

Durham E-Theses

New pyridylboronic acids and their cross-coupling reactions

Paul Richard Parry

How to cite:

Parry, Paul Richard (2003) New pyridylboronic acids and their cross-coupling reactions. Doctoral thesis, Durham University.

Use policy

The full-text may be used and/or reproduced, and given to third parties in any format or medium, without prior permission or charge, for personal research or study, educational, or not-for-profit purposes provided that:

- a full bibliographic reference is made to the original source
- a <https://etheses.durham.ac.uk/id/eprint/3705/> is made to the metadata record in Durham E-Theses
- the full-text is not changed in any way

The full-text must not be sold in any format or medium without the formal permission of the copyright holders.

Please consult the [full Durham E-Theses policy](#) for further details.

The copyright of this thesis rests with the author.
No quotation from it should be published without
his prior written consent and information derived
from it should be acknowledged.

New Pyridylboronic Acids and their Cross-Coupling Reactions

Paul Richard Parry, B.Sc. (Hons)

Graduate Society

Department of Chemistry

University of Durham

A Thesis submitted for the degree of Doctor of Philosophy
at the University of Durham

January 2003


21 MAY 2003

Statement of Copyright

The copyright of this thesis rests with the author. No quotation from it should be published without his prior written consent and information derived from it should be acknowledged.

Declaration

The work described in this thesis was carried out in the Department of Chemistry at the University of Durham between October 1999 and September 2002. All of the work was carried out by the author unless otherwise stated, and has not previously been submitted for a degree at this or any other university.

2.3	X-Ray Crystal Structures of Halo-Substituted Pyridylboronic Acids	70
2.4	Application of Halopyridylboronic Acids	73
2.4.1	<i>Application of Bromo-Substituted Pyridylboronic Acids in the Suzuki Cross-Coupling Reaction</i>	73
2.4.2	<i>Application of Chloro-Substituted Pyridylboronic Acids in the Suzuki Cross-Coupling Reaction</i>	75
2.4.3	<i>Application of Fluoro-Substituted Pyridylboronic Acids in the Suzuki Cross-Coupling Reaction</i>	78
2.5	Conclusions	78
2.6	References	79
3.0	Synthesis of Pyridylboronic Acids with Varying Substituents	81
3.1	Introduction	81
3.2	Synthesis of Mono-Substituted Pyridylboronic Acids	81
3.2.1	<i>Alkoxy-Substituted Pyridylboronic Acids</i>	81
3.2.1.1	<i>Via Metal-Halogen Exchange</i>	81
3.2.1.2	<i>Via Metal-Hydrogen Exchange</i>	83
3.2.2	<i>Synthesis of Di-Substituted Pyridylboronic Acids: Alkoxy- and Halogen-Substituted Pyridylboronic Acids</i>	85
3.3	Application of the Suzuki Cross-Coupling Reaction	86
3.3.1	<i>Application of Mono-Substituted Pyridylboronic Acids In the Suzuki Cross-Coupling Reaction</i>	87
3.3.1.1	<i>Using halobenzenes as the substrate</i>	87
3.3.1.2	<i>Using halopyridines and 3-bromoquinoline as the substrate</i>	88
3.3.1.3	<i>Using electron deficient halides as the substrate</i>	89
3.3.1.4	<i>Using five membered ring halides as the substrate</i>	89
3.3.2	<i>Application of Di-Substituted Pyridylboronic Acid in the Suzuki Cross-Coupling Reaction</i>	91
3.4	Conclusions	93
3.5	References	93
4.0	Synthesis and Application of 5-Formylfuran-2-boronic Acid	95

4.1	Introduction	95
4.2	Synthesis of 5-Formylfuran-2-boronic Acid	95
4.3	Application of 5-Formylfuran-2-boronic Acid in the Suzuki Cross-Coupling Reaction	96
4.4	Functionalisation of Heteroaryl Substituted Furyl Derivatives via Wittig Chemistry	98
4.5	Conclusions	101
4.6	References	102
5.0	Experimental Procedures	104
5.1	General Methods	104
5.2	Experimental Procedures of Chapter 1	106
5.3	Experimental Procedures of Chapter 2	107
5.4	Experimental Procedures of Chapter 3	115
5.5	Experimental Procedures of Chapter 4	131

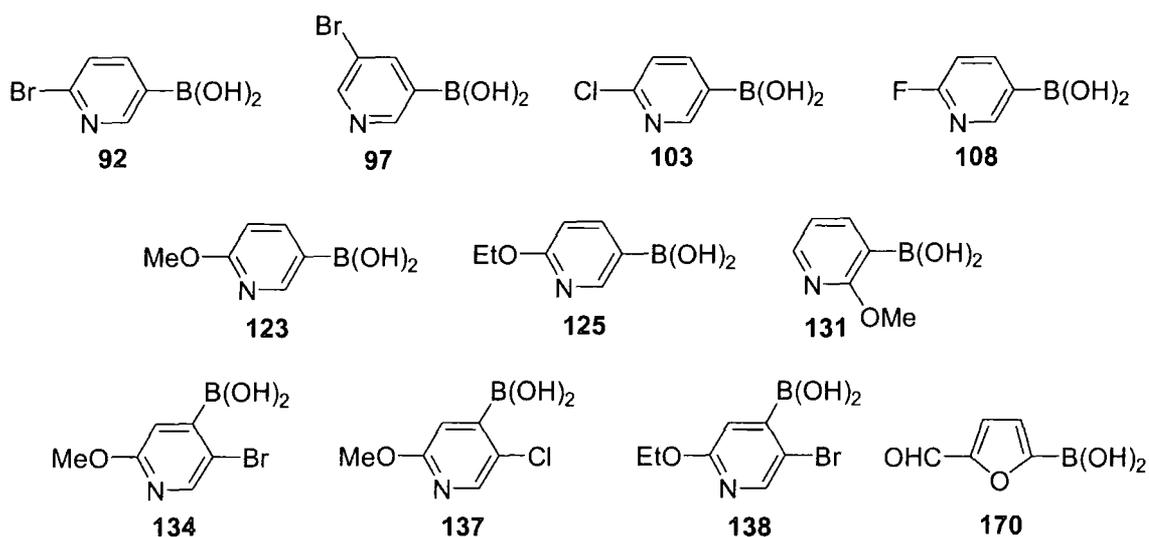
ABSTRACT

New Pyridylboronic Acids and their Cross-Coupling Reactions

Paul Richard Parry, University of Durham, 2003

The novel substituted pyridylboronic acids 2-bromo-5-pyridylboronic acid **92**, 3-bromo-5-pyridylboronic acid **97**, 2-chloro-5-pyridylboronic acid **103**, 2-fluoro-5-pyridylboronic acid **108**, 2-methoxy-5-pyridylboronic acid **123**, 2-ethoxy-5-pyridylboronic acid **125**, 2-methoxy-3-pyridylboronic acid **131**, 3-bromo-6-methoxy-4-pyridylboronic acid **134**, 3-chloro-6-methoxy-4-pyridylboronic acid **137** and 3-bromo-6-ethoxy-4-pyridylboronic acid **138** have been synthesised and shown to undergo palladium-catalysed Suzuki cross-coupling reactions with a vast variety of heteroaryl bromides to yield novel heteroarylpyridine derivatives.

5-Formylfuran-2-boronic acid **170** has been synthesised and isolated and has been shown to undergo palladium-catalysed Suzuki cross-coupling reactions with a variety of heteroaryl bromides to yield novel heteroaryl substituted furyl derivatives. These derivatives have been shown to undergo efficient functionalisation by Wittig chemistry.



ACKNOWLEDGEMENTS

I would like to express my gratitude to the following people who I have had the good fortune to meet and who have been involved in the creation of this work during my time at the University of Durham.

Firstly, I would like to thank my supervisor Prof. M. R. Bryce for offering me a Ph. D., allowing me to research such an interesting topic, and for all his patience and advice over the years. Mr Brian Tarbit for financial support, all of his advice and encouraging words over the years and for giving me an insight into industrial chemistry.

Big thanks to the past and present members of the Bryce group who made me feel welcome and who have made my time in Durham a memorable experience, especially Changsheng, for all his advice and good humour, and Dima, for showing me a lot of practical techniques and some interesting pipetting methods. Christian, who has been a good friend over the years and was the first to welcome me to Durham, what else can I say but top lad. Big thanks to Greg, Ste and Ian 'the chap' Smith, who may not be a member of the Bryce group but he spends so much time there he is now an honorary member. These guys have not only been great housemates, drinking buddies, and teammates, but bloody great friends. What else can I say about these guys, apart from the fact that we obviously see far too much of each other; Greg maybe a narcoleptic, Ste an alcoholic music guru and Ian, a potential 'Don Juan', but they have given me many memories which I will look back on with just a bit of a chuckle.

All the guys I have met from Chembridge and GSAFC, a club I was privileged to captain, who have not only helped keep me reasonably healthy over the years, but who I have had many great nights out with. Special thanks to young Burdon, the 'Scottish Mafia' (aka 'the Craigs' and Ross), Dave Parkin and Troll, who welcomed me to GSAFC. Also, let's not forget all the guys from '*The Cocktail Classic*' tour for an unforgettable trip to Holland and Germany (God Bless North Sea ferries). I eagerly look forward to the next tour. Come on Barcelona 2003.

All of the academic, administrative and technical staff at the Chemistry Department for all the work they put in obtaining various spectra and analyses. Plus, I can't forget all

the girls from the tearoom for all their help and good humour over the years and for keeping the hot beverages flowing.

Many thanks to all the Boyle family for welcoming me into their family and supporting me through my years of study, especially Mrs. B. for all those late night meals after long days in the lab, it was much appreciated.

To my mam, dad, sister and family, nanna and grandad who have been there for me throughout my time in education. I want to thank them for all of their support, both financial and emotional, and for constantly encouraging me to do my best in life. I hope they feel a huge amount of pride from this work.

Last, but certainly not least, to Michelle. They say behind every good man there has to be a great woman, never a truer word spoken. She has been there for me through the hardest times of my life and I feel without whom I would not have achieved so much. She has given me nothing but love, patience and support. For these reasons I dedicate this work to Michelle, my rock.

For Michelle

ABBREVIATIONS

tBOC	tert-Butoxycarbonyl
nBuLi	n-Butyllithium
CNS	Central Nervous System
DCM	Dichloromethane
DMAP	Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DoM	Directed <i>ortho</i> Metallation
dppb	1,4-Bis(diphenylphosphino)butane
EI	Electron Impact
LDA	Lithiumdiisopropylamide
mp	Melting point
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
rt	room temperature
TBB	Tributylborate
TEB	Triethylborate
THF	Tetrahydrofuran
TMB	Trimethylborate
TLC	Thin layer chromatography
TPB	Triisopropylborate
UV	Ultraviolet
Vis	visible

“...he who dares wins...”

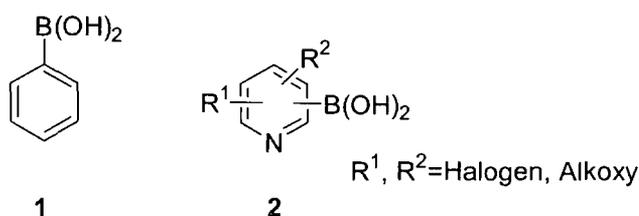
- Del Boy Trotter (Only Fools and Horses)

Chapter 1

**Introduction to Heterocyclic
Boronic Acids**

1.0 Introduction to Heterocyclic Boronic Acids

Arylboronic acids have been known since 1880 when Michaelis and Becker¹ first synthesised phenylboronic acid (**1**). From that early discovery the synthesis and study of phenyl- and substituted-phenylboronic acids has been extensive. This thesis concerns heterocyclic boronic acids, in particular, substituted-pyridylboronic acids (**2**). The main objectives of this work were: (i) to obtain shelf-stable pyridylboronic acids containing substituents that are suitable for subsequent transformations, and (ii) to explore the scope of their reactions with a variety of halogenated ring systems, i.e. heterocyclic or phenyl, under Suzuki cross-coupling conditions, and thereby obtain new aryl- and heteroaryl-substituted pyridine derivatives.

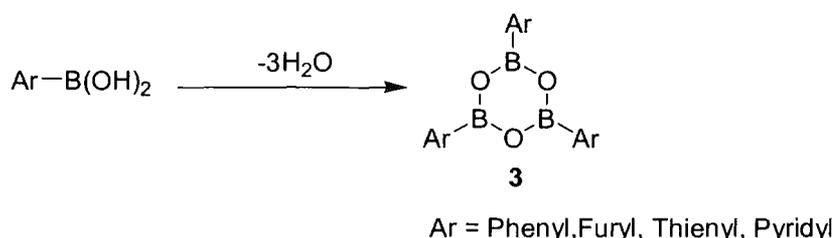


1.1 Why Make Heterocyclic Boronic Acids?

The attraction to heterocyclic boronic acids stems from the fact that many natural products,² modern pharmaceuticals³ and materials⁴ contain at least one heterocycle. So, new reagents that are applicable to the synthesis of such products are valuable tools in the arsenal of the synthetic chemist.

However, many organoboron compounds are air sensitive, and in some cases pyrophoric, for example Me_3B .⁵ Also, organoboron compounds containing boron-hydrogen, oxygen, nitrogen and halogen bonds tend to be easily hydrolysed. Boronic acids, Ar-B(OH)_2 ($\text{Ar} = \text{aryl, heteroaryl}$) on the other hand are an exception to this trend. They are relatively stable to air and moisture, temperature stable, exhibit low toxicity and are environmentally friendly.

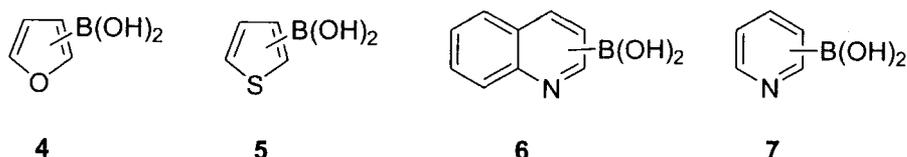
Most boronic acids readily undergo dehydration at room temperature to form the cyclic trimeric anhydride structure (**3**) (Scheme 1.1).



Scheme 1.1: Formation of the Cyclic Trimeric Anhydride by Dehydration.

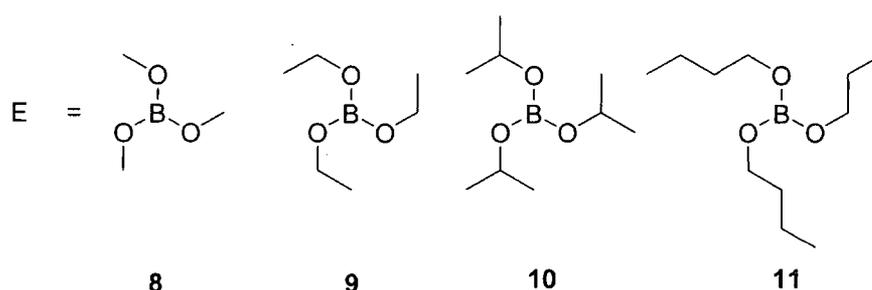
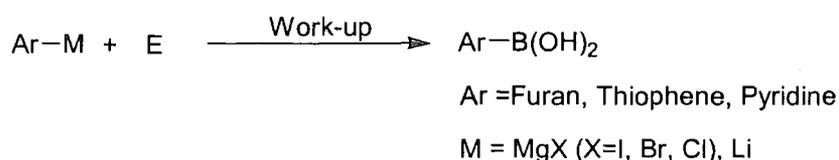
It is often difficult to obtain the free acid from the anhydride. Since, in almost all cases, either the acid or the anhydride will undergo the required reaction, they can be regarded as equivalent reagents.

The main application of boronic acids is in the synthesis of biaryls (Ar-Ar) and their homologues, such as teraryls and polyaryls by a transition metal-catalysed cross-coupling reaction, known as the Suzuki cross-coupling reaction. This chapter will look at the general synthesis of boronic acids and will review the Suzuki reaction. This chapter will also review the history, synthesis and application of heterocyclic boronic acids, such as furyl- (4), thienyl- (5), and quinolylboronic acid (6), concluding with a review of the parent pyridylboronic acids (7).



1.2 Synthesis of Heterocyclic Boronic Acids

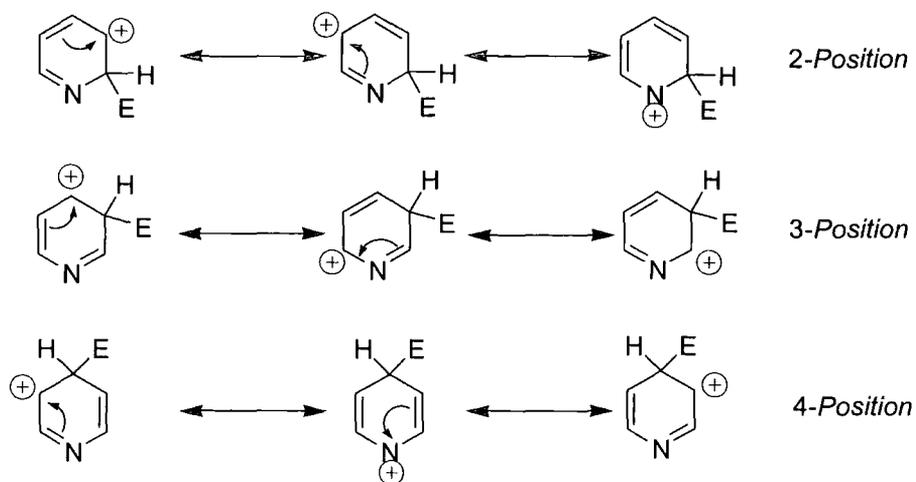
Classically, the synthesis of heterocyclic boronic acids involves the reaction of an *in situ* generated heteroaryl organometallic reagent with a suitable electrophile, usually trimethylborate, TMB (8), triethylborate, TEB (9), triisopropylborate, TPB (10) or tri-*n*-butylborate, TBB (11) (Scheme 1.2).



Scheme 1.2: Formation of Boronic Acids.

The favoured alkylborate is generally TPB, as it avoids the formation of contaminants resulting in multiple alkylation of the borates.⁶ Borates are the electrophile of choice because the boron has a vacant 2p orbital, which can accept electrons.

In the case of pyridine, the organometallic reagents are required to generate a nucleophilic carbon, which will then attack the electrophile, as pyridine undergoes electrophilic substitution with great difficulty.⁷ There are two reasons for this. Firstly, when pyridines are exposed to electrophiles, they tend to form a pyridinium cation, making electrophilic substitution at a carbon atom even more difficult. Secondly, the electrophilic substitution at the carbon atoms of the pyridine ring is a selective reaction. Substitution normally occurs at the 3-position, which leads to the formation of the least destabilized intermediates in the presence of nitrogen. Scheme 1.3 is an illustration of the electrophilic substitution intermediates of pyridine.⁸



Scheme 1.3: Electrophilic Substitution of Pyridine at the 2-, 3-, and 4-positions.

With respect to five-membered heterocycles, such as furan and thiophene, which readily undergo electrophilic substitution, the generation of organometallic reagents complements the electrophilic substitution reaction.⁹

1.2.1 Generation of Organometallic Reagents

Formation of either a Grignard reagent or an organolithium reagent generates the required nucleophilic carbon, due to the polarity of the covalent bond between the carbon and the magnesium or lithium. Figure 1.1 shows the polarization of the carbon-magnesium and carbon-lithium bonds.

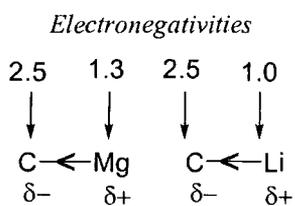
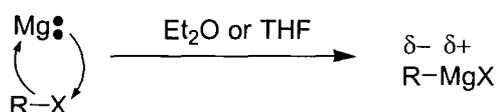


Figure 1.1: Generation of Nucleophilic Carbon.

1.2.1.1 Grignard Reagents

The significance of the Grignard reaction¹⁰ is clearly expressed in the following quotations: "...he who knows and understands the Grignard reaction has a fair grasp of organic chemistry..."¹¹ and "...every chemist has carried out the Grignard reaction at least once in their lifetime..."¹². A Grignard reagent takes the form RMgX ,¹³ where R can be an alkyl, aryl or heteroaryl, and X can be I, Br or Cl. The reactions, which are carried out in ether solutions, involve the 'insertion' of Mg into the C-halogen bond (Scheme 1.4).



Scheme 1.4: Generation of a Grignard Reagent.

After the insertion step, the oxidation state of the magnesium changes from Mg(0) to Mg (II). This means that the reaction is an oxidative insertion or addition. Grignard reagents are not isolated and are reacted *in situ*.¹⁴ The Mg acts as a Lewis acid, due to its empty 3p orbital, and accepts a lone pair of electrons from the solvent (Figure 1.2).

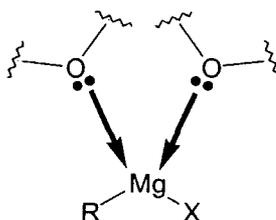


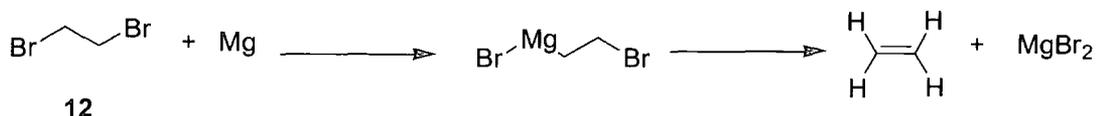
Figure 1.2: Coordination of Solvent to Magnesium.

The success of Grignard reagent generation often depends on the state of the metal surface. Magnesium is often covered with a thin coating of magnesium oxide, so the magnesium needs activating for which there are two main procedures: 1) Activated magnesium by entrainment, 2) Iodine-activated magnesium.¹⁰

Activation by entrainment involves the use of catalytic amounts of a lower, but more reactive alkyl halide to continuously activate the magnesium surface. The reactive

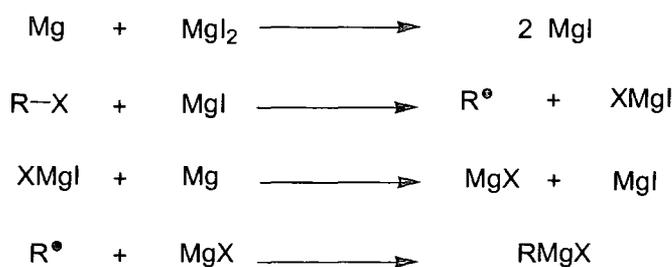
halide cleans and activates the surface of the magnesium, thus allowing the inert halide subsequently to react.

An example of an entrainer is 1,2-dibromoethane (**12**).¹⁵ A proposed mechanism for its action is via 2-bromoethylmagnesium bromide which rapidly eliminates MgBr_2 to give ethene (Scheme 1.5). The MgBr_2 produced subsequently reacts with the inert halide to give the desired Grignard reagent.



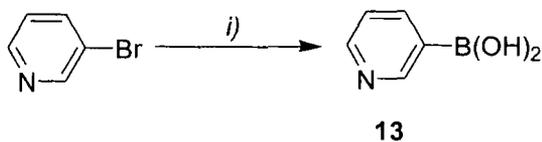
Scheme 1.5: Application of 1,2-Dibromoethane in the Generation of Grignard Reagents.

Iodine is used as a catalyst in the activation of magnesium. Iodine is known to be one of the earliest catalysts in this context.¹⁶ The accepted mechanism involves the formation of magnesium (I) iodide.^{10,17} This is the catalytic species as it is regenerated during the reaction. The mechanism for its formation is illustrated in Scheme 1.6.



Scheme 1.6: Mechanism of Grignard Reagent Formation via Iodine Catalysis.

This methodology has been applied to the synthesis of 3-pyridylboronic acid (**13**) (Scheme 1.7).¹⁸



Scheme 1.7: Formation of 3-Pyridylboronic Acid. Reagents and Conditions: (i) 1. Mg/I₂/1,2-dibromoethane. 2. TBB. 3. Aq. Work-up (Yield, 28%).

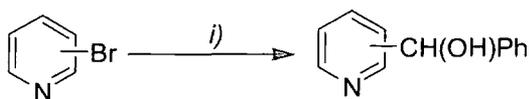
The yield of **13** was low, even when the Grignard reagent was generated using both of the activation techniques previously described. The formation of Grignard reagents from halopyridines is known to be difficult and low yielding.

Alternative routes for the synthesis of Grignard reagents involve the use of halogen-magnesium exchange reactions. These routes are valuable due to the difficulty in forming pyridine Grignard reagents. A review of the literature revealed that successful syntheses of pyridine Grignard reagents had been achieved using iodopyridines (Scheme 1.8).¹⁹



Scheme 1.8: Generation of Grignard Reagents via Halogen-Magnesium Exchange.

Unfortunately, iodopyridines are expensive and are not readily available. Paradies²⁰ and Meunier²¹ have reported results using chloro- and bromopyridines. Paradies has described the bromine- and chlorine-magnesium exchange with phenylmagnesium halides,²⁰ and Meunier obtained bromine-magnesium exchange when isopropylmagnesium chloride, ⁱPrMgCl, was used in THF at -25°C.²¹ Trécourt *et al*²² have optimized conditions to form the Grignard reagent at room temperature. They took 2- and 3-bromopyridine and reacted them with ⁱPrMgCl and trapped the Grignard reagent with various electrophiles. An example of this reaction is illustrated in Scheme 1.9.



Scheme 1.9: Entrapment of Grignard Species Generated by the Action of $^i\text{PrMgCl}$ on 2- and 3-Bromopyridine. Reagents and Conditions: (i) 1. $^i\text{PrMgCl}$, THF, rt. 2). Benzaldehyde. 3). H_2O .

This method has recently been used in the attempted synthesis of **13**,²³ although the route gave unsatisfactory results due to the poor solubility and low conversions.

1.2.1.2 Lithium Reagents

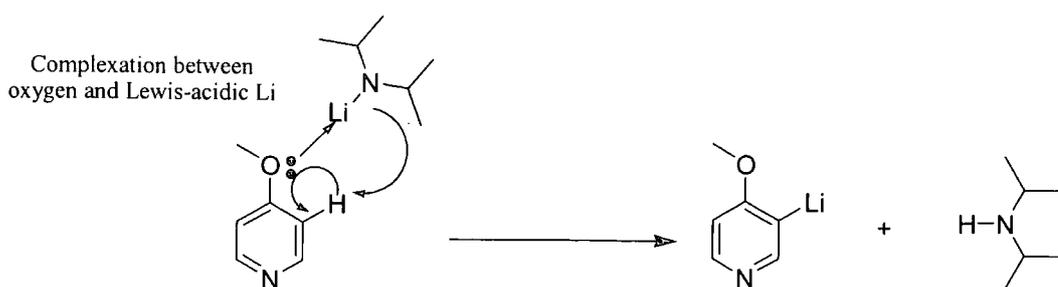
Some of the most important developments in heterocyclic chemistry in the last 20 years have been in the area of organometallic chemistry.⁹ Lithio-heterocycles are most useful as they can react with a whole range of electrophiles. The two main methods for the preparation of this class of compound are metal-hydrogen and metal-halogen exchange.

Metal-hydrogen exchange is achieved using commercially available organolithium reagents, typically *n*-butyllithium, *n*-BuLi, and lithium diisopropylamide, LDA.

The ease of the deprotonation reaction generally depends on two factors:

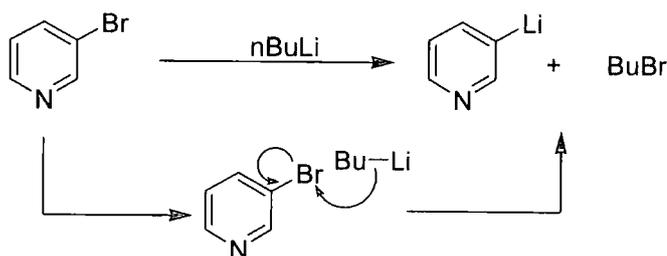
- 1) The acidity of the hydrogen to be removed
- 2) The stability of the carbanion produced.²⁴

The reaction is aided by the presence of functional groups that possess either inductive (e.g. Br, Cl) or chelating effects (e.g. OMe, CH_2OH), which are present *ortho* to the site of metal-hydrogen exchange. This is known as directed *ortho* metallation (DoM). An example of this is the regioselective lithiation of 4-methoxypyridine by LDA.²⁵ The functional group 'guides' the LDA so that it attacks the *ortho* proton, due to the formation of a complex with the Lewis-acidic atom (Scheme 1.10).¹³



Scheme 1.10: Generation of Lithium Reagent via Complexation.

Metal-halogen exchange (Scheme 1.11) is one of the most powerful methods for preparing organometallic compounds.²⁶



Scheme 1.11: Halogen-Lithium Exchange.

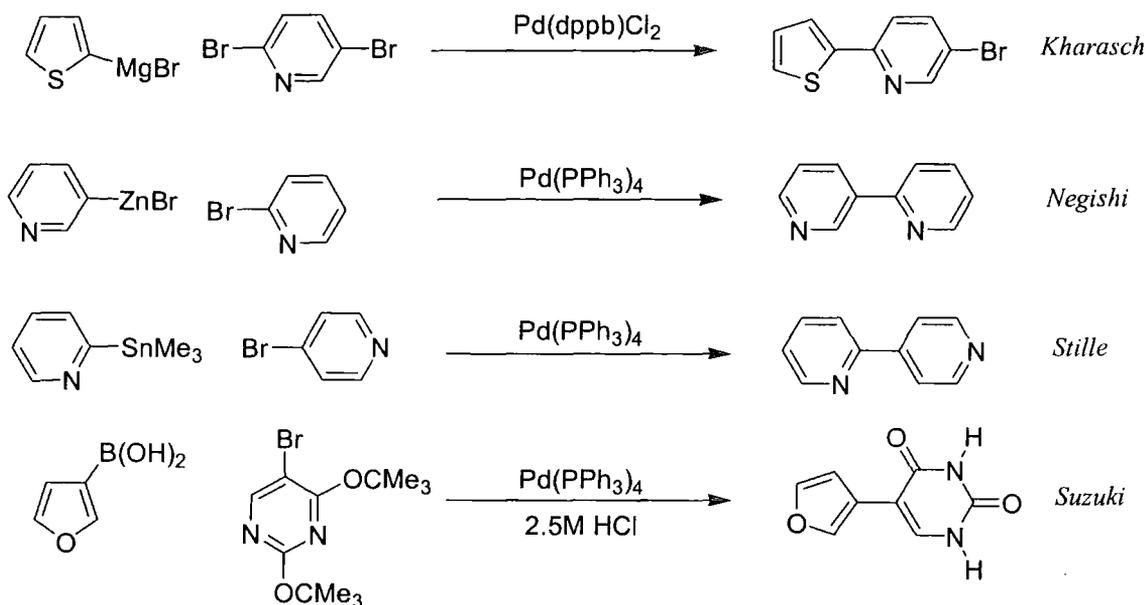
The reagent of choice for this reaction is normally $n\text{BuLi}$, as the by-product, n -butylbromide, does not usually interfere with subsequent steps. The metal-halogen exchange reaction is strongly exothermic,²⁷ which means the addition of $n\text{BuLi}$ has to be performed slowly at low temperatures, typically -100°C to -40°C . These temperatures are not easy to realise industrially, but they are required in order to reduce the possibility of side reactions,²² such as deprotonation, addition of substrate, LiBr elimination yielding pyridynes, bromine migration or ring opening reactions.

The advantages that lithiation has over Grignard reagents, with respect to this work, is that lithiated pyridines are known to display a high reactivity toward many electrophiles;²⁸ they are more convenient to synthesise and behave as typical organometallic reagents.²⁹

1.3 Transition Metal-Mediated Cross-Coupling Reactions

The synthesis of biaryls (Ar-Ar) by transition metal-mediated cross-coupling reactions is important because, along with their homologues, i.e. teraryls, oligoaryls and polyaryls, they are constituents which are present in a number of compounds ranging from natural products, polymers, advanced materials, liquid crystals, ligands and pharmaceuticals.³⁰ Interest in the transition metal-mediated cross-coupling reaction began almost 60 years ago when Kharasch set the stage for catalytic C-C bond formation reactions. Ever since then, the study and development of metal-catalysed cross-coupling reactions of various organometallics (Mg, Li, Cu, Zn, Zr, Al, Sn and B) has grown rapidly.

Kharasch's reaction did not achieve importance as a method for biaryl synthesis until the 1970s.³¹ Kharasch reacted an aryl Grignard reagent with an arylhalide in the presence of an appropriate catalyst to yield the biaryl (Ar-Ar).³⁰ Corriu³² and Kumada³³ also showed the synthetic promise of catalytic ArMgX plus ArX combinations to afford biaryls.³⁴ Negishi³⁵ cross-coupled an arylzinc reagent (ArZnX) with an aryl halide to generate the corresponding biaryl. The late 1970s saw the introduction of the Stille reaction in the formation of biaryls. This involved the reaction of an organostannane reagent (ArSnR₃, R=Me, Bu) with an arylhalide or triflate (trifluoromethanesulfonate). Then, the early 1980s saw the advent of the Suzuki reaction, which involves the reaction of an arylboronic acid (ArB(OH)₂) with ArX to give the desired biaryl. The Kharasch,³⁶ Negishi,³⁷ Stille³⁸ and Suzuki³⁹ cross-coupling reactions are the most common catalytic methods for the synthesis of biaryls. These reactions are used for the production of symmetrical and unsymmetrical biaryls using either nickel or palladium catalysts. Scheme 1.12 shows examples of each of these reactions.



Scheme 1.12: Examples of Transition Metal-Mediated Cross-Coupling Reactions.

All these methods exhibit chemo- and regioselectivity, and the Stille reaction has the advantage that it can tolerate more functionalities on either coupling partner than the Kharasch and Negishi reactions. However, the Stille reaction is avoided whenever possible because of the toxicity of the organotin reagents and the by-products generated. This has resulted in the Suzuki reaction being the first choice cross-coupling reaction.

1.3.1 Suzuki Cross-Coupling Reaction

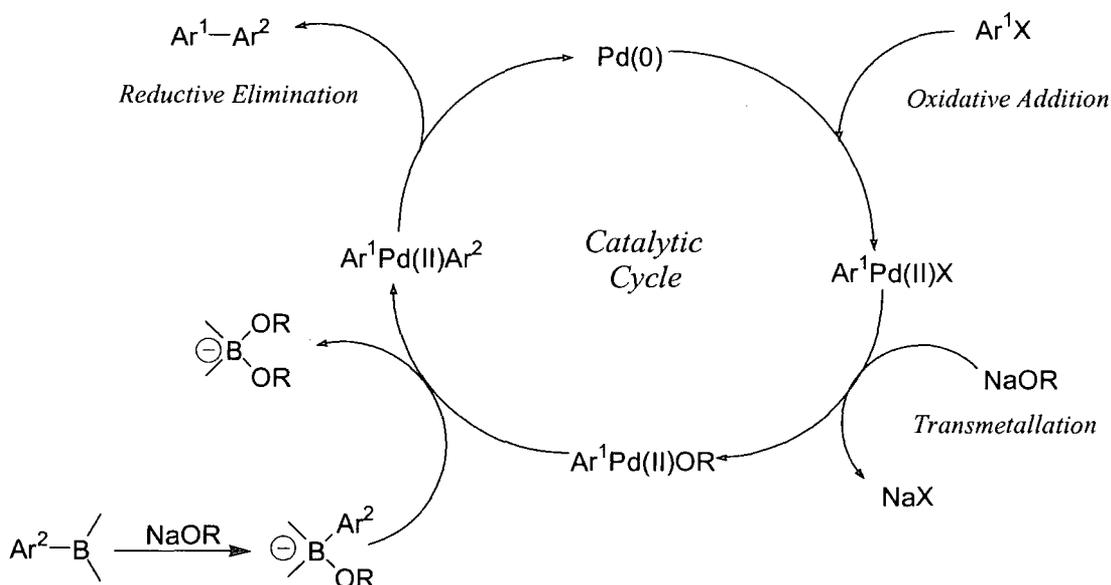
Suzuki *et al*⁴⁰ first published the cross-coupling of an arylboronic acid in 1981. Gronowitz *et al*⁴¹ later modified Suzuki's work, allowing the synthesis of biaryls, heterobiaryls, teraryls and condensed ring systems.

The advantages of the Suzuki cross-coupling reaction are:³⁴

- Boronic acids are often air stable, non-toxic and have long shelf-lives
- Experiences little homocoupling, i.e. self-coupling
- Can tolerate aqueous conditions

- Reaction is applicable with a number of leaving groups, whose reactivity follows this trend: $I > OTf > Br >> Cl$
- Environmentally friendly
- Can tolerate different functional groups on either coupling partner

A wide range of palladium catalysts or precursors can be used for the reaction, tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$, being the most commonly used. The accepted catalytic mechanism involves oxidative addition-transmetallation-reductive elimination sequences as depicted in Scheme 1.13.⁴²



Scheme 1.13: Catalytic Mechanism for the Suzuki Cross-Coupling Reaction.

The process involves oxidative addition of the halide to the palladium(0) complex to form an organopalladium halide (Figure 1.3).

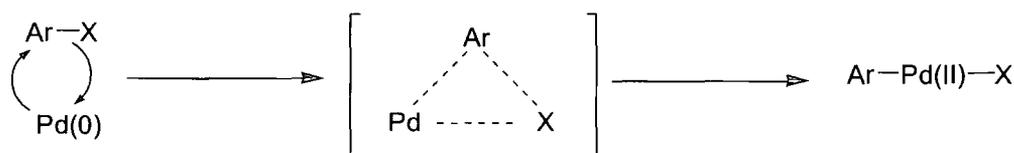


Figure 1.3: Oxidative Addition Step.

This step is seen as the rate-determining step. Although chloro-compounds are often cheaper and more readily available than the corresponding iodo- or bromo-compounds, the reaction is more difficult when Cl is the leaving group because higher energies are needed for the oxidative addition of the chloro-compound to the palladium(0) complex.⁴³ This step is followed by the transmetalation step, which involves the formation of the more reactive organopalladium alkoxide (Figure 1.4).

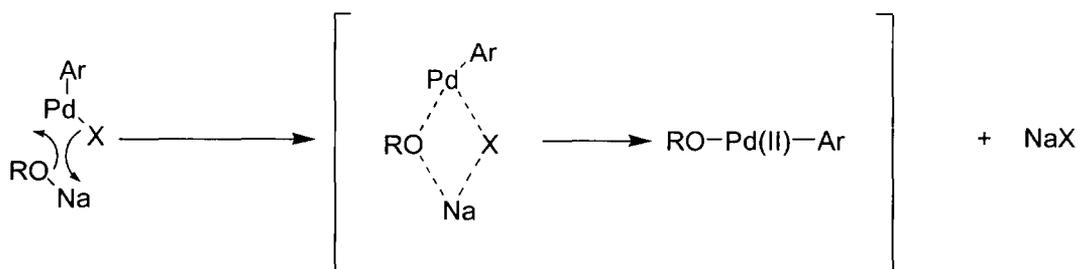


Figure 1.4: Transmetalation Step.

This complex is more reactive (i.e. more electrophilic) than the organopalladium halide complex because the Pd-O bond is more polar than the Pd-X bond. This in turn facilitates the next transmetalation step. Finally, the biaryl is generated by the reductive elimination step, thus regenerating the palladium(0) complex (Figure 1.5).

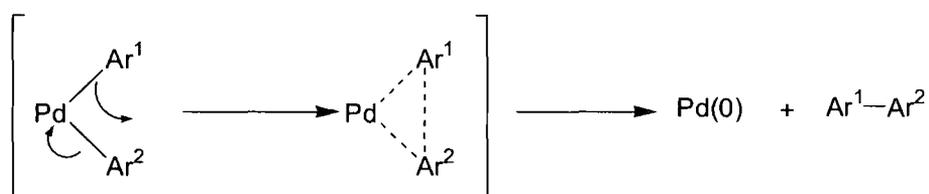


Figure 1.5: Product Formation, i.e. Reductive Elimination Step.

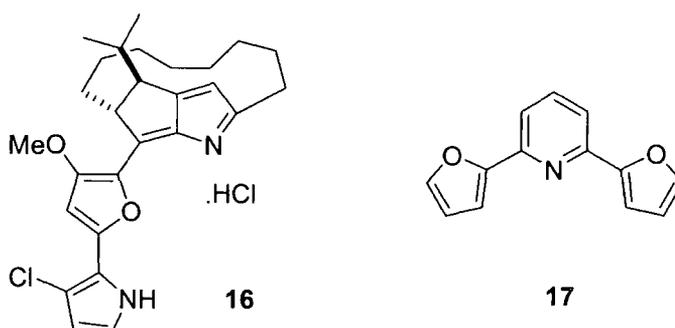
The reductive elimination step occurs because the organopalladium species with two aryl units attached is usually unstable.

This whole process needs at least two equivalents of a suitable base. Firstly, the base is required for the removal of the halide after the oxidative addition of the arylhalide to the Pd(0) complex in order to generate the more reactive organopalladium alkoxide

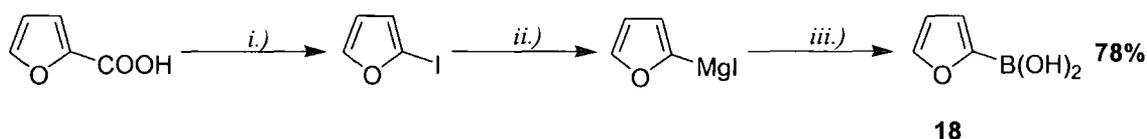
1.4 Heterocyclic Boronic Acids

1.4.1 Furylboronic Acid

The chemistry of furan has been a topic of great interest due to the presence of furan in many natural products and its known versatility, e.g. a component of pharmaceuticals and materials. For example, roseophilin (**16**), an alkaloid isolated from *Streptomyces griseoviridis*, which is a potential anticancer agent;⁴⁶ and 2,6-di-(2-furyl)pyridine⁴⁵ (**17**), a monomer which could be used in the construction of conducting polymers.



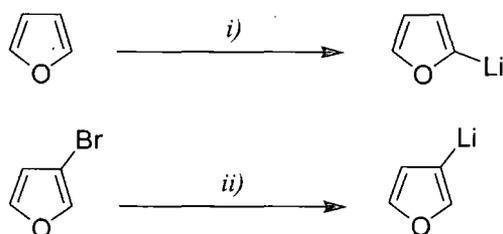
Johnson *et al*⁴⁷ first synthesised 2-furylboronic acid (**18**) in 1938 by reacting 2-furylmagnesium iodide with an excess TMB at low temperature (Scheme 1.15).



Scheme 1.15: Synthesis of 2-Furylboronic Acid. Reagents and Conditions: (i) Aq. NaOH, KI, (ii) Mg turnings, Et₂O, (iii) 1.TMB, low temperature. 2. Aq. Work-up.

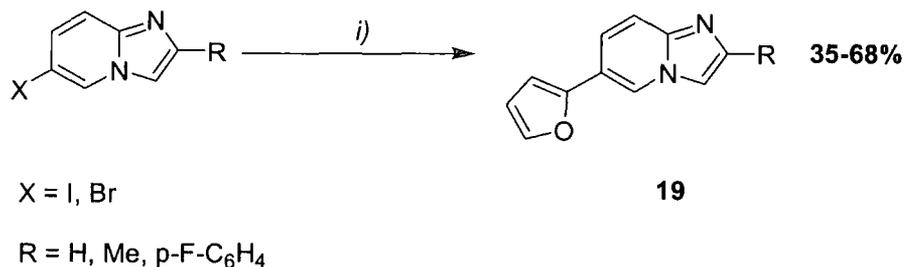
At the time, this route could not be used in the synthesis of 3-furylboronic acid because 3-furylmagnesium iodide was not known,⁴⁸ but can now be formed in modern times. The use of Grignard reagents with borate esters is a conventional procedure for the preparation of boronic acids.⁴⁹ Both the 2- and the 3-isomers have been synthesised by the reaction of their corresponding lithium derivative with TBB⁴⁸ and TPB.⁵⁰ The 2-lithioisomer was synthesised by direct lithiation of the furan ring,⁵¹ and the

3-lithioisomer by halogen-metal exchange between 3-bromofuran and ethyllithium (Scheme 1.16).^{48,52}



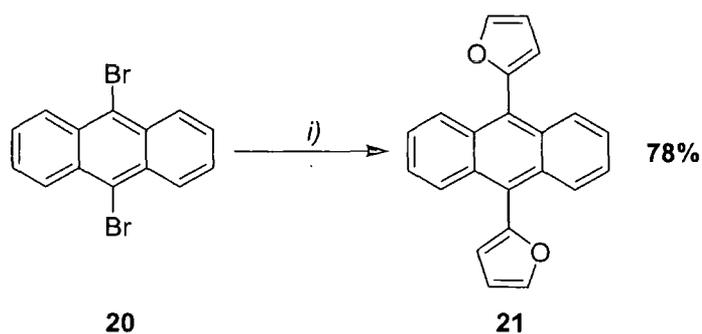
Scheme 1.16: Formation of the lithio-species of Furan. Reagents and Conditions: (i) Et₂O, -40°C, 1M Ethyllithium, (ii) Et₂O, -70°C, 1M Ethyllithium.

Nowadays, furylboronic acid (**18**) is commercially available and it has been widely used in the Suzuki cross-coupling reaction to form various compounds. For example, in the development of rapid pharmacomodulation methods to N-bridgehead heterocycles, which contain a fused imidazole ring (**19**) (Scheme 1.17).⁵³



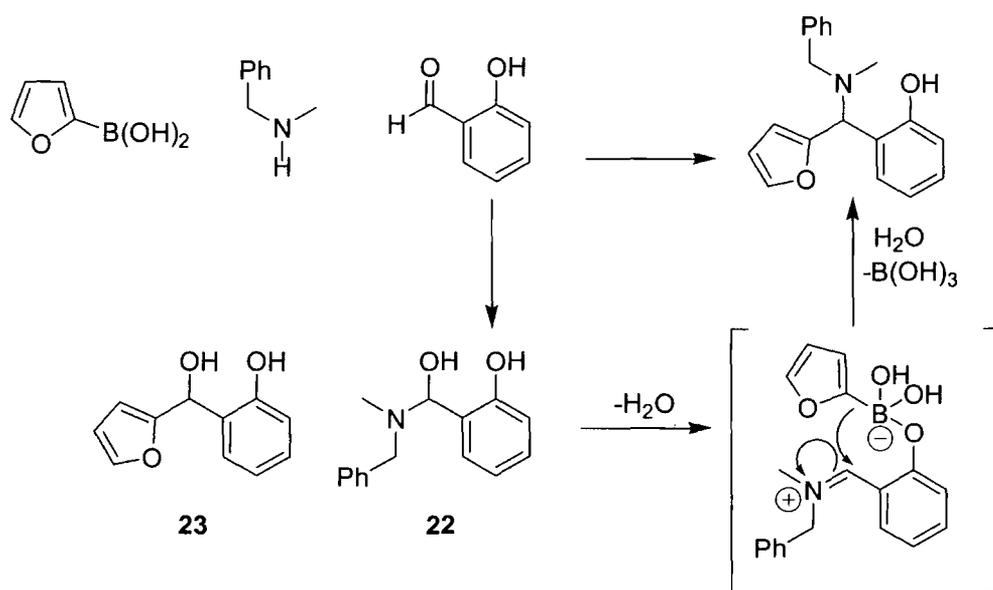
Scheme 1.17: Formation of Functionalised Imidazole Ring. Reagents and Conditions: (i) 18, Pd(0), base, DME-H₂O, Reflux.

Furylboronic acid (**18**) has also been applied in the synthesis of 9,10-difurylanthracenes (**21**) from 9,10-dibromoanthracene (**20**) (Scheme 1.18), for applications in fluorescence, electrochemiluminescence and nonlinear optical materials.⁵⁴



Scheme 1.18: Synthesis of 9,10-Difurylanthracene. Reagents and Conditions: (i) 18, Pd(PPh₃)₄, Na₂CO₃, THF-Toluene, 85°C.

However, the Suzuki reaction is not the only application of furylboronic acid.⁵⁵ This acid has been used in the synthesis of functionalised aminoalkylphenols,⁵⁶ which have attracted interest from both the pharmaceutical and agrochemical sectors. This is a novel one-pot multi-component reaction between boronic acids, amines and salicylaldehyde, which makes use of the fact that boronic acids are weakly electrophilic molecules. Scheme 1.19 shows the mechanism of this reaction.

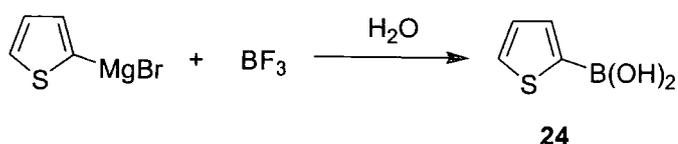


Scheme 1.19: Synthesis of Functionalised Aminofurylphenol.

The amine and carbonyl react initially to give the aminal intermediate (22), which will then react with the boronic acid. A key feature of the reaction is that (23) does not form.

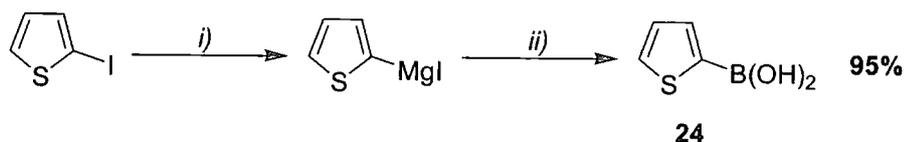
1.4.2 Thienylboronic Acids

2-Thienylboronic acid (24) was first synthesised by Krause and Renwanz⁵⁷ in 1932 by the reaction of 2-thienylmagnesium bromide with boron trifluoride (Scheme 1.20).



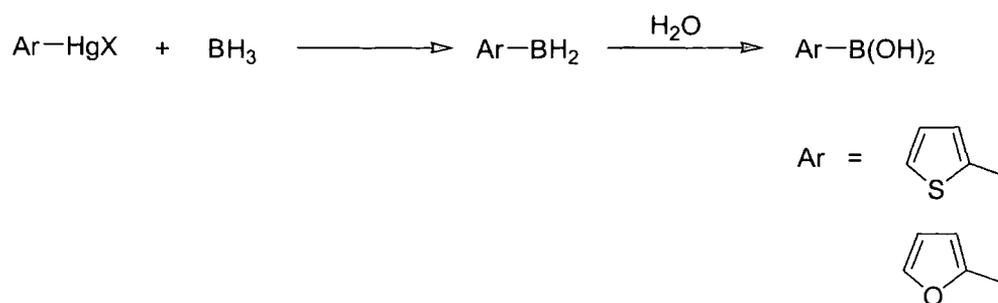
Scheme 1.20: First Synthesis of 2-Thienylboronic Acid.

Later, Johnson *et al*⁴⁷ reported the synthesis of 24 via the reaction of 2-thienylmagnesium iodide with TMB (Scheme 1.21).



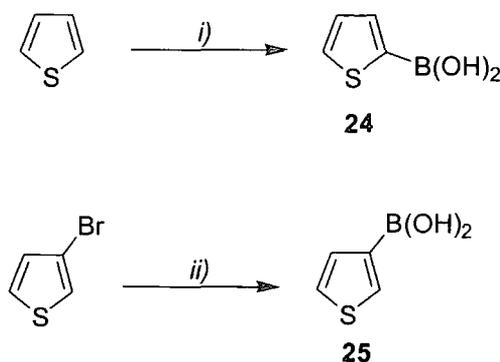
Scheme 1.21: Synthesis of 2-Thienylboronic Acid. Reagents and Conditions: (i) Mg turnings, Et₂O, (ii) 1. TMB, low temperature. 2. Aq. Work-up.

Organomercurials have also been employed in the synthesis of these boronic acids and in high yields (80-90%) (Scheme 1.22).⁵⁸



Scheme 1.22: Synthesis of Boronic Acids via the use of Organomercurial Reagents.

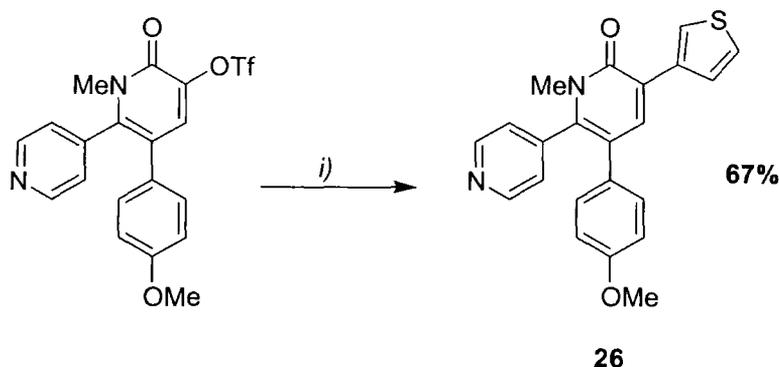
The organomercurial reagent is reacted with an excess of borane. The resulting borohydride is then hydrolysed to give the corresponding boronic acid. This methodology has also been applied to the synthesis of furylboronic acid. Modern methods for the formation of these acids involve the generation of the corresponding lithio-derivative followed by the addition of an alkylborate (Scheme 1.23).



Scheme 1.23: Synthesis of Thienylboronic Acids. Reagents and Conditions: (i) 1. nBuLi, 0°C, 2. TMB, -78°C. 3. Aq. Work-up. (ii) 1. nBuLi, -78°C, 2. TMB, -78°C. 3. Aq. Work-up. 35-100% for 24 and 25.

The parent thiophene can be used to generate 2-lithiothiophene via metal-hydrogen exchange, due to the high reactivity of the 2-position. In order to generate 3-lithiothiophene the metal-halogen exchange route has to be employed. The 2-lithio-derivative can be formed at temperatures as high as 0°C,⁵⁹ but the 3-lithio-derivative has to be formed at low temperature, usually -78°C,⁶⁰ because of its instability at higher temperature, which can lead to ring opening.⁹

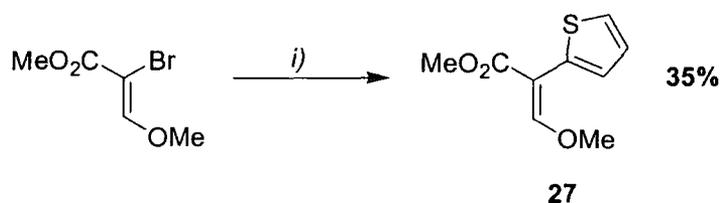
Similar to furylboronic acids, the main applications of thienylboronic acids involve the Suzuki cross-coupling reaction. Over the years it has become apparent that this methodology is a key step in the generation of various pharmaceuticals,⁶¹ fungicides⁶² and materials.⁶³ For example, in the synthesis of functionalised pyridones (**26**), which are known to have widespread pharmaceutical use including analgesic, hypnotic, antifungal and cardiotoxic actions.⁶⁴ An example is illustrated in Scheme 1.24.



Scheme 1.24: Synthesis of a Functionalised Pyridone. Reagents and Conditions: (i) 25, Pd(PPh₃)₄, Na₂CO₃, DME-H₂O, 100°C.

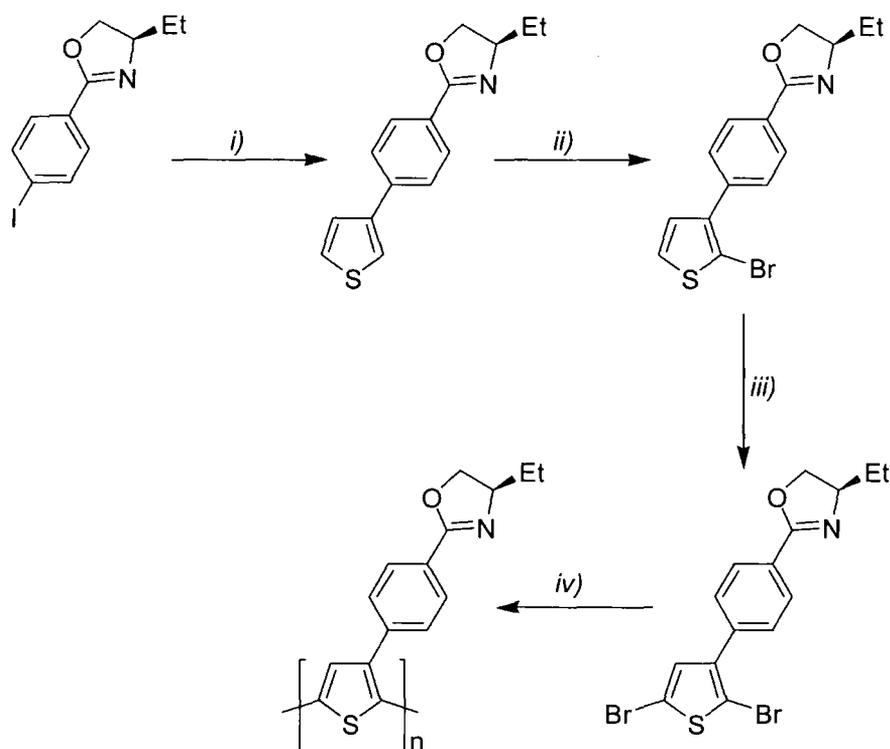
The product of this reaction has the potential for being a selective ligand for the benzodiazepine binding site of GABA-A receptors.

Methyl (E)-2-aryl-3-methoxypropenoates are important in the synthesis of fungicides, because the β -methoxypropenoate unit is active in this context.⁶² Again, the Suzuki methodology can generate a whole host of compounds containing this unit. Scheme 1.25 shows an example involving **24** in the formation of compound **27**.



Scheme 1.25: Synthesis of a Methyl (E)-2-thienyl-3-methoxypropenoates. Reagents and Conditions: (i) 24, Pd(PPh₃)₄, K₃PO₄, dioxane, 80°C.

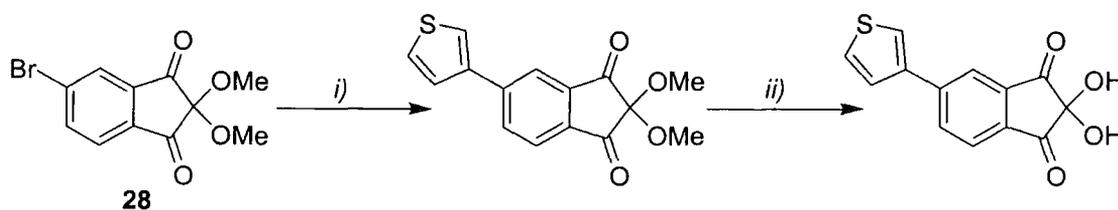
Over the last two decades studies into the synthesis and characterization of molecules with extended π -electron delocalisation have increased.⁶⁵ This class of compound can be applied to areas such as optoelectronics, polymeric light emitting diodes and displays. Thienylboronic acids are used to produce π -conjugated structures.^{66,67} It has been proposed that these new structures offer enhanced material properties, easier processing and even higher stability. An example of the application of **25** in the synthesis of such systems is illustrated in Scheme 1.26.^{66,67}



Scheme 1.26: Synthesis and Polymerisation of Thiophene Monomer. Reagents and Conditions: (i) **25**, Pd(PPh₃)₄, K₃PO₄, toluene, 85°C (85%), (ii) NBS, DMF (90%), (iii) NBS, DMF (74%), (iv) Ni(0), 2,2'-bipyridyl, DMF (74%).

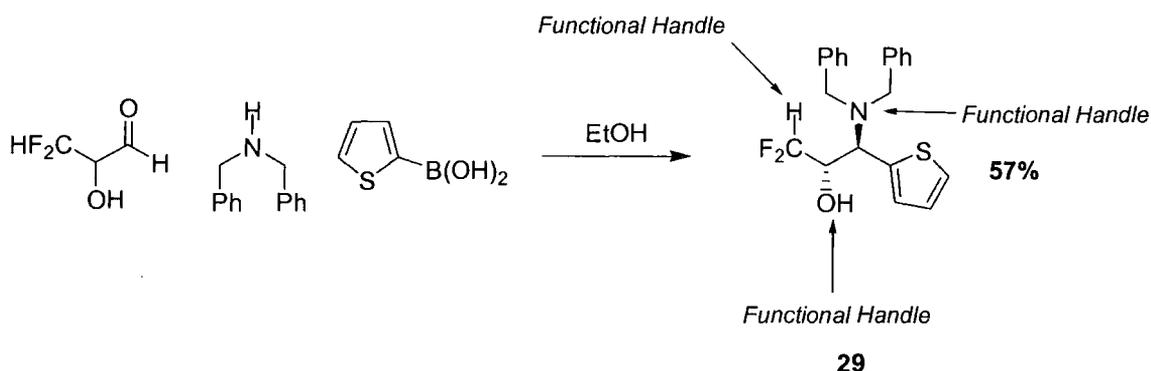
Another interesting application of the Suzuki reaction is in the area of forensic science. This reaction is used to produce ninhydrins, which are used in the chemical enhancement of latent fingerprints.⁶⁸ This involves post-ninhydrin treatment with metal salts, followed by illumination with an appropriate light source. This is a practical and affordable technique adopted by the majority of forensic laboratories. The Suzuki cross-coupling reaction serves to modify the ninhydrins, by enhancing their chromogenic and luminescent properties.⁶⁹ An example of ninhydrin formation is illustrated in Scheme

1.27, showing the cross-coupling of **25** with 5-bromo-2,2-dimethoxy-1,3-indandione (**28**).



Scheme 1.27: Synthesis of Ninhydrins. Reagents and Conditions: (i) **25**, Pd(PPh₃)₄, 2M Na₂CO₃, EtOH-Benzene (55%), (ii) HBr, HOAc, Δ, H₂O.

Like furylboronic acids, thienylboronic acids have other uses apart from the Suzuki reaction. For example, they can be employed in a one-pot 3-component condensation reaction with an amine and a carbonyl compound, in order to form anti- α -(difluoromethyl)- β -amino alcohols (**29**) (Scheme 1.28).⁷⁰

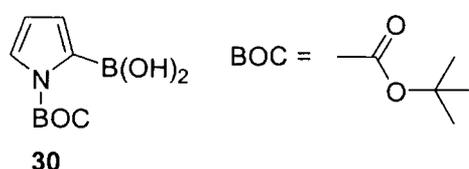


Scheme 1.28: Synthesis of anti- α -(Difluoromethyl)- β -amino alcohols.

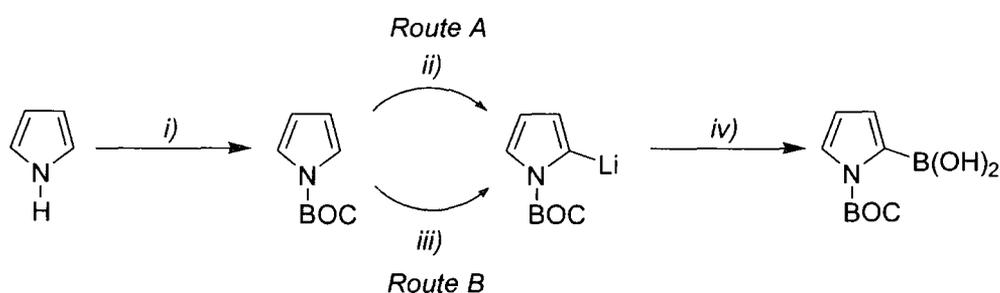
These are an important class of compound as they contain functional handles that allow diverse interactions within biologically active molecules. The added importance of this reaction is that it yields a fluorinated molecule. This is synthetically interesting because of the scarcity of fluorinated molecules in nature and their increasing applications in pharmaceuticals and new materials.⁷⁰

1.4.3 Pyrrolylboronic Acid

Martina *et al*⁷¹ were the first to publish the synthesis of a pyrrolylboronic acid derivative in 1991. They synthesised (1-tert-butoxycarbonylpyrrol-2-yl)boronic acid (**30**) for use in the synthesis of polymers.



They adopted the standard route in boronic acid synthesis; the reactions of a freshly generated organometallic reagent, in this case a lithio-derivative, with TMB (Scheme 1.29).



Scheme 1.29: Synthesis of BOC-protected Boronic Acid. Reagents and Conditions: (i) (BOC)₂O, CH₃CN, DMAP (71%), (ii) tert-butyllithium, -78°C (69%), (iii) lithium 2,2,6,6-tetramethylpiperidide, -78°C, (iv) 1. TMB, -78°C, 2. HCl (60%).

The BOC protecting group is required because the lithiation reaction is complicated by the presence of the acidic hydrogen on the N atom of pyrrole. When choosing a suitable protecting group for this reaction the following criteria have to be met:⁷²

- Stable to strongly basic conditions
- Easily removable under neutral conditions

The protecting group of choice in this reaction was tert-butoxycarbonyl (BOC) which:

- Can be easily removed (hydrolytically)
- Withdraws electrons from the ring, further enhancing the acidity of the α -hydrogen on the pyrrole ring
- Stabilises the lithio-derivative via chelation (Figure 1.6)

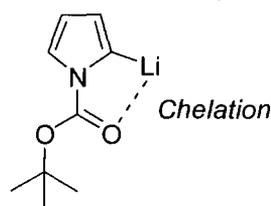
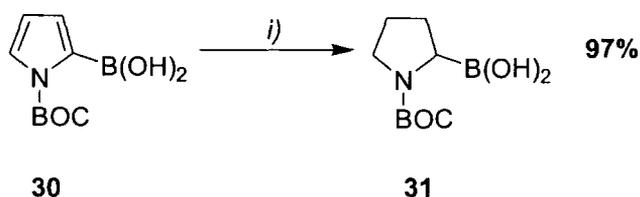


Figure 1.6: Stabilisation by Chelation.

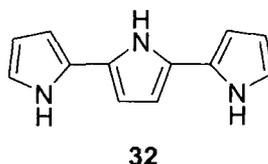
For the lithiation stage, Martina *et al* adopted two possible routes as described by Hasan *et al*. Route A employed tert-butyllithium ($^t\text{BuLi}$) as the lithiating reagent and route B used lithium 2,2,6,6-tetramethylpiperidide (LTMP). LTMP was found to be the more desirable lithiating reagent, due to the fact that $^t\text{BuLi}$ led to unsatisfactory product mixtures, whereas LTMP gave better incorporation of lithium.⁷²

Boronic acid **30** can be used in the generation of boc-prolineboronic acid (**31**),⁷³ which has attracted interest because peptides that incorporate this unit are potent inhibitors of certain post-proline cleaving enzymes implicated in both bacterial infection and regulation of the immune system.⁷³ Acid **31** is simply formed by the reduction of **30** (Scheme 1.30).

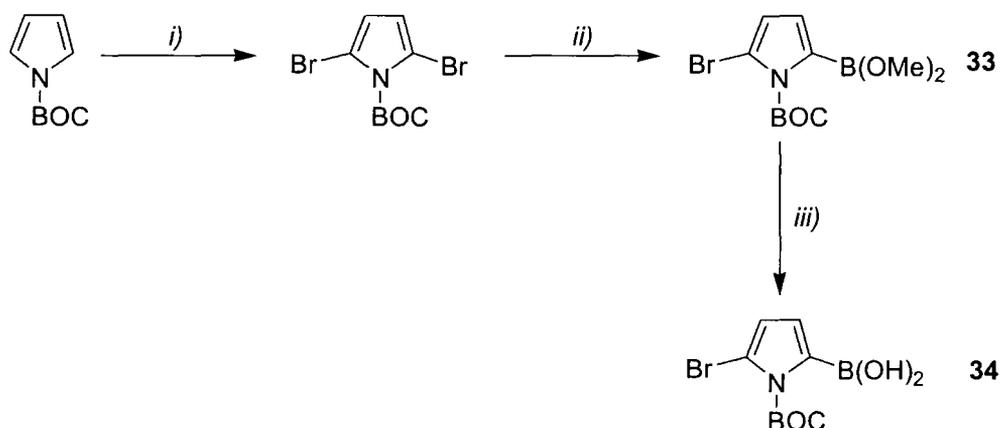


Scheme 1.30: Synthesis of BOC-Prolineboronic acid. Reagents and Conditions: (i) H_2 , Pt-C, EtOAc.

Pyrrolylboronic acid has been employed in the Suzuki cross-coupling reaction in order to generate polymers and pharmaceuticals. For example, in the attempted synthesis of structurally perfect poly(2,5-pyrrole) (**32**), one of the best electrically conducting polymers, when in its oxidised form.^{71b}



This was achieved by coupling an excess of pyrrolylboronic acid with 2,5-dibromopyrrole and polymerisation of 2-bromo-5-pyrrolylboronic acid (**34**), the synthesis of which is illustrated in Scheme 1.31.⁷¹

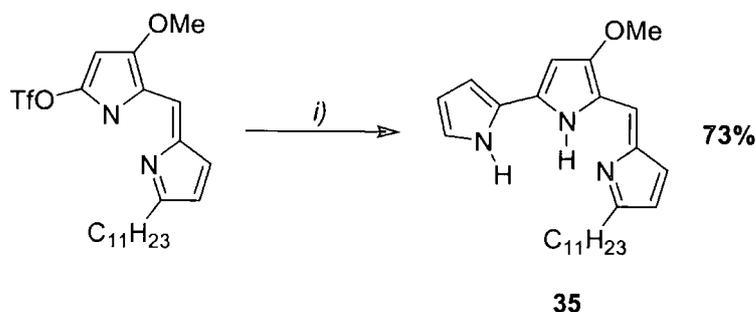


Scheme 1.31: Synthesis of 2-Bromo-5-pyrrolylboronic acid. Reagents and Conditions: (i) NBS, THF (55%), (ii) nBuLi, TMB, -78°C, Aq. Work-up (80%), (iii) HCl.

34 was found to be unstable and decomposes upon removal of the solvent, so **33** was used in the reaction. Derivatives of **32** are synthetic targets because although the molecular structure of polymerised polypyrrole is not known for certain, it is believed to have imperfections.

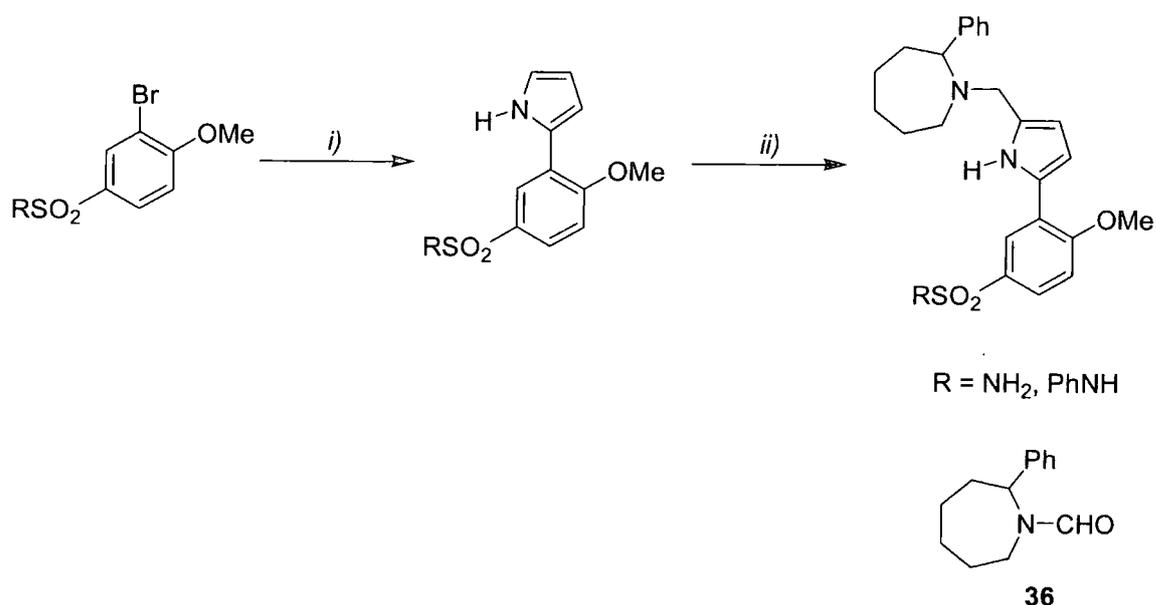
The Suzuki cross-coupling reaction of pyrrolylboronic acid is known to be a key step in the synthesis of many pharmaceuticals, for example undecylprodigiosine (**35**) (Scheme 1.32), an immunosuppressive agent known to inhibit T-cell proliferation.⁷⁴ This

compound is a member of the Prodigiosins, a class of natural pigments produced by *Streptomyces Genus*. These compounds are characterised by a 2,2'-bipyrrolylylpiromethene skeleton.



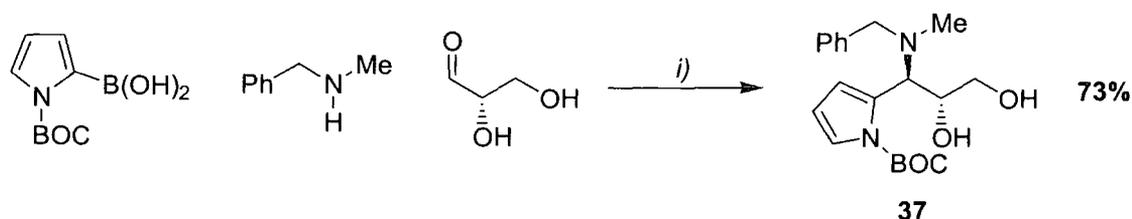
Scheme 1.32: Synthesis of Undecylprodigiosine. Reagents and Conditions: (i) 30, $\text{Pd}(\text{PPh}_3)_4$, K_2CO_3 , dioxane, 90°C .

This methodology is also applied to the synthesis of drugs to combat schizophrenia, which are believed to exert their antipsychotic effects by blocking dopamine receptors (Scheme 1.33).⁷⁵



Scheme 1.33: Synthesis of Dopamine Receptor Blockers. Reagents and Conditions:- (i) 1. 30, $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , DME, 2. TFA, DCM, (ii) Vilsmeier reagent derived from 36, followed by the *in situ* reduction of NaBH_4 .

30 has also been employed in the stereocontrolled synthesis of β -aminoalcohols (**37**) via a one-pot, three-component reaction involving the boronic acid, an amine, and an α -hydroxy aldehyde to give directly the corresponding β -amino alcohol (Scheme 1.34).⁷⁶

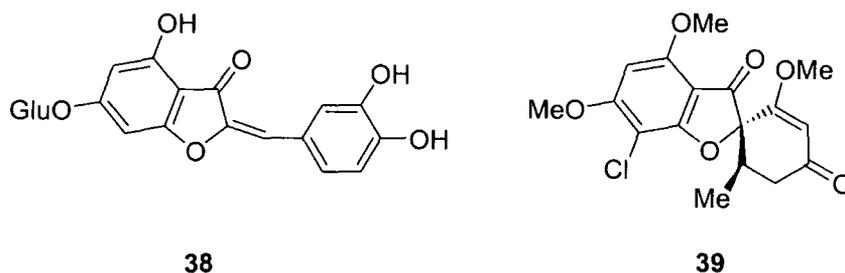


Scheme 1.34: Synthesis of β -Amino Alcohols. Reagents and Conditions: (i) EtOH, 25°C.

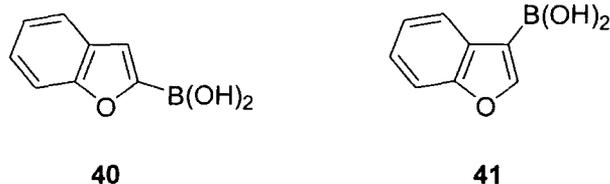
β -aminoalcohols are highly versatile functionalities as they can be converted to other molecules, such as amino acids and can be useful as chiral auxiliaries and transition metal ligands.

1.4.4 Benzofurylboronic Acid

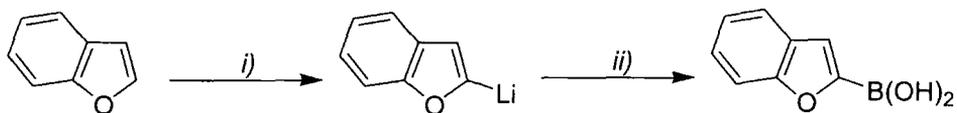
The benzo[b]furan system is known to occur in a range of plant- and microbial-derived natural products.⁹ For example, aureusin (**38**), a member of the aurones, a group of plant pigments. Griseofulvin (**39**), which is obtained from *Penicillium griseofulvum*, can be used in the production of medicines, such as antifungal agents.



There are two known isomers of this boronic acid; 2- (**40**) and 3-benzofurylboronic acid (**41**). There is no known isomer with the boronic acid functional group on the phenyl ring. There are only a few examples of the use of the 2-isomer in the literature.⁷⁷ Although work is unpublished, the 3-isomer is obtainable.⁷⁸

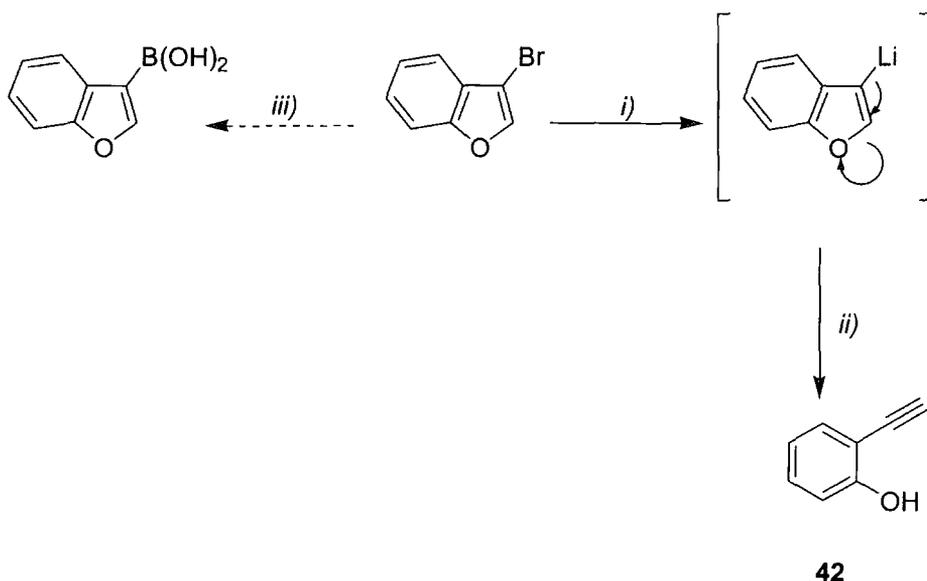


There appears to be no detailed preparation of either boronic acid in the literature. The 2-isomer was reported by Huang *et al* in 1995.^{77a} The 2-lithio species of benzofuran, generated by the action of *n*BuLi on benzofuran, was reacted with TMB, followed by a hydrolytic work-up, yielding the desired boronic acid (Scheme 1.35). Extreme low temperatures are not required, as the lithiation is known to be possible at 0°C.⁹



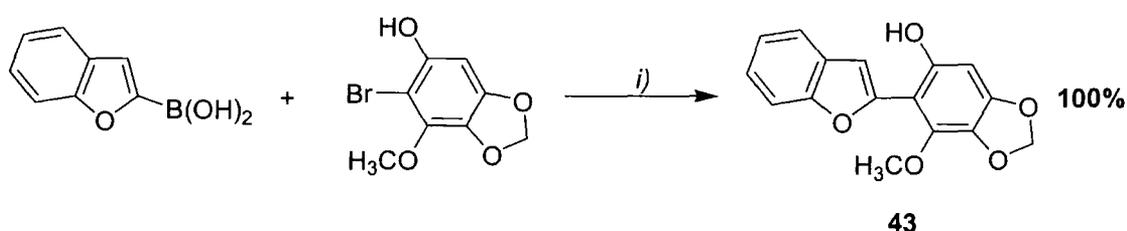
Scheme 1.35: Synthesis of 2-Benzofurylboronic Acid. Reagents and Conditions: (i) *n*BuLi, 0°C, (ii) TMB, Hydrolytic Work-up.

This relatively new boronic acid is now commercially available from Lancaster. The synthesis of the 3-isomer should be possible to synthesise via a metal-halogen exchange procedure, followed by the addition of an alkylborate, i.e. TMB. However, the 3-lithio-derivative should be formed and used at low temperature, i.e. -78°C,⁹ because it is known to fragment at room temperature with the production of 2-hydroxyphenylacetylene (**42**) (Scheme 1.36).⁷⁹



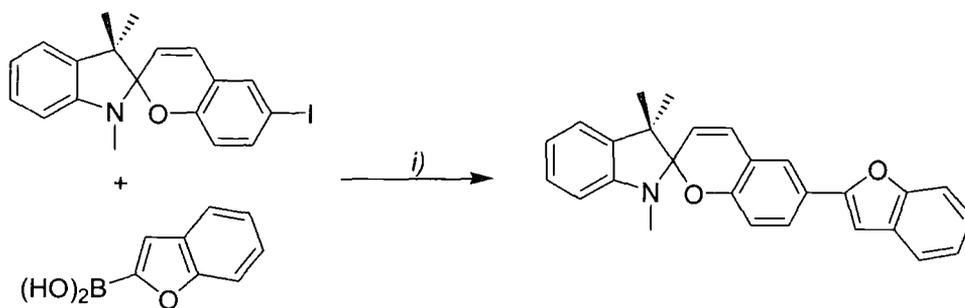
Scheme 1.36: Possible Route and Practical Considerations in the Synthesis of 3-Benzofuranylboronic Acid. Reagents and conditions: (i) $n\text{BuLi}$, r.t., (ii) H_2O , (iii) 1. $n\text{BuLi}$, -78°C , 2. TMB, Work-up.

Like the previous boronic acids, **40** has been used in the Suzuki cross-coupling reaction,⁷⁷ predominantly in the formation of possible pharmaceuticals,⁷⁷ for example, benzofuran derivative (**43**), an antioxidant (Scheme 1.37),⁸⁰ isolated from various yeasts. Compound **43** has been tested for its inhibition of haemolysis of red blood cells.



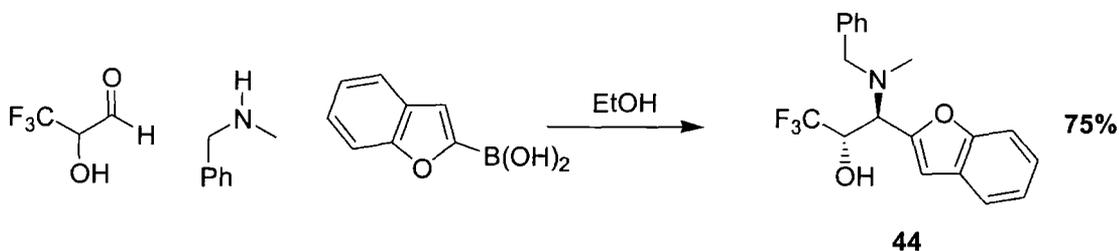
Scheme 1.37: Synthesis of Antioxidant (43). Reagents and Conditions: (i) **40**, $^i\text{Pr}_2\text{NEt}$, $\text{Pd}_2(\text{dba})_3$, DMF.

Acid **40** has also been employed in the synthesis of spiropyran analogues, which are used in photochromic indolinobenzopyran dyes (Scheme 1.38) of use in new technologies that include rewritable optical memory and optical switching, non-linear optics and real-time holography.⁸¹ The stability and properties of this spiropyran structure are dependent on the substituents attached to it.



Scheme 1.38: Synthesis of Spiropyran Analogue. Reagents and Conditions: (i) **40**, Pd(OAc)₂, Na₂CO₃, DMF.

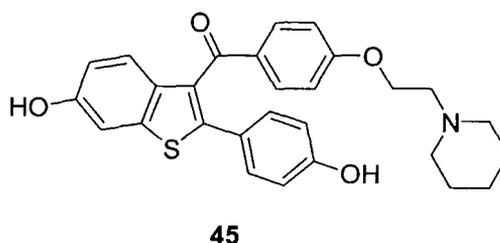
40 has also been employed in the synthesis of anti- α -(trifluoromethyl)- β -aminoalcohols (**44**),⁵⁵ without the need for the Suzuki methodology (Scheme 1.39). The importance of fluorinated compounds has been noted in a previous section.



Scheme 1.39: Synthesis of anti- α -(Trifluoromethyl)- β -aminoalcohols.

1.4.5 Benzothiénylboronic Acid

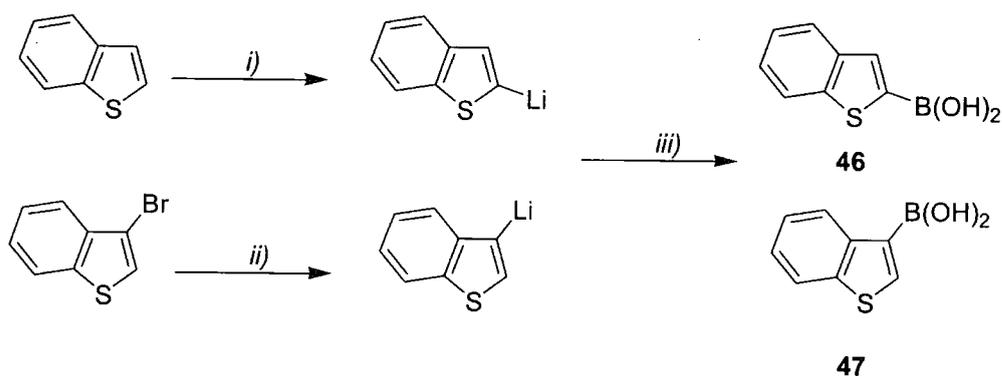
Benzo[b]thiophene has been incorporated into a number of new compounds of pharmaceutical interest, such as Raloxifene (**45**). This compound has been shown to have the potential for preventing osteoporosis, and to bring about a reduction in the incidence of breast cancer.⁹



45

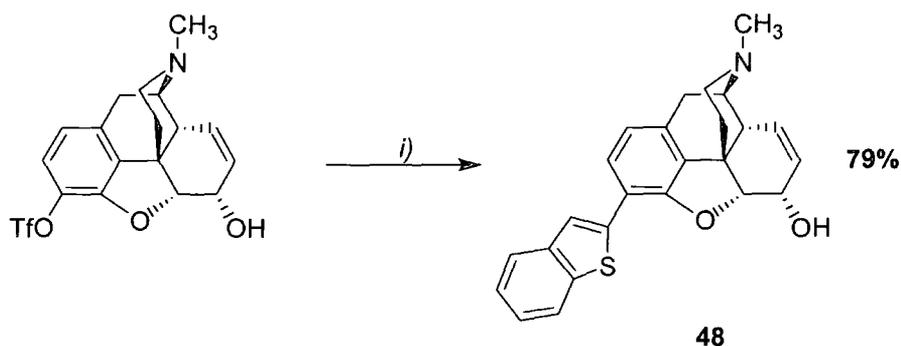
Again there are two known isomers of benzothiénylboronic acid; 2- (46) and 3-benzothiénylboronic acid (47). There is no known isomer with the boronic acid functional group on the phenyl ring.

There are only a few literature references to this class of boronic acid, and there is no detailed preparation of either boronic acid in the literature. Hedberg *et al*⁸² synthesised the 2-isomer by a method described by Thompson and Gaudino,⁵⁰ which involves the reaction of the 2-lithio derivative with TPB, followed by a hydrolytic work-up. The 2-lithio-derivative can be generated by the metal-hydrogen exchange reaction. The 3-isomer is probably generated by the same method, only the lithio-derivative is generated by a metal-halogen exchange reaction (Scheme 1.40).



Scheme 1.40: Synthesis of Benzothiopheneboronic Acids. Reagents and Conditions: (i) nBuLi, 0 → -25°C, (ii) nBuLi, low temperature, i.e. -78°C, (iii) 1. TPB, -78°C. 2. Aq. Work-up.

These acids are used predominantly in the Suzuki cross-coupling reaction in the synthesis of medicinally useful compounds.^{82,83} The 2-isomer is used more; there is only one literature reference showing the use of the 3-isomer. This could be due to the fact that the 2-isomer is commercially available from Lancaster. An example of the use of the 2-isomer is in the modification of morphine (48) (Scheme 1.41).

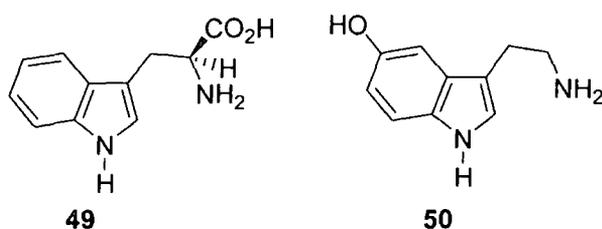


Scheme 1.41: Synthesis of a Morphine Derivative. Reagents and Conditions: (i) **46**, Pd(PPh₃)₄, LiCl, 2M Na₂CO₃, EtOH, DME, 95°C.

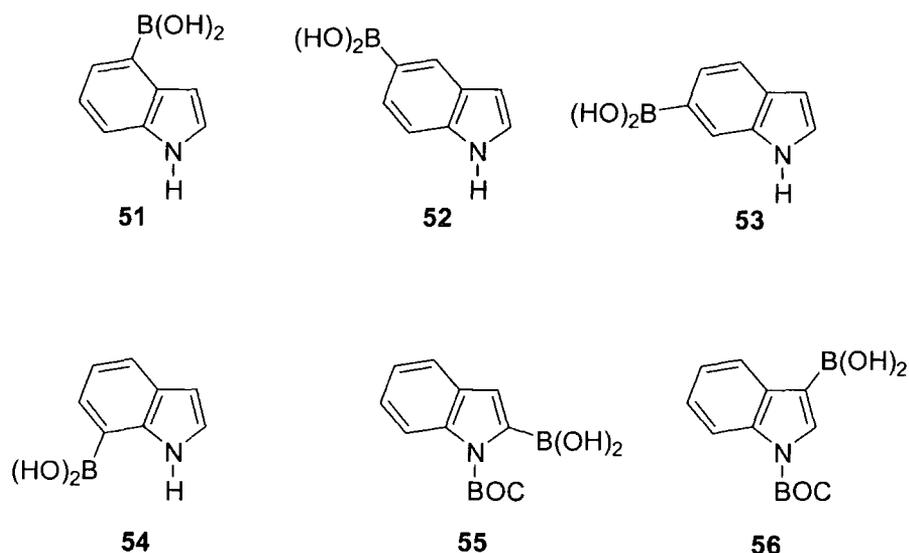
This is an important reaction because numerous structure-activity studies have been undertaken on morphine derivatives in connection with pharmacological effects.⁸²

1.4.6 Indolylboronic Acid

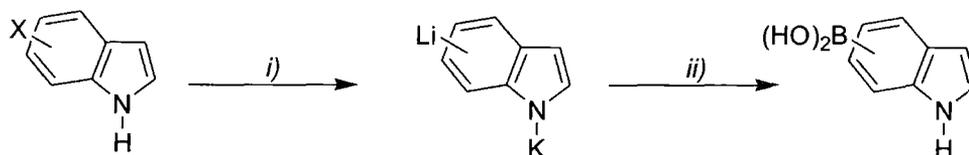
Indoles are probably the most widely distributed heterocyclic compounds in nature.^{9,84} For example, tryptophan (**49**) is an essential amino acid and serotonin (**50**) (5-hydroxytryptamine) is a very important neurotransmitter in the central nervous system.



There are six known isomers of indolylboronic acid; four isomers related to the phenyl ring of indole, 4- (**51**), 5- (**52**), 6- (**53**), and 7-indolylboronic acid (**54**), and two related to the heterocyclic ring of indole, N-protected 2- (**55**) and 3-indoleboronic acid (**56**).



Acids **51**, **52**, **53** and **54** are synthesised by the reaction of the corresponding lithio-derivative, generated by the metal-halogen exchange reaction, with TMB (Scheme 1.42).⁸⁴

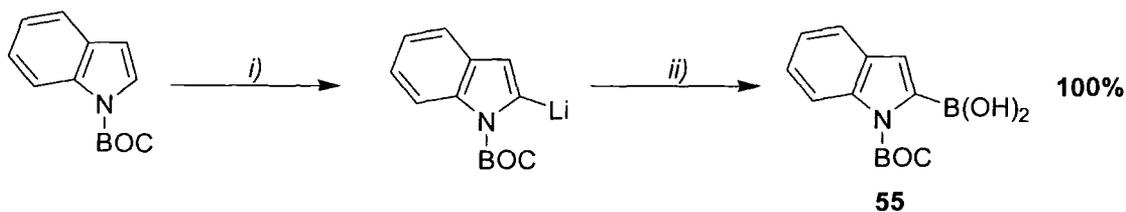


X = 5-Br, 6-Br, 7-Br

Scheme 1.42: Synthesis of Phenyl Ring Substituted Indole Boronic Acids. Reagents and Conditions: (i) 1. KH, Et₂O, 0°C. 2. ^tBuLi, -78°C. (ii) 1. TMB. 2. Aq. Work-up.

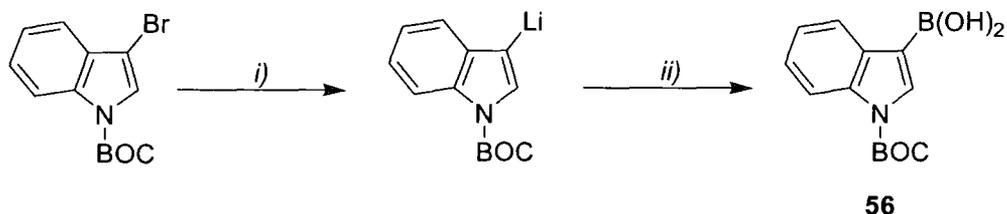
The lithio derivatives were generated following the preparation described by Moyer *et al.*⁸⁵ The lithiation, using ^tBuLi, is facilitated by the removal of the acidic hydrogen on the nitrogen by the action of KH, giving the potassium salt.

The 2-isomer is prepared by the action of the corresponding lithio-derivative, generated by a metal-hydrogen exchange reaction of N-protected (BOC) indole, with TPB (Scheme 1.43).⁸⁶ The BOC group aids the reaction in ways described earlier for pyrrole.



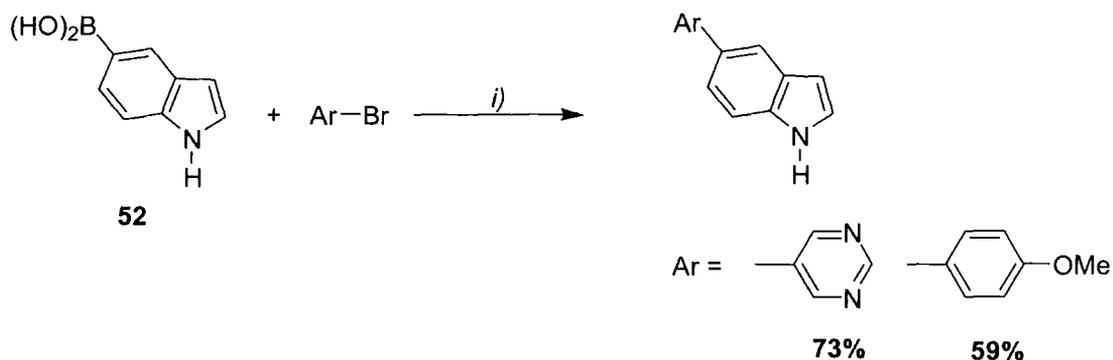
Scheme 1.43: Synthesis of N-Protected 2-Indolylboronic Acid. Reagents and Conditions: (i) LiTMP, THF, -78°C . (ii) TPB, H^+ , H_2O .

The formation of the 3-isomer is not detailed in the literature, but it probably follows the same path as that described for the 2-isomer, except the lithio-derivative is generated by metal-halogen exchange reaction of N-protected- (BOC)-3-bromoindole (Scheme 1.44).⁹



Scheme 1.44: Synthesis of N-Protected 3-Indolylboronic Acid. Reagents and Conditions: (i) $t\text{BuLi}$, Et_2O , -78°C . (ii) TPB, H^+ , H_2O .

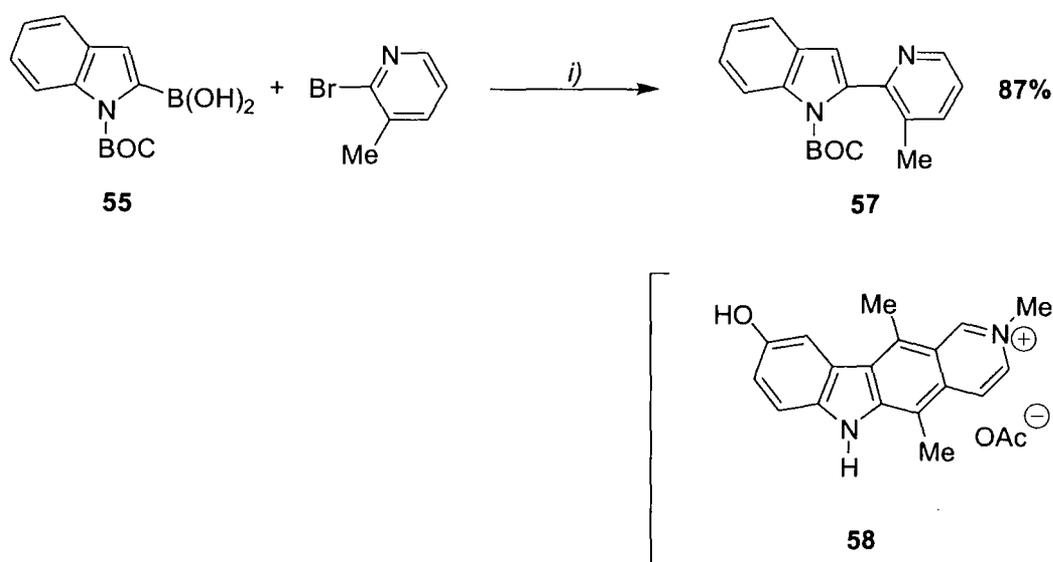
These boronic acids are useful in Suzuki cross-coupling reactions to produce a variety of substituted indoles of potential medicinal value. For example, 5-indolylboronic acid is used in the synthesis of 5-arylated indoles (Scheme 1.45).⁸⁷ The 6- and 7-isomers have been employed in the same manner.



Scheme 1.45: Synthesis of 5-Arylated Indoles. Reagents and Conditions: (i) $\text{Pd}(\text{PPh}_3)_4$, NaHCO_3 , DME, reflux.

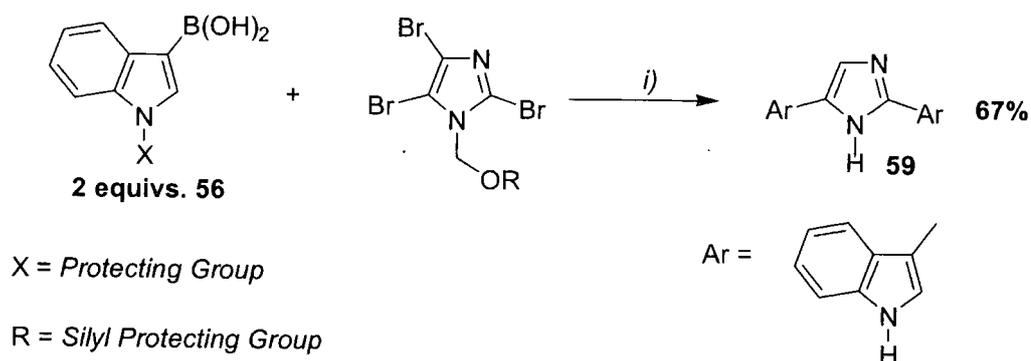
A wide variety of phenyl-substituted indoles are naturally occurring and are biologically active.⁸⁵ These are important intermediates in the synthesis of agonists and antagonists of the CNS neurotransmitter serotonin.⁸⁷

The cross-coupling reaction of indolylboronic acids has been used as a key step in the synthesis of benzo[a]carbazoles and pyrido[2,3-a]carbazoles, for example elliptinium **58**, used clinically for the treatment of cancer. The cross-coupling reaction of **55** forms the intermediate **57**, a precursor to pyridocarbazoles (Scheme 1.46).^{86b}



Scheme 1.46: Key Step in the Synthesis of Pyrido[2,3-a]carbazoles. Reagents and Conditions: (i) 10% $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , DME, reflux.

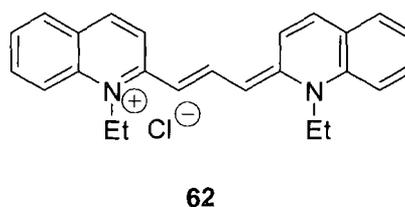
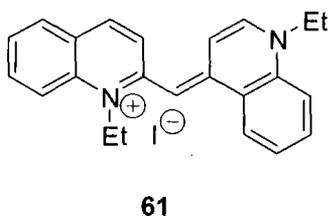
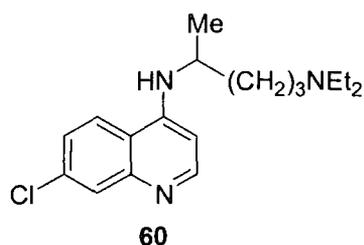
3-Indolylboronic acid plays a key role in the synthesis of 2,4-di(3-indolyl)1H-imidazole (**59**), a marine alkaloid with antifungal properties.⁸⁸ This class of compound is a member of the Nortopsentins. Again the Suzuki reaction is utilized, but on this occasion a dual cross-coupling takes place (Scheme 1.47).



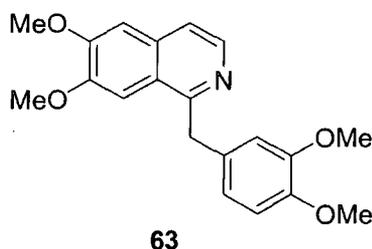
Scheme 1.47: Synthesis of 2,4-Di(3-indolyl)1H-imidazole. Reagents and Conditions: (i) 1. Pd(0), Na₂CO₃, Solvent. 2. nBuLi, H₂O. 3. Buⁿ₄NF.

1.4.7 Benzo-fused Pyridines: Quinolyl- and Isoquinolylboronic Acid

Quinolines occur widely in nature and have valuable chemotherapeutic, tumour-inhibiting and fungicidal properties.⁸⁹ This has led to interest in the synthesis of substituted quinolines, which has resulted in the synthesis of antimalarial drugs such as chloroquine (**60**),⁹⁰ for example. Quinoline compounds also provided the first photographic film sensitizers. The cyanine dye ethyl red (**61**) extended photography from the blue into the green spectral region and then in 1904, with pinacyanol (**62**), into the red.⁹

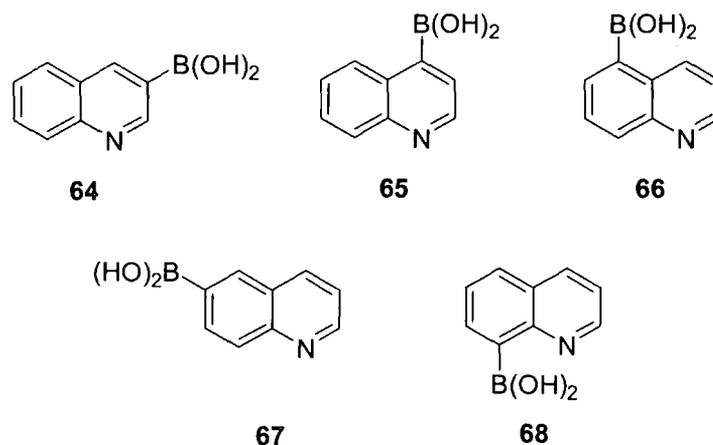


Isoquinoline occurs in a large number of alkaloids, e.g. papaverine (**63**), a member of the opium poppy alkaloids.⁹¹ This compound is a muscle relaxant and can therefore be useful as a coronary vasodilator.

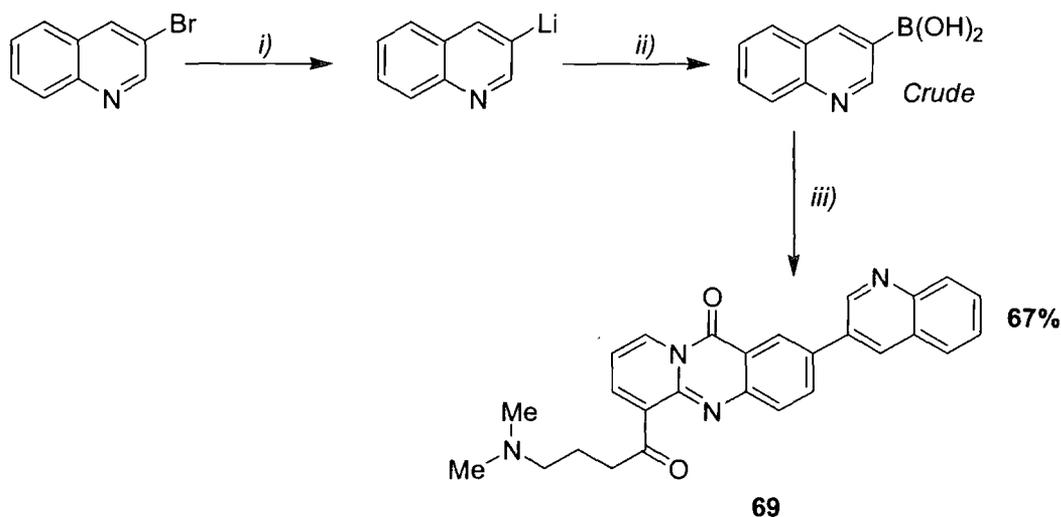


These facts indicate that quinolinyl- and isoquinolinylboronic acids could be advantageous in the synthesis of compounds containing these ring systems.

There are numerous isomers of quinolinylboronic acid, whose syntheses are mainly reported in patents. The 3- (**64**),⁹² 4- (**65**),⁹³ 5- (**66**),^{93,94} 6- (**67**)⁹⁵ and 8-quinolinylboronic (**68**)⁹⁶ isomers exist, but no literature reference has been found to the 2- and 7-isomers. The 3-isomer has been reported the most in the literature.



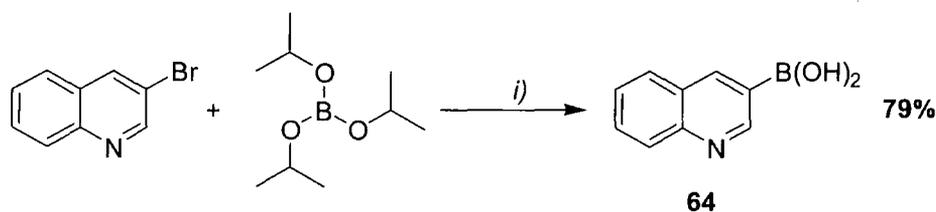
Trova *et al*⁹² described the synthesis of **64** via the 3-lithio-derivative, which was generated by the metal-halogen exchange reaction and subsequent reaction with TMB, followed by the appropriate work-up to yield the desired boronic acid. They did not purify this acid and reacted it directly in a Suzuki cross-coupling reaction aimed at the synthesis of a heterobiaryl-pyridoquinazolinone derivative (**69**) (Scheme 1.48), which is a potential anti-cancer agent.



Scheme 1.48: The Use of 3-Quinolinyboronic Acid in the Synthesis of Hetero-biaryl-pyridoquinazolinone derivative. Reagents and Conditions: (i) $n\text{BuLi}$, Et_2O , -40°C , (ii) TMB, (iii) $\text{Pd}(\text{PPh}_3)_4$, N-[2-(dimethylamino)ethyl]-2-iodo-11-oxo-11H-pyrido[2,1-b]quinazoline-6-carboxamide, $2\text{M Na}_2\text{CO}_3$, toluene, 120°C .

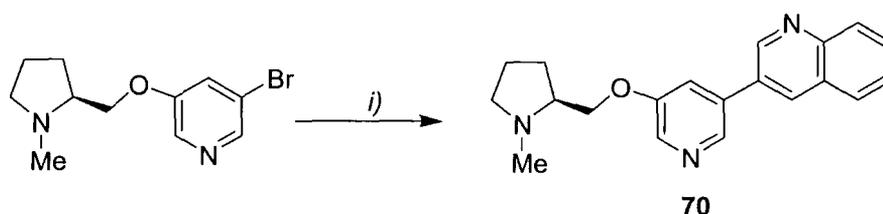
Variations and improvements have been made on this preparation. Recently, Li *et al*⁹⁷ reported the efficient synthesis of **64**, involving the use of an *in situ* quench procedure.

64 was generated by the addition of *n*BuLi to a solution of 3-bromoquinoline and TPB in toluene at -70°C (Scheme 1.49).



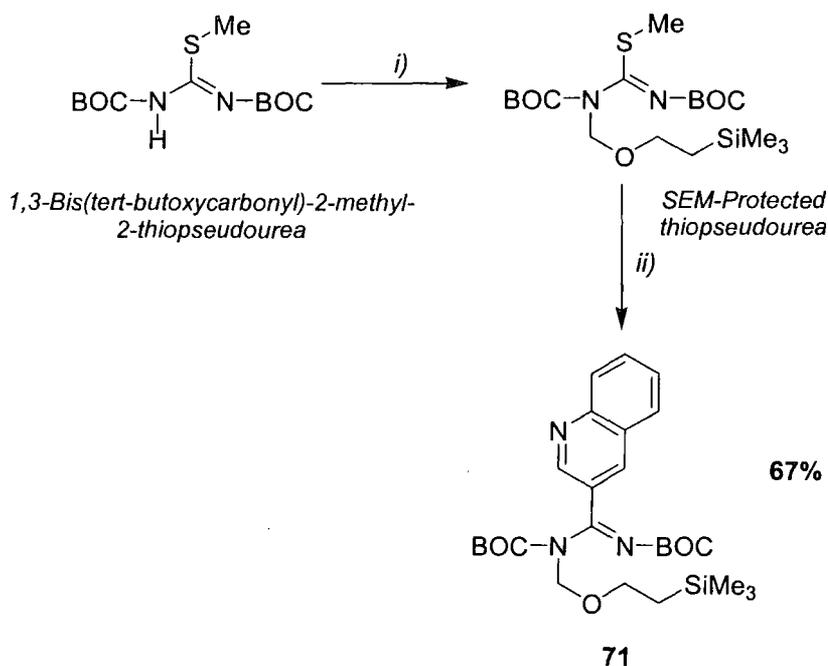
Scheme 1.49: Synthesis of **64**. Reagents and Conditions: (i) *n*BuLi, toluene, -70°C , aq. work-up.

The primary function of **64** has been in the production of pharmaceutical targets via the palladium-catalysed cross-coupling reactions. For example, in the synthesis of a derivative of a 3-pyridyl ether compound (**70**) (Scheme 1.50).⁹⁸ This class of compound has been identified as potent cholinergic channel modulators, and they have the therapeutic potential for the treatment of CNS disorders.



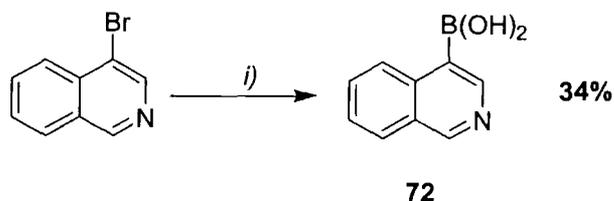
Scheme 1.50: Synthesis of Substituted-3-Pyridyl Ether. Reagents and Conditions: (i) **64**, $\text{Pd}(\text{PPh}_3)_4$.

64 also has potential in the synthesis of protected heteroaryl amidines (**71**).⁹⁹ The amidine functional group is found in many biological molecules. The amine group is firstly protected by deprotonation with NaH followed by treatment with SEM chloride. This protected species can then be reacted with the boronic acid using an extension of the Liebeskind-Srogl thioether cross-coupling methodology (Scheme 1.51).¹⁰⁰



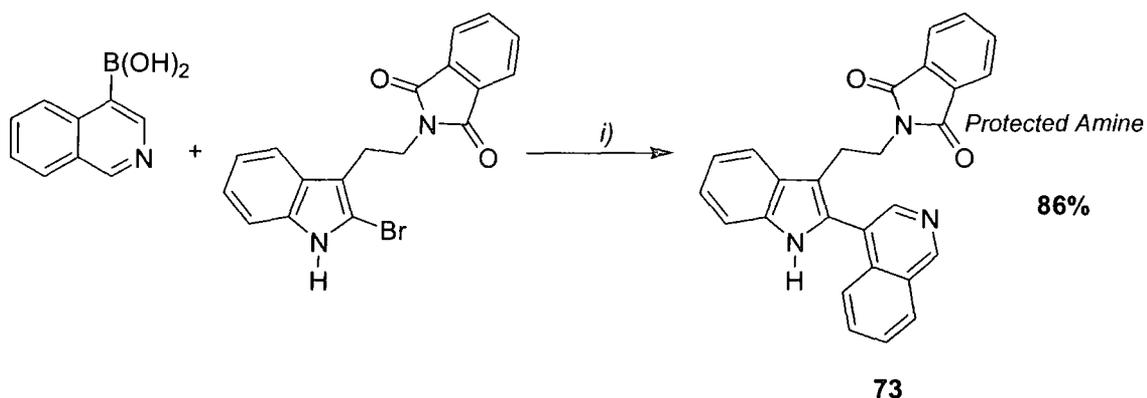
Scheme 1.51: Synthesis of a Protected Heteroaryl Amidine, 71. Reagents and Conditions: (i) 1. NaH, DMF, 2. SEMCl. (ii) 63, CuTC (Cu(I)thiophene-2-carboxylate, Pd₂(dba)₃, TFP (tri-2-furylphosphine), THF, 65°C.

The only known isomer of isoquinolylboronic acid (**72**) is the 4-isomer, and there are only a few references related to this compound.¹⁰¹ The only description of its formation is in a patent. Phebus *et al*^{101a} synthesised the 4-isomer for use in the synthesis of compounds for the treatment of anxiety disorders. The acid was formed via a sequential addition of reagents method. The lithio-derivative was generated at -100°C by the metal-halogen exchange reaction, involving nBuLi. The lithio-derivative was then reacted with TPB to yield the desired boronic acid (Scheme 1.52).



Scheme 1.52: Synthesis of 4-Isoquinolinyboronic Acid. Reagents and Conditions: (i) 1. nBuLi, THF, -100°C. 2. TPB. 3. Aq. Work-up.

This acid has also been employed in the synthesis of 2-aryltryptamines,^{101b} a moiety that is present in many natural products and medicinal chemistry targets that possess various biological activities. The isoquinolyl moiety is introduced into the 2-position of protected-tryptamine (**73**) via a Suzuki reaction (Scheme 1.53).

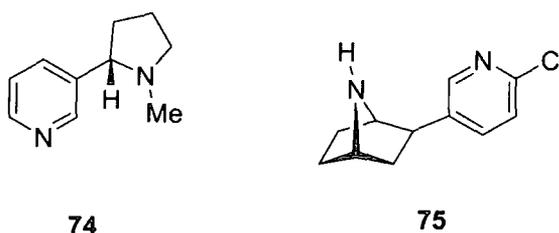


Scheme 1.53: Synthesis of 2-Isoquinolinyltryptamine. Reagents and Conditions: (i) $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , LiCl .

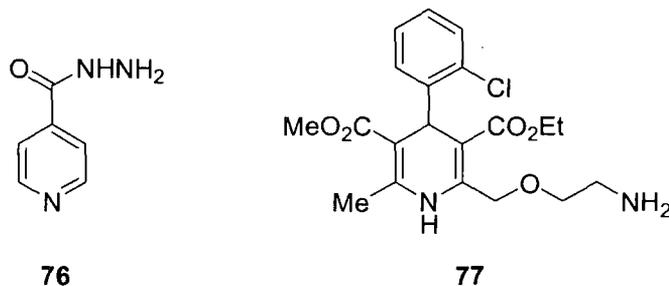
1.4.8 Pyridylboronic Acids

The bulk of the work in this thesis concerns the synthesis and application of substituted-pyridylboronic acids. A review of the background of the parent systems of pyridylboronic acid gives the rationale behind this research.

At the outset of our project there was very little published about the synthesis of pyridylboronic acids.¹⁸ Pyridine derivatives occur widely in nature. For example, the highly toxic alkaloid nicotine (**74**), a major component in tobacco, which is one of the most addictive drugs known.¹⁰² Also, the unique alkaloid epibatidine (**75**), isolated from the Ecuadorian poison frog *Epipedobates tricolor*, exhibits high analgesic activity.¹⁰³

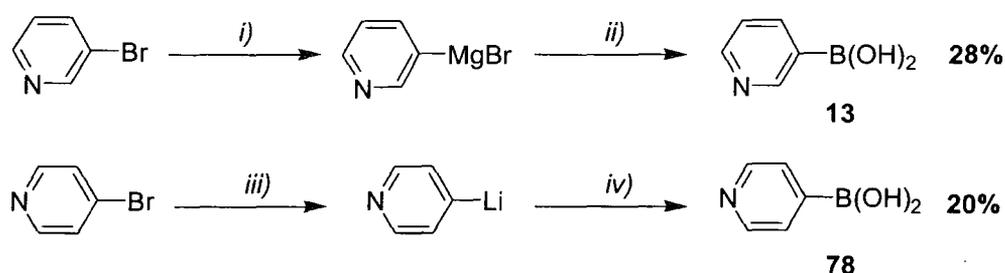


Synthetic pyridine derivatives also have important therapeutic properties. For example, in compounds such as Isoniazide (**76**), a major antituberculosis agent, and Amlodipine (**77**), one of several antihypertensive 1,4-dihydropyridines.⁹



Therefore, like the previously reviewed heterocyclic ring systems, pyridylboronic acids should provide a route into aryl/heteroaryl substituted-pyridines. Such compounds also enjoy various applications in materials science and supramolecular chemistry.^{22b}

Until recently only one literature reference published in 1965¹⁸ described the synthesis of the 3- (**13**) and 4-pyridylboronic acids (**78**). The 3-isomer was obtained via a Grignard reagent and the 4-isomer via a lithio-derivative from their corresponding bromo-compounds. These organometallic species were then reacted with TBB and TMB, respectively, to form **13** and **78** (Scheme 1.54).

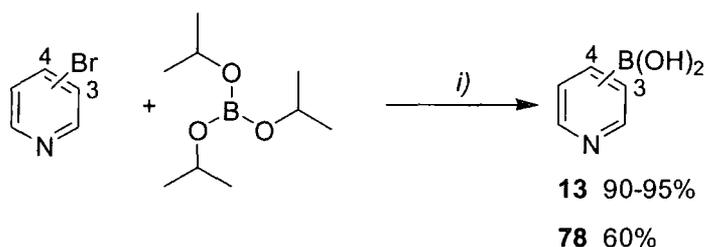


Scheme 1.54: Fischer and Havinga's Synthesis of 3- and 4-Pyridylboronic Acid. Reagents and Conditions: (i) Mg turnings, Et₂O, 20°C, (ii) 1. TBB, -60°C. 2. Work-up, (iii) nBuLi, -60°C, (iv) 1. TMB, -60°C. 2. Work-up.

The problems with these reactions are that they are both low yielding (28 and 20%), require conditions that are not suitable for scale-up, i.e. in the case of the 3-isomer a tedious work-up procedure is required (a 2-week ether extraction), and low temperatures are needed for the formation of the 4-isomer. Also, the analytical data was restricted to the nitrogen content of the compound, hardly conclusive evidence of purity. We

repeated these reactions only to obtain a lower yield for **13** (7%) and obtained no product in the synthesis of **78**.

The factors involved in these reactions, such as reaction times and conditions required are not acceptable by modern standards, i.e. the need for a high throughput of compounds. These acids have been used in various reactions, such as Suzuki cross-coupling reactions since their discovery, but only recently have improved procedures for their formation have been published. Cai *et al*^{23,97} in 2002 published a more efficient synthesis of both **13** and **78** involving an *in situ* quench procedure. This method involved the addition of nBuLi to a solution of bromopyridine and TPB in toluene, a non-coordinating solvent (Scheme 1.55).



Scheme 1.55: Synthesis of 3- and 4-Pyridylboronic Acid. Reagents and Conditions: (i) 1. nBuLi, toluene, -70°C. 2. HCl, -20°C.

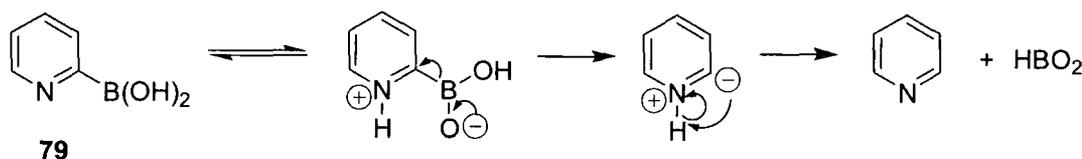
Previous experiments revealed that in the case of 3-bromopyridine the use of toluene gave an almost quantitative conversion to 3-lithiopyridine.²³ Usually, the metal-halogen exchange reaction needs a coordinating solvent, such as THF, to dissociate the BuLi aggregate, but with toluene, the pyridine N serves to activate the metal-halogen exchange reaction.²³ The explanation behind the success of this reaction is that the metal-halogen exchange reaction is faster than any reaction between nBuLi and TPB. Also, the lithio-derivatives generated react immediately with TPB, thus minimizing side reactions.⁹⁷

Other groups have also attempted an improved synthesis of the 4-pyridylboronic acid. Dreos *et al*¹⁰⁴ have synthesised **78** via a sequential addition of reagents method. The lithiation was achieved using nBuLi as the lithiating reagent in the presence of N,N,N',N'-tetramethyl-1,2-ethylenediamine (TMEDA), an activating agent, at very low temperature (-110°C). These conditions were required in order to avoid nucleophilic addition to the 4-bromopyridine. The lithio-derivative was then reacted with TMB to

yield **78**. They only slightly improved on Fischer and Havinga's synthesis (34%), but they obtained full characterisation for the compound. Lamothe *et al*¹⁰⁵ used a sequential addition method for the formation of the **78** and have improved on the syntheses described by all the previous laboratories. They used *n*BuLi in the lithiation of 4-bromopyridine at -78°C, followed by the addition of TPB to give **78** in 65% yield, but they did not quote full characterization for the compound.

To date, there has been no description of the synthesis of the 2-isomer (**79**). We attempted the synthesis of this acid via the routes described by Fischer and Havinga,¹⁸ i.e. via the Grignard- and lithio-species, both to no avail. In 1974, whilst studying the chemical properties of pyridylboronic acids, Fischer and Havinga found that pyridylboronic acids undergo easy protodeboronation.¹⁰⁶ They proposed that this was the reason behind the failure in the synthesis of **79**. They observed that upon UV irradiation in neutral and slightly basic conditions,¹⁰⁷ and attempted quaternisation with MeI in MeOH, **13** and **78** decomposed to pyridine and boric acid. On attempted synthesis of **79**, they noticed that the 2-pyridylboronate was unstable. After dissolving the supposed lithium tributyl-2-pyridineboronate, resulting from the reaction of 2-lithiopyridine with TBB in protic solvents, they observed the formation of pyridine and boric acid (Scheme 1.56). These reactions can be described as S_e1 substitution reactions, which are known to occur in pyridine and pyridinium ions. This observation is analogous to the decarboxylation of 2-pyridylcarboxylic acid, or picolinic acid.^{8,9}

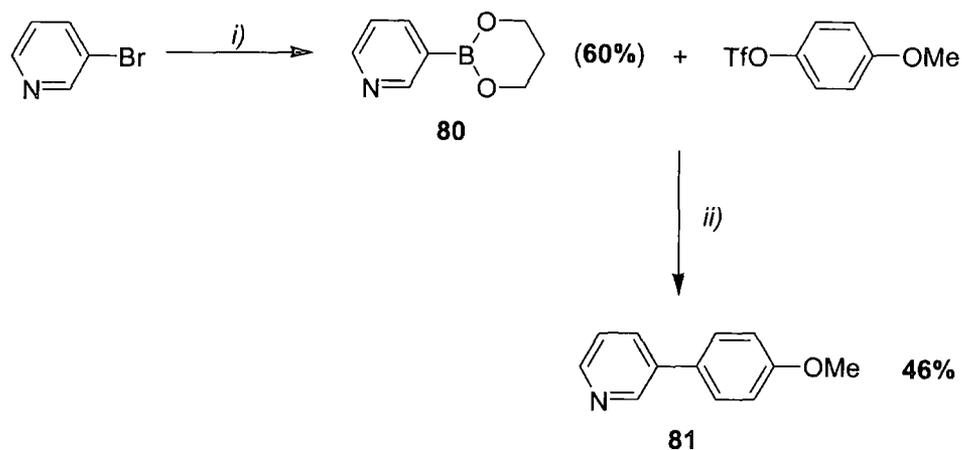
Protodeboronation:



Scheme 1.56: Decomposition of 79.

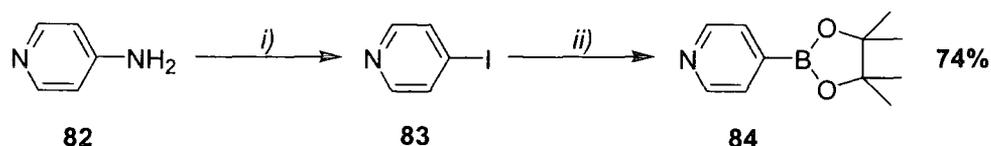
Due to the early difficulties experienced in the synthesis of pyridylboronic acids the related pyridylboronic esters were studied. While studying the Pd-catalysed cross-coupling reactions of organoboron compounds with organic triflates Oh-e *et al* synthesised 2-(3-pyridyl)-1,3,2-dioxaboronane (**80**).¹⁰⁸ The boronic acid was firstly formed via metal-halogen exchange reaction of 3-bromopyridine with *n*BuLi, followed

by the addition of TMB. 1,3-Propanediol was then added in order to form **80**. Oh-e *et al* obtained **80** good yield (60%), and applied this compound in the Suzuki cross-coupling reaction to give **81** (Scheme 1.57). We repeated the synthesis of **80**, but only managed to obtain a 17% yield.



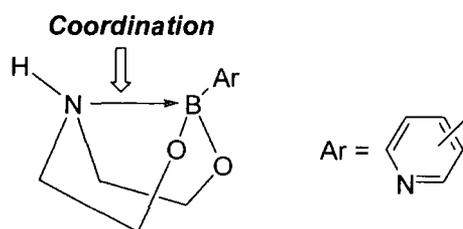
Scheme 1.57: Synthesis and Application of 2-(3-Pyridyl)-1,3,2-dioxaboronane, **80.** Reagents and Conditions: (i) 1. nBuLi, Et₂O, -78°C. 2. TMB, -78°C. 3. 1,3-Propanediol, 0°C; (ii) Pd(PPh₃)₄, K₃PO₄, dioxane, 85°C.

The synthesis of 2-(4-pyridyl)-4,4,5,5-tetramethyl-1,3-dioxaborolane (**84**) has also been investigated by Coudret in the course of the design of photochromic bridging ligands for molecular electronics.¹⁰⁹ The route to **84** involved the metal-halogen exchange reaction of 4-iodopyridine (**83**), which is known to be a convenient source of 4-pyridyl organometallic reagents. The 4-iodopyridine was formed from 4-aminopyridine (**82**) via a Sandmeyer reaction and then lithiated using nBuLi followed by treatment with TBB, pinacol and AcOH to neutralize the reaction (Scheme 1.58). This gave the ester in good yield (74%). As before we repeated the synthesis of this ester and obtained a 21% yield.



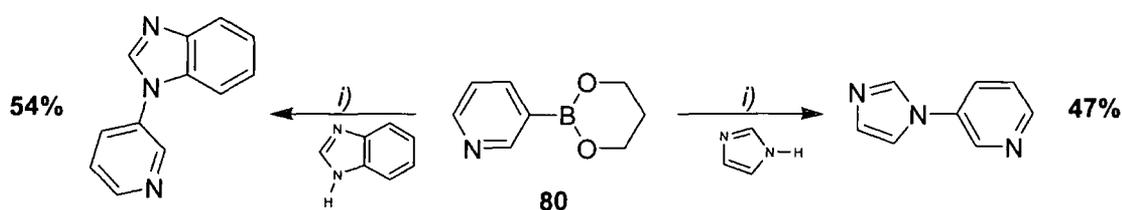
Scheme 1.58: Synthesis of 2-(4-Pyridyl)-4,4,5,5-tetramethyl-1,3-dioxaborolane. Reagents and Conditions: (i) 1. NaNO_2 , HBF_4 , -10°C . 2. KI , acetone- H_2O , (ii) 1. $n\text{BuLi}$, Et_2O , -78°C . 2. TBB, -78°C . 3. Pinacol, then AcOH .

We are not aware of any literature report on the synthesis of the 2-pyridylboronic ester. Another option in the synthesis of pyridylboronic esters is the use of diethanolamine, which can stabilise cyclic boronic esters by N-B bond coordination (Scheme 1.59).¹¹⁰ However, to the best of our knowledge this reagent has not been reported in the synthesis of pyridylboronic esters.



Scheme 1.59: Possible Stabilisation of Pyridylboronic Esters by Coordination.

The ester can sometimes have an advantage over its corresponding acid. Chan *et al* have reported the successful application of **80** in the copper promoted cross-coupling reaction used for the preparation of a range of heteroaryl amines (Scheme 1.60).¹¹¹

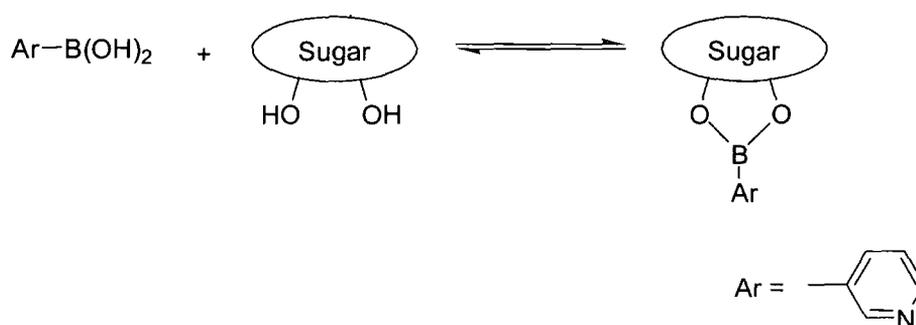


Scheme 1.60: Application of **80** in the Copper Mediated Cross-Coupling Reaction. Reagents and Conditions: (i) $\text{Cu}(\text{OAc})_2$, pyridine, DCM, rt.

In direct comparison, no reaction was observed when **13** was used under identical conditions. This is a useful procedure as it operates under mild conditions and can

tolerate base sensitive functionalities. This was the first reported C-N cross-coupling involving a heterocyclic boronic acid system.

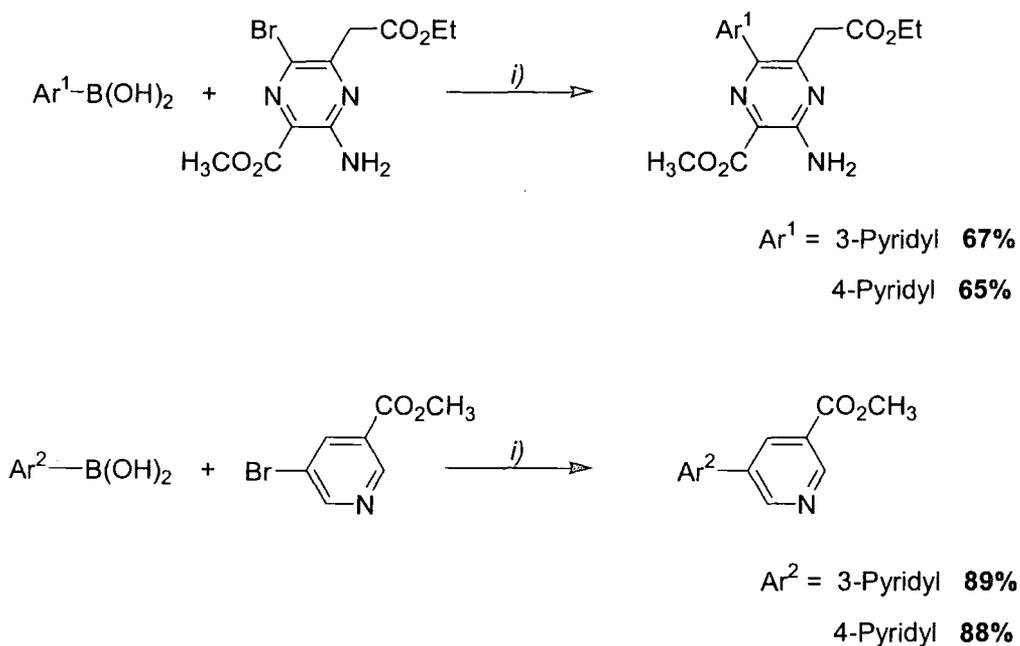
Interesting pyridylboronic esters are obtained by the reaction of **13** with saccharides. Medically, this is a very significant reaction as the boronic acid acts as an artificial sugar receptor in order to transport saccharides through lipid bilayers.¹¹² Boronic acids are of particular interest as they can rapidly form reversible covalent complexes at ambient temperature in aqueous solution.¹¹³ The proposed mechanism for the formation of such esters is illustrated in Scheme 1.61.



Scheme 1.61: Boronic Acid-Saccharide Interaction.

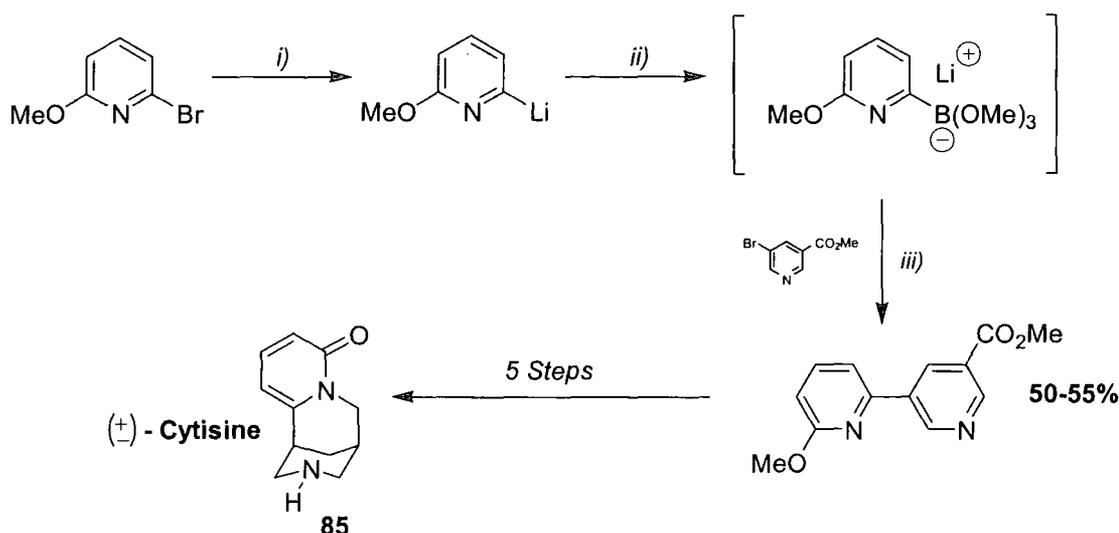
This is a very important process when you understand that selective transportation of saccharides across cell membranes is a ubiquitous cellular activity. For example, a typical human red cell contains around 200,000 glucose transport molecules. A defect in these transportation processes could lead to serious medical problems.

The main application of the parent boronic acids has been their involvement in the Suzuki cross-coupling reaction,¹¹⁴ e.g. in the synthesis of substituted pyrazines and bipyridines (Scheme 1.62).⁴⁴



Scheme 1.62: Synthesis of Substituted Pyrazines and Substituted Bipyridines. Reagents and Conditions: (i) Pd(dppf)(OAc)_2 , DMF, Et_3N , 90°C .

Substituted pyrazines occur widely in nature and are valuable heterocyclic nuclei for the design of pharmaceutical agents. The bipyridine is an important moiety, for example, the 2,2'-bipyridyl ligand plays an important role in organic and inorganic chemistry, photochemistry, and materials science.¹¹⁵ The formation of substituted bipyridine compounds is also an important step in the synthesis of new drug targets. For example, a key step in the formation of cytosine (**85**), a nicotine partial agonist, involves the 'in situ' Suzuki coupling to form a bipyridine (Scheme 1.63).¹¹⁶

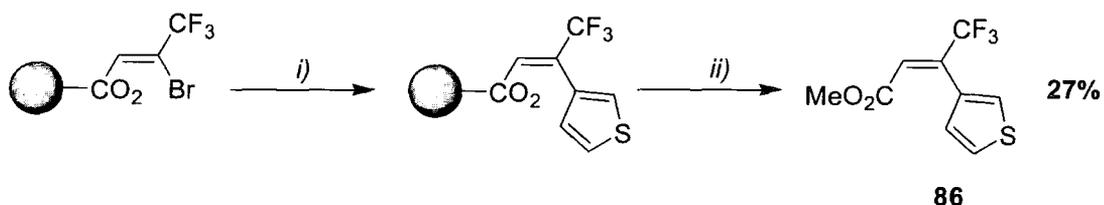


Scheme 1.63: Synthesis of Cytisine. Reagents and Conditions: (i) Et_2O , -40°C , (ii) TMB, Et_2O , (iii) $\text{Pd}(\text{PPh}_3)_4$, CsF , DME , 85°C .

This reaction gives further evidence of the difficulty of synthesising 2-pyridylboronic acids as the intermediate lithium salt was used for the reaction.

1.5 Conclusions

With the variety of heterocyclic boronic acids available, coupled with their application in the Suzuki cross-coupling reaction, we have shown heterocyclic boronic acids to be very versatile reagents and beneficial to organic synthesis. Since its discovery in 1981 the Suzuki reaction has been heavily investigated and is still undergoing improvements to meet the demands of the modern chemical industry. For example, combinatorial chemistry has become an important aspect of the drug discovery process.¹¹⁷ Solid-phase organic synthesis (SPOS) has attracted much attention over the past decade, as a powerful tool in the rapid synthesis of small molecule combinatorial libraries for drug discovery.¹¹⁸ The solid-phase Suzuki cross-coupling reaction has recently been widely investigated.¹¹⁹ Scheme 1.64 shows an example of the Pd-catalysed cross-coupling reaction of 3-thienylboronic acid with a novel resin bound CF_3 -containing building block to give **86**, thus illustrating another method of fluorine incorporation.¹¹⁸

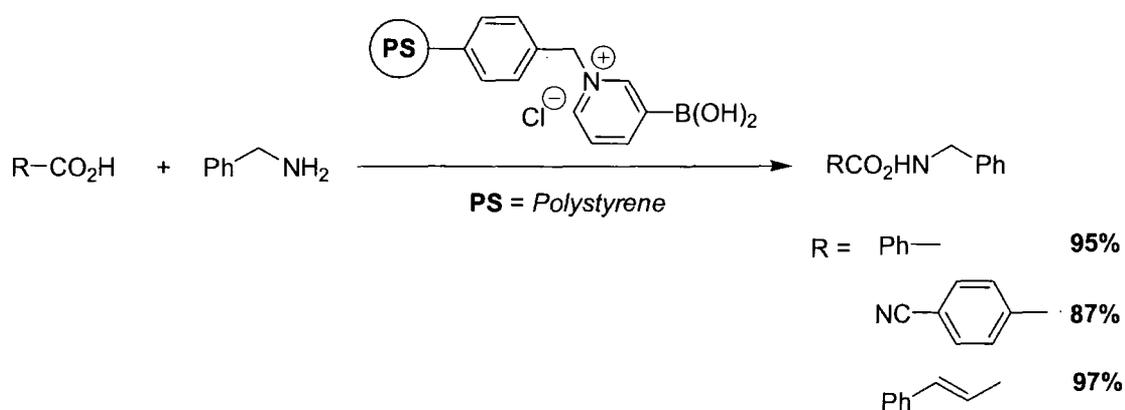


Scheme 1.64: Suzuki Cross-Coupling Reaction of Resin-Bound CF₃-Containing Building Block.
Reagents and Conditions: (i) Pd(PPh₃)₄, 3-Thienylboronic Acid, 2M Na₂CO₃, Xylene/EtOH, 80°C,
(ii) MeONa, MeOH/THF.

The advantages of using SPOS are:¹¹⁷

- Ease at which reagents and solvents are removed.
- Technique allows easy automation.
- Produces a high throughput of compounds.

A polystyrene-bound **13** has been synthesised. A pyridylboronic acid was used in this manner following the success Yamamoto *et al*¹²⁰ had with employing arylboronic acids as amidation catalyts, as many boron-based components such as ClB(OMe)₂, HB(ⁱPr)₂ and catecholborane are known to activate carboxylic acids for amidation reactions via mixed anhydrides. This polystyrene-bound acid has been shown to be an efficient, high yielding, easily recoverable and reusable amidation catalyst providing the first example of a pyridylboronic acid being used in this process (Scheme 1.65).¹²¹



Scheme 1.65: Application of PS-Bound 3-Pyridylboronic Acid.

These examples highlight the scope and possibilities of the Suzuki reaction, which in turn suggests the need for new boronic acids.

The versatility of the Suzuki reaction and the fact that the synthesis of pyridylboronic acids is still a relatively unexplored area of organic chemistry, led us to consider new substituted-pyridylboronic acids to be interesting targets for our research.

1.6 References

- ¹ Seaman, W.; Johnson, J. R. *J. Am. Chem. Soc.* **1931**, *53*, 711, and references therein.
- ² Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817.
- ³ Petasis, N. A.; Boral, S. *Tetrahedron Lett.* **2001**, *42*, 539.
- ⁴ Kotha, S.; Ghosh, A. K. *Synlett* **2002**, *3*, 451.
- ⁵ Vaultier, M.; Carboni, B. *Comprehensive Organometallic Chemistry, II*, Pergamon: New York, **1995**.
- ⁶ Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
- ⁷ Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*, 3rd Edition, Blackwell: Oxford, **1995**.
- ⁸ Gilchrist, T. L. *Heterocyclic Chemistry*, 2nd Edition, Wiley: New York, **1992**.
- ⁹ Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th Edition, Blackwell: Oxford, **2000**.
- ¹⁰ Lai, Y-H. *Synthesis* **1981**, 585.
- ¹¹ Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Non-Metallic Substances*, Prentice-Hall, Inc.: New York, **1954**.
- ¹² Urbanski, T., *Chem. Ber.* **1976**, *12*, 191..
- ¹³ Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*, Oxford: New York, **2001**.
- ¹⁴ Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, Wiley: New York, **1988**.
- ¹⁵ Pearson, D. E.; Cowan, D.; Beckler, J. D. *J. Org. Chem.* **1959**, *24*, 504.
- ¹⁶ Gilman, H.; Peterson, J. M.; Schulze, F. *Recueil* **1928**, *47*, 19.
- ¹⁷ Gomberg, M.; Backmann, W. E. *J. Am. Chem. Soc.* **1927**, *49*, 236.
- ¹⁸ Fischer, F. C.; Havinga, E. *Recueil* **1965**, *84*, 439.

- ¹⁹ Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron* **1987**, *28*, 5845.
- ²⁰ Paradies, H. H.; Görbing, M. *Angew. Chem.* **1969**, *81*, 293; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 279; Paradies, H. H. *Naturwissenschaften* **1974**, *61*, 168.
- ²¹ Martin, G. J.; Mechin, B.; Leroux, Y.; Paulmier, Cl.; Meunier, J. C. *J. Organomet. Chem.* **1974**, *67*, 327.
- ²² (a) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **1999**, *40*, 4339; (b) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349.
- ²³ Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 4285.
- ²⁴ von Ragué Schleyer, P.; Chandrasekhar, J.; Kos, A. J.; Clark, T.; Spitznagel, G. *W. J. Chem. Soc., Chem. Commun.* **1981**, 882.
- ²⁵ Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773.
- ²⁶ Kondo, Y.; Asai, M.; Miura, T.; Uchiyama, M.; Sakamoto, T. *Org. Lett.* **2001**, *3*, 13.
- ²⁷ Cai, D.; Hughes, D. L.; Verhoeven, T. R. *Tetrahedron Lett.* **1996**, *37*, 2537.
- ²⁸ Quéguiner, G.; Marsais, F.; Snieckus, V. *Adv. Heterocycl. Chem.* **1992**, *52*, 187.
- ²⁹ (a) French, H. E.; Sears, K. *J. Am. Chem. Soc.* **1951**, *73*, 469; (b) Ishikura, M.; Ohta, T. *Chem. Pharm. Bull.* **1985**, *33*, 4755.
- ³⁰ Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.
- ³¹ (a) Kharasch, M. S.; Fuchs, C. F. *J. Am. Chem. Soc.* **1943**, *65*, 50; (b) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316.
- ³² Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144.
- ³³ Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.
- ³⁴ Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150.
- ³⁵ Negishi, E.-I.; King, A. O.; Villani, M.; Silveira, R. *J. Org. Chem.* **1978**, *43*, 358.
- ³⁶ Minato, A.; Suzuki, K.; Tamao, K.; Kumada, M. *J. Chem. Soc. Chem. Commun.*, **1984**, 511.
- ³⁷ Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanatia, H. *Tetrahedron Lett.* **1992**, *33*, 5373.
- ³⁸ Malm, J.; Björk, P.; Gronowitz, S. *Tetrahedron Lett.* **1992**, *33*, 2199.
- ³⁹ Peters, D.; Gronowitz, S. *J. Heterocycl. Chem.* **1990**, *27*, 2165.
- ⁴⁰ Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

- 41 (a) Gronowitz, S.; Lawitz, K. *Chem. Scr.* **1983**, 22, 265; Gronowitz, S.; Lawitz, K. *Chem. Scr.* **1984**, 23, 5; (b) Gronowitz, S.; Bobosik, V.; Lawitz, K. *Chem. Scr.* **1984**, 23, 120.
- 42 Martin, A. R.; Yang, Y. *Acta. Chem. Scand.* **1993**, 47, 221.
- 43 Shen, W. *Tetrahedron Lett.* **1997**, 38, 5575.
- 44 Thompson, W. J.; Jones, J. H.; Lyle, P. A.; Thies, J. E. *J. Org. Chem.* **1988**, 53, 2052.
- 45 Gronowitz, S.; Peters, D. *Heterocycles* **1990**, 30, 645.
- 46 Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, 120, 2817.
- 47 Johnson, J. R.; Van Campen, Jr, M. G.; Grummitt, O. *J. Am. Chem. Soc.* **1938**, 60, 111.
- 48 Roques, B. P.; Florentin, D.; Callanquin, M. *J. Heterocycl. Chem.* **1975**, 12, 195.
- 49 (a) Lappert, M. F. *Chem. Rev.* **1956**, 56, 959; (b) Kharasch, M. S.; Reinmuth, O. "Grignard Reactions of Non-Metallic Substances", Prentice-Hall Inc.: New York, **1954**, 1335.
- 50 Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, 49, 5237.
- 51 Brown, R. D.; Buchanan, A. S.; Humffray, A. A. *Aust. J. Chem.* **1965**, 18, 1521.
- 52 Zaluski, M. C.; Thèse de Doctorat es-Sciences, Paris, **1970**.
- 53 Enguehard, C.; Hervet, M.; Théry, I.; Renou, J.-L.; Fauvelle, F.; Gueiffer, A. *Het. Chem. Acta.* **2001**, 84, 3610.
- 54 Kotha, S.; Ghosh, A. K. *Synlett.* **2002**, 451.
- 55 Prakash, G. K. S.; Mandal, M.; Schweizer, S. *Org. Lett.* **2000**, 2, 3173.
- 56 Petasis, N. A.; Boral, S. *Tetrahedron Lett.* **2001**, 42, 539.
- 57 Krause, E.; Renwanz, G. *Ber.* **1932**, 65, 777.
- 58 Breur, S. W.; Thorpe, F.G. *Tetrahedron Lett.* **1974**, 42, 3719.
- 59 (a) Seed, A. J.; Toyne, K. J., Goodby, J. W. *J. Mat. Chem.* **1995**, 5, 653; (b) Caze, C.; El Moualij, N.; Hodge, P.; Lock, C. J. *Polymer* **1995**, 36, 621.
- 60 Lawesson, S. O. *Ark. Kemi.* **1957**, 11, 373.
- 61 (a) Franc, C.; Denonne, F.; Cuisinier, C.; Ghosez, L. *Tetrahedron Lett.* **1999**, 40, 4555; (b) Kaswasaki, I.; Yamashita, M.; Ohta, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2085; (c) Shi, D.-F.; Wheelhouse, R. T.; Sun, D.; Hurley, L. H. *J. Med. Chem.* **2001**, 44, 4509; (d) Gooßen, L. J.; Ghosh, K. *Angew. Chem. Int. Ed.* **2001**, 40, 3458; (e) Yu, S.; Saenz, J.; Srirangam, J. K. *J. Org. Chem.* **2002**, 67, 1699; (f) McCort, G.; Duclos, O.; Cadilhac, C.; Guilpain, E. *Tetrahedron*

- Lett.* **1999**, *40*, 6211; (g) Lakshman, M. K.; Thomson, P. F.; Nuqui, M. A.; Hilmer, J. H.; Sevova, N.; Boggess, B. *Org. Lett.* **2002**, *4*, 1479; (h) Enguehard, C.; Renou, J.-L.; Collot, V.; Hervet, M.; Rault, Gueiffier, A. *J. Org. Chem.* **2000**, *65*, 6572; (i) Burk, M. J.; Lee, J. R.; Martinez, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 10847.
- 62 Rossi, R.; Bellina, F.; Carpita, A. *Synlett.* **1996**, 356.
- 63 (a) Johansson, T.; Mammo, W.; Andersson, M. R.; Inganäs, O. *Chem. Mater.* **1999**, *11*, 3133; (b) Caze, C.; El Moualij, N.; Hodge, P.; Lock, C. J. *Polymer* **1995**, *36*, 621; (c) Effenberger, F.; Grube, G. *Synthesis* **1998**, 1372; (d) Martinez, F.; Naarmann, H. *Syn. Metals* **1990**, *39*, 195; (e) Nicolas, M.; Fabre, B.; Marchand, G.; Simonet, J. *Eur. J. Org. Chem.* **2000**, 1703.
- 64 Collins, I.; Castro, J. L. *Tetrahedron Lett.* **1999**, *40*, 4069.
- 65 Cravino, A.; Zerza, G.; Neugebauer, H.; Maggini, M.; Bucella, S.; Menna, E.; Svensson, M.; Andersson, M. R.; Brabec, C. J.; Sariciftci, N. S. *J. Phys. Chem. B* **2002**, *106*, 70.
- 66 Goto, H.; Okamoto, Y.; Yashima, E. *Macromolecules* **2002**, *35*, 4590.
- 67 Tovar, J. D.; Swager, T. M. *Adv. Mat.* **2001**, *13*, 1775.
- 68 Hark, R. R.; Hauze, D. B.; Petrovskaja, O.; Joullié, M. M.; Jaoukari, R.; McComiskey, P. *Tetrahedron. Lett.* **1994**, *35*, 7719.
- 69 Joullié, M. M.; Thompson, T. R.; Nemeroff, N. H. *Tetrahedron* **1991**, *47*, 8791.
- 70 Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 3718.
- 71 (a) Martina, S.; Enkelmann, V.; Wegner, G.; Schlüter, A.-D. *Synthesis* **1991**, *8*, 613; (b) Martina, S.; Enkelmann, V.; Wegner, G.; Schlüter, A.-D. *Syn. Metals* **1991**, *41*, 403.
- 72 Hasan, I.; Marinelli, E. R.; Chang Lin, L.-C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.
- 73 Kelly, T. A.; Fuchs, V. U.; Perry, C. W.; Snow, R. J. *Tetrahedron* **1993**, *49*, 1009.
- 74 D'Alessio, R.; Rossi, A. *Synlett.* **1996**, 513.
- 75 Bolton, D.; Boyfield, I.; Coldwell, M. C.; Hadley, M. S.; Johns, A.; Johnson, C. N.; Markwell, R. E.; Nash, D. J.; Riley, G. J.; Scott, E. E.; Smith, S. A.; Stemp, G.; Wadsworth, H. J.; Watts, E. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 485.
- 76 Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.

- 77 (a) Huang, H.-C.; Chamberlain, T. S.; Seibert, K.; Koboldt, C. M.; Isakson, P. C.; Reitz, D. B. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2377; (b) Jinno, S.; Okita, T.; Inouye, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1029; (c) Ding, S.; Gray, N. S.; Wu, X.; Ding, Q.; Schultz, P. G. *J. Am. Chem. Soc.* **2002**, *124*, 1594; (d) Chen, C.; Wilcoxon, K.; Huang, C. Q.; Strack, N.; McCarthey, J. R. *J. Fluor. Chem.* **2000**, *101*, 285; (e) DeBoos, G. A.; Fullbrook, J. J.; Percy, J. M. *Org. Lett.* **2001**, *3*, 2859; (f) Cockerill, G. S.; Easterfield, H. J.; Percy, J. M. *Tetrahedron Lett.* **1999**, *40*, 2601; (g) Lee, J. H.; Park, E. S.; Yoon, C. M. *Tetrahedron Lett.* **2001**, *42*, 8311; (h) Böhmer, J.; Grigg, R. *Tetrahedron* **1999**, *55*, 13463; (i) Cockerill, G. S.; Easterfield, H. J.; Percy, J. M.; Pintat, S. *J. Chem. Soc., Perkin Trans 1* **2000**, 2591.
- 78 Armstrong, H. M.; Beresis, R.; Goulet, J. L.; Holmes, M. A.; Hong, X.; Mills, S. G.; Parsons, W. H.; Sinclair, P. J.; Steiner, M. G.; Wong, F.; Zaller, D. M. *PCT Int. Appl. WO 010023*, **2001**.
- 79 (a) Grandclaudon, P.; Lablache-Combiere, A.; Prknyi, C. *Tetrahedron* **1973**, *29*, 651; (b) Reichstein, T.; Baud, J. *Helv. Chem. Acta* **1937**, *20*, 892.
- 80 Jinno, S.; Okita, T.; Inouye, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1029.
- 81 Lee, J. H.; Park, E. S.; Yoon, C. M. *Tetrahedron Lett.* **2001**, *42*, 8311.
- 82 Hedberg, M. H.; Johansson, A. M.; Fowler, C. J.; Terenius, L.; Hacksell, U.O. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2527.
- 83 (a) Scott Weston, G.; Blázquez, J.; Baquero, F.; Shoichet, B. K. *J. Med. Chem.* **1998**, *41*, 4577; (b) Lepifre, F.; Clavier, S.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2001**, *57*, 6969; (c) Bastian, J. A.; Chirgadze, N.; Denney, M. L.; Gifford-Moore, D. S.; Sall, D. J.; Smith, G. F.; Wikel, J. H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 363.
- 84 (a) Crabonelle, A.-C.; Zamora, E. G.; Beugelmans, R.; Roussi, G. *Tetrahedron Lett.* **1998**, *39*, 4467; (b) Yang, Y.; Martin, A. R.; Nelson, D. L.; Regan, J. *Heterocycles* **1992**, *34*, 1169; (c) Jones, K.; Keenan, M.; Hibbert, F. *Synlett.* **1996**, 509.
- 85 Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106.
- 86 (a) Johnson, C. N.; Stemp, G.; Anand, N.; Stephen, S. C.; Gallagher, T. *Synlett.* **1998**, 1025; (b) de Koning, C. B.; Michael, J. P.; Rousseau, A. L. *J. Chem. Soc., Perkin Trans 1* **2000**, 1705.
- 87 Yang, Y.; Mart, A. R. *Heterocycles* **1992**, *34*, 1395.

- 88 Kaswasaki, I.; Yamashita, M.; Ohta, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2085.
- 89 Ishikura, M.; Oda, I.; Terashima, M. *Heterocycles* **1985**, *23*, 2375.
- 90 Surrey, A. R.; Hammer, H. F. *J. Am. Chem. Soc.* **1946**, *68*, 113.
- 91 Pictet, A.; Gams, A. *Chem. Ber.* **1909**, *42*, 2943.
- 92 Trova, M. P.; Zhang, N. *U.S. Patent 5908840*, **1999**.
- 93 (a) Wang, W.-B.; Curtin, M. L.; Fakhoury, S. A.; Gwaltney, S. L., II; Hasvold, L. A.; Hutchins, C. W.; Li, Q.; Lin, N.-H.; Nelson, L. T. J.; O'Conner, S.; Sham, H. L.; Sullivan, G. M.; Wang, G. T.; Wang, X. *U.S. Patent 20020019527*, **2002**;
(b) Wang, W.-B.; Curtin, M. L.; Fakhoury, S. A.; Gwaltney, S. L., II; Hasvold, L. A.; Hutchins, C. W.; Li, Q.; Lin, N.-H.; Nelson, L. T. J.; O'Conner, S.; Sham, H. L.; Sullivan, G. M.; Wang, G. T.; Wang, X. *PCT Int. Appl. WO 0181316*, **2001**.
- 94 Phillips, E.; Schmiesing, R. *PCT Int. Appl. WO 0160821*, **2001**.
- 95 Castro Pineiro, J. L.; Churcher, I.; Guiblin, A. R.; Harrison, T.; Kerrad, S.; Madin, A.; Nadin, A. J.; Owens, A. P.; Sparey, T. J.; Teall, M. R.; Williams, S. *PCT Int. Appl. WO 0190084*, **2001**.
- 96 (a) Claiborne, A. K.; Gwaltney, S. L., Hasvold, L. A.; Li, Q.; Li, T.; Lin, N.-H.; Mantei, R. A.; Rockway, T. W.; Sham, H. L.; Sullivan, G. M.; Tong, .; Wang, G.; Wang, L.; Wang, X.; Wang, W.-B. *U.S. Patent 20020115640*, **2002**;
(b) Wang, T.; Zhang, Z.; Meanwell, N. A.; Kadow, J. F.; Yin, Z. *PCT Int. Appl. WO 0262423*, **2002**;
(c) Nikolic, S.; Bartel, S.; Brands, M.; Niewoehner, U.; Paessens, A.; Graef, E.; Schlemmer, K.-H.; Henninger, K.; Endermann, R.; Weber, O.; Koletzki, D. *PCT Int. Appl. WO 0220509*, **2002**;
(d) Maillaird, M.; Hom, C.; Gailunas, A.; Jagodzinska, B.; Fang, L. Y.; John, V.; Freskos, J. N.; Pulley, S. R.; Beck, J. P.; Tenbrink, R. E. *PCT Int. Appl. WO 0202512*, **2002**.
- 97 Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394.
- 98 Lin, N.-H.; Li, Y.; Yun, H.; Holladay, M. W.; Kuntzweiler, T.; Anderson, D. J.; Campbell, J. E.; Arneric, S. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 631.
- 99 Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4*, 983.
- 100 (a) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979; (b) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91; (c) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

- 101 (a) Phebus, L. A.; Sajdyk, T. J. *Eur. Pat. Appl.* 99305923.7, 1999, (b) Chu, L.;
isher, M. H.; Goulet, M. T.; Wyvratt, M. J. *Tetrahedron Lett.* 1997, 38, 3871.
- 102 'Drugs against drugs', Gaskell, D. *Chem. Brit.* 1998, 27.
- 103 (a) Malpass, J. R.; Cox, C. D. *Tetrahedron Lett.* 1999, 40, 1419; (b) Sirisoma, N.
S.; Johnson, C. R., *Tetrahedron Lett.* 1998, 39, 2059.
- 104 Dreos, R.; Nardin, G.; Randaccio, L.; Siega, P.; Tazher, G.; Vrdoljak, V. *Inorg.*
Chem. 2001, 40, 5536.
- 105 Lamothe, M.; Pauwels, P. J.; Belliard, K.; Schambel, P.; Halazy, S. *J. Med.*
Chem. 1997, 40, 3542.
- 106 Fischer, F. C.; Havinga, E. *Recueil* 1974, 93, 21.
- 107 van Riel, H. C. H. A.; Fischer, F. C.; Lugtenburg, J.; Havinga, E. *Tetrahedron*
Lett. 1969, 36, 3085.
- 108 Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* 1993, 58, 2201.
- 109 Coudret, C. *Syn. Commun.* 1996, 26, 3543.
- 110 Contreras, R.; Garcia, C.; Mancilla, T. *J. Organomet. Chem.* 1983, 246, 213.
- 111 Chan, D. M. T.; Monaco, K. L.; Li, R.; Bonne, D.; Clark, C. G.; Lam, P. Y. S.
Org. Lett., preprint.
- 112 Westmark, P. R.; Gardiner, S. J.; Smith, B. D. *J. Am. Chem. Soc.* 1996, 118,
11093.
- 113 Suenaga, H.; Yamamoto, H.; Shinkai, S. *Pure & Appl. Chem.* 1996, 68, 2179.
- 114 (a) Collins, I.; Castro, J. L. *Tetrahedron Lett.* 1999, 40, 4069; (b) Enguehard, C.;
Allouchi, H.; Debouzy, J.-C.; Leger, J.-M.; Gueiffier, A. *Synthesis* 2001, 595;
(c) Mitchell, M. B.; Wallbank, P. J. *Tetrahedron Lett.* 1991, 32, 2273; (d) Usse,
S.; Guillaumet, G.; Viaud, M.-C. *Tetrahedron Lett.* 1997, 38, 5501; (e) Lamothe,
M.; Pauwels, P. J.; Belliard, K.; Schambel, P.; Halazy, S. *J. Med. Chem.* 1997,
40, 3542; (f) Bromidge, S. M.; Dabbs, S.; Davies, D. T.; Davies, S.; Duckworth,
D. M. *J. Med. Chem.* 2000, 43, 1123.
- 115 Cordaro, J. G.; McCusker, J. K.; Bergman, R. G. *Chem. Commun.* 2002, 1496.
- 116 O'Neill, B. T.; Yohannes, D.; Bundesmann, M. W.; Arnold, E. P. *Org. Lett.*
2000, 2, 4201.
- 117 Zhang, J.; Aszodi, J.; Chartier, C.; L'hermite, N.; Weston, J. *Tetrahedron Lett.*
2001, 42, 6683.
- 118 Wang, H.-J.; Ling, W.; Lu, L. *J. Fluor. Chem.* 2001, 111, 241.

-
- ¹¹⁹ (a) Juteau, H.; Gareau, Y.; Labelle, M.; Lamontagne, S.; Tremblay, N.; Carriere, M.-C.; Sawyer, N.; Denis, D.; Metters, K. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 747; (b) Briehn, C. A.; Kirschbaum, T.; Bouerle, P. *J. Org. Chem.* **2000**, *65*, 352; (c) Li, W.; Burgess, K. *Tetrahedron Lett.* **1999**, *40*, 6527; (d) Yoo, S.-E.; Gong, Y.-D.; Choi, M.-Y.; Seo, J.-S.; Yi, K. Y. *Tetrahedron Lett.* **2000**, *41*, 6415.
- ¹²⁰ Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196.
- ¹²¹ Latta, R.; Springsteen, G.; Wang, B. *Synthesis* **2001**, 1611-1613.

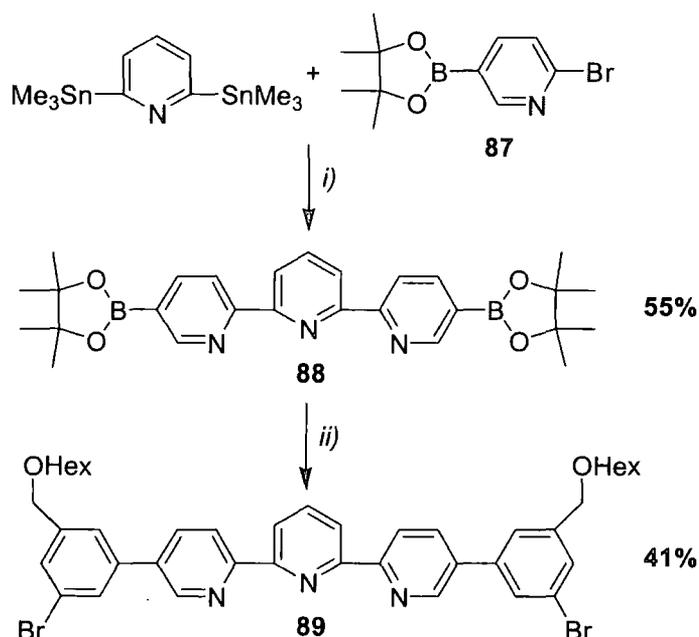
Chapter 2

**Synthesis and Application of
Halogenated Pyridylboronic Acids**

2.0 Synthesis and Application of Halogenated-Pyridylboronic Acids

2.1 Introduction

At the beginning of this project no halopyridylboronic acids had been reported in the literature. In 1999 Schlüter *et al*¹ synthesised a bromo-substituted pyridylboronic acid, but only obtained it in its crude form. They then converted the acid into its corresponding ester, {2-[3-(6-bromo)pyridine]-4,4',5,5'-tetramethyl-1,3-dioxaborolane} (**87**), using pinacol, in order to purify the compound. This ester has been applied in the construction of terpyridines (**88**), which are employed in transition metal complexation and supramolecular assembly. This initial Stille cross-coupling reaction leaves the reactive boronic ester moiety free to undergo further cross-coupling reactions to give **89**, as illustrated in Scheme 2.1.



Scheme 2.1: Synthesis and Functionalisation of Terpyridines. Reagents and Conditions: (i) Pd(PPh₃)₄, KF, toluene, reflux, (ii) 1-Bromo-3-hexyloxymethyl-5-iodobenzene, Pd(PPh₃)₄, 1M Na₂CO₃, toluene, reflux.

During the course of our work a detailed synthesis of halopyridylboronic acids was reported in the literature. Rault *et al*² published a series of papers detailing the halopyridylboronic acids and esters (Figure 2.1).

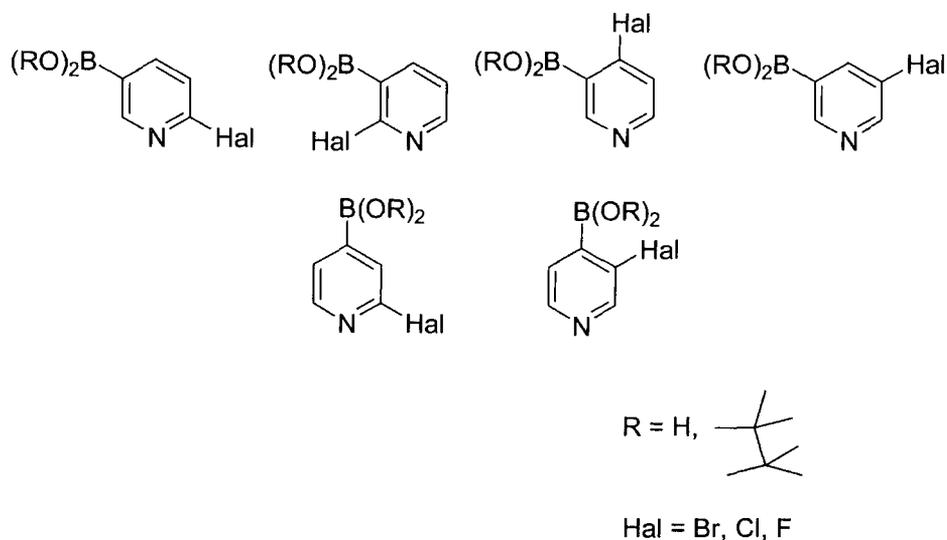


Figure 2.1: Halopyridylboronic Acids and Esters Synthesised by Rault *et al*.

This chapter will describe in detail our synthesis of various Br, Cl and F substituted-pyridylboronic acids. Iodine-substituted pyridylboronic acid was ruled out at an early stage, due to the fact that iodine is known to be a very good leaving group in the Suzuki cross-coupling reaction (see Chapter 1). This could lead to further complications upon the cross-coupling of such a substituted boronic acid, i.e. unwanted extended cross-coupling (or polymerization).

2.2 Synthesis of Halogenated Pyridylboronic Acids

2.2.1 Synthesis of Bromo-Substituted Pyridylboronic Acids

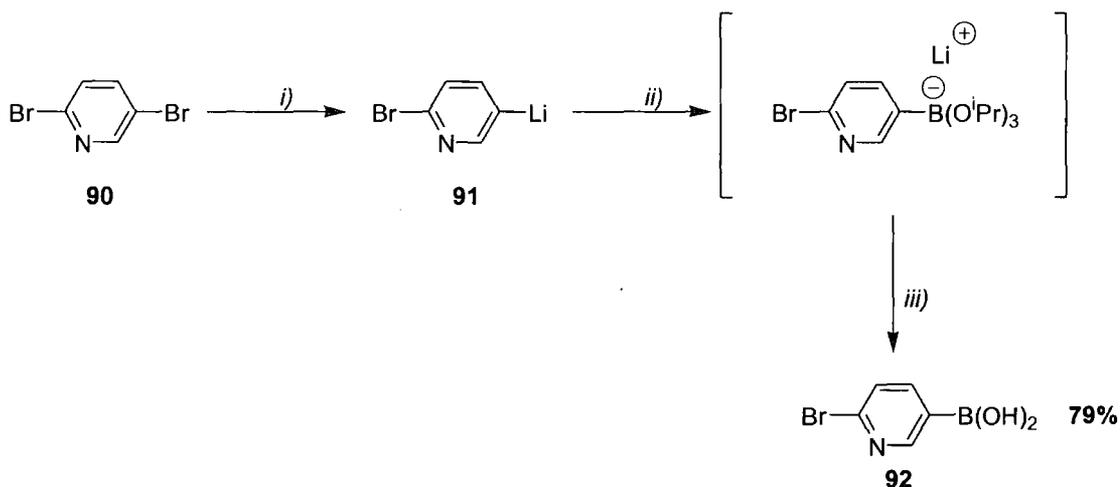
At the beginning of this work we aimed to synthesise various bromo-substituted pyridylboronic acids, with the hope of preparing a bromo-substituted 2-pyridylboronic acid. In the preparation of these acids we avoided the use of Grignard reagents as pyridyl Grignard reagents are difficult to form (see Chapter 1) and lithiated

intermediates are known to be preferable. The routes we adopted in the synthesis of these acids involved either 1) metal-halogen or 2) metal-hydrogen exchange reactions.

2.2.1.1 Via Metal-Halogen Exchange

Our initial target was 2-bromo-5-pyridylboronic acid (**92**). The reasons behind this choice were: 1) the precursor 2,5-dibromopyridine (**90**) was commercially available and cheap, 2) the bromo substituent would allow further synthetic modification after the cross-coupling reaction.

In the preparation of acid **92** we used the classical method for the preparation of a boronic acid, i.e. generation of the corresponding organolithium reagent at low temperature, followed by the addition of an alkylborate, in this case TPB, in order to introduce the boronic acid group (Scheme 2.2).

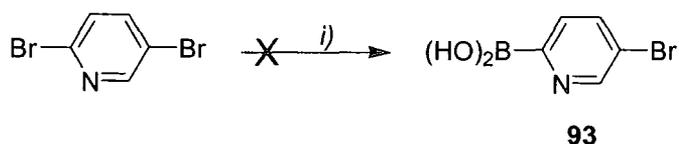


Scheme 2.2: Synthesis of 2-Bromo-5-pyridylboronic Acid. Reagents and Conditions: (i) *n*BuLi, Et_2O , -78°C , (ii) TPB, -78°C , (iii) Aqueous Work-up.

This procedure gave acid **92** in good yield and it was found to be a shelf-stable compound. Comparing this synthesis to that of 3-pyridylboronic acid seemed to indicate that the presence of the bromine on the pyridine ring plays an important role in the synthesis of this acid. The lithio-species employed in this reaction was generated via the metal-halogen exchange reaction. This reaction is known to efficiently produce 2-bromo-5-lithiopyridine (**91**).³ Wang *et al*⁴ have reported that the selectivity of the lithiation reaction of **90** is strongly influenced by the choice of solvent and

concentration of the substrate. They found that **91** is produced when Et₂O is used as the solvent for the lithiation. Bolm *et al*⁵ reported that THF gave complex mixtures when used as the solvent for this reaction. The aqueous work-up yielded **92** without the need for further purification.

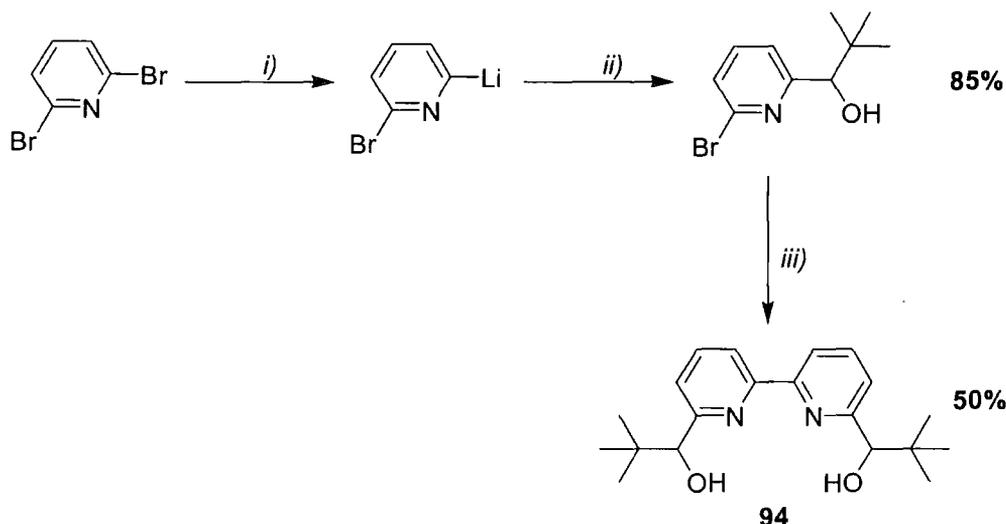
Following the success of the above reaction, we attempted the synthesis of other bromo-substituted pyridylboronic acids. We again used **90**, but in this case we aimed to introduce the boronic acid group at the 2-position of the pyridine ring, a usually inaccessible compound. Recalling the findings of Wang *et al*, they found that the metal-halogen exchange reaction of **90** at the 2-position is possible in toluene at a concentration of 0.085M at -78°C. Unfortunately the corresponding boronic acid (**93**) could not be isolated (Scheme 2.3).



Scheme 2.3: Attempted Synthesis of 5-Bromo-2-pyridylboronic Acid. Reagents and Conditions: (i) 1. Substrate conc.: 0.085M, nBuLi, toluene, -78°C, 2. TPB, -78°C, 3. Aqueous Work-up.

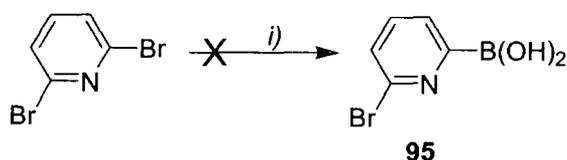
There are 2 possible explanations behind this failure. Firstly, the reaction may have worked, but the boronic acid underwent protodeboronation, the proposed reason behind the failure in the synthesis of 2-pyridylboronic acid.⁶ Secondly, it has been reported that the 2-pyridyl anion, that is generated via the metal-halogen exchange reaction is destabilised by electrostatic repulsion between the lone pair on the nitrogen and the adjacent anion.⁷

The above explanation could also apply in the failure to synthesise 2-bromo-6-pyridylboronic acid (**95**). Bolm *et al* have reported the lithiation of commercially available 2,6-dibromopyridine, a key step in the synthesis of bipyridines (**94**) (Scheme 2.4).⁵



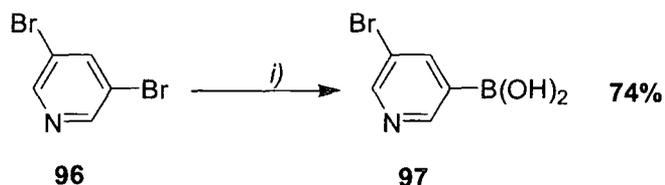
Scheme 2.4: Application of 2,6-Dibromopyridine in the Synthesis of Bipyridines. Reagents and Conditions: (i) $n\text{BuLi}$, Et_2O , -78°C , (ii) ${}^t\text{BuCHO}$, (iii) $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, Zn , PPh_3 , DMF , 70°C .

Following our usual methodology, i.e. addition of TPB to generated lithio-species, followed by aqueous work-up, we were unable to form the corresponding boronic acid (Scheme 2.5). Also the use of TMB did not lead to the desired boronic acid, i.e. no precipitation from aqueous layer. A better route to this lithio-species could be to adopt an 'inverse addition' procedure, i.e. addition of the halide to a solution of $n\text{BuLi}$.⁸



Scheme 2.5: Attempted Synthesis of 2-Bromo-6-Pyridylboronic Acid. Reagents and Conditions: (i) 1. $n\text{BuLi}$, Et_2O , -78°C , 2. TPB, -78°C , 3. Aqueous Work-up.

We then attempted the formation of 3-bromo-5-pyridylboronic acid (**97**), using 3,5-dibromopyridine (**96**) as the starting material. We applied the same conditions that had been successful in the formation of **92** (Scheme 2.6). This reaction gave **97** in good yield. Rault *et al* undertook a similar route in the synthesis of this acid, i.e. employing the metal-halogen exchange reaction, using $n\text{BuLi}$ in Et_2O at -78°C . The difference between the reactions is a different work up procedure.

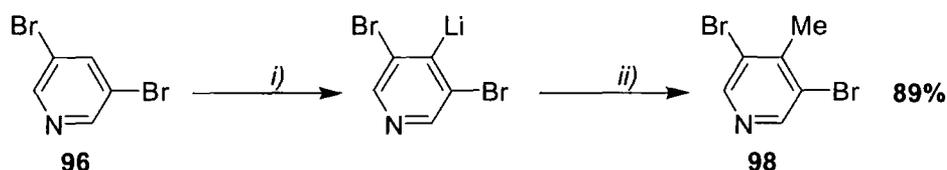


Scheme 2.6: Synthesis of 3-Bromo-5-pyridylboronic Acid. Reagents and Conditions: (i) nBuLi, Et₂O, -78°C, 2. TPB, -78°C, 3, Aqueous Work-up.

2.2.1.2 Via Metal-Hydrogen Exchange

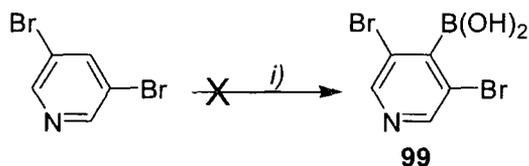
Thus far all of the above reactions have involved the generation (or attempted generation) of the corresponding lithio-species, via the metal-halogen exchange reaction, in order to form the boronic acid. The following reactions involve the application of the metal-hydrogen exchange reaction in a bid to form boronic acids.

An interesting application of this technique was the attempted synthesis of a dibromo-substituted pyridylboronic acid. Gu *et al*⁹ have reported the successful generation of 3,5-dibromo-4-lithiopyridine by the action of LDA. This reaction is an example of a DoM reaction. They then used this derivative to yield an alkyl-substituted 3,5-dibromopyridine (**98**) (Scheme 2.7).



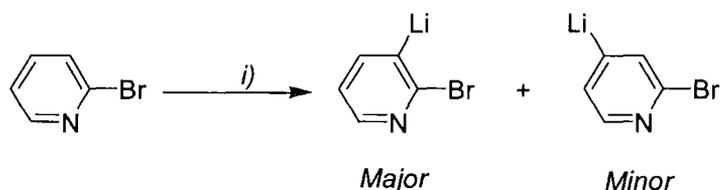
Scheme 2.7: Generation of 3,5-Dibromo-4-lithiopyridine. Reagents and Conditions: (i) LDA, THF, -78°C, (ii) MeI.

We employed this protocol but were unable to obtain **99** even when we deviated from our standard conditions. For example, we used TMB, a less bulky alkylborate, rather than TPB, plus we followed a different reaction work-up procedure (Scheme 2.8).¹⁰



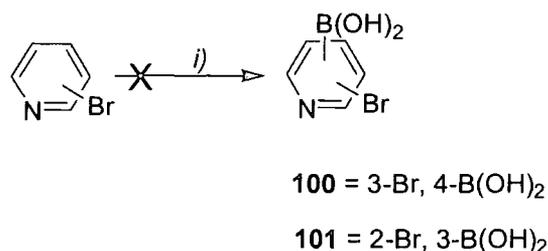
Scheme 2.8: Attempted Synthesis of 3,5-Dibromo-4-pyridylboronic acid. Reagents and Conditions: (i) 1. LDA, THF, -78°C , 2. TPB or TMB, -78°C , 3. Aqueous work-up or alternate work-up (See ref 10).

We also used DoM methodology with mono-brominated pyridines, as halopyridines, particularly chloro- and fluoro-pyridines, and even bromo-pyridines, are known to undergo lithiation by deprotonation ortho to the halogen, normally using LDA as the lithiating reagent.^{8a} Gribble and Saulnier¹¹ described the synthesis of 4-lithio-3-halopyridines using this methodology. Furthermore, Effenberger *et al*¹² have reported that the lithiation of 2-bromopyridine proceeds mainly at the 3-position, with partial lithiation at the 4-position (Scheme 2.9).



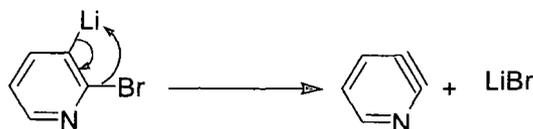
Scheme 2.9: Lithiation of 2-Bromopyridine. Reagents and Conditions: (i) LDA, THF, -78°C .

We employed their procedure in the attempted synthesis of acids **100** and **101**. Again, the reaction failed to yield the desired boronic acid, even when alternate reagents and reaction work-up were employed (Scheme 2.10).



Scheme 2.10: Attempted Synthesis of Acids 100 and 101. Reagents and Conditions: (i) 1. LDA, THF, -78°C, 2. TPB or TMB, -78°C, 3. Aqueous work-up or alternate work-up (See ref 10).

All of the lithiation reactions are known to be successful, as the various groups described above have managed to trap the lithio-species with various electrophiles. However, it is known for pyridyllithium reagents with bromo substituents to be unstable, which results in the formation of pyridyne and lithium bromide (Scheme 2.11).¹³



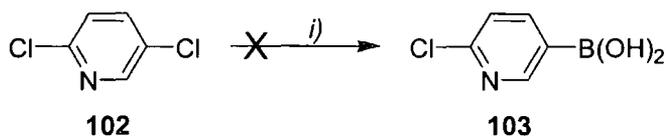
Scheme 2.11: Decomposition of 2-Bromopyridyllithium.

Also, these reactions have all been carried out using a sequential addition method. Following an *in situ* quench pathway may facilitate the formation of the desired boronic acids. Plus, there are the reagents used and reaction work-up to consider. For example, Rault *et al* used freshly generated LDA, formed from the reaction between diisopropylamine and nBuLi at 0°C, in the synthesis of their catalogue of boronic acids.² They also paid particular attention to the reaction work-up. For example, the reaction was 'quenched' very slowly using NaOH, and they carried out their acidification stage using aq. HCl ensuring that the temperature did not go above 5°C in order to prevent protodeboronation.¹⁴ Whereas we used commercial reagents, such as LDA, and even though our work-up was applicable to certain bromo-substituted boronic acids, it may have been too harsh for others.

2.2.2 Synthesis of 2-Chloro-5-Pyridylboronic Acid

We targeted 2-chloro-5-pyridylboronic acid (**103**) following the successful synthesis of **92**.

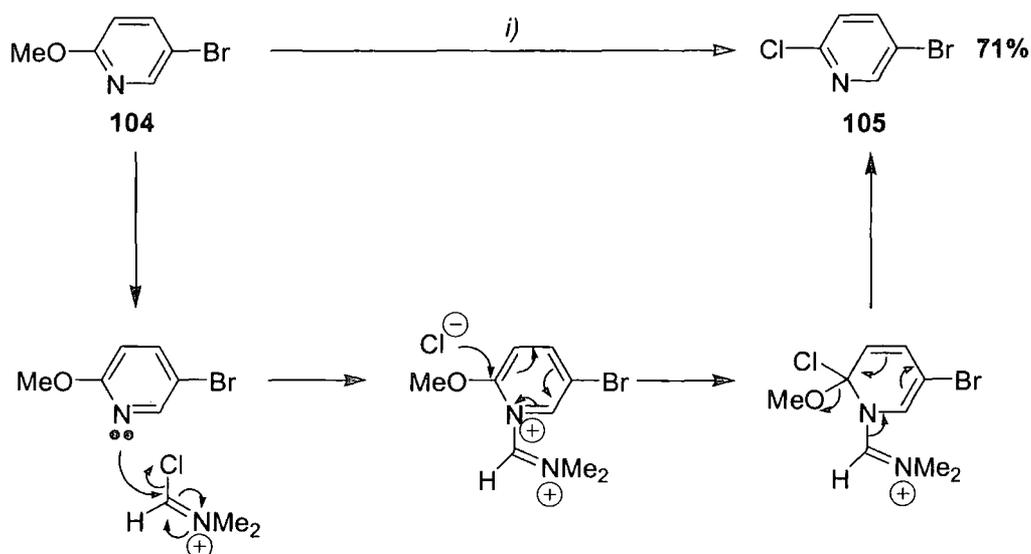
We aimed to follow the same strategy as for **92**. However, at the time 5-bromo-2-chloropyridine (**105**) was not available commercially. So, for time and convenience we attempted the reaction using 2,5-dichloropyridine (**102**), following exactly the same procedure as we had used for the bromo derivative (Scheme 2.12).



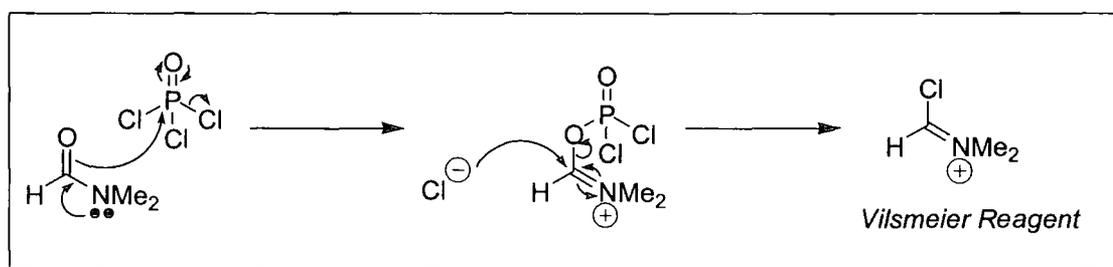
Scheme 2.12: Attempted Synthesis of 2-Chloro-5-Pyridylboronic Acid. Reagents and Conditions: (i) $n\text{BuLi}$, Et_2O , -78°C , (ii) TPB, -78°C , (iii) Aqueous Work-up.

Bromo- or iodo- derivatives are known to react rapidly with alkyllithiums, at temperatures ranging from $\text{rt} \rightarrow -100^\circ\text{C}$, to give the lithio-derivative. Exchange of chlorine is rare, but nonetheless we carried out this reaction. **103** was not formed.

A literature search on **105** revealed that Shiao *et al*¹⁵ conveniently prepared this compound by the transformation of 5-bromo-2-methoxypyridine (**104**) under Vilsmeier-Haack conditions (Scheme 2.13).

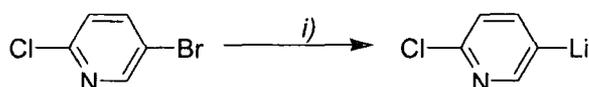


Generation of Vilsmeier Reagent:



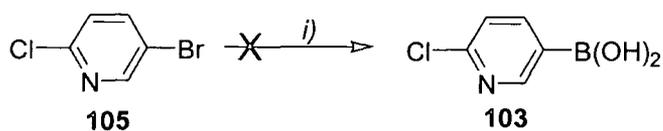
Scheme 2.13: Formation of 5-Bromo-2-chloropyridine via the Vilsmeier Reagent. Reagents and Conditions: (i) POCl₃, DMF.

Johnson and Sirisoma¹⁶ successfully lithiated **105** at the 5-position, i.e. **105** can successfully undergo bromo-lithium exchange (Scheme 2.14).



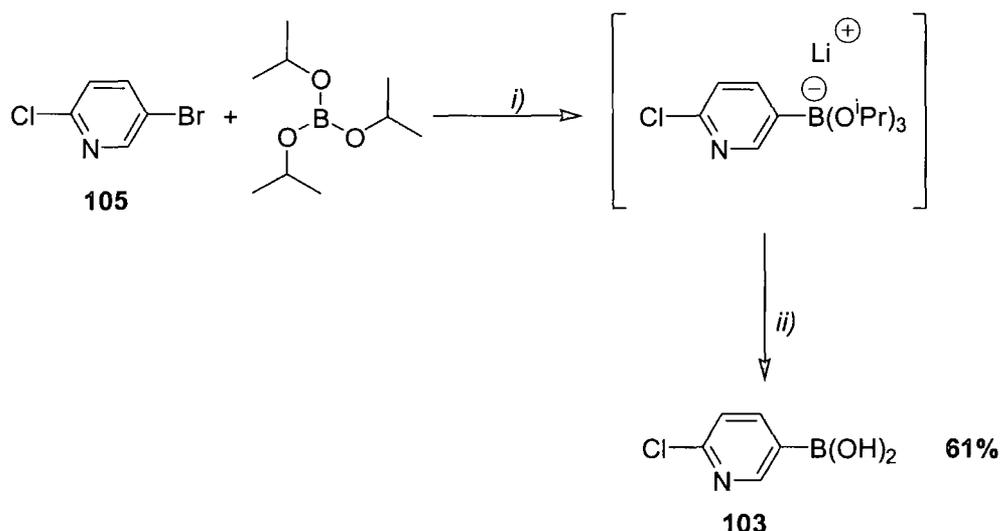
Scheme 2.14: Lithiation of 5-Bromo-2-chloropyridine. Reagents and Conditions: (i) nBuLi, THF, -78°C.

We then applied this methodology in the synthesis of **103**, following a sequential addition method, i.e. starting material \rightarrow nBuLi \rightarrow TPB, which, surprisingly, did not yield **103** (Scheme 2.15).



Scheme 2.15: Attempted Synthesis of 2-Chloro-5-pyridyl boronic Acid. Reagents and Conditions: (i) 1. nBuLi, -78°C, THF, 2. TPB, -78°C, 3. Aqueous Work-up.

We then turned to an *in situ* quench method, i.e. addition of nBuLi to a solution of the bromide and TPB, followed by our standard work-up. This method gave boronic acid **103** in good yield (Scheme 2.16).



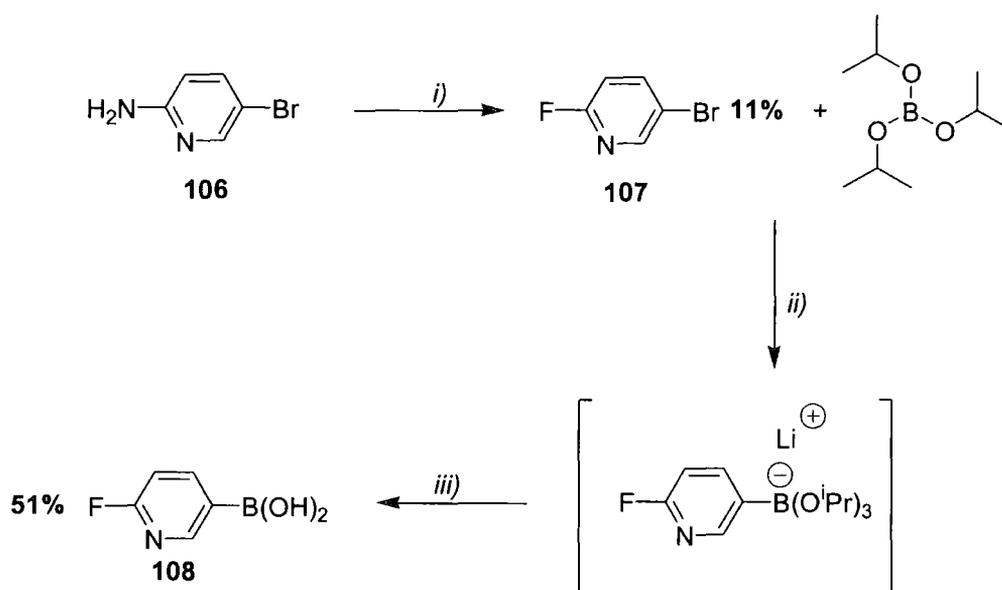
Scheme 2.16: Successful Synthesis of 2-Chloro-5-pyridylboronic Acid. Reagents and Conditions: (i) nBuLi, -78°C, THF, (ii) Aqueous Work-up.

After completion of our work, Rault *et al* reported the synthesis of this acid using the sequential addition method. The differences being that they used Et₂O as the solvent for the reaction and they applied a different work-up procedure.²

2.2.3 Synthesis of 2-Fluoro-5-pyridylboronic Acid

The synthesis of a fluoropyridylboronic acid was seen as completing the set of halo-substituted boronic acids.

The route that we adopted to 2-fluoro-5-pyridylboronic acid (**108**) was to firstly prepare 2-fluoro-5-bromopyridine (**107**) from 2-amino-5-bromopyridine (**106**), via a Balz-Schiemann reaction,¹⁷ then the *in situ* quench method gave **108** in 51% yield (Scheme 2.17).



Scheme 2.17: Synthesis of 2-Fluoro-5-pyridylboronic Acid. Reagents and Conditions: (i) HBF_4 , NaNO_2 , 0°C , (ii) $n\text{BuLi}$, -78°C , THF, (iii) Aqueous Work-up.

2.3 X-Ray Crystal Structures of Halo-Substituted Pyridylboronic Acids 92 & 103

A survey of the April 2002 version of the Cambridge Crystallographic Database¹⁸ found 17 structures containing a $\text{C}(sp^2)\text{-B}(\text{OH})_2$ fragment, *viz.* $\text{PhB}(\text{OH})_2$ ¹⁹ and its various derivatives, including $4\text{-BrC}_6\text{H}_4\text{B}(\text{OH})_2$,²⁰ but no heterocyclic derivatives. This finding prompted us to grow crystals of our halo-substituted pyridylboronic acids.

In all boronic acids, the boron atom has nearly planar trigonal coordination. In the absence of bulky substituents in the *ortho* positions, the CBO₂ plane is often coplanar with the benzene ring, but occasionally the twist around the C-B bond (τ) can be as

large as 28°. The two independent molecules in the structure of PhB(OH)₂ display widely different τ of 6.6° and 21.4°. Thus the rotation around the C-B bond is not hindered much. Crystals of **92** and **103** were obtained from an EtOH/H₂O solvent system and their structures solved by Dr. A Batsanov. Figures 2.2 and 2.3 show that these acids have substantially different crystal structures, notwithstanding the similar size of the Cl and Br atoms (van der Waals radii 1.76 and 1.87 Å, respectively).²¹ This can often produce isomorphous derivatives. **92** has the same structure at 295 and 120 K, i.e. there is no evidence that the crystallographic difference between **92** and **103** is linked to temperature dependent polymorphism.

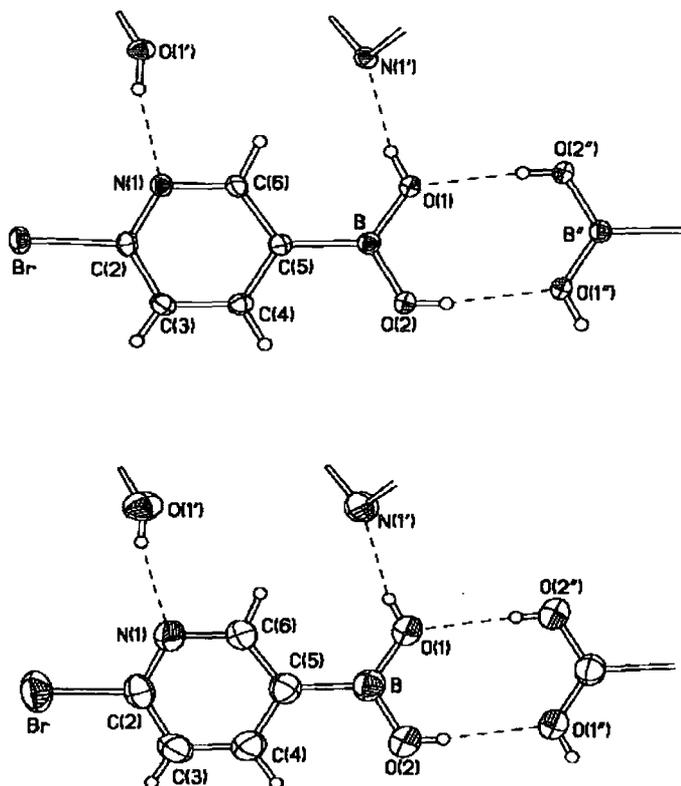


Figure 2.2: X-ray Structure of Br, at 120 K (top) and 295 K (bottom), showing 50% Thermal Ellipsoids and Hydrogen Bonds. Atoms Generated by an *n* plane are Primed, those Generated by an Inversion Centre Double Primed.

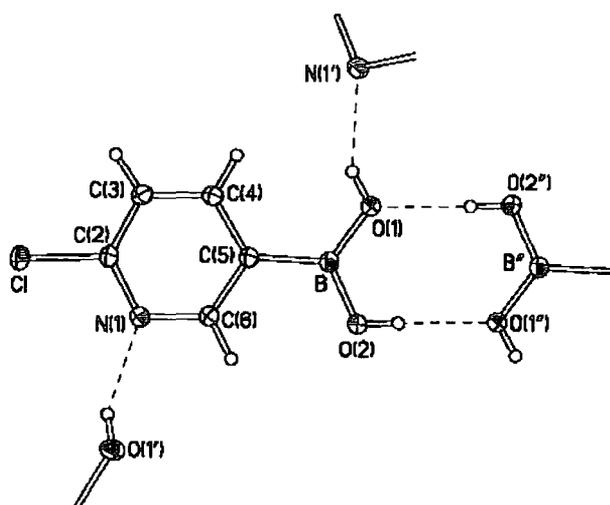


Figure 2.3: X-ray Structure of **103**, Showing 50% Thermal Ellipsoids and Hydrogen Bonds. Atoms Generated by a 2_1 Axis are Primed, those Generated by an Inversion Centre Double-Primed.

92 and **103** adopt slightly twisted conformations: in Br $\tau=10.5^\circ$ (295 K) and 10.9° (120 K), in Cl $\tau=4.0^\circ$. The C-B bond distances in Br and Cl are equal [1.573(2) Å at 120 K] and close to that in PhB(OH)₂ after libration correction [1.565(3) Å]. As with the latter structure, molecules of **92** and **103** related by an inversion centre, form hydrogen-bonded dimers, broadly similar to those existing in the crystals of organic acids. The hydroxyl H atoms not engaged in dimerization, form hydrogen bonds with the O atoms of adjacent dimers in PhB(OH)₂ and with heterocyclic N atoms in **92** and **103**. Due to the latter, the crystal architecture of **92** and **103** is quite different from that of 4-BrC₆H₄B(OH)₂. In both **92** and **103**, the O(1) atom acts as both a donor and an acceptor of hydrogen bonds, and O(2) as a donor only. Correspondingly, the B-O(1) bond is marginally longer than B-O(2): 1.363(2) vs. 1.357(2) Å in **92**, 1.362(2) vs. 1.352(2) Å in **103**, comparing the average of 1.371(7) Å in PhB(OH)₂, where both O atoms act like O(1).

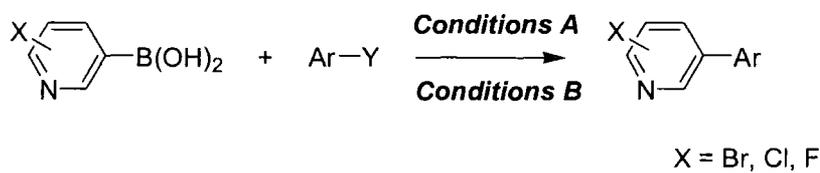
However, the two OH...N bonds (donated and accepted) by the same molecule, in **92** are in a *cis*, and in **103** in a *trans* orientation with respect to the B...Br(Cl) axis of the molecule (see Figures 2.2 and 2.3). In **92** these bonds link the molecules symmetrically related by an *n* glide plane, in **103** those related by a 2_1 axis, giving rise to rather different crystal packing.

To date we have been unable to grow crystals of 2-fluoro-5-pyridylboronic acid (**108**).

2.4 Application of Halopyridylboronic Acids

As we have shown in Chapter 1, the main application of a boronic acid is the Suzuki cross-coupling reaction, so we applied our halo-substituted pyridylboronic acids in this reaction. There are many different solvents, bases, temperatures and catalyst combinations available for this reaction, and we decided on two sets of reaction conditions. Conditions A: DMF as the solvent, Na_2CO_3 as the base, $\text{Pd}(\text{PPh}_3)_4$ as the catalyst and a reaction temperature of 80°C . Conditions B: 1,4-dioxane as the solvent, Cs_2CO_3 as the base, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ as the catalyst and a reaction temperature of 95°C . Having a choice of reaction conditions allowed us to check the results of our cross-coupling reactions to see if the conditions had an effect on the reaction yield.

We cross-coupled our acids with different heteroaryl bromides as the other coupling partner. Scheme 2.18 is a general representation of these reactions.



Scheme 2.18: General Illustration of our Suzuki Cross-Coupling Reactions.

2.4.1 Application of Bromo-Substituted Pyridylboronic Acid in the Suzuki Cross-Coupling Reaction

We initially studied the bromo-substituted pyridylboronic acids. The results are shown in Table 2.1.

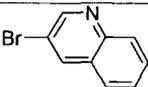
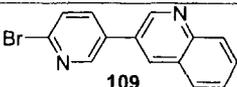
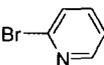
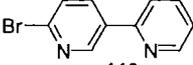
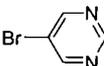
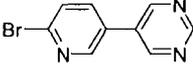
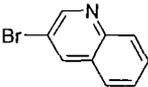
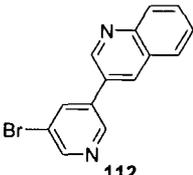
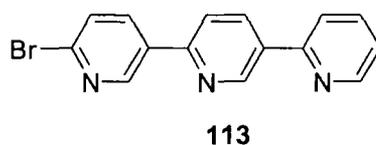
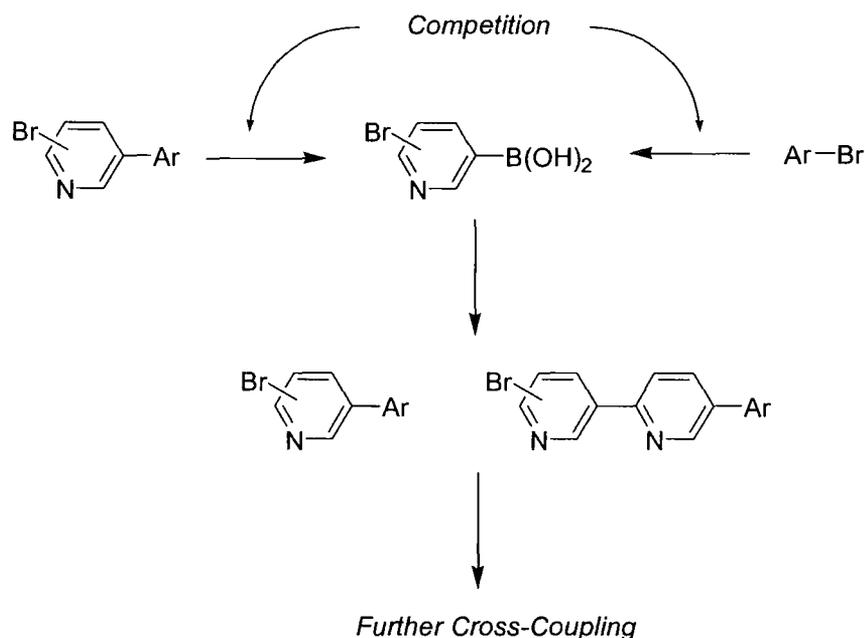
Entry	Boronic Acid	Ar-Y	Product	Isolated Yield/%	
				Conditions A	Conditions B
1	92		 109	32	14
2	92		 110	11	-
3	92		 111	10	-
4	97		 112	-	8

Table 2.1: The Suzuki Cross-Coupling Reactions of 92 and 97.

Table 2.1 shows that we have successfully attached different heteroaryl ring systems to the pyridine ring, albeit in low yield, using both sets of reaction conditions. Upon investigation into possible causes behind these low yields we found that, with respect to entry two of Table 2.1, extended cross-coupling was occurring between the remaining boronic acid and the product bromide, i.e. there was competition between the two bromides for the remaining boronic acid, resulting in the low yield of the biheteroaryl target (Scheme 2.19).

In support of this theory, TLC of the reaction mixtures indicated an extra product being produced in this reaction, which upon isolation was shown by ^1H NMR and mass spectrometry data to be **113** (Figure 2.4).





Scheme 2.19: An Illustration of Extended Cross-Coupling.

On the positive side, we are able to produce bromo-substituted heterobiaryls, which can now be used as the halo-coupling partner in the Suzuki reaction. This can lead to further functionalisation of our pyridyl systems.

2.4.2 Application of Chloro-Substituted Pyridylboronic Acid in the Suzuki Cross-Coupling Reaction

The synthesis of a chloro-substituted pyridylboronic acid was seen as a way of combating the extended cross-coupling observed with the bromo-substituted pyridylboronic acid **92**, because the boronic acid would be less reactive towards the chloro product (see Chapter 1). Also, at the beginning of this project no chloro-substituted pyridylboronic acids had been published.

We firstly used 3-bromoquinoline as the coupling partner in our cross-coupling reaction, because we had used this successfully with **92** & **97**. We thought that the use of this particular reagent would provide a good benchmark to gauge the success of the reaction. The reaction of **103** with 3-bromoquinoline showed an improvement on the analogous bromo reaction (55% yield compared to 32% yield). From this initial success

we carried out similar reactions with different heteroaryl bromides. Table 2.2 shows the results from these cross-coupling reactions.

These analogous reactions with the chloro-substituted boronic acid were found to be much cleaner and more efficient (higher yielding) than the bromo-substituted boronic acids (no TLC evidence of extended cross-coupling).

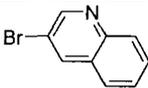
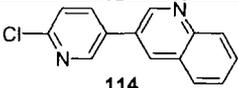
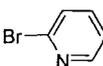
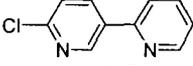
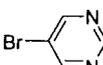
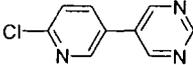
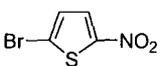
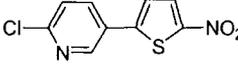
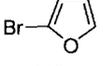
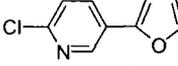
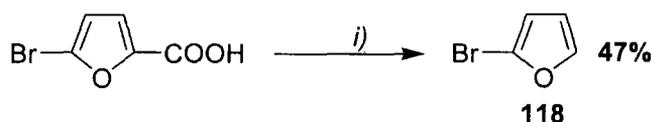
Entry	Boronic Acid	Ar-Y	Product	Isolated Yields/% Conditions A	
1	103		 114	55	64
2	103		 115	61	-
3	103		 116	38	-
4	103		 117	53	-
5	103	 118	 119	-	66

Table 1.2: Results from the Suzuki Cross-Coupling Reactions of 2-Chloro-5-pyridylboronic Acid.

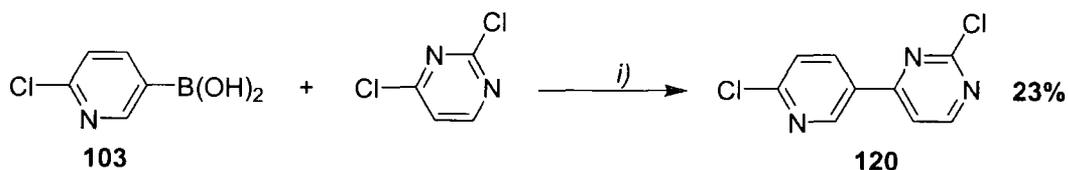
The 2-bromofuran (118) is not available commercially and was formed from the decarboxylation of 2-bromo-5-furoic acid (Scheme 2.20).²²



Scheme 1.20: Synthesis of 2-Bromofuran. Reagents and Conditions: (i) Cu powder, quinoline, Δ .

Investigating this chemistry further, we decided to test the cross-coupling reaction of 103 with heteroaryl chlorides. This follows reports in the literature that chloropyrimidines are good substrates for the Suzuki couplings with phenyl- and substituted-phenylboronic acids.²³ Therefore, we treated 103 with 2,4-

dichloropyrimidine, using our coupling reagents and conditions, and obtained **120** in 23% yield (Scheme 2.21).



Scheme 2.21: Suzuki Cross-Coupling of 103 with 2,4-Dichloropyrimidine. Reagents and Conditions: Conditions A: (i) $\text{Pd}(\text{PPh}_3)_4$, DMF, Na_2CO_3 , 80°C .

We are confident the cross-coupling reaction of 2,4-dichloropyrimidine takes place at the 4 position of the pyrimidine ring and not the 2-position for two reasons: 1) the precedent for such a reaction is that the halogen at C4 is more reactive than the halogen at C2 of the pyrimidine ring,^{23a} and 2) the observed response of **120** in a NOESY spectrum between the proton at C5 of the pyrimidine with the protons at C2 and C4 of the pyridine ring confirms that **120** is the correct isomer structure (Figure 2.5).

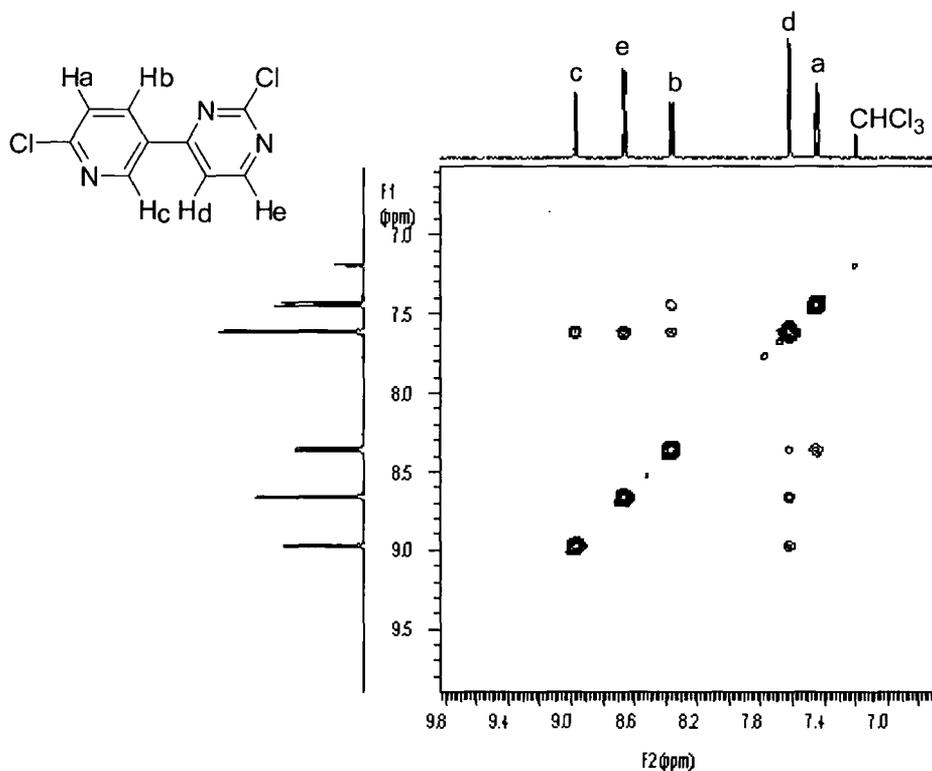
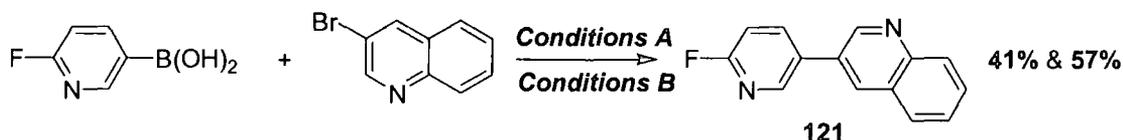


Figure 2.5: NOESY Spectrum of 120.

This reaction verifies the fact that cross-coupling reaction can be carried out using chlorides, and that this reaction has lead **120** with 2 chlorines present, which have the potential to be reactive handles for further cross-coupling reactions.

2.4.3 Application of 2-Fluoro-5-pyridylboronic Acid in the Suzuki Cross-Coupling Reaction

We have proved that the cross-coupling reaction of **103** is more efficient than **92** and **97**. We would expect the cross-coupling of the fluoro-boronic acid (**108**) to be analogous with the chloro-boronic acid. So, rather than give numerous examples of cross-coupling reactions of this acid, we cross-coupled **108** with 3-bromoquinoline for comparison to the other boronic acids. We used conditions A & B, and obtain **121** in 41% and 57% respectively (Scheme 2.22).



Scheme 2.22: Cross-Coupling Reaction of **108** with 3-Bromoquinoline.

This reaction indicates that we can potentially introduce a variety of heteroaryl ring systems to this fluorinated pyridine, following the success of this reaction. The importance of such a reaction, i.e. production of fluorinated compounds, has already been addressed in Chapter 1.

2.5 Conclusions

Rault *et al*, and ourselves, have independently and concurrently shown that a variety of halo-substituted pyridylboronic acids can be formed in high yields and be isolated in their pure state making use of metal-halogen exchange and DoM methodology. We believe this methodology could be extended to give dihalo-substituted pyridylboronic acids, which to date are unknown compounds.

Both research groups have proven that these acids can be applied in the Suzuki cross-coupling reaction, to great effect. However, Rault *et al* cross-coupled their acids with a

variety of substituted phenyl rings, whereas we used only heteroaryl ring systems. We avoided substituted-phenyl ring systems as many of their corresponding boronic acids are known to be available commercially, and thus could be used in the cross-coupling reactions with heteroaryl bromides. We chose heteroaryl bromides as our coupling partners as their boronic acids are difficult to form; therefore, we are producing novel heteroarylpyridines in our work.

2.6 References

- ¹ Lehmann, U.; Henze, O.; Schlüter, A. D. *Chem. Eur. J.* **1999**, *5*, 854.
- ² Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885; Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323; Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369.
- ³ Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 257.
- ⁴ Wang, X.; Rabbat, P.; O'Shea, P.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2000**, *41*, 4335.
- ⁵ Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169.
- ⁶ Fischer, F. C.; Havinga, E. *Recueil* **1974**, *93*, 21.
- ⁷ Walters, M. A.; Shay, J. J. *Syn. Commun.* **1997**, *27*, 3573.
- ⁸ (a) Joule, J. A.; Mills, K., *Heterocyclic Chemistry*, 4th Edition, Blackwell: Oxford, **2000**; (b) Cai, D.; Hughes, D. L.; Verhoeven, T. R. *Tetrahedron Lett.* **1996**, *37*, 2537; (c) Peterson, M. A.; Mitchell, J. R. *J. Org. Chem.* **1997**, *62*, 8237.
- ⁹ Gu, Y. G.; Bayburt, E. K. *Tetrahedron Lett.* **1996**, *37*, 2565.
- ¹⁰ Work-up: Quench reaction with sat. NH₄Cl solution. Add H₂O. Separate aqueous layer from the organic layer. Extraction with Et₂O. Wash Et₂O extracts with brine and dry using MgSO₄.
- ¹¹ Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151.
- ¹² Effenberger, F.; Daub, W. *Chem. Ber.* **1991**, *124*, 2119.
- ¹³ Imahori, T.; Uchiyama, M.; Sakamoto, T.; Kondo, Y. *Chem. Commun.* **2001**, 2450.
- ¹⁴ Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51.
- ¹⁵ Shiao, M.-J.; Shyu, L.-M.; Tarng, K.-Y. *Syn. Commun.* **1990**, *20*, 2971.

- ¹⁶ Sirisoma, N. S.; Johnson, C. R. *Tetrahedron Lett.* **1998**, *39*, 2059.
- ¹⁷ Finger, G. C.; Starr, L. D.; Dickerson, D. R.; Gutowsky, H. S.; Hamer, J. *J. Org. Chem.* **1963**, *28*, 1666.
- ¹⁸ Allen, F.; Kennard, O. *Chem. Des. Autom. News* **1993**, *8*, 1 and 31.
- ¹⁹ Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1977**, *55*, 3071.
- ²⁰ Zvonkova, Z. V.; Glushkova, V. P. *Kristallografiya* **1958**, *3*, 559.
- ²¹ Rowland, R. S.; Taylor, R. *J. Phys. Chem.* **1996**, *100*, 7384.
- ²² Clennan, E. L.; Mehrsheikh-Mohammadi, M. E. *J. Am. Chem. Soc.* **1984**, *106*, 7112.
- ²³ (a) Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125; (b) Cooke, G.; de Cremiers, H. A.; Rotello, V. M.; Tarbit, B.; Vanderstraeten, P. E. *Tetrahedron* **2001**, *57*, 2787.

Chapter 3

**Synthesis and Application of
Pyridylboronic Acids with Varying
Substituents**

3.0 Synthesis of Pyridylboronic Acids with Varying Substituents

3.1 Introduction

At the beginning of this project very little had been published about the parent pyridylboronic acids let alone substituted pyridylboronic acids. After our successes in the synthesis of various halogenated pyridylboronic acids, we turned to the synthesis of various mono- and di-substituted pyridylboronic acids. Our aims were to produce boronic acids with the substituent and the B(OH)₂ groups at varying positions around the pyridine ring. These would be new boronic acids, which could then be applied in the Suzuki cross-coupling reaction to yield new, functionalised heteroaryl systems. The routes adopted in the synthesis of these boronic acids involve the methodologies described in Chapter 1, i.e. lithiation via metal-hydrogen or metal-hydrogen exchange.

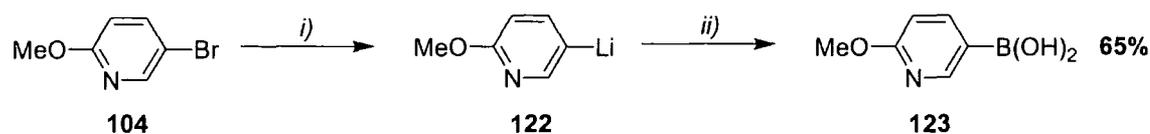
3.2 Synthesis of Mono-Substituted Pyridylboronic Acids

3.2.1 Alkoxy-Substituted Pyridylboronic Acids

3.2.1.1 Via Metal-Halogen Exchange

Our initial target, namely 2-methoxy-5-pyridylboronic acid (**123**) was chosen for two reasons: (i) the starting material, 5-bromo-2-methoxypyridine (**104**) was readily available, and (ii) **104** is known to undergo the metal-halogen exchange reaction to give the corresponding lithio-species.¹

The route we employed proceeded via the reactive lithio intermediate **122** for subsequent reaction with the electrophile, i.e. TPB (Scheme 3.1).



Scheme 3.1: Synthesis of 2-Methoxy-pyridylboronic Acid. Reagents and Conditions: (i) nBuLi, Et₂O, -78°C, (ii) 1. TPB, -78°C, 2. Aqueous Work-up.

The whole procedure followed the sequential addition of reagents and gave **123** in 65% yield.

The low temperature, i.e. -78°C , used to carry out this initial reaction is difficult to realise on an industrial scale. Therefore, we repeated this reaction at a series of elevated temperatures, whilst the other factors, i.e. solvent and reagent quantities, remained the same for each experiment. Table 3.1 shows the results from these experiments.

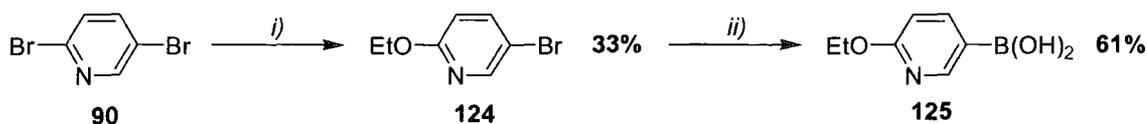
Reaction No.	Temp./ $^{\circ}\text{C}$	Yield/% ^a
1	-78	65
2	-50	63
3	-20	69
4	0	51
5	5	45

Table 3.1: Results from Formation of 123 at Varying Temperature.

Notably the yield of **123** did not vary significantly between -78°C and -20°C . This is an interesting observation that has potential benefits for industrial applications, as -20°C is a temperature that can be realised on an industrial scale. Reactions 4 & 5 then gave the expected reductions in the yield of this reaction, but still gave **123** in workable yields. These findings demonstrate that this reaction is not restricted to very low temperature, i.e. -78°C , in order to achieve significantly useful results.

We then decided to attempt the synthesis of a similar boronic acid having an ethoxy group rather than a methoxy group, to give another example of an alkoxy substituted pyridylboronic acid. At the time this work was carried out, 5-bromo-2-ethoxypyridine **124** was not commercially available. Therefore, **124** was produced from 2,5-dibromopyridine by the method described by Den Hertog *et al.*² The corresponding boronic acid (**125**) was then produced via the same methodology that gave **123** (Scheme 3.2).

^a ^1H NMR determined identification and purity of the products.

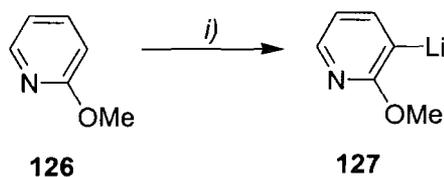


Scheme 3.2: Synthesis of 2-Ethoxy-5-pyridylboronic Acid. Reagents and Conditions: (i) EtOH, NaOH, Δ , (ii) 1. nBuLi, Et₂O, -78°C, 2. TPB, -78°C, 3. Aqueous Work-up.

Scheme 3.2 shows that **125** is produced in similar yield to that of **123**. Both acids are shelf-stable and they represent the first alkoxy-pyridylboronic acids.

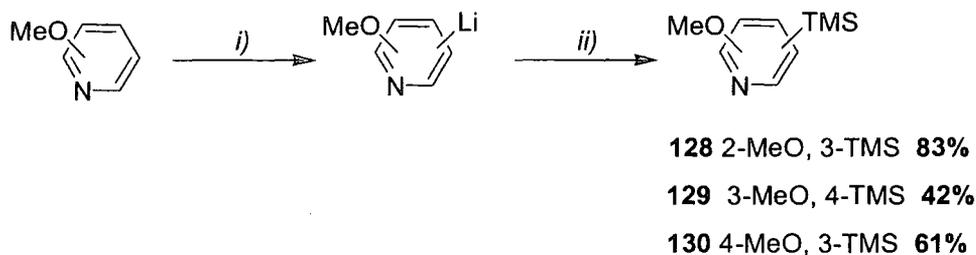
3.2.1.2 Via Metal-Hydrogen Exchange

We then progressed to the formation of other derivatives of **123**. The DoM reaction provides a mechanism that would enable us to vary the positions of the methoxy and boronic acid functional groups around the pyridine ring. Queguiner *et al*³ have employed this methodology in the *ortho* lithiation of 2-methoxypyridine (**126**) in order to produce 3-lithio-2-methoxypyridine (**127**) using LDA as the lithiating reagent (Scheme 3.3).



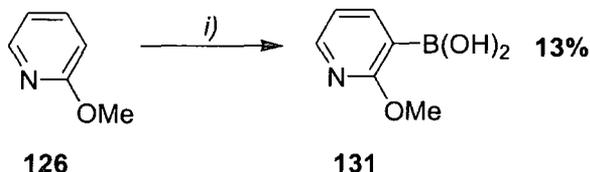
Scheme 3.3: Ortho Lithiation of 2-Methoxypyridine. Reagents and Conditions: (i) LDA, THF, -78°C.

This reaction is possible due to the chelating effect of the methoxy group, which stabilises the lithio intermediate. This concept was described in Chapter 1. However, it was the work of Comins and LaMunyon⁴ that really attracted our interest. They lithiated 2-, 3- and 4-methoxypyridine, *ortho* to the methoxy group, using LDA at 0°C; which they then trapped with trimethylsilylchloride (TMSCl) (Scheme 3.4),



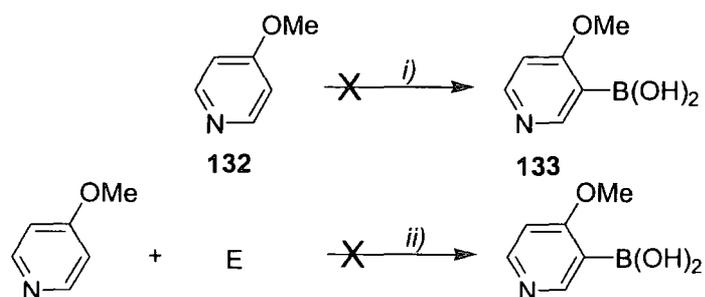
Scheme 3.4: Trimethylsilyllation of Methoxypyridine. Reagents and Conditions: (i) LDA, THF, 0°C, (ii) TMSCl.

The attraction of these reactions is that 0°C is an industrially applicable temperature. We used these conditions in the attempted synthesis of new pyridylboronic acids. Firstly, we aimed to synthesise 2-methoxy-3-pyridylboronic acid (**131**) via the sequential addition of reagents. The lithio-species generated was reacted with TMB followed by an aqueous work-up to give **131** in 13% yield (Scheme 3.5).



Scheme 3.5: Synthesis of 2-methoxy-3-pyridylboronic Acid. Reagents and Conditions: (i) 1. LDA, THF, 0°C, 2. TMB, 0°C, 3. Aqueous Work-up.

The use of TMB instead of TPB as the electrophile of choice was influenced by the possibility of the increased steric hindrance if TPB was to be used in the reaction. The same reaction was attempted using 4-methoxypyridine (**132**), only this reaction gave none of the desired boronic acid (**133**). The use of sequential addition and *in situ* quench methodology was employed using both TMB and TPB as the electrophile for the reaction to no avail (Scheme 3.6).

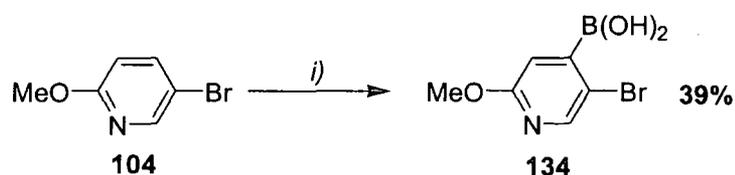


Scheme 3.6: Attempted Synthesis of 4-Methoxy-3-pyridylboronic Acid. Reagents and Conditions: (i) 1. LDA, THF, 0°C, 2. TMB or TPB, 0°C, 3. Aqueous Work-up, (ii) 1. E = TMB or TPB, LDA, THF, 0°C, 3. Aqueous Work-up.

3.2.2 Synthesis of Di-Substituted Pyridylboronic Acids: Alkoxy- and Halogen-Substituted Pyridylboronic Acids

Having synthesised various mono-substituted halogen and alkoxy pyridylboronic acids, respectively, we believed that a di-substituted pyridylboronic acid, containing both of these functional groups, would be a realistic target. Therefore, following a method described by Leeson and Emmett,⁵ we utilised DoM methodology to introduce the boronic acid functional group at the 4-position of various alkoxy- and halogen-substituted pyridine rings.

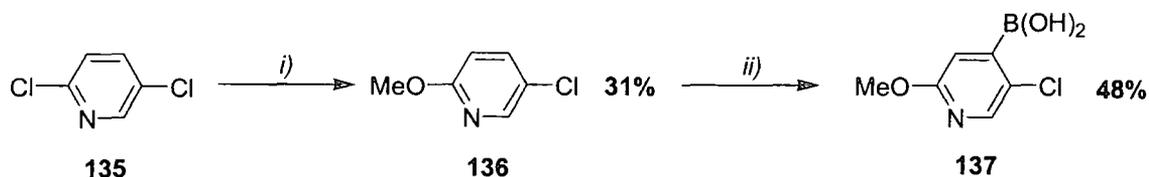
Firstly, we attempted the DoM reaction on **104**, a commercially available substrate. The lithiated species generated by the action of LDA was quenched with TPB followed by an aqueous work-up to give **134** in 39% yield (Scheme 3.7). Evidence (¹H NMR) indicates that the compound we have isolated is **134**.



Scheme 3.7: Synthesis of 3-Bromo-6-methoxy-4-pyridylboronic Acid. Reagents and Conditions: (i) 1. LDA, THF, -78°C, 2. TPB, -78°C, 3. Aqueous Work-up.

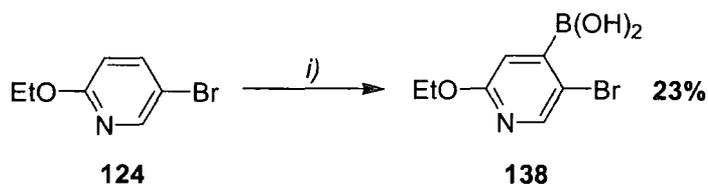
To obtain the chloro-analogue we needed **136**, which was not commercially available at the time of this work. Therefore, following a method described by Bargar *et al.*,⁶ we successfully produced **136** in 31% yield from 2,5-dichloropyridine (**135**) and

subsequently, we subjected **136** to the same conditions as **104** which gave **137** in 48% yield, a slight improvement on the Br derivative (Scheme 3.8).



Scheme 3.8: Synthesis of 3-Chloro-6-methoxy-4-pyridylboronic Acid. Reagents and Conditions: (i) 25% NaOMe (MeOH), MeOH, Δ , (ii) 1. LDA, THF, -78°C , 2. TPB, -78°C , 3. Aqueous Work-up.

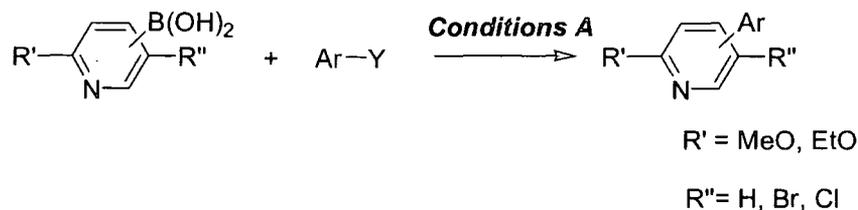
We next employed **124** in our di-substituted pyridylboronic acid reactions, and following the same route as the previous two boronic acids we were able to generate **138** in 23% yield (Scheme 3.9).



Scheme 3.9: Synthesis of 3-Bromo-6-ethoxy-4-pyridylboronic Acid. Reagents and Conditions: (i) 1. LDA, THF, -78°C , 2. TPB, -78°C , 3. Aqueous Work-up.

3.3 Application of the Suzuki Cross-Coupling Reaction

The main purpose in obtaining these new boronic acids was to explore their applications in Suzuki cross-coupling reactions. Therefore, from our successes with the cross-coupling reactions of our other substituted pyridylboronic acids, we decided to utilise the same conditions as described in Chapter 2 for the cross-coupling reactions of these new classes of boronic acids (Scheme 3.10).



Scheme 3.10: General Illustration of the Suzuki Cross-Coupling Reaction. Reagents and Conditions: Conditions A: Pd(PPh₃)₄, DMF, Na₂CO₃, 80°C.

3.3.1 Application of Mono-Substituted Pyridylboronic Acid in the Suzuki Cross-Coupling Reaction

3.3.1.1 Using halobenzenes as the substrate

We initially used phenyl halides to test the cross-coupling reaction using acid **123**. Table 3.2 highlights our initial findings.

Entry	Boronic Acid	Ar-Y	Product	Isolated Yields/% Conditions A
1	123		 139	65
2	123		 140	67
3	123		 141	48

Table 3.2: Results from the Cross-Coupling of acid 123 with Various Substituted Halides.

We began our series of cross-coupling reactions with simple ring systems, as they were readily available and produced new products. Compound **139** is an example of the incorporation of the simplest phenyl halide, bromobenzene. With compounds **140** and **141** we see the easy production of fluorine containing systems. The significance of such a reaction has already been highlighted in Chapter 1.

3.3.1.2 Using halopyridines and 3-bromoquinoline as the substrate

Table 3.3 highlights our findings using this series of cross-coupling partners.

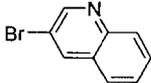
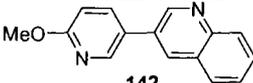
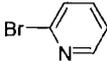
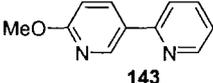
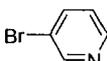
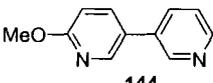
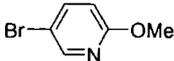
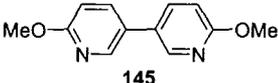
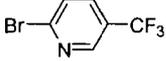
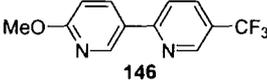
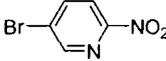
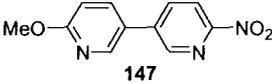
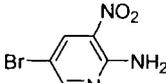
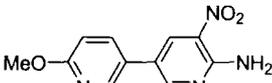
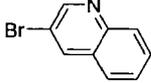
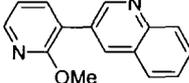
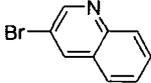
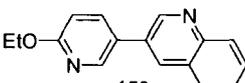
Entry	Boronic Acid	Ar-Y	Product	Isolated Yields/% Conditions A
1	123		 142	76
2	123		 143	50
3	123		 144	58
4	123		 145	83
5	123		 146	32
6	123		 147	66
7	123		 148	45
8	131		 149	61
9	125		 150	49

Table 3.3: Results from the Cross-Coupling Reactions of 123, 125 & 131 with Various Substituted Pyridyl Bromides.

As seen from Table 3.3 we have produced many different biheteroaryl and quinolyl systems with a variety of substituents, with each substituent chosen to have a different electronic effect on the ring system. For example, the alkoxy and amine groups are

electron donating, whereas the nitro and trifluoromethyl groups are electron withdrawing.

3.3.1.3 Using electron deficient halides as the substrates

We decided to investigate what effect more electron deficient heterocyclic halides would have on the Suzuki reaction. We therefore used pyrimidine and pyrazine derivatives as they are known to be more electron deficient than pyridine as the additional nitrogens in the ring lowers the energies of the π molecular orbitals, which results in the increasing difficulty of such systems to undergo electrophilic attack on the ring carbon atoms, therefore allowing the increased ease of nucleophilic attack.

Table 3.4 highlights the results from our cross-coupling reactions.

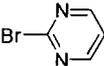
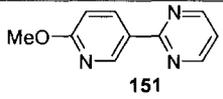
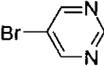
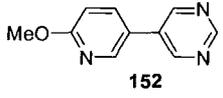
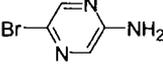
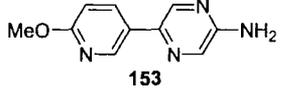
Entry	Boronic Acid	Ar-Y	Product	Isolated Yields/% Conditions A
1	123		 151	28
2	123		 152	35
3	123		 153	26

Table 3.4: Results from the Cross-Coupling of 123 with Various Electron Deficient Ring Systems.

Table 3.4 clearly shows the trend that when an electron deficient substrate is applied in the Suzuki cross-coupling reaction, under conditions A, the desired product is formed in lower yield.

3.3.1.4 Using five membered ring halides as the substrate

In contrast to the previous section, when an electron rich system, such as a thiazole, thiophene or furan ring is employed in the Suzuki reaction, again using conditions A, notably higher product yields are obtained (Table 3.5).

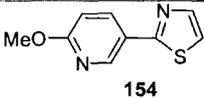
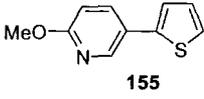
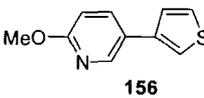
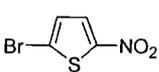
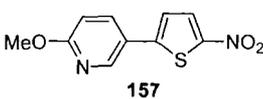
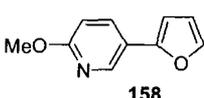
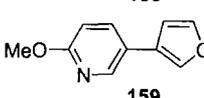
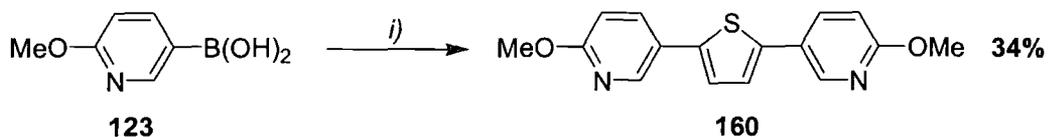
Entry	Boronic Acid	Ar-Y	Product	Isolated Yields/% Conditions A
1	123		 154	85
2	123		 155	87
3	123		 156	77
4	123		 157	94
5	123		 158	67
6	123		 159	54

Table 3.5: Results from the Cross-Coupling of acid 123 with five-membered ring bromides.

123 has also been proved as a suitable reagent for the synthesis of a tris(heteroaryl) derivative, which has been illustrated by the two-fold reaction of 123 with 2,5-dibromothiophene, which gave 160 in 34% yield (Scheme 3.11).



Scheme 3.11: Synthesis of a Tris(heteroaryl) Derivative (160). Reagents and Conditions: (i) 2,5-dibromothiophene, Pd(PPh₃)₄, DMF, 1M Na₂CO₃, 80°C.

This reaction has important implications as linear oligo(heteroaryl) systems of this type are important materials for optoelectronic device applications.⁷

3.3.2 Application of Di-Substituted Pyridylboronic Acid in the Suzuki Cross-Coupling Reaction

This section gives the results from the Suzuki reactions of our di-substituted pyridylboronic acids **134** and **137**, using reaction conditions A. Table 3.6 illustrates our findings.

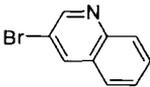
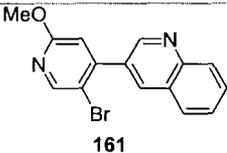
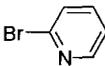
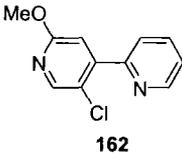
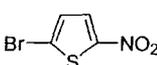
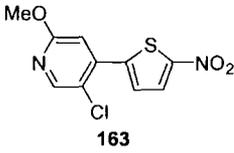
Entry	Boronic Acid	Ar-Y	Product	Isolated Yields/% Conditions A
1	134		 161	50
2	137		 162	35
3	137		 163	28

Table 3.6: Results from the Cross-Coupling of acids 134 & 137 with Various Bromide Substrates.

The yields of the reactions were lower than anticipated, as the corresponding reactions involving the mono-substituted pyridylboronic acid were relatively high yielding. We believe this outcome could be a result of three possible factors:

1. The substituent *ortho* to the boronic acid functional group may sterically hinder the cross-coupling.
2. The set reagents and conditions we have used so far with our coupling reactions may be unsuitable for the reactions involving this class of boronic acid.
3. There is also the possibility that further cross-coupling of our products may be occurring

In an attempt to improve upon the yields of not only the above reactions, but also attempt the synthesis of more novel heteroaryl derivatives using both the mono- and di-substituted pyridylboronic acids, we explored the application of our alternative reaction conditions, conditions B, which we had used earlier in this work (Scheme 3.12). Table 3.7 highlights the results from our cross-coupling reactions under these conditions.



Scheme 3.12: General Illustration of our Cross-Coupling Reaction using Conditions B. Reagents and Conditions: (i) Conditions B: Pd(PPh₃)₂Cl₂, 1,4-dioxane, 1M Cs₂CO₃, 95°C.

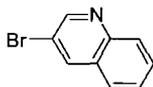
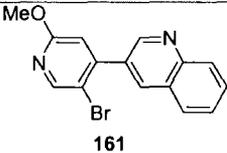
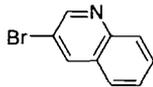
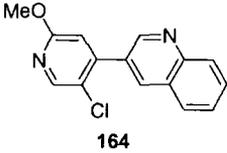
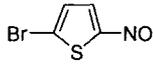
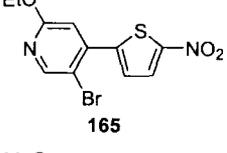
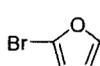
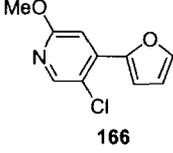
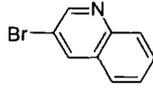
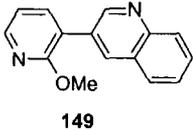
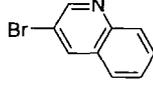
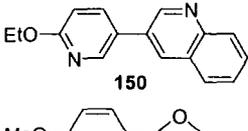
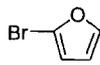
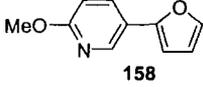
Entry	Boronic Acid	Ar-Y	Product	Isolated Yields/% Conditions B
1	134		 161	50
2	137		 164	60
3	138		 165	44
4	137		 166	30
5	131		 149	77
6	125		 150	59
7	123		 158	91

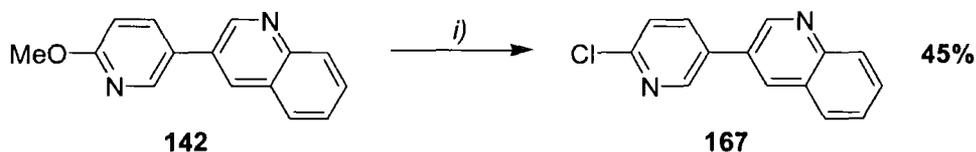
Table 3.7: Results of Suzuki Reactions using our Alternative Conditions (Conditions B).

The table clearly shows vast improvements in the yields of some reactions and the production of new, interesting bisheteroaryl systems.

3.4 Conclusions

In summary, judging by the data from each of our reactions, we can clearly state that these classes of substituted pyridylboronic acids are versatile reagents for the production of novel heteroarylpyridine derivatives, which can contain different ring systems varying from pyridyl, quinolyl, pyrimidyl, pyrazinyl, thienyl, thiazoyl and furyl. An added advantage of these reactions, in particular reactions involving the di-substituted pyridylboronic acids, is that the products obtained are able to undergo further functionalisation. For instance, the compounds that contain a halogen can now be employed as the halo substrate for further cross-coupling reactions, which can lead to numerous possibilities for further functionalisation. An example showing the possibility of such a reaction was highlighted in Chapter 2.

Furthermore, the alkoxy group of the compounds is suitable for functional group interconversion. As an example of such a conversion, we converted the MeO group of **142** into a Cl group to give **167** in 45% yield, following the method described by Shiao *et al*⁸, which involves Vilsmeier-Haack conditions (Scheme 3.13).



Scheme 3.13: Conversion of MeO→Cl under Vilsmeier-Haack Conditions. Reagents and Conditions: (i) POCl₃, DMF, Δ.

3.5 References

- ¹ Sirisoma, N. S.; Johnson, C. R. *Tetrahedron Lett.* **1998**, *39*, 2059.
- ² Den Hertog, H. J.; Jouwersma, C.; Van Der Wal, A. A.; Willebrands-Schogt, E. *C. C. Recueil* **1949**, *68*, 275.

- ³ Gros, Ph.; Fort, Y.; Queguiner, G.; Caubère, P. *Tetrahedron Lett.* **1995**, *36*, 4791.
- ⁴ Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773.
- ⁵ Leeson, P. D.; Emmett, J. C. *J. Chem. Soc. Perkin Trans. 1* **1988**, 3085.
- ⁶ Bargar, T. M.; Wilson, T.; Daniel, J. K. *J. Heterocycl. Chem.* **1985**, *22*, 1583.
- ⁷ Review: Mitsche, U.; Bauerle, P. J. *J. Mater. Chem.* **2000**, *10*, 1471.
- ⁸ Shiao, M.-J.; Shyu, L.-M.; Tarng, K.-Y. *Syn. Commun.* **1990**, *20*, 2971.

Chapter 4

Synthesis and Application of 5-Formylfuran-2-boronic Acid

4.0 Synthesis and Application of 5-Formylfuran-2-boronic Acid

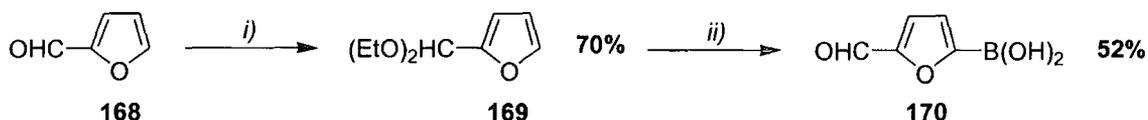
4.1 Introduction

The previous chapters have involved the synthesis and application of new pyridylboronic acids. In this chapter we investigate the synthesis and application of 5-formylfuran-boronic acid (**170**). This compound had previously been reported in the literature and is now commercially available. Our aim was to expand on the work previously carried by Starling *et al*¹ by firstly isolating, and then employing **170** in the production of novel, functionalised heteroaryl substituted furyl derivatives. We then intended to investigate methods for increasing further the functionality of these systems.

4.2 Synthesis of 5-Formylfuran-2-boronic Acid

As we detailed in Chapter 1, furylboronic acids have been known for some time. The attraction of **170** is that the aldehyde substituent can be used as a reactive handle for increasing the functionalisation of the furan ring.

The synthesis of **170** by a lithiation mechanism could be complicated by the presence of the aldehyde group being susceptible to attack from the organolithium reagent at its δ^+ centre. Therefore, following the method described by Thames *et al*,² we firstly protected the aldehyde group on our starting material, 2-furaldehyde (**168**), using triethylorthoformate, which gave the corresponding acetal (**169**) in 70% yield which would be resistant to attack by an organolithium reagent, and can be cleaved after the reaction by acid hydrolysis. Reaction of an organolithium reagent with **169** allows substitution to occur mainly at the 5-position of the furan ring. We obtained acid **170** pure in 52% yield following the method described Starling *et al*.¹ This route involved the generation of the reactive lithium species, by the reaction of nBuLi with **169**, followed by quenching the reaction with TMB, a suitable electrophile (Scheme 4.1).



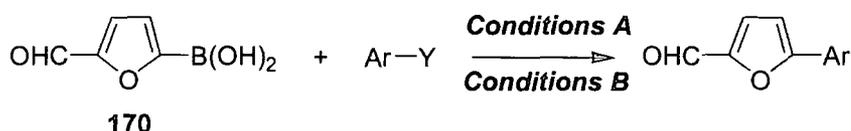
Scheme 4.1: Synthesis of 5-Formylfuran-2-boronic Acid (**170**). Reagents and Conditions: (i) Triethylorthoformate, 130°C, (ii) 1. nBuLi, -78°C, THF, 2. TMB, -78°C, 3. Aqueous Work-up.

We significantly modified the work-up described by Starling *et al.* During our aqueous work-up the protecting group is cleaved and an aldehyde is regenerated. We also found that in order to obtain **170** in a pure state, a post aqueous work-up wash with DCM removes tarry by-products. This procedure is simple, yet effective.

These practical differences have allowed us to obtain **170** in its pure form prior to its application in the Suzuki cross-coupling reaction, whereas Starling *et al* reacted **170** in its crude state.

4.3 Application of 5-Formylfuran-2-boronic Acid in the Suzuki Cross-Coupling Reaction

Following the isolation of pure **170** the main area of interest we envisaged was the formation of various heteroaryl substituted furyl systems, following our Suzuki cross-coupling conditions (Scheme 4.2).



Scheme 4.2: General Scheme of the Suzuki Cross-Coupling Reactions of 170. Reagents and Conditions: Conditions A: Pd(PPh₃)₄, DMF, Na₂CO₃, 80°C, Conditions B: Pd(PPh₃)₂Cl₂, 1,4-dioxane, Cs₂CO₃, 95°C.

The products would be novel and the -CHO group present in the system should allow continued functionalisation of the furyl systems.

Initially, we used conditions A in the production of **171-174** and found that the yield of each cross-coupling reaction was low, in comparison to the good to moderate yields we achieved previously with our pyridyl systems using conditions A. We then repeated the cross-coupling reactions for **171-174** using conditions B. In general, except for **174**, the results were vastly improved. This prompted us to attempt the synthesis of other analogous systems; again using conditions B. Table 4.1 highlights the results from all our Suzuki reactions using both sets of reaction conditions.

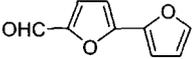
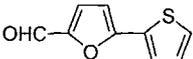
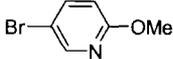
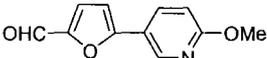
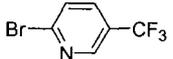
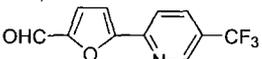
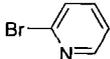
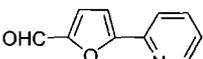
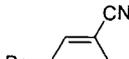
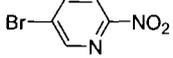
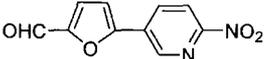
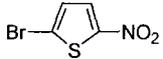
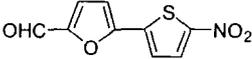
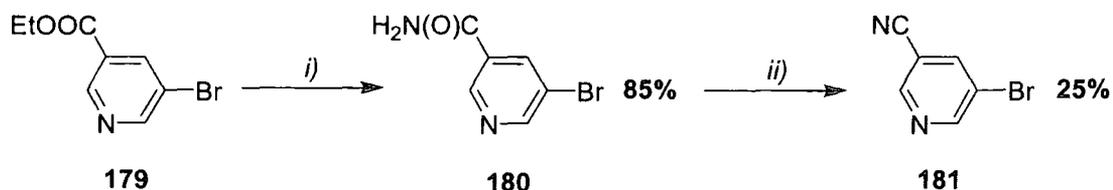
Entry	Boronic Acid	Ar-Y	Product	Isolated Yield/%	
				Conditions A	Conditions B
1	170		 171	34	64
2	170		 172	30	61
3	170		 173	16	52
4	170		 174	24	31
5	170		 175	-	57
6	170		 176	-	15
7	170		 177	-	44
8	170		 178	-	54

Table 4.1: Results from the Suzuki Cross-Coupling Reaction of 170.

The yields were moderate except for compound **176**. As observed with our pyridyl systems, the reaction is low yielding when an electron deficient halide is employed in the Suzuki cross-coupling reaction. This has been a consistent finding throughout our work, a fact that should be considered for future cross-coupling reactions.

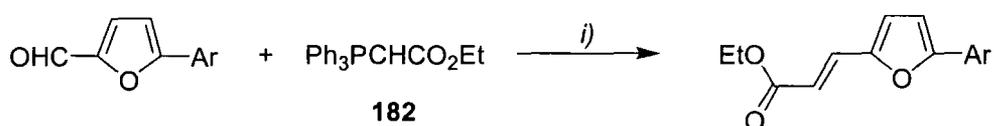
The 3-bromo-5-cyanopyridine (**181**), used in the synthesis of **176**, was not commercially available at the time this work was carried out. We felt that the synthesis of **176** would not only provide further evidence regarding the work involving electron deficient halides, but would also lead to a new, interesting heteroaryl substituted furyl system. Therefore, we obtained the 3-bromo-5-cyanopyridine by the formation of the amide **180** by the reaction of concentrated ammonia on **179**. **179** was then dehydrated using P_2O_5 to give **181** in 25% yield (Scheme 4.3).³



Scheme 4.3: Synthesis of 3-Bromo-5-cyanopyridine (181). Reagents and Conditions: (i) c.NH₃, rt, (ii) P₂O₅, Δ.

4.4 Functionalisation of Heteroaryl Substituted Furyl Derivatives via Wittig Chemistry

From our catalogue of functionalised heteroaryl substituted furyl systems we aimed to increase the functionality around the furan ring by the action of a Wittig reagent at the CHO group.⁴ Therefore, following a method described by Pandey *et al*⁵ we successfully synthesised compounds **183-185** by Wittig olefination, using (ethoxycarbonylmethylene)triphenylphosphorane (**182**) as the Wittig reagent, under simple conditions (Scheme 4.4). The results of these experiments, which are illustrated in Table 4.2, revealed this method of functionalisation to be high yielding and versatile, as the reaction tolerates different functionalities on the heteroaryl substituted furyl systems.



Scheme 4.4: General Illustration of the Wittig Olefination of Heteroaryl Substituted Furyl Systems. Reagents and Conditions: (i) CH₃CN, reflux.

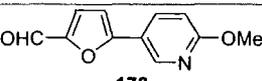
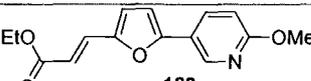
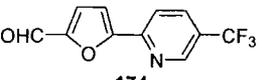
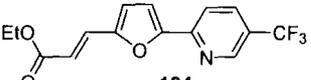
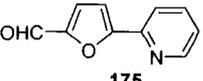
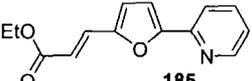
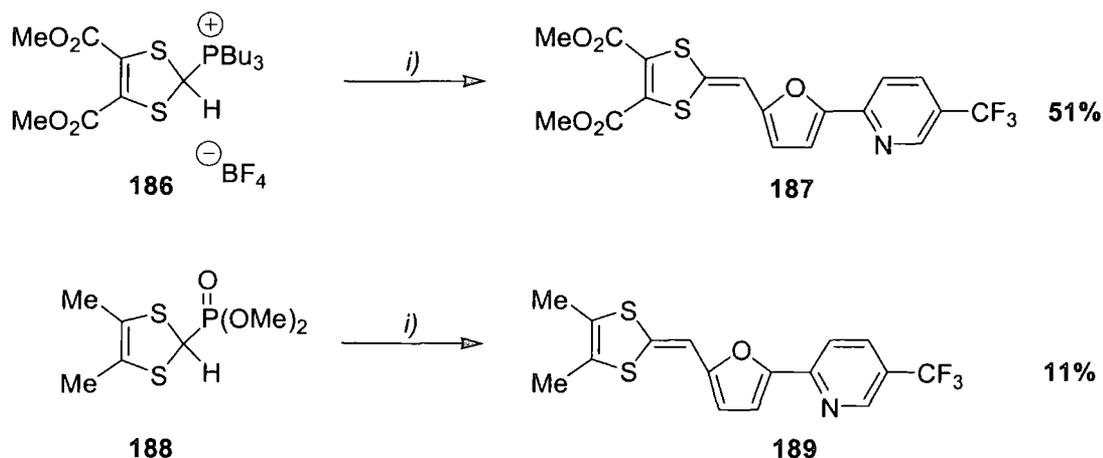
Entry	Heteroaryl Substituted Furyl System	Product	Isolated Yields/%
1	 173	 183	82
2	 174	 184	92
3	 175	 185	75

Table 1.2: Results from the Wittig Olefination Experiments.

To study more elaborate Wittig reactions we turned to the dithiole reagents **186** and **188**, which are readily available in our laboratory. Products containing the 1,3-dithiole heterocycle would be novel conjugated chromophores that contain electron donor and electron acceptor (D- π -A) substituents. We aimed to synthesise these compounds for the following reasons:

1. Use of compound **174** would provide a novel acceptor system, due to the presence of the highly electronegative CF_3 group.
2. The dithiole ring moiety has been previously applied as the donor component in D- π -A systems.⁶
3. The chemistry of 1,3-dithiole heterocycles is well established in our group.

Compounds **187** and **189** were formed by standard routes.⁷ The corresponding carbanions required for the Wittig and Horner-Wadsworth-Emmons reaction with the carbonyl group, are generated by the removal of the proton using $n\text{BuLi}$ at low temperature (Scheme 4.5).



Scheme 4.5: Formation of Compounds 187 and 189. Reagents and Conditions: (i) 1. nBuLi, THF, -78°C, 2. 174, THF, -78°C, 3. -78°C → rt, reflux.

At this time we cannot fully explain why the yield of **189** is so low when past examples have shown that the use of phosphonate esters in such reactions usually give products in reasonably high yield.⁸ However, we can state that **188** is known to be not as stable as **186**, resulting in **188** having to be stored in cold conditions. This reasoning could be a factor in the reaction being low yielding. This theory can be further substantiated by the fact that the production of **187** proceeds more cleanly than that of **189** (more by-products present for **189** than **187** (TLC evidence)).

4.4.1 Intramolecular Conjugation in the Dithiole Heteroaryl Substituted Furyl Derivatives

We targeted **187** and **189** as the substituents on the dithiole rings are known to impart differing donor abilities, i.e. 4,5-dimethyl > 4,5-dimethoxycarbonyl (Figure 4.1).

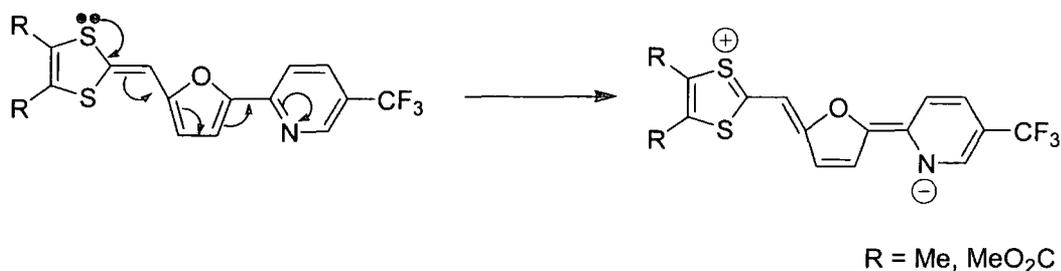


Figure 4.1: Illustration of Proposed Intramolecular Charge Transfer.

The methyl substituents have the greater donor ability due to their inductive effects. Therefore, taking UV-Vis spectroscopic measurements of our starting material **183**, **187** and **189**, we expected to observe a bathochromic shift (or red shift) in λ max values as the donor strength of the dithiole increases. Figure 4.2 illustrates our findings, which concur with our preliminary theories on these experiments.

We might also expect a downfield shift in the proton adjacent to N of the pyridine ring of compound **189**, as a result of the inductive effect of the methyl groups (Figure 4.1). No such shift was observed.

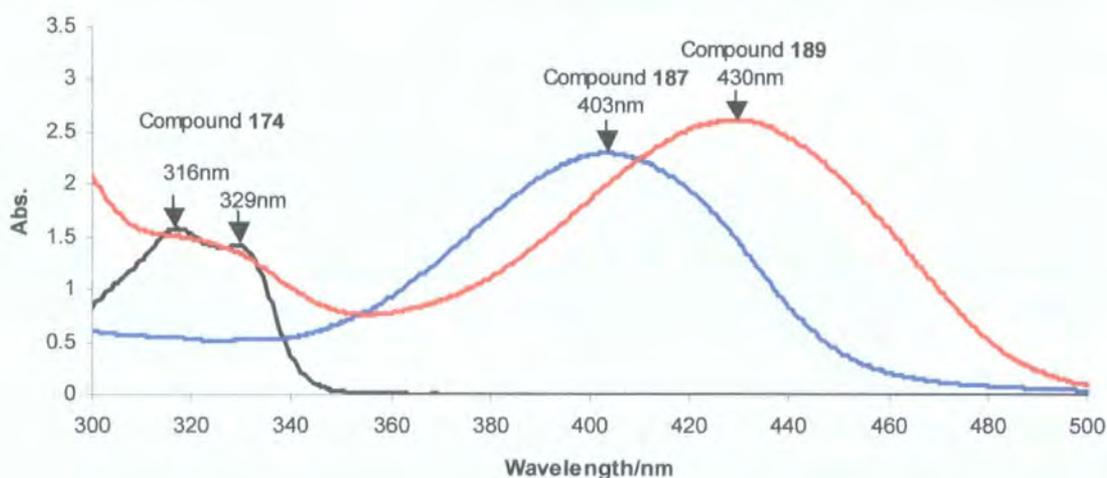


Figure 4.2: UV-Visible Absorption Spectra of Compounds **174**, **187**, and **189** in DCM at rt. All UV measurements were carried out in DCM and at varying concentrations: **174** (Black Line) 1×10^{-4} M, **187** (Blue Line) 1×10^{-4} M and **189** (Red Line) 5.5×10^{-4} M.

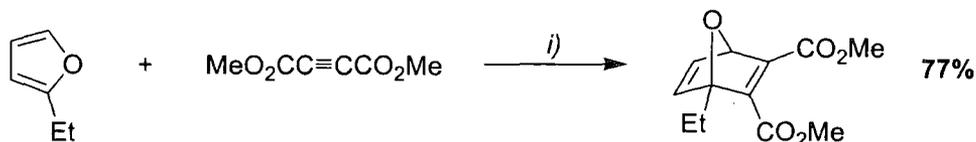
4.5 Conclusions

In summary, we have synthesised a number of different functionalised heteroaryl substituted furyl systems by firstly cross-coupling methodology, which can then subsequently be extended via Wittig chemistry; the boundaries of which we have explored by the synthesis of **187** and **189**, which display interesting intramolecular charge-transfer properties.

However, there is still more scope for further functionalisation, as Wittig chemistry is not the only means of functionalisation of such systems. For example, Diels-Alder chemistry is also another route into functionalisation of these heteroaryl substituted



furyl systems, as it has been well documented that furan, either substituted or non-substituted, can be employed as the diene in a Diels-Alder reaction.⁹ Scheme 4.6 is an example of such a reaction.¹⁰



Scheme 4.6: Diels-Alder Chemistry involving Furan as the Diene. Reagents and Conditions: (i) Δ.

This example illustrates one of numerous possibilities that are available for extending the synthetic chemistry on these new furan-containing systems.

4.6 References

- ¹ Starling, S. M.; Raslan, D. S.; de Oliveira, A. B. *Syn. Commun.* **1998**, *28*, 1013.
- ² Thames, S. F.; Odom, Jr., H. C. *J. Heterocycl. Chem.* **1966**, 490.
- ³ Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th Edition, Longman, UK, **1989**.
- ⁴ (a) Kao, B.-C.; Doshi, H.; Reyes-Rivera, H.; Titus, D. D.; Yin, M.; Dalton, D. R. *J. Heterocycl. Chem.* **1991**, *28*, 1315; (b) Avasthi, K.; Knaus, E. E. *J. Heterocycl. Chem.* **1981**, *18*, 375; (c) Szántay, C.; Kardos-Balogh, Z.; Moldvai, I.; Szántay Jr., C.; Temesvári, E.; Blaskó, G. *Tetrahedron Lett.* **1994**, *35*, 3171.
- ⁵ Pandey, G.; Bagul, T. D.; Sahoo, A. K. *J. Org. Chem.* **1998**, *63*, 760.
- ⁶ Moore, A. J.; Bryce, M. R.; Batsanov, A. S.; Green, A.; Howard, J. A. K.; McKerverey, A.; McGuigan, P.; Ledoux, L.; Ortí, E.; Viruela, R.; Viruela, P. M.; Tarbit, B. *J. Mater. Chem.* **1998**, *8*, 1173.
- ⁷ (a) Benahmed-Gasmi, A. S.; Frère, P.; Garrigues, B.; Gorgues, A.; Jubault, M.; Carlier, R.; Texier, F. *Tetrahedron Lett.* **1992**, *33*, 6457; (b) Roncali, J.; Griffard, M.; Frère, P.; Jubault, M.; Gorgues, A. *J. Chem. Soc., Chem. Commun.* **1993**, 689; (c) Hansen, T. K.; Lakshmikantham, M. V.; Cava, M. P.; Niziurski-Mann, R. E.; Jensen, F.; Becher, J. *J. Am. Chem. Soc.* **1992**, *114*, 5035; (d)

- Takahashi, K.; Nihira, T.; Yoshifuji, M.; Tomitani, K. *Bull. Chem. Soc. Jpn.* **1994**, *66*, 2330.
- ⁸ Elanddaloussi, E. H.; Frère, P.; Roncali, J.; Richomme, P.; Jubault, M.; Gorgues, A. *Adv. Mater.* **1995**, *7*, 390.
- ⁹ (a) McElhanon, J. R.; Wheeler, D. R. *Org. Lett.* **2001**, *3*, 2681; (b) Maeba, I.; Usami, F.; Furukawa, H. *J. Org. Chem.* **1984**, *49*, 1534; (c) Duval, O.; Mavoungou Gomès, L. *Tetrahedron Lett.* **1988**, *26*, 3243; (d) Wright, D. L.; Robotham, C. V.; Aboud, K. *Tetrahedron Lett.* **2002**, *43*, 943.
- ¹⁰ Fry, A. J.; Sherman, L. R.; Beaulieu, A. R.; Sherwin, C. *J. Org. Chem.* **1990**, *55*, 389.

Chapter 5

Experimental Procedures

5.0 Experimental Procedures

This chapter provides the experimental procedures and analytical data for each of the novel compounds presented in this thesis. This chapter also includes the experimental procedures for compounds, which are already known in the literature, that were used in the production of this work. All references given in this chapter correspond to references listed at the end of each chapter.

5.1 General Methods

All reactions which required inert or dry atmosphere, were carried out under a blanket of argon, which was dried by passage through a column of phosphorus pentoxide. All reagents employed were of standard reagent grade and purchased from Aldrich, Lancaster, Avocado, Fluka, Fluorchem or Merck and used as supplied unless otherwise stated. The following solvents were dried and distilled immediately prior to use: acetone, over Drierite (CaSO_4); acetonitrile and DCM, over calcium hydride; diethyl ether and toluene, over sodium metal; THF, over potassium metal. Ethanol and methanol were dried and distilled over magnesium turnings. DMF was dried by standing over 4Å molecular sieves for at least 48 h and was not distilled prior to use. 1,4-Dioxane was distilled prior to its use in the cross-coupling reactions. All other solvents used in the production of this work were used without prior purification.

Column chromatography was carried out on silica (40-60 μm mesh). Solvents used for chromatography were distilled prior to use.

^1H NMR spectra were recorded on a Varian Unity 200, 250 or 300 at 200, 250 or 300 MHz, respectively, or a Varian VXR 400s at 400 MHz or a Varian Inova 500 at 500 MHz using the deuteriated solvent as lock. Chemical shifts are quoted in ppm, relative to tetramethylsilane (TMS), using TMS or the residual solvent as internal reference. ^{13}C NMR were recorded using broad band decoupling on a Varian Unity 200, 250 or 300 at 50, 63 or 75 MHz, respectively, or a Varian VXR 400s or Varian Inova 500 at 100 MHz and 125 MHz, respectively. The following abbreviations are used in listing NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, br = broad.

Electron Impact (EI) mass spectra were recorded on a Micromass Autospec spectrometer operating at 70 eV with the ionization mode as indicated.

Elemental analyses were obtained on an Exeter Analytical Inc. CE-440 elemental analyzer.

UV-vis spectra were recorded using a Shimadzu UV-2101 spectrophotometer at ambient temperature.

Melting points were recorded on a Stuart Scientific SMP3 melting point apparatus and are uncorrected.

General Procedure for all the Cross-Coupling Reactions

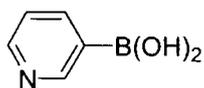
The boronic acid, the halide, and the catalyst (5 mol% relative to the boronic acid) were added sequentially to degassed solvent (10 mL) and the mixture was stirred at rt for 30-60 min. Degassed aqueous base solution was added and the mixture was heated under N₂ until tlc monitoring showed that the reaction was complete. Solvent was evaporated *in vacuo* and ethyl acetate was added. Then the organic layer was purified by column chromatography on silica gel.

Conditions **A**: Pd(PPh₃)₄, Na₂CO₃, DMF, 80°C.

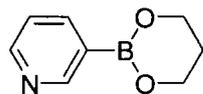
Conditions **B**: Pd(PPh₃)₂Cl₂, Cs₂CO₃, 1,4-dioxane, 95°C.

Note: No carbons attached to boron atoms are observed owing to the effects of the quadrupole moment.

5.2 Experimental Procedures of Chapter 1

3-Pyridylboronic Acid (**13**)¹⁸

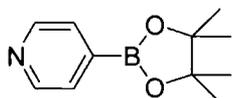
To magnesium turnings (3.0 g, 123.4 mmol) suspended in THF (50 mL) a solution of 3-bromopyridine (8.1 g, 51.2 mmol) and 1,2-dibromoethane (9.6 g, 51.1 mmol) in THF (50 mL) was added portionwise over a period of a few hours at 25 °C. The reaction mixture was then cooled to -78 °C then TBB (11.9 g, 52.0 mmol) was added over a period of 1 h, warmed to 25 °C and then a citric acid solution (25 g in 50 mL of water) was added. The reaction mixture was taken to pH 3 (HCl) and was washed with diethyl ether (1x100 mL). The reaction mixture was then taken to pH 10 (Na₂CO₃) and was again washed with diethyl ether (1x100 mL). The reaction mixture was then taken to pH 6 (HCl) and was concentrated until NaCl began to precipitate out. The NaCl was then removed via filtration and the filtrate underwent a continuous extraction for 2 weeks. This gave a yellow solid which was recrystallised from methanol to give **13** as a white solid (464 mg, 7%), mp >300 °C (lit mp = >300 °C)¹⁸; ¹H NMR (300 MHz, CD₃OD) δ 8.61 (1H, s), 8.52 (1H, d, *J* = 5.7 Hz), 8.39 (1H, d, *J* = 6.9 Hz), 7.67 (1H, t, *J* = 5.7 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 155.24, 151.41, 142.28, 123.80.

2-(3-Pyridyl)-1,3,2-dioxaboronane (**80**)¹⁰⁸

To a solution of 3-bromopyridine (7.3 g, 40.1 mmol) in anhydrous ether (100 mL) at -78 °C, *n*BuLi (1.6 M in hexane, 29.0 mL, 46.4 mmol) was added dropwise. The reaction mixture was then allowed to stir at this temperature for 2 h then TPB (9.0 g, 47.7 mmol) was added dropwise. The reaction mixture was stirred for a further 2 h at -78 °C. The reaction mixture was then allowed to warm to 25 °C and stir overnight. The solution was then cooled to 0 °C and 1,3-propanediol (3.7 g, 48.4 mmol) was added. The solution was then stirred for 1 h. Methanesulfonic acid (4.4 g, 46.2 mmol) was then added to the solution and was stirred for another hour. Celite (10 g) was added to the reaction mixture and was stirred vigorously for 30 mins at 25 °C. The solid was then filtered off and the filtrate was

evaporated to dryness. The crude ester was then recrystallised from ethyl acetate to give **80** as a white powder (1.1 g, 17%), mp 99-101 °C (lit mp = 96 °C)¹⁰⁸; ¹H NMR (250 MHz, CDCl₃) δ 8.89 (1H, s), 8.60 (1H, dd, *J* = 1.5 Hz, *J* = 1.5 Hz), 8.00-7.97 (1H, m), 7.23-7.19 (1H, m), 4.18-4.13 (4H, m), 2.08-2.04 (2H, m); ¹³C NMR (63 MHz, CDCl₃) δ 154.71, 151.30, 141.21, 122.91, 61.98(2C), 27.35. Anal. Calcd for C₈H₁₀BNO₂: C, 58.95%; H, 6.18%; N, 8.59%. Found: C, 58.76%; H, 6.17%; N, 8.59%.

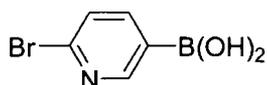
2-(4-Pyridyl)-4, 4, 4, 5-tetramethyl-1, 3-dioxaborolane (**84**)¹⁰⁹



To a slurry of 4-iodopyridine (1.5 g, 7.1 mmol) in anhydrous ether (100 mL) at -78 °C nBuLi (1.6 M in hexane, 5.5 mL, 8.9 mmol) followed 30 minutes later by TPB (1.6 g, 8.7 mmol). The temperature was allowed to rise to 25 °C over a period of 2 h. Pinacol (1.1 g, 9.5 mmol) was then added and 10 minutes later acetic acid (420 mg, 7.0 mmol) was also added. The resulting slurry was filtered through celite, the filter washed with ether. The combined filtrates were then evaporated *in vacuo*. The crude ester was then recrystallised from cyclohexane to give **84** as a white crystalline powder (308 mg, 21%), mp 150-152 °C (lit mp = 151 °C)¹⁰⁹; ¹H NMR (300 MHz, CDCl₃) δ 8.64 (2H, d, *J* = 5.6 Hz), 7.63 (2H, d, *J* = 5.6 Hz), 1.36 (12H, s); ¹³C NMR (100 MHz, acetone-d₆) δ 153.26(2C), 132.86(2C), 88.65, 29.01(4C), 28.75(2C); MS (EI) *m/z* 205 (M⁺, 71%). Anal. Calcd for C₁₁H₁₆BNO₂: C, 64.43%; H, 7.86%; N, 6.83%. Found: C, 63.95%; H, 7.74%; N, 6.53%.

5.3 Experimental Procedures of Chapter 2

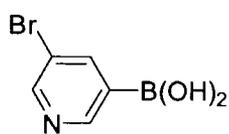
2-Bromo-5-pyridylboronic acid (**92**)



To a solution of 2,5-dibromopyridine (10.0 g, 42.2 mmol) in anhydrous ether (30 mL) at -78 °C was added nBuLi (1.6 M in hexane, 30.0 mL, 48.0 mmol) dropwise. The reaction mixture was stirred for 2 h at -78 °C. TPB (18.6 g, 99.7 mmol) was then added quickly. The reaction mixture was stirred at -78 °C for a further 2 h then allowed to warm to 20 °C and was quenched with water (50 mL). The reaction mixture was stirred overnight.

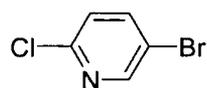
The organic solvent was evaporated *in vacuo* and the remaining aqueous layer was taken to pH 10 (with 5% NaOH), and was washed with diethyl ether (3x100 mL). The aqueous layer was then carefully acidified to pH 4 (with 48% HBr) to give **92** as a white solid (6.7 g, 79%), mp 167-169 °C (lit mp 198 °C)²; ¹H NMR (200 MHz, DMSO-d₆) δ 8.63 (1H, d, *J* = 1.8 Hz), 8.47 (2H, OH, s), 7.99 (1H, dd, *J* = 2.2 Hz, *J* = 2.2 Hz), 7.61 (1H, d, *J* = 8.0 Hz); ¹³C NMR (50 MHz, DMSO-d₆) δ 156.51, 145.65, 144.52, 128.30. Anal. Calcd for C₅H₅BBrNO₂: C, 29.76%; H, 2.50%; N, 6.94%. Found: C, 29.83%; H, 2.60%; N, 6.83%. Crystals for X-ray analysis were grown from aqueous EtOH solution.

3-Bromo-5-pyridylboronic acid (**97**)



To a solution of 3,5-dibromopyridine (2.0 g, 8.4 mmol) in anhydrous ether (30 mL) at -78 °C was added *n*BuLi (1.6 M in hexane, 6.0 mL, 10.0 mmol) dropwise. The reaction mixture was stirred for 2 h at -78 °C. TPB (3.3 g, 17.3 mmol) was then added quickly. The reaction mixture was stirred at -78 °C for a further 2 h then allowed to warm to 20 °C and was quenched with water (50 mL). The reaction mixture was stirred overnight. Workup as described for **92** gave **97** as an off-white solid (1.3 g, 74%), mp >300 °C (lit mp = dec 210 °C)²; ¹H NMR (200 MHz, DMSO-d₆) δ 8.80 (1H, d, *J* = 1.4 Hz), 8.68 (1H, d, *J* = 2.4 Hz), 8.56 (2H, OH, s), 8.25-8.23 (1H, m); ¹³C NMR (50 MHz, DMSO-d₆) δ 153.76, 152.15, 144.79, 121.38. Anal. Calcd for C₅H₅BBrNO₂: C, 29.76%; H, 2.50%; N, 6.94%. Found: C, 29.48%; H, 1.75%; N, 6.77%.

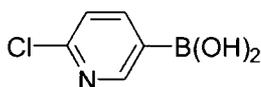
5-Bromo-2-chloro pyridine (**105**)¹⁵



Phosphoryl chloride (773 mg, 5.0 mmol) was added dropwise to stirred solution of 5-bromo-2-methoxy pyridine (189 mg, 1.0 mmol) in dry DMF at 0 °C. The stirring was continued for 1 h then the mixture was heated at 110 °C for 19 h. It was cooled to 0 °C and was quenched with saturated sodium acetate solution (25 mL). The mixture was extracted with EtOAc (4x50 mL). The organic layer was then washed with water (3x100 mL) and was dried over MgSO₄. The residue was chromatographed through a silica gel column; eluent EtOAc:Petroleum Ether(40-60°C) (7:3 v/v) to give **105** as a white solid (136 mg, 71%), mp 70-71 °C (lit

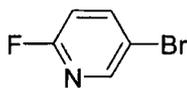
mp = 70-71 °C)¹⁵; ¹H NMR (300 MHz, CDCl₃) δ 8.47 (1H, d, *J* = 2.1 Hz), 7.77 (1H, dd, *J* = 2.4 Hz, *J* = 2.4 Hz), 7.25 (1H, d, *J* = 8.4 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 150.71, 150.07, 141.23, 125.66, 119.11; MS (EI) *m/z* 192 (M⁺, 100%). Anal. Calcd for C₅H₃BrCl: C, 31.21%; H, 1.57%; N, 7.28%. Found: C, 31.59%; H, 1.65%; N, 7.09%.

2-Chloro-5-pyridylboronic acid (103)



To a solution of 2-chloro-5-bromopyridine (742 mg, 3.9 mmol) and TPB (1.5 g, 7.8 mmol) in anhydrous THF (10 mL) at -78 °C was added nBuLi (1.6 M in hexane, 2.5 mL, 4.0 mmol), dropwise. The reaction mixture was stirred for 5 h at -78 °C then quenched with water (10 mL) and allowed to warm to 20 °C with stirring overnight. Workup as described for **92** gave **103** as a white solid (370 mg, 61%), mp 166-167 °C (lit mp 190 °C)²; ¹H NMR (300 MHz, acetone-d₆) δ 8.76 (1H, d, *J* = 1.8 Hz), 8.17 (1H, dd, *J* = 2.1 Hz, *J* = 2.1 Hz), 7.61 (2H, OH, s), 7.43 (1H, d, *J* = 8.1 Hz); ¹³C NMR (75 MHz, acetone-d₆) δ 155.85, 152.76, 145.72, 124.26. Anal. Calcd for C₅H₅BClNO₂: C, 38.16%; H, 3.20%; N, 8.90%. Found: C, 37.82%; H, 3.28%; N, 8.79%. Crystals for X-ray analysis were grown from aqueous EtOH solution.

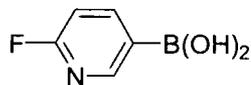
2-Fluoro-5-bromopyridine (107)¹⁷



2-Amino-5-bromopyridine (9.8 g, 56.8 mmol) was added portionwise to 50% fluoroboric acid. This did not readily dissolve so the mixture was heated until it dissolved. The mixture was then cooled to 0 °C, which gave a slurry. Sodium nitrite (4.8 g, 70.0 mmol) was then added slowly. The mixture was stirred at 0 °C for 30 mins. The mixture was then warmed to ~50 °C and then cooled back down to 0 °C. The mixture was then poured onto ice and was neutralized using Na₂CO₃. The mixture was then steam distilled. The distillate was then washed with diethyl ether and was dried using MgSO₄. The distillate was concentrated *in vacuo* and was distilled under reduced pressure to give **107** as a clear liquid (1.1 g, 11%). ¹H NMR (200 MHz, CDCl₃) δ 8.21 (1H, s), 7.86-7.70 (1H, m), 6.81 (1H, dd, *J* = 3.3 Hz, *J* = 3.3 Hz); ¹³C NMR (63 MHz, acetone-d₆) δ 165.62 (*J* =

237.8 Hz), 149.69 ($J = 15.7$ Hz), 145.40 ($J = 8.2$ Hz), 117.48 ($J = 5.7$ Hz), 113.03 ($J = 39.6$ Hz); MS (EI) m/z 176 (M^+ , 100%).

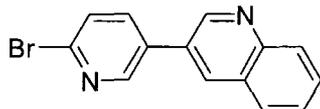
2-Fluoro-5-pyridylboronic acid (108)



To a solution of 2-fluoro-5-bromo pyridine (599 mg, 3.4 mmol) and TPB (1.3 g, 6.9 mmol) in anhydrous THF (10 mL) at -78 °C was added nBuLi (1.6 M in hexane, 2.2 mL, 3.5 mmol), dropwise.

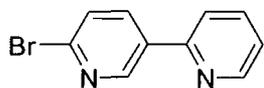
The reaction mixture was stirred for 4 h at -78 °C then quenched with water (10 mL) and allowed to warm to 20 °C with stirring overnight. Workup as described for **92** gave **108** as a white solid (245 mg, 51%), mp 170 - 171 °C (lit mp 172 °C)²; ^1H NMR (400 MHz, acetone- d_6) δ 8.52 (1H, d, $J = 2.0$ Hz), 8.41 (2H, s, OH), 8.27-8.23 (1H, m), 7.14-7.11 (1H, m); ^{13}C NMR (125 MHz, acetone- d_6) δ 165.44 ($J = 238.0$ Hz), 154.02 ($J = 14.8$ Hz), 147.51 ($J = 7.7$ Hz), 108.76 ($J = 36.0$ Hz). Anal. Calcd for $\text{C}_5\text{H}_5\text{BFNO}_2$: C, 42.62%; H, 3.58%; N, 9.94%. Found: C, 42.32%; H, 3.57%; N, 9.81%.

3-(6-Bromo-pyridin-3-yl)-quinoline (109)

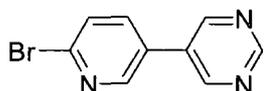


Conditions A: **92** (222 mg, 1.1 mmol), 3-bromoquinoline (153 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (56 mg), DMF and Na_2CO_3 (1 M, 3.5 mL); reaction time 43

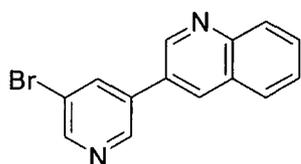
h; eluent petroleum ether (bp 40 - 60 °C):EtOAc (3:2 v/v) gave **109** as a white solid (63 mg, 32%). Conditions B: **92** (100 mg, 0.5 mmol), 3-bromoquinoline (123 mg, 0.6 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (18 mg), 1,4-dioxane and Cs_2CO_3 (1 M, 1.5 mL); reaction time 43 h; eluent petroleum ether (bp 40 - 60 °C):EtOAc (3:2 v/v) gave **109** as a white solid (20 mg, 14%), mp 178 - 179 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.13 (1H, d, $J = 2.0$ Hz), 8.74 (1H, d, $J = 2.5$ Hz), 8.33 (1H, d, $J = 2.5$ Hz), 8.18 (1H, d, $J = 8.5$ Hz), 7.93 (1H, d, $J = 8.0$ Hz), 7.89 (1H, dd, $J = 2.8$ Hz, $J = 2.8$ Hz), 7.80 (1H, t, $J = 7.0$ Hz), δ 7.67-7.63 (2H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 150.40, 148.97, 147.99, 142.17, 137.33, 134.03, 133.20, 130.56, 129.59, 128.69, 128.32(3C), 127.95, 127.85; MS (EI) m/z 286 (M^+ , 100%). HRMS (EI) calcd for $\text{C}_{14}\text{H}_9\text{BrN}_2$ (M^+) 283.9950, found 283.9949.

6'-Bromo-[2,3']bipyridinyl (110)

Conditions A: **92** (222 mg, 1.1 mmol), 2-bromopyridine (163 mg, 0.7 mmol), tetrakis(triphenylphosphino) palladium (56 mg), DMF and Na_2CO_3 (1 M, 3.5 mL); reaction time 43 h; eluent petroleum ether (bp 40-60 °C):EtOAc (3:2 v/v) gave **110** as a white solid (18 mg, 11%), mp 78-82 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.94 (1H, s), 8.77 (1H, s), 8.31 (1H, d, $J = 8.0$ Hz), 7.92 (1H, t, $J = 7.0$ Hz), 7.81 (1H, d, $J = 7.5$ Hz), 7.64 (1H, d, $J = 8.0$ Hz), δ 7.50-7.34 (1H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 153.00, 149.20, 148.53, 143.23, 138.41, 137.16, 128.32, 123.56(2C), 121.08; MS (EI) m/z 234 (M^+ , 100%). HRMS(EI) calcd for $\text{C}_{10}\text{H}_7\text{BrN}_2$ (M^+) 233.9793, found 233.9795. Compound **113** is a by-product of this reaction.

5-(6-Bromo-pyridin-3-yl)-pyrimidine (111)

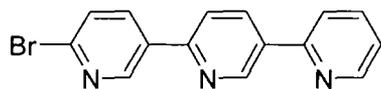
Conditions A: **92** (162 mg, 0.8 mmol), 5-bromopyridine (111 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (40 mg), DMF and Na_2CO_3 (1 M, 2.5 mL); reaction time 22 h; eluent petroleum ether (bp 40-60 °C): EtOAc (1:4 v/v) gave **111** as a white solid (16 mg, 10%), mp 178-179 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.32 (1H, s), 8.97 (2H, s), 8.63 (1H, s), 7.78 (1H, dd, $J = 2.2$ Hz, $J = 2.2$ Hz), 7.69 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 158.82, 155.05, 148.38, 143.32, 136.94, 130.66, 129.77, 129.01; MS (EI) m/z 235 (M^+ , 100%). HRMS(EI) calcd for $\text{C}_9\text{H}_6\text{BrN}_3$ (M^+) 234.9746, found 233.9744.

3-(5-Bromo-pyridin-3-yl)-quinoline (112)

Conditions B: **97** (100 mg, 0.4 mmol), 3-bromoquinoline (153 mg, 0.7 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (15 mg) and Cs_2CO_3 (1 M, 1.2 mL); reaction time 68 h; eluent EtOAc: CH_2Cl_2 (7:3 v/v) gave **112** as a white solid (11 mg, 8%), mp 180-182 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.07 (1H, s), 8.86 (1H, s), 8.71 (1H, s), 8.27 (1H, s), 8.11 (2H, d, $J = 8.0$ Hz), 7.86 (1H, d, $J = 8.5$ Hz), 7.73 (1H, t, $J = 7.0$ Hz), δ 7.58 (1H, t, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 149.20, 147.79, 146.87(2C), 145.44, 136.12, 133.10,

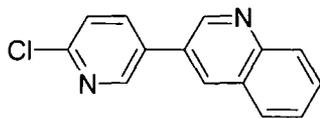
129.39, 128.38(3C), 127.11, 126.60(2C); MS (EI) m/z 284 (M^+ , 100%). HRMS (EI) calcd for $C_{14}H_9BrN_2$ (M^+) 283.9949, found 285.9931.

6''-Bromo-[2,3';6',3'']terpyridine (113)



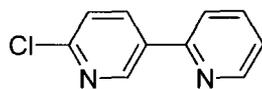
1H NMR (250 MHz, $CDCl_3$) δ 9.28 (1H, d, $J = 2.0$ Hz), 9.01 (1H, d, $J = 2.3$ Hz), 8.75 (1H, d, $J = 6.0$ Hz), 8.45 (1H, dd, $J = 2.0$ Hz, $J = 2.0$ Hz), 8.27 (1H, dd, $J = 2.5$ Hz, $J = 2.5$ Hz), 7.87-7.81 (3H, m), 7.61 (1H, d, $J = 8.3$ Hz), 7.36-7.30 (1H, m); MS (EI) m/z 311 (M^+ , 100%).

3-(6-Chloro-pyridin-3-yl)-quinoline (114)



Conditions A: **103** (100 mg, 0.6 mmol), 3-bromoquinoline (153 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (37 mg), DMF and Na_2CO_3 (1 M, 2.0 mL); reaction time 70 h; eluent DCM: EtOAc (3:7 v/v) gave **114** as a white solid (84 mg, 55%). Conditions B: **103** (100 mg, 0.6 mmol), 3-bromoquinoline (153 mg, 0.7 mmol), $Pd(PPh_3)_2Cl_2$ (23 mg), 1,4-dioxane and Cs_2CO_3 ; eluent DCM: EtOAc (3:7 v/v) gave **114** as a white solid (99 mg, 64%), mp 180-181 °C; 1H NMR (300 MHz, acetone- d_6) δ 9.13 (1H, d, $J = 2.4$ Hz), 8.77 (1H, d, $J = 2.1$ Hz), 8.55 (1H, d, $J = 1.8$ Hz), 8.20 (1H, dd, $J = 2.7$ Hz, $J = 2.7$ Hz), 7.99-7.92 (2H, m), 7.72-7.66 (1H, m), 7.60-7.50 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.29, 148.88, 148.17, 147.48, 137.34, 133.71(2C), 132.60, 130.22, 129.38, 128.05, 127.68, 127.51, 124.59; MS (EI) m/z 240 (M^+ , 100%). Anal. Calcd for $C_{14}H_9ClN_2$: C, 69.86%; H, 3.77%; N, 11.64%. Found: C, 69.40%; H, 3.80%; N, 11.53%.

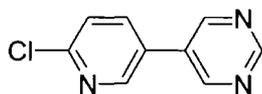
6'-Chloro-[2,3']bipyridinyl (115)



Conditions A: **103** (100 mg, 0.6 mmol), 2-bromopyridine (163 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (37 mg), DMF and Na_2CO_3 (1 M, 2.0 mL); reaction time 70 h; eluent DCM:EtOAc (7:3 v/v) gave **115** as a white solid (75 mg, 61%), mp 71-72 °C; 1H NMR (300 MHz, acetone- d_6) δ 9.10 (1H, d, $J = 2.4$ Hz), 8.73-8.71 (1H, m), 8.51 (1H, dd, $J =$

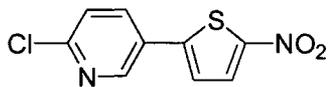
2.4 Hz, $J = 2.4$ Hz), 8.03 (1H, dd, $J = 0.9$ Hz, $J = 0.9$ Hz), 7.96-7.90 (1H,m), 7.57 (1H, d, $J = 8.4$ Hz), 7.44-7.39 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 153.42, 151.53, 150.27, 148.31, 137.54, 137.44, 134.19, 124.40, 123.60, 120.71; MS (EI) m/z 192 ($[\text{M}+2]^+$, 41%), 190 (M^+ , 100%). Anal. Calcd for $\text{C}_{10}\text{H}_7\text{ClN}_2$: C, 63.01%; H, 3.70%; N, 14.70%. Found: C, 63.19%; H, 3.84%; N, 14.45%.

5-(6-Chloropyridin-3-yl)-pyrimidine (116)

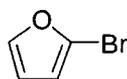


Conditions A: **103** (50 mg, 0.3 mmol), 5-bromopyrimidine (115 mg, 0.7 mmol), tetrakis(triphenylphosphino) palladium (37 mg), DMF and Na_2CO_3 (1 M, 2.0 mL); reaction time 70 h; eluent petroleum ether (bp 40-60 °C) : EtOAc (2:3 v/v) gave **116** as a white solid (24 mg, 38%), mp 177-178.5 °C; ^1H NMR (400 MHz, acetone- d_6) δ 9.22 (1H, s), 9.16 (2H, s), 8.84 (1H, d, $J = 2.4$ Hz), 8.28 (1H, dd, $J = 2.4$ Hz, $J = 2.8$ Hz), 7.66 (1H, dd, $J = 0.8$ Hz, $J = 0.8$ Hz); ^{13}C NMR (100 MHz, acetone- d_6) δ 158.42, 155.25 (2C), 151.68, 148.36, 138.08, 130.49, 130.00, 124.85; MS (EI) m/z 193 ($[\text{M}+2]^+$, 33%), 191 (M^+ , 100%). Anal. Calcd for $\text{C}_9\text{H}_6\text{ClN}_3$: C, 56.41%; H, 3.16%; N, 21.93%. Found: C, 56.48%; H, 3.33%; N, 21.43%.

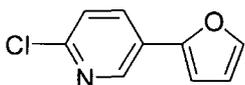
2-Chloro-5-(5-nitrothien-2-yl)-pyridine (117)



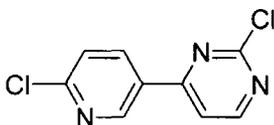
Conditions A: **103** (100 mg, 0.6 mmol), 2-bromo-5-nitrothiophene (115 mg, 0.6 mmol), tetrakis(triphenylphosphino) palladium (37 mg), DMF and Na_2CO_3 (1 M, 2.0 mL); reaction time 70 h; eluent DCM gave **117** as a yellow solid (132 mg, 53%), mp 190-191 °C; ^1H NMR (500 MHz, acetone- d_6) δ 8.74 (1H, d, $J = 3.0$ Hz), 8.13 (1H, dd, $J = 2.5$ Hz, $J = 2.5$ Hz), 7.98 (1H, d, $J = 4.5$ Hz), 7.60 (1H, d, $J = 4.0$ Hz), 7.49 (1H, d, $J = 8.5$ Hz); ^{13}C NMR (125 MHz, acetone- d_6) δ 152.16, 147.40, 146.38, 137.10(2C), 130.43, 127.89, 125.42, 125.05, 122.95; MS (EI) m/z 242 ($[\text{M}+2]^+$, 38%), 240 (M^+ , 100%). Anal. Calcd for $\text{C}_9\text{H}_5\text{ClN}_2\text{O}_2\text{S}$: C, 44.92%; H, 2.09%; N, 11.64%. Found: C, 44.81%; H, 2.19%; N, 11.38%.

2-Bromofuran (118)²²

5-Bromo-2-furoic acid (12.0 g, 62.8 mmol), copper powder (3.0 g, 47.2 mmol) and quinoline (49.2 g, 380.8 mmol) were added together and underwent a fractional distillation. The distillate collected was fractionally distilled at a reduced pressure to give **118** as a clear liquid (4.3 g, 47%). ¹H NMR (250 MHz, acetone-d₆) δ 7.64-7.63 (1H, m), 6.50-6.48 (1H, m), 6.46-6.44 (1H, m); ¹³C NMR (63 MHz, acetone-d₆) δ 146.19, 122.55, 113.83, 112.56; MS (EI) *m/z* 148 ([M+2]⁺, 100%), 146 (M⁺, 94%).

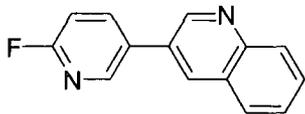
5-(6-Chloro-pyridinyl-3-yl)-furan-2-carbaldehyde (119)

Conditions B: **103** (200 mg, 1.3 mmol), 2-bromofuran (165 mg, 1.1 mmol), Pd(PPh₃)₂Cl₂ (46 mg) and Cs₂CO₃ (1M, 4.0 mL). Reaction time 64 h. Eluent used, DCM gave **119** as a white solid (133 mg, 66%), mp 54-56 °C; ¹H NMR (400 MHz, acetone-d₆) δ 8.62 (1H, d, *J* = 2.4 Hz), 7.98 (1H, dd, *J* = 2.4 Hz, *J* = 2.4 Hz), 7.61-7.60 (1H, m), 7.37 (1H, dd, *J* = 0.8 Hz, *J* = 0.8 Hz), 6.94-6.93 (1H, m), 6.50-6.49 (1H, m); ¹³C NMR (100 MHz, acetone-d₆) δ 150.09, 149.43, 145.07, 144.05, 134.06, 126.32, 124.57, 112.37, 107.85; MS (EI) *m/z* 181 ([M+2]⁺, 30%), 179 (M⁺, 100%). Anal. Calcd for C₉H₆ClNO: C, 60.19%; H, 3.37%; N, 7.80%. Found: C, 60.13%; H, 3.51%; N, 7.74 %.

2-Chloro-4-(6-chloropyridin-3-yl)-pyrimidine (120)

Conditions A: **103** (91 mg, 0.6 mmol), 2,4-dichloropyrimidine (75 mg, 0.5mmol), tetrakis(triphenylphosphino) palladium (34 mg) and Na₂CO₃ (1M, 2.0 mL); reaction time 65 h; eluent DCM:EtOAc; (4:1 v/v) gave **120** as a white solid (26 mg, 23%), mp 188-190°C; ¹H NMR (200 MHz, acetone-d₆) δ 9.06 (1H, d, *J* = 1.8 Hz), 8.74 (1H, d, *J* = 5.4 Hz), 8.48 (1H, dd, *J* = 2.6 Hz, *J* = 2.6 Hz), 8.04 (1H, d, *J* = 5.2 Hz), 7.56 (1H, d, *J* = 8.4 Hz); ¹³C NMR (100 MHz, acetone-d₆) δ 163.91, 161.64, 161.54, 154.17, 149.17, 138.21, 130.61, 124.94, 116.42; MS (EI) *m/z* 226 ([M+2]⁺, 70%), 224 (M⁺, 100%). HRMS(EI) calcd for C₉H₅Cl₂N₃ (M⁺) 224.9861, found 224.9861.

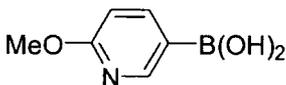
3-(6-Fluoro-pyridin-3-yl)-quinoline (121)



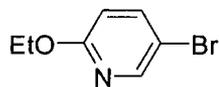
Conditions A: **108** (72 mg, 0.6 mmol), 2,4-dichloropyrimidine (199 mg, 1.0 mmol), tetrakis(triphenylphosphino) palladium (40 mg) and Na_2CO_3 (2M, 1.0 mL); reaction time 65 h; eluent, DCM:EtOAc; (1:1 v/v) gave **121** as a white solid (47 mg, 41%) Conditions B: **108** (100 mg, 0.7 mmol), 3-bromoquinoline (199 mg, 1.0 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (25mg) and Cs_2CO_3 (1M, 2.0 mL); reaction time 67 h; eluent, DCM:EtOAc; (1:1 v/v) gave **121** as a white solid (91 mg, 57%), mp 126-127°C; ^1H NMR (400 MHz, acetone- d_6) δ 9.12 (1H, d, $J = 2.4$ Hz), 8.60-8.59 (1H, m), 8.52 (1H, d, $J = 2.0$ Hz), 8.36-8.31 (1H, m), 7.99-7.91 (2H, m), 7.70-7.66 (1H, m), 7.56-7.52 (1H, m), 7.18-7.15 (1H, m); ^{13}C NMR (100 MHz, acetone- d_6) δ 164.94 ($J = 237.3$ Hz), 149.43, 147.99, 146.60 ($J = 15.1$ Hz), 140.86 ($J = 8.0$ Hz), 133.67, 132.25 ($J = 4.0$ Hz), 130.00, 129.77, 129.42, 128.57, 128.09, 127.43, 110.16 ($J = 38.2$ Hz); MS (EI) m/z 224 (M^+ , 100%). Anal. Calcd for $\text{C}_{14}\text{H}_9\text{FN}_2$: C, 74.99%; H, 4.05%; N, 12.49%. Found: C, 74.54%; H, 4.16%; N, 12.38%.

5.4 Experimental Procedures of Chapter 3

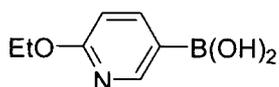
2-Methoxy-5-pyridylboronic acid (123)



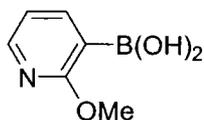
To a solution of 5-bromo-2-methoxypyridine (727 mg, 3.9 mmol) in anhydrous ether (10 mL) at -78 °C was added $n\text{BuLi}$ (1.6 M in hexane, 2.5 mL, 4.0 mmol), dropwise. The reaction mixture was stirred for 1 h at -78 °C then TPB (1.5 g, 7.8 mmol) was added quickly. The reaction mixture was stirred at -78 °C for another 1 h, then quenched with water (15 mL) and allowed to warm to 20 °C with stirring overnight. Workup as described for **92** gave **123** as a white solid (382 mg, 65%), mp 137-138 °C; ^1H NMR (250 MHz, acetone- d_6) δ 8.62 (1H, d, $J = 1.3$ Hz), 8.05 (1H, dd, $J = 2.0$ Hz, $J = 2.0$ Hz), 7.27 (2H, OH, s), 6.73 (1H, d, $J = 10.0$ Hz); ^{13}C NMR (100 MHz, acetone- d_6) δ 166.31, 154.23, 144.85, 110.49, 53.23. Anal. Calcd for $\text{C}_6\text{H}_8\text{BNO}_3$: C, 47.12%; H, 5.27%; N, 9.16%. Found: C, 46.87%; H, 5.30%; N, 8.99%.

5-Bromo-2-ethoxy pyridine (124)²

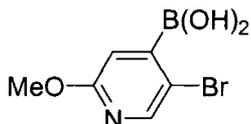
2,5-Dibromopyridine (5.0 g, 21.1 mmol) was refluxed in a solution of sodium hydroxide (2.5 g, 62.5 mmol) in absolute ethanol (20 mL) for 18 h. Concentrated hydrochloric acid was then added to give a faint acidic reaction. Filtered the reaction mixture. The residue was then steam distilled to give **124** as a white solid (1.4 g, 33%), mp 35-37 °C (lit mp = 34-35 °C)²; ¹H NMR (200 MHz, acetone-d₆) δ 8.20 (1H, d, *J* = 2.6 Hz), 7.80 (1H, dd, *J* = 2.7 Hz, *J* = 2.7 Hz), 6.75 (1H, d, *J* = 8.8 Hz), 4.31 (2H, q, *J* = 7.0 Hz), 1.33 (3H, t, *J* = 7.2 Hz); ¹³C NMR (50 MHz, acetone-d₆) δ 163.05, 147.60, 141.44, 113.08, 111.32, 61.94, 14.10; MS (EI) *m/z* 202 (M⁺, 38%).

2-Ethoxy-5-pyridylboronic acid (125)

To a solution of 2-ethoxy-5-bromopyridine (200 mg, 1.0 mmol) in anhydrous ether (5 mL) at -78 °C was added *n*BuLi (1.6 M in hexane, 0.6 mL, 1.0 mmol), dropwise. The reaction mixture was stirred for 1 h at -78 °C then TPB (375 mg, 2.0 mmol) was added dropwise. The reaction mixture was stirred for another 1 h at -78 °C. The reaction was then quenched with water (5 mL) and was then allowed to warm to 20 °C and stir overnight. Workup as described for **92** gave **125** as a white solid (101 mg, 61%), mp 131-134 °C; ¹H NMR (300 MHz, acetone-d₆) δ 8.59 (1H, d, *J* = 1.8 Hz), 8.03 (1H, dd, *J* = 2.0 Hz, *J* = 2.0 Hz), 7.18 (2H, s, OH), 6.69 (1H, d, *J* = 8.1 Hz), 4.35 (2H, q, *J* = 4.2 Hz), 1.33 (3H, t, *J* = 5.1 Hz); ¹³C NMR (100 MHz, acetone-d₆) δ 165.56, 153.79, 144.38, 110.16, 61.25, 14.27. Anal. Calcd for C₇H₁₀BNO₃: C, 50.35%; H, 6.04%; N, 8.39%. Found: C, 50.09%; H, 6.10%; N, 8.26%.

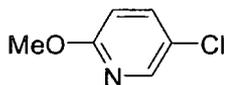
2-Methoxy-3-pyridylboronic acid (131)

To a solution of 2-methoxypyridine (1.2 g, 11.4 mmol) in anhydrous THF (10 mL) at 0 °C was added LDA (2.0 M in heptane/THF/ethylbenzene, 6.9 mL, 13.8 mmol), dropwise. The reaction mixture was stirred for 3 h at 0 °C then TMB (2.4 g, 23.2 mmol) was added dropwise. The reaction mixture was allowed to warm to 20 °C then was quenched with water (10 mL) and allowed to stir overnight. Workup as described for **92** gave **131** as a white solid (235 mg, 13%), mp 143-145 °C; ¹H NMR (300 MHz, acetone-d₆) δ 8.24 (1H, dd, *J* = 2.1 Hz, *J* = 2.1 Hz), 8.12 (1H, dd, *J* = 2.0 Hz, *J* = 2.0 Hz), 7.10 (2H, s, OH), 7.02-6.98 (1H, m), 3.99 (3H, OCH₃, s); ¹³C NMR (125 MHz, acetone-d₆) δ 168.26, 150.09, 146.70, 118.08, 53.56. Anal. Calcd for C₆H₈BNO₃: C, 47.12%; H, 5.27%; N, 9.16%. Found: C, 46.78%; H, 5.18%; N, 8.94%.

3-Bromo-6-methoxy-4-pyridylboronic acid (134)

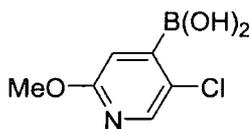
To a solution of 5-bromo-2-methoxypyridine (727 mg, 3.9 mmol) in anhydrous THF (10 mL) at -78 °C was added LDA (2.0 M in heptane/THF/ethylbenzene, 2.0 mL, 4.0 mmol), dropwise. The reaction mixture was stirred for 1 h at -78 °C then TPB (1.5 g, 7.8 mmol) was added dropwise. The reaction mixture was allowed to stir for another hour then quenched with water (10 mL) and allowed to warm to 20 °C and stir overnight. Workup as described for **92a** gave **134** as a white solid (351 mg, 39%), mp 97-99 °C; ¹H NMR (300 MHz, acetone-d₆) δ 8.16 (1H, s), 7.76 (2H, s, OH), 6.84 (1H, s), 3.85 (3H, OCH₃, s); ¹³C NMR (100 MHz, acetone-d₆) δ 162.79, 147.44, 115.67, 114.92, 53.17. Anal. Calcd for C₆H₇BBrNO₃: C, 31.08%; H, 3.04%; N, 6.04%. Found: C, 31.09%; H, 2.90%; N, 6.00%.

5-Chloro-2-methoxypyridine (136)

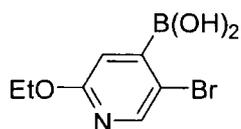


To a stirred suspension of 2,5-dichloropyridine (12.1 g, 81.6 mmol) in methanol (60 mL) was added a 25% solution of sodium methoxide in methanol (30 mL). The mixture was refluxed under an inert atmosphere for 24 h. More of the 25% solution of sodium methoxide in methanol (30 mL) was added and refluxing was continued for a further 80 h. Precipitated sodium chloride was removed via filtration and the filtrate was concentrated *in vacuo* to about ¼ its original volume and was partitioned between ether and water. The aqueous layer was extracted with more ether (4x50 mL). The combined ether layers were then washed with brine and dried using MgSO₄. This was then concentrated to give a brown oil which was distilled under reduced pressure to give **136** as a clear liquid (3.6 g, 31%). ¹H NMR (300 MHz, acetone-d₆) δ 8.12 (1H, d, *J* = 2.7 Hz), 7.68 (1H, dd, *J* = 2.7 Hz, *J* = 2.7 Hz), 6.79 (1H, d, *J* = 8.1 Hz), 3.87 (3H, OCH₃, s); ¹³C NMR (100 MHz, CDCl₃) δ 162.97, 145.22, 138.79, 123.92, 112.29, 53.33; MS (EI) *m/z* 143 (M⁺, 90%). Anal. Calcd for C₆H₆ClNO: C, 50.19%; H, 4.21%; N, 9.76%. Found: C, 50.07%; H, 4.19%; N, 9.76%.

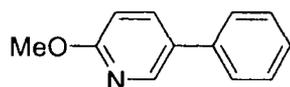
3-Chloro-6-methoxy-4-pyridylboronic acid (137)



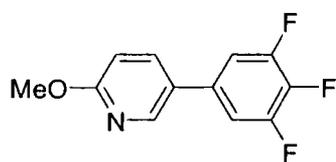
To a solution of 5-chloro-2-methoxypyridine (437 mg, 3.0 mmol) in anhydrous THF (10 mL) at -78 °C was added LDA (2.0 M in heptane/THF/ethylbenzene, 1.8 mL, 3.6 mmol), dropwise. The reaction mixture was stirred for 4 h then TPB (1.4 mL, 6.1 mmol) was added quickly. The reaction mixture was stirred for a further 3 h then quenched with water (10 mL) at -78 °C and allowed to warm to 20 °C with stirring overnight. Workup as described for **92** gave **137** as a white solid (275 mg, 48%), mp 123-125 °C; ¹H NMR (250 MHz, acetone-d₆) δ 8.07 (1H, s), 7.72 (2H, OH, s), 6.89 (1H, s), 3.86 (3H, OMe, s); ¹³C NMR (63 MHz, acetone-d₆) δ 163.42, 145.94, 127.58, 116.35, 54.07. Anal. Calcd for C₆H₇BClNO₃: C, 38.46%; H, 3.77%; N, 7.47%. Found: C, 38.22%; H, 3.64%; N, 7.43%.

3-Bromo-6-ethoxy-4-pyridylboronic acid (138)

To a solution of 5-bromo-2-ethoxypyridine (261 mg, 1.3 mmol) in anhydrous THF (10 mL) at -78°C was added LDA (2.0 M in heptane/THF/ethylbenzene, 0.8 mL, 1.5 mmol), dropwise. The reaction mixture was stirred for 1 h at -78°C then TPB (489 mg, 2.6 mmol) was added dropwise. The reaction mixture was allowed to stir for another hour then quenched with water (1 mL) and allowed to warm to 20°C and stir overnight. Workup as described for **92** gave **138** as a white solid (74 mg, 23%), mp $103\text{-}105^{\circ}\text{C}$; ^1H NMR (400 MHz, acetone- d_6) δ 8.15 (1H, s), 7.70 (2H, s, OH), 6.81 (1H, s), 4.30 (2H, q, $J = 7.2$ Hz), 1.32 (3H, t, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, acetone- d_6) δ 162.48, 147.45, 115.86, 114.67, 61.72, 14.15. Anal. Calcd for $\text{C}_7\text{H}_9\text{BBrNO}_3$: C, 34.20%; H, 3.69%; N, 5.70%. Found: C, 34.90%; H, 3.25%; N, 5.90%.

2-Methoxy-5-phenyl-pyridine (139)

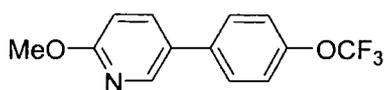
Conditions A: **123** (100 mg, 0.7 mmol), bromobenzene (149 mg, 1.0 mmol), tetrakis(triphenylphosphino) palladium (38 mg) and Na_2CO_3 (1M, 2.0 mL); reaction time 68h; eluent, Petroleum Ether (40-60): EtOAc (9:1 v/v) gave **139** as a yellow oil (79 mg, 65%); ^1H NMR (400 MHz, acetone- d_6) δ 8.44 (1H, d, $J = 2.2$ Hz), 7.94 (1H, dd, $J = 2.8$ Hz, $J = 2.8$ Hz), 7.64-7.61 (2H, m), 7.48-7.44 (2H, m), 7.38-7.34 (1H, m), 3.93 (3H, OCH₃, s); ^{13}C NMR (100 MHz, acetone- d_6) δ 163.86, 145.10, 137.99, 137.59, 130.10, 129.22(2C), 127.50, 126.70(2C), 110.86, 53.00; MS (EI) m/z 185 (M^+ , 100%). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{NO}$: C, 77.81%; H, 5.99%; N, 7.56%. Found: C, 77.53%; H, 6.00%; N, 7.54%.

2-Methoxy-5-(3,4,5-trifluoro-phenyl)-pyridine (140)

Conditions A: (100 mg, 0.7 mmol), 5-bromo-1,2,3-trifluorobenzene (177 mg, 0.8 mmol), tetrakis(triphenylphosphino) palladium (38 mg) and Na_2CO_3 (1M, 2.0 mL); reaction time 68 h; eluent, Petroleum Ether (40-60): EtOAc (9:1 v/v) gave **140** as a white solid (104 mg, 67%), mp $102\text{-}103^{\circ}\text{C}$; ^1H NMR (500 MHz, acetone- d_6) δ

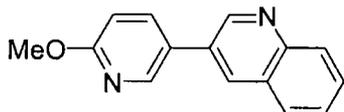
8.52 (1H, d, $J=2.5$ Hz), 8.04 (1H, dd, $J = 2.5$ Hz, $J = 2.5$ Hz), 7.56-7.53 (2H, m), 6.90 (1H, d, $J = 8.5$ Hz), 3.96 (3H, OCH₃, s); ¹³C NMR (125 MHz, acetone-d₆) δ 164.51, 152.53 ($J = 3.8$ Hz), 150.57 ($J = 5.0$ Hz), 145.51, 140.04 ($J = 15.1$ Hz), 138.06 ($J = 15.1$ Hz), 137.61, 134.93 ($J = 3.8$ Hz), 127.11 ($J = 1.4$ Hz), 111.06, 110.97 ($J = 17.3$ Hz), 53.18; MS (EI) m/z 239 (M⁺, 100%). Anal. Calcd for C₁₂H₈F₃NO: C, 60.26%; H, 3.37%; N, 5.86%. Found: C, 60.20%; H, 3.40%; N, 5.82%.

2-Methoxy-5-(3,4,5-trifluoro-phenyl)-pyridine (141)

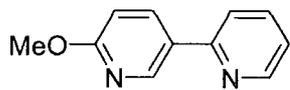


Conditions A: **123** (100 mg, 0.7 mmol), 1-bromo-4-trifluoromethoxy-benzene (195 mg, 0.8 mmol), tetrakis(triphenylphosphino) palladium (38 mg) and Na₂CO₃ (1M, 2.0 mL); reaction time 68 h; eluent, Petroleum Ether (40-60): EtOAc (9:1 v/v) gave **141** as a clear oil (84 mg, 48%); ¹H NMR (400 MHz, acetone-d₆) δ 8.46 (1H, d, $J=2.4$ Hz), 7.98 (1H, dd, $J=2.6$ Hz, $J= 2.6$ Hz), 7.78-7.75 (2H, m), 7.44-7.42 (2H, m), 6.87 (1H, d, $J=8.0$ Hz), 3.94 (3H, OCH₃, s); ¹³C NMR (100 MHz, acetone-d₆) δ 164.11, 148.64 ($J = 1.9$ Hz), 145.31, 137.65, 137.30, 128.69, 128.45(2C), 121.79(2C), 120.82 ($J = 255.4$ Hz), 110.97, 53.06; MS (EI) m/z 269 (M⁺, 100%). Anal. Calcd for C₁₃H₁₀F₃NO₂: C, 58.00%; H, 3.74%; N, 5.20%. Found: C, 58.19%; H, 3.78%; N, 5.28%.

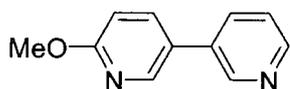
3-(6-Methoxypyridin-3-yl)-quinoline (142)



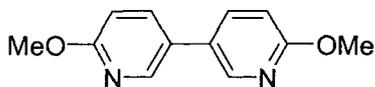
Conditions A: **123** (122 mg, 0.8 mmol), 3-bromoquinoline (307mg, 1.1 mmol), tetrakis(triphenylphosphino)palladium (56 mg), DMF and Na₂CO₃ (1 M, 2.5 mL); reaction time 70 h; eluent petroleum ether (bp 40-60 °C):EtOAc (3:7 v/v) gave **142** as a white solid (144 mg, 76%), mp 125-126 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.13 (1H, d, $J = 2.4$ Hz), 8.52 (1H, d, $J = 2.4$ Hz), 8.26 (1H, d, $J = 1.8$ Hz), 8.14 (1H, d, $J = 8.7$ Hz), 7.94-7.88 (2H, m), 7.76-7.71 (1H, m), 7.62-7.57 (1H, m), 4.02 (3H, OMe, s); ¹³C NMR (100 MHz, CDCl₃) δ 164.11, 149.32, 147.29, 145.43, 137.54, 132.70, 130.70, 129.51, 129.27, 127.95, 127.89, 127.19, 126.89, 111.37, 53.70; MS (EI) m/z 236 (M⁺, 100%). Anal. Calcd for C₁₅H₁₂N₂O: C, 76.25%; H, 5.12%; N, 11.86%. Found: C, 75.99%; H, 5.08%; N, 11.64%.

6'-Methoxy-[2,3']bipyridinyl (143)

Conditions A: **123** (50 mg, 0.3 mmol), 2-bromopyridine (163 mg, 1.0 mmol), tetrakis(triphenylphosphino)palladium (26 mg), DMF and Na₂CO₃ (1 M, 1.0 mL); reaction time 22 h; eluent petroleum ether (bp 40-60 °C):EtOAc (7:3 v/v) gave **143** as a dark red oil (28 mg, 50%). ¹H NMR (300 MHz, CDCl₃) δ 8.73 (1H, d, *J* = 2.4 Hz), 8.68-8.66 (1H, m), 8.24 (1H, dd, *J* = 2.6 Hz, *J* = 2.6 Hz), 7.78-7.72 (1H, m), 7.66 (1H, d, *J* = 7.8 Hz), 7.25-7.20 (1H, m), δ 6.84 (1H, d, *J* = 8.4 Hz), 3.99 (3H, OMe, s); ¹³C NMR (125 MHz, D₂O) δ 167.48, 157.45, 152.59, 148.43, 139.99, 131.33, 125.02(2C), 122.29, 113.35, 55.76; MS (EI) *m/z* 186 (M⁺, 100%). HRMS(EI) calcd for C₁₁H₁₀N₂O (M⁺) 186.0793, found 186.0795.

6-Methoxy-[3,3']-bipyridinyl (144)

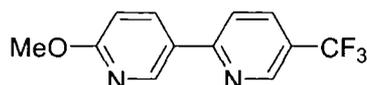
Conditions A: **123** (100 mg, 0.7 mmol), 3-bromopyridine (162 mg, 1.0 mmol), tetrakis(triphenylphosphino)palladium (56 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 48 h; eluent EtOAc gave **144** as a white solid (71 mg, 58%), mp 62-63 °C; ¹H NMR (300 MHz, acetone-d₆) δ 8.86 (1H, d, *J* = 2.4 Hz), 8.57 (1H, d, *J* = 4.8 Hz), 8.49 (1H, d, *J* = 2.4 Hz), 8.02 (1H, dd, *J* = 1.8 Hz, *J* = 1.8 Hz), 7.48-7.43 (1H, m), 6.90 (1H, d, *J* = 8.4 Hz), 3.95 (3H, OMe, s); ¹³C NMR (63 MHz, acetone-d₆) δ 165.23, 149.65, 148.76, 146.30, 138.62, 134.75, 134.44, 128.00, 124.83, 112.06, 54.00; MS (EI) *m/z* 186 (M⁺, 100%). Anal. Calcd for C₁₁H₁₀N₂O: C, 70.95%; H, 5.41%; N, 15.04%. Found: C, 70.52%; H, 5.32%; N, 15.05%.

6,6'-Dimethoxy-[3,3']bipyridinyl (145)

Conditions A: **123** (150 mg, 1.0 mmol), 5-bromo-2-methoxypyridine (145 mg, 0.8 mmol), tetrakis(triphenylphosphino) palladium (50 mg), DMF and Na₂CO₃ (1 M, 3.0 mL); reaction time 65 h; eluent , petroleum ether (bp 40-60 °C):EtOAc 4:1 v/v gave **145** as a white solid (138 mg, 83%), mp 104.5-106 °C (lit. mp 104-105 °C)²; ¹H NMR (300 MHz, CDCl₃) δ 8.33 (2H, d, *J* = 2.1 Hz), 7.72 (2H, dd, *J* =

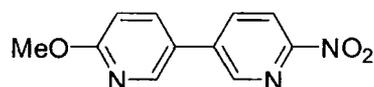
2.4 Hz, $J = 2.4$ Hz), 6.83 (2H, d, $J = 8.7$ Hz), 3.98 (6H, OMe, s); ^{13}C NMR (75 MHz, CDCl_3) δ 163.86(2C), 144.76(2C), 137.70(2C), 127.17(2C), 111.33(2C), 53.83(2C); MS (EI) m/z 216 (M^+ , 100%). Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$: C, 66.65%; H, 5.59%; N, 12.96%. Found: C, 66.42%; H, 5.62%; N, 12.97%.

6'-Methoxy-5-trifluoromethyl-[2,3']-bipyridinyl (146)

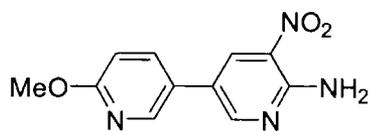


Conditions A: **123** (100 mg, 0.7 mmol), 2-bromo-5-(trifluoromethyl)pyridine (170 mg, 0.8 mmol), tetrakis(triphenylphosphino)palladium (38 mg), DMF and Na_2CO_3 (1 M, 2.0 mL); reaction time 70 h; eluent DCM:EtOAc (9:1 v/v) gave **146** as a yellow solid (53 mg, 32%), mp 78-80 °C; ^1H NMR (400 MHz, acetone- d_6) δ 8.98 (2H, dd, $J = 0.8$ Hz, $J = 0.8$ Hz), 8.47 (1H, dd, $J = 2.6$ Hz, $J = 2.6$ Hz), 8.23-8.15 (2H, m), 6.93 (1H, dd, $J = 0.8$ Hz, $J = 0.8$ Hz), 3.98 (3H, OMe, s); ^{13}C NMR (100 MHz, acetone- d_6) δ 165.56, 158.56, 146.59 ($J = 3.9$ Hz), 145.75, 137.74, 134.61 ($J = 3.5$ Hz), 134.54 ($J = 3.5$ Hz), 127.28, 124.37 ($J = 117.3$ Hz), 119.62, 111.04, 53.31; MS (EI) m/z 253 (M^+ , 100%). Anal. Calcd for $\text{C}_{12}\text{H}_9\text{F}_3\text{N}_2\text{O}$: C, 56.70%; H, 3.57%; N, 11.02%. Found: C, 56.78%; H, 3.61%; N, 10.72%.

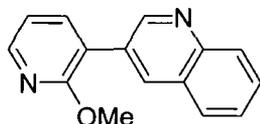
6-Methoxy-6'-nitro-[3,3']bipyridinyl (147)



Conditions A: **123** (100 mg, 0.7 mmol), 5-bromo-2-nitropyridine (140 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (30 mg), DMF and Na_2CO_3 (1 M, 2.0 mL); reaction time 65 h; eluent petroleum ether (bp 40-60 °C):EtOAc (3:2 v/v) gave **147** as a yellow solid (150 mg, 66%), mp 191-192 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.81 (1H, d, $J = 1.8$ Hz), 8.48 (1H, d, $J = 2.1$ Hz), 8.36 (1H, d, $J = 8.7$ Hz), δ 8.16 (1H, dd, $J = 2.3$ Hz, $J = 2.3$ Hz), 7.86 (1H, dd, $J = 2.6$ Hz, $J = 2.6$ Hz), 6.93 (1H, d, $J = 8.4$ Hz), 4.02 (3H, OMe, s); ^{13}C NMR (75 MHz, CDCl_3) δ 165.31, 156.35, 146.71, 146.08, 139.68, 137.50, 137.21, 124.60, 118.62, 112.13, 54.17; 53.83(2C); MS (EI) m/z 231 (M^+ , 100%). Anal. Calcd for $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_3$: C, 57.14%; H, 3.92%; N, 18.17%. Found: C, 56.94%; H, 3.97%; N, 17.92%.

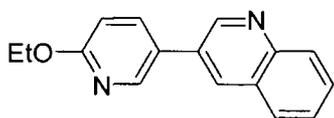
6'-Methoxy-5-nitro-[3,3']bipyridinyl-6-ylamine (148)

Conditions A: **123** (100 mg, 0.7 mmol), 2-amino-5-bromo-2-nitropyridine (109 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (38 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 69 h; eluent petroleum ether (bp 40-60 °C):EtOAc (2:3 v/v) gave **148** as an orange solid (55 mg, 45%), mp 230-231 °C; ¹H NMR (200 MHz, DMSO) δ 8.74 (1H, d, *J* = 2.0 Hz), 8.52 (2H, dd, *J* = 2.3 Hz, *J* = 2.3 Hz), 8.07-7.99 (3H, m), 6.88 (1H, d, *J* = 8.6 Hz), 3.86 (3H, OMe, s); ¹³C NMR (50 MHz, CDCl₃) δ 163.73, 154.88, 153.49, 144.93, 137.81, 132.19, 125.75, 122.57, 117.27, 111.36, 53.97; MS (EI) *m/z* 246 (M⁺, 100%). Anal. Calcd for C₁₁H₁₀N₄O₃: C, 53.66%; H, 4.09%; N, 22.75%. Found: C, 53.56%; H, 4.13%; N, 22.45%.

3-(2-Methoxy-pyridin-3-yl)-quinoline (149)

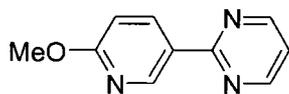
Conditions A: **131** (50 mg, 0.3 mmol), 3-bromoquinoline (107 mg, 0.5 mmol), tetrakis(triphenylphosphino)palladium (19 mg), DMF, Na₂CO₃ (1 M, 1.0 mL); reaction time 68 h; eluent petroleum ether (bp 40-60 °C):EtOAc (3:7 v/v) gave **149** as a white solid (47 mg, 61%). Conditions B: **131** (100 mg, 0.7 mmol), 3-bromoquinoline (153 mg, 0.7 mmol), Pd(PPh₃)₂Cl₂ (20 mg) and Cs₂CO₃ (1M, 2.0 mL); reaction time 95 h; eluent, EtOAc:DCM (1:1 v/v) gave **149** as a white solid (86 mg, 77%), mp 89-90 °C; ¹H NMR (400 MHz, acetone-d₆) δ 9.12 (1H, d, *J* = 2.0 Hz), 8.48 (1H, d, *J* = 2.0 Hz), 8.26 (1H, dd, *J* = 2.0 Hz, *J* = 2.0 Hz), 8.09-8.07 (1H, m), 8.02-7.99 (1H, m), 7.95 (1H, dd, *J* = 2.0 Hz, *J* = 2.0 Hz), 7.80-7.76 (1H, m), 7.66-7.61 (1H, m), 7.18-7.14 (1H, m), 3.98 (3H, OCH₃, s); ¹³C NMR (100 MHz, acetone-d₆) δ 161.21, 151.35 147.52, 147.03, 139.33, 135.42, 130.25, 129.64, 129.33, 128.44, 128.06, 127.00, 121.40, 117.77, 53.21; MS (EI) *m/z* 236 (M⁺, 100%). HRMS(EI) calcd for C₁₅H₁₂N₂O (M⁺) 236.0950, found 236.0950.

3-(6-Ethoxy-pyridin-3-yl)-quinoline (150)

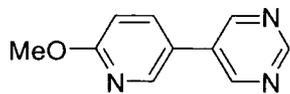


Conditions A: **124** (73 mg, 0.4 mmol), 3-bromoquinoline (153 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (35 mg) and Na_2CO_3 (1M, 1.3 mL); reaction time 63 h; eluent, DCM:EtOAc (9:1 v/v) gave **150** as a white solid (54 mg, 49%). Conditions B: **124** (12 mg, 0.07 mmol), 3-bromoquinoline (21 mg, 0.1 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (3 mg) and Cs_2CO_3 (1M, 0.25 mL); reaction time 63 h; eluent DCM:EtOAc (9:1 v/v) gave **150** as a white solid (10 mg, 59%), mp 104-105°C; ^1H NMR (250 MHz, acetone- d_6) δ 9.21 (1H, d, $J=2.5$ Hz), 8.63 (1H, d, $J=2.0$ Hz), 8.54 (1H, d, $J=2.0$ Hz), 8.16 (1H, dd, $J=2.7$ Hz, $J=2.7$ Hz), 8.10-8.00 (2H, m), 7.80-7.73 (1H, m), 7.67-7.60 (1H, m), 6.93 (1H, d, $J=8.0$ Hz), 4.43 (2H, q, $J=7.0$ Hz), 1.39 (3H, t, $J=7.0$ Hz); ^{13}C NMR (63 MHz, acetone- d_6) δ 164.95, 150.34, 148.58, 146.66, 138.81, 133.38, 131.82(2C), 130.36(2C), 129.30, 128.11, 127.87, 112.31, 62.62, 15.18; MS (EI) m/z 250 (M^+ , 55%). HRMS(EI) calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}$ (M^+) 250.1106, found 250.1106.

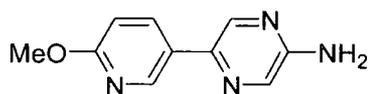
2-(6-Methoxy-pyridin-3-yl)-pyrimidine (151)



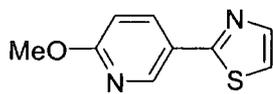
Conditions A: **123** (100 mg, 0.7 mmol), 2-bromopyrimidine (105 mg, 0.7 mmol), tetrakis(triphenylphosphino) palladium (56 mg), DMF and Na_2CO_3 (1 M, 2.0 mL); reaction time 70 h; eluent petroleum ether (bp 40-60 °C):EtOAc (3:2 v/v) gave **151** as a white solid (34 mg, 28%), mp 70-71 °C; ^1H NMR (400 MHz, acetone- d_6) δ 9.09 (1H, d, $J=2.4$ Hz), 8.72 (2H, d, $J=4.8$ Hz), 8.51 (1H, dd, $J=2.2$ Hz, $J=2.2$ Hz), 7.25 (1H, t, $J=5.2$ Hz), 6.77-6.75 (1H, m), 3.85 (3H, OMe, s); ^{13}C NMR (100 MHz, acetone- d_6) δ 166.22, 163.20, 158.02(2C), 148.12, 138.58, 127.55, 119.96, 110.91, 53.56; MS (EI) m/z 186 (M^+ , 100%). Anal. Calcd for $\text{C}_{10}\text{H}_9\text{N}_3\text{O}$: C, 64.16%; H, 4.85%; N, 22.45%. Found: C, 63.79%; H, 4.89%; N, 22.19%.

5-(6-Methoxy-pyridin-3-yl)-pyrimidine (152)

Conditions A: **123** (50 mg, 0.3 mmol), 5-bromopyrimidine (60 mg, 0.4 mmol), tetrakis(triphenylphosphine) palladium (26 mg), DMF and Na₂CO₃ (1 M, 1.0 mL); reaction time 70 h; eluent petroleum ether (bp 40-60 °C):EtOAc (1:9 v/v) gave **152** as a white solid (20 mg, 35%), mp 162-164 °C; ¹H NMR (300 MHz, acetone-d₆) δ 9.14 (1H, s), 9.07 (1H, s), 8.57 (1H, d, *J* = 1.8 Hz), 8.10 (1H, dd, *J* = 2.7 Hz, *J* = 2.7 Hz), 6.95 (1H, dd, *J* = 0.6 Hz, *J* = 0.6 Hz), 3.96 (3H, OMe, s); ¹³C NMR (75 MHz, acetone-d₆) δ 164.66, 157.53, 154.58(2C), 145.61, 137.66, 131.42, 123.77, 111.41, 53.22; MS (EI) *m/z* 187 (M⁺, 100%). HRMS(EI) calcd for C₁₀H₉N₃O (M⁺) 187.0746, found 187.0746.

5-(6-Methoxy-pyridin-3-yl)-pyrazine-2-ylamine (153)

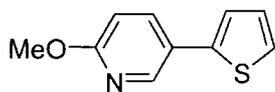
Conditions A: **123** (100 mg, 0.7 mmol), 2-bromo-5-aminopyrazine (63 mg, 0.5 mmol), tetrakis(triphenylphosphino)palladium (38 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 70 h; eluent EtOAc gave **153** as an off-white solid (33 mg, 26%), mp 164-165 °C (from toluene); ¹H NMR (300 MHz, acetone-d₆) δ 8.70 (1H, d, *J* = 2.4 Hz), 8.46 (1H, s), 8.20 (1H, dd, *J* = 2.7 Hz, *J* = 2.7 Hz), 8.05 (1H, s), 6.82 (1H, d, *J* = 8.4 Hz), 5.92 (2H, NH₂, br s), 3.92 (3H, OMe, s); ¹³C NMR (125 MHz, D₂O) δ 166.58, 163.20, 157.76, 146.52, 141.49, 141.17, 138.64, 134.48, 129.83, 113.32, 55.60; MS (EI) *m/z* 202 (M⁺, 100%). HRMS(EI) calcd for C₁₀H₁₀N₄O (M⁺) 202.0855, found 202.0857.

2-Methoxy-5-thiazol-2-yl-pyridine (154)

Conditions A: **123** (100 mg, 0.7 mmol), 2-bromothiazole (184 mg, 0.6 mmol), tetrakis(triphenylphosphino)palladium (38 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 70 h; eluent petroleum ether (bp 40-60 °C):EtOAc (7:3 v/v) gave **154** as an off-white solid (107 mg, 85%), mp 76-79 °C; ¹H NMR (300 MHz, acetone-d₆) δ 8.75 (1H, d, *J* = 2.1 Hz), 8.23 (1H, dd, *J* = 2.7 Hz, *J* = 2.7 Hz), 7.87 (1H, d, *J* = 3.0 Hz), 7.61 (1H, d, *J* = 3.0 Hz), 6.89 (1H, d, *J* = 8.7 Hz), 3.95 (3H, OMe, s); ¹³C NMR (63 MHz, acetone-d₆) δ 166.21,

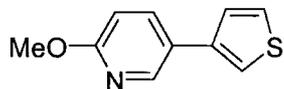
146.20, 144.88, 137.87, 124.95, 122.77, 120.14, 112.20, 54.26; MS (EI) m/z 192 (M^+ , 100%). Anal. Calcd for $C_9H_8N_2OS$: C, 56.23%; H, 4.19%; N, 14.57%. Found: C, 56.10%; H, 4.31%; N, 14.23%.

2-Methoxy-5-thien-2-yl-pyridine (155)

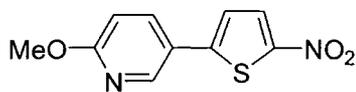


Conditions A: **123** (229 mg, 1.5 mmol), 2-bromothiophene (170 mg, 1.0 mmol), tetrakis(triphenylphosphino)palladium (30 mg), DMF and Na_2CO_3 (1 M, 4.5 mL); reaction time 65 h; eluent petroleum ether (bp 40-60 °C):EtOAc (9:1 v/v) gave **155** as a yellow oil (174 mg, 87%). 1H NMR (300 MHz, $CDCl_3$) δ 8.41 (1H, d, $J = 2.1$ Hz), 7.73 (1H, dd, $J = 2.6$ Hz, $J = 2.6$ Hz), 7.24 (1H, dd, $J = 0.7$ Hz, $J = 0.7$ Hz), 7.18 (1H, dd, $J = 0.6$ Hz, $J = 0.6$ Hz), 7.05-7.03 (1H, m), 6.74 (1H, dd, $J = 0.5$ Hz, $J = 0.5$ Hz), 3.95 (3H, OMe, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.75, 144.15, 140.97, 136.70, 128.30, 124.88, 124.31, 123.14, 111.17, 53.82; MS (EI) m/z 191 (M^+ , 100%). Anal. Calcd for $C_{10}H_9NOS$: C, 62.80%; H, 4.74%; N, 7.32%. Found: C, 62.54%; H, 4.77%; N, 7.33%.

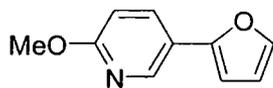
2-Methoxy-5-thien-3-yl-pyridine (156)



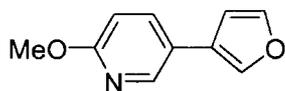
Conditions A: **123** (229 mg, 1.5 mmol), 2-bromothiophene (172 mg, 1.1 mmol), tetrakis(triphenylphosphino)palladium (30 mg), DMF and Na_2CO_3 (1 M, 4.5 mL); reaction time 65 h; eluent petroleum ether (bp 40-60 °C):EtOAc (9:1 v/v) gave **156** as a yellow solid (163 mg, 77%), mp 31-31 °C. 1H NMR (300 MHz, $CDCl_3$) δ 8.41 (1H, d, $J = 2.7$ Hz), 7.75 (1H, dd, $J = 2.7$ Hz, $J = 2.7$ Hz), 7.39-7.31 (3H, m), 6.77 (1H, d, $J = 8.4$ Hz), 3.97 (3H, OMe, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.51, 144.60, 139.08, 137.06, 126.90, 126.08, 125.47, 119.95, 111.10, 53.77; MS (EI) m/z 191 (M^+ , 100%). Anal. Calcd for $C_{10}H_9NOS$: C, 62.80%; H, 4.74%; N, 7.32%. Found: C, 62.75%; H, 4.77%; N, 7.34%.

2-Methoxy-5-(5-nitrothien-2-yl)-pyridine (157)

Conditions A: **123** (50 mg, 0.3 mmol), 2-bromo-5-nitrothiophene (115 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (37 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 63 h; eluent DCM:MeOH (99:1 v/v) gave **157** as a yellow solid (109 mg, 94%), mp 186-187 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.48 (1H, d, *J* = 2.1 Hz), 7.91 (1H, dd, *J* = 0.6 Hz, *J* = 0.6 Hz), 7.79 (1H, dd, *J* = 2.3 Hz, *J* = 2.3 Hz), 7.16 (1H, d, *J* = 4.2 Hz), 6.84 (1H, d, *J* = 8.7 Hz), 4.00 (3H, OMe, s); ¹³C NMR (125 MHz, CDCl₃) δ 165.34, 148.94, 145.12, 136.64, 130.01, 122.12, 111.98, 111.94, 54.21; MS (EI) *m/z* 236 (M⁺, 100%). Anal. Calcd for C₁₀H₈N₂O₃S: C, 50.84%; H, 3.41%; N, 11.86%. Found: C, 50.61%; H, 3.41%; N, 11.90%.

5-Furan-2-yl-methoxy-pyridine (158)

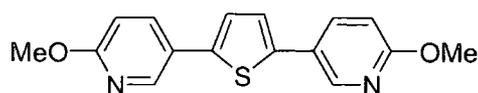
Conditions A: **123** (100 mg, 0.7 mmol), 2-bromofuran (83 mg, 0.6 mmol), tetrakis(triphenylphosphino)palladium (41 mg), DMF and Na₂CO₃ (2 M, 1.0 mL) reaction time 110 h; eluent, DCM gave **158** as a yellow oil (65 mg, 67%). Conditions B **123** (2.0 g, 13.1 mmol), 2-bromofuran (1.7 g, 11.2 mmol), Pd(PPh₃)₂Cl₂ (472 mg) and Cs₂CO₃ (1 M, 39 mL); reaction time 69 h; eluent, DCM gave **158** as a yellow oil (1.8 g, 91%); ¹H NMR (500 MHz, acetone-d₆) δ 8.53 (1H, d, *J* = 2.0 Hz), 7.99 (1H, dd, *J* = 2.5 Hz, *J* = 2.5 Hz), 7.64 (1H, m), 6.84 (1H, dd, *J* = 1.0 Hz, *J* = 1.0 Hz), 6.81 (1H, dd, *J* = 0.5 Hz, *J* = 0.5 Hz), 6.56-6.55 (1H, m), 3.92 (3H, OCH₃, s); ¹³C NMR (125 MHz, acetone-d₆) δ 163.59, 151.63, 142.63, 142.52, 134.66, 121.13, 111.94, 111.02, 104.94, 53.05; MS (EI) *m/z* 175 (M⁺, 100%). HRMS(EI) calcd for C₁₀H₉O₂N (M⁺) 175.0633, found 175.0634.

5-Furan-3-yl-methoxy-pyridine (159)

Conditions A: **123** (122 mg, 0.8 mmol), 3-bromofuran (82 mg, 0.6 mmol), tetrakis(triphenylphosphino)palladium (46 mg), 1,4-dioxane and Na₂CO₃ (2 M, 1.3 mL) reaction time 88 h; eluent, DCM gave **159** as a clear liquid (53 mg, 54%) which rapidly darkened in colour on storage; ¹H NMR (400 MHz, acetone-d₆) δ 8.01 (1H, d, *J* = 0.4 Hz), 7.89 (1H, dd, *J* =

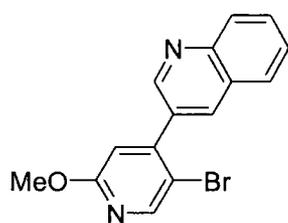
2.4 Hz, $J = 2.4$ Hz), 7.67-7.65 (1H, m), 6.89-6.88 (1H, m), 6.79 (1H, dd, $J = 0.4$ Hz, $J = 0.4$ Hz), 3.90 (3H, OCH₃, s); ¹³C NMR (500 MHz, acetone-d₆) δ 163.43, 144.50, 144.01, 138.73, 136.56, 126.70, 110.90, 108.59, 52.89; MS (EI) m/z 175 (M⁺, 100%).

2,5-Bis(2-methoxy-4-pyridyl)thiophene (160)

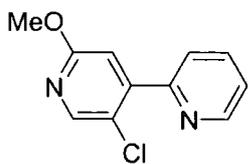


Conditions A: **123** (324 mg, 2.1 mmol), 2,5-dibromothiophene (215 mg, 0.5 mmol), tetrakis(triphenylphosphino) palladium (244 mg), DMF and Na₂CO₃ (1 M, 7.0 mL); reaction time 70 h; eluent DCM:EtOAc (9:1 v/v) gave **160** as a yellow solid (53 mg, 34%), mp 126-127 °C (from cyclohexane). ¹H NMR (200 MHz, acetone-d₆) δ 8.36 (2H, d, $J = 2.3$ Hz), 7.85 (2H, dd, $J = 3.3$ Hz, $J = 3.3$ Hz), 7.29 (2H, s), 6.72 (2H, d, $J = 10.8$ Hz), 3.80 (6H, OMe, s); ¹³C NMR (100 MHz, CDCl₃) δ 163.83(2C), 143.96(2C), 140.13(2C), 136.45(2C), 124.10(2C), 111.29(2C), 53.90(2C); MS (EI) m/z 298 (M⁺, 100%). Anal. Calcd for C₁₆H₁₄N₂O₂S: C, 64.41%; H, 4.73%; N, 9.39%. Found: C, 64.50%; H, 4.84%; N, 9.20%.

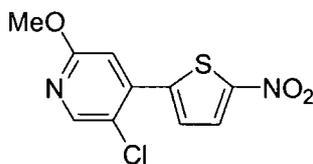
3-(5-Bromo-2-methoxy-pyridin-4-yl)-quinoline (161)



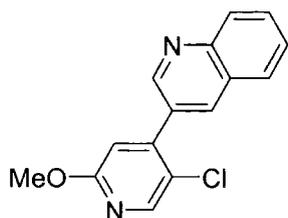
Conditions A: **134** (100 mg, 0.4 mmol), 3-bromoquinoline (123 mg, 0.6 mmol), tetrakis(triphenylphosphine)palladium (25 mg), DMF and Na₂CO₃ (1 M, 1.5 mL); reaction time 46 h; eluent DCM:EtOAc (8:2 v/v) gave **161** as a white solid (68 mg, 50%),
 Conditions B: **134** (100 mg, 0.4 mmol), 3-bromoquinoline (123 mg, 0.6 mmol) Pd(PPh₃)₂Cl₂ (16 mg) and Cs₂CO₃ (1 M, 1.2 mL); reaction time 98 h; eluent, DCM:EtOAc (9:1 v/v) gave **161** as a white solid (68 mg, 50%), mp 120-123 °C; ¹H NMR (400 MHz, acetone-d₆) δ 9.14 (1H, d, $J = 2.0$ Hz), 8.54 (1H, d, $J = 2.4$ Hz), 8.33 (1H, d, $J = 2.8$ Hz), 8.12 (1H, d, $J = 2.4$ Hz), 8.10-8.08 (1H, m), 8.04-8.01 (1H, m), 7.83-7.79 (1H, m), 7.67-7.63 (1H, m), 3.99 (3H, OCH₃, s); ¹³C NMR (125 MHz, acetone-d₆) δ 160.32, 151.04, 147.73, 147.17, 141.32, 135.92, 130.01, 129.35, 128.81, 128.57, 127.94, 127.15, 123.56, 112.09, 53.78; MS (EI) m/z 316 ([M+2]⁺, 98%), 314 (M⁺, 100%). HRMS(EI) calcd for C₁₅H₁₁BrN₂O (M⁺) 314.0055, found 314.0054.

5'-Chloro-2'-methoxy-[2,4']bipyridinyl (162)

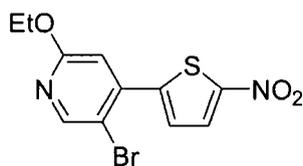
Conditions A: **137** (100 mg, 0.5 mmol), 2-bromopyridine (163 mg, 0.6 mmol), tetrakis(triphenylphosphine)palladium (31 mg), DMF and Na₂CO₃ (1 M, 1.5 mL); reaction time 65 h; eluent DCM:EtOAc (9:1 v/v) gave **162** as a white solid (41 mg, 35%), mp 76.5-78 °C; ¹H NMR (400 MHz, acetone-d₆) δ 8.58-8.56 (1H, m), 8.26 (1H, d, *J* = 2.4 Hz), 8.08 (1H, d, *J* = 2.4 Hz), 8.03-8.01 (1H, m), 7.76-7.71 (1H, m), 7.26-7.22 (1H, m), 3.90 (3H, OMe, s); ¹³C NMR (100 MHz, acetone-d₆) δ 159.90, 152.21, 149.90, 145.05, 138.70, 136.56, 124.63, 124.50, 123.97, 123.22, 53.72; MS (EI) *m/z* 222 ([*M*+2]⁺, 10%), 220 (*M*⁺, 30%). Anal. Calcd for C₁₁H₉ClN₂O: C, 59.88%; H, 4.11%; N, 12.70%. Found: C, 60.12%; H, 4.32%; N, 12.53%.

5-Chloro-2-methoxy-4-(5-nitrothien-2-yl)-pyridine (163)

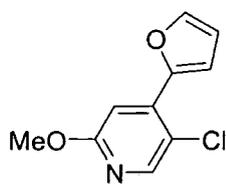
Conditions A: **137** (100 mg, 0.5 mmol), 2-bromo-5-nitrothiophene (129 mg, 0.6 mmol), tetrakis(triphenylphosphino)palladium (31 mg), DMF and Na₂CO₃ (1 M, 1.5 mL); reaction time 65 h; eluent DCM:petroleum ether (bp 40-60 °C) (9:1 v/v) gave **163** as a yellow solid (40 mg, 28%), mp 177-200 °C; ¹H NMR (400 MHz, acetone-d₆) δ 8.32 (1H, d, *J* = 2.4 Hz), 8.13 (1H, d, *J* = 2.4 Hz), 7.95 (1H, d, *J* = 4.4 Hz), 7.80 (1H, d, *J* = 4.4 Hz), 4.04 (3H, OMe, s); ¹³C NMR (125 MHz, acetone-d₆) δ 174.68, 158.08, 146.02, 142.76, 135.92, 128.85, 125.79, 124.83, 116.78, 54.30; MS (EI) *m/z* 272 ([*M*+2]⁺, 18%), 270 (*M*⁺, 40%). Anal. Calcd for C₁₀H₇ClN₂O₃S: C, 44.37%; H, 2.61%; N, 10.35%. Found: C, 43.88%; H, 2.63%; N, 9.91%.

3-(5-Chloro-2-methoxy-pyridin-4-yl)-quinoline (164)

Conditions B: **137** (100 mg, 0.5 mmol), 3-bromoquinoline (123 mg, 0.6 mmol), Pd(PPh₃)₂Cl₂ (20 mg) and Cs₂CO₃ (1 M, 1.6 mL); reaction time 98 h; eluent, DCM : EtOAc (9:1 v/v) gave **164** as a white solid (86 mg, 60%), mp 130-132 °C; ¹H NMR (400 MHz, acetone-d₆) δ 9.02 (1H, d, *J* = 2.0 Hz), 8.50 (1H, d, *J* = 2.0 Hz), 8.34 (1H, s), 8.10 (2H, dd, *J* = 8.2 Hz, *J* = 8.2 Hz), 7.88-7.84 (1H, m), 7.72-7.68 (1H, m), 7.05 (1H, s), 3.97 (3H, OCH₃, s); ¹³C NMR (100 MHz, acetone-d₆) δ 163.58, 150.17, 148.09, 147.41, 146.81, 136.25, 130.56, 130.09, 129.44, 128.72, 127.54, 127.48, 122.71, 112.90, 53.58; MS (EI) *m/z* 270 (M⁺, 100%). HRMS(EI) calcd for C₁₅H₁₁ClN₂O (M⁺) 270.0560, found 270.0559.

5-Bromo-2-ethoxy-4-(5-nitro-thiophen-2-yl)-pyridine (165)

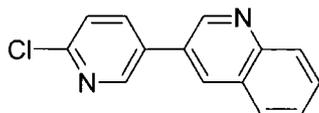
Conditions B: **138** (20mg, 0.08 mmol), 2-bromo-5-nitrothiophene (20 mg, 0.1 mmol), Pd(PPh₃)₂Cl₂ (3 mg) and Cs₂CO₃ (1 M, 0.25 mL); reaction time 59 h; eluent CH₂Cl₂ gave **165** as a yellow solid (11 mg, 45%), mp 84-86 °C; ¹H NMR (500 MHz, acetone-d₆) δ 8.32 (1H, s), 7.99 (1H, d, *J* = 4.0 Hz), 7.51 (1H, d, *J* = 4.5 Hz), 6.96 (1H, s), 4.25 (2H, q, *J* = 4.5 Hz), 1.24 (3H, t, *J* = 7.0 Hz); ¹³C NMR (125 MHz, acetone-d₆) δ 163.80, 152.95, 150.44, 145.21, 142.44, 129.32, 129.00, 112.96, 110.31, 62.57, 14.10; MS (EI) *m/z* 330 (M⁺, 50%). HRMS (EI) calcd for C₁₁H₉BrN₂O₃S (M⁺) 327.9517, found 327.9517.

5-Chloro-4-furan-2-yl-2-methoxy-pyridine (166)

Conditions B: **137** (100 mg, 0.5 mmol), 2-bromofuran (33 mg, 0.2 mmol), Pd(PPh₃)₂Cl₂ (46 mg) and Cs₂CO₃ (1 M, 1.6 mL); reaction time 42 h; eluent, DCM:Hexane (9:1 v/v) gave **166** as a yellow solid (14 mg, 30%), mp 56-58 °C; ¹H NMR (400 MHz, acetone-d₆) δ 8.09 (1H, d, *J* = 0.4 Hz), 7.69 (1H, dd, *J* = 0.8 Hz, *J* = 0.8 Hz), 7.31 (1H, dd, *J* = 0.4 Hz, *J* = 0.4 Hz), 7.04 (1H, d, *J* = 0.4 Hz), 6.58-6.56 (1H, m), 3.78 (3H, OCH₃, s); ¹³C NMR

(100 MHz, acetone- d_6) δ 163.68, 147.96, 147.72, 144.73, 137.74, 119.14, 114.37, 112.54, 106.96, 53.48; MS (EI) m/z 207 (M^+ , 100%).

3-(6-Chloro-pyridin-3-yl)-quinoline (167) ⁸

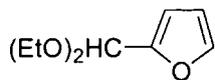


Phosphoryl chloride (345 mg, 2.3 mmol) was added dropwise to stirred solution of **142** (106 mg, 0.5 mmol) in dry DMF at 0 °C. The stirring was continued for 1 h then the mixture was heated at 110 °C for 19 h. It was cooled to 0 °C and was quenched with saturated sodium acetate solution (25 mL). The mixture was extracted with EtOAc (4x50 mL). The organic layer was then washed with water (3x100 mL) and was dried over MgSO₄. The residue was chromatographed through a silica gel column; eluent EtOAc:Petroleum Ether(40-60°C) (7:3 v/v) to give **167** as a white solid (49 mg, 44%), mp 180-181 °C (from MeOH); ¹H NMR (300 MHz, acetone- d_6) δ 9.13 (1H, d, $J = 2.4$ Hz), 8.77 (1H, d, $J = 2.1$ Hz), 8.55 (1H, d, $J = 1.8$ Hz), 8.20 (1H, dd, $J = 2.7$ Hz, $J = 2.7$ Hz), 7.99-7.92 (2H, m), 7.72-7.66 (1H, m), 7.60-7.50 (2H, m); ¹³C NMR (125 MHz, CDCl₃) δ 151.29, 148.88, 148.17, 147.48, 137.34, 133.71(2C), 132.60, 130.22, 129.38, 128.05, 127.68, 127.51, 124.59; MS (EI) m/z , 240 (M^+ , 100%). Anal. Calcd for C₁₄H₉ClN₂: C, 69.86%; H, 3.77%; N, 11.64%. Found: C, 69.40%; H, 3.80%; N, 11.53%.

5.5 Experimental Procedures of Chapter 4

General procedure for the synthesis of 183-185 (Procedure A)

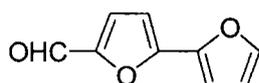
A solution of **182** in CH₃CN (5 mL) was added, while stirring, to a solution of the aldehyde in CH₃CN (5 mL). The reaction mixture was refluxed for 18 h. After the completion of the reaction (TLC), solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography to afford the desired product.

2-Diethoxymethylfuran (169)²

A mixture of **168** (18.6 g, 193.2 mmol), triethylorthoformate (35.6 g, 240.5 mmol) and a warm solution of ammonium nitrate in MeOH (1.0 g in 10 mL) was heated at 130 °C for 4 h. The crude mixture was filtered and sodium carbonate (1.0 g) was added to the filtrate. The filtrate was then fractionally distilled under reduced pressure to give **169** as a clear liquid (23.0 g, 70%). ¹H NMR (300 MHz, acetone-d₆) δ 7.53-7.51 (1H, m), 6.42-6.40 (2H, m), 5.52-5.41 (1H, m), 3.62-3.51 (4H, m), 1.21-1.13 (6H, m).

5-Formylfuran-2-boronic Acid (170)

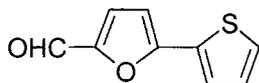
To a solution of **169** (1.0 g, 5.9 mmol) in anhydrous THF (20 mL) at -78 °C was added nBuLi (1.6 M in hexane, 2.2 mL, 3.5 mmol), dropwise. The reaction mixture was stirred for 5 h at -78 °C then TMB (8.15 mg, 9.6 mmol) was added dropwise and the reaction mixture was allowed to warm to 25 °C and stir overnight. Workup as described for **92**, with the addition of washing the precipitated product with ether (10 mL), gave **170** as a brown solid (428 mg, 52%), mp 150-151 °C; ¹H NMR (250 MHz, acetone-d₆) δ 9.70 (1H, s, CHO), 7.92 (2H, s, OH), 7.40 (1H, d, *J* = 3.5 Hz), 7.19 (1H, d, *J* = 3.5 Hz); ¹³C NMR (100 MHz, acetone-d₆) δ 178.44, 155.97, 122.79, 121.63. Anal. Calcd for C₅H₅BO₂: C, 42.93%; H, 3.60%. Found: C, 42.72%; H, 3.70%.

[2,2']Bifuranyl-5-carbaldehyde (171)

Conditions A: **170** (100 mg, 0.7 mmol), 2-bromofuran (99 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (41 mg), DMF and Na₂CO₃ (1 M, 1.1 mL); reaction time 109 h; eluent, DCM gave **171** as a yellow oil (37 mg, 34%). Conditions B: **170** (200 mg, 1.4 mmol), 2-bromofuran (165 mg, 1.4 mmol), Pd(PPh₃)₂Cl₂ (52 mg) and Cs₂CO₃ (1 M, 5.0 mL); reaction time 90 h; eluent, DCM gave **171** as a yellow oil (139 mg, 64%); ¹H NMR (500 MHz, acetone-d₆) δ 9.66 (1H, CHO, s), 7.78 (1H, dd, *J* = 0.5 Hz, *J* = 1.0 Hz), 7.54 (1H, d, *J* = 3.5 Hz), 7.00 (1H, d, *J* = 3.5 Hz), 6.91 (1H, d, *J* = 3.5 Hz), 6.69-6.68 (1H, d, *J* =

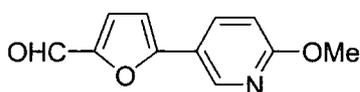
3.5 Hz); ^{13}C NMR (125 MHz, acetone- d_6) δ 177.02, 152.23, 150.89, 145.11, 144.82, 124.03, 112.42, 109.63, 107.73; MS (EI) m/z 162 (M^+ , 100%). HRMS(EI) calcd for $\text{C}_9\text{H}_6\text{O}_3$ (M^+) 162.0317, found 162.0319.

5-Thiophen-2-yl-furan-2-carbaldehyde (172)

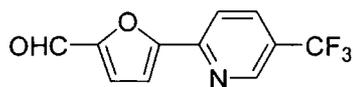


Conditions A: **170** (100 mg, 0.7 mmol), 2-bromothiophene (102 mg, 0.6 mmol), tetrakis(triphenylphosphino)palladium (41 mg), DMF and Na_2CO_3 (1 M, 1.1 mL); reaction time 126 h; eluent, DCM gave **172** as a yellow oil (34 mg, 30%). Conditions B: **170** (200 mg, 1.4 mmol), 2-bromothiophene (170 mg, 1.3 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (52 mg) and Cs_2CO_3 (1 M, 5.0 mL); reaction time 91 h; eluent, DCM gave **172** as a yellow oil (136 mg, 61%); ^1H NMR (500 MHz, acetone- d_6) δ 9.64 (1H, CHO, s), 7.68 (1H, dd, $J = 1.5$ Hz, $J = 1.5$ Hz), 7.66 (1H, dd, $J = 1.3$ Hz, $J = 1.3$ Hz), 7.53 (1H, d, $J = 3.5$ Hz), 7.23-7.21 (1H, m), 6.99 (1H, d, $J = 3.5$ Hz); ^{13}C NMR (125 MHz, acetone- d_6) δ 176.84, 154.57, 152.06, 131.83, 128.63, 128.14, 126.62, 124.46, 107.85; MS (EI) m/z 178 (M^+ , 100%). HRMS(EI) calcd for $\text{C}_9\text{H}_6\text{O}_2\text{S}$ (M^+) 178.0089, found 178.0089.

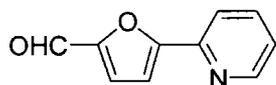
5-(6-Methoxy-pyridin-3-yl)-furan-2-carbaldehyde (173)



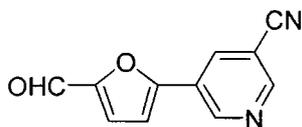
Conditions A: **170** (100 mg, 0.7 mmol), 5-bromo-2-methoxypyridine (116 mg, 0.6 mmol), tetrakis(triphenylphosphino)palladium (41 mg), DMF and Na_2CO_3 (2 M, 1.5 mL); reaction time 112 h; eluent, DCM:EtOAc (9:1 v/v) gave **173** as an orange needles (20 mg, 16%). Conditions B: **170** (200 mg, 1.4 mmol), 5-bromo-2-methoxypyridine (247 mg, 1.3 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (52 mg) and Cs_2CO_3 (1 M, 5.0 mL); reaction time 134 h; eluent, DCM:EtOAc (9:1 v/v) gave **173** as orange needles (137 mg, 52%), mp 121-123 °C (from cyclohexane); ^1H NMR (400 MHz, acetone- d_6) δ 9.66 (1H, CHO, s), 8.71 (1H, dd, $J = 0.8$ Hz, $J = 0.8$ Hz), 8.14 (1H, dd, $J = 2.4$ Hz, $J = 2.4$ Hz), 7.54 (1H, d, $J = 3.6$ Hz), 7.13 (1H, d, $J = 3.6$ Hz), 6.92 (1H, dd, $J = 0.8$ Hz, $J = 0.8$ Hz), 3.96 (3H, OCH_3 , s); ^{13}C NMR (100 MHz, acetone- d_6) δ 177.03, 164.88, 156.89, 152.59, 144.54, 135.74, 124.30, 119.51, 111.44, 107.68, 53.36; MS (EI) m/z 203 (M^+ , 100%). Anal. Calcd for $\text{C}_{11}\text{H}_9\text{NO}_3$: C, 65.02%; H, 4.46%; N, 6.89%. Found: C, 65.07%; H, 4.63%; N, 6.93%.

5-(5-Trifluoromethyl-pyridin-2-yl)-furan-2-carbaldehyde (174)

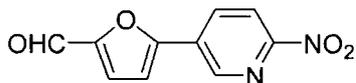
Conditions A: **170** (100 mg, 0.7 mmol), 2-bromo-5-(trifluoromethyl)pyridine (110 mg, 0.6 mmol), tetrakis(triphenylphosphino)palladium (41 mg), DMF and Na_2CO_3 (2 M, 1.5 mL); reaction time 134 h; eluent, DCM:EtOAc (9:1 v/v) gave **174** as an orange needles (37 mg, 24%). Conditions B: **170** (239 mg, 1.7 mmol), 2-bromo-5-(trifluoromethyl)pyridine (354 mg, 2.0 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (62 mg) and Cs_2CO_3 (1 M, 5.0 mL); reaction time 111 h; eluent, DCM:EtOAc (9:1 v/v) gave **174** as orange needles (126 mg, 31%), mp 93-94 °C (from cyclohexane); ^1H NMR (300 MHz, acetone- d_6) δ 9.66 (1H, CHO, s), 8.87 (1H, s), 8.20 (1H, dd, $J = 2.4$ Hz, $J = 2.4$ Hz), 8.02 (1H, d, $J = 8.4$ Hz), 7.49 (1H, d, $J = 3.9$ Hz), 7.36 (1H, d, $J = 3.6$ Hz); ^{13}C NMR (125 MHz, acetone- d_6) δ 178.11, 156.56, 153.82, 151.30, 147.14, 135.06, 125.68 ($J = 32.9$ Hz), 123.29, 122.92, 119.76, 112.96; MS (EI) m/z 241 (M^+ , 100%). Anal. Calcd for $\text{C}_{11}\text{H}_6\text{F}_3\text{NO}_2$: C, 54.78%; H, 2.51%; N, 5.81%. Found: C, 54.67%; H, 2.48%; N, 5.81%.

5-Pyridin-2-yl-furan-2-carbaldehyde (175)

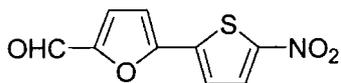
Conditions B: **170** (200 mg, 1.4 mmol), 2-bromopyridine (163 mg, 1.2 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (52 mg) and Cs_2CO_3 (1 M, 5.0 mL); reaction time 110 h; eluent, DCM:EtOAc (9:1 v/v) gave **175** as a yellow solid (121 mg, 57%), mp 88-90 °C; ^1H NMR (400 MHz, acetone- d_6) δ 9.73 (1H, CHO, s), 8.68-8.66 (1H, m), 7.98-7.92 (2H, m), 7.57 (1H, d, $J = 3.6$ Hz), 7.44-7.40 (1H, m), 7.32 (1H, d, $J = 3.6$ Hz); ^{13}C NMR (100 MHz, acetone- d_6) δ 177.79, 158.30, 153.16, 150.40, 148.08, 137.42, 124.21, 123.65, 119.86, 110.83; MS (EI) m/z 173 (M^+ , 100%). Anal. Calcd for $\text{C}_{10}\text{H}_7\text{NO}_2$: C, 69.36%; H, 4.07%; N, 8.09%. Found: C, 69.17%; H, 4.08%; N, 8.14%.

5-(5-Formyl-furan-2-yl)-nicotinonitrile (176)

Conditions B: **170** (200 mg, 1.4 mmol), 3-bromo-5-cyanopyridine (238mg, 1.3 mmol), Pd(PPh₃)₂Cl₂ (52 mg) and Cs₂CO₃ (1 M, 5.0 mL); reaction time 110 h; eluent, DCM:EtOAc (7:3 v/v) gave **176** as an orange solid (39 mg, 15%), mp 219-220 °C (from CH₃CN); ¹H NMR (400 MHz, DMSO) δ 9.67 (1H, CHO, s), 9.04 (1H, d, *J* = 2.0 Hz), 9.31 (1H, d, *J* = 2.0 Hz), 8.78 (1H, t, *J* = 2.0 Hz), 7.71 (1H, d, *J* = 3.6 Hz), 7.56 (1H, d, *J* = 3.6 Hz); ¹³C NMR (100 MHz, acetone-d₆) δ 177.33, 152.25, 151.48, 151.13, 147.89, 134.67, 123.82, 123.52, 115.31, 110.65, 108.52; MS (EI) *m/z* 198 (M⁺, 100%). Anal. Calcd for C₁₁H₆N₂O₂: C, 66.67%; H, 3.05%; N, 14.14%. Found: C, 66.40%; H, 3.08%; N, 14.19 %.

5-(6-Nitro-pyridin-3-yl)-furan-2-carbaldehyde (177)

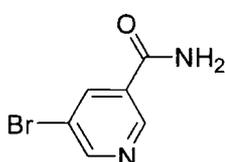
Conditions B: **170** (50 mg, 0.4 mmol), 5-bromo-2-nitropyridine (81 mg, 0.4 mmol), Pd(PPh₃)₂Cl₂ (13 mg) and Cs₂CO₃ (1 M, 1.0 mL); reaction time 48 h; eluent, DCM:EtOAc (9:1 v/v) gave **177** as an orange solid (35 mg, 44%), mp 162-164 °C; ¹H NMR (500 MHz, acetone-d₆) δ 9.83 (1H, CHO, s), 9.46 (1H, d, *J* = 3.0 Hz), 8.77 (1H, dd, *J* = 2.7 Hz, *J* = 2.7 Hz), 8.21 (1H, d, *J* = 8.5 Hz), 7.66 (1H, d, *J* = 4.0 Hz), 7.58 (1H, d, *J* = 4.0 Hz); ¹³C NMR (125 MHz, acetone-d₆) δ 178.38, 156.01, 154.22, 152.28, 145.76, 143.97, 133.08, 123.25, 120.04, 114.30; MS (EI) *m/z* 218 (M⁺, 100%). Anal. Calcd for C₁₀H₆N₂O₄: C, 55.05%; H, 2.77%; N, 12.84%. Found: C, 55.05%; H, 2.89%; N, 12.55%.

5-(5-Nitro-thiophen-2-yl)-furan-2-carbaldehyde (178)

Conditions B: **170** (50 mg, 0.4 mmol), 5-bromo-2-nitrothiophene (90 mg, 0.4 mmol), Pd(PPh₃)₂Cl₂ (13 mg) and Cs₂CO₃ (1 M, 1.0 mL); reaction time 41 h; eluent, DCM:Hexane (9:1 v/v) gave **178** as a yellow solid (43 mg, 54%), mp 150-152 °C; ¹H NMR (400 MHz, acetone-d₆) δ 9.73 (1H, CHO, s), 8.09 (1H, d, *J* = 4.4 Hz), 7.69 (1H, d, *J* = 4.4 Hz), 7.60 (1H, d, *J* = 4.0 Hz), 7.37 (1H, d, *J* = 3.6 Hz); ¹³C NMR (400 MHz,

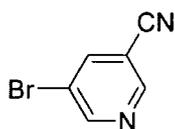
acetone- d_6) δ 177.71, 153.17, 151.46, 138.14(2C), 130.42, 125.45, 123.68, 111.98; MS (EI) m/z 223 (M^+ , 100%). Anal. Calcd for $C_9H_5NO_4S$: C, 48.43%; H, 2.26%; N, 6.28%. Found: C, 48.42%; H, 2.36%; N, 6.24 %.

5-Bromonicotinamide (180)



Ethyl-5-bromonicotinate (5.5 g, 24.0 mmol) was added to a concentrated ammonia solution (100 mL) and was stirred at 25 °C for 24 h. The solution was then evaporated to dryness and the crude product was recrystallised from EtOH to give **180** as a tan solid (4.1 g, 85%), mp 222-223 °C (lit mp^a = 224 °C); ¹H NMR (200 MHz, DMSO- d_6) δ 8.97 (1H, d, J = 1.6 Hz), 8.83 (1H, d, J = 2.2 Hz), 8.41 (1H, t, J = 2.0 Hz), 8.22 (1H, br s), 7.73 (1H, br s); ¹³C NMR (100 MHz, DMSO- d_6) δ 165.63, 153.25, 147.96, 138.22, 131.98, 120.76. Anal. Calcd for $C_6H_5BrN_2O$: C, 35.85%; H, 2.51%; N, 13.94%. Found: C, 35.70%; H, 2.35%; N, 13.64%.

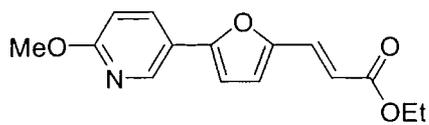
3-Bromo-5-cyanopyridine (181)



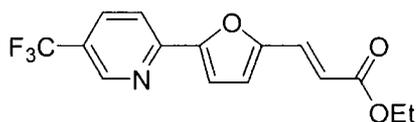
5-Bromonicotinamide (3.9 g, 19.3 mmol) and phosphorus pentoxide (7.7 g, 54.2 mmol) were added together and underwent a solid distillation. The distillate was then recrystallised from petroleum ether (40-60) to give **181** as white needles (883 mg, 25%), mp 104-106 °C (lit mp^b = 105-106 °C); ¹H NMR (200 MHz, $CDCl_3$) δ 8.83 (1H, d, J = 1.8 Hz), 8.75 (1H, d, J = 1.2 Hz), 8.05 (1H, t, J = 1.6 Hz); ¹³C NMR (100 MHz, $CDCl_3$) δ 154.75, 150.59, 141.60, 120.94, 115.31, 111.46; MS (EI) m/z 183 (M^+ , 100%). Anal. Calcd for $C_6H_3BrN_2$: C, 39.38%; H, 1.65%; N, 15.31%. Found: C, 39.37%; H, 1.62%; N, 15.25%.

^a Czuba. *Recueil* **1963**, 82, 988.

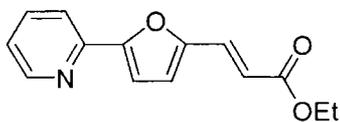
^b Zwart; Wilbaut. *Recueil* **1955**, 74, 1063.

3-[5-(6-Methoxy-pyridin-3-yl)-furan-2-yl]-acrylic acid ethyl ester (183)

Synthesised according to procedure A: **173** (50 mg, 0.3 mmol) and **182** (91 mg, 0.3 mmol). Eluent used, DCM:EtOAc (9:1 v/v) gave **183** as a yellow powder (56 mg, 82%), mp 88-89 °C; ¹H NMR (200 MHz, acetone-d₆) δ 8.68 (1H, d, *J* = 2.0 Hz), 8.13 (1H, dd, *J* = 2.4 Hz, *J* = 2.4 Hz), 7.48 (1H, d, *J* = 15.6 Hz), 7.00-6.95 (2H, m), 6.87 (1H, dd, *J* = 0.6 Hz, *J* = 0.6 Hz), 6.41 (1H, d, *J* = 15.8 Hz), 4.21 (2H, q, *J* = 7.2 Hz), 3.94 (3H, OCH₃, s), 1.29 (3H, t, *J* = 7.0 Hz); ¹³C NMR (100 MHz, acetone-d₆) δ 166.41, 164.21, 153.98, 150.58, 143.54, 135.14, 130.60, 120.19, 117.90, 115.30, 111.21, 107.76, 60.12, 53.21, 13.97; MS (EI) *m/z* 273 (M⁺, 100%). Anal. Calcd for C₁₅H₁₅NO₄: C, 65.92 %; H, 5.53%; N, 5.13%. Found: C, 65.83%; H, 5.59%; N, 5.11%.

3-[5-(5-Trifluoromethyl-pyridin-2-yl)-furan-2-yl]-acrylic acid ethyl ester (184)

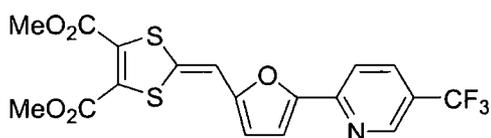
Synthesised according to procedure A: **174** (50 mg, 0.2 mmol) and **182** (77 mg, 0.2 mmol). Eluent used, DCM:EtOAc (9:1 v/v) gave **184** as a yellow powder (60 mg, 92%), mp 96-98 °C; ¹H NMR (400 MHz, acetone-d₆) δ 8.21 (1H, s), 7.53-7.44 (2H, m), 6.81 (1H, d, *J* = 16.0 Hz), 6.65 (1H, d, *J* = 3.6 Hz), 6.35 (1H, d, *J* = 3.6 Hz), 5.82 (1H, d, *J* = 15.6 Hz), 3.50 (2H, q, *J* = 7.2 Hz), 0.57 (3H, t, *J* = 6.8 Hz); ¹³C NMR (100 MHz, acetone-d₆) δ 166.10, 154.34, 152.72, 151.72, 146.96(2C), 134.73, 130.45, 122.80 (*J* = 33.0 Hz), 118.94, 117.66, 113.58, 110.00, 60.35, 13.93; MS (EI) *m/z* 311 (M⁺, 40%). Anal. Calcd for C₁₅H₁₂F₃NO₄: C, 57.88 %; H, 3.89%; N, 4.50%. Found: C, 57.76%; H, 3.99%; N, 4.45%.

3-(5-Pyridin-2-yl)-furan-2-yl]-acrylic acid ethyl ester (185)

Synthesised according to the procedure A: **175** (50 mg, 0.3 mmol) and **182** (101 mg, 0.3 mmol). Eluent used, DCM:EtOAc (7:3 v/v) gave **185** as a yellow powder (53 mg, 75%), mp 121-122 °C; ¹H NMR (400 MHz, acetone-d₆) δ 8.49-8.47 (1H, s), 7.84-7.73 (2H, m), 7.38 (1H, d, *J* = 16.0 Hz), 7.21-7.18 (1H, m), 7.08 (1H, d, *J* = 3.6 Hz), 6.90-6.88 (1H, m), 6.35 (1H, d, *J* = 15.2 Hz), 4.09 (2H, q, *J* = 7.2 Hz), 1.17 (3H, t, *J* =

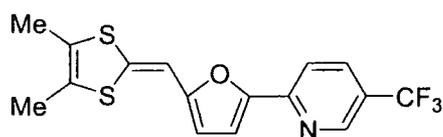
7.2 Hz); ^{13}C NMR (100 MHz, acetone- d_6) δ 166.25, 155.92, 151.53, 150.16, 148.62, 137.16, 130.69, 123.22, 119.14, 117.72, 116.39, 111.19, 60.22, 13.95; MS (EI) m/z 243 (M^+ , 52%). Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_3$: C, 69.12 %; H, 5.39%; N, 5.76%. Found: C, 68.89%; H, 5.51%; N, 5.71%.

2-[5-(5-Trifluoromethylpyridin-2-yl)-furan-2-yl methylene]-[1, 3]-dithiol-4, 5-dicarboxylic acid dimethyl ester (187)



To a solution of (4,5-Bis-methoxycarbonyl-[1,3]dithiol-2-yl) tributylphosphonium tetrafluoroborate (127 mg, 0.3 mmol) in THF (5 mL) at -78°C , $n\text{BuLi}$ (1.6 M in hexane, 0.2 mL, 0.3 mmol) was added dropwise. The mixture was stirred for ~ 10 mins. A solution of **174** (60 mg, 0.3 mmol) in THF (5 mL) was added to the mixture at -78°C . The mixture was allowed to warm to 25°C , and then the mixture was refluxed for 24 h. The THF was removed *in vacuo*. The remaining residue was dissolved in DCM (20 mL), which was washed with water (20 mL) and dry with MgSO_4 . The crude product was purified by silica gel column chromatography, eluent DCM:EtOAc (19:1 v/v) gave **187** as a red solid (56 mg, 51%), mp $135\text{--}138^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.80-8.79 (1H, m), 7.97 (1H, dd, $J = 2.4$ Hz, $J = 2.4$ Hz), 7.78 (1H, d, $J = 8.4$ Hz), 7.27 (1H, d, $J = 3.6$ Hz), 6.42 (1H, s), 6.33 (1H, d, $J = 4.0$ Hz), 3.91 (3H, s, OCH_3), 3.88 (3H, s, OCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 158.98, 158.77, 151.71, 150.65, 150.46, 145.68, 133.05, 130.74, 129.67, 122.78 ($J = 33.0$ Hz), 116.43, 112.42, 108.61(3C), 101.56, 52.48(2C); MS (EI) 443 (M^+ , 100%). HRMS(EI) calcd for $\text{C}_{18}\text{H}_{12}\text{F}_3\text{NO}_5\text{S}_2$ (M^+) 444.2175, found 443.4218.

2-[5-(4,5-Dimethyl-[1,3]-dithiol-2-ylidene)methyl-furan-2-yl]-5-trifluoromethylpyridine (189)



To a solution of (4,5-dimethyl-[1,3]dithiol-2-yl)-phosphonic acid dimethyl ester (100 mg, 0.3 mmol) in THF (5 mL) at -78°C , $n\text{BuLi}$ (1.6 M in hexane, 0.2 mL, 0.3 mmol) was added dropwise. The mixture was stirred for ~ 10 mins. A solution of **174** (60 mg, 0.3 mmol) in THF (5 mL) was added to the mixture at -78°C .

The mixture was allowed to warm to 25 °C, and then the mixture was refluxed for 24 h. The THF was removed *in vacuo*. The remaining residue was dissolved in DCM (20 mL), which was washed with water (20 mL) and dry with MgSO₄. The crude product was purified by silica gel column chromatography, eluent DCM:EtOAc (19:1 v/v) gave **189** as a yellow oil (12 mg, 11%). ¹H NMR (400 MHz, CDCl₃) δ 8.75 (1H, s), 7.86 (1H, d, *J* = 8.4 Hz), 7.70 (1H, d, *J* = 8.4 Hz), 7.07 (1H, d, *J* = 3.6 Hz), 6.36 (1H, d, *J* = 3.2 Hz), 4.72 (1H, t, *J* = 5.6 Hz), 1.86 (3H, s, CH₃), 1.32 (3H, s, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 154.82, 152.19, 150.88, 146.85, 137.24, 134.49, 134.46, 123.09 (*J* = 33.0 Hz), 123.01, 122.01, 117.26, 114.08, 108.07, 99.23, 12.84, 12.24; MS (EI) 355 (M⁺, 2%), 242 (M⁺, 100%). HRMS(EI) calcd for C₁₆H₁₂F₃NO₂S₂ (M⁺) 355.4024, found 355.4023.

