Synthesis and reactions of new N-heteroaryl boronic acids

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SYNTHESIS AND REACTIONS OF NEW *N*-HETEROARYL BORONIC ACIDS

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A thesis submitted for the degree of Doctor of Philosophy at the University of Durham.

October 2008

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DECLARATION

The work described in this thesis was carried out in the Department of Chemistry at the University of Durham between October 2005 and September 2008. All the work was carried out by the author unless otherwise stated and has not been previously submitted for a degree at this or any other university.

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Chapter 1 – Introduction

ABSTRACT

Synthesis and Reactions of New *N*-Heteroaryl Boronic Acids

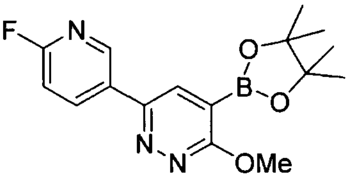
Kate M. Clapham, University of Durham, October 2008

New functionalized pyridazinylboronic acids/esters are reported. A comprehensive study of the reactivity of the C–B bond in palladium-catalyzed cross-couplings with aryl/heteroaryl halides is presented. Aryl/heteroaryl-pyridazines have thereby been obtained in synthetically viable yields (typically 40-75%).

A series of pyridazin-3(2*H*)-one derivatives have been obtained from the corresponding 3-methoxypyridazines in straightforward procedures. Further functionalization of the pyridazin-3(2*H*)-one derivatives through C–C and C–N cross-coupling reactions yielded a number of multiheteroaryl arrays.

The synthesis of trifluoromethyl-substituted pyridylboronic acids and pyrazolylboronic esters is described. An extensive study of their palladium-catalyzed cross-couplings with aryl/heteroaryl halides is presented. CF_3-substituted aryl/heteroaryl-pyridines have thereby been obtained (51-98% yields). Analogous cross-couplings have yielded heteroaryl-3-(trifluoromethyl)pyrazoles (60-85% yields). Regioselective halogenation of the 4-position of selected trifluoromethylated pyrazole derivatives was successful. Subsequent Suzuki-Miyaura cross-couplings yielded tetra-substituted pyrazolyl derivatives.

X-Ray crystal structures are reported for several aryl/heteroaryl-pyridazines and derived pyridazin-3(2*H*)-one derivatives, and selected pyridylboronic acids, pyrazolylboronic esters and derived trifluoromethyl-substituted heterobiaryl systems.



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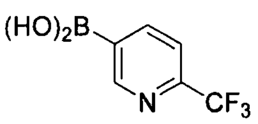

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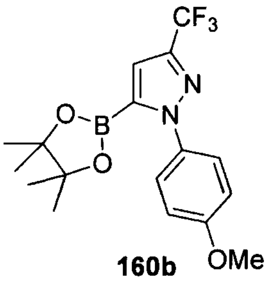

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DEDICATION

This work is dedicated to everyone who has inspired and supported me to get to where I am today.

To my loving parents, thank you so much for your continued love and support. You have made it possible for me to achieve my goals. Mum, Dad, Ella and Stuart, I am so very lucky and grateful to be part of such a close, loving family.

Chris, thank you for your endless love, patience and support.

"A scientist in his laboratory is not a mere technician: he is also a child confronting natural phenomena that impress him as though they were fairy tales."

Marie Curie

PUBLICATIONS

The following papers are based on work described in this thesis:

Clapham, K. M.; Batsanov, A. S.; Greenwood, R. D. R.; Bryce, M. R.; Smith, A. E.; Tarbit, B. **Functionalized Heteroarylpyridazines and Pyridazin-3(2*H*)-one Derivatives via Palladium-Catalyzed Cross-Coupling Methodology,** *J. Org. Chem.* **2008**, *73*, 2176.

Clapham, K. M.; Andrei S. Batsanov, Martin R. Bryce and Brian Tarbit. **(Trifluoromethyl)-substituted Pyridyl- and Pyrazolylboronic Acids and Esters: Synthesis and Suzuki-Miyaura Cross-Coupling Reactions**, manuscript submitted.

The following paper is based on work described in the PhD thesis of Amy E. Smith, University of Durham, 2005 and work described in this thesis:

Clapham, K. M.; Smith, A. E.; Batsanov, A. S.; McIntyre, L.; Pountney, A.; Bryce, M. R.; Tarbit, B. **New Pyrimidylboronic Acids and Functionalized Heteroarylpyrimidines by Suzuki Cross-Coupling Reactions,** *Eur. J. Org. Chem.* **2007**, 5712.

The following paper is based on work described in the PhD thesis of Amy E. Smith, University of Durham, 2005:

Smith, A. E.; Clapham, K. M.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. **(Dimethoxy- and dihalopyridyl)boronic Acids and Highly Functionalized Heteroarylpyridines by Suzuki Cross-Coupling Reactions,** *Eur. J. Org. Chem.* **2008**, 1458.

ABBREVIATIONS

acac	Acetonylacetate
AcOH	Acetic acid
Ar	Aryl
binap	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
B_2pin_2	Bis(pinacolato)diboron
bpy	2,2'-Bipyridine
Boc	*tert*-Butyloxycarbonyl
BuLi	Butyl lithium
Bu	Butyl
CIPE	Complex-induced proximity effect
CF_3	Trifluoromethyl
COD	1,5-Cyclooctadiene
COSY	Correlation spectroscopy
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	*ortho*-Dichlorobenzene
DCM	Dichloromethane
DFT	Density functional theory
DME	Dimethyl ether
DMF	Dimethylformamide
DMG	Directed metalation group
DMPY	Bis(3,5-dimethylpyrazol-1-yl)
DMSO	Dimethylsulfoxide
D*o*M	Directed *ortho* metalation
DPEphos	Bis(2-diphenylphosphinophenyl)ether
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	Diphenyl-1-pyrenylphosphine
D-*t*-BPF	Di-*tert*-butylphosphinoferrocene
dtbpy	4,4'-Di-*tert*-butyl-2.2'-bipyridine

HBMP	Methylpentanediol borane
HBpin	Pinacol borane
Het	Heteroaryl
HMBC	Heteronuclear multiple bond correlation
HSQC	Heteronuclear single quantum correlation
Hx	Hexyl
Hz	Hertz
Ind	Indenyl
LDA	Lithium diisopropylamide
LTMP	Lithium 2,2,6'6'-tetramethylpiperidide
LUMO	Lowest unoccupied molecular orbital
Me	Methyl
MeCN	Acetonitrile
MS	Mass spectrometry
NCS	*N*-Chlorosuccinimide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
OTf	Triflate
pin	Pinacol
PhCN	Benzonitrile
py	Pyridine
RT	Room temperature
S_E	Electrophilic substitution
SEM	[2-(Trimethylsilyl)ethoxy]-methyl
SDS	Sodium dodecyl sulphate
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer Chromatography
UV	Ultra violet

CHAPTER 1 – INTRODUCTION

1.1 Boronic Acids

In modern organic chemistry boronic acids and esters are widespread; the versatility of the C–B bond allows the transformation of organoboron species into new synthetic compounds through functional group conversion[1-4] and carbon-carbon bond forming reactions.[5, 6] In addition they have received considerable attention in macrocyclic chemistry,[7, 8] supramolecular chemistry,[9-12] materials chemistry,[13, 14] organic chemistry[15-19] and as sensors for saccharides[20, 21] due to their intrinsic affinity for the diol functional group. The potent biological activity of organoboron compounds has been shown in several areas, for example artificial lectins (boronolectins),[22] antibiotics,[23] enzyme inhibitors, specifically protease inhibitors[24] and boron neutron capture therapy (BNCT).[25]

Functionalized biaryl and biheteroaryl templates have contemporary pharmaceutical, agrochemical, materials and supramolecular applications. Boronic acids have become valued reagents for modern organic synthesis, largely since the 1979 paper by Miyaura, Yamada and Suzuki,[26] which established the foundations for a very important transformation in the construction of carbon-carbon bonds. Since the discovery of what is now known as the Suzuki-Miyaura reaction the synthesis of novel boron containing reagents and improvements to the parameters have been widely studied. It is essential that new heteroaryl boronic acids are developed; these systems should show widespread reactivity in cross-coupling with a range of halogenated partners, yielding new building blocks of importance for industrial applications.

In this chapter literature methods for the synthesis of arylboronic acids and boronic esters are described, with *N*-heteroarylboronic acids as the main focus. Reactions of boronic acids are reviewed, specifically the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction.

The following chapters detail the syntheses of functionalized pyridazinylboronic acids and esters, and new (trifluoromethyl)-substituted pyridyl- and pyrazolylboronic acids and esters. The importance of pyridazine derivatives and (trifluoromethyl)-substituted heteroarenes and their current syntheses are briefly presented. Furthermore, the preparation and further development of pyridazin-3(2*H*)-one derivatives is described in Chapter 3. The Suzuki-Miyaura reactions of each novel class of boronic acid or ester, with various (hetero)aryl cross-coupling partners, is explored in each chapter.

1.1.1 Structure and Properties of Boronic Acids

Boronic acids are trivalent boron-containing species; the boron has six valence electrons, resulting in a vacant p orbital orthogonal to the three substituents. The mild Lewis acidic nature of boronic acids is a consequence of the valency.

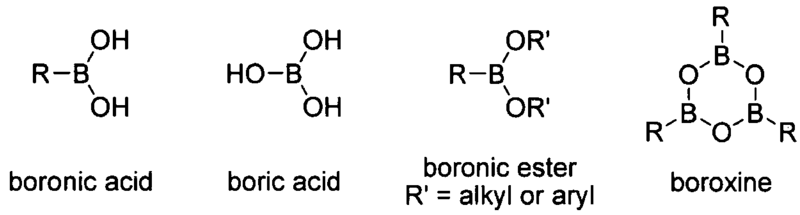
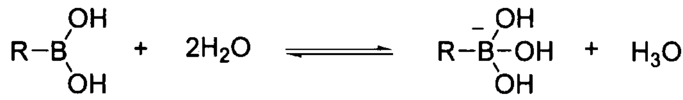


Figure 1.1 Organoboron compounds.

The acidic character of boronic acids in water yields the tetrahedral hydroxyboronate anion (Scheme 1.1), hence, the most acidic boronic acids possess the most electrophilic boron atom that can best form and stabilise the hydroxyboronate anion.



Scheme 1.1 Ionization equilibrium of boronic acids in water.

Most boronic acids are solids which are chemically stable, can be handled in air and show shelf-stability for long periods. They tend to exist as a mixture of the free-acid and oligomeric anhydrides, in particular the cyclic six-membered boroxines, as a result of dehydration of the boronic acid during preparation. Anhydride formation may complicate analysis and spectroscopic characterisation, however, most reactions of boronic acids, including the Suzuki-Miyaura cross-coupling, proceed regardless of the hydrated state.[27] X-ray crystal structures have been reported of aryl[28, 29] and heteroarylboronic acids[30-32] which confirm the almost planar trigonal conformation. Dimeric units bound through a pair of O–H...O hydrogen bonds is a common motif in the crystal structures. Boroxine structures characterized by X-ray analysis[33] are almost planar. Boroxines may possess partial aromaticity due to π orbital overlap of the oxygen lone pair into the vacant boron orbital.

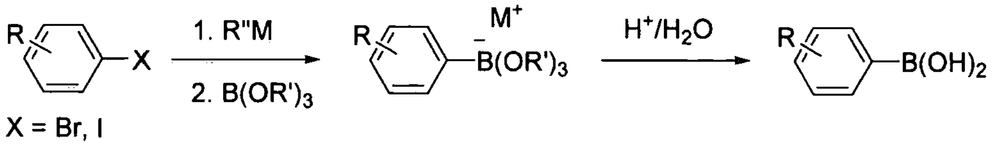
One reason for the stability of boronic acids and their esters is that ligand exchange (the exchange of the hydroxyl substitutents for other ligands) and disproportionation (to the corresponding trialkylborane and borinic or boric acid) are both thermodynamically unfavourable. For example, dehydration techniques are required to drive forward the substitution with alcohols or diols to form boronic esters. Arylboronic acids can readily deboronate by protolysis of the C–B bond in highly acidic or basic aqueous solutions; notably *ortho*-substituted or electron-poor arylboronic acids deboronate under basic conditions.[34] Consequently, competitive protodeboronation can affect the Suzuki-Miyaura reaction which is often carried out under basic aqueous conditions. Hydrolytic protodeboronation of boronic species will be discussed further in section 1.3.3.

1.1.2 Synthesis of Aryl Boronic Acids

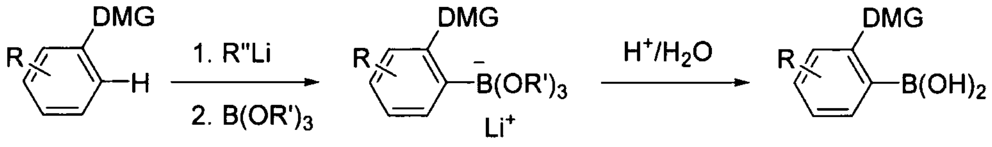
Figure 1.2 outlines three common methods for the synthesis of aryl/heteroaryl boronic acids. One of the earliest methods was the transmetalation of aryl silanes or stannanes with a hard boron halide (BBr_3) (Figure 1.2, scheme c). The thermodynamic drive for this reaction is the higher stability of B–C and Si/Sn–Br bonds compared to the respective bonds in the substrates. Simple arylboronic acids are isolated following hydrolysis of the arylboron dibromide product.[35] Benzene and pyridyldiboronic acids have been prepared through the transmetalation of organotin compounds with borane and subsequent hydrolysis.[36]

The classical synthesis of arylboronic acids is the reaction of an organometallic reagent with a trialkyl borate electrophile.[37] The intermediate is hydrolyzed by the addition of an aqueous acid to yield the corresponding boronic acid (Figure 1.2, schemes a and b). This is, probably, the cheapest and most common way for preparing arylboronic acids, especially on a large scale. On using small trialkyl borates, such as trimethyl borate, products resulting from multiple addition (i.e. borinic acid and borane) were isolated. With triisopropylborate this is not the case and the clean formation of lithium alkoxyboronate salts has been observed by NMR spectroscopy, resulting in good yields of the arylboronic acids upon acidic quench.[38, 39]

a. Electrophilic borate trapping of an arylmetal intermediate from aryl halides



b. Electrophilic borate trapping of an aryllithium intermediate from directed *ortho*-metalation



c. Transmetalation of arylsilanes and arylstannanes

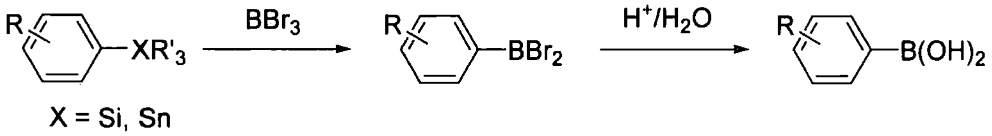
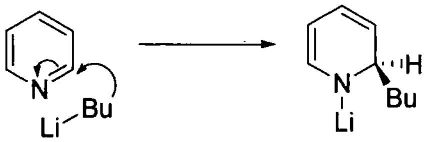


Figure 1.2 Common methods for the synthesis of arylboronic acids.

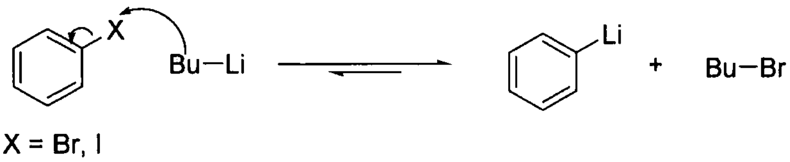
Organomagnesium or organolithium reagents are typically used in arylboronic acid syntheses as the source of nucleophilic carbon.[40] Grignard formation can be conducted at ambient temperature, however, these reagents do not tolerate polar functional groups (e.g. C=O, C≡N, NO_2, COOR). Organolithium formation often requires low temperatures. A wider variety of functional groups are tolerated for organolithium intermediates; problems generally arise as a result of acidic protons being present. Organolithium reagents for boronic acid synthesis, can be generated by lithium-halogen exchange, lithium-hydrogen exchange, or directed *ortho* metalation (D*o*M). Although this section encompasses arene metalation, special consideration will be given to the lithiation of *N*-heteroarenes, specifically pyridines. Excellent reviews have been written on the subject of lithiation of pyridines and related heterocycles.[41-44]

Lithium-hydrogen exchange (or direct lithiation) uses an organolithium reagent which abstracts a proton from the aromatic system; the site of deprotonation depends upon the acidity of the hydrogen to be removed and the stability of the anion formed. Direct lithiation of pyridines often shows complications not usually seen with benzene analogues. Benzene compounds, with pKa of ca. 38-40, can be metalated with a strong base such as *n*-, *sec*- or *tert*-butyllithium, pKa ~ 45. Alkyllithiums add to pyridines very quickly, even at low temperatures, due nucleophilic attack at C-2 (Scheme 1.2).



Scheme 1.2 Nucleophilic attack of butyllithium on pyridine.

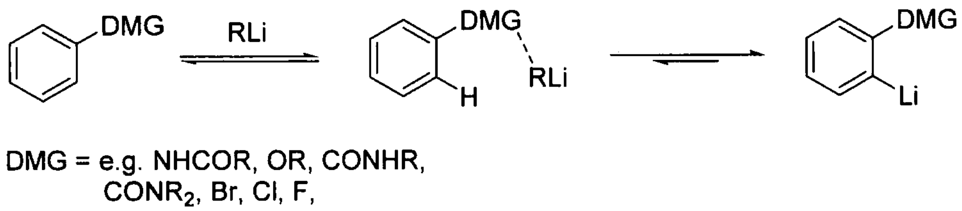
The pyridine ring is more sensitive to deprotonation at the C-2, -4 and -6 positions than benzene. The kinetically favoured α-deprotonation of pyridine is possible due to the directing ability of the pyridyl nitrogen. There is presumably some complexation of the lithium base prior to deprotonation. The resulting C-2 anion can migrate to the thermodynamically more stable C-4 position as a result of repulsion by the lone pair on the pyridine N. Efficient α-lithiation of pyridine occurs when the complex base BuLi·LiO$(CH_2)_2NMe_2$ (BuLi·LiDMAE) is used; trapping with electrophiles leads to 2-substituted pyridines in good to excellent yields.[45] Hindered lithium amide bases show a much greater selectivity for proton abstraction vs. nucleophilic addition (shown in Scheme 1.2), as they are less nucleophilic and weaker bases; LDA pKa 35.7, LTMP pKa 37.3. Thermodynamically favoured deprotonation at C-4 of pyridine generally occurs with lithium amides.[42] Lithium-halogen exchange involves the nucleophilic attack of an alkyllithium, usually *n*-BuLi, on an aryl halide (Scheme 1.3).[46] The equilibrium favours the aryllithium which is less basic than the butyllithium.



Scheme 1.3 Lithium-halogen exchange.

With lithium-halogen exchange, selectivity is usually only an issue when more than one halide is present. Alkyllithiums undergo metal-halogen exchange in preference to deprotonation or nucleophilic attack of halopyridines. Regioselective lithium-halogen exchange of substituted dibromobenzenes is influenced by the electronegative substituent adjacent to bromine (e.g. OMe, F, CF_3), with reaction occurring preferentially at the activated bromine.[47] However, when the non-activated bromine is replaced with iodine, lithiation occurs at this position and not the activated bromine. Halopyridines yield lithiumpyridyls via lithium-halogen exchange, resulting in regioselective lithiation in good yields. Metal-halogen exchange reactions are highly exothermic; low temperatures, between –40 °C and –100 °C and slow addition of *n*-BuLi are required to suppress any side reactions[48, 49] (competitive deprotonation of the acidic halopyridines in THF), and to reduce decomposition of unstable organolithium intermediates. THF is the solvent often used for lithiations since it is coordinating and dissociates any butyl lithium aggregates.[50] Temperatures below 0 °C are required to prevent deprotonation of THF by BuLi; the resulting intermediate is unstable towards reverse [2+3] cycloaddition. Selective lithiation of dihalopyridines can be achieved by selecting the appropriate reaction conditions.[48, 51] For example, monolithiation of 2,5-dibromopyridine favours C-5 with coordinating solvents (Et_2O, THF) and higher concentrations, while non-coordinating solvents (toluene) and lower concentration favour C-2 lithiation.[51] Although lithium-halogen exchange is a versatile method for the rapid, selective lithiation of heteroarenes, drawbacks are the availability and greater expense of halo-substituted heteroaryls.

Directed *ortho* metalation (D*o*M) is an important protocol for selective deprotonation and the Snieckus group has been the forerunner in developing this strategy.[52-54] Snieckus defined directed *ortho* metalation as "deprotonation of a site *ortho* to a heteroatom containing directed metalation group (DMG) by a strong base, leading to an *ortho*-lithiated species" (Scheme 1.4).[55] D*o*M is useful since the starting material does not require a halogen atom. The number of DMGs available is considerable: amides, carbamates, sulfonates are all very good DMGs, while amines, alkoxy, trifluoromethyl, chloro and fluoro groups are also good DMGs.[55] D*o*M usually employs a powerful alkyllithium, for example when DMG = NHCOR, OR, CONHR clean regioselective metalation can occur with alkyllithiums. However, for systems where nucleophilic addition of alkyllithiums is an issue, lithium amide bases have been successfully employed; for instance, DMGs Cl, F, $CONR_2$ can be treated with less basic lithiating agents such as LDA and LTMP for effective deprotonation.[43]



Scheme 1.4 Directed *ortho* metalation.

For successful deprotonation, the DMG must provide a good coordinating site for the lithium reagent and be a poor electrophilic site for attack by a strong base. DMGs influence *ortho* lithiation either through coordination to the lithium reagent or through an inductive effect making the *ortho* hydrogens more acidic.[55] There is evidence that inductive factors dominate in the *ortho* deprotonation step for Br, F and CF_3 groups.[56] In contrast, OMe and NMe_2 groups show enhanced reactivity rates, greater than those expected based solely on inductive effects. Consequently, a coordination component in the deprotonation step has been invoked. For azine and diazine rings, kinetic and thermodynamic factors can rationalize the regioselective D*o*M effects (Figure 1.3). When metal amides are used the regioselectivity is a result of the stabilization by chelation of the metal with the DMG (a), the electron-withdrawing effect of the DMG (b), and destabilization by electronic repulsion between the carbanion and the lone pair on the nitrogen (c). When alkyllithiums are used as the base at low temperature, the reaction mainly proceeds under kinetic control. The course of the reaction is directed by the acid-base (inductive) mechanism (d) and chelation in the transition state (e). Coordination of the DMG to the Lewis acidic metal allows disaggregation of the metalating agent, reinforcing the electron-withdrawing effect of the DMG and increasing the proximity effect of the complexed base.[42, 43]

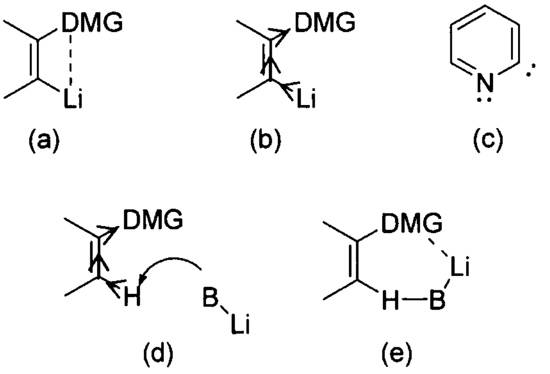


Figure 1.3 D*o*M effects under thermodynamic control (a), (b), (c) and kinetic control (d), (e).[43]

Proposing a mechanism for D*o*M is not always straightforward. For example, Fort *et al.* found that C-3 lithiation of 2-chloro- and 2-methoxypyridine with LDA was not a simple process. They proposed that precomplexation of lithium dialkylamides near the C-6 proton was involved in the formation of a 3,6-dilithiopyridine intermediate.[57, 58] Thinking beyond thermodynamic acidity, the concept of complex-induced proximity effect (CIPE) in deprotonations suggests the formation of a pre-lithiation complex, which brings reactive groups into proximity for directed deprotonation.[59] D*o*M of a compound bearing two potential DMGs can use a CIPE to alter the inductive and association effects and thus the regioselectivity of lithiation. However, it is still unclear whether deprotonative lithiation is a result of CIPE or "kinetically enhanced metalation".[59] The main distinction between the two postulations is the transition-state structure for proton transfer. For CIPE, the reaction proceeds via a complex intermediate, whereas for "kinetically enhanced metalation" this is not the case. Instead proton transfer is the only required step between the reactant and the lithiated product, and is hence the rate-determining step. Therefore, CIPE is a useful concept; however, the detailed mechanism must be investigated on a case by case basis.

Directed *ortho* metalation combined with cross-coupling methodologies presents an efficient nexus for regioselective preparation of (hetero)biaryls.[60] Recently, the D*o*M/boronation of substituted pyridines, and subsequent Suzuki-Miyaura cross-coupling has been combined in a one-pot procedure (see Section 1.2.1).[61]

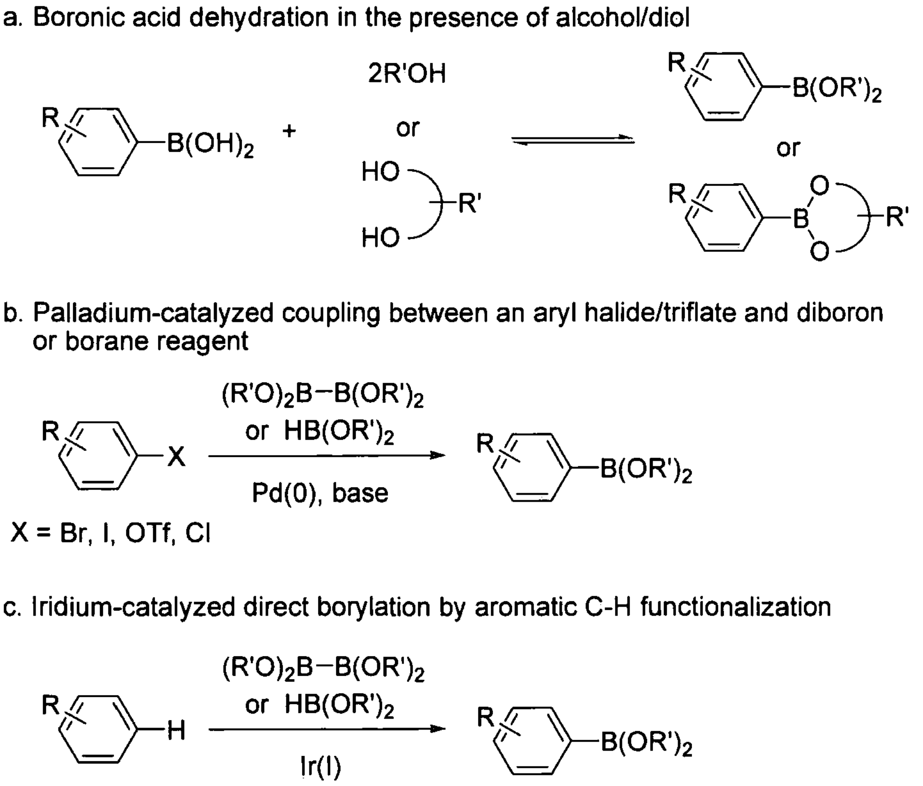
Metalation–boronation techniques are now common for large-scale preparations of (hetero)arylboronic acids. The relatively cheap reagents and wide availability of halo- and DMG-substituted (hetero)arenes make these routes industrially viable.

1.1.3 Synthesis of Aryl Boronic Esters

Boronic esters are often preferred as synthetic intermediates due to their increased ease of handling, characterization and stability compared with their boronic acid derivative.[5, 62] Figure 1.4 shows the main procedures for the preparation of aryl- and heteroarylboronic esters.

The synthesis of boronic esters from boronic acids and alcohols or diols is straightforward (Figure 1.4, scheme a), although it is an equilibrium reaction which requires the removal of water to drive the reaction forward. This is conducted by either using Dean-Stark apparatus[63, 64] or by addition of a dehydrating agent.[65] Cyclic, hindered boronic esters are often prepared as they hydrolyse at a slower rate compared to non-cyclic alkyl based boronic esters. Six-membered ring esters, such as 2,2-dimethyl-1,3-propanediol (neopentylglycol) or 2-methyl-2,4-pentanediol derivatives, are thermodynamically more stable than their five-membered analogues, such as 2,3-

dimethyl-2,3-butanediol (pinacol) boronic esters.[66] An alternative route to boronic esters involves the *ortho*-lithiation–*in situ* trapping of substituted arenes. Following lithiation and boronation with $B(O\textit{i}\text{-}Pr)_3$, the isopropyl boronic ester intermediate generated is reacted with a diol to yield the (hetero)arylboronic esters in high yield.[67] Non-aqueous conditions have also been applied.[68, 69] Using 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the boronating agent following lithiation and upon controlled acidification yields pinacol boronic ester derivatives.

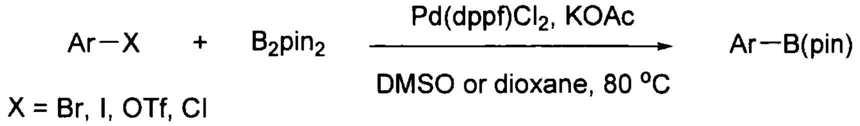

a. Boronic acid dehydration in the presence of alcohol/diol

b. Palladium-catalyzed coupling between an aryl halide/triflate and diboron or borane reagent

c. Iridium-catalyzed direct borylation by aromatic C-H functionalization

Figure 1.4 Common methods for the synthesis of arylboronic esters.

Palladium-catalyzed cross-coupling reactions of B–B, or B–H reagents with aryl, vinyl, allyl and benzyl halides or triflates (Figure 1.4, scheme b) represents a direct method for the borylation of organic electrophiles, without using lithium or magnesium intermediates.[70] Ishiyama *et al.* were the pioneers for the direct preparation of arylboronic esters. They reported the palladium-catalyzed coupling of bis(pinacolato)diboron (B_2pin_2) with bromo- and iodoarenes,[71, 72] and then extended this protocol to aryl triflates[72, 73] and chlorides (Scheme 1.5).[74]



Scheme 1.5 Pd-catalyzed coupling of an aryl electrophile with a diboron reagent.[72, 74]

The coupling reaction occurs in the presence of base and palladium catalyst. KOAc was found to be critical for the reaction to occur. This suggests there is transmetalation between the B_2pin_2 and Ar–Pd–OAc intermediate, as a result of displacement of X in Ar–Pd–X by AcO^-. The catalytic cycle is shown in Figure 1.5.[72] When stronger bases (K_3PO_4, K_2CO_3) were used competitive homocoupling yielded biaryls, reducing the yields of arylboronic esters. For bromo- and iodoarenes $Pd(dppf)Cl_2$ is a good catalyst.[71] Ligandless $Pd(OAc)_2$ is also a suitable catalyst for the coupling of B_2pin_2 with a number of substituted arylbromides.[75] Arylboronates prepared in this way have been used *in situ* for Suzuki-Miyaura cross-coupling reactions to prepare unsymmetrical biaryls.

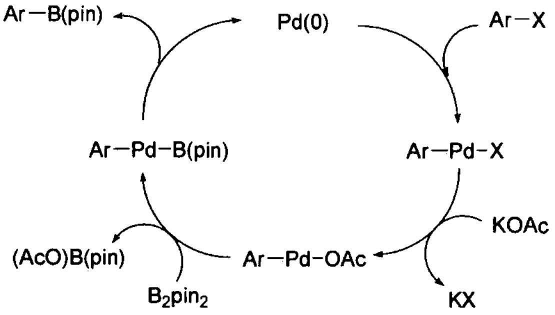
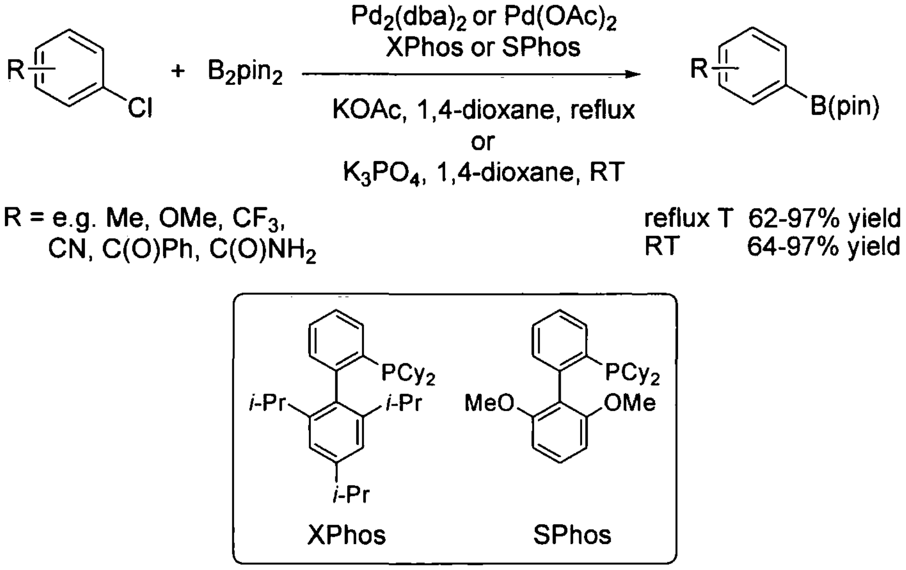


Figure 1.5 Catalytic cycle for cross-coupling of diborons.[72]

When less reactive chloroarene precursors are used $Pd(dba)_2$ and PCy_3 are required.[74] Buchwald *et al.* have demonstrated that biaryl phosphine ligands XPhos and SPhos (see Section 1.3.1) and $Pd(OAc)_2$ or $Pd_2(dba)_3$ form highly stable and efficient catalyst systems for the borylation of substituted aryl chlorides and heteroaryl chlorides with B_2pin_2.[76] At elevated temperatures, the preparation of pinacol arylboronic esters from substituted aryl chlorides (including those bearing electron-donating groups) requires much reduced reaction times of 10 min-24 h (Scheme 1.6),[76] compared to 24-48 h as previously reported.[74] The room temperature cross-coupling of B_2pin_2 and chloroarenes requires a stronger base and extended reaction time to give 64-97% isolated yields of boronic esters (Scheme 1.6).[76] In a further extention of the work pinacol boronic esters have been reacted *in situ* (without work up). After the Pd-catalyzed coupling of B_2pin_2

with aryl chlorides, a second aryl chloride was added and extra base (no additional catalyst was added to the system) to yield unsymmetrial biaryls from chloroarene precursors in yields of 62-92%. This is notable due to the lower cost and wider availability of substituted aryl chlorides, and the cost of commercially available XPhos and SPhos ligands is comparable to other phosphine based ligands.

Examples of other tetra(alkoxo)diborons used include bis(neopentyl glycolato)diboron[77] and bis(1,3-diphenylpropanediol)diboron.[78]



Scheme 1.6 Buchwald *et al.* Borylation of chloroarenes with B_2pin_2.[76]

More recently Murata *et al.* have found that pinacolborane (HBpin) couples to aryl and vinyl electrophiles in the presence of a palladium catalyst and triethylamine (Scheme 1.7).[79-81] Other bases (KOAc, DBU, pyridine) promoted dehalogenation, yielding Ar–H, due to HBpin behaving as a hydride source. Using HBpin is more atom economical than B_2pin_2.

$$\text{Ar–X} \quad + \quad \text{HB(pin)} \xrightarrow[\text{dioxane, 80 °C, 1-6 h}]{\text{Pd(dppf)Cl}_2\text{, Et}_3\text{N}} \text{Ar–B(pin)}$$

X = I, Br, OTf, Cl

Scheme 1.7 Murata *et al.* Pd-catalyzed coupling of an aryl electrophile with pinacolborane.[80, 81]

The exact mechanism for HBpin borylation is unknown; two processes have been proposed leading to the formation of an Ar–Pd–Bpin intermediate. Et_3N could facilitate B–C bond formation through Pd(II)–X displacement with a weakly bound nucleophilic boryl anion $Et_3NH^{\delta+}\cdot Bpin^{\delta-}$ [Figure 1.6, (a)]. However, it is possible that HBpin may oxidatively add to the Pd(0) complex, followed by σ-bond metathesis of the boryl-palladium complex with aryl halides [Figure 1.6, (b)].[80] Other catalyst systems are advantageous for the HBpin borylation of *ortho*-substituted haloarenes ($Pd(OAc)_2$/biphenylphosphine ligand)[82] and electron-donor substituted haloarenes ($Pd(OAc)_2$/DPEphos).[83] In both cases the borylation procedure was extended to a one-pot Suzuki-Miyaura unsymmetrical biphenyl synthesis.

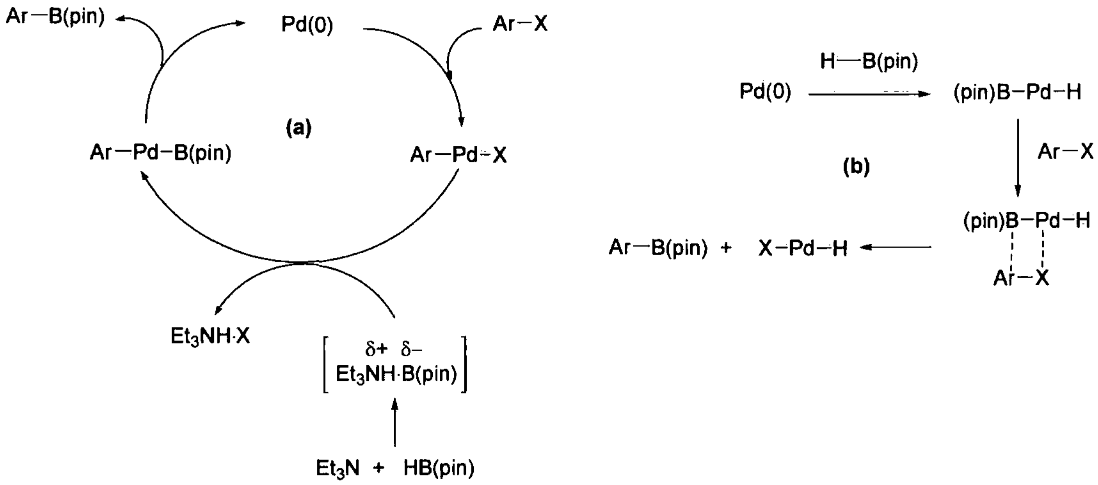
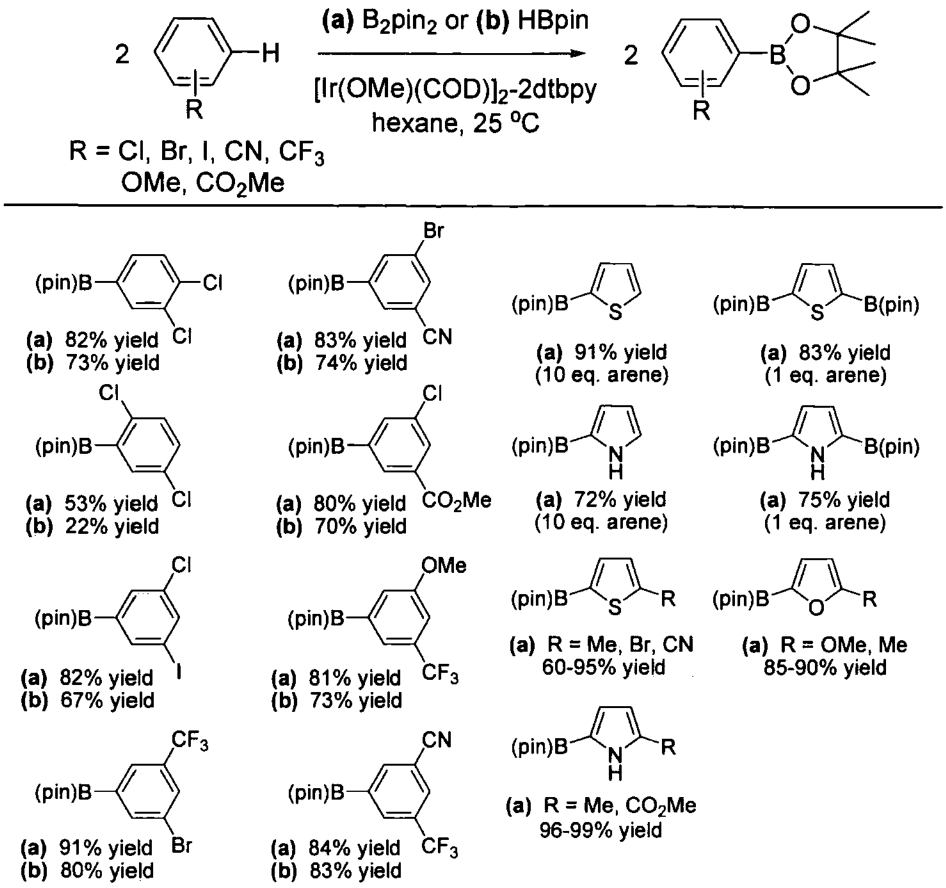


Figure 1.6 Plausible reaction mechanisms for the Pd-catalyzed borylation of arylhalides with HBpin.[80]

Buchwald *et al.* reported an improved system for the Pd-catalyzed borylation of aryl halides with HBpin.[84] Previously Murata *et al.* had successfully borylated only *para*-substituted electron-rich aryl chlorides.[81] The active catalyst system based on $Pd(MeCN)_2Cl_2$ and SPhos was general for aryl iodides, bromides and chlorides with both electron-donating and electron-withdrawing substituents. Higher quantities of palladium catalyst and longer reaction times were required for chloroarenes; however, this system was effective for a range of chlorides giving pinacol boronic esters is good yields (51-96%). Aryl bromides still gave higher yields compared to chloro analogues.[84]

Methylpentanediol borane (HBMP) has been used in Pd-catalyzed borylation of substituted aryl bromides and iodides.[85] The scope of HBMP equals that of HBpin, leading to comparable yields of boronic esters. Suzuki-Miyaura cross-coupling reactions of methylpentanediol boronic esters with aryl iodides give good conversion to the coupling products. There appears to be no advantage to HBMP over HBpin, especially as HBpin is reactive with aryl chlorides. However, the authors report that HBMP is "much less expensive than HBpin, very easily prepared and stable."[85]

An extension of the above methodology was the aliphatic or aromatic C–H borylation. Aromatic C–H borylation is catalyzed efficiently by iridium; extensive work has established some key mechanistic steps in the catalytic cycle.[86, 87] An Ir(I) complex prepared from ½$[IrX(COD)]_2$ (X = OMe or Cl) and bpy or dtbpy exhibits excellent activity and selectivity for aromatic C–H borylation with B_2pin_2[88-91] or HBpin.[92] Initially borylation of (hetero)arenes with B_2pin_2 was conducted at 80 °C with $[IrCl(COD)]_2$ and bpy or dtbpy, using an excess of (hetero)arene to avoid multiple borylations.[88, 89] It was later found that $[Ir(OMe)(COD)]_2$ and dtbpy was an improved system. The reactions are faster in non-polar solvents such as hexane or octane; more coordinating solvents also slow the reaction. The superiority of dtbpy compared to bpy can be attributed to the greater solubility of dtbpy in hexane. The high catalytic efficiency of $[Ir(OMe)(COD)]_2$ compared to the chloro analogue can be ascribed to the more facile conversion into (boryl)iridium complexes (proposed intermediates in the catalytic cycle) meaning that C–H borylation of (hetero)arenes can be conducted at room temperature with stochiometric amounts of either B_2pin_2 or HBpin.[90-92] The reaction is suitable for arenes possessing OMe, I, Br, Cl, CO_2Me, CN and CF_3 substituents (Scheme 1.8).[90, 92] Regioselectivity of borylation largely depends on steric factors rather than on the electronics of the arene. Five-membered heteroarenes such as thiophene, furan and pyrrole yield mono- and di-borylated products depending on the amount of arene employed.[89, 91] Recently a one-pot Ir-catalyzed aromatic C–H borylation–Suzuki-Miyaura cross-coupling procedure was developed for the synthesis of unsymmetrical biaryls.[93] As hydrolysis of pinacolboronates to boronic acids is unfavourable, in some cases lower reactivity is found in Suzuki-Miyaura cross-coupling reactions. Consequently, Hartwig *et al.* have developed a synthesis of arylboronic acids and aryl trifluoroborates through the treatment of crude, isolated pinacol boronic esters prepared from Ir-catalyzed borylation of arenes.[94] This one-pot procedure alleviates the need to prepare boronic acids through organolithium derivatives and generates substitution patterns which complement those available from lithiation of haloarenes.



Scheme 1.8 Ishiyama *et al.* Ir-catalyzed aromatic C–H borylation with B_2pin_2 or HBpin.[90-92]

There is mechanistic evidence for a tris(boryl)Ir(III) intermediate (Figure 1.7, intermediate **B**) in the Ir-catalyzed borylation of arenes.[95] The tris(boryl) intermediate **B** can be produced by oxidative addition of B_2pin_2 to a mono(boryl)Ir(I) complex **A**, formed via σ-bond metathesis or an oxidative addition/reductive elimination sequence between [Ir]–OMe and B_2pin_2. It is unclear whether oxidative addition of Ar–H or σ-bond metathesis occurs at the vacant site of Ir(III) intermediate **C**, to create an Ir(V) species **D**. Reductive elimination of ArB(pin) gives an Ir(III) hydride complex (**E**). Oxidative addition of B_2pin_2 to **E**, followed by reductive elimination of HBpin, regenerates **C**. The resulting HBpin can participate in the catalytic cycle through a sequence of oxidative addition to **E** and hydrogen reductive elimination from a Ir(V) intermediate **F**.[87] Although catalytic cycles involving Ir(III)–Ir(V) are rare, the ease of elimination of HBpin or H_2 from an Ir(V) intermediate should promote borylation under mild conditions.[87] Iridium-catalyzed C–H borylation of (hetero)arenes is a convenient, economical and environmentally benign route to boronic esters, for which some substitution patterns have not previously been reported.

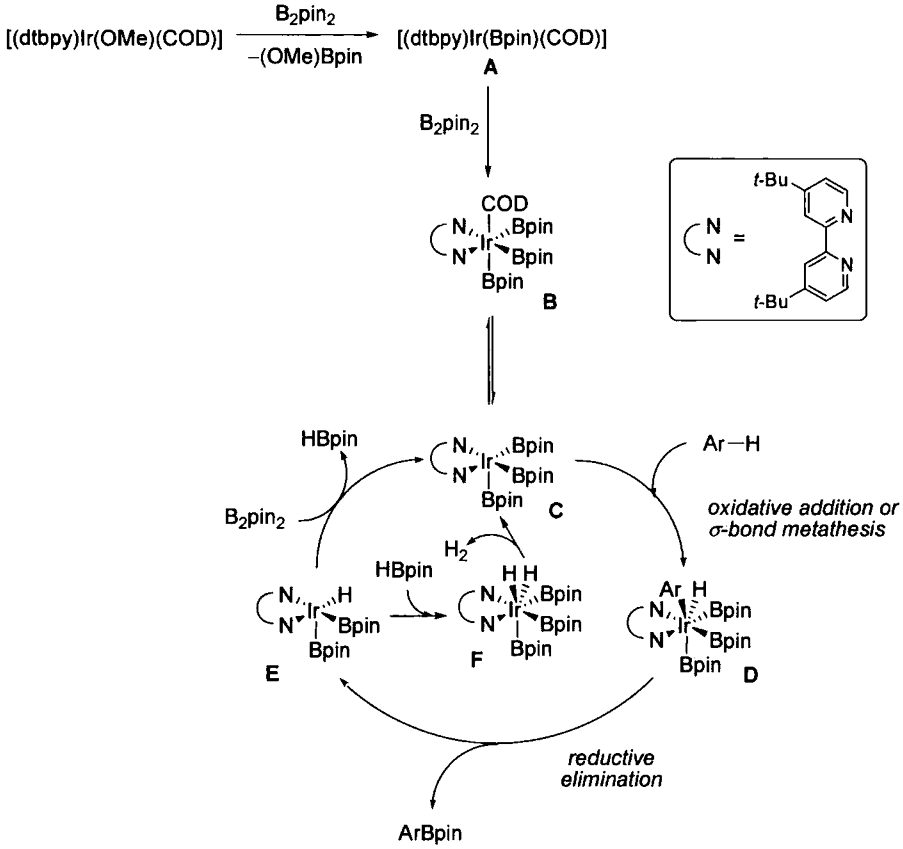


Figure 1.7 Proposed catalytic cycle for Ir-catalyzed arene borylation.[87, 95]

Harrity *et al.* have developed cycloaddition reactions of alkynylboronic esters with an appropriate substrate for the synthesis of (hetero)arylboronic esters.[96] This will be discussed in more detail in Section 1.2. It should be noted that initial preparation of the alkynylboronic ester is required.

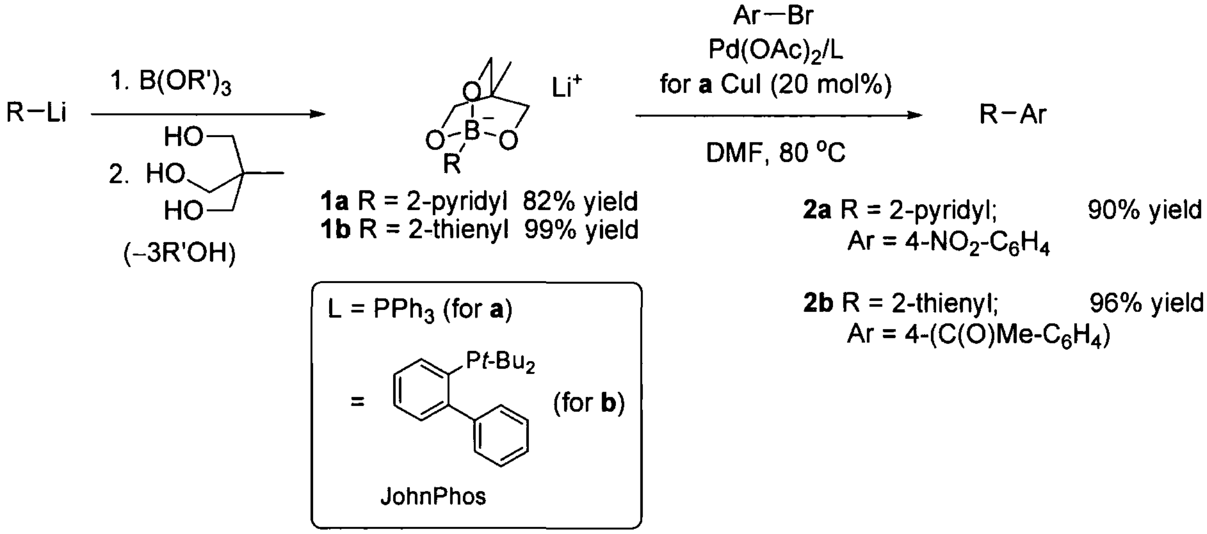
The one-step synthesis of organoboronic esters from organic electrophiles has advantages over traditional lithiation–boronation techniques, for example, protection of functional groups that are sensitive to organometallic reagents is not necessary. Diboron reagents are relatively expensive, therefore, for large-scale syntheses the cross-coupling of HBpin or direct C–H borylation is recommended. If catalytic levels of Pd or Ir can be reduced the preparation of boronic esters through coupling reactions is more economical.

1.1.4 Boronic Acid Alternatives

There are several arylboronic acid alternatives which are competent substrates in many of the same reaction processes that involve free boronic acids. Aryltrifluoroborate salts reported by Molander *et al.* are a class of air-stable arylboronic acid derivatives.[97] Trifluoroborates are easily prepared by the treatment of boronic acids or esters with aqueous KHF_2. They are generally more robust, easily purified and easier to handle. Aryl- and electron-rich heteroaryltrifluoroborates partake in Suzuki-Miyuara cross-coupling reactions, under ligandless conditions, with aryl and activated heteroaryl bromides.[97] However, the metal-catalyzed bond-forming reactions are very slow in the absence of base, due to the high electronegativity of the fluorine atoms.[98, 99] The strong B–F bonds make trifluoroborate salts resistant to electrophilic reaction with a strong oxidant.

Diethanolamine adducts are stable boronic acid derivatives through tetracoordination of the boron moiety.[66] The internal chelation of the nitrogen lone pair to the vacant orbital on boron, makes their hydrolysis less favourable. They are readily formed through dehydration of boronic acid derivatives with a diethanolamine species. 2-Pyridylboronates are renowned for being unstable due to the boronate being α to a heteroatom; however, they have been stabilized as their diethanolamine adduct[100] (see Section 1.2.1).

Cammidge *et al.* and more recently Miyaura *et al.* have reported the preparation of trihydroxyborates[101] and cyclic triolborates,[102] respectively. These tetracoordinated 'ate' complexes are extremely air and water stable, and the procedure for isolation is easy and convenient. The nucleophilicity of organic groups attached to B is enhanced by quaternization with an anionic ligand. Ordinarily in metal-catalyzed coupling reactions of boronic acids, a nucleophile (usually from base or KF) is added and formation of an 'ate' complex occurs. For trihydroxyborates and cyclic triolborates these discrete salts can be used directly in Suzuki-Miyaura rections without the need for an additional nucleophile or base (unlike trifluoroborate salts, as discussed previously). Good to excellent yields are obtained for Suzuki-Miyaura coupling reactions of substituted aryl trihydroxy- and cyclic triolborates with arylbromides.[101, 102] Miyaura *et al.* also found that 2-pyridyl- and 2-thienyl triolborates, whose boronic acid/ester derivatives generally undergo B–C bond cleavage in water, reacted quantitatively with bromoarenes in anhydrous DMF.[102] The presence of CuI increased the coupling yield with 2-pyridylboronate (Scheme 1.9). Cyclic triolborates were also successful in the copper-promoted arylation of the N–H bond in a number of amine and amides.[102, 103]



Scheme 1.9 Coupling reactions of triolborates, usually sensitive to protodeboronation.[102]

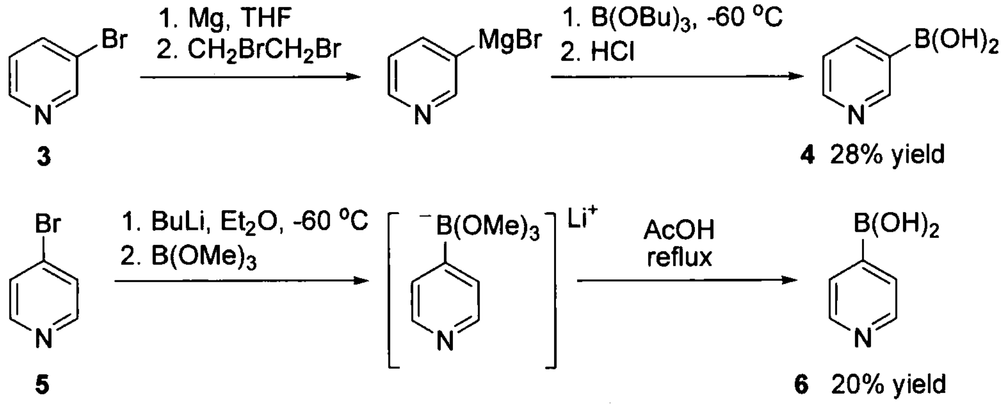
1.2 *N*-Heteroaryl Boronic Acids

Functionalized biheteroaryl systems are of great importance due to their widespread applications in many areas of contemporary interest. The metal-mediated cross-coupling reactions continue to be of paramount importance in their synthesis; currently, the Suzuki-Miyaura cross-coupling protocol[37, 104, 105] or direct arylation approach[106-108] are favoured. Direct arylation of heteroarenes through the activation of an arene C–H bond[109-111] (Ar–H + Ar–X) represents a recent area of research. The catalytic oxidative arene cross-coupling,[112-115] in which neither substrate must be pre-activated (Ar–H + Ar–H), whilst still in its infancy is an exciting prospect in atom-efficient cross-couplings with reduced cost and waste. The Suzuki-Miyaura cross-coupling remains an established and well-practised method for the preparation of biaryls, with a wide commercial availability of boronic acid derivatives and halide coupling partners. The synthesis of heteroaryl systems, where both boronic acid moiety and coupling partner are heteroarenes, is generally underdeveloped in comparison to aryl analogues. The prevalence of heteroaryl boronic acids in the literature is mounting[116] and their commercial availability on the increase.

The next section will specifically focus on the current literature (up to August 2008) surrounding pyridyl-, pyrimidyl-, pyridazinyl- and pyrazolylboronic acid derivatives; other *N*-heteroarylboronic acids will be briefly reviewed. The procedures for the synthesis of boronic acids or esters described in section 1.1 are all applied to the preparation of *N*-heteroarylboronic acid derivatives.

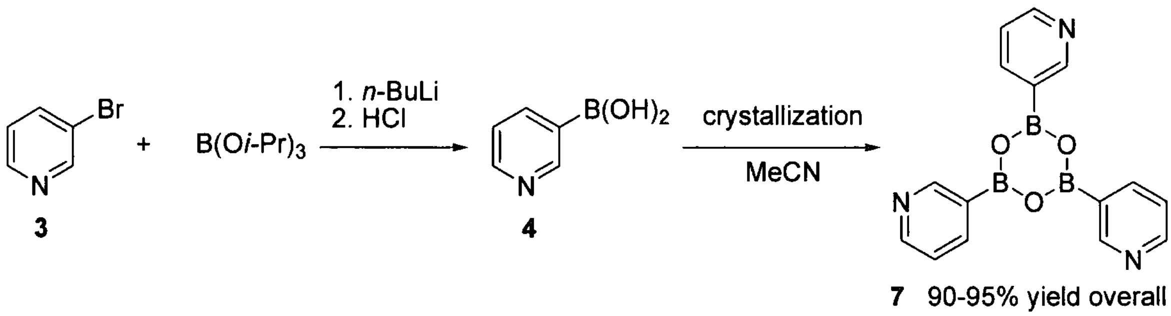
1.2.1 Pyridylboronic Acids

Of all the *N*-heteroarylboronic acids, pyridine derivatives are among the most abundant and earliest reported, reflecting the importance of the pyridine motif in organic chemistry. The parent 3- and 4-pyridylboronic acids **4** and **6**, respectively, are relatively stable compounds and now commercially available in multigram quantities from numerous suppliers. 3- and 4-Pyridylboronic acid decompose to pyridine and boric acid upon UV irradiation in neutral or slightly basic conditions.[117] Original preparations were low yielding, with difficulties in their isolation from aqueous media, due to the hydrophilic nature of the compounds. The reactions of 3-pyridylmagnesium bromide and 4-pyridyllithium at low temperature with tributyl borate or trimethyl borate yielded **4** and **6** in 28 and 20% yields, respectively, after acidic workup (Scheme 1.10).[118] These species were not fully characterized, instead, treated with a diol to afford the ester derivatives which were oxidized and reacted with picric acid to yield the corresponding hydroxypyridine picrates to confirm the initial preparation of **4** and **6**.



Scheme 1.10 Synthesis of 3- and 4-pyridylboronic acid.[118]

More recently, Cai *et al.* reported the preparation of the boroxine derivative **7** on a multigram scale by a lithium-halogen exchange, "*in situ* quench" procedure (Scheme 1.11).[63, 119] They found this procedure to be superior to previous routes. The preparation of **4** via magnesium-halogen exchange showed poor converstion to the boronic acid due to poor solubility of the 3-pyridylmagnesium chloride intermediate.[49] Previous lithium-halogen exchange procedures had identified the importance in the order of reagents and choice of solvent, with the best isolated yield of **4** being 87%.[49] Yields of **7** from the "*in situ* procedure" at –40 °C in THF were 90-95%; at 0 °C the yield was 80%.[63]



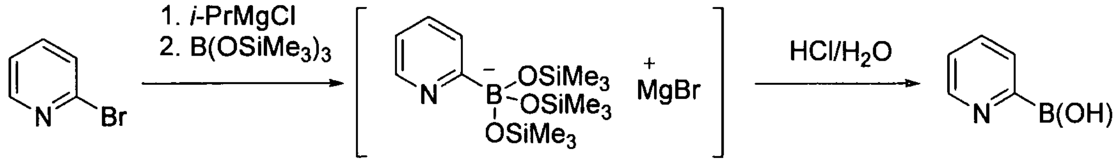
Scheme 1.11 "*In situ* quench" procedure for the preparation of 3-pyridylboronic acid **4**.[63]

It is often difficult to quantify the purity of boronic acids due to the mixture of free boronic acid and anhydride species present in the sample; dehydration to their boroxine derivatives can improve the purity. Suzuki-Miyaura cross-coupling reactions of boroxine **7** are comparable to those of boronic acid **4**. For **7** aqueous conditions are required as the boroxine undergoes initial *in situ* hydrolysis prior to cross-coupling.[27]

In the "*in situ* quench" procedure, unstable aryllithiums, which may be labile or undergo side reactions, are quenched immediately after they are formed, resulting in improved yields of the boronic acid. Employing the "*in situ* quench" procedure with a number of bromoheteroarenes and substituted phenylbromides gave mixed results, compared with the sequential addition approach. For the heteroaryl examples (3- and 4-pyridyl-, 3-thienyl- and 5-pyrimidylboronic acid) the yields of boronic acids when using the "*in situ* quench" procedure were improved or comparable to literature reports. For example, sequential lithium-halogen exchange followed by boronation afforded **6** in 65% yield from **5**[120] and the 4-pyridylboronic ester from 4-iodopyridine in 74% yield.[68] Whilst the "*in situ* quench" procedure yielded **6** in a comparable 60% yield.[63] With substituted phenylbromides, on using the "*in situ* quench" protocol, yields of boronic acids were comparable to sequential addition procedures, or in some cases markedly reduced. In some cases unreacted arylbromide was isolated. This suggests that not only does the stability of the aryllithium species influence the suitability for the "*in situ* quench" procedure, but if the generation of the aryllithium is relatively slow, competitive reaction of *n*-BuLi with triisopropylborate can occur, thus not consuming all of the arylbromide.

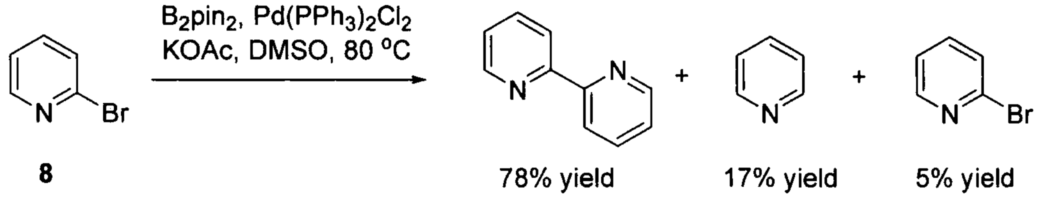
The preparation and Suzuki-Miyaura cross-coupling of 3-pyridyltrifluoroborates has been recently reported.[97, 121, 122] Iridium-catalyzed C–H coupling between bis(pinacolato)diboron and pyridine afforded a mixture of 3- and 4-pyridylboronic ester.[89] Substituted pyridine derivatives have been shown to regioselectively borylate, leading to 2- and 4-pyridylboronic esters.[123]

2-Pyridylboronic acid has remained elusive since early work showed the boronic moiety at the α position of the pyridine ring to be highly prone to protodeboronation.[117] The reaction of 2-pyridyl Grignard with tris(trimethylsilyl)borate has recently been reported to yield the corresponding boronic acid **9** in 70% yield (Scheme 1.12);[124] this procedure was applied to the preparation of 3-pyridyl- and 5-pyrimidylboronic acids, giving yields of 75% and 72%, respectively.



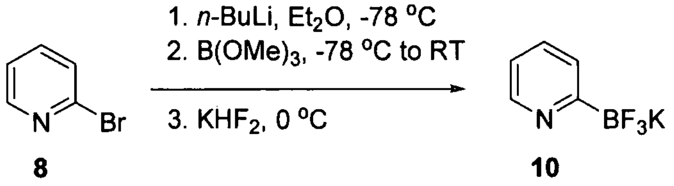
Scheme 1.12 Preparation of 2-pyridylboronic acid.[124]

Diethyl 2-pyridylborane is reported to be a stable compound;[62] however, its attempted palladium catalyzed cross-couplings yielded unreacted starting materials.[125, 126] Dialkyl 3-pyridylboranes are commercially available or easy to prepare;[127] diethyl 3-pyridylborane has been coupled with a pyridyl stannane reagent under palladium catalyzed conditions.[128] Dimethyl 2-pyridylboronic ester has been prepared and cross-coupled under Suzuki-Miyaura conditions; however, there was no acidic work-up during the synthesis and therefore the active species may be the trimethyl 2-pyridylborate complex.[129, 130] The pinacol 2-pyridylboronic ester could not be isolated from the palladium-catalyzed reaction of **8** with bis(pinacolato)diboron. Instead, a mixture of 2,2'-bipyridine, pyridine and unreacted **8** was recovered (Scheme 1.13),[131] resulting from coupling of the boronic ester *in situ* with **8** or protodeboronation of the boronic ester in the reaction mixture.



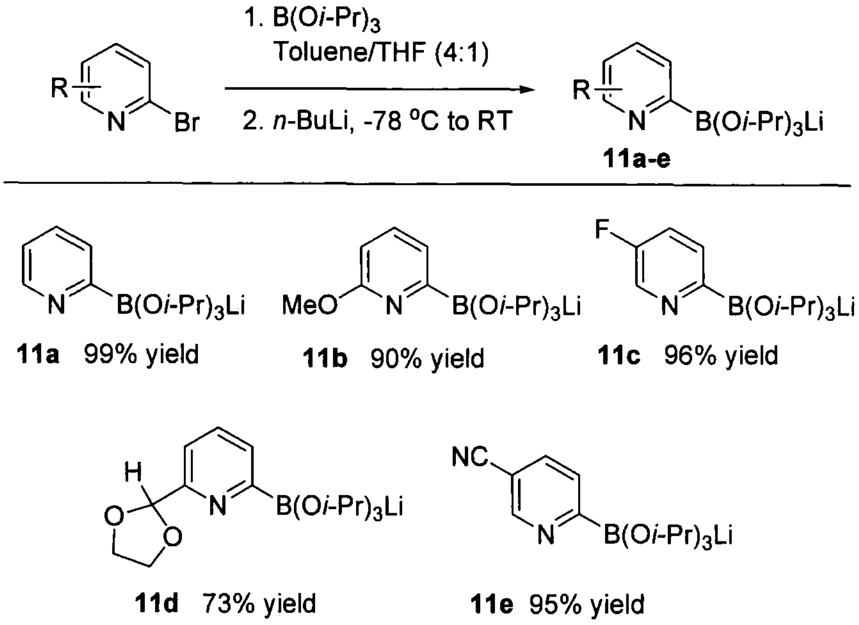
Scheme 1.13 Attempted preparation of pinacol 2-pyridylboronic ester.[131]

The instability of 2-pyridylboronates was highlighted by Molander *et al.*, in their preparation of potassium 2-pyridyltrifluoroborate **10** (Scheme 1.14).[97] The synthesis of **10** was complicated by solubility issues and the product did not show an adequate (extended) shelf life. Attempts to cross-couple **10** were unsuccessful.



Scheme 1.14 Preparation of potassium 2-pyridyltrifluoroborate.[97]

More recently the preparation and Suzuki-Miyaura cross-couplings of diethanolamine stabilized 2-pyridylboronates have been reported,[100, 132, 133] these being the most stable isolated 2-pyridyl adducts reported thus far. Buchwald *et al.* described an efficient method for the Suzuki-Miyaura coupling of 2-pyridyl nucleophiles.[134] They found lithium triisopropyl 2-pyridylborate **11a** to be markedly more reactive than 2-pyridylboronic acid **9**, pinacol boronic ester, *N*-phenyldiethanolamine adduct, and trifluoroborate **10**. Lithium triisopropyl 2-pyridylborate is stable under argon for up to a month and can be synthesized in quantitative yield on a multigram scale; a number of substituted 2-pyridyl borate derivatives have also been prepared **11b-e** (Scheme 1.15). Suzuki-Miyaura cross-coupling reactions of **11a-d** with substituted bromo- and chlorobenzenes or heteroarylbromides yielded bi(hetero)aryl systems in good yields (40-92%) when using phosphine oxides as the ligand; reaction conditions [$Pd_2(dba)_3$ (1.0-1.5 mol%), $Cy_2P(O)H$ or t-$Bu_2P(O)H$ (6 mol%), KF, 1,4-dioxane, reflux, 20 h].[134]

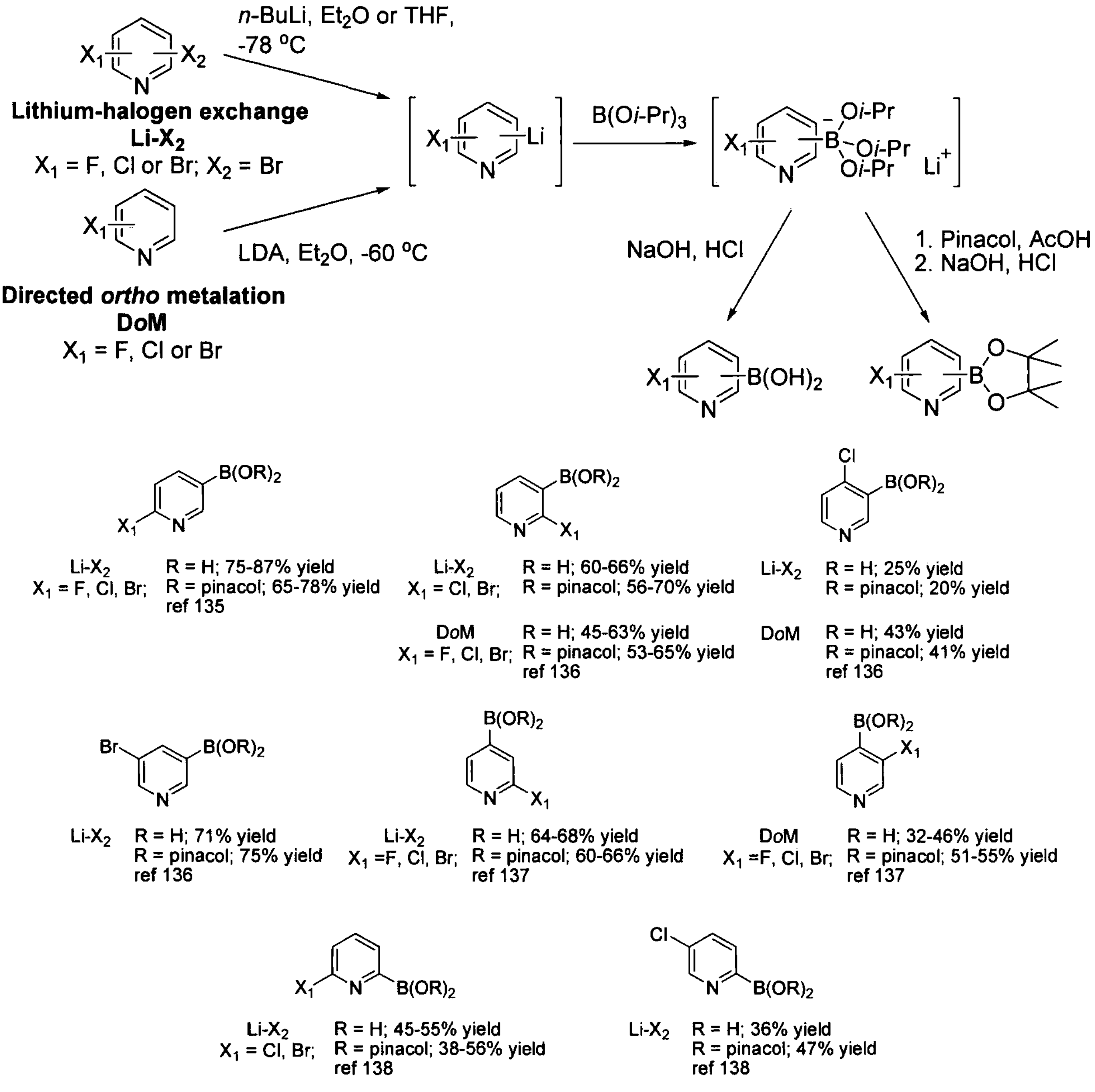


Scheme 1.15 Synthesis of lithium triisopropyl 2-pyridylborate derivatives.[134]

Pyridylboronic acid derivatives substituted with a variety of functional groups (e.g. halo-,[30, 61, 135-143] alkoxy-,[30, 32, 139, 140, 144] cyano-,[65] amido-[61]) have been prepared and successfully cross-coupled under Suzuki-Miyaura conditions to yield bi(hetero)aryl systems. Halopyridylboronic acids have been extensively studied, due to the wide commercial availability of halopyridines. In a series of papers Rault *et al.* described the syntheses of a range of halo-substituted pyridylboronic acids and pinacol esters – a summary of the compounds prepared and synthetic route are shown in Scheme 1.16.[135-138] The reactivity of the halopyridylboronic acids in Suzuki-Miyaura cross-coupling reactions is highlighted in each case.

In the synthesis of 6-halo-3-pyridylboronic acids the dihalopyridines were used. The different reactivities of the halogens towards lithium-halogen exchange was exploited to yield the expected products.[135, 145, 146] Comparable yields were obtained regardless of whether lithium-halogen exchange or directed *ortho* metalation was applied in the synthesis of 2-halo-3-pyridylboronic acids.[136, 147] 4-Halopyridines are more challenging to prepare as the precursor to 4-pyridylboronic acids; as a consequence, directed *ortho* metalation is often employed. For 3-halo-4-pyridylboronic acids, D*o*M of 3-halopyridines is used; the electron-withdrawing effect of the halogens increase the rate of metalation. 3-Halo-4-pyridylboronic acids were isolated in reasonable yields reflecting the selective deprotonation at C-4.[137] The C-4 position is more acidic than C-

2, and significantly more so than C-5 and C-6, due to the inductive electron withdrawal by the halogen.



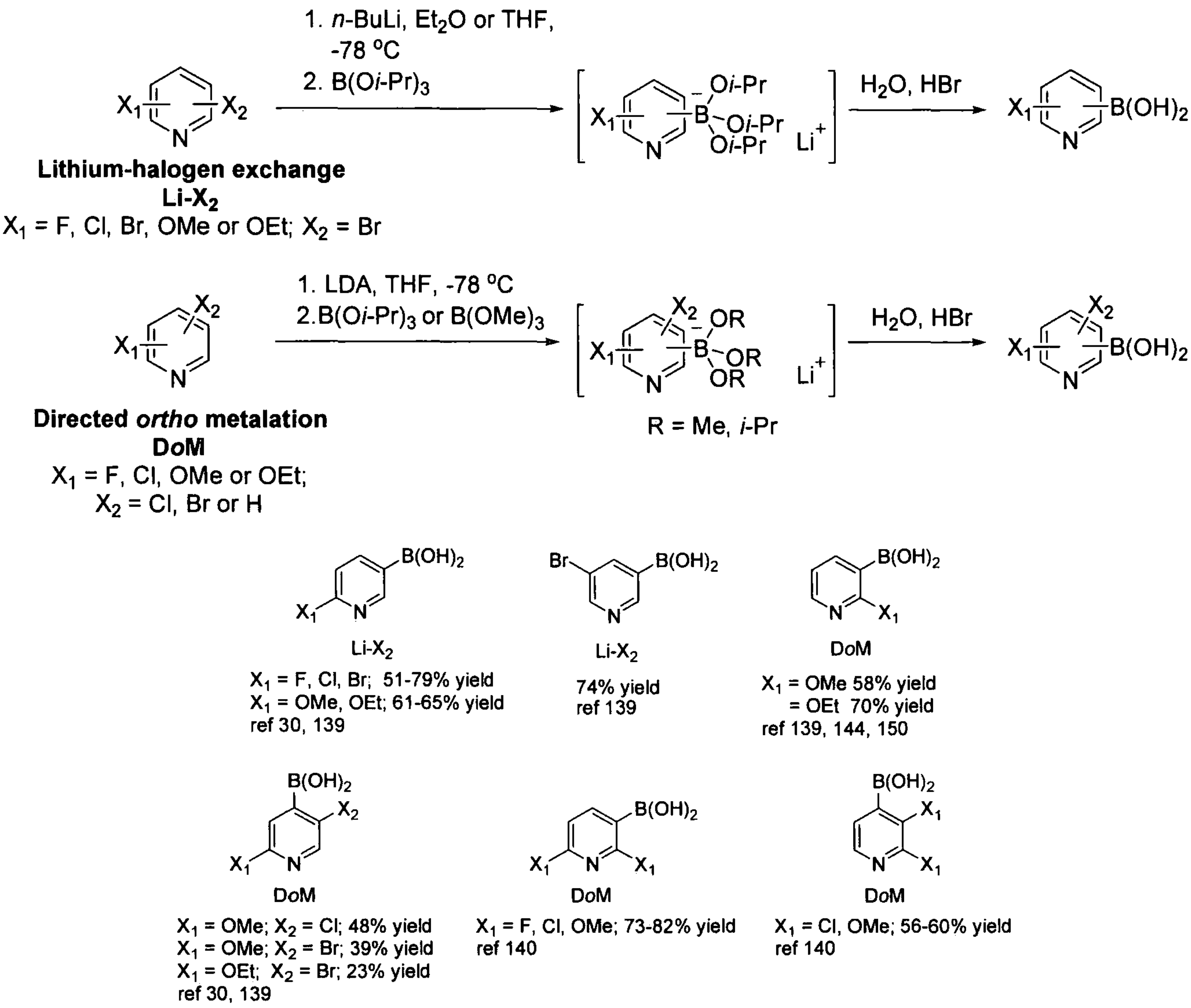
Scheme 1.16 Halopyridylboronic acids and esters prepared by Rault *et al.*[135-138]

5-Chloro- and 6-halo-2-pyridylboronic acids were isolated in acceptable yields considering the unstable nature of boronic acid moieties adjacent to heteroatoms.[138] The first X-ray crystal structure for a 2-pyridylboronic ester moiety was reported,[148] identifying a slight deformation of the boronic ester moiety. The C–B bond is longer than in the corresponding 3-pyridyl derivative (2-pyridyl- 1.578 Å, c.f. 3-pyridyl- 1.557

Å[145]), and may be more fragile. The X-ray structure of the corresponding *N*-methyldiethanolamine 2-pyridylboronate (or *N*-methyldioxazaborocane) confirms the presence of an N→B bond (1.696 Å).[149] In comparison with the 2-pyridylboronic ester the C–B bond is longer (boronic ester 1.578 Å, c.f. dioxazaborocane 1.615 Å), however, the boronate is stabilized by the N→B bond.

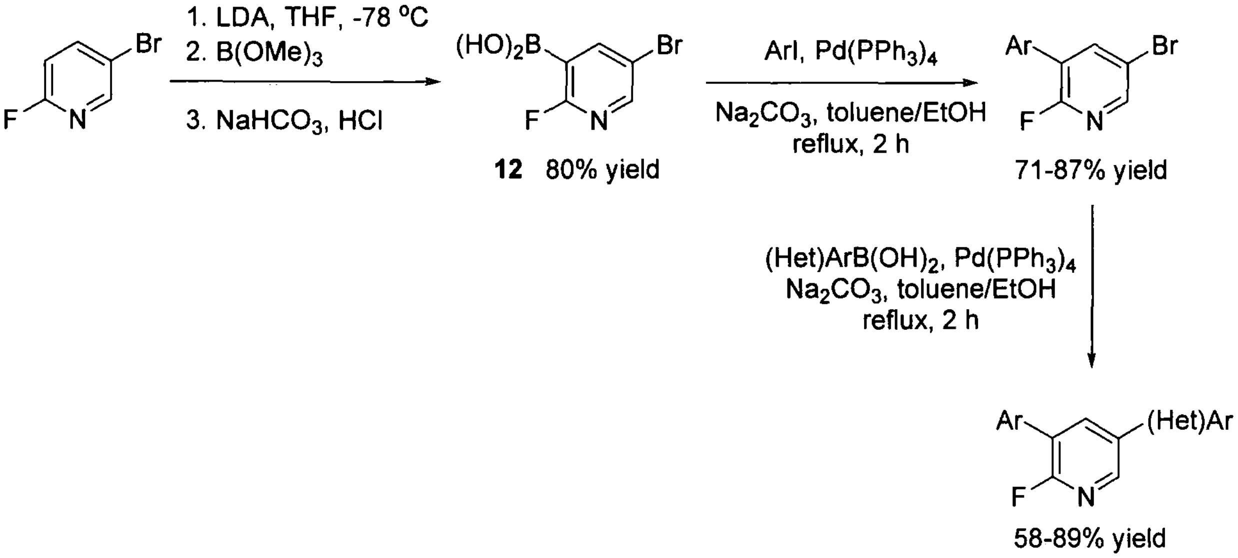
Our group has an established interest in substituted pyridylboronic acids; a summary of the compounds prepared and synthetic routes is shown in Scheme 1.17.[30, 139, 140, 144] The syntheses of 6-halo-3-pyridylboronic acids has also been reported by Bryce *et al.*,[30, 139] with similar reaction conditions and yields to Rault *et al.* Bryce *et al.* extended the lithium-halogen exchange/boronation protocol to the preparation of 6-alkoxy-3-pyridylboronic acids in good yields.[30, 139] The X-ray crystal structures of 6-chloro- and 6-bromo-3-pyridylboronic acid revealed extensive hydrogen-bonding of the boronic acid groups. A study into the Suzuki-Miyaura cross-couplings of these boronic acids with heteroaryl bromides and chlorides gave moderate to good isolated coupling product yields.[30, 150] Good compatibility was found with a variety of functionality on the coupling partner (viz. trifluoromethyl, nitro, primary amine). 6-Fluoro- and 6-chloro-3-pyridylboronic acids have been reported by other groups, with a comparable synthetic strategy being used.[151, 152]

Directed *ortho* metalation is generally preferred in the commercial preparation of functionalized pyridylboronic acids. Di-substituted pyridine starting materials are not required, which is beneficial as they are generally more expensive than their mono-substituted analogues. D*o*M reactions are also more atom efficient than lithium-halogen exchange procedures. Standard directing groups used in D*o*M are halogens and methoxy groups.[43] Methoxy substituents are regarded as having increased chelation to the metalating agent, and are therefore more effective in regioselective metalation[57] However, contrary to this, Bryce *et al.* found that lithiation/boronation of 5-chloro-2-methoxypyridine with LDA gave 5-chloro-2-methoxy-4-pyridylboronic acid in 48% yield.[30] This implies that the stronger chelating ability of the methoxy group, which would have directed lithiation at the C-3 position, is insufficient to overcome the removal of the acidic C-4 proton, which is aided by the directing chloro substituent. The use of the methoxy substituent in D*o*M has the advantage that the reagent is not prone to metal exchange unlike halogen substituted reagents.



Scheme 1.17 Halo- and alkoxy-pyridylboronic acids prepared by Bryce *et al.*[30, 139, 140, 144, 150]

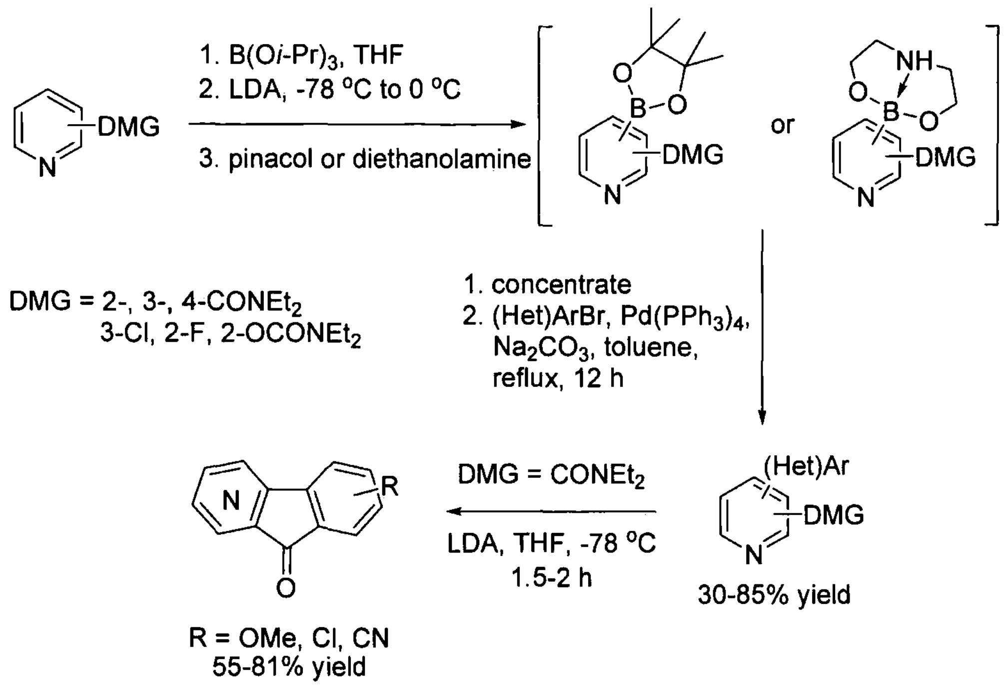
The DoM/boronation protocol was extended to alkoxy substituted pyridylboronic acids.[139, 144] Initial yields of 2-methoxy-3-pyridylboronic acid were only 13%.[139] However, after much experimentation, this compound was prepared, following an optimized procedure in 58% yield on a 75 g scale.[150] 2-Ethoxy-3-pyridylboronic acid was easily synthesized on a 70 g scale, and proved to be a versatile building block for the preparation of a library of functionalized heteroaryl-pyridines.[144] D*o*M of 5-bromo-2-alkoxypyridine with LDA yielded the 4-pyridylboronic acid derivatives, analogous to the preparation of 5-chloro-2-methoxy-4-pyridylboronic acid.[139] Lower yields were obtained for the bromo derivatives, presumably due to the weaker directing ability of the bromo substituents compared to chloro. Interestingly, for 5-bromo-2-fluoropyridine, Gallagher *et al.* found regioselective lithiation occurred *ortho* to fluorine and prepared the 3-pyridylboronic acid derivative **12** (Scheme 1.18).[142] Suzuki-Miyaura cross-coupling of **12** initially occurred at the boronic moiety; extended reaction times lead to debromination of the coupling products. Further cross-coupling at the bromo substituent furnished 3,5-disubstituted-2-fluoropyridines in good yields.[142]



Scheme 1.18 Synthesis of 3,5-disubstituted-2-fluoropyridines.[142]

Dimethoxy- and dihalopyridylboronic acids have been prepared via D*o*M of the corresponding disubstituted pyridine precursor with LDA, followed by reaction with triisopropylborate or trimethylborate (Scheme 1.17).[140] The preparation of 2,3-dimethoxy-4-pyridylboronic acid was low yielding when using LDA (12% yield); following literature conditions for the lithiation, *n*-BuLi (2.2 equiv.) in THF,[153] the yield was improved to 60%. Suzuki-Miyaura cross-couplings of the dimethoxy- and dihalopyridylboronic acids with a number of heteroaryl bromides yielded new highly-functionalized heteroarylpyridines in 42-96% yields.[140]

Snieckus *et al.* have combined the D*o*M/boronation of pyridine derivatives and subsequent Suzuki-Miyaura cross-coupling into a one-pot protocol (Scheme 1.19).[61] Halides or *N*,*N*-diethylamide were employed as DMG, the halide examples being comparable to previous work where the analogous boronic acids had been isolated and subsequently cross-coupled. This one-pot procedure showed good functional group compatibility. The coupling products offer additional synthetic potential in directed remote metalation (DreM) chemistry, as highlighted by cyclization to yield azafluorenones.[61]

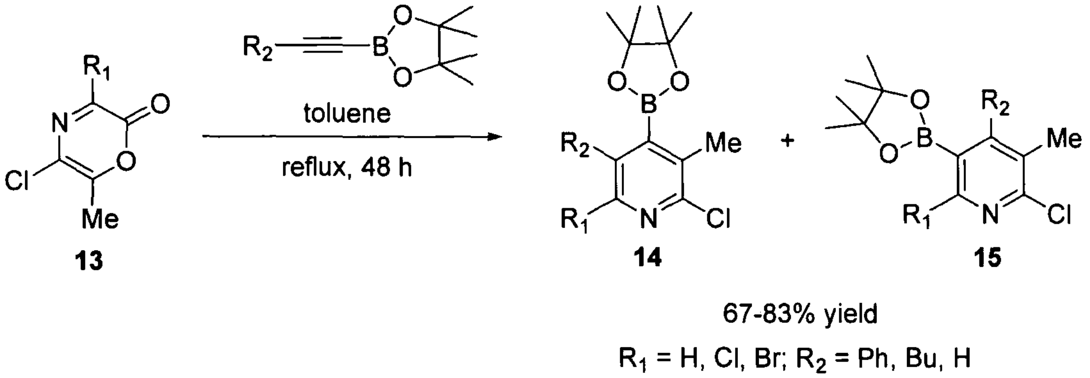


Scheme 1.19 One-pot D*o*M–boronation–Suzuki-Miyaura cross-coupling synthesis of azabiaryls.[61]

Recently Rault *et al.* synthesized *ortho*-cyanopyridylboronic acids leading to cyano-functionalized bipyridines.[65] Their procedure involved the *ortho*-lithiation of the cyanopyridines with LTMP at low temperature and quenching with triisopropylborate. The subsequent low yields of the cross-coupling reactions were explained by the close proximity of the electron-withdrawing cyano group facilitating competitive protodeboronation of the boronic acid. The corresponding pinacol ester derivatives were more stable (with respect to protodeboronation). Novel cyanobipyridines were obtained in 40-60% yields.

Oxybispyridylboronic acids have been prepared from bromo-oxybispyridines, using standard lithium-halogen exchange with *n*-BuLi in THF at –78 °C, followed by boronation with triisopropylborate.[154] Yields of boronic acids were variable, 20-86%, in some cases degradation products were isolated, indicating instability of the oxybispyridylboronic acids. Suzuki-Miyaura cross-couplings were successful, preparing substituted pyridylethers which may be potential ligands for neuronal nicotinic cholinergic receptors (nAChRs).

An alternative strategy to halo-substituted pyridylboronic esters is through the [4+2] cycloaddition of 1,4-oxazin-2-ones with alkynylboronic esters (Scheme 1.20).[141] For 1,4-oxazin-2-one when R_1 = H or Cl, the pericyclic reaction with alkynylboronic esters provides useful levels of regiocontrol for isomer **14** (ca. 5:1, **14**:**15**), when R_1 = Br the regioselectivity is further enhanced (ca. 10:1). Unfortunately, with terminal alkynylboronic esters poor selectivity was found.



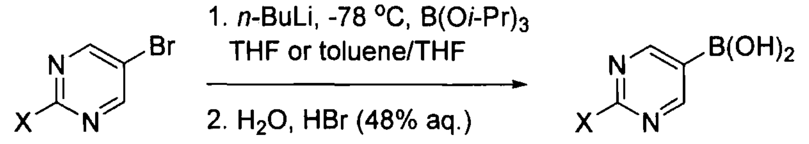
Scheme 1.20 Harrity *et al.* [4+2] cycloaddition route to substituted pyridylboronic esters.[141]

1.2.2 Pyrimidylboronic Acids

There is considerable interest in specifically functionalized pyrimidine derivatives as they are extensive in natural products and molecules with biological activity.[155-159] However, only a limited number of pyrimidylboronic acids have been reported.[31, 63, 160-163] Early work was inspired by the role of organoboron reagents in BNCT, as potential anti-tumour agents. 2,5-Dimethoxy- and 2,5-dibenzyloxy-5-pyrimidylboronic acid were prepared through lithium-halogen exchange and *in situ* treatment with trimethylborate or tributylborate.[160] Gronowitz *et al.* found the couplings of halogenated uracils with boronic acids were unsuccessful; conversely the couplings of the corresponding pyrimidylboronic acid with π-electron deficient heterocyclic halides occurred in good to excellent yields.[164] As noted in Section 1.2.1, the parent 5-pyrimidylboronic acid has been prepared in yields of 72-76% by either the reaction of the 5-pyrimidyl Grignard with tris(trimethylsilyl)borate[124] or halogen-lithium exchange of 5-bromopyrimidine and "*in situ* quench" procedure outlined by Cai *et al.*[63]

More recently Bryce *et al.* synthesized 5-pyrimidylboronic acid in 1-10 g batches via halogen-lithium exchange of 5-bromopyrimidine with *n*-BuLi, and "*in situ* quench" with triisopropylborate in reproducible yields of 45% (Scheme 1.21).[31] The method was extended to 2-methoxy-, and 2-chloro-5-pyrimidylboronic acids yielding **17b**[31] and

17c[162] in 61% and 85%, respectively. X-ray diffraction studies of **17a** and **17c** revealed the structure of the hemi-hydrate of 5-pyrimidylboronic acid and the free boronic acid for **17c**, with intermolecular O–H....N hydrogen bonds present in the crystals. Suzuki-Miyaura cross-couplings of the pyrimidylboronic acids with heteroaryl halides, yield heteroarylpyrimidines (heteroaryl = thienyl, quinolyl and pyrimidyl) in moderate to good yields.[31, 162]



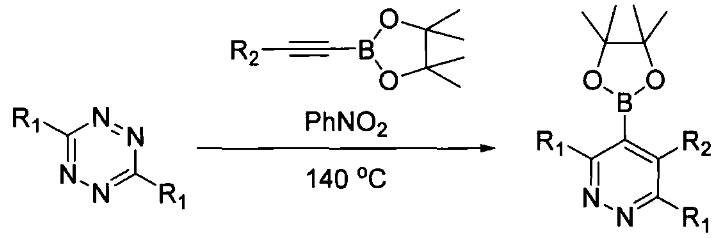
16a X = H
16b X = OMe
16c X = Cl

17a X = H 45% yield
17b X = OMe 61% yield
17c X = Cl 85% yield

Scheme 1.21 Synthesis of 5-pyrimidylboronic acid derivatives by Bryce *et al.*[31, 162]

1.2.3 Pyridazinylboronic Acids

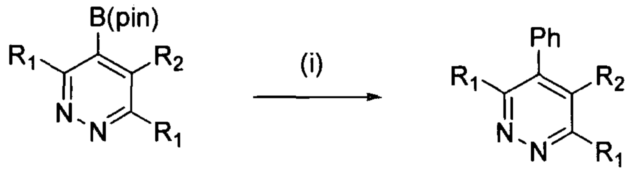
At the outset of this project Harrity *et al.* reported the synthesis of the first pyridazinylboronate species. These were substituted pyridazinylboronic esters obtained in good yields (44-89%) by the inverse electron demand [4+2] cycloaddition of symmetrical and unsymmetrical 3,6-disubstituted-1,2,4,5-tetrazines with an alkynylboronic ester (Scheme 1.22).[165, 166]



R_1 = CO_2Me, DMPY, H
R_2 = Me, *n*-Bu, Ph, TMS, H

Scheme 1.22 Harrity *et al.* preparation of substituted pyridazinylboronic ester.[165]

They were successful in cross-coupling several of the pyridazinylboronic esters with iodobenzene under Suzuki-Miyaura conditions in moderate to good yields (51-72%) (Scheme 1.23). Considering that electron-deficient boronic acids are known to undergo protodeboronation,[167, 168] and the significant steric crowding around the boronate moiety these results are noteworthy.



18a $R_1 = CO_2Me$, $R_2 = Me$
18b $R_1 = DMPY$, $R_2 = Ph$

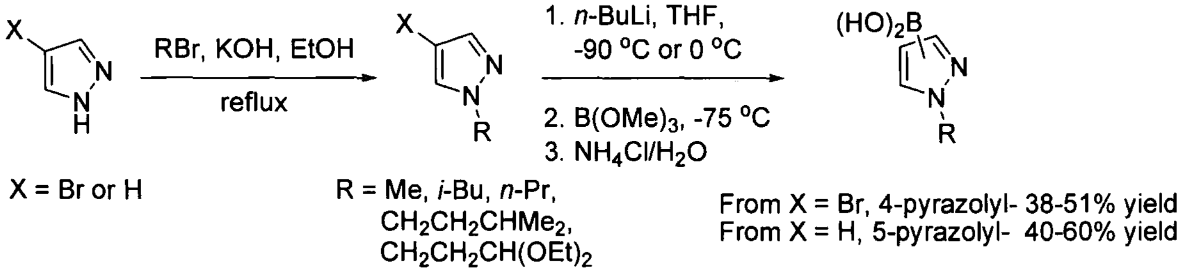
19a $R_1 = CO_2Me$, $R_2 = Me$ 57% yield
19b $R_1 = DMPY$, $R_2 = Ph$ 51% yield

Scheme 1.23 (i) **19a**: PhI, $Pd_2(dba)_3$ (5 mol% PhI), [*t*-$Bu_3PH]BF_4$ (12 mol% PhI), K_3PO_4, MeCN, 50 °C, 90 min. **19b**: PhI, $Pd_2(dba)_3$ (5 mol% PhI), [*t*-$Bu_3PH]BF_4$ (12 mol% PhI), K_3PO_4, MeCN, μW 170 °C, 15 min.[165]

Oxidation of the boronic moiety yielded pyridazin-4(1*H*)-ones in good yields and short reaction times.[165, 169] Prior to our work (Chapter 2) there were no reports of pyridazinylboronic acids prepared via lithiation/boronation techniques.

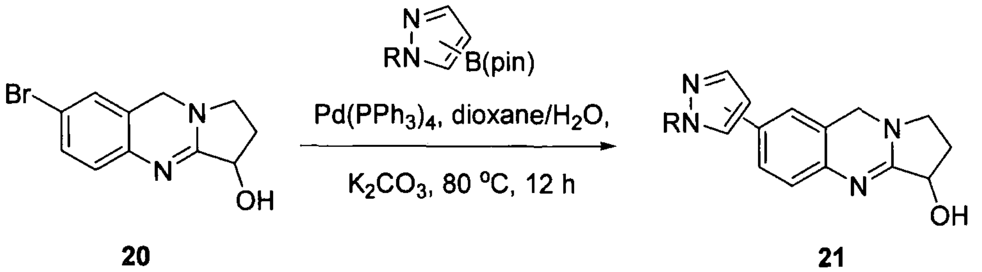
1.2.4 Pyrazolylboronic Acids

Until recently, pyrazolylboronic acids were underdeveloped which is somewhat surprising considering their utility as building blocks for biologically active compounds. A family of 1-alkyl-pyrazolylboronic acids have been prepared in 38-60% yields through lithiation of pyrazole or bromopyrazole derivatives followed by boronation with trimethylborate (Scheme 1.24).[170]



Scheme 1.24 1-Alkylpyrazolylboronic acid derivatives.[170]

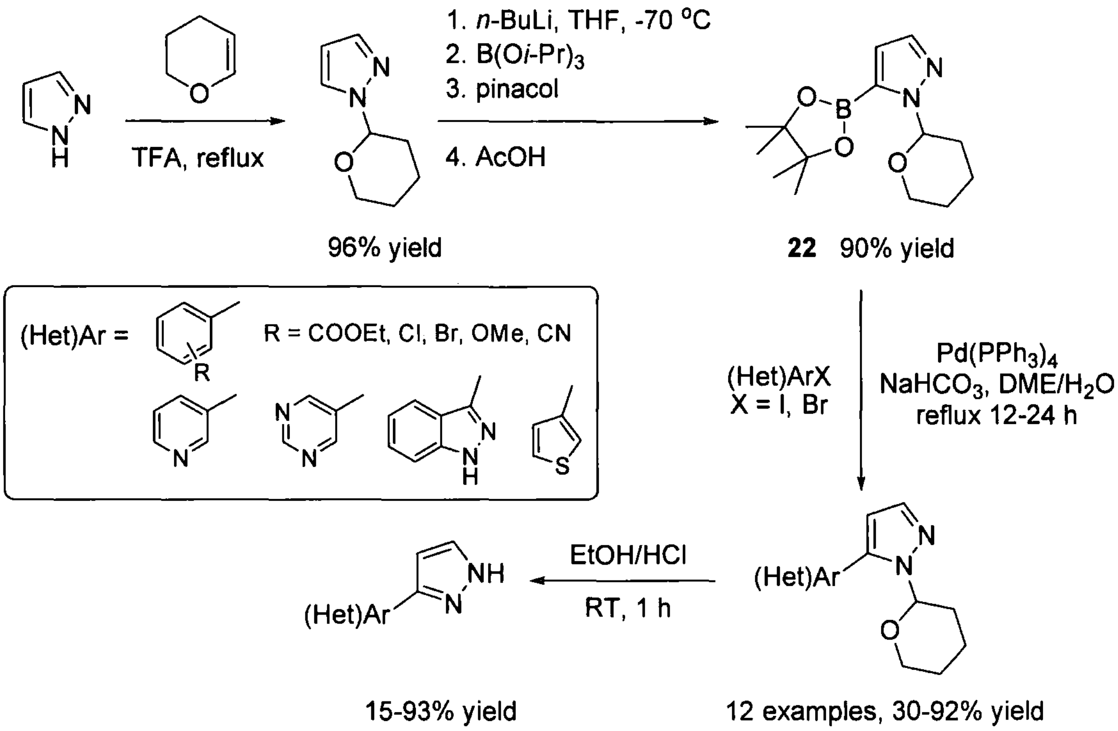
It was observed that the 1-alkyl-4-pyrazolylboronic acids were unstable and easily decomposed in the presence of water yielding 1-alkylpyrazoles. Conversion of the boronic acids into their pinacol ester derivatives increased their stability; no protodeboronation products were observed after 6 months storage of the boronic esters at 5-10 °C.[170] 1-Alkyl-5-pyrazolylboronic acids are less prone to protodeboronation than the 4-pyrazolyl analogues; to prevent decomposition the 5-pyrazolylboronic acids were similarly converted into their pinacol ester derivatives. In further work, introducing functionality at the C-7 position of (±)-vasicine, a quinazoline alkaloid, Suzuki-Miyaura cross-coupling reactions of (±)-7-bromovasicine (**20**) with 1-alkylpyrazolylboronic esters yielded (±)-7-pyrazolylvasicine derivatives (Scheme 1.25).[171]



Scheme 1.25 Suzuki-Miyaura cross-coupling reactions of pyrazolylboronic esters with (±)-7-bromovasicine.[171]

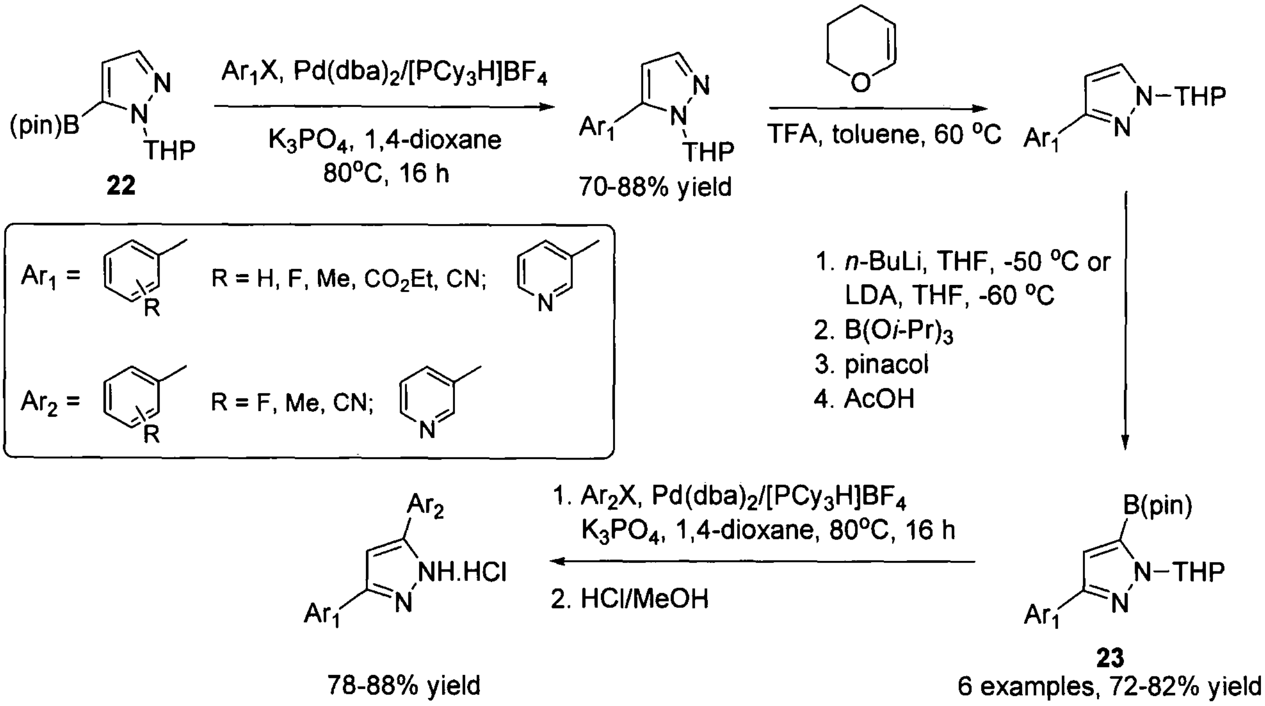
Protection of the pyrazole N–H increased the yields of Suzuki-Miyaura cross-couplings of 4- or 5-pyrazolylboronic acid derivatives.[172] Labile protecting groups such as SEM or THP have been employed in the preparation of *N*-protected 5-pyrazolylboronic acids and esters.[173-176] Following subsequent cross-coupling the SEM or THP protecting groups can be readily removed to yield 3-aryl-1*H*-pyrazole derivatives. Although cross-couplings of 1-SEM-5-pyrazolylboronic ester with iodo- or bromoarenes gave good yields (typically 40-93%), Rault *et al.* found that quite harsh conditions were required (excess *n*-Bu_4NF in refluxing THF, >12 h) to remove the SEM group to yield 3-aryl-1*H*-pyrazoles in 60-95% yield. The SEM group was not removed in the presence of a carboxylate moiety, instead, the carboxylate was converted into the carboxylic acid derivative.[173] THP is suitable for protection of the pyrazole N–H; namely, the presence of an oxygen atom to direct lithiation at C-5, stability to base and lability under acidic conditions. Young *et al.* described the preparation of 1-THP-1*H*-pyrazole, and then used this for the synthesis of 5-pyrazolylboronic acid.[174] Rault *et al.* applied their protocol for the preparation of SEM-protected pyrazolylboronic esters to THP-protected pyrazole and prepared 1-THP-5-pyrazolylboronic ester **22** in 90% yield (Scheme 1.26).[173] **22** was an efficient partner for cross-coupling reactions with a variety of (hetero)aryl halides, giving 1-THP-5-(hetero)aryl-1*H*-pyrazoles. On treatment with ethanolic HCl at room temperature cleavage of the THP resulted in the 3-(hetero)aryl-1*H*-pyrazoles (Scheme 1.26).[173] Pyrazoloisoindolones were prepared through the intramolecular cyclization of

4- and 5-substituted-2-[1*H*-pyrazol-3(5)-yl]benzoic acid derivatives, synthesized from the coupling of **22** with commercially available methyl 2-bromobenzoates.[175]



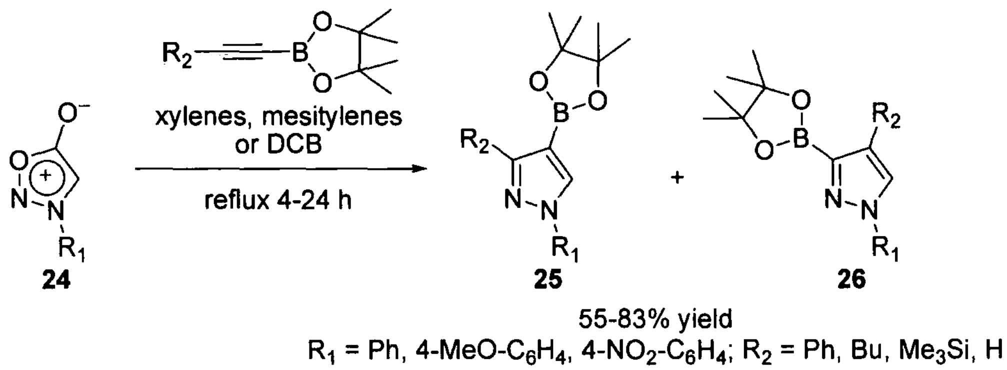
Scheme 1.26 Preparation and Suzuki-Miyaura cross-couplings of 1-THP-5-pyrazolylboronic ester to yield 3-(hetero)aryl-1*H*-pyrazoles.[173, 174]

More recently, substituted pyrazoles have been prepared using *N*-THP as a switchable metal-directing group to enable sequential direct lithation at 3- and 5- positions of the pyrazole ring.[176] Following Suzuki-Miyaura cross-coupling of **22** with substituted bromoarenes, the THP group was equilibrated onto the thermodynamically most stable position (furthest from the aryl substituent), without the need for a deprotection/reprotection sequence (Scheme 1.27).[176] The 1-THP-3-aryl-1*H*-pyrazoles were then regioselectively lithiated at C-5 and the boronic ester derivatives **23** prepared in good yields (72-82%). A further Suzuki-Miyaura cross-coupling yielded 3,5-diarylated pyrazoles, isolated as their HCl salts (Scheme 1.27). Further complexity was introduced into one of the THP-protected diaryl-pyrazoles via bromination at C-4 of the pyrazole ring. Subsequent Suzuki-Miyaura cross-coupling at the 4-bromo site allowed introduction of a third aryl substituent onto the pyrazole ring in good yield.[176]



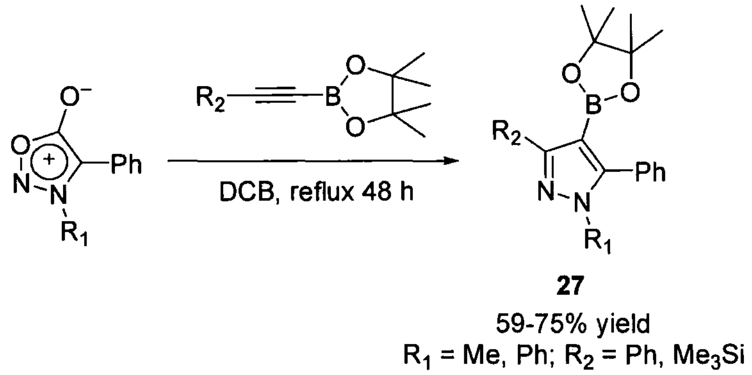
Scheme 1.27 Synthesis of 3,5-diarylated pyrazoles.[176]

Harrity *et al.* expanded their cycloaddition protocol to the synthesis of substituted pyrazolylboronic esters.[177] After investigating the [3+2] cycloadditions of alkynylboronic esters with diazoalkanes and nitrile imines and the cycloaddition/retrocycloaddition of sydnones, it was found that the reaction of alkynylboronic esters with sydnones **24** yielded pyrazolylboronic esters with varying regiocontrol (Scheme 1.28).[177]



Scheme 1.28 Cycloaddition of sydnones in the synthesis of pyrazolylboronic esters.[177]

When employing phenyl alkynylboronate, good selectivity for the 4-pyrazolylboronic esters (**25**) was found for a variety of *N*-aryl sydnones. However, more modest regiocontrol was observed when TMS or butyl alkynylboronates were used (**25**:**26**, ca. 2:1); using terminal alkynylboronate reversed the regioselectivity in favour of **26**. The regioselectivity was found to be essentially uneffected by the sydnone. However, the reaction rate depended on the electronic nature, with more electron-deficient sydnones having faster reaction rates. This is in agreement with other kinetic and computational studies conducted by Harrity *et al.* which suggested that alkynylboronates partake as electron-rich components in cycloadditions.[166] More substituted pyrazolylboronic esters were prepared as single regioisomers **27** (Scheme 1.29),[177] providing access to tetra-substituted pyrazole derivatives. Suzuki-Miyaura cross-coupling reactions of 1-aryl-3-phenyl-1*H*-4-pyrazolylboronic ester with 1-bromo-4-chlorobenzene yielded tri-substituted pyrazole derivatives in good yields (75-88%). Removal of the *N*-(4-methoxybenzene) group from the cross-coupling product occurred by oxidation with ceric ammonium nitrate, revealing the 1*H*-pyrazole derivative in good yield.[177]

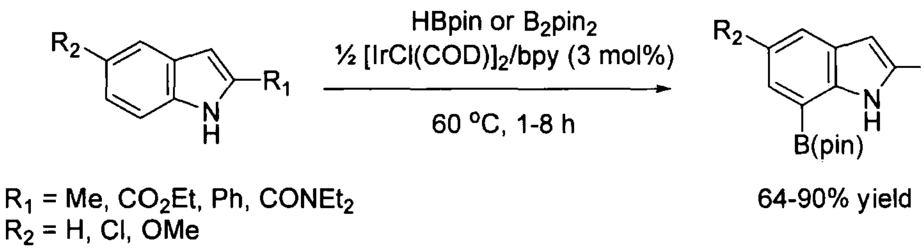


Scheme 1.29 Tri-susbstituted 4-pyrazolylboronic esters.[177]

1.2.5 Other *N*-Heteroaryl Boronic Acids

There are limited reports of other *N*-heteroarylboronic acids. Indolyl- and pyrrolylboronic acid derivatives are quite widespread, most likely due to these motifs being common in natural products and drug candidates. Indole derivatives are extensive in natural products and molecules with biological activity.[178] The synthesis of indolylboronic acids is well established, often requiring protection of the N–H group.[179-186] The choice of protecting group can effect efficiency in the synthesis of indolylboronic acids and their subsequent reactivity. For example, steric hindrance between the *N*-Boc group and the hydrogen at C-7 of *N*-Boc protected 2-indolylboronic acid explained the lower cross-coupling yields, compared to those from the pyrrole analogue.[187] An extensive study into the Suzuki-Miyaura coupling reactions of indoles, using either indolylboronic acids and esters or indole halides concluded that the yields of coupling products depended on the assignment of the partner roles and protection of the indole.[184] Generally, it was found that using bromoindoles with arylboronic acids gave the highest yields. Protecting the indole partner with the strongly electron-withdrawing tosyl group was advantageous.

More recently Ir-catalyzed borylation of substituted indoles has selectively prepared 7-indolylboronic ester derivatives (Scheme 1.30).[185, 186] One-pot Ir-catalyzed boronation–Suzuki-Miyaura reactions were attempted and yielded 7-arylated substituted indoles in good yields,[185] encouraging prospects for synthetic utility. Notably, protection of the indole N–H was not required to give high coupling yields.



Scheme 1.30 Ir-catalyzed borylation of susbstituted indoles.[185]

Since 1991 a few articles have been published on pyrrolylboronic acids. Pyrrole can be lithiated directly or via halogen exchange with initial protection of the nitrogen atom. Schlüter *et al.* reported the first synthesis of 2-pyrrolylboronic acid,[188] and noted that it was susceptible to deboronation and self-coupling under Suzuki-Miyaura reaction conditions. The Suzuki-Miyaura reactions of *N*-phenylsulfonyl protected 2-pyrrolylboronic acid have been reported without evidence of deboronation.[189] Varying yields (39-91%) of the coupling products were obtained; as expected the higher yields were for aryl halides bearing electron-withdrawing groups. Pd-catalyzed borylation of an unprotected iodopyrrole derivative has been reported; successful Suzuki-Miyaura cross-coupling of the resulting 2-pyrrolylboronic ester with a number of dihalo(hetero)arenes yields bis(pyrrol-2-yl)arenes in good yields (69-97%).[190] Ir-catalyzed borylation of pyrrole gave the 2-pyrrolylboronic ester and 2,4-pyrrolyldiboronic ester in 83% and 80% yields, respectively, with high regiocontrol.[89] The regioselectivity could be changed on using *N*-protected pyrrole; 1-methylpyrrole showed preferential reactivity at the 2-position; however, sterically more hindered 1-(triisopropylsilyl)pyrrole provided the 3-boryl isomer selectively.[89]

There are isolated examples of imidazolyl-,[191] oxazolyl-,[192] and triazolopyridyl-[193] boronic acids, although in some cases instability of the C–B bond lessens their synthetic utility.[191, 193] In the case of 4-oxazolylboronic acids Suzuki-Miyaura reactions with less reactive coupling partners (electron-rich or sterically hindered) gave markedly reduced coupling yields and increased levels of homocoupled boronic acid.[192] To our knowledge, thiazolyl- and pyrazinylboronic acids have not been reported.

This review has sought to highlight the recent literature surrounding boronic acids and esters of *N*-heteroaryl motifs, many of which are commonly found in natural products, biologically active compounds or functional compounds for materials chemistry. On the whole *N*-heteroarylboronic acids have shown to be effective reagents in Suzuki-Miyaura cross-coupling reactions with a variety of (hetero)aryl coupling partners, providing efficient routes to functionalized bi(hetero)aryl scaffolds with good functional group compatibility. There are notable deficiencies in the literature for certain species. Given the considerable interest in azabiaryls it is clearly important to explore new *N*-heteroaryl boronic acids, which are thus far unknown or in limited supply.

1.3 Reactions of Boronic Acids

Boronic acids can undergo a number of different synthetic transformations. The most renowned is the Suzuki-Miyaura cross-coupling reaction for the preparation of biaryl systems. Homocoupling of boronic acids is a useful route to symmetrical biaryls. Competitive homocoupling can occur during cross-coupling syntheses, and is often undesired. Some boronic acid derivatives are unstable with respect to protodeboronation. This is often a challenge in Suzuki-Miyaura reactions, when employing electron-deficient boronic acids or those with the boronic acid group adjacent to a heteroatom.

Patent literature holds an extensive number of reports of *N*-heteroarylboronic acids and a recent review by Corbet and Mignani highlighted selected patented cross-coupling reactions, applied in the synthesis of “significant products” (e.g. drugs, materials, optical devices, etc.).[194]

This review will attempt to cover the key aspects of the Suzuki-Miyaura reaction in aromatic bond formation. However, work relevant to the field of heterobiaryl synthesis has been prioritized. Homocoupling and protolytic deboronation are discussed in detail. Other reactions of boronic acids are highlighted.

1.3.1 Suzuki-Miyaura cross-coupling reaction

In recent years, transition metal catalyzed aromatic carbon-carbon bond forming reactions have become of great interest, especially in the development of agrochemicals, pharmaceuticals and other fine chemicals, where the biaryl unit is a recurrent motif. The general reaction is of an aryl halide (or triflate), ArX, an electrophilic source of carbon, with a source of nucleophilic carbon in the form of M–Ar’, where M is an electropositive centre [e.g. Li, MgX, SnR_3, Cu, $B(OR)_2$] bound to an aryl group. The reactions are catalyzed by a transition metal, usually Ni or Pd(0). Boronic acids have a number of advantages over other organometallic reagents; they are generally innocuous, air-, moisture- and temperature-stable, and can tolerate a wide range of functional groups during the cross-coupling reaction.

There are a number of commonly used catalytic methods for biaryl synthesis, for example, Kumada, Negishi, Stille, Suzuki-Miyaura and Hiyama reactions (Figure 1.8).[104, 107] In the mid to late seventies the Kharasch reaction was developed in which an aryl Grignard is reacted with an aryl halide in the presence of an appropriate catalyst. The main disadvantage of the Kharasch reaction is that due to the polar nature of the Grignard reagent, several functional groups, such as aldehydes, ketones, esters or nitro groups are precluded from use in the coupling partners. The reaction of organomagnesium reagents with alkenyl or aryl halides, catalyzed by Ni(II) complexes was reported by Kumada, Tamao and Corriu independently.[195] This transformation is economical, yet is limited to halide partners that do not react with organomagnesium compounds, and again cannot tolerate certain functional groups.

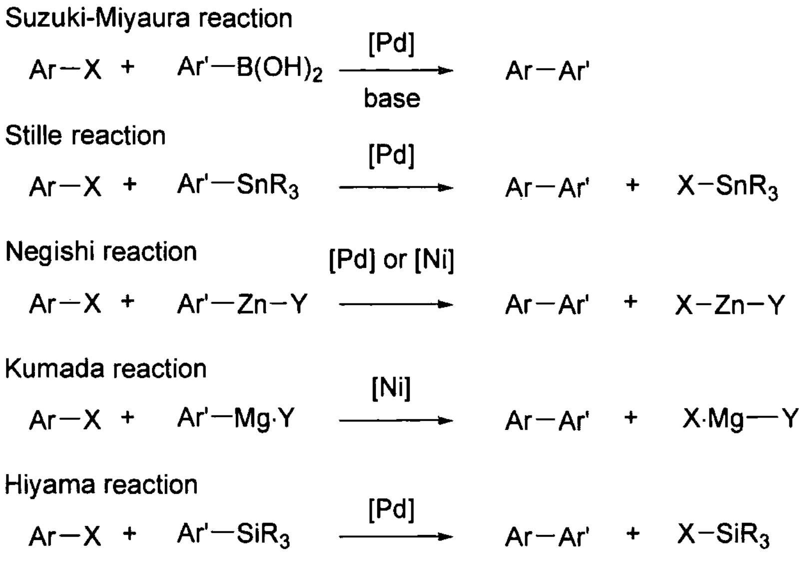


Figure 1.8 Carbon-carbon aromatic bond forming reactions.

The Negishi reaction employs arylzinc reagents with aryl halides or triflates. However, Grignard reagents are required to synthesize the zinc compounds for the starting material of the Negishi reaction. Unlike the Kharasch or Kumada reactions, functional groups are tolerated on the coupling partner. The Negishi reaction has broad scope and is not restricted to the synthesis of biaryls; various aryl, vinyl, benzyl or allyl halides can be coupled to the organozinc reagents in the presence of the nickel or palladium catalyst. There are isolated examples in which aryllithiums have been used in the formation of biaryls; however, they are seldom used due to their highly polar and basic nature. The Stille reaction is a versatile carbon-carbon bond forming reaction using arylstannanes ($ArSnR_3$, R = Me, Bu) and aryl halides or triflates. The reaction tolerates a wide range of functional groups on either coupling partner, and the neutral reaction conditions are an advantage. A disadvantage to the Stille reaction in that the organotin reagents and by-products are toxic. Although arylstannanes are stable and the Stille reaction conditions mild, boronic acids can undergo much of the same chemistry in the Suzuki-Miyaura cross-couplings, without the drawbacks of toxic tin compounds.

The development of the Suzuki-Miyaura reaction in the early 1980s was a major breakthrough. It overcame the problems previously experienced of intolerance towards sensitive functionalities on either coupling partner, the issues of air and moisture sensitivity, and toxicity found with some organometallics. In the Suzuki-Miyaura reaction boronic acids react with aryl halides or triflates, catalyzed by a Pd(0) active species. Suzuki *et al.* first published the cross-coupling of phenylboronic acid with a halobenzene to yield biphenyl in 1981.[196] The versatility of the reaction can be attributed to the commercial availability of the boronic acid reagents and the mild reaction conditions. The aforementioned advantages of organoboronic acids combined with regio- and stereoselectively and tolerance of a wide range of functional groups makes the Suzuki-Miyaura cross-coupling an extremely versatile procedure,[5, 37, 197-199] especially for industrial scale syntheses.[200, 201] The inorganic boron containing by-products are non-toxic and easy to remove from the reaction.

The catalytic cycle for all cross-coupling reactions is generally the same, involving the oxidative addition of the organic halide to the catalyst, usually a palladium(0) species, to form an organopalladium halide; followed by transmetalation with the main-group organometallic or organoboronic acid, resulting in a diorganopalladium complex which undergoes reductive elimination, thereby forming the carbon-carbon bond and regenerating the catalyst.[198] The catalytic cycle for the Suzuki-Miyaura cross-coupling reaction has been well studied, with the mechanisms for each step investigated. More recently DFT studies have predicted the possible intermediates at each stage of the catalytic cycle.[202-204] The catalytic cycle for the Suzuki-Miyaura cross-coupling reaction is represented in Figure 1.9. The active catalytic species is given as $L_2Pd(0)$ (L = phosphine monodentate ligand). There is evidence that the mechanism for Ar–X addition to zerovalent L_2Pd is highly sensitive to the steric bulk and electronic properties of the phosphine ligand, and that some reactions proceed via a monoligated LPd(0) species.[205-209] Reduction of the palladium precursors [usually Pd(II) species, for example $Pd(OAc)_2$ or $Pd(PPh_3)_2Cl_2$] can form anionic Pd(0) complexes i.e. $L_2Pd(0)Cl^-$, $L_2Pd(0)OAc^-$. The rate of oxidative addition can be affected by the anionic ligand.[210-212] Early mechanistic studies by Smith *et al.* noted that water and base were required to activate the boronic acid and that the rate determining step depended on the halide of Ar–X.[213] Arylboronic acids behave as Lewis acids under basic conditions, forming tetrahedral anions through addition of hydroxide (see Section 1.1.1). Therefore, it was suggested that on using water and potassium carbonate the active boronic species is $ArB(OH)_3^-K^+$. The rate-determining step for Ar–Br was found to be the oxidative addition to Pd(0), however, when using Ar–I, transmetalation was the rate-determining step.[213]

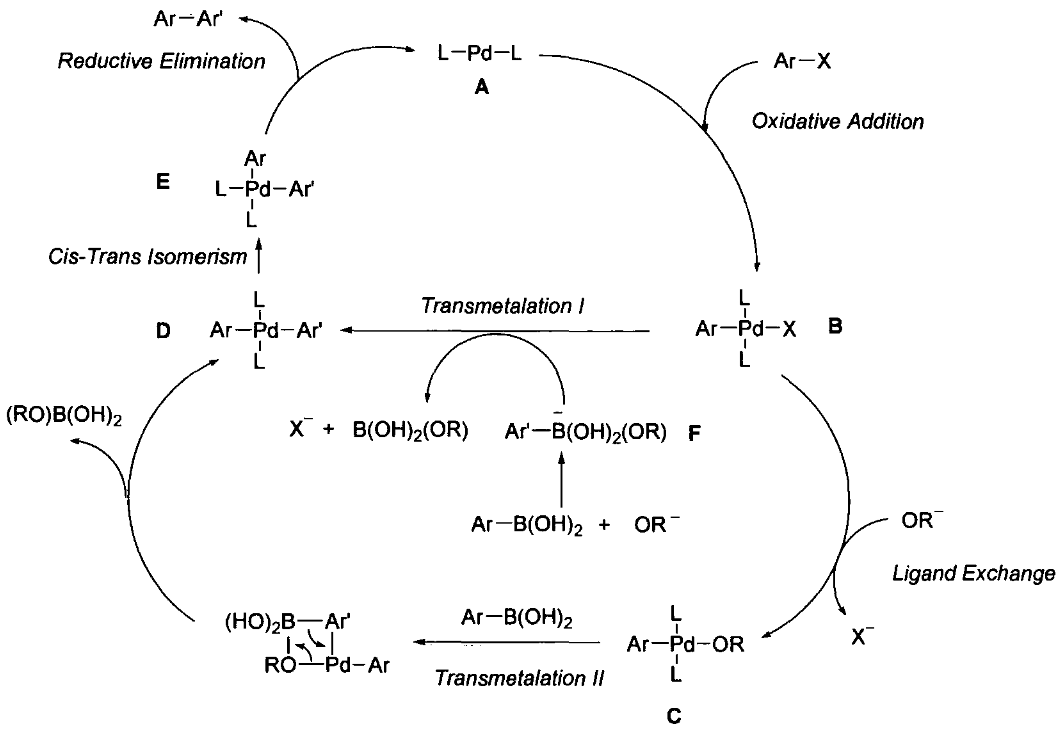
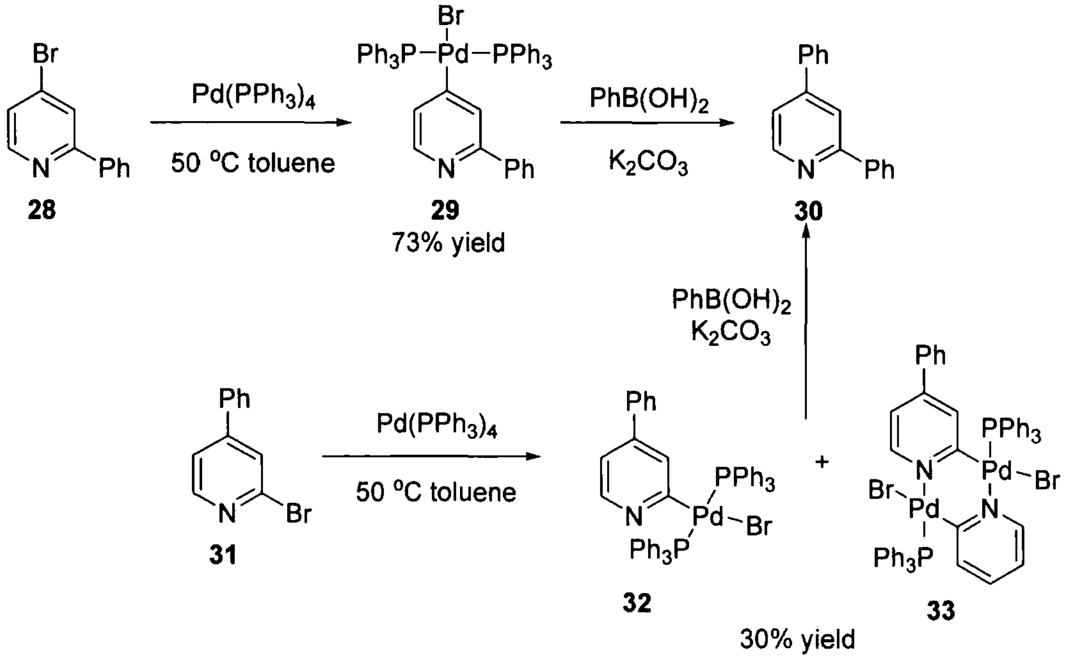


Figure 1.9 Catalytic cycle for the Suzuki-Miyaura cross-coupling reaction.

The catalytic cycle for the Suzuki-Miyaura cross-coupling reaction was initially based on the work by Negishi on organozinc coupling reactions.[213] Aliprantis and Canary confirmed that oxidative addition and transmetalation were occurring during Suzuki-Miyaura reactions. They observed the intermediates **B** and **D** in the reaction mixture of 3-bromopyridine and a phenylboronic acid catalyzed by $Pd(PPh_3)_4$, through electrospray ionization mass spectrometry.[214] In their study on the mechanism of palladium-catalyzed homocoupling of arylboronic acids Adamo *et al.* confirmed the observations made by Aliprantis and Canary, that intermediate **D** formed in the transmetalation step of the Suzuki-Miyaura reaction clearly adopts the *trans* configuration (see Section 1.3.2).[215] Suzuki *et al.* had previously reported the mechanism for the reaction of a 1-alkenylboron compound with a 1-alkenyl halide.[37, 216] Although they had not investigated the mechanism of the coupling between haloarenes and arylboronic acids, from their earlier studies, they believed that intermediate **C** was formed, even for aryl-aryl coupling reactions.[217]

Originally it was established that oxidative addition of the aryl halide to a palladium(0) complex was the rate-determining step in the majority of cases. Initially a *cis*-σ-palladium(II) complex is formed which rapidly isomerizes to the more stable *trans*-σ-palladium(II) intermediate **B**. Sicre and co-workers reacted 4-bromo-2-phenylpyridine and 2-bromo-4-phenylpyridine with 100 mol% of $Pd(PPh_3)_4$ to isolate and characterize the oxidative addition products (Scheme 1.31).[204]



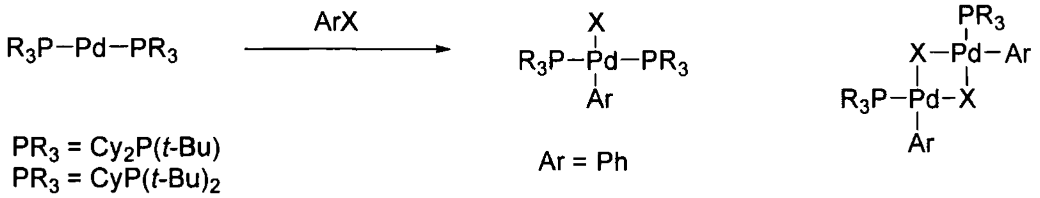
Scheme 1.31 Stepwise Suzuki-Miyaura cross-coupling reaction of bromopyridines **28** and **31**.[204]

For **28**, the *trans* complex **29** was isolated in 73% yield; a singlet in the ^{31}P NMR spectrum (24.13 ppm, CD_2Cl_2) confirmed the *trans* nature of the ligands. With **31** a mixture of mononuclear *trans* complex **32** and dinuclear complex **33** was obtained in 30% yield (the lower yield attributable to difficulties in isolation). The ^{31}P NMR signals appeared at 22.12 and 30.32 ppm, respectively.[204] Based on NMR studies at 50 °C the oxidative addition at position 2 of the pyridine ring was much faster than that at position 4 (10 min vs 10 h). The characterization of mononuclear species **29** and **32** is in agreement with previous work.[205, 214]

The nature of the aryl halide can influence the reactivity in Suzuki-Miyaura cross-coupling, both in terms of the halide and substituents on the aryl ring. In general the rate of reactivity decreases in the order I (> OTf) > Br >> Cl. Electron-withdrawing groups can activate the aryl halide towards oxidative addition by stabilizing the intermediate. The reactions proceed efficiently for aryl and vinyl halides, however, for alkyl halides competing β-hydride elimination can occur from the σ-organopalladium(II) complex resulting from oxidative addition of the alkyl halide. There has been increasing interest into why some ligands can accelerate the reactivity of certain aryl halides. The active catalyst system is intended to activate the carbon-halide bond towards oxidative addition, whilst also enhancing the rate of reductive elimination so that the whole catalytic cycle turns over quickly. There is no universal catalyst system which satisfies the diverse requirements of different Suzuki-Miyaura cross-couplings.[218, 219] A review summarizes the work up to 2006 on the nature of the active species in palladium-catalyzed Suzuki-Miyaura coupling reactions.[220] All forms of palladium were considered (e.g. solid-supported metal complexes, palladium nanoparticles, ligand-free palladium) and the homogeneity or heterogeneity of catalyst systems was evaluated.

The active palladium complex must be in a zero oxidation state for oxidative addition to occur. The most common catalyst is $Pd(PPh_3)_4$ which fulfils the requirements of the complex being electron rich and having ligands which readily dissociate. $Pd_2(dba)_3$ or $Pd(dba)_2$ are also frequently used with the addition of a phosphine ligand, as a method of preparing palladium(0)/phosphine complexes in which the Pd:P ratio can be adjusted to optimize catalytic ability. Other catalyst precursors are palladium(II) complexes such as $Pd(OAc)_2$ or $PdCl_2$/phosphine which are reduced *in situ* to the corresponding palladium(0) complexes. Various phosphine ligands are effective in stabilizing the palladium(0) species; the reactivity of the catalysts towards oxidative addition and transmetalation is dependent on the stoichiometry of phosphine to palladium, and the bulkiness or donating ability of the phosphine ligands.[221, 222] $Pd(PPh_3)_4$ and other Pd(0)/phosphine complexes are in equilibrium with coordinatively unsaturated species. Bulky and highly donating ligands have an accelerating catalytic effect, accredited to their ability to donate electrons to the metal centre and ready dissociation of the ligand to generate a coordinatively unsaturated species. Several ligands for palladium are especially efficient, e.g. trialkylphosphines (e.g. t-Bu_3P, PCy_3), bisphosphines (e.g. dppp, dppf) and N-heterocyclic carbenes. A discussion of different ligands for Suzuki-Miyaura cross-coupling reactions will be considered below.

It has been suggested that the enhanced reactivity of bulky electron-rich phosphines, e.g. t-Bu_3P, may be associated with a change in mechanism of the oxidative addition step, compared to PPh_3 complexes. The presence of a monoligated (t-Bu_3P)Pd species has been implicated in studies on the reductive elimination of Ar–X from palladium(II) species.[223] The mechanism of Ar–X addition to a zerovalent $L_2Pd(0)$ complex has been shown to be highly sensitive to the steric bulk of the phosphine ligand (Scheme 1.32).



34 $PR_3 = Cy_2P(t\text{-}Bu)$
35 $PR_3 = CyP(t\text{-}Bu)_2$
36 R = Cy
37 R = *t*-Bu
38 R = (*o*-tolyl)

39 R = Cy; X = I
40 $R = Cy_2P(t\text{-}Bu)$; X = I
41 $R = Cy_2P(t\text{-}Bu)$; X = Br

42 R = (*o*-tolyl); X = Br
43 $R = CyP(t\text{-}Bu)_2$; X = I
44 R = *t*-Bu; X = I

Scheme 1.32 The observed intermediates resulting from oxidative addition of ArX to Pd(0) with different phosphine ligands.[205]

The addition of PhI to complex **36** in THF occurs very rapidly to give the *trans* biphosphine complex **39**. The reaction of PhOTf is much slower and through electrochemical techniques was shown to follow an associative mechanism. ^1H NMR spectroscopy established an associative mechanism for the reaction of PhI or PhBr with the air-sensitive **34**. The reaction of PhI with **34** was ca. 10^3 times slower than with complex **36**. Product **40** showed characteristic virtual coupling in the *t*-Bu signal associated with *trans*-L_2M. X-Ray crystallography of complex **41** confirmed the structure.[205] In contrast, the addition of ArBr to **38** involves dissociation of one phosphine ligand preceding addition of the electrophile to produce the halide-bridged dimer **42**.[224] On treating **35** with PhBr generation of a monophosphine palladium complex and an equivalent of free phosphine was observed. On addition of PhI to **35**, the ^{31}P NMR spectrum of the resultant **43** indicated a temperature-dependent equilibrium. In a parallel experiment after 4 days at RT the mixture of complex **37** and PhI showed one equivalent of free phosphine and one equivalent of dimer **44**.[205] Overall, less bulky ligands $Cy_2P(t\text{-}Bu)$ and PCy_3 initiate oxidative addition through the initial formation of *trans*-$[Pd(X)L_2Ar]$, whilst bulkier ligands $CyP(t\text{-}Bu)_2$ and $t\text{-}Bu_3P$ generate dimeric $[(Pd(X)LR)_2]$ species from monoligand reactants. The effectiveness of these two ligands in palladium-catalyzed cross-coupling reactions is associated with a propensity to form monophosphine complexes, either as or en route to the true catalytic species.[205] QPhos-tol is a sterically hindered ferrocenyl monodentate phosphine ligand. The oxidative addition of chloro-, bromo- and iodoarenes to the bisphosphine palladium(0) complex $Pd(QPhos\text{-}tol)_2$ occurs via three different mechanisms (Figure

1.10), producing [Pd(QPhos-tol)(Ar)(X)].[206] Addition of PhI occurs by the associative displacement of a phosphine (Path A), PhBr by rate-limiting dissociation of a phosphine (Path B) and PhCl by a reversible dissociation of a phosphine, followed by rate-limiting oxidative addition (Path C). Iodo and bromoarenes yield monomeric complexes **II**, whereas the chloride complex **III** is dimeric in the solid state and solution phase.[206]

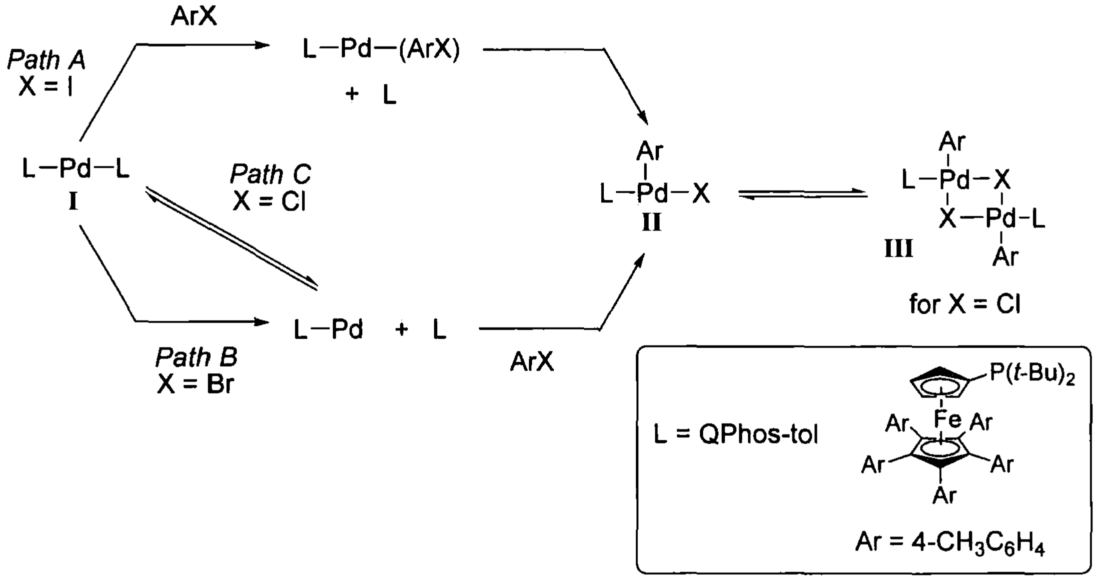


Figure 1.10 Distinct mechanisms for the oxidative addtion of ArX to Pd(QPhos-tol)$_2$.[206]

Theoretical studies into the role of monoligated palladium complexes in cross-coupling reactions have attempted to evaluate why in some cases LPd(0) can out-perform $L_2Pd(0)$ in oxidative addition.[207-209] DFT calculations indicated that monophosphine PR_3Pd was catalytically more active than bisphosphine $(PR_3)_2Pd$ for oxidative addition.[207] Among the different PR_3 ligands (R = Me, Et, *i*-Pr, *t*-Bu, Ph) the free-energy barriers to oxidative addition did not change significantly. In practice, *t*-Bu_3P was the only catalytically active ligand towards aryl chlorides.[207, 221] Through calculations it was proposed that the dissociation energy of *t*-Bu_3P from (*t*-$Bu_3P)_2Pd$ is significantly lower than that of $(PR_3)_2Pd$ (where R = Me, Et, *i*-Pr, Ph). Hence, the difference in dissociation energies from L_2Pd to LPd and L, between various PR_3 ligands could account for their different reactivities in oxidative addition.[207] DFT studies have also demonstrated how the electronic properties of different aryl halides affect the reaction pathways for their oxidative addition to L_2Pd complexes.[208] The results showed that electron-donating groups or electron-withdrawing groups on aryl bromides and aryl chlorides do not quantitatively alter the preferred dissociative LPd pathway. Consequently, bulky or hemilabile ligands promote the oxidative addition of ArCl or ArBr, because such ligands promote the monoligated pathway. For aryl iodides, electron-withdrawing groups favour the L_2Pd pathway, whereas electron-donating groups further enhance the LPd dissociative mechanism for oxidative addition.[208]

To summarize, there is evidence for both L_2Pd and LPd active species. Generally it is thought that biphosphine complexes $L_2Pd(0)$ occur when using chelating bidentate phosphine ligands or monodentate trialkylphosphines with small or moderate steric bulk. It has been shown that biphosphine palladium complexes undergo associative oxidative addition of aryl halides to prepare monoligated [LPd(Ar)(X)] complexes. Monophosphine complexes LPd(0) are a result of (in some cases rate-limiting) dissociation of a phosphine ligand prior to oxidative addition of the aryl halide. This usually occurs for bulky trialkylphosphines. The stability of either mono- or biphosphine palladium(0) complexes is enhanced by electron rich alkylphosphines, through donation of electrons to the palladium.

The role of the base in Suzuki-Miyaura cross-coupling reactions has been widely investigated. It is clear that addition of a base has an accelerating effect on the cross-coupling of boronic acids, which is quite different from the related reactions of other organometallics. The mechanism of transmetalation involves base, and there are two general opinions: (i) the base is required to quaternize the boron prior to transmetalation (Figure 1.9, transmetalation I), or (ii) ligand exchange between Ar–Pd(II)–X and a base (OR^-), with subsequent transmetalation to an alkoxopalladium(II) complex **C** (Figure 1.9, transmetalation II). Owing to the low nucleophilicity of organic groups in organoboron compounds, the transmetalation between organopalladium(II) halides and organoboronic acids does not readily occur. Quaternization of the boron with a negatively charged base increases the nucleophilicity of the organic groups on the boron forming an 'ate' complex. It is known that 'ate' complexes such as $[ArB(R)(OR)_2]Li$ readily couple with organic electrophiles in the presence of a palladium or nickel catalyst.[225] Similarly the hydroxyboronate anion $[ArB(OH)_3^-]$, which exists in equilibrium with the free organoboronic acid, could effect the transmetalation. It has been assumed that the addition of base activates the boronic acid by donating an electron pair into the vacant p orbital on the boron, increasing the nucleophilicity of the adjacent carbon and its reactivity towards attack at the palladium(II) centre.[225]

The choice of base plays an important role; smooth transmetalation is critical for such metalloid compounds with low nucleophilicity. Transmetalation to Ar–Pd–X follows the reactivity order Cl > Br > I, i.e. the opposite to oxidative addition. It is highly dependent on the counter cation of the base used as MX is produced in the process. The effectiveness of the base can be related to its affinity for MX formation. The reaction can be fast for counter ions which have a high stability constant for halide ions, additionally, increasing the base strength ($OH^- > MPO_4^- > MCO_3^- > HCO_3^-$) can increase the concentration of hydroxyboronate anion $[Ar'B(OH)_3]M$ present.[225, 226] For sterically bulky arylboronic acids when using NaOH or Na_2CO_3 no coupling reaction was observed; the strong base KO*t*-Bu was essential for good coupling yields and short reaction times.[227] The counter cation may also affect the solubility of $[Ar'B(OH)_3]M$ in organic solvents. Fluoride ions have a high affinity for boron and are suitable for forming a boronate anion, $ArB(OH)_2F^-$ capable of effecting boron to palladium transmetalation. Fluoride salts (Et_4NF, KF, CsF) allow the cross-coupling reactions of aryl- and vinylboronic acids in essentially non-basic conditions, rapidly and in good yields.[228]

Transmetalation to Ar–Pd–OR, where OR = alkoxo-, hydroxo-, acetoxo- or acetylacetoxo-, generated *in situ* by ligand exchange, may involve the rate-determining coordination of OR^- ligand to the boron atom via the transition state (Figure 1.9 **C**→**D**). The transfer of an activated organic group from boron to palladium then takes place as a result of complex formation. The high basicity of the Pd–OR species and high oxophilicity of the boron centre are both attributed to the high reactivity of the alkoxopalladium(II) complexes. Ar–Pd–OR can undergo transmetalation with boronic acids without base being present.[225] Ag_2O has been used to promote Suzuki-Miyaura reactions.[229] The reaction of Ag_2O with *trans*-$Pd(C_6F_5)I(PEt_3)_2$ generated *trans*-$Pd(C_6F_5)(OH)(PEt_3)_2$ with concomitant generation of AgI.[230] It was suggested that Ag_2O promotes replacement of the iodo ligand with a hydroxyl group of H_2O, to prepare the hydroxopalladium(II) intermediate of transmetalation.

DFT studies suggested that base binds initially to organoboronic acids rather than palladium species.[203] From DFT calculations it was concluded that the transmetalation reaction takes place via a multistep mechanism, where the boronic acid is activated by an external base and attacks the palladium centre as an organoboronate anion.[204] From the comparison of relative energies, DFT studies have shown that transmetalation can proceed smoothly with a palladium species with one or two phosphine ligands, and either the *cis* or *trans* arrangement.[202]

It is not obvious in many cross-coupling reactions of organoboron compounds in alkaline solution, which of the two possible transmetalation processes is predominant. Results depend on the organoboron reagents, bases and organic electrophiles. Matos and Sonderquist proposed that depending on the base affinity for the organoborane species it can either replace the halide on the palladium complex or bind to the organoborane species.[231] Electron-deficient heteroarylboronic acids undergo transmetalation at a relatively slow rate, consequently these reagents often rapidly decompose by a protodeboronation pathway (see Section 1.3.3).

Formation of the *trans*-diarylpalladium(II) intermediate (Figure 1.9, intermediate **D**) has been confirmed. The *cis*-configuration is required for reductive elimination to occur, forming the biaryl and regenerating the active palladium(0) complex. The *trans*-diarylpalladium(II) complex undergoes a form of *cis-trans* isomerism to enable elimination of the biaryl unit from intermediate **E**. Diaryl complexes are the most reactive in undergoing reductive elimination [diaryl- > (alkyl)aryl- > dipropyl- > dimethylpalladium(II)] suggesting π-orbital participation during bond formation. DFT studies into the mechanism of the isomerization of **D** to **E**: via (i) a four-coordinate tetrahedral transition state, (ii) a three-coordinate rearrangement with initial loss of phosphine ligand then re-addition or (iii) a five-coordinate rearrangement, through coordination of a phosphine ligand or solvent molecule,[202] have found that the energy barrier to isomerism was fairly high. It is feasible that the reaction takes place through the necessary loss of one of the phosphine ligands, after which the energy barrier for complex isomerism becomes quite low.[202]

Aryl bromides and iodides are often used in the Suzuki-Miyaura reaction. Milder reaction conditions have been developed for the cross-coupling reactions of aryl triflates; due to their base sensitive and thermally labile nature, more efficient catalysts such as $PdCl_2(dppf)$, and weakly basic, non-aqueous conditions have been employed. The addition of an alkali metal halide promotes the cross-coupling of aryl triflates and also prevents premature catalyst decomposition. Aryl chlorides require a much higher energy for insertion of Pd(0) into the C–Cl bond in the oxidative addition step, resulting in their decreased reactivity.[232] Nevertheless, aryl chlorides are highly desirable coupling partners as they are readily available and inexpensive. An electron withdrawing group on the aryl chloride is advantageous; those at the *ortho* or *para* position being more activating.[232] The reactivity difference between electron-poor and electron-rich aryl chlorides in cross-coupling reactions has been attributed to the higher ligating ability of the electron-deficient aryl chlorides. Electron-poor aryl chlorides allow for more d → π* back-donation from the palladium in the pre-reactive complex (Figure 1.11).[209] Suzuki-Miyaura reactions of fluoroarenes have been reported.[233, 234] Aryl fluorides are not often employed in cross-coupling reactions due to the strength of the C–F bond. Successful cross-coupling reactions with phenylboronic acid derivatives occurred on fluoroarenes activated by an adjacent nitro substituent[233] and perfluorinated arenes *para* to a CF_3 or C_6F_5 substituent.[234]

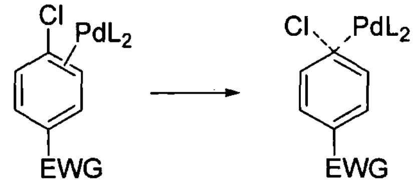


Figure 1.11 Activation of aryl chlorides towards oxidative addition.

New catalytic systems have been developed for the cross-coupling of unreactive chloroarenes. Fu *et al.* investigated the effects of adding a variety of phosphines to the Suzuki-Miyaura cross-coupling of aryl chlorides and arylboronic acids.[221] They established that *t*-Bu_3P was the most effective phosphine, and that the optimal phosphine:Pd ratio is between 1 and 1.5. The steric bulk and electron-richness of *t*-Bu_3P is critical for the unprecedented reactivity, with only PCy_3 being nearly as effective. A further study demonstrated that this catalytic system gave excellent yields of coupling products at room temperature, when aryl bromides and iodides were used.[222] A mechanistic study of the $Pd_2(dba)_3$/*t*-Bu_3P catalyzed cross-couplings showed that a monophosphine complex was the active species. Fu *et al.* concluded that they had a methodology for which electronically and sterically diverse reactants could be cross-coupled, without the need for substrate specific optimization of the reaction conditions.[222] Recently Fu *et al.* have reported the cross-coupling of aryl- and heteroaryl chlorides with a wide range of heterocyclic boronic acids in good to excellent yields.[172] This wide-ranging study includes the coupling of unprotected amine- and hydroxy-substituted pyridines, and utilizes the following reaction parameters; Pd_2dba_3, PCy_3, K_3PO_4, dioxane/water. Air-stable phosphonium salts (e.g. [t-Bu_3PH]BF_4, [Cy_3PH]BF_4) serve as direct replacements for the corresponding phosphines in Suzuki-Miyaura and other palladium-catalyzed cross-coupling reactions.[235]

Buchwald *et al.* have reported a number of different *ortho*-phosphine-substituted biphenyl ligands (Figure 1.12).[236-241] Early work found that ligands **45** and **46** were suitable for Suzuki-Miyaura cross-couplings of aryl bromides and chlorides at room temperature and with low catalyst loadings.[236] Ligand **49** was effective for the coupling of *ortho*-substituted aryl halides with *ortho*-substituted arylboronic acids.[236] Mechanistic studies indicated that increasing the steric bulk on the non-phosphine containing phenyl ring was important for catalyst activity and lifetime. Thus ligand **47** SPhos was developed, and found to be incredibly efficient for the cross-coupling of unactivated aryl chlorides, hindered substrates and heteroaryl halides.[237] Ligand **47** confers unprecedented activity, allowing room temperature cross-couplings of aryl chlorides with low catalyst loadings (0.25-0.5 mol% Pd) to be performed. Cross-coupling reactions of 3-pyridylboronic acid were reported with a range of aryl halides in isolated yields of 81-96%.[238] Incorporation of a water-solubilizing sulfonate group onto **47** gave **51**[239] which proved to be a highly active catalyst system for the Suzuki-Miyaura cross-coupling of a variety of aryl and heteroaryl bromides and chlorides in aqueous media.

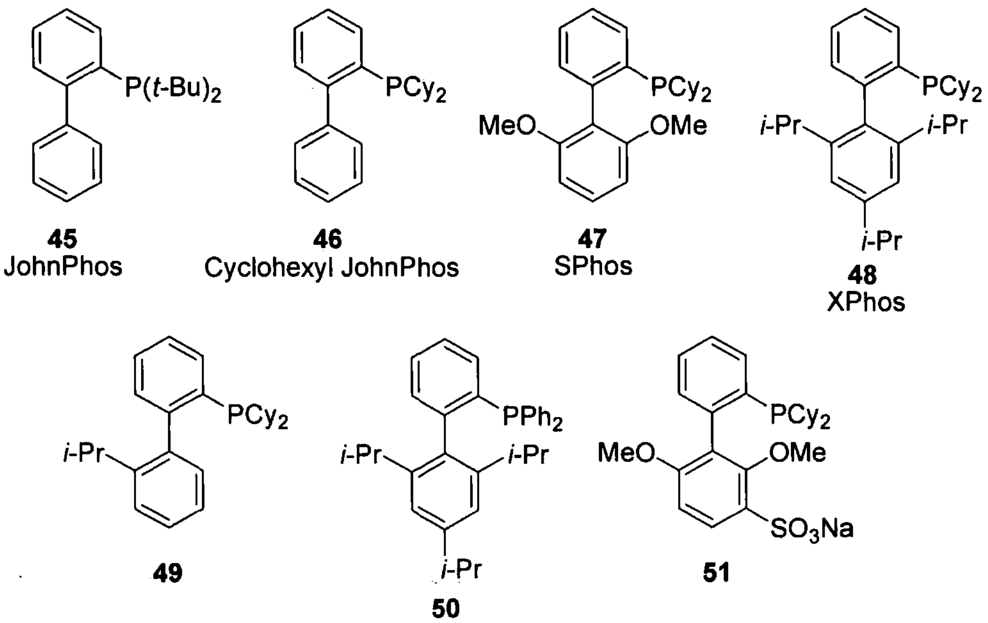


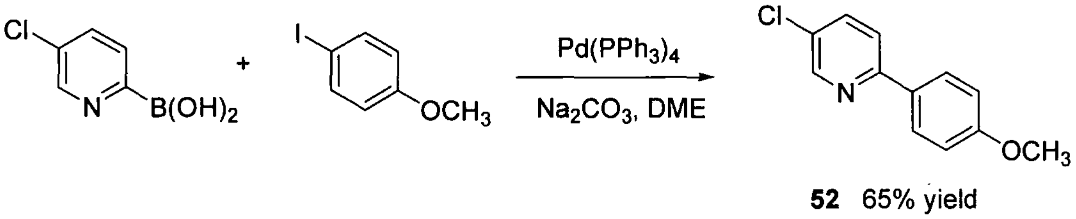
Figure 1.12 Buchwald ligands for Suzuki-Miyaura cross-coupling reactions.[236, 238-241]

Of all the Buchwald ligands **47** SPhos and **48** XPhos show universal activity and efficiency in the Suzuki-Miyaura cross-couplings of aryl and heteroaryl bromides and chlorides. Recently, ligand **48** and to some extent **47**, have shown to provide highly stable and active catalysts for the Suzuki-Miyuara cross-coupling of pyridyl-, pyrrolyl-, indolyl-, thienyl- and furylboronic acids with substituted heteroaryl bromides and chlorides.[240, 241]

Other reports of specific catalyst and ligand systems for Suzuki-Miyuara cross-couplings of aryl chlorides are plentiful. For example, under aerobic conditions,[242] new air-stable catalysts $PdCl_2[R_2P(p\text{-}R'\text{-}Ph)]_2$ (where R = *t*-Bu, Cy and R' = CF_3, H, OMe, NMe_2),[243, 244] ferrocenyl monophosphine ligands,[245, 246] a bowl-shaped phosphine ligand (the depth of the bowl dramatically effecting the catalytic ability)[247] and a PEG(300)-$PdCl_2$ system which promotes the cross-coupling of aryl chlorides with various phenylboronic acids have been studied.[248]

New ligands, catalyst systems, and reaction conditions for Suzuki-Miyaura cross-coupling reactions of (hetero)aryl halides and (hetero)arylboronic acids is a vast topic. However, phosphine based catalyst systems show broad activity and efficiency and are widely commercially available. Microwave conditions have become extensively popular, as have aqueous conditions, in attempts to make the reaction 'greener'.

The applications of heterobiaryl systems in many areas of contemporary chemistry have inspired the use of heteroaryl halides or triflates as the coupling partners in the Suzuki-Miyaura reaction, thus generating a versatile route to bi(hetero)aryls. The activating effect of some nitrogen-containing heterocycles assists the cross-coupling reaction. The electron deficient nature of pyridines aids the oxidative addition of the Pd(0) species. The potential for the synthesis of a wide variety of novel heterobiaryls is fuelled by the Suzuki-Miyaura cross-coupling reaction tolerating many functional groups on either coupling partner. Indeed, Bryce *et al.* have reported the cross-coupling of halo- and alkoxy-substituted pyridylboronic acids with a variety of substituted electron-rich and electron-deficient heteroaryl coupling partners.[30, 139, 140, 144, 150] Rault *et al.* have coupled novel halopyridylboronic acids efficiently with sterically hindered, electron-rich and electron-deficient halides. Under standard Suzuki-Miyaura-type conditions, no products resulting from coupling of the halide substitutent on the pyridylboronic acid with another halopyridylboronic acid unit were observed.[135-138] The coupling of a halopyridylboronic acid with itself should not occur under the basic Suzuki-Miyaura conditions as the boronic acid would most likely be a boronate anion, exerting a deactivating effect on the halogen. After the cross-coupling has taken place the remaining halogen should be available for further coupling. Nevertheless, it is interesting to note that this is not generally the case for Rault *et al.*, who report 47-78% yields of the singly coupled products of the halopyridylboronic acids with an array of substituted halogenated aryls. This may be due to their use of more reactive halo-coupling partners than are obtained from the coupling reaction. Scheme 1.33 shows the absence of a secondary coupling of **52**, due to the inherent lower reactivity of chloro-coupling partners. The iodinated species is very reactive towards oxidative addition and is preferred in the cross-coupling with the 5-chloro-2-pyridylboronic acid, resulting in the singly-coupled product.[138]



Scheme 1.33 Example of the Suzuki-Miyaura cross-couplings undertaken by Rault *et al.*[138]

Traditionally it was thought that compounds bearing labile protons were unsuitable coupling partners; however, couplings have now been reported in the presence of primary amines,[150, 240, 249] carboxylic acids[250] and alcohols.[251] The work done in our laboratory established Suzuki-Miyaura cross-couplings in the presence of an amine group on the halide coupling partner, with no need for protection/deprotection steps in the synthesis.[150] An extensive library of (hetero)arylpyridines was reported from the cross-coupling of 2-methoxy-5- and 2-methoxy-3-pyridylboronic acid with amino-substituted bromo/chloro-(hetero)aryl coupling partners in good yields (bromo-coupling partners 69-84%, chloro-coupling partners 40-69%). The presence of the primary amine group on the highly substituted pyridine coupling products offers scope for further synthetic transformations, as well as applications in supramolecular and coordination chemistry.

Polyhalogenated heterocycles can be regioselectively cross-coupled.[252-256] In cases where the halogens are different the selectivity is related to the relative bond dissociation energies, and the reactivity of the halide towards oxidative addition (following the trend I > Br > Cl > F). Sicre *et al.* highlighted that the oxidative addition of 2-bromo-4-phenylpyridine to $Pd(PPh_3)_4$ occurred much faster than that of 4-bromo-2-phenylpyridine.[204] This reactivity was exploited for the cross-coupling of 2,4-dibromopyridine with a number of phenylboronic acids to prepare 2-aryl-4-bromopyridine derivatives regioselectively.[257] The origin of regioselectivity in palladium-catalyzed cross-coupling reactions of heterocycles bearing multiple identical halogens is a combination of both the strength of the carbon-halogen bond (which is related to the bond dissociation energy) and the LUMO of the heterocycle (which is related to frontier molecular orbital interactions).[253, 258] Handy and Zhang have developed a guide for predicting the most likely oxidative addition reaction, and hence the reactive site, in polyhaloheteroaromatics, based upon the chemical shift values of the parent non-halogenated heteroaromatic species.[259] NMR chemical shift values are very sensitive to the electronic environment. The initial site for coupling in polyhaloheteroaromatics is always the more electron-deficient centre, i.e. the carbon bearing the proton with the more downfield chemical shift. For example, 2,5-dibromopyridine undergoes selective Suzuki-Miyaura cross-coupling at C-2; the chemical shift of the parent pyridine is δ 8.59 and 7.38 ppm for the C-2 and C-5 protons, respectively; the predictive and experimental data are consistent (Figure 1.13).[259] With mixed halogenated heteroaromatics the ^1H NMR chemical shift prediction method can be overcome by the intrinsic reactivities of the different halogens; 2-bromo-4-iodopyridine reacts selectivly at the iodo C-4 position, even though in the parent pyridine the C-2 proton has the higher chemical shift value.

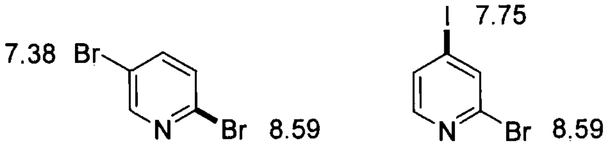


Figure 1.13 ^1H NMR chemical shift method for prediciting regioselectivity in the coupling of polyhaloheteroaromatics.[259] The ^1H NMR chemical shift values of the parent pyridine are given and the site of first coupling identified by the bold bond.

1.3.2 Homocoupling of boronic acids

Self-coupling or homocoupling of the boronic acid can occur as a side reaction when the cross-coupling reaction is very slow or as a result of oxygen being present. This homocoupling has been developed into a useful synthetic method for the preparation of symmetrical biaryls.[260-263] Proposed mechanisms for the homocoupling of boronic acids are somewhat ambiguous. Nevertheless, there is agreement that the presence of oxygen accelerates the reaction,[260] and the reaction can proceed via a catalytic reaction between Pd(II) and a boronic acid.[262, 264] Moreno-Mañas *et al.* established that addition of a base was unnecessary to promote homocoupling and that oxygen accelerated the reaction. They proposed that oxidative addition/transmetalation of a boronic acid entity onto a Pd species occurs twice, followed by reductive elimination to yield the biaryl product (Figure 1.14). Elimination of a tetrahydroxydiborane [$(HO)_2B\text{-}B(OH)_2$] was considered to be thermodynamically improbable. An oxidation step was assumed to release the boron as a boric acid derivative. It was concluded that the oxidative self-coupling of arylboronic acids induced by Pd(II) involved acid-base reactions between the Pd(II) species and arylboronic acid, followed by 1,2-rearrangements of aryl groups to the electron-deficient positive palladium species, (Figure 1.14).[260, 265]

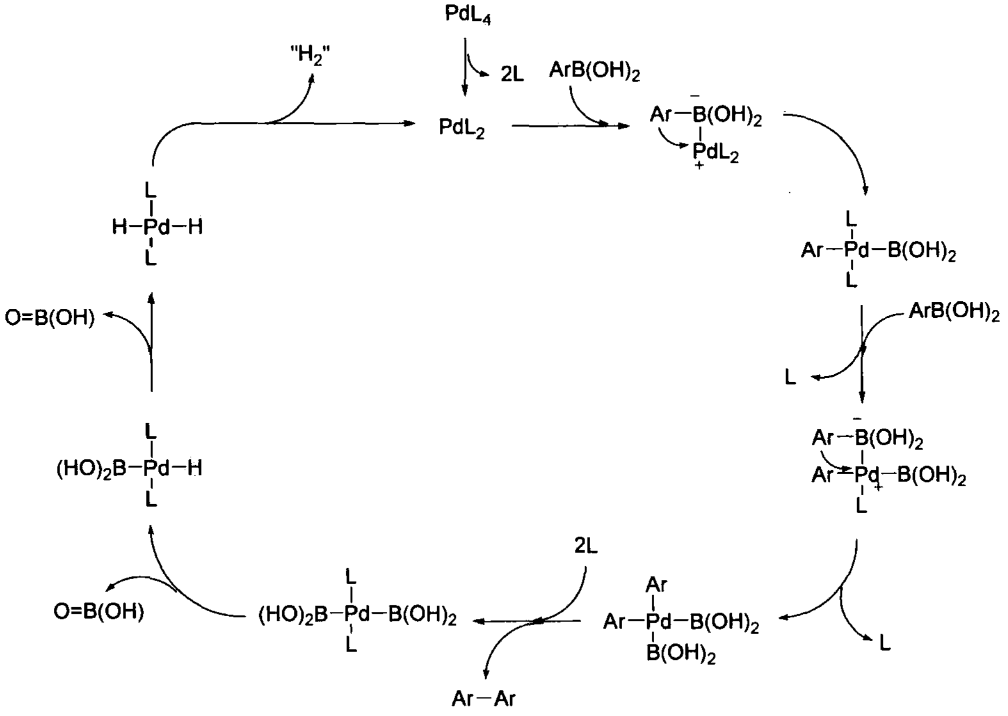


Figure 1.14 Mechanism for oxidative homocoupling of boronic acids proposed by Moreno-Mañas *et al.*[260, 265]

Yoshida *et al.* acknowledged that molecular oxygen was indispensable for the homocoupling of arylboronic esters and proposed the catalytic cycle in Figure 1.15, as it is known that oxygen reacts readily with Pd(0) to afford Pd(II) peroxide.[266] Initially a three-membered Pd(II) peroxide complex (intermediate **A**) is formed by oxidative cyclization of molecular oxygen with the Pd(0) complex. Subsequently a double transmetalation occurs yielding a diorganopalladium species and boron peroxide, then reductive elimination of the homocoupling product follows with regeneration of the Pd(0) species.

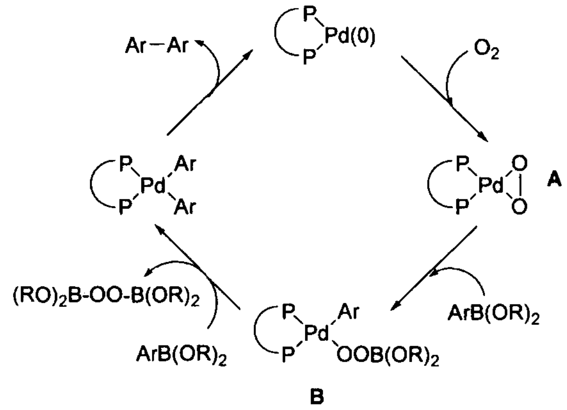


Figure 1.15 Catalytic cycle for the homocoupling of boronic acids proposed by Yoshida *et al.*[266]

A further kinetic and mechanistic study of boronic acid oxidative homocoupling by Adamo *et al.* is consistent with the involvement of a palladium peroxo complex (Figure 1.16).[215] They prepared the (η^2-O_2)-Pd(PPh_3)$_2$ species and used this directly as the catalyst for the homocoupling of arylboronic acids. Intermediate *trans*-**C** and *trans*-**D** were characterized after long reaction times; the *cis*-intermediates were not observed under the reaction conditions. However, reductive elimination must occur from the *cis*-**D** intermediate. In some cases intermediate *trans*-**D** was not observed, suggesting that reductive elimination from *trans*-**D** via *cis*-**D** was fast. It could also be possible that *cis*-**C**/*trans*-**C** isomerization is slower than transmetalation, and consequently transmetalation of *cis*-**C** generates *cis*-**D** which is prone to reductive elimination. Adamo and co-workers do not rule out that intermediate **B** could be trapped by ArB(OH)$_2$, as proposed by Yoshida *et al.*, yielding a boron peroxide species and intermediate *cis*-**D**.

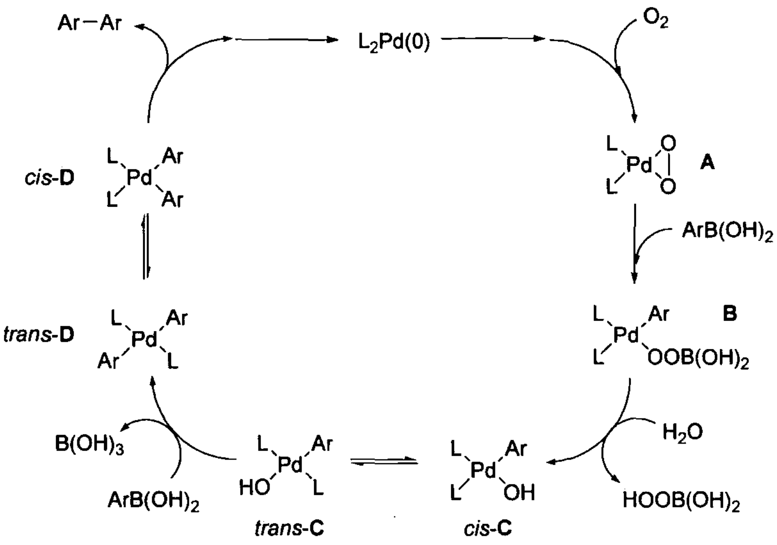


Figure 1.16 Mechanism of oxidative boronic acid homocoupling proposed by Adamo *et al.*, based on the observed **A**, *trans*-**C** and *trans*-**D** complexes.[215]

Adamo *et al.* concluded that since the oxidative homocoupling and Suzuki-Miyaura cross-coupling reactions have the common intermediate $L_2Pd(0)$, the palladium-catalyzed homocoupling reaction may compete with the Suzuki-Miyuara cross-coupling if the reaction is not conducted under an inert atmosphere.[215] However, Miller *et al.* proposed that the oxygen present in the system is not reacting with palladium to create a palladium peroxo complex. Instead, oxygen is acting as an oxidant, increasing the levels of Pd(II) in the system, which promotes the homocoupling.[264] It has been reported that $Pd(OAc)_2$ can catalyze the room temperature homocoupling of arylboronic acids in air without ligands present.[262] Miller *et al.* were also using $Pd(OAc)_2$, palladium on carbon or palladium black as the heterogeneous catalyst in Suzuki-Miyaura cross-coupling reactions. They proposed that the addition of a mild oxidant would minimize the concentration of free Pd(II) in the reaction without causing significant reduction of the product resulting from oxidative addition of the aryl halide to Pd(0). Consequently, the homocoupling would be suppressed whilst still maintaining the cross-coupling reaction (Figure 1.17)

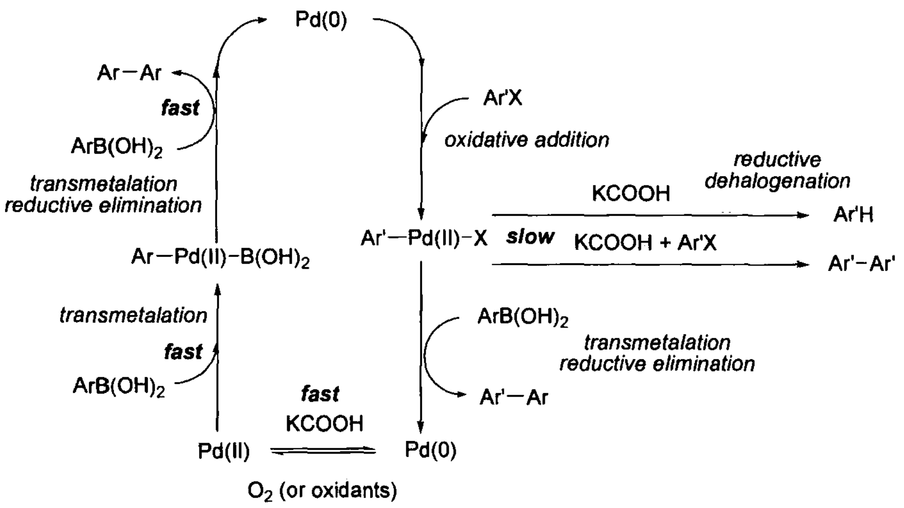
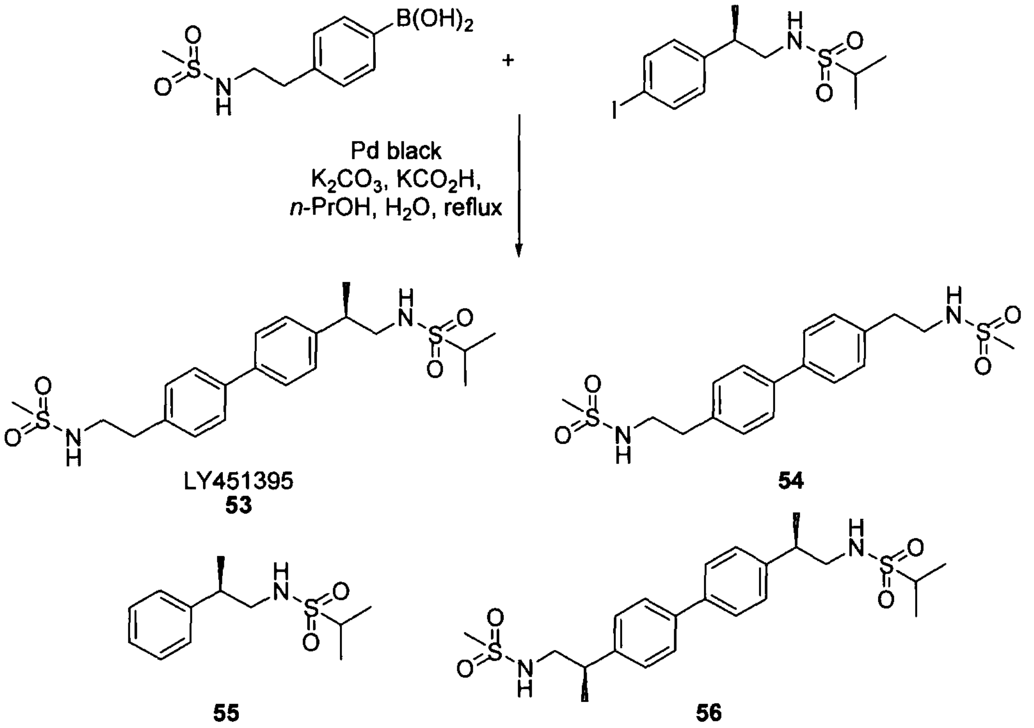


Figure 1.17 Catalytic cycle of Pd(II)-catalyzed homocoupling and Pd(0)-catalyzed Suzuki-Miyaura cross-coupling.[264]

In their system, Miller *et al.* found addition of potassium formate reduced levels of homocoupled dimer **54** from ca. 4% to ca. 0.07% (Scheme 1.34). A slight excess of aryl halide was used during the reaction as, not surprisingly, **55** was observed as a result of reductive dehalogenation in ca. 10% (HPLC analysis), and chiral dimer **56** was observed in ca. 0.5% yield.



Scheme 1.34 Preparation of LY451395, with addition of potassium formate to suppress homocoupling.[264]

1.3.3 Hydrolytic Protodeboronation of boronic acids

Arylboronic acids can be susceptible to protodeboronation. This problem is accentuated for heteroarylboronic acids which are electron-deficient[167, 168] or when the boronic moiety is α to a heteroatom.[74] Protodeboronation can affect the stability of the boronic acid under ambient storage conditions, and the reactivity of boronic acids in Suzuki-Miyaura reactions. Examples of heteroarylboronic acids or esters, reported as being unstable towards protodeboronation, have been noted previously, viz. pyridyl-,[65] 2-pyridyl-,[117, 131] pyrazolyl-,[170] 5-tetrazolyl-,[267] 2-oxazolyl-,[268] triazolopyridyl-.[193]

Early work reported protodeboronation of phenylboronic acid as a result of pyrolysis; refluxing phenylboronic acid in water[269] or heating directly at 200 °C for 25 h[270] yielded benzene and boric acid. NaOH, HCl and Zn^{2+} or Cd^{2+} ions were found to catalyze the pyrolysis in water.[269] Kuivila and co-workers investigated the mechanism of protodeboronation promoted by acids,[271-273] bases[34] and metal ions.[274] After investigating the kinetics of protodeboronation and the effects of different acids, bases, metal ions, concentrations and substituents on the phenylboronic acids they inferred three possible mechanisms (Figure 1.18).

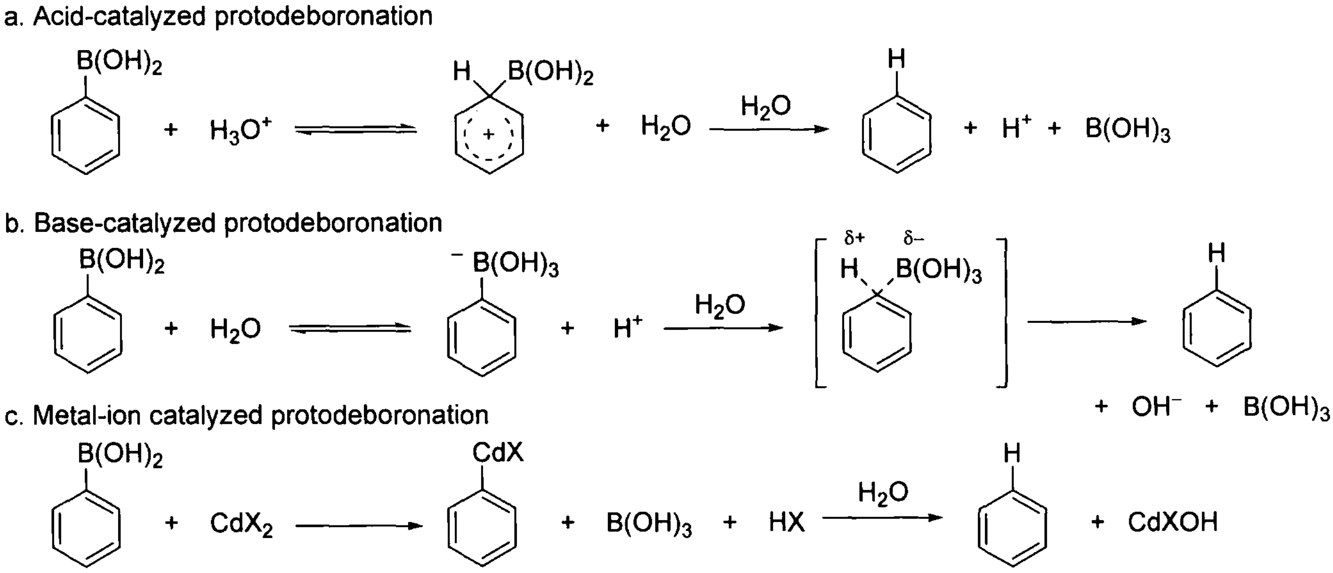


Figure 1.18 Proposed mechanisms for protodeboronation of boronic acids.[34, 272, 274]

Protodeboronation promoted by acid was found to be subject to general acid catalysis and to proceed via an A-S_E2 mechanism.[271-273, 275] Proton transfer to the arene ring is the rate-determining step, followed by rapid ionic cleavage of the B–C bond. Stronger acid resulted in more rapid protodeboronation. Base-promoted protodeboronation of phenylboronic acids was not subject to general base catalysis; consequently, the mechanism was not an S_E1 type.[34] The rate-determining step was the proton transfer to the boronate anion, with little disturbance of the π-electron system in the transition state. An increase in the concentration of base leads only to an increase in the rate of protodeboronation when this promotes an increase in the concentration of boronate anion, through an increase in pH. The mechanism for the metal-ion catalyzed protodeboronation is thought to be approaching an S^*_E2 reaction, with localization of π-electrons occurring in the passage to the transition state. Initially Cd^{2+} ions were found to promote protodeboronation: a number of other metal ions also have the same effect, e.g. Ni^{2+}, Mg^{2+}, Co^{2+}, Zn^{2+}, Pb^{2+}, Cu^{2+}.[274]

Fisher and Havinga reported the photoinduced deboronations of 3- and 4-pyridylboronic acids **4** and **6**.[117] Although **4** and **6** are thermally stable, on UV irradiation they were "split into pyridine and boric acid", in neutral and slightly basic solution. It was reasoned that photoinduced protodeboronation represented an electrophilic aromatic substitution, considering photoprotodeboronation to be analogous to photodecarboxylation of pyridine carboxylic acids. An S_E1 mechanism was suggested on the following grounds. Calculations and UV spectra of aqueous solutions of **4** and **6** show that the neutral forms have the zwitterion structure (a "pyridinium-boronate" structure); pyridine and pyridinium ions undergo S_E1 substitutions (e.g. decarboxylation) and the leaving group in the protodeboronation, boric acid, is very weakly electrophilic like the leaving group in decarboxylation, CO_2. Although the photoreactions of 3- and 4-pyridylboronic acids are considered as S_E1-protodeboronations of the pyridinium boronate form, it is now regarded that boronic acids are not comparable to carboxylic acids in terms of Brønsted acidity (see section 1.1.1). Therefore, it is unlikely that pyridylboronic acids exist as the pyridinium boronate zwitterion and the mechanism for the UV irradiation promoted protodeboronation may not be S_E1 type.

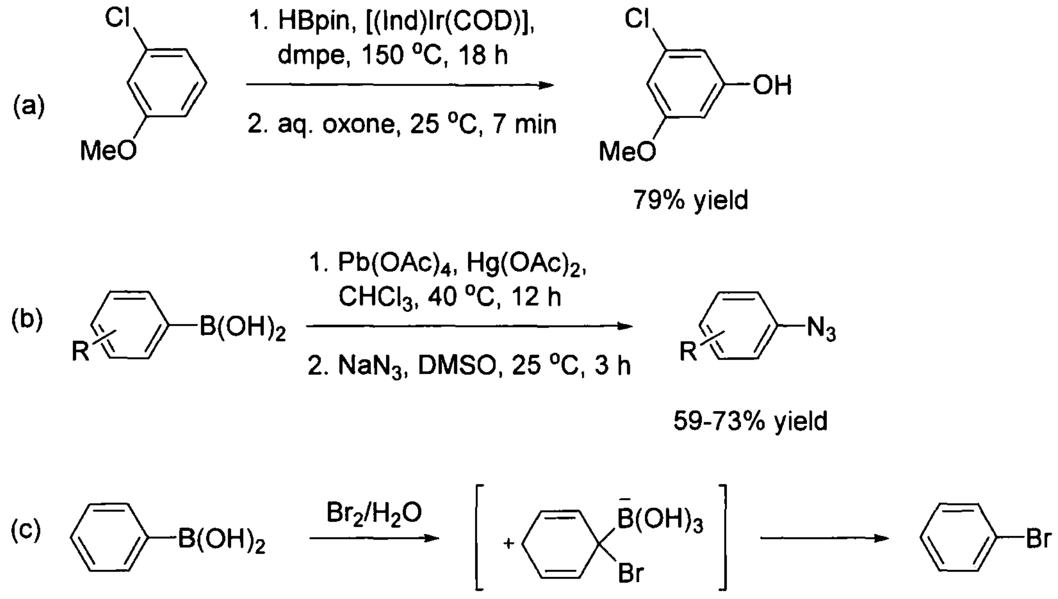
Protodeboronation is partially base promoted and is a common competitive reaction when conducting a Suzuki-Miyaura cross-coupling with a boronic acid derivative which may be prone to C–B bond cleavage. Often alternative catalysts or reaction conditions are used in attempts to suppress protodeboronation. For example, Payack *et al.* found dicyclohexylamine to be an excellent base for the Suzuki-Miyaura cross-coupling of a 2-boronic acid derivative of indole, at the same time preventing protodeboronation previously found when using the usual basic aqueous conditions.[276]

Selective protodeboronation has been a useful tool in the synthesis of 4-methyl-2-thiopheneboronic acid.[277] Regioselective lithiation of 3-methylthiophene followed by treatment with triisopropylborate and hydrolysis provides the regioisomers 4-methyl-2-thiopheneboronic acid and 2-methyl-3-thiopheneboronic acid in a 92:8 ratio. Treatment of the mixture with concentrated acid selectively protodeboronated the undesired regioisomer (2-methyl-3-thiopheneboronic acid), providing only the desired 4-methyl-2-thiopheneboronic acid after crystallization.

1.3.4 Other reactions of boronic acids

In addition to the Suzuki-Miyaura C–C bond forming reaction, arylboronic acids can take part in a number of other reactions, including addition reactions, the replacement of boron and C–heteroatom bond formation.

The boronic acid moiety can be converted into several different substituents. Treatment of arylboronic acids and esters with alkaline hydrogen peroxide yields the corresponding phenols[269, 278] although this is not a popular or economical approach for preparing phenols. Conversely, a one-pot C–H activation–borylation–oxidation procedure successfully prepared a number of *meta*-substituted phenols bearing *ortho*- and *para*- directing groups, that would be difficult to prepare by other means [Scheme 1.35, (a)].[279] Aryl azides can be accessed indirectly from arylboronic acids, via an *in situ* generated aryl lead intermediate [Scheme 1.35, (b)].[280] Halodeboronation of arylboronic acids occurs by action of aqueous chlorine or bromine and aqueous iodine containing KI [Scheme 1.35, (c)].[269] *N*-Bromo- and *N*-iodosuccinimides also convert arylboronic acids into their corresponding aryl halides.[281] This is not generally used as often aryl halides are the precursors to boronic acids, and there are more economical methods for preparing aryl halides.



Scheme 1.35 (a) One-pot C–H activation–borylation–oxidation procedure.[279] (b) Aryl azide via an *in situ* aryl lead.[280] (c) Halogenation of a boronic acid in aqueous bromine.[269]

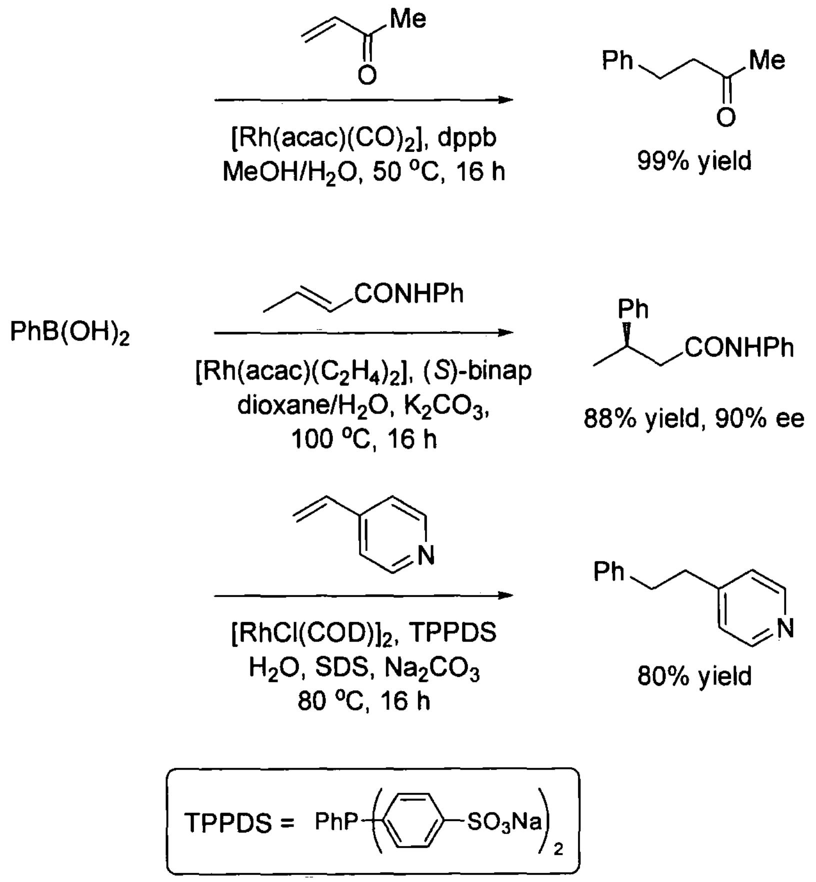
More usefully, arylboronic acids undergo copper-catalyzed C–O, C–N and C–S coupling reactions[282] with phenols,[283, 284] amines, amides and imines,[284, 285] *N*-heteroaromatics[286] and thiols,[287] to give the corresponding diaryl ethers, arylamines or *N*-arylheterocycles and thioethers (Scheme 1.36). The reaction is mediated by copper(II) acetate and a mechanism was suggested based on transmetalation of the boronic acid with copper(II) acetate followed by ligand exchange with the nucleophilic substrate and reductive elimination to give the coupling product.[284] *N*-Heteroarylboronic acids have been applied to the C–N cross-coupling between two heteroarenes;[64] an alternative to the routine copper- or palladium-catalyzed *N*-arylation of heteroarenes with aryl halides.[288, 289]

$$\mathrm{Ar{-}B(OH)_2} + \mathrm{R{-}XH} \xrightarrow[\text{DCM, RT}]{\mathrm{Cu(OAc)_2,\ Et_3N}} \mathrm{Ar{-}X{-}R}$$

R = aryl, heteroaryl, alkenyl
X = O, NR', S

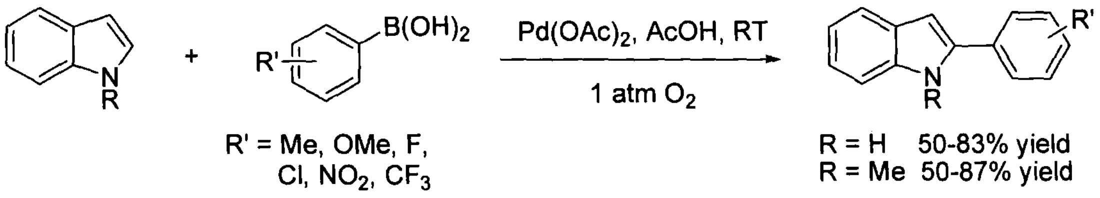
Scheme 1.36 General reaction for the copper-catalyzed coupling of boronic acids with nucleophilic oxygen-, nitrogen- and sulfur-containing compounds.

Rhodium-catalyzed addition of arylboronic acids to carbonyl compounds and electron-deficient alkenes has emerged as a useful system for the formation of such carbon-carbon bonds. Functional group protection is not required, and the reaction shows good chemoselectivity. Initially Miyaura *et al.* reported the conjugate addition of arylboronic acids to α,β-unsaturated ketones, to give good yields of saturated ketones.[290] The reaction was catalyzed by a complex generated from [Rh(acac)$(CO)_2$] and dppb. Asymmetric conjugate addition of arylboronic acids has been established, using chiral bisphosphines, such as (*S*)-binap, and an Rh precursor.[291] The rhodium-catalyzed conjugate addition of arylboronic acids is tolerant of a wide variety of substrates, including, α,β-unsaturated esters,[292, 293] amides,[294] vinyl-substituted *N*-heteroarenes[295] and aldehydes[296-298] (Scheme 1.37). More recently palladium-catalyzed additions of aryl- and heteroarylboronic acids to aldehydes has been reported.[299] There are other reports of palladium-catalyzed systems for the efficient addition of arylboronic acids,[300-302] in some cases higher reactivity is observed, in comparison to using the rhodium catalysts.



Scheme 1.37 Examples of rhodium-catalyzed conjugate addition of phenylboronic acid to alkenes.[290, 294, 295]

The palladium-catalyzed direct arylation of electron-rich (hetero)arenes with arylboronic acids has been reported.[303] This is an efficient procedure for formation of aryl carbon-carbon bonds, without the requirement of aryl halides, like the traditional Suzuki-Miyaura coupling. Previous work on the cross-couplings of C–H bonds with boronic acids was generally low yielding and required directing groups.[304] The palladium(II) catalyzed electrophilic aromatic C–H functionalization with arylboronic acids is promoted by acidic conditions. Homocoupling of arylboronic acids is known to proceed readily in the presence of Pd(II)[262, 264] (see Section 1.3.2). Consequently, it was noted that fast electrophilic attack of the aromatic ring was required, compared to transmetalation of the arylboronic acid onto the Pd(II) species. It was considered that as base is required for transmetalation of boronic acids under Suzuki-Miyaura conditions, and acidic conditions were being applied for direct arylation, this may reduce the rate of transmetalation and thus suppress homocoupling of the boronic acid. Unfortunately, high levels of homocoupled boronic acid were initially observed during the direct arylation reactions. Optimization of the reaction conditions found $Pd(OAc)_2$ to be the best catalyst and O_2 the most efficient terminal oxidant, with $Cu(OAc)_2$ as a cooxidant. A variety of electron-rich arenes and heteroarenes (including pyrroles, indoles, benzothiophene and benzofuran) were successful partners for the Pd(II)-catalyzed direct coupling with phenylboronic acid. Electron-rich substituents were beneficial on the arylboronic acids to promote the coupling reaction, and chloro- and fluoro-substituted boronic acids were tolerated (Scheme 1.38).[303] The proposed mechanism involves electrophilic activation of the aromatic C–H bond by Pd(II), followed by transmetalation of the aryl-palladium species with arylboronic acid and reductive elimination producing the desired product. Pd(0) is reoxidized by O_2 or a Cu(II) species to complete the catalytic cycle.[303]



Scheme 1.38 Palladium(II)-catalyzed direct arylation of indole and *N*-methylindole with various arylboronic acids.[303]

Recently, a copper-mediated C–H bond arylation of arenes with arylboronic acids was reported; multiple C–H bond arylation of nitrogen heterocycles was successful, highlighting the potential for further development and applications.[305] Although still in its infancy, the direct arylation of arenes with arylboronic acids offers scope for biaryl preparation. Clearly, oxidative coupling where neither substrate needs pre-activatation is an elegant and economical procedure for biaryl synthesis, as noted earlier (see Section 1.2). Nevertheless, much effort is needed to enhance the scope of these C–H activated direct arylation reactions, especially for electron-deficient heteroaryl derivatives. For now, the Suzuki-Miyaura cross-coupling still remains superior on account of its widespread utility for a variety of aryl and heteroaryl derivatives.

1.4 Conclusions

The prevalence of *N*-heteroarylboronic acids has escalated in the last few decades. Syntheses of a wide variety of substituted *N*-heteroarylboronic acids and esters have been reported, employing lithiation/boronation techniques, transition metal catalyzed protocols or cycloaddition reactions. Furthermore, *N*-heteroarylboronic acids are increasingly available commercially. Their cross-coupling reactions with a range of halide and triflate coupling partners, under non-toxic and comparatively mild conditions, yield novel (hetero)biaryl systems which otherwise are challenging to synthesize.

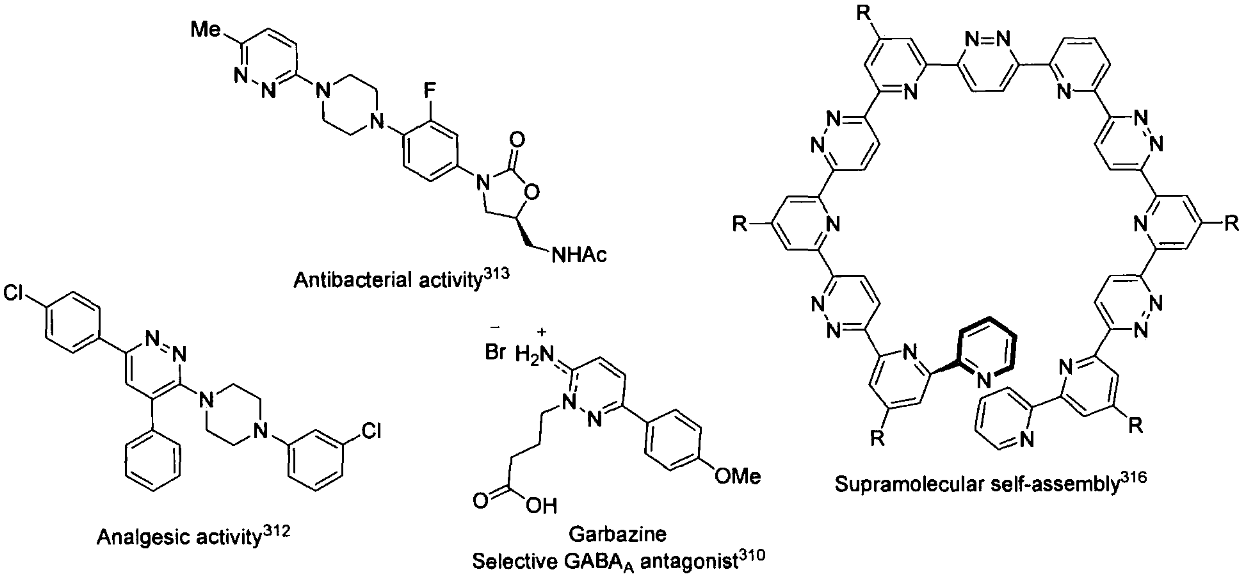
The Suzuki-Miyaura reaction has proved to be a highly useful and versatile synthetic tool for the modern organic chemist; nevertheless many challenges remain. The versatility and scope of application for this essential carbon-carbon bond forming reaction has resulted in unabated research in this area of chemistry. Each aspect of the palladium catalyzed cross-coupling appears to be under review in efforts to improve and broaden the application of the reaction. There is scope for development in, e.g. microwave conditions, lower catalyst loadings, novel palladium catalysts and catalyst precursors, and the industrial, large-scale application of the Suzuki-Miyaura reaction.

The application of *N*-heteroarylboronic acids in other reactions has also gained significance. The conjugate addition of arylboronic acids to alkenes and derivatives shows increasing potential. The use of arylboronic acids in the palladium-catalyzed direct arylation of electron-rich (hetero)arenes is an exciting procedure, where further investigation may demonstrate more universal applicability. Although direct cross-coupling reactions of unactivated arenes is an emerging area of chemistry, aryl- and heteroarylboronic acids and their subsequent Suzuki-Miyaura cross-coupling reactions, currently exhibit widespread utility and functional group tolerance, making them valuable reagents for the synthetic organic chemist.

CHAPTER 2 – PYRIDAZINYLBORONIC ACIDS AND ESTERS

2.1 Introduction

The pyridazine nucleus is a versatile pharmacophore in many biologically active molecules. It is considered a bioisotere of benzene and other heterocycles, whilst having the attractive physicochemical property of high water solubility as a result of its hydrogen bond acceptor abilities.[306] The discovery of the antidepressant aminopyridazine Minaprene[307, 308] stimulated research into pyridazine derivatives, highlighting their potential as bioactive compounds for several different therapeutic areas.[309] For example, aryl-/heteroarylpyridazine derivatives have been used in the treatment of dementia, and other selective $GABA_A$ antagonists.[310, 311] Piperazinyl-pyridazine derivatives show analgesic activity involving both opiate and serotonergic pathways[312] and exhibit antibacterial in vivo potency against *staphylococcus aureus*, comparable to that of the morpholine derivative linezolid.[313] Trisubstituted pyridazine derivatives have been identified as p38 inhibitors, presenting a useful therapeutic strategy as an anti-inflammatory agent.[314] The pyridazine motif is also found in several areas of materials chemistry, e.g. in the preparation of self-assembled supramolecular molecular architectures[315, 316] and π-conjugated organic materials with desirable electronic properties.[317]



Antibacterial activity[313]

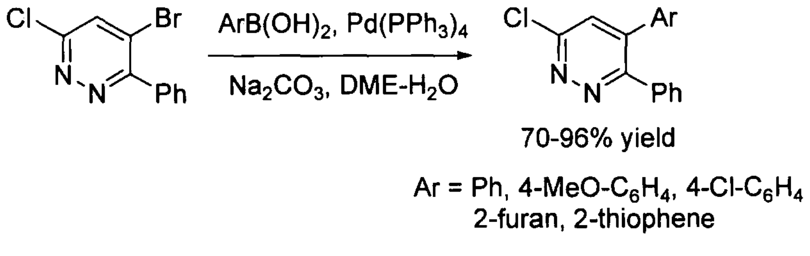
Analgesic activity[312]

Garbazine
Selective $GABA_A$ antagonist[310]

Supramolecular self-assembly[316]

Figure 2.1 Examples of pyridazine motifs in medicinal and materials chemistry.

The methods for preparing substituted pyridazine derivatives are limited which can be attributed to the electron-deficient nature of the pyridazine nucleus making classical methods for direct C-functionalization less available. The standard protocol for pyridazine ring formation is through the addition of hydrazine to a 1,4-dicarbonyl compound, with functionality set up prior to ring closure. There are numerous reports of organometallic pyridazine derivatives,[42, 44] mainly organolithium species, which are reacted with a variety of electrophiles.[318-322] The pyridazinyl-lithium intermediates are generally stable only at low temperatures (< –50 °C), whereas the analogous pyridazinyl Grignard reagents have greater stability (> 0 °C) and comparable reactivity with electrophiles.[323] Pyridazinylzincate species have been prepared;[324, 325] their in situ Negishi cross-couplings yield heteroarylpyridazine derivatives in good yields.[324] As previously noted (see section 1.2.3), reports of pyridazinylboronic acids and their cross-couplings are limited, although halopyridazines are widely employed in palladium-catalyzed cross-coupling reactions.[310, 326-331] Chloropyridazines are readily available, consequently their Suzuki-Miyaura reactions are well reported.[307, 310, 328, 332] Chloroarenes are regarded as being more difficult to cross-couple as a result of their lower reactivity towards oxidative addition, compared to bromo- or iodoarenes. However, the decreased π-electron density of the pyridazine ring promotes the reactivity of chloropyridazines. 3-Amino-6-halopyridazine provided Suzuki-Miyaura coupling products with a range of arylboronic acids in comparable yields whether the iodo- or chloro- derivative was employed.[310] Regioselective Suzuki-Miyaura cross-couplings of di-halopyridazines are reported, in these cases reaction occurs at the other halogen, not the chloro substituent (Scheme 2.1).[329, 333, 334]



Scheme 2.1 Regioselective cross-coupling of 4-bromo-6-chloro-3-phenylpyridazine.[329]

In 2003 our group noted the scarcity of literature surrounding pyridazinylboronic acids. Our approach to their preparation has been to use conventional lithiation, boronation and acidic workup. We identified 3,6-dimethoxypyridazine as a suitable reagent for D*o*M and subsequently 3,6-dimethoxy-4-pyridazinylboronic acid **59** was prepared.[335] In

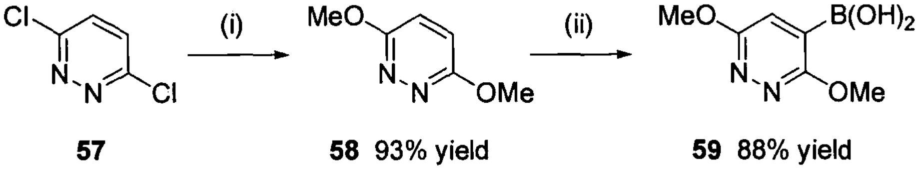
2005 an initial investigation into the Suzuki-Miyaura cross-coupling of **59** was conducted.[336] The present chapter incorporates the previous work surrounding **59**, details the scale-up of **59** and a systematic study into its Suzuki-Miyaura cross-coupling reactions. We have extended the chemistry to a series of 3-methoxy-6-(hetero)aryl-4-pyridazinylboronic acids and investigated the reactivity of the C–B bond under cross-coupling conditions.

2.2 3,6-Dimethoxy-4-pyridazinylboronic acid

2.2.1 Synthesis and Scale-up

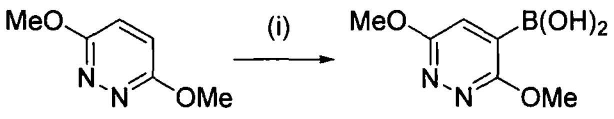
3,6-Dimethoxypyridazine **58** is prepared in good yields (86-93%) via a nucleophilic di-substitution on the commercially available 3,6-dichloropyridazine **57**. It is well documented in the literature that the metalation of diazines is particularly difficult due to their higher reactivity towards nucleophiles than other aromatic compounds. Their affinity for nucleophilic addition is a result of the electron withdrawing effect of the two sp^2 nitrogen atoms which lowers the energy level of their LUMO.[318, 321, 337, 338] Mattson was the first to report the clean *ortho*-lithation of methoxypyridazines and incorporation of electrophiles in high yields.[319] Subsequently there were several investigations into the metalation of pyridazines using lithium alkylamides, which are less prone to nucleophilic addition than alkyl- or aryllithium. The electron-withdrawing effect of the two nitrogen atoms of pyridazines makes the ring hydrogens more acidic, thus allowing less efficient-metalating agents such as LDA or LTMP to be used. As previously noted, the lithiation of **58** at C-4 using *n*-BuLi in THF at –70 °C is documented in the preparation of an organozinc derivative.[324]

Directed *ortho*-lithiation of **58** with LDA[322] in THF at –78 °C followed by addition of triisopropylborate and aqueous workup afforded the boronic acid derivative **59** as an air-stable solid in 88% yield.



Scheme 2.2 (i) Na, MeOH, reflux, 19 h. (ii) *n*-BuLi, HN*i*-Pr_2, THF, –78 °C; B(O*i*-Pr)$_3$; H_2O, HBr (48% aq.).

The feasibility of scaling-up the synthesis of **59** was established; on a 40 g scale a marked decrease in yield was observed when using *n*-BuLi for the LDA preparation; however, when using HxLi, on a 40 g scale, the decrease in yield was not as appreciable. HxLi is used industrially on a large scale due to its ease in handling and greater stability compared to *n*-BuLi. Maintaining low temperatures for a large-scale synthesis is more difficult and requires specialist cooling. Hence, the preparation of **59** was attempted at –20 °C; the yields were poor regardless of the choice of alkyllithium, indicating a lower reaction temperature is beneficial.



58 **59**

Procedure	Reaction Scale	RLi	Temp (°C)	Yield (%)
A	7 g	*n*-BuLi	-78	88
B	40 g	*n*-BuLi	-78	45
C	1 g	*n*-BuLi	-20	14
D	40 g	HxLi	-78	62
E	5 g	HxLi	-20	30

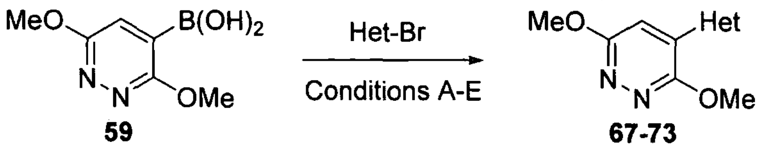
Scheme 2.3 (i) RLi, HN*i*-Pr$_2$, THF, –78 °C or –20 °C; B(O*i*-Pr)$_3$; H_2O, HBr (48% aq.) or AcOH.

2.2.2 Suzuki-Miyaura cross-coupling reactions

Suzuki-Miyaura cross-coupling reactions of **59** were carried out with a variety of heteroaryl halides **60-66** to yield products **67-73**, respectively. The results are collated in Table 2.1. Initial reactions with conditions C, [Pd(PPh$_3$)$_2$Cl$_2$ (5 mol% **59**), 1,4-dioxane, Na$_2$CO$_3$ (1 M), reflux, 65 h] generally gave poor yields. We varied the reaction time (entry 7) and found that after 24 h reflux we obtained 38% yield of **73** and after 4.5 days reflux, 60% yield of **73**. For the reactions to be close to completion, 65 h at reflux was sufficient; low yields were a result of decreased reactivity of boronic acid **59**. Protodeboronation of **59** was not observed, and in one case homocoupled boronic acid was isolated, in ca. 10% yield (entry 5, conditions C). An excess of **59** was used in one reaction (entry 2, conditions C) to assess whether the boronic acid would react with itself more readily than with a coupling partner. An improved yield of 53% of **68** (compared to 30% when using 1.1 equiv. of **59**) indicated that the boronic acid does not degrade under the reaction conditions and since there was an excess of boronic acid, there was a greater possibility for the cross-coupling to occur, resulting in an improvement in the yield.

Stabilizing the Pd(0) active catalytic species can improve reactivity in the cross-coupling reaction, and the addition of bulky and electron-rich phosphines can promote the formation of a monophosphine palladium complex LPd, which is regarded as being the active species.[205, 208, 221, 222] On addition of *t*-Bu$_3$P (Conditions D: [Pd(PPh$_3$)Cl$_2$ (5 mol% **59**)/*t*-Bu$_3$P (5 mol% **59**), 1,4-dioxane, Na$_2$CO$_3$ (1 M), reflux, 65]) little improvement was found in the cross-coupling yields (entries 2 and 5). On using a different Pd source and *t*-Bu$_3$P ligand, good cross-coupling yields were obtained in some cases, for example, entries 2 and 3 conditions B: [Pd(PhCN)$_2$Cl$_2$ (5 mol% **59**)/*t*-Bu$_3$P (5 mol% **59**), 1,4-dioxane, Na$_2$CO$_3$ (1 M), reflux, 65 h], and entry 7 conditions E: [Pd(OAc)$_2$ (5 mol% **59**)/*t*-Bu$_3$P (5 mol% **59**), 1,4-dioxane, Na$_2$CO$_3$ (1 M), reflux, 65 h]. The effect was not universal, with no marked improvement in other yields, c.f. entries 1, 4 and 6 for both conditions B and E.

For coupling partners **60** and **64** we expected the coupling yields to be higher, as the bromine α to the ring nitrogen should be activated towards oxidative addition. The reactions in the presence of a primary amine substituent are notable as new examples of Suzuki-Miyaura reactions where protection of the amine group is not necessary.[150, 249] We considered that the amine and nitro substituents may be chelating to the Pd species and thus could disrupt the catalytic cycle. Itoh et al. proposed that employing a chelating bis-(phosphine) ligand may inhibit the formation of any bis-(amine) complexes resulting from chelation of amino-substituted pyridines or pyrimidines to Pd (Scheme 2.4).[249] They found that using the sterically hindered and electron rich alkyl bidentate phosphine ligand 1,1′-bis(di-*t*-butylphosphino)-ferrocene (D-*t*-BPF), with Pd(OAc)$_2$, to be superior to other bidentate phosphine ligands for the coupling of aminochloropyrimidines/pyridines with phenylboronic acid.



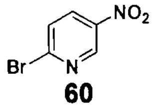
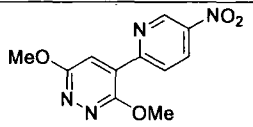
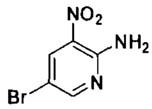
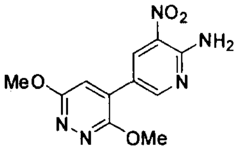
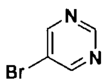
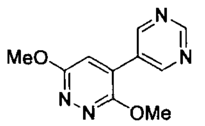
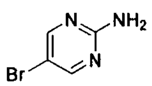
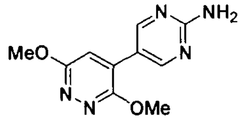
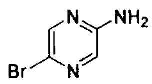
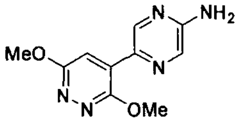
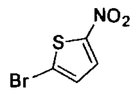
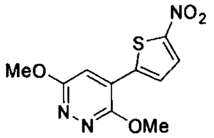
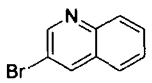
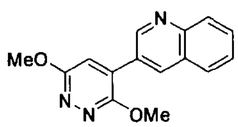
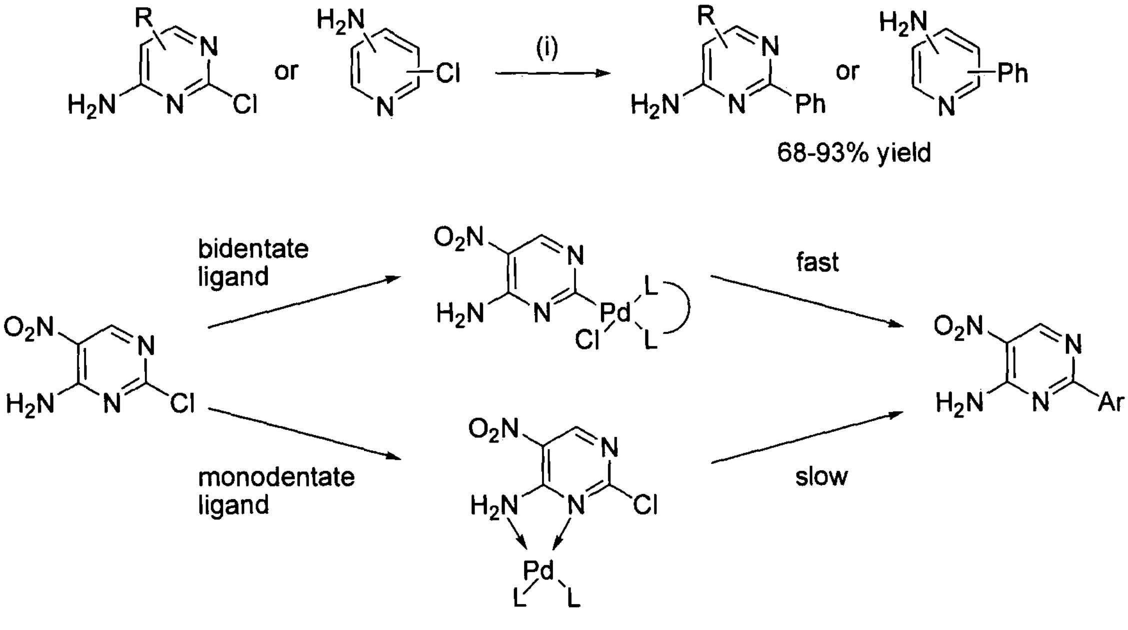
Entry	Het-Br	Product	Conditions	Isolated yield (%)
1	 **60**	 **67**	A B E	90 37 17
2	 **61**	 **68**	A B C D E	69 (67)[a] 60 30 (53)[b] 33 41
3	 **62**	 **69**	A B E	74 78 75
4	 **63**	 **70**	A B E	65 (63)[a] 19 40
5	 **64**	 **71**	A B C D E	38 48 6[c] 11 44
6	 **65**	 **72**	A B C E	77 17 25 19
7	 **66**	 **73**	A C E	95 72 (60)[d] 92

Table 2.1 Conditions: A: $Pd(OAc)_2$ (5 mol% **59**)/D-*t*-BPF (5 mol% **59**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h. B: $Pd(PhCN)_2Cl_2$ (5 mol% **59**)/*t*-Bu_3P (5 mol% **59**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h. C: $Pd(PPh_3)_2Cl_2$ (5 mol% **59**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h. D: $Pd(PPh_3)Cl_2$ (5 mol% **59**)/*t*-Bu_3P (5 mol% **59**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h. E: $Pd(OAc)_2$ (5 mol% **59**)/*t*-Bu_3P (5 mol% **59**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h. [a] Carbon treated instead of silica column chromatography. [b] 2.3 equiv. **59**. [c] ca. 10% homocoupled boronic acid isolated. [d] 4.5 days reflux.

With standard conditions A [Pd(OAc)$_2$ (5 mol% **59**)/D-*t*-BPF (5 mol% **59**), 1,4-dioxane, Na$_2$CO$_3$ (1 M), reflux, 65 h] the reactions of **59** with **60-66** proceeded in moderate to high yields (38-95%). In several cases there were noticeable improvements in coupling yields compared to other conditions attempted, for example entries 1, 4 and 6. We considered that the polar nature and amine substituents of **68** and **70** were making purification by silica column chromatography difficult and hence lowering the isolated yield. However, alternative purification using carbon treatment followed by recrystallization did not improve the yields. Suzuki-Miyaura reactions of **59** provided expedient access to highly functionalized heteroarylpyridazine derivatives, which would be very difficult to obtain by alternative methodology.



Scheme 2.4 (i) PhB(OH)$_2$, Pd(OAc)$_2$ (5 mol%), D-*t*-BPF (5 mol%), K$_3$PO$_4$, 1,4-dioxane, reflux.[249]

When **59** was dissolved in refluxing ethanol, protodeboronation rapidly occurred and X-ray analysis showed that the crystals obtained were a 1:1 molecular complex of **58** and boric acid, **58**·B(OH)$_3$ stabilized by hydrogen bonding. This is interesting as protodeboronation was not observed in Suzuki-Miyaura cross-couplings of **59**. The crystal structure of **58**·B(OH)$_3$ comprises discrete neutral molecules of **58** and orthoboric acid (both planar and forming a dihedral angle of 7°), hydrogen-bonded into a centrosymmetric [**58**·B(OH)$_3$]$_2$ unit. The O(4) and O(5) act as donor of hydrogen bonds, whereas O(3) is both donor and acceptor; the B-O(3) bond is longer (1.378(2) Å) than B-O(4) and B-O(5) (1.359(2) and 1.361(2) Å). In boric acid, $B(OH)_3$, every oxygen atom in two independent molecules is both donor and acceptor; all B-O distances are equivalent within experimental error, but the average (1.368(1) at 105 K)[339] is essentially the same as in **58**•$B(OH)_3$.

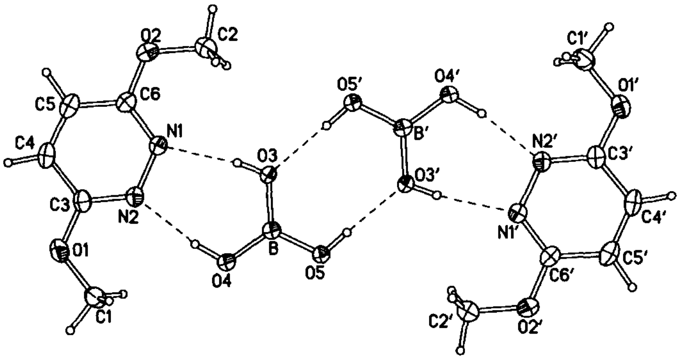


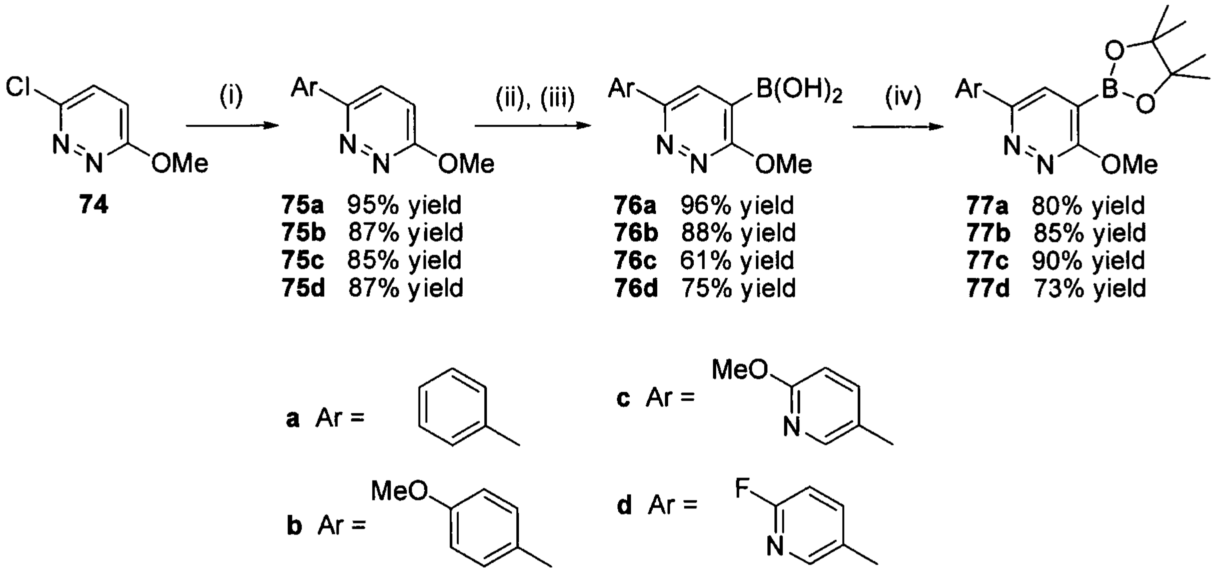
Figure 2.2 X-ray crystal structure of **58**·$B(OH)_3$, the hashed lines are hydrogen bonds, (50% thermal ellipsoids). (CCDC 665174).

2.3 3-Methoxy-6-(hetero)aryl-4-pyridazinylboronic acids and esters

2.3.1 Synthesis and initial reactions

In a further development that has led to more highly functionalized systems, an alternative cross-coupling protocol was explored. Reaction of commercial 3-chloro-6-methoxypyridazine **74** with the readily available benzene-, 4-methoxybenzene-, 2-methoxy-5-pyridyl-[30] and 2-fluoro-5-pyridylboronic acids[139] under standard conditions [$Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h] gave products **75a-d**, respectively, in high yields. This protocol had previously been used in our group to cross-couple **74** with 2-methoxy-3-pyridylboronic acid[139] in 69% yield and provide the first example of the 3-(3-pyridyl)pyridazine system.[340] Treatment of **75a-d** with the standard lithiation-boronation seuqence used for the preparation of boronic acid **59** yielded boronic acids **76a-d** in 61-96% yields (Scheme 2.5).

Electron-deficient boronic acids are known to be susceptible to protodeboronation both during their synthesis (where careful neutralization is required) and during their subsequent reactions.[61, 165, 167, 168] During the synthesis of **76c** instability of the C–B bond was highlighted; prior to acidification, on leaving the reaction mixture at room temperature overnight (in basic pH) formation of **75c** was observed by TLC. The workup and isolation of **76c** was subsequently conducted in a shorter time to minimize protodeboronation. The boronic species may also be unstable at low temperatures which could account for the lower isolated yield of **76c** compared to the other boronic acids.



Scheme 2.5 (i) $ArB(OH)_2$, $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h. (ii) *n*-BuLi, $HN\textit{i}\text{-}Pr_2$, –78 °C, THF or Et_2O. (iii) $B(O\textit{i}\text{-}Pr)_3$, –78 °C then H_2O/HBr (48% aq.) or AcOH. (iv) pinacol, $MgSO_4$, toluene, RT, 17 h.

Initial reactions of **76a** with 2-bromopyridine **78**, and 5-bromopyrimidine **62**, using conditions [$Pd(OAc)_2$ (5 mol% **76a**)/*t*-Bu_3P (5 mol% **76a**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h], gave low cross-coupling yields of ca. 10% (**79**) and 23% (**80**), respectively; the major product isolated was **75a** resulting from hydrolytic protodeboronation of **76a**. On reacting **76a** and 3-bromoquinoline under the same conditions, the isolated crystals were confirmed by X-ray analysis to be homocoupled boronic acid, **81** (Figure 2.3). No cross-coupling was observed in this reaction. Electron-poor boronic acids are more difficult to cross-couple as they are less nucleophilic and undergo transmetalation at a slower rate than electron-rich boronic acids. Undesired homocoupling of boronic acids can compete with slow Suzuki-Miyaura reactions,[260] furthermore, electron-deficient boronic acids are prone to homocoupling[261] and are more susceptible to metal-catalyzed protodeboronation.[274]

In some cases boronic ester derivatives are regarded as being more stable than boronic acids and hence more reactive in Suzuki-Miyaura cross-couplings.[65, 170] Consequently, we converted **76a-d** into their pinacol ester derivatives **77a-d** in good yields by stirring with pinacol and magnesium sulfate in toluene (Scheme 2.5). The direct synthesis of pinacol esters **77c** and **77d** through trapping of the lithiated species from **75c,d** with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in either THF or Et$_2$O was less efficient than the two-step route via **76c,d**. The lithio intermediates of **75c,d** were treated with triisopropylborate, followed by attempts at in situ trapping with pinacol[67] to yield **77c,d**; however, this too was unsuccessful, giving unreacted starting material after work-up.

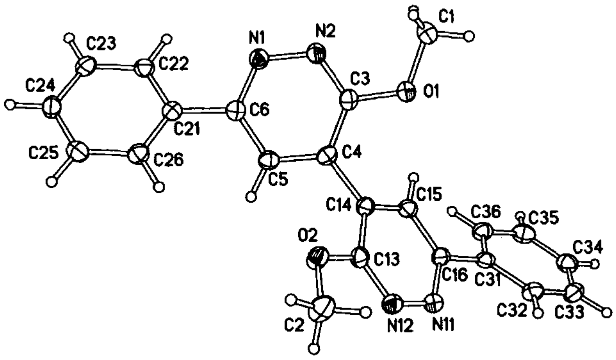


Figure 2.3 X-ray crystal structure of **81**,the homocoupled boronic acid **76a**.

The substitution pattern in the boronated products was confirmed for **77b** and **77d** unequivocally by X-ray crystal structure determinations (Figures 2.4 and 2.5, respectively). For **77c** comparison of the ^{1}H NMR signals confirmed lithiation (and subsequent boronation) occurred on the pyridazine ring (Figure 2.6). It was pleasing to note that despite the presence of a second directed metalation group (DMG) in **75b-d**, lithiation occurred regioselectively on the more electron-deficient pyridazine ring. To our knowledge there are no literature reports which compare the effect of the same DMG on different rings in a biaryl/heteroaryl system, making compounds **75b** and **75c** of particular interest. Quéguiner et al. concluded that the regioselectivity of DMGs on 3- and 3,6-disubstituted pyridazines,[320, 322] was highly dependent on the nature of the metalating agent. They also found that the relative *ortho*-directing power of a wide range of DMGs in the D*o*M reactions of the diazine series (pyridazines, pyrazines and pyrimidines),[44, 341] was F > OMe > Cl. The methoxy group undergoes greater complexation with the metalating agent than the chlorine atom, and regioselectivity favours the methoxy group with increasing bulkiness of the lithium alkylamide. The very strong electron-withdrawing ability of the fluorine atom makes the *ortho* hydrogens much more acidic, so there is no need for complexation to achieve the metalation. For DMG substituted pyridines there are no comprehensive reports on the regioselectivity of D*o*M. Differing reaction conditions can be employed to selectively lithiate *ortho* to one substituent, for example 2-chloro-6-methoxypyridine can be lithiated to form 2-chloro-3-lithio-6-methoxypyridine using PhLi and 5% diisopropylamine,[342] whereas with *t*-BuLi the 2-chloro-5-lithio-6-methoxy isomer is obtained.[343]

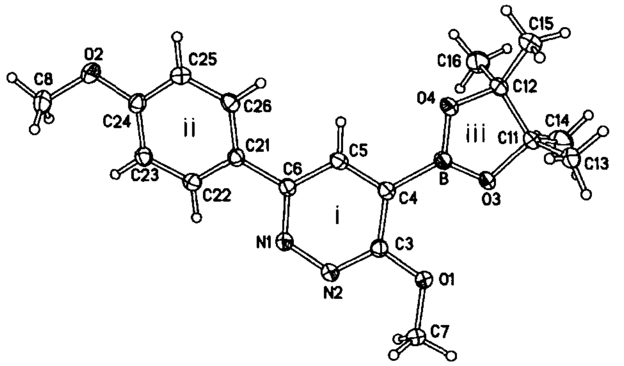


Figure 2.4 X-ray crystal structure of **77b**, (50% thermal ellipsoids). The dihedral angle between rings *i* and *ii* is 22.0°, between ring *i* and the boron atom plane is 28.0°; torsion angles C(7)-O(1)-C(3)-N(2) 8.5(2)°, C(8)-O(2)-C(24)-C(23) 15.6(2)°. Ring *iii* adopts twisted conformation (ca. C_2 symmetry). (CCDC 665168).

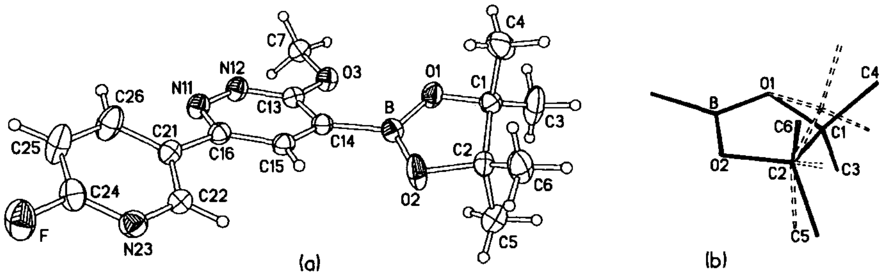
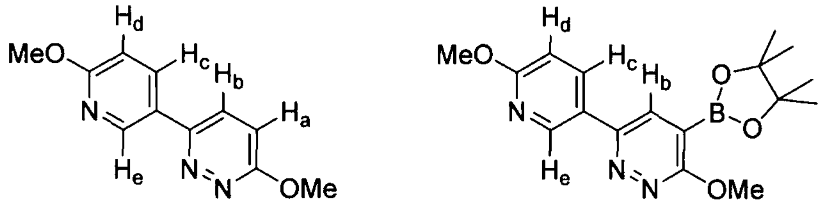


Figure 2.5 X-ray crystal structure of **77d**. (a) major conformation; (b) disorder of the tetramethyl-dioxaborolan moiety. The tetramethyldioxaborolan moiety is disordered between two different conformations with equal probability. The pyridazine ring forms dihedral angles of 21.8° with the pyridine ring and 21.7° with the B atom plane. The methoxy group has an in-plane conformation (torsion angle N(12)-C(13)-O(3)-C(7) 4.6(2)°). (CCDC 665169).

The observed regioselective lithiation of **75d** may be rationalized as follows. The electron-withdrawing effect of the fluoro substituent, making the pyridine protons acidic, was overshadowed by the combined effect of the methoxy-substituent complexing with LDA and higher acidity of pyridazinyl protons (due to the electron deficient nature of the pyridazine ring).

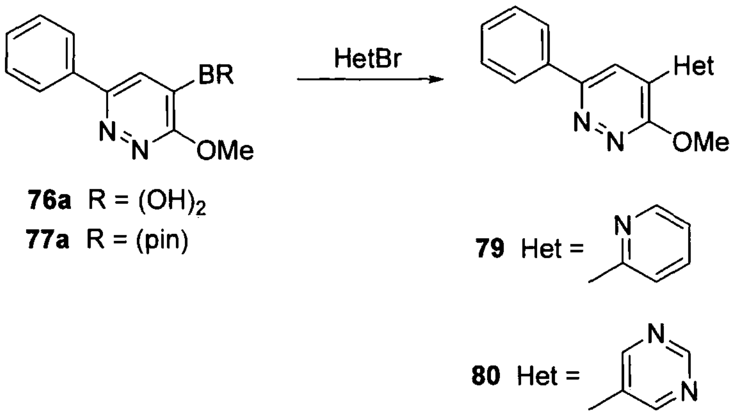


75c **77c**

75c	δ (ppm), multiplet in $CDCl_3$	*J* (Hz)	**77c**	δ (ppm), multiplet in $CDCl_3$	*J* (Hz)
H_a	7.73, d	9.6			
H_b	7.04, d	9.6	H_b	8.03, s	
H_c	8.31, dd	9.0, 2.4	H_c	8.29, d	9.0, 2.4
H_d	6.86, d	9.0	H_d	6.83, dd	9.0, 0.4
H_e	8.70, d	2.4	H_e	8.77, dd	2.4, 0.4

Figure 2.6 ^1H NMR chemical shifts for the aromatic protons in compounds **75c** and **77c** (400 MHz, $CDCl_3$).

Table 2.2 summarizes the Suzuki-Miyaura conditions screened in attempts to increase cross-coupling yields; protodeboronated boronic species was isolated alongside the coupling product in all cases. The yield of **79** was improved when using boronic ester **77a** and the $Pd(OAc)_2$/*t*-Bu_3P conditions, whereas changing reaction conditions to [$Pd(PPh_3)_2Cl_2$ (5 mol% **76a**)/*t*-Bu_3P (5 mol% **76a**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h] with either boronic acid or ester did not dramatically improve the yield of **79**. The conditions reported by Fu et al. for the cross-coupling of nitrogen heterocycles,[172] [$Pd_2(dba)_3$ (1 mol% Het-Br)/PCy_3 (2.4 mol% Het-Br), 1,4-dioxane, K_3PO_4 1.27 M, reflux 24 h] generally gave good yields for our system; using the pinacol ester derivative also improved yields. Attempts to suppress the protodeboronation of **77a** by using an anhydrous base (solid K_3PO_4) were unsuccessful, leading to decreased yields of the coupling products. As previously discussed in section 1.3.3, protodeboronation is strongly base dependent, however, we did not investigate different bases in this case as the thermal instability of boronic acid **76a** had been established; when **76a** was heated in 1,4-dioxane (in the absence of base and palladium catalyst), protodeboronation was observed by TLC monitoring at > 50 °C. As this qualitative assessment was made in neutral conditions we must assume that it is either the temperature or adventitious water in the 1,4-dioxane which caused protodeboronation to occur.[270]



76a R = $(OH)_2$
77a R = (pin)

79 Het =

80 Het =

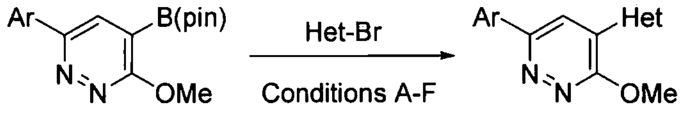
Entry	Boronic species	HetBr	Reaction conditions	Product	Yield (%)
1	**76a**	2-bromo-pyridine **78**	$Pd(OAc)_2$ (5 mol% **76a**)/*t*-Bu_3P (5 mol% **76a**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h	**79**	~10
2	**76a**	**78**	$Pd(PPh_3)_2Cl_2$ (5 mol% **76a**)/*t*-Bu_3P (5 mol% **76a**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h	**79**	55
3	**76a**	**78**	$Pd(PPh_3)_2Cl_2$ (5 mol% **76a**)/*t*-Bu_3P (5 mol% **76a**), 1,4-dioxane, Na_2CO_3 (1 M), 55 °C, 5 days	**79**	40
4	**76a**	**78**	$Pd_2(dba)_3$ (1 mol% **78**)/PCy_3 (2.4 mol% **78**), 1,4-dioxane, K_3PO_4 (1.27 M), reflux, 24 h	**79**	67
5	**77a**	**78**	$Pd(OAc)_2$ (5 mol% **77a**)/*t*-Bu_3P (5 mol% **77a**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h	**79**	40
6	**77a**	**78**	$Pd(PPh_3)_2Cl_2$ (5 mol% **77a**)/*t*-Bu_3P (5 mol% **77a**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h	**79**	44
7	**77a**	**78**	$Pd_2(dba)_3$ (1 mol% **78**)/PCy_3 (2.4 mol% **78**), 1,4-dioxane, K_3PO_4 (1.27 M), reflux, 24 h	**79**	76 (47)*
8	**76a**	5-bromo-pyrimidine **62**	$Pd(OAc)_2$ (5 mol% **76a**)/*t*-Bu_3P (5 mol% **76a**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h	**80**	23
9	**76a**	**62**	$Pd_2(dba)_3$ (1 mol% **62**)/PCy_3 (2.4 mol% **62**), 1,4-dioxane, K_3PO_4 1.27 M, reflux 24 h	**80**	34
10	**77a**	**62**	$Pd_2(dba)_3$ (1 mol% **62**)/PCy_3 (2.4 mol% **62**), 1,4-dioxane, K_3PO_4 1.27 M, reflux 24 h	**80**	47 (46)*

Table 2.2 Catalyst screening for the cross-couplings of **76a** and **77a**. *Using $K_3PO_{4\,(s)}$.

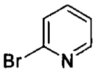
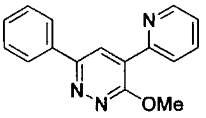
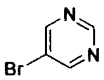
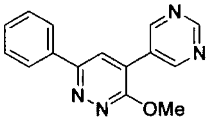
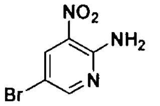
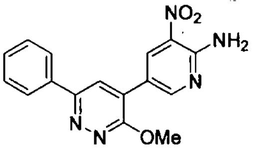
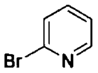
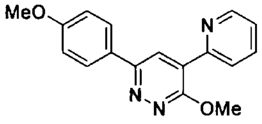
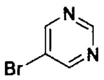
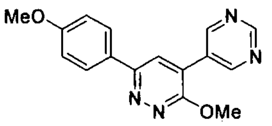
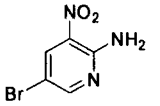
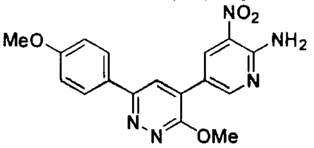
It was decided to use [$Pd_2(dba)_3$ (1 mol%)/PCy_3 (2.4 mol%), 1,4-dioxane, K_3PO_4 1.27 M, reflux 24 h] as standard conditions for the Suzuki-Miyaura cross-couplings of boronic esters **77a-d** and accept that these electron-deficient boronic derivatives would remain prone to hydrolytic protodeboronation under these conditions.

2.3.2 Suzuki-Miyaura cross-coupling reactions

Suzuki-Miyaura cross-coupling reactions of **76a,b** and **77a-d** were carried out with heteroaryl bromides **78**, **62** and **61** under standard conditions [$Pd_2(dba)_3$ (1 mol% Het-Br)/PCy_3 (2.4 mol% Het-Br), 1,4-dioxane, K_3PO_4 1.27 M, reflux 24 h] to yield products **79, 80, 82-91**. The results are collated in Table 2.3. In every case competing protodeboronation occurred yielding pyridazines **75a-d** as by-products, or in some cases as the major isolated product.



77a-d **79, 80, 82-91**

Entry	Boronic acid or ester	Het-Br	Product	Conditions	Isolated yield (%)
1	**77a**	 **78**	 **79**	A B C	76 47 73
2	**76a**			A	67
3	**77a**	 **62**	 **80**	A B	47 46
4	**76a**			A	34
5	**77a**	 **61**	 **82**	A	59
6	**76a**			A	40
7	**77b**	 **78**	 **83**	A	77
8	**76b**			A	62
9	**77b**	 **62**	 **84**	A	28
10	**76b**			A D E	27 43 14
11	**77b**	 **61**	 **85**	A	46
12	**76b**			A	39

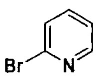
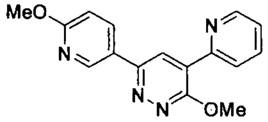
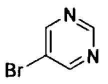
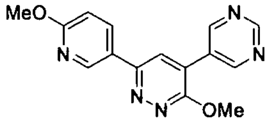
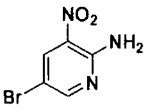
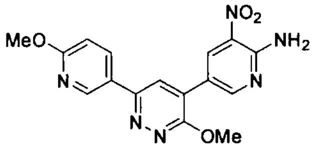
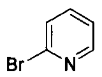
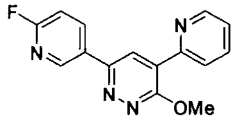
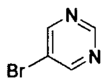
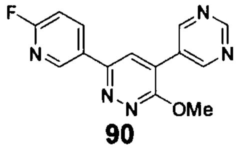
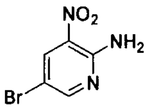
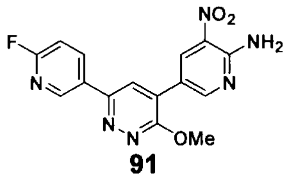
Entry	Boronic acid or ester	Het-Br	Product	Conditions	Isolated yield (%)
13	**77c**	 **78**	 **86**	A	58
14	**77c**	 **62**	 **87**	A	37
15	**77c**	 **61**	 **88**	A	42
16	**77d**	 **78**	 **89**	A	67
17	**77d**	 **62**	 **90**	A	29
18	**77d**	 **61**	 **91**	A F	18 52

Table 2.3 Conditions A: $Pd_2(dba)_3$ (1 mol% Het-Br)/PCy_3 (2.4 mol% Het-Br), 1,4-dioxane, K_3PO_4 (1.27 M), reflux, 24 h. B: $Pd_2(dba)_3$ (1 mol% Het-Br)/PCy_3 (2.4 mol% Het-Br), 1,4-dioxane, $K_3PO_{4\,(s)}$, reflux, 24 h. C: $Pd_2(dba)_3$ (5 mol% Het-Br)/[*t*-Bu_3PH]BF_4 (12 mol% Het-Br), MeCN, $K_3PO_{4\,(s)}$, 85 °C, 1 h. D: $Pd_2(dba)_3$ (1 mol% Het-Br)/PCy_3 (2.4 mol% Het-Br), 1,4-dioxane, K_3PO_4 (1.27 M), μW 120 °C, 1 h. E: $Pd_2(dba)_3$ (1 mol% Het-Br)/PCy_3(2.4 mol% Het-Br), DMF, $K_3PO_4.2H_2O$, μW 160 °C, 5 min. F: $Pd(OAc)_2$ (5 mol% Het-Br)/D-*t*-BPF (5 mol% Het-Br), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 5 h.

As previously established, anhydrous conditions did not suppress the competitive protodeboronation. The catalyst system was changed to [$Pd_2(dba)_3$ (5 mol% Het-Br)/[*t*-Bu_3PH]BF_4 (12 mol% Het-Br), MeCN, $K_3PO_{4\,(s)}$, 85 °C, 1 h] (entry 1, conditions C) which had been used by Harrity et al. for reactions of their pyridazinylboronic esters.[165] However this gave no improvement compared to our standard conditions. Microwave assisted Suzuki-Miyaura reactions are a routine synthetic procedure.[344] It was hoped that applying microwave conditions would promote cross-coupling of our boronic esters over protodeboronation. The yield of cross-coupling product **84** did improve to 43% (entry 10, conditions D) compared to the 27% yield from the standard conditions, however, protodeboronation was again observed and microwave conditions were not further investigated. The yield of coupling product **91** was improved when using the conditions previously used for the cross-coupling of boronic acid **59** (entry 18, conditions F).

In general the overall yields of the cross-coupled products from the two-step protocol via the pyridazinylboronic esters are comparable to the one-step procedure from the boronic acid derivatives. X-Ray diffraction studies confirmed the structures of compounds **80** and **83** (Figures 2.7 and 2.8, respectively).

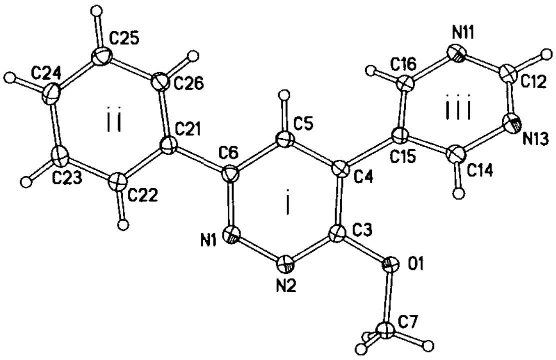


Figure 2.7 X-ray crystal structure of **80**, dihedral angles *i*/*ii* 8.2°, *i*/*iii* 37.2°. The methoxy group is coplanar with the adjacent rings, the torsion angle N(2)-C(3)-O(1)-C(7) and C(23)-C(24)-O(2)-C(8) equals 3.5(2)°. (CCDC 665170).

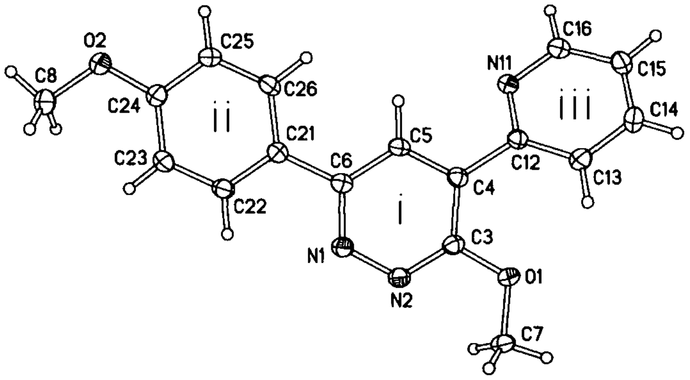
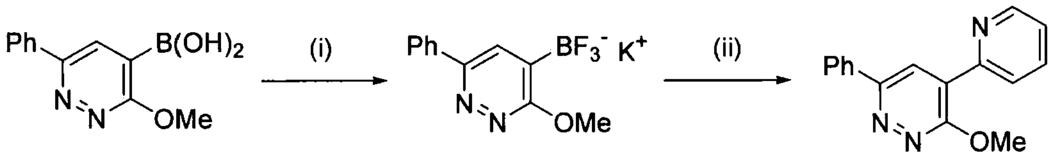


Figure 2.8 X-ray crystal structure of **83**, dihedral angles *i*/*ii* 7.8°, *i*/*iii* 31.8°. The methoxy group is nearly coplanar with the adjacent rings, the torsion angle N(2)-C(3)-O(1)-C(7) and C(23)-C(24)-O(2)-C(8) equals 2.0(2)°. (CCDC 665171).

In some cases the reactivity of organotrifluoroborates in Suzuki-Miyaura coupling reactions is superior to that of the corresponding boronic acid; trifluoroborates are in general more robust, easily purified and easier to handle.[97] Accordingly, **76a** was converted to the potassium trifluoroborate derivative **92** in 97% yield by using the established protocol with KHF_2 in aqueous methanol. In cross-coupling reactions, under a number of different reaction conditions, **92** was less efficient than **76a** (Scheme 2.6). **92** was found to be highly insoluble at reflux temperature and no cross-coupling was observed by TLC analysis; on the addition of water to make the reaction mixture homogeneous protodeboronation occurred yielding **75a** as the major product. This may be anticipated as the formation of such an "ate" complex and higher electron-withdrawing strength of the trifluoroborate group (factors that usually contribute to the higher reactivity of trifluoroborates) assist in polarizing the C–B bond, leading to facile protodeboronation in some α-heteroaryltrifluoroborates.[97]



76a

92 97% yield

79

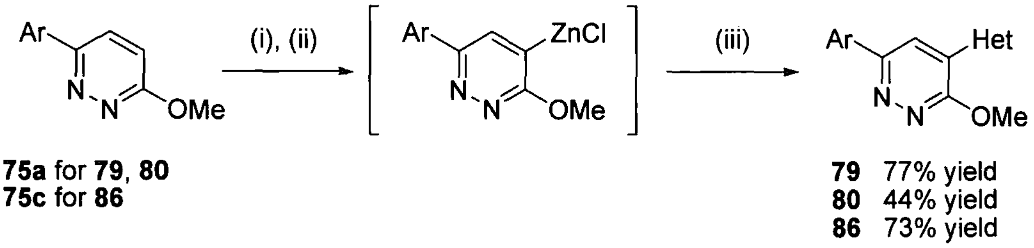
	Conditions	Yield of **79** (%)
A	$Pd(dppf)Cl_2 \cdot DCM$ (1 mol% **78**), Et_3N, EtOH, reflux, 24 h[97]	47
B	$Pd(dppf)Cl_2 \cdot DCM$ (1 mol% **78**), Et_3N, MeCN, reflux, 18 h	X*
C	$Pd_2(dba)_3$ (1 mol% **78**)/PCy_3 (2.4 mol% **78**), Et_3N, 1,4-dioxane, reflux, 24 h	33
D	$Pd_2(dba)_3$ (1 mol% **78**)/PCy_3 (2.4 mol% **78**), $K_3PO_{4(s)}$, DMF, 100 °C, 3.5 h	26 (LCMS yield)

Scheme 2.6 (i) KHF_2, H_2O/MeOH, RT, 1 h → 0 °C, 1 h. (ii) 2-bromopyridine **78**, conditions A-D. *Mainly deboronated species **75a** isolated.

As shown in Table 2.3 we have successfully prepared novel highly functionalized (hetero)arylpyridazine derivatives in synthetically useful yields. Protodeboronation of these pyridazinylboronic species dominates Suzuki-Miyaura cross-coupling especially when less reactive coupling partners are employed.

2.3.3 Optimization of cross-coupling yields

As previously described, organometallic pyridazine derivatives other than organolithiums are reported. As an alternative route to heteroarylpyridazines we explored the formation and reactions of organozincate derivatives. Adapting the procedure outlined by Turck et al.,[324] using LDA as the lithiating agent instead of *n*-BuLi, we prepared and cross-coupled the organozinc derivatives of **75a** and **75c** using the in situ Negishi protocol (Scheme 2.7).



Scheme 2.7 (i) *n*-BuLi, HN*i*-Pr$_2$, –78 °C, THF. (ii) ZnCl$_2$, –78 °C → RT, 1 h. (iii) 2-bromopyridine **78** or 5-bromopyrimidine **62**, Pd(PPh$_3$)$_4$, reflux/sonicate, 3 h.

The overall yields of the cross-coupling products **79**, **80** and **86** (based on the starting pyridazines **75a** and **75c**) were improved to 77%, 44% and 73%, respectively, compared to 64%, 33% and 32% via the boronic acid **76a** or ester **77c**. Nevertheless, the boronic acid/ester route may be more practical due to the isolation and stability of boronic acids/esters compared to organozincate derivatives.

2.4 Conclusions

Through the lithiation/boronation of pyridazines we have successfully provided an efficient entry into a series of new pyridazinylboronic acid/ester derivatives, which are stable to storage under ambient conditions. A systematic study into the reactivity of **59** under Suzuki-Miyaura cross-coupling conditions, with a range of palladium catalyst/phosphine ligand systems, shows that consistently good yields are obtained when using Pd(OAc)$_2$/D-*t*-BPF as the catalytic species, although other catalyst systems provide high coupling yields in some cases.

Boronic esters **77a-d**, and their boronic acid derivatives, undergo palladium-catalyzed cross-coupling reactions to provide aryl/heteroarylpyridazines in synthetically viable yields, although competing protodeboronation is observed. Efforts to promote Suzuki-

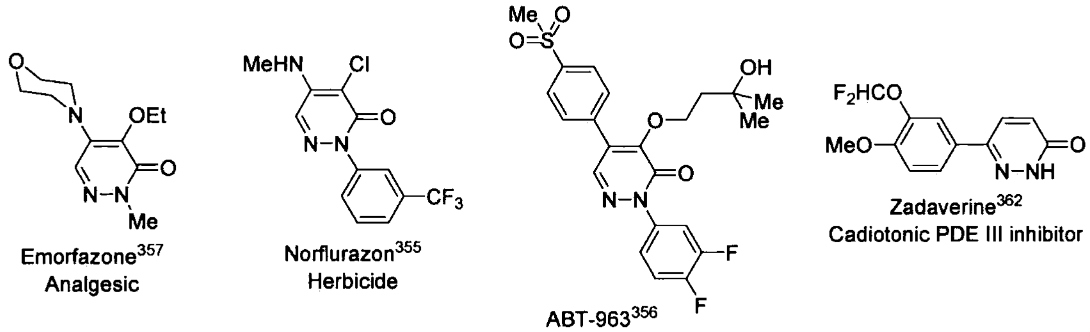
Miyaura cross-coupling, and minimize protodeboronation by-products, through alternative catalyst systems, microwave assisted conditions, anhydrous base conditions and trifluoroborate salts had little effect on improving coupling yields. An alternative cross-coupling protocol, via organozinc pyridazine derivatives, highlights that overall coupling yields may be improved by this in situ method; however, zincates do not have the versatility of boronic acids in terms of handling.

Good functional group tolerance has been shown throughout the preparation and reaction of these pyridazinylboronic species. They provide expedient access to highly functionalized heteroarylpyridazine derivatives, which would be very difficult to obtain by alternative methodology and are attractive as new pharmacophores. Moreover, they offer scope for further synthetic transformations, some examples of which are detailed in Chapter 3.

CHAPTER 3 – PYRIDAZIN-3(2*H*)-ONES

3.1 Introduction

Of the pyridazine derivatives, pyridazin-3(2*H*)-ones are an important class of compounds with a broad array of biological activities.[306, 345-352] Substituted pyridazinones show herbicidal activity,[353] for example the insecticides Chloridazon, used for weed control in sugar beet cultivation, a recent synthesis of which utilized palladium-catalyzed cross-coupling.[354] Norflurazon inhibits carotenoid synthesis causing chlorophyll depletion and inhibition of photosynthesis in plants.[355] Pyridazinone derivatives were identified as selective cyclooxygenase-2 inhibitors, thereby acting as anti-inflammatory drugs.[346, 347, 356] New analgesic agents without the side-effects typical of opioid agonists, or gastro-intestinal problems associated with non-steroidal anti-inflammatory drugs have attracted considerable attention. In this regard a number of pyridazin-3(2*H*)-one derivatives are of particular interest; Emorfazone displays good analgesic activity[357, 358] and preliminary studies have shown 4-carbamoyl-5-aryl- and 4-amino-5-vinyl-pyridazin-3(2*H*)-one analogues show potent antinociceptive activity.[359] Arylpiperazine-pyridazinone-containing compounds show strong affinity for α_1-adrenergic receptors.[345, 348, 360] Several 6-arylpyridazin-3(2*H*)-ones are active cardiotonic agents and platelet aggregation inhibitors, notably 6-(3,4-dialkoxyphenyl)-pyridazin-3(2*H*)-ones, such as Zardaverine.[361-363] Selected structures are shown in Figure 3.1.



Emorfazone[357]
Analgesic

Norflurazon[355]
Herbicide

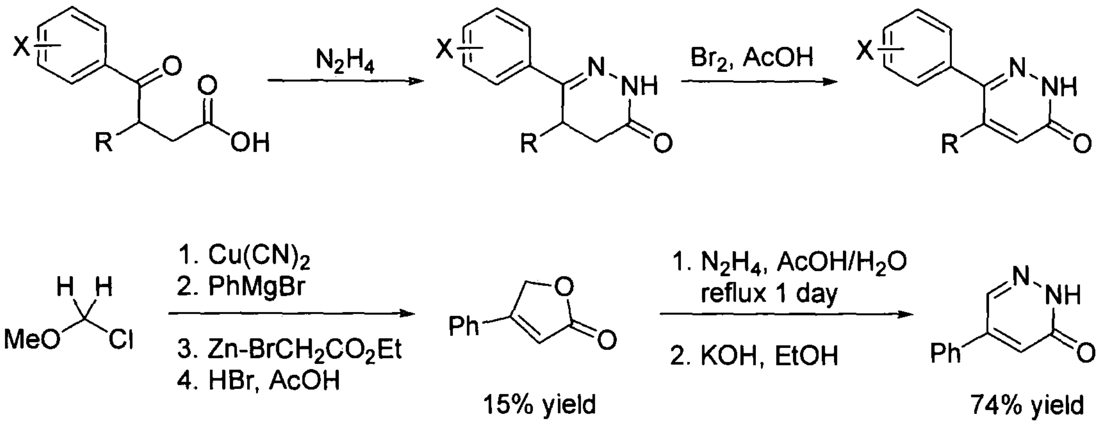
ABT-963[356]
COX-2 inhibitor

Zadaverine[362]
Cadiotonic PDE III inhibitor

Figure 3.1 Examples of biologically active pyridazin-3(2*H*)-one derivatives.

Most syntheses of pyridazin-3(2*H*)-one derivatives proceed via traditional methods (Scheme 3.1). Early literature described the condensation of γ-ketonic acids with hydrazine hydrate, to form a 6-substituted-4,5-dihydropyridazin-3(2*H*)-one which can be dehydrogenated with bromine in acetic acid.[364-366] In order to prepare pyridazin-

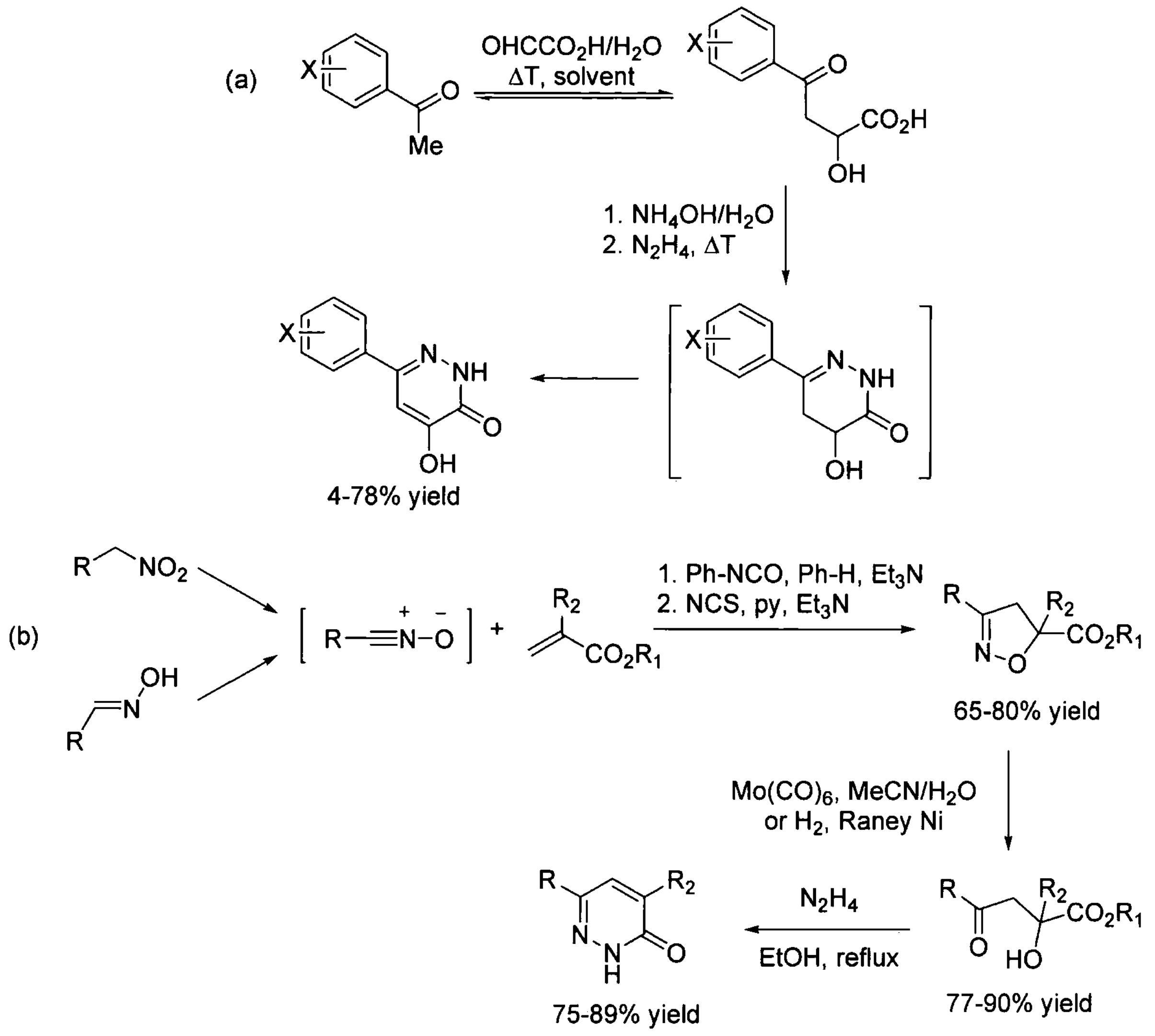
3(2*H*)-one analogues with differing substitution patterns alternative 1,4-dicarbonyl species were required, usually hydroxy γ-lactone derivatives; their reaction with hydrazine hydrate, followed by oxidation, yielded pyridazinones.[367]



Scheme 3.1 Preparation of substituted pyridazin-3(2*H*)-one derivatives through classical methods.[365, 367]

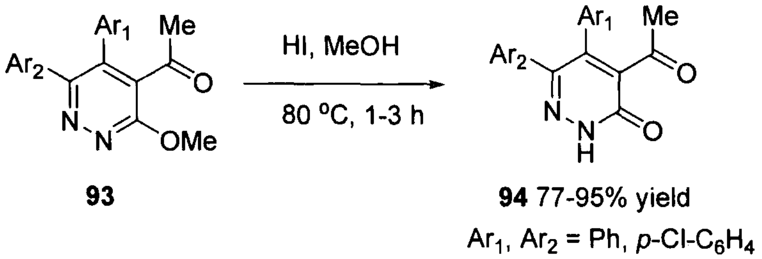
With the demand for pyridazin-3(2*H*)-ones increasing, including large-scale syntheses, more efficient synthetic protocols were developed, including several one-pot syntheses. Commercially available anilines can be converted, in a two step, one-pot procedure, to the corresponding pyridazinones in good to excellent yields.[368] The "self-catalyzed glyoxylic acid process" involves the reaction of glyoxylic acid hydrate with a three-fold excess of methyl ketone at 100 °C to give the aldol intermediate, treatment of which with aqueous ammonia and heating with hydrazine leads to cyclization and dehydration, with isolation of the pyridazinone [Scheme 3.2, (a)].[369] Another alternative strategy to 6-substituted pyridazin-3(2*H*)-ones is based on the [3+2] dipolar cycloaddition of readily available nitrile oxides with an alkyl acrylate to produce 4,5-dihydroisoxazolines, which in turn are ring opened to give α-hydroxy γ-keto ester and subsequently undergo ring closure with hydrazine hydrate to form the pyridazinone [Scheme 3.2, (b)].[370] Harrity et al. developed a novel route to 3,6-dichloropyridazinones through the oxidation of pyridazinylboronic esters (prepared via cycloaddition protocol of tetrazines with alkynylboronic esters, see Section 1.2.3) with hydrogen peroxide.[169]

All of the above methods are useful for preparing substituted pyridazinone derivatives, offering fair structural diversity. However, the major drawback of these routes is the necessity to prepare the specific dicarbonyl components required for each pyridazinone synthesis.



Scheme 3.2 More modern strategies to 6-substituted pyridazin-3(2*H*)-ones: (a) One-pot preparation from ketones.[369] (b) Nitrile oxide [3+2] cycloaddition, followed by ring-opening of 4,5-dihydroisoxazolines.[370]

Methoxy-substituted pyridazines can be converted into their pyridazin-3(2*H*)-one derivatives under acidic conditions.[334, 350] Conditions must be tailored to the substrate as too mild conditions may not result in demethylation, whereas too harsh conditions lead to degradation. For example, the conversion of **93** into the pyridazin-3(2*H*)-one derivative **94** was unsuccessful with boron tribromide in DCM, and hydroiodic acid in water; however, hydroiodic acid in methanol gave good yields of **94** (Scheme 3.3).[334] Chloropyridazines can be readily hydrolyzed to their pyridazin-3(2*H*)-one derivatives under acidic conditions.[366]

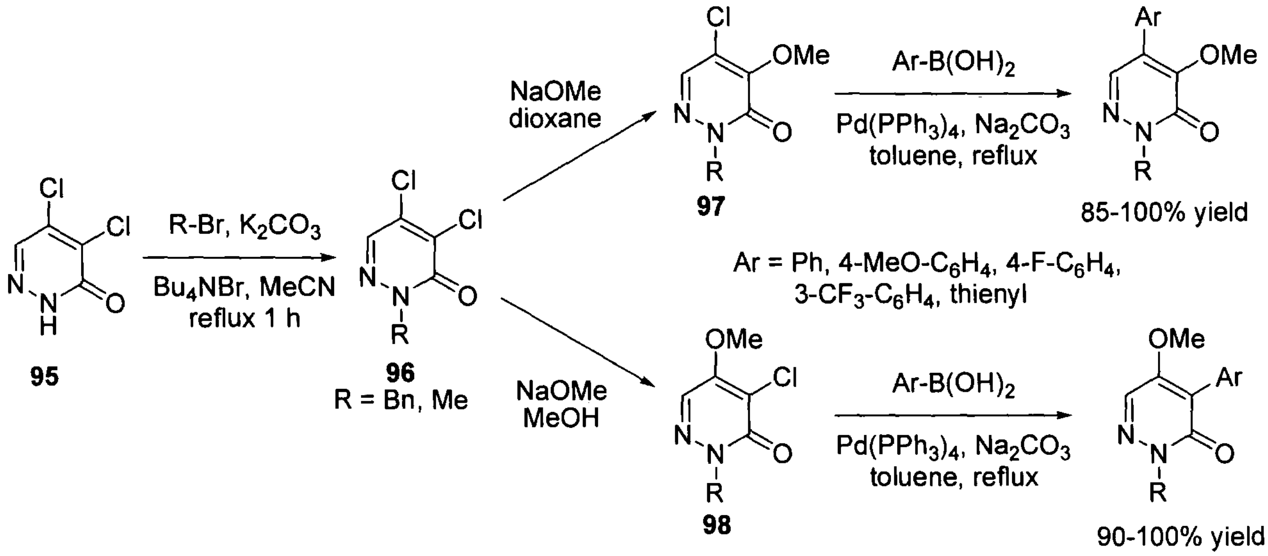


Scheme 3.3 Conversion of methoxy-pyridazines to pyridazin-3(2*H*)-ones.[334]

Substituted pyridazin-3(2*H*)-ones can undergo further synthetic transformations including *N*-alkylation usually to afford the 2-*N*-substituted derivatives, nucleophilic substitution of halopyridazin-3(2*H*)-ones with N-, S- and O-nucleophiles, electrophilic substitution at the 4-position with a variety of electrophiles (viz. nitration, formylation, diazotization) and cycloadditions (in Diels-Alder and 1,3-dipolar addition reactions).[349, 350]

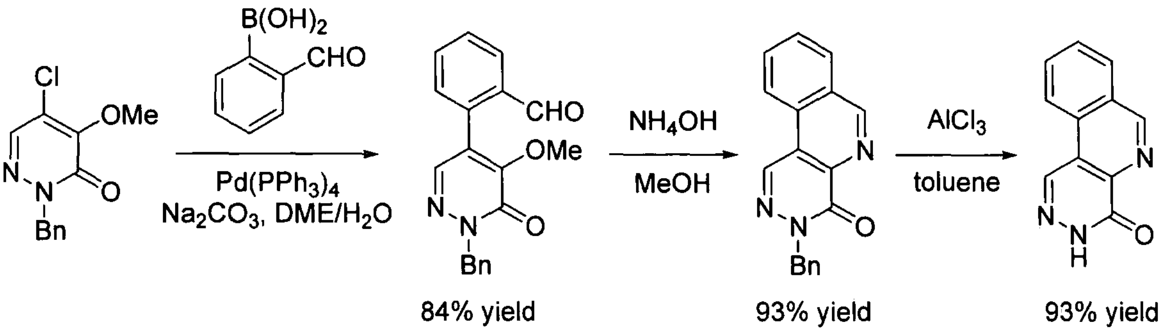
Pyridazinone ring formation or functionalizing pyridazinones through differing substitution reactions, offer reasonable routes to substituted pyridazinones, although there are some drawbacks. The palladium-catalyzed cross-coupling of halopyridazin-3(2*H*)-ones is attractive since it adds the functionality towards the end of the synthesis. This allows one to take advantage of the wide selection of reactive partners (e.g. boronic acids, amines, organotin derivatives, acetylenes), thus enhancing the access to libraries of pyridazin-3(2*H*)-one analogues.[326, 371] The solid-phase synthesis of 6-aryl-pyridazin-3(2*H*)-ones through Suzuki-Miyaura cross-coupling of a grafted pyridazinone derivative is effective.[372, 373] Chloropyridazin-3(2*H*)-ones are commercially available (or easily accessible) and undergo palladium-catalyzed Suzuki-Miyaura reactions in high yields when N-2 is protected with either an alkyl group or a labile (removable) protecting group.[326, 374]

From commercially available 4,5- or 5,6-dichloropyridazin-3(2*H*)-one, *N*-alkylated aryl- and amino-aryl-pyridazin-3(2*H*)-one derivatives have been prepared in high yields using Suzuki-Miyaura cross-coupling.[354, 375-377] Selective arylation of *N*-alkyl-4,5-dichloropyridazin-3(2*H*)-one was unsuccessful, giving a mixture of monoaryl-substituted isomers and the diarylated product.[354, 375] For mono-substitution one chlorine must be replaced with a methoxy group, which can be done selectively with sodium methoxide, depending on the choice of solvent.[375] The electron-donating nature of the methoxy group does not effect the cross-coupling at the chlorine, yielding monoarylated derivatives in excellent yields (Scheme 3.4).[354, 375, 376] The remaining methoxy group can be easily converted into the corresponding triflate which is subsequently used in a second Suzuki-Miyaura cross-coupling to yield unsymmetrically substituted 4,5-diaryl pyridazin-3(2*H*)-ones.[378] One can achieve selective Suzuki-Miyaura cross-couplings on dihalopyridazinones with different halogens; for example, 2-methyl-5-chloro-4-iodopyridazin-3(2*H*)-one reacts with phenylboronic acids to yield only one mono-substituted product resulting from reaction at the iodo position, although disubstitution was not completely suppressed.[353]



Scheme 3.4 Suzuki-Miyaura reactions of 2-alkyl-4-/5-chloro-4-/5-methoxypyridazin-3(2*H*)-one.[354, 375]

Pyridazino-fused ring systems, not easily accessible by other routes, have been prepared using a sequential or one-pot strategy combining palladium-catalyzed C–C bond forming reactions with a C–X (X = N, O) or another C–C bond forming reaction, such as a condensation, lactonization, Buchwald-Hartwig amination or Pschorr reaction.[379] For example, the previously undescribed pyridazino[4,5-*c*]isoquiniolinone, dibenzo[f,h]-phthalazin-1(2*H*)-one and -cinnolin-3(2*H*)-one polycyclic pyridazinone systems were prepared by Maes et al. through the cyclization of the biaryl Suzuki-Miyaura coupling products from the reaction of **97** or **98** with *ortho*-substituted phenylboronic acids.[375, 376] As the yields for the intramolecular cyclizations, affording dibenzo[f,h]-phthalazin-1(2*H*)-one and -cinnolin-3(2*H*)-one, were relatively low an alternative strategy utilizing an in situ Pschorr type thermal cyclization was developed, giving good yields and a new route to phenanthrene units.[376]



Scheme 3.5 Synthesis of pyridazino[4,5-*c*]isoquiniolinone via Suzuki-Miyaura–cyclization.[375]

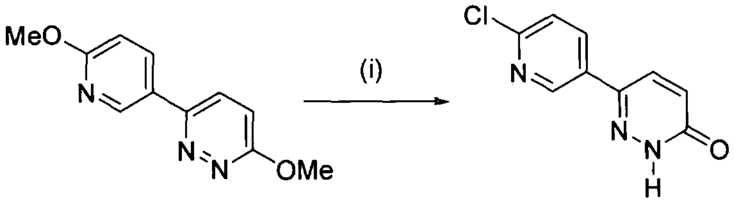
For the preparation of N-2 unsubstituted arylated pyridazin-3(2*H*)-ones, temporary protection of the lactam moiety with a hydroxymethyl group can be employed. It is assumed that initially cross-coupling occurs followed by loss of the protecting group as formaldehyde following a retro-ene fragmentation.[380, 381] This retro-ene assisted Suzuki-Miyaura methodology has been applied to chloro-, bromo- and iodo-pyridazin-3(2*H*)-ones.[363, 380-382]

On the whole chloropyridazin-3(2*H*)-ones are chosen for Suzuki-Miyaura cross-couplings due to their lower cost and greater availability, although bromo- and iodopyridazin-3(2*H*)-ones have been utilized.[326, 353, 371, 383] There appears to be no major advantage to using bromo- or iodopyridazinones as yields with chloropyridazinones are comparable and the bromo- or iodo- derivatives are usually prepared from the commercially available chloro analogues. In all cases palladium-catalyzed cross-couplings (Suzuki-Miyaura, Stille or Sonogashira) occur in higher yields with 2-substituted pyridazinones, indicating that to ensure successful coupling it is critical to block the enolizable carbonyl group.

Palladium-catalyzed cross-coupling reactions of halopyridazin-3(2*H*)-ones is a highly effective method for introducing different substituents on to the pyridazinone core, and is frequently more efficient than the traditional methodology. The remainder of this chapter outlines the conversion of several of our heteroaryl-pyridazine coupling products into their pyridazin-3(2*H*)-one derivatives and further functionalization reactions.

3.2 Preparation of functionalized pyridazin-3(2*H*)-ones

Previously in our group, Greenwood investigated the di-chlorination of **75c** in attempts to increase the structural diversity of heteroarylpyridazines.[340] The conversion of 2-alkoxypyridines to 2-chloropyridines under Vilsmeier-Haack conditions ($POCl_3$/DMF) is reported.[384, 385] Studies in our group also found that different chlorinating agents ($POCl_3$, PCl_3) were successful in converting a 2-methoxypyridine moiety to the 2-chloropyridine derivative, however, in lower yields than when using $POCl_3$/DMF.[340] Interestingly the reaction of **75c** with $POCl_3$ in DMF did not give the dichlorobiheteroaryl product; instead **99** was obtained in 60% yield,[335] representing a new route to the 6-substituted-pyridazin-3(2*H*)-one motif (Scheme 3.6).



75c **99** 60% yield

Scheme 3.6 (i) $POCl_3$, DMF, 110 °C, 19 h.[335]

While the standard methoxy to chloro transformation occurred at the pyridine ring of **75c**, this was not the case at the pyridazine ring, where demethylation occurred instead. There is no literature precedent for the methoxypyridazine to pyridazin-3(2*H*)-one conversion under Vilsmeier-Haack conditions; ordinarily, this transformation occurs under acidic conditions as discussed in Section 3.1. Treatment of 3-methoxypyridazines with HBr or HI, to yield the pyridazin-3(2*H*)-one derivatives, followed by reaction with $POBr_3$ or $POCl_3/PCl_5$ has been applied to prepare the 3-bromo- or 3-chloropyridazines, respectively.[365, 386, 387] Dimethylchloromethleneammonium chloride ($[Me_2N^+{=}CHCl]Cl^-$) has been used as a chlorinating agent in the conversion of 4,5,6-trichloropyridazin-3(2*H*)-one to 3,4,5,6-tetrachloropyridazine.[388] In the reverse procedure, the reaction of 3-(*N*,*N*-dimethylamino)-4,5,6-trichloropyridazine with glacial acetic acid gave 6-(*N*,*N*-dimethylamino)-4,5-dichloropyridazin-3(2*H*)-one in 30% yield.[389] Formylation at C-4 of a 2-alkyl-5-hydroxypyridazin-3(2*H*)-one derivative under Vilsmeier-Haack conditions has been reported.[350] None of the above literature sheds light on the conversion of **75c** into **99** under Vilsmeier-Haack conditions. ^1H and ^{13}C NMR and MS spectra confirmed structure **99**. Figure 3.2 shows the ^1H NMR spectrum of **99**, the pyridazin-3(2*H*)-one N–H signal can be clearly seen at δ 13.4 ppm.

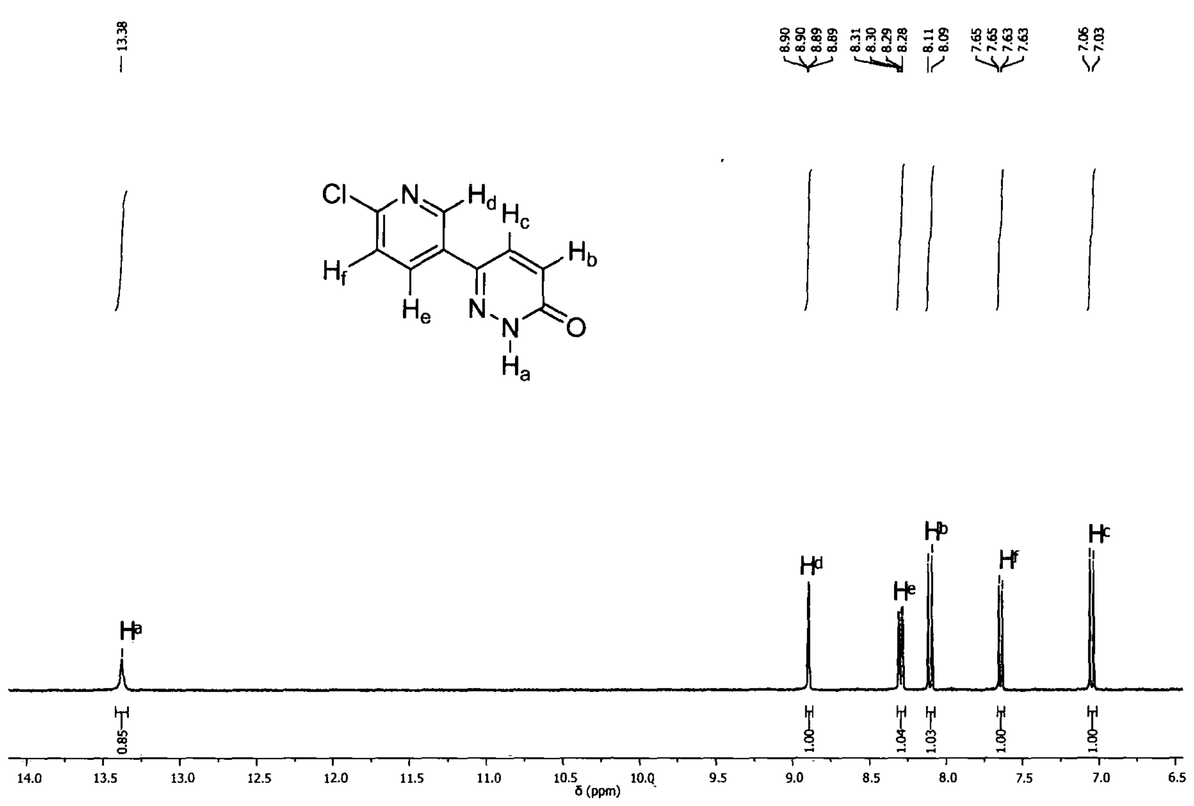
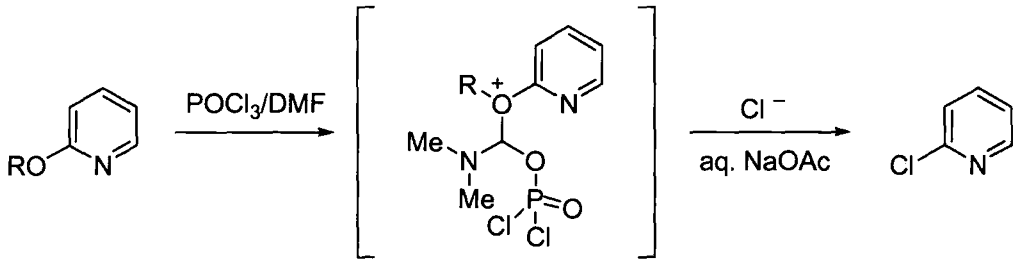


Figure 3.2 ^{1}H NMR spectrum of **99** (400 MHz, DMSO-d$_6$).

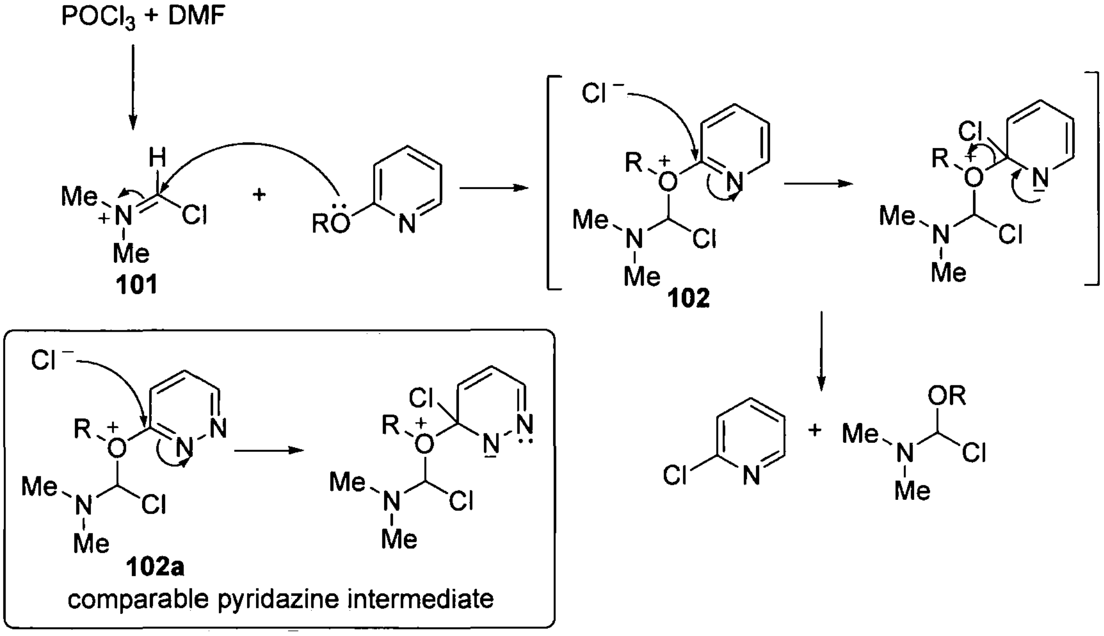
The proposed mechanism for the transformation of 2-alkoxypyridine to 2-chloropyridine involves initial attack of the Vilsmeier-Haack reagent on the oxygen of the alkoxy group, followed by attack of chloride ion at C-2 and cleavage of the ether (Scheme 3.7).[384]



100

Scheme 3.7 Proposed mechanism for the 2-alkoxy- to 2-chloropyridine conversion under Vilsmeier-Haack conditions (as illustrated in reference 384).

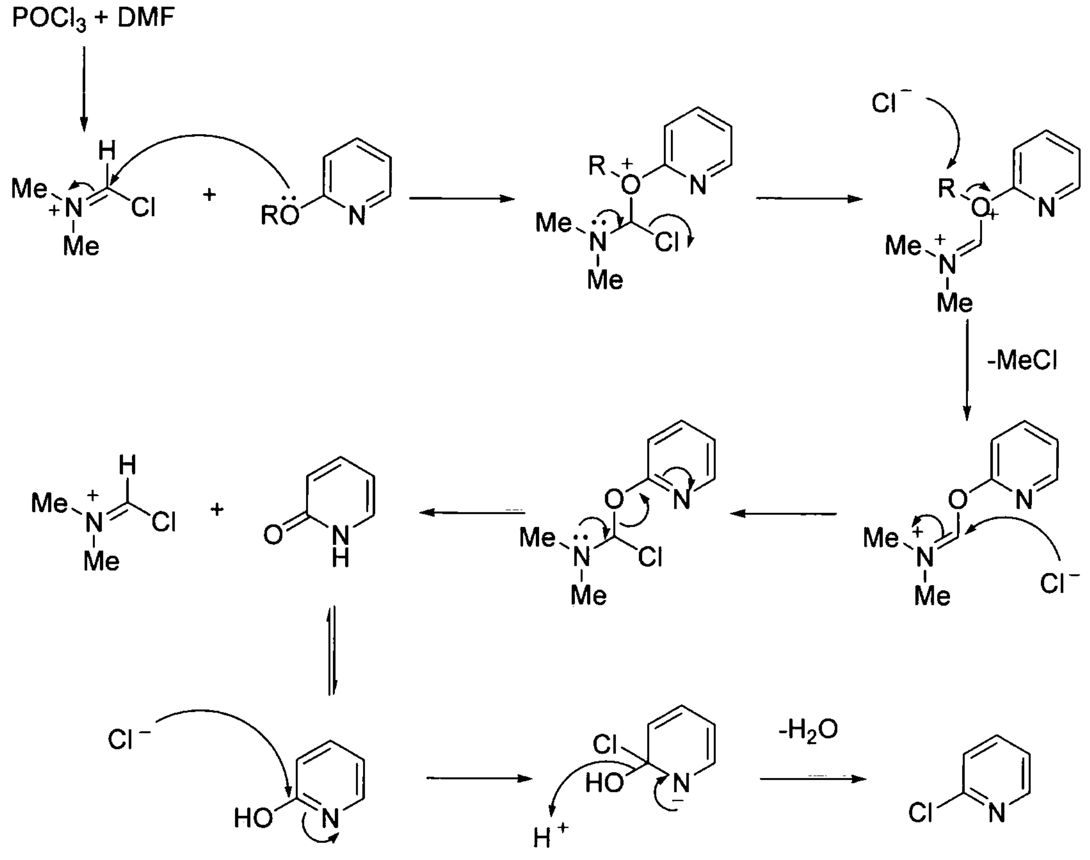
There is some evidence supporting intermediate **100**, however, the active Vilsmeier-Haack reagent is generally regarded as being species **101** (Scheme 3.8). Even so, applying the mechanism proposed in Scheme 3.7 results in a similar outcome, where the product from nucleophilic attack of the chloride ion may be resonance stabilized by the pyridine N (Scheme 3.8, intermediate **102**). If the mechanism in Scheme 3.8 were correct, comparable formation of a resonance stabilized pyridazine-Vilsmeier reagent intermediate (Scheme 3.8, **102a**) would be unfavourable due to repulsion of the negative charge from the adjacent N-1. This could explain why the 3-methoxypyridazine ring does not convert to 3-chloropyridazine, and pyridazin-3(2*H*)-one is isolated instead.



Scheme 3.8 Proposed mechanism for 2-alkoxy- to 2-chloropyridine conversion under Vilsmeier-Haack conditions.

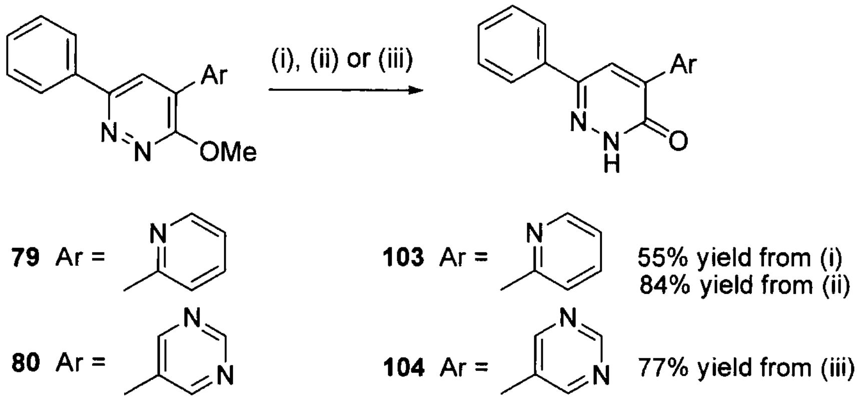
We propose that the Vilsmeier-Haack reagent is acting as an acylating agent, to give the intermediate **102**, but instead of nucleophilic attack at the arene ring, chloride ions attack the methyl of the methoxy substituent, and subsequently the Vilsmeier reagent is reformed along with pyridin-2(1*H*)-one (Scheme 3.9). As the pyridine-pyridinol tautomerization occurs rapidly in solution, nucleophilic attack of chloride ions on the pyridinol tautomer would yield 2-chloropyridine. However, for the 3-methoxypyridazine ring of **75c** the above mechanism would form the pyridazin-3(2*H*)-one which is more stable than the pyridazinol tautomer[390-394] and consequently is less susceptible to nucleophilic attack from chloride ions. Alternatively, the 3-chloropyridazine derivative may be formed and hydrolyzed to **99** during aqueous workup. The 2-chloropyridine function would be relatively more hydrolytically stable. However, as we later found more efficient routes to pyridazin-3(2*H*)-ones from 3-

methoxypyridazines we did not further investigate the reaction mechanism for the transformation under $POCl_3$/DMF.



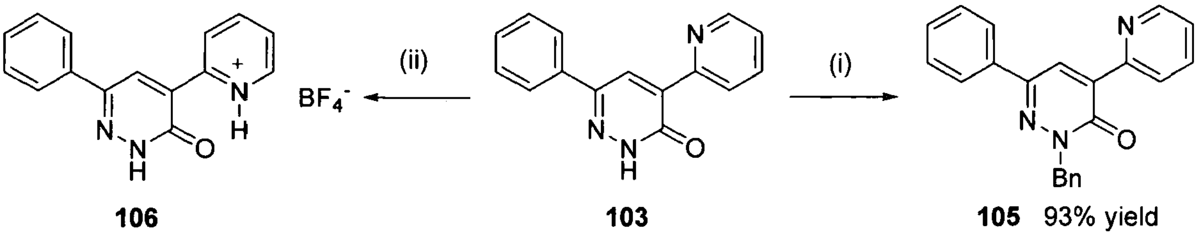
Scheme 3.9 Proposed mechanism for 2-alkoxy- to 2-chloropyridine conversion under Vilsmeier-Haack conditions; the Vilsmeier reagent acting as an acylating agent.

We were interested to see if other methoxy-substituted pyridazines would react with $POCl_3$/DMF to give pyridazin-3(2*H*)-one derivatives. Indeed, compound **79** when treated with $POCl_3$/DMF gave pyridazinone derivative **103** in 55% yield (Scheme 3.10). This transformation has also been repeated under acidic conditions, as highlighted in Section 3.1, although the reaction of **79** with HI (57% aq. soln), heated at reflux, did not yield **103**. No starting material **79** or any other organic species were recovered from the reaction; it is possible that the acid protonated the pyridine ring and formed a salt which was inextractable from the aqueous phase. Consequently, Lewis acidic conditions were considered. On treating **79** with BBr_3 in DCM at reflux an improved yield of **103**, 84%, was obtained. The attempted conversion of **80** to **104** using BBr_3 in DCM was unsuccessful; however, using HBr (48% aq. soln) in acetic acid at 80 °C gave **104** in 77% yield.



Scheme 3.10 (i) $POCl_3$, DMF, 110 °C, 19 h. (ii) BBr_3, DCM, reflux, 4 h. (iii) HBr (48% aq. soln), AcOH, 80 °C, 3.5 h.

We were interested in the structural conformation of **103**, anticipating that the pyridyl N would face in the opposite direction to the pyridazinone carbonyl group to minimize electronic interactions. Compound **103** is not crystalline, so the *N*-benzylated derivative **105** was prepared in 93% yield (Scheme 3.11). Alkylation usually affords N-2 substituted derivatives, some N-1 or *O*-alkylated pyridazinone derivatives have been reported.[395] IR studies of **105** showed a band at 1646 cm^{-1} characteristic of the pyridazinone carbonyl υ(C=O) stretch. X-ray diffraction studies of crystals of **105** confirmed that benzylation had occurred at N-2, and comparison of the C(4)–C(12)–N(11) and C(4)–C(12)–C(13) angles, 115.08(15) and 123.69(16)°, respectively, indicates a pyridyl...O repulsion in **105**, presumably to minimize any electrostatic effects (Figure 3.3). Rings *i* – *iii* are nearly coplanar and there is a weak intramolecular C–H...O hydrogen bond of **105** [C–H 0.94(2), H...O 2.15(2), C(3)–O 1.238(2) Å]. This is also consistent with the conformation of the pyridine ring in the crystal structure of compound **86** (Chapter 2, Figure 2.7).



Scheme 3.11 (i) BnBr, K_2CO_3, Bu_4NCl, MeCN, reflux, 1 h. (ii) HBF_4, MeOH.

Compound **103** was converted into its pyridinium salt **106** with tetrafluoroboric acid.[396] A downfield shift in the ^1H NMR signals of the aromatic protons indicated that the pyridyl N was protonated. X-Ray diffraction studies of **106** (Figure 3.3) revealed a strong N–H...O hydrogen bond in **106**, [N–H 0.95(2), H...O 1.80(2), C(3)–O 1.2474(13) Å], resulting in the co-planarization of rings *i* – *iii*; the orientation of ring *iii* in **106** differs from **105** by ca. 180° rotation. Pyridyl...O attraction in **106** was indicated by the comparison of the C(4)–C(12)–N(11) and C(4)–C(12)–C(13) angles in **106**, 117.92(9) and 124.12(9)°, respectively. The change in conformation (from the neutral pyridazinone) was also observed by a shift in the carbonyl stretching signal to 1669 cm^{-1} in the IR spectrum, due to hydrogen-bonding.

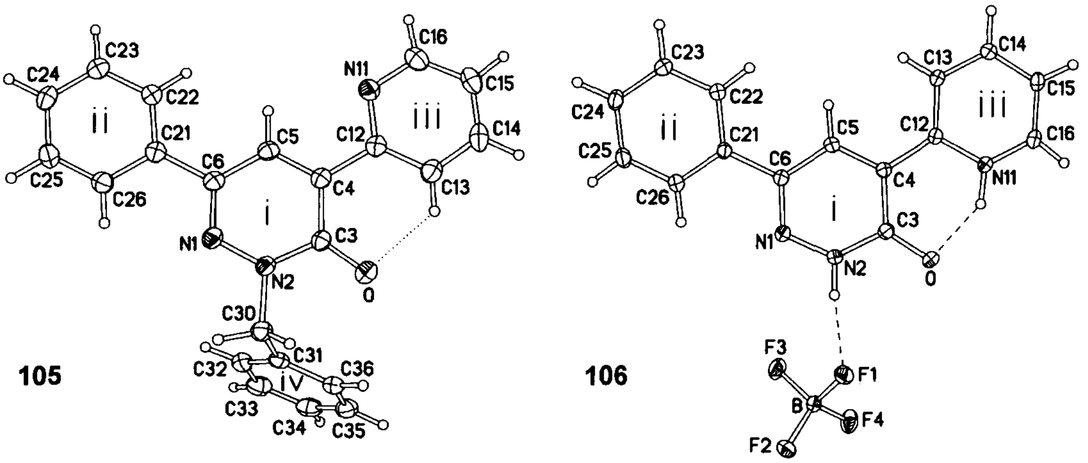


Figure 3.3 X-ray molecular structures of **105** and **106** (50% thermal ellipsoids). Angles between ring planes (°): i/ii 5.2, i/iii 1.3, i/iv 75.8 in **105**, i/ii 12.7, i/iii 2.6 in **106**. Note the much smaller atomic displacements in **106** at the same temperature (120 K). (CCDC **105** 665172, **106** 665173). Dashed lines represent hydrogen bonds.

3.3 Further functionalization of pyridazin-3(2*H*)-ones

N-Alkylation of pyridazin-3(2*H*)-one derivatives is well reported,[351, 361, 395] this motivated us to investigate whether our pyridazinone systems could be further functionalized through *N*-(hetero)arylation at N-2. Initially nucleophilic substitution at N-2 of pyridazinone **103** was attempted with 2-chloropyridine (K_2CO_3, DMF, reflux), however, no reaction occurred. There are few reports in the literature of pyridazinone *N*-(hetero)arylation; several examples of copper-catalyzed C–N bond forming reactions of pyridazinones with aryl halides are detailed,[397-400] although in most cases they are isolated examples rather than a comprehensive study. There are a number of other strategies for C–N coupling of pyridazinones, for example, low yields (19-33%) are obtained in the $Cu(OAc)_2$ promoted *N*-arylation with phenylboronic acids, according to the procedure of Chan and Lam.[286, 401, 402] *N*-Arylation of substituted pyridazin-3(2*H*)-

ones, through the coupling of a C–H bond of benzene or benzene derivative and the N–H bond of pyridazin-3(2H)-one, in the presence of lead tetraacetate/zinc chloride, yields pyridazinone derivatives in 24-71%.[403] To the best of our knowledge there are no reports of Pd-catalyzed Buchwald-Hartwig type amidations of pyridazinones with aryl halides. As copper is significantly less expensive than palladium and the removal of copper from polar products may be easier than trace amounts of palladium, we chose to investigate the copper-catalyzed *N*-(hetero)arylation of our pyridazin-3(2*H*)-one derivatives with aryl halides (preferably bromides).

3.3.1 Copper catalyzed *N*-(Hetero)arylation

Copper-catalyzed C–N coupling reactions have come a long way since the traditional Ullmann systems. Ligand-assisted protocols accelerate reaction rates for the amination or amidation of a variety of (hetero)aryl iodides, bromides and in some cases chlorides.[288, 404] Ligands increase the catalyst solubility and stability and may prevent aggregation of the copper. The scope of the N-containing substrate is also wide; including amines, amides,[400, 405] azoles (pyrazoles, imidazoles,[406-408] pyrroles, indoles, triazoles),[399, 409] and pyridones.[398, 410] Plausible mechanisms for the copper-catalyzed *N*-arylation reactions which have been postulated include radical intermediates or that the mechanism involves oxidative addition/reductive elimination processes. The case for radicals or radical anions has been contested as reactions conducted in the presence of radical scavengers were not inhibited,[399] however, practical and theoretical investigations into the copper complexes proposed as intermediates in copper-catalyzed amidations of aryl halides have shown the potential for the reaction pathway to proceed through radical intermediates.[411]

It is generally regarded that copper-catalyzed C–N bond forming reactions go via an oxidative addition process; this is reflected in the reactivity of aryl halides, with aryl iodides being more reactive than aryl bromides, and aryl chlorides showing very poor reactivity (which parallels the leaving group ability of the halide). As Cu(II) cannot oxidatively insert into a C–X bond it is more likely that the active copper species is Cu(I), regardless of the copper source used. It is still unclear whether the oxidative addition occurs prior to nucleophilic substitution of the N–H species (Figure 3.4, catalytic cycle A), or whether the amino-derivative coordinates to the copper before oxidative addition of the aryl halide (Figure 3.4, catalytic cycle B). In either case the addition of the amine may occur through a nucleophilic coordination to the copper, followed by deprotonation. The binding of the nucleophile enhances the acidity of the amine proton, or the amine may be deprotonated prior to attacking the copper centre. Reductive elimination of the coupling product regenerates the active catalyst. A Cu(I)-catalyzed nucleophilic substitution mechanism would parallel that of the corresponding Pd(0) and Ni(0) species. As Cu(I) is a d_{10} transition metal and isoelectronic with the aforementioned species, this would not be unsurprising. The formation of an arylcopper (III) intermediate is still a contentious issue, as the existence of higher order cuprates is debatable. Recent theoretical studies on the copper-catalyzed cross-coupling of aryl halides with amides, suggest that Cu(III) intermediates would be higher in energy than the Cu(I) complexes and the free aryl halide; however, the Cu(III) species lie at energies that are accessible under mild conditions.[411] Oxidative addition was identified as the rate-limiting step and the Cu(I)→Cu(III) transformation yields a pentacoordinated complex.[412]

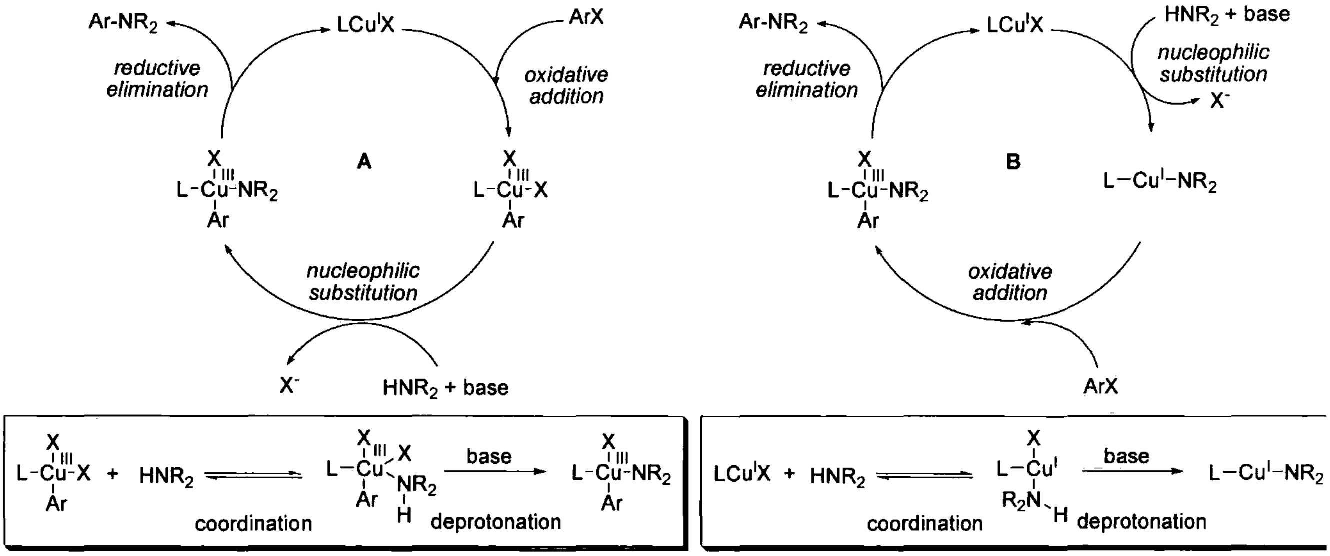
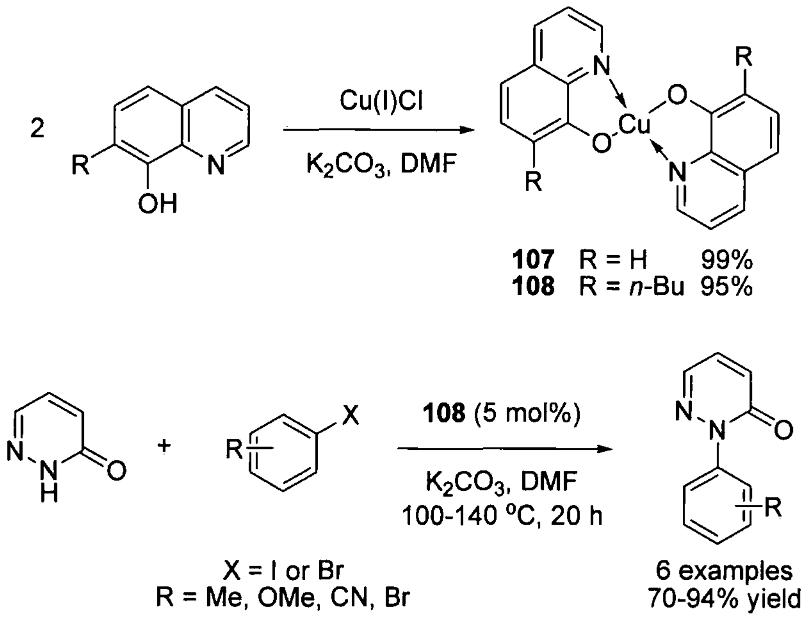


Figure 3.4 Proposed mechanism for the copper-catalyzed N-arylation of aryl halides. Based on the work by Taillefer et al.[399]

As the oxidative addition of an aryl halide to Cu(I) is a reversible process, the role of the additional ligands may be to shift the equilibrium towards the Cu(III) complex through stabilization. Hard donor ligands (such as Lewis bases with N or O binding sites) display a higher affinity towards hard Cu(III) than soft Cu(I).[399] More electron rich ligands stabilize the presumed Cu(III) intermediate, lowering the oxidation potential for the Cu(I)–Cu(III) redox pair, and as a result, accelerate the rate limiting aryl halide activation.[407]

The most comprehensive investigation into the *N*-arylation of pyridazin-3(2*H*)-one was reported while our work was in progress by Pu et al.[397] They found that the palladium-catalyzed *N*-arylation of pyridazin-3(2*H*)-one with aryl bromides "did not succeed under the typical palladium-catalyzed amination or amidation conditions, presumably due to the poor nucleophilicity of this substrate" (no further details were given). Consequently, they investigated copper-catalyzed *N*-arylation and concluded that the optimal reaction conditions for the reaction of pyridazin-3(2*H*)-one (1.5 equiv.) with 4-bromoanisole (1 equiv.) were [CuCl (5 mol%), 8-hydroxyquinoline (10 mol%), K_2CO_3 (1.5 equiv.), DMF, 140 °C, 20 h]. The precatalyst structure was elucidated using the more soluble 7-*n*-propyl-8-hydroxyquinoline ligand. Electrospray ionization mass spectrometry and single crystal X-ray confirmed the structure to be the copper(II)hydroxyquinolate complex **108** (Scheme 3.12).

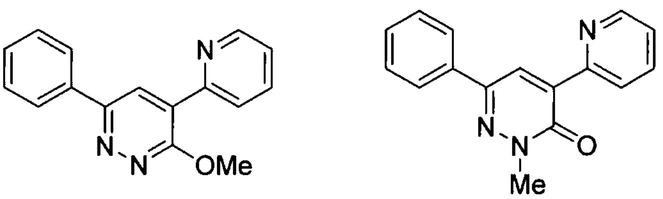


Scheme 3.12 Pyridazin-3(2*H*)-one *N*-arylation using a copper(II) hydroxyquinoline complex.[397]

Pu reported 70-94% isolated yields of 2-arylpyridazin-3(2*H*)-one products, including only one heteroaryl derivative from the reaction of pyridazin-3(2*H*)-one with 6-bromo-2-methylquinoline.[397] A similar catalyst system has been used recently for the *N*-arylation of pyridin-2(1*H*)-ones with aryl bromides and iodides in moderate yields 11-59%, [CuI (15 mol%), 8-hydroxyquinoline (15 mol%), K_2CO_3 (1.1 equiv.), DMSO, 130

°C, 19 h]. Alternative ligands, typically used for amidation of aryl halides, gave much lower yields.[398] Under these conditions one example of *N*-arylation of 6-methylpyridazin-3(2*H*)-one was given.

It is known that the choice of base plays an important role in the reactivity of amidation of aryl halides. The rate of deprotonation of the amide must match the rate of amidation, as an excess of deprotonated amide impedes the amidation reaction presumably through the formation of an unreactive cuprate complex; consequently, the pK_{HA} of the base used should be lower than the pK_{HA} of the amide.[405] 2-Hydroxypyridine, pK_{HA} ~17, is more acidic than indoles and amides, pK_{HA} ~ 21-26, pK_{HA} of imidazole ~ 19, is similar to that of 2-hydroxypyridine. Consequently, catalyst/ligand systems and bases used for the *N*-arylation of imidazole have been applied to 2-hydroxypyridines.[410] For 2-hydroxypyridine, copper-catalyzed arylation favours *N*-arylation instead of *O*-arylation. It has been suggested that the Cu–N binding affinity is significantly stronger than Cu–O binding and isomerization from Cu–N to Cu–O may be slower than Ar–X activation accounting for the selectivity.[410] The pK_A for tautomerisation of pyridazin-3(2*H*)-one and 3-hydroxypyridazine is -1.80, indicating that the tautomeric compound exists in the oxo form to the extent ca. $10^{4.6}$:1.[392] The pK_{HA} for pyridazin-3(2*H*)-one is 10.46, which is more acidic than 2-hydroxypyridine, consequently, we assumed that copper-catalyzed arylation would be selective for *N*-arylation. On applying the conditions outlined by Pu et al.[397] [**107** (5 mol% Ar-X), DMF, Cs_2CO_3 (1.5 equiv.), 140 °C, 24 h] for the reaction of compound **103** with 4-bromoanisole **109** and 5-bromo-2-methoxypyridine **110**, the C–N coupling products **112** and **113** were isolated in 41% and 21%, respectively (Table 3.1), along with a by-product (ca. 50% yield of by-product alongside **113**). The ^{1}H NMR spectrum of the by-product suggested that *N*- or *O*-methylation had occurred to give 3-methoxypyridazine **79**, or the 2-methylpyridazin-3(2*H*)-one isomer **117** (Figure 3.5).



79 **117**

Figure 3.5 Possible structures of the by-product isolated in the copper-catalyzed *N*-arylation of **103** with DMF as solvent.

^{1}H NMR chemical shifts of this by-product were slightly different from **79** (isolated previously from the cross-coupling of boronic ester **77a** with 2-bromopyridine). MS(ES$^+$) showed a molecular ion of *m/z* 264.2 (M+H)$^+$, consistent with either structure proposed and elemental analysis was correct. The IR spectrum of the by-product showed a signal at 1646 cm^{-1} indicative of a carbonyl υ(C=O) stretch. Comparison of the pyridazinyl C-5 proton signal in the ^{1}H NMR spectra of **79**, **103** and **105**, showed a downfield shift in **103** and **105** compared to **79**, from δ 8.54 ppm in **79** to ~δ 8.8 ppm in **103** and **105** (400 MHz, $CDCl_3$). The by-product showed the C-5 pyridazine proton at δ 8.73 ppm (Figure 3.6 shows the superimposed ^{1}H NMR spectra of **79**, **103**, **105** and the by-product). From all the above data we concluded that the by-product was in fact the *N*-methylated derivative **117**. The methyl substituent may originate from the DMF solvent. It is also possible that the methoxy group of the aryl halide (e.g. X–C_6H_4–OMe) provides the methyl group (analogous to deprotonation of phenol). As aryl halides without a methoxy substituent were not employed with DMF as the solvent, the source of methylation can only be speculated.

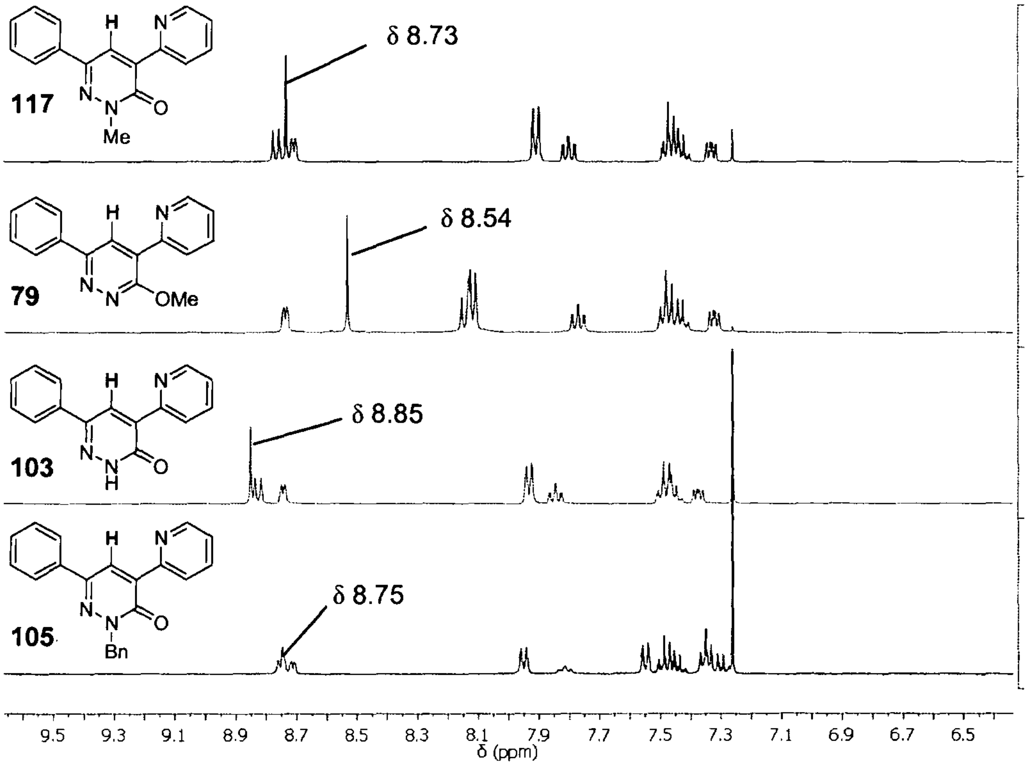
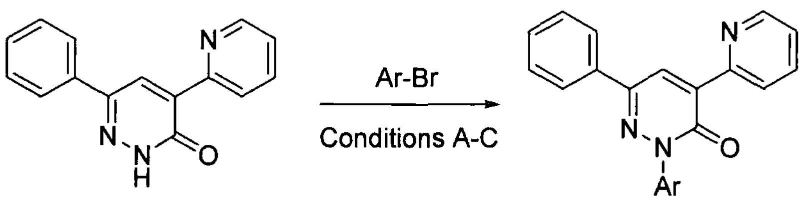


Figure 3.6 ^{1}H NMR spectra of **117** (spectrum 1) **79** (spectrum 2), **103** (spectrum 3) and **105** (spectrum 4), (400 MHz, $CDCl_3$).

On changing the reaction solvent to 1,4-dioxane, for the reaction of **103** with **110**, no by-product was isolated, only the C–N coupling product **113** in 74% yield. All pyridazinone *N*-arylation results are collated in Table 3.1. The reaction rates of copper-catalyzed *N*-arylations can be increased by addition of a solid-liquid phase-transfer agent, such as polyethylene glycol (PEG) with Cs_2CO_3 as base.[407] We investigated the effect of using the copper source (CuI) and ligand (8-hydroxyquinoline) separately instead of as the pre-formed copper complex **107**, and with added PEG. This procedure slightly improved the yield of **113** (entry 2, conditions C) and, therefore, subsequently the standard conditions used for the *N*-arylation of **103** were [CuI (5 mol% Ar-Br)/8-hydroxyquinoline (10 mol% Ar-Br), 1,4-dioxane, Cs_2CO_3 (1.5 equiv.), PEG, reflux, 41-51 h]. The C–N coupling yields were good (63-81%) with a number of bromoheterocycles (entries 2, 3 and 5) and different functional groups (methoxy, trifluoromethyl, nitro). The low yield of *N*-pyrimidyl derivative **115** (35%, entry 4) was unexpected; unreacted **103** was isolated in 50% yield.

The *N*-(hetero)arylation of pyridazin-3(2*H*)-one **103** detailed herein is complementary to the work of Pu et al.[397] and extends the protocol to bromo-heteroaryl coupling partners with a selection of functionality (methoxy, trifluoromethyl, nitro). Another system which may be suitable for the *N*-(hetero)arylation of pyridazin-3(2*H*)-one derivatives is CuI, 4,7-dimethoxy-1,10-phenanthroline, K_2CO_3, DMSO, 110 °C;[410] these conditions have been used for the *N*-(hetero)arylation of pyridin-2(1*H*)-ones with bromo- and iodo(hetero)arenes. As the acidity of the amide N–H of pyridin-2(1*H*)-one and pyridazin-3(2*H*)-one is similar, these conditions could be compatable with pyridazin-3(2*H*)-ones. However, 4,7-dimethoxy-1,10-phenanthroline is not commercially available and requires a multi-step synthesis so it was not investigated as a ligand in the copper-catalyzed *N*-(hetero)arylation of **103**.



103 → **112-116**

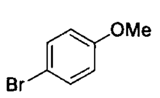
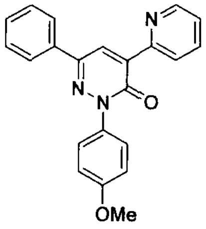
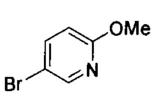
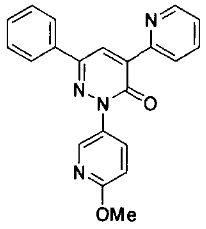
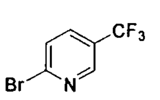
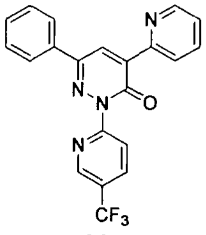
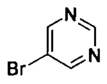
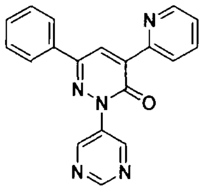
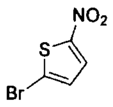
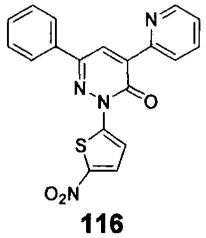
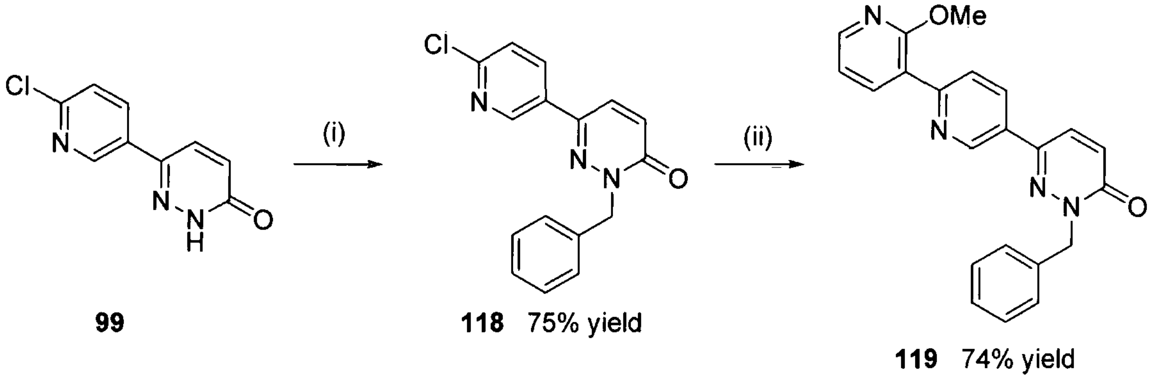
Entry	Ar-Br	Product	Conditions	Isolated yield (%)
1	 **109**	 **112**	A	41*
2	 **110**	 **113**	A B C	21* 74 80
3	 **111**	 **114**	C	81
4	 **62**	 **115**	C	35
5	 **65**	 **116**	C	63

Table 3.1 Conditions A: **107** (5 mol% Ar-Br), DMF, for **112** $K_2CO_{3\,(s)}$; for **113** $Cs_2CO_{3\,(s)}$ (1.5 equiv.), 140 °C, 24-48 h. B: **107** (5 mol% Ar-Br), 1,4-dioxane, $Cs_2CO_{3\,(s)}$ (1.5 equiv.), reflux, 48 h. C: CuI (5 mol% Ar-Br)/8-hydroxyquinoline (10 mol% Ar-Br), 1,4-dioxane, $Cs_2CO_{3\,(s)}$ (1.5 equiv.), PEG, reflux, 41-51 h. *By-product **117** isolated.

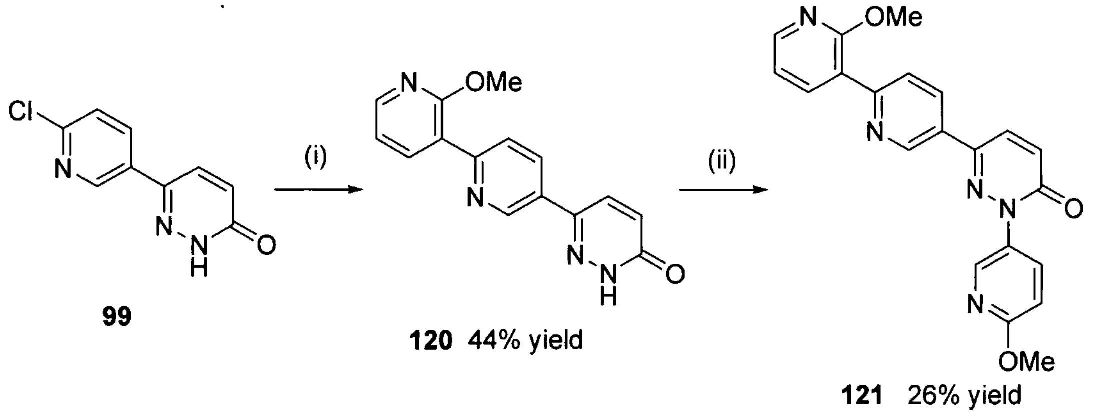
3.3.2 C–C/C–N Cross-couplings of 99

Compound **99** is equipped for both *N*-(hetero)arylation at the pyridazinone and Suzuki-Miyaura reaction at the pyridine ring. As discussed in Section 3.1, palladium-catalyzed cross-couplings of halopyridazin-3(2*H*)-one generally require N-2 protection for high yielding reactions. The protection of **99** with a hydroxymethyl group, following the procedure outlined by Coelho et al,[380] was unsuccessful, yielding a multicomponent mixture that was not further investigated. *N*-Benzylation of **99** was successful, and subsequent Suzuki-Miyaura cross-coupling with 2-methoxy-3-pyridylboronic acid produced the extended pyridazinone structure **119** in 74% yield (Scheme 3.13).



Scheme 3.13 (i) BnBr, K_2CO_3, Bu_4NCl, MeCN, reflux, 1 h. (ii) 2-Methoxy-3-pyridylboronic acid, $Pd(PPh_3)_4$ (5 mol% **118**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 3 h.

The Suzuki-Miyaura cross-coupling of **99** with 2-methoxy-3-pyridylboronic acid, without protection of the pyridazin-3(2*H*)-one, effectively prepared **120** in 44% isolated yield (Scheme 3.14), ^{1}H, ^{13}C NMR and HRMS confirmed the structure of **120**. **120** was subjected to *N*-heteroarylation under the standard copper-catalyzed reaction conditions previously used with **103**. Pyridazinone derivative **121** was isolated in a poor yield of 26% as a result of difficult purification. The structure was confirmed through 2D NMR (see Appendix A2) and HRMS. The ^{1}H and ^{13}C NMR spectra in $CDCl_3$ at room temperature showed broadening of several of the proton and carbon signals as a result of incomplete averaging of the signals. This may be a result of incomplete averaging of rotamers, however the ^{1}H and ^{13}C NMR spectra at 90 °C in 1,1,2,2-tetrachloroethane-d_2 gave no further definition to the proton or carbon signals, which would be expected for restricted rotation. Protonation/deprotonation of the pyridine rings may also be occurring and consequently causing incomplete averaging and downfield shifting of the signals. **121** is a yellow solid and TLC shows fluorescence under 365 nm light. Conjugation between the pyridazinone ring and the *N*-pyridyl ring may be accountable for these observations. These reactions highlight the potential for the further derivatization of pyridazin-3(2*H*)-one **99**, although further optimization of reaction conditions is required. From a sequential strategy we have successfully prepared extended pyridazin-3(2*H*)-one structures which are notable as multiheteroaryl arrays.



Scheme 3.14 (i) 2-Methoxy-3-pyridylboronic acid, $Pd(PPh_3)_2Cl_2$ (5 mol% **99**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 21 h. (ii) 5-Bromo-2-methoxypyridine, CuI (5 mol% Ar-Br), 8-hydroxyquinoline (10 mol% Ar-Br), Cs_2CO_3 $_{(s)}$, PEG, 1,4-dioxane, reflux, 45 h.

3.4 Conclusions

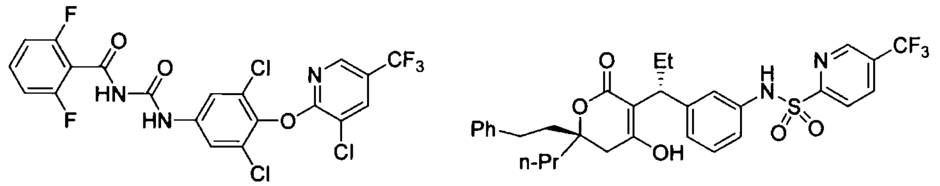
Substituted 3-methoxypyridazines have been converted into the corresponding pyridazin-3(2*H*)-ones with good functional group tolerance via a number of different routes. The pyridazin-3(2*H*)-one derivatives offer scope for further synthetic transformations; primarily the copper-catalyzed *N*-(hetero)arylation of these pyridazin-3(2*H*)-ones has been demonstrated. This work builds on current literature on the *N*-arylation of pyridazin-3(2*H*)-ones, expanding the variety of heteroaryl bromides employed and functionality introduced.

Pyridazinone **99** has shown to be an attractive reagent, compatible with Suzuki-Miyaura cross-couplings and *N*-functionalization. This systematic approach to derivatizing the core pyridazin-3-(2*H*)-one structure has prepared a number of multiheteroaryl motifs. These functionalized heterocycles are attractive candidates as new pharmacophores and scaffolds for drug discovery.

CHAPTER 4 – (TRIFLUOROMETHYL)-SUBSTITUTED PYRIDYL- AND PYRAZOLYLBORONIC ACIDS AND ESTERS

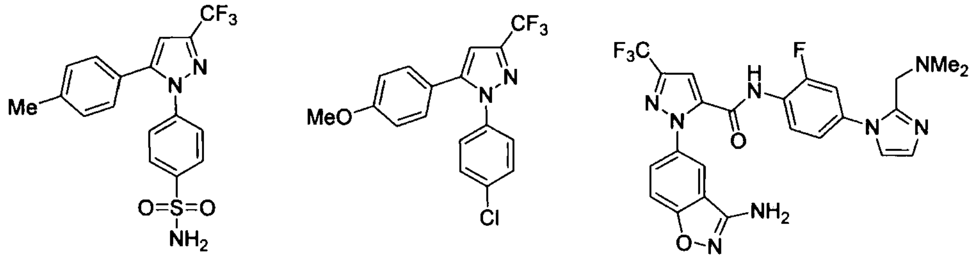
4.1 Introduction

The presence of a trifluoromethyl moiety can dramatically modify the physical and chemical properties of a compound making it a privileged motif in medicinal and materials chemistry when attempting to tailor a specific activity profile.[413] For example, the replacement of a substituent, or addition of a trifluoromethyl group to a lead compound can alter (a) the shape and size of a compound,[414] (b) the acidity,[415] (c) dipole moments,[416] and (d) lipophilicity.[417] Trifluoromethyl-substituted heteroaryls, e.g. pyridines and pyrazoles, are found in several biologically active compounds, for example, the insecticide Chlorfluazuron is a chitin synthesis inhibitor[418] and Aptivus® (Tipranavir) is a commercial HIV protease inhibitor and manufactured by Boehringer Ingelheim.[419, 420] Structures are shown in Figure 4.1.



Chlorfluazuron
Insecticide, chitin synthesis inhibitor[418]

Tipranavir (Aptivus®)
HIV protease inhibitor[419]



Celecoxib (Celexbrex®)
Non-steroidal anti-inflammatory
COX-2 inhibitor[422]

SC-560
Anti-tumour activity
COX-1 inhibitor[423]

Razaxaban
Treatment of thrombotic diseases
factor Xa inhibitor[425]

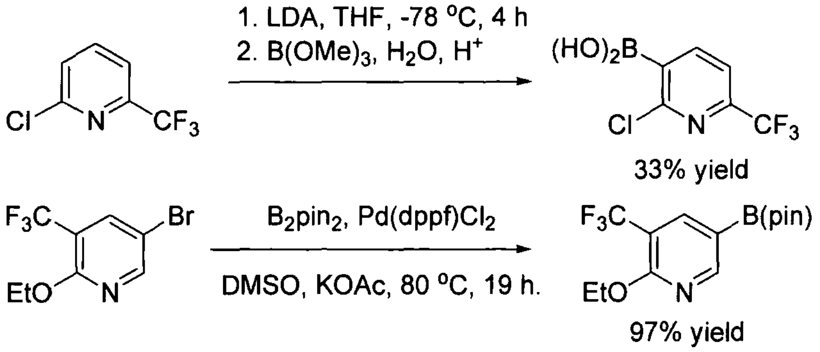
Figure 4.1 Examples of biologically active (trifluoromethyl)-substituted pyridines and pyrazoles.

Pyrazoles bearing a trifluoromethyl group constitute the core structure of pharmaceuticals across a number of therapeutic areas:[421] Celexbrex® (Celecoxib) is a COX-2 inhibitor and non-steroidal anti-inflammatory manufactured by Pfizer,[422] whereas SC-560 is a COX-1 inhibitor and shows anti-tumour activity (Figure 4.1).[423, 424]

Razaxaban and derivatives are factor Xa inhibitors used in the treatment of thrombotic diseases.[425]

Organofluorine compounds are scarce in nature; any fluorine-containing compounds for pharmaceuticals, agrochemicals and advanced materials must therefore be synthesized. In synthetic organic chemistry fluorine generally comes from an inorganic source. The traditional methods for the incorporation of a trifluoromethyl group into organic compounds from an inorganic fluorine source have been supplemented by more convenient procedures. Previous methods include the halogen exchange of a trichloromethyl group using anhydrous hydrogen fluoride or antimony trifluoride (in the presence or absence of antimony pentachloride)[426-428] or the treatment of a carboxylic acid with sulfur tetrafluoride in a pressurized vessel.[429, 430] More recently the copper-promoted reductive coupling of aryl iodides with trifluoromethyl iodide,[431, 432] and the in situ generation of trifluoromethylcopper species from (trifluoromethyl)trimethylsilane ("Ruppert-Prakash reagent"[433, 434]) in the presence of copper(I) iodide and potassium fluoride have been used for the preparation of CF_3-substituted benzene[435] and pyridine derivatives.[436]

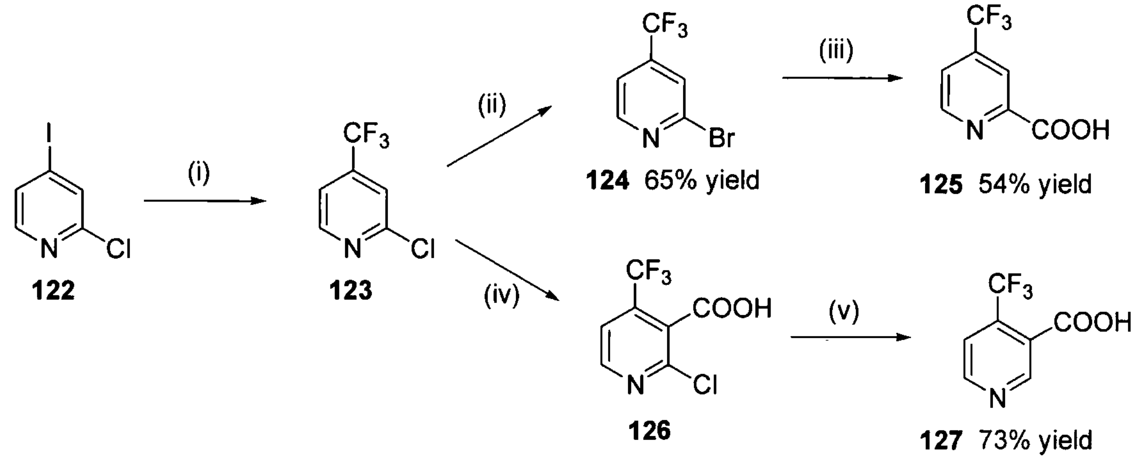
(Trifluoromethyl)-substituted arylboronic acids are valuable building blocks in the synthesis of biaryl systems for pharmaceutical and agrochemical research, and are widely used in combinatorial chemistry. (Trifluoromethyl)phenylboronic acids are extensive commercial availability; there are a handful of accounts of their preparation in the literature, several of those being in patents.[437-444] With the increased availability of CF_3-substituted aryl/heteroaryl halides and phenylboronic acid derivatives bearing CF_3 groups, the Suzuki-Miyaura cross-coupling is being utilized in the preparation of specific aryl/heteroaryl scaffolds or libraries of compounds with trifluoromethyl functionalities.[445-453] On account of the widespread interest in (trifluoromethyl)phenylboronic acids one would anticipate investigation into heteroarylboronic acids containing a (trifluoromethyl)-moiety. Therefore, it is somewhat surprising to observe the distinct lack of literature surrounding trifluoromethylated heteroarylboronic acids, as they are very attractive reagents for the preparation of functionalized heterobiaryl systems. The majority of reports of CF_3-substituted heteroarylboronic acids are in patent literature.[454-465] The preparations of (trifluoromethyl)pyridylboronic acids are vague with little analytical data given to confirm their purity (Scheme 4.1).[454, 456, 459, 460, 465]



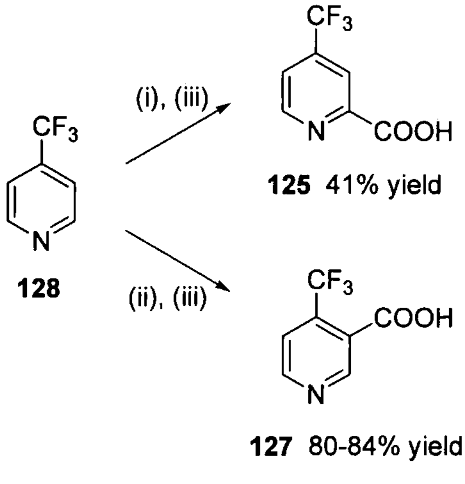
Scheme 4.1 Example syntheses of (trifluoromethyl)-substituted pyridylboronic acids.[454, 459]

Schlosser and co-workers have been innovative in developing the area of trifluoromethyl chemistry.[466] Starting from arenes and heteroarenes functionalized with a CF_3 group they have utilized "regioexhaustive substitution" to prepare a variety of organometallic intermediates; on trapping with electrophiles these yield new fluorinated building blocks.[467-472] They highlight the potential for lithiation of (trifluoromethyl)-(hetero)aromatic compounds. In their work they use carbon dioxide to trap the organometallic intermediates, resulting in extensive libraries of structurally isomeric (hetero)aryl carboxylic acids. The syntheses of (trifluoromethyl)pyridine carboxylic acids involves halogen-lithium exchange or D*o*M on unsubstituted and halo-substituted (trifluoromethyl)pyridines.[467, 468, 473] In cases where the starting pyridines are not commercially available they are prepared using copper-mediated iodine/trifluoromethyl displacement. For example, Scheme 4.2 shows the preparation of **123** from the iodo-precursor and then, via different routes, yields the two carboxylic **125** [54%, step (iii)] and **127** [73%, steps (iv) and (v)].

Carboxylic acids **125** and **127** can alternatively be prepared using 4-(trifluoromethyl)pyridine as the substrate, with the choice of base determining regioselective lithiation.[467] LDA and LTMP abstract protons exclusively from the 3-position, thus generating **127** on carboxylation and neutralization. Caubère's base, lithium 2-(dimethylamino)ethoxide-activated butyllithium, is specific for the 2-position, as demonstrated by the formation of acid **125** (Scheme 4.3). The choice of lithiating agent and conditions can favour the lithiation of a particular available site, balancing any directing effects attributable to the trifluoromethyl group and other substituents on the pyridine ring, and steric hindrance resulting from the trifluoromethyl group.[467, 468, 473, 474] Related work has also been conducted in the regioselective metalation of halo(trifluoromethyl)benzenes, and on the steric and electronic effects of the trifluoromethyl group on the site selectivity.[471, 475, 476]



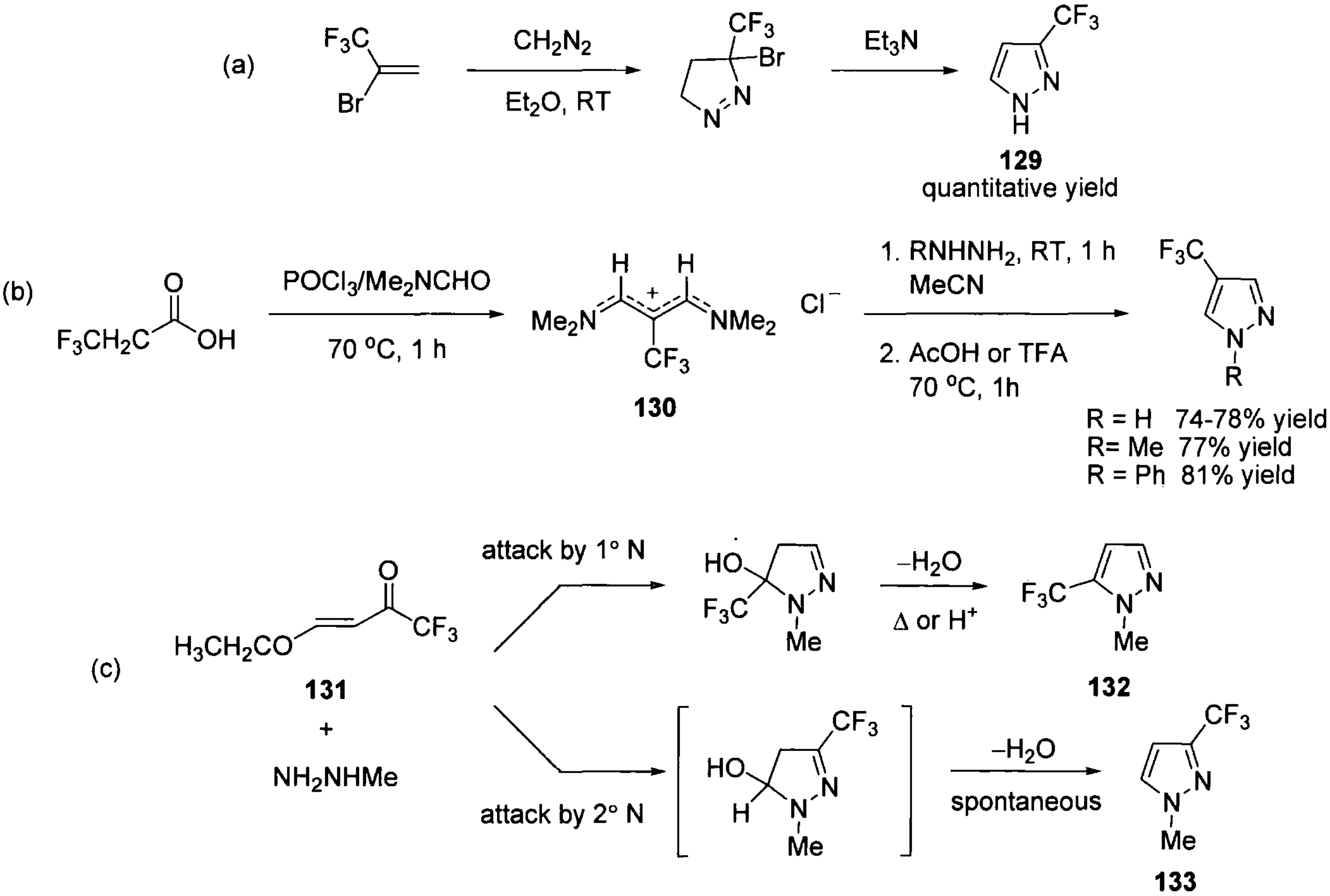
Scheme 4.2 An example preparation of (trifluoromethyl)pyridine carboxylic acids.[473] (i) Me_3SiCF_3, CuI, KF, 25 °C (ii) $BrSiMe_3$ in C_2H_5CN, 100 °C (iii) *n*-BuLi, toluene/THF, –75 °C, CO_2, H^+ (iv) LDA, THF, –75 °C, CO_2, H^+ (v) $HCOONH_4$, Pd/C in MeOH, 25 °C.



Scheme 4.3 Alternative preparation of **125** and **127**.[467] (i) *n*-BuLi in the presence of lithium 2-(dimethylamino)ethoxide, Et_2O, –75 °C, 2 h (ii) LDA or LTMP, THF, –75 °C, 2 h (iii) CO_2, H^+.

The lithiation of (trifluoromethyl)pyridines is now a well known route to new (trifluoromethyl)-bearing heteroaromatic building blocks. The inductive electron-withdrawing nature of the trifluoromethyl group increases substrate acidities and in some cases can stabilize anionic intermediates. However, this does not always facilitate kinetic deprotonation, due to CF_3 being a relatively bulky substitutent. We recognized that these protocols could be adapted for the preparation of (trifluoromethyl)pyridylboronic acids, paving the way for novel pyridylboronates for use in the synthesis of functionalized heterobiaryls.

Trifluoromethylated pyrazoles have been prepared via a number of protocols. In all cases the trifluoromethyl moiety is present on an alkene or carbonyl containing substrate which is used to construct the pyrazole ring via a condensation or [3+2] cycloaddition. For example, the 1,3-dipolar cycloaddition of 2-bromotrifluoropropene and diazomethane occurs regioselectively yielding 3-(trifluoromethyl)pyrazole **129** in quantitative yield [Scheme 4.4, (a)].



Scheme 4.4 Procedures for the preparation of 3-(trifluoromethyl)pyrazole derivatives. (a) 1,3-dipolar cycloaddition of 2-bromotrifluoropropene and diazomethane.[477] (b) Reaction of a β-trifluoromethyl vinamidinium salt with a hydrazine.[478] (c) Condensation of methylhydrazine with 4-ethoxy-1,1,1-trifluoro-3-buten-2-one.[479, 480]

A β-trifluoromethyl vinamidinium salt was reported as a novel trifluoromethylating agent. Following preparation from the reaction of 3,3,3-trifluoropropanoic acid with phosphorus oxychloride in DMF, the vinamidinium salt reacts with bifunctional nitrogen nucleophiles, leading to trifluoromethylated azaheterocycles [Scheme 4.4, (b)]. The reaction of **130** with hydrazine derivatives gave 4-(trifluoromethyl)pyrazole and 1-methyl- or 1-phenyl-4-(trifluoromethyl)pyrazole in good yields (74-81%).[478]

4-Ethoxy-1,1,1-trifluoro-3-buten-2-one **131** has been used in a number of procedures to prepare 3- and 5-(trifluoromethyl)pyrazoles.[480, 481] Treating **131** with methylhydrazine affords a regioisomeric mixture of 1-methyl-3-(trifluoromethyl)pyrazole **133** and 1-methyl-5-(trifluoromethyl)pyrazole **132** in ca. 2.5:1 ratio (**133**:**132**). This is a result of initial competitive Michael attack by the primary and secondary nitrogen atoms of methylhydrazine [Scheme 4.4, (c)]. The mixture can be easily separated as the dihydroxypyrazol-5-ol intermediate to isomer **132** is sufficiently stable to allow isolation, whereas the precursor to **133** undergoes spontaneous dehydration. Reaction of **131** with phenylhydrazine or 2-bromophenylhydrazine yields the 1-phenyl- and 1-(2-bromophenyl)-5-(trifluoromethyl)pyrazole derivatives in good yields (both 78% yield); no comment was made on whether the 3-(trifluoromethyl)pyrazole isomer was observed.[481]

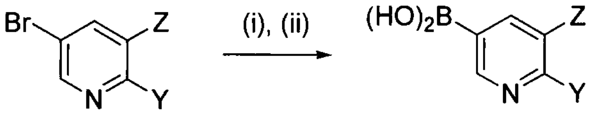
There are numerous methods for the preparation of trifluoromethylated heteroaryls and only a few have been highlighted here. More recently, (trifluoromethyl)-substituted heteroarenes, especially pyridines, have gained wider commercial availability, and at reasonable cost. With the trifluoromethylated heteroaryl building blocks in hand, and the importance of these motifs within pharmaceuticals and agrochemicals, there are incentives for further functionalizations to create new heteroaryl scaffolds.

The present chapter outlines the preparation of CF_3-substituted pyridylboronic acids and pyrazolylboronic esters via lithiation/boronation of commercial CF_3-substituted starting materials. The Suzuki-Miyaura cross-couplings of these boronic acids and esters with functionalized halo-benzene and halo-heteroarene partners provide new trifluoromethylated heterobiaryl systems, including tetra-functionalized pyrazoles.

4.2 (Trifluoromethyl)-substituted pyridylboronic acids

4.2.1 Synthesis and reactions of 2- and 3-(trifluoromethyl)-5-pyridylboronic acid

Prior to our work the preparation of **137** had been reported in a patent although the only analytical data given was the mass spectrum of its hydrochloride salt.[482] One example of a Suzuki-Miyaura cross-coupling reaction of **137** with 3-bromo-l-methyl-l*H*-pyrazolo[3,4-d]pyrimidin-6-ylamine was detailed. Lithium-halogen exchange of 5-bromo-2-(trifluoromethyl)pyridine **134** and 5-bromo-3-(trifluoromethyl)pyridine **135** with *n*-BuLi in THF at –78 °C, then addition of triisopropylborate followed by aqueous workup yielded boronic acid derivatives **136** and **137** as air-stable solids in 95% and 94% yields, respectively, on a ca. 10 g scale (Scheme 4.5). The X-ray crystal structure of **136** was obtained (Figure 4.2). Here and in the X-ray crystallography figures below atomic displacement ellipsoids are drawn at the 50% probability level.



134 Y = CF_3, Z = H
135 Y = H, Z = CF_3
136 X = CF_3, Z = H 95% yield
137 X = H, Z = CF_3 94% yield

Scheme 4.5 (i) *n*-BuLi, $B(Oi\text{-}Pr)_3$, THF, –78 °C, 3 h. (ii) H_2O, AcOH.

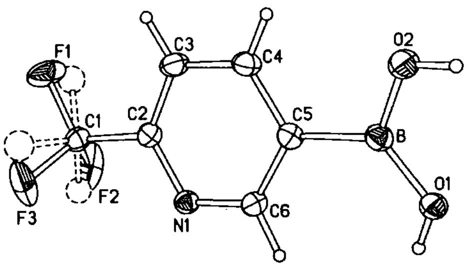
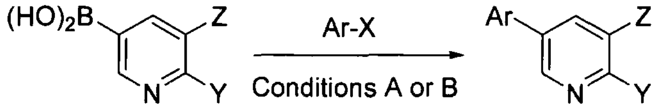


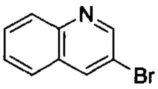
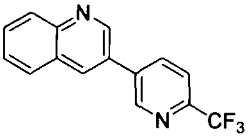
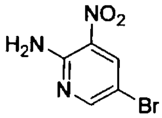
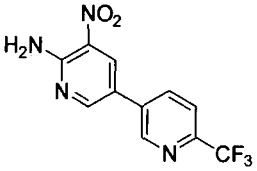
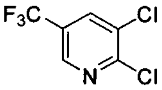
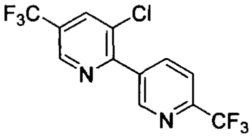
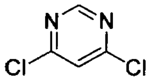
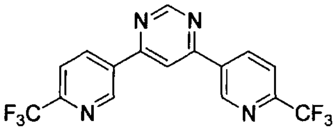
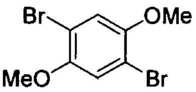
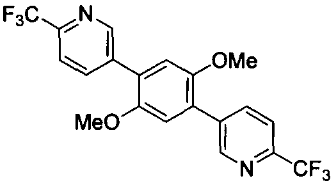
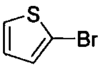
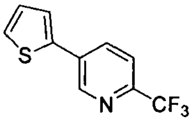
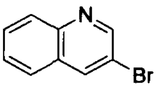
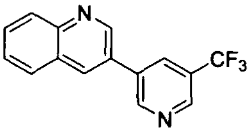
Figure 4.2 X-ray molecular structure of **136**. The rotational disorder of the CF_3 group was modelled as two orientations with the probabilities of 85% (solid) and 15% (dashed). (CCDC-699539).

Suzuki-Miyaura cross-coupling reactions of **136** and **137** were carried out with a variety of (hetero)aryl bromides and chlorides **61**, **66**, **138-142** under standard conditions [$Pd(PPh_3)_2Cl_2$, (t-Bu_3P was added in some cases), 1,4-dioxane, Na_2CO_3, reflux] to yield products **143-153**, respectively. The results presented in Table 1 show that reactions generally proceed in high yields for both electron-rich (entries 5, 6 and 9) and electron-deficient coupling partners (entries 1-4, 7, 8, 10-12). The efficient reactions of heteroaryl chlorides (entries 3, 4, 10-12) are notable due to their wider availability and lower cost than bromide derivatives. Primary amine, nitro and methoxy functionalities on the coupling partners were tolerated.



136 Y = CF_3, Z = H
137 Y = H, Z = CF_3

143-153
Y, Z = CF_3 or H

Entry	Boronic acid	Ar-X	Product	Conditions	Time (h)	Isolated yield (%)
1	**136**	 **66**	 **143**	A	22	94
2	**136**	 **61**	 **144**	A	17	75
3	**136**[a]	 **138**	 **145**	A	4	92
4	**136**[b]	 **139**	 **146**	B	21[d]	81
5	**136**[b]	 **140**	 **147**	A	1	77
6	**136**	 **141**	 **148**	A	3	93
7	**137**	 **66**	 **149**	A	22	98

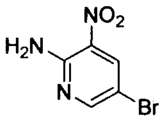
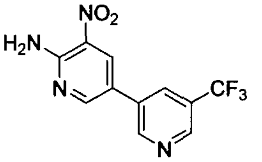
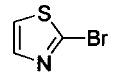
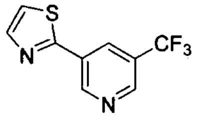
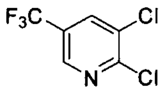
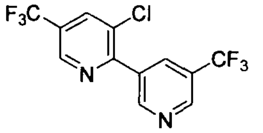
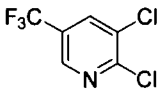
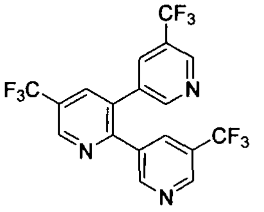
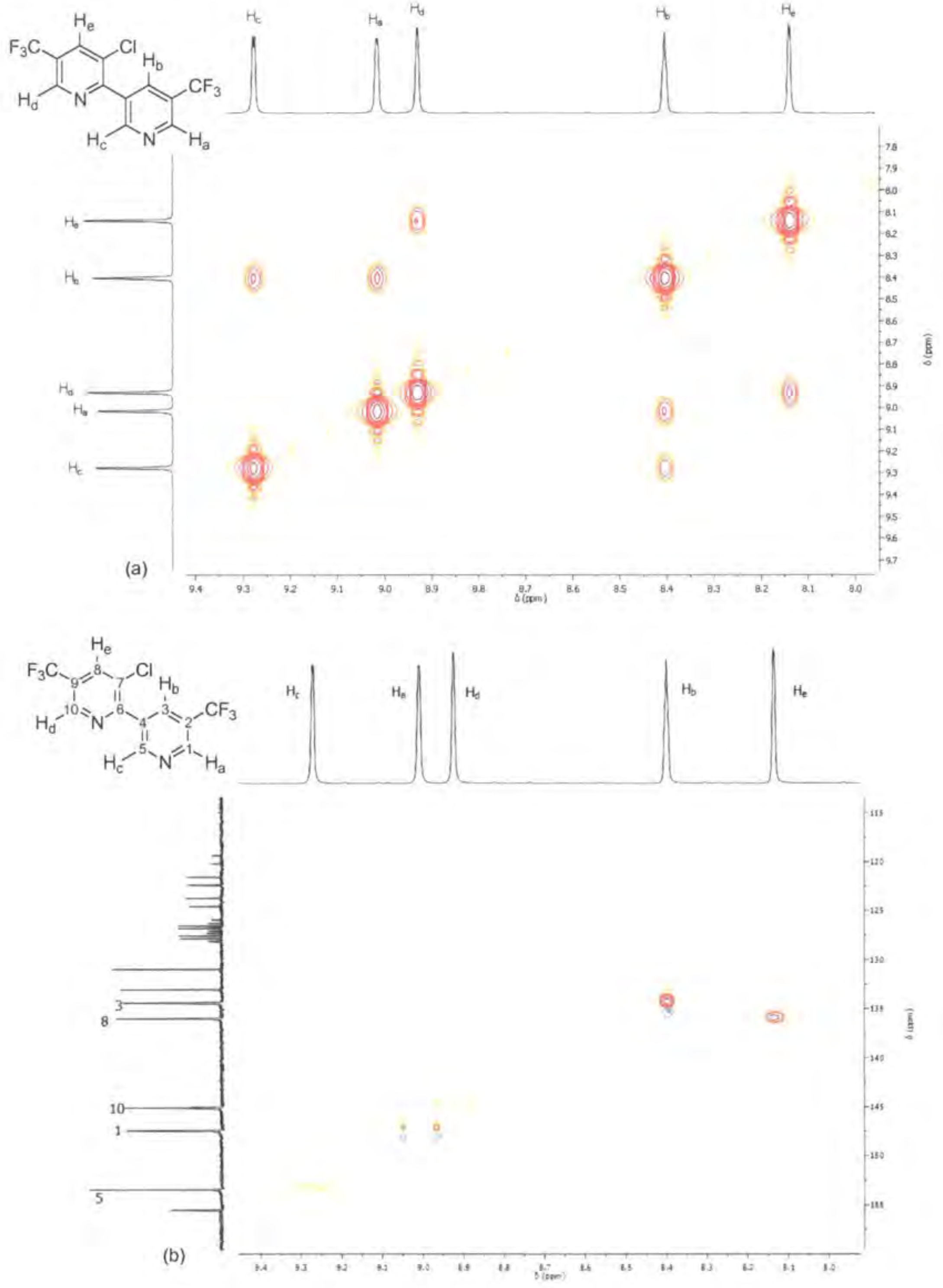
Entry	Boronic acid	Ar-X	Product	Conditions	Time (h)	Isolated yield (%)
8	**137**	 **61**	 **150**	A	17	78
9	**137**	 **142**	 **151**	A	20.5^{d}	51
10	**137**^{c}	 **138**	 **152**	A	3	75
11				A	28.5	83
12	**137**^{b}	 **138**	 **153**	B	55^{e}	58^{f}

Table 4.1 Conditions A: $Pd(PPh_3)_2Cl_2$ (5 mol% Ar-X), 1,4-dioxane, Na_2CO_3 1 M, reflux. B: $Pd(PPh_3)_2Cl_2$ (5 mol% Ar-Br)/*t*-Bu_3P (5 mol% Ar-X), 1,4-dioxane, Na_2CO_3 1 M, reflux. ^{a} 2 equiv. boronic acid. ^{b} 2.1 equiv. boronic acid. ^{c} 1 equiv. boronic acid. ^{d} TLC indicated reaction was complete in 2 h. ^{e} After 28 h reflux a further 5 mol% $Pd(PPh_3)_2Cl_2$ was added and the reaction was left at reflux for a further 27 h. ^{f} 36% of **152** was isolated as the minor product.

Initial attempts to cross-couple 2,3-dichloro-5-(trifluoromethyl)pyridine **138** with two equivalents of boronic acid **136** resulted in high yields of the mono-substituted product **145** (entry 3). It was expected that **138** would react initially at the more activated 2-chloro position (see Section 1.3.1), the 2D NMR spectra (Figure 4.3, ^{1}H COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC) were consistent with the structure **152**. In the HMBC spectrum a 3-bond correlation is observed between C-6 (for numbering identification of **152** see Figure 4.3) and all protons except H_a. C-7 correlates to H_d (4-bond correlation) and H_e (2-bond correlation). Both observations are consistent with cross-coupling at the 2-chloro position of **138**. If cross-coupling had occurred at C-3 of **138** one would expect to observe a nOe interaction. No nOe was observed for any protons in compound **145** indicating that the protons on each pyridine ring were not interacting between the rings, which is the case when **138** is substituted at the C-2 position. An extended reaction time and additional *t*-Bu$_3$P ligand were required to promote the bis-coupling reaction (entry 12) yielding **153** as the major product (58% yield) alongside **152** (36% yield). The ^{1}H COSY, HSQC and HMBC NMR spectra which validate the structure of **153** can be found in Appendix 2.



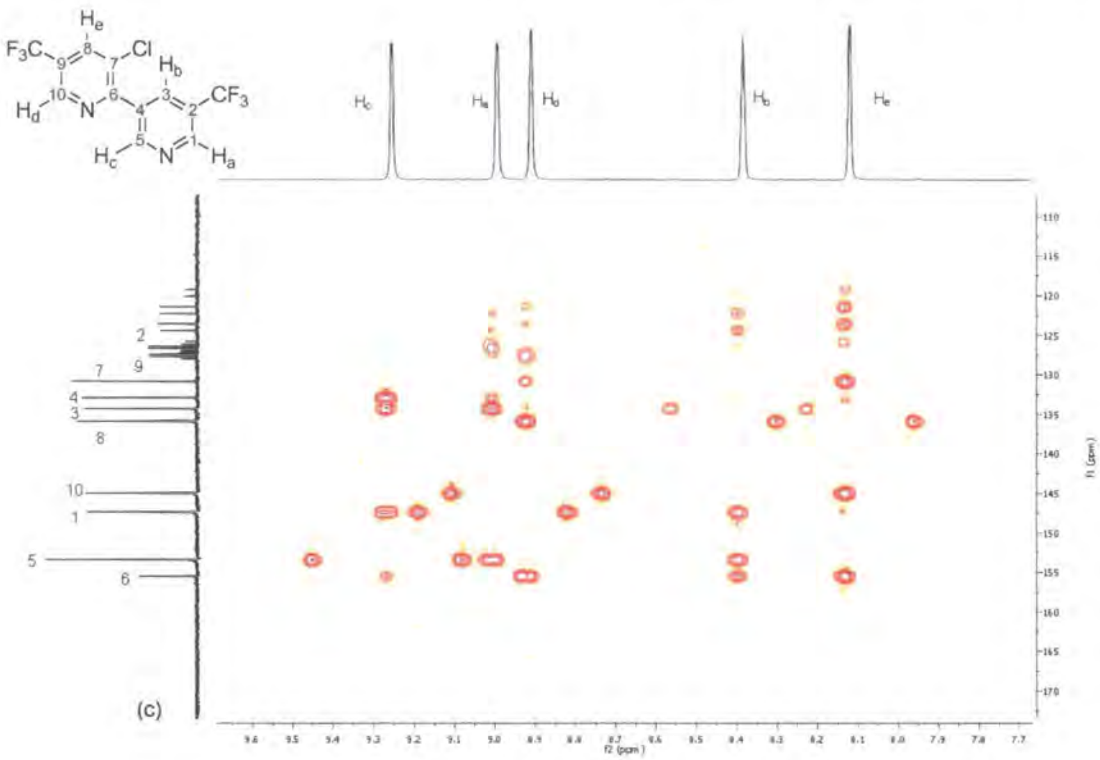
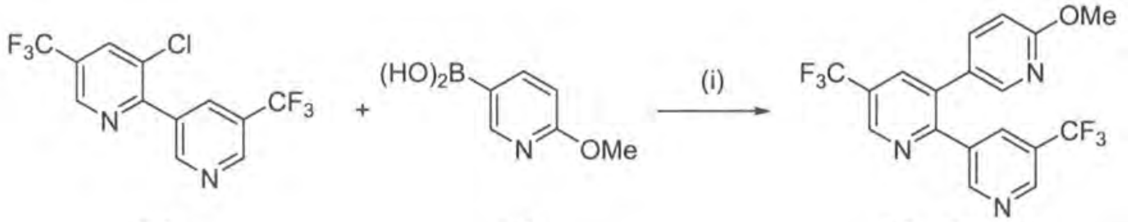


Figure 4.3 (a) ^{1}H COSY NMR spectra of **152** (500 MHz, $CDCl_3$), (b) HSQC ^{1}H NMR (500 MHz, $CDCl_3$), ^{13}C NMR (125 MHz, $CDCl_3$), (c) HMBC ^{1}H NMR (500 MHz, $CDCl_3$), ^{13}C NMR (125 MHz, $CDCl_3$).

The chloro-bipyridyl derivative **152** was further cross-coupled with 2-methoxy-5-pyridylboronic acid **154**, yielding the tripyridyl derivative **155** in 75% yield (Scheme 4.6). These reactions demonstrate the versatility of (trifluoromethyl)-substituted pyridylboronic acids **136** and **137** for the synthesis of functionalized bi- and tri-(hetero)arenes.

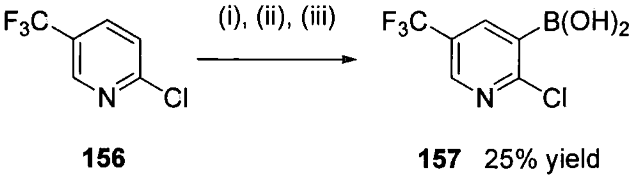


152 **154** **155** 75% yield

Scheme 4.6 (i) $Pd(PPh_3)_2Cl_2$ (5 mol% **152**)/t-Bu_3P (5 mol% **152**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 2.5 h.

4.2.2 Synthesis of 2-chloro-5-(trifluoromethyl)-3- and 4-pyridylboronic acid

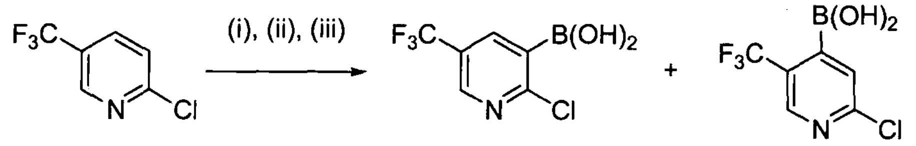
2-Chloro-5-trifluoromethylpyridine **156** is readily available from commercial suppliers and a patent outlines the preparation of 2-chloro-5-(trifluoromethyl)-3-pyridylboronic acid **157** in 25% yield (Scheme 4.7).[456]



Scheme 4.7 Preparation of 2-chloro-5-(trifluoromethyl)-3-pyridylboronic acid **157**: (i) *n*-BuLi, HN(*i*-Pr)$_2$, THF, –78 °C, 2 h. (ii) B(OMe)$_3$, –78 °C, 0.5 h. (iii) H_2O, RT, AcOH.[456]

Adapting the patent by using triisopropylborate instead of trimethylborate the directed *ortho*-lithiation and boronation of **156** yielded a product whose ^{1}H NMR spectrum seemed consistent with the data assigned to **157** in the patent. The authors described the solid product to be a mixture of boronic acid and boroxine structures. Quoting the ^{1}H NMR data of the mixture to be "^{1}H NMR (D_2O, NaOD, MeOD) δ 8.45 – 8.51 (m, 1H), 8.39, 8.36, 8.29 (each of these peaks is d, J = 2.5 Hz, and the number of the proton is totally 1H)".[456] Our ^{1}H NMR spectra, recorded in DMSO-d_6, DCl, showed four proton signals (Figure 4.4). However, the ^{19}F NMR spectrum showed our product to have two distinct fluorine signals, δ_F –61.2 and –58.9 ppm: ca. 1:1.4 ratio; the ^{13}C NMR of the mixture also showed two CF_3 carbon signals.

We speculated that our compound was a mixture of two boronic acid species. From the ^{1}H NMR spectrum (Figure 4.4), we assigned two pairs of protons; H_a and H_b have similar integrals and show fine coupling, resulting from **157** where the protons would interact through a ^4J (H,H). In compound **158** the two protons would not show an observable interaction; consequently, the remaining protons are assigned to **158** (H_c and H_d), their integrals also matched. Subsequently the two isomers **157** and **158** were separated by column chromatography and isolated in 25% and 42% yields, respectively (Scheme 4.8). The ^{1}H NMR spectra of the separated **157** and **158** were consistent with our earlier deductions. X-Ray analysis further confirmed structure **158** (Figure 4.5).



156 **157** 25% yield **158** 42% yield

Scheme 4.8 (i) *n*-BuLi, HN(*i*-Pr)$_2$, THF, –78 °C, 2 h. (ii) B(O*i*-Pr)$_3$, –78 °C, 0.5 h. (iii) H_2O, RT, AcOH.

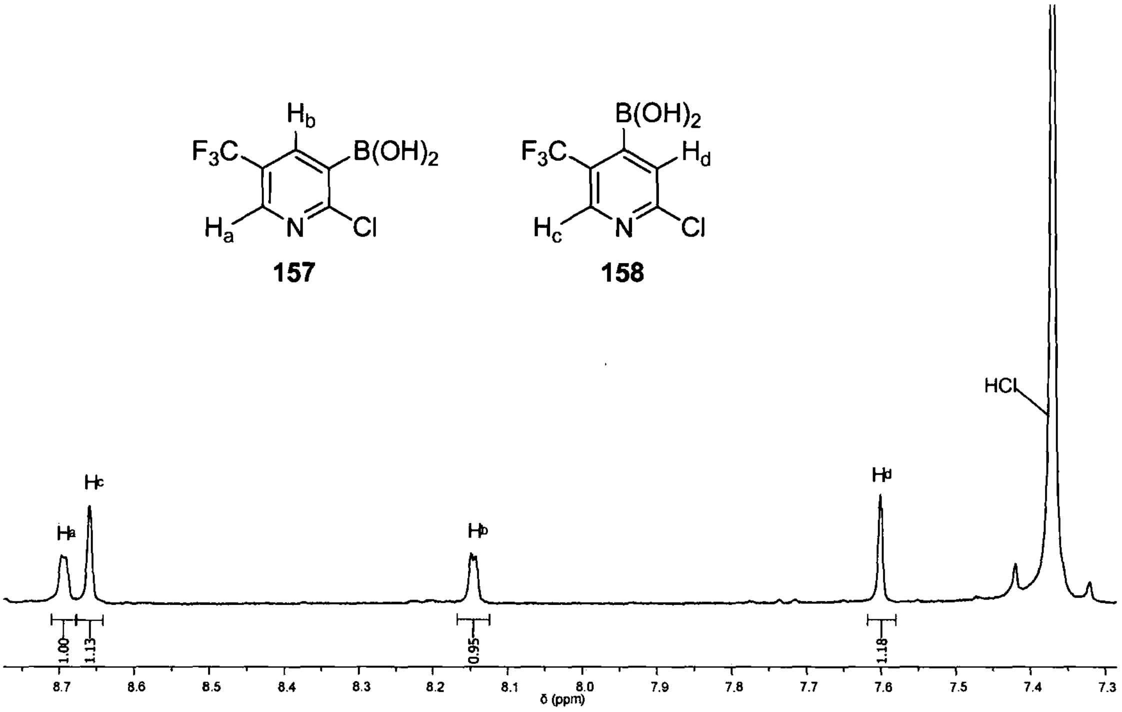


Figure 4.4 ^{1}H NMR spectrum of the mixture of **157** and **158** (400 MHz, DMSO-d$_6$, DCl).

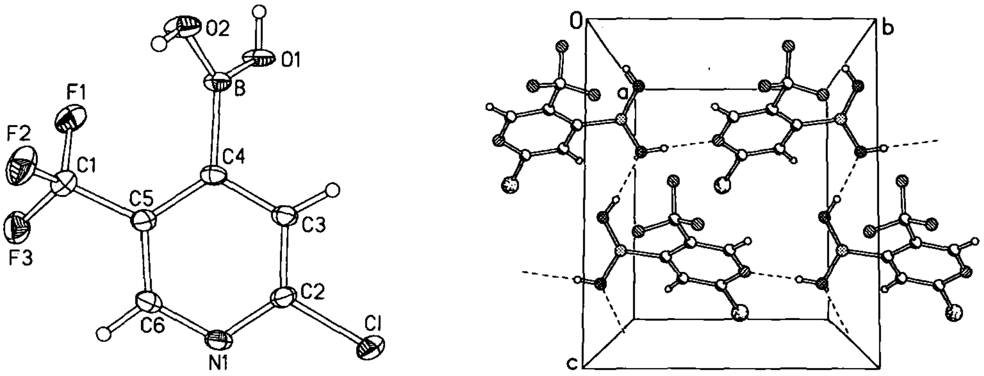


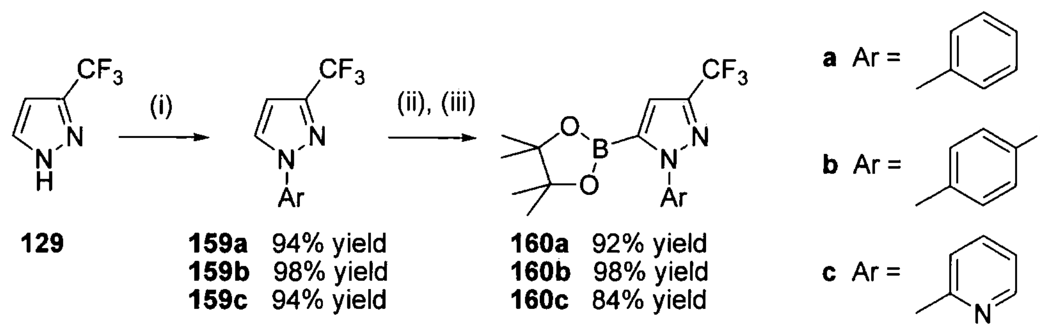
Figure 4.5 X-ray crystal structure of **158**, and hydrogen bonding in the crystal (the dashed lines are hydrogen bonds). (CCDC-699843).

It is possible that both isomers **157** and **158** were also obtained in the patent reference where the ^1H NMR data was wrongly assigned solely to isomer **157**. Methods for the regioselective lithiation of **156** are known.[468] However, the regioselective boronic acid preparation was not investigated after finding that these highly electron-deficient boronic acids did not undergo Suzuki-Miyaura cross-couplings. From the reactions of both **157** and **158** with 2-bromopyridine using conditions [$Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3], cross-coupling was not observed. 2-Chloro-5-(trifluoromethyl)pyridine **156**, as a result of protodeboronation of the boronic acids, and unreacted 2-bromopyridine were isolated. On subjecting **157** and **158** to the Suzuki-Miyaura conditions [$Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3], without a coupling partner present, after only 30 min protodeboronated species **156** was observed by TLC, highlighting the instability of these boronic acids and their facile protodeboronation. Even when using the more reactive 2-iodopyridine and conditions previously used for the cross-coupling of our pyridazinylboronic esters (which we had found to be highly prone to protodeboronation, see Section 2.3.2), [$Pd_2(dba)_3$/PCy_3, 1,4-dioxane, K_3PO_4, reflux] no cross-coupling occurred, only **156** was observed instantaneously and unreacted 2-iodopyridine via TLC. Attempts to oxidize boronic acid **158** with H_2O_2[1] to see if these boronic species had some synthetic use for the preparation of pyridinols were unsuccessful. The ^1H NMR spectrum of the crude product showed a multi-component mixture, and the ^{11}B NMR indicated boronic acid was still present. We concluded that although isomeric boronic acids **157** and **158** seemed relatively stable on storage at ambient temperature, they were both highly susceptible to protodeboronation under Suzuki-Miyaura reaction conditions. This is not surprising considering the electron-deficient nature of the pyridyl ring, combined with two highly electron-withdrawing substituents. It is interesting that changing the electronics of the system dramatically affects the stability of the boronic acid. Without the chloro substituent, analogous boronic acids **136** and **137** were both resistant to protodeboronation and underwent Suzuki-Miyaura cross-coupling reactions readily giving coupling products in high yields.

4.3 (Trifluoromethyl)-substituted pyrazolylboronic esters

4.3.1 Synthesis of 1-(hetero)aryl-3-(trifluoromethyl)-1*H*-4-pyrazolylboronic esters

When employing pyrazolylboronic acids in Suzuki-Miyaura cross-coupling, using $Pd_2(dba)_3/PCy_3$ as the catalyst system, low coupling yields were obtained when the pyrazole NH group is unprotected.[172] To circumvent this sensitivity *N*-protected pyrazolylboronic acids were applied and good coupling yields observed. *N*-aryl pyrazolylboronic esters have been prepared by Harrity and co-workers.[177] As the copper-catalyzed *N*-arylation of 3-(trifluoromethyl)pyrazole with iodobenzene is outlined[483] we followed these conditions for the preparation of several 1-(hetero)aryl-3-(trifluoromethyl)-1*H*-pyrazoles. From the commercially available 3-(trifluoromethyl)pyrazole **129**, *N*-(hetero)arylated pyrazole derivatives **159a-c** were obtained in high yields (94-98%) with conditions [Cu_2O, salicylaldoxime, MeCN, Cs_2CO_3, reflux] (Scheme 4.9).



Scheme 4.9 (i) Ar-I, Cu_2O (5 mol% **129**), salicylaldoxime (20 mol% **129**), Cs_2CO_3, MeCN, reflux, 18 h.[483] (ii) *n*-BuLi, THF, –78 °C, 0.5 h; (iii) 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, –78 °C, 1.5 h; warm to RT over 1 h, AcOH.

It is known that regioselective arylation of pyrazole occurs when a trifluoromethyl substituent is at C-3;[483] i.e. there is no tautomerization of the 3-(trifluoromethyl)pyrazole, unlike other 3-substituted pyrazoles which undergo 3-/5-tautomerization. The structures of **159a-c** were confirmed by the coupling constants of the hydrogen atoms on the pyrazole ring. 1-Aryl-3-substituted pyrazoles exhibit $^3J_{H,H}$ = 2.4 – 2.9 Hz, while 1-aryl-5-substituted pyrazoles exhibit $^3J_{H,H}$ = 1.5 – 1.9 Hz. Lithiation of 1-substituted pyrazoles with *n*-BuLi occurs at the C-5 position when this is free.[484] C-5 lithiation of 3-(trifluoromethyl)pyrazole is well known.[477, 481, 485] Accordingly, treating **159a-c** with *n*-BuLi followed by 2-isopropoxy-4,4,5,5-

tetramethyl-1,3,2-dioxaborolane and acidic workup yielded the pinacol ester derivatives **160a-c** in 92%, 98% and 84% yields, respectively. The X-ray crystal structure of **160b** was obtained, further confirming the boronic ester connectivity at the C-5 position of the pyrazole (Figure 4.6).

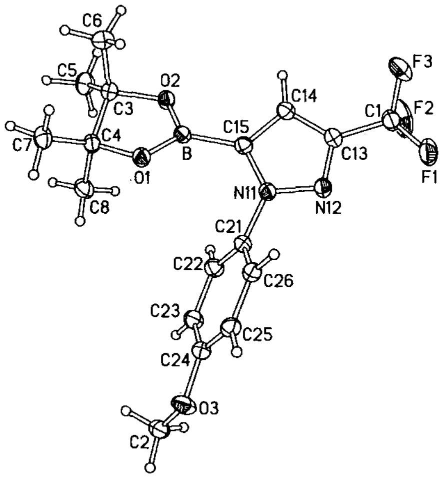
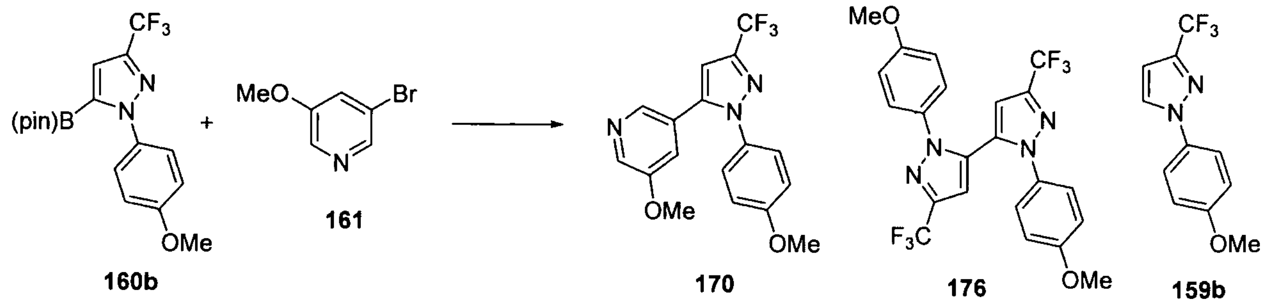


Figure 4.6 X-Ray molecular structure of pyrazolylboronic ester **160b**. (CCDC-699540).

Boronic ester **160c** showed signs of instability during purification. The boronic ester is an oil, so to remove small amounts of unreacted starting material **159c** from the crude product silica column chromatography was attempted. Unfortunately, the boronic ester readily protodeboronated whilst on the acidic silica, yielding more of **159c** alongside the boronic ester. We found that distillation of the unreacted starting material was suitable for purifying **160c** without any degradation of the boronic ester.

4.3.2 Suzuki-Miyaura cross-coupling reactions

Initial Suzuki-Miyaura cross-couplings of **160a**, using the conditions reported by Harrity et al. for the coupling of pyrazolylboronic ester derivatives [Pd(dppf)Cl_2·DCM, 1,4-dioxane, K_3PO_4, 85 °C][177] yielded the desired cross-coupled products alongside products resulting from homocoupling of the boronic ester and hydrolytic protodeboronation (Table 4.3, entries 2 and 4). On cross-coupling boronic ester **160b** and changing the base to KOAc no homocoupling was observed; however, protodeboronation still occurred (Table 4.3, entries 10 and 13). A range of conditions for the cross-coupling of **160b** with 3-bromo-5-methoxypyridine **161** were screened and the ratios of cross-coupled product **170**, homocoupled boronic ester **176** and protodeboronation product **159b** were assessed either from isolated yields or quantitatively by GCMS (Table 4.2).



Entry	Conditions	Results (Isolated yields or GCMS)
1	Pd(dppf)Cl$_2$·DCM, 1,4-dioxane, KOAc, 80 °C	Isolated yields; **170** 42%, **159b** 43%.
2	Pd(dppf)Cl$_2$·DCM, 1,4-dioxane, KOAc, 80 °C, with slow addition of **160b**	Isolated yields; **170** 45%, **159b** 54%.
3	Pd(dppf)Cl$_2$·DCM, 1,4-dioxane, K$_3$PO$_4$, RT to 50 °C	GCMS; **170**:**176** ca. 1:10.
4	Pd(dppf)Cl$_2$·DCM, toluene, K$_3$PO$_4$, RT to 50 °C	GCMS; **170**:**176** ca. 4:1.
5	Pd(PPh$_3$)$_4$, 1,4-dioxane, Na$_2$CO$_3$, 80 °C	Isolated yields; **170** 31%, **159b** 50%.
6	Pd(PPh$_3$)$_4$, Butanol:H$_2$O, 3:1 v/v, Na$_2$CO$_3$, 100 °C	GCMS; **170**:**176**:**159b** 1:4:2.
7	Pd(PPh$_3$)$_4$, THF, Cy$_2$NH, 60 °C	GCMS; **161** and Cy$_2$NH observed, no coupling reaction observed.

Table 4.2 Screening of reaction conditions for the cross-coupling of **160b** with **161**.

Attempts to suppress levels of protodeboronation by slow addition of the boronic ester to the reaction mixture (Table 4.2, entry 2) or using Cy$_2$NH as base[276] (entry 7) were unsuccessful. It is thought that addition of water to a system can promote the cross-coupling of *N*-heteroaryl derivatives by suppressing the coordination of the heteroaryl N to Pd through the formation of hydrogen bonds between the heteroaryl N and water.[486] In our case this had no effect on reducing levels of homocoupling or protodeboronation (entry 6). The stability of boronic ester **160b** was investigated; when **160b** was subjected to the Suzuki-Miyaura conditions [Pd(dppf)Cl$_2$·DCM, 1,4-dioxane, 80 °C] in the absence of a coupling partner in the presence of K$_3$PO$_4$ homocoupled boronic ester was detected: however, with KOAc only protodeboronated product **159b** was observed by GCMS. Protodeboronation of **160b** occurred in 1,4-dioxane only in the presence of base at elevated temperatures (no catalyst or coupling partner present). The boronic ester **160b** was stable to storage at ambient temperature and also stable at room temperature in the presence of base and stable to prolonged heating at 80 °C in 1,4-dioxane.

To improve the yields of the cross-coupled products we suppressed the homocoupling by addition of potassium formate.[264] However, protodeboronation could not be completely eliminated. The conditions [Pd(dppf)Cl_2·DCM, 1,4-dioxane, K_3PO_4, HCOOK, 80 °C] resulted in the highest conversions to the coupling product. The results for the Suzuki-Miyaura cross-coupling reactions of boronic esters **160a-c** with heteroaryl bromides **61-63**, **78**, **143** and **161** are collated in Table 4.3. For **160a** and **160b** the reactions proceeded in moderate to high yields (60-82%) with a variety of heteroaryl bromides as coupling partners, including those bearing nitro and primary amine substituents, yielding compounds **162-173**. The X-ray structure of **163** was obtained (Figure 4.7). The presence of the mild reductant potassium formate may promote reductive dehalogenation of the heteroaryl halide-palladium intermediate (see Section 1.3.2, Figure 1.17). No Het-H was observed or isolated in any cross-couplings of **160a-c** with Het-Br, if the reductive dehalogenation was occurring it was only in negligible amounts, consequently a slight excess of Het-Br was not applied.

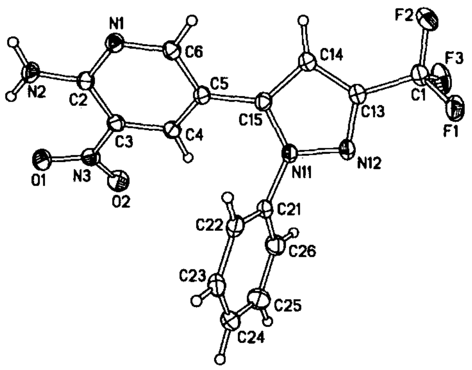
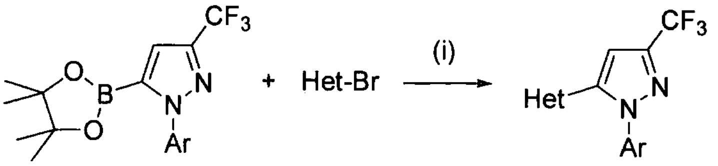
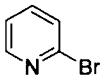
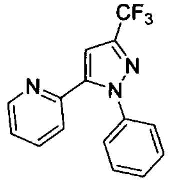
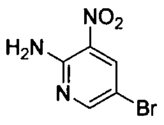
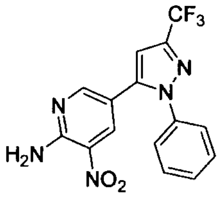
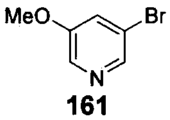
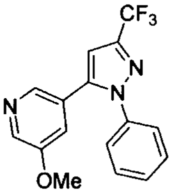
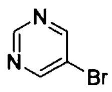
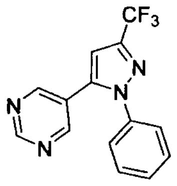
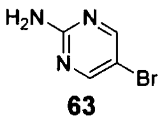
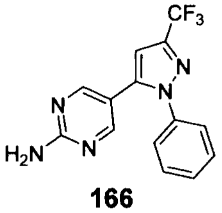
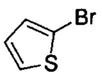
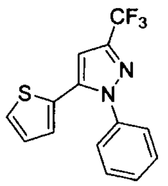
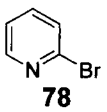
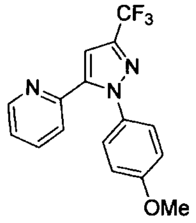
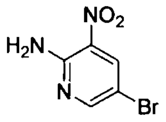
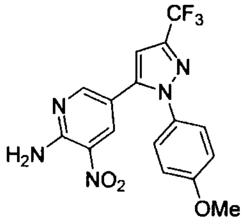
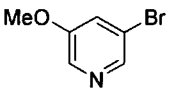
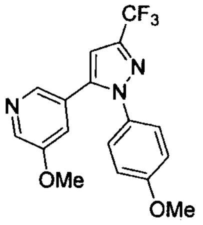
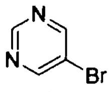
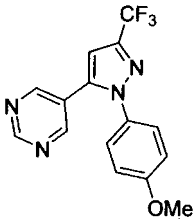
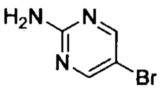
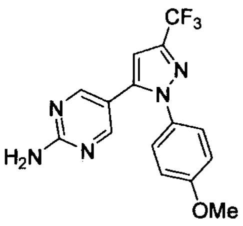
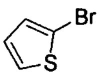
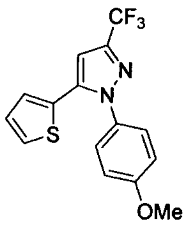


Figure 4.7 X-Ray molecular structure of compound **163**. (CCDC-699541).



160a-c **162-175**

Entry	Boronic ester	Het-Br	Product	Time (h)	Isolated yield (%)
1	**160a**	 **78**	 **162**	4.5	77
2^a				43	59
3	**160a**	 **61**	 **163**	4	82
4^a				26.5	66
5	**160a**	 **161**	 **164**	4	80
6	**160a**	 **62**	 **165**	3	74
7	**160a**	 **63**	 **166**	5	67
8	**160a**	 **143**	 **167**	5	81

Entry	Boronic ester	Het-Br	Product	Time (h)	Isolated yield (%)
9	**160b**	 **78**	 **168**	5.5	63
10^b				17.5	49
11	**160b**	 **61**	 **169**	5	79
12	**160b**	 **161**	 **170**	5	82
13^b				17.5	42
14	**160b**	 **62**	 **171**	3	60
15	**160b**	 **63**	 **172**	5	72
16	**160b**	 **143**	 **173**	5	85

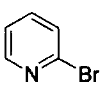
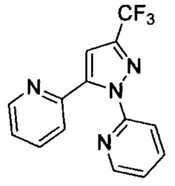
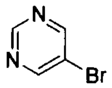
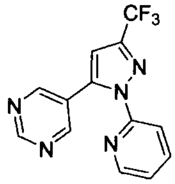
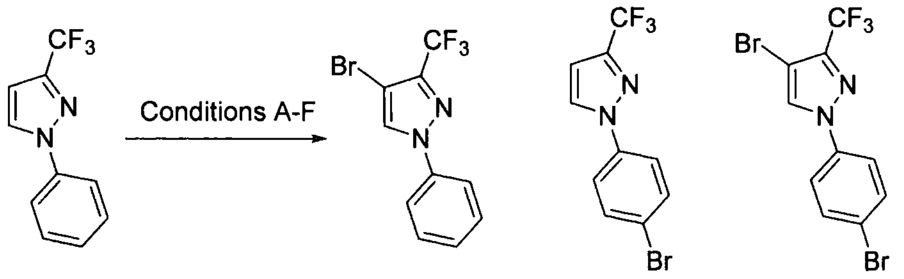
Entry	Boronic ester	Het-Br	Product	Time (h)	Isolated yield (%)
17	**160c**	 **78**	 **174**	4.5	16
18	**160c**	 **62**	 **175**	4.5	30

Table 4.3 (i) Pd(dppf)Cl$_2$·DCM (10 mol% Het-Br), 1,4-dioxane, K$_3$PO$_4$, HCOOK, 80 °C. [a] Without HCOOK. [b] Without HCOOK and using KOAc as base.

For **160c** the coupling reactions were less successful (Table 4.3, entries 17 and 18), the major product was the protodeboronated product **159c**: yields of coupling products **174** and **175** were 16% and 30%, respectively. These results are consistent with the combined electron withdrawing effects of the *N*-pyridyl and trifluoromethyl substituents increasing the instability of the C–B bond and thus making it prone to hydrolytic deboronation under basic conditions. Protodeboronation is known to occur with heteroarylboronic acids, especially electron-deficient derivatives (see Section 1.3.3 for further discussion). Pyrazolylboronic acids and esters are also known to be prone to protodeboronation.[170, 176] On checking **160c** by ^{1}H NMR, after its storage under ambient conditions for 15 days, we found that the boronic ester had started to protodeboronate, the ratio of **160c**:**159c** from the proton integrals was ca. 5:1. The ^{11}B NMR of the sample also showed a second signal resulting from the product of protodeboronation, presumably (pin)B(OH). The stability of **160c** was investigated at elevated temperatures; at 80 °C the sample which had started to protodeboronate on storage, showed no further signs of degradation after heating for 1 h. However, on adding K$_3$PO$_4$ rapid protodeboronation occurred and the boronic ester was fully converted into **159c**.

4.3.3 Bromination of 3-(trifluoromethyl)pyrazole derivatives

Pyrazole can undergo electrophilic attack at the C-4 position. To further increase the structural diversity of the 3-(trifluoromethyl)pyrazole core we looked to introduce a halogen at the C-4 position for use as a handle to prepare a 4-pyrazolylboronic ester analogue. The *N*-phenyl and *N*-(4-methoxyphenyl) derivatives **159a, b** were the main focus. As we had found the 5-pyrazolylboronic ester **160c** to be unstable we did not expect the 4-pyrazolylboronic ester analogue to have improved stability, especially as 4-pyrazolylboronic acids are known to be more unstable, with respect to protodeboronation, than their 5-pyrazolyl derivatives.[170] There are a number of methods reported for the halogenation of pyrazole derivatives.[481, 487-491] We recognized that **159a** and **b** may be more activated towards electrophilic halogenation of the *N*-phenyl or *N*-(4-methoxyphenyl) substituents, particularly as the trifluoromethyl group adjacent to the pyrazole C-4 may deactivate this site towards electrophilic reaction. A number of conditions were screened for the bromination of **159a** (Table 4.4). Using highly activated conditions [Br_2, {Fe}, 100 °C, 1 h], reported for the bromination of 1-methyl 3-(trifluoromethyl)pyrazole,[481] we found that both the pyrazole and phenyl rings of **159a** were activated to bromination and the dibrominated species **179** was isolated. Although in this case it was an undesired product, **179** may be an interesting substrate for cross-coupling reactions. Reviewing the literature, regioselective pyrazole C-4 bromination of 1-phenylpyrazole is known; for example, by reaction with bromine in sulfuric acid at 0 °C[487] or the microwave reaction with NBS in acetic acid.[490] NBS is also used for the preparation of 4-bromo-3,5-dimethyl-1-phenylpyrazole in good yields from 3,5-dimethyl-1-phenylpyrazole using ultrasound irradiation.[489] Our attempts to apply some of these conditions were unsuccessful in preparing **177**, either the phenyl group was brominated (Table 4.4, conditions B), or no reaction occurred (conditions C). It has been stated that when using bromine for the bromination of 1-phenylpyrazole "bromination can be expected to occur preferentially in the 4-position in both 1-phenylpyrazole and the protonated molecule".[487] Consequently, we treated **159a** with bromine in acetic acid at 100 °C and obtained 4-bromo-3-(trifluoromethyl)-1-phenylpyrazole **177** in 51% yield. We also recovered some unreacted **159a**, we assumed that the reaction had not gone to completion, presumably as a result of some bromine evaporation. When using 1.5 equiv. of bromine we were pleased to isolate **177** in 92% yield, without any bromination of the *N*-phenyl substituent.

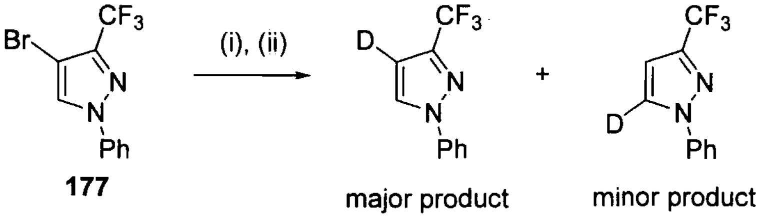


159a **177** **178** **179**

	Conditions	Yield of **177** (%)	Yield of **178** (%)	Yield of **179** (%)
A	Br_2, {Fe}, 100 °C, 1 h[481]	0	evidence by NMR[a]	73
B	Br_2, H_2SO_4, 0 °C[487]	0	evidence by NMR[a]	0
C	NBS, EtOAc, sonicate, 1 h[489]		no reaction occurred	
D	Br_2 (1.0 equiv.), AcOH, 100 °C, 39.5 h	51[b]	0	0
E	NBS (1.1 equiv.), AcOH, 50 °C, 7 h	30[c]	0	0
F	Br_2 (1.5 equiv.), AcOH, 100 °C, 17 h	92	0	0

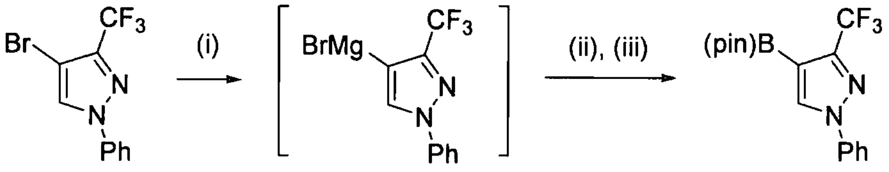
Table 4.4 Bromination of **159a** [a] Mixture with unreacted starting material **159a**. [b] ca. 10% unreacted **159a** recovered. [c] Reaction not to completion.

With **177** in hand we looked to the preparation of the 4-pyrazolylboronic ester. The first question to consider was, on treating **177** with an alkyllithium would lithium-halogen exchange at C-4 occur more rapidly than deprotonation at C-5? Also, would the initial lithium intermediates be stable or would they rearrange to the thermodynamically most stable position? Literature precedent reported the selective C-5 lithiation-halogen exchange of 4-bromo-3-(trifluoromethyl)-1-methylpyrazole with *t*-BuLi.[481] When using LDA, deprotonation of 4-bromo-3-(trifluoromethyl)-1-methylpyrazole occurred at the C-5 position. Analysis of the ^1H NMR from treating **177** with *n*-BuLi and D_2O showed both C-4 and C-5 protons present. The major signal was from the C-5 proton, indicating that the lithium-halogen exchange had occurred preferentially (Scheme 4.10).


177

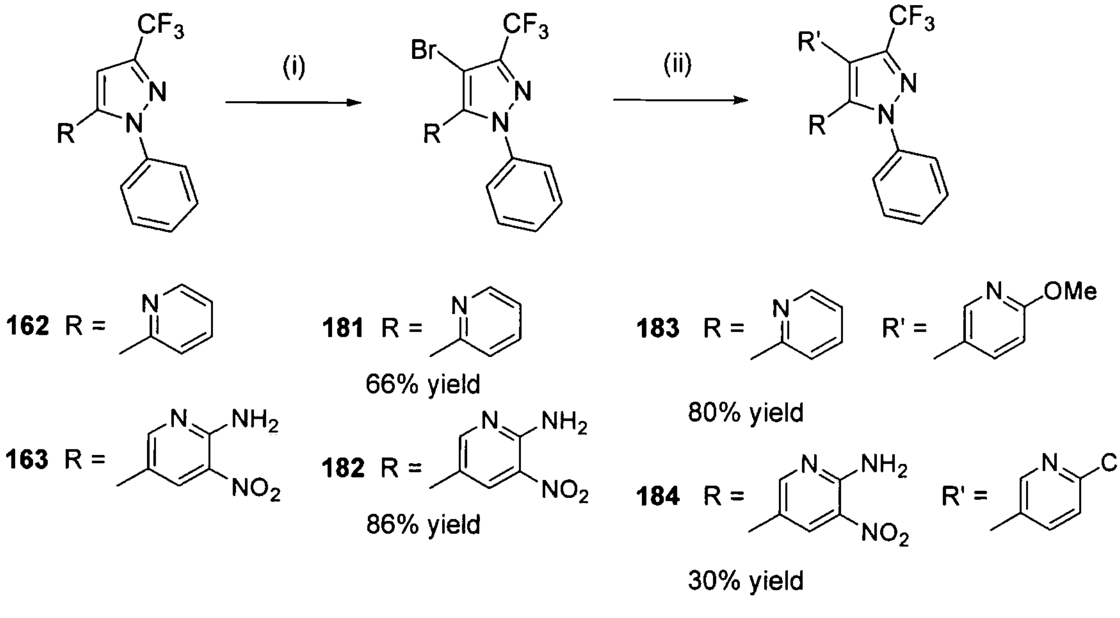
Scheme 4.10 Investigation into the lithiation of **177**. (i) *n*-BuLi, THF, –78 °C, 10 min; (ii) D_2O.

177 was treated with *t*-BuLi, as in the literature, and then quenched with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane; unfortunately, boronic ester was not observed by TLC and the ^1H NMR spectrum of the product indicated lithiation had occurred but not boronation, as the C-4 proton was present. An alternative route was explored, using **177** to prepare a Grignard reagent, which could then be transmetalated with a boron reagent to prepare the boronic ester derivative (Scheme 4.11). Initially the Grignard and the boronate were stirred at room temperature for 10 min before an acid quench. The ^1H NMR spectrum of the resulting product showed the C-4 proton signal, indicating that the Grigard had been prepared, however, the transmetalation to the boronate had been unsuccessful. In further attempts, leaving the reaction mixture for 2 h at room temperature did not improve transmetalation of the Grignard to the boronate – the ^1H NMR spectrum of the isolated product again showed the C-4 proton. Further investigation into both the lithiation and Grignard reaction of **177** may prove fruitful in isolating boronic ester **180**, however, we decided to move on to the functionalization of the pyrazole cross-coupling products.


177 **180**

Scheme 4.11 Attempted synthesis of **180**. (i) Mg, THF; (ii) 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane; (iii) AcOH.

The pyrazolyl coupling products **162** and **163** were further elaborated by preparing their 4-bromo derivatives and subsequent cross-coupling with another heteroarylboronic acid to yield 1,4,5-[tri(hetero)aryl]-3-(trifluoromethyl)pyrazole derivatives (Scheme 4.12). The reaction of **162** and **163** with bromine in acetic acid at 100 °C resulted in regioselective electrophilic bromination at C-4 of the pyrazole ring yielding **181** and **182** in 66% and 86% yields, respectively (Scheme 4.12). In a further Suzuki-Miyaura cross-coupling reaction, **181** and **182** gave the fully functionalized pyrazole derivatives **183** and **184** in 80% and 30% yields, respectively. Unfortunately, in the reaction of **182** with boronic acid **136**, homocoupled boronic acid and debrominated starting material **163**, (which coeluted during column chromatography), and 16% unreacted starting material **182** were recovered alongside the coupling product **184**. The X-ray structure of **183** was obtained (Figure 4.8).



Scheme 4.12 (i) Br_2, AcOH, 100 °C, 19 h. (ii) for **181**, 2-methoxy-5-pyridylboronic acid; for **182**, **136**; $Pd(PPh_3)_4$ (5 mol% Ar-Br), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 3.5-6 h.

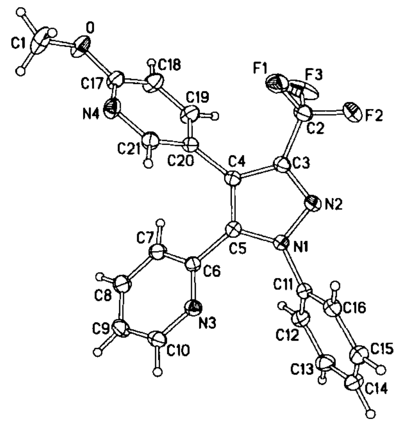
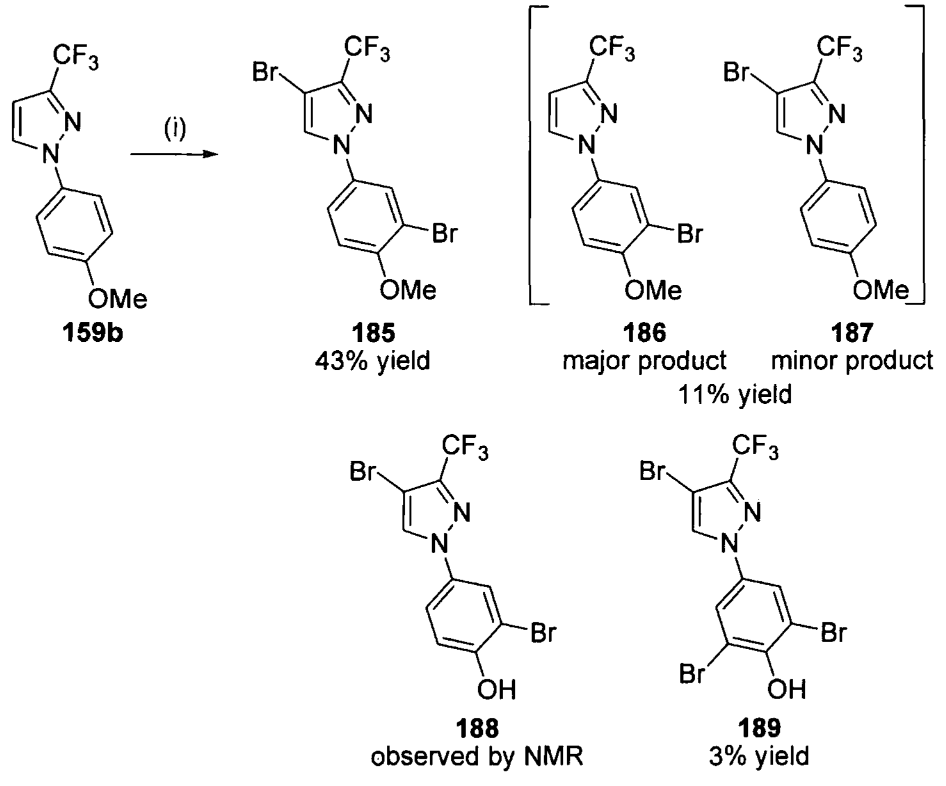


Figure 4.8 X-Ray crystal structure of compound **183**. (CCDC-699542).

Although the boronic ester preparation from **177** had been unsuccessful in our hands we were interested whether the *N*-(4-methoxyphenyl)pyrazole derivatives could be regioselectively brominated at the pyrazole ring, or whether the 4-methoxyphenyl substituent would be too activated towards electrophilic reaction. We then hoped to use this protocol for the bromination of several of the *N*-(4-methoxyphenyl)pyrazole coupling products (analogous to Scheme 4.12). The reaction of **159b** with bromine (1.5 equiv.) in acetic acid at 100 °C gave a multicomponent mixture. Following silica column chromatography the major product isolated was identified as the dibrominated species **185** (Scheme 4.13), as had been expected. A mixture of two monobrominated isomers **186** and **187** was obtained in 11% yield. Separation was not attempted as the undesired **186** was the major isomer (^{1}H NMR spectra indicated a ratio of **186**:**187**, 4:1 from the integrals).



Scheme 4.13 Bromination of **159b**. (i) Br_2 (1.5 equiv.), AcOH, 100 °C, 17 h.

Two further minor products were isolated, both of which showed no OMe signals in the ^{1}H NMR spectra. Based on the ^{1}H NMR and MS data we conclude their structures are **188** and **189**. The MS spectra for **188** and **189** were consistent with two and three bromines, respectively, and a hydroxyl substituent and not a methoxy (in agreement with the ^{1}H NMR spectra). It appears that the methoxyphenyl substituent prevents clean electrophilic bromination on the pyrazole ring. Consequently alternative bromination conditions were not explored, and the *N*-methoxyphenyl substituted pyrazolyl coupling products were not further derivatized. The brominated derivatives of **159b** are new interesting species, that could be used to further expand the diversity of the 3-(trifluoromethyl)pyrazole structure.

4.4 Conclusions

The preparation of new CF_3-substituted pyridylboronic acids which are stable to storage under ambient conditions has been described. These species readily undergo Suzuki-Miyaura cross-coupling reactions to yield aryl/heteroaryl-(trifluoromethyl)pyridines in good to excellent yields. However, if further electron-withdrawing substituents are introduced on the pyridyl ring, as is the case for 2-chloro-5-(trifluoromethyl)pyridine, the boronic acid derivatives are unstable to protolytic deboronation.

3-(Trifluoromethyl)-pyrazolylboronic esters have been synthesized through an expedient procedure. These species undergo palladium-catalyzed cross-coupling reactions to provide heteroaryl-(trifluoromethyl)pyrazoles in synthetically viable yields, although in some cases competing protodeboronation was observed. Regioselective C-4 bromination of 3-(trifluoromethyl)-1-phenylpyrazole derivatives has been established, offering scope for further synthetic transformations, as highlighted by the Suzuki-Miyaura cross-coupling reactions of 4-bromo-5-(heteroaryl)-3-(trifluoromethyl)-1-phenylpyrazoles to prepare highly functionalized tri-substituted trifluoromethylated pyrazole structures.

The fragile stability of electron-deficient *N*-heteroarylboronic acids has been exposed. The successful preparation and storage under ambient conditions is notable, on account of the highly electron-deficient trifluoromethyl group and adjacent pyrazole N. With the trifluoromethyl-substituent having the appeal of tailoring activity profiles, these functionalized CF_3-substituted heterocycles are of potential utility as new pharmacophores and scaffolds for drug discovery.

CHAPTER 5 – EXPERIMENTAL PROCEDURES

5.1 General Considerations

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. Glassware was either flame dried or dried in the oven prior to use. All reagents employed were of standard reagent grade and purchased from Aldrich, Alfa Aesar, Apollo, Frontier Scientific, Fluorochem or supplied by Vertellus Specialties UK Ltd., and were used as supplied unless otherwise stated. $Pd(PPh)_3Cl_2$ and $Pd(PPh_3)_4$ were prepared in house,[492-494] $Pd(OAc)_2$ was purchased from Aldrich, $Pd_2(dba)_3$ was purchased from Alfa Aesar. *t*-Bu_3P and D-*t*-BPF were purchased from Strem, PCy_3 was purchased from Molekula. Anhydrous THF, diethyl ether (Et_2O), DMF, DCM and methanol were dried through a HPLC column on an Innovative Technology Inc. solvent purification system. All other solvents in this work were used without prior purification. All reactions were set up outside of a glovebox, including the weighing of solid substrates. Column chromatography was carried out using 40-60 μm mesh silica. Thin-layer chromatography (TLC) were performed on 20 mm precoated plates of silica gel (Merck, silica gel $60F_{254}$), visualisation was made using ultraviolet light (254 nm).

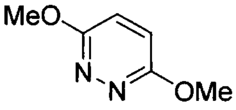
NMR spectra were recorded on; Bruker Avance-400 (^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{11}B NMR (128 MHz)), Varian 500 (^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz)), Varian 400 (^{19}F NMR (372 MHz)), Varian 200 (^{19}F NMR (188 MHz)), Varian VNMRS 700 (^{13}C NMR (175 MHz), using deuterated solvent as a lock. Chemical shifts are quoted in ppm, relative to tetramethylsilane (TMS), using TMS or the residual solvent as internal reference for ^{1}H and ^{13}C, and $CFCl_3$ for ^{19}F NMR. The following abbreviations are used in listing NMR spectra: s = singlet, d = doublet, t = triplet, m = multiplet. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Electron Impact (EI) mass spectra were recorded on a Thermo-Finnigan Trace or Thermo-Finnigan DSQ with positive ionisation mode. Electro Spray (ES^+) mass spectra were recorded on a Waters Micromass LCT mass spectrometer. HRMS (ES^+) mass spectra were recorded on a Thermo-Finnigan LTQ FT mass spectrometer. All measured mass for bromine containing compounds corresponds to ^{79}Br, which displays expected isotope profile for bromine. Elemental analyses were obtained on an Exeter analytical Inc. CE-440 elemental analyser.

X-Ray Crystallographic Data

Single-crystal diffraction experiments were carried out on Bruker 3-circle diffractometers with SMART 1K CCD area detector, using graphite-monochromated Mo-K_α radiation (λ=0.71073 Å) and Cryostream (Oxford Cryosystems) open-flow N_2 cryostats. The structures were solved by direct methods and refined by full-matrix least squares against F^2 of all data, using SHELXTL software.[495] Non-hydrogen atoms were refined in anisotropic, H atoms is isotropic approximation or (in **77b** and **77d**) in "riding" model. Full structural data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre, deposition numbers are given with the X-ray crystal structures. Thermal ellipsoids are drawn at the 50% probability level. Primed atoms are generated by the crystallographic inversion center.

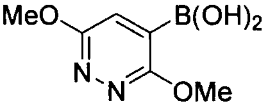
5.2 Experimental details for Chapter 2

3,6-Dimethoxypyridazine (58)[496]



To a solution of sodium methoxide from sodium (6.50 g, 0.28 mol) in dry methanol (130 mL), was added a solution of 3,6-dichloropyridazine **57** (9.70 g, 0.065 mol) in anhydrous methanol (50 mL). The reaction mixture was heated at reflux for 19 h, cooled to room temperature then carefully neutralized with 37% HCl aq and evaporated in vacuo to dryness. The solid was extracted with EtOAc (200 mL) and washed twice with deionised water (2 × 100 mL). EtOAc was removed to leave **58** as a white crystalline solid (8.47 g, 93%) which was not further purified: mp 103.6-104.8 °C, lit. mp[496] 108 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.22 (1H, s), 3.97 (3H, s); ^{13}C NMR (100 MHz, DMSO-d$_6$), δ 162.7, 122.4, 55.0; MS (EI) *m/z* 140.1 (M$^+$, 100%). Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.19. Found: C, 51.30; H, 5.78; N, 19.48%.

3,6-Dimethoxy-4-pyridazinylboronic acid (59)



Procedure A: Diisopropylamine (13.4 mL, 0.10 mol) was added to *n*-butyllithium (2.5 M in hexane, 41.0 mL, 0.10 mol) in anhydrous THF (400 mL) at –78 °C under argon. The mixture warmed to 0 °C and left to stir for 0.5 h. The reaction was then cooled to –78 °C and a solution of 3,6-dimethoxypyridazine, **58** (6.73g, 0.048 mol) in anhydrous THF (100 mL) was added over 1 h. The reaction was stirred for a further 0.5 h. Triisopropylborate (33.2 mL, 0.14 mol) was added at –78 °C and the mixture was stirred for 1.5 h. The mixture was warmed to –10 °C and quenched with deionised water (100 mL) and left to stir at room temperature overnight. The organic solvent and most of the water were removed in vacuo. The resulting slurry was then dissolved in water and filtered. The filtrate was washed with Et_2O (2 × 150 mL) and acidified to pH 4 using HBr (48% aq. solution) to precipitate **59** as a white solid (7.78 g, 88%): mp 152.1-153.2 °C; ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 8.50 (2H, s), 7.13 (1H, s), 3.95 (6H, s); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 163.99, 162.46, 125.35, 54.96, 54.84. ^{11}B NMR (128 MHz, DMSO-d$_6$) δ 28.9; Anal. Calcd. for $C_6H_9BN_2O_4$: C, 39.17; H, 4.93; N, 15.23. Found: C, 39.00; H, 4.93; N, 15.11%.

Procedure B: Diisopropylamine (83 mL, 0.59 mol) was added to *n*-butyllithium (2.5 M in hexane, 236 mL, 0.59 mol) in THF (500 mL) at –78 °C under nitrogen. The mixture warmed to 0 °C and left to stir for 0.5 h. The reaction was then cooled to –78 °C and a solution of 3,6-dimethoxypyridazine, **58** (40 g, 0.29 mol) in THF (500 mL) was added over 2 h. The reaction was stirred for a further 0.5 h. Triisopropylborate (198 mL, 0.86 mol) was added at –78 °C and the mixture was stirred for 1 h. The mixture was warmed to –25 °C and quenched with water (500 mL) and left to stir at room temperature overnight. The mixture was filtered, the organic phase was separated and washed with water (250 mL), the aqueous phases were combined and washed with MTBE (3 × 250 mL). The resulting aqueous phase basified to pH 12 using NaOH (50 mL, 10% aq.), then slowly acidified to pH 4 using AcOH to precipitate **59** as a white solid (23.5 g, 45%) spectroscopically identical with the sample from Procedure A.

Procedure C: Diisopropylamine (2.1 mL, 15 mmol) was added to *n*-butyllithium (2.5 M in hexane, 5.9 mL, 15 mmol) in anhydrous THF (60 mL) at –78 °C under argon. The mixture warmed to 0 °C and left to stir for 0.5 h. The reaction was then cooled to –20 °C and a solution of 3,6-dimethoxypyridazine, **58** (1.0 g, 7.1 mmol) in anhydrous THF (40 mL) was added over 1 h. The reaction was stirred for a further 0.5 h. Triisopropylborate (4.9 mL, 21 mmol) was added at –20 °C and the mixture was stirred for 1.5 h. The mixture was warmed to –10 °C and quenched with deionised water (50 mL) and left to stir at room temperature overnight. The organic solvent and most of the water were removed in vacuo. The resulting slurry was then dissolved in water (50 mL) and filtered. The filtrate was washed with Et_2O (2 × 50 mL) and acidified to pH 4 using HBr (48% aq. solution) to precipitate **59** as a beige solid (0.184 g, 14%) spectroscopically identical with the sample from Procedure A.

Procedure D: Diisopropylamine (83 mL, 0.59 mol) was added to hexyllithium (2.5 M in hexane, 236 mL, 0.59 mol) in THF (1 L) at –78 °C under nitrogen. The mixture warmed to 0 °C and left to stir for 0.5 h. The reaction was then cooled to –78 °C and a solution of 3,6-dimethoxypyridazine, **58** (40 g, 0.29 mol) in THF (500 mL) was added over 1.25 h. The reaction was stirred for a further 0.5 h. Triisopropylborate (198 mL, 0.86 mol) was added at –78 °C and the mixture was stirred for 1 h. The mixture was warmed to room temperature and quenched with water (500 mL) and left to stir at room temperature overnight. The mixture was filtered, the organic phase was separated, the aqueous phase was washed with MTBE (2 × 250 mL). The resulting aqueous phase was slowly acidified to pH 4 using AcOH to precipitate **59** as a white solid (32.8 g, 62%) spectroscopically identical with the sample from Procedure A.

Procedure E: Diisopropylamine (10.4 mL, 0.074 mol) was added to hexyllithium (2.3 M in hexane, 32 mL, 0.074 mol) in THF (100 mL) at –78 °C under nitrogen. The mixture warmed to 0 °C and left to stir for 0.5 h. The reaction was then cooled to –20 °C and a solution of 3,6-dimethoxypyridazine, **58** (5.1 g, 0.036 mol) in THF (120 mL) was added over 1.25 h. The reaction was stirred for a further 1.25 h. Triisopropylborate (24.7 mL, 0.11 mol) was added at –20 °C and the mixture was stirred for 1 h. The mixture was warmed to room temperature and quenched with water (150 mL) and left to stir at room temperature overnight. The organic phase was separated, and the resulting aqueous phase was washed with MTBE (4 × 200 mL). The resulting aqueous phase was slowly acidified to pH 4 using AcOH to precipitate **59** as a white solid (2.0 g, 30%) spectroscopically identical with the sample from Procedure A.

Typical Procedure for the Suzuki-Miyaura Cross-Coupling Reactions in Table 2.1

The boronic acid **59** (1.0 equiv.) the aryl halide (0.9 equiv.) and catalyst (ca. 5 mol% **59**) were sequentially added to degassed 1,4-dioxane (10 mL) 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 65 h. Solvent was removed in vacuo, then EtOAc 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 followed if needed by recrystallization.

Conditions A: $Pd(OAc)_2$ (5 mol% **59**)/D-*t*-BPF (5 mol% **59**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h.

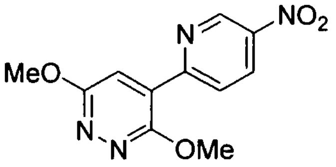
Conditions B: $Pd(PhCN)_2Cl_2$ (5 mol% **59**)/*t*-Bu_3P (5 mol% **59**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h.

Conditions C: $Pd(PPh_3)_2Cl_2$ (5 mol% **59**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h.

Conditions D: $Pd(PPh_3)Cl_2$ (5 mol% **59**)/*t*-Bu_3P (5 mol% **59**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h.

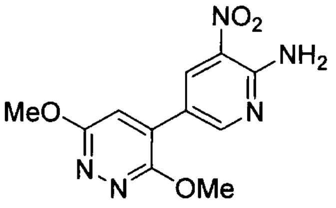
Conditions E: $Pd(OAc)_2$ (5 mol% **59**)/*t*-Bu_3P (5 mol% **59**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h.

2-(3,6-Dimethoxypyridazin-4-yl)-5-nitropyridine (67)



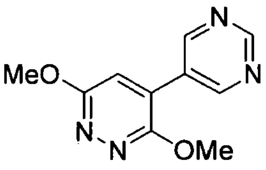
Compound **59** (313 mg, 1.7 mmol), 2-bromo-5-nitropyridine **60** (305 mg, 1.5 mmol), $Pd(OAc)_2$ (19.0 mg, 0.085 mmol), D-*t*-BPF (38.0 mg, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (1 M, 4 mL); reaction time 65 h; eluent EtOAc gave **67** as a light brown crystalline solid (353 mg, 90%): mp 144.4-145.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (1H, d, J = 2.4 Hz), 8.57 (1H, dd, J = 11.2 Hz, J = 2.8 Hz), 8.37 (1H, d, J = 8.8 Hz), 7.74 (1H, s), 4.21 (3H, s), 4.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$), δ 163.4, 158.8, 156.1, 145.1, 143.9, 131.7, 129.4, 125.0, 121.0, 55.3, 55.0; MS (ES$^+$) *m/z* 263.1 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.84; N, 21.37. Found: C, 50.36; H, 3.84; N, 21.27%.

2-Amino-3-nitro-5-(3,6-dimethoxypyridazin-4-yl)-pyridine (68)



Compound **59** (313 mg, 1.7 mmol), 2-amino-5-bromo-3-nitropyridine **61** (327 mg, 1.5 mmol), $Pd(OAc)_2$ (19.0 mg, 0.085 mmol), D-*t*-BPF (38.0 mg, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (1 M, 4 mL); reaction time 65 h; eluent EtOAc gave **68** as a yellow crystalline solid (288 mg, 69%): mp 235.0-236.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (2H, s), 8.23 (2H, s), 7.45 (1H, s), 4.02 (3H, s), 3.98 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 158.6, 156.1, 153.5, 135.1, 128.6, 126.1, 117.7, 117.0, 54.6, 54.2; MS (ES$^+$) *m/z* 278.0 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{11}H_{11}N_5O_4$: C, 47.66; H, 4.00; N, 25.26. Found: C, 47.47; H, 3.91; N, 24.90%.

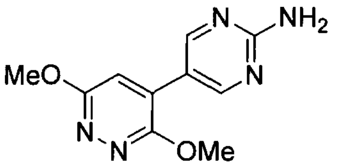
5-(3,6-Dimethoxypyridazin-4-yl)-pyrimidine (69)



Compound **59** (313 mg, 1.7 mmol), 5-bromopyrimidine **62** (238 mg, 1.5 mmol), $Pd(PhCN)_2Cl_2$ (33.0 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (1 M, 4 mL); reaction time 65 h; eluent EtOAc gave **69** as a yellow solid (258 mg, 78%): mp 168.8-169.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (1H, s), 8.99 (2H, s), 7.01 (1H, s), 4.11 (3H, s), 4.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 159.0, 158.9, 156.7, 127.9, 127.6, 119.4, 55.3, 55.0; MS (ES$^+$) *m/z* 219.4 ([M+H]$^+$, 100%); HRMS (EI) calcd for $C_{10}H_{10}N_4O_2$ 218.0804, found: 218.0806. Anal.

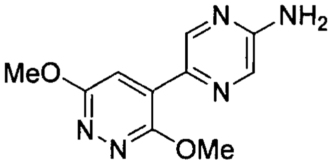
Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 54.72; H, 4.61; N, 25.24%.

2-Amino-5-(3,6-dimethoxypyridazin-4-yl)-pyrimidine (70)



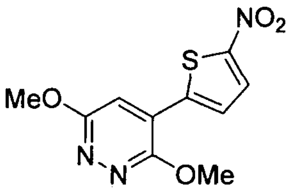
Compound **59** (313 mg, 1.7 mmol), 2-amino-5-bromopyrimidine **63** (261 mg, 1.5 mmol), $Pd(OAc)_2$ (19.0 mg, 0.085 mmol), D-*t*-BPF (38.0 mg, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (1 M, 4 mL); reaction time 65 h; eluent EtOAc gave **70** as a beige solid (234 mg, 65%): mp 253.2-254.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (2H, s), 6.92 (1H, s), 5.46 (2H, s), 4.10 (3H, s), 7.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 162.7, 159.2, 158.5, 128.7, 117.6, 117.2, 55.1, 54.8; MS (ES$^+$) *m/z* 234.1 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 51.50; H, 4.75; N, 30.03. Found: C, 51.41; H, 4.75; N, 29.97%.

2-Amino-5-(3,6-dimethoxypyridazin-4-yl)-pyrazine (71)



Compound **59** (313 mg, 1.7 mmol), 2-amino-5-bromopyrazine **64** (281 mg, 1.5 mmol), $Pd(PhCN)_2Cl_2$ (33.0 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL, 1 M); reaction time 65 h; recrystallized from toluene to give **71** as a yellow/orange solid (168 mg, 48%): mp 233.3-235.4 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.72 (1H, d, *J* = 1.2 Hz), 8.03 (1H, d, *J* = 1.2 Hz), 7.48 (1H, s), 7.04 (2H, s), 4.07 (3H, s), 3.97 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6), δ 162.6, 158.4, 155.8, 143.5, 132.7, 132.1, 129.6, 115.4, 54.5, 54.2; MS (ES$^+$) *m/z* 234.1 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 51.50; H, 4.75; N, 30.03. Found: C, 51.21; H, 4.74; N, 29.73%.

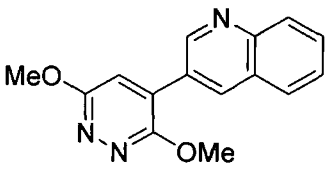
2-Nitro-5-(3,6-dimethoxypyridazin-4-yl)-thiophene (72)



Compound **59** (313 mg, 1.7 mmol), 2-bromo-5-nitrothiophene **65** (312 mg, 1.5 mmol), $Pd(OAc)_2$ (19.0 mg, 0.085 mmol), D-*t*-BPF (38.0 mg, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (1 M, 4 mL); reaction time 65 h; eluent EtOAc gave **72** as a brown powder (309 mg, 77%): mp 185.1-186.9 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, d, *J* = 4.0 Hz), 7.64 (1H, d, *J* = 4.0 Hz), 7.24 (1H, s), 4.26 (3H, s), 4.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 157.2, 140.6, 128.1, 127.1, 124.6, 115.9, 55.4, 55.1;

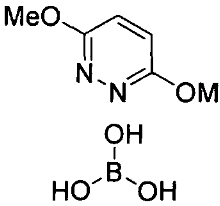
MS (ES$^+$) *m/z* 268.1 ([M+H]$^+$, 100%). HRMS (ES$^+$) calcd for $C_{10}H_{10}N_3O_4S$ 268.0392, found 268.0387. Anal. Calcd. for $C_{10}H_9N_3O_4S$: C, 44.94; H, 3.39; N, 15.72. Found: C, 44.79; H, 3.47; N, 15.01%.

3-(3,6-Dimethoxypyridazin-4-yl)-quinoline (73)



Compound **59** (313 mg, 1.7 mmol), 3-bromoquinoline **66** (0.2 mL, 1.5 mmol), Pd(OAc)$_2$ (19.0 mg, 0.085 mmol), D-*t*-BPF (38.0 mg, 0.080 mmol), 1,4-dioxane (10 mL), Na_2CO_3 (1 M, 4 mL); reaction time 65 h; eluent EtOAc gave **73** as a white solid (381 mg, 95%): mp 146.6-147.1 °C; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 9.22 (1H, d, *J* = 2.0 Hz), 8.69 (1H, d, *J* = 2.8 Hz), 8.14 (1H, d, *J* = 9.2 Hz), 8.08 (1H, d, *J* = 9.6 Hz), 7.81 – 7.88 (1H, m), 7.67 – 7.71 (1H, m), 7.34 (1H, s), 4.13 (3H, s), 4.10 (3H, s); ^{13}C NMR (100 MHz, acetone-d$_6$), δ 163.5, 160.2, 150.9, 148.8, 137.1, 131.5, 131.0, 129.9, 129.3, 128.2, 127.9, 127.7, 120.0, 54.9, 54.6; MS (ES$^+$) *m/z* 268.2 ([M+H]$^+$, 100%). Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.37; H, 4.85; N, 15.55%.

58·B(OH)$_3$ Complex

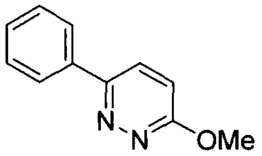


3,6-Dimethoxy-4-pyridazinylboronic acid **59** was refluxed in the minimal amount of ethanol, upon cooling and evaporation of the solvent crystals grew which X-ray structural analysis confirmed to be complex **58·B(OH)$_3$**.

General Procedure for the preparation of 75a-d.

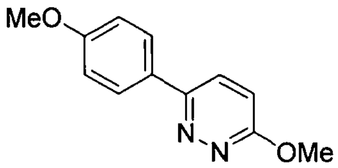
Boronic acid (1.0 equiv.), 3-chloro-6-methoxypyridazine **74** (0.9 equiv.) and Pd(PPh$_3$)$_2$Cl$_2$ (ca. 5 mol% boronic acid) were sequentially added to degassed 1,4-dioxane (100 mL) and the mixture was stirred at 20 °C for 30 min. Degassed aqueous Na_2CO_3 solution (1 M, 56 mL) was added and the reaction mixture was heated under argon at reflux for 65 h. Solvent was removed in vacuo then EtOAc (50 mL) was added and the organic layer was washed with brine (50 mL), separated, and dried over $MgSO_4$. The mixture was purified by chromatography on a silica gel column, followed by recrystallization in some cases.

3-Methoxy-6-phenylpyridazine (75a)[328, 331]



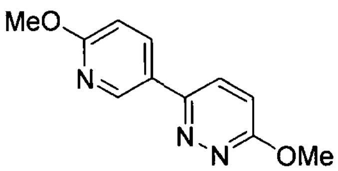
Benzeneboronic acid (2.86 g, 0.024 mol), 3-chloro-6-methoxypyridazine **74** (3.0 g, 0.021 mol), $Pd(PPh_3)_2Cl_2$ (0.82 g, 1.2 mmol); eluent petroleum ether (bp 40–60 °C):EtOAc 1:4 v/v, yielded **75a** as a white solid (3.68 g, 95%): mp 119.8-121.4 °C, lit. mp[328] 116 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, d, *J* = 8.0 Hz), 7.73 (1H, d, *J* = 9.2 Hz), 7.42 – 7.47 (3H, m), 7.00 (1H, d, *J* = 9.2 Hz), 4.15 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 155.2, 136.2, 129.4, 128.9, 127.2, 126.5, 117.7, 54.9; MS (ES^+) *m/z* 187.1 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.88; H, 5.37; N, 15.14%.

3-Methoxy-6-(4-methoxyphenyl)pyridazine (75b)[328]



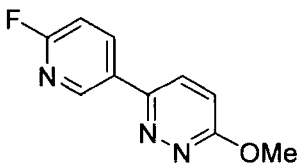
4-Methoxyphenylboronic acid (2.38 g, 0.016 mol), 3-chloro-6-methoxypyridazine **74** (2.0 g, 0.014 mol), $Pd(PPh_3)_2Cl_2$ (0.55 g, 0.78 mmol). Recrystallization from toluene yielded **75b** as a white solid (2.59 g, 87%): mp 137.4-139.0 °C, lit. mp[328] 134 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, *J* = 8.8 Hz), 7.71 (1H, d, *J* = 9.2 Hz), 7.01 – 6.98 (3H, m), 4.16 (3H, s), 3.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 160.9, 155.0, 128.9, 127.9, 126.7, 117.8, 114.5, 55.5, 54.9; MS (ES^+) *m/z* 217.1 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.75; H, 5.62; N, 13.10%.

3-Methoxy-6-(2-methoxypyridin-5-yl)-pyridazine (75c)



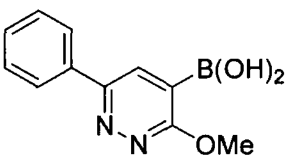
2-Methoxy-5-pyridylboronic acid (3.6 g, 0.024 mol), 3-chloro-6-methoxypyridazine **74** (3.0 g, 0.021 mol), $Pd(PPh_3)_2Cl_2$ (0.82 g, 1.17 mmol); eluent EtOAc, yielded **75c** as a white solid (3.85 g, 85%): mp 146.8-148.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (1H, d, *J* = 2.4 Hz), 8.31 (1H, dd, *J* = 9.0 Hz, *J* = 2.4 Hz), 7.73 (1H, d, *J* = 9.6 Hz), 7.04 (1H, d, *J* = 9.6 Hz), 6.86 (1H, d, *J* = 9.0 Hz), 4.17 (3H, s), 3.99 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.4, 153.1, 145.1, 137.0, 126.4, 125.7, 118.0, 111.4, 55.0, 53.91; MS (ES^+) *m/z* 218.1 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.73; H, 5.15; N, 19.29%.

3-Methoxy-6-(2-fluoropyridin-5-yl)-pyridazine (75d)



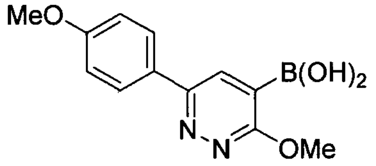
2-Fluoro-5-pyridylboronic acid (2.2 g, 0.016 mol), 3-chloro-6-methoxypyridazine **74** (2.0 g, 0.014 mol), $Pd(PPh_3)_2Cl_2$ (0.55 g, 0.78 mmol); eluent petroleum ether (bp 40–60 °C):EtOAc 1:4 v/v, yielded **75d** as a pink solid (2.48 g, 87%): mp 147.7-149.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (1H, d, *J* = 2.4 Hz), 8.52 (1H, td, *J* = 8.2 Hz, *J* = 2.4 Hz), 7.78 (1H, d, *J* = 8.8 Hz), 7.09 (1H, d, *J* = 9.2 Hz), 7.06 (1H, d, *J* = 3.2 Hz), 4.19 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (1C, d, *J* = 241 Hz), 164.8, 152.0, 145.8 (1C, d, *J* = 15 Hz), 139.6 (1C, d, *J* = 9 Hz), 130.4 (1C, d, *J* = 5 Hz), 126.7, 118.2, 110.1 (1C, d, *J* = 38 Hz), 55.2; MS (ES^+) *m/z* 206.1 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{10}H_8FN_3O$: C, 58.53; H, 3.93; N, 20.48. Found: C, 58.25; H, 3.94; N, 20.97%.

3-Methoxy-6-phenyl-4-pyridazinylboronic acid (76a)



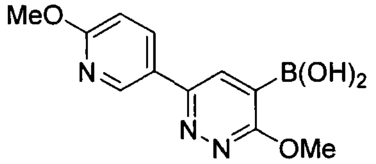
Diisopropylamine (3.13 mL, 0.022 mol) was added to *n*-butyllithium (2.5 M in hexane, 8.9 mL, 0.022 mol) in anhydrous THF (50 mL) at −78 °C under argon. The mixture warmed to 0 °C and left to stir for 0.5 h. The reaction was then cooled to −78 °C and a solution of 3-methoxy-6-phenylpyridazine **75a** (2.1 g, 0.011 mol) in anhydrous THF (20 mL) was added over 1.5 h. The reaction was stirred for a further 0.5 h. Triisopropylborate (7.4 mL, 0.032 mol) was added at −78 °C and the mixture was stirred for 1.5 h before warming gradually to −10 °C when it was quenched with deionised water (100 mL) and left to stir at room temperature overnight. The organic solvent was removed in vacuo. The resulting aqueous phase was then washed with Et_2O (3 × 50 mL) and treated with NaOH to obtain pH 10, then acidified to pH 6 using HBr (48% aq. solution) to precipitate **76a** as a white solid (2.38 g, 96%): mp 155.6-156.4 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.55 (2H, s), 8.11 (1H, s), 8.06 (2H, d, *J* = 6.8 Hz), 7.46 – 7.54 (3H, m), 4.07 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.5, 154.0, 136.3, 131.1, 129.2, 128.9, 126.2, 54.3; ^{11}B NMR (128 MHz, DMSO-d_6) δ 29.8; Anal. Calcd. for $C_{11}H_{11}BN_2O_3$: C, 57.44; H, 4.82; N, 12.18. Found: C, 57.00; H, 4.78; N, 11.82%.

3-Methoxy-6-(4-methoxyphenyl)-4-pyridazinylboronic acid (76b)



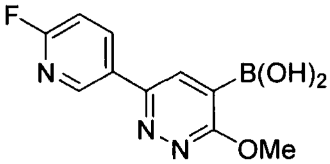
Diisopropylamine (0.65 mL, 4.6 mmol) was added to *n*-butyllithium (2.5 M in hexane, 1.8 mL, 4.6 mmol) in anhydrous ether (20 mL) at –78 °C under argon. The mixture warmed to 0 °C and left to stir for 0.5 h. The reaction was then cooled to –78 °C and a solution of 3-methoxy-6-(4-methoxyphenyl)pyridazine **75b** (0.5 g, 2.3 mmol) in anhydrous ether (40 mL) was added over 1 h (the solid was not entirely dissolved in ether at room temperature). The reaction was stirred for a further 1 h. Triisopropylborate (1.6 mL, 6.9 mmol) was added at –78 °C and the mixture was stirred for 1.5 h. The mixture was warmed to room temperature and stirred for 0.5 h before quenching with deionised water (50 mL) and then left to stir at room temperature for 1 h. The organic solvent was removed in vacuo. The resulting aqueous phase was then washed with Et_2O (3 × 50 mL) and treated with NaOH to obtain pH 10, then acidified to pH 6 using HBr (48% aq. solution) to precipitate a white solid. The mixture was stirred overnight at pH 6. On further acidification to pH 2 more precipitate formed; after filtration and drying **76b** was obtained as a white solid (0.53 g, 88%): mp 170.4-171.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (2H, s), 8.05 (1H, s), 8.01 (2H, d, *J* = 8.4 Hz), 7.07 (2H, d, *J* = 8.4 Hz), 4.04 (3H, s), 3.82 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 160.2, 153.6, 130.5, 128.6, 127.5, 114.3, 55.2, 54.2; ^{11}B NMR (128 MHz, DMSO-d_6) δ 28.9; Anal. Calcd. for $C_{12}H_{13}BN_2O_4$: C, 55.42; H, 5.04; N, 10.77. Found: C, 55.39; H, 5.03; N, 10.56%.

3-Methoxy-6-(2-methoxypyridin-5-yl)-4-pyridazinylboronic acid (76c)



Diisopropylamine (1.3 mL, 9.2 mmol) was added to *n*-butyllithium (2.5 M in hexane, 3.7 mL, 9.2 mmol) in anhydrous ether (70 mL) at –10 °C under argon. The mixture warmed to 0 °C and left to stir for 0.5 h. The reaction was then cooled to –78 °C and a solution of 3-methoxy-6-(2-methoxypyridin-5-yl)-pyridazine **75c** (1.0 g, 4.6 mmol) in anhydrous ether (80 mL) was added over 1.25 h. The reaction was stirred for a further 1 h. Triisopropylborate (3.2 mL, 13.8 mmol) was added at –78 °C and the mixture was stirred for 1.5 h before warming gradually to room temperature, before quenching with deionised water (70 mL). After stirring for a further 15 min the organic solvent was removed in vacuo. The resulting aqueous phase was then washed with Et_2O (1 × 150 mL) to remove any remaining starting material. The aqueous phase was cooled in an ice bath and acidified with glacial acetic acid to pH 5, where a precipitate formed. The solid was filtered and dried to yield **76c** as a pale orange solid (379 mg). TLC analysis of the aqueous phase still showed a baseline spot. The aqueous phase was further acidified to pH 3 and then extracted with EtOAc until a TLC of the aqueous phase no longer showed boronic acid. The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to dryness in vacuo, yielding an orange solid which NMR confirmed to be **76c** (352 mg). Total yield of boronic acid **76c** (731 mg, 61%): mp 144.4-145.9 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.84 (1H, d, *J* = 2.4 Hz), 8.56 (2H, s), 8.38 (1H, dd, *J* = 11.6 Hz, *J* = 2.4 Hz), 8.12 (1H, s), 6.97 (1H, d, *J* = 8.8 Hz), 4.05 (3H, s), 3.92 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 164.7, 152.4, 145.4, 137.4, 131.0, 126.2, 111.2, 54.8, 53.9; ^{11}B NMR (128 MHz, DMSO-d_6) δ 29.3; Anal. Calcd. for $C_{11}H_{12}BN_3O_4$: C, 50.61; H, 4.63; N, 16.10. Found: C, 50.32; H, 4.60; N, 16.12%.

3-Methoxy-6-(2-fluoropyridin-5-yl)-4-pyridazinylboronic acid (76d)

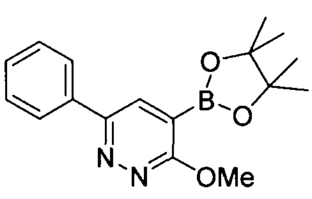


Diisopropylamine (1.4 mL, 9.8 mmol) was added to *n*-butyllithium (2.5 M in hexane, 3.9 mL, 9.8 mmol) in anhydrous THF (50 mL) at –78 °C under argon. The mixture warmed to 0 °C and left to stir for 0.5 h. The reaction was then cooled to –78 °C and a solution of 3-methoxy-6-(2-fluoropyridin-5-yl)-pyridazine **75d** (1.0 g, 4.9 mmol) in anhydrous THF (35 mL) was added over 1.5 h. The reaction was stirred for a further 0.5 h. Triisopropylborate (3.4 mL, 14.6 mmol) was added at –78 °C and the mixture was stirred for 1.5 h before warming gradually to –10 °C when it was quenched with deionised water (100 mL) and left to stir at room temperature overnight. The organic solvent was removed in vacuo. The resulting aqueous phase was then washed with Et_2O (4 × 50 mL) and treated with NaOH to obtain pH 10. The aqueous phase was acidified to pH 4 using HBr (48% aq. solution), and then extracted with EtOAc (4 × 50 mL). The organic layer was reduced in vacuo and the product **76d** was isolated as a light orange solid (0.91 g, 75%) Recrystallizations were unsuccessful and the product was not further purified: mp ca. 149 °C (decomp.); ^1H NMR (400 MHz, DMSO-d_6) δ 8.90 (1H, d, *J* = 2.8 Hz), 8.65 (1H, td, *J* = 8.6 Hz, *J* = 2.0 Hz), 8.60 (2H, s), 8.21 (1H, s), 7.36 (1H, dd, *J* = 8.6 Hz, *J* = 2.8 Hz), 4.07 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.0 (1C, d, *J* = 263 Hz), 165.7, 151.1, 145.5, (1C, d, *J* = 16 Hz), 139.9 (1C, d, *J* = 9 Hz), 131.0, 130.6 (1C, d, *J* = 4 Hz), 109.8 (1C, d, *J* = 38 Hz), 54.5; Anal. Calcd. for $C_{10}H_9BFN_3O_3$: C, 48.23; H, 3.64; N, 16.88. Found: C, 45.05; H, 3.63; N, 14.60%. Characterization indicated that **76d** is a mixture of boronic acid and anhydride, resulting in the C, H, N analysis being incorrect for pure boronic acid.

General Procedure for the preparation of 77a-d.

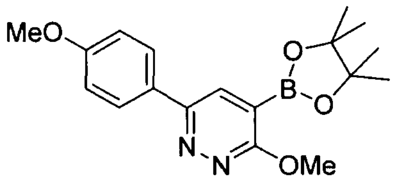
A solution of the boronic acid **76a-d** (1.0 equiv.), pinacol (1.0 equiv.) and $MgSO_4$ (2 g) in toluene (25 mL) was stirred for 17 h at room temperature (TLC monitoring). The suspension was filtered and the resulting solution washed with brine (3 × 15 mL). The aqueous phase was washed with DCM (1 × 25 mL). The combined organic layers were dried over $MgSO_4$ and reduced in vacuo to yield pinacol esters **77a-d**.

3-Methoxy-6-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine (77a)



3-Methoxy-6-phenyl-4-pyridazinylboronic acid **76a** (0.350 g, 1.5 mmol), pinacol (0.18 g, 1.5 mmol), $MgSO_4$ (2 g), toluene (25 mL); 12 h at room temperature (TLC monitoring); evaporation of the organic layer gave the product **77a** as a white solid (0.378 g, 80%): mp 151.6-152.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, s), 8.06 (2H, dd, *J* = 9.6 Hz, *J* = 2.0 Hz), 7.44 – 7.51 (3H, m), 4.22 (3H, s), 1.39 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 154.9, 136.5, 133.8, 129.4, 129.0, 126.7, 85.0, 55.4, 31.0, 25.0; ^{11}B NMR (128 MHz, DMSO-d_6) δ 30.1; MS (ES$^+$) *m/z* 313.2 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{17}H_{21}BN_2O_3$: C, 65.41; H, 6.78; N, 8.97. Found: C, 65.09; H, 6.68; N, 8.69%.

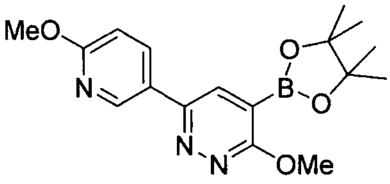
3-Methoxy-6-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine (77b)



3-Methoxy-6-(4-methoxyphenyl)-4-pyridazinylboronic acid **76b** (1.0 g, 3.85 mmol), pinacol (0.45 g, 3.85 mmol), $MgSO_4$ (2.0 g) in toluene (25 mL); 20 h at room temperature (TLC monitoring); evaporation of the organic phase gave the product **77b** as a white solid (1.1 g, 85%): mp 176.4-177.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (1H, s), 7.98 (2H, d, *J* = 8.8 Hz), 6.97 (2H, d, *J* =

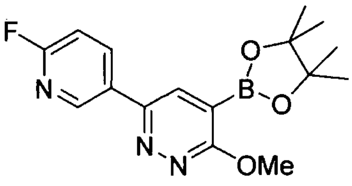
8.8 Hz), 4.17 (3H, s), 3.82 (3H, s), 1.35 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 160.7, 154.4, 133.2, 128.9, 127.8, 114.3, 84.8, 55.4, 55.2, 24.8; ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.2; MS (ES^+) *m/z* 343.4 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{18}H_{23}BN_2O_4$: C, 63.18; H, 6.77; N, 8.19. Found: C, 63.10; H, 6.82; N, 8.21%. Crystals for X-ray diffraction analysis were grown from hexane.

3-Methoxy-6-(2-methoxypyridin-5-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine (77c)



3-Methoxy-6-(2-methoxypyridin-5-yl)-4-pyridazinylboronic acid **76c** (0.290 g, 1.1 mmol), pinacol (0.13 g, 1.1 mmol), $MgSO_4$ (2 g), toluene (10 mL); 17 h at room temperature (TLC monitoring); evaporation of the combined organic phase gave the product **77c** as a white solid (0.337 g, 90%): mp 146.8-148.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (1H, dd, *J* = 2.4 Hz, *J* = 0.4 Hz), 8.29 (1H, dd, *J* = 9.0 Hz, *J* = 2.4 Hz), 8.03 (1H, s), 6.83 (1H, dd, *J* = 9.0 Hz, *J* = 0.4 Hz), 4.19 (3H, s), 3.98 (3H, s), 1.36 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.0, 152.7, 145.3, 136.9, 133.1, 125.8, 111.2, 85.0, 55.4, 53.8, 24.9; ^{11}B NMR (128 MHz, $CDCl_3$) δ 29.97; MS (ES^+) *m/z* 344.3 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{17}H_{22}BN_3O_4$: C, 59.50; H, 6.46; N, 12.24. Found: C, 58.82; H, 6.47; N, 11.86%.

3-Methoxy-6-(2-fluoropyridin-5-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine (77d)



3-Methoxy-6-(2-fluoropyridin-5-yl)-4-pyridazinyl boronic acid **76d** (0.600 g, 2.4 mmol), pinacol (0.28 g, 2.4 mmol), $MgSO_4$ (2 g), toluene (25 mL); 12 h at room temperature (TLC monitoring). evaporation of the combined organic layers yielded **77d** as a white solid (0.583 g, 73%): mp 198.2-199.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (1H, d, *J* = 2.4 Hz), 8.49 (1H, td, *J* = 8.0 Hz, *J* = 2.4 Hz), 8.04 (1H, s), 7.02 (1H, dd, *J* = 8.6 Hz, *J* = 3.0 Hz), 4.18 (3H, s), 1.35 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 164.2 (1C, d, *J* = 242 Hz), 151.5, 145.8 (1C, d, *J* = 16 Hz), 139.4 (1C, d, *J* = 8 Hz), 133.2, 130.4 (1C, d, *J* = 4 Hz), 109.8 (1C, d, *J* = 38 Hz), 85.1, 55.4, 24.8, 24.6; ^{11}B NMR (128 MHz, DMSO-d_6) δ 29.9; MS (ES^+) *m/z* 332.2 ($[M+H]^+$, 100%). HRMS (ES^+) calcd for $C_{16}H_{20}BFN_3O_3$ 332.1576, found 332.1573. Anal. Calcd.

for $C_{16}H_{19}BFN_3O_3$: C, 58.03; H, 5.78; N, 12.69. Found: C, 56.46; H, 5.76; N, 12.21%. Crystals for X-ray diffraction analysis were grown from toluene/hexane.

Typical Procedure for the Suzuki-Miyaura Cross-Coupling Catalyst Screening in Table 2.2

The boronic acid **76a** or ester **77a** (1.1 equiv.) the aryl halide (1.0 equiv.) and Pd source and phosphine ligand were sequentially added to degassed 1,4-dioxane (10 mL) and the mixture was stirred at 20 °C for 30 min. Degassed aqueous base or solid K_3PO_4 was added and the reaction mixture was heated under argon at reflux or the temperature stated for the time stated. Solvent was removed in vacuo then EtOAc 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.

Typical Procedure for the Suzuki-Miyaura Cross-Coupling Reactions in Table 2.3

The boronic ester **77a-d** or acid **76a, b** (1.1 equiv.) the aryl halide (1.0 equiv.) and $Pd_2(dba)_3$ (ca. 1 mol% ArX), PCy_3 (ca. 2.4 mol% ArX) were sequentially added to degassed 1,4-dioxane (2.7 mL) and the mixture was stirred at 20 °C for 30 min. Degassed aqueous K_3PO_4 solution (1.27 M, 1.7 equiv.) was added and the reaction mixture was heated under argon at reflux for 24 h. Solvent was removed in vacuo then EtOAc 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 followed if needed by recrystallization.

Conditions A: $Pd_2(dba)_3$ (1 mol% ArX)/PCy_3 (2.4 mol% ArX), 1,4-dioxane, K_3PO_4 (1.27 M), reflux, 24 h.

Conditions B: $Pd_2(dba)_3$ (1 mol% ArX)/PCy_3 (2.4 mol% ArX), 1,4-dioxane, K_3PO_4 $_{(s)}$, reflux, 24 h.

Conditions C: $Pd_2(dba)_3$ (5 mol% ArX)/[*t*-Bu_3PH]BF_4 (12 mol% ArX), MeCN, K_3PO_4 $_{(s)}$, 85 °C, 1 h.

Conditions D: $Pd_2(dba)_3$ (1 mol% ArX)/PCy_3 (2.4 mol% ArX), 1,4-dioxane, K_3PO_4 (1.27 M), μW 120 °C, 1 h.

Conditions E: $Pd_2(dba)_3$ (1 mol% ArX)/PCy_3(2.4 mol% ArX), DMF, $K_3PO_4.2H_2O$, μW 160 °C, 5 min.

Conditions F: $Pd(OAc)_2$ (5 mol% ArX)/D-*t*-BPF (5 mol% ArX), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 5 h.

3-Methoxy-6-phenyl-4-(pyridin-2-yl)pyridazine (79)

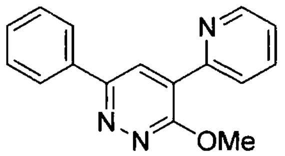


Table 2.2, entry 7: Compound **77a** (343 mg, 1.1 mmol), 2-bromopyridine **78** (0.095 mL, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.67 mL) and K_3PO_4 (1.27 M, 1.33 mL); reaction time 24 h; eluent EtOAc:hexane, 2:3 v/v gave **79** as a yellow oil, which solidified on standing (200 mg, 76%): mp 68.0-70.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (1H, d, *J* = 4.8 Hz), 8.54 (1H, s), 8.15 (1H, d, *J* = 8.4 Hz), 8.12, (2H, d, *J* = 8.0 Hz), 7.78 (1H, td, *J* = 7.6 Hz, *J* = 2.0 Hz), 7.41 – 7.50 (3H, m), 7.33 (1H, t, *J* = 6.2 Hz), 4.29 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 156.3, 151.1, 150.1, 136.5, 136.4, 129.4, 128.9, 127.8, 126.7, 126.2, 125.3, 124.1, 55.3; MS(ES^+) *m/z* 264.2 ($[M+H]^+$, 100%). HRMS (ES^+) calcd for $C_{16}H_{14}N_3O$ 264.1137, found 264.1131. Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.60; H, 5.06; N, 15.58%.

Synthesis via the organozincate:[324] A solution of *n*-butyllithium (2.5M in hexane, 0.92 mL, 2.3 mmol), was added to cold (–30 °C) anhydrous THF (20 mL) under an argon atmosphere. Diisopropylamine (0.34 mL, 2.4 mmol) was added and the solution was then allowed to stir at 0 °C for 15 min. The solution was then cooled to –78 °C and 3-methoxy-6-phenylpyridazine **75a** (186 mg, 1.0 mmol) dissolved in 5 mL of anhydrous THF was added dropwise and the mixture was stirred for 1.5 h at –78 °C. A solution of zinc chloride (previously dried under vacuum with a heat gun, 272 mg, 2.0 mmol) dissolved in 5 mL of anhydrous THF was added to the lithiated pyridazine at –78 °C, the mixture was allowed to warm to room temperature over 1 h. To the pyridazinylzincate solution, at room temperature, was added $Pd(PPh_3)_4$ (4 mol%, 46.2 mg, 0.04 mmol) and 2-bromopyridine (0.11 mL, 1.2 mmol), the mixture was fitted with a reflux condenser and heated whilst placed in a sonication bath for 3 h (the reaction mixture gradually reached reflux whilst under sonication). The reaction mixture was then hydrolysed with a solution of ethylenediamine tetraacetic acid (584 mg, 2.0 mmol) in 10 mL deionized water and made slightly basic with a saturated aqueous solution of potassium carbonate. The aqueous layer was extracted with DCM (3 × 25 mL) and the resulting organic layer dried over $MgSO_4$ and reduced in vacuo. The resulting crude product was purified by column chromatography, eluent EtOAc: petroleum ether (bp 40–60 °C), 1:4 v/v, yielding **79** was an off-white solid (202 mg, 77%). Spectroscopically identical with the sample previously described.

Table 2.2, entry 1: Compound **76a** (391 mg, 1.7 mmol), 2-bromopyridine **78** (0.14 mL, 1.5 mmol), $Pd(OAc)_2$ (19.0 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (1 M, 4 mL); reaction time 65 h; eluent petroleum ether (bp 40–60 °C): EtOAc 1:4 v/v gave **79** as a opaque oil which solidified to an off-white solid on standing (39 mg, 10%). Spectroscopically identical with the sample previously described.

Table 2.2, entry 2: Compound **76a** (391 mg, 1.7 mmol), 2-bromopyridine **78** (0.14 mL, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (60.0 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (1 M, 4 mL); reaction time 65 h; eluent EtOAc:hexane 1:4 v/v gave **79** as a pale yellow solid (216 mg, 55%). Spectroscopically identical with the sample previously described.

Table 2.2, entry 3: Compound **76a** (391 mg, 1.7 mmol), 2-bromopyridine **78** (0.14 mL, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (60.0 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (1 M, 4 mL); reaction time 5 days at 55 °C, reaction monitored by TLC. Eluent EtOAc:hexane 1:1 v/v gave **79** as a pale yellow solid (157 mg, 40%). Spectroscopically identical with the sample previously described.

Table 2.2, entry 4: Compound **76a** (253 mg, 1.1 mmol), 2-bromopyridine **78** (0.10 mL, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.67 mL) and K_3PO_4 (1.27 M, 1.33 mL); reaction time 24 h; eluent EtOAc:hexane, 2:3 v/v gave **79** as a yellow oil (176 mg, 67%). Spectroscopically identical with the sample previously described.

Table 2.2, entry 5: Compound **77a** (530 mg, 1.7 mmol), 2-bromopyridine **78** (0.14 mL, 1.5 mmol), $Pd(OAc)_2$ (19.0 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (1 M, 4 mL); reaction time 65 h; eluent EtOAc:hexane 1:1 v/v gave **79** as an off-white solid (157 mg, 40%). Spectroscopically identical with the sample previously described.

Table 2.2, entry 6: Compound **77a** (530 mg, 1.7 mmol), 2-bromopyridine **78** (0.14 mL, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (60.0 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (1 M, 4 mL); reaction time 24 h; eluent EtOAc:hexane 2:3 v/v gave **79** as an oil which solidified on standing (173 mg, 44%). Spectroscopically identical with the sample previously described.

Table 2.2, entry 7 with $K_3PO_{4\,(s)}$: Compound **77a** (343 mg, 1.1 mmol), 2-bromopyridine **78** (0.10 mL, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.67 mL) and K_3PO_4 $_{(s)}$ (425 mg, 2.0 mmol); reaction time 24 h; eluent EtOAc:hexane, 2:3 v/v gave **79** as a yellow oil, which solidified on standing (124 mg, 47%). Spectroscopically identical with the sample previously described.

3-Methoxy-6-phenyl-4-(pyrimidin-5-yl)pyridazine (80)

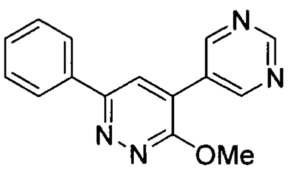


Table 2.2, entry 10: Compound **77a** (343 mg, 1.1 mmol), 5-bromopyrimidine **62** (159 mg, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.67 mL) and K_3PO_4 (1.27 M, 1.33 mL); reaction time 24 h; eluent EtOAc gave **80** as an off-white solid (126 mg, 47%): mp 165.7-166.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (1H, s), 9.08 (2H, s), 8.04 (2H, dd, J = 10 Hz, J = 2 Hz), 7.83 (1H, s), 7.47 – 7.54 (3H, m), 4.26 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 159.0, 156.8, 156.2, 135.8, 130.0, 129.2, 128.2, 126.7, 125.5, 123.9, 55.7; MS (EI) *m/z* 264.0 (M^+, 100%). Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 67.92; H, 4.53; N, 21.23%. Crystals for X-ray diffraction analysis were grown from EtOAc.

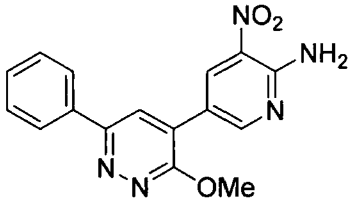
Synthesis via the organozincate: Procedure followed as for the preparation of **79** via this protocol. *n*-Butyllithium (2.5M in hexane, 0.92 mL, 2.3 mmol), diisopropylamine (0.34 mL, 2.4 mmol), 3-methoxy-6-phenylpyridazine **75a** (186 mg, 1.0 mmol), $ZnCl_2$ (272 mg, 2.0 mmol), $Pd(PPh_3)_4$ (4 mol%, 46.2 mg, 0.04 mmol), 5-bromopyrimidine (191 mg, 1.2 mmol). Heated and sonicated for 3 h, unsure if reaction was complete (from TLC monitoring), reaction mixture left to stand at room temperature overnight, then heated and sonicated for a further 3 h; eluent EtOAc: petroleum ether (bp 40–60 °C), 2:3 v/v, gave **80** as a pale yellow solid (117 mg, 44%). Spectroscopically identical with the sample previously described.

Table 2.2, entry 8: Compound **76a** (391 mg, 1.7 mmol), 5-bromopyrimidine **62** (238 mg, 1.5 mmol), $Pd(OAc)_2$ (19.0 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (1 M, 4 mL); reaction time 65 h; eluent EtOAc gave **80** as an orange solid (92 mg, 23%). Spectroscopically identical with the sample previously described.

Table 2.2, entry 9: Compound **76a** (253 mg, 1.1 mmol), 5-bromopyrimidine **62** (159 mg, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.67 mL) and K_3PO_4 (1.27 M, 1.33 mL); reaction time 24 h; eluent EtOAc gave **80** as a pale yellow solid (89 mg, 34%). Spectroscopically identical with the sample previously described.

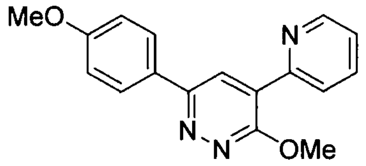
Table 2.2, entry 10 with K_3PO_4 $_{(s)}$: Compound **77a** (343 mg, 1.1 mmol), 5-bromopyrimidine **62** (159 mg, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.67 mL) and K_3PO_4 $_{(s)}$ (425 mg, 2.0 mmol); reaction time 24 h; eluent EtOAc gave **80** as a white solid (122 mg, 46%). Spectroscopically identical with the sample previously described.

2-Amino-3-nitro-5-(3-methoxy-6-phenylpyridazin-4-yl)-pyridine (82)



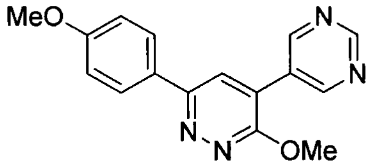
Compound **77a** (343 mg, 1.1 mmol), 2-amino-5-bromo-3-nitropyridine **61** (218 mg, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.67 mL) and K_3PO_4 (1.27 M, 1.33 mL); reaction time 24 h; eluent EtOAc:petroleum ether (bp 40–60 °C) 2:3 v/v, gave **82** as a yellow solid (190 mg, 59%): mp 214.6-216.9 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.90 (2H, dd, *J* = 6.8 Hz, *J* = 2.0 Hz), 8.33 (1H, s), 8.25 (2H, s), 8.17 (2H, d, *J* = 8.4 Hz), 7.48 – 7.56 (3H, m), 4.16 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 156.4, 155.3, 153.5, 136.0, 135.3, 129.4, 128.8, 126.6, 126.2, 124.9, 124.8, 117.3, 55.0; MS (ES^+) *m/z* 324.2 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{16}H_{13}N_5O_3$: C, 59.44; H, 4.05; N, 21.66. Found: C, 59.58; H, 4.04; N, 21.50%.

3-Methoxy-6-(4-methoxyphenyl)-4-(pyridin-2-yl)pyridazine (83)



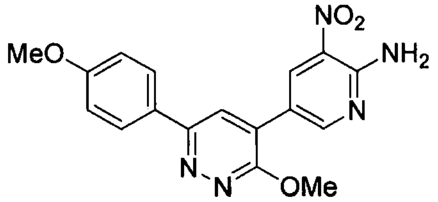
Compound **77b** (376 mg, 1.1 mmol), 2-bromopyridine **78** (0.095 mL, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (10 mL) and K_3PO_4 (1.27 M, 1.33 mL); reaction time 24 h; eluent petroleum ether (bp 40–60 °C):EtOAc, 2:3 v/v, gave **83** as a pale yellow solid (227 mg, 77%): mp 129.1-131.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (1H, d, *J* = 3.6 Hz), 8.50 (1H, s), 8.17 (1H, d, *J* = 8.0 Hz), 8.10 (2H, dd, *J* = 7.0 Hz, *J* = 2.0 Hz), 7.82 (1H, td, *J* = 7.8 Hz, *J* = 1.6 Hz), 7.03 (2H, dd, *J* = 6.8 Hz, *J* = 2.0 Hz), 4.30 (3H, s), 3.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 160.9, 156.0, 151.3, 150.1, 136.6, 129.0, 128.1, 127.9, 125.7, 125.4, 124.1, 114.4, 55.5, 55.3; MS (ES^+) *m/z* 294.2 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.46; H, 5.16; N, 14.39%. Crystals for X-ray diffraction analysis were grown from EtOAc.

3-Methoxy-6-(4-methoxyphenyl)-4-(pyrimidin-5-yl)pyridazine (84)



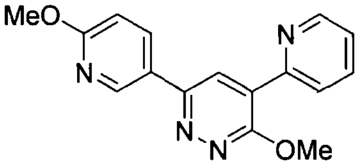
Compound **77b** (180 mg, 0.69 mmol), 5-bromopyrimidine **62** (100 mg, 0.62 mmol), $Pd_2(dba)_3$ (5.8 mg, 0.0062 mmol), PCy_3 (4.2 mg, 0.015 mmol), 1,4-dioxane (5 mL) and K_3PO_4 (1.27 M, 2 mL); microwave heating 120 °C, 1 h; eluent EtOAc, gave **84** as a white solid (87 mg, 43%): mp 191.4-192.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (1H, s), 9.07 (2H, s), 8.01 (2H, dd, *J* = 6.8 Hz, *J* = 2 Hz), 7.78 (1H, s), 7.04 (2H, dd, *J* = 6.8 Hz, *J* = 2 Hz), 4.25 (3H, s), 3.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 160.8, 159.0, 156.8, 155.8, 128.34, 128.30, 128.1, 125.1, 123.9, 114.7, 55.58, 55.56; MS (ES^+) *m/z* 295.2 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.12; H, 4.88; N, 18.66%.

5-(3-Methoxy-6-(4-methoxyphenyl)pyridazin-4-yl)-3-nitropyridin-2-amine (85)



Compound **77b** (284 mg, 0.83 mmol), 2-amino-5-bromo-3-nitropyridine **61** (164 mg, 0.75 mmol), $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), PCy_3 (5.1 mg, 0.018mol), 1,4-dioxane (10 mL) and K_3PO_4 (1.27 M, 1.0 mL); reaction time 24 h; eluent petroleum ether (bp 40–60 °C):EtOAc, 2:3 v/v, gave **85** as a yellow solid (120 mg, 46%): mp 222.9-225.8 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.89 (2H, q, *J* = 6.4 Hz, *J* = 2.0 Hz), 8.29 (1H, s), 8.25 (2H, s), 8.14 (2H, d, *J* = 8.8 Hz), 7.09 (2H, d, *J* = 8.8 Hz), 4.14 (3H, s), 3.84 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.54, 160.46, 156.5, 155.0, 153.6, 135.4, 128.4, 128.0, 125.0, 124.3, 117.4, 114.2, 79.2, 55.3, 54.9: MS (ES$^+$) *m/z* 354.2 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{17}H_{15}N_5O_4$: C, 57.79; H, 4.28; N, 19.82. Found: C, 58.04; H, 4.25; N, 19.39%.

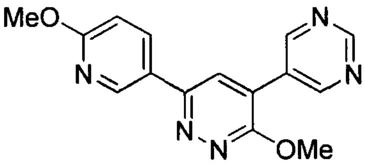
3-Methoxy-6-(2-methoxypyridin-5-yl)-4-(pyridin-2-yl)pyridazine (86)



Compound **77c** (378 mg, 1.1 mmol), 2-bromopyridine **78** (0.095 mL, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (10 mL) and K_3PO_4 (1.27 M, 1.33 mL); reaction time 24 h; eluent petroleum ether (bp 40–60 °C):EtOAc 2:3 v/v, gave **86** as a white solid (170 mg, 58%): mp 156.0-157.7 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.83 (1H, d, *J* = 2.4 Hz), 8.72 (1H, d, *J* = 4.4 Hz), 8.46 (1H, s), 8.32 (1H, dd, *J* = 9.8 Hz, *J* = 2.8 Hz), 8.13 (1H, d, *J* = 8.0 Hz), 7.77 (1H, td, *J* = 7.6 Hz, *J* = 1.6 Hz), 7.30 – 7.34 (1H, m), 6.82 (1H, d, *J* = 8.0 Hz), 4.26 (3H, s), 3.96 (3H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 165.1, 161.6, 154.3, 151.0, 150.2, 145.5, 137.0, 136.6, 128.1, 125.8, 125.5, 125.4, 124.3, 111.2, 55.4, 53.9; MS (ES$^+$) *m/z* 295.2 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.20; H, 4.83; N, 18.99%.

Synthesis via the organozincate: Procedure followed as for the preparation of **79** via this protocol. *n*-Butyllithium (2.5M in hexane, 0.92 mL, 2.3 mmol), diisopropylamine (0.34 mL, 2.4 mmol), 3-methoxy-6-(2-methoxypyridin-5-yl)pyridazine **75c** (217 mg, 1.0 mmol), $ZnCl_2$ (272 mg, 2.0 mmol), $Pd(PPh_3)_4$ (4 mol%, 46.2 mg, 0.04 mmol), 2-bromopyridine (0.11 mL, 1.2 mmol). Heated and sonicated for 4 h, until the reaction was complete (from TLC monitoring); eluent EtOAc: petroleum ether (bp 40–60 °C), 2:3 v/v, gave **86** as an off-white solid (215 mg, 73%). Spectroscopically identical with the sample previously described.

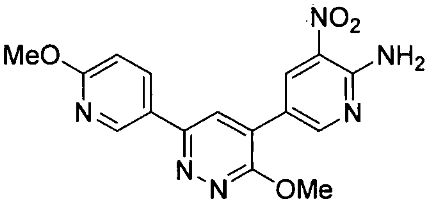
3-Methoxy-6-(2-methoxypyridin-5-yl)-4-(pyrimidin-5-yl)pyridazine (87)



Compound **77c** (343 mg, 1.0 mmol), 5-bromopyrimidine **62** (145 mg, 0.91 mmol), $Pd_2(dba)_3$ (8.3 mg, 0.0091 mmol), PCy_3 (6.1 mg, 0.022 mmol), 1,4-dioxane (2.67

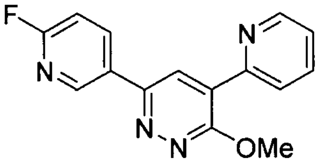
mL) and K_3PO_4 (1.27 M, 1.33 mL); reaction time 24 h; eluent EtOAc, gave **87** as a white solid (102 mg, 37%): mp 192.0-194.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (1H, s), 9.06 (2H, s), 8.74 (1H, d, *J* = 2.8 Hz), 8.31 (1H, dd, *J* = 8.8 Hz, *J* = 2.4 Hz), 7.76 (1H, s), 6.87 (1H, d, *J* = 8.8 Hz), 4.24 (3H, s), 3.99 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 160.9, 158.9, 156.6, 153.8, 145.1, 136.8, 127.8, 125.0, 124.5, 124.0, 111.4, 55.5, 53.8; MS (ES$^+$) *m/z* 296.2 ([M+H]$^+$, 100%). HRMS (ES$^+$) calcd for $C_{15}H_{14}N_5O_2$ 296.1142, found 296.1141. Anal. Calcd. for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 60.39; H, 4.39; N, 23.25%.

5-(3-Methoxy-6-(2-methoxypyridin-5-yl)-pyridazin-4-yl)-3-nitropyridin-2-amine (88)



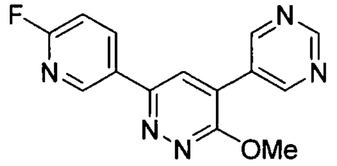
Compound **77c** (337 mg, 0.98 mmol), 2-amino-5-bromo-3-nitropyridine **61** (195 mg, 0.89 mmol), $Pd_2(dba)_3$ (8.2 mg, 0.0089 mmol), PCy_3 (6.0 mg, 0.021 mmol), 1,4-dioxane (10 mL) and K_3PO_4 (1.27 M, 1.33 mL); reaction time 24 h; eluent petroleum ether (bp 40–60 °C):EtOAc 1:1 v/v, final elution with EtOAc gave **88** as a yellow solid (134 mg, 42%): mp 249.5-252.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (1H, d, *J* = 2.4 Hz), 8.91 (2H, s), 8.48 (1H, dd, *J* = 8.6 Hz, *J* = 2.4 Hz), 8.38 (1H, s), 8.26 (2H, s), 7.00 (1H, d, *J* = 8.8 Hz), 4.16 (3H, s), 3.94 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3, 160.8, 156.5, 153.6, 153.3, 145.5, 137.3, 135.4, 126.2, 125.5, 125.1, 124.4, 117.2, 110.7, 55.0, 53.5; MS (ES$^+$) *m/z* 355.2 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{16}H_{14}N_6O_4$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.62; H, 4.00; N, 23.43%.

3-Methoxy-6-(2-fluoropyridin-5-yl)-4-(pyridin-2-yl)pyridazine (89)



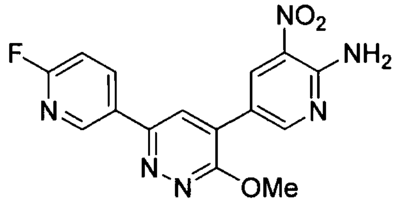
Compound **77d** (310 mg, 0.94 mmol), 2-bromopyridine **78** (0.081 mL, 0.85 mmol), $Pd_2(dba)_3$ (7.8 mg, 0.0085 mmol), PCy_3 (5.5 mg, 0.020 mmol), 1,4-dioxane (2.5 mL) and K_3PO_4 (1.27 M, 1.1 mL); reaction time 24 h; eluent petroleum ether (bp 40–60 °C):EtOAc 1:1 v/v, gave **89** as an off-white solid (160 mg, 67%): mp 190.3-191.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (1H, d, *J* = 2.4 Hz), 8.75 (1H, d, *J* = 4.8 Hz), 8.57 (1H, td, *J* = 7.8 Hz, *J* = 2.4 Hz), 8.55 (1H, s), 8.19 (1H, d, *J* = 8.0 Hz), 7.81 (1H, td, *J* = 7.8 Hz, *J* =1.6 Hz), 7.35 – 7.39 (1H, m), 7.06 (1H, dd, *J* = 8.4 Hz, *J* = 2.8 Hz), 4.31 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (1C, d, *J* = 242 Hz), 161.9, 153.0, 150.5, 150.2, 146.0 (1C, d, J = 15 Hz), 139.5 (1C, d, J = 8 Hz), 136.7, 130.5 (1C, d, J = 4 Hz), 128.1, 125.6, 125.4, 124.4, 109.9 (1C, d, J = 38 Hz), 55.5; MS (ES$^+$) *m/z* 336.9 ([M+MeOH+Na]$^+$, 100%). Anal. Calcd. for $C_{15}H_{11}FN_4O$: C, 63.83; H, 3.93; N, 19.85. Found: C, 63.58; H, 3.89; N, 19.69%.

3-Methoxy-6-(2-fluoropyridin-5-yl)-4-(pyrimidin-5-yl)pyridazine (90)



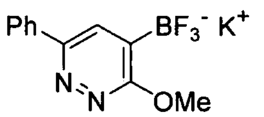
Compound **77d** (364 mg, 1.1 mmol), 5-bromopyrimidine **62** (159 mg, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (3 mL) and K_3PO_4 (1.27 M, 1.3 mL); reaction time 24 h; eluent EtOAc, gave **90** as a white solid (82 mg, 29%): mp 256.1-257.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (1H, s), 9.09 (2H, s), 8.83 (1H, d, J = 2.5 Hz), 8.57 (1H, td, J = 8.1 Hz, J = 2.5 Hz), 7.83 (1H, s), 7.12 (1H, dd, J = 8.6 Hz, J = 3.0 Hz), 4.29 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6 (1C, d, J = 242 Hz), 161.5, 159.2, 156.8, 152.9, 145.9 (1C, d, J = 16 Hz), 139.7 (1C, d, J = 9 Hz), 129.9 (1C, d, J = 5 Hz), 127.8, 125.0, 124.4, 110.3 (1C, d, J = 37 Hz), 55.9; MS (ES$^+$) *m/z* 284.2 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{14}H_{10}FN_5O$: C, 59.36; H, 3.56; N, 24.72. Found: C, 59.30; H, 3.56; N, 24.45%.

5-(6-(2-Fluoropyridin-5-yl)-3-methoxypyridazin-4-yl)-3-nitropyridin-2-amine (91)



Compound **77d** (189 mg, 0.57 mmol), 2-amino-5-bromo-3-nitropyridine **61** (109 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), D-*t*-BPF (12 mg, 0.025 mmol), 1,4-dioxane (7 mL) and Na_2CO_3 (1 M, 2 mL); reaction time 5 h; eluent hexane:EtOAc 1:1 v/v, recrystallization from EtOAc/hexane, gave **91** as a yellow solid (91 mg, 52%): mp 281.5 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (1H, s), 8.91 (2H, s), 8.74 (1H, t, J = 7.8 Hz), 8.45 (1H, s), 8.28 (1H, br. s), 7.34 (1H, d, J = 8.1 Hz), 4.17 (3H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.6 (1C, d, J = 238 Hz), 161.1, 156.4, 153.6, 152.3, 146.0 (1C, d, J = 15 Hz), 140.2, (1C, d, J = 9 Hz), 135.4, 130.3 (1C, d, J = 4 Hz), 126.2, 125.1, 124.7, 117.0, 109.8 (1C, d, J = 38 Hz), 55.2; MS (ES$^+$) *m/z* 343.2 ([M+H]$^+$, 95%), 365.2 ([M+Na]$^+$, 100%). HRMS (ES$^+$) calcd for $C_{15}H_{12}N_6O_3F$ 343.0949, found 343.0950.

Potassium 3-methoxy-6-phenyl-4-pyridazinyltrifluoroborate salt (92)



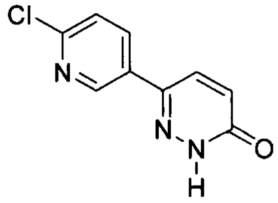
3-Methoxy-6-phenyl-4-pyridazinylboronic acid **76a** (640 mg, 2.8 mmol) and potassium hydrogen fluoride (650 mg, 8.3 mmol) were stirred in methanol (5 mL) at room temperature; on addition of water (3 mL) a white precipitate formed. The reaction mixture was stirred at room temperature for 1 h before standing in an ice bath for 1 h. The precipitate was filtered and recrystallized from hot MeCN to yield **92** as a white solid (792 mg, 97%): mp 209.4-210.8 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.96 (2H, dd, *J* = 8.4 Hz, *J* = 1.6 Hz), 7.82 (1H, s), 7.52 – 7.46 (2H, m), 7.43 – 7.39 (1H, m), 3.97 (3H, s); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 167.8, 153.7, 137.7, 129.6, 128.7, 128.3, 125.9, 53.4; ^{11}B NMR (128 MHz, DMSO-d$_6$) δ 3.5; ^{19}F NMR (376 MHz, DMSO-d$_6$) δ -136.5.

Typical Procedure for the Suzuki-Miyaura Cross-Coupling Reactions of 92 in Scheme 2.6

The trifluoroborate salt **92** (1.1 equiv.), 2-bromopyridine **78** (1.0 equiv.), Pd(dppf)Cl$_2$·DCM or Pd$_2$(dba)$_3$ (ca. 1 mol% **78**), PCy$_3$ (ca. 2.4 mol% **78**) in certain cases, Et$_3$N or K$_3$PO$_4$ $_{(s)}$ were sequentially added to degassed solvent (3 mL). The reaction mixture was heated under argon at reflux for the time stated. In some cases several drops of deionized water were added in attempts to make the reaction mixture homogeneous. Solvent was removed in vacuo then EtOAc 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 or analyzed by LCMS.

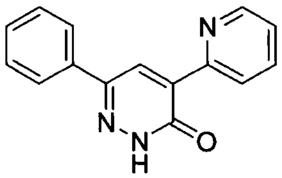
5.3 Experimental details for Chapter 3

6-(6-Chloropyridin-3-yl)pyridazin-3(2*H*)-one (99)



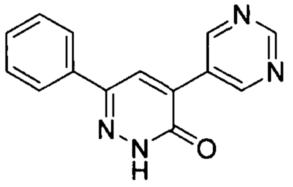
Phosphorus oxychloride (1.86 mL, 20 mmol) was added dropwise to a stirred solution of **75c** (434 mg, 2.0 mmol) in anhydrous DMF (40 mL) at 0 °C. Stirring was continued for 1 h then the mixture was heated at 110 °C for 19 h. The reaction was cooled to 0 °C and quenched with saturated NaOAc solution (60 mL). The mixture was transferred to a separating funnel with the addition of deionized water (25 mL). The mixture was extracted with EtOAc (3 × 200 mL) and washed with deionized water (3 × 150 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The solid was recrystallized from EtOAc to give **99** as a beige solid (249 mg, 60%): mp 262.4-263.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 13.40 (1H, s), 8.89 (1H, s), 8.29 (1H, dd, *J* = 8.9 Hz, *J* = 1.3 Hz), 8.10 (1H, d, *J* = 10.4 Hz),7.64 (1H, d, *J* = 8.3 Hz), 7.05 (1H, d, *J* = 9.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 151.1, 147.6, 141.2, 137.2, 131.8, 130.8, 130.4, 124.9; MS (ES$^+$) *m/z* 208.1 ([M+H]$^+$, 100%). Anal. Calcd. for $C_9H_6ClN_3O$: C, 52.07; H, 2.91; N, 20.24. Found: C, 52.10; H, 2.95; N, 20.06%.

6-Phenyl-4-(pyridin-2-yl)pyridazin-3(2*H*)-one (103)



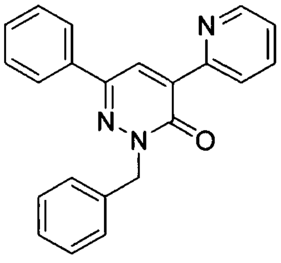
Boron tribromide (1 M in DCM, 3.6 mL, 3.6 mmol) was added dropwise to a solution of **79** (232 mg, 0.89 mmol) in anhydrous DCM (30 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 15 min before warming to room temperature. The reaction mixture was then heated at reflux for 4 h. The reaction was cooled and deionized water (40 mL) added. The mixture was neutralized with a saturated $NaHCO_3$ solution to pH 7, before being extracted with DCM (2 × 50 mL). The combined organic phase was dried over Na_2SO_4, evaporated to dryness and recrystallized from chloroform/petroleum ether (bp 40–60 °C) to give **103** as a yellow solid (186 mg, 84%): mp 247.6-248.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.57 (1H, s), 8.77 – 8.68 (3H, m), 7.94 – 7.90 (3H, m), 7.54 – 7.47 (4H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.8, 150.2, 149.7, 144.5, 136.7, 135.8, 134.8, 129.2, 129.0, 127.7, 125.6, 124.64, 124.57; MS (ES$^+$) *m/z* 250.2 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 71.99; H, 4.38; N, 16.77%.

6-Phenyl-4-(pyrimidin-5-yl)pyridazin-3(2*H*)-one (104)



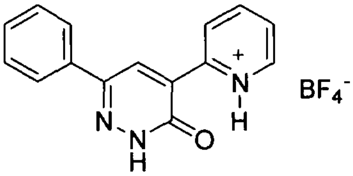
A mixture of **80** (100 mg, 0.38 mmol), HBr (5 mL, 48% aq. solution) and acetic acid glacial (1 mL) were stirred at 80 °C for 3.5 h (TLC monitored). After cooling to room temperature deionized water (15 mL) was added and the reaction neutralized using $NaHCO_{3(s)}$. The mixture was extracted with DCM (2 × 100 mL) and washed with deionized water (1 × 100 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness. After passing through a silica plug **104** was isolated as a cream colored solid (73 mg, 77%): mp 258.3-261.8 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 13.56 (1H, s), 9.39 (2H, s), 9.25 (1H, s), 8.46 (1H, s), 8.02 – 7.99 (2H, m), 7.52 – 7.48 (3H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.2, 158.3, 156.4, 144.5, 134.6, 133.2, 129.3, 128.8, 128.5, 127.8, 125.9; MS (EI) *m/z* 250.3 (M^+, 100%); HRMS (EI) calcd for $C_{14}H_{10}N_4O$ 250.0855, found 250.0855.

2-Benzyl-6-phenyl-4-(pyridin-2-yl)pyridazin-3(2*H*)-one (105)



A mixture of **103** (46 mg, 0.18 mmol), benzyl bromide (0.02 mL, 0.19 mmol), potassium carbonate (64 mg, 0.46 mmol) and tetrabutylammonium bromide (2.9 mg, 0.009 mmol) in acetonitrile (10 mL) was heated at reflux for 1 h. The solvent was then removed in vacuo before column chromatography on silica, eluent EtOAc to yield **105** as yellow needles after recrystallization from hexane (58 mg, 93%): mp 157.1-159.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 – 8.71 (3H, m), 7.95 (2H, d, $J = 6.8$ Hz), 7.81 (1H, t, $J = 8.8$ Hz), 7.55 (2H, d, $J = 6.8$ Hz), 7.51 – 7.42 (3H, m), 7.37 – 7.27 (4H, m), 5.54 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 151.2, 149.7, 145.0, 136.8, 136.7, 136.6, 135.3, 129.5, 129.01, 128.97, 128.7, 128.2, 128.0, 126.3, 125.5, 124.3, 56.5; MS (ES^+) *m/z* 340.2 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{22}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38. Found: C, 77.42; H, 4.98; N, 12.29%. Crystals for X-ray structure determination were grown from hexane.

Pyridinium salt (106)

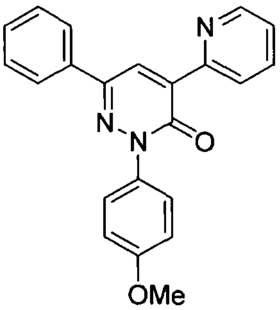


To a methanol solution of compound **103** (30 mg), HBF_4 solution in Et_2O (Fluka, 54%) was added slowly until precipitation was complete. The solids were redissolved by heating the mixture. Slow evaporation of the cooled solution gave orange crystals of **106** suitable for X-ray structural analysis.

Typical Procedure for the *N*-(Hetero)arylation of 103 in Table 3.1

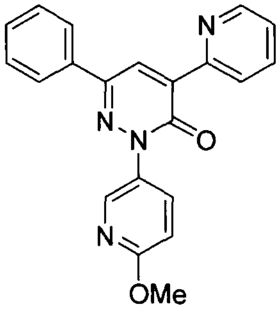
Compound **103** (1.05 equiv.), aryl halide (1.0 equiv.), CuI (ca. 5 mol%), 8-hydroxyquinoline (ca. 10 mol%), Cs_2CO_3 (1.5 equiv.) and poly(ethyleneglycol) methyl ether (average M_n 2000, 85 mg) were sequentially added to degassed 1,4-dioxane (4 mL). The reaction mixture was heated under argon at reflux for the time stated. The reaction mixture was cooled slightly and then paseed through a celite pad which was rinsed with EtOAc. The organic solvent was removed in vacuo. The mixture was purified by chromatography on a silica gel column followed if needed by recrystallization.

2-(4-Methoxyphenyl)-6-phenyl-4-(pyridin-2-yl)pyridazin-3(2*H*)-one (112)



Compound **103** (90 mg, 0.36 mmol), 4-bromoanisole **109** (0.03 mL, 0.24 mmol), 8-hydroxyquinoline copper (II) salt **107** (4.2 mg, 0.012 mmol), K_2CO_3 (50 mg, 0.36 mmol) and DMF (4 mL); reaction time 24 h; eluent acetone:hexane 1:4 v/v, gave **112** as a yellow solid (35 mg, 41%): mp 178.4-180.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (1H, s), 8.76 – 8.74 (2H, m), 7.97 (2H, d, *J* = 7.2 Hz), 7.81 (1H, td, *J* = 7.8 Hz, *J* = 1.8 Hz), 7.65 (2H, d, *J* = 8.9 Hz), 7.51 – 7.43 (3H, m), 7.38 – 7.34 (1H, m), 7.05 (2H, d, *J* = 8.9 Hz), 3.89 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 159.4, 151.1, 149.7, 145.3, 137.4, 136.7, 135.4, 135.1, 129.6, 129.0, 128.3, 127.2, 126.4, 125.5, 124.5, 114.1, 55.7; MS (ES$^+$) *m/z* 356.3 ([M+H]$^+$, 100%). HRMS (ES$^+$) calcd for $C_{22}H_{18}N_3O_2$ 356.1393, found 356.1394.

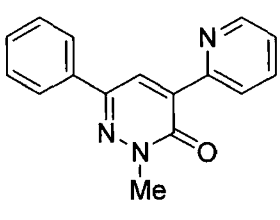
2-(6-Methoxypyridin-3-yl)-6-phenyl-4-(pyridin-2-yl)pyridazin-3(2H)-one (113)



Conditions C: Compound **103** (102 mg, 0.41 mmol), 5-bromo-2-methoxypyridine **110** (0.05 mL, 0.39 mmol), CuI (3.7 mg, 0.020 mmol), 8-hydroxyquinoline (5.7 mg, 0.040 mmol), Cs_2CO_3 (191 mg, 0.59 mmol), PEG (85 mg) and 1,4-dioxane (4 mL); reaction time 51 h; eluent EtOAc, gave **113** as a white solid (111 mg, 80%): mp 179.0-182.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (1H, s), 8.75 – 8.70 (2H, m), 8.56 (1H, d, *J* = 2.6 Hz), 7.98 (1H, dd, *J* = 8.8 Hz, *J* = 2.7 Hz), 7.95 (2H, dd, *J* = 5.2 Hz, *J* = 3.2 Hz), 7.80 (1H, td, *J* = 7.9 Hz, *J* = 1.8 Hz), 7.51 – 7.42 (3H, m), 7.35 (1H, ddd, *J* = 7.5 Hz, *J* = 4.7 Hz, *J* = 1.0 Hz), 6.87 (1H, d, *J* = 8.8 Hz), 4.01 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 159.5, 150.8, 149.7, 145.8, 144.2, 137.5, 136.7, 136.3, 134.8, 133.2, 129.8, 129.1, 128.6, 126.3, 125.4, 124.6, 110.5, 54.0; MS (ES$^+$) *m/z* 357.3 ([M+H]$^+$, 60%), 379.2 ([M+Na]$^+$, 100%). Anal. Calcd. for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.53; N, 15.72. Found: C, 70.42; H, 4.53; N, 15.42%.

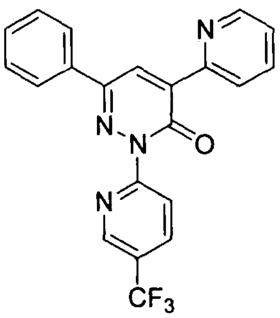
Conditions A: Compound **103** (100 mg, 0.40 mmol), 5-bromo-2-methoxypyridine **110** (0.05 mL, 0.38 mmol), 8-hydroxyquinoline copper (II) salt **107** (6.7 mg, 0.020 mmol), Cs_2CO_3 (186 mg, 0.57 mmol) and DMF (4 mL); 140 °C reaction time 48 h; eluent hexane + 5% acetone to hexane:acetone 1:1 v/v, gave **113** as a yellow solid (29 mg, 21%). Spectroscopically identical to the sample previously described. Compound **117** was obtained as the major product, as a cream coloured solid (54 mg, 54%).

2-Methyl-6-phenyl-4-(pyridin-2-yl)pyridazin-3(2H)-one (117)



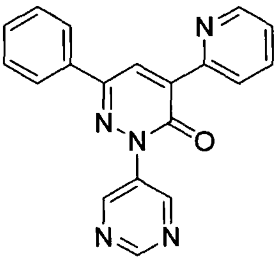
Isolated from the above reaction as a cream coloured solid (54 mg, 54%): mp 136.4-138.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (1H, dt, *J* = 8.0, 0.9 Hz), 8.73 (1H, s), 8.71 (1H, ddd, *J* = 4.7 Hz, *J* = 1.8 Hz, *J* = 0.9 Hz), 7.94 – 7.87 (2H, m), 7.83 – 7.77 (1H, m), 7.51 – 7.39 (3H, m), 7.33 (1H, ddd, *J* = 7.5 Hz, *J* = 4.7 Hz, *J* = 1.1 Hz), 3.99 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 151.1, 149.6, 144.9, 136.6, 136.1, 135.2, 129.4, 129.0, 128.2, 126.2, 125.4, 124.3, 41.4; MS (ES$^+$) *m/z* 264.2 ([M+H]$^+$, 100%), 286.1 ([M+Na]$^+$, 40%). Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.72; H, 5.09; N, 15.73%.

2-(5-(Trifluoromethyl)pyridin-2-yl)-6-phenyl-4-(pyridin-2-yl)pyridazin-3(2H)-one (114)



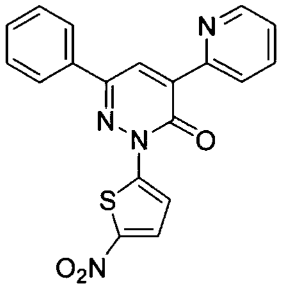
Compound **103** (102 mg, 0.41 mmol), 2-bromo-5-(trifluoromethyl)pyridine **111** (88 mg, 0.39 mmol), CuI (3.7 mg, 0.020 mmol), 8-hydroxyquinoline (5.7 mg, 0.040 mmol), Cs_2CO_3 (191 mg, 0.59 mmol), PEG (85 mg) and 1,4-dioxane (4 mL); reaction time 41.5 h; eluent petroleum ether (bp 40–60 °C):EtOAc 1:3 v/v, followed by recrystallzation from toluene/hexane gave **114** as white needles (125 mg, 81%): mp 206.7-208.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (dd, 1H, *J* = 1.5 Hz, *J* = 0.7 Hz), 8.88 (1H, s), 8.76 – 8.73 (1H, m), 8.72 (1H, d, *J* = 8.0 Hz), 8.17 (1H, dd, *J* = 8.3 Hz, *J* = 2.1 Hz), 7.97 – 7.93 (2H, m), 7.89 (1H, d, *J* = 8.4 Hz), 7.81 (1H, td, *J* = 7.8 Hz, *J* = 1.9 Hz), 7.51 – 7.44 (3H, m), 7.37 (1H, ddd, *J* = 7.6 Hz, *J* = 4.7 Hz, *J* = 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 156.8 (1C, q, *J* = 1 Hz), 150.4, 149.8, 146.7 (1C, q, *J* = 4 Hz), 146.5, 138.1, 136.8, 135.7 (1C, q, *J* = 4 Hz), 134.7, 130.0, 129.4, 129.1, 126.8 (1C, q, *J* = 33 Hz), 126.6, 125.5, 124.8, 123.2 (1C, q, *J* = 271 Hz), 121.7; MS (ES$^+$) *m/z* 394.9 (M$^+$, 100%), 395.9 ([M+H]$^+$, 20%), 416.9 ([M+Na]$^+$, 30%). Anal. Calcd. for $C_{21}H_{13}F_3N_4O$: C, 63.96; H, 3.32; N, 14.21. Found: C, 63.75; H, 3.35; N, 14.30%.

6-Phenyl-4-(pyridin-2-yl)-2-(pyrimidin-5-yl)pyridazin-3(2*H*)-one (115)



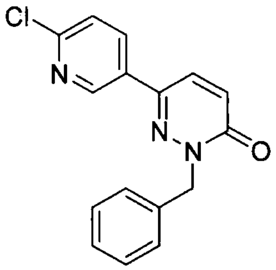
Compound **103** (102 mg, 0.41 mmol), 5-bromopyrimidine **62** (62 mg, 0.39 mmol), CuI (3.7 mg, 0.020 mmol), 8-hydroxyquinoline (5.7 mg, 0.040 mmol), Cs_2CO_3 (191 mg, 0.59 mmol), PEG (85 mg) and 1,4-dioxane (4 mL); reaction time 41.5 h; eluent petroleum ether (bp 40–60 °C):EtOAc 1:3 v/v, followed by recrystallzation from hexane/toluene gave **115** as a white solid (45 mg, 35%): mp 259.4-261.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (2H, s), 9.24 (1H, s), 8.86 (1H, s), 8.76 (1H, d, *J* = 4.6 Hz), 8.68 (1H, d, *J* = 8.0 Hz), 7.98 – 7.95 (2H, m), 7.84 (1H, td, *J* = 7.8 Hz, *J* = 1.8 Hz), 7.54 – 7.50 (3H, m), 7.40 (1H, ddd, *J* = 7.5 Hz, *J* = 4.7 Hz, *J* = 0.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 157.2, 153.2, 150.3, 149.9, 147.0, 138.1, 137.4, 136.9, 134.3, 130.3, 129.2, 126.4, 125.5, 124.9; MS (ES$^+$) *m/z* 328.2 ([M+H]$^+$, 100%). HRMS (ES$^+$) calcd for $C_{19}H_{14}N_5O$ 328.1193, found 328.1194. Anal. Calcd. for $C_{19}H_{13}N_5O$: C, 69.71; H, 4.00; N, 21.39. Found: C, 68.83; H, 4.15; N, 20.67%.

2-(5-Nitrothiophen-2-yl)-6-phenyl-4-(pyridin-2-yl)pyridazin-3(2*H*)-one (116)



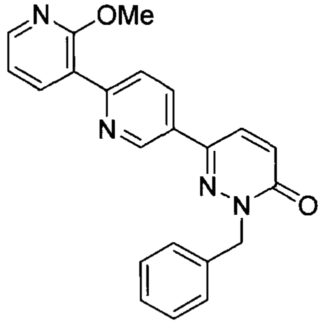
Compound **103** (102 mg, 0.41 mmol), 2-bromo-5-nitrothiophene **65** (81 mg, 0.39 mmol), CuI (3.7 mg, 0.020 mmol), 8-hydroxyquinoline (5.7 mg, 0.040 mmol), Cs_2CO_3 (191 mg, 0.59 mmol), PEG (85 mg) and 1,4-dioxane (4 mL); reaction time 42 h; eluent DCM:Et_2O 1:1 v/v, followed by recrystallzation from chloroform/hexane gave **116** as an orange crystalline solid (98 mg, 67%): mp 248.2-250.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (1H, s), 8.78 – 8.75 (1H, m), 8.73 (1H, d, *J* = 8.1 Hz), 8.06 – 8.00 (2H, m), 7.96 (1H, d, *J* = 4.8 Hz), 7.91 – 7.83 (2H, m), 7.59 – 7.52 (3H, m), 7.42 (1H, ddd, *J* = 7.5 Hz, *J* = 4.7 Hz, *J* = 1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 150.0, 149.7, 147.8, 147.2, 146.6, 137.6, 137.0, 134.0, 130.7, 129.3, 128.3, 127.2, 126.8, 125.7, 125.2, 116.7; MS (ES$^+$) *m/z* 377.2 ([M+H]$^+$, 60%), 774.7 ([Dimer+Na]$^+$, 100%). HRMS (ES$^+$) calcd for $C_{19}H_{13}N_4O_3S$ 377.0703, found 377.0702. Anal. Calcd. for $C_{19}H_{12}N_4O_3S$: C, 60.63; H, 3.21; N, 14.89. Found: C, 60.14; H, 3.21; N, 14.85%.

2-Benzyl-6-(6-chloropyridin-3-yl)pyridazin-3(2*H*)-one (118)



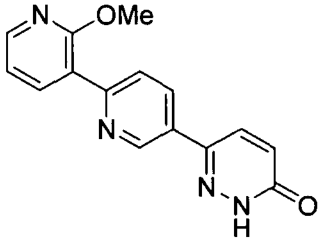
A mixture of **99** (70 mg, 0.34 mmol), benzyl bromide (0.04 mL, 0.35 mmol), potassium carbonate (116 mg, 0.84 mmol) and tetrabutylammonium bromide (6.0 mg, 0.02 mmol) in acetonitrile (10 mL) was heated at reflux for 1 h. The solvent was then removed in vacuo before column chromatography on silica, eluent EtOAc to yield **118** as a cream coloured solid (76 mg, 75%): mp 156.3-157.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (1H, d, *J* = 2.5 Hz), 8.07 (1H, dd, *J* = 8.4 Hz, *J* = 2.6 Hz), 7.63 (1H, d, *J* = 9.7 Hz), 7.50 – 7.47 (2H, m), 7.43 (1H, d, *J* = 8.4 Hz), 7.38 – 7.28 (3H, m), 7.07 (1H, d, *J* = 9.7 Hz), 5.41 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 152.5, 147.1, 140.9, 136.0, 136.0, 131.1, 129.7, 129.3, 129.1, 128.8, 128.3, 124.6, 55.8; MS (ES$^+$) *m/z* 320.0 ([M+Na]$^+$, 100%), 298.0 ([M+H]$^+$, 40%). Anal. Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.06; N, 14.11. Found: C, 64.34; H, 4.13; N, 14.04%.

2-Benzyl-6-(6-(2-methoxypyridin-3-yl)pyridin-3-yl)pyridazin-3(2*H*)-one (119)



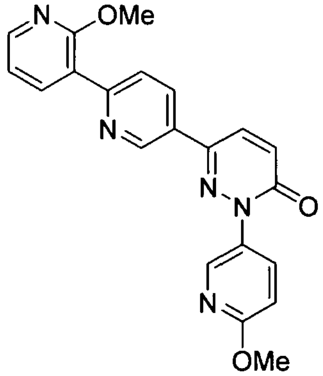
Compound **118** (68 mg, 0.23 mmol), 2-methoxy-3-pyridylboronic acid (38 mg, 0.25 mmol), $Pd(PPh_3)_4$ (13 mg, 0.012 mmol) were charged to flask, purged with argon, 10 mL degassed 1,4-dioxane was added. Degassed Na_2CO_3 (1 mL, 1 M) was added and the reaction mixture heated at reflux for 3 h. The solvent was then removed in vacuo, 50 mL EtOAc and 50 mL brine added, before separating the organic phase. The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness and purified before column chromatography on silica, eluent EtOAc. Recrystallization from hexane/toluene gave **119** as a white solid (63 mg, 74%): mp 129.7-130.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (1H, t, *J* = 1.6 Hz), 8.32 (1H, dd, *J* = 7.5 Hz, *J* = 2.0 Hz), 8.25 (1H, dd, *J* = 4.9 Hz, *J* = 2.0 Hz), 8.13 (2H, d, *J* = 1.6 Hz), 7.70 (1H, d, *J* = 9.7 Hz), 7.53 – 7.50 (2H, m), 7.38 – 7.28 (3H, m), 7.09 – 7.05 (2H, m), 5.43 (2H, s), 4.06 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 159.6, 154.9, 147.6, 147.0, 142.0, 139.6, 136.2, 133.3, 130.9, 129.6, 129.1, 128.9, 128.8, 128.2, 124.6, 122.3, 117.6, 55.8, 53.8; MS (ES$^+$) *m/z* 371.2 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{22}H_{18}N_4O_2$: C, 71.34; H, 4.90; N, 15.13. Found: C, 71.16; H, 4.86; N, 14.89%.

6-(6-(2-Methoxypyridin-3-yl)pyridin-3-yl)pyridazin-3(2*H*)-one (120)



Compound **99** (75 mg, 0.36 mmol), 2-methoxy-3-pyridylboronic acid (61 mg, 0.40 mmol), $Pd(PPh_3)_2Cl_2$ (13 mg, 0.018 mmol) were charged to flask, purged with argon, 6 mL degassed 1,4-dioxane was added. Degassed Na_2CO_3 (1 mL, 1 M) was added and the reaction mixture heated at reflux for 21 h. The solvent was then removed in vacuo, 50 mL EtOAc and 50 mL brine added, before separating the organic phase. The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness and purified before column chromatography on silica, eluent EtOAc to yield **120** as a yellow solid following recrystallization from toluene (45 mg, 44%): mp 256.6 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.36 (1H, s), 9.16 (1H, d, *J* = 1.7 Hz), 8.35 – 8.25 (3H, m), 8.13 (2H, t, *J* = 9.1 Hz), 7.18 (1H, dd, *J* = 7.4 Hz, *J* = 4.9 Hz), 7.06 (1H, d, *J* = 9.9 Hz), 3.99 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5, 160.1, 153.3, 147.4, 146.6, 141.6, 139.2, 133.3, 131.3, 130.3, 128.9, 124.0, 121.5, 117.6, 53.5; MS (ES$^+$) *m/z* 281.3 ([M+H]$^+$, 100%), 303.3 ([M+Na], 65%). HRMS (ES$^+$) calcd for $C_{15}H_{13}O_2N_4$ 281.1033, found 281.1033.

2-(6-Methoxypyridin-3-yl)-6-(6-(2-methoxypyridin-3-yl)pyridin-3-yl)pyridazin-3(2*H*)-one (121)

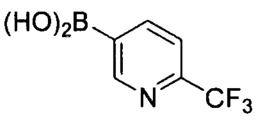


Compound **120** (45 mg, 0.16 mmol), 5-bromo-2-methoxypyridine **110** (0.02 mL, 0.15 mmol), CuI (1.4 mg, 0.0075 mmol), 8-hydroxyquinoline (2.2 mg, 0.015 mmol), Cs_2CO_3 (75 mg, 0.23 mmol), PEG (50 mg) and 1,4-dioxane (5 mL) were charged to a reaction flask and heated at reflux for 45 h. The reaction mixture was then cooled slightly before being passed through a silica/celite pad, rinsing the EtOAc. The organic solvent was evaporated in vacuo and the crude product purified by silica column chromatography, eluent EtOAc to yield **121** as a yellow solid (15 mg, 26%): mp 162.7 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (1H, s), 8.54 (1H, s), 8.32 (1H, d, *J* = 6.9 Hz), 8.24 (1H, d, *J* = 4.3 Hz), 8.17 (2H, m), 7.95 (1H, dd, *J* = 8.9 Hz, *J* = 2.7 Hz), 7.80 (1H, d, *J* = 9.7 Hz), 7.18 (1H, d, *J* = 9.7 Hz), 7.06 (1H, dd, *J* = 7.2 Hz, *J* = 4.9 Hz), 6.86 (1H, d, *J* = 8.9 Hz), 4.05 (3H, s), 3.99 (3H, s; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 161.3, 159.4, 155.3, 147.7, 143.7, 142.9, 139.6, 135.7, 133.5, 132.5, 131.8, 129.9, 117.6, 110.7, 54.1, 53.8. (Due to line-broadening not all of the carbon signals could be identified); HRMS (ES$^+$) calcd for $C_{21}H_{17}N_5O_3$ 388.1404, found 388.1405. Elemental analysis was incorrect, unfortunately there was insufficient sample remaining for recrystallization to improve purity.

For ^{1}H COSY, HSQC and HMBC spectra which aided confirmation of the structure see Appendix A2.

5.4 Experimental details for Chapter 4

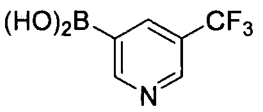
6-(Trifluoromethyl)-3-pyridylboronic acid (136)



n-Butyllithium (2.5 M in hexane, 19.5 mL, 49 mmol) was added to a mixture of 5-bromo-2-(trifluoromethyl)pyridine **134** (10.0 g, 44 mmol) and triisopropylborate (12.3 mL, 53 mmol) in anhydrous THF (80 mL) at –78 °C under argon. The reaction was stirred at –78 °C for 3 h before warming gradually to –10 °C when the reaction was quenched with deionised water (100 mL). The organic solvent was removed in vacuo. The resulting aqueous phase was treated with solid NaOH to obtain pH 10, then washed with Et_2O (50 mL) and acidified to pH 5 using acetic acid. The solution was extracted with EtOAc (200 mL) and evaporated to dryness in vacuo to yield **136** as a white solid (8.04 g, 95%): mp 255 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6, DCl) δ 8.98 (1H, s), 8.35 (1H, d, *J* = 7.8 Hz), 7.82 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (125 MHz, DMSO-d_6, DCl) δ 155.3, 144.6, 120.5 (1C, q, *J* = 3 Hz); ^{11}B NMR (128 MHz, DMSO-d_6, DCl) δ 29.2; ^{19}F NMR (188 MHz, DMSO-d_6, DCl) δ -66.2.

Crystals of **136** suitable for X-ray structure determination were grown on slow recrystallization from EtOAc.

5-(Trifluoromethyl)-3-pyridylboronic acid (137)



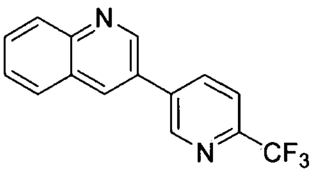
n-Butyllithium (2.5 M in hexane, 19.5 mL, 49 mmol) was added to a mixture of 3-bromo-5-(trifluoromethyl)pyridine **135** (10.0 g, 44 mmol) and triisopropylborate (12.3 mL, 53 mmol) in anhydrous THF (80 mL) at –78 °C under argon. The reaction was stirred at –78 °C for 3.5 h before warming gradually to –10 °C when the reaction was quenched with deionised water (80 mL). The organic solvent was removed in vacuo. The resulting aqueous phase was treated with $NaOH_{(s)}$ to obtain pH 10, then washed with Et_2O (1 × 80 mL) and acidified to pH 5 using acetic acid. The solution was extracted with EtOAc (1 × 250 mL) and evaporated to dryness in vacuo to yield **137** as an off-white solid (7.91 g, 94%): mp 300.8 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6, DCl) δ 9.43 (1H, s), 9.23 (1H, s), 9.11 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6, DCl) δ 151.6, 145.7 (1C, q, *J* = 3 Hz), 142.2 (1C, q, *J* = 4 Hz), 126.9 (1C, q, *J* = 35 Hz), 122.7 (1C, q, *J* = 273 Hz);

^{11}B NMR (128 MHz, DMSO-d$_6$, DCl) δ 27.8; ^{19}F NMR (188 MHz, DMSO-d$_6$, DCl) δ -61.0.

Typical Procedure for the Suzuki-Miyaura Cross-Coupling Reactions in Table 4.1

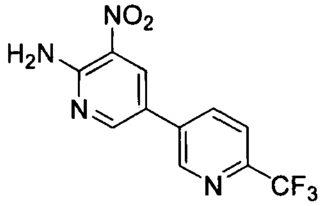
The boronic acid **136** or **137** (1.0-2.1 equiv.) the aryl halide (1.0 equiv.) and Pd(PPh$_3$)$_2$Cl$_2$ (ca. 5 mol% Ar-X), (for conditions b; *t*-Bu$_3$P (ca. 5 mol% Ar-X)) were sequentially added to degassed 1,4-dioxane (7 mL) and the mixture was stirred at 20 °C for 30 min. Degassed aqueous Na$_2$CO$_3$ solution (1 M, 2 equiv.) was added and the reaction mixture was heated under argon at reflux for the time stated. The mixture was transferred to a separating funnel, EtOAc 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 followed on some occasions by recrystallization or Kügelrohr distillation.

3-[6-(Trifluoromethyl)pyridin-3-yl]quinoline (143)



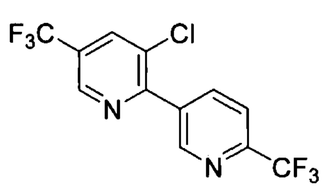
Compound **136** (216 mg, 1.13 mmol), 3-bromoquinoline **66** (0.14 mL, 1.0 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 mL) and Na$_2$CO$_3$ (1 M, 3 mL); reaction time 22 h reflux; eluent petroleum ether (bp 40–60 °C): EtOAc 1:1 v/v and subsequent recrystallization from cyclohexane gave **143** as a white crystalline solid (259 mg, 94%): mp 173.0-174.7 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.16 (1H, d, J = 2.5 Hz), 9.07 (1H, d, J = 2.0 Hz), 8.37 (1H, d, J = 2.1 Hz), 8.18 – 8.16 (2H, m), 7.93 (1H, d, J = 8.0 Hz), 7.85 (1H, d, J = 8.0 Hz), 7.84 – 7.80 (1H, m), 7.66 – 7.64 (1H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ 149.0, 148.7, 148.1, 147.7 (1C, q, J = 35 Hz), 136.6, 136.0, 134.4, 130.7, 129.6, 129.3, 128.3, 127.8, 127.7, 121.6 (1C, q, J =274 Hz), 120.9 (1C, q, J = 3 Hz); ^{19}F NMR (188 MHz, CDCl$_3$) δ -68.3; MS (ES$^+$) *m/z* 275.0 ([M+H]$^+$, 100%). Anal. Calcd. for C$_{15}$H$_9$F$_3$N$_2$: C, 65.69; H, 3.31; N, 10.21. Found: C, 65.62; H, 3.31; N, 10.18%.

5-[6-(Trifluoromethyl)pyridin-3-yl]-2-amino-3-nitropyridine (144)



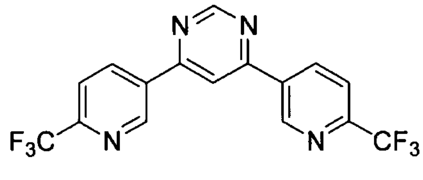
Compound **136** (216 mg, 1.13 mmol), 2-amino-5-bromo-3-nitro-pyridine **61** (218 mg, 1.0 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 mL) and Na$_2$CO$_3$ (1 M, 3 mL); reaction time 17 h reflux; eluent EtOAc and subsequent recrystallization from toluene gave **144** as a yellow solid (214 mg, 75%): mp 124.2-126.5 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.24 (1H, d, *J* = 1.7 Hz), 9.00 (1H, d, *J* = 2.3 Hz), 8.89 (1H, d, *J* = 2.2 Hz), 8.53 (1H, dd, *J* = 8.2 Hz, *J* = 2.2 Hz), 8.29 (2H, br s, NH_2), 8.06 (1H, d, *J* = 8.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.8, 153.5, 147.6, 144.9 (1C, q, *J* = 34 Hz), 135.3, 134.8, 133.1, 126.8, 121.8 (1C, q, *J* = 273 Hz), 120.8 (1C, q, *J* = 3 Hz), 120.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ -68.3; MS (EI) *m/z* 284.0 (M^+, 100%). Anal. Calcd. for $C_{11}H_7F_3N_4O_2$: C, 46.49; H, 2.48; N, 19.71. Found: C, 46.57; H, 2.47; N, 19.73%.

3-Chloro-5-(trifluoromethyl)-2-[6-(trifluoromethyl)pyridin-3-yl]pyridine (145)



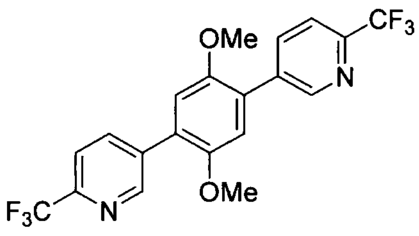
Compound **136** (383 mg, 2.0 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine **138** (0.14 mL, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 mL) and Na_2CO_3 (1 M, 3 mL); reaction time 4 h reflux; eluent DCM:Et_2O 95:5 v/v, gave a yellow oil which after Kügelrohr distillation, gave **145** as a white crystalline solid (298 mg, 92%): mp 90.9-93.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (1H, d, *J* = 1.4 Hz), 8.90 (1H, s), 8.31 (1H, dd, *J* = 8.1 Hz, *J* = 2.0 Hz), 8.11 (1H, d, *J* = 1.8 Hz), 7.83 (1H, d, *J* = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 150.6, 148.7 (1C, q, *J* = 35 Hz), 145.0 (1C, q, *J* = 4 Hz), 138.5, 135.8 (1C, q, *J* = 4 Hz), 135.6, 130.9, 127.6 (1C, q, *J* = 34 Hz), 122.5 (1C, q, *J* = 272 Hz), 121.5 (1C, q, *J* = 273 Hz), 120.0 (1C, q, *J* = 3 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.9, -68.5; MS (ES^+) *m/z* 327.1 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{12}H_5ClF_6N_2$: C, 44.13; H, 1.54; N, 8.58. Found: C, 44.26; H, 1.49; N, 8.71%.

4,6-Bis[6-(trifluoromethyl)pyridin-3-yl]pyrimidine (146)



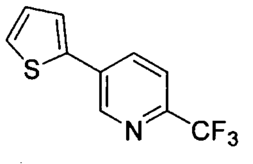
Compound **136** (601 mg, 3.2 mmol), 4,6-dichloropyrimidine **139** (224 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (53.0 mg, 0.075 mmol), *t*-Bu_3P (0.02 mL, 0.075 mmol), 1,4-dioxane (7 mL) and Na_2CO_3 (1 M, 6 mL); reaction time 21 h reflux; eluent hexane:EtOAc 1:1 v/v, and subsequent recrystallization from cyclohexane gave a crystalline yellow solid **146** (456 mg, 81%): mp 156.9-158.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (1H, d, *J* = 1.3 Hz), 9.45 (2H, d, *J* = 1.9 Hz), 8.68 (2H, dd, *J* = 8.3 Hz, *J* = 1.5 Hz), 8.23 (1H, d, *J* = 1.3 Hz), 7.89 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 160.1, 150.4 (1C, q, *J* = 35 Hz), 148.8, 136.5, 134.9, 121.4 (1C, q, *J* = 274 Hz), 120.9, 113.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.5; MS (ES$^+$) *m/z* 371.2 ([M+H]$^+$, 35%). Anal. Calcd. for $C_{16}H_8F_6N_4$: C, 51.90; H, 2.18; N, 15.13. Found: C, 51.86; H, 2.16; N, 15.18%.

2-(Trifluoromethyl)-5-{4-[6-(trifluoromethyl)pyridin-3-yl]-2,5-dimethoxyphenyl}pyridine (147)



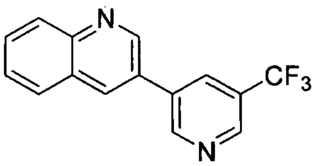
Compound **136** (400 mg, 2.1 mmol), 1,4-dibromo-2,5-dimethoxybenzene **140** (296 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.05 mmol), 1,4-dioxane (7 mL) and Na_2CO_3 (1 M, 3 mL); reaction time 1 h reflux; recrystallization from toluene gave a white crystalline solid **147** (331 mg, 77%): mp 224.7-226.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (2H, s), 8.09 (2H, dd, *J* = 8.1 Hz, *J* = 1.8 Hz), 7.76 (2H, d, *J* = 8.1 Hz), 7.01 (2H, s), 3.84 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 150.5, 146.9 (2C, q, *J* = 35 Hz), 138.1, 136.7, 127.1, 121.8 (2C, q, *J* = 274 Hz), 120.0 (2C, q, *J* = 3 Hz), 114.4, 56.5; ^{19}F NMR (188 MHz, $CDCl_3$) δ -68.3; MS (ES$^+$) *m/z* 429.2 ([M+H]$^+$, 100%), Anal. Calcd. for $C_{20}H_{14}F_6N_2O_2$: C, 56.08; H, 3.29; N, 6.54. Found: C, 56.21; H, 3.28; N, 6.56%.

2-(Trifluoromethyl)-5-(thiophen-2-yl)pyridine (148)



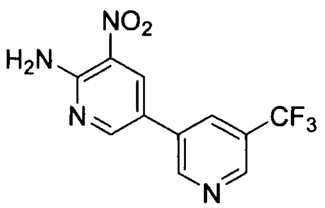
Compound **136** (216 mg, 1.13 mmol), 2-bromothiophene **141** (0.1 mL, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.05 mmol), 1,4-dioxane (7 mL) and Na_2CO_3 (1 M, 3 mL); reaction time 3 h reflux; eluent Et_2O:DCM 1:9 v/v, gave a beige crystalline solid **148** (221 mg, 93%): mp 65.2-66.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (1H, d, *J* = 2.0 Hz), 8.02 (1H, dd, *J* = 8.1 Hz, *J* = 2.3 Hz), 7.69 (1H, d, *J* = 8.1 Hz), 7.46 – 7.44 (2H, m), 7.18 – 7.16 (1H, m); ^{13}C NMR (175 MHz, $CDCl_3$) δ 147.1, 146.6 (1C, q, *J* = 35 Hz), 138.8, 133.9, 133.3, 128.8, 127.6, 125.8, 121.7 (1C, q, *J* = 273 Hz), 120.7 (1C, q, *J* = 3 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -68.2; MS (ES$^+$) *m/z* 230.4 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{10}H_6F_3NS$: C, 52.40; H, 2.64; N, 6.11. Found: C, 52.66; H, 2.65; N, 6.09%.

3-[5-(Trifluoromethyl)pyridin-3-yl]quinoline (149)



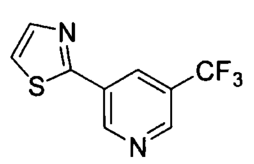
Compound **137** (216 mg, 1.13 mmol), 3-bromoquinoline **66** (0.14 mL, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 mL) and Na_2CO_3 (1 M, 3 mL); reaction time 22 h reflux; eluent EtOAc and subsequent recrystallization from cyclohexane gave **149** as a white crystalline solid (268 mg, 98%): mp 164.9-166.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.170 (1H, s), 9.166 (1H, s), 8.97 (1H, s), 8.38 (1H, d, *J* = 2.1 Hz), 8.24 (1H, s), 8.19 (1H, d, *J* = 8.5 Hz), 7.94 (1H, d, *J* = 8.1Hz), 7.83 – 7.78 (1H, m), 7.65 (1H, t, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 148.9, 148.1, 146.1 (1C, q, *J* = 4 Hz), 134.4, 134.0, 131.7 (1C, q, *J* = 4 Hz), 130.7, 129.6, 129.2, 128.3, 127.84, 127.76 (1C, q, *J* = 33 Hz), 127.2 (1C, q, *J* = 33 Hz), 123.5 (1C, q, *J* = 271 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.9; MS (ES$^+$) *m/z* 275.0 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{15}H_9F_3N_2$: C, 65.69; H, 3.31; N, 10.21. Found: C, 65.57; H, 3.28; N, 10.16%.

5-[5-(Trifluoromethyl)pyridin-3-yl]-2-amino-3-nitropyridine (150)



Compound **137** (216 mg, 1.13 mmol), 2-amino-5-bromo-3-nitro-pyridine **61** (218 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 mL) and Na_2CO_3 (1 M, 3 mL); reaction time 17 h reflux; eluent EtOAc gave **150** as a yellow solid (220 mg, 78%): mp 247.2-250.0 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (1H, d, *J* = 2.0 Hz), 8.94 (1H, s), 8.93 (1H, d, *J* = 2.2 Hz), 8.85 (1H, d, *J* = 2.2 Hz), 8.6 (1H, s), 8.18 (2H, br s, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.8, 153.5, 151.0, 144.7 (1C, q, *J* = 4 Hz), 133.2, 131.8, 130.8 (1C, q, *J* = 3 Hz), 126.8, 125.4 (1C, q, *J* = 32 Hz), 123.7 (1C, q, *J* = 271 Hz), 120.0; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 284.0 (M$^+$, 100%). Anal. Calcd. for $C_{11}H_7F_3N_4O_2$: C, 46.49; H, 2.48; N, 19.71. Found: C, 46.43; H, 2.49; N, 19.50%.

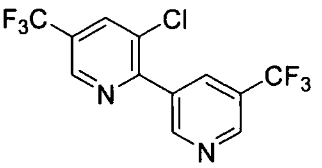
3-(Trifluoromethyl)-5-(thiazol-2-yl)pyridine (151)



Compound **137** (324 mg, 1.7 mmol), 2-bromothiazole **142** (0.14 mL, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (52.0 mg, 0.075 mmol), 1,4-dioxane (7 mL) and Na_2CO_3 (1 M, 3 mL); reaction time 20.5 h reflux; eluent Et_2O:DCM 1:9 v/v, gave a white crystalline solid **151** (175 mg, 51%): mp 69.2-71.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (1H, d, *J* = 2.0 Hz), 8.90 (1H, d, *J* = 1.3 Hz), 8.50 – 8.49 (1H, m), 7.96 (1H, d, *J* = 3.3 Hz), 7.48 (1H, d, *J* = 3.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 150.7 (1C, q, *J* = 2 Hz), 147.3 (1C, q, *J* = 4 Hz), 144.6, 130.7 (1C, q, *J* = 3 Hz), 129.7, 127.2 (1C, q, *J* = 34 Hz), 123.3 (1C, q, *J* = 273 Hz), 120.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ -63.0; MS (ES$^+$) *m/z* 231.4 ([M+H]$^+$, 100%).

Anal. Calcd. for $C_9H_5F_3N_2S$: C, 46.96; H, 2.19; N, 12.17. Found: C, 47.16; H, 2.25; N, 12.08%.

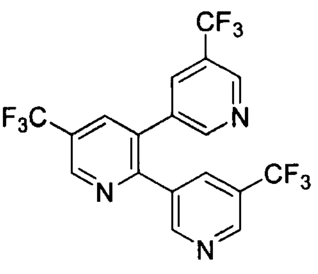
3-Chloro-5-(trifluoromethyl)-2-[5-(trifluoromethyl)pyridin-3-yl]pyridine (152)



Compound **137** (192 mg, 1.0 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine **138** (0.14 mL, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 mL) and Na_2CO_3 (1 M, 3 mL); reaction time 3 h reflux; eluent gradient DCM:EtOAc, 1:0 to 0:1 v/v, gave a yellow oil which with subsequent distillation of the crude fraction, using Kügelrohr apparatus, gave **152** as a white crystalline solid (244 mg, 75%): mp 47.5-48.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (1H, d, $J = 2.0$ Hz), 9.00 (1H, d, J 1.3 Hz), 8.91 (1H, s), 8.39 – 8.38 (1H, m), 8.12 (1H, d, $J = 2.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 153.4, 147.4 (1C, q, $J = 4$ Hz), 145.0 (1C, q, $J = 4$ Hz), 135.9 (1C, q, $J = 3$ Hz), 134.2 (1C, q, $J = 4$ Hz), 132.9, 130.9, 127.6 (1C, q, $J = 33$ Hz), 126.6 (1C, q, $J = 33$ Hz), 124.0 (1C, q, $J = 271$ Hz), 121.9 (1C, q, $J = 271$ Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8, -62.9; MS (ES$^+$) *m/z* 327.1 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{12}H_5ClF_6N_2$: C, 44.13; H, 1.54; N, 8.58. Found: C, 44.06; H, 1.51; N, 8.62%.

Compound **137** (383 mg, 2.0 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine **138** (0.14 mL, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 mL) and Na_2CO_3 (1 M, 3 mL); reaction time 28.5 h reflux; eluent hexane:EtOAc, 1:1 v/v, gave a yellow oil which with subsequent distillation using Kügelrohr apparatus, gave **152** as a white crystalline solid (270 mg, 83%) spectroscopically identical with the sample previously prepared. A minor product was also isolated after column chromatography and distilled using a Kügelrohr apparatus to give a colourless oil which was identified as **153** from ^{1}H NMR, COSY and ^{19}F NMR spectra.

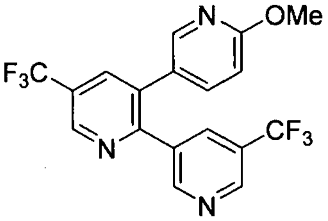
5-(Trifluoromethyl)-2,3-bis[5-(trifluoromethyl)pyridin-3-yl]pyridine (153)



Compound **137** (401 mg, 2.1 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine **138** (0.14 mL, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), *t*-Bu_3P (0.02 mL, 0.050 mmol), 1,4-dioxane (7 mL) and Na_2CO_3 (1 M, 3 mL); TLC monitored, after 28 h reflux a second amount of $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol) was added, and left at reflux for a further 27 h; total reaction time 55 h reflux; eluent gradient hexane:EtOAc, 1:1 v/v, recrystallization from petroleum ether (bp 40–60 °C) gave **153** a white crystalline solid (255 mg, 58%): mp 73.7-75.8 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.11 (1H, s), 8.92 (1H, s), 8.86 (1H, s), 8.66 (1H, d, *J* = 1.7 Hz), 8.64 (1H, d, *J* = 1.8 Hz), 8.08 (1H, d, *J* = 1.9 Hz), 8.04 (1H, s), 7.81 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 153.6, 153.0, 147.2 (1C, q, *J* = 4 Hz), 147.0 (1C, q, *J* = 4 Hz), 146.8 (1C, q, *J* = 4 Hz), 136.2 (1C, q, *J* = 3 Hz), 134.7 (1C, q, *J* = 3 Hz), 133.7 (1C, q, *J* = 4 Hz), 133.7, 133.4, 131.8, 127.2 (1C, q, *J* = 34 Hz), 127.0 (1C, q, *J* = 34 Hz), 126.8 (1C, q, *J* = 34 Hz), 123.1 (2C, q, *J* = 273 Hz), 122.9 (1C, q, *J* = 273 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.7, -63.1, -63.2; MS (ES^+) *m/z* 437.9 (M^+, 100%). Anal. Calcd. for $C_{18}H_8F_9N_3$: C, 49.44; H, 1.84; N, 9.61. Found: C, 49.56; H, 1.82; N, 9.56%.

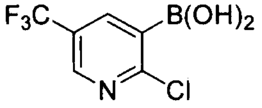
A second product was identified as **152** (117 mg, 36%) spectroscopically identical to the sample previously prepared.

5-(Trifluoromethyl)-2-[5-(trifluoromethyl)pyridin-3-yl]-3-(6-methoxypyridin-3-yl)pyridine (155)

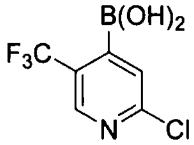


2-Methoxy-5-pyridylboronic acid **154** (53 mg, 0.35 mmol), **152** (100 mg, 0.31 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 0.016 mmol), *t*-Bu_3P (0.004 mL, 0.016 mmol), 1,4-dioxane (5 mL) and Na_2CO_3 (1 M, 1 mL); reaction time 2.5 h reflux; eluent hexane:EtOAc, 1:1 v/v, and subsequent Kügelrohr distillation gave **155** a colourless oil (93 mg, 75%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.98 (1H, d, *J* = 1.3 Hz), 8.81 (1H, d, *J* = 1.0 Hz), 8.70 (1H, d, *J* = 1.8 Hz), 8.10 (1H, s), 8.02 (1H, d, *J* = 2.5 Hz), 7.98 (1H, d, *J* = 2.0 Hz), 7.34 (1H, dd, *J* = 8.7 Hz, *J* = 2.5 Hz), 6.73 (1H, d, *J* = 8.6 Hz), 3.92 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 156.0, 153.7, 147.3, 146.4, (1C, q, *J* = 4 Hz), 146.0 (1C, q, *J* = 4 Hz), 139.2, 136.0 (1C, q, *J* = 4 Hz), 134.6, 134.5 (1C, q, *J* = 4 Hz), 133.6, 126.8 (1C, q, *J* = 3 Hz), 126.5 (1C, q, *J* = 4 Hz), 126.1, 123.3 (1C, q, *J* = 273 Hz), 121.9 (1C, q, *J* = 273 Hz), 111.6, 53.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7, -63.1; MS (ES^+) *m/z* 400.2 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{18}H_{11}F_6N_3O$: C, 54.14; H, 2.78; N, 10.52. Found: C, 53.90; H, 2.92; N, 10.41%.

2-Chloro-5-(trifluoromethyl)-3-pyridylboronic acid (157) and 2-chloro-5-(trifluoromethyl)-4-pyridylboronic acid (158)



157



158

A solution consisting of diisopropylamine (2.1 mL, 15 mmol), and anhydrous THF (15 mL) was cooled to −10 °C and *n*-butyllithium (2.5 M in hexanes, 6.0 mL, 15 mmol) was added dropwise, and then stirred at 0 °C for 30 min. The lithium diisopropylamine solution was cooled to −78 °C and a solution of 2-chloro-5-(trifluoromethyl)pyridine **156** (1.82 g, 10 mmol) in anhydrous THF (10 mL) was added dropwise over 15 min. The reaction mixture was stirred for a further 2 h at −78 °C, before adding triisopropylborate (3.5 mL, 15 mmol) dropwise. After stirring at −78 °C for 0.5 h the reaction mixture was warmed to −10 °C and quenched with deionised water (20 mL). Et_2O (20 mL) was added and the aqueous phase separated and taken to pH 10 with $NaOH_{(s)}$. The aqueous phase was then acidified with glacial acetic acid, at pH 6 the solution turned opaque, the aqueous solution was further acidified to pH 5 then extracted with EtOAc (100 mL). In attempts to decolourize, the organic phase was treated with carbon and filtered through a celite pad. The organic solvent was removed in vacuo resulting in an orange solid. The crude product was then purified by column chromatography, eluent EtOAc to EtOAc:MeOH 1:1 v/v to yield **158** as a cream solid (0.94 g, 42%), followed by **157**, an off-white solid, (0.58 g, 25%).

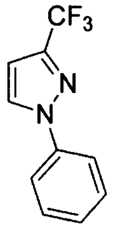
157: mp 138.9-141.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6, DCl) δ 8.68 (1H. s), 8.12 (1H, d, *J* = 2.2 Hz); ^{13}C NMR (175 MHz, DMSO-d_6, DCl) δ 156.6, 146.8 (1C, q, *J* = 5 Hz) 140.4 (1C, q, *J* = 4 Hz), 124.0 (1C, q, *J* = 33 Hz), 123.8 (1C, q, *J* = 269 Hz); ^{11}B NMR (128 MHz, DMSO-d_6, DCl) δ 28.3; ^{19}F NMR (376 MHz, DMSO-d_6, DCl) δ -61.2; Anal. Calcd. for $C_6H_4BClF_3NO_2$: C, 31.98; H, 1.79; N, 6.22. Found: C, 30.95; H, 1.93; N, 5.95%.

158: mp 147.9-149.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6, DCl) δ 8.61 (1H, s), 7.54 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6, DCl) δ 153.6 (1C, q, *J* = 2 Hz), 146.8 (1C, q, *J* = 5 Hz), 127.4, 126.6 (1C, q, *J* = 31 Hz), 124.1 (1C, q, *J* = 272 Hz); ^{11}B NMR (128 MHz, DMSO-d_6, DCl) δ 27.2; ^{19}F NMR (376 MHz, DMSO-d_6, DCl) δ -59.0. Anal. Calcd. for $C_6H_4BClF_3NO_2$: C, 31.98; H, 1.79; N, 6.22. Found: C, 32.39; H, 1.88; N, 6.10%. Crystals for X-ray diffraction analysis were grown from EtOAc.

Typical Procedure for the preparation of 159a-c

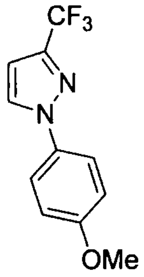
A flame-dried round-bottomed flask, purged with argon was charged with Cu_2O (5 mol%), salicylaldoxime (20 mol%), 3-(trifluoromethyl)pyrazole **129** (1.0 equiv.), anhydrous Cs_2CO_3 (2.0 equiv.) and iodo(hetero)aryl (1.5 equiv.). To the reaction flask degassed acetonitrile (20 mL) was added, the reaction mixture was stirred at reflux for 18 h. The reaction mixture was cooled to room temperature, diluted with DCM and filtered through a celite pad and further washed with DCM (~100 mL). The filtrate was concentrated in vacuo, the residue was further purified by column chromatography on silica gel.

3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazole (159a)[483]



3-(Trifluoromethyl)pyrazole **129** (2.0 g, 14.7 mmol), iodobenzene (2.5 mL, 22.0 mmol), Cu_2O (106 mg, 0.74 mmol), salicylaldoxime (398 mg, 2.9 mmol), anhydrous Cs_2CO_3 (9.6 g, 29.4 mmol) and acetonitrile (20 mL); reaction time 18 h reflux; eluent petroleum ether (bp 40–60 °C):DCM, 100:0 to 1:1 v/v. The crude product a yellow oil was further distilled using Kügelrohr apparatus (69–75 °C/0.6–0.75 mbar) to give **159a** as a pale yellow oil (2.92 g, 94%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (1H, d, J = 2.0 Hz), 7.70 (2H, d, J = 8.5 Hz), 7.49 (2H, t, J = 7.7 Hz), 7.37 (1H, t, J = 7.4 Hz), 6.72 (1H, d, J = 2.6 Hz); ^{13}C NMR (175 MHz, $CDCl_3$) δ 144.1 (1C, q, J = 38 Hz), 139.6, 129.7, 128.4, 127.9, 121.4 (1C, q, J = 268 Hz), 120.1, 106.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.5; MS (EI) *m/z* 212.0 (M^+, 100%). HRMS (EI) calcd for $C_{10}H_7F_3N_2$ 212.0561, found 212.0561.

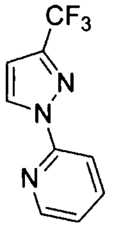
3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazole (159b)



3-(Trifluoromethyl)pyrazole **129** (2.0 g, 14.7 mmol), 4-iodoanisole (5.15 g, 22.0 mmol), Cu_2O (106 mg, 0.74 mmol), salicylaldoxime (398 mg, 2.9 mmol), anhydrous Cs_2CO_3 (9.6 g, 29.4 mmol) and acetonitrile (20 mL); reaction 19.5 h reflux; eluent DCM:petroleum ether (bp 40–60 °C) 1:9 v/v to give **159b** as a pale yellow oil (3.48 g, 98%); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.37 (1H, dd, J = 2.5 Hz, J = 1.0 Hz), 7.76 (2H, d, J = 9.2 Hz), 7.07 (2H, d, J = 9.2 Hz), 6.85 (1H, dd, J = 2.5 Hz, J = 0.4 Hz), 3.84 (3H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.3, 143.7 (1C, q, J = 38 Hz), 134.0, 130.3, 122.7 (1C, q, J = 267 Hz), 122.1, 115.6, 106.0 (1C, q, J = 2 Hz), 56.0; ^{19}F NMR (188 MHz,

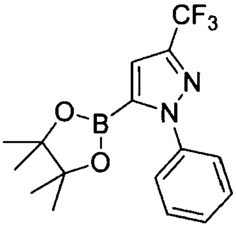
$CDCl_3$) δ -62.4; MS (EI) *m/z* 242.0 (M^+, 100%), 226.9 ($[M-CH_3]^+$, 80%). Anal. Calcd. for $C_{11}H_9F_3N_2O$: C, 54.55; H, 3.75; N, 11.57. Found: C, 54.90; H, 3.80; N, 11.96%.

3-(Trifluoromethyl)-1-(pyridin-2-yl)-1*H*-pyrazole (159c)



3-(Trifluoromethyl)pyrazole **129** (2.0 g, 14.7 mmol), 2-iodopyridine (2.3 mL, 22.0 mmol), Cu_2O (106 mg, 0.74 mmol), salicylaldoxime (398 mg, 2.9 mmol), anhydrous Cs_2CO_3 (9.6 g, 29.4 mmol) and acetonitrile (20 mL); reaction 22 h reflux; eluent EtOAc:petroleum ether (bp 40–60 °C) 1:9 v/v to give **159c** as a white crystalline solid (2.95 g, 94%); mp 81.2-82.6 °C. ^1H NMR (400 MHz, acetone-d_6) δ 8.79 – 8.77 (1H, m), 8.52 (1H, ddd, J = 4.9 Hz, J = 1.7 Hz, J = 1.0 Hz), 8.09 – 8.01 (2H, m), 7.45 (1H, ddd, J = 8.0 Hz, J = 3.6 Hz, J = 1.6 Hz), 6.93 (1H, dd, J = 2.7 Hz, J = 0.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 148.3, 144.9 (1C, q, J = 38 Hz), 139.1, 128.5, 122.7, 121.2 (1C, q, J = 267 Hz), 113.1, 106.0 (1C, q, J = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -63.0; MS (EI) *m/z* 212.9 (M^+, 100%). Anal. Calcd. for $C_9H_6F_3N_3$: C, 50.71; H, 2.84; N, 19.71. Found: C, 50.60; H, 2.88; N, 19.75%.

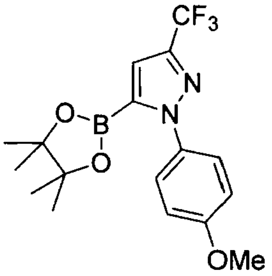
3-(Trifluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-phenyl-1*H*-pyrazole (160a)



n-Butyllithium (2.5 M in hexane, 1.4 mL, 3.5 mmol) was added dropwise to a solution of 3-(trifluoromethyl)-1-phenyl-1*H*-pyrazole **159a** (617 mg, 2.9 mmol) in 20 mL anhydrous THF at –78 °C under argon. The reaction mixture was stirred for 45 min at –78 °C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.62 mL, 3.1 mmol) was added dropwise to the reaction mixture at –78 °C, and the mixture was stirred for 1.5 h. The mixture was warmed to room temperature over 1 h and glacial acetic acid (0.18 mL, 3.2 mmol) was added. The mixture was filtered through a celite pad which was washed with EtOAc (1 × 100 mL). The organic solvent was removed in vacuo and the crude product distilled to remove any unreacted starting material and boron-containing species, the remaining pale-brown solid was confirmed to be **160a** (906 mg, 92%); mp 77.7-79.3 °C. ^1H NMR (400 MHz, acetone-d_6) δ 7.65 – 7.62 (2H, m), 7.54 – 7.48 (3H, m), 7.19 (1H, s), 1.29 (12H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 143.8 (1C, q, J = 38 Hz), 141.6, 129.54, 129.53, 125.9, 122.8 (1C, q, J = 266 Hz), 115.8 (1C, q, J = 2 Hz), 85.7, 25.0; ^{11}B NMR (128 MHz, acetone-d_6) δ 27.9; ^{19}F NMR (188

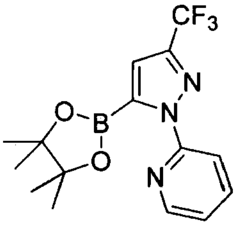
MHz, acetone-d$_6$) δ -62.5; MS (EI) *m/z* 337.8 ([M(**160a**)]$^+$, 80%), 211.9 ([M(**159a**)]$^+$, 60%). Anal. Calcd. for $C_{16}H_{18}BF_3N_2O_2$: C, 56.83; H, 5.37; N, 8.28. Found: C, 56.72; H, 5.37; N, 8.07%.

3-(Trifluoromethyl)-1-(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (160b)



n-Butyllithium (2.5 M in hexane, 4.0 mL, 10.0 mmol) was added dropwise to a solution of 3-(trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazole **159b** (2.0 g, 8.3 mmol) in 20 mL anhydrous THF at –78 °C under argon. The reaction mixture was stirred for 30 min at –78 °C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.9 mL, 9.1 mmol) was added dropwise to the reaction mixture at –78 °C, and the mixture was stirred for 1.5 h. The mixture was warmed to room temperature over 1 h and glacial acetic acid (0.52 mL, 9.1 mmol) was added. The mixture was filtered through a celite pad which was washed with EtOAc (1 × 100 mL). The organic solvent was removed in vacuo, recrystallization of the crude product from hexane with external cooling precipitated **160b** as an off-white crystalline solid (2.99 g, 98%): mp 97.8-99.7 °C. ^{1}H NMR (400 MHz, acetone-d$_6$) δ 7.52 (2H, d, *J* = 9.1 Hz), 7.11 (1H, s), 7.06 (2H, d, *J* = 9.1 Hz), 3.88 (3H, s), 1.28 (12H, s); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 160.9, 143.3 (1C, q, *J* = 36 Hz), 135.0, 127.2, 122.8 (1C, q, *J* = 266 Hz), 115.4, 114.6, 85.7, 56.0, 25.0; ^{11}B NMR (128 MHz, acetone-d$_6$) δ 27.9; ^{19}F NMR (188 MHz, acetone-d$_6$) δ -62.5; MS (EI) *m/z* 368.0 (M$^+$, 100%). Anal. Calcd. for $C_{17}H_{20}BF_3N_2O_3$: C, 55.46; H, 5.48; N, 7.61. Found: C, 55.27; H, 5.44; N, 7.46%. Crystals suitable for X-ray diffraction analysis were grown on slow recrystallization from hexane.

3-(Trifluoromethyl)-1-(pyridin-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (160c)

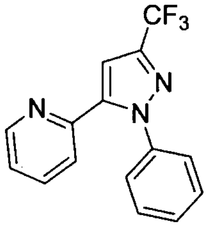


n-Butyllithium (2.5 M in hexane, 3.3 mL, 8.4 mmol) was added dropwise to a solution of 3-(trifluoromethyl)-1-(pyridin-2yl)-1*H*-pyrazole **159c** (1.5 g, 7.0 mmol) in 50 mL anhydrous THF at –78 °C under argon. The reaction mixture was stirred for 45 min at –78 °C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.6 mL, 7.7 mmol) was added dropwise to the reaction mixture at –78 °C, and the mixture was stirred for 1.5 h. The mixture was warmed to room temperature over 1 h and glacial acetic acid (0.44 mL, 7.7 mmol) was added. The mixture was filtered through a celite pad which was washed with EtOAc (1 × 100 mL). The organic solvent was removed in vacuo and the crude product distilled to remove any unreacted starting material and boron-containing species, the remaining colorless opaque oil was confirmed to be **160c** (1.98 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (1H, ddd, *J* = 4.9 Hz, *J* = 1.8 Hz, *J* = 0.9 Hz), 8.00 (1H, dt, *J* = 8.2, 0.9 Hz), 7.85 (1H, ddd, *J* = 8.3 Hz, *J* = 7.4 Hz, *J* = 1.8 Hz), 7.26 (1H, ddd, *J* = 7.5 Hz, *J* = 5.0 Hz, *J* = 1.0 Hz), 6.83 (1H, s), 1.42 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 146.7, 145.1 (1C, q, *J* = 38 Hz), 139.3, 122.5, 121.1 (1C, q, *J* = 267 Hz), 113.2, 111.5 (1C, q, *J* = 2 Hz), 84.6, 24.8; ^{11}B NMR (128 MHz, $CDCl_3$) δ 28.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.6; MS (EI) *m/z* 323.9 ($[M-CH_3]^+$, 100%). Anal. Calcd. for $C_{15}H_{17}BF_3N_3O_2$: C, 53.13; H, 5.05; N, 12.39. Found: C, 53.40; H, 5.09; N, 12.29%.

Typical Procedure for the Suzuki-Miyaura Cross-Coupling Reactions of 160a-c in Table 4.3.

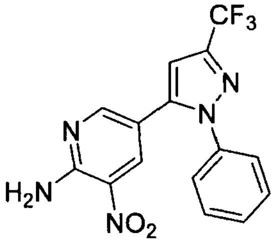
The boronic esters **160a-c** (1.1 equiv.) the aryl halide (1.0 equiv.), Pd(dppf)Cl_2·DCM (ca. 10 mol%), K_3PO_4 (3.0 equiv.) and HCOOK (46 mol% with respect to the boronic ester) were sequentially added to degassed 1,4-dioxane (7 mL) and the mixture was heated under argon at 80 °C for the time stated. The mixture was filtered through a celite pad, which was rinsed with EtOAc. The organic solvent was removed in vacuo and the resulting mixture was purified by chromatography on a silica gel column followed on some occasions by recrystallization.

2-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]pyridine (162)



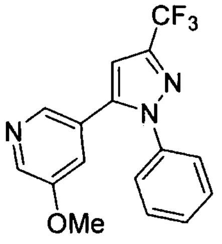
Compound **160a** (279 mg, 0.83 mmol), 2-bromopyridine **78** (0.07 mL, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 4.5 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **162** as a light yellow oil (167 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (1H, d, *J* = 4.1 Hz), 7.61 (1H, td, *J* = 7.8 Hz, *J* = 1.8 Hz), 7.40 – 7.30 (5H, m), 7.24 (1H, ddd, *J* = 7.6 Hz, *J* = 4.9 Hz, *J* = 1.1 Hz), 7.15 (1H, dt, *J* = 7.9, 1.0), 7.03 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 148.4, 144.0, 143.3 (1C, q, *J* = 39 Hz), 139.7, 136.6, 129.2, 128.8, 125.7, 123.7, 123.5, 121.3 (1C, q, J = 269 Hz), 106.8 (1C, q, J = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.7; MS (EI) *m/z* 288.0 ($[M{-}H]^+$, 100%), 289.1 (M^+, 40%). Anal. Calcd. for $C_{15}H_{10}F_3N_3$: C, 62.28; H, 3.48; N, 14.53. Found: C, 62.30; H, 3.68; N, 14.37%.

5-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]-3-nitropyridin-2-amine (163)



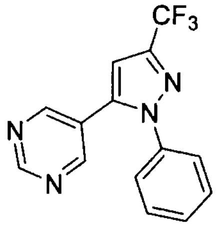
Compound **160a** (279 mg, 0.83 mmol), 2-amino-5-bromo-3-nitropyridine **61** (164 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 4 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **163** as a yellow solid (215 mg, 82%): mp 166.6-168.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, d, J = 2.2 Hz), 8.18 (1H, d, J = 2.2 Hz), 7.47 – 7.42 (3H, m), 7.37 – 7.32 (2H, m), 6.81 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 152.8, 143.6 (1C, q, J = 38 Hz), 139.7, 138.5, 134.5, 129.7, 129.3, 127.4, 125.7, 121.0 (1C, q, J = 260 Hz), 115.6, 105.5 (1C, q, J = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 348.8 (M^+, 100%). Anal. Calcd. for $C_{15}H_{10}F_3N_5O_2$: C, 51.58; H, 2.89; N, 20.05. Found: C, 51.47; H, 2.91; N, 20.15%. Crystals suitable for X-ray diffraction analysis were grown from EtOAc/hexane.

3-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]-5-methoxypyridine (164)



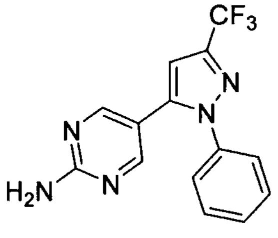
Compound **160a** (279 mg, 0.83 mmol), 3-bromo-5-methoxypyridine **161** (141 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 4 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **164** as a pale pink oil (192 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, d, J = 2.8 Hz), 8.12 (1H, d, J = 1.7 Hz), 7.41 – 7.37 (3H, m), 7.33 – 7.29 (2H, m), 6.92 (1H, dd, J = 2.8 Hz, J = 1.8 Hz), 6.83 (1H, s), 3.69 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 143.5 (1C, q, J = 39 Hz), 141.5, 141.3, 138.9, 138.4, 129.6, 129.1, 125.8, 121.1 (1C, q, J = 267 Hz), 120.1, 106.2, 55.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.7; MS (EI) *m/z* 319.0 (M^+, 80%), 317.9 ($[M{-}H]^+$, 100%). Anal. Calcd. for $C_{16}H_{12}F_3N_3O$: C, 60.19; H, 3.79; N, 13.16. Found: C, 59.89; H, 3.94; N, 13.53%.

5-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]pyrimidine (165)



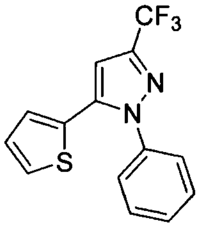
Compound **160a** (279 mg, 0.83 mmol), 5-bromopyrimidine **62** (119 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 3 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **165** as a pale orange crystalline solid (161 mg, 74%): mp 117.3-118.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (1H, s), 8.60 (2H, s), 7.46 – 7.42 (3H, m), 7.33 – 7.28 (2H, m), 6.91 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 156.0, 144.1 (1C, q, $J = 39$ Hz), 138.4, 138.2, 129.9, 129.7, 125.8, 124.1, 121.1 (1C, q, $J = 267$ Hz), 106.6 (1C, q, $J = 2$ Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 290.0 (M^+, 90%), 289.0 ($[M-H]^+$, 100%). Anal. Calcd. for $C_{14}H_9F_3N_4$: C, 57.93; H, 3.13; N, 19.30. Found: C, 57.93; H, 3.24; N, 19.42%.

5-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]pyrimidin-2-amine (166)



Compound **160a** (279 mg, 0.83 mmol), 2-amino-5-bromopyrimidine **63** (131 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:1 v/v gave **166** as a white solid (153 mg, 67%): mp 172.3-174.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (2H, s), 7.46 – 7.40 (3H, m), 7.37 – 7.32 (2H, m), 6.74 (1H, s), 5.28 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 157.9, 143.7 (1C, q, $J = 38$ Hz), 139.5, 138.9, 129.7, 129.2, 125.8, 121.2 (1C, q, $J = 264$ Hz), 114.2, 105.2 (1C, q, $J = 2$ Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 305.0 (M^+, 100%). HRMS (EI) calcd for $C_{14}H_{10}F_3N_5$ 305.0994, found 305.0994.

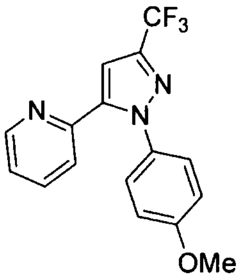
3-(Trifluoromethyl)-1-phenyl-5-(thiophen-2-yl)-1*H*-pyrazole (167)



Compound **160a** (279 mg, 0.83 mmol), 2-bromothiophene **143** (0.07 mL, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to petroleum ether (bp 40–60 °C):DCM 1:1 v/v gave **167** as a pale yellow solid (178 mg, 81%): mp 78.7-80.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ

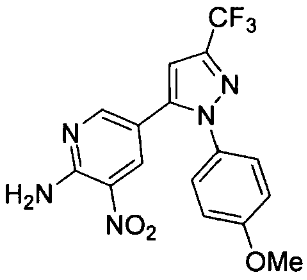
7.47 – 7.39 (5H, m), 7.32 (1H, dd, J = 5.1 Hz, J = 1.2 Hz), 6.96 (1H, dd, J = 5.1 Hz, J = 3.7 Hz), 6.86 (1H, dd, J = 3.7 Hz, J = 1.2 Hz), 6.80 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1 (1C, q, J = 38 Hz), 138.9, 138.7, 129.7, 129.3, 129.2, 128.1, 127.50, 127.45, 126.3, 121.3 (1C, q, J = 267 Hz), 105.3 (1C, q, J = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 293.9 (M^+, 100%). Anal. Calcd. for $C_{14}H_9F_3N_2S$: C, 57.14; H, 3.08; N, 9.52. Found: C, 57.01; H, 3.11; N, 9.67%.

2-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyridine (168)



Compound **160b** (304 mg, 0.83 mmol), 2-bromopyridine **78** (0.07 mL, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5.5 h at 80 °C; eluent EtOAc:petroleum ether (bp 40–60 °C) 1:4 v/v gave **168** as an off-white crystalline solid (150 mg, 63%): mp 107.6-109.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (1H, ddd, J = 4.9 Hz, J = 1.7 Hz, J = 1.0 Hz), 7.60 (1H, td, J = 7.8 Hz, J = 1.8 Hz), 7.27 – 7.20 (m, 3H), 7.12 (1H, dt, J = 8.0 Hz, J = 1.0 Hz), 7.03 (1H, s), 6.88 (2H, d, J = 9.0 Hz), 3.82 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 149.9, 148.3, 143.9, 142.9 (1C, q, J = 38 Hz), 136.4, 132.7, 126.9, 123.4, 123.3, 121.2 (1C, q, J = 267 Hz), 114.3, 106.3 (1C, q, J = 2 Hz), 55.50.; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.7; MS (EI) *m/z* 318.0 ($[M-H]^+$, 100%), 319.1 (M^+, 40%). Anal. Calcd. for $C_{16}H_{12}F_3N_3O$: C, 60.19; H, 3.79; N, 13.16. Found: C, 59.89; H, 3.78; N, 13.12%.

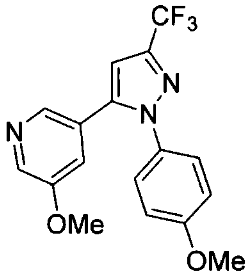
5-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]-3-nitropyridin-2-amine (169)



Compound **160b** (304 mg, 0.83 mmol), 2-amino-5-bromo-3-nitropyridine **61** (164 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5 h at 80 °C; eluent EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **169** as a yellow solid (225 mg, 79%): mp 190.9-193.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (1H, d, J = 2.2 Hz), 8.18 (1H, d, J = 2.2 Hz), 7.26 (2H, d, J = 9.0 Hz), 6.93 (2H, d, J = 9.0 Hz), 6.79 (1H, s), 3.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 154.9, 152.9, 143.3 (1C, q, J = 39 Hz), 139.9, 134.7, 131.6, 127.6, 127.2, 121.2 (1C, q, J = 267 Hz), 115.9, 114.9, 105.3 (1C, q, J = 2 Hz), 55.7; ^{19}F

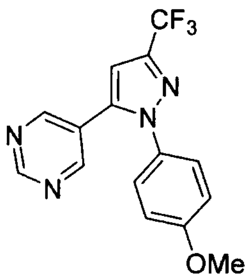
NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 378.9 (M^+, 100%). Anal. Calcd. for $C_{16}H_{12}F_3N_5O_3$: C, 50.67; H, 3.19; N, 18.46. Found: C, 50.38; H, 3.20; N, 18.51%.

3-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]-5-methoxypyridine (170)



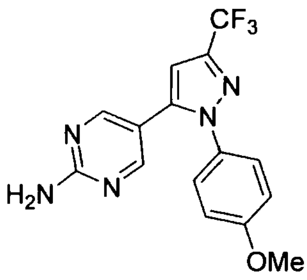
Compound **160b** (304 mg, 0.83 mmol), 3-bromo-5-methoxypyridine **161** (141 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **170** as a pink oil, which solidified and was recrystallized from hexane (214 mg, 82%): mp 88.2-90.2 °C ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, d, *J* = 2.8 Hz), 8.10 (1H, d, *J* = 1.7 Hz), 7.21 (2H, d, *J* = 9.1 Hz), 6.95 (1H, dd, *J* = 2.8 Hz, *J* = 1.8 Hz), 6.87 (2H, d, *J* = 9.0 Hz), 6.79 (1H, s), 3.79 (3H, s), 3.72 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 155.2, 143.1 (1C, q, *J* = 28 Hz), 141.3, 141.1, 137.9, 131.8, 127.0, 125.8, 121.1 (1C, q, *J* = 267 Hz), 120.1, 114.5, 105.7 (1C, q, *J* = 2 Hz), 55.53, 55.52; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.6; MS (EI) *m/z* 349.0 (M^+, 100%), 348.0 ($[M-H]^+$, 90%). Anal. Calcd. for $C_{17}H_{14}F_3N_3O_2$: C, 58.45; H, 4.04; N, 12.03. Found: C, 58.40; H, 4.08; N, 12.06%.

5-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyrimidine (171)



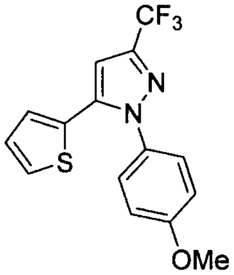
Compound **160b** (304 mg, 0.83 mmol), 5-bromopyrimidine **62** (119 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 3 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **171** as a pale orange solid (143 mg, 60%): mp 94.4-95.9 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.14 (1H, s), 8.58 (2H, s), 7.20 (2H, d, *J* = 9.1 Hz), 6.90 (2H, d, *J* = 9.0 Hz), 6.87 (1H, s), 3.80 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 158.4, 155.9, 143.6 (1C, q, *J* = 39 Hz), 138.2, 131.3, 127.2, 124.1, 121.0 (1C, q, *J* = 268 Hz), 115.0, 106.1 (1C, q, *J* = 2 Hz), 55.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.7; MS (EI) *m/z* 319.9 (M^+, 100%). Anal. Calcd. for $C_{15}H_{11}F_3N_4O$: C, 56.25; H, 3.46; N, 17.49. Found: C, 56.33; H, 3.59; N, 17.09%.

5-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyrimidin-2-amine (172)



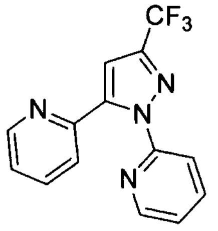
Compound **160b** (304 mg, 0.83 mmol), 2-amino-5-bromopyrimidine **63** (131 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:1 v/v gave **172** as a white solid (180 mg, 72%): mp 171.3-173.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (2H, s), 7.23 (2H, d, *J* = 9.0 Hz), 6.89 (2H, d, *J* = 9.0 Hz), 6.70 (1H, s), 5.61 (2H, s), 3.80 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 160.0, 157.8, 143.2 (1C, q, *J* = 38 Hz), 139.6, 131.8, 127.2, 121.2 (1C, q, *J* = 268Hz), 114.8, 114.0, 104.7 (1C, q, *J* = 2 Hz), 55.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.7; MS (EI) *m/z* 334.8 (M^+, 100%). HRMS (EI) calcd for $C_{15}H_{12}F_3N_5O$ 335.0994, found 335.0994. Anal. Calcd. for $C_{15}H_{12}F_3N_5O$: C, 53.73; H, 3.61; N, 20.89. Found: C, 53.48; H, 3.77; N, 20.32%.

3-(Trifluoromethyl)-1-(4-methoxyphenyl)-5-(thiophen-2-yl)-1*H*-pyrazole (173)



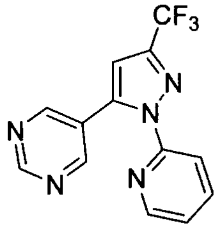
Compound **160b** (304 mg, 0.83 mmol), 2-bromothiophene **143** (0.07 mL, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to petroleum ether (bp 40–60 °C):DCM 1:1 v/v gave **173** as a pale yellow solid (206 mg, 85%): mp 107.5-109.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (3H, m), 6.97 – 6.93 (3H, m), 6.88 (1H, dd, *J* = 3.6 Hz, *J* = 1.0 Hz), 6.79 (1H, s), 3.86 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 143.0 (1C, q, *J* = 38 Hz), 139.1, 132.0, 130.0, 128.0, 128.0, 127.6, 127.5, 121.3 (1C, q, *J* = 268 Hz), 114.5, 104.8 (1C, q, *J* = 2 Hz), 55.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 323.9 (M^+, 100%). Anal. Calcd. for $C_{15}H_{11}F_3N_2OS$: C, 55.55; H, 3.42; N, 8.64. Found: C, 55.33; H, 3.43; N, 8.55%.

2-[3-(Trifluoromethyl)-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl]pyridine (174)



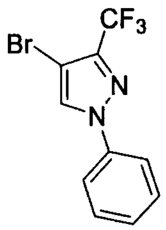
Compound **160c** (280 mg, 0.83 mmol), 2-bromopyridine **78** (0.07 mL, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 4.5 h at 80 °C; eluent EtOAc:petroleum ether (bp 40–60 °C) 1:1 v/v gave **174** as a yellow oil (35 mg, 16%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (1H, ddd, *J* = 4.8 Hz, *J* = 1.6 Hz, *J* = 0.9 Hz), 8.26 (1H, ddd, *J* = 4.8 Hz, *J* = 1.7 Hz, *J* = 0.7 Hz), 7.89 – 7.82 (1H, td, *J* = 8.0 Hz, *J* = 2.0 Hz), 7.75 – 7.67 (2H, m), 7.41 (1H, dt, *J* = 7.9 Hz, *J* = 1.0 Hz), 7.28 – 7.24 (2H, m), 6.96 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 149.5, 149.1, 148.2, 144.4, 143.7 (1C, q, *J* = 39 Hz), 138.8, 136.5, 123.7, 123.6, 123.4, 121.2 (1C, q, *J* = 268 Hz), 119.1, 107.2 (1C, q, *J* = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.9; MS (EI) *m/z* 220.7 ($[M-CF_3]^+$, 90%), 289.0 ($[M-H]^+$, 50%), 290.1 (M^+, 30%). HRMS (ES^+) calcd for $C_{14}H_{10}F_3N_4$ 291.0852, found 291.0852. Anal. Calcd. for $C_{14}H_9F_3N_4$: C, 57.93; H, 3.13; N, 19.30. Found: C, 57.03; H, 3.35; N, 18.39%.

5-[3-(Trifluoromethyl)-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl]pyrimidine (175)



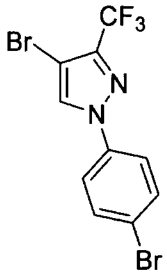
Compound **160c** (280 mg, 0.83 mmol), 5-bromopyrimidine **62** (119 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7mL), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 4.5 h at 80 °C; eluent EtOAc:petroleum ether (bp 40–60 °C) 1:1 v/v gave **175** as an white solid (65 mg, 30%): mp 116.5-117.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (1H, s), 8.76 (2H, s), 8.21 (1H, ddd, *J* = 4.8 Hz, *J* = 1.7 Hz, *J* = 0.9 Hz), 7.95 – 7.87 (m, 2H), 7.29 (1H, ddd, *J* = 6.9 Hz, *J* = 4.9 Hz, *J* = 1.5 Hz), 6.85 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.6, 151.6, 147.9, 144.23 (1C, q, *J* = 38 Hz), 139.4, 138.9, 125.7, 123.7, 120.9 (1C, q, *J* = 267 Hz), 117.4, 108.6 (1C, q, *J* = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -63.1; MS (EI) *m/z* 290.0 ($[M-H]^+$, 100%). Anal. Calcd. for $C_{13}H_8F_3N_5$: C, 53.61; H, 2.77; N, 24.05. Found: C, 53.44; H, 2.83; N, 23.91%.

4-Bromo-3-(trifluoromethyl)-1-phenyl-1*H*-pyrazole (177)



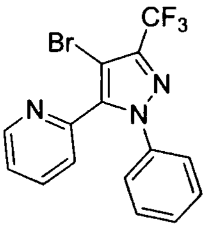
Bromine (0.4 mL, 7.4 mmol) was added to a solution of compound **159a** (1.05 g, 5.0 mmol) in 10 mL glacial acetic acid. The mixture was heated to 100 °C for 17 h. The reaction mixture was allowed to cool slightly before quenching with deionised water (10 mL), the mixture was then neutralised with NaOH solution (1M). A saturated solution of $Na_2S_2O_3$ (50 mL) was added and the product then extracted with EtOAc (2 × 100 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness in vacuo. Following column chromatography, eluent DCM:petroleum ether (bp 40–60 °C) 1:4 v/v, **177** was isolated as a colourless oil (1.33 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, d, *J* = 0.9 Hz), 7.66 – 7.59 (2H, m), 7.50 – 7.44 (2H, m), 7.41 – 7.35 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8 (1C, q, *J* = 38 Hz), 138.9, 129.78, 129.75, 128.3, 120.7 (1C, q, *J* = 268 Hz), 93.6 (1C, q, *J* = 1Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.5; MS (EI) *m/z* 289.8 ($M^+[^{79}Br]$, 100%). Anal. Calcd. for $C_{10}H_6BrF_3N_2$: C, 41.26; H, 2.08; N, 9.62. Found: C 41.61; H, 2.15; N, 9.78%.

4-Bromo-1-(4-bromophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (179)



Bromine (0.65 mL, 12.7 mmol) and iron powder (140 mg, 2.5 mmol) were added to compound **159a** (1.0 g, 4.7 mmol). The mixture was heated to 100 °C for 1 h. $Na_2S_2O_3$ (2.5 g, 16.0 mmol) in 10 mL water was added to the mixture. The product was then extracted with Et_2O (3 × 50 mL). The organic phase was combined and washed with brine (2 × 25 mL) and water (1 × 50 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness in vacuo. Following column chromatography, eluent petroleum ether (bp 40–60 °C) + 5% DCM, **179** was isolated as a white solid (1.28 g, 73%): mp 51.5-53.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, s), 7.54 (2H, d, *J* = 8.7 Hz), 7.46 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1412.0 (1C, q, *J* = 37 Hz), 137.7, 132.8, 129.5, 124.8, 120.8, 120.5 (1C, q, *J* = 268 Hz), 94.0 (1C, q, *J* = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 369.7 ($M^+[^{79}Br]$, 100%). Anal. Calcd. for $C_{10}H_5Br_2F_3N_2$: C, 32.46; H, 1.36; N, 7.57. Found: C, 32.72; H, 1.42; N, 7.50%.

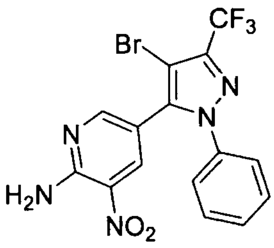
2-[4-Bromo-3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]pyridine (181)



Bromine (0.02 mL, 0.48 mmol) was added to a solution of compound **162** (92 mg, 0.32 mmol) in 5 mL glacial acetic acid. The mixture was heated to 100 °C for 17 h. The reaction mixture was allowed to cool slightly before quenching with deionised water (10 mL), the mixture was then neutralised with NaOH solution (1M). A saturated solution of $Na_2S_2O_3$ (40 mL) was added and the product then extracted with EtOAc (2 × 75 mL).

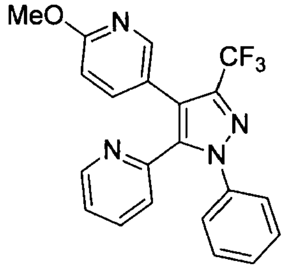
The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness in vacuo. Following column chromatography, eluent DCM, **181** was isolated as a white solid (78 mg, 66%): mp 106.4-108.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (1H, d, *J* = 4.2 Hz), 7.77 (1H, td, *J* = 7.7 Hz, *J* = 1.6 Hz), 7.47 (1H, d, *J* = 7.8 Hz), 7.32 – 7.30 (4H, m), 7.26 – 7.23 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 147.2, 142.3, 141.4 (1C, q, *J* = 37 Hz), 139.4, 136.7, 129.2, 128.8, 125.9, 125.0, 124.1, 120.8 (1C, q, *J* = 269 Hz), 94.1 (1C, q, *J* = 1.4 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.9; MS (EI) *m/z* 367.8 ($M^+[^{79}Br]$, 100%). HRMS (EI) calcd for $C_{15}H_9BrF_3N_3$ 366.9932, found 366.9932. Anal. Calcd. for $C_{15}H_9BrF_3N_3$: C, 48.94; H, 2.46; N, 11.41. Found: C, 48.22; H, 2.49; N, 11.20%.

5-[4-Bromo-3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]-3-nitropyridin-2-amine (182)



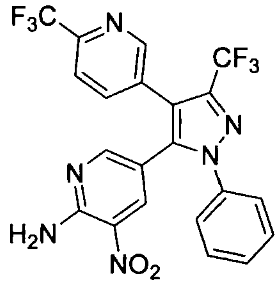
Bromine (0.012 mL, 0.24 mmol) was added to a solution of compound **163** (55 mg, 0.16 mmol) in 5 mL glacial acetic acid. The mixture was heated to 100 °C for 18 h. The reaction mixture was allowed to cool slightly before quenching with deionised water (25 mL), the mixture was then neutralised with a saturated solution of $NaHCO_3$. A saturated solution of $Na_2S_2O_3$ (50 mL) was added and the product then extracted with DCM (3 × 50 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness in vacuo. The crude product was passed through a silica pad and then recrystallized from cyclohexane to yield **182** as a yellow crystalline solid (58 mg, 86%): mp 183.9-185.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (1H, d, *J* = 2.2 Hz), 8.20 (1H, d, *J* = 2.2 Hz), 7.44 – 7.40 (3H, m), 7.31 – 7.27 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 153.2, 141.8 (1C, q, *J* = 37 Hz), 138.7, 138.5, 136.4, 129.8, 129.6, 127.6, 125.5, 120.6 (1C, q, *J* = 267 Hz), 113.8, 94.3 (1C, q, *J* = 1 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -63.0; MS (EI) *m/z* 426.8 ($M^+[^{79}Br]$, 100%). Anal. Calcd. for $C_{15}H_9BrF_3N_5O_2$: C, 42.08; H, 2.12; N, 16.36. Found: C, 41.96; H, 2.14; N, 15.97%.

2-[3-(Trifluoromethyl)-4-(6-methoxypyridin-3-yl)-1-phenyl-1*H*-pyrazol-5-yl]pyridine (183)



Compound **181** (120 mg, 0.33 mmol), 2-methoxy-5-pyridylboronic acid (55 mg, 0.36 mmol), Pd(PPh_3)$_4$ (5 mol%, 19 mg, 0.016 mmol) and degassed1,4-dioxane (4 mL) were added sequentially to a reaction flask, under an argon atmosphere, the mixture was placed stirred at room temperature for 20 min. Degassed Na_2CO_3 (1M, 1.0 mL, 1.0 mmol) was added and the reaction mixture heated to reflux. After 6 h at reflux the reaction was complete, the mixture was cooled slightly before adding EtOAc (50 mL) and brine (50 mL). The organic phase was extracted and dried over Na_2SO_4, filtered and evaporated to dryness in vacuo. The crude product was purified by column chromatography, eluent EtOAc, followed by recrystallization from hexane/DCM to yield **183** as light yellow/orange, rectangular crystals (104 mg, 80%): mp 127.8-130.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (1H, ddd, *J* = 4.9 Hz, *J* = 1.8 Hz, *J* = 1.0 Hz), 8.06 (1H, d, *J* = 2.2 Hz), 7.59 – 7.51 (2H, m), 7.34 – 7.28 (5H, m, 5H), 7.20 (1H, ddd, *J* = 7.7 Hz, *J* = 4.9 Hz, *J* = 1.2 Hz), 7.06 (1H, dt, *J* = 7.8, 1.1 Hz), 6.71 (1H, dd, *J* = 8.6 Hz, *J* = 0.8 Hz), 3.92 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 150.2, 148.3, 147.9, 141.2, 141.6 (1C, q, *J* = 36 Hz), 140.5 (1C, q, *J* = 1 Hz), 139.4, 136.6, 129.1, 128.5, 126.0, 125.3, 123.7, 121.6 (1C, q, *J* = 268 Hz), 119.2, 118.6, 110.6, 53.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ -60.1; MS (EI) *m/z* 395.0 ([M−H]$^+$, 100%), 396.1 (M$^+$, 25%). Anal. Calcd. for $C_{21}H_{15}F_3N_4O$: C, 63.63; H, 3.81; N, 14.14. Found: C, 63.60; H, 3.86; N, 14.33%. Crystals, obtained as described above, were suitable for X-ray diffraction analysis.

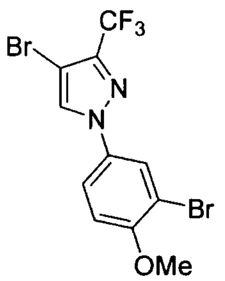
5-[3-(Trifluoromethyl)-4-(6-(trifluoromethyl)pyridin-3-yl)-1-phenyl-1*H*-pyrazol-5-yl]-3-nitropyridin-2-amine (184)



Compound **182** (43 mg, 0.10 mmol), 6-(trifluoromethyl)-3-pyridylboronic acid **136** (21 mg, 0.11 mmol), Pd(PPh_3)$_4$ (5 mol%, 5.8 mg, 0.005 mmol) and degassed1,4-dioxane (10 mL) were added sequentially to a reaction flask, under an argon atmosphere, the mixture was placed stirred at room temperature for 10 min. Degassed Na_2CO_3 (1M, 0.30 mL, 0.30 mmol) was added and the reaction mixture heated to reflux. After 3.5 h at reflux the reaction was complete, the reaction solvent was removed in vacuo before EtOAc (50 mL) and brine

(50 mL) were added to the reaction mixture. The organic phase was extracted and solvent removed in vacuo, the crude product was filtered through a silica pad, washing with EtOAc. The combined organic solvent was removed in vacuo and the crude product was purified by column chromatography, eluent DCM to yield **184** as a yellow solid (15 mg, 30%): mp 164.9 °C darkens, >200 °C decomp.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (1H, d, *J* = 1.8 Hz), 8.04 (1H, d, *J* = 2.2 Hz), 7.97 (1H, d, *J* = 2.2 Hz), 7.88 (1H, dd, *J* = 8.0 Hz, *J* = 1.7 Hz), 7.75 (1H, d, *J* = 8.0 Hz), 7.48 – 7.43 (3H, m), 7.37 – 7.31 (2H, m), 6.01 (2H, br. s); ^{13}C NMR (175 MHz, $CDCl_3$) δ 155.8, 153.1, 150.8, 147.9 (1C, q, *J* = 33 Hz), 141.5 (1C, q, *J* = 37 Hz), 139.1, 138.7, 138.1, 136.3, 129.9, 129.7, 129.2, 127.5, 125.8, 121.4 (1C, q, *J* = 271 Hz), 121.1 (1C, q, *J* = 270 Hz), 120.5 (1C, q, *J* = 2 Hz), 116.9, 113.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ -60.0, 68.4; MS (ES$^+$) *m/z* 495.1 ([M+H]$^+$, 100%). HRMS (ES$^+$) calcd for $C_{21}H_{13}F_6N_6O_2$ 495.09987, found 495.09995.

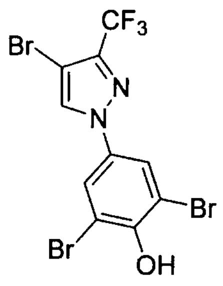
4-Bromo-1-(3-bromo-4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazole (185)



Bromine (0.31 mL, 6.0 mmol) was added to a solution of compound **159b** (971 mg, 4.0 mmol) in 10 mL glacial acetic acid. The mixture was heated to 100 °C for 17 h. The reaction mixture was allowed to cool slightly before quenching with deionised water (25 mL), the mixture was then neutralised with a saturated solution of $NaHCO_3$. A saturated solution of $Na_2S_2O_3$ (50 mL) was added and the product then extracted with DCM (3 × 50 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness in vacuo. The crude product was purified by silica column chromatography eluent petroleum ether (bp 40–60 °C):DCM 1:1 v/v, to yield **185** as a cream coloured solid (695 mg, 43%): mp 84.1-86.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, d, *J* = 0.9 Hz), 7.87 (1H, d, *J* = 2.7 Hz), 7.56 (1H, dd, *J* = 8.9 Hz, *J* = 2.7 Hz), 6.97 (1H, d, *J* = 8.9 Hz), 3.94 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 141.9 (1C, q, *J* = 37 Hz), 132.9, 129.8, 125.3, 120.6 (1C, q, *J* = 268 Hz), 120.1, 112.6, 112.2, 93.7 (1C, q, *J* = 2 Hz), 56.8; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.6; MS (EI) *m/z* 397.7 (M$^+$[^{79}Br], 50%). Anal. Calcd. for $C_{11}H_7Br_2F_3N_2O$: C, 33.03; H, 1.76; N, 7.00. Found: C, 32.99; H, 1.95; N, 6.81%.

Also isolated from the reaction mixture were minor products: isomers **186** and **187** as a mixture (142 mg, 11% yield) confirmed by ^{1}H NMR. **188** observed by ^{1}H NMR, as a mixture with another species, GCMS (EI) *m/z* 383.8 (M$^+$[^{79}Br], 100%). **189** recrystallized from hexane to yield an off-white solid (53 mg, 3%). For the ^{1}H NMR spectra of the **186** and **187** mixture and **188** see Appendix 2.

2,6-Dibromo-4-(4-bromo-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenol (189)



Isolated from the above reaction, following recrystallization from hexane after column chromatography (53 mg, 3%): mp 159.3-161.6 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 (1H, d, *J* = 0.9 Hz), 7.81 (2H, s), 6.02 (1H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.8, 142.3 (1C, q, *J* = 37 Hz), 133.1, 129.8, 123.6, 120.4 (1C, q, *J* = 269 Hz), 110.5, 94.2 (1C, q, *J* = 1 Hz); ^{19}F NMR (188 MHz, CDCl$_3$) δ -62.6; MS (EI) *m/z* 463.6 (M$^+$[^{79}Br], 100%. Anal. Calcd. for $C_{10}H_4Br_3F_3N_2O$: C, 25.84; H, 0.87; N, 6.03. Found: C, 25.86; H, 0.87; N, 5.97%.

CHAPTER 6 – REFERENCES

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APPENDIX 1 – 2-AMINO-5-PYRIMIDYLBORONIC ACID

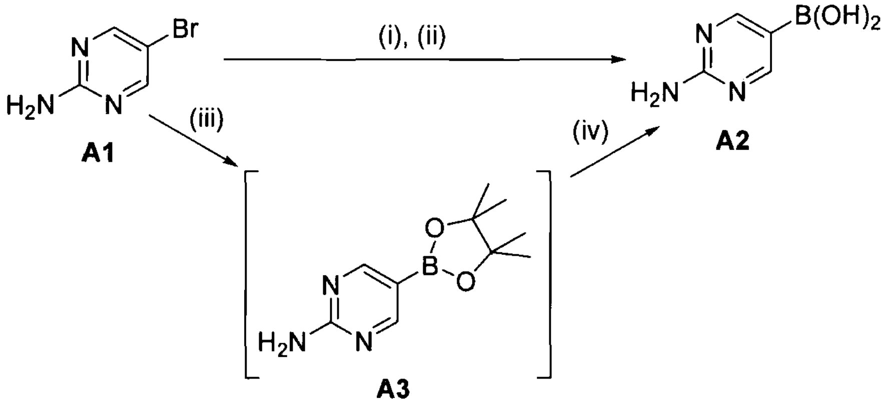
A1.1 Introduction

Pyrimidylboronic acids are important reagents in the preparation of functionalized pyrimidine derivatives,[1-3] however there are far fewer reports of substituted pyrimidylboronic acids than pyridylboronic acid derivatives, as discussed previously. Our group were interested in the Suzuki-Miyaura cross-coupling reactions of (hetero)aryl halides in the presence of an unprotected primary amine substituent.[4, 5] Previous to our work, it was generally regarded that compounds bearing labile protons were unsuitable as coupling partners[6] and that reactions would occur only when the amine was protected. However, a systematic study into the Suzuki-Miyaura reactivity of a variety of amine-substituted halogenated-benzenes, -pyridines, -pyrazines and -pyrimidines with a number of pyridylboronic acids and aryldiboronic acids showed the suitability of these substrates without need for protection/deprotection of the amine, yielding highly functionalized bi(hetero)aryls in moderate to good yields, 35-84%.[5] At this time other groups were also reporting the synthesis of biheteroaryl compounds containing an unprotected amine group, in good yields, via the Suzuki-Miyaura reaction.[7, 8] Our research was extended to the preparation of 2-amino-5-pyrimidylboronic acid **A2**; there are several reports of aniline boronic acids[9-11] and amino-pyridylboronic acids,[12, 13] both of which are commercially available, however, the aminopyrimidine derivative had not been reported.

In this appendix the background work regarding the synthesis and reactions of 2-amino-5-pyrimidylboronic acid **A2** is outlined. Optimization of the Suzuki-Miyaura reaction conditions, gave synthetically viable yields for the cross-coupling of **A2** with a variety of (hetero)aryl bromides.

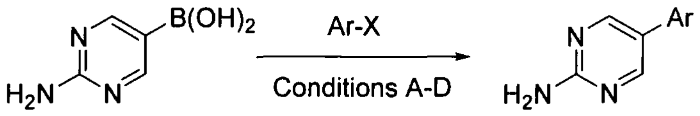
A1.1.1 Synthesis of A2 and initial Suzuki-Miyaura cross-couplings

The commercially available 2-amino-5-bromopyrimidine **A1** was treated with *n*-BuLi in the presence of triisopropylborate in THF at –78 °C to yield boronic acid **A2** in typically 25% yield (a yield of 40% was obtained on one occasion)[4] (Scheme A1.1). Competitive deprotonation of the amine substituent was thought to account for the low isolated yields of boronic acid **A2**; optimum yields were obtained when at least 3 equivalents of *n*-BuLi was used. Lithium-halogen exchange in the presence of the free 2-amino group, combined with the in situ boronic acid preparation,[14] was successful for the pyrimidine derivative. However, analogous lithiation/borylation procedures on 2-amino-5-bromopyridine and 1-amino-4-bromobenzene gave complex product mixtures; the corresponding boronic acid/ester derivatives could not be isolated. One may anticipate that for **A1** the negative charge resulting from deprotonation of the amine group will be delocalized over the two nitrogen atoms, and therefore will significantly influence the lithium-halogen exchange. However, for the pyridine and benzene derivatives there would be less stabilization of the negative charge, which may possibly have prevented the lithium-halogen exchange from occurring efficiently. We have found that a more reliable route to **A2** is via the pinacol ester derivative **A3** which was generated by reaction of **A1** with HxLi in THF at –78 °C, in the presence 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, then intermediate **A3** was hydrolyzed in situ to **A2** (46% optimized yield from **A1**).[15]



Scheme A1.1 (i) *n*-BuLi, B(O*i*-Pr)$_3$, THF , –78 °C. (ii) H_2O, 48% aq. HBr. (iii) HxLi, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, THF, –78 °C. (iv) H_2O, AcOH.[4, 15]

Suzuki-Miyaura reactions of **A2** with (hetero)aryl halides **66**, **78**, **A4-A9** were carried out under a variety of conditions to yield (hetero)arylpyrimidine derivatives **A10-A16**. The results are collated in Table A1.1.[16] Initially reactions of **A2** with heteroaryl bromides yielded coupling products in low yields (entries 1 and 2) with iodoheterocycles generally giving higher coupling yields, typically 27-60% (entries 3-8). Reaction conditions [Pd(PPh$_3$)$_2$Cl$_2$ (5 mol% **A2**)/*t*-Bu$_3$P (5 mol% **A2**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 24 h] were found to give reliably moderate to good yields; however, protodeboronation of **A2** to give 2-aminopyrimidine was a competing side-reaction. The overall yield of cross-coupled product could be further improved by a second addition of **A2** (1.1 equiv.) to the reaction mixture after 24 h reflux (entries 3 and 5, conditions D) to overcome the loss of **A2** by protodeboronation, and maintain a viable amount of **A2** in the reaction mixture. However, for practical purposes the advantage of higher product yield is offset by the use of more of compound **A2**.



A2 **A10-A16**

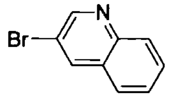
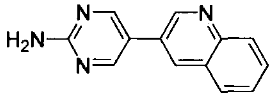
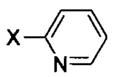
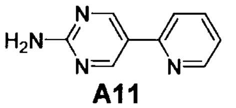
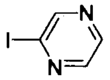
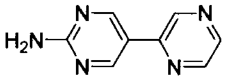
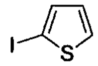
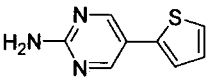
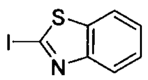
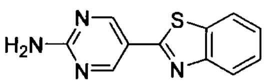
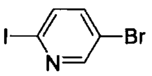
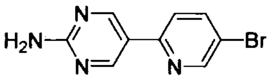
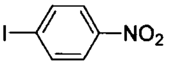
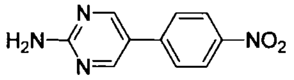
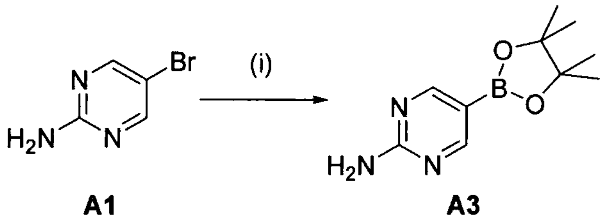
Entry	Ar-X	Product	Conditions	Isolated yield (%)
1	 **66**	 **A10**	A C	45 45 (39)*
2	 **78** X = Br **A4** X = I	 **A11**	A (from **78**)	6
3			A (from **A4**) B (from **A4**) D (from **A4**)	47 56 96
4	 **A5**	 **A12**	A B	33 60
5	 **A6**	 **A13**	B D	49 76
6	 **A7**	 **A14**	B	40
7	 **A8**	 **A15**	B	27
8	 **A9**	 **A16**	A	42

Table A1.1 Conditions: A: $Pd(PPh_3)_2Cl_2$ (5 mol% **A2**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 24 h. B: $Pd(PPh_3)_2Cl_2$ (5 mol% **A2**)/*t*-Bu_3P (5 mol% **A2**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 24 h. C: $Pd(OAc)_2$ (5 mol% **A2**)/D-*t*-BPF (5 mol% **A2**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h. D: Conditions B, with a second addition of boronic acid **A2** (1.1 equiv.) after 24 h reflux. *$K_3PO_{4(s)}$ used (2 equiv.).[16]

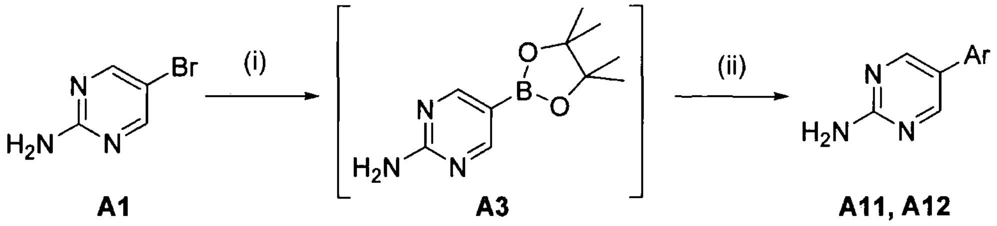
A1.1.2 Boronic ester synthesis and in situ cross-coupling reactions

In attempts to improve the cross-coupling yields we looked to stabilize the boronic species. From literature precedents there is no general rule as to whether the boronic acid or an ester derivative is more suitable for cross-coupling. One must evaluate each system on a case-by-case basis; for example, Rault et al. showed that *o*-cyanopyridylboronic esters are more suitable than the acids,[17] however, as shown in Chapter 2 the improvement in the cross-coupling yields may not be significant when employing boronic ester derivatives (compared to the analogous boronic acid). Instead of isolating the boronic ester **A3** from the lithium-halogen exchange/boronation protocol outlined in Scheme A1.1, one could alternatively prepare **A3** through the palladium catalyzed reaction of 2-amino-5-bromopyrimidine **A1** with bis(pinacolato)diboron (B_2pin_2). Miyaura et al. have worked extensively on the palladium-catalyzed borylation of (hetero)aryl halides[18, 19] as discussed in Chapter 1.



Scheme A1.2 (i) B_2pin_2, $Pd(OAc)_2$ (5 mol% **A1**), KOAc, DMF, 90 °C, 17 h.[20]

On treating **A1** with B_2pin_2, $Pd(OAc)_2$ and KOAc in DMF, boronic ester **A3** was readily synthesized (Scheme A1.2); to achieve optimum yields 2.5 equivalents of B_2pin_2 were required, using fewer equivalents resulted in a significant proportion of unreacted **A1** being recovered.[20] Purification of the boronic ester was particularly problematic, after silica column chromatography, **A3** was isolated along with a second boron-containing species. We assume this species to be 'pinacol acetate' resulting from transmetalation during the catalytic cycle. Further column chromatography using a more polar eluent resulted in the isolation of **A3** in very low yields (ca. 2%). The polar nature of the amine and pyrimidine functionality of **A3** presumably makes column chromatography more difficult. Recrystallization was also unsuccessful in purifying **A3**. As isolation of boronic ester **A3** proved difficult, in situ Suzuki-Miyaura cross-coupling reactions were performed.[21] The boronic ester **A3** was prepared as before, and the reaction mixture was cooled prior to addition of the Suzuki-Miyaura cross-coupling reagents. Unfortunately, when using the Suzuki-Miyaura conditions previously used for the cross-coupling of boronic acid **A2**, [Pd(PPh$_3$)$_2$Cl$_2$ (5 mol% Ar-X)/*t*-Bu$_3$P (5 mol% Ar-X), 1,4-dioxane, Na$_2$CO$_3$ (1 M), reflux, 65 h], isolated yields of coupling products **A11** and **A12** (with respect to **A1**) were poor, even when using heteroaryl iodides as coupling partners (Table A1.2).[20]



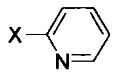
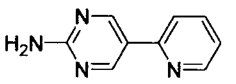
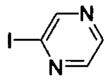
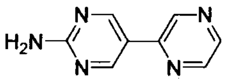
Entry	Ar-X	Product	Conditions	Isolated yield (%)
1	 **78** X = Br **A4** X = I	 **A11**	A (from **78**)	13
2			B (from **A4**)	29
3	 **A5**	 **A12**	B	9

Table A1.2 (i) B$_2$pin$_2$, Pd(OAc)$_2$ (5 mol% **A1**), KOAc, 1,4-dioxane, 80 °C, 17 h. (ii) Ar-X, Conditions A: Pd(PPh$_3$)$_2$Cl$_2$ (5 mol% Ar-X), Na$_2$CO$_3$ (1 M), reflux, 65 h. Conditions B: Pd(PPh$_3$)$_2$Cl$_2$ (5 mol% Ar-X)/*t*-Bu$_3$P (5 mol% Ar-X), Na$_2$CO$_3$ (1 M), reflux, 65 h.[20]

Alongside coupling products **A11** and **A12**, 2-aminopyrimidine was isolated indicating that the boronic ester **A3** was unstable towards protodeboronation under the reaction conditions; this may occur during the boronic ester preparation or the subsequent Suzuki-Miyaura cross-coupling. The isolated yields for cross-coupling products (with respect to **A1**) were slightly improved when using the boronic ester/in situ Suzuki-Miyaura protocol, compared to the overall yields when using the boronic acid; yield of **A11**, from 2-iodopyridine **A4**, via boronic ester/in situ route 29%, via boronic acid 26%. Nonetheless, as in situ Suzuki-Miyaura reactions of boronic ester **A3** were ineffective in improving the preparation, stability and cross-coupling yields (compared to the boronic acid **A2**) we re-investigated alternative Suzuki-Miyaura reaction conditions.

A1.2 Improved Suzuki-Miyaura cross-coupling reactions

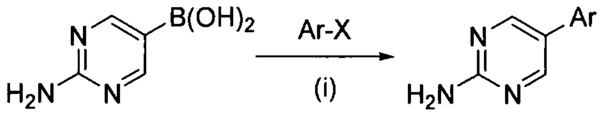
The reactions of less expensive (hetero)aryl bromides or chlorides with **A2** were attractive. However, as previously the reactivity of **A2** with (hetero)aryl iodides was shown to be fairly poor, we anticipated that cross-coupling with bromo- and chloro-coupling partners would be difficult. We found that for the electron-deficient coupling partners using bromo derivatives and conditions [$Pd_2(dba)_3$ (1 mol% Ar-X)/PCy_3 (2.4 mol% Ar-X), 1,4-dioxane, K_3PO_4 (1.27 M), reflux][22] resulted in similar or improved yields of **A10**, **A11**, **A15** and **A16** compared to previous reactions with the comparable iodo coupling partners (Table A1.3, entries 1, 2, 9 and 10). Chloropyrazine gave **A12** in a synthetically useful yield of 51% (entry 4), compared to the 72% yield of **A12** from iodopyrazine (entry 3).

The overall improved reactivity of boronic acid **A2** when using $Pd_2(dba)_3/PCy_3$ as the catalyst system applies when utilizing (hetero)aryl bromides, which are far more appealing reagents than (hetero)aryl iodides, mainly due to their lower cost. This system is far more efficient than the boronic ester/in situ Suzuki-Miyaura protocol in terms of general cost of reagents and ease of isolation of final cross-coupling products.

A1.3 Conclusions

2-Amino-5-pyrimidylboronic acid can be prepared on a relatively large-scale (70 g) in good yield, considering the competitive deprotonation of the amine substituent which can occur. Boronic acid **A2** is stable to storage under ambient conditions and should prove to be a valuable reagent in pyrimidine chemistry. Preparation of the boronic acid from cheap commercial reagents and superior reactivity in Suzuki-Miyaura cross-coupling reactions renders the boronic ester derivative obsolete.

Protection/deprotection steps of the primary amine are not required at any stage in order to prepare novel 5-heteroarylpyrimidine scaffolds in synthetically viable yields. A selection of heterocycles (quinoline, pyridine, pyrimidine, pyrazine, thiophene, benzothiazole) with primary amine, bromo and nitro functional groups were shown to be applicable and compatible with the reaction conditions.



A1.2 **A1.10-A1.16**

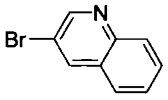
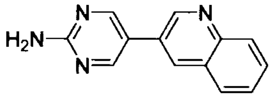
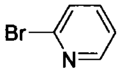
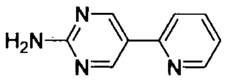
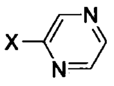
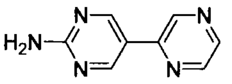
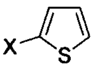
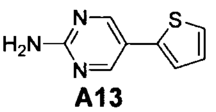
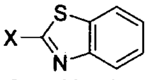
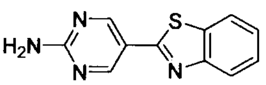
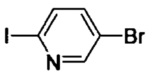
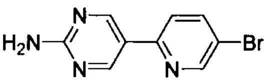
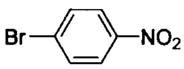
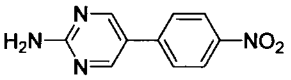
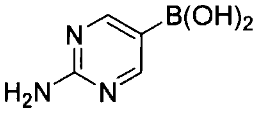
Entry	Ar-X	Product	Isolated yield (%)
1	 **66**	 **A10**	72
2	 **78**	 **A11**	75
3	 **A5** X = I **A17** X = Cl	 **A12**	72 (from **A5**)
4			61 (from **A17**)
5	 **A6** X = I **141** X = Br	 **A13**	37 (from **A6**)
6			26 (from **141**)
7	 **A7** X = I **A18** X = Br	 **A14**	45 (from **A7**)
8			33 (from **A18**)
9	 **A8**	 **A15**	49
10	 **A18**	 **A16**	43

Table A1.3 Conditions: (i) $Pd_2(dba)_3$ (1 mol% Ar-X)/PCy_3 (2.4 mol% Ar-X), 1,4-dioxane, K_3PO_4 (1.27 M), reflux, 1-30 h.

A1.4 Experimental details for Appendix 1

Several compounds reported in Appendix 1 were prepared prior to this work; synthesis of **A2**,[4, 15] initial Suzuki-Miyaura cross-couplings of **A2** (Section A1.1.1),[16] synthesis of **A3** and in situ Suzuki-Miyaura cross-couplings.[20] For general considerations refer to Chapter 5.

2-Amino-5-pyrimidylboronic acid (A2)



To a solution of 2-amino-5-bromopyrimidine **A1** (69.6 g, 0.4 mol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (223 g, 1.2 mol) in THF (2 L) at –78 °C, HxLi (2.5 M in hexane, 640 mL, 1.6 mol) was added dropwise over 1 h. The reaction was stirred for 2.5 h at –78 °C, then allowed to warm to room temperature overnight. The reaction mixture was quenched with water (1.5 L) and stirred for 30 min. The aqueous phase was separated and washed with EtOAc (2 × 1 L) then carbon treated and stirred for 30 min at room temperature before filtration through celite. The resulting aqueous filtrate was acidified slowly to pH 6 using glacial acetic acid (maintaining the temperature below 30 °C) and stirred for a further 30 min before filtering the white precipitate which formed. The white solid was oven dried at 50 °C and identified as boronic acid **A2** (25.6 g, 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 164.1, 163.9.

Alternative route: To a solution of 2-amino-5-bromopyrimidine **A1** (1.74 g, 10 mmol) and triisopropylborate (2.9 mL, 12 mmol) in anhydrous THF (50 mL) at –78 °C, *n*-BuLi (2.5 M in hexane, 10 mL, 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 mL) 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 × 50 mL) to remove unreacted starting material and the aqueous layer filtered to remove inorganic salts. The filtrate was then acidified to pH 6 (with 48% aq. HBr) to precipitate **A2** as a white solid (347 mg, 25%), spectroscopically identical to the sample previously described.

Typical Procedure for the Suzuki-Miyaura Cross-Coupling Reactions in Table A1.1

The boronic acid (1.1 equiv.) the arylhalide (1.0 equiv.) and catalyst (ca. 5 mol%) were sequentially added to degassed 1,4-dioxane (10 mL) and the mixture stirred at 20 °C for 30 min. Degassed aqueous Na_2CO_3 (1 M, 3.0 equiv.) was added and the reaction mixture was heated under argon at reflux (typically for 24 h). The solvent was removed in vacuo then EtOAc 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 an additional recrystallization was necessary.

Conditions A: $Pd(PPh_3)_2Cl_2$ (5 mol% **A2**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 24 h.
Conditions B: $Pd(PPh_3)_2Cl_2$ (5 mol% **A2**)/*t*-Bu_3P (5 mol% **A2**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 24 h.
Conditions C: $Pd(OAc)_2$ (5 mol% **A2**)/D-*t*-BPF (5 mol% **A2**), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h.
Conditions D: Conditions B, with a second addition of boronic acid **A2** (1.1 equiv.) after 24 h reflux.

Typical Procedure for the Suzuki-Miyaura Cross-Coupling Reactions in Table A1.3

The boronic acid **A2** (1.1 equiv.) the arylhalide (1.0 equiv.) $Pd_2(dba)_3$ (ca. 1 mol%) and PCy_3 (ca. 2.4 mol%) were sequentially added to degassed 1,4-dioxane (2.7 mL) and the mixture stirred at 20 °C for 30 min. Degassed aqueous K_3PO_4 solution (1.27 M, 1.7 equiv.) was added and the reaction mixture was heated under argon at reflux (typically between 1-30 h). The solvent was removed in vacuo then EtOAc 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 or by recrystallization.

3-(2-Aminopyrimidin-5-yl)-quinoline (A10)

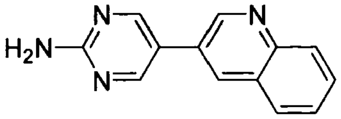


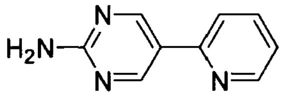
Table A1.3: Boronic acid **A2** (153 mg, 1.1 mmol), 3-bromoquinoline **66** (0.14 mL, 1.0 mmol), $Pd_2(dba)_3$ (9.2

mg, 0.01 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.7 mL) and K_3PO_4 (1.3 mL); reflux 24 h; eluent MeOH:EtOAc 1:4 v/v gave **A10** as a cream solid (160 mg, 72%); mp 267.5-269.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.08 (1H, d, *J* = 2.4 Hz), 8.67 (2H, s), 8.24 (1H, d, *J* = 2.3 Hz), 8.16 (1H, d, *J* = 8.4 Hz), 7.89 (1H, d, *J* = 8.2 Hz), 7.75 (1H, t, *J* = 7.7 Hz), 7.61 (1H, t, *J* = 7.6 Hz), 5.22 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2, 156.4, 154.8, 153.8, 148.5, 146.5, 130.7, 129.2, 128.7, 128.4, 128.1, 127.0, 119.2. MS (ES^+) *m/z* 223.5 ($[M+1]^+$). Anal. Calcd. for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.00; H, 4.40; N, 24.86%.

Conditions C: Boronic acid **A2** (236 mg, 1.7 mmol), 3-bromoquinoline **66** (0.2 mL, 1.5 mmol), $Pd(OAc)_2$ (19 mg, 0.085 mmol), D-*t*-BPF (38 mg, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reflux 65 h; eluent EtOAc gave impure **A10** as a red/brown solid. To remove the colouration (thought to be caused by D-*t*-BPF) the product was columned again to give **A10** as a white solid (149 mg, 45%), spectroscopically identical with the sample previously described.

Conditions A: Boronic acid **A2** (236 mg, 1.7 mmol), 3-bromoquinoline **66** (0.2 mL, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reaction time 65 h; eluent methanol:EtOAc (1:9 v/v) and recrystallization from toluene/hexane gave **A10** as a white solid (72 mg, 22%), spectroscopically identical with the sample previously described.

2-(2-Aminopyrimidin-5-yl)-pyridine (A11)



Conditions D: Boronic acid **A2** (236 mg, 1.7 mmol), 2-iodopyridine **A4** (0.16 mL, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reflux 24 h then addition of boronic acid **A2** (236 mg, 1.7 mmol), further reflux for 48 h; eluent methanol:EtOAc (1:9 v/v) and recrystallization from toluene gave **A11** as a pale yellow crystalline solid (249 mg, 96%); mp 192.5-194.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (2H, s), 8.65 (1H, d, *J* = 4.1 Hz), 7.74 (1H, t, *J* = 8.0 Hz), 7.60 (1H, d, *J* = 8.0 Hz), 7.22 (1H, t, *J* = 6.1 Hz), 5.41 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 157.1, 153.3, 150.1, 137.1, 123.5, 122.3, 119.0. MS (ES^+) *m/z* 173.1 ($[M+1]^+$). Anal. Calcd. for $C_9H_8N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 62.64; H, 4.66; N, 32.79%.

Conditions B: Boronic acid **A2** (236 mg, 1.7 mmol), 2-iodopyridine **A4** (0.16 mL, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), *t*-Bu_3P (30 mg, 0.15 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reaction time 65 h; eluent MeOH:EtOAc 1:9 v/v gave **A11** as an off-white solid (145 mg, 56%), spectroscopically identical with the sample previously described.

Table A1.3: Boronic acid **A2** (160 mg, 1.15 mmol), 2-bromopyridine **78** (0.10 mL, 1.05 mmol), $Pd_2(dba)_3$ (9.6 mg, 0.011 mmol), PCy_3 (7.0 mg, 0.025 mmol), 1,4-dioxane (2.7 mL) and K_3PO_4 (1.3 mL); reflux 3 h; recrystallization from toluene gave **A11** as a white crystalline solid (135 mg, 75%), spectroscopically identical with the sample previously described.

2-Amino-5-pyrazinylpyrimidine (A12)

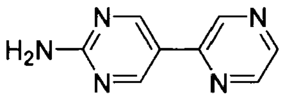
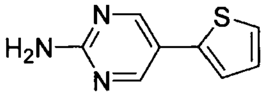


Table A1.3: Boronic acid **A2** (153 mg, 1.1 mmol), iodopyrazine **A5** (0.1 mL, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.7 mL) and K_3PO_4 (1.3 mL); reflux 2.5 h; recrystallization from toluene gave **A12** as a white solid (126 mg, 72%); mp 213.0-215.5 °C, lit. mp[23] 213-216°C. ^1H NMR (500 MHz, DMSO-d_6) δ 9.16 (1H, d, J = 1.5 Hz), 8.97 (2H, s), 8.62 (1H, m), 8.52 (1H, d, J = 2.4 Hz), 7.16 (2H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.9, 156.7, 144.8, 144.1, 142.6, 140.5, 118.2. MS (EI) *m/z* 173.0 (M^+). Anal. Calc. for $C_8H_7N_5$: C, 55.48; H, 4.07; N, 40.44. Found: C, 55.24; H, 4.02; N, 40.77%.

Conditions B: Boronic acid **A2** (236 mg, 1.7 mmol), iodopyrazine **A5** (0.15 mL, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reflux 65 h; eluent EtOAc gave **A12** as a white solid (155 mg, 60%), spectroscopically identical with the sample previously described.

Table A1.3: Boronic acid **A2** (236 mg, 1.7 mmol), chloropyrazine **A17** (0.13 mL, 1.5 mmol), $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol), PCy_3 (10.1 mg, 0.036 mmol), 1,4-dioxane (2.7 mL) and K_3PO_4 (1.3 mL); reflux 2.5 h; recrystallization from toluene gave **A12** as an off-white solid (158 mg, 61%), spectroscopically identical with the sample previously described.

2-(2-Aminopyrimidin-5-yl)-thiophene (A13)



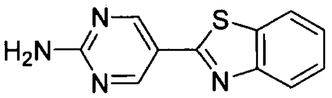
Conditions D: Boronic acid **A2** (236 mg, 1.7 mmol), 2-iodothiophene **A6** (0.17 mL, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reflux 24 h then addition of boronic acid **A2** (236 mg, 1.7 mmol), further reflux for 48 h; eluent methanol:EOAc (1:9 v/v) and recrystallization from toluene gave **A13** as a pale yellow solid (203 mg, 76%); mp 171.2-172.9 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (2H, s), 7.30 (1H, dd, J = 5.1, 1.2 Hz), 7.18 (1H, dd, J = 3.6, 1.2 Hz), 7.09 (1H, dd, J = 5.2, 3.6 Hz), 5.14 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 155.7, 137.9, 128.3, 124.8, 122.9, 119.6. MS (EI) *m/z* 177.0 (M^+). Anal. Calc. for $C_8H_7N_3S$: C, 54.22; H, 3.98; N, 23.71. Found C, 54.05; H, 3.93; N, 23.60%.

Conditions B: Boronic acid **A2** (236 mg, 1.7 mmol), 2-iodothiophene **A6** (0.17 mL, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reflux 65 h; eluent methanol:EtOAc (1:9 v/v), recrystallization from toluene/hexane to give **A13** as a pale yellow solid (131 mg, 49%), spectroscopically identical with the sample previously described.

Table A1.3: Boronic acid **A2** (153 mg, 1.1 mmol), 2-iodothiophene **A6** (0.11 mL, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.7 mL) and K_3PO_4 (1.3 mL); reflux 3 h; recrystallization from toluene gave **A13** as a beige solid (66 mg, 37%), spectroscopically identical with the sample previously described.

Table A1.3: Boronic acid **A2** (153 mg, 1.1 mmol), 2-bromothiophene **141** (0.1 mL, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.7 mL) and K_3PO_4 (1.3 mL); reflux 24 h; eluent EtOAc gave **A13** as a yellow solid (46 mg, 26%), spectroscopically identical with the sample previously described.

2-Amino-5-benzothiazol-2-ylpyrimidine (A14)



Conditions B: Boronic acid **A2** (236 mg, 1.7 mmol), 2-iodobenzothiazole **A7** (342 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reflux 65 h; eluent EtOAc followed by recrystallization from toluene/hexane gave **A14** as an orange solid (136 mg, 40%); mp 267.0-269.5 °C. ^1H

NMR (400 MHz, DMSO-d_6) δ 8.89 (2H, s), 8.11 (1H, d, *J* = 7.8 Hz), 7.98 (1H, d, *J* = 8.1 Hz), 7.51 (1H, t, *J* = 7.9 Hz), 7.44 (2H, s), 7.42 (1H, t, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.3, 163.5, 157.1, 153.3, 133.6, 126.6, 125.1, 122.2, 122.2, 116.4. MS (EI) *m/z* 227.9 (M^+). HRMS (EI) calcd. for $C_{11}H_8N_4S$ 228.0470, found 228.0473.

Table A1.3: Boronic acid **A2** (153 mg, 1.1 mmol), 2-iodobenzothiazole **A7** (628 mg, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.7 mL) and K_3PO_4 (1.3 mL); reflux 24 h; recrystallization from toluene gave **A14** as an orange-brown solid (102 mg, 45%), spectroscopically identical with the sample previously described.

Table A1.3: Boronic acid **A2** (153 mg, 1.1 mmol), 2-bromobenzothiazole **A18** (214 mg, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.7 mL) and K_3PO_4 (1.3 mL); reflux 30 h; eluent EtOAc gave **A14** as a light brown solid (76 mg, 33%), spectroscopically identical with the sample previously described.

3-Bromo-6-(2-aminopyrimidin-5-yl)-pyridine (A15)

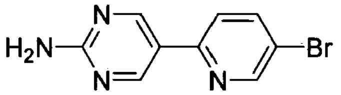
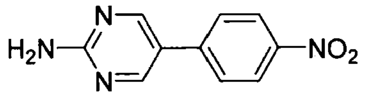


Table A1.3: Boronic acid **A2** (96 mg, 0.69 mmol), 5-bromo-2-iodopyridine **A8** (179 mg, 0.63 mmol), $Pd_2(dba)_3$ (5.8 mg, 0.007 mmol), PCy_3 (4.2 mg, 0.015 mmol), 1,4-dioxane (2.7 mL) and K_3PO_4 (1.3 mL); reflux 2 h; recrystallization from toluene gave **A15** as a white solid (77 mg, 49%); mp 237.0-239.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 (2H, s), 8.68 (1H, d, *J* = 2.3 Hz), 8.05 (1H, dd, *J* = 8.6, 2.5 Hz), 7.85 (1H, d, *J* = 8.6 Hz), 7.07 (2H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.7, 156.5, 151.8, 150.1, 139.6, 120.2, 119.8, 118,0. MS (ES^+) *m/z* 251.2, 253.2 ($[M+1]^+$). Anal. Calc. for $C_9H_7BrN_4$: C, 43.05; H, 2.81; N, 22.31. Found: C, 43.21; H, 2.78; N, 21.89%.

Conditions B: Boronic acid **A2** (236 mg, 1.7 mmol), 5-bromo-2-iodopyridine **A8** (426 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), *t*-Bu_3P (0.02 mL, 0.080 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reflux 65 h; eluent EtOAc and recrystallization from toluene gave **A15** as an off-white solid (103 mg, 27%), spectroscopically identical with the sample previously described.

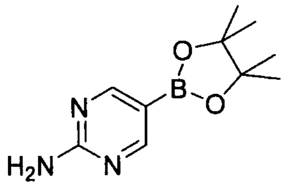
4-(2-Aminopyrimidin-5-yl)-nitrobenzene (A16)



Conditions A: Boronic acid **A2** (196 mg, 1.4 mmol), 1-iodo-4-nitrobenzene **A9** (311 mg, 1.25 mmol), $Pd(PPh_3)_2Cl_2$ (50 mg, 0.071 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reflux 65 h; eluent methanol:EtOAc 1:9 v/v, gave **A16** as an orange solid (113 mg, 42%); mp 279.5-281.0 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 8.74 (2H, s), 8.25 (2H, d, J = 9.2 Hz), 7.94 (2H, d, J = 9.2 Hz), 7.09 (2H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.5, 156.8, 146.0, 142.2, 125.8, 124.2, 119.6. MS (EI) *m/z* 216.00 (M^+). Anal. Calc. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.91. Found: C, 55.81; H, 3.74; N, 25.95%.

Table A1.3: Boronic acid **A2** (153 mg, 1.1 mmol), 1-bromo-4-nitrobenzene **A18** (202 mg, 1.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), PCy_3 (6.7 mg, 0.024 mmol), 1,4-dioxane (2.7 mL) and K_3PO_4 (1.3 mL); reflux 1 h; recrystallization from toluene gave **A16** as a brown crystalline solid (93 mg, 43%), spectroscopically identical with the sample previously described.

Representative procedure for the synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (A3)



2-Amino-5-bromopyrimidine **A1** (0.50 g, 2.87 mmol), bis(pinacolato)diboron (1.80 g, 7.18 mmol), KOAc (2.3 g, 23 mmol), $Pd(OAc)_2$ (15 mg, 0.14 mmol) and degassed anhydrous DMF (10 mL) was heated to 90 °C for 17 hours. The reaction was allowed to cool and the DMF was removed in vacuo. EtOAc was added (25 mL) and the organic layer was washed with brine (25 mL), and extracted with EtOAc (2 × 25 mL), the organic phase was dried over $MgSO_4$. The organic solvents were removed in vacuo and the resulting yellow solid appeared to be compound **A3**, from ^1H, ^{11}B and ^{13}C NMR evidence, alongside a second boron-containing species. Recrystallization from hexane did not improve the purity. Column chromatography with eluent EtOAc also had little effect on isolating the boronic ester **A3** with increased purity. Therefore in further work compound **A3** was reacted in situ.

Typical Procedure for the Suzuki-Miyaura Cross-Coupling Reactions in Table A1.2

2-Amino-5-bromopyrimidine **A1** (1.0 equiv.), bis(pinacolato)diboron (2.5 equiv.), $Pd(OAc)_2$ (5 mol% **A1**) and degassed 1,4-dioxane were stirred at room temperature for 30 min under argon. KOAc (12 equiv.) was added and the reaction was stirred at 80 °C for 17 h. The reaction mixture was allowed to cool to room temperature before addition of the heteroaryl halide (1.0 equiv.), $Pd(PPh_3)_2Cl_2$ (ca. 5 mol% Ar-X), *t*-Bu_3P (ca. 5 mol% Ar-X), and degassed Na_2CO_3 (1M, 3 equiv.), and the reaction was stirred at reflux for 65 h. The reaction mixture was cooled and filtered to remove any palladium salts; the solvent was then removed in vacuo, EtOAc 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 an additional recrystallization of the product was necessary to obtain a pure compound.

A1.5 References for Appendix 1

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