Palladium-Catalysed Heterocycle Synthesis

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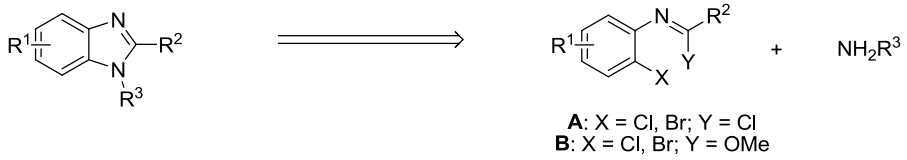
Abstract

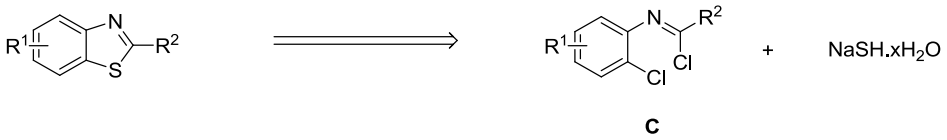
Chapter 1 is a literature review of selected palladium-catalysed aryl C-N and C-S bond forming reactions. The application of these reactions to the synthesis of heterocycles is also discussed.

Chapter 2 highlights the importance of the benzimidazole motif and gives a brief discussion of the existing routes to this scaffold. The utility of *N*-(*o*-halophenyl)imidoyl chlorides (**A**) and imidates (**B**) as precursors to heterocycles is demonstrated in a palladium-catalysed reaction with *N*-nucleophiles to afford benzimidazole products (Scheme 1).



Scheme 1

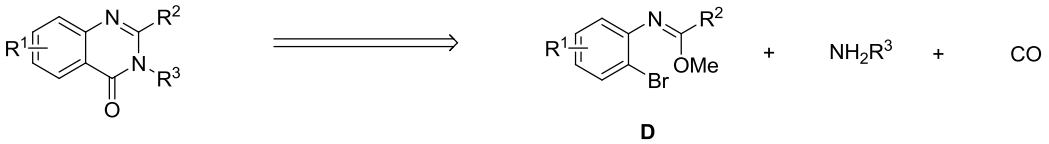
Chapter 3 provides a brief introduction to the synthesis of benzothiazoles and describes efforts towards the use of our established substrates for the preparation of these heterocycles. This is achieved *via* reaction of *N*-(*o*-chlorophenyl)imidoyl chlorides (**C**) with a sulfur nucleophile in a metal-free process (Scheme 2).



Scheme 2

Chapter 4 is a literature review of palladium-catalysed carbonylation chemistry with specific focus on aminocarbonylation and thiocarbonylation reactions of aryl halides. Heterocycle syntheses which employ such carbonylative methods are also discussed.

Chapter 5 describes existing protocols for the synthesis of quinazolinones. A novel palladium-catalysed synthesis of these heterocycles from the reaction of our imidate substrates (**D**) with an amine and carbon monoxide is described (Scheme 3). This further demonstrates their utility as general heterocycle precursors.



D

Scheme 3

Acknowledgements

Firstly I would like to thank Dr. Michael Willis for the opportunity to work in his group. He has been a great supervisor, always willing to listen even when I was speaking rubbish.

Next a massive thanks go to "my twin" SJ for being so supportive and always being up for drinking wine with me. Thanks go to Fiona and Maria for being there from day one and enduring the moaning and stress as well as the good times. Thanks to Myriam for being a good friend and listener. Thank you to Radleigh for being a constant source of entertainment and never taking anything too seriously. Many thanks to Cat for the gossip and doing my proof reading so thoroughly. Thank you Ed for being a "football friend" and all the heartache and joys we have endured watching United play. Thanks to Charlie for being so happy yet sometimes aggressive.

I'd like to say thanks to others from the group: Carlos, Joel, Phil, Paul, Rob, Lewis, Caitlin, Holly and Rhian for making lab such a great place to work!

Thanks go to my "JR friends." Thank you to Kiri for being so awesome and enjoying gin so much. Thanks to Liz for being so caring and helping fuel my M&S obsession. Thank you both for making Cripley Rd such a nice home to live in. Many thanks to Chris for all the sports watching and listening to my random rants. Thanks to Sarah and George for all the fun times we have had together. I promise to try and keep up the standard 6 tradition! Thanks to my good friends Jon and Carina who have been great at keeping me going through my undergrad and DPhil. Thank you to my housemates for a fun final year!

Thanks to the NMR, Mass Spec and CRL staff.

Finally, thanks to my family for all their love and support.

Contents

Abbreviations and Acronyms

δ	Chemical shift (ppm)
µw	Microwave
λ	Wavelength
ν	Frequency
Å	Angstrom
Ac	Acetyl
app.	Apparent
aq.	Aqueous
Ar	Aryl
atm	Atmosphere
BINAP	2,2'-Bis(diphenylphophino)-1,1'-binapthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
Bu	Butyl
^{n}Bu	Normal butyl
BTF	α,α,α-Trifluorotoluene or benzotrifluoride
^{t}Bu	Tertiary butyl
°C	Degrees Celsius
cata*C*Xium® A	Di(1-adamantyl)-*n*-butylphosphine
cm	Centimetre
conc.	Concentrated
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
d	doublet
DavePhos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dba	*trans*, *trans*-Dibenzylidene-acetone

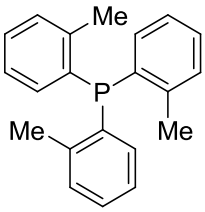
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DCPP	1,3-Bis(dicyclohexylphosphino)propane
DEPT	Distortionless Enhancement by Polarization Transfer
DMA	*N*,*N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMEDA	*N*,*N*'-Dimethyl-ethylenediamine
DMF	*N*,*N*-Dimethylformamide
DMPP	Tris(2,6-dimethoxyphenyl)phosphine
DMSO	Dimethylsulfoxide
DPEPhos	Bis(2-diphenylphosphino)-phenyl ester
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
D^iPPF	1,1′-Bis(di-isopropylphosphino)ferrocene
DPPP	1,3-Bis(diphenylphosphino)-propane
E	Entgegen
equiv	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
g	Gram(s)
h	Hour(s)
Hex	Hexyl
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
Hz	Hertz
IR	Infrared
J	Coupling constant (Hz)
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
Kg	Kilogram(s)
L	Litre(s)
L_n	Ligand(s)
LRMS	Low resolution mass spectrometry
M	Molar/molarity
m	Multiplet

m-	*meta*-
Me	Methyl
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mol	Mole(s)
mmol	Millimole(s)
mp	melting point
MS	Molecular sieves
Ms	Methanesulfonyl (Mesyl)
m/z	Mass to charge ratio
Nf	Nonafluorobutanesulfonyl
NHC	*N*-heterocyclic carbene
nm	Nanometre(s)
NMR	Nuclear Magnetic Resonance
NMP	1-Methyl-2-pyrrolidinone
o-	*ortho*-
Oct	Normal octyl
p-	*para*-
PEPPSI	Pyridine-enhanced precatalyst preparation stabilization and initiation
1,10-Phen	1,10-Phenanthroline
Ph	Phenyl
PPA	Phosphonoacetic acid
ppm	Parts per million
psi	Pounds per square inch
Pr	Propyl
^{i}Pr	Isopropyl
^{i}Pr-MOP	2-Diisopropylphophino-2’-methoxy-1,1’-binapthyl
p-TSA	*para*-Toluenesulfonic acid
Py	Pyridine

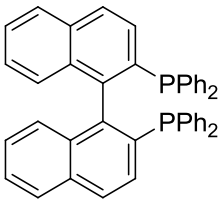
QPhos	1,2,3,4,5-Pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene
q	Quartet
quin	Quintet
R	Generic group/substituent
r.t.	Room temperature
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
s	Singlet
sex	Sextet
S_NAr	Nucleophilic aromatic substitution
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
t	triplet
Tf	Trifluoromethanesulfonyl (Trifyl)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
Tol	Tolyl
TriPhos	1,1,1-Tris(diphenylphosphinomethyl)ethane
Ts	*p*-Toluenesulfonyl (Tosyl)
X	Generic halide or pseudo halide (unless defined)
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
Z	Zusammen

Ligands

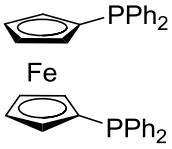
Phosphine ligands



P(*o*-Tol)$_3$



BINAP



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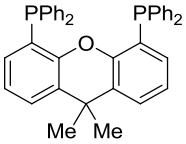

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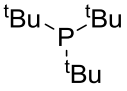

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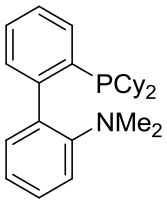
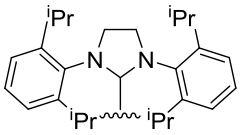


DavePhos



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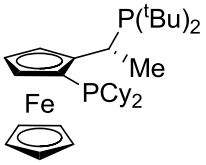

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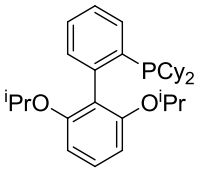
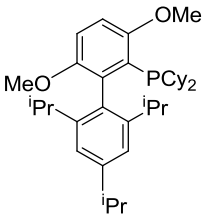


RuPhos



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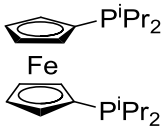

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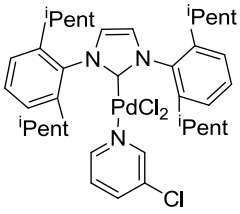

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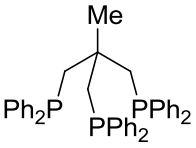

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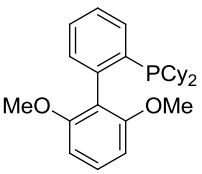

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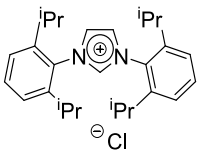

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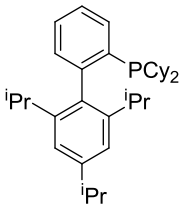

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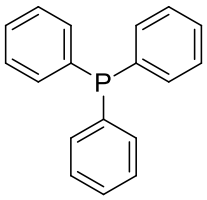
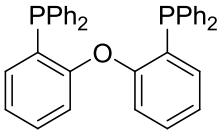


PPh_3



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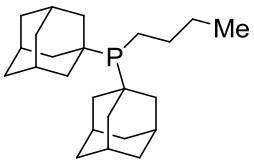
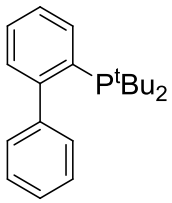


cata*C*Xium® A



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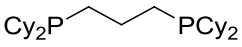

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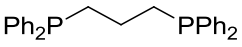

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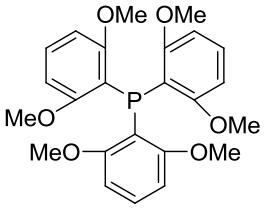

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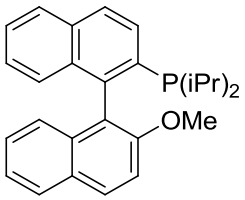
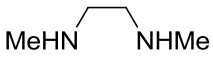


^{i}Pr-MOP

Ligands for copper catalysis



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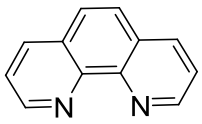
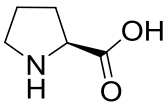
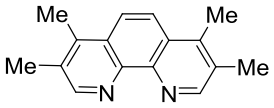


1,10-Phen

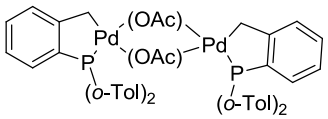


***L*-proline**

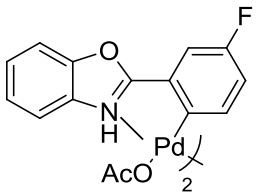


L2

Palladacycles



Hermann's palladacycle



Palladacycle 1

Chapter 1: Palladium-catalysed aryl C-X bond forming reactions and their application in aromatic heterocycle synthesis

1.1 Palladium-catalysed aryl C-X bond forming reactions

1.1.1 Introduction

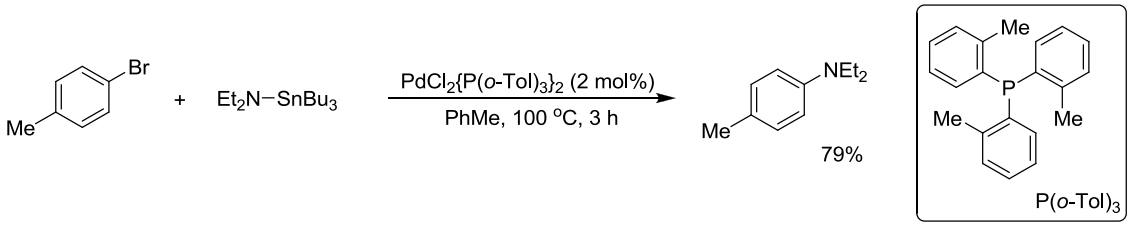
Aryl amines, ethers and thioethers are commonly found in a range of important and useful molecules such as pharmaceuticals, herbicides, polymers and organic light-emitting diodes. As classical methods to prepare these functionalities possess several limitations, milder and more efficient methods based on the use of transition-metal catalysis have been developed.[1, 2] These include numerous important protocols for aryl C-X bond forming reactions catalysed by copper,[3-7] iron,[8] cobalt,[9-12] nickel[13-17] and rhodium;[18] however, it is palladium-catalysed strategies which have arguably become the most general and powerful.[1, 19-21] The background of the discovery and consequent progress of some of these processes, as well as their application to the synthesis of aromatic heterocycles will be discussed here.[i]

1.1.2 Palladium-catalysed aryl C-N bond forming reactions

Procedures for the synthesis of arylamines include nitration and reduction,[22] nucleophilic substitution of aryl halides,[23] addition of amines to benzyne intermediates[24] and Ullmann couplings.[25-28] However these suffer from several drawbacks such as the requirement of numerous steps, use of excesses of reagents, pre-activated substrates and/or high reaction temperatures. Furthermore, functional groups which are compatible in these reactions are limited and product yields can be low.

[i] This has been limited to palladium-catalysed aryl C-N and C-S bond forming reactions and their role specifically in aromatic heterocycle synthesis, as this forms an introduction to the methods used in subsequent chapters.

The first example of a palladium-catalysed amination reaction of an aryl halide was published in 1983 by Migita *et al*.[29] This protocol made use of tributyltin diethylamide, which was successfully coupled with aryl bromides, utilising a $[PdCl_2\{P(o\text{-Tol})_3\}_2]$ catalyst (Scheme 1.1). However, the scope was limited to unhindered dialkyltin amides and only electron-neutral aryl bromides afforded good yields.

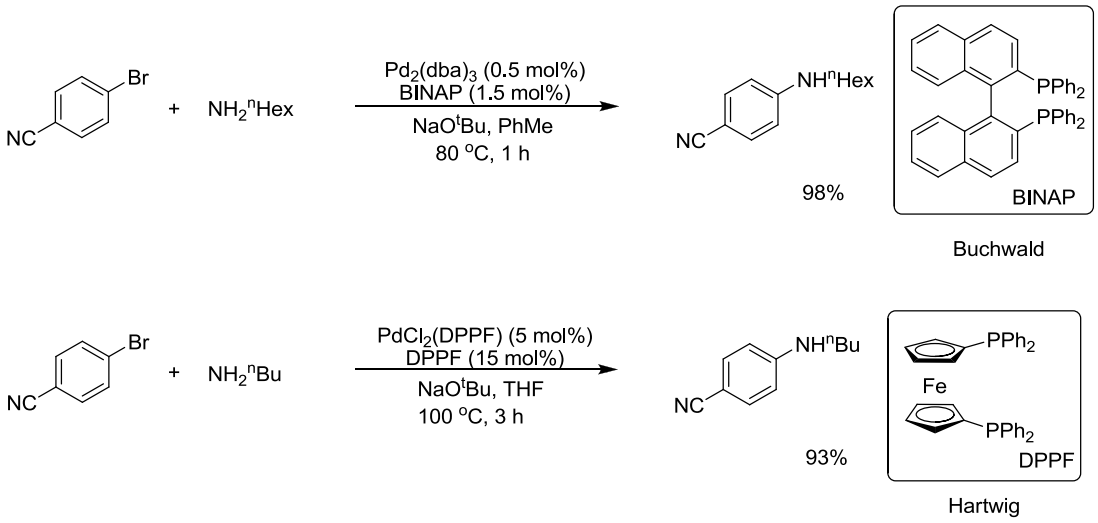


Scheme 1.1

This reaction did not appear in the literature again until 1994 when Hartwig *et al*. published insights into the mechanism and improvements to the catalyst,[30] while the Buchwald group simultaneously reported improvements to the scope of the aryl halide by use of *in situ* generated tin amides.[31] However, the use of toxic and unstable tin reagents as well as poor substrate scope proved significant limitations and prompted further investigations.

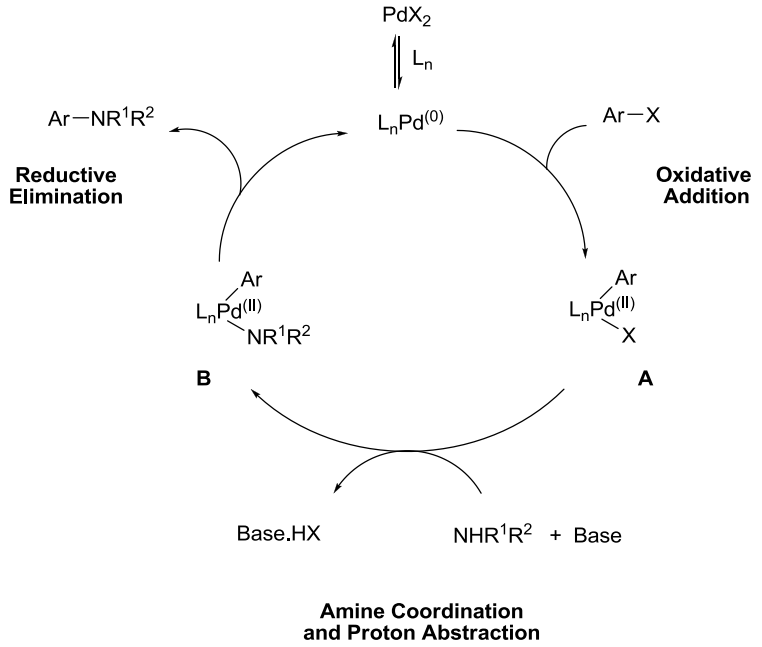
In the following year, both groups reported examples of tin-free palladium-catalysed aminations of aryl bromides in the presence of either an alkoxide[32] or silylamide base.[33] Although these new procedures gave good yields with secondary amines, the coupling of primary amines was not as successful. Thus, second generation catalysts were developed which encompassed reactions of primary amines and generally gave higher yields under milder conditions. This increased reactivity was attributed to the use of chelating

bisphosphine ligands (as opposed to the previously used monophosphine P(*o*-Tol)$_3$ ligand). Buchwald utilised palladium complexes of BINAP[34] while Hartwig favoured DPPF derived catalysts[35] (Scheme 1.2).



Scheme 1.2

Extensive investigations have been carried out into various aspects of the mechanism of the palladium-catalysed amination reaction,[36-40] especially into the Pd(BINAP) system for the amination of aryl bromides.[41-44] As a result a general mechanism has been postulated, which is broadly accepted to proceed *via* three basic steps (Scheme 1.3).



Scheme 1.3

Several studies have also been carried out into the generation of the active palladium catalyst, from either palladium(II) sources[45, 46] or palladium(0) precursors.[41-43, 47, 48] The resultant monoligated Pd(0) species are widely accepted to be the active catalysts and can either be 14-electron complexes when ligated with bidentate ligands (such as BINAP) or 12-electron complexes with monodentate ligands.[49] They are nucleophilic in nature and oxidatively add to the aryl halide bond in the first step, generating organopalladium(II) complex **A**. This is generally the rate-limiting step, particularly for aryl chlorides as they contain a stronger Ar-X bond. The next step involves co-ordination of the amine and deprotonation by the base to afford aryl palladium(II) amide intermediate **B**. This can then undergo reductive elimination to form the desired C-N bond of the arylamine product and regenerate the active palladium(0) species. This step may control the yield and selectivity of the reaction. For example, a competing β-hydride elimination pathway may occur from palladium-bound amines which contain a β-hydrogen. This affords an imine, a reduced arene product and regenerated palladium(0) catalyst and is particularly

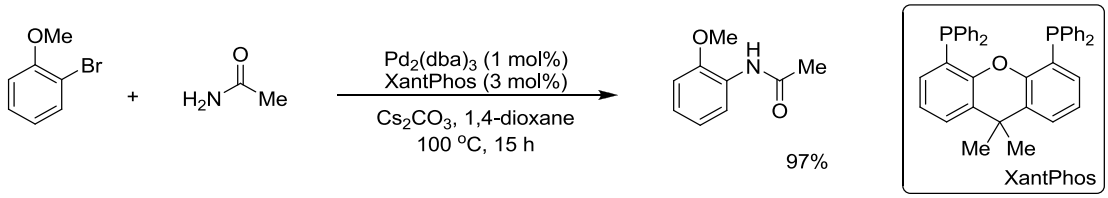
problematic for the coupling of primary alkyl amines. Other side reactions such as protonolysis of the metal amide or ligand displacement by a second equivalent of amine may also occur, affording low yields and undesirable products.

The nature of the ligand in palladium-catalysed C-N bond forming reactions plays a key role. For example, electron-rich phosphines can aid oxidative addition as they increase the electron density around the palladium centre. Conversely electron-poor ligands facilitate reductive elimination. The steric bulk of the ligand is also important. Sterically demanding ligands can shift the equilibrium in favour of the LPd(0) catalytically active species and also accelerate reductive elimination. Additionally, the use of chelating bidendate ligands, such as BINAP can suppress side reactions such as β-hydride elimination and formation of catalytically inactive $Pd(amine)_2(Ar)X$ complexes through formation of four co-ordinate palladium(II) complexes.[50]

Further advancements which have been made to this methodology in order to broaden the scope of both coupling partners, reduce catalyst loadings and/or utilise milder and more efficient processes have been primarily as a result of the development of new classes of ligands. Consequently a vast number of systems now exist for the Buchwald-Hartwig amination reaction; however a selection of the most significant are discussed herein.

Following on from the successful use of BINAP in C-N bond forming reactions, Buchwald demonstrated the use of other bisphosphine ligands. For example, the successful coupling of a wide variety of aryl bromides with primary anilines was possible using DPEPhos.[51] The group also showed the use of a structurally similar bisphosphine,

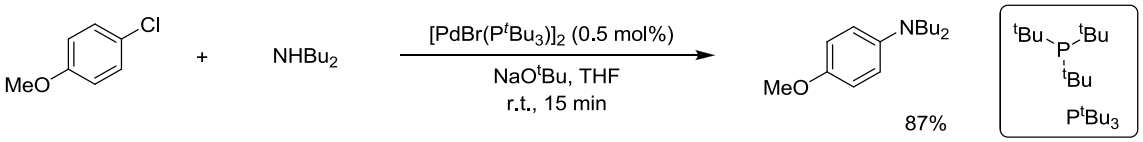
namely XantPhos as a general ligand for the cross-coupling of aryl iodides, bromides and triflates with electron deficient nucleophiles such as amides, sulfonamides, carbamates and ureas.[52, 53] This system also successfully incorporated unactivated electron-rich aryl halides in this amidation process (Scheme 1.4). However, in order to avoid the formation of by-products, more carefully controlled conditions were required.



Scheme 1.4

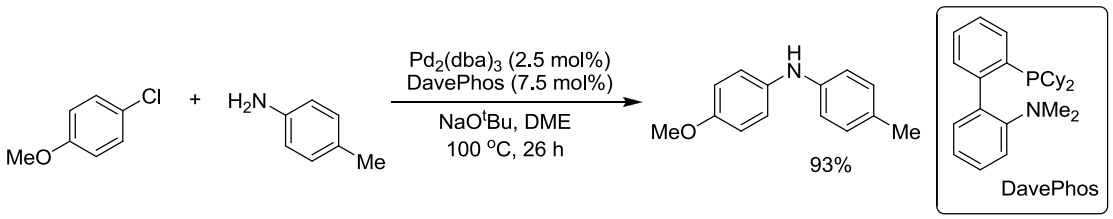
Several groups then turned their attention to developing a third generation of ligands, namely sterically hindered monophosphines. The first example was the use of tri-*tert*-butylphosphine for the coupling of aryl halides and heteroaryl halides to piperazine published in 1998 by researchers at the Tosoh Company.[54] This catalyst system exhibited very high reactivity and selectivity, which is attributed to the strong electron donating properties and bulkiness of the alkyl groups of the ligand. For example, high conversions of aryl bromides to the desired product were obtained with catalyst loadings as low as 0.5 mol%. A single example of the coupling of an aryl chloride at this low loading gave a good conversion of 88%, albeit at a high reaction temperature of 140 °C. A year later, Hartwig went on to show that a catalyst system comprising of $Pd(dba)_2$ and this ligand could catalyse the room temperature coupling of a wide range of aryl bromides with secondary alkylamines and primary and secondary arylamines.[55] The coupling of aryl chlorides was also achieved under milder conditions than any of the established procedures at that time. It was found that these reactions occurred faster when a 1:1 ratio

of palladium to ligand was used. This can be attributed to more efficient generation of a monoligated Pd(0) species, which is highly active towards oxidative addition.[49] Consequently, the use of catalysts based on palladium(I) dimers, such as $[PdBr(P^tBu_3)]_2$, which is an air stable solid, was reported in 2002.[56] These could be cleaved into two monomeric units, namely Pd(II) dibromide and the catalytically active monoligated Pd(0) complex. Thus, these complexes exhibited extremely high reaction rates for the coupling of secondary alkylamines to aryl chlorides with reaction times as low as 15 minutes (Scheme 1.5). Since these publications, several related ligands have been developed.[57] Examples include Q-Phos,[58] diadamantylalkyl phosphines (e.g. cata*C*Xium® A),[59] and 9-fluorenyldialkyl phosphines and related derivatives (cata*C*Xium® F).[60]



Scheme 1.5

A major contribution from the Buchwald group has been the development of dialkylbiaryl monophosphine ligands.[61-63] In 1998, they first demonstrated the use of ligands such as DavePhos for the room temperature coupling of aryl bromides to both primary and secondary aliphatic amines as well as to an arylamine.[64] This ligand was also successfully used for the coupling of unactivated aryl chlorides (Scheme 1.6).

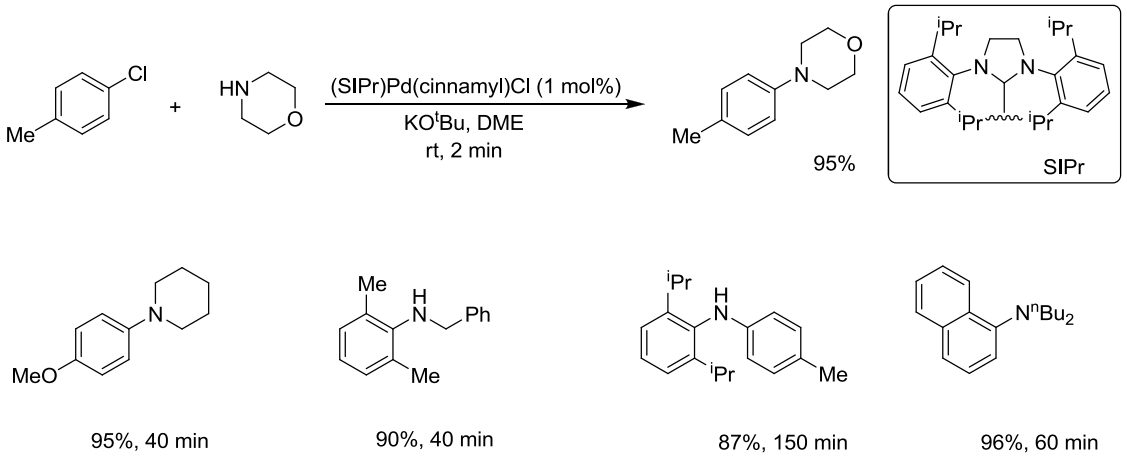


Scheme 1.6

Since this discovery, several structurally similar ligands have been developed such as JohnPhos,[65] SPhos,[66] RuPhos[66], XPhos,[67] and BrettPhos,[68, 69] which provide improvements such as a broader scope of both coupling partners as well as increased reactivity and selectivity. The success of these ligands has been attributed to several of their structural features. For example, the steric bulk and strong electron-donating ability of the alkyl moieties on the phosphine group encourage formation of the active monoligated Pd(0) species, facilitating oxidative addition. The lower aryl ring and its substituents have also been shown to play an important role in promoting catalyst stability. This is possibly due to palladium-arene interactions, which may result in increased electron-density at the metal-centre. As a result of their high reactivity, ease of synthesis and stability, this family of ligands has been utilised in many palladium-catalysed C-N bond forming reactions for the synthesis of pharmaceuticals, heterocycles, natural products and in material science.[61] Beller *et al*. have demonstrated the use of structurally similar dialkylphosphino-*N*-arylindoles and -pyrroles (cata*C*Xium® P) as successful ligands for the amination of aryl and hetero aryl chlorides.[70]

A structurally different class of ligands was introduced in 2006 by Nolan and co-workers for the amination of aryl bromides and chlorides.[71] These NHC-bearing palladium(allyl)Cl complexes (NHC = *N*-heterocyclic carbene), exhibited remarkable

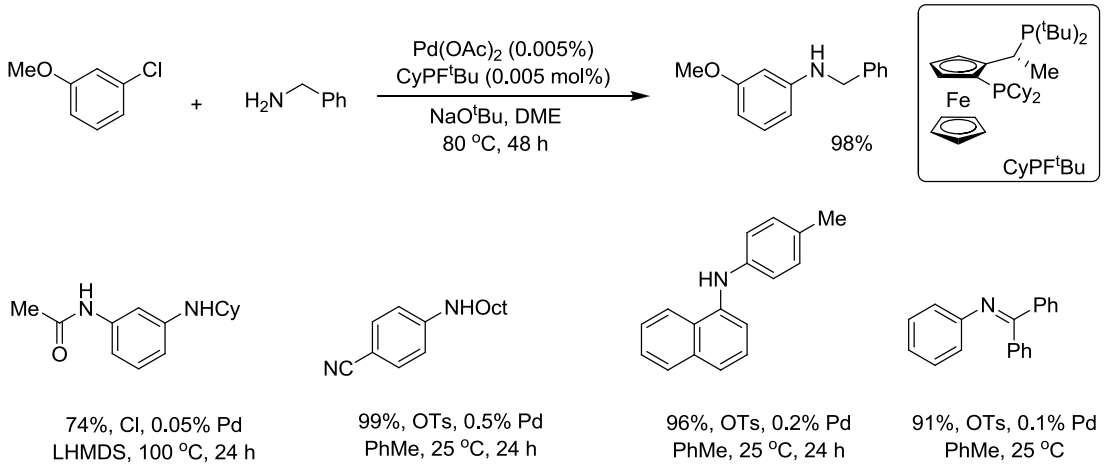
activity. Reactions could be carried out at room temperature with low catalyst loadings affording excellent yields in very short reaction times. This high reactivity was attributed to the ease of formation of the active Pd(0) complexes, by facile elimination of the labile allyl and chloride groups as well as the strong electron donating and sterically demanding properties of the NHC. Synthesis and testing of a series of structurally similar complexes showed that the (SIPr)Pd(cinnamyl)Cl complex was the most active for Buchwald-Hartwig reactions. Examples of the scope of this reaction are shown in Scheme 1.7. These complexes act as well-defined single component catalyst systems and benefit from being air and moisture stable and easy to synthesise.[72]



Scheme 1.7

A major break-through from the Hartwig laboratory has been the development of a highly active class of ligands, known as JosiPhos derivatives.[73] The structure of this fourth generation ligand family combined the bulky electron donating properties of alkylphosphines with the chelating properties of bisphosphines. Thus, alkyl bisphosphine moieties were arranged on a rigid ferrocenyl-1-ethyl backbone, which pre-organised them towards metal binding. A variant, which comprised of one dicyclohexylphosphino group

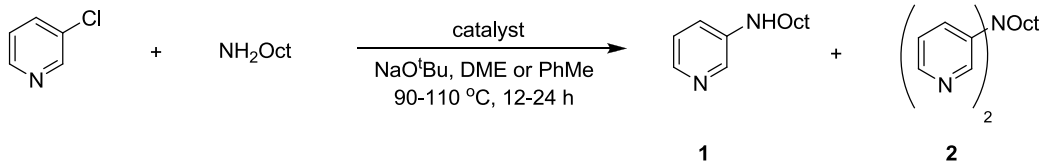
and one di-*tert*-butylphosphino group (CyPF^{t}Bu) was shown to catalyse reactions of aryl and heteroaryl iodides, bromides and chlorides as well as tosylates with a wide range of amines using catalyst loadings as low as 0.005 mol% (Scheme 1.8).[74-77] The use of aryl tosylates as coupling partners is highly attractive as they are less expensive to prepare than aryl triflates and are generally air stable solids.[67, 78, 79] In addition, a wide range of functional groups on the aryl and heteroaryl coupling partners could be tolerated.



Scheme 1.8

Comparative studies undertaken of the reactivities of CyPF^{t}Bu, XPhos and the (SIPr)Pd(cinnamyl)Cl carbene ligand complex revealed the CyPF^{t}Bu ligand to be exceptionally more reactive for the coupling of 3-chloropyridine with octylamine (Table 1.1).[76] Full conversion to desired monoarylated product **1** was observed with loadings as low as 0.005 mol% for CyPF^{t}Bu (entry 1), however the other ligands required higher loadings and afforded a mixture of **1** and diarylation product **2** (entries 2 and 3).

Table 1.1 Comparative ligand study[a]



1 **2**

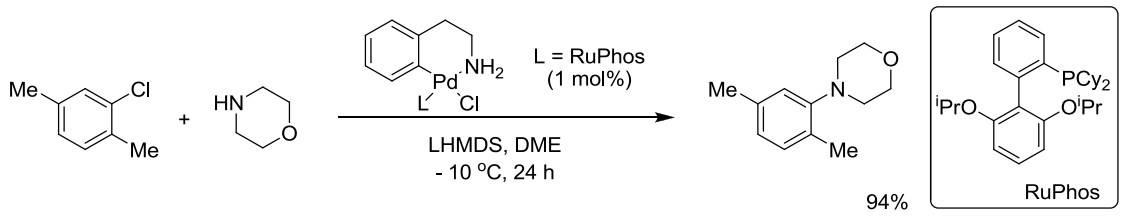
Entry	Catalyst (mol%)	Conversion[b]	Yield[c] (%)	1:2
1	$Pd(OAc)_2$/CyPF^{t}Bu (0.005)	100	92	100:0
2	$Pd(OAc)_2$/XPhos (0.1)	85	80	2.4:1
3	(SIPr)Pd(cinnamyl)Cl (0.5)	100	71	7.6:1

[a] Reaction conditions: 3-chloropyridine (1.0 equiv), octylamine (1.2 equiv), NaO^{t}Bu (1.4 equiv), 1:1 ratio of Pd/CyPF^{t}Bu or 1:2 ratio of Pd/XPhos. [b] Determined from ^{1}H NMR spectrum of crude reaction mixture. [c] Isolated yields.

The CyPF^{t}Bu ligand was also reported as a successful ligand for the first palladium-catalysed coupling of aryl halides with ammonia to form primary amines.[80, 81] Excellent selectivity for the primary aniline over the diaryl amine (as a result of a second amination reaction of the desired product) was observed. Additionally, the use of a solid ammonia surrogate, lithium amide, allowed for a more practical protocol. Since this publication, Buchwald,[82] Beller[83] and Stradiotto[84] have reported similar couplings.

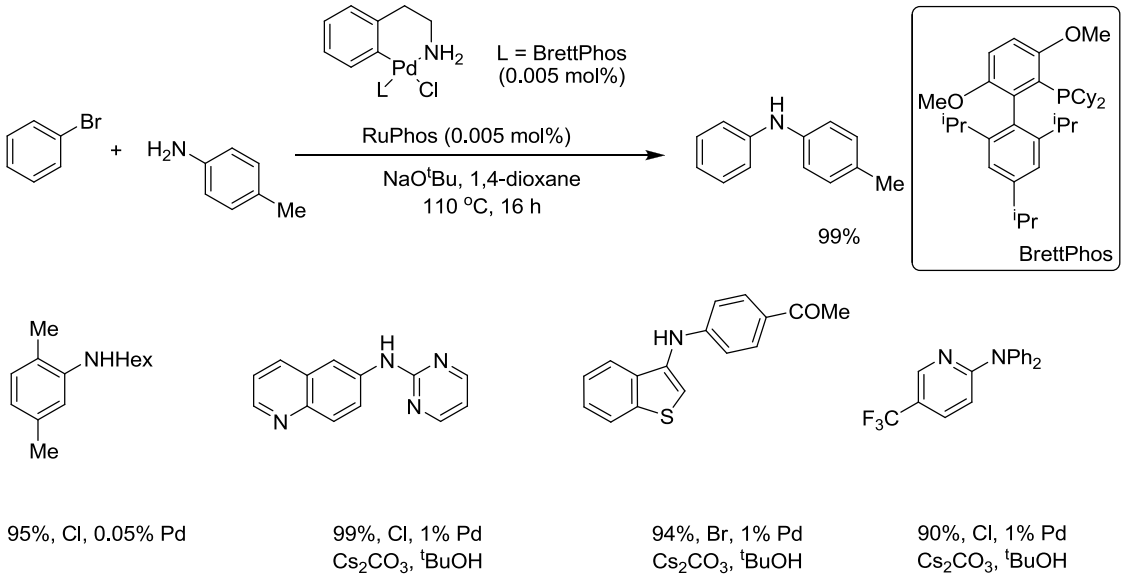
In 2008 Buchwald demonstrated the use of a new class of palladium precatalysts, as highly active systems for C-N bond forming reactions of aryl chlorides with a variety of amines.[85] These complexes, comprising of intramolecularly co-ordinated amines bearing dialkylbiarylphosphine ligands such as RuPhos, were easily converted to their active LPd(0) species under mild conditions. Thus, high reactivity even at very low reaction temperatures was possible as shown in Scheme 1.9. This methodology was extended to the use of aryl mesylates as successful coupling partners.[68] The group has also demonstrated the generation of highly active Pd(0) catalysts from water-mediated

preactivation of $Pd(OAc)_2$ and dialkylbiarylphosphine ligands, which allow the efficient coupling of aryl chlorides to a range of amines and amides.[86]



Scheme 1.9

An alternative approach to catalyst development was reported in 2010 by the Buchwald group.[87] A multi-ligand based catalyst system incorporated the high reactivity of BrettPhos with primary amines and RuPhos with secondary amines in order to attain a wider substrate scope. Thus, a wide variety of amines were successfully coupled with aryl halides in high yields using exceptionally low catalyst loadings as shown in Scheme 1.10.



Scheme 1.10

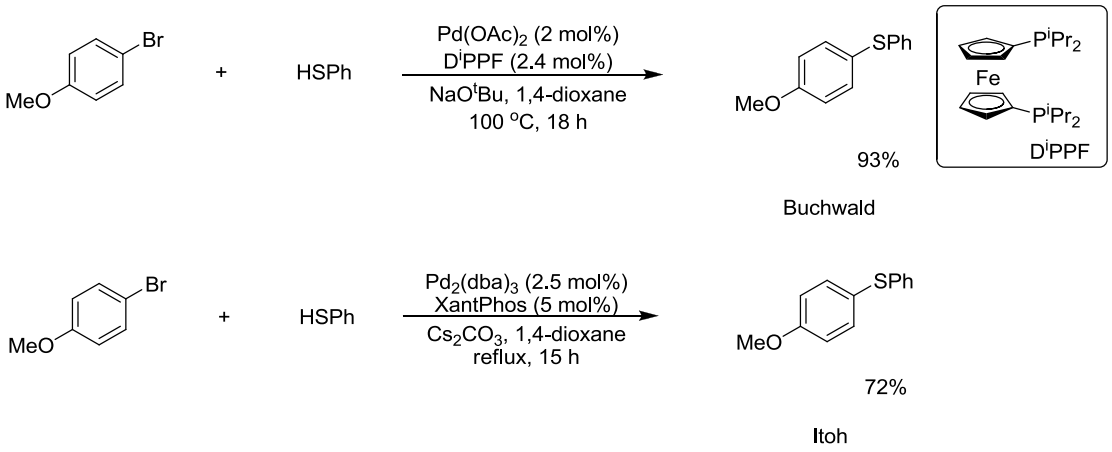
1.1.3 Palladium-catalysed aryl C-S bond forming reactions

Classical routes to aryl thioethers include reactions of arenes[88, 89] or Grignard reagents[90, 91] with sulfur, nucleophilic aromatic substitution reactions (S_NAr) of aryl halides with metal sulfides,[92, 93] reduction of disulfides,[94, 95] and the Newman-Kwart rearrangement.[96] However these procedures present several limitations such as high reaction temperatures, use of harsh reagents, limited substrate compatibility and the requirement for multiple steps as well as the formation of side products.

The development of efficient transition-metal catalysed C-S bond forming reactions has been somewhat slower in comparison to other C-X bond forming processes. This is due to the strong co-ordinating properties of sulfur containing compounds which can render them as catalyst poisons.[97, 98] However recent progress, such as the employment of new ligand types has resulted in numerous useful protocols for this transformation.[2, 99] The development of palladium-catalysed aryl C-S bond forming reactions will be discussed herein.

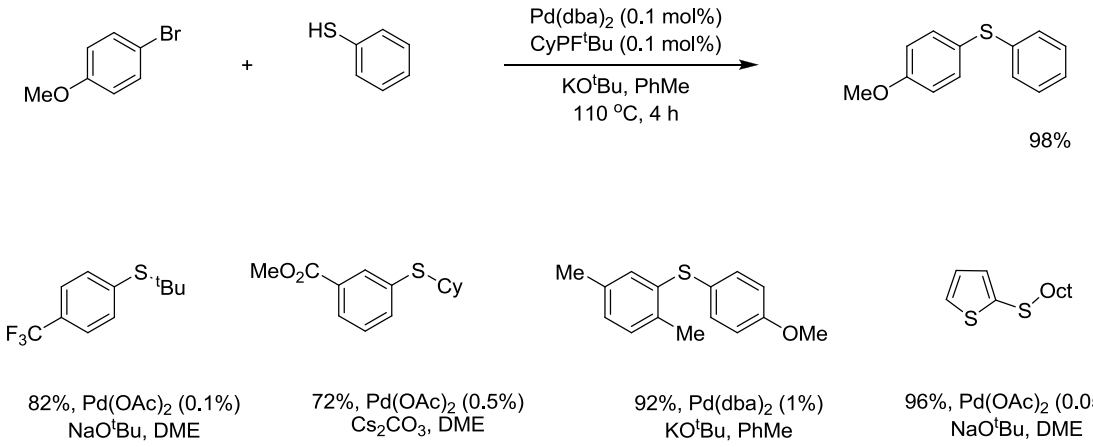
In 1978 and 1980 Migita *et al*. published the first examples of palladium-catalysed couplings of aryl iodides and bromides with alkyl and aryl thiols, utilising a $Pd(PPh_3)_4$ catalyst.[100, 101] However, the use of only a small number of thiols was demonstrated and the coupling of aryl chlorides was not possible. Since these reports, a number of other catalyst systems have been developed, which utilised different classes of ligands but were again somewhat limited in scope.[102-106]

A more general and efficient system remained unreported until 2004 when Buchwald[107] and Itoh[108] published work towards the development of this reaction. The Buchwald group utilised a chelating bisphosphine D^{i}PPF ligand, to successfully couple a range of aryl bromides and chlorides to alkyl as well as aryl thiols. Itoh *et al*. employed a XantPhos based system for the coupling of aryl bromides, activated aryl chlorides and aryl triflates with a variety of aryl and alkyl thiols. An example from each laboratory is shown in Scheme 1.11.



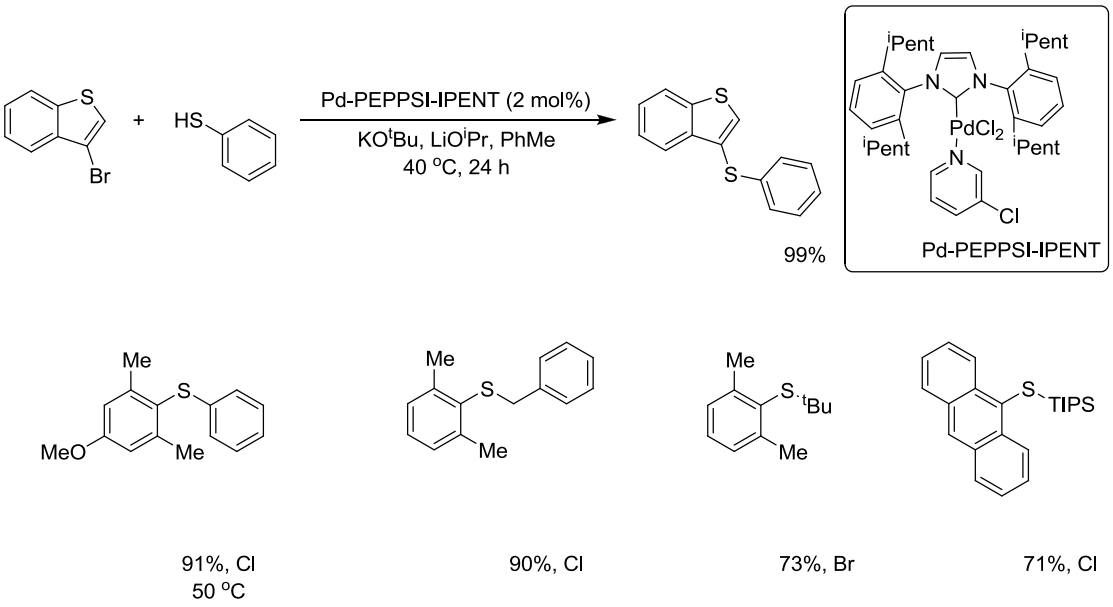
Scheme 1.11

A major development came from the Hartwig group in 2006 when they disclosed a highly active catalyst system based on their CyPF^{t}Bu JosiPhos ligand for the coupling of aryl chlorides with thiols.[109, 110] A large variety of alkyl and aryl thiols, as well as a wide range of substituents on the aryl chloride substrates, were tolerated by the reaction conditions and the products were obtained in high yields using low catalyst loadings (Scheme 1.12). This system was successful for the coupling of thiols to aryl iodides and bromides as well.[111] The group have also disclosed several reports on the mechanistic aspects of palladium-catalysed C-S bond forming reactions.[112-114]



Scheme 1.12

The use of a NHC-palladium complexes as catalysts for C-S bond forming cross couplings of aryl halides with thiols was first demonstrated in 2010 by Liu *et al*.[115] The group utilised a [(NHC)Pd(PPh_3)Cl_2] pre-catalyst, which afforded high yields of biaryl thioethers from aryl iodides and bromides, however poor yields were obtained when alkyl thiol coupling partners were used. The use of a pyridine-enhanced precatalyst preparation stabilization and initiation (PEPPSI^{TM})[116] [(SIPr)Pd(py)Cl_2] complex was reported a year later by the Shi group. This displayed higher reactivity as unactivated aryl chlorides could be coupled successfully with aryl or benzyl thiols in excellent yields.[117] Further improvements to substrate scope and reactivity were demonstrated by Organ *et al*. in the same year by utilising a similar [Pd-PEPPSI-IPENT] complex.[118] This catalyst displayed remarkable activity for the coupling of a wide range of aryl and hetero aryl bromides and chlorides to aryl, alkyl and silyl thiols under mild reaction temperatures as shown in Scheme 1.13.

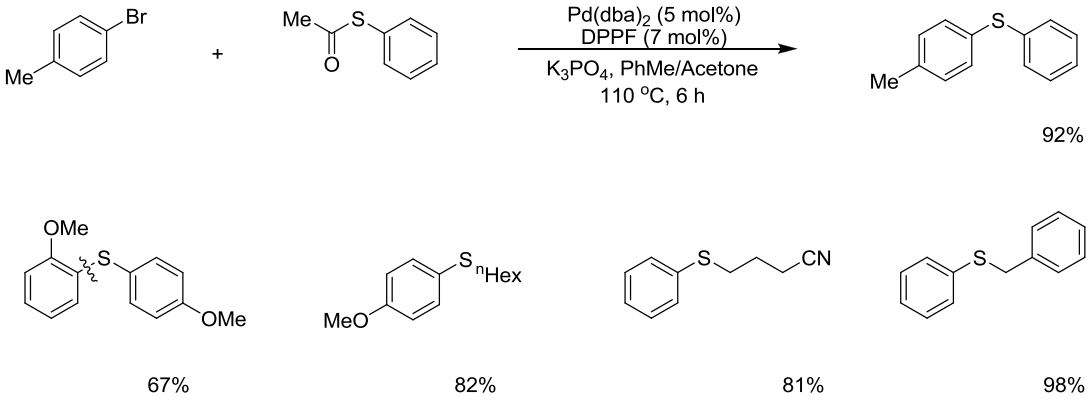


Scheme 1.13

Other recent developments include the palladium-catalysed coupling of aryl bromides with alkyl and aryl thiols under mildly basic conditions,[119] a ligand-free palladium system for the synthesis of aryl thioethers from aryl iodides and bromides in water under microwave irradiation[120] and use of a resin-supported palladium complex for the C-S coupling of aryl bromides and aryl thiols in water.[121]

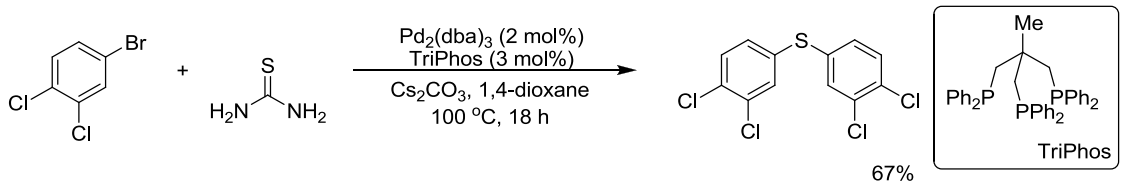
However, the wider use of aryl thiols as coupling partners is unfavourable due to their instability and limited availability. In 2010, Hartwig reported an attractive alternative route to unsymmetrical diaryl thioethers from the palladium-catalysed one-pot reaction of two aryl bromides and a thiol surrogate, namely triisopropylsilanethiol.[122] This coupling was catalysed by a $Pd(OAc)_2$ and CyPF^{t}Bu system and utilised low palladium loadings. A similar protocol was published in 2011 by Lee *et al*. which demonstrated the use of potassium thioacetate as the sulfur source for the synthesis of unsymmetrical diaryl thioethers, however in this case, the use of an aryl iodide and bromide was required.[123]

The coupling of *S*-alkyl and *S*-aryl thioacetates with aryl bromides was possible and a wide range of thioethers were synthesised and selected examples are shown in Scheme 1.14.



Scheme 1.14

The use of thioacetates as sulfur sources in palladium-catalysed C-S bond forming reactions has also been utilised for the synthesis of *S*-aryl thioacetates from the coupling of aryl bromides and triflates to potassium thioacetate[124] and for the synthesis of benzyl aryl thioethers from aryl bromides and benzyl thioacetates.[125] Recently, Fu and Guo have reported the use of sodium thiosulfate as a cheap and non-toxic sulfur source for the palladium-catalysed synthesis of aryl thiols from aryl bromides, chlorides and triflates.[126] Paradies *et al*. have demonstrated the use of thiourea as a cheap and easy to handle dihydrosulphide surrogate for the synthesis of symmetrical diaryl thioethers (Scheme 1.15).[127]



Scheme 1.15

1.2 Applications of palladium-catalysed aryl C-X bond forming reactions in aromatic heterocycle synthesis

1.2.1 Introduction

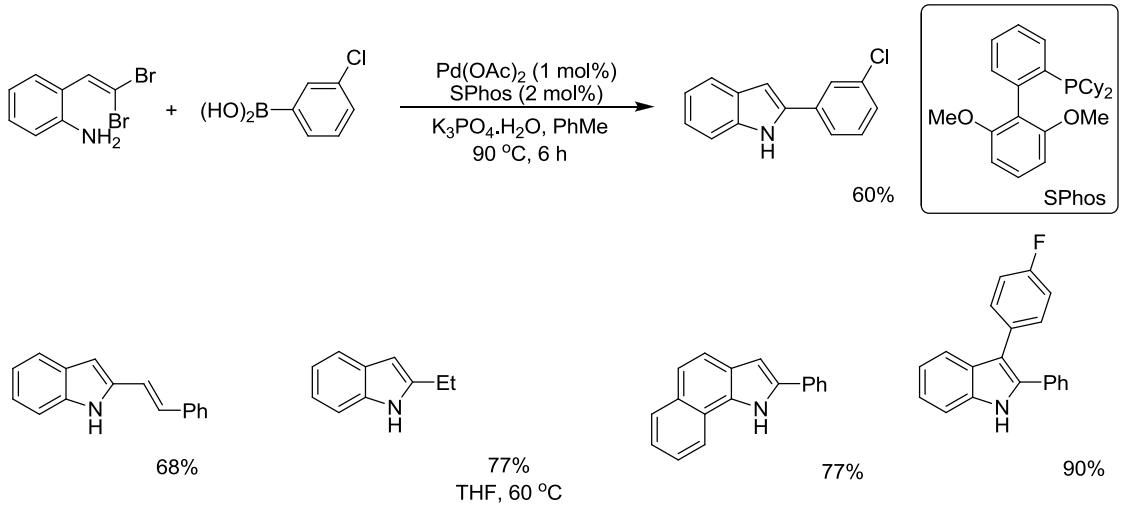
Palladium catalysis has played a huge role in the development of routes to important heterocyclic compounds, offering efficient construction of complex molecules from readily available starting materials under mild conditions.[128-133] Many of these syntheses include the use of intermolecular, intramolecular or tandem aryl C-X bond forming processes. A recent review detailing the use of such palladium- and copper- catalysed aryl C-X bond forming reactions for the synthesis of aromatic heterocycles has been published by Willis and Sadig.[134] Thus, only a brief overview of some palladium-catalysed approaches will be presented here in order to provide an introduction to the work presented in the following chapters.

1.2.2 Palladium-catalysed aryl C-N bond forming reactions in aromatic heterocycle synthesis

A whole host of aromatic heterocycles, in particular five- and six-membered benzo-fused structures have been constructed using palladium-catalysed amination reactions. Of these, indoles have proved to be a popular target, as this scaffold is commonly found in biologically active natural products and designed compounds.[135-138]

A number of groups have developed palladium-catalysed cascade routes to indoles from key precursors, for example Willis *et al*. have reported syntheses, which utilise 2-(2-haloakenyl)aryl halides and their corresponding alkenyl triflates.[139-143] These routes (as well as additional work from the group) will be further elaborated on in section 1.2.4.

The Lautens group have demonstrated the utility of *gem*-dihalovinyl anilines which,[ii] for example, undergo tandem intramolecular C-N arylation/Suzuki coupling reactions with organoboron reagents under palladium catalysis, affording 2-substituted indoles.[144, 145] A wide range of substituents were tolerated on the aniline substrate and a variety of organoboron reagents could be successfully coupled as shown in Scheme 1.16.



Scheme 1.16

The group showcased the use of this methodology as the key step in the synthesis of KDR kinase inhibitors[146] and extended it to the synthesis of azaindoles from pyridine analogues.[147] They have also demonstrated the combination of different palladium-

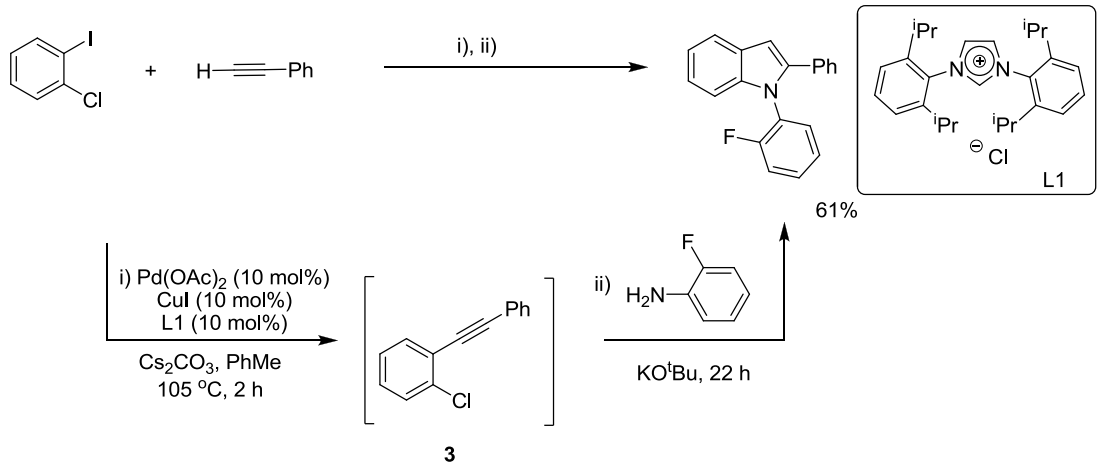
[ii] Although these processes involve aminations of alkenyl halides (as opposed to aryl halides), they have been included due to their significance to the development of Pd-catalysed routes to indoles.

catalysed processes in this sequence, namely Heck,[148] Sonogashira[149] and direct arylation[150] couplings for the synthesis of 2-vinylic, 2-alkynyl and polycyclic indoles respectively. The inclusion of a carbonylation process for the synthesis of 2-carboxyindoles[151] or carbonylation/Suzuki couplings affording 2-aroylindoles[152] has been reported by other groups.

Recently, Lautens *et al*. have reported the impressive synthesis of 2-bromo indoles from *gem*-dibromovinyl anilines.[153] The use of the bulky P^tBu_3 ligand, facilitated successful catalyst turnover by allowing reversible oxidative addition of palladium into the C-Br bond of the bromo indole product.

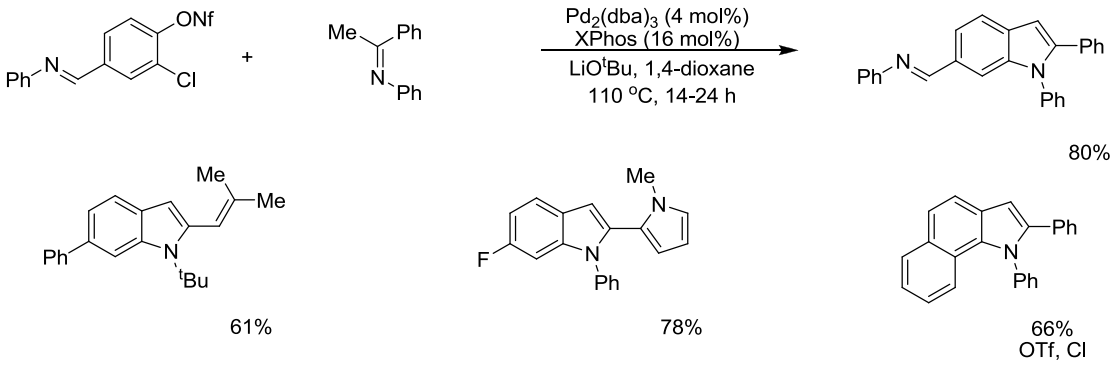
Alternative precursors, namely *o*-alkynylhaloarenes, have been developed by Ackermann *et al*.[154-157] and others[158-160] for the palladium- (and copper-) catalysed synthesis of indoles *via* coupling with primary amines. Recently, Stradiotto *et al*. have demonstrated the first use of ammonia as a successful coupling partner in these reactions for the synthesis of N-H indoles by the use of a Hartwig JosiPhos ligand.[161]

The Ackermann group have also reported an elegant three-component synthesis of indoles, involving the tandem coupling of *o*-chloroiodobenzenes with terminal alkynes followed by introduction of a nitrogen nucleophile.[162] The reaction was catalysed by a combined palladium/copper system, with the initial coupling occurring at the aryl iodide to afford intermediate **3** (Scheme 1.17). Although this protocol provides a shorter route to indoles, the range of amines, dihalo substrates and alkynes tolerated was limited.



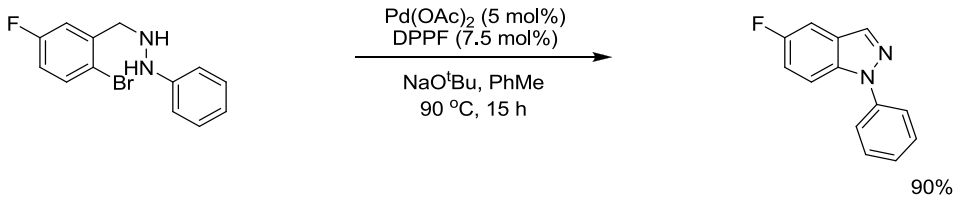
Scheme 1.17

The Barluenga group have developed an indole synthesis based on the palladium-catalysed coupling of 1,2-dihaloarenes with ketimines.[163] These reactions proceed *via* an initial α-arylation of the ketimine to form an intermediate imine, which upon tautomerisation to its enamine form, undergoes an intramolecular amination/cyclisation. The further development of *o*-chloroaryl triflate and nonaflate precursors allowed for a wider scope of substituted indoles to be synthesised (Scheme 1.18).[164] Recently, the use of a combined "on-water" microwave protocol has allowed for additional improvements such as reduction in reaction times and catalyst loadings.[165]



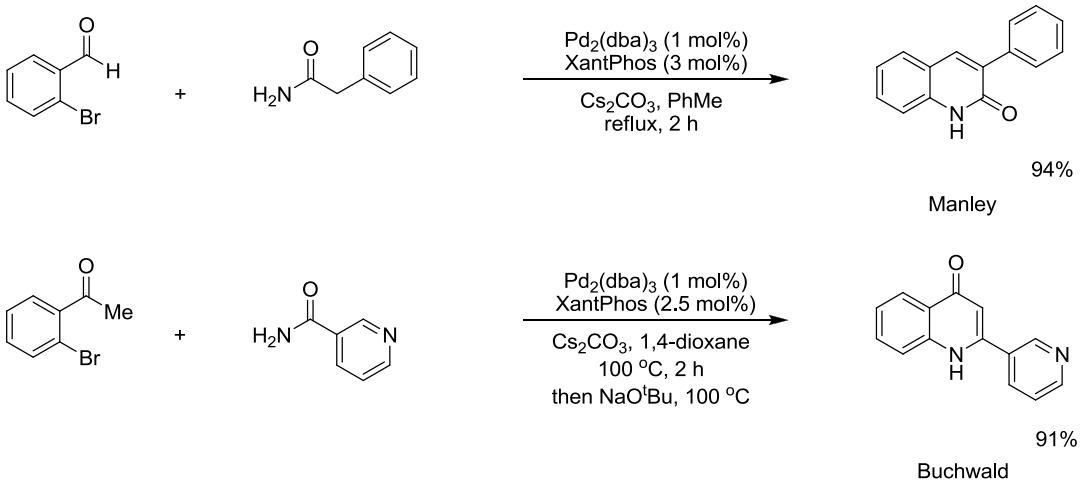
Scheme 1.18

Five-membered benzo-fused heterocycles containing more than one nitrogen atom, specifically benzimidazoles and indazoles (and their related derivatives), have also been synthesised by a range of palladium-catalysed amination reactions. The former will be discussed in Chapter 2. The syntheses of 2-aryl-2*H*-indazoles and 1-aryl-1*H*-indazoles *via* an intramolecular amination cyclisation of *N*-aryl-*N*-(*o*-bromobenzyl)hydrazines and *N*-aryl-*N*'-(*o*-bromobenzyl)hydrazines respectively have been reported by the Song group.[166, 167] In both cases, aromatisation was found to occur spontaneously under the reaction conditions. An example of an 1*H*-indazole synthesised by this method is shown in Scheme 1.19.



Scheme 1.19

The use of a palladium-catalysed intermolecular amidation reaction has been utilised for the synthesis of 2-quinolones by Manley *et al*.[168] and 4-quinolones by Huang *et al*.[169] The Manley group demonstrated that readily available *o*-bromobenzaldehydes can be successfully coupled to enolisable amides using a $Pd_2(dba)_3$/XantPhos catalyst system with a subsequent aldol condensation affording the desired heterocycle. Similarly, Huang and co-workers utilised this catalyst system to couple *o*-acetylbromoarenes with amides. The resulting intermediates were found to undergo an intramolecular cyclisation following the addition of a second base. An example from each group is shown in Scheme 1.20.

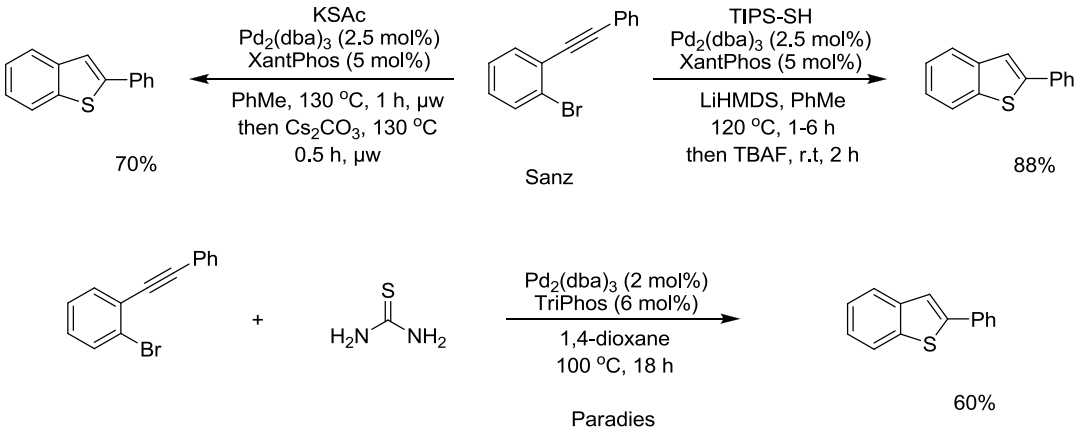


Scheme 1.20

Palladium-catalysed syntheses of six-membered benzo-fused heterocycles containing more than one nitrogen atom have also been reported. For example phenazines have been prepared *via* intramolecular aryl amination of 2-amino-2'-bromodiphenylamines by Kamikawa *et al.*[170] and Beifuss *et al.*[171] Routes to structurally similar heterocycles, specifically quinazolinones will be discussed in Chapter 5.

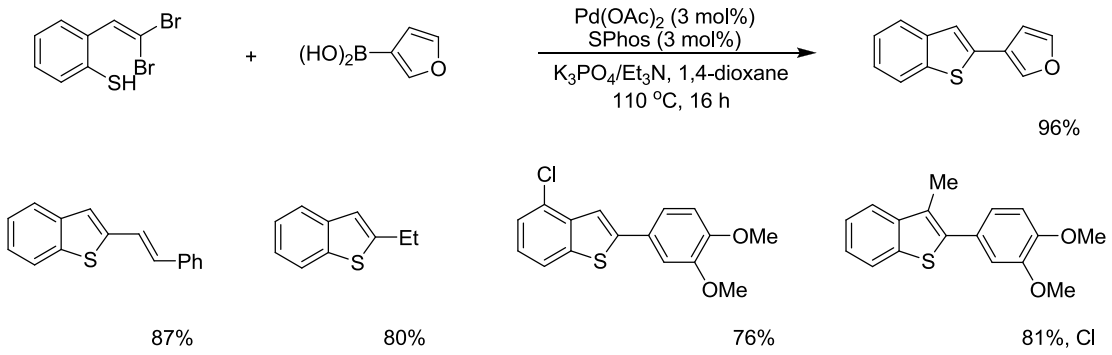
1.2.3 Palladium-catalysed aryl C-S bond forming reactions in aromatic heterocycle synthesis

In comparison to the previous section, relatively few palladium-catalysed aryl thioetherification reactions have been reported for the synthesis of aromatic heterocycles. Sanz *et al.*[172] and Paradies *et al.*[127] have reported the intermolecular coupling of *o*-alkynylbromobenzenes and dihydrosulfide surrogates for the synthesis of benzothiophenes. Sanz and co-workers showed that either potassium thioacetate (followed by treatment by cesium carbonate) or triisopropylsilanethiol (followed by addition of TBAF) could be utilised successfully; the Paradies group employed thiourea as the sulfur source. An example from each laboratory is shown in Scheme 1.21.



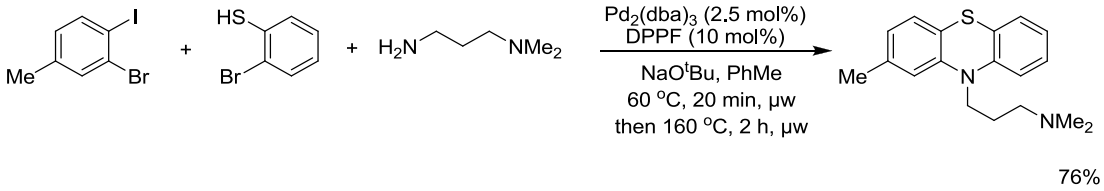
Scheme 1.21

In an analogous fashion to their indole synthesis (see Scheme 1.16), Lautens *et al*. reported the use of *gem*-dihalovinyl thiophenols as precursors for benzothiophenes.[173] The group utilised the reaction of these substrates with a variety of boronic acids under palladium-catalysed conditions to prepare a range of 2-substituted benzothiophenes. The reaction proceeded *via* an intramolecular C-S bond formation/Suzuki-Miyaura coupling sequence. Additionally, other catalytic process, such as Heck and Sonogashira couplings could also be used in this sequence. Examples of the heterocycles synthesised *via* these methods are shown in Scheme 1.22.



Scheme 1.22

An impressive three component synthesis of phenothiazines was reported by Jørgensen *et al.*[174] The one-pot palladium-catalysed cascade reaction between primary amines, 2-bromothiophenols and 1-bromo-2-iodobenzenes was found to proceed *via* an initial thioetherification of the aryl iodide moiety, followed by successive inter- and intramolecular aminations of the aryl bromide moieties. This protocol was used to synthesise a range of phenothiazines as well as members of the promazine class of antipsychotics, such as methylpromazine, which was obtained in a high 76% yield as shown in Scheme 1.23.

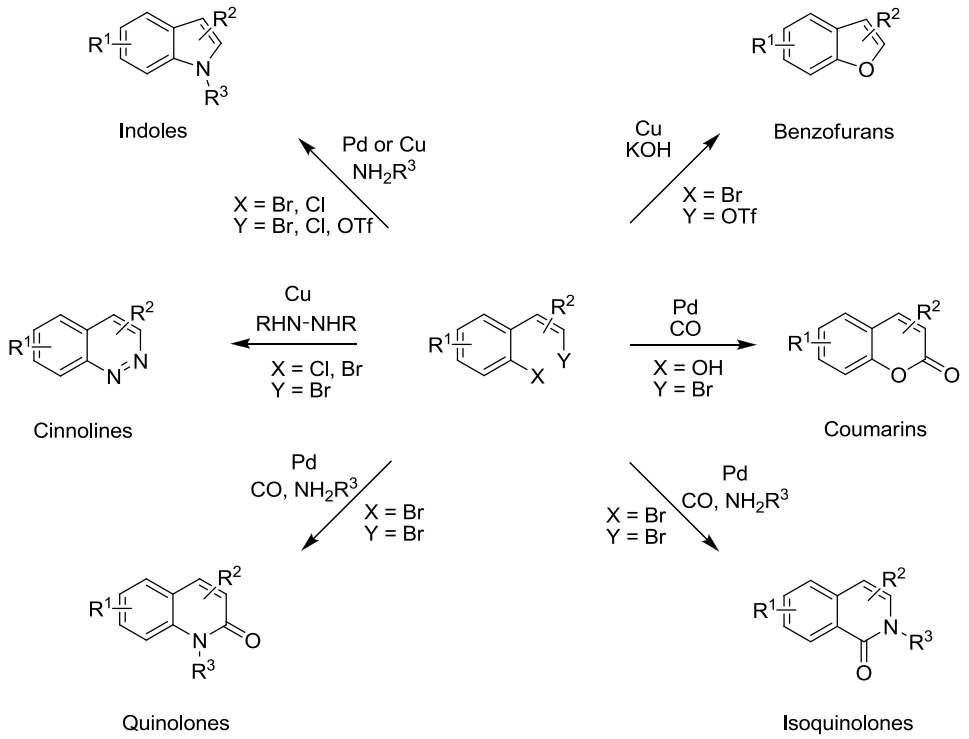


Scheme 1.23

A number of palladium-catalysed routes to benzothiazoles (and their derivatives) involving aryl C-S bond forming reactions have been developed; these will be discussed in Chapter 3.

1.2.4 Previous work from the Willis laboratory

A significant number of palladium- (and copper-) catalysed routes to important aromatic heterocycles have been developed as part of ongoing research within the Willis group. The main focus has been on designing key substrates, which as a result of tandem C-X bond forming reactions with various nucleophiles afford a variety of heterocyclic products. Examples of this are the 2-(2-haloalkenyl)aryl halides and the corresponding alkenyl triflates, which are shown in Scheme 1.24.

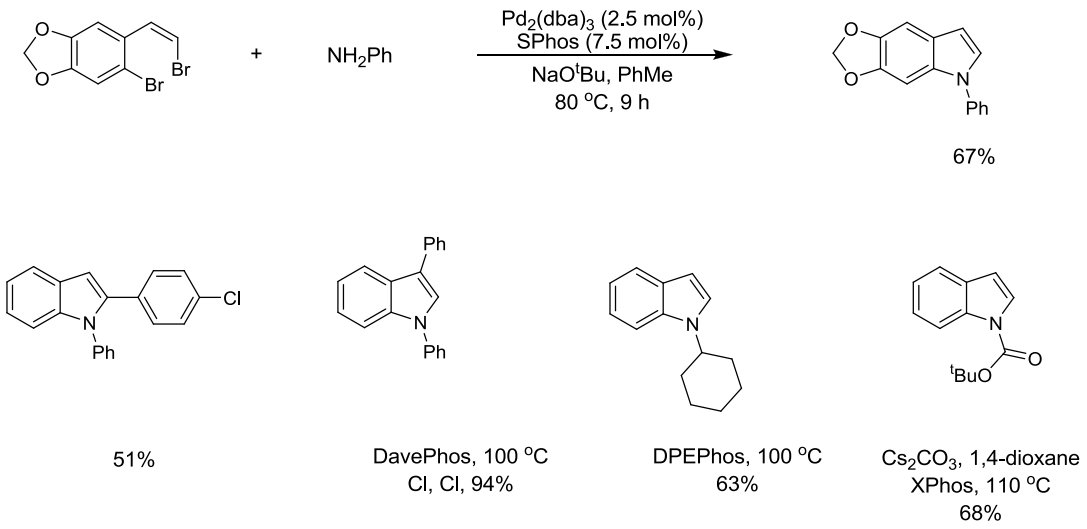


Scheme 1.24

In 2005, a novel route to *N*-substituted indoles, utilising the aryl halide/alkenyl triflate substrate and primary amines was described.[139] This occurred *via* an initial palladium-catalysed intermolecular amination at the alkenyl triflate, affording an enamine intermediate, which cyclised by means of a subsequent intramolecular amination. The starting material was easily synthesised from a two step process and the established catalyst system allowed good variation of both the carbon backbone and the nitrogen nucleophile, affording 2,3-disubstituted indoles in excellent yields. This method however was limited, as synthesis of the precursor substrates for mono- or non-substituted indoles proved difficult.

Alternatively, the use of the similar 2-(2-haloalkenyl)aryl halide starting materials allowed for access to a wider variety of substitution patterns.[140] This starting material was

easily synthesised *via* a one-step Wittig reaction from the (often) commercially available 2-halo benzaldehyde in varying *E/Z* ratios. However, either isomer (or a mixture) could be used as indole precursors due to isomerisation of the enamine intermediate obtained after the initial alkenyl amination. Both the alkenyl and aryl bromides and chlorides successfully afforded the desired heterocycle and the reaction conditions displayed good tolerance for a number of coupling partners. A few examples of the indoles synthesised are shown in Scheme 1.25.



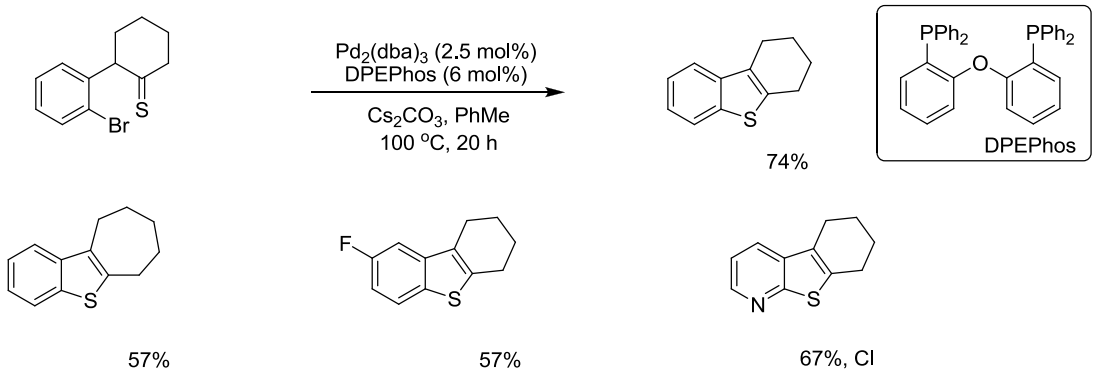
Scheme 1.25

The palladium-catalysed coupling of sterically demanding nitrogen nucleophiles was also shown to be possible and was utilised in the synthesis of the natural product demethylasterriquinone A.[141] This chemistry has also been extended to synthesis of 4-, 5-, 6- and 7-chloroindoles from the trihalogenated precursors.[142] The use of related pyridine-substrates in this tandem process has also proved to be successful in the synthesis of 7-azaindoles.[143] Unfortunately, a general catalyst system was not established, but coupling partners including amines, anilines and carbamates as well as good variation of the

substrate backbone were all tolerated when the appropriate ligand was selected. Access to the other azaindole isomers proved to be less successful due to the instability of their precursors. A copper-catalysed route to *N*-functionalised indoles from similar precursors have also been reported by Willis *et al.*[175] as well as syntheses of cinnolines[176] and benzofurans.[177]

The preparation of 2-quinolones form the aryl bromide/alkenyl bromide substrate *via* a palladium-catalysed carbonylation/intramolecular amidation cascade reaction has been reported.[178] This will be discussed further in chapters 4 and 5.

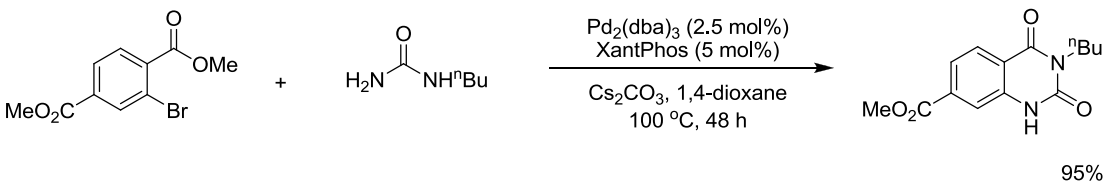
The Willis group has also developed α-(*o*-haloaryl) ketones and thioketones as heterocycle precursors; for example the synthesis of benzofurans and benzothiophenes *via* palladium-catalysed intramolecular enolate *O*-arylation or thioenolate *S*-arylation respectively.[179, 180] Some examples of the sulfur heterocycles synthesised are shown in Scheme 1.26.



Scheme 1.26

The ketone substrates could further be utilised for the synthesis of isocoumarins when subjected to an atmosphere of carbon monoxide *via* an aryl-carbonylation/intramolecular *O*-enolate acylation reaction.[181]

A palladium-catalysed strategy for the synthesis of 3-substituted quinazolinediones has also been developed.[182] This route utilised an initial amidation coupling reaction of monosubstituted ureas with *o*-bromobenzoates, which occurred regioselectively at the less substituted *N*-atom. A subsequent base-promoted intramolecular cyclisation gave the desired heterocycles in high yields; a representative example is shown in Scheme 1.27.



Scheme 1.27

1.3 Concluding comments

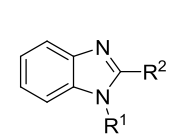
As this discussion demonstrates, the palladium-catalysed C-X bond forming reaction has become a highly versatile synthetic tool. A wide range of aryl and hetero aryl halides and pseudo halides can now be efficiently coupled to a large variety of nucleophiles under mild reaction conditions. The invaluable application of these reactions for the synthesis of important aromatic heterocycles has also been shown. However, development of this methodology is ongoing, with efforts being directed into finding truly universal catalyst systems, which will undoubtedly bring about further improvements to this field of chemistry.

Chapter 2: Palladium-catalysed synthesis of benzimidazoles

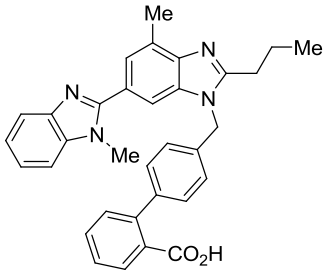
2.1 Introduction

2.1.1 The importance of benzimidazoles

Heterocyclic compounds such as benzimidazoles (Figure 2.1) can be found in a vast array of bioactive, naturally occurring compounds as well as designed pharmaceutical molecules. Specifically, 1,2-disubstituted benzimidazoles have been shown to possess a wide variety of biological properties such as hepatitis C virus NS5B polymerase inhibitors.[183] Examples of the pharmacological properties they exhibit include analgesic,[184] chemotherapeutic,[185] antidiabetic,[186] antiviral[187] and antihistamine.[188] As a result, several commercial pharmaceutical products based on this motif have been developed such as telmisartan, an antihypertensive.[189] These privileged structures also have uses in fungicides and herbicides[190] as well as intermediates for dyes and polymers[191] and ligands for copper-catalysed reactions.[192]



1,2-benzimidazole motif



telmisartan

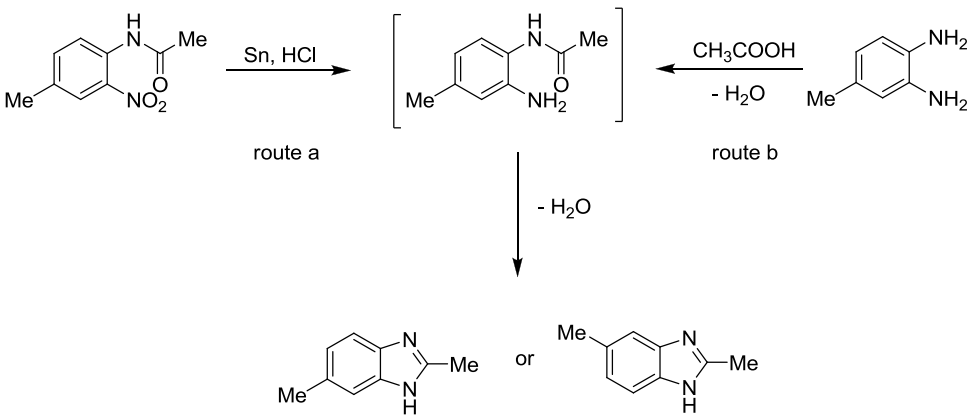
Figure 2.1

2.1.2 Synthesis of benzimidazoles

As a consequence of their importance, a vast number of methods for the synthesis of benzimidazoles exist, including a large number of classical routes. As many existing books[193-199] and reviews[200-208] detail these, only a few will be highlighted in this section.

The latter discussion will focus on modern metal-catalysed methods, which are of more importance to the work presented in this chapter.

The majority of classical syntheses of benzimidazoles involve aryl starting materials which have two nitrogen containing functionalities positioned *ortho* to one another. The first benzimidazole synthesis to appear in the literature dates back to 1872. Hoebrecker achieved this by reduction of *N*-(4-methyl-2-nitrophenyl)acetamide to the corresponding amine, which after a condensation reaction yielded 2,5- and 2,6-dimethylbenzimidazole (Scheme 2.1, route a).[209] In 1875, Ladenburg synthesised the same heterocycles by refluxing 3,4-diaminotoluene with acetic acid (route b).[210]



Scheme 2.1

Methods based on route (a) have become popular ways of synthesising benzimidazoles.[199] A number of reductants have been found to successfully allow cyclisation of *o*-(*N*-acylamino and arylamino) arylamines from their corresponding nitro compounds. Examples include tin and acetic acid, tin(II) chloride and hydrochloric acid, iron and acetic acid, hydrogen-palladium-carbon, sodium dithionite or sodium borohydride. This method is often superior to those following route (b), with higher yields and a wider variety of benzimidazoles being obtained.

Route (b), namely the condensation of *o*-diaminobenzenes with a carboxylic acid, however is still a common way of synthesising benzimidazoles.[199] The Phillips method, which involves heating the reagents together in the presence of hydrochloric acid, is the most widely used set of conditions, however many more have been developed.[211] These include use of other acid catalysts (such as PPA and boric acid), heating with a titanium catalyst, heating under high pressure or the use of photolysis. Carboxylic acid derivatives such as esters, amides, anhydrides and acid chlorides, nitriles, imidates and *ortho*-esters can similarly be used. Aldehydes can also be utilised, however in this case, the use of an oxidant (e.g. nitrobenzene) is required.

The main drawbacks of these methods is the use of harsh reaction conditions, such as high reaction temperatures or pressures, use of stoichiometric or excess amounts of acids or other toxic reagents and generation of environmentally hazardous by-products. Reaction times can also be long and often mixtures of regioisomeric products are afforded in low isolated yields. They are also restricted by the availability of the starting materials, thus limiting the complexity of the heterocycles that can be synthesised.

Modern approaches to benzimidazoles, which overcome some of the limitations of classical methods, rely on transition metal-catalysed reactions. Recent reviews by Willis[134] and others[212, 213] cover many of these existing routes to benzimidazoles, thus an overview of these will be presented here as an introduction to the syntheses we have developed. Figure 2.2 shows the main disconnection approaches to benzimidazoles which

utilise palladium- as well as copper-catalysed[iii] processes and primarily focuses on the aryl halide starting material used.

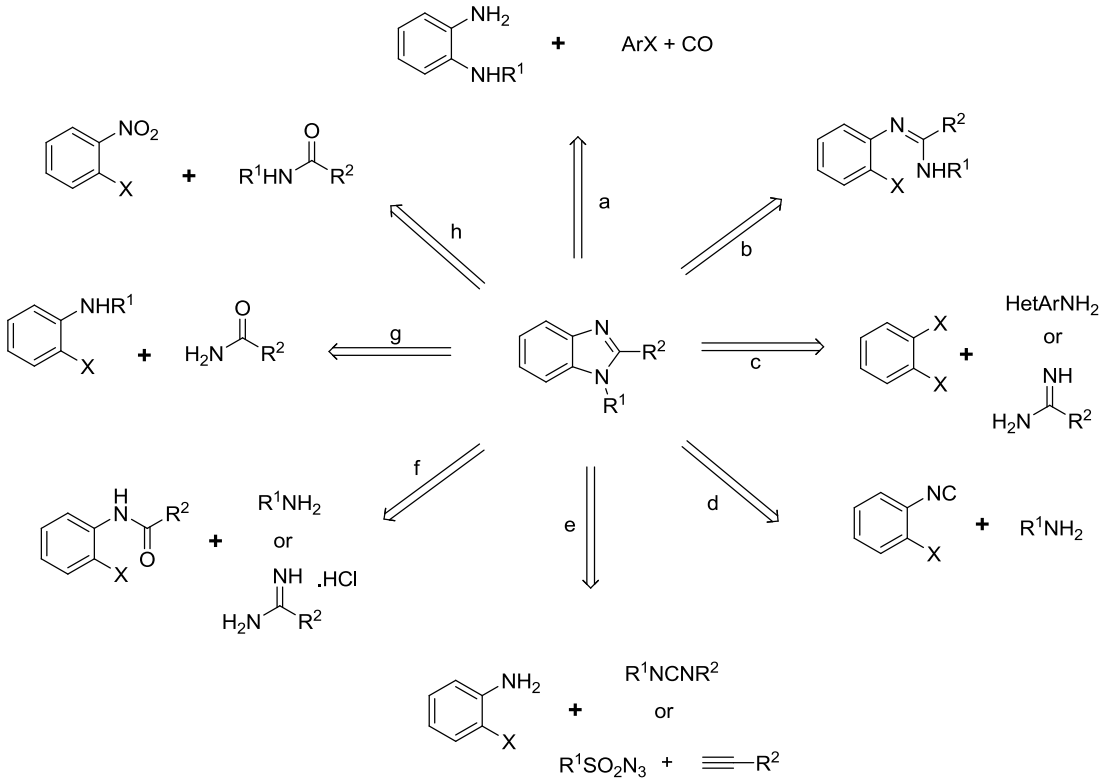
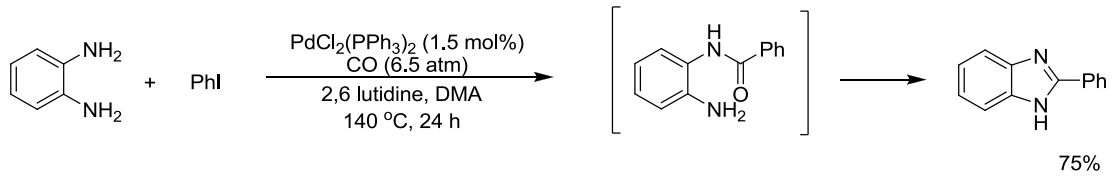


Figure 2.2

The first example of a palladium-catalysed benzimidazole synthesis was described by Perry *et al*. in 1993.[214] This method exploited an aminocarbonylation reaction of an *o*-aminoanilines with an aryl iodide or bromide (Figure 2.2, disconnection a) to form intermediate benzamides (an example is shown in Scheme 2.2). These successfully cyclise under the basic reaction conditions to form 2-aryl (or heteroaryl) benzimidazoles in mostly high yields, with a good variety of functional groups tolerated. Although this method offered a complimentary route to classical syntheses when benzoic acid

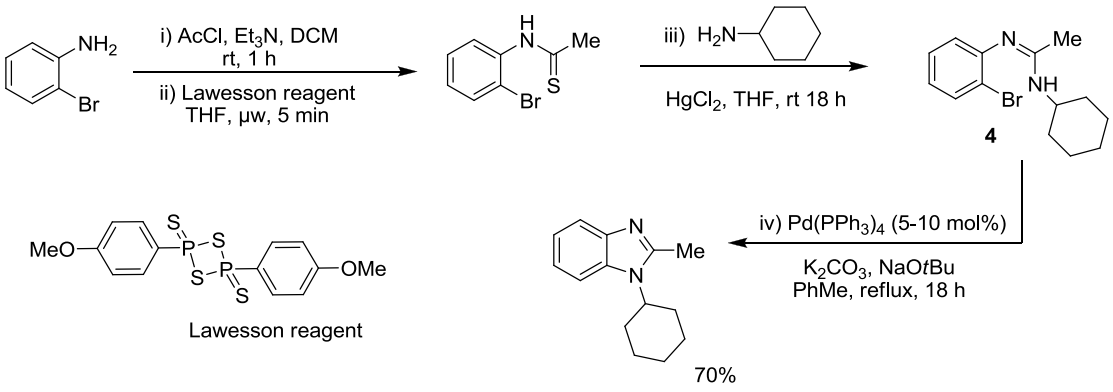
[iii] These have also been included due to their importance in the development of catalytic routes to benzimidazoles.

derivatives are unavailable, it required high pressures of carbon monoxide gas (*ca*. 6.5 atm).



Scheme 2.2

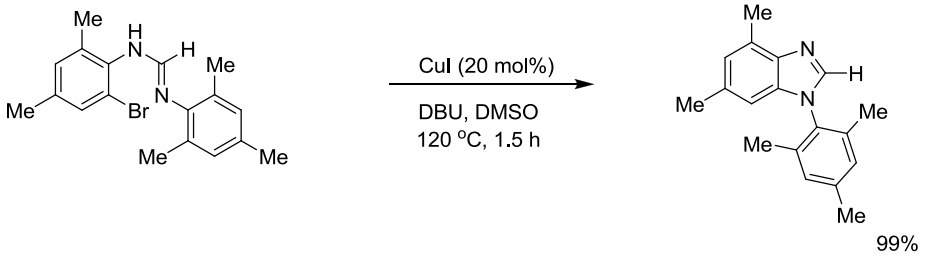
As discussed in Chapter 1, palladium-catalysed aryl C-N bond forming reactions have played an important role in the development of novel syntheses of heterocycles and the benzimidazole scaffold is no exception. In particular, routes which utilise *N*-arylation reactions of amidines have proved to be efficient ways to construct benzimidazoles.[213] The first example of this was reported in 2002 by Brain *et al*. who demonstrated the use of *N*-(*o*-bromophenyl)amidines as starting materials for the synthesis of benzimidazoles, *via* an intramolecular palladium-catalysed C-N bond forming reaction (Figure 2.2, disconnection b).[215, 216] Although this route afforded the desired heterocycles in high yields, additional steps were required to make the precursor. For example, amidine **4** (Scheme 2.3) was synthesised from *o*-bromoaniline *via* the corresponding thioamide in three steps. Other examples were made more directly from the reaction of *o*-bromoanilines with amides using $POCl_3$. A more efficient second generation synthesis was developed by the group, which used lower catalyst loadings, microwave irradiation allowing for shorter reaction times and an improved purification strategy.[216]



Scheme 2.3

Bernotas *et al*. have since shown that *N*-(*o*-chloroaryl)amidines can also be used as precursors to benzimidazoles.[217] The same palladium catalyst was utilised, however use of xylenes or DMF as the solvent at elevated temperatures was required to afford higher yields. A full scope has not been examined, with only three examples presented in this publication.

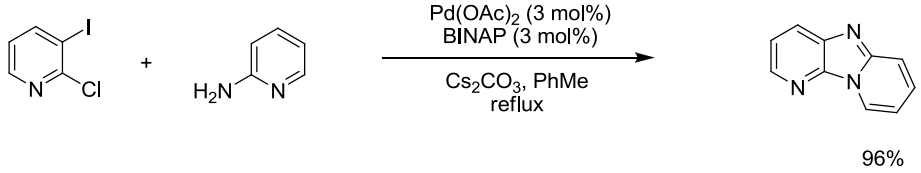
Glorius *et al*. have reported a related copper-catalysed intramolecular arylation of *N*-(*o*-haloaryl)-formamidines for the synthesis of 2-unsubstituted, *N*-substituted benzimidazoles.[218] The starting materials were easily synthesised and excellent yields were observed for the bromide substrates (an example is shown in Scheme 2.4). Only two examples of the chloride substrates are given, both obtained in moderate yields after very long reaction times.[219]



Scheme 2.4

Recently Chen and Peng have published a similar copper-catalysed cyclisation of *N*-(*o*-haloaryl)-amidines for the synthesis of 1*H*-benzimidazoles using water as the reaction solvent.[220] Use of iodide or bromide substrates was necessary as chloride substrates gave decomposition products.

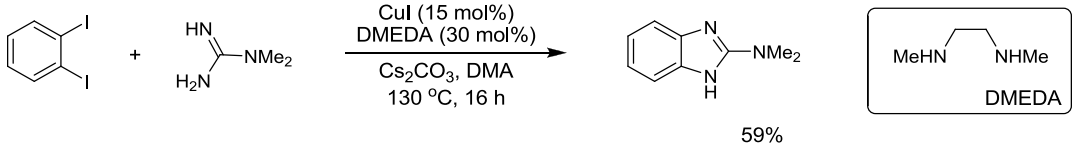
A more concise route has been developed by Maes *et al.* who demonstrated that benzo-fused benzimidazoles can be accessed *via* a palladium-catalysed cascade amination strategy (Figure 2.2, disconnection c).[221] For example 2-chloro-3-iodopyridine was coupled with 2-picoline to afford the corresponding dipyridoimidazole in an excellent yield (Scheme 2.5). Related cascade processes have also been used for preparation of a number of benzo- and aza-fused benzimidazole analogues.[222-225]



Scheme 2.5

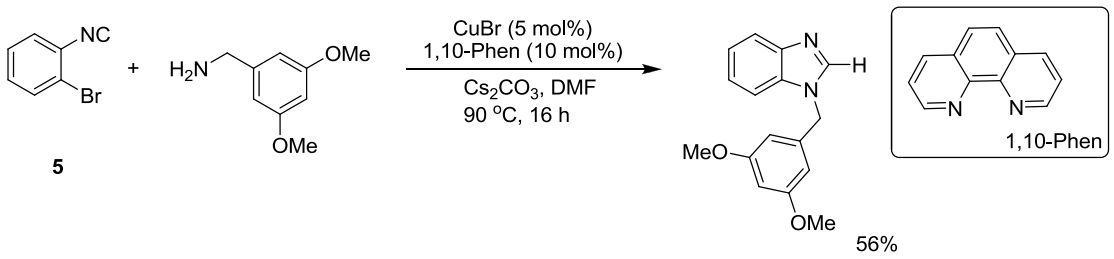
1*H*-Benzimidazoles and 1*H*-benzimidazol-2-amines have been synthesised *via* copper-catalysed coupling of 1,2-dihalobenzenes with amidines or guanidines respectively.[226,227] An example from the Deng laboratory, which utilises 1,2 diiodobenzene, is shown in Scheme 2.6. However use of 1-bromo-2-iodobenzene and 1-chloro-2-iodobenzene afforded the product heterocycles in poor isolated yields. The scope of the coupling partners (both amidine and guanidine) was also limited and high temperatures of up to 170 °C were required with only moderate yields being afforded along with decomposition side-products. The same group also developed a regioselective synthesis of 1,2-

disubstituted benzimidazoles from *N*-substituted amidines, however most examples were isolated in low yields.[228]



Scheme 2.6

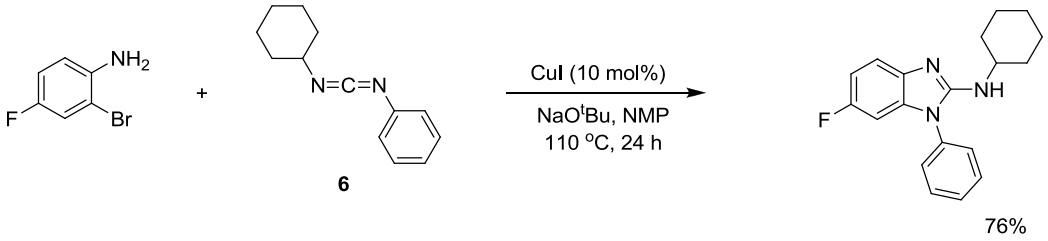
An elegant tandem approach to 2-unsubstituted, *N*-substituted benzimidazoles was reported by De Meijere and Lygin (Figure 2.2, disconnection d).[229] They combined the copper-catalysed *in-situ* formation of amidines (from *o*-bromophenyl isocyanide **5** and primary amines) and their subsequent intramolecular amination to afford the heterocyclic products (Scheme 2.7). A wide scope of the primary amine coupling partner was explored with unsubstituted isocyanide **5** affording a variety of benzimidazoles in moderate yields.



Scheme 2.7

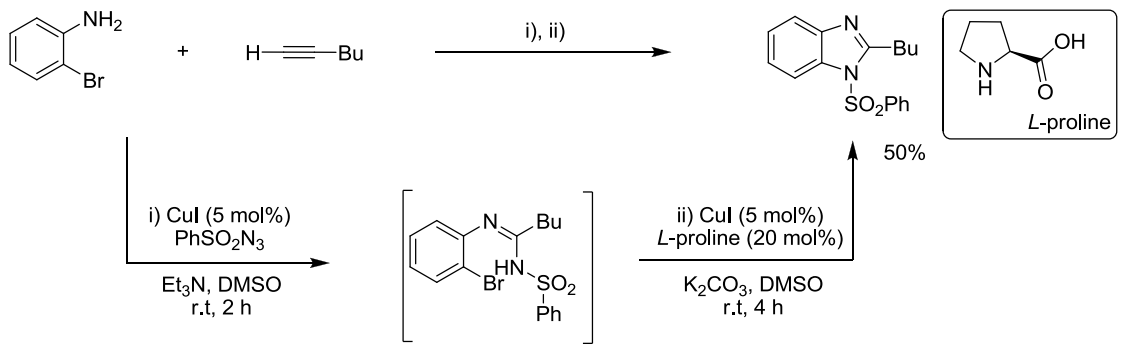
Bao *et al.* have developed a concise strategy for the synthesis of *N*-aryl-2-aminobenzimidazole derivatives (Figure 2.2, disconnection e).[230] This one-pot process involved a copper-catalysed coupling of readily available *o*-haloanilines to diphenylcarbodiimide, followed by cyclisation and was carried out successfully under ligand-free conditions. Recently Xi *et al*. have extended the scope of both the aniline and

carbodiimide coupling partner, synthesising a large range of substituted 2-aminobenzimidazoles in good to excellent yields.[231] Carbodiimides possessing both aryl and alkyl substituents, such as **6** (Scheme 2.8) were shown to display highly regioselectivity, with intramolecular cyclisation of the intermediate guanidine occurring preferentially at the aryl-NH over the alkyl-NH moiety.



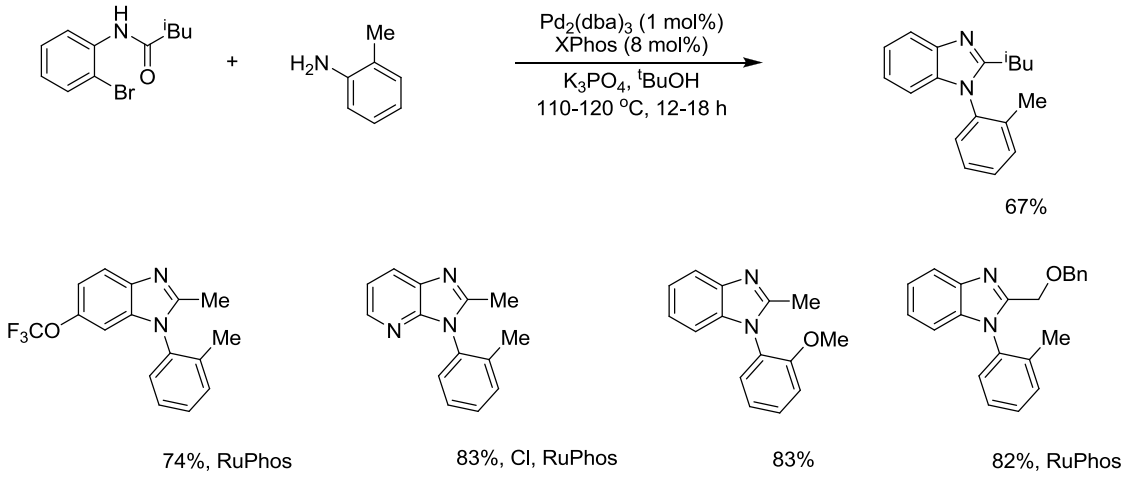
Scheme 2.8

The three component copper-catalysed coupling of *o*-bromoanilines, sulfonyl azides and alkynes has been utilised for the efficient synthesis of 2-substituted 1-sulfonylbenzimidazoles (Scheme 2.9).[232] The proposed mechanism involves a copper-catalysed condensation of the sulfonyl azide and the alkyne, forming a ketenimine intermediate. Attack of the aniline yields an *N*-sulfonylamidine, which can undergo copper-catalysed intramolecular amination affording the heterocyclic product in moderate to high isolated yields.



Scheme 2.9

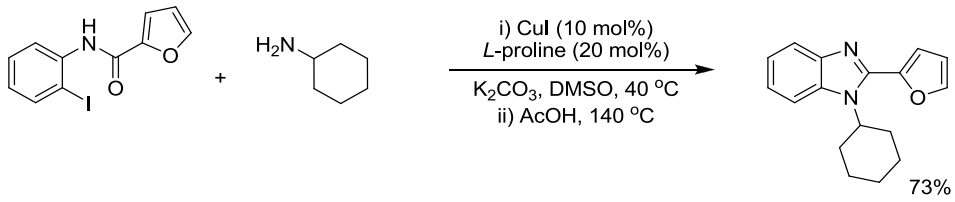
An alternative approach to benzimidazoles utilises intermolecular aryl amination reactions of *o*-haloacetanilides with *N*-nucleophiles (Figure 2.2, disconnection f). These starting materials offer the advantage of being easily synthesised (often requiring just one step) and isolated. For example, Buchwald *et al*. have reported a palladium-catalysed route to *N*-arylbenzimidazoles *via* the coupling of *o*-bromo or *o*-chloroacetanilides to anilines.[233] The resultant *o*-aminoamide intermediate underwent dehydration under the reaction conditions to afford the desired heterocyclic product. Most examples were isolated in high yields; however variation of the ligand (XPhos or RuPhos) was required for some substrates (Scheme 2.10).



Scheme 2.10

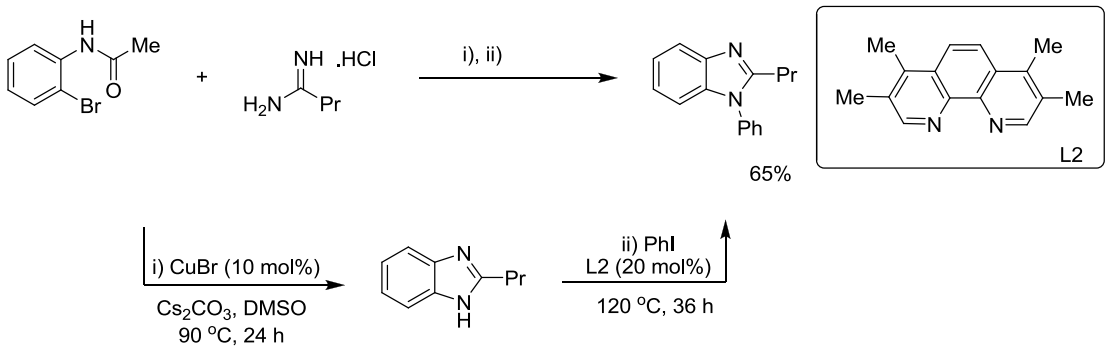
Ma *et al*. have reported a number of similarly efficient copper-catalysed routes.[234] Their first in 2007 demonstrated that *o*-haloacetanilides can be coupled to primary amines using copper(I) iodide and *L*-proline, which upon cyclisation (either under the reaction conditions or after heating with acid) afforded the benzimidazole products (Scheme 2.11). Both iodides and bromides could be used and a wide variety of amines were tolerated. The same catalyst system was also shown to affect the conversion of *o*-iodoarylcarbamates to benzimidazolones.[235] A route to the N-H derivatives of both

heterocycles was also developed *via* the use of aqueous ammonia as the nitrogen nucleophile.[236]



Scheme 2.11

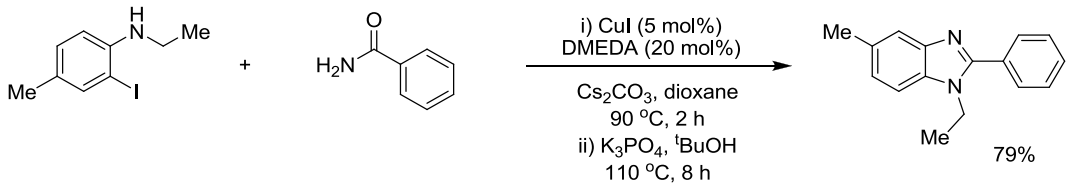
In 2008, Fu and Hu developed a copper-catalysed synthesis of 2-substituted benzimidazoles from the reaction of *o*-haloacetanilides with readily available amidine hydrochlorides (Scheme 2.12, step i).[237] They also demonstrated a one-pot protocol for the synthesis of 1,2-disubstituted benzimidazoles which combined the initial heterocycle forming process with an arylation reaction (step ii). Although the first step is ligand-free, the use of L2 was required for the second step.



Scheme 2.12

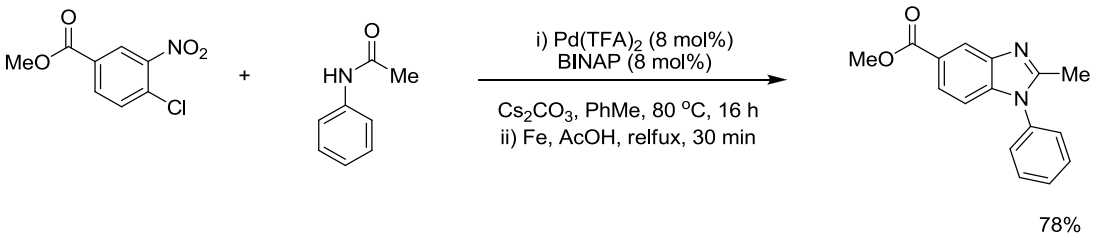
A copper-catalysed route based on an aryl amidation of *o*-iodo-*N*-alkylanilines, to afford *N*-alkylbenzimidazoles has been developed by Buchwald (Figure 2.2, disconnection g).[238] A wide variety of amides were tolerated in the reaction; however a second cyclisation step was required (Scheme 2.13). This route proves a complementary method to their

previously mentioned palladium-catalysed synthesis of *N*-arylbenzimidazoles and both provide regioisomerically pure products.



Scheme 2.13

A related process has recently been published by Lidenschmidt and co-workers.[239] This method utilises a palladium-catalysed amidation of *o*-halonitrobenzenes, followed by a reductive cyclisation reaction (Figure 2.2, disconnection h). A variety of functional groups were tolerated on the aryl chloride substrate when coupled to *N*-phenyl-acetamide and a wide range of secondary amides were successfully coupled to *o*-iodonitrobenzene in high yields. The example shown in Scheme 2.14 was prepared on a 5 gram scale.



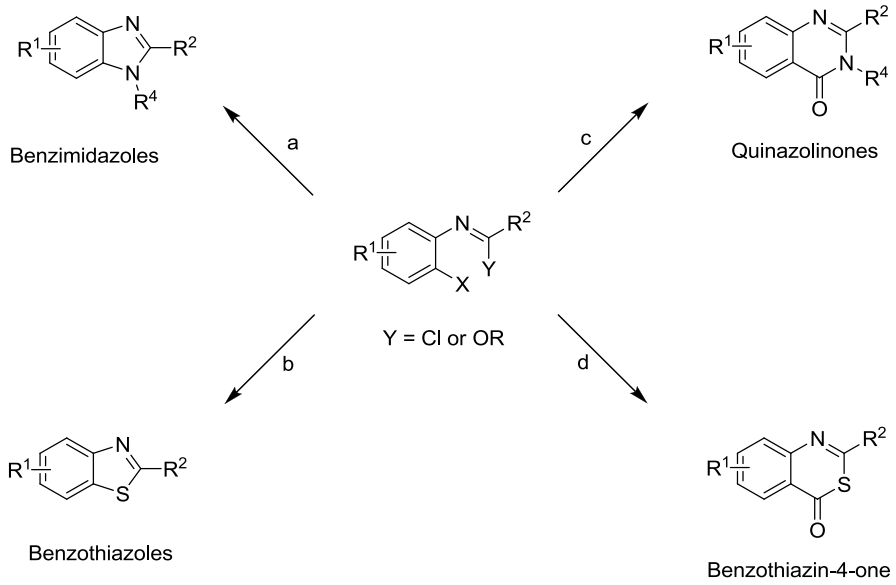
Scheme 2.14

It should be noted that other palladium- and copper-catalysed benzimidazole syntheses also appear in the literature. These include a palladium-catalysed C-H functionalisation/C-N bond formation approach,[240] copper-catalysed C-H functionalisation routes[241-243] and palladium-catalysed intramolecular sulfonamidation/oxidation of imines.[244]

2.2 Results and Discussion

2.2.1 Proposed route to 1,2-disubstituted benzimidazoles and initial goals

As discussed in section 1.2.4, work within the Willis group focuses on the development of a number of key starting materials which could act as building blocks for the synthesis of heterocycles. Prompted by the success of 2-(2-haloalkenyl)aryl halides and the corresponding alkenyl triflates (Scheme 1.24), we envisaged the use of structurally similar precursors, namely *N*-(*o*-halophenyl)imidoyl chlorides (Y = Cl) or imidates (Y = OR) for the synthesis of other important heterocycles (Scheme 2.15).

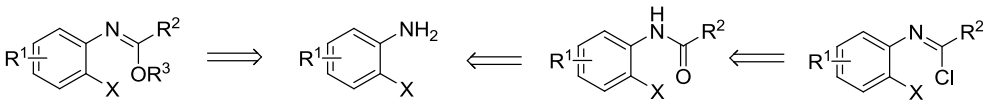


Scheme 2.15

In routes (a) and (b) the five-membered ring fused heterocycles could be formed by reacting with an appropriate nucleophile under palladium-catalysed conditions. This could occur either *via* an initial nucleophile substitution reaction at Y followed by a metal-catalysed cyclisation or *via* an intermolecular C-X bond formation then cyclisation. This sequence would be determined by the leaving group ability of Y on the imidoyl portion (Cl > OR) and the rate at which the metal-catalysed step occurs. Routes (c) and

(d) combine a palladium-catalysed carbonylation step to furnish six-membered benzo-fused heterocycles and will be discussed in Chapter 5.

The straight-forward synthesis of both precursors from commercially available *o*-haloanilines was foreseen, which would allow facile variation of the substrate backbone (Scheme 2.16).



Scheme 2.16

Our initial goal was to investigate the use of these substrates as starting materials for the synthesis of benzimidazoles (their use in benzothiazole synthesis will be discussed in Chapter 3). Although a number of palladium- and copper-catalysed routes to benzimidazoles have been developed (see section 2.1.2), we envisaged that the use of our substrates would provide a novel and practical synthesis of these important heterocycles. We were also keen to develop a set of reaction conditions, which would allow for the incorporation of a variety of *N*-nucleophiles and afford regioisomerically pure 1,2-disubstituted benzimidazoles in a single-step process.

During our investigations, two reports were published which demonstrated the use of *N*-(*o*-halophenyl)imidoyl chlorides in the copper-catalysed synthesis of benzimidazoles. In the work carried out by Wu *et al*., a ligand-free copper(I) iodide catalyst system was used for the coupling of a limited number of *N*-(*o*-iodophenyl)imidoyl chlorides to a variety of amine nucleophiles affording the heterocycles in high yields.[245] The Zhang group were able to extend this to *N*-(*o*-bromo) and *N*-(*o*-chlorophenyl)imidoyl chlorides, however

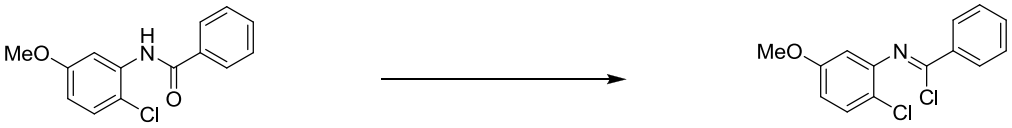
only a small number of examples were synthesised.[246] A major limitation of both reports is the need for an electron-withdrawing substituent (e.g. CF_3) on the imidoyl chloride, thus only *N*-substituted 2-fluoroalkylbenzimidazoles could be synthesised.

2.2.2 The use of *N*-(*o*-halophenyl)imidoyl chlorides as precursors for benzimidazole synthesis: Initial investigations- scope of an established catalyst system

Initial work was carried out into the viability of *N*-(*o*-chlorophenyl)imidoyl chloride substrates as precursors for benzimidazoles. As discussed in Chapter 1, aryl chlorides have been shown to successfully participate in palladium-catalysed amination reactions and provide a cheaper alternative to bromides and iodides.

Imidoyl chlorides can be synthesised from the corresponding secondary amides, with a large number of procedures for this conversion documented in the literature.[247-249] Of these methods, reaction of amide **7** with thionyl chloride[250] or phosphorous pentachloride[251] were tested, as shown in Table 2.1.

Table 2.1 Synthesis of imidoyl chloride 8[a]



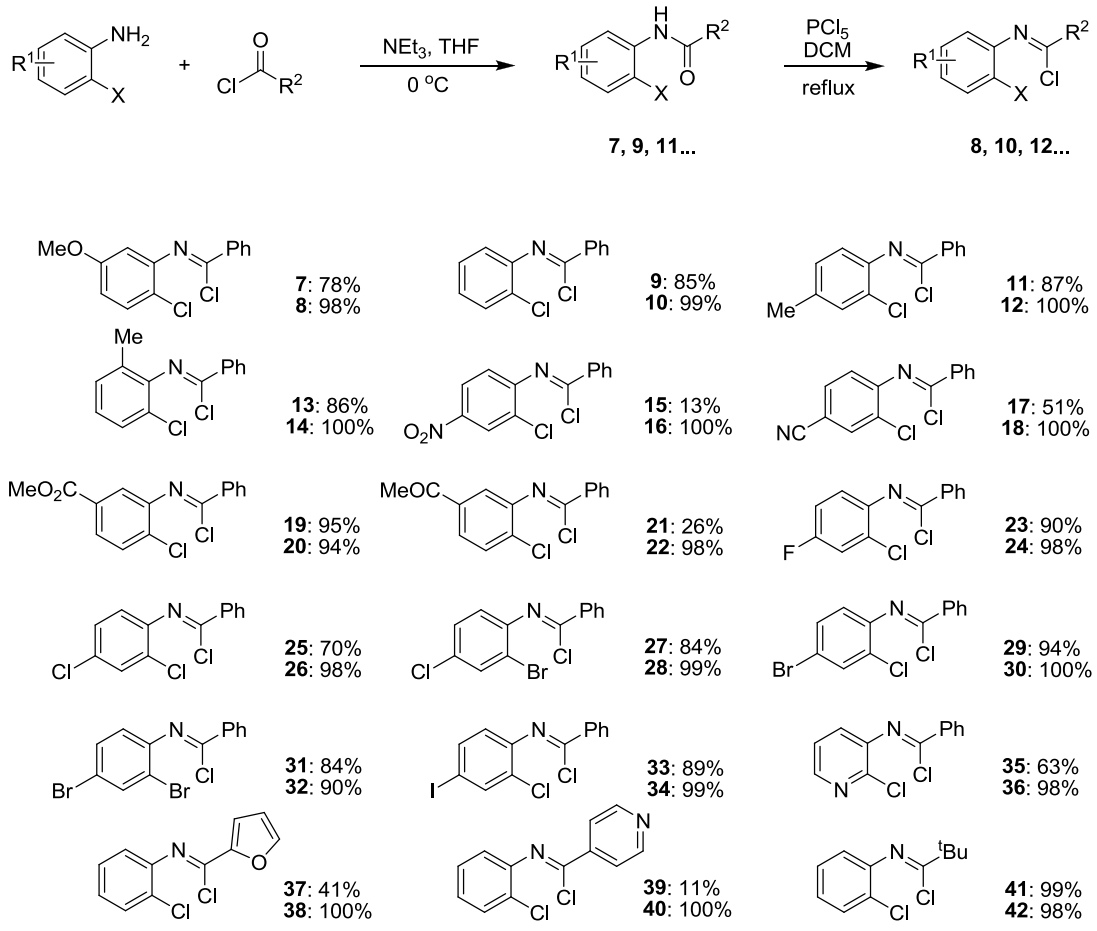
7 **8**

Entry	Reaction conditions	Conversion (%)[b]
1	$SOCl_2$ (7 equiv), DMF (cat) PhMe, reflux	81
2	$SOCl_2$ (14 equiv), DMF (cat) PhMe, reflux	91
3	PCl_5 (1.05 equiv) DCM, reflux	98

[a] Reaction conditions: amide **7** (1.0 equiv), 18 h. [b] Conversion determined from ^{1}H NMR spectrum of crude reaction mixture.

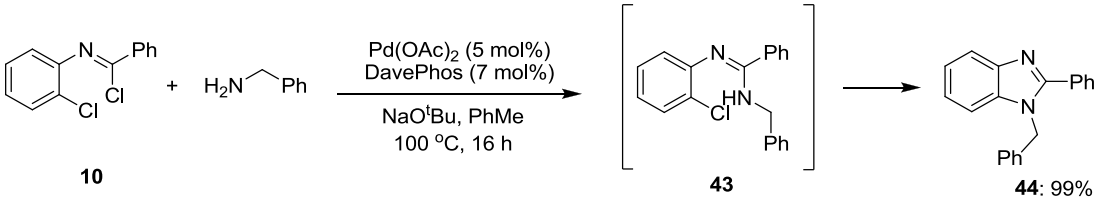
Use of seven equivalents of thionyl chloride was required to afford an 81% conversion of amide **7** to imidoyl chloride **8** (entry1). When this was increased to fourteen equivalents, a higher conversion was obtained (entry 2). However, use of phosphorous pentachloride proved to be more successful. A lower number of equivalents of reagent was used to afford imidoyl chloride **8** in an excellent 98% conversion and the reaction was carried out at a lower temperature (entry 3). Isolation was obtained after heating *in vacuo* (to remove the $POCl_3$) and the purity of these starting materials was confirmed by ^{31}P NMR spectroscopy. Subjection to palladium-catalysed benzimidazole forming test reactions also showed that greater yields of product heterocycle were observed with starting materials synthesised by use of phosphorous pentachloride. This may due to contamination of imidoyl chlorides with sulphur residues as a result of the use of thionyl chloride.

A number of examples were synthesised (Scheme 2.17); in each case the isolated yield of the amide is given followed by their conversion (as determined by ^{1}H NMR spectroscopy) to the imidoyl chloride. An isolated yield was not obtained due to their air and moisture sensitive nature.[251]



Scheme 2.17

Initial palladium-catalysed test reactions had been carried out previously within the group.[252] These revealed that when *N*-(*o*-chlorophenyl)imidoyl chloride **10** and benzylamine were subjected to catalytic palladium conditions benzimidazole **44** was obtained (Scheme 2.18). This was presumed to occur *via* initial nucleophilic substitution at the imidoyl chloride affording amidine intermediate **43** (not isolated), followed by intramolecular metal-catalysed amination cyclisation yielding the desired heterocycle.

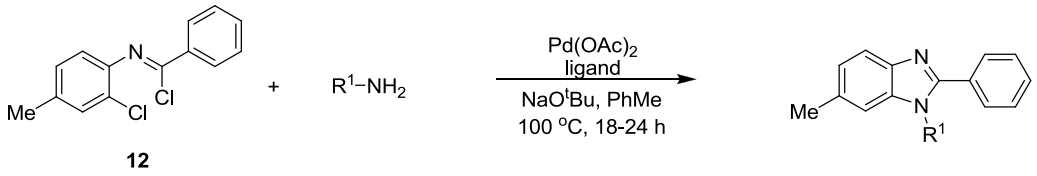


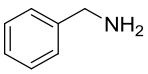
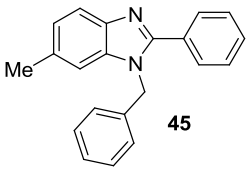
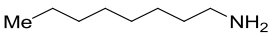
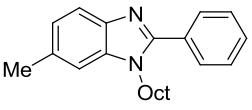
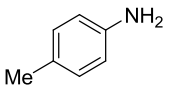
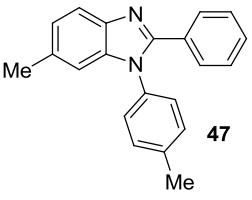
Scheme 2.18

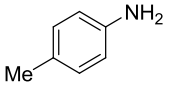
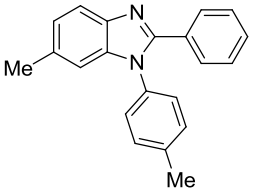
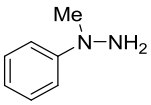
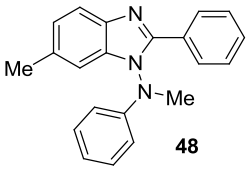
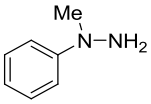
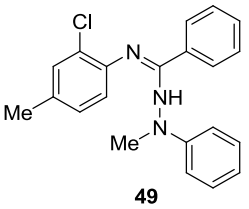
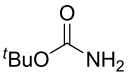
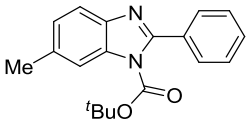
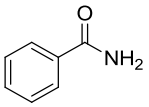
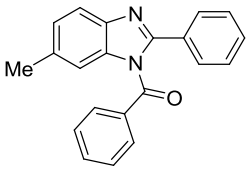
Optimisation of this reaction was carried out including screening of the palladium source, ligand, base, solvent and reaction temperature in order to establish ideal conditions. A catalyst system based on $Pd(OAc)_2$ (5 mol%) and a dialkylbiaryl monophosphine ligand DavePhos (7 mol%), (developed by Buchwald *et al*. for use in amination reactions- see section 1.1.2)[64] along with use of sodium *tert*-butoxide in toluene at 100 °C for 16 hours afforded benzimidazole **44** in an excellent 99% yield.

With this result in hand, the scope of this catalyst system was tested by reaction of imidoyl chloride **12** with a variety of *N*-nucleophile coupling partners. Work was carried out in collaboration with R. Foster and the results are shown in Table 2.2.

Table 2.2- Variation of the *N*-nucleophile[a]



Entry	*N*-nucleophile	Ligand	Product	Yield (%)[b]
1[c]		DavePhos	 **45**	98
2		DavePhos	 **46**	65
3[c]		DavePhos	 **47**	10

4[c]		RuPhos		43
5		DavePhos	 **48**	16
6[d]		DavePhos	 **49**	27
7		DavePhos		0
8[c]		DavePhos		0

[a] Reaction conditions: imidoyl chloride **12** (1.0 equiv), *N*-nucleophile (1.5 equiv), $Pd(OAc)_2$ (5 mol%), ligand (7 mol%), NaO^tBu (3 equiv), PhMe, 100 °C, 18-24 h. [b] Isolated yield. [c] Reaction performed by R. Foster. [d] Reaction carried out at 80 °C.

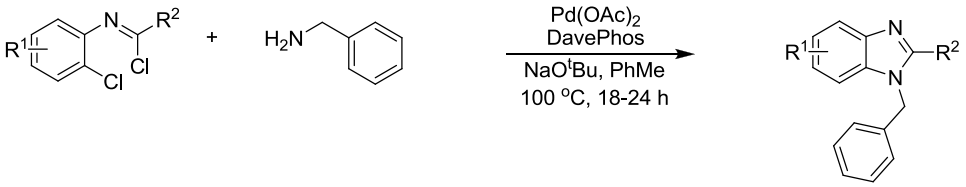
When an alkyl amine was employed, *N*-alkyl benzimidazole **46** was obtained in a moderate yield (entry 2). Use of an aromatic amine, namely *p*-toluidine, afforded *N*-aryl benzimidazole **47** in poor yield (entry 3), due to its reduced nucleophilicity. As previously mentioned in section 2.1.2, Buchwald has shown that *o*-bromoacetanide can be coupled successfully with anilines affording *N*-aryl benzimidazoles.[253] It was shown that DavePhos gave poor conversions in this reaction, however use of RuPhos gave excellent conversions and isolated yields thus it was hoped this may prove to be successful in our reaction. Although use of this ligand gave an increased yield of 43%

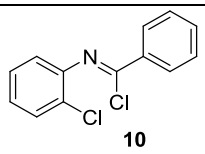
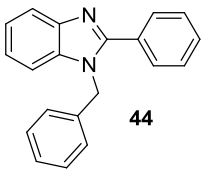
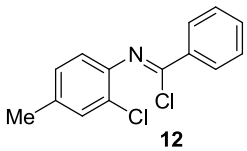
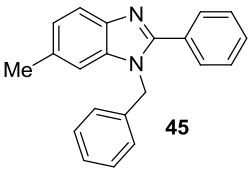
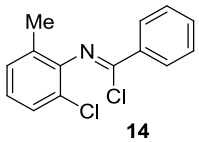
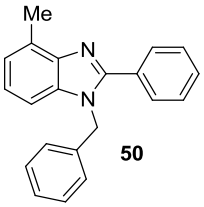
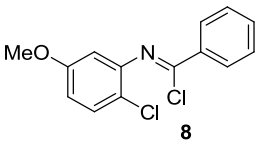
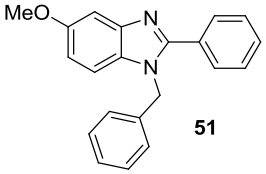
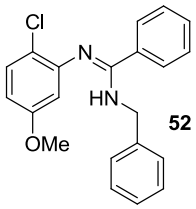
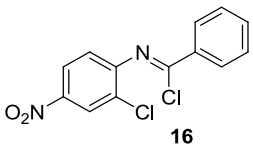
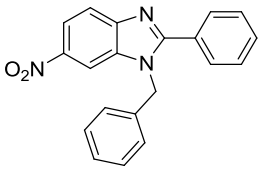
(entry 4), this did not compare to those of Buchwald. The coupling of hydrazines was tested as they were shown to be successful partners in the synthesis of indoles (see section 1.2.4), thus 1-methyl-1-phenylhydrazine was reacted with imidoyl chloride **12** (entry 5). Despite the use of a range of ligands (RuPhos, SPhos and $^{t}Bu_3P.HBF_4$), only low isolated yields of required heterocycle **48** were obtained. This was believed to be due to the instability of the hydrazine at such high reaction temperatures, however when this was lowered to 80 °C only intermediate **49** was isolated in a poor 27% yield (entry 6). Unfortunately, only decomposition products were observed for the carbamate and amide coupling partners (entries 7 and 8), again due to their reduced nucleophilicity.

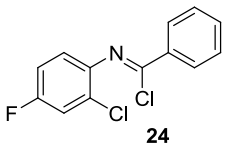
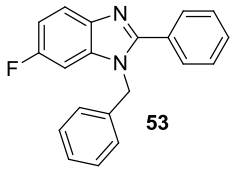
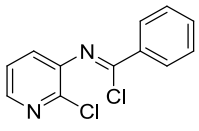
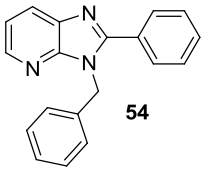
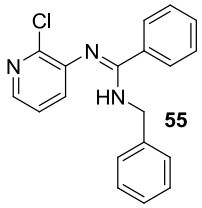
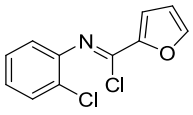
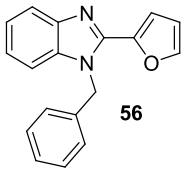
It is worth noting that no starting material was observed in the crude ^{1}H NMR spectrum or recovered from all these reactions, thus suggesting that decomposition may be occurring, resulting in the poor mass recovery observed.

Although these results revealed the reaction's limited tolerance for the nature of the *N*-nucleophile, namely that alkyl and benzyl amines were favoured due to their high nucleophilicity, it was hoped that it would exhibit good functional group tolerance with respect to the imidoyl chloride starting material. Thus, in order to test the reaction scope, a number of imidoyl chlorides were reacted with benzylamine under the established conditions and the results are summarised in Table 2.3.

Table 2.3- Variation of the substrate[a]



Entry	Substrate	Product	Yield (%)[b]
1[c]	 **10**	 **44**	99
2[c]	 **12**	 **45**	98
3	 **14**	 **50**	10
4	 **8**	 **51**	4
		 **52**	18
5	 **16**		0

6[d]	 **24**	 **53**	35
7[d]	 **36**	 **54**	8
		 **55**	47
8[d]	 **38**	 **56**	47

[a] Reaction conditions: imidoyl chloride (1.0 equiv), benzylamine (1.5 equiv), $Pd(OAc)_2$ (5 mol%), DavePhos (7 mol%), NaO^{t}Bu (3 equiv), PhMe, 100 °C, 18-24 h. [b] Isolated yield. [c] Reaction performed by R. Foster. [d] Reaction carried out at 120 °C.

As shown in entries 1 and 2, when unsubstituted imidoyl chloride **10** or imidoyl chloride **12** were used, the product benzimidazoles were obtained in excellent yields. However, when a methyl group was introduced *ortho* to the imidoyl chloride functionality a very poor yield of product was observed (entry 3). Incorporation of an electron-donating methoxy group *para* to the aryl chloride resulted in a very poor yield of benzimidazole **51** product being obtained (entry 4) along with intermediate amidine **52** and decomposition products. Unfortunately, inclusion of a strongly electron-withdrawing nitro group in the starting imidoyl chloride was not tolerated in the reaction, with no benzimidazole formation observed (entry 5). However, the decomposition of nitroarenes under strongly basic palladium-catalysed conditions has been previously reported.[254] A fluorine atom was somewhat tolerated by the reaction conditions with a moderate 35% yield of

benzimidazole **53** being obtained at 120 °C (entry 6). Replacement of the benzene ring with that of a pyridine resulted in a very poor 8% yield of the corresponding aza-benzimidazole **54** and 47% of intermediate amidine **55** was also isolated along with decomposition products (entry 7). Variation of the benzene ring in the 2 position (product numbering) to a furan yielded corresponding benzimidazole product **56** in a modest 47%, again at an elevated reaction temperature of 120 °C (entry 8).

2.2.3 Further optimisation

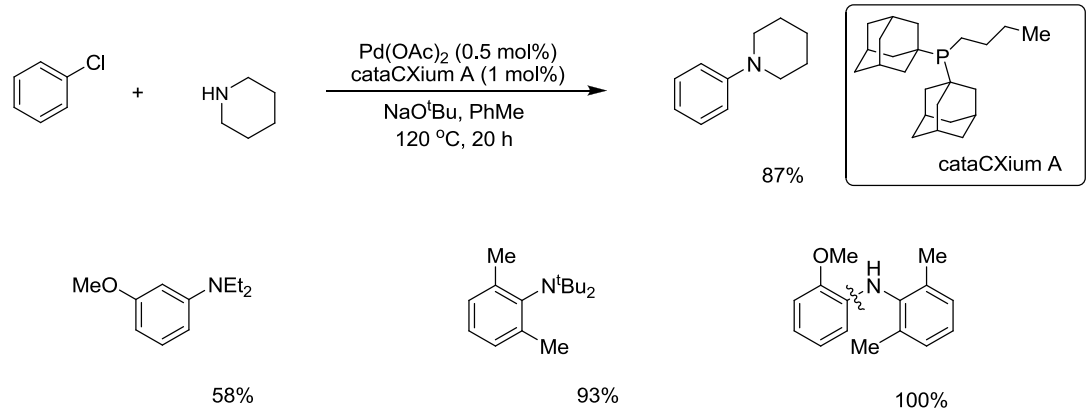
The initial reaction scope revealed the ineffectiveness of the established catalyst system as very poor product yields were obtained for more demanding substrates such as electron-rich imidoyl chloride **8**. The reaction conditions also displayed poor functional group tolerance as decomposition products were also observed. Thus, it was decided that further optimisation of reaction parameters was required.

As discussed in Chapter 1, phosphine ligands have been shown to play a huge part in the success of transition metal-catalysed reactions such as aminations of aryl halides. The discovery of new classes of ligands, which have different electronic and steric properties, has led to major improvements in the scope, mildness and efficiency of this reaction. Those which are most important for our system are ones which allow effective coupling of amines to unactivated aryl chlorides.

Previous studies carried out by the group into the screening of ligands were limited to dialkylbiaryl monophosphines, namely DavePhos and SPhos and chelating biphosphines such as XantPhos and DPEPhos, with the latter displaying very little reactivity. In order to gain a broader scope of ligand effects, different ligands were considered.

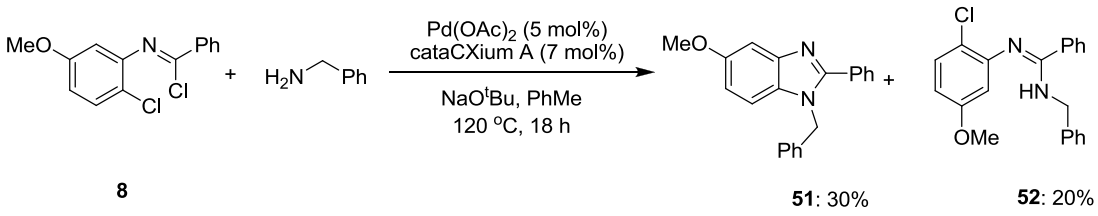
In order to establish a more effective catalyst system, optimisation was carried out on a challenging substrate, namely imidoyl chloride **8**, which previously gave very poor yields of benzimidazole product as well as a number of decomposition products (see Table 2.3). Test reactions using Buchwald's SPhos and XPhos palladium precatalysts (see section 1.1.2, scheme 1.9) gave poor yields of benzimidazole product as did the bisphosphine DPPF ligand.

A class of ligand yet to be explored in this system was trialkyl monophosphines. A review of the literature revealed the di-1-adamantyl(*n*-butyl)phosphine ligand (cata*CX*ium® A), developed originally by the Beller group, as an active ligand for Heck[255] and Suzuki[59] couplings of aryl chlorides. In 2002, they showed that their novel ligand is also very active for the coupling of a wide range of sterically congested aryl chlorides with hindered amines.[256] Their system utilised $Pd(OAc)_2$ at 0.5 mol%, 1 mol% of ligand along with NaO^tBu in toluene (Scheme 2.19). The reactions were run at 120 °C for 20 hours, affording good to excellent yields of the product anilines. Direct comparison studies were carried out with eight other alkyl monophosphines, with cata*CX*ium® A affording the most superior conversions and yields in three out the four reactions investigated.



Scheme 2.19

Thus, this ligand was tested in the reaction between imidoyl chloride **8** with benzylamine under our standard conditions. A moderate 30% yield of benzimidazole product **51** was obtained along with 20% of uncyclised amidine intermediate **52** and once again some decomposition products were also observed (Scheme 2.20).

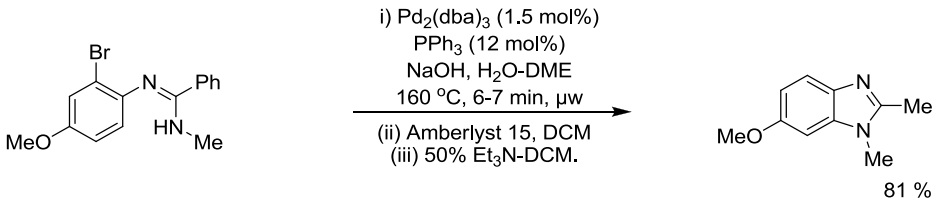


Scheme 2.20

The area of microwave assisted organic synthesis (MAOS) has become fast growing since the first discovery by Gedye[257] and Giguere[258] in 1986 that organic chemical transformations can be greatly accelerated by the use of microwave heating. Further studies have led to not only significant decreases in reaction times but also improvements in yields, reproducibility and reduction in side-products. This has rendered this technique as an established tool for both industrial and academic laboratories with uses including optimisation of reactions, high throughput synthesis as well as discovery of new reactivity.[259-263]

Transition-metal catalysed reactions are one of the best studied processes in MAOS.[264] The first example of high speed aminations of aryl bromides was developed in 2002 by Alterman *et al*.[265] Products were afforded in moderate to good yields in reaction times of only 4 minutes. A year later this protocol was extended to aryl chlorides by work from the Caddick[266] and Maes[267] groups independently with both achieving good to excellent yields again in short (maximum of 10 minutes) reaction times.

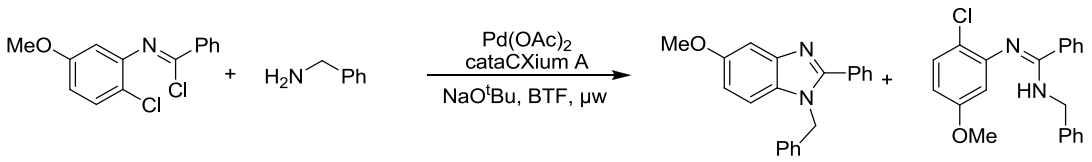
As mentioned in section 2.1.2, the Brain group have developed a benzimidazole synthesis based on an intramolecular C-N coupling of amidines under palladium-catalysis (see Scheme 2.3).[215] Notably, the authors were able to improve on the efficiency of their procedure by use of microwave irradiation allowing the heterocycles to be obtained in short reaction times (Scheme 2.21).[216]



Scheme 2.21

Thus, it was reasoned that the use of MAOS could similarly be applied to our investigations for improving the efficiency of our benzimidazole synthesis. During their investigations into the scale up of microwave-assisted palladium-catalysed aminations, Maes *et al*. demonstrated the use of α-α-α-trifluorotoluene (or benzotrifluoride, BTF) as a successful toluene substitute as it displayed better heating properties.[268] Thus, test reactions were carried out using this solvent and a number of the results are displayed in Table 2.4.

Table 2.4- Optimisation using imidoyl chloride 8 [a]



8 **51** **52**

Entry	Temperature (°C)	Time (h)	Yield (%)[b] 51:52
1	120	2	38:25
2	135	2	71:trace
3	150	2	decomposition
4[c]	**135**	**2**	**80:0**

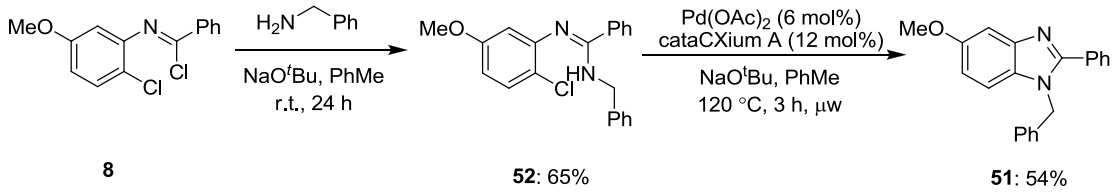
[a] Reaction conditions: imidoyl chloride **8** (1.0 equiv), benzylamine (1.5 equiv), $Pd(OAc)_2$ (5 mol%), cata*C*Xium® A (7 mol%), NaO^{t}Bu (3 equiv), BTF. [b] Isolated yields. [c] 2.2 equiv of base used.

Reaction at 120 °C for 2 hours encouragingly gave similar results to those carried out under conventional heating for 18 hours (entry 1), however yields were still moderate. Increasing the temperature to 135 °C gave a more pleasing 71% yield of benzimidazole **51**, with no intermediate amidine **52** observed (entry 2); but further increase to 150 °C afforded only decomposition products (entry 3). Previous screening showed that use of weak bases such as cesium carbonate gave a very poor (<5%) yield of benzimidazole product and a strong base such as sodium *tert*-butoxide was essential. This may be undesirable as it has been shown to limit the functional group tolerance of the substrates which can be used.[254] Thus, reduction of the equivalence of base was tested and pleasingly use of 2.2 equivalents instead of 3 gave an increased isolated yield of 80% (entry 4). Although not all reaction parameters were fully explored, the successful optimisation of this substrate was encouraging.

Interestingly, optimisation reactions using similar bulky monophosphine ligands namely, tri-*tert*-butylphosphonium tetrafluoroborate, cata*CX*ium® ABn and cata*CX*ium® PIntB gave poor yields (<30%) of benzimidazole product.

2.2.4 Proposed mechanism

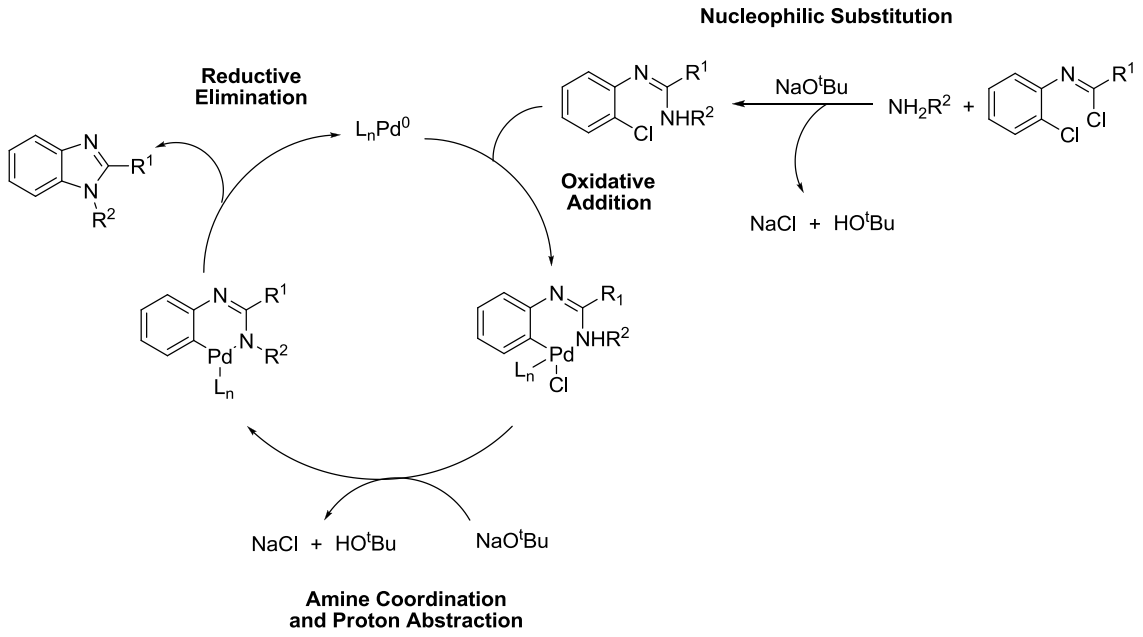
In order to probe the reaction mechanism, imidoyl chloride **8** was reacted with benzylamine in the absence of a palladium catalyst (Scheme 2.22). This afforded amidine **52** in a 65% yield. This was then subjected to palladium-catalyzed conditions and indeed benzimidazole **51** was isolated (as well as 41% of recovered amidine **52**).



8 **52**: 65% **51**: 54%

Scheme 2.22

Based on these findings, a reaction mechanism is proposed in Scheme 2.23. We postulate this involves initial nucleophilic substitution by the amine at the imidoyl chloride to afford an amidine intermediate followed by intramolecular palladium-catalyzed amination. The low yields obtained for electron-deficient nucleophiles such as anilines can be attributed to their reduced reactivity in the initial substitution step, thus less of the intermediate *N*-aryl amidine was available to participate in the subsequent palladium-catalysed step.

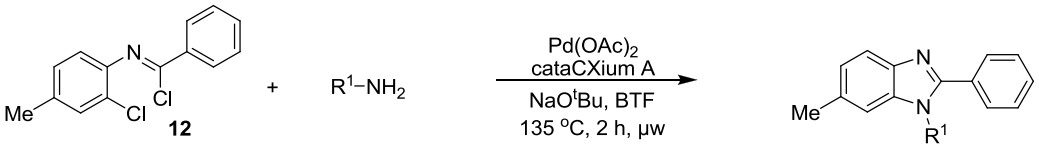


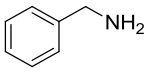
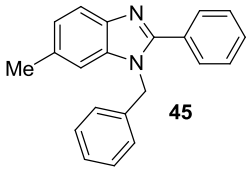
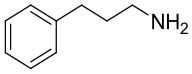
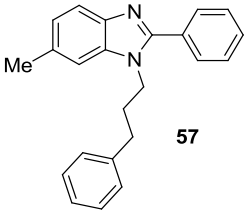
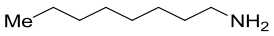
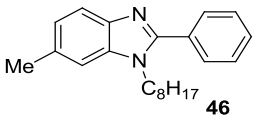
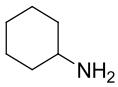
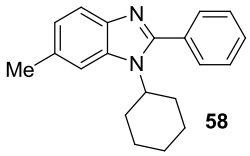
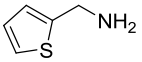
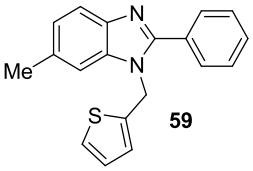
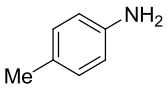
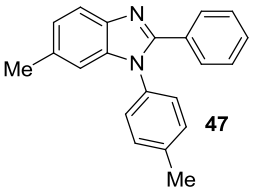
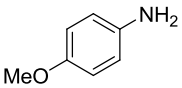
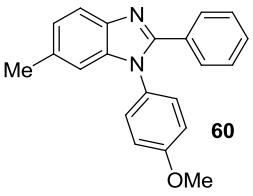
Scheme 2.23

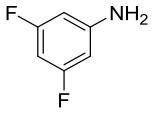
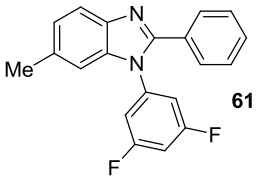
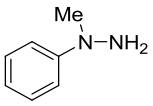
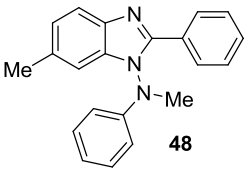
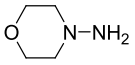
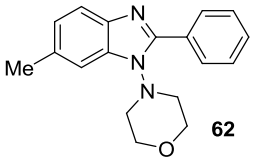
2.2.5 Investigating the scope of benzimidazole synthesis: variation of the nitrogen nucleophile

With new optimised conditions for the synthesis of *N*-benzyl benzimidazole **51** in hand, the variety of nucleophiles that could be tolerated in this reaction was again explored. Thus imidoyl chloride **12** was reacted with a variety of nucleophiles; the products and yields obtained are shown in Table 2.5.

Table 2.5- Variation of the *N*-nucleophile[a]



Entry	*N*-nucleophile	Product	Yield (%)[b]
1		 **45**	69
2		 **57**	75
3		 **46**	73
4[c]		 **58**	94
5[c]		 **59**	48
6[c]		 **47**	53
7		 **60**	46

8[c]		 **61**	45
9[d]		 **48**	38
10[c]		 **62**	47

[a] Reaction conditions: imidoyl chloride **12** (1.0 equiv), *N*-nucleophile (1.5 equiv), $Pd(OAc)_2$ (5 mol%), cata*C*Xium® A (7 mol%), NaO^{t}Bu (2.2 equiv), BTF, 50 °C, 30 min then 135 °C, 2 h, µw. [b] Isolated yield. [c] Reaction carried out at 50 °C, 0.5 h, µw then 135 °C, 2 h, µw. [d] Reaction carried out at 125 °C, 1 h, µw.

Entries 1-3 illustrate the effectiveness of primary amines as coupling partners in this reaction, as high yields of *N*-alkyl benzimidazole products were obtained. When a bulky nucleophile, namely cyclohexylamine was employed, it was found that carrying the reaction out at 50 °C for 30 minutes first (in order to encourage the initial nucleophilic substitution step) followed by 135 °C for 2 hours afforded benzimidazole **58** in an excellent yield (entry 4). The use of an alkyl amine with a heterocyclic group attached to the chain was tolerated under the reaction conditions, yielding structurally interesting benzimidazole **59** (entry 5). Unfortunately, the reactivity of anilines once again proved to be less successful with only moderate yields of *N*-aryl benzimidazoles obtained along with decomposition products (entries 6-8). Increasing the loading of palladium to 7 mol% and ligand to 10 mol% gave comparably low yields. Similarly, hydrazines gave poor yields (entries 9 and 10).

Despite this new, more reactive system, carbamates, amides (both aryl and alkyl) and sulfonamides failed to afford the desired benzimidazoles. Those tested under the standard reaction conditions are shown in Figure 2.3.

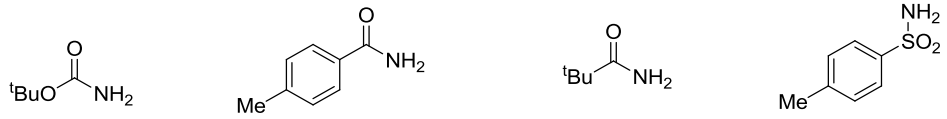


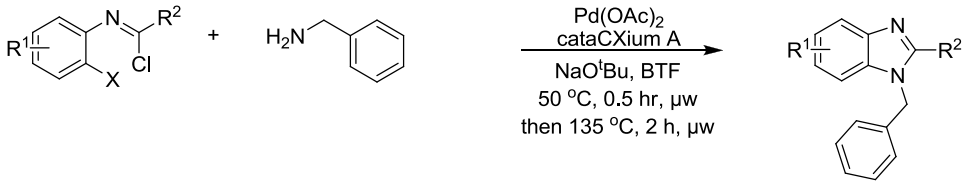
Figure 2.3

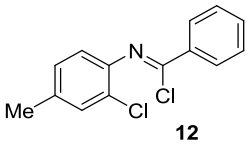
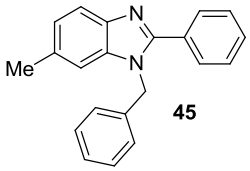
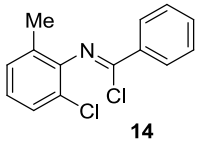
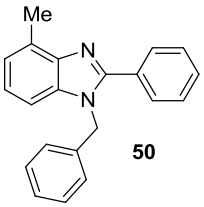
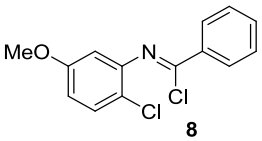
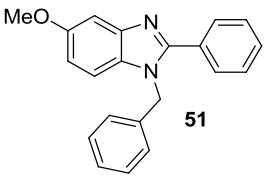
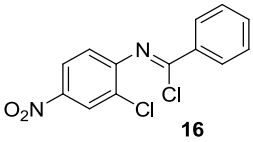
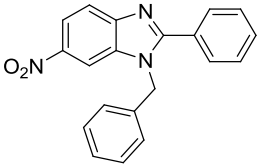
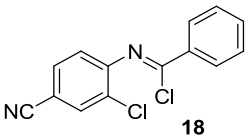
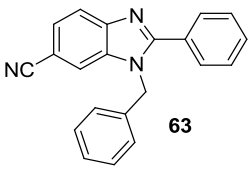
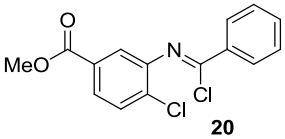
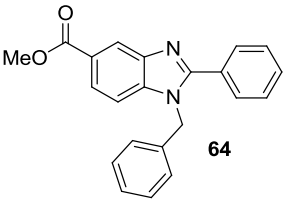
Although disappointing, this was not surprising, as problems were also encountered when these electron-deficient nucleophiles were used in the group's synthesis of indoles from 2-(2-bromoalkenyl)aryl bromides.[140] The cross-coupling of *tert*-butylcarbamate was only possible after an optimised ligand, base and solvent combination was utilised and use of an alkyl amide gave low (<20%) isolated yields.[269] Furthermore, there are few examples in the literature of high yielding palladium-catalysed amidations of *ortho*-substituted aryl chlorides[270] and only very recently has the successful coupling of bulky amides to *ortho*-substituted aryl chlorides (by use of unsymmetrical bisphosphine ligands) been demonstrated.[271] Thus, further optimisation is needed in order to allow for the successful incorporation of these nucleophiles into this process.

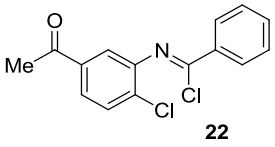
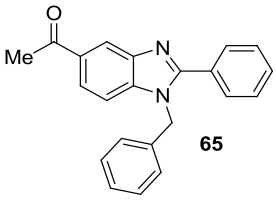
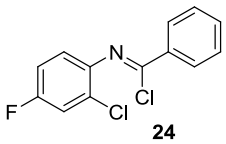
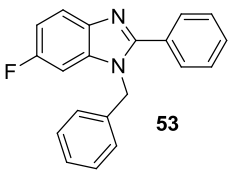
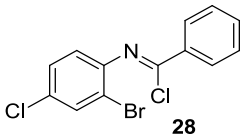
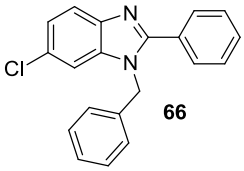
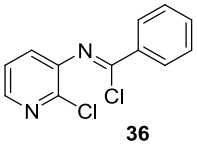
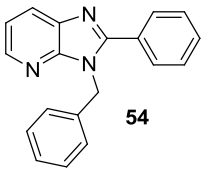
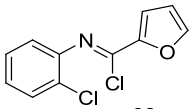
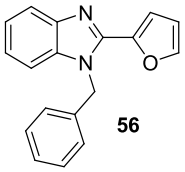
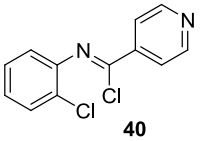
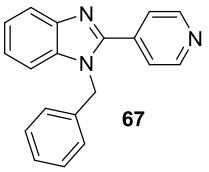
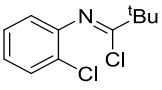
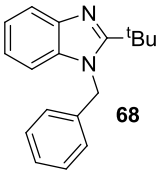
2.2.6 Investigating the scope of benzimidazole synthesis: variation of the substrate

We then sought to extend the scope of the reaction with respect to the substrate, as optimisation had been carried out using imidoyl chloride **8** which possessed an electron-donating group (see section 2.2.3). Thus, a range of substrates possessing electronically different substituents were reacted with benzylamine under the new optimised conditions and the results are summarised in Table 2.6.

Table 2.6- Variation of the substrate[a]



Entry	Substrate	Product	Yield (%)[b]
1[c]	 **12**	 **45**	69
2	 **14**	 **50**	91
3[c]	 **8**	 **51**	80
4	 **16**		0
5	 **18**	 **63**	47
6	 **20**	 **64**	26

7	 **22**	 **65**	71
8	 **24**	 **53**	75
9[d]	 **28**	 **66**	67
10	 **36**	 **54**	50
11[c]	 **38**	 **56**	80
12[e]	 **40**	 **67**	72
13	 **42**	 **68**	84

[a] Reaction conditions: imidoyl chloride (1.0 equiv), *N*-nucleophile (1.5 equiv), $Pd(OAc)_2$ (5 mol%), cata*C*Xium® A (7 mol%), NaO^{t}Bu (2.2 equiv), BTF, 50 °C, 0.5 h, µw then 135 °C, 2 h, µw. [b] Isolated yield. [c] Reaction carried out at 135 °C, 2 h, µw. [d] Reaction carried out at 50 °C, 0.5 h, µw then 120 °C, 2 h, µw. [e] Reaction carried out with $Pd(OAc)_2$ (10 mol%), cata*C*Xium® A (14 mol%) at 50 °C, 0.5 h, µw then 135 °C, 4 h, µw.

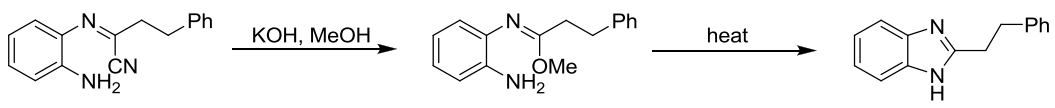
Pleasingly, incorporation of a methyl group *ortho* to the imidoyl chloride moiety afforded the corresponding benzimidazole **50** in an excellent yield (entry 2). Unfortunately, once again a nitro group was not tolerated in this reaction (entry 4), however an electron withdrawing nitrile group gave a modest 47% yield of benzimidazole **63** (entry 5). A methyl ester moiety was less well tolerated affording benzimidazole **64** in a low 26% yield (entry 6) along with 12% of the carboxylic acid benzimidazole formed by hydrolysis of the ester under these strongly basic conditions and trace amounts of the corresponding amidine intermediates. Methyl ketone substituted benzimidazole **65** was successfully synthesised in a good 71% yield (entry 7). A fluorine atom was well tolerated affording halogenated heterocycle **53** in a high 75% yield. Unfortunately, similar 6-chloro, bromo and iodo-benzimidazoles could not be obtained in good yield from the corresponding *N*-(*o*-chlorophenyl)imidoyl chloride starting materials. In all cases, the more exposed halogen preferentially reacted affording a mixture of products. A similar result was observed within the group for the synthesis of 6-chloro indole from (*Z*)-1-(2-bromovinyl)-2,4-dichlorobenzene.[269] However, use of *N*-(2-bromo-4-chlorophenyl) imidoyl chloride **28** successfully afforded chloro-substituted benzimidazole **66** in a good 67% yield (entry 9) under a reduced reaction temperature of 120 °C. This is a useful substituent as it allows a handle for further functionalisation.[142] Entry 10 demonstrates the application of these reaction conditions for the successful synthesis of aza-benzimidazole **54**. Variation at the 2-position (product numbering) was then tested. Both furan and pyridine moieties could be incorporated successfully (entries 11 and 12). The later however, required higher catalyst loading and a prolonged reaction time in order to obtain a good conversion of the intermediate imidamide to benzimidazole product **67**. This may be due to interaction of the pyridine lone pair with the palladium metal. A bulky *tert*-butyl group afforded 2-alkyl benzimidazole **68** in an excellent yield (entry 13).

Unfortunately, it was found that imidoyl chlorides containing a straight alkyl chain (e.g. *n*-pentyl) could not be obtained with good conversions using PCl_5 (this was similarly observed by Cunico *et al*.);[272] thus the synthesis of 2-*n*-alkyl substituted benzimidazoles is not possible *via* this route.

2.2.7 The use of *N*-(*o*-halophenyl)imidates as precursors for benzimidazole synthesis: Proposed route

Having demonstrated that *N*-(*o*-chlorophenyl)imidoyl chlorides can successfully be utilised as starting materials for the synthesis of benzimidazoles, we then investigated the use of *N*-(*o*-halophenyl)imidates. As discussed in section 2.2.1, we envisaged that the nature of the alkoxy leaving group on the imidoyl moiety may allow for a difference in reactivity between the two substrates, thus perhaps affording the product heterocycle *via* a different mechanism.

The acid-catalysed reaction of *o*-diaminobenzenes and imidates (as mentioned in section 2.1.2) is an established method for the synthesis of benzimidazoles. This is believed to proceed *via* an initial attack of the aniline amine onto the imidate salt which upon loss of ammonium chloride, affords an *N*-(o-aminophenyl)imidate intermediate. In fact, Walia *et al*. have showed that when subjected to heat, intermediate **70** (synthesised from the corresponding 2-aminonitrile **69**) does indeed undergo a hetero-cyclisation reaction to afford benzimidazole **71** (Scheme 2.24).[273]



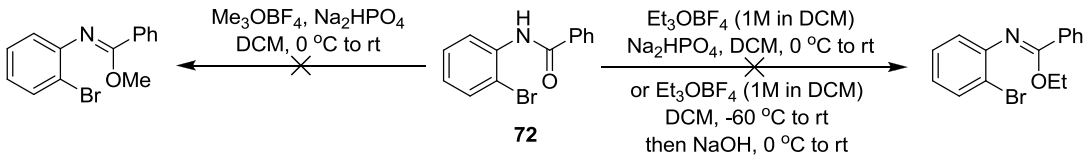
69 **70** **71**: 95%

Scheme 2.24

This provided good precedent for our proposed route to benzimidazoles using *N*-(*o*-halophenyl)imidates and amines *via* a one-pot metal-catalysed C-N bond formation/cyclisation strategy.

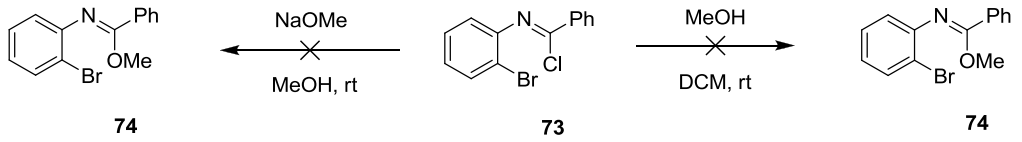
2.2.8 Starting material synthesis

Imidates are a well known class of compound with a number of their syntheses appearing in the literature.[248] One route is *via* the deprotonation of alkoxymethyleniminium salts formed from a reaction of amides with trialkyloxonium tetrafluoroborate.[274, 275] Unfortunately, a number of attempts to transform amide **72** into either the corresponding methyl or ethyl imidates failed to yield product as shown in Scheme 2.25.



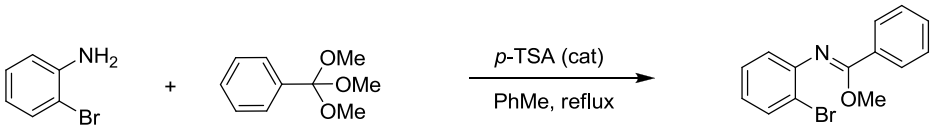
Scheme 2.25

The action of alcohols on imidoyl chlorides (often in the presence of a base) is a standard procedure. Attempted reaction of imidoyl chloride **73** (synthesised by reaction of amide **72** with phosphorous pentachloride) with sodium *tert*-butoxide in the presence of methanol produced only decomposition products and reaction with methanol also failed, affording only a trace amount of imidate **74** (Scheme 2.26).



Scheme 2.26

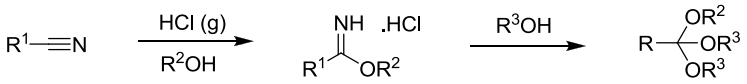
The acid-catalysed reaction of *ortho*-esters with compounds containing primary amine functional groups has also been utilised for the preparation of imidates. Thus, following a literature procedure,[276] *o*-bromoaniline and trimethyl *ortho*-benzoate were reacted in the presence of a catalytic amount of *p*-toluenesulfonic acid to give imidate **74** in an excellent 89% yield (Scheme 2.27). It was also found that heating the aniline with an excess of *ortho*-ester to between 90 °C and 110 °C afforded the imidate product.[277]



74: 89%

Scheme 2.27

Although this method allowed for the one-step preparation of imidates, only straight chain alkyl and benzene substituted trimethyl *ortho*-esters were commercially available.[iv] In order to fully test the scope of our benzimidazole synthesis from these substrates, *ortho*-esters with varying types of substituent were required. These are traditionally prepared using a two-step process named the Pinner method.[278, 279] This involves synthesis of imidic ester hydrochlorides by the reaction of nitriles with alcohols and anhydrous hydrogen chloride gas and their subsequent alcoholysis to afford the corresponding *ortho*-ester (Scheme 2.28).

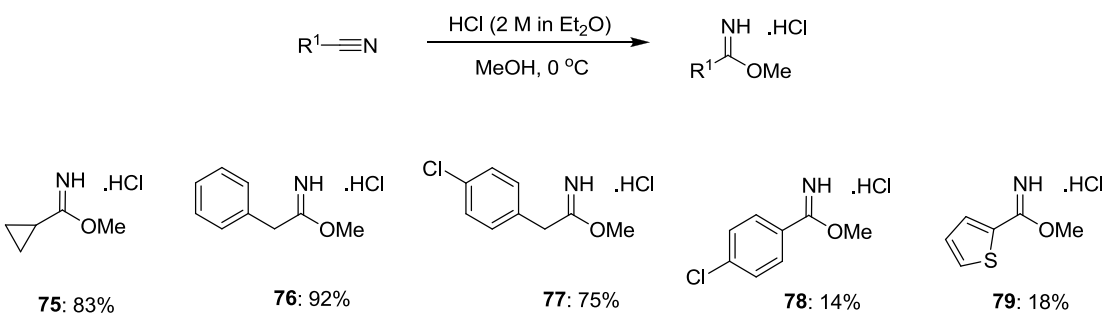


Scheme 2.28

[iv] Chemical suppliers searched: Aldrich, Alfa Aesar, Acros Organics, Strem Chemicals and Fluorochem.

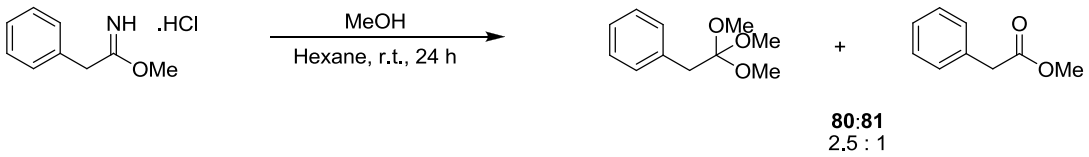
Although this is a well studied process, it does suffer from a number of drawbacks.[280] The rate at which nitriles are converted to the imidic salts is influenced by both steric and electronic factors. Synthesis of simple alkyl substituted imidic salts can be achieved successfully in a few hours, however higher aliphatic nitriles and those containing bulkier substituents can require reaction times of up to a few days. A competing decomposition reaction of the imidic salts to their corresponding amides and alkylchlorides can affect yields. Although this process can be minimised by carrying out the reaction at low temperatures, it is problematic for nitriles substituted with electron-withdrawing groups. The alcoholysis step is particularly capricious as the *ortho*-ester products are extremely susceptible to acid-catalysed hydrolysis. Thus, it is essential that the imidate ester salts be completely free of excess hydrogen chloride and that anhydrous alcohol and solvents are used.

It was envisaged that the use of commercially available hydrogen chloride solution (2 M in diethyl ether) would provide a more practical alternative to the use of hydrogen chloride gas for the synthesis of the imidic salts. Washing of the product salts with anhydrous ether would also ensure removal of excess acid. Indeed, when a number of nitriles were reacted with methanol in this acidic solution at 0 °C and left to crystallise at 4 °C for several days, the corresponding imidic salts were obtained (Scheme 2.29).



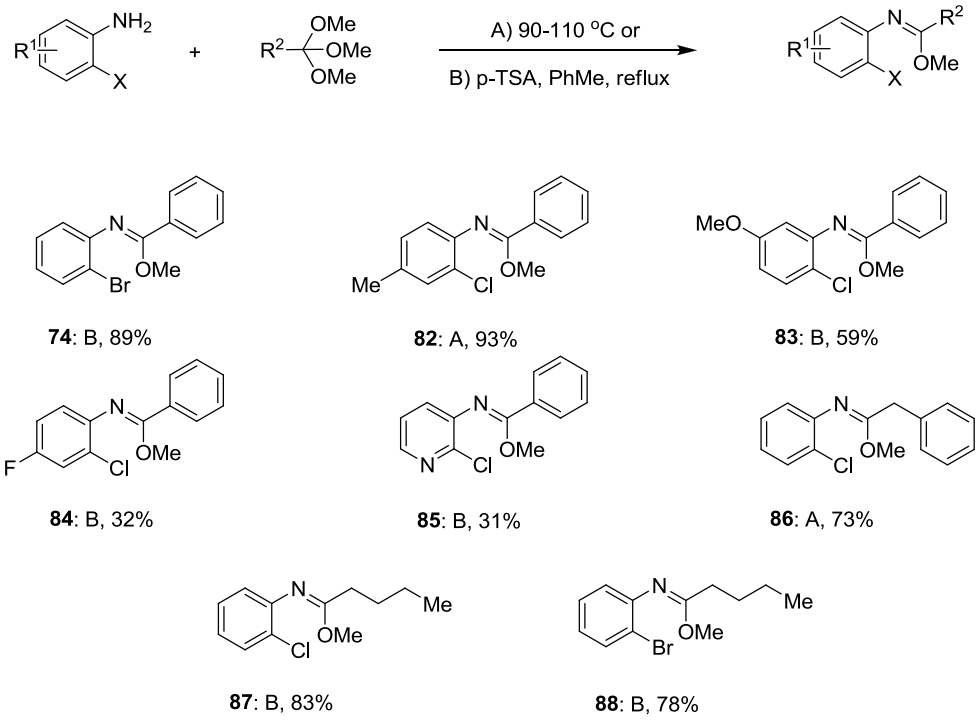
Scheme 2.29

Following literature conditions for the alcoholysis of imidic salts to their corresponding *ortho*-esters unfortunately gave poor results.[281] In most cases, the corresponding ester (as a result of a competing hydrolysis reaction) was observed as the sole product. However, benzyl substituted imidic salt **76** gave a crude 2.5:1 mixture of *ortho*-ester **80** and ester **81** (Scheme 2.30), which was successfully used for the synthesis of the required imidate starting material without further purification.



Scheme 2.30

Several imidates with varying substituents were thus synthesised in order to test the scope of these substrates as precursors for the synthesis of benzimidazoles (Scheme 2.31).

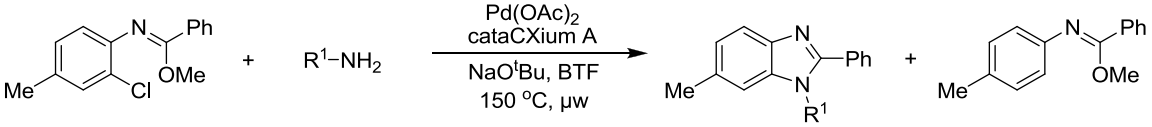


Scheme 2.31

2.2.9 Initial investigations and optimisation

In order to assess the reactivity of these substrates, test reactions of *N*-(*o*-chlorophenyl)imidate **82** with various nucleophiles were carried out. The use of the established reaction conditions was trialled and the results are summarised in Table 2.7.

Table 2.7- Optimisation using *N*-(*o*-chlorophenyl)imidate 82[a]



82 — **45**: R^1 = benzyl; **46**: R^1 = octyl; **47**: R^1 = *p*-tol — **89**

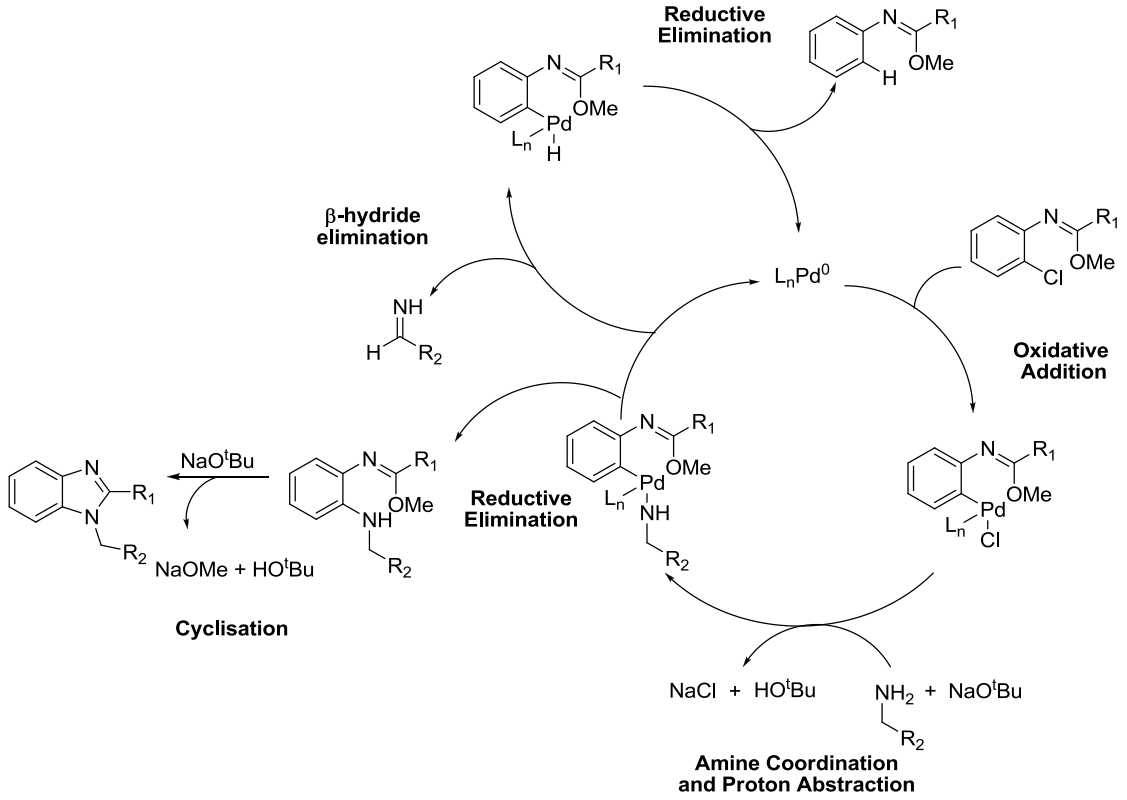
Entry	R^1	Temperature (°C)	Time (h)	Yield (%)[b] benzimidazole:89
1	benzyl	150	1.5	trace:100[c]
2	octyl	150	3	14:80
3[d]	octyl	150	3	trace:100[c]
4	*p*-tol	150	3	87:13

[a] Reaction conditions: imidate **82** (1.0 equiv), amine (1.5 equiv), $Pd(OAc)_2$ (5 mol%), cata*C*Xium® A (7 mol%), NaO*t*Bu (3 equiv), BTF, 150 °C, μw. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy.[d] Cs_2CO_3 used as the base

Employment of benzylamine as the coupling partner at 150 °C yielded exclusively reduction of imidate **82** to imidate **89** (entry 1). Use of octylamine gave a poor 14% isolated yield of benzimidazole **46** and 80% of imidate **89** was also obtained (entry 2). Use of a weaker base unfortunately gave reduction product **89** exclusively (entry 3).

These results revealed that the reaction was proceeding *via* a different mechanism to that observed in the synthesis of benzimidazoles from *N*-(*o*-chlorophenyl)imidoyl chlorides. Isolation of reduced imidate **89** indicates that in this case an initial amination pathway must be occurring followed by nucleophilic substitution at the imidate moiety (Scheme 2.32). The reduction product can be rationalised as a result of a *β*-hydride elimination

process competing with reductive elimination, which is a known pathway in the amination reaction of alkyl amines.[282]



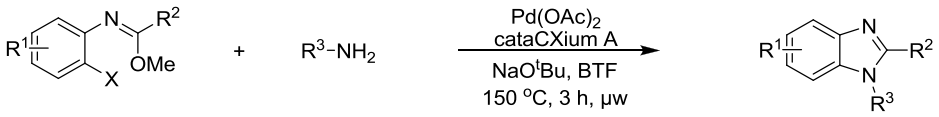
Scheme 2.32

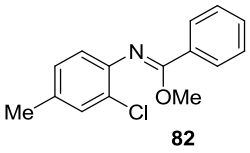
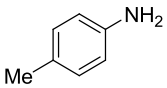
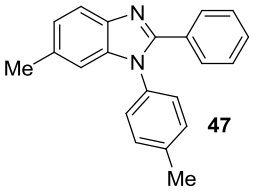
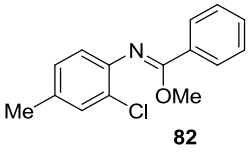
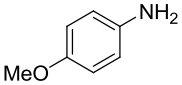
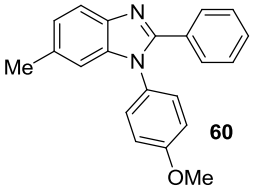
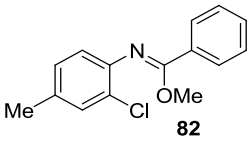
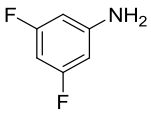
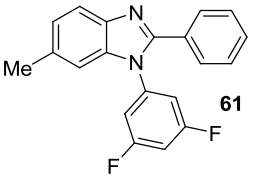
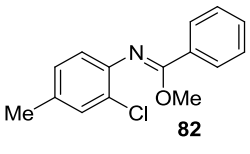
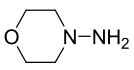
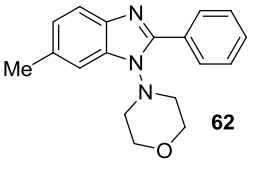
Thus it was rationalised that use of a nucleophile lacking *β*-hydrogens would shut down this process. When *p*-toluidine was utilised, pleasingly an excellent 87% yield of the corresponding *N*-aryl benzimidazole **47** was obtained (entry 4). However a 13% yield of reduction product **89** was also isolated. It is worth noting a similar result was observed during Buchwald's studies on the palladium-catalysed synthesis of *N*-aryl benzimidazoles from *o*-bromoacetanilides and anilines (see section 2.1.2).[253]

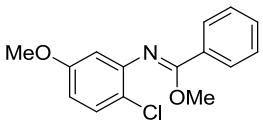
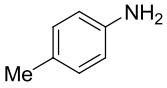
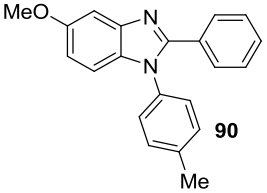
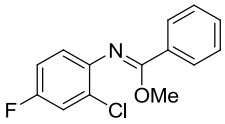
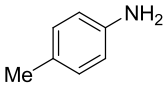
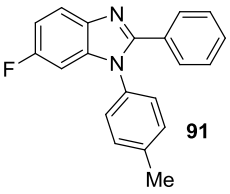
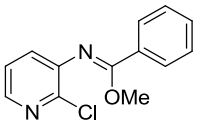
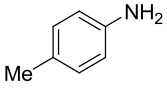
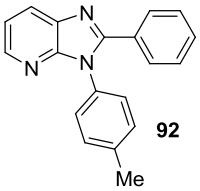
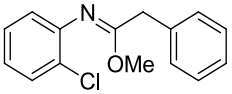
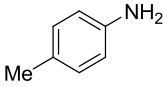
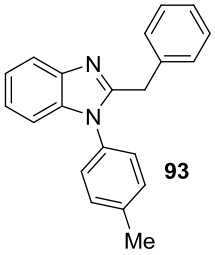
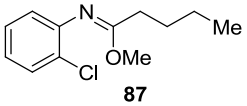
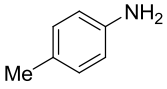
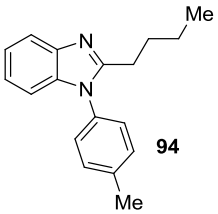
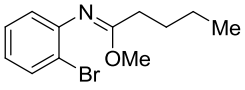
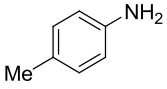
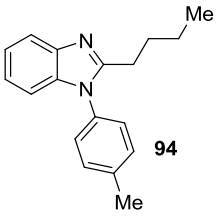
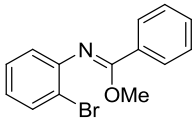
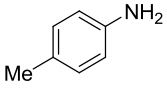
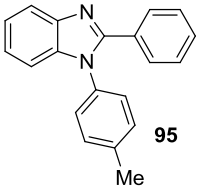
2.2.10 Investigating the scope of benzimidazole synthesis: variation of the nucleophile and substrate

Although screening revealed the limited scope of the *N*-nucleophile coupling partner which can be used in this reaction; it demonstrated that the same set of conditions can be utilised for the synthesis of 1,2-disubstituted benzimidazoles from *N*-(*o*-chlorophenyl)imidoyl chlorides and imidates. In order to test this generality, the scope of the nucleophile and substrate was carried out, as summarised in Table 2.8.

Table 2.8- Scope of the *N*-nucleophile and substrate[a]



Entry	Substrate	Amine	Product	Yield (%)[b]
1	 **82**		 **47**	87
2	 **82**		 **60**	86
3	 **82**		 **61**	42
4	 **82**		 **62**	56

5	 **83**		 **90**	42
6	 **84**		 **91**	80
7	 **85**		 **92**	80
8	 **86**		 **93**	76
9	 **87**		 **94**	64
10[c]	 **88**		 **94**	94
11[c]	 **74**		 **95**	80

[a] Reaction conditions: imidate (1.0 equiv), *N*-nucleophile (1.5 equiv), $Pd(OAc)_2$ (5 mol%), cata*C*Xium® A (7 mol%), NaO^{t}Bu (2.2 equiv), BTF, 150 °C, 3 h, µw. [b] Isolated yield. [c] Reaction carried out at 135 °C, 2 h, µw.

Entry 2 shows the successful incorporation of an electron-rich aniline into this process, affording heterocycle **60** in an 86% yield. Electron-poor 3,5-difluoroaniline gave a moderate 42% yield of benzimidazole **61** as well as 29% of imidate **89** (entry 3). The use of a hydrazine coupling partner was also tolerated yielding 56% of desired product **62** and 21% of side-product **89** (entry 4). Entry 5 demonstrates the difficulty in using electron-rich substrates in amination reactions as a 42% yield of product **42** was obtained as well 40% of the starting imidate also recovered from the reaction. Pleasingly a fluorine substituent could be successfully incorporated as shown in entry 6 and *N*-aryl azabenzimidazole **92** was also isolated in a high 80% yield (entry 7). Variation of the 2-position (product numbering) to a benzyl group was well tolerated affording a 76% isolated yield of benzimidazole **93** (entry 8). 2-alkyl substituted benzimidazole **94** was successfully synthesised in a good yield as shown in entry 9. This is worth noting as this transformation was not possible from the corresponding imidoyl chloride starting material (as shown in section 2.2.4). Entries 10 and 11 confirm the increased reactivity of aryl bromides in this amination reaction as excellent yields of benzimidazole products **94** and **95** were obtained at a reduced reaction temperature.

2.3 Concluding Comments

We have demonstrated the use of *N*-(*o*-chlorophenyl)imidoyl chlorides and *N*-(*o*-halophenyl)imidates as successful precursors for the palladium-catalysed synthesis of 1,2-disubstituted benzimidazoles. The vast majority of these examples have utilised cheap and readily available *o*-chloroanilines, making these routes practical and attractive. The facile synthesis of a wide variety of imidoyl chlorides in excellent conversions from their corresponding amides has been shown. Although problems were encountered with methods for the synthesis of the imidate starting material, good variation of the substituents on the aryl backbone was still achieved.

Identification of a single catalyst system has proved to be general for both substrates as good variation of the carbon backbone was achieved. This included the synthesis of two examples of azabenzimidazoles and a chloro-substituted benzimidazole. The difference in reactivity with respect to the *N*-nucleophile has allowed for complementary and efficient routes to *N*-alkyl substituted benzimidazoles from *N*-(*o*-chlorophenyl)imidoyl chlorides and *N*-aryl subsitituted benzimidazoles from *N*-(*o*-halophenyl)imidates. In total 28 benzimidazoles have been synthesised in short reactions times (as a result of the use of microwave irradiation) in moderate to excellent yields.[283]

The utility of both these substrates as general heterocycle precursors will be further demonstrated in Chapters 3 and 5.

Chapter 3: Synthesis of benzothiazoles

3.1 Introduction

3.1.1 The importance of benzothiazoles

The 2-substituted benzothiazole scaffold (Figure 3.1) is a prominent motif in biologically active molecules which display antitumor,[284-286] antimicrobial[287] and antiglutamate[288] properties. A number of drugs containing this pharmacophore have been developed[289] such as Zopolrestat for the treatment of diabetes.[290] Additional applications include use as bioluminogenic substrates for *in vivo* imaging[291] and fluorescent pH indicators.[292]

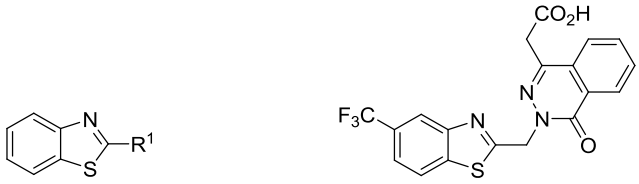
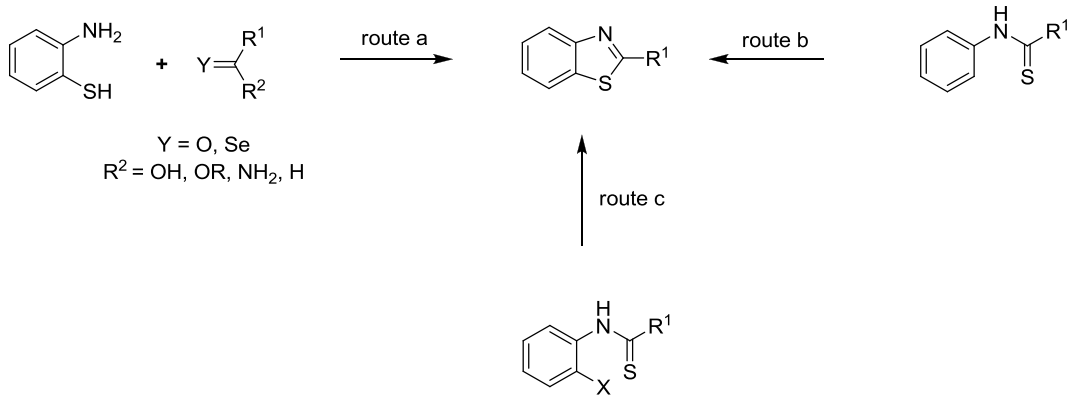


Figure 3.1

3.1.2 Synthesis of benzothiazoles

Classical routes to benzothiazoles involve the condensation of *o*-aminothiophenols with carbonyl compounds (Scheme 3.1, route a). Examples include use of selenoesters,[293] selenoamides[294] or carboxylic acids in the presence of acid,[285, 295-297] catalytic base and NMP,[298] thionyl chloride,[299] molecular iodine[300] or Lawesson reagent.[301] However, these protocols required excesses of reagent and/or prolonged reaction times. When aldehydes were utilised as the condensation partner, the use of strong oxidants such as molecular O_2,[302-304] H_2O_2[305] or MnO_2[306] were required. However, all these approaches are limited by the difficulty in preparation of substituted *o*-aminothiophenols, which are readily oxidisable.

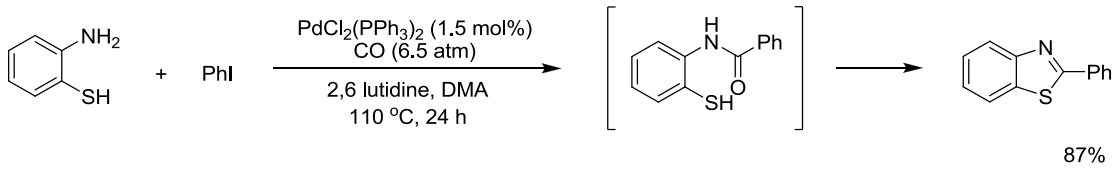


Scheme 3.1

An alternative route is the oxidative radical cyclisation of thioanilides by potassium ferricyanide (route b),[285, 286, 307] however this protocol can lead to a mixture of regioisomers. The syntheses of benzothiazoles *via* intramolecular nucleophilic aromatic substitution reactions of *o*-halo thiobenzamides have been reported (route c).[308-315] The majority of studies have been carried out using *o*-fluoro, *o*-bromo and/or *o*-iodo thiobenzamides. A single example of a chloride substrate has been demonstrated, however this afforded the product benzothiazole in a lower yield than its other halogen analogues.[311] However, these protocols utilise Lawesson's reagent for the conversion of benzamides to the desired thiobenzamides starting material. This is undesirable as it is toxic, malodorous and incompatible with functional groups such as ketones, esters and amides.

An early example of a palladium-catalysed benzothiazole synthesis was described by Perry *et al*. in 1994.[316] This utilised an aminocarbonylation coupling of *o*-aminothiophenols with aryl iodides or bromides to form an amide intermediate (Scheme 3.2). A subsequent condensation/cyclisation reaction under the reaction conditions afforded the 2-aryl benzothiazole product. A good variety of functional groups could be tolerated on the halide coupling partner. However, only a small number of substituted *o*-

aminothiophenols were utilised and high pressures of carbon monoxide gas (*ca*. 6.5 atm) were required.



Scheme 3.2

As discussed in Chapter 1, several palladium-catalysed C-S bond forming protocols for the effective synthesis of aryl thioethers have been reported and utilised in the preparation of aromatic heterocycles such as benzothiophenes. A recent review by Willis and Sadig[134] covers palladium- and copper-catalysed thioetherification reactions for the synthesis of benzothiazoles, thus only a brief overview of the palladium-catalysed routes (Figure 3.2) will be discussed herein.

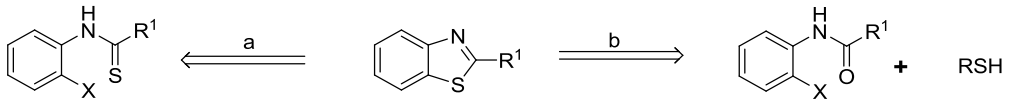
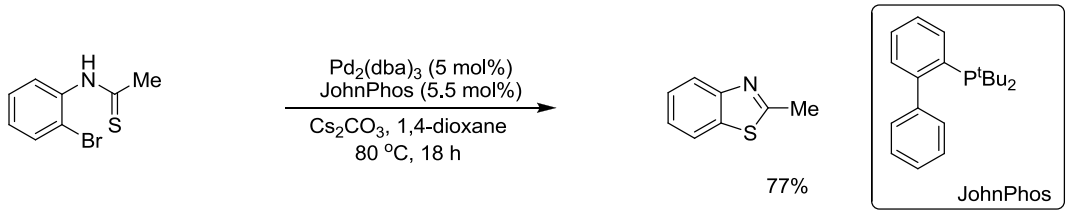


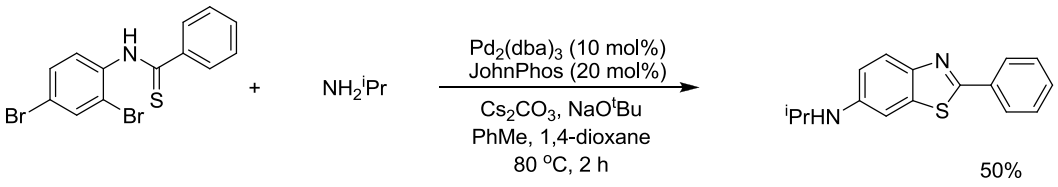
Figure 3.2

Several groups have utilised a palladium-catalysed intramolecular cyclisation reaction for the synthesis of benzothiazoles (Figure 3.2, disconnection a). For example, Castillón *et al*. demonstrated the use of *o*-bromophenylthioamide and *o*-bromophenylthioureas as precursors to 2-substituted and 2-aminobenzothiazoles respectively.[317] An example of the former is shown in Scheme 3.3. The use of a catalyst allowed for lower reaction temperatures than those utilised in the analogous metal-free protocols.



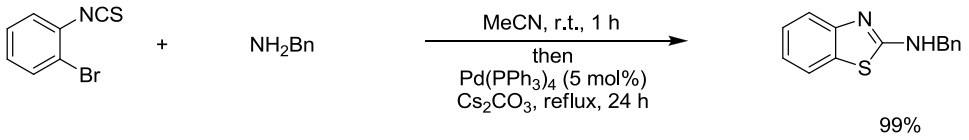
Scheme 3.3

Vera *et al*. have reported the synthesis of amino-substituted benzothiazoles from dibromophenylthioamides and primary amines *via* a tandem palladium-catalysed C-S cyclisation/Buchwald-Hartwig amination sequence.[318] Impressively, a single catalyst system affected both couplings; a representative example is shown in Scheme 3.4. However, these protocols were also limited by the use of Lawesson's reagent for the preparation of the starting material.



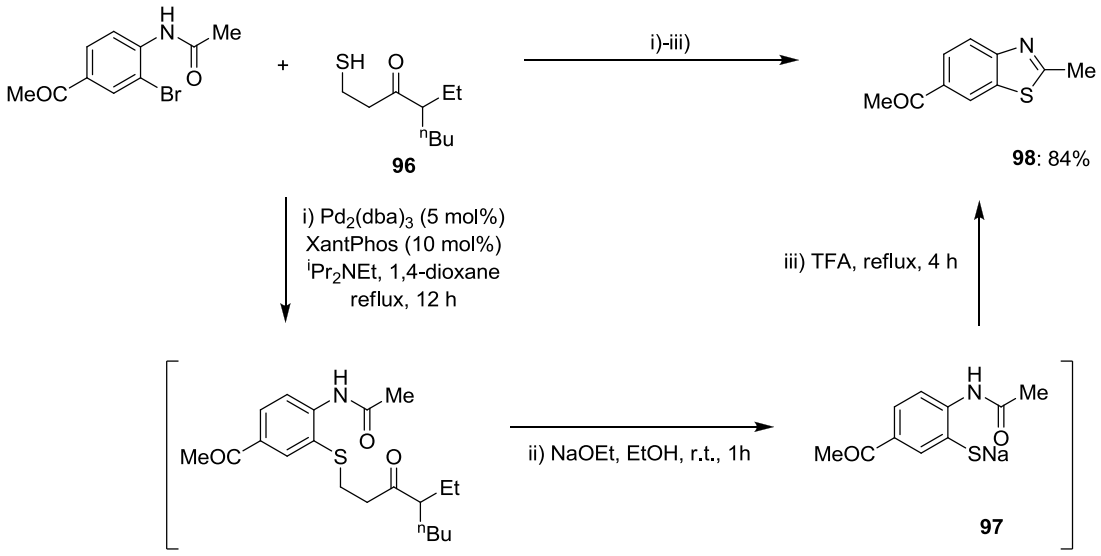
Scheme 3.4

Alternatively, Batey *et al*. have reported the palladium-catalysed synthesis of 2-aminobenzothiazoles from *o*-iodo or *o*-bromoarylthioureas.[319] The starting materials were readily prepared from either the reaction of readily available *o*-haloanilines with isothiocyanates or *o*-halo isothiocyanates with amines. A wide variety of substituted heterocycles were successfully prepared. Additionally, an example of a one-pot benzothiazole synthesis from the reaction of *o*-bromophenylisothiocyanate with benzylamine was also demonstrated (Scheme 3.5).



Scheme 3.5

A different approach to the benzothiazole scaffold has been reported by Itoh *et al*. (Figure 3.2, disconnection b).[320] This route utilised a palladium-catalysed intermolecular cross-coupling of easily synthesised *o*-bromoanilides with alkyl thiol **96** (an inexpensive and odourless thiol) (Scheme 3.6). The resultant sulfide intermediate was treated with NaOEt, affording the corresponding sodium thiolate **97**. Upon subjection to acidic conditions, the resultant thiophenol underwent a condensation cyclisation to benzothiazole **98**. The synthesis of a wide variety of substituted heterocycles was possible employing this protocol.



Scheme 3.6

Other palladium-catalysed benzothiazole syntheses have been reported; these however utilise a C-H functionalisation/C-S bond formation approach.[321-323]

3.2 Results and Discussion

3.2.1 Proposed route to 2-substituted benzothiazoles

The use of *N*-(*o*-halophenyl)imidoyl chlorides and imidates as precursors for the palladium-catalysed synthesis of benzimidazoles was successfully demonstrated in the previous chapter. Thus, we were keen to further display the utility of these starting materials *via* the synthesis of another important heterocyclic scaffold, namely benzothiazole (see section 3.1.1). We envisaged that this would be possible *via* the reaction of these substrates with a suitable sulfur nucleophile under similar palladium-catalysed conditions (Figure 3.3). Once again, the reaction may proceed by two mechanisms depending on whether an initial C-S bond formation occurs at the imidoyl centre or at the aryl halide moiety of the two different starting materials.

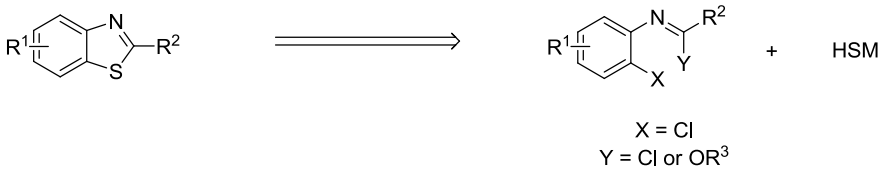


Figure 3.3

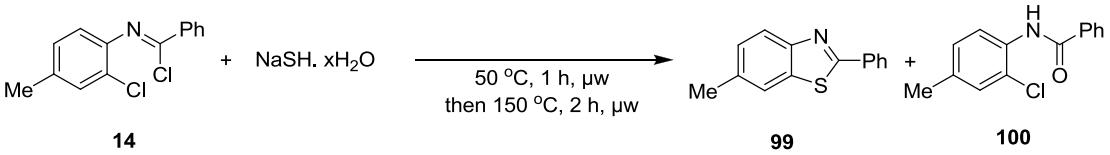
A recent report by Wu demonstrated the synthesis of 2-trifluoromethylbenzothiazoles *via* the palladium-catalysed reaction of trifluoromethylimidoyl chlorides and sodium hydrosulfide hydrate.[324] The proposed mechanism proceeded *via* initial formation of a trifluoromethylthiobenzamide intermediate, which then underwent a metal-catalysed C-H functionalisation/C-S bond formation cyclisation sequence. A good range of substituents were tolerated on the aryl ring and most products were isolated in moderate to high yields. A related protocol was recently developed by Zhang and Li involving the copper-catalysed coupling of *N*-(*o*-haloaryl)trifluoroacetimidoyl chlorides again with sodium hydrosulfide hydrate.[325] The catalyst system utilised required no ligand. However,

substrates were limited to use of iodides or bromides; chlorides gave poor yields even at elevated temperatures. A major limitation of both reports is the need for an electron-withdrawing substituent (e.g. CF_3) on the imidoyl chloride, thus only 2-fluoroalkylbenzothiazoles could be synthesised.

3.2.2 The use of *N*-(*o*-halophenyl)imidoyl chlorides as precursors for benzothiazole synthesis: Initial investigations

Initial work focused on the use of our *N*-(*o*-chlorophenyl)imidoyl chloride substrates as precursors for benzothiazoles. It was envisaged that when reacted with a sulfur nucleophile, an initial substitution reaction would occur at the imidoyl chloride portion, forming a thiobenzamide intermediate, which would cyclise in the presence of a palladium-catalyst. Thus, the reactivity of one of our precursors, namely imidoyl chloride **14** (which was synthesised by the method described in section 2.2.2) with sodium hydrosulfide hydrate as the sulfur source was tested under various palladium-catalysed conditions; the results are summarised in Table 3.1.

Table 3.1- Optimisation using imidoyl chloride 14[a]



14 **99** **100**

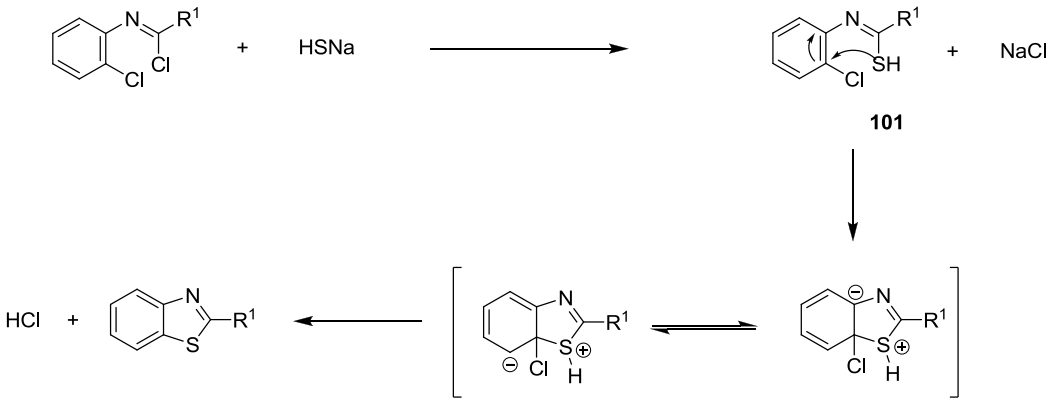
Entry	Pd catalyst (mol%)	Ligand (mol%)	Base	Solvent	Yield (%)[b] 99:100
1[c]	$Pd(OAc)_2$ (5)	cata*C*Xium® A (7)	NaO^tBu	BTF	trace
2[c]	$Pd(OAc)_2$ (5)	cata*C*Xium® A (7)	Cs_2CO_3	BTF	<10:41
3	$Pd(OAc)_2$ (5)	cata*C*Xium® A (7)	Cs_2CO_3	BTF	30:23
4	$Pd(OAc)_2$ (5)	cata*C*Xium® A (7)	Cs_2CO_3	DMF	80:12
5	$Pd(OAc)_2$ (5)	cata*C*Xium® A (7)	Cs_2CO_3	DMA	81:14
6	$Pd(OAc)_2$ (5)	cata*C*Xium® A (7)	K_3PO_4	DMF	40:54
7	**-**	**-**	**Cs_2CO_3**	**DMA**	**73:14**
8	-	-	-	DMA	63:16

[a] Reaction conditions: imidoyl chloride **14** (1.0 equiv), NaSH. xH_2O (3.0 equiv), base (2.2 equiv), 50 °C, 1 h, µw then 150 °C, 2 h, µw. [b] Isolated yields. [c] 50 °C, 0.5 h, µw then 135 °C, 2 h, µw.

The reaction was first carried out at 50 °C under microwave irradiation, in order to ensure the formation of the intermediate and then the temperature was raised in order to affect the coupling. Initially, the catalyst system established for our benzimidazole synthesis was applied to this reaction (entry 1). Unfortunately this gave a complex reaction mixture and only a trace amount of desired benzothiazole **99** was observed by ^1H NMR spectroscopy. Due to the nucleophilic nature of the sulfide, it was hoped that a weaker base could be compatible with this reaction. However, use of cesium carbonate afforded a poor yield of benzothiazole **99** as well as 41% of amide **100** (entry 2). It has been shown that *o*-halobenzamides do not cyclise to the corresponding benzoxazoles under palladium-catalysed conditions.[317, 326] Interestingly, no thioamide intermediate was observed, presumably as this underwent rapid cyclisation to the product benzothiazole. Pleasingly,

increasing the reaction temperature and time gave a moderate 30% yield of **99** (entry 3). The use of polar solvents was next investigated as these may increase the solubility of the reagents and catalysts of the reaction mixture. Comparably high yields were achieved when DMF or DMA were the reaction solvents (entries 4 and 5). When potassium phosphate was used, a poorer yield of benzothiazole **99** and higher amount of amide **100** was obtained (entry 6). A reaction omitting the palladium catalyst was then carried out in order to determine the effect of it on the reaction. A yield of 73% benzothiazole **99** was obtained (entry 7), which although lower than that obtained with catalyst (entry 5) was nonetheless acceptable. When no base was added, a lower yield of **99** was afforded (entry 8).

A similar cyclisation of *o*-fluoro thiobenzamides (formed *in situ* from the reaction of *o*-fluoro anilines, acid chlorides and Lawesson reagent), under metal-free microwave irradiation or conventional heating has been recently reported by Bose *et al*.[314] They proposed that the reaction proceeds *via* a nucleophilic aromatic substitution reaction (S_NAr).[327] It was postulated that a similar mechanism would be plausible for our reaction (Scheme 3.7). Initial formation of intermediate sulfide **101** could occur from the reaction of imidoyl chloride and sodium hydrosulfide. The sulfur atom of which could attack the aromatic ring at the C-Cl bond, resulting in loss of aromaticity. The resultant anion would be stabilised through delocalisation around the aryl ring. Subsequent loss of the chloride would restore the aromaticity of the aryl ring and afford the product benzothiazole.

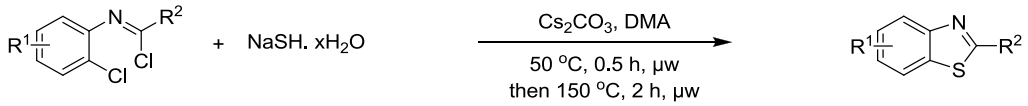


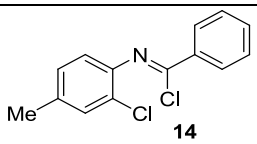
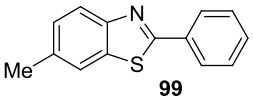
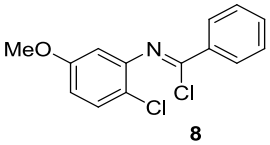
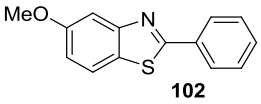
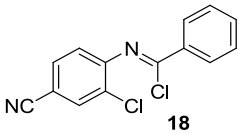
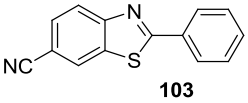
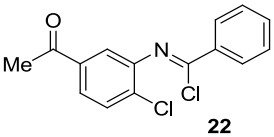
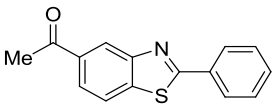
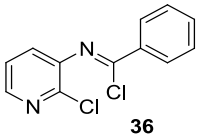
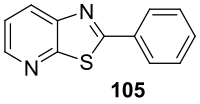
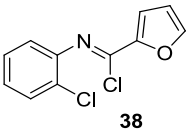
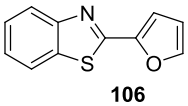
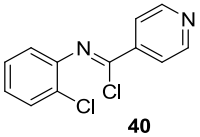
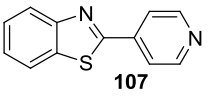
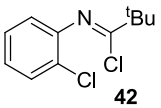
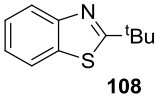
Scheme 3.7

3.2.3 Investigating the scope of benzothiazole synthesis: variation of the substrate

Initial investigations revealed that *N*-(*o*-chlorophenyl)imidoyl chloride **14** successfully reacted with sodium hydrosulfide hydrate under metal-free conditions to afford benzothiazole **99** in a good isolated yield of 73%. Amide **100** was also obtained in a 14% yield, however the two products were easily separated. In order to explore the scope and generality of this reaction a range of substrates possessing electronically different substituents were tested as is summarised in Table 3.2.

Table 3.2- Variation of the substrate[a]



Entry	Substrate	Product	Yield (%)[b]
1	 **14**	 **99**	73
2	 **8**	 **102**	37
3	 **18**	 **103**	48
4	 **22**	 **104**	74
5	 **36**	 **105**	77
6	 **38**	 **106**	81
7	 **40**	 **107**	56
8	 **42**	 **108**	83

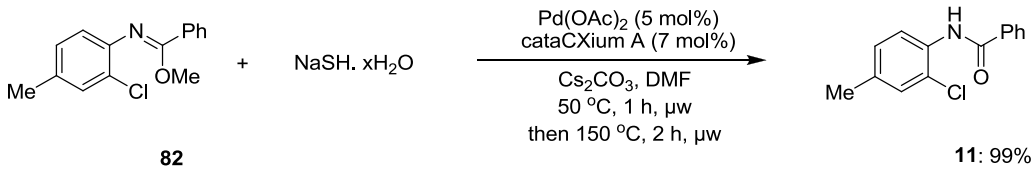
[a] Reaction conditions: imidoyl chloride (1.0 equiv), NaSH. xH_2O (3.0 equiv), Cs_2CO_3 (2.2 equiv), DMA, 50 °C, 1 h, µw then 150 °C, 2 h, µw. [b] Isolated yields

Inclusion of an electron-donating methoxy group unfortunately gave a low yield of benzothiazole **102** (entry 2). This reduced reactivity is attributed to the increased electron density on the aromatic ring, making it less electrophilic thus less susceptible to intramolecular attack by the sulfur of the thioamide moiety. Pleasingly electron-withdrawing nitrile and ketone moieties were tolerated in moderate to good yields respectively (entries 3 and 4). Entry 5 demonstrates the application of these reactions conditions for the successful synthesis of azabenzothiazole **105**. Variation of the 2-position (product numbering) was successfully demonstrated as furan, pyridine and a tertiary alkyl moiety could be incorporated in good yields (entries 6-8).

3.2.4 The use of *N*-(*o*-halophenyl)imidates as precursors for benzothiazole synthesis

As shown in Chapter 2, subjection of *N*-(*o*-halophenyl)imidates to palladium-catalysed amination conditions results in an initial reaction at the aryl halide moiety, followed by base promoted cyclisation to afford a benzimidazole product. It was envisaged that use of a sulfur nucleophile may yield a benzothiazole product *via* an analogous mechanism.

Thus, a test reaction of imidate **82** with sodium hydrosulfide hydrate, utilising conditions which previously gave an 81% yield of benzothiazole **99** from imidoyl chloride **14** (see section 3.2.2., table 3.1) was conducted. Unfortunately, this failed to give the desired heterocycle and amide **11** was observed as the sole product (Scheme 3.8).



Scheme 3.8

This reaction was repeated without the palladium catalyst under various conditions however, either recovered starting material or amide **11** were obtained. As no incorporation of the sulfur nucleophile (either by a palladium-catalysed thioetherification or as a result of a substitution reaction) had been seen in these test reactions, further screening of reaction conditions was not carried out.

3.3 Concluding comments

A metal-free route to benzothiazoles, utilising *N*-(*o*-chlorophenyl)imidoyl chlorides and sodium hydrosulfide hydrate has been developed. This provides advantages over existing metal-free routes as it makes use of cheap and readily available *o*-chloroanilines and avoids the use of Lawesson's reagent. A small substrate scope demonstrated that a good variety of benzothiazoles can be synthesised by this protocol, including 2-aryl, heteroaryl and alkyl substituted benzothiazoles, which was not possible *via* previously reported palladium- and copper-catalysed strategies.

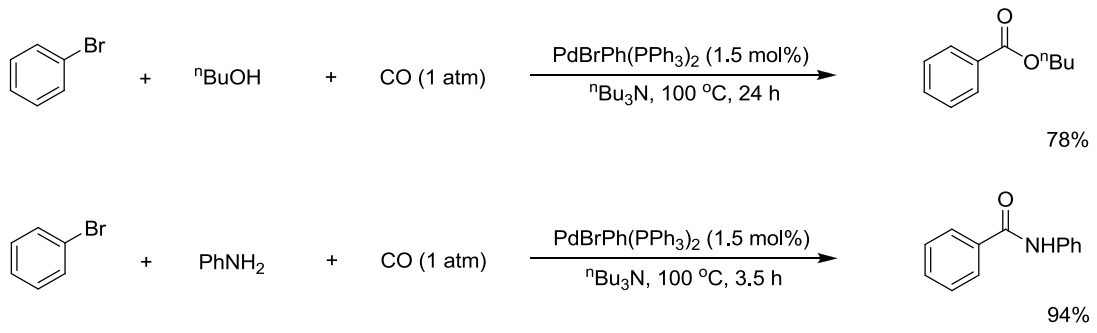
Unfortunately, *N*-(*o*-chlorophenyl)imidates did not yield benzothiazoles under test reaction conditions; however the use of these as precursors for the synthesis of quinazolinones will be demonstrated in Chapter 5.

Chapter 4: Palladium-catalysed carbonylation reactions of aryl halides and their application in heterocycle synthesis

4.1 Palladium-catalysed carbonylation reactions of aryl halides

4.1.1 Introduction

The palladium-catalysed reaction of aryl, alkenyl and heterocyclic halides with an appropriate nucleophile under a carbon monoxide atmosphere to afford, esters or amides was first reported by Heck *et al*. in 1974.[328, 329] Examples of these alkoxy- and aminocarbonylation reactions are shown in Scheme 4.1.



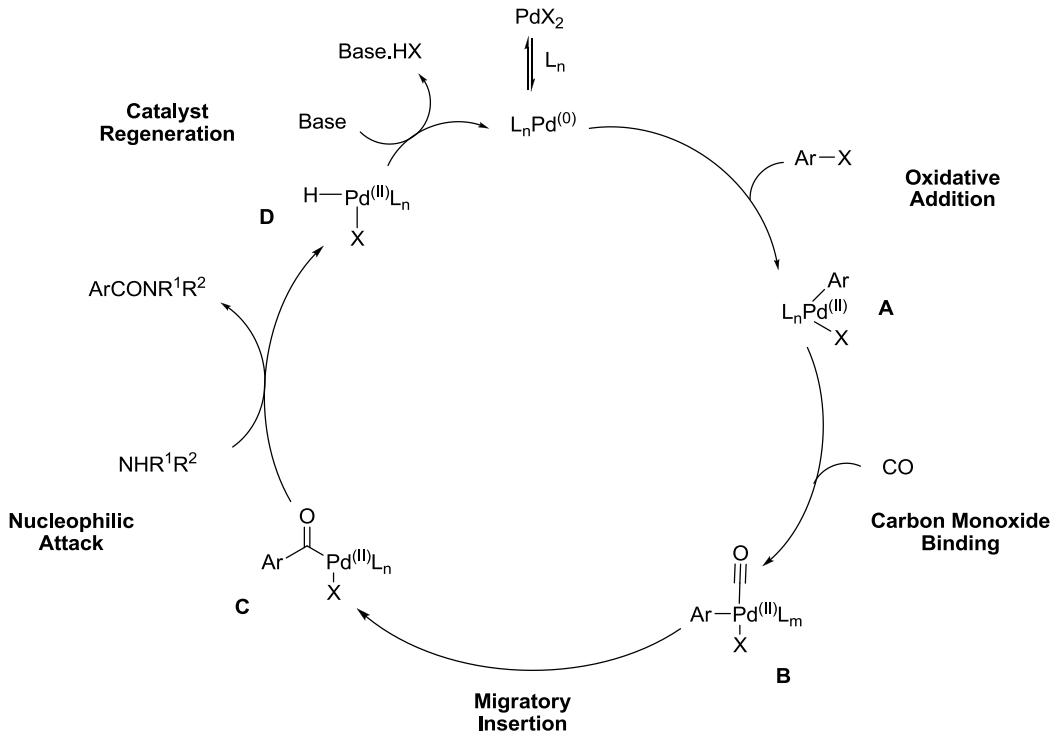
Scheme 4.1

Since these early reports, palladium-catalysed carbonylation reactions have received significant attention and as a result a broader scope now exists for these transformations.[330-335] For example, aryl chlorides, pseudo halides,[336, 337] and diazonium salts[338] may be successfully utilised as coupling partners. Additionally, a wide variety of nucleophiles can be employed; meaning that a range of products can be synthesised *via* carbonylative methods. Examples include carboxylic acids, anhydrides, acid fluorides, aldehydes, ketones and alkynones.[339]

This discussion will primarily focus on the development of palladium-catalysed amino and thiocarbonylation reactions of aryl halides and their application in heterocycle synthesis, as an introduction to the methods utilised in the following chapter.

4.1.2 Mechanism

Several mechanistic studies have been performed into these related carbonylation reactions.[340-342] Scheme 4.2 depicts the main steps for the generally accepted palladium-catalysed aminocarbonylation reaction. A detailed discussion of each step has been disclosed by Barnard,[333] thus a brief overview of the cycle will be presented here.



Scheme 4.2

As discussed in Chapter 1, a catalytically active monoligated Pd(0) complex can be generated from either palladium(II) or palladium(0) sources. Once formed, this undergoes oxidative addition into the aryl halide bond. This is thought to occur from a palladium

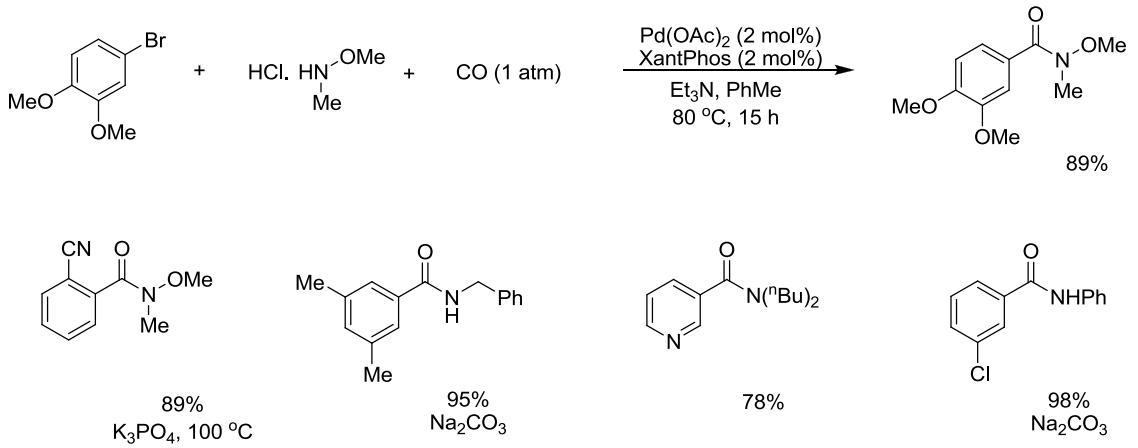
species which does not have carbon monoxide ligands bound to the metal centre. This is because, as a π acceptor, carbon monoxide reduces electron density on the metal centre by back donation, thus making the metal less susceptible to oxidation.[341] The next step is coordination of a carbonyl ligand to form complex **B**; this is generally rapid for simple phenyl complexes.[340] However, steric bulk around the aryl halide moiety can lead to a decrease in reactivity and rate as it hinders the binding of the carbonyl ligand. Migratory insertion then occurs from the aryl group to a *cis*-bound carbonyl ligand, thus forming acyl palladium species **C**. The formation of the product can then occur by two routes; direct nucleophilic attack at the acyl carbon by the amine or by initial bonding of the amine to palladium followed by reductive elimination. Although the full nature of this step has yet to be understood, it is believed to occur *via* the former for most aminocarbonylation reactions.[333] Thus, the resultant product amide is generated in tandem with palladium(II) species **D**, which in the presence of base can be converted to the active palladium(0) catalyst.

4.1.3 Palladium-catalysed aminocarbonylation reactions of aryl halides

The amide bond is an important moiety as it is found in many natural products and pharmaceutical molecules.[343, 344] Despite this, no one synthetic method has dominated, with numerous techniques existing. Common amide syntheses involve addition of amines to activated carboxylic acids by use of so-called coupling reagents[345] or various enzymatic approaches.[346] However high costs, formation of by-products and poor substrate compatibility mean that these methods can be unattractive. Methods based on metal-catalysed reactions provide alternative routes, which are more atom economical and utilise readily available starting materials.[347] Of these, palladium-catalysed aminocarbonylation of aryl halides has become a prominent way to synthesis benzamides

and has found application in the synthesis of pharmaceuticals.[348] As this process has been reviewed by Barnard[333] and Beller *et al*.,[334] only selected recent developments will be discussed herein.

A general system for the aminocarbonylation of aryl bromides under atmospheric pressure of carbon monoxide was reported by Buchwald *et al*. in 2008.[349] The use of the bisphosphine ligand XantPhos allowed the successful synthesis of a large variety of Weinreb amides[350] as well as coupling to a wide range of amines in mostly excellent yields. Several examples are shown in Scheme 4.3. (Six methyl esters were also prepared *via* an analogous alkoxycarbonylation reaction with methanol).

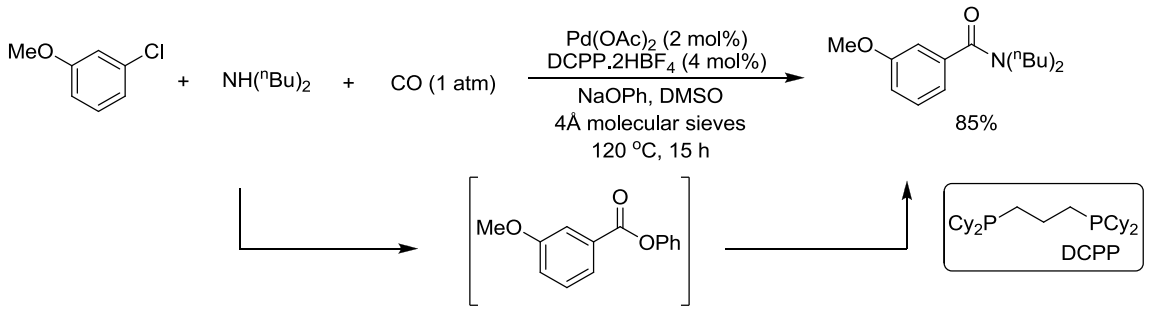


Scheme 4.3

Examples of more recent developments include aminocarbonylations of aryl iodides in water,[351] microwave-assisted aminocarbonylations of aryl bromides[352] and carbonylative couplings of aryl iodides or bromides with electron deficient nucleophiles such as ureas.[353, 354]

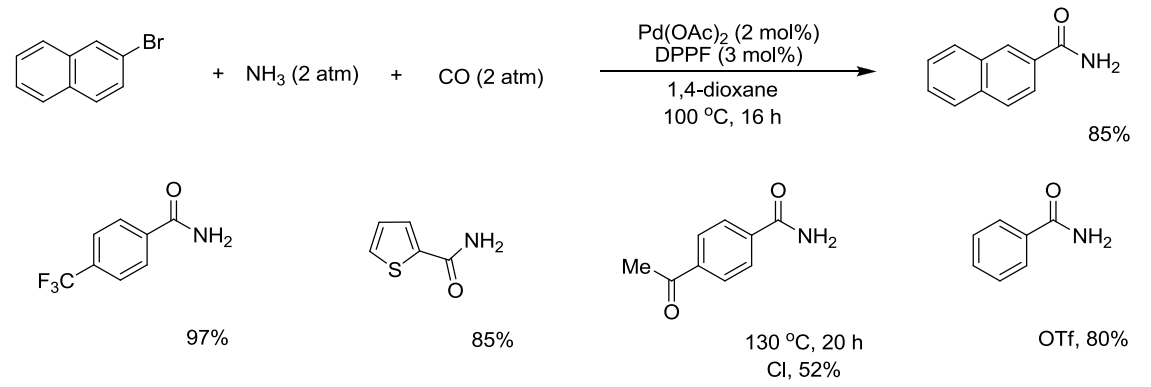
Although many examples of systems which utilise aryl iodides, bromides and triflates have been reported, a relatively small number of palladium-catalysed aminocarbonylation reactions of aryl chlorides exist in the literature. As discussed, the presence of carbon monoxide can hinder the oxidative addition step. This becomes even more difficult in these reactions due to the increased strength of the Ar-Cl bond; thus resulting in more forcing conditions being required to achieve reactivity. The first example of a system which successfully accomplished this coupling was reported by Milstein *et al.* in 1989.[355] This was based on the use of the bidendate phosphine ligand *bis*(diisopropylphosphino)propane at a high (*ca*. 4.8 atm) pressure of carbon monoxide. Additionally, only three examples were reported. More recently, the Beller group have reported the use of a JosiPhos derived ligand, which exhibited higher catalyst efficiency under 1 atm pressure of carbon monoxide.[356] However, their study focused mainly on alkoxycarbonylation reactions, with only a single example of an amine nucleophile being successfully employed.

A different approach was reported by Buchwald *et al*. in which aminocarbonylations of aryl chlorides were carried out at atmospheric pressures of carbon monoxide at relatively moderate temperatures.[357] This was possible through use of a sodium phenoxide additive, which acted both as a base and an acyl transfer agent. Thus, the reaction proceeded *via* formation of an intermediate phenyl ester (due to its greater nucleophilicity relative to the non-deprotonated amine) and subsequent reaction of this with an amine nucleophile afforded the desired amide product. A representative example is shown in Scheme 4.4. A good variety of substrates and amines were successfully coupled in mostly high yields.



Scheme 4.4

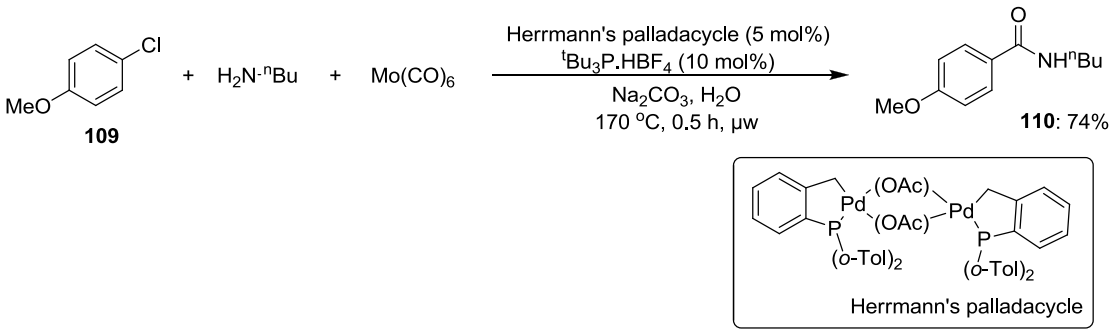
Although several syntheses of primary amides *via* aminocarbonylation protocols have been reported, these indirect approaches utilise ammonia synthons.[334] Recent contributions from the Beller laboratory provide a more straightforward approach by the use of ammonia gas.[358, 359] Due to its relatively low basicity, ammonia had not previously been used in a catalytic carbonylation reaction. However, a range of aryl and heteroaryl bromides and chlorides were shown to successfully react under relatively low pressures (2 atm) of carbon monoxide and ammonia gas to afford the desired amide products (Scheme 4.5). The initial system developed utilised the bulky monophosphine cata*C*Xium® A ligand,[358] which has previously been used in several other carbonylation reactions.[83, 360-363] However, development of a second generation catalyst system based on DPPF exhibited improved reactivity.[359]



Scheme 4.5

Although modern carbonylation reactions employ low pressures of carbon monoxide gas, thus circumventing the use of high pressure reactors, the handling and storage of this toxic and odourless gas are still disadvantageous. Therefore, this has led to a number of groups developing gas-free protocols.[364] A selection of recent examples, used for aminocarbonylation reactions will be highlighted here.

Numerous reports in which molybdenum hexacarbonyl is utilised as a solid source of carbon monoxide in a wide range of carbonylation reactions have been published by the Larhed group and others.[365] When heated to above 150 °C, this metal carbonyl complex is known to decompose to release carbon monoxide and solid molybdenum metal.[366] In order to do so safely, these pressurised reactions are generally conducted in microwave reactors (however, conventional heating has also been utilised). An example of such a protocol from the Larhed laboratory of the rapid synthesis of amide **110** from aryl chloride **109** in water is shown in Scheme 4.6.[367] However, molybdenum hexacarbonyl is toxic and the requirement of a near stoichiometric amount of an additional transition metal is not particularly attractive.

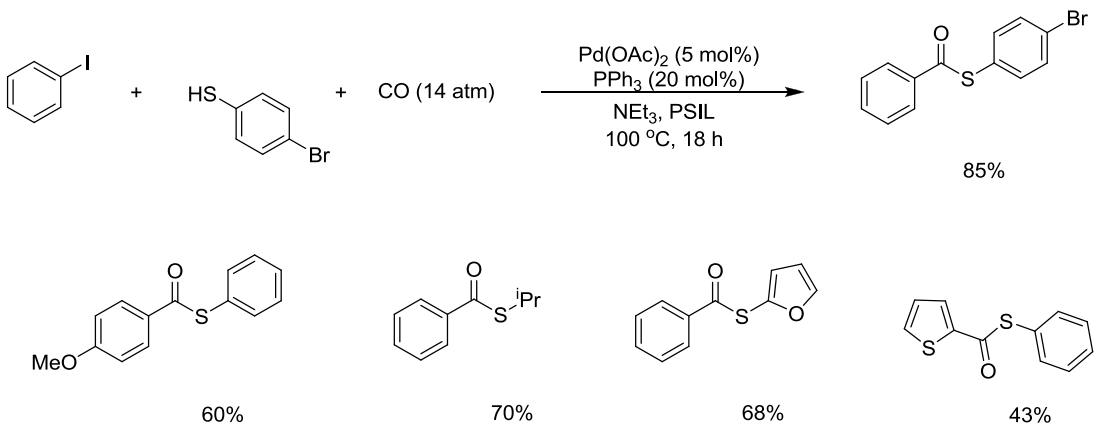


Scheme 4.6

Several aminocarbonylation reactions of aryl halides, which utilise non-metallic sources of carbon monoxide, have also been developed. These include use of carbamoylsilane,[368] formamides with a strong base[265, 369] and formamides in the presence of $POCl_3$.[370, 371] Recently, Skrydstrup *et al*. have reported the use of tertiary acid chlorides[372, 373] or silacarboxylic acids[374] as alternative sources of carbon monoxide gas in a range of carbonylation reactions. However, these protocols present limitations such as the use of toxic reagents for the preparation of the surrogates, high reaction temperatures, limited scope of aryl halide and the use of a glovebox and specialist equipment.

4.1.4 Palladium-catalysed thiocarbonylation reactions of aryl halides

Relative to related aminocarbonylation reactions, few palladium-catalysed thiocarbonylation protocols of aryl halides have currently been reported in the literature. The first example was published in 2008 by Alper *et al*.[375] Their system entailed the carbonylative coupling of aryl iodides with thiols and use of a phosphonium salt ionic liquid (PSIL), as the reaction solvent. Although a wide variety of thiols were successfully coupled, a high pressure of carbon monoxide (*ca*. 14 atm) was necessary (Scheme 4.7).



Scheme 4.7

Lei *et al*. have shown that preparation of aryl thioesters is possible *via* palladium-catalysed thiocarbonylation of aryl iodides with alkyl thiols in the presence of a sodium alkylthiolate additive.[376] Various aryl halides were transformed into the desired thioesters in high yields again, as a result of high pressures (10-30 atm) of carbon monoxide.

Recently, Yorimitsu and Oshima *et al*. have demonstrated the use of *bis*(cyclopentadienyldicarbonyliron) as a carbon monoxide source in a range of carbonylation reactions including thiocarbonylation of a limited number of aryl iodides.[377]

4.2 Application of palladium-catalysed carbonylation reactions in heterocycle synthesis

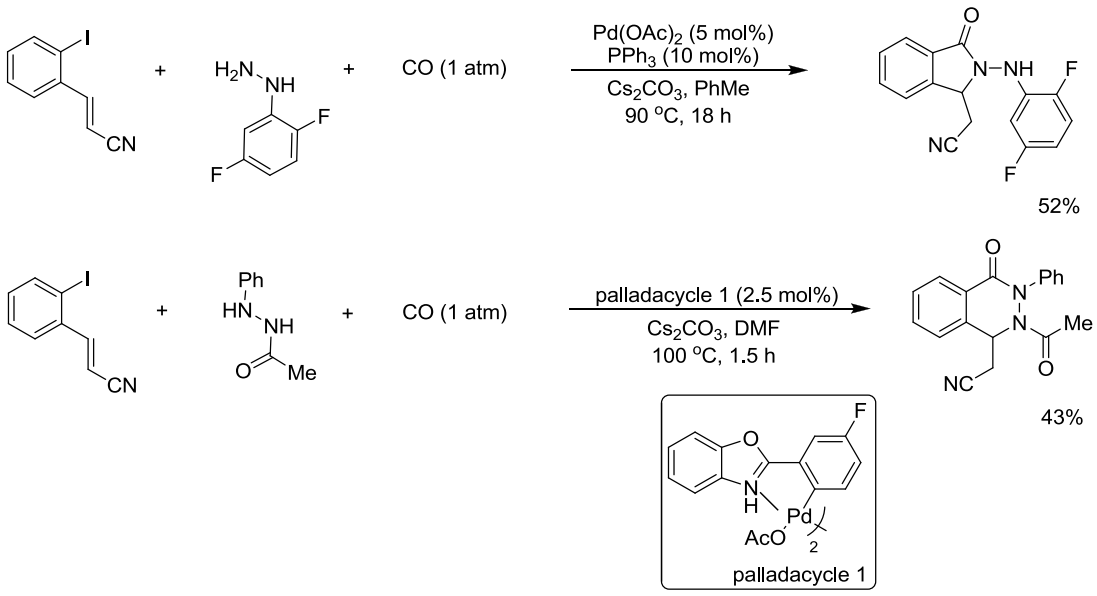
4.2.1 Introduction

Palladium-catalysed carbonylative-cyclisation reactions have become a valuable tool for the synthesis of a large variety of heterocyclic compounds.[128, 132, 335, 339, 378, 379] They enable the construction of complex scaffolds, through formation of multiple bonds in a single step. Selected protocols which utilise only palladium-catalysed aminocarbonylation reactions of aryl halides to form heterocycles will be the focus of this introductory discussion.

4.2.2 Palladium-catalysed aminocarbonylation reactions of aryl halides in heterocycle synthesis

Numerous palladium-catalysed aminocarbonylation protocols for isoindolinones (and related derivatives) have been reported.[380-386] An interesting report from the Grigg

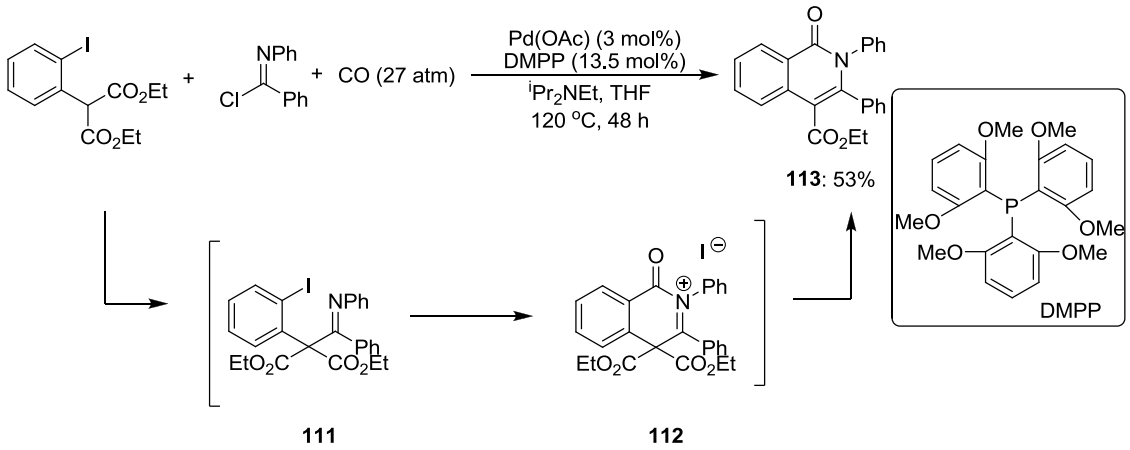
laboratory utilised a three component reaction between an aryl iodide/Michael acceptor, a hydrazine and carbon monoxide for the efficient synthesis of *N*-aminoisoindolones or phthalazones.[386] Regioselectivity was achieved by the selection of a mono or disubstituted hydrazine respectively. Both reactions proceeded *via* an initial aminocarbonylation at the aryl iodide moiety to form an acyl hydrazine, which subsequently underwent a Michael addition in either a 5-*exo*-*trig* or 6-*endo*-*trig* ring closure. An example of the synthesis of both heterocycles is shown in Scheme 4.8.



Scheme 4.8

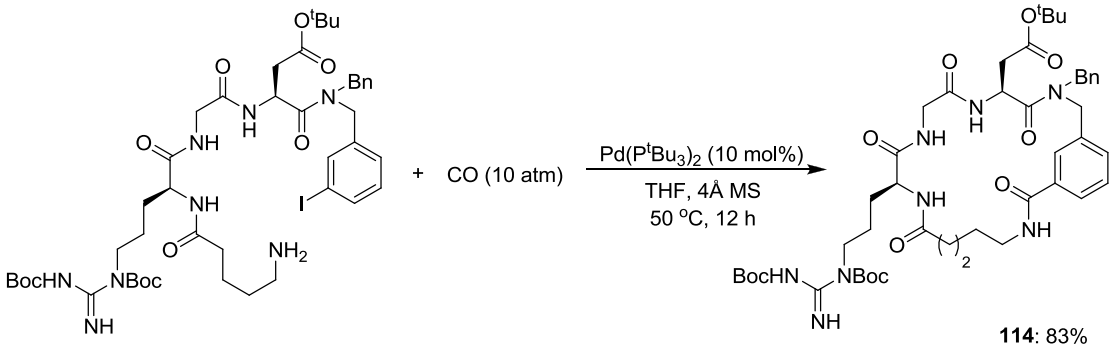
The Alper group have reported the synthesis of several carbonyl-containing heterocyclic scaffolds which employ a variety of cyclocarbonylation reactions.[387-395] This includes a number of routes which utilise aminocarbonylations of aryl halides for the synthesis of quinazolinones[396-399] and isoquinolinones derivatives;[400, 401] the former will be discussed at the beginning of Chapter 5. A representative example for the synthesis of isoquinolin-1(2*H*)-ones is the palladium-catalysed cyclisation of diethyl(*o*-iodoaryl)malonates with imidoyl chlorides and carbon monoxide.[401] The authors postulated that the reaction

proceeded *via* formation of intermediate **111**, followed by aminocarbonylation between the aryl iodide and imine moiety of **111**, to form isoquinolone salt **112** (Scheme 4.9). This subsequently underwent a base promoted decarboxylation reaction to afford heterocyclic product **113**. Twelve examples were synthesised in moderate to high yields, however a high pressure of carbon monoxide (*ca*. 27 atm) was required.



Scheme 4.9

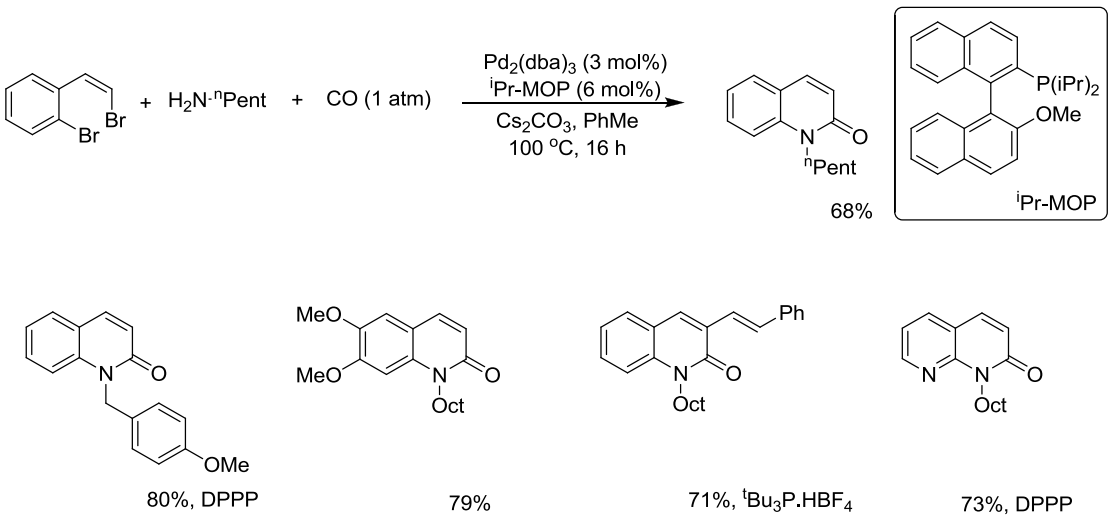
Palladium-catalysed aminocarbonylations have also been utilised for the synthesis of large ring systems.[395, 402, 403] For example, Doi *et al*. have reported the synthesis of cyclic peptide **114** *via* an impressive carbonylative macrolactamisation reaction (Scheme 4.10).[403]



Scheme 4.10

4.2.3 Previous work from the Willis laboratory

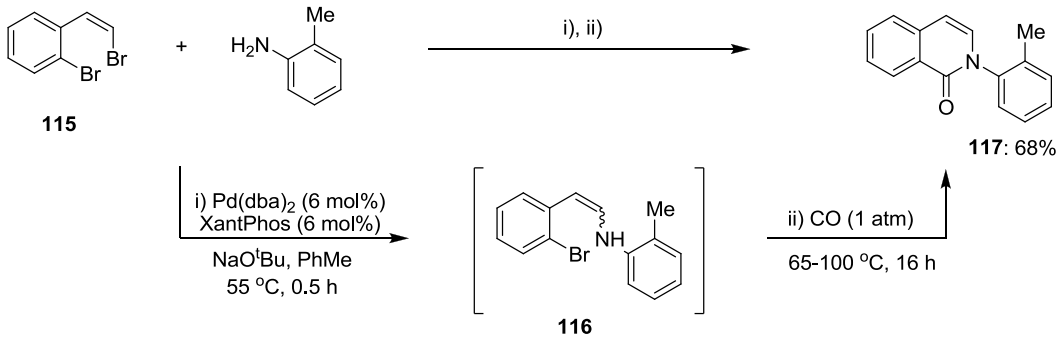
In 2009, Willis *et al*. reported the synthesis of 2-quinolones from a palladium-catalysed coupling of 2-(2-bromoalkenyl)aryl bromides with amines under atmospheric pressure of carbon monoxide.[178] The tandem reaction occurred *via* an initial aminocarbonylation at the alkenyl moiety to form an intermediate amide, which underwent an intramolecular amidation/cyclisation to afford the desired heterocycle. Some variation of the ligands was required in order to incorporate a range of nucleophiles and substituents on the substrate backbone successfully. A few examples are shown in Scheme 4.11.



Scheme 4.11

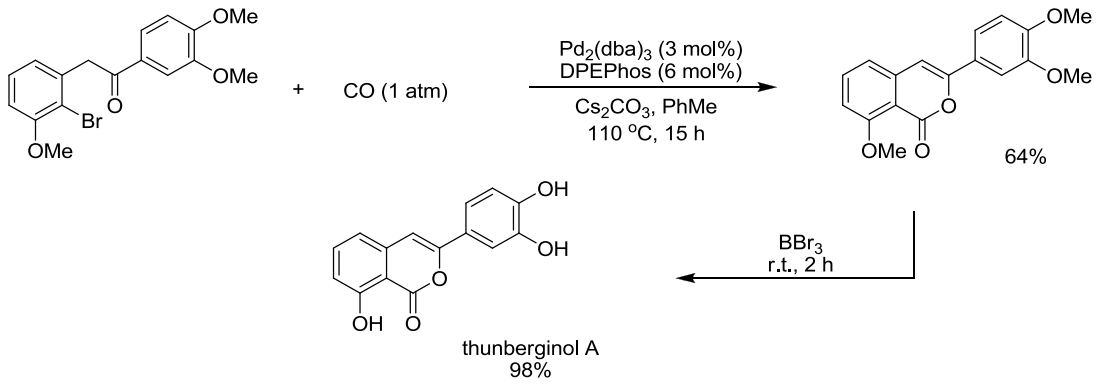
A route to isoquinolones from the same precursor, which entailed a two step process, was also explored. For example, dibromide **115** was initially reacted with *o*-toluidine in the presence of a palladium catalyst to form enamine intermediate **116** (Scheme 4.12). This was then subjected to a carbon monoxide atmosphere, which triggered carbonylation at the aryl bromide and subsequent ring closure to afford isoquinolone product **117**. Unfortunately, this protocol proved not to be as general as the related quinolone synthesis. Poor yields were obtained for other nucleophiles tested and problems were

encountered with competing formation of indole and decomposition products. A similar route has recently been published by Florent *et al*.[404] However, the scope of both the aryl halide and amine were poor with most isoquinolones isolated in low to moderate yields.



Scheme 4.12

Similarly, the Willis group have published a route to isocoumarins, which utilised an aryl carbonylation reaction.[181] When α-(*o*-bromoaryl) ketones were treated with a palladium catalyst under a low pressure of carbon monoxide, an aryl carbonylation/intramolecular *O*-enolate acylation sequence occurred, resulting in the heterocyclic product. This methodology was showcased in the concise synthesis of the natural product thunberginol A as shown in Scheme 4.13.



Scheme 4.13

4.3 Concluding comments

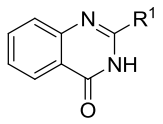
Since Heck's early work, significant developments have meant that numerous aryl halides and nucleophiles can now be carbonylatively coupled to form a wide variety of products. In addition, milder protocols which utilise relatively low pressures of carbon monoxide mean these reactions are more attractive as specialist equipment is no longer required. Several gas-free methods have also been described. Finally, use of aminocarbonylations for the efficient synthesis of important heterocycles has additionally been highlighted here.

Chapter 5: Palladium-catalysed carbonylation in the synthesis of quinazolinones and benzothiazinones

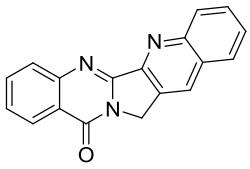
5.1 Introduction

5.1.1 The importance of quinazolinones

The fused six-membered heterocyclic motif of quinazolinones is a prominent scaffold in both naturally occurring compounds and synthetic drugs.[405-407] Specifically, quinazolin-4(3*H*)-ones (Figure 5.1) exhibit a vast range of biologically active properties[408] including antimalarial,[409] antidiabetic[410] and antiallergy activities.[411] Additionally, luotonin A (a naturally occurring alkaloid extracted from a Chinese medicinal plant)[412] has been shown to exhibit potent cytotoxic properties,[412, 413] which has led to its use as a lead compound in anticancer drug development.[413, 414]



quinazolin-4(3*H*)-one motif



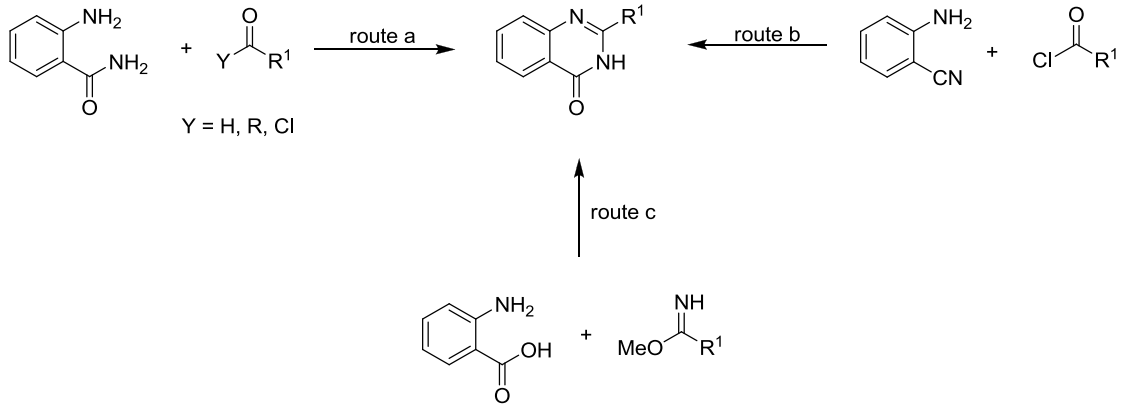
luotonin A

Figure 5.1

5.1.2 Synthesis of quinazolinones

A number of comprehensive reviews have been written covering classical syntheses of quinazolinones,[407, 415-420] thus only a brief description of these methods will be discussed. This will be followed by transition metal-catalysed protocols, which form the main focus of this introduction.

The synthesis of 2-phenylquinazolin-4(3*H*)-one was first reported by Körner in 1877 by the action of aqueous potassium hydroxide on *N*-benzoylorthoanilamide.[421] This, in turn was obtained from anthranilamide, which has been utilised in further quinazolinone syntheses (Scheme 5.1, route a).[422] Examples of these include cyclisation with aldehydes[423] and ketones or acid chlorides under acidic and basic conditions.[424-426] Related approaches to quinazolinones involve the amidation of *o*-aminobenzonitriles followed by oxidative ring closure (route b)[427-430] and condensation of *o*-aminobenzoic acids with imidates (route c).[431-433]



Scheme 5.1

However, these classical syntheses suffer from a requirement for multiple steps and harsh conditions and can afford the product heterocycles in low yields. A number of palladium-catalysed routes to quinazolinones have been reported which allow facile synthesis from readily available starting materials in fewer steps. Several of these utilise carbonylation reactions; the main disconnection approaches are shown in Figure 5.2.

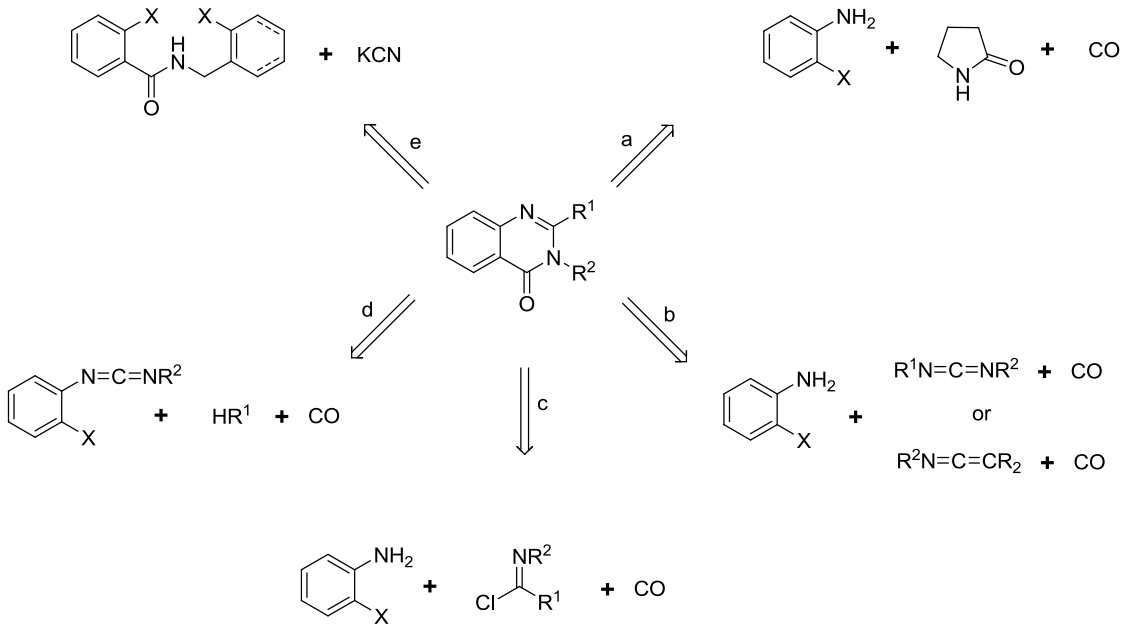
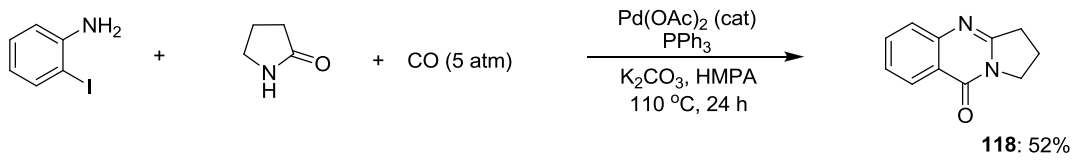


Figure 5.2

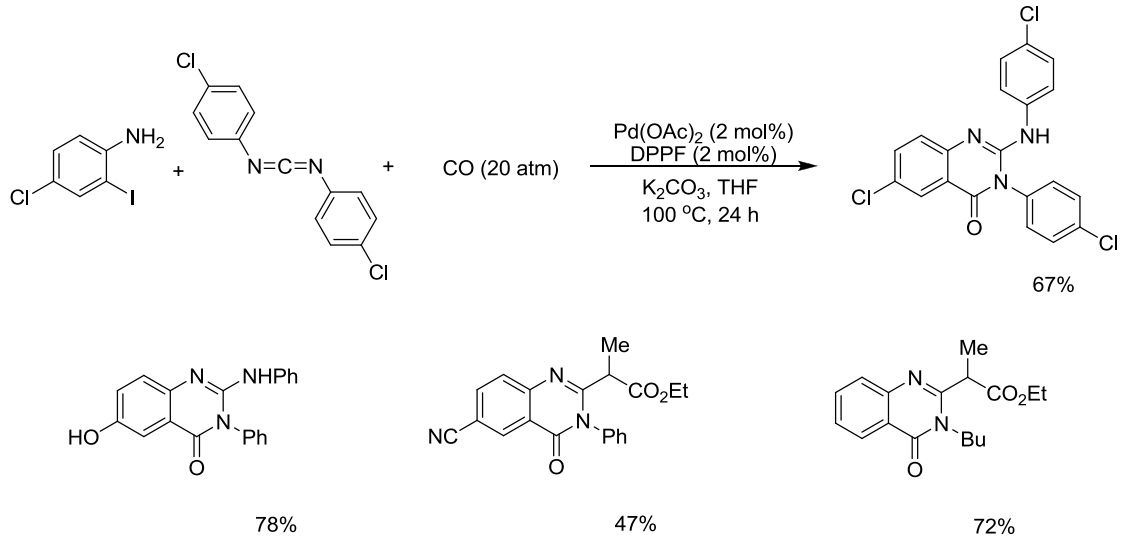
An early example of a palladium-catalysed synthesis of quinazolinones was reported by Mori *et al*. in 1985 (Figure 5.2, disconnection a).[434] The group showed that when *o*-iodoaniline and 2-pyrrolidone were reacted in the presence of a catalytic amount of palladium under 5 atm pressure of carbon monoxide, quinazolinone **118** was obtained in a 52% yield (Scheme 5.2). This occurred *via* an aminocarbonylation reaction followed by ring closing attack of the amino group onto the imide carbonyl. However, this protocol was very limited as six and seven membered lactams gave very poor yields of the desired heterocycles.



Scheme 5.2

Several routes to quinazolinones have been developed by the Alper group.[396-399] Their first protocol, published in 2000, utilised palladium-catalysed aminocarbonylation

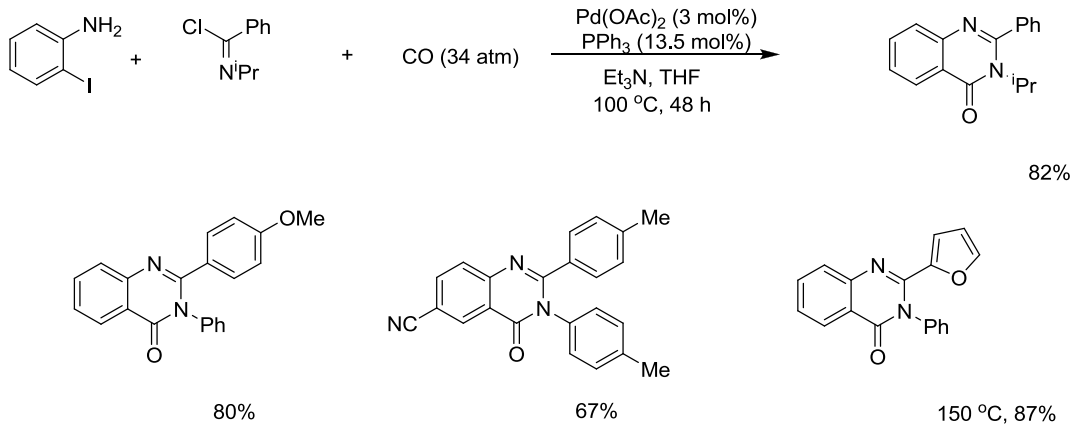
reactions of *o*-iodoanilines with carbodiimides or ketenimines to afford 2-amino quinazolin-4(3*H*)-ones or 2-alkyl quinazolin-4(3*H*)-ones respectively (Figure 5.2, disconnection b).[396] The proposed mechanism involved formation of guanidine or amidine intermediates respectively, oxidative addition of palladium and aminocarbonylative ring closure. Although the reactions were carried out with low loadings of catalyst and ligand (2 mol%), a high pressure of carbon monoxide was required (*ca*. 20 atm). Examples of the heterocycles synthesised by this method are shown in Scheme 5.3.



Scheme 5.3

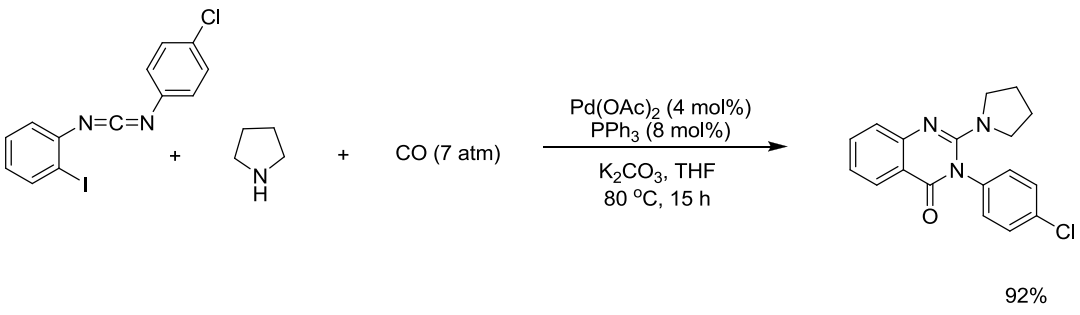
In 2008, the same group demonstrated an alternative approach to quinazolinones, which involved the palladium-catalysed coupling of *o*-iodoanilines to imidoyl chlorides in the presence of carbon monoxide (Figure 5.2, disconnection c).[397] A similar mechanism was postulated; this proceeded *via* formation of an amidine intermediate followed by aminocarbonylation cyclisation. The imidoyl chlorides were easily prepared from the corresponding amides and thionyl chloride, thus allowing a wide range of substituted 2,3-disubstituted quinazolin-4(3*H*)-ones to be synthesised (Scheme 5.4). However, this

protocol also required high pressures of carbon monoxide (*ca*. 34 atm), long reaction times and was limited to use of iodide starting materials.



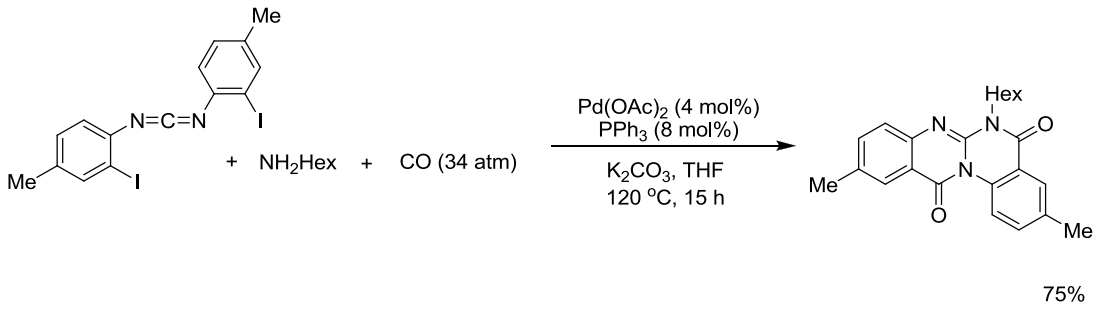
Scheme 5.4

More recently, Alper *et al*. have reported an efficient and mild protocol for the synthesis of 2-hetero substituted quinazolin-4(3*H*)-ones (Figure 5.2, disconnection d).[398] This entailed the intermolecular addition of nitrogen or oxygen nucleophiles to *N*-(*o*-iodophenyl)-*N*'-aryl carbodiimides, followed by palladium-catalysed aminocarbonylation/intramolecular cyclisation reactions. A lower pressure of carbon monoxide was successfully utilised (7 atm) at a lower reaction temperature. A variety of nucleophiles could be incorporated; an example of a 2-amino quinazolinone prepared *via* this method is shown in Scheme 5.5.



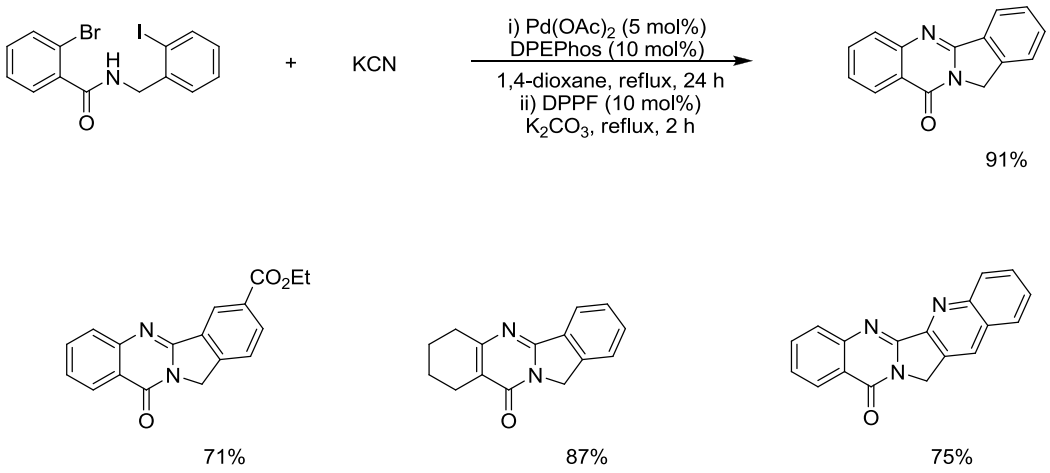
Scheme 5.5

In an elegant extension to this work, the group demonstrated the synthesis of 6-substituted quinazolino[3,2,*a*]quinazolinones by the reaction of *N*,*N*'-di-*o*-iodophenyl carbodiimides with nitrogen nucleophiles under high pressures of carbon monoxide (34 atm) (Scheme 5.6).[399] The authors proposed that the reaction proceeded *via* an addition/palladium-catalysed domino carboxamidation sequence in which five bonds were formed in a single step. A very recent publication by He *et al*. utilised a similar palladium-catalysed tandem reaction of *N*,*N*'-di-*o*-iodophenyl carbodiimides, amines and in this case isocyanides in order to prepare imine- substituted quinazolino[3,2,*a*]quinazolinones.[435]



Scheme 5.6

The use of a palladium-catalysed cyanation reaction in combination with sequential *N*-addition/*N*-arylation was reported by Li *et al.* for the synthesis of isoindolo[1,2,*b*]quinazolin-10(12*H*)-ones (Figure 5.2, disconnection e).[436] The reaction of *o*-bromo-*N*-(*o*-iodobenzyl)benzamides with potassium cyanide in the presence of a palladium catalyst afforded the product heterocycles in good to excellent yields (Scheme 5.7). This method was also utilised for the facile synthesis of the luotonin A and its derivatives from the corresponding dibromide starting materials.



Scheme 5.7

Other palladium-catalysed quinazolinone syntheses have been reported; however these utilise C-H functionalisation approaches. Examples include direct *ortho*-carboxylation of anilides[437] or intramolecular carboxamidation of *N*-arylamidines.[438]

It should be noted that a number of copper-catalysed protocols for the synthesis of quinazolinones appear in the literature. These routes include heteroannulation of alkynes,[439, 440] the coupling of *o*-halobenzamides with imidamides,[441] α-amino acids[442] or (aryl)methanamines,[443] and *o*-halocarboxylic acids with guanidines[444] or amidines.[445]

5.2 Results and Discussion

5.2.1 Proposed route to 2,3-disubstituted quinazolin-4(3*H*)-ones

Previous work from the group involved the synthesis of 2-quinolones and isoquinolones from palladium-catalysed reactions of 2-(2-bromoalkenyl)aryl bromides with nitrogen nucleophiles under atmospheric pressure of carbon monoxide (see section 4.2.3). In an analogous fashion, we envisaged the use of *N*-(*o*-halophenyl)imidoyl chlorides (Y = Cl) or imidates (Y = OR) for the synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones (Figure 5.3). During our studies into the use of these precursors for benzimidazole synthesis, the two starting materials were shown to react *via* different mechanisms (see chapter 2). Hence, in this case, initial nucleophilic substitution may occur at the imidoyl moiety followed by aminocarbonylative cyclisation. Alternatively, an aminocarbonylation reaction may occur at the aryl halide moiety first to form an amide intermediate, followed by a condensation/cyclisation reaction. Likewise, this sequence would be determined by the leaving group ability of Y on the imidoyl portion (Cl > OR) and the rate at which the metal-catalysed step occurs.

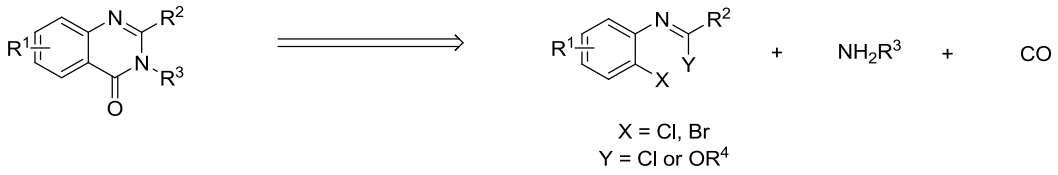
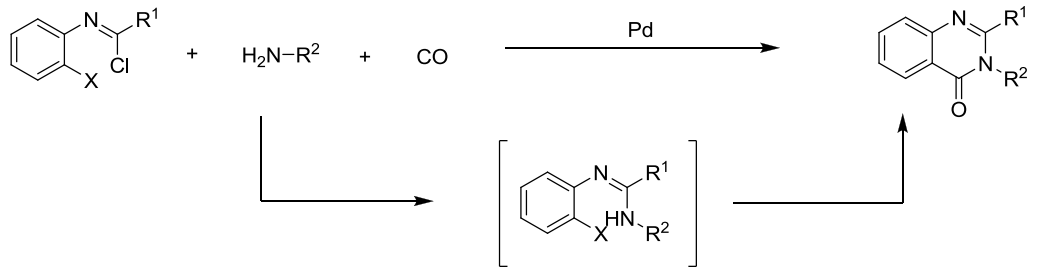


Figure 5.3

Although a number of palladium-catalysed routes to quinazolinones exist (section 5.1.2), these are limited by the use of iodide precursors, high pressures of carbon monoxide and high reaction temperatures. Thus, we were keen to develop a quinazolinone synthesis from readily available and cheaper *o*-chloro or *o*-bromoanilines, utilising an atmospheric pressure of carbon monoxide under mild reaction conditions.

5.2.2 The use of *N*-(*o*-halophenyl)imidoyl chlorides as precursors for quinazolinone synthesis: Initial investigations

During our studies into the use *N*-(*o*-halophenyl)imidoyl chlorides for benzimidazole synthesis, it was found that the nucleophilic substitution reaction occurred initially at the imidoyl chloride portion, forming an amidine intermediate. This subsequently underwent an intramolecular palladium-catalysed C-N bond formation to yield the heterocycle product (see section 2.2.2). Thus, if a carbon monoxide atmosphere was introduced to this process, an aminocarbonylation reaction between the aryl halide moiety and free nitrogen of the amidine intermediate could occur, affording a quinazolinone product (Scheme 5.8).

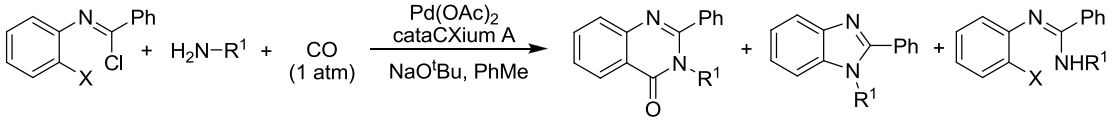


Scheme 5.8

Investigations began with a two-step reaction of imidoyl chloride **10** with *p*-toluidine. The reagents were initially reacted in the presence of a base and then subjected to an atmospheric pressure of carbon monoxide. (This was achieved by simply attaching a balloon of carbon monoxide to the reaction vessel). It was envisaged that use of a weak nucleophile would decrease the competitive formation of the unwanted benzimidazole heterocycle over the desired quinazolinone product. The initial catalyst system used in these test reactions utilised the hindered monophosphine cata*C*Xium® A ligand as it proved to be the optimal ligand during our benzimidazole studies. Additionally, several reports by Beller *et al*. showed its use in a range of carbonylation reactions,[360, 362, 446] including aminocarbonylations.[358, 361] In these reports, the authors noted the use of a high

ratio of ligand to palladium catalyst (3:1) is crucial for good catalyst efficiency. Carbon monoxide acts as a π-acceptor ligand thus decreasing the electron density at the palladium centre and impeding oxidative addition into the aryl halide bond. Moreover, inactive species can be formed by agglomeration and clustering of palladium atoms in the presence of carbon monoxide. Thus, use of higher concentrations of such phosphine ligands was shown to overcome these undesirable interactions. Initial optimisation results are summarised in Table 5.1.

Table 5.1- Optimisation using imidoyl chlorides 10 and 73[a]



10: X = Cl
73: X = Br

119: R^1 = *p*-tol
120: R^1 = benzyl

95: R^1 = *p*-tol
44: R^1 = benzyl

121: X = Br
R^1 = *p*-tol
122: X = Br
R^1 = benzyl

Entry	X	R^1	Conditions	Yield (%)[b]
1	Cl	*p*-Tol	50 °C, 0.5 h then CO, 100 °C, 18 h	-
2	Cl	*p*-Tol	50 °C, 0.5 h then CO, 140 °C, 18 h	0:61:0
3	Br	*p*-Tol	55 °C, 0.5 h then CO, 85 °C, 18 h	14:trace:0
4	Br	*p*-Tol	55 °C, 0.5 h then CO, 100 °C, 18 h	27:14:0
5	Br	*p*-Tol	55 °C, 0.5 h then CO, 120 °C, 18 h	1:2:0[c]
6	Br	CH_2Ph	55 °C, 0.5 h then CO, 85 °C, 18 h	27:26:15
7[d]	Br	CH_2Ph	55 °C, 0.5 h then CO, 85 °C, 18 h	30:40:22
8	Br	CH_2Ph	CO, 85 °C, 18 h	1:3:trace[c]

[a] Reaction conditions: imidoyl chloride (1.0 equiv), amine (1.5 equiv), $Pd(OAc)_2$ (6 mol%), cata*C*Xium® A (18 mol%), NaO^{t}Bu (3 equiv), PhMe then CO (balloon). [b] Isolated yields. [c] Ratio determined from ^{1}H NMR spectrum of crude reaction mixture. [d] Cs_2CO_3 used as the base

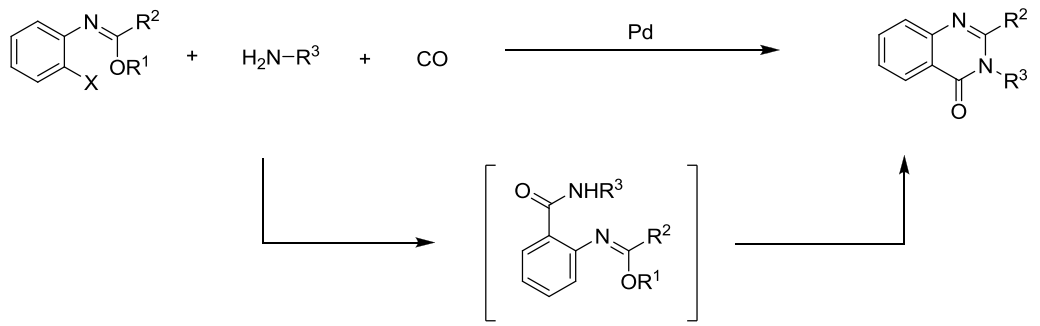
Entry 1 shows that when the carbonylation reaction between *N*-(*o*-chlorophenyl)imidoyl chloride **10** and *p*-toluidine was carried out at 100 °C, no products were cleanly isolated from the crude reaction mixture. Beller *et al*. have shown that aminocarbonylations of aryl chlorides, employing the same catalyst system, typically require higher temperatures (130-150 °C) than those of aryl bromides (100 °C).[358] However, increasing reaction

temperature to 140 °C resulted in benzimidazole **95** being isolated in a 61% yield with no desired quinazolinone being observed in this reaction (entry 2). As preliminary reactions with imidoyl chloride **10** proved to be problematic, *N*-(*o*-bromophenyl)imidoyl chloride **73** was then tested in the hope that the more activated aryl bromide moiety would undergo aminocarbonylation under milder conditions. An initial reaction between **73** and *p*-toluidine utilising the same catalyst system and carrying out the carbonylation reaction at 85 °C did indeed afford quinazolinone product **119**, albeit in a low yield (entry 3). Trace amounts of benzimidazole **95** and decomposition products were also observed. Increasing the temperature of the second step of the reaction to 100 °C yielded quinazolinone **119** in a higher 27% isolated yield (entry 4). However benzimidazole **95** was also afforded in a 14% yield as well as products resembling amidine **121**, which decomposed on isolation, thus a reliable yield could not be obtained. When this reaction temperature was further increased to 120 °C, a 2:1 ratio of benzimidazole **95** to quinazolinone **119** was observed in the crude ^{1}H NMR spectrum of the reaction mixture (entry 5). As these reactions often yielded decomposition products, the use of benzylamine was then tested, as this gave cleaner reactions during our benzimidazole synthesis studies. Carrying out a two-step reaction of imidoyl chloride **73** with benzylamine afforded amidine intermediate **122**, benzimidazole **44** and quinazolinone **120**, with the later obtained in similarly poor yields (entry 6). Use of a weaker base increased the ratio of benzimidazole **44** to quinazolinone **120** (entry 7). When the reaction was carried out in a single step, namely heating the mixture to 85 °C under an atmosphere of carbon monoxide, a 3:1 ratio of benzimidazole **44** to quinazolinone **120** was observed (entry 8). This suggested that benzimidazole formation is faster relative to quinazolinone formation.

Although not extensive, these initial investigations resulted in low yields of the desired heterocycle and competitive benzimidazole formation proved problematic in these reactions. Thus, an alternative approach was considered.

5.2.3 The use of *N*-(*o*-halophenyl)imidates as precursors for quinazolinone synthesis: Initial investigations

As shown in Chapter 2, the reaction of *N*-(*o*-halophenyl)imidates with nitrogen nucleophiles in the presence of a palladium catalyst also successfully yielded benzimidazole products. This occurred *via* a different mechanism and it was envisaged that this alternative reactivity could be utilised for the more effective synthesis of quinazolinones. An initial aminocarbonylation reaction could plausibly occur at the aryl halide, affording an amide intermediate, which could then undergo a condensation/cyclisation reaction (Scheme 5.9).

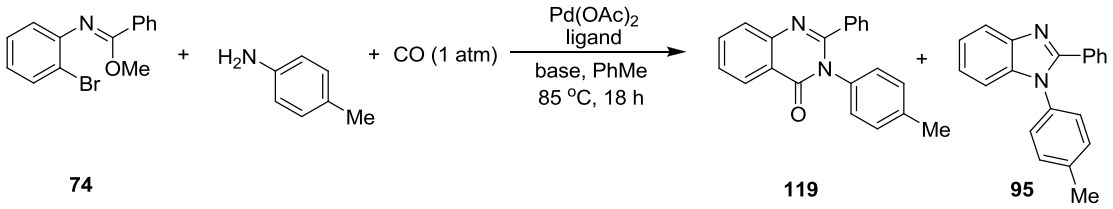


Scheme 5.9

Literature precedent suggests that carbonylation should be faster than an intermolecular amination reaction (as demonstrated by the numerous heterocycle syntheses presented in sections 4.2.2 and 4.2.3). Thus, competitive benzimidazole formation should be less problematic in this case. Additionally, a two-step process would not be required, making

it an experimentally easier reaction. Initial investigations were carried out for the reaction of *N*-(*o*-bromophenyl)imidate x with *p*-toluidine; the results are shown in Table 5.2.

Table 5.2- Optimisation using imidate 74[a]



74 119 95

Entry	Ligand	Base	Yield (%)[b] 74:119:95
1	cata*C*Xium® A	NaO^{t}Bu	14:86:0[c]
			17:65:2
2[d]	cata*C*Xium® A	NaO^{t}Bu	0:58:9
3[e]	cata*C*Xium® A	NaO^{t}Bu	100:0:0[c]
4	**cata*C*Xium® A**	**Cs_2CO_3**	**14:75:0**
5[f]	cata*C*Xium® A	Cs_2CO_3	20:70:0[c]
6[g]	cata*C*Xium® A	Cs_2CO_3	24:64:0
7[h]	cata*C*Xium® A	Cs_2CO_3	63:37:0[c]
8	cata*C*Xium® A	K_2CO_3	37:62:0
9	^{t}Bu$_3$P.HBF$_4$	Cs_2CO_3	67:33:0[c]
10	^{i}PrMOP	Cs_2CO_3	43:46:0
11	XPhos	Cs_2CO_3	33:49:2
12	SPhos	Cs_2CO_3	54:46:0[c]
13	DavePhos	Cs_2CO_3	70:30:0[c]
14	XantPhos	Cs_2CO_3	100:0:0[c]
15	DPPP	Cs_2CO_3	82:18:0[c]
16	DPPF	Cs_2CO_3	62:38:0[c]

[a] Reaction conditions: imidate **74** (1.0 equiv), *p*-toluidine (1.5 equiv), $Pd(OAc)_2$ (6 mol%), ligand (18 mol%), CO (balloon), base (3 equiv), PhMe, 85 °C, 18 h. [b] Isolated yields. [c] Ratio determined from ^{1}H NMR spectrum of crude reaction mixture. [d] Reaction carried out at 90 °C. [e] $Pd(OAc)_2$ (6 mol%), cata*C*Xium® A (12 mol%) used. [f] $Pd(OAc)_2$ (4 mol%), cata*C*Xium® A (12 mol%) used. [g] $Pd_2(dba)_3$ used as the catalyst. [h] 1,4-dioxane used as the solvent.

Initially, the same catalyst system under similar conditions to those utilised in the previous investigations were applied to this reaction. Pleasingly, an 86% conversion of starting material to quinazolinone **119** was observed in the crude ^{1}H NMR spectrum (entry 1). After purification, a moderate isolated yield of 65% quinazolinone **119** was obtained as well as 17% recovered starting material and only 2% of benzimidazole **95**.

Increasing the reaction temperature to 90 °C resulted in full conversion of the starting material. However, a lower isolated yield of desired heterocycle **119** was obtained as well as an increased 9% yield of benzimidazole **95** (entry 2). The ratio of palladium catalyst to ligand was then reduced to 1:2 and no conversion of starting material to either product was observed (entry 3). This confirmed the dependence on these reactions on the concentration of phosphine ligand. Use of cesium carbonate resulted in an increased yield of quinazolinone product, however full conversion was not observed as 14% of the starting material **74** was recovered (entry 4). Reducing the catalyst and ligand loading, unfortunately gave a poorer conversion (entry 5). Employment of an alternative palladium catalyst (entry 6), solvent (entry 7) or base (entry 8), failed to give an improvement in yield. A variety of ligands, which have been utilised in aminocarbonylation reactions were then tested (entries 9-16). It was found that monophosphine ligands generally preformed better than bisphosphine ligands in this reaction. However, none of the ligands tested gave a higher conversion than cata*C*Xium® A.

During these reactions, a non-polar side product was often observed in small amounts (<10%). Although this was not isolated cleanly, the ^{1}H NMR spectrum contained signals which were consistent with the ester product shown in Figure 5.4. A singlet at 4.02 ppm was assigned as the protons of the imidate methoxy group as these appear at 4.05 ppm in the starting material. Another singlet, which has an equal integration, appeared at 3.79 ppm. This is consistent with the methoxy group of an ester group. A distinct doublet of doublets at 7.80 ppm was found to integrate to one proton relatively. When compared to the equivalent proton of the starting material [(7.53 (1H, dd, J = 8.0 Hz, J = 1.4 Hz))], it

was consistent to it now being *ortho* to an electron withdrawing ester group on the benzene ring.

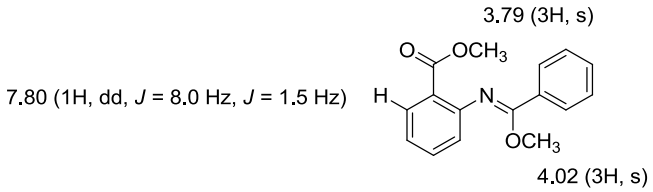
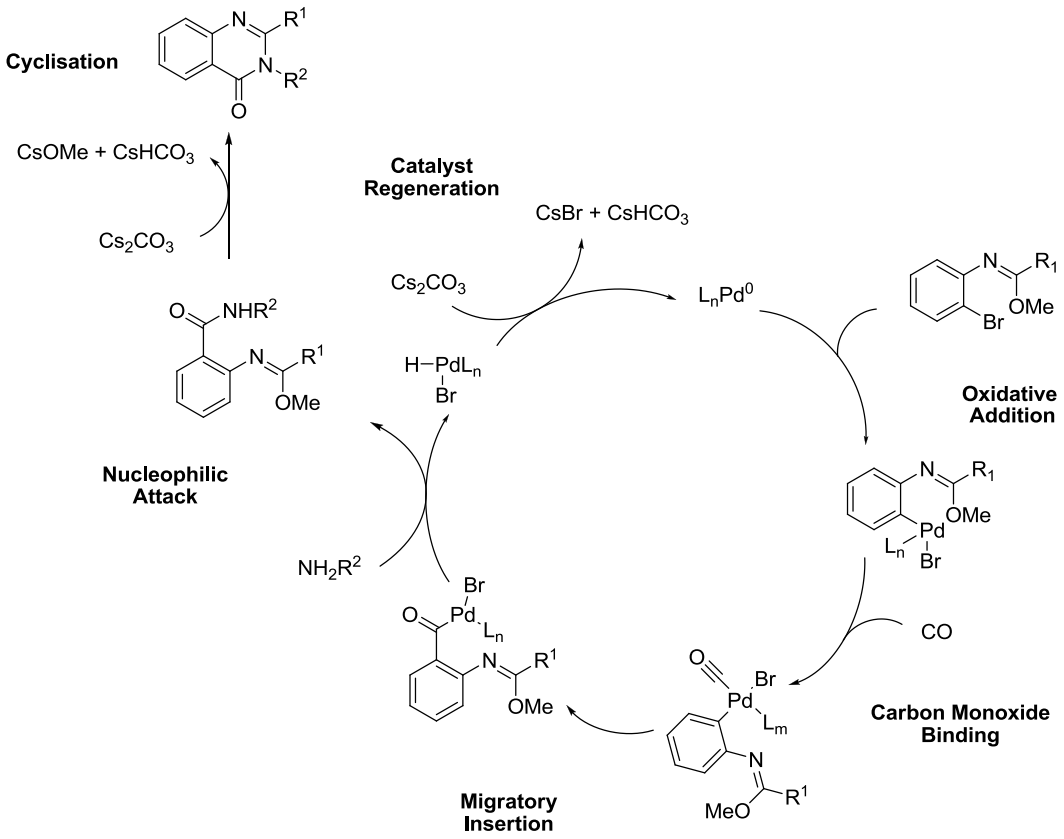


Figure 5.4

The observation of this side product indicated that indeed an initial palladium-catalysed carbonylation at the aryl bromide moiety was occurring, as shown in Scheme 5.10. This would form an acyl palladium intermediate, which could be attacked by either the amine nucleophile added or methoxide generated in the reaction mixture to afford an intermediate amide or the ester side product (not shown in Scheme 5.10) respectively. The amide could then undergo cyclisation (through the nitrogen atom) in the presence of the base to afford the desired quinazolinone heterocycle.

Alternatively, cyclisation through the amide oxygen would afford a regioisomeric heterocycle (not shown in Scheme 5.10). However, comparisons of ^{1}H NMR, ^{13}C NMR and IR spectra of the heterocycle obtained from our reaction matched those of quinazolinones synthesised by Alper *et al.* (see scheme 5.4), which have been assigned by X-ray crystallography.[397] In addition, heterocyclic products obtained *via* our imidoyl chloride route (wherein cyclisation through the oxygen is not plausible) produced the same products (as determined by ^{1}H NMR, ^{13}C NMR and IR spectroscopy) to those from our corresponding imidate precursors. Thus, we were confident of the proposed mechanism and the identity of the quinazolinone products produced *via* our route.

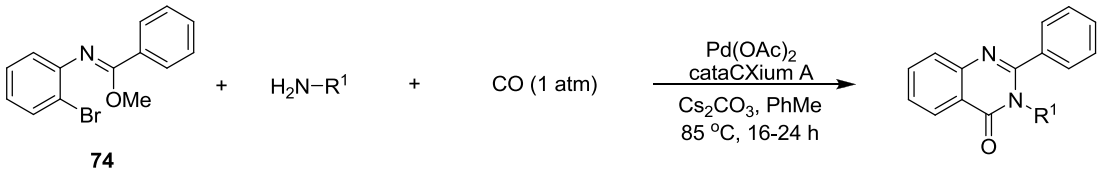


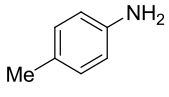
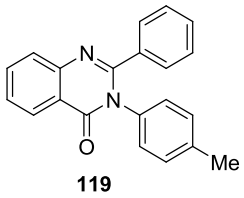
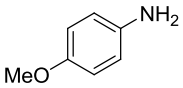
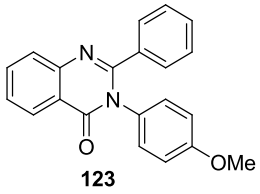
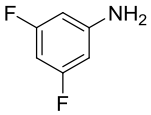
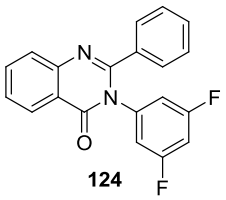
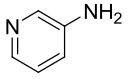
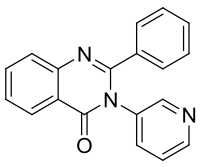
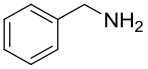
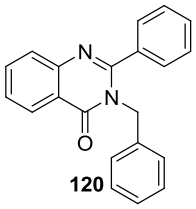
Scheme 5.10

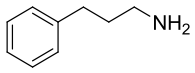
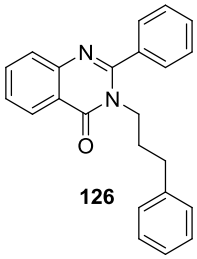
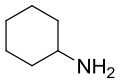
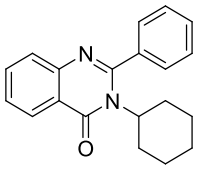
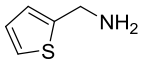
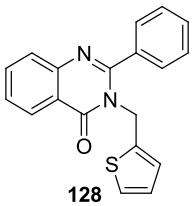
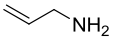
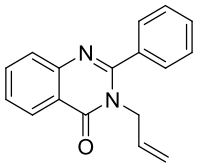
5.2.4 Investigating the scope of quinazolinone synthesis: variation of the nitrogen nucleophile

Initial investigation revealed that the palladium-catalysed reaction of *N*-(*o*-bromophenyl)imidate **74** with *p*-toluidine in the presence of a carbon monoxide atmosphere afforded quinazolinone **119** in a good isolated yield of 75%. Although 14% of the starting material was also recovered, the two products were easily separated. In order to explore the scope and generality of this reaction a range of *N*-nucleophiles were tested as is summarised in Table 5.3.

Table 5.3- Variation of the *N*-nucleophile[a]

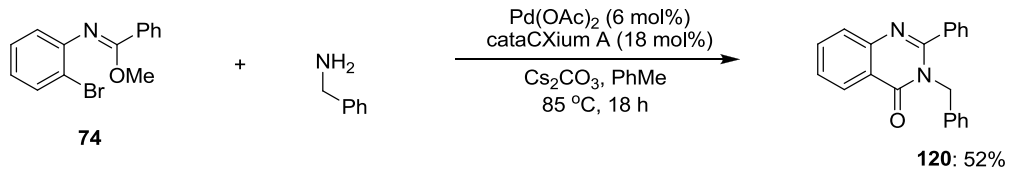


Entry	*N*-nucleophile	Product	Yield (%)[b]
1		 **119**	75
2		 **123**	65
3		 **124**	89
4[c]		 **125**	76
5[d]		 **120**	59

6[d]		 **126**	72
7[d]		 **127**	54
8[d]		 **128**	67
9		 **129**	41

[a] Reaction conditions: imidate **74** (1.0 equiv), *N*-nucleophile (1.5 equiv), $Pd(OAc)_2$ (6 mol%), cata*C*Xium® A (18 mol%), Cs_2CO_3 (3.0 equiv), CO (balloon), PhMe, 85 °C, 16-24 h. [b] Isolated yield. [c] Reaction carried out at 90 °C. [d] Reaction carried with *N*-nucleophile (3.0 equiv) and at 95 °C.

The use of aniline nucleophiles bearing varying substituents gave high yields (entries 1-4). When an alkyl amine, namely benzylamine was employed as the nucleophile under the standard reaction conditions a moderate 52% yield of desired quinazolinone **120** was obtained (Scheme 5.11).



Scheme 5.11

In addition, small amounts (<10%) of side products were obtained and tentatively identified as products **130**-**132** (figure 5.5). Although the formation of ester **130** and imidate **131** were unsurprising, the observation of un-cyclised amide **132** was unexpected. Similar un-cyclised intermediates were also observed for all other alkyl amines tested under these reaction conditions; however these were not observed when aniline nucleophiles were used.

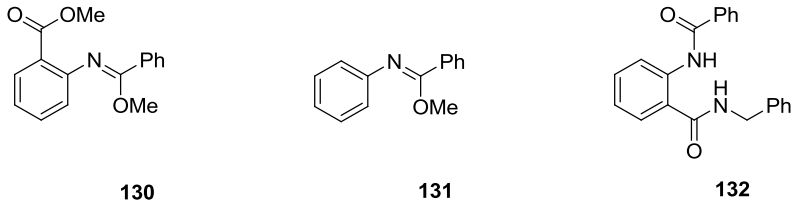


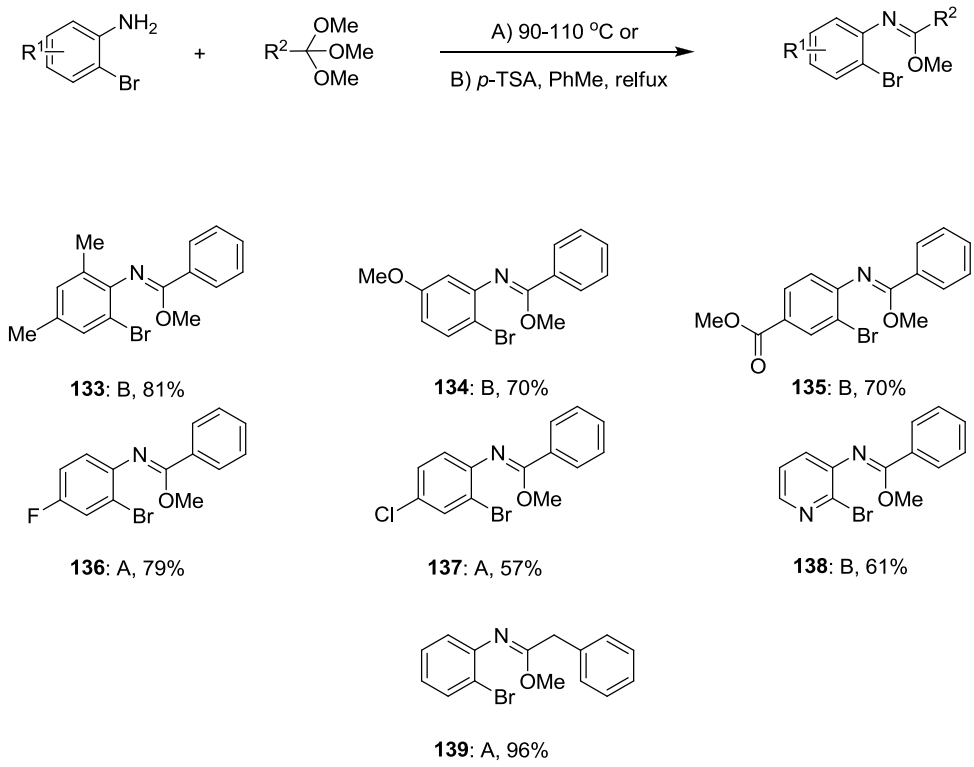
Figure 5.5

In order to aid cyclisation and discourage formation of ester **131**, the reaction temperature was increased to 95 °C and more equivalents of amine were used in these cases. Pleasingly, this gave higher yields of quinazolinone products (table 5.3, entries 5-8). The reaction of allyl amine gave a poor yield perhaps due to its high volatility at this reaction temperature (entry 9).

5.2.5 Investigating the scope of quinazolinone synthesis: variation of the substrate

The scope of the *N*-(*o*-halophenyl)imidate coupling partner was then investigated. As described in Chapter 2, readily available anilines react with *ortho*-esters when either

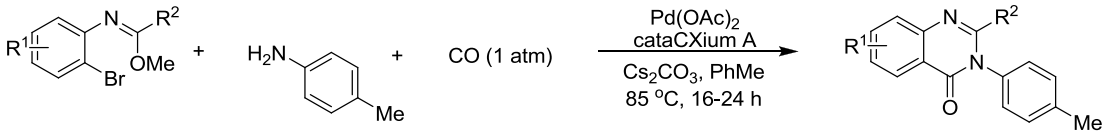
heated together or in the presence of catalytic acid to afford the required staring materials. Thus, utilising this method a range of substituted *N*-(*o*-halophenyl)imidates were synthesised in mostly high yields (Scheme 5.12).

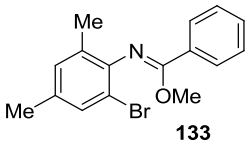
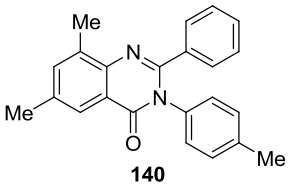
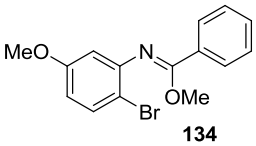
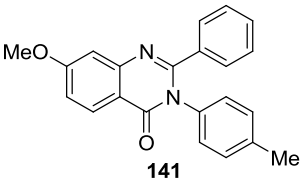
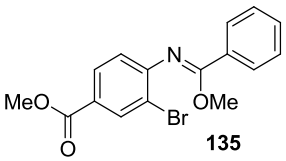
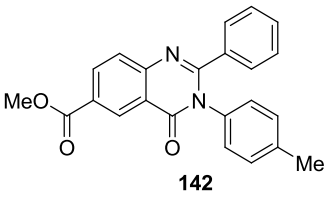
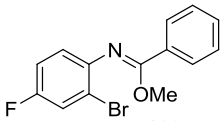
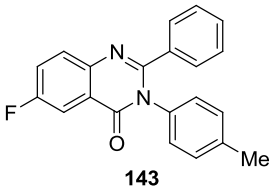
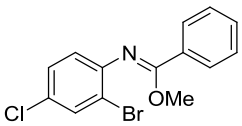
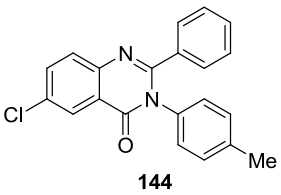
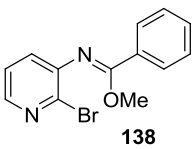
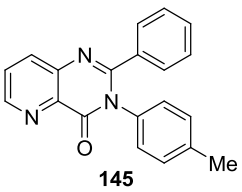


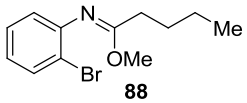
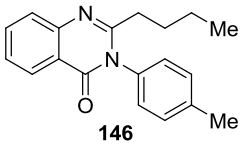
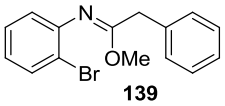
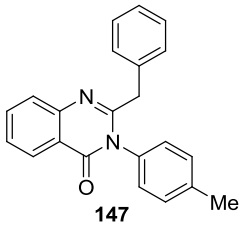
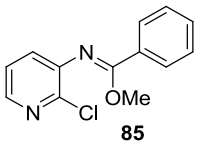
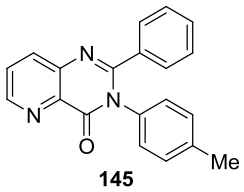
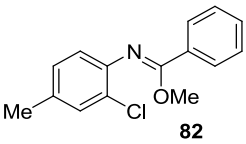
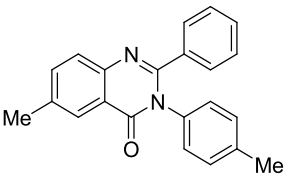
Scheme 5.12

These were then subjected to the standard conditions for quinazolinone synthesis; the results are shown in Table 5.4.

Table 5.4- Variation of the substrate[a]



Entry	Substrate	Product	Yield (%)[b]
1[c]	 **133**	 **140**	81
2[c]	 **134**	 **141**	71
3	 **135**	 **142**	76
4	 **136**	 **143**	58
5	 **137**	 **144**	74
6	 **138**	 **145**	90

7	 **88**	 **146**	71
8	 **139**	 **147**	67
9[d]	 **85**	 **145**	0
10[e]	 **82**		0

[a] Reaction conditions: imidate (1.0 equiv), *N*-nucleophile (1.5 equiv), $Pd(OAc)_2$ (6 mol%), cata*C*Xium® A (18 mol%), Cs_2CO_3 (3.0 equiv), CO (balloon), PhMe, 85 °C, 16-24 h. [b] Isolated yield. [c] Reaction carried out at 90 °C. [d] Reaction carried out at 100 °C. [e] Reaction carried out at 120 °C.

Carbonylation reactions are known to be susceptible to steric bulk around the aryl moiety which can result in reduced yields.[333] Pleasingly, use of di-substituted imidate **133** afforded quinazolinone **140** in a high 81% yield (entry 1). An electron-rich group was successfully incorporated, affording desired product **141** in a good 71% yield (entry 2). An electron-withdrawing group was also tolerated (entry 3). Fluoro- and chloro-substituted quinazolinones were synthesised in good yields, with no side reactions occurring at chloride substituent (entries 4 and 5). Azaquinazolinone **145** was successfully synthesised in an excellent 90% yield (entry 6). Pleasingly, alkyl groups

were well tolerated, affording 2-alkyl quinazolinones **85** and **82** in good yields (entries 7 and 8). Unfortunately, when *N*-(*o*-chlorophenyl)imidates were employed, no reaction was observed and only recovered starting material was isolated even at elevated reaction temperatures (entries 9 and 10). This highlights the difficulties associated with using unactivated aryl chlorides in aminocarbonylation reactions.

5.2.6 Benzothiazinone synthesis

Investigations were then carried out into the use of our precursors for the synthesis of 2-substituted benzothiazin-4-ones. It was envisaged that this could occur *via* an analogous thiocarbonylation to the aminocarbonylation reaction established for the preparation of quinazolinones (Figure 5.6).

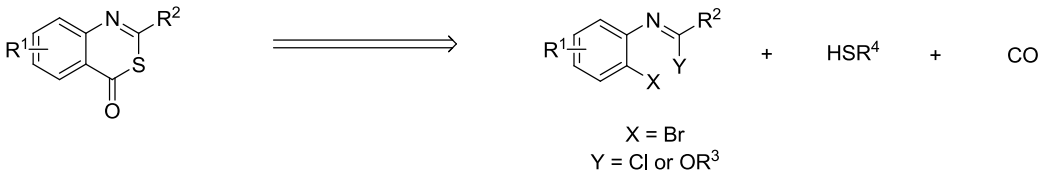
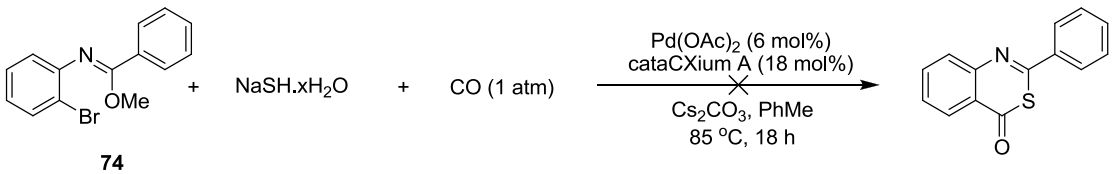


Figure 5.6

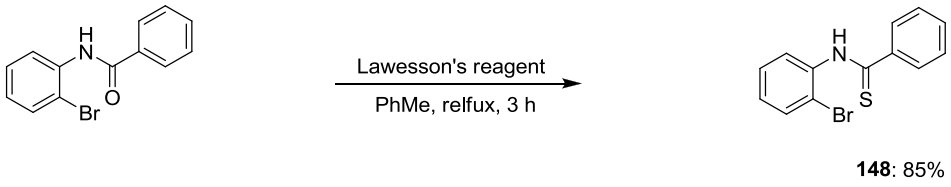
Investigations began with the reaction of *N*-(*o*-bromophenyl)imidate **74** with sodium hydrosulfide hydrate under an atmosphere of carbon monoxide (Scheme 5.13). This sulfur nucleophile was chosen as it was successfully utilised for the synthesis of benzothiazoles from *N*-(*o*-chlorophenyl)imidoyl chlorides (see Chapter 3).



Scheme 5.13

Unfortunately, application of our standard quinazolinone forming conditions to this reaction resulted in only starting material being observed in the ^{1}H NMR spectrum of the crude reaction mixture. Increasing the reaction temperature to 100 °C gave the same result. A possible explanation for this lack of reactivity is the observation that upon heating these reactions rapidly turn a black colour. This indicates decomposition of the palladium catalyst, perhaps as a result of poisoning by the sulfur nucleophile. Although disappointing, these results were unsurprising as test reaction of *N*-(*o*-halophenyl)imidates with the same sulfur source in the presence of a palladium catalyst also failed to afford the desired benzothiazole product (see section 3.2.4). As shown in section 4.1.4, the few reports which exist for the thiocarbonylation of aryl halides utilise high pressures of carbon monoxide and are limited to aryl iodides.

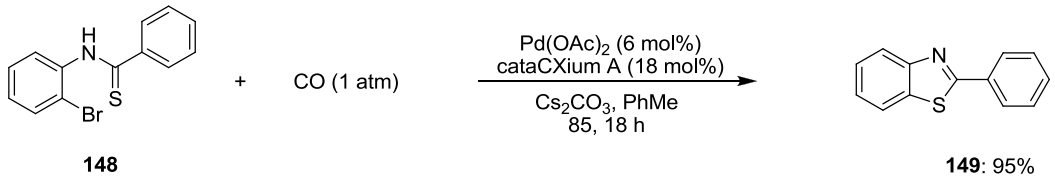
An alternative approach was then considered. The reaction of our *N*-(*o*-halophenyl)imidoyl chloride precursors with sodium hydrosulfide hydrate was shown to form *o*-halothioamides, which underwent an S_NAr reaction to yield benzothiazoles (see section 3.2.2). Thus, carrying out this reaction in the presence of a palladium catalyst under an atmosphere of carbon monoxide may result in benzothiazinone formation *via* an intramolecular thiocarbonylation reaction. In order to test this, thioamide **148** was synthesised from the reaction of amide **9** with Lawesson's reagent (Scheme 5.14).



148: 85%

Scheme 5.14

Disappointingly, test reactions of thioamide **148** utilising our standard conditions failed to afford any of the desired carbonylated heterocycle. Full conversion to benzothiazole **149** was instead observed and an isolated yield of 95% was obtained (Scheme 5.15). Reduction of the reaction temperature gave the same result.



148 **149**: 95%

Scheme 5.15

This result can be attributed to the fact that the competing formation of benzothiazole **149** can occur *via* two mechanisms; S_NAr or a palladium-catalysed C-S bond formation. However, thiocarbonylation can only proceed *via* one pathway. Additionally, upon oxidative addition into the aryl bromide bond, the palladium may bind to the sulfur atom of the thioamide. As this process is an intramolecular one and only a low pressure of carbon monoxide is present in the reaction, the chance for coordination by a carbon monoxide ligand is decreased. Thiocarbonylation is less likely to occur thus, formation of the benzothiazole product becomes prevalent. However, the use of higher carbon monoxide pressures may achieve the desired transformation.

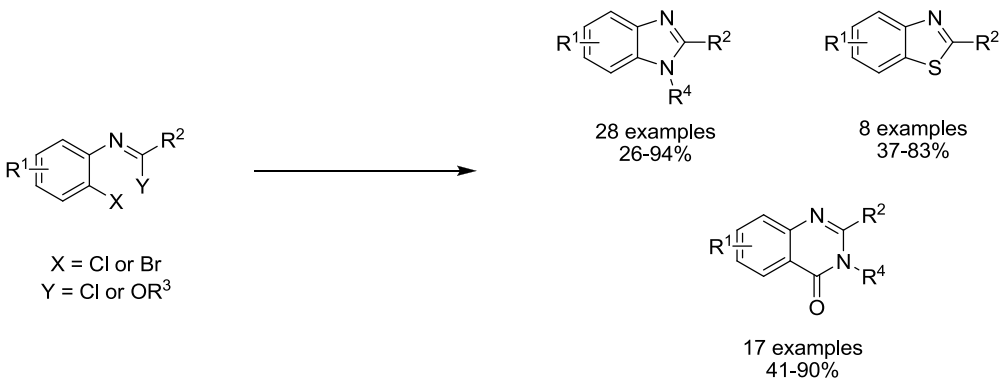
5.3 Concluding comments

We have demonstrated the use of *N*-(*o*-halophenyl)imidates as precursors for the synthesis of quinazolinones *via* a palladium-catalysed aminocarbonylation/cyclisation reaction sequence. This novel route provides advantages over existing carbonylative quinazolinone syntheses as it utilises aryl bromide starting materials, low pressures of carbon monoxide and milder conditions. In total, 17 examples were synthesised in mostly high yields with a good variety of amines and functional groups tolerated in this reaction.

The work presented here, along with that discussed in previous chapters demonstrates the utility of *N*-(*o*-halophenyl)imidoyl chlorides and imidates as easily prepared, common precursors for the synthesis of a variety of heterocycles (benzimidazoles, benzothiazoles and quinazolinones).[283]

Chapter 6: Summary and future work

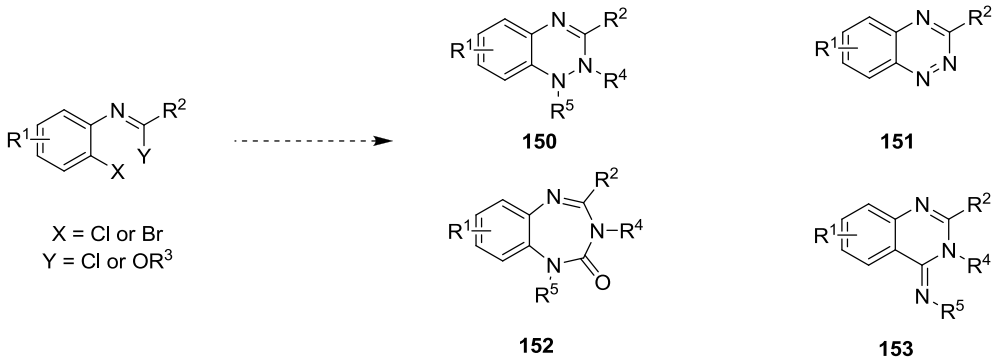
Employing catalytic processes for the synthesis of important heterocycles from common substrates is part of ongoing work within the Willis group. This study has involved the introduction of *N*-(*o*-halophenyl)imidoyl chlorides and imidates as precursors in palladium-catalysed and metal-free syntheses of several heterocyclic scaffolds (Scheme 6.1). This is significant as it allows the facile synthesis of these motifs from readily available starting materials in few (2-3) steps. Additionally, the successful incorporation of a variety of *N*-nucleophiles has been demonstrated in the synthesis of *N*-substituted benzimidazoles and quinazolinones as well as a wide range of functional groups in all of these reactions.[283]



Scheme 6.1

Future studies could investigate the utilisation of these substrates for the synthesis of other heterocycles (Scheme 6.2). For example, benzotriazine derivatives **150** and **151** could be accessed *via* reaction with *N*-*N*-disubstituted hydrazines. This would be analogous to the group's recent copper-catalysed preparation of cinnolines from 2-(2-haloalkenyl)-aryl halides.[176] Other nucleophiles such as ureas could also be incorporated in palladium- or copper-catalysed reactions to afford benzotriazepinone **152** derivatives.

The successful use of these nucleophiles in palladium-catalysed heterocycle syntheses has previously been reported by Willis[182] and others.[447] Finally, the palladium and copper-catalysed insertion of isonitriles into aryl halides has been utilised for a number of heterocycle syntheses.[213, 435, 448-450] Thus, a coupling reaction with our precursors may afford imine substituted quinazolinone **153**.



Scheme 6.2

Chapter 7: Experimental

7.1 General Considerations

Chemicals were purchased from either Sigma Aldrich, Alfa Aesar, Acros Organics Ltd., or Strem Chemicals Inc. and used without further purification. Anhydrous methanol, α,α,α- trifluorotoluene, toluene, methanol, hexane and *N*,*N*-dimethylacetamide were purchased from either Sigma Aldrich or Alfa Aesar. Dichloromethane and tetrahydrofuran used as reaction solvents were obtained dry from an in-house solvent purification system (Innovative Technology Inc. PS-400-7) having passed through anhydrous alumina columns. Triethylamine was distilled under reduced pressure from calcium hydride and stored over 4 Å molecular sieves. Molecular sieves were activated by heating at >200 ^{o}C for 24 h. HPLC grade solvents were purchased from Sigma Aldrich, Fisher Scientific or Rathburn and used directly without further purification. 'Petrol' refers to the fraction of light petroleum ether boiling in the range 40-60 ^{o}C.

All experiments were conducted with continuous magnetic stirring under a nitrogen atmosphere unless otherwise stated, using standard Schlenk techniques and all glassware was oven-dried overnight (>200 °C) and allowed to cool under a flow of nitrogen (passed through a Drierite® filled tube) prior to use. Cooling of reaction vessels to 0 °C was achieved by an ice-water bath. Microwave reactions were carried out in a CEM Discover® S microwave using 10 mL CEM microwave tubes.

Flash column chromatography was performed using Apollo scientific silica gel 60 (particle size 0.040-0.063 nm) with the indicated eluents. Thin Layer Chromotography (TLC) was performed on Merck Kieselgel 60 F254 pre-coated aluminium backed sheets

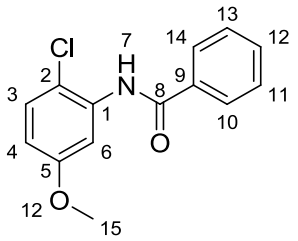
and visualised either by UV fluorescence (λ_{max}254 nm) and/or stained with vanillin or potassium permanganate ($KMnO_4$).

NMR spectra were recorded at ambient temperature on either Brüker DPX200 (200 MHz), DQX400 (400 MHz) or AVC500 (500 MHz) spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and referenced relative to the residual solvent peak(s) (as specified). Coupling constants (*J*) are given in Hertz (Hz) and rounded to the nearest 0.1 Hz. Assignments were made on the basis of chemical shifts, coupling constants, DEPT, COSY, HSQC and comparison with spectra of related compounds. Signal multiplicities are denoted as: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sex, sextet; m, multiplet; br., broad; app., apparent.

Melting points were measured using a Leica Gallen III hot-stage microscope. Low resolution mass spectra were recorded on a Fisons Platform spectrometer (ESI). High resolution mass spectra were measured by the internal service at the University of Oxford using a Bruker Daltronics microTOF spectrometer. *m/z* ratio values are reported in Daltons; high resolution values are calculated to four decimal places from the molecular formula, all found within a tolerance of 5 ppm. Infrared spectra were determined neat using a Bruker Tensor 27 FT spectrometer with an internal range of 600-4000 cm^{-1}.

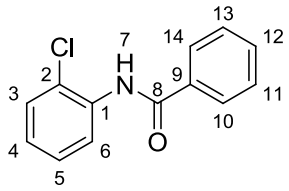
7.2 Procedures and characterisation data

General procedure A for the preparation of amides, exemplified by the preparation of *N*-(2-Chloro-5-methoxyphenyl)benzamide 7



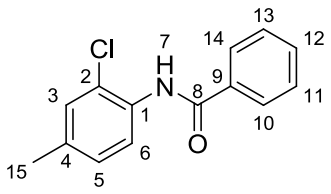
To a solution of 2-chloro-5-methoxyaniline (2.0 g, 13.0 mmol) and triethylamine (1.9 mL, 14.0 mmol) in tetrahydrofuran (40 mL) at 0 °C was added drop wise benzoyl chloride (1.8 mL, 15.0 mmol). The solution was stirred at this temperature for 3 h then quenched with brine (60 mL) and the aqueous phase extracted with diethyl ether (3 × 60 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/diethyl ether 4:1) afforded the title compound as a white crystalline solid (2.6 g, 78%). mp: 82-83 °C, ν_{max} (KBr)/cm^{-1} 3223 (br), 3012 (m), 2956 (m), 2835 (m), 1776 (s), 1636 (s), 1600 (s), 1579 (s), 1519 (s), 1481 (s); δ_H (400 MHz, $CDCl_3$) 8.48 (1H, br. s, H-7), 8.32-8.29 (1H, m, H-6), 7.95-7.91 (2H, m, H-10 and H-14), 7.63-7.57 (1H, m, H-12), 7.56-7.50 (2H, m, H-11 and H-13), 7.32-7.26 (1H, m, H-3), 6.69-6.64 (1H, m, H-4), 3.88-3.85 (3H, m, H-15); δ_C (100 MHz, $CDCl_3$) 165.3, 159.1, 135.4, 134.6, 132.3, 129.2 (C-3), 129.0 (C-11 and C-13), 127.0 (C-10 and C-14), 114.1, 111.4 (C-4), 106.2 (C-6), 55.7 (C-15); HRMS (ESI) found *m/z* 284.0447 $[M+Na]^+$, $C_{14}H_{12}{}^{35}ClNNaO_2$ requires 284.0449.

_N_-(2-Chlorophenyl)benzamide 9*



General procedure A was followed using 2-chloroaniline (10.0 g, 78.0 mmol) and benzoyl chloride (11.0 mL, 94.0 mmol). Recrystallisation from dichloromethane afforded the title compound as a white crystalline solid (15.4 g, 85 %). δ_H (400 MHz, $CDCl_3$) 8.59 (1H, dd, *J* = 7.8 Hz, *J* = 1.4 Hz, H-6), 8.47 (1H, br. s, H-7), 7.93-7.95 (2H, m, H-10 and H-14), 7.58-7.62 (1H, m, H-12), 7.54 (2H, m, H-11 and H-13), 7.43 (1H, dd, *J* =7.8, *J* = 1.4 Hz, H-3), 7.35 (1H, dd, *J*= 7.8, *J* = 1.4 Hz, H-5), 7.10 (1H, dd, *J* = 7.8, *J* = 1.5 Hz, H-4); δ_C (100 MHz, $CDCl_3$) 165.3, 134.7, 134.6, 132.2, 129.0, 128.9, 127.9, 127.1, 124.7, 123.0, 121.5; LRMS (ESI) *m/z* 232.1 (40%, [^{37}Cl M-H]$^-$), 230.1 (100%, [^{35}Cl M-H]$^-$). Data was consistent with literature data.[451] * Reaction carried out by R.Foster

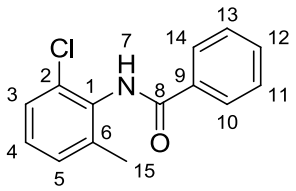
_N_-(2-Chloro-4-methylphenyl)benzamide 11



General procedure A was followed using 2-chloro-4-methylaniline (5.0 g, 35.0 mmol) and benzoyl chloride (4.9 mL, 42.0 mmol). Recrystallisation from ethanol afforded the title compound as a white crystalline solid (7.5 g, 87%). δ_H (400 MHz, $CDCl_3$) 8.43 (1H, d, *J* = 8.4 Hz, H-6), 8.37 (1H, br. s, H-7), 7.94-7.91 (2H, m, H-10 and H-14), 7.61-7.57 (1H, m, H-12), 7.54-7.51 (2H, m, H-11 and H-13), 7.26 (1H, d, *J* = 1.4 Hz, H-3), 7.15 (1H, dd, *J* = 8.4 Hz, *J* = 1.4 Hz, H-5), 2.34 (3H, s, H-15); δ_C (100 MHz, $CDCl_3$) 165.2, 134.9, 134.7, 132.1, 132.0, 129.3, 128.9, 128.5, 127.1, 122.9, 121.4, 20.7 (C-15); LRMS

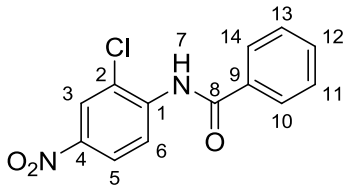
(ESI) *m/z* 246.1 (40%, [^{37}Cl M-H]$^-$), 244.1 (100%, [^{35}Cl M-H]$^-$). Data consistent with literature data.[452]

_N_-(2-Chloro-6-methylphenyl)benzamide 13



General procedure A was followed using 2-chloro-6-methylaniline (0.5 g, 3.5 mmol) and benzoyl chloride (0.5 mL, 4.2 mmol). Flash chromatography (SiO_2, petrol/diethyl ether 3:1) afforded the title compound as a white solid (0.7 g, 86%). δ_H (400 MHz, $CDCl_3$) 7.96 (2H, d, *J* = 7.6 Hz, Ar-H), 7.69 (1H, br. s, H-7), 7.61-7.57 (1H, m, Ar-H), 7.53-7.49 (2H, m, Ar-H), 7.31-7.15 (3H, m, Ar-H), 2.34 (3H, s, H-15); δ_C (100 MHz, $CDCl_3$) 165.8, 138.2, 134.0, 132.7, 132.0, 131.4, 129.3, 128.8, 127.9, 127.4, 127.0, 19.1 (C-15); LRMS (ESI) *m/z* 246.1 (40%, [^{37}Cl M-H]$^-$), 244.1 (100%, [^{35}Cl M-H]$^-$). Data consistent with literature data.[453]

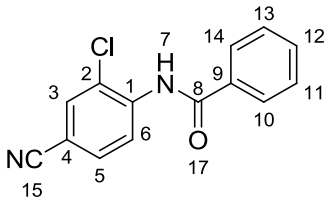
_N_-(2-Chloro-4-nitrophenyl)benzamide 15



General procedure A was followed using 2-chloro-4-nitroaniline (5.0 g, 29.0 mmol) and benzoyl chloride (4.1 mL, 35.0 mmol). Flash chromatography (SiO_2, petrol/diethyl ether 6:1) afforded the title compound as a yellow solid (1.0 g, 13%). mp: 136-138 °C; ν_{max} (KBr)/cm^{-1} 3308 (br), 1666 (s), 1582 (s), 1505 (s), 1466 (s), 1393 (s), 1349 (s), 1312 (s), 1278 (s), 1139 (m); δ_H (400 MHz, $CDCl_3$) 8.89 (1H, d, *J* = 9.2 Hz, H-6), 8.73 (1H, br. s,

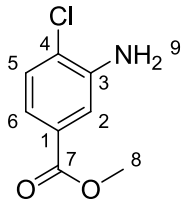
H-7), 8.37 (1H, d, *J* = 2.5 Hz, H-3), 8.25 (1H, dd, *J* = 9.2 Hz, *J* = 2.5 Hz, H-5), 7.97- 7.96 (2H, m, H-10 and H-14), 7.68- 7.64 (1H, m, H-12), 7.59-7.56 (2H, m, H-11 and H-13); δ_C (100 MHz, $CDCl_3$) 165.3, 143.0, 140.4, 133.6, 133.0, 129.2, 127.2 (C-10 and C-14), 124.7 (C-3), 123.8 (C-5), 122.6, 120.2 (C-6); HRMS (ESI) found *m/z* 299.0192 $[M+Na]^+$, $C_{13}H_9{}^{35}ClN_2NaO_3$ requires 299.0194.

_N_-(2-Chloro-4-cyanophenyl)benzamide 17



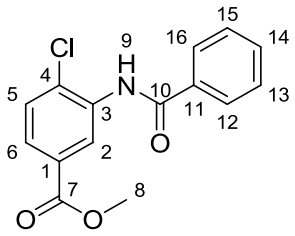
General procedure A was followed using methyl 4-amino-3-chlorobenzonitrile (3.0 g, 20.0 mmol) and benzoyl chloride (2.7 mL, 24.0 mmol). Recrystallisation from ethanol afforded the title compound as an orange crystalline solid (2.6 g, 51%). mp: 136-137 °C; ν_{max} (neat)/cm^{-1} 3429 (w), 3412 (w), 3065 (br), 2224 (s), 1686 (s), 1596 (m), 1578 (m), 1508 (s), 1494 (s), 1464 (m); δ_H (400 MHz, $CDCl_3$) 8.81 (1H, d, *J* = 8.7 Hz, H-6), 8.64 (1H, br. s, H-7), 7.95-7.91 (2H, m, H-10 and H-14), 7.74 (1H, d, *J* = 1.8 Hz, H-3), 7.67-7.61 (2H, m, H-5 and H-12), 7.59-7.53 (2H, m, H-11 and H-13); δ_C (100 MHz, $CDCl_3$) 165.3, 138.9, 133.7, 132.9, 132.5, 132.1, 129.2 (C-11 and C-13), 127.2 (C-10 and 14), 122.8, 121.0 (C-6), 117.5, 107.7; HRMS (ESI) found *m/z* 257.0481 $[M+H]^+$, $C_{14}H_{10}{}^{35}ClN_2O$ requires 257.0476.

Methyl 3-amino-4-chlorobenzoate[454]



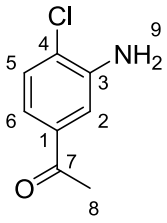
A 1 L, 3 neck flask was charged with 3-amino-4-chlorobenzoic acid (10.0 g, 58.0 mmol), methanol (70 mL) and trimethyl orthoformate (7.0 mL, 64.0 mmol). The flask was fitted with a condenser and a pressure equalising addition funnel. The reaction was heated to 60 °C and conc. sulphuric acid (3.4 mL, 64.0 mmol) was added slowly so as to keep reflux from being too vigorous. The reaction was refluxed for 1.5 h, cooled and the solvent removed *in vacuo*. To the resulting material was added ethyl acetate (500 mL) and left to stand overnight. The resulting solid was collected by filtration and water (100 mL) and ethyl acetate (400 mL) were added. After all the material dissolved, the solution was treated with KOH (3.0 g). The organic layer was collected and washed twice with 300 mL portions of aqueous 5 M KOH, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a pink solid (2.9 g, 27%). δ_H (400 MHz, $CDCl_3$) 7.46 (1H, d, J = 1.9 Hz, H-2), 7.36 (1H, dd, J = 8.3 Hz, J = 1.9 Hz, H-6), 7.31 (1H, d, J = 8.3 Hz, H-5), 4.25 (2H, br. s, H-9), 3.89 (3H, s, H-8); δ_C (100 MHz, $CDCl_3$) 166.6, 142.9, 129.6, 129.4 (C-6), 123.9, 119.9 (C-5), 116.6 (C-2), 52.2 (C-8); LRMS (ESI) *m/z* 188.0 (40%, $[^{37}Cl\ M+H]^+$), 186.0 (100%, $[^{35}Cl\ M+H]^+$). Data consistent with literature data.[454]

Methyl 3-benzamido-4-chlorobenzoate 19



General procedure A was followed using methyl 3-amino-4-chlorobenzoate (1.0 g, 5.4 mmol) and benzoyl chloride (0.8 mL, 6.5 mmol). Recrystallisation from dichloromethane afforded the title compound as a light pink crystalline solid (1.5 g, 95%). mp: 98-100 °C; ν_{max} (KBr)/cm^{-1} 3283 (br), 1897 (s), 1789 (s), 1726 (s), 1653 (s), 1579 (s), 1532 (s), 1463 (s), 1441 (s), 1227 (m); δ_H (400 MHz, $CDCl_3$) 9.22-9.20 (1H, m, H-2), 8.47 (1H, br. s, H-9), 7.94 (2H, app. d, *J* = 8.0 Hz, H-12 and H-16), 7.81-7.80 (1H, m, H-6), 7.63-7.59 (1H, m, H-14), 7.56-7.49 (3H, m, H-5, H-13 and H-15), 3.94 (3H, s, H-8); δ_C (100 MHz, $CDCl_3$) 166.1, 165.3, 134.8, 134.2, 132.4 (C-14), 129.9, 129.1, 129.0, 127.7, 127.1 (C-12 and C-16), 125.9 (C-6), 122.43 (C-2), 52.4 (C-8); HRMS (ESI) found *m/z* 312.0392 $[M+Na]^+$, $C_{15}H_{12}{}^{35}ClNNaO_3$ requires 312.0398.

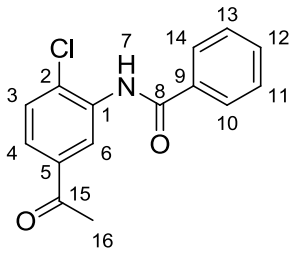
1-(3-Amino-4-chlorophenyl)ethanone



To a solution of 4′-chloro-3′-nitroacetophenone (1.5 g, 7.5 mmol) in absolute ethanol (25 mL) was added iron powder (1.3 g, 23.0 mmol) and HCl (3.2 mL, 37%). The mixture was heated at reflux for 24 h and then allowed to cool. The resultant solution was diluted with water (50 mL) and dichloromethane (50 mL) and filtered through a Celite® pad, washing with dichloromethane (250 mL). The organic layer was then separated and water (150

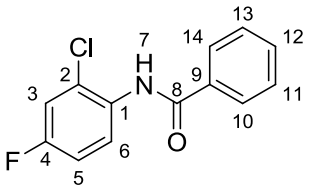
mL) was added. The aqueous layer was then basified with anhydrous solid K_2CO_3. The organic layer was removed and dried ($MgSO_4$) and then concentrated *in vacuo* to afford the title compound as a yellow crystalline solid (1.1 g, 88%). mp: 104-106 °C; ν_{max} (neat)/cm^{-1} 3482 (m), 3369 (m), 1675 (s), 1619 (m), 1580 (m), 1571 (m), 1489 (m), 1427 (m), 1325 (w), 1323 (m); δ_H (400 MHz, $CDCl_3$) 7.36 (1H, d, *J* = 2.0 Hz, H-2), 7.33 (1H, d, *J* = 8.2 Hz, H-5), 7.27-7.24 (1H, m, H-6), 4.20 (2H, br. s, H-9), 2.55 (3H, s, H-8); δ_C (100 MHz, $CDCl_3$) 197.4, 143.1, 136.6, 129.5 (C-5), 124.2, 119.0 (C-6), 114.8 (C-2), 26.6 (C-8); HRMS (ESI) found *m/z* 170.0362 $[M+H]^+$, $C_8H_9{}^{35}ClNO$ requires 170.0367.

_N_-(5-Acetyl-2-chlorophenyl)benzamide 21



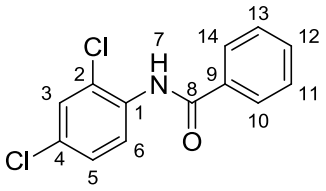
General procedure A was followed using methyl 1-(3-amino-4-chlorophenyl)ethanone (1.0 g, 6.0 mmol) and benzoyl chloride (0.8 mL, 7.0 mmol). Recrystallisation from ethanol afforded the title compound as a light yellow crystalline solid (0.4 g, 26%); mp: 114-116 °C; ν_{max} (neat)/cm^{-1} 3282 (w), 1681 (m), 1655 (s), 1574 (m), 1524 (m), 1491 (w), 1450 (m), 1408 (m), 1355 (m); δ_H (400 MHz, $CDCl_3$) 9.20 (1H, d, *J* = 2.1 Hz, H-6), 8.51 (1H, br. s, H-7), 7.97-7.92 (2H, m, H-10 and H-14), 7.71 (1H, dd, *J* = 8.4 Hz, *J* = 2.1 Hz, H-4), 7.64-7.60 (1H, m, H-12), 7.58-7.50 (3H, m, H-3, H-11 and H-13), 2.66 (3H, s, H-16); δ_C (100 MHz, $CDCl_3$) 197.1, 165.4, 136.6, 135.0, 134.1, 132.5 (C-12), 129.3, 129.1, 127.6 (C-10 and C-14), 127.1, 124.0 (C-4), 121.7 (C-6), 26.7 (C-16); HRMS (ESI) found *m/z* 296.0447 $[M+Na]^+$, $C_{15}H_{12}{}^{35}ClNNaO_2$ requires 296.0449.

_N_-(2-Chloro-4-fluorophenyl)benzamide 23



General procedure A was followed using 2-chloro-4-fluoroaniline (2.0 g, 14.0 mmol) and benzoyl chloride (1.9 mL, 17.0 mmol). Recrystallisation from dichloromethane afforded the title compound as a light pink crystalline solid (3.1 g, 90%). mp: 110-112 °C; ν_{max} (KBr)/cm^{-1} 3201 (br), 3095 (br), 2833 (m), 2678 (m), 1988 (m), 1818 (m), 1778 (s), 1647 (s), 1595 (s), 1579 (s), 1519 (m), 1493 (m), 1390 (m); δ_H (400 MHz, $CDCl_3$) 8.47 (1H, dd, *J* = 9.1 Hz, *J* = 5.7 Hz, H-6), 8.33 (1H, br. s, H-7), 7.91 (2H, app. d, *J* = 7.5 Hz, H-10 and H-14), 7.60-7.56 (1H, m, H-12), 7.52-7.49 (2H, m, H-11 and H-13), 7.16 (1H, dd, *J* = 8.0 Hz, *J* = 2.8 Hz, H-3), 7.07-7.02 (1H, m, H-5); δ_C (100 MHz, $CDCl_3$) 165.3, 158.5 (d, *J* = 247.3 Hz, C-4), 134.3, 132.3 (C-12), 131.2 (d, *J* = 3.3 Hz), 128.9 (C-11 and C-13), 127.1 (C-10 and C-14), 123.9 (d, *J* = 10.3 Hz), 122.9 (d, *J* = 8.2 Hz, C-6), 116.3 (d, *J* = 25.9 Hz, C-3), 114.7 (d, *J* = 21.7 Hz, C-5); δ_F (376 MHz, $CDCl_3$) -116.0 (1F, s); HRMS (ESI) found *m/z* 272.0249, $[M+Na]^+$, $C_{13}H_9{}^{35}ClFNNaO$ requires 272.0249.

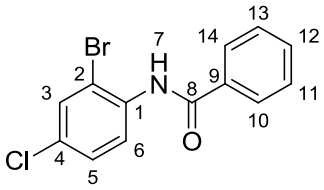
_N_-(2,4-Dichlorophenyl)benzamide 25



General procedure A was followed using 2,4-dichloroaniline (5.0 g, 31.0 mmol) and benzoyl chloride (4.3 mL, 37.0 mmol). Recrystallisation from ethanol afforded the title compound as a white crystalline solid (5.7 g, 70%). mp: 113-115 °C; ν_{max} (neat)/cm^{-1} 3290 (br), 3071 (w), 3031 (w), 1648 (s), 1601 (w), 1590 (w), 1576 (m), 1510 (m), 1488

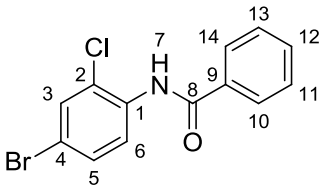
(m), 1466 (m); δ_H (400 MHz, $CDCl_3$) 8.56 (1H, d, *J* = 8.9 Hz, H-6), 8.40 (1H, br. s, H-7), 7.93-7.89 (2H, m, H-10 and 14), 7.63-7.58 (1H, m, H-12), 7.56-7.51 (2H, m, H-11 and H-13), 7.22 (1H, d, *J* = 2.4 Hz, H-3), 7.32 (1H, dd, *J* = 8.9 Hz, *J* = 2.4 Hz, H-5); δ_C (100 MHz, $CDCl_3$) 165.2, 134.3, 133.5, 132.4 (C-12), 129.2, 129.0 (C-11 and C-13), 128.7 (C-3), 128.0 (C-5), 127.1 (C-10 and C-14), 123.5, 122.2 (C-6); HRMS (ESI) found *m/z* 287.9951 $[M+Na]^+$, $C_{13}H_9{}^{35}Cl{}^{35}ClNNaO$ requires 287.9953.

***N*-(2-Bromo-4-chlorophenyl)benzamide 27**



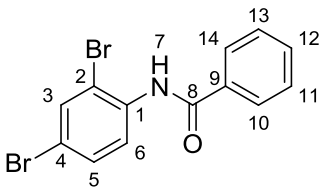
General procedure A was followed using 2-bromo-6-chloroaniline (2.5 g, 12.0 mmol) and benzoyl chloride (1.7 mL, 14.0 mmol). Recrystallisation from ethanol afforded the title compound a white crystalline solid (3.1 g, 84%). δ_H (400 MHz, $CDCl_3$) 8.54 (1H, d, *J* = 8.9 Hz, H-6), 8.42 (1H, br. s, H-7), 7.95-7.91 (2H, m, H-10 and H-14), 7.63-7.58 (2H, m, H-3 and H-12), 7.56-7.51 (2H, m, H-11 and H-13), 7.36 (1H, dd, *J* = 8.9 Hz, *J* = 2.3 Hz, H-5); δ_C (100 MHz, $CDCl_3$) 165.2, 134.6, 134.3, 132.4, 131.7, 129.5, 129.0, 128.7, 127.1 (C-10 and C-12), 122.3 (C-6), 113.8; LRMS (ESI) *m/z* 308.0 (80%, $[^{79}Br\ ^{35}Cl\ M-H]^-$), 310.0 (100%, $[^{81}Br\ ^{35}Cl\ M-H]^-$ and $[^{79}Br\ ^{37}Cl\ M-H]^-$), 312.0 (30%, $^{81}Br\ ^{37}Cl\ M-H]^-$). Data consistent with literature data.[455]

_N_-(4-Bromo-2-chlorophenyl)benzamide 29



General procedure A was followed using 2-chloro-4-iodoaniline (4.0 g, 19.0 mmol) and benzoyl chloride (2.7 mL, 23.0 mmol). Recrystallisation from ethanol afforded the title compound as an off white crystalline solid (5.5 g, 94%). mp: 140-143 °C; ν_{max} (neat)/cm^{-1} 3286 (br), 3068 (br), 1644 (s), 1601 (w), 1574 (m), 1505 (s), 1487 (m), 1462 (s), 1377 (s), 1296 (m); δ_H (400 MHz, $CDCl_3$) 8.51 (1H, d, *J* = 8.9 Hz, H-6), 8.40 (1H, br. s, H-7), 7.92 (2H, app. d, *J* = 7.3 Hz, H-10 and H-14), 7.63-7.51 (4H, m, H-3, H-11, H-12 and H-13), 7.47 (1H, dd, *J* = 8.9 Hz, *J* = 1.9 Hz, H-5); δ_C (100 MHz, $CDCl_3$) 165.2, 134.3, 134.0, 132.4, 131.5 (C-5), 131.0, 129.0, 127.1, 123.6, 122.5 (C-6), 116.4; HRMS (ESI) found *m/z* 331.9449 $[M+Na]^+$, $C_{13}H_9{}^{79}Br^{35}ClNNaO$ requires 331.9448.

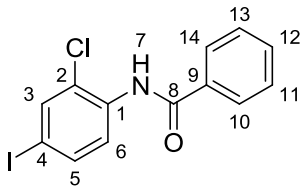
_N_-(2,4-Dibromophenyl)benzamide 31



General procedure A was followed using 2,4-dibromoaniline (2.5 g, 10.0 mmol) and benzoyl chloride (1.4 mL, 12.0 mmol). Recrystallisation from ethanol afforded the title compound a white crystalline solid (3.0 g, 84%). mp: 136-139 °C; ν_{max} (neat)/cm^{-1} 3273 (br), 1655 (s), 1602 (w), 1578 (m), 1568 (m), 1509 (m), 1488 (s), 1461 (m), 1376 (m), 1304 (m), 1252 (m); δ_H (400 MHz, $CDCl_3$) 8.50 (1H, d, *J* = 8.9 Hz, H-6), 8.43 (1H, br. s, H-7), 7.96-7.91 (2H, m, H-10 and H-14), 7.74 (1H, d, *J* = 2.2 Hz, H-3), 7.64-7.58 (1H, m, H-12), 7.57-7.48 (3H, m, H-5, H-11 and H-13); δ_C (100 MHz, $CDCl_3$)165.2, 135.1, 134.4

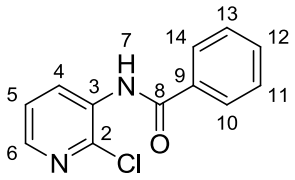
(C-3), 134.2, 132.4 (C-12), 131.6 (C-5), 129.0 (C-11 and C-13), 127.1 (C-10 and C-14), 122.6 (C-6), 116.8, 114.0; HRMS (ESI) found *m/z* 377.8924 $[M+Na]^+$, $C_{13}H_9{}^{81}Br^{79}BrNNaO$ requires 377.8923.

_N_-(2-Chloro-4-iodophenyl)benzamide 33



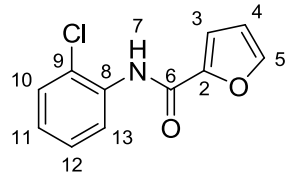
General procedure A was followed using 2-chloro-4-iodoaniline (3.0 g, 12.0 mmol) and benzoyl chloride (1.6 mL, 14.0 mmol). Recrystallisation from ethanol afforded the title compound as a white crystalline solid (3.8 g, 89%). mp: 163-165 °C; ν_{max} (neat)/cm^{-1} 3285 (br), 3059 (w), 1645 (s), 1600 (w), 1578 (m), 1568 (s), 1503 (s), 1485 (s), 1460 (s), 1366 (m); δ_H (400 MHz, $CDCl_3$) 8.41 (1H, br. s, H-7), 8.38 (1H, d, *J* = 8.7 Hz, H-6), 7.91 (2H, app. d, *J* = 7.2 Hz, H-10 and H-14), 7.76 (1H, d, *J* = 1.9 Hz, H-3), 7.65 (1H, dd, *J* = 8.7 Hz, *J* = 1.9 Hz, H-5), 7.60 (1H, m, H-12), 7.57-7.51 (2H, m, H-11 and H-13); δ_C (100 MHz, $CDCl_3$) 165.2, 137.1, 136.9, 134.7, 134.3, 132.4, 129.0, 127.1 (C-10), 123.6, 122.7 (C-6), 86.4 (C-4); HRMS (ESI) found *m/z* 379.9310 $[M+Na]^+$, $C_{13}H_9{}^{35}ClINNaO$ requires 379.9310.

_N_-(2-Chloropyridin-3-yl)benzamide 35



General procedure A was followed using 3-amino-2-chloropyridine (3.0 g, 23.0 mmol) and benzoyl chloride (3.3 mL, 28.0 mmol). Recrystallisation from ethanol afforded the title compound as a light pink crystalline solid (3.4 g, 63%). δ_H (400 MHz, $CDCl_3$) 8.93 (1H, dd, *J* = 8.1 Hz, *J* = 0.8 Hz, H-6), 8.45 (1H, br. s, H-7), 8.17 (1H, dd, *J* = 4.6 Hz, *J* = 0.8 Hz, H-4), 7.93 (2H, app. d, *J* = 7.8 Hz, H-10 and H-14), 7.65-7.61 (1H, m, H-12), 7.57-7.53 (2H, m, H-11 and H-13), 7.34 (1H, dd, *J* = 8.1 Hz, *J* = 4.6 Hz, H-5); δ_C (100 MHz, $CDCl_3$) 165.7, 143.9 (C-4), 140.1, 133.8, 132.6 (C-12), 132.1 (C-6), 129.1 (C-11 and C-13), 128.9, 127.1 (C-10 and C-14), 123.5 (C-5); LRMS (ESI) *m/z* 257.0 (70%, $[^{37}Cl\ M+Na]^+$) 255.0 (100%, $[^{35}Cl\ M+Na]^+$), 233.0 (30%, $[^{35}Cl\ M+H]^+$). Data consistent with literature data.[456]

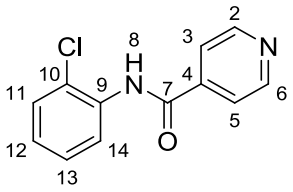
_N_-(2-Chlorophenyl)furan-2-carboxamide 37



To a solution of 2-chloroaniline (2.0 g, 15.7 mmol) and triethylamine (2.4 mL, 17.0 mmol) in tetrahydrofuran (50 mL) at 0 °C was added drop wise 2-furoyl chloride (1.9 mL, 19.0 mmol). The solution was stirred at this temperature for 4 h then quenched with brine (25 mL) and the aqueous phase extracted with diethyl ether (3 × 25 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from ethanol afforded the title compound as a white crystalline solid

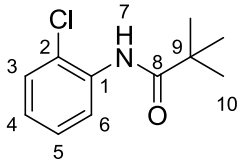
(1.4 g, 41%). δ_H (400 MHz, $CDCl_3$) 8.70 (1H, br. s, H-7), 8.52 (1H, app. d, *J* = 8.3 Hz, H-13), 7.55 (1H, app. s, H-5), 7.40 (1H, app. d, *J* = 8.0 Hz, H-10), 7.34-7.26 (2H, m, H-3 and H-12), 7.06 (1H, app. t, *J* = 7.7 Hz, H-11), 6.59-6.56 (1H, m, H-4); δ_C (100 MHz, $CDCl_3$) 155.8, 147.5, 144.5 (C-5), 134.2, 129.0 (C-10), 127.7 (C-12), 124.6 (C-11), 122.7, 121.2 (C-13), 115.6 (C-3), 112.6 (C-4); LRMS (ESI) *m/z* 246.0 (40%, $[^{37}Cl\ M+Na]^+$), 244.0 (100%, $[^{35}Cl\ M+Na]^+$). Data consistent with literature data.[457]

_N_-(2-Chlorophenyl)isonicotinamide 39



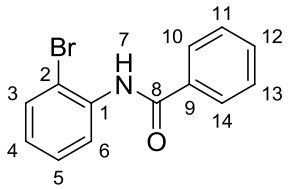
General procedure A was followed using 2-chloroaniline (2.4 g, 19.0 mmol), isonicotinoyl chloride hydrochloride (4.0 g, 22.0 mmol) and triethylamine (6.3 mL, 45.0 mmol). Recrystallisation from ethanol afforded the title compound as a yellow crystalline solid (0.6 g, 11%). δ_H (400 MHz, $CDCl_3$) 8.84 (2H, dd, *J* = 4.4 Hz, *J* = 1.6 Hz, H-2 and H-6), 8.52 (1H, dd, *J* = 8.2 Hz, *J* = 1.2 Hz, H-14), 8.48 (1H, br. s, H-8), 7.76 (2H, dd, *J* = 4.4 Hz, *J* = 1.6 Hz, H-3 and H-5), 7.44 (1H, dd, *J* = 8.0 Hz, *J* = 1.4 Hz, H-11), 7.39-7.33 (1H, m H-13), 7.14 (1H, td, *J* = 7.7 Hz, *J* = 1.4 Hz, H-12); δ_C (100 MHz, $CDCl_3$) 163.3, 151.0 (C-2 and C-6), 141.6, 134.0, 129.2 (C-11), 128.0 (C-13), 125.5 (C-12), 123.3, 121.7 (C-14), 120.8 (C-3 and C-5); LRMS (ESI) *m/z* 257.0 (80%, $[^{37}Cl\ M+Na]^+$), 255.0 (100%, $[^{35}Cl\ M+Na]^+$), 235.0 (55%, $[^{37}Cl\ M+H]^+$), 233.0 (80%, $[^{35}Cl\ M+H]^+$). Data consistent with literature data.[458]

_N_-(2-Chlorophenyl)pivalamide 41



General procedure A was followed using 2-chloroaniline (3.0 g, 24.0 mmol), pivaloyl chloride (3.6 mL, 29.0 mmol) and triethylamine (3.7 mL, 26.0 mmol) affording the title compound as a white crystalline solid (5.0 g, 99%). δ_H (400 MHz, $CDCl_3$) 8.42 (1H, dd, *J* = 8.3 Hz, *J* = 1.2 Hz, H-6), 8.02 (1H, br. s, H-7), 7.37 (1H, dd, *J* = 8.0 Hz, *J* = 1.2 Hz, H-3), 7.31-7.24 (1H, m, H-5), 7.03 (1H, td, *J* = 7.7 Hz, *J* = 1.2 Hz, H-4), 1.36 (9H, s, H-10); δ_C (100 MHz, $CDCl_3$) 176.6, 134.8, 128.8 (C-3), 127.7 (C-5), 124.3 (C-4), 122.9, 121.4 (C-6), 40.2 (C-9), 27.6 (C-10); LRMS (ESI) *m/z* 447.1 (90%, $[^{37}Cl\ ^{35}Cl\ 2M+Na]^+$), 445.1 (100%, $[^{35}Cl\ ^{35}Cl\ 2M+Na]^+$), 236.4 (75%, $[^{37}Cl\ M+Na^+]$, 234.0 (80%, $[^{35}Cl\ M+Na]^+$), 212.1 (30%, $[^{35}Cl\ M+H]^+$). Data consistent with literature data.[459]

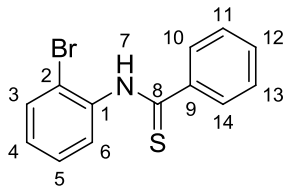
_N_-(2-Bromophenyl)benzamide 72



General procedure A was followed using 2-bromoaniline (2.0 g, 12.0 mmol) and benzoyl chloride (2.3 mL, 20.0 mmol). Recrystallisation from ethanol afforded the title compound as a light pink crystalline solid (1.6 g, 52%). δ_H (400 MHz, $CDCl_3$) 8.57 (1H, app. d, *J* = 8.2 Hz, H-6), 8.48 (1H, br. s, H-7), 7.95 (2H, app. d, *J* = 7.3 Hz, H-10 and H-14), 7.63-7.49 (4H, m, H-3, H-11 and H-13, H-12), 7.39 (1H, app. t, *J* = 7.8 Hz, H-5), 7.03 (1H, app. t, *J* = 7.7 Hz, H-4); δ_C (100 MHz, $CDCl_3$) 165.3, 135.9, 134.6, 132.3, 132.2, 129.0, 128.6 (C-5), 127.1 (C-10 and C-14), 125.3 (C-4), 121.8 (C-6), 113.8; LRMS (ESI) *m/z*

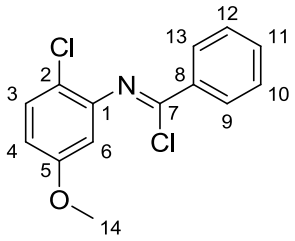
276.0 (95%, [^{81}Br M-H]$^-$), 274.0 (100%, [^{79}Br M-H]$^-$). Data consistent with literature data.[460]

_N_-(2-bromophenyl)benzothioamide[461] 148



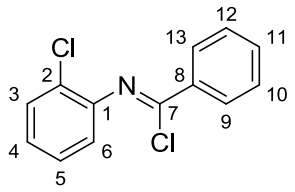
To a solution of *N*-(2-Bromophenyl)benzamide **72** (1.0 g, 3.6 mmol) in toluene (40 mL) was added Lawesson reagent (0.9 g, 2.2 mmol). The reaction was refluxed for 3 h before cooling to room temperature. The resultant mixture was concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/ethyl acetate 6:1) afforded the title compound as a as a green solid (0.9 g, 85%). δ_H (400 MHz, $CDCl_3$) 9.29 (1H, app. br. s, Ar-H), 8.67 (1H, br. s, H-7), 7.93 (1H, br. d, *J* = 5.4 Hz, Ar-H), 7.68 (1H, dd, *J* = 8.0 Hz, *J* = 1.2 Hz, Ar-H), 7.58-7.38 (5H, m, Ar-H), 7.21 (1H, td, *J* = 7.8 Hz, *J* = 1.5 Hz, Ar-H); δ_C (100 MHz, $CDCl_3$) 198.5, 142.7, 137.0, 132.9, 131.6, 128.8, 128.2, 127.9, 127.0, 125.9, 118.1; LRMS (ESI) *m/z* 292.0 (95%, [^{81}Br M-H]$^-$), 290.0 (100%, [^{79}Br M-H]$^-$). Data consistent with literature data.[455]

General procedure B for the preparation of benzimidoyl chlorides, exemplified by the preparation of (*Z*)-*N*-(2-Chloro-5-methoxyphenyl)benzimidoyl chloride 8



To *N*-(2-chloro-5-methoxyphenyl)benzamide **7** (0.6 g, 3.8 mmol), in dichloromethane (10 mL) was added phosphorous pentachloride (0.8 g, 4.2 mmol). The reaction was refluxed at 50 °C for 22 h before cooling to room temperature. The resulting solution was stirred and heated at 50 °C under reduced pressure until ^{31}P NMR confirmed the complete removal of all phosphoryl trichloride. This yielded the title compound as a yellow oil (98% conversion). δ_H (400 MHz, $CDCl_3$) 8.21 (2H, app. d, *J* = 7.6 Hz, H-9 and H-13), 7.61-7.55 (1H, m, H-11), 7.54-7.48 (2H, m, H-10 and H-12), 7.35 (1H, d, *J* = 8.8 Hz, H-3), 6.71 (1H, dd, *J* = 8.8 Hz, *J* = 2.9 Hz, H-4), 6.53 (1H, d, *J* = 2.9 Hz, H-6), 3.82 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 158.7, 146.5, 145.9, 134.9, 132.5 (C-11), 130.2 (C-3), 129.6 (C-9 and C-13), 128.5 (C-10 and C-12), 116.1, 111.6 (C-4), 106.6 (C-6), 55.6 (C-14). Full characterisation data was unattainable due to low stability of the molecule.[251]

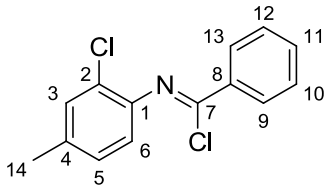
(*Z*)-*N*-(2-Chlorophenyl)benzimidoyl chloride 10*



General procedure B was followed using *N*-(2-chlorophenyl)benzamide **9** (5.0 g, 21.5 mmol), affording the title compound as a pale green liquid (99% conversion). δ_H (400 MHz, $CDCl_3$) 8.24 (2H, app. d, *J* = 7.8 Hz, H-9 and H-13), 7.58-7.62 (1H, m, H-11),

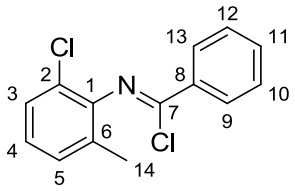
7.48-7.54 (3H, m, H-3, H-10 and H-13), 7.33 (1H, app. dd, *J* = 7.8, *J* = 1.4 Hz, H-5), 7.16 (1H, app. dd, *J* = 7.8, *J* = 1.4 Hz, H-4), 7.00 (1H, dd, *J* = 8.0, 1.4 Hz, H-6); δ_C (100 MHz, $CDCl_3$) 146.2, 145.3, 134.9, 132.4, 129.8, 129.6, 128.5, 127.2, 125.8, 124.8, 121.1. Full characterisation data was unattainable due to low stability of the molecule.[251] * Reaction carried out by R.Foster

(*Z*)-*N*-(2-Chloro-4-methylphenyl)benzimidoyl chloride 12



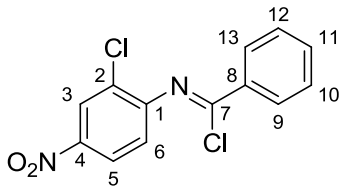
General procedure B was followed using *N*-(2-chloro-4-methylphenyl)benzamide **11** (1.0 g, 4.1 mmol), affording the title compound as an amorphous yellow solid (100% conversion). δ_H (400 MHz, $CDCl_3$) 8.21 (2H, app. d, *J* = 7.7 Hz, H-9 and H-13), 7.59-7.56 (1H, m, H-11), 7.52-7.48 (2H, m, H-10 and H-12), 7.29 (1H, app. s, H-3), 7.12 (1H, app. d, *J* = 8.0 Hz, H-5), 6.90 (1H, d, *J* = 8.0 Hz, H-6), 2.37 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 145.8, 142.6, 135.9, 135.1, 132.3 (C-11), 130.2 (C-3), 129.6 (C-9 and C-13), 128.5 (C-10 and 12), 127.9 (C-5), 124.6, 120.9 (C-6), 20.8 (C-14). Full characterisation data was unattainable due to low stability of the molecule.[251]

(*Z*)-*N*-(2-Chloro-6-methylphenyl)benzimidoyl chloride 14



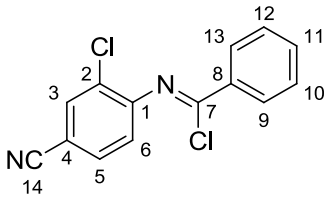
General procedure B was followed using *N*-(2-chloro-6-methylphenyl)benzamide **13** (0.4 g, 1.4 mmol), affording the title compound as an amorphous yellow solid (100% conversion). δ_H (400 MHz, $CDCl_3$) 7.95-7.90 (2H, m, H-9 and H-13), 7.59-7.52 (1H, m, H-11), 7.49-7.43 (2H, m, H-10 and H-12), 7.29 (1H, dd, *J* = 6.7 Hz, *J* = 2.0 Hz, Ar-H), 7.18-7.13 (2H, m, Ar-H), 2.29 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 138.2, 133.9, 132.8, 132.0, 131.5, 129.3, 128.7, 127.9, 127.5 (2C), 127.0, 19.0 (C-14). Full characterisation data was unattainable due to low stability of the molecule.[251]

(*Z*)-*N*-(2-Chloro-4-nitrophenyl)benzimidoyl chloride 16



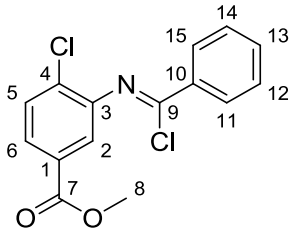
General procedure B was followed using *N*-(2-chloro-4-nitrophenyl)benzamide **15** (0.5 g, 1.8 mmol), affording the title compound as an amorphous yellow solid (100% conversion). δ_H (400 MHz, $CDCl_3$) 8.39 (1H, d, *J* = 2.3 Hz, H-3), 8.22-8.18 (3H, m, H-5 and H-9 and H-13), 7.67-7.61 (1H, m, H-11), 7.57-7.51 (2H, m, H-10 and H-12), 7.11 (1H, d, *J* = 8.7 Hz, H-6); δ_C (100 MHz, $CDCl_3$) 150.9, 148.5, 144.9, 134.1, 133.3 (C-11), 129.7, 129.2, 128.7 (C-10 and C-12), 125.6 (C-3), 122.9, 121.4 (C-6). Full characterisation data was unattainable due to low stability of the molecule.[251]

(*Z*)-*N*-(2-Chloro-4-cyanophenyl)benzimidoyl chloride 18



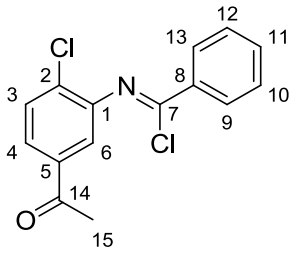
General procedure B was followed using *N*-(2-chloro-4-cyanophenyl)benzamide **17** (2.0 g, 3.3 mmol), affording the title compound as a colourless oil (100% conversion). δ_H (400 MHz, $CDCl_3$) 8.20 (2H, app. d, *J* = 7.8 Hz, H-9 and H-13), 7.78-7.76 (1H, m, H-3), 7.65-7.58 (2H, m, H-5 and H-11), 7.53 (2H, t, *J* = 7.7 Hz, H-10 and H-12), 7.06 (1H, d, *J* = 8.2 Hz, H-6); δ_C (100 MHz, $CDCl_3$) 149.4, 148.2, 134.4, 133.5, 133.2, 131.2, 129.7 (C-9 and C-13), 128.7 (C-10 and C-12), 125.8, 121.9 (C-6), 117.7, 109.4. Full characterisation data was unattainable due to low stability of the molecule.[251]

(*Z*)-Methyl 4-chloro-3-(chloro(phenyl)methyleneamino)benzoate 20



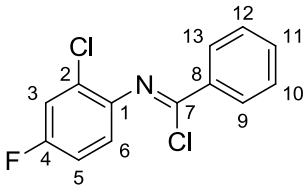
General procedure B was followed using methyl 3-benzamido-4-chlorobenzoate **19** (0.6 g, 2.0 mmol), affording the title compound as an amorphous yellow solid (94% conversion). δ_H (400 MHz, $CDCl_3$) 8.21 (2H, app. d, *J* = 7.8 Hz, H-11 and H-15), 7.84-7.81 (1H, m, H-6), 7.67 (1H, d, *J* = 1.6 Hz, H-2), 7.63-7.58 (1H, m, H-13), 7.56-7.48 (3H, m, H-5 and H-12 and H-14), 3.93 (3H, s, H-8); δ_C (100 MHz, $CDCl_3$) 166.0, 147.4, 145.4, 134.7, 132.7 (C-12), 130.0, 129.9, 129.6, 129.4, 128.6, 126.7 (C-6), 122.4 (C-2), 52.4 (C-8). Full characterisation data was unattainable due to low stability of the molecule.[251]

(*Z*)-*N*-(5-Acetyl-2-chlorophenyl)benzimidoyl chloride 22



General procedure B was followed using *N*-(5-acetyl-2-chlorophenyl)benzamide **21** (0.4 g, 1.5 mmol), affording the title compound as an orange oil (98% conversion). δ_H (400 MHz, $CDCl_3$) 8.21 (2H, app. d, *J* = 7.6 Hz, H-9 and H-13), 7.74 (1H, dd, *J* = 8.3 Hz, *J* = 1.8 Hz, H-4), 7.63-7.48 (5H, m, H-3, H-6, H-10, H-11 and H-12), 2.61 (3H, s, H-15); δ_C (100 MHz, $CDCl_3$) 196.6, 147.5, 145.6, 136.2, 134.6, 132.8, 130.2, 130.1, 129.6, 128.6, 125.5 (C-4), 121.1, 26.7 (C-14). Full characterisation data was unattainable due to low stability of the molecule.[251]

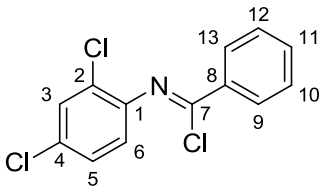
(*Z*)-*N*-(2-Chloro-4-fluorophenyl)benzimidoyl chloride 24



General procedure B was followed using *N*-(2-chloro-4-fluorophenyl)benzamide **23** (1.0 g, 4.0 mmol), affording the title compound as an amorphous white solid (98% conversion). δ_H (400 MHz, $CDCl_3$) 8.22-8.20 (2H, m, H-9 and 13), 7.61-7.58 (1H, m, H-11), 7.53-7.49 (2H, m, H-10 and H-12), 7.28-7.22 (1H, m, H-3), 7.08-7.03 (1H, m, H-5), 7.00-6.96 (1H, m, H-6); δ_C (100 MHz, $CDCl_3$) 159.7 (d, *J* = 247.0 Hz, C-4), 146.8, 141.6 (d, *J* = 3.3 Hz), 134.9, 132.6 (C-11), 129.6 (C-9 and C-13), 128.6 (C-10 and C-12), 125.8 (d, *J* = 10.3 Hz), 122.0 (d, *J* = 8.7 Hz, C-6), 117.1 (d, *J* = 25.6 Hz, C-3), 114.4 (d, *J* =

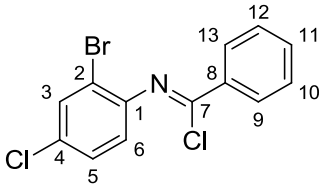
22.4 Hz, C-5); δ_F (376 MHz, $CDCl_3$) -116.5 (1F, s). Full characterisation data was unattainable due to low stability of the molecule.[251]

(*Z*)-*N*-(2,4-Dichlorophenyl)benzimidoyl chloride 26



General procedure B was followed using *N*-(2,4-dichlorophenyl)benzamide **25** (1.0 g, 3.8 mmol), affording the title compound as an amorphous white solid (98% conversion). δ_H (500 MHz, $CDCl_3$) 8.21-8.16 (2H, m, H-9 and H-13), 7.61-7.55 (1H, m, H-11), 7.53-7.46 (3H, m, H-3, H-10 and H-12), 7.28 (1H, dd, *J* = 8.5 Hz, *J* = 2.2 Hz, H-5), 6.93 (1H, d, *J* = 8.5 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 147.0, 143.9, 134.7, 132.7 (C-11), 130.5, 129.6 (2C), 128.6, 127.5 (C-5), 125.8, 122.0 (C-6). Full characterisation data was unattainable due to low stability of the molecule.[251]

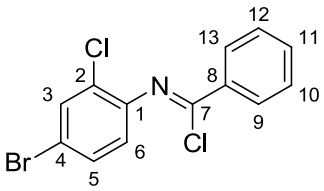
(*Z*)-*N*-(2-Bromo-4-chlorophenyl)benzimidoyl chloride 28



General procedure B was followed using *N*-(2-bromo-4-chlorophenyl)benzamide **27** (1.0 g, 3.4 mmol), affording the title compound as an amorphous yellow solid (99% conversion). δ_H (400 MHz, $CDCl_3$) 8.21 (2H, app. d, *J* = 7.2 Hz, H-9 and H-13), 7.66 (1H, d, *J* = 2.0 Hz, H-3), 7.62-7.57 (1H, m, H-11), 7.54-7.48 (2H, m, H-10 and H-12), 7.34 (1H, dd, *J* = 8.5 Hz, *J* = 2.0 Hz, H-5), 6.93 (1H, d, *J* = 8.5 Hz, H-6); δ_C (100 MHz, $CDCl_3$) 146.7, 145.3, 134.8, 132.7 (C-11), 132.4 (C-3), 130.7, 129.6 (C-9 and C-13),

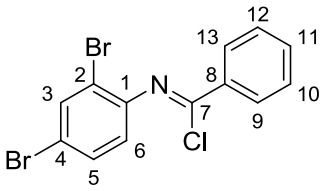
128.6 (C-10 and C-12), 128.1 (C-5), 121.9 (C-6), 115.3. Full characterisation data was unattainable due to low stability of the molecule.[251]

(*Z*)-*N*-(4-Bromo-2-chlorophenyl)benzimidoyl chloride 30



General procedure B was followed using *N*-(4-bromo-2-chlorophenyl)benzamide **29** (2.0 g, 6.5 mmol), affording the title compound as an amorphous yellow solid (100% conversion). δ_H (400 MHz, $CDCl_3$) 8.20 (2H, app. d, *J* = 7.7 Hz, H-9 and H-13), 7.63 (1H, d, *J* = 1.6 Hz, H-3), 7.59 (1H, app. d, *J* = 7.3 Hz, H-11), 7.51 (2H, t, *J* = 7.6 Hz, H-10 and H-12), 7.44 (1H, dd, *J* = 8.4 Hz, *J* = 1.6 Hz, H-5), 6.88 (1H, d, *J* = 8.4 Hz, H-6); δ_C (100 MHz, $CDCl_3$) 147.0, 144.4, 134.7, 132.7, 132.4, 130.5 (C-5), 129.6, 128.6, 126.1, 122.4 (C-6), 117.8. Full characterisation data was unattainable due to low stability of the molecule.[251]

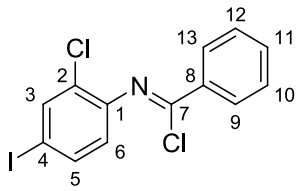
(*Z*)-*N*-(2,4-Dibromophenyl)benzimidoyl chloride 32



General procedure B was followed using *N*-(2,4-dibromophenyl)benzamide **31** (1.0 g, 2.7 mmol), affording the title compound as an amorphous yellow solid (90% conversion). δ_H (400 MHz, $CDCl_3$) 8.23-8.19 (2H, m, H-9 and H-13), 7.01 (1H, d, *J* = 2.1 Hz, H-3), 7.62-7.46 (4H, m, H-5, H-10, H-11 and H-12), 6.87 (1H, d, *J* = 8.5 Hz, H-6); δ_C (100 MHz,

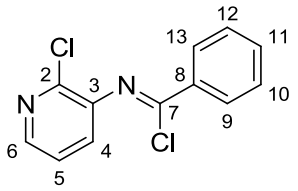
$CDCl_3$) 146.7, 145.8, 135.1 (C-3), 134.7, 132.7, 131.0, 129.6, 128.6, 122.3 (C-6), 118.0, 115.6. Full characterisation data was unattainable due to low stability of the molecule.[251]

(*Z*)-*N*-(2-Chloro-4-iodophenyl)benzimidoyl chloride 34



General procedure B was followed using *N*-(2-chloro-4-iodophenyl)benzamide **33** (1.5 g, 4.0 mmol), affording the title compound as an amorphous yellow solid (99% conversion). δ_H (400 MHz, $CDCl_3$) 8.20 (2H, app. d, *J* = 7.6 Hz, H-9 and H-13), 7.81 (1H, d, *J* = 1.7 Hz, H-3), 7.62 (1H, dd, *J* = 8.3 Hz, *J* = 1.7 Hz, H-5), 7.59 (1H, app. d, *J* = 7.4 Hz, H-11), 7.51 (2H, t, *J* = 7.6 Hz, H-10 and H-12), 6.74 (1H, d, *J* = 8.3 Hz, H-6); δ_C (100 MHz, $CDCl_3$) 146.9, 145.1, 138.0 (C-3), 136.3 (C-5), 134.7, 132.7 (C-11), 129.6 (C-9 and C-13), 128.6 (C-10 and C-12), 126.1, 122.7 (C-6), 88.1 (C-4). Full characterisation data was unattainable due to low stability of the molecule.[251]

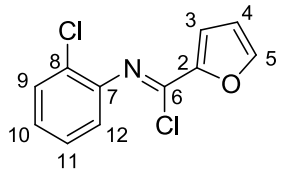
(*Z*)-*N*-(2-Chloropyridin-3-yl)benzimidoyl chloride 36



General procedure B was followed using *N*-(2-chloropyridin-3-yl)benzamide **35** (1.0 g, 4.3 mmol), affording the title compound as an amorphous yellow oil (98% conversion). δ_H (400 MHz, $CDCl_3$) 8.27 (1H, dd, *J* = 4.5 Hz, *J* = 1.9 Hz, H-6), 8.22 (2H, app. d, *J* = 7.9 Hz, H-9 and H-13), 7.64-7.59 (1H, m, H-11), 7.56-7.48 (2H, m, H-10 and H-12), 7.37-7.29 (2H, m, H-5 and H-4); δ_C (100 MHz, $CDCl_3$) 148.4, 145.5 (C-6), 142.3, 141.9,

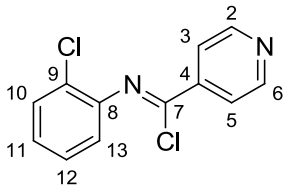
134.5, 132.9 (C-11), 129.7, 129.5, 128.7, 122.7. Full characterisation data was unattainable due to low stability of the molecule.[251]

(*Z*)-*N*-(2-Chlorophenyl)furan-2-carbimidoyl chloride 38



General procedure B was followed using *N*-(2-chlorophenyl)furan-2-carboxamide **37** (1.0 g, 4.5 mmol), affording the title compound as a brown oil (100% conversion). δ_H (400 MHz, $CDCl_3$) 7.68 (1H, app. s, H-5), 7.46 (1H, app. d, *J* = 8.0 Hz, H-9), 7.33-7.25 (2H, m, H-3, H-11), 7.17-7.12 (1H, app. t, *J* = 7.7 Hz, H-10), 6.99 (1H, app. d, *J* = 7.9 Hz, H-12), 6.56 (1H, app. s, H-4); δ_C (100 MHz, $CDCl_3$) 148.0, 147.2 (C-5), 144.5, 134.9, 129.8 (C-9), 127.2 (C-11), 126.1 (C-10), 125.2, 121.5 (C-12), 119.0 (C-3), 112.5 (C-4). Full characterisation data was unattainable due to low stability of the molecule.[251]

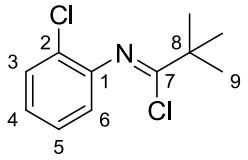
(*Z*)-*N*-(2-Chlorophenyl)isonicotinimidoyl chloride 40



General procedure B was followed using *N*-(2-chlorophenyl)isonicotinamide **39** (0.5 g, 4.3 mmol), affording the title compound as an amorphous yellow solid (100% conversion). δ_H (500 MHz, $CDCl_3$) 8.95 (2H, d, *J* = 6.5 Hz, H-2 and H-6), 8.49 (2H, d, *J* = 6.5 Hz, H-3 and H-5), 7.53 (1H, dd, *J* = 8.1 Hz, *J* = 1.3 Hz, H-10), 7.38 (1H, td, *J* = 7.8 Hz, *J* = 1.3 Hz, H-12), 7.30-7.24 (1H, m, H-11), 7.06 (1H, dd, *J* = 7.9 Hz, *J* = 1.5 Hz, H-13); δ_C (125 MHz, $CDCl_3$) 146.7, 144.4 (C-2 and C-6), 143.5, 141.8, 130.2 (C-10), 127.6,

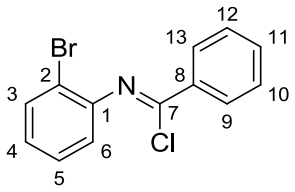
127.4, 125.3, 125.2, 120.5 (C-13). Full characterisation data was unattainable due to low stability of the molecule.[251]

(*Z*)-*N*-(2-Chlorophenyl)pivalimidoyl chloride 42



General procedure B was followed using *N*-(2-chlorophenyl)pivalamide **41** (2.0 g, 9.5 mmol), affording the title compound as a yellow oil (98% conversion). δ_H (400 MHz, $CDCl_3$) 7.40 (1H, app. d, *J* = 8.0 Hz, H-6), 7.26-7.22 (1H, m, H-4), 7.08 (1H, td, *J* = 7.7 Hz, *J* = 1.2 Hz, H-5), 6.82 (1H, dd, *J* = 7.9 Hz, *J* = 1.2 Hz, H-3), 1.42 (9H, s, H-9); δ_C (100 MHz, $CDCl_3$) 158.3, 145.1, 129.7 (C-6), 127.1 (C-4), 125.7 (C-5), 124.2, 120.9 (C-3), 44.0 (C-8), 28.3 (C-9). Full characterisation data was unattainable due to low stability of the molecule.[251]

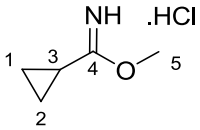
(*Z*)-*N*-(2-Bromophenyl)benzimidoyl chloride 73



General procedure B was followed using *N*-(2-bromophenyl)benzamide **72** (1.0 g, 3.7 mmol) affording the title compound as a yellow oil (92% conversion). δ_H (500 MHz, $CDCl_3$) 8.26-8.21 (2H, m, H-9 and H-13), 7.66 (1H, dd, *J* = 8.1 Hz, *J* = 1.2 Hz, H-3), 7.71-7.57 (1H, m, H-11) 7.54-7.49 (2H, m, H-10 and H-12), 7.37 (1H, td, *J* = 7.7 Hz, *J* = 1.2 Hz, H-5), 7.09 (1H, td, *J* = 7.7 Hz, *J* = 1.4 Hz, H-4), 7.00 (1H, dd, *J* = 7.9 Hz, *J* = 1.4 Hz, H-6); δ_C (125 MHz, $CDCl_3$) 146.7, 146.0, 135.0, 132.8, 132.4, 129.6 (C-9 and C-13),

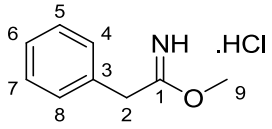
128.5, 127.8, 126.0 (C-4), 121.1 (C-6), 114.6. Full characterisation data was unattainable due to low stability of the molecule.[251]

General procedure C for the preparation of imidate salts, exemplified by the preparation of Methyl cyclopropanecarbimidate hydrochloride 75



To a mixture of HCl solution (34.0 mL, 2M in diethyl ether, 70.0 mmol) and methanol (1.1 mL, 30.0 mmol) at 0 °C was added cyclopropanecarbonitrile (1.5 g, 20.0 mmol). The resulting solution was kept at 4 °C for 5 days to complete the imidate hydrochloride crystallisation. The resultant solid was filtered and washed with anhydrous diethyl ether and concentrated *in vacuo* to afford the title compound as a white crystalline solid (2.5 g, 83%). mp; 111-113 °C; ν_{max} (neat)/cm^{-1} 3094 (br), 2991 (br), 2836 (br), 2727 (br), 2645 (br), 1635 (s), 1557 (m), 1482 (m), 1461 (m), 1442 (m); δ_H (400 MHz, $CDCl_3$) 12.45 (1H, br. s, N-H), 11.31 (1H, br. s, N-H), 4.21 (3H, s, H-5), 2.47-2.38 (1H, m, H-3), 1.30-1.17 (4H, m, H-1 and H-2); δ_C (100 MHz, $CDCl_3$) 180.4, 60.3 (C-5), 12.9 (C-3), 10.9 (C-1 and C-2); HRMS (ESI) found *m/z* 100.0755 $[M-Cl]^+$, $C_5H_{10}NO$ requires 100.0757.

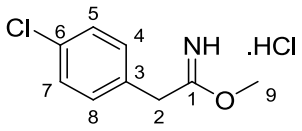
Methyl 2-phenylacetimidate hydrochloride 76



General procedure C was followed using phenylacetonitrile (2.8 mL, 20.0 mmol) and left to crystallise for 11 days. The title compound was afforded as a white crystalline solid (4.1 g, 92%). δ_H (400 MHz, $CDCl_3$) 12.85 (1H, br. s, N-H), 11.84 (1H, br. s, N-H), 7.46-

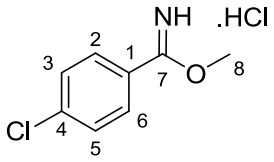
7.25 (5H, m, Ar-H), 4.27 (3H, s, H-9), 4.07 (2H, s, H-2); δ_C (100 MHz, $CDCl_3$) 178.5 (C-1), 131.3, 129.8, 129.4, 128.6, 61.3 (C-9), 39.3 (C-2). LRMS (ESI) *m/z* 150.1 (100%, $[M-Cl]^+$). Data consistent with literature data.[462]

Methyl 2-(4-chlorophenyl)acetimidate hydrochloride 77



General procedure C was followed using (4-chlorophenyl)acetonitrile (3.0 g, 20.0 mmol) and left to crystallise for 7 days. The title compound was afforded as a white crystalline solid (3.3 g, 75%). mp: 112-115 °C (decomposition); ν_{max} (neat)/cm^{-1} 3345 (br), 2838 (br), 2730 (br), 2643 (br), 2557 (br), 1733 (s), 1650 (m), 1597 (m), 1482 (m); δ_H (400 MHz, $CDCl_3$) 12.94 (1H, br. s, N-H), 11.86 (1H, br. s, N-H), 7.43-7.30 (4H, m, Ar-H), 4.27 (3H, s, H-9), 4.06 (2H, s, H-2); δ_C (100 MHz, $CDCl_3$) 177.8, 134.6, 130.9, 129.4, 129.3, 61.1 (C-9), 38.3 (C-2); HRMS (ESI) found *m/z* 184.0520 $[M-Cl]^+$, $C_9H_{11}{}^{35}ClNO$ requires 184.0524.

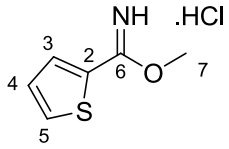
Methyl 4-chlorobenzimidate hydrochloride 78



General procedure C was followed using 4-chlorobenzonitrile (3.0 g, 20.0 mmol) and left to crystallise for 6 days. Recrystallisation from dichloromethane afforded the title compound as a white crystalline solid (0.64 g, 14%). mp 139-141 °C (decomposition); ν_{max} (neat)/cm^{-1} 3033 (br), 2839 (br), 1638 (s), 1593 (m), 1496 (w), 1456 (m), 1436 (m), 1404 (m), 1383 (w); δ_H (400 MHz, $CDCl_3$) 12.86 (1H, br. s, N-H), 12.14 (1H, br. s, N-H

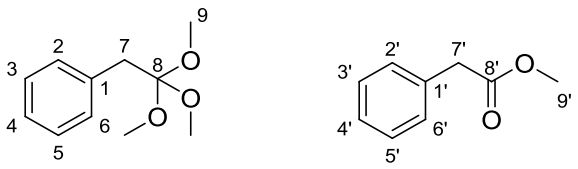
), 8.38 (2H, d, *J* = 8.7 Hz, Ar-H), 7.56 (2H, d, *J* = 8.7 Hz, Ar-H), 4.57 (3H, s, H-8); δ_C (100 MHz, $CDCl_3$) 171.0, 142.8, 131.1, 129.7, 123.3, 61.5 (C-8); HRMS (ESI) found *m/z* 192.0192 $[M\text{-}Cl]^+$, $C_8H_8{}^{35}ClNNaO$ requires 192.0187.

Methyl thiophene-2-carbimidate hydrochloride 79



General procedure C was followed using 2-thiophenecarbonitrile (2.6 mL, 30.0 mmol) and left to crystallise for 4 days. The title compound was afforded as a yellow crystalline solid (0.9 g, 18%). mp: 121-123 °C (decomposition); ν_{max} (neat)/cm^{-1} 3355 (br), 3093 (br), 3044 (br), 2888 (br), 1609 (s), 1533 (m), 1458 (m), 1446 (m), 1409 (m); δ_H (400 MHz, $CDCl_3$) 12.64 (1H, br. s, N-H), 11.86 (1H, br. s, N-H) 9.04 (1H, dd, *J* = 4.0 Hz, *J* = 1.0 Hz, Ar-H), 7.83 (1H, dd, *J* = 4.9 Hz, *J* = 1.0 Hz, Ar-H), 7.29-7.25 (1H, m, H-4), 4.51 (3H, s, H-7); δ_C (100 MHz, $CDCl_3$) 166.8, 138.3, 136.8, 129.8 (C-4), 127.3, 61.3 (C-7); HRMS (ESI) found *m/z* 142.0325 $[M\text{-}Cl]^+$, C_6H_8NOS requires 142.0321.

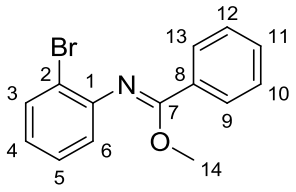
(2,2,2-Trimethoxyethyl)benzene 80 and Methyl 2-phenylacetate 81



To a suspension of methyl 2-phenylacetimidate hydrochloride **76** (1.0 g, 5.4 mmol) in anhydrous hexane (11 mL) was added methanol (0.7 mL, 16.0 mmol). The mixture was stirred at room temperature for 24 h. The resultant mixture was filtered to remove the precipitated ammonium chloride and concentrated *in vacuo* to afford a crude 2.5:1 mixture of ortho-ester and ester as a colourless liquid (0.8 g). This crude mixture was

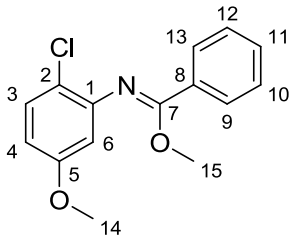
used immediately and without further purification. δ_H (400 MHz, $CDCl_3$) 7.34-7.22 (10H, m, Ar-H), 3.71 (3H, s, H-9'), 3.65 (2H, s, H-7'), 3.32 (9H, s, H-9), 3.11 (2H, s, H-7); δ_C (100 MHz, $CDCl_3$) 172.0, 135.4, 134.0, 129.7, 129.3, 128.6, 128.1, 127.1, 126.4, 115.2, 52.0 (C-9'), 49.7 (C-9), 41.2 (C-7'), 37.0 (C-7). Data consistent with literature data.[463, 464]

General procedure D for the preparation of benzimidates, exemplified by the preparation of (*Z*)-Methyl *N*-2-bromophenylbenzimidate 74



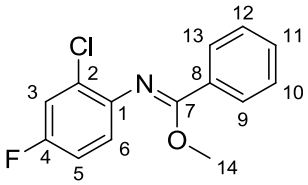
A mixture of 2-bromoaniline (2.0 g, 12.0 mmol), trimethyl orthobenzoate (2.3 mL, 13.0 mmol) and *p*-toluenesulfonic acid (cat.) in toluene (60 mL) was heated under reflux for 3 h with the aid of Dean-Stark apparatus. The mixture was cooled and concentrated *in vacuo*. The residue was re-dissolved in diethyl ether (20 mL), washed with a saturated aqueous solution of sodium bicarbonate (20 mL) and then brine (20 mL). This was then dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/ethyl acetate 25:1) afforded the title compound as colourless oil and as a single isomer (3.0 g, 89%). ν_{max} (neat)/cm^{-1} 3055 (br), 2986 (br), 2947 (br), 1721 (w), 1667 (s), 1602 (w), 1584 (w), 1493 (w), 1469 (m), 1447 (m); δ_H (400 MHz, $CDCl_3$) 7.53 (1H, dd, *J* = 8.0 Hz, *J* = 1.4 Hz, H-3), 7.36-7.30 (3H, m, H-10, H-11 and H-12), 7.28-7.22 (2H, m, H-9 and H-13), 7.09 (1H, td, *J* = 7.7 Hz, *J* = 1.4 Hz, H-5), 6.83 (1H, td, *J* = 7.7 Hz, *J* = 1.5 Hz, H-4), 6.64 (1H, dd, *J* = 7.9 Hz, *J* = 1.5 Hz, H-6), 4.05 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 159.9, 147.1, 132.7 (C-3), 131.3, 130.2, 128.7, 128.0, 127.9, 123.8 (C-4), 122.5 (C-6), 116.3, 54.4 (C-14); HRMS (ESI) found *m/z* 311.9996 $[M+Na]^+$, $C_{14}H_{12}{}^{79}BrNNaO$ requires 311.9994.

(*Z*)-Methyl *N*-2-chloro-5-methoxyphenylbenzimidate 83



General procedure D was followed using 2-chloro-5-methoxyaniline (1.0 g, 6.3 mmol) and trimethyl orthobenzoate (2.3 mL, 13.0 mmol). Flash chromatography (SiO_2, petrol/diethyl ether 12:1) afforded the title compound as a crystalline colourless solid as a single isomer (1.0 g, 59 %). mp: 67-69 °C; ν_{max} (neat)/cm^{-1} 3006 (br), 2950 (br), 1666 (s), 1593 (m), 1573 (m), 1493 (m), 1479 (m), 1461 (m), 1445 (m), 1434 (m), 1399 (m), 1317 (m); δ_H (400 MHz, $CDCl_3$) 7.39-7.31 (3H, m, Ar-H), 7.28-7.22 (2H, m, Ar-H), 7.18 (1H, d, *J* = 8.8 Hz, H-3), 6.48 (1H, dd, *J* = 8.8 Hz, *J* = 2.9 Hz, H-4), 6.27 (1H, d, *J* = 2.9 Hz, H-6), 4.03 (3H, s, H-15), 3.67 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 160.2, 158.7, 146.5, 131.4, 130.3, 130.0, 128.5, 128.0, 117.3, 109.6 (C-4), 108.0 (C-6), 55.4 (C-14), 54.4 (C-15); HRMS (ESI) found *m/z* 276.0795 $[M+H]^+$, $C_{15}H_{15}{}^{35}ClNO_2$ requires 276.0786.

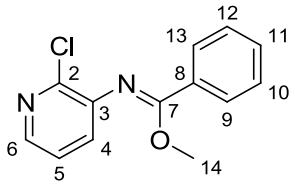
(*Z*)-Methyl *N*-2-chloro-4-fluorophenylbenzimidate 84



General procedure D was followed using 2-chloro-4-fluoroaniline (2.0 g, 14.0 mmol) and trimethyl orthobenzoate (2.6 mL, 15.0 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 20:1) afforded the title compound as a yellow oil and as a single isomer (1.2 g, 32%). ν_{max} (neat)/cm^{-1} 2989 (w), 2946 (w), 1737 (w), 1662 (s), 1661 (m), 1579 (m), 1518 (m), 1485 (s), 1458 (m), 1447 (m), 1434 (m); δ_H (400 MHz, $CDCl_3$) 7.36-7.31 (3H, m,

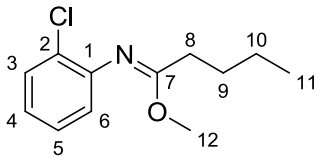
Ar-H), 7.29-7.24 (2H, m, Ar-H), 7.10 (1H, dd, *J* = 8.4 Hz, *J* = 2.8 Hz, H-3), 6.82-6.76 (1H, m, H-5), 6.62 (1H, dd, *J* = 8.8 Hz, *J* = 5.6 Hz, H-6), 4.05 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 160.2 (d, *J* = 155.8 Hz, C-4), 157.0, 142.3 (d, *J* = 3.2 Hz), 131.3, 130.3, 128.6, 128.1, 126.1 (d, *J* = 10.4 Hz), 123.2 (d, *J* = 8.3 Hz, C-6), 116.7 (d, *J* = 25.3 Hz, C-3), 114.3 (d, *J* = 22.1 Hz, C-5), 54.4 (C-14); δ_F (376 MHz, $CDCl_3$) -119.7 (1F, s); HRMS (ESI) found *m/z* 264.0591 $[M+H]^+$, $C_{14}H_{12}{}^{35}ClFNO$ requires 264.0586.

(*Z*)-Methyl *N*-2-chloropyridin-3-ylbenzimidate 85



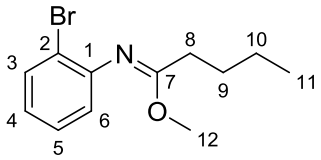
General procedure D was followed using 3-amino-2-chloropyridine (2.0 g, 16.0 mmol) and trimethyl orthobenzoate (2.9 mL, 17.0 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 10:1) afforded the title compound as an orange oil and as a single isomer (1.2 g, 31%). ν_{max} (neat)/cm^{-1} 3057 (w), 2946 (w), 1721 (w), 1656 (s), 1601 (m), 1580 (m), 1554 (m), 1493 (m), 1443 (s), 1396 (m); δ_H (400 MHz, $CDCl_3$) 8.02 (1H, dd, *J* = 4.7 Hz, *J* = 1.8 Hz, H-6), 7.37-7.22 (5H, m, H-9, H-10, H-11, H-12 and H-13), 7.03 (1H, dd, *J* = 7.8 Hz, *J* = 4.7 Hz, H-5), 6.95 (1H, dd, *J* = 7.8 Hz, *J* = 1.8 Hz, H-4), 4.05 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 161.6, 143.6, 143.3 (C-6), 142.6, 130.8, 130.6, 130.3, 128.5, 128.3, 122.8 (C-5), 54.7 (C-14); HRMS (ESI) found *m/z* 247.0633 $[M+H]^+$, $C_{13}H_{12}{}^{35}ClN_2O$ requires 247.0633.

(*Z*)-Methyl *N*-2-chlorophenylpentanimidate 87



General procedure D was followed using 2-chloroaniline (1.0 g, 7.8 mmol) and trimethyl orthovalerate (1.4 mL, 8.6 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 20:1) afforded the title compound as colourless oil and as a single isomer (1.5 g, 83%). ν_{max} (neat)/cm^{-1} 2962 (br), 1713 (s), 1670 (s), 1589 (w), 1437 (m), 1360(m), 1267 (w),1220 (m); δ_H (400 MHz, $CDCl_3$) 7.37 (1H, dd, *J* = 8.0 Hz, *J* = 1.3 Hz, H-3), 7.18 (1H, td, *J* = 7.6 Hz, *J* = 1.3 Hz, H-5), 6.97 (1H, td, *J* = 7.8 Hz, *J* = 1.5 Hz, H-4), 6.80 (1H, dd, *J* = 7.8 Hz, J_{6-4} = 1.5 Hz, H-6), 3.85 (3H, s, H-12), 2.12 (2H, t, *J* = 7.7 Hz, H-8), 1.51 (2H, quin, *J* = 7.6 Hz, H-9), 1.24 (2H, sex, *J* = 7.4 Hz, H-10), 0.83 (3H, t, *J* = 7.3 Hz, H-11); δ_C (100 MHz, $CDCl_3$) 165.4, 145.9, 129.7 (C-3), 127.2 (C-5), 125.6, 123.7 (C-4), 122.6 (C-6), 53.5 (C-12), 30.0 (C-8), 27.9 (C-9), 22.3 (C-10), 13.7 (C-11); HRMS (ESI) found *m/z* 226.0992 $[M+H]^+$, $C_{12}H_{17}{}^{35}ClNO$ requires 226.0993.

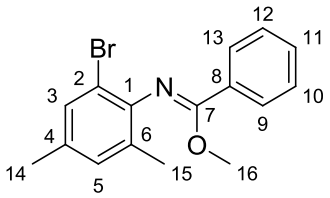
(*Z*)-Methyl *N*-2-bromophenylpentanimidate 88



General procedure D was followed using 2-bromoaniline (2.0 g, 11.6 mmol) and trimethyl orthovalerate (2.2 mL, 13.0 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 20:1) afforded the title compound as a yellow oil and as a single isomer (2.5 g, 78%). ν_{max} (neat)/cm^{-1} 2960 (br), 2872 (w), 1715 (w), 1668 (s), 1586 (w), 1466 (w), 1435 (m), 1357 (w), 1313 (m), 1267 (m); δ_H (400 MHz, $CDCl_3$) 7.55 (1H, dd, *J* = 8.0 Hz, *J* = 1.1 Hz, H-3), 7.23 (1H, td, *J* = 7.6 Hz, *J* = 1.1 Hz, H-5), 6.90 (1H, td, *J* = 7.7 Hz, *J* = 1.5

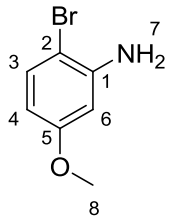
Hz, H-4), 6.78 (1H, dd, *J* = 7.8 Hz, *J* = 1.5 Hz, H-6), 3.86 (3H, s, H-12), 2.11 (2H, t, *J* = 7.7 Hz, H-8), 1.51 (2H, quin, *J* = 7.6 Hz, H-9), 1.24 (2H, sex, *J* = 7.6 Hz, H-10), 0.83 (3H, t, *J* = 7.3 Hz, H-11); δ_C (100 MHz, $CDCl_3$) 165.2, 147.2, 132.7 (C-3), 127.9 (C-5), 123.9 (C-4), 122.3 (C-6), 116.1, 53.6 (C-12), 30.0 (C-8), 27.9 (C-9), 22.4 (C-10), 13.7 (C-11); HRMS (ESI) found *m/z* 270.0494 $[M+H]^+$, $C_{12}H_{17}{}^{79}BrNO$ requires 270.0488.

(*Z*)-Methyl *N*-2-bromo-4,6-dimethylphenylbenzimidate 133



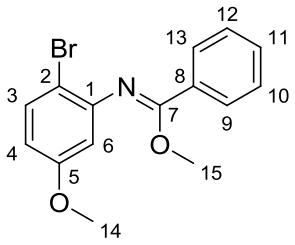
General procedure D was followed using 2-bromo-4,6-dimethylaniline (2.0 g, 10.0 mmol) and trimethyl orthobenzoate (1.9 mL, 11.0 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 50:1) afforded the title compound as a colourless oil and as a single isomer (2.6 g, 81%). mp: 39-42 °C; ν_{max} (neat)/cm^{-1} 3052 (w), 2941 (w), 1663 (s), 1601 (w), 1493 (m), 1438 (m), 1317 (m), 1298 (s), 1264 (s); δ_H (400 MHz, $CDCl_3$) 7.39-7.31 (3H, m, Ar-H), 7.27-7.22 (2H, m, Ar-H), 7.18 (1H, app. s, H-5), 6.84 (1H, app. s, H-3), 4.05 (3H, s, H-16), 2.23 (3H, s, H-15), 2.02 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 159.0, 142.8, 133.0, 132.1, 130.7, 130.3 (2C), 129.2, 128.0, 128.0, 115.2, 54.3 (C-16), 20.4 (C-15), 18.9 (C-14); HRMS (ESI) found *m/z* 318.0491 $[M+H]^+$, $C_{16}H_{17}{}^{79}BrNO$ requires 318.0488.

2-Bromo-5-methoxyaniline



To a solution of 4-bromo-3-nitroanisole (1.4 g, 6.0 mmol) in absolute ethanol (20 mL) was added iron powder (1.0 g, 18.0 mmol) and HCl (2.5 mL, 37%). The mixture was heated at reflux for 24 h and then allowed to cool. The resultant solution was diluted with water (40 mL) and dichloromethane (40 mL) and filtered through a Celite® pad, washing with dichloromethane (200 mL). The organic layer was then separated and water (100 mL) added. The aqueous layer was basified with anhydrous solid K_2CO_3. The organic layer was removed and dried ($MgSO_4$) and then concentrated *in vacuo* to afford the title compound as a yellow oil (0.9 g, 70%). δ_H (400 MHz, $CDCl_3$) 7.26 (1H, d, *J* = 8.1 Hz, H-3), 6.30 (1H, d, *J* = 2.8 Hz, H-6), 6.21 (1H, dd, *J* = 8.1 Hz, *J* = 2.8 Hz, H-4), 4.02 (2H, br. s, H-7), 3.72 (3H, s, H-8); δ_C (100 MHz, $CDCl_3$) 160.2, 145.0, 133.0, 105.7, 101.5, 100.7, 55.5 (C-8); LRMS (ESI) *m/z* 204.0 (95%, $[^{79}Br\ M+H]^+$), 202.0 (100%, $[^{81}Br\ M+H]^+$). Data consistent with literature data.[465]

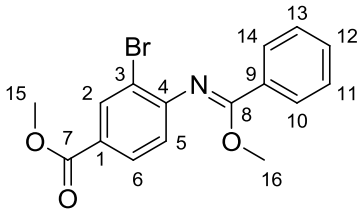
(*Z*)-Methyl *N*-2-bromo-5-methoxyphenylbenzimidate 134



General procedure D was followed using 2-bromo-5-methoxyaniline (0.8 g, 4.0 mmol) and trimethyl orthobenzoate (1.3 mL, 7.5 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 18:1) afforded the title compound as white crystalline solid and as a

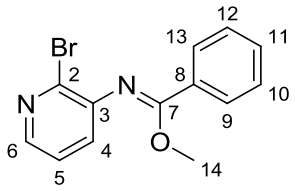
single isomer (1.0 g, 70%). mp: 76-78 °C; ν_{max} (neat)/cm^{-1} 3025 (w), 3006 (w), 2966 (w), 2835 (w), 1662 (s), 1585 (m), 1570 (m), 1492 (m), 1476 (m), 1443 (m); δ_H (400 MHz, $CDCl_3$) 7.39-7.31 (4H, m, H-3 and Ar-H), 7.28-7.23 (2H, m, Ar-H), 6.43 (1H, dd, *J* = 8.8 Hz, *J* = 2.9 Hz, H-4), 6.23 (1H, d, *J* = 2.9 Hz, H-6), 4.03 (3H, s, H-15), 3.65 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 159.9, 159.4, 147.9, 133.0, 131.3, 130.2, 128.6, 128.0, 110.1 (C-4), 107.9 (C-6), 107.0, 55.4 (C-15), 54.4 (C-14); HRMS (ESI) found *m/z* 320.0280 $[M+H]^+$, $C_{15}H_{15}{}^{79}BrNO_2$ requires 320.0281.

(*Z*)-Methyl 3-bromo-4-(methoxy(phenyl)methyleneamino)benzoate 135



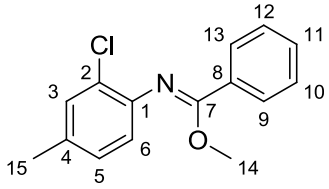
General procedure D was followed using methyl 4-amino-3-bromobenzoate (0.4 g, 1.7 mmol) and trimethyl orthobenzoate (0.3 mL, 1.9 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 18:1) afforded the title compound as a thick colourless oil and as a single isomer (0.4 g, 70%). ν_{max} (neat)/cm^{-1} 3062 (w), 2991 (w), 2948 (w), 2842 (w), 1718 (s), 1659 (s), 1591 (s), 1548 (w), 1494 (m), 1433 (s), 1391 (m); δ_H (400 MHz, $CDCl_3$) 8.22 (1H, d, *J* = 1.8 Hz, H-2), 7.77 (1H, dd, *J* = 8.3 Hz, *J* = 1.8 Hz, H-6), 7.37-7.30 (3H, m, Ar-H), 7.27-7.22 (2H, m, Ar-H), 6.66 (1H, d, *J* = 8.3 Hz, H-5), 4.05 (3H, s, H-16), 3.87 (3H, s, H-15); δ_C (100 MHz, $CDCl_3$) 165.9, 159.9, 151.7, 134.3 (C-2), 130.8, 130.6, 129.5, 128.6, 128.2, 125.5, 122.0 (C-5), 116.0, 54.7 (C-16), 52.1 (C-15); HRMS (ESI) found *m/z* 370.0044 $[M+Na]^+$, $C_{16}H_{14}{}^{79}BrNNaO_3$ requires 370.0049.

(*Z*)-Methyl *N*-2-bromopyridin-3-ylbenzimidate 138



General procedure D was followed using 3-amino-2-bromopyridine (0.6 g, 3.5 mmol) and trimethyl orthobenzoate (0.7 mL, 3.8 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 10:1) afforded the title compound as an orange oil and as a single isomer (0.6 g, 61%). ν_{max} (neat)/cm^{-1} 3460 (br), 3322 (br), 3187 (w), 2947 (w), 1720 (m), 1653 (s), 1601 (m), 1580 (m), 1549 (m), 1493 (w); δ_H (400 MHz, $CDCl_3$) 7.99 (1H, dd, *J* = 4.6 Hz, *J* = 1.6 Hz, H-6), 7.37-7.22 (5H, m, H-9, H-10, H-11, H-12 and H-13), 7.03 (1H, dd, *J* = 7.8 Hz, *J* = 4.6 Hz, H-5), 6.86 (1H, dd, *J* = 7.8 Hz, *J* = 1.6 Hz, H-4), 4.05 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 161.5, 144.5, 143.7 (C-6), 136.8, 130.7, 130.6, 129.6, 128.6, 128.3, 123.1 (C-5), 54.7 (C-14); HRMS (ESI) found *m/z* 312.9939 $[M+Na]^+$, $C_{13}H_{11}{}^{79}BrN_2NaO$ requires 312.9947.

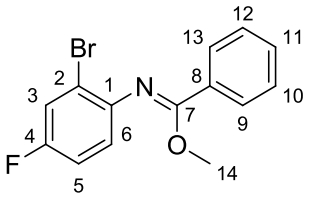
General procedure E for the preparation of benzimidates, exemplified by the preparation of (*Z*)-Methyl *N*-2-chloro-4-methylphenylbenzimidate 82



A mixture of 2-chloro-4-methylaniline (1.6 mL, 13.0 mmol) and trimethyl orthobenzoate (4.7 mL, 27.0 mmol) was heated at 90 °C for 53 h with the aid of Dean-Stark apparatus. Flash chromatography (SiO_2, petrol/diethyl ether 12:1) afforded the title compound as a yellow oil and as a single isomer (3.1 g, 93%). ν_{max} (neat)/cm^{-1} 3026 (br), 2985 (s), 1667 (s), 1609 (s), 1493 (m), 1435 (w), 1285 (s); δ_H (400 MHz, $CDCl_3$) 7.35-7.29 (3H, m, Ar-

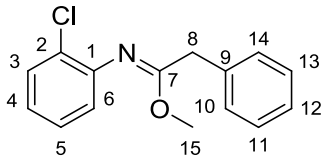
H), 7.25-7.22 (2H, m, Ar-H), 7.14-7.12 (1H, m, H-3), 6.84 (1H, dd, *J* = 8.0 Hz, *J* = 1.1 Hz, H-5), 6.54 (1H, d, *J* = 8.0 Hz, H-6), 4.03 (3H, s, H-14), 2.25 (3H, s, H-15); δ_C (100 MHz, $CDCl_3$) 160.2, 143.1, 133.3, 131.6, 130.0, 130.0, 128.6, 128.0 (2C), 125.3, 122.4 (C-6), 54.3 (C-14), 20.5 (C-15); HRMS (ESI) found *m/z* 282.0652 $[M+Na]^+$, $C_{15}H_{14}{}^{35}ClNNaO$ requires 282.0656.

(*Z*)-Methyl *N*-2-bromo-4-fluorophenylbenzimidate 84



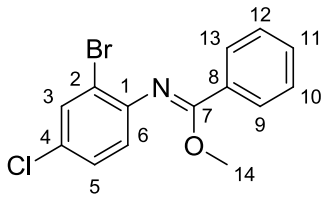
General procedure E was followed using 2-bromo-4-fluoroaniline (0.6 mL, 5.0 mmol) and trimethyl orthobenzoate (1.8 mL, 10.0 mmol) and was heated at 100 °C for 19 h. Flash chromatography (SiO_2, petrol/diethyl ether 30:1) afforded the title compound as a colourless oil and as a single isomer (1.2 g, 79%). ν_{max} (neat)/cm^{-1} 3065 (w), 2981 (w), 2945 (w), 2840 (w), 1723 (w), 1658 (s), 1599 (m), 1580 (w), 1493 (m), 1447 (s); δ_H (400 MHz, $CDCl_3$) 7.37-7.24 (6H, m, H-3, H-9, H-10, H-11, H-12 and H-13), 6.85-6.79 (1H, m, H-5), 6.56 (1H, dd, *J* = 8.8 Hz, *J* = 5.5 Hz, H-6), 4.04 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 160.1 (d, *J* = 138.7 Hz, C-4), 156.9, 143.6 (d, *J* = 3.2 Hz), 131.2, 130.3, 128.6, 128.1, 122.8 (d, $J_{6\text{-}F}$ = 8.1 Hz, C-6), 119.6 (d, *J* = 25.2 Hz), 116.1 (d, *J* = 21.9 Hz), 114.9 (d, $J_{5\text{-}F}$ = 21.9 Hz, C-5), 54.5 (C-14); δ_F (376 MHz, $CDCl_3$) -119.9 (1F, s); HRMS (ESI) found *m/z* 308.0083 $[M+H]^+$, $C_{14}H_{12}{}^{79}BrFNO$ requires 308.0081.

(*Z*)-Methyl *N*-2-chlorophenyl-2-phenylacetimidate 86



General procedure E was followed using 2-chloroaniline (0.3 g mL, 1.7 mmol) and (2,2,2-trimethoxyethyl)benzene **80** (0.7 g, 3.3 mmol) and was heated at 90 °C for 22 h. Flash chromatography (SiO_2, petrol/diethyl ether 18:1) afforded the title compound as a colourless oil and as a single isomer (0.62 g, 73%). ν_{max} (neat)/cm^{-1} 3063 (w), 3029 (w), 2986 (w), 2945 (w), 2842 (w), 1651 (s), 1603 (w), 1588 (m), 1495 (m), 1474 (m), 1455 (m); δ_H (400 MHz, $CDCl_3$) 7.42 (1H, app. d, *J* = 8.0 Hz, H-3), 7.32-7.19 (4H, m, H-5, H-11, H-12, and H-13), 7.14 (2H, app. d, *J* = 7.3 Hz, H-10 and H-14), 7.05-7.00 (1H, m, H-4), 6.84 (1H, dd, *J* = 7.8 Hz, *J* = 1.4 Hz, H-6), 3.89 (3H, s, H-15), 3.50 (2H, s, H-8); δ_C (100 MHz, $CDCl_3$) 163.0, 145.6, 135.2, 129.8, 129.1, 128.4, 127.3, 126.7, 125.7, 124.1 (C-4), 122.9 (C-6), 54.0 (C-15), 36.8 (C-8); HRMS (ESI) found *m/z* 260.0841 $[M+H]^+$, $C_{15}H_{15}{}^{35}ClNO$ requires 260.0837.

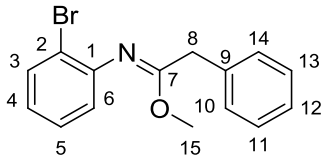
(*Z*)-Methyl *N*-2-bromo-4-chlorophenylbenzimidate 137



General procedure E was followed using 2-bromo-4-chloroaniline (1.0 g mL, 4.8 mmol) and trimethyl orthobenzoate (1.7 mL, 9.6 mmol) and was heated at 110 °C for 24 h. Flash chromatography (SiO_2, petrol/diethyl ether 30:1) afforded the title compound as an orange oil and as a single isomer (0.9 g, 57%). ν_{max} (neat)/cm^{-1} 3055 (w), 2944 (w), 1654 (s), 1601 (m), 1580 (w), 1493 (m), 1433 (s), 1381 (w), 1283 (s); δ_H (400 MHz, $CDCl_3$)

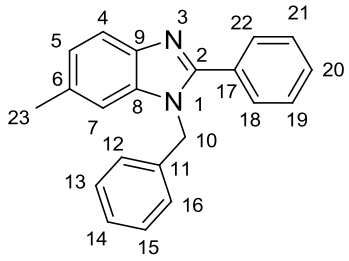
7.53 (1H, d, *J* = 2.2 Hz, H-3), 7.38-7.24 (5H, m, H-9, H-10, H-11, H-12 and H-13), 7.06 (1H, dd, *J* = 8.5 Hz, *J* = 2.2 Hz, H-5), 6.54 (1H, d, *J* = 8.5 Hz, H-6), 4.04 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 160.5, 146.0, 132.2 (C-3), 131.0, 130.4, 128.6, 128.2, 128.1, 128.0, 123.1 (C-6), 116.7, 54.6 (C-14); HRMS (ESI) found *m/z* 323.9790 $[M+H]^+$, $C_{14}H_{12}{}^{79}Br^{35}ClNO$ requires 323.9785.

(*Z*)-Methyl *N*-2-bromophenyl-2-phenylacetimidate 139



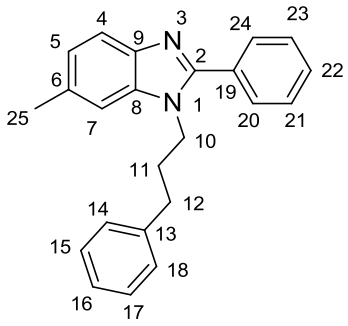
General procedure E was followed using 2-bromoaniline (0.4 g, 2.6 mmol) and (2,2,2-trimethoxyethyl)benzene **80** (1.0 g, 5.0 mmol) and was heated at 90 °C for 20 h. Flash chromatography (SiO_2, petrol/diethyl ether 18:1) afforded the title compound as a colourless oil and as a single isomer (0.76 g, 96%). ν_{max} (neat)/cm^{-1} 3062 (w), 3029 (w), 2944 (w), 2841 (w), 1650 (s), 1602 (w), 1585 (m), 1495 (m), 1468 (m), 1455 (m); δ_H (400 MHz, $CDCl_3$) 7.60 (1H, app. d, *J* = 8.0 Hz, H-3), 7.32-7.23 (4H, m, H-5, H-11, H-12 and H-13), 7.14 (2H, app. d, *J* = 7.1 Hz, H-10 and H-14), 6.95 (1H, app. t, *J* = 8.1 Hz, H-4), 6.82 (1H, app. d, *J* = 7.8 Hz, H-6), 3.89 (3H, s, H-15), 3.49 (2H, s, H-8); δ_C (100 MHz, $CDCl_3$) 162.9, 146.9, 135.1, 132.9 (C-3), 129.1, 128.4, 128.0, 126.7, 124.3 (C-4), 122.7 (C-6), 116.2, 54.1 (C-15), 36.8 (C-8); HRMS (ESI) found *m/z* 304.0335 $[M+H]^+$, $C_{15}H_{15}{}^{79}BrNO$ requires 304.0332.

General procedure F for the preparation of benzimidazoles from benzimidoyl chlorides, exemplified by the preparation of 1-Benzyl-6-methyl-2-phenyl-1*H*-benzo[*d*]imidazole 45



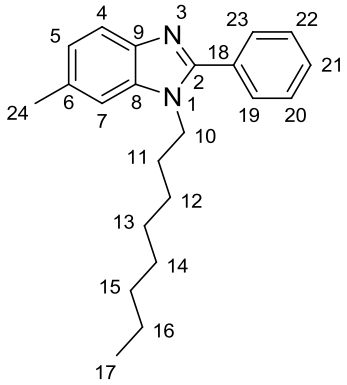
To a 5 mL microwave vial was added (*Z*)-*N*-(2-chloro-4-methylphenyl)benzimidoyl chloride **12** (100 mg, 0.4 mmol), palladium (II) acetate (4.0 mg, 0.02 mmol), cata*C*Xium® A (10 mg, 0.03 mmol) and sodium *t*-butoxide (80 mg, 0.8 mmol). This was capped and purged with N_2 three times and α,α,α-trifluorotoluene (1.0 mL) and benzylamine (60 µL, 0.6 mmol) were then added. This was heated in a microwave for 2 h at 135 °C. After cooling to room temperature the reaction mixture was diluted with diethyl ether (2 mL) and filtered through a Celite® pad, washing with diethyl ether (40 mL). This was then and concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/diethyl ether 2:1) afforded the title compound as a colourless solid (79 mg, 69%). δ_H (400 MHz, $CDCl_3$) 7.77 (1H, d, *J* = 8.2 Hz, H-4), 7.71-7.66 (2H, m, H-18 and H-22), 7.48-7.40 (3H, m, H-19 and H-20, H-21), 7.38-7.29 (3H, m, H-13 and H-14, H-15), 7.15 (1H, app. d, *J* = 8.2 Hz, H-5), 7.12 (2H, d, *J* = 6.9 Hz, H-12 and H-16), 7.02 (1H, app. s, H-7), 5.42 (2H, s, H-10), 2.45 (3H, s, H-23); δ_C (100 MHz, $CDCl_3$) 153.7, 141.3, 136.6, 136.4, 133.1, 130.2, 129.8, 129.2, 129.1, 128.7, 127.7, 125.9, 124.3, 119.5 (C-4), 110.3 (C-7), 48.2 (C-10), 21.9 (C-23); LRMS (ESI) *m/z* 299.2 (100%, $[M+H]^+$). Data consistent with literature data.[228]

6-Methyl-2-phenyl-1-(3-phenylpropyl)-1*H*-benzo[*d*]imidazole 57



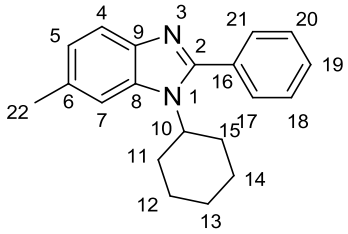
General procedure F was followed using (*Z*)-*N*-(2-chloro-4-methylphenyl)benzimidoyl chloride **12** (100 mg, 0.4 mmol) and 3-phenyl-1-propylamine (80 µL, 0.6 mmol). Flash chromatography (SiO_2, petrol/diethyl ether 2:1) afforded the title compound as a yellow crystalline solid (93 mg, 75%). mp: 80-82 °C; ν_{max} (neat)/cm^{-1} 3030 (br), 2980 (w), 2910 (br), 2850 (w), 1650 (m), 1621 (m), 1604 (w), 1585 (w), 1543 (w), 1497 (w), 1479 (s); δ_H (400 MHz, $CDCl_3$) 7.74 (1H, d, *J* = 8.2 Hz, H-4), 7.69-7.64 (2H, m, H-20 and H-24), 7.50-7.44 (3H, m, H-21 and H-22, H-23), 7.32-7.26 (2H, m, H-15 and H-17), 7.25-7.20 (1H, m, H-16), 7.14 (1H, app. d, *J* = 8.2 Hz, H-5), 7.12-7.07 (3H, m, H-7, H-14 and H-18), 4.20 (2H, t *J* = 7.7 Hz, H-10), 2.61 (2H, t, *J* = 7.4 Hz, H-12), 2.53 (3H, s, H-25), 2.16 (2H, quin, *J* = 7.6 Hz, H-11); δ_C (100 MHz, $CDCl_3$) 153.1, 141.3, 140.4, 135.9, 132.7, 130.7, 129.5, 129.2, 128.7, 128.6, 128.3, 126.3, 124.0, 119.5 (C-4), 110.0 (C-7), 43.9 (C-10), 32.8 (C-12), 31.0 (C-11), 21.9 (C-25); HRMS (ESI) found *m/z* 327.1855 $[M+H]^+$, $C_{23}H_{23}N_2$ requires 327.1856.

6-Methyl-1-octyl-2-phenyl-1*H*-benzo[*d*]imidazole 46



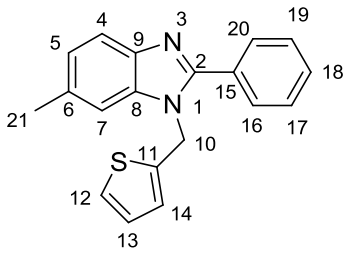
General procedure F was followed using (*Z*)-*N*-(2-chloro-4-methylphenyl)benzimidoyl chloride **12** (100 mg, 0.4 mmol) and octylamine (90 µL, 0.6 mmol). Flash chromatography (SiO_2, petrol/diethyl ether 3:1) afforded the title compound as a colourless oil (88 mg, 73%). ν_{max} (neat)/cm^{-1} 3423 (br), 2927 (s), 2856 (s), 1652 (m), 1486 (s), 1393 (m), 1331 (m), 1277 (w); δ_H (400 MHz, $CDCl_3$) 7.72- 7.69 (3H, m, H-4, H-19 and H-23), 7.54-7.49 (3H, m, H-20, H-21 and H-22), 7.20 (1H, app. s, H-7), 7.13 (1H, app. d, *J* = 8.2 Hz, H-5), 4.20-4.16 (2H, m, H-10), 2.54 (3H, s, H-24), 1.82-1.77 (2H, m, H-11), 1.29-1.17 (10H, m, H-12, H-13, H-14, H-15 and H-16), 0.87 (3H, t, *J* = 7.0 Hz, H-17); δ_C (100 MHz, $CDCl_3$) 153.3, 141.2, 135.8, 132.6, 130.9, 129.5, 129.3, 128.6, 123.9 (C-5), 119.4, 110.9 (C-19 and C-23), 44.6 (C-10), 31.7, 29.7, 29.1 (C-11), 28.9, 26.6, 22.6 (C-24), 21.9, 14.1 (C-17); HRMS (ESI) found *m/z* 321.2328 $[M+H]^+$, $C_{22}H_{29}N_2$ requires 321.2325.

1-Cyclohexyl-6-methyl-2-phenyl-1*H*-benzo[*d*]imidazole 58



General procedure F was followed using (*Z*)-*N*-(2-chloro-4-methylphenyl)benzimidoyl chloride **12** (100 mg, 0.4 mmol) and cyclohexylamine (70 µL, 0.6 mmol) and heated in the microwave for 30 min at 50 °C then 2 h at 135 °C. Flash chromatography (SiO_2, petrol/diethyl ether 2:1) afforded the title compound as an orange oil (103 mg, 94%). ν_{max} (neat)/cm^{-1} 3061 (w), 3031 (w), 2930 (br), 2856 (br), 1609 (m), 1580 (w), 1526 (w), 1495 (s), 1467 (s), 1449 (s); δ_H (400 MHz, $CDCl_3$); 7.70 (1H, d, *J* = 8.2 Hz, H-4), 7.65-7.61 (2H, m, H-17 and H-21), 7.54-7.49 (3H, m, H-18, H-19 and H-20), 7.45 (1H, app. s, H-7), 7.11 (1H, app. d, *J* = 8.2 Hz, H-5), 4.34 (1H, tt, *J* = 12.4 Hz, *J* = 3.8 Hz, H-10), 2.54 (3H, s, H-22), 2.41-2.28 (2H, m, Cy-H), 2.01-1.88 (4H, m, Cy-H), 1.80-1.73 (1H, m, Cy-H), 1.39-1.29 (3H, m, Cy-H); δ_C (125 MHz, $CDCl_3$) 153.3, 141.8, 134.2, 131.9, 131.3, 129.5, 129.4, 128.6, 123.5 (C-5), 119.7 (C-4), 112.5 (C-7), 56.9 (C-10), 31.4, 25.9, 25.3, 22.0 (C-22); HRMS (ESI) found *m/z* 291.1852 $[M+H]^+$, $C_{20}H_{23}N_2$ requires 291.1856.

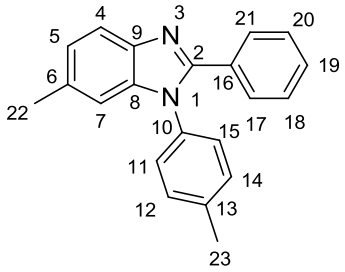
6-Methyl-2-phenyl-1-(thiophen-2-ylmethyl)-1*H*-benzo[*d*]imidazole 59



General procedure F was followed using (*Z*)-*N*-(2-chloro-4-methylphenyl)benzimidoyl chloride **12** (200 mg, 0.8 mmol) and 2-thiophenemethylamine (0.1 mL, 1.2 mmol) and heated in the microwave for 30 min at 50 °C then for 2 h at 135 °C. Flash

chromatography (SiO_2, petrol/diethyl ether 2:1) afforded the title compound as a brown crystalline solid (111 mg, 48%). mp: 170-172 °C; ν_{max} (neat)/cm^{-1} 3227 (br), 3066 (br), 3031 (br), 2929 (br), 2857 (w), 1714 (w), 1646 (m), 1620 (m), 1580 (w), 1531 (w), 1480 (m); δ_H (400 MHz, $CDCl_3$); 7.78-7.72 (3H, m, H-4, H-16 and H-20), 7.52-7.47 (3H, m, H-17, H-18 and H-19), 7.24 (1H, dd, *J* = 5.1 Hz, *J* = 0.9 Hz, H-12), 7.18-7.13 (2H, m, H-5 and H-7), 6.95 (1H, dd, *J* = 5.1 Hz, *J* = 3.5 Hz, H-13), 6.85 (1H, dd, *J* = 3.5 Hz, *J* = 0.9 Hz, H-14), 5.53 (2H, s, H-10), 2.49 (3H, s, H-21); δ_C (125 MHz, $CDCl_3$) 153.3, 141.3, 139.4, 136.0, 133.1, 130.1, 129.9, 129.3, 128.8, 127.1 (C-13), 125.4, 125.3, 124.4 (C-5), 119.6 (C-4), 110.2 (C-7), 44.1 (C-10), 21.9 (C-21); HRMS (ESI) found *m/z* 305.1098 $[M+H]^+$, $C_{19}H_{17}N_2S$ requires 305.1107.

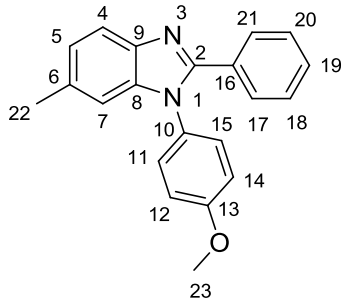
6-Methyl-2-phenyl-1-*p*-tolyl-1*H*-benzo[*d*]imidazole 47



General procedure F was followed using (*Z*)-*N*-(2-chloro-4-methylphenyl)benzimidoyl chloride **12** (100 mg, 0.4 mmol) and *p*-toluidine (61 mg, 0.6 mmol) and heated in the microwave for 30 min at 50 °C then for 2 h at 135 °C. Flash chromatography (SiO_2, petrol/ethyl acetate 6:1) and recrystalisation from diethyl ether afforded the title compound as a pale pink crystalline solid (60 mg, 53%). δ_H (400 MHz, $CDCl_3$) 7.78 (1H, d, *J* = 8.2 Hz, H-4), 7.61-7.57 (2H, m, H-17 and H-21), 7.35-7.26 (5H, m, H-12, H-14, H-18, H-19 and H-20), 7.22-7.15 (3H, m, H-5, H-11 and H-15), 7.03 (1H, app. s, H-7), 2.45 (6H, s, H-22 and H-23); δ_C (125 MHz, $CDCl_3$) 152.0, 141.1, 138.5, 137.6, 134.5, 133.3,

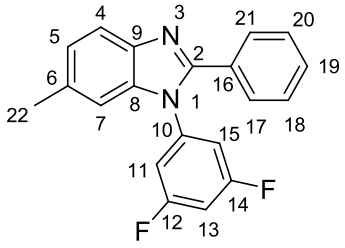
130.4, 130.2, 129.3, 129.2, 128.2, 127.2, 124.4, 119.3 (C-4), 110.3 (C-7), 21.8, 21.3; LRMS (ESI) *m/z* 299.2 (100%, $[M+H]^+$). Data consistent with literature data.[466]

1-(4-Methoxyphenyl)-6-methyl-2-phenyl-1*H*-benzo[*d*]imidazole 60



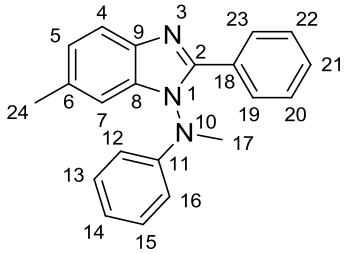
General procedure F was followed using (*Z*)-*N*-(2-chloro-4-methylphenyl)benzimidoyl chloride **12** (100 mg, 0.4 mmol) and *p*-anisidine (70 mg, 0.6 mmol) and heated in the microwave for 30 min at 50 °C then for 2 h at 135 °C. Flash chromatography (SiO_2, petrol/diethyl ether 1:2) and recrystalisation from diethyl ether afforded the title compound as a pink crystalline solid (55 mg, 46%). mp: 140-141 °C; ν_{max} (neat)/cm^{-1} 3042 (br), 2918 (br), 2850 (w), 1609 (m), 1582 (w), 1511 (s), 1471 (m), 1451 (m), 1389 (m), 1332 (m), 1310 (m); δ_H (400 MHz, $CDCl_3$) 7.77 (1H, d, *J* = 8.1 Hz, H-4), 7.61-7.58 (2H, m, H-17 and H-21), 7.34-7.27 (3H, m, H-18, H-19 and H-20), 7.25-7.20 (2H, m, H-11 and H-15), 7.16 (1H, app. d, *J* = 8.1 Hz, H-5), 7.03-6.98 (3H, m, H-7, H-12 and H-14) 3.87 (3H, s, H-23), 2.45 (3H, s, H-22); δ_C (125 MHz, $CDCl_3$) 159.4, 152.0, 141.0, 137.9, 133.3, 130.2, 129.8, 129.3, 129.2, 128.6, 128.2, 124.4 (C-5), 119.3 (C-4), 115.0, 110.3, 55.5 (C-23), 21.8 (C-22); HRMS (ESI) found *m/z* 315.1491 $[M+H]^+$, $C_{21}H_{19}N_2O$ requires 315.1492.

1-(3,5-Difluorophenyl)-6-methyl-2-phenyl-1*H*-benzo[*d*]imidazole 61



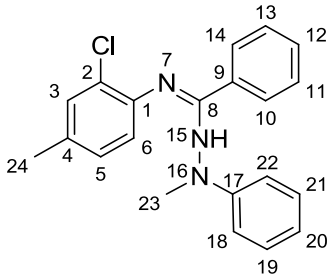
General procedure F was followed using (*Z*)-*N*-(2-chloro-4-methylphenyl)benzimidoyl chloride **12** (200 mg, 0.8 mmol) and 3,5-difluoroaniline (146 mg, 1.1 mmol) and heated in the microwave for 30 min at 50 °C then for 2 h at 135 °C. Flash chromatography (SiO_2, petrol/diethyl ether 2:1) and recrystalisation from diethyl ether afforded the title compound as pale pink crystalline solid (115 mg, 45%). mp: 164-167 °C; ν_{max} (neat)/cm^{-1} 3055 (br), 1712 (m), 1615 (m), 1603 (s), 1480 (m), 1445 (m), 1362 (m), 1338 (m), 1309 (m); δ_H (400 MHz, $CDCl_3$) 7.77 (1H, d, *J* = 8.2 Hz, H-4), 7.56 (2H, app. d, *J* = 7.2 Hz, H-17 and H-21), 7.43-7.33 (3H, m, H-18 and H-10, H-20), 7.19 (1H, app. d, *J* = 8.2 Hz, H-5), 7.08 (1H, app. s, H-7), 6.94 (1H, td, *J* = 8.7 Hz, *J* = 2.0 Hz, H-13), 6.90-6.84 (2H, m, H-11 and H-15), 2.49 (3H, s, H-22); δ_C (125 MHz, $CDCl_3$) 163.3 (dd, *J* = 251.4 Hz, *J* = 14.1 Hz), 151.7, 141.1, 139.3 (t, *J* = 12.2 Hz), 136.7, 134.0, 129.7, 129.5, 129.3, 128.5, 125.0 (C-5), 119.7 (C-4), 111.1 (dd, *J* = 27.4 Hz, *J* = 11.5 Hz, C-11 and C-15), 109.9, 104.3 (*J* = 25.3 Hz, C-13), 21.8 (C-22); δ_F (376 MHz, $CDCl_3$) -106.66 (2F, s); HRMS (ESI) found *m/z* 321.1195 $[M+H]^+$, $C_{20}H_{15}F_2N_2$ requires 321.1198.

_N_,6-Dimethyl-_N_,2-diphenyl-1_H_-benzo[_d_]imidazol-1-amine 48



General procedure F was followed using (*Z*)-*N*-(2-chloro-4-methylphenyl)benzimidoyl chloride **12** (100 mg, 0.4 mmol) and 1-methyl-1-phenylhydrazine (0.07 mL, 0.6 mmol) and heated in the microwave for 1 h at 125 °C. Flash chromatography (SiO_2, petrol/diethyl ether 3:1) afforded the title compound as a brown oil (45 mg, 38%). ν_{max} (neat)/cm^{-1} 3423 (br), 1599 (m), 1499 (m), 1335 (w), 1274 (w); δ_H (400 MHz, $CDCl_3$) 8.04-8.02 (2H, m, Ar-H), 7.75 (1H, app. d, *J* = 8.2 Hz, H-5), 7.44-7.40 (3H, m, Ar-H), 7.33-7.27 (2H, m, H-20 and H-22), 7.14 (1H, d, *J* = 8.2 Hz, H-4), 6.97 (1H, t, *J* = 7.4 Hz, H-21), 6.85 (1H, app. s, H-7), 6.73-6.70 (2H, m, H-19 and H-23) 3.42 (3H, s, H-17), 2.40 (3H, s, H-24); δ_C (100 MHz, $CDCl_3$) 151.2, 147.6, 139.5, 133.5, 133.2, 130.0, 129.7, 129.2, 128.6, 128.4, 124.9 (C-5), 120.5, 120.2, 112.7 (C-19 and 23), 110.3 (C-7), 39.8 (C-17), 21.8 (C-24); HRMS (ESI) found *m/z* 314.1652 $[M+H]^+$, $C_{21}H_{20}N_3$ requires 314.1653.

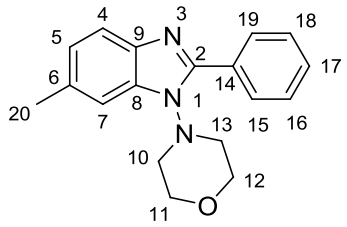
(_Z_)-_N_'-(2-Chloro-4-methylphenyl)-_N_'-methyl-_N_'-phenylbenzimidohydrazide 49



To a 5 mL microwave vial was added (*Z*)-*N*-(2-chloro-4-methylphenyl)benzimidoyl chloride **12** (100 mg, 0.4 mmol), palladium (II) acetate (4.0 mg, 0.02 mmol), Davephos (10.0 mg, 0.03 mmol) and sodium *t*-butoxide (109 mg, 1.2 mmol). This was capped and

purged with N_2 three times and toluene (1 mL) and 1-methyl-1-phenylhydrazine (0.07 mL, 0.6 mmol) were then added. The reaction mixture was heated at 80 °C for 23 h. After cooling to room temperature the reaction mixture was diluted with diethyl ether (2 mL) and filtered through a Celite® pad, washing with diethyl ether (40 mL) and then concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/diethyl ether 2:1) afforded the title compound as a dark red oil (54 mg, 27%). ν_{max} (neat)/cm^{-1} 3318 (br), 1595 (s), 1569 (m), 1493 (s), 1374 (w), 1300 (w); δ_H (400 MHz, $CDCl_3$) 7.98 (1H, br. s, H-15), 7.58 (2H, d, *J* = 7.2 Hz, Ar-H), 7.44-7.27 (5H, m, Ar-H), 7.16 (1H, app. s, H-3), 7.09 (2H, d, *J* = 8.0 Hz Ar-H), 6.95-6.91 (1H, t, *J* = 7.3 Hz, Ar-H), 6.72 (1H, app. d, *J* = 8.2 Hz, H-5), 6.44 (1H, d, *J* = 8.2 Hz, H-6), 3.18 (3H, s, H-23), 2.23 (3H, s, H-24); δ_C (100 MHz, $CDCl_3$) 159.8, 151.2, 134.4, 134.2, 132.7, 130.2, 130.0, 128.9, 128.7, 128.4, 127.6 (C-5), 125.9, 124.2 (C-6), 120.4, 115.8 (C-3), 41.5 (C-23), 20.5 (C-24); HRMS (ESI) found *m/z* 350.1420 $[M+H]^+$, $C_{21}H_{21}{}^{35}ClN_3$ requires 350.1419.

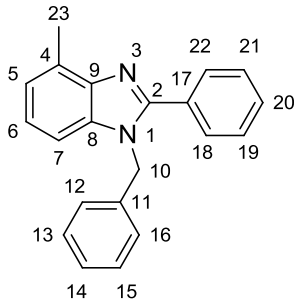
4-(6-Methyl-2-phenyl-1*H*-benzo[*d*]imidazol-1-yl)morpholine 62



General procedure F was followed using (*Z*)-*N*-(2-chloro-4-methylphenyl)benzimidoyl chloride **12** (100 mg, 0.4 mmol) and 4-aminomorpholine (60 µL, 0.6 mmol) and heated in the microwave for 30 min at 50 °C then for 2 h at 135 °C. Flash chromatography (SiO_2, petrol/diethyl ether 1:1) and recrystalisation from diethyl ether afforded the title compound as a white crystalline solid (52 mg, 47%). mp: 169-170 °C; ν_{max} (neat)/cm^{-1} 3024 (br), 2961 (w), 2899 (w), 2859 (br), 1602 (w), 1580 (w), 1521 (w), 1473 (m), 1456 (m), 1445 (m); δ_H (400 MHz, $CDCl_3$) 8.12-8.07 (2H, m, H-15 and H-19), 7.70 (1H, d, *J* =

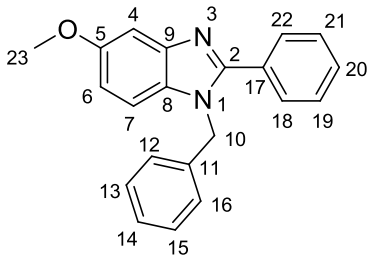
8.2 Hz, H-4), 7.53-7.43 (4H, m, H-7, H-16 and H-17, H-18), 7.12 (1H, app. d, *J* = 8.2 Hz, H-5), 4.07-3.96 (4H, m, H-11 and H-12), 3.86-3.73 (2H, m, H-10 and H-13), 3.14-3.07 (2H, m, H-10' and H-13'), 2.53 (3H, s, H-20); δ_C (125 MHz, $CDCl_3$) 151.2, 139.8, 133.0, 132.7, 129.9, 129.6, 129.4, 128.1, 124.1 (C-5), 120.4 (C-4), 111.6, 67.0, 52.8 (C-10 and 13, C-11 and C-12), 21.9 (C-20); HRMS (ESI) found *m/z* 294.1603 $[M+H]^+$, $C_{18}H_{20}N_3O$ requires 294.1601.

1-Benzyl-4-methyl-2-phenyl-1*H*-benzo[*d*]imidazole 50



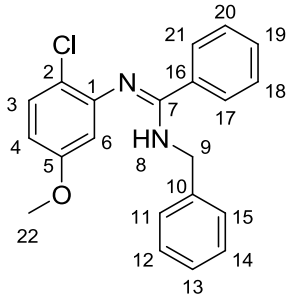
General procedure F was followed using (*Z*)-*N*-(2-chloro-6-methylphenyl)benzimidoyl chloride **14** (200 mg, 0.8 mmol) and benzylamine (0.1 mL, 1.1 mmol) and heated in the microwave for 30 min at 50 °C then for 2 h at 135 °C. Flash chromatography (SiO_2, petrol/diethyl ether 3:1) afforded the title compound as a yellow solid (205 mg, 91%). δ_H (500 MHz, $CDCl_3$) 7.69-7.66 (2H, m, Ar-H), 7.48-7.43 (3H, m, Ar-H), 7.35-7.29 (3H, m, Ar-H), 7.17-7.08 (4H, m, Ar-H), 7.06 (1H, d, *J* = 7.9 Hz, Ar-H), 5.43 (2H, s, H-10), 2.77 (3H, s, H-23); δ_C (125 MHz, $CDCl_3$) 153.5, 142.4, 136.5, 135.5, 130.1, 129.8, 129.6, 129.4, 128.9, 128.7, 127.7, 126.0, 123.0, 122.9, 107.9, 48.4 (C-10), 16.8 (C-23); LRMS (ESI) *m/z* 321.1 (100%, $[M+Na]^+$). Data consistent with literature data.[243]

1-Benzyl-5-methoxy-2-phenyl-1*H*-benzo[*d*]imidazole 51



General procedure F was followed using (*Z*)-*N*-(2-chloro-5-methoxyphenyl)benzimidoyl chloride **8** (100 mg, 0.4 mmol) and benzylamine (60 µL, 0.6 mmol). Flash chromatography (SiO_2, petrol/diethyl ether 1:3) afforded the title compound as a pale yellow crystalline solid (89 mg, 80%). δ_H (500 MHz, $CDCl_3$) 7.71-7.68 (2H, m, Ar-H), 7.49-7.44 (3H, m, Ar-H), 7.39-7.30 (4H, m, Ar-H), 7.13-7.07 (3H, m, Ar-H), 6.90 (1H, dd, *J* = 8.8 Hz, *J* = 2.3 Hz, H-6), 5.45 (2H, s, H-10), 3.89 (3H, s, H-23); δ_C (125 MHz, $CDCl_3$) 156.6, 154.3, 143.9, 136.4, 130.6, 130.1, 129.8, 129.2, 129.0, 128.7, 127.8, 125.9, 113.1, 110.9 (C-6), 102.0, 55.8 (C-23), 48.4 (C-10); LRMS (ESI) *m/z* 315.1 (100%, $[M+H]^+$). Data consistent with literature data.[243]

(*Z*)-*N*-Benzyl-*N*'-(2-chloro-5-methoxyphenyl)benzimidamide 52

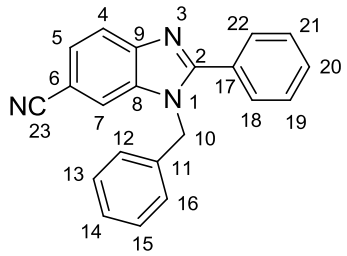


To a 5 mL microwave vial was added (*Z*)-*N*-(2-chloro-5-methoxyphenyl)benzimidoyl chloride **8** (100 mg, 0.4 mmol), palladium (II) acetate (4.0 mg, 0.02 mmol), Davephos (10 mg, 0.03 mmol) and sodium *t*-butoxide (103 mg, 1.2 mmol). This was capped and purged with N_2 three times and toluene (1 mL) and benzylamine (0.06 mL, 0.6 mmol) were then added. The reaction mixture was heated at 100 °C for 42 h. After cooling to room

temperature the reaction mixture was diluted with diethyl ether (2 mL) and filtered through a Celite® pad, washing with diethyl ether (40 mL) and then concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/diethyl ether 3:1) afforded the title compound as a yellow crystalline solid (22 mg, 18%). mp: 88-91 °C; ν_{max} (neat)/cm^{-1} 3423 (br), 1625 (s), 1586 (m), 1513 (m), 1471 (m), 1289 (w), 1130 (w); δ_H (400 MHz, $CDCl_3$) 7.55-7.49 (2H, m, Ar-H), 7.45-7.28 (8H, m, Ar-H), 7.15 (1H, d, *J* = 8.7 Hz, H-3), 6.42-6.36 (1H, m, H-4), 6.23-6.16 (1H, m, H-6), 5.18 (1H, br. s, H-8), 4.75 (2H, br. s, H-9), 3.63 (3H, s, H-22); δ_C (125 MHz, $CDCl_3$) 158.4, 157.9, 138.7, 135.0, 129.5, 129.0, 128.7 (2C), 128.3, 128.1, 127.9, 127.4, 118.8, 109.4 (C-6), 108.7 (C-4), 55.3 (C-9), 46.1 (C-22); HRMS (ESI) found *m/z* 351.1252 $[M+H]^+$, $C_{21}H_{20}{}^{35}ClN_2O$ requires 351.1259.

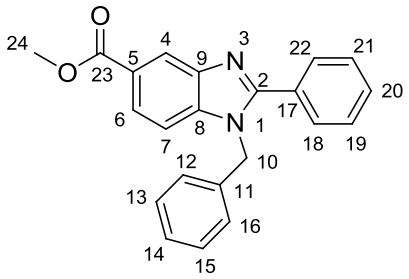
To a 5 mL microwave vial was added (*Z*)-*N*-(2-chloro-5-methoxyphenyl)benzimidoyl chloride **8** (150 mg, 0.5 mmol) and sodium *t*-butoxide (77 mg, 0.9 mmol). This was capped and purged with N_2 three times and then toluene (1.5 mL) and benzylamine (90 µL, 0.9 mmol) were added. The reaction mixture was heated at room temperature for 24 h. The reaction mixture was then diluted with diethyl ether (2 mL) and filtered through a Celite® pad, washing with diethyl ether (40 mL) and concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/diethyl ether 3:1) afforded the title compound as yellow crystalline solid (123 mg, 65%). Data as reported previously.

1-Benzyl-2-phenyl-1*H*-benzo[*d*]imidazole-6-carbonitrile 63



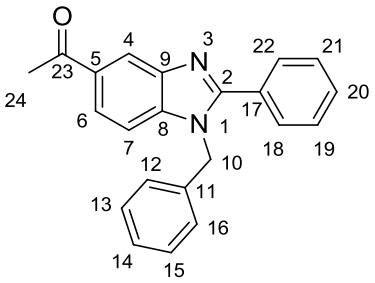
General procedure F was followed using (*Z*)-*N*-(2-Chloro-4-cyanophenyl)benzimidoyl chloride **18** (200 mg, 0.7 mmol) and benzylamine (0.1 mL, 1.1 mmol) and heated in the microwave for 30 min at 50 °C then 2 h at 135 °C. Flash chromatography (SiO_2, petrol/diethyl ether 2:1) afforded the title compound as a yellow crystalline solid (105 mg, 47%). mp: 161-163 °C; ν_{max} (neat)/cm^{-1} 3020 (br), 2226 (m), 1606 (m), 1579 (m), 1517 (m), 1497 (m), 1461 (m); δ_H (400 MHz, $CDCl_3$) 7.88 (1H, d, *J* = 8.3 Hz, H-4), 7.70 (2H, app. d, *J* = 7.5 Hz, H-18 and H-22), 7.56-7.44 (5H, m, H-5, H-7, H-19, H-20 and H-21), 7.30-7.30 (3H, m, H-13, H-14 and H-15), 7.07 (2H, app. d, *J* = 7.1 Hz, H-12 and H-16), 5.48 (2H, s, H-10); δ_C (100 MHz, $CDCl_3$) 157.4, 146.1, 135.6, 135.2, 130.7, 129.3, 129.3, 129.0, 129.0, 128.3, 126.2, 125.9 (C-12 and C-16), 120.9 (C-4), 119.8, 115.4, 105.7, 48.7 (C-10); HRMS (ESI) found *m/z* 310.1329 $[M+H]^+$, $C_{21}H_{16}N_3$ requires 310.1339.

Methyl 1-benzyl-2-phenyl-1*H*-benzo[*d*]imidazole-5-carboxylate 64



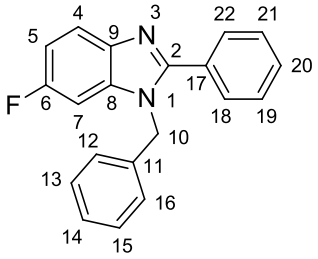
General procedure F was followed using (*Z*)-methyl 4-chloro-3-(chloro(phenyl) methyleneamino)benzoate **20** (200 mg, 0.8 mmol) and benzylamine (0.1 mL, 1.0 mmol) and heated in the microwave for 30 min at 50 °C then 2 h at 135 °C. Flash chromatography (SiO_2, petrol/diethyl ether 2:1) afforded the title compound as a thick yellow oil (58 mg, 26%). ν_{max} (neat)/cm^{-1} 3054 (br), 2953 (br), 1713 (s), 1618 (w), 1525 (w), 1496 (w), 1475 (m), 1462 (m), 1436 (m), 1382 (m); δ_H (400 MHz, $CDCl_3$) 8.58 (1H, d, *J* = 1.1 Hz, H-4), 7.98 (1H, dd, *J* = 8.5 Hz, *J* = 1.1 Hz, H-6), 7.71-7.67 (2H, m, H-18 and H-22), 7.54-7.44 (3H, m, H-19, H-20 and H-21), 7.37-7.30 (3H, m, H-13, H-14 and H-15), 7.23 (1H, d, *J* = 8.5 Hz, H-7), 7.10-7.06 (2H, m, H-12 and H-16), 5.48 (2H, s, H-10), 3.95 (3H, s, H-24); δ_C (125 MHz, $CDCl_3$) 167.6, 155.9, 142.8, 139.3, 135.8, 130.3, 129.6, 129.3, 129.2, 128.9, 128.0, 125.9 (C-12 and C-16), 124.9, 124.6 (C-6), 122.3 (C-4), 110.2 (C-7), 52.1 (C-23), 48.5 (C-10); HRMS (ESI) found *m/z* 343.1431 $[M+H]^+$, $C_{22}H_{19}N_2O_2$ requires 343.1441.

1-(1-Benzyl-2-phenyl-1*H*-benzo[*d*]imidazol-5-yl)ethanone 65



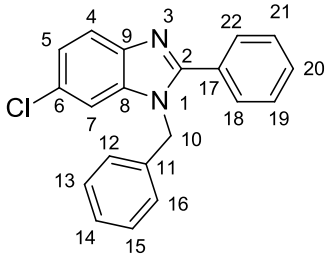
General procedure F was followed using (*Z*)-*N*-(5-acetyl-2-chlorophenyl)benzimidoyl chloride **22** (100 mg, 0.3 mmol) and benzylamine (0.06 mL, 0.5 mmol) and heated in the microwave for 30 min at 50 °C then 2 h at 135 °C. Flash chromatography (SiO_2, petrol/ethyl acetate 6:1) afforded the title compound as thick orange oil (80 mg, 71%). ν_{max} (neat)/ cm^{-1} 3054 (br), 1676 (s), 1614 (m), 1475 (w), 1453 (m), 1432 (w), 1382 (m), 1357 (m), 1333 (w); δ_H (400 MHz, $CDCl_3$) 8.47 (1H, d, *J* = 1.2 Hz, H-4), 7.93 (1H, dd, *J* = 8.5 Hz, *J* = 1.2 Hz, H-6), 7.71-7.67 (2H, m, H-18 and H-22), 7.51-7.44 (3H, m, H-19, H-20 and H-21), 7.36-7.29 (3H, m, H-13, H-14 and H-15), 7.24 (1H, d, *J* = 8.5 Hz, H-7), 7.09-7.04 (2H, m, H-12 and H-16), 5.48 (2H, s, H-10), 2.67 (3H, s, H-24); δ_C (100 MHz, $CDCl_3$) 197.9, 156.0, 142.8, 139.3, 135.8, 132.5, 130.3, 129.5, 129.2, 129.2, 128.9, 128.0, 125.9 (C-12 and C-16), 123.3 (C-6), 121.5 (C-4), 110.5 (C-7), 48.5 (C-10), 26.7 (C-24); HRMS (ESI) found *m/z* 327.1495 $[M+H]^+$, $C_{22}H_{19}N_2O$ requires 327.1492.

1-Benzyl-6-fluoro-2-phenyl-1*H*-benzo[*d*]imidazole 53



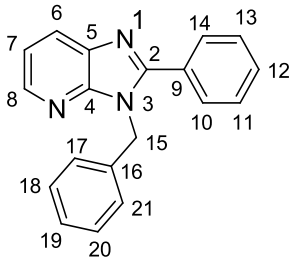
General procedure F was followed using (*Z*)-*N*-(2-chloro-4-fluorophenyl)benzimidoyl chloride **24** (100 mg, 0.4 mmol) and benzylamine (70.0 µL, 0.6 mmol) and heated in the microwave for 30 min at 50 °C then for 2 h at 135 °C. Flash chromatography (SiO_2, petrol/diethyl ether 3:1) afforded the title compound as pale pink crystalline solid (85 mg, 75%). mp: 132-135 °C; ν_{max} (neat)/cm^{-1} 3423 (br), 1620 (s), 1439 (s), 1391 (m), 1143 (m), 1106 (m); δ_H (400 MHz, $CDCl_3$) 7.79 (1H, dd, *J* = 8.8 Hz, *J* = 4.8 Hz, H-7) 7.70-7.66 (2H, m, Ar-H), 7.51-7.41 (3H, m, Ar-H), 7.38-7.29 (3H, m, Ar-H), 7.12-7.02 (3H, m, H-5 and Ar-H), 6.88 (1H, dd, *J* = 8.6 Hz, *J* = 2.4 Hz, H-4), 5.41 (2H, s, H-10); δ_C (100 MHz, $CDCl_3$) 159.7 (d, *J* = 240.1 Hz, C-6), 154.9 (d, *J* = 2.9 Hz), 139.6, 136.2 (d, *J* = 13.0 Hz), 135.8, 130.0, 129.8, 129.2 (2C), 128.8, 128.0, 125.9, 120.7 (d, *J* = 10.0 Hz, C-7), 111.0 (d, *J* = 25.2 Hz, C-5), 97.3 (d, *J* = 27.5 Hz, C-4), 48.5 (C-10); δ_F (376 MHz, $CDCl_3$) -118.1 (1F, s); HRMS (ESI) found *m/z* 325.1112 $[M+Na]^+$, $C_{20}H_{15}FN_2Na$ requires 325.1111.

1-Benzyl-6-chloro-2-phenyl-1*H*-benzo[*d*]imidazole 66



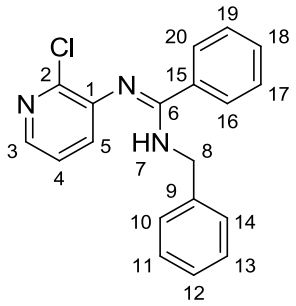
General procedure F was followed using (*Z*)-*N*-(2-bromo-4-chlorophenyl)benzimidoyl chloride **28** (100 mg, 0.5 mmol) and benzylamine (70 µL, 0.6 mmol) and heated in the microwave for 30 min at 50 °C then 2 h at 100 °C. Flash chromatography (SiO_2, petrol/ethyl acetate 7:1) afforded the title compound as a colourless crystalline solid (98 mg, 67%). mp: 159-161 °C; ν_{max} (neat)/cm^{-1} 3066 (w), 1611 (w), 1525 (w), 1497 (s), 1461 (s), 1442 (m), 1386 (m), 1358 (s), 1327 (m); δ_H (400 MHz, $CDCl_3$) 7.77 (1H, d, *J* = 8.6 Hz, H-4), 7.70-7.65 (2H, m, H-18 and H-22), 7.50-7.42 (3H, m, H-19, H-20 and H-21), 7.38-7.31 (3H, m, H-13, H-14, and H-15), 7.28 (1H, dd, *J* = 8.6 Hz, *J* = 1.8 Hz, H-5), 7.20 (1H, d, *J* = 1.8 Hz, H-7), 7.09 (2H, app. d, *J* = 6.8 Hz, H-12 and H-16), 5.42 (2H, s, H-10); δ_C (100 MHz, $CDCl_3$) 155.0, 141.8, 136.7, 135.8, 130.2, 129.6, 129.2, 129.2, 128.8, 128.7, 128.0, 125.9 (C-12 and C-16), 123.4 (C-5), 120.8 (C-4), 110.6 (C-7), 48.5 (C-10); HRMS (ESI) found *m/z* 319.1000 $[M+H]^+$, $C_{20}H_{16}{}^{35}ClN_2$ requires 319.0997.

3-Benzyl-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine 54



General procedure F was followed using (*Z*)-*N*-(2-chlorophenyl)nicotinimidoyl chloride **36** (100 mg, 0.4 mmol) and benzylamine (0.07 mL, 0.6 mmol) and heated in the microwave for 30 min at 50 °C then 2 h at 135 °C. Flash chromatography (SiO_2, petrol/diethyl ether 1:1) afforded the title compound as a brown crystalline solid (57 mg, 50%). mp: 117-119 °C; ν_{max} (neat)/cm^{-1} 2923 (s), 1597 (s), 1470 (m), 1451 (s), 1418 (m), 1381 (m), 1296 (m); δ_H (500 MHz, $CDCl_3$) 8.49 (1H, d, *J* = 4.6 Hz, H-8), 8.24 (1H, d, *J* = 8.0 Hz, H-6), 7.73 (2H, app. d, *J* = 7.5 Hz, H-10 and H-14), 7.58-7.47 (3H, m, H-11, H-13, H-19), 7.37 (1H, dd, *J* = 8.0 Hz, *J* = 4.6 Hz, H-7), 7.33-7.25 (3H, m, H-12, H-18 and H-20), 7.10 (2H, app. d, *J* = 7.0 Hz, H-17 and H-21) 5.66 (2H, s, H-15); δ_C (125 MHz, $CDCl_3$) 154.1, 148.0, 145.1 (C-8), 136.2, 131.1, 129.4, 129.0, 129.0, 128.8, 128.2, 127.9, 126.9, 126.5, 119.6 (C-7), 47.0 (C-15); HRMS (ESI) found *m/z* 308.1161 $[M+Na]^+$, $C_{19}H_{15}N_3Na$ requires 308.1158.

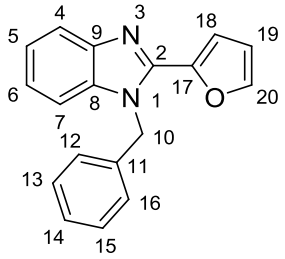
(*Z*)-*N*-Benzyl-*N*'-(2-chloropyridin-3-yl)benzimidamide 55



To a 5 mL microwave vial was added (*Z*)-*N*-(2-chlorophenyl)nicotinimidoyl chloride **36** (100 mg, 0.4 mmol), palladium (II) acetate (4.0 mg, 0.02 mmol), Davephos (11 mg, 0.03 mmol) and sodium *t*-butoxide (115 mg, 1.2 mmol). This was capped and purged with N_2 three times and toluene (1.0 mL) and benzylamine (70.0 µL, 0.6 mmol) were then added. The reaction mixture was heated at 120 °C for 42 h. After cooling to room temperature the reaction mixture was diluted with diethyl ether (2 mL) and filtered through a Celite® pad, washing with diethyl ether (40 mL) and then concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/diethyl ether 1:1) afforded and the title compound as a colourless solid (59 mg, 47%). mp: 117-119 °C; ν_{max} (neat)/cm^{-1} 3244 (br), 3025 (w), 1618 (s), 1598 (m), 1536 (m), 1493 (m), 1452 (m), 1425 (w), 1397 (m); δ_H (500 MHz, $CDCl_3$) 7.84-7.79 (1H, m, Ar-H), 7.51-7.19 (10H, m, Ar-H), 6.92-6.80 (2H, m, Ar-H), 5.29 (1H, br. s, H-7), 4.74 (2H, br. s, H-8); δ_C (125 MHz, $CDCl_3$) 158.8, 145.0, 145.0, 141.9, 138.5, 134.2, 131.5, 129.9, 128.7, 128.5, 128.1, 127.9, 127.5, 122.5, 44.0 (C-8); HRMS (ESI) found *m/z* 322.1098 $[M+H]^+$, $C_{19}H_{17}{}^{35}ClN_3$ requires 322.1106.

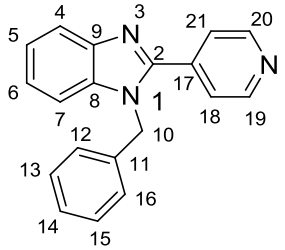
3-Benzyl-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine 54 was also isolated by flash column chromatography as a brown crystalline solid (5.0 mg, 8%). Data as reported previously.

1-Benzyl-2-(furan-2-yl)-1*H*-benzo[*d*]imidazole 56



General procedure F was followed using (*Z*)-*N*-(2-chlorophenyl)furan-2-carbimidoyl chloride **38** (100 mg, 0.4 mmol) and benzylamine (70 µL, 0.6 mmol) and heated in the microwave for 30 min at 50 °C then for 2 h at 135 °C. Flash chromatography (SiO_2, petrol/diethyl ether 2:1) afforded the title compound as a yellow solid (88 mg, 80%). δ_H (500 MHz, $CDCl_3$) 7.84 (1H, app. d, *J* = 7.9 Hz, H-4), 7.56 (1H, app. d, *J* = 1.2 Hz, H-20), 7.32-7.22 (6H, m, H-5, H-6, H-7, H-13, H-14 and H-15), 7.13 (2H, app. d, *J* = 6.9 Hz, H-12 and H-16), 7.07 (1H, app. d, *J* = 3.5 Hz, H-18), 6.54 (1H, dd, *J* = 3.5 Hz, *J* = 1.8 Hz, H-19), 5.67 (2H, s, H-10); δ_C (125 MHz, $CDCl_3$) 145.2, 144.5, 144.0, 143.1, 136.4, 135.8, 128.9, 127.7, 126.2 (C-12 and C-16), 123.2, 122.9, 119.9, 112.7 (C-18), 111.9 (C-19), 110.0, 48.3 (C-10); LRMS (ESI) *m/z* 297.1 (100%, $[M+Na]^+$). Data consistent with literature data.[243]

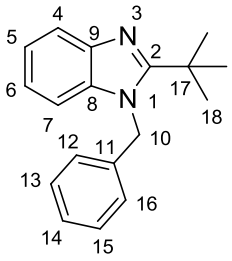
1-Benzyl-6-methyl-2-(pyridin-4-yl)-1*H*-benzo[*d*]imidazole 67



General procedure F was followed using (*Z*)-*N*-(2-chlorophenyl)isonicotinimidoyl chloride **40** (200 mg, 0.8 mmol), palladium (II) acetate (18 mg, 0.08 mmol), cataCXium A (40 mg, 0.1 mmol) and benzylamine (0.1 mL, 1.6 mmol) and heated in the microwave

at 50 °C for 30 min then 135 °C for 4 h. Flash chromatography (SiO_2, petrol/ethyl acetate 1:3) afforded the title compound as a thick orange oil (163 mg, 72%). ν_{max} (neat)/cm^{-1} 3050 (br), 2979 (w), 2928 (w), 1605 (m), 1554 (w), 1518 (w), 1497 (m), 1476 (m), 1453 (w), 1415 (w); δ_H (400 MHz, $CDCl_3$) 8.72 (2H, d, *J* = 5.7 Hz, H-19 and H-20), 7.91 (1H, app. d, *J* = 7.9 Hz, H-4), 7.61 (2H, dd, *J* = 4.5 Hz, *J* = 1.5 Hz, H-18 and H-21), 7.39-7.28 (6H, m, H-5, H-6, H-7, H-13, H-14 and H-15), 7.10 (2H, app. d, *J* = 7.1 Hz, H-12 and H-16), 5.50 (2H, s, H-10); δ_C (100 MHz, $CDCl_3$) 151.1, 150.4 (C-19 and C-20), 143.1, 137.7, 136.3, 135.8, 129.3, 128.1, 125.8 (C-12 and C-16), 124.0, 123.2, 123.2, 120.5 (C-4), 110.6, 48.4 (C-10); HRMS (ESI) found *m/z* 286.1336 $[M+H]^+$, $C_{19}H_{16}N_3$ requires 286.1339.

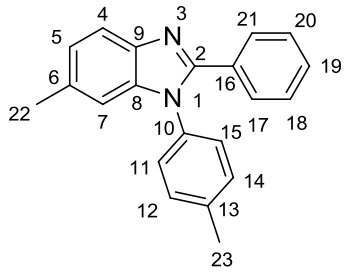
1-Benzyl-2-*tert*-butyl-1*H*-benzo[*d*]imidazole 68



General procedure F was followed using (*Z*)-*N*-(2-chlorophenyl)pivalimidoyl chloride **42** (200 mg, 0.9 mmol) and benzylamine (0.2 mL, 1.4 mmol) and heated in the microwave for 30 min at 50 °C then for 2 h at 135 °C. Flash chromatography (SiO_2, petrol/diethyl ether 2:1) afforded the title compound as a yellow crystalline solid (200 mg, 84%). mp: 161-163 °C; ν_{max} (neat)/cm^{-1} 3056 (w), 3026 (w), 2992 (br), 2964 (br), 2925 (br), 2867 (w), 1646 (m), 1612 (m), 1590 (m), 1494 (s), 1452 (s); δ_H (400 MHz, $CDCl_3$) 7.82 (1H, app. d, *J* = 8.0 Hz, H-4), 7.32-7.20 (4H, m, H-5, H-13, H-14 and H-15), 7.13 (1H, app. t, *J* = 7.5 Hz, H-6), 7.01 (1H, app. d, *J* = 8.1 Hz, H-7), 6.97 (2H, app. d, *J* = 7.1 Hz, H-12 and H-16), 5.62 (2H, s, H-10), 1.54 (9H, s, H-18); δ_C (125 MHz, $CDCl_3$) 161.2, 141.8,

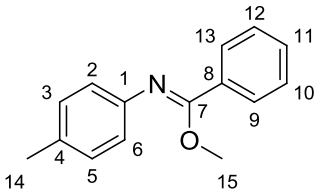
136.7, 136.3, 128.8, 127.5, 125.7 (C-12 and C-16), 122.4, 121.9, 119.5 (C-4), 109.9 (C-7), 48.7 (C-10), 34.1 (C-17), 29.8 (C-18); HRMS (ESI) found *m/z* 265.1698 $[M+H]^+$, $C_{18}H_{21}N_2$ requires 265.1699.

General procedure G for the preparation of benzimidazoles from benzimidates, exemplified by the preparation of 6-Methyl-2-phenyl-1-*p*-tolyl-1*H*-benzo[*d*]imidazole 47



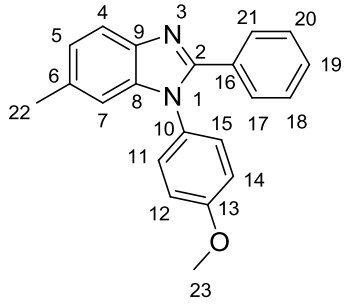
To a 5 mL microwave vial was added (*Z*)-methyl *N*-2-chloro-4-methylphenylbenzimidate **82** (100 mg, 0.4 mmol), palladium (II) acetate (4.0 mg, 0.02 mmol), cataCXium A (10 mg, 0.03 mmol), *p*-toluidine (62 mg, 0.6 mmol) and sodium *t*-butoxide (82 mg, 0.9 mmol). This was capped and purged with N_2 three times and α,α,α-trifluorotoluene (1.0 mL) was then added. This was heated in a microwave for 3 h at 150 °C. After cooling to room temperature the reaction mixture was diluted with diethyl ether (2 mL) and filtered through a Celite® pad, washing with diethyl ether (40 mL) and then concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a pale pink crystalline solid (100 mg, 87%). Data as reported previously.

A side-product, **(*Z*)-methyl *N*-*p*-tolylbenzimidate 89** was also isolated from flash chromatography as a yellow oil (16 mg, 13%).



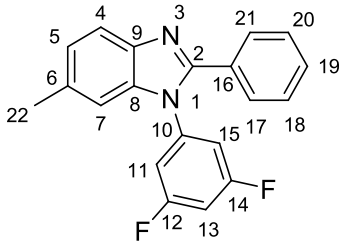
δ_H (400 MHz, $CDCl_3$) 7.35-7.20 (5H, m, H-9, H-10, H-11, H-12 and H-13), 6.99 (2H, d, *J* = 8.0 Hz, H-3 and H-5), 6.63 (2H, d, *J* = 8.0 Hz, H-2 and H-6), 3.98 (3H, s, H-15), 2.27 (3H, s, H-14); δ_C (100 MHz, $CDCl_3$) 159.1, 145.7, 131.9, 131.6, 129.7, 129.5, 129.3, 127.9, 121.5 (C-2 and C-6), 53.9 (C-15), 20.8 (C-14); LRMS (ESI) *m/z* 226.1 (100%, $[M+H]^+$).

1-(4-Methoxyphenyl)-6-methyl-2-phenyl-1*H*-benzo[*d*]imidazole 60



General procedure G was followed using (*Z*)-methyl *N*-2-chloro-4-methylphenylbenzimidate **82** (100 mg, 0.4 mmol) and *p*-anisidine (70 mg, 0.6 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a pink crystalline solid (104 mg, 86%). Data as reported previously.

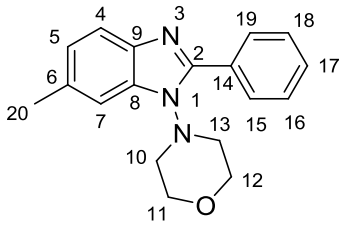
1-(3,5-Difluorophenyl)-6-methyl-2-phenyl-1*H*-benzo[*d*]imidazole 61



General procedure G was followed using (*Z*)-methyl *N*-2-chloro-4-methylphenylbenzimidate **82** (100 mg, 0.4 mmol) and 3,5-difluoroaniline (75 mg, 0.6 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a pale pink crystalline solid (52 mg, 42%). Data as reported previously.

A side-product, **(*Z*)-methyl *N*-*p*-tolylbenzimidate 89** was also isolated from flash chromatography as a yellow oil (25 mg, 29%). Data as reported previously.

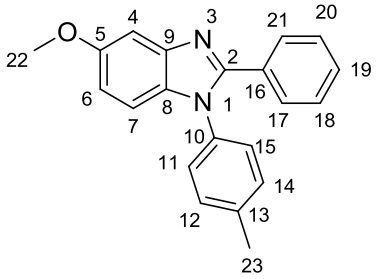
4-(6-Methyl-2-phenyl-1*H*-benzo[*d*]imidazol-1-yl)morpholine 62



General procedure G was followed using (*Z*)-methyl *N*-2-chloro-4-methylphenylbenzimidate **82** (100 mg, 0.4 mmol) and 4-aminomorpholine (60 µL, 0.6 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 7:1) and afforded the title compound as a white crystalline solid (62 mg, 56%). Data as reported previously.

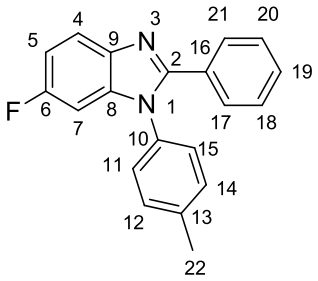
A side-product, **(*Z*)-methyl *N*-*p*-tolylbenzimidate 89** was also isolated from flash chromatography as a yellow oil (21 mg, 21%). Data as reported previously.

5-Methoxy-2-phenyl-1-*p*-tolyl-1*H*-benzo[*d*]imidazole 90



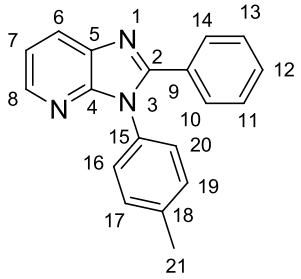
General procedure G was followed using (*Z*)-methyl *N*-2-chloro-5-methoxyphenyl benzimidate **83** (100 mg, 0.4 mmol) and *p*-toluidine (58 mg, 0.6 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a pale yellow solid (48 mg, 42%). mp: 118-120 °C; ν_{max} (neat)/cm^{-1} 2961 (w), 2923 (w), 2853 (w), 1617 (m), 1594 (m), 1581 (m), 1485 (s), 1470 (s), 1450 (s), 1429 (s); δ_H (400 MHz, $CDCl_3$) 7.58 (2H, app. d, *J* = 7.2 Hz, H-17 and H-21), 7.38 (1H, d, *J* = 2.2 Hz, H-4), 7.35-7.26 (5H, m, H-12, H-14, H-18, H-19 and H-20), 7.18 (2H, d, *J* = 8.1 Hz, H-11 and H-15), 7.11 (1H, d, *J* = 8.8 Hz, H-7), 6.90 (1H, dd, *J* = 8.8 Hz, *J* = 2.2 Hz, H-6), 3.90 (3H, s, H-22), 2.44 (3H, s, H-23); δ_C (100 MHz, $CDCl_3$) 156.7, 152.6, 143.6, 138.5, 134.4, 132.1, 130.4, 130.1, 129.3, 129.2, 128.2, 127.0, 113.3 (C-6), 110.9 (C-7), 101.8 (C-4), 55.8 (C-22), 21.2 (C-23); HRMS (ESI) found *m/z* 315.1488 $[M+H]^+$, $C_{21}H_{19}N_2O$ requires 315.1492.

6-Fluoro-2-phenyl-1-*p*-tolyl-1*H*-benzo[*d*]imidazole 91



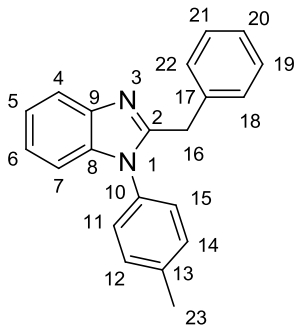
General procedure G was followed using (*Z*)-methyl *N*-2-chloro-4-fluorophenylbenzimidate **84** (100 mg, 0.4 mmol) and *p*-toluidine (61 mg, 0.6 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a dark red solid (96 mg, 83%). mp: 121-123 °C; ν_{max} (neat)/cm^{-1} 3051 (w), 1620 (w), 1515 (m), 1484 (m), 1474 (s), 1454 (s), 1441 (m), 1384 (m), 1264 (s); δ_H (400 MHz, $CDCl_3$) 7.79 (1H, dd, *J* = 8.8 Hz, *J* = 4.8 Hz, H-7), 7.57 (2H, d, *J* = 6.8 Hz, H-17 and H-21), 7.36-7.28 (5H, m, H-12, H-14, H-18, H-19 and H-20), 7.17 (2H, app. d, *J* = 8.2 Hz, H-11 and H-15), 7.07 (1H, td, *J* = 9.2 Hz, *J* = 2.4 Hz, H-5), 6.92 (1H, dd, *J* = 8.7 Hz, *J* = 2.4 Hz, H-4), 2.45 (3H, s, H-22); δ_C (100 MHz, $CDCl_3$) 160.0 (d, *J* = 240.2 Hz, C-6), 153.1 (d, *J* = 3.0 Hz), 139.3, 138.9, 137.5 (d, *J* = 13 Hz), 134.0, 130.6, 129.8, 129.5, 129.3, 128.3, 126.9 (C-11 and C-15), 120.5 (d, *J* = 9.9 Hz, C-7), 111.2 (d, *J* = 25.2 Hz, C-5), 97.2 (d, *J* = 28.0 Hz, C-4), 21.2 (C-22); δ_F (376 MHz, $CDCl_3$) -118.1 (1F, s); HRMS (ESI) found *m/z* 303.1298 $[M+H]^+$, $C_{20}H_{16}FN_2$ requires 303.1292.

2-Phenyl-3-*p*-tolyl-3*H*-imidazo[4,5-*b*]pyridine 92



General procedure G was followed using (*Z*)-methyl *N*-2-chloropyridin-3-ylbenzimidate **85** (100 mg, 0.4 mmol) and *p*-toluidine (65 mg, 0.6 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a pale yellow solid (114 mg, 80%). mp: 156-158 °C; ν_{max} (neat)/cm^{-1} 3044 (w), 1595 (m), 1517 (s), 1472 (s), 1444 (m), 1424 (m), 1378 (m), 1341 (s), 1292 (m), 1244 (m); δ_H (400 MHz, $CDCl_3$) 8.37 (1H, dd, *J* = 4.8 Hz, *J* = 1.4 Hz, H-8), 8.14 (1H, dd, *J* = 8.0 Hz, *J* = 1.4 Hz, H-6), 7.64-7.61 (2H, m, H-10 and H-14), 7.38-7.23 (8H, m, H-7, H-11, H-12, H-13, H-16, H-17, H-19 and H-20), 2.42 (3H, s, H-21); δ_C (100 MHz, $CDCl_3$) 153.4, 149.7, 144.6, 138.8, 135.2, 132.9, 130.3, 129.9, 129.7, 129.4, 128.4, 127.5, 127.3, 119.1, 21.3 (C-21); HRMS (ESI) found 286.1338 $[M+H]^+$, $C_{19}H_{16}N_3$ requires 286.1339.

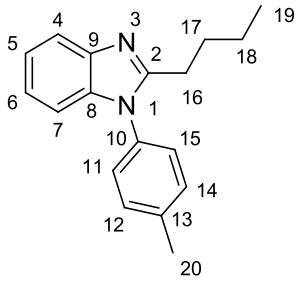
2-Benzyl-1-*p*-tolyl-1*H*-benzo[*d*]imidazole 93



General procedure G was followed using (*Z*)-methyl *N*-2-chlorophenyl-2-phenylacetimidate **86** (100 mg, 0.4 mmol) and *p*-toluidine (62 mg, 0.6 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as an orange

solid (114 mg, 80%). mp: 116-118 °C; ν_{max} (neat)/cm^{-1} 3055 (br), 3031 (w), 2907 (w), 1673 (w), 1602 (s), 1514 (2), 1494 (m), 1475 (m), 1455 (m), 1421 (s); δ_H (400 MHz, $CDCl_3$) 7.85 (1H, app. d, *J* = 8.0 Hz, H-4), 7.32-7.26 (3H, m, H-5, H-12 and H-14), 7.24-7.15 (4H, m, H-6 and Ar-H), 7.12-7.04 (5H, m, H-18, 22 and Ar-H), 4.20 (2H, s, H-16), 2.47 (3H, s, H-23); δ_C (100 MHz, $CDCl_3$) 153.5, 142.6, 139.0, 136.9, 136.7, 133.1, 130.3, 128.7, 128.4, 127.4, 126.6, 122.7, 122.3, 119.4, 110.2, 34.2 (C-16), 21.3 (C-23); HRMS (ESI) found *m/z* 299.1543 $[M+H]^+$, $C_{21}H_{19}N_2$ requires 299.1543.

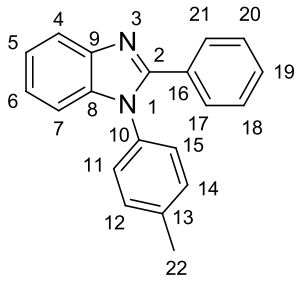
2-Butyl-1-p-tolyl-1*H*-benzo[*d*]imidazole 94



General procedure G was followed using (*Z*)-methyl *N*-2-chlorophenylpentanimidate **87** (100 mg, 0.4 mmol) and *p*-toluidine (71 mg, 0.7 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a white solid (75 mg, 64%). mp: 96-98 °C; ν_{max} (neat)/cm^{-1} 3057 (br), 3038 (w), 2948 (s), 2925 (m), 2864 (w), 1614 (w), 1584 (w), 1519 (s), 1511 (s), 1476 (s); δ_H (400 MHz, $CDCl_3$) 7.80-7.76 (1H, m, H-4), 7.40-7.35 (2H, m, H-12 and 14), 7.29-7.15 (4H, m, H-5, H-6, H-11 and H-15), 7.11-7.06 (1H, m, H-7), 2.78 (2H, t, *J* = 7.8 Hz, H-16), 2.49 (3H, s, H-20), 1.77 (2H, quin, *J* = 7.7 Hz, H-17), 1.35 (2H, sex, *J* = 7.4 Hz, H-18), 0.88 (3H, t, *J* = 7.3 Hz, H-19); δ_C (100 MHz, $CDCl_3$) 155.5, 142.5, 138.9, 136.6, 133.4, 130.5 (C-12 and C-14), 127.1, 122.4, 122.2, 119.0 (C-4), 109.9 (C-7), 29.9 (C-17), 27.4 (C-16), 22.4 (C-18), 21.2 (C-20), 13.7 (C-19); HRMS (ESI) found *m/z* 265.1702 $[M+H]^+$, $C_{18}H_{21}N_2$ requires 265.1699.

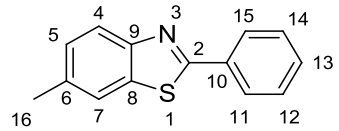
General procedure G was followed using (*Z*)-methyl *N*-2-bromophenylpentanimidate **88** (100 mg, 0.4 mmol) and *p*-toluidine (60 mg, 0.6 mmol) and heated in a microwave for 2 h at 135 °C. Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a white solid (110 mg, 94%). Data as reported previously.

2-Phenyl-1-*p*-tolyl-1*H*-benzo[*d*]imidazole 95



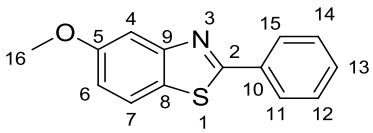
General procedure G was followed using (*Z*)-methyl *N*-2-bromophenylbenzimidate **74** (100 mg, 0.4 mmol) and *p*-toluidine (55 mg, 0.5 mmol) and heated in a microwave for 2 h at 135 °C. Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a pale yellow solid (78 mg, 80%). δ_H (400 MHz, $CDCl_3$) 7.89 (1H, app. d, *J* = 8.1 Hz, H-4), 7.60 (2H, app. d, *J* = 7.6 Hz, H-17 and H-21), 7.38-7.25 (8H, m, H-5, H-6, H-7, H-12, H-14, H-18, H-19 and H-20), 7.20 (2H, d, *J* = 7.6 Hz, H-11 and H-15), 2.46 (3H, s, H-22); δ_C (100 MHz, $CDCl_3$) 152.4, 142.9, 138.6, 137.4, 134.3, 132.9, 130.4, 129.4, 128.8, 128.3, 127.2, 123.2, 122.9, 119.8, 110.5, 21.3 (C-22); LRMS (ESI) *m/z* 285.1 (90%, $[M+H]^+$). Data consistent with literature data.[467]

General procedure H for the preparation of benzothiazoles from benzimidoyl chlorides, exemplified by the preparation of 6-Methyl-2-phenylbenzo[*d*]thiazole 99



To a 5 mL microwave vial was added (*Z*)-*N*-(2-chloro-4-methylphenyl)benzimidoyl chloride **14** (100 mg, 0.4 mmol), sodium hydrosulphide hydrate (63 mg, 1.1 mmol) and cesium carbonate (272 mg, 0.83 mmol). This was capped and purged with N_2 three times and *N*,*N*-dimethylacetamide (1.0 mL) was then added. This was heated in a microwave for 1 h at 50 °C then 2 h at 150 °C. After cooling to room temperature the reaction mixture was diluted with ethyl acetate (25 mL) and washed with brine (2 × 25 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/ethyl acetate 20:1) afforded the title compound as white solid (61 mg, 73%). δ_H (400 MHz, $CDCl_3$) 8.11-8.07 (2H, m, H-11 and H-15), 7.98 (1H, d, *J* = 8.3 Hz, H-4), 7.67 (1H, app. s, H-7), 7.51-7.47 (3H, m, H-12, H-13 and H-14), 7.31 (1H, dd, *J* = 8.3 Hz, *J* = 1.3 Hz, H-5), 2.50 (3H, s, H-16); δ_C (100 MHz, $CDCl_3$) 167.0, 152.3, 135.3, 135.2, 133.8, 130.7, 129.0, 127.9, 127.4, 122.7 (C-4), 121.4 (C-7), 21.6 (C-16); LRMS (ESI) *m/z* 226.1 (85%, $[M+H]^+$). Data consistent with literature data.[468]

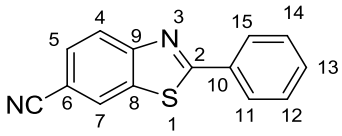
5-Methoxy-2-phenylbenzo[*d*]thiazole 102



General procedure H was followed using (*Z*)-*N*-(2-chloro-5-methoxyphenyl)benzimidoyl chloride **8** (100 mg, 0.4 mmol) and sodium hydrosulphide hydrate (60 mg, 1.1 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 20:1) afforded the title compound as a

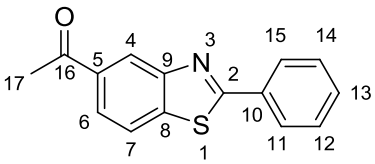
pale yellow solid (33 mg, 37%). δ_H (400 MHz, $CDCl_3$) 8.10-8.07 (2H, m, H-11 and H-15), 7.75 (1H, d, *J* = 8.8 Hz, H-7), 7.59 (1H, d, *J* = 2.4 Hz, H-4), 7.51-7.48 (3H, m, H-12, H-13 and H-14), 7.05 (1H, dd, *J* = 8.8 Hz, *J* = 2.4 Hz, H-6), 3.92 (3H, s, H-16); δ_C (100 MHz, $CDCl_3$) 169.3, 159.1, 155.3, 133.7, 130.9, 129.0, 127.4, 126.9, 121.8 (C-7), 115.5 (C-6), 105.5 (C-4), 55.6 (C-16); LRMS (ESI) *m/z* 242.1 (100%, $[M+H]^+$). Data consistent with literature data.[323]

2-Phenylbenzo[*d*]thiazole-6-carbonitrile 103



General procedure H was followed using (*Z*)-*N*-(2-chloro-4-cyanophenyl)benzimidoyl chloride **18** (100 mg, 0.4 mmol) and sodium hydrosulphide hydrate (61 mg, 1.1 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 4:1) afforded the title compound as a pale yellow solid (41 mg, 48%). δ_H (400 MHz, $CDCl_3$) 8.22 (1H, d, *J* = 1.5 Hz, H-7), 8.13-8.07 (3H, m, H-4, H-11 and H-15), 7.73 (1H, dd, *J* = 8.5 Hz, *J* = 1.5 Hz, H-5), 7.59-7.50 (3H, m, H-12, H-13 and H-14); δ_C (100 MHz, $CDCl_3$) 172.2, 156.4, 135.5, 132.7, 132.1, 129.5, 129.3, 127.9, 126.4 (C-7), 123.9, 118.7, 108.5; LRMS (ESI) *m/z* 259.0 (100%, $[M+Na]^+$). Data consistent with literature data.[323]

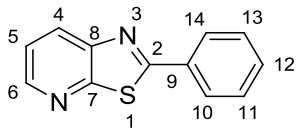
1-(2-Phenylbenzo[*d*]thiazol-5-yl)ethanone 104



General procedure H was followed using (*Z*)-*N*-(5-acetyl-2-chlorophenyl)benzimidoyl chloride **22** (35 mg, 0.1 mmol) and sodium hydrosulphide hydrate (20 mg, 0.3 mmol).

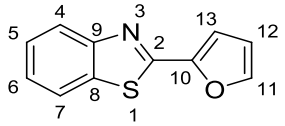
Flash chromatography (SiO_2, petrol/ethyl acetate 20:1) afforded the title compound as a pale yellow solid (25 mg, 74%). mp: 105-107 °C; ν_{max} (neat)/cm^{-1} 3054 (br), 2987 (w), 1739 (s), 1682 (m), 1690 (w), 1546 (m), 1516 (w), 1481 (m), 1445 (m); δ_H (400 MHz, $CDCl_3$) 8.65-8.63 (1H, m, H-4), 8.13-8.08 (2H, m, H-11 and H-15), 8.03 (1H, dd, *J* = 8.4 Hz, *J* = 1.4 Hz, H-6), 7.97 (1H, d, *J* = 8.4 Hz, H-7), 7.55-7.50 (3H, m, H-12, H-13 and H-14), 2.72 (3H, s, H-17); δ_C (100 MHz, $CDCl_3$) 197.5 (C-16), 169.6, 154.0, 140.0, 135.7, 133.1, 131.5, 129.2, 127.6, 124.3 (C-6), 123.7 (C-4), 121.7 (C-7), 26.7 (C-17); HRMS (ESI) found *m/z* 276.0455 $[M+Na]^+$, $C_{15}H_{11}NNaOS$ requires 276.0454.

2-Phenylthiazolo[5,4-*b*]pyridine 105



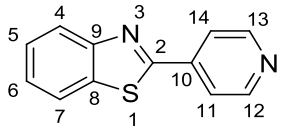
General procedure H was followed using (*Z*)-*N*-(2-chloropyridin-3-yl)benzimidoyl chloride **36** (100 mg, 0.4 mmol) and sodium hydrosulphide hydrate (67 mg, 1.2 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 10:1) afforded the title compound as a pale yellow solid (65 mg, 77%). δ_H (400 MHz, $CDCl_3$) 8.54 (1H, dd, *J* = 4.6 Hz, *J* = 1.4 Hz, H-6), 8.24 (1H, dd, *J* = 8.2 Hz, *J* = 1.4 Hz, H-4), 8.08-8.05 (2H, m, H-10 and H-14), 7.50-7.46 (3H, m, H-11, H-12 and H-13), 7.39 (1H, dd, *J* = 8.2 Hz, *J* = 4.6 Hz, H-5); δ_C (100 MHz, $CDCl_3$) 168.6, 158.4, 147.2, 147.0 (C-6), 133.4, 131.5, 129.9, 129.1, 127.6 (C-10 and C-14), 121.4 (C-5); LRMS (ESI) *m/z* 213.0 (95%, $[M+H]^+$). Data consistent with literature data.[469]

2-(Furan-2-yl)benzo[*d*]thiazole 106



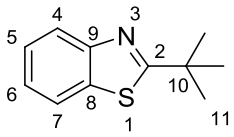
General procedure H was followed using (*Z*)-*N*-(2-chlorophenyl)furan-2-carbimidoyl chloride **38** (100 mg, 0.4 mmol) and sodium hydrosulphide hydrate (70 mg, 1.3 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 20:1) afforded the title compound as a pale yellow solid (68 mg, 81%). δ_H (400 MHz, $CDCl_3$) 8.05 (1H, d, *J* = 8.2 Hz, Ar-H), 7.87 (1H, d, *J* = 8.0 Hz, Ar-H), 7.60-7.58 (1H, m, H-11), 7.48 (1H, t, *J* = 7.7 Hz, Ar-H), 7.36 (1H, t, *J* = 7.5 Hz, Ar-H), 7.19 (1H, d, *J* = 3.4 Hz, H-13), 6.58 (1H, dd, *J* = 3.4 Hz, *J* = 1.7 Hz, H-12); δ_C (100 MHz, $CDCl_3$) 157.5, 153.7, 148.7, 144.7 (C-11), 134.3, 126.5, 125.2, 123.1, 121.6, 112.5 (C-13), 111.4 (C-12); LRMS (ESI) *m/z* 224.0 (100%, $[M+Na]^+$). Data consistent with literature data.[470]

2-(Pyridin-4-yl)benzo[*d*]thiazole 107



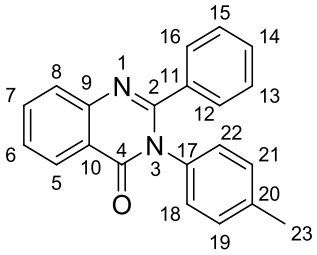
General procedure H was followed using (*Z*)-*N*-(2-chlorophenyl)isonicotinimidoyl chloride **40** (100 mg, 0.4 mmol) and sodium hydrosulphide hydrate (67 mg, 1.2 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 6:1) afforded the title compound as a pale yellow solid (47 mg, 56%). δ_H (400 MHz, $CDCl_3$) 8.74 (2H, d, *J* = 6.0 Hz, H-12 and H-13), 8.10 (1H, d, *J* = 8.1 Hz, Ar-H), 7.92-7.89 (3H, m, H-11, H-14 and Ar-H), 7.52 (1H, t, *J* = 7.7 Hz, Ar-H), 7.43 (1H, t, *J* = 7.6 Hz, Ar-H); δ_C (100 MHz, $CDCl_3$) 165.0, 153.9, 150.7 (C-12 and C-13), 140.4, 135.2, 126.8, 126.2, 123.9, 121.8, 121.1; LRMS (ESI) *m/z* 213.0 (100%, $[M+H]^+$). Data consistent with literature data.[471, 472]

2-*Tert*-butylbenzo[*d*]thiazole 108



General procedure H was followed using (*Z*)-*N*-(2-chlorophenyl)pivalimidoyl chloride **42** (100 mg, 0.4 mmol) and sodium hydrosulphide hydrate (73 mg, 1.3 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 25:1) afforded the title compound as a colourless oil (69 mg, 83%). δ_H (400 MHz, $CDCl_3$) 8.02 (1H, d, *J* = 8.2 Hz, Ar-H), 7.85 (1H, d, *J* = 8.0 Hz, Ar-H), 7.45 (1H, t, *J* = 8.2 Hz, Ar-H), 7.33 (1H, t, *J* = 8.0 Hz, Ar-H), 1.54 (9H, s, H-11); δ_C (100 MHz, $CDCl_3$) 181.8, 153.3, 135.0, 125.7, 124.5, 122.7, 121.4, 38.3 (C-10), 30.7 (C-11); LRMS (ESI) *m/z* 192.1 (100%, $[M+H]^+$). Data consistent with literature data.[473]

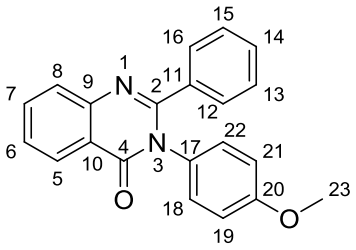
General procedure I for the preparation of quinazolin-4(3*H*)-ones from benzimidates, exemplified by the preparation of 2-Phenyl-3-*p*-tolylquinazolin-4(3*H*)-one 119



To a 50 mL Schlenk tube was added palladium (II) acetate (5.0 mg, 0.02 mmol), cata*C*Xium® A (22 mg, 0.06 mmol), cesium carbonate (326 mg, 1.0 mmol) and *p*-toluidine (55 mg, 0.5 mmol) under N_2. A solution of (*Z*)-methyl *N*-2-bromophenylbenzimidate **74** (100 mg, 0.3 mmol) in anhydrous toluene (0.65 mL) was then added. A balloon fitted with a glass tap attachment was filled with N_2 and evacuated three times. The balloon was then filled with carbon monoxide from a lecture bottle

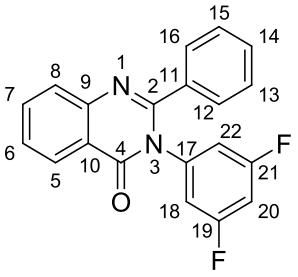
(Aldrich) or cylinder (BOC) and attached to the top of the Schlenk tube. The inert atmosphere was then exchanged for carbon monoxide by briefly exposing the reaction vessel to vacuum (1-2 seconds) through the side arm of the Schlenk tube and filling the vessel with carbon monoxide *via* the balloon. This was performed three times. The reaction was then left under an atmosphere of carbon monoxide and stirred vigorously, heating at 85 °C for 18 h. The reaction was then allowed to cool to room temperature and the carbon monoxide balloon removed. The reaction mixture was diluted with ethyl acetate (10 mL) and filtered through a Celite® pad, washing with ethyl acetate (40 mL) and DCM (40 mL) and then concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/diethyl ether 3:1) afforded the title compound as a white crystalline solid (88 mg, 73%). δ_H (400 MHz, $CDCl_3$) 8.36 (1H, app. d, J = 8.0 Hz, H-5), 7.85-7.77 (2H, m, H-7 and H-8), 7.55-7.50 (1H, m, H-6), 7.39-7.34 (2H, m, Ar-H), 7.30-7.20 (3H, m, Ar-H), 7.11 (2H, d, J = 8.2 Hz, Ar-H), 7.04 (2H, d, J = 8.2 Hz, Ar-H), 2.31 (3H, s, H-23); δ_C (100 MHz, $CDCl_3$) 162.4, 153.4, 147.5, 138.3, 135.6, 135.0, 134.7, 129.7, 129.3, 129.2, 129.0, 128.8, 128.0, 127.7, 127.2, 121.0, 21.2 (C-23); LRMS (ESI) *m/z* 647.2 (100%, $[2M+Na]^+$). Data consistent with literature data.[397]

3-(4-Methoxyphenyl)-2-phenylquinazolin-4(3*H*)-one 123



General procedure I was followed using (*Z*)-methyl *N*-2-bromophenylbenzimidate **74** (100 mg, 0.3 mmol) and *p*-anisidine (64 mg, 0.5 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a pale yellow crystalline solid (72 mg, 65%). δ_H (400 MHz, $CDCl_3$) 8.36 (1H, app. d, J = 7.6 Hz, H-5), 7.83-7.78 (2H, m, H-7 and H-8), 7.55-7.51 (1H, m, H-6), 7.37-7.34 (2H, m, Ar-H), 7.28-7.21 (3H, m, Ar-H), 7.08-7.04 (2H, m, Ar-H), 6.85-6.80 (2H, m, Ar-H), 3.77 (3H, s, H-23); δ_C (100 MHz, $CDCl_3$) 162.5, 159.2, 155.5, 147.5, 135.6, 134.6, 130.3, 130.0, 129.2, 129.0, 128.0, 127.7, 127.2, 121.0, 114.2, 55.4 (C-23); LRMS (ESI) *m/z* 679.2 (100%, $[2M+Na]^+$). Data consistent with literature data.[397]

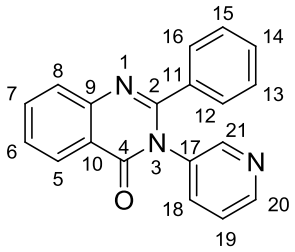
3-(3,5-Difluorophenyl)-2-phenylquinazolin-4(3*H*)-one 124



General procedure I was followed using (*Z*)-methyl *N*-2-bromophenylbenzimidate **74** (100 g, 0.3 mmol) and 3,5-difluoroaniline (67 mg, 0.5 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 10:1) afforded the title compound as a white crystalline solid (101 mg, 89%). mp: 227-228 °C ; ν_{max} (neat)/cm^{-1} 3068 (br), 1675 (s), 1606 (m), 1587 (m), 1574 (m), 1561 (w), 1494 (m), 1460 (w), 1446 (m), 1357 (w); δ_H (400 MHz, $CDCl_3$)

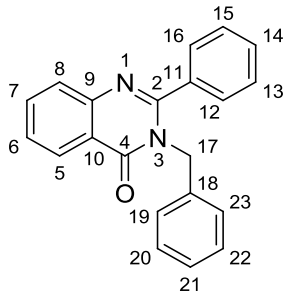
8.37-8.34 (1H, m, H-5), 7.86-7.83 (2H, m, H-7 and H-8), 7.59-7.55 (1H, m, H-6), 7.39-7.28 (5H, m, H-12, H-13, H-14, H-15 and H-16), 7.80-6.74 (3H, m, H-18, H-20 and H-22); δ_C (125 MHz, $CDCl_3$) 162.7 (dd, *J* = 250.8 Hz, *J* = 13.6 Hz), 161.8, 154.2, 147.2, 139.7 (t, *J* = 12.4 Hz), 135.1, 134.7, 129.9, 128.7, 128.4, 127.9, 127.7, 127.2, 120.6, 113.2 (dd, *J* = 27.7 Hz, *J* = 14.1 Hz), 104.5 (t, *J* = 25.2 Hz); δ_F (376 MHz, $CDCl_3$) -108.3 (2F, s); HRMS (ESI) found *m/z* 357.0809 $[M+Na]^+$, $C_{20}H_{12}F_2N_2NaO$ requires 357.0810.

2-Phenyl-3-(pyridin-3-yl)quinazolin-4(3*H*)-one 125



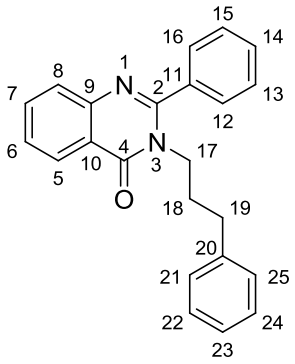
General procedure I was followed using (*Z*)-methyl *N*-2-bromophenylbenzimidate **74** (100 mg, 0.3 mmol) and 3-aminopyridine (48 mg, 0.5 mmol) at 90 °C. Flash chromatography (SiO_2, petrol/ethyl acetate 4:1) afforded the title compound as a pale yellow crystalline solid (101 mg, 89%). mp: 174-176 °C; ν_{max} (neat)/cm^{-1} 3062 (br), 1681 (s), 1604 (m), 1593 (m), 1580 (w), 1565 (m), 1495 (w), 1472 (w), 1445 (m), 1425 (w); δ_H (400 MHz, $CDCl_3$) 8.50 (1H, br. app. s, H-20), 8.39 (1H, br. s, H-21), 8.33 (1H, app. d, *J* = 8.0 Hz, H-5), 7.83 (2H, app. d, *J* = 4.0 Hz, Ar-H), 7.58-7.52 (2H, m, Ar-H), 7.33-7.20 (6H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 162.1, 154.5, 149.7, 149.2, 147.3, 136.6, 135.1, 134.7, 129.8, 129.1 (2C), 128.4, 127.9, 127.6, 127.2, 123.5, 120.6; HRMS (ESI) found *m/z* 322.0949 $[M+Na]^+$, $C_{19}H_{13}N_3NaO$ requires 322.0951.

3-Benzyl-2-phenylquinazolin-4(3*H*)-one 120



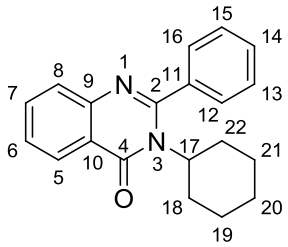
General procedure I was followed using (*Z*)-methyl *N*-2-bromophenylbenzimidate **74** (100 mg, 0.3 mmol) and benzylamine (0.1 mL, 1.0 mmol) at 95 °C. Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a yellow crystalline solid (63 mg, 59%). mp: 131-133 °C; ν_{max} (neat)/cm^{-1} 3281 (br), 3033 (w), 1675 (s), 1603 (w), 1584 (m), 1567 (m), 1521 (w), 1494 (w), 1474 (w), 1433 (m); δ_H (400 MHz, $CDCl_3$) 8.41-8.37 (1H, m, H-5), 7.80-7.77 (2H, m, H-7 and H-8), 7.56-7.51 (1H, m, H-6), 7.50-7.45 (1H, m, H-14), 7.44-7.33 (4H, m, H-12, H-13, H-15 and H-16), 7.24-7.19 (3H, m, H-20, H-21 and H-22), 6.97-6.91 (2H, m, H-19 and H-23), 5.29 (2H, s, H-17); δ_C (100 MHz, $CDCl_3$) 162.5, 156.4, 147.3, 136.6, 135.3, 134.6, 129.9, 128.6, 128.5, 128.0, 127.6, 127.4, 127.2, 127.1, 127.0, 120.9, 48.8 (C-17); HRMS (ESI) found *m/z* 335.1148 $[M+Na]^+$, $C_{21}H_{16}N_2NaO$ requires 335.1155.

2-Phenyl-3-(3-phenylpropyl)quinazolin-4(3*H*)-one 126



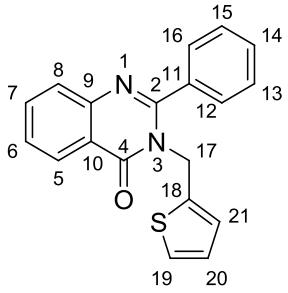
General procedure I was followed using (*Z*)-methyl *N*-2-bromophenylbenzimidate **74** (100 mg, 0.3 mmol) and 3-phenylpropylamine (0.1 mL, 1.0 mmol) at 95 °C. Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a yellow crystalline solid (83 mg, 72%). mp: 120-123 °C; ν_{max} (neat)/cm^{-1} 3062 (br), 3027 (br), 2933 (br), 1673 (s), 1605 (m), 1587 (m), 1566 (m), 1496 (w), 1472 (w); δ_H (400 MHz, $CDCl_3$) 8.35 (1H, app. d, *J* = 8.5 Hz, H-5), 7.79-7.72 (2H, m, H-7 and H-8), 7.54-7.47 (6H, m, H-6, H-12, H-13, H-14, H-15 and H-16), 7.22-7.11 (3H, m, H-22, H-23 and H-24), 7.01-6.97 (2H, m, H-21 and H-25), 4.04-3.99 (2H, m, H-17), 2.52 (2H, t, *J* = 7.6 Hz, H-19), 1.96 (2H, quin, *J* = 7.8 Hz, H-18); δ_C (100 MHz, $CDCl_3$) 162.1, 156.1, 147.2, 140.5, 135.4, 134.3, 129.8, 128.8, 128.4, 128.0, 127.7, 127.5, 127.0, 126.8, 125.9, 120.9, 45.5 (C-17), 32.9 (C-19), 29.7 (C-18); HRMS (ESI) found *m/z* 341.1646 $[M+H]^+$, $C_{23}H_{21}N_2O$ requires 341.1648.

3-Cyclohexyl-2-phenylquinazolin-4(3*H*)-one 127



General procedure I was followed using (*Z*)-methyl *N*-2-bromophenylbenzimidate **74** (100 mg, 0.3 mmol) and cyclohexylamine (0.1 mL, 1.0 mmol) at 95 °C. Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a pale yellow crystalline solid (56 mg, 54%). mp: 133-135 °C; ν_{max} (neat)/cm^{-1} 3033 (br), 2935 (br), 2857 (w), 1672 (s), 1605 (m), 1586 (m), 1567 (w), 1497 (w), 1474 (w), 1454 (m); δ_H (400 MHz, $CDCl_3$) 8.29 (1H, dd, *J* = 7.8 Hz, *J* = 2.6 Hz, H-5), 7.74-7.66 (2H, m, Ar-H), 7.53-7.43 (6H, m, Ar-H), 3.91-3.80 (1H, m, H-17), 2.73 (2H, q, *J* = 12.4 Hz, Cy-H), 1.82-1.64 (4H, m, Cy-H), 1.57-1.48 (1H, m, Cy-H), 1.23-1.15 (1H, m, Cy-H), 0.96 (2H, qd, *J* = 13.0 Hz, *J* = 3.2 Hz, Cy-H); δ_C (100 MHz, $CDCl_3$) 162.6, 156.9, 146.8, 136.5, 134.1, 129.7, 128.9, 127.2, 127.1, 126.8, 126.5, 122.2, 62.6 (C-17), 28.8, 26.2, 24.9; HRMS (ESI) found *m/z* 327.1470 $[M+Na]^+$, $C_{20}H_{20}N_2NaO$ requires 327.1468.

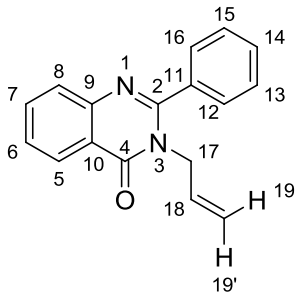
2-Phenyl-3-(thiophen-2-ylmethyl)quinazolin-4(3*H*)-one 128



General procedure I was followed using (*Z*)-methyl *N*-2-bromophenylbenzimidate **74** (100 mg, 0.3 mmol) and 2-thiophenemethylamine (0.1 mL, 1.0 mmol) at 95 °C. Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a pale

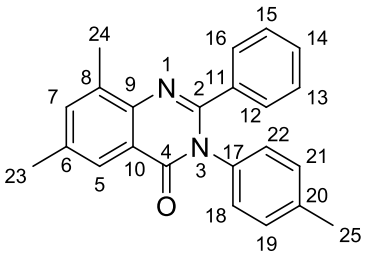
yellow crystalline solid (73 mg, 67%). mp: 130-132 °C; ν_{max} (neat)/cm^{-1} 3064 (br), 1671 (s), 1605 (m), 1586 (m), 1566 (m), 1496 (w), 1472 (w), 1445 (m), 1426 (m), 1378 (m); δ_H (400 MHz, $CDCl_3$) 8.39 (1H, app. d, *J* = 8.0 Hz, H-5), 7.79-7.72 (2H, m, H-7 and H-8), 7.56-7.47 (6H, m, H-6, H-12, H-13, H-14, H-15 and H-16), 7.17 (1H, dd, *J* = 5.1 Hz, *J* = 1.0 Hz, H-19), 6.84 (1H, m, H-20), 6.61 (1H, app. d, *J* = 3.1 Hz, H-21), 5.38 (2H, s, H-17); δ_C (100 MHz, $CDCl_3$) 162.2, 155.7, 147.1, 138.2, 135.0, 134.6, 130.1, 128.8, 128.3, 127.6, 127.3, 127.2, 127.0, 126.3, 126.0, 120.9, 44.1 (C-17); HRMS (ESI) found *m/z* 341.0716 $[M+Na]^+$, $C_{19}H_{14}N_2NaOS$ requires 341.0719.

3-Allyl-2-phenylquinazolin-4(3*H*)-one 129



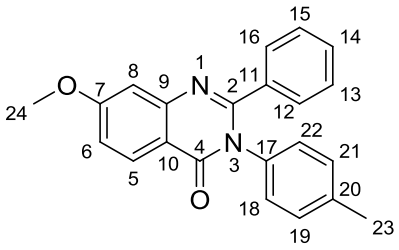
General procedure I was followed using (*Z*)-methyl *N*-2-bromophenylbenzimidate **74** (100 mg, 0.3 mmol) and allylamine (40 µL, 0.5 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 7:1) afforded the title compound as a yellow crystalline solid (36 mg, 41%). mp: 79-81 °C; ν_{max} (neat)/cm^{-1} 3059 (br), 2927 (w), 1679 (s), 1603 (m), 1583 (m), 1566 (m), 1495 (w), 1472 (m), 1445 (w), 1425 (m); δ_H (400 MHz, $CDCl_3$) 8.35 (1H, app. d, *J* = 7.9 Hz, H-5), 7.79-7.74 (2H, m, H-7 and H-8), 7.57-7.46 (6H, H-6, H-12, H-13, H-14, H-15 and H-16), 5.93-5.82 (1H, m, H-18), 5.17 (1H, dd, *J* = 10.4 Hz, *J* = 1.0 Hz, H-19'), 4.94 (1H, dd, *J* = 17.2 Hz, *J* = 0.9 Hz, H-19), 4.63-4.58 (2H, m, H-17); δ_C (100 MHz, $CDCl_3$) 162.0, 156.3, 147.2, 135.2, 134.4, 132.2, 130.0, 128.6, 128.0, 127.5, 127.1, 126.9, 120.8, 117.5 (C-19), 48.2 (C-17); HRMS (ESI) found *m/z* 285.1000 $[M+Na]^+$, $C_{17}H_{14}N_2NaO$ requires 285.0998.

6,8-Dimethyl-2-phenyl-3-*p*-tolylquinazolin-4(3*H*)-one 140



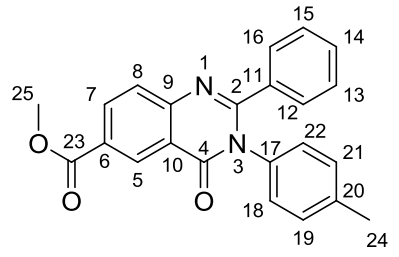
General procedure I was followed using (*Z*)-methyl *N*-2-bromo-4,6-dimethyl phenyl benzimidate **133** (100 mg, 0.3 mmol) and *p*-toluidine (51 mg, 1.0 mmol) at 95 °C. Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a white crystalline solid (78 mg, 81%). mp: 207-209 °C; ν_{max} (neat)/cm^{-1} 3054 (br), 1676 (s), 1616 (w), 1590 (m), 1564 (m), 1512 (m), 1494 (w), 1475 (w), 1446 (m), 1379 (m); δ_H (400 MHz, $CDCl_3$) 8.01 (1H, app. s, H-5), 7.49 (1H, app. s, H-7), 7.40 (2H, app. d, *J* = 7.4 Hz, H-12 and H-16), 7.29-7.19 (3H, m, H-13, H-14 and H-15), 7.13 (2H, d, *J* = 8.1 Hz, H-19 and H-21), 7.05 (2H, d, *J* = 8.1 Hz, H-18 and H-22), 2.66 (3H, s, H-24), 2.49 (3H, s, H-23), 2.33 (3H, s, H-25); δ_C (100 MHz, $CDCl_3$) 162.9, 152.8, 144.1, 138.1, 136.8, 136.7 (C-7), 136.0, 135.4, 129.6, 129.4 (2C), 129.0, 128.8, 127.7, 124.2 (C-5), 120.6, 21.4, 21.2, 17.3 (C-25); HRMS (ESI) found *m/z* 341.1646 $[M+H]^+$, $C_{23}H_{21}N_2O$ requires 341.1648.

7-Methoxy-2-phenyl-3-*p*-tolylquinazolin-4(3*H*)-one 141



General procedure I was followed using (*Z*)-methyl *N*-2-bromo-5-methoxyphenylbenzimidate **134** (100 mg, 0.3 mmol) and *p*-toluidine (50 mg, 0.5 mmol) at 90 °C. Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a pale pink crystalline solid (76 mg, 71%). mp: 217-219 °C; ν_{max} (neat)/cm^{-1} 3060 (br), 3037 (br), 2921 (w), 1674 (s), 1613 (m), 1591 (m), 1561 (m), 1513 (w), 1484 (m), 1445 (m); δ_H (400 MHz, $CDCl_3$) 8.24 (1H, d, *J* = 8.8 Hz, H-5), 7.37-7.33 (2H, m, Ar-H), 7.28-7.19 (4H, m, H-8 and Ar-H), 7.12-7.07 (3H, m, H-6, H-19 and H-21), 7.05-7.00 (2H, m, H-18 and H-22), 3.93 (3H, s, H-24), 2.30 (3H, s, H-23); δ_C (100 MHz, $CDCl_3$) 164.8, 161.9, 156.1, 149.7, 138.2, 135.7, 135.0, 129.6, 129.2, 128.9, 128.8, 128.8, 128.0, 117.3, 114.4, 108.3, 55.7 (C-24), 21.1 (C-23); HRMS (ESI) found *m/z* 343.1440 $[M+H]^+$, $C_{22}H_{19}N_2O_2$ requires 343.1441.

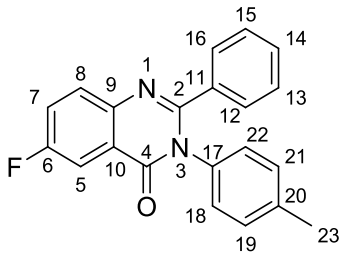
Methyl 4-oxo-2-phenyl-3-*p*-tolyl-3,4-dihydroquinazoline-6-carboxylate 142



General procedure I was followed using (*Z*)-methyl-3-bromo-4-(methoxy(phenyl) methyleneamino)benzoate **135** (0.1 g, 0.3 mmol) and *p*-toluidine (46 mg, 0.4 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a

pale pink crystalline solid (82 mg, 76%). mp: 229-232 °C; ν_{max} (neat)/cm^{-1} 3035 (br), 2952 (w), 1721 (s), 1688 (s), 1605 (w), 1587 (m), 1554 (m), 1512 (m), 1495 (w), 1436 (m); δ_H (400 MHz, $CDCl_3$) 9.00 (1H, d, *J* = 1.9 Hz, H-5), 8.40 (1H, dd, *J* = 8.5 Hz, *J* = 1.9 Hz, H-7), 7.83 (1H, d, *J* = 8.5 Hz, H-8), 7.38-7.34 (2H, m, Ar-H), 7.28-7.20 (3H, m, Ar-H), 7.12 (2H, d, *J* = 8.2 Hz, H-19 and H-21), 7.03 (2H, d, *J* = 8.2 Hz, H-18 and H-22), 3.96 (3H, s, H-25), 2.31 (3H, s, H-24); δ_C (100 MHz, $CDCl_3$) 166.0, 161.9, 157.3, 150.5, 138.6, 135.2, 134.9, 134.7, 129.7, 129.7, 129.6, 129.0, 128.6, 128.6, 128.0, 128.0, 120.7, 52.4 (C-25), 21.2 (C-24); HRMS (ESI) found *m/z* 371.1389 $[M+H]^+$, $C_{23}H_{19}N_2O_3$ requires 371.1390.

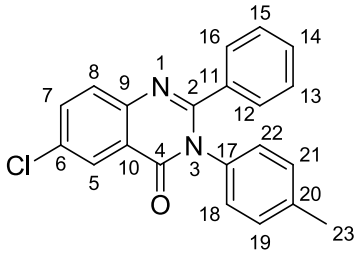
6-Fluoro-2-phenyl-3-*p*-tolylquinazolin-4(3*H*)-one 143



General procedure I was followed using (*Z*)-methyl *N*-2-bromo-4-fluorophenylbenzimidate **136** (100 mg, 0.3 mmol) and *p*-toluidine (52 mg, 0.5 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 8:1) afforded the title compound as a pale pink crystalline solid (60 mg, 58%). mp: 207-209 °C; ν_{max} (neat)/cm^{-1} 3054 (br), 1693 (s), 1679 (s), 1622 (w), 1590 (m), 1565 (m), 1512 (w), 1485 (m), 1446 (m), 1346 (m); δ_H (400 MHz, $CDCl_3$) 7.98 (1H, dd, *J* = 8.4 Hz, *J* = 3.0 Hz, H-5), 7.83 (1H, dd, *J* = 8.9 Hz, *J* = 4.8 Hz, H-8), 7.55-7.50 (1H, m, H-7), 7.37-7.32 (2H, m, Ar-H), 7.29-7.20 (3H, m, Ar-H), 7.14-7.10 (2H, m, H-19 and H-21), 7.05-7.01 (2H, m, H-18 and H-22), 2.31 (3H, s, H-23); δ_C (100 MHz, $CDCl_3$) 161.7 (d, *J* = 3.4 Hz), 161.1 (d, *J* = 248.7 Hz, C-6), 154.7 (d, *J* = 2.2 Hz), 144.2, 138.5, 135.3, 134.8, 130.1 (d, *J* = 8.4 Hz, C-8), 129.7,

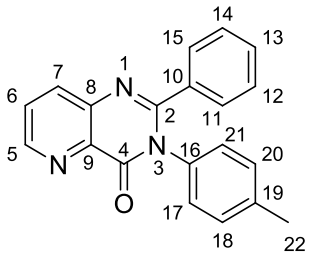
129.3, 129.0, 128.6, 128.0, 123.2 (d, *J* = 24.2 Hz, Ar-C), 122.3 (d, *J* = 8.8 Hz, C-7), 112.0 (d, *J* = 23.8 Hz, C-5), 21.2 (C-23); δ_F (376 MHz, $CDCl_3$) -112.1 (1F, s); HRMS (ESI) found *m/z* 331.1237 $[M+H]^+$, $C_{21}H_{16}FN_2O$ requires 331.1241.

6-Chloro-2-phenyl-3-*p*-tolylquinazolin-4(3*H*)-one 144



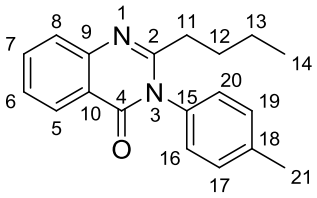
General procedure I was followed using (*Z*)-methyl *N*-2-bromo-4-chlorophenylbenzimidate **137** (100 mg, 0.3 mmol) and *p*-toluidine (50 mg, 0.5 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 9:1) afforded the title compound as a pale pink crystalline solid (82 mg, 74%). mp: 234-236 °C; ν_{max} (neat)/cm^{-1} 3326 (br), 2962 (w), 2920 (w), 1685 (s), 1599 (w), 1586 (w), 1549 (m), 1511 (m), 1491 (m), 1471 (m); δ_H (400 MHz, $CDCl_3$) 8.31 (1H, d, *J* = 2.2 Hz, H-5), 7.78-7.70 (2H, m, H-7 and H-8), 7.37-7.32 (2H, m, Ar-H), 7.29-7.20 (3H, m, Ar-H), 7.12 (2H, d, *J* = 8.2 Hz, H-19 and H-21), 7.02 (2H, d, *J* = 8.2 Hz, H-18 and H-22), 2.31 (3H, s, H-23); δ_C (100 MHz, $CDCl_3$) 161.4, 155.6, 146.0, 138.6, 135.3, 135.1, 134.7, 132.9, 129.7, 129.4, 129.4, 129.0, 128.6, 128.0, 126.5 (C-5), 122.0, 21.2 (C-23); HRMS (ESI) found *m/z* 347.0949 $[M+H]^+$, $C_{21}H_{16}{}^{35}ClN_2O$ requires 347.0946.

2-Phenyl-3-*p*-tolylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one 145



General procedure I was followed using (*Z*)-methyl *N*-2-bromopyridin-3-ylbenzimidate **138** (100 mg, 0.3 mmol) and *p*-toluidine (55 mg, 0.5 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 4:1) afforded the title compound as a brown solid (95 mg, 90%). mp: 219-221 °C; ν_{max} (neat)/cm^{-1} 3060 (br), 2922 (br), 1705 (s), 1640 (w), 1606 (m), 1573 (w), 1555 (m), 1511 (m), 1495 (w), 1495 (w); δ_H (400 MHz, $CDCl_3$) 8.93 (1H, dd, *J* = 4.3 Hz, *J* = 1.4 Hz, H-5), 8.16 (1H, dd, *J* = 8.3 Hz, *J* = 1.5 Hz, H-6), 7.73 (1H, dd, *J* = 8.3 Hz, *J* = 4.3 Hz, H-7), 7.31-7.22 (5H, m, H-11, H-12, H-13, H-14 and H-15), 7.15-7.11 (2H, m, H-18 and H-20), 7.07-7.03 (2H, m, H-17 and H-21), 2.32 (3H, s, H-22); δ_C (100 MHz, $CDCl_3$) 160.9, 156.4, 150.1 (C-5), 144.2, 138.7, 137.8, 136.0 (C-6), 135.1, 134.6, 129.8, 129.5, 128.9, 128.7, 128.6, 128.0, 21.2 (C-22); HRMS (ESI) found *m/z* 336.1101 $[M+Na]^+$, $C_{20}H_{15}N_3NaO$ requires 336.1107.

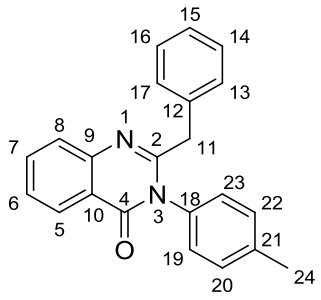
2-Butyl-3-*p*-tolylquinazolin-4(3*H*)-one 146



General procedure I was followed using (*Z*)-methyl *N*-2-bromophenylpentanimidate **88** (100 mg, 0.4 mmol) and *p*-toluidine (60 mg, 0.6 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 9:1) afforded the title compound as a pink crystalline solid (80 mg, 71%). mp: 112-113 °C; ν_{max} (neat)/cm^{-1} 3053 (br), 2961 (br), 2873 (w), 1680 (s), 1593

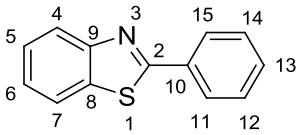
(m), 1570 (m), 1511 (w), 1473 (m), 1421 (m), 1380 (w); δ_H (400 MHz, $CDCl_3$) 8.27 (1H, app. d, *J* = 7.9 Hz, H-5), 7.77-7.68 (2H, m, H-7 and H-8), 7.46-7.41 (1H, m, H-6), 7.34 (2H, d, *J* = 8.2 Hz, H-17 and H-19), 7.14 (2H, d, *J* = 8.2 Hz, H-16 and H-20), 2.47-2.42 (5H, m, H-11 and H-21), 1.68 (2H, quin, *J* = 7.7 Hz, H-12), 1.26 (2H, sex, *J* = 7.5 Hz, H-13), 0.82 (3H, t, *J* = 7.4 Hz, H-14); δ_C (100 MHz, $CDCl_3$) 162.6, 157.4, 147.6, 139.2, 134.7, 134.4, 130.5, 128.0, 127.0, 127.0, 126.4, 120.7, 35.5 (C-11), 29.3 (C-12), 22.3 (C-13), 21.3 (C-21), 13.7 (C-14); HRMS (ESI) found 293.1643 $[M+H]^+$, $C_{19}H_{21}N_2O$ requires 293.1648.

2-Benzyl-3-*p*-tolylquinazolin-4(3*H*)-one 147



General procedure I was followed using (*Z*)-methyl *N*-2-bromophenyl-2-phenylacetimidate **139** (100 mg, 0.3 mmol) and *p*-toluidine (53 mg, 0.5 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 9:1) afforded the title compound as a yellow crystalline solid (72 mg, 67%). mp: 204-208 °C; ν_{max} (neat)/cm^{-1} 3304 (br), 3031 (br), 2922 (w), 1685 (s), 1608 (m), 1592 (m), 1568 (m), 1510 (w), 1496 (m), 1472 (m); δ_H (400 MHz, $CDCl_3$) 8.29 (1H, app. d, *J* = 7.9 Hz, H-5), 7.81-7.78 (2H, m, H-7 and H-8), 7.52-7.47 (1H, m, H-6), 7.22-7.14 (5H, m, H-14, H-15, H-16, H-20 and H-22), 6.94-6.89 (2H, m, H-13 and H-17), 6.85 (2H, d, *J* = 8.2 Hz, H-19 and H-23), 3.93 (2H, s, H-11), 2.42 (3H, s, H-24); δ_C (100 MHz, $CDCl_3$) 162.7, 155.6, 147.4, 139.2, 135.5, 134.5, 134.2, 130.0, 128.6, 128.3 (2C), 127.3, 127.1, 126.9, 126.8, 120.9, 42.6 (C-11), 21.3 (C-24); HRMS (ESI) found *m/z* 327.1491 $[M+H]^+$, $C_{22}H_{19}N_2O$ requires 327.1492.

Reaction of *N*-(2-bromophenyl)benzothioamide using general procedure I intended to afford 2-phenyl-4H-benzo[*d*][1,3]thiazin-4-one, afforded 2-Phenylbenzo[*d*]thiazole 149 as the sole product



General procedure H was followed using *N*-(2-bromophenyl)benzothioamide **148** (100 mg, 0.3 mmol). Flash chromatography (SiO_2, petrol/ethyl acetate 9:1) afforded the title compound as a yellow solid (69 mg, 95%). δ_H (400 MHz, $CDCl_3$) 8.14-8.09 (3H, m, Ar-H), 8.04 (1H, d, *J* = 8.0 Hz, Ar-H), 7.50-7.48 (4H, m, Ar-H), 7.42-7.37 (1H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 168.1, 154.2, 135.1, 133.6, 131.0, 129.0, 127.6, 126.3, 125.2, 123.3, 121.6. LRMS (ESI) *m/z* 212.0 (100%, $[M+H]^+$). Data consistent with literature data.[474]

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