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METAL-CATALYSED CROSS-COUPLING REACTIONS OF NITROGEN HETEROCYCLES

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METAL-CATALYSED CROSS-COUPLING REACTIONS OF NITROGEN HETEROCYCLES

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DECLARATION

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CONTENTS

ABSTRACT
Metal-Catalysed Cross-Coupling Reactions of Nitrogen Heterocycles

Described herein are copper-catalysed N-C heteroarylations of benzimidazole, 1-methylbenzimidazolone, imidazole and pyrrole. The products of these reactions then undergo palladium-catalysed C-C cross-couplings with aryl or heteroarylboronic acids under Suzuki-Miyaura conditions to provide a rapid entry to tris(hetero)aryl scaffolds comprising two or three *N*-heterocyclic rings. The sequential N-C and C-C couplings can be performed in a one-pot process.

1,5-Di(hetero)arylated-pyridin-2(1*H*)-one derivatives have been synthesised in good yields starting from (2-fluoro-5-pyridyl)boronic acid. The sequence comprises three steps: (i) palladium-catalysed Suzuki-Miyaura reaction; (ii) basic hydrolysis; (iii) copper-catalysed C-N coupling. X-ray crystal structures are reported for selected pyridin-2(1*H*)-one derivatives. These compounds are of interest as new scaffolds for drug discovery.

A one-pot synthesis of 2-chloro-3,4-diiodopyridine from 2-chloropyridine is described *via* a Directed *ortho* Metallation (D*o*M)/Halogen Dance (HD) mechanism in 26-28% yields. By performing sequential iterative Suzuki-Miyaura cross-couplings using a variety of functionalised heteroaryl and arylboronic acids, a series of novel 2,3,4-triheteroarylpyridine scaffolds have been accessed in synthetically viable yields, including sterically hindered derivatives. An iterative two-fold Sonogashira/Suzuki-Miyaura reaction sequence gave access to 5-[3,4-bis(2-phenylethynyl)pyridine-2-yl]-2-fluoropyridine in 48% overall yield.

Disclosed is a novel route towards benzimidazolo[1,2-*f*]phenanthridines starting from 4-*tert*-butyl-*N*-(2-iodophenyl)benzamide *via* a intermolecular palladium-catalysed N-C bond formation and dehydration to form 2-(4-*tert*-butylphenyl)-1-(2-bromophenyl)-1*H*-benzo[*d*]imidazole. Performing an intramolecular C-H activation reaction on this provided 6-*tert*-butylbenzimidazolo[1,2-*f*]phenanthridine. This compound could be of interest to materials science or as a new scaffold for drug discovery.

Synthesis of novel soluble, shielding auxiliary ligand 4-(4-(2-ethylhexyloxy)-2,6-dimethylphenyl)pyridine-2-carboxylic acid (G1pic) has been achieved *via* a five step synthesis from commercially available starting materials utilising the Suzuki-Miyaura reaction on demanding substrates. A route towards a more shielded auxiliary ligand have been explored eventually providing 3-(4-pyridyl)-1,5-bis(4-(2-ethylhexyloxy)phenyl)-2,4-dimethylbenzene as an intermediate for future work. Ir(III) complexes have been synthesised with G1pic and picolinic acid.

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DEDICATION

This thesis is dedicated to my loving wife Louise. Without her endless love, support, time and often unacknowledged effort none of this would have been possible.

"If you want to have good ideas you must have many ideas. Most of them will be wrong, and what you have to learn is which ones to throw away."

LINUS PAULING

PUBLICATIONS

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

Siddle, J. S.; Batsanov, A. S.; Bryce, M. R. **Sequential Metal-Catalyzed *N*-Heteroarylation and C-C Cross-Coupling Reactions: An Expedient Route to Tris(hetero)aryl Systems**, *Eur. J. Org. Chem.* **2008**, 2746-2750.

Daykin, L. M.; Siddle, J. S.; Ankers, A. L.; Batsanov, A. S.; Bryce, M. R. **Iterative and Regioselective Cross-Couplings of 2-Chloro-3,4-diiodopyridine Leading to 2,3,4-Triheteroarylpyridines**, *Tetrahedron* **2010,** *66*, 668-675.

Siddle, J. S.; Batsanov, A. S.; Caldwell, S. T.; Cooke, G.; Bryce, M. R. **Divergent Synthesis of Arylated Pyridin-2(1*H*)-one Derivatives *via* Metal-Catalysed Cross-Coupling Processes**, *Tetrahedron* **2010,** *66*, 6138-6149.

ABBREVIATIONS

AcO	Acetate
AcOH	Acetic Acid
APCI	Atmospheric Pressure Chemical Ionisation
APGC	Atmospheric Pressure Gas Chromatography
Ar	Aryl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bu	Butyl
Chxn-Py-Al	(1R,2R,7E,14E)-*N*,*N*'-bis((pyridin-2-yl)methylene)cyclohexane-1,2-diamine
CuFAP	Copper Exchanged Fluorapatite
Cy	Cyclohexyl
Cy-JohnPhos	2-(Dicyclohexylphosphino)biphenyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DFT	Density Functional Theory
DMA	*N*,*N*-Dimethylacetamide
DMCDA	*N*,*N*'-dimethylcyclohexanediamine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulphoxide
D*o*M	Directed *ortho* metallation
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
D^{t}BPF	1,1'-Bis(di-*tert*-butylphosphino)ferrocene
DTPF	1,1'-Bis(di-*ortho*-tolylphosphino)ferrocene
EI	Electron ionisation
ES	Electrospray
Et	Ethyl
EtOAc	Ethylacetate
EQE	External quantum efficiency
FAP	Fluorapatite

Firpic	Iridium(III)[bis(4,6-difluorophenyl)pyridinato-*N*,C²']picolinate
FTIR	Fourier Transform Infrared Spectroscopy
G0	Generation 0: mesityl shielding
G1	Generation 1: 4-(2-ethylhexyloxy)-2,6-dimethylphenyl shielding
G2	Generation 2: 3-(1,5-bis(4-(2-ethylhexyloxy)phenyl)-2,4-dimethylbenzenyl) shielding
GC	Gas chromatography
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HD	Halogen dance
Het	Heteroaryl
HPLC	High performance liquid chromatography
8HQ	8-Hydroxyquinoline
Hz	Hertz
ITO	Indium tin oxide
JosiPhos	(*R*)-1-[(*S*$_P$)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine
KHMDS	Potassium bis(trimethylsilyl)amide
LiHDMS	Lithium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
Me	Methyl
MeCN	Acetonitrile
MS	Mass spectrometry
MIDA	*N*-Methyliminodiacetic acid
mCPBA	*meta*-Chloroperbenzoic acid
neocup	2,9-Dimethyl-1,10-phenanthroline
NMR	Nuclear magnetic resonsonace spectroscopy
OLED	Organic light emitting diode
OTf	Triflate
PEG	Polyethylene glycol
Ph	Phenyl
phen	1,10-Phenanthroline
pic	Picolinic acid

|	
PivOH	Pivalic acid
PMB	Paramethoxybenzyl ether – protecting group
Pr	Propyl
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
S_NAr	Nucleophilic aromatic substitution reaction
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBAF	Tetra-*n*-butylammonium fluoride
TEAC	Bis(tetraethylammonium) carbonate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
tol	Tolyl
UV	Ultraviolet
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XPS	X-ray photoelectron spectroscopy

CHAPTER 1 - INTRODUCTION

Convenience in the synthesis of families of multi-heteroaryl systems has been a goal for chemists seeking to create highly functionalised compounds to screen for pharmaceutical and agrochemical studies. Cross-coupling methodologies have, to an extent, addressed these needs by enabling functionality to be incorporated into starting materials to quickly create large families of highly functionalised compounds using few steps under mild, catalysed reaction conditions. Suzuki, Sonogashira, Heck, Stille, and Negishi carbon-carbon cross-coupling reactions have been used to this effect by a number of groups by using known biologically active heterocycles as the skeleton for these compounds.[1] Carbon-heteroatom cross-coupling reactions have also experienced a renaissance of late thanks to pioneering work by Buchwald and Hartwig (palladium catalysed *N* & *O*-arylations with aryl halides and nitrogen or oxygen nucleophiles),[2] Buchwald (copper catalysed *N*-arylations with aryl halides)[3] and the groups of Chan, Lam and Evans (copper catalysed *N*, *O* & *S*-arylations with aryl boronic acids and esters).[4-6]

1.1   Cu-Catalysed C-N Cross-Coupling: Ullmann Reaction

From the dawn of the 20th century, cross-coupling reactions have been studied and improved upon resulting in one of the most rapid growing fields in organic chemistry.[7] In 1901, Fritz Ullmann published work on the homo-coupling of nitro substituted aryl halides[8] leading to many variations on the theme of Cu mediated C-C bond formation.[7,9-11] Subsequently his 1903 publication on the condensation of amines with aryl halides[12] and work on the amidation of aryl halides by Goldberg[13] paved the way for future successes in C-N and C-heteroatom bond forming reactions.

The Ullmann and Goldberg reactions rely usually (although not always) on stoichiometric use of copper powder or copper salts, strong bases and high reaction temperatures.. The limitations on functionality imposed by the reaction conditions, the low and often unpredictable yields and the associated problems in dealing with large amounts of copper waste limited widespread use. The ability to synthesise *N*-arylheterocycles, diarylamines, diarylamides, diarylethers and diarylthioethers in an efficient manner is of great importance considering their incorporation in a vast amount of natural products, biologically active compounds, drugs and agrochemicals.

Among the many reports of improvements in the Ullmann condensation reaction, the increased solubility of the copper source was thought to play a key role. Amide co-solvents such as DMF effectively solvate cuprous salts and purportedly increase stability of the catalyst.[14-15] It was noted that the Ullmann condensation of potassium phenoxide with bromobenzene in diglyme suffered from reduced yields after treatment of the solvent with LiAlH$_4$. Upon investigation, the source of the rate enhancement was found to be a diester impurity in the diglyme, absence of which not only reduced yields but resulted in the observed precipitation of copper.[16] An observed rate enhancement in the Ullmann-type methanolysis of aryl bromides was attributed to an increased solubility of a catalytic copper species with esters, with a tentative assignment of a tetrahedral copper complex **1** participating in the reaction (Scheme 1).[17]
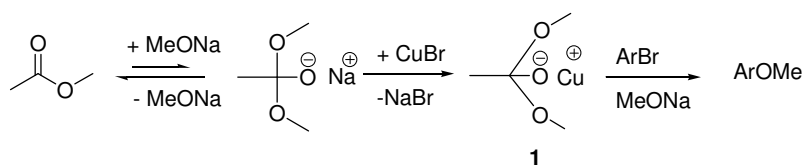
Scheme 1:   Ate complex **1**.[17]

The use of amines as ligands for copper mediated Ullmann-type reactions had been reported previously,[18] although publications by Goodbrand,[19] Buchwald[20,3] (1,10-phenanthroline) and Ma[21] (α-amino acids) are often credited as the genesis of the ligand-accererated Ullmann reaction.[22] Catalytic Ullmann-type reactions have been reviewed by Ley and Thomas,[22] and by Monnier and Taillefer.[23]

1.1.1   Mechanism

Both the copper-catalysed amination (Ullmann) and amidation (Goldberg) of aryl halides come under the banner of "Ullmann-like", varying in the nature of the nitrogen nucleophile. These two reactions share common intermediates and in this work, both shall be assessed.

The ligand-accelerated Ullmann reaction occurs between aryl halides or pseudohalides and heteroatom nucleophiles with the *ipso*-substitution of the halide with the nucleophile. The observed trend for reactivity of the electrophile is Ar-I > Ar-Br > Ar-Cl >> Ar-F, consistent with the increasing strength of the carbon-halogen bond as the group is

ascended. This is the opposite trend to that observed for nucleophilic aromatic substitution (S_NAr) reactions whereby increased rates are observed with the more electronegative halogens. The S_NAr reaction occurs *via* a Meisenheimer intermediate (Scheme 2) where the increase in electron density from the *ipso*-addition of the nucleophile to the aryl halide is stabilised by the electron withdrawing ability of the halide and the resonance stabilisation of *ortho* and *para* nitro groups.[24]
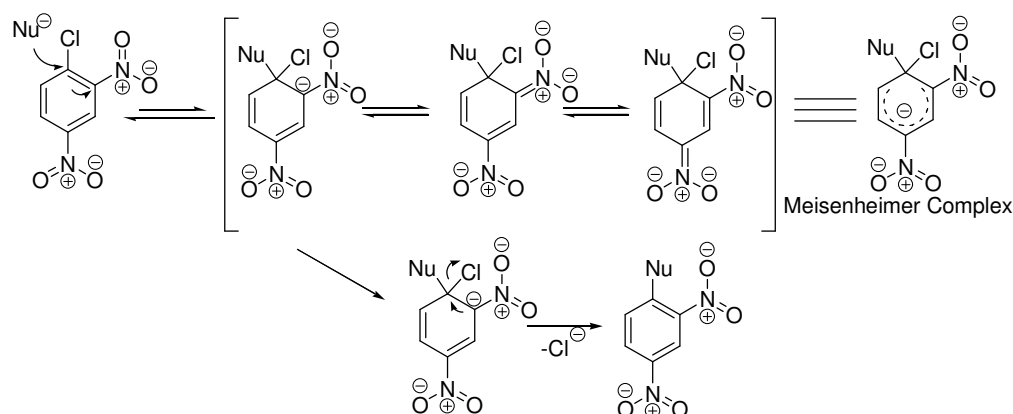
Scheme 2:   Meisenheimer Complex stabilisation in the S_NAr reaction.

Early work on the Ullmann reaction led to the proposal of a copper π-stabilisation of an *ipso*-substitution in a Meisenheimer-like transition state[16] (Scheme 3, A) which was discounted after evaluation of the ring substituents on the aryl halide.[25] Observations such as: the slight rate increasing effect of electron withdrawing groups on the aryl halide, the greater reactivity of more easily polarisable halogens, and a positive effect of *ortho*-chelating groups indicated a copper insertion into the C-X bond (Scheme 3, B).
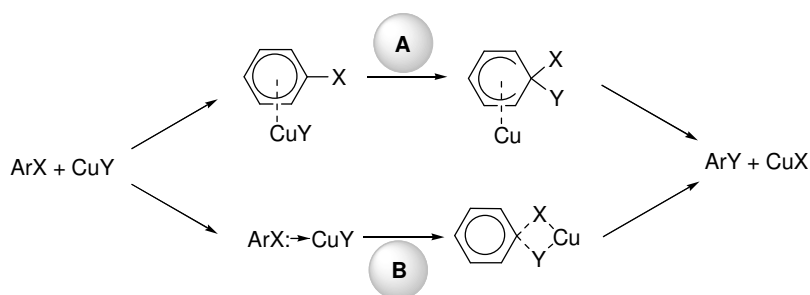
Scheme 3:   Proposed π-stabilisation or copper insertion pathways in the Ullmann reaction.[25]

Recently Cristau *et al.*[26] proposed two alternative catalytic pathways (Scheme 4) for this reaction based on an initial activation of either the aryl halide (path A) or the nucleophile (path B). Significant progress has been made in elucidating the nature of the nucleophile activation and the aryl halide activation steps by determining the order of activation, the nature of the active catalytic species and the effect of the ligand..
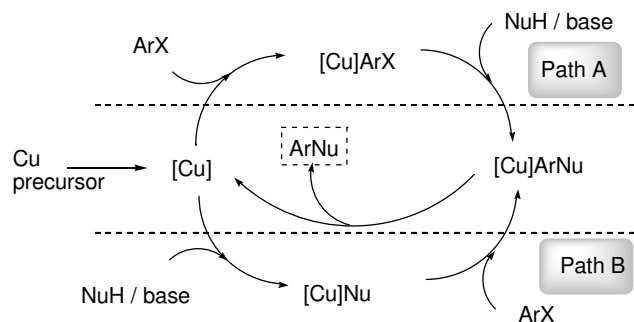
Scheme 4:   Two proposed catalytic cycles based on either an oxidative addition / nucleophilic substitution / reductive elimination cycle (Path A); or nucleophilic substitution / oxidative addition / reductive elimination cycle (Path B).

1.1.2   Nucleophile Activation

In 2005, Choudary *et al.*[27] proposed that imidazole coordination to copper exchanged fluorapatite (CuFAP) occurred prior to aryl halide activation and used XPS and FTIR studies to prove their claims.[27-28] In 2007, Altman *et al.*[29] speculated on the formation of a $Cu(II)L_2$ species *in situ* followed by coordination of the imidazole nucleophile and subsequent deprotonation . Aryl halide activation onto this is followed by reductive elimination steps. Whilst investigating a butadienylphosphine ligand for the arylation of phenols and pyrazole, a crystal structure of a $Cu(II)L_2$ **2** species was obtained by Kaddouri *et al.*[30] They conducted ^{31}P NMR studies on the stoichiometric reaction of **2** with pyrazole and base and concluded that $[Cu(II)LNu]^-M^+$ species **3** was formed as a result, which led to 100% yield of ArNu after treatment with PhBr (Scheme 5). They found no change in the ^{31}P NMR signal when reacting **2** with PhBr thereby adding evidence in favour of pathway B (Scheme 4).
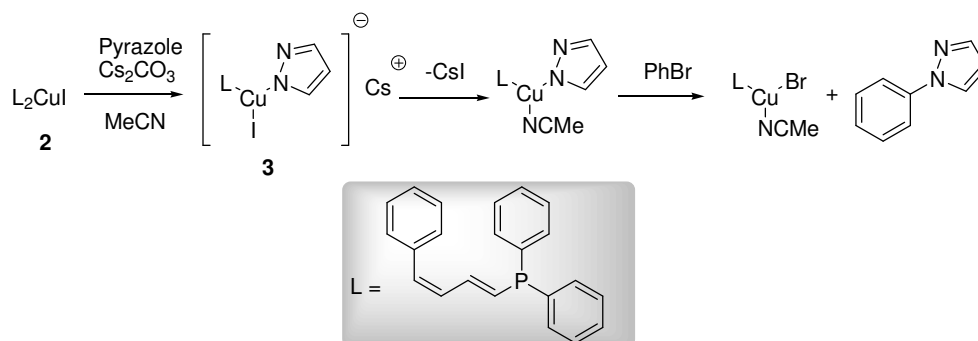
Scheme 5: ^{31}P NMR studies on the role of nucleophile coordination prior to aryl halide activation.

For the amidation reaction, Strieter *et al.*[31-32] conducted kinetic studies and proposed that copper complex **4** is formed from CuI in high ligand concentrations, existing in an equilibrium with an isolable and characterisable iodo-bridging homo-dimer (see Scheme 6). When depronated by a base, a nucleophile can displace the halide from **4** to generate active copper amidate **5**. This allows the aryl halide activation step to become rate limiting. At lower concentrations of ligand, multiply amide ligated species **6** is formed which must dissociate and lose one amide *via* ligand coordination to give active amidate **5**. They showed that the aryl halide activation step is always rate limiting at high ligand concentrations, but did not firmly conclude the nature of the activation.
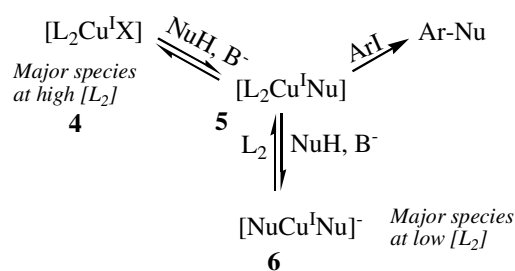
Scheme 6:   Proposed mechanism for generation of active amidate complex in amidation reaction. L_2 = trans-N,N'-dimethylcyclohexane-1,2-diamine (DMCDA), NuH = amide, B$^-$ = base, X = I.[32]

In 2008, Tye *et al.*[33] isolated crystals of imidate and amidate Cu(I) complexes from the room temperature reaction of [CuO^{t}Bu]$_4$ with a ligand and either phthalidimide or pyrrolidinone in THF. These structures clearly show the presence of two species: 1) a 3-coordinate $L_2Cu^INR_2$ complex 7 (where L_2 = 1,10-phenanthroline and NR_2 = phthalidimide) formed by sequential addition of L_2 then Nu to the reaction and 2) an ionic

species 8 with one cationic tetrahedral $[L_2CuL_2]^+$ and one anionic 2-coordinate $[Cu(NR_2)_2]^-$ (where L_2 = 1,10-phenanthroline and NR_2 = pyrrolidinone or L_2 = 4,4'-di-*tert*-butylbipyridine and NR_2 = phthalidimide) formed by addition of L_2 and NR_2 to the reaction at the same time.
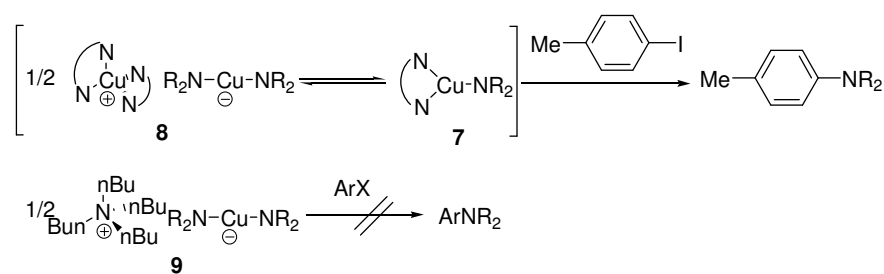
Scheme 7:   Equilibrium and reactions of isolated ionic **8** and neutral **9** copper amidate / imidate complexes with aryl halides.

They reported that aryl halide activation did not occur when the cation was changed to $[^nBu_4N]^+$ (giving with $[^nBu_4N][Cu(NR_2)_2]$ **9**) but did occur from both $[L_2CuL_2][Cu(NR_2)_2]$ 8 and $L_2Cu^INR_2$ 7. They conducted studies and concluded that $L_2Cu^INR_2$ 7 is the active species with an equilibrium existing between $L_2Cu^INR_2$ 7 and $[L_2CuL_2][Cu(NR_2)_2]$ 8 (Scheme 7).

1.1.3   Aryl halide Activation

Cohen *et al.* proposed a Cu(III) intermediate in the Ullmann-like halogen exchange reaction, from which ArCl is reductively eliminated from ArCu(III)Cl$_2$.[34] Much later, Cristau *et al.* discussed the mechanism of the ligand-accelerated Ullmann reaction.[26] They disproved involvement of radical intermediates through experimental studies and proposed a Cu(III) intermediate and associated oxidative addition/reductive elimination pathways. They noted that the ligands used in this study were σ–donor and π–accepting, thus potentially stabilising a Cu(III) transition state especially considering the high affinity expected for hard donor ligands (*i.e.* tertiary amines, etc.) to a hard acceptor such as Cu(III). Tye *et al.*[33] proposed three possible mechanisms for the reaction (Scheme 8) where the first (Path A) occurs *via* a direct activation of the aryl halide by $[L_2CuL_2][Cu(NR_2)_2]$ 8.[16] This was discounted as the reaction did not proceed when the counter-ion was exchanged (*vide supra*). Paths (B) and (C) both occur *via* the formation of $L_2Cu^INR_2$ 7

followed by an aryl halide activation by either electron transfer followed by either dissociation of halide from the aryl halide radical anion, or by oxidative addition to Cu(III). They discard path (B) due to limited evidence of radicals, either free or in a solvent cage. Computational studies suggested that a Cu(III) intermediate was accessible under mild reaction conditions and they conclude path (C) is most likely to occur by either a concerted oxidative addition (10 to 11) or by an internal electron transfer process (10 to 12).
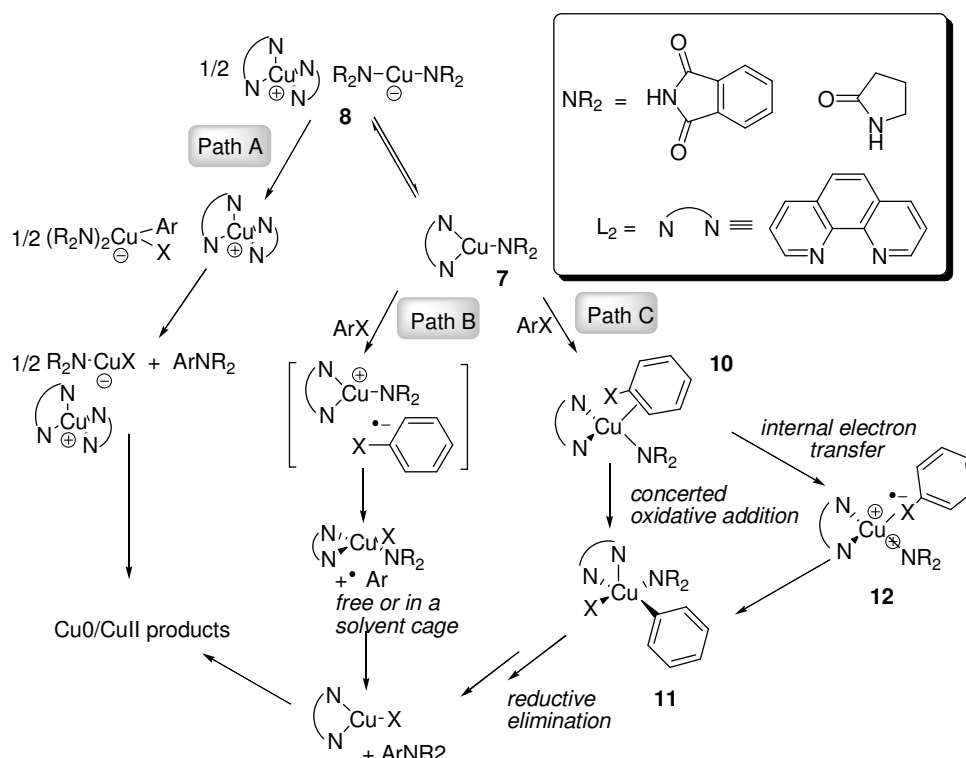
Scheme 8: Three mechanisms proposed by Tye *et al.*[33]
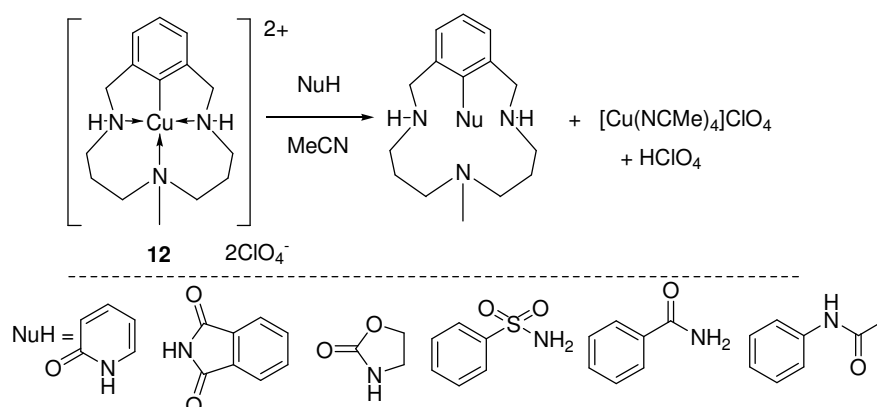
Scheme 9: *N*-arylation reaction of structurally defined Cu(III)-aryl complex **12** with nitrogen nucleophiles.

Zhang *et al.*[35] conducted a computational study on the copper-catalysed amidation of aryl halides by acetamide. They concluded that a trigonal L_2Cu^INHAc was the most reactive

species in the reaction mixture for the oxidative addition of the aryl halide (especially when L_2 = DMCDA) whilst the $Cu^I(NHAc)_2$ complex (favoured with low concentrations of L_2) is the least reactive and thereby retards oxidative addition. These conclusions support those reported experimentally by Strieter *vide supra*.[31-32]

Until 2008, no firm conclusion as to the nature of the aryl halide activation step had been established due to the rarity of Cu(III) species.[36-41] Huffman and Stahl[42] reported that the square planar Cu(III)-aryl species **12**[39] reacted at room temperature within 2 h with a variety of nitrogen nucleophiles (Scheme 9). This lends great support to the involvement of Cu(III) in the Ullmann reaction. In this case, the oxidative addition stage has essentially occurred before the nucleophile activation, but nevertheless shows that such species can exist and react. They reported that more acidic nucleophiles reacted faster, indicating that the nucleophilic substitution occurs first *via* a deprotonation of the nucleophile, rather than a bimolecular coordination followed by deprotonation sequence. Phipps *et al.* proposed a Cu(III) intermediate in an oxidative direct-arylation of indoles and argued that Cu(III) (formed from oxidation by iodine(III)) is d_8 like Pd(II) so ought to facilitate metalation like the electrophilic palladium species.[43] Their proposal is that the nucleophilic indole attacks the electrophilic Cu(III) species and subsequent reductive elimination gives the C3-arylated indole species (Scheme 10). This postulate does not, however, translate to Hartwig's proposed pathway for the Ligand-Accelerated Ullmann reaction,[33] where the nucleophile is added to the Cu(I) species *via* a nucleophilic substitution which then, by an oxidative addition step, gives the Cu(III) by reaction with the electrophile (Scheme 8, Path C).
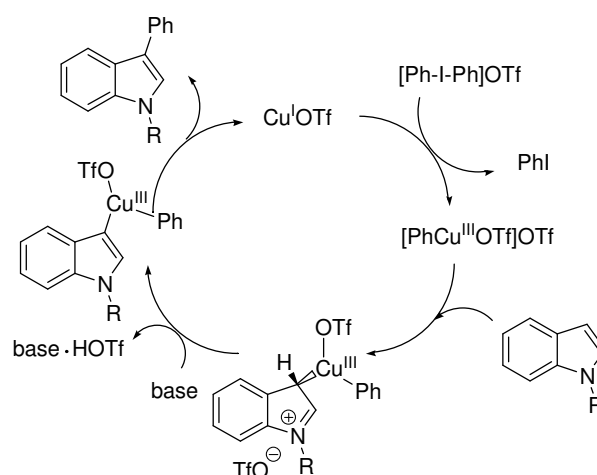
Scheme 10:   Cu(III) participating in catalytic C-3 arylation of indole.[43]

1.1.4　Precatalyst

In the early Ullmann reaction many copper sources have been applied from the Cu(0), Cu(I) and Cu(II) oxidation states including Cu bronze, CuI, CuBr, CuCl, $CuCl_2$, $(CuOTf)_2$.benzene and $Cu(OAc)_2$.[8,12,44,13,3] All sources seemed to promote the reaction, with Cu(I) salts giving slightly greater performances. Mansour *et al.*[45] published an electrochemical study on the activation of aryl halides by Cu(0) and 1,10-phenanthroline and concluded that electrochemically generated $Cu^0(phen)$ can be transformed into $Cu^I(phen)S_2^+$ (where S = acetonitrile solvent) by the reduction of an aryl halide. The implication is that this complex is then free to undergo the catalytic Ullmann cross-coupling as an active Cu(I) species, thereby explaining how Cu(0) can promote Ullmann reactions.

1.1.5　Ligands

A variety of ligands accelerate Ullmann-type reactions. Most recent examples tend to be bidenatate, although mono- and even polydentate ligands have been employed. Coordination to Cu is achieved *via* N, O or P atoms and many useful reviews have been published.[1,7,22-23] No one ligand has been adopted for all transformations, indicating the challenges in the Ullmann reaction, as well as the breadth of substrate variety sought by modern chemistry.

Esters have been reported as potential ligands[16-17] *vide supra*, although utilisation of these in Ullmann reactions is impractical considering the strength of the base often required, but the idea of using ligating small molecules as ligands to solubilise the catalyst was further expanded on with examples of crown ethers giving increased yields in some cases.[46]

A 1997 publication by Marcoux *et al.*[20] showed a strong rate acceleration effect in the formation of diarylethers from aryl iodides when using catalytic amounts of EtOAc in conjunction with $(CuOTf)_2$.benzene precatalyst. In this case, the employment of Cs_2CO_3 as the base and toluene as solvent led to highly efficient conversion (Scheme 11). Aryl bromides and less nucleophilic phenols were active under these conditions when 1-naphthoic acid was used as an additive, which is thought to aid the solubility of the copper catalyst by forming a copper-naphtholate complex. More recently, a three-component catalytic system based on CuI, oxalyldihydrazide, and hexane-2,5-dione has been found to promote the coupling of benzimidazoles with aryl bromides and iodides.[47]
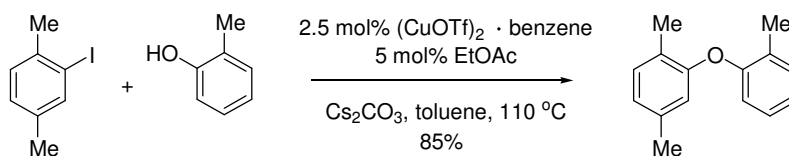
Scheme 11: Ligand acceleration by EtOAc in formation of diarylethers.

Goodbrand and Hu published the synthesis of hole-conducting triarylamines using catalytic CuCl and 1,10-phenanthroline (phen) as a ligand which substantially lowered the temperature required for the conversion when compared to classic conditions, but was limited to aryl iodides at this lower temperature (Scheme 12).[19] In the same year, Buchwald published the arylation of imidazoles and benzimidazole using 1,10-phenanthroline as the ligand with his previously reported Cu(OTf)$_2$.benzene[20] complex as copper source.[3] Of note are good yields using unactivated and sterically hindered *ortho*-bromoxylene as electrophile when using dba as an additive (Scheme 13). Both authors proposed increased solubility as a key effect of the ligand but also emphasised the complexing ability of the two pyridyl nitrogens leading to a stabilisation of the active species. Buchwald also proposed that the phen ligand stops the multiple chelation of imidazole to the copper leading to inactive copper species.[3]
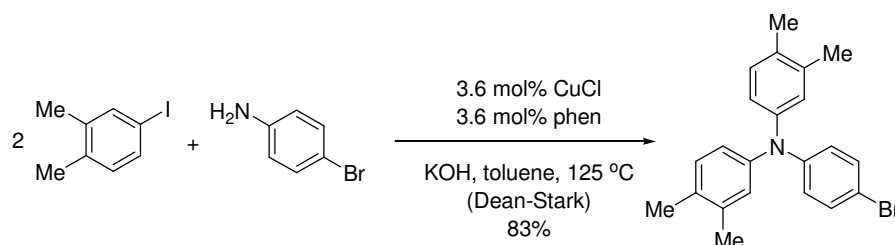
Scheme 12: 1,10-Phenanthroline as the ligand for double *N*-arylation of anilines.
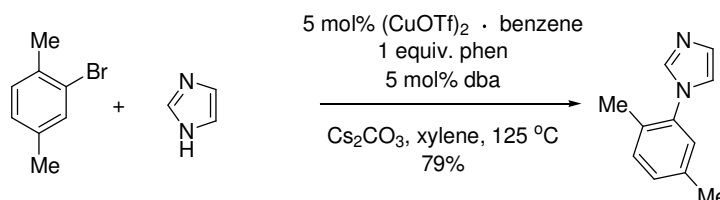
Scheme 13: 1,10-Phenanthroline as the ligand for the *N*-arylation of imidazole.

Gujadhur used preformed Cu(PPh$_3$)$_3$Br,[48] Cu(phen)(PPh$_3$)Br and Cu(neocup)(PPh$_3$)Br[49] species (Scheme 14) in the coupling of aryl halides to aryl- and diarylamines. Although this system was compatible with unactivated aryl chlorides, yields were low and intolerance to *ortho*-steric hindrance was observed. A study of various ligands for the

arylation of arylamines was undertaken by Kelkar[50] showing a good yields for 2,2'-bipyridines, pyridine, monophosphines and some bisphosphines (Scheme 15).
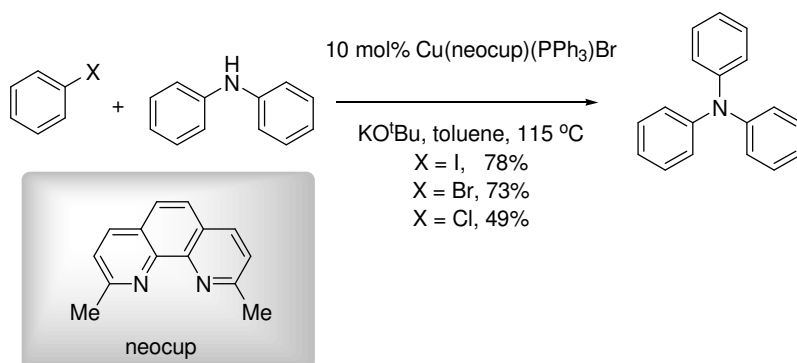
Scheme 14: Neocup as the ligand for the *N*-arylation of diarylamines with aryl halides.
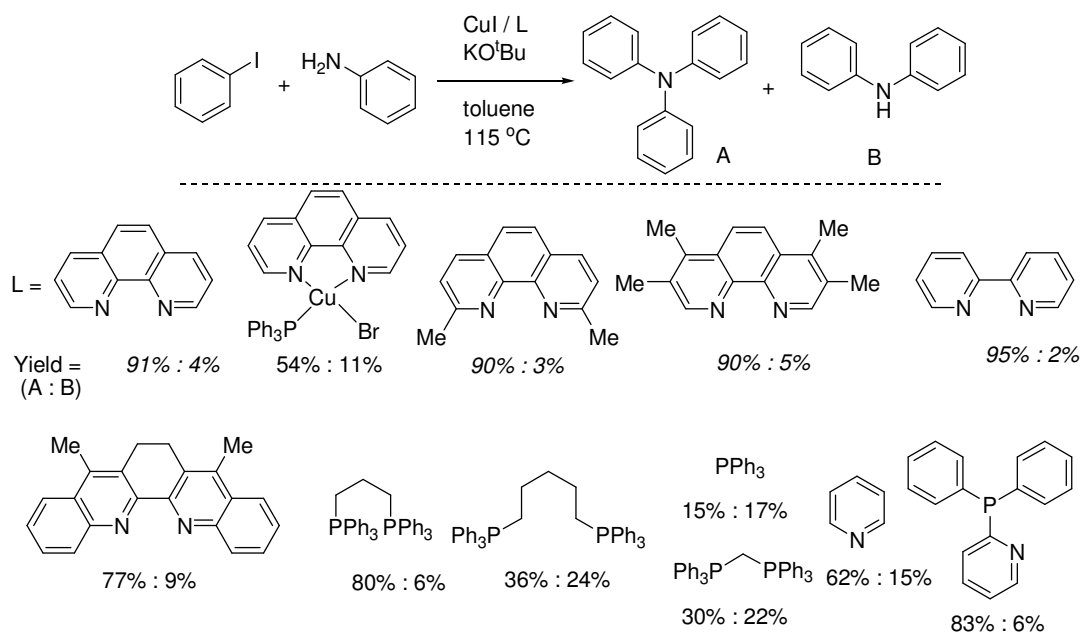
Scheme 15: *N*-Arylation of aniline showing yield improvement with certain chelating ligands.

1,10-Phenanthroline and its derivatives have been widely employed for the arylation of NH-heterocycles, arylamines and amides. The 2,2'-bipyridine framework allows bidentate Cu coordination and isolation of these copper species has been accomplished.[33] Modifications to 1,10-phenanthroline have included neocup[49] and 3,4,7,8-tetramethyl-1,10-phenanthroline (Scheme 15).[50] Buchwald demonstrated that 4,7-dimethoxy-1,10-phenanthroline was superior to 1,10-phenanthroline in the arylation of imidazoles.[29] Using this ligand and with optimised conditions, coupling at relatively low temperatures was achieved with imidazoles, benzimidazoles and hydroxypyridine derivatives.[29,51-52]
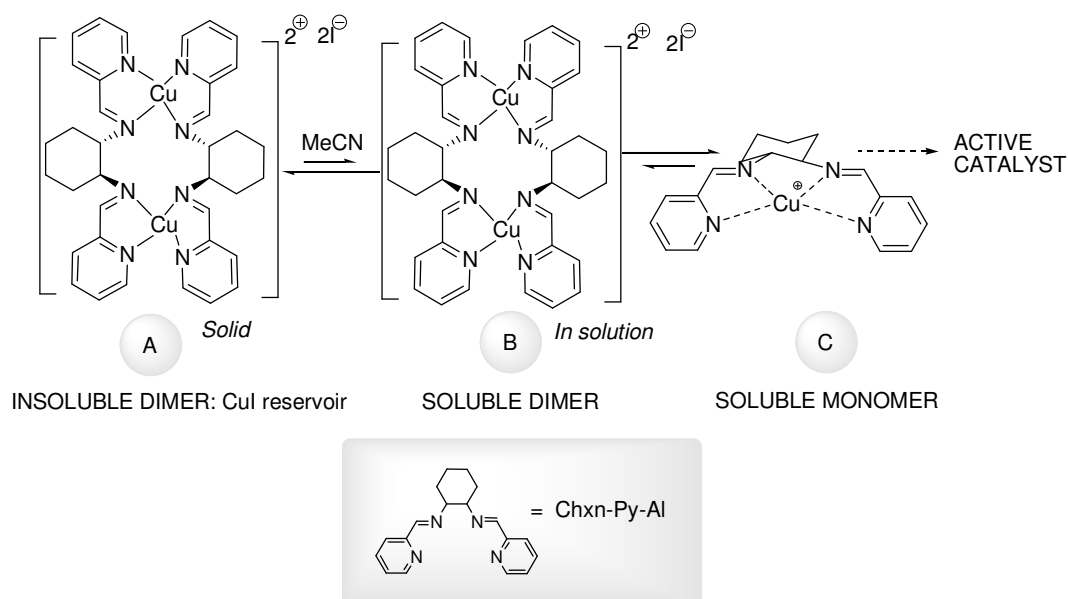
Scheme 16:   Copper complexes of Chxn-Py-Al involved in active catalyst formation.

Along with Buchwald in 2002,[53] the Taillifer group reported breakthrough work on C-N cross-couplings using a ligand-accelerated Ullmann-reaction approach,[54] demonstrating that the potentially tetradentate Schiff-base ligand (Chxn-Py-Al – name derived from cycohexanediamine and pyridine-2-carbaldehyde starting materials) was effective for the arylation of NH-heterocycles[55,26] and phenols.[56-58] When mixing CuI and Chxn-Py-Al in acetonitrile, an insoluble dicopper complex is formed (Scheme 16, **A**) which, being sparingly soluble, leads to solubilised species **B** which was then shown to form monomeric Cu(I) species C.[59] Thus, the ligand is thought to act as: a) a solubilising agent for CuI, b) an aid to a 'reservoir' of Cu(I) (species **A**), and c) by adding electron density on Cu(I) due to the σ-donor ability of the pyridine N atoms. This interplay between electronic manipulation of the catalytic species by different chelating groups was investigated in the arylation of phenols. Ligands with both imine and pyridyl nitrogen centres performed best, especially when the imine was more electron deficient and the pyridine more electron rich. These observations suggested that the more electron rich (pyridyl chelation dominating) the Cu(I) species, the lower the oxidation potential of Cu(I) to Cu(II), thereby favouring the oxidative addition step. On the other hand, the more electron deficient the copper species (imine chelation dominating), the lower the reduction potential of Cu(II) to Cu(I) so stabilising the Cu centre when a more electrophilic species is needed, *i.e.* the nucleophilic substitution onto Cu(I) and reductive elimination from Cu(III).

At around the same time as Taillefer's reports, the Buchwald group also reported   ligand-accelerated Ullmann reactions.[53] They based their work on diamine ligands and their initial publications (post patent) focused on ethylenediamine, cyclohexanediamine and 1,10-phenanthroline giving rise to arylation of a wide variety of NH-heterocycles, amides, hydrazones, hydrazides and secondary amines.[60-64] Their later work focuses on modifying 1,10-phenanthroline and further mechanistic studies, *vide supra*.

Ma *et al.*[21] published a paper in 1998 on the CuI catalysed arylation of α-amino acids indicating that the structure of the amino acid is key to rate acceleration. A Cu-amino acid chelate was postulated as an active catalytic species. Amino acids such as *N*-methylglycine, L-proline and *N,N*-dimethylglycine increase the rate of arylation of various substrates.[65]

Other ligands that have been effectively used in Ullmann-like reactions include oximes,[26,55] 1,1'-bi-2-naphthol (BINOL),[66] *N*-phenylhydrazone,[67] diketones,[68-69] phosphine-oximes,[70] phosphinidenes,[71] benzotriazoles,[72-73] 8-hydroxyquinoline,[74] ninhydrin,[75] carbenes,[76] *N,N*-diethylsalicylamide[77] and picolinic acid,[78] to name a few. Catalytic systems utilising "ligand-free" conditions have been reported by various groups and generally incorporate sometimes large amounts of copper source[79] with carbonate[80] or phosphate bases.[81] It is believed that in such systems either the base, the solvent, or both, behave as ligands to varying degrees but such systems can lead to inconsistent results.[23] Other "ligand-free" systems include the use of CuFAP which can arylate heterocycles using aryl halides or arylboronic acids.[27,82] Reusable catalysts have also been explored as greener methods for Ullmann-like reactions using Cu nanoparticles[83] or supported copper systems.[84]

1.1.6   Base

The deprotonation of the nucleophile at some stage in the catalytic cycle is required. Inorganic bases such as Cs_2CO_3, K_2CO_3, K_3PO_4 and KOH have been used in the arylation of *N*-heterocycles, amides, primary and secondary amines and other nitrogen nucleophiles.[22] Cristau *et al.* found that Cs_2CO_3 was superior to K_2CO_3 in the arylation of pyrazine with bromobenzene.[55] They reasoned that this was, in part, due to the lesser ion-pairing of Cs^+ compared to K^+ resulting in a greater nucleophilicity of the pyrazinyl anion. The greater solubility of Cs_2CO_3 in organic solvents was also regarded as a positive contributing factor. The use of CsOAc has been reported using ligand-free conditions for the intramolecular C-N coupling of secondary amines.[85] This is probably a case where the

base and/or solvent are acting as ligands in the copper species. Strong organic bases such as KO^{t}Bu have been used for the arylation of *N*-heterocycles and primary and secondary amines,[69] although the strength of this base makes it unsuitable in the presence of sensitive functionality. As part of a study into the arylation of anilines to give triarylamines, NaO^{t}Bu, KOH, NaOMe and DBU were much less efficient than KO^{t}Bu.[50] The soluble organic base bis(tetraethylammonium) carbonate (TEAC) has been successfully used to arylate benzimidazole and imidazole where it outperformed Cs_2CO_3 in comparable reactions (see Scheme 17).[86]

base = Cs_2CO_3, ligand = phen; yield = 20%
base = TEAC, ligand = DMCDA; yield = 32%
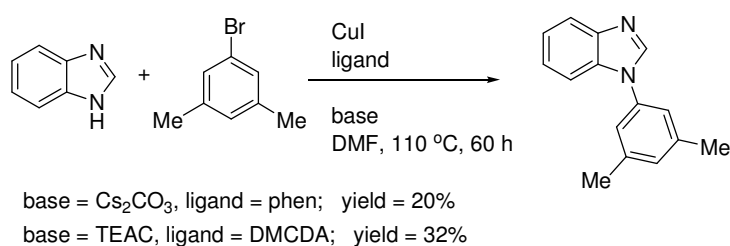
Scheme 17: Arylation of benzimidazole using TEAC or Cs_2CO_3 bases.[86]

For the Goldberg arylation of amides, Klapars *et al.*[64] found that the choice of base plays an important role. When using K_3PO_4, the reaction proceeded faster than with K_2CO_3 for the amidation of aryl iodides, while the reverse was true if the electrophile was changed to an aryl bromide.[64] They also observed that by adding the strong base KHMDS slowly to the amidation of aryl iodides, the reaction proceeded well; however, when added in one portion, the reaction failed. They suggest that the rate of deprotonation of the amide should match the rate of the arylation reaction, otherwise the excess of deprotonated amide could form unreactive cuprate complexes (see Scheme 18). Aryl iodides will undergo oxidative addition more rapidly than aryl bromides (*vide supra*) therefore, stronger bases (K_3PO_4) can be used for aryl iodides but the decreased reactivity of aryl-bromides requires weaker bases (K_2CO_3).
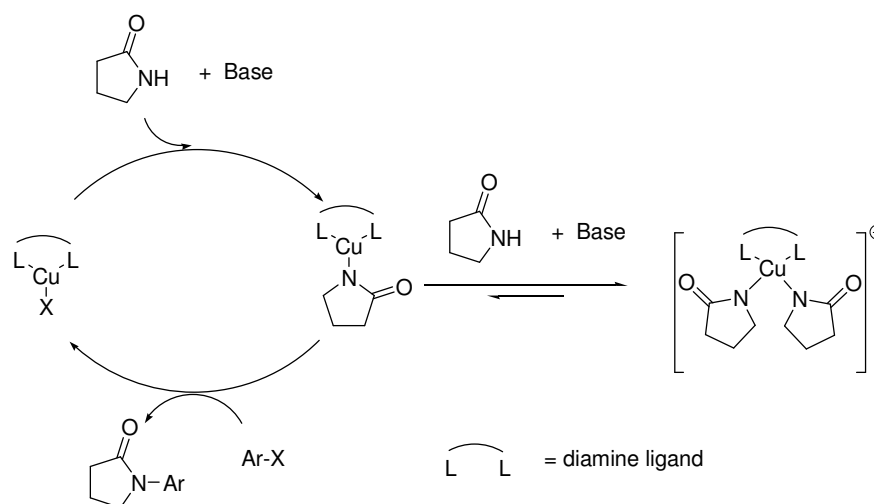
Scheme 18: Simplified reaction mechanism for Goldberg amide arylation showing deactivation of the catalyst with an excess of deprotonated amide.[64]

1.1.7 Scope

Buchwald *et al.*,[87] (*vide infra*) significantly improved upon the classic Ullmann condensation reaction by employing (CuOTf)$_2$·benzene as a catalyst with 1,10-phenanthroline as a ligand for the *N*-arylation of imidazoles and benzimidazole[88] and also for diaryl ether synthesis.[29] *N*-arylations were carried out with stoichiometric amounts of Cs$_2$CO$_3$ base, catalytic amounts of Cu(OTf)$_2$·benzene, stoichiometric amounts of 1,10-phenanthroline, dba and xylenes at 110 - 125 ^{o}C under an argon atmosphere for up to 48 h. His paper gave the first *N*-arylbenzimidazole synthesised *via* modern copper-catalysed C-N cross-coupling (Scheme 19).
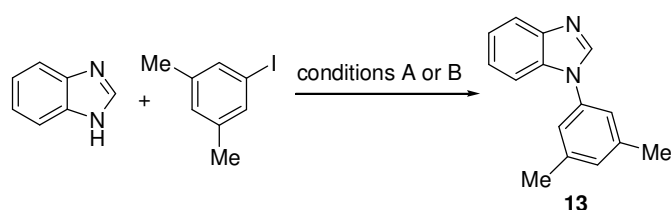
Scheme 19: Conditions: A) 0.5 mol% Cu(OTf)$_2$.PhH, Cs$_2$CO$_3$, phen, dba, xylenes, 125 ^{o}C, 40 h, 91% yield;[88] B) 10 mol% CuI, Cs$_2$CO$_3$, phen, DMF, 110 ^{o}C, 24 h, 91% yield.[89]

A variety of *N*-aryl indoles, indazoles, benzimidazoles and imidazoles were subsequently reported. The general procedure included CuI and either 1,10-phenanthroline or diamine ligands. In Scheme 19 1-(3,5-dimethylphenyl)-1*H*-benzo[*d*]imidazole **13**, was synthesised

using 1,10-phenanthroline as the ligand and DMF as the solvent, affording the product in 91% yield.[89]

A study of the applicability of indoles for this reaction was performed by Buchwald using a series of diamine ligands. Various aryl bromides and aryl iodides were coupled to indole and substituted indoles. Aryl donors included 2- and 4-bromotoluene and 2-isopropyliodobenzene.[90] Toluene was used as the solvent for these reactions with CuI as copper source and K_3PO_4 as base.

N,N'-Dimethylethylenediamne was used as the ligand for the *N*-arylation of oxindoles using CuI, K_2CO_3 in acetonitrile. Electron-withdrawing and electron-donating groups on either oxindole or aryl donor gave products in reasonable yields.[91] Sterically hindered aryl donors were examined using diamine ligands with catalytic amounts of CuI and Cs_2CO_3 in DMF or dioxane. *N*-Mesitylimidazole was synthesised in 54% yield and more hindered *N*-arylations of 1-iodo-2,6-diisopropylbenzene proceeded in lower yields. Reaction temperatures were high at 95 – 170 ^{o}C leading the authors to conclude that the Chan, Lam, Evans protocol was more suited to sterically hindered substrates. An optimisation study focusing on *N*-arylation of sterically hindered substrates with benzimidazole was undertaken by Alcalde. By comparing aryl halide substrates with arylboronic acid and aryltrifluroborate salts, the authors concluded that the ligand-accelerated Ullmann reaction was the most effective in these difficult *N*-arylation reactions.[92]
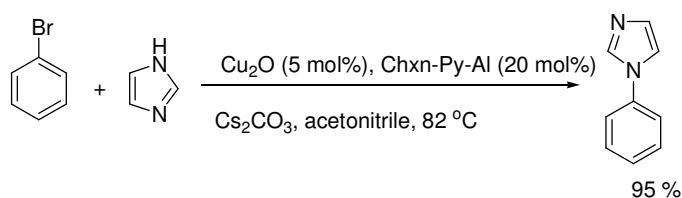
Scheme 20:   Mild conditions for arylation of imidazoles with unactivated aryl bromides.

Taillefer studied *N*-arylation of azoles under mild reaction conditions and described how Chxn-Py-Al performs especially well with a broad array of azoles and aryl donors.[93] This ligand was also shown to catalyse *O*- and *C*-arylations using similar conditions. Cu_2O was used as the copper source with best yields occurring with acetonitrile as solvent and 2.2 equivalents of Cs_2CO_3 as base. Reaction temperatures were as low as 50 ^{o}C using both aryl iodides and aryl bromides. *N*-Phenylimidazole was formed in excellent yield by the reaction of imidazole with bromobenzene at 82 ^{o}C (see Scheme 20). The trend in reactivity of azole substrates was shown to be:
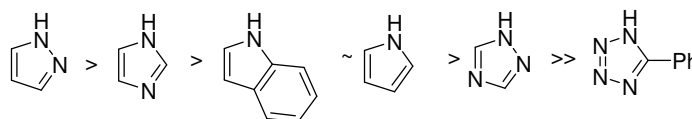
A selection of aryl donors was used to assess the suitability of 4,7-dimethoxy-1,10-phenanthroline as a ligand by Buchwald.[51] Yields were typically very high with even 0.05 mol % of Cu_2O in butyronitrile at 110 °C. Functionalities tolerated in this study include free amines, alcohols, carboxylic acids and nitrile, with arylations occurring in very high yields with both iodo- and bromoaryl donors (Scheme 21). 8-Hydroxyquinoline[86,94] was used as a ligand with 10 mol % CuI in DMF and $(Et_4N)_2CO_3$ base for arylation of a selection of imidazoles and benzimidazoles (Scheme 22). Interestingly, by applying this methodology, two examples of arylation with aryl chlorides were observed after 60 h at 130 °C. Although not the first report of *N*-arylation of an azole with aryl chlorides using copper,[95-96] it was the first with a ligand-accelerated Ullmann procedure.
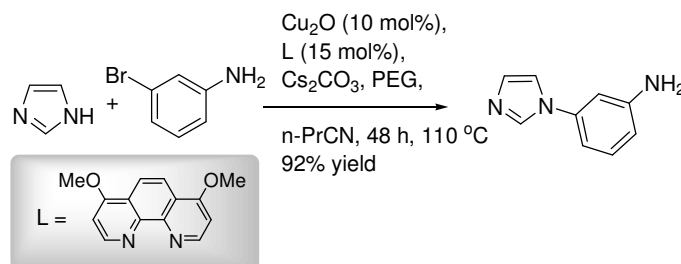
Scheme 21:   *N*-Arylation of imidazoles using 4,7-dimethoxy-1,10-phenanthroline as a ligand.
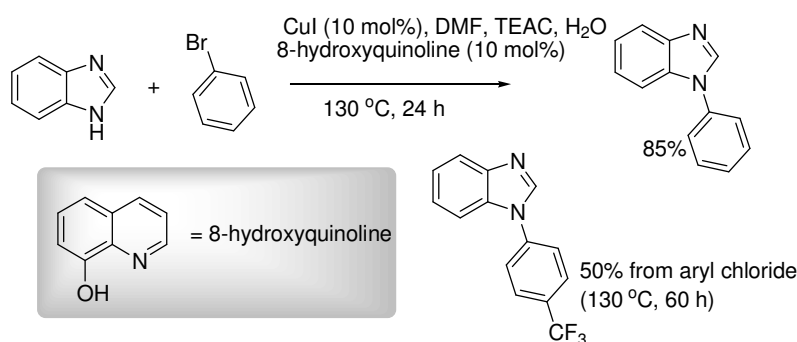
Scheme 22:   *N*-Arylation using 8-hydroxyquinoline.

N-Arylation of pyrazoles with a variety of aryl donors was carried out to screen some potentially interesting ligands including oximes[55] (see Scheme 23). Yields for some of these arylations were very high (*N*-phenylpyrazole up to 96% GC yields).
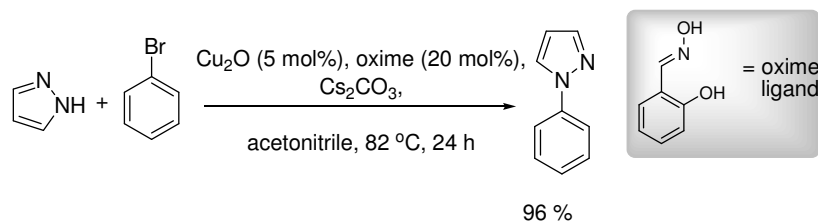
Scheme 23:   *N*-Arylation using an oxime as ligand.

Amino acids have been used in conjunction with catalytic amounts of CuI, base and a selection of solvents to arylate azoles in very high yields. L-Proline was used in the arylation of indoles and pyrrole with a selection of aryl iodides,[97] while pipecolinic acid was used for arylation of indoles and imidazoles with aryl iodide, bromide and even chlorides.[78] A solvent-free method for ligand-accelerated Ullmann *N*-arylations was published by Li.[98] 2-Aminopyrimidine-4,6-diol was used in conjunction with *n*-Bu$_4$NF as base to provide a greener route to *N*-aryl benzimidazoles and imidazoles. It also provided a selection of interesting heteroarylated benzimidazoles including 1-(pyrimidin-2-yl)-1*H*-benzimidazole and 1-(thiazol-2-yl)-1*H*-benzimidazole from 2-chloropyrimidine and 2-bromothiazole in 100% and 55% yields, respectively (see Scheme 24).
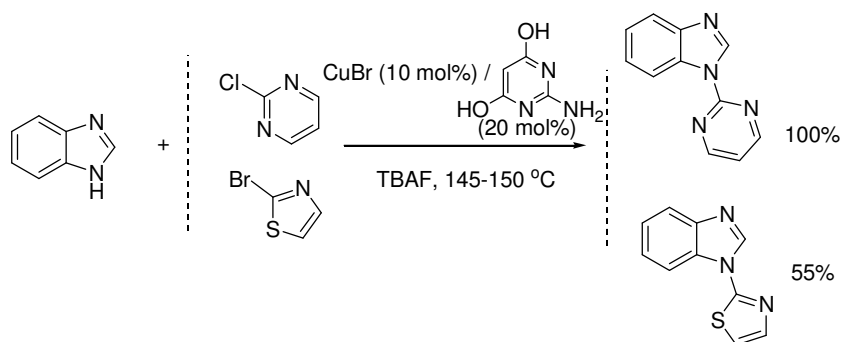
Scheme 24:   Solvent-free *N*-arylations of benzimidazole.

You[99] also provided a synthesis of *N*-heteroarylated imidazoles with the employment of (*S*)-pyrrolidinylmethylimidazole ligands with catalytic amounts of CuI and an excess of Cs$_2$CO$_3$ in DMF. This protocol also used activated aryl chlorides as aryl donor in very good yields (4-chloronitrobenzene and 4-chlorobenzonitrile in 98% and 92% yields, respectively). Benzotriazole was recently reported as a good ligand for *N*-arylation of indoles and pyrroles.[73]

Exceptional functional group tolerance has been observed in ligand-free Cu-catalysed C-N coupling of azoles with aryl bromides containing thermally sensitive groups, as well as displaying chemoselective coupling to the NH-heterocycle in the presence of functionality that are known to undergo coupling to aryl halides in the presence of Cu catalysts, *i.e.* -OH, -C≡C-H, -CON(H)R and –NH$_2$ groups (see Scheme 25).[100]
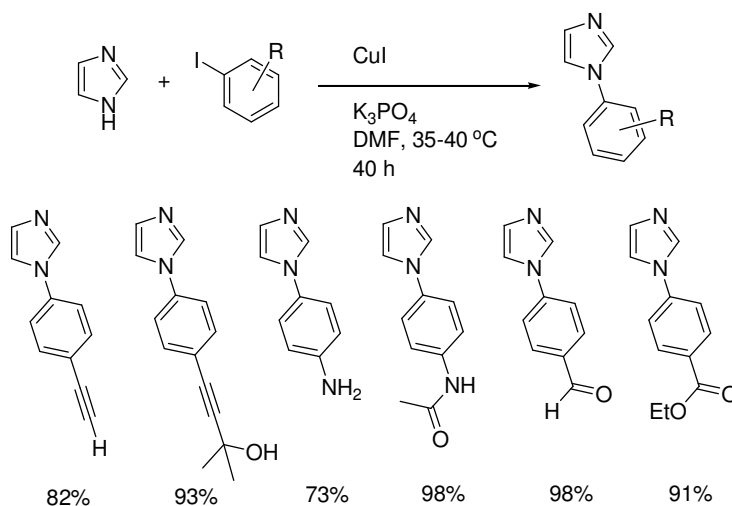
Scheme 25:   Ligand-free *N*-arylation of imidazole under mild conditions.

 "Ligand-free-like" synthesis of *N*-arylated benzimidazoles, indoles, imidazoles, pyrroles, pyrazoles and triazoles was achieved[47] using Cu powder in a nitrile solvent. The use of MeCN as solvent was crucial and was assumed to act as a monodentate ligand.[79]

1.1.8   Conclusion

In conclusion, ligand-accelerated Ullmann reactions provide an efficient route to the *N*-arylation of NH-heterocycles. A large variety of conditions for such coupling reactions have been developed and good functional group tolerance is noteworthy. Despite the range of substrates and conditions covered there has been fairly limited investigation of the *N*-heteroarylation of NH-heterocycles, a motif expected to be of great interest to pharmaceutical research.

1.2   Pd-Catalysed C-N Cross-Coupling: Buchwald-Hartwig Reaction

While Ullmann and Goldberg type reactions utilise copper for the formation of C-N bonds, the Buchwald-Hartwig reaction uses palladium. Although a much more expensive metal,[101] there are many benefits to using this reaction. Firstly, unactivated aryl bromides and aryl chlorides can be successfully coupled to various amines and amides; substrates normally considered challenging for Ullmann-type reactions. Very low catalyst loadings can be achieved with palladium couplings: this reduces both costs and trace metal contamination, which are important factors to consider for active pharmaceutical ingredients (API's) in GMP synthesis.

The first report of a palladium catalysed method for the arylation of amines was in 1983 by Kosugi.[102] The protocol required the use of nucleophilic tin-amides (*c.f.* the Stille reaction[103]) and aryl bromides using catalytic amounts of $PdCl_2(o\text{-tol}_3P)_2$. This procedure was limited to electron neutral aryl bromides, with both electron rich and electron deficient electrophiles resulting in poor yields of the aryl amine. Iodobenzene and chlorobenzene failed to couple under the conditions presented. The authors rejected a radical or aryne mechanism through observations on reactivity.

The earliest palladium-catalysed route to aromatic amides was by Schoenberg and Heck[104] in 1974 where aryl, heteroaryl and vinylic bromides were reacted with amines, including aniline, in a carbon monoxide atmosphere with either $Pd(PPh_3)_2Br_2$ or $Pd(PPh_3)_2(Ph)(Br)$ catalyst (Scheme 26). Although not a C_{arom}-N bond forming procedure like the Ullmann reaction, it is an amidation process and provided the products in good yields under catalytic conditions.
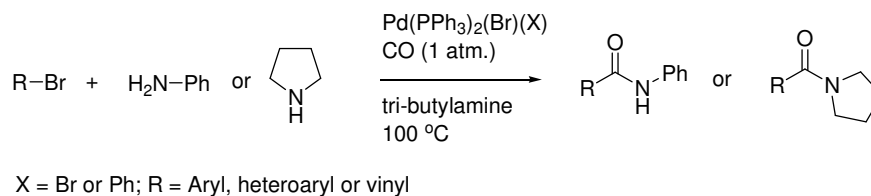
Scheme 26:   Palladium-catalysed amidation of aryl halides by Schoenberg and Heck.

1.2.1   Mechanism

Like many other transition-metal catalysed cross-coupling reactions,[105,103,22] the mechanism is based upon a combination of oxidative addition of the electrophile (in this case an aryl halide), transmetallation of the nucleophile (in this case an amine or amide)

and a reductive elimination of the cross-coupled product and regeneration of the catalytic species (Scheme 27). Many of the insights into the mechanism of the Buchwald-Hartwig reaction were based upon stoichiometric studies on either tin-mediated aminations or tin-free aminations, although many catalytic studies have complimented these.
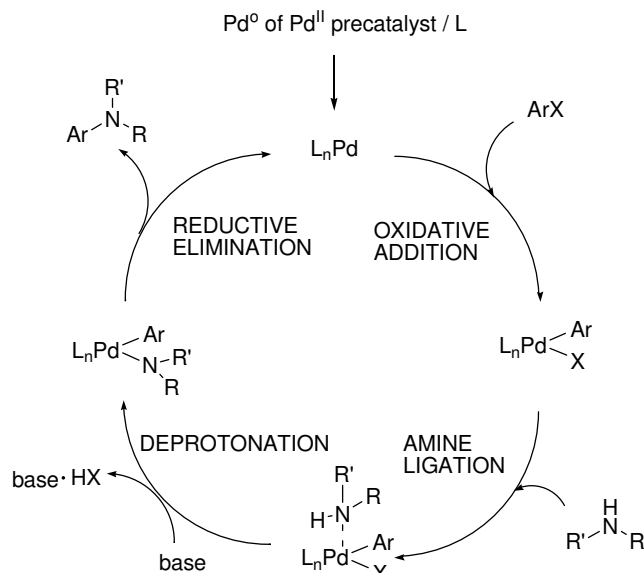
Scheme 27: General catalytic cycle for Buchwald-Hartwig reaction.

1.2.2   Oxidative Addition

The oxidative addition step involves the addition of Ar-X to a Pd^0 species, cleaving the Ar-X bond and forming an oxidised Pd^{II} species with the general order of reactivity I > Br > Cl. Mechanistic investigations conducted by Hartwig[106] in the early 1990s pointed to an active catalytic species of the form $Pd(o\text{-tol}_3P)_2$ which was confirmed by an X-ray molecular structure of the linear Pd(0) complex.[107] This air-stable 14-electon species did not react with tin-amides but rapidly underwent oxidative addition with aryl bromides to afford an isolated dimeric palladium complex **14**.[106-107] It was shown (Scheme 28) that this process occurred by formation of the active catalytic species *in situ* by loss of a phosphine ligand giving 12-electron one-coordinate [PdL] either as free species, a solvated one or transient as the aryl halide displaces L.[108] This finding was surprising as previous examples of oxidative addition had only occurred onto PdL_2 species.[109-110,103]
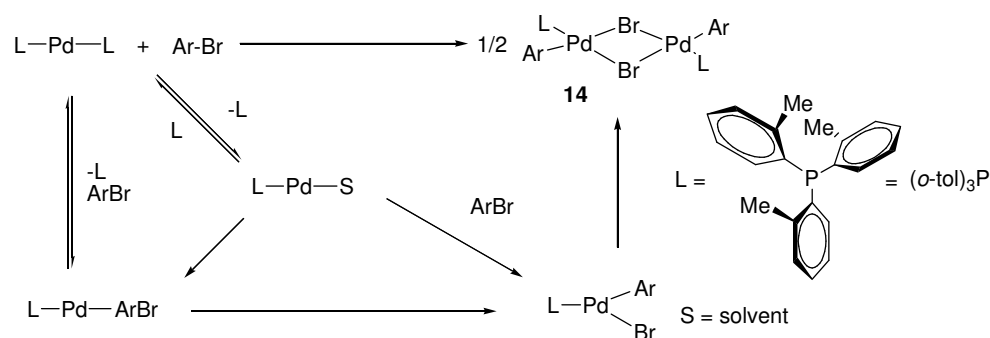
Scheme 28:   Proposed oxidative addition pathways using (o-tol)$_3$P as ligand with aryl bromides.

More recently, studies have shown that the nature of the halide plays a key role in the oxidative addition palladium species (see Scheme 29).[111] When using a variety of bulky alkyl mono-phosphine ligands, the general trend for the oxidative addition step was reversible reaction with mono-phosphine palladium(0) for aryl chlorides (dissociative substitution, Path A) and irreversible reaction with bis-phosphine Pd(0) for aryl iodides (associative substitution, Path B). Aryl bromides reacted by a combination of both pathways. The authors concluded that the more reactive aryl iodides reacted with the bisphosphine species while aryl chlorides require the more reactive monophosphine species to cleave the stronger Ar-Cl bond.
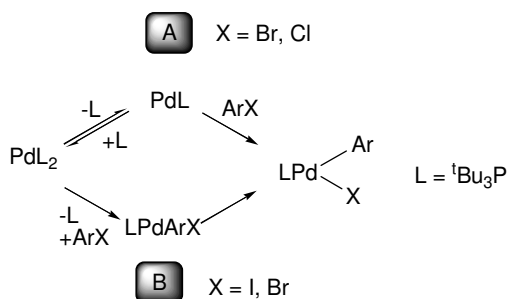
Scheme 29:   Oxidative addition occurrs *via* different pathways depending on nature of halide.

The same authors reported the oxidative addition with bulky phosphine complex **15**.[112] They found the process for PhI, PhBr and PhCl occurred by three distinct pathways: for aryl iodides, *via* an associative displacement of a phosphine (Scheme 30, Path A); for aryl bromides, *via* a rate-limiting non-reversible dissociation of a phosphine from Pd^{0}L$_2$

followed by oxidative addition (Path B); for aryl chlorides, *via* a reversible dissociation of a phosphine from Pd^0L_2 followed by a rate-limiting oxidative addition step (Path C).[112]
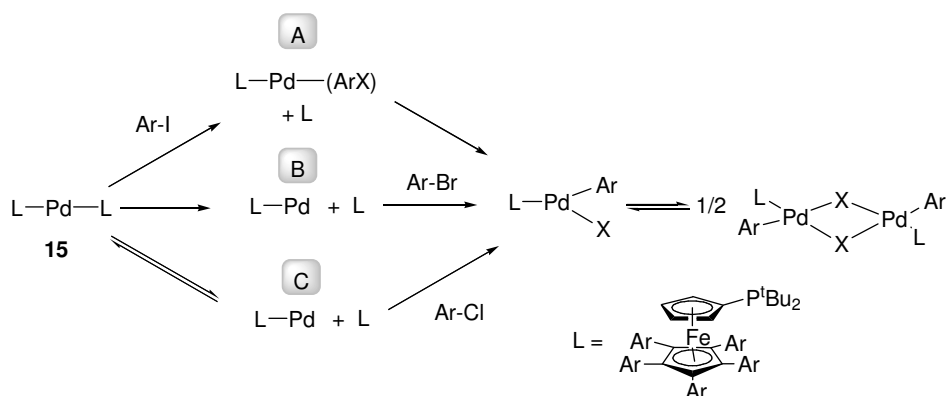
Scheme 30: Distinction between oxidative addition pathways of aryl chlorides, bromides and iodides using bulky ligand Q-Phos.

1.2.3 Transmetallation

For tin-mediated reactions, the dimeric oxidative addition product **16** was found to exist in an equilibrium with its monomeric form **17**, which then formed transmetallation product **18** upon addition of Bu_3SnNEt_2.[113] The dimeric species **16** did not undergo transmetallation directly and the monomeric tetra-coordinate species **19** was also incapable of transmetallating (Scheme 31). Chelating ligands were ineffective in promoting the reaction in the same way as (*o*-tolyl)$_3$P or PPh$_3$, no doubt due to the requirement for mono-phosphine-ligated palladium intermediates.[114] These reactions are limited to secondary amines. The transmetallation step involves a reversible loss of trialkyltinbromide (the presence of which is inhibitory[113]) giving the three-coordinate species **18**.

Scheme 31:   Transmetallation step occurs from monomeric species **17** in tin-mediated aminations.

Hartwig proposed a mechanism for this reaction,[106] which could be made catalytic (Scheme 32). This relied upon the Pd(*o*-tol$_3$P) species **20** undergoing oxidative addition to the aryl bromide to give mono-palladium species **21** which exists in an equilibrium with the dimeric species **22**. The next step would be a transmetallation with the tin-amide followed by a reductive elimination to afford the coupled product.

Scheme 32:   Mechanism for tin-mediated Pd-catalysed amination proposed by Hartwig.

In the same year, Buchwald showed that the reaction could be carried out by *in situ* generation of the tin-amide.[114] This reaction was found to be catalytic with loading as low as 1 mol% $PdCl_2(o\text{-}tol_3P)_2$ and capable of coupling primary and secondary amines, including anilines, with both electron rich and electron deficient aryl bromides (Scheme 33).
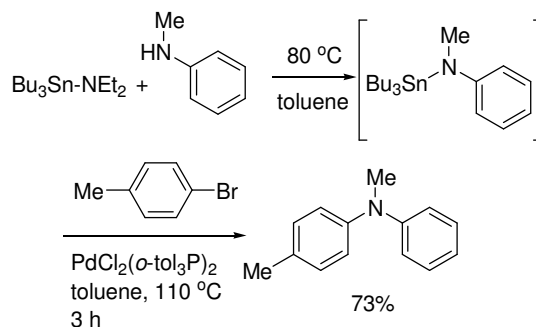
Scheme 33:   Amination of aryl bromides with *in situ* generation of aminostannanes.

In tin-free aminations, transmetallation with a variety of amines is possible including primary amines and amides. The dimeric oxidative addition species **22** was shown to react with amines to give monomeric species **23** (Scheme 34, top).[107] Deprotonation of the ligated amine by alkoxide or silylamide base occurred readily to give arylamine products with the transient anionic species **24** being observed by NMR (Scheme 34, bottom).[115]
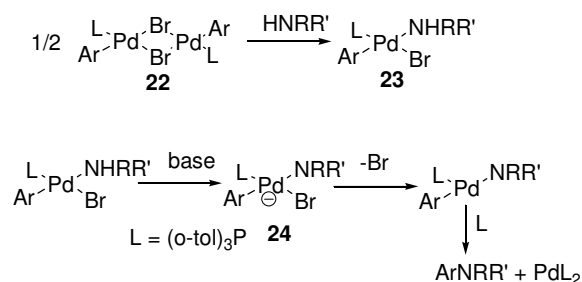
Scheme 34:   Cleavage of dimeric **22** by amine (*top*) and subsequent deprotonation *in situ* giving anionic species and eventual formation of arylamines (*bottom*).

When using chelating ligands such as DPPF, a different mechanism for transmetallation is observed. When alkoxopalladium complex **26a** (where R = 4-*tert*-buytlphenyl) was treated with primary and secondary amines and PPh₃, *with no base present,* the corresponding coupled arylamine was formed indicating formation of an amide complex *via* a proton transfer mechanism *not* by external deprotonation. It was proposed that when using an alkoxide base and amine, the exchange of the halide from **25** for the alkoxide occurs first to give **26a** which then exchanges with the amine to give **26b** (Scheme 35). Reductive elimination then gives the arylamine. The exact mechanism in the case of chelating ligands is not clear but these results show that it is possible to access Pd-amido complexes from Pd-alkoxides.[116]
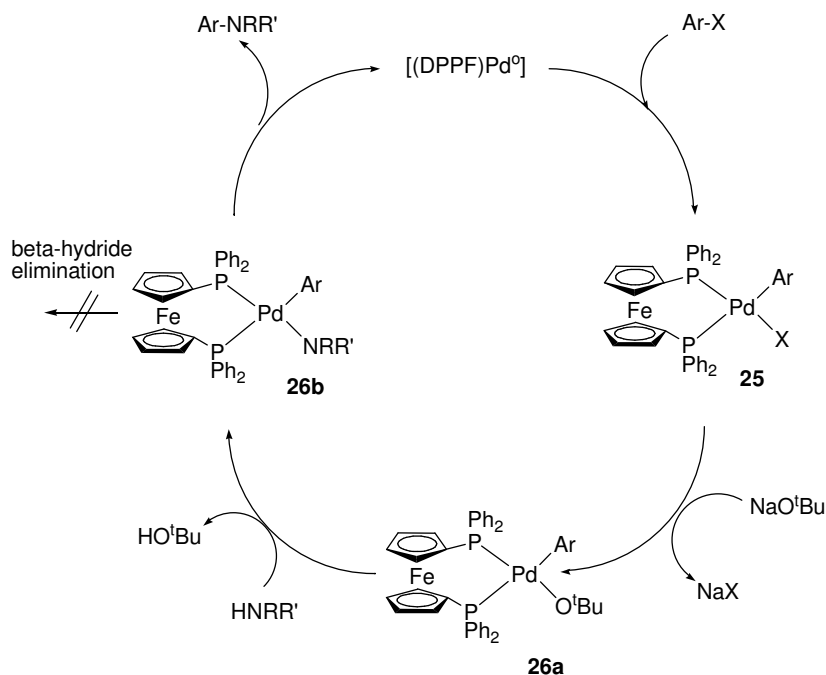
Scheme 35:   Catalytic cycle for DPPF-type ligands as proposed by Hartwig.[116]

For monophosphine ligands, Hartwig proposed two possible pathways, involving neutral or anionic processes.[117] In the anionic pathway, alkoxide attack on **20** forms alkoxide-palladium species **27** which facilitates oxidative addition with loss of halide as the sodium salt giving alkoxopalladium **28**. Transmetallation has been observed previously on alkoxopalladium species in stoichiometric reactions.[118] In the neutral pathway, the amine is deprotonated first by NaO^{t}Bu, then undergoes transmetallation (Scheme 36).
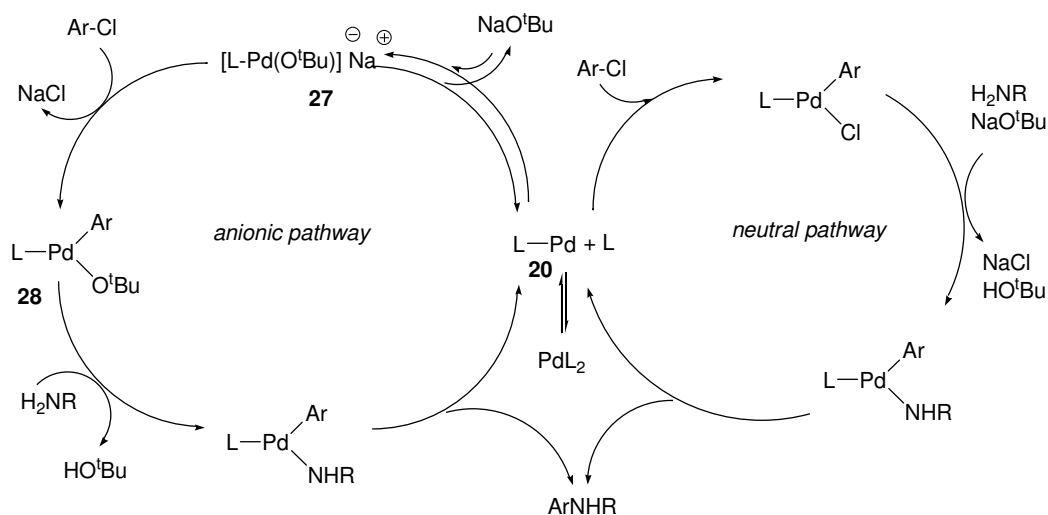
Scheme 36:   Anionic and neutral pathways proposed for aminations based on bulky monophosphine ligands (L = P^{t}Bu$_3$).

Many bases have been used in Buchwald-Hartwig reactions with the most common being NaO^{t}Bu (KO^{t}Bu tends to promote formation of palladium black and LiO^{t}Bu is a poor base);[119] carbonate bases are also suitable when mild conditions are required.[120] Buchwald proposed an alternative mechanistic pathway when the chelating BINAP (see Abbreviations) is employed as supporting ligand, where coordination of the amine to the Pd^0(BINAP) complex occurs first, with oxidative addition accelerated by this pre-coordination effect (Scheme 37).[121] Also of note here is that the base deprotonates the bound amine without alkoxo-palladium intermediates as described in previous mechanisms.[117]

$$Pd_2(dba)_3 \ + \ BINAP \ \rightleftharpoons \ (BINAP)Pd(dba)$$
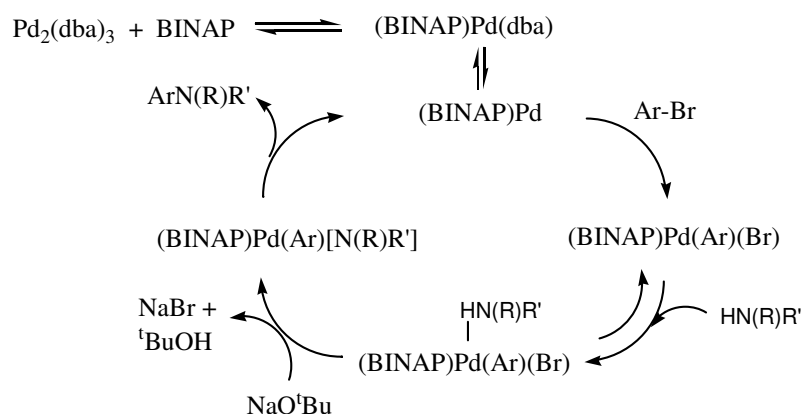
Scheme 37:   Alternative mechanism proposed by Buchwald when BINAP is used.

1.2.4   Reductive Elimination

In the reductive elimination stage, the Pd(II) species formed in the transmetallation step eliminates the arylamine and regenerates the Pd(0) species, which in catalytic systems rejoins the catalytic cycle. Studies have shown that, although both monomeric and dimeric Pd-amido complexes have been isolated, only monomeric species directly react to give reductive elimination products.[122] Dimeric complexes **29** are first cleaved to give 3-coordinate 14-electron species **30** which then undergos reductive elimination with C-N bond formation (Scheme 38).[122] With monomeric species (*i.e.* **31**) it was observed that the reaction occurred *via* two pathways: a 3-coordinate 14-electron species after ligand dissociation **33** or by 4-coordinate 16-electron species after *trans-cis* isomerism **32** (see Scheme 39).
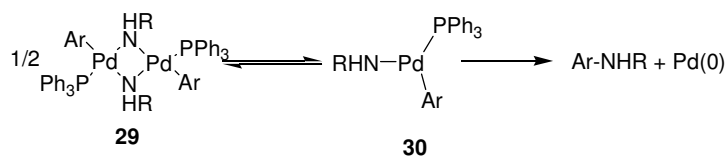
Scheme 38:   Cleavage of dimeric transmetallation product affords 3-coordinate species from which reductive elimination occurs. R = ^{t}Bu.
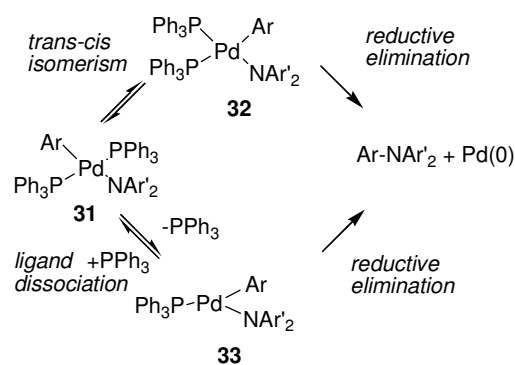
Scheme 39:   Reductive elimination pathways for monomeric transmetallation species.

These observations of a 4-coordinate intermediate led to the study of chelating phosphine ligands such as DPPF[123] and BINAP,[124] which both gave very good product yields with less hydrodehalogenated by-product (*vide infra*). The chelation forces the transmetallation product to be *cis*, therefore, the reductive elimination step goes *via* the 4-coordinate 16-electron species without the need for *trans-cis* isomerism.[125] When using DPPF, the general rule for reactivity is alkylamido > arylamido > diarylamido, suggesting that the more electron rich the amine, the better the reductive elimination, *i.e.* the amido group is acting as a nucleophile.[122] Electronic effects of the electrophilic aryl group were probed leading to the conclusion that electron-withdrawing groups increase the rate of reductive elimination, again consistent with the amido moiety acting as a nucleophile and the aryl as the electrophile.[126]

1.2.5   β-Hydride Elimination

The major side-products from Buchwald-Hartwig type reactions are arenes, formed by a reductive β-hydride elimination pathway. For mono-phosphine ligands [*i.e.* (*o*-tol)$_3$P] the β-hydride elimination was found to occur from the amido group leading to imine as well as arene formation.[127] It was also shown that an alternative pathway can exist whereby arene formation occurs from the reduction of Pd(II) catalyst precursors when Pd(II) catalysts are employed. Exploration of electronic effects showed that electron deficient aryl halides gave less arene by-product, judged to be an effect of a more electrophilic aryl group (see "Reductive Elimination"). The β-hydride elimination pathway is in direct competition with the reductive elimination step and selectivity towards C-N bond formation can be controlled by using more sterically bulky ligands. β-Hydride elimination occurs from the amido leading to the arene and imine.[128] The process involves either imine coordination (Scheme 40, path A), therefore increasing the coordination number on the Pd centre, or, if

the imine is not coordinated but extruded (Scheme 40, path B), then the coordination number remains the same. Larger ligands can force a lower coordination geometry onto the Pd centre which favours reductive elimination (Scheme 40, path C).[116] For chelating ligands, the opposite trend was revealed, with the bulkier DTPF giving more arene by-product than DPPF.[129] The authors conclude that arene by-products are not formed by β-hydride elimination, but by another unknown pathway. It was also noted that electron poor groups on the phosphine gave more arene by-product which was not expected as electron poor complexes tend to favour reductive elimination.[130]
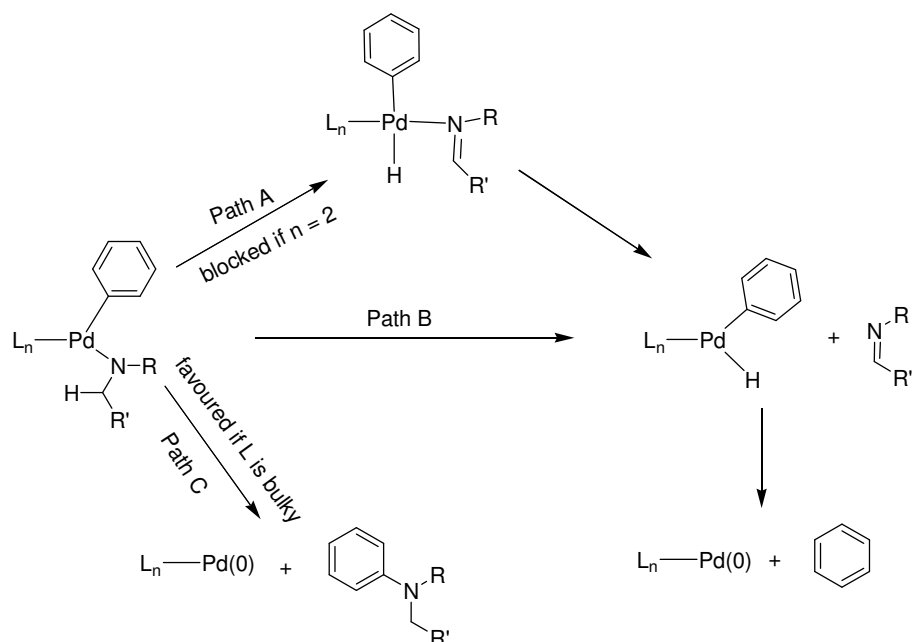
Scheme 40:   Pathways for β-hydride elimination *vs.* reductive elimination.

1.2.6   Ligands

As described above, ligands serve an important role in the catalytic cycle. The original monophosphine ligands such as P(o-tol)$_3$ and PPh$_3$ afford cross-coupled products with aryl bromides and various amines.[102,106,107,114,119,123,131-133] Buchwald demonstrated that aryl iodides[133] and aryl bromides[131] were able to undergo amination using P(o-tol)$_3$ as the ligand with primary, secondary and cyclic alkylamines, anilines and *N*-alkylanilines. Primary alkylamines were shown to be unreactive using a similar system, as noted by Louie and Hartwig.[119] It has been noted that primary alkylamines are challenging substrates,[134] presumably due to their tendancy to react further to form the tertiary amine.[135]

The "second generation" monodentate PCy$_3$ was one of the first reported ligands to be used in the amination of aryl chlorides.[136] Using the bulkier ^{t}Bu$_3$P, Yamamoto *et al.* showed that

diarylamines could be arylated using excess chlorobenzenes in very high yields in low catalyst loadings[134] at elevated temperatures when using a 1 : 4 ratio of Pd : ligand.[137] In 1999, Hartwig *et al.* showed that by carefully controlling the Pd : ligand ratio, $^{t}Bu_3P$ could provide aminations of aryl chlorides at room temperature.[138] This catalytic system was also applied to amides and a selection of azoles at elevated temperatures (see Scheme 41). Azoles are reported to undergo reductive elimination slowly, with DPPF as the ligand and Cs_2CO_3 base being optimal to avoid low yields,[139] therefore, making this study all the more interesting.[138]
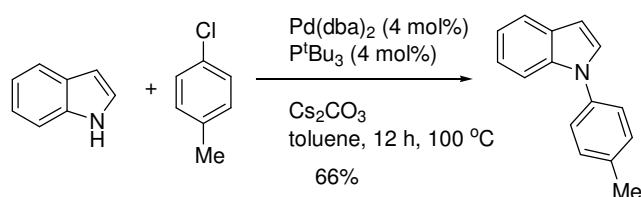
Scheme 41:   *N*-Arylation of indole using aryl chlorides.

Bulky trialkylphosphine **34** has been used very successfully for the coupling of primary and secondary alkylamines and anilines with unactivated and sterically hindered aryl chlorides, outperforming most other monodentate ligands tested over a series of reactions (Scheme 42).[134]

L	=	**34**	P^tBu_3	PCy_3	$PhPCy_2$	Cy-JohnPhos	$BuPCy_2$	BuP^tBu_2	PPh_3
Yield(%)	=	70	52	56	51	44	45	54	2
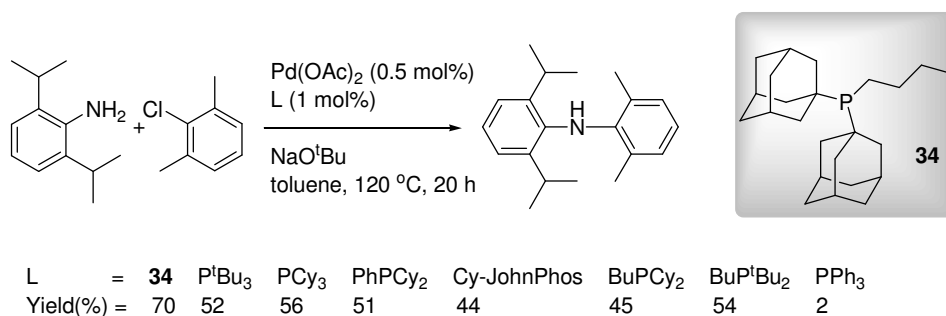
Scheme 42:   Coupling of sterically hindered aniline with deactivated and hindered aryl chloride using **34** as ligand.

From initial study of the "first generation" of ligands (PPh_3 and o-tol$_3$P) by Buchwald[140] and Hartwig,[119] both groups independently moved towards "second generation" chelating ligands. Buchwald and others have described BINAP as being a good ligand providing excellent yields[141,124,142] while Hartwig found DPPF to be effective in many coupling scenarios.[123,143] As described above, mechanistic insights have pointed to a 4-coordinate Pd

complex as oxidative addition complex, with PdL$_2$ as the active catalyst where chelating ligands are used. The steric bulk associated with both BINAP and DPPF aid reductive elimination and it has been proposed that β-hydride elimination is reduced when using DPPF (*vide supra*). DPPF is also strongly electron rich, favouring oxidative addition.[116] Structurally related D^{t}BPF (see Figure 1) has been very successful in coupling aryl chlorides.[144] The authors speculated that the increased sterics could favour oxidative addition by allowing mono-phosphine dissociation to form a bent Pd^0 species,[129] while the increased electron density of the bis-alkylphosphine moiety, compared to DPPF, also favours oxidative addition. They also point out that more electron rich phosphines disfavour reductive elimination, and they reasoned that the increase in steric bulk attenuates for the negative effect of increased electron density.

The monophosphine ligand **35** (see Figure 1) has been effective in the amination of aryl chlorides, arybromides and aryl iodides (Scheme 43, bottom). An oxidative addition complex containing two similar ligands with P-Pd bonds (**36**) and also a complex with one ligand but coordination *via* P-Pd and O-Pd bonds (**37**) have been observed (Figure 1, top).[145]
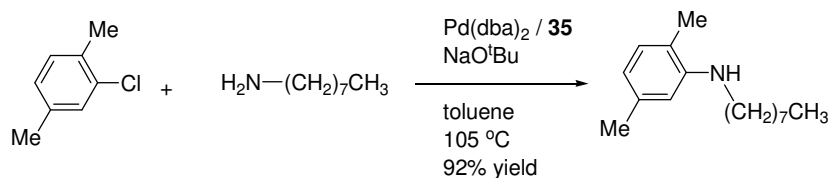
Scheme 43:   Ambidentate ligand (**35**) used in the study of the amination of aryl chlorides with primary amines (*bottom*).[145]

The Buchwald group have had much success with ligand design for the Buchwald-Hartwig reactions,[146] as well as other cross-coupling protocols.[147] Their *ortho*-biphenyldialkylphosphine ligands (a selection is shown in Figure 1) have been shown to afford cross-coupling with deactivated substrates under mild conditions.[148,146,149] They exist as LPd^0 complexes in an equilibrium with the L$_2$Pd^0 complexes.[150] Structurally, the ^{t}Bu- and Cy- groups add bulk, as does the *ortho*-biphenyl moiety. Further substituents on the aryl rings, especially on the 2',6'- positions, add bulk and favour oxidative addition and reductive elimination by forcing a reduction in coordination number (*vide supra*). The alkyl substituents on the phosphorus atom also allow the phosphine to donate more electron density to the Pd centre, aiding oxidative addition. There also exists a possibility

of Pd-arene interactions,[151-154] as shown in Figure 1, which could stabilise oxidative addition (B) and reductive elimination species (C),[152] and increase electron density on the palladium atom (A).[146]
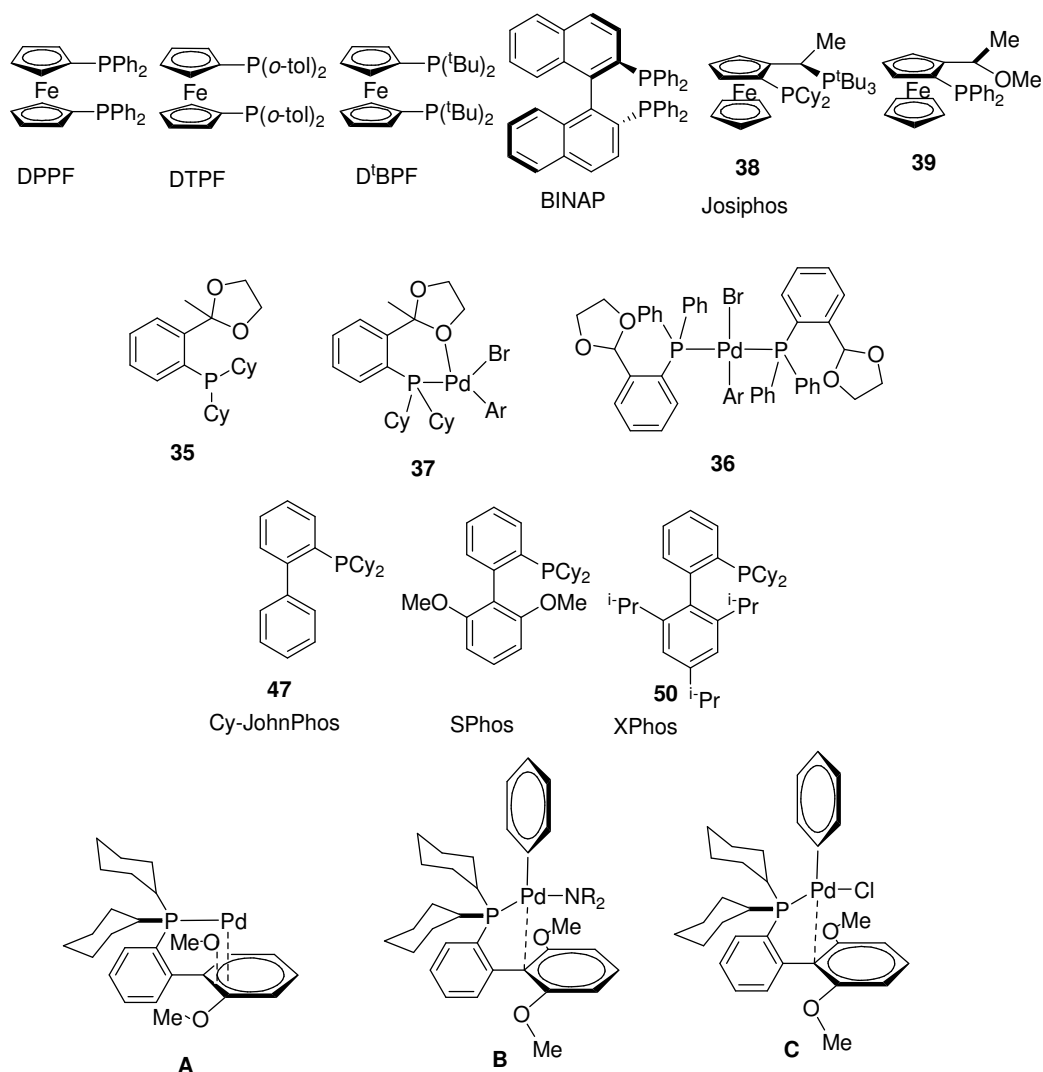
Figure 1:   Bis-chelating, ambidentate ligands and Pd complexes of ambidentate ligands observed (*top*). Also, Buchwald's *ortho*-biphenyldialkylphosphine ligands and proposed stabilisation *via* Pd-arene interactions for the amination of chlorobenzene (*bottom*).

Primary alkylamines are problematic nucleophiles with many catalytic systems due to issues with bis-arylation if there is no *ortho*-substituent on the aryl halide or if there is not an excess of amine.[135] This problem has been tackled effectively by using very bulky "fourth generation" ligands such as JosiPhos **38** (although Buchwald classes this as third generation and XPhos as fourth generation[155]).[144,135,2] The steric bulk is thought to inhibit further coupling of the secondary amine product. Like DPPF and related chelating ligands

(*vida supra*), the ferrocenyl moiety imparts strong electron richness, favouring oxidative addition. However, unlike DPPF, the rigid backbone of the JosiPhos ligand allows stronger binding to the metal centre with more preorganisation.[2] Problems encountered previously of ligand displacement by basic *N*-heterocycles or even primary amine substrates[107,156] leading to deactivated catalyst, are thought to be negated through the binding affinity of the JosiPhos structure. Prior to Hartwig's publication of the use of JosiPhos ligands, Buchwald studied the structurally similar Hayashi ligands and obtained very good results with **39** (structures shown in Figure 1).[128]

1.2.7   Scope

The intolerance of Buchwald-Hartwig amination and amidation reactions initially to non-activated aryl bromides, aryl chlorides, aryl iodides and bulky substrates led to a variety of different approaches as well as a better understanding of the reaction mechanism. The Buchwald-Hartwig reaction has been applied to heterocycles in a number of different ways, either by "decoration" of heterocycles,[1] reactions of NH-heterocycles or by formation of heterocyclic ring systems.[157] A few leading papers displaying the scope and limitations of the reaction in regards to *N*-heterocycles will now be considered.

Coupling can occur between aryl and heteroaryl halides[158] and pseudohalides,[149] and vinylic halides in both an inter-[159] and intra-molecular fashion.[160] The choice of nucleophile is also vast, with primary and secondary alkylamines being tolerated (with secondary amines generally being better substates[116]) and cyclic secondary amines being particularly good. Amides, both primary and secondary (including cyclic) are good substrates.[161] Aryl, diaryl and alkylarylamines are well tolerated substrates, as are various heteroarylamines.[146] Sulfonamides,[162] hydrazines,[163] and hydrazones[164] are also well tolerated. Routes to primary arylamines are also available through the Buchwald-Hartwig reaction utilising either "ammonia surrogates"[165-167] or, more recently, gaseous ammonia[168] with optimised conditions. The *N*-arylation of NH-heterocycles is also achievable using Buchwald-Hartwig methodology with varying success.[119] Intramolecular couplings to synthesise *N*-heterocycles are an interesting application of the Buchwald-Hartwig reaction with many examples in the literature.[159,169]

Although generally accepted as superior electrophiles in many cross-coupling protocols, aryl iodides have been known as poor substrates in the Buchwald-Hartwig reaction.[102]

Several groups[135,120] have shown that retardation by alkali metal iodides (one of the by-products from the reaction) is a contributing factor. Buchwald succeeded in improving coupling of 4-iodoanisole with aniline by changing from DME to toluene, stating that the decreased solubility of sodium iodide in toluene facilitates a greater conversion.[120] The authors postulate that inhibition could occur not only at the oxidative addition stage (Scheme 45, top) but also at the transmetallation stage (Scheme 45, bottom).
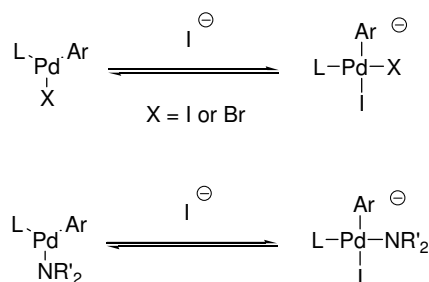
Scheme 45:   Iodide inhibition at either oxidative addition stage (*top*) or transmetallation stage (bottom).

It has been proposed that the formation of reactive monomeric oxidative addition complexes by cleavage of the dimeric bridging complexes is endergonic with bridging iodides.[140] The stability of these bridging dimers is believed to impede reactions of aryl iodides and prevention of their formation by using specialised ligands has been explored by Fors *et al.* (Scheme 46).[120]
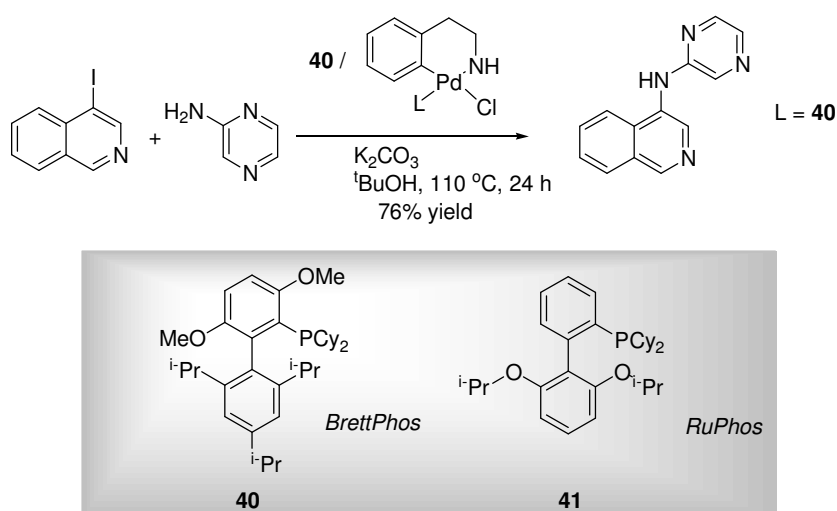
Scheme 46:   Specialised ligands for the amination of heteroaryl iodides.

BrettPhos **40** and RuPhos **41** are designed to favour formation of monomeric oxidation complexes in solution, thereby aiding amine coordination and transmetallation.[120] Good yields have been obtained using deactivated heteroarylamines and heteroaryl iodides when combined with palladacyclic sources of precatalyst. Hartwig found that low catalyst loadings and high conversions can be accomplished in the reaction between primary amines and aryl iodides when utilising the JosiPhos ligand **38** (Scheme 47).[158]
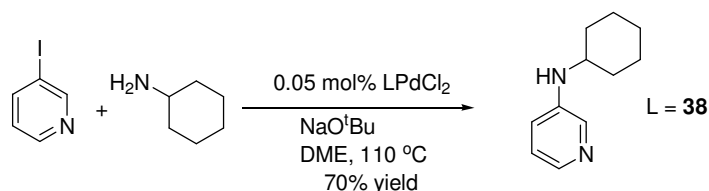
Scheme 47:   Dichloropalladium-JosiPhos complex as efficient catalyst for heteroaryl iodide amination with primary amines (see Figure 1 for structure of **38**).

The synthesis of functionalised chloroindoles through cascade cyclisation of gem-*ortho*-gem-dibromostyrenes has been achieved by Pd-catalysed amination with biarylphosphine ligand **42**.[159] An initial Suzuki cross-coupling allowed momo-arylation of the dibromoalkenyl moiety, followed by a tandem dual C-N amination with various primary amines and carbamates, which allowed cyclisation to provided the indole. This methodology allowed regiochemical control of the 4, 5, 6 or 7 chloro substituent (Scheme 48).
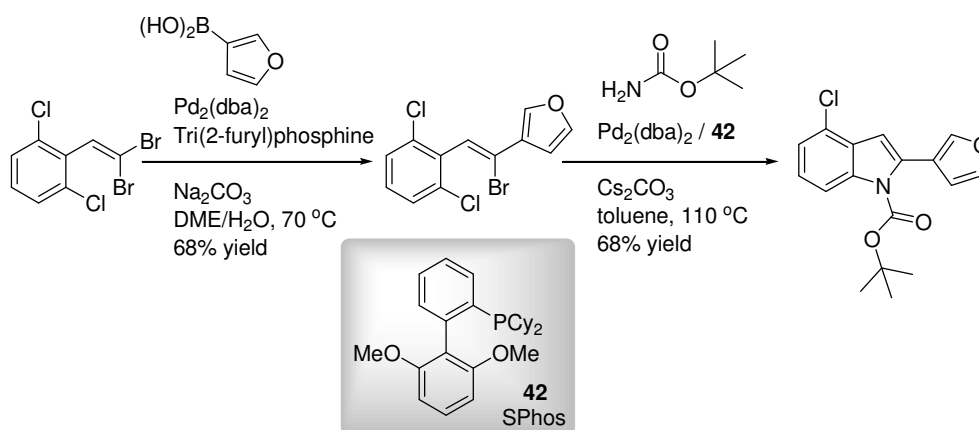
Scheme 48:   The formation of indoles by cascade cyclisation utilising Pd-catalysed amidation step.

The C-N coupling of 2-chloropyridine to various hydrazides using a JosiPhos/Pd$_2$(dba)$_3$ catalytic system followed by a dehydrative cyclisation gave access to functionalised triazolopyridines in good yields (Scheme 49).[163]
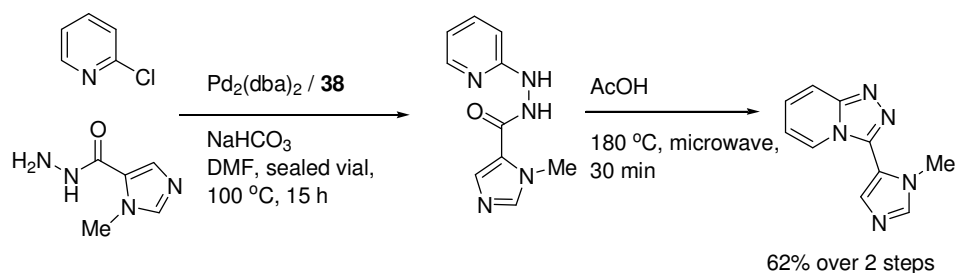
Scheme 49:   Sequential hydrazide C-N coupling / cyclisation route to triazolopyridines (microwave reactor power was not disclosed).

Amidations of aryl- and heteroarylmesitylates have been achieved in high yields using **40** as the ligand (Scheme 50).[161]
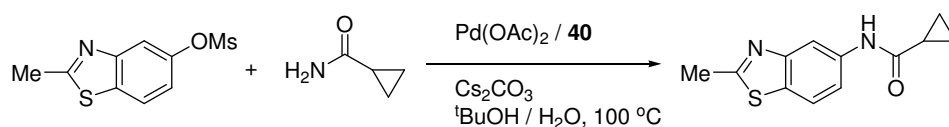
Scheme 50:   Amidation of heteroaryl mesylates.

Amination of indoles (Scheme 51),[170] indazoles (Scheme 52),[171] pyridazinones (Scheme 53),[172] tetrahydroquinolines (Scheme 54)[132] using various Pd catalyst systems highlights the useful role of the Buchwald-Hartwig reaction in the decoration of heterocycles relevant in the pharmaceutical sector.
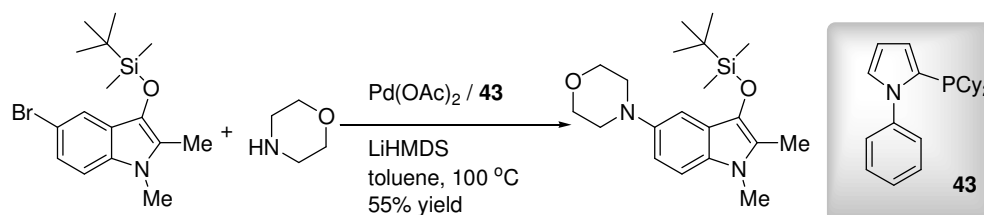
Scheme 51:   Amination of an electron-rich indole derivative using sterically hindered **43**.
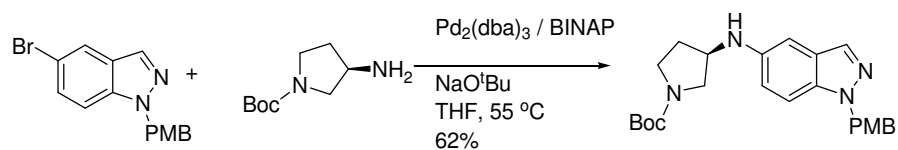
Scheme 52:   Amination of selectively protected indazoles using BINAP.
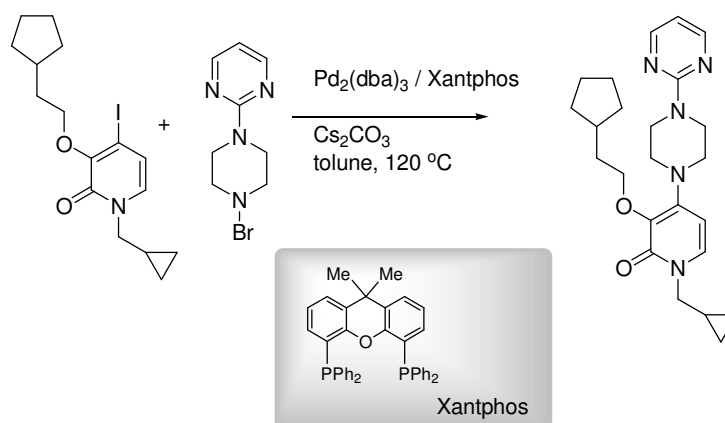
Scheme 53: Amination of iodopyridazinones using Xantphos as part of drug optimisation at Pfizer.
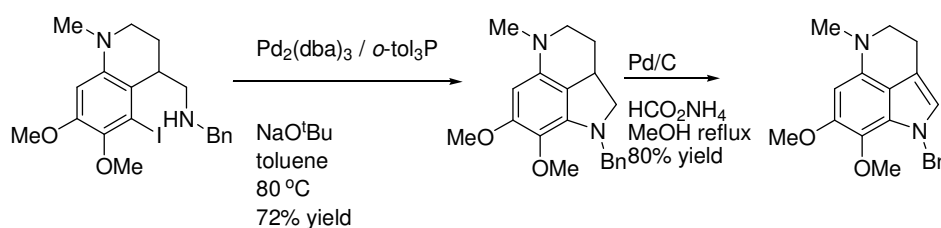
Scheme 54: Intra-molecular cyclisation of tetrahydroquinoline.

N-Arylation of azoles has been relatively under explored using the Buchwald-Hartwig reaction, compared to the Ullmann reaction, although progress has been made using DPPF and ^{t}Bu$_3$P ligands.[139,138,173] Indoles and pyrroles can be arylated with aryl bromides and aryl chlorides in good yields when ^{t}Bu$_3$P is used (Scheme 55),[138] and even carbazoles and imines have been arylated with DPPF (Scheme 56).[139] Tris-coupling can be performed in reasonable yields to give tris-carbazole system **44** by employing a ^{t}Bu$_3$P / Pd(OAc)$_2$ catalyst system with K$_2$CO$_3$ as base (Scheme 57).[173]
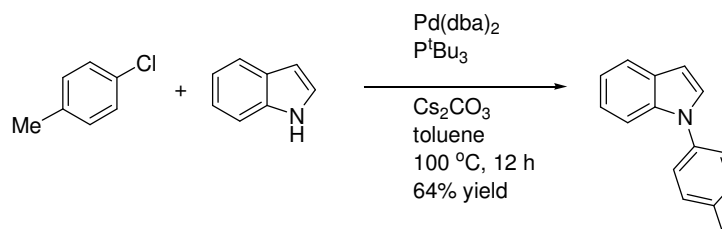
Scheme 55: Arylation of indole using 4-methylchlorobenzene.
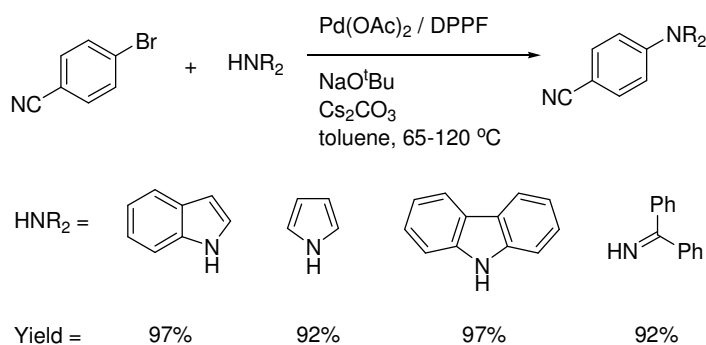
Scheme 56:   Arylations of azoles and imines.
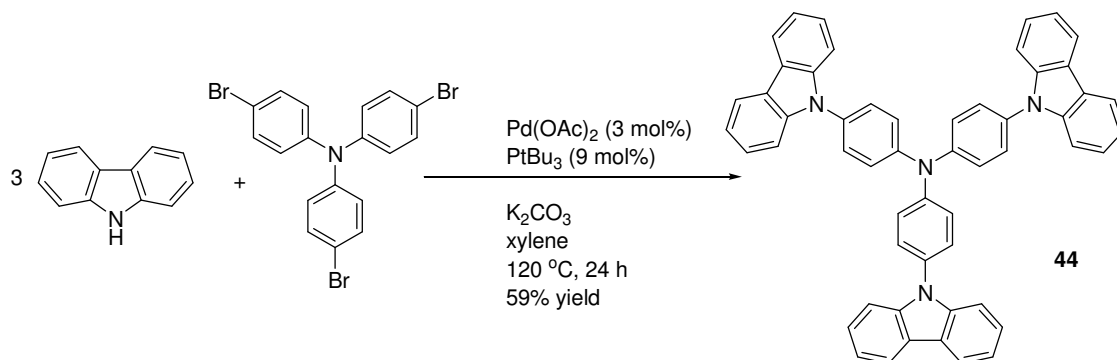
Scheme 57:   Arylations of azoles.

As described earlier, Hartwig found that reductive elimination of azolyl-palladium complexes required higher temperatures than the reductive elimination of anilines. The rationale for this observed difference in reactivity was the reduced nucleophilicity of azoles due to the nitrogen-lone pair electrons are delocalised within the heteroaromatic π-electron system.[139]

1.2.8   Conclusion

In conclusion, recent progress in the field of palladium-catalysed C-N coupling has made this a relevant reaction in modern synthetic chemistry. The range of designer ligands and optimised conditions allows for the coupling of substrates which are challenging for Ullmann-type protocols (primary alkylamines, aryl chlorides, *etc.*). Heterocyclic substrates are well tolerated; however, fewer examples of the amination of NH-heterocycles are shown in the literature than for the Ligand-Accelerated Ullmann reaction. Limitations include lower reactivity for aryl chlorides and the employment of often very expensive ligands and Pd-precatalysts.

1.3   Pd-Catalysed C-C Cross-Coupling: Suzuki-Miyaura Reaction

The prevalence of biaryl systems in pharmaceuticals, agrochemicals, natural products and in materials science necessitates efficient procedures to form C_{SP2}-C_{SP2} bonds. For biaryl formation, the Suzuki-Miyaura cross-coupling reaction is one of the most popular and versatile chemical transformations. The reaction involves the *ipso*-substitution of an aryl halide (or pseudohalide) by an arylboronic nucleophile, catalysed by palladium (or nickel) species. The identity of the nucleophile differentiates the type of C-C bond forming cross-coupling reaction with a wide variety available to the synthetic chemist.[7,174] These reactions include the Stille reaction (tin nucleophile), the Kumada or Kharasch reaction (magnesium nucleophile), Negishi (zinc nucleophile) and the Hiyama reaction (silicon nucleophile). A major drawback of the Stille reaction is the generation of toxic tin byproducts, although the generation of any stoichiometric metal-byproduct is common to these transformations and limits their industrial applications. Lack of substrate functionality, especially with the Kumada reaction of aryl Grignard nucleophiles is an issue, as is stability and ease of accessibility of these nucleophiles.

In contrast to the above named reactions, the Suzuki-Miyaura reaction generates innocuous boronic by-products, maintains good functional group tolerance and the boronic nucleophiles are generally stable species. Aryl boronic acid and boronic esters are readily accessed through various simple protocols such as Directed *ortho* Metallation (D*o*M),[175] halogen-metal-exchange,[176] Pd-catalysed coupling of B-B or B-H species to aryl halides[177] or catalytic C-H borylation by Ir catalysis.[178] More recently, C-H activation by palladium or rhodium catalysis has provided atom efficient cross-coupling methodologies by either coupling of an arene/heteroarene/heteroaryl C-H with an aryl halide,[179] or by oxidative coupling of two arene C-H groups.[180] Metal-free cross-coupling of benzene with aryl iodides, aryl bromides and aryl chlorides using organocatalysts has been achieved with evidence of a radical mechanism.[181]

1.3.1   Mechanism

The catalytic cycle for the Suzuki-Miyaura reaction is essentially similar to many metal-catalysed cross-coupling reactions. Like the Ullmann and Buchwald-Hartwig reaction (*vide supra*), it involves oxidative addition of the electrophile to a catalytic species, a transmetallation step of the nucleophile and a reductive elimination to generate the coupled

product and the active catalyst. In the Suzuki-Miyaura reaction the catalytic cycle has been extensively investigated experimentally[112] and by DFT calculations,[182] describing active catalytic species and intermediates. The general catalytic cycle is outlined in Scheme 58. The active Pd^0L_n species undergoes oxidative addition with Ar-X to give *trans* $L_nPd^0(Ar)X$, observed by mass spectrometry.[183] This species then undergoes transmetallation with the activated arylboronate $[Ar'-B(OH)_2OR]^-$ (from the arylboronic activated by base) with loss of X^-. This *trans* complex, also observable by mass spectrometry,[183] then undergoes isomerisation to the *cis* Pd^{II} complex and the final step is the reductive elimination of Ar-Ar' from the $L_nPd^{II}(Ar)Ar'$ species, generating Ar-Ar' and the regenerated active catalytic species.
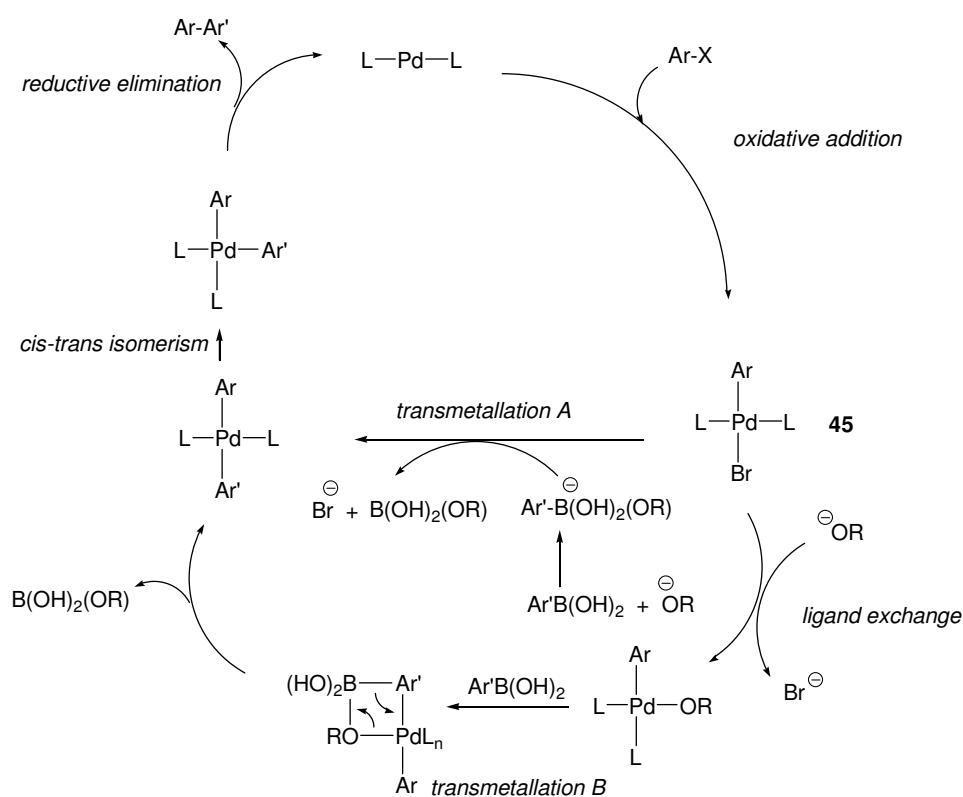
Scheme 58: General catalytic cycle of the Suzuki-Miyaura reaction.[183]

1.3.2 Oxidative Addition

This stage of the catalytic cycle is essentially the same as the Buchwald-Hartwig reaction (*vide supra*) with non-bulky monophosphine ligands (such as PPh_3) leading to the active L_2Pd^0 species. Practically, this is formed either by ligand dissociation from the commonly used Pd^0 precatalyst $Pd(PPh_3)_4$ to give $Pd(PPh_3)_2$ (Scheme 59)[184] or by activation of Pd^{II} precatalysts, such as $Pd(PPh_3)_2Cl_2$ (Scheme 60),[184] or $Pd(OAc)_2$ (Scheme 61).[185]

$$Pd(PPh_3)_4 \underset{+PPh_3}{\overset{-PPh_3}{\rightleftharpoons}} Pd(PPh_3)_3 \underset{+PPh_3}{\overset{-PPh_3}{\rightleftharpoons}} Pd(PPh_3)_2$$
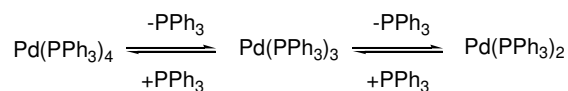
Scheme 59: Formation of active species from $Pd(PPh_3)_4$.

$$Pd(PPh_3)_2Cl_2 + 2OH^{\ominus} \longrightarrow Pd(PPh_3) + O{=}PPh_3 + 2 Cl^{\ominus} + H_2O$$
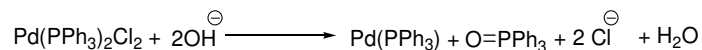
Scheme 60: Formation of active species from $Pd(PPh_3)_2Cl_2$.

$$Pd(OAc)_2 + n\,PPh_3 + H_2O \longrightarrow Pd(PPh_3)n^{-1} + O{=}PPh_3 + 2AcOH$$
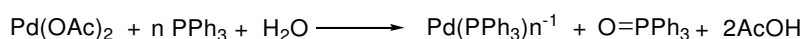
Scheme 61: Formation of active species from $Pd(OAc)_2$.

The coordination number of the active Pd^0 species depends upon the cone angle of the phosphine ligand with bulky phosphines reducing the coordination number.[186] As either Pd^0L_2 or Pd^0L can be the active catalytic species steric bulk (*vide infra*) on the ligand can force the formation of Pd^0L.[187-189] The *trans*-bisphosphine oxidative addition structure was observed for PPh_3 ligands after isolation of intermediates in the Suzuki-Miyaura cross-coupling of 2- and 4-bromopyridine derivatives.[190] Based on ^{31}P NMR studies, oxidative addition occurred faster at the C2 than the C4 position

Generally, oxidative addition with bulky phosphines (*i.e.* $^tBu_3P$ and *o*-tol$_3$P), chelating ligands (BINAP, DPPF, JosiPhos) and *ortho*-biaryldialkylphosphines occurs as in the Buchwald-Hartwig reaction, with the active catalytic Pd^0 species existing as a reactive monoligated 12-electron Pd^0L species (*vide supra*). This was aptly demonstrated by Littke *et al.*[189] who observed only one phosphine species by ^{31}P NMR during the Suzuki reaction with the L : Pd ratio of 1 : 1. This was assigned as the $Pd(^tBu_3P)_2$ species which did not seem to participate in the reaction directly. They postulated that phosphine-free palladium (half the palladium in the reaction mixture) is present with the active species being monoligated Pd^0L. As described in the Buchwald-Hartwig section previously, the nature of the oxidative addition complex is not only ligand dependent but also halide dependant.[111] For PPh_3 as a ligand, it has been shown by ^{31}P NMR that oxidative addition of PhBr occurs onto $Pd(PPh_3)_2$ leading to the $PdL_2Ph(Br)$ oxidative addition complex.[191] More recently, DFT calculations have countered this argument and have shown that, although endergonic, the dissociative loss of a phosphine from both $Pd(^tBu_3P)_2$ and $Pd(PPh_3)_2$ leads to much more reactive 12-electron Pd^0L species, able to participate better in the oxidative addition of aryl halides.[192] It was shown that the oxidative addition transition state for Pd^0L_2 is very

high energy when L = PPh$_3$ and does not even exist when L = P^{t}Bu$_3$. Lam *et al.*[193] have reported similar conclusions based on DFT calculations: the aryl bromides and chlorides require a monoligated-Pd pathway with electronic effects on the electrophile not altering the necessity for a dissociative pathway. They concluded that bulky or hemilabile ligands are required to enable oxidative addition of aryl bromides and chlorides. They also found that with bisphosphine-palladium complexes, oxidative addition occurred much more slowly due to the high energy barriers involved. Bisphosphine-palladium complexes do play a significant role in the oxidative addition of aryl iodides, however, with electron-withdrawing groups favouring a PdL$_2$Ar(I) transition state and electron-donating groups favouring a PdLAr(I) transition state. Apart from the steric effect and chelating *vs.* mono-ligating effects, the electronics of the phosphine also greatly affect the oxidative addition capability of the Pd^0 complex, with more electron rich species accelerating oxidative addition due to increased electron density on the Pd centre.[189]

1.3.3   Transmetallation

Owing to the low nucleophilicity of organoboron compounds, transmetallation does not generally occur; however, activation by negatively charged base can dramatically increase the rate of the reaction. This quaternisation of the organoboronic species to generate negatively charged 'ate' complexes, increases the nucleophilicity, thereby aiding transmetallation. For example, [RB(R')(OR'')$_2$]Li readily undergoes transmetallation.[194] Matos *et al.*[191] have shown that transmetallation occurs with retention of stereochemistry (Figure 62) owing to a β-hydroxybridged transition state, either by reaction of a hydroxypalladium intermediate (path A) or by a quaternised boronate (path B).
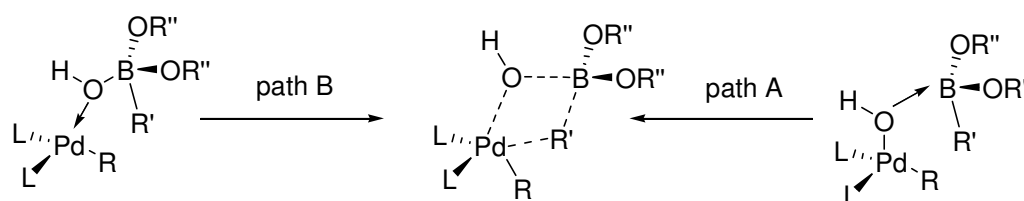
Scheme 62:   Transmetallation occurring by quaternisation of the boronic acid.

This alternative transmetallation step (Scheme 58, transmetallation B) in the catalytic cycle is also widely accepted whereby the oxidative addition complex **45** undergoes ligand

exchange with either an alkoxide or a hydroxide anion to form the alkoxy- or hydroxy-palladium complex.[195]

The oxidative addition step is generally rate limiting, especially for aryl chlorides and deactivated aryl bromides with the reactivity of the aryl halide decreasing as the group is descended (*vide supra*). The transmetallation step, however, follows the opposite reactivity order; Cl > Br > I in line with the greater Pd-X bond strength as the group is descended, due to the required ligand exchange of the halide form the Pd^{II} complex.

Due to the base-promoted quaternisation of the boronic acid, the nature of the base plays a significant role in the rates of the reaction. Generally, increasing the base strength (*i.e.* $MOH > M_3PO_4 > M_2CO_3 > MHCO_3$) increases the concentration of the ate complex in the reaction system, with cesium bases generally being stronger than the corresponding sodium bases.[196] However, the affinity of the counter cation for displaced halide also plays a large effect, whether transmetallation occurs *via* Path A or Path B (Scheme 62). The observed rates are in line with the stability constants for the halides: $Ag^+ > Tl^+ >> Ba^+ > Cs^+ > K^+$.[197] When employing sterically bulky arylboronics the reactivity follows the order: $TlOH > Ba(OH)_3, Tl_2CO_3 > NaOH > Cs_2CO_3, K_3PO_4 > Na_2CO_3 > NaHCO_3$ and can be attributed to the concentration of the ate complex and stability of the MX species, as outlined above. In another study, bulky arylboronic acids coupled best when the base strength was increased with the reactivity order: $KO^tBu > NaOEt > NaOH > Na_2CO_3$.[198] It has been speculated that the large size of the K^+ counter cation could template the boronate attack of the alkoxypalladium intermediate (Scheme 63) so increasing the rate of reaction.[199] Other methods for increasing the reaction rates of sterically hindered boronic acids are outlined in chapter 6.
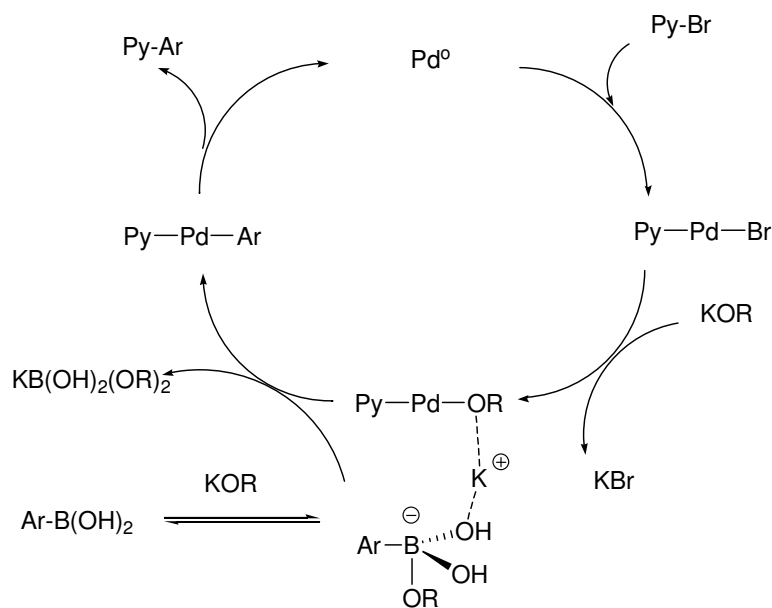
Scheme 63:   Possible intervention of K^+ cation as template for nucleophilic attack of boronate to alkoxypalladium intermediate.[199]

In the presence of base sensitive functionality, the use of KF as a mild base for the Suzuki-Maiyura reaction has been explored. The high affinity of F^- for boron is responsible for the formation of ate complexes of the type $[RB(OR'')_2F]K$.[200] Electron deficient boronic species transmetalate slower due to their decreased nucleophilicity and, therefore, can decompose under the reactions conditions.

1.3.4   Reductive Elimination

After the transmetallation step, *trans-cis* isomerisation occurs, bringing the aryl groups from the electrophile and nucleophile into the required geometry for reductive elimination. This could occur *via* three possible mechanisms: a 3-coordinate transition state by loss of a phosphine ligand (LPdR(R')); a 4-coordinate tetrahedral intermediate; or a 5 coordinate transition state by association of a phosphine or solvent molecule.[182] As with the Buchwald–Hartwig reaction, more electron deficient ligands promote reductive elimination by lowering the energy barrier for the reduction of the Pd^{II} species. However, as the oxidative addition step is generally the rate limiting step, the employment of electron rich ligands that favour oxidative addition has little impact on the reaction rates.

1.3.5   Improved Ligands and Conditions

As described above (oxidative addition), PPh$_3$ performs well as a ligand; however, it is not effective when employing electron rich aryl chlorides. Bulky and electron rich alkylphosphines enable oxidative addition of electron rich aryl chlorides by increasing electron density on the Pd centre and favouring more reactive monophosphine complexes. It seems, however, less bulky phosphines can improve sluggish reactions using aryltriflates as electrophiles, with PCy$_3$ providing more stable complexes at higher temperature than the corresponding P^{t}Bu$_3$ ligand.[189]

Using *ortho*-biphenylbisalkylphosphines,[151] bulky substrates coupled in higher yields when less bulky phosphines **46**-**48** were used compared with the bulky **49**.[201] For electron deficient heteroarylboronic acids and challenging heteroaryl halides, XPhos **50** is particularly effective, providing coupled products in excellent yields.[202]
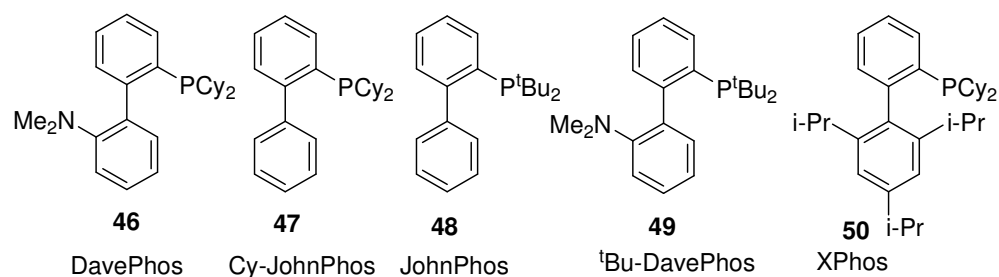
Figure 2:   *ortho*-Biphenylphosphine ligands.

The pyrophoric nature of alkylphosphines, such as ^{t}Bu$_3$P, serves to limit the usefulness of this very active ligand in cross-coupling procedures. This issue has been addressed by the use of HBF$_4$[203] salts of the phosphines.

The use of water as a reaction solvent has been achieved by employing phase-transfer agents, enabling insoluble aromatics and heteroaromatics to couple effectively.[204-206]

Coupling of electron deficient boronic acids[207-208] or boronic acids with an α-heteroatom[209] often give protodeboronation byproducts due to the slow transmetallation of the ate species. Protodeboronation occurs under Suzuki-Miyaura reaction conditions *via* a base promoted mechanism, although HCl, Zn^{2+} and Cd^{2+} ions also catalyse this reaction.[210] Methods of combating these sluggish reactions and side-reactions have included modified ligand design, with RuPhos capable of coupling 3-pyridylboronic acids in excellent yields.[211]

1.3.6 Conclusions

As a method for forming aryl-aryl bonds, the Suzuki-Miyaura reaction is unchallenged in its versatility and widespread applications. Many different conditions have been investigated to improve on yields for sluggish systems, tolerate sensitive functionality and to reduce catalyst loadings. Heterocyclic systems, especially heteroarylboronic acids are challenging substrates and methods used to couple such species are therefore of interest. The wide choice of ligands and conditions can be overwhelming, however choosing logically based on the electronics of the nucleophile or electrophile, steric considerations and the sensitivity of any functionality *in situ*, a good starting point can be made.

CHAPTER 2 - SEQUENTIAL CROSS-COUPLINGS ON AZOLES

2.1   Introduction

Arylated heterocycles are key structural motifs in a wide range of pharmaceuticals, agrochemicals, and organic functional materials; hence, great effort has been devoted to their synthesis by a range of metal-catalysed protocols.[22,179,212-216] Contemporary procedures can be readily performed with low catalyst loadings and good functional-group tolerance, as reviewed in Chapter 1. These include C–heteroaryl bond formation by palladium catalysed Suzuki–Miyaura cross-coupling reactions of arylboronic acids/esters with heteroaryl halides,[176,217] or by direct functionalisation of heterocyclic C–H bonds with aryl halides[214] catalysed by palladium or copper species.[218] For heterocyclic *N*-arylation, which is relevant to the present work, the classical copper-promoted Ullmann reaction has been improved by the addition of a variety of ligands, such as diamines,[26,55,61-62,219] pipecolinic acid,[78] sterically hindered phosphanes,[220] a mixture of 1,10-phenanthroline and dibenzylideneacetone,[3]   4,7-dimethoxy-1,10-phenanthroline,[51]   (*S*)-pyrrolidinylmethylimidazole,[99] *N*-hydroxyimides[221] or ninhydrin.[75] A CuCl-catalysed *N*-arylation of imidazole with arylboronic acids has been developed in the absence of an additional chelating ligand.[222] Combined N(1)- and C(3)-arylations of 3-iodoindazole using boronic acids and Cu(OAc)$_2$ have been reported.[223] However, these methods require additional steps to synthesise the arylboronic acid. You *et al.* have recently shown that imidazoles can be *N*-arylated with aryl and heteroaryl halides in the presence of base and a catalytic amount of CuI: an excess of imidazole improved the product yield and it was noted that the imidazole substrate may also function as a ligand in this process.[224] The CuOAc-mediated *N*-arylation of indoles and carbazole with aryl iodides under base-free and ligandless conditions has been reported.[225] Developments in iron-catalysed[226] *N*-arylations have also been reported although warnings over the possible role of trace Cu contamination in these catalysts have been noted recently.[227]

While many important results have been achieved for *N*-arylations, it is notable that much less progress has been made for *N*-heteroarylations, *i.e.* analogous reactions with heteroaryl halides.[224] The development of this methodology is, therefore, of considerable interest. To this end, we undertook a series of heterocyclic *N*-heteroarylation reactions and then exploited further reaction at an active halide site in the products *via* Suzuki–Miyaura cross-coupling reactions, leading to the expedient construction of tris(hetero)aryl scaffolds

comprising two or three *N*-heterocyclic rings. Tris(aryl) compounds containing two or three heteroaryl rings have found applications in medicinal chemistry,[228] fluorophores[229] and liquid crystals[230] (see Figure 3).

(A)

(B)   (C)

R =   -O₂C-C₆H₄-OC₁₆H₃₉
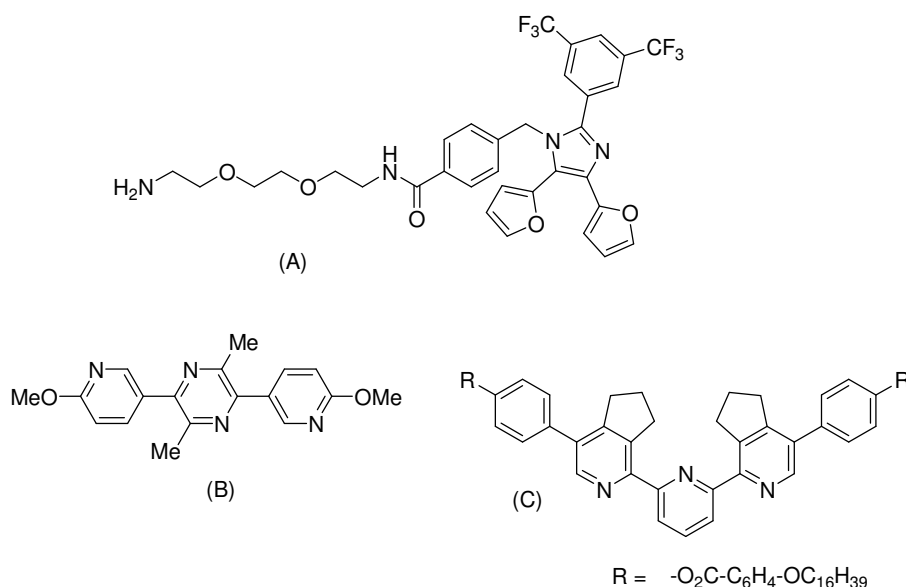
Figure 3:   Tris(aryl)systems   containing   three   heteroaryl   rings.   A   potential neurogenesis agent for the treatment of neurodegenerative diseases (A); a fluorophore (B); and a liquid crystalline material (C).

N-aryl azoles have seen potential applications in a variety of drugs (see Figure 4) such as: platelet derived growth factor inhibitors as anticancer agents **51**,[231] nephritis treatment **52**,[232] immunosuppression drugs **53**,[233] potential antitumour drugs **54**,[234] potential cancer treatment agent **55**[235] and as treatments for obesity **56**.[236] The bioactivity of benzimidazole and its analogues is not surprising considering the similarity in structure of natural compounds such as histidine and the purines. As direct analogues to histidine, benzimidazoles and related indoles, oxindoles and benzimidazolones have been used to create multi-ring compounds for a variety of biological studies.[237-239]
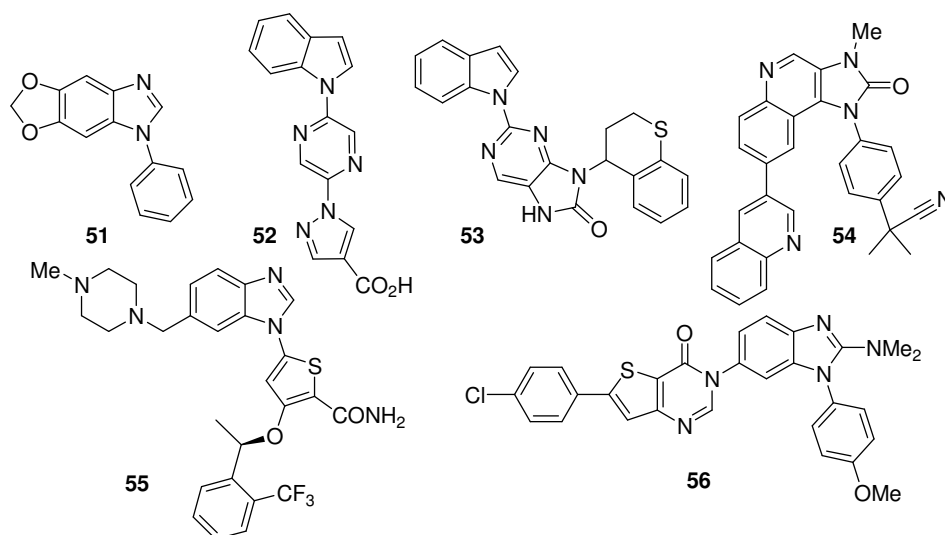
Figure 4:   *N*-(Hetero)aryl azoles investigated as potential drug molecules.

2.2   Results and Discussion

2.2.1   Ligand-accelerated Ullmann-Reactions

We chose benzimidazole **57** and 1-methylbenzimidazolone **58** as starting reagents for the optimisation of our strategy for two reasons: (i) their derivatives are widespread in structures of biological and medicinal importance;[240-244] (ii) their arylation reactions have been relatively neglected compared to other NH heterocycles; imidazole is most commonly used in this context.[3,75,99,224,245,246] To confirm the versatility of the procedures, analogous reactions were also performed for imidazole **59** and pyrrole **60**. The general concept of sequential N–C and C–C couplings leading to tris(hetero)aryl systems is depicted for benzimidazole in Scheme 64. The higher reactivity of iodides compared to bromides was exploited for selectivity in the reactions of the dihaloarenes in step 1. Scheme 65 depicts the N–C couplings and the specific examples are shown in Table 1.
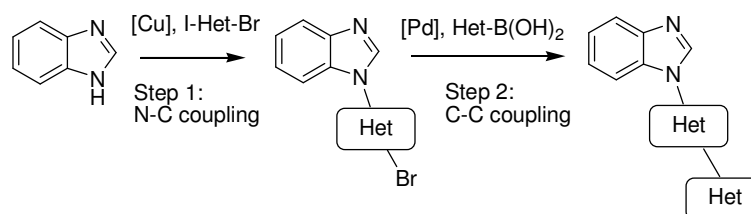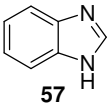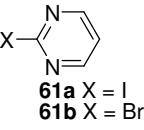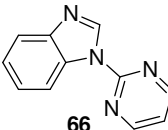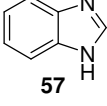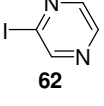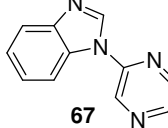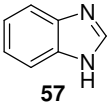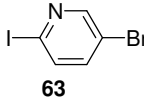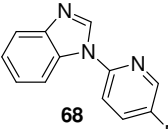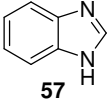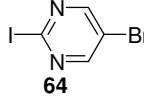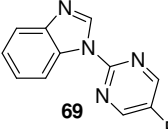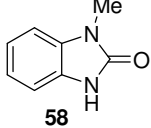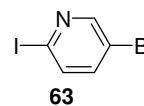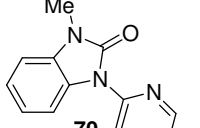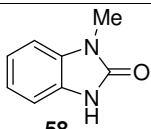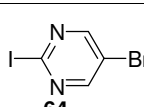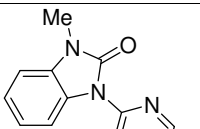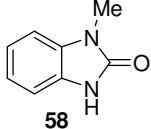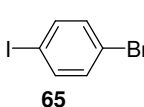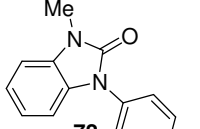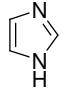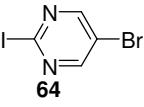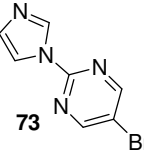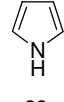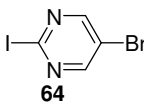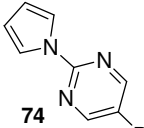
Scheme 64:   Construction of tris(hetero)aryl scaffolds by sequential N–C and C–C couplings.
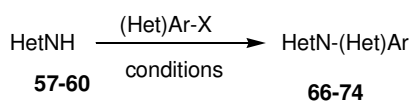
Scheme 65:   Synthesis of **66-74**. For conditions see Table 1.

Table 1:   Copper catalysed C-N cross-couplings.[a]

Entry	Het-NH	(Het)Ar-X	Product	Conditions, Isolated Yield (%)[B]	
1	**57**	**61a** X = I **61b** X = Br	**66**	a b	50 (X=I) 78 (X=Br)
2	**57**	**62**	**67**	a	70
3	**57**	**63**	**68**	c	90
4	**57**	**64**	**69**	c	57
5	**58**	**63**	**70**	c	94
6	**58**	**64**	**71**	c	76
7	**58**	**65**	**72**	d	81
8	**59**	**64**	**73**	c	65
9	**60**	**64**	**74**	c	84

[a] Reaction Conditions: (a) **61a**, Cs_2CO_3, CuI, 1,10-phenanthroline, DMF, 110 °C, 6 h; (b) **61b**, Cs_2CO_3, Cu_2O, Chxn-py-al, acetonitrile, 87 °C, 64 h; (c) Cs_2CO_3, CuI, 1,10-phenanthroline, DMF, 70 → 80 °C, 18 → 24 h; (d) Cs_2CO_3, CuI, 1,10-phenanthroline, DMF, 80 → 110 °C, 24 → 65 h. [b] The quoted yields are for isolated product after purification by chromatography and/or recrystallisation.

In test reactions benzimidazole **57** reacted smoothly with 2-iodopyrimidine **61a** and 2-iodopyrazine **62** under modified Ullmann conditions (Cs_2CO_3, CuI, 1,10-phenanthroline, DMF, 110 °C)[60] to afford the *N*-heteroarylated products **66** and **67** in 50% and 70% isolated yields, respectively (Table 1, Entries 1 and 2). The comparable reaction of **57** with 2-bromopyrimidine **61b** using the conditions developed by Cristau, Taillefer, *et al.*[26] (Cs_2CO_3, Cu_2O, Chxn-py-al, acetonitrile, reflux) gave **66** in 78% yield. These workers found that the reaction of imidazole with 4-bromo-1-iodobenzene (1 equiv.) took place with complete regioselectivity at the iodine site. We have found that for reactions of the dihalo reagents **63** and **64** with the NH heterocycles **57-60** the optimum conditions to achieve selective displacement of the iodo substituent[247] are: **57-60** (1.2 equiv.), **63** or **64** (1.0 equiv.) Cs_2CO_3 (2.0 equiv.) CuI (10 mol-%) and 1,10-phenanthroline (10 mol-%) in DMF at 80 °C (Table 1, Entries 3–6, 8 and 9). Other ligands that were trialed using these conditions for the reaction of benzimidazole and 2-iodopyrimidine included 8-hydroxyquinoline[74] and DMCDA[61] however, lower conversions were noted upon completion check by GCMS, qualitatively. Higher reaction temperatures (e.g. 110 °C as used in Entries 1 and 2) resulted in considerably lower product yields for reactions of **63** and **64**. The reaction of the less activated 4-bromo-1-iodobenzene (**65**) with benzimidazolone **58** (Entry 7) required a higher temperature (100 °C) to drive the reaction to completion to form **72**. Table 1, Entries 3–9, show that moderate to high isolated yields were obtained for all the products **68-74**, which possess a bromo substituent suitable for a subsequent C–C (hetero)arylation reaction. The reactions of 5-bromo-2-iodopyridine (**63**) were especially efficient (Entries 3 and 5).
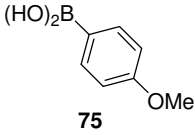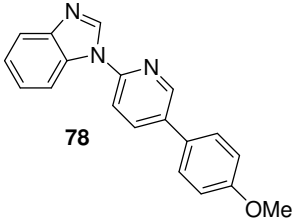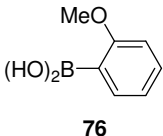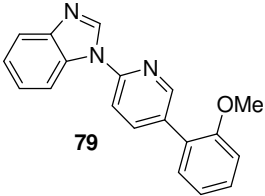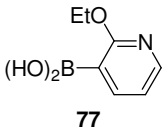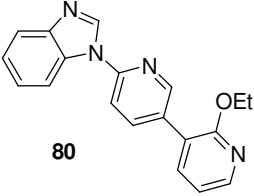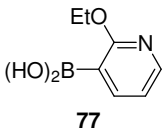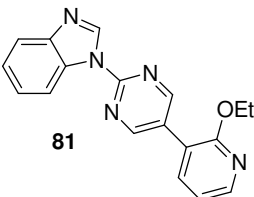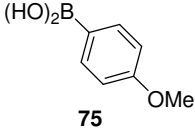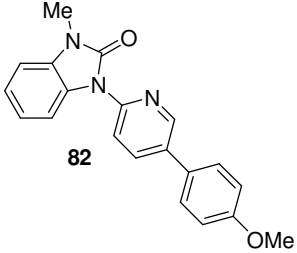
2.2.2 Suzuki-Miyaura Reactions
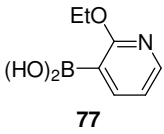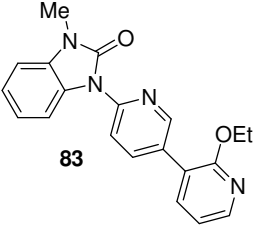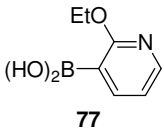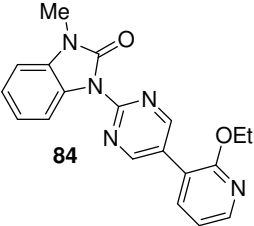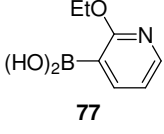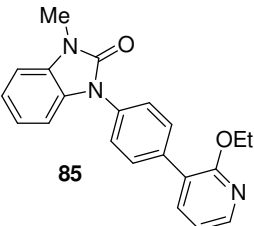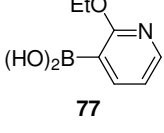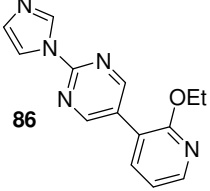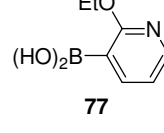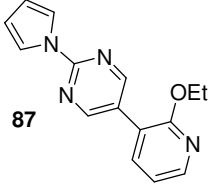
To accomplish step 2 of our strategy (Scheme 64) the compounds **68-74** were treated with the commercially available methoxyphenylboronic acid derivatives **75** and **76**, and the previously synthesised[248] pyridylboronic acid derivative **77** in Pd-catalysed Suzuki–Miyaura reactions[176,249,217,250] to obtain the tris(hetero)aryl scaffolds **78–87** comprising two or three *N*-heterocyclic rings (Scheme 66).

$$\text{HetN-Ar-Br} \xrightarrow[\text{conditions}]{\text{Ar'-B(OH)}_2} \text{HetN-Ar-Ar'}$$
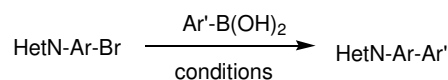
Scheme 66:   Synthesis of **78-87**. For conditions see Table 2.

Table 2:   Palladium catalysed C-C cross-couplings.[a]

Entry	Het-N-Ar-Br	Ar-B(OH)$_2$	Product	Conditions, isolated yield (%)[b]	
1	**68**	**75**	**78**	a	74
2	**68**	**76**	**79**	a	96
3	**68**	**77**	**80**	a	96
4	**69**	**77**	**81**	a	79
5	**70**	**75**	**82**	a	76

Entry	Het-N-Ar-Br	Ar-B(OH)$_2$	Product	Conditions, isolated yield (%)[b]	
6	**70**	**77**	**83**	a	**0**
7	**71**	**77**	**84**	a	0
				b	43
8	**72**	**77**	**85**	a	30
				b	83
9	**73**	**77**	**86**	a	48
10	**74**	**77**	**87**	a	78

[a] Reaction conditions, (a) Pd(PPh$_3$)$_2$Cl$_2$, 1,4-dioxane, aq. Na$_2$CO$_3$ (1 M), 80 °C; (b) Pd(PPh$_3$)$_4$, 1,4-dioxane, Na$_2$CO$_3$ (1 M), 80–90 °C; (c) [Pd$_2$(dba)$_3$], 1,4-dioxane, aq. K$_3$PO$_4$ (1.27 M), 100 °C. [b] The quoted yields are for the isolated product after purification by chromatography and/or recrystallisation.

There is considerable current interest in the cross-coupling of pyridylboronic acids.[251-254] The alkoxy substituents on the aryl/heteroaryl boronic acids were chosen to ensure good solubility of the products. The results are collated in Table 2. Standard conditions using Pd(PPh$_3$)$_2$Cl$_2$ (*ca.* 5 mol-%) as catalyst, Na$_2$CO$_3$ (1 M) as base, in dioxane at 80 °C gave the products **78**-**82** in high yields (Entries 1–5). The molecular structure of **78** determined by X-ray crystallographic analysis is shown in Figure 5. A dihedral twist between benzimidazole-pyridine (30.7 °) and pyridine-benzene (27.2 °) resulted in an out-of-plane geometry with the pyridyl nitrogen lone pair facing toward the benzene ring of benzimidazole.
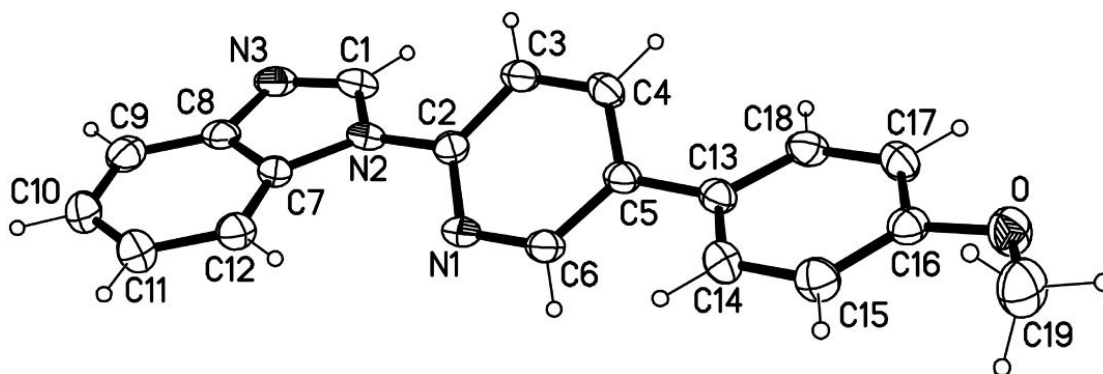
Figure 5: X-ray molecular structure of compound **78** (50% thermal ellipsoids). Dihedral angles [°]: benzimidazole/pyridine 30.7, pyridine/benzene 27.2, benzene/methoxy 10.2. Courtesy of Dr. Andrei S. Batsanov (Durham).

To our surprise, applying these conditions to attempted reactions of **70** and **71** with boronic acid derivative **77** failed to yield any product – unreacted **70** and **71** were recovered in 83% and 88% yield respectively (Entries 6 and 7, conditions a). When the catalyst was changed to Pd(PPh$_3$)$_4$ (with Na$_2$CO$_3$ as base) or [Pd$_2$(dba)$_3$] (with K$_3$PO$_4$ as base)[255] product **83** was obtained in 67 and 54% yields, respectively (Entry 6, conditions b, c). Similarly, conditions b gave **84** in 43% yield. Pd(PPh$_3$)$_4$ is a more active catalyst than Pd(PPh$_3$)$_2$Cl$_2$, being a Pd^o pre-catalyst, therefore, explaining the increased yields. The low yields when using Pd(PPh$_3$)$_2$Cl$_2$ could be as a result of phosphine ligand displacement by the benzimidazolone substrate.[107,156]
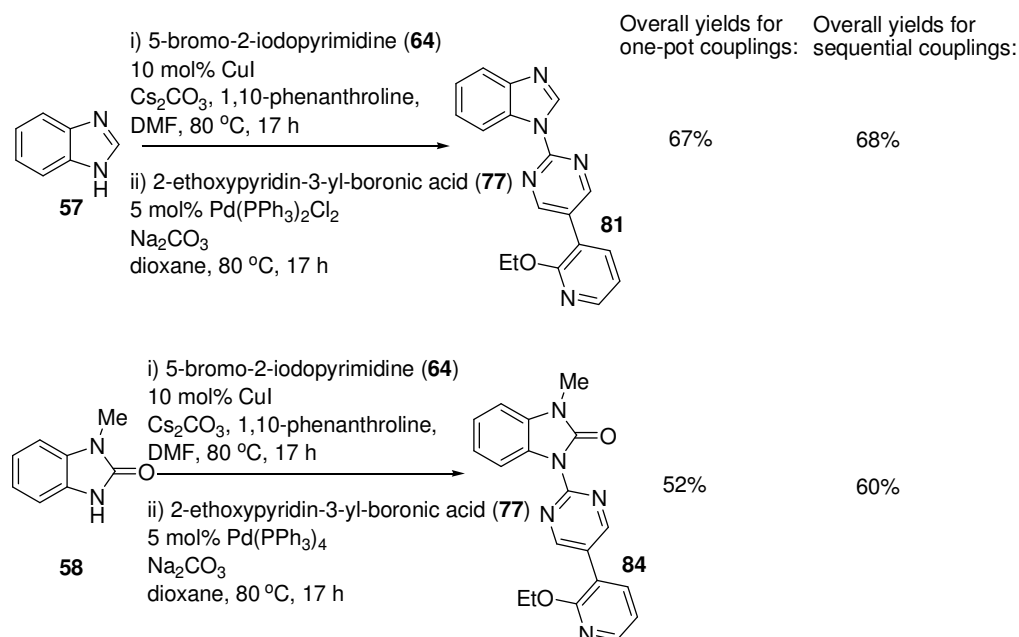
Scheme 67:   One-pot C-N/C-C cross-coupling protocol *vs.* sequential procedure.

A general trend was that the Suzuki–Miyaura reactions were less efficient in the benzimidazolone series, especially Entries 6–8, compared to benzimidazole, imidazole and pyrrole analogs (Entries 1–4, 9, 10). Analogous one-pot, two-stage procedures gave compounds **81** and **84** starting from benzimidazole (**57**) and 1-methylbenzimidazolone (**58**) in 67% and 52% overall yields, respectively (Scheme 67).

2.3   Conclusions

In summary, this work[256] established a series of reactions which constitute expedient and powerful methodology for the synthesis of new multi-heteroaryl scaffolds by a combination of N–C heteroarylation and C–C cross-couplings. Functionalised benzimidazole, benzimidazolone, imidazole and pyrrole derivatives were thereby obtained. This protocol complements existing strategies which are of great importance in diverse areas of heterocyclic chemistry, especially the development of new molecular templates for drug discovery and materials chemistry applications. The practical benefits include readily-available and inexpensive starting materials, substrate versatility, experimentally straightforward procedures and good product yields. One significant aspect of the work is that the sequential N–C and C–C couplings can be performed in a one-pot process in >50% overall yields.

CHAPTER 3 - PYRIDIN-2(1*H*)-ONES

3.1 Introduction

Functionalised pyridones are of continued interest due to their prevalence in naturally occurring compounds,[257-259] bioactive compounds and drugs,[260-270] coordination chemistry[271] and also for their catalytic acitivity.[272] New routes for the synthesis and functionalisation of pyridones continue to be developed.[273-274] Metal-catalysed cross-coupling reactions have revolutionised the modification of pyridones[275] and related heterocycles, with C-C, C-N, C-O bond forming processes now widely utilised.[22,1] As reviewed in Chapter 1, Suzuki-Miyaura, Buchwald-Hartwig and Ullmann-type reactions have become ubiquitous in the post-functionalisation of heterocycles. Access to *N*-arylpyridones was traditionally achieved using harsh Ullmann-Goldberg conditions[276] resulting in low yields and poor functional group tolerance. Ligand-accelerated and copper-catalysed approaches have led to much milder coupling conditions. [26,52,277-280,] Other methods for *N*-arylating pyridones and related heterocycles include: copper mediated coupling with arylboronic acids,[278,4-5] lead-mediated coupling to aryl halides[281-282] and HATU-mediated coupling of arylamides to 4-hydroxyquinazolines.[283] Following our work in Chapter 2, and in the light of general interest in sequential metal-catalysed routes to functionalised heteroaryl systems, [284-285,256,286,254,252] we set out to develop an efficient divergent route to tri-(hetero)aryl systems based on the pyridin-2(1*H*)-one framework, starting from the commercially-available 2-fluoro-5-pyridylboronic acid **88**.[287] This work is described in this Chapter, along with related reactions of 2,6-difluoro-5-pyridylboronic acid **117**.

3.2 Results and Discussion

3.2.1 Suzuki-Miyaura Cross-Coupling and Hydrolysis

An overview of our methodology is shown in Scheme 68. Suzuki-Miyaura cross-coupling of 2-fluoro-5-pyridylboronic acid **88** with (hetero)aryl bromides **89-91** furnished compounds **92-94** under standard conditions[288-289] in high isolated yields (Table 3). Conversion of **92-94** into the 2-pyridone derivatives **95-97** was achieved in high yields by hydrolysis under basic conditions (Table 3). Acidic hydrolysis of 2-fluoropyridines to yield 2-pyridones has been utilised by Cheng *et al.*[253] Compounds **93** and **94** reacted faster than

92 (see Table 3), presumably due to the increased electrophilicity imparted by the electron withdrawing effect of the quinolyl and pyridyl substituents, respectively.
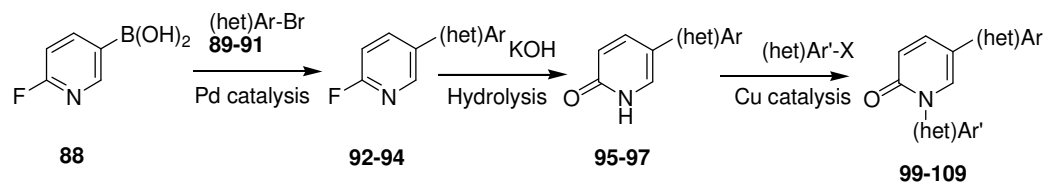
Scheme 68: Protocol for the three-step synthesis of 1,5-di(hetero)arylpyridin-2(1*H*)-one derivatives.

Table 3: Pd-catalysed cross-coupling of **88** with (hetero)arylbromides **89-91** and subsequent basic hydrolysis.

Entry	(het)Ar-Br	Cross-coupling product[c]	Yield (%)[a]	Hydrolysis product[e]	Yield[b] (%)
1	**89**	**92**	98	**95**[f]	83
2	**90**	**93**[d]	89	**96**	88
3	**91**	**94**	97	**97**	92

[a] The quoted yields are for isolated product after purification by chromatography and/or recrystallisation. [b] The quoted yields are for isolated product after purification. [c] Reagents and conditions: **88** (1.2-1.5 equiv), (hetero)arylbromide (1.0 equiv), Pd(PPh$_3$)$_2$Cl$_2$, (2.5 mol%), aq. Na$_2$CO$_3$ (1 M), 1,4-dioxane, reflux, 1-20 h under argon. [d] 1.5 mol% Pd(PPh$_3$)$_2$Cl$_2$ used. [e] Reagents and conditions: compound **92**, **93** or **94**, aq. KOH (1 M), 1,4-dioxane, reflux, 24 h. [f] 66 h reaction time.

3.2.2   Ligand-Accelerated Ullmann Cross-Coupling

It has previously been observed that the copper-catalysed coupling of 2-pyridones can lead to both C-N and C-O arylated products.[52,74] To explore this reaction in our system, pyridone derivative **95** was reacted with 2-bromo-5-(trifluoromethyl)pyridine **98** (Scheme 69). After isolation and full analysis (*vide infra*) of the *N*-heteroarylated product **99a**, a comparison with the crude ^{1}H NMR spectrum and GC-MS traces confirmed that **99a** was the major product. The other product displayed an identical *m/z* in the GCMS trace and was presumed to be **99b**, but could not be obtained pure. An initial screening was undertaken utilising commonly employed conditions and ligands for the C-N coupling of 2-pyridones, 2-pyridazinones and NH-heterocycles (Table 4). Using 1,10-phenanthroline (phen) with conditions used previously for the *N*-heteroarylation of benzimidazole and other NH-heterocycles,[256] conversion was complete after 24 h with a 79:21 ratio of **99a:99b** (Table 4, entry 1). Buchwald's 4,7-dimethoxy-1,10-phenanthroline ligand has proved to be effective for the copper-catalysed *N*-arylation of 2-pyridone;[52] however, the high cost of the ligand led us to try cheaper alternatives. Whilst keeping the same base (Cs_2CO_3), the solvent was changed to dioxane, 8-hydroxyquinoline (8-HQ) was employed as the ligand and PEG was added as a solid-liquid transfer catalyst.[51] However, despite 8-HQ being previously used to *N*-arylate pyridones[74] and pyridazinones,[280] these conditions resulted in a low conversion and a reduced ratio of **99a:99b** (Table 4, entry 2). When *N,N'*-dimethylcyclohexane-1,2-diamine (DMCDA) was employed using K_2CO_3 in toluene[279] (Table 4, entry 3) the conversion was complete with a high ratio (95:5) of **99a:99b** and **99a** was isolated in 80% yield (Table 5, entry 3). By changing the solvent to DMSO,[52] **99a** was the sole product observed (Table 4, entry 4). It has been observed previously that more polar solvents favour the 2-(1*H*)pyridone tautomer.[26] Utilising the potentially tetradentate Schiff base ligand Chxn-Py-Al with conditions developed by Cristau *et al.*, for the *N*-arylation of 2-pyridone,[26] conversion was improved compared to 8-HQ with an enhanced **99a:99b** ratio of 50:11 (Table 4, entry 5).
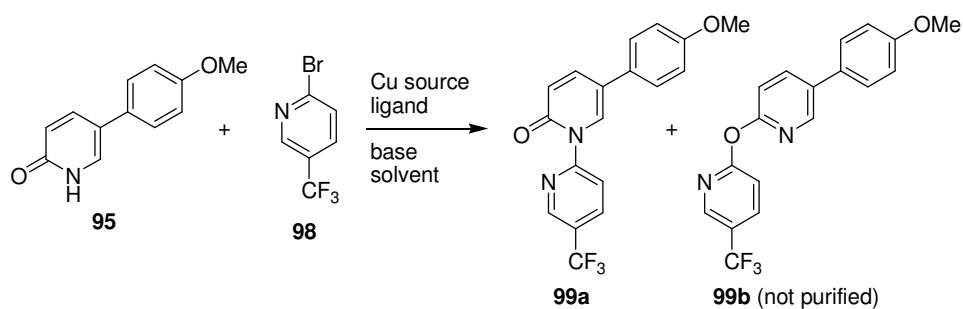
Scheme 69:   Coupling of **95** and **98**. For conditions see Table 4.

Table 4:   Screening conditions for Cu-catalysed cross-coupling of **95** with **98**.[a]

Entry	Cu source	Ligand	Base	Solvent	GC-MS analysis[c] 98 : 99a : 99b
1	CuI	phen	Cs_2CO_3	DMF	0 : 79 : 21
2	CuI	8-HQ	Cs_2CO_3	dioxane[b]	69 : 20 : 11
3	CuI	DMCDA	K_2CO_3	toluene	0 : 95 : 5
4	CuI	DMCDA	K_2CO_3	DMSO	3 : 97 : 0
5	Cu_2O	Chxn-Py-Al	Cs_2CO_3	MeCN	39 : 50 : 11

[a] Conditions and reagents: **95** (0.735 mmol), **98** (0.700 mmol), Cu source (0.07 mmol), ligand (0.140 mmol), base (1.40 mmol), anhydrous solvent (2 mL), 100 °C, 36 h under argon. [b] PEG (43 mg) additive used. [c] A sample (0.2 mL) of the stirred reaction mixture was diluted with dioxane (5 mL), filtered through a pipette with a cotton wool plug and injected directly into the GCMS. Ratios calculated based upon integrations of the GC traces of **98**, **99a** and **99b**.

4-Bromoanisole **89** was chosen as a more challenging substrate to couple with pyridone **95** as it is a deactivated halogen due to the *para*-methoxy group. Using the best conditions from Table 4 (entry 3: CuI, DMCDA, K_2CO_3 in toluene) gave clean conversion to **100**, which was isolated in 82% yield: no other product was detected by GC analysis (Table 5, entry 2) (Scheme 70). However, when changing the ligands to those used in the previous screening (Table 4, entries 1, 2 and 5), no reaction of **95** with **89** was observed. The structure of **100** was confirmed by single crystal X-ray analysis (Figure 6) showing a large torsion angle between the pyridone and C-N bound anisole ring (68.6 °) and a much smaller angle between the pridone and the C-C bound anisole ring (28.7 °). IR observation of a strong C=O stretching band at 1662 cm^{-1}, a ^{1}H NMR signal at 6.7 ppm for the proton *ortho-* to the carbonyl and the crystal structure all clearly indicate the C-N and not the C-O isomer. 2D NMR (NOESY) analysis did indicate an interaction between the proton *ortho-* to the pyridone nitrogen and the protons of the C-N bound anisole ring, an interaction not expected for the C-O isomer.
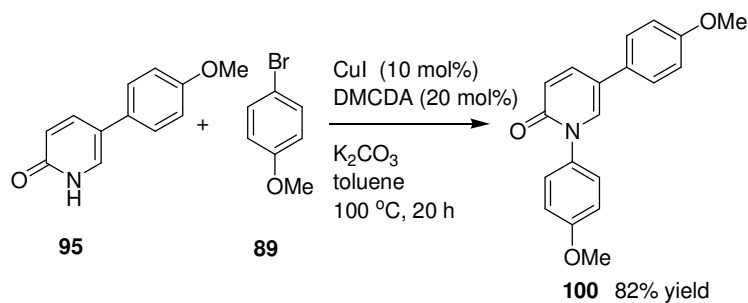
Scheme 70:   Coupling of **95** and **89** to yield **100.**
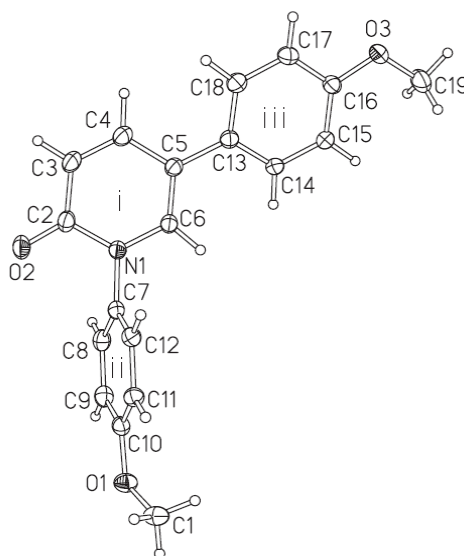
Figure 6:   X-ray molecular structure of **100**. Interplanar angles (°): i/ii 68.6, i/iii 28.7.

Having found suitable conditions for *N*-arylation, 2-pyridone derivatives **95**, **96** and **97** were coupled with a variety of aryl and heteroaryl halides to give the functionalised 2-pyridones **99-107** (Table 5, entries 1-12 and Scheme 71). High yields were also obtained when using more activated heteroaryl bromides (Table 5, entries 1, 3 and 4). Pyridone **96** coupled with both 4-bromoanisole **89** and 2-bromo-5-(trifluoromethyl)pyridine **98** giving **103** (66%) and **104a** (72%), respectively (Table 5, entries 5 and 6). Alongside the major product **104a**, the C-O coupled product **104b** was isolated in low yield (Table 5, entry 6). A comparison of IR stpectra indicate a lack of strong C=O stretching band in **104b** as observed in **104a** (1609 cm^{-1}). A comparison of ^{1}H NMR signals shows that the signal for the proton *ortho*- to the C-O/C=O is 7.27 ppm for **104b** and 6.81 ppm for **104a** indicating a
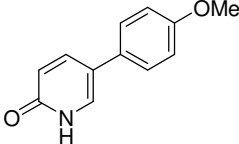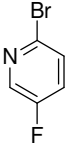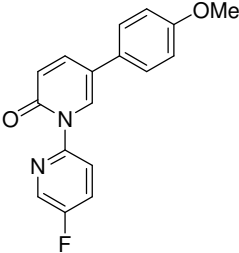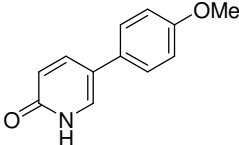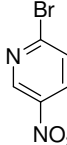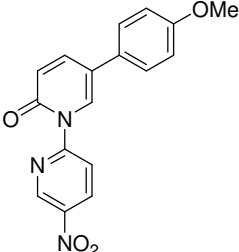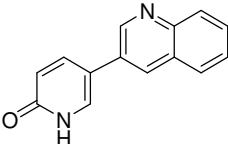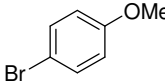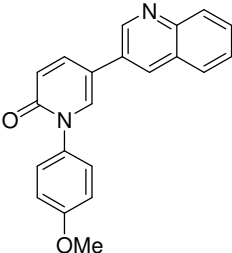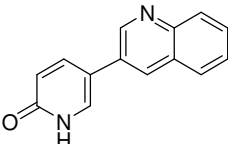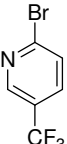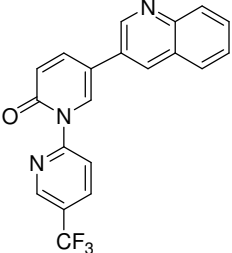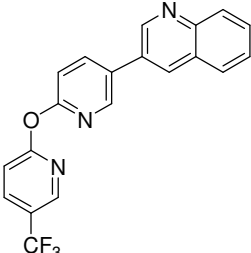
much more aromatic, deshielded environment for the C-O isomer. Coupling of **97** was also performed with **91** giving **105** in a good yield. Pyridone **97** coupled to **89** under the same conditions, giving **106** in 74% isolated yield. Coupling at the iodo site of **112** afforded **107** (entry 10) leaving an active bromo group for further functionalisation. Aminopyrazine derivative[290] **113** coupled to **97** to give **108** in 40% yield (entry 11). 2-Bromo-5-nitrothiophene **114** coupled to **97** to give **109** in 60% yield. Functional group tolerance is notable, with fluoro, trifluoromethyl, methoxy, primary amino and nitro-substituted (hetero)aryl bromides coupling in good yields.
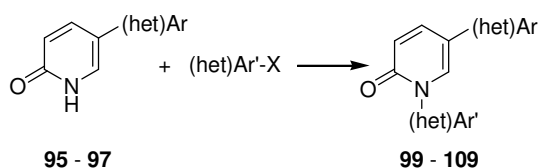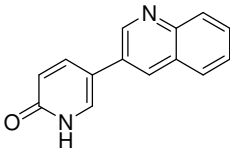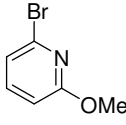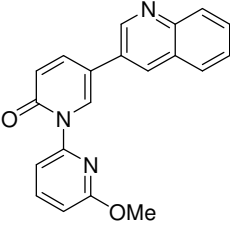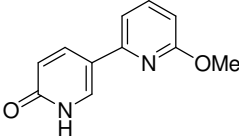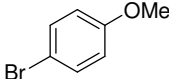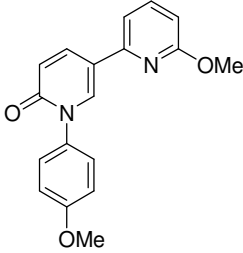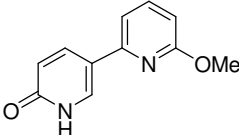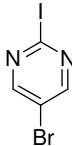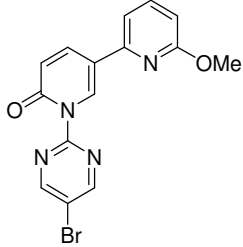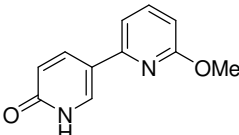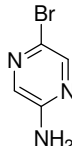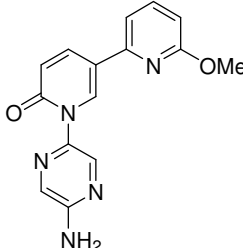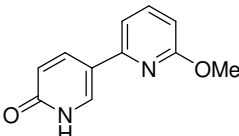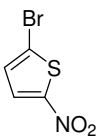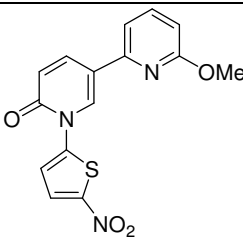
Scheme 71:   Coupling of 2-pyridones **95-97** to (hetero)aryl halides.

Table 5:   Cu-catalysed cross-coupling of 2-pyridones leading to C-N and C-O coupled products.

Entry	Pyridone	(het)Ar-X	Product	Yield (%)[a]
1	**95**	**98**	**99a**	80
2	**95**	**89**	**100**	82

Entry	Pyridone	(het)Ar-X	Product	Yield (%)[a]
3	**95**	**110**	**101**	77
4	**95**	**111**	**102**	83
5	**96**	**89**	**103**	66
6	**96**	**98**	**104a**	72
			104b	5

Entry	Pyridone	(het)Ar-X	Product	Yield (%)[a]
7	96	91	105	70
9	97	89	106	74
10	97	112	107	51
11	97	113	108	40
12	97	114	109	60

[a] The quoted yields are for isolated product after purification by chromatography and/or recrystallisation. Conditions and reagents: Pyridone, (hetero)aryl halide, CuI (10-20 mol%), DMCDA (20-40 mol%), K_2CO_3, anhydrous toluene, 100 °C, 20-88 h under argon.

Two-fold coupling of **95** with 2,6-dibromopyridine **115** (2.2 equiv) provided the penta-aryl system **116** in 69% yield (Scheme 72) with no mono-coupled product isolated or observed

in the crude ^{1}H NMR spectrum. X-ray crystallographic analysis of **116** confirmed the bis-C-N coupled structure, with both amide carbonyls lying parallel to each other, facing away from the lone pair of the pyridyl nitrogen and out of the plane of the pyridine ring (Figure 7). Being a highly π-conjugated molecule it displayed blue luminescence under UV-irradiation. An attempt to protonate the pyridyl nitrogen using HBF$_4$ gave a solution with red-shifted emission (qualitative observation). Attempts to grow crystals of this protonated **116** of suitable form for X-ray structure determination failed due to the instability of the crystals. It was thought that by protonating the central ring, a 3-point hydrogen bonding system could form, planarising the molecule and, therefore, red-shifting the emission (Scheme 73).
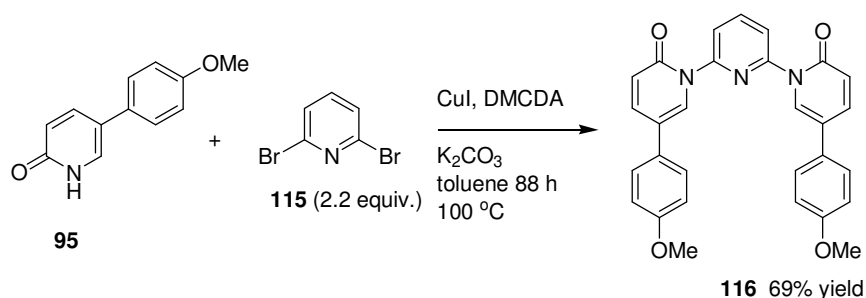
Scheme 72:   Synthesis of penta-aryl **116** from **95** and **115**.
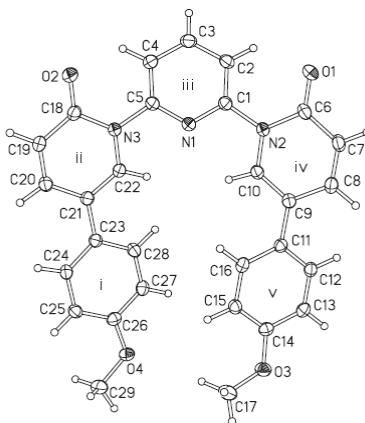
Figure 7:   X-Ray molecular structure of **116**. Interplanar angles (^{o}): i/ii 36.0, ii/iii 25.1, iii/iv 34.6, iv/v 10.9, i/v 4.3.

116
Strong "blue" fluorescence in EtOAc

116⁻H⁺
Weak "green" fluorescence in EtOAc
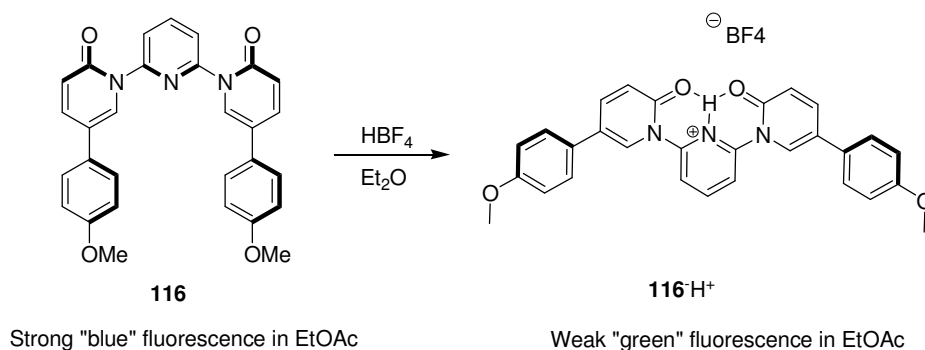
Scheme 73:   Possible product from acidification of **116** with HBF$_4$ in Et$_2$O, explaining the change in fluorescence intensity and colour**.**

3.2.3   Fluoropyridine-2(1*H*)-ones

3-Aryl-2,6-difluoropyridines **119** and **120** were synthesised *via* Suzuki cross-coupling of 2,6-difluoro-3-pyridylboronic acid **117** with **89** and **118** in good yields (Scheme 74 and Table 6). Hydrolysis of **119** gave a 1:1.4 ratio of **121a** and **121b**, as judged by ^{1}H NMR analysis of the crude mixture, indicating a slight preference for nucleophilic attack by the hydroxide anion at the less hindered C(6) site of **119.** The isolated crude yield of **121a+121b** was *ca.* 80%. Separation was very difficult and samples of each of the two isomers were isolated pure in 10 and 8% yields, respectively after successive chromatography. To test C-N coupling reactions on these fluoropyridones (*vide infra*) without exhausting supplies of **121a** and **121b**, the parent compound **123**[291] was synthesised from 2,6-difluoropyridine **122** *via* basic hydrolysis; the reaction was sluggish, giving **123** in 62% yield after 114 h at reflux (Scheme 75).

117   119, 120   121a   121b
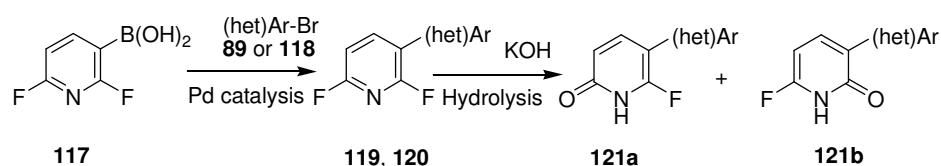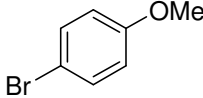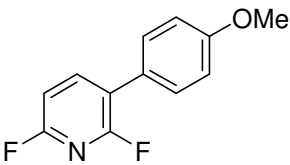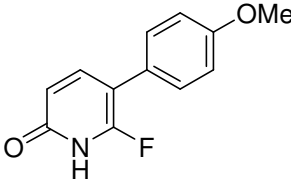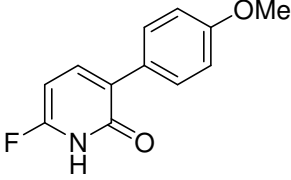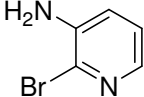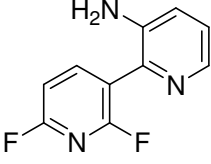
Scheme 74:   Two-step synthesis of 3- and 5-((hetero)aryl-6-fluoro-2-pyridones.

122   123
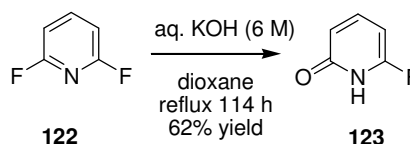
Scheme 75:   Synthesis of 6-fluoropyridin-2(1*H*)-one **123** *via* basic hydrolysis of 2,6-difluoropyridine (**122**).

Table 6:   Pd-catalysed cross-coupling of **117** with (hetero)aryl bromides and subsequent basic hydrolysis.

Entry	(het)Ar-Br	Cross-coupling product / difluoropyridine	Yield (%)[a]	Hydrolysis product[d]	Yield (%)[a]
1	**89**	**119**	76[b]	**121a**	(80) 10
				121b	8
2	**118**	**120**	83[c]	-	-

[a] The quoted yields are for isolated product after purification by chromatography and/or recrystallisation. Yield in parenthesis refers to combined isolated yield of both isomers **121a** and **121b** before purification.

[b] Reagents and conditions: **117** (1.2 equiv), **89** (1.0 equiv), Pd(PPh$_3$)$_2$Cl$_2$, Na$_2$CO$_3$ (3 equiv, 1 M in H$_2$O), 1,4-dioxane, reflux, 1 h under argon.

[c] Reagents and conditions: **117** (1.5 equiv), **118** (1.0 equiv), Pd$_2$(dba)$_3$, PCy$_3$, Na$_2$CO$_3$ (3 equiv, 1 M in H$_2$O), 1,4-dioxane, reflux, 22 h under argon.

[d] Reagents and conditions: KOH (1 M in H$_2$O), 1,4-dioxane, reflux, 16 h.

Related 2- and 5-arylpyridone derivatives have been synthesised by Cheng *et al.*[253] Fluoropyridones have been reported as potential bioactive compounds in previous studies.[261,292]
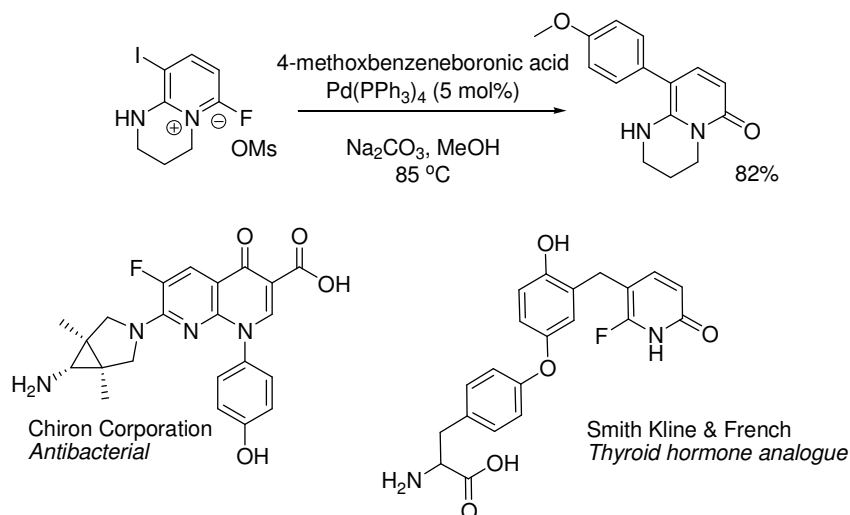
Figure 8:   5-Arylpyridin-2-one synthesis by Gallagher (*top*); Antibacterial fluoro pyridine-4-one (*bottom left*); Thyroid hormone analogue with 6-fluoropyridin-2-one core (*bottom right*)

X-ray crystal structure determinations of fluoropyridone derivatives **121b** and **123** (Figure 9) revealed that both exist as lactim (2-hydroxypyridine) tautomers. In both structures, pairs of hydroxypyridine groups related by a crystallographic inversion centre and practically coplanar, are linked together by pairs of strong linear hydrogen bonds O-H/N, with the proton unequivocally localised at the oxygen. Tautomerism of 2-pyridones has been extensively investigated.[293-298] In the solid state, the parent 2-pyridone exists as the lactam tautomer as do 5-chloro-2-pyridone, 2-thiopyridone, 4-hydroxy-2-pyridone and 5-nitro-2-pyridone.[297,296] Functionalisation of 2-pyridones at C-6 with inductively electron withdrawing groups affects the acidity of the O-H group (in the 2-hydroxypyridine form) and the N-H group (in the 2-pyridone form) *via* a bimolecular proton transfer mechanism leading to the lactim tautomer.[297] Polar solvents favour the lactam tautomer and interaction with another nonsolvent species can have an effect on the tautomeric equilibrium.[272,298]
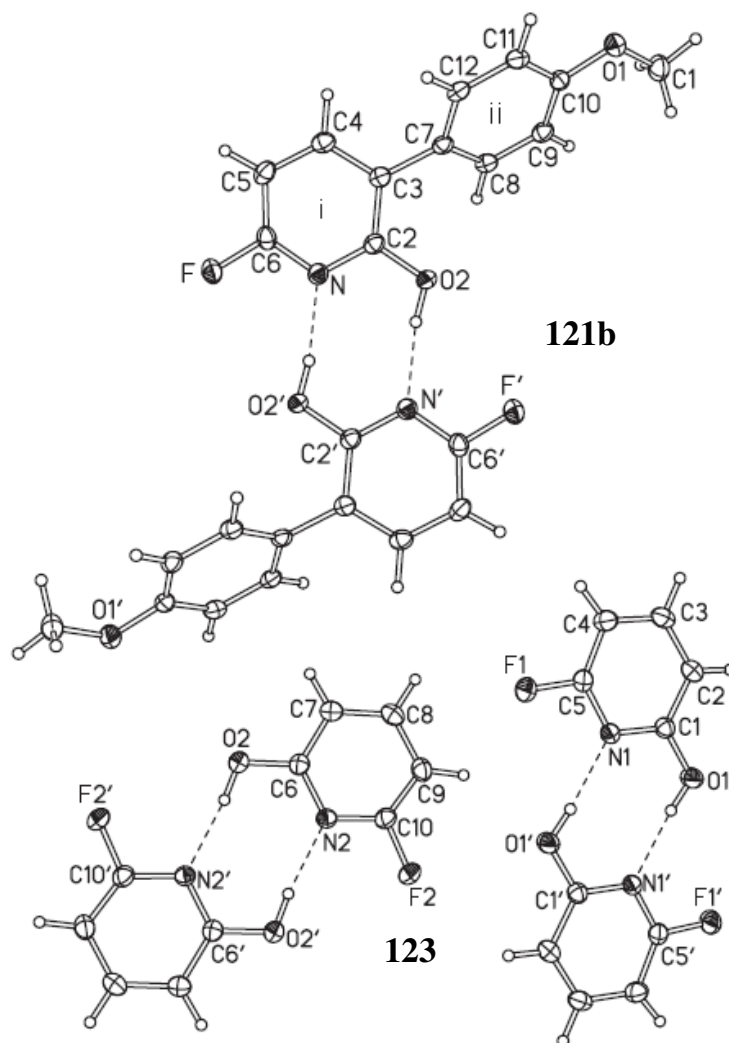
Figure 9:   X-ray molecular structures of **121b** and **123**, showing independent molecules, their inversion equivalents (primed) and hydrogen bonds (dashed lines). Interplanar angle i/ii 50.1°. Bond distances (Å): C(2)-O(2) 1.337(2), N-C(2) 1.339(2), N-C(6) 1.323(2), O(2)/N0 2.758(2), O(2)-H 0.92(2) in **121b**; C(1)-O(1) 1.330(1), N(1)-C(1) 1.342(1), N(1)-C(5) 1.320, C(6)-O(2) 1.335(1), N(2)-C(6) 1.342(1), N(2)-C(10) 1.323(1), O(1)/N(10) 2.735(1), O(1)-H 0.88(2), O(2)/N(20) 2.760(1), O(2)-H 0.89(2) in **123** indicate 2-hydroxypyridine tautomeric structures.

Arylation of 6-fluoro-2-pyridone **123** was attempted using the optimised conditions for the arylation of 2-pyridone **95** (Table 4, entry 3). However, no reaction was observed after 72 h at reflux and starting material was recovered. Copper-catalysed arylation of amides is known to be very dependent on base strength with the optimal pK_a below that of the amide.[64] Although the solubility of K_2CO_3 in toluene is expected to be low, if the acidity of

the 6-fluoro-2-pyridone is significantly greater than 2-pyridone (pK_a=17.0 in DMSO),[299] then deprotonation could occur faster than arylation leading to inactive cuprate complexes. A screening of different bases was carried out whilst keeping all other conditions unchanged. Despite changing to weak inorganic bases such as $KHCO_3$ and weak organic bases such as Et_3N (pK_a=9.0 in DMSO)[300] and pyridine (pK_a=3.4 in DMSO),[300] no reaction was observed after 48 h at reflux. On the basis of these results it is more likely that the steric effect of a 6-fluoro substituent hampers the arylation of **123**, as well as the electron withdrawing effect of the fluorine atom resulting in a reduced nucleophilicity.[74] An attempt to arylate **123** by copper-catalysed coupling with phenylboronic acid (DCM, room temperature, 48 h)[278] gave an intractable reaction mixture.
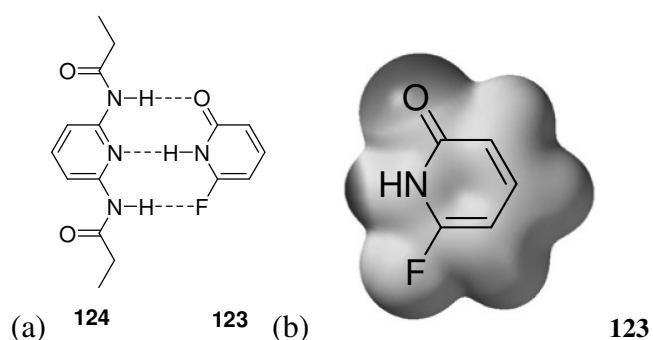
Figure 10:   (a) Possible hydrogen bonding interactions between **124** and **123**. (b) DFT (B3LYP-/6-31G*) derived electrostatic potential map for compound **123**.

On the premise that a compound with complementary hydrogen bonding sites could form host-guest complexes with **123**, we have investigated the interaction of this compound with diaminopyridine derivative **124** (Figure 10a). DFT calculations on structure **123** performed in Dr. G. Cooke's group at Glasgow University (Figure 10b) predict that although the carbonyl oxygen possess a significantly larger negative electrostatic potential than the fluoride, this derivative could have the propensity to form complementary hydrogen bonds with **124** (principally through the carbonyl oxygen and NH components of the pyridinone moiety with the amide N-H and pyridyl nitrogen of **124**, respectively).[301] The ability of **123** to form hydrogen bonding interactions with **124** was assessed in Dr Cooke's group using ^1H and ^{19}F NMR spectroscopy in CDCl$_3$. A 1:1 admixture of **123** and **124** resulted in a broadening and a small downfield shift (0.2 ppm) of the pyridinone NH resonance in the ^1H NMR spectra, which is characteristic of weak hydrogen bonding interactions. The proton-decoupled ^{19}F spectrum of the admixture revealed a 2 ppm shift from -75 ppm to -73 ppm in the single fluorine resonance,[300] suggesting that weak F/H-N interactions may

be occuring.[302] Thus, the data are consistent with the formation of a low-affinity complex between **123** and **124** in CDCl$_3$.

3.3   Conclusion

We have established efficient and flexible procedures that afford a range of 1,5-di(hetero)arylated-pyridin-2(1*H*)-one derivatives starting from the readily-available 2-fluoro-5-pyridylboronic acid **88**.[303] These protocols should be amenable to further exploitation in the synthesis of libraries of functionalised heterocycles of high diversity derived from **88**, especially compounds of potential utility as new pharmacophores and scaffolds for drug discovery.

Although **121a**, **121b** and **123** proved unreactive towards *N*-arylation, one could envisage that the pyridine tautomer could be converted to, for example, a triflate. This would provide a very active leaving group capable of being deisplaced in metal-catalysed processes (see scheme below). Access to ethers or thioethers could be achieved using alcohols or thiols in conjunction with Buchwald-Hartwig or Ullmann conditions. Using these conditions, displacement by amines or amides could be achieved. Utilising boronic nucleophiles (Suzuki-Miyaura reaction) access to an aryl/heteroaryl, alkyl or alkenyl moieties could be possible. Also, by using the Sonogashira reaction, alkynes could be incorporated into the fluoropyridine structure. Variation of **121a**, **121b**, **123** or other anologues which could be synthesised would make a wide ranging study and provide novel compound of interest to pharmaceutical/agrochemical research.
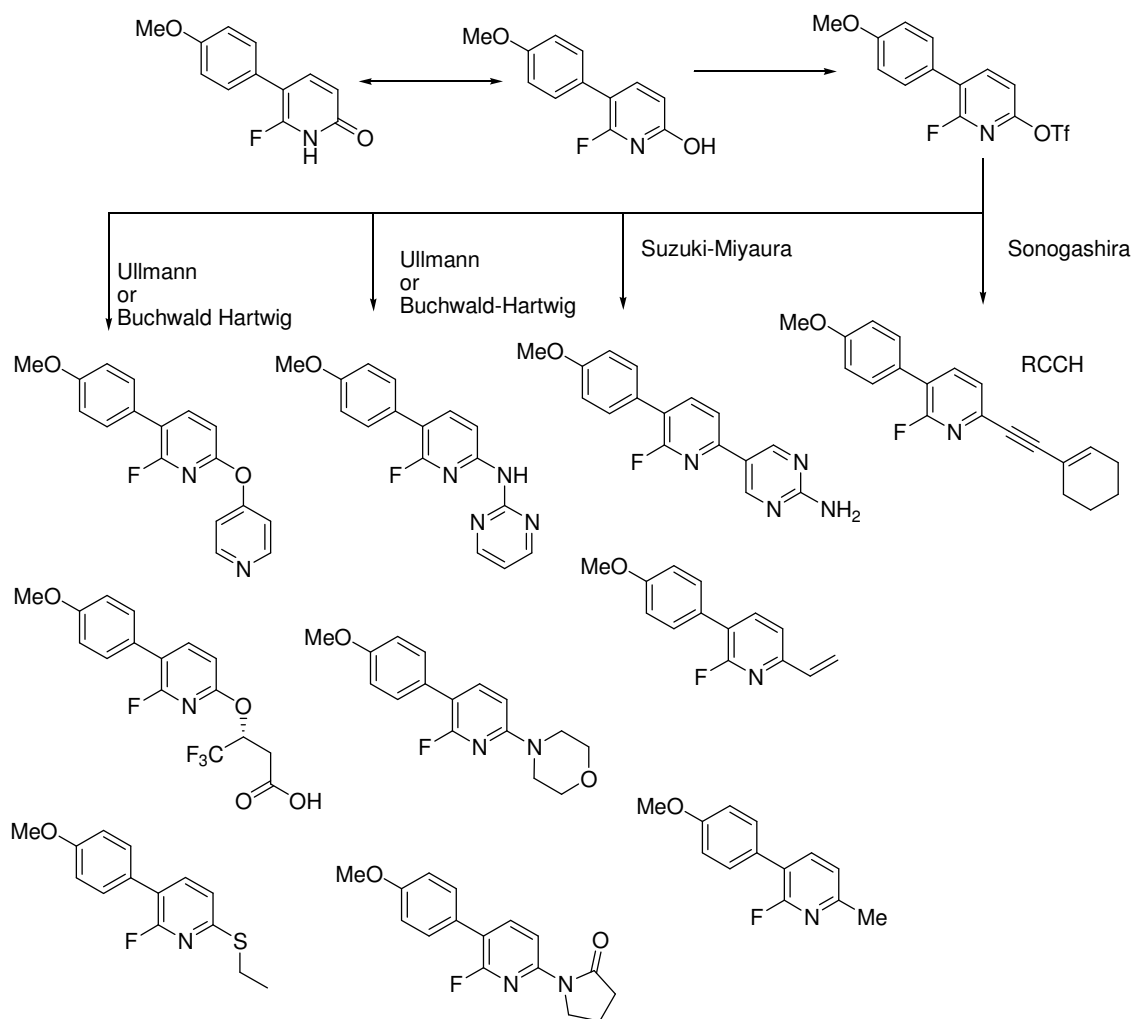
Scheme 76:   Possible routes towards novel fluoropyridines through modification of **121a** to the triflate and subsequent metal-catalysed coupling with various nucleophiles.

CHAPTER 4 – 2-CHLORO-3,4-DIIODOPYRIDINE

4.1   Introduction

Highly-substituted pyridine scaffolds are of contemporary interest due to their prevalence in bioactive compounds,[304-306] as ligands for organometallics[307] and in materials chemistry applications.[308] As discussed in Chapter 1, metal-catalysed cross-coupling methodologies have considerably expanded the scope of substitutions on heteroaryls by giving access to aryl–aryl, aryl–alkyl, aryl–alkenyl, aryl–alkynyl and aryl–heteroatom bond formations.[1,22,215,309] These substitutions have also been achieved *via* rhodium catalysed CH activation[310] and iridium catalysed borylations,[311] as well as palladium catalysed direct arylations. [179,213] The more commonly used coupling reactions, require pre-activation in the form of a halide or other leaving group on the electrophilic substrate. Many such halogenated heteroaryl compounds are commercially available; however, the 2,3,4-trihalopyridine substitution pattern is not well exploited. 4-Bromo-2-chloro-3-iodopyridine has recently been employed in the synthesis of potential drug treatments for rheumatoid arthritis[312] and 2-chloro-3-fluoro-4-iodo-5,6-dimethylpyridine has been used in the synthesis of Streptonigrin analogues.[313]

Organometallic bases regioselectively deprotonate aryl rings by Directed ortho Metallation (DoM) allowing electrophilic halogenation and access to a range of halogenated products.[314,315] It has been well documented that 'halogen dance' (HD) reactions are amenable to the regioselective synthesis of multihalogenated pyridines.[316-319] For example, Rocca *et al.*[320] reported that 2-chloro-3-iodopyridine **125** can be selectively deprotonated ortho to iodine with LDA leading to the 4-lithio species **126**. Subsequent isomerism (HD) gave the 3-lithio species **127** (with stability imparted by a strongly inductive electron withdrawing effect of chlorine and chelation of the lithium to chlorine in the intermediate **127**).[319-321] Electrophilic attack by molecular iodine on **127** then leads to 2-chloro-3,4-diiodopyridine **128** in 71% yield (Scheme 76).[320]

We were interested in developing metal-catalysed cross-couplings of halogenated pyridines. Previous work in our laboratory[322] had established that **128** could be synthesised in an unoptimised one-pot reaction from cheap and readily available[323] 2-chloropyridine using combined DoM and HD methodology. It was, therefore, timely to build on this initial result. We first sought to optimise the synthesis of **128**, and to demonstrate the utilisation of **128** in metal-catalysed cross-couplings for the first time. This has been achieved,

resulting in the regioselective synthesis of novel 2,3,4-triheteroarylpyridines, as described in this Chapter.
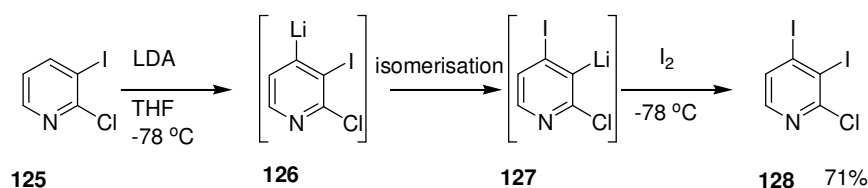
Scheme 76:   Synthesis of **128** by Rocca *et al.*[320]

4.2   Results and Discussion

4.2.1   Synthesis of 2-Chloro-3,4-diiodopyridine

The overview of our synthetic strategy is shown in Scheme 77. Lithiation of 2-chloropyridine **129** at -78 ^{o}C or -100 ^{o}C using 2 equiv. of LDA (prepared in situ from *n*-butyllithium or *n*-hexyllithium and diisopropylamine) followed by addition of iodine (2.9 equiv.) and aqueous workup reproducibly afforded 2-chloro-3,4-diiodopyridine **128** in 26–28% yields for *ca.* 4–5 g batches of product. This was achieved on three occasions, and we believe this to be the optimal yield for our one-pot protocol. Lower yields of **128** were obtained under the following conditions: (i) scale-up of the reaction; (ii) use of 2,2,6,6-tetramethylpiperidine as base at -100 to -85 ^{o}C. It is presumed that initial directed *ortho* lithiation of 2-chloropyridine **129** gives the 3-lithio intermediate **130** and electrophilic attack by I_2 then gives 2-chloro-3-iodopyridine **125**. In the GC–MS analysis of the crude product mixture, along with the signal for **128**, two smaller signals were observed both of m/z 238.9 which are consistent with 2-chloro-3-iodopyridine **125** and 2-chloro-4-iodopyridine as minor products. Subsequent directed lithiation and HD as reported previously[320] and a final electrophilic attack affords product **128** (Scheme 78).While the route of Rocca *et al.* gives a greater yield, our method uses much cheaper 2-chloropyridine as a starting material. In order to obtain **125** to use in Rocca's protocol, it will inevitably have to be synthesised from 2-chloropyridine *via* a D*o*M and iodination protocol. Due to these factors our route is potentially more cost effective and has fewer steps in the synthesis.
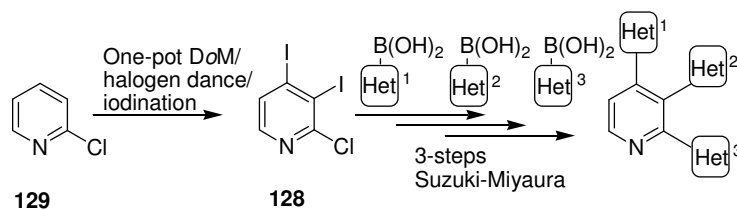
Scheme 77:   Our general strategy for the synthesis of 2,3,4-tri(heteroaryl)pyridines.
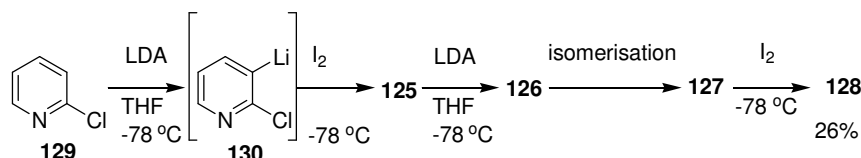
Scheme 78:   Our synthesis of **128** from readily available **129** in one pot.

4.2.2   Suzuki-Miyaura Cross-Coupling at C4

With stocks of **128** in hand we explored Suzuki–Miyaura[176,217] cross-coupling reactions on **128** using a variety of heteroarylboronic acids to give a range of functional mono-heteroarylated products **131–134** (Scheme 78 and Table 7). The formation of heteroaryl–heteroaryl bonds is of great interest to many areas of synthetic chemistry, including the synthesis of pharmaceuticals.[234,324-325] Cross-couplings of heteroarylboronic acids are often complicated by lower yields than arylboronic acids due to deactivation and instability. When using $Pd(PPh_3)_4$, aq. Na_2CO_3 in dioxane at reflux and less than 1 equiv of the boronic acid **135** a mixture of unreacted **128**, mono- and bis-coupled products was obtained. In attempts to optimise the conversion of **128** (Table 7, entries 2 and 3) by using 2.5 equiv. of boronic acids **136** and **88**, products **132** and **133** were obtained in 38% and 50% yields, respectively, along with bis-coupled side-products observed *via* GC–MS. When using 0.75 equiv. **137**, **134** was isolated in a low yield of 13% using $Pd(PPh_3)_2Cl_2$ as the catalyst. This low yield prevented further reactions on **134**, although further trials using more active catalysts could have been carried out in a bid to optimise the reaction.
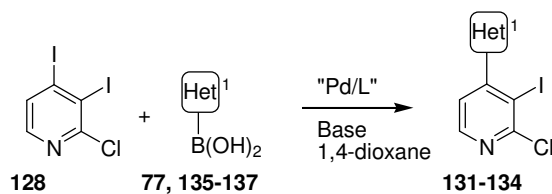
Scheme 79: Synthesis of **131**-**134** *via* Suzuki cross-coupling reactions. For conditions see Table 7.

Table 7: Suzuki-Miyaura cross-coupling of 2-chloro-3,4-diiodopyridine **128** with heteroarylboronic acids yielding mono-coupled products.

Entry	R-X	Boronic acid	Product	Yield (%)[a]
1	**128**	**135** (0.9 equiv.)	**131**	44[b] 22[c]
2	**128**	**136** (2.5 equiv.)	**132**	38[b]
3	**128**	**88** (2.5 equiv)	**133**	50[b]
4	**128**	**137** (0.75 equiv.)	**134**	13[c]

[a] Isolated yields after purification *via* chromatography and/or recrystallisation.

[b] Reagents and conditions: Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, 1,4-dioxane, reflux, 20–24 h.

[c] Reagents and conditions: Pd(PPh$_3$)$_2$Cl$_2$, Na$_2$CO$_3$, 1,4-dioxane, reflux, 19–70 h.

The increased yield for the more electron deficient fluoropyridylboronic acid **88** compared to the methoxypyridylboronic acid **136** (see Table 7, entries 2 & 3) is counter-intuitive as electron deficient boronic acids tend to transmetallate slower due to their lower nucleophilicity (*vide supra*). A higher isolated yield of **131** was obtained for the reaction of **128** when using Pd(PPh$_3$)$_4$ as catalyst rather than the air stable Pd(PPh$_3$)$_2$Cl$_2$ (Table 7, entry 1), a phenomenon noted in Chapter 2.

4.2.3   Suzuki-Miyaura Cross-Coupling at C3

Performing the Suzuki–Miyaura reaction on **128** using 2.5 equiv of **135** yielded the bis-coupled product **142** in 47% yield (see Table 8, entry 1) with **131** also observed *via* GC–MS analysis of the product mixture. The activated 4-position of **128** reacts first, followed by reaction at the less electronically active and more sterically hindered 3-position.[247] X-ray diffraction studies confirmed the regioselectivity for mono- and bis-coupled products **131** and **146** (see Figure 10).

Twofold cross-coupling of the boronic acids **135, 136** or **75** at both the 4- and 3-positions of **128** gave **142–144** in optimised yields of 47– 64% (Scheme 80 and Table 8, entries 1–3). Tris-coupled products were not observed in any of the reactions shown in Schemes 80–81. Entries 4–6 in Table 8 show the products of stepwise reactions where the pyridyl substituents at C3 and C4 are different in each case. This was achieved by further reaction of **131–133** with a selection of pyridylboronic acids under Suzuki-Miyaura conditions (see Table 8) furnishing compounds **145–147** in variable yields. The inherent regioselectivity, *vide supra*, led to the second coupling occurring exclusively at the 3-position giving excellent control over the substitution pattern on the pyridine core. When using boronic acid **135**, the resulting product **146** was obtained in only 23% yield (Table 8, entry 5) presumably due to the added steric hindrance of the ortho-methoxy group on **135**. The X-ray molecular structure of **146** is shown in Figure 10 showing the expected regioselectivity and large dihedral angles between the central pyridine ring and the rings at C3 and C4.
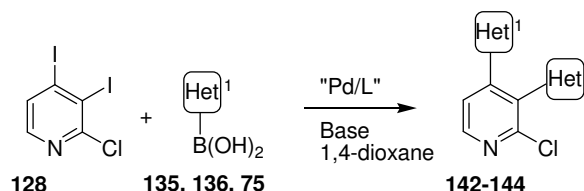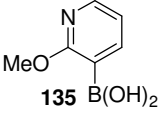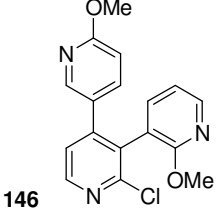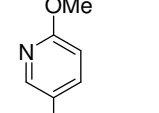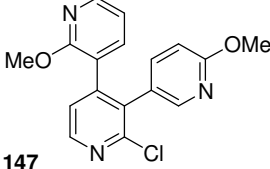
Scheme 80:   Synthesis of **142**-**144** *via* Suzuki-Miyaura cross-coupling. For conditions see Table 8.
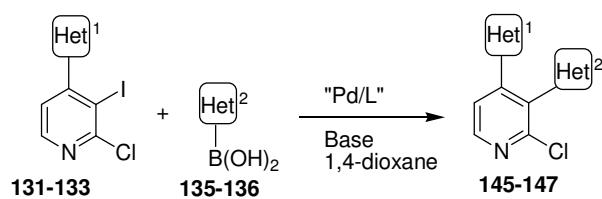
Scheme 81:   Synthesis of **145**-**147** *via* Suzuki-Miyaura cross-coupling. For conditions see Table 8.

Table 8:   Suzuki-Miyaura cross-coupling with pyridylboronic acids to yield bis-coupled products.

Entry	R-X	Boronic acid	Product	Yield (%)[a]
1	**128**	**135** B(OH)₂ (2.5 equiv.)	**142**	47[b]
2	**128**	**136** B(OH)₂ (2.0 equiv.)	**143**	50[b]
3	**128**	**75** B(OH)₂ (2.0 equiv.)	**144**	64[b]
4	**133**	**136** B(OH)₂ (1.5 equiv.)	**145**	90[c]

Entry	R-X	Boronic acid	Product	Yield (%)[a]
5	**132**	**135** B(OH)$_2$ (MeO-pyridine) (1.5 equiv.)	**146**	23[c]
6	**131**	**136** B(OH)$_2$ (OMe-pyridine) (1.1 equiv.)	**147**	74[d]

[a] Isolated yields after purification *via* chromatography and/or recrystallisation. [b] Reagents and conditions: Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, 1,4-dioxane, reflux, 20 h. [c] Reagents and conditions: Pd(PPh$_3$)$_2$Cl$_2$, Na$_2$CO$_3$, 1,4-dioxane, reflux, 18–70 h. [d] Reagents and conditions: Pd$_2$(dba)$_3$, P(t-Bu)$_3$.HBF$_4$, 1,4-dioxane, KF, 80 $^{\circ}$C, 7 h.

Compound **133** does not suffer this steric interference and furthermore, the electron withdrawing 5-yl-2-fluoropyridine substituent at C4 of **133** would be expected to enhance reactivity at C3, thus explaining the high yield in this case (Table 8, entry 4). In attempts to mitigate anticipated low yields for the coupling of the sterically encumbered **131** with boronic acid **136**, Fu's conditions (which have been reported to provide excellent yields for sterically crowded substrates)[189] were employed. Using **136** (1.1 equiv) we were gratified to obtain **147** in 74% yield (Table 8, entry 6).
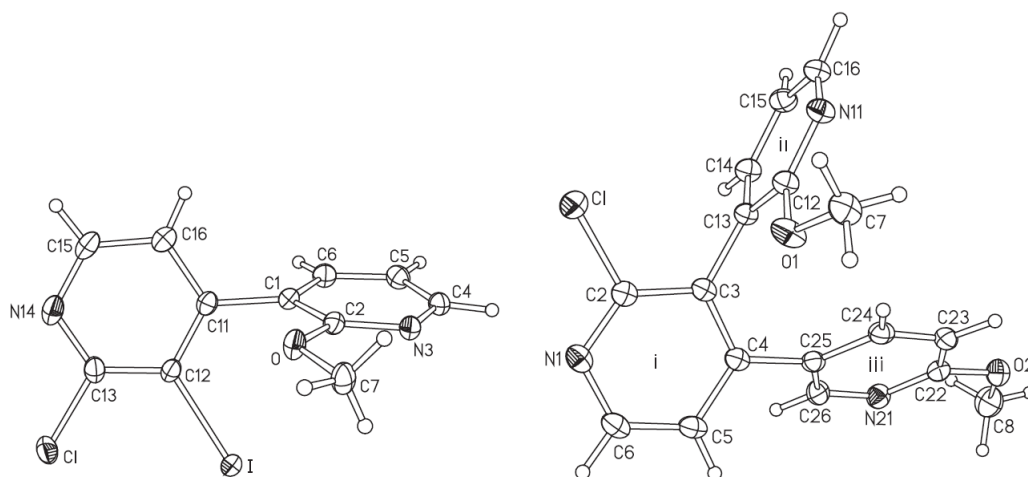
Figure 10:   X-ray molecular structures of **131** (*left*) and **146** (*right*). Dihedral angles between pyridyl rings: 72.4° in **131**, i/ii 85.3° and i/iii 52.8° in **146**.
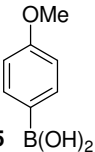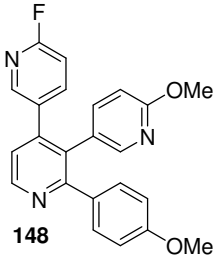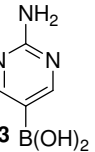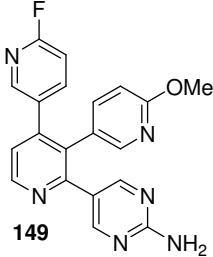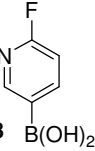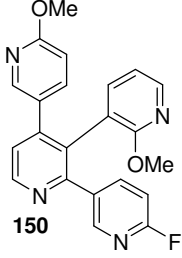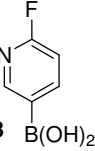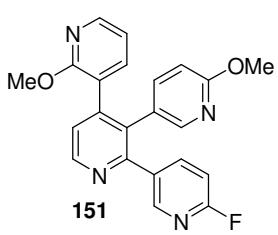
4.2.4   Suzuki-Miyaura Cross-Coupling at C2

As stated above, on no occasion was a tris-coupled product observed *via* GC-MS in the reactions shown in Schemes 80–81 (Tables 7 and 8). This provided the opportunity to introduce regioselectively a third heteroaryl substituent into the pyridine core by reactions of the remaining 2-chloro functionality.[326-327] For this purpose a selection of the bis-coupled products (**145**, **146** and **147**) were reacted with a range of aryl and heteroarylboronic acids to gain access to 2,3,4-tri(hetero)arylpyridines **148–151** in 23–51% yields (Scheme 82 and Table 9).
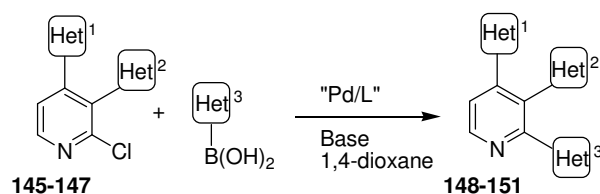
Scheme 82:   Synthesis of **148**-**151** *via* Suzuki-Miyaura cross-coupling. For conditions see Table 9.

Table 9:   Suzuki-Miyaura coupling of arylboronic acids and heteroarylboronic acids with compounds **145**, **146** and **147**.

Entry	R-X	Boronic acid	Product	Yield (%) [a]
1	**145**	**75** B(OH)$_2$ (1.2 equiv.)	**148**	30[b]
2	**145**	**153** B(OH)$_2$ (1.2 equiv.)	**149**	23[b]
3	**146**	**88** B(OH)$_2$ (1.2 equiv.)	**150**	45[b]
4	**147**	**88** B(OH)$_2$ (1.2 equiv.)	**151**	51[b] 50[c]

[a] Isolated yields after purification *via* chromatography and/or recrystallisation. [b] Reagents and conditions: Pd$_2$(dba)$_3$, PCy$_3$, 1,4-dioxane, K$_3$PO$_4$, 100 °C, 2-20 h. [c] Reagents and conditions: Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, 1,4-dioxane, reflux, 24 h.

The reactions were performed using the conditions designed for coupling heteroaryl chlorides with nitrogen-containing heteroarylboronic acids[255] [*viz.* Pd$_2$(dba)$_3$, PCy$_3$, K$_3$PO$_4$, 1,4-dioxane, H$_2$O, reflux]. However, a similar yield of **151** was obtained on the one occasion when Pd(PPh$_3$)$_4$/Na$_2$CO$_3$ was used (Table 9, entry 4). Suzuki–Miyaura reactions

are known to be tolerant to unprotected amine functionality,[328] and accordingly, coupling of 2-aminopyrimidin-5-yl-5-boronic acid **152** with **145** gave **149** in 23% yield. With all of these third couplings (Scheme 82) a varying amount of dechlorinated side-product was observed *via* GC–MS, thus accounting for the modest yields of **148-151**. This can be explained by the steric crowding in the bis-coupled substrate **145-147** inhibiting transmetallation of the boronic acid in the transition state leading to competing protodechlorination. It is noteworthy that, to our knowledge, compounds **149-151** represent the first reported 2,3,4-triheteroarylpyridine derivatives.
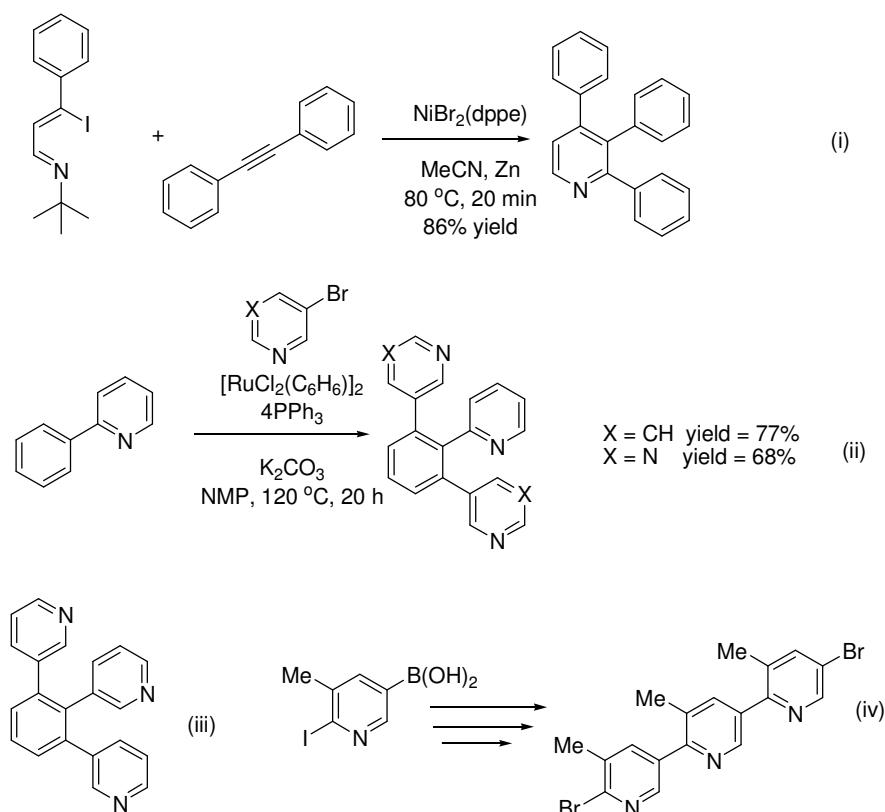
Figure 11:   (i) Triphenylpyridine synthesised by Ni catalysed annulation; (ii) triheterarylbenzene synthesised by Ru catalysed *ortho*-metalation; (iii) tripyridylbenzene used as electron transport material; and (iv) linear tripyridyl synthesised in sequential manner using the Suzuki-Miyaura reaction.

Related structures in the literature include the following examples (see Figure 11): (i) 2,3,4-triphenylpyridine has been synthesised by the nickel catalysed annulation of 2-iodobenzaldimine;[329] (ii) 2-(2,6-di(pyridin-3-yl)phenyl)pyridine and 5-(2-(pyridin-2-yl)-3-(pyrimidin-5-yl)phenyl)pyrimidine were synthesised *via* the ruthenium catalysed ortho-arylation of 2-phenylpyridine;[330] (iii) the phenyl core analogue 3-[2,3-di(pyridin-3-

yl)phenyl]pyridine has been used as an electron transport material in electroluminescent devices;[331] and (iv) related bis(pyridyl)pyridines and linear quaterpyridines have recently been synthesised *via* Suzuki–Miyaura reactions by Burzicki *et al.* starting from dihalopyridines.[332]

4.2.5   Sonogashira Cross-Coupling
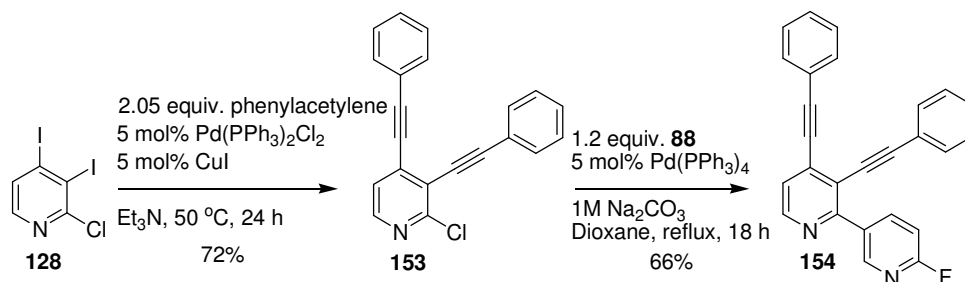
Scheme 83:   Synthesis of **154** *via* sequential two-fold Sonogashira and Suzuki-Miyaura reactions.

To extend further the scope of **128** in cross-coupling reactions, a Sonogashira reaction[105,286] was performed (Scheme 83). Compound **128** reacted with phenylacetylene (2.05 equiv) under standard conditions [5 mol % Pd(PPh$_3$)$_2$Cl$_2$, 5 mol % CuI, Et$_3$N] to give **153** in 72% yield. No dehalogenation was observed in this case. A subsequent Suzuki–Miyaura reaction of **88** on the remaining 2-chloro substituent of **153** gave **154** in 66% yield. The higher yield in this case when comparing to the reaction of the same boronic acid **88** with the chloro substituent of **147** (Table 9, entry 4) can be attributed to the reduced steric hindrance in **153** compared to **147**. We note that (arylethynyl)pyridines have been synthesised for pharmacological applications[333] and bis(arylethynyl)pyridines are of interest for their optoelectronic properties.[334]

4.3   Conclusions

We have described a new one-pot synthesis of 2-chloro-3,4-diiodopyridine **128** in 4–5 g batches from 2-chloropyridine *via* a Directed *ortho* Metallation–Halogen Dance–iodination sequence. Utilising **128** as a starting material has led to a versatile range of mono-, bis- and trisheteroarylpyridine derivatives in a series of iterative and regioselective Suzuki–Miyaura cross-coupling reactions.[285] These procedures have provided the first examples of pyridine derivatives bearing heteroaryl units in the 2, 3 and 4 positions. The yields of the products

are synthetically viable, even for the more sterically hindered derivatives, especially in view of the known challenges of cross-coupling heteroaryl halides with heteroarylboronic acids/esters.[202,255,326-327] We have also established that compound **128** is a suitable reagent for Sonogashira reactions. These protocols are versatile and can be further exploited in the synthesis of libraries of small molecules derived from **128** for drug discovery and for materials chemistry applications.

CHAPTER 5 - BENZIMIDAZOLO[1,2-*F*]PHENANTHRIDINE

5.1   Introduction

Fused *N*-heterocyclic ring systems are prevalent in biologically active compounds, especially marine alkaloids.[132,335] Of the myriad structures investigated, azolo[1,2-*f*]phenanthridine structures have only been noted on a few occasions (see Scheme 84 and Figure 11).[336-337] Indolophenanthridines have been synthesised *via* a palladium catalysed process from arylindoles and an *in situ* generated aryne (Scheme 84).[337] Disadvantages to this process are the lack of functionality available on the aryne, difficulties in accessing unsymmetrical arynes and incorporating this regioselectivly into the product. The employment of benzimidazolophanthridines as ligands for blue electrophosphorescent OLED materials were disclosed in a patent in 2007 (Figure 11).[336]
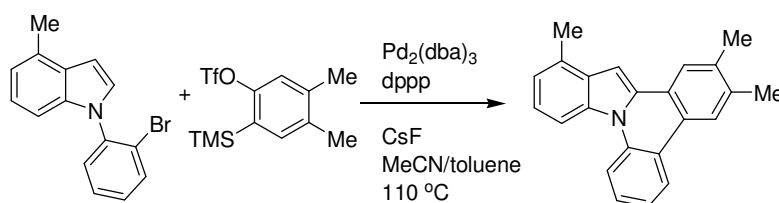
Scheme 84:   Indolo[1,2-*f*]phenanthridine synthesised by Pd catalysed process.
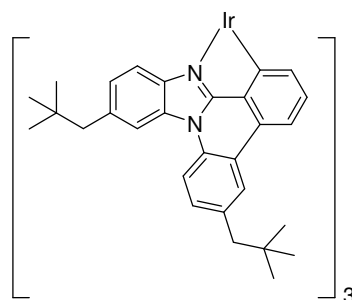
Figure 11:   Azolophenanthridines reported in literature.

Many palladium-catalysed routes to fused *N*-heterocyclic rings have been reported leading to three or four fused rings[338-344] and also routes where palladium does not play any role.[345-347]

Routes to new heterocyclic structures based upon sequential metal-catalysed processes is of interest in the context of this work, both as a proof of concept as well as a possible convenient synthesis of elusive structures. Based upon work by Zheng *et al.*[169] (see Scheme 85, top) a route was devised whereby construction of an *ortho*-haloacetanilide precursor was followed by the palladium catalysed amination using a functionalised aniline

followed by a dehydradive cyclisation to form the benzimidazole structure. This 1,2-diarylbenzimidazole could then be cyclised by an intramolecular direct arylation (see Scheme 86) modified from the intermolecular protocols championed by the late, great Keith Fagnou (see Scheme 85, *bottom*).[348]
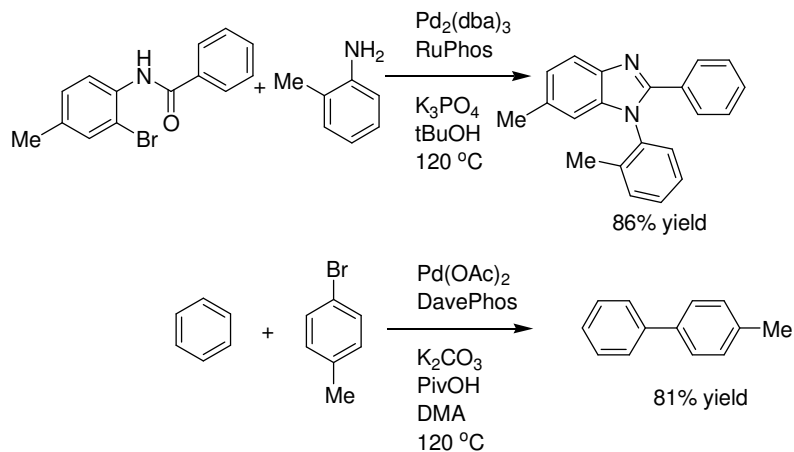
Scheme 85:   Palladium-catalysed amination/dehydrative cyclisation to make 1,2-bisarylbenzimidazoles "Zheng method" (*top*) and intermolecular direct arylation reactions "Lafrance method" (*bottom*).
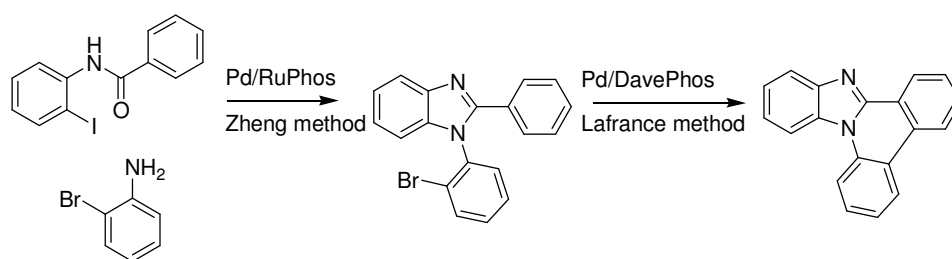
Scheme 86:   Our proposed route to benzimidazolo[1,2-*f*]phenanthridine.

5.2   Results and Discussion

As outlined in Scheme 86 above, *ortho*-haloacetanilides were required as precursors. Iodine was chosen as the halogen in this instance due to the complication of site selectivity in the amination step. Although Pd-catalysed amination of aryl iodides is known, it is often slow and low yielding (*vide supra*). In a bid to circumvent the expected solubility issues in the final product and to give us a fairly electronically neutral starting point, 4-*tert*-butylbenzoylchloride **155** was used to form the anilide **157** using 2-iodoaniline **156** after refluxing in EtOAc for 24 h (see Scheme 87).[169]
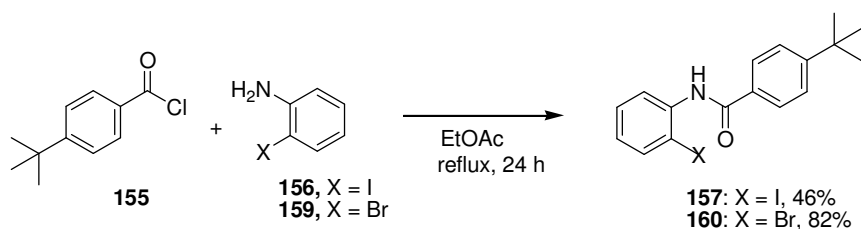
Scheme 87:   Synthesis of **157** and **160**.

Compound **157** was then reacted with 2-bromoaniline using RuPhos/Pd$_2$(dba)$_3$ catalyst system (see Scheme 88).[169] The desired product **158** was obtained after dehydrative cyclisation in 4 M HCl in only 14% yield. The de-halogenated arene by-product from the starting material **157** was observed by GC-MS. Attempts to improve the yield of **158** by using the *ortho*-bromoacetanilide **160** [from 2-bromoaniline **159** (see Scheme 87)] failed to give any product with starting materials recovered in quantitative yield.
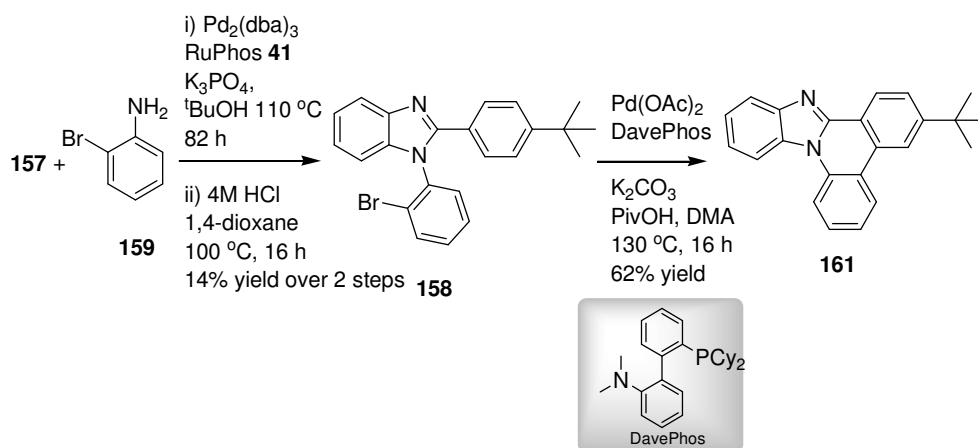
Scheme 88:   Synthesis of **161** by Buchwald-Hartwig amination/dehydrative cyclisation and intramolecular direct arylation reactions.

A reaction was carried out using Lafrance's method[348] for direct arylation, forming a C-C bond between the Ar-Br and Ar-H of **158** (see Scheme 88). This was achieved giving **161** in 62% yield. The structure **161** was assigned based on ES$^+$ mass spectrometry (M$^+$+H peak), ^{1}H, ^{13}C and COSY/HMBC/HSQC NMR analysis and C, H, N elemental analysis which were all consistent with **161**. Efforts to grow a single crystal suitable for X-ray structural analysis were unsuccessful with all solvents tried (including perfluorobenzene/hexane combinations) resulting in fine needles.

5.3   Conclusions

Due to the low yielding amination/cyclisation step only one reaction was taken through to the desired benzimidazolo[1,2-*f*]phenanthridine system. Efforts to improve the yield failed. Should this route be pursued further, the use of masked halides (*i.e.* alcohols) on the aniline component could be tried to allow the supposedly more reactive aryl bromide to react first in the amination step. Unmasking of the halide (by creating –OTf or bromination) could then lead to a good system for the ring closing direct activation step (Scheme 89). One-pot methodologies could also be investigated.
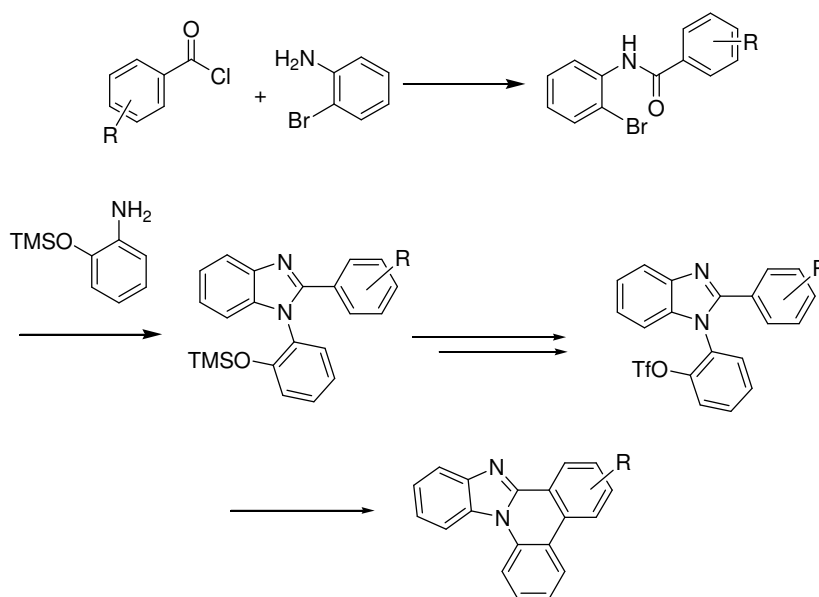
Scheme 89:   Proposed route to benzimidazol0[1,2-f]phenanthridine using masked halide.

CHAPTER 6 – PHOSPHORESCENT IRIDIUM(III) COMPLEXES

6.1   Introduction

OLEDs or "organic light emitting diodes" are an emerging lighting technology based upon singlet or triplet emission from organic materials under an applied voltage. A device is composed of layers of charge transporting materials sandwiched between a metal cathode and a transparent anode (usually indium tin oxide, ITO) to allow the generated light to escape (Figure 12).
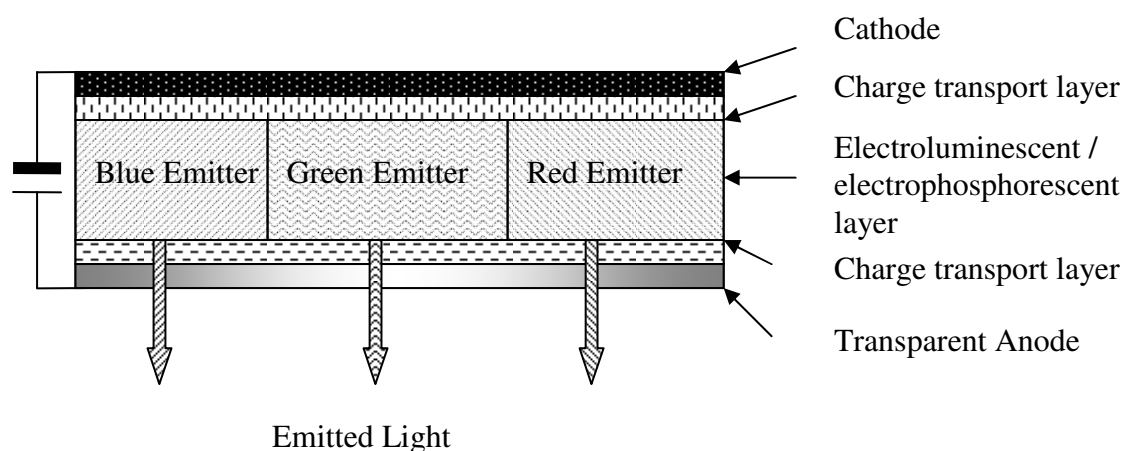
Figure 12:   A simplistic OLED device architecture.

Ir^{III} complexes are widely used in these devices as triplet emitters, whereby a triplet excited state is generated on the complex. There is the potential for 100% internal device quantum efficiency (photons emitted : electrons injected) and colour tunability.[349] With an aim of producing efficient white lighting technology based on printing methodology, a collaboration between industry partners and Durham University has been investigating various components for these devices. White light requires blue, green and red components which are provided from the differing band-gap energies of the materials. Blue triplet emission is challenging due to the high band-gap energy associated with blue emitters.
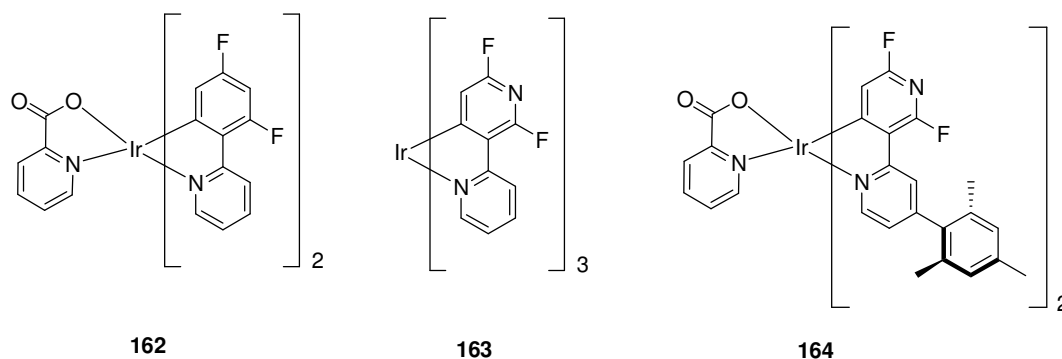
Figure 13:   Blue phosphorescent Ir[III] complexes **162** - **164.**

The complex **162** (FIrpic) is promising due to its near blue emission;[349] however, its use in printed devices is limited due to its insolubility. Bluer complexes such as **163** are available.[350] One major challenge is to inhibit triplet-triplet annihilation pathways that reduce device efficiency. These occur when the phosphorescent emitters interact with each other and so ways of shielding these interactions have been investigated by the use of dendritic systems.[351-352] Simpler systems have been envisioned in our group by the use of shielding units which are shown below.
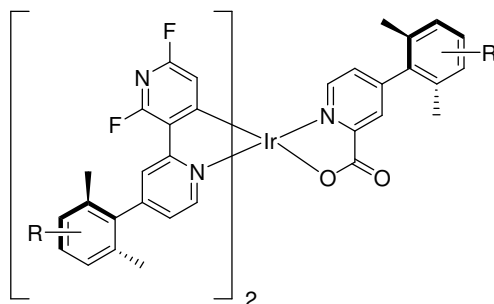
Figure 14:   Proposed Ir[III] complex with sterically twisted aryl groups on both ligands and auxiliary picolinic acid ligand where R = solubilising group.

Our recent unpublished work[353] on the blue emitting complex **164** (Figure 13) demonstrated the positive effect of aryl shielding on the external quantum efficiency (EQE) of devices. The aryl shielding groups must be "twisted" out of the plane of the phenyl-pyridine moiety using a 2,6-dimethyl system in order to reduce π-conjugation and placement at the position *para-* to the Ir results in a bluer colour. Issues affecting these complexes are low solubility in organic solvents and a desire for bluer emission. By functionalising the picolinic acid auxillary ligand with shielding substituents (see Figure 14), it was hoped that EQEs could be raised further, while retaining the blue colour.

6.2   Results and Discussion

6.2.1   Scale-up of "G0" Complex

Scale-up synthesis of "G0" complex "G0PyF2-Ir-pic" **164** was required by our industrial partners, so 2-chloro-4-iodopyridine **165** was reacted with mesitylboronic acid using K_3PO_4 and a $Pd_2(dba)_3$ / PCy_3 catalyst system with the yield of **166** increased to 85%, (see Scheme 88) compared to previous yields of 57% using aqueous Na_2CO_3 in DME at 85 ^{o}C with $Pd(OAc)_2$ / PPh_3.[353] Coupling with 2,6-difluoropyridin-3-yl-3-boronic acid to the chloro site of **166** led to poor yields[353] of **168**, so MIDA protected boronic acid **167** was used (this has previously been used to couple this electron deficient boronic acid).[353] MIDA protection has been shown to allow a slow release of boronic acid into the reaction medium when performed at <60 ^{o}C.[354] As the transmetallation of this electron deficient boronic acid will be slow, having an excess of boronic acid in solution leads to protodeboronation pathways (*vide supra*). By using **167**, SPhos and $Pd(OAc)_2$ we had previously made **168** in 68% yield.[353] When changing to $Pd_2(dba)_3$ and PCy_3 this was reduced to 46% yield (see Scheme 90) showing these couplings to be highly sensitive to the catalyst system.
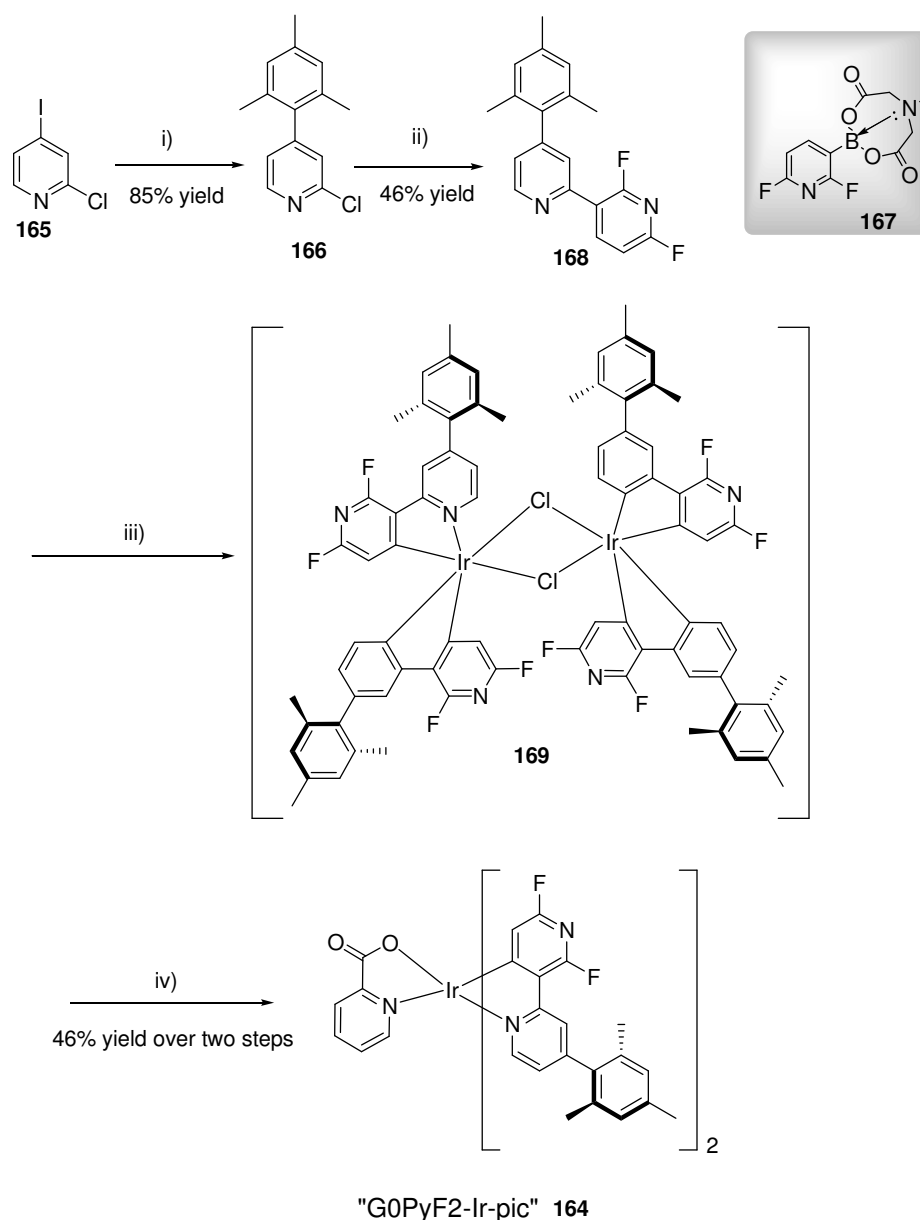
Scheme 90:   Synthesis of **164**. Conditions: i) Mesitylboronic acid / Pd$_2$(dba)$_3$ / PCy$_3$ / K$_3$PO$_4$ (1.27 M) / dioxane, 80 – 100 ^{o}C, 20 h; ii) 2,6-difluoropyridin-3-yl-3-boronic acid MIDA ester **167** / Pd$_2$(dba)$_3$ / PCy$_3$ / K$_3$PO$_4$ (3 M) / dioxane, 60 ^{o}C, 88 h; iii) IrCl$_3$.3H$_2$O / 2-ethoxyethanol / H$_2$O, 110 ^{o}C, 16 h; iv) picolinic acid / 2-ethoxyethanol, 110 ^{o}C, 16 h.

Compound **168** was reacted with IrCl$_3$.3H$_2$O in water with ethoxyethanol to furnish the dichloro-bridged complex **169** (see Scheme 90) which was then reacted with an excess of picolinic acid in ethoxyethanol to give the complex **164** in 46% yield after chromatography. An X-ray molecular structure of **164** (see Figure 15) shows a twist of 85.1^o between the shielding G0 group and the phenyl-pyridine moiety. The structure also

shows that the picolinic acid ligand is exposed, leading us to begin work on shielding this area of the complex.
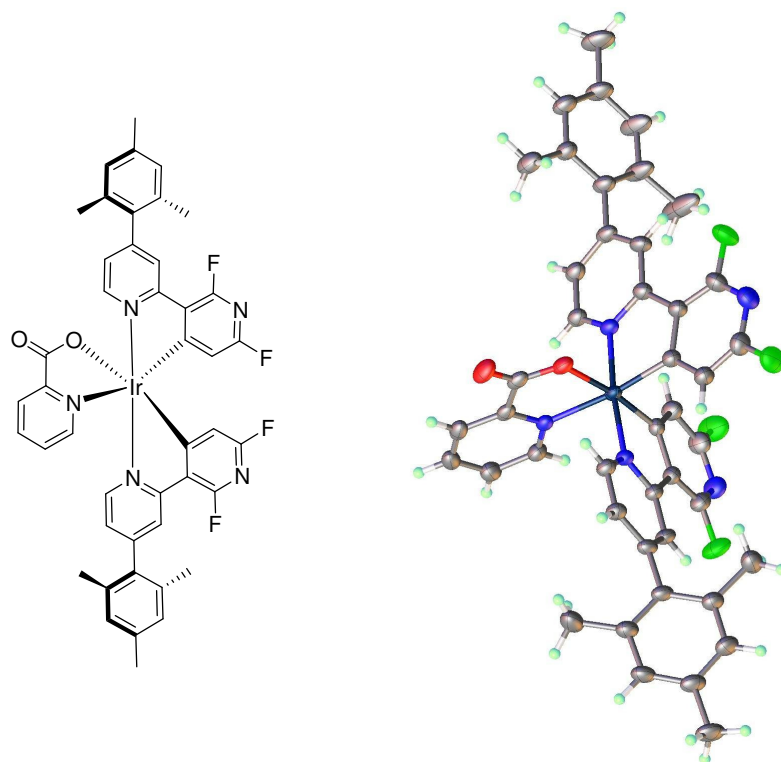
Figure 15: X-ray molecular structure of **164**. Mesitylene units twisted as shown in "poles" of the complex and unshielded picolinic acid moiety in the "equator" of the complex.

6.2.2   Preparation of "G1pic" Auxiliary Ligand

To enhance the solubility of the complexes, 2-ethylhexyloxy groups were installed on the phenyl rings (Scheme 91). Bromophenol **170** was alkylated using 2-ethylhexylbromide in DMF with K_2CO_3 as the base at 75 ^{o}C overnight. The resulting oil **171** was isolated in 89% yield. The conversion of **171** to a boronic acid was low yielding with debrominated by-product observed but not isolated. These reactions were carried at -78 ^{o}C using ^{n}BuLi to form the lithio intermediate with electrophilic trapping by triisopropyl borate. Acidic aqueous work-up gave **172** in up to 40% yield as a white solid. Subsequently, a Suzuki-Miyaura cross-coupling reaction of **172** with 4-bromopyridine hydrochloride using Pd(PPh$_3$)$_4$ and K_3PO_4 giving **173** in 91% yield. To access the picolinic acid motif, a route from **173** *via* the 2-cyano intermediate **174** was devised.[355] Treatment of **173** with mCPBA at room temperature provided the *N*-oxide which was not purified but used directly in the subsequent cyanation reaction. The crude oil was treated with TMS-CN and *N,N*-dimethylcarbamoyl chloride to afford the cyanated product **174** in 33% yield.
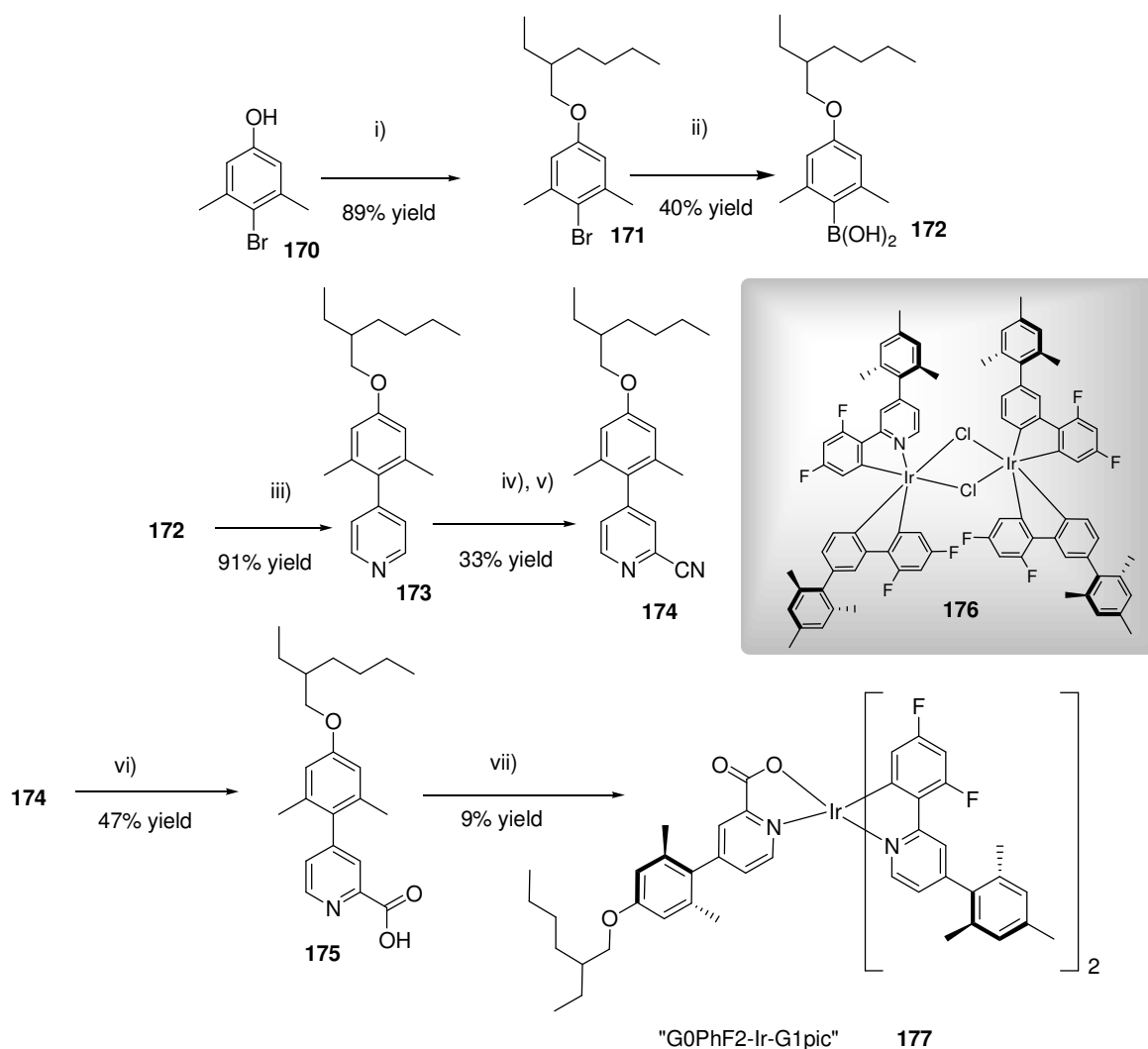
Scheme 91:   Synthesis of **177**. Conditions: i) 2-ethylhexylbromide / K$_2$CO$_3$ / DMF, 78 °C, 15 h; ii) ^{n}BuLi / B(O^{i}Pr)$_3$ / THF, -78 °C, NH$_4$Cl work-up; iii) 4-bromopyridine hydrochloride / Pd(PPh$_3$)$_4$ / K$_3$PO$_4$ / dioxane / H$_2$O, 100 °C, 48 h; iv) mCPBA / DCM, room temp., 24 h; v) TMS-CN / dimethylcarbamyl chloride / anhydrous DCM, room temp. 16 h; vi) 6 M HCl / dioxane, reflux, 48 h; vii) **176** / Na$_2$CO$_3$ / ethoxyethanol, 130 °C, 16 h.

This was hydrolysed under acidic conditions and "G1pic" **175** was isolated in 47% yield. Reaction of **175** with dichloro-bridged iridium complex **176** synthesised by other members of the group[353] in ethoxyethanol and Na$_2$CO$_3$ at 130 °C for 48 h led to a complex mixture of compounds from which **177** was isolated in 9% yield after two successive purifications by chromatography. The batch of **175** was not pure due to the possible presence of amide by-product. A better work-up procedure for **175** resulted in pure compound; however, there was insufficient time available to process this to the iridium complex.

6.2.3   Preparation of "G2pic" Auxilary Ligand

In a bid to further shield these complexes, a larger group was required on both the phenyl-pyridine ligand and the auxillary ligand. To reduce π–conjugation between the shielding group and the picolinic acid moiety, the G2 unit was chosen as the best group. The methyl substituents should achieve a twist between the picolinic acid and the phenyl ring as well causing the two alkoxyphenyl rings to be twisted with respect to the central phenyl ring. This would allow a larger, bulkier shielding unit with no impact on the electronics of the system and afford more solubility with more alkyl groups per ligand. To gain access to the triaryl bromide unit **183**, **180** was prepared in a two step process; firstly, bromination of **178** in AcOH using Br_2 to give **179** (previously synthesised by a different bromination approach[356]), then by a Sandmeyer reaction[357] to convert the amine to an iodo group giving **180**.[358] This then underwent a Hart reaction[359] when reacted with excess of the Grignard derivative of **181**[360] (formed from the product of the Williamson etherification of **182**) to give **183**. Attempts to make the boronic acid from this led predominantly to dehalogenation byproducts when attempted by other members of the group when using halogen-metal exchange reaction at -78 ^{o}C using ^nBuLi and $B(O^iPr)_3$. To circumvent this problem, 4-pyridylboronic acid pinacol ester **185** was synthesised by the two-step literature process from 4-aminopyridine; namely, a Sandmeyer reaction to give 4-iodopyridine then reaction with ^nBuLi and $B(O^iPr)_3$ at -78 ^{o}C and a pinacol / AcOH quench to give **185**.[361] The Suzuki-Miyaura reaction of **183** with **185** using the highly active $Pd_2(dba)_3$ / $P^tBu_3.HBF_3$ / K_3PO_4 catalytic system gave **184** in 63% yield. Due to time constraints the remainder of the synthesis towards G2pic and complexes containing G2pic was carried out by other members of the group.
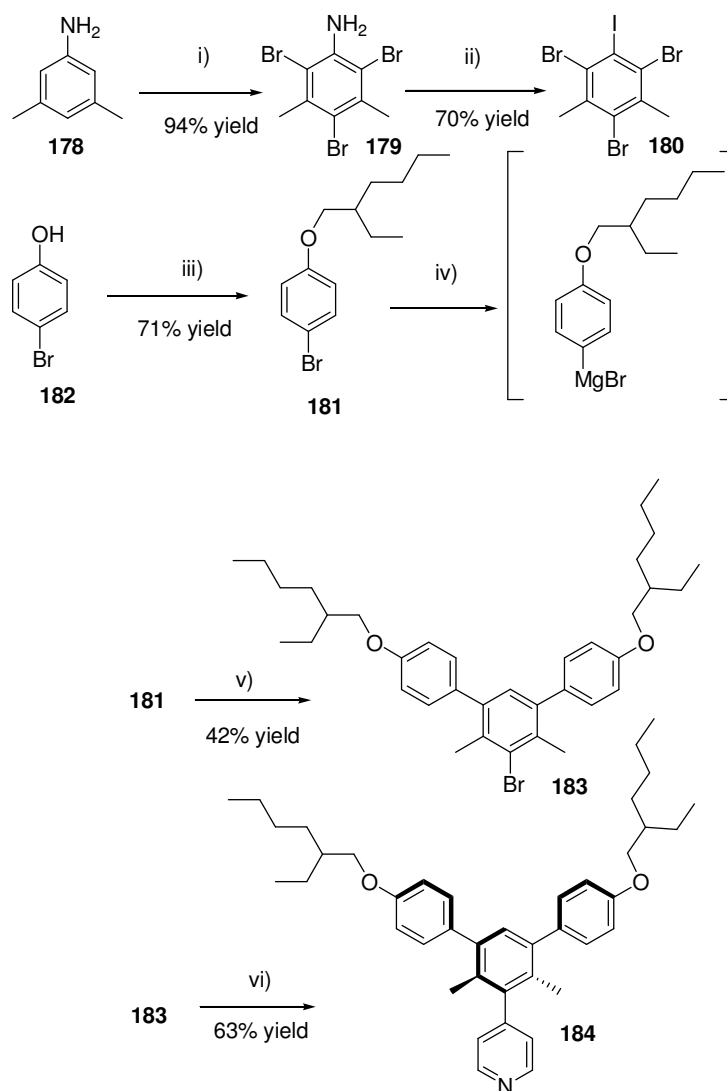
Scheme 92: Synthesis of **184**. Conditions: i) Br$_2$ / AcOH / 0 ^{o}C; ii) NaNO$_2$ / HCl then KI; iii) 2-ethylhexylbromide / K$_2$CO$_3$ / DMF, 70 ^{o}C, 15 h; iv) Mg turnings / I$_2$ / THF, 50 ^{o}C, 2h; v) **180** / THF, reflux, overnight; vi) **185** / Pd$_2$(dba)$_3$ / P^{t}Bu$_3$.HBF$_4$ / K$_3$PO$_4$ / dioxane / water, 100 ^{o}C 24 h.
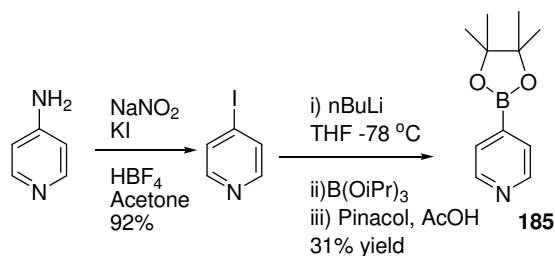
Scheme 93: Synthesis of **185** using the method of Coudret.[361]

6.3   Conclusions

The synthesis of novel and soluble aryl-shielded picolinic acid derivative has been achieved. These compounds show promise as auxillary ligands in Ir[III] complexes in OLED applications. The routes described are not optimised although some issues have been circumnavigated such as the low yielding formation of the boronic acid of **183**. Complex **164** has been successfully scaled up to provide *ca.* 0.5 g to our industrial partners. Two novel complexes have been synthesised, incorporating **175** ligand. The synthesis of **184** has been accomplished successfully and is being taken towards the picolinic acid derivative and subsequent Ir[III] complex by other members of the Bryce research group.
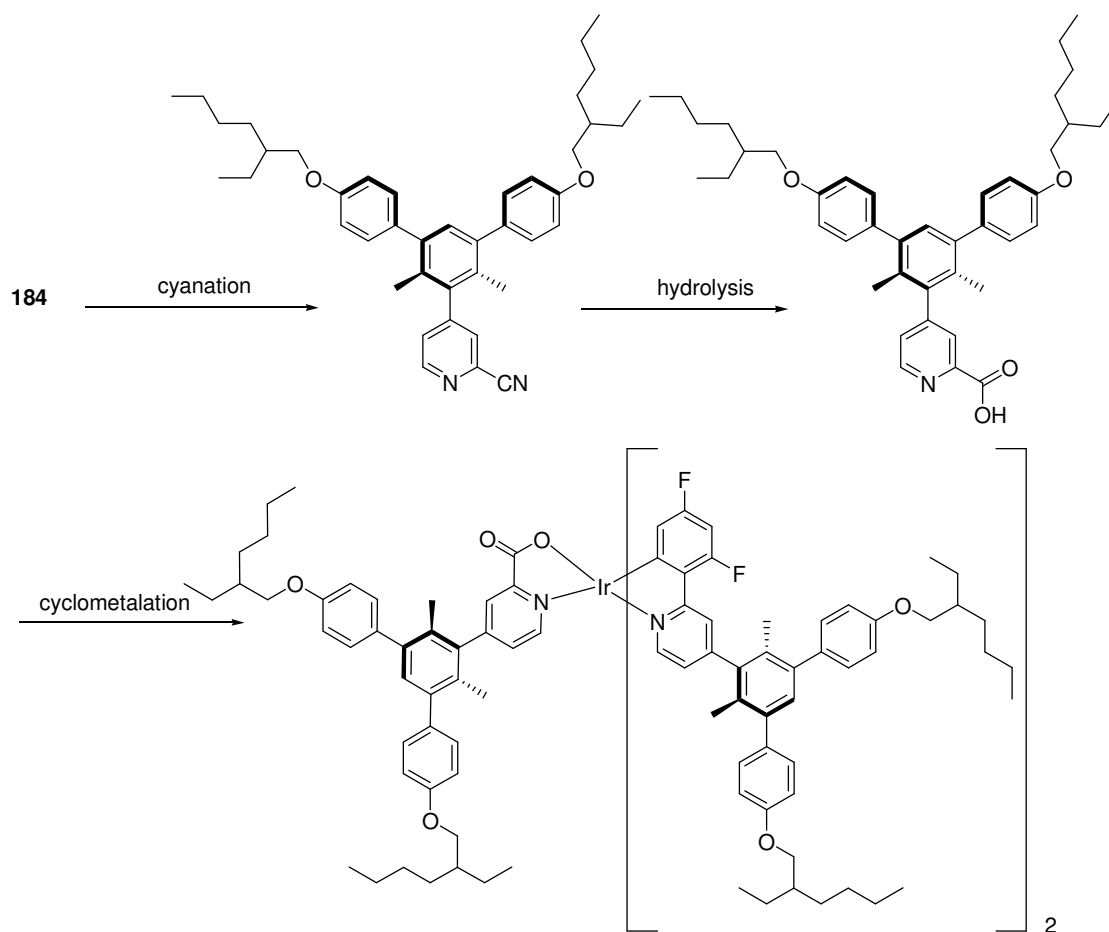
Scheme 94:   Proposed route to modify 184 towards G2Pic and the associated Ir[III] complex. This work is being carried out by other members of the Bryce research group.

CHAPTER 7 - EXPERIMENTAL PROCEDURES

7.1   General Considerations

All reactions were performed under an argon atmosphere, which was dried by passage through a column of phosphorus pentoxide. Glassware was flame dried prior to use for moisture sensitive reactions. All reagents used were of standard reagent grade, used as supplied unless otherwise stated and purchased from Sigma–Aldrich or Alfa Aesar, except for methoxypyridylboronic acid derivatives **135**[248,329] and **136**[248,329] which were supplied by Vertellus Specialities UK Ltd., 2-fluoro-5-pyridylboronic acid **88**[287] 2-amino-5-pyrimidylboronic acid **152**[362] Pd(PPh$_3$)$_4$ and Pd(PPh$_3$)$_2$Cl$_2$,[363] which were prepared in-house. 2-Amino-5-bromopyrazine **113**[364] and 5-bromo-2-iodopyrimidine **64**[365] were prepared in our group by literature methods. Anhydrous THF, toluene, DMF and DCM were dried through a HPLC column on an Innovative Technology Inc. solvent purification system. Anhydrous triethylamine was dried over calcium hydride, distilled and stored under dry nitrogen prior to use. All other solvents were used without prior purification. Solvents were degassed by bubbling dry argon at a steady rate through the solvent for *ca.* 20 min. Column chromatography was carried out using 40–63 mm mesh silica. Thin-layer chromatography (TLC) was performed on 20 mm pre-coated plates of silica gel (Merck, silica gel ^{60}F$_{254}$), visualisation was made using ultraviolet light (254 nm). NMR spectra were recorded on: a Bruker Avance-400 spectrometer [δ_H (400 MHz), δ_C (100 MHz)], a Varian Inova-500 spectrometer [δ_H (500 MHz), δ_C (125 MHz)] and a Varian NMR system 700 MHz spectrometer using deuterated solvent as a lock. Chemical shifts are quoted in ppm, relative to the residual solvent as internal reference for ^{1}H and ^{13}C. The following abbreviations are used in listing NMR spectra: s=singlet, d=doublet, dd=doublet of doublets, t=triplet, ddd=doublet of doublet of doublets, dt=doublet of triplets, td=triplet of doublets, m=multiplet, br=broad. *J* values are quoted in Hz. 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-FinniganTrace mass spectrometer with positive ionisation mode. Electrospray (ES$^+$) mass spectra were recorded on a Thermo-Finnigan LTQ FT mass spectrometer or a Micromass Autospec LCT mass spectrometer. High resolution ES$^+$ mass spectra were recorded on a Thermo-Finnigan LTQ FT mass spectrometer. High resolution atmospheric pressure chemical ionisation (APCI$^+$) mass spectra were obtained courtesy of Mr Liam Brady of Waters Ltd on a Waters LCT

Premier XE using atmospheric pressure chemical ionisation with an ASAP probe or on a Waters Xevo QToF equipped with Atmospheric Pressure Gas Chromatography (APGC). Elemental analyses were obtained on an Exeter Analytical Inc. CE-440 elemental analyser. IR spectra were recorded on a Perkin-Elmer Paragon FT-IR spectrometer as a film using "golden-gate" setup.

7.2   Experimental Details for Chapter 2

General procedure for Ligand-accelerated Ullmann Reactions

The azole/azolone, base and copper source (5 – 20 mol% relative to the aryl halide) were added to an argon purged, flame-dried, round-bottom flask. To this was added degassed solvent *via* syringe followed sequentially by the aryl halide and ligand. The reaction mixture was stirred and heated under a blanket of argon until TLC monitoring showed the reaction was complete (approximately 24 h). The reaction mixture was diluted with EtOAc (10 mL) and washed through a short silica pad with EtOAc (40 mL). The collected eluent was concentrated under reduced pressure and the product was either recrystallised or further purified by chromatography on silica.

1-(Pyrimidin-2-yl)-1*H*-benzimidazole 66
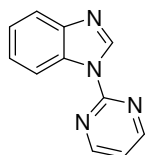
Procedure A: Benzimidazole **57** (0.284 g, 2.4 mmol), Cs_2CO_3 (1.304 g, 4 mmol), CuI (0.038g, 0.2 mmol, 10 mol%), DMF (4 mL), 2-iodopyrimidine **61a** (0.412 g, 2 mmol) and 1,10-phenanthroline (0.072 g, 0.4 mmol) were reacted at 110 °C for 6 h. Filtration and concentration yielded a white solid which was purified by column chromatography on silica (eluent EtOAc : Et_2O 9:1 *v/v*) yielding **66** as a white powder (0.196 g, 50%). mp 149.1-150.1 °C; δ_H (400 MHz, CDCl$_3$) 9.03 (1H, s, C(2)$\underline{H}$$_{benzimidzole}$), 8.66 (2H, d, *J* 4.8, C(3+5)$\underline{H}$$_{pyrimidyl}$), 8.53 (1H, d, *J* 6.8, C(4)$\underline{H}$$_{benzimidazole}$), 7.81 (1H, d, *J* 7.3, C(7)$\underline{H}$$_{benzimidazole}$), 7.39-7.31 (2H, m, C(5+6)$\underline{H}$$_{benzimidazole}$), 7.09 (1H, t, *J* 4.8, C(4)$\underline{H}$$_{pyrimidyl}$); δ_C (100 MHz, CDCl$_3$) 158.7 ($\underline{C}$(2) $_{pyrimidyl}$), 156.5 (2C, $\underline{C}$(4+6)H$_{pyrimidyl}$), 145.3 ($\underline{C}$(2)H$_{benzimidazole}$), 142.0 ($\underline{C}$(3)$_{benzimidazole}$), 132.1 ($\underline{C}$(8)$_{benzimidazole}$), 124.8 ($\underline{C}$(5)H$_{benzimidazole}$), 124.0 ($\underline{C}$(6)H$_{benzimidazole}$), 120.6 ($\underline{C}$(4)H$_{pyrimidyl}$), 118.2 ($\underline{C}$(4)H$_{benzimidazole}$), 115.9 ($\underline{C}$(7)H$_{benzimidazole}$); *m/z* (EI) 196 (M$^+$, 100%); *Anal.* Calcd. for C$_{11}$H$_8$N$_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.12; H, 4.07; N, 28.74; ν_{max} (film)/cm^{-1} 3127, 3066, 1570, 1463, 1440, 1300, 742.

Procedure B: Benzimidazole **57** (0.260 g, 2.2 mmol), Cs_2CO_3 (1.303 g, 4 mmol), Cu_2O (0.014g, 0.1 mmol, 5 mol%), acetonitrile (4 mL), 2-bromopyrimidine **61b** (0.318 g, 2 mmol) and the ligand Chxn-Py-Al (0.123 g, 0.4 mmol), were reacted at 87 °C for 64 h. Work-up as for Procedure A yielded **66** (0.275 g, 78%) spectroscopically identical to the sample prepared by procedure A.

1-(Pyrazin-2-yl)-1*H*-benzimidazole 67
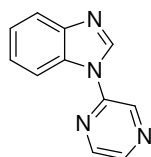
Benzimidazole **57** (0.144 g, 1.22 mmol), Cs_2CO_3 (0.660 g, 2.025 mmol), CuI (0.019 g, 0.10 mmol, 7 mol%), DMF (2 mL), 2-iodopyrazine **62** (0.309 g, 1.50 mmol) and 1,10-phenanthroline (0.037 g, 0.20 mmol), were reacted at 110 °C for 65 h. Filtration and concentration yielded a white solid which was purified by chromatography using a silica column (eluent EtOAc : Et_2O 9:1 *v/v*) yielding **67** as a white powder (0.228 g, 70%). mp 149.5-150.8 °C; δ_H (400 MHz, $CDCl_3$) 9.03 (1H, d, *J* 1.6, C(2)<u>H</u>benzimidazole), 8.63-8.58 (3H, m, C(3+4+5)<u>H</u>pyrazinyl), 8.11 (1H, dd, *J* 6.8, 1.6, C(4)<u>H</u>benzimidazole), 7.90 (1H, dd, *J* 5.2, 2.4, C(7)<u>H</u>benzimidazole), 7.46-7.38 (2H, m, C(5+6)<u>H</u>benzimidazole); δ_C (100 MHz, $CDCl_3$) 147.1 (<u>C</u>(2)pyrazinyl), 145.1 (<u>C</u>(6)Hpyrazinyl), 143.6 (<u>C</u>(2)H benzimidazole), 142.6 (<u>C</u>(5)Hpyrazinyl), 140.9 (<u>C</u>(3)benzimidazole), 136.5 (<u>C</u>(3)Hpyrazinyl), 129.6(<u>C</u>(8)Hbenzimidazole), 125.2 (<u>C</u>(6)Hbenzimidazole), 124.3 (<u>C</u>(5)Hbenzimidazole), 121.4 (<u>C</u>(4)Hbenzimidazole), 113.0 (<u>C</u>(7)Hbenzimidazole); *m/z* (EI) 196 (M⁺, 100%); *Anal.* Calcd. for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.11; H, 4.13; N, 28.33; ν_{max} (film)/cm⁻¹ 3082, 2975, 1501, 1478, 1305, 748.

1-(5-Bromopyridin-2-yl)-1*H*-benzimidazole 68
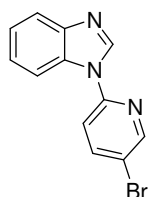
Benzimidazole **57** (0.523 g, 4.8 mmol), Cs_2CO_3 (2.608 g, 8.0 mmol), CuI (0.076 g, 0.2 mmol, 5 mol%), DMF (4 mL), 5-bromo-2-iodopyridine **63** (1.160 g, 4.1 mmol) and 1,10-phenanthroline (0.1440 g, 0.80 mmol), were reacted at 80 °C for 22 h. Filtration and concentration yielded a pale yellow solid which was purified by chromatography on silica (9:1 EtOAc : Et_2O *v/v*) yielding **68** as a white solid (1.008 g, 90%). m.p 159.6-160.5 °C; δ_H (400 MHz, $CDCl_3$) 8.62 (1H, d, *J* 2.3 C(6)<u>H</u>pyridyl), 8.52 (1H, s, C(2)<u>H</u>benzimidazole), 8.03-7.95 (2H, m, C(4)<u>H</u>benzimidazole + <u>C</u>(4)Hpyridyl), 7.88-7.84 (1H, m, C(7)<u>H</u>benzimidazole), 7.45 (1H, d, *J* 8.6, C(3)<u>H</u>pyridyl), 7.34-7.25 (2H, m, C(5+6)<u>H</u>benzimidazole); δ_C (100 MHz, $CDCl_3$) 150.4 (<u>C</u>(2)pyridyl), 148.5 (<u>C</u>(6)Hpyridyl), 144.7 (<u>C</u>(2)Hbenzimidazole), 141.4 (<u>C</u>(3)benzimidazole), 141.0 (<u>C</u>(4)Hpydridyl), 131.9 (<u>C</u>(8)benzimidazole), 124.5 (<u>C</u>(6)Hbenzimidazole), 123.6 (<u>C</u>(5)Hbenzimidazole), 120.8 (<u>C</u>(3)Hpyridyl),

117.6 ($\underline{C}$(5)Br$_{pyridyl}$), 115.2 ($\underline{C}$(4)H$_{benzimidazole}$), 112.6 ($\underline{C}$(7)H$_{benzimidazole}$); *m/z* 273 (M$^+$ [^{79}Br], 100%), 275 (M$^+$ [^{81}Br], 97%); *Anal.* Calc. for $C_{12}H_8N_3Br$: C, 52.58; H, 2.94; N, 15.33. Found: C, 52.53; H, 2.83; N, 15.19.

1-(5-Bromopyrimidin-2-yl)-1*H*-benzimidazole 69
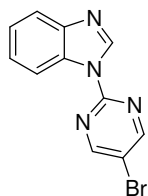
Benzimidazole **57** (0.284 g, 2.4 mmol), Cs_2CO_3 (1.304 g, 4.0 mmol), CuI (0.038 g, 0.20 mmol, 10 mol%), DMF (4 mL), 5-bromo-2-iodopyrimidine **64** (0.570 g, 2.0 mmol) and 1,10-phenanthroline (0.072 g, 0.40 mmol), were reacted at 70 °C for 24 h. Filtration and concentration yielded a white solid which was purified by column chromatography on silica (eluent EtOAc : Et$_2$O 9:1 *v/v*) yielding **69** as a white solid (0.230 g, 57%). mp 189.1-189.6 °C; δ_H (400 MHz, CDCl$_3$) 9.03 (1H, s, C(2)$\underline{H}$$_{benzimidazole}$), 8.80 (2H, s, C(4+6)$\underline{H}$$_{pyrimidyl}$), 8.52 (1H, dd, *J* 7.2, 1.6 C(7)$\underline{H}$$_{benzimidazole}$), 7.85 (1H, dd, *J* 6.8, 1.2, C(4)$\underline{H}$$_{benzimidazole}$), 7.45-7.37 (2H, m C(5+6)$\underline{H}$$_{benzimidazole}$); δ_C (125 MHz, CDCl$_3$) 159.4 ($\underline{C}(2)_{pyrimidyl}$), 154.9 (2C, $\underline{C}$(4+6)$_{pyrimidyl}$), 145.4 ($\underline{C}$(2)H$_{benzimidazole}$), 142.1 ($\underline{C}$(3)$_{benzimidazole}$), 132.0 ($\underline{C}$(8)$_{benzimidazole}$), 125.2 ($\underline{C}$(5)H$_{benzimidazole}$), 124.4 ($\underline{C}$(6)H$_{benzimidazole}$), 120.9 ($\underline{C}$(4)H$_{benzimidazole}$), 115.83 ($\underline{C}$(7)H$_{benzimidazole}$), 115.77 ($\underline{C}$(5)$_{pyrimidyl}$); *m/z* 274 (M$^+$ [^{79}Br], 100%), 276 (M$^+$ [^{81}Br], 97%); *Anal.* Calcd. for $C_{11}H_7N_4Br$: C, 48.02; H, 2.56; N, 20.37. Found: C, 47.86; H, 2.52; N, 20.37; ν_{max} (film)/cm^{-1} 3124, 3022, 1462, 1439, 1298, 747.

1-(5-Bromopyridin-2-yl)-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 70

1-Methyl-2-benzimidazolone **58** (1.305 g, 8.8 mmol), Cs_2CO_3 (5.213 g, 16 mmol), CuI (0.152g, 0.8 mmol, 10 mol%), DMF (20 mL), 2-iodo-5-bromopyridine **63** (2.271 g, 8.0 mmol) and 1,10-phenanthroline (0.288 g, 1.6 mmol) were reacted at 80 °C for 24 h. Filtration and concentration yielded a pale brown solid which was purified by column chromatography on silica (eluent DCM : EtOAc 9:1 *v/v*) yielding **70** as a white solid (2.27 g, 94%). mp 148.2-148.6 °C; δ_H (500 MHz, CDCl$_3$) 8.59 (1H, d, *J* 2.0, C(6)$\underline{H}$$_{pyridyl}$), 8.16 (1H, d, *J* 8.5, C(4)$\underline{H}$$_{pyridyl}$), 8.10 (1H, d, *J* 8.0, C(8)$\underline{H}$$_{benzimidazolone}$), 7.94 (1H, dd, *J* 8.5, 2.5, C(3)$\underline{H}$$_{pyridyl}$), 7.23-7.14 (2H, m, C(6+7)$\underline{H}$$_{benzimidazolone}$), 7.03 (1H, d, *J* 8.0, C(5)$\underline{H}$$_{benzimidazolone}$), 3.48 (3H, s, N-C$\underline{H}$$_3$); δ_C (125 MHz, CDCl$_3$) 153.3 ($\underline{C}$(2)=O$_{benzimidazolone}$), 149.5 ($\underline{C}(2)_{pyridyl}$), 149.1 ($\underline{C}$(6)H$_{pyridyl}$), 141.0 ($\underline{C}$(4)H$_{pyridyl}$), 130.5 ($\underline{C}(9)_{benzimidazolone}$), 127.6 ($\underline{C}(4)_{benzimidazolone}$), 123.4 ($\underline{C}$(7H)$_{benzimidazolone}$), 122.4 ($\underline{C}$(6)H$_{benzimidazolone}$), 118.7 ($\underline{C}$(3)H$_{pyridyl}$), 116.9 ($\underline{C}(5)_{pyridyl}$), 113.7 ($\underline{C}$(8H)$_{benzimidazolone}$), 107.8 ($\underline{C}$(5)H$_{benzimidazolone}$), 27.5 (N-$\underline{C}H_3$); *m/z* 303 (M$^+$ ^{79}Br],
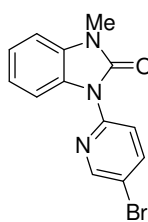
100%), 305 (M$^+$ [^{81}Br], 97%); *Anal.* Calcd. for C$_{13}$H$_{10}$BrN$_3$O: C, 51.34; H, 3.31; N, 13.82. Found: C, 51.13; H, 3.20; N, 13.67; ν_{max} (film)/cm^{-1} 3057, 3013, 1727, 1493, 1472, 1392, 746.

1-(5-Bromopyrimidin-2-yl)-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 71
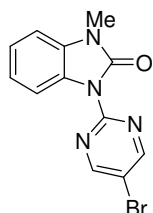
1-Methyl-2-benzimidazolone **58** (0.652 g, 4.4 mmol), Cs$_2$CO$_3$ (2.607 g, 8 mmol), CuI (0.076g, 0.4 mmol, 10 mol%), DMF (10 mL), 2-iodo-5-bromopyrimidine **64** (1.134 g, 4.0 mmol) and 1,10-phenanthroline (0.144 g, 0.8 mmol) were reacted at 80 ^{o}C for 18 h. Filtration and concentration yielded a yellow solid which was chromatographed on a silica column (eluent DCM : EtOAc 3:1 *v/v*) yielding **71** as a white solid (0.92 g, 76%). mp 175.4-176.7 ^{o}C; δ_H (400 MHz, CDCl$_3$) 8.87 (2H, s, C(4+6)$\underline{H}$$_{pyrimidyl}$), 7.93 (d, 1H, *J* 9.4, C(8)$\underline{H}$$_{benzimidazolone}$), 7.23-7.11 (2H, m, C(6+7)$\underline{H}$$_{benzimidazolone}$), 7.01 (d, 1H, *J* 7.8, C(2)$\underline{H}$$_{benzimidazolone}$), 3.46 (s, 3H, N-C$\underline{H}$$_3$); δ_C (125 MHz, CDCl$_3$) 159.4 ($\underline{C}(2)_{pyrimidyl}$), 155.1 ($\underline{C}$(4+6)H$_{pyrimidyl}$), 152.3 ($\underline{C}$(2)=O$_{benzimidazolone}$), 130.6 ($\underline{C}(9)_{benzimidazolone}$), 127.2 ($\underline{C}(4)_{benzimidazolone}$), 123.9 ($\underline{C}$(7)H$_{benzimidazolone}$), 122.3 ($\underline{C}$(6)H$_{benzimidazolone}$), 116.2 ($\underline{C}(5)_{pyrimidyl}$), 113.4 ($\underline{C}$(8)H$_{benzimidazolone}$), 107.0 ($\underline{C}$(5)H$_{benzimidazolone}$), 27.6 (N-$\underline{C}H_3$); *m/z* 304 (M$^+$ [^{79}Br], 100%), 306 (M$^+$ [^{81}Br], 97%); *Anal.* Calcd. for C$_{12}$H$_9$N$_4$BrO: C, 47.24; H, 2.97; N, 18.36. Found: C, 47.27; H, 2.98; N, 18.43; ν_{max} (film)/cm^{-1} 3060, 3031, 1735, 1498, 1413, 1384, 745.

1-(4-Bromophen-2-yl)-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 72

1-Methyl-2-benzimidazolone **58** (0.593 g, 4.0 mmol), Cs$_2$CO$_3$ (3.37g, 7.3 mmol), CuI (0.076g, 0.40 mmol, 10 mol%), DMF (5.5 mL), 1-bromo-4-iodobenzene **65** (1.136 g, 3.6 mmol) and 1,10-phenanthroline (0.072 g, 0.4 mmol) were reacted at 80 ^{o}C for 16 h, then at 90 ^{o}C for 6 h and finally at 100 ^{o}C for 2 h to drive to completion by TLC monitoring. Filtration and concentration yielded a white solid which was chromatographed on a silica column (eluent DCM : EtOAc 3:1 *v/v*) yielding **72** as a white solid which was recrystallized from DCM/hexane mixture to give white crystals (0.893 g, 81%). mp 157.7-158.6 ^{o}C; δ_H (400 MHz, CDCl$_3$) 7.65 (d, 2H, *J* 8.8, C(3+5)$\underline{H}$$_{phenyl}$), 7.44 (d, 2H, *J* 8.8, C(2+6)$\underline{H}$$_{phenyl}$), 7.20-7.04 (m, 4H, C(5+6+7+8)$\underline{H}$$_{benzimidazolone}$), 3.49 (s, 3H, N-C$\underline{H}$$_3$); δ_C (125 MHz, CDCl$_3$) 153.6 ($\underline{C}$(2)=O$_{benzimidazolone}$), 134.2 ($\underline{C}(1)_{phenyl}$), 133.0 ($\underline{C}(9)_{benzimidazolone}$), 130.5 (2C, $\underline{C}$(3+5)H$_{phenyl}$), 129.2 ($\underline{C}$(4)$_{benzimidazolone}$), 127.8 ($\underline{C}$(7)$_{benzimidazolone}$), 122.6 ($\underline{C}$(6)$_{benzimidazolone}$),

121.9 (2C, $\underline{C}$(2+6)$_{phenyl}$), 121.4 ($\underline{C}$(8)$_{benzimidazolone}$), 108.9 ($\underline{C}$(5)$_{benzimidazolone}$), 108.2 ($\underline{C}$(4)$_{phenyl}$), 27.6 (N-$\underline{C}H_3$); *m/z* 302 (M$^+$ [^{79}Br], 100%), 304 (M$^+$ [^{81}Br], 97%); *Anal.* Calcd. for $C_{14}H_{11}BrN_2O$: C, 55.47; H, 3.66; N, 9.24; Found: C, 54.95; H, 3.60; N, 9.62; *m/z* (ES$^+$) 305.01087 (M$^+$+H, $C_{14}H_{11}BrN_2O$+H requires 305.01071); ν_{max} (film)/cm^{-1} 3056, 2932, 1712, 1501, 1400, 1204, 745.

5-Bromo-2-(1H-imidazol-1-yl)pyrimidine 73

Imidazole **59** (0.150 g, 2.2 mmol), Cs_2CO_3 (1.303 g, 4 mmol), CuI (0.038 g, 0.2 mmol, 10 mol%), DMF (5 mL), 5-bromo-2-iodopyrimidine **64** (0.570 g, 2.2 mmol) and 1,10-phenanthroline (0.072 g, 0.4 mmol) were reacted at 80 ^{o}C for 18 h. Filtration and concentration yielded an off-white solid which was chromatographed on a silica column (eluent EtOAc : Et$_2$O 9:1 *v/v*) yielding **73** as a white solid (0.292 g, 65%). mp *ca.* 160 ^{o}C (dec.); δ_H (400 MHz, CDCl$_3$) 8.72 (s, 2H, C(4+6)$\underline{H}_{pyrimidyl}$), 8.56 (s, 1H, C(2)$\underline{H}_{imidazole}$), 7.83 (t, 1H, *J* 1.2, C(5)$\underline{H}_{imidazole}$), 7.17 (m, 1H, C(4)$\underline{H}_{imidazole}$); δ_C (125 MHz, CDCl$_3$) 159.6 ($\underline{C}(2)_{pyrimidyl}$), 153.5 (2C, $\underline{C}$(4+6)H$_{pyrimidyl}$), 136.6 ($\underline{C}$(2)H$_{imidazole}$), 131.4 ($\underline{C}$(4)H$_{imidazole}$), 116.9 ($\underline{C}$(5)H$_{imidazole}$), 116.7 ($\underline{C}$(5)$_{pyrimidyl}$). *m/z* 223.9 (M$^+$ [^{79}Br], 100%), 225.9 (M$^+$ [^{81}Br], 97%); *Anal.* Calcd. for $C_7H_5BrN_4$: C, 37.36; H, 2.24; N, 24.90. Found: C, 36.99; H, 2.22; N, 24.61; ν_{max} (film)/cm^{-1} 3134, 1557, 1471, 1446, 754, 648.

5-Bromo-2-(1H-pyrrol-1-yl)pyrimidine 74

Pyrrole **60** (0.295 g, 4.4 mmol), Cs_2CO_3 (2.607 g, 8 mmol), CuI (0.076 g, 0.4 mmol, 10 mol%), DMF (10 mL), 5-bromo-2-iodopyrimidine **64** (1.140 g, 4.4 mmol) and 1,10-phenanthroline (0.144 g, 0.8 mmol) were reacted at 80 ^{o}C for 18 h. Filtration and concentration yielded an off-white solid which was chromatographed on a silica column (eluent EtOAc : hexane 1:9 *v/v*) yielding **74** as a white solid (0.756 g, 84%). mp *ca.* 217 ^{o}C (dec.); δ_H (400 MHz, CDCl$_3$) 8.63 (s, 2H, C(4+6)$\underline{H}_{pyrimidyl}$), 7.71 (t, 2H, *J* 2.0, C(2+5)$\underline{H}_{pyrrole}$), 6.35 (t, 2H, *J* 2.4, C(3+4)$\underline{H}_{pyrrole}$); δ_C (125 MHz, CDCl$_3$) 159.2 ($\underline{C}$(2)$_{pyrimidyl}$), 153.3 (2C, $\underline{C}$(4+6)H$_{pyrimidyl}$), 119.9 (2C, $\underline{C}$(2+5)$_{pyrrole}$), 114.8 (2C, $\underline{C}$(3+4)$_{pyrrole}$), 112.6 ($\underline{C}$(5)$_{pyrimidyl}$); *Anal.* Calcd. for $C_8H_6BrN_3$: C, 42.88; H, 2.70; N, 18.75. Found: C, 42.49; H, 2.81; N, 18.82; *m/z* (ES$^+$) 223.98210 (M$^+$+H, $C_8H_6N_3$Br+H requires 223.98178); ν_{max} (film)/cm^{-1} 3150, 1555, 1470, 1443, 735, 610.

General method for Suzuki–Miyaura cross-coupling reactions

To an argon purged flask was added the (het)aryl halide, boronic acid, palladium source and additional ligand (when applicable). Degassed solvent and base were added and the mixture was heated to reflux, with stirring. The reaction was monitored by TLC and on completion (2–70 h) the reaction was cooled to room temperature and the solvent was removed *in vacuo*. The residue was extracted into EtOAc and washed with brine. The organic layers were dried over Na_2SO_4, filtered and then concentrated *in vacuo*. Purification was achieved by flash chromatography on a silica gel column followed in some cases by recrystallisation.

1-(5-(4-Methoxyphenyl)pyridin-2-yl)-1*H*-benzo[*d*]imidazole 78

Compound **68** (0.139 g, 0.505 mmol), 4-methoxybenzeneboronic acid **75** (0.085 g, 0.561 mmol), $Pd(PPh_3)_2Cl_2$ (0.020 g, 0.03 mmol, 6 mol%), 1,4-dioxane (5 mL) and Na_2CO_3 (1 M, 1.7 mL) were reacted at 80 ^{o}C for 24 h. Standard work-up and evaporation yielded a white solid which was chromatographed on a silica column (eluent DCM : EtOAc 1:1 *v/v*) to yield **78** which was recrystallized from hexane as large white crystals (0.112 g, 74%). mp 155.0-156.2 ^{o}C; δ_H (400 MHz, CDCl$_3$) 8.75 (1H, d, *J* 2.5, C(6)$\underline{H}_{pyridyl}$), 8.58 (1H, s, C(2)$\underline{H}_{benzimidazole}$), 8.07 (1H, dd, *J* 7.0, 1.8, C(4)$\underline{H}_{pyridyl}$), 7.98 (1H, d, *J* 8.5, C(4)$\underline{H}_{benzimidazole}$), 7.88 (1H, d, *J* 7.1, C(7)$\underline{H}_{benzimidazole}$), 7.56-7.52 (3H, m, C(5+6)$\underline{H}_{benzimidazole}$+ C(3)$\underline{H}_{pyridyl}$), 7.41-7.33 (2H, m, C(2+6)$\underline{H}_{phenyl}$), 7.02 (2H, d, *J* 8.6, C(3+5)$\underline{H}_{phenyl}$), 3.85 (3H, s, O-C$\underline{H}_3$); δ_C (100 MHz , CDCl$_3$) 160.3 ($\underline{C}(4)O_{phenyl}$), 148.6 ($\underline{C}(2)_{pyridyl}$), 147.4 ($\underline{C}(6)H_{pyridyl}$), 145.0 ($\underline{C}(2)H_{benzimidazole}$), 141.6 ($\underline{C}(3)_{benzimidazole}$), 136.9 ($\underline{C}(5)_{pyridyl}$), 134.9 ($\underline{C}(8)_{benzimidazole}$), 132.5 ($\underline{C}(4)H_{pyridyl}$), 129.3 ($\underline{C}(1)_{phenyl}$), 128.3(2C, $\underline{C}(2+6)H_{phenyl}$), 124.5 ($\underline{C}(5)H_{benzimidazole}$), 123.5 ($\underline{C}(6)H_{benzimidazole}$), 120.9 ($\underline{C}(4)_{benzimidazole}$), 115.0 ($\underline{C}(7)H_{benzimidazole}$), 114.3 ($\underline{C}(3)H_{pyridyl}$), 112.9 ($\underline{C}(3+5)H_{phenyl}$), 55.7 (O-$\underline{C}H_3$); *m/z* (EI) 301 (M$^+$, 100%); *Anal.* Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.39; H, 4.97; N, 13.84; ν_{max} (film)/cm^{-1} 3056, 2933, 2833, 1598, 1487, 1455, 1245, 830, 740.

1-(5-(2-Methoxyphenyl)pyridin-2-yl)-1*H*-benzo[*d*]imidazole 79

Compound **68** (0.493 g, 1.8 mmol), 2-methoxybenzeneboronic acid **76** (0.304 g, 2.0 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.07 g, 0.1 mmol, 6 mol%), 1,4-dioxane (8 mL) and Na$_2$CO$_3$ (1 M, 4 mL) were reacted at 80 ^{o}C for 4 h. Standard work-up and concentration yielded a white solid which was chromatographed on a silica column (eluent EtOAc : DCM 10:1 *v/v*) yielding **79** as a white solid (0.519 g, 96%). mp 69.1-72.0 ^{o}C; δ_H (500 MHz, CDCl$_3$) 8.77 (1H, d, *J* 2.0, C(6)$\underline{H}$$_{pyridyl}$), 8.62 (1H, s, C(2)$\underline{H}$$_{benzimidazole}$), 8.12-8.09 (2H, m, C(4)$\underline{H}$$_{pyridyl}$), 7.89 (1H, d, *J* 7.0, C(4)$\underline{H}$$_{benzimidazole}$), 7.61 (1H, dd, *J* 8.5, 0.5, C(7)$\underline{H}$$_{benzimidazole}$), 7.44-7.36 (4H, m, C(5+6)$\underline{H}$$_{benzimidazole}$+ C(3+5)$\underline{H}$$_{phenyl}$), 7.12-7.04 (2H, m, C(4+6)$\underline{H}$$_{phenyl}$), 3.88 (3H, s, O-C$\underline{H}$$_3$); δ_C (125 MHz, CDCl$_3$) 156.9 ($\underline{C}$(4)O$_{phenyl}$), 150.0 ($\underline{C}(2)_{pyridyl}$), 148.6 ($\underline{C}$(6)H$_{pyridyl}$), 145.0 ($\underline{C}$(2)H$_{benzimidazole}$), 141.8 ($\underline{C}(3)_{benzimidazole}$), 140.1 ($\underline{C}(5)_{pyridyl}$), 133.0 ($\underline{C}(8)_{benzimidazole}$), 132.5 ($\underline{C}$(4)H$_{pyridyl}$), 130.8 ($\underline{C}$(5)H$_{phenyl}$), 130.2 ($\underline{C}$(3)H$_{phenyl}$), 126.2 ($\underline{C}(2)_{phenyl}$), 124.5 ($\underline{C}$(5)H$_{benzimidazole}$), 123.6 ($\underline{C}$(6)H$_{benzimidazole}$), 121.5 ($\underline{C}$(4)H$_{phenyl}$), 121.0 ($\underline{C}$(4)H$_{benzimidazole}$), 113.9 ($\underline{C}$(7)H$_{benzimidazole}$), 113.0 ($\underline{C}$(3)H$_{pyridyl}$), 111.7 ($\underline{C}$(6)H$_{phenyl}$), 55.9 (O-$\underline{C}H_3$); *m/z* (EI) 301 (M$^+$, 100%); *Anal.* Calcd. for C$_{19}$H$_{15}$N$_3$O: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.45; H, 4.98; N, 13.95; ν_{max} (film)/cm^{-1} 3099, 3054, 2833, 1597, 1505, 1480, 1245, 746.
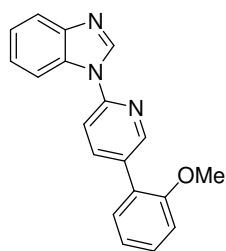
1-(5-(2-Ethoxypyridin-3-yl)pyridin-2-yl)-1*H*-benzo[*d*]imidazole 80
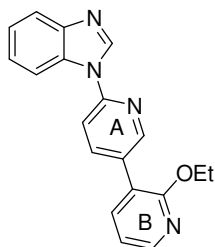
Compound **68** (0.493 g, 1.8 mmol), 2-ethoxypyridin-3-yl-3-boronic acid **77** (0.304 g, 2 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.07 g, 0.1 mmol, 6 mol%), degassed 1,4-dioxane (8 mL), degassed 1 M Na$_2$CO$_3$ (4 mL), were reacted at 80 ^{o}C for 4 h. Standard work-up and concentration yielded a white solid which was purified by chromatography using a silica column (10:1 EtOAc : DCM *v/v*) yielding **80** as a white solid (0.519 g, 96%). m.p. 106.9-107.7 ^{o}C; δ_H (400 MHz, CDCl$_3$) 8.80 (1H, d, *J* 2.0, C(6)$\underline{H}$$_{pyridyl-A}$), 8.63 (1H, s, C(2)$\underline{H}$$_{benzimidazole}$), 8.23 (1H, dd, *J* 5.1, 1.8, C(6)$\underline{H}$$_{pyridyl-B}$), 8.15 (1H, dd, *J* 8.5, 2.4, C(4)$\underline{H}$$_{pyridyl-A}$), 8.11 (1H, d, *J* 7.3, C(7)$\underline{H}$$_{benzimidazole}$), 7.89 (1H, d, *J* 7.1, C(4)$\underline{H}$$_{benzimidazole}$), 7.69 (1H, dd, *J* 7.3, 2.0, C(4)$\underline{H}$$_{pyridyl-B}$), 7.63 (1H, d, *J* 8.1, C(3)$\underline{H}$$_{pyridyl-A}$), 7.45-7.34 (2H, m, C(5+6)$\underline{H}$$_{benzimidazole}$), 7.04-7.01 (1H, m, C(5)$\underline{H}$$_{pyridyl-B}$), 4.40 (2H, q, *J* 7.1, O-C$\underline{H}$$_2$), 1.31 (3H, t, *J* 7.1, CH$_2$-C$\underline{H}$$_3$); δ_C (100 MHz , CDCl$_3$) 160.6 ($\underline{C}$(2)O$_{pyridyl-B}$), 149.4 ($\underline{C}(2)_{pyridyl-A}$), 148.7 ($\underline{C}(6)_{pyridyl-B}$), 147.0 ($\underline{C}(6)_{pyridyl-A}$), 144.8 ($\underline{C}$(2)H$_{benzimidazole}$), 144.4 ($\underline{C}$(3)H$_{benzimidazole}$), 139.4 ($\underline{C}$(5)H$_{pyridyl-A}$), 138.2 ($\underline{C}(8)_{benzimidazole}$), 132.2 ($\underline{C}$(4)H$_{pyridyl-B}$), 131.0 ($\underline{C}$(4)H$_{pyridyl-A}$), 124.3 ($\underline{C}(3)_{pyridyl-B}$), 123.3 ($\underline{C}$(5)H$_{benzimidazole}$), 120.7 ($\underline{C}$(6)H$_{benzimidazole}$), 120.0 ($\underline{C}$(4)H$_{benzimidazole}$), 117.1

($\underline{C}(3)H_{pyridyl-A}$), 113.5 ($\underline{C}(7)H_{benzimidazole}$), 112.7 ($\underline{C}(5)H_{pyridyl-B}$), 63.0 (O-$\underline{C}H_2$), 15.2 (CH$_2$-$\underline{C}H_3$); *m/z* (EI) 316 (M$^+$, 100%); *Anal.* Calc. for $C_{19}H_{16}N_4O$: C, 72.14; H, 5.10; N, 17.71. Found: C, 70.68; H, 5.08; N, 17.21.

1-(5-(2-Ethoxypyridin-3-yl)pyrimidin-2-yl)-1*H*-benzo[*d*]imidazole 81
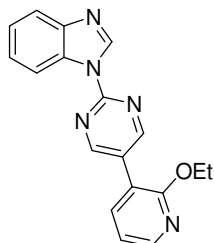
Procedure A: Compound **69** (0.113 g, 0.41 mmol), 2-ethoxypyridin-3-yl-3-boronic acid **77** (0.076 g, 0.46 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.016 g, 0.02 mmol, 5 mol%), 1,4-dioxane (5 mL) and Na$_2$CO$_3$ (1 M, 1.4 mL) were reacted at 80 ^{o}C for 18 h. Standard work-up and concentration yielded a white solid which was purified by column chromatography on silica (eluent chloroform : EtOAc 1:1 *v/v*) followed by recrystallization from hexane to yield **81** as a white solid (0.098 g, 79%). mp 229.0-230.2 ^{o}C; δ_H (400 MHz, CDCl$_3$) 9.14 (1H, s, C(2)$\underline{H}_{benzimidazole}$), 9.00 (2H, s, C(4+6)$\underline{H}_{pyrimidyl}$), 8.66 (1H, d, *J* 7.6 ,C(7)$\underline{H}_{benzimidazole}$), 8.25 (1H, dd, *J* 5.2, 1.6, C(6)$\underline{H}_{pyridyl}$), 7.87 (1H, d, *J* 7.6, C(4)$\underline{H}_{benzimidazole}$), 7.71 (1H, dd, *J* 7.2, 2.0, C(4)$\underline{H}_{pyridyl}$), 7.47-7.37 (2H, m, C(5+6)$\underline{H}_{benzimidazole}$), 7.05 (1H, dd, *J* 4.8, 7.2, C(5)$\underline{H}_{pyridyl}$), 4.49 (2H, q, *J* 7.2, O-C$\underline{H}_2$), 1.43 (3H, t, *J* 6.8, CH$_2$-C$\underline{H}_3$); δ_C (175 MHz, CDCl$_3$) 160.9 ($\underline{C}(2)_{pyrimidyl}$), 158.5 ($\underline{C}(2)O_{pyridyl}$), 155.4 (2C, $\underline{C}(4+6)H_{pyrimidyl}$), 148.0 ($\underline{C}(6)H_{pyridyl}$), 145.4 ($\underline{C}(2)H_{benzimidazole}$), 142.3 ($\underline{C}(3)_{benzimidazole}$), 138.2 ($\underline{C}(4)H_{pyridyl}$), 132.2 ($\underline{C}(8)_{benzimidazole}$), 127.8 ($\underline{C}(5)_{pyrimidyl}$), 125.0 ($\underline{C}(3)_{pyridyl}$), 124.2 ($\underline{C}(5)H_{benzimidazole}$), 120.8 ($\underline{C}(6)H_{benzimidazole}$), 117.6 ($\underline{C}(4)H_{benzimidazole}$), 117.5 ($\underline{C}(7)H_{benzimidazole}$), 110.4 ($\underline{C}(5)_{pyridyl}$), 62.7 (O-$\underline{C}H_2$), 15.0 (CH$_2$-$\underline{C}H_3$); *m/z* (EI) 317 (M$^+$, 100%); *Anal.* Calcd. for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07. Found: C, 68.02; H, 4.40; N, 22.42; ν_{max} (film)/cm^{-1} 3128, 2983, 2922, 1587, 1480, 1448, 1300, 735.

Procedure B (one-pot): To a mixture of benzimidazole **57** (0.284 g, 2.4 mmol), Cs$_2$CO$_3$ (1.304 g, 4.0 mmol), CuI (0.038 g, 0.20 mmol, 10 mol%) in dry degassed DMF (4 mL) was added 5-bromo-2-iodopyrimidine **64** (0.570 g, 2.0 mmol) and 1,10-phenanthroline (0.072 g, 0.40 mmol). The mixture was stirred and heated under argon at 80 ^{o}C for 17 h, until TLC monitoring showed the reaction was complete. To this was added, under argon, 2-ethoxypyridin-3-yl-3-boronic acid **77** (0.367 g, 2.2 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.084 g, 0.12 mmol, 6 mol%), 1,4-dioxane (10 mL) and Na$_2$CO$_3$ (1 M, 4.4 mL) and the mixture reacted at 80 ^{o}C for 17 h. The reaction was cooled to room temperature and the solvent removed *in vacuo.* The residue was extracted with EtOAc (100 mL) and the organic phase was washed with brine (3 x 50 mL). The combined organics were dried (MgSO$_4$) and concentrated *in*

vacuo. The product was purified by column chromatography on silica (eluent DCM : EtOAc 1:1 *v/v*) to yield **81** as a white solid (0.425 g, 67 %) spectroscopically identical to the sample prepared by procedure A.

1-(5-(4-Methoxyphenyl)pyridin-2-yl)-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 82
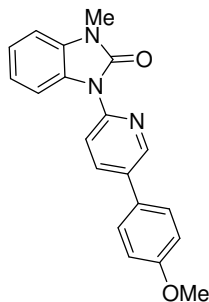
Compound **70** (0.366 g, 1.20 mmol), 4-methoxybenzeneboronic acid **75** (0.228 g, 1.50 mmol), $Pd(PPh_3)_2Cl_2$ (0.053 g, 0.08 mmol, 7 mol%), degassed 1,4-dioxane (6 mL) and degassed Na_2CO_3 (1 M, 5.7 mL) were reacted at 80 ^{o}C for 24 h. Standard work-up and concentration yielded a white solid which was chromatographed on a silica column (eluent DCM : EtOAc 1:1 *v/v*) yielding **82** as a white solid (0.300 g, 76 %). mp 195.9-196.7 ^{o}C; δ_H (500 MHz, CDCl$_3$) 8.74 (1H, dd, *J* 2.5, 0.5 Hz, C(6)$\underline{H}$$_{pyridyl}$), 8.17 (1H, dd, *J* 8.5, 0.5, C(3)$\underline{H}$$_{pyridyl}$), 8.09 (1H, dd, *J* 8.0, 1.0, C(5)$\underline{H}$$_{benzimidazolone}$), 8.01 (1H, dd, *J* 8.5, 2.5, C(4)$\underline{H}$$_{pyridyl}$), 7.57 (2H, d, *J* 9.0, C(2+6)$\underline{H}$$_{phenyl}$), 7.22-7.15 (2H, m, C(3+4)$\underline{H}$$_{benzimidazolone}$), 7.06-7.02 (3H, m, C(2)$\underline{H}$$_{benzimidazolone}$ + C(3+5)$\underline{H}$$_{phenyl}$), 3.88 (3H, s, O-C$\underline{H}$$_3$), 3.50 (3H, s, N-C$\underline{H}$$_3$); δ_C (125 MHz, CDCl$_3$) 160.1 ($\underline{C}$(4)O$_{phenyl}$), 153.5 ($\underline{C}(2)_{pyridyl}$), 149.2 ($\underline{C}$(2)O$_{benzimidazolone}$), 146.1 ($\underline{C}$(6)H$_{pyridyl}$), 134.1 ($\underline{C}$(4)H$_{pyridyl}$), 130.5 ($\underline{C}(9)_{benzimidazolone}$), 130.1 ($\underline{C}(4)_{benzimidazolone}$), 128.4 ($\underline{C}(1)_{phenyl}$), 128.1 (2C, $\underline{C}$(2+6)H$_{phenyl}$), 123.0 ($\underline{C}$(5)$_{pyridyl}$), 122.2 ($\underline{C}$(7)H$_{benzimidazolone}$), 117.6 ($\underline{C}$(6)H$_{benzimidazolone}$), 144.9 ($\underline{C}$(8)H$_{benzimidazolone}$), 113.3 (2C, $\underline{C}$(3+5)H$_{phenyl}$), 110.0 ($\underline{C}$(5)H$_{benzimidazolone}$) 107.7 ($\underline{C}$(3)H$_{pyridyl}$), 55.7 (O-$\underline{C}$H$_3$), 27.4 (N-$\underline{C}$H$_3$); *m/z* (EI) 332.2 ((M+H)$^+$, 100 %), 354.2 ((M+Na)$^+$, 72 %), 684.9 ((2M+Na)$^+$, 96 %); *Anal.* Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68; O, 9.66. Found: C, 72.26; H, 5.14; N, 12.62; ν_{max} (film)/cm^{-1} 3065, 2935, 2837, 1711, 1607, 1483, 1382, 824, 745.

1-(5-(2-Ethoxypyridin-3-yl)pyridin-2-yl)-3-methyl-1H-benzo[*d*]imidazol-2(3*H*)-one 83
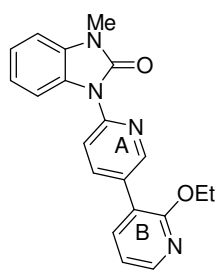
A mixture of **70** (0.401 g, 1.315 mmol), 2-ethoxypyridin-3-yl-3-boronic acid **77** (0.278 g, 1.46 mmol), $Pd(PPh_3)_4$ (0.085 g, 0.07 mmol, 5 mol%), degassed 1,4-dioxane (6 mL) and degassed Na_2CO_3 (1 M, 2.9 mL) were reacted at 80 ^{o}C for 19 h. Standard work-up and concentration yielded a white solid which was chromatographed on a silica column (eluent DCM : EtOAc 6:1 *v/v*) yielding **83** as a white solid (0.304 g, 67 %). mp 183.6-184.1 ^{o}C; δ_H (400 MHz, CDCl$_3$) 8.77 (1H, d, *J* 1.6, C(6)$\underline{H}$$_{pyridyl-A}$), 8.21-8.19 (2H, m, C(6)$\underline{H}$$_{pyridyl-B}$+ C(3)$\underline{H}$$_{pyridyl-A}$), 8.14 (d, 1H, J 8.0, C(8)$\underline{H}$$_{benzimidazolone}$), 8.09 (1H, dd, *J* 7.2,

2.0, C(4)$\underline{\text{H}}$_{pyridyl-A}), 7.68 (1H, dd, *J* 5.6, 1.2, C(4)$\underline{\text{H}}$_pyridyl-B_), 7.23-7.16 (2H, m, C(6+7)$\underline{\text{H}}$_benzimidazolone_), 7.05 (d, 1H, *J* 5.2, C(5)$\underline{\text{H}}$_benzimidazolone_), 7.01 (dd, 1H, *J* 5.6, 4.0, C(5)$\underline{\text{H}}$_pyridyl-B_), 4.46 (q, 2H, *J* 5.6, O-C$\underline{\text{H}}_2$), 3.51 (s, 3H, N-C$\underline{\text{H}}_3$), 1.41 (t, 3H, *J* 5.6, CH$_2$-C$\underline{\text{H}}_3$); δ_C (125 MHz, CDCl$_3$) 161.0 ($\underline{\text{C}}$(2)O_pyridyl-B_), 153.5 ($\underline{\text{C}}$(2)_pyridyl-A_), 149.6 ($\underline{\text{C}}$(2)O_benzimidazolone_), 148.3 ($\underline{\text{C}}$(6)H_pyridyl-B_), 147.0 ($\underline{\text{C}}$(6)H_pyridyl-A_), 139.0 ($\underline{\text{C}}$(4)H_pyridyl-A_), 138.7 ($\underline{\text{C}}$(4)H_pyridyl-B_), 130.5 ($\underline{\text{C}}$(9)_benzimidazolone_), 130.4 ($\underline{\text{C}}$(4)_benzimidazolone_), 128.0 ($\underline{\text{C}}$(3)H_pyridyl-B_), 123.1 ($\underline{\text{C}}$(5)H_pyridyl-A_), 122.3 ($\underline{\text{C}}$(7)H_benzimidazolone_), 120.9 ($\underline{\text{C}}$(6)H_benzimidazolone_), 117.4 ($\underline{\text{C}}$(8)H_benzimidazolone_), 117.1 ($\underline{\text{C}}$(5)H_benzimidazolone_), 113.4 ($\underline{\text{C}}$(3)H_pyridyl-A_), 107.8 ($\underline{\text{C}}$(5)H_benzimidazolone_), 62.4 (O-$\underline{\text{C}}$H$_2$), 27.5 (N-$\underline{\text{C}}$H$_3$), 15.0 (CH$_2$-$\underline{\text{C}}$H$_3$); *m/z* 347.3 ((M+H)$^+$, 100 %); *m/z* (ES$^+$) 369.1319 (M$^+$+Na, C$_{20}$H$_{18}$N$_4$O$_2$+Na requires 369.1322); ν_{max} (film)/cm^{-1} 3058, 2988, 2932, 1723, 1447, 1400, 739.

1-(5-(2-Ethoxypyridin-3-yl)pyrimidin-2-yl)-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 84
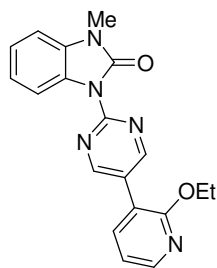
Procedure A: A mixture of **71** (0.458 g, 1.50 mmol), 2-ethoxypyridin-3-yl-3-boronic acid **77** (0.278 g, 1.67 mmol), Pd(PPh$_3$)$_4$ (0.0965 g, 0.08 mmol, 5 mol%), degassed 1,4-dioxane (10 ml) and degassed Na$_2$CO$_3$ (1 M, 3.3 mL) were reacted at 90 ^{o}C for 78 h. Work-up as described for **83** and column chromatography (eluent EtOAc : DCM 10:1 *v/v*) yielded **84**

as a white solid (0.223 g, 43%). mp 197.1-198.5 ^{o}C (decomp.); δ_H (400 MHz, CDCl$_3$) 9.10 (s, 2H, C(3+5)$\underline{\text{H}}$_pyrimidyl_), 8.24 (dd, 1H, *J* 5.2, 2.0, C(6)$\underline{\text{H}}$_pyridyl_), 8.03 (d, 1H, *J* 6.8 C(8)$\underline{\text{H}}$_benzimidazolone_), 7.70 (dd, 1H, *J* 7.5, 2.0, C(4)$\underline{\text{H}}$_pyridyl_), 7.25-7.21 (m, 2H, C(6+7)$\underline{\text{H}}$_benzimidazolone_), 7.06-7.02 (m, 2H, C(5)$\underline{\text{H}}$_benzimidazolone_+C(5)$\underline{\text{H}}$_pyridyl_), 4.48 (q, 2H, *J* 7.2, O-C$\underline{\text{H}}_2$), 3.51 (s, 3H, N-C$\underline{\text{H}}_3$), 1.41 (t, 3H, *J* 7.2, CH$_2$-C$\underline{\text{H}}_3$); δ_C (100 MHz, CDCl$_3$) 161.0 ($\underline{\text{C}}$(2)_pyrimidyl_), 158.4 ($\underline{\text{C}}$(2)O_pyridyl_), 155.5 (2C, $\underline{\text{C}}$(4+6)H_pyrimidyl_), 152.6 ($\underline{\text{C}}$(2)O_benzimidazolone_), 148.0 ($\underline{\text{C}}$(6)H_pyridyl_), 138.4 ($\underline{\text{C}}$(4)H_pyridyl_), 130.7 ($\underline{\text{C}}$(9)_benzimidazolone_), 127.8 ($\underline{\text{C}}$(4)_benzimidazolone_), 127.7 ($\underline{\text{C}}$(3)_pyr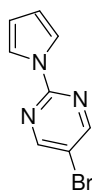idyl_), 123.6 ($\underline{\text{C}}$(7)H_benzimidazolone_), 122.2 ($\underline{\text{C}}$(6)H_benzimidazolone_), 117.6 $\underline{\text{C}}$(5)_pyrimidyl_), 117.5 ($\underline{\text{C}}$(8)H_benzimidazolone_), 113.3 ($\underline{\text{C}}$(5)H_pyridyl_), 107.8 ($\underline{\text{C}}$(5)H_benzimidazolone_), 62.7 (O-$\underline{\text{C}}$H$_2$), 27.5 (N-$\underline{\text{C}}$H$_3$), 14.6 (CH$_2$-$\underline{\text{C}}$H$_3$); *m/z* 348.2 ((M+H)$^+$, 41 %), 370.2 ((M+Na)$^+$, 33 %), 717.1 ((2M+Na)$^+$, 100 %); *Anal.* Calcd. for C$_{19}$H$_{17}$N$_5$O$_2$: C, 65.69; H, 4.93; N, 20.16. Found: C, 65.38; H, 4.88; N, 20.09; ν_{max} (film)/cm^{-1} 3060, 2984, 2928, 1723, 1423, 1385, 747.

Procedure B (one-pot): To a mixture of 1-methyl-2-benzimidazolone **58** (0.163 g, 1.1 mmol), Cs_2CO_3 (0.652 g, 2 mmol), CuI (0.019 g, 0.1 mmol, 10 mol%) in dry degassed DMF (4 mL) was added 5-bromo-2-iodopyrimidine **64** (0.284 g, 1.0 mmol) and 1,10-phenanthroline (0.036 g, 0.2 mmol). The mixture was stirred and heated under argon at 80 °C for 24 h, until TLC monitoring showed the reaction was complete. To this was added, under argon, 2-ethoxypyridin-3-yl-3-boronic acid **77** (0.129 g, 1.1 mmol), $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol, 5 mol%), 1,4-dioxane (5 mL) and Na_2CO_3 (1 M, 2.2 mL) and the mixture reacted at 80 °C for 24 h. The reaction was cooled to room temperatrue, solvent removed *in vacuo* and EtOAc (100 mL) was added to the residue which was washed with brine (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography on silica (eluent DCM : EtOAc 3:1 *v/v*) to yield **84** as a white solid (0.179 g, 52%) spectroscopically identical to the sample prepared by procedure A.

1-(4-(2-Ethoxypyridin-3-yl)phenyl)-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 85
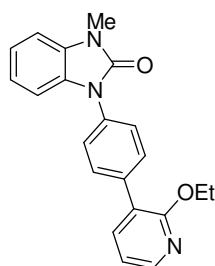
Procedure A: A mixture of **72** (0.294 g, 0.97 mmol), 2-ethoxypyridin-3-yl-3-boronic acid **77** (0.165 g, 1.08 mmol), $Pd(PPh_3)_2Cl_2$ (0.038 g, 0.05 mmol, 5 mol%), 1,4-dioxane (5 mL) and Na_2CO_3 (1 M, 3.2 mL) were reacted at 80 °C for 40 h. Filtration and concentration yielded a white solid which was chromatographed on a silica column (eluent hexane : EtOAc 1:1 *v/v*) to yield **85** as a white solid (0.101 g, 30%). mp 186.6-187.2 °C; δ_H (500 MHz, CDCl$_3$) 8.17 (dd, 1H, *J* 5.0, 2.0, C(6)$\underline{H}_{pyridyl}$), 7.74 (d, 2H, *J* 9, C(5+3)$\underline{H}_{phenyl}$), 7.67 (dd, 1H, *J* 7.5, 2.0, C(4)$\underline{H}_{pyridyl}$), 7.59 (d, 2H, *J* 9.0, C(2+6)$\underline{H}_{phenyl}$), 7.19-7.16 (m, 2H, C(6+8)$\underline{H}_{benzimidazolone}$), 7.11-7.06 (m, 2H, C(5+7)$\underline{H}_{benzimidazolone}$), 6.98 (dd, 1H, *J* 7.0, 5.0, C(5)$\underline{H}_{pyridyl}$), 4.47 (q, 2H, *J* 7.0, O-C$\underline{H}_2$), 3.52 (s, 3H, N-C$\underline{H}_3$), 1.41 (t, 3H, *J* 7.0, CH$_2$-C$\underline{H}_3$); δ_C (125 MHz, CDCl$_3$) 160.9 ($\underline{C}$(2)O$_{pyridyl}$), 153.9 ($\underline{C}$(2)O$_{benzimiazolone}$), 146.3 ($\underline{C}$(6)H$_{pyridyl}$), 139.0 ($\underline{C}$(1)$_{phenyl}$), 136.5 ($\underline{C}$(9)$_{benzimidazolone}$), 134.3 ($\underline{C}$(4)H$_{pyridyl}$), 130.6 ($\underline{C}$(4)$_{benzimidazolone}$), 130.5 (2C, $\underline{C}$(3+5)H$_{phenyl}$), 129.6 ($\underline{C}$(7)H$_{benzimidazolone}$), 125.8 ($\underline{C}$(4)$_{phenyl}$), 124.0 ($\underline{C}$(3)$_{pyridyl}$), 122.4 ($\underline{C}$(6)H$_{benzimidazolone}$), 121.8 ($\underline{C}$(8)H$_{benzimidazolone}$), 117.3 5 (2C, $\underline{C}$(2+6)H$_{phenyl}$), 109.2 ($\underline{C}$(5)H$_{benzimidazolone}$), 109.0 ($\underline{C}$(5)H$_{pyridyl}$), 62.3 (O-$\underline{C}$H$_2$), 27.6 (N-$\underline{C}$H$_3$), 15.0 (CH$_2$-$\underline{C}$H$_3$); *m/z* 346.3 ((M+1)$^+$, 50 %), 368.2 ((M+Na)$^+$, 67 %), 712.9 ((2M+Na)$^+$, 100 %); *m/z* (ES$^+$) 368.13715 (M$^+$+Na, C$_{21}$H$_{19}$N$_3$O+Na requires 368.13695); ν_{max} (film)/cm^{-1} 3056, 2989, 2920, 1723, 1450, 1407, 734.

Procedure B: A mixture of **72** (0.294 g, 0.97 mmol), 2-ethoxypyridin-3-yl-3-boronic acid **77** (0.165 g, 1.08 mmol), Pd(PPh$_3$)$_4$ (0.062 g, 0.05 mmol, 5 mol%), 1,4-dioxane (5 mL) and Na$_2$CO$_3$ (1 M, 3.2 mL) were reacted at 80 ^{o}C for 40 h. Work-up as described above gave **85** as a white solid (0.808 g, 83%) spectroscopically identical to the sample prepared by procedure A.

5-(2-Ethoxypyridin-3-yl)-2-(1H-imidazol-1-yl)pyrimidine 86
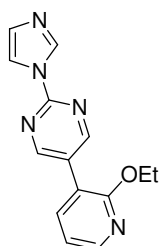
A mixture of **73** (0.132 g, 0.59 mmol), 2-ethoxypyridin-3-yl-3-boronic acid **77** (0.109 g, 0.65 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.023 g, 0.03 mmol, 5 mol%), 1,4-dioxane (4 mL) and Na$_2$CO$_3$ (1 M, 2.0 mL) were reacted at 80 ^{o}C for 22 h. Filtration and concentration yielded a white solid which was recrystallized once from hexane and once from toluene as white crystals of **86** (0.091 g, 48%). mp 155.5-156.6 ^{o}C; δ_H (400 MHz, CDCl$_3$) 8.91 (s, 2H, C(3+5)$\underline{H}$$_{pyrimidyl}$), 8.66 (t, 1H, *J* 1.2, C(2)$\underline{H}$$_{imidazole}$), 8.24 (dd, 1H, *J* 5.2, 1.6, C(4)$\underline{H}$$_{pyridyl}$), 7.93 (t, 1H, *J* 1.6, C(5)$\underline{H}$$_{imidazole}$), 7.67 (dd, 1H, *J* 7.6, 1.6, C(6)$\underline{H}$$_{pyridyl}$), 7.20-7.19 (m, 1H, C(4)$\underline{H}$$_{imidazole}$), 7.04 (dd, 1H, *J* 7.6, 5.2, C(5)$\underline{H}$$_{pyridyl}$), 4.47 (q, 2H, *J* 7.2, O-C$\underline{H}$$_2$), 1.41 (t, 3H, *J* 6.8, CH$_2$-C$\underline{H}$$_3$); δ_C (125 MHz, CDCl$_3$) 160.9 ($\underline{C}(2)_{pyrimidyl}$), 158.6 ($\underline{C}$(2)O$_{pyridyl}$), 153.8 (2C, $\underline{C}$(4+6)H$_{pyrimidyl}$), 148.1 ($\underline{C}$(6)H$_{pyridyl}$), 138.2 ($\underline{C}$(2)H$_{imidazole}$), 136.6 ($\underline{C}$(4)H$_{pyridyl}$), 131.1 ($\underline{C}$(5)$_{pyrimidyl}$), 128.6 ($\underline{C}$(4)H$_{imidazole}$), 117.6 ($\underline{C}$(3)H$_{pyridyl}$), 117.2 ($\underline{C}$(5)H$_{imidazole}$), 116.9 ($\underline{C}$(5)H$_{pyridyl}$), 62.7 (O-$\underline{C}$H$_2$), 14.9 (CH$_2$-$\underline{C}$H$_3$); *m/z* (ES$^+$) 268.11953 (M$^+$+H, C$_{14}$H$_{13}$N$_5$O+H requires 268.11929); ν_{max} (film)/cm^{-1} 3130, 3114, 2974, 1586, 1436, 769.

5-(2-Ethoxypyridin-3-yl)-2-(1H-pyrrol-1-yl)pyrimidine 87

A mixture of **74** (0.132 g, 0.59 mmol), 2-ethoxypyridin-3-yl-3-boronic acid **77** (0.109 g, 0.65 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.023 g, 0.03 mmol, 5 mol%), 1,4-dioxane (4 mL) and Na$_2$CO$_3$ (1 M, 2.0 mL) were reacted at 80 ^{o}C for 22 h. Filtration and concentration yielded a white solid which was chromatographed on a silica column (eluent hexane : EtOAc 4:1 *v/v*) to yield **87** which was recrystallized once from hexane and once from toluene as crystals (0.122 g, 78%). mp 109.7-110.1 ^{o}C; δ_H (400 MHz, CDCl$_3$) 8.85 (s, 2H, C(3+5)$\underline{H}$$_{pyrimidyl}$), 8.21 (dd, 1H, *J* 4.8, 2.0, C(4)$\underline{H}$$_{pyridyl}$), 7.82 (t, 2H, *J* 2.0, C(2+5)$\underline{H}$$_{pyrrole}$), 7.66 (t, 1H, *J* 5.2, 2.8, C(6)$\underline{H}$$_{pyridyl}$), 7.02 (dd, 1H, *J* 5.2, 4.8, C(5)$\underline{H}$$_{pyridyl}$), 6.37 (t, 2H, *J* 2.0, C(3+4)$\underline{H}$$_{pyrrole}$), 4.46 (q, 2H, *J* 7.2, O-C$\underline{H}$$_2$), 1.41 (t, 3H, *J* 6.8, CH$_2$-C$\underline{H}$$_3$); δ_C (125 MHz, CDCl$_3$) 160.9 ($\underline{C}(2)_{pyrimidyl}$), 158.4 ($\underline{C}$(2)O$_{pyridyl}$), 153.6 (2C, $\underline{C}$(4+6)H$_{pyrimidyl}$), 147.6

(<u>C</u>(6)H_{pyridyl}), 138.0 (<u>C</u>(4)H_{pyridyl}), 126.7 (<u>C</u>(3)H_{pyridyl}), 119.4 (2C, <u>C</u>(2+5)H_{pyrrole}), 117.9 (<u>C</u>(5)_{pyrimidyl}), 117.5 (2C, <u>C</u>(2+5)H_{pyrrole}), 112.4 (<u>C</u>(5)H_{pyridyl}), 62.6 (O-<u>C</u>H$_2$), 15.0 (CH$_2$-<u>C</u>H$_3$); *m/z* 266.1 (M$^+$, 100%); *Anal.* Calcd. for C$_{15}$H$_{14}$N$_4$O: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.39; H, 5.33; N, 20.81; v_{max} (film)/cm^{-1} 3100, 1985, 1588, 1479, 1442, 730.

7.3   Experimental Details for Chapter 3

2-Fluoro-5-(4-methoxyphenyl)pyridine 92

In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted (2-fluoro-5-pyridyl)boronic acid **88** (1.18 g, 8.40 mmol), 4-bromoanisole **89** (1.31 g, 7 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.122 g, 0.18 mmol, 2.6 mol%) and Na$_2$CO$_3$ (21 mL, 21 mmol, 1 M in water) in 1,4-dioxane (50 mL) at reflux for 14 h. Standard work-up and concentration gave a brown solid which was purified *via* column chromatography (SiO$_2$, eluent 5: 1 EtOAc: hexane *v/v*) yielding **92** as a white solid (1.39 g, 98%). mp 69.8-70.9 °C; δ_H (400 MHz, CDCl$_3$) 8.35 (1H, d, *J* 1.9, C(6)<u>H</u>_{pyridyl}), 7.91 (1H, dt, *J* 8.1, 2.8 C(4)<u>H</u>_{pyridyl}), 7.45 (2H, d, *J* 8.9, C(2+6)<u>H</u>_{phenyl}), 6.98 (2H, d, *J* 8.9, C(3+5)<u>H</u>_{phenyl}), 6.95 (1H, dd, *J* 8.5, 2.6, C(3)<u>H</u>_{pyridyl}), 3.84 (3H, s, C<u>H</u>$_3$); δ_C (126 MHz, CDCl$_3$) 162.9 (d, *J*$_{CF}$ 238.4, <u>C</u>(6)F_{pyridyl}), 159.9 (<u>C</u>(4)_{phenyl}), 145.5 (d, *J*$_{CF}$ 14.7, <u>C</u>(2)H_{pyridyl}), 139.5 (d, *J*$_{CF}$ 7.8, <u>C</u>(4)H_{pyridyl}), 134.7 (d, *J*$_{CF}$ 4.6, <u>C</u>(3)_{pyridyl}), 129.3 (<u>C</u>(1)_{phenyl}), 128.4 (2C, <u>C</u>(2+6)H_{phenyl}), 114.8 (2C, <u>C</u>(3+5)H_{phenyl}), 109.5 (d, *J*$_{CF}$ 37.5, <u>C</u>(5)H_{pyridyl}), 55.6 (O-<u>C</u>H$_3$); *Anal.* Calcd for C$_{12}$H$_{10}$FNO: C, 70.93; H, 4.96; N, 6.89. Found: C, 70.99; H, 4.94; N, 6.85; *m/z* (EI) 203 (M$^+$, 100%); v_{max} (film)/cm^{-1} 2939, 2833, 1612, 1594, 1518, 1476, 1373, 1246, 1187, 1047, 1013, 1000, 826, 813, 796.

3-(6-Fluoropyridin-3-yl)quinoline 93

In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted (2-fluoro-5-pyridyl)boronic acid **88** (2.03 g, 14.4 mmol), 3-bromoquinoline **90** (2.40 g, 12.0 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.126 g, 0.180 mmol, 1.5 mol%) and Na$_2$CO$_3$ (36 mL, 36 mmol, 1 M in water) in 1,4-dioxane (65 mL) at reflux for 20 h. Standard work-up and concentration yielded an off-white solid which was purified *via* column chromatography (SiO$_2$, eluent 1: 1 EtOAc: hexane *v/v*) yielding **93** as an off-white solid (2.39 g, 89%). mp

265 ^{o}C (decomp.); δ_H (700 MHz, CDCl$_3$) 9.10 (1H, d, *J* 2.1, C(2)$\underline{H}$$_{quinolyl}$), 8.55 (1H, d, *J* 1.9, C(6)$\underline{H}$$_{pyridyl}$), 8.30 (1H, s, C(4)$\underline{H}$$_{quinolyl}$), 8.16 (1H, d, *J* 8.4, C(8)$\underline{H}$$_{quinolyl}$), 8.10 (1H, td, *J* 8.4, 2.8, C(4)$\underline{H}$$_{pyridyl}$), 7.90 (1H, d, *J* 8.1, C(5)$\underline{H}$$_{quinolyl}$), 7.77 (1H, t, *J* 7.7, C(6)$\underline{H}$$_{quinolyl}$), 7.62 (1H, t, *J* 7.5, C(7)$\underline{H}$$_{quinolyl}$), 7.10 (1H, dd, *J* 8.4, 2.6 C(3)$\underline{H}$$_{pyridyl}$); δ_C (175 MHz, CDCl$_3$) 163.8 (d, J_{CF} 241.1, $\underline{C}$(6)F$_{pyridyl}$), 149.1 ($\underline{C}$(2)H$_{quinolyl}$), 147.7 ($\underline{C}$(10)$_{quinolyl}$), 146.5 (d, J_{CF} 15.1, $\underline{C}$(2)H$_{pyridyl}$), 140.2 (d, J_{CF} 8.1, $\underline{C}$(4)F$_{pyridyl}$), 134.0 ($\underline{C}$(4)H$_{quinolyl}$), 132.0 (d, J_{CF} 4.7, $\underline{C}$(3)$_{pyridyl}$), 130.4 ($\underline{C}$(3)$_{quinolyl}$), 129.8 ($\underline{C}$(8)H$_{quinolyl}$), 129.5 ($\underline{C}$(9)H$_{quinolyl}$), 128.2 ($\underline{C}$(5)$_{quinolyl}$), 128.0 ($\underline{C}$(6)H$_{quinolyl}$), 127.8 ($\underline{C}$(7)H$_{quinolyl}$), 110.3 (d, J_{CF} 37.6, $\underline{C}$(5)$_{pyridyl}$); *m/z* (EI) 224 (M$^+$, 100%); *Anal.* Calcd for C$_{14}$H$_9$FN$_2$: C, 74.99; H, 4.05; N, 12.49. Found: C, 74.97; H, 4.13; N; ν_{max} (film)/cm^{-1} 3041, 2921, 2845, 1597, 1583, 1570, 1491, 1394, 1345, 1298, 1255, 1124, 1052, 1023, 954, 913, 825, 788, 741, 668.
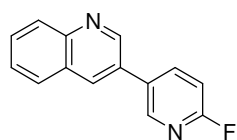
2-(6-Fluoropyridin-3-yl)-6-methoxypyridine 94
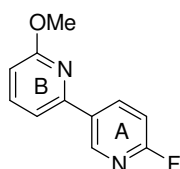
In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted (2-fluoro-5-pyridyl)boronic acid **88** (1.69 g, 12.0 mmol), 2-bromo-6-methoxypyridine **91** (1.88 g, 10 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.176 g, 0.25 mmol, 2.5 mol%) and Na$_2$CO$_3$ (30 mL, 30 mmol, 1 M in water) in 1,4-dioxane (60 mL) at reflux for 14 h although completion by TLC noted after 10 min at reflux. Standard work-up and concentration gave a black residue which was purified *via* column chromatography (SiO$_2$, eluent 5: 1 EtOAc: hexane) yielding **94** as a white solid (1.98 g, 97%). mp 67.2-67.7 ^{o}C; δ_H (700 MHz, CDCl$_3$) 8.83 (1H, d, *J* 1.6, C(6)$\underline{H}$$_{pyridyl-A}$), 8.42 (1H, td, *J* 8.5, 2.5, C(4)$\underline{H}$$_{pyridyl-A}$), 7.64 (1H, dd, *J* 8.2, 7.5, C(4)$\underline{H}$$_{pyridyl-B}$), 7.29 (1H, d, *J* 7.5, C(3)$\underline{H}$$_{pyridyl-B}$), 6.99 (1H, dd, *J* 8.5, 2.9, C(3)$\underline{H}$$_{pyridyl-A}$), 6.73 (1H, d, *J* 8.2, C(5)$\underline{H}$$_{pyridyl-B}$), 4.00 (3H, s, O-C$\underline{H}$$_3$); δ_C (175 MHz, CDCl$_3$) 164.2 ($\underline{C}$(6)O$_{pyridyl-B}$), 164.1 (d, J_{CF} 240.5, $\underline{C}$(6)F$_{pyridyl-A}$), 151.2 ($\underline{C}$(2)$_{pyridyl-B}$), 146.4 (d, J_{CF} 1`5.3, $\underline{C}$(2)H$_{pyridyl-A}$), 139.7 (d, J_{CF} 8.1, $\underline{C}$(4)H$_{pyridyl-A}$), 139.6 ($\underline{C}$(4)H$_{pyridyl-B}$), 133.0 (d, J_{CF} 4.7, $\underline{C}$(3)H$_{pyridyl-A}$), 112.8 ($\underline{C}$(5)H$_{pyridyl-B}$), 110.5 ($\underline{C}$(3)H$_{pyridyl-B}$), 109.5 (d, J_{CF} 37.5, $\underline{C}$(5)H$_{pyridyl-A}$), 53.56; *m/z* (EI) 204 (M$^+$, 68%), 203 (100, M$^+$ - H); *Anal.* Calcd for C$_{11}$H$_9$FN$_2$O: C, 64.70; H, 4.44; N, 13.72. Found: C, 64.82; H, 4.50; N, 13.63; ν_{max} (film)/cm^{-1} 2957, 1607, 1579, 1494, 1463, 1434, 1372, 1329, 1291, 1245, 1165, 1029, 797, 685.

5-(4-Methoxyphenyl)pyridin-2(1*H*)-one 95

To **92** (1.40 g, 6.89 mmol) was sequentially added 1,4-dioxane (26 mL) and KOH (1 M, 40 mL) and the resulting mixture was heated at reflux and judged complete by TLC (SiO$_2$, eluent 2: 1 hexane: EtOAc) after 66 h. The mixture was cooled to room temperature and acidified to pH 6 with 4 M HCl. The precipitate was filtered and washed with hexane (2 x 50 mL), water (2 x 50 mL) and acetone (2 x 20 mL) followed by drying *in vacuo* yielding **95** as a white solid (1.145g, 83%). mp 191 ^{o}C (decomp.); δ_H (400 MHz, CDCl$_3$) 13.04 (1H, s, N$\underline{H}$), 7.72 (1H, dd, *J* 9.4, 2.6, C(4)$\underline{H}$$_{pyridone}$), 7.52 (1H, d, *J* 2.6, C(6)$\underline{H}$$_{pyridone}$), 7.32 (2H, d, *J* 8.7, C(2+6)$\underline{H}$$_{phenyl}$), 6.94 (2H, d, *J* 8.7, C(3+5)$\underline{H}$$_{phenyl}$), 6.66 (1H, d, *J* 9.4, C(3)$\underline{H}$$_{pyridone}$), 3.82 (3H, s, O-C$\underline{H}$$_3$); δ_C (175 MHz, *d$_6$*-DMSO) 161.6 ($\underline{C}$(4)O$_{phenyl}$), 158.3 ($\underline{C}$(2)O$_{pyridone}$), 140.0 ($\underline{C}$(4)H$_{pyridone}$), 131.8 ($\underline{C}(1)_{phenyl}$), 128.6 (2C, $\underline{C}$(2+6)H$_{phenyl}$), 126.4 ($\underline{C}$(5)H$_{pyridone}$), 119.9 ($\underline{C}$(6)H$_{pyridone}$), 117.7($\underline{C}$(3)H$_{pyridone}$), 114.3 (2C, $\underline{C}$(3+5)H$_{phenyl}$), 55.1; *m/z* (APCI$^+$) 202 (M$^+$ + H, 100%), 201 (69, M$^+$); *Anal.* Calcd for C$_{12}$H$_{11}$NO$_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.47; H, 5.89; N, 6.78; ν_{max} (film)/cm^{-1} 2843, 1738, 1657 (C=O), 1622, 1514, 1468, 1283, 1244, 1183, 1037, 1020, 950, 881, 821.

5-(Quinolin-3-yl)pyridin-2(1*H*)-one 96

To **93** (2.24 g, 10 mmol) was sequentially added 1,4-dioxane (26 mL) and KOH (1 M, 50 mL) and the resulting mixture was heated at reflux and the reaction was *J*udged complete by TLC (SiO$_2$, eluent 2: 1 hexane: EtOAc, R$_f$ = 0) after 24 h. The mixture was cooled to room temperature and acidified to pH 6 with 4 M HCl. The precipitate was filtered and washed with hexane (2 x 50 mL), water (2 x 50 mL) and acetone (2 x 20 mL) followed by drying *in vacuo* yielding **96** as an off-white solid (1.95 g, 88%). mp 290 ^{o}C (decomp.); δ_H (700 MHz, *d$_6$*-DMSO) 12.03 (1H, s, N$\underline{H}$), 9.17 (1H, d, *J* 2.3, C(2)$\underline{H}$$_{quinolyl}$), 8.52 (1H, d, *J* 2.2, C(4)$\underline{H}$$_{quinolyl}$), 8.06 – 7.99 (3H, m, C(4+6)$\underline{H}$$_{pyridone}$ + C(8)$\underline{H}$$_{quinolyl}$), 7.97 (1H, d, *J* 7.9, C(5)$\underline{H}$$_{quinolyl}$), 7.73 (1H, t, *J* 7.6, C(6)$\underline{H}$$_{quinolyl}$), 7.62 (1H, t, *J* 7.4, C(7)$\underline{H}$$_{quinolyl}$), 6.52 (1 H, d, *J* 9.5, C(3)$\underline{H}$$_{pyridone}$); δ_C (176 MHz, *d$_6$*-DMSO) 161.7 ($\underline{C}$(2)O$_{pyridone}$), 148.5 ($\underline{C}$(4)H$_{pyridone}$), 146.3 ($\underline{C}(10)_{quinolyl}$), 139.9 ($\underline{C}$(2)H$_{quinolyl}$), 133.8 ($\underline{C}$(4)H$_{pyridone}$), 130.7 ($\underline{C}$(4)H$_{quinolyl}$), 129.1 ($\underline{C}(3)_{quinolyl}$), 129.1 ($\underline{C}$(8)H$_{quinolyl}$), 128.6 ($\underline{C}(5)_{quinolyl}$), 128.0 ($\underline{C}$(6)H$_{pyridone}$), 127.6 ($\underline{C}$(9)H$_{quinolyl}$), 127.0 ($\underline{C}$(6)H$_{quinolyl}$), 120.4 ($\underline{C}(5)_{pyridone}$), 114.8 ($\underline{C}$(3)H$_{pyridone}$); *m/z* (APCI$^+$) 223 (M$^+$+H); *Anal.* Calcd. for C$_{14}$H$_{10}$N$_2$O: C, 75.66; H, 4.54; N, 7.20. Found: C, 75.56; H, 4.53; N, 7.03; ν_{max}

(film)/cm^{-1} 2823, 1659 (C=O), 1618, 1590, 1435, 1316, 1297, 1258, 1122, 952, 866, 832, 784, 752, 672.

5-(6-Methoxypyridin-2-yl)pyridin-2(1*H*)-one 97

To **94** (2.04 g, 10 mmol) was sequentially added 1,4-dioxane (26 mL) and KOH (1 M, 40 mL) and the resulting mixture was heated at reflux and the reaction was *J*udged complete by TLC (SiO$_2$, eluent 2: 1 hexane: EtOAc, R$_f$ = 0) after 24 h. The mixture was cooled to room temperature and acidified to pH 6 with 4 M HCl. The precipitate was filtered and washed with hexane (2 x 50 mL), water (2 x 50 mL) and acetone (2 x 20 mL) followed by drying *in vacuo* yielding **97** as a white solid (1.85 g, 92%). mp 277 ^{o}C (decomp.); δ_H (400 MHz, *d*6-DMSO) 11.92 (1H, s, N$\underline{H}$), 8.17 (1H, dd, *J* 2.7, 9.6, C(4)$\underline{H}_{pyridone}$), 8.15-8.07 (1H, m, C(6)$\underline{H}_{pyridone}$), 7.70 (1H, dd, *J* 8.2, 7.5, C(4)$\underline{H}_{pyridine}$), 7.38 (1H, d, *J* 7.5, C(3)$\underline{H}_{pyridine}$), 6.67 (1H, d, *J* 8.2, C(5)H$_{pyridine}$), 3.96 (3H, s, O-CH_3); δ_C (125 MHz, CDCl$_3$) 165.4 ($\underline{C}$(6)O$_{pyridine}$), 164.0 ($\underline{C}$(2)O$_{pyridone}$), 150.8 ($\underline{C}$(2)$_{pyridine}$), 140.2 ($\underline{C}$(4)H$_{pyridone}$), 139.6 ($\underline{C}$(4)H$_{pyridine}$), 133.8 ($\underline{C}$(6)H$_{pyridone}$), 119.9 ($\underline{C}$(5)$_{pyridone}$), 119.7 ($\underline{C}$(3)H$_{pyridone}$), 110.9 ($\underline{C}$(5)H$_{pyridine}$), 109.5 ($\underline{C}$(3)H$_{pyridine}$), 53.5 (O-$\underline{C}$H$_3$); *m/z* (ES$^+$) 202 (M$^+$+H, 100%), *Anal.* Calcd. for C$_{11}$H$_{10}$N$_2$O$_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.47; H, 5.04; N, 13.66; ν_{max} (film)/cm^{-1} 2842, 1666 (C=O), 1576, 1466, 1433, 1327, 1263, 1123, 1077, 1029, 790, 745, 693.

General proceedure for pyridone C-N cross-coupling

To an argon purged flask was added pyridone, aryl halide, copper source, ligand, additive (where applicable), base and dry degassed solvent. The mixture was heated to 100 ^{o}C under argon and monitored by TLC. Upon completion, the reaction mixture was allowed to cool to room temp. and passed through a silica plug, eluting with EtOAc. The concentrated residue was purified *via* column chromatography.

1-(5-(Trifluoromethyl)pyridin-2-yl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one 99a

In accordance with the general procedure for pyridone C-N cross-coupling, **95** (0.211 g, 1.05 mmol), 2-bromo-6-(trifluoromethyl)pyridine **89** (0.226 g, 1.00 mmol), CuI (0.038 g, 0.200 mmol, 20 mol%), DMCDA (0.057 g, 0.400 mmol) and K$_2$CO$_3$ (0.276 g, 2.00 mmol) in toluene (6 mL) were reacted for 20 h.

Standard work-up and column chromatography (SiO$_2$, eluent 1: 1 EtOAc: hexane *v/v*) yielded **99a** as a white solid (0.276 g, 80%). mp 101.1-102.7 ^{o}C; δ_H (500 MHz, CDCl$_3$) 8.40 (1H, d, *J* 3.0, C(6)$\underline{H}$$_{pyridyl}$), 8.01 (1H, d, *J* 8.9, C(4)$\underline{H}$$_{pyridyl}$), 7.97 (1H, dd, *J* 2.7, C(6)$\underline{H}$$_{pyridone}$), 7.66 (1H, dd, *J* 9.5, 2.7, C(4)$\underline{H}$$_{pyridone}$), 7.56 (1H, dd, *J* 8.9, 3.0, C(3)$\underline{H}$$_{pyridyl}$), 7.38 (2H, d, *J* 8.9, C(2+6)$\underline{H}$$_{phenyl}$), 6.94 (2H, d, *J* 8.9, C(2+5)$\underline{H}$$_{phenyl}$), 6.71 (1H, d, *J* 9.5, C(3)$\underline{H}$$_{pyridone}$), 6.72 (1H, dd, *J* 9.5, 0.7), 3.83 (4H, s, O-C$\underline{H}$$_3$); δ_C (175 MHz, CDCl$_3$) 161.6 ($\underline{C}$(2)O$_{pyridone}$), 159.6 ($\underline{C}$(4)O$_{phenyl}$), 154.5 ($\underline{C}$(4)H$_{pyridone}$), 146.1 (q, *J* 4.1, $\underline{C}$(6)H$_{pyridyl}$), 141.0 ($\underline{C}$(2)$_{pyridyl}$), 135.3 (q, *J* 3.2 $\underline{C}$(4)H$_{pyridyl}$), 131.2 (2C, $\underline{C}$(2+6)H$_{phenyl}$), 128.8 ($\underline{C}$(1)$_{phenyl}$), 127.3 ($\underline{C}$(5)$_{pyridone}$), 126.0 (q, *J* 33.6, $\underline{C}$(5)$_{pyridyl}$), 123.4 (q, *J* 272.4, $\underline{C}$F$_3$), 122.4 ($\underline{C}$(3)H$_{pyridone}$), 121.4 (2C, $\underline{C}$(3+5)H$_{phenyl}$), 120.9 ($\underline{C}$(6)H$_{pyridone}$), 114.7 ($\underline{C}$(4)H$_{pyridyl}$), 55.6 (O-$\underline{C}$H$_3$); *m/z* (APCI$^+$) 347.1006 (M$^+$+H, C$_{18}$H$_{13}$F$_3$N$_2$O$_2$ requires 347.1007); ν_{max} (film)/cm^{-1} 3056, 2801, 1659 (C=O), 1600, 1587, 1269, 1248, 1297, 1156, 1001, 809.
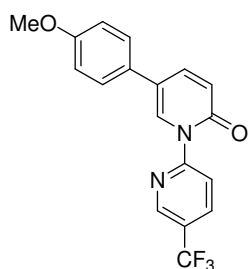
1,5-Bis(4-methoxyphenyl)pyridin-2(1*H*)-one 100
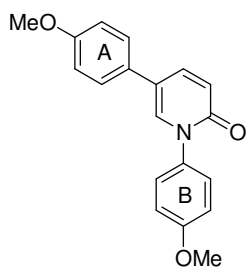
In accordance with the general procedure for pyridone C-N cross-coupling, **95** (0.211 g, 1.05 mmol), 4-bromoanisole **89** (0.187 g, 1.00 mmol), CuI (0.019 g, 0.100 mmol, 10 mol%), DMCDA (0.029 g, 0.200 mmol) and K$_2$CO$_3$ (0.276 g, 2.00 mmol) in toluene (3 mL) were reacted for 20 h. Standard work-up and column chromatography (SiO$_2$, eluent EtOAc) yielded **100** as a white solid which was recrystallised from hexane/DCM (0.251g, 82%). mp 147.0-148.2 ^{o}C; δ_H (400 MHz, CDCl$_3$) 7.64 (1H, dd, *J* 9.5, 2.7, C(4)$\underline{H}$$_{pyridone}$), 7.46 (1H, d, *J* 2.7, C(6)$\underline{H}$$_{pyridone}$), 7.33 (2H, d, *J* 8.9, C(2+6)$\underline{H}$$_{phenyl-B}$), 7.32 (2H, d, *J* 8.7, C(2+6)$\underline{H}$$_{phenyl-A}$), 6.99 (2H, d, *J* 8.9, C(3+5)$\underline{H}$$_{phenyl-B}$), 6.92 (2H, d, *J* 8.7, C(3+5)$\underline{H}$$_{phenyl-A}$), 6.71 (1H, d, *J* 9.5, C(3)$\underline{H}$$_{pyridone}$), 3.83 (3H, s, O-C$\underline{H}$$_{3\ phenyl-B}$), 3.81 (3H, s, O-C$\underline{H}$$_{3\ phenyl-A}$); δ_C (176 MHz, CDCl$_3$) 162.1 ($\underline{C}$(2)O$_{pyridone}$), 159.7 ($\underline{C}$(4)O$_{phenyl-A}$), 159.4 ($\underline{C}$(4)O$_{phenyl-B}$), 139.9 ($\underline{C}$(4)H$_{pyridone}$), 135.0 ($\underline{C}$(3)H$_{pyridone}$), 134.2 ($\underline{C}(1)_{phenyl-B}$), 129.0 (2C, $\underline{C}$(2+6)H$_{phenyl-B}$), 127.9 (2C, $\underline{C}$(2+6)H$_{phenyl-A}$), 127.2 ($\underline{C}$(1)$_{phenyl-A}$), 121.8 ($\underline{C}$(3)H$_{pyridone}$), 120.0 ($\underline{C}$(5)$_{pyridone}$), 114.8 (2C, $\underline{C}$(3+5)H$_{phenyl-B}$), 114.7 (2C, $\underline{C}$(3+5)H$_{phenyl-A}$), 55.8 (O-$\underline{C}$H$_{3\ phenyl-A}$), 55.6 (O-$\underline{C}$H$_{3\ phenyl-B}$); *m/z* (EI) 307 (M$^+$, 100%); *Anal.* Calcd. for C$_{19}$H$_{17}$NO$_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.34; H, 5.60; N, 4.49; ν_{max} (film)/cm^{-1} 3058, 2834, 1662 (C=O), 1610, 1598, 1514, 1275, 1249, 1180, 1026, 818.

1-(5-Fluoropyridin-2-yl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one 101

In accordance with the general procedure for pyridone C-N cross-coupling, **95** (0.423 g, 2.10 mmol), 2-bromo-5-fluoropyridine **110** (0.352 g, 2.00 mmol), CuI (0.038 g, 0.200 mmol, 10 mol%), DMCDA (0.057 g, 0.400 mmol) and K_2CO_3 (0.553 g, 4.00 mmol) in toluene (6 mL) were reacted for 20 h.   Standard work-up and column chromatography (SiO_2, eluent EtOAc) yielded **101** as a white solid (0.533, 77%). mp 140.9-142.2 $^{\circ}$C; δ_H (500 MHz, CDCl$_3$) 8.40 (1H, ddd, *J* 2.6, 1.2, 0.9, C(6)$\underline{H}_{pyridine}$), 8.01 (1H, ddd, *J* 8.9, 7.9, 4.0, C(4)$\underline{H}_{pyridyl}$), 7.98 (1H, dd, *J* 2.7, 0.6, C(6)$\underline{H}_{pyridone}$), 7.66 (1H, dd, *J* 9.5, 2.7, C(4)$\underline{H}_{pyridone}$), 7.56 (1H, ddd, *J* 8.9, 7.5, 3.0, C(3)$\underline{H}_{pyridyl}$), 7.38 (2H, d, *J* 8.9, C(2+6)$\underline{H}_{phenyl}$), 6.94 (2H, d, *J* 8.8, C(3+5)$\underline{H}_{phenyl}$), 6.71 (1H, dd, *J* 9.5, 0.6 C(3)$\underline{H}_{pyridone}$), 3.82 (3H, s, O-C$\underline{H}_3$); δ_C (125 MHz, CDCl$_3$) 161.6 ($\underline{C}$(2)O$_{pyridone}$), 159.4 ($\underline{C}$(4)O$_{phenyl}$), 158.8 (d, J_{CF} 257.1, $\underline{C}$(5)F$_{pyridyl}$), 148.0 (d, J_{CF} 2.9, $\underline{C}$(2)$_{pyridyl}$), 140.8 ($\underline{C}$(4)H$_{pyridone}$), 136.9 (d, J_{CF} 25.8, $\underline{C}$(6)H$_{pyridyl}$), 132.6 ($\underline{C}$(1)$_{phenyl}$), 129.0 ($\underline{C}$(5)$_{pyridone}$), 127.3 (2C, $\underline{C}$(2+6)H$_{phenyl}$), 125.0 (d, J_{CF} 19.8, $\underline{C}$(4)H$_{pyridyl}$), 122.9 (d, J_{CF} 5.0, $\underline{C}$(3)H$_{pyridyl}$), 122.2 ($\underline{C}$(3)H$_{pyridone}$), 120.7 ($\underline{C}$(6)H$_{pyridone}$), 114.7 (2C, $\underline{C}$(3+5)H$_{phenyl}$), 55.6 (O-$\underline{C}$H$_3$); *m/z* (EI) 296 (M$^+$, 100%); *Anal.* Calcd. for C$_{17}$H$_{13}$FN$_2$O$_2$: C, 68.91; H, 4.42; N, 9.45. Found: C, 69.07; H, 4.39; N, 9.21; ν_{max} (film)/cm^{-1} 3076, 2940, 2834, 1674 (C=O), 1619, 1514, 1473, 1394, 1286, 1248, 1184, 1024, 819.

5-(4-Methoxyphenyl)-1-(5-nitropyridin-2-yl)pyridin-2(1*H*)-one 102

In accordance with the general procedure for pyridone C-N cross-coupling, **95** (0.211 g, 1.05 mmol), 2-bromo-5-nitropyridine **111** (0.203 g, 1.00 mmol), CuI (0.019 g, 0.100 mmol, 10 mol%), DMCDA (0.028 g, 0.200 mmol) and K_2CO_3 (0.276 g, 2.00 mmol) in toluene (2 mL) were reacted for 20 h. Standard work-up yielded **102** as a yellow solid which was purified by an EtOAc slurry and filtration (0.268, 83%). mp 184.9-185.5 $^{\circ}$C; δ_H (400 MHz, CDCl$_3$) 9.38 (1 H, dd, *J* 2.7, 0.6, C(6)$\underline{H}_{pyridine}$), 8.60 (1H, dd, *J* 9.0, 2.7, C(4)$\underline{H}_{pyridine}$), 8.44 (1H, dd, *J* 9.0, 0.6, C(3)$\underline{H}_{pyridine}$), 8.22 (1H, dd, *J* 2.6, 0.6, C(6)$\underline{H}_{pyridone}$), 7.68 (1H, dd, *J* 9.5, 2.6, C(4)$\underline{H}_{pyridone}$), 7.40 (2 H, d, *J* 8.9), 6.96 (2H, d, *J* 8.9), 6.73 (1H, dd, *J* 9.5, 0.6, C(3)$\underline{H}_{pyridone}$), 3.84 (3H, d, *J* 3.7, O-C$\underline{H}_3$); δ_C (125 MHz, CDCl$_3$) 161.6 ($\underline{C}$(2)O$_{pyridone}$), 159.7 ($\underline{C}$(4)O$_{phenyl}$), 155.6 ($\underline{C}$(2)N$_{pyridyl}$), 149.1 ($\underline{C}$(4)H$_{pyridone}$), 144.7 ($\underline{C}$(6)H$_{pyridyl}$), 141.3 ($\underline{C}$(4)H$_{pyridyl}$), 133.3 ($\underline{C}$(5)N$_{pyridyl}$), 131.1 (2C, $\underline{C}$(2+6)H$_{phenyl}$), 128.6 ($\underline{C}$(1)$_{phenyl}$), 127.4 ($\underline{C}$(5)$_{pyridone}$), 122.6 ($\underline{C}$(3)H$_{pyridone}$), 121.4 (2C,

$\underline{C}$(3+5)H$_{phenyl}$), 121.3 ($\underline{C}$(6)H$_{pyridone}$), 114.8 ($\underline{C}$(3)H$_{pyridyl}$), 55.6 (O-$\underline{C}$H$_3$); *m/z* (APCI$^+$) 323 (M$^+$, 100%); *Anal.* Calcd. for C$_{17}$H$_{13}$N$_3$O$_4$: C, 68.16; H, 4.05; N, 13.00. Found: C, 68.06; H, 4.19; N, 12.70; ν_{max} (film)/cm^{-1} 3073, 2839, 1680 (C=O), 1610, 1576, 1513, 1464, 1393, 1348, 1298, 1248, 1230, 1191, 1142, 1119, 1038, 1019, 858, 814, 770.

1-(4-Methoxyphenyl)-5-(quinolin-3-yl)pyridin-2(1*H*)-one 103

In accordance with the general procedure for pyridone C-N cross-coupling, **96** (0.355 g, 1.60 mmol), 4-bromoanisole **89** (0.285 g, 1.52 mmol), CuI (0.058 g, 0.304 mmol, 20 mol%), DMCDA (0.087 g, 0.609 mmol) and K$_2$CO$_3$ (0.421 g, 3.04 mmol) in toluene (4.5 mL) were reacted for 72 h. Standard work-up and column chromatography (SiO$_2$, eluent 1: 1 hexane: EtOAc *v/v*) yielded **103** as a yellow solid which was purified by an EtOAc slurry and filtration (0.328 g, 66%). mp 179.8-181.2 ^{o}C; δ_H (500 MHz, CDCl$_3$) 9.05 (1H, d, *J* 2.3, C(2)$\underline{H}$$_{quinolyl}$), 8.19 (1H, dd, *J* 2.3, 0.9, C(4)$\underline{H}$$_{quinolyl}$), 8.15 (1H, d, *J* 8.1, C(9)$\underline{H}$$_{quinolyl}$), 7.87 (1H, d, *J* 7.8, C(6)$\underline{H}$$_{quinolyl}$), 7.83 (1H, dd, *J* 9.5, 2.8, C(4)$\underline{H}$$_{pyridone}$), 7.79 – 7.72 (2H, m, , C(6)$\underline{H}$$_{pyridone}$ + C(8)$\underline{H}$$_{quinolyl}$), 7.61 (1H, ddd, *J* 7.8, 7.0, 0.9, C(7)$\underline{H}$$_{quinolyl}$), 7.41 (2H, d, *J* 9.0, C(2+6)$\underline{H}$$_{phenyl}$), 7.06 (2H, d, *J* 9.0, C(3+5)$\underline{H}$$_{phenyl}$), 6.86 (1H, dd, *J* 9.5, 0.6, C(3)$\underline{H}$$_{pyridone}$), 3.89 (3H, s); δ_C (125 MHz, CDCl$_3$) 162.1 ($\underline{C}$(2)O$_{pyridone}$), 159.9 ($\underline{C}$(4)O$_{phenyl}$), 148.6 ($\underline{C}$(4)H$_{pyridone}$), 147.5 ($\underline{C}$(10)$_{quinolyl}$), 146.4 ($\underline{C}$(2)H$_{quinolyl}$), 141.1 ($\underline{C}$(4)H$_{quinolyl}$), 139.5 ($\underline{C}$(6)H$_{pyridone}$), 136.5 ($\underline{C}$(8)H$_{quinolyl}$), 133.8 ($\underline{C}$(3)$_{quinolyl}$), 132.0 ($\underline{C}$(9)H$_{quinolyl}$), 129.8 ($\underline{C}$(5)$_{quinolyl}$), 129.5 ($\underline{C}$(6)H$_{quinolyl}$), 128.0 ($\underline{C}$(1)$_{phenyl}$), 127.9 (2C, $\underline{C}$(2+6)H$_{phenyl}$), 127.6 ($\underline{C}$(7)H$_{quinolyl}$), 122.6 ($\underline{C}$(5)H$_{pyridone}$), 117.0 ($\underline{C}$(3)H$_{pyridone}$), 115.0 (2C, $\underline{C}$(3+5)H$_{phenyl}$), 55.8 (O-$\underline{C}$H$_3$); *m/z* (EI) 328 (M$^+$, 100%); *Anal.* Calcd. for C$_{21}$H$_{16}$N$_2$O$_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 77.08; H, 4.99; N, 8.32; ν_{max} (film)/cm^{-1} 3061, 2830, 1650 (C=O), 1613, 1587, 1510, 1282, 1247, 1175, 1020, 809.

1-(5-(Trifluoromethyl)pyridin-2-yl)-5-(quinolin-3-yl)pyridin-2(1*H*)-one 104a and
3-(6-(5-(Trifluoromethyl)pyridin-2-yloxy)pyridin-3-yl)quinoline 104b

In accordance with the general procedure for pyridone C-N cross-coupling, **96** (0.233 g, 1.05 mmol), 2-bromo-5-(trifluoromethyl)pyridine **89** (0.226 g, 1.00 mmol), CuI (0.038 g, 0.200 mmol, 20 mol%), DMCDA (0.057 g, 0.400 mmol) and K$_2$CO$_3$ (0.276 g, 2.00 mmol) in toluene (3 mL) were reacted for 48 h. Standard work-up and column chromatography

(SiO$_2$, eluent 4: 1 EtOAc: hexane *v/v*) yielded **104a** as a white solid (0.264g, 72%) followed by **104b** as a white solid (0.017 g, 5%).
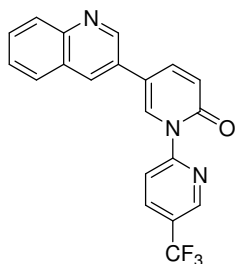
104a mp.156.0-157.8 ^{o}C; δ$_H$ (700 MHz, CDCl$_3$) 9.04 (1H, d, *J* 2.3, C(2)$\underline{H}$$_{quinolyl}$), 8.37 (1H, d, *J* 2.6, C(6)$\underline{H}$$_{pyridyl}$), 8.28 (1H, d, *J* 8.6, C(9)$\underline{H}$$_{quinolyl}$), 8.19 (1H, d, *J* 2.3, C(4)$\underline{H}$$_{quinolyl}$), 8.13 – 8.04 (2H, m, C(4)$\underline{H}$$_{pyridyl}$ + C(6)$\underline{H}$$_{pyridone}$), 7.83 (1H, d, *J* 8.1, C(6)$\underline{H}$$_{quinolyl}$), 7.79 (1H, dd, *J* 9.5, 2.7, C(4)$\underline{H}$$_{pyridone}$), 7.71 (1H, ddd, *J* 8.3, 6.9, 1.3, C(8)$\underline{H}$$_{quinolyl}$), 7.61 – 7.54 (2H, m, C(3)$\underline{H}$$_{pyridyl}$ + C(7)$\underline{H}$$_{quinolyl}$), 6.81 (1H, d, *J* 9.5, C(3)$\underline{H}$$_{pyridone}$); δ$_C$ (175 MHz, CDCl$_3$) 161.4 ($\underline{C}$(2)O$_{pyridone}$), 154.1 ($\underline{C}$(10)$_{quinolyl}$), 148.5 ($\underline{C}$(2)H$_{quinolyl}$), 147.6 ($\underline{C}$(4)H$_{pyridone}$), 146.2 (q, *J*$_{CF}$ 4.1, ($\underline{C}$(4)H$_{pyridyl}$), 140.3 ($\underline{C}$(4)H$_{quinolyl}$), 135.5 (q, *J*$_{CF}$ 3.2, ($\underline{C}$(6)H$_{pyridyl}$), 133.3 ($\underline{C}$(2)$_{pyridyl}$), 132.3($\underline{C}$(5)$_{pyridone}$), 129.9 ($\underline{C}$(8)H$_{quinolyl}$), 129.5 ($\underline{C}$(3)$_{quinolyl}$), 129.2 ($\underline{C}$(9)H$_{quinolyl}$), 127.98 ($\underline{C}$(5)H$_{quinolyl}$), 127.95 ($\underline{C}$(6)H$_{quinolyl}$), 127.6 ($\underline{C}$(7)H$_{quinolyl}$), 126.4 (q, *J*$_{CF}$ 33.6, ($\underline{C}$(5) $_{pyridyl}$), 123.3 (q, *J*$_{CF}$ 272.4, ($\underline{C}$F$_3$), 123.2 ($\underline{C}$(6)H$_{pyridone}$), 121.3 ($\underline{C}$(3)H$_{pyridone}$), 118.0 ($\underline{C}$(3)H$_{pyridyl}$; *m/z* (APCI$^+$) 367 (M$^+$, 100%); *Anal.* Calcd. for C$_{20}$H$_{12}$F$_3$N$_3$O: C, 65.40; H, 3.29; N, 11.44. Found: C, 65.73; H, 3.50; N, 11.42; ν$_{max}$ (film)/cm^{-1} 3023, 2836, 1628 (C=O), 1555, 1304, 1281, 1257, 1220, 1183, 1002.
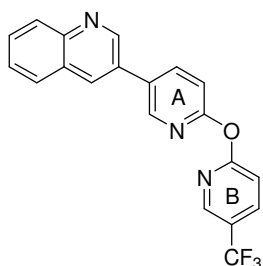
104b mp 127.8-128.3 ^{o}C; δ$_H$ (700 MHz, CDCl$_3$) 9.13 (1H, d, *J* 2.2, C(2)$\underline{H}$$_{quinolyl}$), 8.65 (1H, d, *J* 2.2, C(4)$\underline{H}$$_{quinolyl}$), 8.54 (1H, d, *J* 2.2, C(6)$\underline{H}$$_{pyridyl-B}$), 8.30 (1H, d, *J* 2.6, C(6)$\underline{H}$$_{pyridyl-A}$), 8.14 (1H, d, *J* 8.7, C(9)$\underline{H}$$_{quinolyl}$), 8.13 (1H, dd, *J* 8.1, 2.6, C(4)$\underline{H}$$_{pyridyl-A}$), 8.00 (1H, dd, *J* 8.6, 2.2, C(4)$\underline{H}$$_{pyridyl-B}$), 7.89 (1H, d, *J* 8.1, C(3)$\underline{H}$$_{pyridyl-A}$), 7.75 (1H, t, *J* 7.5, C(8)$\underline{H}$$_{quinolyl}$), 7.60 (1H, t, *J* 7.5, C(7)$\underline{H}$$_{quinolyl}$), 7.28 (1H, d, *J* 8.4, C(6)$\underline{H}$$_{quinolyl}$), 7.23 (1H, d, *J* 8.6, C(3)$\underline{H}$$_{pyridyl-B}$); δ$_C$ (175 MHz, CDCl$_3$) 164.4 ($\underline{C}$(2)O$_{pyridyl-A}$), 161.0 ($\underline{C}$(2)O$_{pyridyl-B}$), 149.33 ($\underline{C}$(2)H$_{quinolyl}$), 147.9 ($\underline{C}$(10) $_{quinolyl}$), 147.0 ($\underline{C}$(6)H$_{pyridyl-A}$), 145.9 (q, *J*$_{CF}$ 4.3, $\underline{C}$(4)H$_{pyridyl-B}$), 138.9 ($\underline{C}$(4)H$_{quinolyl}$), 137.3 (q, *J*$_{CF}$ 3.2, $\underline{C}$(6)H$_{pyridyl-B}$), 133.7 ($\underline{C}$(4)H$_{pyridyl-A}$), 131.4 ($\underline{C}$(3)$_{quinolyl}$), 130.2 ($\underline{C}$(5)$_{pyridyl-A}$), 130.1 ($\underline{C}$(8)H$_{quinolyl}$), 129.6 ($\underline{C}$(9)H$_{quinolyl}$), 128.2 ($\underline{C}$(5)$_{quinolyl}$), 128.0 ($\underline{C}$(6)H$_{quinolyl}$), 127.6 ($\underline{C}$(7)H$_{quinolyl}$), 123.7 (q, *J*$_{CF}$ 271.7, $\underline{C}$F$_3$), 123.3 (q, *J*$_{CF}$ 33.4, $\underline{C}$(5)$_{pyridyl-B}$), 115.2 ($\underline{C}$(3)H$_{pyridyl-A}$), 113.7 ($\underline{C}$(3)H$_{pyridyl-B}$); *Anal.* Calcd. for C$_{20}$H$_{12}$F$_3$N$_3$O: C, 65.40; H, 3.29; N, 11.44. Found: C, 65.48; H, 3.20; N, 11.09; ν$_{max}$ (film)/cm^{-1} 3033, 2858, 1609, 1583, 1299, 1280, 1235, 1177, 1016.

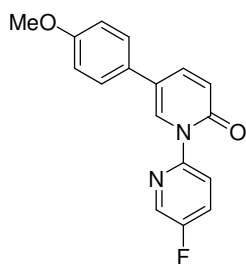**1-(6-Methoxypyridin-2-yl)-5-(quinolin-3-yl)pyridin-2(1*H*)-one 105**
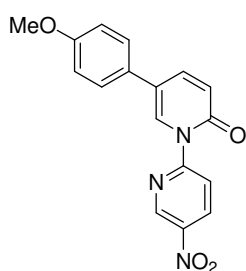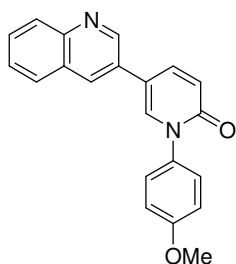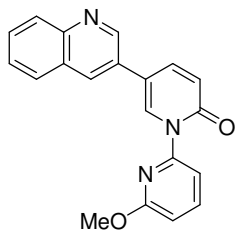
In accordance with the general procedure for pyridone C-N cross-coupling, **96** (0.233 g, 1.05 mmol), 2-bromo-6-methoxypyridine **91** (0.188 g, 1.00 mmol), CuI (0.038 g, 0.200 mmol, 20 mol%), DMCDA (0.057 g, 0.400 mmol) and K_2CO_3 (0.276 g, 2.00 mmol) in toluene (6 mL) were reacted for 20 h. Standard work-up and column chromatography (SiO_2, eluent EtOAc) yielded **105** as a white solid (0.230 g, 70%). mp 187 ^{o}C (decomp.); δ_H (700 MHz, $CDCl_3$) 9.07 (1H, d, *J* 2.3, C(2)$\underline{H}_{quinolyl}$), 8.28 (1H, d, *J* 2.6, C(6)$\underline{H}_{pyridone}$), 8.19 (1H d, *J* 2.3, C(4)$\underline{H}_{quinolyl}$), 8.11 (1H, d, *J* 8.5, C(9)$\underline{H}_{quinolyl}$), 7.84 (1H, d, *J* 8.0, C(6)$\underline{H}_{quinolyl}$), 7.77 (1H, dd, *J* 9.5, 2.7, C(4)$\underline{H}_{pyridone}$), 7.76 – 7.73 (1H, m, C(8)$\underline{H}_{quinolyl}$), 7.71 (1H, ddd, *J* 8.3, 6.9, 1.4, C(7)$\underline{H}_{quinolyl}$), 7.62 – 7.53 (2H, m, C(4)$\underline{H}_{pyridyl}$ + C(3)$\underline{H}_{pyridone}$), 6.85 – 6.76 (2H, m, C(3)$\underline{H}_{pyridyl}$ + C(5)$\underline{H}_{pyridyl}$), 3.94 (3H, s, O-C$\underline{H}_3$); δ_C (175 MHz, $CDCl_3$) 164.1 ($\underline{C}$(6)$O_{pyridyl}$), 161.6 ($\underline{C}$(2)$O_{pyridone}$), 148.9 ($\underline{C}$(10)$H_{quinolyl}$), 148.7 ($\underline{C}$(4)$H_{pyridone}$), 147.5 ($\underline{C}$(2)$_{pyridyl}$), 140.5 ($\underline{C}$(4)$H_{pyridyl}$), 139.5 ($\underline{C}$(2)$H_{quinolyl}$), 134.2 ($\underline{C}$(4)$H_{quinolyl}$), 132.1 ($\underline{C}$(3)$_{quinolyl}$), 129.8 ($\underline{C}$(8)$H_{quinolyl}$), 129.7 ($\underline{C}$(5)$_{quinolyl}$), 129.6 ($\underline{C}$(6)$H_{quinolyl}$), 128.1 ($\underline{C}$(9)$H_{quinolyl}$), 128.0 ($\underline{C}$(7)$H_{quinolyl}$), 127.6 ($\underline{C}$(5)$_{pyridone}$), 123.1 ($\underline{C}$(6)$H_{pyridone}$), 117.1 ($\underline{C}$(3)$H_{pyridone}$), 113.7 ($\underline{C}$(5)$H_{pyridyl}$), 110.6 ($\underline{C}$(3)$H_{pyridyl}$), 54.0 (O-$\underline{C}H_3$); *m/z* (APCI$^+$) 330.1252 (M$^+$+H, $C_{20}H_{16}N_3O_2$ requires 330.1243); ν_{max} (film)/cm^{-1} 2983, 2892, 1680 (C=O), 1620, 1574, 1470, 1434, 1414, 1321, 1286, 1249, 1215, 1148, 1073, 918, 821, 739.

1-(4-Methoxyphenyl)-5-(6-methoxypyridin-2-yl)pyridin-2(1*H*)-one 106
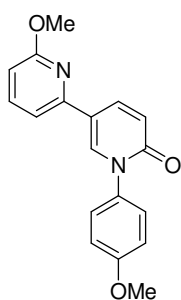
In accordance with the general procedure for pyridone C-N cross-coupling, **97** (0.302 g, 1.49 mmol), 4-bromoanisole **89** (0.266 g, 1.42 mmol), CuI (0.054 g, 0.285 mmol, 20 mol%), DMCDA (0.081 g, 0.569 mmol) and K_2CO_3 (0.393 g, 2.85 mmol) in toluene (4.5 mL) were reacted for 72 h. Standard work-up and column chromatography (SiO_2, eluent EtOAc) yielded **106** as a white solid (0.326 g, 74%). mp 62.9-64.0 ^{o}C; δ_H (500 MHz, $CDCl_3$) 8.13 (1H, d, *J* 2.5, C(6)$\underline{H}_{pyridone}$), 8.02 (1H, dd, *J* 9.6, 2.6, C(4)$\underline{H}_{pyridone}$), 7.57 (1H, dd, *J* 8.1, 7.6, C(4)$\underline{H}_{pyridyl}$), 7.34 (2H, d, *J* 8.9, C(2+6)$\underline{H}_{phenyl}$), 7.07 (1H, d, *J* 7.4, C(5)$\underline{H}_{pyridyl}$), 7.00 (2H, d, *J* 8.9, C(3+5)$\underline{H}_{phenyl}$), 6.71 (1H, d, *J* 9.6 C(3)$\underline{H}_{pyridone}$), 6.62 (1H, d, *J* 8.2, C(3)$\underline{H}_{pyridyl}$), 3.92 (3H, s, O-C$\underline{H}_{3\ pyridyl}$), 3.84 (3H, s, O-C$\underline{H}_{3\ phenyl}$); δ_C (126 MHz, $CDCl_3$) 164.0 ($\underline{C}$(6)$O_{pyridyl}$), 162.7 ($\underline{C}$(2)$O_{pyridone}$), 159.8 ($\underline{C}$(6)O_{phenyl}), 151.0 ($\underline{C}$(2)$_{pyridyl}$), 139.7 ($\underline{C}$(4)$H_{pyridone}$), 138.5 ($\underline{C}$(4)$H_{pyridyl}$), 137.5 ($\underline{C}$(6)$H_{pyridone}$), 134.1 ($\underline{C}$(1)N_{phenyl}), 127.9

(2C, $\underline{C}$(2+6)H$_{phenyl}$), 121.3 ($\underline{C}$(5)$_{pyridone}$), 118.5 ($\underline{C}$(3)H$_{pyridone}$), 114.9 (2C, $\underline{C}$(3+5)H$_{phenyl}$), 111.1 $\underline{C}$(5)H$_{pyridyl}$, 109.2 ($\underline{C}$(3)H$_{pyridyl}$), 55.8 (O-$\underline{C}$H$_3$ $_{pyridyl}$), 53.5 (O-$\underline{C}$H$_3$ $_{phenyl}$); *m/z* (EI) 308 (M$^+$, 100%); *Anal.* Calcd. for C$_{18}$H$_{16}$N$_2$O$_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.27; H, 5.39; N, 9.34; ν_{max} (film)/cm^{-1} 3010, 2949, 1736, 1664 (C=O), 1588, 1575, 1506, 1409, 1314, 1244, 1124, 1023, 901, 830, 799.

1-(5-Bromopyrimidin-2-yl)-5-(6-methoxypyridin-2-yl)pyridin-2(1*H*)-one 107
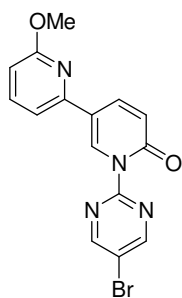
In accordance with the general procedure for pyridone C-N cross-coupling, **97** (0.202 g, 1.000 mmol), 5-bromo-2-iodopyrimidine **112** (0.313 g, 1.10 mmol), CuI (0.042 g, 0.220 mmol, 20 mol%), DMCDA (0.063 g, 0.440 mmol) and K$_2$CO$_3$ (0.304 g, 2.22 mmol) in toluene (4 mL) were reacted for 28 h. Standard work-up and column chromatography (SiO$_2$, eluent 1: 1 hexane: EtOAc) yielded **107** as an off-white solid (0.203 g, 51%). mp 172.3-173.9 ^{o}C; δ_H (400 MHz, CDCl$_3$) 9.06 (2H, s, C(4+6)$\underline{H}$$_{pyrimidyl}$), 8.38 (1H, d, *J* 2.6, C(6)$\underline{H}$$_{pyridone}$), 8.06 (1H, ddd, *J* 9.7, 2.6, 1.7, C(4)$\underline{H}$$_{pyridone}$), 7.58 (1H, td, *J* 7.4, 3.7 C(4)$\underline{H}$$_{pyridyl}$), 7.10 (1H, ddd, *J* 7.4, 1.0, 0.6, C(5)$\underline{H}$$_{pyridyl}$), 6.73 (1H, ddd, *J* 9.7, 1.7, 0.7, C(3)$\underline{H}$$_{pyridyl}$), 6.64 (1H, dt, *J* 8.2, 0.7, C(3)$\underline{H}$$_{pyridone}$), 3.94 (3H, s, O-C$\underline{H}$$_3$); δ_C (126 MHz, CDCl$_3$) 164.8 ($\underline{C}$(2)N$_{pyrimidyl}$), 164.0 ($\underline{C}$(6)O$_{pyridyl}$), 161.6 ($\underline{C}$(2)O$_{pyridone}$), 161.6 (2 C, $\underline{C}$(4+6)H$_{pyrimidyl}$), 160.0 ($\underline{C}$(6)$_{pyridyl}$), 150.5 ($\underline{C}$(4)H$_{pyridone}$), 139.6 ($\underline{C}$(4)H$_{pyridyl}$), 139.2 ($\underline{C}$(5)$_{pyridone}$), 134.4 ($\underline{C}$(6)H$_{pyridone}$), 122.3 ($\underline{C}$(3)H$_{pyridone}$), 118.9 ($\underline{C}$(5)H$_{pyridyl}$), 111.2 ($\underline{C}$(3)H$_{pyridyl}$), 109.6 ($\underline{C}$(5)Br$_{pyrimidyl}$), 53.5 (O-$\underline{C}$H$_3$); *m/z* (EI) 358 (M$^+$ [^{79}Br], 60%), 360 (M$^+$ [^{81}Br], 55%), 279 (100, M$^+$ - Br); *Anal.* Calcd. for C$_{15}$H$_{11}$BrN$_4$O$_2$: C, 50.16; H, 3.09; N, 15.60. Found: C, 50.44; H, 3.30; N, 15.37; ν_{max} (film)/cm^{-1} 2937, 2899, 1707, 1645 (C=O), 1573, 1549, 1509, 1387, 1234, 1100, 1094, 1006, 914, 824.

1-(5-Aminopyrazin-2-yl)-5-(6-methoxypyridin-2-yl)pyridin-2(1*H*)-one 108
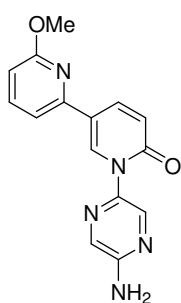
In accordance with the general procedure for pyridone C-N cross-coupling, **97** (0.425 g, 2.10 mmol), 2-amino-5-bromopyrazine **113** (0.348 g, 2 mmol), CuI (0.076 g, 0.400 mmol, 20 mol%), DMCDA (0.114 g, 0.800 mmol) and K$_2$CO$_3$ (0.553 g, 4.00 mmol) in toluene (6 mL) were reacted for 42 h. The reaction mixture was quenched by stirring in saturated ammonium chloride solution (50 mL) for 1 h then the organic component was extracted into EtOAc (3 x 250 mL), the combined extracts were washed with brine (2 x 50 mL). After drying over Na$_2$SO$_4$, filtration, concentration and a

precipitation from EtOAc, the yellow solid was purified twice consecutively by column chromatography: (SiO$_2$, eleuent 20: 1 EtOAc: MeOH *v/v*) then (SiO$_2$, eluent 20: 1 DCM : MeOH *v/v*) yielding **108** as a yellow solid (0.238 g, 40%). mp 169 ^{o}C (decomp.); δ_H (500 MHz, d_6-DMSO) 8.48 (1H, d, *J* 2.4, C(6)$\underline{H}_{pyridone}$), 8.28 – 8.24 (2H, m, C(6)$\underline{H}_{pyrazinyl}$ + C(4)$\underline{H}_{pyridone}$), 7.85 (1H, d, *J* 1.3, C(3)$\underline{H}_{pyrazinyl}$), 7.72 (1H, t, *J* 7.8, C(4)$\underline{H}_{pyridyl}$), 7.43 (1H, d, *J* 7.5, C(6)$\underline{H}_{pyridyl}$), 6.81 (2H, br s, N$\underline{H}_2$), 6.70 (1H, d, *J* 8.1, C(3)$\underline{H}_{pyridyl}$), 6.61 (1H, d, *J* 9.6, C(3)$\underline{H}_{pyridone}$), 3.88 (3H, s, O-C$\underline{H}_3$); δ_C (126 MHz, d_6-DMSO) 163.1 ($\underline{C}$(6)O$_{pyridyl}$), 161.0 ($\underline{C}$(2)O$_{pyridone}$), 155.6, ($\underline{C}$(2)$_{pyridyl}$), 150.3 ($\underline{C}$(4)H$_{pyridone}$), 140.3 ($\underline{C}$(5)N$_{pyrazinyl}$), 140.1 ($\underline{C}$(2)N$_{pyrazinyl}$), 138.8 ($\underline{C}$(4)H$_{pyridyl}$), 137.5 ($\underline{C}$(3)H$_{pyrazinyl}$), 136.3 ($\underline{C}$(6)H$_{pyrazinyl}$), 129.8 ($\underline{C}$(5)$_{pyridone}$), 120.1 ($\underline{C}$(6)H$_{pyridone}$), 117.2 ($\underline{C}$(3)H$_{pyridone}$), 111.4 ($\underline{C}$(5)H$_{pyridyl}$), 108.6 ($\underline{C}$(3)H$_{pyridyl}$), 52.9 (O-$\underline{C}$H$_3$); *m/z* (APCI$^+$) 295 (M$^+$, 100%), 296 (69, M$^+$+H); *Anal.* Calcd. for C$_{15}$H$_{13}$N$_5$O$_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 61.33; H, 4.60; N, 23.65; ν_{max} (film)/cm^{-1} 3333, 3174, 1666 (C=O), 1577, 1538, 1465, 1398, 1331, 1269, 1156, 1125, 1013, 826, 788.

5-(6-Methoxypyridin-2-yl)-1-(5-nitrothiophen-2-yl)pyridin-2(1*H*)-one 109
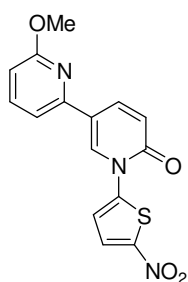
In accordance with the general procedure for pyridone C-N cross-coupling, **97** (0.212 g, 1.05 mmol), 2-bromo-5-nitrothiophene **114** (0.208 g, 1.00 mmol), CuI (0.038 g, 0.200 mmol, 20 mol%), DMCDA (0.057 g, 0.400 mmol) and K$_2$CO$_3$ (0.276 g, 2.00 mmol) in toluene (6 mL) were reacted for 20 h. Standard work-up and column chromatography (SiO$_2$, eluent 3: 2 hexane: EtOAc) yielded **109** as a yellow solid (0.196 g, 60%). mp 227 ^{o}C (decomp.); δ_H (400 MHz, d_6-DMSO) 8.93 (1H, d, *J* 2.1, C(6)$\underline{H}_{pyridone}$), 8.38 (1H, dd, *J* 9.6, 2.1, C(4)$\underline{H}_{pyridone}$), 8.21 (1H, d, *J* 5.0, C(4)$\underline{H}_{thiophenyl}$), 7.94 (1H, d, *J* 5.1, C(3)$\underline{H}_{thiophenyl}$), 7.87 – 7.76 (1H, m, C(4)$\underline{H}_{pyridyl}$), 7.70 (1H, d, *J* 7.4, C(5)$\underline{H}_{pyridyl}$), 6.90 (1H, d, *J* 9.6, C(3)$\underline{H}_{pyridone}$), 6.79 (1H, d, *J* 8.1, C(3)$\underline{H}_{pyridyl}$), 3.96 (3H, s, O-C$\underline{H}_3$); δ_C (126 MHz, CDCl$_3$) 164.2 ($\underline{C}$(6)O$_{pyridyl}$), 162.9 ($\underline{C}$(2)O$_{pyridone}$), 160.2 ($\underline{C}$(2)H$_{pyridyl}$), 149.2($\underline{C}$(2)N$_{thiophenyl}$), 144.3 ($\underline{C}$(4)H$_{pyridone}$), 139.9 ($\underline{C}$(4)H$_{pyridyl}$), 138.3 ($\underline{C}$(5)N$_{thiophenyl}$), 130.4 ($\underline{C}$(5)H$_{pyridone}$), 126.1 ($\underline{C}$(4)H$_{thiophenyl}$), 121.5 ($\underline{C}$(2)N$_{thiophenyl}$), 121.4 ($\underline{C}$(6)H$_{pyridone}$), 114.4 ($\underline{C}$(3)H$_{pyridone}$), 111.8 ($\underline{C}$(5)H$_{pyridyl}$), 110.6 ($\underline{C}$(3)H$_{pyridyl}$), 53.6 (O-$\underline{C}$H$_3$); *m/z* (APCI$^+$) 329 (M$^+$ 66%), 330 (100, M$^+$+H); *Anal.* Calcd. for C$_{15}$H$_{11}$N$_3$O$_4$S: C, 54.71; H, 3.37; N, 12.76. Found: C, 55.00; H, 3.56; N, 12.40; ν_{max} (film)/cm^{-1} 2924, 2848, 1667 (C=O), 1611, 1575, 1542, 1494, 1460, 1425, 1334, 1284, 1258, 1017, 800, 701.

## 2,6-Di(5-(4-methoxyphenyl)-2-oxopyridin-1(2H)-yl)pyridine 116
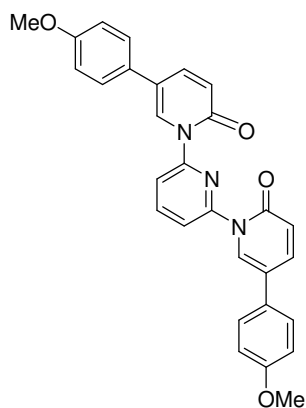
In accordance with the general procedure for pyridone C-N cross-coupling, **95** (0.460 g, 2.28 mmol), 2,6-dibromopyridine **115** (0.246 g, 1.04 mmol), CuI (0.079 g, 0.415 mmol, 20 mol%), DMCDA (0.118 g, 0.830 mmol) and K_2CO_3 (0.574 g, 4.15 mmol) in toluene (12 mL) were reacted for 88 h. Standard work-up and column chromatography (SiO$_2$, eluent 19: 1 EtOAc: Et$_3$N *v/v*) yielded **116** as a white solid which was recrystallised from refluxing EtOAc/hexane (0.340 g, 69%).

mp 229.9-231.1 ^{o}C; δ_H (700 MHz, CDCl$_3$) 8.06 – 7.98 (3H, m, C(3+4+5)$\underline{H}_{pyridyl}$), 7.96 (2H, d, *J* 2.5, C(6+6')$\underline{H}_{pyridone}$), 7.68 (2H, dd, *J* 9.5, 2.7, C(4+4')$\underline{H}_{pyridone}$), 7.35 (4H, d, *J* 8.8, C(2+2'+6+6')$\underline{H}_{phenyl}$), 6.92 (4H, d, *J* 8.8, C(3+3'+5+5')$\underline{H}_{phenyl}$), 6.74 (2H, d, *J* 9.5, C(3+3')$\underline{H}_{pyridone}$), 3.80 (6H, s, 2 x O-C$\underline{H}_3$); δ_C (176 MHz, CDCl$_3$) 161.5 (2C, $\underline{C}$(6+6')O$_{pyridone}$), 159.5 (2C, $\underline{C}$(4+4')O$_{phenyl}$), 151.3 (2C, $\underline{C}$(2+6)N$_{pyridyl}$), 140.8 (2C, $\underline{C}$(4+4')H$_{pyridone}$), 139.8 ($\underline{C}$(4)H$_{pyridyl}$), 132.5 (2C, $\underline{C}$(1+1')$_{phenyl}$), 128.8 (4C, $\underline{C}$(2+2'+6+6')H$_{phenyl}$), 127.3 (2C, $\underline{C}$(5+5')$_{pyridone}$), 122.2 (2C, $\underline{C}$(3+3')H$_{pyridone}$), 121.1 (4C, $\underline{C}$(3+3'+5+5')H$_{phenyl}$), 120.7 (2C, $\underline{C}$(6+6')H$_{pyridone}$), 114.7 (2C, $\underline{C}$(3+5)H$_{pyridyl}$), 55.5 (2C, O-$\underline{C}$H$_3$); *m/z* (APCI$^+$) 478 (M$^+$, 100%); *Anal.* Calcd. for C$_{29}$H$_{23}$FN$_3$O$_4$: C, 72.94; H, 4.85; N, 8.80. Found: C, 73.02; H, 4.5.13; N, 8.69; ν_{max} (film)/cm^{-1} 2959, 1683 (C=O), 1610, 1516, 1436, 1295, 1246, 1205, 1181, 1025, 821, 798.

2,6-Difluoro-3-(4-methoxyphenyl)pyridine 119
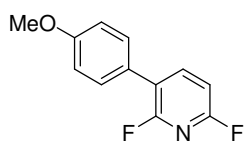
In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted (2,6-difluoro-3-pyridyl)boronic acid **117** (0.953 g , 6 mmol), 4-bromoanisole **89** (0.935 g, 5 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.175 g, 0.25 mmol, 5 mol%) and Na$_2$CO$_3$ (15 mL, 15 mmol, 1 M in water) in 1,4-dioxane (40 mL) at reflux for 1 h. Standard work-up and concentration followed by column chromatography (SiO$_2$, eluent 1: 3 EtOAc: hexane) yielded **119** as a white solid (0.839 g, 76%). mp 33.4-34.9 ^{o}C; δ_H (700 MHz, d_6-DMSO) 8.18 (1H, dd, *J* 17.9, 8.0, C(4)$\underline{H}_{pyridyl}$), 7.48 (2H, dd, *J* 8.6, 1.2, C(2+6)$\underline{H}_{phenyl}$), 7.14 (1H, dd, *J* 8.1, 2.6, C(5)$\underline{H}_{pyridyl}$), 7.02 (2H, d, *J* 8.8, C(3+5)$\underline{H}_{phenyl}$), 3.80 (3H, s, O-C$\underline{H}_3$); δ_C (176 MHz, d_6-DMSO) 157.8 ($\underline{C}$(4)O$_{phenyl}$), 157.6 (dd, *J* 243.2, 13.9, $\underline{C}$(2)F$_{pyridyl}$), 155.3 (dd, *J* 245.4, 14.5, $\underline{C}$(6)F$_{pyridyl}$), 144.0 ($\underline{C}$(1)$_{phenyl}$), 128.2 (2C, $\underline{C}$(2+6)H$_{phenyl}$), 122.9 (d, *J* 4.8, $\underline{C}$(4)H$_{pyridyl}$), 118.3 (dd, *J* 25.4, 5.8, $\underline{C}$(3)$_{pyridyl}$), 112.5 (2C, $\underline{C}$(3+5)H$_{phenyl}$), 105.3 (dd, *J*

40.1, 9.3, $\underline{C}$(5)F$_{pyridyl}$), 53.5 (O-$\underline{C}$H$_3$); *m/z* (EI) 221 (M$^+$, 100%), *Anal.* Calcd. for C$_{12}$H$_9$F$_2$NO: C, 65.16; H, 4.10; N, 6.33. Found: C, 65.05; H, 4.11; N, 6.20; (film)/cm^{-1} 3095, 1642, 1602, 1589, 1511, 1370, 1245, 1176, 1053, 1004, 995, 831, 780.

2-(2,6-Difluoropyridin-3-yl)-3-aminopyridine 120
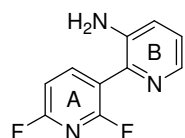
In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted (2,6-difluoro-3-pyridyl)boronic acid **117** (1.50 g , 9.44 mmol), 3-amino-2-bromopyridine **118** (1.09 g, 6.29 mmol), Pd$_2$(dba)$_3$ (0.144 g, 0.157 mmol, 5 mol% Pd), PCy$_3$ (0.088 g, 0.315 mmol) and Na$_2$CO$_3$ (18.9 mL, 18.9 mmol, 1 M in water) in 1,4-dioxane (45 mL) at reflux for 22 h. Standard work-up and concentration followed by column chromatography (SiO$_2$, eluent 2: 1 EtOAc: hexane *v/v*) yielded **120** as a white solid (1.09 g, 83%). mp 156.9-157.7 ^{o}C; δ_H (400 MHz, d_6-DMSO) 8.16 (1H, dt, *J* 9.5, 8.1, C(4)$\underline{H}$$_{pyridyl-A}$), 7.86 (1H, dd, *J* 4.2, 1.8, C(6)$\underline{H}$$_{pyridyl-B}$), 7.25 (1H, ddd, *J* 8.1, 2.5, 0.8, C(5)$\underline{H}$$_{pyridyl-A}$), 7.18 – 7.03 (2H, m, C(4+5)$\underline{H}$$_{pyridyl-B}$), 5.25 (2H, s, N$\underline{H}$$_2$); δ_C (126 MHz, d_6-DMSO) 160.0 (dd, *J* 243.0, 14.0, $\underline{C}$(2)F$_{pyridyl-A}$), 157.7 (dd, *J* 245.4, 14.6, $\underline{C}$(6)F$_{pyridyl-A}$), 147.8 (dd, *J* 8.0, 5.1, $\underline{C}$(4)H$_{pyridyl-A}$), 143.2 ($\underline{C}$(3)N$_{pyridyl-B}$), 137.2 ($\underline{C}$(6)H$_{pyridyl-B}$), 135.8 (d, *J* 4.1, $\underline{C}$(2)$_{pyridyl-B}$), 124.3 ($\underline{C}$(5)H$_{pyridyl-B}$), 121.8 ($\underline{C}$(4)H$_{pyridyl-B}$), 118.7 (dd, *J* 28.7, 5.6, $\underline{C}$(3)$_{pyridyl-A}$), 106.8 (dd, *J* 34.6, 5.3, $\underline{C}$(5)H$_{pyridyl-A}$); *m/z* (APCI$^+$) 208 (M$^+$ + H, 100%); *Anal.* Calcd. for C$_{10}$H$_7$F$_2$N$_3$: C, 57.97; H, 3.41; N, 20.28. Found: C, 58.31; H, 3.77; N, 20.08; ν_{max} (film)/cm^{-1} 3384, 3308, 3201, 1640, 1602, 1587, 1478, 1458, 1444, 1402, 1307, 1274, 1254, 1226, 1211, 1106, 1023, 997, 972, 846, 834, 804, 736.

6-Fluoro-5-(4-methoxyphenyl)pyridin-2(1*H*)-one 121a and 6-fluoro-3-(4-methoxyphenyl)pyridin-2(1*H*)-one 121b

To **119** (0.481 g, 2.17 mmol) was sequentially added 1,4-dioxane (4 mL) and KOH (1 M, 11 mL) and the resulting mixture was heated at reflux and judged complete by TLC (SiO$_2$, eluent 2: 1 hexane : EtOAc *v/v*) after 16 h. The mixture was cooled to room temperature and acidified to pH 6 with 4 M HCl. The mixture was extracted into EtOAc, dried over Na$_2$SO$_4$, filtered and concentrated. The crude mixture was purified by column chromatography (SiO$_2$, eluent 2: 1 hexane : EtOAc *v/v*) to give a mixture of **121a** and **121b** as a white solid (0.383 g, 80%, judged as ratio 1 : 1.4 **121a** : **121b** by ^{1}H NMR). The mixture was separated by column

chromatography (SiO$_2$, eluent 3: 1 hexane : EtOAc *v/v*) followed by preparative TLC (SiO$_2$, eluent 3: 1 hexane : EtOAc *v/v*) giving **121b** as a white solid which was recrystallised from hexane (0.036 g, 8%). Further column chromatography provided **121a** as a white solid which was recrystallised from hexane (0.046 g, 10%). The remaing material was recovered from chromatography as mixed product fractions.

121a mp 195 °C (decomp.); δ$_H$ (400 MHz, CDCl$_3$) 7.80 (1H, dd, *J* 10.1, 8.2, C(4)H$_{pyridone}$), 7.42 (2H, dd, *J* 8.9, 1.5, C(2+6)H$_{phenyl}$), 6.96 (2H, d, *J* 8.9, C(3+5)H$_{phenyl}$), 6.72 (1H, dd, *J* 8.2, 0.9, C(4)H$_{pyridone}$), 3.84 (3H, s, O-CH$_3$); δ$_C$ (176 MHz, *d$_6$*-DMSO) 161.4 (d, *J* 15.7, C(2)O$_{pyridone}$), 158.6 (C(4)O$_{phenyl}$), 157.7 (d, *J* 238.1, C(6)F$_{pyridone}$), 143.4 (d, *J* 4.6, C(4)H$_{pyridone}$), 129.4 (d, *J* 3.0, C(2+6)H$_{phenyl}$), 126.0 (d, *J* 5.1, C(1)$_{phenyl}$), 114.1 (C(3+5)H$_{phenyl}$), 112.4 (d, *J* 27.0, C(5)$_{pyridone}$), 106.9 (d, *J* 4.8, C(3)H$_{pyridone}$), 55.1 (O-CH$_3$); *m/z* (APCI$^+$) 220 (M$^+$+H, 100%), *Anal.* Calcd. for C$_{12}$H$_{10}$FNO$_2$: C, 65.75; H, 4.60; N, 6.39. Found: C, 65.70; H, 4.60; N, 6.41; ν$_{max}$ (film)/cm^{-1} 2936, 1613, 1591, 1509, 1448, 1390, 1290, 1200, 1192, 1104, 1003, 855, 817, 760, 707.

121b mp 200 °C (decomp.); δ$_H$ (700 MHz, CDCl$_3$) 10.32 (1H, s, NH), 7.73 (1H, t, *J* 8.0, C(5)H$_{pyridone}$), 7.53 (2H, d, *J* 8.9, C(2+6)H$_{phenyl}$), 6.97 (2H, d, *J* 8.8, C(3+5)H$_{phenyl}$), 6.53 (1H, dd, *J* 8.0, 1.7, C(4)H$_{pyridone}$), 3.84 (3H, s, O-CH$_3$); δ$_C$ (126 MHz, CDCl$_3$) 160.5 (d, *J* 244.7, C(6)F$_{pyridone}$), 159.4 (C(4)O$_{phenyl}$), 159.4 (d, *J* 11.2, C(2)O$_{pyridone}$), 143.9 (d, *J* 8.1, C(4)H$_{pyridone}$), 130.3 (2C, C(2+6)H$_{phenyl}$), 127.8 (C(1)$_{phenyl}$), 120.3 (d, *J* 5.3, C(3)$_{pyridone}$), 114.2 (C(3+5)H$_{phenyl}$), 100.4 (d, *J* 32.3, C(5)H$_{pyridone}$), 55.6 (O-CH$_3$); *m/z* (APCI$^+$) 220 (M$^+$+H, 100%), *Anal.* Calcd. for C$_{12}$H$_{10}$FNO$_2$: C, 65.75; H, 4.60; N, 6.39. Found: C, 65.89; H, 4.87; N, 6.23; ν$_{max}$ (film)/cm^{-1} 2927, 1613, 1590, 1516, 1448, 1379, 1285, 1253, 1217, 1178, 1100, 1034, 1019, 841, 806, 773, 742.

6-Fluoropyridin-2(1*H*)-one 123

To 2,6-difluoropyridine **122** (2.24 g, 10 mmol) was sequentially added 1,4-dioxane (26 mL) and KOH (6 M, 50 mL) and the resulting mixture was heated at reflux and judged complete by TLC (SiO$_2$, eluent 1 : 1 hexane : EtOAc *v/v*) after 114 h. The mixture was cooled to room temperature, concentrated *in vacuo* and acidified to pH 6 with 4 M HCl. After extraction into DCM (2 x 200 mL) and the combined organic layers were washed with brine (2 x 50 mL) and dried over Na$_2$SO$_4$, filtered and concentrated. The resulting residue was recrystallised from a mixture of DCM and hexane yielding **123** as white needles (0.703 g, 62%). mp 127.2-128.2 °C; δ$_H$ (400 MHz, CDCl$_3$) 11.87 (1H, s, NH), 7.71 (1H, dd, *J* 16.2, 8.1, C(4)H), 6.73 – 6.53 (1H, m, C(3)H), 6.53 – 6.35 (1H, m,

C(5)$\underline{H}$); δ$_C$ (101 MHz, CDCl$_3$) 163.7 (d, J_{CF} 11.7, $\underline{C}$(2)O), 161.8 (d, J_{CF} 245.7, $\underline{C}$(6)F), 144.6 (d, J_{CF} 8.7, $\underline{C}$(4)H), 107.4 (d, J_{CF} 5.0, $\underline{C}$(3)H), 99.5 (d, J_{CF} 31.6, $\underline{C}$(5)H); *m/z* (APCI$^+$) 114 (M$^+$+H, 100%), 113 (35, M$^+$); *Anal.* Calcd. for C$_5$H$_4$FNO: C, 53.10; H, 3.57; N, 16.80. Found: C, 52.86; H, 3.39; N, 17.11; ν$_{max}$ (film)/cm^{-1} 3320, 2696, 1632, 1596, 1574, 1486, 1456, 1344, 1242, 1143, 1070, 1017, 996, 787, 744, 723.

7.4   Experimental Details for Chapter 4

2-Chloro-3,4-diiodopyridine 128.

Method A. A solution of diisopropylamine (12.33 mL, 88 mmol) and anhydrous THF (100 mL) was cooled to -10 ^{o}C under an argon atmosphere. To this *n*-hexyllithium (2.3 M in hexane, 35.2 mL, 88 mmol) was added dropwise over 10 min. Following the addition, the mixture was stirred at 0 ^{o}C for 0.5 h, yielding a clear yellow solution. The solution was cooled to -78 ^{o}C and treated dropwise over 0.5 h with 2-chloropyridine **129** (4.2 mL, 44 mmol) in THF (50 mL). The solution was stirred for 1 h and became clear orange. To this solution iodine (32.4 g, 128 mmol) in THF (100 mL) was added over 45 min, after which the reaction was stirred at -78 ^{o}C for a further 30 min. The solution was allowed to warm to 0 ^{o}C before quenching with water (200 mL), followed by addition of saturated aqueous sodium sulfite (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 400 mL). The combined organic extracts were dried over MgSO$_4$, filtered and then concentrated to yield a dark brown crude solid (10.4 g). This product was dried and slurried in acetonitrile. Filtration yielding 2-chloro-3,6-diiodopyridine **128** as a white solid (4.42 g, 28%). mp 161.1–162.5 ^{o}C; δ$_H$ (700 MHz, CDCl$_3$) 7.96 (1H, d, *J* 5.0, C(6)$\underline{H}$), 7.67 (1H, d, *J* 5.0, C(5)$\underline{H}$); δ$_C$ (176 MHz, CDCl$_3$) 155.0 ($\underline{C}$(2)Cl), 148.4 ($\underline{C}$(6)H), 133.2 ($\underline{C}$(5)H), 122.5 ($\underline{C}$(4)I), 110.5 ($\underline{C}$(3)I); *m/z* (EI) 365 (M$^+$), 238 (62%, M$^+$-I). *Anal.* Calcd. for C$_5$H$_2$ClI$_2$N: C, 16.44; H, 0.55; N, 3.83. Found: C, 16.32; H, 0.56; N, 3.68; ν$_{max}$ (film)/cm^{-1} 2359, 2337, 1535, 1408, 1331, 1180, 1141, 1001, 828.

Method B. The experimental procedure of Method A was followed using ^{n}butyllithium (2.5 M in hexane, 35.2 mL, 88 mmol) instead of *n*-hexyllithium. The crude solid (13.1 g) was recrystallised from acetonitrile yielding **128** as a white solid (4.18 g, 26%). Scale-up using diisopropylamine (24.67 mL, 180 mmol), *n*-butyllithium (70.50 mL, 176 mmol), 2-chloropyridine **129** (8.30 mL, 88 mmol), iodine (65.0 g, 260 mmol), THF (350 mL) gave **128** (5.50 g, 17%). Analytical data were consistent with those obtained by Method A.

Method C. Method B was followed but with the temperature maintained between -100 and -85 °C during the addition of 2-chloropyridine and iodine. Iodine was added over 1.25 h. This gave **128** as a white solid (4.16 g, 26%). Analysis was consistent with that obtained by Method A.

3-(2-Chloro-3-iodopyridin-4-yl)-2-methoxypyridine 131.

Method A. The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **128** (2.0 g, 5.5 mmol), **135** (0.754 g, 4.9 mmol), Pd(PPh$_3$)$_4$ (0.316 g, 0.27 mmol, 5 mol%), 1,4-dioxane (20 mL), Na$_2$CO$_3$ (1 M, 10.94 mL, 10.94 mmol) was stirred at reflux for 24 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, hexane/EtOAc, 4:1 *v/v*) yielded **131** as a white solid (0.75 g, 44%). A sample was recrystallised from hexane and EtOAc for mp determination and CHN analysis. mp 169.5–171.0 °C; δ_H (500 MHz, CDCl$_3$) 8.32 (1H, d, *J* 4.8, C(6)$\underline{H}$$_{pyridyl-A}$), 8.26 (1H, dd, *J* 5.1, 1.9, C(6)$\underline{H}$$_{pyridyl-B}$), 7.37 (1H, dd, *J* 7.3, 1.9, C(4)$\underline{H}$$_{pyridyl-B}$), 7.04 (1H, d, *J* 4.8, C(5)$\underline{H}$$_{pyridyl-A}$), 6.99 (1H, dd, *J* 7.3, 5.1, C(4)$\underline{H}$$_{pyridyl-B}$), 3.91 (3H, s, O-C$\underline{H}$$_3$); δ_C (125 MHz, CDCl$_3$) 159.8 ($\underline{C}$(2)O$_{pyridyl-B}$), 156.0 ($\underline{C}$(6)Cl$_{pyridyl-A}$), 154.9 ($\underline{C}(4)_{pyridyl-A}$), 148.5 ($\underline{C}$(6)H$_{pyridyl-A}$), 148.1 ($\underline{C}$(6)H$_{pyridyl-B}$), 138.4 ($\underline{C}$(4)H$_{pyridyl-B}$), 125.9 ($\underline{C}(3)_{pyridyl-B}$), 123.7 ($\underline{C}$(5)H$_{pyridyl-A}$), 116.8 ($\underline{C}$(5)H$_{pyridyl-B}$), 101.6 ($\underline{C}$(3)I$_{pyridyl-A}$), 53.9 (O-$\underline{C}H_3$); *m/z* (EI) 346 (M$^+$, 45%), 219 (100, M$^+$-I). *Anal.* Calcd. for C$_{11}$H$_8$ClIN$_2$O: C, 38.12; H, 2.33; N, 8.08. Found: C, 38.14; H, 2.34; N, 7.97; ν_{max} (film)/cm^{-1} 3032, 2993, 2949, 1581, 1463, 1402, 1342, 1017, 840, 783.

Method B. The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **128** (5.80 g, 16 mmol), **135** (2.20 g, 14 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.557 g, 0.79 mmol, 5 mol%), 1,4-dioxane (30 mL), Na$_2$CO$_3$ (1 M, 29.0 mL, 29 mmol) was stirred at reflux for 19 h. Standard work-up and cconcentration gave a brown residue which was purified by chromatography (SiO$_2$, hexane/EtOAc, 4:1 *v/v*) yielded **128** (1.05 g, 22%). Analytical data were identical to those obtained in method A.

5-(2-Chloro-3-iodopyridin-4-yl)-2-methoxypyridine 132.

The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **128** (3.0 g, 8.0 mmol), **136** (3.10 g, 21 mmol), Pd(PPh$_3$)$_4$ (0.474 g, 0.41 mmol, 5 mol%,), 1,4-dioxane (30 mL), Na$_2$CO$_3$ (1 M, 41 mL, 41 mmol) was stirred at reflux for 20 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, hexane/EtOAc, 3:1 *v/v*) yielded **132** as a cream solid (1.05 g, 38%), used in subsequent reactions without further purification. A sample was recrystallised from hexane and EtOAc for mp determination and CHN analysis. mp 130.1–130.6 ^{o}C; δ_H (700 MHz, CDCl$_3$) 8.31 (1H, d, *J* 4.8, C(6)$\underline{H}$$_{pyridyl-A}$), 8.13 (1H, dd, *J* 2.5, 0.6, C(6)$\underline{H}$$_{pyridyl-B}$), 7.57 (1H, dd, *J* 8.5, 2.5, C(4)$\underline{H}$$_{pyridyl-B}$), 7.07 (1H, d, *J* 4.8, C(5)$\underline{H}$$_{pyridyl-A}$), 6.82 (1H, dd, *J* 8.5, 0.6, C(3)$\underline{H}$$_{pyridyl-B}$), 3.98 (3H, s, O-C$\underline{H}$$_3$); δ_C (175 MHz, CDCl$_3$) 164.5 ($\underline{C}$(2)O$_{pyridyl-B}$), 156.6 ($\underline{C}$(2)Cl$_{pyridyl-A}$), 155.6 ($\underline{C}(4)_{pyridyl-A}$), 148.7 ($\underline{C}$(6)H$_{pyridyl-A}$), 146.5 ($\underline{C}(6)_{pyridyl-B}$), 139.1 ($\underline{C}(4)_{pyridyl-B}$), 131.6 ($\underline{C}(5)_{pyridyl-B}$), 123.3 ($\underline{C}$(5)H$_{pyridyl-A}$), 110.7 ($\underline{C}(3)_{pyridyl-B}$), 100.8 ($\underline{C}$(3)I$_{pyridyl-A}$), 54.0 (O-C$\underline{H}$$_3$); *m/z* (EI) 346 (M$^+$); *Anal.* Calcd. for C$_{11}H_8$ClIN$_2$O: C, 38.12; H, 2.33; N, 8.08. Found: C, 38.07; H, 2.32; N, 7.90; ν_{max} (film)/cm^{-1} 3038, 3012, 2950, 1599, 1490, 1372, 1061, 1002, 828.
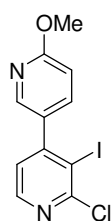
5-(2-Chloro-3-iodopyridin-4-yl)-2-fluoropyridine 133.

The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **128** (1.61 g, 4.4 mmol), **88** (1.60 g, 11 mmol), Pd(PPh$_3$)$_4$ (0.255 g, 0.22 mmol, 5 mol%), 1,4-dioxane (20 mL), Na$_2$CO$_3$ (1M, 22 mL, 22 mmol) was stirred at reflux for 24 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, 0–50% EtOAc in hexane) yielded **133** as a white solid (0.740 g, 50%), used in subsequent reactions without further purification. A sample was recrystallised from hexane and DCM for mp determination and CHN analysis. mp 152.9–153.9 ^{o}C; δ_H (700 MHz, CDCl$_3$) 8.36 (1H, d, *J* 4.8, C(6)$\underline{H}$$_{pyridyl-A}$), 8.19 (1H, dd, *J* 2.5, 1.5, C(6)$\underline{H}$$_{pyridyl-B}$), 7.78 (1H, ddd, *J* 8.4, 2.5, 2.3, C(4)$\underline{H}$$_{pyridyl-B}$), 7.09 (1H, d, *J* 4.8, C(2)$\underline{H}$$_{pyridyl-A}$), 7.04 (1H, dd, *J* 8.4, 2.5, C(3)$\underline{H}$$_{pyridyl-B}$); δ_C (175 MHz, CDCl$_3$) 163.7 (d, *J*$_{CF}$ 242.5, $\underline{C}$(2)F$_{pyridyl-B}$), 156.8 ($\underline{C}$(2)Cl$_{pyridyl-A}$), 154.2 ($\underline{C}$(4)$_{pyridyl-A}$), 148.9 ($\underline{C}$(6)H$_{pyridyl-A}$), 147.3 (d, *J*$_{CF}$ 15.4, $\underline{C}$(4)H$_{pyridyl-B}$), 141.6 (d, *J*$_{CF}$ 8.3, $\underline{C}$(6)H$_{pyridyl-B}$), 136.2 (d, *J*$_{CF}$ 4.8, $\underline{C}$(5)$_{pyridyl-B}$), 123.2 ($\underline{C}$(5)H$_{pyridyl-A}$), 109.6 (d, *J*$_{CF}$ 37.6, $\underline{C}$(3)H$_{pyridyl-B}$), 100.6 ($\underline{C}$(3)I$_{pyridyl-A}$); *m/z* (EI) 334 (M$^+$, 32%), 207 (15, M$^+$ - I), 127 (100,

M^+ - $C_{10}H_5ClFN_2$). *Anal.* Calcd. for $C_{10}H_5ClFIN_2$: C, 35.90; H, 1.51; N, 8.37. Found: C, 35.73; H, 1.50; N, 8.31; v_{max} (film)/cm^{-1} 3048, 1588, 1485, 1376, 1260, 850, 828.

3-(2-Chloro-3-iodopyridin-4-yl)quinoline 134.

The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **128** (2.80 g, 7.7 mmol), **137** (0.994 g, 5.75 mol), Pd(PPh$_3$)$_2$Cl$_2$ (0.269 g, 0.383 mmol, 5 mol%), 1,4-dioxane (30 mL), Na$_2$CO$_3$ (1 M, 11 mL, 11 mmol) was stirred at reflux for 67 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, EtOAc/hexane, 4:1 *v/v*) and recrystallisation from hexane / DCM yielded **134** as a white solid (0.277 g, 13%). mp 199.1–199.9 ^{o}C; δ_H (700 MHz, CDCl$_3$) 8.90 (1H, d, *J* 2.3, C(2)$\underline{H}_{quinolyl}$), 8.40 (1H, d, *J* 4.7, C(6)$\underline{H}_{pyridyl}$), 8.17 (1H, d, *J* 8.5, C(9)$\underline{H}_{quinolyl}$), 8.11 (1H, d, *J* 2.3, C(4)$\underline{H}_{quinolyl}$), 7.88 (1H, d, *J* 8.1, C(6)$\underline{H}_{quinolyl}$), 7.81 (1H, ddd, *J* 8.5, 6.9, 1.2, C(8)$\underline{H}_{quinolyl}$), 7.63 (1H, ddd, *J* 8.1, 6.9, 1.2, C(7)$\underline{H}_{quinolyl}$), 7.19 (1H, d, *J* 4.7, C(5)$\underline{H}_{pyridyl}$); δ_C (175 MHz, CDCl$_3$) 156.7 ($\underline{C}$(2)Cl$_{pyridyl}$), 155.5 ($\underline{C}$(4)$_{pyridyl}$), 149.7 ($\underline{C}$(6)H$_{pyridyl}$), 148.9 ($\underline{C}$(2)H$_{quinolyl}$), 148.0 ($\underline{C}$(10)$_{quinolyl}$), 135.7 ($\underline{C}$(4)H$_{quinolyl}$), 135.5 ($\underline{C}$(3)$_{quinolyl}$), 130.8 ($\underline{C}$(9)H$_{quinolyl}$), 129.8 ($\underline{C}$(8)H$_{quinolyl}$), 128.4 ($\underline{C}$(5)$_{quinolyl}$), 127.8 ($\underline{C}$(6)H$_{quinolyl}$), 127.2 ($\underline{C}$(7)H$_{quinolyl}$), 123.5 ($\underline{C}$(5)H$_{pyridyl}$), 100.6 ($\underline{C}$(3)I$_{pyridyl}$); *m/z* (ES$^+$) 366.94959 (M$^+$ + H, $C_{14}H_9{}^{35}Cl^{127}IN_2$ requires 366.94935); v_{max} (film)/cm^{-1} 3060, 3036, 1565, 1329, 850, 786.

3-[2-Chloro-3-(2-methoxypyridin-3-yl)pyridin-4-yl]-2-methoxypyridine 142.

The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **128** (2.00 g, 5.5 mmol), **135** 2.09 g, 13.69 mmol), Pd(PPh$_3$)$_4$ (0.316 g, 0.274 mmol, 5 mol%), 1,4-dioxane (20 mL), Na$_2$CO$_3$ (1 M, 10.95 mL, 10.95 mmol) was stirred at reflux for 20 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, hexane/EtOAc, 2:1 *v/v*) yielded **142** as a pale yellow waxy solid (0.897 g, 47%). A sample was recrystallised from hexane and EtOAc for mp determination and CHN analysis. mp 111.5–112.2 ^{o}C; δ_H (500 MHz, CDCl$_3$) 8.42 (1H, d, *J* 5.0, C(6)$\underline{H}_{pyridyl-A}$), 8.05 (1H, dd, *J* 5.0, 1.9, C(4)$\underline{H}_{pyridyl-B}$), 8.03 (1H, dd, *J* 5.0, 1.9 C(4)$\underline{H}_{pyridyl-C}$), 7.29–7.25 (2H, m, C(6)$\underline{H}_{pyridyl-B}$ + C(6)$\underline{H}_{pyridyl-C}$), 7.23 (1H, d, *J* 5.0 C(5)$\underline{H}_{pyridyl-A}$), 6.78–6.75 (2H, m, C(5)$\underline{H}_{pyridyl-B}$ + C(5)$\underline{H}_{pyridyl-C}$), 3.77 (3H, s, O-C$\underline{H}_{3 \; pyridyl-B}$), 3.69 (3H, s, O-C$\underline{H}_{3 \; pyridyl-C}$); δ_C (125 MHz, CDCl$_3$) 160.9 ($\underline{C}$(2)O$_{pyridyl-BA}$), 160.0 ($\underline{C}$(2)O$_{pyridyl-C}$), 151.8 ($\underline{C}$(6)H$_{pyridyl-A}$), 148.6 ($\underline{C}(4)_{pyridyl-A}$), 148.5($\underline{C}$(6)H$_{pyridyl-B}$), 147.5 ($\underline{C}$(6)H$_{pyridyl-C}$), 147.3

($\underline{C}$(2)Cl$_{pyridyl-A}$), 139.7 ($\underline{C}$(4)H$_{pyridyl-B}$), 138.8 ($\underline{C}$(4)H$_{pyridyl-C}$), 131.7 ($\underline{C}$(3)H$_{pyridyl-A}$), 124.3 ($\underline{C}$(3)$_{pyridyl-B}$), 121.4 ($\underline{C}$(3)$_{pyridyl-C}$), 119.7 ($\underline{C}$(5)H$_{pyridyl-A}$), 116.5 ($\underline{C}$(5)H$_{pyridyl-B}$), 116.3 ($\underline{C}$(5)H$_{pyridyl-C}$), 53.6 (O-$\underline{C}$H$_{3\ pyridyl-B}$), 53.5 (O-$\underline{C}$H$_{3\ pyridyl-C}$); *m/z* (EI) 327 (M$^+$, 60%), 292 (100, M$^+$-Cl). *Anal.* Calcd. for $C_{17}H_{14}ClN_3O_2$: C, 62.30; H, 4.31; N, 12.82. Found: C, 62.19; H, 4.32; N, 12.78; ν_{max} (film)/cm^{-1} 2989, 2952, 1578, 1468, 1400, 1366, 1300, 1188, 1017.
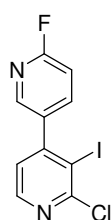
2-Chloro-3,4-bis(6-methoxypyridin-3-yl)pyridine 143.

The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **128** (0.500 g, 1.37 mmol), **136** (0.419 g, 2.74 mmol), Pd(PPh$_3$)$_4$ (0.081 g, 0.07 mmol, 5 mol%), 1,4-dioxane (20 mL) and Na$_2$CO$_3$ (1 M, 5.5 mL, 5.5 mmol) was stirred at reflux for 20 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, petroleum ether/EtOAc, 1:1 *v/v*) yielded **143** as a white powder (0.255 g, 50%). mp 145.6–147.9 ^{o}C; δ_H (400 MHz, CDCl$_3$) 8.44 (1H, d, *J* 5.0, C(6)$\underline{H}_{pyridyl-A}$), 7.97 (1H, d, *J* 2.7, C(2)$\underline{H}_{pyridyl-B}$), 7.91 (1H, d, *J* 2.5, C(2)$\underline{H}_{pyridyl-C}$), 7.39 (1H, dd, *J* 2.5, 8.6, C(4)$\underline{H}_{pyridyl-C}$), 7.29 (1H, d, *J* 5.0, C(5)$\underline{H}_{pyridyl-A}$), 7.20 (1H, dd, *J* 2.7, 8.6, C(4)$\underline{H}_{pyridyl-B}$), 6.73 (1H, d, *J* 8.6, C(5)$\underline{H}_{pyridyl-C}$), 6.60 (1H, d, *J* 8.6, C(5)$\underline{H}_{pyridyl-B}$), 3.93 (3H, s, O-C$\underline{H}_{pyridyl-B}$) 3.90 (3H, s, O-C$\underline{H}_{pyridyl-C}$); δ_C (100 MHz, CDCl$_3$) 163.8 ($\underline{C}$(6)O$_{pyridyl-B}$), 163.5 ($\underline{C}$(6)O$_{pyridyl-C}$), 152.3 ($\underline{C}$(6)H$_{pyridyl-A}$), 149.0 ($\underline{C}(4)_{pyridyl-A}$), 148.7 ($\underline{C}$(2)Cl$_{pyridyl-A}$), 148.2 ($\underline{C}$(2)H$_{pyridyl-B}$), 147.0 ($\underline{C}$(2)H$_{pyridyl-C}$), 140.6 ($\underline{C}$(4)H$_{pyridyl-B}$), 139.1 ($\underline{C}$(4)H$_{pyridyl-C}$), 131.9 ($\underline{C}(3)_{pyridyl-A}$), 127.7 ($\underline{C}(3)_{pyridyl-B}$), 126.9 ($\underline{C}(3)_{pyridyl-C}$), 124.8 ($\underline{C}$(5)H$_{pyridyl-B}$), 123.7 ($\underline{C}$(3)H$_{pyridyl-C}$), 110.6 ($\underline{C}(5)_{pyridyl-A}$), 53.6 (O-$\underline{C}H_{3\ pyridyl-B}$), 53.5 (O-$\underline{C}H_{3\ pyridyl-C}$); *m/z* (ES$^+$) 328.08469 (M$^+$, $C_{17}H_{14}{}^{35}ClN_3O_2$ requires 328.08473); ν_{max} (film)/cm^{-1} 3039, 3010, 2945, 1602, 1560, 1498, 1456, 1359, 1302, 1289, 1257, 1188, 1012, 830, 776.

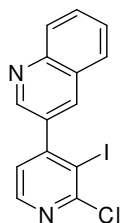### 2-Chloro-3,4-bis(4-methoxyphenyl)pyridine 144.

The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **128** (0.500 g, 1.37 mmol), **75** (0.416 g, 2.74 mmol), Pd(PPh$_3$)$_4$ (0.081 g, 0.07 mmol, 5 mol%), 1,4-dioxane (20 mL) and Na$_2$CO$_3$ (1 M, 5.5 mL, 5.5 mL) was stirred at reflux for 20 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, petroleum ether/EtOAc, 3:2 *v/v*) yielded **144** as a white crystalline powder (0.288 g, 64%). mp 126.4–129.9 ^{o}C; δ_H (400 MHz, *d*6-acetone) 8.37 (1H, d, *J* 5.0,

C(6)$\underline{H}$$_{pyridyl}$), 7.39 (1H, d, *J* 5.0, C(5)$\underline{H}$$_{pyridyl}$), 6.80 (2H, d, *J* 8.8, C(2+6)$\underline{H}$$_{phenyl-A}$), 7.10 (2H, d, *J* 8.8, C(2+6)$\underline{H}$$_{phenyl-B}$), 6.88 (2H, d, *J* 8.8, C(3+5)$\underline{H}$$_{phenyl-A}$), 6.80 (2H, d, *J* 8.8, C(3+5)$\underline{H}$$_{phenyl-B}$), 3.78 (3H, s, O-C$\underline{H}$$_{phenyl-B}$), 3.75 (3H, s, O-C$\underline{H}$$_{phenyl-C}$); δ$_C$ (100 MHz, *d$_6$*-acetone) 160.4 ($\underline{C}$(4)O$_{phenyl-A}$), 160.1 ($\underline{C}$(4)O$_{phenyl-B}$), 152.6 ($\underline{C}$(4)$_{pyridyl}$), 152.4 ($\underline{C}$(6)H$_{pyridyl}$), 148.8 ($\underline{C}$(2)Cl$_{pyridyl}$), 135.6 ($\underline{C}$(3)$_{pyridyl}$), 132.5 ($\underline{C}$(1)$_{phenyl-A}$), 131.6 (2C, $\underline{C}$(2+6)H$_{phenyl-A}$), 131.4 (2C, $\underline{C}$(2+6)H$_{phenyl-B}$), 129.8 ($\underline{C}$(1)$_{phenyl-B}$), 125.0 ($\underline{C}$(5)H$_{pyridyl}$), 114.4 (2C, $\underline{C}$(3+5)H$_{phenyl-A}$), 114.3 (2C, $\underline{C}$(3+5)H$_{phenyl-B}$), 55.5 (O-$\underline{C}$H$_{3\ phenyl-D}$), 55.5 (O-$\underline{C}$H$_{3\ phenyl-C}$); *m/z* (APCI$^+$) 326.0938 (M$^+$ + H, C$_{19}$H$_{17}$^{35}ClNO$_2$ requires 326.0948); ν$_{max}$ (film)/ cm^{-1} 2963, 2838, 1606, 1577, 1511, 1454, 1371, 1289, 1246, 1173, 1110, 1060, 1027, 998, 812, 767.

5-[2-Chloro-3-(6-methoxypyridin-3-yl)pyridin-4-yl]-2-fluoropyridine 145.

The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **133** (0.480 g, 1.43 mmol), **136** (0.330 g, 2.2 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.0504 g, 0.072 mmol, 5 mol%), 1,4-dioxane (20 mL), Na$_2$CO$_3$ (1 M, 4.0 mL, 4.0 mmol) was stirred at reflux for 18 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, hexane/EtOAc, 2:1 *v/v*) yielded **145** as a yellow oil (0.410 g, 90%). δ$_H$ (700 MHz, CDCl$_3$) 8.45 (1H, d, *J* 5.0, C(6)$\underline{H}$$_{pyridyl-A}$), 7.97 (1H, d, *J* 2.2, C(6)$\underline{H}$$_{pyridyl-B}$), 7.84 (1H, d, *J* 1.8, C(6)$\underline{H}$$_{pyridyl-C}$), 7.42 (1H, ddd, *J* 8.4, 2.5, 2.2, C(4)$\underline{H}$$_{pyridyl-B}$), 7.33 (1H, dd, *J* 8.5, 2.4, C(4)$\underline{H}$$_{pyridyl-C}$), 7.27 (1H, d, *J* 5.0, C(5)$\underline{H}$$_{pyridyl-A}$), 6.79 (1H, dd, *J* 8.4, 2.6, C(3)$\underline{H}$$_{pyridyl-B}$), 6.68 (1H, dd, *J* 8.5, 0.5, C(6)$\underline{H}$$_{pyridyl-C}$), 3.88 (3H, s, O-C$\underline{H}$$_3$); δ$_C$ (175 MHz, CDCl$_3$) 163.8 ($\underline{C}$(6)O$_{pyridyl-C}$), 163.2 (d, *J*$_{CF}$ 242.3, $\underline{C}$(2)F$_{pyridyl-B}$), 152.7 ($\underline{C}$(6)H$_{pyridyl-A}$), 149.1 ($\underline{C}$(4)$_{pyridyl-A}$), 148.3 ($\underline{C}$(2)Cl$_{pyridyl-A}$), 147.8 (d, *J*$_{CF}$ 15.2, $\underline{C}$(4)H$_{pyridyl-B}$), 147.8 ($\underline{C}$(2)$_{pyridyl-C}$), 141.8 (d, *J*$_{CF}$ 8.2, $\underline{C}$(6)H$_{pyridyl-B}$), 140.6 ($\underline{C}$(4)H$_{pyridyl-C}$), 132.4 ($\underline{C}$(3)$_{pyridyl-A}$), 131.9 (d, *J*$_{CF}$ 4.8, $\underline{C}$(5)$_{pyridyl-B}$), 124.4 ($\underline{C}$(3)$_{pyridyl-C}$), 123.8 ($\underline{C}$(5)$_{pyridyl-C}$), 111.0 ($\underline{C}$(5)F$_{pyridyl-A}$), 109.6 (d, *J*$_{CF}$ 37.6, $\underline{C}$(3)H$_{pyridyl-B}$), 53.8 (O-$\underline{C}$H$_3$); *m/z* (APCI$^+$) 315.05770 (M$^+$, C$_{16}$H$_{11}$^{35}ClFN$_3$O requires 315.05692); ν$_{max}$ (film)/cm^{-1} 2950, 1594, 1498, 1362, 1286, 1250, 1017, 830.
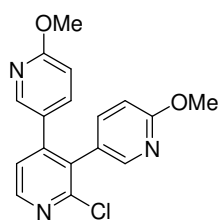
5-[2-Chloro-3-(2-methoxypyridin-3-yl)pyridin-4-yl]-2-methoxypyridine 146.
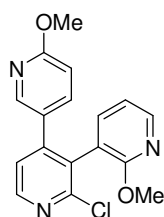
The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **132** (0.680 g, 1.96 mmol), **135** (0.450 g, 2.9 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.0689 g, 0.0981 mmol, 5 mol%), 1,4-dioxane (20 mL), Na$_2$CO$_3$ (1 M, 6.0 mL, 6.0 mmol) was stirred at reflux for 70 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, diethyl ether/petroleum ether, 2:1 *v/v*) yielded **146** as a white solid (0.146 g, 23%). A sample was recrystallised from hexane and EtOAc for mp determination and CHN analysis. mp 149.6–150.2 $^{\circ}$C; δ_H (500 MHz, CDCl$_3$) 8.42 (1H, d, *J* 5.0, C(6)$\underline{H}$$_{pyridyl-A}$), 8.13 (1H, dd, *J* 5.0, 1.9, C(6)$\underline{H}$$_{pyridyl-C}$), 7.93 (1H, d, *J* 2.5, C(6)$\underline{H}$$_{pyridyl-B}$), 7.30 (1H, dd, *J* 7.3, 1.9, C(4)$\underline{H}$$_{pyridyl-C}$), 7.25 (1H, d, *J* 5.0, C(5)$\underline{H}$$_{pyridyl-A}$), 7.20 (1H, dd, *J* 8.6, 2.5, C(4)$\underline{H}$$_{pyridyl-B}$), 6.84 (1H, dd, *J* 7.3, 5.0, C(5)$\underline{H}$$_{pyridyl-C}$), 6.55 (1H, d, *J* 8.6, C(3)$\underline{H}$$_{pyridyl-B}$), 3.86 (3H, s, O-C$\underline{H}$$_3$ $_{pyridyl-B}$), 3.78 (3H, s, O-C$\underline{H}$$_3$ $_{pyridyl-C}$); δ_C (125 MHz, CDCl$_3$) 164.0 ($\underline{C}$(2)O$_{pyridyl-B}$), 161.0 ($\underline{C}$(2)O$_{pyridyl-C}$), 152.3 ($\underline{C}$(6)H$_{pyridyl-A}$), 149.4 ($\underline{C}$(4)$_{pyridyl-A}$), 148.9 ($\underline{C}$(6)H$_{pyridyl-C}$), 147.6 ($\underline{C}$(2)Cl$_{pyridyl-A}$), 146.6 ($\underline{C}$(6)H$_{pyridyl-B}$), 140.2 ($\underline{C}$(4)H$_{pyridyl-C}$), 138.7 ($\underline{C}$(4)H$_{pyridyl-B}$), 130.9 ($\underline{C}$(3)$_{pyridyl-A}$), 127.3 ($\underline{C}$(3)$_{pyridyl-C}$), 123.5 ($\underline{C}$(5)H$_{pyridyl-B}$), 119.7 ($\underline{C}$(5)H$_{pyridyl-A}$), 116.8 ($\underline{C}$(5)H$_{pyridyl-B}$), 110.5 ($\underline{C}$(3)H$_{pyridyl-B}$), 53.8 (O-$\underline{C}$H$_3$ $_{pyridyl-B}$), 53.8 (O-$\underline{C}$H$_3$ $_{pyridyl-C}$); *m/z* (EI) 327 (M$^+$), 292 (100, M$^+$-Cl). *Anal.* Calcd. for C$_{17}$H$_{14}$ClN$_3$O$_2$: C, 62.30; H, 4.31; N, 12.82. Found: C, 62.32; H, 4.37; N, 12.73; ν_{max} (film)/cm^{-1} 2978, 2939, 1574, 1492, 1464, 1376, 1287, 1016, 784.

3-[2-Chloro-3-(6-methoxypyridin-3-yl)pyridin-4-yl]-2-methoxypyridine 147.
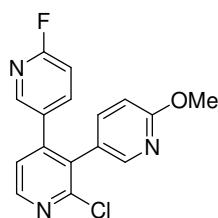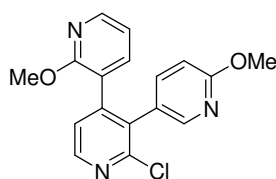
The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **131** (2.00 g, 5.77 mmol), **136** (0.970 g, 6.3 mmol), Pd$_2$(dba)$_3$ (0.159 g, 0.173 mol, 3 mol%), P(t-Bu)$_3$.HBF$_4$ (6 mol %, 0.100 g, 0.346 mmol) 1,4-dioxane (20 mL), KF (1.10 g, 19 mmol) was stirred at reflux for 6 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, hexane/EtOAc, 4:1 *v/v*) yielded **147** as a white solid (1.40 g, 74%). mp 102.7–105.3 $^{\circ}$C; δ_H (700 MHz, CDCl$_3$) 8.41 (1H, d, *J* 4.9, C(6)$\underline{H}$$_{pyridyl-A}$), 8.06 (1H, dd, *J* 5.0, 1.8, C(4)$\underline{H}$$_{pyridyl-B}$), 7.83 (1H, s, C(6)$\underline{H}$$_{pyridyl-C}$), 7.35 (1H, d, *J* 7.4, C(4)$\underline{H}$$_{pyridyl-C}$), 7.30 (1H, dd, *J* 7.2, 1.7, C(6)$\underline{H}$$_{pyridyl-B}$), 7.22 (1H, d, *J* 4.9, C(3)$\underline{H}$$_{pyridyl-A}$), 6.82 (1H, dd, *J* 7.2, 5.0, C(5)$\underline{H}$$_{pyridyl-B}$), 6.62 (1H, d, *J* 7.4, C(3)$\underline{H}$$_{pyridyl-C}$), 3.86 (3H, s), 3.68 (3H, s); δ_C (175 MHz, CDCl$_3$) 163.6 ($\underline{C}$(6)O$_{pyridyl-C}$), 159.8 ($\underline{C}$(2)O$_{pyridyl-B}$), 151.8 ($\underline{C}$(6)H$_{pyridyl-A}$), 148.6 ($\underline{C}$(4)$_{pyridyl-A}$), 148.4 ($\underline{C}$(6)H$_{pyridyl-B}$),

147.7 (2C, $\underline{C}$(2)Cl$_{pyridyl-A}$ + $\underline{C}$(2)H$_{pyridyl-C}$), 140.4 ($\underline{C}$(2)H$_{pyridyl-C}$), 139.1 ($\underline{C}$(4)H$_{pyridyl-B}$), 133.3 ($\underline{C}$(4)H$_{pyridyl-C}$), 125.3 ($\underline{C}$(3)$_{pyridyl-B}$), 124.6 ($\underline{C}$(3)$_{pyridyl-C}$), 121.5 ($\underline{C}$(5)H$_{pyridyl-A}$), 116.8 ($\underline{C}$(5)H$_{pyridyl-B}$), 110.1 ($\underline{C}$(5)H$_{pyridyl-C}$), 53.7 (O-$\underline{C}$H$_3$ $_{pyridy-C}$), 53.5 (O-$\underline{C}$H$_3$ $_{pyridy-B}$); *m/z* (ES$^+$) 328.08494 (M$^+$+H, C$_{17}$H$_{15}$^{35}ClN$_3$O$_2$ requires 328.08473); ν_{max} (film)/cm^{-1} 2952, 1469, 1400, 1375, 1284, 1016, 839, 788.

2-Fluoro-5-[2-(4-methoxyphenyl)-3-(6-methoxypyridin-3-yl)pyridin-4-yl]pyridine 148.
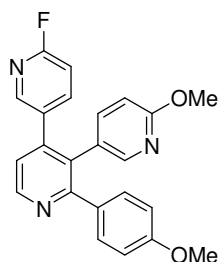
The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **145** (0.175 g, 0.554 mmol), **75** (0.100 g, 0.67 mmol), Pd$_2$(dba)$_3$ (0.010 g, 0.011 mmol, 2 mol%), PCy$_3$ (4.8 mol%, 0.008 g, 0.027 mmol) 1,4-dioxane (7 mL), K$_3$PO$_4$ (1.27 M, 0.74 mL, 0.94 mmol) was stirred at reflux for 20 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, EtOAc/hexane, 3:1 *v/v*) yielded **148** as a pale yellow solid (0.0640 g, 30%). mp 139.2–140.2 ^{o}C; δ_H (700 MHz, CDCl$_3$) 8.72 (1H, d, *J* 5.0, C(6)$\underline{H}$$_{pyridyl-A}$), 7.98 (1H, d, *J* 1.9 C(6)$\underline{H}$$_{pyridyl-B}$), 7.63 (1H, d, *J* 2.3, C(2)$\underline{H}$$_{pyridyl-C}$), 7.40 (1H, dd, *J* 8.5, 2.3, C(4)$\underline{H}$$_{pyridyl-C}$), 7.25 (1H, d, *J* 5.0, C(5)$\underline{H}$$_{pyridyl-A}$), 7.17 (2H, d, *J* 8.7, C(2+6)$\underline{H}$$_{phenyl}$), 7.04 (1H, dd, *J* 8.5, 2.4, 1.9, C(4)$\underline{H}$$_{pyridyl-B}$), 6.79 (1H, dd, *J* 8.5, 2.6, C(3)$\underline{H}$$_{pyridyl-B}$), 6.73 (2H, d, *J* 8.8, C(3+5)$\underline{H}$$_{phenyl}$), 6.50 (1H, d, *J* 8.5, C(5)$\underline{H}$$_{pyridyl-C}$), 3.83 (3H, s), 3.74 (3H, s); δ_C (175 MHz, CDCl$_3$) 163.1 ($\underline{C}$(6)O$_{pyridyl-C}$), 163.0 (d, J_{CF} 241.2, $\underline{C}$(2)F$_{pyridyl-B}$), 159.6 ($\underline{C}$(4)O$_{phenyl}$), 159.2 ($\underline{C}$(2)$_{pyridyl-A}$), 149.0 ($\underline{C}$(6)H$_{pyridyl-A}$), 148.8 ($\underline{C}$(4)$_{pyridyl-A}$), 147.9 (d, J_{CF} 15.0, $\underline{C}$(4)H$_{pyridyl-B}$), 145.8 ($\underline{C}$(3)$_{pyridyl-A}$), 142.0 (d, J_{CF} 8.0, $\underline{C}$(6)H$_{pyridyl-B}$), 141.3 ($\underline{C}$(4)H$_{pyridyl-C}$), 133.1 (d, J_{CF} 4.7, $\underline{C}$(5)$_{pyridyl-B}$), 132.3 ($\underline{C}$(1)$_{phenyl}$), 131.4 (2C, $\underline{C}$(2+6)H$_{phenyl}$), 130.9 ($\underline{C}$(3)H$_{pyridyl-C}$), 126.1 ($\underline{C}$(2)$_{pyridyl-C}$), 123.3 ($\underline{C}$(5)H$_{pyridyl-A}$), 113.7 (2C, $\underline{C}$(3+5)H$_{phenyl}$), 110.8 $\underline{C}$(5)H$_{pyridyl-C}$, 109.4 (d, J_{CF} 37.5, $\underline{C}$(3)H$_{pyridyl-B}$), 55.4 (O-$\underline{C}$H$_3$ $_{pyridy-C}$), 53.6 (O-$\underline{C}$H$_3$ $_{phenyl}$); *m/z* (EI) 387 (M$^+$, 85%), 386 (100, M$^+$-H). *Anal.* Calcd. for C$_{23}$H$_{18}$FN$_3$O$_2$: C, 71.31; H, 4.68; N, 10.85. Found: C, 70.88; H, 4.74; N, 10.67; ν_{max} (film)/cm^{-1} 3030, 2940, 1604, 1499, 1252, 1178, 1016, 836.

## 5-[4-(6-Fluoropyridin-3-yl)-3-(6-methoxypyridin-3-yl)pyridin-2-yl]pyrimidin-2-amine 149.
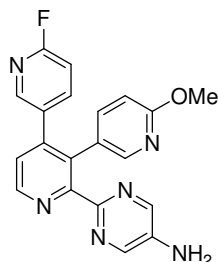
The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **145** (0.175 g, 0.5543 mmol), **152** (0.0920 g, 0.67 mmol), Pd$_2$(dba)$_3$ (0.0102 g, 0.011 mmol, 2 mol%), PCy$_3$ (4.8 mol%, 0.00750 g, 0.027 mmol) 1,4-dioxane (7 mL), K$_3$PO$_4$ (1.27 M, 0.742 mL, 0.942 mmol) was stirred at reflux for 2 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, EtOAc/methanol, 4:1 *v/v*) yielded **149** as a white solid (0.0470 g, 23%). mp 200.2–202.5 °C; v_{max} (film)/cm^{-1} 3454 and 3305 (NH$_2$), 3184, 1638, 1585, 1487, 1410, 1285, 1251, 828; δ_H (700 MHz, CDCl$_3$) 8.76 (1H, d, *J* 4.9, C(6)$\underline{H}$$_{pyridyl-A}$), 8.24 (2H, s, C(4+6)$\underline{H}$$_{pyrimidyl}$), 7.99 (1H, d, *J* 1.6, C(2)$\underline{H}$$_{pyridyl-B}$), 7.72 (1H, d, *J* 1.8, C(2)$\underline{H}$$_{pyridyl-C}$), 7.40 (1H, ddd, *J* 8.5, 2.4, 1.6, C(4)$\underline{H}$$_{pyridyl-B}$), 7.30 (1H, d, *J* 4.9, C(5)$\underline{H}$$_{pyridyl-A}$), 7.12 (1H, dd, *J* 8.5, 2.6, C(5)$\underline{H}$$_{pyridyl-B}$), 6.81 (1H, dd, *J* 8.4, 2.6, C(4)$\underline{H}$$_{pyridyl-C}$), 6.60 (1H, d, *J* 8.5, C(5)$\underline{H}$$_{pyridyl-C}$), 5.20 (2H, br s, N$\underline{H}_2$), 3.86 (3H, s); δ_C (175 MHz, CDCl$_3$) 163.6 ($\underline{C}$(6)O$_{pyridyl-C}$), 163.2 (d, J_{CF} 242.0, $\underline{C}$(6)F$_{pyridyl-B}$), 161.5 ($\underline{C}$(2)$_{pyridyl-A}$), 159.2 (2C, $\underline{C}$(3+6)H$_{pyrimidyl}$), 154.1 ($\underline{C}$(2)H$_{pyrimidyl}$), 149.7 ($\underline{C}$(6)H$_{pyridyl-A}$), 148.8 ($\underline{C}$(4)H$_{pyridyl-A}$), 147.9 (d, J_{CF} 15.1, $\underline{C}$(4)H$_{pyridyl-B}$), 146.3 ($\underline{C}$(5)N$_{pyrimidyl}$), 141.9 (d, J_{CF} 8.0, $\underline{C}$(2)H$_{pyridyl-B}$), 141.0 ($\underline{C}$(2)H$_{pyridyl-C}$), 132.6 (d, J_{CF} 5.0, $\underline{C}$(3)$_{pyridyl-B}$), 131.1 ($\underline{C}$(4)H$_{pyridyl-C}$), 125.1 ($\underline{C}$(6)H$_{pyridyl-A}$), 124.2 ($\underline{C}$(3)$_{pyridyl-C}$), 123.9 ($\underline{C}$(5)H$_{pyridyl-A}$), 111.5 ($\underline{C}$(5)H$_{pyridyl-C}$), 109.5 (d, J_{CF} 37.5, $\underline{C}$(5)H$_{pyridyl-B}$), 53.8 ($\underline{C}$(5)H$_{pyridyl-C}$); *m/z* (ES$^+$) 375.13660 (M$^+$+H), C$_{20}$H$_{15}$FN$_6$O+H requires 375.13641.

5-[2-(6-Fluoropyridin-3-yl)-3-(2-methoxypyridin-3-yl)pyridin-4-yl]-2-methoxypyridine 150.

The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **147** (0.100 g, 0.31 mmol), **88** (0.052 g, 0.37 mmol), Pd$_2$(dba)$_3$ (0.0056 g, 0.0061 mmol, 2 mol%), PCy$_3$ (4.8 mol%, 0.0041 g, 0.015 mmol) 1,4-dioxane (5 mL), K$_3$PO$_4$ (1.27 M, 0.4 mL, 0.052 mmol) was stirred at reflux for 5 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, EtOAc/hexane, 3:1 *v/v*) yielded **150** as a clear colourless oil (0.0540 g, 45%). δ_H (700 MHz, CDCl$_3$) 8.73 (1H, d, *J* 5.0, C(6)$\underline{H}$$_{pyridyl-A}$), 8.07 (1H, d, *J* 1.8, C(2)$\underline{H}$$_{pyridyl-D}$), 8.01 (1H, dd, *J* 5.0, 1.8, C(6)$\underline{H}$$_{pyridyl-C}$), 7.93 (1H, d, *J* 2.4, C(6)$\underline{H}$$_{pyridyl-B}$), 7.66 (1H, ddd, *J* 8.4, 2.4, 1.8, C(4)$\underline{H}$$_{pyridyl-D}$), 7.33 (1H, d, *J* 5.0, C(5)$\underline{H}$$_{pyridyl-A}$), 7.16 (1H, dd, *J* 8.4, 2.5,

C(5)$\underline{\text{H}}$_{pyridyl-D}), 7.09 (1H, dd, *J* 7.3, 1.8, C(4)$\underline{\text{H}}$_{pyridyl-C}), 6.76 (1H, dd, *J* 8.4, 2.4, C(4)$\underline{\text{H}}$_{pyridyl-B}), 6.70 (1H, dd, *J* 7.3, 5.0, C(5)$\underline{\text{H}}$_{pyridyl-C}), 6.55 (1H, d, *J* 8.4, C(3)$\underline{\text{H}}$_{pyridyl-B}), 3.87 (3H, s, O-C$\underline{\text{H}}_3$ _{pyridyl-C}), 3.56 (3H, s, O-C$\underline{\text{H}}_3$ _{pyridyl-B}); δ_C (176 MHz, CDCl₃) 163.9 ($\underline{\text{C}}$(2)O_{pyridyl-B}), 163.0 (d, *J*_{CF} 240.4, $\underline{\text{C}}$(6)F_{pyridyl-D}), 160.7 ($\underline{\text{C}}$(2)O_{pyridyl-C}), 155.3 ($\underline{\text{C}}$(2)_{pyridyl-A}), 149.3 ($\underline{\text{C}}$(6)H_{pyridyl-A}), 148.2 (d, *J*_{CF} 15.1, $\underline{\text{C}}$(4)H_{pyridyl-D}), 147.8 ($\underline{\text{C}}$(4)_{pyridyl-A}), 147.5 ($\underline{\text{C}}$(6)H_{pyridyl-C}), 146.6 ($\underline{\text{C}}$(6)H_{pyridyl-B}), 141.8 (d, *J*_{CF} 8.0, $\underline{\text{C}}$(2)H_{pyridyl-D}), 140.9 ($\underline{\text{C}}$(4)H_{pyridyl-B}), 138.8 ($\underline{\text{C}}$(4)H_{pyridyl-C}), 134.4 (d, *J*_{CF} 4.6, $\underline{\text{C}}$(3)_{pyridyl-D}), 130.3 ($\underline{\text{C}}$(3)_{pyridyl-A}), 127.7 ($\underline{\text{C}}$(3)_{pyridyl-C}), 124.2 ($\underline{\text{C}}$(5)_{pyridyl-B}), 120.3 ($\underline{\text{C}}$(5)H_{pyridyl-A}), 117.0 ($\underline{\text{C}}$(5)H_{pyridyl-C}), 110.4 ($\underline{\text{C}}$(3)H_{pyridyl-B}), 108.7 (d, *J*_{CF} 37.4, $\underline{\text{C}}$(5)F_{pyridyl-D}), 53.8 (O-$\underline{\text{C}}$H₃ _{pyridyl-C}), 53.5 (O-$\underline{\text{C}}$H₃ _{pyridyl-B}); *m/z* (ES⁺) 389.14105 (M⁺+H, C₂₂H₁₈FN₄O₂ requires 389.14083); ν_{max} (film)/cm⁻¹ 2963, 1592, 1488, 1462, 1397, 1369, 1286, 1257, 1097, 1015, 827, 797, 732.

3-[2-(6-Fluoropyridin-3-yl)-3-(6-methoxypyridin-3-yl)pyridin-4-yl]-2-methoxypyridine 151.
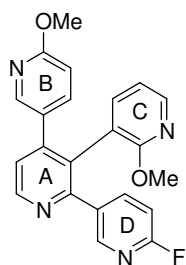

Method A. The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **146** (0.500 g, 1.5 mmol), **88** (0.260 g, 1.8 mmol), Pd₂(dba)₃ (0.0279 g, 0.0305 mmol, 2 mol%), PCy₃ (4.8 mol%, 0.0205 g, 0.073 mmol) 1,4-dioxane (15 mL), K₃PO₄ (1.27 M, 2.04 mL, 2.59 mmol) was stirred at reflux for 17 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO₂, EtOAc/hexane, 3:1 *v/v*) yielded **151** as a clear colourless oil (0.302 g, 51%). δ_H (700 MHz, CDCl₃) 8.69 (1H, d, *J* 4.9, C(6)$\underline{\text{H}}$_{pyridyl-A}), 8.06 (1H, d, *J* 2.2, C(2)$\underline{\text{H}}$_{pyridyl-D}), 8.04 (1H, dd, *J* 5.1, 1.8, C(6)$\underline{\text{H}}$_{pyridyl-B}), 7.71 (1H, dd, *J* 8.4, 2.4, 2.2, C(4)$\underline{\text{H}}$_{pyridyl-D}), 7.61 (1H, s, C(2)$\underline{\text{H}}$_{pyridyl-C}), 7.32 (1H, dd, *J* 7.2, 1.8, C(4)$\underline{\text{H}}$_{pyridyl-B}), 7.27 (1H, d, *J* 4.9, C(5)$\underline{\text{H}}$_{pyridyl-A}), 7.02 (1H, d, *J* 7.5, C(4)$\underline{\text{H}}$_{pyridyl-C}), 6.81 (1H, dd, *J* 7.2, 5.1, C(5)$\underline{\text{H}}$_{pyridyl-B}), 6.77 (1H, dd, *J* 8.4, 2.5, C(5)$\underline{\text{H}}$_{pyridyl-D}), 6.43 (1H, d, *J* 7.2, C(5)$\underline{\text{H}}$_{pyridyl-C}), 3.76 (3H, s, O-C$\underline{\text{H}}_3$ _{pyridyl-B}), 3.60 (3H, s, O-C$\underline{\text{H}}_3$ _{pyridyl-C}); δ_C (175 MHz, CDCl₃) 163.1 ($\underline{\text{C}}$(6)O_{pyridyl-C}), 162.9 (d, *J*_{CF} 240.8, $\underline{\text{C}}$(6)F_{pyridyl-D}), 159.9 ($\underline{\text{C}}$(2)O_{pyridyl-B}), 154.4 ($\underline{\text{C}}$(2)_{pyridyl-A}), 149.1 ($\underline{\text{C}}$(6)H_{pyridyl-A}), 149.0 (d, *J*_{CF} 15.1, $\underline{\text{C}}$(4)H_{pyridyl-D}), 148.1 ($\underline{\text{C}}$(6)H_{pyridyl-B}), 147.4 ($\underline{\text{C}}$(4)_{pyridyl-A}), 146.8 ($\underline{\text{C}}$(2)H_{pyridyl-C}), 142.6 (d, *J*_{CF} 8.0, $\underline{\text{C}}$(2)H_{pyridyl-D}), 140.5 ($\underline{\text{C}}$(4)H_{pyridyl-B}), 139.1 ($\underline{\text{C}}$(4)H_{pyridyl-C}), 134.1 (d, *J*_{CF} 4.4, $\underline{\text{C}}$(3)_{pyridyl-D}), 132.5 ($\underline{\text{C}}$(3)_{pyridyl-B}), 125.9 (C(3)_{pyridyl-A}), 124.8 ($\underline{\text{C}}$(3)_{pyridyl-C}), 121.9 ($\underline{\text{C}}$(5)H_{pyridyl-A}), 116.8 ($\underline{\text{C}}$(5)H_{pyridyl-B}), 110.3 ($\underline{\text{C}}$(5)H_{pyridyl-C}), 108.9 (d, *J*_{CF} 37.4, $\underline{\text{C}}$(5)H_{pyridyl-D}), 53.5 (O-$\underline{\text{C}}$H₃ _{pyridyl-C}), 53.3 (O-$\underline{\text{C}}$H₃ _{pyridyl-B}); *m/z* (ES⁺) 389.14105 (M⁺+H,

$C_{22}H_{17}FN_4O_2+H$ requires 389.14083); ν_{max} (film)/cm^{-1} 2949, 1592, 1463, 1400, 1285, 1249, 1016, 830.

Method B. The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **146** (0.250 g, 0.763 mmol), **88** (0.130 g, 0.92 mmol), Pd(PPh$_3$)$_4$ (0.0441 g, 0.038 mmol, 5 mol%), 1,4-dioxane (12 mL), Na$_2$CO$_3$ (1 M, 1.8 mL, 1.8 mmol) was stirred at reflux for 24 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, EtOAc/hexane, 3:1 *v/v*) yielded **151** as a clear colourless oil (0.150 g, 50%).

2-Chloro-3,4-bis(2-phenylethynyl)pyridine 153.

To a flask fitted with a septum was added 2-chloro-3,4-diiodopyridine **128** (1.500 g, 4.11 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.144 g, 0.21 mmol, 5 mol%) and CuI (0.039 g, 0.21 mmol, 5 mol%). The flask was evacuated and backfilled with dry argon three times. Dry, degassed triethylamine (40 mL) was added *via* a cannula and phenylacetylene (0.860 g, 8.42 mmol) was added *via* syringe. The reaction mixture was heated to 50 °C for 18 h by which time the reaction was complete by TLC. The reaction was cooled to room temperature, triethylamine was removed *in vacuo* and the residue was passed through a silica plug eluting with EtOAc (300 mL). After concentration, the residue was purified by flash chromatography (SiO$_2$, DCM/hexane, 1:1 *v/v*) followed by recrystallisation from methanol yielding **153** as a white solid (1.01 g, 72%). mp 100.5– 101.7 °C; δ_H (400 MHz, CDCl$_3$) 8.26 (1H, d, *J* 5.1, C(6)$\underline{H}$$_{pyridyl}$), 7.63–7.53 (4H, m, C(2+2'+6+6')$\underline{H}$$_{phenyl-A+B}$), 7.44–7.31 (7H, m, C(6)$\underline{H}$$_{pyridyl-A}$ + C(3+4+5)$\underline{H}$$_{phenyl-A}$ + C(3+4+5)$\underline{H}$$_{phenyl-B}$); δ_C (175 MHz, CDCl$_3$) 152.9 ($\underline{C}$(2)Cl$_{pyridyl}$), 147.3 ($\underline{C}$(6)H$_{pyridyl}$), 136.2 ($\underline{C}(4)_{pyridyl}$), 132.3 (2C, $\underline{C}$(2+6)H$_{phenyl-A}$), 132.0 (2C, $\underline{C}$(2+6)H$_{phenyl-B}$), 129.9 (2C, $\underline{C}$(3+5)H$_{phenyl-A}$), 129.5 (2C, $\underline{C}$(3+5)H$_{phenyl-B}$), 128.8 ($\underline{C}$(4)H$_{phenyl-A}$), 128.7 ($\underline{C}$(4)H$_{phenyl-B}$), 124.1 ($\underline{C}$(5)H$_{pyridyl}$), 122.7 ($\underline{C}$(1)$_{phenyl-A}$), 122.11 ($\underline{C}$(3)$_{pyridyl}$), 122.07 ($\underline{C}$(1)$_{phenyl-B}$), 101.0 (C≡$\underline{C}$-Ph$_A$), 99.5 (C≡$\underline{C}$-Ph$_B$), 85.9 ($\underline{C}$≡C-Ph$_A$), 84.1 ($\underline{C}$≡C-Ph$_B$); *m/z* (ES$^+$) 314.07294 (M$^+$+H, C$_{21}$H$_{12}$^{35}ClN+H requires 314.07310); ν_{max} (film)/cm^{-1} 3046, 2365, 2323, 2235, 2202, 1596, 1567, 1519, 1490, 1442, 1389, 1279, 1160, 901, 841, 754.

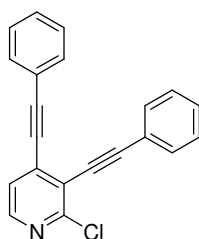**5-[3,4-Bis(2-phenylethynyl)pyridin-2-yl]-2-fluoropyridine 154.**
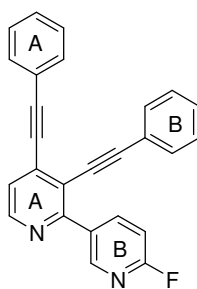
The general method for Suzuki–Miyaura cross-couplings was followed. A mixture of compound **153** (0.400 g, 1.38 mmol), **88** (0.216 g, 1.53 mmol), Pd(PPh$_3$)$_4$ (0.074 g, 0.06 mmol, 5 mol%), 1,4-dioxane (20 mL), Na$_2$CO$_3$ (1 M, 2.55 mL, 2.55 mmol) was stirred at reflux for 18 h. Standard work-up and concentration gave a brown residue which was purified by chromatography (SiO$_2$, EtOAc/hexane, 1:2 *v/v*) followed by recrystallisation from hexane and DCM yielded **154** as white needles (0.314 g, 66%). mp 124.3–124.9 ^{o}C; δ_H (700 MHz, CDCl$_3$) 8.95 (1H, d, *J* 2.4, C(6)$\underline{H}$$_{pyridyl-B}$), 8.58 (1H, d, *J* 5.0, C(6)$\underline{H}$$_{pyridyl-A}$), 8.50–8.37 (1H, m, C(4)$\underline{H}$$_{pyridyl-B}$), 7.65–7.51 (2H, m, C(2+6)$\underline{H}$$_{phenyl-A}$ + C(2+6)$\underline{H}$$_{phenyl-B}$), 7.50–7.28 (9H, m, C(2+3+4+6)$\underline{H}$$_{phenyl-A}$ + C(2+3+4+6)$\underline{H}$$_{phenyl-B}$ + C(5)$\underline{H}$$_{pyridyl-A}$), 7.04 (1H, dd, *J* 8.5, 2.7, C(3)$\underline{H}$$_{pyridyl-B}$); δ_C (175 MHz, CDCl$_3$) 163.9 (d, J_{CF} 241.2, $\underline{C}$(2)F$_{pyridyl-B}$), 156.1 ($\underline{C}$(2)$_{pyridyl-A}$), 148.8 (d, J_{CF} 15.4, $\underline{C}$(4)H$_{pyridyl-B}$), 148.2 ($\underline{C}$(6)$_{pyridyl-A}$), 142.3 (d, J_{CF} 8.0, $\underline{C}$(6)H$_{pyridyl-B}$), 135.6 ($\underline{C}$(4)$_{pyridyl-A}$), 133.4 (d, J_{CF} 4.6, $\underline{C}$(5)$_{pyridyl-B}$), 132.2 (2C, $\underline{C}$(2+6)H$_{phenyl-B}$), 131.7 (2C, $\underline{C}$(2+6)H$_{phenyl-A}$), 129.8 ($\underline{C}$(4)H$_{phenyl-B}$), 129.4 ($\underline{C}$(4)H$_{phenyl-A}$), 128.80 (2C, $\underline{C}$(3+5)H$_{phenyl-B}$), 128.77 (2C, $\underline{C}$(3+5)H$_{phenyl-A}$), 124.4 ($\underline{C}$(5)H$_{pyridyl-A}$), 122.6 ($\underline{C}$(1)$_{phenyl-B}$), 122.3 ($\underline{C}$(1)$_{phenyl-A}$), 119.8 ($\underline{C}$(3)$_{pyridyl-A}$), 108.9 (d, J_{CF} 37.4, $\underline{C}$(3)H$_{pyridyl-B}$), 99.8 (C≡$\underline{C}$-Ph$_B$), 98.9 (C≡$\underline{C}$-Ph$_A$), 86.4 ($\underline{C}$≡C-Ph$_B$), 85.9 ($\underline{C}$≡C-Ph$_A$); *m/z* (APCI$^+$) 375.1294 (M$^+$+H, C$_{26}$H$_{15}$N$_2$F+H requires 375.1298); ν_{max} (film)/cm^{-1} 3056, 2360, 2339, 2212, 1590, 1552, 1491, 1442, 1408, 1367, 1256, 1130, 1023, 899, 831, 740, 684.

7.5   Experimental Details for Chapter 5

4-*tert*-Butyl-*N*-(2-iodophenyl)benzamide 157

To a stirred solution of 2-iodoaniline **156** (6.571 g, 30 mmol) in EtOAc (60 mL) at room temperature was added 4-*tert*-butylbenzoyl chloride **155** (12.98 g, 66 mmol) dropwise, giving a cloudy white mixture which was heated to reflux for 24 h. The resulting homogeneous solution was cooled to room temperature and adjusted to pH 8 with 3 M NaOH. The organic components were separated and sequentially washed with water (50 mL), sat. aq. NaHCO$_3$ (50 mL) and brine (100 mL), dried over MgSO$_4$, filtered and concentrated, the residue was purified by column chromatography (SiO$_2$, eluent 8: 1 hexane: EtOAc *v/v*) yielding **157** as

a white solid (5.20 g, 46%). mp 157.1-158.0 °C. δ_H (400 MHz, CDCl$_3$) 8.68-8.59 (1 H, m, C(3)$\underline{H}$$_{phenyl-A}$), 8.01 (1 H, br s, N$\underline{H}$), 7.91 (2 H, d, *J* 8.5, C(2+6)$\underline{H}$$_{phenyl-B}$), 7.57-7.44 (1 H, m, C(6)$\underline{H}$$_{phenyl-A}$), 7.53 (2 H, d, *J* 8.5, C(3+5)$\underline{H}$$_{phenyl-B}$), 7.46 – 7.35 (1 H, m, C(5)$\underline{H}$$_{phenyl-A}$), 6.99 – 6.90 (1 H, m, C(4)$\underline{H}$$_{phenyl-A}$), 1.35 (9 H, s, C(C$\underline{H}$$_3$)$_3$); δ_C (100 MHz, CDCl$_3$) 164.9 ($\underline{C}$=O), 155.0 ($\underline{C}(4)_{phenyl-B}$), 136.7 ($\underline{C}$(1)N$_{phenyl-A}$), 131.6 ($\underline{C}$(3)H$_{phenyl-A}$), 131.3 ($\underline{C}(1)_{phenyl-B}$), 128.3 ($\underline{C}$(5)H$_{phenyl-A}$), 127.6 (2 C, $\underline{C}$(2+6)H$_{phenyl-B}$), 126.4 ($\underline{C}$(4)H$_{phenyl-A}$), 125.3 (2 C, $\underline{C}$(2+6)H$_{phenyl-B}$), 124.6 ($\underline{C}$(6)H$_{phenyl-A}$), 122.1 ($\underline{C}$(2)I$_{phenyl-A}$), 41.0 ($\underline{C}$(CH$_3$)$_3$), 31.4 (3 C, C($\underline{C}$H$_3$)$_3$); *m/z* (ES$^+$) 380.3 (M$^+$ + H); *Anal.* Calcd. for C$_{17}$H$_{18}$INO: C, 51.84; H, 4.78; N, 3.69. Found: C, 51.99; H, 4.50; N, 3.41.
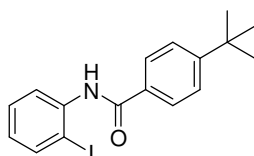
4-*tert*-Butyl-*N*-(2-bromophenyl)benzamide 160
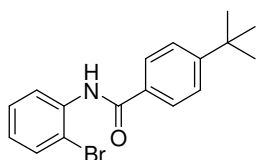
Dropwise addition of 4-*tert*-butylbenzoyl chloride **155** (4.72 g, 24 mmol) to a stirred solution of EtOAc (120 mL) and 2-bromoaniline **157** (3.44 g, 20 mmol) at room temperature gave a cloudy white mixture which was heated to reflux for 24 h. The homogeneous solution was cooled to room temperature and adjusted to pH 8 with 3 M NaOH. The organic components were separated and washed with brine (50 mL). The collected organic layer was dried over MgSO$_4$, filtered and concentrated and the residue was purified by column chromatography (SiO$_2$, eluent 10: 1 hexane: EtOAc *v/v*) yielding **160** as a white crystalline solid (5.45 g, 82%). mp 121.9-123.0 °C; δ_H (400 MHz, CDCl$_3$) 8.55 (1 H, dd, *J* 8.3, 1.5, C(3)$\underline{H}$$_{phenyl-A}$), 8.44 (1 H, br s, N$\underline{H}$), 7.86 (2 H, d, *J* 8.5, C(2+6)$\underline{H}$$_{phenyl-B}$), 7.56 (1 H, dd, *J* 8.0, 1.5, C(6)$\underline{H}$$_{phenyl-A}$), 7.52 (2 H, d, *J* 8.5, C(3+5)$\underline{H}$$_{phenyl-B}$), 7.40 – 7.31 (1 H, m, C(5)$\underline{H}$$_{phenyl-A}$), 7.03 – 6.96 (1 H, m, C(4)$\underline{H}$$_{phenyl-A}$), 1.35 (9 H, s, C(C$\underline{H}$$_3$)$_3$); δ_C (100 MHz, CDCl$_3$) 166.0 ($\underline{C}$=O), 154.3 ($\underline{C}(4)_{phenyl-B}$), 137.3 ($\underline{C}$(1)N$_{phenyl-A}$), 131.8 ($\underline{C}$(3)H$_{phenyl-A}$), 131.4 ($\underline{C}$(5)H$_{phenyl-A}$), 128.1 ($\underline{C}(1)_{phenyl-B}$), 127.7 (2C, $\underline{C}$(2+6)H$_{phenyl-B}$), 126.5 ($\underline{C}$(4)H$_{phenyl-A}$), 125.0 (2C, $\underline{C}$(3+5)H$_{phenyl-B}$), 124.1 ($\underline{C}$(6)H$_{phenyl-A}$), 122.0 ($\underline{C}$(2)Br$_{phenyl-A}$), 41.0 ($\underline{C}$(CH$_3$)$_3$), 31.4 (C($\underline{C}$H$_3$)$_3$); *m/z* (ES$^+$) 333.3 (M$^+$ + H); *Anal.* Calcd. for C$_{17}$H$_{18}$BrNO: C, 61.46; H, 5.46; N, 4.22. Found: C, 61.27; H, 5.50; N, 64.31.

2-(4-*tert*-Butylphenyl)-1-(2-bromophenyl)-1*H*-benzo[*d*]imidazole 158

4-*tert*-Butyl-*N*-(2-iodophenyl)benzamide **157** (3.03 g, 8.00 mmol), 2-bromoaniline **159** (2.06 g, 12.0 mmol), K_3PO_4 (5.10 g, 24.0 mmol), RuPhos **41** (0.299 g, 0.640 mmol) and $Pd_2(dba)_3$ (0.073 g, 0.080 mmol, 1 mol%) were added to an argon purged round-bottom flask fitted with a condenser. To this, degassed *t*-butanol (24 mL) was added *via* syringe and the mixture was stirred under argon at reflux. The reaction was judged complete by TLC after 82 h. The mixture was allowed to cool to room temperature and passed through celite eluting with DCM: EtOAc 3:1 *v/v* (400 mL). The eluent was concentrated *in vacuo* and redissolved in 1,4-dioxane (30 mL). To this was added 4 M HCl (32 mL) and the stirred mixture was heated to 100 °C for 16 h, allowed to cool to room temperature and followed by slow addition of 3 M NaOH (53 mL). The 1,4-dioxane was removed *in vacuo* and the residue was extracted into EtOAc (3 x 150 mL) and washed with $NaHCO_3$, the combined organic organic layers were dried over Na_2SO_4, filtered and concentrated to yield a black residue which was purified by chromatography (SiO_2, 3 : 1 hexane : EtOAc *v/v*) and recrystallised from hexane/DCM to give **158** as colourless crystals (0.45 g, 14%). mp 100.9-101.6 °C; δ_H (700 MHz, d_6-acetone) 7.91 (1H, d, *J* 8.0, C(7)$\underline{H}$benzimidazole), 7.77 (1H, d, *J* 8.0, C(3)$\underline{H}$phenyl-B), 7.70 – 7.62 (2H, m, C(2+6)$\underline{H}$phenyl-A), 7.60 – 7.56 (3H, m, C(5+6+8)$\underline{H}$benzimidazole), 7.40 (2H, d, *J* 8.5, C(3+5)$\underline{H}$phenyl-A), 7.31 (1H, dd, *J* 8.0, 7.6, C(5)$\underline{H}$phenyl-B), 7.25 (1H, dd, *J* 8.0, 7.6 C(4)$\underline{H}$phenyl-B), 6.98 (1H, d, *J* 8.0, C(6)$\underline{H}$phenyl-B), 1.30 (9H, s, C(C$\underline{H}_3$)$_3$); δ_C (175 MHz, $d6$-acetone) 152.6 ($\underline{C}$(4)phenyl-A), 151.9 ($\underline{C}$(2)benzimidazole), 143.2 ($\underline{C}$(1)Nphenyl-B), 137.2 ($\underline{C}$(4)benzimidazole), 136.7 ($\underline{C}$(11)benzimidazole), 134.0 ($\underline{C}$(3)Hphenyl-B), 131.3 ($\underline{C}$(4)Hphenyl-B), 130.9 ($\underline{C}$(5)Hphenyl-B), 129.4 ($\underline{C}$(1)phenyl-A), 128.3 (2C, $\underline{C}$(2+6)Hphenyl-A), 127.6 ($\underline{C}$(6)Hphenyl-B), 125.2 (2C, $\underline{C}$(3+5)Hphenyl-A), 123.1 ($\underline{C}$(5)Hbenzimidazole), 122.7 ($\underline{C}$(6)Hbenzimidazole), 122.6 ($\underline{C}$(4)Hbenzimidazole), 119.5 ($\underline{C}$(7)Hbenzimidazole), 110.3 ($\underline{C}$(2)Brphenyl-B), 34.4 ($\underline{C}$(CH$_3$)$_3$), 30.5 (3C, C($\underline{C}$H$_3$)$_3$); *m/z* (ES$^+$) 405.3 (M$^+$), 407.2 (M$^+$+H); *Anal.* Calcd. for $C_{23}H_{21}BrN_2$: C, 68.15; H, 5.22; N, 6.91. Found: C, 68.19; H, 5.28; N, 6.88.

6-*tert*-Butylbenzimidazolo[1,2-*f*]phenanthridine 161

To a Schlenk tube was added **158** (0.200 g, 0.4934 mmol), Pd(OAc)$_2$ (0.0033 g, 0.0148 mmol, 3 mol%), DavePhos (0.0058 g, 0.0148 mmol), pivalic acid (0.0151 g, 0.1480 mmol) and K$_2$CO$_3$ (0.1705 g, 1.234 mmol). The tube was evacuated and backfilled twice with argon. Degassed DMA (10.5 mL) was added and the mixture was stirred at 130 $^{\circ}$C under argon for 16 h whereupon TLC analysis showed completion. The reaction mixture was concentrated *in vacuo* and the residue filtered through a silica plug with EtOAc (350 mL). The filtrate was concentrated *in vacuo* and purified *via* column chromatography (SiO$_2$, 13 : 1 toluene : EtOAc *v/v*) to give **161** as a white solid (0.099 g, 62%). mp 144.5-145.1 $^{\circ}$C; δ_H (400 MHz, CDCl$_3$) 8.81 (1 H, d, *J* 8.4, C(6)<u>H</u>), 8.61 (1 H, d, *J* 7.9, C(9)<u>H</u>), 8.57 (1 H, d, *J* 7.0, C(4)<u>H</u>), 8.42 (1 H, d, *J* 1.8, C(19)<u>H</u>), 8.38 (1 H, d, *J* 7.7, C(12)<u>H</u>), 8.10 – 7.98 (1 H, m, C(10)<u>H</u>), 7.77 (1 H, dd, *J* 8.5, 1.8, C(17)<u>H</u>), 7.76 – 7.68 (1 H, m, C(11)<u>H</u>), 7.60 – 7.42 (3 H, m, C(3+5+6)<u>H</u>), 1.50 (9 H, s, C(C<u>H</u>$_3$)$_3$); δ_C (100 MHz, CDCl$_3$) 153.0 (<u>C</u>(18)), 149.8 (<u>C</u>(1)), 138.5 (<u>C</u>(2)), 137.7 (<u>C</u>(14)H), 135.6 (<u>C</u>(7)), 131.0 (<u>C</u>(8)), 129.4 (<u>C</u>(10)H), 129.0 (<u>C</u>(9)H), 128.9 (<u>C</u>(16)H), 127.8 (<u>C</u>(12)H), 127.6 (<u>C</u>(11)H), 125.0 (<u>C</u>(17)H), 124.4 (<u>C</u>(13)), 123.3 (<u>C</u>(19)H), 123.1 (<u>C</u>(4)H), 123.0 (<u>C</u>(5)H), 118.1 (<u>C</u>(15)), 115.4 (<u>C</u>(3)H), 115.3 (<u>C</u>(6)H), 40.9 (<u>C</u>(CH$_3$)$_3$), 31.1 (3C, C(<u>C</u>H$_3$)$_3$); *m/z* (ES$^+$) 325.2 (M$^+$+H), 309.2 (M$^+$-CH$_3$); *Anal.* Calcd. for C$_{23}$H$_{20}$N$_2$: C, 85.15; H, 6.21; N, 8.63. Found: C, 85.26; H, 5.97; N, 8.60.

7.6   Experimental Details for Chapter 6

2-Chloro-4-mesitylpyridine 166

In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted mesitylboronic acid (1.39 g , 5.05 mmol), 2-chloro-4-iodopyridine **165** (1.20 g, 5.00 mmol), Pd$_2$(dba)$_3$ (0.023 g, 0.025 mmol, 0.5 mol%), PCy$_3$ (0.017 g, 0.060 mmol) and K$_3$PO$_4$ (3.7 mL, 8.50 mmol, 1.27 M in water) in 1,4-dioxane (13.5 mL) at 80 $^{\circ}$C for 16 h then at 100 $^{\circ}$C for a further 4 h. Standard work-up and concentration gave a yellow oil which was purified *via* column chromatography (SiO$_2$, eluent 1 : 5 EtOAc: hexane *v/v*) followed by vacuum distillation (Kugel Rohr, 120 $^{\circ}$C, 0.27 mbar) yielding **166** as a colourless oil (0.990 g, 85%

yield). δ_H (400 MHz; CDCl$_3$) 8.46 (1H, d, *J* 5.1, C(6)$\underline{H}$$_{pyridyl}$), 7.18 (1H, d, *J* 1.4, C(3)$\underline{H}$$_{pyridyl}$), 7.06 (1H, dd, *J* 1.4, 5.1, C(5)$\underline{H}$$_{pyridyl}$), 6.97 (2H, s, C(3+5)$\underline{H}$$_{phenyl}$), 2.02 (6H, s, 2 x C$\underline{H}$$_3$), 2.35 (3H, s, C$\underline{H}$$_3$; δ_C (125 MHz; CDCl$_3$) 153.1 ($\underline{C}(4)_{pyridyl}$), 152.1 ($\underline{C}$(6)H$_{pyridyl}$), 150.1 ($\underline{C}$(2)Cl$_{pyridyl}$), 138.3 ($\underline{C}(4)_{phenyl}$), 135.19 ($\underline{C}(1)_{phenyl}$), 135.16 (2C, $\underline{C}$(2+6)$_{phenyl}$), 128.7 (2C, $\underline{C}$(3+5)H$_{phenyl}$), 125.4 ($\underline{C}$(5)H$_{pyridyl}$), 123.9 ($\underline{C}$(3)H$_{pyridyl}$), 21.3 (2 x CH$_3$), 20.8 ($\underline{C}$H$_3$); *m/z* (EI) 230.9 (M$^+$), 196.0 (M$^+$-Cl); *m/z* (APCI$^+$) 231.0808 (M$^+$, C$_{14}$H$_{14}$NCl requires 231.0815).

2,6-Difluoro-3-(4-mesitylpyridin-2-yl)pyridine 168

In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted 2,6-difluoropyridin-3-yl-3-boronic acid MIDA ester **167** (2.10 g , 7.77 mmol), **166** (1.50 g, 6.47 mmol), Pd$_2$(dba)$_3$ (0.089 g, 0.097 mmol, 1.5 mol%), PCy$_3$ (0.065 g, 0.233 mmol) and K$_3$PO$_4$ (16.2 mL, 48.6 mmol, 1.27 M in water) in 1,4-dioxane (80 mL) at 60 ^{o}C h. Standard work-up and concentration gave a brown solid which was purified *via* column chromatography (SiO$_2$, eluent EtOAc: hexane 1: 4 *v/v*) and recrystallisation from methanol yielding **168** as a white solid (0.69 g, 34% yield). mp 74.5-75.9 ^{o}C; δ_H (400 MHz, CDCl$_3$) 8.96 – 8.65 (2 H, m, C(6)$\underline{H}$$_{pyridyl-A}$ + C(4)$\underline{H}$$_{pyridyl-B}$), 7.71 (1 H, d, *J* 1.5, C(3)$\underline{H}$$_{pyridyl-B}$), 7.18 (1H, dd, *J* 5.0, 1.5, C(5)$\underline{H}$$_{pyridyl-A}$), 7.03 (1H, dd, *J* 8.2, 3.0, C(5)$\underline{H}$$_{pyridyl-B}$), 7.00 (2H, s, C(3+5)$\underline{H}$$_{phenyl}$), 2.37 (3H, s, (2 x C$\underline{H}$$_3$)), 2.06 (6H, s, (C$\underline{H}$$_3$)); δ_C (125 MHz, CDCl$_3$) 164.8 (dd, *J*$_{CF}$ 244.0, 13.6, $\underline{C}$(2)F$_{pyridyl-B}$), 163.5 (dd, *J*$_{CF}$ 246.3, 14.7, $\underline{C}$(2)F$_{pyridyl-B}$), 151.9 ($\underline{C}$(2)$_{pyridyl-A}$), 151.0 ($\underline{C}$(4)$_{pyridyl-A}$), 148.5 ($\underline{C}$(6)$_{pyridyl-A}$), 145.0 (d, *J*$_{CF}$ 4.4, $\underline{C}$(4)F$_{pyridyl-B}$), 138.9 ($\underline{C}$(4)$_{phenyl}$), 138.0 ($\underline{C}$(1)$_{phenyl}$), 137.2 (2C, $\underline{C}$(2+6)$_{phenyl}$), 128.1 (2C, $\underline{C}$(3+5)H$_{phenyl}$), 120.8 (dd, *J*$_{CF}$ 26.2, 5.7, $\underline{C}$(3)$_{pyridyl-B}$), 118.7 ($\underline{C}$(3)H$_{pyridyl-A}$), 114.3 ($\underline{C}$(5)H$_{pyridyl-A}$), 107.7 (dd, *J*$_{CF}$ 35.5, 5.2, $\underline{C}$(3)$_{pyridyl-B}$), 24.7 (C$\underline{H}$$_3$), 18.1 (2 x C$\underline{H}$$_3$); *m/z* (ES$^+$) 311.3 (M$^+$ + H); *Anal.* Calcd. for C$_{19}$H$_{16}$F$_2$N$_2$: C, 73.53; H, 5.20; N, 9.03. Found: C, 73.70; H, 5.09; N, 9.12.

G0PyF$_2$-Ir-pic 164

To a round bottom flask was added **168** (1.20 g, 3.88 mmol), IrCl$_3$.3H$_2$O (0.583 g, 1.65 mmol) followed by 2-ethoxyethanol (32 mL) and water (12 mL). The mixture was stirred at 110 ^{o}C under argon for 16 h then water (130 mL) was added and the resulting yellow precipitate was collected by filtration and washed sequentially with water (100 mL) and a mixture of ethanol and acetone (1: 1 *v/v* 80 mL). The yellow solid was transferred to a reaction flask along with picolinic acid (0.952 g, 7.733 mmol) and ethoxyethanol (20 mL) and stirred at 110 ^{o}C under argon for 16 h and purified by chromatography (SiO$_2$, 2 : 1 hexane : EtOAc *v/v*), (SiO$_2$, 4 : 1 DCM : EtOAc *v/v*), (SiO$_2$, 5 : 1 *v/v* DCM : EtOAc) to yield **164** as a pale yellow solid (0.708 g, 46%). mp > 300 ^{o}C; δ_H (400 MHz, CDCl$_3$) 8.81 (1H, d, *J* 5.8), 8.42 (1H, d, *J* 7.7), 8.17 – 8.02 (3H, m), 7.89 (1H, dd, *J* 5.4, 0.5), 7.61 – 7.51 (1H, m), 7.46 (1H, d, *J* 5.8), 7.16 (1H, dd, *J* 5.8, 1.6), 7.08 – 6.87 (5H, m), 5.81 (1H, t, *J* 1.7), 5.55 (1H, t, *J* 1.7), 2.34 (6H, s), 2.13 (3H, s), 2.10 (3H, s), 2.07 (3H, s), 1.95 (3H, s); δ_C (125 MHz, CDCl$_3$) 172.7, 171.7 – 169.5 (2C, m), 163.9, 162.4 (d), 162.3 – 161.5 (2C, m), 160.1 (d, *J* 67.6), 159.0, 157.5 – 156.0 (3C, m), 153.8 (d, *J* 3.9), 151.5, 148.9, 148.6, 148.2, 139.5, 138.9 (d, *J* 5.8), 135.5, 135.1 (d, *J* 36.1), 134.8 (d, *J* 3.6), 129.1 (dd, *J* 35.1, 17.7), 125.8 – 124.1 (2C, m), 109.6 (t, *J* 31.7), 31.9, 21.3, 21.1, 20.9; *m/z* (MALDI$^+$) 933.2 (M$^+$); *m/z* (ES$^+$) 932.23382 (M$^+$+H, C$_{44}$H$_{35}$O$_2$N$_5$F$_4$Ir requires 932.23274).

5-(2-Ethylhexyloxy)-2-bromo-1,3-dimethylbenzene 171

A mixture of 4-bromo-3,5-dimethylphenol **170** (53.80 g, 267.6 mmol), 2-ethylhexylbromide (62.02 g, 321.1 mmol) and K$_2$CO$_3$ (55.47 g, 401.4 mmol) in DMF (300 mL) was reacted at 78 ^{o}C overnight. The mixture was allowed to cool to room temperature and filtered, washing the filtercake with Et$_2$O (3 x 300 mL). The filtrate was diluted with water (900 mL) and the layers were separated. The aqueous layer was extracted with Et$_2$O (2 x 300 mL) and the combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated *in vacuo* . The oil was purified by washing through a SiO$_2$ plug with 4 : 1 *v/v* hexane : EtOAc (*ca.* 1L) to give **171** as a clear oil (74.24 g, 89% yield). δ_H (400 MHz; CDCl$_3$) 6.66 (2H, s, C(4+6)$\underline{H}_{phenyl}$), 3.80 (2H, dd, *J* 5.6, 1.6, O-C$\underline{H}_2$), 2.39 (6H, s, 2 x C$\underline{H}_{3\ phenyl}$), 1.71 (1H, heptet, *J* 6.1, C$\underline{H}$), 1.37 - 1.54 (4H, m, 2 x CH$_2$C$\underline{H}_2$), 1.28 - 1.37 (4H, m, 2 x C$\underline{H}_2$CH$_3$),

0.93 (3H, t, *J* 7.6, CH$_2$C$\underline{H}_3$), 0.92 (3H, t, *J* 7.0, CH$_2$C$\underline{H}_3$); δ$_C$ (100 MHz; CDCl$_3$) 157.9 ($\underline{C}$(5)O$_{phenyl}$), 139.0 (2C, $\underline{C}$(1+3)$_{phenyl}$), 117.9 ($\underline{C}$(2)Br$_{phenyl}$), 114.4 (2C, $\underline{C}$(4+6)H$_{phenyl}$), 70.6 (O-$\underline{C}$H$_2$), 39.4 ($\underline{C}$H), 30.5 (CH-$\underline{C}$H$_2$), 29.1 (CH$_2$-$\underline{C}$H$_2$), 24.0 ($\underline{C}$H$_2$-CH$_3$), 23.9 ($\underline{C}$H$_2$-CH$_3$), 23.0 (CH$_2$-$\underline{C}$H$_3$), 14.1 (CH$_2$-$\underline{C}$H$_3$), 11.1 (2C, 2 x $\underline{C}$H$_3$ $_{phenyl}$); *m/z* (APCI$^+$) 314.1093 (M$^+$, C$_{16}$H$_{25}$BrO requires 314.1068).

4-(2-Ethylhexyloxy)-2,6-dimethylphenylboronic acid 172

To a stirred solution of 5-(2-ethylhexyloxy)-2-bromo-1,3-dimethylbenzene **171** (20 g, 63.84 mmol) in dry THF (400 mL) at -78 ^{o}C under argon was added ^{n}BuLi (2.5 M in hexane, 29.88 mL, 74.7 mmol) dropwise, maintaining the reaction temperature at -78 ^{o}C. The resulting solution was stirred for 1.5 h followed by slow addition of triisopropyl borate (22.1 mL, 95.76 mmol). The resulting mixture was allowed to react for 1 h. The reaction was quenched at -78 ^{o}C with sat. aq. NH$_4$Cl (700 mL) and stirred at room temperature overnight. The organics were extracted into EtOAc (3 x 600 mL), dried over MsSO$_4$, filtered and concentrated *in vacuo*. The resulting crude oil was purified by chromatography (SiO$_2$, hexane : EtOAc 2 : 1 *v/v*) followed by recrystallisation from hexane to give **172** as a white solid (7.11 g, 40%). mp 36.2-37.9 ^{o}C; δ$_H$ (400 MHz; *d$_6$*-acetone) 6.56 (2H, s, C(4+6)$\underline{H}_{phenyl}$), 3.85 (2H, dd, *J* 5.8, 0.8, O-C$\underline{H}_2$), 2.90 (2H, s, B(O$\underline{H}$)$_2$), 2.25 (6H, s, 2 x C$\underline{H}_3$ $_{phenyl}$), 1.70 (1H, heptet, *J* 6.0, C$\underline{H}$), 1.39 – 1.58 (4H, m, 2 x CH$_2$C$\underline{H}_2$), 1.28 – 1.39 (4 H, m, 2 x C$\underline{H}_2$CH$_3$), 0.94 (3H, t, *J* 7.4, CH$_2$C$\underline{H}_3$), 0.92 (3H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ$_C$ (125 MHz; *d$_6$*-acetone) 159.5 ($\underline{C}$(5)O$_{phenyl}$), 140.9 (2C, $\underline{C}$(1+3)$_{phenyl}$), 112.3 (2C, $\underline{C}$(4+6)H$_{phenyl}$), 69.8 (O-$\underline{C}$H$_2$), 39.6 ($\underline{C}$H), 30.7 (CH-$\underline{C}$H$_2$), 29.1 (CH$_2$-$\underline{C}$H$_2$), 23.1 ($\underline{C}$H$_2$-CH$_3$), 23.4 ($\underline{C}$H$_2$-CH$_3$), 21.9 (CH$_2$-$\underline{C}$H$_3$), 13.7 (CH$_2$-$\underline{C}$H$_3$), 10.8 (2C, 2 x $\underline{C}$H$_3$ $_{phenyl}$); *Anal.* Calcd. for C$_{16}$H$_{27}$BO$_3$: C, 69.08; H, 9.78. Found: C, 69.40; H, 9.98

4-(4-(2-Ethylhexyloxy)-2,6-dimethylphenyl)pyridine 173

In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted 4-bromopyridine hydrochloride (4.667 g, 24 mmol), 4-(2-ethylhexyloxy)-2,6-dimethylphenylboronic acid **172** (6.677 g, 24 mmol), Pd(PPh$_3$)$_4$ (0.2773 g, 0.24 mmol, 1 mol%) and K$_3$PO$_4$ (33.92 g, 108 mmol) in degassed dioxane/H$_2$O (170 mL / 54 mL) at 100 ^{o}C for 48 h. Standard work-up conditions and purification *via* chromatography (SiO$_2$, 2 : 1 *v/v* hexane : EtOAc) provided **173** as a yellow oil (6.80 g, 91%). δ$_H$ (400 MHz; *d$_6$*-acetone)

8.65 (2H, d, *J* 6.0, C(2+6)$\underline{H}_{pyridyl}$), 7.16 (2H, d, *J* 6.0, C(3+5)$\underline{H}_{pyridyl}$), 6.75 (2H, s, C(3+5)$\underline{H}_{phenyl}$), 3.93 (2H, d, *J* 5.6, O-C$\underline{H}_2$), 2.00 (6H, s, 2 x C$\underline{H}_{3\ phenyl}$), 1.75 (1H, heptet, *J* 6.0, C$\underline{H}$), 1.42 – 1.61 (4H, m, 2 x CH$_2$C$\underline{H}_2$, 2 x CH$_2$C$\underline{H}_2$), 1.29 – 1.42 (4H, m, 2 x C$\underline{H}_2$CH$_3$), 0.97 (3H, t, *J* 7.6, CH$_2$C$\underline{H}_3$), 0.93 (3H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; *d$_6$*-acetone) 158.8 ($\underline{C}$(5)O$_{phenyl}$), 149.9 (2C, $\underline{C}$(2,6)H$_{pyridyl}$), 148.9 ($\underline{C}$(4)$_{pyridyl}$), 136.3 (2C, $\underline{C}$(1+3)$_{phenyl}$), 131.6 ($\underline{C}$(2)$_{phenyl}$), 128.7 ($\underline{C}$(5)O$_{phenyl}$), 113.5 (2C, $\underline{C}$(4+6)H$_{phenyl}$), 69.9 ($\underline{C}$(5)O$_{phenyl}$), 39.4 ($\underline{C}$H), 30.4 (CH-$\underline{C}$H$_2$), 29.1 (CH$_2$-$\underline{C}$H$_2$), 23.7 ($\underline{C}$H$_2$-CH$_3$), 22.8 ($\underline{C}$H$_2$-CH$_3$), 20.0 (CH$_2$-$\underline{C}$H$_3$), 13.4 (CH$_2$-$\underline{C}$H$_3$), 10.5 (2C, 2 x $\underline{C}$H$_{3\ phenyl}$); *m/z* (APCI$^+$) 312.2324 (M+H$^+$, C$_{21}$H$_{30}$NO$^+$ requires 312.2327).

2-Cyano-4-(4-(2-ethylhexyloxy)-2,6-dimethylphenyl)pyridine 174

    To 4-(4-(2-ethylhexyloxy)-2,6-dimethylphenyl)pyridine **173** (6.6 g, 21.19 mmol) in DCM (220 mL) was added *meta*-chloroperoxybenzoic acid (16.07 g, 4.40 mmol) and the resulting mixture stirred at room temperature with TLC monitoring. After 24 h, NaOH (200 mL, 3M) was added and the organic layer was separated, washed with brine and the organics dried over MgSO$_4$, filtered and concentrated *in vacuo*. The resulting residue, presumed to contain 4-(4-(2-ethylhexyloxy)-2,6-dimethylphenyl)pyridine-*N*-oxide (*ca.* 8 g), was dissolved in dry DCM (33 mL) under dry argon. To this stirred mixture was added TMS-CN (3.5 mL, 27.65 mmol) slowly *via* syringe followed by *N,N*-dimethylcarbamyl chloride (2.5 mL, 27.55 mmol) slowly *via* syringe. The reaction was stirred at room temperature under argon with TLC monitoring. After 24 h, the reaction was quenched with K$_2$CO$_3$ (21.2 mL, 1 M) and stirred open to the air for *ca.* 1 h. The mixture was separated, washing with DCM (2 x 150 mL) and the combined organic fractions were dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The resulting residue was purified *via* column chromatography (SiO$_2$, 1 : 1 *v/v* hexane : EtOAc) yielding **174** as a yellow oil (2.35 g, 33%). δ_H (400 MHz, CDCl$_3$) 8.73 (1 H, dd, *J* 5.0, 0.9, C(5)$\underline{H}_{pyridyl}$), 7.50 (1 H, dd, *J* 1.6, 0.9, C(3)$\underline{H}_{pyridyl}$), 7.31 (1 H, dd, *J* 5.0, 1.6, C(6)$\underline{H}_{pyridyl}$), 6.67 (2 H, s, C(3+5)$\underline{H}_{phenyl}$), 3.94 – 3.76 (2 H, m, O-C$\underline{H}_2$), 1.97 (6 H, s, 2 x C$\underline{H}_{3\ phenyl}$), 1.70 (1 H, heptet, *J* 6.0, C$\underline{H}$), 1.60 – 1.30 (8 H, m, 4 x C$\underline{H}_2$), 0.91 (6 H, 2 x d, *J* 10.9, 7.1, 2 x CH$_2$C$\underline{H}_3$); δ_C (175 MHz, CDCl$_3$) 159.6 ($\underline{C}$(5)O$_{phenyl}$), 151.4 ($\underline{C}$(4)$_{pyridyl}$), 151.4 ($\underline{C}$(6)H$_{pyridyl}$), 136.6 (2C, $\underline{C}$(1+3)H$_{phenyl}$), 134.5, ($\underline{C}$(2)CN$_{pyridyl}$), 130.3 ($\underline{C}$(2)$_{phenyl}$), 129.4 ($\underline{C}$(3)H$_{pyridyl}$), 128.8 ($\underline{C}$(5)H$_{pyridyl}$), 117.5 ($\underline{C}$≡N), 114.1 (2C, $\underline{C}$(4+6)H$_{phenyl}$), 70.6 ($\underline{C}$(5)O$_{phenyl}$), 39.6 ($\underline{C}$H), 30.8 (CH-$\underline{C}$H$_2$), 29.3 (CH$_2$-$\underline{C}$H$_2$), 24.1 ($\underline{C}$H$_2$-

CH$_3$), 23.3 (C$\underline{H}_2$-CH$_3$), 21.1 (CH$_2$-C$\underline{H}_3$), 14.3 (CH$_2$-C$\underline{H}_3$), 11.3 (2C, 2 x C$\underline{H}_3$ $_{phenyl}$); *m/z* (APCI$^+$) 337.2267 (M$^+$ + H, C$_{22}$H$_{29}$N$_2$O requires 337.2280).

4-(4-(2-Ethylhexyloxy)-2,6-dimethylphenyl)pyridine-2-carboxylic acid "G1pic" 175

To a solution of 2-cyano-4-(4-(2-ethylhexyloxy)-2,6-dimethylphenyl)pyridine **174** (2.20 g, 6.54 mmol) in 1,4-dioxane (50 mL) was added HCl (82 mL, 6 M) and the resulting mixture was stirred at reflux for 48 h with TLC monitoring. The reaction was allowed to cool to room temperature and remaining starting material was carefully extracted into hexane (2 x 50 mL). The product was then extracted from the aqueous layer with EtOAc (2 x 150 mL) and the organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated. The yellow solid was recrystallised from a mixture of hexane and EtOAc to yield **175** as white, plate-like crystals (1.10 g, 47%). mp 150.4-151.6 ^{o}C; δ_H (500 MHz, CDCl$_3$) 8.65 (1H, d, *J* 5.0, C(6)$\underline{H}$$_{pyridyl}$), 8.03 (1H, s C(3$\underline{H}$$_{pyridyl}$), 7.37 (1H, d, *J* 5.0, C(5)$\underline{H}$$_{pyridyl}$), 6.65 (2H, s, C(4+6)$\underline{H}$$_{phenyl}$), 3.87 – 3.77 (2H, m, O-C$\underline{H}_2$), 1.95 (6H, s, 2 x C$\underline{H}_3$ $_{phenyl}$), 1.70 (1H, hept, *J* 5.9, C$\underline{H}$), 1.57 – 1.18 (8H, m, 4 x C$\underline{H}_2$), 0.97 – 0.82 (6H, m, , 2 x CH$_2$C$\underline{H}_3$); δ_C (125 MHz, CDCl$_3$) 164.4 ($\underline{C}$(O)OH), 159.4 ($\underline{C}$(5)O$_{phenyl}$), 153.0 ($\underline{C}$(4) $_{pyridyl}$, 148.3 ($\underline{C}$(6)H$_{pyridyl}$), 146.5 ($\underline{C}$(2)$_{pyridyl}$), 136.7 (2C, $\underline{C}$(1+3)$_{phenyl}$), 130.1 ($\underline{C}$(2)$_{phenyl}$), 129.8 ($\underline{C}$(5)H$_{pyridyl}$), 125.6 ($\underline{C}$(3)H$_{pyridyl}$), 114.0 (2C, $\underline{C}$(4+6)H$_{phenyl}$), 70.5 ($\underline{C}$O$_{Alk}$), 39.7 $\underline{C}$H $\underline{C}$(5)O$_{phenyl}$), 30.8 (CH-$\underline{C}$H$_2$), 29.3 (CH$_2$-$\underline{C}$H$_2$), 24.1 (C$\underline{H}_2$-CH$_3$), 23.3 (C$\underline{H}_2$-CH$_3$), 21.2 (CH$_2$-$\underline{C}$H$_3$), 14.4 (CH$_2$-$\underline{C}$H$_3$), 11.4 (2C, 2 x C$\underline{H}_3$ $_{phenyl}$); *m/z* (ES$^+$) 356.2233 (M$^+$ + H, C$_{22}$H$_{30}$NO$_3$ requires 356.2226).
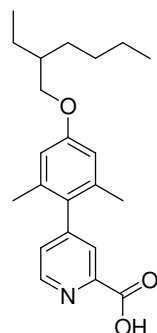
"G0PhF$_2$-Ir-G1Pic" 177
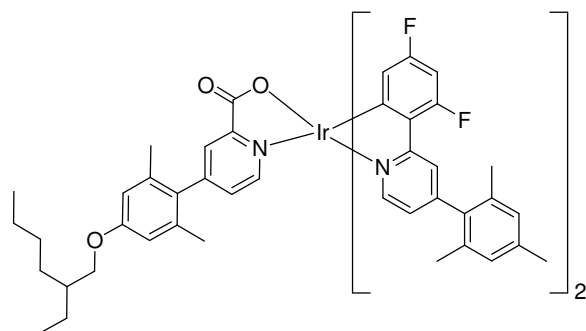
A mixture of **176** (0.100 g, 0.059 mmol), **175** (0.126 g, 0.355 mmol) and Na$_2$CO$_3$ (0.038 g, 0.355 mmol) in ethoxyethanol (12 mL) was stirred at 130 ^{o}C under argon for 16 h. After cooling to room temp., the product mixture was purified by chromatography (SiO$_2$, DCM : EtOAc 10 : 1 *v/v*), (SiO$_2$, DCM : EtOAc 15 : 1 *v/v*) to yield **177** as a yellow solid (0.012 g, 9%). mp > 300 ^{o}C; δ_H (700 MHz, CDCl$_3$) 8.85 (1H, d, *J* 5.1), 8.18 (1H, s), 8.13 (1H, s), 8.06 (1H, s), 7.87 (1H, d, *J* 4.9), 7.58 (1H, d, *J* 5.1), 7.25 (1H, s), 7.06 (1H, d, *J* 5.0), 6.99 (4H, t, *J*

22.8), 6.84 (1H, d, *J* 5.0), 6.66 (2H, d, *J* 13.6), 6.47 (1H, t, *J* 10.2), 6.40 (1H, t, *J* 10.4), 5.86 (1H, d, *J* 8.6), 5.71 (1H, d, *J* 8.3), 3.83 (2H, s), 2.35 (6H, s), 2.18 (3H, s), 2.13 (3H, s), 2.11 (3H, s), 1.91 (3H, s), 1.75 – 1.68 (1H, m), 1.54 – 1.29 (8H, m), 0.97 – 0.86 (6H, m); δ_C (175 MHz, CDCl$_3$) 173.0, 165.9 (d, *J* 6.3), 164.3 (d, *J* 7.5), 162.3 (ddd, *J* 266.5, 258.3, 9.8), 162.2 (ddd, *J* 355.9, 257.5, 9.0), 159.3, 152.9 (d, *J* 11.6), 152.6, 152.3 (d, *J* 8.5), 151.7, 151.3 (d, *J* 7.3), 148.5, 148.0, 147.8, 138.2 (d, *J* 11.2), 136.1 (4C), 135.3 (d, *J* 3.0), 135.1 (dd, *J* 99.6, 48.0), 130.1 (d, *J* 30.7), 129.5 (4C), 129.0 – 128.1 (6C, m), 124.9 – 123.3 (3C, m), 114.4 (t, *J* 18.6), 113.8 (2C), 98.1 (t, *J* 27.2), 97.7 (t, *J* 26.9), 70.3, 39.4, 30.5, 29.1, 23.9 (2C), 23.0 (2C), 21.0 (2C), 20.9, 20.6, 20.5, 20.3, 14.1, 11.1; *m/z* (ES$^+$) 1098.36872 (M$^+$+H, C$_{62}$H$_{61}$F$_4$IrN$_3$O$_3$ requires 1098.36898).

2,4,6-Tribromo-3,5-dimethylbenzenamine 179[356]
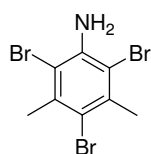
To a solution of 3,5-dimethylaniline **178** (19.42 g, 160 mmol) in AcOH (340 mL) at 0 °C was added Br$_2$ (26 mL, 500 mmol) dropwise. After the addition, the reaction was allowed to warm to room temp. and H$_2$O (500 mL) added. The precipitate was filtered and washed with H$_2$O (2 x 500 mL). The pink solid was triturated with MeOH to afford the desired product as a light pink solid (53.9 g, 94%). mp 195.7-196.7 °C; δ_H (400 MHz, CDCl$_3$) 4.69 (2H, br s, N$\underline{H}_2$), 2.57 (6H, s, 2 x C$\underline{H}_3$); δ_C (101 MHz, CDCl$_3$) 141.50 ($\underline{C}$(1)N), 136.91 (2C, $\underline{C}$(3+5)), 114.83 ($\underline{C}$(4)Br), 108.90 (2C, $\underline{C}$(2+6)Br), 25.79 (6C, 2 x C$\underline{H}_3$); *m/z* (EI) 356.7 (100%, [^{79}Br$_2$][^{81}Br]M$^+$), 358.7 (97%, [^{79}Br][^{81}Br$_2$]M$^+$); *Anal.* Calcd. for C$_8$H$_8$Br$_3$N: C, 26.85; H, 2.25; N, 3.91. Found: C, 26.44; H, 1.78; N, 3.51.

1,3,5-Tribromo-2-iodo-4,6-dimethylbenzene 180[358]
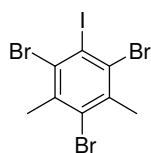
To a solution of **179** (40 g, 111.8 mmol) dissolved in conc. HCl (320 mL) at 0 °C was added NaNO$_2$ (8.799 g, 127.5 mmol) dissolved in H$_2$O (64 mL) dropwise whilst maintining the temp at 0 °C. The reaction was stirred at 0 °C for 90 min then the mixture was carefully poured through glass wool into a stirred solution of KI (128.0 g, 771.1 mmol). The mixture was stirred at 60 °C for 1 h then allowed to cool to room temp. The solution was extracted into DCM (3 x 1 L) and dried over MgSO$_4$, filterd and concentrated to afford the desired product as a beige solid (36.8 g, 70%). mp 244.0-245.6 °C; δ_H (400 MHz, CDCl$_3$) 2.76 (6H, s, 2 x C$\underline{H}_3$); δ_C (101 MHz, CDCl$_3$) 138.7 (2C, $\underline{C}$(4+6)), 130.6 (2C, $\underline{C}$(1+3)), 128.2 ($\underline{C}$(5)Br), 111.1 ($\underline{C}$(2)I, 9.3 (6C, 2 x C$\underline{H}_3$); *m/z*

(APCI⁺) 467.7 (100%, [^{79}Br$_2$][^{81}Br]M⁺) 469.7 (97%, [^{79}Br][^{81}Br$_2$]M⁺); *m/z* (APCI⁺) 465.7055 (35%, [^{79}Br$_3$]M⁺, C$_8$H$_6$^{79}Br$_3$^{127}I) requires 465.7064.

1-(2-Ethylhexyloxy)-4-bromobenzene 181[360]
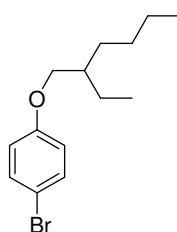
A mixture of 4-bromophenol **182** (90.0 g, 520.2 mmol), 2-ethylhexylbromide (120.6 g, 624.3 mmol) and K$_2$CO$_3$ (107.8 g, 401.4 mmol) in DMF (500 mL) was reacted at 78 °C overnight. The mixture was allowed to cool to room temperature and filtered, washing the filtercake with Et$_2$O (3 x 500 mL). The filtrate was diluted with water (500 mL) and the layers were separated. The aqueous layer was re-extracted with Et$_2$O (2 x 500 mL) and the combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated *in vacuo* . The oil was purified by washing through a SiO$_2$ plug with hexane (*ca.* 5 L) to give **181** as a colourless oil (106 g, 71% yield). δ$_H$ (400 MHz, CDCl$_3$) 7.34 (2H, d, *J* 9.0, C(3+5)$\underline{H}$), 6.76 (2H, d, *J* 9.0, C(2+6)$\underline{H}$), 3.78 (2H, dd, *J* 5.8, 1.0, ($\underline{C}$(1)O$_{phenyl}$)), 1.69 (1H, ddd, *J* 12.2, 6.1, 5.9, C$\underline{H}$), 1.55 – 1.21 (8H, m, 4 x C$\underline{H}_2$-CH$_2$), 0.93 – 0.84 (6H, m, 2 x CH$_2$C$\underline{H}_3$); δ$_C$ (101 MHz, CDCl$_3$) 158.7 ($\underline{C}$(1)O$_{phenyl}$), 132.4 ($\underline{C}$(5)H$_{phenyl}$), 116.5 ($\underline{C}$(2+6)H$_{phenyl}$), 112.7 ($\underline{C}$(4)Br$_{phenyl}$), 71.0 $\underline{C}$(5)O$_{phenyl}$, 39.5, 30.7, 29.3, 24.0, 23.3, 14.3, 11.3; *m/z* (APCI⁺) 284.1 (100%, [^{79}Br]M⁺).

3-Bromo-1,5-bis(4-(2-ethylhexyloxy)phenyl)-2,4-dimethylbenzene 183
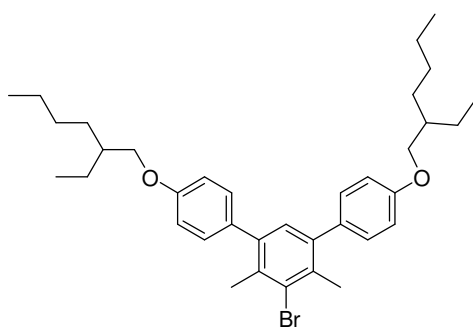
Magnesium turnings (2.837 g, 116.7 mmol) were activated under argon in a flame dried flask with a few crystals of I$_2$ by heating until purple vapours formed. To this was added **181** (33.74 g, 118.30 mmol) dissolved in dry THF (200 mL) dropwise over 40 min. and the resulting solution was stirred at 50 °C for 2 h. To this, **180** (18.49 g, 39.44 mol) dissolved in dry THF (260 mL) was added dropwise and the resulting mixture was stirred at reflux overnight. The mixture was allowed to cool to room temp and quenched with 2M HCl (200 mL). The mixture was concentrated *in vacuo* and extracted into DCM (200 mL). The aqueous layers were re-extracted with DCM (2 x 200 mL) and the combined organic layers were washed with Na$_2$SO$_3$, dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purifacation made by chromatography (SiO$_2$, 20 : 1 *v/v* hexane : DCM) to give **183** as a yellow oil (9.82 g, 42%); δ$_H$ (400 MHz, CDCl$_3$) 7.19 (4H, d, *J* 8.7), 7.06 (1H, s), 6.91 (4H,

d, *J* 8.7), 3.85 (4H, d, *J* 5.6), 2.38 (6H, s), 1.80 – 1.64 (2H, m), 1.52 – 1.19 (16H, m), 0.98 – 0.80 (12H, m); δ_C (101 MHz, CDCl$_3$) 158.7, 140.7, 134.8, 134.1, 130.7, 130.6, 130.4, 114.3, 70.8, 39.64, 30.8, 29.3, 24.1, 23.3, 22.3, 14.3, 11.4; *m/z* (APCI$^+$) 593.3 (100%, [^{79}Br]M$^+$), 595.3 (97%, [^{81}Br]M$^+$).

3-(4-Pyridyl)-1,5-bis(4-(2-ethylhexyloxy)phenyl)-2,4-dimethylbenzene 184
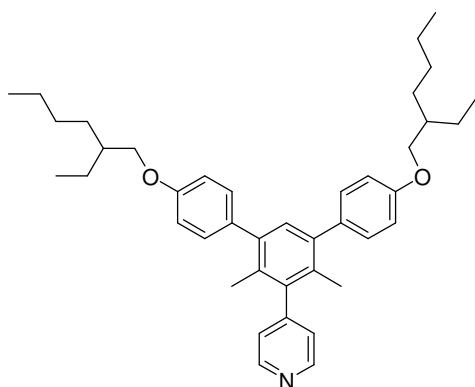
In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted **187** (4.75 g, 8.00 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine **185** (2.29 g, 11.2 mmol), Pd$_2$(dba)$_3$ (0.073 g, 0.08 mmol, 1 mol%), P^{t}Bu$_3$.HBF$_4$ (0.056 g, 0.024 mmol) and degassed fresh aqueous K$_3$PO$_4$ (21.4 mL, 1.27 M, 27.2 mmol) in degassed dioxane (50 mL) at 100 °C for 24 h. Standard work-up conditions and purification *via* chromatography (SiO$_2$, 8 : 1 *v/v* hexane : EtOAc) provided **184** as a yellow oil (3.00 g, 63%); δ_H (400 MHz, CDCl$_3$) 8.74 (2H, s), 7.32 – 7.24 (6H, m), 7.23 (1H, s), 6.99 – 6.93 (4H, m), 3.89 (4H, d, *J* 5.9), 1.95 (6H, s), 1.82 – 1.71 (2H, m), 1.62 – 1.31 (16H, m), 1.02 – 0.90 (12H, m); δ_C (101 MHz, CDCl$_3$) 158.7, 150.1, 148.5, 140.6, 140.0, 134.0, 131.7, 131.6, 130.6, 125.0, 114.4, 70.8, 39.7, 30.8, 29.3, 24.1, 23.3, 19.1, 14.3, 11.4; *m/z* (APCI$^+$) 592.4 (100%, M$^+$+H), 591.4 (15%, M$^+$); *m/z* (APCI$^+$) 591.4087 (15%, M$^+$, C$_{41}$H$_{53}$NO$_2$ requires 591.4076).

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