Functionalised Pyridyl- and Pyrimidyl- Boronic acids and derived new Biheteroaryls

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A Thesis Entitled

Functionalised Pyridyl- and Pyrimidyl- Boronic Acids and Derived New Biheteroaryls

Submitted by

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MEMORANDUM

The work presented within this thesis was carried out at the University of Durham between October 2002 and September 2005. The thesis is the work of the author, except where acknowledged by reference and has not been submitted for any other degree. The copyright of this thesis lies solely with the author and no quotation from it should be published without prior written consent and information derived from it should be acknowledged.

Part of this work has been the subject of the following publications:

- A. E. Thompson, G. Hughes, A. S. Batsanov, M. R. Bryce, P. R. Parry, and B. Tarbit; *J. Org. Chem.* **2005**, *70*, 388.
- A. E. Thompson, A. S. Batsanov, M. R. Bryce, N. Saygili, P. R. Parry, and B. Tarbit, *Tetrahedron*, **2005**, *61*, 5131.

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- Seal Sands Chemistry Day, Ramside Hall 2004
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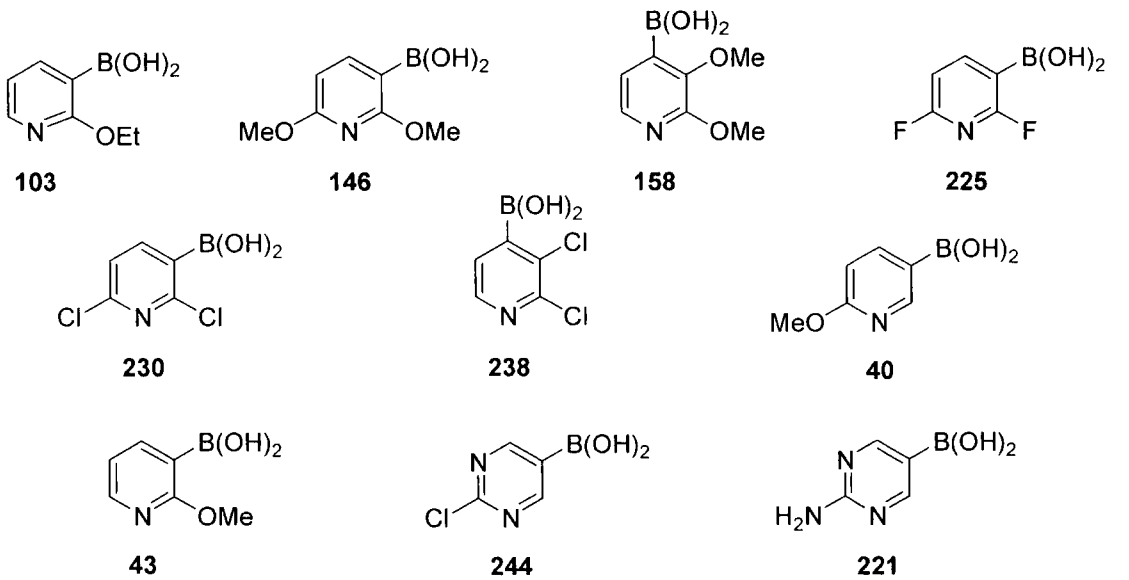
ABBREVIATIONS

DMF	Dimethylformamide
THF	Tetrahydrofuran
NMR	Nuclear Magnetic Resonance
TMEDA	*N,N,N',N'*-Tetramethyl-1,2-ethylenediamine
DMSO	Dimethylsulfoxide
HPLC	High Pressure Liquid Chromatography
nOe	nuclear Overhauser effect
DCM	Dichloromethane
DPA	Diisopropylamine
LDA	Lithium Diisopropylamide
TLC	Thin Layer Chromatography
dba	dibenzylideneacetone
dppf	diphenylphosphinoferrocene
Cy	cyclohexyl
TPB	Triisopropylborate
TMB	Trimethylborate
TBB	Tributylborate
n-BuLi	*n*-butyllithium
DoM	directed *ortho*-metallation
DMGs	directing metallating groups
LTMP	Lithium 2,2,6,6-tetramethylpiperidide
DME	dimethylether
ROESY	Rotating frame Overhauser Enhancement Spectroscopy
COSY	Correlation Spectroscopy

HSQC	Heteronuclear Single Quantum Coherence
HMBC	Heteronuclear Multiple Bond Correlation
EtOAc	Ethyl acetate

ABSTRACT

The novel substituted pyridylboronic acids 2-ethoxy-3-pyridylboronic acid **103**, 2,6-dimethoxy-3-pyridylboronic acid **146**, 2,3-dimethoxy-4-pyridylboronic acid **158**, 2,6-difluoro-3-pyridylboronic acid **225**, 2,6-dichloro-3-pyridylboronic acid **230** and 2,3-dichloro-4-pyridylboronic acid **238** have been synthesised, and the synthesis of existing alkoxy pyridylboronic acids 2-methoxy-5-pyridylboronic acid **40** and 2-methoxy-3-pyridylboronic acid **43** has been optimized and scaled up. The novel substituted pyrimidylboronic acids 2-chloro-5-pyrimidylboronic acid **244** and 2-amino-5-pyrimidylboronic acid **221** have been synthesised. All of the above mentioned boronic acids were shown to undergo palladium-catalysed Suzuki cross-coupling reactions with a variety of heteroaryl halides to yield novel heteroarylpyridine derivatives.



A range of halogenated aromatics and heteroaromatics bearing primary amine groups have been shown to be suitable substrates for Suzuki-Miyaura cross-coupling reactions with arylboronic acids and pyridylboronic acids under standard conditions, without the need for protection/deprotection steps. New amino-substituted arylpyridines, bipyridines, pyrazinopyridines, indolinopyridines, carbazolopyridines and indolopyridines have thereby been obtained. One derivative was further functionalised via diazotisation.

PAGE NUMBER

Chapter 1

Introduction

1.0 Introduction

Functionalised aryl and heteroaryl systems are important synthetic templates for industries such as agrochemicals, fine chemicals and pharmaceuticals. Small multi-substituted ring systems may be incorporated into larger systems by utilising substituted boronic acid moieties in Suzuki-Miyaura cross-coupling reactions. It is therefore imperative that newly functionalised boronic acid ring systems are developed. These systems must also cross-couple successfully with a range of halogenated partners in order to satisfy the need for building blocks for the next generation of industrial products.

In this first chapter the literature methods used to synthesise heteroaryl boronic acids are discussed in detail. In addition to this, the palladium catalysed Suzuki-Miyaura cross-coupling reactions of these boron containing species are also reviewed.

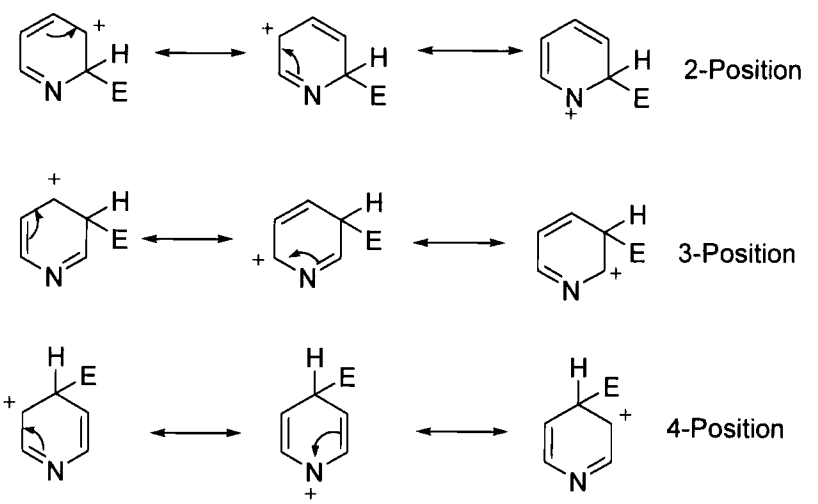
The following chapters encompass the syntheses of heteroaryl boronic acids containing alkoxy, amine and halogen substituents, respectively. Furthermore, the successful large-scale (*ca.* 100 g) syntheses of several alkoxy-substituted heteroaryl boronic acids are also reported. The later part of each chapter explores the Suzuki-Miyaura reactions of each novel class of boronic acids with various cross-coupling partners.

Chapter 3 examines in detail the Suzuki-Miyaura cross-coupling reactions of a range of heteroaryl and aryl halides bearing amine groups with a range of aryl and heteroaryl boronic acids.

1.1 Synthesis of Aryl and Heteroarylboronic Acids

The main method used in the syntheses of boronic acids is the reaction of an organometallic reagent with an electrophile, in this case a trialkylborate such as triisopropylborate (TPB).[1] This route is also useful for the syntheses of boronate esters.[2] The reaction of an organometallic reagent, such as *n*-butyllithium (*n*-BuLi) with an arylhalide forms the organolithium reagent.[3] The subsequent addition of an electrophilic borate species allows the formation of a carbon-boron bond. The boronic acid can then be generated by acidification of the reaction mixture. Pyridine undergoes

electrophilic substitution with difficulty for two reasons; pyridine and electrophiles tend to form pyridinium cations, thereby making electrophilic substitution at a carbon even more difficult[3], and secondly the electrophilic substitution of pyridine is a selective reaction[4] (Scheme 1.1a) which normally occurs at the C-3 position where the least destabilising intermediate is.[5]



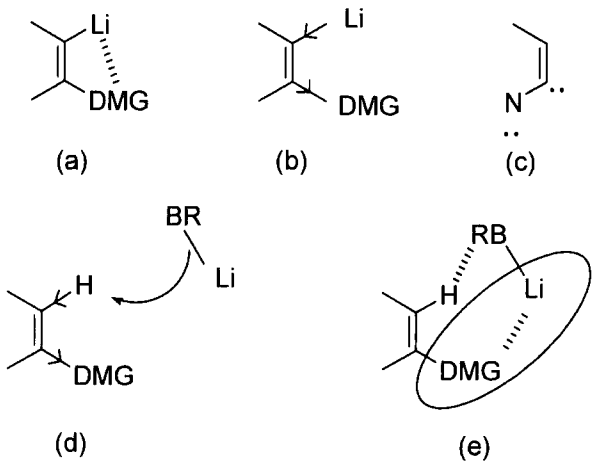
Scheme 1.1a: Electrophilic Substitution of Pyridine at the 2-, 3- and 4-positions.

The organometallic reagents used are either Grignard [6] or organolithium species[7]. Both reagents are formed by adding the corresponding alkyl- or arylhalide to the appropriate metal and they contain a metal-carbon bond which is highly polarised.

A Grignard reagent (R-Mg-X, where X is bromine, chlorine or iodine) is generated by the oxidative insertion, or addition, of magnesium into a carbon-halogen bond.[3] However, Grignard reagents react with water and oxygen, so they require anhydrous conditions and are in general neither isolated nor stored, but are generated and reacted *in situ*.[4] The magnesium atom acts as a Lewis acid due to its empty 3p orbital which accepts a lone pair of electrons from the solvent. The order of halide activity is I > Br > Cl, although aryl chlorides require the use of THF or another higher boiling solvent instead of the usual ether. Due to the poor reactivity of some organic halides, modifications such as the use of higher reaction temperatures, catalysts and activated magnesium have been used to form Grignard reagents.[8] Magnesium can be activated by a number of different methods. Iodine-activated magnesium turnings may

form magnesium iodide which is more soluble and reactive than magnesium alone. Entrainment is the use of catalytic amounts of a lower but more reactive alkyl halide, *e.g.* 1,2-dibromoethane, to initiate the Grignard reaction. Also using finely powdered magnesium with increased surface area facilitates the Grignard reagent formation.[8] Grignard reagents can also be generated by halogen-magnesium exchange, normally using iodopyridines which are expensive.[9] Using bromo- and chloropyridines is reported in magnesium exchange,[10-14] but an attempt by Cai *et al.* to synthesise 3-pyridylboronic acid using this method gave a poor yield of the desired product (36%).[15]

Lithium reagents are generated by either metal-hydrogen exchange or metal-halogen exchange. The former can be achieved using *n*-BuLi or lithium diisopropylamide (LDA). First deprotonation occurs, the ease of which depends upon the acidity of the hydrogen to be removed and the stability of the carbanion produced.[16] Electron-deficient six-membered aromatic heterocycles, such as pyridine, can be deprotonated with lithium amides where as alkyllithiums prefer addition to the electron-deficient ring over deprotonation.[1] Metal-hydrogen exchange is facilitated by the presence of certain functional groups; this process is termed directed *ortho*-metallation (DoM). It is possible to achieve clean metallation with alkyllithiums for many directing metallating groups (DMGs) such as OR, NHCOR, CONHR, where the DMG cannot undergo halogen exchange. For substrates carrying substituents which can undergo halogen-metal exchange, such as I, Br, Cl, F, the harder and less basic LDA (pKa 35.7) and LTMP (lithium 2,2,6,6-tetramethylpiperidide, pKa 37.3) can usually be relied upon for deprotonation.[12] The regioselective DoM effect can be rationalised in terms of kinetic or thermodynamic control of the reaction. There are three main factors that affect DoM: the inductive electron-withdrawing effect of the DMG; the strength of coordination between the heteroatom containing the DMG and the metal, and the electronic repulsion between the carbanion and the lone pair of the nitrogen in the ring. When metal amides are used, the reaction is normally thermodynamically controlled (Scheme 1.1b). The DoM observed is a result of the stabilisation from the chelation of the metal with the DMG (a) and the inductive effect of the DMG (b) and the destabilisation by the repulsion between the carbanion and the lone pair on the nitrogen (c). As a result, the formation of the pyridine 3- and 4- carbanions is more favourable than the formation of the 2-carbanion.



Scheme 1.1b: DoM effects under thermodynamic control (a), (b), (c) and kinetic control (d) and (e).

When alkyllithiums are used at low temperatures the reaction normally proceeds under kinetic control, where the inductive mechanism (d) and chelation in the transition state (e) direct the reaction (Scheme 1.1b). The coordination of the DMG to the metal allows disaggregation of the metallating agent, reinforcing the electron-withdrawing effect of the DMG and increasing the proximity effect of the alkyllithium. The pyridyl nitrogen can promote deprotonation at C-2 *via* coordination with a base when a strong DMG is absent. In such cases it is important to use a chelating solvent, such as THF, to stop this occurring.

Due to the addition problems associated with the treatment of electron-deficient six-membered rings with alkyllithiums, the simplest way to produce pyridyllithium species is by halogen-lithium exchange. The disadvantage of this route is the greater expense of the starting halo-substituted ring systems. Metal-halogen exchange is normally achieved by using *n*-BuLi because the by-product *n*-butylbromide rarely interferes with subsequent steps in the reaction. Metal-halogen exchange is extremely exothermic, therefore, low temperature and slow rate of addition of *n*-BuLi are needed to avoid side-reactions occurring, such as deprotonation, addition of the substrate, elimination of lithium bromide, bromine migration ("dance") or even ring opening reactions.[14]

A different route is available to synthesise boronic esters, namely metal-catalysed borylation of alkenes, alkynes and organic electrophiles with diboron

compounds or pinacolborane.[17] This route has been investigated in the last few years and extended to cross-coupling reactions of borating agents, most commonly bis(pinacolato)diboron or pinacolborane,[18] with aryl and vinyl halides or triflates and allyl chlorides or acetates to yield aryl-, vinyl-, and allylboronates in high yields in the presence of a base and a palladium catalyst. This route has advantages over traditional methods, for example, the protection of functional groups sensitive to organometallic reagents is not required. Moreover, it is a one-step procedure for the synthesis of organoboronic esters from organic electrophiles. A weaker base, for example KOAc, is the most efficient for aryl iodides and bromides because stronger bases, such as K_3PO_4 and K_2CO_3, promote the further coupling of arylboronates with the haloarenes, resulting in a substantial amount of the symmetrical biaryl.[19] The boronic esters obtained can then be used in the same manner as other boronic esters and acids in Suzuki-Miyaura coupling reactions with halide compounds or they can be deprotected to produce the corresponding boronic acids.[17] For examples 2,4-dimethoxy-5-pyrimidylboronic acid was synthesised *via* cedranediolborane being cross-coupled with the corresponding aryl iodide and then a deprotection step.[20] 2-Pyridylboronic esters, known to be troublesome, have been generated by cross-coupling 2-bromopyridines with bis(pinacolato)diboron in the presence of a base and catalyst. Depending on the reaction conditions used, varying amounts of protodeboronated products were observed. It was stated that due to the instability of the esters, they were reacted *in situ* producing a nearly statistical mixture of homo- and cross-coupled products.[21]

Why make boronic acids?

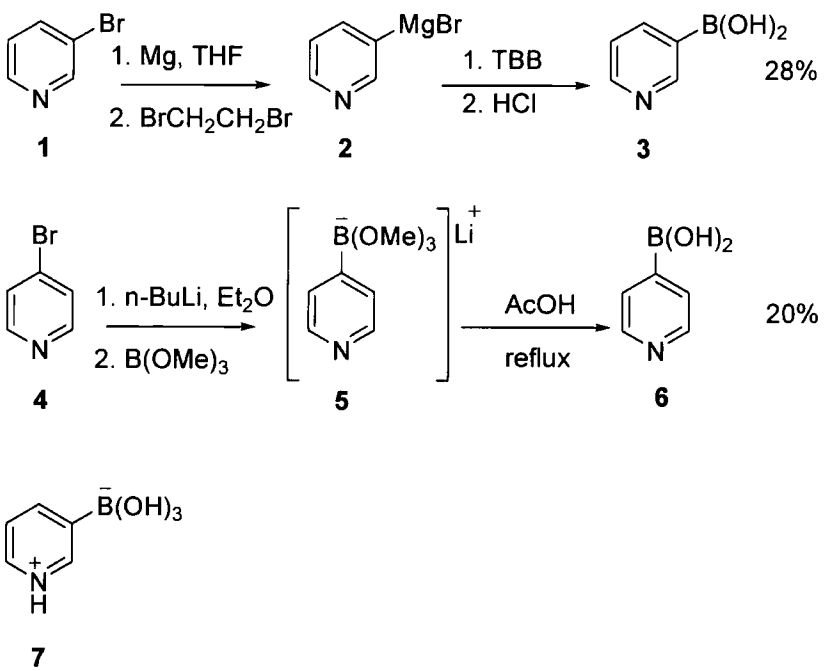
Many phenylboronic acids possessing functionality such as amino-, halo-, formyl-, cyano-, acetyl-, alkyl- and tri(alkylsilyl)-substituents are now commercially available. There are also a number of heterocyclic boronic acids available, the syntheses of some have been reported, but they do not possess such diverse functionalities. Heterocyclic boronic acids are valued for their important role in the syntheses of bi(hetero)aryls *via* Suzuki-Miyaura cross-coupling. Many natural products[22] and modern pharmaceuticals[23] contain at least one heterocycle and thus using boronic acids for the syntheses of novel analogues for high through-put screening has intensified. These biaryls also have applications in materials science[24] and

supramolecular chemistry.[24] An example is the synthesis of a modern pharmaceutical namely nemertelline,[25] the neurotoxin isolated from a Hoplonemertine sea worm. Suzuki-Miyaura cross-coupling reactions performed on halopyridylboronic acids provide an efficient two-step rapid synthesis of nemertelline, compared to the other routes, where a minimum of five steps are required.

Boronic acids have also recently been investigated for other uses, for example, fluorescent sensors containing boronic acid moieties have been synthesised for non-invasive and continuous glucose monitoring.[26]

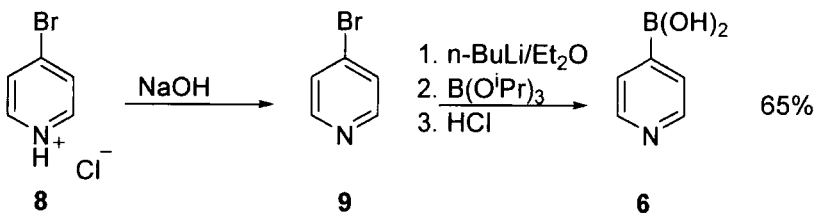
Pyridylboronic acids

Until 2002, there was only very limited literature on pyridylboronic acid syntheses with 3- and 4-pyridylboronic acids first reported in 1965.[6] 3-Pyridylboronic acid (**3**) was obtained in a 28% yield *via* a Grignard reaction, where as 4-pyridylboronic acid (**6**) was generated *via* the organolithium derivative in a 20% yield (Scheme 1.1c).



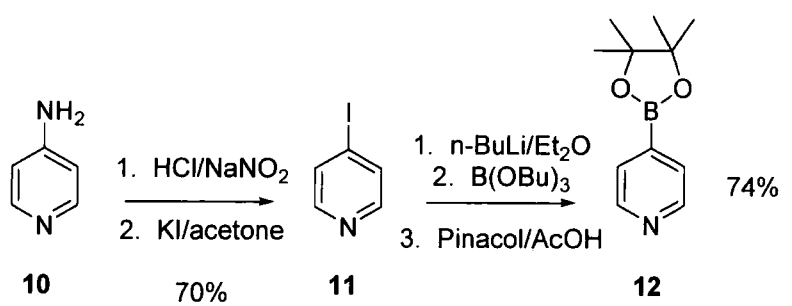
Scheme 1.1c: Syntheses of 3- and 4-Pyridylboronic acids.[6]

The low yields reflect the difficulty in isolating the products, which was suggested to be due to the amphoteric nature of 3-pyridylboronic acid at pH 7, where it could exist predominantly as the zwitterionic pyridinium boronate (**7**). The presence of the zwitterionic structure was not supported by any characterisation data.[2] The hydrophilic nature of both isomers **3** and **6**, was also stated to hinder their isolation from the aqueous phase. The isolated compounds were not fully characterised; only their nitrogen content was given as evidence of purity. The low yields, tedious work up and extreme reaction conditions needed, for the preparation makes this method unattractive for large-scale industrial use. More recently, new improved syntheses have been published. Halazy *et al.* synthesised 4-pyridylboronic acid (**6**) in 65% yield *via* halogen-lithium exchange from 4-bromopyridine (**9**) (Scheme 1.1d).[27]



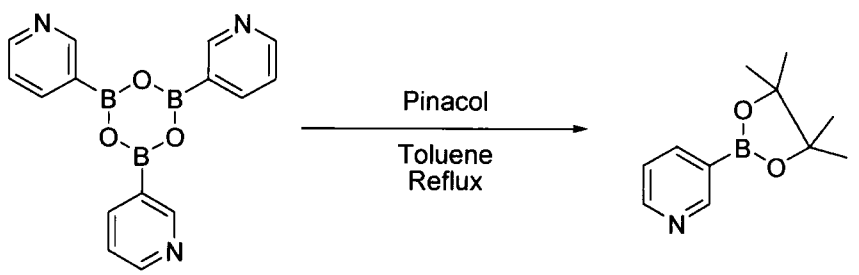
Scheme 1.1d: 4-Pyridylboronic acid synthesis.[27]

Coudret also developed a route to **6**, however, using 4-iodopyridine that was converted to the boronic acid and then immediately protected as the pinacol borate (**12**) (Scheme 1.1e).[28] The resulting 4-pyridylpinacolylboronic ester (**12**) was obtained in a 74% yield.



Scheme 1.1e: 4-Pyridylboronic acid synthesis.[28]

In 2002, Cai *et al.* published the use of a lithium-halogen exchange to produce 3-pyridyllithium from 3-bromopyridine.[15] The pyridyllithium species was then reacted with a variety of building blocks *in situ*, e.g. with TPB to give 3-pyridylboronic acid (**3**) in 87% yield. Cai *et al.* noted that the isolated product was a mixture of free boronic acid and anhydride (**13**) based on C, H, N analysis. Cai *et al.* then studied the order of addition of the various reagents[29] and stated that sequential addition produced poor yields (20-30%). A "reverse" addition procedure (3-bromopyridine added to *n*-BuLi followed by the addition of TPB) gave better yields but had to be carried out at low temperatures. However, in order to achieve consistent high yields an "*in situ*" procedure was required; the *n*-BuLi was added to a solution of 3-bromopyridine and TPB, followed by an aqueous work up. This approach is reported to be tolerant of temperature giving the best yields (90-95%) at – 40 °C and yielding 80% even at 0 °C. This procedure allowed the synthesis of 19.6 g of 3-pyridylboroxine (**13**), using the same lithium-halogen exchange to obtain the 3-pyridylboronic acid, and then a further cyclisation step. The characterisation of the anhydride (**13**) was difficult due to the presence of varying amounts of hydrates, so it was converted to the pinacol ester (**14**), in 81% yield, which was then fully characterised. Cai extended the *in situ* procedure to a number of other heterocyclic boronic acids including 5-pyrimidylboronic acid, 3-quinolylboronic acid and 3-thienylboronic acid.[29]



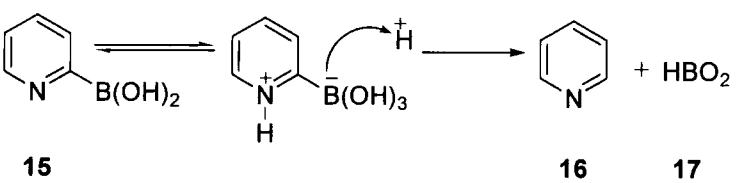
13 **14**

Scheme 1.1f: 3-Pyridylboroxin and pinacol ester synthesis of Cai *et al.*[29]

In 2005, Cai *et al.* published work on a kilogram scale utilising the same procedure,[30] and also coupled the boronic ester (**14**) with 3-bromoquinoline to obtain 3-pyridin-3-ylquinoline in 87% yield.

Dreos *et al.* published the synthesis of "almost pure" 4-pyridylboronic acid (**6**) *via* the previously described reverse addition procedure, although it was only in a 34% yield; full analysis of the compound was given.[31] It was claimed that lower yields were obtained when the reaction was carried out at – 60 °C due to nucleophilic additions to the 4-bromopyridine occurring competitively with the halogen metal exchange reaction and the low reactivity of 4-pyridyllithium towards trimethoxyborane. To overcome this problem the reaction was carried out at -110 °C and *N,N,N',N'*-tetramethyl-1,2-ethylenediamine (TMEDA) was added as an activating agent.

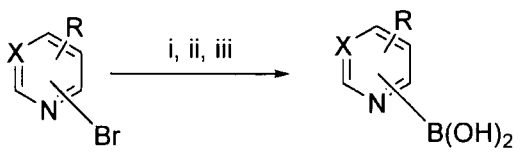
The salt of 2-pyridyllithium borate has been isolated as a stable compound,[32] but the synthesis of 2-pyridylboronic acid (**15**), until recently, has remained elusive.[33] The proposed reason behind the failure of this synthesis was that the pyridylboronic acid underwent protodeboronation.[34] It was observed by Fischer *et al.* that the 3- and 4-pyridylboronic acids, upon UV irradiation in neutral and slightly basic conditions, decompose to produce pyridine (**16**) and boric acid (**17**). The proposed deprotonation of the 2-pyridylboronic acid (**15**) is a S_e1 substitution reaction, which is known to occur with pyridine and pyridinium ions (Scheme 1.1g). It was also observed that although 3- and 4-pyridylboronic acids were thermally stable, they decomposed upon treatment with methyl iodide.[34]



Scheme 1.1g: Decomposition of 2-pyridylboronic acid.[34]

The first claim of the synthesis of 2-pyridylboronic acid was by Matondo *et al.* who in 2002 described the coupling of 2-pyridylboronic acid (**15**) with 2-bromopyridine, amongst couplings of other boronic acids.[35] The synthesis and characterisation of the coupling products were detailed but the synthesis of **15** was not. Matondo's subsequent work, described the synthesis of a new family of azaheteroarylboronic acids in good yields (62-75%) by transmetallation between Grignard azine reagents and *tris*-trimethylsilylborate.[36] This procedure gave the parent heterocyclic boronic acids such

as 2-pyridylboronic acid (**15**), 3-pyridylboronic acid (**3**), 5-pyrimidylboronic acid (**18**) and quinolinyl-3-boronic acid (**19**) and two substituted derivatives, namely 6-methyl- (**20**) and 6-bromo-2 pyridylboronic acid (**21**) (Scheme 1.1h). It is noteworthy that the work-up had to be carried out at no higher than 20 °C and at a pH between 6-7 or deboronation of the product occurred.

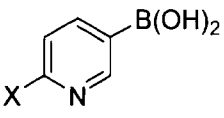


R = H,	X = CH,	2-$B(OH)_2$	**15**
R = H,	X = CH,	3-$B(OH)_2$	**3**
R = H,	X = N,	5-$B(OH)_2$	**18**
R = C_4H_4,	X = CH,	3-$B(OH)_2$	**19**
R = 6-Me,	X = CH,	2-$B(OH)_2$	**20**
R = 6-Br,	X = CH,	2-$B(OH)_2$	**21**

Scheme 1.1h: (i) ^{i}PrMgCl, 20 °C, 2 h; (ii) $[(CH_3)_3SiO]_3B$, 0 °C to RT, 24 h; (iii) HCl/H_2O(6<pH<7), 0 °C to RT.[36]

Matondo *et al.* also published the syntheses of the novel 3-alkoxy-2-pyridylboronic acids containing linear alkoxy or perfluoroalkoxy chains with *n* carbon atoms (*n* = 6,8,10,12 and 18). The yields ranged from 60 to 75% although it was stated that higher yields may have been obtained had it not been for difficulties with product extraction and purification.[37]

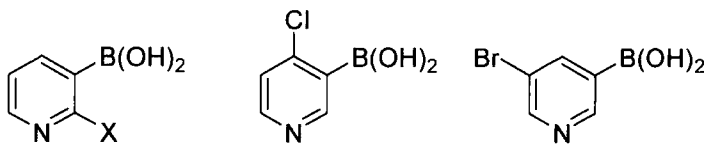
At the outset of the present work Rault *et al.* published the syntheses of a number of halopyridylboronic acids and esters.[33, 38-44] The 6-halo-3-pyridylboronic acids (Scheme 1.1i; compounds **22-24**) were prepared, on a multi-gram scale, using halogen-metal exchange from the corresponding 2,5-dihalopyridines. Bromine substituted pyridine starting materials gave much greater yields in metal-halogen exchange and subsequent boronic acid formation than the corresponding chloro-, fluoro- and iodo- derivatives. The synthesis of 6-iodo-3-pyridylboronic acid (**25**) was unsuccessful from both 5-bromo-2-iodopyridine and 2,5-diiodopyridine. The 2-substituted boronic acids were not obtained, even when using conditions that selectively lithiated in the 2-position.[45] It was suggested that this was due to the known instability of these compounds.[46] The boronic acids were coupled with sterically hindered, electron-rich, or electron-poor phenylhalides under standard Suzuki-Miyaura conditions, although only three examples were reported.



X = Br = 75% **22**
X = Cl = 87% **23**
X = F = 76% **24**
X = I = 0% **25**

Scheme 1.1i: 6-Halo-3-pyridylboronic acids.[41]

Rault *et al.* published the syntheses of 2-, 4- and 5-halo-3-pyridylboronic acids (compounds **26-30**) *via* halogen-metal exchange using *n*-BuLi or *via* directed *ortho*-lithiation (hydrogen-metal exchange) using LDA.[42] Five novel pyridylboronic acids were thereby obtained (Scheme 1.1j). The highest yields (compounds **26** and **27**) were achieved using halogen-metal exchange from the corresponding dihalopyridine. However, starting from 3-bromo-4-chloropyridine gave compound **29** in only 25% yield, compared to 43% when carrying out a directed *ortho*-lithiation on 4-chloropyridine. It was concluded that no one method gave higher yields for all compounds.



X = Br = 60% **26**
X = Cl = 66% **27**
X = F = 63% **28**

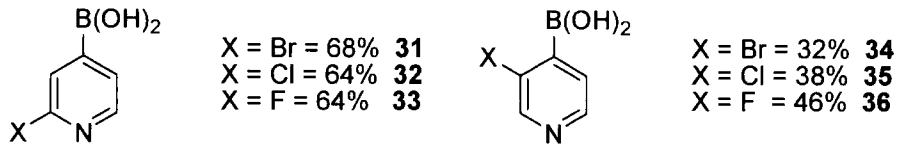
43%
29

71%
30

Scheme 1.1j: 2-, 4-, and 5-Halo-3-pyridylboronic acids.[42]

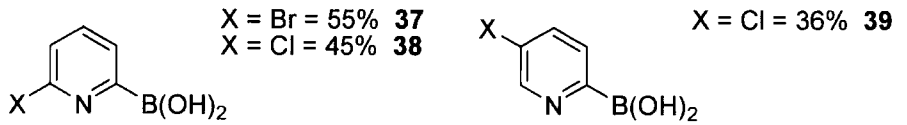
The boronic acids were also coupled with sterically hindered, electron-rich, or electron-poor phenylhalides under standard Suzuki-Miyaura conditions, again only three examples of these were reported.

Rault *et al.* published the synthesis of 2- and 3-halo-4-pyridylboronic acids (compounds **31-36**).[43] The 2-halo-4-pyridylboronic acids were synthesised *via* a halogen-metal exchange, using *n*-BuLi, in good yields. However, the 3-halo-4-pyridylboronic acids were produced *via* directed *ortho*-metallation in lower yields. Two cross-coupling examples were reported on this occasion.



Scheme 1.1k: 2- and 3-Halo-4-pyridylboronic acids.[43]

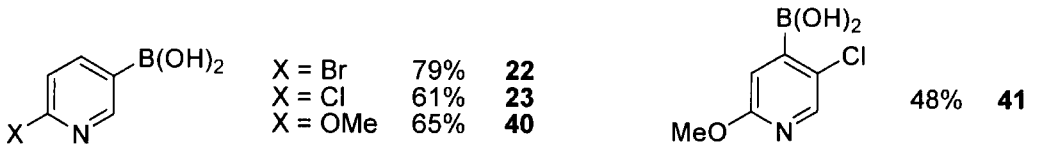
The second report of a 2-pyridylboronic acid synthesis by Rault *et al.* (Scheme 1.1l)[33] comprised the synthesis, purification, some X-ray crystallographic data and the reactivity of the new 5- and 6-halo-2-pyridylboronic acids. No difficulties in the syntheses of these compounds were noted and it was claimed that they were stable to storage at < 5 °C. The only stated problem was in the synthesis of 5-bromo-2-pyridylboronic acid. 2,5-Dibromopyridine could not be selectively lithiated at the 2-position, and all attempted reactions resulted in 6-bromo-3-pyridylboronic acid. Almost full characterisation was given for compounds **37** to **39** (no ^{13}C NMR), but an X-ray crystal structure of the corresponding pinacol ester of compound **37** was conclusive proof that the compound had been obtained.[38]



Scheme 1.1l: 2- and 3-Halo-6-pyridylboronic acids.[33]

Compounds **37** and **39** were coupled under standard Suzuki-Miyaura conditions in moderate yield with two substituted iodobenzenes and bromobenzene. Interestingly, compound **37** did not react as both the boronic acid and the halide, and only the desired monocoupled product was isolated.

Earlier work in our laboratory established routes to novel pyridylboronic acids with halo and/or methoxy functionality which was supported by the first X-ray crystal structures of pyridylboronic acid derivatives.[7] 2-Bromo-5-pyridylboronic acid (**22**), 2-chloro-5-pyridylboronic acid (**23**), 2-methoxy-5-pyridylboronic acid (**40**) and 5-chloro-2-methoxy-4-pyridylboronic acid (**41**) were synthesised *via* halogen-metal exchange using *n*-BuLi (Scheme 1.1m).



Scheme 1.1m: Pyridylboronic acid derivatives.[7]

The X-ray crystal structures of **22** and **23** (**22** is shown in Figure 1.1a) confirm the presence of the free boronic acid which is extensively hydrogen bonded. The boronic acids were cross-coupled under Suzuki-Miyaura conditions with a wide range of heteroaryl bromides, including quinolines, pyridines, pyrimidines, pyrazines and thiazoles to produce a new biheteroaryl library containing 21 compounds.

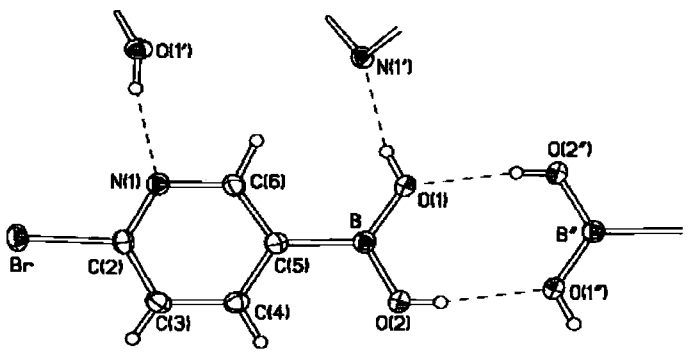
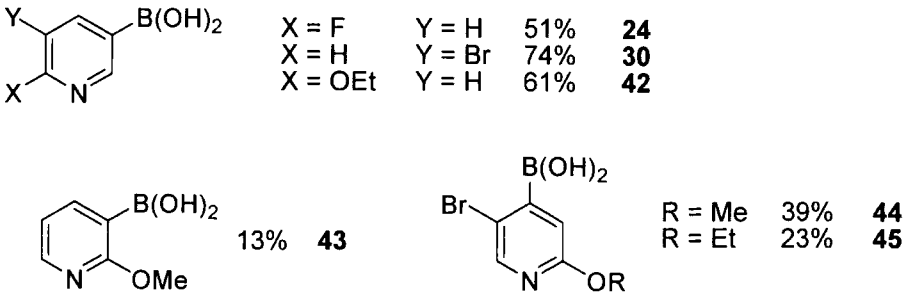


Figure 1.1a: X-Ray structure of 2-bromo-5-pyridylboronic acid (**22**), at 120 K. Dashed lines are hydrogen bonds.

Contrary to the couplings carried out by Rault, in our laboratory, coupling of compound **22** consistently gave multicomponent product mixtures (TLC evidence) from which only low yields (10 – 32%) of bi(heteroaryl) products were isolated. Further details of these Suzuki-Miyaura couplings will be discussed in part 2 of this introduction (1.2).

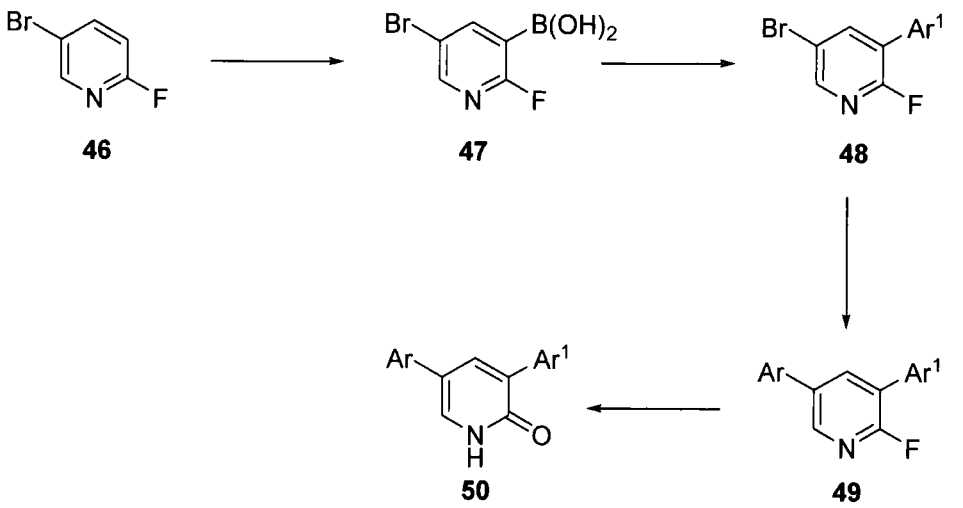
Bryce *et al.* published more halo- and alkoxy- substituted pyridylboronic acids in 2003 (Scheme 1.1n).[47] 2-Fluoro-5-pyridylboronic acid (**24**), 3-bromo-5-pyridylboronic acid (**30**) and 2-ethoxy-5-pyridylboronic acid (**42**) were synthesised using metal-halogen exchange followed by reaction with TPB. 2-Methoxy-3-pyridylboronic acid (**43**), 3-bromo-6-methoxy-4-pyridylboronic acid (**44**) and 3-bromo-6-ethoxy-4-pyridylboronic acid (**45**) were synthesised using metal-hydrogen exchange.[47]



Scheme 1.1n: Pyridylboronic acids.[47]

Each boronic acid was coupled with 3-bromoquinoline, to confirm their suitability as a cross-coupling partner for Suzuki-Miyaura reactions, to afford the corresponding pyridylquinoline products. Derivative **30** coupled in a very low yield (8%) and this was due to the formation of numerous other products (TLC evidence) that probably arose from further couplings of the reactive bromine substituent on **30**. It is noteworthy that no such further couplings were observed with **44** and **45**, presumably due to the steric effect of the heterocyclic substituent adjacent to the bromine.

The synthesis of 5-bromo-2-fluoro-3-pyridylboronic acid (**47**) in 80 %, was published by Gallagher *et al.* in 2002,[48] by directed *ortho*-lithiation of 5-bromo-2-fluoropyridine (**46**) followed by reaction with trimethylborate. The Suzuki-Miyaura reactions of **47** with a range of aryl iodides gave 3-monosubstituted 5-bromo-2-fluoropyridines (**48**) in excellent yields. Suzuki-Miyaura cross-coupling reactions of **47** with aryl bromides were unsuccessful. Gallagher *et al.* then carried out a second Suzuki-Miyaura cross-coupling reaction utilising the bromo substituent on **48** with aryl and heteroaryl boronic acids to generate 3,5-disubstituted 2-fluoropyridines (**49**), which in turn were converted to the corresponding pyridones (**50**) (Scheme 1.1o).



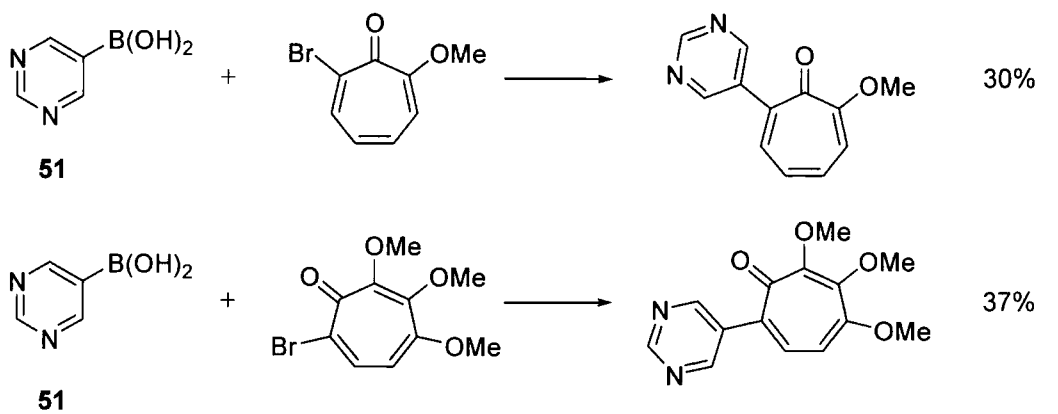
Scheme 1.1o: Pyridone synthesis.[48]

Pyridylboronic acids are occasionally mentioned in other literature,[49] for example, Peukert *et al.* detailed the Suzuki coupling of 3-*tert*-butyl ethylcarbamate-4-pyridylboronic acid and 1-(2-bromophenyl)-2-methoxyethanone as one step in a multi-stage synthesis of a pharmaceutical. The synthesis and isolation of the product was detailed, however, no characterisation data were given and it was stated to have been used in its crude form with no purification.

Pyrimidylboronic acids

Substituted pyrimidylboronic acids were first isolated by Liao *et al.* during the syntheses of anti-tumour reagents, by lithiating pyrimidyl ethers and reacting *in situ* with trimethylborate or tributylborate.[50] Some of the resulting boronic acids were unstable and thus converted to 5-uracilboronic acid by a catalytic hydrogenation process. Attempted couplings between halogenated uracil and appropriate boronic acids, in the hope of achieving nucleoside syntheses, were unsuccessful. The pyrimidylboronic acids did couple with π-electron deficient heterocyclic halides in good yields. The parent pyrimidin-5-ylboronic acid (**51**) was first synthesised in 1986 by Gronowitz *et al.* in a 52% yield *via* halogen-lithium exchange and then an *in situ* quench using tributylborate (TBB).[51] Full characterisation of **51** was given. In 1997, in

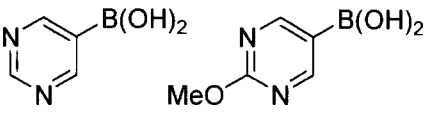
a study into the synthesis of novel potent inositol monophosphate inhibitors, **51** was coupled to a number of tropolone derivatives in modest yields (Scheme 1.1p).



Scheme 1.1p: Couplings of boronic acids with tropolone derivatives.[51]

Matondo *et al.* published the detailed synthesis of **51** in 72% yield by a trans-metallation between Grignard azine reagent and *tris*-trimethylsilylborate, followed by an aqueous work up. [36] Cai also obtained **51**, stating that the order of addition of reagents was crucial.[29] In their hands, a sequential addition procedure yielded the product in only 28% yield, whereas an "*in situ* quench" (the borate being present during the halogen-lithium exchange) gave **51** in a much higher yield of 76%.

In our laboratory in 2004, the detailed synthesis of **51** was investigated. In our hands both literature routes gave an impure product (by ^{1}H NMR) in low yields (< 30%). A modified synthesis (still using an "*in situ* quench") reproducibly and cleanly gave **51** in 1 – 10 g batches. The route was extended to the synthesis of 2-methoxy-5-pyrimidylboronic acid (**52**).[52] Compound **51,** obtained by this route, was isolated as an air-stable hemi-hydrate as confirmed by its X-ray crystal structure. Both **51** and **52** were coupled under Suzuki-Miyaura conditions to produce a range of biheteroaryls and, in one example, a two fold reaction gave 4,6-di(pyrimidin-5-yl)pyrimidine. Yields were low when coupling 2-bromopyrimidine with **51** and **52** (9 and 4%, respectively) and **51** with 3-bromoquinoline (18%). Using 2-chloropyrimidine instead of 2-bromopyrimidine increased the yields to 34% and 50%, respectively.



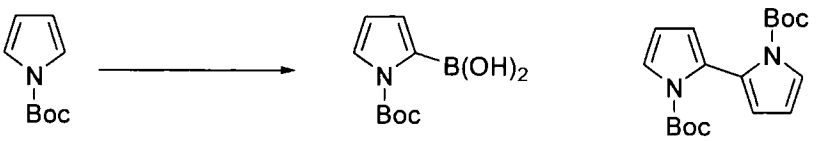
51 **52**

Scheme 1.1q: Pyrimidylboronic acids.[52]

Other Nitrogen-Containing Heterocyclic Boronic Acids

Pyrrole

In 1991, the first report of a pyrrolylboronic acid appeared,[53] namely 2-pyrrolylboronic acid by Schluter *et al.* Pyrrole could be lithiated directly or could undergo metal-halogen exchange, when the nitrogen atom was protected by *tert*-butoxycarbonyl (Boc), triisopropylsilyl (TIPS) or phenylsulphonyl groups. Schluter *et al.* used *tert*-butoxycarbonyl in their synthesis of *N*-(Boc)-2-pyrrolylboronic acid (**53**) in 40% yield. Unfortunately, **53** could not be used in any Suzuki-Miyaura cross-coupling reactions as it was susceptible to deboronation, and homocoupling to give product (**54**) when heated (Scheme 1.1r).

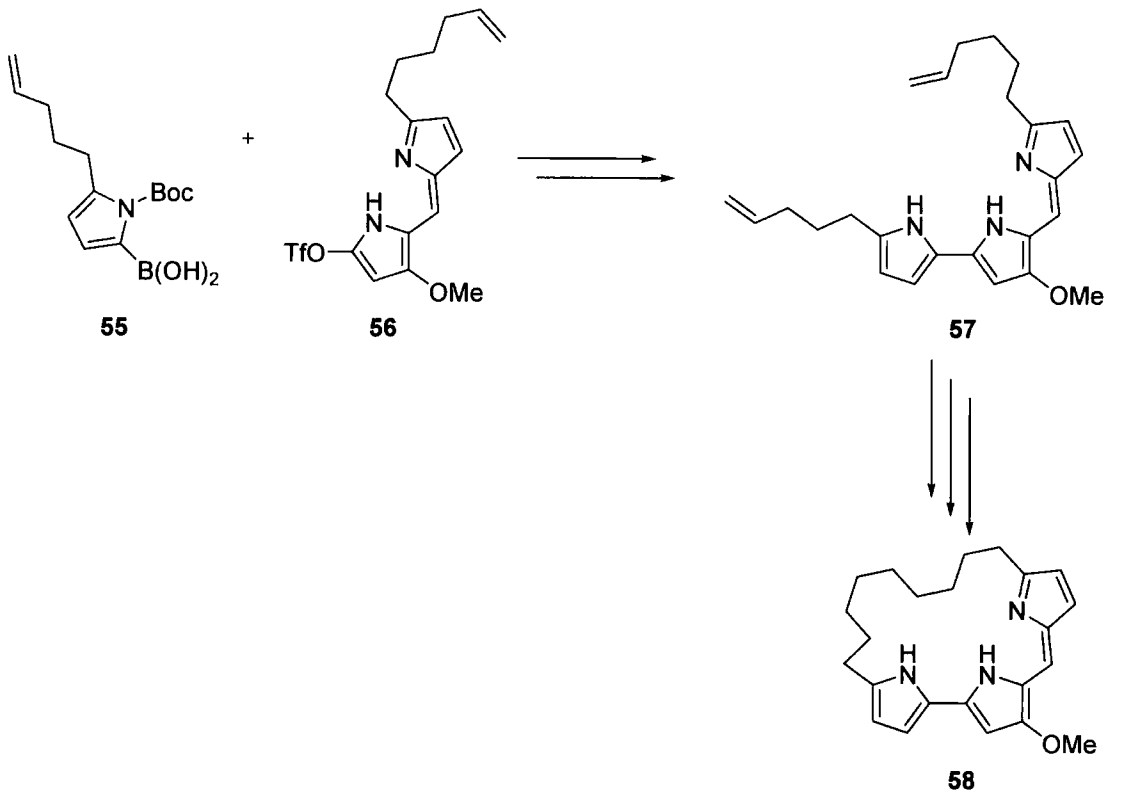


40%

53 **54**

Scheme 1.1r: *N*-(Boc)-pyrrole-2-boronic acid (**53**) and homocoupled product (**54**).[53]

N-(Boc)-5-(pent-4-enyl)-2-pyrrolylboronic acid (**55**) was produced by Furstner *et al.* in the synthesis of a potent cytotoxic prodigiosin alkaloid, *via* directed *ortho*-metallation of *N*-Boc protected 2-(pent-4-enyl)pyrrole. The aim was to cross-couple **55** with a triflate (**56**) (Scheme 1.1s).[54] The diene (**57**) produced underwent further transformation finally to produce the desired product nonylprodigiosin (**58**). It was again observed that 2-pyrrolylboronic acid was unstable and underwent protodeboronation during attempts to couple it.



Scheme 1.1s: Nonylprodigiosin (**58**) synthesis[54]

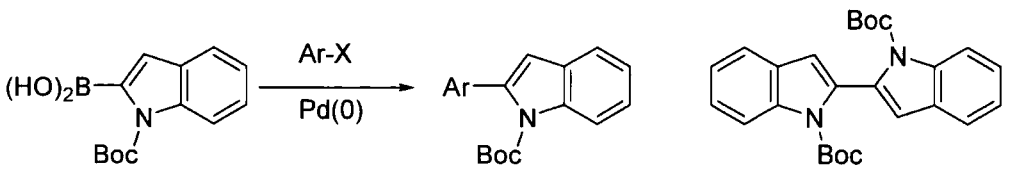
Ketcha *et al.* discovered that 1-(phenylsulfonyl)pyrrole competitively desulfonylated when attempting to lithiate at the C-2 position and for this reason the boronic acid was obtained in only 8% yield. However, Suzuki-Miyaura reactions of the boronic acid took place in yields of 39-91%, without deboronation occurring.[2]

Muchowski *et al.*[55] published the only synthesis of 3-pyrrolylboronic acid using a triisopropylsilyl protecting group. The protected pyrrole first underwent selective iodination at C-3 then metal-halogen exchange using *n*-BuLi, to produce the boronic acid in 43% yield.

Indole

Indole boronic acids are known to possess sugar binding properties, and the indole motif is an integral part of a wide variety of natural properties. The following protecting groups have been used prior to making the boronic acid: *N*-tosyl, *N*-SO_2Ph,

N-Boc, *N*-Me, *N*-OMe, *N*-TBS and *N*-potassio salt. Johnson *et al.*[56] published the synthesis of 2-indolylboronic acid using *N*-Boc protected indole in 65% overall yield; the boronic acid (**59**) was then coupled under Suzuki-Miyaura conditions with a range of aryl halides, but only low yields of products (**60**) were obtained and this was explained by steric hindrance and preferential homocoupling. A significant amount of homocoupled boronic acid (**61**) was obtained.

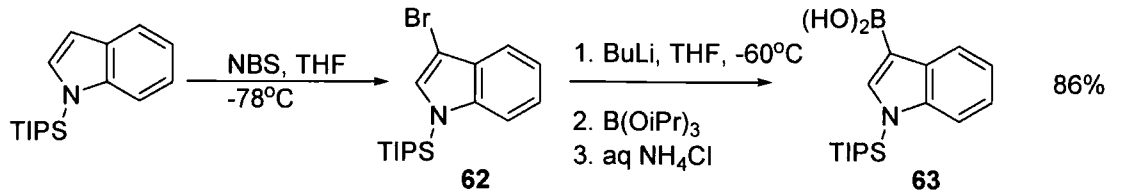


59 **60** **61**

Scheme 1.1t: Cross- and homo-coupling of *N*-Boc-2-indolylboronic acid (**59**).[56]

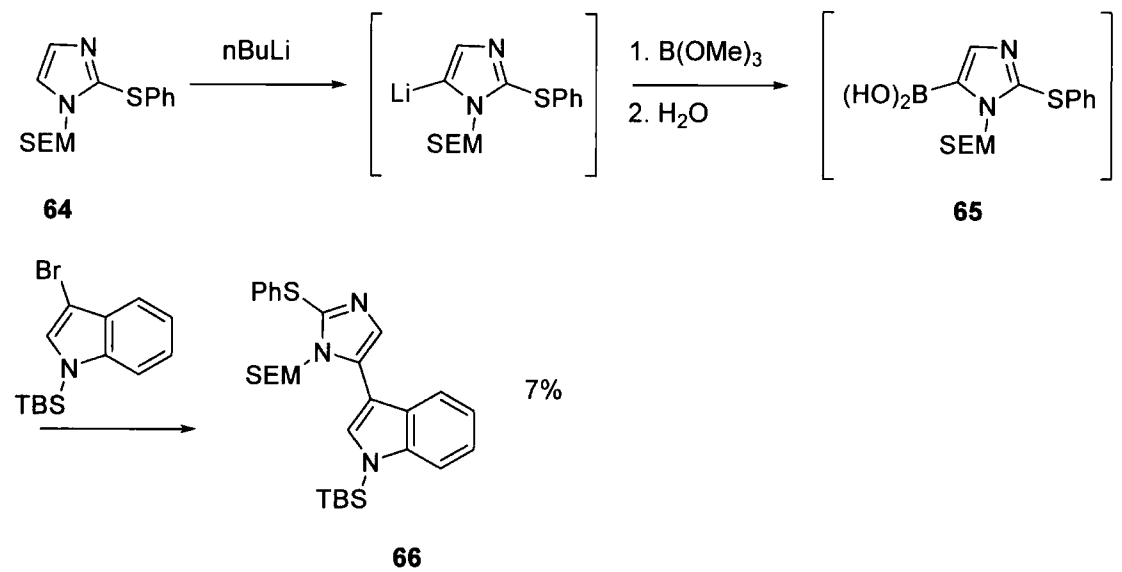
Ishikura *et al.* studied a range of *N*-substituted indol-2-ylboronates and found that the reaction yields (0 – 80%) when the boronic acids were coupled with aryl-, 2- and 3-pyridyl and 3-thienyl groups depended on the protecting group *e.g.* ~ 15% for SO_2Ph to ~ 80% for Me.[57]

The ease of the synthesis of 3-indolylboronic acid seems to be influenced by the protecting group, with silicon-based groups being favoured. The synthesis of 3-indolylboronic acid using a phenylsulphonyl protecting group must take place at temperatures below –100 °C, or rearrangement to the more stable 2-lithio derivative occurs.[58] If a different protecting group, such as *N*-TBS, is used the reaction is much less temperature sensitive; this protecting group is used in the synthesis of the antiviral/antitumour bis(indoyl)imidazole derivative topsentin.[59] The lithiation was carried out at –78 °C and no isomerisation was observed, the boronic acid was used without purification, so therefore, a yield was not recorded. *N*-TIPS is another protecting group that has a stabilising influence on the boronic acid. The *N*-TIPS-3-bromoindole (**62**) was converted to the *N*-TIPS-3-indolylboronic acid (**63**) in an overall yield of 86%.[60]



Scheme 1.1u: Synthesis of *N*-TIPS-3-indolylboronic acid (**63**).[60]

The only syntheses published for 5-, 6- and 7-indolylboronic acids have used the *N*-potassio-salt protecting group,[61, 62] and moderate yields (~ 44 %) were obtained. It was established that a halogen-lithium exchange takes place without metallation occurring at the C-2 position. The only imidazolylboronic acid synthesis[63] to be published utilises a 1,2-protected imidazole (**64**) (Scheme 1.1v). No yield was quoted as the crude boronic acid (**65**) was reacted in Suzuki-Miyaura coupling reactions where only a 7% yield of (**66**) was obtained. The author stated that the instability of **65** was responsible for the low coupling yields and not the inefficiency of the coupling reaction themselves. No evidence to support this statement was given.



Scheme 1.1v: Synthesis of Imidazolylboronic acid (**65**).[63]

Quinolinylboronic acids

The syntheses of 8-quinolinylboronic acid[64] and 2-chloroquinolyl-3-boronic acid[65] have been reported. 8-Quinolylboronic acid was obtained in 79% yield and Letsinger *et al.* failed to synthesise any other isomers and proposed that it was the only isomer achievable due to the need to facilitate the metal-halogen exchange by the coordination of the *n*-BuLi with the heterocyclic nitrogen atom. Recently, the synthesis of 2-chloroquinolyl-3-boronic acid (85%) was published by a DoM reaction due to the chlorine in the 2-position.[10]

There are also a number of sulphur and oxygen heterocyclic boronic acids known but despite many attempted syntheses thiazolyl, oxazolyl, and pyrazinylboronic acids remain unknown.

1.2 Application of Boronic Acids

Boronic acids have a number of advantages over organolithium, organomagnesium and other organometallic reagents. They are generally innocuous, air-, moisture- and temperature-stable, unlike many other organoboron compounds e.g. Me_3B. The main application for boronic acids, amongst others, is the synthesis of biaryls by transition metal catalysed cross-coupling reactions. The biaryl unit is present in several types of compounds of current interest including natural products, polymers, advanced materials, liquid crystals and molecules of medicinal interest.

There are a number of commonly used catalytic methods in biaryl synthesis for example; Kumada, Negishi, Stille and Suzuki-Miyaura reactions. These reactions prepare both symmetrical and unsymmetrical biaryls and invariably proceed using either nickel or palladium catalysts. In 1972, Kumada, Tamao and Corriu reported independently that the reaction of organomagnesium reagents with alkenyl or aryl halides could be catalysed by Ni(II) complexes.[66] The coupling of a Grignard reagent (Ar^1MgX) with alkyl, vinyl or aryl halides under Ni-catalysis provides an economical transformation. However, there are disadvantages, the reaction is limited to halide partners that do not react with organomagnesium compounds and the polar nature of the Grignard reagent precludes the use of several types of functional groups in the coupling partner such as aldehydes, ketones, esters and nitro groups.[67] The advantage of this reaction is the direct coupling of Grignard reagents, which avoids additional reaction steps such as the conversion of Grignard reagents to zinc compounds for the starting materials in the Negishi coupling.[67] An example is in the industrial-scale production of styrene derivatives, and the Kumada coupling is generally the method of choice for the low-cost synthesis of unsymmetrical biaryls.

The Negishi coupling, first published in 1977, was the first reaction that allowed the preparation of unsymmetrical biaryls in good yields. The versatile nickel- or palladium-catalysed coupling of organozinc compounds with various halides (aryl, vinyl, benzyl, or allyl) has broad scope and is not restricted to the formation of biaryls. Unlike the Kumada

reaction, functional groups are tolerated in the coupling partner. Arylmagnesium and arylzinc reagents are precursors to biaryls in the Kumada and Negishi reactions, respectively. Aryllithiums are not generally used due to their highly polar and basic nature. There are, however, some isolated examples which have been successful. The Stille Coupling is a versatile C-C bond forming reaction between stannanes (Ar^1SnR_3, R = Me, Bu) and halides, with very few limitations on the R-groups. Well-elaborated methods allow the preparation of different products from all of the combinations of halides and stannanes. The main drawback is the toxicity of the tin compounds and their low polarity, which makes them poorly soluble in water. Stannanes are stable, but boronic acids and their derivatives undergo much the same chemistry in the Suzuki-Miyaura coupling (see below), without the drawbacks of using tin compounds.

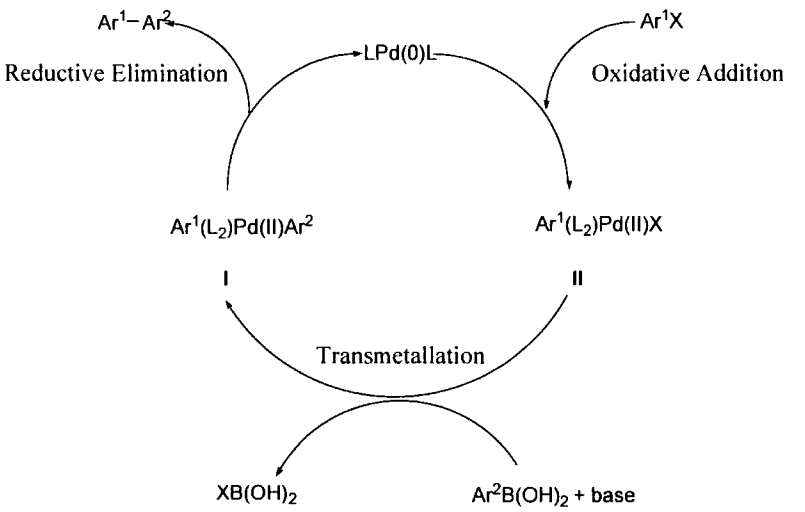
The palladium catalysed reaction of a boronic acid [$Ar^1B(OH)_2$] with an aryl halide (Ar^2X) is a general method for the formation of carbon-carbon bonds. Since the late 1990s this type of reaction has been called Suzuki coupling, Suzuki reaction or Suzuki-Miyaura coupling. The reaction is extremely versatile due to the availability of the reagents and the mild reaction conditions. The reaction is unaffected by the presence of water, tolerates a broad range of functional groups, generally proceeds regio- and stereo-selectively and the inorganic by-product is non-toxic and easily removed.[68]

Due to the extensive synthetic possibilities using Suzuki-Miyaura couplings, the parameters of the reaction and the mechanism are constantly under investigation.

Mechanism

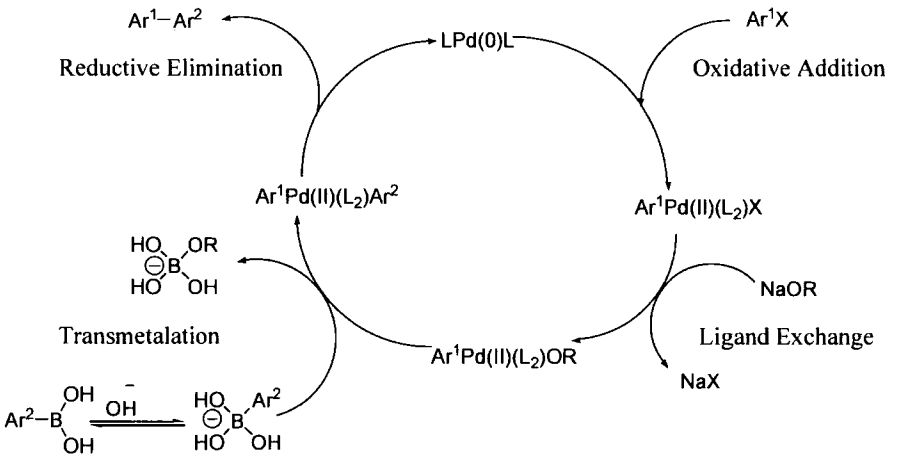
The cross-coupling reactions of organoboron compounds follow a similar catalytic cycle to that of other main metal reagents, involving: (a) oxidative addition of organic halide or other electrophiles to a palladium(0) complex yielding R^1-Pd-X; (b) transmetallation between R^1-Pd-X and R^2-B with the aid of base; and (c) reductive elimination of R^1-R^2 to regenerate the palladium(0) complex. Water and base are necessary to activate the boronic acid.[69] The coupling reaction of 3-bromopyridine and a phenyl boronic acid has been analysed using electrospray ionisation mass spectrometry (ESI-

MS).[70] From this study it was concluded that the reaction mixture contained two key intermediates (I and II) as shown in scheme 1.2a.



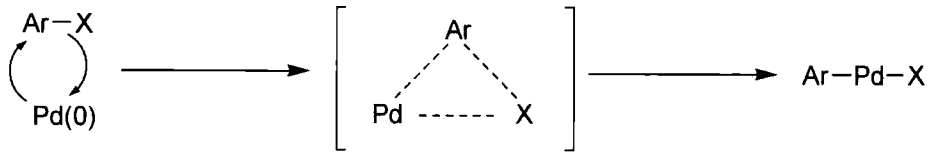
Scheme 1.2a: Studies of mechanism by Canary *et al.*[70]

Other studies, including that of Suzuki *et al.,* have shown the formation of three intermediates during the coupling of 1-alkenyl halide and 1-alkenylboron compounds. The generally accepted catalytic mechanism is depicted in Scheme 1.2b.[71]



Scheme 1.2b: Catalytic Mechanism for Suzuki-Miyaura Cross-Coupling Reaction.

Although the two steps of oxidative addition and reductive elimination are reasonably well understood, less is known about the transmetallation process. Oxidative addition of the halide to the palladium(0) complex forms an organopalladium halide (Scheme 1.2c).

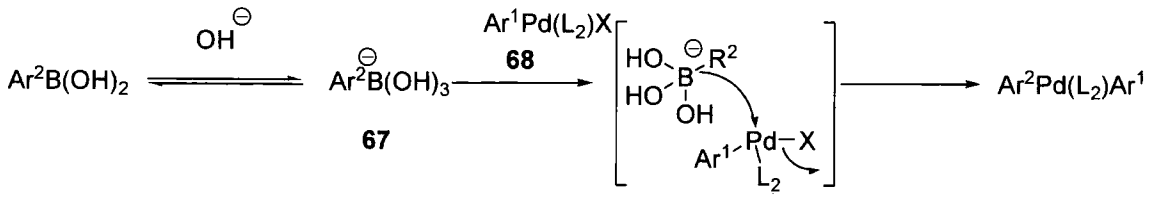


Scheme 1.2c: Oxidative addition step.

This step is generally accepted to be rate-determining,[69] although it has been shown by Smith *et al.* that when using an aryl iodide, instead of an aryl bromide or chloride, the transmetallation step is rate determining.[69] Recent literature has shown that the oxidative addition of chloro-, bromo- and iodoarenes to a bisphosphine palladium(0) complex (containing hindered ligands) occurs *via* three different mechanisms.[72] Addition of PhI occurs by the associative displacement of a phosphine, PhBr by rate-limiting dissociation of a phosphine and that of PhCl occurs by a reversible dissociation of a phosphine, followed by rate-limiting oxidative addition.

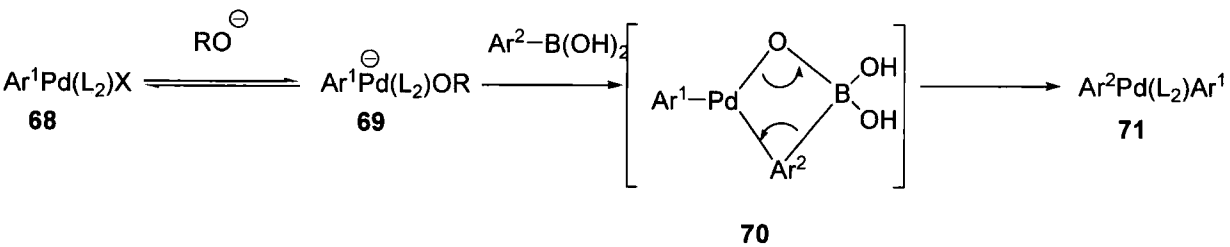
Next is the transmetallation step where two alternative processes are hypothesised. Available information indicates that there are several processes for transferring the organic group onto the organopalladium halide (**68**).[73] The addition of sodium hydroxide and other bases exerts a remarkable accelerating effect on the transmetallation between **68** and organoboronic acids. Quarternization of the boron atom with a negatively charged base enhances the nucleophilicity of the organic group on the boronic acid for alkylation of **68**. Similarly a hydroxyboronate anion (**67**), which exists in equilibrium with the free boronic acid, could alkylate Ar^1-Pd-X (Scheme 1.2d). Phenylboronic acid has a pKa of 8.8, therefore the concentration of hydroxyboronate anions will increase at pH 9 and above. The rate of the coupling reaction of phenylboronic acid and 3-iodobenzoic acid is significantly increased upon raising the pH from 8 to 10.[73] However, the rate is retarded

above pH 11. Kinetic studies using NMR spectroscopy also support this mechanism by showing the formation of the hydroxyboronate anion.[73]



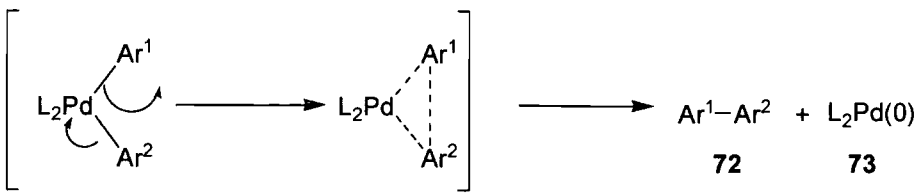
Scheme 1.2d: Transmetallation step.

An alternative process is transmetallation to an alkoxo-, hydroxo-, acetoxo-, or (acetylacetoxo)palladium(II) complex (**69**), formed by the *in situ* ligand exchange between Ar^1-Pd-X (**68**) and a base (RO^-) (Scheme 1.2e). This species is more electrophilic than the organopalladium halide complex (**68**) due to the Pd-O bond being more polar than the Pd-X bond. These complexes undergo transmetallation without the aid of base. The reaction may involve the rate determining coordination of the RO^- ligand to the boron atom *via* a transition state depicted as **70**. The high basicity of the Pd(0) species and the high oxophilicity of the boron centre are the reasons for the strong reactivity of the RO-Pd complexes. This latter scheme is generally accepted to be the mechanism due to Suzuki *et al.* showing the formation of Ar^1Pd(II)OR.



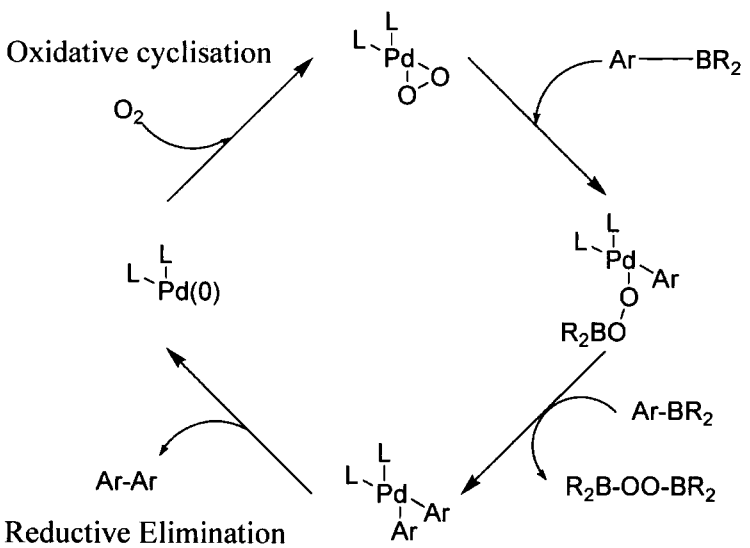
Scheme 1.2e: Transmetallation step.

As the organopalladium species with two aryl units (**71**) attached are unstable, the biaryl (**72**) is produced and the palladium(0) complex (**73**) is regenerated,.



Scheme 1.2f: Reductive Elimination Step

For a homocoupling reaction of a boronic acid to proceed there needs to be a step replacing the aryl group from the coupling partner (Ar^1) with that from the boronic acid (Ar^2). Proposed mechanisms for homocoupling involve two transmetallations stages.[74, 75] Yoshida *et al.* proposed the catalytic cycle in Scheme 1.2g as it is known that oxygen readily reacts with palladium(0) to afford palladium(II) peroxide.



Scheme 1.2g: Proposed pathway of homocoupling[74]

In this cycle a three-membered palladium(II) peroxide complex is formed by oxidative cyclization of molecular oxygen with the palladium(0) complex. Subsequently a double transmetallation of the organic moiety attached to the boronic acid to the palladium(II),

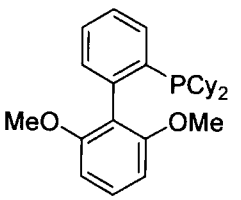
with the aid of base gives diorganopalladium and boron peroxide. Reductive elimination of the homcoupling product regenerates the palladium(0) complex.

The Suzuki-Miyaura reaction can be carried out using a variety of catalysts, bases and solvents, where their combinations significantly affect the yields and selectivity of the products. However, the influence of the parameters depends upon the nature of the substrate and for this reason, in this chapter, only the most relevant literature will be reported.

Catalysts and Ligands

$Pd(PPh_3)_4$ is a commonly used catalyst for Suzuki-Miyaura reactions; however, it is air sensitive so alternative species have been investigated.[73] Idealy, a universal catalyst would satisfy the diverse requirements of every different Suzuki-Miyaura coupling and obtain a high yield using low loading. To date this has not been realised, but a number of research groups have reported different catalysts/catalytic systems relevant to heterocyclic boronic acid couplings. The use of bulky trialkylphosphine ligands is thought to assist in Suzuki-Miyaura cross-couplings by stabilising and promoting the generation of the unsaturated Pd(0) and Pd(II) intermediates and thereby enhancing the catalytic activity of Pd complexes in coupling reactions.[76] Buchwald *et al.* reported a number of different ligands, some for use in room temperature couplings, and some for extremely low loadings of catalyst (0.000001 mol %).[77] They have however, only published one example using heterocyclic boronic acids. In 2004, they reported a catalyst system that enabled the coupling of both electron-rich and electron-poor heteroaryl boronic acids with hindered aryl halides and a variety of heteroaryl halides at exceptionally low loadings.[78] The catalyst system, 2-(2',6'-dimethoxybiphenyl)-dicyclohexylphosphine, SPhos (**74**) and Pd_2dba_3 (dba = dibenzylideneacetone) was used to cross-couple 3-pyridylboronic acid with a range of aryl halides in isolated yields of 81 – 96%, reactions times of 15 – 24 h and catalyst loadings of 2 – 3%.[79] Aryl couplings carried out using 2-(2',4',6'-triisopropylbiphenyl)diphenylphosphine (**75**) were not as high yielding; this was claimed to be due to the importance of ligand bulk and electron-donating ability in the high activity of

catalysts. Interestingly, it was found that when aryl bromides became too hindered (three *t*-Bu groups) the desired coupling product was not obtained.



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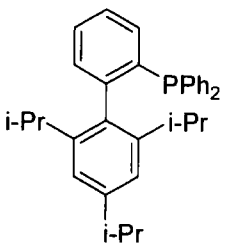


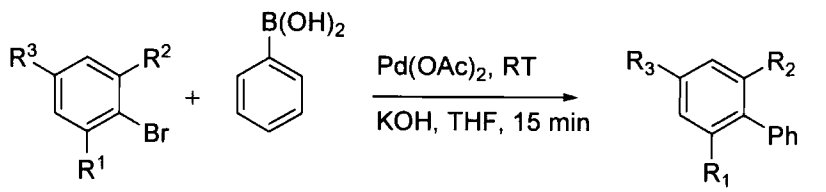
75

Scheme 1.2h: Ligands investigated by Buchwald *et al.*[79]

Many phosphines are sensitive to air and moisture and can undergo conversion to other species, for example, phosphine oxide species. For this reason and economical and environmental reasons, especially from an industrial perspective, new recyclable catalytic systems are being sought. Li *et al.* reported the $Pd(OAc)_2$/ DABCO (trimethylenediamine) catalytic system for use in Suzuki-Miyaura cross-coupling reactions.[80] This system can be recovered and recycled five times without any loss of catalytic activity; the system is, however, limited to aryl iodides and bromides. Capretta *et al.* used a catalytic system based upon $Pd_2dba_3.CHCl_3$ on a 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane framework for solid-phase Suzuki-Miyaura cross-couplings of aryl halides with aryl and thienylboronic acids.[81] The reactions proceed at room temperature with low palladium loadings (2 mol %) giving moderate to high conversions (42 – 100%). Alternatively, the catalyst can be polymer supported. Le Drian *et al.* reported the same product yields from the Suzuki-Miyaura cross-coupling of phenylboronic acid and bromoaromatic compounds using a polymer supported catalyst or "free" catalyst.[82] Recovery and reuse of the catalyst was stated to be straightforward and only 0.6% of the initial palladium content was lost during the reaction. Williams *et al.* carried out Suzuki-Miyaura cross-coupling reactions using reverse-phase glass beads in aqueous media.[83] The beads were coated with $Pd(PPh_3)_4$, which is assumed to be still mobile on the surface, and the reaction occurs at the interface. 3 mol% $Pd(PPh_3)_4$ on polymer beads was used to couple aryl boronic acids with

heteroaryl iodides and bromides to afford the desired products in moderate to excellent yields (47 – 100%).

The advances in catalytic systems have enabled Suzuki-Miyaura reactions to be carried out at a range of temperatures, some even at room temperature, *e.g.* the synthesis of **76 – 80** using hindered aryl bromides (Scheme 1.2i).[84] The concentration of base used made no difference to the yields obtained.



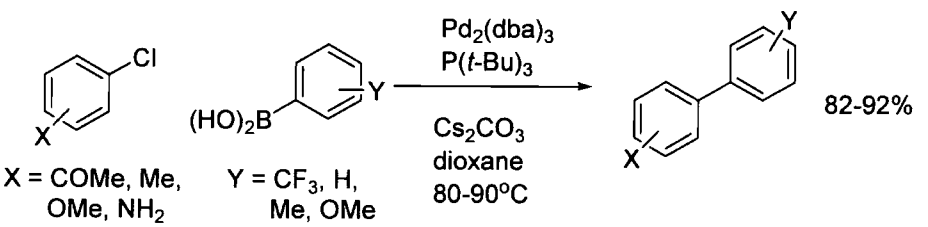
76	R^1 = H	R^2 = H	R^3 = CH_3	95%
77	R^1 = CN	R^2 = H	R^3 = H	92%
78	R^1 = CF_3	R^2 = H	R^3 = H	90%
79	R^1 = OCH_3	R^2 = H	R^3 = H	96%
80	R^1 = CH_3	R^2 = CH_3	R^3 = H	84%

Scheme 1.2i: Suzuki-Miyaura cross-coupling reactions.[84]

Halo partners: I, Br, Cl, F

A range of halo partners can be used in Suzuki-Miyaura cross-coupling reactions. Aryl triflates are also sometimes used, but are base sensitive and thermally labile. Mild reaction conditions have been developed for the coupling of arylboronic acids with triflates using efficient catalysts and weak non-aqueous bases in polar solvents. To prevent premature catalyst decomposition and/or to promote cross-coupling, an alkali metal halide may also be added. An investigation by Martin *et al.* to extend the reaction from electron-rich aryl triflates to less reactive aryl sulphonates and aryl chlorides discovered that alternative sulphonate leaving groups were active in these reactions. Although aryl mesylates, benzenesulphonates and tosylates are much less expensive than triflates, they are inactive towards palladium catalysts.[85-87] It has been shown that, due to the differing reactivities of iodo-, bromo- and chloro-aryls, selective coupling can be achieved under the Suzuki-Miyaura reaction conditions.[88] Although chloro-compounds are often cheaper and

more readily available than the corresponding iodo- or bromo-analogues, 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.[89] Aryl chlorides as coupling partners participate in Suzuki-Miyaura coupling reactions more readily if used in conjunction with electron-deficient groups. For these reasons, bromides and iodides are traditionally the aryl halides used. Aryl chlorides were, until recently, not used as they were known to be a lot less reactive and in many cases unreactive.[90] Over the last few years, however, new catalytic systems have been developed for unreactive chlorides. In 1998, Fu *et al.* reported the use of $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ as a catalytic system to cross-couple a wide range of aryl chlorides in good yields (82 – 92%) (Scheme 1.2j).[91] They observed no coupling in the absence of a phosphine and lower yields using phosphines other than P(*t*-Bu)$_3$. The phosphine was used in high loading (3.6%) and electron-withdrawing groups were present to activate the aryl chlorides.

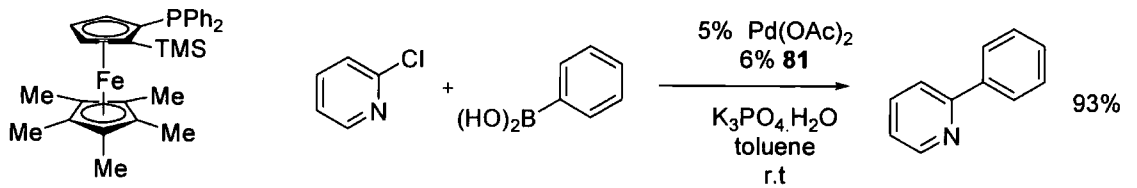


Scheme 1.2j: Suzuki-Miyaura cross coupling of aryl chlorides.[91]

Fu *et al.* then extended this system to a range of aryl iodides, aryl bromides and activated chlorides (*i.e.* heteroaryl chlorides and aryl chlorides that bear an electron withdrawing group) at room temperature.[92] They stated that CsF was an effective alternative base to Cs_2CO_3. The ratio of phosphine to catalyst was found to be an important parameter: a 1:1 ratio furnished a very active catalytic system, whereas a 2:1 ratio produced extremely slow reactions. $Pd_2(dba)_3$ was stated to be superior to $Pd(OAc)_2$, although no evidence was given. Chloro-substituted pyridine and thiophenes were coupled at room temperature and

this was related to their ability to bind to palladium through nitrogen or sulphur, respectively.

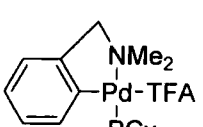
In 2001, triarylphosphine derivative (**81**), $Pd_2(dba)_3$ and $Pd(OAc)_2$ were shown to be successful in coupling a range of sterically-demanding and electronically-deactivated substrates.[93] Included was the example of 2-chloropyridine (**82**) and phenylboronic acid (**83**) at room temperature producing 2-phenylpyridine (**84**) in 93% yield (Scheme 1.2k).



81 **82** **83** **84**

Scheme 1.2k: Suzuki-Miyaura cross coupling of aryl chlorides.[93]

Bedford *et al.* published the first coupling of aryl chlorides (both electron-rich and electron-poor) under aerobic conditions.[94] The number of complexes derived from di- or tri-alkyl substituted phosphine ligands was limited due to their laborious synthesis, which is reflected in their high commercial cost compared to the more common catalysts. They deduced that an ideal catalyst for use with aryl chlorides should contain tricyclohexylphosphine, which is easy to synthesise from cheap, commercially available materials, is easy to handle and shows good activity at low loadings. Tricyclohexylphosphine adducts of palladium complexes with *ortho*-metallated *N*-donor ligands, *e.g.* **85**, showed high activity. Complex **85** was synthesised from the commercially available *N,N*-dimethylbenzylamine. A brief investigation of solvents and bases to optimise the coupling conditions showed that the catalyst activity was greatly affected by reaction conditions and worked best using dioxane and Cs_2CO_3 with a 0.01 mol% catalyst loading.



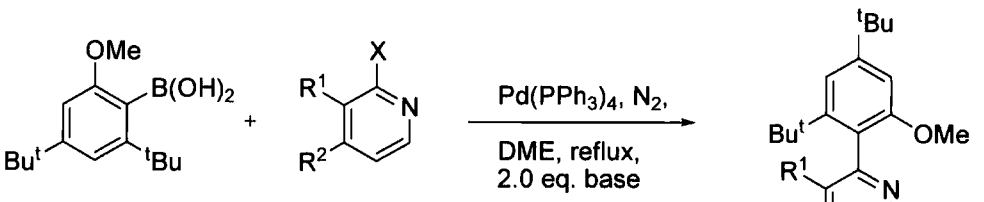
85

Scheme 1.2l: Complex **85**.[94]

In 2003, Widdowson and Wilhelm published the first Suzuki couplings on aryl fluorides. However, a nitro group in the 2-position of the fluoroarene was essential for the reaction to occur. It was stated that the nitro group facilitated by coordinating with the palladium atom of the catalyst. These authors found that when attempting to couple fluoroarenes with other groups e.g. COOMe, CF_3 and F in the 2-posistion, no product could be detected.[95]

Choice of Base

Cross-coupling reactions of organoboronic acids and organic halides require the presence of a negatively charged base, such as an aqueous solution of sodium or potassium carbonate, phosphate or hydroxide. Although, in general, aqueous sodium carbonate is used as a base in Suzuki-Miyaura cross-coupling reactions, there are other used in the literature for example; $Ba(OH)_2$,[96] K_2CO_3,[68] and Cs_2CO_3. Various groups claim that whilst investigating a range of couplings in certain conditions certain bases are best, but no systematic study has been carried out. In 1996, Chan *et al.*[97] stated that the type of base had a remarkable accelerating effect upon the rate of coupling of sterically bulky boronic acids with halopyridines in dimethyl ether (DME) (Scheme 1.2m).



86

87 $R^1 = R^2 = H$, X = Br
88 R^1 = Me, $R^2 = H$, X = Br
89 $R^1 = R^2 = (CH)_4$, X = Cl

90 $R^1 = R^2 = H$
91 R^1 = Me, $R^2 = H$
92 $R^1 = R^2 = (CH)_4$

Scheme 1.2m: Couplings used in investigations into accelerating effects of different bases[97]

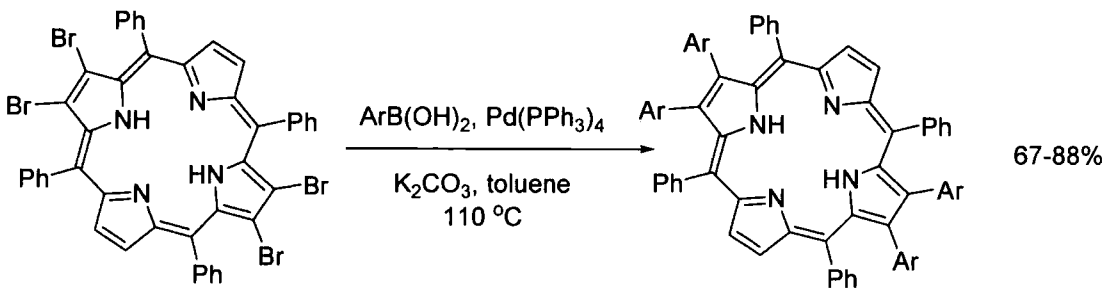
In DME, using their standard base (aq. NaOH) low yields of the desired products were obtained or no coupling was observed (**90** = 26%, **91** and **92** = 0%), after 90 h. By increasing the base strength from using NaOH or $NaOC_2H_5$ to *t*-BuOK, the yields increased with shorter reaction times (4 – 10 h). Using *t*-BuOK high yields were obtained of **90**, **91** and **92** (86, 83 and 77%, respectively). Chan *et al.* also reported the synthesis of **86** and mentioned that DME was used as a solvent for the coupling reactions to suppress deboronation of **86**.[98]

Microwave Reactions

Microwave-assisted Suzuki-Miyaura reactions have been carried out using a number of polar solvents, for example water,[99, 100] ethyleneglycol[101] and DMF[102] which efficiently absorb microwaves. These conditions significantly decrease the amount of time needed to carry out a coupling,[103] and can increase the efficiency of ligandless catalysts.[73]

Miscellaneous examples of Suzuki-Miyaura reactions

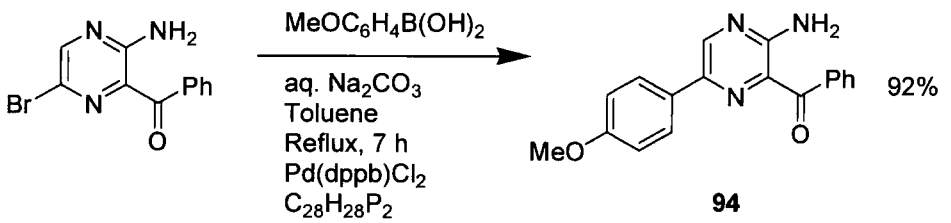
A few instances are now given in which the Suzuki-Miyaura cross coupling reaction has facilitated the synthesis of a number of important molecules. β-Substituted porphyrins are of continuous interest due to their biological properties. β-Brominated porphyrins are easily obtained from the controlled bromination of porphyrins, and derived tetraphenylporphyrins **93** have been obtained in high yields (Scheme 1.2n).[90]



93

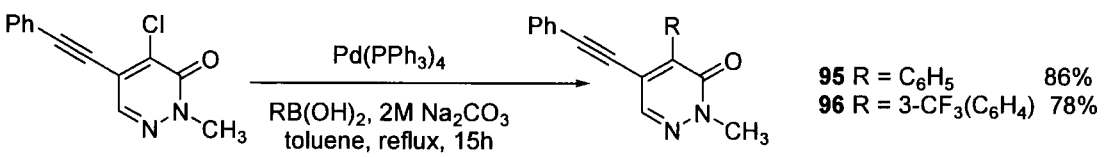
Scheme 1.2n: Synthesis of tetra-aryl-tetra-phenylporphyrins.[90]

The field of non-linear optics has also advanced due to Suzuki-Miyaura cross-couplings. Few 1,8-di(hetero)arylnaphthalenes, used in this field, were known due to the lack of general synthetic methods. Grahn *et al.* developed a process for their production using two Suzuki-Miyaura cross-coupling reactions. This work showed that nitro-substituents on the halo-coupling partner were tolerated when phenyl boronic acids were used.[104] Suzuki-Miyaura couplings of 5-halopyrazine with arylboronic acids have simplified the syntheses of arylpyrazines (**94**), which are building blocks for luminescent imidazopyrazine. Using 1,4-bis(diphenylphosphine)butane palladium(II) chloride as a catalyst gave excellent yields (Scheme 1.2o).[105] The primary amine substituent on the coupling partner was tolerated in this reaction.



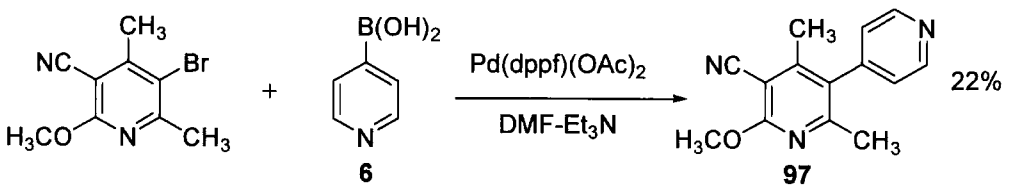
Scheme 1.2o: Example of the synthesis of arylpyrazines.[105]

Highly functionalised and sterically hindered coupling partners can be tolerated in couplings with phenylboronic acids and functionalised phenylboronic acids[106] as illustrated in the syntheses of pyridazinone derivatives **95** and **96** by R'kyek *et al.*



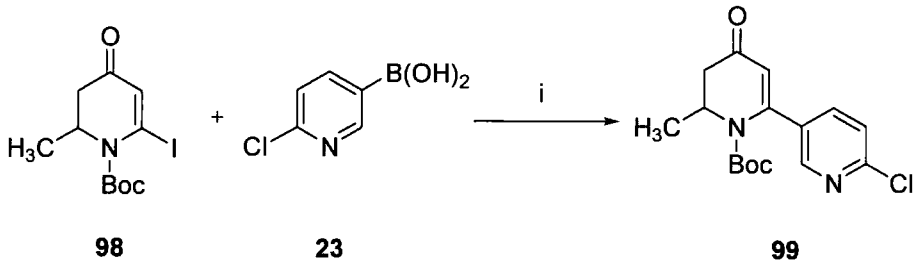
Scheme 1.2p: Synthesis of **95** and **96**.[106]

Thompson *et al.* published the coupling of 4-pyridylboronic acid to produce the fully substituted 2-(4'-pyridyl)pyridine (**97**), showing that sterically hindered reagents containing methyl, methoxy and nitrile groups can undergo coupling reactions (Scheme 1.2q).[107] The source or synthesis of **6** was not noted in the publication.



Scheme 1.2q: Suzuki-Miyaura cross coupling reactions[107]

In 2004, Rault *et al.* extended his cross-coupling to non halo aromatics and published the Suzuki-Miyaura cross coupling of **23** with *tert*-butyl 3,4-dihydro-6-iodo-2-methyl-4-oxopyridine-1(2*H*)-carboxylate (**98**) to give **99** in an 80% yield (Scheme 1.2r).[39]



Scheme 1.2r: 2-Chloro-5-pyridylboronic acid Suzuki-Miyaura cross coupling[39] (i) Reagents and conditions; $NaHCO_3$, $Pd(PPh_3)_4$, DME/H_2O, 6 h, reflux.

1.3 Conclusions

A wide variety of heterocyclic boronic acids are available and their cross-coupling reactions have established that they are extremely versatile reagents for organic syntheses. The parameters of the Suzuki-Miyaura reaction are under constant investigation and modification to meet the demands of the modern chemical industry. These important considerations led us to consider larger-scale syntheses (up to 100 g batches) of new and existing pyridylboronic acids and their subsequent Suzuki-Miyaura cross-coupling reactions (up to 5 g batches).

At the outset of the work described in this thesis the versatility and scope of the Suzuki-Miyaura cross-coupling had not been explored for systems where both the boronic acid and the coupling partner were heteroaromatics. Also no systematic study had addressed the effect of specific substituents upon each of the coupling partners. This has led us to synthesise new functionalised pyridyl- and pyrimidyl- boronic acids, and to couple them with a large range of substituted partners in order to produce some heterobiaryl systems, which would be very difficult to obtain by other routes.

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Chapter 2

Alkoxyboronic acids: Scale-up of existing preparations and the synthesis of new examples

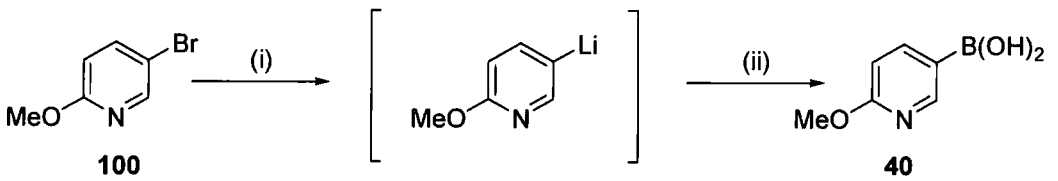
2.0 Chapter 2

2.1 Introduction

At the beginning of this project very little had been published on the syntheses of pyridylboronic acids, and larger-scale syntheses (>*ca.* 10 g batches) had not been reported. To extend the work already published in our group on small-scale (1 g) synthesis of various alkoxy-substituted pyridylboronic acids,[1, 2] we turned our attention to larger scale methodology. These investigations were important in assisting in the ultimate industrial aim of carrying out the syntheses on plant scale. Our initial aim was to produce *ca.* 100 g batches of the known alkoxy-substituted pyridylboronic acids **40** and **43**. We later extended the chemistry to produce novel pyridylboronic acids.

2.2 Large-scale Syntheses of Previously Published Alkoxy-sustituted Pyridylboronic Acids.

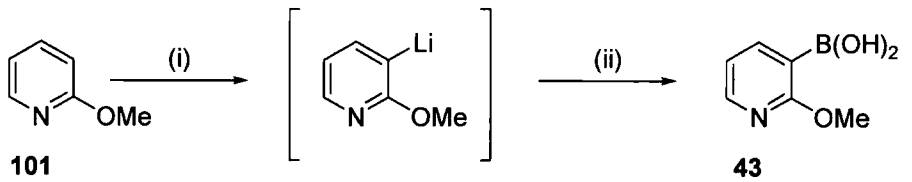
Bryce *et al.* previously published small-scale syntheses (250-350 mg batches) of 2-methoxy-5-pyridylboronic acid (**40**) and 2-methoxy-3-pyridylboronic acid (**43**) in 65% and 13% yields, respectively. The starting materials were readily available in large quantities, and the syntheses could be carried out at relatively high temperatures (-20 °C)[3] which would be achievable in industry. Compound **40** was synthesised *via* lithium-halogen exchange of 2-methoxy-5-bromopyridine (**100**), at –78 °C (or –20 °C) and subsequent reaction with the electrophile TPB (Scheme 2.2a).



100 **40**

Scheme 2.2a: 2-Methoxy-5-pyridylboronic acid synthesis. Reagents and Conditions: (i) *n*-BuLi, Et_2O, -78 °C, (ii) 1. TPB, -78 °C, 2. aqueous work-up.

Comins and Killpack published the lithiation of 2-, 3- and 4-methoxypyridine using mesityllithium and interest grew when Queguiner *et al.* established methodology for the *ortho*-lithiation of 2-methoxypyridine using LDA at 0 °C. [4,5] Compound **43** was thus synthesised *via* the directed *ortho*-metallation of 2-methoxypyridine (**101**) (Scheme 2.2b).



Scheme 2.2b: 2-Methoxy-3-pyridylboronic acid synthesis. Reagents and Conditions: (i) LDA, THF, 0 °C, (ii) 1. TMB, 0 °C, 2. aqueous work-up.[3]

Commercially purchased lithium diisopropylamide (LDA) was added to **101** in THF at 0 °C, followed by the addition of trimethylborate (TMB) and an aqueous work up. The use of TMB instead of TPB as the electrophile was to minimise steric hindrance.

The initial aim was to increase the small-scale yield of **43**. A repeat of the synthesis of **43** using diisopropylamine (DPA) and *n*-BuLi to produce LDA *in situ*, followed by dropwise addition of **101** to this mixture afforded an increased yield of 70% from 13%.

Applying these small-scale procedures to a 50 g scale resulted in impure **40** and **43**. After much experimentation, we optimised procedures to afford *ca.* 75 g batches of analytically pure **40** and **43** in 65% and 58% yields, respectively. These scaled-up reactions are not a straightforward extrapolation of the procedures used in the small-scale reactions. In particular, additional filtration and washing were needed on scale-up to remove unreacted starting material and inorganic salts before isolation of the product could occur easily. Moreover, the pH needed to be precisely controlled at this stage (pH 10) and during acidification which induces precipitation of the pure product (pH 4 and 6, for **40** and **43**, respectively). The greater amounts of **40** and **43** prompted us to attempt crystal growth, which had previously been unsuccessful.[3] Crystals of **40** were grown over 10 months from a water/ethanol mixture and the structure was solved by Dr. A Batsanov (Figure 2.2a).

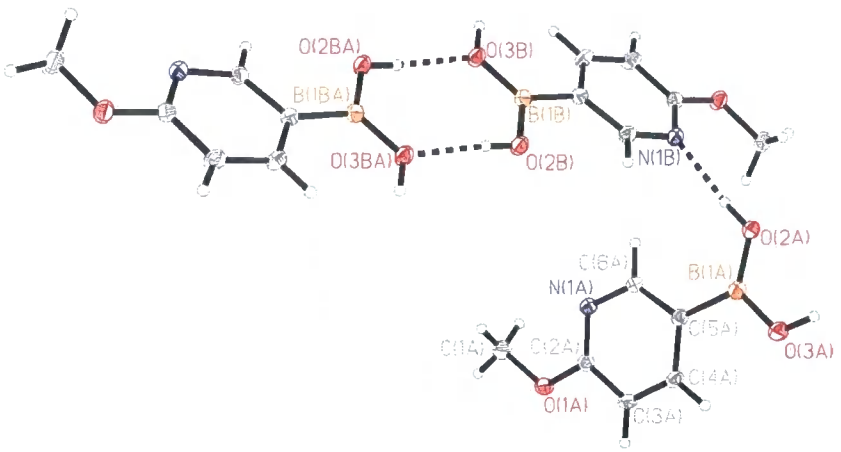


Figure 2.2a: X-ray crystal structure of **40**. Dashed lines are hydrogen bonds.

The X-ray crystal structure of **40** provided further proof that the free boronic acid had been obtained and not the anhydride. Extensive hydrogen bonding is present (intermolecular O-H....N and dimer formation) and is similar to that found in the X-ray crystal structures of **22** and **23** previously published.[2] However, the packing diagram showed that, due to the presence of the methoxy group, the crystals of **40** do not pack together as closely as **22** and **23**. The attempted crystal growth of **43** was unfortunately unsuccessful.

2.3 Novel Alkoxypyridylboronic Acids

2.3.1 2-Ethoxy-3-pyridylboronic Acid

Due to successful scale up of **40** and **43** we attempted to extend the synthesis to new alkoxypyridylboronic acids. 2-Ethoxypyridine **102** is cheap and readily available from commercial suppliers and with the idea that the ethoxy group may increase solubility of the corresponding boronic acid, this was our next target. The synthesis of **103** was readily achieved by a directed *ortho*-metalation reaction[6] of **102** (LDA in THF) followed by addition of triisopropylborate and an aqueous workup. The initial attempts were carried out at 0 °C using the same protocol as that used for 2-methoxy-3-pyridylboronic acid (**43**). It was shown that using DPA and *n*-BuLi, or commercially available LDA made no difference to the yield. We repeated the synthesis at a range of temperatures, whilst other

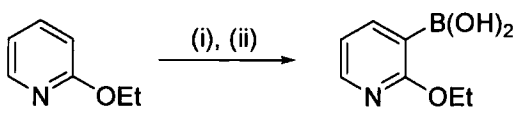
factors, *i.e.* solvent and reagent quantities, remained the same for each experiment. Table 2.3.1a shows the results from these experiments.

Entry	Temp. / °C	Yield / %[a]
1	- 78	55
2	-50	70
3	-20	42
4	0	35

[a] identification and purity of the products (>98% pure in all cases) established by ^{1}H NMR spectra.

Table 2.3.1a: Results from the syntheses of **103** at varying temperatures (conditions stated in Scheme 2.3.1a).

This procedure, using the optimum temperature of - 50 °C, was scaled-up to give *ca.* 70 g batches of analytically-pure **103** (Scheme 2.3.1a) in 48% yield. Compound **103** has the following attractive features: (i) it is stable at room temperature (no observable decomposition after 18 months storage), (ii) as predicted, the hydrophobic ethoxy substituent ensures good solubility of **103** in organic solvents which makes extraction from the aqueous phase easier than for most other pyridylboronic acid derivatives we have studied and (iii) for cross-coupled products the 2-ethoxy group leads to sterically-induced twisting of the biaryl system (peri-interactions) and hence increased solubility, which assists chromatographic separation from any minor byproducts.



102 **103**

Scheme 2.3.1a: 2-Ethoxy-3-pyridylboronic acid (**103**) synthesis. Reagents and conditions: (i) LDA, THF, - 50 °C, (ii) triisopropylborate, aqueous work up.[7]

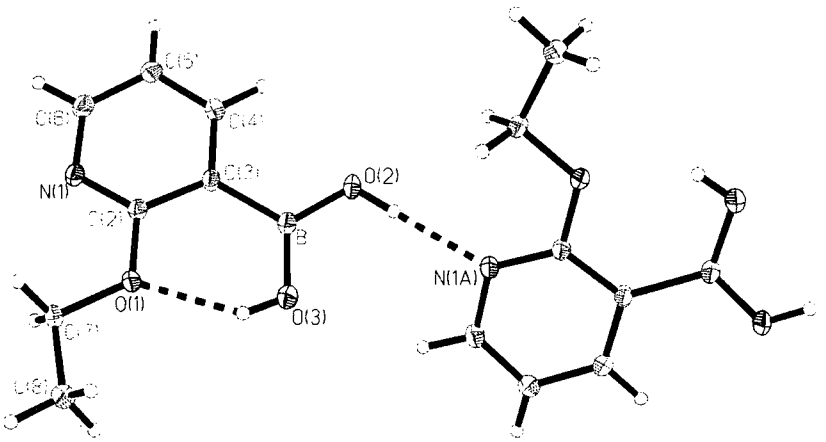
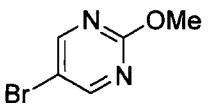
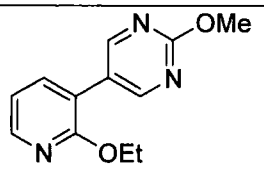
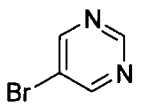
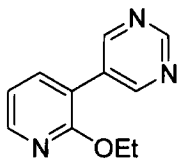
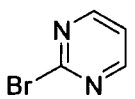
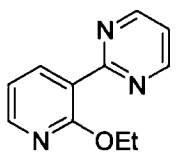
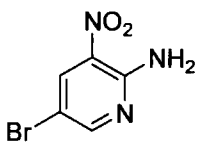
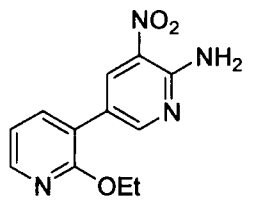
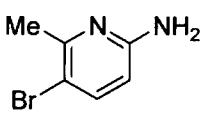
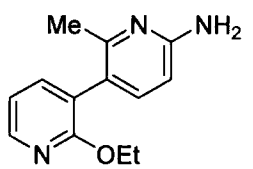


Figure 2.3.1a: X-Ray structure of **103**, showing thermal ellipsoids (50% probability) and hydrogen bonds. Symmetry transformations: (i) x+½, ½–y, z–½; (ii) x–½, ½–y, z+½.

The X-ray crystal structure of **103**, solved by Dr A. Batsanov, shows a nearly planar conformation of the molecule, stabilised by an intramolecular O-H···O hydrogen bond which forms a geometrically favourable six-membered ring (Figure 2.3.1a), while the other hydroxyl group forms an intermolecular O-H···N bond linking the molecules into an infinite chain. This structure is unusual as arylboronic acids (like carboxylic acids) typically form H-bonded dimers in crystals (see Figure 2.1a);[1, 8] this does not occur with compound **103**.

Suzuki cross-coupling reactions of **103** were carried out with a range of aryl/heteroaryl halides **104-112** under standard conditions [$Pd(PPh_3)_2Cl_2$, dioxane, reflux] to yield products **113-121**, respectively. The results are collated in Table 2.3.1.b.

Table 2.3.1b. 103 + R-X $\xrightarrow{i}$ **113-121**

Entry	Boronic Acid	R-X	Product	Isolated yield (%)
1	**103**	 **104**	 **113**	82
2	**103**	 **105**	 **114**	90
3	**103**	 **106**	 **115**	89
4	**103**	 **107**	 **116**	74
5	**103**	 **108**	 **117**	75

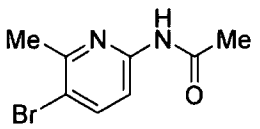
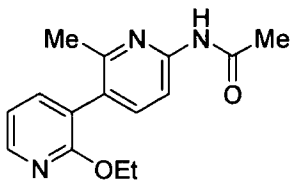
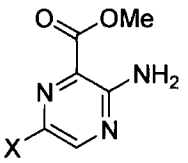
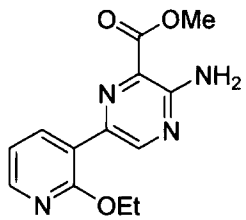
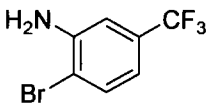
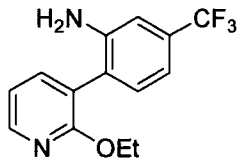
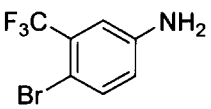
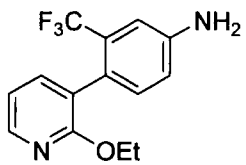
6	**103**	 **109**	 **118**	78
7	**103**	 **110** **a** = Br **b** = Cl	 **119**	90 (from **110a**) 62 (from **110b**)
8	**103**	 **111**	 **120**	71
9	**103**	 **112**	 **121**	68

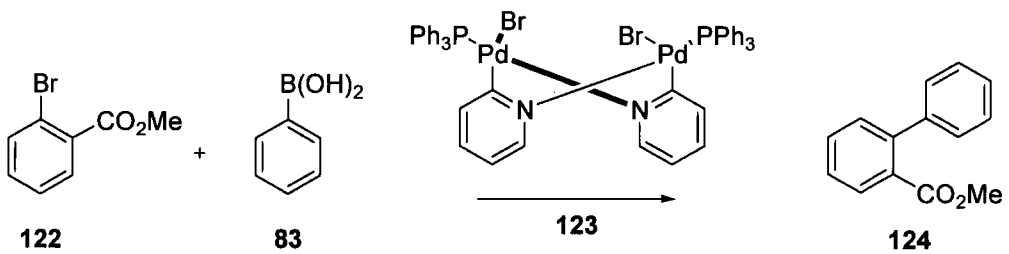
Table 2.3.1b Suzuki-Miyaura cross-coupling of **103**. (i) Reagents and conditions: $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 24 h; for **110a**, 20 °C, 16 h; for **110b**, 60 °C, 15 min.

The reactions are high-yielding with a variety of halogenated coupling partners (*viz.* pyridyl, pyrimidyl, pyrazyl and phenyl derivatives). The reaction is versatile with respect to functional group tolerance (*viz.* nitro, amine, amide, ester and trifluoromethyl) thereby allowing access to highly-functionalised 2-ethoxy-3-aryl/heteroaryl-pyridine derivatives, which are attractive as candidates for pharmaceutical and agrochemical uses. The high-yielding reactions in the presence of a primary amine substituent (entries 4, 5 and 7) are

notable, as protection of the amino group was previously generally considered to be necessary for Suzuki reactions (see chapter 3).[9]

Substrates **104-112** gave the optimized yield of products after 24 h at reflux, as judged by TLC and ^{1}H NMR monitoring of the reaction mixture. Reagent **110a** is a notable exception. A high yield of product **119** (78%) was obtained after only 15 minutes reflux; the yield decreased after 2 h and 8 h to 40% and 12%, respectively; with 24 h reflux an intractable green product was obtained. Indeed, the reaction of **103** with **110a** at 20 °C for 16 h gave **119** in 90% yield. The chloro-analogue **110b** was also very reactive: 62% yield of **119** was obtained after only a 15 minutes reaction time at 60 °C. Refluxing analytically pure compound **119** in dioxane in the presence of base led to the decomposition of **119** to yield an insoluble green solid which accounted for the reduced isolated yield of **119** at longer reaction times. The reasons for the increased reactivity of **110a** and **110b**, compared to **104-109** and **111-112**, were investigated. Some relevant literature and model reactions, as described below.

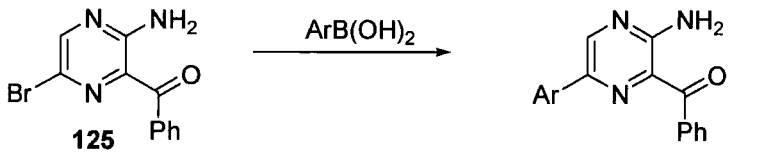
Cross-coupling reactions of organoboronic acids and organic halides require the presence of a negatively charged base, such as an aqueous solution of sodium or potassium carbonate, phosphate or hydroxide. The difficulties that can be encountered during a reaction in a basic solution are side reactions, such as the saponification of esters, racemization of optically active compounds, or Aldol condensations of carbonyl compounds.[10] The literature precedents are that esters can remain intact during Suzuki-Miyaura cross couplings.[11-20] For example, Beeby *et al.* published the cross coupling of methyl 2-bromobenzoate (**122**), where the methyl ester group is *ortho* to the halide, with phenylboronic acid in 62% yield at reflux for 4 h in the presence of aqueous sodium carbonate (Scheme 2.3.1b).[21]



122 **83** **123** **124**

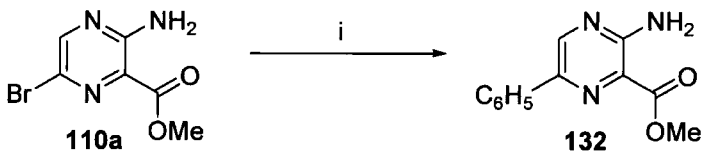
Scheme 2.3.1b: Reagents and Conditions; 0.2 mol% **123**, 1 M Na_2CO_3, THF, 60 °C.[21]

Suzuki-Miyaura cross-coupling reactions where the aryl-X species contains both amine and ketone functionalities have also been published by Jones *et al.* (Scheme 2.3.1c). The reacting halide is *ortho* to a nitrogen and *meta* to the methyl ester group. This coupling took place over 3-48 h to give the products shown in high yields (82-96%).[22]



Scheme 2.3.1c: Reagents and Conditions; 1,4-bis(diphenylphosphino)butane, bis(benzonitrile)palladium(II) dichloride, 1 M Na_2CO_3, toluene, reflux.[22]

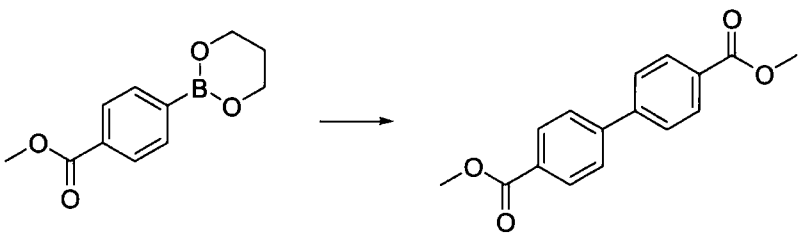
Thompson *et al.* published the cross coupling of areneboronic acids with 6-halo-2-aminopyrazinoate esters in the presence of triethylamine and a range of palladium catalysts in DMF at 90 °C for 12 h (Scheme 2.3.1d).[23] This first proved that **110a** could be used in Suzuki-Miyaura cross coupling reactions.



Scheme 2.3.1d: Reagents and Conditions; (i) $Pd(PPh_3)_4$, **83**, DMF, Et_3N, 90 °C, 12 h.[23]

However, ester groups have been found to be problematic for some Suzuki-Miyaura cross coupling reactions.[17, 18] Yoshida *et al.* published base-free reaction conditions for the homo-coupling of arylboronic esters, stating that it was possible to couple arylboronic

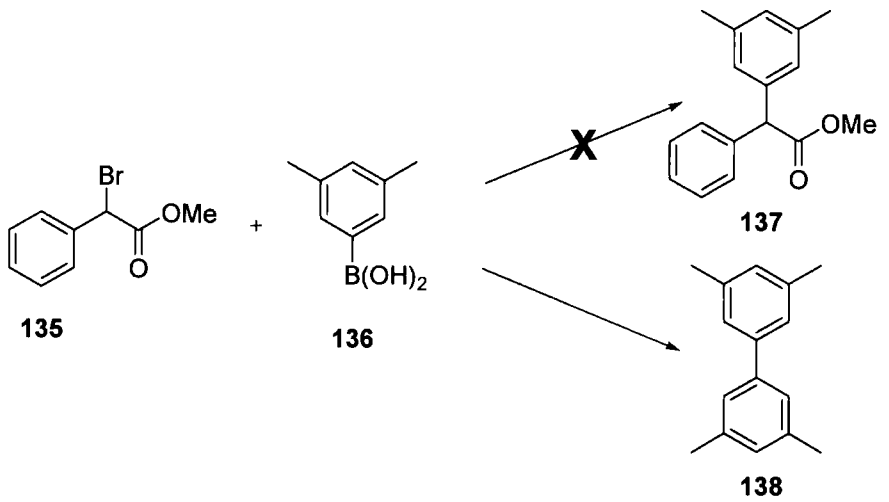
esters bearing base-sensitive functional groups, namely methyl ester groups. They showed that arylboronic esters bearing electron-withdrawing groups or an electron-donating group at the *para* position afforded the homocoupled-product in excellent yields (87-99%). However, even in the base-free conditions, the homocoupling of 4-methyl ester phenylboronic ester (**133**) (*para*- methyl ester group to the reacting site), and other base sensitive groups, was carried out at a lower temperature of 60 °C (all other couplings were carried out at 80 °C). The reason for the lower temperature was not explained in the paper. The homo-coupled product (**134**) was obtained in 51% yield after 72 h at 60 °C (Scheme 2.3.1e).



133 **134**

Scheme 2.3.1.e: Reagents and Conditions; 3 mol% $Pd(OAc)_2$, 4.5 mol% DPPP, DMSO, 60 °C, O_2.[18]

Zhang and Lei published the homo-coupling of arylboronic acids initiated by the transmetallation of palladium enolates.[17] This was discovered whilst attempting to couple α-bromophenylacetate (**135**) and 3,5-dimethylphenyl boronic acid (**136**). They were unable to couple the ester to obtain the expected product (**137**) and obtained only the homo-coupled product (**138**) (Scheme 2.3.1f). In the absence of an α-bromo ester no coupling product could be obtained. Interestingly, when coupling **136** and ethyl α-bromo acetate the homo-coupling and cross-coupling reaction compete and both products are obtained.



Scheme 2.3.1f: Reagents and Conditions; $Pd_2(dba)_3.CHCl_3$, rac-BINAP, Cs_2CO_3, dioxane, 100 °C.[17]

Our investigation into the stability and reactivity of **110a** in Suzuki-Miyaura cross-coupling reactions is detailed in Table 2.3.1c. We considered that **110a** might be highly reactive with all pyridylboronic acids, but coupling reactions with **40** and **43** showed that this was not the case. The anomalously high reactivity of **103** may be due to the increased solubility of **103**, affording faster reaction rates at lower temperatures. The *meta* methyl ester in conjunction with a nitrogen *ortho* to the reacting bromide may assist with the coordination of the palladium catalyst thereby accelerating oxidative addition. The reason for the lower reactivity of **139** (entry 1) is at present not fully understood and may be due to absence of the *ortho* nitrogen. Entries 2 and 3 show that (predictably) there is no steric interference from the reacting ester.

Table 2.3.1c. Boronic Acid + R-X $\xrightarrow{i}$ **141-143**

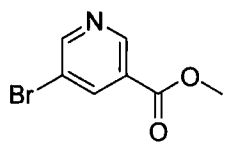
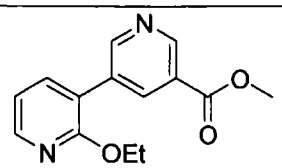
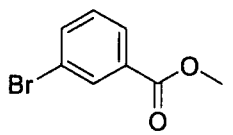
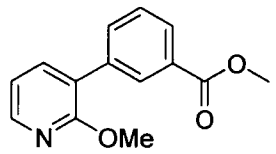
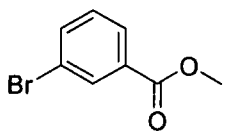
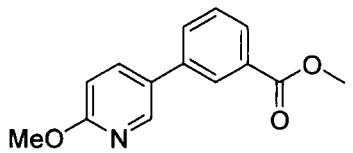
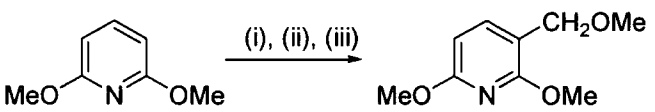
Entry	Boronic Acid	R-X	Product	Isolated yield (%)
1	**103**	 **139**	 **141**	67 (21[a])
2	**43**	 **140**	 **142**	77
3	**40**	 **140**	 **143**	79

Table 2.3.1c: Reagents and conditions: $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 15 min, ([a] room temp, 19 h).

Compounds **139** and **140** are stable at reflux in both neat dioxane, and in dioxane with $Pd(PPh_3)_2Cl_2$. However, refluxing in dioxane with 1 M Na_2CO_3 resulted in an intractable solid. This leads us to believe that a heat-induced, base-initiated polymerasation. Due to the Suzuki-Miyaura cross coupling reactions that Thompson *et al.* published (Scheme 2.3.1d) the base-initiated reaction must only occur in the presence of selected bases.

2.3.2 2,6-Dimethoxy-3-pyridylboronic Acid

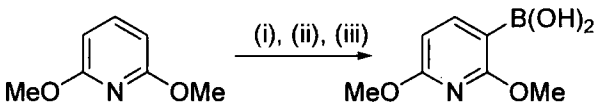
The metallation of 2,6-dimethoxypyridine (**144**)[24, 25] was published by Khanapure *et al.* and unlike 2-methoxypyridine (**101**), no additional compounds were observed when **144** was treated with *n*-BuLi (Scheme 2.3.2a).



144 **145**

Scheme 2.3.2a: 2,6-Dimethoxy-3-(methoxymethyl)pyridine (**145**) synthesis. Reagents and Conditions: (i) *n*-BuLi, THF, 10 °C, 30 min, (ii) $ClCH_2OMe$, (iii) hydrolysis.[24]

We therefore applied the methodology developed for the synthesis of 2-ethoxy-3-pyridylboronic acid (**103**) to 2,6-dimethoxypyridine (**144**). Accordingly, **146** was readily obtained by the directed *ortho*-metallation reaction[6] of **144** (LDA in THF) followed by the addition of triisopropylborate and an aqueous workup (Scheme 2.3.2b).



(144) **(146)**

Scheme 2.3.2b: 2,6-Dimethoxy-3-pyridylboronic acid (**146**) synthesis. Reagents and Conditions: (i) DPA, *n*-BuLi, THF, -10 °C, 30 min, (ii) **147**, -78 °C, 3 h (iii) TPB and aqueous work-up.

Crystals of **146** grew over 4 months from a water/ethanol mixture and the X-ray structure, which was solved by Dr. A Batsanov, is shown in figure 2.3.2a.

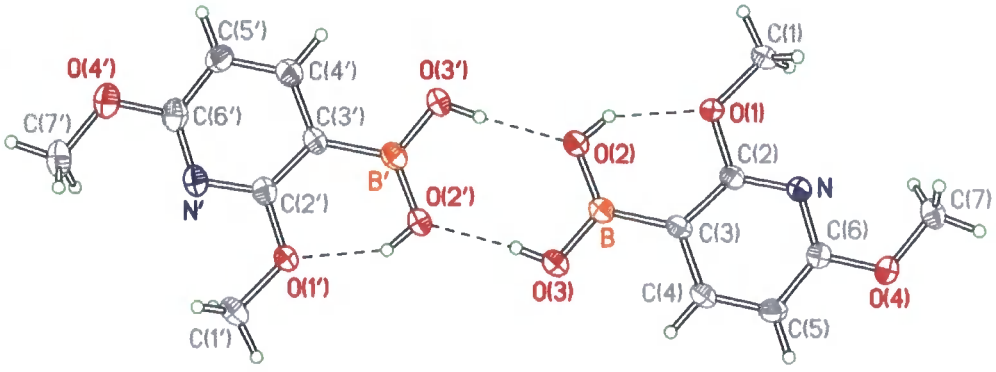


Figure 2.3.2a: X-ray crystal structure of **146** (dashed lines are H-bonds).

The X-ray crystal structure of **146** provided proof that the free boronic acid had been obtained and not the anhydride, *i.e.* the boroxin. The X-ray crystal structure of **146**, showed a H-bonded dimer, like the X-ray crystal structures of **22** and **23** (figure 1.1a) previously published[2] and the structure of **40** (figure 2.2a). An intramolecular O-H···O hydrogen bond which forms a geometrically favourable six-membered ring (Figure 2.3.2a) is also observed.

The initial reactions (1-5 g scale) were carried out at - 78 °C, although the reaction was successful at - 10 °C on scale up (100 g) to obtain a 45% yield of **146**. It was shown, on a 1 g scale, that using DPA and *n*-BuLi gave a higher yield (82%) than using commercial LDA (52%). Suzuki-Miyaura cross-coupling reactions of **146** were carried out with **147**, **110a** and **148** under standard conditions [$Pd(PPh_3)_2Cl_2$, dioxane, reflux] to yield products **149-152**, respectively, in good yields. The results are collated in Table 2.3.2a.

Table 2.3.2a **Boronic Acid** + R-X $\xrightarrow{i}$ **149-152**

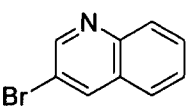
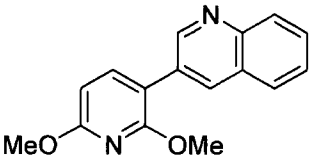
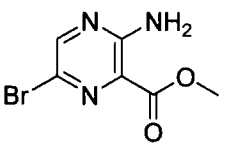
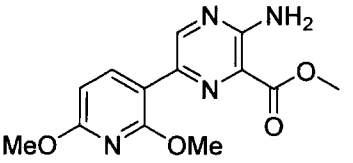
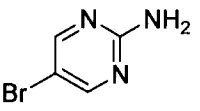
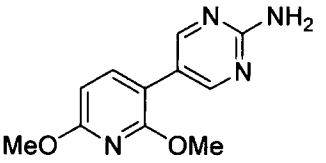
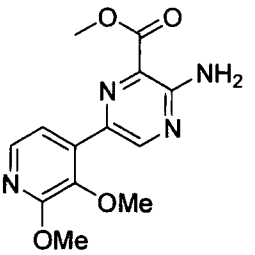
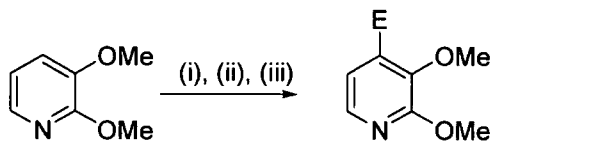
Entry	Boronic Acid	R-X	Product	Isolated yield (%)
1	**146**	 **147**	 **149**	83
2	**146**	 **110a**	 **150**	74
3	**146**	 **148**	 **151**	75
4	**158**	 **110a**	 **152**	86

Table 2.3.2a: Suzuki-Miyaura cross-coupling of **146** and **158**. (i) Reagents and conditions: $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 24 h; for **110a** 15 min.

2.3.3 2,3-Dimethoxy-4-pyridylboronic Acid

It is known that lithiation at C4 of 2,3-dimethoxypyridine (**153**) proceeds using 2 equivalents of *n*-BuLi at 0 °C to produce **154** - **157** (Scheme 2.3.3a).[26] It was stated that no lithiation was observed when **153** was treated with 2.2 equiv of *n*-BuLi at -70 °C. Using 1.2 equivalents of *n*-BuLi at 0 °C gave only a very poor metallation yield (5-15 %). It was stated that this was due to 1 equivalent of the base being entirely chelated by the two methoxy groups and/or the nitrogen atom of the pyridine.

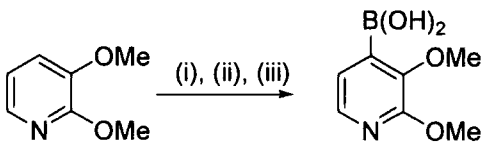


153

154 a) E = D
155 b) E = Br
156 c) E = CH(OH)Ph
157 d) E = OH

Scheme 2.3.3a: 156 a-d synthesis. Reagents and Conditions: (i) 2 eq. *n*-BuLi, THF, 0 °C, 1 h, (ii) E^+, (iii) hydrolysis (60-99%).[26]

This may be the reason we found that the synthesis of 2,3-dimethoxy-4-pyridylboronic acid (**158**) was not readily achieved by the directed *ortho*-metallation reaction of 2,3-dimethoxypyridine (**153**). Due to the high cost and limited availability of **153**, the synthesis of **158** was only attempted once. We followed the methodology developed for the synthesis of 2,6-dimethoxy-3-pyridylboronic acid (**146**) apart from using TMB instead of TPB to limit the effects of steric hindrance (Scheme 2.3.3b).



153 **158**

Scheme 2.3.3b: 2,3-Dimethoxy-4-pyridylboronic acid (**158**) synthesis. Reagents and Conditions: (i) DPA, *n*-BuLi, THF, -10 °C, 30 min, (ii) **153**, -78 °C, 3h (iii) TMB and aqueous work-up.

One equivalent of *n*-BuLi was used, as using two equivalents for the synthesis of other 2,3-disubstituted-4-pyridylboronic acid had been found to not increase the yield (see Chapter 4). **158** was thereby synthesised in 12% yield which meant there was only a limited quantity for use in further reactions. For this reason only one cross-coupling was carried out with **110a** as the coupling partner, this halide was chosen as the product would be a very highly functionalised biheteroaryl (**152**) (Entry 4, Table 2.3.2a) which was obtained in 86% yield.

2.4 Conclusion

A range of novel alkoxy- and dialkoxy-substituted pyridylboronic acids have been synthesized and the synthesis of existing boronic acids have been optimized and scaled up. These have been shown to serve as versatile compounds for the preparation of highly-functionalised aryl/heteroaryl-pyridine libraries.

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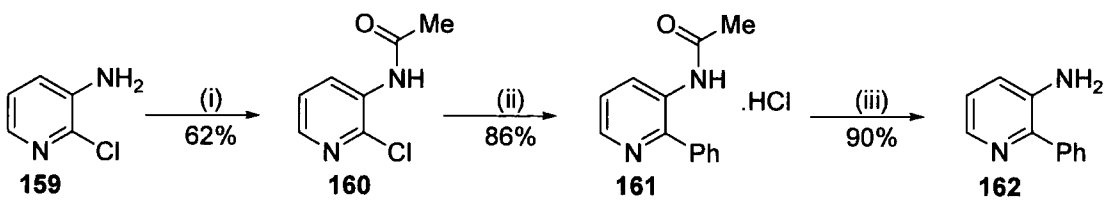
Chapter 3

Amine Substituted Couplings and Amine Substituted Boronic acid

3.0 Chapter 3

3.1 Introduction

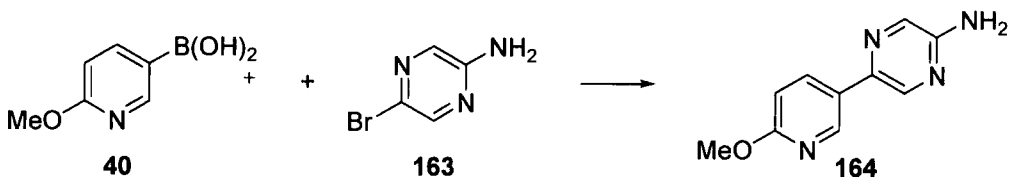
At the beginning of this project there were publications stating that Suzuki-Miyaura cross-coupling reactions could not be carried out with compounds bearing labile protons (especially primary amines, carboxylic acids and alcohols) and thereby additional protection/deprotection steps were necessary.[1-3] Ali *et al.* obtained no product from attempted Suzuki-Miyaura cross-coupling reactions with 2-chloropyridine-3-carboxamide and 5-chloropyridin-2(1*H*)-one and similar reactions of 2-chloro-3-hydroxypyridine gave only a very low yield (15%) of cross-coupled product.[4] 3-Iodoanthranilic acid failed to react with a range of arylboronic acids.[5] More recently, Caron *et al.* reported that the attempted cross-coupling reaction between phenylboronic acid (**83**) and 2-chloro-3-aminopyridine (**159**) was unsuccessful.[1] However, when the aminopyridine was first protected as the acetamide (**160**), the coupling proceeded efficiently in an 86% yield (Scheme 3.1a).



Scheme 3.1a: Synthesis of 2-phenyl-3-aminopyridine (**162**). Reagents and Conditions; (i) AcCl, Et_3N, CH_2Cl_2; (ii) a, **83**, Na_2CO_3 (aq.), EtOH, $PhCH_3$, $Pd(PPh_3)_4$, (ii) b, MeOH, HCl; (iii) HCl.[1]

It should be noted that during the course of our work Meier *et al.* reported successful Suzuki coupling reactions of unprotected bromopyridylcarboxylic acids with 4-

formylphenylboronic acid.[6] There are only isolated examples in the literature of successful reactions in the presence of an NH_2 group, and many of these are low yielding.[6-14] One example, *viz.* the preparation of **164**, was published previously by our group, in 26% yield, but at the time its significance was not appreciated (Scheme 3.1b).[15]



Scheme 3.1b: Suzuki-Miyaura cross-coupling in the presence of an amine group. Reagents and conditions; $Pd(PPh_3)_4$, DMF, 1 M Na_2CO_3, 80 °C, 65 h.[15]

Prior to our work no systematic study using the same catalyst and reaction conditions while varying the amino-containing substrate and the arylboronic acids was available. Therefore, we decided to carry this out and this work is discussed in the following section.[16]

3.2 Suzuki-Miyaura Cross-Couplings with a Partner Bearing a Primary Amine Group

Initially we utilized the 2-methoxy-5-pyridylboronic (**40**) and 2-methoxy-3-pyridylboronic acids (**43**) in these reactions as we had successfully scaled up their syntheses (Chapter 2). In addition to this, there is widespread interest in pyridylboronic acid derivatives and their derived libraries of aryl/heteroarylpyridines.[15, 17-28] Examples of reactions using other boronic acids were carried out for comparison (Chart 3.2a).

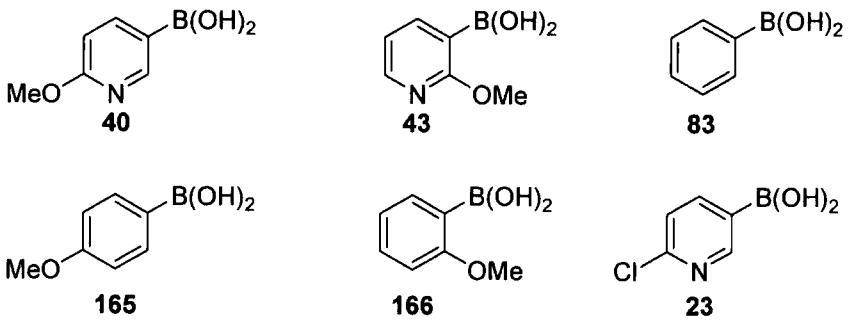
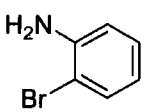
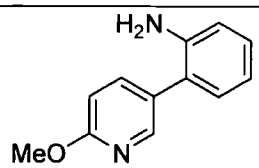
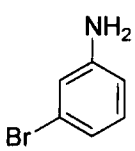
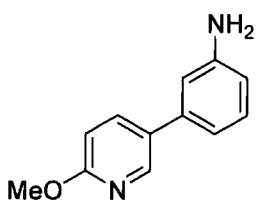
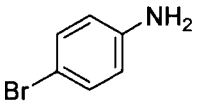
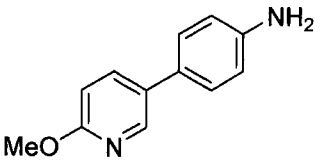
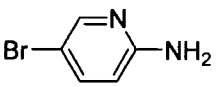
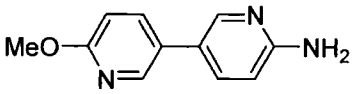
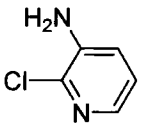
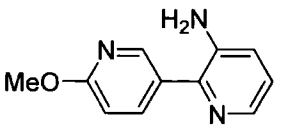
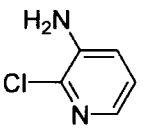
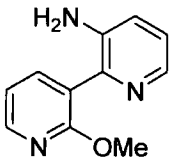
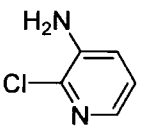
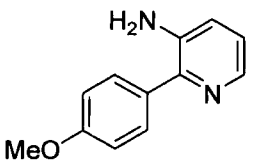
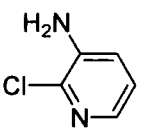
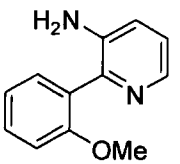
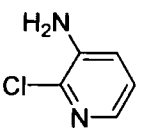
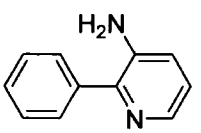


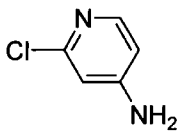
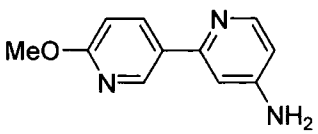
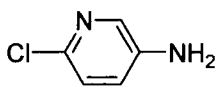
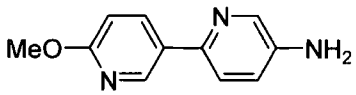
Chart 3.2a; Structures of boronic acids used in this study

The standard reagents and conditions used for most of these Suzuki-Miyaura cross-coupling reactions were aqueous sodium carbonate as base and bis(triphenylphosphino)palladium dichloride as catalyst in 1,4-dioxane at 95 °C, although other conditions were used (Table 3.2a). The results clearly show that many reactions proceed in moderate or high yields in the presence of a primary amine group, thereby directly affording novel amino-substituted biaryl/heteroaryl systems without the need for protection/deprotection steps. The table has been split into sections to allow several trends to be discussed.

Table 3.2a. **Boronic Acid + R-X** $\xrightarrow{i}$ **173-183**

Entry	Boronic Acid	R-X	Product	Isolated yield (%)
1	**40**	 **167**	 **173**	81
2	**40**	 **168**	 **174**	78

3	**40**	 **169**	 **175**	80
4	**40**	 **170**	 **176**	77
5	**40**	 **159**	 **177**	82
6	**43**	 **159**	 **178**	69
7	**165**	 **159**	 **179**	80
8	**166**	 **159**	 **180**	70
9	**83**	 **159**	 **181**	86

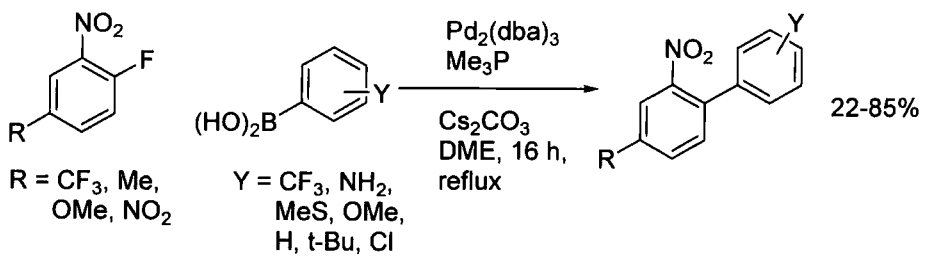
10	**40**	 **171**	 **182**	40*
11	**40**	 **172**	 **183**	40*

* problems with isolation caused a slightly lower yield of isolated product.

Table 3.2a: Suzuki-Miyaura cross-coupling reactions. Reagents and conditions: $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 aq (1 M), reflux, 28 h.

Entries 1-4 show that the position of the bromine on the ring relative to the amine substituent made no difference to the reactivity, whether on a phenyl or pyridyl ring (yields 77-81%). π–Deficient heteroaryl chlorides are known to be reactive partners in Suzuki reactions,[4, 12] but comparing entries 4 and 11 shows that, under these conditions, chloro-coupling partners are significantly less reactive than the equivalent bromo-partner (40 and 77% yields, respectively). It is known that Suzuki Miyaura cross-couplings of arylboronic acids and less-reactive (electron-rich) chloroaromatics proceed in the presence of $P^tBu_3/[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) under conditions where $[Pd_2(dba)_3]$ alone is ineffective. Indeed, we have shown that product yields using 2,3-dichloro-4-pyridylboronic acid and 2,6-dichloro-3-pyridylboronic acid with 3-bromoquinoline, are significantly increased using $P^tBu_3/Pd(PPh_3)_2Cl_2$ compared to $Pd(PPh_3)_2Cl_2$ alone (see Chapter 4). However, the addition of P^tBu_3 (10 mol %) to the reaction mixtures in entries 10 and 11 had no effect on these selected lower-yielding reactions in Table 3.2a. A comparison of entries 5, 10 and 11 shows that 3-amino-2-chloropyridine (**159**) is a more reactive substrate than the 4-amino- and 5-amino- isomers **171** and **172**, respectively. Indeed, **159** also reacted with the 4-methoxyphenyl- (**165**) and phenyl- (**83**) boronic acids to give the expected cross-coupled products (**179** and **181**) in 80 and 86% yields, respectively (Entries 7 and 9). The lower yield obtained from reacting **159** with 2-methoxyphenylboronic acid

(**166**) (Entry 8) and 2-methoxy-3-pyridylboronic acid (**43**) (Entry 6) is presumably due to steric hindrance. The increased reactivity of **159** is presumed to be due to the amino group's ability to coordinate with the palladium atom of the catalyst (possibly with displacement of a PPh_3 ligand), and the high yield with **159** is ascribed to steric factors in the complexed intermediate facilitating the displacement of the *ortho*-halogen. This concept of coordination has been noted in several publications to be discussed below. Chatani *et al.* stated that the coordination of the nitrogen to palladium is the key step in efficient reactions of 2-pyridyl esters with phenylboronic acids.[29] To date, Widdowson and Wilhelm published the only examples of Suzuki-Miyaura cross coupling using uncomplexed fluoroarenes as the reactive partner (Scheme 3.2a).[30] The reaction tolerated a wide range of boronic acids, however, a nitro group *ortho* to the fluorine was essential for the reaction to occur. The 2-nitro group is required to assist oxidative addition of the palladium into the C-F bond by both electron withdrawing effects and, more importantly, by coordinating the palladium atom. Schroter *et al.* reported that cross-couplings show a high regioselectivity at the C-2 position on a number of ring systems (*e.g.* thiophenes, benzothiophenes, furans, benzofurans, pyrroles).[31]



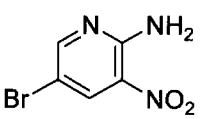
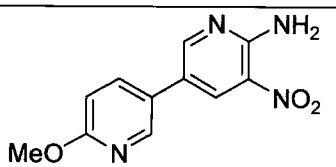
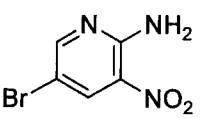
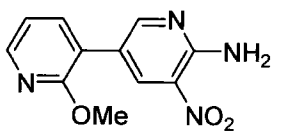
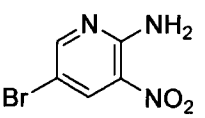
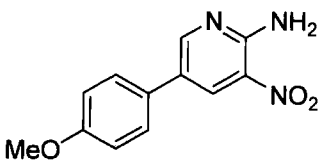
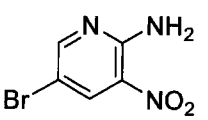
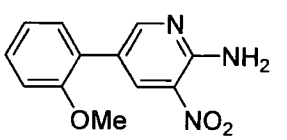
Scheme 3.2a: Suzuki-Miyaura cross-couplings of fluoroarenes.[30]

Ali *et al.* stated that 2,5-dichloropyridine underwent selective cross-coupling at the C-2 position and suggested that this may be due to coordination of the palladium to the pyridine nitrogen.[4] Fu *et al.* found that chloro- substituted pyridines had the potential to bind to the

palladium through the nitrogen and were therefore suitable substrates for room-temperature Suzuki-Miyaura cross-coupling reactions.[10] In their hands 2-chloropyridine coupled with **83** in a higher yield of 97% than 3-chloropyridine (77%).

The reactions of the substrates detailed in entries 5 and 10 were also carried out on 5 g scales; products **177** and **182** were obtained in 80 and 60% yields, respectively. The increased yield of 60% was due to less material being lost during isolation of the product.

Table 3.2b. Boronic Acid + R-X $\xrightarrow{i}$ 184-194

Entry	Boronic Acid	R-X	Product	Isolated yield (%)
12	**40**	 **107**	 **184**	69
13	**43**	 **107**	 **185**	75
14	**165**	 **107**	 **186**	75
15	**166**	 **107**	 **187**	69

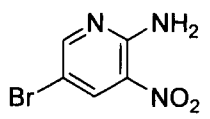
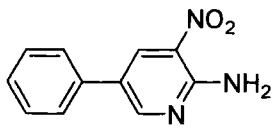
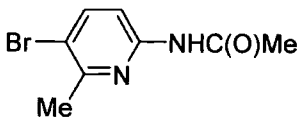
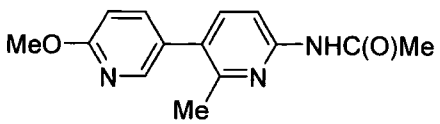
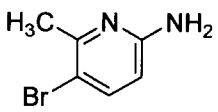
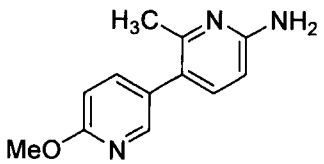
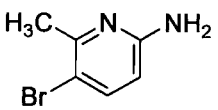
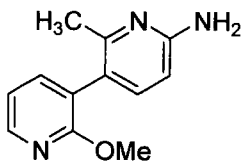
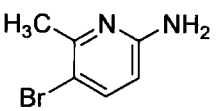
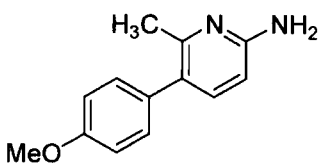
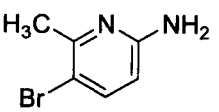
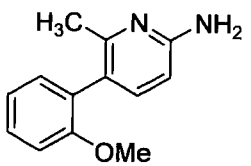
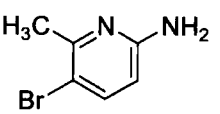
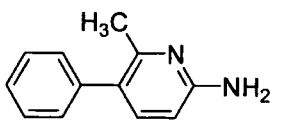
16	**83**	 **107**	 **188**	80
17	**40**	 **109**	 **189**	81
18	**40**	 **108**	 **190**	73
19	**43**	 **108**	 **191**	75
20	**165**	 **108**	 **192**	65
21	**166**	 **108**	 **193**	75
22	**83**	 **108**	 **194**	68

Table 3.2b: Suzuki-Miyaura cross-coupling reactions. Reagents and conditions: (i) $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 8 h.

Entries 12-22, using substrates **107-109**, demonstrate that more highly-functionalised amino-substituted bipyridines can also be obtained in synthetically viable yields. The conditions of the reaction shown in entry 12 were varied to establish the optimum mol% of catalyst, amount of base and reaction time needed. The reaction was repeated using three different molar ratios of catalyst while keeping all the other parameters the same. The results which are shown in Table 3.2c, established that when using $Pd(PPh_3)_2Cl_2$ for these couplings 5 mol% is required and that there is no advantage in using more than this.

Reaction No.	Mol% $Pd(PPh_3)_2Cl_2$	Isolated yield (%)[a]
1	1	37
2	5	69
3	10	67

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

Table 3.2c: Results from the formation of **184** with varying molar ratios of catalyst.

The reaction was then repeated using 5 mol% catalyst but varying the reaction time; the results are shown in Table 3.2d. No increase in yield was observed after 8 h. The reaction was also carried out for 8 h, using 5 mol% catalyst and varying the base (Na_2CO_3, K_2CO_3, Cs_2CO_3 and Ba_2CO_3). Yields were found to be independent of the base used (yields 67-69%).

Reaction No.	Time (h)	Isolated yield (%)[a]
1	2	32
2	8	69
3	12	64
4	24	61

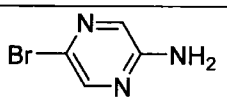
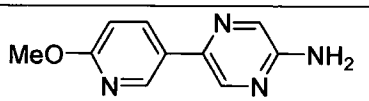
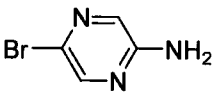
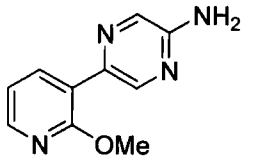
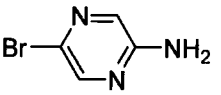
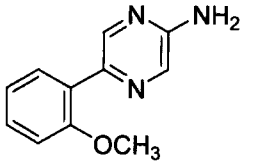
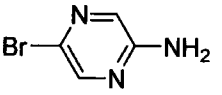
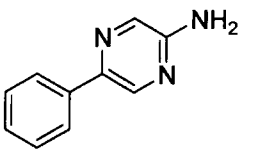
5	48	66
6	65	68

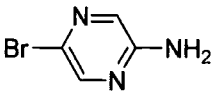
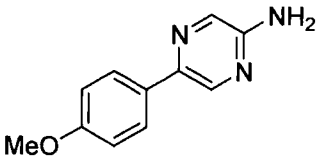
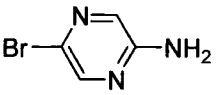
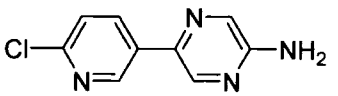
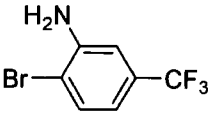
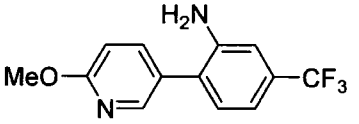
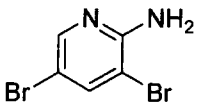
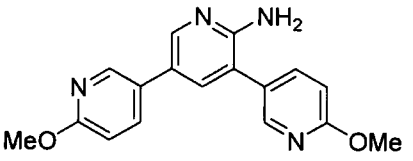
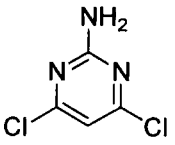
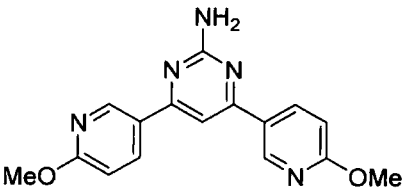
[a] ^{1}H NMR determined identification and purity of the products (>98% pure in all cases).

Table 3.2d: Results for the formation of **184**, for varying times (h).

Protection of amine **108** was carried out using a modification of the procedure of Wright *et al.*[32] to give the analytically-pure acetamide derivative **109** in 93% yield. Entry 17 shows that **109** reacted in a similarly high yield to the free amine (Entry 18).

Table 3.2e. Boronic Acid + R-X $\xrightarrow{i}$ **198-206**

Entry	Boronic Acid	R-X	Product	Isolated yield (%)
23	**40**	 **163**	 **198**	60
24	**43**	 **163**	 **199**	70
25	**166**	 **163**	 **200**	71
26	**83**	 **163**	 **201**	68

27	**165**	 **163**	 **202**	69
28	**23**	 **163**	 **203**	62
29	**40**	 **195**	 **204**	84
30	**40**	 **196**	 **205**	76*
31	**40**	 **197**	 **206**	35

* Reaction was repeated using 1.2 equiv of **40**.

Table 3.2e: Suzuki-Miyaura cross-coupling reactions. Reagents and conditions: (i) $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 aq (1 M), reflux, 8 h.

The reactions were extended using 2-amino-5-bromopyrazine **163** which reacted in moderate yield with the boronic acids **40**, **43**, **165**, **166**, **83** and **23** (entries 23-28) to provide novel pyrazinylpyridine derivatives **198-203**. Entry 28 establishes that 2-chloro-5-pyridylboronic acid **23** shows comparable reactivity to the methoxy analogues **40** and **43**.

Entries 30 and 31 extend the scope of the reaction and involve two-fold cross-couplings with the dihalo derivatives **196** and **197** to yield products **205** and **206**, respectively. When compound **40** was used in 1.2 equivalents in the reaction with **196**, the yield of compound **205** was reduced to 32% and a trace amount (<1% yield) of mono-coupled product was also isolated, but not obtained analytically pure. We are confident based on ^{1}H NMR, ^{13}C NMR, gCOSY, ROESY, NOESY, gHSQC and gHMBC data that the mono-substituted product was that derived from the Suzuki cross-coupling *ortho* to the amine, *i.e.*, 5-bromo-3-(6-methoxypyridin-3-yl)pyridin-2-amine (**207**).

Figure 3.2a: Formula and nomenclature for 5-bromo-3-(6-methoxypyridin-3-yl)pyridin-2-amine (**207**)

This would be consistent with concept of the free amine group coordinating to the palladium atom of the catalyst. For ease of discussion for the spectra below the nomenclature shown above (Figure 3.2a) will be used and the peaks will be labelled as shown below (Figure 3.2b).

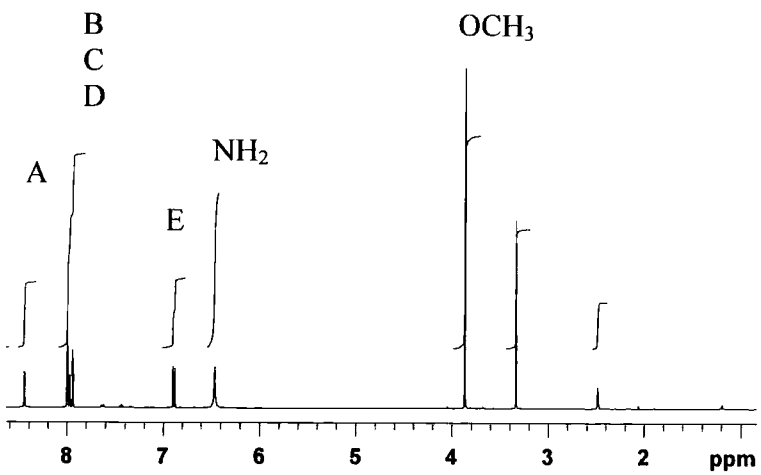


Figure 3.2b: ^{1}H NMR spectrum of **207** in d_6-DMSO.

From the ^{1}H NMR spectrum the amine and methoxy group protons can be easily assigned. The NMR solvent DMSO peak can be seen at 2.5 ppm and a H_2O peak can be seen at ~ 3.3 ppm. The methoxy group protons are next furthest up field as they are aliphatic protons attached to a carbon that is attached to an oxygen at ~ 3.85 ppm. The amine group has a characteristic broad peak at ~ 6.5 ppm. The remaining 5 peaks (Labelled A-E from left to right for ease of discussion) can be assigned to the protons attached directly to the two rings (V – Z). The ^{13}C NMR spectrum shows the correct number of carbons (11), supporting the monocoupled product structure (with a trace of impurity at δ 127 and 129).

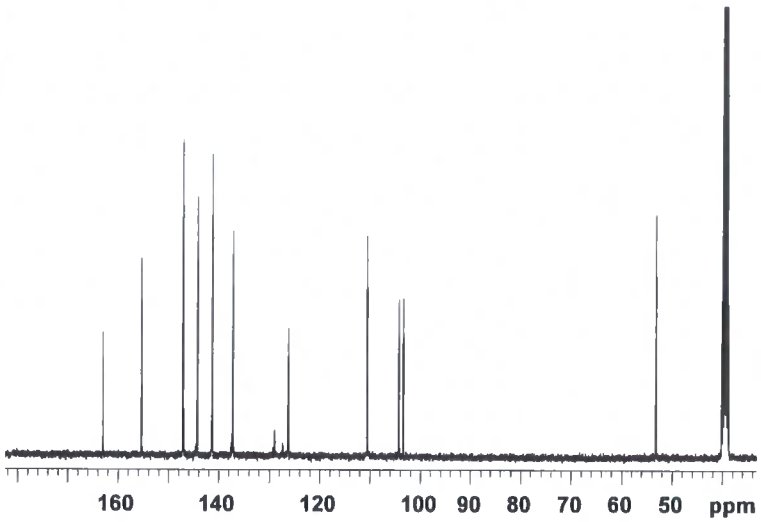


Figure 3.2c: ^{13}C NMR spectrum of **207** in d_6-DMSO (peaks at ~40 ppm)

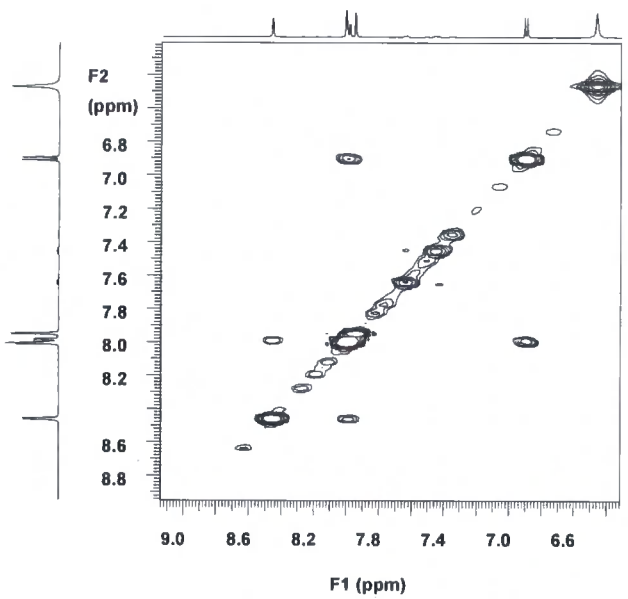


Figure 3.2d: ROESY (Rotating frame Overhauser Enhancement Spectroscopy) spectrum of **207**

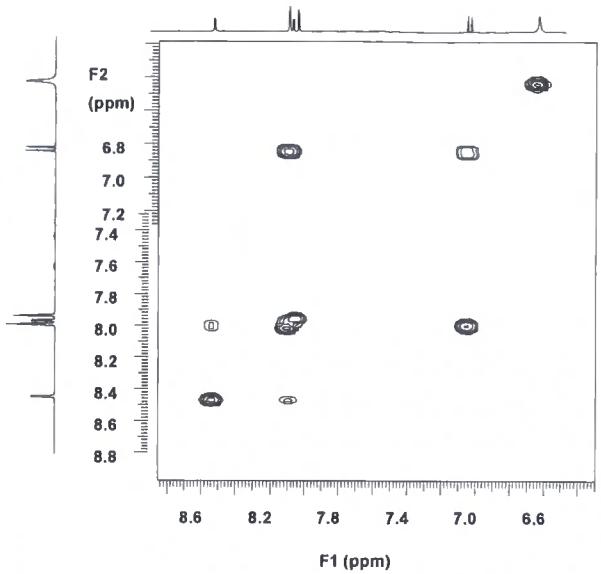


Figure 3.2e: COSY (Correlation Spectroscopy) spectrum of **207**

The observed responses from protons V to Z seen in ROESY and COSY NMR spectra tell us that the proton that gives rise to peak C couples with the protons that give rise to peaks A, and E. Therefore, peaks A, C and E are observed from 3 protons on one ring system (V, W and X). The coupling constants (larger from protons V and W) establish that peak A relates to proton X, peak C relates to proton W and peak E relates to proton V. Peaks B and D relate to protons Y and Z, due to the electronegativity of the nitrogen adjacent carbon 1 (see Figure 3.2a), proton Y is observed further downfield; therefore, Y relates to peak B and Z to D. No response can be seen in the ROESY or COSY NMR spectra from protons Z and Y, this could be due to the bulky amine group restricting rotation of the molecule. If the other mono coupled isomer had been formed, observable coupling between protons Y and X, and Y and W would be predicted to be seen in the ROESY spectrum.

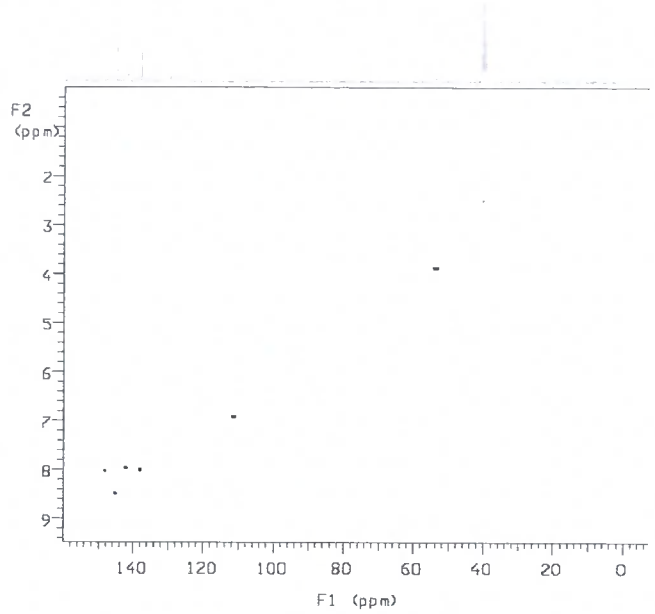


Figure 3.2f: Part of HSQC (Heteronuclear Single Quantum Coherence) spectrum of **207**

A HSQC spectrum shows which proton is directly attached to which carbon, therefore the proton peaks relating to; the carbon that is attached to the bromine (2 or 4) and the carbon that is attached to the amine group (5) were identified, as neither carbons couple to any protons.

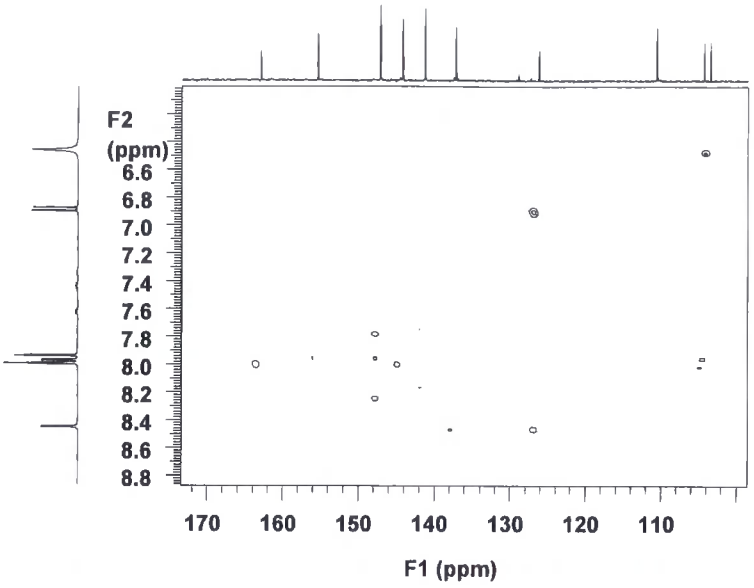
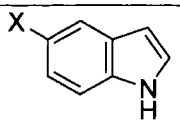
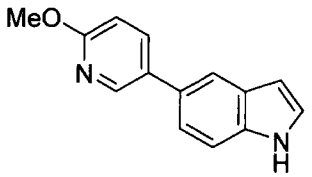
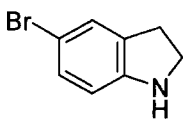
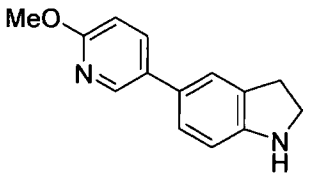
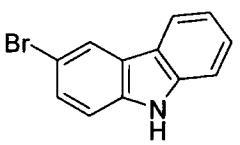
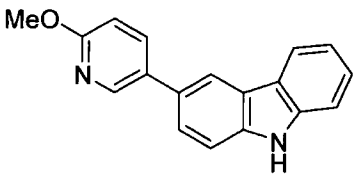
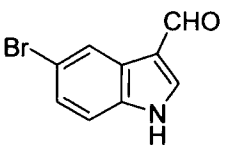
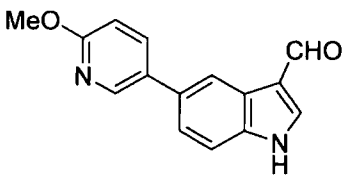
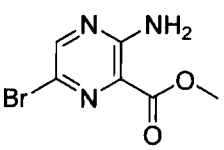
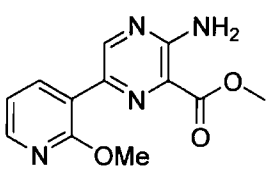


Figure 3.2g: Part of HMBC (Heteronuclear Multiple Bond Correlation) spectrum of **207**

The HMBC allows the peak relating to the carbon attached to the amine group to be identified, therefore the other carbon, of the two identified by the HSQC, is the one attached to the bromine. That carbon attached to the bromine has long-range coupling with the protons that give rise to peaks B and D (protons Y and Z respectively). The long-range coupling with proton Y confirms the structure in Figure 3.2a. If the cross-coupling reaction had occurred at the carbon which is *para* to the amine group, this coupling in the HMBC spectrum between the carbon attached to the bromine and proton Y should not be observable, as it would be a 4-bond coupling.

Table 3.2f. Boronic Acid + R-X $\xrightarrow{i}$ **213-218**

Entry	Boronic Acid	R-X	Product	Isolated yield (%)
32	**40**	 **208** **a** X = Br **b** X = I	 **213**	45 (from **208a**) 36 (from **208b**)
33	**40**	 **209**	 **214**	22
34	**40**	 **210**	 **215**	52
35	**40**	 **211**	 **216**	54
36	**43**	 **110a**	 **217**	82*

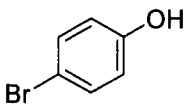
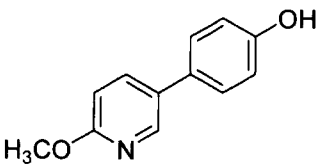
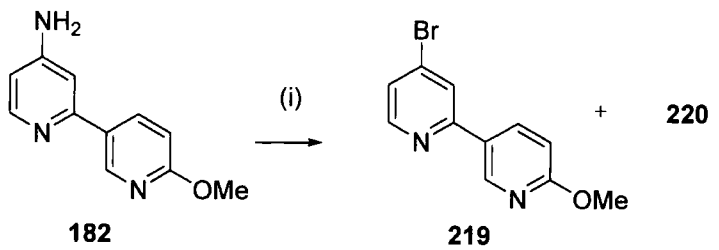
37 **40**  **212**  **218** 82

Table 3.2f: Suzuki-Miyaura cross-coupling reactions. Reagents and conditions: (i) $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 aq (1 M), reflux, 24 h. *15 min, reflux.

Entry 32 suggests there is no significant difference in reactivity between 5-bromo- and 5-iodo-indole under these conditions. However, we cannot generalise, as no other examples were tried. Entries 32 – 35 show that reactions using indole, 2,3-dihydroindole and carbazole derivatives also gave the expected products in moderate yields. Entry 37 was carried out to show that these conditions are not confined to free amine groups, but that hydroxyl groups (which also have labile hydrogens) could also be coupled with **40** in high yields.

3.3 Transformation of 182 via Diazotization

The amine group in the above compounds is a possible site for further reactions, *e.g.* diazotization.[33] Diazonium salts can react with a number of different nucleophiles to form a range of products. Diazotization of 2-(6-methoxypyridin-3-yl)pyridin-4-amine **182** following the standard procedure used previously in our group on other molecules (Scheme 3.3a),[34] gave the expected product **219** in 32% yield where the amino group was replaced with a bromine. A second product **220** was isolated in 30% yield, and 32% of the starting material was also recovered. Structure **220** had an amine group and a bromine group attached this was supported by a combination of mass spectra, elemental analysis, ^{1}H NMR and ^{13}C NMR spectroscopic data.



Scheme 3.3a: Diazotization of **182**. Reagents and Conditions: (i) HBr, $NaNO_2$, NaOH

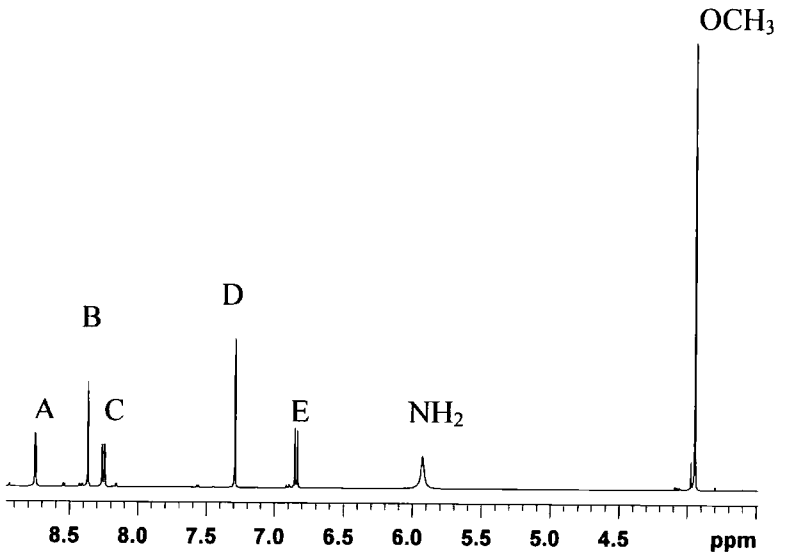


Figure 3.3a: ^1H NMR spectrum of **220** in d_6-acetone

^1H NMR spectra of the second product (**220**) showed 5 aromatic protons (labelled A to E from left to right for ease of discussion) and the broad singlet at 5.8 ppm from the amine protons. The *J* values and splitting of the peaks confirm that the protons resulting in peaks A, C and E are on one ring system, and those resulting in peaks C and E are on adjacent carbons. The two singlets (B and D) relate to two protons on another ring system. Therefore only five protons are present and the amine group (peak at ~5.9 ppm). From this it was concluded that a proton had been displaced by a bromine.

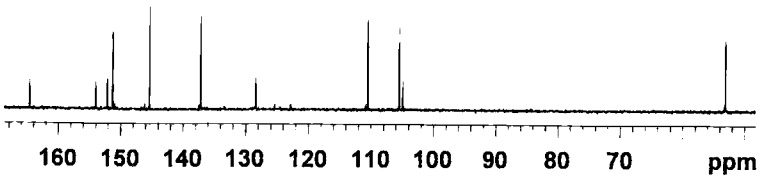


Figure 3.3b: ^{13}C NMR spectrum of **220** in d_6-acetone

The ^{13}C NMR spectrum (Figure 3.3b) shows 11 carbons as expected if the bromine had displaced any proton. Replacing a proton with a bromine causes an upfield shift of the carbon to which it is attached by *ca.* 6 ppm.[35]

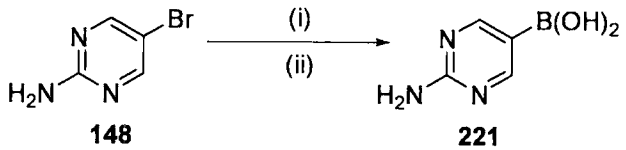
3.4 2-Amino-5-pyrimidylboronic Acid Synthesis

To date, there have been several reports regarding the syntheses of aminophenylboronic acids[36] but no amine-substituted heterocyclic boronic acids have been described. After our success with the synthesis of various amine-substituted bi(hetero)aryls, we turned to an amine-substituted heterocyclic boronic acid, with the view to synthesising a bi(hetero)aryl with amine group(s) on either or both rings.

Our target, 2-amino-5-pyrimidylboronic acid, was chosen for two reasons: (i) the starting material, 2-amino-5-bromopyrimidine (**148**), was readily available and (ii) we had recently successfully synthesised pyrimidylboronic acids (see chapter 4). Compound **148** allowed only one site for halogen-lithium exchange, as the DoM methodology could further complicate the reaction. The reactive lithio-species then reacted with the already present borate. As previous work in our group on the synthesis of other pyrimidylboronic acids,[27] had employed the "reverse addition route" instead of the sequential addition route, this was attempted first.

We recognized that the acidic amino hydrogens of **148** could be problematic under strongly basic conditions; nonetheless, the synthesis was attempted on unprotected **148**

(Scheme 3.4a) using a range of equivalents of lithium, on a 2 g scale, as shown below in Table 3.4a.



Scheme 3.4a: 2-Amino-5-pyrimidylboronic acid synthesis. Reagents and Conditions: (i) TPB, THF, -78 °C, *n*-BuLi, (ii) Aqueous work-up.

Reaction No.	Equiv. *n*-BuLi used	Isolated Yield of 221 (%)[a]
1	1.2	12
2	2.5	46
3	5.0	45
4	10.0	-

[a] ^{1}H NMR determined identification and purity of the products.

Table 3.4a: Results for the formation of **221** using varing equivalents of *n*-BuLi.

The results show that the desired product was obtained in a synthetically-useful yield, and there is no advantage in using more than 2.5 equiv. of *n*-BuLi. As far as we are aware this is the first reported example of lithium-halogen exchange on **148**.

Two examples of Suzuki-Miyaura cross-coupling reactions of **221** were carried out with **147** and **163** under standard conditions [$Pd(PPh_3)_2Cl_2$, dioxane, reflux] to yield products **222** and **223**, respectively, in moderate yields (Table 3.5).

Table 3.4b. **221** + R-X $\xrightarrow{i}$ **222** and **223**

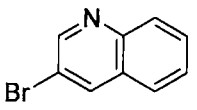
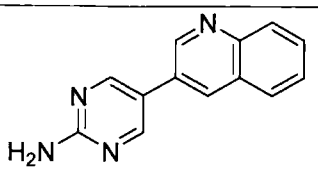
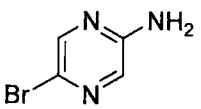
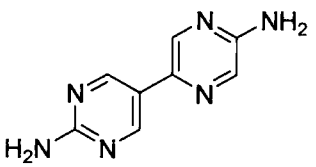
Entry	Boronic Acid	R-X	Product	Isolated yield (%)
1	**221**	 **147**	 **222**	60
2	**221**	 **163**	 **223**	40

Table 3.4b: Suzuki-Miyaura cross-coupling of **221**. Reagents and conditions: (i) $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 aq (1 M), reflux, 24 h.

The versatility of the reactions with respect to functional group tolerance (*viz.* nitro, amide, ester and trifluoromethyl) needs further investigation. This would allow access to highly-functionalised pyrimidine derivatives, which are attractive drug and agrochemical candidates.

3.5 Conclusion

A range of halogenated aromatics and heteroaromatics bearing primary amine groups have been shown to be suitable substrates for Suzuki-Miyaura cross-coupling reactions with arylboronic acids and pyridylboronic acids under standard conditions, without the need for protection/deprotection steps. New amino-substituted arylpyridines, bipyridines, pyrazinopyridines, indolinopyridines, carbazolopyridines and indolopyridines have thereby been obtained. Since our publication on this work,[16] another group has published different cross-couplings in the presence of primary amine groups.[37] In this work, Itoh *et al.* also showed that 3-amino-2-chloropyridine (**159**) is more reactive in Suzuki-Miyaura cross-coupling reactions than other isomers (**171** and **172**).[37]

The first amino-heterocyclic boronic acid, namely 2-amino-5-pyridimidylboronic acid (**221**), has been successfully synthesised in moderate yield. Suzuki-Miyaura cross-coupling reactions have been carried out using **221** to synthesise novel pyrazinopyrimidine and quinolinopyrimidine derivatives. This paves the way for the synthesis of other heterocyclic boronic acids bearing free amine substituents.

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Chapter 4

Synthesis and Application of Novel Halopyridylboronic Acids

4.0 Synthesis and Application of Novel Halopyridylboronic Acids

4.1 Introduction

At the outset of this project there was one publication in the literature of a dihalopyridylboronic acid.[1] As stated in Chapter 1, Gallagher *et al.* had prepared 5-bromo-2-fluoro-3-pyridylboronic acid (**47**) in 80% yield by a DoM reaction of 5-bromo-2-fluoropyridine (**46**), followed by reaction with trimethylborate and described a sequence leading to 3,5-disubstituted 2-fluoropyridines which were converted into the corresponding 2-pyridone derivatives (Scheme 1.1o).

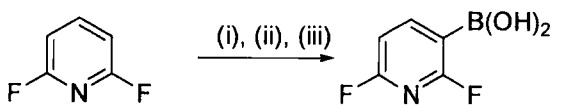
In 2002, Rault *et al.* published the synthesis and Suzuki-Miyaura cross coupling of a number of chloropyridylboronic acids; 2-chloro-3-pyridylboronic acid (**27**) and 2-chloro-5-pyridylboronic acid (**23**) with 2-bromobenzonitrile in 57 and 72% yields respectively,[2] and 4-chloro-3-pyridylboronic acid (**29**) with 4-bromotoluene in 54% yield, although no characterisation of the coupled products was given.[3]

It was our aim to synthesise a series of dihalopyridylboronic acids via DoM methodology. DoM methodology does not require brominated starting materials and therefore cheaper and more readily available reagents can be used which makes the procedure more commercially viable on an industrial scale. We later extended the chemistry to produce a halopyrimidylboronic acid by using halogen-lithium exchange methodology.

4.2 2,6-Difluoro-3-pyridylboronic Acid

Following the successful synthesis of 2,6-dimethoxy-3-pyridylboronic acid (**146**), we applied the methodology to 2,6-difluoro-3-pyridylboronic acid (**225**) which was expected to be readily accessible by a DoM reaction[4] of **224** (LDA in THF) followed by the addition of triisopropylborate and an aqueous workup. The initial attempts using an aqueous workup were unsuccessful, upon acidification of the aqueous layer to pH 6 no solid precipitated even after prolonged stirring (24 h). The aqueous layer was further

acidified to pH 1 but still no precipitate formed. TLC analysis of the aqueous layer showed a base line spot characteristic of a boronic acid. Extraction with ethyl acetate and recrystallisation gave product **225** in 68% yield. Using TMB instead of TPB gave a similar yield (70%). However, the yield of **225** increased to 82% when DPA and *n*-BuLi were used to generate LDA instead of using commercial LDA (Scheme 4.2a). The reaction was scaled-up to give 50 g of **225** in 34% unoptimised yield.

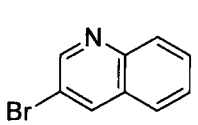
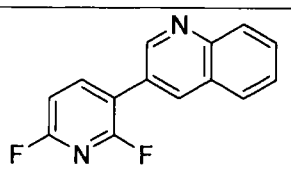


224 **225**

Scheme 4.2a: 2,6-Difluoro-3-pyridylboronic acid (**225**) synthesis. Reagents and Conditions: (i) DPA, *n*-BuLi, THF, -10 °C, 30 min, (ii) 2,6-dimethoxypyridine, -78 °C, 3 h (iii) TPB and aqueous work-up (including ethyl acetate extractions).

Suzuki-Miyaura cross-coupling reactions of **225** were carried out with a range of aryl/heteroaryl halides **147**, **110a** and **148** under our standard conditions [$Pd(PPh_3)_2Cl_2$, dioxane, reflux] to yield products **226-228**, respectively. The results are collated in Table 4.2a.

Table 4.2a. **225** + R-X $\xrightarrow{i}$ **226-228**

Entry	Boronic Acid	R-X	Product	Isolated yield (%)
1	**225**	 **147**	 **226**	81 84[a]

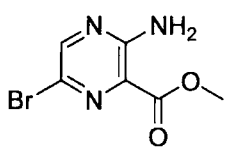
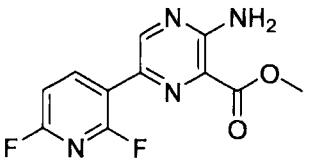
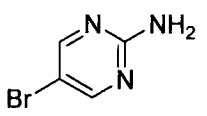
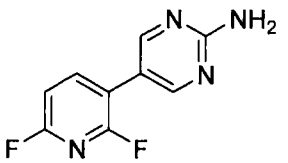
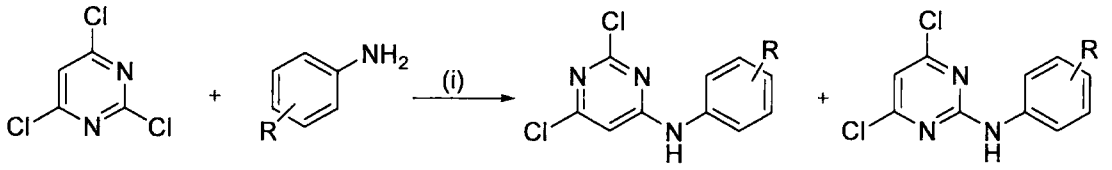
2	**225**	 **110a**	 **227**	82
3	**225**	 **148**	 **228**	69

Table 4.2a: Suzuki-Miyaura cross-couplings of **225** (i) Reagents and conditions: $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 24 h; for **110a** 15 min. ([a] 10 mol% $^tBu_3P$)

Bromo-heteroaryls bearing primary amine groups have been shown to be suitable substrates for Suzuki-Miyaura cross-coupling reactions with arylboronic acids and pyridylboronic acids under standard conditions, without the need for protection/deprotection steps (see Chapter 3). Compounds **147** and **148** coupled with **225** in high yields and new amino-substituted pyrimidopyridines, quinolinopyridines, have thereby been obtained. The reaction was extended to couple **110a** to show its versatility with respect to functional group tolerance (ester) thereby allowing access to a highly-functionalised 2,6-difluoro-3-pyrazinopyridine derivative. Substrates **147** and **148** gave the optimized yield of products after 24 h at reflux, as judged by TLC and ^1H NMR monitoring of the reaction mixture. Reagent **110a** is a notable exception, as previously discussed. A high yield of product **227** (82%) was obtained after only 15 minutes reflux. Products **226**, **227**, **228** are attractive as candidates for pharmaceutical and agrochemical uses.

4.3 2,6-Dichloro-3-pyridylboronic Acid

Suzuki-Miyaura reactions on chloro-aryls are well known in the literature.[5-7] In 2005 (after completion of our work) Itoh and Mase published the cross-couplings of phenylboronic acid with amine-substituted heteroaryl chlorides. Substituted 2-chloropyrimidines and 2-chloropyridines reacted with phenylboronic acid in moderate to good yields (68 – 93%).[8] In 2004, Gong *et al.* reported that in refluxing dioxane the amine group on various halo-substituted phenyls reacted with various heteroaryl chlorides by nucleophilic heteroaromatic substitution (Scheme 4.3a).

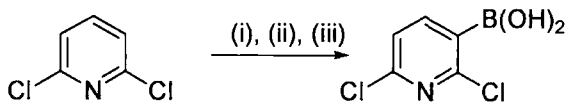


Scheme 4.3a: Intermediates in the synthesis of 2,4-diamino-N_4,6-diarylpyrimidines[9] Reagents and conditions; (i) reflux dioxane.

In our laboratory, the mono-chloropyridylboronic acids, namely 2-chloro-5-pyridylboronic acid (**23**) and 5-chloro-2-methoxy-4-pyridylboronic acid (**41**), had been shown to couple in moderate yields with both electron-rich and electron-deficient heteroaryl bromides.[10]

As the synthesis of 2,6-difluoro-3-pyridylboronic acid (**225**) was successful, we applied analogous DoM methodology to 2,6-dichloropyridine (**229**) and 2,6-dichloro-3-pyridylboronic acid (**230**) was thereby readily obtained in 70-75% yields (Scheme 4.3b) on 2.5 g, 5 g and 10 g scales reactions. Various parameters and conditions of the synthesis were changed to examine their effect on the product yield. Using commercial LDA, instead of LDA formed *in situ* (DPA and *n*-BuLi) decreased the yield to 50%. Using conc. HCl in the aqueous work up step, instead of HBr, decreased the yield to 51%. Using commercial LDA and HCl in the same reaction further decreased the yield to 34%. Stirring for > 1 h

after the addition of the borate, did not increase the yield above 73%. Adding the triisopropylborate at the start of the reaction (reverse addition method) lowered the yield to 42%. An unoptimised scale-up of the synthesis using LDA formed *in situ* and HBr, which had given **230** in 73% yield on 10 g scale, was used to synthesise 70 g of **230** but it required an additional recrystallisation from toluene to obtain pure product in 22% yield.



229 **230**

Scheme 4.3b: 2,6-Dichloro-3-pyridylboronic acid (**230**) synthesis. Reagents and Conditions: (i) DPA, *n*-BuLi, THF, -10 °C, 30 min, (ii) 2,6-dichloropyridine, -78 °C, 3 h (iii) TPB and aqueous work-up.

Crystals of **230** grew over a number of months from a water/ethanol mixture and the X-ray structure, which was solved by Dr. A Batsanov, is shown in figure 4.3a.

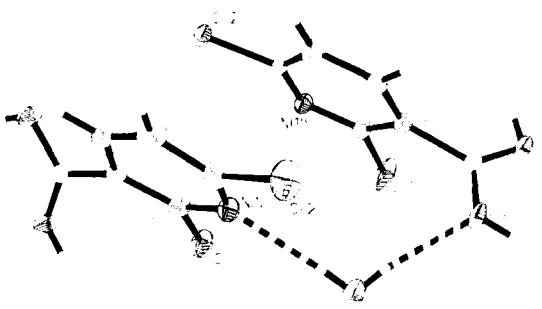


Figure 4.3a: X-ray crystal structure of **230·0.5H_2O** (dashed lines are H-bonds).

The X-ray crystal structure of **230** shows a hemi-hydrate and provided proof that the free boronic acid had been obtained and not the anhydride, *i.e.* the boroxin. Hydrogen bonding is present between the water molecule, and the pyridyl N(1) and O(2') of the boronic acid group. Unlike the X-ray crystal structures of **22** and **23** previously published[11]

and the structure of **40** (figure 2.1a) no H-bonded dimer was observed for **230**. The lack of dimer is presumably due to preferred H-bonding to OH of water than to the OH of the boronic acid.

The crystals of **230** were grown from the 70 g scale synthesis and an unexpected byproduct co-crystallised along with **230**. The X-ray analysis established the bipyridyl structure **231** shown in figure 4.3b. There was no evidence to suggest this byproduct was present in any other samples and therefore we considered that its mechanism of formation could be explained by either: (i) oxygen being present during the large-scale synthesis; (ii) an impurity in the starting material **229**; (iii) or homocoupling of **230** occurring during crystallisation. To test these possibilities, the synthesis of **230** was carried out in the presence of oxygen (flask was not evacuated to remove oxygen at the start of the experiment) and a lower yield of **230** (15%) was obtained but **231** was not present in the product isolated (^{1}H and ^{13}C NMR). Homocoupling of the boronic acid was unlikely, due to no catalyst or base being present and to date no examples of Suzuki coupling without catalyst or base are known. Therefore, it was concluded that **231** was probably already present as an impurity in the starting material or was derived from an impurity; however, there was no sample remaining of this batch of starting material, so we could not prove its origin conclusively.

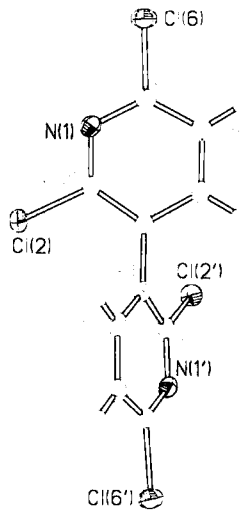


Figure 4.3b: X-ray crystal structure of **231**.

Suzuki-Miyaura cross-coupling reactions of **230** were carried out with **147** and **148** under our standard conditions [$Pd(PPh_3)_2Cl_2$, dioxane, reflux] to yield products **232** and **233**, respectively. Due to the low yields of the desired coupling products, other conditions were investigated and the results are collated in Table 4.3b. We drew on the work of Fu *et al.* who reported $Pd_2(dba)_3/{}^tBu_3P$ as a catalyst for cross-coupling a wide range of aryl halides with arylboronic acids in very good yields (75-95%).[12] The catalyst system produced biaryls with a range of substituents (NH_2, OMe, COMe, Me) and was extended to couple aryl boronic acids with chloropyridines. A range of phosphanes and bases were used in couplings; using ${}^tBu_3P$ with either $Pd(OAc)_2$ or $Pd(PPh_3)_2Cl_2$ in the presence of Cs_2CO_3 or Na_2CO_3 gave slightly increased yields (54-57%).[13]

Table 4.3a. **230 + R-X** $\xrightarrow{\text{a - h}}$ **232 or 233**

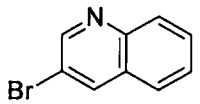
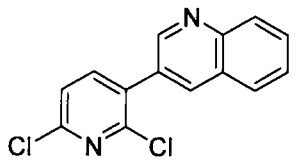
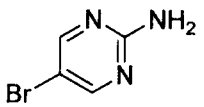
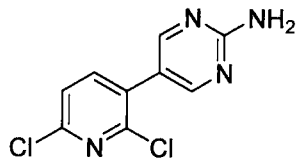
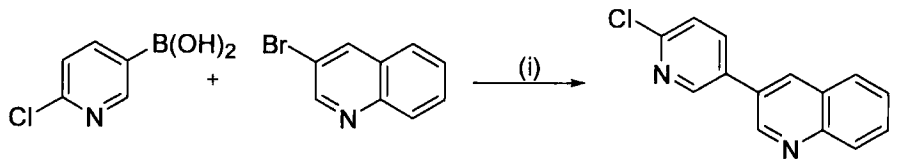
Entry	Boronic Acid	R-X	Product	Conditions	Isolated yield (%)
1	**230**	 **147**	 **232**	a	36
2				b	54
3				c	56
4				d	57
5				e	55
6				f	38
7				g	24
8				h	30
9	**230**	 **148**	 **233**	b	46

Table 4.3a: Suzuki-Miyaura cross-coupling of **230**. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h, (b) $Pd(PPh_3)_2Cl_2$, $^tBu_3P$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h, (c) $Pd(PPh_3)_2Cl_2$, $^tBu_3P$, 1,4-dioxane, Cs_2CO_3 (1 M), reflux, 65 h, (d) $Pd(OAc)_2$, $^tBu_3P$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h, (e) $Pd(OAc)_2$, $^tBu_3P$, 1,4-dioxane, Cs_2CO_3 (1 M), reflux, 65 h, (f) $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 8 h, (g) $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), 150 °C, 5 min @ 150 W, (h) $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), 150 °C, 20 min @ 150 W.

Entry 2 - 5 shows that changing the aqueous base from sodium carbonate to cesium carbonate had no effect on the yield. Adding $^tBu_3P$ [12, 13] increased the yield of the coupled product (*cf.* entry 1 - 2). Changing the catalyst to from $Pd(PPh_3)_2Cl_2$ to $Pd(OAc)_2$ made no difference to the yield (entries 2 and 4).

Previously in our hands, 2-chloro-5-pyridylboronic acid (**23**) had coupled with 3-bromoquinoline (**147**) in 55% yield (scheme 4.3c). The same reaction carried out using conditions a and b of table 4.3a gave 58 and 71% yields of **234**, respectively, demonstrating a modest increase in yield with added $^tBu_3P$.

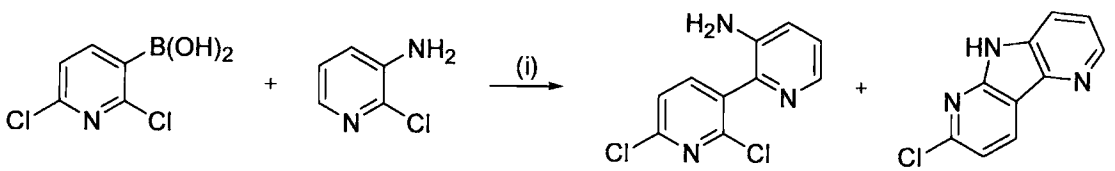


23 **147** **234**

Scheme 4.3c: Suzuki coupling of **23**. Reagents and conditions; (i) $Pd(PPh_3)_4$, DMF, Na_2CO_3 (1 M), 80 °C.

As previously discussed (Chapters 1 and 3) other reactions, especially homocoupling of the boronic acid, can occur with halogen-substituted boronic acids under Suzuki conditions. Although no homocoupled products were isolated, **236** was isolated from the cross-coupling of 2,6-dichloro-3-pyridylboronic acid (**230**) and 3-amino-2-

chloropyridine (**159**) (Scheme 4.3d). Product **236** was obtained in 32% yield along with ca 15% yield of the expected coupled product, but **235** was not obtained analytically pure. Cyclisation had occurred with the amino group of **235** attacking C2 (attached to the chlorine); base present in the reaction mixture then removes a proton from the positively charged nitrogen. Overall this gives compound **236** and a molecule of hydrochloric acid.



230 **159** **235** **236**

Scheme 4.3d: Suzuki coupling of **230** and **159**. Reagents and conditions; (i) $Pd(PPh_3)_2Cl_2$, $^tBu_3P$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h,

This structure of **236** was supported by mass spectra, ^1H NMR, ^{13}C NMR, gCOSY, ROESY, gHSQC and gHMBC data (Figs 4.3c – 4.3h).

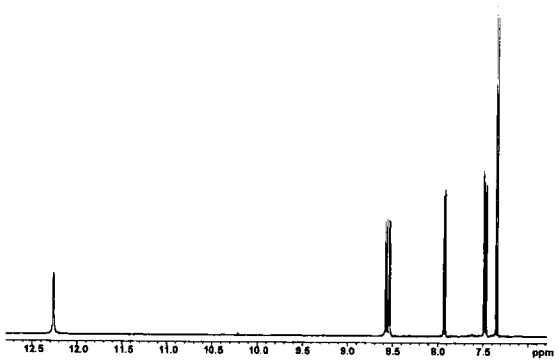


Figure 4.3c: ^1H NMR spectrum of **236** in d_6-DMSO.

The ^{1}H NMR spectrum showed five aromatic protons (Fig. 4.3c) with no broad singlet from a free amine group. A singlet at δ 12.23 ppm with an integral of one proton was assigned to the NH of **236**.

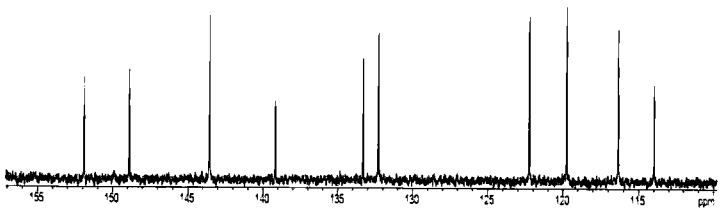


Figure 4.3d: ^{13}C NMR spectrum of **236**.

The ^{13}C NMR spectrum showed 10 carbons as expected for **236** (Fig 4.3d).

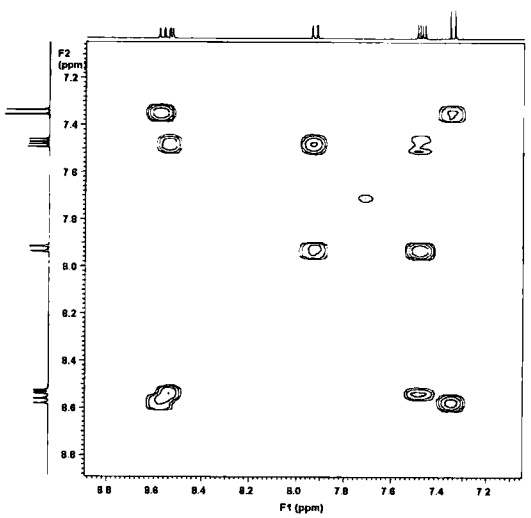


Figure 4.3e: ROESY spectrum of **236**.

The ROESY spectrum confirmed that the protons producing the two doublets at δ 8.6 and 7.3 ppm are on adjacent carbons, and the quartet at 7.5 ppm is from a proton on the carbon adjacent to both carbons that carry protons, causing the doublet of doublets at 7.9 and 8.5 ppm. Overall this confirms that on one ring system two protons are present and on the other ring system three protons are present.

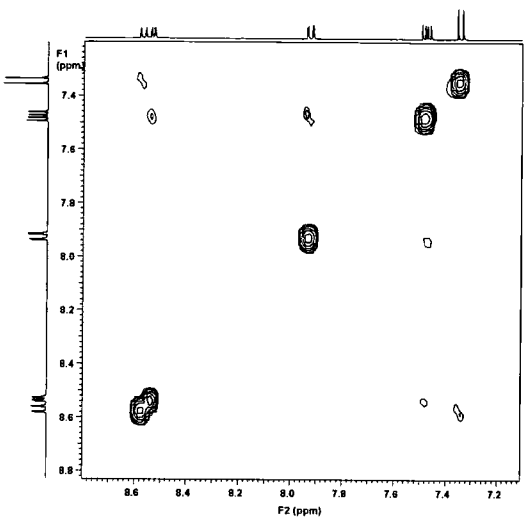


Figure 4.3f: COSY spectrum of **236**.

The COSY spectrum further supported a structure with two separate ring systems and no interaction is observed between the two ring systems grouped previously by the ROESY spectrum.

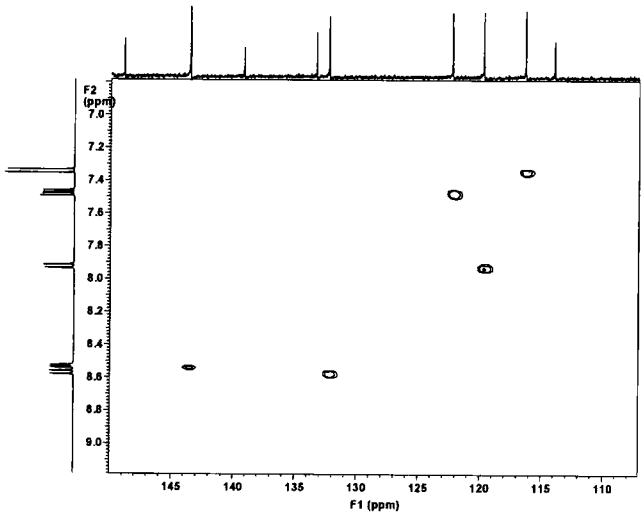


Figure 4.3g: HSQC spectrum of **236**.

The HSQC spectrum assigned the carbons to which each of the five aromatics protons are attached, and identified those carbons not bearing protons.

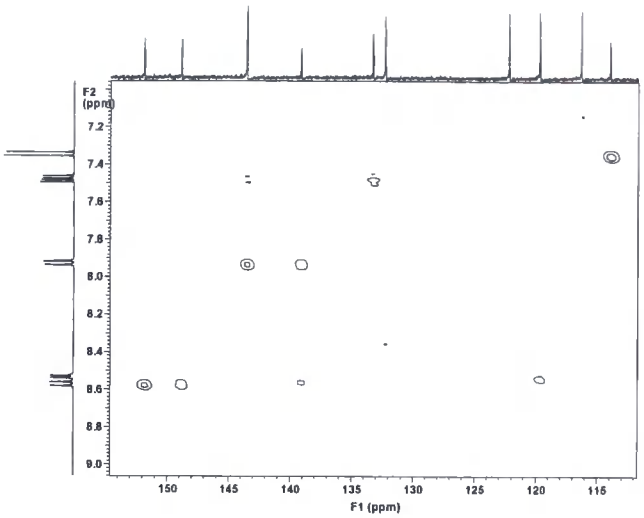


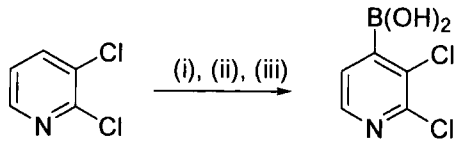
Figure 4.3h: HMBC spectrum of **236**.

The HMBC spectrum identified which carbons the five aromatic protons couple with through 2 or 3 bonds. Quaternary carbons can sometimes be observed by this technique. Taken together, all the data points unambiguously to structure **236**.

4.4 2,3-Dichloro-4-pyridylboronic Acid

The DoM methodology used for 2,6-dichloro-3-pyridylboronic acid (**230**) was applied to 2,3-dichloropyridine (**237**). Reaction of **237** [LDA (1.1 equiv.) in THF] followed by the addition of triisopropylborate and an aqueous workup gave **238** in only 40% yield on 2.5 - 15 g scales of product. Using DPA and *n*-BuLi, instead of commercial LDA, gave a disappointing 30 % yield. Lithiation of **237** could occur at both C(4) and C(6) and using 2 equivalents of LDA increased the yield of **238** to 56% (Scheme 4.4a) suggesting that the lower than expected yield was, indeed, at least partly due to both positions lithiating. If lithiation had occurred at C6 the derived boronic acid would deboronate, so the 56% yield suggests lithiation at C4 is preferred. Interestingly, when HCl was used in the aqueous

workup instead of HBr, **238** deboronated and only starting material (**237**) was obtained, even when the aqueous work up was carried out at 0 °C. An unoptimised scale-up of the synthesis detailed in Scheme 4.4a gave a 70 g batch of pure **253**, in a lower yield of 22% after recrystallisation from toluene.



237 **238**

Scheme 4.4a: 2,3-Dichloro-4-pyridylboronic acid (**238**) synthesis. Reagents and Conditions: (i) 2.0 equiv. LDA, THF, -10 °C, 30 min, (ii) 2,3-dichloropyridine, -78 °C, 3 h (iii) TPB and aqueous work-up.

Crystals of **238** were grown over a number of months from a water/ethanol mixture and the structure was solved by Dr. A Batsanov. The X-ray crystal structure of **238** is shown in figure 4.4a.

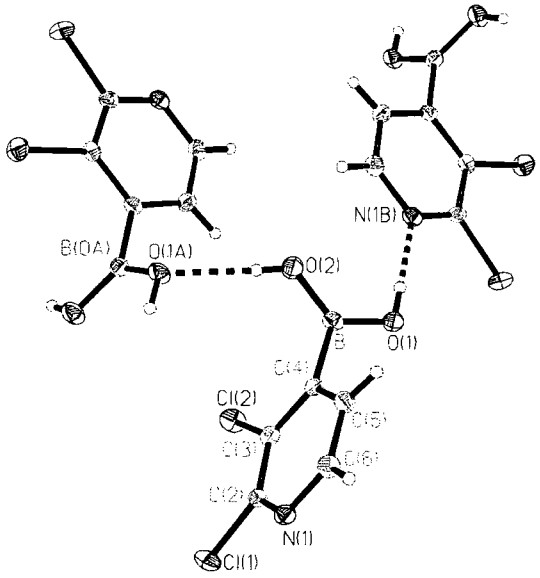


Figure 4.4a: X-ray crystal structure of **238**. Dashed lines are H-bonds.

Similar to the structures of **40**, **23** and **230** the free boronic acid was observed and not the anhydride. Extensive intermolecular hydrogen bonding is present. No intermolecular dimer formation between two boronic acid moieties was observed.

Cross-coupling reactions of **238** with **147**, **148**, **1** and **239** under our standard conditions [$Pd(PPh_3)_2Cl_2$, dioxane, reflux] yielded products **240-242**, respectively. Due to the disappointing yields of the desired coupling products, other conditions were investigated; the results are collated in Table 4.4a.

Table 4.4a. **238** + **R-X** $\xrightarrow{\text{a-f}}$ **240-242**

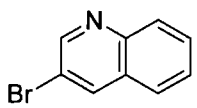
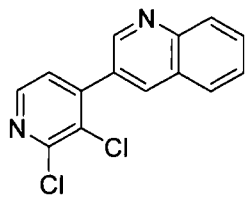
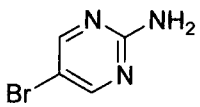
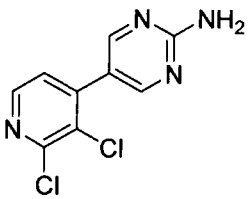
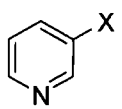
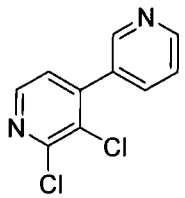
Entry	Boronic Acid	R-X	Product	Conditions	Isolated yield (%)
1	**238**	 **147**	 **240**	a	34
2				b	48
3				c	54
4				d	54
5				e	56
6				f	57
7	**238**	 **148**	 **241**	b	42
8	**238**	 **1 X = Br** **239 X = I**	 **242**	b	**1** = 41 **239** = 50

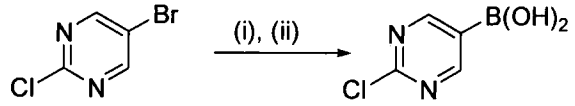
Table 4.4a: Suzuki-Miyaura cross-coupling of **238**. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h, (b) $Pd(PPh_3)_2Cl_2$, $^tBu_3P$, 1,4-

dioxane, Na_2CO_3 (1 M), reflux, 65 h, (c) $Pd(PPh_3)_2Cl_2$, $^tBu_3P$, 1,4-dioxane, Cs_2CO_3 (1 M), reflux, 65 h, (d) $Pd(OAc)_2$, $^tBu_3P$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h, (e) $Pd(OAc)_2$, $^tBu_3P$, 1,4-dioxane, Cs_2CO_3 (1 M), reflux, 65 h, (f) $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 8 h.

Similar trends can be seen as previously described for reactions of 2,6-dichloro-3-pyridylboronic acid **230** (Table 4.3a). The addition of a ligand to the standard reaction conditions increased the yield of **240** from 34 to 54% (Entry 1 and 3). Entry 8 shows that using iodoaryl coupling partners increased the yield slightly compared to the bromo analogue.

4.5 2-Chloro-5-pyrimidylboronic Acid

2-Chloro-5-pyrimidylboronic acid (**244**) was an attractive target for comparison with **221** and the dichloropyridylboronic acids (**230** and **238**). The initial synthesis of **244** following the route for **221** produced impure **244**. However, the halogen-lithium exchange of **243** (*n*-BuLi in THF/ toluene) in the presence of triisopropylborate and then an aqueous workup gave pure **244** in 85% yield. A sequential addition method (adding the TPB after the lithiation) gave **244** in a lower yield of 15%.



243 **244**

Scheme 4.5a: 2-Chloro-5-pyrimidylboronic acid (**244**) synthesis. Reagents and Conditions: (i) *n*-BuLi, TPB, -78 °C, toluene:THF (ii) aqueous work-up.

Crystals of **244** were grown over a two months from a water/ethanol mixture and the structure was solved by Dr. A Batsanov. The X-ray crystal structure of **244** is shown in figure 4.5a.

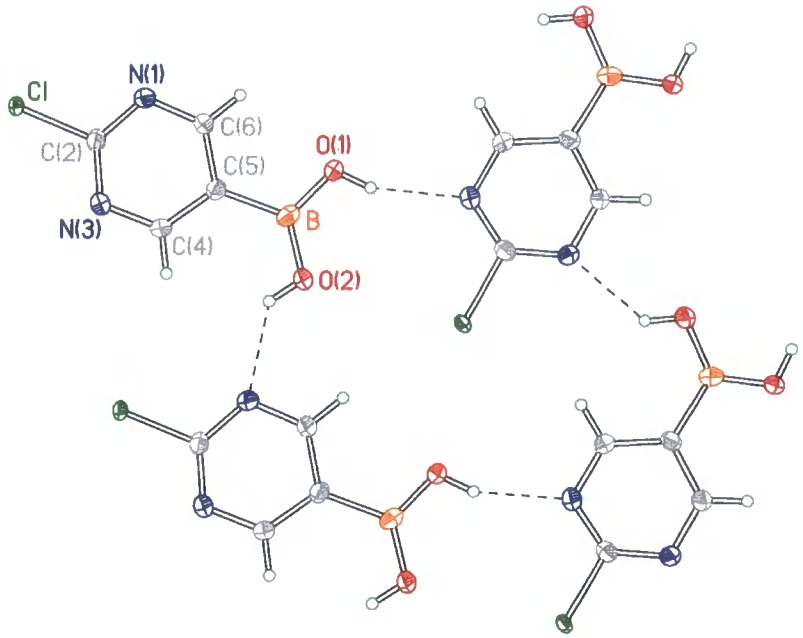
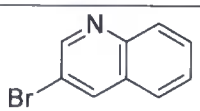
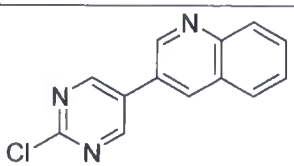


Figure 4.5a: X-ray crystal structure of **244**. Dashed lines are H-bonds.

Similar to the structures of **40**, **23** and **230** the free boronic acid was observed and not the anhydride. Extensive intermolecular hydrogen bonding is present but no intermolecular dimer formation between two boronic acid moieties was observed.

Cross-coupling reactions of **244** with **147** [$Pd(PPh_3)_2Cl_2$, dioxane, reflux] gave product **245** in only 21% yield. Addition of tributylphosphine increased the yield to 47% (Table 4.5a; entry 2), so this ligand was also used in the reactions in entries 3 and 4. These procedures gave novel functionalised heteroaryl-pyrimidines **245-247** in moderate and synthetically-viable yields (45-48%).

Table 4.5a. **244** + **R-X** $\xrightarrow{\text{a-b}}$ **245-247**

Entry	Boronic Acid	R-X	Product	Conditions	Isolated yield (%)
1	**244**	 **147**		a	21
2				b	47

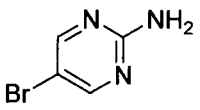
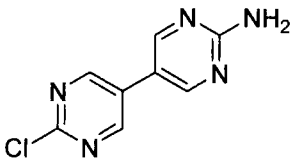
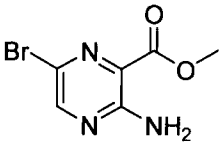
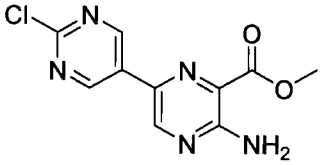
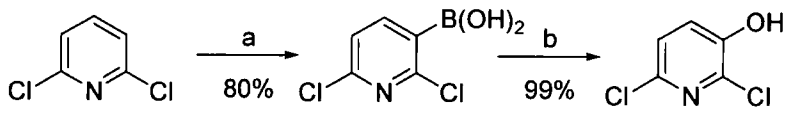
			245		
3	**244**	 **148**	 **246**	b	48
4	**244**	 **110a**	 **247**	b	45

Table 4.5a; Suzuki-Miyaura cross-coupling of **244**. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h, (b) $Pd(PPh_3)_2Cl_2$, $^tBu_3P$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h; for **110a** 15 min.

During the course of our work Rault *et al.* published syntheses of 2,6-dichloro-3-pyridylboronic acid **230**, and 2,5-dichloro-4-pyridylboronic acid in 80 and 56% yields, respectively, also using DoM methodolgy.[14] No cross-coupling reactions were reported; hydroxydeboronation in the presence of hydrogen peroxide yielded **248** (Scheme 4.5b).



229 **230** **248**

Scheme 4.5b: Recent synthesis of **230**.[14] Reagents and conditions (a) LDA, TPB, - 80 °C, THF (b) aq. H_2O_2, CH_2Cl_2, rt, 20 h.

4.6 Conclusion

A range of novel halo substituted pyridylboronic acids and a pyrimidyl boronic acid have been synthesized and the syntheses of **230** and **237** have been scaled up to produce 50 g quantities. These compounds serve as versatile reagents for the production of highly-functionalised aryl/heteroaryl-pyridyl/pyrimidyl libraries. An added advantage of these reactions is that the products obtained are able to undergo further functionalisation. For instance, the compounds that contain a amine group can be employed in a diazotisation reaction An example showing the possibility of such a reaction was highlighted in the previous chapter. Furthermore the compounds that contain a chloro can be employed as the halo substrate for further cross-coupling reactions, which can then lead to numerous possibilities for further functionalisation.

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Chapter 5

Experimental Procedures

5.0 Experimental Procedures

This chapter describes 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 during the course of this work.

5.1 General Methods

All reactions that 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, or Fluorochem, or supplied by Seal Sands Chemicals, and were used as supplied unless otherwise stated. The following solvents were dried and distilled immediately prior to use: diethyl ether and toluene, over sodium metal; THF, over potassium metal; DMF, dried by standing over 4 Å molecular sieves for at least 48 h. All other solvents in this work were used without prior purification. Column chromatography was carried out on silica (40-60 μm mesh).

^{1}H NMR spectra were recorded on a Varian Unity 300 MHz, a Varian VXR 400s MHz or a Varian Inova 500 spectrometer at 500 MHz using 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 spectra were recorded using broad band decoupling on a Varian Unity 200, 250 or 300 spectrometer at 50, 63 or 75 MHz, respectively, or a Varian VXR 400s or Varian Inova 500 spectrometer 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 ionisation mode as indicated. Electro Spray (ES) mass spectra were recorded on a Micromass LCT mass spectrometer.

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

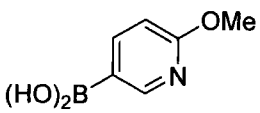
Melting points were recorded on a Stuart Scientific SMP3 melting point apparatus and are uncorrected.

5.1.1 General Procedure for all the Cross-Coupling Reactions

The boronic acid (1.0 equiv.) the arylhalide (0.9 equiv.) and $Pd(PPh_3)_2Cl_2$ (ca. 5 mol%) were sequentially added to degassed 1,4-dioxane and the mixture was stirred at 20 °C for 30 min. Degassed aqueous Na_2CO_3 solution (1 M, 3.0 equiv.) was added and the reaction mixture was heated under argon at reflux for the time specified. The solvent was removed *in vacuo* then ethyl acetate was added and the organic layer was washed with brine, separated, and dried over $MgSO_4$. The mixture was purified by chromatography on a silica gel column. On some occasions additional recrystallisation was necessary to remove traces of Ph_3PO which co-eluted with the desired product.

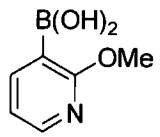
5.2 Experimental Procedures of Chapter 2

2-Methoxy-5-pyridylboronic acid (40)



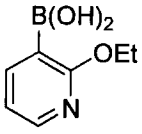
To a solution of 5-bromo-2-methoxypyridine (**100**) (100 cm^3, 773 mmol) in anhydrous ether (500 cm^3) at –78 °C, *n*-BuLi (1.6 M in hexane, 580 cm^3, 928 mmol) was added dropwise. The reaction was stirred for 1 h at –78 °C then triisopropylborate (360 cm^3, 1.56 mol) was added quickly. The reaction mixture was stirred at –78 °C for another 1 h, then quenched with water (1.0 dm^3) and allowed to warm to room temperature with stirring 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 (3 x 400 cm^3) to remove unreacted starting material. The aqueous layer was then acidified to pH 4 (with 48% HBr) to precipitate **40** as white solid (70.0 g, 65 %), analytically pure and spectroscopically identical with the sample described previously.[1]

2-Methoxy-3-pyridylboronic acid (43)



To a solution of diisopropylamine (142 cm^3, 1.01 mol) in anhydrous THF (1.0 dm^3) at 0 °C, *n*-BuLi (2.5 M in hexane, 424 cm^3, 1.06 mol) was added dropwise. The reaction was stirred for 1 h at 0 °C then 2-methoxypyridine (**101**) (96 cm^3, 920 mmol) in anhydrous THF (500 cm^3) was added dropwise. The reaction was stirred for 1 h at 0 °C then triisopropylborate (254 cm^3, 1.10 mol) was added slowly. The reaction mixture was stirred at 0 °C for another 0.5 h, then quenched with water (500 cm^3) and allowed to warm to room temperature with stirring overnight. The organic solvent was evaporated *in vacuo* and the remaining aqueous layer was adjusted to pH 10 (with 5% NaOH: on some occasions this addition of NaOH was not necessary) and then filtered. The filtrate was washed with diethyl ether (3 x 500 cm^3) to remove unreacted starting material. The aqueous layer was then acidified to pH 6 (with 48% HBr) to precipitate **43** as white solid (80.7 g, 58 %), analytically pure and spectroscopically identical with the sample described previously.[2]

2-Ethoxy-3-pyridylboronic acid (103)

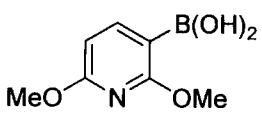


Procedure A: To a solution of diisopropylamine (5.9 cm^3, 41.69 mmol) in anhydrous THF (50 cm^3) at -10 °C, *n*-BuLi (2.5 M in hexane, 17.4 cm^3, 43.59 mmol) was added dropwise. The reaction was stirred for 0.5 h at -10 °C then cooled to -50 °C. 2-Ethoxypyridine (**102**) (4.5 cm^3, 37.9 mmol) in anhydrous THF (10 cm^3) was added dropwise. The reaction was stirred for 1 h at -50 °C then triisopropylborate (10.5 cm^3, 45.5 mmol) was added slowly. The reaction mixture was stirred at -50 °C for another 1 h, then allowed to warm to -10 °C and quenched with water (50 cm^3). The reaction was left at room temperature with stirring overnight. The organic solvent was evaporated *in vacuo* and the remaining aqueous layer, pH 10, was filtered. The filtrate was washed with diethyl ether (2 x 50 cm^3). The aqueous layer was then acidified to pH 4 (with 48% HBr) to give **103** as a white solid (4.4 g, 70%), mp 103.0-103.8 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.16 (1H, dd, J = 2.0 Hz, J = 4.8 Hz), 7.87 (1H, dd, J = 2.0 Hz, J = 7.0 Hz), 7.83 (2H, s), 6.94 (1H, dd, J = 4.8 Hz, J = 7.0 Hz), 4.33 (2H, q, J = 6.8 Hz), 1.31 (3H,

t, J = 6.8 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.0, 148.4, 144.8, 116.9, 61.2, 14.5; MS (EI) *m/z* 166.9 (M^+, 100%). Anal. Calcd. for $C_7H_{10}BNO_3$: C, 50.35; H, 6.04; N, 8.39. Found: C, 50.32; H, 5.92; N, 8.34%.

Procedure B: Following procedure A, diisopropylamine (96.7 g, 0.96 mol) in anhydrous THF (500 cm^3), *n*-BuLi (2.5 M in hexane, 400 cm^3, 1.00 mol), 2-ethoxypyridine (**102**) (107 g, 0.87 mol) and triisopropylborate (196 g, 1.04 mol) were used. After quenching with water the reaction was left at room temperature with stirring overnight. The organic layer was discarded and the aqueous layer, pH 10, was then filtered. The filtrate was washed with diethyl ether (200 cm^3) until no starting material was detected in the ether washings by tlc. The aqueous layer was then acidified to pH 7 (with 48% HBr) to give **103** as an analytically-pure off-white solid (69.7 g, 48 %) spectroscopically identical with the sample from Procedure A.

2,6-Dimethoxy-3-pyridylboronic acid (146)

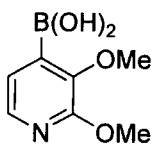


To a solution of diisopropylamine (6.5 cm^3, 46.45 mmol) in anhydrous THF (100 cm^3) at - 10 °C, *n*-BuLi (2.5 M in hexane, 20.0 cm^3, 50 mmol) was added dropwise. The reaction was stirred for 0.5 h at 0 °C and was then cooled to -78 °C before 2,6-dimethoxypyridine (**144**) (56 cm^3, 42 mmol) was added dropwise. The reaction was stirred for 3 h at -78 °C then triisopropylborate (6.2 cm^3, 54 mmol) was added slowly. The reaction mixture was stirred at -78 °C for another 1 h, then quenched with water (100 cm^3) and allowed to warm to room temperature with stirring overnight. The organic solvent was evaporated *in vacuo* and then filtered. The filtrate was washed with diethyl ether (3 x 50 cm^3) to remove unreacted starting material. The aqueous layer was then acidified to pH 6 (with 48% HBr) to precipitate **146** as white solid (6.3 g, 82 %), mp 108.2-109.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (1H, d, J = 8.0 Hz), 7.53 (2H, s), 6.36 (1H, d, J = 8.0 Hz), 3.89 (3H, s), 3.86 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.85, 164.65, 148.60, 101.62, 53.67,

53.57. MS (EI) *m/z* 183.0 (M^+, 100%). Anal. Calcd. for $C_7H_{10}BNO_4$: C, 45.95; H, 5.51; N, 7.66. Found: C, 45.46; H, 5.34; N, 7.79%.

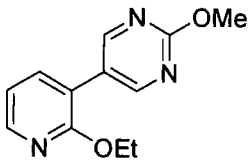
Procedure B: Following procedure A, diisopropylamine (106.3 cm^3, 0.76 mol) in anhydrous THF (500 cm^3), *n*-BuLi (2.5 M in hexane, 312 cm^3, 0.78 mol), 2,6-dimethoxypyridine (**144**) (107 g, 0.69 mol) and triisopropylborate (196 g, 0.86 mol) were added at −10 °C. The filtrate was washed with diethyl ether (250 cm^3) until no starting material was detected in the ether washings by tlc. The aqueous layer was then acidified to pH 6 (with 48% HBr) to give **146** as an analytically-pure off-white solid (57.2 g, 45 %) spectroscopically identical with the sample from Procedure A.

2,3-Dimethoxy-4-pyridylboronic acid (158)



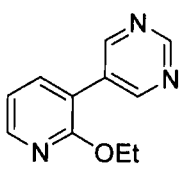
To a solution of diisopropylamine (2.6 cm^3, 18.5 mmol) in anhydrous THF (50 cm^3) at -10 °C, *n*-BuLi (2.5 M in hexane, 8 cm^3, 20 mmol) was added dropwise. The reaction was stirred for 0.5 h at 0 °C and was then cooled to -78 °C before 2,3-dimethoxypyridine (**153**) (2 cm^3, 16.8 mmol) in anhydrous THF (10 cm^3) was added dropwise. The reaction was stirred for 3 h at -78 °C then trimethyl borate (2.5 cm^3, 21.5 mmol) was added slowly. The reaction mixture was stirred at -78 °C for another 1 h, then quenched with water (50 cm^3) and allowed to warm to room temperature with stirring overnight. The organic solvent was evaporated *in vacuo* and then filtered. The filtrate was washed with diethyl ether (2 x 50 cm^3) to remove unreacted starting material. The aqueous layer was then acidified to pH 2 (with 48% HBr) to precipitate **158** as white solid (0.3 g, 12 %), mp 125.8-126.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (1H, d, J = 8.0 Hz), 7.54 (2H, s), 6.35 (1H, d, J = 8.0 Hz), 3.89 (3H, s), 3.85 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.48, 164.25, 148.15, 101.28, 53.19, 53.12. MS (ES+) *m/z* 182.0 (M^+, 100%). Anal. Calcd. for $C_7H_{10}BNO_4$: C, 45.95; H, 5.51; N, 7.66. Found: C, 45.96; H, 5.07; N, 6.60%.

5-(2-Ethoxy-3-pyridyl)-2-methoxypyrimidine (113)



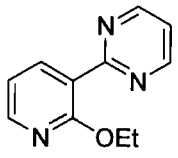
Boronic acid **103** (284 mg, 1.7 mmol), 5-bromo-2-methoxypyrimidine (**104**) (283 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc:hexane (1:2 v/v), gave **113** as a white solid (284 mg, 82%) mp 70.9-71.6 °C; ^1H NMR (400 MHz, acetone-d_6) δ 8.79 (2H, s), 8.17 (1H, dd, J = 1.6 Hz, J = 4.8 Hz), 7.82 (1H, dd, J = 1.6 Hz, J = 7.2 Hz), 7.06 (1H, dd, J = 4.8 Hz, J = 7.2 Hz), 4.42 (2H, q, J = 7.2 Hz), 3.98 (3H, s), 1.34 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.70, 160.42, 158.80, 146.80, 137.38, 124.10, 117.69, 116.91, 96.11, 61.99, 54.82, 14.57; MS (EI) *m/z* 231.1 (M^+, 100%). Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.42; H, 5.74; N, 17.93%.

5-(2-Ethoxy-3-pyridyl)pyrimidine (114)



Boronic acid **103** (284 mg, 1.7 mmol), 5-bromopyrimidine (**105**) (239 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc:hexane (1:1 v/v), gave **114** as a white solid (271 mg, 90%) mp 119.0-119.8 °C; ^1H NMR (400 MHz, acetone-d_6) δ 9.10 (1H, s), 9.01 (2H, s), 8.23 (1H, dd, J = 1.6 Hz, J = 4.8 Hz), 7.89 (1H, dd, J = 1.6 Hz, J = 8.0 Hz), 7.11 (1H, dd, J = 5.2 Hz, J = 7.6 Hz), 4.43 (2H, q, J = 7.2 Hz), 1.34 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 157.3, 156.4, 147.7, 138.0, 130.6, 117.5, 117.0, 96.2, 62.2, 14.6; MS (EI) *m/z* 201.1 (M^+, 100%). Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.46; H, 5.51; N, 20.63%.

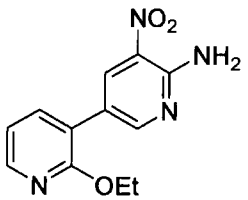
2-(2-Ethoxy-3-pyridyl)pyrimidine (115)



Boronic acid **103** (284 mg, 1.7 mmol), 2-bromopyrimidine (**106**) (239 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc:hexane (1:2 v/v), gave **115** as a colourless viscous oil (268 mg, 89%); ^1H NMR (200 MHz, $CDCl_3$) δ 8.68

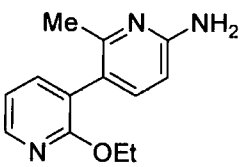
(2H, d, J = 4.8 Hz), 8.11 (1H, d, J = 4.8 Hz), 7.94 (1H, d, J = 7.3 Hz), 7.03 (1H, t, J = 4.8 Hz), 6.83 (1H, dd, J = 5.1 Hz, J = 7.2 Hz), 4.37 (2H, q, J = 7.0 Hz), 1.23 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 161.1, 156.8 (2C), 148.0, 140.1, 122.3, 118.7, 116.3, 62.0, 14.2; HRMS (EI) calcd for $C_{11}H_{11}N_3O$ (M^+) 201.09121, found 201.09133.

2'-Ethoxy-5-nitro-[3,3']bipyridinyl-6-ylamine (116)



Boronic acid **103** (284 mg, 1.7 mmol), 5-bromo-2-amino-3-nitropyridine (**107**) (327 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc, gave **116** as a yellow solid (289 mg, 74%) mp 193.0-193.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (2H, dd, J = 2.0 Hz, J = 16.0 Hz), 8.15 (1H, dd, J = 2.0 Hz, J = 4.8 Hz), 8.03 (2H, br s, NH_2), 7.90 (1H, dd, J = 2.0 Hz, J = 4.8 Hz), 7.07 (1H, dd, J = 4.8 Hz, J = 7.6 Hz), 4.37 (2H, q, J = 7.2 Hz), 1.31 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7, 156.0, 152.7, 146.0, 137.9, 134.2, 126.2, 120.5, 118.7, 117.4, 61.5, 14.3; MS (EI) *m/z* 260.0 (M^+, 100%). Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.12; H, 4.58; N, 21.36%.

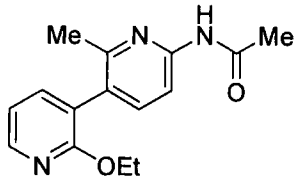
5-(2-Ethoxypyridin-3-yl)-6-methylpyridin-2-amine (117)



Boronic acid **103** (284 mg, 1.7 mmol), 6-amino-3-bromo-2-methylpyridine (**108**) (281 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc, gave **117** as a crystalline solid (258 mg, 75%) mp 138.6-139.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (1H, dd, J = 2.0 Hz, J = 4.8 Hz), 7.47 (1H, dd, J = 2.0 Hz, J = 7.2 Hz), 7.12 (1H, d, J = 8.4 Hz), 6.99 (1H, dd, J = 4.8 Hz, J = 7.2 Hz), 6.30 (1H, d, J = 8.4 Hz), 5.88 (2H, br s, NH_2), 4.29 (2H, q, J = 7.2 Hz), 2.05 (3H, s), 1.22 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.2, 158.5, 153.6, 145.3, 139.6, 139.0, 123.3, 119.0, 116.8, 104.9, 60.9, 22.3, 14.5; MS (EI) *m/z* 229.1

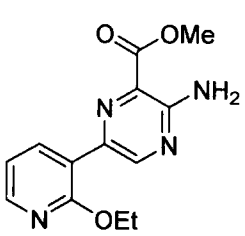
(M^+, 100%). Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.23. Found: C, 67.85; H, 6.54; N, 17.96%.

N-(2'-Ethoxy-2-methyl-[3,3']bipyridinyl-6-yl)-acetamide (118)



Boronic acid **103** (284 mg, 1.7 mmol), *N*-(5-bromo-6-methyl-pyridin-2-yl)-acetamide (**109**)[15] (334 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc, gave **118** as a crystalline solid (317 mg, 78%) mp 147.7-148.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (1H, br s, NH), 8.17 (1H, dd, J = 2.0 Hz, J = 4.8 Hz), 7.94 (1H, d, J = 8.4 Hz), 7.57 (1H, dd, J = 2.0 Hz, J = 7.2 Hz), 7.51 (1H, d, J = 8.4 Hz), 7.04 (1H, dd, J = 4.8 Hz, J = 7.2 Hz), 4.31 (2H, q, J = 7.2 Hz), 2.20 (3H, s), 2.08 (3H, s), 1.20 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.2, 160.0, 154.3, 150.7, 146.3, 139.7, 139.6, 126.7, 122.0, 116.9, 110.4, 61.1, 23.3, 22.1, 14.4; MS (EI) *m/z* 271.0 (M^+, 100%). Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.18; H, 6.25; N, 15.31%.

Methyl 2-amino-5-(2-ethoxy-3-pyridyl)-3-pyrazinoate (119)

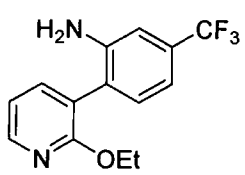


Boronic acid **103** (284 mg, 1.7 mmol), 3-amino-6-bromopyrazine-2-carboxylic acid methyl ester (**110a**)[3] (345 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 16 h at 20 °C; eluent EtOAc, gave **119** as a yellow solid (440 mg, 90%) mp 156.6-157.0 °C; ^{1}H NMR (400MHz, DMSO-d_6) δ 8.89 (1H, s), 8.17 (1H, dd, J = 2.0 Hz, J = 4.8 Hz), 8.12 (1H, dd, J = 2.0 Hz, J = 7.6 Hz), 7.46 (2H, br s, NH_2), 7.11 (1H, dd, J = 4.8 Hz, J = 7.6 Hz), 4.41 (2H, q, J = 7.2 Hz), 3.87 (3H, s), 1.35 (3H, t, J = 7.2 Hz) ; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.3, 159.8, 154.3, 148.0, 146.5, 138.0, 136.7, 122.4, 119.3, 117.4, 61.6, 52.2, 14.4; MS (EI) *m/z* 274.0 (M^+, 100%). Anal. Calcd. for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.63; H, 4.97; N, 20.33%.

When the reaction was carried out at reflux for 15 min, product **119** (321 mg, 78% yield) was obtained.

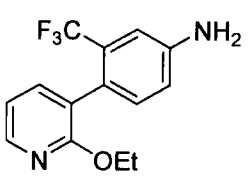
A comparable reaction with 3-amino-6-chloropyrazine-2-carboxylic acid methyl ester **110b**[3] 15 min at 60 °C, gave **119** in 62% yield.

3-(2-Amino-4-trifluoromethylbenzene)-2-ethoxypyridine (120)



Boronic acid **103** (284 mg, 1.7 mmol), 2-bromo-5-(trifluoromethyl)aniline (**111**) (360 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent DCM, gave **120** as a clear brown oil (300 mg, 71%); ^1H NMR (400 MHz, acetone-d_6) δ 8.27 (1H, dd, J = 2.0 Hz, J = 3.2 Hz), 7.70 (1H, dd, J = 2.0 Hz, J = 5.2 Hz), 7.26 (1H, d, J = 7.8 Hz), 7.20 (1H, s), 7.12 (1H, dd, J = 2.0 Hz, J = 4.8 Hz), 7.04 (1H, d, J = 7.8 Hz), 4.90 (2H, t, s), 4.48 (2H, q, J = 7.2 Hz), 1.36 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.3, 147.5, 140.8, 132.4, 130.9 (q, J = 32 Hz), 125.5 (q, J = 270 Hz), 122.2, 117.8, 113.5, 112.2, 62.2, 14.8; HRMS (EI) calcd for $C_{14}H_{13}F_3N_2O$ (M^+) 282.09800, found 282.09820.

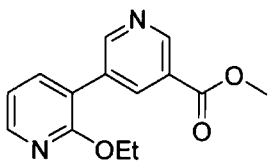
4-(2-ethoxypyridin-3-yl)-3-(trifluoromethyl)aniline (121)



Boronic acid **103** (284 mg, 1.7 mmol), 4-bromo-3-(trifluoromethyl)aniline (**112**) (360 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent DCM, gave **121** as a clear oil (288 mg, 68%); ^1H NMR (400 MHz, acetone-d_6) δ 8.23 (2H, m), 7.55 (2H, dd, J = 2.0 Hz, J = 7.2 Hz), 7.18 (1H, d, J = 2.0 Hz), 5.27 (2H, s), 4.69 (2H, t, J = 7.2 Hz), 1.30 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 161.6, 148.9, 146.6, 140.0, 133.5, 129.5 (q, J =

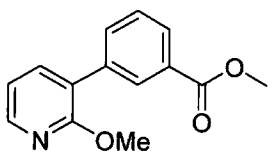
29.2 Hz), 126.5, 123.8 (d, J = 250 Hz), 120.7, 117.4, 116.5, 111.7, 61.6, 14.5; HRMS (EI) calcd for $C_{14}H_{13}F_3N_2O$ (M^+) 282.09800, found 282.09812.

Methyl 5-(2-ethoxypyridin-3-yl)pyridine-3-carboxylate (141)



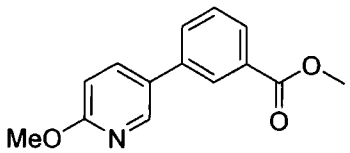
Boronic acid **103** (284 mg, 1.7 mmol), methyl 5-bromopyridine-3-carboxylate (**139**) (324 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 15 min; eluent EtOAc gave **141** as a yellow solid (260 mg, 67%) mp 69.2-70.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (1H, d, J = 2.0 Hz), 8.99 (1H, d, J = 2.0 Hz), 8.42 (1H, t, J = 2.0 Hz), 8.26 (1H, dd, J = 4.8 Hz, J = 2.0 Hz), 7.92 (1H, dd, J = 7.2 Hz, J = 2.0 Hz), 7.15 (1H, dd, J = 4.8 Hz, J = 7.2 Hz), 4.37 (2H, q, J = 7.2 Hz), 3.90 (3H, s), 1.34 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.56, 160.16, 153.28, 148.63, 147.13, 139.25, 136.60, 131.97, 125.40, 119.30, 117.67, 61.26, 53.49, 14.01; MS (EI) *m/z* 258.0 (M^+, 100%). Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.96; H, 5.36; N, 11.10%.

Methyl 3-(2-methoxypyridin-3-yl)benzoate (142)



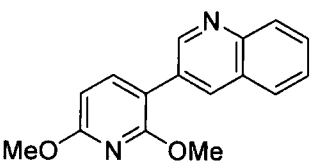
Boronic acid **43** (260 mg, 1.7 mmol), methyl 3-bromobenzoate (**140**) (323 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 15 min; eluent EtOAc gave **142** as clear yellow crystals (280 mg, 77%) mp 76.2-77.1 °C (from toluene:hexane); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.19 (2H, m), 7.99 (1H, m), 7.84 (1H, m), 7.77 (1H, dd, J = 7.2 Hz, J = 2.0 Hz), 7.57 (1H, t, J = 7.2 Hz), 7.09 (1H, dd, J = 7.2 Hz, J = 0.8 Hz), 3.92 (3H, s), 3.90 (3H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.87, 161.26, 147.04, 139.33, 137.91, 134.33, 130, 91, 130.54, 129.10, 128.87, 123.83, 118.00, 53.49, 52.18; MS (ES+) *m/z* 243.0 (M^+, 100%). Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.70; H, 5.34; N, 5.47%.

Methyl 3-(6-methoxypyridin-3-yl)benzoate (143)



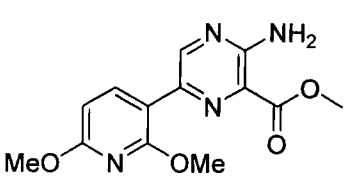
Boronic acid **40** (260 mg, 1.7 mmol), methyl 3-bromobenzoate (**140**) (323 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 15 min; eluent EtOAc gave **143** as a grey solid (289 mg, 79%) mp 89.2-90.5 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.49 (1H, d, J = 1.6 Hz), 8.14 (1H, t, J = 1.6 Hz), 8.03 (1H, dd, J = 8.8 Hz, J = 1.6 Hz), 7.93 (2H, m), 7.60 (1H, t, J = 8.0 Hz), 6.91 (1H, d, J = 8.8 Hz), 3.89 (3H, s), 3.87 (3H,s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.02, 163.33, 144.85, 137.63, 131.09, 130.40, 129.47, 128.93, 128.27, 127.91, 126.72, 110.66, 53.26, 52.71; MS (ES+) *m/z* 244.1 (M^+, 100%). Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.40; H, 5.39; N, 5.85%.

3-(2,6-Dimethoxypyridin-3-yl)quinoline (149)



Boronic acid **146** (311 mg, 1.7 mmol), 3-bromoquinoline (**147**) (312 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent DCM:EtOAc (1:1 v/v) gave **149** as an off white solid (333 mg, 83%) mp 98.0-98.7 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.06 (1H, d, J = 2.0 Hz), 8.42 (1H, d, J = 2.0 Hz), 8.02 (1H, d, J = 8.0 Hz), 7.97 (1H, d, J = 8.0 Hz), 7.91 (1H, t, J = 8.0 Hz), 7.73 (1H, t, J = 8.0 Hz), 7.60 (1H, t, J = 8.0 Hz), 6.55 (1H, d, J = 8.0 Hz), 3.94 (3H, s), 3.91 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.38, 159.15, 151.09, 146.17, 142.24, 134.47, 129.50, 129.31, 128.59, 128.15, 127.51, 126.79, 111.68, 101.86, 53.48, 53.46; MS (EI) *m/z* 266.1 (M^+, 100%). Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.67; H, 5.28; N, 10.50%.

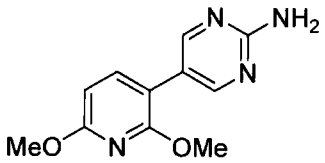
Methyl 3-amino-6-(2,6-dimethoxypyridin3-yl)pyrazine-2-carboxylate (150)



Boronic acid **146** (311 mg, 1.7 mmol), methyl 3-amino-6-bromopyrazine-2-carboxylate (**110a**) (348 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3)

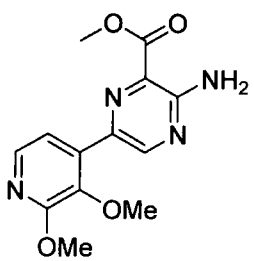
and Na_2CO_3 (1 M, 4 cm^3); reaction time 15 min; eluent EtOAc gave **150** as a yellow needles (320 mg, 74%) mp 191.8-192.3 °C (from toluene); ^1H NMR (400 MHz, DMSO-d_6) δ 8.79 (1H, s), 8.08 (1H, d, J = 8.0 Hz), 7.36 (2H, br s, NH_2), 6.54 (1H, d, J = 8.0 Hz), 3.98 (3H, s), 3.91 (3H, s), 3.87 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.52, 162.16, 158.90, 154.04, 147.70, 141.16, 137.12, 122.01, 110.96, 102.02, 53.49, 53.49, 52.22; MS (EI) *m/z* 291.2 (M^+, 100%). Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.64; H, 4.81; N, 19.07%.

5-(2,6-Dimethoxypyridin-3-yl)pyrimidin-2-amine (151)



Boronic acid **146** (311 mg, 1.7 mmol), 2-amino-5-bromopyrimidine (**148**) (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent EtOAc gave **151** as a pale yellow solid (261 mg, 75%) mp 201.2-202.5 °C (from toluene); ^1H NMR (400 MHz, DMSO-d_6) δ 8.36 (2H, s), 7.70 (1H, d, J = 8.0 Hz), 6.67 (2H, s), 6.45 (1H, d, J = 8.0 Hz), 3.89 (3H, s), 3.88 (3H, s); ^{13}C NMR (100 MHz, DMSO- d_6) δ 162.21, 161.57, 158.67, 157.22, 140.51, 118.31, 109.84, 101.35, 53.28, 53.24; MS (ES+) *m/z* 233.1 (M^+, 100%). Anal. Calcd. for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 57.18; H, 5.21; N, 24.08%.

Methyl 3-amino-6-(2,3-dimethoxypyridin-4-yl)pyrazine-2-carboxylate (152)

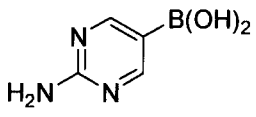


Boronic acid **158** (311 mg, 1.7 mmol), methyl 3-amino-6-bromopyrazine-2-carboxylate (**110a**) (348 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 15 min; eluent EtOAc gave **152** as yellow crystals (375 mg, 86%) mp 195.6-196.1 °C (from toluene); ^1H NMR (400 MHz, DMSO-d_6) δ 8.79 (1H, s), 7.94 (1H, d), 7.60 (2H, br s), 7.31 (1H, d, J = 5.2 Hz), 3.94 (3H, s), 3.88 (3H, s), 3.76 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.16, 157.89, 154.76, 148.29, 140.58, 140.41, 136.87, 135.89,

122.58, 116.55, 60.136, 53.43, 52.26; HRMS (EI) calcd for $C_{13}H_{14}N_4O_4$ (M^+) 290.10150, found 290.10148.

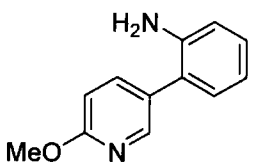
5.3 Experimental Procedures of Chapter 3

2-Amino-5-pyrimidylboronic acid (221)



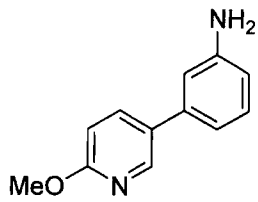
To a solution of 2-amino-5-bromopyrimidine (**148**) (1.74 g, 10 mmol) and triisopropylborate (2.9 cm^3, 12 mmol) in anhydrous THF (50 cm^3) at –78 °C, *n*-BuLi (2.5 M in hexane, 10 cm^3, 25 mmol) was added dropwise over 1 h. The reaction was stirred for 3.5 h at –78 °C, then allowed to warm to -20 °C and quenched with water (50 cm^3) before being stirred for 30 min. The organic solvent was evaporated *in vacuo* and the remaining aqueous layer filtered to remove inorganic salts. The filtrate was washed with diethyl ether (3 x 50 cm^3) to remove unreacted starting material and the aqueous layer filtered to remove inorganic salts. The filtrate was then acidified to pH 6 (with 48% HBr) to precipitate **221** as a white solid (640 mg, 46 %), mp > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (2H, s), 7.96 (2H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.11, 163.89. Anal. Calcd. for $C_4H_6BN_3O_2$: C, 34.58; H, 4.35; N, 30.25. Found: C, 34.46; H, 4.34; N, 30.37%.

2-(6-Methoxypyridin-3-yl)-phenylamine (173)



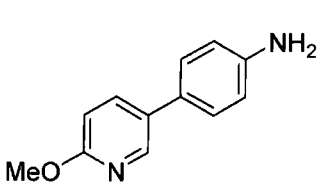
Boronic acid **40** (258 mg, 1.7 mmol), 2-bromoaniline (**167**) (258 mg, 1.5 mmol), $Pd[PPh_3]_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent EtOAc, gave **173** as a white solid (243 mg, 81%) mp 66.8-67.5 °C (from toluene); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.22 (1H, d, J = 2.0 Hz), 7.78 (1H, dd, J = 8.8 Hz, J = 2.8 Hz), 7.13 (1H, m), 7.05 (1H, dd, J = 8.2 Hz, J = 1.2 Hz), 6.86 (2H, d, J = 8.0Hz), 6.74 (1H, m), 4.50 (2H, br s, NH_2), 3.96 (3H, s, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.75, 147.34, 146.17, 140.14, 130.92, 129.54, 129.26, 123.81, 118.12, 116.12, 111.10, 53.33; MS (EI) *m/z* 200.1 (M^+, 100%). Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.76; H, 6.08; N, 13.85%.

3-(6-Methoxypyridin-3-yl)-phenylamine (174)



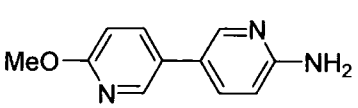
Boronic acid **40** (258 mg, 1.7 mmol), 3-bromoaniline (**168**) (158 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM:EtOAc (4:1 v/v) gave **174** as a brown solid (234 mg, 78%) mp 65.2-66.3 °C (from toluene:hexane); ^1H NMR (400 MHz, acetone-d_6) δ 8.39 (1H, d, J = 2.4 Hz), 7.90 (1H, dd, J = 8.4 Hz, J = 2.4 Hz), 7.18 (1H, t, J = 7.6 Hz), 6.95 (1H, t, J = 2.0 Hz), 6.85 (2H, m), 6.71 (1H, m), 4.77 (2H, br s, NH_2), 3.95 (3H, s, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 145.54, 145.28, 137.92, 130.18, 121.49, 119.05, 117.99, 115.58, 114.08, 112.94, 111.08, 53.37; MS (EI) *m/z* 199.1 (M^+, 100%). Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.48; H, 6.02; N, 13.99%.

4-(6-Methoxypyridin-3-yl)-phenylamine (175)



Boronic acid **40** (258 mg, 1.7 mmol), 4-bromoaniline (**169**) (258 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM, gave **175** as a dark brown solid (240 mg, 80%), mp 100.4-101.6 °C; ^1H NMR (200 MHz, acetone-d_6) δ 8.35 (1H, d, J = 2.6 Hz) 7.87 (1H, dd, J = 8.6 Hz, J = 2.0 Hz), 7.37 (2H, dd, J = 8.9 Hz, J = 2.3 Hz), 6.81 (3H, m), 4.81 (2H, br s), 3.94 (3H, s, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.34, 148.80, 148.76, 144.34, 137.18, 131.15, 127.79, 126.59, 115.42, 115.33, 111.00, 53.26; MS (EI) *m/z* 200.1 (M^+, 100%). Anal Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.10; H, 6.10; N 13.79%.

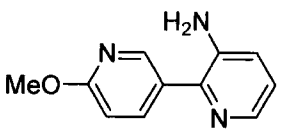
6'-Methoxy-[3,3']bipyridinyl-6-ylamine (176)



Boronic acid **40** (258 mg, 1.7 mmol), 2-amino-5-bromopyridine (**170**) (260 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h. Yielded **176** as off white needles (232 mg, 77%) mp 155.2-

156.1 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.37 (1H, d, J = 2.4 Hz), 8.27 (1H, d, J = 2.4 Hz), 7.89 (1H, dd, J = 2.4 Hz, J = 8.4 Hz), 7.70 (1H, dd, J = 2.4 Hz, J = 8.4 Hz), 6.84 (1H, d, J = 8.4 Hz), 6.67 (1H,d, J = 8.4 Hz), 5.56 (2H, br s, NH_2), 3.94 (3H, s, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.74, 159.90, 146.51, 144.44, 137.22, 135.98, 128.56, 123.06, 111.25, 53.34; MS (EI) *m/z* 201.1 (M^+, 100%). Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.90; H, 5.51; N, 21.10%.

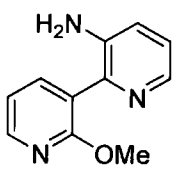
6'-Methoxy-[2,3']bipyridinyl-3-ylamine (177)



Boronic acid **40** (258 mg, 1.7 mmol), 3-amino-2-chloropyridine (**159**) (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM:EtOAc (4:1 v/v) gave **177** as a brown crystalline solid (247 mg, 82%) mp 84.0-84.4 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.55 (1H, s), 8.03 (2H, m), 7.23 (1H, d, J = 7.8 Hz), 7.09 (1H, m), 6.87 (1H, d, J = 8.4 Hz), 4.80 (2H, br s, NH_2), 3.97 (3H, s, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 164.12, 147.34, 142.51, 142.03, 139.72, 139.57, 129.42, 123.66, 123.07, 110.87, 53.40; MS (EI) *m/z* 201.2 (M^+, 100%). Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.39; H, 5.54; N, 20.72%.

When the reaction was carried out on 5 g scale, product **177** (4.10 g, 80% yield) was obtained.

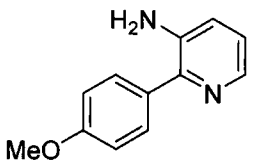
2'-Methoxy-[2,3']bipyridinyl-3-ylamine (178)



Boronic acid **43** (258 mg, 1.7 mmol), **159** (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM, yielded **178** as a pale yellow powder (207 mg, 69%) mp 184.1-185.2 °C (from toluene); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.21 (1H, dd, J = 5.0 Hz, J = 1.6 Hz), 7.95 (1H, dd, J = 4.4 Hz, J = 1.6 Hz), 7.70 (1H, dd, J = 7.2 Hz, J = 2.0 Hz), 7.14 (1H, m), 7.07 (2H, m), 4.56 (2H, br s, NH_2), 3.91 (3H, s, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.38, 146.49, 142.65,

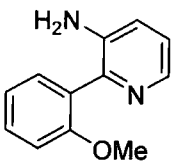
140.39, 140.23, 137.17, 123.31, 122.32, 121.40, 117.16, 53.16; MS (EI) *m/z* 201.0 (M^+, 100%). Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.83; H, 5.50; N, 20.43%.

3-Amino-2-(4-methoxyphenyl)pyridine (179)



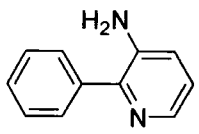
Boronic acid **165** (260 mg, 1.7 mmol), **159** (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent EtOAc yielded **179** as a brown crystalline solid (240 mg, 80%) mp 99.2-100.1 °C; ^1H NMR (500 MHz, acetone-d_6) δ 7.96 (1H, dd, J = 6.0 Hz, J = 3.5 Hz), 7.66 (2H, dd, J = 9.0 Hz, J = 5.0 Hz), 7.13 (1H, dd, J = 9.0 Hz, J = 6.0 Hz), 7.0 (3H, m), 4.63 (2H, br s, NH_2), 3.82 (3H, s, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.22, 148.03, 142.24, 133.96, 133.35, 131.33, 126.13, 125.75, 125.58, 117.35, 116.67, 58.30; MS (EI) *m/z* 200.1 (M^+, 78%), 199.0 (M^+-1, 100%). HRMS Calcd. for $C_{12}H_{11}N_2O$: 199.08714 (M^+-1), found: 199.08710.

3-Amino-2-(2-methoxyphenyl)pyridine (180)



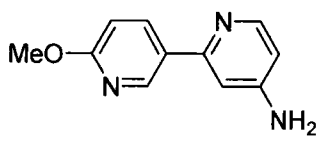
Boronic acid **166** (260 mg, 1.7 mmol), **159** (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent EtOAc yielded **180** as a brown crystalline solid (210 mg, 70%) mp 99.2-100.1 °C (from toluene); ^1H NMR (400 MHz, acetone-d_6) δ 7.94 (1H, dd, J = 4.4 Hz, J = 1.2 Hz), 7.38 (1H, m), 7.30 (1H, dd, J = 7.2 Hz, J = 2.0 Hz), 7.10 (2H, m), 7.05 (2H, m), 4.40 (2H, br s, NH_2), 3.82 (3H, s, OCH_3); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.52, 144.39, 143.26, 138.89, 132.41, 130.13, 129.47, 123.53, 122.13, 121.50, 111.97, 55.74; MS (EI) *m/z* 200.1 (M^+, 100%). Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.69; H, 6.01; N, 13.79%.

3-Amino-2-phenylpyridine (181)



Boronic acid **83** (207 mg, 1.7 mmol), **159** (193 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent EtOAc yielded **181** a pale brown crystalline solid (219 mg, 86%) analytically pure and spectroscopically identical with the sample described previously.[4]

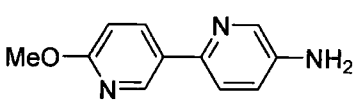
2-(6-Methoxypyridin-3-yl)pyridin-4-amine (182)



Boronic acid **40** (258 mg, 1.7 mmol), 4-amino-2-chloropyridine (**171**) (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent EtOAc, yielded **182** as a pale brown crystalline solid (120 mg, 40%) mp 148.9-149.6 °C (from toluene and hexane); ^1H NMR (400 MHz, acetone-d_6) δ 8.75 (1H, s), 8.24 (1H, d, J = 8.8 Hz), 8.14 (1H, d, J = 5.2 Hz), 7.08 (1H, s), 6.80 (1H, m), 6.54 (1H, dd, J = 5.6 Hz, J = 2.4 Hz), 5.62 (2H, br s), 3.92 (3H, s, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ167.76, 158.68, 158.32, 153.40, 148.66, 140.54, 132.80, 133.64, 111.45, 108.10, 56.33; MS (EI) *m/z* 201.1 (M^+, 100%). Anal. calcd for $C_{11}H_{11}N_3O$; C, 65.66; H, 5.51; N, 20.86. Found: C, 65.58; H, 5.42; N, 20.98%.

When the reaction was carried out on 5 g scale, product **182** (3.08 g, 60% yield) was obtained.

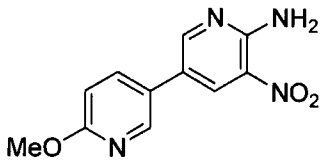
6-(6-Methoxypyridin-3-yl)pyridin-3-amine (183)



Boronic acid **40** (258 mg, 1.7 mmol), 5-amino-2-chloropyridine (**172**) (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent EtOAc, gave **183** as a pale brown crystalline solid (120 mg, 40%) mp 147.0-147.7 °C (from toluene); ^1H NMR (500 MHz, acetone-d_6) δ 8.75 (1H, d, J = 2.5 Hz), 8.27 (1H, dd, J = 8.5 Hz, J = 2.5 Hz), 8.17 (1H, d, J = 2.5 Hz), 7.63

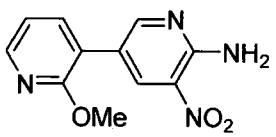
(1H, d, J = 8.5 Hz), 7.15 (1H, dd, J = 8.5 Hz, J = 2.5 Hz), 6.82 (1H, d, J = 8.5 Hz), 5.03 (2H, br s), 3.95 (3H, s, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.14, 147.56, 147.38, 146.78, 140.38, 139.73, 132.91, 124.76, 123.20, 113.85, 56.36; MS (EI) *m/z* 201.1 (M^+, 100%). Anal. Calcd for $C_{11}H_{11}N_3O$; C, 65.66; H, 5.51; N, 20.86. Found: C, 65.63; H, 5.53; N, 21.18%.

5-(6-Methoxypyridin-3-yl)-3-nitropyridin-2-amine (184)



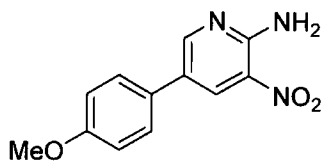
Boronic acid **40** (258 mg, 1.7 mmol), 2-amino-5-bromo-3-nitropyridine (**107**) (327 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM:EtOAc (3:2 v/v) gave **184** as an orange solid (253 mg, 69%) mp 228.9-229.5 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.81 (1H, d, J = 2.4 Hz), 8.61 (1H, d, J = 2.4 Hz), 8.56 (1H, d, J = 2.4 Hz), 8.10 (1H, dd, J = 8.4 Hz, J = 2.4 Hz), 8.07 (2H, br s, NH_2) 6.95 (1H, dd, J = 8.4 Hz, J = 0.8 Hz), 3.38 (3H, s, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.99, 155.21, 153.78, 145.21, 138.11, 132.48, 127.60, 126.03, 122.80, 111.66, 54.27; MS (EI) *m/z* 246.0 (M^+, 100%). Anal. Calcd. for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.75. Found: C, 53.18; H, 4.09; N, 21.69%.

5-(2-Methoxypyridin-3-yl)-3-nitropyridin-2-amine (185)



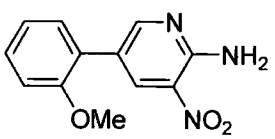
Boronic acid **43** (258 mg, 1.7 mmol), **107** (327 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (98 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM:EtOAc (4:1 v/v) gave **185** as a yellow solid (277 mg, 75%), mp 222.1-223.2 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.63 (1H, d, J = 2.0 Hz), 8.56 (1H, d, J = 2.0 Hz), 8.18 (1H, dd, J = 4.8 Hz, J = 2.0 Hz), 8.06 (2H, br s, NH_2), 7.89 (1H, dd, J = 7.2 Hz, J = 2.0 Hz), 7.10 (1H, dd, J = 7.2 Hz, J = 4.8 Hz) 3.90 (3H, s, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.76, 156.85, 153.47, 146.75, 138.82, 134.90, 126.81, 121.15, 119.62, 118.36, 54.20; MS (EI) *m/z* 246.0 (M^+, 100%). Anal. Calcd. for $C_{11}H_{10}N_4O_3$: C, 53.75; H, 4.09; N, 22.75. Found: C, 53.45; H, 4.09; N, 22.66%.

5-(4-Methoxyphenyl)-3-nitropyridin-2-amine (186)



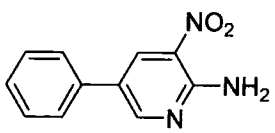
Boronic acid **165** (258 mg, 1.7 mmol), **107** (327 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (98 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM, yielded **186** as an orange solid (276 mg, 75%), mp 182.1-182.9 °C (from toluene); ^1H NMR (400 MHz, acetone-d_6) δ 8.68 (1H, d, J = 2.4 Hz), 8.55 (1H, d, J = 2.4 Hz), 7.63 (2H, d, J = 8.8 Hz), 7.49 (2H, br s, NH_2), 7.04 (2H, d, J = 8.8 Hz), 3.84 (3H, s, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.95, 154.20, 152.51, 130.95, 127.86, 127.23, 126.60, 124.68, 114.53, 55.21; MS (EI) *m/z* 245.0 (M^+, 100%). Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.42; H, 4.46; N, 16.75%.

5-(2-methoxyphenyl)-3-nitropyridin-2-amine (187)



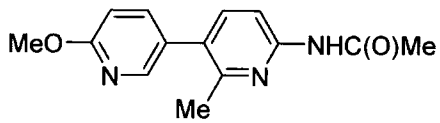
Boronic acid **166** (258 mg, 1.7 mmol), **107** (327 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (98 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent EtOAc, gave **187** as a mustard-yellow solid (254 mg, 69%), mp 164.0-165.0 °C; ^1H NMR (400 MHz, acetone-d_6) δ 8.68 (1H, d, J = 2.4 Hz), 8.55 (1H, d, J = 2.4 Hz), 7.63 (2H, d, J = 8.8 Hz), 7.49 (2H, br s, NH_2), 7.04 (2H, d, J = 8.8 Hz), 3.84 (3H, s, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.95, 154.20, 152.51, 130.95, 127.86, 127.23, 126.60, 124.68, 114.53, 55.21; MS (EI) *m/z* 245.0 (M^+, 100%). Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.82; H, 4.52; N, 17.17%.

2-Amino-3-nitro-5-phenylpyridine (188)



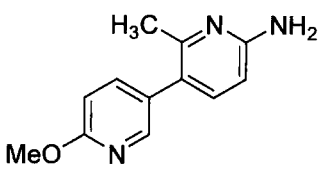
Boronic acid **83** (207 mg, 1.7 mmol), **107** (327 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM:EtOAc (4:1 v/v) yielded **188** as a yellow solid (257 mg, 80%) analytically pure and spectroscopically identical with the sample described previously.[5]

_N_-[5-(6-Methoxypyridin-3-yl)-6'-methylpyridin-2-yl]acetamide (189)



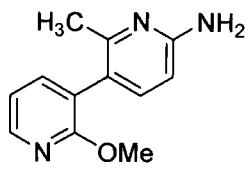
Boronic acid **40** (258 mg, 1.7 mmol), *N*-(5-bromo-6-methylpyridin-2-yl)acetamide (**109**)[3] (334 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 8 h; eluent EtOAc gave **189** as a white solid (310 mg, 81%) mp 142.6-143.1 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.50 (1H, br s, NH), 8.11 (1H, dd, J = 2.4 Hz, J = 0.8 Hz), 7.93 (1H, d, J = 8.8 Hz), 7.69 (1H, dd, J = 8.8 Hz, J = 2.4 Hz), 7.54 (1H, d, J = 8.8 Hz), 6.83 (1H, dd, J = 8.8 Hz, J = 0.8 Hz), 3.83 (3H, s), 2.31 (3H, s), 2.04 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.0, 163.4, 154.4, 151.4, 147.2, 140.5, 140.1, 128.9, 128.7, 111.4, 110.7, 53.9, 24.5, 23.2; MS (EI) *m/z* 257.1 (M^+, 100%). Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.28; H, 5.82; N, 16.32%.

6'-Methoxy-2-methyl-[3,3']bipyridinyl-4-ylamine (190)



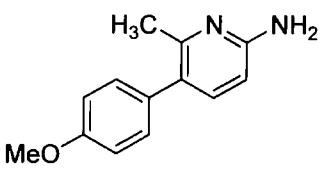
Boronic acid **40** (258 mg, 1.7 mmol), 2-amino-5-bromo-6-methylpyridine (**108**) (281mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM:EtOAc (1:4 v/v) yielded **190** as off-white needles (235 mg, 73%) mp 181.7-182.1 °C (from toluene); ^1H NMR (400 MHz, acetone-d_6) δ 8.10 (1H, d, J = 2.4 Hz), 7.65 (1H, dd, J = 8.4 Hz, J = 2.4 Hz), 7.28. (1H, d, J = 8.4 Hz), 6.83 (1H, d, J = 8.4 Hz), 6.49 (1H, d, J = 8.4 Hz), 5.41 (2H, br s, NH_2), 3.95 (3H, s, OCH_3), 2.87 (3H, s, CH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.50, 159.27, 154.42, 147.33, 140.35, 139.49, 130.50, 122.40, 110.61, 106.10, 53.32, 23.08; MS (EI) *m/z* 215.1 (M^+, 100%). Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.74; H, 6.03; N, 19.44%.

2'-Methoxy-2-methyl-[3,3']bipyridinyl-4-ylamine (191)



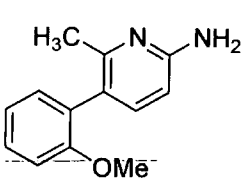
Boronic acid **43** (258 mg, 1.7 mmol), **108** (281mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM:EtOAc (1:4 v/v) yielded **191** as off-white needles (241 mg, 75%) mp 151.2-151.9 °C; ^1H NMR (500 MHz, acetone-d_6) δ 7.08 (1H, d, J = 3.5 Hz), 7.43 (1H, dd, J = 7.0 Hz, J = 1.5 Hz), 7.12 (1H, d, J = 8.0 Hz), 6.94 (1H, m), 6.49 (1H, d, J = 8.4 Hz), 6.37 (1H, d, J = 8.0 Hz), 5.40 (2H, br s, NH_2), 3.80 (3H, s, OCH_3), 2.04 (3H, s, CH_3); ^{13}C NMR (125 MHz, acetone-d_6) δ 161.87, 159.27, 154.91, 146.27, 140.00, 139.75, 124.34, 120.83, 117.43, 105.57, 53.22, 22.55; MS (EI) *m/z* 215.0 (M^+, 100%). Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.66; H, 6.12; N, 19.10%.

2-Amino-6-methyl-5-(4-methoxyphenyl)pyridine (192)



Boronic acid **165** (258 mg, 1.7 mmol), **108** (281 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM:EtOAc (3:7 v/v) yielded **192** as off-white needles (207 mg, 65%) mp 160.1-160.9 °C (from toluene); ^1H NMR (400 MHz, acetone-d_6) δ 7.20 (3H, d, J = 8.8 Hz), 6.94 (2H, d, J = 8.8 Hz), 6.42 (1H, d, J = 8.0 Hz), 5.35 (2H, br s, NH_2), 3.81 (3H, s, OCH_3), 2.37 (3H, s, CH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 159.09, 158.72, 153.81, 139.39, 133.86, 130.84, 125.85, 114.17, 105.95, 55.25, 23.07; MS (EI) *m/z* 214.1 (M^+, 100%). Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.72; H, 6.53; N, 12.73%.

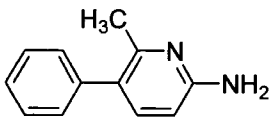
2-Amino-6-methyl-5-(2-methoxyphenyl)pyridine (193)



Boronic acid **166** (258 mg, 1.7 mmol), **108** (281 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and

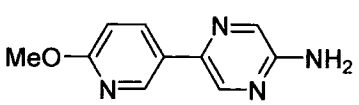
Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM:EtOAc (1:4 v/v) yielded **193** as an off-white powder (241 mg, 75%) mp 158.7-159.2 °C (from toluene); ^1H NMR (400 MHz, acetone-d_6) δ 7.09 (1H, d, J = 8.4 Hz), 7.05 (1H, dd, J = 7.4 Hz, J = 2.0 Hz), 7.00 (1H, d, J = 8.4 Hz), 6.93 (1H, t, J = 7.4 Hz), 7.27 (1H, m), 6.36 (1H, d, J = 8.4 Hz), 5.26 (2H, br s, NH_2), 3.71 (3H, s, OCH_3), 2.04 (3H, s, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.24, 156.47, 153.56, 139.04, 130.96, 129.21, 128.37, 120.85, 120.34, 111.09, 104.83, 55.14, 22.29; MS (EI) *m/z* 214.0 (M^+, 100%). Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 73.04; H, 6.60; N, 12.62%.

2-Amino-5-phenyl-6-methylpyridine (194)



Boronic acid **83** (207 mg, 1.7 mmol), **108** (281 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent EtOAc yielded **194** white crystalline solid (188 mg, 68%) mp 117.2-118.4 °C (from toluene:hexane); ^1H NMR (400 MHz, acetone-d_6) δ 7.43 (2H, m), 7.33 (3H, m), 7.28 (1H, d, J = 8.4 Hz), 6.49 (1H, d, J = 8.4 Hz), 5.44 (2H, br s, NH_2), 2.30 (3H, s, CH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 162.00, 156.84, 144.76, 142.39, 132.86, 131.83, 129.97, 129.18, 109.01, 26.09; MS (EI) *m/z* 184.1 (M^+, 100%). Anal. calcd for $C_{12}H_{12}N_2$ C, 78.23; H, 6.57; N, 15.21. Found: C, 78.27; H, 6.63; N, 15.51%.

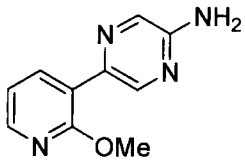
5-(6-Methoxypyridin-3-yl)-pyrazin-2-ylamine (198)



Boronic acid **40** (258 mg, 1.7 mmol), 2-amino-5-bromopyrazine (**163**)[3] (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent EtOAc gave **198** as a brown crystalline solid (182 mg, 60%), mp 166.1-166.6 °C (from toluene); ^1H NMR (400 MHz, acetone-d_6) δ 8.75 (1H, dd, J = 2.6 Hz, J = 0.6 Hz), 8.50 (1H, d, J = 1.6 Hz), 8.24 (1H, dd, J = 8.6 Hz, J = 2.6 Hz), 8.09 (1H, d, J = 1.2 Hz), 6.86 (1H, dd, J = 8.4 Hz, J = 0.8 Hz), 5.98 (2H, br s), 3.96 (3H, s); ^{13}C NMR (100 MHz, acetone-d_6); δ 164.36, 155.54, 144.29, 139.25, 138.97, 136.41, 132.23,

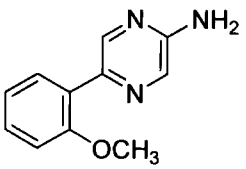
127.60, 111.11, 53.41; MS (EI) *m/z* 202.1 (M^+, 100%). Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.16; H, 4.98; N, 27.69%.

5-(2-Methoxypyridin-3-yl)-pyrazin-2-ylamine (199)



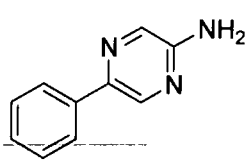
Boronic acid **43** (258 mg, 1.7 mmol), **163** (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent EtOAc, gave **199** as a off white powder (213 mg, 70%), mp 134.7-135.2 °C (from toluene); ^1H NMR (500 MHz, acetone-d_6) δ 8.70 (1H, d, J = 1.5 Hz), 8.26 (1H, dd, J = 9.5 Hz, J = 5.5 Hz), 8.11 (1H, dd, J = 6.5 Hz, J = 3.0 Hz), 8.08 (1H, d, J = 1.0 Hz), 7.04 (1H, dd, J = 12.0 Hz, J = 2.5 Hz), 6.02 (2H, br s), 4.00 (3H, s); ^{13}C NMR (125 MHz, acetone-d_6) δ 163.97, 158.19, 149.16, 146.28, 141.00, 140.64, 135.29, 124.32, 120.84, 56.37; MS (EI) *m/z* 202.1 (M^+, 100%). HRMS Calcd for $C_{10}H_{10}N_4O$: 202.08546 (M^+), found: 202.08550.

5-(2-Methoxyphenyl)-pyrazin-2-ylamine (200)



Boronic acid **166** (261 mg, 1.7 mmol), **163** (261 mg, 1.5 mmol), $Pd(PPh_3)_4$ (98 mg, 0.085 mmol), THF (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h. Purified by column chromatography and recrystallised using toluene to yield **200** as a beige solid (214 mg, 71%), mp 99.8-100.2 °C; ^1H NMR (400 MHz, acetone-d_6) δ 8.60 (1H, d, J = 1.6 Hz), 8.11 (1H, d, J = 1.2 Hz), 7.85 (1H, dd, J = 1.8 Hz, J = 7.8 Hz), 7.34 (1H, m) 7.13 (1H, d, J = 8.4 Hz), 7.10 (1H, m) 5.80 (2H br s, NH_2), 3.93 (3H, s, OCH_3); ^{13}C HMR (125 MHz, acetone-d_6) δ 157.40, 154.85, 143.71, 139.90, 131.98, 130.45, 129.45, 127.32, 121.30, 112.09, 55.62; MS (EI) *m/z* 200.8 (M^+, 100%). Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.38; H, 5.47; N 20.58%.

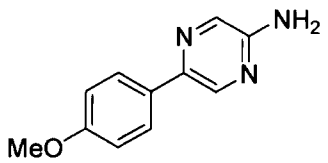
5-Phenylpyrazin-2-amine (201)



Boronic acid **83** (207 mg, 1.7 mmol), **163** (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and

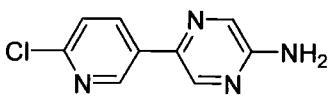
Na_2CO_3 (1 M, 4 cm^3); reaction time 8 h; eluent EtOAc, gave **201** as a yellow powder (174 mg, 68%), analytically pure and spectroscopically identical with the sample described previously.[6]

5-(4-Methoxyphenyl)pyrazin-2-amine (202)



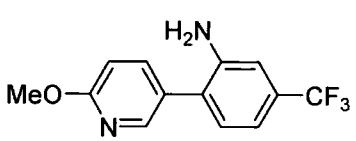
Boronic acid **165** (258 mg, 1.7 mmol), **163**(261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 8 h; eluent EtOAc, gave **202** as a brown needles (208 mg, 69%), analytically pure and spectroscopically identical with the sample described previously.[7]

5-(6-Chloropyridin-3-yl)pyrimidin-2-amine (203)



Boronic acid **23**[3] (267 mg, 1.7 mmol), **163** (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h; eluent DCM:Et_2O (1:2 v/v) gave **203** as an off-white solid (193 mg, 62%), mp 205.5-205.8 °C; ^1H NMR (300 MHz, acetone-d_6) δ 8.99 (1H, d, J = 2.4 Hz), 8.63 (1H, d, J = 1.2 Hz), 8.38 (1H, dd, J = 8.4 Hz, J = 2.7 Hz), 8.13 (1H, d, J = 1.5 Hz), 7.54 (1H, d, J = 8.4 Hz), 6.02 (2H, br s, NH_2); ^{13}C NMR (100 MHz, acetone-d_6) δ 156.28, 150.41, 147.04, 140.16, 137.49, 136.10, 133.23, 132.63, 124.77; MS (EI) *m/z* 205.9 (M^+, 100%). Anal. Calcd. for $C_9H_7ClN_4$: C, 52.31; H, 3.41; N, 27.11. Found: C, 51.99; H, 3.33; N, 26.67%.

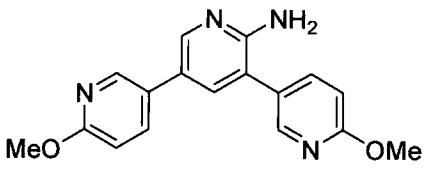
2-(6-Methoxypyridin-3-yl)-5-(trifluoromethyl)-phenylamine (204)



Boronic acid **40** (258 mg, 1.7 mmol), 1-amino-2-bromo-5-(trifluoromethyl)benzene (**195**) (360 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 8 h; eluent EtOAc gave **204** as a white crystalline solid (337 mg, 84%) mp 63.9-64.2 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.16 (1H, dd, J = 2.4 Hz, J = 1.0 Hz), 7.71 (1H, dd, J = 8.8 Hz, J = 2.4 Hz), 7.06 (2H, m), 6.85 (2H, m), 5.31 (2H, s, NH_2), 3.85 (3H, s, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.9, 146.6, 146.4,

139.5, 131.1, 129.1 (J = 30.9 Hz), 127.5, 125.9, 112.3, 111.1, 110.6, 53.2; MS (EI) *m/z* 268.2 (M^+, 100%). Anal. Calcd. for $C_{13}H_{11}N_2F_3O$: C, 58.21; H, 4.13; N, 10.44. Found: C, 58.01; H, 4.24; N, 10.47%.

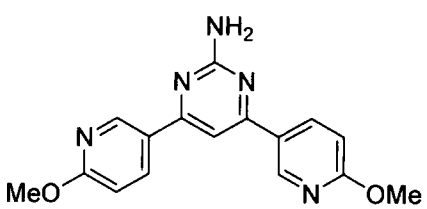
3,5-Bis(6-methoxypyridin-3-yl)pyridin-2-amine (205)



Boronic acid **40** (550 mg, 3.6 mmol), 2-amino-3,5-dibromopyridine (**196**) (378 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 8 h; eluent EtOAc gave **205** as a white crystalline solid (350 mg, 76%) mp 144.0-144.5 °C; ^1H NMR (400 MHz, acetone-d_6) δ 8.42 (1H, dd, J = 2.4 Hz, J = 0.8 Hz), 8.30 (1H, dd, J = 2.4 Hz, J = 0.8 Hz), 8.28 (1H, d, J = 2.4 Hz), 7.94 (1H, dd, J = 8.8 Hz, J = 2.4 Hz), 7.85 (1H, dd, J = 8.8 Hz, J = 2.4 Hz), 7.64 (1H, d, J = 2.4 Hz), 6.87 (2H, dd, J = 8.8 Hz, J = 0.8 Hz), 6.83 (1H, dd, J = 8.8 Hz, J = 0.8 Hz), 5.49 (2H, s, NH_2), 3.93 (3H, s, OCH_3), 3.90 (3H, s, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 164.0, 163.7, 157.0, 147.3, 145.6, 144.4, 139.8, 137.2, 135.3, 127.9, 127.7, 124.0, 118.3, 111.2, 111.1, 53.7 (2C); MS (EI) *m/z* 308.3 (M^+, 100%). Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.01; H, 5.32; N, 18.02%.

When boronic acid **40** (1.2 equiv.) was used in this reaction, the yield of compound **205** was reduced to 32%, and a trace amount (<1% yield) of mono-coupled product was isolated, but not obtained analytically pure.

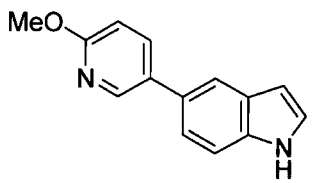
4,6-Bis(6-methoxypyridin-3-yl)pyrimidin-2-amine (206)



Boronic acid **40** (550 mg, 3.6 mmol), 2-amino-3,5-dichloropyrimidine (**202**) (247 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 8 h; from toluene gave **206** as a green crystalline solid (163 mg, 35%) mp 226.3-227.0 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.98 (2H, d, J = 2.4 Hz), 8.42

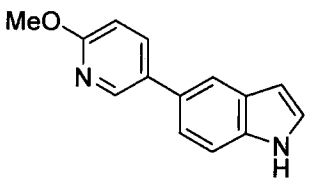
(2H, dd, J = 8.8 Hz, J = 2.4 Hz), 7.68 (1H, s), 6.91 (2H, dd, J = 8.8 Hz, J = 1.0 Hz), 6.73 (2H, s, NH_2), 3.89 [6H, s, $(OCH_3)_2$]; ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 164.5 (2C), 163.3 (2C), 147.1 (2C), 138.3 (2C), 127.3 (2C), 111.1 (2C), 110.1, 54.3 (2C); MS (EI) *m/z* 309.3 (M^+, 100%). Anal. Calcd. for $C_{16}H_{15}N_5O_2$: C, 62.13; H, 4.89; N, 22.64. Found: C, 62.20; H, 4.89; N, 22.35%.

5-(6-Methoxy-pyridin-3-yl)-1*H*-indole (213)



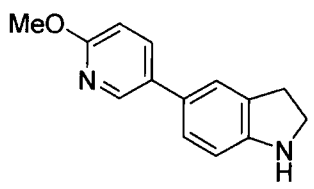
Boronic acid **40** (258 mg, 1.7 mmol), 5-bromoindole (**208a**) (294 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h. Yielded **213** as an off-white waxy solid (150 mg, 45%), mp 94.3-97.7 °C, ^1H NMR (400 MHz, acetone-d_6) δ 10.37 (1H, br s, NH), 8.29 (1H, d, J = 2.4 Hz), 7.98 (1H, dd, J = 2.6 Hz, J = 8.6 Hz), 7.84 (1H, m), 7.56 (1H, dd, J = 0.8 Hz, J = 8.4 Hz) 7.42 (2H, m), 6.87 (1H, dd, J = 0.8 Hz, J = 8.4 Hz), 6.58 (1H, m), 3.79 (3H, s, OCH_3); ^{13}C NMR (125 MHz, acetone-d_6) δ 163.41, 145.17, 138.05, 136.38, 132.10, 129.55, 129.39, 126.18, 120.99, 118.75, 112.34, 110.88, 102.43, 53.19; MS (EI) *m/z* 224.0 (M^+, 100%). Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.88; H, 5.39; N, 12.49. Found: C, 74.39; H, 5.46; N, 12.46%.

5-(6-Methoxy-pyridin-3-yl)-1*H*-indole (213)



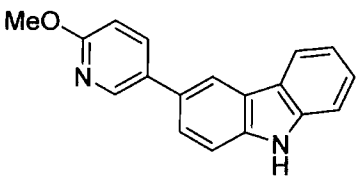
Boronic acid **40** (258 mg, 1.7 mmol), 5-iodoindole (**208b**) (364.6 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h. Yielded **213** as an off-white waxy solid (121 mg, 36%), mp 98.2-98.8 °C, analytically pure and spectroscopically identical with the sample described previously.

5-(6-Methoxy-pyridin-3-yl)-2,3,dihydro-1*H*-indole (214)



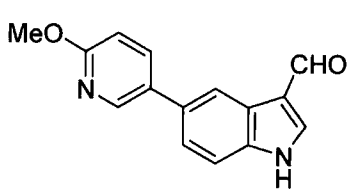
Boronic acid **40** (258 mg, 1.7 mmol), 5-bromoindoline (**209**) (297 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h. Yielded **214** as a green oil (75 mg, 22%); ^1H NMR (400 MHz, acetone-d_6) δ8.43 (1H, s), 7.93 (1H, dd, J = 8.4 Hz, J = 2.4 Hz), 7.43 (1H, s), 7.31 (1H, d, J = 8.4 Hz), 6.89 (1H, d, J = 8.4 Hz), 6.75 (1H, d, J = 8.4 Hz), 5.08 (1H, br s, NH), 4.02 (3H, s, OCH_3), 3.67 (2H, t, J = 8.4 Hz), 3.13 (2H, t, J = 8.4 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ145.27, 144.40, 138.16, 137.30, 126.15, 123.20, 121.07, 118.85, 112.39, 110.91, 109.47, 102.44, 53.22, 47.57; MS (EI) *m/z* 225.8 (M^+, 100%).

3-(6-Methoxy-pyridin-3-yl)-9*H*-carbazole (215)



Boronic acid **40** (258 mg, 1.7 mmol), 3-bromo-9*H*-carbazole (**210**) (369.2 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h. Yielded **215** as a white powder (215 mg, 52%) mp 188.1-189.5 °C; ^1H NMR (400 MHz, acetone-d_6) δ 10.47 (1H, br s, NH), 8.57 (1H, dd, J = 2.4 Hz, J = 0.8 Hz), 8.44 (1H, m), 8.25 (1H, d, J = 3.6 Hz), 8.08 (1H, dd, J = 8.4 Hz, J = 2.4 Hz), 7.70 (1H, m), 7.64 (1H, m), 7.58 (1H, m), 7.46 (1H, m), 7.25 (1H, m), 6.91 (1H, dd, J = 8.4 Hz, J = 0.8 Hz), 3.99 (3H, s, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.66, 145.34, 141.24, 140.18, 138.12, 131.70, 129.39, 126.50, 125.12, 124.45, 123.75, 120.91, 119.60, 118.72, 111.99, 111.64, 111.09, 53.32; HRMS (EI) calcd for $C_{18}H_{14}N_2O$ 274.11061; Found 274.11055.

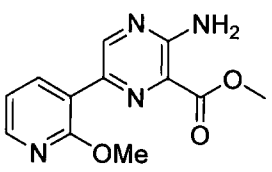
5-(6-Methoxy-pyridin-3-yl)-1*H*-indole-3-carbaldehyde (216)



Boronic acid **40** (258 mg, 1.7 mmol), 5-bromoindole-3-carboxaldehyde (**211**) (336 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 65 h. Yielded **216** as a white powder (204 mg, 54%) mp 224.8-225.2 °C; ^1H NMR (400 MHz, acetone-d_6) δ 10.11 (1H, s, NH),

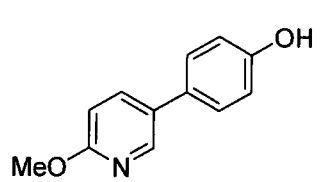
8.49 (2H, dd, J = 2.4 Hz, J = 8.4 Hz), 8.29 (1H, s), 8.03 (1H, dd, J = 2.4 Hz, J = 8.4 Hz), 7.68 (1H, dd, J = 8.4 Hz, J = 0.8 Hz), 7.59 (1H, dd, J = 2.4 Hz, J = 8.4 Hz), 6.92 (1H, dd, J = 0.8 Hz, J = 8.4 Hz), 3.98 (3H, s, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 185.21, 163.99, 145.61, 138.52, 138.40, 133.02, 131.60, 126.05, 123.52, 120.01, 119.91, 113.42, 111.27, 53.42; HRMS (EI) calcd for $C_{15}H_{12}N_2O_2$ 252.26798; Found 251.26521.

Methyl 3-amino-6-(2-methoxypyridin3-yl)pyrazine-2-carboxylate (217)



Boronic acid **43** (260 mg, 1.7 mmol), methyl 3-amino-6-bromopyrazine-2-carboxylate **110a** (348 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 15 min; eluent EtOAc gave **217** as a yellow solid (320 mg, 82%) mp 185.3-186.0 °C (from toluene); ^1H NMR (400 MHz, DMSO-d_6) δ 8.84 (1H, s), 8.20 (1H, dd, J = 4.8 Hz, J = 2.0 Hz), 8.11 (1H, dd, J = 7.6 Hz, J = 2.0 Hz), 7.48 (2H, br s, NH_2), 7.14 (1H, dd, J = 7.6 Hz, J = 4.8 Hz), 3.96 (3H, s), 3.87 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.40, 160.15, 154.49, 148.19, 146.54, 138.13, 136.63, 122.46, 119.49, 117.65, 53.52, 52.28; MS (ES+) *m/z* 261.1 (M^+, 100%). Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.02; H, 4.41; N, 21.23%.

4-(6-Methoxypyridin-3-yl)phenol (218)

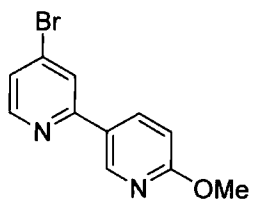


Boronic acid **40** (260 mg, 1.7 mmol), 4-bromophenol (**212**) (259 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 8 h; eluent EtOAc:DCM (4:1 v/v) gave **218** as peach needles (249 mg, 82%) mp 166.9-167.9 °C; ^1H NMR (400 MHz, acetone-d_6) δ 8.50 (1H, s), 8.34 (1H, dd, J = 2.8 Hz, J = 0.8 Hz), 7.85 (1H, dd, J = 8.8 Hz, J = 2.8 Hz), 7.45 (2H, m), 6.93 (2H, m), 6.79 (1H, dd, J = 8.8 Hz, J = 0.8 Hz), 3.90 (3H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.6, 157.7, 144.7, 137.5, 130.5, 129.6, 128.2, 116.4, 111.0, 53.2; MS (EI) *m/z* 201.0 (M^+, 100%). Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.61; H, 5.51; N, 6.96%.

Diazotisation[8]

2-(6-Methoxypyridin-3-yl)pyridin-4-amine (**182**) (500 mg, 2.48 mmol) was suspended in 48% hydrobromic acid (2.5 cm^3) and the mixture sonicated for 10 min then cooled to -5 °C. To this solution, maintained at -5 °C, a solution of sodium nitrite (520 mg) in water (0.5 cm^3) was added dropwise with vigorous stirring over 0.5 h. The mixture was then allowed to warm up to room temperature and stirred for an additional 1 h. Sodium hydroxide solution (5% aqueous) was then added carefully to adjust the pH to ca. 10 before being extracted with DCM (50 cm^3). The extract was dried over magnesium sulphate, evaporated and the solid purified by column chromatography (eluent EtOAc). Two products were obtained along with unreacted **182**, in the following order of elution.

4-Bromo-2-(6-methoxypyridin-3-yl)pyridine (219)

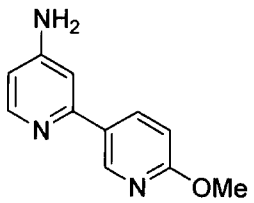


219 a white solid (210 mg, 32%) mp 70.0-71.0 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.90 (1H, dd, J = 2.4 Hz, J = 0.8 Hz), 8.51 (1H, dd, J = 5.2 Hz, J = 0.4 Hz), 8.38 (1H, dd, J = 8.8 Hz, J = 2.4 Hz), 8.12 (1H, dd, J = 2.0 Hz, J = 0.4 Hz), 7.53 (1H, dd, J = 5.2 Hz, J = 2.0 Hz), 6.87 (1H, dd, J = 8.8 Hz, J = 0.8 Hz), 3.95 (3H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 165.72, 157.00, 151.42, 146.71, 137.97, 133.80, 127.85, 125.84, 123.28, 111.27, 53.69; HRMS (EI) calcd for $C_{11}H_9BrN_2O$ (M^+) 263.98983, found 263.98955.

220 (unknown structure)

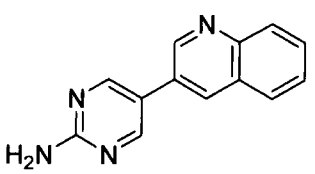
220 colourless needles (208 mg, 30%) mp 177.0-178.0 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.72 (1H, dd, J = 2.4 Hz, J = 0.4 Hz), 8.34 (1H, s), 8.23 (1H, dd, J = 8.8 Hz, J = 2.4 Hz), 7.26 (1H, s), 6.81 (1H, dd, J = 8.8 Hz, J = 0.8 Hz), 5.88 (2H, br s), 3.92 (3H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 165.19, 154.54, 152.56, 151.71, 145.88, 137.62, 128.90, 110.95, 105.96, 105.40, 53.52; HRMS (EI) calcd for $C_{11}H_{10}BrN_3O$ (M^+) 279.00072, found 279.00100.

2-(6-Methoxypyridin-3-yl)pyridin-4-amine (182)



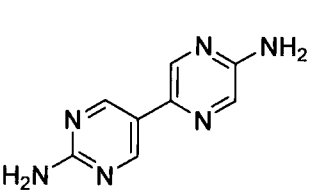
(210 mg, 32%) of the starting material spectroscopically identical to previously described.

5-(Quinolin-3-yl)pyrimidin-2-amine (222)



Boronic acid **221** (236 mg, 1.7 mmol), 3-bromoquinoline (**147**) (312 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); eluent EtOAc gave **222** as a pale yellow solid (200 mg, 60%) mp 265.9-266.9 °C (from toluene: hexane); ^1H NMR (400 MHz, DMSO-d_6) δ 9.21 (1H, d, J = 2.8 Hz), 8.79 (2H, s), 8.59 (1H, d, J = 2.0 Hz), 8.02 (1H, d, J = 8.0 Hz), 7.98 (1H, d, J = 8.0 Hz), 7.72 (1H, t, J = 8.0 Hz), 7.64 (1H, t, J = 7.2 Hz), 6.94 (2H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.15, 156.42, 148.43, 146.47, 150.71, 129.13, 128.66, 128.36, 128.04, 127.71, 126.97, 119.18; MS (ES+) *m/z* 223.1 (M^+, 100%). Anal. Calcd. for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.02; H, 4.41; N, 25.23%.

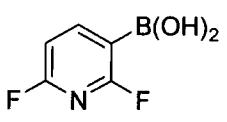
5-(2-Aminopyrimidin-5-yl)pyrazin-2-amine (223)



Boronic acid **221** (236 mg, 1.7 mmol), 2-amino-5-bromopyrazine (**163**) (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); eluent EtOAc gave **223** as a pale yellow solid (113 mg, 40%) mp 132.4-133.5 °C (from toluene); ^1H NMR (400 MHz, DMSO-d_6) δ 8.71 (1H, s), 8.47 (1H, s), 8.38 (1H, d, J = 1.6 Hz), 7.90 (1H, d, J = 1.6 Hz), 6.74 (2H, s), 6.46 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.82, 154.66, 154.62, 137.32, 136.09, 131.42, 128.85, 128.16; MS (ES+) *m/z* 188.1 (M^+, 100%). Anal. Calcd. for $C_8H_8N_6$: C, 51.06; H, 4.28; N, 44.66. Found: C, 51.02; H, 4.41; N, 44.23%.

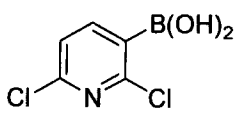
5.4 Experimental Procedure of Chapter 4

2,6-Difluoro-3-pyridylboronic acid (225)



To a solution of diisopropylamine (6.5 cm^3, 47.7 mmol) in anhydrous ether (50 cm^3) at 0 °C, *n*-BuLi (2.5 M in hexane, 20 cm^3, 52.1 mmol) was added dropwise. The reaction was stirred for 0.5 h at 0 °C and was then cooled to -78 °C before 2,6-difluoropyridine (**224**) (5.0 g, 43.4 mmol) was added dropwise. The reaction was stirred for 3 h at -78 °C then triisopropylborate (15 cm^3, 65.0 mmol) was added slowly. The reaction mixture was stirred at -78 °C for another 0.5 h, then quenched with water (50 cm^3) and allowed to warm to room temperature with stirring overnight. The organic solvent was evaporated *in vacuo* and washed with diethyl ether (3 x 50 cm^3) to remove unreacted starting material. The aqueous layer was then acidified to pH 6 (with 48% HBr) and then extracted with ethyl acetate (3 x 50 cm^3). The organic layer was reduced *in vacuo* and the crude product recrystallised from toluene to give **225** as a white solid (5.6 g, 82 %), mp 136.7-137.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (1H, q, J = 8.4 Hz), 7.47 (2H, s), 7.03 (1H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.58 (1C, dd, J = 178.4 Hz, J =13.6 Hz), 162.14 (1C, dd, J = 178.4 Hz, J =13.6 Hz), 153.02, 106.59 (1C, dd, J = 32.4 Hz, J =5.4 Hz). Anal. Calcd. for $C_5H_4BF_2NO_2$: C, 37.79; H, 2.54; N, 8.81. Found: C, 37.92; H, 2.34; N, 8.67%.

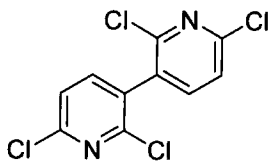
2,6-Dichloro-3-pyridylboronic acid (230)



To a solution of diisopropylamine (5.2 cm^3, 37.2 mmol) in anhydrous THF (50 cm^3) at 0 °C, *n*-BuLi (2.5 M in hexane, 15.2 cm^3, 38.0 mol) was added dropwise. The reaction was stirred for 0.5 h at 0 °C and was then cooled to -78 °C before 2,6-dichloropyridine (**229**) (5.0 g, 33.8 mmol) in anhydrous THF (25 cm^3) was added dropwise. The reaction was stirred for 3 h at -78 °C then triisopropylborate (9.3 cm^3, 40.5 mmol) was added slowly. The reaction mixture was stirred at -78 °C for another 1 h, then quenched with water (50 cm^3) and allowed to warm to room temperature with stirring overnight. The organic solvent was evaporated *in vacuo* and then filtered. The filtrate was washed with diethyl ether (3 x 50 cm^3) to remove

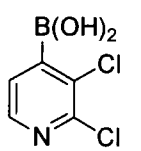
unreacted starting material. The aqueous layer was then acidified to pH 6 (with 48% HBr) to precipitate **230** as white solid (4.7 g, 73%), mp 155.2-156.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (1H, d, J =8.0 Hz), 7.48 (1H, d, J =8.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.50, 149.12, 146.25, 122.80. Anal. Calcd. for $C_5H_4BCl_2NO_2$: C, 31.31; H, 2.10; N, 7.30. Found: C, 31.11; H, 2.05; N, 7.40%. Recrystallisation of the product from toluene increased the melting point to 275.1-276.3 °C. This is assumed to be due to the formation of the anhydride although ^{1}H NMR was inconclusive.

2,6-dichloro-3-(2,6-dichloropyridin-3-yl)pyridine (231)



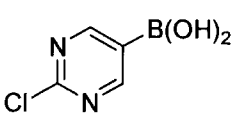
231 cocrystallised with **230** from a reaction that had been carried out to obtain 70 g of product.

2,3-Dichloro-4-pyridylboronic acid (238)



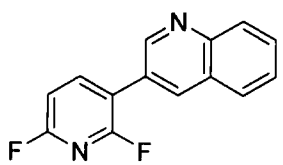
To a solution of diisopropylamine (5.2 cm^3, 37.2 mmol) in anhydrous THF (50 cm^3) at 0 °C, *n*-BuLi (2.5 M in hexane, 15.2 cm^3, 38.0 mmol) was added dropwise. The reaction was stirred for 0.5 h at 0 °C and was then cooled to -78 °C before 2,3-dichloropyridine (**237**) (5.0 g, 33.8 mmol) in anhydrous THF (25 cm^3) was added dropwise. The reaction was stirred for 3 h at -78 °C then triisopropylborate (9.3 cm^3, 40.5 mmol) was added slowly. The reaction mixture was stirred at -78 °C for another 1 h, then quenched with water (50 cm^3) and allowed to warm to room temperature with stirring overnight. The organic solvent was evaporated *in vacuo* and then filtered. The filtrate was washed with diethyl ether (3 x 25 cm^3) to remove unreacted starting material. The aqueous layer was then acidified to pH 6 (with 48% HBr) to precipitate **238** as white solid (3.6 g, 56%), mp 140.2-141.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (1H, d, J = 4.4 Hz), 7.41 (1H, d, J = 4.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.36, 146.86, 130.94, 126.80. MS (EI) *m/z* 190.8 (M^+, 100%). Anal. Calcd. for $C_5H_4BCl_2NO_2$: C, 31.31; H, 2.10; N, 7.30. Found: C, 30.71; H, 1.94; N, 6.90%.

2-Chloro-5-pyrimidylboronic acid (244)



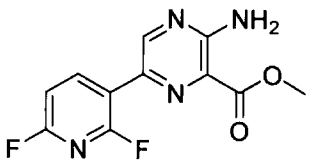
To a solution of 5-bromo-2-chloropyrimidine (**243**) (2.5 g, 13.0 mmol) and triisopropylborate (4.2 cm^3, 18.2 mmol) in anhydrous THF (20 cm^3) and toluene (5 cm^3) at –78 °C, *n*-BuLi (2.5 M in hexane, 6.2 cm^3, 15.6 mmol) was added dropwise. The reaction was stirred for 4 h at –78 °C then the reaction mixture was then quenched with water (40 cm^3) and allowed to warm to room temperature with stirring overnight. The organic solvent was evaporated *in vacuo* and the remaining aqueous layer was washed with diethyl ether (3 x 10 cm^3) to remove unreacted starting material. The aqueous layer was then acidified to pH 5 (with 48% HBr) to precipitate **244** as white solid (1.75 g, 85 %), mp. 200 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.33, 161.77. MS (EI) *m/z* 157.8 (M^+, 100%). Anal. Calcd. for $C_4H_4BClN_2O_2$: C, 30.34; H, 2.55; N, 17.69. Found: C, 30.62; H, 1.94; N, 17.10%.

3-(2,6-Difluoropyridin-3-yl)quinoline (226)



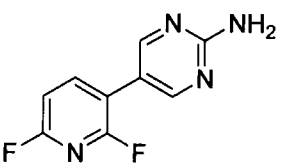
Boronic acid **225** (270 mg, 1.7 mmol), 3-bromoquinoline (**147**) (312 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent DCM:EtOAc (1:1 v/v) gave **226** as a white solid (303 mg, 84%) mp 155.5-156.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (1H, t, J = 2.0 Hz), 8.61 (1H, s), 8.54 (1H, q, J = 10.0 Hz, J = 8.0 Hz), 8.06 (2H, t, J = 8.0 Hz), 7.82 (1H, t, J = 8.0 Hz), 7.67 (1H, t, J = 8.0 Hz), 7.38 (1H, dd, J = 8.0 Hz, J = 2.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.13 (dd, J = 244 Hz, J = 14.5 Hz), 157.37 (dd, J = 244 Hz, J = 14.5 Hz), 150.04 (d, J = 8.0 Hz), 147.04 (d, J = 8.0 Hz), 146.95 (d, J = 6.2 Hz), 135.82 (d, J = 3.4 Hz),130.40, 128.72, 128.48, 127.33, 127.13, 125.63 (d, J = 4.9 Hz), 117.31 (dd, J = 25.6 Hz, J = 5.4 Hz), 107.58 (dd, J = 34.3 Hz, J = 5.7 Hz); MS (EI) *m/z* 242.1 (M^+, 100%). Anal. Calcd. for $C_{14}H_8F_2N_2$: C, 69.19; H, 3.22; N, 11.57. Found: C, 69.19; H, 3.22; N, 11.35%.

Methyl 3-amino-6-(2,6-difluoropyridin3-yl)pyrazine-2-carboxylate (227)



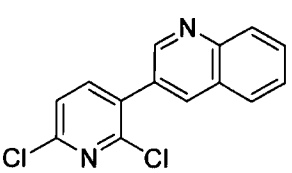
Boronic acid **225** (270 mg, 1.7 mmol), methyl 3-amino-6-bromopyrazine-2-carboxylate (**110a**) (348 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 15 min; eluent EtOAc gave **227** as a yellow powder (327 mg, 82%) mp 201.8-202.3 °C (from toluene); ^1H NMR (400 MHz, DMSO-d_6) δ 8.68 (1H, d, J = 2.4 Hz), 8.52 (1H, q, J = 8.0 Hz), 7.63 (2H, br s, NH_2), 7.32 (1H, dd, J = 8.0 Hz, J = 2.4 Hz), 3.88 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.01, 154.72, 147.36, 147.26, 145.53, 133.33, 122.79, 107.63, 107.31, 107.23, 52.29; MS (ES+) *m/z* 267.0 (M^+, 100%). Anal. Calcd. for $C_{11}H_8F_2N_4O_2$: C, 49.63; H, 3.03; N, 21.05. Found: C, 49.46; H, 2.76; N, 20.95%.

5-(2,6-Difluoropyridin-3-yl)pyrimidin-2-amine (228)



Boronic acid **225** (270 mg, 1.7 mmol), 2-amino-5-bromopyrimidine (**148**) (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc gave **228** as a white solid (215 mg, 69%) mp 221.1-222.0 °C (from toluene); ^1H NMR (400 MHz, acetone-d_6) δ 8.51 (2H, d, J = 1.6 Hz), 8.28 (1H, dt, J = 8.0 Hz, J = 1.6 Hz), 7.18 (1H, dd, J = 8.0 Hz, J = 2.8 Hz), 6.33 (2H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 164.20, 160.90 (dd, J = 194.5 Hz, J = 11.1 Hz), 158.38 (dd, J = 194.5 Hz, J = 11.1 Hz), 158.34 (d, J = 2.6 Hz), 145.55 (dd, J = 6.4 Hz, J = 3.8 Hz); MS (ES+) *m/z* 208.2 (M^+, 100%). Anal. Calcd. for $C_9H_6F_2N_4$: C, 51.93; H, 2.91; N, 26.91. Found: C, 52.06; H, 3.03; N, 27.01%.

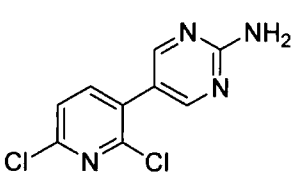
3-(2,6-Dichloropyridin-3-yl)quinoline (232)



Boronic acid **230** (326 mg, 1.7 mmol), 3-bromoquinoline (**147**) (312 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), tri-t-butylphosphine (30 mg, 0.15 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent DCM:EtOAc (1:1 v/v) gave **232** as a white solid (235 mg, 57%) mp 162.2-163.0 °C (from toluene); ^1H

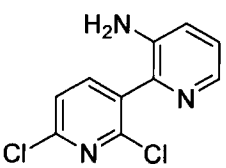
NMR (400 MHz, acetone-d_6) δ 9.03 (1H, d, J = 2.0 Hz), 8.48 (1H, d, J = 2.0 Hz), 8.13 (1H, s), 8.11 (1H, s), 8.05 (1H, d, J = 8.0 Hz), 7.84 (1H, t, J = 8.0 Hz), 7.68 (2H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.39, 148.53, 147.75, 146.93, 143.82, 136.51, 132.60, 130.53, 129.06, 128.75, 128.49, 127.36, 126.92, 124.09; MS (EI) *m/z* 274.0 (M^+, 100%). Anal. Calcd. for $C_{14}H_8Cl_2N_2$: C, 61.12; H, 2.93; N, 10.18. Found: C, 60.79; H, 2.92; N, 10.09%.

5-(2,6-Dichloropyridin-3-yl)pyrimidin-2-amine (233)

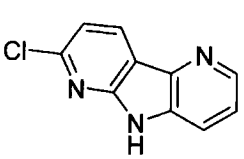


Boronic acid **230** (326 mg, 1.7 mmol), 2-amino-5-bromopyrimidine (**148**) (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), tri-t-butylphosphine (30 mg, 0.15 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc gave **233** as a pale yellow solid (166 mg, 46%) mp 245.2-245.9 °C (from toluene); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (2H, s), 7.99 (1H, d, J = 8.0 Hz), 7.65 (1H, d, J = 8.0 Hz), 7.00 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.04, 158.09, 147.56, 147.48, 142.80, 130.89, 123.98, 118.01; MS (ES+) *m/z* 240.0 (M^+, 100%). Anal. Calcd. for $C_9H_6Cl_2N_4$: C, 44.84; H, 2.51; N, 23.24. Found: C, 44.76; H, 2.52; N, 22.88%.

2-(2,6-Dichloropyridin-3-yl)pyridin-3-amine (235)



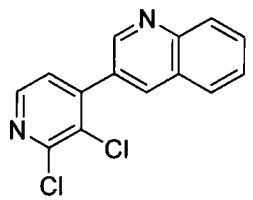
Boronic acid **230** (326 mg, 1.7 mmol), 2-chloro-3-aminopyridine (**159**) (193 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), tri-t-butylphosphine (30 mg, 0.15 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc gave **235** as a white solid (ca 54 mg, ca 15%); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.90 (2H, m), 7.67 (1H, m), 7.14 (1H, m), 5.23 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.8, 143.6, 138.8, 138.3, 129.5, 125.0, 124.5, 124.3, 122.7, 122.2.



followed by **236** as a white solid (98 mg, 32%) mp dec 310 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.2 (1H, s), 8.58 (1H, dd, J = 8.8 Hz, J = 0.8 Hz), 7.93 (1H, dd, J = 8.0 Hz, J = 1.6 Hz), 7.49 (1H, dd, J =

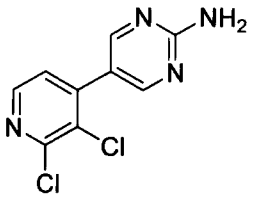
8.0 Hz, J = 4.8 Hz), 7.35 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.92, 148.91, 143.56, 139.18, 133.31, 132.30, 122.27, 119.77, 116.35, 113.99; MS (ES+) *m/z* 204.1 (M^+, 100%). HRMS Calcd for $C_{11}H_6ClN_3$: 203.62774 (M^+), found: 203.62780.

3-(2,3-Dichloropyridin-4-yl)quinoline (240)



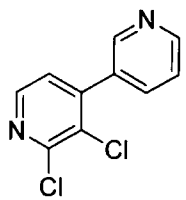
Boronic acid **237** (326 mg, 1.7 mmol), 3-bromoquinoline (**147**) (312 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), tri-t-butylphosphine (30 mg, 0.15 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent DCM:EtOAc (3:7 v/v) gave **240** as a white solid (236 mg, 57%) mp 162.2-163.0 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.03 (1H, d, J = 2.0 Hz), 8.60 (1H, d, J = 2.0 Hz), 8.52 (1H, d, J = 4.8 Hz), 8.10 (2H, t, J = 8.0 Hz), 7.87 (1H, t, J = 8.0 Hz), 7.71 (2H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.76, 149.04, 147.71, 147.69, 147.18, 136.46, 130.86, 129.39, 128.78, 128.67, 128.04, 127.48, 126.77, 125.85; MS (EI) *m/z* 274.0 (M^+, 100%). Anal. Calcd. for $C_{14}H_8Cl_2N_2$: C, 61.12; H, 2.93; N, 10.18. Found: C, 60.94; H, 2.75; N, 9.89%.

5-(2,3-Dichloropyridin-4-yl)pyrimidin-2-amine (241)



Boronic acid **237** (326 mg, 1.7 mmol), 2-amino-5-bromopyrimidine (**148**) (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), tri-t-butylphosphine (30 mg, 0.15 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc gave **241** as a yellow solid (151 mg, 42%) mp 197.5-198.9 °C (from toluene); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.49 (2H, s), 8.38 (1H, d, J = 4.8 Hz), 7.49 (1H, d, J = 4.8 Hz), 6.46 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.28, 158.11, 149.02, 147.50, 145.91, 127.323, 124.67, 118.35; MS (ES+) *m/z* 240.0 (M^+, 100%). Anal. Calcd. for $C_9H_6Cl_2N_4$: C, 44.84; H, 2.51; N, 23.24. Found: C, 44.76; H, 2.52; N, 22.68%.

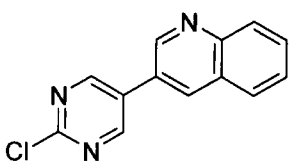
3-(2,3-Dichloropyridin-4-yl)pyridine (242)



Boronic acid **237** (326 mg, 1.7 mmol), 3-bromopyridine (**1**) (237 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), tri-t-butylphosphine (30 mg, 0.15 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc gave **242** as a off white solid (138 mg, 41%) mp 192.2-193.0 °C (from hexane); ^1H NMR (500 MHz, acetone-d_6) δ 8.72 (1H, s), 8.69 (1H, d, J = 5.0 Hz), 8.48 (1H, d, J = 5.0 Hz), 7.99 (1H, d, J = 8.0 Hz), 7.57 (2H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.16, 148.98, 147.64, 147.61, 136.61, 132.14, 127.88, 125.53, 123.44; MS (EI) *m/z* 224.0 (M^+, 100%). Anal. Calcd. for $C_{10}H_6Cl_2N_2$: C, 53.36; H, 2.69; N, 12.45. Found: C, 53.72; H, 2.92; N, 12.09%.

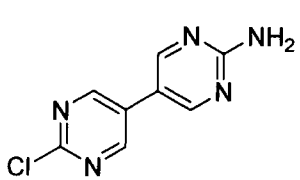
When the reaction was repeated using 3-iodopyridine (**239**) (169 mg, 50%), **242** was obtained.

3-(2-Chloropyrimidin-5-yl)quinoline (245)



Boronic acid **244** (269 mg, 1.7 mmol), 3-bromoquinoline (**147**) (312 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc gave **245** as a white solid (170 mg, 47%) mp 214.3-215.2 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.34 (3H, s), 8.86 (1H, d, J = 2.0 Hz), 8.07 (2H, dd, J = 8.4 Hz), 7.84 (1H, t, J = 8.4 Hz), 7.69 (1H, t, J = 8.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.47, 158.51, 148.85, 147.37, 134.22, 130.58, 129.87, 128.82, 128.55, 127.51, 127.25, 125.73; MS (EI) *m/z* 240.9 (M^+, 100%). Anal. Calcd. for $C_{13}H_8ClN_3$: C, 64.61; H, 3.34; N, 17.39. Found: C, 64.36; H, 3.36; N, 17.10%.

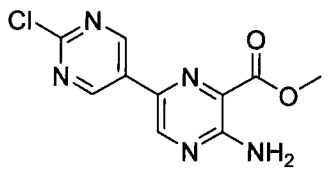
5-(2-chloropyrimidin-5-yl)pyrimidin-2-amine (246)



Boronic acid **244** (269 mg, 1.7 mmol), 2-amino-5-bromopyrimidine (**148**) (261 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), tri-t-butylphosphine (30 mg, 0.15 mmol), 1,4-

dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc gave **246** as a white solid (140 mg, 45%) mp 196.8-197.2 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.12 (2H, s), 8.75 (2H, s), 7.10 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.5, 158.3, 156.4, 156.3, 128.3, 114.8; MS (EI) *m/z* 207.03 (M^+, 100%). Anal. Calcd. for $C_{13}H_8ClN_5$: C, 46.28; H, 2.91; N, 33.73. Found: C, 46.02; H, 2.99; N, 33.29%.

Methyl 3-amino-6-(2-chloropyrimidin-5-yl)pyrazine-2-carboxylate (247)



Boronic acid **244** (269 mg, 1.7 mmol), methyl 3-amino-6-bromopyrazine-2-carboxylate (**110a**) (348 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), tri-t-butylphosphine (30 mg, 0.15 mmol), 1,4-dioxane (10 cm^3) and Na_2CO_3 (1 M, 4 cm^3); reaction time 24 h; eluent EtOAc gave **247** as a yellow solid (191 mg, 48%) dec 230 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.21 (2H, s), 8.96 (1H, s), 7.65 (2H, s), 3.85 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 159.0, 156.6, 155.3, 145.8, 128.8, 99.5; MS (EI) *m/z* 266.0 (M^+, 100%). Anal. Calcd. for $C_{10}H_8ClN_5O_2$: C, 45.21; H, 3.04; N, 26.36. Found: C, 45.68; H, 3.33; N, 26.62%.

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