Tribromo-*N*-(4-nitrobenzyl)pyrrole (211)



A solution of 2,3,4,5-tetrabromo-*N*-(4-nitrobenzyl)pyrrole (1.04 g, 2 mmol) in dry THF (15 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (0.8 mL, 2.5 M in hexanes, 2 mmol) was added dropwise over 10 min and the resulting solution stirred at -78 ºC for 1 h. Aq. HCl (4 mL, 0.5 M) was then added and the solution stirred to room temperature over a period of 1 h. Water (25 mL) was added, the aqueous layer extracted with DCM (3 × 25 mL) and the combined organics dried ($MgSO_4$) before being concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel using a gradient of hexane/EtOAc (0-20% EtOAc) as the eluent to yield *2,3,4-tribromo-N-(4-nitrobenzyl)pyrrole* (0.23 g, 26%) as an off white solid; Mp 151-153 ºC. ^{1}H NMR (Chloroform-d, 700 MHz) δ 8.25 – 8.18 (2H, m, C**3'**H), 7.25 – 7.22 (2H, m, C**2'**H), 6.89 (1H, s, C**5**H), 5.21 (2H, s, C**6**H). ^{13}C NMR (Chloroform-d, 176 MHz) δ 147.9 (s, C**4'**), 143.2 (s, C**1'**), 127.7 (s, C**2'**), 124.4 (s, C**3'**), 122.3 (s, C**5**), 104.1 (s, C**2**), 102.7 (s, C**4**), 99.8 (s, C**3**), 52.8 (s, C**6**). HRMS (ASAP) m/z calculated for $[M]^+$ $C_{11}H_7Br_3N_2O_2$ 435.8058; found 435.8062.

3,4-Dibromo-*N*-benzylpyrrole (231)

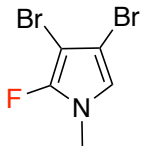


A solution of 2,3,4-tribromo-*N*-benzylpyrrole (7.10 g, 18 mmol) in dry THF (150 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (7.2 mL, 2.5 M in hexanes,

18 mmol) was added dropwise over 15 min and the resulting solution stirred at -78 ºC for 1 h. Aq. HCl (36 mL, 0.5 M) was then added and the solution stirred to room temperature over a period of 1.5 h. Water (200 mL) was added, the aqueous layer extracted with DCM (3 × 100 mL) and the combined organics dried ($MgSO_4$) before being concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel using hexane/Et_2O (100:1) as the eluent and recrystallized from hexane to yield *3,4-dibromo-N-benzylpyrrole* (3.36 g, 59%) as white crystals; Mp 75-77 ºC (lit 59-62 ºC).[163] ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.39 – 7.31 (3H, m, C**3'**H/C**4'**H), 7.18 – 7.10 (2H, m, C**2'**H), 6.68 (2H, s, C**2**H/C**5**H), 4.97 (2H, s, C**6**H). ^{13}C NMR (Chloroform-d, 176 MHz) δ 136.4, 129.1, 128.5, 127.6, 121.2, 98.8, 54.6. The data were consistent with those previously reported in the literature.[163]

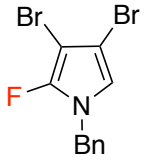
7.3.2 Fluorination of Brominated Pyrrole Substrates

2-Fluoro-3,4-dibromo-*N*-methylpyrrole (198)



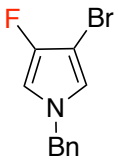
A solution of 2,3,4-tribromo-*N*-methylpyrrole (100 mg, 0.31 mmol) in dry THF (10 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (0.13 mL, 2.5 M in hexanes, 0.31 mmol) was added dropwise over 10 min and the resulting solution stirred at -78 ºC for 1 h. NFSI (99 mg, 0.31 mmol) in dry THF (5 mL) was then added and the solution stirred overnight to room temperature. Water (20 mL) was added, the aqueous layer extracted with DCM (3 × 15 mL) and the combined organics dried ($MgSO_4$) before being concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel using a gradient of hexane/EtOAc (0 – 10% EtOAc) as the eluent to give *2-fluoro-3,4-tribromo-N-methylpyrrole* (33 mg, 43%) as a yellow oil; ^{1}H NMR (Chloroform-d, 400 MHz) δ 6.30 (1H, d, $^4J_{HF}$ 2.2, C**5**H), 3.51 (3H, d, $^4J_{HF}$ 0.8, NCH_3). ^{19}F NMR (Chloroform-d, 376 MHz) δ -138.84 – -138.87 (m). HRMS (ASAP) m/z calculated for $[M+H]^+$ $C_5H_5NBr_2F$ 255.8773; found 255.8789.

2-Fluoro-3,4-dibromo-*N*-benzylpyrrole (203)



A solution of 2,3,4-tribromo-1-benzylpyrrole (3.55 g, 9 mmol) in dry THF (180 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (3.6 mL, 2.5 M in hexanes, 9 mmol) was added dropwise over 10 min and the resulting solution stirred at -78 ºC for 1 h. NFSI (2.84 g, 9 mmol) in dry THF (40 mL) was then added and the solution stirred overnight to room temperature. Water (150 mL) was added, the aqueous layer extracted with DCM (3 × 100 mL) and the combined organics dried ($MgSO_4$) before being concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel using hexane as the eluent to give *2-fluoro-3,4-tribromo-N-benzylpyrrole* (2.10 g, 70 %) as a clear oil which crystallised on storage at -18 ºC; ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.42 – 7.29 (3H, m, C**3'**H/C**4'**H), 7.19 – 7.15 (2H, m, C**2'**H), 6.32 (1H, d, $^{4}J_{HF}$ 2.0, C**5**H), 4.94 (2H, s, C**6**H). ^{19}F NMR (Chloroform-d, 376 MHz) δ -138.35 (d, $^{4}J_{HF}$ 2.0). ^{13}C NMR (Chloroform-d, 176 MHz) δ 143.5 (d, $^{1}J_{CF}$ 260.9, *C*F), 135.5 (s, C**1'**), 129.2 (s, C**3'**), 128.6 (s, C**4'**), 127.5 (s, C**2'**), 111.7 (d, $^{3}J_{CF}$ 1.9, C**5**), 96.4 (d, $^{3}J_{CF}$ 4.3, C**4**), 76.4 (d, $^{2}J_{CF}$ 14.0, C**3**), 49.9 (d, $^{3}J_{CF}$ 0.9, C**6**). HRMS (ASAP) m/z calculated for $[M]^{+}$ $C_{11}H_8NBr_2F$ 330.9007; found 330.8990.

3-Fluoro-4-bromo-*N*-benzylpyrrole (232)

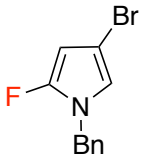


A solution of 3,4-dibromo-*N*-benzylpyrrole (158 mg, 0.5 mmol) in dry THF (10 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (0.20 mL, 2.5 M in hexanes, 0.5 mmol) was added dropwise over 5 min and the resulting solution stirred at -78 ºC for 1 h. NFSI (158 mg, 0.5 mmol) in dry THF (2 mL) was then added dropwise and the

solution stirred to room temperature over a period of 1 h. Water (10 mL) was added and the aqueous layer extracted with Et_2O (3 × 8 mL). The combined organics were washed with brine (15 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel using a gradient of hexane/Et_2O (0-10% Et_2O) as the eluent to yield *3-fluoro-4-bromo-N-benzylpyrrole* (56 mg, 44%) as an off white solid; Mp 51-53 ºC. ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.40 – 7.27 (3H, m, C**3'**H/C**4'**H), 7.18 – 7.10 (2H, m, C**2'**H), 6.47 (1H, dd, $^3J_{HF}$ 3.6, $^4J_{HH}$ 2.8, C**2**H), 6.43 (1H, dd, $^4J_{HF}$ 3.6, $^4J_{HH}$ 2.8, C**5**H), 4.91 (2H, s, C**6**H). ^{19}F NMR (Chloroform-d, 376 MHz) δ -166.07 (app t, $^3J_{HF}$ 3.6, $^4J_{HF}$ 3.6). ^{13}C NMR (Chloroform-d, 101 MHz) δ 149.2 (d, *J* 240.7), 136.7, 129.1, 128.4, 127.4, 118.6 (d, *J* 2.2), 105.2 (d, *J* 26.4), 83.4 (d, *J* 17.8), 54.8. HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{11}H_{10}BrFN$ 253.9981; found 253.9995.

7.3.3 Derivatisation of Fluorinated Pyrrole Substrates

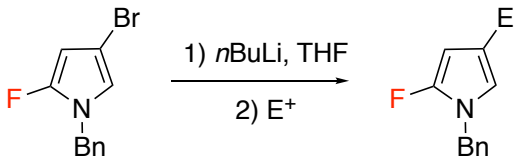
2-Fluoro-4-bromo-*N*-benzylpyrrole (213)



A solution of 2-fluoro-3,4-dibromo-*N*-benzylpyrrole (1.33 g, 4 mmol) in dry THF (40 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (1.6 mL, 2.5 M in hexanes, 4 mmol) was added dropwise over 10 min and the resulting solution stirred at -78 ºC for 1 h. Aq. HCl (8 mL, 0.5 M) was then added and the solution stirred to room temperature over a period of 1 h. Water (100 mL) was added, the aqueous layer extracted with DCM (3 × 50 mL) and the combined organics dried ($MgSO_4$) before being concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel using hexane as the eluent to give *2-fluoro-4-bromo-N-benzylpyrrole* (0.79 g, 78 %) as a clear oil; ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.39 – 7.29 (3H, m, C**3'**H/C**4'**H), 7.20 – 7.15 (2H, m, C**2'**H), 6.22 (1H, dd, $^4J_{HH}$ 2.2, $^4J_{HF}$ 1.4, C**5**H), 5.61 (1H, dd, $^3J_{HF}$ 4.2, $^4J_{HH}$ 2.2, C**3**H), 4.92 (2H, s, C**6**H). ^{19}F NMR (Chloroform-d, 376 MHz) δ -138.97 (dd,

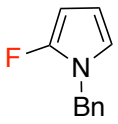
$^{3}J_{HF}$ 4.2, $^{4}J_{HF}$ 1.4). ^{13}C NMR (Chloroform-d, 176 MHz) δ 146.2 (d, $^{1}J_{CF}$ 262.7, *C*F), 136.3 (s, C**1'**), 129.0 (s, C**3'**), 128.2 (s, C**4'**), 127.3 (s, C**2'**), 112.0 (d, $^{3}J_{CF}$ 2.0, C**5**), 93.2 (d, $^{3}J_{CF}$ 9.4, C**4**), 89.2 (d, $^{2}J_{CF}$ 12.3, C**3**), 48.8 (d, $^{3}J_{CF}$ 1.5, C**6**). HRMS (ESI) m/z calculated for $[M+H]^{+}$ $C_{11}H_{10}NBrF$ 253.9981; found 253.9987.

General Procedure A



A solution of 2-fluoro-4-bromo-*N*-benzylpyrrole (128 mg, 0.5 mmol) in dry THF (10 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (0.20 mL, 2.5 M in hexanes, 0.5 mmol) was added dropwise over 5 min and the resulting solution stirred at -78 ºC for 1 h. A solution of the appropriate electrophile (0.9 mmol) in dry THF (2 mL) was then added dropwise and the solution stirred at -78 ºC for 1 h before being quenched with sat. aq. NH_4Cl (10 mL) and allowed to warm to room temperature. The solution was diluted with water (10 mL) and the products extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (15 mL) and brine (15 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel to give the respective product.

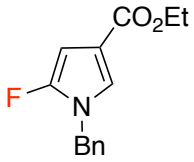
2-Fluoro-*N*-benzylpyrrole (215)



Aq. HCl (1.8 mL, 0.5 M) was reacted using general procedure A. Purification by column chromatography on silica gel using hexane as the eluent gave *2-fluoro-N-benzylpyrrole* (51 mg, 58%) as a clear oil; ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.37 – 7.27 (3H, m, C**3'**H/C**4'**H), 7.17 – 7.11 (2H, m, C**2'**H), 6.18 (1H, ddd, $^{3}J_{HH}$ 3.5, $^{4}J_{HH}$ 2.1, $^{4}J_{HF}$ 1.3,

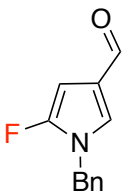
C**5**H), 5.96 (1H, ddd, $^{4}J_{HF}$ 5.1, $^{3}J_{HH}$ 3.8, $^{3}J_{HH}$ 3.5, C**4**H), 5.49 (1H, ddd, $^{3}J_{HF}$ 4.0, $^{3}J_{HH}$ 3.8, $^{4}J_{HH}$ 2.1, C**3**H), 4.96 (2H, s, C**6**H). ^{19}F NMR (Chloroform-d, 376 MHz) δ -142.77 – -142.81 (m). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{11}H_{11}FN$ 176.0876; found 176.0882.

Ethyl 2-fluoro-*N*-benzylpyrrole-3-carboxylate (217)



Ethyl chloroformate (82 mg, 0.9 mmol) was reacted using general procedure A. Purification by column chromatography on silica gel using toluene as the eluent gave *ethyl 2-fluoro-N-benzylpyrrole-3-carboxylate* (88 mg, 71%) as a clear oil; ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.39 – 7.28 (3H, m, C**3'**H/C**4'**H), 7.19 – 7.15 (2H, m, C**2'**H), 6.90 (1H, dd, $^{4}J_{HH}$ 2.2, $^{4}J_{HF}$ 2.1, C**5**H), 5.95 (1H, dd, $^{3}J_{HF}$ 4.2, $^{4}J_{HH}$ 2.2, C**3**H), 4.98 (2H, s, C**6**H), 4.24 (2H, q, $^{3}J_{HH}$ 7.1, $CO_2CH_2CH_3$), 1.31 (3H, t, $^{3}J_{HH}$ 7.1, $CO_2CH_2CH_3$). ^{19}F NMR (Chloroform-d, 376 MHz) δ -140.06 (dd, $^{3}J_{HF}$ 4.2, $^{4}J_{HF}$ 2.1). ^{13}C NMR (Chloroform-d, 101 MHz) δ 164.5 (d, $^{4}J_{CF}$ 3.7, *C*=O), 146.7 (d, $^{1}J_{CF}$ 261.9, *C*F), 135.9 (s, C**1'**), 129.1 (s, C**3'**), 128.4 (s, C**4'**), 127.4 (s, C**2'**), 118.1 (d, $^{3}J_{CF}$ 1.9, C**5**), 113.1 (d, $^{3}J_{CF}$ 5.8, C**4**), 86.7 (d, $^{2}J_{CF}$ 11.0, C**3**), 60.0 (s, $CO_2CH_2CH_3$), 49.3 (d, $^{3}J_{CF}$ 1.4, C**6**), 14.6 (s, $CO_2CH_2CH_3$). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{14}H_{15}FNO_2$ 248.1087; found 248.1085.

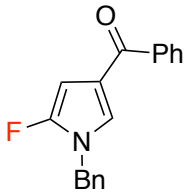
2-Fluoro-*N*-benzylpyrrole-3-carbaldehyde (218)



Ethyl formate (67 mg, 0.9 mmol) was reacted using general procedure A. Purification by column chromatography on silica gel using a gradient of hexane/EtOAc (0-20% EtOAc)

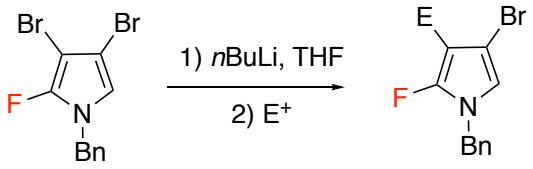
as the eluent gave *ethyl 2-fluoro-N-benzylpyrrole-3-carbaldehyde* (95 mg, 93%) as a pale yellow oil; ^{1}H NMR (Chloroform-d, 400 MHz) δ 9.62 (1H, d, $^{4}J_{HH}$ 3.2, C*H*O), 7.43 – 7.30 (3H, m, C**3'**H/C**4'**H), 7.22 – 7.18 (2H, m, C**2'**H), 6.88 (1H, app t, $^{4}J_{HH}$ 2.2, $^{4}J_{HF}$ 2.2, C**5**H), 6.00 (1H, dd, $^{3}J_{HF}$ 4.2, $^{4}J_{HH}$ 2.2, C**3**H), 5.03 (2H, s, C**6**H). ^{19}F NMR (Chloroform-d, 376 MHz) δ -138.06 – -138.11 (m). ^{13}C NMR (Chloroform-d, 176 MHz) δ 185.2 (d, ^{4}JCF 3.4, *C*=O), 148.4 (d, $^{1}J_{CF}$ 265.7, *C*F), 135.2 (s, C**1'**), 129.3 (s, C**3'**), 128.7 (s, C**4'**), 127.6 (s, C**2'**), 123.3 (d, $^{3}J_{CF}$ 4.3, C**4**), 122.2 (s, C**5**), 84.3 (d, $^{2}J_{CF}$ 10.5, C**3**), 49.6 (d, $^{3}J_{CF}$ 1.3, C**6**). HRMS (ESI) m/z calculated for $[M+H]^{+}$ $C_{12}H_{11}FNO$ 204.0825; found 204.0829.

2-Fluoro-4-benzoyl-*N*-benzylpyrrole (219)



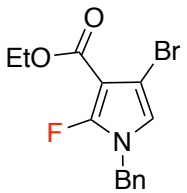
Benzoyl chloride (127 mg, 0.9 mmol) was reacted using general procedure A. Purification by column chromatography on silica gel using a gradient of hexane/EtOAc (0-10% EtOAc) as the eluent gave *2-fluoro-4-benzoyl-N-benzylpyrrole* (46 mg, 33%) as a clear oil;^{1}H NMR (Chloroform-d, 400 MHz) δ 7.80 – 7.76 (2H, m, C**2''**H), 7.55 – 7.49 (1H, m, C**4''**H), 7.47 – 7.42 (2H, m, C**3''**H), 7.39 – 7.30 (3H, m, C**3'**H/C**4'**H), 7.20 – 7.16 (2H, m, C**2'**H), 6.82 (1H, app t, $^{4}J_{HH}$ 2.2, $^{4}J_{HF}$ 2.2, C**5**H), 6.10 (1H, dd, $^{3}J_{HF}$ 4.2, $^{4}J_{HH}$ 2.2, C**3**H), 5.03 (2H, s, C**6**H). ^{19}F NMR (Chloroform-d, 376 MHz) δ -139.47 (dd, $^{3}J_{HF}$ 4.2, $^{4}J_{HF}$ 2.2). ^{13}C NMR (Chloroform-d, 176 MHz) δ 190.3 (d, $^{4}J_{CF}$ 3.1, *C*=O), 147.6 (d, $^{1}J_{CF}$ 264.3, *C*F), 139.4 (s, C**1''**), 135.7 (s, C**1'**), 131.6 (s, C**4''**), 129.2 (s, C**3'**), 129.0 (s, C**2''**), 128.5 (s, C**4'**), 128.4 (s, C**3''**), 127.3 (s, C**2'**), 121.2 (d, $^{3}J_{CF}$ 4.3, C**4**), 120.4 (d, $^{3}J_{CF}$ 2.0, C**5**), 87.3 (d, $^{2}J_{CF}$ 10.3, C**3**), 49.4 (d, $^{3}J_{CF}$ 1.2, C**6**). HRMS (ASAP) m/z calculated for $[M+H]^{+}$ $C_{18}H_{15}FNO$ 280.1138; found 280.1149.

General Procedure B



A solution of 2-fluoro-3,4-dibromo-*N*-benzylpyrrole (167 mg, 0.5 mmol) in dry THF (10 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (0.20 mL, 2.5 M in hexanes, 0.5 mmol) was added dropwise over 5 min and the resulting solution stirred at -78 ºC for 1 h. A solution of the appropriate electrophile (0.9 mmol) in dry THF (2 mL) was then added dropwise and the solution stirred at -78 ºC for 1 h before being quenched with sat. aq. NH_4Cl (10 mL) and allowed to warm to room temperature. The solution was diluted with water (10 mL) and the products extracted with Et_2O (3 $\times$ 8 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (15 mL) and brine (15 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel to give the respective product.

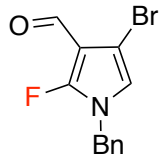
Ethyl 2-fluoro-4-bromo-*N*-benzylpyrrole-3-carboxylate (221)



Ethyl chloroformate (82 mg, 0.9 mmol) was reacted using general procedure B. Purification by column chromatography on silica gel using toluene as the eluent gave *ethyl 2-fluoro-4-bromo-N-benzylpyrrole-3-carboxylate* (138 mg, 85%) as a clear oil; ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.40 – 7.31 (3H, m, C**3'**H/C**4'**H), 7.20 – 7.16 (2H, m, C**2'**H), 6.29 (1H, d, $^4J_{HF}$ 2.4, C**5**H), 4.94 (2H, s, C**6**H), 4.31 (2H, q, $^3J_{HH}$ 7.1, $CO_2CH_2CH_3$), 1.34 (3H, t, $^3J_{HH}$ 7.1, $CO_2CH_2CH_3$). ^{19}F NMR (Chloroform-d, 376 MHz) δ -124.37 (d, $^4J_{HF}$ 2.4). ^{13}C NMR (Chloroform-d, 176 MHz) δ 161.7 (d, $^3J_{CF}$ 5.2, *C*=O), 147.6 (d, $^1J_{CF}$ 277.3, *C*F), 134.9 (s, C**1'**), 129.2 (s, C**3'**), 128.7 (s, C**4'**), 127.6 (s, C**2'**), 113.5 (d, $^3J_{CF}$ 2.5, C**5**), 94.9 (d, $^2J_{CF}$ 5.3, C**3**), 94.7 (d, $^3J_{CF}$ 5.0, C**4**),

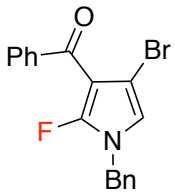
60.2 (s, $CO_2CH_2CH_3$), 49.1 (d, $^3J_{CF}$ 1.3, C**6**), 14.5 (s, $CO_2CH_2CH_3$). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{14}H_{14}FNO_2Br$ 326.0192; found 326.0168.

2-Fluoro-4-bromo-*N*-benzylpyrrole-3-carbaldehyde (222)



Ethyl formate (67 mg, 0.9 mmol) was reacted using general procedure B. Purification by column chromatography on silica gel using a gradient of hexane/EtOAc (0-20% EtOAc) as the eluent gave *2-fluoro-4-bromo-N-benzylpyrrole-3-carbaldehyde* (95 mg, 67%) as a yellow oil; ^{1}H NMR (Chloroform-d, 400 MHz) δ 9.75 (1H, s, C*H*O), 7.42 – 7.35 (3H, m, C**3'**H/C**4'**H), 7.22 – 7.18 (2H, m, C**2'**H), 6.29 (1H, d, $^4J_{HF}$ 2.4, C**5**H), 4.96 (2H, s, C**6**H). ^{19}F NMR (Chloroform-d, 376 MHz) δ -127.90 (s). ^{13}C NMR (Chloroform-d, 176 MHz) δ 182.7 (d, $^3J_{CF}$ 2.6, *C*=O), 148.4 (d, $^1J_{CF}$ 283.7, *C*F), 134.3 (s, C**1'**), 129.4 (s, C**3'**), 129.0 (s, C**4'**), 127.7 (s, C**2'**), 113.9 (d, $^3J_{CF}$ 2.7, C**5**), 103.4 (d, $^3J_{CF}$ 2.7, C**4**), 95.0 (d, $^2J_{CF}$ 6.4, C**3**), 49.2 (d, $^3J_{CF}$ 1.4, C**6**). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{12}H_{10}FNOBr$ 281.9930; found 281.9920.

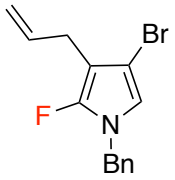
2-Fluoro-3-benzoyl-4-bromo-*N*-benzylpyrrole (223)



Benzoyl chloride (127 mg, 0.9 mmol) was reacted using general procedure B. Purification by column chromatography on silica gel using a gradient of hexane/EtOAc (0-10% EtOAc) as the eluent gave *2-fluoro-3-benzoyl-4-bromo-N-benzylpyrrole* (86 mg, 46%) as an off white solid; Mp 92-93 ºC. ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.84 – 7.76 (2H, m, C**2''**H), 7.60 – 7.51 (1H, m, C**4''**H), 7.50 – 7.40 (2H, m, C**3''**H), 7.43 – 7.30 (3H, m, C**3'**H/C**4'**H), 7.24 – 7.16 (2H, m, C**2'**H), 6.39 (1H, d, $^4J_{HF}$ 2.2, C**5**H), 4.96

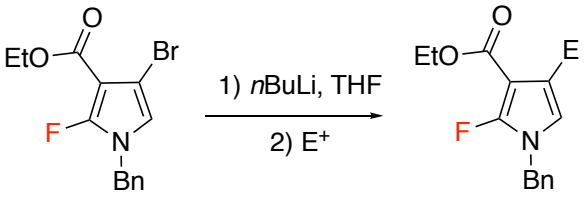
(2H, s, C**6**H). ^{19}F NMR (Chloroform-d, 376 MHz) δ -124.95 – -125.00 (m). ^{13}C NMR (Chloroform-d, 176 MHz) δ 187.7 (d, $^{3}J_{CF}$ 4.0, *C*=O), 146.5 (d, $^{1}J_{CF}$ 275.3, *C*F), 138.9 (s, C**1''**), 134.8 (s, C**1'**), 132.5 (s, C**4''**), 129.31 (d, $^{5}J_{CF}$ 1.7, C**2''**), 129.30 (s, C**3'**), 128.8 (s, C**4'**), 128.3 (s, C**3''**), 127.6 (s, C**2'**), 114.5 (d, $^{3}J_{CF}$ 2.7, C**5**), 102.6 (d, $^{2}J_{CF}$ 6.5, C**3**), 95.2 (d, $^{3}J_{CF}$ 6.1, C**4**), 49.3 (d, $^{3}J_{CF}$ 1.3, C**6**). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{18}H_{14}FNOBr$ 358.0243; found 358.0224. Crystals suitable for x-ray diffraction were grown by slow evaporation from hexane/DCM.

2-Fluoro-3-allyl-4-bromo-*N*-benzylpyrrole (224)



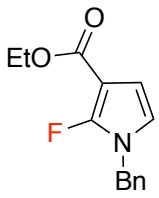
A solution of 2-fluoro-3,4-dibromo-*N*-benzylpyrrole (167 mg, 0.5 mmol) in dry THF (10 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (0.20 mL, 2.5 M in hexanes, 0.5 mmol) was added dropwise over 5 min and the resulting solution stirred at -78 ºC for 1 h. CuCl (5 mg, 10 mol%) was added and the solution stirred for 5 min before the dropwise addition of allyl bromide (109 mg, 0.9 mmol) in dry THF (2 mL) and the solution stirred at -78 ºC for a further 1 h before being quenched with sat. aq. NH_4Cl (10 mL) and allowed to warm to room temperature. The solution was diluted with water (10 mL) and the products extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (15 mL) and brine (15 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by Kugelrohr distillation (100 ºC, 1 mbar) to give *2-fluoro-3-allyl-4-bromo-N-benzylpyrrole* (56 mg, 38 %) as a clear oil; ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.40 – 7.25 (3H, m, C**3'**H/C**4'**H), 7.19 – 7.12 (2H, m, C**2'**H), 6.22 (1H, d, $^{4}J_{HF}$ 1.8, C**5**H), 5.98 – 5.84 (1H, m, CH_2CH=CH_2), 5.09 – 5.00 (2H, m, CH_2CH=CH_2), 4.90 (2H, s, C**6**H), 3.14 (2H, dt, $^{3}J_{HH}$ 5.9, $^{4}J_{HH}$ 1.8, CH_2CH=CH_2). ^{19}F NMR (Chloroform-d, 376 MHz) δ -143.69 (d, $^{4}J_{HF}$ 1.8). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{14}H_{14}FNBr$ 294.0294; found 294.0307.

General Procedure C



A solution of ethyl 2-fluoro-4-bromo-*N*-benzylpyrrole-3-carboxylate (163 mg, 0.5 mmol) in dry THF (10 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (0.20 mL, 2.5 M in hexanes, 0.5 mmol) was added dropwise over 5 min and the resulting solution stirred at -78 ºC for 1 h. A solution of the appropriate electrophile (0.9 mmol) in dry THF (2 mL) was then added dropwise and the solution stirred at -78ºC for 1 h before being quenched with sat. aq. NH_4Cl (10 mL) and allowed to warm to room temperature. The solution was diluted with water (10 mL) and the products extracted with Et_2O (3 $\times$ 8 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (15 mL) and brine (15 mL) before being dried ($MgSO_4$) and concentrated in vacuo. The crude product was then purified by column chromatography on silica gel to give the respective product.

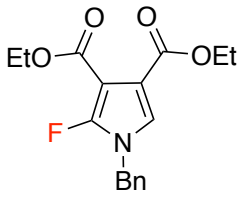
Ethyl 2-fluoro-*N*-benzylpyrrole-3-carboxylate (220)



Aq. HCl (1.8 mL, 0.5 M) was reacted using general procedure C. Purification by column chromatography on silica gel using hexane/EtOAc (0-10% EtOAc) as the eluent gave *ethyl 2-fluoro-N-benzylpyrrole-3-carboxylate* (103 mg, 83%) as a pale yellow oil; ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.38 – 7.28 (3H, m, C**3'**H/C**4'**H), 7.19 – 7.14 (2H, m, C**2'**H), 6.40 (1H, dd, $^4J_{HF}$ 4.6, $^3J_{HH}$ 3.7, C**5**H), 6.16 (1H, dd, $^3J_{HF}$ 3.7, $^4J_{HF}$ 2.1, C**4**H), 4.97 (2H, s, C**6**H), 4.28 (2H, q, $^3J_{HH}$ 7.1, $CO_2CH_2CH_3$), 1.33 (3H, t, $^3J_{HH}$ 7.1, $CO_2CH_2CH_3$). ^{19}F NMR (Chloroform-d, 376 MHz) δ -129.22 (dd, $^3J_{HF}$ 4.6, $^4J_{HF}$ 2.1).

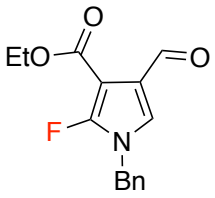
^{13}C NMR (Chloroform-d, 176 MHz) δ 163.1 (d, $^{3}J_{CF}$ 5.0, *C*=O), 148.0 (d, $^{1}J_{CF}$ 274.9, *C*F), 135.8 (s, C**1'**), 129.1 (s, C**3'**), 128.4 (s, C**4'**), 127.3 (s, C**2'**), 112.6 (s, C**4**), 107.4 (d, $^{3}J_{CF}$ 1.6, C**5**), 95.0 (d, $^{2}J_{CF}$ 3.8, C**3**), 59.9 (s, $CO_2CH_2CH_3$), 48.9 (d, $^{3}J_{CF}$ 1.4, C**6**), 14.6 (s, $CO_2CH_2CH_3$). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{14}H_{15}FNO_2$ 248.1087; found 248.1077.

Diethyl 2-fluoro-*N*-benzylpyrrole-3,4-dicarboxylate (225)



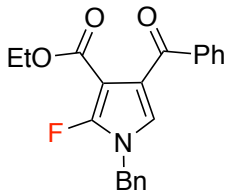
Ethyl chloroformate (82 mg, 0.9 mmol) was reacted using general procedure C. Purification by column chromatography on silica gel using hexane/EtOAc (0-20% EtOAc) as the eluent gave *diethyl 2-fluoro-N-benzylpyrrole-3,4-dicarboxylate* (66 mg, 41%) as a yellow oil; ^{1}H NMR (Chloroform-d, 700 MHz) δ 7.38 – 7.32 (3H, m, C**3'**H/C**4'**H), 7.20 – 7.18 (2H, m, C**2'**H), 6.84 (1H, d, $^{4}J_{HF}$ 3.0, C**5**H), 4.97 (2H, s, C**6**H), 4.30 (2H, q, $^{3}J_{HH}$ 7.1, $CO_2CH_2CH_3$), 4.26 (2H, q, $^{3}J_{HH}$ 7.1, $CO_2CH_2CH_3$), 1.33 (3H, t, $^{3}J_{HH}$ 7.1, $CO_2CH_2CH_3$), 1.30 (3H, t, $^{3}J_{HH}$ 7.1, $CO_2CH_2CH_3$). ^{19}F NMR (Chloroform-d, 376 MHz) δ -128.37 (d, $^{4}J_{HF}$ 3.0). ^{13}C NMR (Chloroform-d, 176 MHz) δ 163.2 (d, $^{4}J_{CF}$ 3.0, *C*=O), 161.9 (d, $^{3}J_{CF}$ 5.1, *C*=O), 148.1 (d, $^{1}J_{CF}$ 275.8, *C*F), 134.7 (s, C**1'**), 129.3 (s, C**3'**), 128.8 (s, C**4'**), 127.7 (s, C**2'**), 118.8 (d, $^{3}J_{CF}$ 1.6, C**5**), 113.4 (d, $^{3}J_{CF}$ 2.2, C**4**), 95.3 (d, $^{2}J_{CF}$ 4.9, C**3**), 60.60 (s, $CO_2CH_2CH_3$), 60.56 (s, $CO_2CH_2CH_3$), 49.4 (d, $^{3}J_{CF}$ 1.2, C**6**), 14.40 (s, $CO_2CH_2CH_3$), 14.39 (s, $CO_2CH_2CH_3$). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{17}H_{19}FNO_4$ 320.1298; found 320.1301.

Ethyl 2-fluoro-4-formyl-*N*-benzylpyrrole-3-carboxylate (226)



Ethyl formate (67 mg, 0.9 mmol) was reacted using general procedure C. Purification by column chromatography on silica gel using hexane/EtOAc (0-20% EtOAc) as the eluent gave *ethyl 2-fluoro-4-formyl-N-benzylpyrrole-3-carboxylate* (63 mg, 43%) as a yellow solid; Mp 83-84 ºC. ^{1}H NMR (Chloroform-d, 400 MHz) δ 10.30 (1H, s, C*H*O), 7.41 – 7.33 (3H, m, C**3'**H/C**4'**H), 7.23 – 7.19 (2H, m, C**2'**H), 6.99 (1H, d, $^{4}J_{HF}$ 3.1, C**5**H), 5.01 (2H, s, C**6**H), 4.34 (2H, q, $^{3}J_{HH}$ 7.1, $CO_2CH_2CH_3$), 1.36 (3H, t, $^{3}J_{HH}$ 7.1, $CO_2CH_2CH_3$). ^{19}F NMR (Chloroform-d, 376 MHz) δ -125.37 (d, $^{4}J_{HF}$ 3.1). ^{13}C NMR (Chloroform-d, 176 MHz) δ 187.7 (t, *J* 2.7, C*H*O), 162.3 (d, $^{3}J_{CF}$ 5.4, $CO_2CH_2CH_3$), 148.6 (d, $^{1}J_{CF}$ 280.3, *C*F), 134.1 (s, C**1'**), 129.4 (s, C**3'**), 129.0 (s, C**4'**), 127.9 (s, C**2'**), 121.4 (s, C**4**), 117.4 (d, $^{3}J_{CF}$ 2.1, C**5**), 95.0 (d, $^{2}J_{CF}$ 2.7, C**3**), 60.7 (s, $CO_2CH_2CH_3$), 49.8 (d, $^{3}J_{CF}$ 1.1, C**6**), 14.5 (s, $CO_2CH_2CH_3$). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{15}H_{15}FNO_3$ 276.1036; found 276.1044.

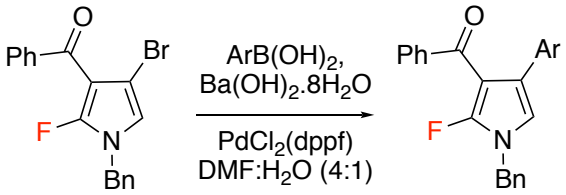
Ethyl 2-fluoro-4-benzoyl-*N*-benzylpyrrole-3-carboxylate (227)



Benzoyl chloride (127 mg, 0.9 mmol) was reacted using general procedure C. Purification by column chromatography on silica gel using hexane/EtOAc (0-20% EtOAc) as the eluent gave *ethyl 2-fluoro-4-benzoyl-N-benzylpyrrole-3-carboxylate* (102 mg, 58%) as a yellow solid; Mp 105-106 ºC. ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.89 – 7.77 (2H, m, ArH), 7.56 – 7.48 (1H, m, ArH), 7.44 – 7.32 (5H, m, ArH), 7.25 – 7.21 (2H, m, ArH), 6.64 (1H, d, $^{4}J_{HF}$ 2.9, C**5**H), 5.03 (2H, s, C**6**H), 3.97 (2H, q, $^{3}J_{HH}$ 7.1, $CO_2CH_2CH_3$), 0.94 (3H, t, $^{3}J_{HH}$ 7.1, $CO_2CH_2CH_3$). ^{19}F NMR (Chloroform-d, 376 MHz) δ -128.31 (d, $^{4}J_{HF}$ 2.9). ^{13}C NMR (Chloroform-d, 151 MHz) δ 190.80 (d, $^{4}J_{CF}$ 2.2, *C*OPh), 161.93 (d, $^{3}J_{CF}$ 5.2, $CO_2CH_2CH_3$), 148.50 (d, $^{1}J_{CF}$ 278.7, *C*F), 138.93 (s, ArC), 134.61 (s, ArC), 132.55 (s, ArC), 129.43 (s, ArC), 129.34 (s, ArC), 128.84 (s, ArC), 128.30 (s, ArC), 127.74 (s, ArC), 121.45 (s, C**4**), 117.24 (d, $^{3}J_{CF}$ 1.3, C**5**), 95.72 (d, $^{2}J_{CF}$ 3.3, C**3**), 60.36 (s, $CO_2CH_2CH_3$), 49.43 (s, C**6**), 13.83 (s, $CO_2CH_2CH_3$). HRMS (ESI) m/z

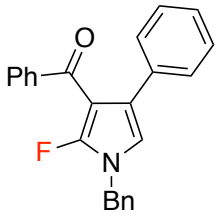
calculated for $[M+H]^+$ $C_{21}H_{19}FNO_3$ 352.1349; found 352.1359. Crystals suitable for x-ray diffraction were grown by slow evaporation from hexane/DCM.

General Procedure D



To a 10 mL microwave vial was charged 2-fluoro-3-benzoyl-4-bromo-*N*-benzylpyrrole (54 mg, 0.15 mmol), $Ba(OH)_2.8H_2O$ (72 mg, 0.23 mmol), $PdCl_2$(dppf) (11 mg, 10 mol%) and the appropriate boronic acid (0.23 mmol). The vial was sealed with a PTFE cap before being evacuated and back filled with argon three times. A degassed mixture of DMF:H_2O (4:1) (3 mL) was then added via syringe and the vial placed in a preheated oil bath at 80 ºC for 10 min. The vial was removed from the oil bath, allowed to cool to temperature before being diluted with EtOAc (10 mL) and water (10 mL). After filtration on a Celite® pad, the layers were separated, and the aqueous layer extracted with EtOAc (10 mL). The combined organics were washed with water (2 × 10 mL) and brine (10 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel to give the respective product.

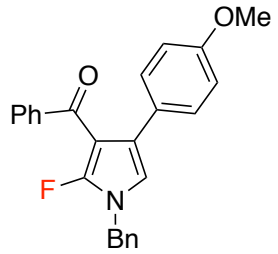
2-Fluoro-3-benzoyl-4-phenyl-*N*-benzylpyrrole (230a)



Phenylboronic acid (28 mg, 0.23 mmol) was reacted using general procedure D. Purification by column chromatography on silica gel using hexane/EtOAc (0-20% EtOAc) as the eluent gave *2-fluoro-3-benzoyl-4-phenyl-N-benzylpyrrole* (51 mg, 96%) as an amorphous solid; ^{1}H NMR (Methylene Chloride-d_2, 700 MHz) δ 7.81 – 7.77 (2H, m, ArH), 7.51 –

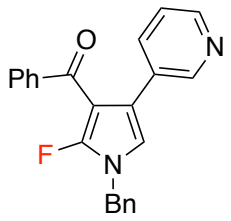
7.47 (1H, m, ArH), 7.43 – 7.34 (5H, m, ArH), 7.30 – 7.28 (2H, m, ArH), 7.27 – 7.25 (2H, m, ArH), 7.24 – 7.20 (2H, m, ArH), 7.18 – 7.15 (1H, m, ArH), 6.43 (1H, d, $^{4}J_{HF}$ 2.4, C**5**H), 5.05 (2H, s, C**6**H). ^{19}F NMR (Methylene Chloride-d$_2$, 376 MHz) δ -128.34 (d, $^{4}J_{HF}$ 2.4). ^{13}C NMR (Methylene Chloride-d$_2$, 176 MHz) δ 189.4 (d, $^{3}J_{CF}$ 3.9, *C*=O), 148.5 (d, $^{1}J_{CF}$ 273.4, *C*F), 140.0 (d, *J* 1.0, ArC), 136.2 (s, ArC), 135.0 (d, *J* 1.5, ArC), 132.6 (s, ArC), 129.7 (d, *J* 1.2, ArC), 129.6 (s, ArC), 128.9 (s, ArC), 128.8 (s, ArC), 128.6 (s, ArC), 128.5 (s, ArC), 128.0 (s, ArC), 126.9 (s, ArC), 124.3 (d, $^{3}J_{CF}$ 2.2, C**4**), 112.5 (d, $^{3}J_{CF}$ 2.0, C**5**), 102.0 (d, $^{2}J_{CF}$ 4.5, C**3**), 49.4 (d, $^{3}J_{CF}$ 1.3, C**6**). HRMS (ESI) m/z calculated for [M+H]$^+$ $C_{24}H_{19}FNO$ 356.1451; found 356.1462.

2-Fluoro-3-benzoyl-4-(4-methoxyphenyl)-*N*-benzylpyrrole (230b)



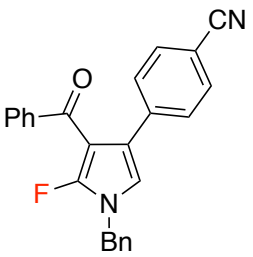
4-Methoxyphenylboronic acid (35 mg, 0.23 mmol) was reacted using general procedure D. Purification by column chromatography on silica gel using hexane/EtOAc (0-20% EtOAc) as the eluent gave *2-fluoro-3-benzoyl-4-(4-methoxyphenyl)-N-benzylpyrrole* (43 mg, 74%) as a yellow oil; ^{1}H NMR (Methylene Chloride-d$_2$, 400 MHz) δ 7.79 – 7.74 (2H, m, ArH), 7.52 – 7.47 (1H, m, ArH), 7.43 – 7.32 (5H, m, ArH), 7.30 – 7.25 (2H, m, ArH), 7.21 – 7.16 (2H, m, ArH), 6.79 – 6.74 (2H, m, ArH), 6.36 (1H, d, $^{4}J_{HF}$ 2.4, C**5**H), 5.03 (2H, s, C**6**H), 3.75 (3H, s, OCH_3). ^{19}F NMR (Methylene Chloride-d$_2$, 376 MHz) δ -128.29 (d, $^{4}J_{HF}$ 2.4). ^{13}C NMR (Methylene Chloride-d$_2$, 176 MHz) δ 189.5 (d, $^{3}J_{CF}$ 3.8, *C*=O), 159.0 (s, ArC), 148.5 (d, $^{1}J_{CF}$ 273.2, *C*F), 140.1 (s, ArC), 136.3 (s, ArC), 132.5 (s, ArC), 129.9 (s, ArC), 129.7 (d, *J* 1.3, ArC), 129.6 (s, ArC), 128.8 (s, ArC), 128.6 (s, ArC), 128.0 (s, ArC), 127.4 (d, *J* 1.3, ArC), 124.0 (d, $^{3}J_{CF}$ 2.2, C**4**), 114.0 (s, ArC), 111.9 (d, $^{3}J_{CF}$ 2.1, C**5**), 101.9 (d, $^{2}J_{CF}$ 4.3, C**3**), 55.7 (s, O*C*H$_3$), 49.3 (s, C**6**). HRMS (ESI) m/z calculated for [M+H]$^+$ $C_{25}H_{21}FNO_2$ 386.1556; found 386.1557.

2-Fluoro-3-benzoyl-4-(3-pyridinyl)-*N*-benzylpyrrole (230c)



3-Pyridinylboronic acid (28 mg, 0.23 mmol) was reacted using general procedure D. Purification by column chromatography on silica gel using hexane/EtOAc (20-50% EtOAc) as the eluent gave *2-fluoro-3-benzoyl-4-(3-pyridinyl)-N-benzylpyrrole* (41 mg, 77%) as a white solid; Mp 71-74 ºC. ^{1}H NMR (Methylene Chloride-d_2, 400 MHz) δ 8.52 (1H, d, *J* 2.3, ArH), 8.39 (1H, dd, *J* 4.8, *J* 1.7, ArH), 7.80 – 7.75 (2H, m, ArH), 7.63 – 7.57 (1H, m, ArH), 7.54 – 7.48 (1H, m, ArH), 7.44 – 7.34 (5H, m, ArH), 7.32 – 7.27 (2H, m, ArH), 7.14 (1H, dd, *J* 7.9, *J* 4.8, ArH), 6.49 (1H, d, $^{4}J_{HF}$ 2.5, C**5**H), 5.06 (2H, s, C**6**H). ^{19}F NMR (Methylene Chloride-d_2, 376 MHz) δ -126.86 (d, $^{4}J_{HF}$ 2.5). ^{13}C NMR (Methylene Chloride-d_2, 176 MHz) δ 189.1 (d, $^{3}J_{CF}$ 3.9, *C*=O), 149.4 (s, ArC), 148.7 (d, $^{1}J_{CF}$ 273.9, *C*F), 148.1 (s, ArC), 139.9 (d, *J* 1.2, ArC), 136.1 (s, ArC), 135.9 (s, ArC), 132.7 (s, ArC), 130.9 (s, ArC), 129.61 (s, ArC), 129.60 (s, ArC), 129.0 (s, ArC), 128.7 (s, ArC), 128.1 (s, ArC), 123.2 (s, ArC), 120.8 (d, $^{3}J_{CF}$ 2.6, C**4**), 113.1 (d, $^{3}J_{CF}$ 2.0, C**5**), 102.1 (d, $^{2}J_{CF}$ 4.8, C**3**), 49.5 (d, $^{3}J_{CF}$ 1.2, C**6**). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{23}H_{18}FN_2O$ 357.1403; found 357.1408. Crystals suitable for x-ray diffraction were grown by slow evaporation from hexane.

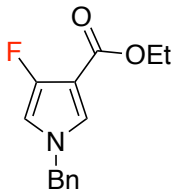
2-Fluoro-3-benzoyl-4-(4-cyanophenyl)-*N*-benzylpyrrole (230d)



4-Cyanophenylboronic acid (34 mg, 0.23 mmol) was reacted using general procedure D. Purification by column chromatography on silica gel using hexane/EtOAc (10-30%

EtOAc) as the eluent gave *2-fluoro-3-benzoyl-4-(4-cyanophenyl)-N-benzylpyrrole* (46 mg, 81%) as an amorphous solid; ^{1}H NMR (Methylene Chloride-d_2, 400 MHz) δ 7.80 – 7.75 (2H, m, ArH), 7.55 – 7.48 (3H, m, ArH), 7.44 – 7.35 (7H, m, ArH), 7.31 – 7.26 (2H, m, ArH), 6.52 (1H, d, $^{4}J_{HF}$ 2.4, C**5**H), 5.06 (2H, s, C**6**H). ^{19}F NMR (Methylene Chloride-d_2, 376 MHz) δ -126.84 (d, $^{4}J_{HF}$ 2.4). ^{13}C NMR (Methylene Chloride-d_2, 151 MHz) δ 189.1 (d, $^{3}J_{CF}$ 3.8, *C*=O), 148.8 (d, $^{1}J_{CF}$ 274.3, *C*F), 139.8 (d, *J* 1.6, ArC), 139.7 (s, ArC), 135.8 (s, ArC), 132.9 (s, ArC), 132.3 (s, ArC), 129.7 (d, *J* 1.3, ArC), 129.6 (s, ArC), 129.2 (s, ArC), 129.0 (s, ArC), 128.7 (s, ArC), 128.1 (s, ArC), 122.7 (d, $^{3}J_{CF}$ 2.7, C**4**), 119.6 (s, ArC), 113.8 (d, $^{3}J_{CF}$ 2.0, C**5**), 110.3 (s, ArC), 102.0 (d, $^{2}J_{CF}$ 5.0, C**3**), 49.6 (d, $^{3}J_{CF}$ 1.3, C**6**). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{25}H_{18}FN_2O$ 381.1403; found 381.1408.

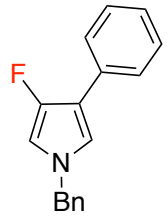
Ethyl 3-fluoro-*N*-benzylpyrrole-4-carboxylate (234)



A solution of 3-fluoro-4-bromo-*N*-benzylpyrrole (101 mg, 0.4 mmol) in dry THF (10 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (0.16 mL, 2.5 M in hexanes, 0.4 mmol) was added dropwise over 5 min and the resulting solution stirred at -78 ºC for 1 h. A solution of ethyl chloroformate (78 mg, 0.7 mmol) in dry THF (2 mL) was then added dropwise and the solution stirred at -78 ºC for 1 h before being quenched with sat. aq. NH_4Cl (10 mL) and allowed to warm to room temperature. The solution was diluted with water (10 mL) and the products extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with brine (15 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel using a gradient of hexane/EtOAc (0-10% EtOAc) as the eluent to yield *ethyl 3-fluoro-N-benzylpyrrole-4-carboxylate* (43 mg, 44%) as a pale yellow oil; ^{1}H NMR (Chloroform-d, 400 MHz) δ 7.38 – 7.32 (3H, m, C**3'**H/C**4'**H), 7.17 – 7.13 (2H, m, C**2'**H), 7.07 (1H, dd, $^{4}J_{HF}$ 3.6, $^{4}J_{HH}$ 2.9, C**5**H), 6.39 (1H, t, $^{3}J_{HF}$ 3.1,

$^{4}J_{HH}$ 2.9, C**2**H), 4.95 (2H, s, C**6**H), 4.28 (2H, q, $^{3}J_{HH}$ 7.1, $CO_2CH_2CH_3$), 1.33 (3H, t, $^{3}J_{HH}$ 7.1, $CO_2CH_2CH_3$). ^{19}F NMR (Chloroform-d, 376 MHz) δ -160.70 – -160.73 (m). ^{13}C NMR (Chloroform-d, 176 MHz) δ 163.1 (d, $^{3}J_{CF}$ 3.6, *C*=O), 150.6 (d, $^{1}J_{CF}$ 250.7, *C*F), 136.0 (s, C**1'**), 129.2 (s, C**3'**), 128.6 (s, C**4'**), 127.5 (s, C**2'**), 123.4 (s, C**5**), 106.3 (d, $^{2}J_{CF}$ 27.3, C**2**), 104.8 (d, $^{2}J_{CF}$ 10.1, C**4**), 60.0 (s, $CO_2CH_2CH_3$), 54.8 (s, C**6**), 14.6 (s, $CO_2CH_2CH_3$). HRMS (ESI) m/z calculated for $[M+H]^+$ $C_{14}H_{15}FNO_2$ 248.1097; found 248.1096.

3-Fluoro-4-phenyl-*N*-benzylpyrrole (235)

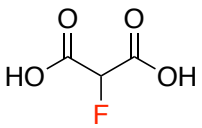


To a 10 mL microwave vial was charged 3-fluoro-4-bromo-*N*-benzylpyrrole (64 mg, 0.25 mmol), $Ba(OH)_2.8H_2O$ (118 mg, 0.38 mmol), $PdCl_2$(dppf) (19 mg, 10 mol%) and phenylboronic acid (46 mg, 0.38 mmol). The vial was sealed with a PTFE cap before being evacuated and back filled with argon three times. A degassed mixture of DMF:H_2O (4:1) (5 mL) was then added via syringe and the vial placed in a preheated oil bath at 80 ºC for 30 min. The vial was removed from the oil bath, allowed to cool to temperature before being diluted with EtOAc (10 mL) and water (10 mL). After filtration on a Celite® pad, the layers were separated, and the aqueous layer extracted with EtOAc (10 mL). The combined organics were washed with water (2 × 10 mL) and brine (10 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel using a gradient of hexane/toluene (0-15% toluene) as the eluent to yield *3-fluoro-4-phenyl-N-benzylpyrrole* (46 mg, 73%) as a yellow oil that solidified on standing; ^{1}H NMR (Methylene Chloride-d_2, 400 MHz) δ 7.57 – 7.51 (2H, m, ArH), 7.40 – 7.30 (5H, m, ArH), 7.23 – 7.16 (3H, m, ArH), 6.78 (1H, dd, $^{4}J_{HF}$ 4.5, $^{4}J_{HH}$ 2.9, C**5**H), 6.54 (1H, t, $^{3}J_{HF}$ 3.0, $^{4}J_{HH}$ 2.9, C**2**H), 4.99 (2H, s, C**6**H). ^{19}F NMR (Methylene Chloride-d_2, 376 MHz) δ -167.31 – -167.36 (m). ^{13}C NMR (Methylene Chloride-d_2, 151 MHz) δ 150.2 (d, $^{1}J_{CF}$ 242.6, *C*F), 138.0 (s, ArC), 133.6

(d, *J* 3.4, ArC), 129.4 (s, ArC), 129.2 (s, ArC), 128.5 (s, ArC), 127.8 (s, ArC), 126.3 (s, ArC), 126.2 (s, ArC), 116.3 (d, $^{3}J_{CF}$ 4.2, C**5**), 112.5 (d, $^{2}J_{CF}$ 10.3, C**4**), 106.4 (d, $^{2}J_{CF}$ 28.4, C**2**), 54.8 (s, C**6**). HRMS (ESI) m/z calculated for $[M+H]^{+}$ $C_{17}H_{15}FN$ 252.1189; found 252.1190.

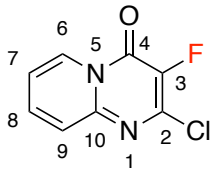
7.4 Experimental to Chapter 4

2-Fluoromalonic acid (262)



To a solution of diethyl fluoromalonate (45.0 g, 253 mmol) in EtOH (500 mL) and H_2O (45 mL) was added LiOH.H_2O (24.3 g, 579 mmol) and the mixture heated to 60 ºC for 16 h before being cooled to room temperature. The resulting solid was filtered, dissolved in H_2O (70 mL) and MTBE (300 mL) and acidified to pH 1 with conc. HCl. The aqueous layer was extracted with MTBE (3 × 150 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo* to give *2-fluoromalonic acid* (30.9 g, 88%) as an off white solid; Mp 70-72 ºC. ^{1}H NMR (Acetone-d_6, 400 MHz) δ 11.45 (2H, s, O*H*), 5.54 (1H, d, $^{2}J_{HF}$ 48.1, C**2**H). ^{19}F NMR (Acetone-d_6, 376 MHz) δ -195.01 (d, $^{2}J_{HF}$ 48.1). ^{13}C NMR (Acetone-d_6, 101 MHz) δ 165.8 (d, $^{2}J_{CF}$ 24.1, C**1**/C**3**), 86.1 (d, $^{1}J_{CF}$ 191.1, C**2**). HRMS (ESI) m/z calculated for $[M-H]^{-}$ $C_3H_2O_4F$ 120.9937; found 120.9914.

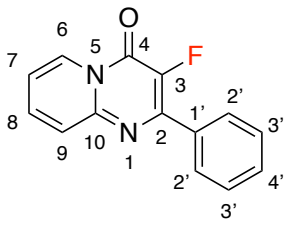
2-Chloro-3-fluoro-4*H*-pyrido[1,2-a]pyrimidin-4-one (284)



To fluoromalonic acid (1.96 g, 16 mmol) and benzyltriethylammonium chloride (7.29 g, 32 mmol) in dry MeCN (20 mL) was added $POCl_3$ (15 mL, 160 mmol) and the mixture heated to 50 ºC under an argon atmosphere. 2-aminopyridine (1.50 g, 16 mmol) in dry

MeCN (10 mL) was then added dropwise and the mixture heated to 80 ºC for 24 h before being allowed to cool to room temperature. MeCN was then removed *in vacuo* upon which a solid began to crystallise. The resulting solid was triturated with water and filtered to give *2-chloro-3-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one* (1.61 g, 51%) as an ochre powder; Mp 192-194 ºC. ^{1}H NMR (DMSO-d$_6$, 700 MHz) δ 8.94 (1H, m, C**6**H), 8.04 (1H, ddd, $^{3}J_{HH}$ 8.6, $^{3}J_{HH}$ 6.8, $^{4}J_{HH}$ 1.4, C**8**H), 7.76 (1H, m, C**9**H), 7.47 (1H, td, $^{3}J_{HH}$ 6.8, $^{4}J_{HH}$ 1.4, C**7**H). ^{19}F NMR (DMSO-d$_6$, 376 MHz) δ -153.25 (s). ^{13}C NMR (DMSO-d$_6$, 176 MHz) δ 150.7 (d, $^{2}J_{CF}$ 25.2, *C*=O), 146.0 (d, $^{4}J_{CF}$ 4.9, C**10**), 141.9 (d, $^{2}J_{CF}$ 16.5, C**2**), 138.0 (d, $^{6}J_{CF}$ 2.4, C**8**), 137.8 (d, $^{1}J_{CF}$ 242.8, *C*F), 127.7 (d, $^{4}J_{CF}$ 4.4, C**6**), 125.3 (d, $^{5}J_{CF}$ 1.1, C**9**), 117.2 (s, C**7**). HRMS (ASAP) m/z calculated for [M+H]$^{+}$ $C_8H_5ClFN_2O$ 199.0074; found 199.0069.

2-Phenyl-3-fluoro-4*H*-pyrido[1,2-a]pyrimidin-4-one (287)

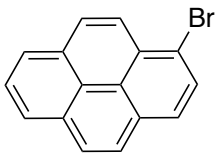


To a solution of 2-chloro-3-fluoro-4*H*-pyrido[1,2-a]pyrimidin-4-one (100 mg, 0.5 mmol), phenylboronic acid (64 mg, 0.53 mmol) in DME (10 mL) was added 1 M $NaHCO_3$ (1.1 mL) and $Pd(PPh_3)_4$ under an argon atmosphere. The mixture was then heated to 80 ºC for 18 h before being allowed to cool to room temperature. The solution was poured into H_2O (15 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (1:1) as the eluent to give *2-phenyl-3-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one* (104 mg, 87%) as an off white solid; Mp 158-159 ºC. ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 8.93 – 8.89 (1H, m, C**6**H), 8.07 – 7.99 (2H, m, C**2'**H), 7.92 (1H, ddd, $^{3}J_{HH}$ 8.5, $^{3}J_{HH}$ 6.9, $^{4}J_{HH}$ 1.6, C**8**H), 7.82 – 7.74 (1H, m, C**9**H), 7.63 – 7.52 (3H, m, C**3'**H/C**4'**H), 7.37 (1H, td, $^{3}J_{HH}$ 6.9, $^{4}J_{HH}$ 1.3, C**7**H). ^{19}F NMR (DMSO-d$_6$, 376 MHz) δ -156.10 (t, $^{5}J_{HF}$ 1.5). ^{13}C NMR (DMSO-d$_6$, 176 MHz) δ 151.6 (d, $^{2}J_{CF}$ 26.4, *C*=O), 146.3 (d, $^{4}J_{CF}$ 5.0, C**10**), 145.9 (d,

$^{2}J_{CF}$ 8.4, C**2**), 140.4 (d, $^{1}J_{CF}$ 246.1), 136.1 (d, $^{6}J_{CF}$ 2.3, C**8**), 133.5 (d, $^{3}J_{CF}$ 5.5, C**1'**), 130.6 (s, C**3'**), 129.0 (d, $^{4}J_{CF}$ 6.4, C**2'**), 128.7 (s, C**4'**), 127.0 (d, $^{4}J_{CF}$ 4.4, C**6**), 126.2 (s, C**9**), 116.2 (s, C**7**). HRMS (ASAP) m/z calculated for $[M+H]^+$ $C_{14}H_{10}FN_2O$ 241.0777; found 241.0780.

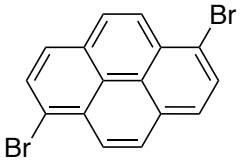
7.5 Experimental to Chapter 5

1-Bromopyrene (291)



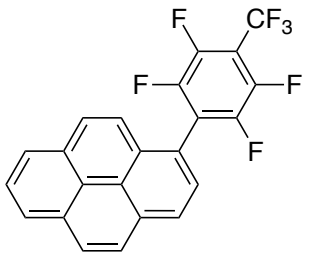
To a methanol/ether (1:1) solution of pyrene (2.02 g, 10 mmol) and hydrobromic acid (1.25 mL, 48 wt% aq., 11 mmol) was slowly added hydrogen peroxide (1.05 mL, 30 wt% aq., 10 mmol) over a period of 15 min and stirred at room temperature for 15 h. The solvent was removed and the product partitioned between DCM (100 mL) and water (100 mL). The aqueous layer extracted with DCM (2 × 50 mL) and the combined organic extracts washed with saturated sodium bicarbonate solution (2 × 100 mL) and saturated brine solution (100 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane as the eluent to yield *1-bromopyrene* (0.97 g, 35%) as a white solid; Mp 98-101 ºC (lit 102-105 ºC).[164] ^{1}H NMR (400 MHz, Chloroform-d) 8.40 (1H, d, $^{3}J_{HH}$ 9.2), 8.24 – 8.16 (3H, m), 8.12 (1H, d, $^{3}J_{HH}$ 9.3), 8.07 – 7.92 (4H, m). ^{13}C NMR (101 MHz, Chloroform-d) 131.2, 131.0, 130.7, 130.1, 129.7, 129.0, 127.8, 127.2, 126.6, 126.0, 125.9, 125.8, 125.6, 125.6, 120.0. HRMS (ASAP) m/z calculated for $[M]^+$ $C_{16}H_9Br$ 279.9888; found 279.9875.

1,6-Dibromopyrene (292)



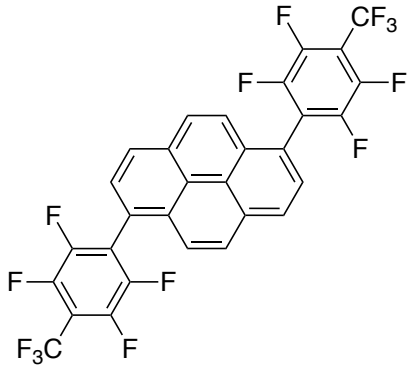
To a solution of pyrene (1.26 g, 5 mmol) in dry DCM (40 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (DBMH) (1.54 g, 5.5 mmol) and stirred at room temperature for 48 h. The resulting precipitate was filtered, washed with EtOH (10 mL) and twice recrystallised from toluene to give *1,6-dibromopyrene* (0.18 g, 10%) as a white solid; Mp 224-226 ºC (lit. 230-231 ºC).[165] ^{1}H NMR (Chloroform-d, 400 MHz) δ 8.46 (2H, d, $^{3}J_{HH}$ 9.2), 8.27 (2H, d, $^{3}J_{HH}$ 8.2), 8.12 (2H, d, $^{3}J_{HH}$ 9.2), 8.06 (2H, d, $^{3}J_{HH}$ 8.2). ^{13}C NMR (Chloroform-d, 101 MHz) δ 130.90, 130.60, 129.86, 128.84, 126.49, 126.15, 125.41, 120.95. HRMS (ASAP) m/z calculated for $[M]^{+}$ $C_{16}H_8Br_2$ 357.8993; found 357.9018.

1-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)pyrene (294)



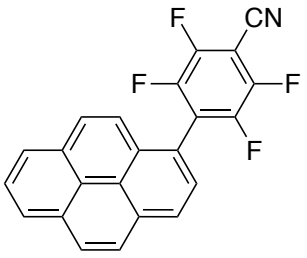
A solution of 1-bromopyrene (0.42 g, 1.5 mmol) in dry THF (15 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (0.88 mL, 2.5 M in hexanes, 2.2 mmol) was added dropwise over 15 min and the solution stirred at -78 ºC for 2 h. Octafluorotoluene (0.89 g, 3.75 mmol) was then added and the solution stirred overnight to room temperature before quenching with water (50 mL) and extracted with DCM (3 × 30 mL). The combined organic extracts were washed with water (100 mL) and saturated brine solution (100 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then recrystallized from hexane/DCM to yield *1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pyrene* (0.31 g, 49 %) as a green solid; Mp 214-216 ºC. ^{1}H NMR (400 MHz, Chloroform-d) 8.34 – 8.03 (7H, m), 7.94 (1H, d, $^{3}J_{HH}$ 7.9), 7.73 (1H, dt, $^{3}J_{HH}$ 9.2, $^{5}J_{HF}$ 2.1). ^{19}F NMR (376 MHz, Chloroform-d) -56.09 (3F, t, $^{4}J_{FF}$ 21.7), -137.35 – -137.56 (2F, m), -140.09 – -140.47 (2F, m). HRMS (ASAP) m/z calculated for $[M]^{+}$ $C_{23}H_9F_7$ 418.0589; found 418.0592.

1,6-Di(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pyrene (295)



A suspension of 1,6-dibromopyrene (0.72 g, 2 mmol) in dry THF (30 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (2.4 mL, 2.5 M in hexanes, 6 mmol,) was added dropwise over 15 min and the resulting solution stirred at -78 °C for 2 h. Octafluorotoluene (2.08 g, 8.8 mmol) was then added and the solution stirred overnight to room temperature before quenching with water (100 mL) and extracted with DCM (3 × 100 mL). The combined organic extracts were washed with water (100 mL) and saturated brine solution (100 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel using a gradient of hexane/DCM as the eluent followed by recrystallisation from hexane/DCM to yield *1,6-di(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pyrene* (0.44 g, 35 %) as an off white solid; Mp 305-308 °C. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) 8.42 (2H, d, $^{3}J_{HH}$ 7.9), 8.26 (2H, d, $^{3}J_{HH}$ 9.2), 8.06 (2H, d, $^{3}J_{HH}$ 7.9), 7.88 (2H, dt, $^{3}J_{HH}$ 9.2, $^{5}J_{HF}$ 2.0). ^{19}F NMR (376 MHz, Methylene Chloride-d_2) -56.56 (6F, t, $^{4}J_{FF}$ 21.7), -138.13 – -138.28 (4F, m), -140.78 – -141.11 (4F, m). HRMS (ASAP) m/z calculated for $[M]^+$ $C_{30}H_8F_{14}$ 634.0402; found 634.0413.

1-(2,3,5,6-Tetrafluorobenzonitrile)pyrene (297)



A solution of 1-bromopyrene (0.84 g, 3 mmol) in dry THF (30 mL) was cooled to -78 ºC under an argon atmosphere. *n*BuLi (1.76 mL, 2.5 M in hexanes, 4.4 mmol,) was added dropwise over 15 min and the solution stirred at -78 °C for 2 h. Pentafluorobenzonitrile (1.45 g, 7.5 mmol) was then added and the solution stirred overnight to room temperature before quenching with water (100 mL) and extracted with DCM (3 × 50 mL). The combined organic extracts were washed with water (100 mL) and saturated brine solution (100 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then recrystallized from hexane/DCM to yield 1-(2,3,5,6-tetrafluorobenzonitrile)pyrene (0.42 g, 37 %) as a yellow solid; Mp 204-207 ºC. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.32 – 8.06 (7H, m), 7.92 (1H, d, $^3J_{HH}$ 7.9), 7.69 (1H, dt, $^3J_{HH}$ 9.2, $^5J_{HF}$ 2.1). ^{19}F NMR (376 MHz, Chloroform-d) δ -132.00 – -132.15 (2F, m), -135.88 – -136.03 (2F, m). HRMS (ASAP) m/z calculated for $[M]^+$ $C_{23}H_9F_4N$ 375.0671; found 375.0662.

References

[1] J. Fried, E. F. Sabo, *J. Am. Chem. Soc.*, 1954, **76**, 1455–1456.

[2] C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven, J. Scheiner, *Nature*, 1957, **179**, 663–666.

[3] P. Kirsch in *Mod. Fluoroorg. Chem.*, Wiley-VCH Verlag GmbH & Co. KGaA, 2013, pp. 299–350.

[4] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330.

[5] A. Harsanyi, G. Sandford, *Org. Process Res. Dev.*, 2014, **18**, 981–992.

[6] J. Hu, Y. Zeng, *Reports Org. Chem.*, 2015, **5**, 19–39.

[7] E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 2832–2842.

[8] B. R. Smith, C. M. Eastman, J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 9764–9773.

[9] Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.*, 2016, **116**, 422–518.

[10] A. M. Shestopalov, A. A. Shestopalov, L. A. Rodinovskaya, A. V. Gromova in *Fluorinated Heterocycl. Compd. Synth. Chem. Appl.*, V. A. Petrov (Ed.), John Wiley & Sons, Inc., 2009, pp. 243–271.

[11] A. Shestopalov, L. Rodinovskaya, V. Mortikov, A. Fedorov in *Fluor. Heterocycl. Chem. Vol. 2 6-Membered Heterocycles*, V. Nenajdenko (Ed.), Springer International Publishing, 2014, pp. 1–58.

[12] T. Kosjek, E. Heath in *Halogenated Heterocycles Synth. Appl. Environ.*, Vol. 27 of *Topics in Heterocyclic Chemistry*, J. Iskra (Ed.), Springer Berlin Heidelberg, 2012, pp. 219–246.

[13] A. Gakh in *Halogenated Heterocycles Synth. Appl. Environ.*, Vol. 27 of *Topics in Heterocyclic Chemistry*, J. Iskra (Ed.), Springer Berlin Heidelberg, 2012, pp. 33–63.

[14] G. C. Finger, L. D. Starr, *J. Am. Chem. Soc.*, 1959, **81**, 2674–2675.

[15] G. C. Finger, L. D. Starr, D. R. Dickerson, H. S. Gutowsky, J. Hamer, *J. Org. Chem.*, 1963, **28**, 1666–1668.

[16] T. Fukuhara, N. Yoneda, A. Suzuki, *J. Fluorine Chem.*, 1988, **38**, 435–438.

[17] O. P. Shkurko, S. G. Baram, V. P. Mamaev, *Chem. Heterocycl. Compd.*, 1972, **8**, 1159–1162.

[18] E. D. Bergmann, S. Cohen, I. Shahak, *J. Chem. Soc.*, 1959, **1**, 3278.

[19] A. Takaoka, M. K. Ibrahim, S. R. F. Kagaruki, N. Ishikawa, *Nippon Kagaku Kaishi*, 1985, 2169–2176.

[20] A. Harsanyi, G. Sandford, *Green Chem.*, 2015, **17**, 3000–3009.

[21] P. D. Schuman, P. Tarrant, D. A. Warner, G. Westmoreland, *US 3954758*, 1976.

[22] S. E. de Laszlo, N. J. Liverton, G. S. Ponticello, H. G. Selnick, N. B. Mantlo, *US 5837719*, 1998.

[23] H. Onda, H. Toi, Y. Aoyama, H. Ogoshi, *Tetrahedron Lett.*, 1985, **26**, 4221–4224.

[24] W. Ando, D. Bellus, U. Bergsträßer, D. Black, H. Heydt, B. König, G. Maas, F. Mathey, M. Regitz, J. Schatz, *Science of Synthesis: Houben-Weyl Methods of*

Molecular Transformations Vol. 9: Fully Unsaturated Small-Ring Heterocycles and Monocyclic Five-Membered Hetarenes with One Heteroatom, Thieme, 2014.

[25] S. Fornarini, G. Cerichelli, M. E. Crestoni, *Gazz. Chim. Ital.*, 1990, **120**, 749–755.

[26] J. Wang, A. Scott, *Tetrahedron Lett.*, 1994, **35**, 3679–3682.

[27] F. C. Gozzo, D. R. Ifa, M. N. Eberlin, *J. Org. Chem.*, 2000, **65**, 3920–3925.

[28] Y. Zhang, K. Shibatomi, H. Yamamoto, *Synlett*, 2005, 2837–2842.

[29] K. Hiramatsu, H. Tamamura, *Eur. J. Org. Chem.*, 2016, 3491–3494.

[30] K. D. Barnes, Y. Hu, D. A. Hunt, *Synth. Commun.*, 1994, **24**, 1749–1755.

[31] A. Bondon, E. Porhiel, C. Pebay, L. Thouin, J. Leroy, C. Moinet, *Electrochim. Acta*, 2001, **46**, 1899–1903.

[32] J. Leroy, E. Porhiel, A. Bondon, *Tetrahedron*, 2002, **58**, 6713–6722.

[33] S. Yamada, A. Gavryushin, P. Knochel, *Angew. Chemie Int. Ed.*, 2010, **49**, 2215–2218.

[34] E. Dvornikova, M. Bechcicka, K. Kamieńska-Trela, A. Krówczyński, *J. Fluorine Chem.*, 2003, **124**, 159–168.

[35] M. B. Wallace, M. E. Adams, T. Kanouni, C. D. Mol, D. R. Dougan, V. A. Feher, S. M. O'Connell, L. Shi, P. Halkowycz, Q. Dong, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4156–4158.

[36] S. Martín-Santamaría, M. A. Carroll, C. M. Carroll, C. D. Carter, H. S. Rzepa, D. A. Widdowson, V. W. Pike, *Chem. Commun.*, 2000, 649–650.

[37] M. S. McCammant, S. Thompson, A. F. Brooks, S. W. Krska, P. J. H. Scott, M. S. Sanford, *Org. Lett.*, 2017, **19**, 3939–3942.

[38] J. Leroy, C. Wakselman, *Tetrahedron Lett.*, 1994, **35**, 8605–8608.

[39] E. K. Woller, V. V. Smirnov, S. G. DiMagno, *J. Org. Chem.*, 1998, **63**, 5706–5707.

[40] G. Buhr, *Chem. Ber.*, 1973, **106**, 3544–3558.

[41] Z.-M. Qiu, D. J. Burton, *Tetrahedron Lett.*, 1994, **35**, 4319–4322.

[42] S. K. Kim, C. Jun, K. Kwak, K. Park, K. Chai, *Bull. Korean Chem Soc.*, 2007, **28**, 2324–2328.

[43] Z.-M. Qui, D. J. Burton, *Tetrahedron Lett.*, 1995, **36**, 5119–5122.

[44] B.-M. Kim, Q.-Z. San, L. R. Bhatt, S.-K. Kim, K.-Y. Chai, *Bull. Korean Chem Soc.*, 2010, **31**, 31–34.

[45] H. Uno, K. Sakamoto, T. Tominaga, N. Ono, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 1441–1448.

[46] H. Takaya, S. Kojima, S. I. Murahashi, *Org. Lett.*, 2001, **3**, 421–424.

[47] Y. Wang, S. Zhu, *Org. Lett.*, 2003, **5**, 745–748.

[48] T. Xu, X. Mu, H. Peng, G. Liu, *Angew. Chemie Int. Ed.*, 2011, **50**, 8176–8179.

[49] T. Cogswell, C. Donald, R. Marquez, *Org. Biomol. Chem.*, 2016, **14**, 183–190.

[50] M. S. Novikov, A. F. Khlebnikov, E. S. Sidorina, R. R. Kostikov, *J. Fluorine Chem.*, 1998, **90**, 117–119.

[51] M. S. Novikov, A. F. Khlebnikov, E. S. Sidorina, R. R. Kostikov, *J. Chem. Soc. Perkin Trans. 1*, 2000, 231–237.

[52] A. F. Khlebnikov, M. S. Novikov, S. A. Dolgikh, J. Magull, *Arkivoc*, 2008, 94.

[53] T.-P. Yang, J.-H. Lin, Q.-Y. Chen, J.-C. Xiao, *Chem. Commun.*, 2013, **49**, 9833.

[54] L. Demange, A. Ménez, C. Dugave, *Tetrahedron Lett.*, 1998, **39**, 1169–1172.

[55] R. Surmont, G. Verniest, F. Colpaert, G. Macdonald, J. W. Thuring, F. Deroose, N. De Kimpe, *J. Org. Chem.*, 2009, **74**, 1377–1380.

[56] M. El Borai, A. H. Moustafa, M. Anwar, E. I. Abdel Hay, *Pol. J. Chem.*, 1981, **55**, 1659–1665.

[57] K. Albertshofer, N. S. Mani, *J. Org. Chem.*, 2016, **81**, 1269–1276.

[58] M. R. Bryce, R. D. Chambers, S. T. Mullins, A. Parkin, *ChemInform*, 1987, **18**.

[59] J. C. Sloop, J. L. Jackson, R. D. Schmidt, *Heteroat. Chem.*, 2009, **20**, 341–345.

[60] Z. Jiang, T. Ni, C. Wei, S. Tian, Y. Li, L. Dai, H. Liu, D. Zhang, *Synlett*, 2012, **24**, 215–218.

[61] X. Yuan, J.-F. Yao, Z.-Y. Tang, *Org. Lett.*, 2017, **19**, 1410–1413.

[62] J. Breen, G. Sandford, B. Patel, J. Fray, *Synlett*, 2014, **26**, 51–54.

[63] K. L. Kirk, L. A. Cohen, *J. Am. Chem. Soc.*, 1971, **93**, 3060–3061.

[64] K. L. Kirk, L. A. Cohen, *J. Org. Chem.*, 1973, **38**, 3647–3648.

[65] B. Dolensky, Y. Takeuchi, L. A. Cohen, K. L. Kirk, *J. Fluorine Chem.*, 2001, **107**, 147–148.

[66] K. Takahashi, K. L. Kirk, L. A. Cohen, *J. Org. Chem.*, 1984, **49**, 1951–1954.

[67] F. Fabra, J. Vilarrasa, J. Coll, *J. Heterocycl. Chem.*, 1978, **15**, 1447–1449.

[68] F. Fabra, E. Fos, J. Vilarrasa, *Tetrahedron Lett.*, 1979, **20**, 3179–3180.

[69] E. C. Coad, H. Liu, P. G. Rasmussen, *Tetrahedron*, 1999, **55**, 2811–2826.

[70] H. Sun, S. G. DiMagno, *Chem. Commun.*, 2007, 528–529.

[71] S. Pazenok, H. M. Thomas, F. Volz, *WO 2016174121*, 2016.

[72] K. Burger, K. Geith, D. Hübl, *Synthesis*, 1988, 189–194.

[73] J. R. Breen, G. Sandford, D. S. Yufit, J. A. K. Howard, J. Fray, B. Patel, *Beilstein J. Org. Chem.*, 2011, **7**, 1048–1054.

[74] R. Surmont, G. Verniest, N. De Kimpe, *Org. Lett.*, 2010, **12**, 4648–4651.

[75] J. Ichikawa, M. Kobayashi, Y. Noda, N. Yokota, K. Amano, T. Minami, *J. Org. Chem.*, 1996, **61**, 2763–2769.

[76] J. Qian, Y. Liu, J. Zhu, B. Jiang, Z. Xu, *Org. Lett.*, 2011, **13**, 4220–4223.

[77] A. Prieto, D. Bouyssi, N. Monteiro, *J. Org. Chem.*, 2017, **82**, 3311–3316.

[78] B. Troegel, T. Lindel, *Org. Lett.*, 2012, **14**, 468–71.

[79] P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent, C.-H. Wong, *Angew. Chem. Int. Ed. Engl.*, 2004, **44**, 192–212.

[80] T. H. Chao, J. March, *J. Polym. Sci. Part A Polym. Chem.*, 1988, **26**, 743–753.

[81] J. K. Howard, K. J. Rihak, A. C. Bissember, J. A. Smith, *Chem. - An Asian J.*, 2016, **11**, 155–167.

[82] R. E. Banks, N. J. Lawrence, A. L. Popplewell, *Synlett*, 1994, 831–832.

[83] M. Krayer, T. Balasubramanian, C. Ruzié, M. Ptaszek, D. L. Cramer, M. Taniguchi, J. S. Lindsey, *J. Porphyr. Phthalocyanines*, 2009, **13**, 1098–1110.

[84] E. M. Beck, N. P. Grimster, R. Hatley, M. J. Gaunt, *J. Am. Chem. Soc.*, 2006, **128**, 2528–2529.

[85] M. Kakushima, P. Hamel, R. Frenette, J. Rokach, *J. Org. Chem.*, 1983, **48**, 3214–3219.

[86] G. Sandford, *J. Fluorine Chem.*, 2007, **128**, 90–104.

[87] T. T. Dang, R. Ahmad, T. T. Dang, H. Reinke, P. Langer, *Tetrahedron Lett.*, 2008, **49**, 1698–1700.

[88] A. Wakamiya, N. Sugita, S. Yamaguchi, *Chem. Lett.*, 2008, **37**, 1094–1095.

[89] S.-M. T. Toguem, O. Fatunsin, A. Villinger, P. Langer, *Tetrahedron Lett.*, 2011, **52**, 3732–3735.

[90] S.-M. Toguem, P. Langer, *Synlett*, 2011, 513–516.

[91] S. Schröter, T. Bach, *Synlett*, 2005, 1957–1959.

[92] T. Bach, S. Schröter, *Heterocycles*, 2007, **74**, 569.

[93] F. Ullah, T. Dang, J. Heinicke, A. Villinger, P. Langer, *Synlett*, 2009, 838–842.

[94] S.-M. T. Toguem, I. Knepper, P. Ehlers, T. T. Dang, T. Patonay, P. Langer, *Adv. Synth. Catal.*, 2012, **354**, 1819–1826.

[95] J. Shi, I. Murtaza, S. Shao, X. Zhu, Y. Zhao, M. Zhu, O. Goto, H. Meng, *Sci. China Chem.*, 2017, **60**, 90–98.

[96] S. T. Handy, Y. Zhang, *Chem. Commun.*, 2006, 299–301.

[97] E. A. John, P. Pollet, L. Gelbaum, J. Kubanek, *J. Nat. Prod.*, 2004, **67**, 1929–1931.

[98] F. Faigl, S. Deák, Z. Mucsi, T. Hergert, L. Balázs, B. Sándor, B. Balázs, T. Holczbauer, M. Nyerges, B. Mátravölgyi, *Tetrahedron*, 2016, **72**, 5444–5455.

[99] M. G. Banwell, B. L. Flynn, E. Hamel, D. C. R. Hockless, *Chem. Commun.*, 1997, **2**, 207–208.

[100] B. L. Bray, P. H. Mathies, R. Naef, D. R. Solas, T. T. Tidwell, D. R. Artis, J. M. Muchowski, *J. Org. Chem.*, 1990, **55**, 6317–6328.

[101] H. M. Gilow, D. E. Burton, *J. Org. Chem.*, 1981, **46**, 2221–2225.

[102] M. Schnürch, M. Spina, A. F. Khan, M. D. Mihovilovic, P. Stanetty, *Chem. Soc. Rev.*, 2007, **36**, 1046–1057.

[103] Z. Zou, Z. Deng, X. Yu, M. Zhang, S. Zhao, T. Luo, X. Yin, H. Xu, W. Wang, *Sci. China Chem.*, 2012, **55**, 43–49.

[104] G. Bartoli, G. Palmieri, M. Bosco, R. Dalpozzo, *Tetrahedron Lett.*, 1989, **30**, 2129–2132.

[105] T. Fukuda, T. Ohta, E.-i. Sudo, M. Iwao, *Org. Lett.*, 2010, **12**, 2734–2737.

[106] E. Differding, G. M. Rüegg, *Tetrahedron Lett.*, 1991, **32**, 3815–3818.

[107] E. Differding, M. Wehrli, *Tetrahedron Lett.*, 1991, **32**, 3819–3822.

[108] Y. Ikenoue, Y. Saida, M.-A. Kira, H. Tomozawa, H. Yashima, M. Kobayashi, *J. Chem. Soc. Chem. Commun.*, 1990, 1694.

[109] X. Wu, T. A. Chen, L. Zhu, R. D. Rieke, *Tetrahedron Lett.*, 1994, **35**, 3673–3674.

[110] R. G. Pearson, *J. Am. Chem. Soc.*, 1963, **85**, 3533–3539.

[111] T. Fukuda, E.-i. Sudo, K. Shimokawa, M. Iwao, *Tetrahedron*, 2008, **64**, 328–338.

[112] L. Ghosez, C. Franc, F. Denonne, C. Cuisinier, R. Touillaux, *Can. J. Chem.*, 2001, **79**, 1827–1839.

[113] C. E. Inman, R. E. Oesterling, E. A. Tyczkowski, *J. Am. Chem. Soc.*, 1958, **80**, 6533–6535.

[114] O. Lerman, S. Rozen, *J. Org. Chem.*, 1983, **48**, 724–727.

[115] S. T. Purrington, W. A. Jones, *J. Org. Chem.*, 1983, **48**, 761–762.

[116] W. E. Barnette, *J. Am. Chem. Soc.*, 1984, **106**, 452–454.

[117] S. Singh, D. D. DesMarteau, S. S. Zuberi, M. Witz, H. N. Huang, *J. Am. Chem. Soc.*, 1987, **109**, 7194–7196.

[118] D. S. Reddy, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chemie Int. Ed.*, 2008, **47**, 164–168.

[119] P. Kirsch, A. Hahn, R. Fröhlich, G. Haufe, *Eur. J. Org. Chem.*, 2006, 4819–4824.

[120] T. A. Miller, D. L. Sloman, M. G. Stanton, K. J. Wilson, D. J. Witter, *WO 2007087129*, 2007.

[121] J. Close, R. W. Heidebrecht, S. Kattar, T. A. Miller, D. Sloman, M. G. Stanton, P. Tempest, D. J. Witter, *WO 2007055941*, 2007.

[122] T. Müh, P. Fiedler, H. Weintritt, W. Westerkamp, A. Reinecke, *WO 2002016304*, 2002.

[123] A. Günther, H. Weintritt, S. Böhm, *WO 2005019154*, 2005.

[124] M. Braun, C. Brosch, *WO 2002050838*, 2002.

[125] N. Ishikawa, A. Takaoka, *Chem. Lett.*, 1981, **10**, 107–110.

[126] N. Ishikawa, A. Takaoka, M. Ibrahim, *J. Fluorine Chem.*, 1984, **25**, 203–212.

[127] G. Romeder in *Encycl. Reagents Org. Synth.*, John Wiley & Sons, Chichester, UK, 2001.

[128] E. D. Bergmann, S. Cohen, I. Shahak, *J. Chem. Soc.*, 1959, 3286–3289.

[129] G. Quin, B. Norton, X. Liao, A. N. Knox, Y. Fang, J. Lee, J. C. Dreabit, S. B. Christiensen, A. B. Benowitz, K. M. Aubart, *WO 2009061879*, 2009.

[130] Y. Zhao, L. Zhu, D. P. Provencal, T. A. Miller, C. O'Bryan, M. Langston, M. Shen, D. Bailey, D. Sha, T. Palmer, T. Ho, M. Li, *Org. Process Res. Dev.*, 2012, **16**, 1652–1659.

[131] B. Li, Z. Zhang, M. Mangano, *Org. Process Res. Dev.*, 2008, **12**, 1273–1275.

[132] I. Hermecz, Z. Mészáros, *Med. Res. Rev.*, 1988, **8**, 203–230.

[133] R. L. Smith, R. J. Barrett, E. Sanders-Bush, *J. Pharmacol. Exp. Ther.*, 1995, **275**, 1050–1057.

[134] I. Hermecz, T. Breining, Z. Meszaros, B. Podanyi, L. Pusztay, K. Simon, P. Dvortsak, L. Seres, *Acta Chim. Acad. Sci. Hung.*, 1986, **122**, 135–145.

[135] C. Fenton, L. J. Scott, *CNS Drugs*, 2005, **19**, 429–444.

[136] Y. Yanagihara, H. Kasai, T. Kawashima, T. Shida, *Jpn. J. Pharmacol.*, 1988, **48**, 91–101.

[137] C. La Motta, S. Sartini, L. Mugnaini, F. Simorini, S. Taliani, S. Salerno, A. M. Marini, F. Da Settimo, A. Lavecchia, E. Novellino, M. Cantore, P. Failli, M. Ciuffi, *J. Med. Chem.*, 2007, **50**, 4917–4927.

[138] U. Mane, H. Li, J. Huang, R. Gupta, S. Nadkarni, R. Giridhar, P. Naik, M. Yadav, *Bioorg. Med. Chem.*, 2012, **20**, 6296–6304.

[139] T. George, C. L. Kaul, R. S. Grewal, R. Tahilramani, *J. Med. Chem.*, 1971, **14**, 913–915.

[140] Á. Ábrahám, Z. Baranyai, G. Gyulai, E. Pári, K. Horváti, S. Bosze, É. Kiss, *Colloids Surf. B. Biointerfaces*, 2016, **147**, 106–115.

[141] A. E. Chichibabin, *Chem. Ber.*, 1924, **57**, 1168–1172.

[142] M. Abass, A. S. Mayas, *Heteroat. Chem.*, 2007, **18**, 19–27.

[143] H. Bregman, J. L. Buchanan, N. Chakka, E. F. Dimauro, H. Gunaydin, P. A. Guzman, Z. Hua, X. Huang, *WO 2014036022*, 2014.

[144] R. Cassis, R. Tapia, J. A. Valderrama, *Synth. Commun.*, 1985, **15**, 125–133.

[145] A. F. Stepan, M. M. Claffey, M. R. Reese, G. Balan, G. Barreiro, J. Barricklow, M. J. Bohanon, B. P. Boscoe, G. D. Cappon, L. K. Chenard, J. Cianfrogna, L. Chen, K. J. Coffman, S. E. Drozda, J. R. Dunetz, S. Ghosh, X. Hou, C. Houle, K. Karki, J. T. Lazzaro, J. Y. Mancuso, J. M. Marcek, E. L. Miller, M. A. Moen, S. O'Neil, I. Sakurada, M. Skaddan, V. Parikh, D. L. Smith, P. Trapa, J. B. Tuttle, P. R. Verhoest, D. P. Walker, A. Won, A. S. Wright, J. Whritenour, K. Zasadny, M. M. Zaleska, L. Zhang, C. L. Shaffer, *J. Med. Chem.*, 2017, **60**, 7764–7780.

[146] S. N. Basahel, N. S. Ahmed, K. Narasimharao, M. Mokhtar, *RSC Adv.*, 2016, **6**, 11921–11932.

[147] I. I. Roslan, Q.-X. Lim, A. Han, G.-K. Chuah, S. Jaenicke, *Eur. J. Org. Chem.*, 2015, 2351–2355.

[148] Z. Chen, Y. Wen, H. Ding, G. Luo, M. Ye, L. Liu, J. Xue, *Tetrahedron Lett.*, 2017, **58**, 13–16.

[149] M. G. Woll, H. Qi, A. Turpoff, N. Zhang, X. Zhang, G. Chen, C. Li, S. Huang, T. Yang, Y. C. Moon, C. S. Lee, S. Choi, N. G. Almstead, N. A. Naryshkin, A. Dakka, J. Narasimhan, V. Gabbeta, E. Welch, X. Zhao, N. Risher, J. Sheedy, M. Weetall, G. M. Karp, *J. Med. Chem.*, 2016, **59**, 6070–6085.

[150] D.-S. Park, E. Jo, J. Choi, M. Lee, S. Kim, H.-Y. Kim, J. Nam, S. Ahn, J. Y. Hwang, M. P. Windisch, *Eur. J. Med. Chem.*, 2017, **140**, 65–73.

[151] H. Guan, C. Wu, T. Yu, D. Hao, B. Gao, J. Sun, N. Shi, S. Chen, *US 20170129888*, 2017.

[152] M. Volgraf, J. Yu, E. Villemure, B. Sellers, G. Wu, A. Lu, *WO 2016166078*, 2016.

[153] K. Matsuo, M. Shindo, *Org. Lett.*, 2011, **13**, 4406–4409.

[154] W. Zhao, *Handbook for Chemical Process Research and Development*, CRC Press, 2016.

[155] M. J. Robins, B. Uznański, *Can. J. Chem.*, 1981, **59**, 2601–2607.

[156] S. K. Guchhait, G. Priyadarshani, *J. Org. Chem.*, 2015, **80**, 6342–6349.

[157] A. Molnár, A. Kapros, L. Párkányi, Z. Mucsi, G. Vlád, I. Hermecz, *Org. Biomol. Chem.*, 2011, **9**, 6559.

[158] J. Liu, H. Zhang, H. Dong, L. Meng, L. Jiang, L. Jiang, Y. Wang, J. Yu, Y. Sun, W. Hu, A. J. Heeger, *Nat. Commun.*, 2015, **6**, 10032.

[159] A. Facchetti, M.-H. Yoon, C. L. Stern, G. R. Hutchison, M. A. Ratner, T. J. Marks, *J. Am. Chem. Soc.*, 2004, **126**, 13480–13501.

[160] F. Babudri, G. M. Farinola, F. Naso, R. Ragni, *Chem. Commun.*, 2007, 1003–1022.

[161] X. Gong, X. Xie, N. Chen, C. Zheng, J. Zhu, R. Chen, W. Huang, D. Gao, *Chinese J. Chem.*, 2015, **33**, 967–973.

[162] T. Dohi, K. Morimoto, N. Takenaga, A. Goto, A. Maruyama, Y. Kiyono, H. Tohma, Y. Kita, *J. Org. Chem.*, 2007, **72**, 109–116.

[163] D.-S. Choi, S. Huang, M. Huang, T. S. Barnard, R. D. Adams, J. M. Seminario, J. M. Tour, *J. Org. Chem.*, 1998, **63**, 2646–2655.

[164] Y. Guo, L. Wang, J. Zhuo, B. Xu, X. Li, J. Zhang, Z. Zhang, H. Chi, Y. Dong, G. Lu, *Tetrahedron Lett.*, 2017, **58**, 3951–3956.

[165] J. Grimshaw, J. Trocha-Grimshaw, *J. Chem. Soc. Perkin Trans. 1*, 1972, 1622–1623.

Appendix A

X-ray Crystallography Data

X-ray crystallographic data related to all compounds analysed can be found in the electronic appendix.