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Regioselective Routes to Tetrasubstituted Aromatic Compounds

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Submitted to the University of Sussex in part fulfilment of the requirements of the
degree of Doctor of Philosophy, January 2016

Declaration

I hereby declare that the work presented in this thesis was carried out at the University of Sussex under the supervision of Prof J Spencer between the dates of April 2012 and September 2015. The work presented in this thesis is my own, unless otherwise stated, and has not been submitted in whole or in part form for award of another degree.

Adam J. Close

Acknowledgements

Firstly I would like to thank my supervisor Prof John Spencer for his guidance and constant enthusiasm throughout my Ph.D. He was always there to point or sometimes to give a necessary push in the right direction and for that I shall be forever grateful.

I would like to thank the School of Life Sciences (Sussex) and AstraZeneca for funding my studies.

I would like to thank my industrial supervisor Dr. Paul Kemmitt who helped me throughout my Ph.D. especially during my work placement. I would also like to thank Dr. Stephen Stokes and Dr. Matthew Grist who made my transition into my industrial work place far easier.

I would like to thank my colleges, Gavin Roffe, Rhiannon Jones, Melvin Ansell, Jose Gascon, Bradley Springett, Antonino (Nino) Puglisi, Supojjane (Po) Sansook, Raysa Khan and Matthew Emmerson. Their help, support, interest and friendship in the laboratory and group meetings made the Ph.D. journey a more enjoyable experience.

I would like to thank Daniel Guest, Tom Moore, Oran O'Doherty, Jessica Frey, Chris Gallop and Katie Duffell for the help in proof reading this document, the writing of which has been the most demanding academic achievement of my life. I would thank the aforementioned along with Alistair Frey, Jess Dwyer, Dave Neil-Hall, Hayley Rand and Kyle Baldwin for general support, camaraderie and close friendship.

I would like to thank the staff within the chemistry department at University of Sussex. In particular Dr. Alaa Abdul-Sada for performing mass spectrometry measurements, Dr. Iain Day for guidance and consultations with NMR and Prof. Mark Bagley for conversations and general interest in this work.

The EPSRC National Mass Spectrometry Service of the University of Swansea and National X-Ray Diffraction Units of the University of Southampton are acknowledged for carrying out HRMS measurements and X-ray crystallographic measurements.

I would like to thank all my teachers and mentors from Nottingham Trent University and Brookfield Community School. In particular David Grafton, John Lees, David Arnold, Dr Gareth Cave and Prof John Wallis.

Last, but by no means least I would like to thank my family, especially Mum, Dad, my brothers, Daniel and Timothy, Uncle Steven and my partner Laura, for their love and unconditional support throughout this process.

List of Symbols and abbreviations

ABL1	Abelson murine leukemia viral oncogene homolog 1
Ac	acetate, CH_3CO
AcOH	acetic acid, $\text{C}_2\text{H}_4\text{O}_2$
ATP	adenosine triphosphate
BCR	breakpoint cluster region protein
BOC	tert-butyloxycarbonyl, $\text{C}_5\text{H}_9\text{O}_2$
Bu	Butyl, C_4H_9
CML	chronic myeloid leukemia
Cy	cyclohexyl
<i>d</i>	deuterated
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene, $\text{C}_9\text{H}_{16}\text{N}_2$
DCM	dichloromethane, CH_2Cl_2
DEA	Diethylamine, $\text{C}_4\text{H}_{11}\text{N}$
DIPEA	<i>N,N</i> -Diisopropylethylamine, $\text{C}_8\text{H}_{19}\text{N}$
DME	dimethoxyethane, $\text{C}_4\text{H}_{10}\text{O}_2$
DMF	dimethylformamide, $\text{C}_3\text{H}_7\text{NO}$
EGFR	epidermal growth factor receptor
ESI	electrospray ionization
Et	ethyl, CH_2CH_3
eq	equivalent
EtOAc	ethyl acetate, $\text{C}_4\text{H}_8\text{O}_2$
EtOH	ethanol, $\text{C}_2\text{H}_6\text{O}$
FDA	food and drug administration
GIST	gastrointestinal stromal tumor
h	hour
IC_{50}	half maximal inhibitory concentration
LCMS	liquid chromatography mass spectrometry
MAPK	mitogen-activated protein kinase
Me	methyl, CH_3
MeCN	acetonitrile, $\text{C}_2\text{H}_3\text{N}$
MeOH	methanol, CH_3OH
MIDA	methyliminodiacetic acid, $\text{CH}_3\text{N}(\text{CH}_2\text{CO}_2\text{H})_2$
MOM	methoxymethyl ethers
MW	molecular weight or microwave

NMR	nuclear magnetic resonance
Pd-118m / Pd(dtbpf)Cl ₂	dichloro[1,1'-bis(di-tert-butylphosphino)ferrocene]palladium(II)
Ph	phenyl, C ₆ H ₅
pin	pinacol
p <i>K</i> _a	acid dissociation constant
Piv	pivaloyl, <i>t</i> -BuCO
PMB	4-methoxybenzyl ether
PTSA	<i>p</i> -toluenesulfonic acid
py	pyridine, C ₅ H ₅ N
R _f	retention factor
r.t.	room temperature
STAB	sodium triacetoxymethylborohydride, C ₆ H ₁₀ BNaO ₆
T	temperature
TEA	triethylamine, C ₆ H ₁₅ N
THF	tetrahydrofuran, C ₄ H ₈ O
TLC	thin layer chromatography
TMS	tetramethylsilane, C ₄ H ₁₂ Si
tol	toluene, C ₇ H ₈
ν	frequency
δ	chemical shift
σ	sigma

Abstract

Polysubstituted aromatics are highly desirable in medicinal chemistry for library generation and the tetrasubstituted aryl motif appears in many pharmaceuticals. Current methods to access 1,2,4,5- and 1,2,3,4- tetrasubstituted aromatics are problematic. Therefore new routes giving defined regiochemical outcomes with four different orthogonal functionalities were sought.

This work took two directions; 1) the bromination and nitration of trisubstituted aryl MIDA boronates, and 2) the nitration of trisubstituted aryl bromides, both leading to the desired tetrasubstituted aromatics.

MIDA boronates are boronic acids masked with N-methyliminodiacetic acid (MIDA). This allows for iterative palladium cross-coupling reactions. The first step in the work was developing a new rapid microwave-mediated method (5-15 min) towards MIDA boronates using ether poly-ethylene glycol 300, acetonitrile or dimethylformamide as a solvent. This methodology gave a library of over 20, mainly aryl or heteroaryl MIDABoronates.^{1,2}

Trisubstituted aryl-MIDABoronates were then brominated or nitrated giving 6 novel tetrasubstituted aromatic compounds. The 3 new tetrasubstituted aryl-MIDABoronates bromides were then used in a selection of iterative Suzuki–Miyaura cross coupling reactions (SM) to show the potential uses of the compound in library generation.

Three different bromo-fluorobenzaldehyde regioisomers were nitrated giving 3 different tetrasubstituted aromatics. These 3 compounds were then subjected to several different conditions to modify them i.e. nitro reduction, Sonogashira couplings, reductive aminations, Clauson-Kaas pyrrole synthesis. A number of tetrasubstituted anilines were reacted with 4-chloro-6,7-dimethoxyquinazoline to afford novel, potential kinase inhibitors.

Publications:

- (1) Close, A. J.; Kemmitt, P.; Emmerson, M. K.; Spencer, J. *Tetrahedron* **2014**, 70, 9125–9131.
- (2) Close, A. J.; Corden, V.; Spencer, J. Use of a camera to monitor reaction stirring and reagent dissolution during a reaction; a MIDA boronate library generation case study. <http://www.cemmicrowave.co.uk/assets/cameramida-boronate---app-note.pdf> (accessed Nov 15, 2015).

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1. Introduction

Importance of tetrasubstituted aromatic compounds

Polyfunctional aromatic compounds containing orthogonal functionality, allowing for independent group transformations, are desirable scaffolds for exploration in medicinal chemistry. The reactivity of the different functional groups allows for efficient library generation and consequently development of new small molecule therapeutics. Often the seemingly simple, desired tetrasubstituted scaffolds are not commercially available and are highly expensive, thus new methodology towards these molecules is required.¹ For these reasons AstraZeneca funded this CASE award with the outlined objectives:

1. Synthesised tetrasubstituted aromatics must contain 4 different orthogonal groups.
2. Synthesised tetrasubstituted aromatics must have either a 1,2,3,4 or a 1,2,4,5-substitution pattern.
3. Methods of preparation must be scalable.

Tetrasubstituted aromatics in drugs and natural products

Tetrasubstituted arenes appear in different formats within drugs as highlighted in Figure 1.1 below.

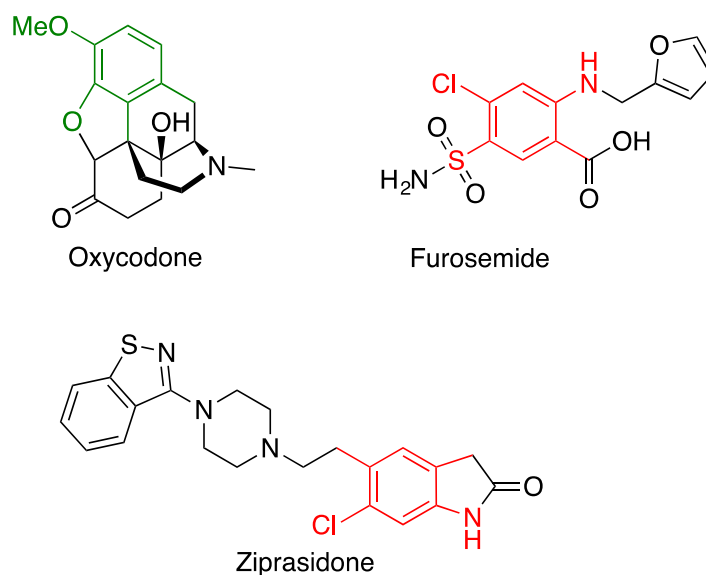


Figure 1.1. Example of pharmaceuticals with tetrasubstituted framework (1,2,3,4-substitution pattern, green) (1,2,4,5-substitution pattern, red)

Oxycodone is an example of a synthetic opioid and is used in the treatment of pain.² Oxycodone and other opioids such as morphine or codeine contain a phenanthrene type ring with one 1,2,3,4-functionalised aromatic ring, as highlighted in red.³ The HCl salt of oxycodone is under licence by Pfizer and Acura Pharmaceuticals and is sold as OxectaTM. This is an abuse-deterrent formulation that only allows oral consumption of the product.⁴ A plethora of thiazide diuretics were discovered in the late 50s and early 60s. These compounds typically contain a 1,2,4,5-functionalised aromatic i.e. hydrochlorothiazide or furosemide (Figure 1.1).^{5,6} In the case of furosemide there are four different functional groups that link to one aromatic core, showing the importance of polysubstituted aromatic cores in bioactive molecules. Oxycodone and furosemide are both drugs of high value and are required to run a basic healthcare system, as outlined on the 2015 list of essential medicines from the World Health Organisation (WHO).⁷ Ziprasidone is a antipsychotic treatment for schizophrenia and has a 1,2,3,4-functionalised aromatic ring as part of a heterocyclic core.^{8,9} It was first synthesized in 1989 as one of a series of compounds in a patent, which involved joining two pre-made heterocyclic cores together by a S_N2 reaction.¹⁰ A later synthesis built the molecule up from 1,4-dichloro-2-methyl-5-nitrobenzene. This outlines the potential of tetrasubstituted aromatics as a starting material for on-the-market pharmaceuticals.¹¹ The tetrasubstituted motif also appears in Nature, as shown in the natural products in Figure 1.2. This exemplar of molecules show either the 1,2,3,4- or 1,2,4,5-substitution

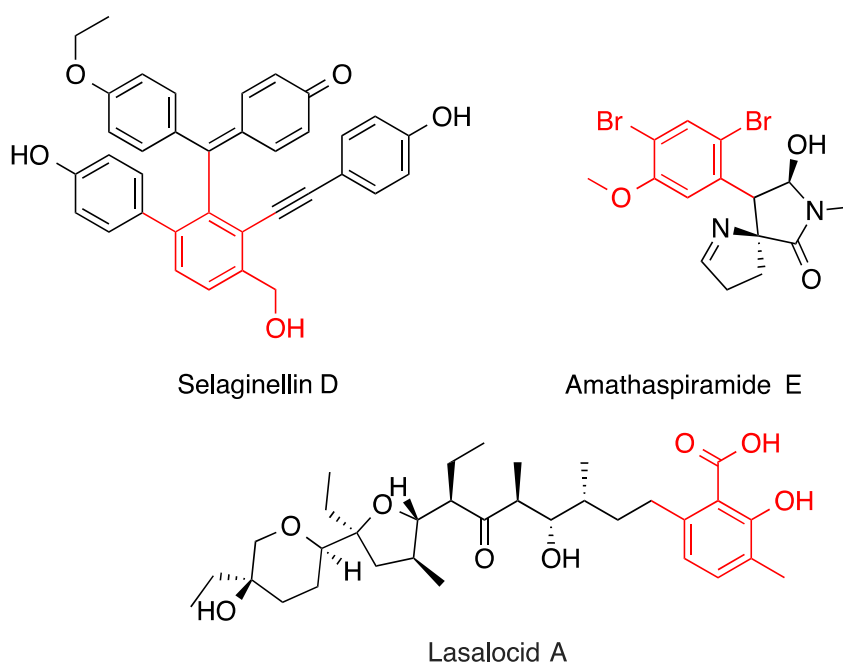


Figure 1.2. Natural products with tetrasubstituted frameworks

framework and they also exhibited some pharmacological activity. Selaginellin D was extracted using ethyl acetate from *Selaginella pollinate*; this plant has been used historically in Chinese medicine. It has activity as an anti-microbial and an anti-fungal chemical.¹²

The Amathaspiramide compounds were extracted from a New Zealand marine bryozoans called *Amathia Wilsoni*, by Prinsep *et al* in 1999.¹³ They also found that amathaspiramide E (Figure 1.2) has activity against poliovirus as well as antimicrobial activity. Due to the interest around this group a total synthesis has been accomplished to allow further investigations into these compounds.¹⁴

Lasalocid A was first isolated from *Streptomyces*. Within this first publication it was noted as an antibiotic.¹⁵ It was later recognised that this molecule was part of the polyether antibiotics group. These compounds are veterinary medicines of high value, and often mixed with animal feeds to prevent and control coccidiaes.³

The natural product and pharmaceutical examples above illustrate the importance of tetrasubstituted scaffolds and highlights the need for new methodology towards them, which will allow drug discovery groups to take advantage of these complex motifs.

Kinase inhibitors

Normal cell growth is typically governed by external signals, in the form of growth factor ligands, which instruct the cell when to grow and divide. The growth factors bind to the extracellular domain of a growth receptor and a signal is passed to the intercellular domain. This allows phosphorylation of a tyrosine, threonine or serine on a protein at the intercellular domain, starting an intercellular cascade of pathways that, result in cell growth and or cell division.¹⁶

Uncontrolled cell division, known as proliferation, is a quintessential cancer characteristic. Cancer cells can produce their own growth factors and transport them in to the extracellular domain, which allows them to divide with reduced external stimulation. This is known as autocrine stimulation. Cancer cells also, often exhibit a mutation in a gene encoding for the regulation of growth receptors. The lack of regulation leads to the over production of growth receptors, and this over expression gives an increased potential for a tumour to be triggered into its growth stage. Growth factor receptor over expression can also lead to ligand independent signalling. These factors all lead to uncontrolled tumour growth.¹⁷

Existing therapeutics can be made that target different aspects of the signalling pathway. The key areas are shown in Figure 1.3(a,b,c):

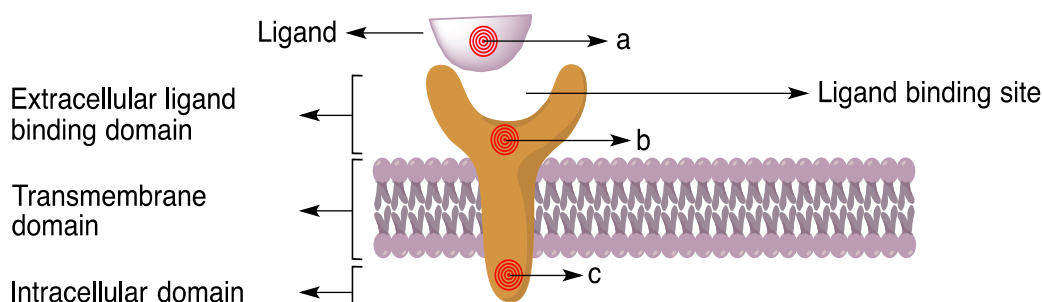


Figure 1.3. Representation of a growth factor receptor, showing three therapeutic targeting areas labelled a, b and c.

- a) Antibodies can be employed to intercept the ligand before it is able to bind to the receptor. Bevacizumab is a monoclonal antibody that binds vascular endothelial growth factor (VEGF). Bevacizumab, alongside chemotherapy gives a significantly improved response compared to chemotherapy alone in the treatment of colorectal cancer.¹⁸
- b) The extracellular part of the receptor can be targeted by antibodies, which bind to the ligand-binding site, thereby inhibiting the receptor. Cetuximab is used to treat advanced-stage colorectal cancer, expressing epidermal growth factor receptors (EGFR).¹⁹
- c) Small molecule inhibitors can also be used to block receptor function, via an interaction at the intracellular domain. These compounds competitively inhibit the binding of adenosine triphosphate (ATP) (Figure 1.4.) to the growth receptor. This prevents the phosphorylation of a tyrosine, threonine or serine on a downstream protein, and thereby arrests the following signalling pathway.²⁰ Gefitinib (Figure 1.5) (marketed as Iressa®) is an orally-available EGFR kinase inhibitor that improves disease-related symptoms and shows induced tumour regressions in non-small cell lung cancer (NSCLC).^{21,22}

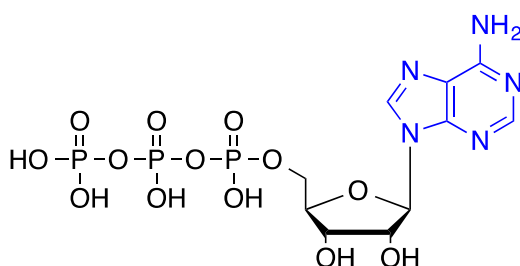


Figure 1.4. Adenosine triphosphate (ATP) with the adenine heterocycle in blue

Small molecule kinase inhibitors are of interest in this project as they commonly incorporate polysubstituted aromatics, as shown in Figure 1.5. For example vemurafenib, which is used for the treatment of metastatic melanoma, contains a 1,2,3,4-substituted aromatic core.²³

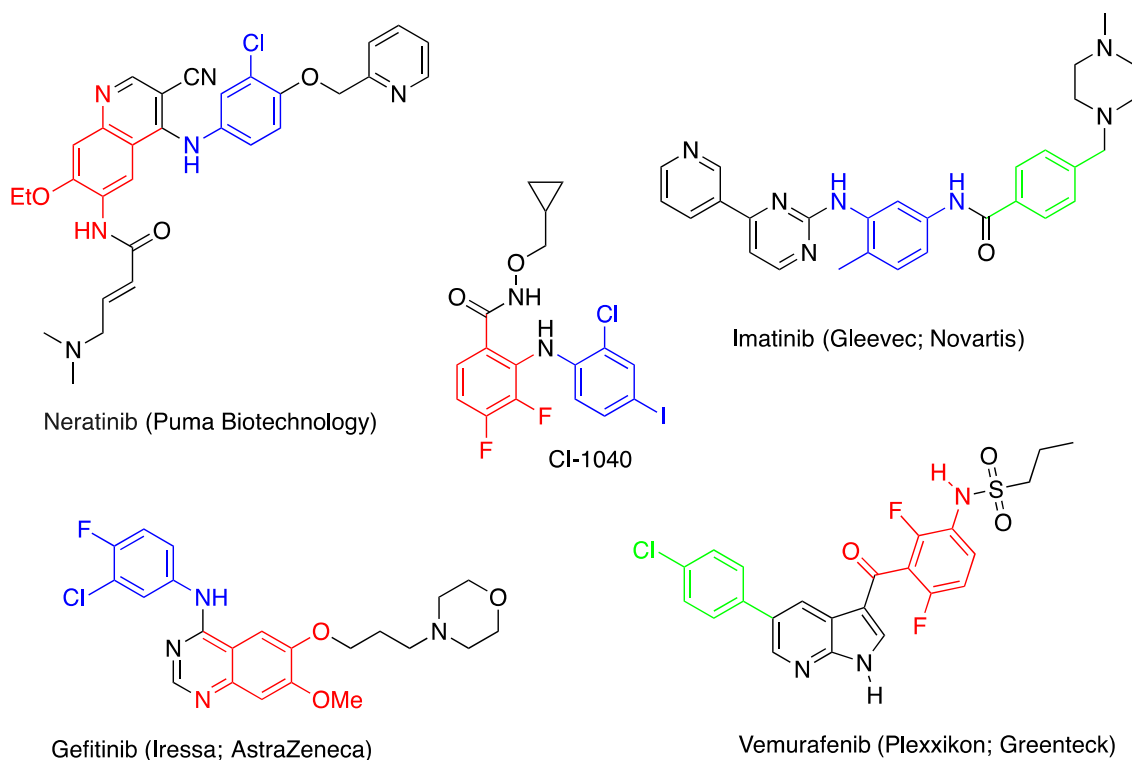


Figure 1.5. Small molecule kinase inhibitors with highlighted polysubstituted aromatics (tetrasubstituted in red, trisubstituted in blue and disubstituted in green)

Protein kinases have a cleft, which forms the ATP binding site. Within this cleft there is the hinge, which interacts with the adenine heterocycle (Figure 1.4). This acts as the target for the majority of inhibitors. Most kinase inhibitors do not utilise the ribose or the triphosphate binding sites. Small molecule kinase inhibitors can be placed into four different types.²⁴

1. Type one. Protein kinases exist in equilibrium between active and inactive conformations, with the active conformer responsible for protein phosphorylation. Type one inhibitors bind to the active conformation of the protein, by mimicking ATP. These competitive inhibitors interact with the purine-binding site at the hinge, forming 1-3 hydrogen bonds. The molecules comprise of a heterocyclic core to mimic the adenine, with complementary functionalities to target the subtle environmental differences within the protein cleft, to give selectivity and potency.

2. Type two. These inhibitors bind to the ATP binding site of the inactive conformer. Upon binding, the inhibitor will stabilise the inactive conformer of the protein kinase therefore denaturing it.
3. Allosteric inhibitors. Allosteric inhibitors interact with the protein kinases outside the ATP binding site, causing a change in the shape of the active site, which prevents ATP binding. These inhibitors are the most selective as the allosteric sites targeted are unique to the protein kinase. An example of this type of inhibitor is CI-1040 shown Figure 1.5, which inhibits MEK1 and MEK2.²⁵ MEK1 and MEK2 are found in the mitogen-activated protein kinase (MAPK) signalling pathway. This pathway is exhibited in 30 % of all human cancers, resulting in undesirable cellular transformations.²⁶
4. Covalent inhibitors. Covalent inhibitors irreversibly bind to the ATP pocket by means of a covalent bond. This is typically achieved by the incorporation of a Michael acceptor that is susceptible to nucleophilic attack, normally by a cysteine thiol moiety.

Three out of the four types of kinase inhibitors rely on binding to the ATP binding site, emphasising the importance of good selectivity, as there are over 500 different protein kinases in the human body.²¹ This selectivity is achieved by rational drug design with the aid of structural data and computational modelling and assessed by counter screening the new analogues against an array of protein kinases, evaluating at each step to develop new inhibitors with high potency.²⁹

The EGFR type one inhibitor gefitinib is an excellent example of successful drug discovery.²³ The first lead compound was *N*-(3-bromophenyl)-6,7-dimethoxyquinazolin-4-amine, compound **1** (Figure 1.6) which has an $IC_{50} = 15$ nM, was found via a high throughput screening approach. This compound was synthesised from 3-bromoaniline and the 4-chloro-6,7-dimethoxyquinazoline to form the secondary amine. This approach allowed for quick modification of the quinazoline and aniline, followed by the linking of the two units to make new analogues.

Modification of the quinazoline unit in the 5,6,7 or 8 positions showed that electron-donating units were required in the 6 and 7 positions. This increases the pK_a of the nitrogen atoms in quinazoline, making them better hydrogen bond acceptors. Modifications of the aniline moiety showed that a small lipophilic group in the 3 (*meta*) position improved activity. This produced a new lead compound with an $IC_{50} = 5$ nM, 7-

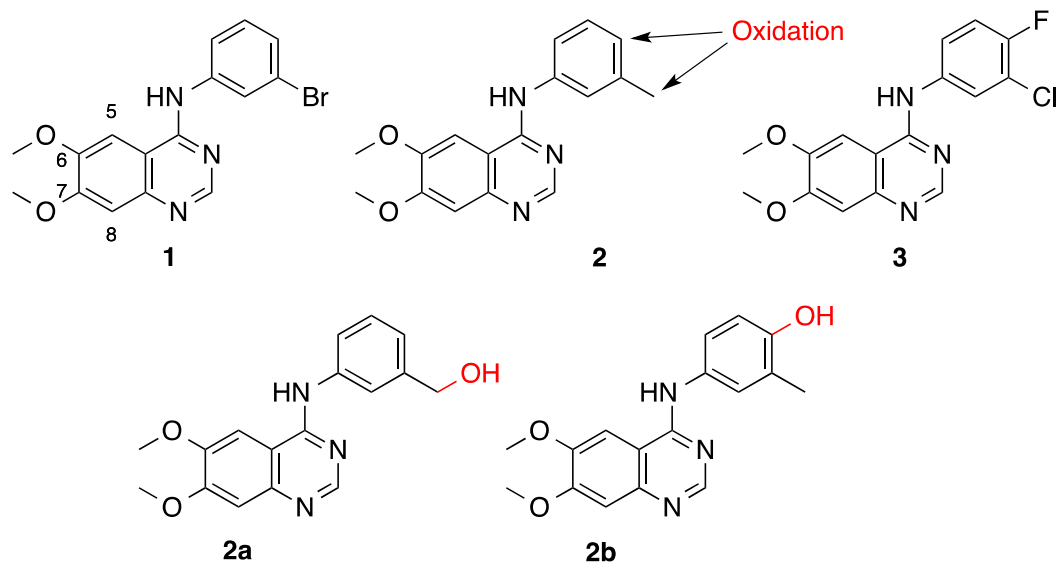


Figure 1.6. Analogues explored in synthesis towards Gefitinib

dimethoxy-*N*-(*m*-tolyl)quinazolin-4-amine, compound **2** (Figure 1.6).

Compound **2** suffers with a short half-life of approximately 1 h due to metabolism by the P450 enzyme to the two metabolites **2a** and **2b**, which reduced the *in vivo* activity. This problem was navigated by the installation of a chloro group in the *meta* position and a fluoro substituent in the *para* position (compound **3**). Compound **3** had better activity *in*

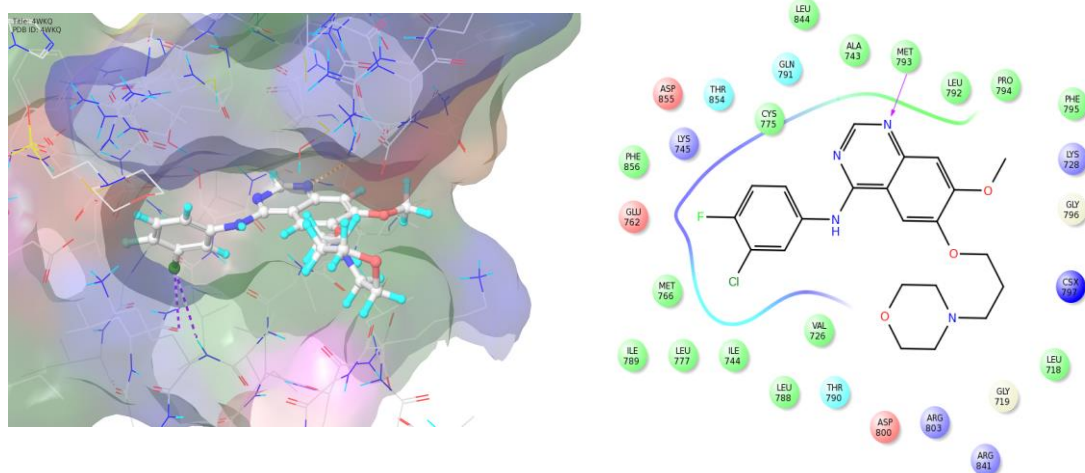


Figure 1.7. Left; co-crystal 3D image of the EGFRs ATP binding cleft with Gefitinib binding. Right; 2D cleft representation of Gefitinib bound to EGFRs. PDB 4WKQ¹⁵⁵

vivo due to its resistance to P450, but it was less active *in vitro*, $IC_{50} = 9$ nM.²⁴

Whilst the activity of the lead had been improved, the lipophilicity remained unacceptably high, and therefore further modifications were required to reduce this. It was found that adding a morpholine moiety at the 6 position was found to solve the solubility issue, due to the basic nitrogen allowing the formation of water-soluble salts. Gefitinib, is such that the chloro fits into a hydrophobic pocket. The nitrogen atoms in the quinazoline act as hydrogen bond acceptors for the methionine amide bond in Figure 1.7, and bridging water molecules enable a bond with a threonine residue. The morpholine sits outside of the binding site in the aqueous environment and does not desolvate when the drug binds, therefore there is no associated energy penalty.

Chronic myeloid leukemia (CML) is a rare life-threatening cancer that is responsible for around 1 in 100,000 cases of leukemia. It is caused by a specific chromosomal translocation, referred to as the Philadelphia chromosome. This creates a new hybrid protein BCR-Abl from Abelson murine leukemia viral oncogene homolog 1 (ABL1) from chromosome 9 and breakpoint cluster region protein (BCR) from gene on chromosome 22. This fusion protein BCR-Abl has oncogenic properties due to tyrosine kinase activity leading to cellular proliferation. Given that BCR-Abl appears essential for cell survival, it was identified as a promising drug target, and the subsequent investigation led to the discovery of Gleevec, Figure 1.5.³¹ This was the first orally available compound for the treatment of CML.

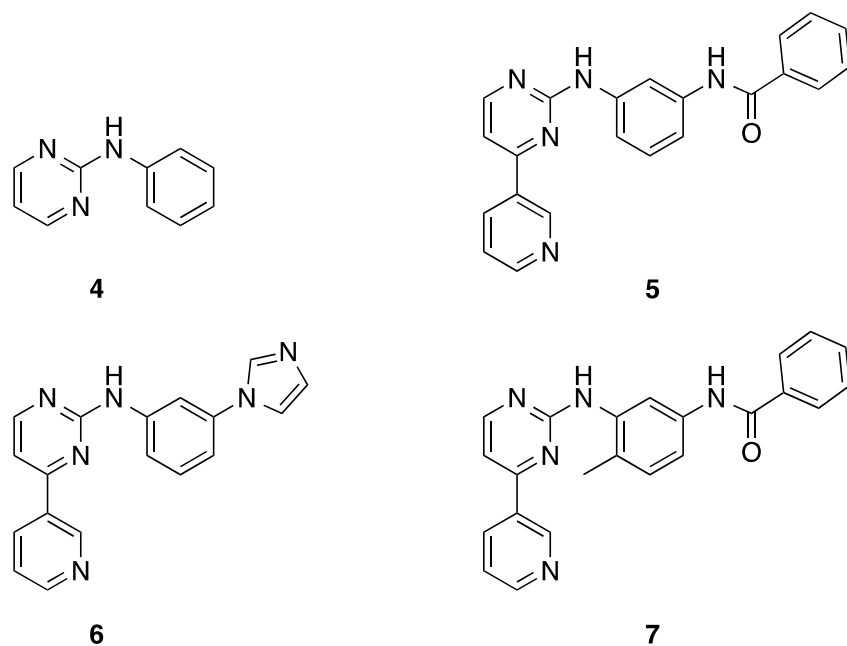


Figure 1.8. Analogues explored in synthesis towards Gleevec.

A screening based approach found the original lead, *N*-phenylpyrimidin-2-amine (Figure 1.8, compound **4**), eventually afforded Gleevec, which has improved selectivity

Compound **4** became the first lead of interest via a high throughput-screening program, and provoked a study involving over 300 molecules. Compound **5** became the next compound of interest following early studies; the improvement came from the addition of a 3-pyridyl group on the 3 position of the pyrimidine ring Table 1.1.

Table 1.1. Compound activity of Gleevec analogues.

Activity IC ₅₀ (μm)	Abl	PKCα	PKCβ
5	>10	-	-
6	0.4	1.2	23
7	0.4	72	>500
Gleevec	0.038	>100	>100

After this a benzamide group was added (compound **7**), which decreased the IC₅₀ to 0.4 μM, but unfortunately following SAR studies showed that the selectivity was low as compound **5** also inhibited protein kinase C (PKC). The addition of a methyl group to the diamino moiety (compound **7**) increased potency without loss of activity, as the conformation was locked in to a shape complimentary to BCR-Alb binding site, Figure 1.9. This compound exhibited solubility issues and it was found that the addition of a benzyl *N*-methylpiperazine solved this problem. Benzyl amine moieties are preferred over

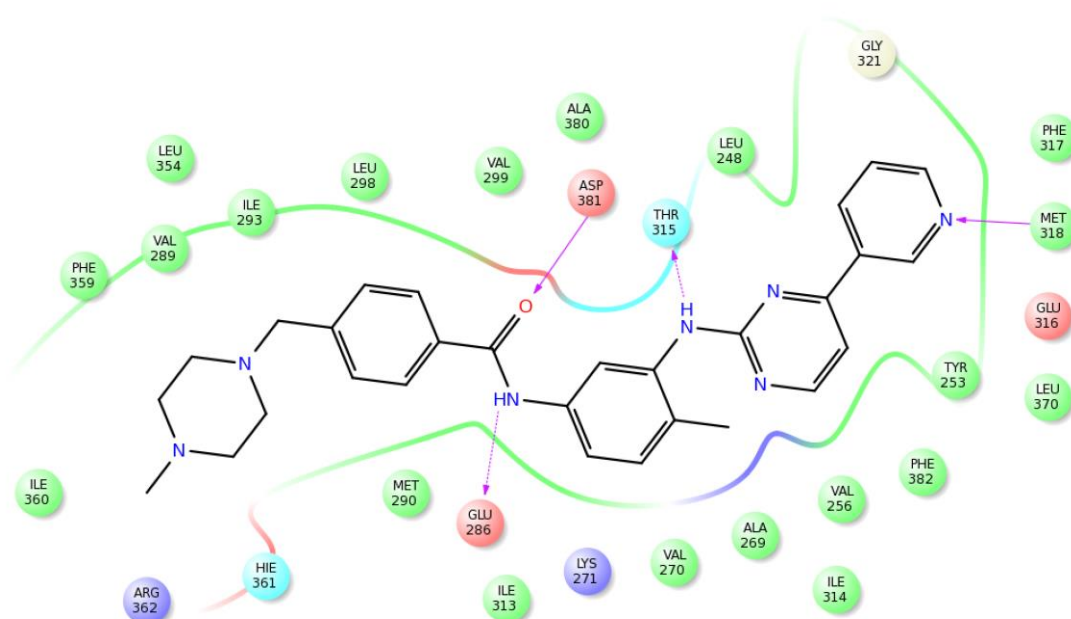


Figure 1.9. 2D pocket representation of Imatinib (Gleevec) bound to ABL. PDB 2HYY¹⁵⁶

aniline derivatives due to their lower genotoxicity. The resulting compound, Imatinib is sold as the mesylate salt under the brand name Gleevec.³²

Gleevec also has therapeutic use in gastrointestinal stromal tumours (GIST).³³ It has been shown that it can halt or reverse GIST with an acceptable safety profile and has made it onto the WHO's list of essential medicines.⁷

Unfortunately, despite continuing efforts to develop effective protein kinase inhibitors there remains a vast amount of work to be done. Tumours can develop resistance to kinase inhibitors, because the drugs enforce selective pressures on the cell, which induce the tumour to evolve coping mechanisms. This happens in several ways e.g. increased function and expression of transporters involved in drug efflux, evolution of a drug resistant alternative of the target protein, mutation of the ATP binding pocket and upregulation of alternate pathways which are able to compensate for the loss of protein function. Indeed, resistance of CML to Gleevec treatment follows these trends.³⁴

Gleevec is a type 2 inhibitor and still the most selective treatment for CML due to its binding mode, which relies upon the dynamic equilibrium between conformations of BCR-Abl.²⁹ The ATP binding site in BCR-Abl is only accessible in the inactive conformation and therefore Gleevec stabilizes this conformation, inactivating BCR-Abl. The high selectivity of Gleevec allows small mutations in the binding domain of BCR-Abl to reduce its activity, such that ATP is able to bind. Some new inhibitors have necessarily been created to target these mutants. In other cases poorly selective inhibitors from other protein kinase targets can be utilized, although these must often be given in a poly-therapeutic dose i.e. multiple therapy treatment.³⁵ Nilotinib and Dasatinib have been shown to be active against Gleevec resistant CML. Sunitinib has been used in the treatment of GIST and has shown activity in Gleevec resistance tumors.^{36–38}

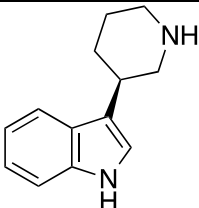
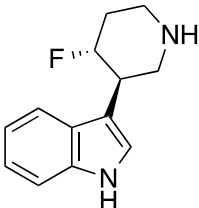
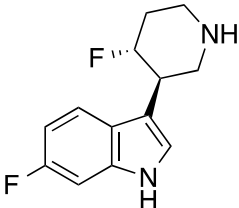
It is likely that over time NSCLC can become resistant to treatment with gefitinib as mutations can develop on EGFR.³⁹ However, Neratinib (Figure 1.5), a new pipeline treatment is a covalent inhibitor and therefore includes a Michael acceptor and forms a bond irreversibly with a cysteine upon binding.⁴⁰ This cysteine in EGFR arises from a mutation, making this a useful technique to combat resistant tumours.

This selection of kinase inhibitors demonstrates the necessary requirement for new tetrasubstituted aromatic starting materials. These will supplement the synthesis of new inhibitors with improved affinity and selectivity and help to overcome the problem with drug resistance.

Fluorine in drugs

Approximately 25% of pipeline pharmaceuticals include at least one or more fluorine, demonstrating the high importance of organofluorine compounds in medicinal chemistry. Fluorine being the most electronegative atom, can be used to modulate the pK_a of compounds.⁴¹ This approach has improved the bioavailability of a series of 3-piperidinyndole antipsychotic drugs by decreasing the basicity of the amines (Table 1.2).⁴² Lowering the pK_a reduces the amount of protonated amine (ammonium species), which in turn affects the absorption process since unionised drug can pass through cell membranes.

Table 1.2. Basicity and bioavailability (F) of a series of 3-piperidinyndole

Indole	5-HT _{2A} (nM)	pK_a	F (%)
	0.99	10.4	Poor
	0.43	8.5	18
	0.06	-	80

The 5-HT₂ receptors normally bind to the neurotransmitter 5-hydroxytryptamine (5-HT). This series binds selectively to the 5-HT₂ receptors over the dopamine D₂ receptor. The first addition of the fluorine to the piperidine moiety improved the bioavailability by reducing the pK_a by 1.9 units. This compound was metabolised by hydroxylation in the 6 position of the indole; this was blocked by the addition of fluorine. The resulting molecule's bioavailability was vastly improved further and enhanced the binding affinity by an order of magnitude.

Drugs are commonly metabolized typically by oxidation by P450 enzymes prior to elimination. Oxidation decreases the lipophilicity, allowing rapid clearance from the body. Fluorine substituents have been used to block metabolism at labile sites on compounds.⁴³

$$\log p_{\text{oct/wat}} = \log \left(\frac{[\text{solute}]_{\text{octanol}}^{\text{uninoised}}}{[\text{solute}]_{\text{water}}^{\text{uninoised}}} \right)$$

Equation 1

Lipophilicity can be regulated by fluorine functionalities. Lipophilicity ($\log p$) is usually measured as a partition-coefficient between water and octanol as shown in Equation 1. Selective fluorination of alkyl groups (*e.g.* mono, di or trifluoromethyl) typically decreases lipophilicity due to the strong electron withdrawing effect of fluorine. In contrast, fluorination adjacent to π -bonds *i.e.* aromatic fluorine, increases lipophilicity due to the C–F bond being highly non-polarisable, as the 2p orbitals overlap with the

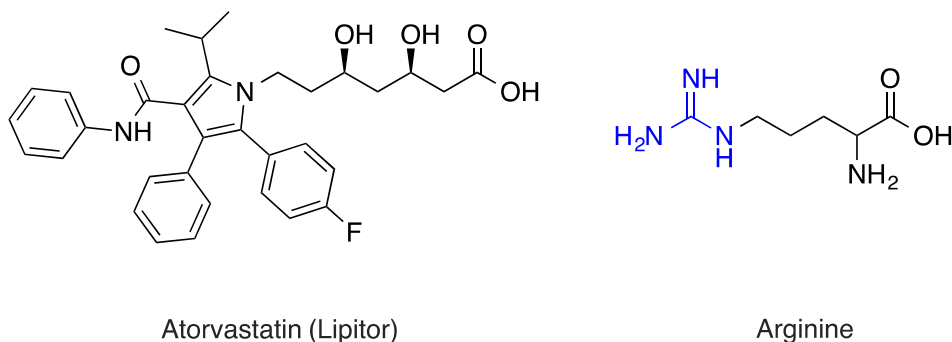


Figure 1.10. Showing left Atorvastatin (Lipitor) and right arginine (blue highlights the guanidinium group).

corresponding orbitals on carbon; the exception to this is when α to a carbonyl.⁴⁴

Atorvastatin, which is marketed under the name Lipitor, is part of the statin drug class, which are used in the treatment of hypercholesterolemia (Figure 1.10). Atorvastatin's fluorophenyl group is involved in the binding to its target, as it forms a bond to the guanidinium group of an arginine.⁴⁵ This is a polar interaction between the nitrogens.

Fluorine incorporation brings a wide range of positive properties as outlined above. For this reason fluorine or fluorine containing substituents have been incorporated within the tetrasubstituted molecules that we will present later in this work.

Boron in medicinal chemistry⁴⁶

Phenyl boronic acids were noted for their antibacterial properties for over 100 years,⁴⁷ and aromatic boronic acids have also been used in the application of carbohydrate recognition.^{48,49} This is due to boron having a vacant p-orbital (see section 0, Figure 1.14.

Boron sp^3 vs. sp^2) this allows it to make dative covalent bonds to nucleophilic moieties within a targeted binding site. These dative covalent bonds are stronger than typical non-covalent hydrophobic interactions that are utilised in the bulk of pharmaceuticals.⁵⁰ Dative covalent bonds are also reversible, unlike standard covalent inhibitors (section 0, the 4th type of kinase inhibitor).

The first boronic acid containing pharmaceutical was Bortezomib (marketed at Velcade, Figure 1.11).⁵¹ Bortezomib was approved by the FDA in 2003 for the treatment of

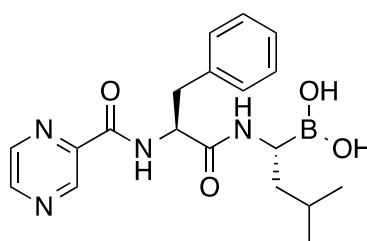


Figure 1.11. Bortezomib.

relapsed multiple myeloma (a bone marrow cancer) and mantle cell lymphoma.⁵² Bortezomib's method of action involves the boronic acid functionality forming a complex with the threonine hydroxyl group of the enzyme inside the active site.

Neratinib (Figure 1.5), is a new pipeline treatment for NSCLC resistant to treatment with Gefitinib (section 0). It is a covalent inhibitor and therefore includes a Michael acceptor which forms an irreversible bond with a cysteine residue in EGFR upon binding (section 0).⁴⁰ Nakamura *et al* tested boron to pick up the same residue using a dative covalent bond, Figure 1.12.⁵³ Docking studies showed an O-B dative covalent bond to an aspartic acid residue within this same region and formed hydrogen bonds to a cysteine. This shows

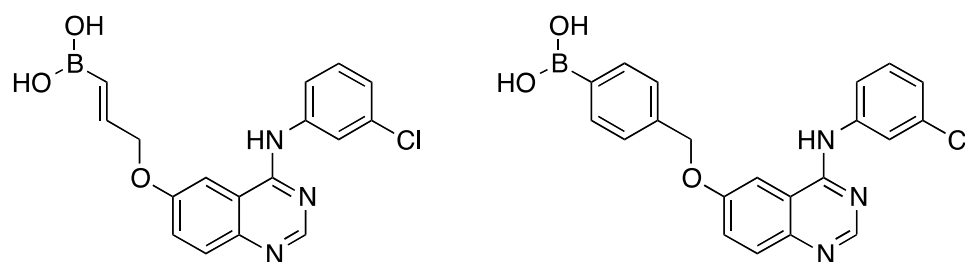


Figure 1.12, Kinase inhibitors containing boronic acids.

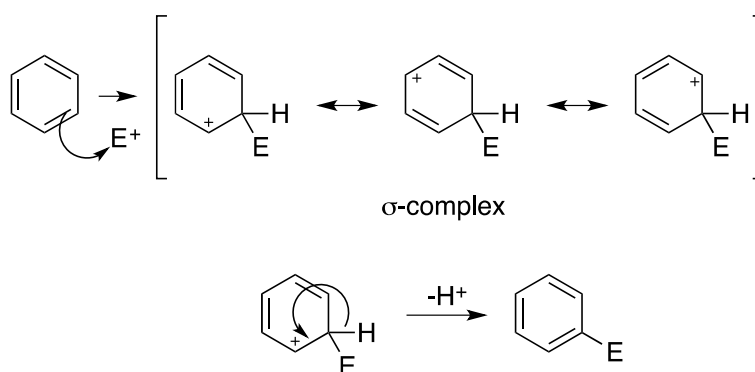
the potential of boronic acids to be used for prolonged inhibition through covalent bond formation.

Boric acid is considered not to be very toxic, as it has a similar LD₅₀ to that of table salt.⁵⁴ This, linked with the properties above show that boron has potential to be utilised in medicinal chemistry but is often overlooked.

Synthesis of tetrasubstituted aromatics

Electrophilic aromatic substitution⁵⁵

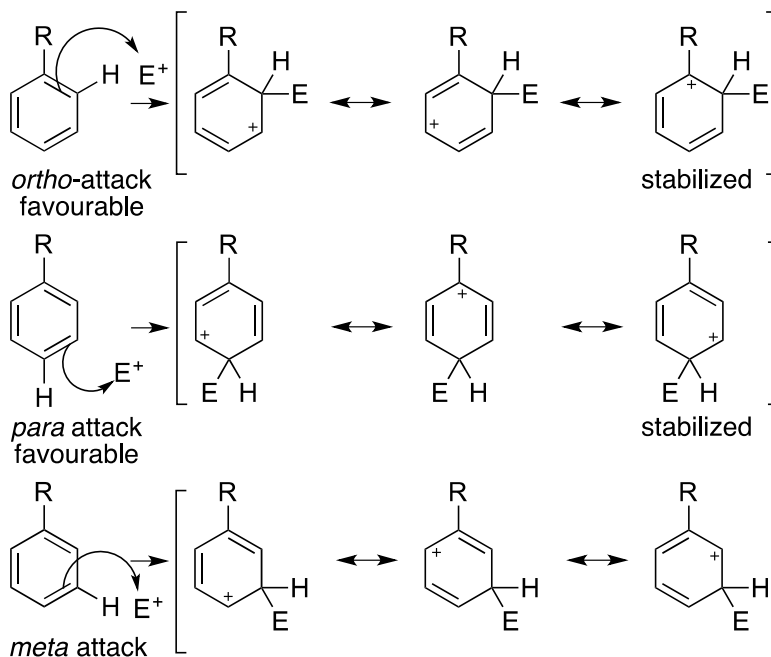
Electrophilic aromatic substitution is one of the most common ways of functionalizing aromatic compounds. The aromaticity of benzene, by virtue of its 6 π electrons, gives it higher levels of stability, thus the reactions require much stronger electrophiles than for the electrophilic addition of alkenes. The first step of the mechanism requires the formation of a σ -complex (arenium ion). The formation of this sp³ carbon atom interrupts the aromaticity, usually making the nature of this step highly endothermic. The aromaticity is restored via reversal of the first step, or loss of the proton from the sp³ carbon giving the product (Scheme 1.1).



Scheme 1.1. Mechanism of Electrophilic Aromatic Substitution.

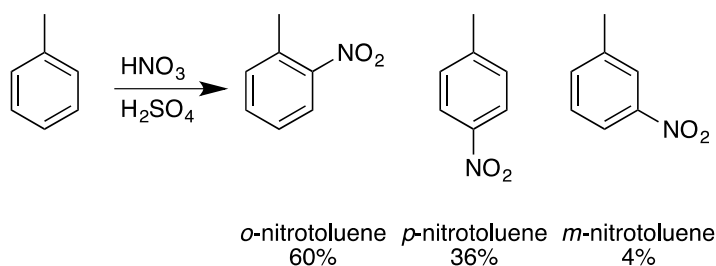
Effects of alkyl groups

Toluene, while undergoing electrophilic aromatic substitution, reacts around 25 times faster than benzene under the same reaction conditions. All alkyl groups cause a similar increase in reactivity and are considered activating groups, due to the alkyl groups donating electron density back through the σ bond via hyperconjugation. This electron density facilitates stabilization of the rate-determining step, the formation of the σ complex; this is known as inductive stabilization.



Scheme 1.2. σ complexes for, *ortho*, *para* and *meta* substitution respectively.

Alkyl groups also have an *ortho-para* directing effect. The canonical forms in Scheme 1.2 show the positive charge is stabilized by the alkyl group making these forms more favourable, therefore the transition state energy required to form the intermediate is lower when the alkyl group is *ortho* or *para* with respect to the substitution site. This is summarized by substitution ratios shown in Scheme 1.3 for the nitration of toluene.



Scheme 1.3. Nitration of toluene.⁵⁶

It is noteworthy that, for the electrophilic aromatic substitution at the *meta* position of toluene, the intermediate has a lower energy transition state than that of the electrophilic aromatic substitution of benzene, Figure 1.13. This shows that the inductive effect still causes a small amount of stabilization at the *meta* position.⁵⁵

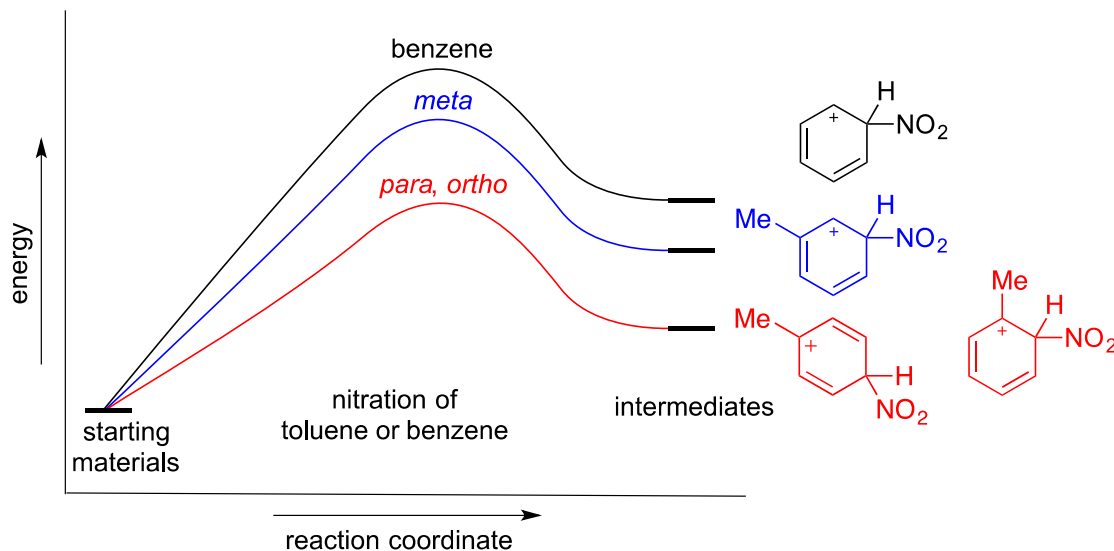
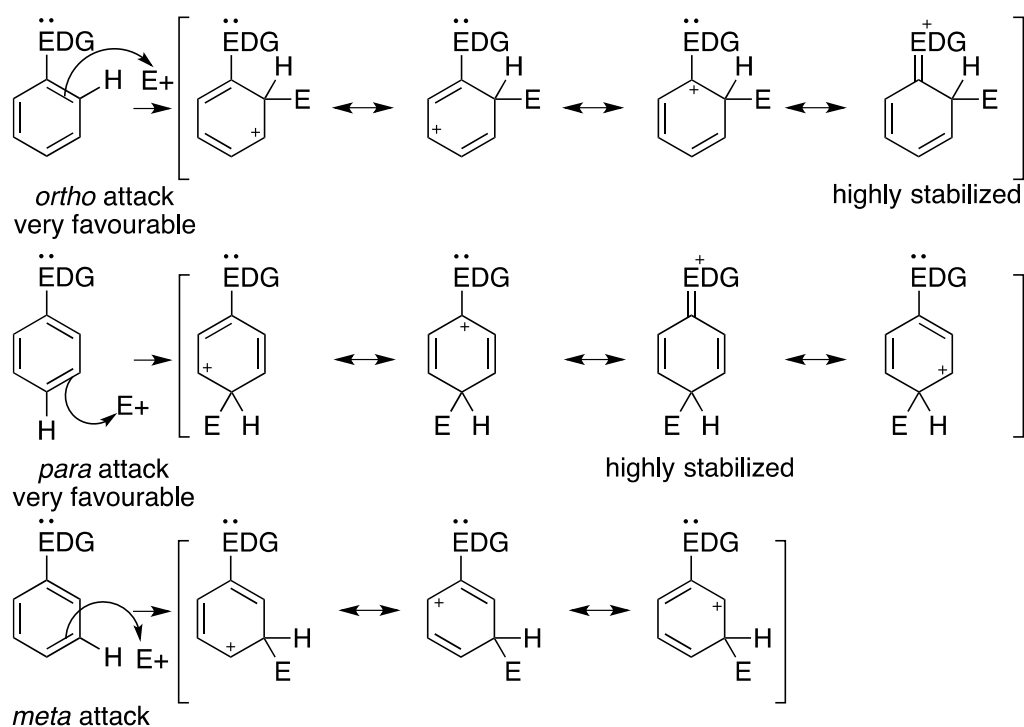


Figure 1.13. Hammond postulate comparing reactivity of toluene to benzene.

Electron donating substituents

Aryls substituted with groups that contain non-bonding electrons e.g. oxygen and nitrogen, increase the rate of electrophilic aromatic substitution, even though these groups are more electronegative than carbon. A lone, non-bonding pair of electrons from the substituent can stabilize the carbocation, formed in the intermediate by donating electron density through the formation of a π bond as one of the canonical forms. Electron donating groups (EDG) are *ortho*, *para*-directing, resulting from especially stable intermediates formed by the π -donating effect (Scheme 1.4).



Scheme 1.4. σ complexes of, *ortho*, *para* and *meta* substitution respectively with EDGs.

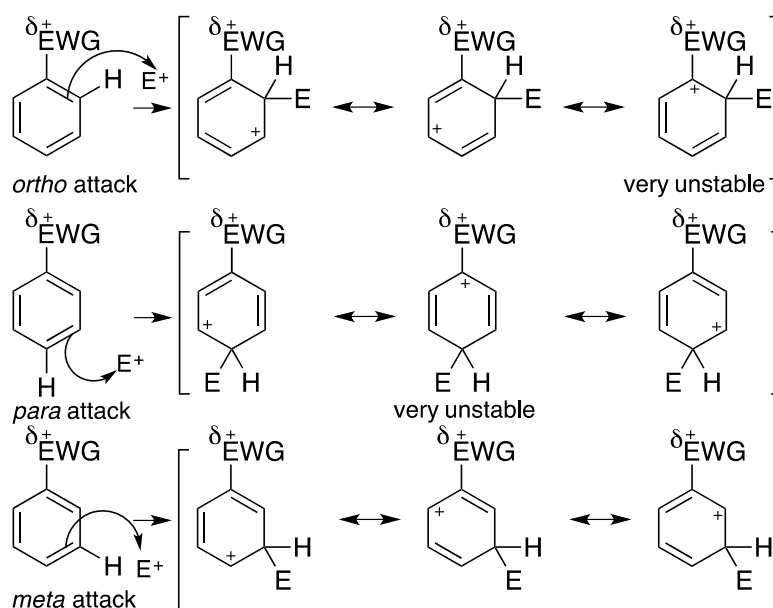
In the case of anisole the π -donation stabilising effect, described above result in nitration 400 times faster than toluene, and 10,000 times faster than benzene.

The effect of halogen substituents

Halogen substituents are strongly electronegative and due to the negative inductive effect react slower with electrophiles than benzene. However they do have non-bonding electrons and do form a halonium ion as their intermediate and this in turn stabilises this rate-determining step by π donation. The mechanism for this is similar to that shown in Scheme 1.4 (the rate of reaction is slower) leading to halogen substituents having an *ortho*, *para*-directing effect.

Effects of electron withdrawing substituents

Electron withdrawing groups (EWG) slow down the rates of reaction of electrophilic aromatic substitutions. In the case of nitrobenzene it is around 100,000 times less reactive than benzene. EWGs are known as deactivating groups and remove electron density predominantly from the *ortho* and *para* positions. The strongest deactivating group is the nitro group due to the positive charge on the nitrogen atom, but with different EWGs a δ^+ can be placed on the adjoining atom.




Scheme 1.5. σ complexes of, *ortho*, *para* and *meta* substitution respectively with EWGs.

The canonical forms in Scheme 1.5 demonstrate how only the substitution at the *meta* position proceeds through an intermediate which is not destabilized by adjacent positive or δ^+ -positives.

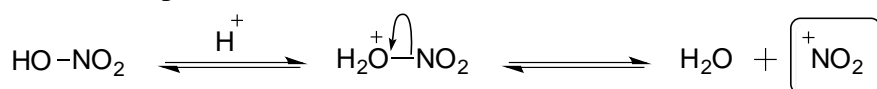
Effect of multiple substituents

When combining different functional groups, several factors need to be considered before making a prediction regarding the outcome of the reaction; the strength of the directing group, whether it is *para* or *ortho* directing and the steric factors involved. The balance of the three factors governs the outcome of these reactions. In some cases all directing groups direct to the same position making prediction of the site of substitution simpler, but sometimes mixtures cannot be avoided. The relative strength of the directing group has the greatest effect on the overall reaction outcome. This information is summarized in Table 1.3 below.

Table 1.3. Summary of directing groups and their relative strengths of activation effecting electrophilic aromatic substitution.

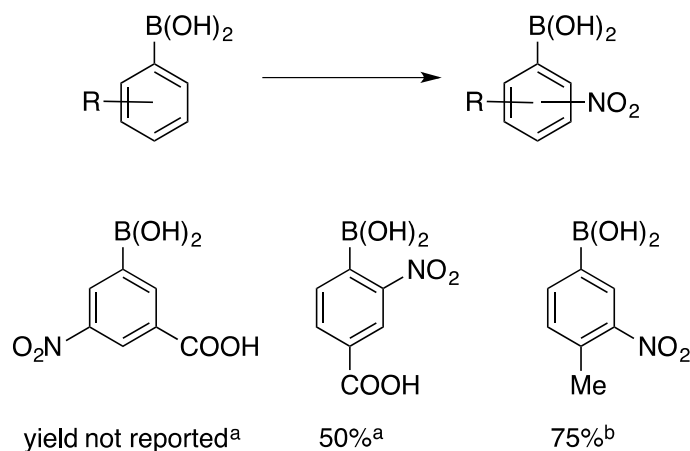
Activating Groups				Deactivating Groups				
π Donors		σ Donors		Halogens				
-OR	Stronger than	-R	Stronger than	-F	Weaker than	-CF ₃	Weaker than	-SO ₃ R
-NR ₂	>		>	-Cl	<	-NR ₃ ⁺	<	-NO ₂
				-Br				-CN
				-I				-COR
								-COOR
Ortho, para-directing substituents						Meta-directing substituents		

The formation of the electrophile is a key step in the reaction, as this needs to be formed in situ. The formation of the nitronium ion (NO₂⁺) requires the use of strong acids, normally concentrated sulphuric acid and concentrated nitric acid (Scheme 1.6). A



Scheme 1.6 Formation of nitronium electrophile.

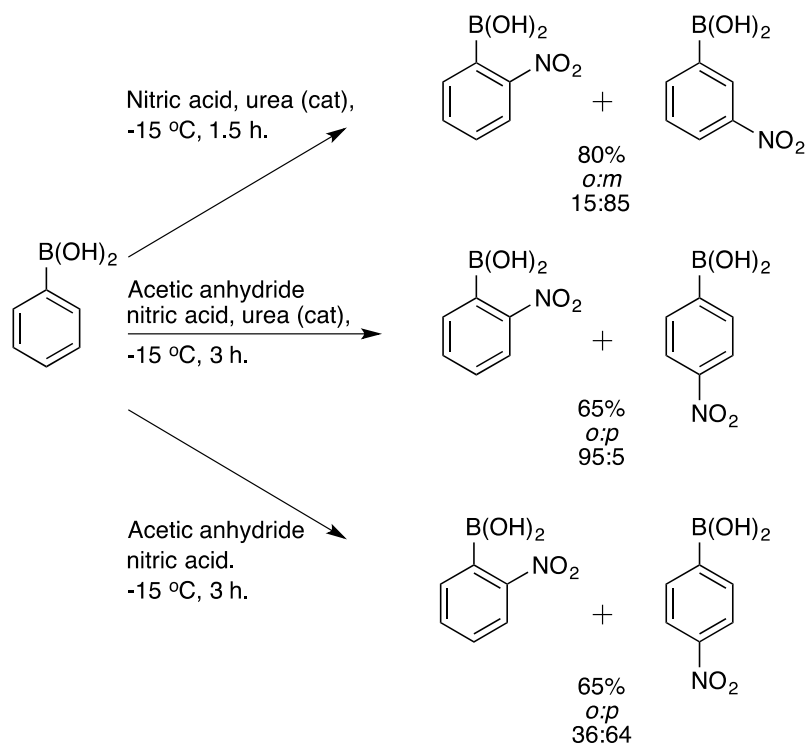
selection of arylboronic acids were synthesised using these strong conditions (Scheme 1.7).^{57,58} These results show the stability of the boronic acid under these strong acid conditions (Scheme 1.7).



Scheme 1.7. Compound made via nitration.

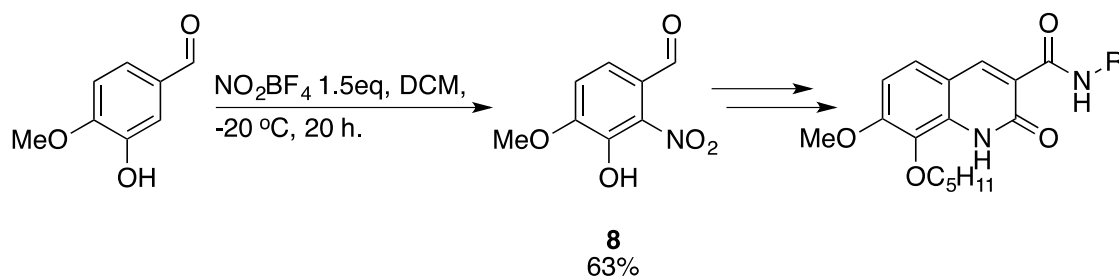
^a fuming nitric acid in sulphuric acid, rt, 30 min. ^b fuming nitric acid, -30 °C, 45 min.

Seaman and Johnson showed that phenylboronic acid could be nitrated selectively, giving mainly meta or ortho product depending on the reaction conditions used (Scheme 1.8, top and middle).⁴⁷ They found that using nitric acid alone gave 85% meta substitution with a total reaction yield of 80%. Whereas, when acetic anhydride was used with catalytic urea, 95% ortho substitution with a total reaction yield of 65% were observed. Van Der Eycken et al later used this methodology, and found that the catalytic urea was crucial to the ortho selectivity.⁵⁹ In this case they found that the para substituted product was the predominant product, 64%, with an overall yield of 58% (Scheme 1.8, bottom reaction). This shows how the boronic acid can be manipulated to direct nitration of the phenyl ring. Van Der Eycken et al hypothesised that this control is due to formation of a boronate species between the boronic acid and urea facilitating ortho substitutions, but no evidence has been found.



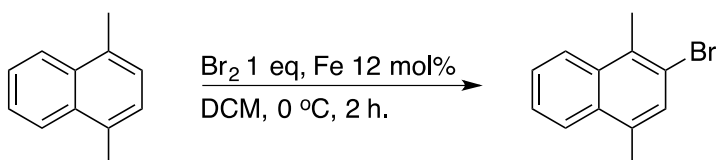
Scheme 1.8. Nitration of phenylboronic acid under different conditions.

Different nitronium sources can be used, such as nitronium tetrafluoroborate (NO_2BF_4), which has been studied in depth.^{60,61} Raitio *et al* synthesized 3-hydroxy-4-methoxy-2-nitrobenzaldehyde (**8**) as an intermediate towards a series of CB2 cannabinoid receptor ligands (Scheme 1.9).⁶² This series of compounds showed anti-inflammatory properties *in vivo*; the R group was changed throughout the study. They used NO_2BF_4 as it improved regioselectivity, as using standard nitric acid in sulphuric acid gave **8** in only a 10% yield.



Scheme 1.9 Nitration forming 3-hydroxy-4-methoxy-2-nitrobenzaldehyde, as an intermediate towards a series of CB2 cannabinoid receptor ligands.

Halogenation typically requires the formation of an electrophilic complex with a Lewis acid, to form the reactive electrophile in the reaction. Harvey *et al* used this in the synthesis of 2-bromo-1,4-dimethylnaphthalene, from which they made a variety of polyaromatic hydrocarbons for biological testing of carcinogenic affects (Scheme 1.10).⁶³ They used a catalytic amount of iron powder to form the Lewis acid iron (III) bromide *in situ*. The formation of this catalyst *in situ* is standard procedure due to the reactivity of

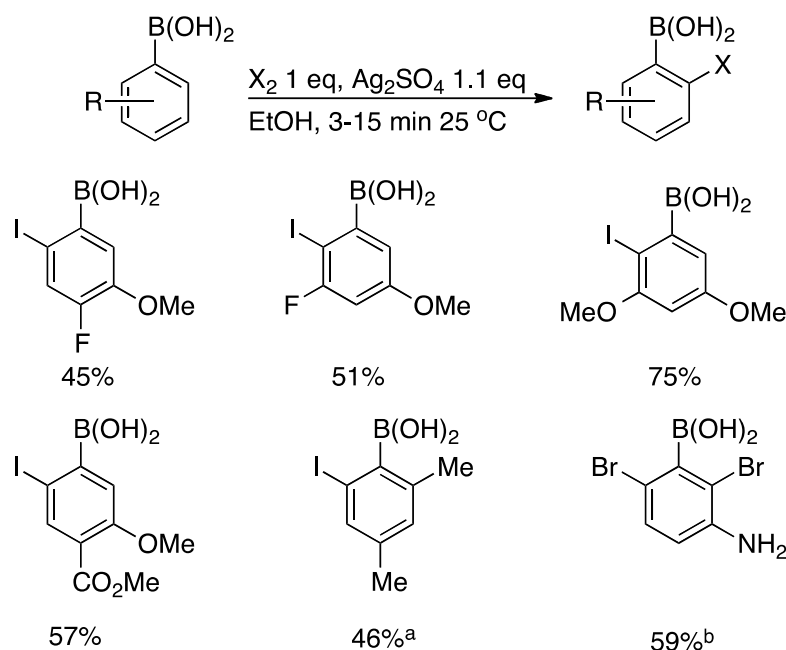


Scheme 1.10 Bromination with iron catalyst.

iron (III) bromide to moisture and air. Different Lewis acids can be used with bromine to produce similar Lewis acid complexes such as BF_3 .⁶⁴

Hall *et al* produced a wide array of *ortho* halogenated tetrasubstituted aromatic boronic acids using stoichiometric silver sulphate at room temperature (Scheme 1.11).⁶⁵ Within this work there are no examples of deactivated aromatics being halogenated.

N-Bromosuccinimide (NBS) is used more often as a brominating agent in modern times due to its ease of handling and since it produces succinimide as a relatively inert side



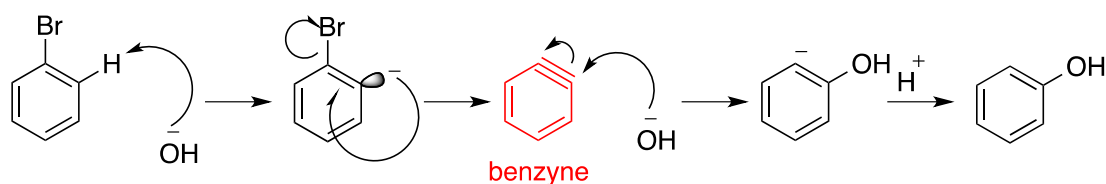
Scheme 1.11 *Ortho* halogenated aromatic boronic acids.

^aAgNO₃ 1 eq. was used. ^bBr₂ 2 eq was used.

product.⁶⁶ Saiganesh *et al* showed that bromination on highly deactivated substrates can be achieved using NBS in sulphuric acid.⁶⁷

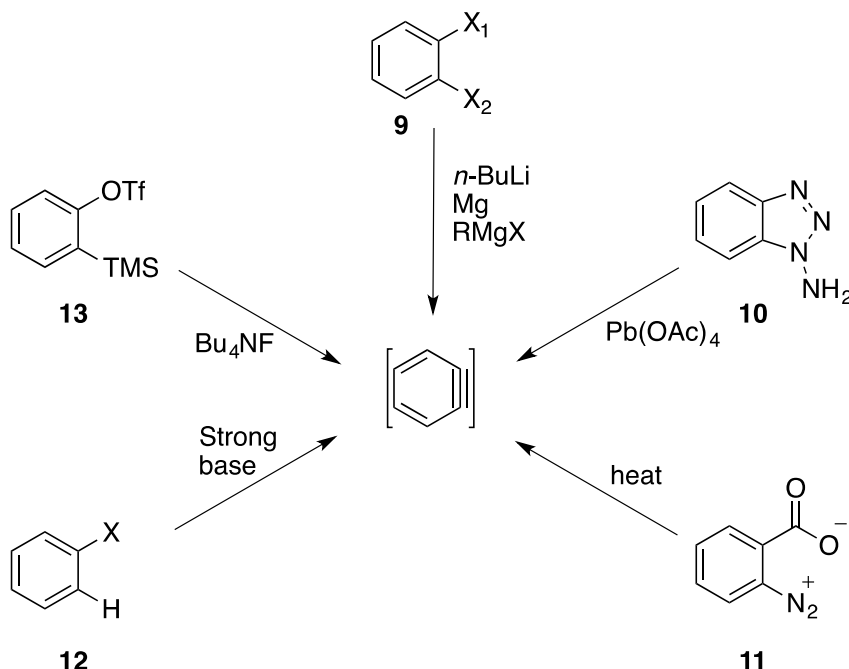
Benzynes

Treatment of bromobenzene in a sodium hydroxide melt would appear to give a nucleophilic substitution reaction to afford phenol, but this pathway for aromatic rings is highly unlikely. In a S_N2 process, the carbon bromine bond is in plane with the aromatic ring, and the nucleophile would need to attack the σ* orbital from the back of the C-Br bond; this would require the nucleophile to be inside the ring to attack, this attack would lose the ring's planar shape. If this were to go via an S_N1 it would require the unaided loss of the bromine making an unstable phenyl cation with an empty sp² orbital.⁵⁶ This reaction proceeds via a benzyne intermediate, formed via the deprotonation using a strong base *ortho* to the bromine. Elimination of the bromine is the next step of the reaction forming the benzyne (Scheme 1.12).



Scheme 1.12 Mechanisms for benzyne formation.

Then benzyne is not a true alkyne, it only has one normal π bond, which is part of the aromatic system. The newly formed π bond is made from two sp^2 orbitals that sit outside the ring, making it very weak and unstable. This weak bond allows the attack of nucleophiles.



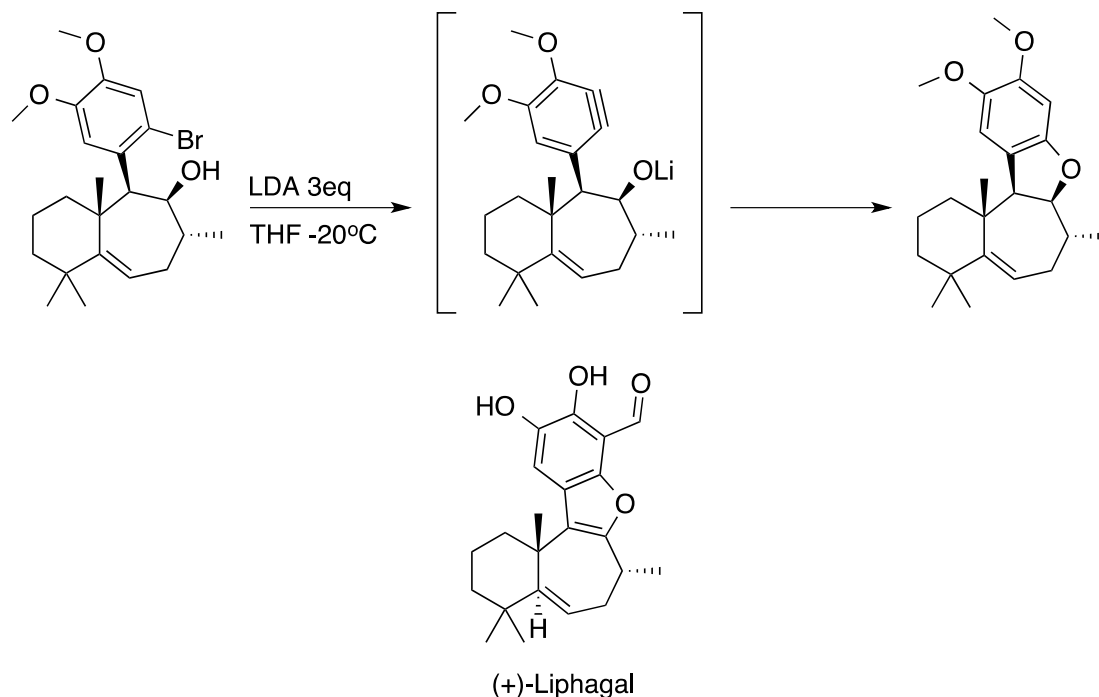
Scheme 1.13 Methods to generate benzyne.

Benzyne can be synthesised in several different ways as shown above in Scheme 1.13 aside from a sodium hydroxide melt. Strong bases can be used to deprotonate, *ortho* to the halogen (Scheme 1.13, **12**). Similarly *ortho* dihalide arenes can be used to prepare a Grignard or a lithium halogen exchange (Scheme 1.13, **9**). Both these processes lead to metalation *ortho* to the halogen, allowing for the elimination step to occur.⁶⁸

Benzyne can be made via methods that generate gas, thus are entropically driven. The first example of this was using arenediazonium-2-carboxylate (Scheme 1.13, **11**), which was produced *in situ* from the corresponding aniline. Compound **11** was heated to give off nitrogen and carbon dioxide gas, forming the benzyne.⁶⁹ 1-Aminobenzotriazole (Scheme 1.13, **10**) amino-protons can be oxidatively removed with lead (IV) acetate, this then fragments to give the benzyne and two nitrogen gas molecules.⁷⁰

Milder, more modern methods have been developed e.g. silyl triflates have become a milder way to form benzyne, without use of pyrophoric bases, shock-sensitive materials or toxic oxidants. Benzyne can be synthesised from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (Scheme 1.13, **13**), at room temperature using tetrabutylammonium fluoride.

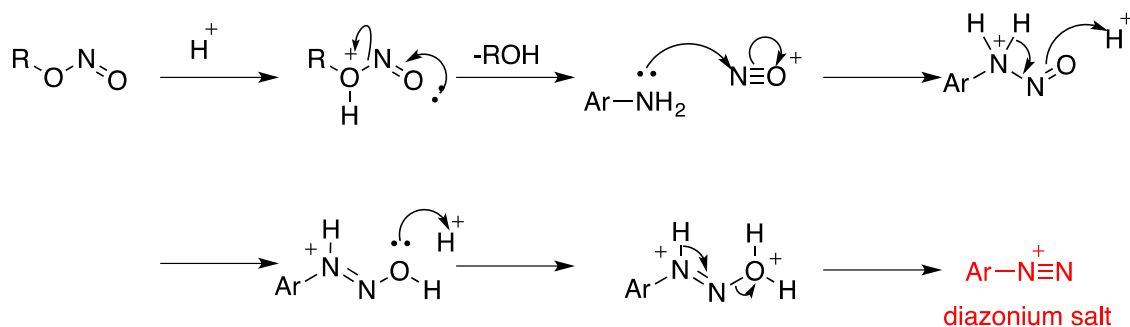
Benzynes are used regularly in the production of natural products such as in the synthesis of (+)-Liphagal, Scheme 1.14. This molecule has shown activity as a selective kinase inhibitor against phosphatidylinositol 3-kinase.⁷¹



Scheme 1.14 Synthesis of (+)-Liphagal.

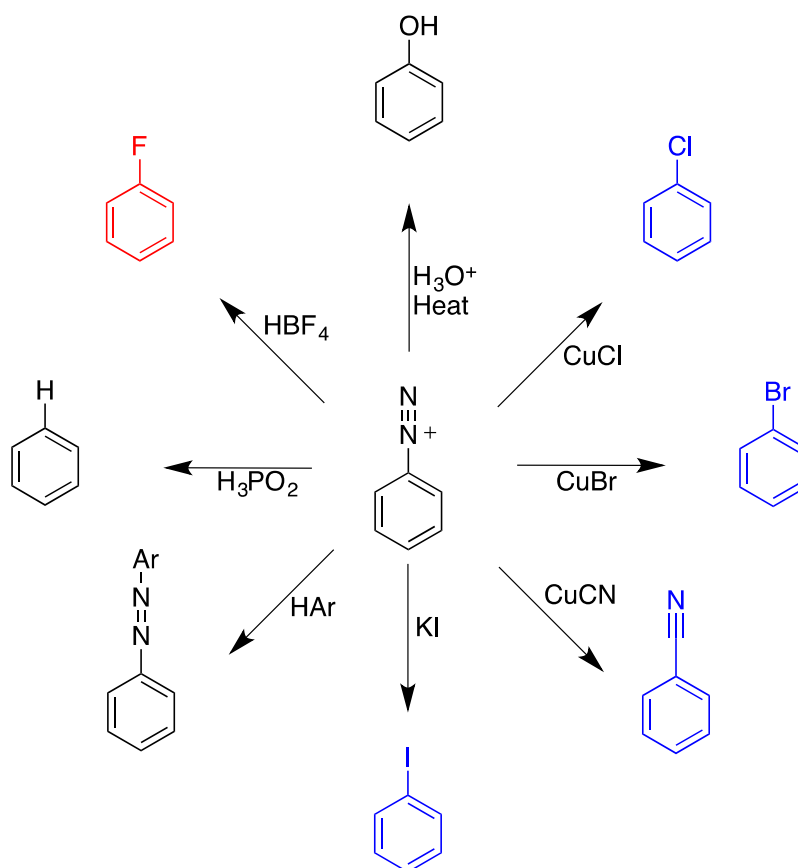
Diazonium salts

Aromatic diazonium salts, considering their structure, are surprising stable at temperatures below 5 °C, in the presence of water. This is due to the lack of stability of the carbocation formed on the loss of nitrogen, making nitrogen loss slower, allowing for controlled reactivity in S_N1 reactions. The diazonium salts can be installed from an aniline, using nitric acid, sodium nitrite in HCl, or an alkyl nitrite in HCl; the mechanism is shown below, Scheme 1.15.⁵⁶



Scheme 1.15 Mechanisms for the formation of diazonium salt.

The diazonium salt's anion is usually the conjugate base of the acid used in the preparation. Typically these salts are used *in-situ*, due to instability at room temperature, but room temperature stable analogues can be isolated via anion exchange to make the tetrafluoroborate salt.⁵⁶



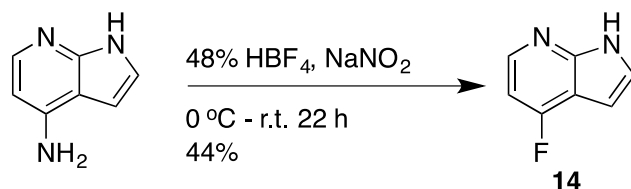
Scheme 1.16 Reactions that can be performed with diazonium salts.⁵⁵

In Scheme 1.16 the reactions outlined in blue are known as Sandmeyer reactions, and typically use copper salts, with the exception of iodination. Iodo groups are useful in aromatic compounds as they can be used in a large array of organometallic chemistry. Unfortunately iodine is not a good electrophile, unlike chlorine and bromine. This makes the Sandmeyer reaction a powerful method of group inter-conversion since iodine cannot be introduced via nucleophilic iodide. Krasnokutskaya *et al* have recently published a paper on these iodinations, using an efficient one-pot method. Starting from variety of different anilines, reactions took between 20 min and 2 h.⁷²

The example highlighted in red is an example of the Balz-Schiemann Reaction. This reaction forms the tetrafluoroborate aryl diazonium salt and is then heated to cause decomposition of the salts to nitrogen and boron trifluoride producing the desired arylfluoride. This reaction has been used in the synthesis of 4-fluoro-1*H*-

pyrrolo[2,3]pyridine (Scheme 1.17, **14**), the compound was formed via spontaneous decomposition from the tetrafluoroborate, on heating from 0 °C to r.t.⁷³ As highlighted in section 0 fluorine is highly desirable in medicinal chemistry, showing the importance of these methods.

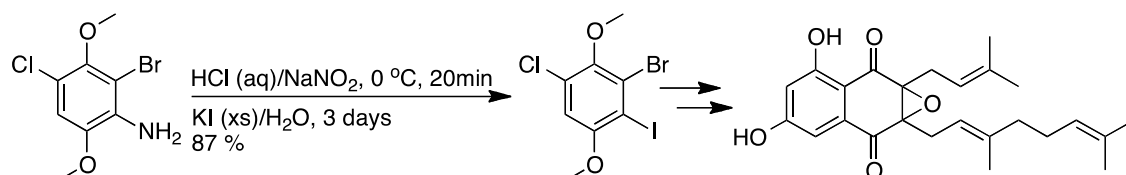
Nakata *et al* used the Sandmeyer reaction to iodinate an intermediate in the synthesis of



Scheme 1.17 Example of Balz-Schiemann reaction.

(±)-A80915G, which is a natural product with antibiotic properties, Scheme 1.18.⁷⁴ The iodine gave selectivity over the bromine in two subsequent Stille cross-coupling reactions.

The use of diazonium salts goes hand in hand with electrophilic aromatic substitution, as

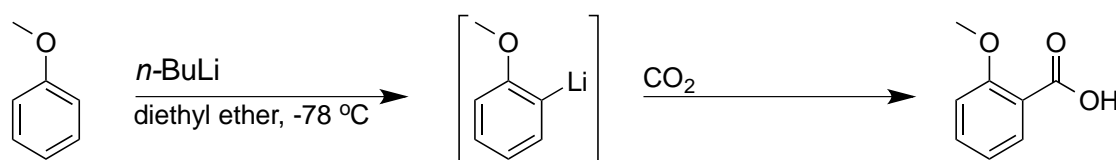


Scheme 1.18 Sandmeyer step in the synthesis of (±)-A80915G.

it allows for selective use of these two methods to give the desired compound. When taking into account that the nitro group is *meta* directing, this can be reduced to the corresponding aniline, which is *ortho*, *para* directing. This aniline can be transformed into a wide range of functionalities using diazonium salts, including the use of hypophosphorous acid reducing back to an aromatic proton, Scheme 1.16. Using these with foresight, can lead to selective functionalization of an aromatic ring.

Directed Ortho Metalation (DoM)

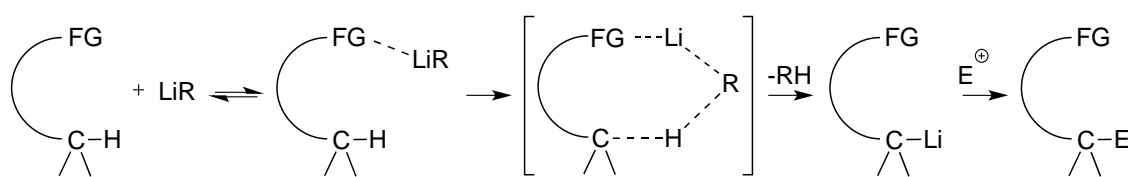
Butyllithium can deprotonate sp^2 hybridized carbons even in the presence of sp^3 carbons, because sp^2 protons are more acidic shown in Scheme 1.19. The independent research



Scheme 1.19 Directed *ortho* lithiation.

groups of Wittig and Gilman discovered this methodology of *ortho* lithiation of anisole.^{75,76} The aryllithium can then be quenched with a plethora of electrophiles, leading

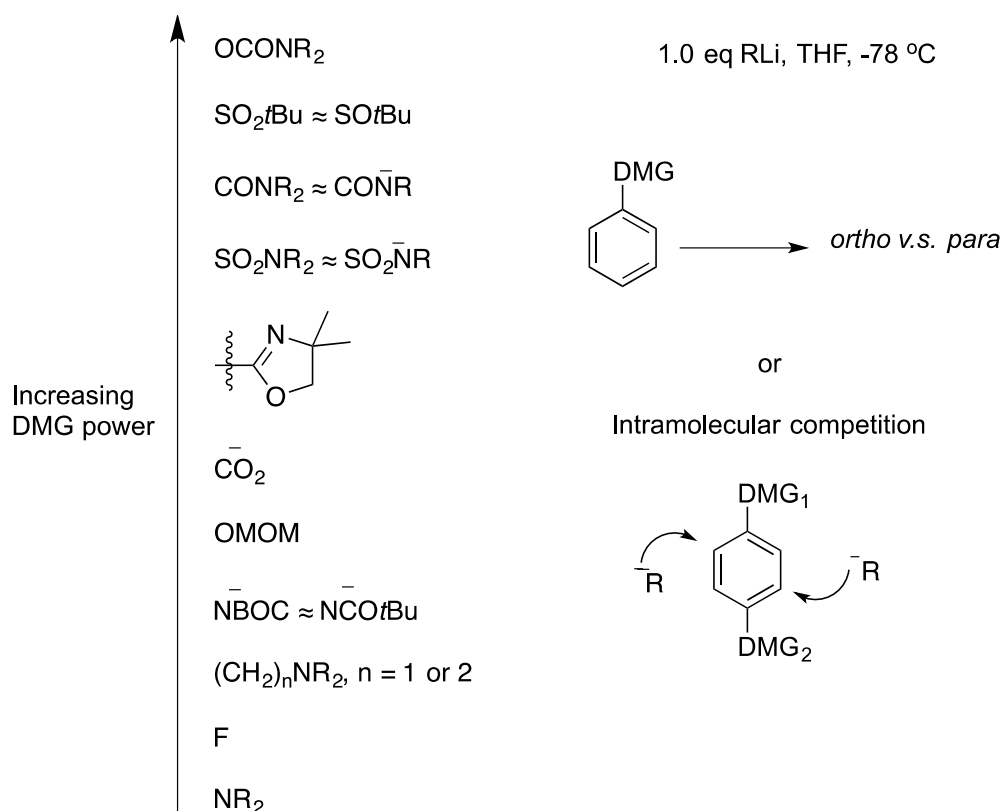
to different functionalities regioselectively at the ortho position e.g. DMF to make the



Scheme 1.20 Mechanism for direct *ortho* metalation.

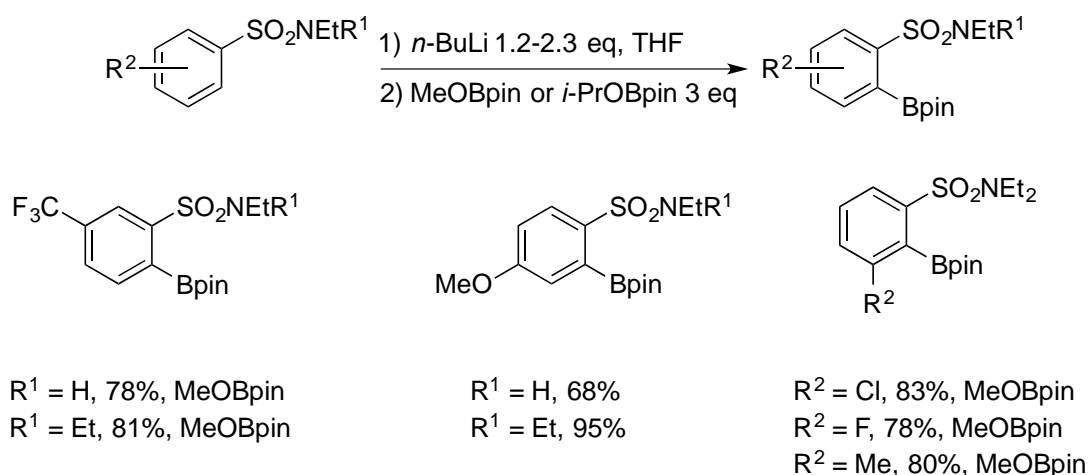
corresponding aldehyde, methyl iodide to make the corresponding methyl group or bromine to make corresponding bromide.

The mechanism of lithiation requires the directing group to complex to the lithium before the deprotonation occurs, shown in Scheme 1.20.



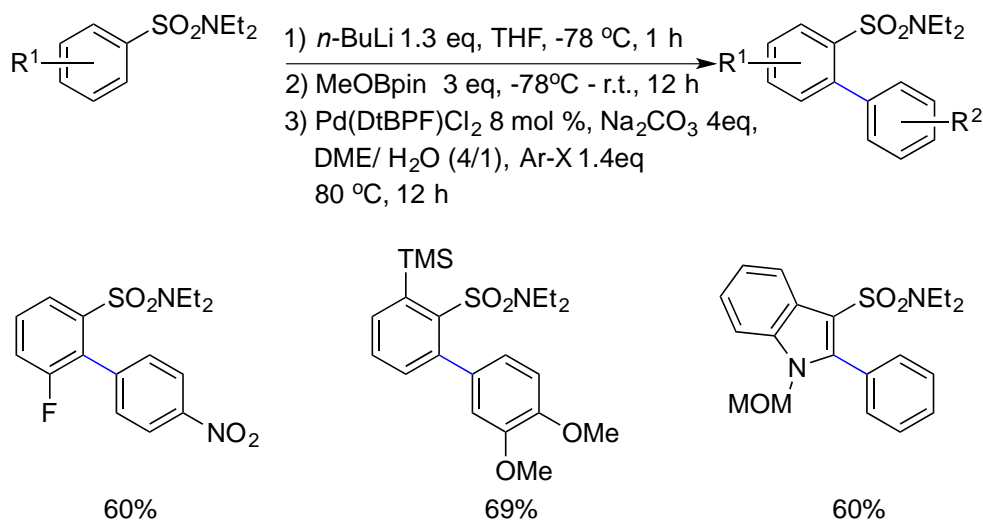
Scheme 1.21 Strength of directing effect.

This is known as the complex-induced proximity effect (CIPE).⁷⁷ The directing groups can be ordered in strength of their relative directive effect shown in Scheme 1.21. These are based on competition studies and rankings can change due to reaction temperature and the solvent used.⁷⁸



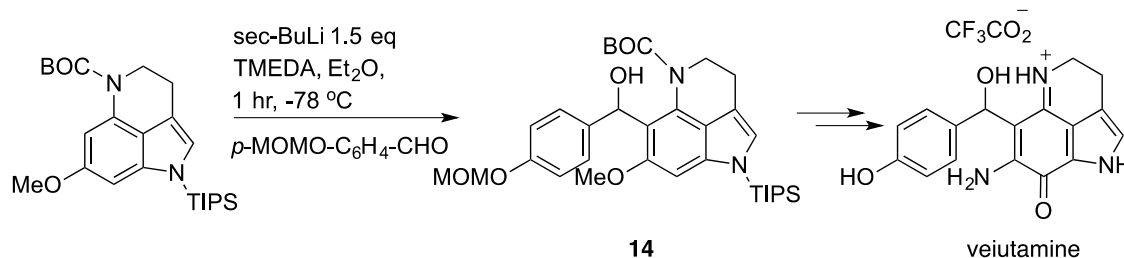
Scheme 1.22 *Ortho*-boropinacolatoaryls prepared via DOM.

Snieckus *et al* used this methodology to prepare an array of *ortho*-boropinacolato aryl and heteroaryl sulfonamides, some aromatic examples of which are shown in Scheme 1.22.⁷⁹ Within this publication they also showed its use as the first part of a two stage, one pot synthesis. The second stage was a Suzuki reaction following the DOM borylation; this was achieved by adding an aryl halide, base and a palladium catalyst to the same reaction mixture, Scheme 1.23. The yields were good considering that this methodology removed an aqueous work up / purification procedure.



Scheme 1.23 Suzuki reaction following the borylation.

The Iwao group used DOM in the first total synthesis of veitamine.⁸⁰ This marine alkaloid was of particular interest due to its antitumor activity. The aryl lithium was reacted with a *para* substituted benzaldehyde forming the alcohol (**14**), which was later cyclised as part of a larger synthetic route, Scheme 1.24.



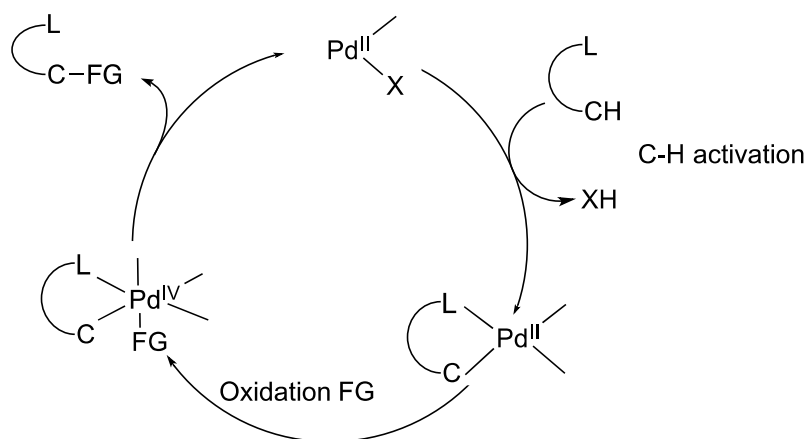
Scheme 1.24 A crucial DOM step in the synthesis of veitamine.

C-H activation

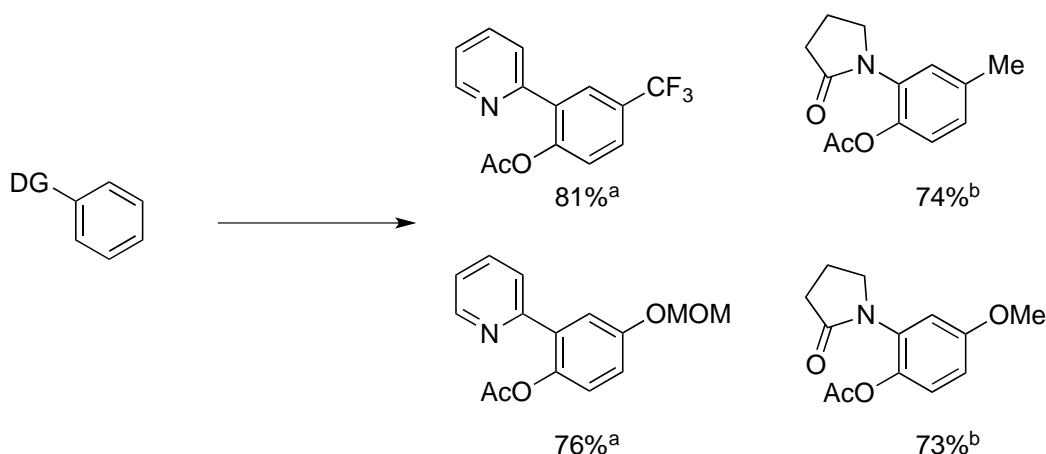
C-H activation is often transition metal-catalysed functionalization of a carbon-hydrogen bond forming a large variety of different, carbon-carbon,^{81,82} or carbon-heteroatom bonds, improving the atom economy of the reaction. These can be split into two groups, 1) without directing group functionalities,⁸³ 2) with directing groups functionalities.⁸⁴

Palladium is used in a large variety of different C-H transformations and in most cases they are directed by functionalities attached to the starting material. For this body of work, only aromatic examples will be given.

One of the first examples of palladium C-H activation was acetoxylation with (diacetoxyiodo)benzene ($\text{PhI}(\text{OAc})_2$).^{85,86} These reactions use a palladium (II) / palladium (IV) catalytic cycle, Scheme 1.25. The C-H activation does not change the oxidation state of the palladium centre and the selectivity of this step is driven by the directing effect of the ligand. In acetoxylation, $\text{PhI}(\text{OAc})_2$ is the oxidant used in the catalytic cycle, which allows the product to reductively eliminate, but other oxidants can be used.



Scheme 1.25 General catalytic cycle for palladium-mediated C-H activation.



Scheme 1.26 Products formed via acetoxylation with $\text{PhI}(\text{OAc})_2$.

^a, $\text{Pd}(\text{OAc})_2$ 5 mol%, $\text{PhI}(\text{OAc})_2$, benzene/ AcOH or benzene/ Ac_2O , 100 °C, 0.5- 4 h. ^b, $\text{Pd}(\text{OAc})_2$ 5 mol%, $\text{PhI}(\text{OAc})_2$, AcOH or Ac_2O , 100 °C, 3-12 h

This methodology was used to prepare a variety of different examples, some are shown in Scheme 1.26. In this scheme the directing groups shown are pyridine derivatives and 2-pyrrolidinone moieties, but other examples include e.g. diazenes, pyrazole.

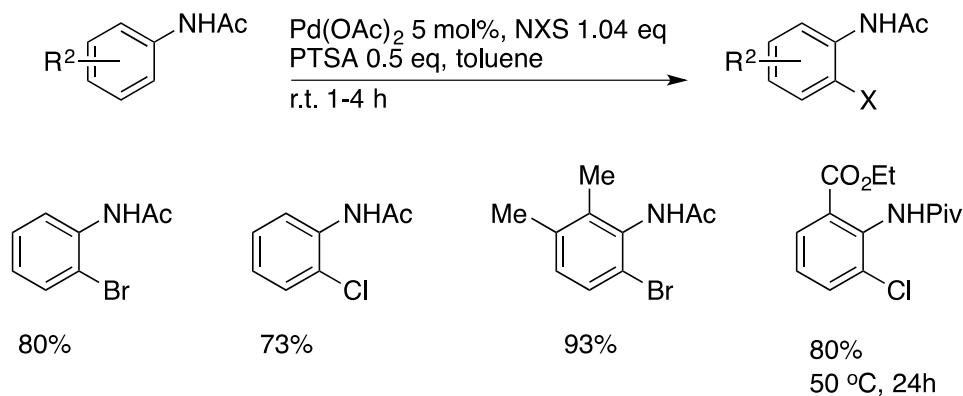
Table 1.4 Showing different parameters and isolated yields.⁸⁵

Oxidant	Solvent	Product (X)	Time (h)	Yield (%)
$\text{PhI}(\text{OAc})_2$	MeCN	OAc/OH 11:1	12	86
$\text{PhI}(\text{OAc})_2$	MeOH	OMe	12	95
$\text{PhI}(\text{OAc})_2$	EtOH	OEt	12	80
$\text{PhI}(\text{OAc})_2$	i-PrOH/ AcOH	OiPr	12	72
$\text{PhI}(\text{OAc})_2$	$\text{CF}_3\text{CH}_2\text{OH}$	OCH_2CF_3	12	71
NCS	MeCN	Cl	24-72	95
NBS	MeCN	Br	24-72	93

In the first acetoxylation publication, the authors demonstrated that different solvents and different oxidants changed the reaction outcome, shown in Table 1.4.⁸⁷ When an alcoholic solvent was used it was incorporated into the product. It also highlighted that the addition of excess lithium halide (Cl or Br) gave the corresponding halogenated species.

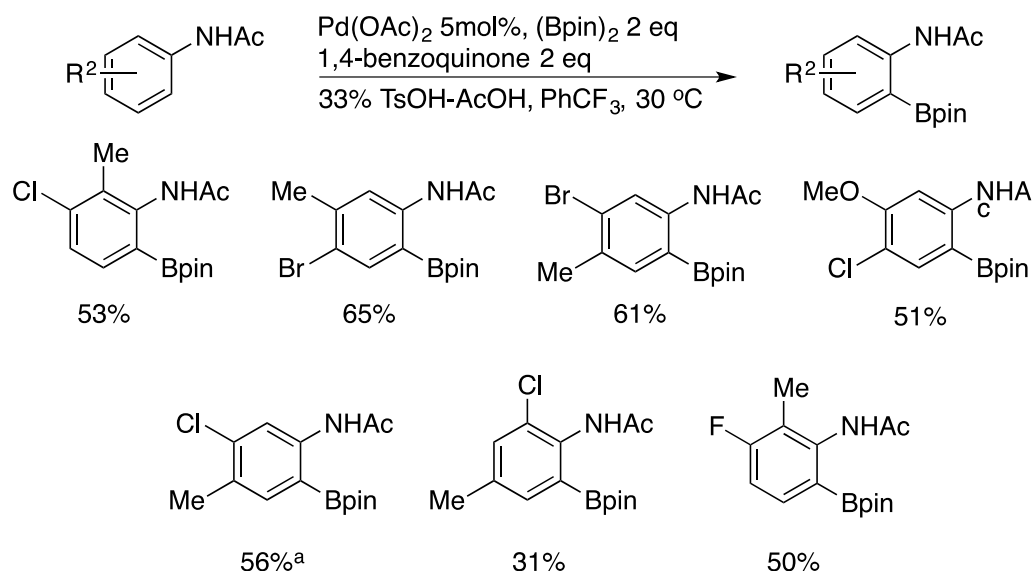
Halogenation did require optimisation; this was done by changing the oxidant to the *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide.

The Bedford group later used this approach in the C-H halogenation of anilides.⁸⁷ A selection of these halogenations is shown in Scheme 1.27, note that when pivaloyl (Piv) is used the reaction conditions required modification.



Scheme 1.27 Showing examples of C-H halogenation of anilides.

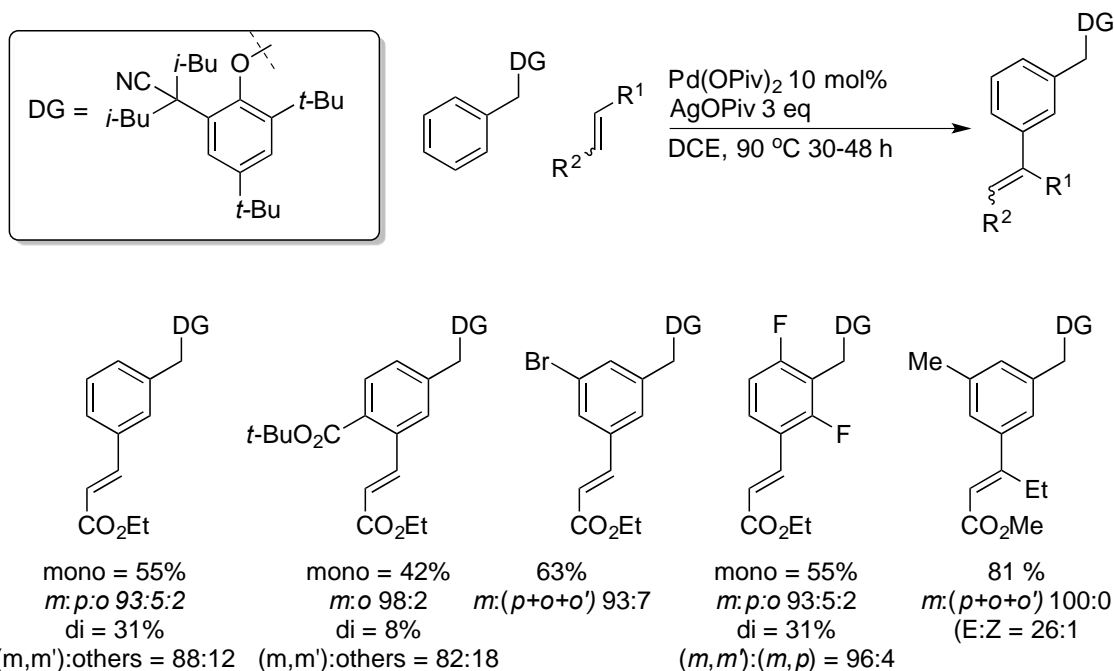
Fu *et al* achieved *ortho* borylation via a palladium C-H activation route using 1,4-benzoquinone as an oxidant.⁸⁸ With their results they attained seven different tetrasubstituted aromatics all of which contain four different orthogonal groups Scheme 1.28. Scheme 1.28 highlights this technique, as being highly functional group tolerant.



Scheme 1.28 Tetrasubstituted aromatics prepared via *ortho* borylation.

Yu's lab recently advanced the scope of C-H activation by the addition of *meta* directing ligands.^{89,90} In order to achieve this, they developed the *meta* directing ligand, shown in Scheme 1.29. which also enables a diverse array of olefinations. This ligand gave the highest selectivity, as highlighted in the schemes *ortho*: *meta*: *para* ratios, but not absolute

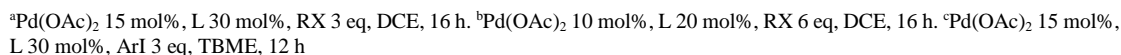
selectivity. They also synthesized a tetrasubstituted aromatic, giving a 1,2,3,4-



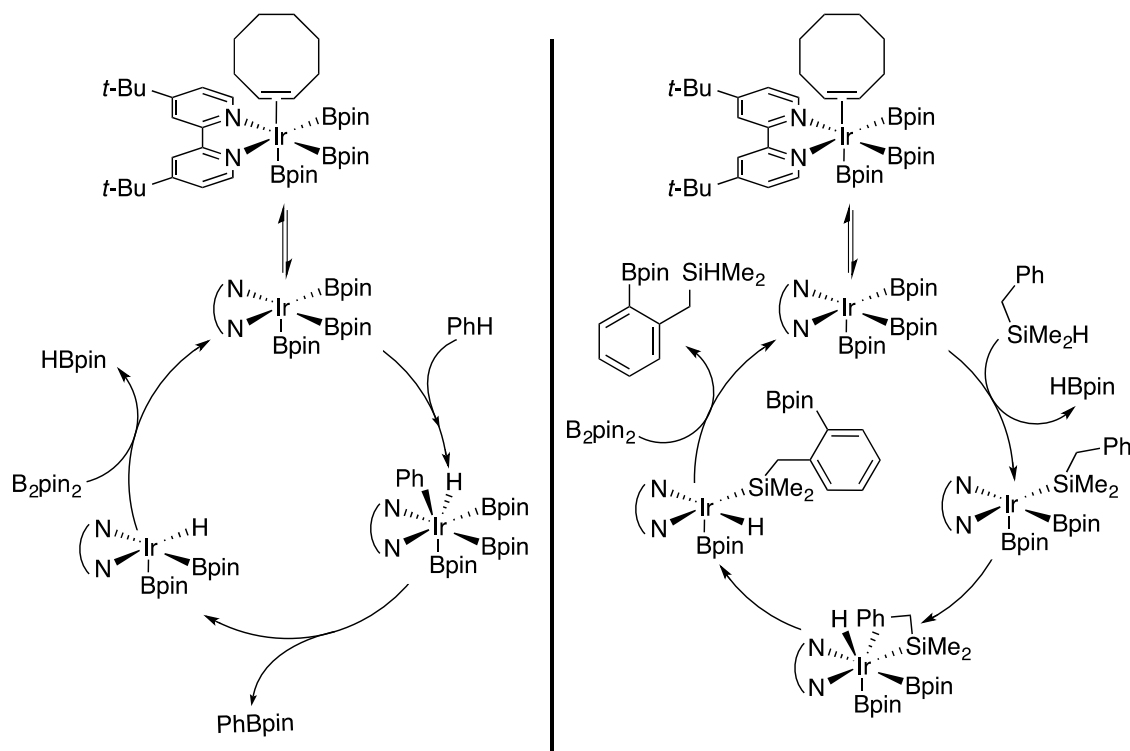
Scheme 1.29 *Meta* selective C–H olefination.

substitution pattern when the starting material is di-*ortho* substituted.

Yu's lab have also published a procedure for transforming an *ortho* directing group C-H activation into a *meta* C-H activation using norbornene as a transient mediator, shown in Scheme 1.30.⁹¹ They had optimised against pitfalls such as mono *ortho* functionalization, *ortho-meta* difunctionalization and reductive elimination forming an *ortho-meta* norbornene adduct. On testing of a wide range of ligands they found the pyridine based group shown in Scheme 1.30, gave the best results. This highlights a powerful technique for synthesising *meta* substituted compounds without the need to form unique internal directing ligands.



Iridium can be used to achieve catalytic C-H borylation of aromatic compounds.⁹⁵ Ishiyama and Miyaura's group developed the original undirected methodology in collaboration with the Hartwig group. This reaction can be performed *via* a directed route or an undirected route. The mechanisms are shown in Scheme 1.31.^{96,97} Note that the 4,4'-di-*tert*-butyl-2,2'-dipyridine (dtbpy) is the ligand throughout the catalytic cycle. The

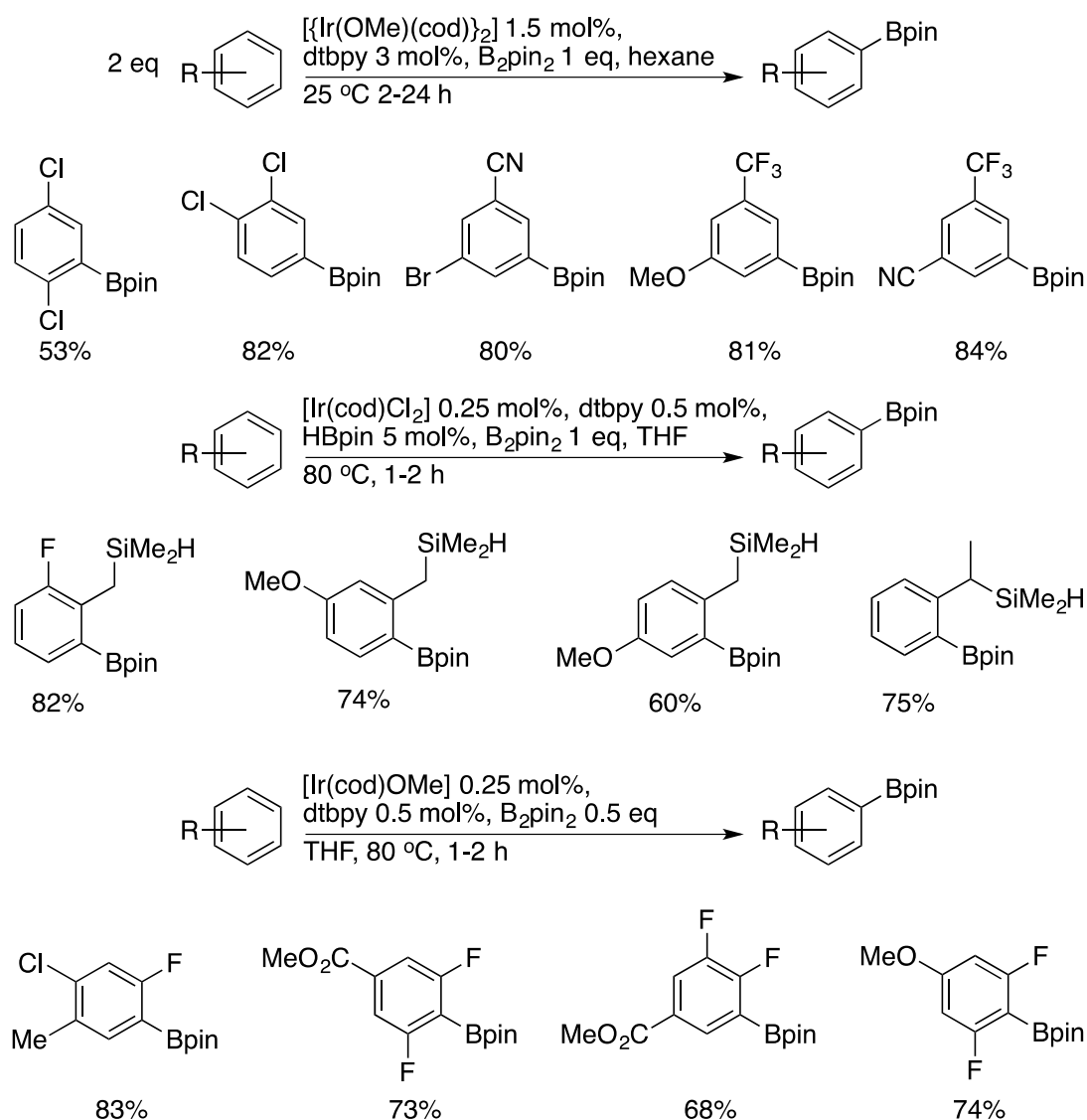


Scheme 1.31 Catalytic cycles for iridium-catalysed borylation of arenes, left nondirected method, right directed method.

selectivity of the reactions are governed by the sterics of the starting material, electronics only playing a small role. This was shown in an in-depth study of *para* substituted compounds, and the products that were synthesised.⁹⁸

Scheme 1.32 shows examples of products formed by this technique; the top example is the non-directed route,⁹⁹ the bottom shows some silyl-directed examples.⁹⁷ Clark *et al* also showed that benzylic amines could be used to *ortho* direct borylation.^{100,101}

Hartwig later published methodology towards tetrasubstituted aromatic compounds shown in Scheme 1.32.¹⁰² Within this publication a method for a one pot Suzuki was incorporated into the reactions, allowing for borylation, followed by cross-coupling with no work up.



Scheme 1.32 Iridium borylation; top, non-directed method; middle, directed method; bottom, non-directed method forming tetrasubstituted motifs.

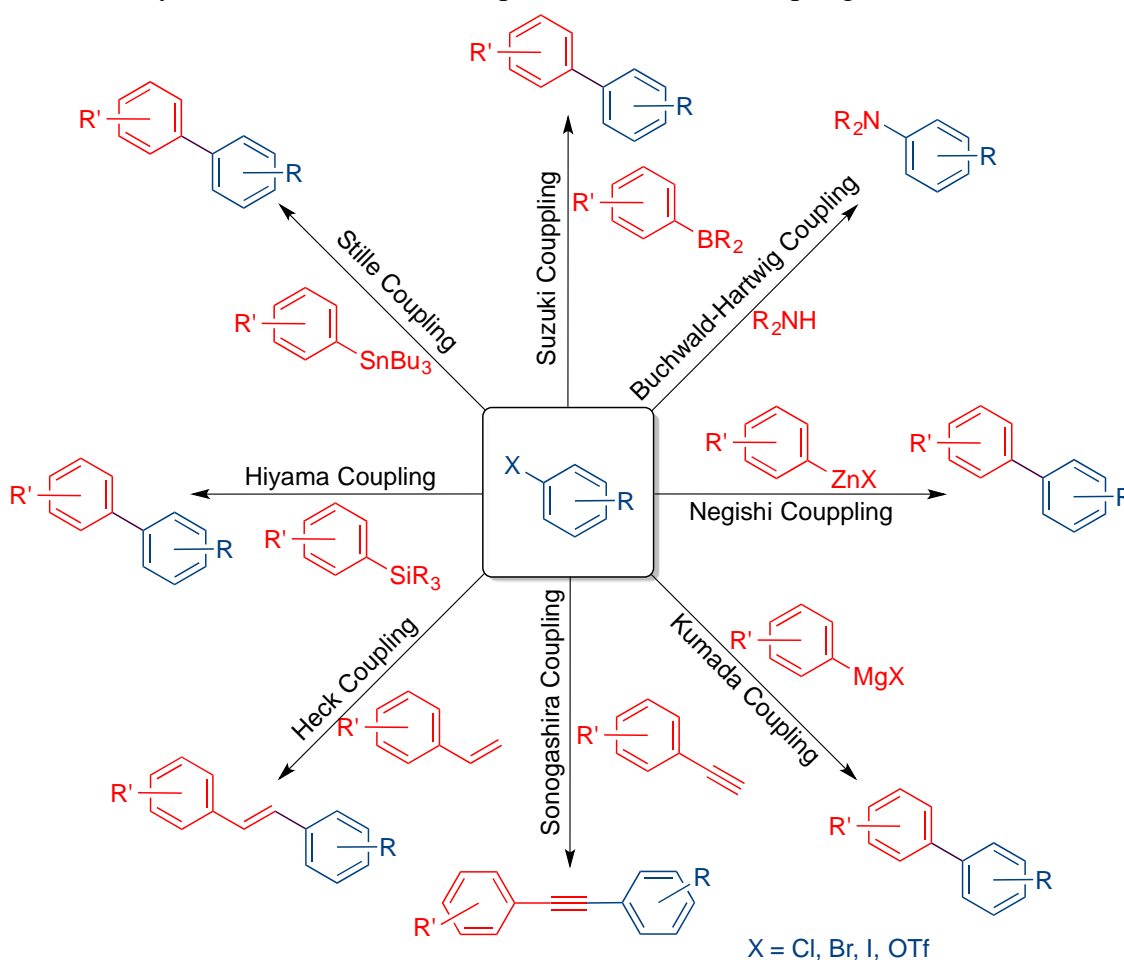
Li *et al* borylated a series of MIDA boronate containing aromatic and heteroaromatic compounds, Scheme 1.52. These were able undergo iterative coupling, elaborated further in section 0.¹⁰³

The reaction times have been improved by the use of microwave-assisted synthesis by Steel *et al*.¹⁰⁴ This development reduced reaction times to under an hour and in some cases as fast as five minutes. They also applied the one pot cross-coupling technique, achieving cross-couplings in 5 minutes, with yields above 90%.

These examples show the high functional group tolerances, yields and selectivity of these reactions.

Palladium cross-coupling reactions

Palladium-catalysed coupling reactions have become one of the most used synthetic tools in the organic chemist's arsenal. These reactions involve cross-coupling an organometallic nucleophilic reagent with an electrophilic organic halogen or pseudo-halogen reagent. These types of reactions are typically used for the formation of carbon-carbon bonds but are also used in carbon-nitrogen bond construction (Scheme 1.33). The scope of the organometallic reagent has been expanded to include Mg, Zn, B, Sn, or Si, over the 50 years since the first use of palladium in cross-coupling reactions.¹⁰⁵



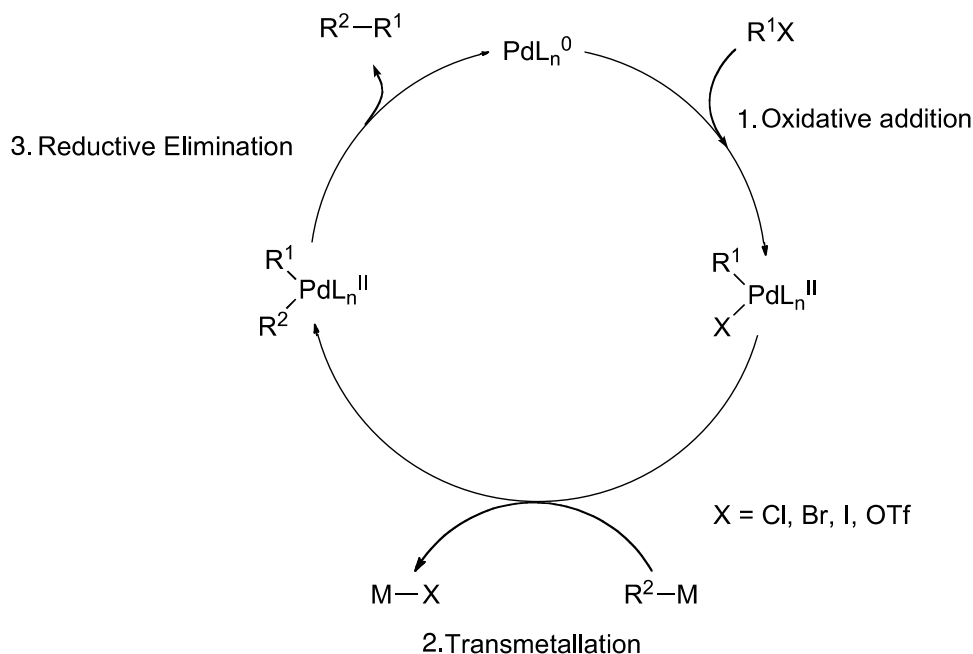
Scheme 1.33 Showing different palladium cross-coupling reactions.

All palladium cross couplings follow a similar general mechanism, with three key steps, shown in Scheme 1.34:¹⁰⁶

1. Oxidative addition of the organic electrophile, oxidising the palladium(0) to the palladium(II) species.

2. Transmetalation of the nucleophilic organometallic component.
3. Reductive elimination, releasing the coupled product, regenerating the palladium(0) species, thus restarting the catalytic cycle.

The Heck reaction follows a slightly different pathway, of migratory insertion followed



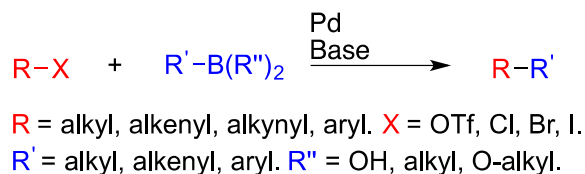
Scheme 1.34 Palladium cross-coupling general mechanism.

by β -hydride elimination.

Palladium cross-couplings are used regularly because of high functional group tolerance, low catalytic loading (on optimized systems) and the development of new ligands and co-catalysts allowing for the control of reactivity. These reactions are used on gram scale in academic and medicinal research labs, to ton-scale in the pharmaceutical and fine chemical industries.¹⁰⁷ The fathers of this chemistry Heck, Negishi and Suzuki received a combined Nobel Prize in 2010 for their work in founding this area of chemistry.¹⁰⁸ During this project Suzuki and Sonogashira reactions were the only palladium cross-coupling reactions used; these will be discussed in greater detail in section 0 and 0

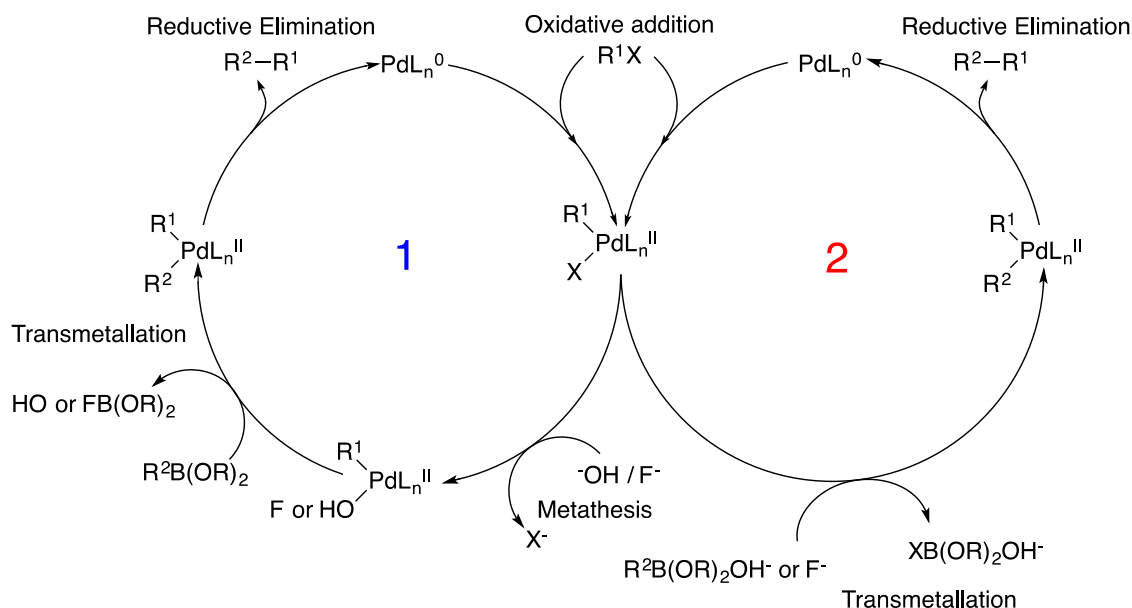
Suzuki cross coupling

The first palladium cross-coupling of alkenylboranes with alkenyl or aryl halides was performed by Suzuki, Miyaura and Yamada in 1979.^{109,110} This is known as the Suzuki



Scheme 1.35. General Suzuki cross-coupling conditions.

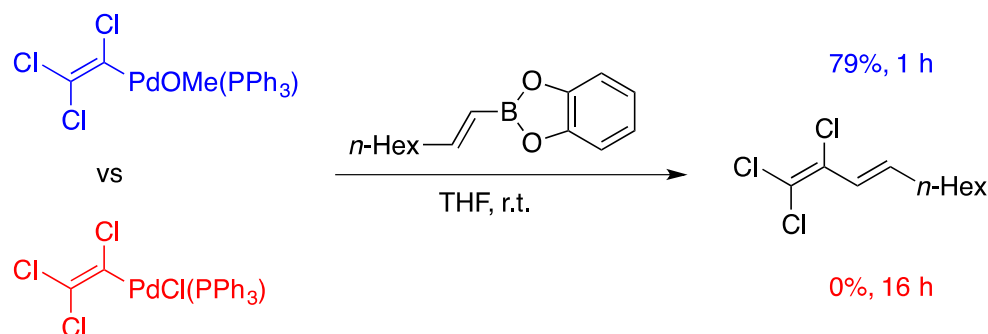
or Suzuki-Miyaura coupling. The Suzuki reaction is the most common synthesis of the biphenyl motif, which is considered a privileged structure in medicinal chemistry and appeared in 4.3 % of drugs in 2000.¹¹¹ Biphenyls have shown diversity in receptor selectivity, as they can be functionalised with substitution patterns that enable complementary binding to aromatic and or hydrophobic sites with a protein.¹¹² Biphenyls have various applications, for example in the synthesis of dialkylbiaryl phosphine ligands,¹¹³ chiral biaryl compounds,¹¹⁴ liquid crystals,^{115–117} and natural products *e.g.* selaginellin D (Figure 1.2). These all demonstrate the importance of the Suzuki coupling. The Suzuki reaction is the favoured method due to the mild reaction conditions, high functional group tolerance, the commercial availability of starting materials, also the reaction by-products are much less toxic than other reactions (*e.g.* tin in the Stille coupling) and the reactions are high yielding when optimised. For these reasons highlighted above, the number of publications and patents using this reactions between the years 2001-2010 out numbers any other palladium cross-coupling by almost 3000.¹⁰⁵ There are differing proposals for the Suzuki coupling catalytic cycle. Earlier proposals are represented in Scheme 1.37 general cycle 2.¹¹⁸ This cycle involves the negatively charged boronate *in situ e.g.* $\text{R}^2\text{B(OR)}_2\text{OH}^-$, formed from the base, and facilitates transmetalation.



Scheme 1.37. Different general catalytic cycles for Suzuki couplings. 1) modern, 2) general.

One of the modifications which defines cycle 2 was the addition of the metathesis step, whereby the ligand exchanges in the palladium coordination sphere. The halogen or *pseudo*-halogen from oxidative addition, exchanges to a hydroxyl, which is shown as the metathesis step. This enables the transmetalation; evidence for this came from Suzuki *et al*, Scheme 1.36. These works show the chloro-compound to be unreactive, whereas the methoxy compound resulted in the production of palladium black and was complete within one hour. This highlights a role of the base in enabling transmetallation.¹¹⁹

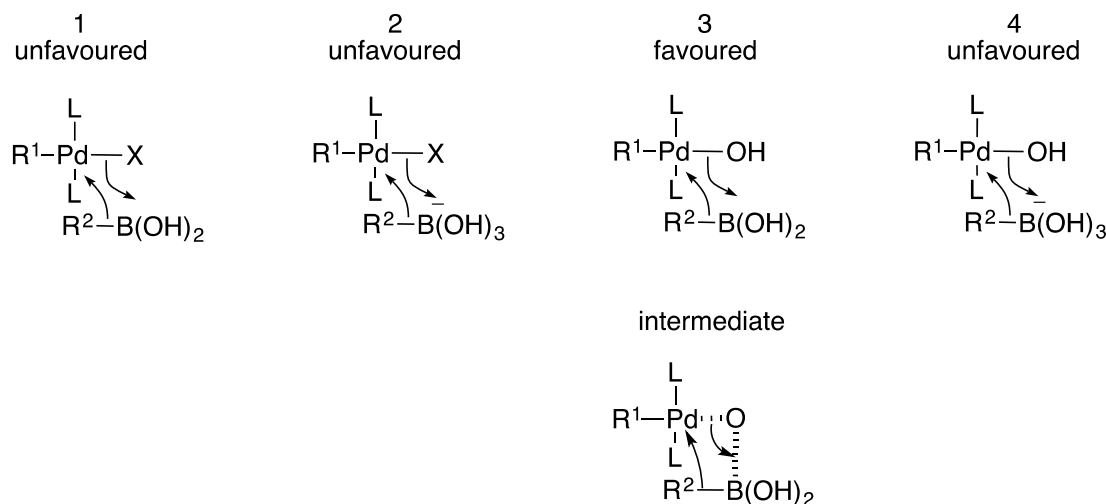
Amatore and Jutand *et al*, did selective reaction probing, showing detailed evidence for



Scheme 1.36. Differences in reactivity between chloro compound vs methoxy compound.

the role of the base in the transmetallation step.¹²⁰ They showed that the boronate was not the reactive species in transmetalation, as the rate of reaction became very slow at high OH^- concentrations, as shown in Scheme 1.38 pathway 4. At these concentrations the boronate ($\text{PhB}(\text{OH})_3^-$) and the $[\text{Pd}(\text{Ar})(\text{PPh})_2(\text{OH})]$ both exist together, as they demonstrated the shift in equilibrium at high OH^- concentrations shown in ^{11}B and ^{31}P

NMR spectroscopic experiments respectively. This showed that the boronate was unfavourably disposed towards transmetallation. In this series of experiments the starting material was the premade product of stoichiometric oxidative addition i.e. [(*p*-NC₆H₄)Pd(PPh)₂Br]. This removed the oxidative addition step from the rate mechanistic investigation. The introduction of this species into a system with no hydroxide ions present exhibited no reaction, thus discounting pathway 1 as the likely mechanism. This was conducive with the example described in Scheme 1.36. Experiments to explore the



Scheme 1.38. Mechanism of the transmetallation through different pathways.

role of pathway 2 required the preformed boronate species to be added to a reaction system with excess halogen concentration, thus ensuring the Pd-halogen bond remained intact. Pathway 2 was ruled out as no reaction was observed, in that case.

These observations showed that pathway 3 was the most favoured and they postulated a four-centred transition state, which was supported by DFT calculations.¹²¹

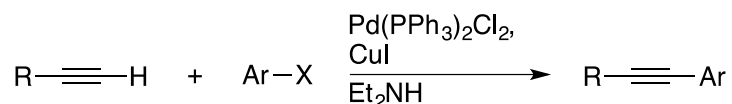
This body of work supports that cycle 1 from Scheme 1.37 is the more likely mechanism for Suzuki reactions.

Several examples of Suzuki couplings appear throughout sections 0 and 0.

Sonogashira cross-coupling

Castro and Stephens, in 1963, showed that cuprous acetylides could be coupled with aryl iodides to effectively prepare arylated alkynes.¹²² This seminal work was improved with the use of catalytic palladium with alkynes and aryl iodides. These sp-sp² C bond-forming reactions led to independent publications by the groups of Heck and Cassar.^{123,124}

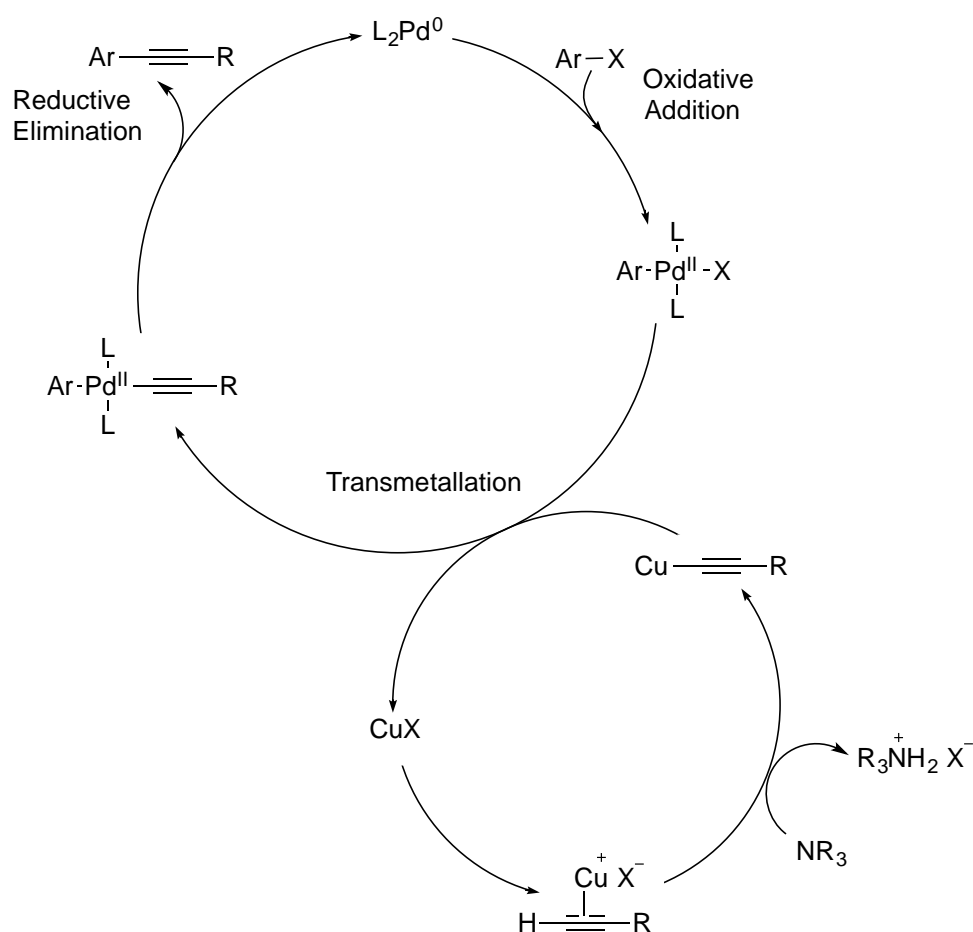
Sonogashira *et al* improved reaction conditions furthered by the addition of catalytic



Scheme 1.39. General Sonogashira coupling reaction.

amounts of copper (I) iodide, Scheme 1.39.¹²⁵ This enabled a room temperature reaction as it formed copper acetylides *in situ*. This methodology has become the standard for the preparation of arylated alkynes.¹²⁶

The generally accepted mechanism of the Sonogashira coupling has changed little from the original publication. There are two simultaneous catalytic cycles as shown in Scheme 1.40.



Scheme 1.40. General mechanism of Sonogashira cross couplings.

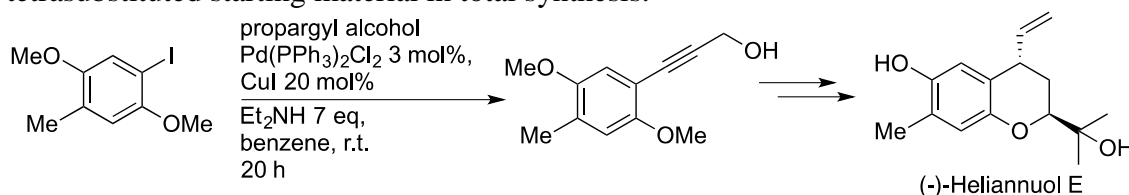
The palladium catalytic cycle is typical of most palladium cross coupling reactions, oxidative addition of an aryl halide, with a transmetalation of a copper acetylide. The copper catalytic cycle is less understood, but the most accepted hypothesis is the presence of a copper (I) salt allows for the deprotonation of the terminal alkyne.¹²⁷

Table 1.5. pK_a of typical compounds used in Sonogashira cross couplings.

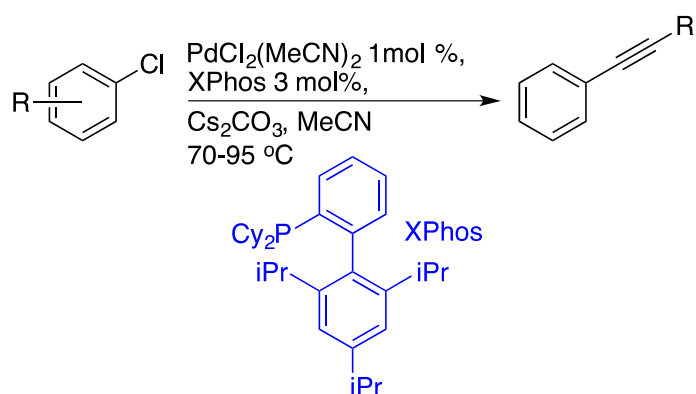
Compound	pK_a
Phenyl acetylene	23
Triethylamine	11
Potassium carbonate	10

Phenyl acetylene cannot be deprotonated directly by the traditional base used in the reaction e.g. triethylamine, potassium carbonate, as they are not strong enough bases see (Table 1.5). It is assumed that the copper forms a π -complex with the alkyne, in a similar manner to the formation of silver acetylides.¹²⁸ This enables the deprotonation of the alkyne by enhancing the acidity of the terminal hydrogen. Transmetalation can then occur followed by reductive elimination, forming the product and the palladium(0) species.

This methodology has been used in the total synthesis of (-)-heliannuol E as show in Scheme 1.41.¹²⁹ This was a quantitative yielding reaction and this highlights the use of a tetrasubstituted starting material in total synthesis.

**Scheme 1.41.** Outlining Sonogashira coupling in the total synthesis of (-)-Heliannuol E.

Aryl chlorides have also been used in Sonogashira reactions; Buchwald *et al* performed a selection of copper-free reactions using $[PdCl_2(CH_3CN)_2]$ and XPhos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) as ligands (Scheme 1.42).¹²⁷ Yi *et al* showed that similar chlorides could be coupled using the $PdCl_2(PCy_3)_2$ as the catalyst

**Scheme 1.42.** Copper-free Sonogashira reaction, XPhos ligand shown in blue.

at high temperatures (150 °C) in DMSO.¹³⁰ Lipshutz *et al* used the PTS surfactant to achieve copper-free Sonogashira of aryl bromides at room temperature, therefore removing organic solvents from these alkyne couplings.¹³¹

N-methyliminodiacetic acid (MIDA) boronates

sp^3 vs. sp^2

When boronic acids are protected with *N*-methyliminodiacetic acid the boron atom becomes sp^3 hybridized via a dative covalent bond. Transmetallation requires a Lewis acidic, vacant p-orbital, making MIDA boronates poor coupling partners in palladium cross coupling reactions as shown in Figure 1.14.¹³²

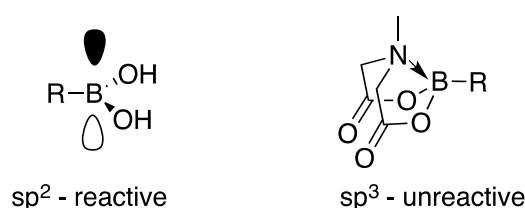


Figure 1.14. Boron sp^3 vs. sp^2 .

Different protecting groups can form an sp^3 centre i.e. *N*-methyldiethanolamine boronates but the strength of the dative covalent bond differs. Burke *et al* showed this via comparison of variable temperature (VT) NMR studies (Figure 1.15).¹³³

Burke showed that there were no major differences in the X-ray crystallography between

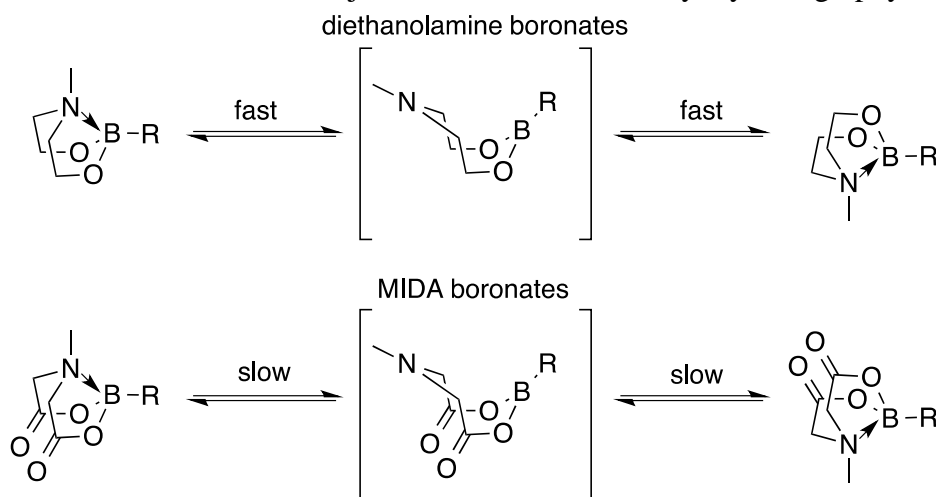


Figure 1.15. Variable temperatures comparison of two different boronates conformational rigidity, at NMR time scale.

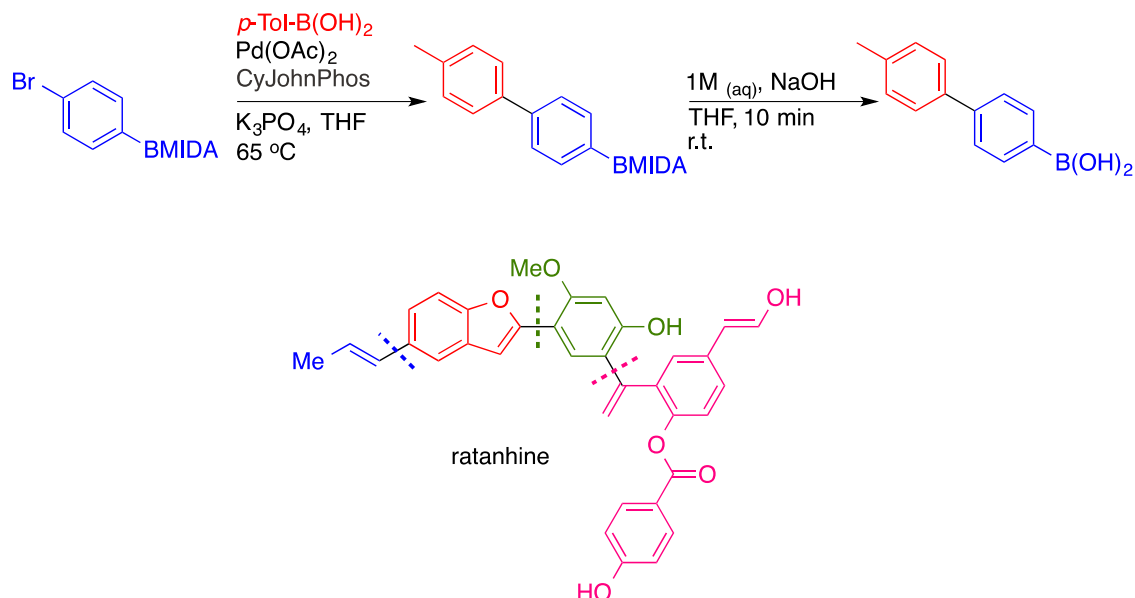
the structures of both boronates. The methylenes in the backbone of both boronates have protons that are diastereotopic; on heating these coalesce due to an equilibrium between the two states (Figure 1.15). The MIDA boronate showed no coalescence on heating to 150 °C, whereas *N*-methyldiethanolamine boronate showed coalescence

between 23 °C - 60 °C. This shows that at room temperature the p-orbital of the *N*-methyldiethanolamine boronate is accessible due to the dynamic dative covalent bond, whereas the p-orbital of the MIDA boronate is not kinetically accessible at less than 150 °C.

The boron reagent tends to be the most nucleophilic part in the SM coupling, and comparisons have been made between reactions with the same electrophile to give them a rating of nucleophilicity.¹³⁴ The MIDA boronate was the least nucleophilic of the common reagents including the aforementioned *N*-methyldiethanolamine boronate. This is due to the electron withdrawing effect from the carbonyls, even with the quaternization of the nitrogen. As in the case of the *N*-methyldiethanolamine boronate the electron density given via the dative covalent bond increases its nucleophilicity.

Use of MIDA boronates in iterative couplings

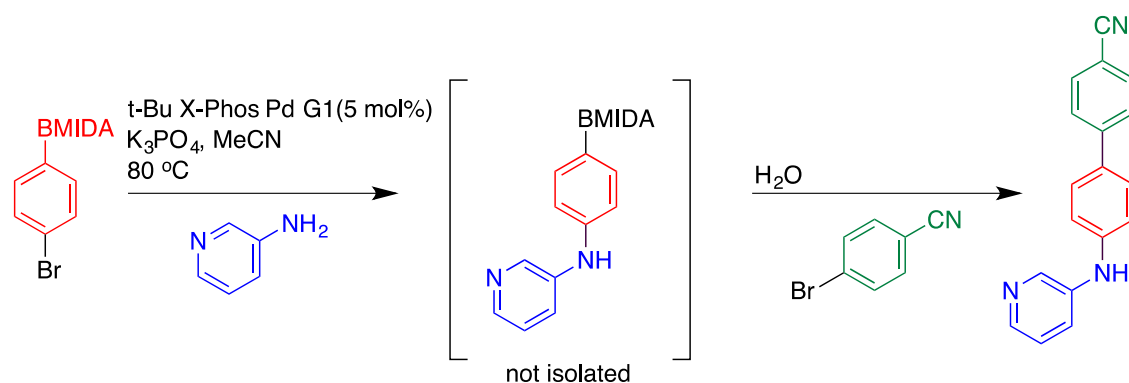
The MIDA boronate functionality is cleaved to give unmasked boronic acid under aqueous basic conditions.¹³⁵ The inertness of the MIDA boronate functionality allows for it to be used in iterative anhydrous palladium cross coupling reactions. This chemistry allows for protection, anhydrous coupling, deprotection and secondary coupling cycles.¹³⁶ Within this publication this methodology was applied to several simple molecules as shown in Scheme 1.43.



Scheme 1.43. Reaction showing simple cross-coupling and deprotection cycle. Ratanhine natural product formed by iterative cross couplings, with dashed lines showing new bonds.

They also applied this to the preparation of Ratanhine, which is a complex natural product. This was made up from 3 coupling / deprotection cycles of different units. These

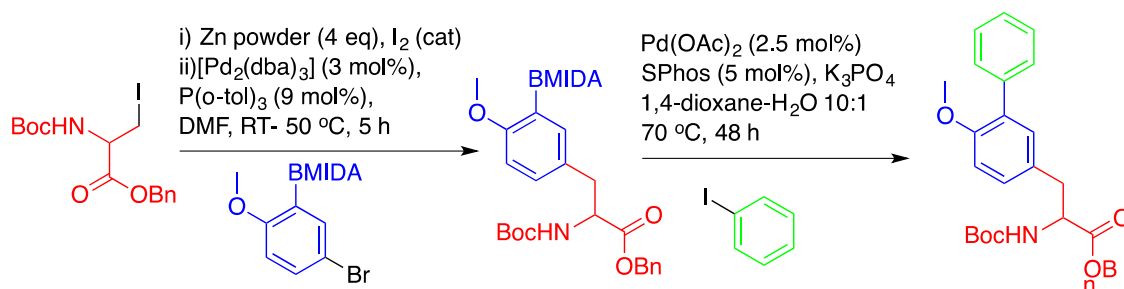
units and the bonds formed are shown in Scheme 1.43 highlighted by the dashed lines. This, including the two MOMO group deprotections (giving the phenols) was the first synthesis of Ratanhine.



Scheme 1.44. One-pot Buchwald-Hartwig followed by Suzuki coupling.

MIDA boronates can be used as a protecting group in different types of palladium cross-couplings. Grob *et al* have made use of this in a selection of one-pot Buchwald-Hartwig couplings, followed by *in situ* release of the masked boronic acid for Suzuki coupling as shown in Scheme 1.44. This uses the same catalyst throughout, one work up and one purification, thus cutting down on solvent and reagent, making a greener telescopic reaction.¹³⁷

The Negishi coupling reaction has also been achieved using this methodology shown in Scheme 1.45. A MIDA boronate improved the synthesis of the amino acid derivative, as they found that aryl pinacol boronates were problematic to purify and maintain stereoselectivity.¹³⁸



Scheme 1.45. Negishi reaction followed by a Suzuki coupling.

Many examples of this type iterative chemistry have been done on a wide variety of different palladium cross-coupling reactions *i.e.* Sonogashira (with ethynyl MIDA boronate), Heck and Stille.^{139–142}

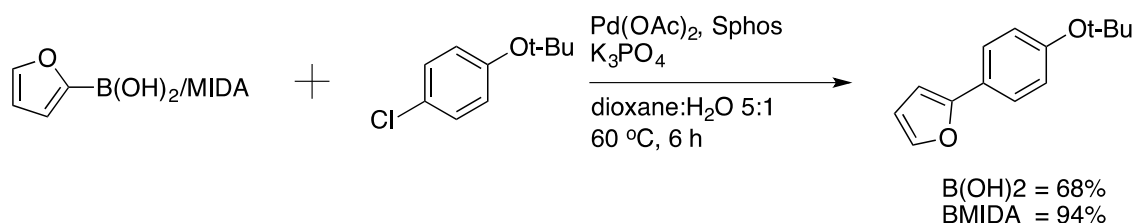
Automation is a powerful tool in increasing production speed in iterative chemical synthesis. For instance, the use of a peptide synthesiser in peptide synthesis allows for

the user to work more productively, as the machine will perform reactions, cleavages and cleaning cycles to the “recipe” the user instructed. This has long been awaited for in small molecule synthesis as outlined by Glorius and Wang.¹⁴³ Burke published a paper in 2015, that outlines a machine that has synthesised 14 distinct classes of small molecules in a fully automated process.¹⁴⁴ This uses a catch and release method of purification, absorbing the crude MIDA boronate by passing it over silica gel, immobilising it onto the gel with 1.5 % methanol in diethyl ether; this solution is used to elute the remaining organic impurities. THF is then used to elute the now purified MIDA boronate, which is then used in the next step of the automated synthesis.

This shows the potential for MIDA boronates to enable quick library generation. Current stumbling blocks involve low availability of interesting MIDA boronate starting materials. This outlines the importance to make new, scalable methodologies towards aromatic MIDA boronate cores.

MIDA boronate use for slow release cross-coupling.

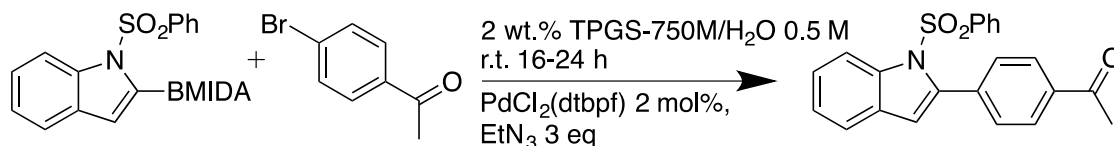
2-Heterocyclic boronic acids have limited bench stability, due to protodeboronation, oxidation, or polymerization, and this instability has a tendency to increase under reaction conditions. It has been found that making the corresponding MIDA boronate analogues vastly increases the shelf-life of these compounds. It has also improved the yields under



Scheme 1.46. Difference in yield between slow release BMIDA and B(OH)_2

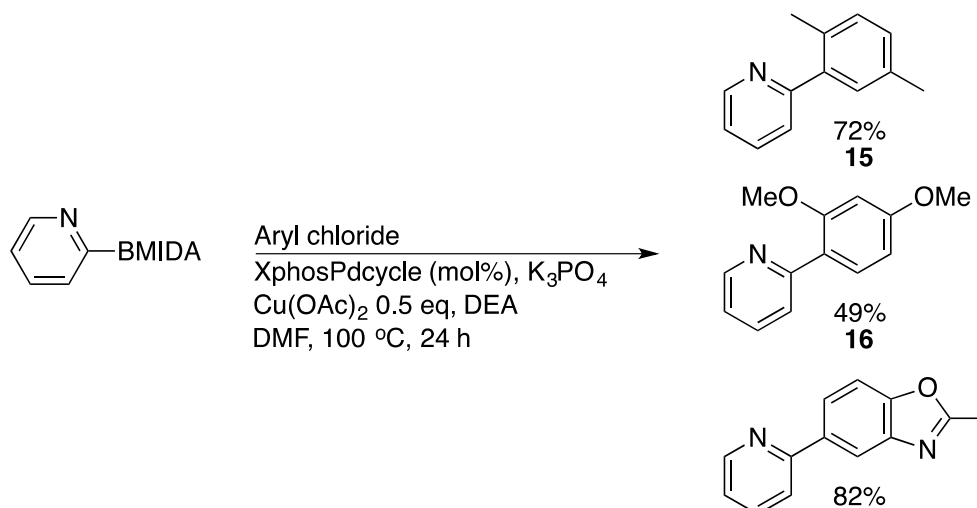
Suzuki conditions compared to free boronic acid analogues. This is due to the MIDA group cleavage being slow under the reaction conditions, thus having a syringe pump affect.¹⁴⁵ In effect the catalysis is in excess of the reagent, thus the reaction can take place before reagent decomposition. Representative yields are shown in Scheme 1.46. The purity of the boronic acid in Scheme 1.46 drops to 7% after 15 days, under bench conditions. The MIDA boronate shows higher stability, as its purity remains >95 % after 60 days under bench conditions. Within this paper similar results were observed in a large number of examples, showing how MIDA boronate chemistry can improve the coupling and storage of many 2-heterocyclic, alkyl and vinyl boronic acids.

Lipshutz *et al* have improved on this work by demonstrating slow release couplings at room temperature, in water with the commercially available surfactant TPGS-750-M.¹⁴⁶ Within this system they used Pd(dtbpf)Cl₂ (Pd118) as the catalyst and triethylamine as a base (Scheme 1.47). They found that adding water caused precipitation of pure product, making a green synthetic process.



Scheme 1.47. Slow release couplings at room temperature in water.

The 2-pyridyl subunit is found in a wide range of pharmaceuticals and natural products. The incorporation of this unit via cross-coupling methodologies is often difficult because of a lack of air stable building blocks and inefficient couplings. Burke *et al* used the slow release methodology and also optimised coupling conditions to enable incorporation of this motif. The addition of copper acetate and diethylamine (DEA) as a ligand improved yields. The role of the DEA is unclear and they suggested two different pathways for DEA incorporation. Firstly, DEA could chelate to the copper aiding the transmetallation of the MIDA boronate to the copper, before it entered the palladium catalytic cycle.

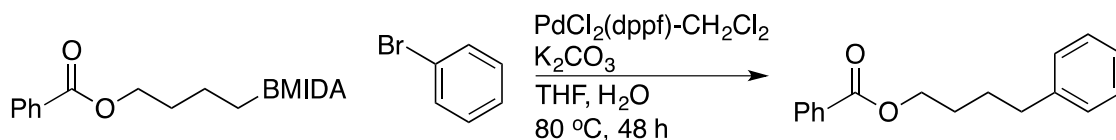


Scheme 1.48. 2-Pyridyl MIDA boronate coupling with chloro aromatics.

Secondly, DEA could displace the MIDA making the DEA boronate, which would allow transmetallation on to the copper. Selective reaction probing the different reagents found that the first suggested pathway was the most likely, but could not prove this systematically.

These slow release reactions of the 2-pyridyl MIDA boronate couple difficult coupling partners, in good yields. This shows that more electron-rich chlorides do cause a reduction

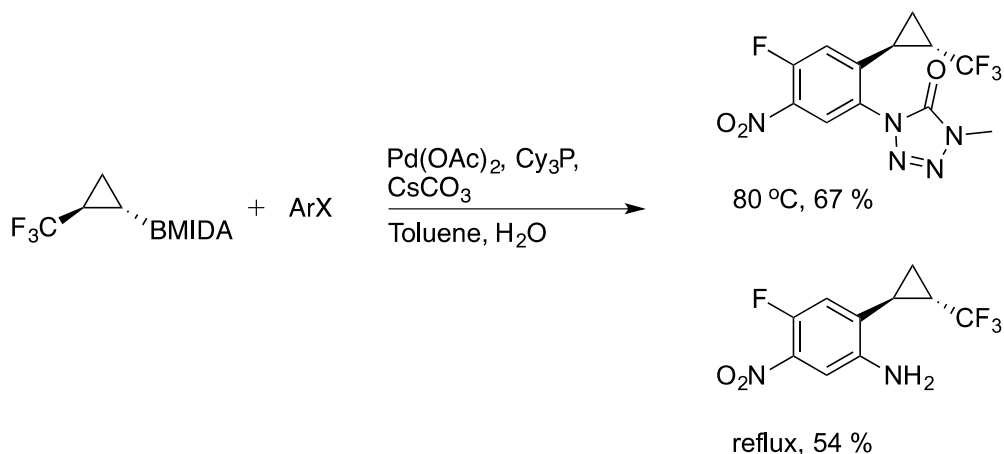
in the yield, as shown by the 2,4-dimethoxy groups in **16** in Scheme 1.48. Sterics factors would also seem not to pose a major problem as demonstrated by the 2,5-dimethyl groups of **15**.



Scheme 1.49. sp²-sp³ couplings.

This process has been applied to sp²-sp³ couplings, allowing the additions of alkanes via a Suzuki coupling.¹⁴⁷ Scheme 1.49 shows the use of the technique in the synthesis of a long aliphatic chain. Within the paper there are over 30 examples using different chain length MIDAs and different haloaryls and heteroaryl groups.

Scheme 1.50 shows the addition of trans-2-(trifluoromethyl)cyclopropane groups, with a variety of different haloaryl and heteroaryl substituents. The example given shows two



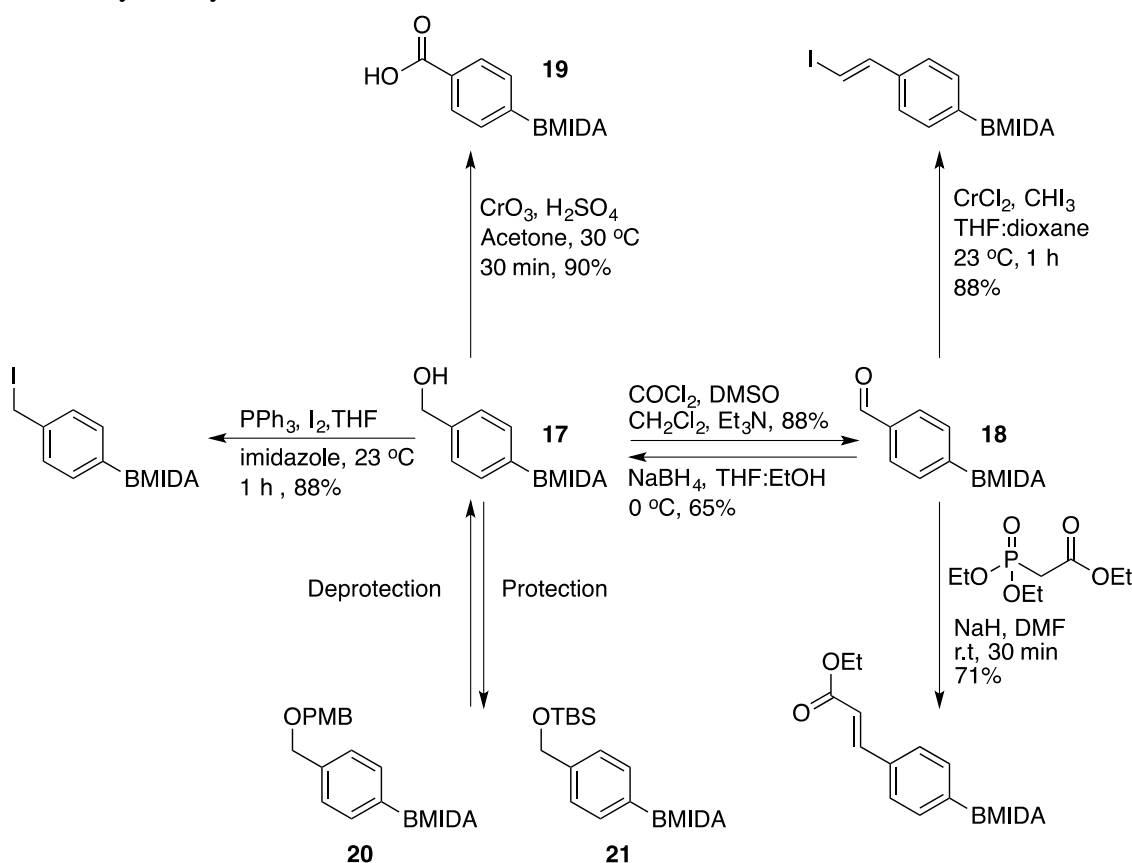
Scheme 1.50. sp²-sp³ couplings¹⁴⁹

different tetrasubstituted aromatic compounds each with four orthogonal groups. This vastly improves the scope of C-C bond formation, allowing for “the clipping” of building blocks in a more efficient process.

Functionalization in the presence of MIDA boronates.

Burke *et al* outlined a plethora of intergroup conversions, showing the compatibility of the MIDA boronate functionality, Scheme 1.51.¹³³ Oxidation of the *p*-hydroxymethylphenyl MIDA boronate (**17**) to the corresponding aldehyde (**18**) was performed using Swern conditions. However, they found that other oxidants were also tolerated i.e. Dess-Martin periodinane, tetrapropylammonium perruthenate (TPAP) with *N*-methylmorpholine *N*-oxide (NMO) as a co-oxidant. They also found that direct oxidation to the corresponding carboxylic acid (**19**) could be achieved under harsh Jones conditions. Jones conditions lead to the decomposition of the corresponding, pinacol boronic acid ester, trifluoroborate salt, *N*-methyldiethanolamine boronate, and the 1,8-diaminonaphthalene adduct. This shows the impressive relative stability of the MIDA boronate group.

Reduction of the aldehyde **18** back to **17** was achieved using sodium borohydride. Reductive amination of this aldehyde was also enabled with morpholine and sodium triacetoxyborohydride as the reductant.

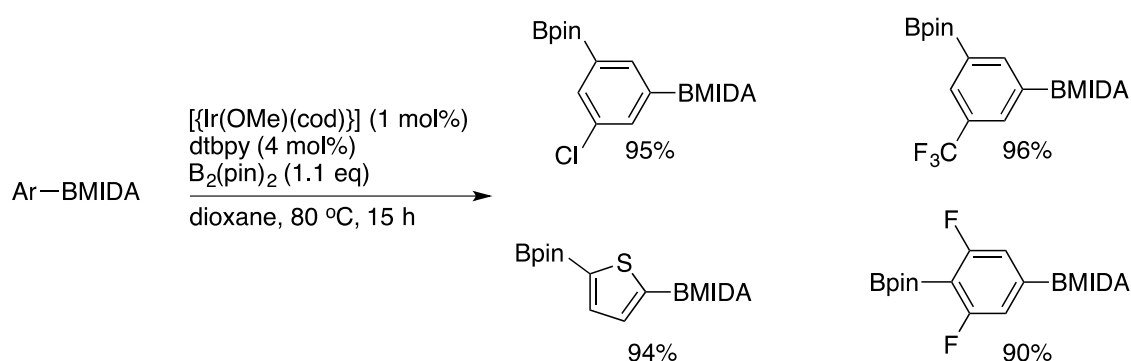


Scheme 1.51. Hydroxyl group transformations.

The protection of **17** shows the tolerance against stronger acids, as trifluoromethanesulfonic acid (TfOH) facilitates acid-catalysed *p*-methoxybenzylation

(OPMB) protection forming compound **20**. Cleavage was achieved with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The cleavage of the *tert*-butyldiphenylsilyl ether (**21**) was enabled with hydrogen fluoride pyridine, as the MIDA boronate was found to be incompatible with tetrabutylammonium fluoride (TBAF). Other incompatibilities include lithium aluminium hydride, diisobutylaluminium hydride (DIBAL) and metal alkoxide bases.

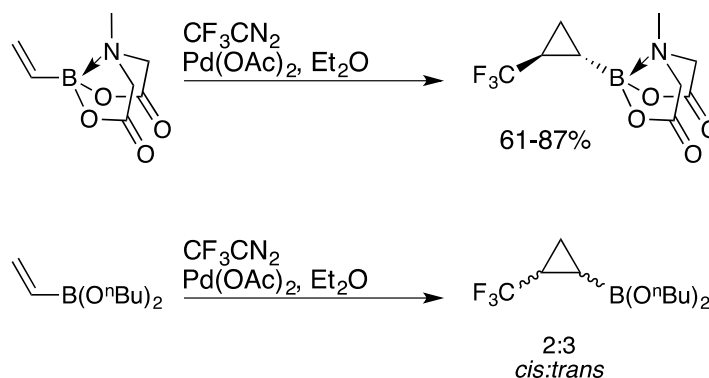
As mentioned above, reductive aminations are tolerated and Grob *et al* continued this work to prepare a library of compounds,¹⁴⁸ by reductive amination on formyl MIDA boronate cores, followed by a one pot iterative Suzuki coupling.



Scheme 1.52. Compounds prepared by borylation.

A fantastic piece of work by Xu and co-workers used iridium C-H borylations of aromatic MIDA boronates to make a library of molecules able to do iterative Suzuki couplings, Scheme 1.52.¹⁰³ This methodology made an array of poly-functional aromatics containing two orthogonal boron species.

The *trans*-2-(trifluoromethyl)cyclopropyl MIDA boronate, shown in Section 0 was made from vinyl MIDA boronate, Scheme 1.53.¹⁴⁹



Scheme 1.53. *Trans*-2-(trifluoromethyl)cyclopropyl MIDA boronate synthesis.

In this synthesis they found the vinyl MIDA boronate to be a far superior starting material as it was solid, bench stable and the product could be purified safely via column chromatography. MIDA has the bonus of being a bulky rigid conformer and this promotes the *trans* isomer because it only allows for a single faced attack, unlike the problematic dibuty-1-2-(trifluoromethyl)-cyclopropylboronate which was synthesised in a 2:3 ratio of the *cis* and *trans* isomers because of a lack of steric constraints in the starting material Scheme 1.53.

This section demonstrates the use of MIDA boronates underlining their usefulness in modern synthesis, as they increase efficiency and allow for the construction of more complex building blocks.

Microwave-Assisted Organic Synthesis (MAOS)

Microwave-assisted organic synthesis has been used since the mid-1980s and has increased in popularity since then. Microwaves are electromagnetic radiation that has a frequency range between 0.3-300 GHz. They consist of two components, an electric field and a magnetic field and the heating effect is caused by the electric component. There are two main mechanisms for microwave heating, dipolar polarisation and ionic conduction.¹⁵⁰ Dipolar polarisation is when a molecule that contains a dipole aligns itself to an applied electrical field. Oscillation of the applied field causes friction between the molecules, generating heat. A frequency of 2.45 GHz is used in commercial microwave systems, as it gives the best time profile to allow dipoles to produce heat. Ionic conduction is where dissolved ionic particles are oscillated due to the applied field, causing collisions, leading to heating.¹⁵¹

The nature of heating the reaction matrix rather than heating the outside of the reaction

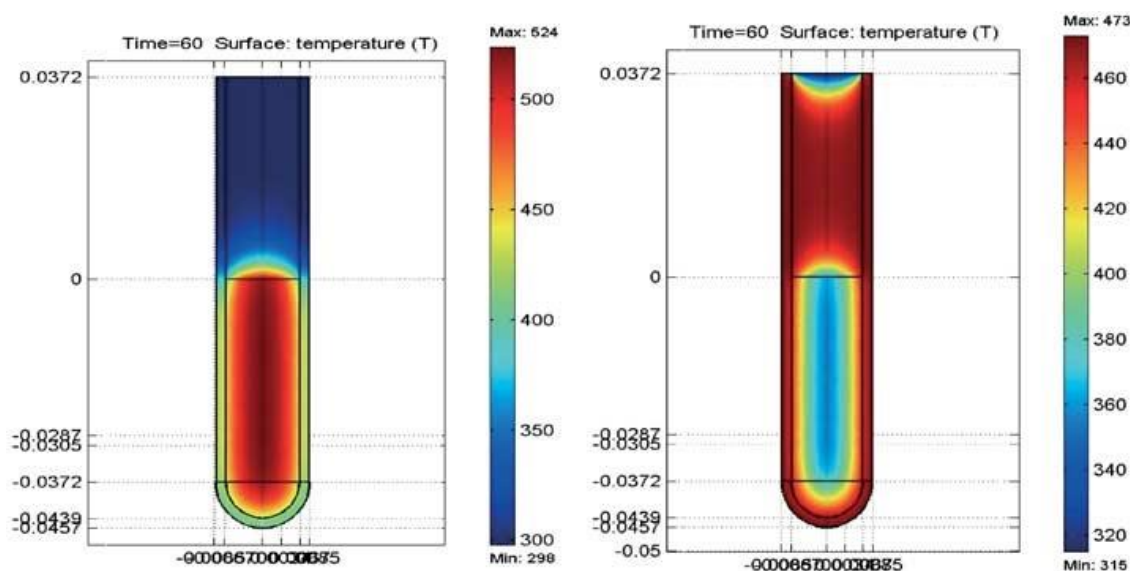
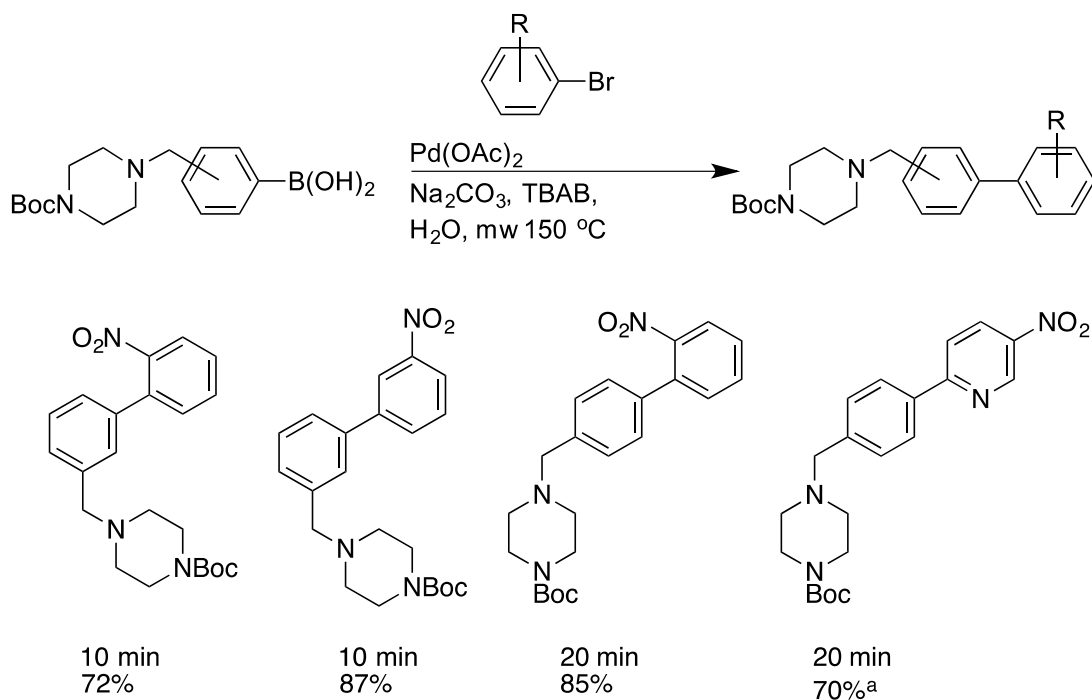


Figure 1.16. Heating after 60 seconds (right) effected by microwave heating (left) compared to oil bath.¹⁵⁷

vessel (as with traditional reaction heating) reverses the heating profile of a reaction (Figure 1.16). This leads to far shorter ramping times in reaction heating. Modern-day purpose built microwave reactors use a closed vessel system allowing for the safe, controlled heating of solvents above their boiling point and elevated reaction pressures.

These combined advantages give quicker reactions times and higher yield due to a reduction in side product formation owing to homogenous controlled heating.¹⁵²

Leadbeater *et al* showed an example of a microwave Suzuki coupling using water as a sole solvent with palladium(II) acetate and tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst.¹⁵³ This work is considered greener than a typical Suzuki reaction



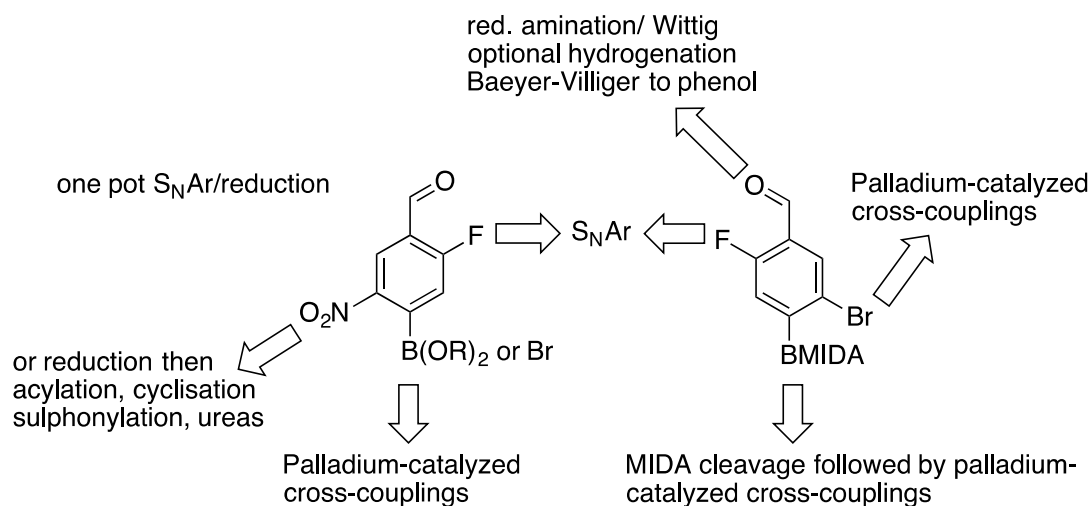
Scheme 1.54. Biaryl compounds by Suzuki reaction.

^aPd(PPh₃)₄ used, Na₂CO₃, toluene/EtOH/H₂O (1:1:1), 150 °C

as the procedure avoids the use of unfavourable organic solvents. The Spencer group used this procedure in rapid synthesis of biaryls (Scheme 1.54) used in a larger library generation project.¹⁵⁴ Steel *et al* also achieved a series of iridium borylations using microwave heating to speed up reaction times, as mentioned in Section 0.¹⁰⁴

Synthetic design and consideration

Commercially available trisubstituted starting materials will be used to elaborate the desired aryl scaffolds; this will be mainly achieved by electrophilic aromatic substitution. This methodology will be used to enable simple, cost-effective, and scalable reactions to be discussed hereafter.



Scheme 1.55. Rough retrosynthetic plan.

Fluorinated, and boronated aromatics are highly desirable due to their medicinal chemistry applications and their added synthetic potential. Structural diversity will be added to the aryl template demonstrating their chemical potential for making drug-like small molecules. Scheme 1.55 is a rough retrosynthetic plan showing the synthetic potential of some of the desired scaffolds.

Bibliography

- (1) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.
- (2) Ordóñez Gallego, A.; González Barón, M.; Espinosa Arranz, E. *Clin. Transl. Oncol.* **2007**, *9*, 298–307.
- (3) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach: Third Edition*; John Wiley and Sons, 2009.
- (4) Waters, H. *Nat. Med.* **2011**, *17*, 905.
- (5) Destevens, G.; Halamandaris, a; Ricca, S.; Werner, L. H. *J. Med. Pharm. Chem.* **1959**, *1*, 565–576.
- (6) Sneader, W. *Drug Discovery: A History*; John Wiley & Sons, Ltd, 2006.
- (7) World Organization Health. Model List of Essential Medicines http://www.who.int/medicines/organization/par/edl/expcom13/eml13_en.pdf.
- (8) Jack Li, J.; Johnson, D. S.; Sliskovic, D. R.; Roth, B. D. *Contemporary Drug Synthesis*; John Wiley & Sons, Inc, 2004.
- (9) Keck, P. E.; Versiani, M.; Potkin, S.; West, S. a; Giller, E.; Ice, K. *Am. J. Psychiatry* **2003**, *160*, 741–748.
- (10) Lowe, J. A.; Nagel, A. A. Aryl piperazinyl-(C2 or C4) alkylene heterocyclic compounds having neuroleptic activity. US4831031, 1989.
- (11) Fox, D. E.; Lambert, J. F.; Sinay, T. G.; Walinsky, S. W. Aryl piperazinyl-(C2 or C4) alkylene heterocyclic compounds having neuroleptic activity. US4831031, 2000.
- (12) Cao, Y.; Chen, J. J.; Tan, N. H.; Oberer, L.; Wagner, T.; Wu, Y. P.; Zeng, G. Z.; Yan, H.; Wang, Q. *Bioorganic Med. Chem. Lett.* **2010**, *20*, 2456–2460.
- (13) Morris, B. D.; Prinsep, M. R. *J. Nat. Prod.* **1999**, *62*, 688–693.
- (14) Chiyoda, K.; Shimokawa, J.; Fukuyama, T. *Angew. Chemie - Int. Ed.* **2012**, *51*, 2505–2508.
- (15) Berger, J.; Rachlin, A. I.; Scott, W. E.; Sternbach, L. H.; Goldberg, M. W. *J. Am. Chem. Soc.* **1951**, *73*, 5295–5298.
- (16) Garrett, R. H.; Grisham, C. M. *Biochemistry*; 4th ed.; 2008.
- (17) Pecorino, L. *Molecular Biology of Cancer: Mechanisms, Targets, and Therapeutics*; 2nd ed.; Oxford University Press, 2008.
- (18) Los, M.; Roodhart, J. M. L.; Voest, E. E. *Oncologist* **2007**, *12*, 443–450.
- (19) Li, S.; Schmitz, K. R.; Jeffrey, P. D.; Wiltzius, J. J. W.; Kussie, P.; Ferguson, K.

- M. *Cancer Cell* **2005**, 7, 301–311.
- (20) Gad, S. C. *Drug Discovery Handbook*; Wiley-VCH, 2005.
 - (21) Kris, M. G.; Natale, R. B.; Herbst, R. S.; Lynch, T. J.; Prager, D.; Belani, C. P.; Schiller, J. H.; Kelly, K.; Spiridonidis, H.; Sandler, A.; Albain, K. S.; Cella, D.; Wolf, M. K.; Averbuch, S. D.; Ochs, J. J.; Kay, A. C. *JAMA* **2003**, 290, 2149–2158.
 - (22) Sordella, R.; Bell, D. W.; Haber, D. A.; Settleman, J. *Science* **2004**, 305, 1163–1167.
 - (23) Bollag, G.; Hirth, P.; Tsai, J.; Zhang, J.; Ibrahim, P. N.; Cho, H.; Spevak, W.; Zhang, C.; Zhang, Y.; Habets, G.; Burton, E. A.; Wong, B.; Tsang, G.; West, B. L.; Powell, B.; Shellooe, R.; Marimuthu, A.; Nguyen, H.; Zhang, K. Y. J.; Artis, D. R.; Schlessinger, J.; Su, F.; Higgins, B.; Iyer, R.; D'Andrea, K.; Koehler, A.; Stumm, M.; Lin, P. S.; Lee, R. J.; Grippo, J.; Puzanov, I.; Kim, K. B.; Ribas, A.; McArthur, G. A.; Sosman, J. A.; Chapman, P. B.; Flaherty, K. T.; Xu, X.; Nathanson, K. L.; Nolop, K. *Nature* **2010**, 467, 596–599.
 - (24) Zhang, J.; Yang, P. L.; Gray, N. S. *Nat. Rev. Cancer* **2009**, 9, 28–39.
 - (25) Barrett, S. D.; Bridges, A. J.; Dudley, D. T.; Saltiel, A. R.; Fergus, J. H.; Flamme, C. M.; Delaney, A. M.; Kaufman, M.; LePage, S.; Leopold, W. R.; Przybranowski, S. A.; Sebolt-Leopold, J.; Van Becelaere, K.; Doherty, A. M.; Kennedy, R. M.; Marston, D.; Howard, W. A.; Smith, Y.; Warmus, J. S.; Tecle, H. *Bioorganic Med. Chem. Lett.* **2008**, 18, 6501–6504.
 - (26) Ohren, J. F.; Chen, H.; Pavlovsky, A.; Whitehead, C.; Zhang, E.; Kuffa, P.; Yan, C.; McConnell, P.; Spessard, C.; Banotai, C.; Mueller, W. T.; Delaney, A.; Omer, C.; Sebolt-Leopold, J.; Dudley, D. T.; Leung, I. K.; Flamme, C.; Warmus, J.; Kaufman, M.; Barrett, S.; Tecle, H.; Hasemann, C. A. *Nat Struct Mol Biol* **2004**, 11, 1192–1197.
 - (27) Jack Li, J.; Johnson, D. S.; Sliskovic, D. R.; Roth, B. D. *Contemporary Drug Synthesis*; John Wiley & Sons, Inc, 2004.
 - (28) Patrick, G. L. *An Introduction to Drug Synthesis*; 1st ed.; Oxford University Press, 2015.
 - (29) Uitdehaag, J. C. M.; Verkaar, F.; Alwan, H.; De Man, J.; Buijsman, R. C.; Zaman, G. J. R. *Br. J. Pharmacol.* **2012**, 166, 858–876.
 - (30) Barker, A. J.; Gibson, K. H.; Grundy, W.; Godfrey, A. A.; Barlow, J. J.; Healy, M. P.; Woodburn, J. R.; Ashton, S. E.; Curry, B. J.; Scarlett, L.; Henthorn, L.;

- Richards, L. *Bioorganic Med. Chem. Lett.* **2001**, *11*, 1911–1914.
- (31) *Textbook of Drug Design and Discovery*; Stromgaard, K.; Krogsgaard-Larsen, P.; Madsen, U., Eds.; 4th ed.; CRC Press, 2009.
- (32) Traxler, P.; Bold, G.; Buchdunger, E.; Caravatti, G.; Furet, P.; Manley, P.; O'Reilly, T.; Wood, J.; Zimmermann, J. *Med. Res. Rev.* **2001**, *21*, 499–512.
- (33) Demetri, G. D. *Eur. J. Cancer* **2002**, *38 Suppl 5*, S52–S59.
- (34) Daub, H.; Specht, K.; Ullrich, A. *Nat. Rev. Drug Discov.* **2004**, *3*, 1001–1010.
- (35) Shah, N. P.; Tran, C.; Lee, F. Y.; Chen, P.; Norris, D.; Sawyers, C. L. *Science* **2004**, *305*, 399–401.
- (36) Kantarjian, H.; Giles, F.; Wunderle, L.; Bhalla, K.; O'Brien, S.; Wassmann, B.; Tanaka, C.; Manley, P.; Rae, P.; Mietlowski, W.; Bochinski, K.; Hochhaus, A.; Griffin, J. D.; Hoelzer, D.; Albitar, M.; Dugan, M.; Cortes, J.; Alland, L.; Ottmann, O. G. *N. Engl. J. Med.* **2006**, *354*, 2542–2551.
- (37) Wills, B. a; Dung, N. M.; Loan, H. T.; Tam, D. T. H.; Thuy, T. T. N.; Minh, L. T. T.; Diet, T. V; Hao, N. T.; Chau, N. V; Stepniewska, K.; White, N. J.; Farrar, J. J. *N. Engl. J. Med.* **2006**, *354*, 2531–2541.
- (38) Demetri, G. D.; van Oosterom, A. T.; Garrett, C. R.; Blackstein, M. E.; Shah, M. H.; Verweij, J.; McArthur, G.; Judson, I. R.; Heinrich, M. C.; Morgan, J. a.; Desai, J.; Fletcher, C. D.; George, S.; Bello, C. L.; Huang, X.; Baum, C. M.; Casali, P. G. *Lancet* **2006**, *368*, 1329–1338.
- (39) Engelman, J. a.; Jänne, P. a. *Clin. Cancer Res.* **2008**, *14*, 2895–2899.
- (40) Minami, Y.; Shimamura, T.; Shah, K.; LaFramboise, T.; Glatt, K. a; Liniker, E.; Borgman, C. L.; Haringsma, H. J.; Feng, W.; Weir, B. a; Lowell, a M.; Lee, J. C.; Wolf, J.; Shapiro, G. I.; Wong, K.-K.; Meyerson, M.; Thomas, R. K. *Oncogene* **2007**, *26*, 5023–5027.
- (41) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *ChemMedChem* **2007**, *2*, 1100–1115.
- (42) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330.
- (43) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886.
- (44) Smart, B. E. *J. Fluor. Chem.* **2001**, *109*, 3–11.
- (45) Istvan, E. S.; Deisenhofer, J. *Science*. **2001**, *292*, 1160–1164.
- (46) Trippier, P. C.; McGuigan, C. *Med. Chem. Commun.* **2010**, *1*, 183–198.

- (47) Seaman, W.; Johnson, J. R. *J. Am. Chem. Soc.* **1931**, *53*, 711–723.
- (48) James, T. D.; Sandanayake, K. R. a S.; Shinkai, S. **1996**.
- (49) Hansen, J. S.; Christensen, J. B.; Solling, T. I.; Jakobsen, P.; Hoeg-Jensen, T. *Tetrahedron* **2011**, *67*, 1334–1340.
- (50) Baker, S. J.; Tomsho, J. W.; Benkovic, S. J. *Chem. Soc. Rev.* **2011**, *40*, 4279–4285.
- (51) Paramore, A.; Frantz, S. *Nat. Rev. Drug Discov.* **2003**, *2*, 611–612.
- (52) Bonvini, P.; Zorzi, E.; Basso, G.; Rosolen, a. *Leuk. Off. J. Leuk. Soc. Am. Leuk. Res. Fund, U.K* **2007**, *21*, 838–842.
- (53) Nakamura, H.; Kuroda, H.; Saito, H.; Suzuki, R.; Yamori, T.; Maruyama, K.; Haga, T. *ChemMedChem* **2006**, *1*, 729–740.
- (54) Baker, S. J.; Ding, C. Z.; Akama, T.; Zhang, Y.-K.; Hernandez, V.; Xia, Y. *Future Med. Chem.* **2009**, *1*, 1275–1288.
- (55) Wade, L. G. *Organic Chemistry*; 8th ed.; Pearson Education, Inc, 2012.
- (56) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Weissrnel, K.; Arpe, H.-J., Eds.; Brooks/Cole, 2001; Vol. 40.
- (57) Soloway, A. H. *J. Am. Chem. Soc.* **1959**, *81*, 3017–3019.
- (58) Bean, F. R.; Johnson, J. R. *J. Am. Chem. Soc.* **1932**, *54*, 4415–4425.
- (59) Appukkuttan, P.; Dehaen, W.; Van Der Eycken, E. *Chem. - A Eur. J.* **2007**, *13*, 6452–6460.
- (60) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1961**, *83*, 4581–5485.
- (61) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1961**, *83*, 4571–4580.
- (62) Raitio, K. H.; Savinainen, J. R.; Vepsäläinen, J.; Laitinen, J. T.; Poso, A.; Järvinen, T.; Nevalainen, T. *J. Med. Chem.* **2006**, *49*, 2022–2027.
- (63) Harvey, R. G.; Dai, Q.; Ran, C.; Penning, T. M. *J. Org. Chem.* **2004**, *69*, 2024–2032.
- (64) Rozen, S.; Lerman, O. *J. Org. Chem.* **1993**, *58*, 239–240.
- (65) Al-Zoubi, R. M.; Hall, D. G. *Org. Lett.* **2010**, *12*, 2480–2483.
- (66) Mo, F.; Yan, J. M.; Qiu, D.; Li, F.; Zhang, Y.; Wang, J. *Angew. Chemie Int. Ed.* **2010**, *49*, 2028–2032.
- (67) Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K. K. *J. Org. Chem.* **2007**, *72*, 5867–5869.
- (68) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701–730.
- (69) Stiles, M.; Miller, R. G.; Burckhardt, U. *J. Am. Chem. Soc.* **1963**, *85*, 1792–1797.
- (70) Campbell, C. D.; Rees, C. W. *J. Chem. Soc. C* **1969**, 742–747.

- (71) Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angew. Chemie - Int. Ed.* **2011**, *50*, 6814–6818.
- (72) Krasnokutskaya, E. a.; Semenischeva, N. I.; Filimonov, V. D.; Knochel, P. *Synthesis (Stuttg.)* **2007**, 81–84.
- (73) Thibault, C.; L'Heureux, A.; Bhide, R. S.; Ruel, R. *Org. Lett.* **2003**, *5*, 5023–5025.
- (74) Takemura, S.; Hirayama, A.; Tokunaga, J.; Kawamura, F.; Inagaki, K.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **1999**, *40*, 7501–7505.
- (75) Wittig, G.; Fuhrmann, G. *Berichte der Dtsch. Chem. Gesellschaft A B Ser.* **1940**, *73*, 1197–1218.
- (76) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109.
- (77) Snieckus, V. *Chem Rev* **1990**, *90*, 879–933.
- (78) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chemie - Int. Ed.* **2004**, *43*, 2206–2225.
- (79) Schneider, C.; Broda, E.; Snieckus, V. *Org. Lett.* **2011**, *13*, 3588–3591.
- (80) Moro-Oka, Y.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* **1999**, *40*, 1713–1716.
- (81) Zhang, L.-S.; Chen, K.; Chen, G.; Li, B.-J.; Luo, S.; Guo, Q.-Y.; Wei, J.-B.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 10–13.
- (82) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 5713–5715.
- (83) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chemie Int. Ed.* **2012**, *51*, 10236–10254.
- (84) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169.
- (85) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301.
- (86) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149–4152.
- (87) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chemie Int. Ed.* **2011**, *50*, 5524–5527.
- (88) Xiao, B.; Li, Y.-M.; Liu, Z.-J.; Yang, H.-Y.; Fu, Y. *Chem. Commun.* **2012**, *48*, 4854–4856.
- (89) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518–522.
- (90) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215–220.
- (91) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. *Nature* **2015**, *519*, 334–338.
- (92) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877–5884.
- (93) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593–1597.
- (94) Luo, J.; Preciado, S.; Larrosa, I. *Chem. Commun.* **2015**, *51*, 3127–3130.

- (95) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992–2002.
- (96) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263–14278.
- (97) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534–7535.
- (98) Chotana, G. A.; Rak, M. A.; Smith, M. R. *J. Am. Chem. Soc.* **2005**, *127*, 10539–10544.
- (99) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chemie Int. Ed.* **2002**, *41*, 3056–3058.
- (100) Roering, A. J.; Hale, L. V. A.; Squier, P. A.; Ringgold, M. A.; Wiederspan, E. R.; Clark, T. B. *Org. Lett.* **2012**, *14*, 3558–3561.
- (101) Hale, L. V. A.; Emmerson, D. G.; Ling, E. F.; Roering, A. J.; Ringgold, M. A.; Clark, T. B. *Org. Chem. Front.* **2015**, *2*, 661–664.
- (102) Robbins, D. W.; Hartwig, J. F. *Org. Lett.* **2012**, *14*, 4266–4269.
- (103) Xu, L.; Ding, S.; Li, P. *Angew. Chemie Int. Ed.* **2014**, *53*, 1822–1826.
- (104) Harriison, P.; Morris, J.; Marder, T.; Steel, P. *Org. Lett.* **2009**, *11*, 3586–3589.
- (105) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chemie - Int. Ed.* **2012**, *51*, 5062–5085.
- (106) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710.
- (107) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027–3043.
- (108) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chemie Int. Ed.* **2010**, *49*, 9047–9050.
- (109) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440.
- (110) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866–867.
- (111) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443–3447.
- (112) Horton, D. a; Bourne, G. T.; Smythe, M. L. *Cancer Res.* **2003**, *103*, 893–930.
- (113) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.
- (114) Zhang, D.; Wang, Q. *Coord. Chem. Rev.* **2015**, *286*, 1–16.
- (115) Keith, C.; Dantlgraber, G.; Reddy, R. A.; Baumeister, U.; Tschierske, C. *Chem. Mater.* **2007**, *19*, 694–710.
- (116) Montani, R. S.; Hegguilustoy, C. M.; Del Rosso, P. G.; Donnio, B.; Guillon, D.; Garay, R. O. *Tetrahedron Lett.* **2009**, *50*, 5231–5234.
- (117) Tandel, R. C.; Patel, N. K. *Mol. Cryst. Liq. Cryst.* **2014**, *593*, 114–125.
- (118) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457–2483.

- (119) Miyaura, N.; Yamada, K.; Sugimoto, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972–980.
- (120) Amatore, C.; Le Duc, G.; Jutand, A. *Chem. - A Eur. J.* **2013**, *19*, 10082–10093.
- (121) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. - A Eur. J.* **2011**, *17*, 2492–2503.
- (122) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313–3315.
- (123) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253–257.
- (124) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259–263.
- (125) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
- (126) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.
- (127) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084–5121.
- (128) Halbes-Letinois, U.; Weibel, J.-M.; Pale, P. *Chem. Soc. Rev.* **2007**, *36*, 759–769.
- (129) Sato, K.; Yoshimura, T.; Shindo, M.; Shishido, K. *J. Org. Chem.* **2001**, *66*, 309–314.
- (130) Yi, C.; Hua, R. *J. Org. Chem.* **2006**, *71*, 2535–2537.
- (131) Lipshutz, B. H.; Chung, D. W.; Rich, B. *Org. Lett.* **2008**, *10*, 3793–3796.
- (132) Gillis, E. P.; Burke, M. D. **2007**, 5161–5175.
- (133) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084–14085.
- (134) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412–443.
- (135) Burke, M.; Gillis, E.; Lee, S. System for Controlling the Reactivity of Boronic Acids. *Espacenet*, 2011, 1–26.
- (136) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717.
- (137) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Null, Ed.; Oxford University Press, 1998.
- (138) Colgin, N.; Flinn, T.; Cobb, S. L. *Org. Biomol. Chem.* **2011**, *9*, 1864–1870.
- (139) Chan, J. M. W.; Amarante, G. W.; Toste, F. D. *Tetrahedron* **2011**, *67*, 4306–4312.
- (140) Burns, A. R.; McAllister, G. D.; Shanahan, S. E.; Taylor, R. J. K. *Angew. Chemie Int. Ed.* **2010**, *49*, 5574–5577.
- (141) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466–468.
- (142) Woerly, E. M.; Struble, J. R.; Palyam, N.; O'Hara, S. P.; Burke, M. D. *Tetrahedron* **2011**, *67*, 4333–4343.
- (143) Wang, C.; Glorias, F. *Angew. Chemie* **2009**, *48*, 5240–5244.
- (144) Li, J.; Ballmer, S. G.; Gillis, E. P.; Fujii, S.; Schmidt, M. J.; Palazzolo, A. M. E.; Lehmann, J. W.; Morehouse, G. F.; Burke, M. D. *Science (80-.)*. **2015**, *347*, 1221–

1226.

- (145) Knapp, D. M.; Gillis, E. P.; Burke, M. D. **2009**, 6961–6963.
- (146) Isley, N.; Gallou, F.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2013**, *135*, 17707–17710.
- (147) St Denis, J. D.; Scully, C. C. G.; Lee, C. F.; Yudin, A. K. *Org. Lett.* **2014**, *16*, 1338–1341.
- (148) Grob, J. E.; Nunez, J.; Dechantsreiter, M. a; Hamann, L. G. *J. Org. Chem.* **2011**, *76*, 4930–4940.
- (149) Duncton, M. J.; Singh, R. *Org. Lett.* **2013**, *15*, 4284–4287.
- (150) Kappe, C. O.; Dallinger, D.; Murphree, S. S. *Practical Microwave Synthesis for Organic Chemists: Strategies, Instruments, and Protocols*; John Wiley and Sons, 2009.
- (151) Kappe, C. O. *Angew. Chemie Int. Ed.* **2004**, *43*, 6250–6284.
- (152) Oliver Kappe, C. *Chem. Soc. Rev.* **2008**, *37*, 1127–1139.
- (153) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888–892.
- (154) Spencer, J.; Baltus, C. B.; Press, N. J.; Harrington, R. W.; Clegg, W. *Tetrahedron Lett.* **2011**, *52*, 3963–3968.
- (155) Yosaatmadja, Y.; SQUIRE, C. J. PDB-4WKQ, 2014.
- (156) Cowan-Jacob, S. W.; Fendrich, G.; Floersheimer, A.; Furet, P.; Liebetanz, J.; Rummel, G.; Rheinberger, P.; Centeleghe, M.; Fabbro, D.; Manley, P. W. *Acta Crystallogr.* **2007**, *D*, 80–93.
- (157) Schanche, J.-S. *Mol. Divers.* **2003**, *7*, 293–300.

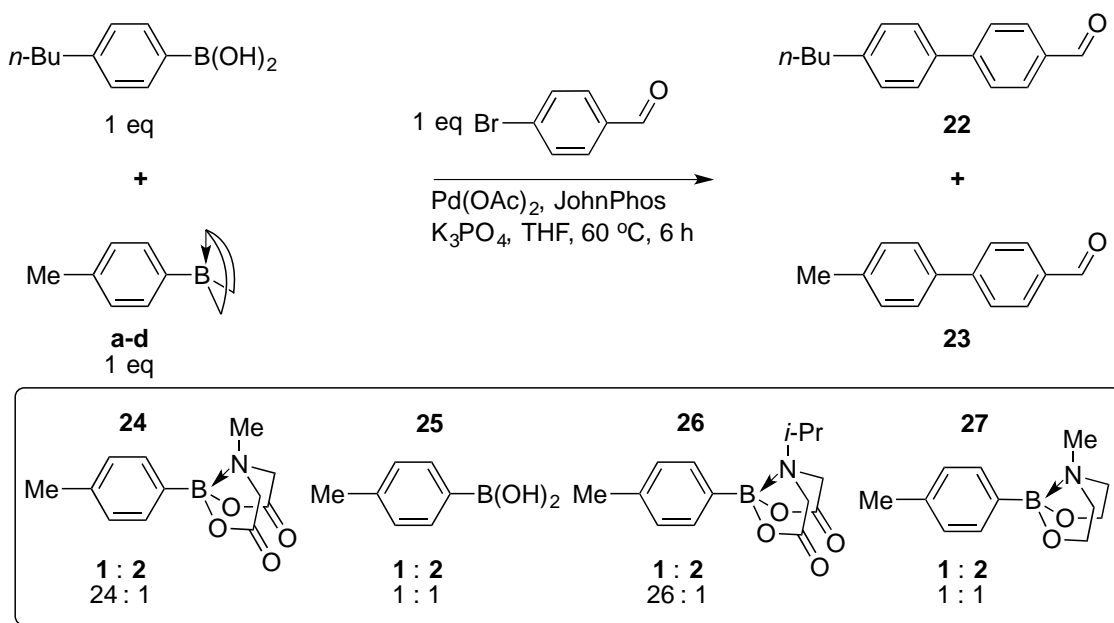
2. MIDA boronate synthesis

2.1. Overview

The aim of this Chapter is to produce new rapid synthetic methodologies towards MIDA protected aromatic boronic acids, as these compounds were key starting materials for work discussed later in Chapters 3 and 4. The hypothesis was that microwave heating could reduce reactions times, making a more efficient synthesis. The use of DMSO with the addition of benzene to aid azeotropic removal of water was unattractive; we postulated that alternative solvents could be used making a “greener,” safer process.

2.2. Introduction

As elaborated in the large review in Chapter 1 (0) Burke’s group has produced pioneering work into MIDA boronate chemistry. This work shows that MIDA boronates are orthogonal to boronic acids in Suzuki reactions, by virtue of the sp^3 hybridized boron in MIDA boronates (Figure 1.14).¹ This electron rich boronate is less prone to transmetalation, exemplified by the competitive Suzuki cross-coupling reaction, shown in Scheme 2.1.²



Scheme 2.1. Competitive Suzuki cross-coupling experiments showing ratios of products.

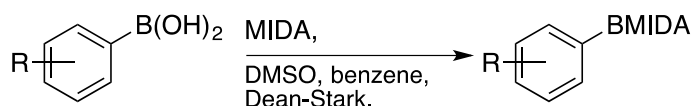
The series of experiments illustrated in Scheme 2.1, demonstrate that the MIDA protecting group slows the transmetalation step, exhibited in the significant differences in the ratios of the final products. This effect could only be due to the sp^3 hybridisation

at boron of the compound **24** or **27**, as it was the only variable changed throughout, these experiments. Compounds **24** and **26** have been shown to have a stronger dative covalent bond compared to that of the *N*-methyldiethanolamine derivative shown in compound **27**.³ This explains why there was no observed difference in the destitution of compound **22** and **23** in this case.

This selective reactivity under anhydrous conditions has enabled iterative palladium cross-couplings. The MIDA boronate can be demasked after an initial cross-coupling to give its parent boronic acid under basic aqueous conditions to enable a second cross-coupling. *In situ* cleavage of the MIDA boronates allows for a greener, multistep one-pot process reducing time taken, work-up time and solvent usage. The scope to which this has been applied is highlighted in-depth in Chapter 1 *e.g.* Negishi, Heck, Sonogashira, Stille and Buchwald–Hartwig amination,^{4–8} and in various functional group interconversions on arenes. Examples of the latter include oxidations under Swern or Jones conditions, and cycloisomerization of arylethynyl MIDA boronates.^{3,9} These *telescopic* reactions are desirable in medicinal chemistry as modern industry favours processes with reduced reaction times, fewer reaction steps and lower solvent volumes.¹⁰ Additionally, MIDA boronates are also crystalline solids, stable and silica-gel column-compatible.¹¹ These attributes have been employed to improve the shelf life and stability of otherwise unstable boronic acids, which tend to protodeboronate.^{12–15}

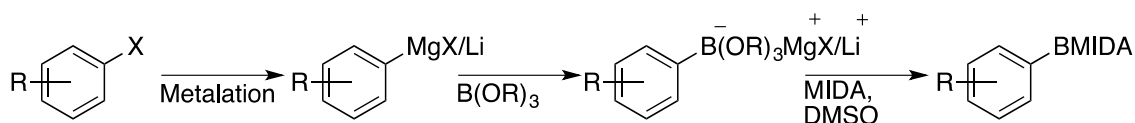
Due to their many advantageous attributes numerous MIDA boronates are now, not unsurprisingly, commercially available.¹⁶ However, more complex MIDA boronates still require individual syntheses.

Mancilla *et. al.* in 1986 were the first to syntheses MIDA boronates (Scheme 2.2).¹⁷ Their synthesis involved the esterification of a boronic acid with MIDA in DMSO, with the addition of ether benzene or toluene to aid the azeotropic removal of water with a Dean-Stark apparatus. This method remains as one of the core methods of MIDA boronate synthesis.



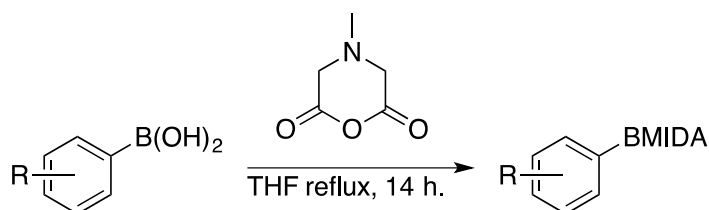
Scheme 2.2. Synthesis of MIDA boronates using Dean-Stark trap.

Burke *et al* later introduced an alternate method of MIDA boronate synthesis by means of intercepting a trialkylboronate, synthesised *in situ* via metalation, with MIDA in DMSO (Scheme 2.3).¹⁸ The trialkylboronate species was synthesised from an aromatic halide via lithium halogen exchange using an organolithium reagent, alternately Grignard reagents have been used. This metalated species under went borylation, typically using either trimethyl- or triisopropyl borate. To avoid an unnecessary work-up and purification at this point, the reaction mixture was added directly to a heated mixture of MIDA in DMSO.



Scheme 2.3. Formation of MIDA boronates via *in situ* intercepting a triolboronate species.

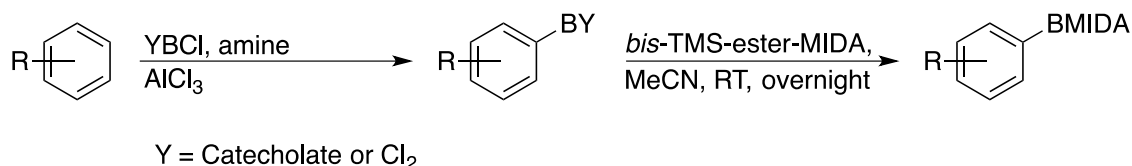
Burke also outlined within this publication, the MIDA esterification of boronic acids with 4-methylmorpholine-2,6-dione (MIDA anhydride) at reflux in THF (Scheme 2.4). Advantageously this method avoids azeotropic removal of water, or high boiling point solvents *i.e.* DMSO or DMF.



Scheme 2.4. MIDA esterification of a boronic acid using MIDA anhydride.

Ingleson *et al* developed a method of electrophilic arene borylation.¹⁹ The borylation typically utilises the BCl_2 or the boron catecholate adduct, which are then reacted to form a MIDA boronate. The MIDA esterification is achieved in most cases using the bis-trimethylsilyl ester of MIDA, however some examples also employ the disodium salt of MIDA or MIDA alone.

Grob *et al* synthesized a wide array of aryl MIDA boronates from their parent boronic acids.²⁰ The esterification was achieved *via* heating a mixture of the aryl boronic acid with MIDA in DMF at 85 °C for 18 h. In a similar procedure, Cheon *et al.* found that



Scheme 2.5. Electrophilic arene borylation followed by MIDA esterification.

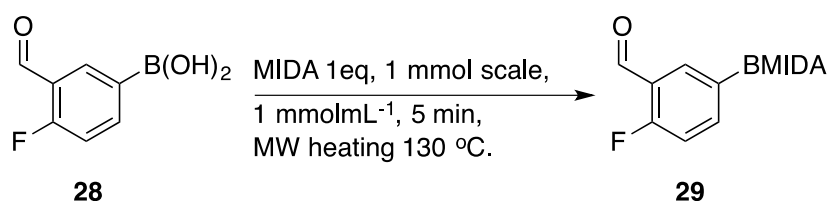
MIDA boronates can be prepared from unstable 2-hydroxyphenylboronic acids.²¹ The MIDA boronates were synthesised by heating MIDA in DMF at 120 °C for 3 h, in the presence of molecular sieves.

Due to the orthogonal functional group requirements in this project the MIDA boronate group became a desirable group to incorporate into tetrasubstituted aromatic compounds being synthesised. Many of the synthetic methods outlined towards MIDA boronates require a multistep process, large solvent volume and/or extensive period of heating. In addition to scalability being a key project objective, there was need for generation of a large amount of examples for later experiments, and this required the development of new, faster methodology. To shorten reaction times it was proposed to perform this chemistry using microwave heating, which has been shown to enable quick, more efficient reactions and was anticipated to be advantageous in MIDA boronate synthesis.^{22–24}

This work was also performed with particular emphasis on removing the requirement of unattractive solvents *e.g.* with high boiling point, or high toxicity, from the MIDA esterification, described in examples above.

Discussion

Large amounts of the MIDA ester of 4-fluoro-3-formyl boronic acid **29** was required for the chemistry described in Chapter 3. A rapid screen of solvents and potential additives was performed under microwave conditions to ascertain the optimum conditions. Small volumes of deuterated solvents were employed in the screening process to facilitate yield calculation via ¹H-NMR spectroscopy. This was achieved via taking a small aliquot of the reaction mixture after cooling and diluting it in an NMR tube prior to inspection. Results from this survey are summarised in Table 2.1.

Table 2.1. Solvent screen optimisation.

Entry	Solvent / Additive	%
1	Acetonitrile- <i>d</i> ₃	95 ^a
2	Acetonitrile- <i>d</i> ₃ + 3 Å molecular sieves	93 ^a
3	Water	5 ^b
4	DMSO- <i>d</i> ₆	60 ^a
5	DMSO- <i>d</i> ₆ + 4 Å molecular sieves	0 ^a
6	DMF dry	97 ^{a,c}
7	DMF reagent grade	72 ^{a,c}
8	PEG 300	69 ^b

^a% conversion calculated from ¹H-NMR spectroscopy analysis of crude mixture. ^bisolated yield, ^cexperiments performed by Matthew Emerson.

Table 2.1 entries 4 and 5 shows that, DMSO gave the poorest results out of the solvents trialled, with the exception of water, entry 3. These reaction mixtures using DMSO tended to blacken and the odour of dimethylsulphide was detectable. This was particularly apparent when molecular sieves were employed. The observed increase in decomposition present visually and by the large amounts of impurities in the crude ¹H-NMR spectrum, could be due to the Lewis acidic nature of the molecular sieves.²⁵ DMF (entry 6) was notable as it gave the highest conversion of all solvents trialled. Entry 7 gave a lower conversion than dry DMF, the proposed cause of this was the decomposition of DMF at high temperatures, generating dimethylamine. These basic conditions can induce the *in situ* MIDA boronate cleavage, due to the small amounts of water present in reagent grade DMF.²⁶ Employing acetonitrile (entry 1) gave comparable conversions to that of entry 6, but entry 1 was deemed to be the most encouraging, due to the favourable properties of this solvent *e.g.* reduced toxicity, lower boiling point.^{27,28} In entry 2 the use of molecular sieves with acetonitrile did not cause the reaction to completion. PEG 300 (entry 8) was considered as a worthy choice of candidate solvent in this study as it has similar solvent properties to DMSO. As highlighted by Jessop, in terms of polarity and hydrogen bond acceptability PEG 300 appears in a similar sector in two Kamlet–Taft plots of common solvents.²⁹ PEG 300 also has desirable green solvent properties *e.g.* low flammability,

negligible vapour pressure, reduced environmental damage and a complete toxicity report which outlines its approval by the FDA for human consumption.³⁰ These factors led to its inclusion in this study, and to our delight a good yield was obtained, shown in entry 8 Table 2.1.

Whilst carrying out the solvent screen it was observed that the starting materials had poor solubility at room temperature, leading to an investigation of these reactions employing an *in situ* microwave camera. This enabled the observation of the solubility of each reaction component at different temperatures. These experiments involved heating MIDA alone in each of acetonitrile, dimethylformamide or PEG 300, to find its solubility in each solvent under the reactions conditions. The observations of these test reactions after 4 minutes of heating are shown in Figure 2.1.

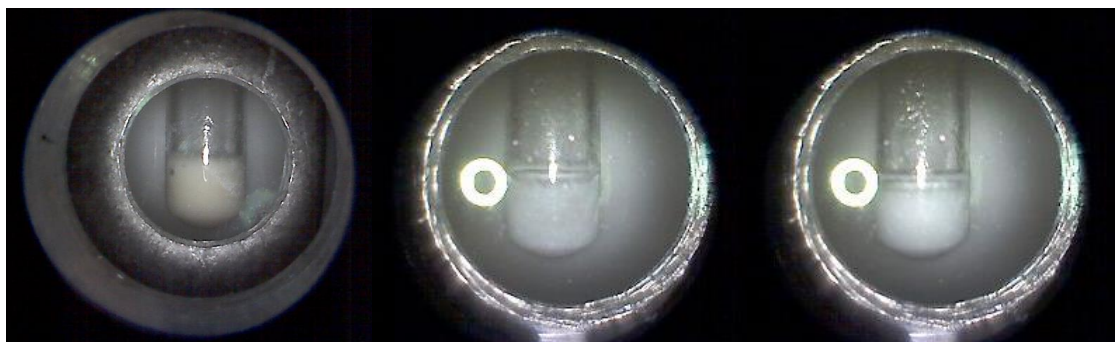


Figure 2.1. From left to right, (a) neat MIDA (1 mmol) in MeCN (1 mL) heated at 130 °C for 4 min. (b) neat MIDA (1 mmol) in DMF (dry 1 mL) heated at 130 °C for 4 min. (c) neat MIDA (1 mmol) in PEG 300 (1 mL) heated at 130 °C for 4 min. Note: the small rings are reflections from lighting LEDs.

As shown in Figure 2.1 MIDA did not dissolve fully in any of the solvents used at the reaction concentration. It was also observed that initiation of stirring proved difficult in these studies due to the flocculation of the MIDA. Stirring of microwave reactions is of high importance, as it enables uniform heating of the reaction mixture. It has been shown that heating in microwave assisted processes can differ up to 30 °C between the middle and the edge of the reaction vessel in the absence of adequate stirring.³¹

In this body of work we have only monitored reactions via an IR thermometer that measures the temperature of the external surface of the vial; this makes effective stirring key to reporting reproducible results. The use of the camera to monitor the reaction allows observations in real time of the effectiveness of stirring and gives a *qualitative* measure of heat distribution in the microwave vial, without the need for internal optical fibre temperature probes.

Real time observation also enabled the visual monitoring of the reaction progress. On heating the reaction, shown in Table 2.1 (entry 1), to 130 °C it initially appeared cloudy. After maintaining heating for a further 3 minutes the reaction became clear. This showed that the reaction had gone to completion as the MIDA, which was insoluble in its unreacted form, had been consumed forming the protected boronate product, which was soluble in hot MeCN (Figure 2.2).

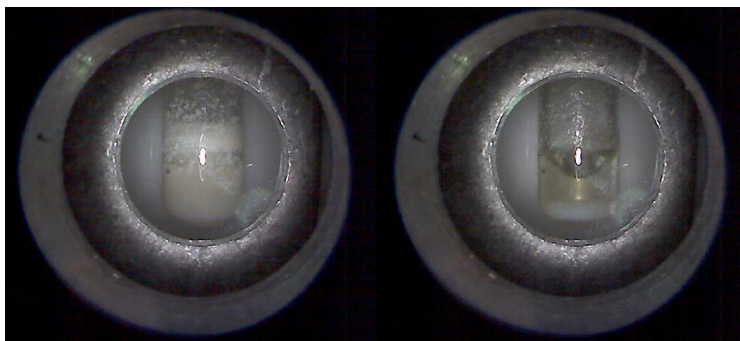


Figure 2.2. (a) initial reaction mixture; heating to 130 °C in MeCN.
(b) Mixture after a further 3 minutes of heating.

Similar observations were noted when the reactions were performed in DMF (Table 2.1 entry 6). This reaction progressed much faster than in MeCN as the disappearance of the cloudy suspension was seen after 1 minute.

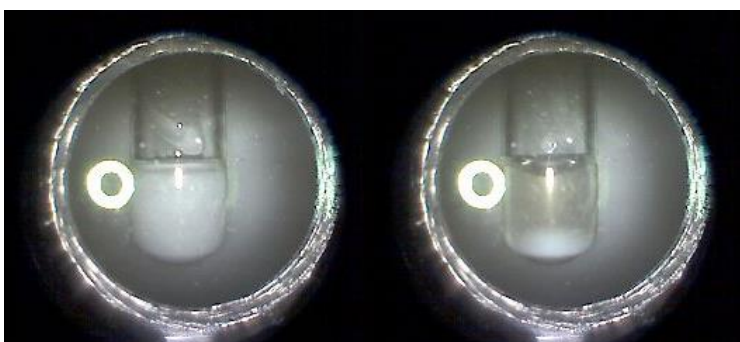


Figure 2.3(a) initial reaction heating 130 °C in DMF. (b) reaction after a further 1 minute of heating.

The reaction in PEG 300 (Table 2.1 entry 8) did not follow this pattern as at no point did the reaction mixture fully dissolve (Figure 2.4). This is potentially why there was a noticeable difference between the conversions in MeCN and DMF (95% and 97%) compared to that of the isolated yield of PEG (69 %).



Figure 2.4 Reaction mixture after 4 minutes of heating in PEG 300.

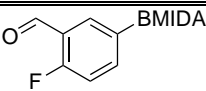
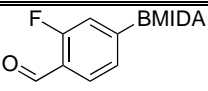
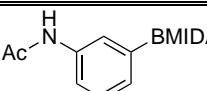
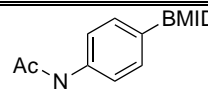
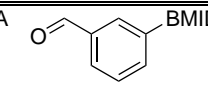
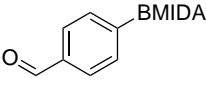
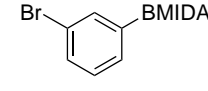
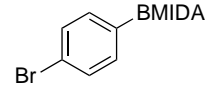
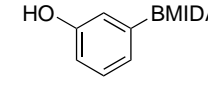
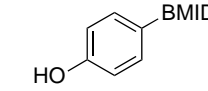
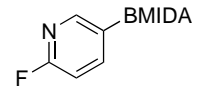
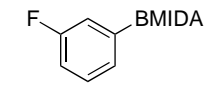
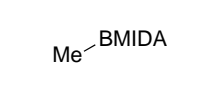
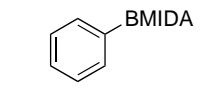
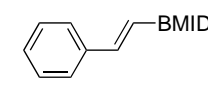
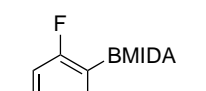
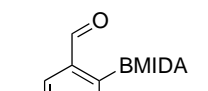
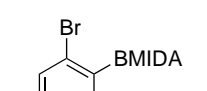
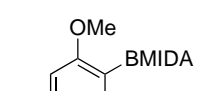
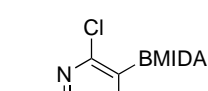
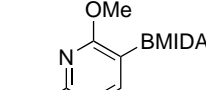
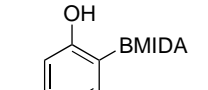
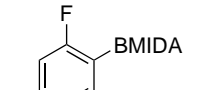
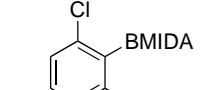
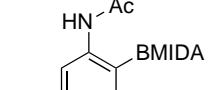
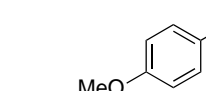
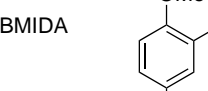
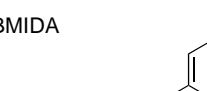
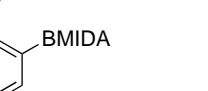
The low solubility of MIDA in the reaction mixture can lead to sedimentation at the bottom of the microwave vial making it difficult to initiate stirring. When the reaction was performed in MeCN its low boiling point caused agitation of the sedimented MIDA, which freed the magnetic stirrer thus initiating stirring. When the reaction is performed in PEG 300, the viscosity in the reaction medium was higher than in MeCN, and this has been shown to limit the stirring rate in the microwave vial.^{32,33} This, along with the sedimentation of the MIDA, causes difficulties in initiating stirring in the reaction vial. Due to the high boiling point of PEG 300, heating to 130 °C did not cause agitation and initiation of stirring, unlike with the more volatile MeCN. We found that using the hot keys to start and stop the stirring and the use of cross-shaped stirrer bars during the heating phase of the reaction helped dislodge the stirrer at the low speed setting. At elevated temperatures the stirrer could be turned up to a faster setting. A consequence of low speed stirring during the heating phase of PEG 300 was overheating. Upon increasing the stirrer speed, this caused the heat to rapidly transfer from the centre to the outer surface of the vial, making the reaction temperature overheat by up to 40 °C in some cases. We found that reducing the maximum power from 200 W to 40 W increased the duration of the heating phase; this allowed for uniform heating at the low stirring rate and removed the problem of overshooting.

Due to the nature of the solvents that were used in this early optimisation study (i.e. DMF, PEG 300 and MeCN), no lengthy work up was required. The simple addition of water caused precipitation of the product; this then could be filtered and washed with water to remove any residual reaction solvent. The high stability of the MIDA boronates enabled fast efficient drying of product in an oven.

2.3. Results

From the optimisation study, a library of MIDA boronates was synthesised. This fast methodology has led to 3 general methods using MeCN, DMF or PEG 300; the results are shown in Table 2.2.

Table 2.2 Isolated yields (%) for MIDA boronates using general method A, B or C.

$ \begin{array}{c} \text{R}-\text{B}(\text{OH})_2 \\ \textbf{3} \end{array} \xrightarrow[\text{MW heating 130 } ^\circ\text{C, 5-10 min}]{\text{MIDA 1 eq, 1 mmol mL}^{-1}} \begin{array}{c} \text{R}-\text{BMIDA} \\ \textbf{4} \end{array} $ <p>General method A- MeCN, B- DMF, C- PEG 300</p>				
 29 81 ^a 69 ^a	 30 84 ^a 73 ^a	 31 79 ^a , 85 ^b 77 ^a	 32 80 ^a , 76 ^b 87 ^a	 33 76 ^a 51 ^a
 34 99 ^a 87 ^a	 35 88 ^a 70 ^a	 36 89 ^a , 79 ^b 83 ^a , 72 ^c , 82 ^d	 37 80 ^a	 38 35 ^a
 39 60 ^a 48 ^a	 40 92 ^a 68 ^a	 41 99 ^a 51 ^a	 42 53 ^a 55 ^a	 43 52% ^a , 53 ^b 29% ^a
 44 0 ^a 62 ^{a,e} , 56 ^c 14 ^a	 45 44 ^{a,e}	 46 72 ^{a,e} 52 ^a	 47 97 ^{a,e} , 87 ^c , 92 ^d 51 ^a	 48 25 ^{a,e} 82 ^a
 49 83 ^{a,e} 60 ^a	 50 42 ^{a,e}	 51 80 ^{a,e} , 79 ^c	 52 69 ^{a,e}	 53 0 ^{a,e}
 54 70 ^a	 55 93 ^a	 56 85 ^c	 57 72 ^d	

^a1 mmol scale, ^b3.5 mmol scale, ^c5 mmol scale, ^d10 mmol scale, ^e experiments performed by Matthew Emerson.

The initial solvent tested was acetonitrile shown in Table 2.2 (general method A, orange highlight), these reactions were done employing a 5 minute time hold microwave method. In general, the reaction showed good functional group tolerance and yields were good to exceptional, *e.g.* **30**, **31**, **37**. A close to quantitative yield was achieved in the preparation of **41**, a simple alkyl MIDA boronate. However, for unknown reasons **38** was formed in a low yield and **44** was a notable exception, which was unable to be synthesised. In the case of **44**, the presence of two ortho substituents flanking the boronic acid functionality was hypothesised to have caused the low yield. This led to the use of higher boiling point solvent and/or extended reaction times that might facilitate formation of **44**.

31, **32**, **36** and **43** were all attempted on a larger scale, and all exhibited similar yields to the smaller scale examples. Some technical adjustments were required for the larger scale reactions. When attempting 5 mmol scale reactions in a 35 mL CEM microwave vial increased pressurisation was observed, resulting from reduction in relative head space in the closed system. This was resolved by adopting a like-for-like mmol mL⁻¹ ratio to that used original 1 mmol conditions, enabling the same relative head space, regardless of vial size. Therefore a 3.5 mmol scale reactions were performed in a 35 mL vial. This was the limit of scale for using MeCN as its lower boiling point did not facilitate open vessel reactions.

The use of DMF as solvent required increasing the reaction time to 10 min, as a rapid screen showed incomplete reactions after a 5 min heating period. This led to **44** being prepared in yield of 62% and series heteroaryl MIDA and 2-substituted aryl boronates were now included in the library (Table 2.2) mostly in reasonable to good yields. Poor yields were recorded for the 2-phenol derivative **50** the chloropyridine **48**, and additionally **53** was unproductive. An acceptable 44% yield was achieved for the benzaldehyde derivative **45**, which Grob *et al* reported a yield of 0% in their 18 hour DMF heating methodology.²⁰ Due to the higher boiling point of DMF increasing the scale of the reactions was less problematic than those carried out in MeCN. 5 mmol scale reactions, as could be achieved using a 35 mL reaction vial and yields were comparable to the smaller scale reactions shown with **44** and **51**. Open vessel reactions were also achievable with DMF as the solvent, allowing for the 10 mmol scale synthesis of **47** yielding over 2 g of product.

Yields in PEG 300 were generally good, as shown in Table 2.2 (general method C, green highlight). Synthesis of 2-substituted MIDA boronates in PEG 300 tended to be lower yielding than those obtained using DMF, for example, **47** (51% vs 97%), **49** (60% vs

83%) and **44** (14% vs 62%) showing that DMF would be a solvent of choice. Although, PEG 300 showed comparable yields in the synthesis of **36** on a range of scales, and a yield of 82% was observed in the preparation of **48**. As with DMF increasing the scale of reactions was done with ease due to PEG 300's low vapour pressure and enabled open vessel MW reaction on a 10 mmol scale for example **57**. The work up procedure using PEG 300 proved easy: precipitation of the pure MIDA boronate product, after cooling, was achieved using water.

2.4. Conclusion

The rapid microwave-mediated synthesis in either acetonitrile, DMF or PEG 300 was developed in this Chapter, facilitating the generation of a library of MIDA boronates. This reaction in most cases gave high yields, using minimal solvent, with reduced reaction times. A range of different functional groups were tolerated at a variety of positions on the aromatic ring with respect to the boronic acid, although the isolated yields varied depending on the solvent used. Generally DMF gave higher yields than either acetonitrile or PEG 300, with substrates that had functional groups on the aromatic ring *ortho* to the boronic acid. This rapid synthesis could be performed on larger scales giving yields comparable to the 1 mmol reactions. The higher boiling point solvents, DMF and PEG 300, facilitated open vessel microwave reactions at 130 °C, this enabled much larger multigram scale reactions.

The work led to the first publications from this thesis, with the aid of Matthew Emmerson, a Spencer lab MChem student, who, under my supervision achieved some of the results using DMF.³⁴ The observations using the microwave camera were of interest to CEM and published as a CEM applications note on their website.³⁵

This work enables the synthesis of key compounds that are used in Chapter 3 for the examination of polysubstituted arene synthesis *via* bromination and nitration reactions. This work also meets the aims outlined by AstraZeneca, as methods are scalable, utilising cheap starting materials.

2.5. Experimental

Solvents and reagents were purchased from commercial suppliers and used without further purification. Reactions were heated using a CEM Discovery microwave fitted with an Explorer unit; ensure a ventilated fumehood with the sash lowered is used as these reactions are under high pressure and temperature. NMR spectra were recorded on a Varian 500 MHz or 400 MHz spectrometer. Chemical shifts are reported in ppm and are referenced to the residual solvent peak or to TMS used as an internal standard; note that in some cases the carbon bonded to the boron is not detectable in the ^{13}C NMR²³. LCMSs were ran on a Shimadzu LCMS-2020 equipped with a Gemini® 5 μm C18 110 Å column. Percentage purities were performed using a 30 minutes method in water/acetonitrile with 0.1% Formic acid (5min at 5%, 5%-95% over 20 min, 5min at 95%) with the UV set to 254 nm. High resolution mass spectrometry (HRMS) was done either internally or by the National Mass Spectrometry Facility, Swansea. A number of the products described below are commercially available or known, e.g. in patents. In these cases, ^1H , ^{13}C , HRMS and % purity data are presented since in many cases these data are not published. For compounds that appear to be novel, more analytical data are presented including ^{11}B NMR.

General procedure for MIDA boronate formation with acetonitrile (General Method A)

The boronic acid (1 mmol) was added to a 10 mL microwave vial equipped with a magnetic stirrer, and then acetonitrile (1 mL) was added, followed by methyliminodiacetic acid (MIDA) (147 mg, 1 mmol). The Teflon cap was added and the reaction was heated using the dynamic heating method, with the maximum power set to 300 W, max pressure 250 psi, max temperature 130 °C, high stirring throughout and power max turned off. This method was used to hold the reaction mixture at 130 °C for 5 min. After cooling, the magnetic stirrer was retrieved and the acetonitrile was removed under reduced pressure giving a crude white powder. This crude material was first triturated via sonication with deionised water (5 mL), cooled in an ice bath, collected by filtration and washed with cold water (5 mL). This solid was then further triturated with diethyl ether (5 mL), cooled in an ice bath, collected by filtration and washed with diethyl ether (5 mL) giving pure product as a white precipitate (if not otherwise quoted) which was air dried.

Note: The 3.5 mmol scale reaction was done using a 35 mL microwave vial, with the same heating profile.

General procedure for MIDA boronate formation with DMF (General Method B)

The boronic acid (1 mmol) was added to a 10 mL microwave vial equipped with a magnetic stirrer, followed by methyliminodiacetic acid (MIDA) (1 mmol) and dry DMF (1 mL) was added to the vial. The Teflon cap was added and the reaction was heated using the dynamic heating method, with max power set to 300 W, max pressure 300 psi, max temperature 130 °C, high stirring throughout and power max turned off. This method was used to hold the reaction mixture at 130 °C for 10 min.

After cooling, the DMF was removed under reduced pressure giving crude yellow oil. The latter was triturated via sonication with deionised water (5 mL), cooled in an ice bath collected by filtration and washed with cold water (5 mL). This solid was then further triturated with diethyl ether (5 mL), cooled in an ice bath, collected by filtration and washed with diethyl ether (5 mL) then air dried giving pure product as a white precipitate.

General procedure for MIDA boronate formation with PEG 300 (General Method C)

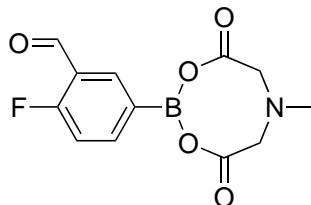
The boronic acid (1 mmol) was added to a 10 mL microwave vial equipped with a magnetic stirrer, and then PEG 300 (1 mL) was added followed by methyliminodiacetic acid (MIDA) (147 mg, 1 mmol). The Teflon cap was added and the reaction was heated using the dynamic heating method, with max power set to 40 W, max pressure 250 psi, max temperature 130 °C, high stirring throughout and power max turned off. This method was used to hold the reaction mixture at 130 °C for 5 min.

After cooling, the mixture was added to water (9 mL). This mixture was stirred forming a white precipitate, then cooled in an ice bath allowing flocculation, then collected by filtration and washed with cold water (5 mL). The precipitate was allowed to dry in an oven set to 100°C, giving pure product as a white precipitate (if not otherwise quoted).

Notes: The 5 mmol scale reaction was performed using a 35 mL microwave vial and the 10 mmol scale was carried out using a 100 mL round bottomed flask with a small air condenser attached with the open vessel attenuator installed. The heating parameters

were kept the same but the hold time was changed to 7.5 min for the 5 mmol scale and 10 min for the 10 mmol scale reactions.

4-Fluoro-3-formylphenyl MIDA boronate, 29.²⁰



Made following General Method A.

Yield: 226 mg (81%) as a white precipitate.

Made following General Method C.

Yield: 193 mg (69%) as a white precipitate.

HRMS-ESI (m/z) found 302.0607, calcd for $[\text{C}_{12}\text{H}_{11}^{10}\text{BNO}_5\text{Na}]^+$ 302.0607.

^1H NMR (500 MHz, Acetonitrile- D_3) δ 10.30 (s, 1H), 7.96 (dd, $^4J_{\text{FH}} = 7.5$, $^4J_{\text{HH}} = 2.0$ Hz, 1H), 7.82 (ddd, $^3J_{\text{HH}} = 8.5$, $^4J_{\text{FH}} = 5.5$, $^4J_{\text{HH}} = 2.0$ Hz, 1H), 7.27 (dd, $^3J_{\text{FH}} = 11.5$, $^3J_{\text{HH}} = 8.5$ Hz, 1H), 4.10 (d, $J = 17.0$ Hz, 2H), 3.93 (d, $J = 17.0$ Hz, 2H), 2.54 (s, 3H).

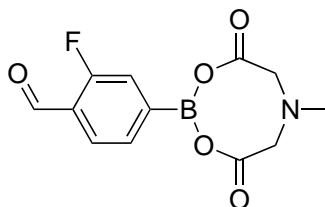
^{13}C NMR (126 MHz, Acetonitrile- D_3) δ 187.9 (d, $^3J_{\text{FC}} = 6.0$ Hz), 168.3, 165.0 (d, $^1J_{\text{FC}} = 260.0$ Hz), 140.9 (d, $^3J_{\text{FC}} = 9.0$ Hz), 134.0 (d, $^3J_{\text{FC}} = 2.0$ Hz), 123.7 (d, $^2J_{\text{FC}} = 8.0$ Hz), 116.1 (d, $^2J_{\text{FC}} = 20.0$ Hz), 62.1, 47.7.

^{19}F NMR (376 MHz, Acetonitrile- D_3) δ -110.85 (ddd, $J = 11.5$, 7.5, 5.5 Hz).

^{11}B NMR (128 MHz, Acetonitrile- D_3) δ 10.6.

LCMS purity UV = 96%, Ret. time = 14.10 min.

3-Fluoro-4-formylphenyl MIDA boronate, 30.²⁰



Made following General Method A.

Yield: 235 mg (84%) as a white precipitate.

Made following General Method C.

Yield: 204 mg (73%) as a white precipitate.

HRMS-ESI (m/z) found 302.0605, calcd for $[\text{C}_{12}\text{H}_{11}^{10}\text{BFNO}_5\text{Na}]^+$ 302.0607

^1H NMR (500 MHz, Acetonitrile- D_3) δ 10.34 (s, 1H), 7.87 (appt, $^3J_{\text{HH}}, ^4J_{\text{FH}}$ $J = 7.5$ Hz, 1H), 7.49 (d, $^3J_{\text{HH}} = 7.5$ Hz, 1H), 7.43 (d, $^3J_{\text{FH}} = 11.5$ Hz, 1H), 4.15 (d, $J = 17.0$ Hz, 2H), 3.98 (d, $J = 17.0$ Hz, 2H), 2.59 (s, 3H).

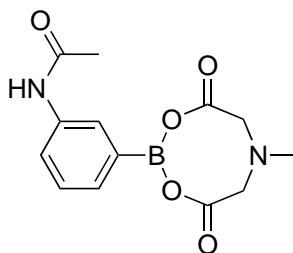
^{13}C NMR (126 MHz, Acetonitrile- D_3) δ 188.7 (d, $^3J_{\text{FC}} = 6.0$ Hz), 169.2, 164.9 (d, $^1J_{\text{FC}} = 258.0$ Hz), 129.8, (d, $^3J_{\text{FC}} = 4.0$ Hz), 129.4, 125.7 (d, $^2J_{\text{FC}} = 9.0$ Hz), 121.3 (d, $^2J_{\text{FC}} = 19.0$ Hz), 63.2, 48.7.

^{19}F NMR (376 MHz, Acetonitrile- D_3) δ -112.46 (dd, $J = 11.7, 7.3$ Hz).

^{11}B NMR (128 MHz, Acetonitrile- D_3) δ 10.6.

LCMS purity UV 94%, Ret. time = 14.24 min.

3-Acetamidophenyl MIDA boronate, 31.



Made following General Method A

Yield: 230 mg (1 mmol scale, 79%), 861 mg (3.5 mmol scale, 85%) as a pink precipitate.

Made following General Method C.

Yield: 223 mg (77%) as a pink precipitate.

HRMS-FTMS (m/z) found 290.1180, calcd for $[\text{C}_{13}\text{H}_{15}^{10}\text{BN}_2\text{O}_5\text{H}]^+$ 290.1183.

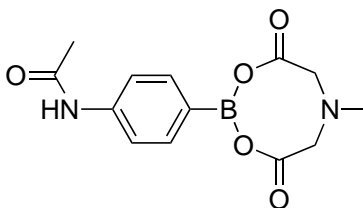
^1H NMR (500 MHz, DMSO- D_6) δ 9.87 (s, 1H), 7.79 – 7.74 (m, 1H), 7.46 (s, 1H), 7.31 – 7.24 (m, 1H), 7.12 – 7.06 (m, 1H), 4.33 (d, $J = 17.0$ Hz, 2H), 4.09 (d, $J = 17.0$ Hz, 2H), 2.49 (s, 3H), 2.02 (s, 3H).

^{13}C NMR (126 MHz, DMSO- D_6) δ 169.2, 168.1, 138.7, 128.0, 127.0, 122.9, 119.7, 61.6, 47.5, 23.9.

^{11}B NMR (128 MHz, DMSO- D_6) δ 11.3.

LCMS purity >99% (UV), Ret. time = 11.76 min.

4-Acetamidophenyl MIDA boronate, 32.



Made following General Method A.

Yield: 232 mg (80%), 768 mg (3.5 mmol scale, 76%) as a brown crystalline solid.

Made following General Method C.

Yield: 252 mg (1 mmol scale, 87%) as a brown crystalline solid.

HRMS-FTMS (m/z) found 290.1181, calcd for $[C_{13}H_{15}^{10}BN_2O_5H]^+$ 290.1183.

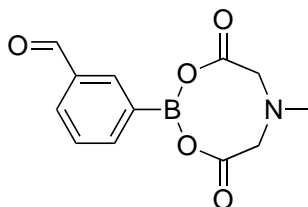
1H NMR (500 MHz, DMSO- D_6) δ 9.90 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.30 (d, J = 17.0 Hz, 2H), 4.08 (d, J = 17.0 Hz, 2H), 2.48 (s, 3H), 2.04 (s, 3H).

^{13}C NMR (126 MHz, DMSO- D_6) δ 169.3, 168.2, 139.9, 132.8, 118.2, 61.7, 47.5, 24.0.

^{11}B NMR (128 MHz, DMSO- D_6) δ 10.4.

LCMS purity >99% (UV), Ret. time = 11.37 min.

3-Formylphenyl MIDA boronate, 33.²⁰



Made following General Method A.

Yield: 200 mg (76%) as a white precipitate.

Made following General Method C.

Yield: 264 mg (51%) as a white precipitate.

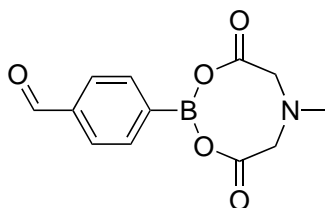
HRMS-ESI (m/z) found 284.0701, calcd for $[C_{12}H_{12}^{10}BNO_5Na]^+$ 284.0701.

1H NMR (500 MHz, DMSO- D_6) δ 10.04 (s, 1H), 8.00 (s, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.60 (app, J = 7.5 Hz, 1H), 4.37 (d, J = 17.2 Hz, 2H), 4.17 (d, J = 17.2 Hz, 2H), 2.53 (s, 3H).

^{13}C NMR (126 MHz, DMSO- D_6) δ 193.5, 169.2, 138.6, 135.5, 133.9, 129.8, 128.4, 62.0, 47.7. ^{11}B NMR (128 MHz, DMSO- D_6) δ 11.3.

LCMS purity UV = 98%, Ret. time = 13.45 min.

4-Formylphenyl MIDA boronate, 34.²⁰



Made following General Method A.

Yield: 264 mg (99%) as a white precipitate.

Made following General Method C.

Yield: 227 mg (87%) as a white precipitate.

HRMS-ESI (m/z) found 284.0699, calcd for $[\text{C}_{12}\text{H}_{12}^{10}\text{BNO}_5\text{Na}]^+$ 284.0701.

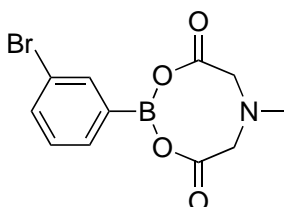
^1H NMR (500 MHz, Acetonitrile- D_3) δ 10.04 (s, 1H), 7.89 (d, $J = 8.0$ Hz, 2H), 7.72 (d, $J = 8.0$ Hz, 2H), 4.10 (d, $J = 17.1$ Hz, 2H), 3.93 (d, $J = 17.1$ Hz, 2H), 2.52 (s, 3H).

^{13}C NMR (126 MHz, $\text{DMSO}-\text{D}_6$) δ 193.4, 169.2, 136.5, 133.1, 128.5, 62.0, 47.7.

^{11}B NMR (128 MHz, $\text{DMSO}-\text{D}_6$) δ 10.8.

LCMS purity >99% (UV), Ret. time = 11.76 min.

3-Bromophenyl MIDA boronate, 35.²



Made following General Method A.

Yield: 274 mg (88%) as a white precipitate.

Made following General Method C.

Yield: 218 mg (70%) as a white precipitate.

HRMS-ESI (m/z) found 333.9851, calcd for $[\text{C}_{11}\text{H}_{11}^{10}\text{B}^{79}\text{BrNO}_4\text{H}]^+$ 333.9857.

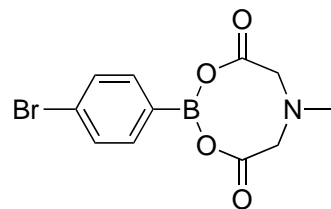
^1H NMR (500 MHz, Acetonitrile- D_3) δ 7.65 (s, 1H), 7.63 – 7.59 (m, 1H), 7.53 – 7.48 (m, 1H), 7.37 – 7.33 (m, 1H), 4.07 (d, $J = 17.1$ Hz, 2H), 3.91 (d, $J = 17.1$ Hz, 2H), 2.53 (s, 3H).

^{13}C NMR (126 MHz, Acetonitrile- D_3) δ 169.3, 136.2, 133.2, 132.3, 131.0, 123.4, 63.0, 48.7.

^{11}B NMR (128 MHz, Acetonitrile- D_3) δ 11.3.

LCMS purity UV >99%, Ret. time = 16.73 min.

4-Bromophenyl MIDA boronate, 36.²



Made following General Method A.

Yield: 278 mg (1 mmol scale, 89%), 861 mg (3.5 mmol scale, 79 %) as a white precipitate.

Made following General Method C.

Yield: 259 mg (1 mmol scale, 83%), 1.127 g (5 mmol scale, 72%), 2.551 g (10 mmol scale, 82%) as a white precipitate.

HRMS-ESI (m/z) found 333.9857, calcd for $[\text{C}_{11}\text{H}_{11}^{10}\text{BBrNO}_4\text{H}]^+$ 333.9857.

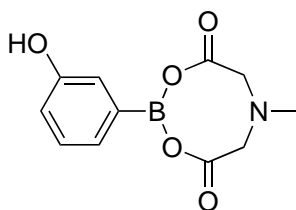
^1H NMR (500 MHz, Acetonitrile- D_3) δ 7.55 (d, $J = 8.0$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 2H), 4.07 (d, $J = 17.0$ Hz, 2H), 3.89 (d, $J = 17.0$ Hz, 2H), 2.51 (s, 3H).

^{13}C NMR (126 MHz, Acetonitrile- D_3) δ 169.4, 135.6, 132.0, 124.4, 62.9, 48.6.

^{11}B NMR (128 MHz, Acetonitrile- D_3) δ 11.2.

LCMS purity UV >99%, Ret. time = 16.87 min.

3-Hydroxyphenyl MIDA boronate 37.



Made following General Method A.

Yield: 199 mg (80%) as a white precipitate.

HRMS-ESI (m/z) found 250.0878, calcd for $[\text{C}_{11}\text{H}_{12}^{10}\text{BNO}_5\text{H}]^+$ 250.0881.

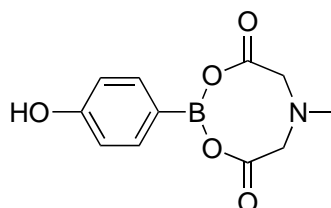
^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 9.26 (s, 1H), 7.25 (d, $J = 8.0$ Hz, 1H), 6.96 – 6.90 (m, 2H), 6.84 (d, $J = 8.0$ Hz, 1H), 4.40 (d, $J = 17.0$ Hz, 2H), 4.18 (d, $J = 17.0$ Hz, 2H), 2.58 (s, 3H).

^{13}C NMR (126 MHz, DMSO- D_6) δ 169.3, 156.7, 128.8, 122.9, 119.0, 115.8, 61.7, 47.5.

^{11}B NMR (128 MHz, DMSO- D_6) δ 11.7.

LCMS purity >99% (UV), Ret. time = 11.61 min.

4-Hydroxyphenyl MIDA boronate, 38.



Made following General Method A.

Yield: 87 mg (35%) as a white precipitate.

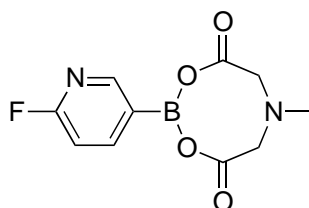
HRMS-ESI (m/z) found 272.0700, calcd for $[\text{C}_{11}\text{H}_{12}^{10}\text{BNO}_5\text{Na}]^+$ 272.0701.

^1H NMR (500 MHz, Acetonitrile- D_3) δ 7.33 (d, J = 8.0 Hz, 2H), 6.93 (s, 1H), 6.82 (d, J = 8.0 Hz, 2H), 4.02 (d, J = 17.0 Hz, 2H), 3.84 (d, J = 17.0 Hz, 2H), 2.48 (s, 3H).

^{13}C NMR (100 MHz, Acetonitrile- D_3) δ 169.6, 159.0, 135.0, 115.9, 62.7, 48.4. ^{11}B NMR (128 MHz, Acetonitrile- D_3) δ 11.6.

LCMS purity >99% (UV), Ret. time = 11.14 min.

2-Fluoropyridine-5 MIDA boronate, 39.



Made following General Method A.

Yield: 152 mg (60%) as a white precipitate.

Made following General Method C.

Yield: 121 mg (48%) as a white precipitate.

HRMS-ESI (m/z) found 253.0789, calcd for $[\text{C}_{10}\text{H}_{10}^{10}\text{BN}_2\text{O}_4\text{H}]^+$ 253.0790.

^1H NMR (500 MHz, DMSO- D_6) δ 8.26 – 8.23 (m, 1H), 8.03 – 7.97 (m, 1H), 7.17 – 7.13 (m, 1H), 4.36 (d, J = 17.0 Hz, 2H), 4.16 (d, J = 17.0 Hz, 2H), 2.58 (s, 3H).

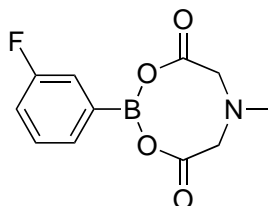
^{13}C NMR (100 MHz, DMSO- D_6) δ 169.0, 164.0 (d, $^1J_{\text{FC}} = 236.0$ Hz), 151.6 (d, $^3J_{\text{FC}} = 14.0$ Hz), 146.4 (d, $^3J_{\text{FC}} = 7.5$ Hz), 108.7 (d, $^2J_{\text{FC}} = 36.0$ Hz), 62.0, 47.7.

^{19}F NMR (376 MHz, DMSO- D_6) δ -68.77 (d, $J = 9.0$ Hz).

^{11}B NMR (128 MHz, DMSO- D_6) δ 11.2.

LCMS purity UV >99%, Ret. time = 12.13 min.

3-Fluorophenyl MIDA boronate, 40.



Made following General Method A.

Yield: 231 mg (92%) as a white precipitate.

Made following General Method C.

Yield: 171 mg (68%) as a white precipitate.

HRMS-FTMS (m/z) found 274.0664, calcd for $[\text{C}_{11}\text{H}_{11}\text{O}_4\text{NBfNa}]^+$ 274.0664.

^1H NMR (500 MHz, DMSO- D_6) δ 7.44 – 7.38 (m, 1H), 7.26 (d, $J = 7.3$ Hz, 1H), 7.23 – 7.12 (m, 2H), 4.34 (d, $J = 17.0$ Hz, 2H), 4.14 (d, $J = 17.0$ Hz, 2H), 2.53 (s, 3H).

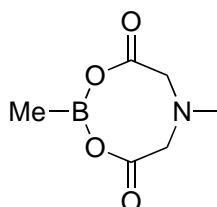
^{13}C NMR (126 MHz, DMSO- D_6) δ 169.2, 162.0 (d, $J = 244.0$ Hz), 129.8 (d, $J = 7.5$ Hz), 128.3 (d, $J = 2.5$ Hz), 118.6 (d, $J = 18.5$ Hz), 115.6 (d, $J = 21.0$ Hz), 61.9, 47.6.

^{19}F NMR (376 MHz, DMSO- d_6) δ -114.11 (td, $J = 9.5, 6.0$ Hz).

^{11}B NMR (128 MHz, DMSO- D_6) δ 10.7.

LCMS purity UV >99%, Ret. time = 15.22 min.

Methyl MIDA boronate, 41.



Made following General Method A.

Yield: 171 mg (99%) as a white precipitate.

Made following General Method C.

Yield: 87 mg (51%) as a white precipitate.

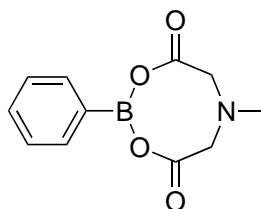
HRMS-ESI (m/z) found 194.0594, calcd for $[\text{C}_6\text{H}_{10}^{10}\text{BNO}_4\text{Na}]^+$ 194.0595

^1H NMR (500 MHz, Acetonitrile- D_3) δ 3.92 (d, $J = 17.0$ Hz, 2H), 3.78 (d, $J = 17.0$ Hz, 2H), 2.84 (s, 3H), 0.10 (s, 3H).

^{13}C NMR (126 MHz, Acetonitrile- D_3) δ 169.1, 62.6, 46.9.

^{11}B NMR (128 MHz, Acetonitrile- D_3) δ 13.4.

Phenyl MIDA boronate, 42.¹⁷



Made following General Method A.

Yield: 123 mg (53%) as a white precipitate.

Made following General Method C.

Yield: 128 mg (55%) as a white precipitate.

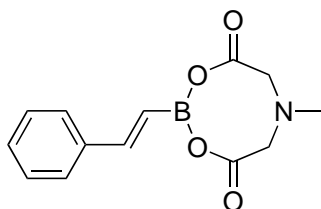
HRMS-ESI (m/z) found 256.0750, calcd for $[\text{C}_{11}\text{H}_{12}^{10}\text{BNO}_4\text{Na}]^+$ 256.0752

^1H NMR (500 MHz, Acetonitrile- D_3) δ 7.53 – 7.47 (m, 2H), 7.44 – 7.36 (m, 3H), 4.06 (d, $J = 17.0$ Hz, 2H), 3.88 (d, $J = 17.0$ Hz, 2H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, Acetonitrile- D_3) δ 169.6, 133.4, 130.3, 128.9, 62.8, 48.5.

LCMS purity UV >99%, Ret. time = 14.38 min.

(E)-Styryl MIDA boronate, 43.



Made following General Method A.

Yield: 135 mg (52%), 480 mg (3.5 mmol scale, 53%).

Made following General Method C.

Yield: 75 mg (29%).

HRMS-FTMS (m/z) found 259.1005, calcd for $[\text{C}_{13}\text{H}_{14}\text{BNO}_4\text{H}]^+$ 259.1016.

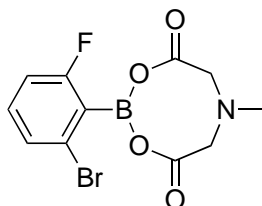
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.52 – 7.47 (m, 2H), 7.39 – 7.32 (m, 2H), 7.29 – 7.24 (m, 1H), 6.83 (d, $J = 18.0$ Hz, 1H), 6.28 (d, $J = 18.0$ Hz, 1H), 4.25 (d, $J = 17.0$ Hz, 2H), 4.04 (d, $J = 17.0$ Hz, 2H), 2.81 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ 169.0, 141.0, 137.8, 128.5, 127.8, 126.4, 61.3, 46.7, 39.5.

^{11}B NMR (128 MHz, $\text{DMSO}-d_6$) δ 10.5.

LCMS purity UV = >99%, Ret. time = 1.75 min.

2-Bromo-6-fluorophenyl MIDA boronate, 44.



Made following General Method B.

Yield: 205 mg (62%), 924 mg (5 mmol scale, 56%)

Made following General Method C.

Yield: 46 mg (14%).

HRMS-FTMS (m/z) found 328.9971, calcd for $[\text{C}_{11}\text{H}_{10}^{10}\text{BBrFNO}_4\text{H}]^+$ 328.9979.

^1H NMR (500 MHz, $\text{DMSO}-D_6$) δ 7.49 (d, $^3J_{\text{HH}} = 8.0$ Hz, 1H), 7.36 (dd, $^3J_{\text{HH}} = 8.0$, 8.5 Hz, 1H), 7.19 (dd, $^3J_{\text{FH}} = 11.0$, $^3J_{\text{HH}} = 8.5$ Hz, 1H), 4.42 (d, $J = 17.5$ Hz, 2H), 4.16 (d, $J = 17.5$ Hz, 2H), 2.72 (s, 3H).

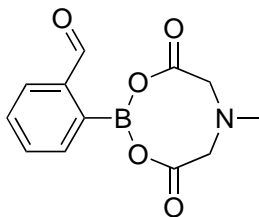
^{13}C NMR (126 MHz, $\text{DMSO}-D_6$) δ 168.6, 166.5 (d, $^1J_{\text{CF}} = 248.0$ Hz), 132.6 (d, $^3J_{\text{FC}} = 11.0$ Hz), 130.5 (d, $^4J_{\text{FC}} = 3.0$ Hz), 127.8 (d, $^3J_{\text{FC}} = 9.0$ Hz), 115.2 (d, $^2J_{\text{FC}} = 27.0$ Hz), 63.0, 47.9

^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -97.67 (dd, $J = 11.0$, 6.3 Hz).

^{11}B NMR (128 MHz, $\text{DMSO}-D_6$) δ 10.6.

LCMS purity UV = >99%, Ret. time = 15.42 min.

2-Formylphenyl MIDA boronate, 45.



Following General Method B

Yield: 116 mg (44%) as a white precipitate.

Following General Method C

Yield: 23 mg (9%) as a white precipitate.

HRMS-FTMS (m/z) found 262.0880, calcd for $[\text{C}_{12}\text{H}_{12}^{10}\text{BNO}_5\text{H}]^+$ 262.0881.

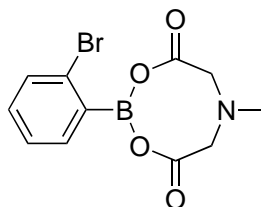
^1H NMR (500 MHz, Acetonitrile- D_3): δ 10.11 (s, 1H), 7.93 (m, 1H), 7.80 (m, 1H), 7.66 (m, 2H), 4.14 (d, $J=18.0$, 2H), 4.14 (d, $J=18.0$, 2H), 2.68 (s, 3H).

^{13}C NMR (126 MHz, Acetonitrile- D_3): 196.8, 169.9, 142.1, 136.8, 135.2, 134.0, 130.7, 65.7, 50.0.

^{11}B NMR (128 MHz, Acetonitrile- D_3): 11.8.

LCMS purity UV = >99%, Ret. time = 12.94 min.

2-Bromophenyl MIDA boronate, 46.²



Made following General Method B

Yield: 224 mg (72%) as a white precipitate.

Made following General Method C

Yield: 218 mg (70%) as a white precipitate.

HRMS-FTMS (m/z) found 333.9862, calcd for $[\text{C}_{11}\text{H}_{11}^{10}\text{B}^{79}\text{BrNO}_4\text{Na}]^+$ 333.9857.

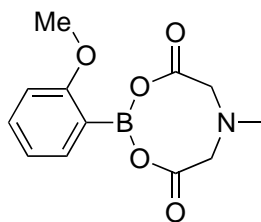
^1H NMR (500 MHz, Acetonitrile- D_3): δ 7.67 (d, $J=7.4$, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 7.39 (dd, $J = 7.4$, 7.5 Hz, 1H), 7.30 (dd, $J = 7.8$, 7.5 Hz, 1H), 4.13 (d, $J = 17.0$ Hz, 2H), 4.03 (d, $J = 17.0$ Hz, 2H), 2.71 (s, 3H).

^{13}C NMR (126 MHz, Acetonitrile- D_3): 169.5, 137.4, 134.6, 132.4, 128.7, 128.0, 65.3, 49.6.

^{11}B NMR (128 MHz, Acetonitrile- D_3): 11.6.

LCMS purity UV = >99%, Ret. time = 15.44 min.

2-Methoxyphenyl MIDA boronate, 47.



Made following General Method B

Yield: 254 mg (97%), 1144 mg (5 mmol scale, 87%), 2420 mg (10 mmol scale, 92%) as a white precipitate.

Made following General Method C

Yield: 134 mg (51%) as a white precipitate.

HRMS-FTMS (*m/z*) found 286.0860, calcd for [C₁₂H₁₄¹⁰BNO₅Na]⁺ 286.0857.

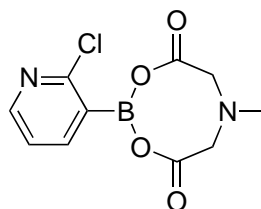
¹H NMR (500 MHz, Acetonitrile-D₃): δ 7.56 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.39 (ddd, *J* = 8.0, 7.0, 2.0 Hz, 1H), 6.97 (m, 2H), 4.06 (d, *J* = 17.0 Hz, 2H), 3.95 (d, *J* = 17.0 Hz, 2H), 3.77 (s, 3H), 2.61 (s, 3H).

¹³C NMR (126 MHz, DMSO-D₆): 169.2, 162.0, 133.9, 130.7, 120.2, 110.3, 63.2, 54.8, 47.2.

¹¹B NMR (128 MHz, Acetonitrile-D₃): 7.7.

LCMS purity UV = >99%, Ret. time = 14.76 min.

2-Chloro-3-pyridyl MIDA boronate, 48.



Made following General Method B

Yield: 67 mg (25%) as a white precipitate.

Made following General Method C

Yield: 220 mg (82%) as a white precipitate.

HRMS-FTMS (*m/z*) found 269.0429, calcd for [C₁₀H₁₀¹⁰BClN₂O₄H]⁺ 269.0495.

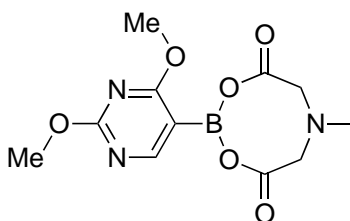
^1H NMR (500 MHz, Acetonitrile- D_3): δ 8.39 (dd, J = 5.0, 2.0 Hz, 1H), 8.11 (dd, J = 2.0, 7.5 Hz, 1H), 7.35 (dd, J = 7.5, 5.0 Hz, 1H), 4.16 (d, J = 17.5 Hz, 2H), 4.05 (d, J = 17.5 Hz, 2H), 2.75 (s, 3H).

^{13}C NMR (126 MHz, Acetonitrile- D_3): 169.3, 151.6, 146.6, 123.5, 111.0, 65.2, 49.3.

^{11}B NMR (128 MHz, Acetonitrile- D_3): 11.0.

LCMS purity UV = >99%, Ret. time = 11.43 min.

2,4-Dimethoxypyrimidine-5-MIDA boronate, 49.



Made following General Method B

Yield: 245 mg (83%) as a white precipitate.

Made following General Method C

Yield: 177 mg (60%) as a white precipitate.

HRMS-FTMS (m/z) found 296.1046, calcd for $[\text{C}_{11}\text{H}_{14}^{10}\text{BN}_3\text{O}_6\text{H}]^+$ 296.1048.

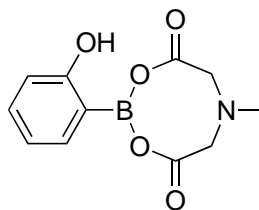
^1H NMR (500 MHz, Acetonitrile- D_3): δ 8.38 (s, 1H), 4.08 (d, J = 17.0 Hz, 2H), 3.95 (s, 3H), 3.94 (d, J = 17.0 Hz, 2H), 3.91 (s, 3H), 2.66 (s, 3H).

^{13}C NMR (126 MHz, Acetonitrile- D_3): δ 174.8, 169.3, 167.9, 164.9, 111.0, 64.0, 55.2, 54.3, 48.2.

^{11}B NMR (128 MHz, Acetonitrile- D_3): δ 11.2 (s).

LCMS purity UV = 97%, Ret. time = 10.34 min.

2-Hydroxyphenyl MIDA boronate, 50.



Made following General Method B

Yield: 105 mg (42%) as a white precipitate.

Following General Method B

Yield: 105 mg (42%) as a white precipitate.

HRMS-FTMS (m/z) found 272.0702, calcd for $[\text{C}_{11}\text{H}_{12}^{10}\text{BNO}_5\text{Na}]^+$ 272.0701.

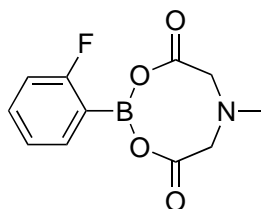
^1H NMR (500 MHz, DMSO- D_6): δ 9.53 (s, 1H), 7.38 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.17 (ddd, $J = 8.0, 7.5, 1.5$ Hz, 1H), 6.80-6.73 (m, 2H), 4.32 (d, $J = 17.0$ Hz, 2H), 4.03 (d, $J = 17.0$ Hz, 2H), 2.63 (s, 3H).

^{13}C NMR (126 MHz, DMSO- D_6): 169.3, 160.0, 134.0, 130.2, 118.7, 114.6, 63.1, 47.1.

^{11}B NMR (128 MHz, DMSO- D_6): 11.8.

LCMS purity UV = >99%, Ret. time = 12.76 min.

2-Fluorophenyl MIDA boronate, 51.



Following General Method B

Yield: 208 mg (83%), 991 mg (5 mmol scale, 79%) as a white precipitate.

HRMS-FTMS (m/z) found 274.0661, calcd for $[\text{C}_{11}\text{H}_{11}^{10}\text{BFNO}_4\text{Na}]^+$ 274.0657.

^1H NMR (500 MHz, Acetonitrile- D_3): 7.59 (dd, $J = 7.5$ Hz, 1H), 7.49-7.41 (m, 1H), 7.22 (dd, $J = 7.5$ Hz, 1H), 7.08 (dd, $J = 10.5, 8.5$ Hz, 1H), 4.12 (d, $J = 17.0$ Hz, 2H), 3.95 (d, $J = 17.0$ Hz, 2H), 2.64 (s, 3H).

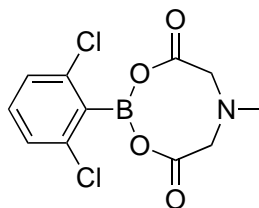
^{13}C NMR (126 MHz, DMSO- D_6): 168.9, 165.5 (d, $J = 241.0$ Hz), 134.7 (d, $J = 9.0$ Hz), 131.6 (d, $J = 8.5$ Hz), 124.1 (d, $J = 2.5$ Hz), 114.9 (d, $J = 25.0$ Hz), 62.4 (d, $J = 2.0$ Hz), 47.5.

^{19}F NMR (376 MHz, DMSO- D_6): -107.5 (m).

^{11}B NMR (128 MHz, Acetonitrile- D_3): 10.5.

LCMS purity UV = >99%, Ret. time = 14.72 min.

2, 6-Dichlorophenyl MIDA boronate, 52.



Following General Method B

Yield: 104 mg (35%) as a white precipitate.

HRMS-FTMS (m/z) found 323.9967, calcd for $[\text{C}_{11}\text{H}_{10}^{10}\text{BCl}_2\text{NO}_4\text{Na}]^+$ 323.9972.

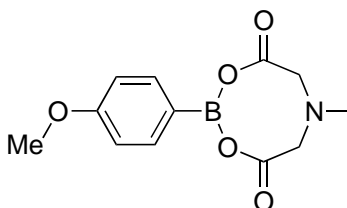
^1H NMR (500 MHz, Acetonitrile- D_3): δ 7.40 (m, 1H), 7.34 – 7.29 (m, 2H), 4.15 (d, J = 17.5 Hz, 2H), 4.01 (d, J = 17.5 Hz, 2H), 2.83 (s, 3H).

^{13}C NMR (126 MHz, Acetonitrile- D_3): δ 169.2, 142.0, 132.4, 130.9, 65.4, 49.7.

^{11}B NMR (128 MHz, Acetonitrile- D_3): δ 11.4 (s).

LCMS purity UV = >99%, Ret. Time = 15.56 min.

4-Methoxyphenyl MIDA boronate, 54.



Made following General Method C

Yield: 184 mg (70%) as a white precipitate.

HRMS-ESI (m/z) found 286.0869, calcd for $[\text{C}_{12}\text{H}_{14}^{10}\text{BNO}_5\text{Na}]^+$ 286.0857

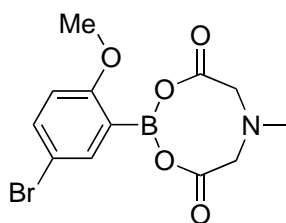
^1H NMR (500 MHz, Acetonitrile- D_3) δ 7.42 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 4.03 (d, J = 17.1 Hz, 2H), 3.86 (d, J = 17.1 Hz, 2H), 3.80 (s, 3H), 2.49 (s, 3H).

^{13}C NMR (126 MHz, Acetonitrile- D_3) δ 169.6, 161.8, 134.9, 114.5, 62.7, 55.8, 48.4.

^{11}B NMR (128 MHz, Acetonitrile- D_3) δ 11.6.

LCMS purity UV >99%, Ret. time = 14.36 min.

5-Bromo-2-methoxyphenyl MIDA boronate, 55.



Made following General Method B

Yield: 318 mg (93%) as a white precipitate.

FTMS APCI MS (m/z) found 344.0118, calcd for $[\text{C}_{12}\text{H}_{13}\text{B}^{81}\text{BrNO}_5\text{H}]^+$ 344.0123.

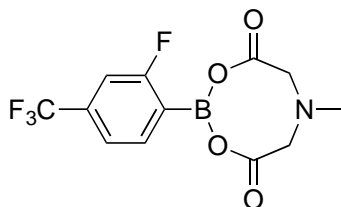
^1H NMR (399 MHz, DMSO- D_6) δ 7.50 – 7.45 (m, 2H), 6.91 (d, J = 9.5 Hz, 1H), 4.33 (d, J = 17.0 Hz, 2H), 3.99 (d, J = 17.0 Hz, 2H), 3.69 (s, 3H), 2.59 (s, 3H).

^{13}C NMR (100 MHz, DMSO- d_6) δ 169.6, 161.7, 136.6, 133.5, 113.4, 112.8, 63.7, 55.8, 47.8.

^{11}B NMR (128 MHz, DMSO- D_6) δ 11.1.

Elemental analysis CHN (%) found C: 42.25, H: 3.88 N: 4.15, calcd for $\text{C}_{12}\text{H}_{13}\text{BBBrF}_4\text{NO}_5$: 40.15, H: 3.83, N: 4.10.

2-Fluoro-4-(trifluoromethyl)phenyl MIDA boronate, 56.



Made following General Method C

Yield: 1.36 g (85%) as a white precipitate.

FTMS ESI (m/z) found 337.0975, calcd for $[\text{C}_{12}\text{H}_{10}\text{BF}_4\text{NO}_4\text{NH}_4]^+$ 337.0977.

^1H NMR (500 MHz, DMSO- D_6) δ 7.78 – 7.68 (m, 1H), 7.64 – 7.52 (m, 2H), 4.50 – 4.43 (m, 2H), 4.19 – 4.10 (m, 2H), 2.67 (d, J = 3.0 Hz, 3H), 4.51 – 4.41 (m, 2H).

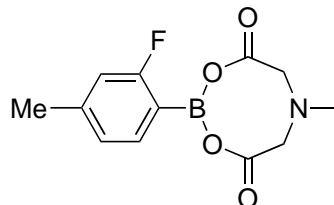
^{13}C NMR (126 MHz, DMSO- D_6) δ 169.2, 165.67 (d, $^1J_{\text{CF}}$ = 243.5 Hz), 136.7 (d, $^3J_{\text{CF}}$ = 9.5 Hz), 132.5 (qd, $^2J_{\text{CF}}$ = 32.5, $^3J_{\text{CF}}$ = 9.0 Hz), 123.6 (qd, $^1J_{\text{CF}}$ = 272.0, $^4J_{\text{CF}}$ = 3.0 Hz), 121.35 – 121.20 (m), 112.7 (dq, $^3J_{\text{CF}}$ = 29.0, $^4J_{\text{CF}}$ = 4.0 Hz), 63.0, 48.0.

^{19}F NMR (376 MHz, DMSO- D_6) δ -61.46, -103.26 – -103.40 (m).

^{11}B NMR (128 MHz, DMSO- D_6) δ 11.1.

LCMS purity UV >99%, Ret. time = 17.38 min.

2-Fluoro-4-methylphenyl MIDA boronate, 57.



Made following General Method C

Yield: 1.90 g (72%) as a white precipitate.

HRMS-ESI (m/z) found 288.0814, calcd for $[\text{C}_{12}\text{H}_{13}^{10}\text{BFNO}_4\text{Na}]^+$ 288.0814

^1H NMR (500 MHz, DMSO- D_6) δ 7.37 (pt, $^3J_{\text{HH}}$, $^4J_{\text{HF}} = 7.0$ Hz, 1H), 7.02 (d, $^3J_{\text{HH}} = 7.5$ Hz, 1H), 6.95 (d, $^3J_{\text{HF}} = 11.0$ Hz, 1H), 4.40 (d, $J = 17.0$ Hz, 2H), 4.08 (d, $J = 17.0$ Hz, 2H), 2.61 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (126 MHz, DMSO- D_6) δ 169.4, 166.0 (d, $^1J_{\text{CF}} = 240.5$ Hz), 142.3 (d, $^3J_{\text{CF}} = 8.7$ Hz), 135.0 (d, $^3J_{\text{CF}} = 10.0$ Hz), 125.3 (d, $^4J_{\text{CF}} = 2.5$ Hz), 115.8 (d, $^2J_{\text{CF}} = 24.5$ Hz), 62.8, 47.9, 21.1.

^{19}F NMR (376 MHz, DMSO- D_6) δ -106.68 (dd, $J = 11.0, 7.0$ Hz).

^{11}B NMR (128 MHz, DMSO- D_6) δ 11.1.

LCMS purity UV >99%, Ret. time = 15.90 min.

2.6. Bibliography

- (1) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, 43, 412–443.
- (2) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, 129, 6716–6717.
- (3) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, 130, 14084–14085.
- (4) Colgin, N.; Flinn, T.; Cobb, S. L. *Org. Biomol. Chem.* **2011**, 9, 1864–1870.
- (5) Grob, J. E.; Dechantsreiter, M. A.; Tichkule, R. B.; Connolly, M. K.; Honda, A.; Tomlinson, R. C.; Hamann, L. G. *Org. Lett.* **2012**, 14, 5578–5581.
- (6) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, 130, 466–468.
- (7) Woerly, E. M.; Struble, J. R.; Palyam, N.; O'Hara, S. P.; Burke, M. D. *Tetrahedron* **2011**, 67, 4333–4343.
- (8) Burns, A. R.; McAllister, G. D.; Shanahan, S. E.; Taylor, R. J. K. *Angew. Chemie Int. Ed.* **2010**, 49, 5574–5577.
- (9) Chan, J. M. W.; Amarante, G. W.; Toste, F. D. *Tetrahedron* **2011**, 67, 4306–4312.
- (10) Bryan, M. C.; Dillon, B.; Hamann, L. G.; Hughes, G. J.; Kopach, M. E.; Peterson, E. A.; Pourashraf, M.; Raheem, I.; Richardson, P.; Richter, D.; Sneddon, H. F. *J. Med. Chem.* **2013**, 56, 6007–6021.
- (11) Gillis, E.; Burke, M. *Aldrichimica Acta* **2009**, 42, 17–27.
- (12) Duncton, M. J.; Singh, R. *Org. Lett.* **2013**, 15, 4284–4287.
- (13) St Denis, J. D.; Scully, C. C. G.; Lee, C. F.; Yudin, A. K. *Org. Lett.* **2014**, 16, 1338–1341.
- (14) Isley, N.; Gallou, F.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2013**, 135, 17707–17710.
- (15) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, 131, 6961–6963.
- (16) Nakhla, J. *ChemFiles* **2009**, 9, 1–10.
- (17) Mancilla, T.; Contreras, R.; Wrackmeyer, B. *J. Organomet. Chem.* **1986**, 307, 4–

6.

- (18) Burke, M.; Dick, G.; Knapp, D. METHODS FOR FORMING PROTECTED ORGANOBORONIC ACIDS. US 2011/0201806 A1, 2011.
- (19) Bagutski, V.; Del Grosso, A.; Carrillo, J. A.; Cade, I. A.; Helm, M. D.; Lawson, J. R.; Singleton, P. J.; Solomon, S. A.; Marcelli, T.; Ingleson, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 474–487.
- (20) Grob, J. E.; Nunez, J.; Dechantsreiter, M. a; Hamann, L. G. *J. Org. Chem.* **2011**, *76*, 4930–4940.
- (21) Ahn, S.-J.; Lee, C.-Y.; Cheon, C.-H. *Adv. Synth. Catal.* **2014**, *356*, 1767–1772.
- (22) Kappe, C. O. *Angew. Chemie Int. Ed.* **2004**, *43*, 6250–6284.
- (23) Spencer, J.; Baltus, C. B.; Patel, H.; Press, N. J.; Callear, S. K.; Male, L.; Coles, S. J. *ACS Comb. Sci.* **2011**, *13*, 24–31.
- (24) Gronnow, M. J.; White, R. J.; Clark, J. H.; Macquarrie, D. J. *Org. Process Res. Dev.* **2005**, *9*, 516–518.
- (25) Mésangeau, C.; Yous, S.; Pérès, B.; Lesieur, D.; Besson, T. *Tetrahedron Lett.* **2005**, *46*, 2465–2468.
- (26) Muzart, J. *Tetrahedron* **2009**, *65*, 8313–8323.
- (27) Material Safety Data Sheet, S.-A. Material Safety Data Sheet, 2014, 271004.
- (28) Material Safety Data Sheet, S.-A. Material Safety Data Sheet, 2014, D4551.
- (29) Jessop, P. G. *Green Chem.* **2011**, *13*, 1391–1398.
- (30) Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. *Green Chem.* **2005**, *7*, 64–82.
- (31) Herrero, M. A.; Kremsner, J. M.; Kappe, C. O.; Graz, K. V; Graz, A. *J. Org. Chem.* **2008**, *73*, 36–47.
- (32) Hayden, S.; Damm, M.; Kappe, C. O. *Macromol. Chem. Phys.* **2013**, *214*, 423–434.

- (33) Obermayer, D.; Damm, M.; Kappe, C. O. *Org. Biomol. Chem.* **2013**, *11*, 4949–4956.
- (34) Close, A. J.; Kemmitt, P.; Emmerson, M. K.; Spencer, J. *Tetrahedron* **2014**, *70*, 9125–9131.
- (35) Close, A. J.; Corden, V.; Spencer, J. Use of a camera to monitor reaction stirring and reagent dissolution during a reaction; a MIDA boronate library generation case study.
<http://www.cemmicrowave.co.uk/assets/cameramida-boronate---app-note.pdf> (accessed Nov 15, 2015).

3 Electrophilic Aromatic Substitution

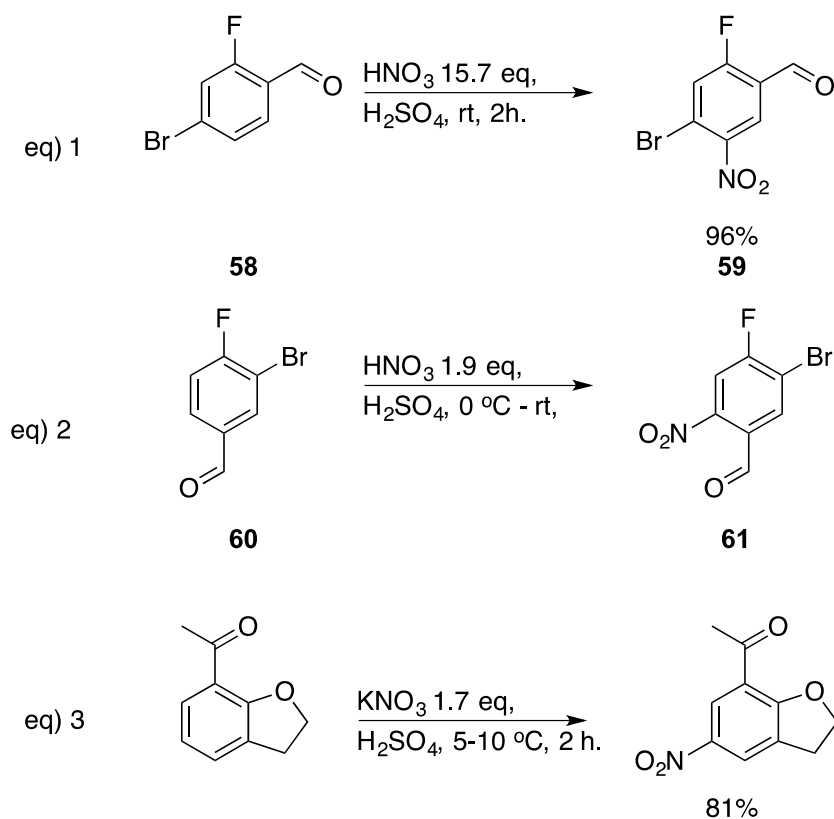
3.1 Overview

The aim of this Chapter is to produce novel tetrasubstituted aromatic compounds using a scalable methodology. The initial study will be based around the nitration of three different regioisomers of bromofluorobenzaldehyde. The later studies will involve the electrophilic aromatic substitution (nitration and bromination) of tri and di substituted phenyl MIDA boronates, with the hypothesis that the MIDA boronates functionality will be able to withstand the harsh reaction conditions.

3.2 Introduction

Historically, electrophilic aromatic substitution is the principal way of synthesising polyfunctionalised aromatic compounds. The review in the introduction (0) highlights the different techniques other than electrophilic aromatic substitution used to synthesise polyfunctionalised aromatic compounds. Due to the need for high scalability, electrophilic aromatic substitution was the focus of this project to achieve bromination and nitration, forming tetrasubstituted aromatics.

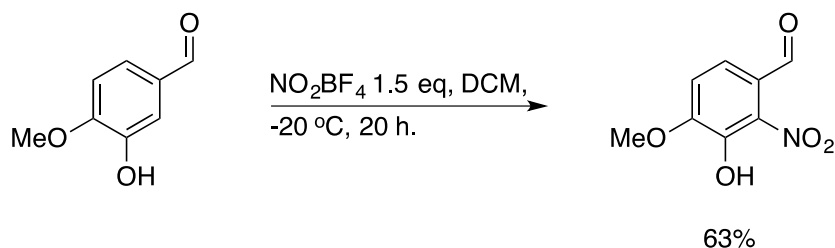
Synthesizing tetrasubstituted aromatics via nitration chemistry has been achieved before as outlined in Scheme 3.1. Equations 1 and 2 show two examples from patents on the use of nitric acid in sulphuric acid to perform nitration.^{1,2} Note that equation 1 has a much



Scheme 3.1. Tetrasubstituted aromatics formed via nitration.

faster reaction time due to the large excess of nitric acid. The use of potassium nitrate in sulphuric acid is a standard method for nitration, as used by Gaster *et al.* in the synthesis towards 5-HT_{1B} (5-hydroxytryptamine, serotonin) receptor agonists (Scheme 3.1 equation 3).³ This method produces the nitric acid *in situ* from the potassium nitrate. This is advantageous as nitric acid is sold in approximate concentration ($\approx 69\%$) and so allows for more accurate stoichiometry.

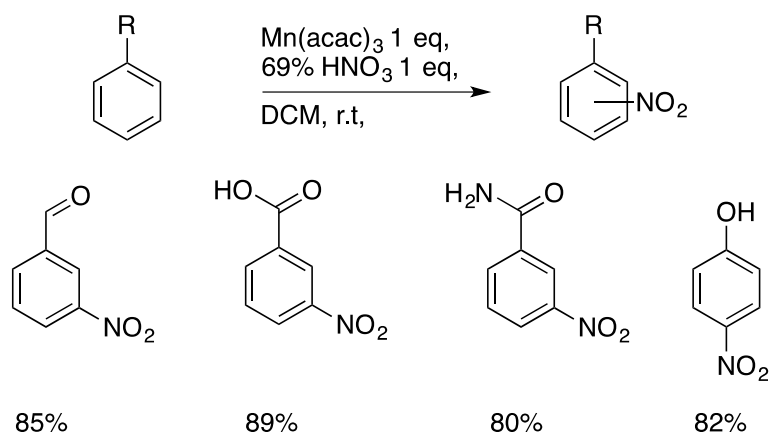
Nitronium tetrafluoroborate is also used to perform nitrations, having the advantage of being milder and that it can be added stoichiometrically. Raitio *et al* used nitronium tetrafluoroborate to synthesize 3-hydroxy-4-methoxy-2-nitrobenzaldehyde as an



Scheme 3.2. Nitronium tetrafluoroborate use in nitration.

intermediate towards a series of CB₂ cannabinoid receptor ligands (Scheme 3.2 and Scheme 1.9).⁴ They used NO₂BF₄ as it improved regioselectivity; using standard nitric acid in sulphuric acid only gave a 10 % yield of 3-hydroxy-4-methoxy-2-nitrobenzaldehyde.

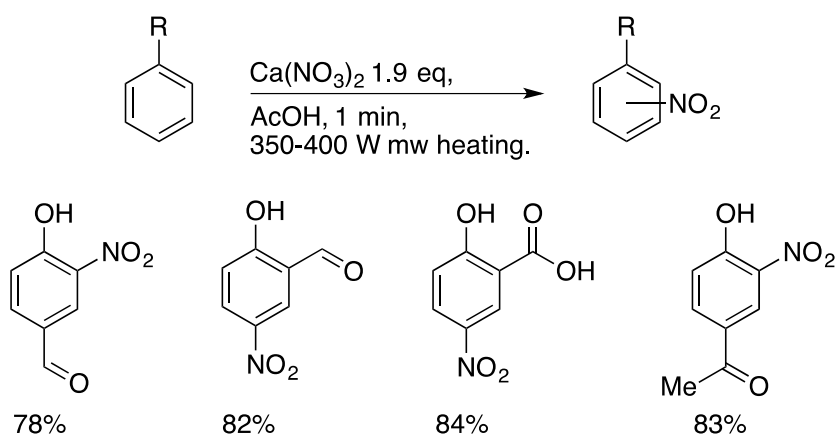
Werner-type transition-metal complexes have been used as catalysts for nitration by Abdulla *et al.*, which were performed in DCM using one equivalent of 69 % nitric acid.⁵



Scheme 3.3. Mn(acac)₃ nitrations.

In this work they showed that stoichiometric Mn(acac)₃ gave the best results for deactivated arenes, in particular using the conditions as shown in Scheme 3.3.

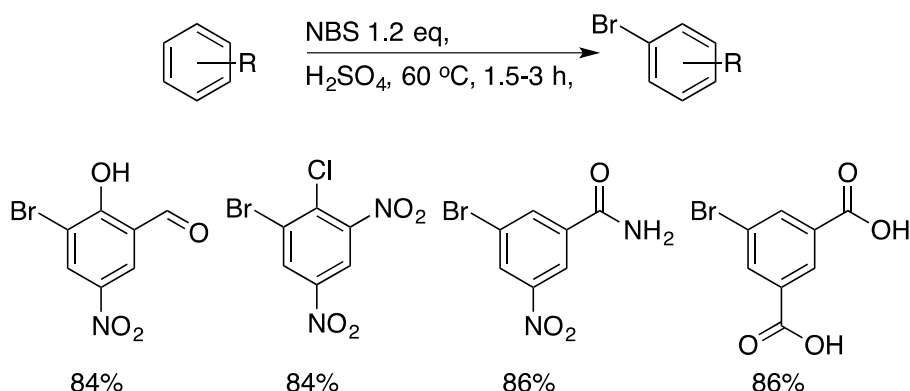
Nitration using microwave-assisted synthesis has been achieved using different metal nitrates. Bose *et al.* used calcium nitrate in glacial acetic acid with microwave heating to perform nitrations on different phenols (Scheme 3.4).⁶ In a similar microwave-mediated



Scheme 3.4. Calcium nitrate nitrations performed in a microwave.

method Ghalsasi *et al.* nitrated phenol using copper (II) nitrate in acetic acid.⁷ This work gave a mixture of *ortho*- and *para*-nitrophenol with low regioselectivity.

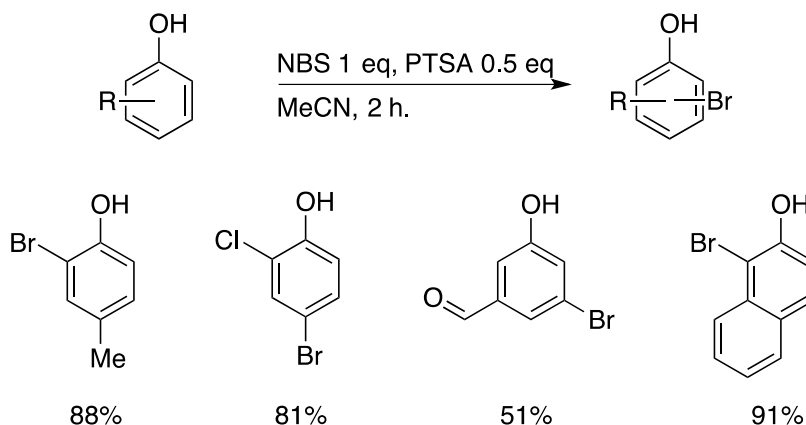
The use of NBS in electrophilic aromatic bromination reactions is standard practice due to its ease of handling and the formation of the moderately inert succinimide as by-product.⁸ Dolbier *et al.* published a procedure for the bromination of deactivated compounds using NBS in a mixture of trifluoroacetic acid (TFA) with the addition of a catalytic amount of sulphuric acid.⁹ Saiganesh *et al.* have used a protocol for bromination similar to that of Dolbier's method where sulphuric acid is used as a solvent, rather than an additive (Scheme 3.5).¹⁰



Scheme 3.5. Saiganesh *et al.*'s protocol for bromination.

Bovonsombat *et al.* showed that using NBS in MeCN with *p*-toluenesulfonic acid (PTSA) gave high selectivity in the bromination of phenols.¹¹ It should be noted that in this publication they reported similar results using sulphuric acid as the catalyst in place of PTSA. This work produced an array of diverse *ortho*- and *para*-substituted phenols in high yields, some of which are shown in Scheme 3.6.

In 2010 Wang *et al.* published two papers both outlining the use of gold (III) chloride as

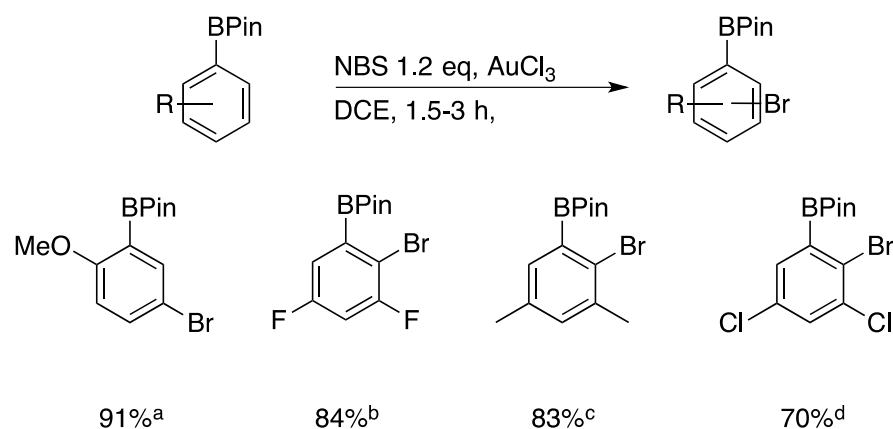


Scheme 3.6. Bromination of phenols with PTSA, NBS.

a Lewis acid catalyst in the bromination of aromatic compounds using NBS in 1,2-dichloroethane. Wang's first paper showed the bromination of substituted aromatic

compounds.⁸ The second publication described the bromination of substituted phenyl boronic acid pinacol esters (Scheme 3.7).¹²

Hall *et al.* also in 2010 demonstrated direct bromination and iodination of phenyl boronic

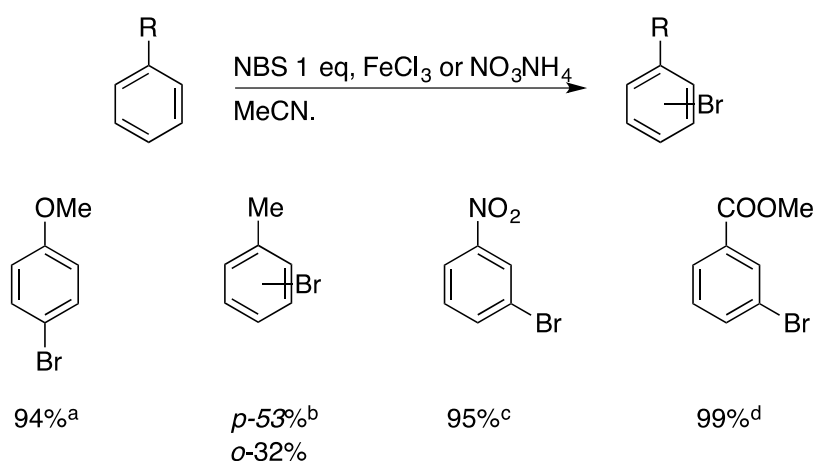


Scheme 3.7. Bromination with gold (III) chloride.

Reaction conditions: ^a 1 eq NBS, rt, 6 h. ^b 40 °C, 6 h. ^c 70 °C, 24 h. ^d 80 °C, 48 h.

acids using silver(I) sulphate and one equivalent of respective neat halogen in ethanol (Scheme 1.11).¹³ As with Wang's research, Hall has only produced results with activated systems and showed that the presence of deactivating groups on the aromatic ring lowered yields and inhibited the reactions.

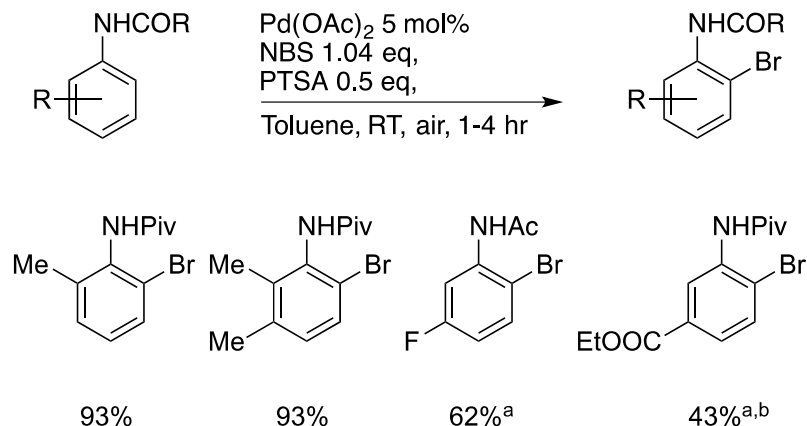
Tanemura *et al.* combined NBS with iron(III) chloride or ammonium nitrate, in either catalytic or stoichiometric quantities, to afford a wide range of brominated products.¹⁴ Their reactions were high yielding on both activated and deactivated aromatics. They found that iron(III) chloride gave better results comparatively when deactivated arenes were the target substrate (Scheme 3.8).



Scheme 3.8. Bromination with NO₃NH₄ or FeCl₃.

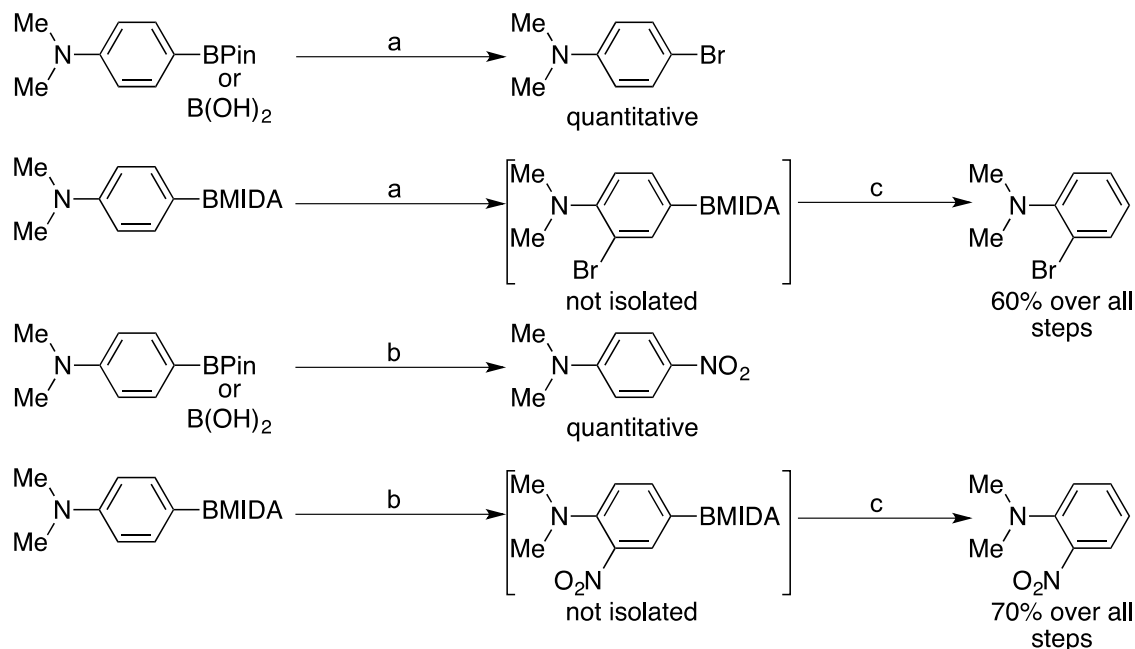
Reaction conditions: ^a NO₃NH₄ 10 mol%, rt, 10 min. ^b NO₃NH₄ 10 mol%, 60 °C, 8 h. ^c FeCl₃ 1 eq, 150 °C, no solvent, 2 h. ^d FeCl₃ 1 eq, 100 °C, 7 h.

Bedford *et al.* synthesised a variety of different *ortho*-bromophenylanilides *via ortho* directed palladium catalysed C-H halogenation (Scheme 3.9).¹⁵ This work employed ether acetate or pivaloyl anilide as a directing ligand to afford high selectivity in these bromination reactions.



Scheme 3.9. Bromination via palladium *ortho* C-H activation.
Reaction conditions: ^a 50 °C. ^b 24 h.

In 2014 Cheon *et al.* showed that under mild conditions MIDA boronates can be used as a para-blocking group affording selective *ortho* electrophilic substitution, whereas the corresponding boronic acid or pinacol ester, quantitatively yields the *ipso* substituted isomer (Scheme 3.10).¹⁶ This demonstrates a different way to achieve selectivity with an



Scheme 3.10. MIDA boronate used as a blocking group.

Reaction conditions: ^aNBS 1eq, DCM, rt, 10 min. ^bNBS 1eq, AgNO₃ 1 eq, EtCN, reflux, 3 h. ^ci) NaOH, THF, 10 min, ii) wet DMSO 100 °C, 24 h.

ortho para directing group. This work was published after the body of work in this chapter.

Using the variety of aromatic electrophilic substitution techniques outlined above tetrasubstituted aromatic compounds were synthesised. This work will have particular implications in the use of phenyl MIDA boronates in bromination and nitration reactions. This is both as a protecting group of the boronic acid moiety, and also as an orthogonal group upon bromination, which will enable iterative palladium cross coupling reactions.

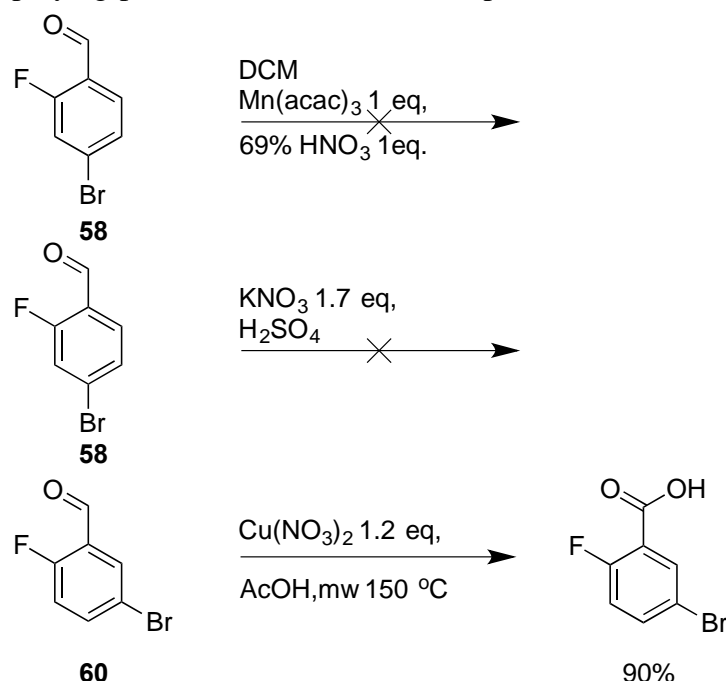
3.3 Results and Discussion: Nitration

3.3.1 Nitration of bromo-fluoro-benzaldehydes

The initial aim of this project was to study nitration of three different regioisomers of bromo-fluoro-benzaldehydes **58**, **60** and **62**, focusing on finding a successful method amenable to scale. Methods of nitration for compounds **58** and **60** were already known as shown in Scheme 3.1 equations 1 and 2, although we wanted to explore milder conditions that would be applicable to a wider variety of substrates. This made **58** and **60** ideal compounds for testing different methods as ¹H-NMR spectroscopic data are known from the literature. Several literature methods were trialled on **58**, as this was predicted to give one regioisomer due to the directing effects (0) of all the functionalities being complementary to the same site of substitution.

When compound **58** was subjected to the nitration procedure of Abdulla *et al.*, using Mn(acac)₃, poor results were observed (Scheme 3.11). Comparison of **58** to the benzaldehyde used in the original publication, showed **58** to be a more deactivated aryl due to the presence of the two electron-withdrawing halogen groups. This was speculated to be the cause of the poor result.

Nitration of **58** employing potassium nitrate was attempted under similar conditions to



Scheme 3.11. Attempted nitrations on compound **1a** and **2b**.

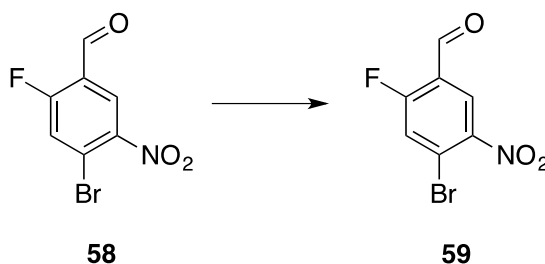
those of Gaster *et al.* (Scheme 3.11). A crude ^1H NMR spectroscopic analysis revealed that this reaction had not gone to completion, even after being left overnight. Using an excess of potassium nitrate still gave low yielding results, thus different conditions were explored.

Microwave synthesis using copper (II) nitrate in acetic acid was also trialled on 5-bromo-2-fluorobenzaldehyde (**60**) giving poor results.⁷ This method resulted in no nitration of **60** and formation of the corresponding benzoic acid derivative was observed resulting from the oxidation of benzaldehyde functionality (Scheme 3.11). The crude ^1H -NMR spectrum after an ethyl acetate work up matched with a known spectrum of 5-bromo-2-fluorobenzoic acid, also by ^{13}C -NMR spectrum and showed the disappearance of the aldehyde peak.¹⁷ Copper (II) salts are known to oxidize aldehydes - for example Benedict's reagent which is used to detect presence of reducing sugars.¹⁸ In the original protocol, the use of phenol gave much higher reactivity than compound **60**. Therefore, it was postulated that the nitronium ion generated in this system was not strong enough to nitrate such a deactivated aryl. In Bose *et al.*'s microwave nitration method using calcium (II) nitrate in acetic acid they nitrated *p*-hydroxybenzaldehyde in 78% yield without oxidation of the aldehyde.⁶ This aryl system is much more electron rich due to π donation from the hydroxyl group, thus this chemistry was not attempted due to the previous two methods not providing encouraging results.

Using nitronium tetrafluoroborate, in a similar method to that of Raitio *et al.*, **58** was successfully nitrated in high yield (**Table 3.1**, entry 1) giving one major product, 4-bromo-2-fluoro-5-nitrobenzaldehyde (**59**). We also found that adopting a protocol using nitric acid in sulphuric acid, akin to conditions used in Scheme 3.1 equation 1 and 2, gave high yielding results.

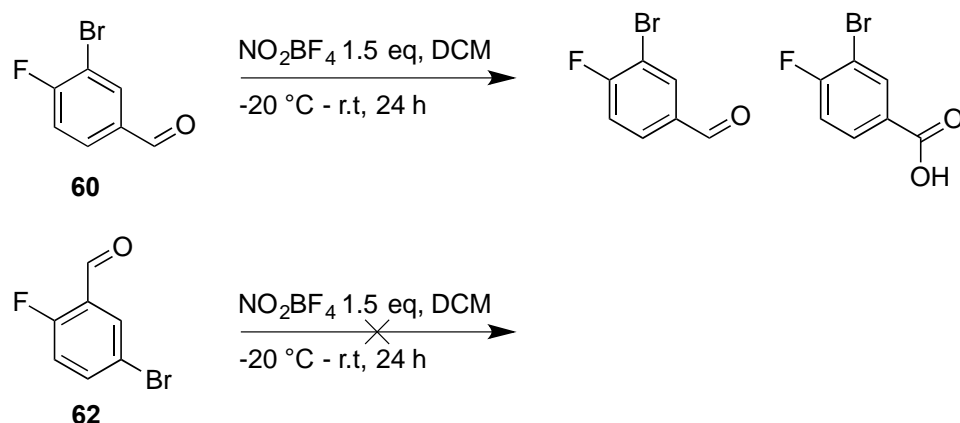
Table 3.1. Nitration of **1a**.

^a 12 mmol scale, ^b25 mmol scale, ^c 99 mmol scale.



Entry	Nitration Method	Product	Yield (%)
1	NO ₂ BF ₄ -20 °C – r.t, 16 h	 59	88 ^a
2	H ₂ SO ₄ /HNO ₃ 0 °C – r.t, 16 h	 59	84 ^b 94 ^c

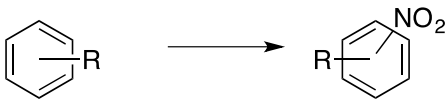
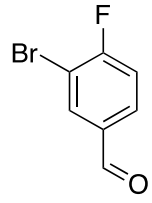
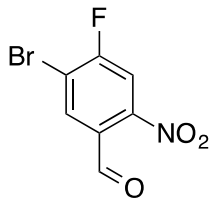
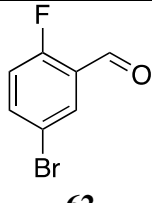
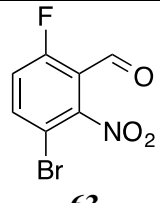
Comparing the nitronium tetrafluoroborate nitration protocol used on **58** (**Table 3.1** entry 1) with the nitration of 3-bromo-4-fluoro-benzaldehyde (**59**) under similar conditions, no reaction was observed after four days via TLC analysis. A crude ¹H-NMR spectrum after work up showed a mixture of starting material and oxidized starting material to give the corresponding 3-bromo-4-fluoro-benzoic acid (Scheme 3.12). 5-Bromo-2-fluorobenzaldehyde (**62**, Scheme 3.12) indicated no reaction under these conditions after four days via TLC, and this was confirmed by crude ¹H-NMR spectrum analysis.



Scheme 3.12. Attempted NO_2BF_4 nitration on **2a** and **3a**.

5-Bromo-4-fluoro-2-nitrobenzaldehyde (**61**) and 3-bromo-6-fluoro-2-nitrobenzaldehyde (**63**) were successfully prepared employing the same nitric acid, nitration conditions used in the synthesis of compound **59** (Table 3.2, entry 1 and 2).

Table 3.2. Bromofluoronitrobenzaldehydes formed by nitration

				
Entry	Starting material	Nitration Method	Product	Yield (%)
1	 60	$\text{H}_2\text{SO}_4/\text{HNO}_3$ $0\text{ }^\circ\text{C} - \text{RT}, 16\text{ h}$	 61	61 ^a 74 ^b
2	 62	$\text{H}_2\text{SO}_4/\text{HNO}_3$ $0\text{ }^\circ\text{C} - \text{RT}, 16\text{ h}$	 63	30 ^a 27 ^b

^a30 mm scale, ^b 99 mmol scale

Recrystallization was found to be the most efficient purification method of crude material in this series of bromofluoronitrobenzaldehydes in **Table 3.1** and Table 3.2. Side products usually consisted of small amounts of regioisomers, and were found to be inseparable via column chromatography. Recrystallization was achieved by dissolving the bromofluoronitrobenzaldehyde in the minimum amount hot of diethyl ether, with hexane.

This purification method is more applicable on a large scale than flash column chromatography (used in one the original patents) as it requires less solvent making it a greener process. Compound **61** showed slow oxidation of the aldehyde, potentially due to some residual acid in the sample catalysing the reaction. This led to adaption of the work up incorporating monitoring of the pH of the brine washings until they were no longer acidic. This method was implemented rather than washing with aqueous base, as Cannizzaro reactions are possible with the aldehyde group present.

The synthesis of compound **63** was found to be low yielding and analysis of the crude ^1H -NMR spectrum showed one major compound (**63**) was present; a large number of overlapping smaller peaks were observed, which could not be assigned. Analysis of the crude reaction mixture by LCMS indicated that no residual starting material remained

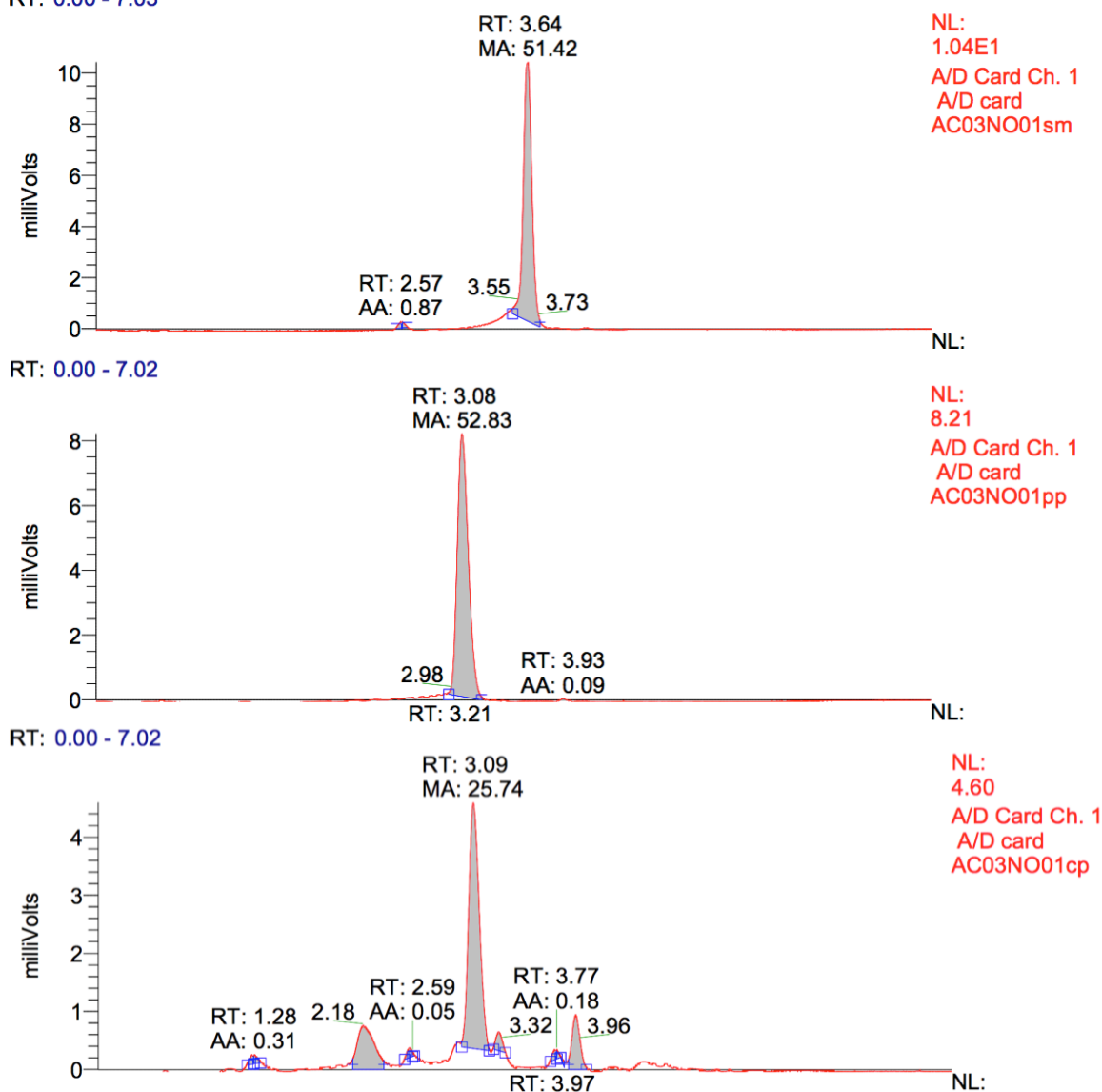


Figure 3.1. Chromatograms of reaction to synthesise **63**: top chromatogram of **62**, middle chromatogram of pure **63**, bottom crude reaction mixture.

and **63** was the major component (Figure 3.1). It was concluded that directing groups present in compound **62** were not conducive with one particular site of substitution. This led to the lower yield due to a wide variety of side products being formed.

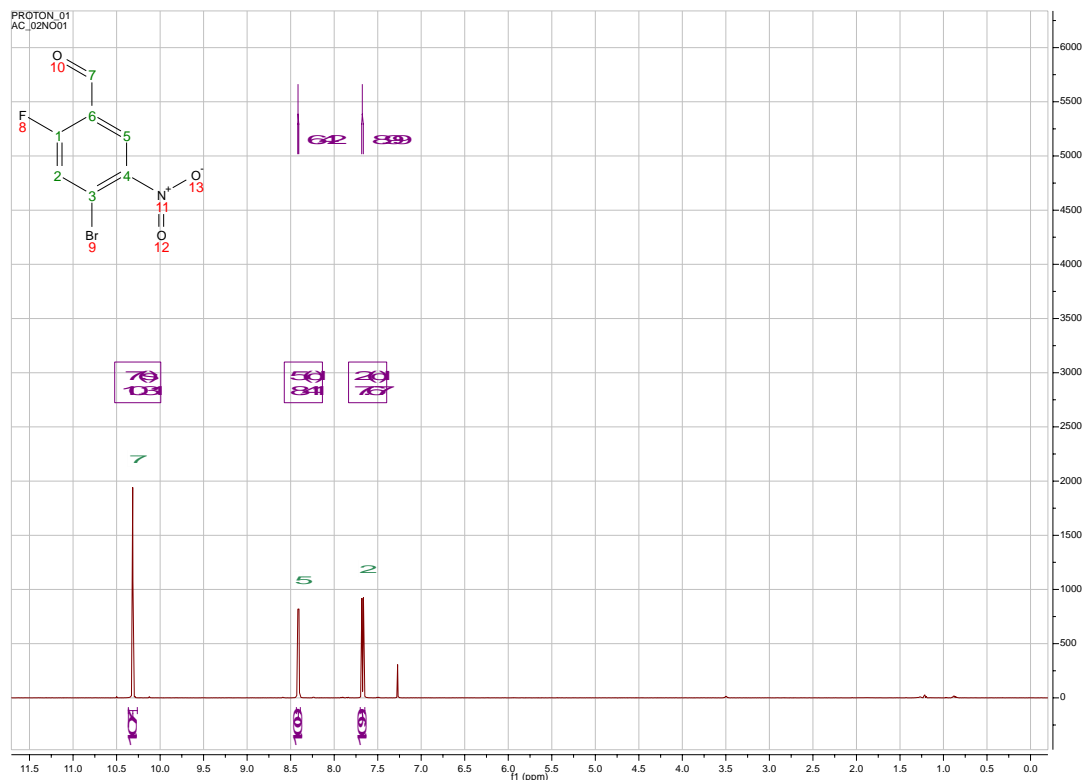


Figure 3.2. ^1H NMR spectra of compound **59**.

Assignment of a compound's regiochemistry was initially performed using NMR spectroscopy techniques. An example of this is shown for compound **59**, Figure 3.2. This ^1H NMR spectrum shows 3 different proton environments and these were assigned using the distinct J_{HF} coupling constants. The 9 Hz suggests a $^3J_{\text{HF}}$ coupling constant whereas the 6.5 Hz suggests a $^4J_{\text{HF}}$ coupling constant, thus these were assigned to positions 2 and 5 respectively.¹⁹ The third proton environment, 10.31 ppm (position 7), is therefore assigned to the aldehyde proton. This peak is 0.1 ppm downfield of the typical range of 9.9 - 10.2 ppm,²⁰ which is possibly due to the fluorine atom in position 8 of compound **59**. 2-Fluorobenzaldehyde also exhibits this downfield movement of its benzaldehyde proton, which is observed at 10.32 ppm.²¹

The ^{13}C NMR spectra (Figure 3.3) is assigned for compound **59**, this was done with the

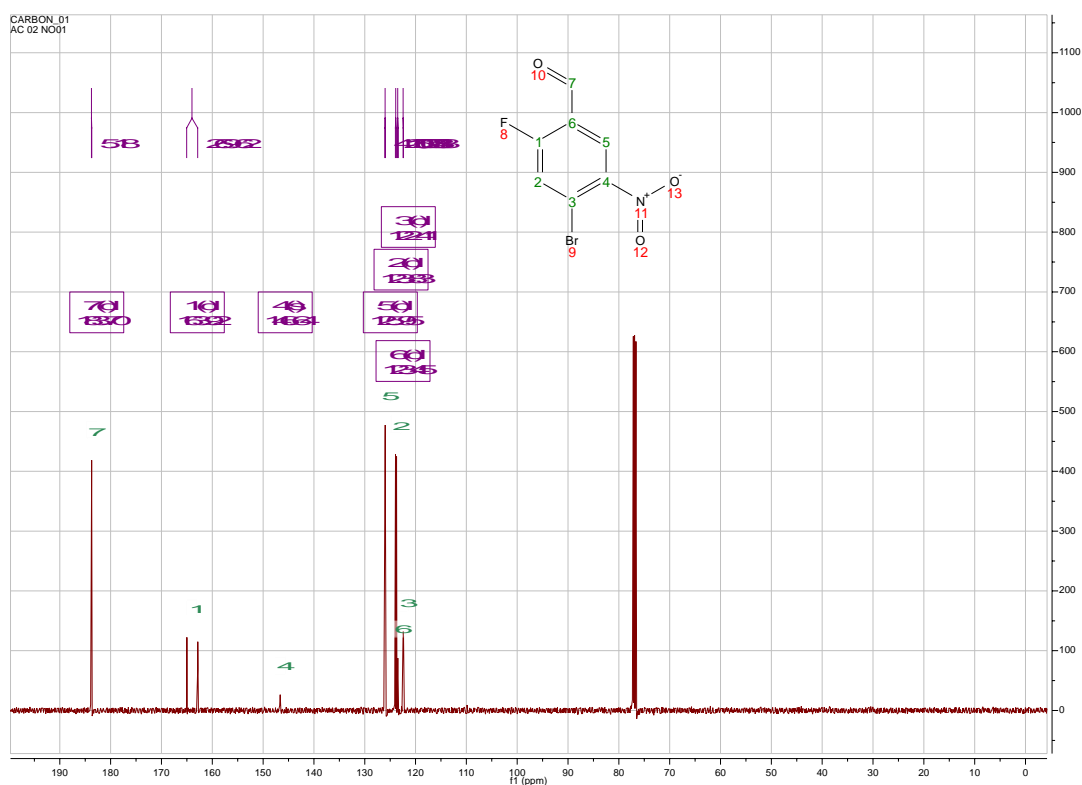


Figure 3.3. ^{13}C NMR spectra of compound **59**.

aid of 2D NMR spectroscopy. The peak at 163.9 ppm has a distinct $^1J_{\text{CF}}$ coupling constant of 269.5 Hz due to the fluorine atom at position 8, this allowed an assignment to carbon 1.

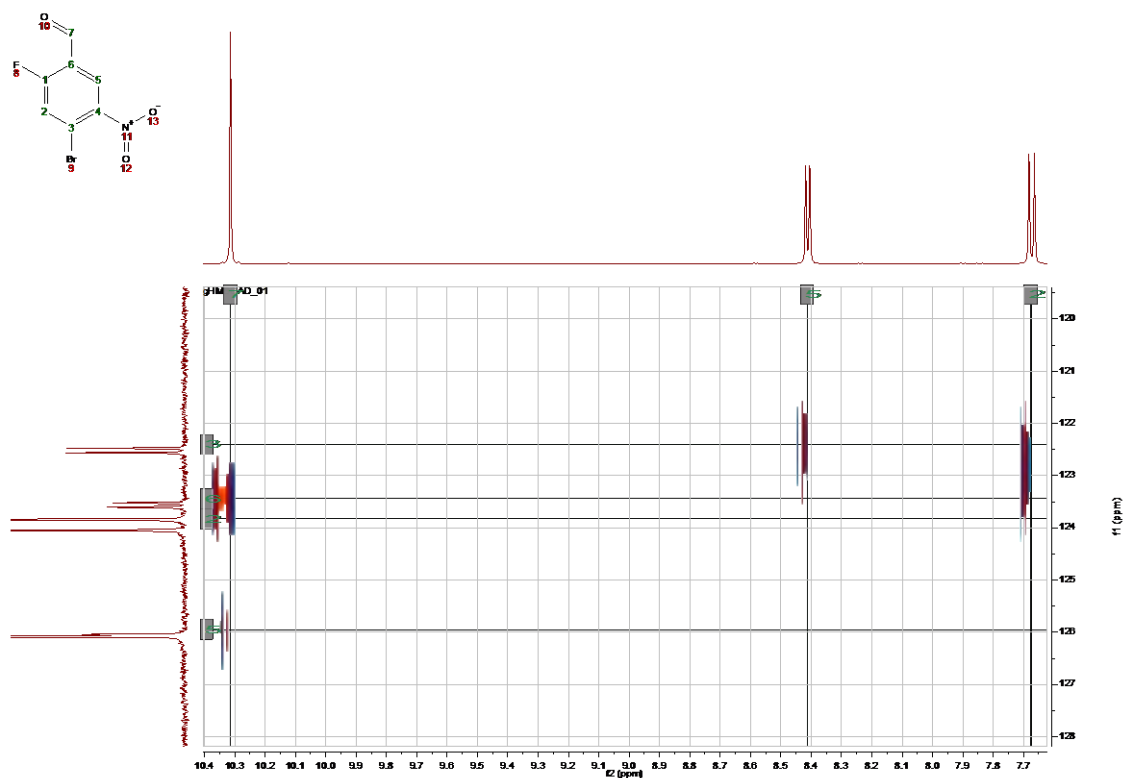


Figure 3.4. HMBC NMR spectra of compound **59**.

HMQC spectrum shows correlations between connected protons and carbons (Figure

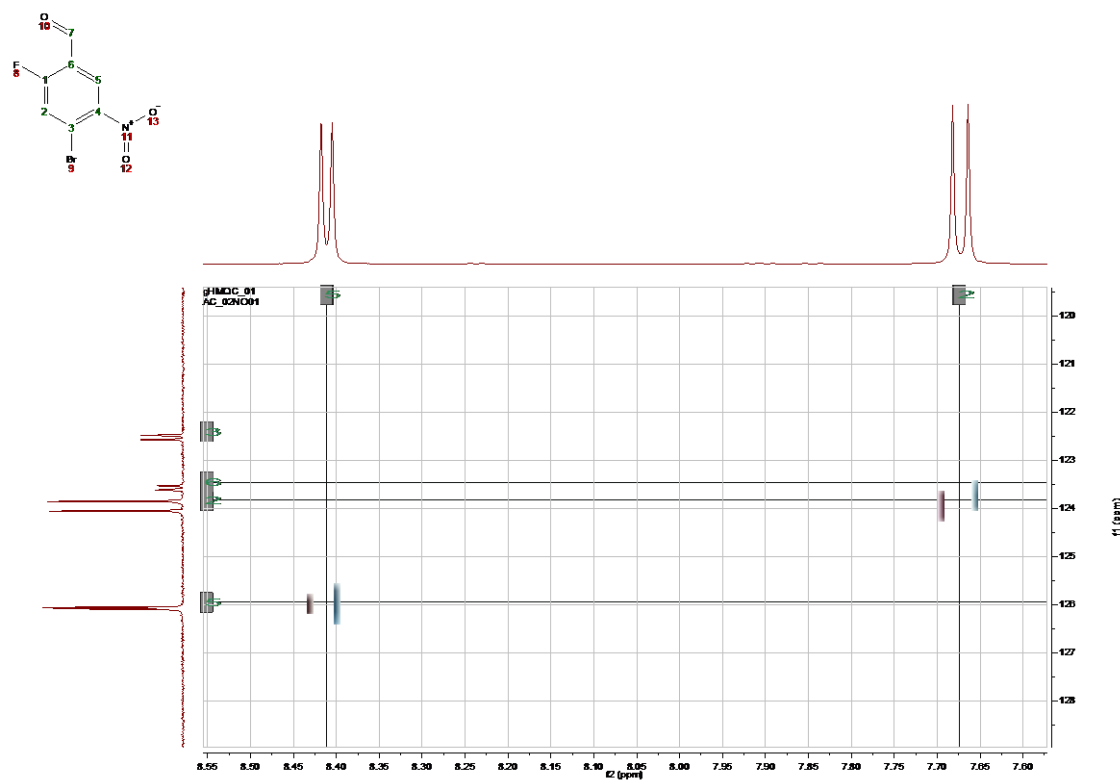


Figure 3.5. HMQC NMR spectra of compound **59**.

3.5). This technique allowed simple assignment of the peaks at positions 2 (123.8 ppm),

5 (126.0 ppm) and 7 (183.7 ppm) due to previous assignment of the ^1H NMR spectrum. A carbon *para* to a fluorine atom in an aromatic ring typically has a coupling constant of 3.3 Hz or lower. The peak at 146.9 ppm showed no carbon fluorine coupling thus it was assigned to position 4, as this is the carbon *para* to the fluorine in compound **59** (Figure 3.3).

HMBC NMR spectroscopy is a 2D NMR technique showing the correlation between protons and carbons 2 to 4 bonds away. An HMBC NMR spectrum is shown in Figure 3.4 for compound **59**, this assisted in the assignment of the two remaining carbon peaks at 122.4 ppm and 123.5 ppm. The ^1H peak at 10.31 ppm, previously assigned to the aldehyde at position 7, correlates with the ^{13}C peak at 123.5 ppm and is therefore assigned to the carbon at position 6, *ipso* to the aldehyde. This left the remaining carbon peak at 122.4 ppm to be assigned to position 3 on the aromatic ring.

This NMR assignment was performed on all compounds to identify the regiochemistry of the major isolated products. The structures were later confirmed for compounds **59**, **61** and **63** by single crystal x-ray diffraction, shown in Figure 3.6. The crystals were crystallised from diethyl ether in hexane and show the expected regiochemistry for the products.

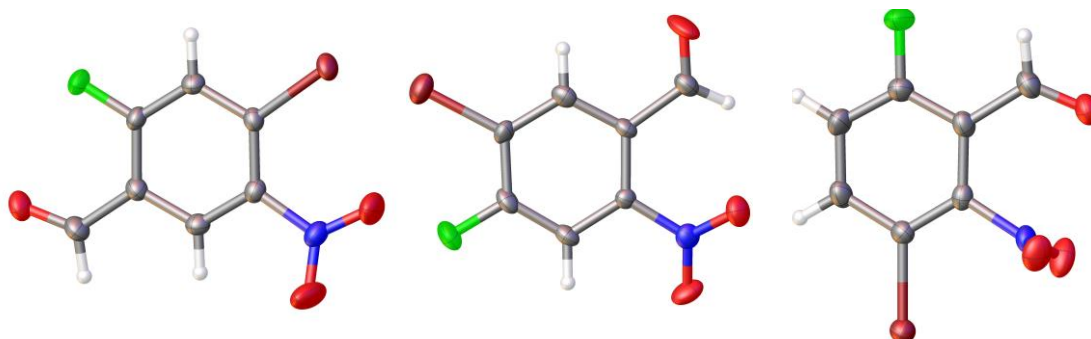


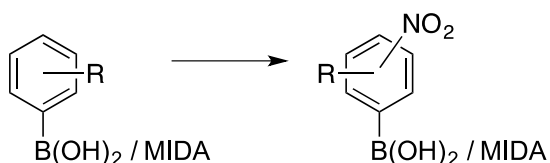
Figure 3.6. ORTEP diagrams showing crystal structures of **59** (left), **61** (middle) and **63** (right). **1b** is shown in Table 3.1, **2b** and **3b** are shown in **Table 3.2** entry 1 and 2 respectively. Red = oxygen
blue = nitrogen, brown = bromine, green = fluorine, grey = carbon and white = hydrogen

3.3.2 Arylboronic Acids

This body of work involved an investigation of the nitration of several trisubstituted phenyl boronic acids and their corresponding MIDA boronates and pinacol ester derivatives. The preparation of pinacol boronic acid esters are simple and high yielding reactions, which have been well documented in the literature on different boronic acids and therefore posed no problems.^{22,23} The MIDA boronates used in the work were synthesized using the methods described within chapter 2 of this thesis.

Compounds containing aryl boronic acids, MIDAs or pinacol groups were found to be incompatible with nitrations involving nitronium tetrafluoroborate. The use of strong acids on phenyl boronic acid pinacol ester caused cleavage of the pinacol group and an inseparable mixture of products were formed. Due to these early negative results the nitronium tetrafluoroborate and the pinacol-protected reagents were withdrawn from this study.

3-Fluoro-4-formylphenyl boronic acid (**64**) and its corresponding MIDA boronate (**30**) were very acid stable and both gave products in high yields (Table 3.3 entries 1 and 2) using the nitric acid method described above. It is also noteworthy that the MIDA group also worked as a handle to aid solubility, as the MIDA dissolved with far greater ease than its parent boronic acid. Compound **65** required no purification after a diethyl ether extraction; basic washes were avoided as this could extract the boronic acid into the aqueous layer. The stability of MIDA boronates under these conditions was expected, as MIDA boronates have been shown to withstand conditions for Jones oxidation, as using sulphuric acid (0).²⁴ Phenyl boronic acids have also shown high stability under very similar nitration conditions in the synthesis of trisubstituted aromatic compounds.²⁵

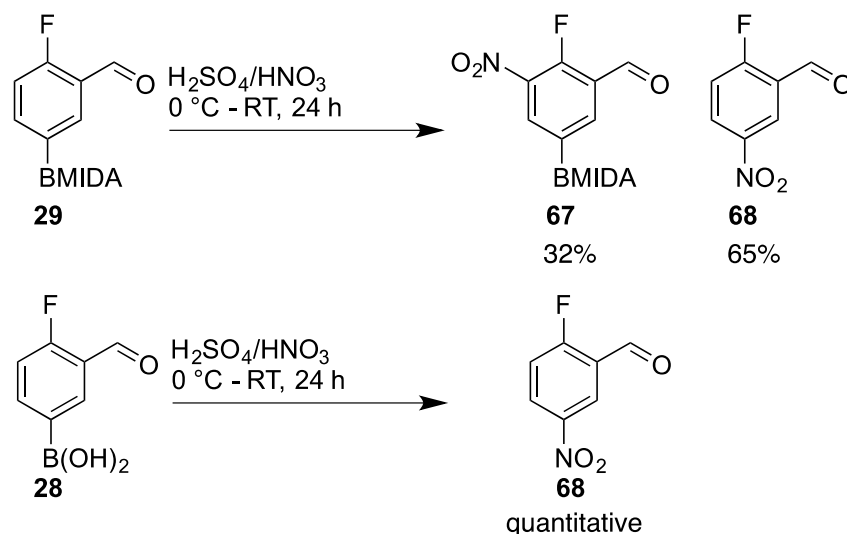
Table 3.3. Boron containing compounds formed by nitration.

Entry	Starting material	Nitration Method	Product	Yield (%)
1	<p style="text-align: center;">64</p>	$\text{H}_2\text{SO}_4/\text{HNO}_3$ $0\text{ }^\circ\text{C} - \text{RT}, 16\text{ h}$	<p style="text-align: center;">65</p>	88 ^a
2	<p style="text-align: center;">30</p>	$\text{H}_2\text{SO}_4/\text{HNO}_3$ $0\text{ }^\circ\text{C} - \text{RT}, 16\text{ h}$	<p style="text-align: center;">66</p>	85 ^b
3	<p style="text-align: center;">29</p>	$\text{H}_2\text{SO}_4/\text{HNO}_3$ $0\text{ }^\circ\text{C} - \text{RT}, 16\text{ h}$	<p style="text-align: center;">67</p>	32 ^b

^a12 mmol scale, ^b1 mmol scale, yield calculated by ¹H NMR

Conversely the **30** regioisomer, 4-fluoro-3-formylphenyl MIDA boronate (**29**), nitrated in the 5-position (Table 3.3 entry 3) to form compound **67**. This reaction was low yielding due to the major product being the *ipso* nitration of the MIDA boronate forming 2-fluoro-5-nitrobenzaldehyde (**68**) (Scheme 3.13). When the reaction conditions were attempted on the corresponding free boronic acid **28** no nitration in the 5-position was observed, forming the *ipso* nitrated **68** exclusively, observed via ¹H-NMR spectra analysis of the

crude mixture (Scheme 3.13). *Ips*o nitration of boronic acids under these conditions has previously been observed by Soloway.²⁵



Scheme 3.13 Nitrations with phenylboronic acid / MIDA boronates containing compounds.

This publication showed that if directing effects are all complementary making the site of substitution *ip*so to the boronic acid, then nitration of this position would be observed over an unsubstituted position on the aromatic ring. More recently, boronic acids have been used for an array of inter functional group conversions, including the formation of hydroxyl,^{26,27} nitro,^{28,29} amine,³⁰ and fluoro groups.³¹

Cheon *et al.* have used MIDA boronate as a blocking group, and this might explain why less *ip*so nitration was observed for the MIDA boronate **29**, over **28** (Scheme 3.10, section 3.1). This is shown by the quantitative yield of **68** observed when the corresponding boronic acid was used (Scheme 3.13). The yield of **67** is lower than the similar reactions described in Cheon's publication. This is possibly due to either the reaction conditions being harsher than in Cheon's work. Alternatively the directing effects of the functionalities of compound **29** are not leading to high *ortho* selectivity with respect to the fluorine group. The fluorine gives higher *para* selectivity over *ortho*,²⁹ compared to the aniline used in their work.^{32,33}

2-Fluoro-4-(trifluoromethyl)phenyl (**56**) was nitrated under the same conditions forming 2-fluoro-5-nitro-4-(trifluoromethyl)phenyl MIDA boronate (**69**) in a very high yield (Table 3.3 entry 4).

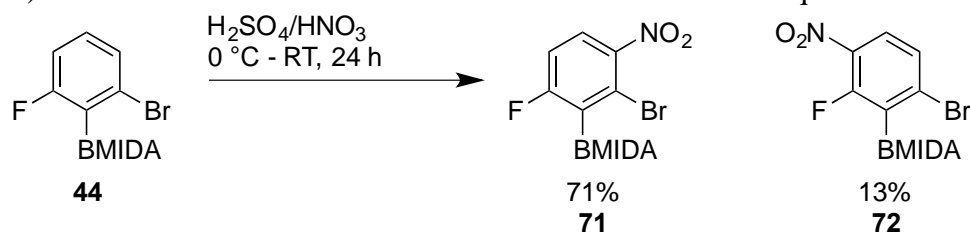
Compounds **66** and **69** only required simple purification involving precipitation of a solid from ice. In some cases diethyl ether washes were used to remove any non-MIDA boronate organic impurities from the filtrate.

Table 3.4. Boron containing compounds formed by nitration.

Entry	Starting material	Nitration Method	Product	Yield (%)
1	 56	$\text{H}_2\text{SO}_4/1.02 \text{ eq}$ HNO_3 $0^\circ\text{C} - \text{r.t.}, 24 \text{ h}$	 69	92 ^a
2	 57	$\text{H}_2\text{SO}_4/1.02 \text{ eq}$ HNO_3 $0^\circ\text{C} - \text{r.t.}, 24 \text{ h}$	 70	39 ^b
3	 44	$\text{H}_2\text{SO}_4/1.02 \text{ eq}$ HNO_3 $0^\circ\text{C} - \text{r.t.}, 24 \text{ h}$	 71	71 ^c

^a1 mmol scale, ^b2 mmol scale, ^c1 mmol scale, yield calculated by ¹H NMR spectra.

2-Fluoro-4-methylphenyl MIDA boronate (**57**) was nitrated using the standard nitric acid nitration method to give 2-fluoro-4-methyl-5-nitrophenyl MIDA boronate (**70**), Table 3.4 entry 2). The amount of nitric acid used was decreased to 1.02 equivalents due to the



Scheme 3.14. Nitration of compound **44**, yield calculated by ¹H NMR spectra, this also included 4 % **44**.

increased reactivity of this compound due to the presence of the activating methyl group.

The nitration of 2-bromo-6-fluorophenyl MIDA boronate (**44**) gave one main product, 2-bromo-6-fluoro-3-nitrophenyl MIDA boronate (**71**, Scheme 3.14, Table 3.4 entry 3). Purification of this compound to remove the regioisomer, 2-bromo-6-fluoro-5-nitrophenyl MIDA (**72**) boronate was unsuccessful. Recrystallization from a variety of solvent systems, or chromatographic purification using either normal or reverse phase, only achieved the separation of starting material from the crude material. Structural similarities between the regioisomers were proposed as the likely cause of the purification

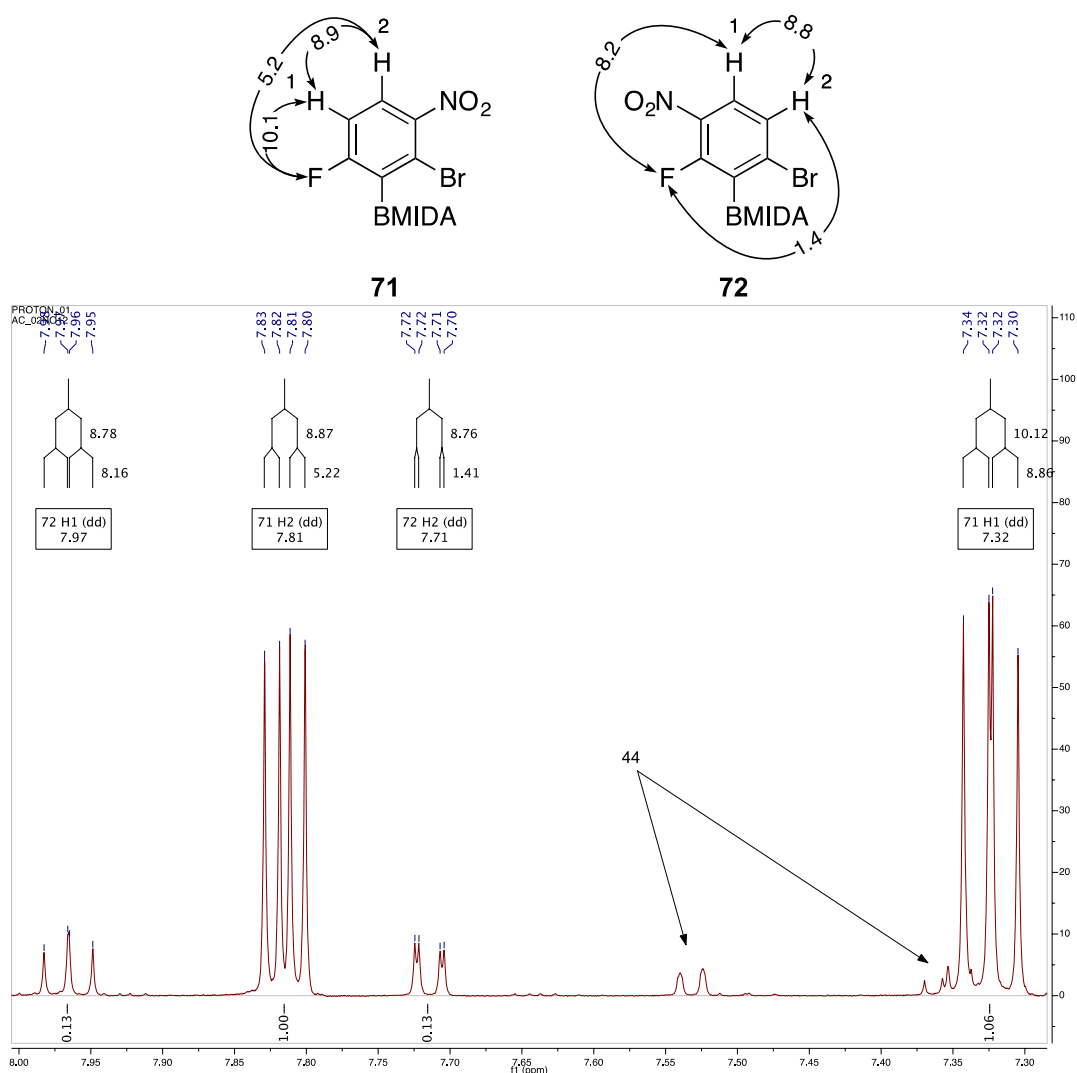


Figure 3.7 Coupling constants in $^1\text{H-NMR}$ shown in Hz, showing remaining compound **44**.

issues.

Identification of the two different regioisomers via crude $^1\text{H-NMR}$ spectra was achieved by measuring J_{HF} coupling constants. Figure 3.7 highlights the different couplings and how they were used in assignment. Regioisomer **71** exhibits a large $^3J_{\text{FH}}$ coupling of 10.1 Hz not observed in **72**.

3.4 Bromination

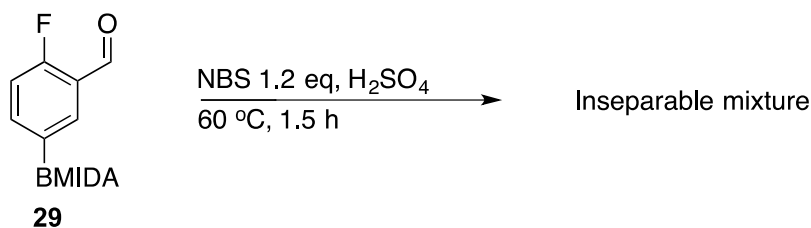
Cheon *et al.* achieved the direct bromination of aryl MIDA boronates, however the products have never been isolated as shown above in Scheme 3.10, as the MIDA boronate was used as a removable blocking group.¹⁶ Kamei *et al* attempted the bromination of 3-methoxyphenyl MIDA boronate using NBS in DMF, but this was reportedly unsuccessful due to decomposition and the formation of a complex mixture of products.³⁴

As with the nitration of phenyl MIDA boronates, the bromination of compound **5a** was the first synthetic foray of this subproject. Wang *et al.*'s methodology was considered impractical for scale up, due to the use of gold(III) catalyst, making it expensive even with the low catalyst loading (Scheme 3.7).¹² Furthermore, it was considered incompatible with the highly deactivated systems that were used in this project, as Wang worked with more activated compounds *i.e.* anisole, toluene, and ortho/meta/para xylenes. Hall *et al.* use of silver(I) sulphate to brominate phenyl boronic acids, would require MIDA protection after the bromination to allow orthogonality, in palladium cross-couplings. Hall's work also has only produced results with activated systems; he showed that the presence of a trifluoromethyl group on an aryl boronic acid inhibits bromination, making these methods unsuitable in this body of work.

Deactivated arenes have been brominated using NBS by Dolbier *et al* using TFA with catalytic sulphuric acid and by Saiganesh *et al.* using sulphuric acid as a solvent.^{9,10} The use of TFA as a solvent would be considerably more expensive than sulphuric acid alone. More importantly, TFA is toxic via inhalation and harmful to aquatic life, making it undesirable.^{35,36} This, combined with the positive results from the earlier nitration studies, meant that the use of sulphuric acid was the preferred method of study.

Using NBS, method the bromination of **30** was achieved, giving 2-bromo-5-fluoro-4-formylphenyl MIDA boronate (**73**) in acceptable yield (Table 3.5, entry 1).

The bromination of compound **29** gave a mixture, including starting material and the product of *ipso* bromination Scheme 3.15. Unfortunately no ratio of products could be deduced as the mixture could not be purified to give any single isolated product.



Scheme 3.15. Bromination of compound **3a**.

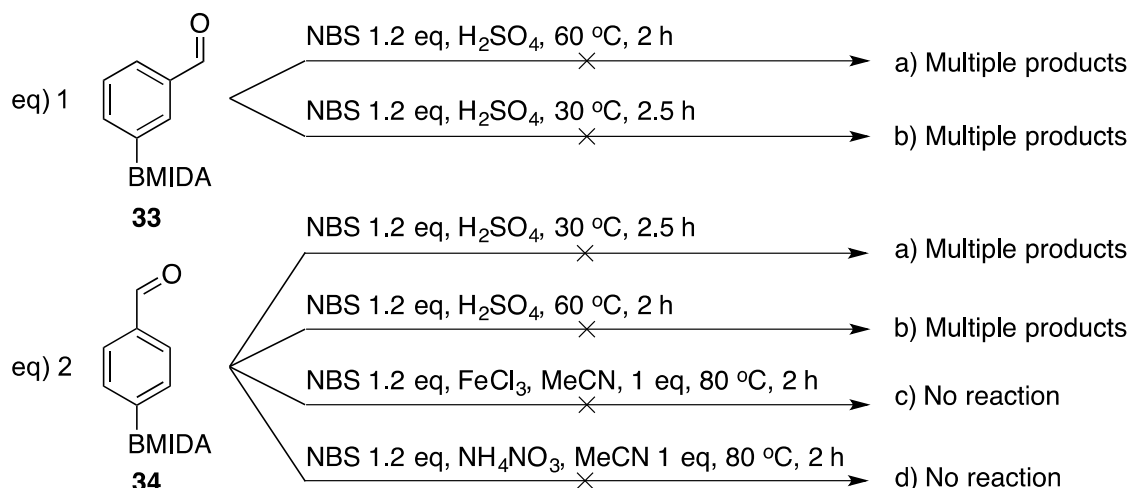
Table 3.5. Bromination of phenyl MIDA boronates.

Entry	Starting material	Bromination Method	Product	Yield (%)
1	<p style="text-align: center;">30</p>	NBS 1.2 eq, H ₂ SO ₄ 60 °C, 2 h	<p style="text-align: center;">73</p>	54
2	<p style="text-align: center;">56</p>	NBS 1.2 eq, H ₂ SO ₄ 30 °C, 2 h	<p style="text-align: center;">74</p>	99

The bromination of **56** initially gave poor yields of the product, 5-bromo-2-fluoro-4-(trifluoromethyl)phenyl MIDA boronate (**74**). Saiganesh found that some substrates could form by-products at higher temperatures. For this reason the reaction temperature was adjusted to 30 °C. Despite the fact this reaction required a longer reaction time, after four hours total conversion was observed by TLC analysis giving an excellent yield of the isolated product **774** (Table 3.5, entry 2).

Due to the availability of an array of MIDA boronates synthesised in Chapter 2, a study of selectivity and stability of substituted phenyl MIDA boronates was carried out. The first substrates for bromination were the 3-formylphenyl MIDA boronate (**33**) and 4-

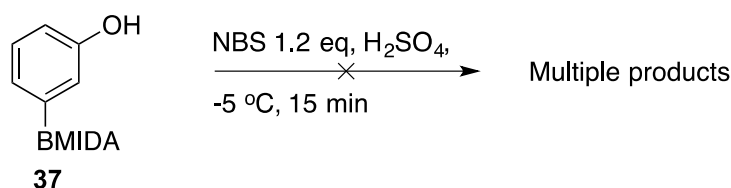
formylphenyl MIDA boronate (**34**), as these compounds were expected to be compatible with this methodology. Compound **33** was used to test the stability of the MIDA boronate as it would expect to undergo *meta*-bromination with respect to the formyl moiety. This would lead to either *ipso*-bromination of the MIDA boronate or formation of the 1,3,5-trisubstituted aromatic compounds. These reactions (Scheme 3.16, eq 1a and 1b) yielded only a small amount of crude material which was a complex mixture of compounds, at both 30 °C and 60 °C.



Scheme 3.16. Attempted bromination conditions used on **33** and **34**.

Compound **34** would be expected to brominate to form a 1,2,4-trisubstituted aromatic MIDA boronate derivative. However, reaction under the sulphuric acid /NBS conditions at both 30 °C and 60 °C led to a mixture of inseparable compounds (Scheme 3.16, eq 2a and 2b). Tanemura *et al.* used iron(III) chloride and ammonium nitrate in a wide range of NBS-mediated brominations.¹⁴ Unfortunately, attempting using these conditions on **34** led to no reaction (Scheme 3.16, eq 2c and 2d). Due to the lack of selectivity observed under conditions that did cause bromination and purification been non-trivial, the formylphenyl MIDA boronates were withdrawn from further work.

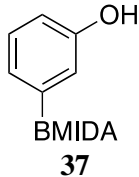
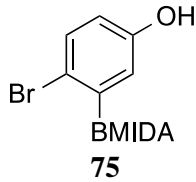
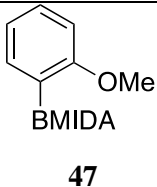
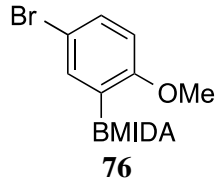
3-Hydroxyphenyl MIDA boronate (**37**) was the next target of this investigation and the first bromination trialled was the sulphuric acid /NBS methodology. Taking into account the increased reactivity of this substrate, the reaction temperature and duration were



Scheme 3.17. Attempted bromination on 3-hydroxyphenyl MIDA boronate.

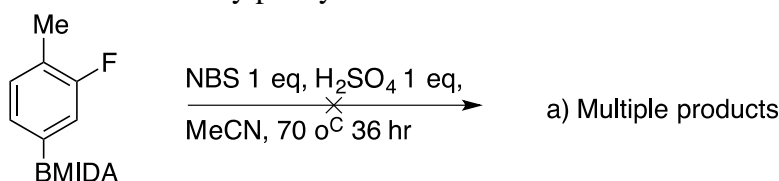
decreased as shown in Scheme 3.17. This reaction also gave multiple products even after only 15 minutes. Bovonsombat *et al.* showed that using NBS in MeCN with *p*-toluenesulfonic acid (PTSA) provided high selectivity towards *para* bromination of phenols (Scheme 3.6).¹¹ Using this method with sulphuric acid, **37** was successfully brominated *para* to the hydroxyl group giving a high yield of **75** (Table 3.6, entry 1). Sulphuric acid was used over PTSA as this made the work-up easier by a simple separation. Employing Bovonsombat's protocol also produced 5-bromo-2-methoxyphenyl MIDA boronate (**76**) (Table 3.6, entry 2).

Table 3.6. Bromination of phenyl MIDA boronates.

Entry	Starting material	Bromination Method	Product	Yield (%)
1	 37	NBS 1 eq, H ₂ SO ₄ 0.5 eq, MeCN, rt, 12 hr	 75	76
2	 47	NBS 1 eq, H ₂ SO ₄ 0.5 eq MeCN, rt, 12 hr	 76	87

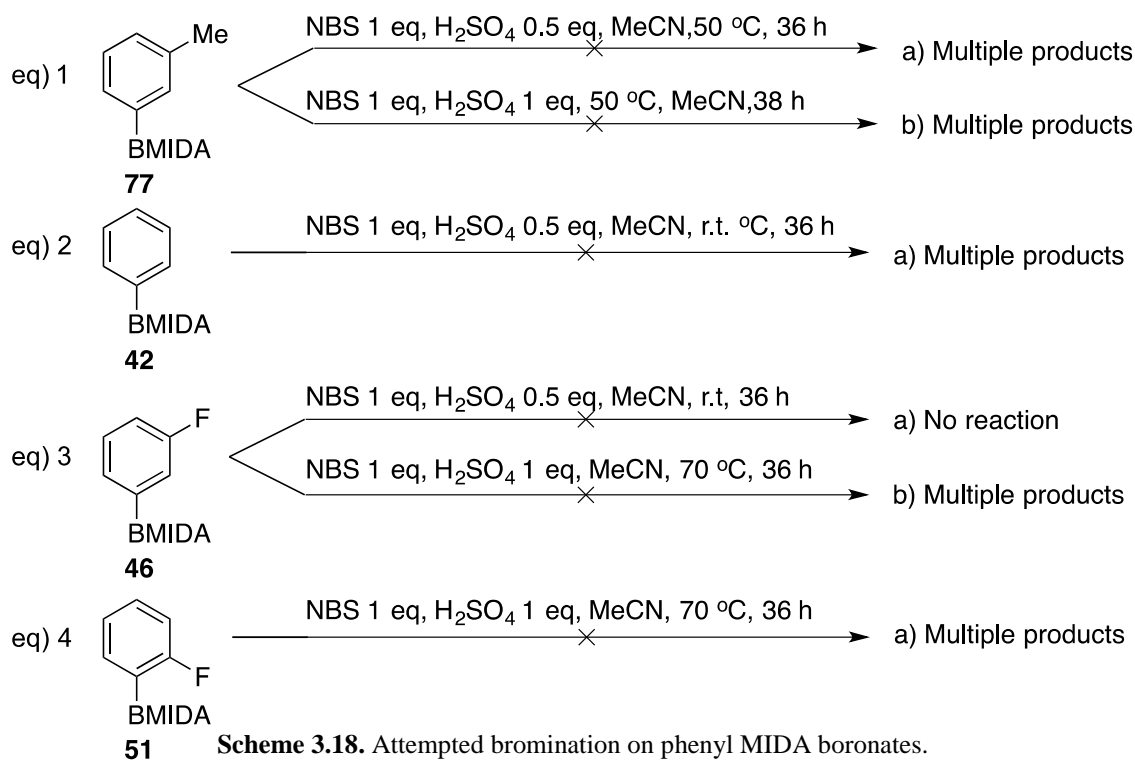
Using a similar procedure to that used on the phenols above test reactions were attempted on *m*-tolyl MIDA boronate (**77**), phenyl MIDA boronate (**42**), 3-fluorophenyl MIDA boronate (**46**) and 2-fluorophenyl MIDA boronate (**61**) (Scheme 3.18, eq) 1, 2, 3 and 4). All of these reactions showed poor results, under a variety of different conditions including increasing the amount of acid and / or altering the temperature. This shows that high selectivity is key in order to obtain brominated products; otherwise purification of the resultant mixtures is nontrivial and does not yield the desired pure product at all.

Bromination of 3-fluoro-4-methylphenyl MIDA boronate and 2-fluoro-4-methylphenyl



Scheme 3.19. Attempted bromination of fluoro-4-methylphenyl MIDA boronate

MIDA boronate (**57**) became the next synthetic challenge. Initial attempts using 3-fluoro-4-methylphenyl MIDA boronate led to multiple products, suggesting that its functionality did not have complementary directing effects (Scheme 3.19). However, the regioisomer **57** gave the desired compound 5-bromo-2-fluoro-4-methylphenyl MIDA boronate (**77**), as the major product. The reaction conditions required a small amount of modification



Scheme 3.18. Attempted bromination on phenyl MIDA boronates.

from those used on the phenolic compounds, to tune them to the reduced reactivity of this compound (Table 3.7, entry 1). The reaction temperature was increased from room

temperature to 70 °C, and the amount of sulfuric acid used was increased to one equivalent. In an earlier experiment it was noted that there was a small amount of side product formed as a result of the bromination of the benzyl methyl moiety. Excluding light from the reaction mixture prevented this, as these types of radical reactions have shown to be initiated by household fluorescent lamps.³⁷

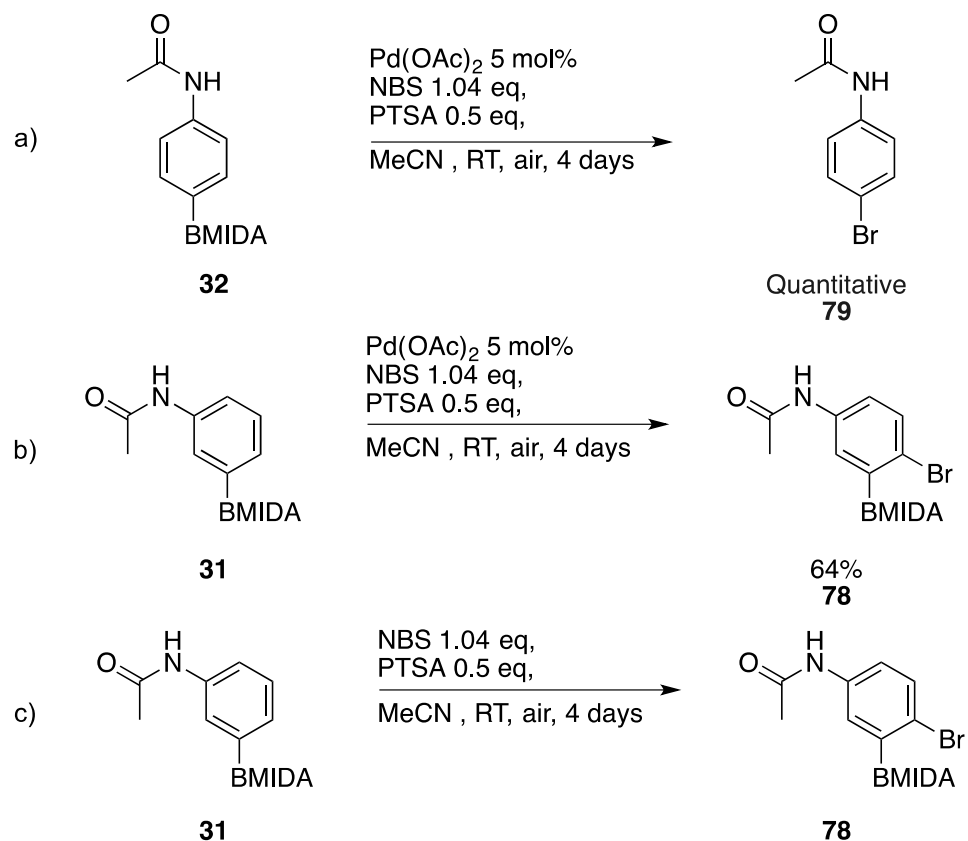
Table 3.7 Bromination of phenyl MIDA boronates.

Entry	Starting material	Bromination Method	Product	Yield (%)
1	 57	NBS 1 eq, H ₂ SO ₄ 0.5 eq MeCN, 70 °C, 12 h	 77	72
2	 31	NBS 1 eq, PTSA 0.5 eq MeCN, rt, 12 h	 78	60

Bedford *et al.* synthesised a variety of different *ortho*-bromophenylacetamides *via ortho*-selective palladium catalysed C-H halogenation (Scheme 3.9).¹⁵ This protocol was employed for the bromination of acetamidophenyl MIDA boronates, except the solvent was changed from toluene to MeCN due the poor solubility of the MIDA boronate. 4-Acetamidophenyl MIDA boronate (**32**) led to complete *ipso*-bromination of the MIDA boronate, forming *N*-4-bromophenylacetamide (**79**) in a quantitative yield (Scheme 3.20a). This shows that no C-H activation was achieved on this compound under these conditions, and that the *para*-substituted product was prevalent.

3-Acetamidophenyl MIDA boronate (**31**) was also subjected to the *ortho*-selective C-H halogenation and in this case only *para*-substitution occurred leading to 5-acetamido-2-bromophenyl (**78**) (Scheme 3.20b). These same conditions were also investigated using DMF as the solvent, giving **78** in comparable yield; hence MeCN was kept as the solvent of choice due to its relative ease of handling *i.e.* low boiling point. The reaction was also attempted without the palladium(II) acetate in MeCN (Scheme 3.20c); **78** was again

obtained in comparable yield (Table 3.7 entry 6). This expected due to the lack of C-H



Scheme 3.20. Bromination via C-H activation.

activation observed in the previous reaction on **78**. Upon crystallization of **78** corresponding boronic acid formed, X-ray crystallography confirmed the regiochemistry shown.

3.5 Conclusion

In this chapter, twelve tetrasubstituted aromatics were synthesised, ten of which were novel. Furthermore, three trisubstituted phenyl MIDA boronates were synthesised *via* bromination methodology. These methods were shown to be scalable and gave the desired products containing orthogonal groups, with the preferred regiochemistry.

The methodologies of direct bromination and nitration *via* electrophilic aromatic substitution of phenyl MIDA boronates described within this chapter are novel. They show that this masked boronic acid functionality can withstand these harsh reaction conditions. This work has highlighted the importance of having complementary directing groups, as the purification of the substituted-phenyl MIDA boronates *via* flash chromatography is nontrivial, particularly in regard to removing undesired regioisomers. The MIDA boronate group in these specific examples do not appear to give a directing effect, and the other functionalities govern reaction selectivity.

We are now in a position to show the potential and chemical relevance of multiple scaffolds through exploring the orthogonal behaviour of these functional group handles in a range of different processes. In chapter 4 the brominated MIDA boronates are used in iterative Suzuki cross coupling reactions. Chapter 5 consists of multiple modifications on three different bromo-fluoro-nitro-benzaldehyde scaffolds to afford novel, potential kinase inhibitors.

3.6 Experimental

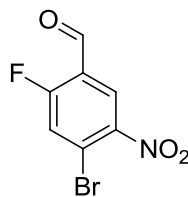
Solvents and reagents were purchased from commercial suppliers and used without further purification. NMR spectra were recorded on a Varian 500 MHz or 400 MHz spectrometer. Chemical shifts are reported in ppm and are referenced to the residual solvent peak or to TMS used as an internal standard; note that in some cases the carbon bonded to the boron is not detectable in the ^{13}C NMR²³. LCMSs were ran on a Shimadzu LCMS-2020 equipped with a Gemini® 5 μm C18 110 Å column. Percentage purities were performed using a 30 minutes method in water/acetonitrile with 0.1% Formic acid (5min at 5%, 5%-95% over 20 min, 5min at 95%) with the UV set to 254 nm. High resolution mass spectrometry (HRMS) was done either internally or by the National Mass Spectrometry Facility, Swansea University. A number of the products described below are commercially available or known, e.g. in patents. In these cases, ^1H , ^{13}C , HRMS and % purity data are presented since in many cases these data are not published. For compounds that appear to be novel, more analytical data are presented including ^{11}B NMR.

3.6.1 Nitration

General procedure for nitration of benzaldehyde derivatives.

A benzaldehyde derivative (12 mmol) was dissolved in sulphuric acid (98%, 25 mL) then cooled to 0 °C. Nitric acid (70%, 3 mL, 47 mmol) in sulphuric acid (98%, 30 mL) then was added drop-wise over 20 minutes maintaining the internal temperature at 0 °C. The mixture was allowed to warm to RT and left overnight. The mixture was poured onto ice (300 g). This was allowed to warm to RT and then extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with brine. The pH of the brine washings was monitored until they were no longer acidic and reached pH 7. The organic layer was then dried (MgSO_4) and evaporated under reduced pressure.

4-Bromo-2-fluoro-5-nitrobenzaldehyde, 59.¹



Method A

The general nitration procedure was used on a 25 mmol scale and the crude material was recrystallised from diethyl ether/hexane to give the title compound as a yellow crystalline solid.

Yield: 5.13 g (84%) Analytical data are presented below.

Method B

Nitronium tetrafluoroborate (2.62 g, 20 mmol) was stirred at -20 °C under anhydrous conditions dry DCM (15 mL). A solution of 4-bromo-2-fluoro-benzaldehyde (2.50 g, 12.3 mmol) in dry DCM (15 mL) was added drop wise over 20 minutes whilst maintaining the internal temperature at -20 °C. The mixture was allowed to warm to room temperature and left to stir over night. Water (30 mL) was added slowly to the reaction. Ethyl acetate (3 x 30 mL) was used to extract from the aqueous layer, then the combined organic layers were then washed with brine (3 x 30 mL). The organic layer was then dried (MgSO₄) and evaporated under reduced pressure. It was then purified via flash chromatography (diethyl ether: hexane 2:8) to give the title compound as a yellow crystalline solid.

Yield: 2.58 g (88%).

Mpt: 36-39 °C.

TLC (hexane:diethyl ether 8:2) R_f = 0.37.

FTMS + p APCI (m/z) found 247.9357, calcd for [C₇H₃⁷⁹BrFNO₃H]⁺ 247.9353.

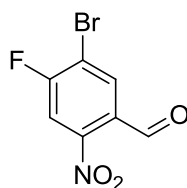
¹H NMR (500 MHz, CDCl₃) δ 10.30 (s, 1H), 8.39 (d, ⁴J_{FH} = 6.5 Hz, 1H), 7.66 (d, ³J_{FH} = 9.0 Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 184.0 (d, $^3J_{\text{FC}} = 5.5$ Hz), 164.2 (d, $^1J_{\text{FC}} = 269.5$ Hz), 146.9 (s), 126.2 (d, $^3J_{\text{FC}} = 4.0$ Hz), 124.1 (d, $^2J_{\text{FC}} = 25.0$ Hz), 123.7 (d, $^4J_{\text{FC}} = 10.5$ Hz), 122.7 (d, $^2J_{\text{FC}} = 11.0$ Hz).

^{19}F NMR (376 MHz, CDCl_3) δ -113.1 (dd, $J = 9.0, 6.5$ Hz).

Elemental analysis CHN (%) found C: 34.00, H: 1.18, N: 5.73, calcd for $\text{C}_7\text{H}_3\text{BrFNO}_3$ C: 33.90, H: 1.22, N: 5.65.

5-Bromo-4-fluoro-2-nitrobenzaldehyde, 61.²



The general nitration procedure was used on a 30 mmol scale and the crude material was recrystallised from diethyl ether/hexane to give the title compound as an orange crystalline solid.

Yield: 4.52 g (61%).

Mpt: 52-55 °C.

FTMS + p APCI (m/z) found 247.9354, calcd for $[\text{C}_7\text{H}_3^{79}\text{BrFNO}_3\text{H}]^+$ 247.9353.

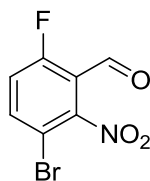
^1H NMR (500 MHz, CDCl_3) δ 10.38 (s, 1H), 8.22 (d, $^3J_{\text{FH}} = 6.5$ Hz, 1H), 7.90 (d, $^4J_{\text{FH}} = 7.5$ Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 185.6, 161.4 (d, $^1J_{\text{FC}} = 260.0$ Hz), 149.4, 135.4, 128.3 (d, $^4J_{\text{FC}} = 4.0$ Hz), 117.1 (d, $^2J_{\text{FC}} = 21.5$ Hz), 113.4 (d, $^2J_{\text{FC}} = 28.0$ Hz).

^{19}F NMR (376 MHz, CDCl_3) δ -94.1 (pt, $J = 7.0$ Hz).

Elemental analysis CHN (%) found C: 34.01, H: 1.23, N: 5.73, calcd for $\text{C}_7\text{H}_3\text{BrFNO}_3$ C: 33.90, H: 1.22, N: 5.65.

3-Bromo-6-fluoro-2-nitrobenzaldehyde, 63.



The general nitration procedure was used on a 30 mmol scale and the crude material was twice recrystallised from diethyl ether/hexane to give title compound as a light yellow crystalline solid.

Yield: 2.18 g (30%).

Mpt: 71-75 °C.

FTMS + p APCI (m/z) found 247.9357, calcd for $[\text{C}_7\text{H}_3^{79}\text{BrFNO}_3\text{H}]^+$ 247.9353.

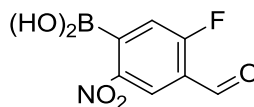
^1H NMR (500 MHz, CDCl_3) δ 10.20 (s, 1H), 7.92 (dd, $^3J_{\text{HH}} = 9.0$, $^4J_{\text{HF}} = 5.0$ Hz, 1H), 7.32 (pt, $^3J_{\text{HH}}$, $^3J_{\text{FH}}$ $J = 9.0$ Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 182.0 (d, $^3J_{\text{FC}} = 8.0$ Hz), 163.2 (d, $^1J_{\text{FC}} = 263.5$ Hz), 148.6 (s), 140.4 (d, $^3J_{\text{FC}} = 9.5$ Hz), 120.1 (d, $^2J_{\text{FC}} = 22.5$ Hz), 117.5 (d, $^2J_{\text{FC}} = 12.5$ Hz), 110.1 (d, $^3J_{\text{FC}} = 4.0$ Hz).

^{19}F NMR (376 MHz, CDCl_3) δ -118.3 (dd, $^3J_{\text{FH}} = 9.0$, $^4J_{\text{FH}} = 5.0$ Hz).

Elemental analysis CHN (%) found C: 33.86, H: 1.17, N: 5.57, calcd for $\text{C}_7\text{H}_3\text{BrFNO}_3$ C: 33.90, H: 1.22, N: 5.65.

5-Fluoro-4-formyl-2-nitrophenyl boronic acid, 65.



3-Fluoro-4-formylphenyl boronic acid (2.02 g, 12 mmol) was dissolved in sulphuric acid (98%, 12 mL) at rt then cooled to 0 °C. Nitric acid (70%, 1.46 mL, 22 mmol) in sulphuric acid 98% (15 mL) was added drop-wise over 20 minutes and maintained at 0 °C. The mixture was allowed to warm to RT and left overnight. The mixture was poured on to ice (150g) then was allowed to warm to RT and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine. The pH of the brine washings was monitored until they were no longer acidic and reached pH 7. The organic layer was then

dried (MgSO₄) and evaporated under reduced pressure to give the title compound as a light yellow powder.

Yield: 2.26 g (88%).

Mpt: decomposes at 135 °C.

HRMS-ES (m/z) found 238.0430, calcd for (ethlyglycol adduct)[C₉H₇O₅NBF]+ 238.0432.

¹H NMR (500 MHz, DMSO-D₆) δ 10.20 (s, 1H), 8.54 (d, ⁴J_{FH} = 5.5 Hz, 1H), 8.46 (s, 2H), 7.61 (d, ³J_{FH} = 10.0 Hz, 1H).

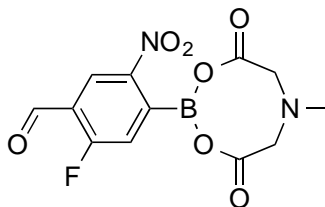
¹³C NMR (126 MHz, DMSO-D₆) δ 186.8 (d, ³J_{FC} = 2.0 Hz), 165.3 (d, ¹J_{FC} = 268.0 Hz), 146.3 (d, ⁴J_{FC} = 2.0 Hz), 145.1, 124.7 (d, ³J_{FC} = 2.0 Hz), 123.7 (d, ²J_{FC} = 11.0 Hz), 120.7 (d, ²J_{FC} = 21.5 Hz).

¹⁹F NMR (376 MHz, DMSO-D₆) δ -111.7 (dd, ³J_{FH} = 10.0, ⁴J_{FH} = 5.5 Hz).

¹¹B NMR (128 MHz, DMSO-D₆) δ 27.8.

Elemental analysis CHN (%) found C: 39.36, H: 2.50, N: 6.39, calcd for C₇H₅BFNO₅ C: 39.49, H: 2.37, N: 6.58

5-Fluoro-4-formyl-2-nitrophenyl MIDA boronate, 66.



3-Fluoro-4-formylphenyl MIDA boronate (250 mg, 1 mmol) was dissolved in sulphuric acid (98%, 1.5 mL) at rt then cooled to 0 °C. Nitric acid (70%, 0.5 mL, 7.7 mmol) in sulphuric acid (98% 1.5 mL) was added drop-wise over 20 minutes and the reaction temperature was maintained at 0 °C. The mixture was allowed to warm to RT and was left to stir overnight. The mixture was poured on to ice (8 g); this then formed a precipitate was filtered under reduced pressure. The precipitate was then washed with water (3 x 10 mL) and then cold diethyl ether (3 x 5 mL) and then oven dried (100 °C) to give the title compound as a light yellow powder.

Yield: 275 mg (85%).

TLC (diethyl ether:MeCN 7:3) R_f = 0.47.

FTMS APCI (m/z) found 325.0638, calcd for $[\text{C}_{12}\text{H}_{10}\text{BFN}_2\text{O}_7\text{H}]^+$ 325.0638.

^1H NMR (500 MHz, DMSO- d_6) δ 10.17 (s, 1H), 8.23 (d, $^4J_{\text{FH}}$ = 5.5 Hz, 1H), 7.67 (d, $^3J_{\text{FH}}$ = 11.0 Hz, 1H), 4.46 (d, J = 17.5 Hz, 2H), 4.25 (d, J = 17.5 Hz, 2H), 2.89 (s, 3H).

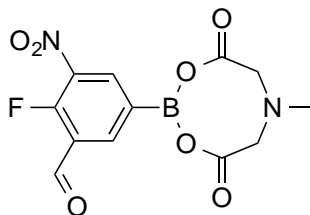
^{13}C NMR (126 MHz, DMSO- d_6) δ 187.0 (d, $^3J_{\text{FC}}$ = 3.5 Hz), 169.2, 163.4 (d, $^1J_{\text{FC}}$ = 264.7 Hz), 151.4 (d, $^4J_{\text{FC}}$ = 2.5 Hz), 125.6 (d, $^3J_{\text{FC}}$ = 3.0 Hz), 125.2 (d, $^2J_{\text{FC}}$ = 11.0 Hz), 125.0 (d, $^2J_{\text{FC}}$ = 21.5 Hz), 64.8, 49.9.

^{19}F NMR (376 MHz, DMSO- d_6) δ -114.38 (dd, $^3J_{\text{FH}}$ = 11.0, $^4J_{\text{FH}}$ = 6.0 Hz).

^{11}B NMR (128 MHz, DMSO- d_6) δ 10.1.

LCMS purity >95 % (UV), Ret. time = 11.09 min.

4-Fluoro-3-formyl-5-nitrophenyl MIDA boronate, 67.



4-Fluoro-3-formylphenyl MIDA boronate (250 mg, 1 mmol) was dissolved in sulphuric acid (98%, 1.5 mL) at rt then cooled to 0 °C. Nitric acid (70 %, 0.5 mL, 7.7 mmol) in sulphuric acid (98 %, 1.5 mL) was added drop-wise over 20 minutes and maintained at 0 °C. The mixture was allowed to warm to RT and left overnight. The mixture was poured on to ice (8 g); this formed a precipitate which was collected by vacuum filtration. The precipitate was then washed with water (3 x 10 mL) and then cold diethyl ether (3 x 5 mL). This was then oven dried (100 °C) to give the title compound as a light yellow powder.

Yield: 105 mg (32 %).

TLC (diethyl ether:MeCN 7:3) R_f = 0.44.

FTMS APCI (m/z) found 325.0638, calcd for $[\text{C}_{12}\text{H}_{10}\text{BFN}_2\text{O}_7\text{H}]^+$ 325.0638.

^1H NMR (399 MHz, DMSO- d_6) δ 10.28 (s, 1H), 8.44 (d, $^4J_{\text{FH}} = 7.0$ Hz, 1H), 8.27 (d, $^4J_{\text{FH}} = 6.0$ Hz, 1H), 4.40 (d, $J = 17.0$ Hz, 2H), 4.19 (d, $J = 17.0$ Hz, 2H), 2.62 (s, 3H).

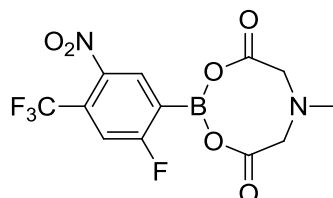
^{13}C NMR (126 MHz, DMSO- d_6) δ 187.4 (d, $^3J_{\text{FC}} = 5.5$ Hz), 169.52, 156.9 (d, $^1J_{\text{FC}} = 275.5$ Hz), 139.7 (d, $^3J_{\text{FC}} = 2.5$ Hz), 137.7 (d, $^2J_{\text{FC}} = 6.5$ Hz), 135.7, 125.5 (d, $^2J_{\text{FC}} = 7.0$ Hz), 62.9, 48.5.

^{19}F NMR (376 MHz, DMSO- d_6) δ -128.36 (s).

^{11}B NMR (128 MHz, DMSO- d_6) δ 10.3.

LCMS purity >99% (UV), Ret. time = 10.43 min.

2-Fluoro-5-nitro-4-(trifluoromethyl)phenyl MIDA boronate, 69.



2-Fluoro-(trifluoromethyl)phenyl MIDA boronate (321 mg, 1 mmol) was dissolved in sulphuric acid (98%, 2 mL) and cooled to 0 °C. Nitric acid (70%, 315 μL , 22 mmol) was added to the mixture at 0 °C, which was allowed to warm to RT and left overnight. The mixture was poured onto ice (20 g) and then was allowed to warm to RT forming a precipitate, which was collected by filtration, washed with water (3 x 50 mL) and then diethyl ether (10 mL). This was then dried overnight in a vacuum desiccator over CaCl_2 giving title compound as a bright yellow powder.

Yield: 344 mg (92 %).

Mpt: decomposes at 232-234°C.

FTMS (m/z) found 381.0865, calcd for $[\text{C}_{12}\text{H}_9\text{BF}_4\text{N}_2\text{O}_6\text{NH}_4]^+$ 381.0864.

^1H NMR (500 MHz, MeCN- d_3) δ 8.20 (d, $J = 5.5$ Hz, 1H), 7.65 (d, $J = 9.5$ Hz, 1H), 4.20 (d, $J = 17.5$ Hz, 2H), 4.01 (d, $J = 17.5$ Hz, 2H), 2.72 (s, 3H).

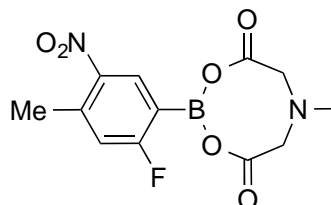
^{13}C NMR (126 MHz, MeCN- d_3) δ 168.8, 167.8 ($^1J_{\text{FC}} = 251.5$ Hz), 145.0, 134.0 (d, $^1J_{\text{FC}} = 11.5$ Hz), 127.4 (qd, $^2J_{\text{FC}} = 35.0$, $^3J_{\text{FC}} = 10.0$ Hz), 122.7 (qd, $^1J_{\text{FC}} = 272.5$, $^4J_{\text{FC}} = 2.1$ Hz), 117.2 (dq, $^2J_{\text{FC}} = 32.5$, $^3J_{\text{FC}} = 5.5$ Hz), 63.9(s), 48.8.

^{19}F NMR (376 MHz, MeCN- d_3) δ -61.03 (s), -97.13 (dd, $^3J_{\text{FH}} = 9.5$, $^4J_{\text{FH}} = 5.5$ Hz).

^{11}B NMR (128 MHz, MeCN- d_3) δ 10.13.

Elemental analysis CHN (%) found C: 39.49, H: 2.47, N: 7.68, calcd for $C_{12}H_9BF_4N_2O_6$
C: 39.59, H: 2.49, N: 7.70.

2-Fluoro-4-methyl-5-nitrophenyl MIDA boronate, 70.



2-Fluoro-4-methylphenyl MIDA boronate (530 mg, 2 mmol) was dissolved in sulphuric acid (98%, 6 mL) and cooled to 0 °C. Nitric acid (70%, 126 μ L, 2.04 mmol) was added to the mixture at 0 °C, which was allowed to warm to RT and left overnight. The mixture was poured onto ice (10 g) and this was allowed to warm to RT forming a precipitate, which was collected by filtration, washed with water (3 x 50 mL) and then diethyl ether (10 mL). This was then dried over night in a vacuum desiccator over $CaCl_2$ giving title compound as a white powder.

Yield: 242 mg (39 %).

FTMS APCI MS m/z found 381.0865, calcd for $[C_{12}H_{12}BFN_2O_6H]^+$ 311.0845.

TLC (DCM:MeCN 7:3) R_f = 0.80

1H NMR (399 MHz, DMSO- d_6) δ 8.11 (d, $^4J_{FH}$ = 6.0 Hz, 1H), 7.35 (d, $^3J_{FH}$ = 10.0 Hz, 1H), 4.45 (d, J = 17.5 Hz, 2H), 4.13 (d, J = 17.5 Hz, 2H), 2.68 (s, 3H), 2.56 (s, 3H).

^{13}C NMR (126 MHz, DMSO- d_6) δ 168.7, 166.9 (d, $^1J_{FC}$ = 251.0 Hz), 145.1, 138.2 (d, $^3J_{FC}$ = 11.0 Hz), 131.8 (d, $^3J_{FC}$ = 12.0 Hz), 119.2 (d, $^2J_{FC}$ = 27.5 Hz), 62.5, 47.6, 19.7.

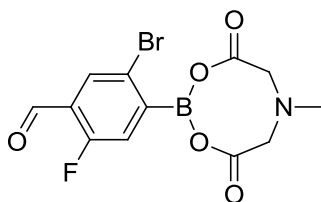
^{19}F NMR (376 MHz, DMSO- d_6) δ -98.29 (dd, $^4J_{FH}$ = 10.0, $^3J_{FH}$ = 6.0 Hz).

^{11}B NMR (128 MHz, DMSO- d_6) δ 10.47.

LCMS purity 95 % (UV), Ret. time = 16.29 min.

3.6.2 Bromination

2-Bromo-5-fluoro-4-formylphenyl MIDA boronate, 73.



3-Fluoro-4-formylphenyl MIDA boronate (279 mg, 1 mmol) was dissolved in sulphuric acid (98%, 4 mL) and the temperature was then increased to 60 °C. *N*-Bromosuccinimide (214 mg, 1.2 mmol) was added in three portions at 15 min intervals. After a further 1.5 h, the cooled reaction mixture was poured onto crushed ice (20 g). This resulted in a white precipitate, which was collected by vacuum filtration. The resulting powder was purified by flash chromatography on silica gel (DCM:MeCN 7:3) to afford the title compound as a white powder.

Yield: 93 mg (54%).

Mpt: decomposes at 232-234 °C.

TLC (DCM:MeCN 7:3) R_f = 0.53.

FTMS APCI (m/z) found 356.9928, calcd for $[C_{12}H_{10}B^{79}BrFNO_5H:]^+$ 356.9929.

1H NMR (500 MHz, DMSO- d_6) δ 10.15 (s, 1H), 7.97 (d, $^4J_{FH}$ = 6.0 Hz, 1H), 7.50 (d, $^3J_{FH}$ = 11.5 Hz, 1H), 4.46 (d, J = 17.5 Hz, 2H), 4.20 (d, J = 17.5 Hz, 2H), 2.75 (s, 3H).

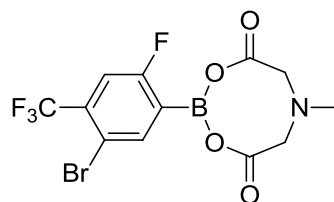
^{13}C NMR (126 MHz, DMSO- d_6) δ 187.0 (d, $^3J_{FC}$ = 3.5 Hz), 169.0, 161.2 (d, $^1J_{FC}$ = 259.0 Hz), 133.6 (d, $^3J_{FC}$ = 2.0 Hz), 125.5 (d, $^2J_{FC}$ = 10.0 Hz), 124.5 (d, $^2J_{FC}$ = 21.0 Hz), 121.9 (d, $^4J_{FC}$ = 3.0 Hz), 64.2, 48.4.

^{19}F NMR (376 MHz, DMSO- d_6) δ -123.4 (dd, $^3J_{FH}$ = 11.5, $^4J_{FH}$ = 6.0 Hz).

^{11}B NMR (128 MHz, DMSO- d_6) δ 10.4.

Elemental analysis CHN (%) found C: 40.31, H: 2.81, N: 4.04, calcd for $C_{12}H_{10}BBBrFNO_5$ C: 40.27, H: 2.82, N: 3.91.

5-Bromo-2-fluoro-4-(trifluoromethyl)phenyl MIDA boronate, 74.



2-Fluoro-4-(trifluoromethyl)phenyl MIDA boronate (321 mg, 2 mmol) was dissolved in sulphuric acid (98%, 8 mL). The temperature was increased to 30 °C and then *N*-bromosuccinimide (427 mg, 2.4 mmol) was added in three portions at 15 min intervals. After a further 4 h the cooled reaction mixture was poured on to crushed ice (20 g) resulting in a white precipitate, which was filtered under vacuum. This resulting white powder required no further purification giving the title compound.

Yield: 787 mg (99%).

FTMS APCI MS *m/z* found 397.9818, calcd for $[\text{C}_{12}\text{H}_9\text{B}^{79}\text{BrF}_4\text{NO}_4\text{H}]^+$ 397.9817.

TLC (DCM:MeCN 7:3) R_f = 0.72.

Mpt: decomposes at 232-234 °C.

^1H NMR (500 MHz, MeCN- d_3) δ 7.93 (d, $^4J_{\text{FH}}$ = 6.0 Hz, 1H), 7.51 (d, $^3J_{\text{FH}}$ = 10.0 Hz, 1H), 4.16 (d, J = 17.0 Hz, 2H), 3.98 (d, J = 17.0 Hz, 2H), 2.70 (s, 3H).

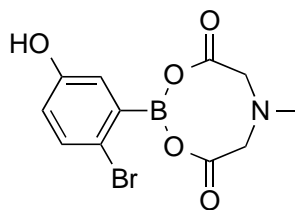
^{13}C NMR (126 MHz, MeCN- d_3) δ 168.8, 165.5 (d, $^1J_{\text{FC}}$ = 243.5 Hz), 142.4 (d, J^3J_{FC} = 9.5 Hz), 133.0 (dq, $^2J_{\text{FC}}$ = 32.5 Hz, $^3J_{\text{FC}}$ = 9.0 Hz), 123.4 (dq, $^1J_{\text{FC}}$ = 272.5, $^4J_{\text{FC}}$ = 2.5 Hz), 116.8 (dq, $^2J_{\text{FC}}$ = 31.5, $^3J_{\text{FC}}$ = 6.0 Hz), 115.0, 63.8, 48.7.

^{19}F NMR (376 MHz, MeCN- d_3) δ -63.7 (s), -107.3 (dd, $^3J_{\text{FH}}$ = 10.0, $^4J_{\text{FH}}$ = 6.0 Hz).

^{11}B NMR (128 MHz, MeCN- d_3) δ 10.3 (s).

Elemental analysis CHN (%) found C: 36.18, H: 2.30, N: 3.61, calcd for $\text{C}_{12}\text{H}_9\text{BBBrF}_4\text{NO}_4$: 36.22, H: 2.28, N: 3.52.

2-Bromo-5-hydroxyphenyl MIDA boronate, 75.



3-Hydroxyphenyl MIDA boronate (498 mg, 2 mmol) was dissolved in acetonitrile (40 mL), and sulphuric acid (98%, 1 mmol, 55 μ L) was added to this mixture. *N*-Bromosuccinimide (356 mg, 2 mmol) was added in three portions at 15 min intervals and the reaction was left to stir overnight at RT. The reaction mixture was evaporated directly on to Celite. The resulting powder was purified by flash chromatography on silica gel (acetonitrile: diethyl ether 10 %: 30 %) to afford the title compound as a white powder.

Yield: 501 mg (76 %).

TLC (diethyl ether:MeCN 7:3) R_f = 0.78.

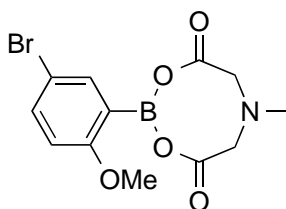
(FTMS m/z) found 327.0023, calcd for $[C_{11}H_{11}B^{79}BrNO_5H]^+$ 327.9986 .

1H NMR (500 MHz, Acetonitrile- d_3) δ 7.41 (d, J = 8.5 Hz, 1H), 7.14 (d, J = 3.0 Hz, 1H), 7.02 (s, 1H), 6.75 (dd, J = 8.5, 3.0 Hz, 1H), 4.11 (d, J = 17.5 Hz, 2H), 4.01 (d, J = 17.5 Hz, 2H), 2.73 (s, 3H).

^{13}C NMR (126 MHz, Acetonitrile- d_3) δ 169.5, 157.0, 135.6, 124.1, 119.2, 117.8, 65.2, 49.5.

Elemental analysis CHN (%) found C: 40.18, H: 3.31 N: 4.46, calcd for $C_{11}H_{11}BBBrF_4NO_5$: 40.29, H: 3.38, N: 4.40.

5-Bromo-2-methoxyphenyl MIDA boronate, 76.



2-Methoxyphenyl MIDA boronate (263 mg, 1 mmol) was dissolved in acetonitrile (40 mL), and sulphuric acid (98%, 0.5 mmol, 28 μ L) was added to this mixture. *N*-bromosuccinimide (178 mg, 1 mmol) was added in three portions at 15 min intervals and the reaction was left to stir over night at RT. The reaction mixture was evaporated directly

onto Celite. The resulting powder was purified by flash chromatography on silica gel (acetonitrile: diethyl ether 10 %: 30 %) to afford the title compound as a white powder.

Yield: 298 mg (87 %).

TLC (diethyl ether:MeCN 7:3) R_f = 0.82.

FTMS APCI MS m/z found 342.0123, calcd for $[C_{12}H_{13}^{79}BBrNO_5H]^+$ 342.0141.

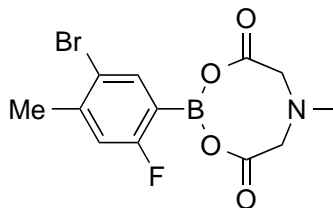
1H NMR (399 MHz, DMSO- d_6) δ 7.50 – 7.45 (m, 2H), 6.91 (d, J = 9.4 Hz, 1H), 4.33 (d, J = 17.1 Hz, 2H), 3.99 (d, J = 17.1 Hz, 2H), 3.69 (s, 3H), 2.59 (s, 3H).

^{13}C NMR (100 MHz, DMSO- d_6) δ 169.6, 161.7, 136.6, 133.5, 113.4, 112.8, 63.7, 55.8, 47.8.

^{11}B NMR (128 MHz, DMSO- d_6) δ 11.1.

Elemental analysis CHN (%) found C: 40.25, H: 3.88 N: 4.15, calcd for $C_{12}H_{13}BBrF_4NO_5$: 40.15, H: 3.83, N: 4.10.

5-Bromo-2-fluoro-4-methylphenyl MIDA boronate, 77.



2-Fluoro-4-methylphenyl MIDA boronate (3.69 g, 13.9 mmol) was dissolved in acetonitrile (70 mL), and sulphuric acid (98%, 13.9 mmol, 778 μ L) was added to this mixture and it was then heated to 70 $^{\circ}C$. *N*-Bromosuccinimide (2.72 g, 15.3 mmol) was added in three portions at 15 min intervals and the reaction was left to stir overnight. The reaction mixture was evaporated directly to dryness under reduced pressure. Water (100 mL) was added, and this aqueous layer was extracted with 50 % ethyl acetate in acetone (3 x 150 mL). The combined organic layers were washed with brine (3 x 100 mL), then dried with $MgSO_4$ and evaporated under reduced pressure. The resulting powder was dissolved in the minimum amount of DMSO and loaded on to a reversed phase flash chromatography column. A 0.1 % formic acid modifier was used throughout the column chromatography; 5 column volumes at 100 % water (removing the DMSO) then a gradient of 20 %-90 % acetonitrile in water was used to elute the desired product. The

desired samples were dried by lyophilisation to afford the title compound as a white powder.

Yield: 3.457 mg (72 %).

TLC (diethyl ether:MeCN 7:3) R_f = 0.69.

(FTMS m/z) found 342.0141, calcd for $[C_{12}H_{12}B^{79}BrFNO_4H]^+$ 342.0143.

1H NMR (500 MHz, DMSO- d_6) δ 7.58 (d, $^4J_{FH}$ = 6.0 Hz, 1H), 7.20 (d, $^3J_{FH}$ = 10.0 Hz, 1H), 4.41 (d, J = 17.5 Hz, 2H), 4.09 (d, J = 17.5 Hz, 2H), 2.66 (s, 3H), 2.35 (s, 3H).

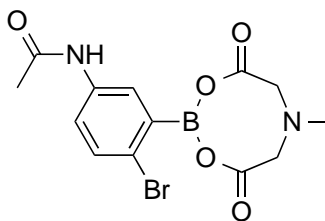
^{13}C NMR (100 MHz, DMSO- d_6) δ 169.3, 164.9 (d, $^1J_{FC}$ = 242.0 Hz), 141.5 (d, $^3J_{FC}$ = 9.5 Hz), 138.0 (d, $^3J_{FC}$ = 10.0 Hz), 119.4 (d, $^4J_{FC}$ = 2.5 Hz), 118.3 (d, $^2J_{FC}$ = 26.5 Hz), 62.9, 48.1, 22.8.

^{19}F NMR (376 MHz, DMSO- d_6) δ -108.43 (dd, $^3J_{FH}$ = 10.0, $^4J_{FH}$ = 6.0 Hz).

^{11}B NMR (128 MHz, DMSO- d_6) δ 10.5.

LCMS purity >99% (UV), Ret. time = 16.21 min.

5-Acetamido-2-bromophenyl MIDA boronate, 78.



3-Acetamidophenyl MIDA boronate (290 mg, 1 mmol) was dissolved in acetonitrile (4 mL), and *p*-toluenesulfonic acid (0.5 mmol, 95 mg) was added to this mixture. *N*-bromosuccinimide (185 mg, 1.04 mmol) was added in three portions at 15 min intervals and the reaction was left to stir over night at RT. The reaction mixture was evaporated directly on to celite. The resulting powder was purified by flash chromatography on silica gel (acetonitrile: DCM 0 %: 40 %) to afford the title compound as a white powder.

Yield: 222 mg (60 %).

TLC (DCM:MeCN 7:3) R_f = 0.57.

(FTMS m/z) found 371.0233, calcd for $[C_{13}H_{14}B^{81}BrN_2O_5H]^+$ 371.0232.

^1H NMR (399 MHz, DMSO- d_6) δ 10.03 (s, 1H), 7.78 (dd, $J = 8.5, 3.0$ Hz, 1H), 7.52 (d, $J = 3.0$ Hz, 1H), 7.46 (d, $J = 8.5$ Hz, 1H), 4.39 (d, $J = 17.5$ Hz, 2H), 4.14 (d, $J = 17.5$ Hz, 2H), 2.66 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (100 MHz, DMSO- d_6) δ 169.5, 168.8, 138.7, 134.0, 127.0, 122.1, 120.7, 64.3, 48.9.

^{11}B NMR (128 MHz, DMSO- d_6) δ 11.0.

LCMS purity >99% (UV), Ret. time = 13.13 min.

3.7 Bibliography

- (1) Barbachyn, M. R.; Dobrowolski, P. J.; Hurd, A. R.; Mcnamara, D. J.; Romero, A. G.; Ruble, J. C.; Sherry, D. A.; Thomasco, L. M.; Toogood, P. L. Tricyclic Tetrahydroquinoline Antibacterial Agents. WO 2004/031195 A1, 2004.
- (2) Baxter, E. 2-Amino-quinoline Derivatives Useful as Inhibitors of β -Secretase (BACE). WO 2009/097401 A1, 2009.
- (3) Gaster, L. M.; Blaney, F. E.; Davies, S.; Duckworth, D. M.; Ham, P.; Jenkins, S.; Jennings, A. J.; Joiner, G. F.; King, F. D.; Mulholland, K. R.; Wyman, P. A.; Hagan, J. J.; Hatcher, J.; Jones, B. J.; Middlemiss, D. N.; Price, G. W.; Riley, G.; Roberts, C.; Routledge, C.; Selkirk, J.; Slade, P. D. *J. Med. Chem.* **1998**, 2623, 1218–1235.
- (4) Raitio, K. H.; Savinainen, J. R.; Vepsäläinen, J.; Laitinen, J. T.; Poso, A.; Järvinen, T.; Nevalainen, T. *J. Med. Chem.* **2006**, 49, 2022–2027.
- (5) Abdulla; Amina, S.; Kumar, Y. *Synth. Commun.* **2011**, 41, 2946–2951.
- (6) Bose, A. K.; Ganguly, S. N.; Manhas, M. S.; Rao, S.; Speck, J.; Pekelny, U.; Pombo-Villars, E. *Tetrahedron Lett.* **2006**, 47, 1885–1888.
- (7) Yadav, U.; Mande, H.; Ghalsasi, P. *J. Chem. Educ.* **2012**, 89, 268–270.
- (8) Mo, F.; Yan, J. M.; Qiu, D.; Li, F.; Zhang, Y.; Wang, J. *Angew. Chemie Int. Ed.* **2010**, 49, 2028–2032.
- (9) Duan, J.; Zhang, L. H.; Dolbier, Jr, W. R. *Synlett* **1999**, 1999, 1245–1246.
- (10) Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K. K. *J. Org. Chem.* **2007**, 72, 5867–5869.
- (11) Bovonsombat, P.; Ali, R.; Khan, C.; Leykajarakul, J.; Pla-on, K.; Aphimanchindakul, S.; Pungcharoenpong, N.; Timsuea, N.; Arunrat, A.; Punpongjareorn, N. *Tetrahedron* **2010**, 66, 6928–6935.
- (12) Qiu, D.; Mo, F.; Zheng, Z.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, 12, 5474–5477.
- (13) Al-Zoubi, R. M.; Hall, D. G. *Org. Lett.* **2010**, 12, 2480–2483.
- (14) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Lett.* **2003**, 32, 932–933.
- (15) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chemie Int. Ed.* **2011**, 50, 5524–5527.
- (16) Ahn, S. J.; Lee, C. Y.; Kim, N. K.; Cheon, C. H. *J. Org. Chem.* **2014**, 79, 7277–7285.
- (17) Sedinkin, S. L.; Rath, N. P.; Bauer, E. B. *J. Organomet. Chem.* **2008**, 693, 3081–3091.
- (18) Benedict, S. *J. Biol. Chem.* **1909**, 5, 485–487.
- (19) Dolbier, W. R. *Guide to Fluorine NMR for Organic Chemists*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2009.
- (20) Richards, S. A.; Hollerton, J. C. *Essential Practical NMR for Organic Chemistry*; John Wiley & Sons, Ltd: Chichester, UK, 2010.
- (21) Feng, Q.; Song, Q. *J. Org. Chem.* **2014**, 79, 1867–1871.
- (22) Holland, E.; Spencer, J.; Deadman, J. J. *Synthesis (Stuttg.)* **2002**, 16, 2379–2382.

- (23) Spencer, J.; Baltus, C. B.; Patel, H.; Press, N. J.; Callear, S. K.; Male, L.; Coles, S. J. *ACS Comb. Sci.* **2011**, *13*, 24–31.
- (24) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084–14085.
- (25) Soloway, A. H. *J. Am. Chem. Soc.* **1959**, *81*, 3017–3019.
- (26) Mulakayala, N.; Kumar, K. M.; Rapolu, R. K.; Kandagatla, B.; Rao, P.; Oruganti, S.; Pal, M. *Tetrahedron Lett.* **2012**, *53*, 6004–6007.
- (27) Zhu, C.; Falck, J. R. *Adv. Synth. Catal.* **2014**, *356*, 2395–2410.
- (28) Wu, X.-F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun. (Camb)*. **2011**, *47*, 12462–12463.
- (29) Prakash, G. K. S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2004**, *8*, 11–13.
- (30) Zhu, C.; Li, G.; Ess, D. H.; Falck, J. R.; Kürti, L. *J. Am. Chem. Soc.* **2012**, 1–4.
- (31) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860–2863.
- (32) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1961**, *83*, 4581–5485.
- (33) Nowrouzi, N.; Mehranpour, A. M.; Bashiri, E.; Shayan, Z. *Tetrahedron Lett.* **2012**, *53*, 4841–4842.
- (34) Kamei, T.; Ishibashi, A.; Shimada, T. *Tetrahedron Lett.* **2014**, *55*, 4245–4247.
- (35) Sigma-Aldrich Company Ltd. Trifluoroacetic acid Material Safety Data Sheet, 2015, T6508.
- (36) Sigma-Aldrich Company Ltd. Sulfuric acid Material Safety Data Sheet, 2015, 258105.
- (37) Cantillo, D.; De Frutos, O.; Rincon, J.; Mateos, C.; Kappe, O. *J. Org. Chem.* **2014**, *79*, 223–229.

4. Iterative Suzuki Cross-Couplings

4.1. Overview

The aim of this chapter is to demonstrate the value and orthogonal behaviour of the bromophenyl MIDA boronates synthesised in Chapter 3 to produce a range of tetrasubstituted aromatic targets. This will be performed using iterative Suzuki cross-couplings to introduce new aromatic and heteroaromatic groups. The target was to produce a faster method for the anhydrous cross coupling, with the hypothesis that microwave heating could enhance reaction times of these iterative Suzuki cross-couplings reactions.

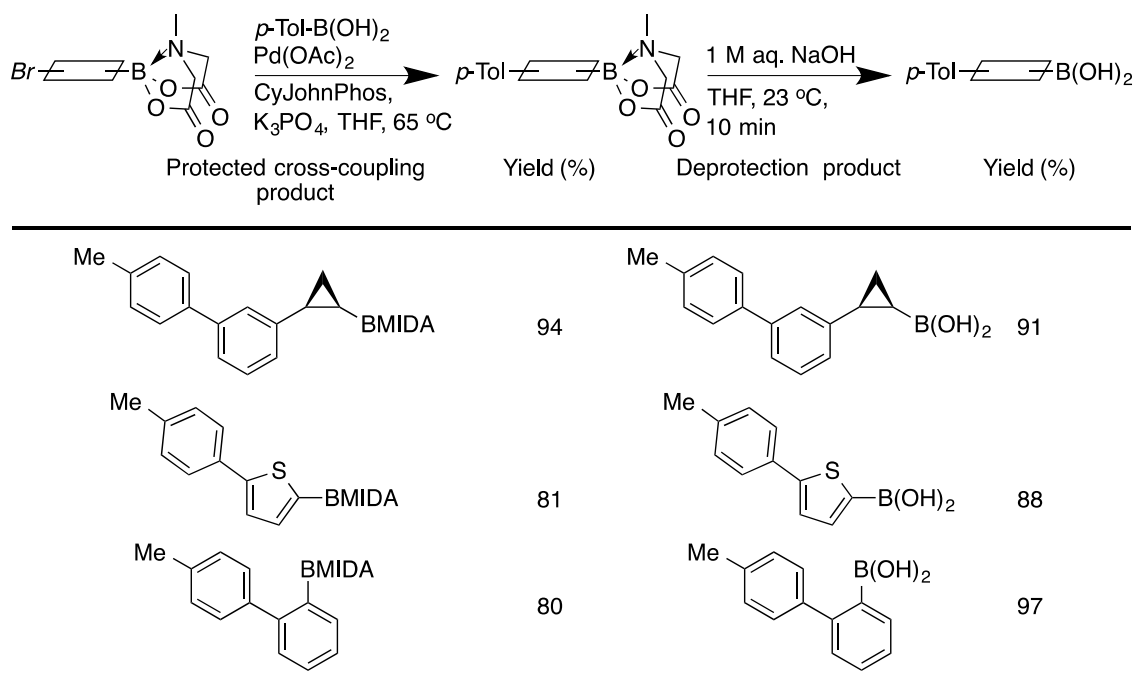
4.2. Introduction

Suzuki, Miyaura and Yamada first reported the Suzuki reaction in 1979, when they outlined the cross-couplings of alkenylboranes with alkenyl or aryl halides.^{1,2} Since then, Suzuki reactions have become the most used palladium catalysed cross-coupling reaction. Between 2001-2010 the number of publications and patents concerning Suzuki cross-couplings by far outweighed all other cross-couplings.³

Suzuki cross-couplings are favoured due to their mild reaction conditions, high functional group tolerance, wide-ranging commercial availability of precursors, lower toxicity of by-products than other reactions (e.g. tin in Stille reactions) and high yielding reactions when optimised. For these reasons the Suzuki reaction has become the principal synthetic pathway towards the biphenyl motif. The biphenyl motif is considered a privileged structure in medicinal chemistry, appearing in 4.3% of drugs in the year 2000.⁴

In 1986 Mancilla employed *N*-methyliminodiacetic acid reacting it with boronic acids to form the bicyclic aryl boronic ester now known as a MIDA boronate.⁵ Mancilla demonstrated that MIDA boronates could easily be prepared from the free phenyl boronic acid and *N*-methyliminodiacetic acid in DMSO with the addition of benzene, to aid the azeotropic removal of water. Burke *et al.* in 2008 outlined the use of MIDA boronates in interactive Suzuki cross-couplings.⁶ The MIDA boronate enables iterative coupling by means of inhibiting transmetalation of the boron. This is due to the formation of a very stable dative covalent bond between the nitrogen and boron, making an sp³-hybridized boron.

Examples of Burke's earlier work are shown in Scheme 4.1. This work shows parallels to peptide synthesis, as it uses coupling cycles followed by deprotection facilitating a second coupling. The coupling cycles in the presence of a MIDA boronate require anhydrous Suzuki cross-coupling conditions, as aqueous basic conditions cause the deprotection of the MIDA boronate. Within this first publication by Burke, his group achieved the first total synthesis of the natural product ratanhine, using 3 different protection deprotection cycles (Scheme 1.43).



Scheme 4.1. Examples of Burke's protected Suzuki cross-coupling followed by deprotection.

Different anhydrous palladium cross-coupling reactions have been achieved since this original publication *i.e.* Buchwald-Hartwig, Negishi, Sonogashira (with ethynyl MIDA boronate), Heck and Stille.⁷⁻¹² This work is reviewed in greater depth within the Introduction (0).

Burke has recently published papers outlining the automated synthesis of different complex molecules using iterative cross coupling reactions.^{18,19} This machine can do

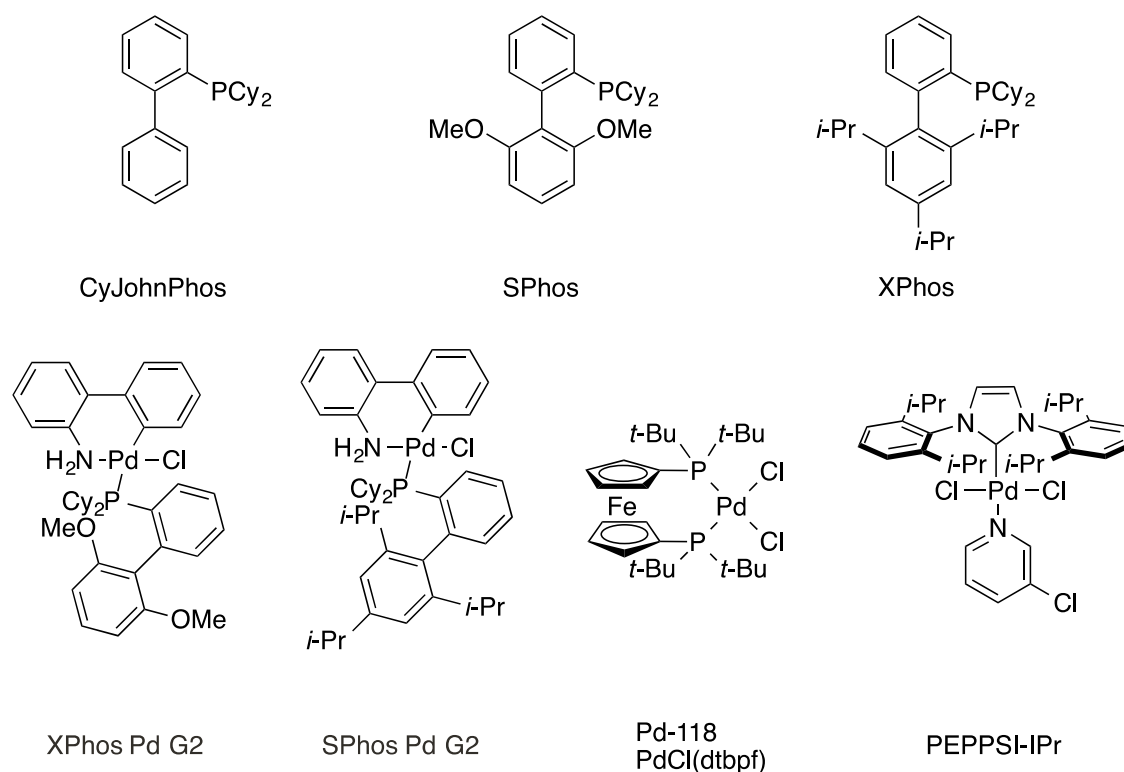
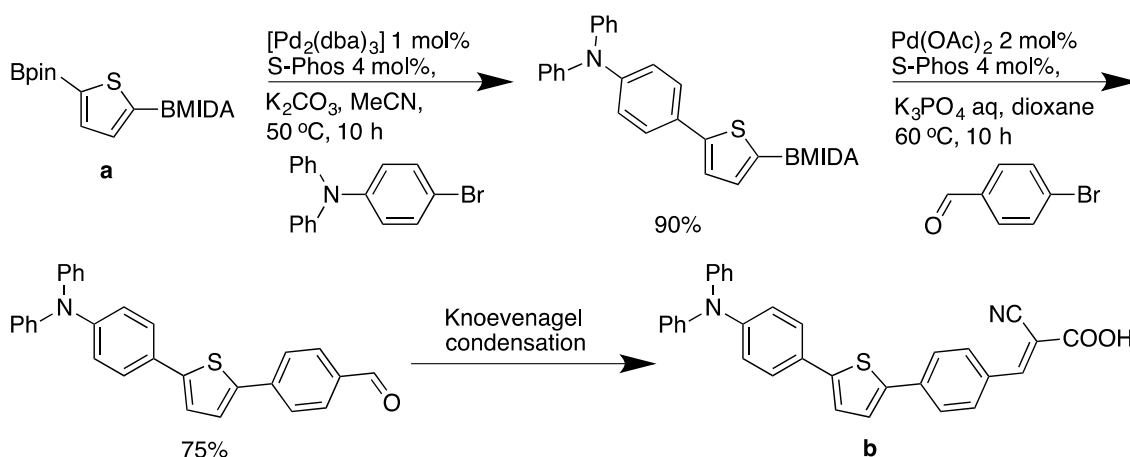


Figure 4.1. Examples of ligands and precatalysts used in palladium cross coupling reactions.

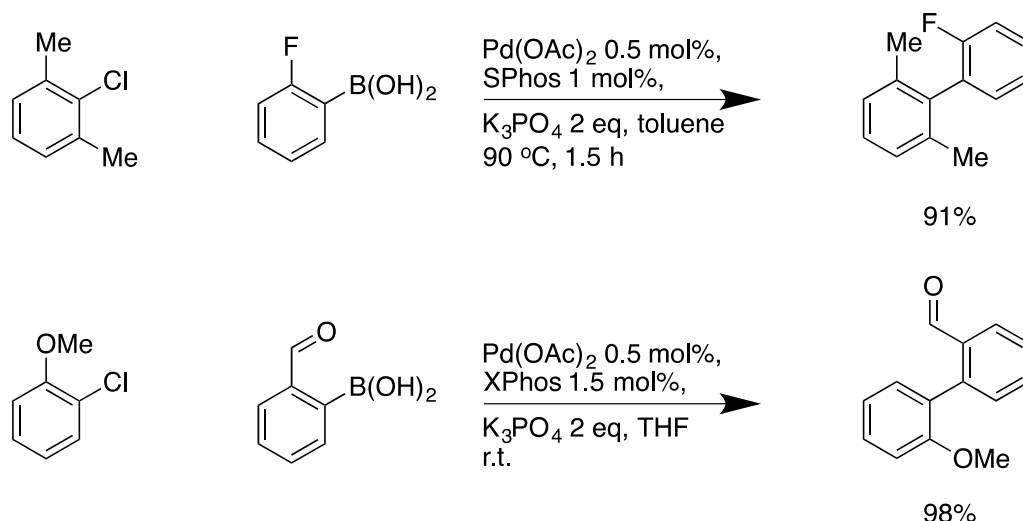
coupling, deprotection and purification cycles. Purification is enabled using a catch and



Scheme 4.3. Synthesis of a high-performance donor–acceptor dye for use in dye-sensitized solar cells, using iterative cross-couplings.

release method, the crude MIDA boronate is passed over silica gel and immobilised onto the gel with 1.5 % methanol in diethyl ether. The 1.5 % methanol in diethyl ether which is used to elute the remaining organic impurities and then THF is used to elute the purified MIDA boronate.

The bulk of early palladium cross-coupling reactions typically used triaryl phosphines as ligands. These ligands are used to aid the formation of the active Pd(0) catalyst during the reaction, from palladium sources such as palladium acetate. Since 1998 there has been a large amount of development in the field of ligands that facilitate cross-couplings with more difficult coupling partners i.e. aryl chlorides, with higher efficiency and selectivity.²⁰ Dialkylbiaryl phosphines, known as Buchwald ligands, are extensively used, examples of which included CyJohnPhos, SPhos, and XPhos Figure 4.1. Examples of the use of CyJohnPhos and SPhos are shown in Scheme 4.1 and Scheme 4.3. Buchwald showed examples of SPhos, and XPhos's high activity in the coupling aryl chlorides with catalyst loadings below 1 mol% (Scheme 4.4).²¹ In this publication they also outlined room temperature couplings with XPhos, but the duration of these reactions was not disclosed.



Scheme 4.4. Examples of the use of Buchwald ligands in Suzuki couplings.

Buchwald later introduced a second generation precatalysts Figure 4.1.²² The XPhos Pd G2 in the publication showed a very high yielding, 30 min coupling of aryl chlorides at room temperature with 2 mol % catalyst loading. The conditions were faster than the rate of protodeboronation of 2-heteroaryl boronic acids, and so facilitated the coupling of these sensitive compounds.

1,10-Bis(di-tert-butylphosphino) ferrocene palladium dichloride (Pd(dbpf)Cl₂, or Pd-118) is an air stable palladium precatalyst that is made up from a bidentate ferrocene containing phosphorus ligand, Figure 4.1. Colacot *et al* were the first to use Pd0118 in Suzuki couplings showing that aryl chlorides could be coupled with 1 mol% catalyst

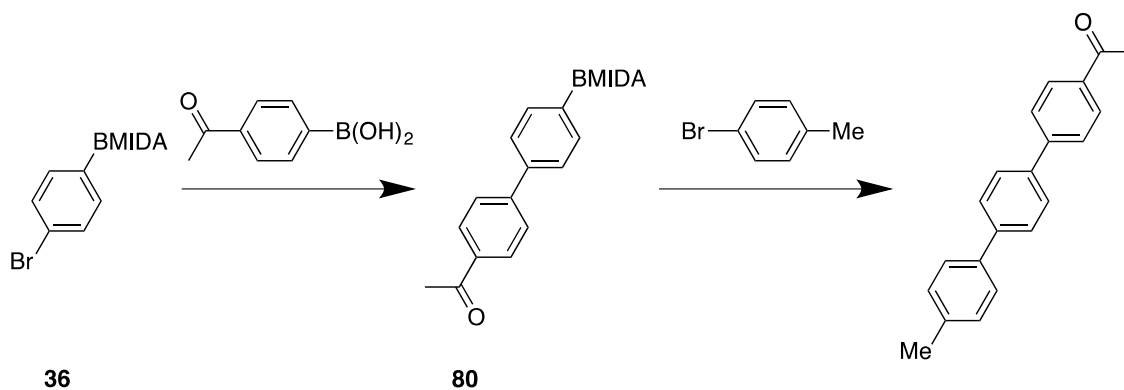
loading.²³ Moseley *et al* improved upon this work by demonstrating that this catalyst can couple sterically and electronically challenging aryl bromides, with 100% conversion showed by LCMS analysis after 2 hours, in acetonitrile and water at 60 °C.²⁴ They also found that these conditions could be used to couple aryl chlorides. The reaction times did increase to 24 hours but they showed that super-heating the reaction mixture to 120 °C reduced reaction times to two hours. Phosphorus containing ligands still are used the most, but closely followed by the use of *N*-heterocyclic carbenes.³

Organ *et al* first synthesized PEPPSI-IPr, which is a *N*-heterocyclic carbene palladium precatalyst that has shown use in Suzuki reactions.²⁵ This publication outlined the coupling of aryl chlorides that showed conversions as high as 97% at 60 °C in less than 2 hours in dioxane, with potassium carbonate. They also showed examples of room temperature coupling under these conditions but conversions dropped to 74%. They adopted the use of potassium *tert*-butoxide in isopropanol to regain conversion as high as 97%. All of the ligands and precatalysts that have been discussed have become commercially available.

Within this chapter the bromophenyl MIDA boronates synthesised in Chapter 3 will be used in anhydrous Suzuki cross-couplings followed by subsequent aqueous MIDA cleavage Suzuki reactions. This will be done with particular emphasise on using standard Schlenk line techniques.

4.3. Anhydrous Suzuki cross-couplings.

The aim of this chapter was to achieve iterative Suzuki cross-coupling reactions on the compounds synthesised via bromination in Chapter 3. The work had a particular emphasis on fast coupling methods that do not require the use of a glove box. The system that was

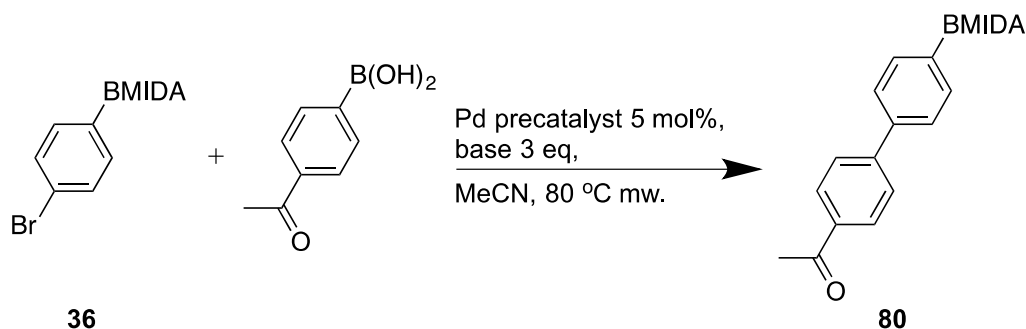


Scheme 4.5. System used for Suzuki coupling optimisation.

used to optimise the Suzuki cross-coupling is shown in Scheme 4.5. This was due to

having ready access to bromophenyl MIDA boronate, and its synthesis is quick and high yielding as outlined in Chapter 2. The final product in Scheme 4.5 is a known compound thus making its characterisation of the final product undemanding, enabling faster optimisation. Unlike Burke's work, outlined in Scheme 4.2, the electronics of the coupling partners in both steps were chosen to be electronically unattractive coupling partners *i.e.* an electron poor 4-acetylphenylboronic acid and electron-rich 4-bromotoluene. These more demanding cross coupling partners were chosen, as the final optimised conditions would be effective on a wider range of coupling partners.

Microwave heating was trialled to reduce reaction times, as this has shown positive results in a number of studies.^{26–29} A catalyst screen of commercially available precatalysts commenced. Percentage conversions were calculated by LCMS comparing the bromide peak (**36**) to product peak (**80**).

Table 4.1. Precatalysts microwave optimisation.

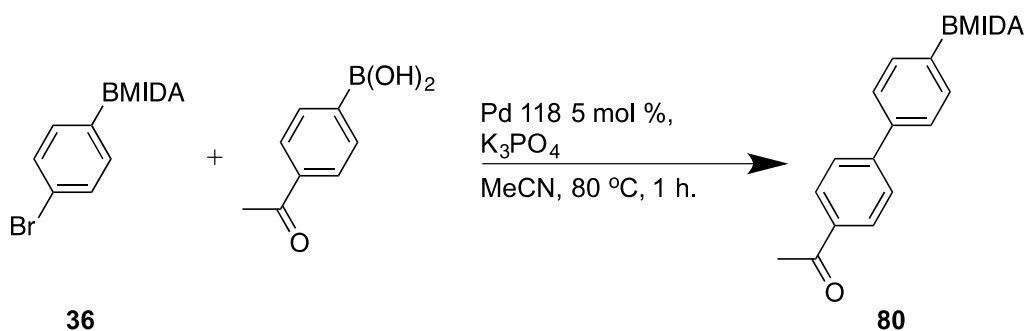
Entry	Catalyst	Base	Time (min)	Conversion (%) ^a
1	XPHOS Pd G2	K ₃ PO ₄	30	47
2	XPHOS Pd G2	K ₃ PO ₄	60	49
3	SPHOS Pd G2	K ₃ PO ₄	30	35
4	SPHOS Pd G2	K ₃ PO ₄	60	56
5	PEPPIS iPr	K ₃ PO ₄	30	33
6	PEPPSI-iPr	K ₃ PO ₄	60	40
7	Pd 118	K ₃ PO ₄	30	38
8	Pd 118	K ₃ PO ₄	60	61
9	Pd 118	KF	60	35
10	Pd 118	Cs ₂ CO ₃	60	50
11	Pd 118	MeONa	60	52

^a Calculated by LCMS. Reactions performed with the bromide (0.25 mmol, 78 mg), boronic acid (1.1 eq, 28 mmol, 45mg) all other solid components were added to a microwave vial sealed, degassed and purged with nitrogen then dry MeCN (1 mL) was added to the mixture.

Pd 118 showed the best conversions but the reaction never proceeded to completion. A theory as to why the reactions never reached completion was that due to the anhydrous nature of these reactions the inorganic bases formed a sediment at the bottom of the microwave vial, which disabled stirring of the reaction. As discussed in Chapter 2 stirring is key to uniform heating of the reaction mixture. In the absence of adequate stirring, temperatures within a microwave can differ up to 30 °C between the middle and outside of the vessel. Due to a lack of efficient stirring, hot spots can occur within the reaction mixture, which could cause the decomposition of the catalyst. Unfortunately, at the time this research was conducted, at AstraZeneca, the microwave camera, which could have

confirmed this hypothesis was not available but similar observations of sedimentation of low solubility materials were discussed in Chapter 2. Considering this, the best conditions from Table 4.1 were attempted using thermal heating, as the stirring could be monitored visually throughout the reaction, as in Table 4.2.

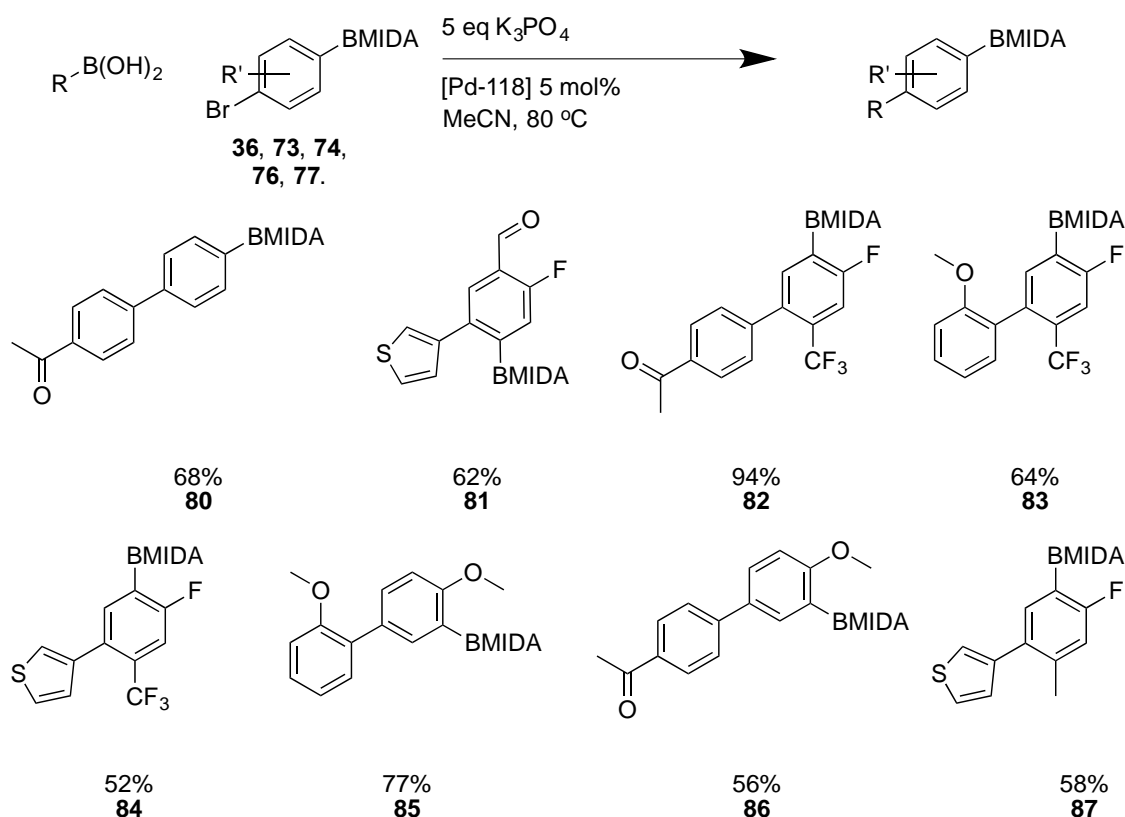
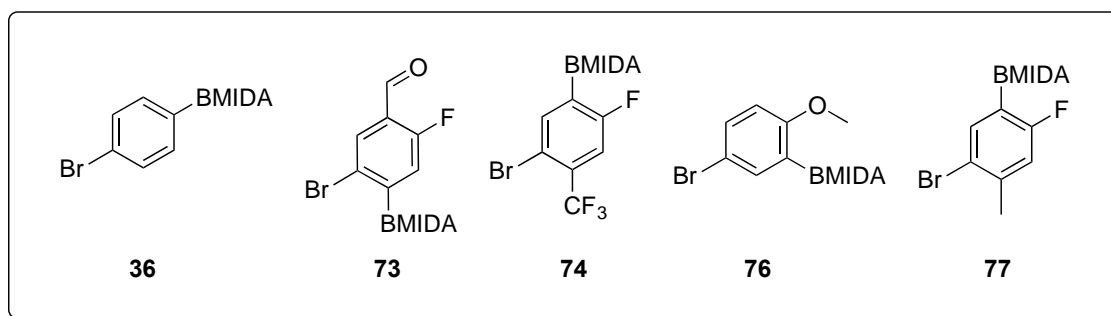
Table 4.2. Cross-couplings with Pd 118 using thermal heating.



Entry	Equivalents of base	Conversion (%) ^a
1	5	>99
2	3	97

Reactions done with the bromide (0.25 mmol, 78 mg), boronic acid (1.1eq, 0.28 mmol, 45mg) all other solid components were added reaction vessel, degassed and purging with nitrogen then dry MeCN (1 mL) was added to the mixture and stirred for 1h. ^a conversion calculated by LCMS.

Thermal heating led to higher conversion than microwave heating after 1 hour, comparing Table 4.1 entry 8 to Table 4.2 entry 2. Using 5 equivalents of base led to a slight improvement, showing no residual starting bromide. Scaling up this reaction gave a isolated yield of 68 % shown in Scheme 4.6, of **80**.



Scheme 4.6. Compounds synthesised via anhydrous Suzuki cross-couplings.

Using these conditions an array of different coupling partners were synthesised utilising the compounds formed via bromination in Chapter 3, with many based on a tetrasubstituted aromatic core.

The isolated yields varied from very good for example **82**, to satisfactory *i.e.* **84**. The conversions in these reactions had to be high, as the separation of two different MIDA boronate-containing species (starting material and product) proved problematic, as discussed in Chapter 3. Monitoring the loss of the bromide starting material via LCMS showed that conversions were high but the isolation of pure product proved difficult and this was reflected in the isolated yields. In most cases the trituration of product using ethyl acetate, with the addition of diethyl ether gave the pure compound, but some reactions

required Burke's catch and release method using 1.5 % methanol in diethyl ether to wash off by-products followed by THF to release the MIDA boronate.

Different boronic acid coupling partners were trialled in this study, shown in Figure 4.2.

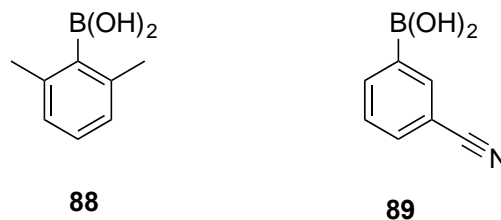


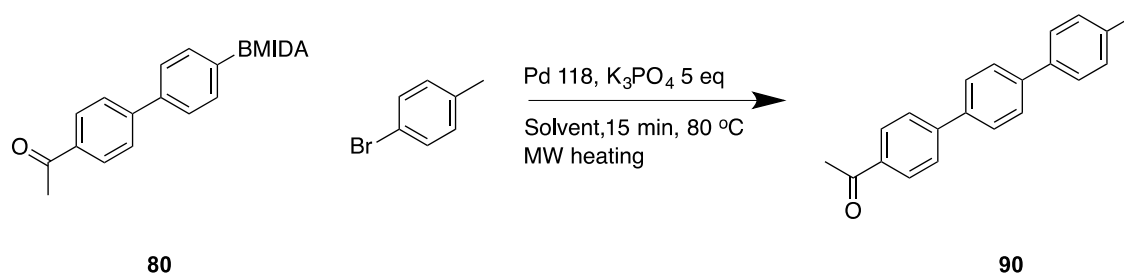
Figure 4.2 Boronic acid coupling partners that showed poor results under these conditions; left, 2,6-dimethylphenyl boronic acid; right, 3-cyanophenyl boronic acid.

2,6-Dimethylphenyl boronic acid (**88**) was used to test this coupling methodology with a sterically demanding substrate. This proved to be too sterically challenging as, no reaction was shown with either 2-bromo-5-fluoro-4-formylphenyl MIDA boronate (**73**) or 5-bromo-2-fluoro-4-trifluoromethylphenyl MIDA boronate (**74**) even after 24 h. LCMS showed no loss of either starting material or 2,6-dimethylphenyl boronic acid and no appearance of a new peak in either case. 3-Cyanophenyl boronic acid (**89**) showed no reaction with **73**, and only a small amount of conversion when used with **74** but this was only a minor product and could therefore not be isolated.

4.1. Deprotection Suzuki cross-couplings.

Microwave heating was used for the second aqueous coupling, with Pd-118, and potassium phosphate. A solvent optimization study for this second stage is shown in Table 4.3. The conversions of the different conditions were calculated via NMR spectra after using a hydrophobic phase separator to remove any inorganic impurities.

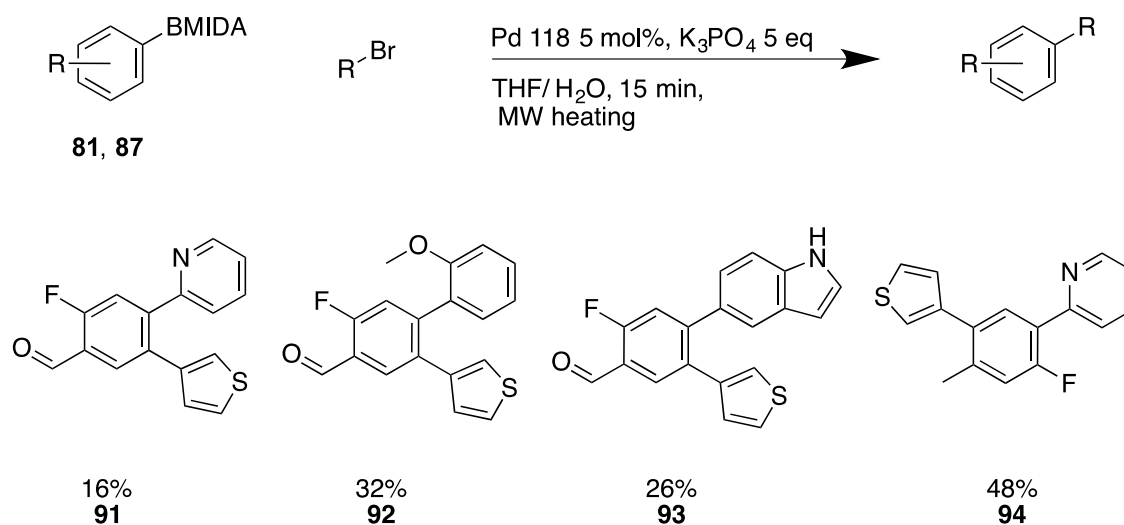
Table 4.3. Showing optimisation of aqueous Suzuki coupling.



Entry	Solvent	Catalyst loading (mol %)	Conversion (%) ^a
1	THF/H ₂ O	5	>99
2	MeCN/H ₂ O	5	70
3	Dioxane/H ₂ O	5	56
4	THF/H ₂ O	2.5	73

Reactions performed with the bromide (0.11 mmol, 18.8 mg), **1b** (0.1 mmol, 35 mg) all other solid components were Solid materials added to a 10 mL microwave vial, degassed and purging with nitrogen then degassed solvent was added to the reactions (0.5 mL organic solvent, 0.2 mL water) this was then heated at 80 °C for 15 min. ^a calculated via ¹H-NMR spectra.

Table 4.3 entry 1 showed the best results of the solvent systems trialled. Maintaining this solvent system but reducing catalyst loading as shown in entry 4, led to a lower conversion. These microwave conditions were used on some of the compounds synthesized by the anhydrous cross-coupling methodologies (shown in Scheme 4.6) with the resulting compounds shown in Scheme 4.7.



Scheme 4.7. Compounds synthesised via aqueous coupling cross-conditions

The low yields shown in Scheme 4.7 were of concern, in comparison to the conversions in Table 4.3. Due to the time constraints of this project, an investigation into this could not proceed. Reflecting on this work, the acetyl-containing compound **80** may have not been the best candidate for use in optimisation even though it produced a known compound. A better candidate for optimisation would have included its corresponding formyl derivative due to observations by Moseley *et al*, that a formyl functionality can increase the reaction duration.²⁴ Also the increased steric bulk around the bond around the MIDA boronate in **81** and **87** in Scheme 4.7, *i.e.* thiophene could have made these couplings more troublesome.

This methodology led to a 15 min microwave-mediated, deprotection and cross-coupling method from which we synthesized four novel final compounds. This highlights that this approach is applicable for masking a boronic acid, to enable a late stage Suzuki reaction. In a medicinal chemistry context a small library has been formed and compounds are available to test for bioactivity.

4.4. Conclusion

Examples of iterative Suzuki cross-couplings were found, illustrating the potential of some of the tetrasubstituted aromatic compounds synthesised in Chapter 3. The iterative cross-couplings validate that these compounds contain orthogonal groups, meeting the original project aims. Following Chapter 2 through to the current chapter, demonstrates how complex polyaromatics with tetrasubstituted cores can be synthesised in a simple four-step procedure *i.e.* MIDA protection, bromination, anhydrous cross-coupling and aqueous cross-coupling. This was done using inexpensive reagents starting from commercially available trisubstituted boronic acids and the procedure was partially automated via the use of a robotic microwave unit. Due to the nature of the first anhydrous cross-coupling, it could not be applied to a microwave heating reaction format, as stirring could not be initiated.

The Suzuki cross-coupling reactions, both anhydrous and aqueous, suffered from low yields, particularly the latter. In the case of the anhydrous cross-coupling, purification created difficulties, since isolating pure product led to low yields, even though observed conversions were high by analysis of LCMS data. These reactions were quicker than the examples reported in Xu's or Burke's work in the introduction of this chapter.^{6,17}

The aqueous cross-coupling required further study to optimise yields in the reactions with tetrasubstituted compounds. Unfortunately the time constraints of this project became too tight to finalise this study; this would be of high priority if this project were to continue.

4.5. Experimental

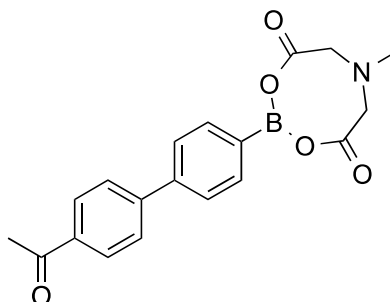
Solvents and reagents were purchased from commercial suppliers and used without further purification. NMR spectra were recorded on a Varian 500 MHz or 400 MHz spectrometer. Chemical shifts are reported in ppm and are referenced to the residual solvent peak or to TMS used as an internal standard; note that in some cases the carbon bonded to the boron is not detectable in the ^{13}C NMR.²⁷ LCMSs were ran on a Shimadzu LCMS-2020 equipped with a Gemini® 5 μm C18 110 Å column. Percentage purities were performed using a 30 minutes method in water/acetonitrile with 0.1% Formic acid (5min at 5%, 5%-95% over 20 min, 5min at 95%) with the UV set to 254 nm. High resolution mass spectrometry (HRMS) was done either internally or by the National Mass Spectrometry Facility, Swansea University. A number of the products described below are commercially available or known, e.g. in patents. In these cases, ^1H , ^{13}C , HRMS and % purity data are presented since in many cases these data are not published. For compounds that appear to be novel, more analytical data are presented including ^{11}B NMR.

General procedure for anhydrous Suzuki cross-couplings on a 1 mmol scale.

A bromophenyl MIDA boronate (1 mmol), potassium phosphate (5 mmol, 1.06 g), Pd 118 (5 mol %, 33 mg) and an aromatic boronic acid (1.1 mmol) were loaded into a reaction tube and sealed. This mixture was placed under vacuum and purged with argon 3 times. Then dry degassed acetonitrile (5 mL) was added to this mixture to form a yellow suspension, this stirred mixture was then heated to 80 °C and monitored via LCMS. After completion of the reaction the mixture was cooled filtered through a pad of celite, which was then washed through with dry acetonitrile (40 mL). The combined filtrates were then evaporated under reduced pressure to yield crude product.

Specific examples of purification are given below.

4'-Acetyl-[1,1'-biphenyl]-4-yl MIDA boronate, 80.



The reaction was followed by LCMS and after 1h 50 min it had gone to completion. The crude material was triturated with ethyl acetate, and then this solid was washed with 5 mL of cold ethyl acetate, to give the title compound as a light brown powder.

Yield: 231 mg (68 %).

(TOFMS EI⁺) found 350.1193, calcd for [C₁₉H₁₇¹¹BNO₅]⁻ 350.1200.

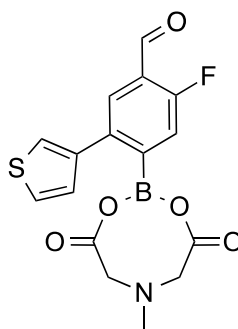
¹H NMR (400 MHz, DMSO-D₆) δ 8.04 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 4.37 (d, *J* = 17.0 Hz, 2H), 4.15 (d, *J* = 17.0 Hz, 2H), 2.61 (s, 3H), 2.57 (s, 3H).

¹³C NMR (101 MHz, DMSO-D₃) δ 197.4, 169.2, 144.4, 139.1, 135.6, 133.1, 128.8, 126.7, 126.1, 61.8, 47.6, 26.7.

¹¹B NMR (128 MHz, Acetonitrile-D₃) δ 11.21.

LCMS purity 95% (UV), Ret. time = 16.59 min.

5-Fluoro-4-formyl-2-(thiophen-3-yl)phenyl MIDA boronate, 81.



The reaction was followed by LCMS and after 12 hours it had gone to completion. The crude material was triturated with ethyl acetate, and then this solid was then washed with

5 mL of cold ethyl acetate. This was then absorbed on to silica and loaded onto a silica column washed with a solution of 1.5 % methanol in diethyl ether. The compound was then eluted with 100 % THF, then evaporated to give the title compound.

Yield: 223 mg (62 %).

^1H NMR (500 MHz, Acetonitrile- D_3) δ 10.32 (s, 1H), 7.65 (d, $^3J_{\text{FH}} = 12.0$ Hz, 1H), 7.61 (d, $^4J_{\text{FH}} = 7.0$ Hz, 1H), 7.45 (dd, $J = 5.0, 3.0$ Hz, 1H), 7.34 (dd, $J = 3.0, 1.5$ Hz, 1H), 7.11 (dd, $J = 5.0, 1.5$ Hz, 1H), 3.88 (d, $J = 17.0$ Hz, 2H), 3.39 (d, $J = 17.0$ Hz, 2H), 2.54 (s, 3H).

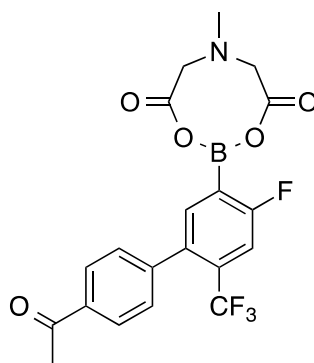
^{13}C NMR (126 MHz, Acetonitrile- D_3) δ 187.56 (d, $^3J_{\text{FC}} = 5.0$ Hz), 167.6, 162.7 (d, $^1J_{\text{FC}} = 258.0$ Hz), 141.5, 139.0 (d, $^4J_{\text{FC}} = 4.0$ Hz), 131.5, 130.0, 125.8, 124.5, 123.8 (d, $^3J_{\text{FC}} = 9.0$ Hz), 122.2 (d, $^4J_{\text{FC}} = 20.0$ Hz), 62.8, 47.8.

^{19}F NMR (376 MHz, Acetonitrile- D_3) δ -125.61 (dd, $J = 12.0, 7.0$ Hz).

^{11}B NMR (128 MHz, Acetonitrile- D_3) δ 10.84.

LCMS purity 90% (UV), Ret. time = 16.65 min.

4'-Acetyl-4-fluoro-6-(trifluoromethyl)-[1,1'-biphenyl]-3-yl MIDA boronate, 82.



The reaction was followed by LCMS and after 2 hours the reaction had gone to completion. The crude material was absorbed on to silica immobilizing it and then loaded onto a silica column. This was washed with 1.5 % methanol in diethyl ether and then the compound was then eluted with 100 % THF, then evaporated to give the title compound as a light brown solid.

Yield: 411 mg (94 %).

FTMS APCI (m/z) found 436.0977, calcd for $[\text{C}_{20}\text{H}_{15}\text{BF}_4\text{NO}_5]^-$ 436.0985.

^1H NMR (500 MHz, Acetonitrile- D_3) δ 8.08 – 8.02 (m, 2H), 7.59 – 7.54 (m, 2H), 7.53 – 7.48 (m, 2H), 4.20 (d, J = 17.0 Hz, 2H), 4.02 (d, J = 17.0 Hz, 2H), 2.75 (s, 3H), 2.64 (s, 3H).

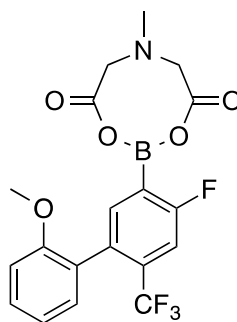
^{13}C NMR (100 MHz, Acetonitrile- D_3) δ 198.6, 169.0, 166.0 (d, $^1J_{\text{FC}}$ 243.0 Hz), 144.7, 139.9 (d, $^3J_{\text{FC}}$ = 9.5 Hz), 137.6, 136.9 (dd, $^3J_{\text{FC}}$ = 4.0, $^4J_{\text{FC}}$ = 2.0 Hz), 131.5 (dd, $^2J_{\text{FC}}$ = 31.1, $^3J_{\text{FC}}$ = 9.0 Hz), 130.5 (d, $^5J_{\text{FC}}$ = 1.0 Hz), 128.9, 124.5 (dd, $^1J_{\text{FC}}$ = 273.5, $^4J_{\text{FC}}$ = 2.5 Hz), 114.4 (dq, $^2J_{\text{FC}}$ = 30.0, $^3J_{\text{FC}}$ = 5.5 Hz), 63.8, 48.7, 27.1.

^{19}F NMR (376 MHz, Acetonitrile- D_3) δ -57.91 (s), -107.07 – -107.16 (m).

^{11}B NMR (128 MHz, Acetonitrile- D_3) δ 10.72.

LCMS purity 94 % (UV), Ret. time = 18.50 min.

4-Fluoro-2'-methoxy-6-(trifluoromethyl)-[1,1'-biphenyl]-3-yl MIDA boronate, 83.



The reaction was done on a 0.86 mmol scale of **3c** and had gone to completion after 2 hours. The crude material was absorbed on to silica immobilizing it and then loaded onto a silica column. This was washed with 1.5% methanol in diethyl ether and then the compound was then eluted off the column with 100% ethyl acetate, then was evaporated to give the title compound as a light white solid.

Yield: 234 mg (64%).

(TOFMS EI^+) found 448.0942, calcd for $[\text{C}_{19}\text{H}_{16}^{11}\text{BNO}_5\text{F}_4\text{Na}]^+$ 448.0942.

^1H NMR (500 MHz, Acetonitrile- D_3) δ 7.44 (d, $^4J_{\text{FH}}$ = 6.5 Hz, 1H), 7.37 (d, $^3J_{\text{FH}}$ = 10.0 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.05 – 7.02 (m, 1H), 6.98 – 6.95 (m, 1H), 6.91 – 6.85 (m, 1H), 4.36 (d, J = 17.0 Hz, 2H), 4.11 (d, J = 17.0 Hz, 2H), 3.61 (s, 3H), 2.88 (s, 3H).

^{13}C NMR (126 MHz, Acetonitrile- D_3) δ 167.6, 164.6 (d, $^1J_{\text{FC}}$ = 242.5 Hz), 157.0, 139.5 (d, $^3J_{\text{FC}}$ = 9.5 Hz), 133.4, 131.4 (dd, $^2J_{\text{FC}}$ = 31.0, $^3J_{\text{FC}}$ = 9.0 Hz), 130.5, 129.5, 127.6, 123.4

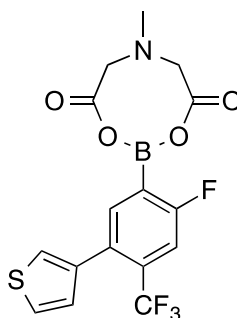
(dd, $^1J_{\text{FC}} = 274.0$, $^4J_{\text{FC}} = 2.0$ Hz), 119.6, 112.6 (dq, $^2J_{\text{FC}} = 29.5$, $^3J_{\text{FC}} = 5.5$ Hz), 110.7, 62.7, 54.8, 47.5.

^{19}F NMR (376 MHz, Acetonitrile- D_3) δ -60.32, -107.91 (dd, $^3J_{\text{FH}} = 10.0$, $^4J_{\text{FH}} = 6.5$ Hz).

^{11}B NMR (128 MHz, Acetonitrile- D_3) δ 10.80.

LCMS purity >99% (UV), Ret. time = 19.23 min.

2-Fluoro-5-(thiophen-3-yl)-4-(trifluoromethyl)phenyl MIDA boronate, 84.



The reaction was followed by LCMS and, after 1 hour, had gone to completion. The crude material was triturated with ethyl acetate, and then this solid was then washed with 2.5 mL of cold ethyl acetate, to give the title compound as a white solid.

Yield: 105 mg (52%).

(TOFMS EI⁺) found 402.0590, calcd for $[\text{C}_{16}\text{H}_{13}^{11}\text{BNO}_4\text{F}_4\text{S}]^+$ 402.0594.

^1H NMR (399 MHz, Acetonitrile- D_3) δ 7.60 (d, $^4J_{\text{FH}} = 6.5$ Hz, 1H), 7.51 (d, $^3J_{\text{FH}} = 10.0$ Hz, 1H), 7.48 (dd, $^3J_{\text{HH}} = 5.0$, $^4J_{\text{HH}} = 3.0$ Hz, 1H), 7.41 (d, $^4J_{\text{FH}} = 3.0$ Hz, 1H), 7.18 (d, $^3J_{\text{HH}} = 5.0$ Hz, 1H), 4.16 (d, $J = 17.0$ Hz, 2H), 3.98 (d, $J = 17.0$ Hz, 2H), 2.71 (s, 3H)

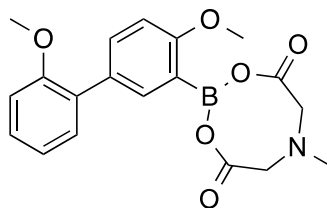
^{13}C NMR (100 MHz, Acetonitrile- D_3) δ 169.0, 165.7 (d, $^1J_{\text{FC}} = 243.0$ Hz), 140.3 (d, $^3J_{\text{FC}} = 9.5$ Hz), 139.6, 133.0 – 132.8 (m), 131.6 (qd, $^2J_{\text{FC}} = 31.0$, $^3J_{\text{FC}} = 9.0$ Hz), 130.1 (d, $^6J_{\text{FC}} = 2.0$ Hz), 126.5, 125.31 (d, $^5J_{\text{FC}} = 2.0$ Hz), 124.5 (dd, $^1J_{\text{FC}} = 273.0$, $^4J_{\text{FC}} = 3.0$ Hz), 114.4 (dq, $^2J_{\text{FC}} = 30.0$, $^3J_{\text{FC}} = 5.5$ Hz), 63.8, 48.7.

^{19}F NMR (376 MHz, Acetonitrile- D_3) δ -58.84 (s), -107.68 (dd, $^3J_{\text{FH}} = 10.0$, $^4J_{\text{FH}} = 6.5$ Hz).

^{11}B NMR (128 MHz, Acetonitrile- d_3) δ 10.81.

LCMS purity > 99% (UV), Ret. time = 19.39 min.

2',4-Dimethoxy-[1,1'-biphenyl]-3-yl MIDA boronate, 85.



The reaction was followed by LCMS and after 2 hours, had gone to completion. The crude material was triturated with ethyl acetate, and then this solid was washed with 5 mL of cold ethyl acetate, to give the title compound as a white solid.

Yield: 285 mg (56%).

(TOFMS EI⁺) found 408.1028, calcd for [C₂₀H₂₀¹¹BNO₆K]⁺ 408.1021

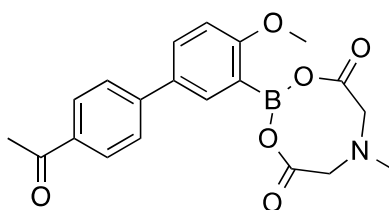
¹H NMR (600 MHz, Acetonitrile-D₃) δ 7.66 (s, 1H), 7.61 – 7.55 (m, 1H), 7.36 – 7.29 (m, 2H), 7.11 – 6.97 (m, 3H), 4.10 (d, J = 17.0 Hz, 2H), 3.99 (d, J = 17.0 Hz, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 2.68 (s, 3H).

¹³C NMR (100 MHz, Acetonitrile-d₃) δ 168.7, 161.5, 156.5, 135.5, 132.0, 130.7, 130.4, 128.3, 120.8, 111.6, 109.8, 63.5, 55.2, 54.8, 47.3.

¹¹B NMR (128 MHz, Acetonitrile-D₃) δ 11.95.

LCMS purity >99% (UV), Ret. time = 17.69 min.

4'-Acetyl-4-methoxy-[1,1'-biphenyl]-3-yl MIDA boronate, 86.



The reaction was followed by LCMS and after 2 hours, had gone to completion. The crude material was triturated with ethyl acetate, and then this solid was then washed with 5 mL of cold ethyl acetate, to give the title compound as a white solid.

Yield: 214 mg (56%).

(FTMS m/z) found 380.1307, calcd for [C₂₀H₁₉BNO₆]⁻ 380.1311.

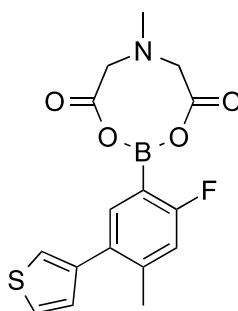
^1H NMR (500 MHz, Acetonitrile- D_3) δ 8.06 – 8.00 (m, 2H), 7.92 – 7.89 (m, 1H), 7.79 – 7.73 (m, 3H), 7.10 – 7.06 (m, 1H), 4.10 (d, J = 17.0 Hz, 2H), 3.99 (d, J = 17.0 Hz, 2H), 3.83 (s, 3H), 2.67 (s, 3H), 2.59 (s, 3H).

^{13}C NMR (126 MHz, Acetonitrile- D_3) δ 198.5, 169.7, 163.9, 146.3, 136.5, 134.4, 130.8, 129.9, 127.5, 111.9, 111.0, 64.6, 56.0, 48.4, 27.0.

^{11}B NMR (128 MHz, Acetonitrile- D_3) δ 12.00.

LCMS purity > 99% (UV), Ret. time = 16.46 min.

2-Fluoro-4-methyl-5-(thiophen-3-yl)phenyl MIDA boronate, 87.



This was followed by LCMS and after 30 minutes the reaction had gone to completion. The crude material was triturated with ethyl acetate, and then this solid was then washed with 5 mL of cold ethyl acetate, to give the title compound as a yellow solid.

Yield: 202 mg (56%).

(TOFMS EI^+) found 347.0792, calcd for $[\text{C}_{16}\text{H}_{15}^{11}\text{BNO}_4\text{FS}]^+$ 347.0799.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.62 (dd, J = 5.0, 3.0 Hz, 1H), 7.51 (dd, J = 3.0, 1.5 Hz, 1H), 7.36 (d, $^4J_{\text{FH}}$ = 7.0 Hz, 1H), 7.23 (dd, J = 5.0, 1.5 Hz, 1H), 7.07 (d, $^3J_{\text{FH}}$ = 11.0 Hz, 1H), 4.39 (d, J = 17.5 Hz, 2H), 4.08 (d, J = 17.5 Hz, 2H), 2.66 (s, 3H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 168.9, 164.5 (d, $^1J_{\text{FC}}$ = 241.5 Hz), 140.7, 139.2 (d, $^3J_{\text{FC}}$ = 9.0 Hz), 135.8 (d, $^2J_{\text{FC}}$ = 10.0 Hz), 132.0 (d, $^4J_{\text{FC}}$ = 3.0 Hz), 128.9, 125.8, 123.1, 116.5 (d, $^2J_{\text{FC}}$ = 25.0 Hz), 62.3, 47.6, 20.3.

^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -109.15 – -109.25 (m).

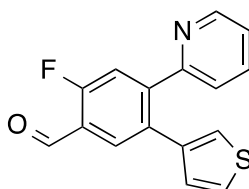
^{11}B NMR (128 MHz, $\text{DMSO-}d_6$) δ 10.59.

LCMS purity >99% (UV), Ret. time = 18.52 min.

General procedure for one-pot MIDA deprotection Suzuki cross-couplings.

The phenyl MIDA analogue (0.20 mmol), aryl bromide (0.22 mmol), potassium phosphate (1.00 mmol, 212 mg) and Pd-118 (0.004 mmol, 6.5 mg) were added to a 10mL microwave vial equipped with a magnetic stirrer and a Teflon cap. Then this mixture was placed under vacuum and purged with argon 3 times. Next, dry degassed THF (1 mL), followed by degassed water (0.4 mL) were added to this mixture to form a yellow solution. This reaction mixture was heated using the dynamic heating method, with the power set to 150 W, max pressure 300 psi, max temperature 80 °C, high stirring throughout and power max turned off. This method was used to hold the reaction mixture at 80 °C for 15 min. After cooling, sodium hydroxide solution was added (5 mL, 2 M), this aqueous phase was then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), and then dried with MgSO₄ and evaporated under reduced pressure. This crude material was then absorbed on to silica and purified by flash chromatography. Specific examples of flash chromatography mobile phases are given below.

2-Fluoro-4-(pyridin-2-yl)-5-(thiophen-3-yl)benzaldehyde, 91.



This was purified by flash chromatography on silica gel on a gradient of 0-20 % ethyl acetate in hexane.

Yield: 9 mg (16%).

(TOFMS EI⁺) found 284.0551, calcd for [C₁₆H₁₁NOFS]⁺ 284.0545.

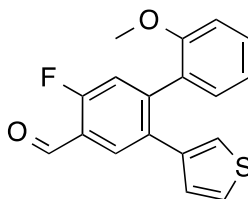
¹H NMR (500 MHz, Acetone-D₆) δ 10.39 (s, 1H), 8.68 – 8.64 (m, 1H), 7.94 (d, ⁴J_{FH} = 7.0 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.57 (d, ³J_{FH} = 11.5 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.36 – 7.32 (m, 1H), 7.32 – 7.30 (m, 1H), 7.16 – 7.10 (m, 1H), 6.78 – 6.73 (m, 1H).

¹³C NMR (126 MHz, Acetone-D₆) δ 186.4 (d, ³J_{FC} = 5.0 Hz), 162.9 (d, ¹J_{FC} = 258.0 Hz), 156.7, 149.7, 147.3 (d, ²J_{FC} = 8.5 Hz), 139.7, 135.9, 132.4 (d, ³J_{FC} = 3.5 Hz), 130.7 (d, ³J_{FC} = 2.5 Hz), 128.5, 125.7, 124.5, 123.8, 122.9, 118.3 (d, ²J_{FC} = 22.0 Hz).

¹⁹F NMR (376 MHz, Benzene-D₆) δ -120.15 (dd, ³J_{FH} = 11.5, ⁴J_{FH} = 7.0 Hz).

LCMS purity >99% (UV), Ret. time = 19.75 min.

5-Fluoro-2'-methoxy-2-(thiophen-3-yl)-[1,1'-biphenyl]-4-carbaldehyde, 92.



This was purified by flash chromatography on silica gel on a gradient of 0-3 % diethyl ether in hexane.

Yield: 20 mg (32%).

(FTMS m/z) found 313.0690, calcd for $[C_{18}H_{13}FO_2SH]^+$ 313.0693.

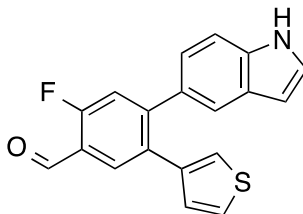
1H NMR (500 MHz, Chloroform- D) δ 10.41 (s, 1H), 7.96 (d, $^4J_{FH} = 7.0$ Hz, 1H), 7.36 – 7.29 (m, 1H), 7.18 (d, $^3J_{FH} = 11.0$ Hz, 1H), 7.18 – 7.11 (m, 1H), 7.13 – 7.10 (m, 1H), 7.00 – 6.95 (m, 1H), 6.94 – 6.89 (m, 1H), 6.84 – 6.78 (m, 1H), 6.78 – 6.75 (m, 1H), 3.46 (s, 3H).

^{13}C NMR (126 MHz, Chloroform- D) δ 186.8 (d, $^3J_{FC} = 6.0$ Hz), 163.3 (d, $^1J_{FC} = 259.0$ Hz), 156.1, 146.1 (d, $^2J_{FC} = 9.0$ Hz), 140.2, 133.5 (d, $^3J_{FC} = 3.5$ Hz), 130.6, 129.9, 129.1 (d, $^4J_{FC} = 2.5$ Hz), 128.7, 128.0, 124.5, 122.9 (d, $^3J_{FC} = 8.5$ Hz), 122.6, 120.7, 118.9 (d, $^2J_{FC} = 21.0$ Hz), 111.1, 55.2.

^{19}F NMR (376 MHz, Chloroform- D) δ -125.16 (dd, $^3J_{FH} = 11.0$, $^4J_{FH} = 7.0$ Hz).

LCMS purity >99% (UV), Ret. time = 23.46 min.

2-Fluoro-4-(1H-indol-5-yl)-5-(thiophen-3-yl)benzaldehyde, 93.



This was purified by flash chromatography on silica gel on a gradient of 0-10% DCM in hexane.

Yield: 17 mg (26%).

(TOFMS EI^+) found 344.0505, calcd for $[C_{19}H_{12}NOFSNa]^+$ 344.0521.

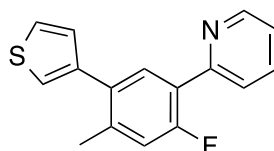
^1H NMR (500 MHz, Acetone- D_6) δ 10.36 (s, 1H), 10.35 (bs, 1H), 7.93 (d, $^4J_{\text{FH}} = 7.0$ Hz, 1H), 7.55 – 7.52 (m, 1H), 7.39 – 7.33 (m, 3H), 7.31 – 7.27 (m, 1H), 7.26 – 7.21 (m, 1H), 6.95 – 6.90 (m, 1H), 6.71 – 6.67 (m, 1H), 6.49 – 6.45 (m, 1H).

^{13}C NMR (126 MHz, Acetone- D_6) δ 187.3 (d, $^3J_{\text{FC}} = 5.0$ Hz), 163.8 (d, $^1J_{\text{FC}} = 258.0$ Hz), 151.5 (d, $^2J_{\text{FC}} = 9.0$ Hz), 141.5, 137.0, 133.4 (d, $^3J_{\text{FC}} = 3.5$ Hz), 131.5, 131.3 (d, $^4J_{\text{FC}} = 2.5$ Hz), 129.6, 129.2, 127.0, 126.0, 124.4, 123.6, 123.4 (d, $^3J_{\text{FC}} = 9.0$ Hz), 122.1, 119.4 (d, $^2J_{\text{FC}} = 21.0$ Hz), 112.0, 103.0.

^{19}F NMR (376 MHz, Acetone- D_6) δ -125.64 (dd, $^3J_{\text{FH}} = 11.5$, $^4J_{\text{FH}} = 7.0$ Hz).

LCMS purity 96% (UV), Ret. time = 17.28 min.

2-(2-Fluoro-4-methyl-5-(thiophen-3-yl)phenyl)pyridine, **94**.



This was purified by flash chromatography on silica gel, 10% ethyl acetate in hexane.

Yield: 26 mg (48%).

TLC (hexane 90%: ethyl acetate, 10%) $R_f = 0.48$.

(TOFMS EI^+) found 270.0748, calcd for $[\text{C}_{16}\text{H}_{13}\text{NFS}]^+$ 270.0753.

^1H NMR (500 MHz, Acetone- D_6) δ 8.70 – 8.67 (m, 1H), 8.02 (d, $^3J_{\text{FH}} = 8.5$ Hz, 1H), 7.88 – 7.85 (m, 2H), 7.57 (dd, $J = 5.0, 3.0$ Hz, 1H), 7.47 (d, $J = 3.0$ Hz, 1H), 7.36 – 7.32 (m, 1H), 7.26 (dd, $J = 5.0, 1.5$ Hz, 1H), 7.18 (d, $^4J_{\text{FH}} = 12.5$ Hz, 1H), 2.39 (s, 3H).

^{13}C NMR (126 MHz, Acetone- D_6) δ 160.4 (d, $^1J_{\text{FC}} = 248.5$ Hz), 153.8 (d, $^3J_{\text{FC}} = 3.5$ Hz), 150.7, 141.9, 139.9 (d, $^3J_{\text{FC}} = 8.5$ Hz), 137.4, 134.2 (d, $^4J_{\text{FC}} = 3.5$ Hz), 132.9 (d, $^3J_{\text{FC}} = 3.5$ Hz), 129.7, 126.4, 125.6 (d, $^2J_{\text{FC}} = 12.0$ Hz), 124.9 (d, $^4J_{\text{FC}} = 10.0$ Hz), 124.0, 123.4, 118.6 (d, $^2J_{\text{FC}} = 23.5$ Hz), 20.7.

^{19}F NMR (376 MHz, Acetone- D_6) δ -121.13 (dd, $^3J_{\text{FH}} = 12.5$, $^3J_{\text{FH}} = 8.5$ Hz).

LCMS purity >99% (UV), Ret. time = 22.27 min.

4.2. Bibliography

- (1) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440.
- (2) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866–867.
- (3) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chemie - Int. Ed.* **2012**, *51*, 5062–5085.
- (4) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443–3447.
- (5) Mancilla, T.; Contreras, R.; Wrackmeyer, B. *J. Organomet. Chem.* **1986**, *307*, 4–6.
- (6) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717.
- (7) Grob, J. E.; Dechantsreiter, M. A.; Tichkule, R. B.; Connolly, M. K.; Honda, A.; Tomlinson, R. C.; Hamann, L. G. *Org. Lett.* **2012**, *14*, 5578–5581.
- (8) Colgin, N.; Flinn, T.; Cobb, S. L. *Org. Biomol. Chem.* **2011**, *9*, 1864–1870.
- (9) Chan, J. M. W.; Amarante, G. W.; Toste, F. D. *Tetrahedron* **2011**, *67*, 4306–4312.
- (10) Burns, A. R.; McAllister, G. D.; Shanahan, S. E.; Taylor, R. J. K. *Angew. Chemie Int. Ed.* **2010**, *49*, 5574–5577.
- (11) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466–468.
- (12) Woerly, E. M.; Struble, J. R.; Palyam, N.; O'Hara, S. P.; Burke, M. D. *Tetrahedron* **2011**, *67*, 4333–4343.
- (13) Burke, M.; Gillis, E.; Lee, S. System for Controlling the Reactivity of Boronic Acids. *Espacenet*, 2011, 1–26.
- (14) Bryan, M. C.; Dillon, B.; Hamann, L. G.; Hughes, G. J.; Kopach, M. E.; Peterson, E. A.; Pourashraf, M.; Raheem, I.; Richardson, P.; Richter, D.; Sneddon, H. F. *J. Med. Chem.* **2013**, *56*, 6007–6021.
- (15) Miguez, J. M. A.; Adrio, L. A.; Sousa-Pedrares, A.; Vila, J. M.; Hii, K. K. M.; Kuok, K.; Hii, M. *J. Org. Chem.* **2007**, *72*, 7771–7774.
- (16) Xu, L.; Ding, S.; Li, P. *Angew. Chemie Int. Ed.* **2014**, *53*, 1822–1826.
- (17) Chang, Y. J.; Chow, T. J. *Tetrahedron* **2009**, *65*, 9626–9632.
- (18) Li, J.; Grillo, A. S.; Burke, M. D. *Acc. Chem. Res.* **2015**, *48*, 2297–2307.
- (19) Li, J.; Ballmer, S. G.; Gillis, E. P.; Fujii, S.; Schmidt, M. J.; Palazzolo, A. M. E.; Lehmann, J. W.; Morehouse, G. F.; Burke, M. D. *Science (80-.)*. **2015**, *347*, 1221–1226.
- (20) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.
- (21) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
- (22) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073–14075.
- (23) Colacot, T. J.; Shea, H. a. *Org. Lett.* **2004**, *6*, 3731–3734.

- (24) Moseley, J. D.; Murray, P. M.; Turp, E. R.; Tyler, S. N. G.; Burn, R. T. *Tetrahedron* **2012**, 68, 6010–6017.
- (25) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. a.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. - A Eur. J.* **2006**, 12, 4743–4748.
- (26) Nun, P.; Martinez, J.; Lamaty, F. *Synlett* **2009**, 2009, 1761–1764.
- (27) Spencer, J.; Baltus, C. B.; Patel, H.; Press, N. J.; Callear, S. K.; Male, L.; Coles, S. J. *ACS Comb. Sci.* **2011**, 13, 24–31.
- (28) Namboodiri, V. V.; Varma, R. S. *Green Chem.* **2001**, 3, 146–148.
- (29) Spencer, J.; Baltus, C. B.; Press, N. J.; Harrington, R. W.; Clegg, W. *Tetrahedron Lett.* **2011**, 52, 3963–3968.

5. Library generation towards potential kinase inhibitors

5.1. Overview

The focus of this chapter was to evaluate the potential for forming bioactive molecules from the bromofluoronitrobenzaldehydes synthesised via nitration in Chapter 3 (Figure 5.1). To showcase the orthogonal behaviour of the different functional groups in compounds **59**, **61**, and **63** they were elaborated via Pd-catalysed coupling, reduction and reductive amination reactions. As a test of hypothesis these compounds were converted into EGFR inhibitors related to Gefitinib.

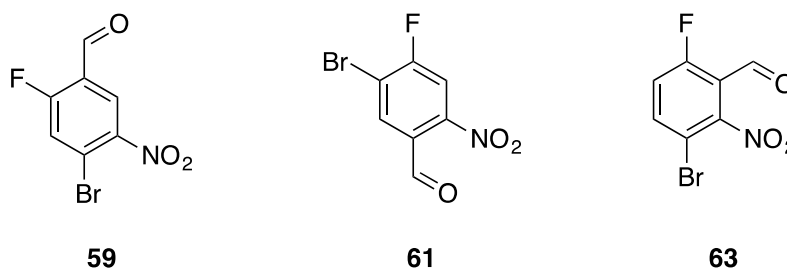


Figure 5.1. Compounds prepared via nitration.

5.2. Introduction

During the synthesis of compounds **59**, **61**, and **63** it was noted that they had potential for transformations towards potential kinase inhibitors. A larger review of the action and types of kinase inhibitors can be found in the introduction (Chapter 1). Figure 5.2 shows 5 examples of different EGFR kinase inhibitors.¹⁻⁴ The aromatic moieties highlighted in blue show some of the functionality incorporated into these molecules. In the case of the compounds synthesised in Chapter 3, these contain complementary functionalities *e.g.* halogens and nitro groups. Vandetanib (Figure 5.2) is an example where bromides can be incorporated into this family of molecules. Also, one of the early lead compounds in the development of Gefitinib contained a bromo group (Chapter 1 Figure 1.6).⁵ Bromides also enable Sonogashira cross-coupling reactions leading to alkyne derivatives, which have been included in kinase inhibitors *e.g.* Erlotinib (Figure 5.2). This made the incorporation of the bromo group a multi-purpose addition. The nitro functionality, after reduction to an aniline, could facilitate the link to the quinazoline portion of the molecule.

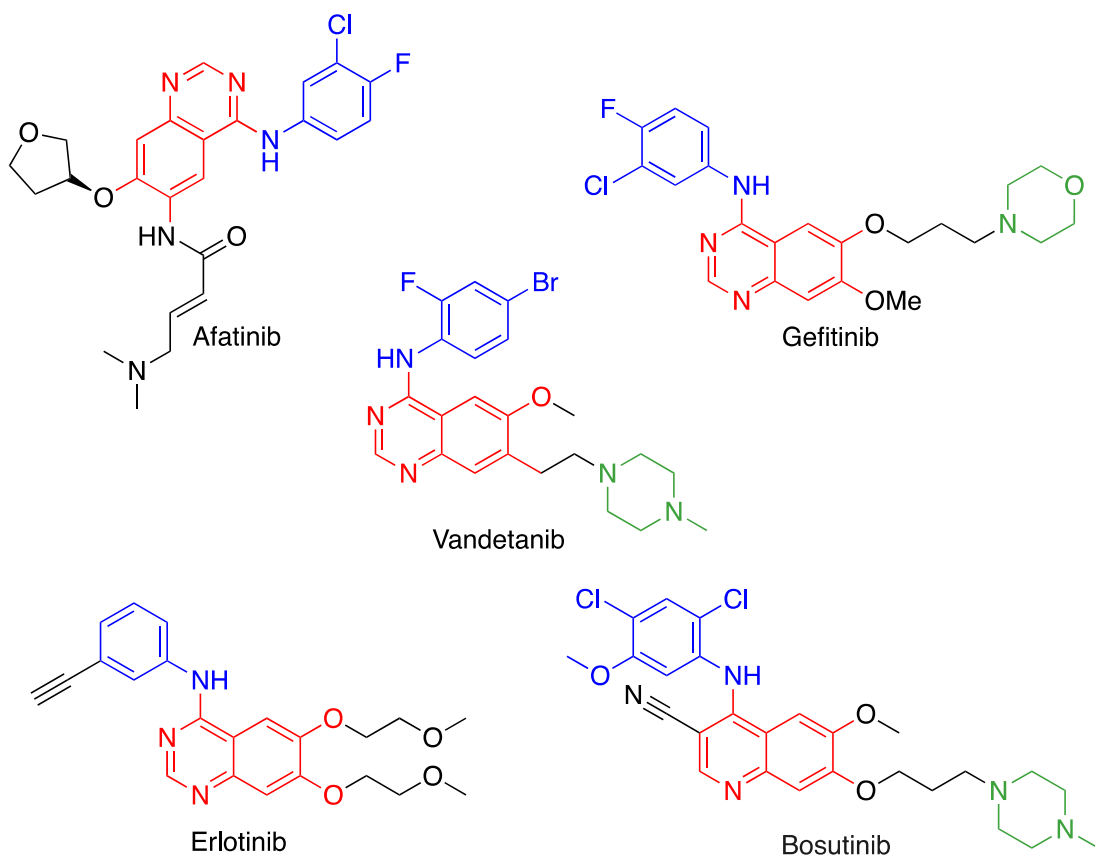
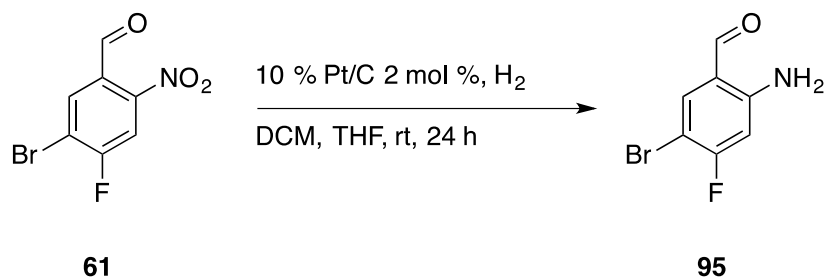


Figure 5.2. Examples of EGFR kinase inhibitors.

The quinazoline unit of these molecules (highlighted in red, Figure 5.2) serves as a mimic for the purine functionality in ATP. These competitive inhibitors interact to form 1 to 3 hydrogen bonds at the hinge of the purine-binding site.⁶ The quinazoline groups usually incorporate electron donating groups at the 6- and 7-positions, to modulate the p*K*_a of the quinazoline or quinolone nitrogen atoms, making them better hydrogen bond acceptors.⁷ Kinase inhibitors usually include solubilizing groups, highlighted in green.

5.2.1. Nitro reduction

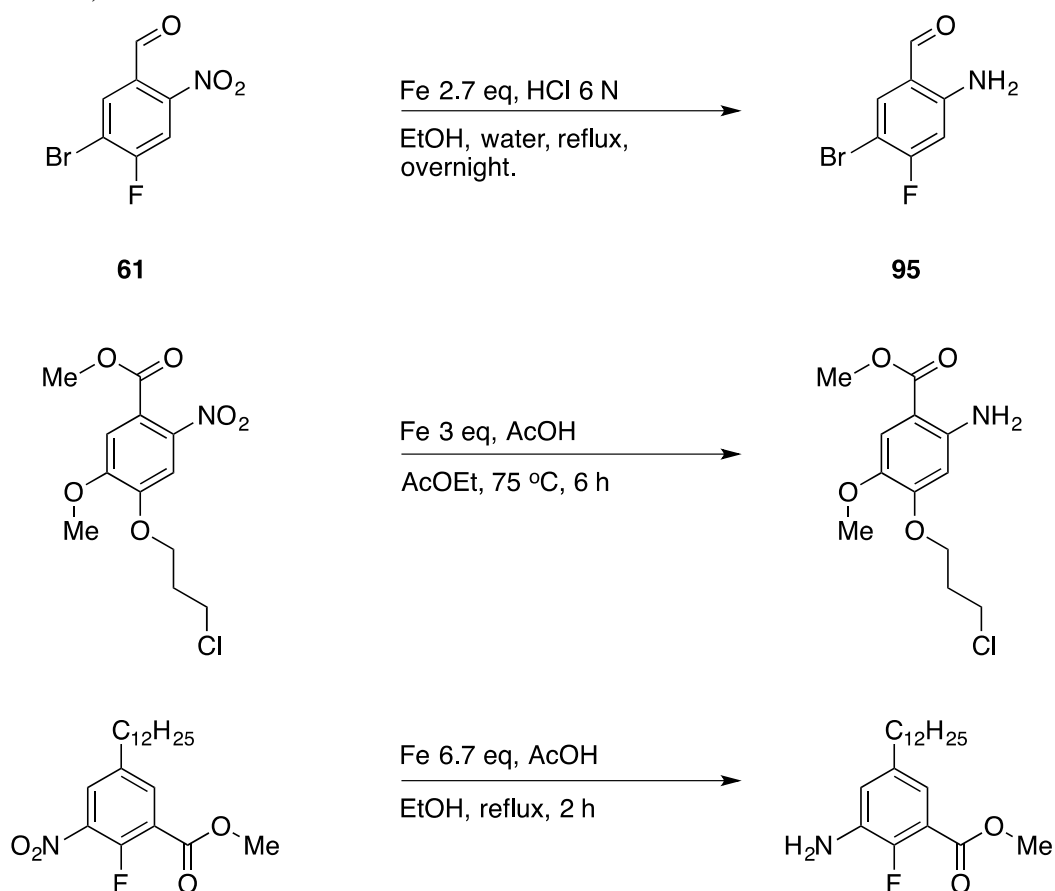
The reduction of aromatic nitro groups can be carried out a number of ways taking into account the different functionalities in the molecule and under what conditions they are sensitive. An example is outlined in a patent, where they prepared one of the desired



Scheme 5.1. Platinum catalysis reduction of 5-bromo-4-fluoro-2-nitrobenzaldehyde.

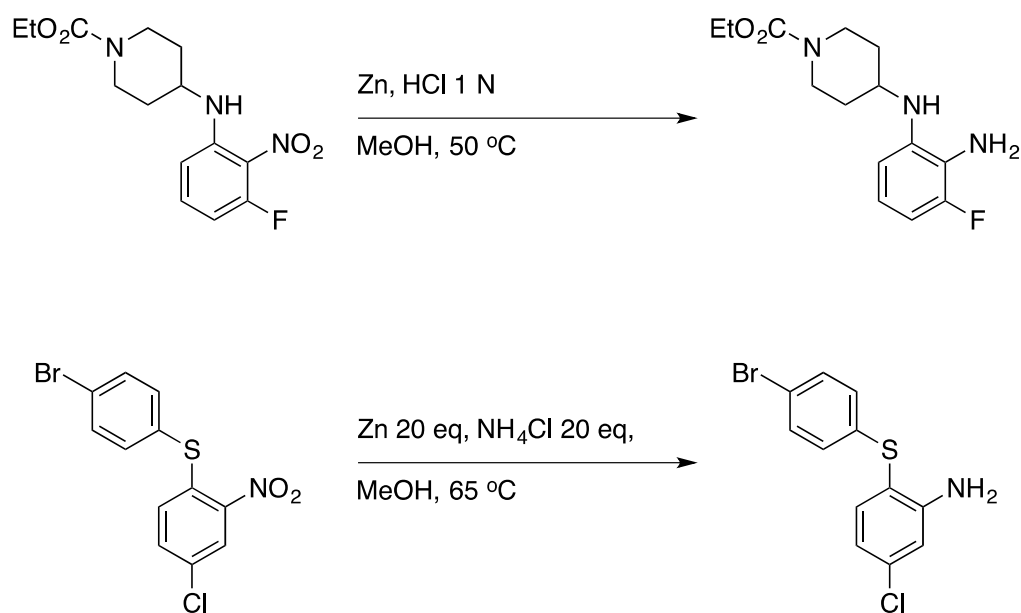
compounds, 2-amino-5-bromo-4-fluorobenzaldehyde (**95**) by a platinum catalysed reduction of 5-bromo-4-fluoro-2-nitrobenzaldehyde (**61**) (Scheme 5.1).⁸ Most powered metal hydrogenation catalysts have an associated hazard of ignition related to their use *e.g.* platinum, palladium, nickel, or the pyrophoric Raney nickel.⁹ However, most of these materials are non-pyrophoric and in fact it is the heat associated with the exothermic oxidation of the finely powdered metal that causes ignition of the solvent vapours.

A modern approach to this transformation is the use of an H-cube™, which is a flow reactor that generates hydrogen *in situ* from water. This enables the use of a large amount of different catalyst cartridges, safely at high temperatures.¹⁰ The H-cube™ is designed to heat cartridges that are packed with a catalyst with filters attached to either end of the casing. This design enables high mixing of reactants with catalysts and hydrogen, and enables safe handling of pyrophoric catalysts as it limits handling steps *e.g.* weighing and filtering.¹¹ The suggested range of different catalysts for the selective reduction of nitro groups includes: 10 % Pd/C, Raney Ni (for the reduction in the presence of benzyl groups), 5 % Ru/C or RuO₂ (both ruthenium catalysts enable reductions in the presence of halides).¹²



Scheme 5.2. Example of iron powder reductions.

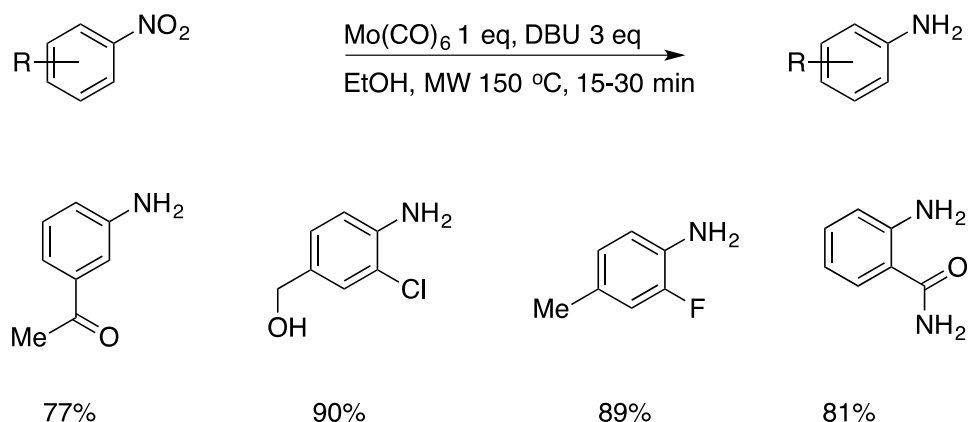
Another common approach is the use of acids with metal powders *e.g.* zinc or iron. Examples of iron powder reductions are shown in Scheme 5.2. The top example is taken from a different patent where they produced the same product **61** using HCl as an acid source.¹³ The middle¹⁴ and bottom¹⁵ examples used acetic acid with an additional solvent *i.e.* ethanol or ethyl acetate. This methodology showed excellent functional group tolerance and short reactions times when heated with acetic acid.



Scheme 5.3. Zinc reduction of nitro group.

Examples of similar zinc reductions are shown in Scheme 5.3. The top example¹⁶ achieves reduction using HCl, whereas the bottom example¹⁷ uses ammonium chloride which enables reduction of more acid sensitive compounds.

Spencer *et al.* achieved nitro reduction by a microwave mediated route using stoichiometric molybdenum hexacarbonyl and 1,8-diazabicyclo[5.4.0]undec-7-ene



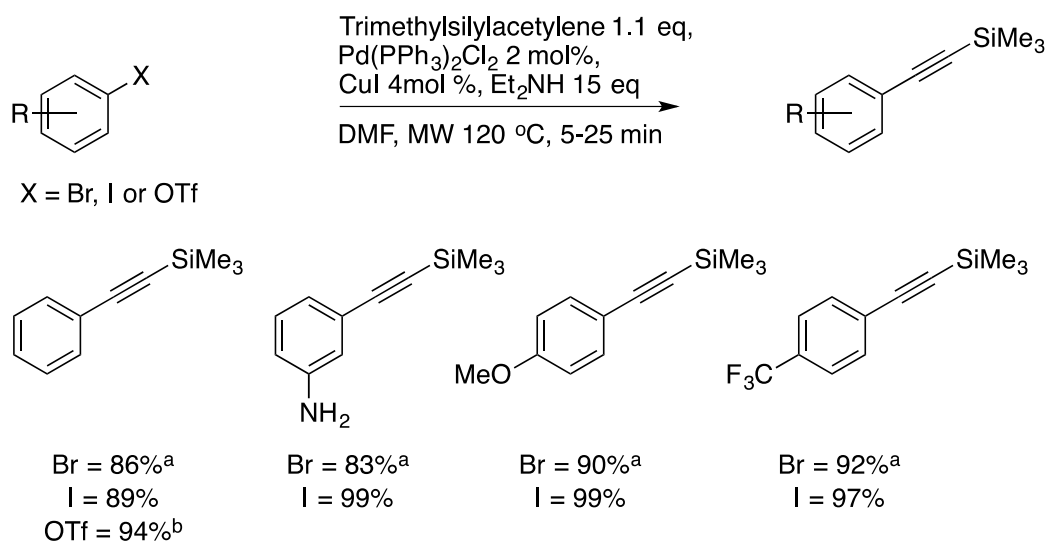
Scheme 5.4. Microwave mediated reduction using molybdenum hexacarbonyl.

(DBU) (Scheme 5.4).^{18,19} The microwave heating facilitates superheating of the ethanol

in the reaction mixture to 150 °C, which enables a fast 15-30 minute reaction, compared to the 24 hour reaction times of the corresponding conductive heating processes.

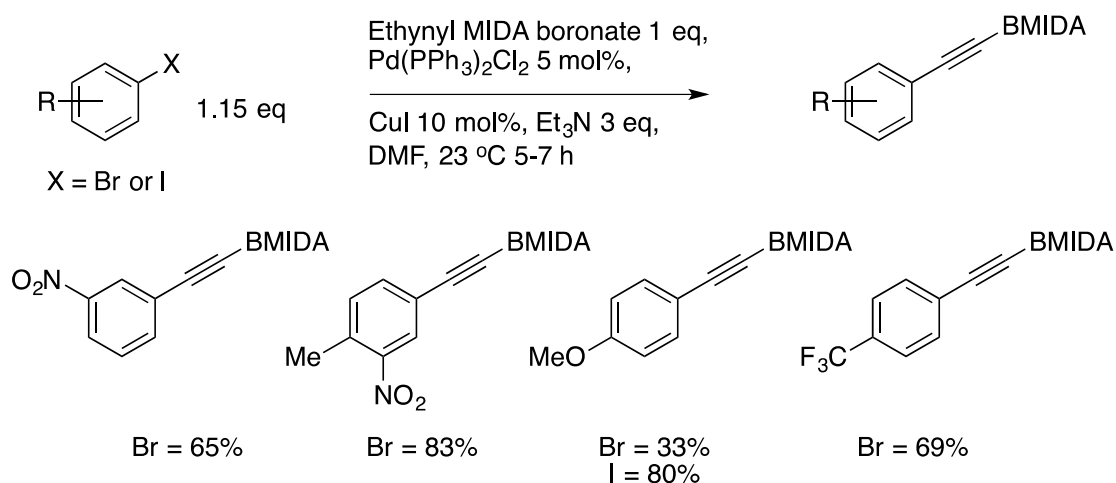
5.2.2. Sonogashira coupling

The Sonogashira reaction mechanism and some general conditions have been reviewed in Chapter 1. However a small review of specific examples will be included within this chapter.



Scheme 5.5. Microwave mediated Sonogashira reactions (yields calculated by ¹H-NMR).
^atriphenylphosphine was added, ^blithium chloride was added.

Erdélyi *et al.* published work on microwave enhanced Sonogashira cross-couplings, reducing reaction times to between 5 and 25 minutes (Scheme 5.5).²⁰ Within the work they included reactions under room temperature conditions, to illustrate the reduction in reaction times.



Scheme 5.6 Sonogashira cross-couplings prepared with ethynyl MIDA boronate.

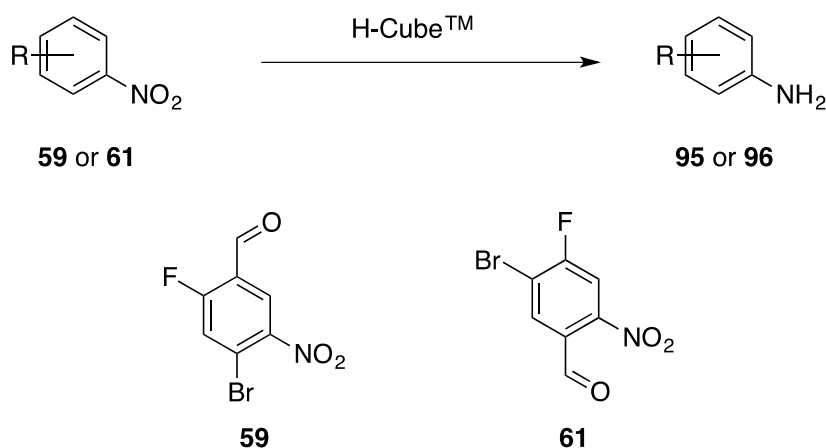
Burke *et al.* synthesised ethynyl MIDA boronate and outlined a selection of Sonogashira cross-couplings.²¹ Some examples of the products prepared via Sonogashira cross-couplings are shown in Scheme 5.6. Within Burke's work he outlined Suzuki reactions and different functional group inter conversions with these MIDA boronates; also Toste *et al* achieved cyclisomerization forming indoles and benzofurans.²²

5.3. Results and discussion

5.3.1. Nitro reduction

The initial focus of the work was the reduction of the nitro group. We hoped that use of the H-cube flow reactor would facilitate this. Unfortunately this did not give reproducible results (Table 5.1).

Table 5.1. Attempted nitro reduction optimisations using H-Cube™



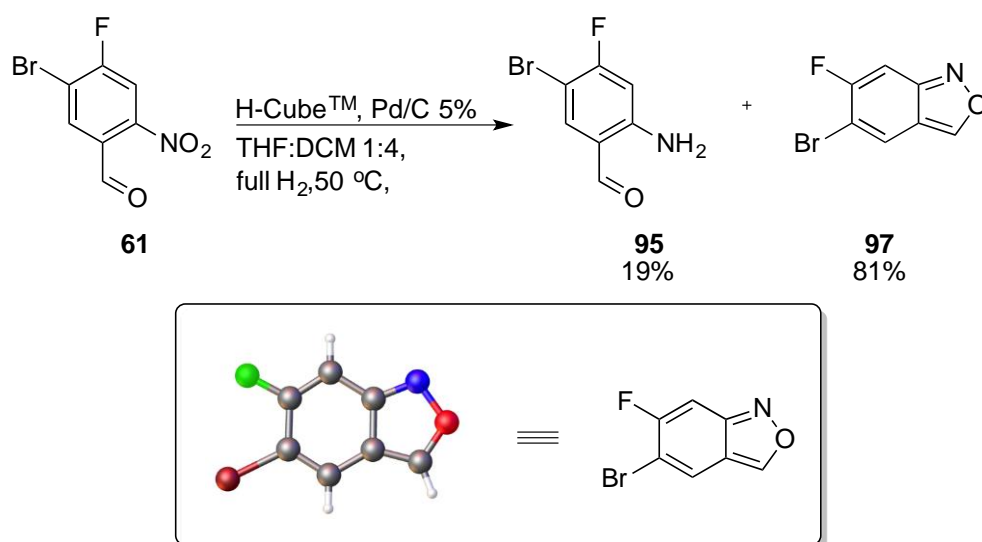
Entry (Substrate)	Cat-card	Solvent	Temperature (°C)	Pressure mode (bar)	Conversion ^a (%)
1 (59)	Pd/C 5%	THF/DCM ^b	50	Full H ₂	0 ^e
2 (61)	Pt/C 5%	THF/DCM ^b	50	Full H ₂	19
3 (61)	Pt/C 5%	THF/DCM ^b	100	70	100 ^{d,e}
4 (61)	Pt/C 5%	EtOAc	100	70	30
5 (61)	RuO ₂	EtOAc	20	70	100 ^d
6 (61)	RuO ₂	EtOAc	60	70	70
7 (61)	RuO ₂	EtOAc	100	70	0 ^f
8 (61)	RuO ₂ ^c	EtOAc	20	70	23 ^e

^aConversions calculated by ¹H-NMR spectra, ^b1:4 ratio of THF DCM, ^c Repeated best conditions with new catalysis cartridge, ^dresults not reproducible, ^emixtures of different materials not aromatic, ^fno benzaldehyde peak observed.

A palladium on carbon route was trialled first for the reduction of compound **59** (Table 5.1, entry 1) and a mixture of different compounds was observed by ¹H-NMR spectra.

This could potentially be due to palladium reacting with bromide making a complex mixture of side products.

The next attempted conditions were inspired from Scheme 5.1, a literature example of the reduction of compound **61** with platinum on carbon.⁸ Optimisation of these conditions achieved 100 % conversion with a high purity, observed for the formation of 2-amino-5-bromo-4-fluorobenzaldehyde (**95**) shown in Table 5.1 entry 3. Unfortunately the yields under these conditions suffered from inconsistencies. It was noted that the side product from these reactions was the 2,1-benzisoxazole (anthranil) analogue (**97**) shown in Scheme 5.7. Formation of 2,1-benzisoxazoles has been observed before when reducing nitro groups ortho to aldehydes or ketones.²³



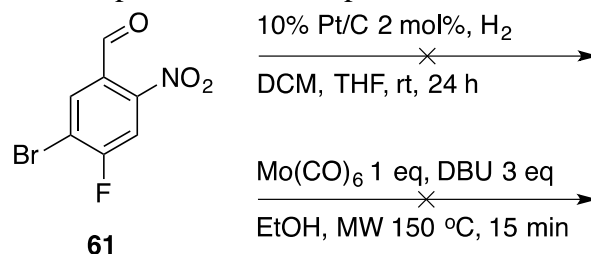
Scheme 5.7. Side product formed by reduction of compound (yields calculated by ¹H-NMR) **61** with platinum on carbon and X-ray structure.

Also, solvent incompatibilities with the tubing of the flow reactor caused unexpected peaks being observed in the aliphatic region of the ¹H-NMR spectra. To remove this problem ethyl acetate was chosen as the solvent for future experiments with the H-cube, but lower yields were obtained, Table 5.1 entry 4.

In the ThalesNano quick start guide, it was suggested that ruthenium (IV) oxide catalyst cartridge gave positive results when reducing nitro groups in the presence of bromo functionalities.¹² It suggested running the ruthenium(IV) oxide catalyst at 30 °C at a pressure of 70 bar. Whilst maintaining the pressure at 70 bar, a range of different temperatures were tested. It was found at higher temperatures the benzaldehyde peak was no longer seen in the ¹H-NMR spectrum, suggesting reduction to the corresponding benzyl alcohol. However lower temperatures yielded an impressive 100 % conversion,

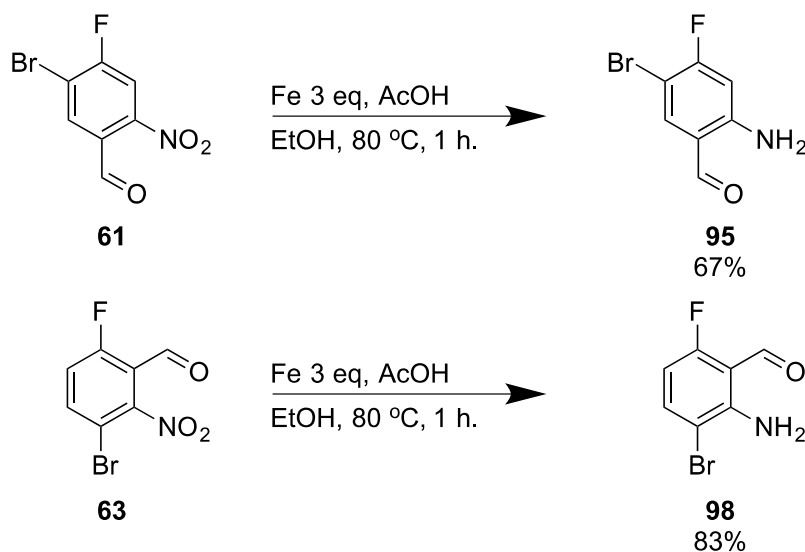
but, as with the platinum on carbon catalyst yields for the reactions were inconsistent and irreproducible.

Due to the lack of reproducibility of the H-cube, the literature method shown in Scheme 5.1 was trialled on compound **61** (Scheme 5.8). This method gave poor results when analysed via crude $^1\text{H-NMR}$ spectra. The attempted microwave heated nitro reduction



Scheme 5.8. Attempted nitro reductions of **61**.

with molybdenum hexacarbonyl (Scheme 5.8) also gave poor results, as crude $^1\text{H-NMR}$ spectra analysis showed a large amount of different aromatic peaks, none of which corresponded to the product.



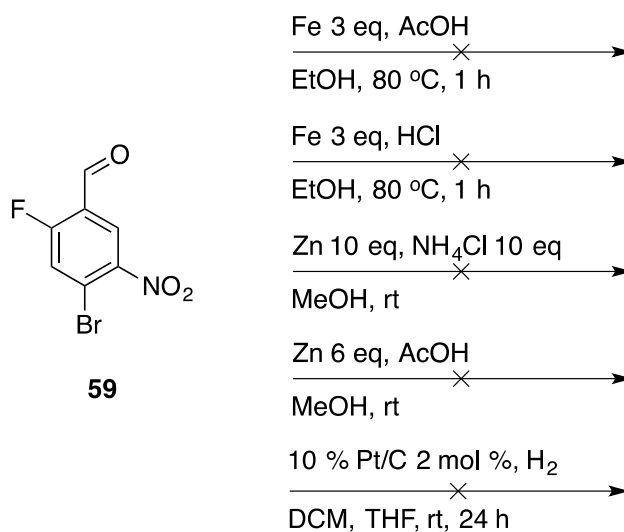
Scheme 5.9. Results from iron reduction, on compound **62** and **63**.

Adopting a literature iron reduction protocol achieved the reduction of **61**, shown in Scheme 5.9.²⁴ Iron reduction with HCl to form compound **95**, has been achieved in a patent before, see top example of Scheme 5.2.¹³

Using the iron in acetic acid also produced compound 2-amino-3-bromo-6-fluorobenzaldehyde (**98**) in a high yield (Scheme 5.9).

The reduction of compound 4-bromo-2-fluoro-5-nitrobenzaldehyde (**59**) was not trivial. The iron powder in acetic acid reductions that yield compounds **95** and **98** produced an inseparable mixture of compounds according to $^1\text{H-NMR}$ spectra analysis of the crude product, Scheme 5.10. This led to several different methods being attempted (*i.e.* iron/ hydrochloric acid, zinc/ hydrochloric acid, zinc/ammonium chloride and platinum on carbon/ hydrogen), none of which yielded the desired product, Scheme 5.10.

Due to the demanding nature of compound **59** it was decided to continue down the



Scheme 5.10. Attempted nitro reductions on compound **59**.

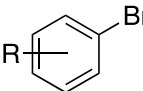
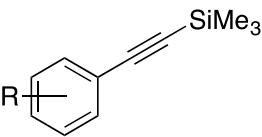
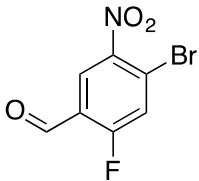
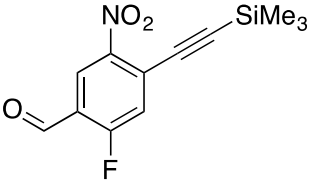
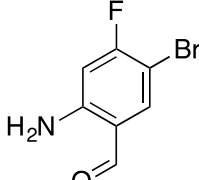
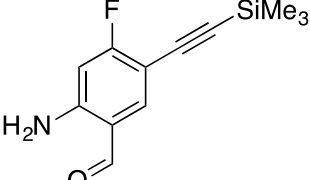
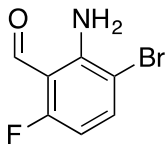
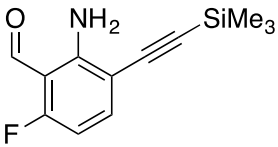
planned path and attempt the nitro reduction at a later stage in the synthesis.

5.3.2. Sonogashira coupling

The microwave conditions highlighted in Scheme 5.5 were trialled on compound **2b**; after 30 minutes of heating at 80 °C the reactions only showed starting material by LCMS analysis.

Standard conductive heating was attempted next, which yielded the product shown in Table 5.2.

Table 5.2. Compounds synthesised via thermal Sonogashira reactions.

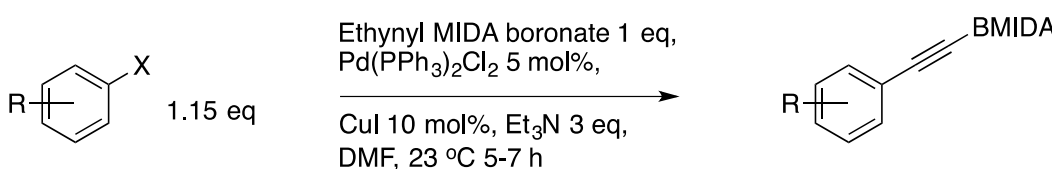
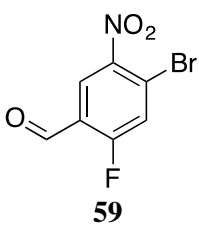
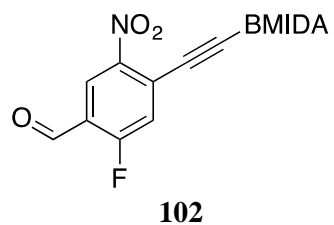
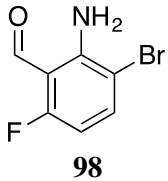
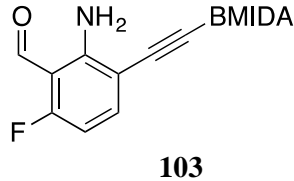
<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center; margin-right: 20px;">  </div> <div style="text-align: center; margin-right: 20px;"> <p>Trimethylsilylacetylene 1.2 eq, Pd(PPh₃)₂Cl₂ 5 mol%, CuI 10 mol%, Et₃N 3 eq</p> <hr/> <p>DMF, 80 °C, 4 h</p> </div> <div style="text-align: center; margin-left: 20px;">  </div> </div>			
Entry	Starting material	Product	Yield (%)
1	 59	 99	66 ^a
2	 95	 100	45
3	 98	 101	74

^a reaction ran at rt for 1 hour.

Table 5.2 entries 1 and 3 showed good yields, better than that of entry 2, which had poor yields due to the purification, as the compound could only be purified via reversed phase chromatography. The temperature of the reactions needed adjustment in the case of Table 5.2 entry 1 as it was found that the reactions gave better yields if left for 1 hour and not heated above room temperature. This was probably due to the bromide in compound **59** being more activated because the nitro group was present.

Synthesising ethynyl MIDA boronate using Sonogashira cross-couplings similar to those shown in Scheme 5.6, was attempted on compounds **59**, **95** and **98**. Compounds **59** and **98** both gave the desired the product and in the case of **98** high yields were observed, Table 5.3.

Table 5.3. Compounds synthesised Sonogashira reactions with ethynyl MIDA boronate.

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;">  </div> </div>			
Entry	Starting material	Product	Yield (%)
1	 <p style="text-align: center;">59</p>	 <p style="text-align: center;">102</p>	38
2	 <p style="text-align: center;">98</p>	 <p style="text-align: center;">103</p>	86

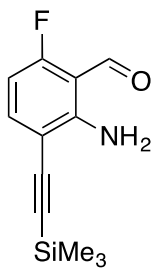
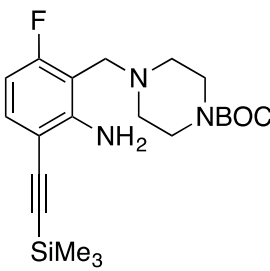
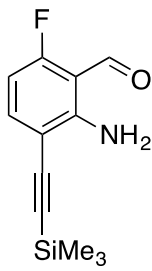
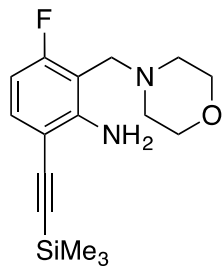
Compound **95** gave positive results according to ¹H-NMR spectra, but could not be purified, due to poor solubility of the compound in a range of solvents.

5.3.3. Reductive amination

Solubilising groups were added to the aromatic core via reductive aminations of the aldehyde. Sodium triacetoxyborohydride (STAB) is a mild reducing reagent that can be used in a simple one-pot procedure; it is one of the most convenient methods and considered the method of choice.^{25,26} The STAB method was applied to some of the compounds that have been discussed previously, either morpholine or tert-butyl piperazine-1-carboxylate (1-Boc-piperazine) as the amines, shown in Table 5.4.

Table 5.4. Compounds formed by reductive aminations.

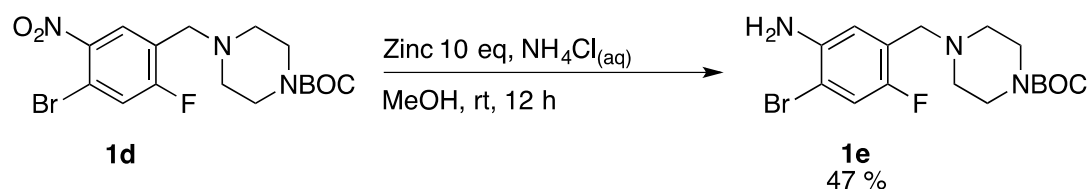
<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;"> <p>STAB 2-2.5 eq, amine 1.1 eq, THF, rt overnight</p> </div> <div style="margin-left: 20px;"> <p>Y = O or NBoc</p> </div> </div>			
Entry	Starting material	Product	Yield (%)
1 ^e	<p>59</p>	<p>104</p>	47 ^a 77 ^b
2 ^f	<p>95</p>	<p>105</p>	83 ^a 91 ^c
3 ^f	<p>95</p>	<p>106</p>	97 ^a
4 ^e	<p>98</p>	<p>107</p>	82 ^a 95 ^d
5 ^e	<p>98</p>	<p>108</p>	95 ^a

6 ^e	 101	 109	28 ^a
7 ^e	 101	 110	63 ^a

^a 0.5 mmol scale, ^b 8 mmol scale, ^c 3 mmol scale, ^d 6.3 mmol scale, ^e 2 eq of STAB, ^f 2.5 eq of STAB.

Yields throughout Table 5.4 are high with the exception of entries 6 and 7. These reactions showed improved yield when reactions were scaled up and in the case of entry 1 compound **104** was prepared on an 8 mmol scale producing 2.5 g of product.

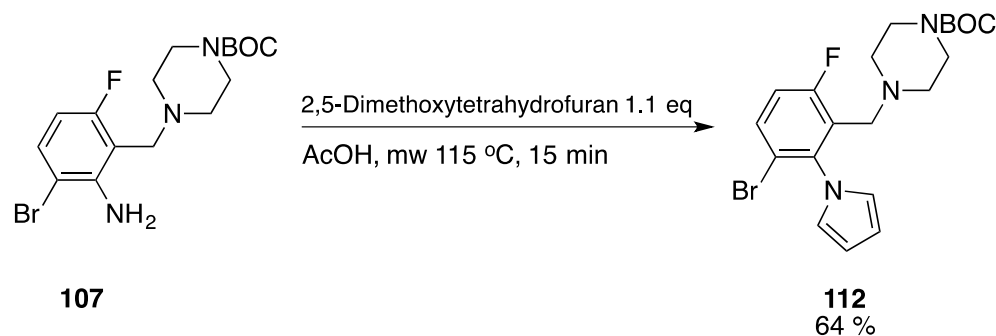
At this point the nitro reduction of compound **104** could be achieved using a zinc ammonium chloride mixture. Under these conditions the nitro group was successfully



Scheme 5.11. Zinc reductions of compound **104**.

reduced forming compound **111** without BOC deprotection, Scheme 5.11. This formed the missing aniline required for formation of the linker to the quinazoline unit.

To show the utility of these compounds a Clauson-Kaas pyrrole synthesis under



Scheme 5.12. Clauson-Kaas pyrrole synthesis under microwave conditions on compound **3e**.

microwave conditions was achieved on compound **107** (Scheme 5.12). To our surprise the BOC protecting group withstood these harsh acid conditions and gave the product **112** in a high yield. Microwave conditions for this pyrrole synthesis have been published and have been shown to be quick and high yielding.^{27,28} This highlights the different chemical processes that can be selectively achieved with these compounds.

5.3.4. Reactions with 4-chloro-6,7-dimethoxyquinazoline

This next step involved linking the 4-chloro-6,7-dimethoxyquinazoline unit via the aniline functionality incorporated in the tetrasubstituted aromatic compounds synthesised in this Chapter. We chose this quinazoline as a representative privileged kinase inhibitor core in order to exemplify the application of this methodology. It was not our intention to perform a drug discovery project, since at its onset we were not guaranteed any biological feedback. Moreover our target compounds were high molecular weight and non-Lipinski like.

As some of the aromatic compounds synthesised contained a 1-Boc-piperazine moiety, methods of linking the quinazoline unit involving acidic conditions were avoided e.g. Spencer *et. al.*²⁹ There are also literature methods that achieve the formations of the linker via heating the aniline with the 4-chloro-6,7-dimethoxyquinazoline using microwave heating in isopropyl alcohol, or acetonitrile.^{30,31} Trialling this acetonitrile method gave very poor results according to ¹H-NMR spectra analysis of the crude reaction mixture. It was found that adopting a synthesis from a patent, where by sodium bis(trimethylsilyl)amide (NaHMDS) was employed to deprotonate the aniline, yielded the desired products.³² Table 5.5 show the compounds synthesised via this methodology.

Table 5.5. Linking of the quinazoline unit.

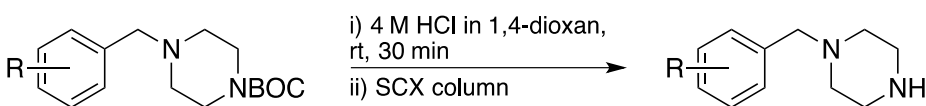
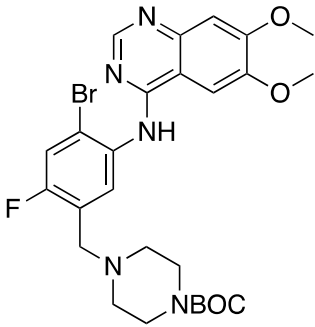
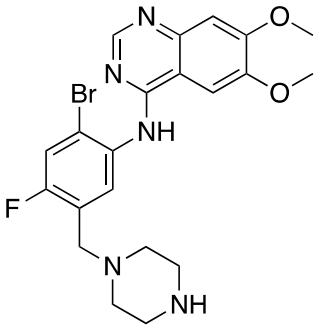
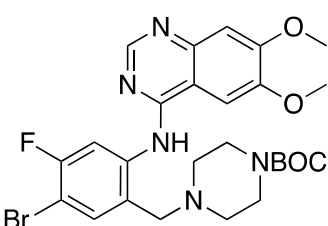
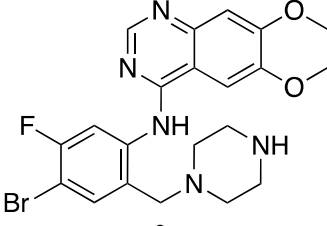
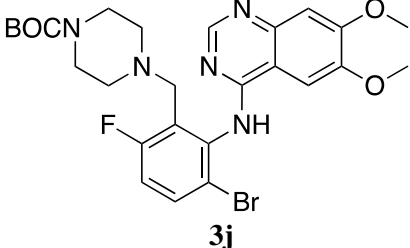
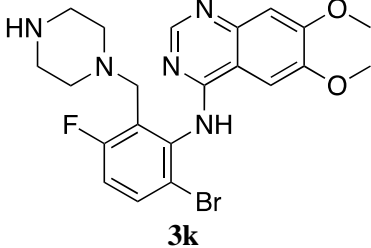
Entry	Starting material	Product	Yield (%)
1	 111	 113	48
2	 105	 114	42
3	 107	 115	72

In the case of compound **114** purification by column chromatography did not yield pure product and this compound required an additional recrystallization, from a minimum amount of ethyl acetate, which led to a lower yield.

5.3.5. BOC deprotection and late stage modification to piperazine

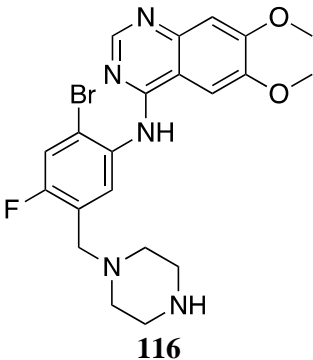
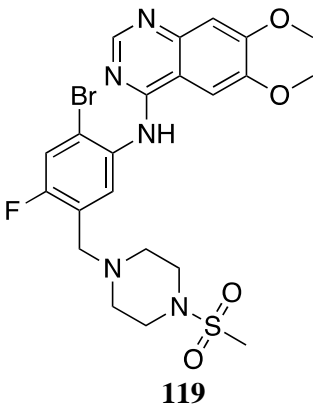
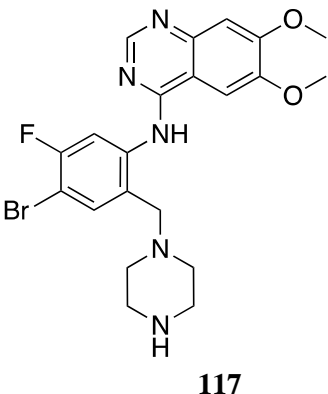
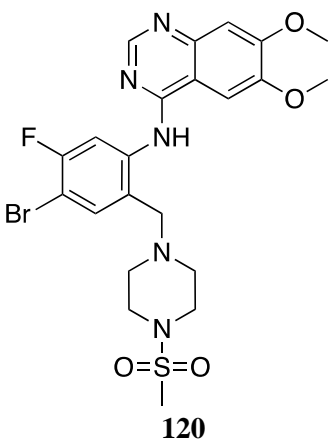
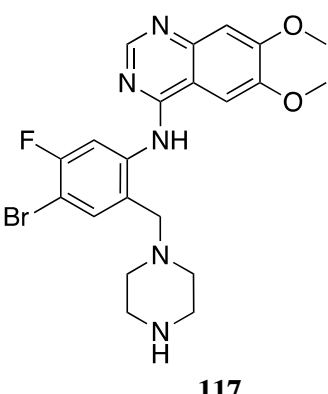
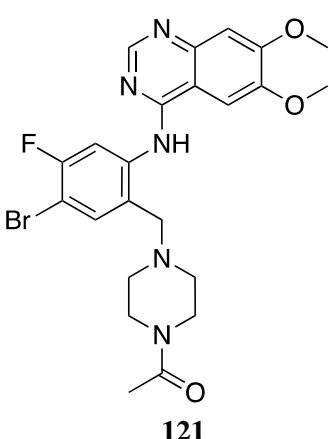
The removal of the BOC protecting group would enable further functionalization of the compounds from the newly formed secondary amine of the piperazine. The BOC group was successfully removed in good yields using 4 M hydrochloric acid in 1,4-dioxane (Table 5.6).

Table 5.6. Showing yields for BOC cleavage step.

<div style="text-align: center;">  </div>			
Entry	Starting material	Product	Yield (%)
1	 1f	 1g	84
2	 2f	 2g	55
3	 3j	 3k	72

The compounds synthesised in Table 5.7 were then functionalised at the newly deprotected secondary amine. These reactions were achieved by adding an acid chloride and *N,N*-diisopropylethylamine (DIPEA) and results are shown in Table 5.7.

Table 5.7. Functionalization of the piperazine unit.

$ \text{R}-\text{C}_6\text{H}_4-\text{CH}_2-\text{N}(\text{CH}_2\text{CH}_2)_2\text{NH}_2 \xrightarrow[1\text{ h, rt.}]{\text{R}'\text{Cl } 1.1\text{ eq, DIPEA } 2\text{ eq}} \text{R}-\text{C}_6\text{H}_4-\text{CH}_2-\text{N}(\text{CH}_2\text{CH}_2)_2\text{NHR}' $			
Entry	Starting material	Product	Yield (%)
1	 <p>116</p>	 <p>119</p>	63
2	 <p>117</p>	 <p>120</p>	99
3	 <p>117</p>	 <p>121</p>	98

The modifications where higher yielding with **2g** as the both entries 2 and 3 gave yields of 99% and 98% respectively.

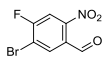


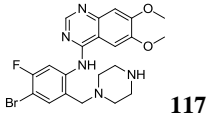
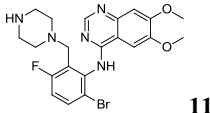
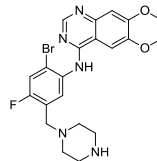
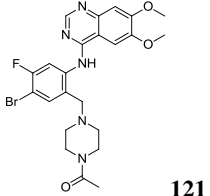
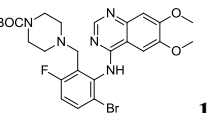
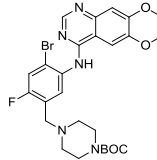
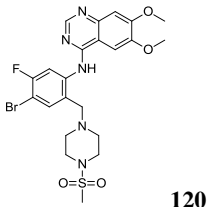
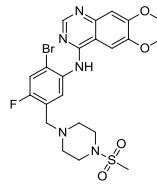
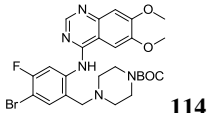
5.4. Biological data

Nine of the compounds synthesised in this Chapter were sent to AstraZeneca for assay testing activity in inhibiting EGFR in wild type cells. The results and starting substrate are shown in Table 5.8.

These results show that the compounds containing a BOC protecting group had low activity with the best activity shown by **115**, which had an IC₅₀ of 21.5 µM. The compounds derived from **59**, *i.e.* **113**, **116** and **119**, showed the lowest activity of 3 different precursors. The most active compound was **117**, which gave an IC₅₀ of 18.4 nM. All of the compounds in series **61** gave good results *i.e.* all IC₅₀'s were less than 1 µM, with the exception of the BOC protected compound **114**.

Unfortunately the percentage hERG inhibition increased as the activity of the compounds improved. There are ways in which to design out hERG inhibition *e.g.* reducing lipophilicity, reducing the pK_a of the nitrogen atoms, increasing steric constraints around nitrogen atoms or decreasing the number of hydrogen bond acceptors.³⁴ These would be considered in future work.

Table 5.8. EGFR wild type cell assay IC₅₀.³³

Compounds synthesised from 61			Compounds synthesised from 63			Compounds synthesised from 59		
								
Compound	EGFR IC ₅₀ ^a	hERG inhibition (%) ^b	Compound	EGFR IC ₅₀ ^a	hERG inhibition (%) ^b	Compound	EGFR IC ₅₀ ^a	hERG inhibition (%) ^b
 117	0.0184	61.1	 118	0.935	44.5	 116	>21.3	33.7
 121	0.377	96.5	 115	21.5	21.5	 113	27.1	46.4
 120	0.546	55.6				 119	>30	43.9
 114	>30	19.5						

^aEGFR Ex20 WT HTRF CR GMean IC₅₀ (μM), ^bhERG Hu CHO IF EPhs SS GD mean, at 10 μM.

5.5. Conclusion

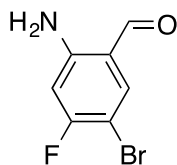
The elaboration of the bromofluoronitrobenzaldehydes synthesised via nitration in Chapter 3 (Figure 5.1.) has led to an EGFR kinase inhibitor that has IC₅₀ of 18.4 nM (**117**). This proves the hypothesis that these tetrasubstituted building blocks have the potential to be EGFR inhibitors when incorporated into bioactive scaffolds. Although this compound did have a high hERG inhibition, this could be designed out of molecules as discussed in Section 5.4.

A vast amount of orthogonal chemistry modifications has been done on compounds **59**, **61** and **63** *e.g.* nitro reduction, Sonogashira couplings, reductive aminations, Clauson-Kaas pyrrole, and the linking of these aromatics to 4-chloro-6,7-dimethoxyquinazoline unit forming novel potential kinase inhibitors. This shows how **59**, **61** and **63** fit the brief of including orthogonal of set by AstraZeneca. This demonstrates how these complex building blocks can be manipulated to form novel interesting compounds in a small amount of steps. Although some of the perceived simpler manipulations were not as trivial as anticipated, *e.g.* the nitro reduction of **59**, many problems were overcome by postponing this until a later stage in the synthetic sequence. Uniquely, these products appear to show that a water solubilising piperazine group, as in **116**, can possibly be incorporated a hydrophobic pocket of a kinase although this would need an X-ray co-crystal structure to confirm this.

5.6. Experimental

Solvents and reagents were purchased from commercial suppliers and used without further purification. NMR spectra were recorded on a Varian 500 MHz or 400 MHz spectrometer. Chemical shifts are reported in ppm and are referenced to the residual solvent peak or to TMS used as an internal standard. LCMSs were ran on a Shimadzu LCMS-2020 equipped with a Gemini® 5 µm C18 110 Å column. Percentage purities were performed using a 30 minutes method in water/acetonitrile with 0.1% Formic acid (5 min at 5%, 5%-95% over 20 min, 5min at 95%) with the UV set to 254 nm. High resolution mass spectrometry (HRMS) was done either internally or by the National Mass Spectrometry Facility, Swansea University. A number of the products described below are commercially available or known, *e.g.* in patents. In these cases, ¹H, ¹³C, HRMS and % purity data are presented since in many cases these data are not published.

2-Amino-5-bromo-4-fluorobenzaldehyde, 95.⁸



5-Bromo-4-fluoro-2-nitrobenzaldehyde (2.678 g, 10.8 mmol) and iron powder (1.819 g, 32.4 mmol) were added to a round-bottomed flask, this was purged with argon for 5 min. Ethanol (16 mL) followed by acetic acid (16 mL) were added and this mixture was heated to 80 °C and monitored via TLC (15 % EtOAc in hexane). After 1 hr the reaction had gone to completion, and the mixture was filtered through a Celite pad, this was then washed through with ethyl acetate (3 x 10 mL). Water (50 mL) was added followed by sodium hydrogen carbonate (saturated) to adjust to pH 4, this was extracted with ethyl acetate (3 x 100 mL), the combined organic layers were washed with brine (3 x 100 mL), dried with sodium sulphate. The organic layer was then evaporated under reduced pressure on to silica. The silica pad was then loaded on to a silica gel column and purified using a gradient of 0 % to 15 % ethyl acetate in hexane to give the title compound as a yellow solid.

Yield: 1.571 g (67 %).

TLC (EtOAc: hexane 15 %) R_f = 0.33.

FTMS APCI (m/z) found 217.9616, calcd for $[C_7H_5^{79}BrF_1N_1O_1H]^+$ 217.9611.

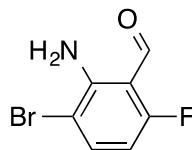
1H NMR (500 MHz, chloroform-d) δ 9.75 (s, 1H), 7.64 (d, $^4J_{FH}$ = 7.5 Hz, 1H), 6.42 (d, $^3J_{FH}$ = 10.5 Hz, 1H), 6.30 (s, 2H).

^{13}C NMR (126 MHz, chloroform-d) δ 191.7, 163.4 (d, $^1J_{FC}$ = 255.2 Hz), 151.2 (d, $^3J_{FC}$ = 12.6 Hz), 140.7 (d, $^3J_{FC}$ = 4.4 Hz), 117.4, 103.3 (d, $^2J_{FC}$ = 25.8 Hz), 95.3 (d, $^2J_{FC}$ = 23.1 Hz).

^{19}F NMR (376 MHz, chloroform-d) δ -97.63 (dd, J = 10.5, 7.5 Hz).

LCMS purity >99% (UV), Ret. time = 18.83 min.

2-Amino-3-bromo-6-fluorobenzaldehyde, 98.



3-Bromo-6-fluoro-2-nitrobenzaldehyde (7.44 g, 30 mmol) and iron powder (5.02 g, 90 mmol) were added to a round-bottomed flask, this was purged with argon for 5 min. Ethanol (30 mL) followed by acetic acid (30 mL) were added and this mixture was heated to 80 °C and monitored via TLC (15 % EtOAc in hexane). After 1 hr the reaction had gone to completion, and the mixture was filtered through a Celite pad, this was then washed though with ethyl acetate (3 x 30 mL). Water (150 mL) was added followed by sodium hydrogen carbonate (saturated) to adjust to pH 4, this was extracted with ethyl acetate (3 x 100 mL), the combined organic layers were washed with brine (3 x 300 mL), dried with sodium sulphate. The organic layer was then evaporated under reduced pressure on to silica. This silica pad was then loaded on to a silica gel column and purified using a gradient of 0 % to 15 % ethyl acetate in hexane to give the title compound as a yellow solid.

Yield: 5.40 g (83 %).

TLC (EtOAc: hexane 15 %) R_f = 0.61.

FTMS APCI (m/z) found 219.9593, calcd for $[C_7H_5^{81}Br_1F_1N_1O_1H]^+$ 219.9591.

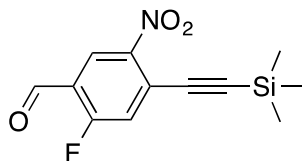
1H NMR (500 MHz, acetone- D_6) δ 10.23 (s, 1H), 7.71 (dd, $^3J_{HH}$ = 8.5, $^4J_{FH}$ = 6.0 Hz, 1H), 7.32 (s, 2H), 6.43 (dd, $^3J_{FH}$ = 11.0, $^3J_{HH}$ = 8.5 Hz, 1H).

^{13}C NMR (126 MHz, acetone- D_6) δ 188.9 (d, $^3J_{FC}$ = 12.5 Hz), 166.7 (d, $^1J_{FC}$ = 254.7 Hz), 149.4 (d, $^3J_{FC}$ = 4.8 Hz), 140.1 (d, $^3J_{FC}$ = 11.9 Hz), 109.1 (d, $^3J_{FC}$ = 10.7 Hz), 104.9 (d, $^4J_{FC}$ = 3.4 Hz), 103.4 (d, $^2J_{FC}$ = 22.9 Hz).

^{19}F NMR (376 MHz, chloroform- D) δ -123.05 (dd, J = 11.0, 6.0 Hz).

LCMS purity >99% (UV), Ret. time = 19.68 min.

2-Fluoro-5-nitro-4-((trimethylsilyl)ethynyl)benzaldehyde, 99.



4-Bromo-2-fluoro-5-nitrobenzaldehyde (2.480 g, 8.0 mmol), copper iodide (181 mg, 1.0 mmol) and bis(triphenylphosphine)palladium(II) dichloride (351 mg, 0.5 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon and cycled 3 times. DMF (dry, 24 mL), triethylamine (dry, 4.28 mL, 30.0 mmol) were added followed by the drop wise addition of trimethylsilylacetylene (1.34 mL, 12.0 mmol). This mixture was stirred at rt for 1h. The bulk of the DMF was evaporated under reduced pressure, then diethyl ether (100 mL) was added to the mixture, this was then filtered through a pad of Celite, which was then washed with more diethyl ether (3 x 20 mL). Water (150 mL) was added and the organic layer separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (5 x 150 mL), dried with magnesium sulphate and evaporated under reduced pressure on to silica. This crude was then loaded on to a silica gel column which was ran at a gradient of 0 % - 15 % diethyl ether in hexane, to give the title compound as a yellow solid.

Yield: 1.736 g (66%).

TLC (Diethyl ether: hexane 10%) R_f = 0.40.

FTMS (m/z) found 266.0638, calcd for $[C_{12}H_{12}FNO_3SiH]^+$ 266.0643.

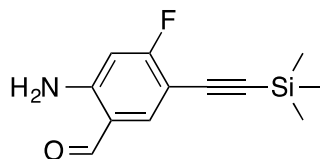
1H NMR (500 MHz, chloroform-D) δ 10.31 (s, 1H), 8.56 (d, $^4J_{FH}$ = 6.5 Hz, 1H), 7.46 (d, $^3J_{FH}$ = 10.0 Hz, 1H), 0.30 (d, J = 1.0 Hz, 9H).

^{13}C NMR (100 MHz, chloroform-D) δ 184.3 (d, $^3J_{FC}$ = 5.5 Hz), 165.1 (d, $^1J_{FC}$ = 267.0 Hz), 146.9, 126.1, 126.0 (d, $^3J_{FC}$ = 4.5 Hz), 123.6 (d, $^2J_{FC}$ = 11.0 Hz), 123.2 (d, $^4J_{FC}$ = 24.0 Hz), 111.2, 97.8, -0.5.

^{19}F NMR (376 MHz, chloroform-D) δ -114.40 (dd, J = 10.0, 6.5 Hz).

LCMS purity >99 % (UV), Ret. time = 23.46 min.

2-Amino-4-fluoro-5-((trimethylsilyl)ethynyl)benzaldehyde, 100.



2-Amino-5-bromo-4-fluorobenzaldehyde (218 mg, 1.00 mmol), copper iodide (18 mg, 0.10 mmol) and bis(triphenylphosphine)palladium(II) dichloride (35 mg, 0.05 mmol) were added to a MPS tube, this was placed under vacuum and purged with argon and cycled 3 times. DMF (dry 3 mL), triethylamine (dry, 417 μ L, 3.00 mmol) were added followed by the drop wise addition of trimethylsilylacetylene (170 μ L, 1.20 mmol). This mixture was heated to 80 $^{\circ}$ C for 4 hr. The reaction mixture was cooled to rt and diethyl ether (20 mL) was added to the mixture, this was then filtered through a pad of Celite, which was then washed with more diethyl ether (3 x 5 mL). Water (50 mL) was added and the organic layer separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (5 x 50 mL), dried with sodium sulphate and evaporated under reduced pressure. The crude material was dissolved in the minimum amount of DMSO and loaded on to a reverse phase flash chromatography column, the column was ran at 100% water (0.1% formic acid modifier) for 1-3 column volumes i.e. until the UV trace normalised from the DMSO. The column was then run at a gradient of 45% to 95% acetonitrile (0.1% formic acid) in water (0.1% formic acid). The fractions containing product were then lyophilized to the title compound as a yellow solid.

Yield: 105 mg (45%).

FTMS (m/z) found 236.0903, calcd for $[\text{C}_{12}\text{H}_{14}\text{ONFSiH}]^{+}$ 236.0901.

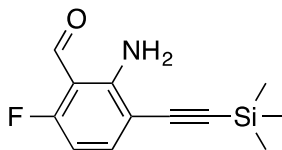
^1H NMR (500 MHz, chloroform-D) δ 9.75 (s, 1H), 7.64 (d, $^4J_{\text{FH}} = 7.5$ Hz, 1H), 6.40 (bs, 2H), 6.31 (d, $^3J_{\text{FH}} = 11.0$ Hz, 1H), 0.25 (s, 9H).

^{13}C NMR (126 MHz, chloroform-D) δ 192.2, 167.0 (d, $^1J_{\text{FC}} = 259.5$ Hz), 151.9 (d, $^3J_{\text{FC}} = 13.5$ Hz), 142.8 (d, $^3J_{\text{FC}} = 5.5$ Hz), 116.1, 102.0 (d, $^2J_{\text{FC}} = 25.0$ Hz), 101.4 (d, $^2J_{\text{FC}} = 18.5$ Hz), 97.9 (d, $^2J_{\text{FC}} = 2.5$ Hz), 97.4, 0.1.

^{19}F NMR (376 MHz, chloroform-D) δ -100.02 (appt, $J = 9.5$ Hz).

LCMS purity >99 % (UV), Ret. time = 23.09 min.

2-Amino-6-fluoro-3-((trimethylsilyl)ethynyl)benzaldehyde, 101.



2-Amino-3-bromo-6-fluorobenzaldehyde (1.144 g, 8.00 mmol), copper iodide (145 mg, 0.80 mmol) and bis(triphenylphosphine)palladium(II) dichloride (281 mg, 0.4 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon and cycled 3 times. DMF (dry 24 mL), triethylamine (dry, 3.34 mL, 24.00 mmol) were added followed by the drop wise addition of trimethylsilylacetylene (1.34 mL, 9.6 mmol). This mixture was heated to 80 °C for 4 h. The reaction mixture was cooled to rt and the diethyl ether (150 mL) was added to the mixture, this was then filtered through a pad of Celite, which was then washed with more diethyl ether (3 x 15 mL). Water (150 mL) was added and the organic layer separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (5 x 150 mL), dried with sodium sulphate and evaporated under reduced pressure on to silica. This crude was then loaded on to a silica gel column which was ran at a gradient of 0 % - 10 % diethyl ether in hexane, to give the title compound as a green solid.

Yield: 1.398 g (74%).

TLC (Diethyl ether: hexane 10 %) R_f = 0.70.

FTMS (m/z) found 236.0904, calcd for $[C_{12}H_{14}ONFSiH]^+$ 236.0901.

1H NMR (500 MHz, chloroform-D) δ 10.28 (s, 1H), 7.43 (dd, $^3J_{HH}$ = 8.5, $^4J_{FH}$ = 6.0 Hz, 1H), 6.28 (dd, $^3J_{FH}$ = 10.5, $^3J_{HH}$ = 8.5 Hz, 1H), 0.27 (s, 9H).

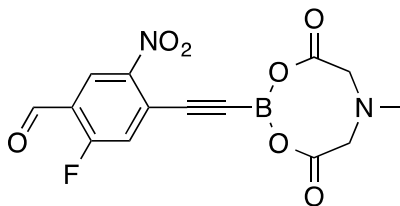
^{13}C NMR (126 MHz, chloroform-D) δ 188.8 (d, $^3J_{FC}$ = 12.0 Hz), 166.6 (d, $^1J_{FC}$ = 259.5 Hz), 152.3 (d, $^3J_{FC}$ = 5.0 Hz), 139.7 (d, $^2J_{FC}$ = 12.5 Hz), 107.6 (d, $^3J_{FC}$ = 10.5 Hz), 105.7 (d, $^4J_{FC}$ = 3.5 Hz), 102.0 (d, $^2J_{FC}$ = 22.0 Hz), 101.6 (d, $^5J_{FC}$ = 1.5 Hz), 99.2, 0.2.

^{19}F NMR (376 MHz, chloroform-D) δ -119.33 (dd, J = 11.0, 6.0 Hz).

LCMS purity >99% (UV), Ret. time = 24.74 min.

2-Fluoro-4-((6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)ethynyl)-5-n, 102.

4-Bromo-2-fluoro-5-nitrobenzaldehyde (143 mg, 0.575 mmol), copper iodide (9 mg, 0.05



mmol), bis(triphenylphosphine)palladium(II) dichloride (18 mg, 0.025 mmol) and ethynylboronic acid MIDA ester (90 mg, 0.5 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon 3 times. DMF (dry, 1.5 mL), triethylamine (dry, 209 μ L, 1.5 mmol) were added this mixture was stirred at rt over night. The DMF was evaporated under reduced pressure heptane was added and evaporated under reduced pressure (3 x 5 mL) to azeotropically remove any residual DMF. The residues were dissolved in acetone (15 mL) and evaporated under reduced pressure on to silica. This crude powder was then loaded on to a silica gel column which was ran at a gradient of 30% - 40% acetonitrile in DCM, to give title compound as a yellow solid.

Yield: mg 67 (38%).

TLC (MeCN:DCM 30%) R_f = 0.78.

FTMS (m/z) found 349.0638, calcd for $[C_{14}H_{10}BFN_2O_7H]^+$ 349.0638.

1H NMR (500 MHz, acetonitrile- D_3) δ 10.25 (s, 1H), 8.51 (d, $^4J_{FH}$ = 6.5 Hz, 1H), 7.70 (d, $^3J_{FH}$ = 10.0 Hz, 1H), 4.11 (d, J = 17.0 Hz, 2H), 3.98 (d, J = 17.0 Hz, 2H), 3.18 (s, 3H).

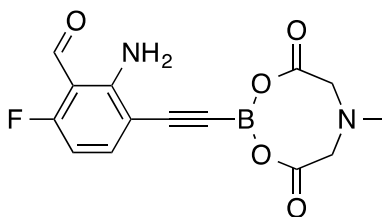
^{13}C NMR (126 MHz, acetonitrile- D_3) δ 185.4 (d, $^3J_{FC}$ = 4.5 Hz), 167.5, 164.7 (d, $^1J_{FC}$ = 266.0 Hz), 146.5, 126.2 (d, $^3J_{FC}$ = 4.5 Hz), 124.8 (d, $^2J_{FC}$ = 12.0 Hz), 124.2 (d, $^3J_{FC}$ = 11.0 Hz), 123.5 (d, $^2J_{FC}$ = 25.0 Hz), 61.7, 48.1.

^{19}F NMR (376 MHz, acetonitrile- D_3) δ -114.33 (dd, J = 10.0, 6.5 Hz).

^{11}B NMR (128 MHz, acetonitrile- D_3) δ 6.18.

LCMS purity >99% (UV), Ret. time = 23.46 min.

2-Amino-6-fluoro-3-((6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)ethynyl)benzaldehyde, 103.



2-Amino-3-bromo-6-fluorobenzaldehyde (429 mg, 1.97 mmol), copper iodide (31 mg, 0.17 mmol), bis(triphenylphosphine)palladium(II) dichloride (60 mg, 0.09 mmol) and ethynylboronic acid MIDA ester (310 mg, 1.71 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon and cycled 3 times. DMF (dry 6 mL), triethylamine (dry, 751 μ L, 5.13 mmol) were added this mixture was stirred at rt overnight. The DMF was evaporated under reduced pressure, heptane was added and evaporated under reduced pressure (3 x 5 mL) to azeotropically remove any residual DMF. The residue was dissolved in acetone (15 mL) and evaporated under reduced pressure on to silica. This crude powder was then loaded on to a silica gel column which was ran at a gradient of 30% - 40% acetonitrile in DCM, to give the title compound as a white solid.

Yield: 470 mg (86%).

TLC (MeCN:DCM 30%) R_f = 0.69.

FTMS (m/z) found 319.0900, calcd for $[C_{14}H_{12}BFN_2O_5H]^+$ 319.0896.

1H NMR (500 MHz, acetonitrile- d_3) δ 10.24 (s, 1H), 7.53 (dd, $^3J_{HH}$ = 8.5, $^4J_{FH}$ = 6.0 Hz, 1H), 7.04 (bs, 2H), 6.38 (dd, $^3J_{FH}$ = 11.5, $^4J_{HH}$ = 8.5 Hz, 1H), 4.04 (d, J = 17.0 Hz, 2H), 3.93 (d, J = 17.0 Hz, 2H), 3.09 (s, 3H).

^{13}C NMR (100 MHz, acetonitrile- D_3) δ 188.7 (d, $^3J_{FC}$ = 12.0 Hz), 167.7, 166.6 (d, $^1J_{FC}$ = 257.5 Hz), 152.2 (d, $^3J_{FC}$ = 5.5 Hz), 140.2 (d, $^2J_{FC}$ = 12.5 Hz), 107.2 (d, $^3J_{FC}$ = 10.5 Hz), 105.1 (d, $^4J_{FC}$ = 3.5 Hz), 101.6 (d, $^2J_{FC}$ = 22.5 Hz), 94.0, 61.6, 48.0.

^{19}F NMR (376 MHz, acetonitrile- D_3) δ -120.70 (dd, J = 11.5, 6.0 Hz).

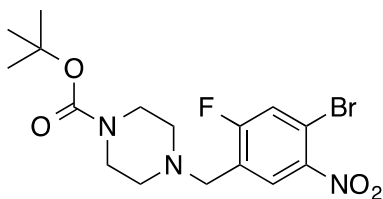
^{11}B NMR (128 MHz, acetonitrile- D_3) δ 6.50.

LCMS purity >99% (UV), Ret. time = 16.41 min.

General procedure for reductive aminations.

A benzaldehyde derivative (1 eq), sodium triacetoxyborohydride (2-2.5 eq) and a secondary amine (1.1 eq) were added to a round-bottomed flask and purged with argon. This was dissolved in THF (5 mLmmol⁻¹), acetic acid (1 eq) was added to the resulting stirred mixture and then left at rt overnight. Once there was no starting material observed via TLC water was added to quench. This was then extracted with ethyl acetate (3 times) then combined organic layers were washed with brine (3 times), the organic layer was dried (Na₂SO₄). Alternatively on scales less than 1 mmol, hydrophobic phase separators were used with DCM extractions (3 times). The organic layer was then evaporated under reduced pressure on to silica. This silica pad was then loaded on to a silica gel column and purified using a gradient of ethyl acetate in hexane.

tert-Butyl 4-(4-bromo-2-fluoro-5-nitrobenzyl)piperazine-1-carboxylate, 104.



The general reductive amination procedure was used on a 0.5 mmol and 8 mmol scale, with 1-Boc-piperazine and 2 eq of sodium triacetoxyborohydride. The crude material was purified by column chromatography using a 0% to 20% gradient of EtOAc in hexane, giving the title compound as a orange solid.

Yield: 98 mg (0.5 mmol scale, 47%) 2.579 g (8.0 mmol scale, 77%).

TLC (EtOAc: hexane 20%) R_f = 0.20.

HRMS-ESI (m/z) found 418.0766, calcd for [C₁₆H₂₁⁷⁹BrFN₃O₄H]⁺ 418.0772.

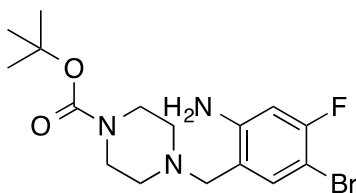
¹H NMR (500 MHz, chloroform-D) δ 8.06 (d, ⁴ J_{FH} = 6.5 Hz, 1H), 7.43 (d, ³ J_{FH} = 8.5 Hz, 1H), 3.56 (s, 2H), 3.46 -3.41 (m, 4H), 2.46 -2.40 (m, 4H), 1.45 (s, 9H).

¹³C NMR (126 MHz, chloroform-D) δ 162.2 (d, ¹ J_{FC} = 259.0 Hz), 154.8, 146.3, 128.5 (d, ³ J_{FC} = 6.5 Hz), 126.6 (d, ² J_{FC} = 16.5 Hz), 122.3 (d, ² J_{FC} = 27.0 Hz), 114.5 (d, ³ J_{FC} = 10.5 Hz), 80.0, 54.4, 53.0, 43.7, 28.6.

¹⁹F NMR (376 MHz, chloroform-D) δ -108.27 (appt, J = 7.5 Hz).

LCMS purity >99% (UV), Ret. time = 15.09 min.

***tert*-Butyl 4-(2-amino-5-bromo-4-fluorobenzyl)piperazine-1-carboxylate, 105.**



The general reductive amination procedure was used on a 0.5 mmol scale, with 1-Boc-piperazine 2.5 eq of sodium triacetoxyborohydride. The crude material was purified by column chromatography using a 0% to 20% gradient of EtOAc in hexane, giving the title compound as a yellow solid.

Yield: mg 161 mg (0.5 mmol scale, 83%) 1.048 g (2.95 mmol scale, 91%).

TLC (EtOAc: hexane 20%) R_f = 0.26.

HRMS-ESI (m/z) found 388.1017, calcd for $[C_{16}H_{23}^{79}BrFN_3O_2H]^+$ 388.1030.

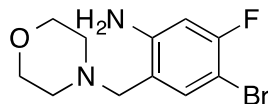
1H NMR (500 MHz, chloroform- D) δ 7.08 (d, $^4J_{FH}$ = 7.5 Hz, 1H), 6.40 (d, $^3J_{FH}$ = 10.0 Hz, 1H), 4.87 (s, 2H), 3.43 (s, 2H), 3.42- 3.37 (m, 4H), 2.39- 2.31 (m, 4H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, chloroform- D) δ 159.2 (d, $^1J_{FC}$ = 244.0 Hz), 154.7, 148.0 (d, $^3J_{FC}$ = 10.0 Hz), 134.3 (d, $^3J_{FC}$ = 2.0 Hz), 119.2 (d, $^4J_{FC}$ = 3.0 Hz), 103.3 (d, $^2J_{FC}$ = 25.0 Hz), 94.6 (d, $^2J_{FC}$ = 21.5 Hz), 79.8, 61.0, 52.5, 43.7, 28.5.

^{19}F NMR (376 MHz, chloroform- D) δ -109.56 (dd, J = 10.0, 7.5 Hz).

LCMS purity >99% (UV), Ret. time = 12.81 min.

4-Bromo-5-fluoro-2-(morpholinomethyl)aniline, 106.



The general reductive amination procedure was used on a 0.5 mmol scale, with morpholine and 2.5 eq of sodium triacetoxyborohydride. The crude material was purified by column chromatography using a 0% to 20% gradient of EtOAc in hexane, giving the title compound as a yellow solid.

Yield: mg 140 mg (97%).

TLC (EtOAc: hexane 20%) R_f = 0.30.

HRMS-ESI (m/z) found 289.0355, calcd for $[C_{11}H_{14}^{79}BrFN_2OH]^+$ 289.0346

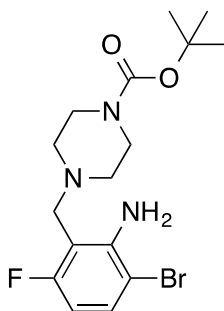
1H NMR (500 MHz, chloroform- D) δ 7.08 (d, $^4J_{FH}$ = 7.5 Hz, 1H), 6.38 (d, $^3J_{FH}$ = 10.5 Hz, 1H), 4.90 (s, 2H), 3.69–3.62 (m, 4H), 3.41 (s, 2H), 2.44–2.32 (m, 4H).

^{13}C NMR (126 MHz, chloroform- D) δ 159.2 (d, $^1J_{FC}$ = 244.0 Hz), 148.0 (d, $^3J_{FC}$ = 10.0 Hz), 134.3 (d, $^3J_{FC}$ = 2.0 Hz), 119.1 (d, $^4J_{FC}$ = 3.0 Hz), 103.2 (d, $^2J_{FC}$ = 25.0 Hz), 94.6 (d, $^2J_{FC}$ = 21.0 Hz), 67.0, 61.3, 53.2.

^{19}F NMR (376 MHz, chloroform- D) δ -109.58 – -109.67 (m).

LCMS purity >99% (UV), Ret. time = 9.38 min.

***tert*-Butyl 4-(2-amino-3-bromo-6-fluorobenzyl)piperazine-1-carboxylate, 107.**



The general reductive amination procedure was used on either a 0.5 mmol or a 6.3 mmol scale, with 1-Boc-piperazine and 2 eq of sodium triacetoxyborohydride. The crude material was columned using a 0% 10% gradient of EtOAc in hexane to give the title compound as a white crystalline solid.

Yield: 160 mg (0.5 mmol scale, 82%) 2.336 g (6.3 mmol scale, 95%).

TLC (EtOAc: hexane 20%) R_f = 0.52.

HRMS-ESI (m/z) found 388.1017, calcd for $[C_{16}H_{23}^{79}BrFN_3O_2H]^+$ 388.1030.

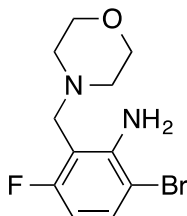
1H NMR (500 MHz, acetone- D_6) δ 7.35 (dd, $^3J_{HH}$ = 9.0, $^4J_{FH}$ = 6.0 Hz, 1H), 6.38 (pt, $^3J_{HH}$ = 9.0 Hz, 1H), 5.62 (s, 2H), 3.59 (m, 2H), 3.37 (m, 4H), 2.40 (t, J = 5.0 Hz, 4H), 1.43 (s, 9H).

^{13}C NMR (126 MHz, acetone- D_6) δ 162.1 (d, $^1J_{FC}$ = 241.5 Hz), 155.0, 147.7 (d, $^3J_{FC}$ = 6.5 Hz), 132.8 (d, $^3J_{FC}$ = 11.0 Hz), 110.4 (d, $^2J_{FC}$ = 17.5 Hz), 105.2 (d, $^2J_{FC}$ = 25.5 Hz), 104.3 (d, $^4J_{FC}$ = 3.0 Hz), 79.7, 53.2, 52.9, 44.5 (d, $^3J_{FC}$ = 4.5 Hz), 28.6.

^{19}F NMR (376 MHz, acetone- D_6) δ -121.00--121.09 (m).

LCMS purity > 92% (UV), Ret. time = 13.93 min.

6-Bromo-3-fluoro-2-(morpholinomethyl)aniline, 108.



The general reductive amination procedure was used on a 0.5 mmol scale, with morpholine and 2 eq of sodium triacetoxyborohydride. The crude material purified by column chromatography using a 0%-20% gradient of EtOAc in hexane, giving the title compound as a yellow solid.

Yield: 137 mg (95%).

TLC (EtOAc: hexane 20%) R_f = 0.50.

HRMS-ESI (m/z) found 289.0351, calcd for $[\text{C}_{11}\text{H}_{14}^{79}\text{BrFN}_2\text{OH}]^+$ 289.0346.

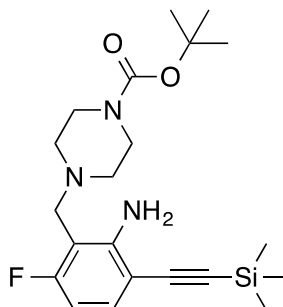
^1H NMR (500 MHz, acetone- D_6) δ 7.25 (dd, $^3J_{\text{HH}}$ 9.0, $^4J_{\text{FH}}$ = 5.5 Hz, 1H), 6.29 (pt, $^3J_{\text{HH}}$, $^3J_{\text{FH}}$ = 9.0 Hz, 1H), 5.55 (s, 2H), 3.57 – 3.51 (m, 4H), 3.49 (d, $^4J_{\text{FH}}$ = 2.0 Hz, 2H), 2.36 – 2.30 (m, 4H).

^{13}C NMR (126 MHz, acetone- D_6) δ 162.4 (d, $^1J_{\text{FC}}$ = 241.5 Hz), 147.9 (d, $^3J_{\text{FC}}$ = 6.5 Hz), 132.9 (d, $^3J_{\text{FC}}$ = 10.5 Hz), 110.5 (d, $^2J_{\text{FC}}$ = 17.5 Hz), 105.5 (d, $^2J_{\text{FC}}$ = 26.0 Hz), 104.5 (d, $^4J_{\text{FC}}$ = 2.5 Hz), 67.7, 54.1, 53.5 (d, $^3J_{\text{FC}}$ = 4.0 Hz).

^{19}F NMR (376 MHz, acetone- D_6) δ -121.22 – -121.32 (m).

LCMS purity >99% (UV), Ret. time = 14.11 min.

***tert*-Butyl 4-(2-amino-6-fluoro-3-((trimethylsilyl)ethynyl)benzyl)piperazine-1-carboxylate, 109.**



The general reductive amination procedure was used on a 0.5 mmol scale, with 1-Boc-piperazine 2 eq of sodium triacetoxyborohydride. The crude material was subjected to column chromatography using a gradient of 0% to 10% EtOAc in hexane, giving the title compound as an orange solid.

Yield: 56 mg (28%).

TLC (EtOAc: hexane 20%) R_f = 0.63.

HRMS-ESI (m/z) found 406.2307, calcd for $[C_{21}H_{32}BrFN_3O_2SiH]^+$ 406.2321.

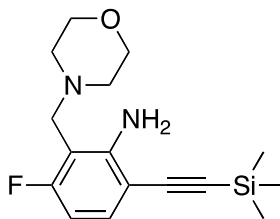
1H NMR (500 MHz, chloroform- D) δ 7.18 (dd, $^3J_{HH}$ = 8.5, $^4J_{FH}$ = 6.0 Hz, 1H), 6.32 (pt, $^3J_{HH}$, $^3J_{FH}$ = 9.0 Hz, 1H), 5.50 (s, 2H), 3.56 (d, $^4J_{FH}$ = 1.5 Hz, 2H), 3.46-3.35 (m, 4H), 2.44-2.34 (m, 4H), 1.44 (s, 9H), 0.25 (s, 9H).

^{13}C NMR (126 MHz, chloroform- D) δ 162.2 (d, $^1J_{FC}$ = 246.5 Hz), 154.8, 151.1 (d, $^3J_{FC}$ = 7.0 Hz), 132.5 (d, $^3J_{FC}$ = 11.0 Hz), 108.0 (d, $^2J_{FC}$ = 17.0 Hz), 104.3 (d, $^4J_{FC}$ = 2.5 Hz), 104.2 (d, $^2J_{FC}$ = 25.0 Hz), 101.4, 99.5 (d, $^5J_{FC}$ = 25.0 Hz), 79.9, 52.5, 52.2 (d, $^3J_{FC}$ = 4.0 Hz), 43.8, 28.5, 0.3.

^{19}F NMR (376 MHz, chloroform- D) δ -115.18 – -115.76 (m).

LCMS purity >99% (UV), Ret. time = 18.45 min.

3-Fluoro-2-(morpholinomethyl)-6-((trimethylsilyl)ethynyl)aniline, 110.



The general reductive amination procedure was used on a 0.5 mmol scale, with morpholine and 2 eq of sodium triacetoxyborohydride. The crude material was purified by column chromatography using a 0% to 10% gradient of EtOAc in hexane, giving the title compound as an orange solid.

Yield: 96 mg (63%).

TLC (EtOAc: hexane 20%) R_f = 0.59.

HRMS-ESI (m/z) found 307.1625, calcd for $[C_{16}H_{22}BrFN_2OSiH]^+$ 307.1636.

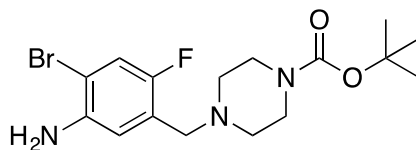
1H NMR (500 MHz, chloroform- D) δ 7.18 (dd, $^3J_{HH}$ = 8.55, $^4J_{FH}$ = 6.0 Hz, 1H), 6.33 (t, $^3J_{HH}$, $^3J_{FH}$ = 9.0 Hz, 1H), 5.54 (s, 2H), 3.67 (appt, J = 4.5 Hz, 4H), 3.56 (d, J = 1.5 Hz, 2H), 2.48 - 2.39 (m, 4H), 0.26 (d, J = 0.8 Hz, 9H).

^{13}C NMR (126 MHz, chloroform- D) δ 162.3 (d, $^1J_{FC}$ = 246.5 Hz), 151.1 (d, $^3J_{FC}$ = 7.5 Hz), 132.4 (d, $^3J_{FC}$ = 11.0 Hz), 107.8 (d, $^2J_{FC}$ = 17.0 Hz), 104.2 (d, $^2J_{FC}$ = 25.0 Hz), 104.2 (d, $^4J_{FC}$ = 3.0 Hz), 101.5, 99.4 (d, $^5J_{FC}$ = 1.5 Hz), 67.2, 53.1, 52.5 (d, $^3J_{FC}$ = 4.0 Hz), 0.3.

^{19}F NMR (376 MHz, chloroform- D) δ -115.25 – -115.60 (m).

LCMS purity >99% (UV), Ret. time = 13.75 min.

***tert*-Butyl 4-(5-amino-4-bromo-2-fluorobenzyl)piperazine-1-carboxylate, 111.**



tert-Butyl 4-(4-bromo-2-fluoro-5-nitrobenzyl)piperazine-1-carboxylate (1.254 mg, 3 mmol) was dissolved in methanol (11 mL). To this mixture zinc powder (1.950 mg, 30 mmol) was added followed by saturated ammonium chloride (11 mL). This mixture was allowed to stir at rt for 14 h before it was filtered through a bed of celite, this was then washed with ethyl acetate (3 x 10 mL). This mixture was then extracted with ethyl acetate (3 x 30 mL), the combined organic layers were then washed with brine (2 x 20 mL) dried with sodium sulphate and evaporated onto silica. This silica pad was then loaded onto a silica gel column and was purified using ethyl acetate: hexane 50%. This gave title compound as a light yellow solid.

Yield: 546 mg (47%).

TLC (EtOAc: hexane 50%) R_f = 0.30.

HRMS-ESI (m/z) found 388.1017, calcd for $[C_{16}H_{23}^{79}BrFN_3O_2H]^+$ 388.1030.

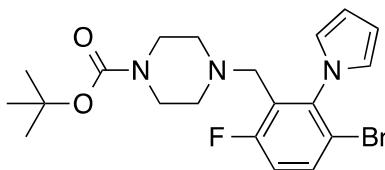
1H NMR (500 MHz, chloroform- D) δ 7.13 (d, $^3J_{FH}$ = 9.0 Hz, 1H), 6.80 (d, $^4J_{FH}$ = 6.5 Hz, 1H), 3.91 (s, 2H), 3.46 (s, 2H), 3.45 – 3.39 (m, 4H), 2.45 – 2.36 (m, 5H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, chloroform- D) δ 154.9, 154.1 (d, $^1J_{FC}$ = 240.5 Hz), 140.6 (d, $^4J_{FC}$ = 2.5 Hz), 125.0 (d, $^2J_{FC}$ = 16.0 Hz), 119.2 (d, $^2J_{FC}$ = 26.5 Hz), 117.3 (d, $^3J_{FC}$ = 4.0 Hz), 107.5 (d, $^3J_{FC}$ = 10.0 Hz), 79.8, 55.2, 52.9, 43.8, 28.6.

^{19}F NMR (376 MHz, Chloroform- D) δ -129.75 – -129.83 (m).

LCMS purity >99% (UV), Ret. time = 11.19 min.

***tert*-Butyl 4-(3-bromo-6-fluoro-2-(1*H*-pyrrol-1-yl)benzyl)piperazine-1-carboxylate, 112.**



tert-Butyl 4-(2-amino-3-bromo-6-fluorobenzyl)piperazine-1-carboxylate (58 mg, 0.15 mmol), 2,5-Dimethoxytetrahydrofuran (22 mg, 0.17 mmol) and acetic acid (1.5 mL) were added to a 10 mL microwave vial. This was loaded in to the microwave and heated at 115 °C for 15 min. The cooled reaction mixture was transferred to round-bottomed; ethyl acetate was used to transfer washing from the microwave vial and evaporated under reduced pressure. The residues were dissolved in DCM (3 mL) then saturated sodium hydrogen carbonate was added (5 mL), a hydrophobic phase separators was used with DCM extractions (3 x 3 mL). The combined organic layer was then evaporated under reduced pressure on to silica. This silica pad was then loaded on to a silica gel column and purified using a gradient of 10 % - 20% ethyl acetate in hexane, to the give title compound as a white solid.

Yield: 42 mg (64%).

TLC (EtOAc:Hexane 20%) R_f = 0.54.

HRMS-ESI (m/z) found 338.0663, calcd for product without BOC [$C_{15}H_{18}N_3F^{79}BrH$]⁺ 338.0663.

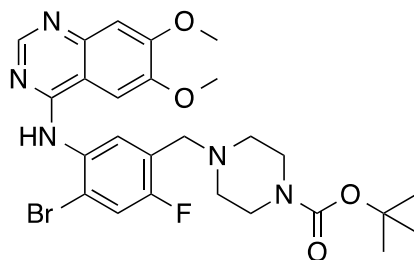
¹H NMR (500 MHz, chloroform-D) δ 7.58 (dd, $^3J_{HH}$ = 9.0, $^4J_{FH}$ = 5.5 Hz, 1H), 7.04 (appt, $^3J_{HH}$, $^3J_{FH}$ = 9.0 Hz, 1H), 6.72 (t, J = 2.0 Hz, 2H), 6.30 (t, J = 2.0 Hz, 2H), 3.33-3.29 (m, 4H), 3.22 (d, $^4J_{FH}$ = 2.0 Hz, 2H), 2.29-2.21 (m, 4H), 1.43 (s, 9H).

¹³C NMR (126 MHz, chloroform-D) δ 160.8 (d, $^1J_{FC}$ = 249.0 Hz), 154.8, 142.3 (d, $^3J_{FC}$ = 6.0 Hz), 132.7 (d, $^3J_{FC}$ = 9.5 Hz), 126.7 (d, $^2J_{FC}$ = 16.5 Hz), 122.7, 118.3 (d, $^4J_{FC}$ = 3.5 Hz), 116.8 (d, $^2J_{FC}$ = 24.5 Hz), 108.9, 79.7, 52.7, 51.7, 43.9, 28.6.

¹⁹F NMR (376 MHz, chloroform-D) δ -114.53 – -114.85 (m).

LCMS purity >99% (UV), Ret. time = 16.86 min.

***tert*-Butyl 4-(4-bromo-5-((6,7-dimethoxyquinazolin-4-yl)amino)-2-fluorobenzyl)-piperazine-1-carboxylate, 113.**



tert-Butyl 4-(5-amino-4-bromo-2-fluorobenzyl)piperazine-1-carboxylate (533 mg, 1.37 mmol) and 4-chloro-6,7-dimethoxyquinazoline (341 mg, 1.51 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon 3 times. DMF (dry 15 mL) was added, this mixture was cooled to 0 °C, then sodium bis(trimethylsilyl)amide (1M, 6.00 mL) was added drop wise over 5 min. The mixture was allowed to stir at 0 °C for 30 min, then the mixture was stirred for further 30 min at rt. The bulk of the DMF was evaporated under reduced pressure, and then ethyl acetate (30 mL) was added to the mixture. This organic layer was washed with water (50 mL) this water layer was extracted with ethyl acetate (2 x 30 mL), the combined organic layer was washed with brine (5 x 30 mL) dried with magnesium sulphate and evaporated under reduced pressure on to silica. This crude was then loaded on to a silica gel column which was ran at a gradient of 5% - 20% methanol in dichloromethane, this also needed recrystallization from the minimum amount of hot ethyl acetate, to the give title compound as a white solid.

Yield: 378 mg (48%).

TLC (MeOH:DCM 10%) R_f = 0.68.

HRMS-ESI (m/z) found 576.1616, calcd for $[\text{C}_{26}\text{H}_{31}^{79}\text{BrFN}_5\text{O}_4\text{H}]^+$ 576.1616.

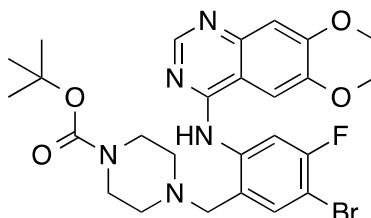
^1H NMR (500 MHz, chloroform- D) δ 8.68 (s, 1H), 8.63 (d, $^4J_{\text{FH}} = 7.0$ Hz, 1H), 7.51 (s, 1H), 7.35 (d, $^3J_{\text{FH}} = 8.5$ Hz, 1H), 7.29 (s, 1H), 7.08 (s, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 3.63 (d, $^4J_{\text{FH}} = 1.5$ Hz, 2H), 3.49 – 3.42 (m, 4H), 2.53 – 2.45 (m, 4H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, chloroform- D) δ 157.0 (d, $^1J_{\text{FC}} = 248.0$ Hz), 155.9, 155.2, 154.9, 153.6, 150.1, 147.9, 133.0, 125.48 (d, $^3J_{\text{FC}} = 3.0$ Hz), 125.2 (d, $^2J_{\text{FC}} = 15.5$ Hz), 119.3 (d, $^2J_{\text{FC}} = 27.0$ Hz), 113.5 (d, $^3J_{\text{FC}} = 10.0$ Hz), 109.5, 108.4, 99.0, 79.8, 56.5, 56.4, 55.3, 52.8, 28.6. One carbon missing from piperazine carbamate.

^{19}F NMR (376 MHz, chloroform-D) δ -120.70 – -121.00 (m).

LCMS purity >99% (UV), Ret. time = 9.94 min.

***tert*-Butyl 4-(5-bromo-2-((6,7-dimethoxyquinazolin-4-yl)amino)-4-fluorobenzyl)-piperazine-1-carboxylate, 114.**



tert-Butyl 4-(2-amino-5-bromo-4-fluorobenzyl)piperazine-1-carboxylate (388 mg, 1.00 mmol) and 4-chloro-6,7-dimethoxyquinazoline (225 mg, 1.10 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon 3 times. DMF (dry 16 mL) was added, this mixture was cooled to 0 °C, then sodium bis(trimethylsilyl)amide (1M, 2.00 mL) was added drop wise over 5 min. The mixture was allowed to stir at 0 °C for 30 min, then the mixture was stirred for further 30 min at rt. The bulk of the DMF was evaporated under reduced pressure, and then ethyl acetate (25 mL) was added to the mixture. This organic layer was washed with water (50 mL) this water layer was extracted with ethyl acetate (2 x 25 mL), the combined organic layer was washed with brine (5 x 50 mL) dried with sulphate and evaporated under reduced pressure on to silica. This crude was then loaded on to a silica gel column which was ran at a gradient of 90% - 100% ethyl acetate in hexane, to give the title compound as a light orange solid.

Yield: 245 mg (42%).

TLC (EtOAc 100%) R_f = 0.45.

HRMS-ESI (m/z) found 576.1626, calcd for $[\text{C}_{26}\text{H}_{31}^{79}\text{BrFN}_5\text{O}_4\text{H}]^+$ 576.1616.

^1H NMR (399 MHz, chloroform-D) δ 10.04 (s, 1H), 8.70 (s, 1H), 8.43 (d, $^3J_{\text{FH}}$ = 11.0 Hz, 1H), 7.33 (d, $^4J_{\text{FH}}$ = 7.5 Hz, 1H), 7.29 (s, 1H), 7.12 (s, 1H), 3.68 (s, 2H), 3.61-3.50 (m, 4H), 2.58-2.48 (m, 4H), 1.47 (s, 9H).

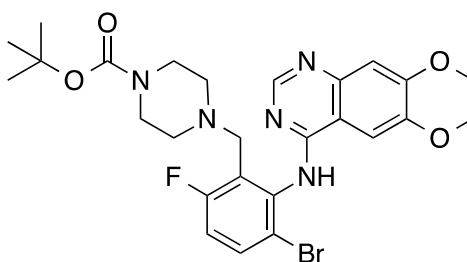
^{13}C NMR (100 MHz, chloroform-D) δ 158.9 (d, $^1J_{\text{FC}}$ = 245.0 Hz), 156.1, 155.7, 154.7, 153.7, 150.0, 148.5, 140.2 (d, $^3J_{\text{FC}}$ = 10.5 Hz), 134.3 (d, $^4J_{\text{FC}}$ = 2.0 Hz), 122.9 (d, $^3J_{\text{FC}}$ =

3.5 Hz), 110.6 (d, $^2J_{\text{FC}} = 28.0$ Hz), 110.1, 108.5, 101.9, 101.4 (d, $^2J_{\text{FC}} = 21.5$ Hz), 80.5, 61.6, 57.5, 56.4, 52.8, 43.6, 28.5.

^{19}F NMR (376 MHz, chloroform-D) δ -106.28 --106.41 (m).

LCMS purity >99% (UV), Ret. time = 10.59 min.

***tert*-Butyl 4-(3-bromo-2-((6,7-dimethoxyquinazolin-4-yl)amino)-6-fluorobenzyl)-piperazine-1-carboxylate, 115.**



tert-Butyl 4-(2-amino-3-bromo-6-fluorobenzyl)piperazine-1-carboxylate (1.164 g, 3.00 mmol) and 4-chloro-6,7-dimethoxyquinazoline (0.743 g, 3.3 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon 3 times. DMF (dry 48 mL) was added, this mixture was cooled to 0 °C, then sodium bis(trimethylsilyl)amide (1M, 6.00 mL) was added drop wise over 5 min. The mixture was allowed to stir at 0 °C for 30 min, then the mixture was stirred for further 30 min at rt. The bulk of the DMF was evaporated under reduced pressure, and then ethyl acetate (75 mL) was added to the mixture. This organic layer was washed with water (100 mL) this water layer was extracted with ethyl acetate (2 x 75 mL) the combined organic layer was washed with brine (5 x 100 mL) dried with sulphate and evaporated under reduced pressure on to silica. This crude was then loaded on to a silica gel column which was ran at a gradient of 90% - 100% ethyl acetate in hexane, to give the title compound as a light yellow solid.

Yield: 1.235 mg (72%).

TLC (EtOAc 100%) $R_f = 0.32$.

HRMS-ESI (m/z) found 576.1613, calcd for $[\text{C}_{25}\text{H}_{31}^{79}\text{BrFN}_5\text{O}_4\text{H}]^+$ 576.1616.

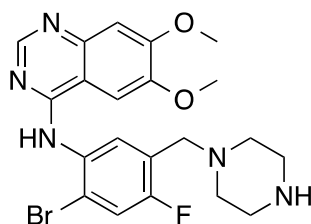
^1H NMR (399 MHz, DMSO- D_6) δ 8.20 (s, 1H), 7.78 (s, 1H), 7.68 (dd, $^3J_{\text{HH}} = 9.0$, $^4J_{\text{FH}} = 5.5$ Hz, 1H), 7.19 (s, 1H), 7.10 (appt, $^3J_{\text{FH}}$, $^3J_{\text{HH}} = 9.0$ Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.52 (s, 2H), 3.09-3.02 (m, 4H), 2.26-2.20 (m, 4H), 1.37 (s, 9H).

^{13}C NMR (126 MHz, chloroform- D) δ 160.6 (d, $^1J_{\text{FC}} = 247.5$ Hz), 156.5, 155.2, 154.4, 153.7, 149.8, 147.7, 140.5, 133.64 (d, $^3J_{\text{FC}} = 9.5$ Hz), 120.8 (d, $^2J_{\text{FC}} = 15.5$ Hz), 116.8, 113.9 (d, $^2J_{\text{FC}} = 24.5$ Hz), 110.0, 107.9, 100.1, 80.2, 56.4, 56.3, 52.8, 52.5, 43.7, 28.3.

^{19}F NMR (376 MHz, DMSO- D_6) δ -116.09 – -116.24 (m).

LCMS purity 94% (UV), Ret. time = 10.6 min.

***N*-(2-Bromo-4-fluoro-5-(piperazin-1-ylmethyl)phenyl)-6,7-dimethoxyquinazolin-4-amine, 116.**



tert-Butyl 4-(4-bromo-5-((6,7-dimethoxyquinazolin-4-yl)amino)-2-fluorobenzyl)-piperazine-1-carboxylate (99 mg, 0.17 mmol) was added to a round bottomed flask then hydrogen chloride solution in dioxane (4M, 1.4 mL) was added. This mixture was stirred for 15 min and the sonicated for a 15 min. This mixture was then evaporated under reduced pressure, the residues were then dissolved in methanol (4 mL) and the minimum amount of water was added to aid to dissolve the residues. This solution was then loaded onto a SCX column, the column was then washed with methanol (20 mL) and then acetonitrile (20 mL). This was then eluted with ammonia in methanol (2 M) then was then evaporated under reduced pressure to give the title compound as a white solid.

Yield: 130mg (55%).

HRMS-ESI (m/z) found 476.1082, calcd for $[\text{C}_{21}\text{H}_{23}^{79}\text{BrFN}_5\text{O}_2\text{H}]^+$ 476.1092.

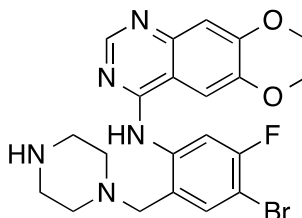
^1H NMR (500 MHz, methanol- D_4) δ 8.27 (s, 1H), 7.69 (s, 1H), 7.62 (d, $^4J_{\text{FH}} = 7.0$ Hz, 1H), 7.52 (d, $^3J_{\text{FH}} = 9.0$ Hz, 1H), 7.17 (s, 1H), 4.01 (s, 3H), 4.00 (s, 3H), 3.59 (s, 2H), 2.87 (t, $J = 5.0$ Hz, 4H), 2.54 (s, 4H).

^{13}C NMR (126 MHz, methanol- D_4) δ 159.3 (d, $^1J_{\text{FC}} = 249.5$ Hz), 158.2, 155.5, 152.4, 149.9, 146.2, 133.6 (d, $^3J_{\text{FC}} = 4.0$ Hz), 131.9, 124.6 (d, $^2J_{\text{FC}} = 16.1$ Hz), 121.1 (d, $^3J_{\text{FC}} = 7.0$ Hz), 119.6 (d, $^2J_{\text{FC}} = 27.0$ Hz), 108.8, 105.8, 101.2, 55.5, 55.2, 54.6, 52.7, 44.7.

^{19}F NMR (376 MHz, methanol- D_4) δ -109.74 – -109.81 (m).

Elemental analysis CHN (%) found C: 45.97, H: 4.30, N: 12.02, calcd for $C_{21}H_{23}BrFN_5O_2 \cdot HCl \cdot 0.6CCl_2H_2$: 46.02, H: 4.51, N: 12.42.

***N*-(4-Bromo-5-fluoro-2-(piperazin-1-ylmethyl)phenyl)-6,7-dimethoxyquinazolin-4-amine, 117.**



tert-Butyl 4-(5-bromo-2-((6,7-dimethoxyquinazolin-4-yl)amino)-4-fluorobenzyl)-piperazine-1-carboxylate (288 mg, 0.5 mmol) was added to a round bottomed flask then hydrogen chloride solution in dioxane (4M, 4 mL) was added. This mixture was stirred for 15 min and the sonicated for a 15 min. This mixture was then evaporated under reduced pressure, the residues were then, methanol (5 mL) and the minimum amount of water was added to aid to dissolve the residues. This solution was then loaded onto a SCX column, the column was then washed with methanol (20 mL) and then acetonitrile (20 mL). This was then eluted with ammonia in methanol (2 M) which was then evaporated under reduced pressure to give the compound as a white solid.

Yield: 199 mg (84%).

HRMS-ESI (m/z) found 476.1091, calcd for $[C_{21}H_{23}^{79}BrFN_5O_2H]^+$ 476.1092.

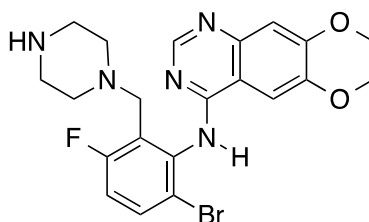
1H NMR (500 MHz, methanol- D_4) δ 8.49 (s, 1H), 8.29 (d, $^3J_{FH} = 11.0$ Hz, 1H), 7.53 (d, $^4J_{FH} = 7.5$ Hz, 1H), 7.33 (s, 1H), 7.19 (s, 1H), 4.01 (s, 3H), 4.00 (s, 3H), 3.68 (s, 2H), 2.93 – 2.86 (m, 4H), 2.58 – 2.48 (m, 4H).

^{13}C NMR (126 MHz, methanol- D_4) δ 159.7 (d, $^1J_{FC} = 243.5$ Hz), 157.9, 157.6, 154.0, 151.6, 148.4, 141.0 (d, $^3J_{FC} = 10.5$ Hz), 135.5 (d, $^4J_{FC} = 1.5$ Hz), 126.8 (d, $^3J_{FC} = 3.0$ Hz), 112.3 (d, $^2J_{FC} = 27.5$ Hz), 110.9, 107.9, 104.0, 102.9 (d, $^2J_{FC} = 21.5$ Hz), 61.7, 58.2, 56.7, 54.2, 46.3.

^{19}F NMR (376 MHz, methanol- D_4) δ -119.49 – -119.64 (m).

LCMS purity >99% (UV), Ret. time = 9.06 min.

***N*-(6-Bromo-3-fluoro-2-(piperazin-1-ylmethyl)phenyl)-6,7-dimethoxyquinazolin-4-amine, 118.**



tert-Butyl 4-(3-bromo-2-((6,7-dimethoxyquinazolin-4-yl)amino)-6-fluorobenzyl)-piperazine-1-carboxylate (99 mg, 0.17 mmol) was added to a round bottomed flask then hydrogen chloride solution in dioxane (4M, 1.4 mL) was added. This mixture was stirred for 15 min and then sonicated for a 15 min. This mixture was then evaporated under reduced pressure, the residues were then dissolved in methanol (4 mL) and the minimum amount of water was added to aid to dissolve the residues. This solution was and then loaded onto a SCX column, the column was then washed with methanol (20 mL) and then acetonitrile (20 mL). The product was then eluted with ammonia in methanol (2 M) and this was then evaporated under reduced pressure to give title compound as a white solid.

Yield: 80 mg (99%).

HRMS-ESI (m/z) found 476.1087, calcd for $[\text{C}_{25}\text{H}_{31}^{79}\text{BrFN}_5\text{O}_4\text{H}]^+$ 476.1092.

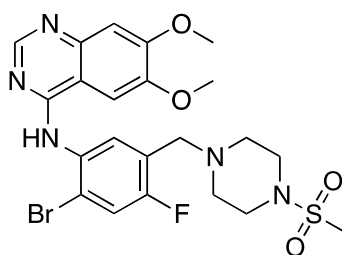
^1H NMR (399 MHz, methanol- d_4) δ 8.24 (s, 1H), 7.72 – 7.64 (m, 2H), 7.19 (s, 1H), 7.09 (t, J = 9.0 Hz, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.71 – 3.40 (m, 1H), 2.77 – 2.66 (m, 4H), 2.46 – 2.37 (m, 4H).

^{13}C NMR (100 MHz, methanol- d_4) δ 161.1 (d, J = 246.5 Hz), 157.5, 155.6, 152.0, 150.1, 146.1, 139.8, 132.9 (d, J = 9.5 Hz), 124.6 (d, J = 16.0 Hz), 118.6, 115.0 (d, J = 25.0 Hz), 109.3, 106.2, 101.6, 55.7, 55.3, 52.0, 51.8, 44.4.

^{19}F NMR (376 MHz, chloroform- d) δ -105.68.

LCMS purity >99% (UV), Ret. time = 12.26 min.

***N*-(2-bromo-4-fluoro-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)-6,7-dimethoxyquinazolin-4-amine, 119.**



N-(2-Bromo-4-fluoro-5-(piperazin-1-ylmethyl)phenyl)-6,7-dimethoxyquinazolin-4-amin (29 mg, 0.06 mmol) was added to a round bottomed flask, then dichloromethane (dry, 0.5 mL) followed by *N,N*-diisopropylethylamine was added (21 μ L, 0.122 mmol). To this stirred mixture methanesulfonyl chloride (5 μ L, 0.066 mmol) was added. After 1 h of stirring at room temperature the reaction had gone to completion, dichloromethane (5 mL) was added followed by water (5 mL). This mixture was then added to a phase separator, the aqueous layer was washed with dichloromethane (2 x 5 mL). The combined organic washes were evaporated under reduced pressure. No further purification was required giving the title compound as a white solid.

Yield: 21 mg (63%).

HRMS-ESI (m/z) found 554.0864, calcd for $[\text{C}_{22}\text{H}_{26}^{79}\text{BrFN}_5\text{O}_4\text{SH}]^+$ 554.0867.

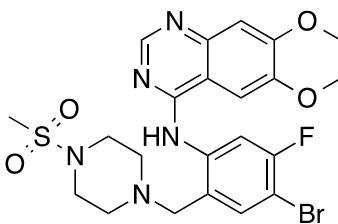
^1H NMR (500 MHz, chloroform- D) δ 9.92 (s, 1H), 8.71 (s, 1H), 8.54 (d, $^3J_{\text{FH}} = 11.0$ Hz, 1H), 7.36 (d, $^4J_{\text{FH}} = 7.5$ Hz, 1H), 7.32 (s, 1H), 7.20 (s, 1H), 4.04 (s, 3H), 3.99 (s, 3H), 3.74 (s, 2H), 3.45 – 3.34 (m, 4H), 2.82 (s, 3H), 2.77 – 2.66 (m, 4H).

^{13}C NMR (126 MHz, chloroform- D) δ 159.0 (d, $^1J_{\text{FC}} = 246.0$ Hz), 156.0, 153.7, 149.8, 148.4, 140.0, 134.2, 122.1, 109.8, 108.6, 104.0, 60.9, 58.4, 56.3, 52.3, 45.3, 35.4. Three carbons missing as the compound had low solubility in low boiling point NMR solvents.

^{19}F NMR (376 MHz, methanol- d_4) δ -118.78 – -118.83 (m).

LCMS purity 90 % (UV), Ret. time = 9.19 min.

***N*-(4-bromo-5-fluoro-2-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)-6,7-dimethoxyquinazolin-4-amine, 120.**



N-(4-Bromo-5-fluoro-2-(piperazin-1-ylmethyl)phenyl)-6,7-dimethoxyquinazolin-4-amine (29 mg, 0.06 mmol) was added to a round bottomed flask, then dichloromethane (dry, 0.5 mL) followed by *N,N*-diisopropylethylamine was added (21 μ L, 0.122 mmol). To this stirred mixture methanesulfonyl chloride (5 μ L, 0.066 mmol) was added. After 1 hr of stirring at room temperature the reaction had gone to completion, dichloromethane (5 mL) was added followed by water (5 mL). This mixture was then added to a phase separator, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic were evaporated under reduced pressure. No further purification was required giving the title compound as a white solid.

Yield: 33 mg (99%).

HRMS-ESI (*m/z*) found 554.0868, calcd for $[\text{C}_{22}\text{H}_{26}^{79}\text{BrFN}_5\text{O}_4\text{SH}]^+$ 554.0867.

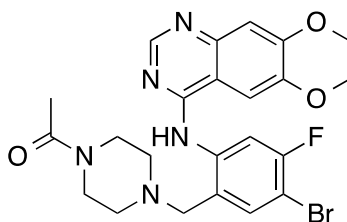
^1H NMR (500 MHz, chloroform-*D*) δ 8.64 (s, 1H), 8.54 (d, $^4J_{\text{FH}} = 7.0$ Hz, 1H), 7.84 (s, 1H), 7.38 (d, $^4J_{\text{FH}} = 8.5$ Hz, 1H), 7.31 (s, 1H), 7.18 (s, 1H), 4.08 (s, 3H), 4.05 (s, 3H), 3.68 (d, $J = 1.5$ Hz, 2H), 3.31 – 3.25 (m, 4H), 2.78 (s, 3H), 2.71 – 2.64 (m, 4H).

^{13}C NMR (126 MHz, chloroform-*D*) δ 156.9.8 (d, $J = 256.5$ Hz), 155.3, 152.6, 150.1, 132.8, 125.7, 124.4, 119.5, 119.2, 114.2, 109.1, 107.3, 99.2, 88.3, 56.4, 56.3, 54.8, 52.1, 45.8, 34.4.

^{19}F NMR (376 MHz, chloroform-*D*) δ -105.60 – -105.77 (m).

LCMS purity 90% (UV), Ret. time = 10.93 min.

1-(4-(5-bromo-2-((6,7-dimethoxyquinazolin-4-yl)amino)-4-fluorobenzyl)piperazin-1-yl)ethanone, 121.



N-(4-Bromo-5-fluoro-2-(piperazin-1-ylmethyl)phenyl)-6,7-dimethoxyquinazolin-4-amine (29 mg, 0.061 mmol) was added to a round bottomed flask, then dichloromethane (dry, 0.5 mL) followed by *N,N*-diisopropylethylamine (21 μ L, 0.122 mmol) were added. To this stirred mixture acetyl chloride (5 μ L, 0.067 mmol) was added, this reaction was monitored via TLC (10% methanol in dichloromethane). After 1 hr of stirring at room temperature the reaction had gone to completion, dichloromethane (5 mL) was added followed by water (5 mL). This mixture was then added to a phase separator, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic extracts were evaporated under reduced pressure on to silica. This crude was then loaded on to a silica gel column which was ran with 100 % dichloromethane to give the title compound as a white solid.

Yield: 31 mg (98%).

TLC (MeOH: DCM 10%) R_f = 0.62.

HRMS-ESI (m/z) found 518.1190, calcd for $[C_{23}H_{25}^{79}BrFN_5O_3H]^+$ 518.1198.

1H NMR (500 MHz, chloroform- D) δ 9.88 (s, 1H), 8.68 (s, 1H), 8.47 (d, $^3J_{FH}$ = 11.5 Hz, 1H), 7.32 (d, $^3J_{FH}$ = 7.5 Hz, 1H), 7.28 (s, 1H), 7.10 (s, 1H), 4.02 (s, 3H), 3.97 (s, 3H), 3.78 – 3.70 (m, 2H), 3.68 (s, 2H), 3.58 – 3.52 (m, 2H), 2.62 – 2.51 (m, 4H), 2.09 (s, 3H).

^{13}C NMR (126 MHz, chloroform- D) δ 169.0, 159.0 (d, $^1J_{FC}$ = 245.5 Hz), 156.1, 155.9, 153.7, 150.0, 148.5, 140.2 (d, $^3J_{FC}$ = 10.5 Hz), 134.3, 122.6 (d, $^3J_{FC}$ = 3.5 Hz), 110.6 (d, $^2J_{FC}$ = 28.0 Hz), 110.0, 108.6, 102.3, 101.4 (d, $^2J_{FC}$ = 22.0 Hz), 61.4, 57.7, 56.4, 53.0, 52.9, 46.10, 41.3, 21.3.

^{19}F NMR (376 MHz, methanol- d_4) δ -117.81 – -118.02 (m).

LCMS purity 96% (UV), Ret. time = 9.57 min.

5.7. Bibliography

- (1) Uitdehaag, J. C. M.; Verkaar, F.; Alwan, H.; De Man, J.; Buijsman, R. C.; Zaman, G. *J. R. Br. J. Pharmacol.* **2012**, *166*, 858–876.
- (2) Remsing Rix, L. L.; Rix, U.; Colinge, J.; Hantschel, O.; Bennett, K. L.; Stranzl, T.; Müller, a; Baumgartner, C.; Valent, P.; Augustin, M.; Till, J. H.; Superti-Furga, G. *Leuk. Off. J. Leuk. Soc. Am. Leuk. Res. Fund, U.K* **2009**, *23*, 477–485.
- (3) Martin, P.; Oliver, S.; Kennedy, S. J.; Partridge, E.; Hutchison, M.; Clarke, D.; Giles, P. *Clin. Ther.* **2012**, *34*, 221–237.
- (4) Finlay, M. R. V.; Anderton, M.; Ashton, S.; Ballard, P.; Bethel, P. A.; Box, M. R.; Bradbury, R. H.; Brown, S. J.; Butterworth, S.; Campbell, A.; Chorley, C.; Colclough, N.; Cross, D. A. E.; Currie, G. S.; Grist, M.; Hassall, L.; Hill, G. B.; James, D.; James, M.; Kemmitt, P.; Klinowska, T.; Lamont, G.; Lamont, S. G.; Martin, N.; Mcfarland, H. L.; Mellor, M. J.; Orme, J. P.; Perkins, D.; Perkins, P.; Richmond, G.; Smith, P.; Ward, R. A.; Waring, M. J.; Whittaker, D.; Wells, S.; Wrigley, G. L. *J. Med. Chem.* **2014**, *57*, 8249–8267.
- (5) Patrick, G. L. *An Introduction to Drug Synthesis*; 1st ed.; Oxford University Press, 2015.
- (6) Zhang, J.; Yang, P. L.; Gray, N. S. *Nat. Rev. Cancer* **2009**, *9*, 28–39.
- (7) Barker, A. J.; Gibson, K. H.; Grundy, W.; Godfrey, A. a.; Barlow, J. J.; Healy, M. P.; Woodburn, J. R.; Ashton, S. E.; Curry, B. J.; Scarlett, L.; Henthorn, L.; Richards, L. *Bioorganic Med. Chem. Lett.* **2001**, *11*, 1911–1914.
- (8) Paras, N. A.; Brown, J.; Cheng, Y.; Hitchcock, S.; Judd, T.; Lopez, P.; Minatti, A. E.; Nixey, T.; Powera, T.; Tegley, C. M.; Xue, Q.; Yang, B.; Zhong, W. Amino Heteroaryl Compounds as Beta-Secret Modulators and Methods of Use. WO 2011/090911 A1, 2011.
- (9) Reynolds, M. P.; Greenfield, H. *Catalysis of Organic Reactions*; Malz, R. E. J., Ed.; 1st ed.; Marcel Dekker INC, 1996.
- (10) ThalesNano. H-Cube® Continuous-flow Hydrogenation Reactor <http://www.thalesnano.com/products/h-cube> (accessed Nov 24, 2015).
- (11) Jones, R. V.; Godorhazy, L.; Varga, N.; Szalay, D.; Urge, L.; Darvas, F. *J. Comb. Chem.* **2006**, *8*, 110–116.
- (12) ThalesNano. Flow Hydrogenation Quick Start Reaction Guide http://thalesnano.com/application-note?category_id=30.
- (13) Carroll, W. A.; Chen, Y.; Holladay, M. W.; Kort, M. E.; Kym, P. R.; Sullivan, J. P.; Tang, R.; Yi, L.; Zhang, H. Q.; Drizin, I. Potassium Channel Openers. US 6593335 B1, 2003.
- (14) Cai, J.; Sun, M.; Wu, X.; Chen, J.; Wang, P.; Zong, X.; Ji, M. *Eur. J. Med. Chem.* **2013**, *63*, 702–712.
- (15) Ren, C.; Xu, S.; Xu, J.; Chen, H.; Zeng, H. *Org. Lett.* **2011**, *13*, 3840–3843.
- (16) Burgey, C. S.; Stump, C. A.; Nguyen, D. N.; Deng, J. Z.; Quigley, A. G.; Norton, B.

- R.; Bell, I. M.; Mosser, S. D.; Salvatore, C. A.; Rutledge, R. Z.; Kane, S. A.; Koblan, K. S.; Vacca, J. P.; Graham, S. L.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5052–5056.
- (17) Stump, B.; Eberle, C.; Kaiser, M.; Brun, R.; Krauth-Siegel, R. L.; Diederich, F. *Org. Biomol. Chem.* **2008**, *6*, 3935–3947.
- (18) Spencer, J.; Anjum, N.; Patel, H.; Rathnam, R. P.; Verma, J. *Synlett* **2007**, *16*, 2557–2558.
- (19) Spencer, J.; Rathnam, R. P.; Patel, H.; Anjum, N. *Tetrahedron* **2008**, *64*, 10195–10200.
- (20) Erdélyi, M.; Gogoll, A. *J. Org. Chem.* **2001**, 4165–4169.
- (21) Struble, J. R.; Lee, S. J.; Burke, M. D. *Tetrahedron* **2010**, *66*, 4710–4718.
- (22) Chan, J. M. W.; Amarante, G. W.; Toste, F. D. *Tetrahedron* **2011**, *67*, 4306–4312.
- (23) Chauhan, J.; Fletcher, S. *Tetrahedron Lett.* **2012**, *53*, 4951–4954.
- (24) Mercer, S. E.; Chaturvedulam, P. V. Constrained Compounds as CGRP-Recepto Antagonists. US 2007/0259850 A1, 2007.
- (25) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
- (26) Abdel-Magid, A. F.; Mehrman, S. J. *Org. Process Res. Dev.* **2006**, *10*, 971–1031.
- (27) Miles, K. C.; Mays, S. M.; Southerland, B. K.; Auvil, T. J.; Ketcha, D. M. *Arkivoc* **2009**, *2009*, 181–190.
- (28) Spencer, J.; Baltus, C. B.; Press, N. J.; Harrington, R. W.; Clegg, W. *Tetrahedron Lett.* **2011**, *52*, 3963–3968.
- (29) Amin, J.; Chuckowree, I.; Tizzard, G. J.; Coles, S. J.; Wang, M.; Bingham, J. P.; Hartley, J. A.; Spencer, J. *Organometallics* **2013**, *32*, 509–513.
- (30) Goldberg, K.; Hamilton, N.; Jones, S.; Jordan, A.; Lyons, A.; Newton, R.; Ogilvie, D.; Waszkowycz, B. Quinazoline Compounds. WO 2015/079251, 2015.
- (31) Marzaro, G.; Guiotto, A.; Pastorini, G.; Chilin, A. *Tetrahedron* **2010**, *66*, 962–968.
- (32) Hennequin, L.; Foote, K. M.; Gibson, K. H. Quinazoline Derivatives for use in the Treatment of Cancer. WO 2004/004732, 2004.
- (33) Harmer, A. R.; Abi-Gerges, N.; Easter, A.; Woods, A.; Lawrence, C. L.; Small, B. G.; Valentin, J.-P.; Pollard, C. E. *J. Pharmacol. Toxicol. Methods* **2008**, *57*, 30–41.
- (34) Aronov, A. M. *J. Med. Chem.* **2006**, *49*, 6917–6921.

6. Conclusions and future work.

6.1. Conclusions

Tetrasubstituted aromatics have been outlined in Chapter 1 to be key synthons in medicinal chemistry. AstraZeneca funded this CASE award into the synthesis of new tetrasubstituted aromatic scaffolds. They outlined a specific set of key objectives at the start this project:

- Synthesised tetrasubstituted aromatics must contain 4 different orthogonal groups.
- Synthesised tetrasubstituted aromatics must have either a 1,2,3,4 or a 1,2,4,5-substitution pattern.
- Methods of preparation must be scalable.

Chapter 2 highlights the development of a new rapid microwave-mediated synthesis leading to a library of MIDA boronates, prepared from their parent boronic acids. This work meets the project objectives, as methods are scalable as they can be performed on multigram scales using cheap starting materials. These reactions in most cases gave high yields, using low solvent volumes and high tolerance to an array of different functional groups. Moreover, this method meets many of the requirements of green chemistry since it employs low energy, rapid routes and environmentally friendly solvents.

Chapter 3 first discusses the synthesis of new tetrasubstituted building blocks. This was achieved via bromination or nitration of compounds described and synthesised in the previous chapter; some of these compounds are shown in Figure 6.1. Twelve

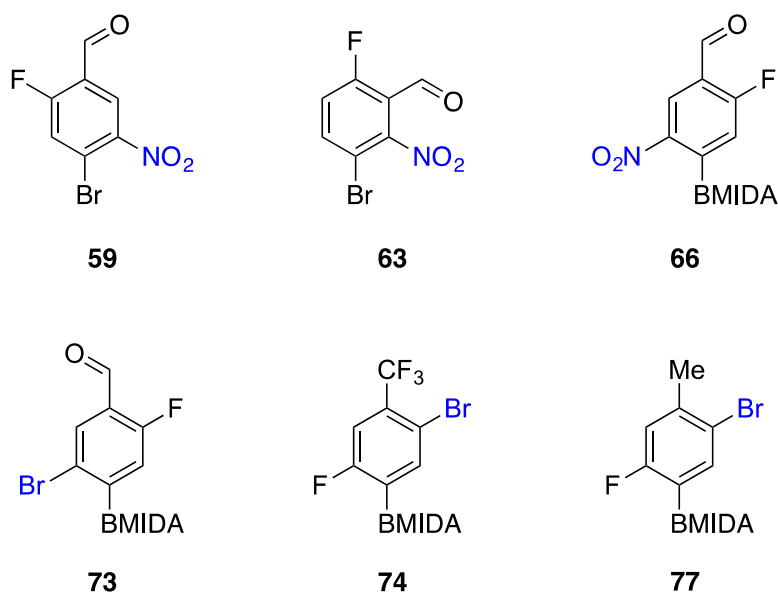
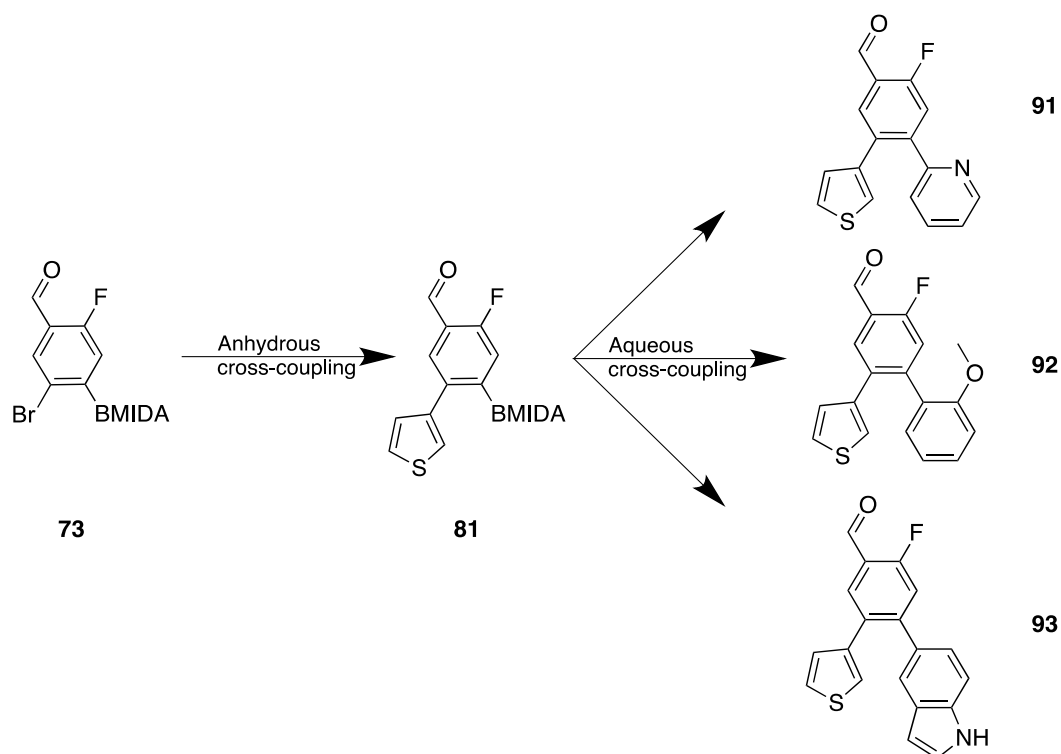


Figure 6.1 Compounds synthesised by nitration or bromination with the new functional group highlighted in blue.

tetrasubstituted aromatics were synthesised, 10 of which were novel. The bulk of these compounds use trisubstituted MIDA boronates which were formed in Chapter 2. We found that MIDA boronates could be nitrated utilising classical methods and in fact the MIDA functionality provided a good handle to aid solubilisation in sulphuric acid. This was also true in the case of bromination, and mixed classical chemistry with contemporary iterative palladium cross-coupling methodology. This gave the desired compounds that contained four different orthogonal functionalities as outlined in the objectives. These methods were also scalable, using cheap and simple reagents.

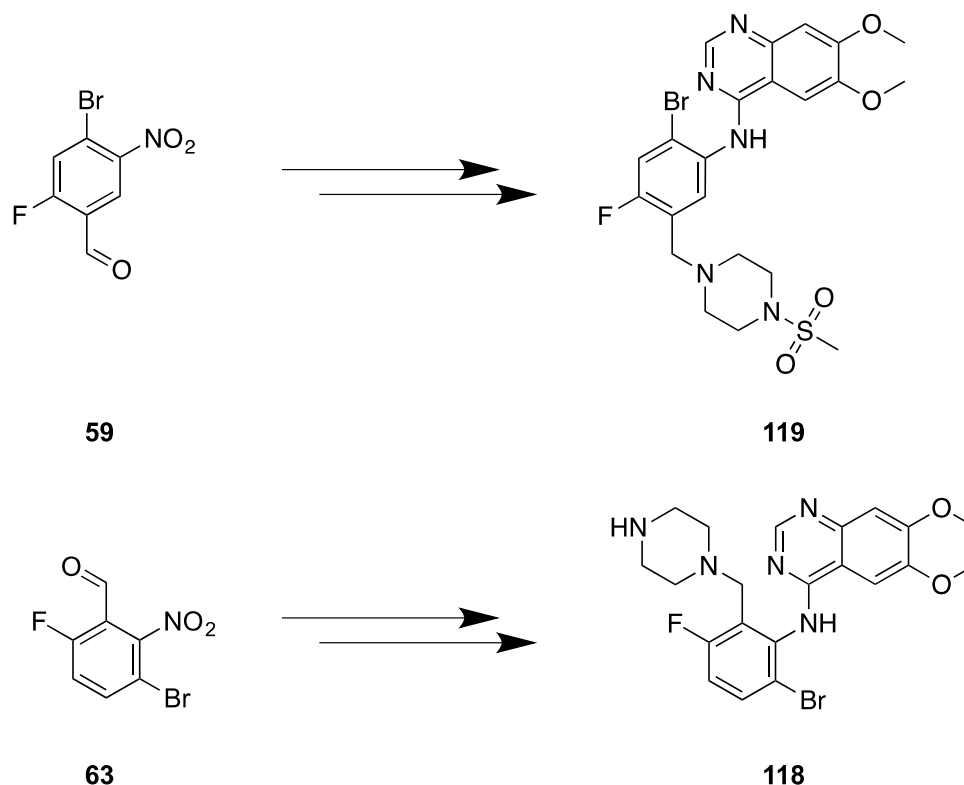
Chapter 4 highlights the brominated MIDA boronates, many of which are described in Figure 6.1 can be used in iterative Suzuki cross-coupling reactions. These iterative cross-couplings validated that these compounds contain orthogonal groups, meeting the project brief and show how complex polyaromatic compounds with tetrasubstituted cores can be synthesised in a simple procedure. There are two different types of cross-couplings shown in Scheme 6.1 anhydrous and aqueous, this is to enable the iterative methodology. A total



Scheme 6.1 Some examples of cross-couplings discussed in Chapter 4.

of 7 compounds were synthesised via the anhydrous and 4 by the aqueous cross-coupling methodology.

Chapter 5 consists of the elaboration on the bromo-fluoro-nitro-benzaldehydes synthesised via nitration in Chapter 3. Multiple modifications on these three different bromo-fluoro-nitro-benzaldehyde scaffolds were achieved *i.e.* nitro reduction, trifluoromethylation, Sonogashira couplings, reductive aminations, Clauson-Kaas pyrrole synthesis and the reaction of polysubstituted amines with 4-chloro-6,7-dimethoxyquinazoline. Scheme 6.2 shows how the 4-chloro-6,7-dimethoxyquinazoline was used to afford novel compounds that have potential as kinase inhibitors.



Scheme 6.2. Potential kinase inhibitors synthesised from bromo-fluoro-nitro-benzaldehydes.

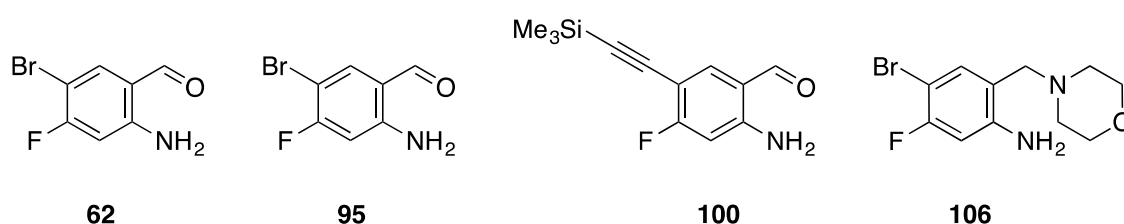
Nine of these potential kinase inhibitors were submitted to AstraZeneca for EGFR wild type cell assay. The best compound had an impressive IC_{50} of 18 nM, but unfortunately gave a large hERG inhibition. The assays were performed after all of the chemical synthesis had ceased. No further development to improve on these first compounds could be done.

A vast amount of orthogonal chemistry modifications has been achieved in chapters 4 and 5 on tetrasubstituted aryls synthesized in chapter 3. All of this work was maintaining attention towards the original brief and this was key to this work. This demonstrates how these complex tetrasubstituted building blocks can be manipulated to forming novel interesting compounds.

6.2. Future work

A number of studies merit further investigation these including,

- Improvement the methodology of the MIDA boronate deprotection aqueous Suzuki cross-couplings step in Chapter 4, to improve the yields.
- Link the quinazoline unit to different scaffold synthesised via reductive amination and Sonogashira reactions, in Chapter 5. This will be done with the series of compounds synthesised from compound **62** (Scheme 6.3) as they gave the most active compounds in the assays. The morpholine compound would hopefully lower the hERG inhibition



Scheme 6.3. Scaffolds **62**, **95**, **100** and **106** are key compounds for investigation after addition of the quinazoline.

- Commence a study developing the lead compounds from the AstraZeneca EGFR wild type cell assay, aiming to reduce their hERG inhibition.
- Look at alternative “ATP” like scaffolds other than quinazoline to address Lipinski and other drug like limitations of the prototypical EGFR inhibitors synthesized.