Novel One-Pot Methods for the Synthesis of Heterocycles and Functional Aromatic Compounds

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A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

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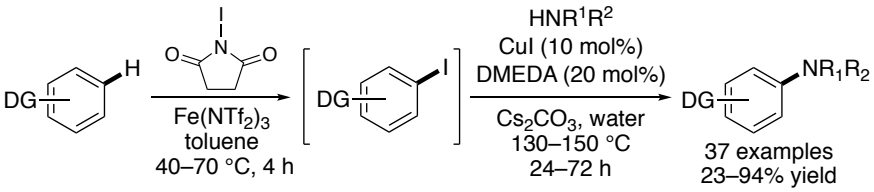
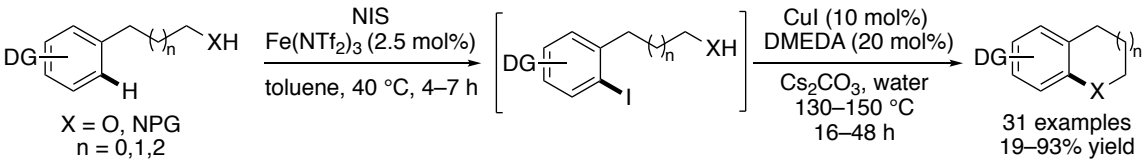
July 2020

Abstract

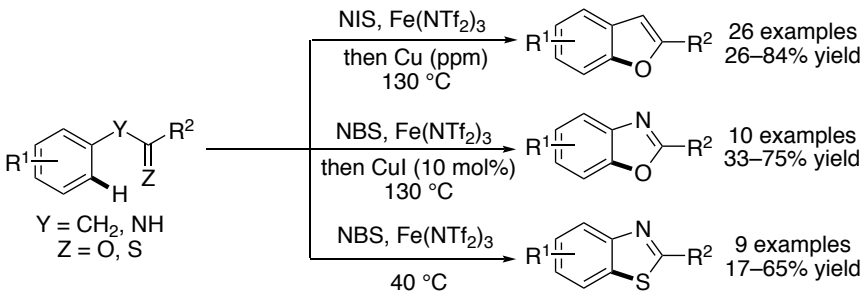
This PhD focused on the development of transition metal-catalysed one-pot processes for the rapid and selective formation of aryl C–N and C–O bonds from unactivated aryl C–H bonds. The key feature, common to all the processes, was the activation of aryl rings *via* a regioselective, iron triflimide-catalysed halogenation. After a brief description of a new iodination process in the first R&D section of this thesis, the second section details the development of a one-pot intermolecular aryl C–N bond forming process by copper-catalysed cross-coupling of *in situ* generated aryl iodides with unactivated *N*-nucleophiles.



The third section describes the extension of this methodology for the synthesis of indolines and 2,3-dihydrobenzofurans by intramolecular cross-coupling with pendant *N*- or *O*-nucleophiles. In addition to the synthesis of small libraries of heterocycles, this one-pot process was used as the key reaction in the 8-step total synthesis of neolignan natural product, (+)-obtusafuran.



The fourth and fifth sections detail the development of several one-pot processes for the synthesis of benzo[*b*]furans, benzoxazoles and benzothiazoles directly from the corresponding α-arylketones, *N*-arylbenzamides and *N*-arylthiobenzamides. Mechanistic insights as well as the synthesis of a range of biologically active heterocycles are presented.



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Acknowledgements

Firstly, I would like to thank my supervisor Dr Andy Sutherland for allowing me to undertake a PhD within his group. His help, support and guidance has been invaluable over the past four years.

I would like to express my appreciation of all the technical staff in the Joseph Black building for their help and assistance throughout my PhD: Andy and Jim (MS), David Adam (NMR), Ted, Finlay and Karen (Stores), Stuart and Arlene (IT), Jim McIver (ICP-AES) and Frank McGeoch.

Huge thank you to all the members of the Sutherland group past and present—Nikki, Alex, Kerry, Réka, Maria, Mirco, Holly, Leanne, Beckie, Amy, Rochelle and Nina. You have all made the Loudon lab a fantastic place to work. I want to thank Tim, for all his help throughout my PhD and for appreciating the excellence of Rush, to the distaste of others. Also, thanks to Mohamed for passing on his wisdom and teaching me the ways of the halogenation. Honourable mentions to Lewis Williams, for his insightful discussions and Jonathan, for organising the fateful Loudon lab cup. Thank you to my project students Rochelle and Jessica, it was a good experience working with you both. Thanks to all the members of the Hartley group, especially BSL and Stuart, as well as the Prunet group for contributing to the fantastic atmosphere of the Loudon lab.

Finally, thanks to my mum and dad for their infinite support and help with everything. Abi, thank you for all your support and keeping me sane throughout my PhD. You're an ok person.

Financial support from the EPSRC is gratefully acknowledged.

Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis represents the original work of Martyn C. Henry and has not been submitted for any other degree at the University of Glasgow or any other institution. The research was carried out at the University of Glasgow in the Loudon Laboratory under the supervision of Dr Andrew Sutherland between October 2016 and February 2020. Aspects of the work described herein have been published elsewhere as listed below.

M. C. Henry, M. A. B. Mostafa and A. Sutherland, Recent Advances in Transition Metal-Catalyzed, Directed Aryl C–H/N–H Cross-Coupling Reactions, *Synthesis*, 2017, **49**, 4586–4598.

M. A. B. Mostafa, R. M. Bowley, D. T. Racys, **M. C. Henry** and A. Sutherland, Iron(III)-Catalyzed Chlorination of Activated Arenes, *J. Org. Chem*. 2017, **82**, 7529–7537.

M. C. Henry, R. McGrory, R. J. Faggyas, M. A. B. Mostafa and A. Sutherland, One-Pot *ortho*-Amination of Aryl C–H Bonds Using Consecutive Iron and Copper Catalysis, *Org. Biomol. Chem*., 2019, **17**, 4629–4639.

M. C. Henry, H. M. Senn and A. Sutherland, Synthesis of Functionalized Indolines and Dihydrobenzofurans by Iron and Copper Catalyzed Aryl C–N and C–O Bond Formation, *J. Org. Chem*., 2019, **84**, 346–364.

M. C. Henry and A. Sutherland, Synthesis of Benzo[*b*]furans by Intramolecular C–O Bond Formation Using Iron and Copper Catalysis, *Org. Lett*., 2020, **22**, 2766–2770.

M. C. Henry, V. M. Abbinante and A. Sutherland, Iron-Catalyzed Regioselective Synthesis of 2-Arylbenzoxazoles and 2-Arylbenzothiazoles *via* Alternative Reaction Pathways, *Eur. J. Org. Chem*., 2020, 2819–2826.

Signature _____

Printed Name Martyn C. Henry

Abbreviations

Ac	Acetyl
AIBN	Azobisisobutyronitrile
Ar	Aromatic
BMIM	1-Butyl-3-methylimidazolium
Bn	Benzyl
br	Broad
Boc	*tert*-Butyloxycarbonyl
bpy	2,2′-Bipyridine
Bz	Benzoyl
Cbz	Carboxybenzyl
dba	Dibenzylideneacetone
COSY	Correlated spectroscopy
Cp*	Pentamethylcyclopentadiene
d	Doublet
DAIPEN	1,1-Bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless enhancement polarisation transfer
DFT	Density functional theory
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMEDA	*N*,*N*′-Dimethylethylenediamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPEphos	Bis[(2-diphenylphosphino)phenyl]ether
dr	Diastereomeric Ratio
e.e.	Enantiomeric Excess
EDCI	Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	Electron impact
equiv.	Equivalents
er	Enantiomeric Ratio

ESI	Electrospray ionisation
Et	Ethyl
g	Grams
GI_{50}	Concentration for 50% of maximal inhibition of cell proliferation
h	Hour
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate
hfacac	Hexafluoroacetylacetone
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMBC	Heteronuclear multiple bond correlation
HOBt	1-Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
^{i}Bu	Isobutyl
IC_{50}	Half maximal inhibitory concentration
^{i}Pr	Isopropyl
J	Coupling constant
HMDS	Hexamethyldisilazide
lit.	Literature
LUMO	Lowest unoccupied molecular orbital
M	Molar
m	Multiplet
m-	*meta*
m-CPBA	*meta*-Chloroperoxylbenzoic acid
Me	Methyl
MHz	Megahertz
min	Minutes
mol	Moles
Mp	Melting point
Ms	Mesyl
m/z	Mass to charge ratio

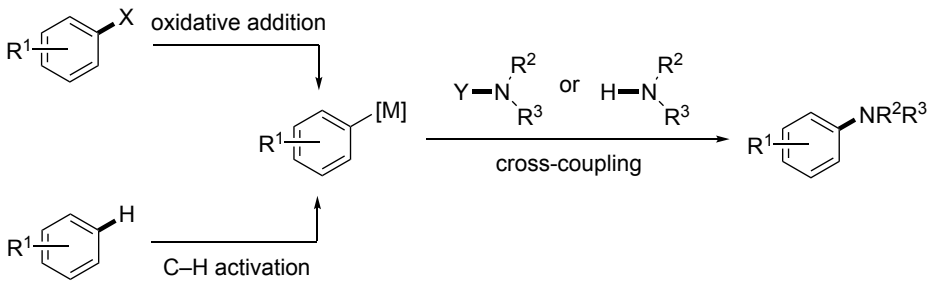
NBS	*N*-Bromosuccinimide
^{n}Bu	*n*-Butyl
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine *N*-oxide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
o-	*ortho*
p-	*para*
PCC	Pyridinium chlorochromate
PET	Positron emission tomography
Ph	Phenyl
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
ppm	Parts per million
q	Quartet
quin.	Quintet
rt	Room temperature
s	Singlet
SAR	Structural activity relationship
DM-Seghos	5,5′-Bis(diphenylphosphino)-4,4-bi-1,3-benzodioxole
sept	Septet
SET	Single electron transfer
S_NAr	Nucleophilic aromatic substitution
SPECT	Single-photon emission computed tomography
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

TLC	Thin-layer chromatography
TMHD	2,2,6,6-Tetramethyl-3,5-heptanedione
TMS	Trimethylsilyl
Ts	Tosyl
UV	Ultraviolet
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
°C	Degrees centigrade

1.0 Introduction

1.1 Transition Metal-Catalysed Aromatic C–N Bond Formation

Arene C–N bonds are prevalent in valuable natural products, pharmaceutical agents, biologically active compounds and organic materials, hence, a wide range of methods have been developed for the synthesis of this motif.[1,2] In particular, transition metal catalysis has proved indispensable in this endeavor.[3] There are three significant pathways through which this can occur: pre-functionalisation of aryl substrates then cross-coupling with *N*-nucleophiles; C–H activation then cross-coupling with pre-functionalised amino sources; or direct C–H/N–H coupling of unactivated aromatic compounds and amines (Scheme 1). The latter approach, known as cross-dehydrogenative coupling, is a highly desirable and long sought reaction mode and is in the early stages of development with work currently ongoing to fully realise its potential.[4–7]

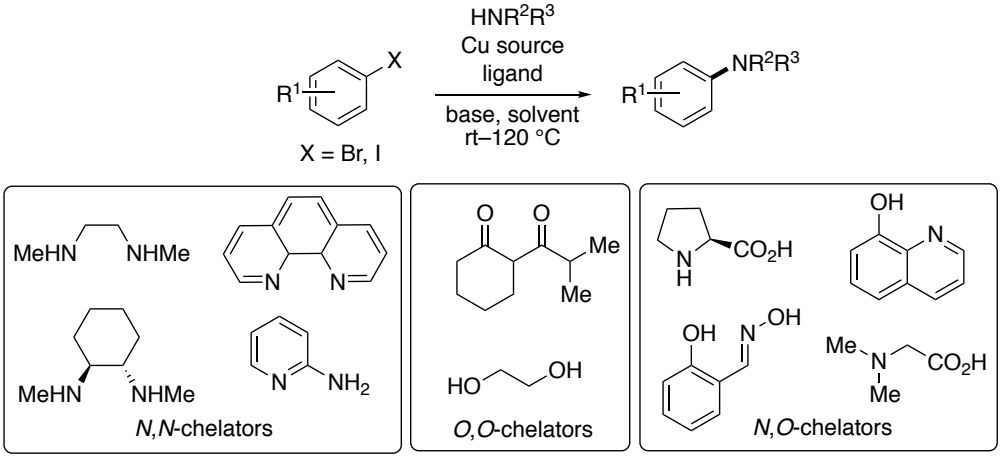


Scheme 1: Transition metal-mediated C–N bond formation

1.1.1 Pre-Functionalisation of the Arene Partner

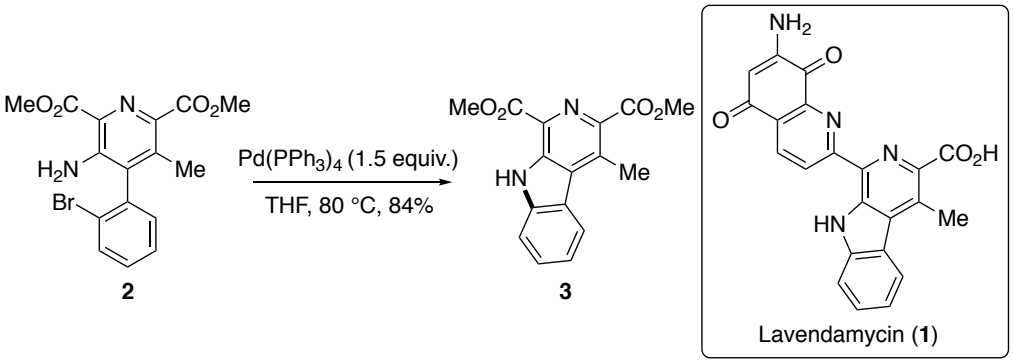
In the opening years of the 20th century, Ullmann and Goldberg discovered the reaction of aryl halides with amines or alcohols in the presence of copper which allowed regioselective C–N or C–O bond formation.[8,9] Despite its potential, this reaction failed to gain wide applicability in the synthetic community due to the harsh reaction conditions, with the reaction temperature often exceeding 200 °C and requiring the use of stoichiometric copper reagents. This changed around the year 2000, with reports from Ma,[10,11] Goodbrand,[12] Nicolaou,[13] Liebkind[14] and Buchwald[15–18] demonstrating that bidentate, chelating copper ligands resulted in a substantial rate acceleration and allowed for this transformation to be carried out under comparatively mild conditions. These reports brought about a resurgence of

interest in this copper-catalysed transformation and as a result, this reaction has since become the focus of intense research in a bid to widen the scope and utility.[19–21] This focus has allowed the development of a 'copper-catalysis toolbox' in which a vast array of protocols have been optimised using a range of copper sources and bidentate ligands, including *N*,*N*-, *O*,*O*- and *N*,*O*-chelators (Scheme 2).[22] With careful selection of copper salt, bidentate ligand and base, this transformation can be used for a wide variety of aryl halide and amine coupling partners under relatively mild reaction conditions.[23–25]



Scheme 2: Ullmann-Goldberg 'copper-catalysis toolbox'

The Ullmann-Goldberg reaction has largely been superseded by the development of palladium-catalysed methods which have since become the primary method for the formation of aryl C–N bonds. Beginning in 1983, Migita disclosed a cross-coupling reaction between aryl bromides and tin amides using palladium-catalysis.[26] The following year, Panek and Boger discovered a facile palladium-mediated intramolecular amination which allowed for the synthesis of a carboline ring system as a key step in their total synthesis of anti-tumour antibiotic, lavendamycin (**1**).[27] After attempts at the ring closure of **2** using an intramolecular S_NAr reaction failed to give any product due to the non-coplanarity of the biaryl system, the use of tetrakis(triphenylphosphine)palladium(0) was investigated. Despite requiring an excess of the palladium complex, the C–N bond formation was efficient and allowed the formation of β-carboline **3** in 84% yield (Scheme 3). It was thought that the success of this transformation was the accessibility of a twisted 6-membered palladacycle from which reductive elimination could readily occur.

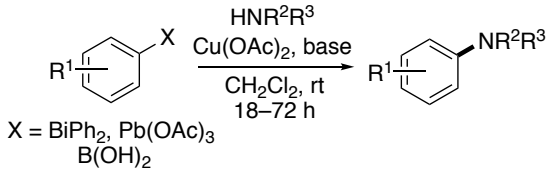


Scheme 3: Panek and Boger's palladium-mediated C–N bond formation

The palladium-catalysed C–N bond forming reaction remained underexploited until the 1990s, when Buchwald and Hartwig independently offered mechanistic insights and improved the scope of Migita's original work for the coupling of aryl halides and tin amides.[28,29] Soon after this, both groups reported that this transformation could be undertaken using tin-free conditions, avoiding toxic reagents and non-trivial work-up procedures, while allowing the coupling of unactivated alkyl amines, including secondary cyclic amines.[30,31] The use of sterically hindered, large cone-angle phosphine ligands in combination with a suitable base and solvent was vital for this reaction. Since these initial studies, this methodology rapidly evolved into a general cross-coupling procedure with a wide scope and functional group tolerance, allowing the coupling of aryl halides with a wide variety of *N*-nucleophiles.[32,33] For more difficult cross-coupling reactions, the reactivity can be easily improved by altering the phosphine ligands, affecting the σ-donation and π-back donation and hence, tuning the electronic and steric environment at the palladium metal centre. To date, there are multiple generations of phosphine ligands as well as a range of palladium complexes which offer this possibility.[34,35] Limitations of this methodology endure however, with the requirement for strongly basic conditions, generally high reaction temperatures and the use of expensive and toxic palladium pre-catalysts.[36]

Contemporaneous with the development of the Buchwald-Hartwig amination, a distinctive oxidative cross-coupling approach for aryl C–N formation was under investigation (Scheme 4). In the 1980s, the *N*-arylation of amine derivatives was studied involving the cross-coupling of nucleophilic arylbismuth or aryllead compounds with catalytic quantities of copper(II) acetate.[37,38] These reactions used an inexpensive source of copper and proceeded at room temperature however,

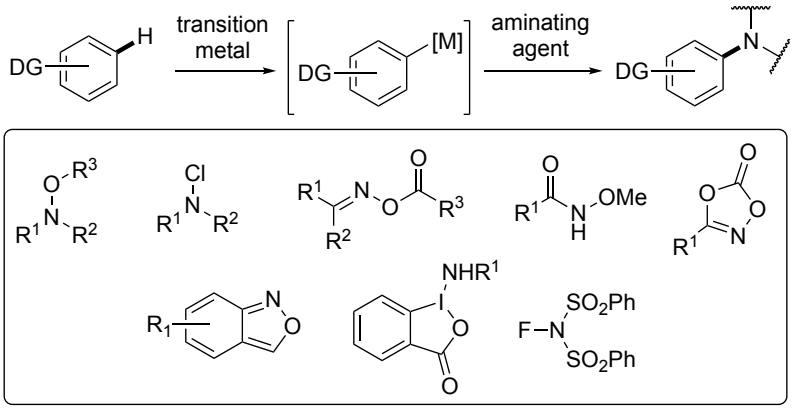
there was considerable toxicity associated with the metalated aryl reagents alongside their difficult preparation. For example, aryllead triacetate reagents are typically prepared by the reaction of lead tetraacetate with the desired aryl stannane in the presence of catalytic quantities of mercury trifluoroacetate.[39] To address these issues, the copper-mediated Chan-Evans-Lam reaction was developed and first described in 1998.[40–42] This method substitutes the aromatic bismuth or lead reagents for commercially available or readily accessible aryl boronic acids, uses mild reaction conditions under an atmosphere of air and allows the coupling with a wide range of *N*-nucleophiles such as anilines, amides, sulfonamides, ureas and alkyl amines. The Chan-Evans-Lam coupling has since become the focus of many mechanistic investigations and has found wide applicability in natural product synthesis and medicinal chemistry.[43]



Scheme 4: Nucleophile-nucleophile cross-coupling for C–N bond formation

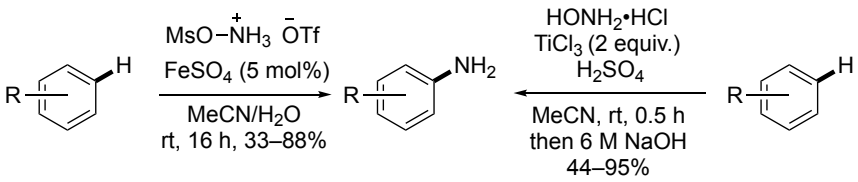
1.1.2 Pre-Functionalisation of the Amino Source

An alternative method involves the direct amination of aromatic C–H bonds with activated, electrophilic amino reagents. This approach allows selective activation of inert aromatic C–H bonds with transition-metals and then reaction of the *in situ* generated nucleophilic metalated intermediate with an electrophilic aminating reagent, resulting in C–N bond formation (Scheme 5). As well as insertion into C–H bonds, the transition-metal catalyst can oxidatively cleave the polarised N–X bonds of the electrophilic amines hence, no external oxidants are required in this process. A wide variety of novel aminating agents have been reported including hydroxylamines,[44,45] chloroamines,[46–50] substituted oximes,[51] *N*-methoxyamides,[52] 1,4,2-dioxazol-5-ones,[53] anthranils[54] and hypervalent amidobenziodoxolones[55] each with individually optimised catalytic conditions. In addition, the use of *N*-fluorobenzenesulfonamide (NFSI) has gained attention as an efficient amidating agent in a wide range of palladium-catalysed cross-coupling protocols.[56–58]



Scheme 5: C–H amination with activated aminating agents

In a distinct process, transition metals and electrophilic hydroxylamines have been used for the direct preparation of anilines, presumably *via* radical-mediated pathways.[59] For example, the Morandi group developed a practical synthesis of anilines using iron(II)-catalysis while Sanford and co-workers reported a room temperature, titanium(III)-mediated aryl-C–H amination with hydroxylamine hydrochloride as the inexpensive amine source (Scheme 6).[60,61] These protocols are operationally simple and use inexpensive, stable reagents under mild conditions however, *ortho*/*para*-selectivity was often poor with unsymmetrical aromatic substrates. For example, the reaction of anisole with hydroxylamine hydrochloride under Sanford's conditions resulted in a 1:2.2 mixture of *ortho*- to *para*-regiosiomers in 76% yield as well as some di-aminated product (<20% yield). Similar iron-promoted redox processes have been reported by Ritter[62] and Jiao[63] for the synthesis of anilines by C–H amination of unactivated aryl compounds.

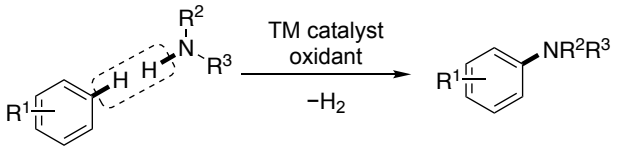


Scheme 6: Morandi and Sanford's aniline synthesis by C–H amination

1.2 Direct C–H/N–H Cross-Dehydrogenative Coupling

Aryl C–N bond formation by direct C–H/N–H cross-dehydrogenative coupling (Scheme 7) represents the most step- and atom economical route as there is no requirement for pre-activation of either coupling partner, avoiding tedious starting

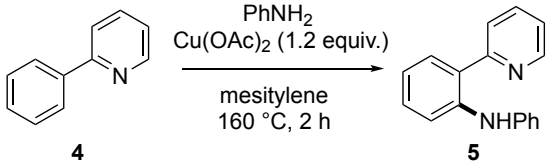
material synthesis and stoichiometric waste such as halide-salts. These advantages notwithstanding, several challenges need to be overcome before this method is generally applicable to the same extent as the Ullmann-Goldberg, Buchwald-Hartwig and Chan-Evans-Lam cross-coupling reactions. Primarily, formation of a C–N bond with formal loss of H_2 is a thermodynamically unfavourable process as the strong C–H and N–H bonds of the reactants are converted into weaker bonds. As a consequence, a sacrificial oxidant is almost always required as an appropriate external driving force. The high activation barrier associated with this transformation can also be reduced by careful selection of transition metal and ligand combinations while ensuring the compatibility of the oxidative conditions with the chosen catalytic system. Furthermore, the highly nucleophilic unactivated amines and amides, present in excess, bind strongly to transition metal centres and often results in catalyst deactivation. With highly active primary amine nucleophiles, regioselectivity is a non-trivial issue and requires the use of auxiliary directing groups, particularly with intermolecular cross-couplings.



Scheme 7: C–N bond formation by cross-dehydrogenative coupling

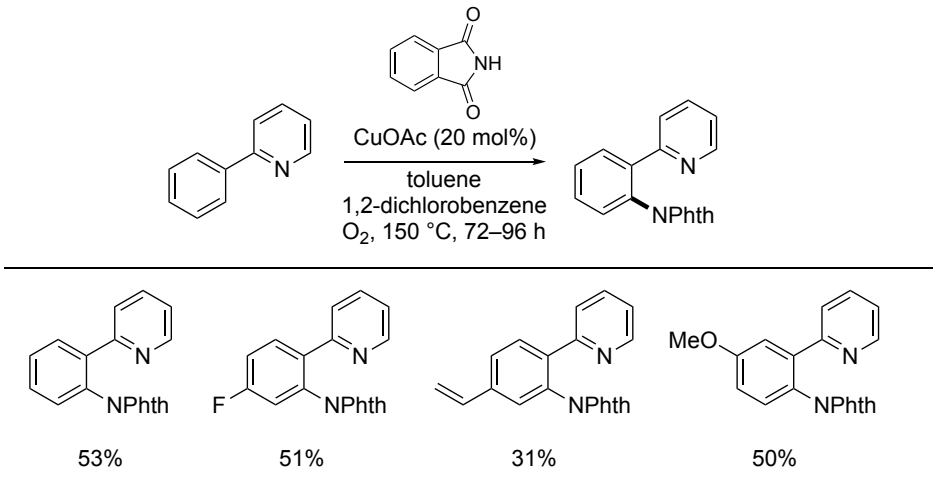
1.2.1 Intermolecular *ortho*-C–N Bond Formation with Copper Catalysis

The first known examples of transition metal-mediated intermolecular cross-dehydrogenative amidation with unactivated *N*-nucleophiles were reported by Yu and Chatani in 2006.[64,65] In both processes, a 2-pyridyl group was used as a directing group to facilitate the copper-mediated cleavage of the inert *ortho*-C–H bond of **4** which then permitted cross-coupling with aniline to give **5** (Scheme 8). Yu evoked a radical-mediated C–H activation mechanism, with single electron transfer from the coordinated copper(II)-metal centre to the arene ring.[64] Due to the difficult nature of this transformation, stoichiometric quantities of the copper(II) species were required as well as a very high reaction temperature.



Scheme 8: Copper-promoted intermolecular *ortho*-C–H amidation of 2-phenylpyridine

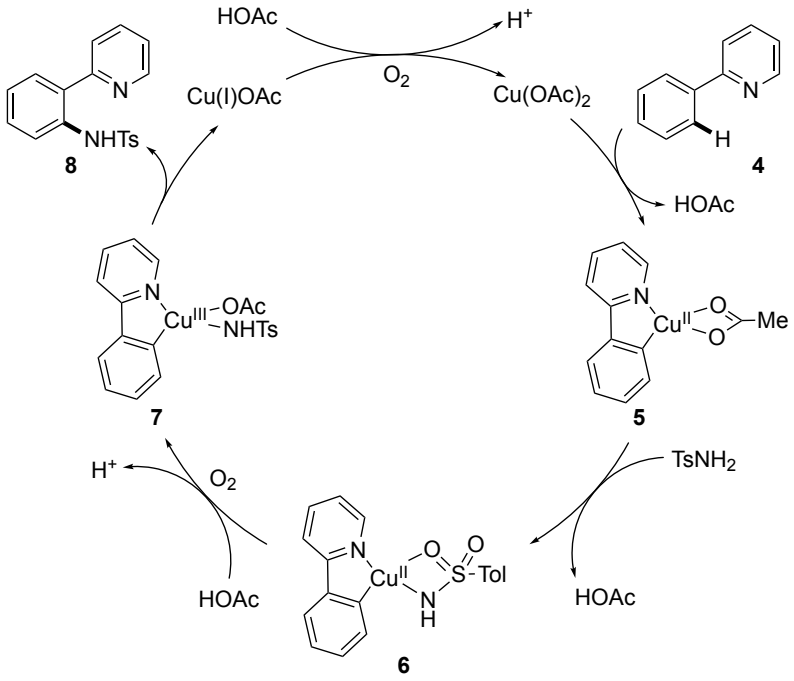
These early observations encouraged intense research in the field of cross-dehydrogenative amination and led to the development of catalytic protocols for the *ortho*-C–H amination of 2-arylpyridines with unactivated amines and amides.[66–71] For example, Shen and co-workers reported a copper-catalysed cross-dehydrogenative coupling of 2-arylpyridines with phthalimide as the aminating source and with molecular oxygen as a terminal oxidant (Scheme 9).[68] This method used only 10 mol% of copper acetate however, the reactions required high temperature (150 °C) and extended reaction times of up to 72 h. The authors proposed that this amidation procedure represented an efficient access to arylamines, as phthalimide acts as an ammonia surrogate and can be converted to the primary aniline derivative by reaction with hydrazine using the Gabriel reaction.



Scheme 9: Copper-catalysed *ortho*-C–H amidation with phthalimide

Similarly, John and Nicholas found that this C–H amination/amidation process was efficient using copper(II) acetate (20 mol%) and oxygen for the coupling of 2-phenylpyridine with a range of *N*-nucleophiles including sulfonamides, benzamides and electron-deficient anilines.[67] The exact mechanism of copper(II)-catalysed aryl C–N bond formation is still not established however, a plausible catalytic cycle has been proposed (Scheme 10).[67] The first step involves coordination of copper(II)

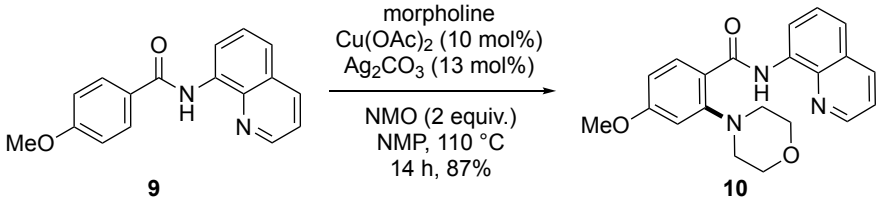
acetate to the 2-pyridine nitrogen atom of **4** followed by C–H activation, either by single-electron transfer or electrophilic aromatic substitution, to give organocopper intermediate **5**. Ligand exchange of the acetate with the *N*-nucleophile results in the formation of complex **6** which is followed by protonation and one-electron oxidation to give a copper(III) intermediate **7**. Reductive elimination of **7** then gives *ortho*-amidated 2-phenylpyridine compound **8** with simultaneous release of copper(I) acetate, which then undergoes aerobic oxidation to regenerate the active catalyst.



Scheme 10: Proposed mechanism for the intermolecular C–H amidation of 2-phenylpyridines

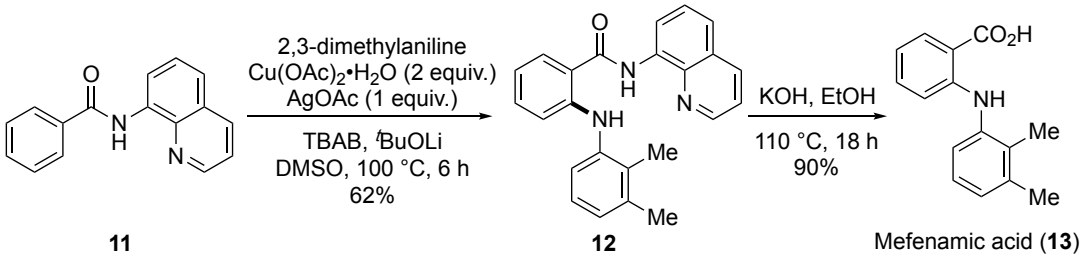
With the 2-pyridine directing group, these copper-catalysed C–H amination reactions required strong oxidants, high temperatures and long reaction times. Furthermore, the 2-pyridine functionality is intrinsic to the compound and cannot be removed, further limiting the synthetic utility of these protocols. To address these issues, new removeable auxiliary directing groups, derived from simple carboxylic acid and aniline compounds were developed.[72] In 2013, Daugulis and co-workers demonstrated that 8-aminoquinoline was an effective bidentate chelator and permitted the selective activation and amination of inert *ortho*-C–H bonds.[73] This procedure used a copper and silver catalytic system with *N*-methylmorpholine *N*-oxide (NMO) as an oxidant and allowed the coupling of **9** with morpholine which gave **10** in 87% yield (Scheme 11). This procedure tolerated a wide range of cyclic

and acyclic secondary amines under relatively mild conditions. No explicit mechanistic studies were undertaken however, similar to other copper-catalysed cross-coupling procedures, this reaction was thought to proceed *via* an aryl-copper(III) intermediate.[74] The group were then able to expand the scope of this process to include electron-rich primary amines and electronically neutral anilines with a lower reaction temperature (80 °C), albeit with the requirement for one equivalent of copper(II) acetate. This new protocol was efficient in the absence of the silver co-catalyst and with tetrabutylammonium iodide as the oxidant.[75] A modified system using copper carbonate hydroxide and tetramethylguanidine as a base allowed the cross-coupling of a range of *N*-heterocycles including pyrazole, carbazole and 7-azaindole.



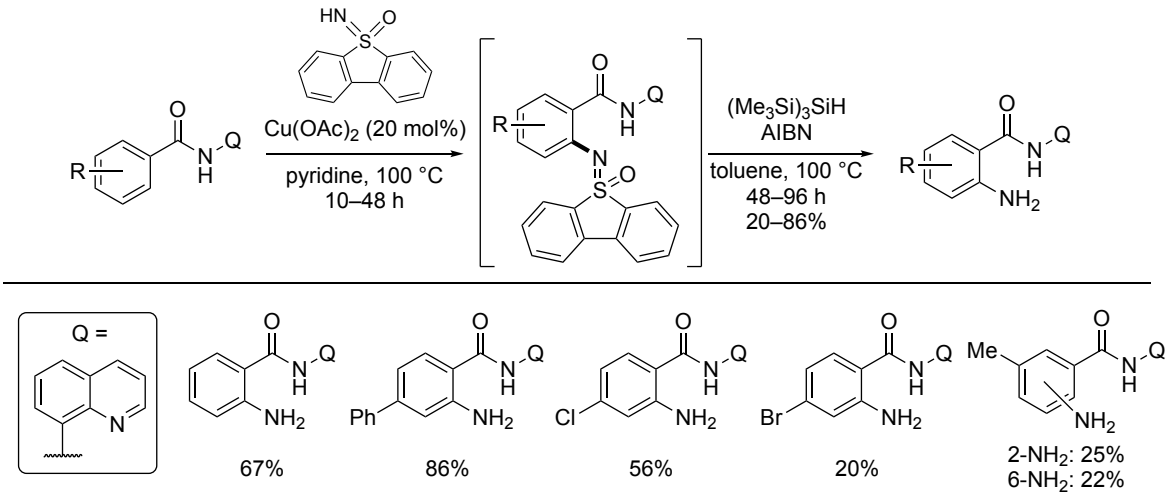
Scheme 11: 8-Aminoquinoline directed, intermolecular C–H amination of benzamides

The 8-aminoquinoline auxiliary has since found wide utility in a variety of cross dehydrogenative coupling reactions.[76–78] For example, Jana and co-workers were able to use this directing group and expand the scope of the transformation to include electron-rich anilines under basic conditions, although two equivalents of copper(II) acetate were required.[77] In most cases, the presence of even a trace amount of molecular oxygen was found to be detrimental to the reaction therefore, a mixture of silver(I) acetate and tetrabutylammonium bromide were found to be the optimal oxidising agents. In their study, the coupling of 8-aminoquinoline protected benzoic acid **11** with 2,3-dimethylaniline, gave coupled product **12** in 62% yield. Alkaline hydrolysis of **12** gave mefenamic acid (**13**), a non-steroidal anti-inflammatory drug (Scheme 12).



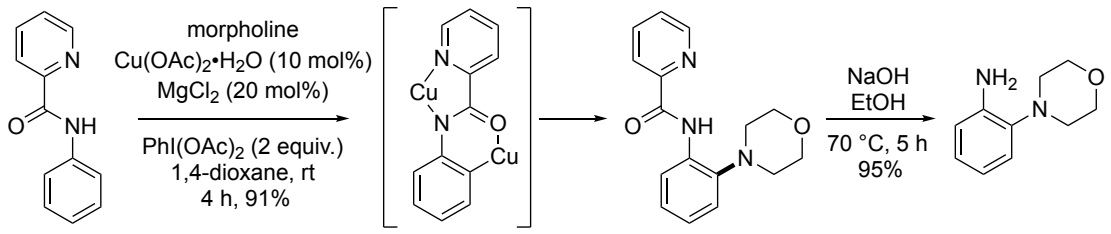
Scheme 12: Synthesis of mefenamic acid (13) by copper-mediated C–H amination

The Bolm group has recently undertaken several studies into the cross-dehydrogenative coupling of unreactive C–H bonds and *N*-sulfoximines.[69,79] More specifically, the group developed a one-pot, two-step process for the synthesis of free anilines which used an 8-aminoquinoline auxiliary to direct copper(II) acetate-catalysed cross-dehydrogenative coupling of dibenzothiophene sulfoximine as an ammonia surrogate (Scheme 13).[78] This process was efficient for a range of substituted benzamides however, some limitations were noted. With a 4-bromo analogue, reductive dehalogenation was found to be a significant side-reaction, while with a 3-methyl substituted benzamide, a mixture of regioisomers was obtained. Without isolation of the *N*-arylated sulfoximines, radical mediated S=N bond cleavage was achieved using a mixture of tris(trimethylsilyl)silane and AIBN in toluene at 100 °C which gave the parent aniline and completed the one-pot process. This methodology does provide selective access to 2-aminobenzamides however, is limited due to atom inefficiency and the requirement of extended reaction times (up to six days in some cases).



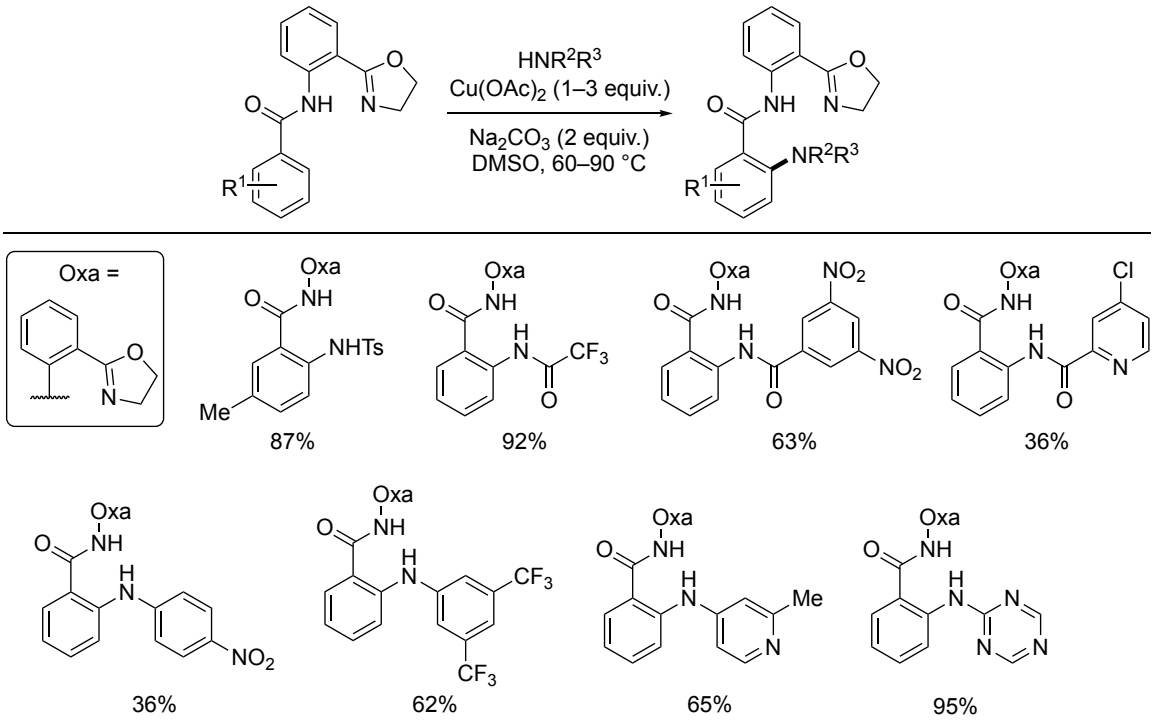
Scheme 13: *ortho*-C–H Amination with dibenzothiophene sulfoximine as an ammonia surrogate

Arrayas and Rodrigues reported that picolinamide protected aniline derivatives are good substrates for intermolecular copper-catalysed amination.[80] With (diacetoxyiodo)benzene as an oxidant and a reaction temperature of 80 °C, this cross dehydrogenative coupling was efficient for a range of cyclic, secondary amines. A few months after this report, Chen and co-workers disclosed the same picolinamide directed, oxidative C–H amination process.[81] With $PhI(OAc)_2$ as an oxidant and in the presence of magnesium chloride, this reaction proceeded at room temperature, was complete in 4 h and generally gave a wide-range of *ortho*-aminated aromatic compounds in excellent yields. The facile nature of this transformation was ascribed to the binding of the imidate *O*-atom to copper, facilitating C–H amination through the formation of a stable 6-membered *O*-ligated metallacycle (Scheme 14). Although this organometallic pathway was hypothesised, the authors could not rule out a single electron transfer mechanism as the addition of TEMPO was shown to inhibit the reactions. Due to the electron-deficient pyridine ring, the picolinic acid auxiliary was easily removed under basic conditions and gave the *ortho*-aminated aniline in 95% yield.



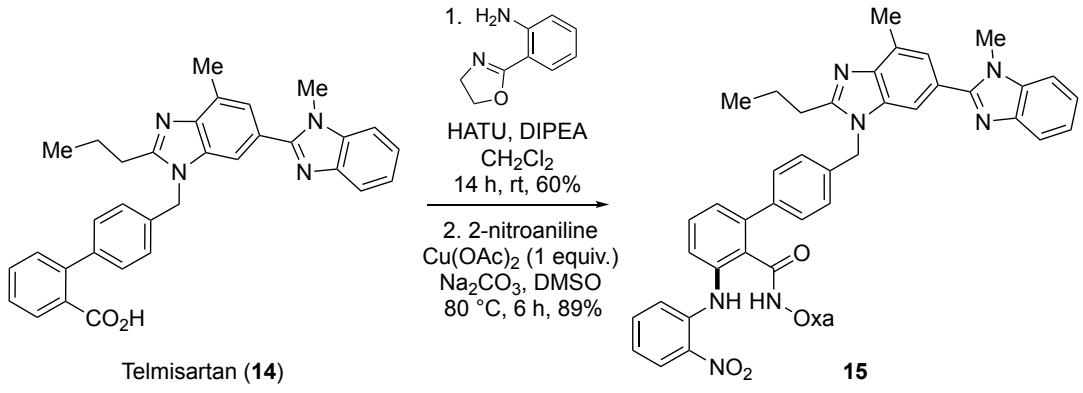
Scheme 14: Copper-catalysed *ortho*-C–H amination of picolinamide protected anilines

Yu and Dai exploited the well-known strong coordinating ability of oxazoline to copper(II) catalysts[82] and developed an amide tethered oxazoline directing group for the direct cross-dehydrogenative coupling of aryl-C–H bonds and *N*-nucleophiles.[83–85] This protocol used stoichiometric or excess quantities of copper(II) acetate and allowed the efficient coupling of oxazoline-substituted *N*-arylbenzamides and heteroaryl substrates with a wide range of sulfonamides, benzamides and electron-deficient anilines (Scheme 15).[83] The scope of this process has recently been expanded to include a wide range of *N*-heterocycles including imidazole, pyrazole, pyridine, purine as well as azaindoles.[84]



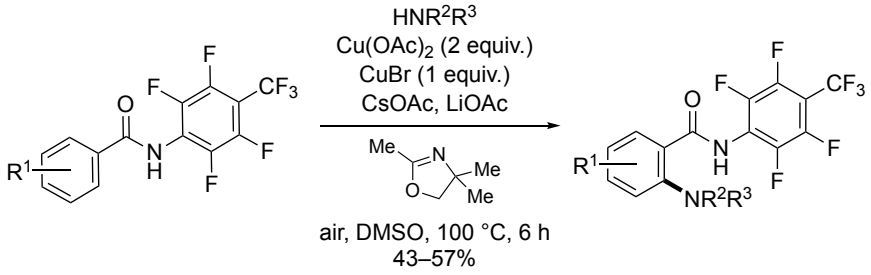
Scheme 15: Oxazoline directed, copper-catalysed C–N bond formation

The Yu group then applied this C–H amination and amidation methodology for the late-stage functionalisation of telmisartan (**14**), an angiotensin II receptor antagonist, used in the treatment of high-blood pressure and heart failure (Scheme 16).[85] The oxazoline auxiliary was installed using a simple amide coupling reaction between the carboxylic acid functional group and 2-(4,5-dihydrooxazol-2-yl)aniline using HATU. This was followed by directed activation of the *ortho*-C–H bond with copper(II) acetate which permitted cross-coupling with 2-nitroaniline and gave **15** in 89% yield.



Scheme 16: Late-stage functionalisation of telmisartan (14)

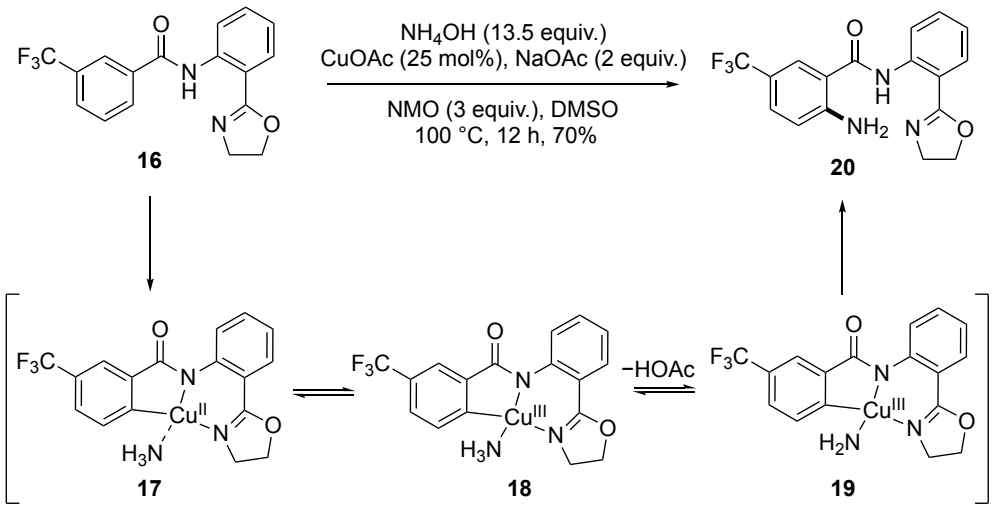
Subsequent studies within the Yu and Dai groups investigated the use of weakly coordinating amide auxiliaries with the assistance of a monodentate oxazoline ligand for cross dehydrogenative coupling reactions (Scheme 17).[86] They proposed that while strongly chelating auxiliaries are efficient for C–H activation, they often form 5- or 6-membered cyclometalated intermediates which are thermodynamically stable and hence, less reactive in the subsequent functionalisation step.[87] This limits the scope and utility of such a process. A drastic reduction of the electron density of the benzamide auxiliary necessarily decreases the ability of the amide nitrogen to donate electrons to the vacant d-orbitals of the metal centre. It is then reasoned that this decreased electron donation will lead to a less stable metallacycle, thereby kinetically assisting the amination step. In this context, the very electron deficient 2,3,5,6-tetrafluoro-4-trifluoromethyl)phenyl-substituted amide was used as a directing group in this copper-mediated, oxazoline accelerated C–H amination procedure (Scheme 17). This worked with electron-rich, unprotected cyclic secondary amines and gave the desired coupled products in moderate yields.



Scheme 17: Intermolecular *ortho*-C–H amination with weakly coordinating directing group

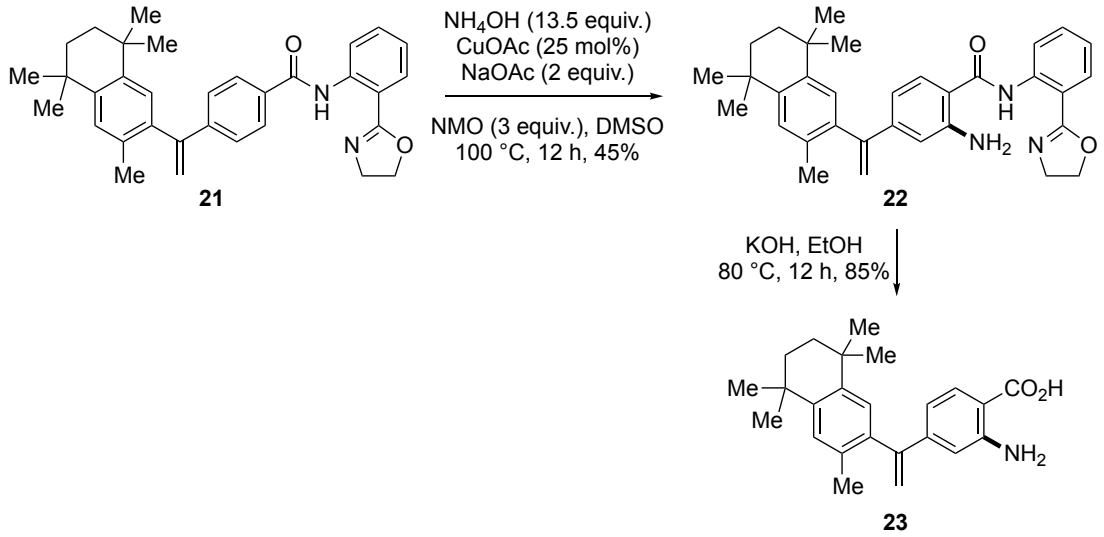
In 2017, Chang and co-workers developed an elegant copper-mediated, oxazoline-directed C−H amination with aqueous ammonia as the amino source.[88] The use of ammonia as an amino source for the direct cross-coupling amination of unreactive C–H bonds remains a significant challenge in synthetic chemistry.[89,90] Firstly, transition metal-catalysed activation of N–H bonds of ammonia is a difficult, energetically demanding process with a bond dissociation energy of 107 kcal/mol. Secondly, ammonia is an excellent ligand for transition metals, binding almost exclusively *via* the σ-donation of the nitrogen lone pair, resulting in rapid formation of a metal-amido ‘Werner’ complex, inevitably leading to inhibition of the catalytic turnover in the desired amination reaction.[91]

Critical to the success of Chang's method was the use of a soft, d^{10} copper(I)-complex which avoided the strong coordination of ammonia and minimised catalyst deactivation. After initial coordination of copper(I) to the bidentate, oxazoline auxiliary of **16**, oxidation is assumed to occur to give a copper(II) intermediate (Scheme 18). Activation of the *ortho*-C–H bond then occurs, presumably by acetate-assisted deprotonative cupration to afford a cyclometalated copper(II) intermediate which then undergoes ligand exchange with ammonia and gives intermediate **17**. Interestingly, DFT calculations revealed that deprotonation of ammonia from copper(II) intermediate **17** was thermodynamically not feasible however, it was found that **17** can disproportionate and produce a lower energy copper(III) intermediate. The hard Lewis acidic nature of copper(III) complex **18** increases the strength of the metal-ligand interactions and lowers the energy of **18** relative to copper(II) intermediate **17**. As a consequence, the acidity of the amine ligand drastically increases, with the energy barrier for deprotonation of metal-amino complex **18** being reduced by 13 pK_a units. After deprotonation of metal-amino complex **18**, facile reductive elimination from **19** then gives aniline **20** in 70% yield.



Scheme 18: Copper-catalysed *ortho*-C–H amination with aqueous ammonia

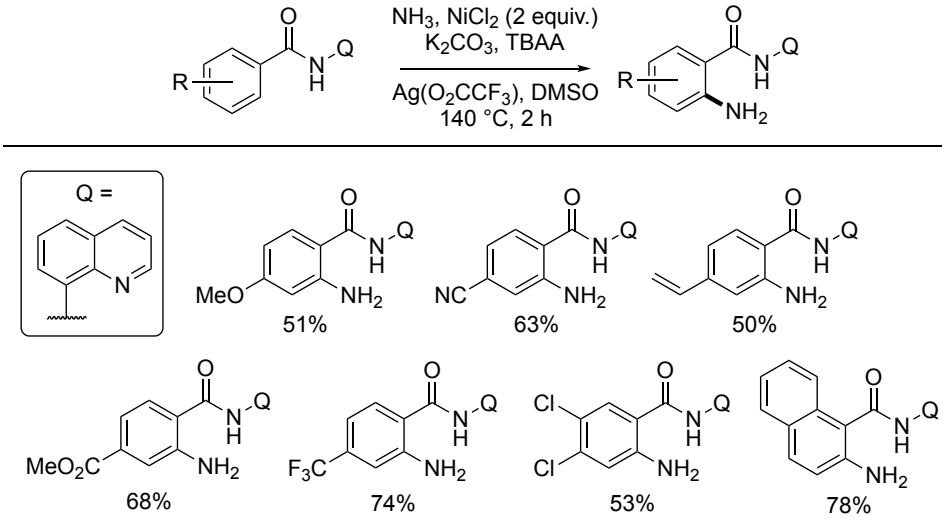
This methodology was used for the late-stage amination of pharmaceutically relevant compounds, including oxazoline-substituted bexarotene (**21**) (Scheme 19). Treatment of **21** with excess aqueous ammonia, copper(I) acetate, sodium acetate and NMO allowed the selective installation of an amino group and gave **22** in 45% yield. Alkaline hydrolysis of the oxazoline auxiliary gave the amino derivative of bexarotene (**23**) in 85% yield.



Scheme 19: Late-stage functionalisation of bexarotene (21)

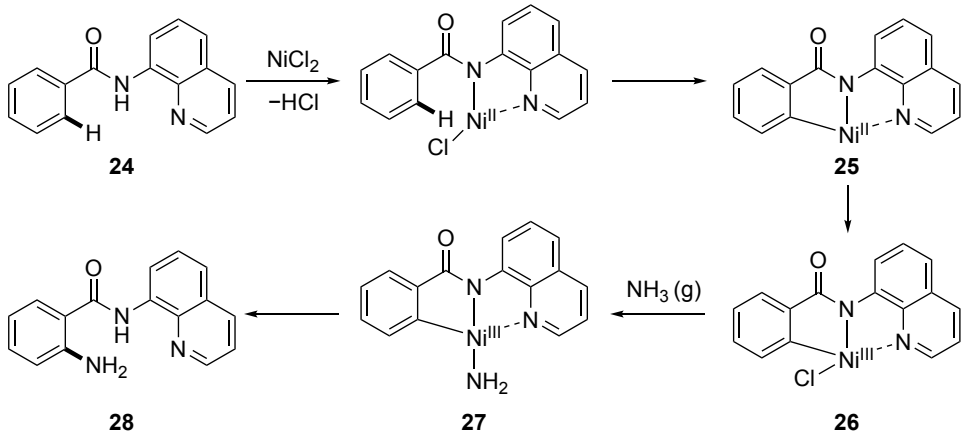
1.2.2 Intermolecular *ortho*-C–N Bond Formation with Other Transition Metals

In addition to copper-catalysis, other inexpensive and abundant first-row transition metals in conjunction with bidentate, chelating auxiliaries have been successfully used for cross-dehydrogenative coupling reactions.[92–95] For example, Liu and Zhang reported an 8-aminoquinoline directed, nickel-catalysed *ortho*-C–H amination of benzamides with cyclic and acyclic secondary amines.[92] Elevated reaction temperatures (140 °C) were necessary for high yields of the coupled products, while primary aliphatic amines and anilines were incompatible with the oxidising conditions of this protocol. Very recently, Tan and co-workers directly employed ammonia gas in a nickel-mediated cross dehydrogenative amination, also directed by an 8-aminoquinoline auxiliary (Scheme 20).[93] This method required a stoichiometric quantity of nickel(II) chloride in combination with tetrabutylammonium acetate (TBBA) to allow conversion to the aminated benzamide products and avoid the poisoning of the nickel species. Despite the harsh reaction conditions (140 °C), the functional *ortho*-amino adducts were isolated in moderate to high yields. While silver trifluoroacetate was not required for an efficient transformation, higher yields were obtained when two equivalents of this additive were used.



Scheme 20: Nickel-promoted *ortho*-C–H amination with ammonia

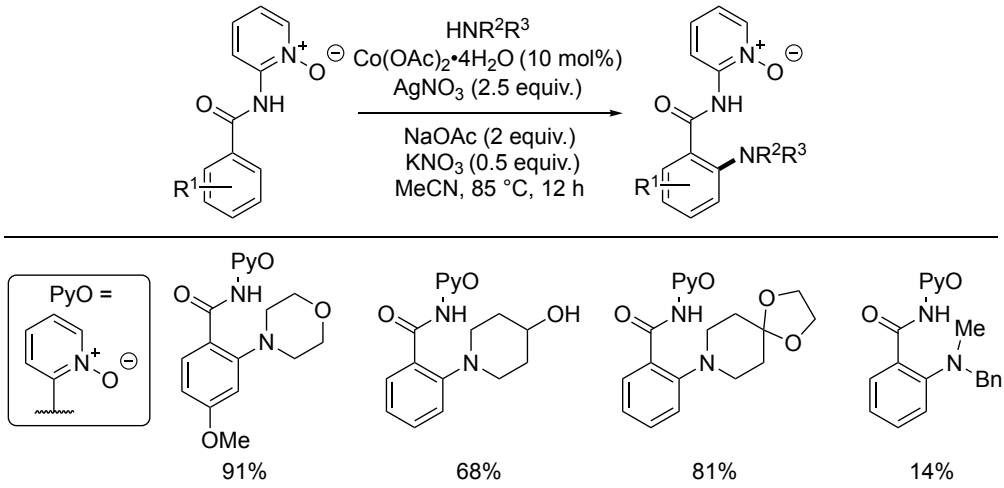
A plausible mechanism for this transformation was proposed in this study (Scheme 21)*.* The nickel(II) salt reacts with **24** to give an 8-aminoquinoline-coordinated intermediate, which then undergoes base-assisted cleavage of the *ortho*-C–H bond to give nickel(II) intermediate **25**. Nickel(III) intermediate **26** is formed by oxidation of **25**, presumably by a nickel-mediated disproportionation pathway and perhaps promoted by the presence of the silver(I) salt. After reaction of intermediate **26** with gaseous ammonia, deprotonation of the bound amino complex gives nickel(III) intermediate **27**. Reductive elimination then provides 2-aminobenzamide **28**.



Scheme 21: Nickel(II)-mediated amination mechanism

New methods have been developed for the selective dehdrogenative C–H/N–H coupling with cobalt-catalysis.[94,95] Specifically, cobalt(II) catalysis has been exploited for the amination of 2-benzamidopyridine *N*-oxides with secondary alkyl

amines in a simple reaction protocol (Scheme 22).[94] A bidentate *N*,*O*-chelating group in combination with silver nitrate as an oxidant were found to be the most efficient combination, resulting in the formation of a range of C–N coupled products in high yields and at a relatively low reaction temperature (85 °C). Similar to copper-catalysed methods, catalyst deactivation of the cobalt catalyst was observed when acyclic secondary amines were used in this procedure. The functional group tolerance was demonstrated as cyclic secondary amines bearing an unprotected secondary alcohol and a cyclic ketal were efficient substrates in this cross-coupling. The use of ferrocene as an oxidant and with the 8-aminoquinoline directing group subsequently allowed the expansion of this methodology to include aniline *N*-nucleophiles for the dual C–H/N–H cross-coupling, which allowed the synthesis of highly substituted triarylamines.[95]

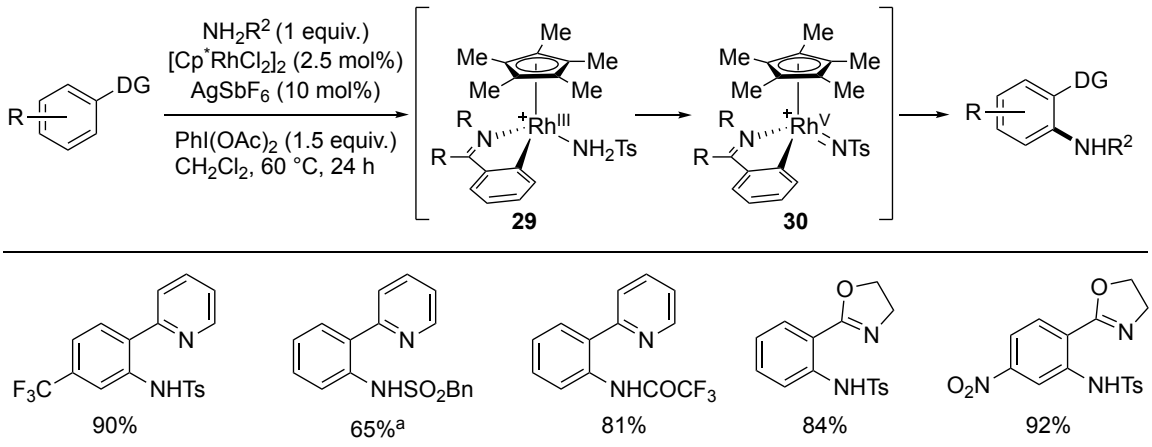


Scheme 22: Cobalt(II)-catalysed cross-dehydrogenative coupling

Similar auxiliary directed, cobalt-catalysed cross-dehydrogenative coupling reactions have been reported in which electrochemistry is utilised in the modulation of the transition metal oxidation state, thus removing the requirement for external oxidants.[96–100] These procedures tolerate a wide range of benzamides and secondary cyclic amines and operate under mild conditions with green solvents, driven by the evolution of hydrogen gas.

Second and third row transition metals such as palladium,[101–103] silver,[104] ruthenium,[105,106] rhodium[107–110] and iridium[111,112] have also been successful in enabling directed *ortho*-C–H/N–H cross-dehydrogenative coupling reactions. More

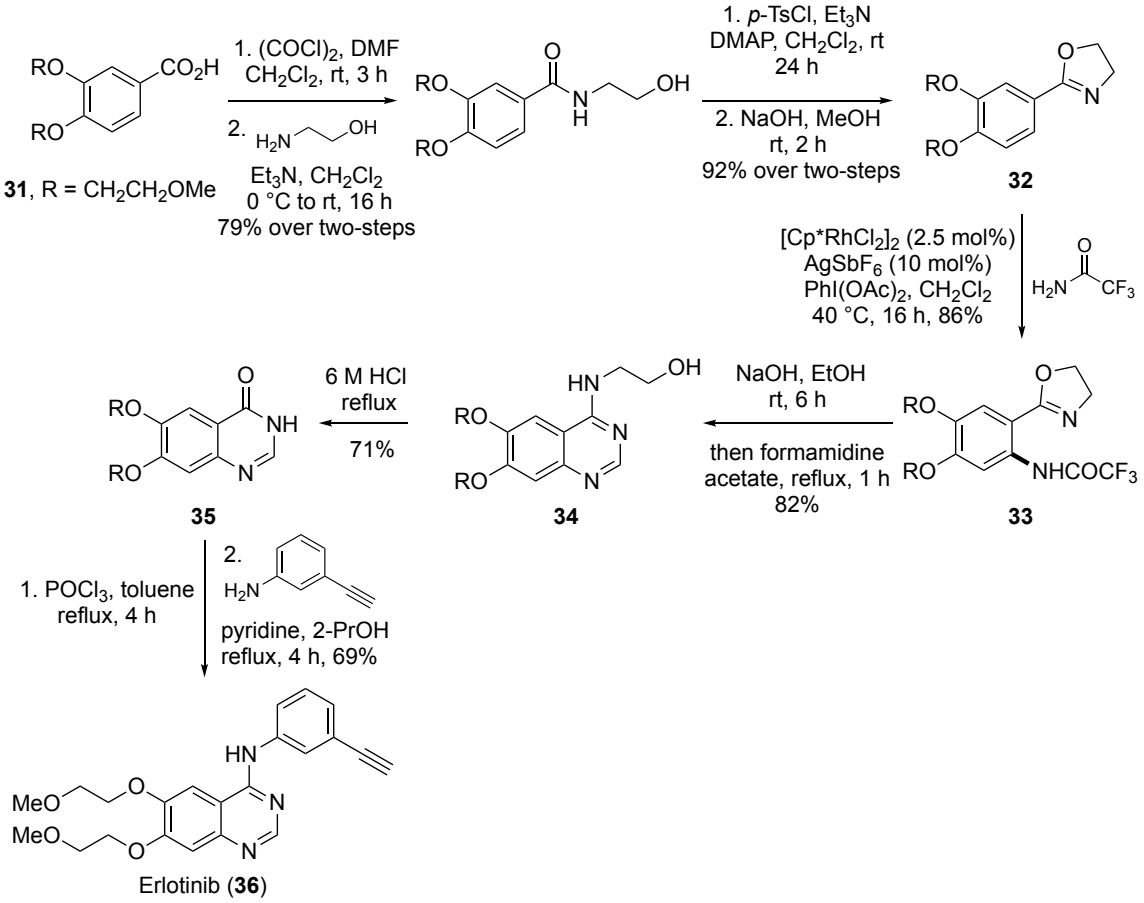
specifically, d^6 Ru(II), Rh(III) and Ir(III) complexes are known to facilitate a wide range of C–H activation reactions due to their ability to form metalacycles under mild conditions.[113,114] First reported by Bergman in 1982,[115] half-sandwich pentamethylcyclopentadiene (Cp*) rhodium and iridium complexes have shown remarkable activity towards the activation of inert C(sp^3)–H and C(sp^2)–H bonds.[116–119] This exceptional C–H bond activation does come with a cost however, as the subsequent amination step is more difficult due to the inherent stability of these rhoda- and iridacyclic complexes. This necessitates the careful selection of oxidants, additives and reaction conditions to effect this transformation. In this regard, Su and co-workers developed a rhodium(III)-catalysed *ortho*-C–H amidation with sulfonamides and amides which operated under relatively mild conditions compared with previously developed copper-promoted methods (Scheme 23).[107] It was proposed that the mildness of this protocol was due to the facile activation of the inert *ortho*-C–H bond *via* the formation of half-sandwich rhodacycle **29**. Oxidation of this rhodium(III) intermediate results in the formation of very electron-deficient rhodium(V) nitrenoid intermediate **30** which readily undergoes rapid reductive elimination to form the C–N bond followed by protonolysis to release the desired coupled products. As well as 2-pyridine, a range of auxiliaries were screened and the easily installable oxazoline functionality was shown to be the most efficient directing group.



Scheme 23: Rhodium(III)-catalysed intermolecular *ortho*-C–H amidation; [a]Reaction performed at 100 °C

Harrity and co-workers later expanded the scope of this oxazoline directed, rhodium(III)-catalysed *ortho*-C–H amidation of a wide range of aromatic compounds

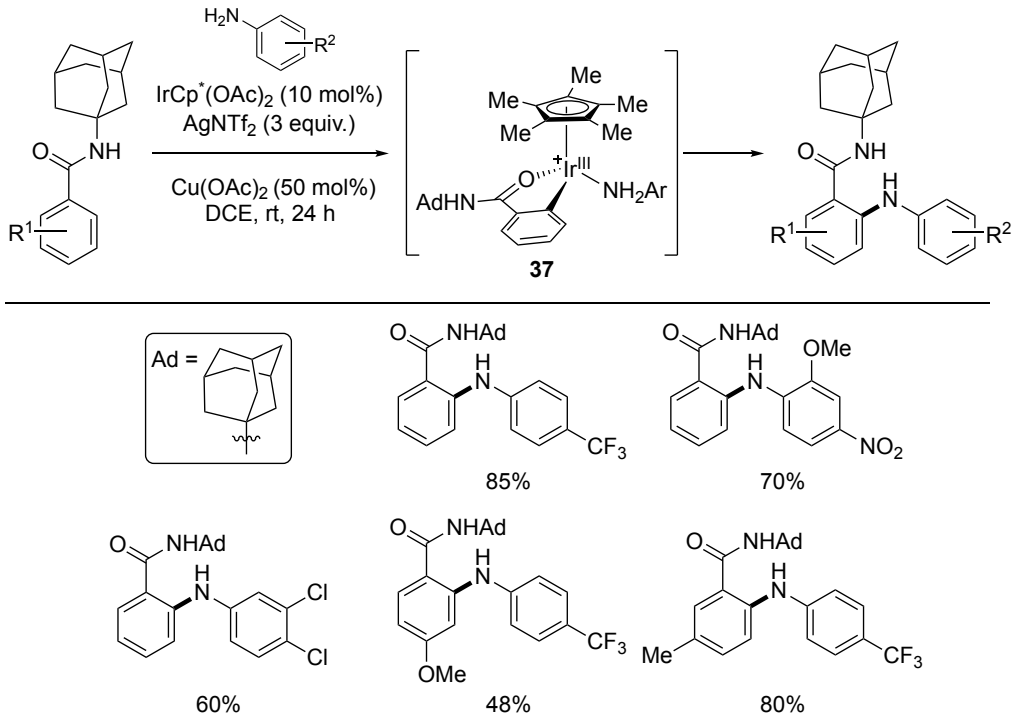
including π-deficient pyridines.[108,109] In addition, the *ortho*-amidated products synthesised by this method were hydrolysed and cyclised with formamidine acetate, providing an efficient route towards functionalised 4-aminoquinazolines and quinazolinones. This was demonstrated with the total synthesis of erlotinib (**36**), a tyrosine kinase inhibitor used in the treatment of pancreatic and lung cancers (Scheme 24).[108] The synthesis began by the installation of the oxazoline auxiliary directing group which was easily achieved in four-steps from benzoic acid **31**. After conversion of **31** to the corresponding amide by coupling of the acyl chloride with 2-aminoethanol, tosylation of the alcohol then effected cyclisation of the amide under basic conditions. The rhodium(III)-catalysed cross-dehydrogenative coupling with trifluoroacetamide was then performed on **32** with only 2.5 mol% catalyst loading under very mild conditions (40 °C for 16 h) and gave coupled product **33** in 86% yield. Alkaline hydrolysis of trifluoromethylamide adduct **33** gave the crude aniline, which then underwent reaction with formamidine acetate and gave 4-aminoquinazoline **34** in 82% yield. Following this, **34** was converted to the corresponding quinazolinone **35** in 71% yield under acidic conditions. Introduction of a chlorine atom at the 4-position by reaction with phosphoryl chloride was followed by nucleophilic aromatic substitution with 3-ethynylaniline, which completed the total synthesis of erlotinib (**36**) in 25% yield over ten-steps.



Scheme 24: Total synthesis of erlotinib (36)

Around the same time as these rhodium(III)-catalysed amination reports, Chang and co-workers developed a room temperature, iridium-catalysed oxidative C–H amination reaction with unactivated, electron-deficient anilines in the presence of a silver(I) salt (Scheme 25).[111] The authors proposed that the use of a bulky *N*-adamantyl group, would favour carbonyl *O*-coordination and facilitate the activation of the *ortho*-C–H bond *via* a stable, half sandwich iridacycle **37**, analogous to the rhodium(III)-catalysed mechanism. Pentamethylcyclopentadienyl iridium(III) acetate (10 mol%), silver triflimide and copper acetate were found to be the optimal combination to allow the selective *ortho*-amination to proceed with a wide-range of electron-deficient anilines in high yields. The desired amination reaction did not occur in the absence of the silver(I) salt but instead resulted in the quantitative formation of cationic iridacycle adduct **37**, an analogue of which was isolated and characterised by X-ray crystallography. In addition, with this catalytic system, electron-rich or *N*-substituted anilines exhibited very poor reactivity. With these observations, it was proposed that the reaction proceeds through a high-valent iridium(V) nitrenoid intermediate, accessible through several silver(I)-promoted

proton-coupled electron transfers. This then undergoes nitrenoid insertion followed by proto-demetalation to deliver the C–N coupled products.



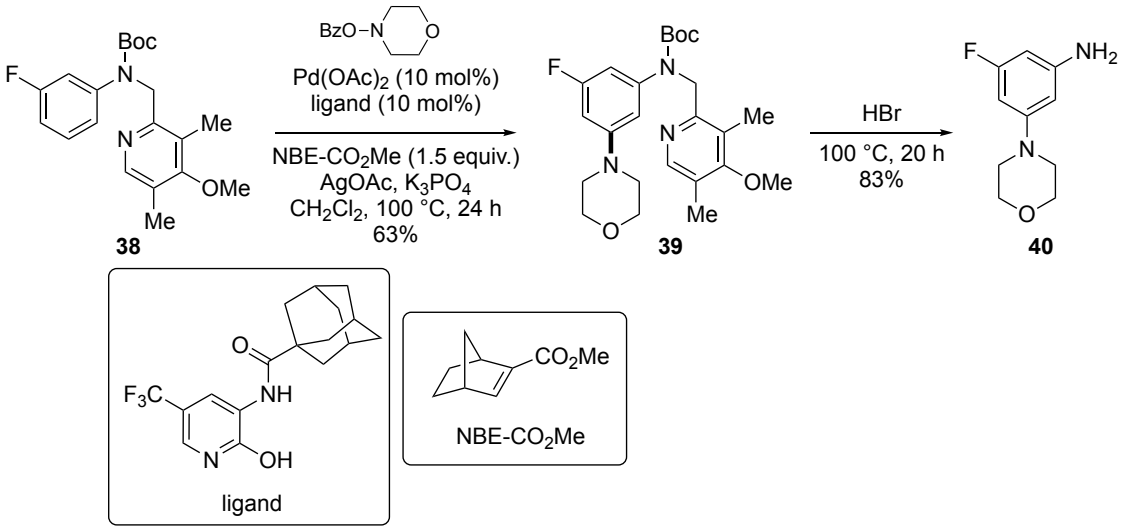
Scheme 25: Iridium(III)-catalysed intermolecular *ortho*-C–H amination

With the success of the iridium-catalysed cross-coupling of benzamides and unactivated anilines, the procedure was then extended to include more challenging alkyl amine nucleophiles by careful tuning and optimisation of the catalytic system.[112] The use of a 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and 1,2-dichloroethane solvent combination was critical to prevent catalyst deactivation, presumably my mitigation of the nucleophilicity of the alkyl amine due to hydrogen bonding with the solvent.[120]

1.2.3 *meta*- and *para*-C–N Bond Formation

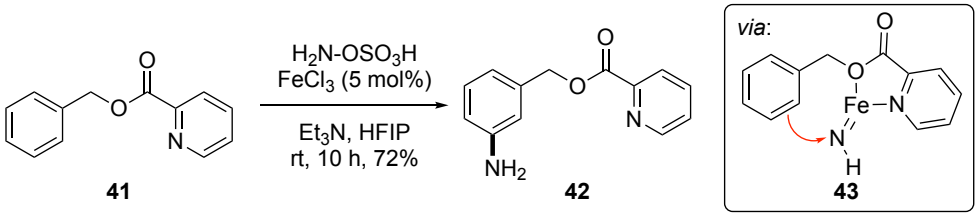
All early methods of C–H/N–H cross-dehydrogenative coupling rely on the presence of a metal coordinating substituent which directs the cleavage of only the *ortho*-C–H bond. Between 2015 and 2017, Yu and co-workers disclosed a series of *meta* selective aryl-C–H functionalisation procedures,[121–123] including *meta*-C–H amination albeit with an activated hydroxylamine as an amino source.[122] This methodology exploits Catellani's palladium-catalysed, norbornene-promoted relay reaction for an overall *meta*-functionalised product.[124] This palladium(II)-catalysed

amination procedure required an *N*-adamantyl substituted 3-amino-2-hydroxypyridine ligand, a pendant pyridine directing group, a modified norbornene derivative and a silver salt for maximum efficiency. For example, treatment of **38** with this intricate combination of reagents gave *meta*-coupled product **39** in 63% yield (Scheme 26). The Boc protecting group and pyridine auxiliary could then be removed by reaction of **39** with HBr which gave aniline **40**, a key intermediate in the synthesis of a BRAF inhibitor, in 83% yield. The high yields of *meta*-coupled products and broad reaction scope notwithstanding, this method does require an electrophilic nitrogen source and suffers from poor atom economy due to necessity of an *N*-protecting group, a chelating auxiliary and norbornene as a transient mediator.



Scheme 26: *meta*-Directed, palladium-catalysed C–H amination with activated amines

To tackle some of these issues and improve this work, Falck and co-workers developed a more practical *meta*-selective amination procedure (Scheme 27).[125] Although still requiring an electrophilic source of nitrogen, this method used an earth abundant, inexpensive iron catalyst in conjunction with a simpler, weakly basic pyridyl directing group. The iron(III) chloride-catalysed reaction of picolinate protected benzyl alcohol **41** with hydroxylamine-*O*-sulfonic acid (HOSA) in the presence of triethylamine and HFIP gave *meta*-substituted aniline **42** in 72% yield at room temperature. The authors reasoned that the selectivity originates from the formation of 5-membered iron nitrenoid intermediate **43** which then undergoes intramolecular electrophilic aromatic substitution.

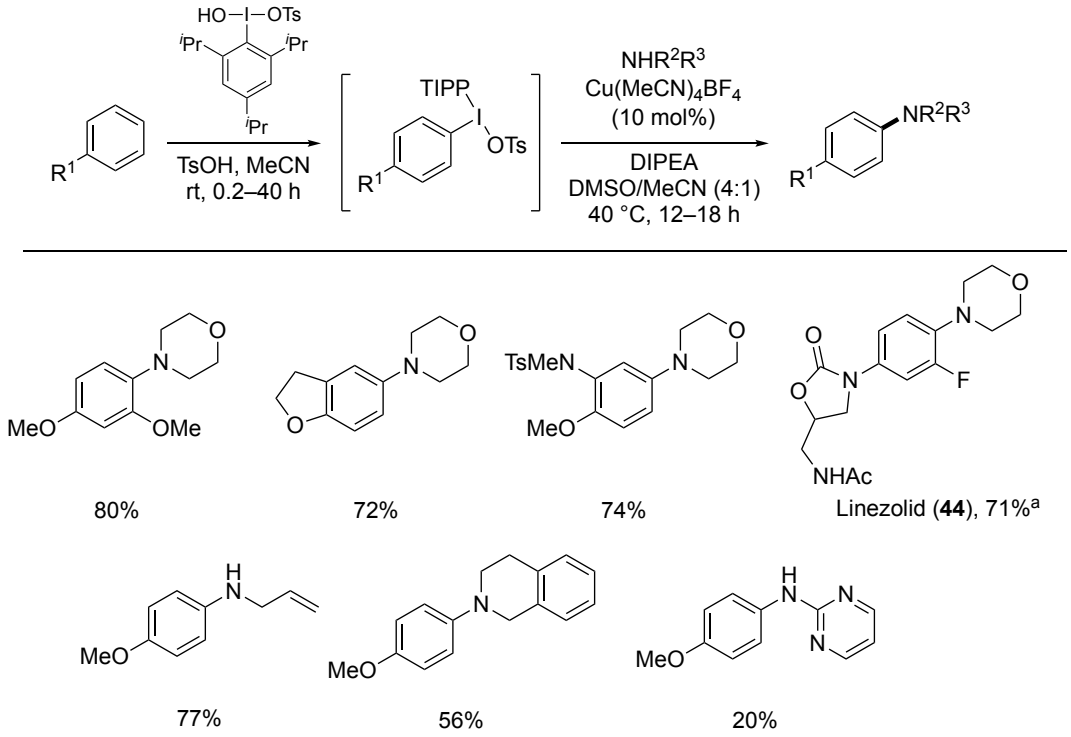


Scheme 27: Iron-catalysed *meta*-C–H amination

Similarly, the use of cross-dehydrogenative coupling for selective *para*-amination remains underdeveloped. Over the past decade there have been significant efforts into the development of extended template directing groups which enable the selective transition metal-catalysed functionalisation of the *para*-C–H bond however, these have yet to be extended to more challenging amination reactions.[126,127] Hartwig and co-workers reported a direct palladium-catalysed intermolecular aryl-C–H/N–H coupling reaction of phthalimides which gave *para*-products.[128] Arene substrates with either blocked *ortho*-positions or bulky ^{i}Pr or ^{t}Bu groups were required but this still resulted in equal mixtures of *meta*- and *para*-*N*-aryl phthalimides. The regioselectivity of this method was partially improved by the DeBoef group who developed an electrophilic aromatic metalation procedure using gold(I)-catalysis.[129] By activating *N*-nucleophiles *in situ* through treatment with $PhI(OAc)_2$, the iodane derived phthalimide can then react with a gold(III) arene intermediate, to give the C–N coupled products by reductive elimination. A major limitation to both these procedures is the requirement of these reactions to be performed in neat arene which inevitably limits the substrate scope to relatively simple aromatic compounds. Very recently, a *para*-selective C–H amidation reaction by the copper-catalysed dimerisation of anilide substrates *via* a radical addition mechanism was reported.[130]

A more general approach was described by Suna and co-workers who showed that electron-rich aromatic compounds can first be activated by reaction with hypervalent iodonium reagents (Scheme 28).[131,132] The corresponding unsymmetrical diaryl λ^3-iodane species were then coupled with a range of unactivated amines in a copper-catalysed one-pot process. Various aromatic compounds were coupled with primary amines, secondary cyclic amines, electron-deficient anilines and *N*-heterocycles in excellent yields, under very mild reaction conditions. In the first step, the use of a sterically encumbered 2,4,6-triisopropylphenyl (TIPP) substituted iodonium reagent

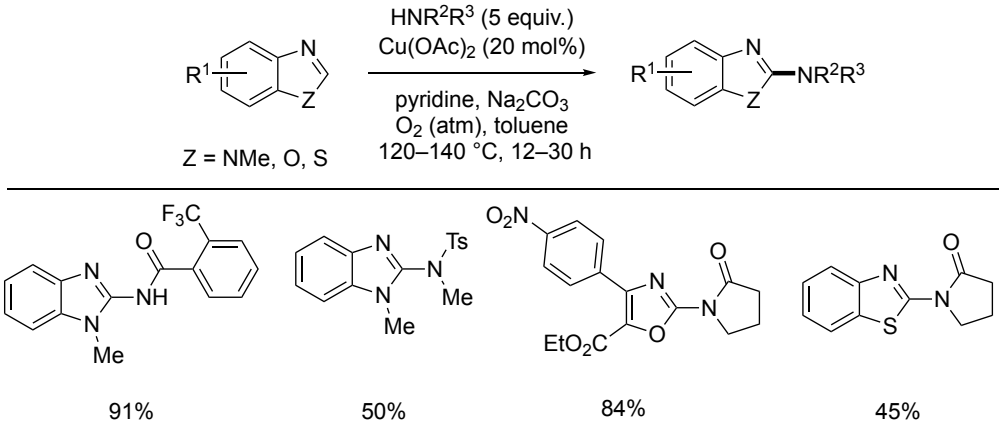
as well as strong, alkoxy electronic directing groups were responsible for the observed *para*-selectivity of the electron aromatic substitution. The versatility of this method was demonstrated with the synthesis of gram-negative antibiotic linezolid (**44**) by cross-coupling with morpholine.



Scheme 28: *para*-C–H Amination *via* hypervalent iodine intermediates; [a] With one equivalent of $Cu(MeCN)_4BF_4$

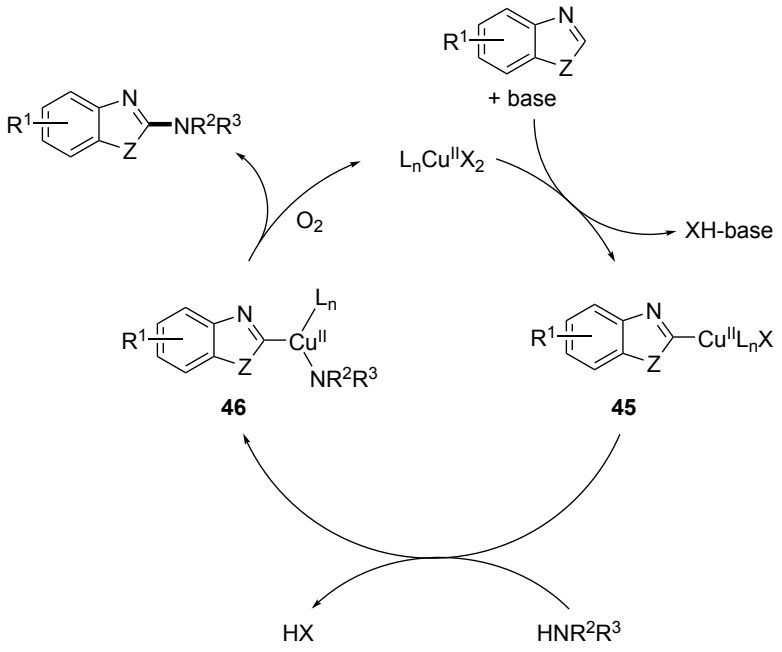
1.3 Intermolecular C–H/N–H Cross-Dehydrogenative Coupling of Acidic C–H Bonds

Another significant approach to dehydrogenative aromatic C–N bond formation is the activation and coupling of electron-deficient (hetero)arenes with unactivated *N*-nucleophiles. The first reports of this type of cross-dehydrogenative amination reaction came from simultaneous publications from the groups of Mori and Schreiber in 2009, which showed the feasibility of the coupling of the C-2 position of azoles with amines and amides (Scheme 29).[133,134]



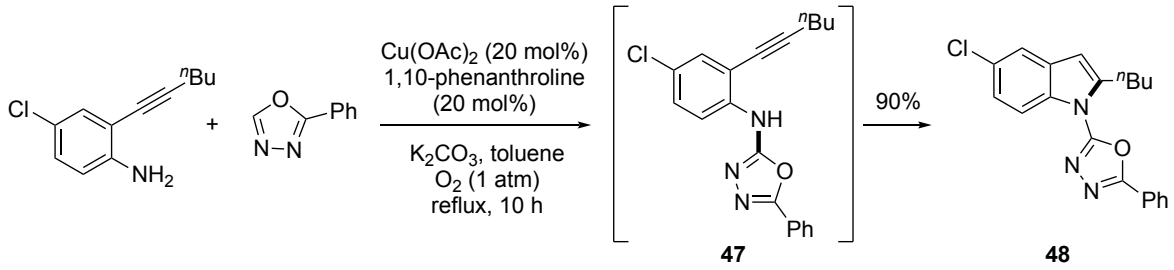
Scheme 29: Intermolecular amination of acidic C–H bonds

The exact mechanistic details of this copper-catalysed oxidative C–H amination/amidation process remain uncertain however, both groups have proposed a mechanism to account for the observed reactivity (Scheme 30). The first step involves the base-promoted formation of organocopper intermediate **45**. Ligand exchange with the *N*-nucleophile would give intermediate **46** which is then followed by reductive elimination to generate the C–N coupled heterocycle. Molecular oxygen is then responsible for the regeneration of the active copper(II) catalyst, completing the catalytic cycle.



Scheme 30: Proposed catalytic cycle for the copper-catalysed amination of azoles

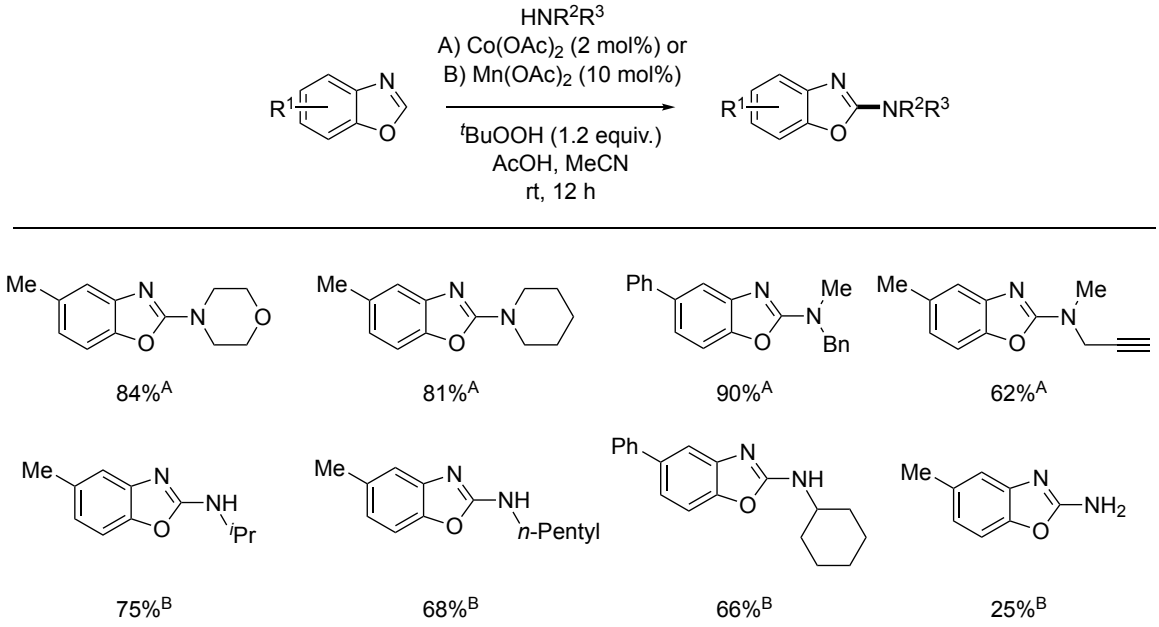
Successive investigations provided significantly improved reaction conditions of this copper-catalysed cross-dehydrogenative coupling which allowed for a broader scope of heterocycle and (hetero)arene substrates as well as *N*-nucleophiles.[135–139] For example, Bolm and Miura reported the cross-coupling of oxadiazoles, benzoxazoles and benzothiazoles with *N*-sulfoximines, while Shi and co-workers used copper(II) chloride complexes for the direct amination of benzoxazoles with primary amines, with both methods operating under ambient temperatures.[135,136] This was further elaborated by Miura and co-workers who showed that a range of *ortho*-alkynylanilines can undergo oxidative C–H/N–H cross-coupling with oxadiazoles and other functional azoles, which was followed by benzannulation to form *N*-azoylindoles in a high yielding one-pot process (Scheme 31).[137] The copper(II) catalyst serves a dual purpose, first by catalysing the cross-coupling of the acidic C–H bond of azoles with anilines, then acting as a π-acid for activation of the alkyne functional group of **47**, enabling *5-endo-dig* cyclisation which gave **48** in 90% yield.



Scheme 31: Miura's domino sequence for the synthesis of *N*-azolylindoles

In addition to the acidic C–H bonds of azole analogues, other acidic aromatic C–H bonds have been employed in these cross-coupling reactions. Su and co-workers demonstrated that polyfluoroarenes were sufficiently electron-poor to undergo cross-coupling with electron-deficient aniline substrates in a copper-catalysed, TEMPO mediated reaction for the synthesis of biarylamines.[140] Moreover, this copper-catalysed functionalisation of acidic C–H bonds has been applied to the selective C-2 amination and amidation reactions of quinoline *N*-oxides.[79,141,142] With selectfluor as an oxidant, the direct C-2 amination of quinolines with *N*-heterocycles was achieved without having to first synthesise the *N*-oxide derivative.[143]

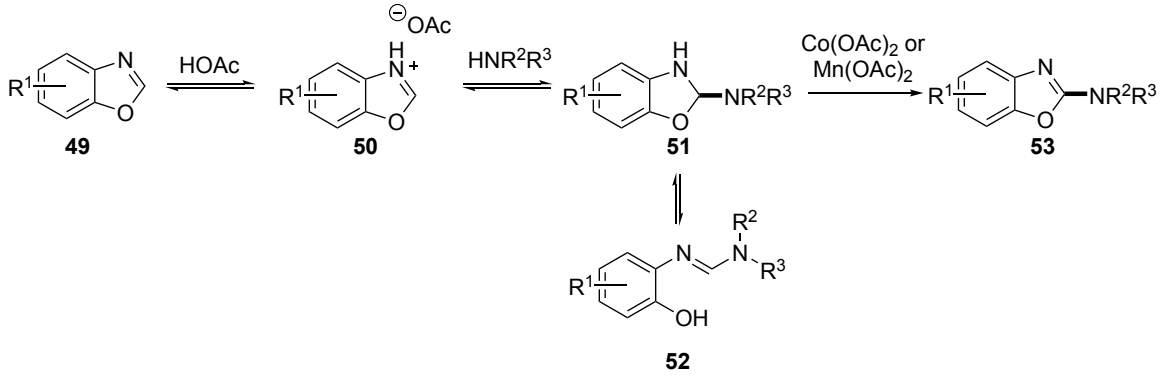
As well as these copper-catalysed methods, other first-row transition metals such as cobalt,[144] manganese[144,145] and nickel[146] have been used for cross-dehydrogenative coupling reactions. The Chang group has developed a mechanistically distinct process, assisted with a Brønsted acid, for the C-2 amination of benzoxazoles with aliphatic amines (Scheme 32).[144] This procedure used low catalyst loadings of cobalt(II) acetate (2 mol%) and tolerated cyclic and acyclic secondary amines under mild conditions however, no coupled products were obtained when primary amines were used. When the cobalt(II) catalyst was exchanged with manganese(II) acetate (10 mol%) and with an elevated reaction temperature (70 °C), primary amines were coupled with benzoxazoles, with even aqueous ammonia being tolerated as a nucleophile, albeit in 25% yield.



Scheme 32: Cobalt or manganese-catalysed amination of benzoxazoles

During the course of these studies, a significant by-product was ring-opened amidine species **52**. In addition, with a deuterium label at the C-2 position, no kinetic isotope effect was detected, which implies that the cleavage of the acidic C–H bond is not involved in the rate-determining step. On the basis of these observations, a plausible mechanism of this transformation was suggested (Scheme 33). The Brønsted acid additive initially protonates benzoxazole **49** to produce the substantially more electrophilic oxazolium salt **50**, which is then susceptible to nucleophilic attack by the unactivated amine. The resulting oxazolidine adduct **51** is in equilibrium with ring-opened amidine species **52**, which is favoured with primary

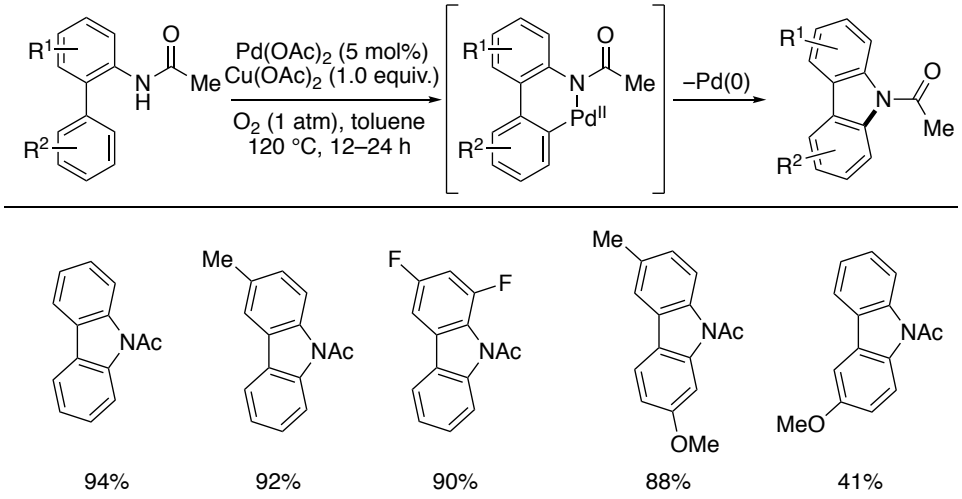
amines and ammonia. The cobalt or manganese metal catalyst, in combination with aqueous *tert*-butyl hydroperoxide solution (TBHP), facilitates the rearomatisation of adduct **51** *via* two single electron transfer steps, generating 2-aminobenzoxazolidine species **53**.



Scheme 33: Proposed mechanism for the C–H amination of benzoxazoles

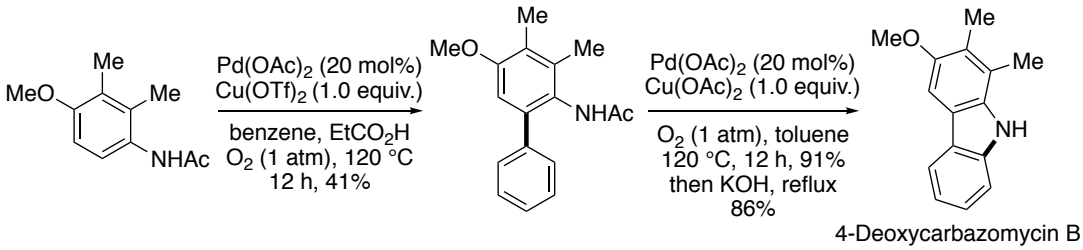
1.4 Intramolecular C–H/N–H Cross-Dehydrogenative Coupling

In 2005, Buchwald and co-workers reported the first known intramolecular oxidative cross-dehydrogenative coupling process for the synthesis of *N*-acylcarbazoles (Scheme 34).[147] In this process, coordination of palladium acetate to the amide nitrogen facilitated the activation of the *ortho*-C–H bond and allowed the formation of an intermediate 6-membered palladacycle, from which reductive elimination then provided the carbazole products in excellent yields while releasing Pd(0).[148] The Pd(0) species was then re-oxidised to Pd(II) by stoichiometric quantities of copper(II) acetate in the presence of molecular oxygen, in a similar manner to the Wacker process.



Scheme 34: Buchwald's synthesis of *N*-acylcarbazoles

Inspired by Buchwald's novel intramolecular cross-dehydrogenative amination procedure, the Shi group used sequential palladium(II)-catalysed C–H activation reactions to construct both the biaryl system and the *N*-acylcarbazole ring.[149] This methodology was then used for the preparation of natural product 4-deoxycarbazomycin B, without the requirement of pre-activated starting materials (Scheme 35).

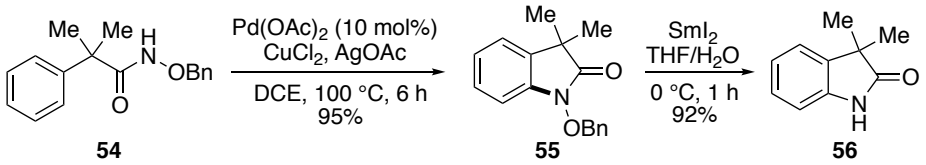


Scheme 35: The use of C–H functionalisation reactions for the synthesis of 4-deoxycarbazomycin B

Following Buchwald's seminal study, the use of other oxidants such as oxone[150] or hypervalent iodine species ($PhI(OAc)_2$)[151] have been shown to expedite the C–N reductive elimination step. This occurs by oxidation of the Pd(II) intermediate to a high-valent Pd(IV)-palladacycle, allowing this transformation to take place at room temperature. Oxidation of Pd(II) intermediates to high oxidation state Pd(IV)-complexes followed by reductive elimination has emerged as a significant paradigm in catalysis and has been implicated in a wide range of C–H functionalisation reactions.[152–155] In addition to palladium catalysis, the Chang group reported that this oxidative carbazole synthesis can be catalysed using copper while Miura and co-workers developed an iridium(III)/copper(I)-catalytic system for the cyclisation of 2-aminobiphenyls.[156,157]

This general approach for intramolecular C–H/N–H using palladium- or copper-catalysis has been applied to the preparation of a wide range of benzannulated heterocycles, such as benzimidazoles,[158] pyrido[1,2-*a*]benzimidazoles,[159] 2-oxindoles,[160] 2-quinolinones[161] and 3-arylindazoles.[162] For instance, Yu and co-workers used a range of *N*-methoxy- or *N*-benzyloxyamides as substrates in a palladium(II)-catalysed C–H lactamisation reaction for the synthesis of 2-oxindoles and 3,4-dihydroquinolinones in a high yielding process (Scheme 36).[160] Excess quantities of copper(II) chloride and silver acetate were required for re-oxidation of

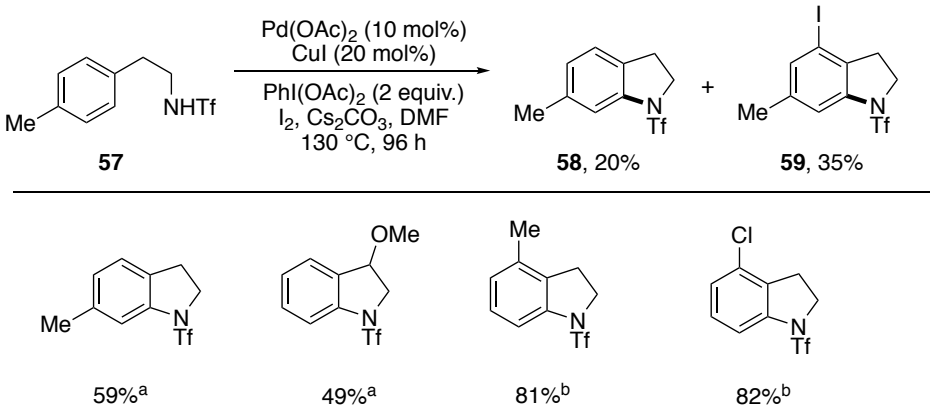
the palladium catalyst. Despite the harsh reaction conditions, cyclised product **55** was isolated in 95% yield from *N*-benzyloxyamide **54**. Reductive cleavage of the N–O bond of **55** using samarium iodide provided parent γ-lactam **56** in 92% yield.



54 **55** **56**

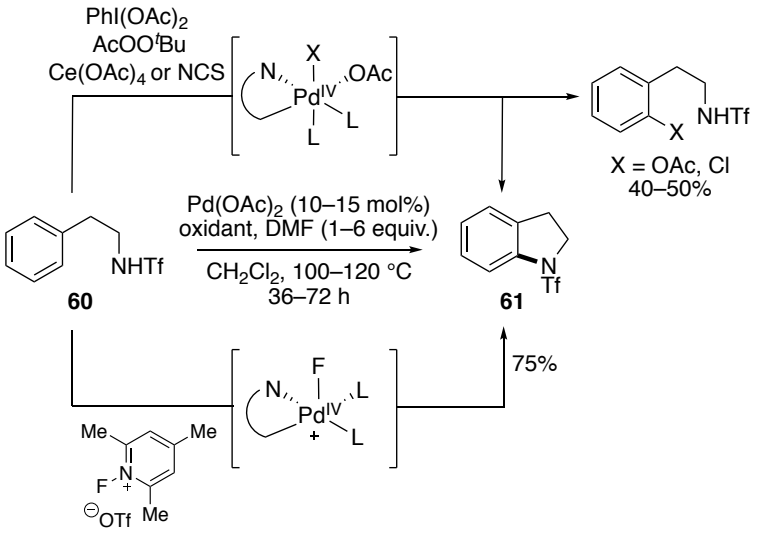
Scheme 36: Palladium(II)-catalysed synthesis of 2-oxoindoles

In 2008, the Yu group developed a tandem-catalytic process for the synthesis of indolines and tetrahydroisoquinolines from arylethylamines utilising a Pd(II)-catalysed C–H activation reaction.[163] In this distinct process, palladium(II) acetate and iodoacetate, formed *in situ* by the reaction of (diacetoxyiodo)benzene and iodine, are used for the activation and iodination of aromatic C–H bonds. This is followed by intramolecular amination with copper(I) iodide providing indolines in a compatible one-pot process. As well as requiring a high temperature (130 °C) and an extended reaction time (96 h), this reaction suffered from poor regioselectivity. The use of *N*-triflimide protected phenylethylamine **57** in this one-pot process, resulted in the formation of mono- and di-iodinated compounds during the first step, both of which underwent subsequent *N*-heterocyclisation and gave **58** and **59** in 20% and 35% yield, respectively (Scheme 37). This lack of selectivity was circumvented either by using a stoichiometric amount of copper iodide to accelerate the amination reaction of the mono-iodinated precursor, or by blocking the position *ortho*- to the aminoethyl side-chain.



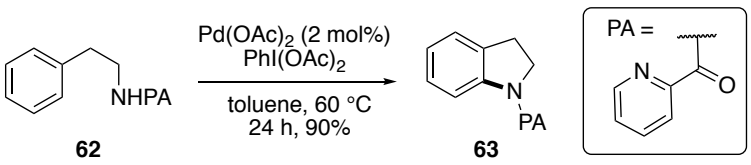
Scheme 37: Yu's synthesis of indolines *via* intramolecular C–H amination; [a]Reaction performed using 1 equiv. CuI; [b]Reaction performed using 0.5 equiv. CuI.

The Yu group improved this methodology by the development of a procedure for direct, oxidative intramolecular C–H amination for the synthesis of indolines from phenylethylamines (Scheme 38).[164] This new approach avoided the requirement of incorporation of the oxidant into the products. Similar to previous methods, the first step involved the coordination of the triflimide nitrogen of **60** to palladium, facilitating the C–H insertion reaction and delivering a 6-membered palladium(II) intermediate. Next, oxidation of this intermediate to yield a Pd(IV) intermediate from which facile C–N reductive elimination could occur, gave indoline product **61**. A wide range of oxidants were screened however, in most cases this resulted in no formation of the indoline and often led to undesired reductive elimination from the palladium(IV) intermediate, forming acetoxylated or halogenated by-products in significant yields (40–50%). There was some success when using the one-electron oxidant, cerium(IV) sulfate, and a small library of indolines were produced in moderate to good yields however, it was proposed that the presence of sulfate ions was impeding the reaction by forming unreactive palladium sulfate as the reaction progressed. To avoid these unwanted reductive elimination events, an established F^+ oxidant, 1-fluoro-2,4,6-trimethylpyridinium triflate,[165,166] was used instead. It was proposed that the strength of the Pd–F bond prevented undesired reductive elimination and encouraged the Pd(IV) complex to eliminate along the desired pathway, forming the C–N bond. The use of DMF in stoichiometric quantities or excess was found to be essential, possibly due to its role as a labile ligand in this process.



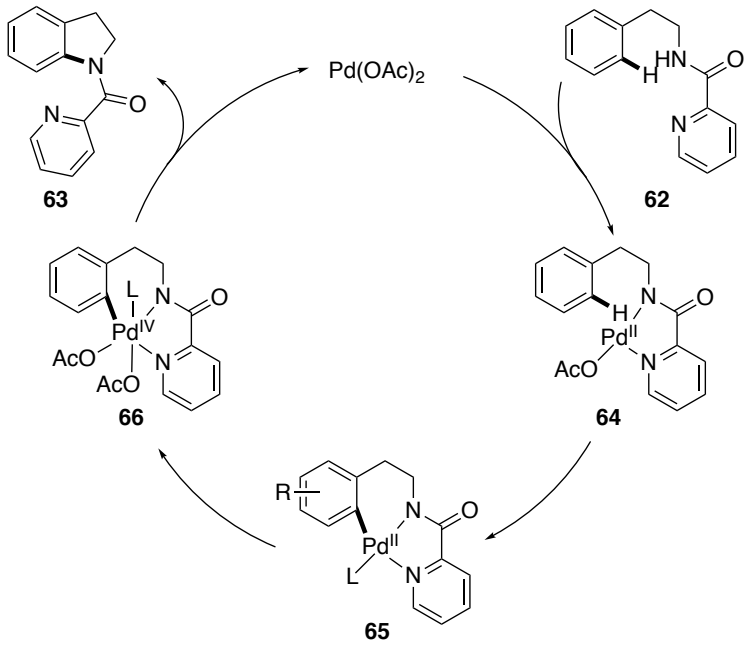
Scheme 38: Role of oxidants in palladium-catalysed *N*-heterocyclisation

The use of chelating groups to assist transition metal-catalysed C–H activation has allowed this transformation to proceed with milder conditions and lower catalyst loadings. For example, the groups of Chen and Daugulis independently reported the use of picolinamide (PA) as an auxiliary to direct palladium-catalysed activation of aryl-C–H bonds and intramolecular cross-coupling with tethered *N*-nucleophiles (Scheme 39).[167,168] Under these conditions, picolinamide protected phenylethyamine **62** was converted to indoline **63** in 90% yield.



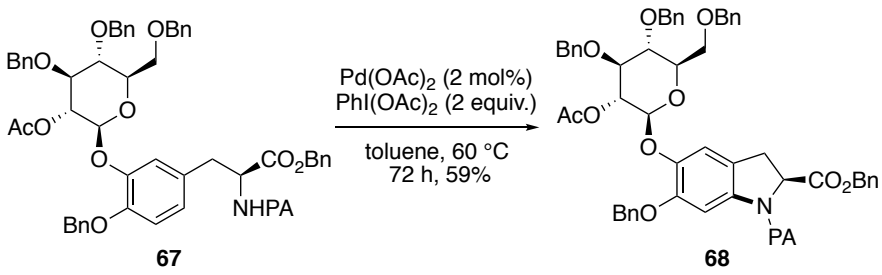
Scheme 39: Picolinamide-assisted intramolecular C–H amination

Similar to previous methods, this transformation likely proceeds through a Pd(II)/Pd(IV) catalytic cycle (Scheme 40). The first step involves the coordination of palladium to the amide and pyridine functionality of *N*-phenylethylpicolinamide (**62**), giving intermediate **64**. The close proximity of the coordinatively unsaturated palladium(II) centre to the *ortho*-C–H bond results in an agostic interaction and subsequent insertion, and provides Pd(II) intermediate **65**. Oxidation of Pd(II) intermediate **65** with an excess of (diacetoxyiodo)benzene gives palladium(IV) intermediate **66**, which can then undergo selective reductive elimination to form the new C–N bond and indoline product **63**.



Scheme 40: Proposed mechanism for the chelation-controlled *N*-heterocyclisation

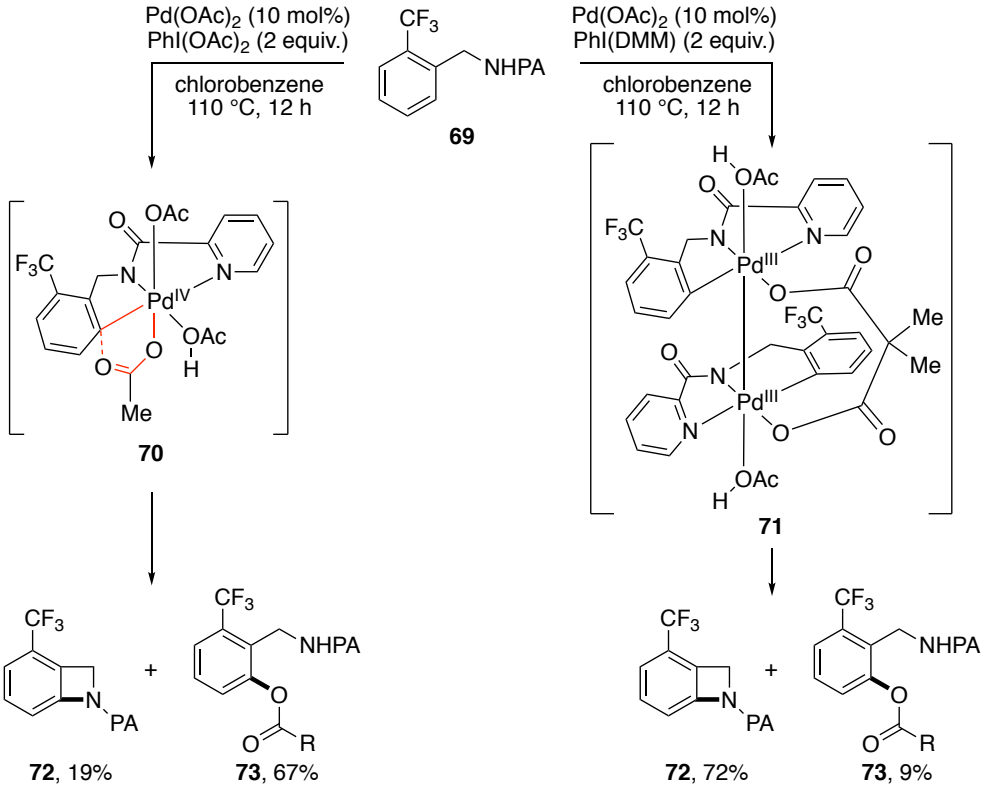
The mild nature of this picolinamide directed intramolecular C–H amination was exemplified by Chen and co-workers.[169] This reaction was found to proceed at 60 °C with catalyst loadings as low as 0.5 mol% and tolerated a wide range of sensitive and labile functionality, such as aryl C–I bonds. The methodology was used for the cyclisation of phenylethylamine **67** which gave indoline **68**, a key intermediate in the total synthesis of natural product and glycosidic food dye, betanin (Scheme 41).



Scheme 41: Key step in the formal synthesis of betanin

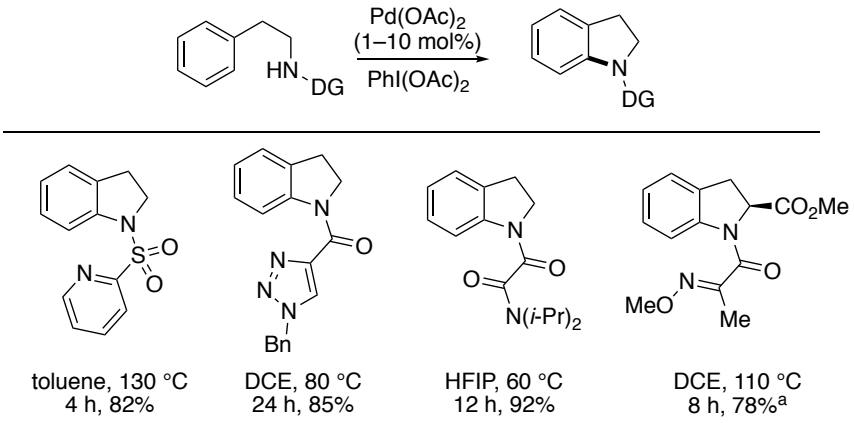
This picolinamide directed, palladium-catalysed C−H functionalisation approach has been applied to the more demanding synthesis of benzazetidines by the Chen group.[170] Treatment of picolinamide protected benzylamine **69** with palladium acetate and excess (diacetoxyiodo)benzene resulted in thermodynamically favoured *ortho*-acetoxylation and gave C–H oxygenated product **73** in 67% yield (Scheme 42). It is believed that the mechanism proceeds as a result of C–OAc

reductive elimination from putative Pd(IV) intermediate **70**, which computational studies have shown typically occurs through a five-membered transition state with the new C–O bond formed from the carbonyl oxygen.[171,172] Interestingly, in this reaction, benzazetidine **72** was formed in 19% yield, despite the significant ring strain. To optimise this reaction for benzazetidine formation, the group used a novel oxidising agent, phenyliodonium dimethyl malonate (PhI[DMM]), which was proposed to facilitate the thermodynamically unfavorable C–N bond formation. By tethering the carboxylate ligands with a rigid linker, the conformation of the high-valent palladium intermediates were constrained, which would suppress C–O reductive elimination, while encouraging the kinetically controlled formation of the strained 4-membered ring. This theory was confirmed as using PhI(DMM), C–N reductive elimination from Pd(III) was found to be the major reaction pathway and gave benzazetidine **72** in 72% yield, while *ortho*-C–H acetoxylation product **73** was isolated in only 9% yield. In this case, DFT calculations suggested bimetallic Pd(III)/Pd(III) intermediate **71** with bridging dimethyl malonate as a catalytic resting state before reductive elimination. Palladium(III) species have been previously implicated in C–H activation reactions however, it is usually unclear whether disproportionation to Pd(II) and Pd(IV) occurs during the catalytic cycle.[172–174] This strategy to minimise C–OAc reductive elimination from highly strained palladium species was highly effective for the synthesis of a range of benzazetidines. In addition, the group observed that with *ortho*-arylbenzylamine substrates, the formation of 4-membered cyclisation products was favoured over thermodynamically stable six-membered rings.



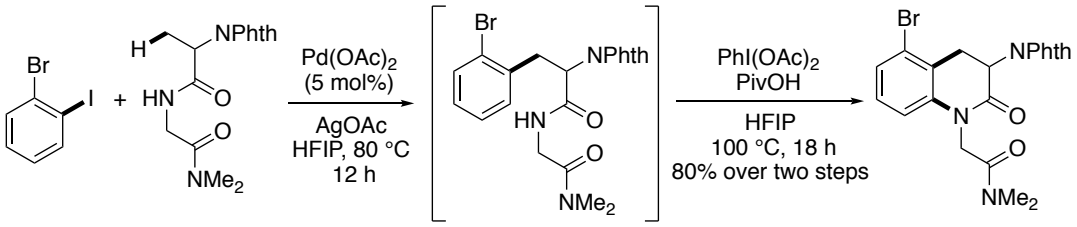
Scheme 42: Benzazetidine synthesis with a novel oxidant

Since these initial reports involving the use of picolinamide auxiliaries, a variety of *N*-directing groups have been used for palladium-catalysed intramolecular C–N bond forming reactions.[175–178] These chelating groups include 2-pyridinesulfonyl,[175] 1-benzyl-1,2,3-triazole-4-carboxylate,[176] oxalyl amides[177] and *N*-methoxyiminoacyl,[178] which have all been employed in this oxidative transformation and gave the corresponding indolines in excellent yields (Scheme 43).



Scheme 43: Auxiliaries as directing groups for the synthesis of indolines; [a]1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate used as an oxidant

A modified directing group featuring a glycine dimethylamide (GDMA) motif allowed Zhao and co-workers to perform multiple C–H activation reactions in a palladium-catalysed cascade process.[179] This one-pot methodology comprises sequential intermolecular β-C(sp^3)–H arylation and C(sp^2)–H amidation reactions for the synthesis of a range of 2-quinolinones from various GDMA-protected 2-phthalimidopropanoic acid derivatives and aryl iodides. Upon completion of the first step, the palladium catalyst was re-utilised in the intramolecular cross-dehydrogenative coupling step, with the addition of the hypervalent iodine reagent which facilitated oxidation to Pd(IV) and subsequent reductive elimination. This gave a series of 3-phthalimido-2-quinolinones in good yields, with no oligomerisation by arylation of the amide observed. The chemoselectivity was demonstrated when 2-bromoiodobenzene was applied in the one-pot process, as the reactive C–Br is unaffected throughout the palladium-catalysed arylation and amidation steps (Scheme 44).

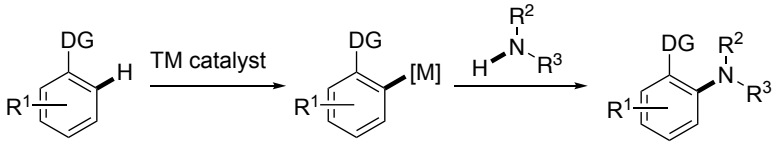


Scheme 44: Palladium-catalysed cascade process for the synthesis of 2-quinolinone heterocycles

1.5 Conclusions

Of the principle methods of C–N bond formation, C–H/N–H cross-dehydrogenative coupling reactions offer the most promise in terms of efficiency and atom economy (Scheme 45). The majority of these intermolecular transformations used copper-catalysis in combination with an auxiliary directing group as well as an external oxidant for selective *ortho*-C–N bond formation. With careful tuning of catalytic conditions and using other transition metals such as nickel, cobalt, ruthenium, rhodium and iridium, milder conditions and a broader scope of *N*-nucleophile could be achieved. In contrast, very few methods exist for *para*-selective C–N bond formation while there are no methods for *meta*-directed transition metal-catalysed C–H/N–H cross-coupling reactions to date. In addition, acidic C–H bonds of arenes

and (hetero)arenes are more reactive in these transition metal-catalysed processes and can readily undergo intermolecular cross-coupling with unactivated amines and amides. Since these reports of intermolecular cross-dehydrogenative coupling reactions, there has been a surge in methods for related intramolecular amination for the synthesis of a wide variety of functional *N*-heterocycles such as carbazoles, indolines, benzazetidines and quinolinones.



Scheme 45: C–H/N–H cross-dehydrogenative coupling

The advantages of this dehydrogenative, transition metal-catalysed C–H amination approach are apparent, with no requirement for substrate pre-functionalisation which results in a high atom economy and a large reservoir of potential aromatic hydrocarbon staring materials. The high atom economy notwithstanding, several challenges remain before this method is made more practical and widely applicable. These include the need to further expand the scope of the *N*-nucleophile while ensuring compatibility with the transition metal catalyst, the use of environmentally benign oxidants in the process and the removal of the requirement for auxiliary directing groups in order to control the regioselectivity. Further to this, the amination of more distal *meta*- and *para*-positions is yet to be achieved with unactivated amine nucleophiles.

2.0 Results and Discussion

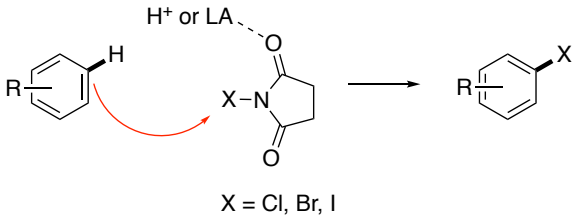
2.1 Regioselective Iodination of Arenes *via* Lewis Acid-Catalysed Activation of *N*-Iodosuccinimide

2.1.1 Introduction

Aryl halides and (hetero)aryl halides are very important synthetic intermediates in organic chemistry, used in a vast range of synthetic transformations, not least the construction of C–C, C–N, C–O and C–S bonds *via* transition metal-catalysed cross-coupling reactions.[180,181] They also find great utility in the formation of organometallic reagents and as precursors for nucleophilic aromatic substitution reactions.[182] In these processes, the much weaker C–X bonds of aryl iodides and bromides find more utility compared to aryl chlorides and fluorides. In addition to their synthetic importance, the use of halogenated arenes are indispensable in the field of medical imaging and in the understanding of diseases associated with neurology and oncology, through the use of aryl compounds containing radioactive halogen isotopes.[183]

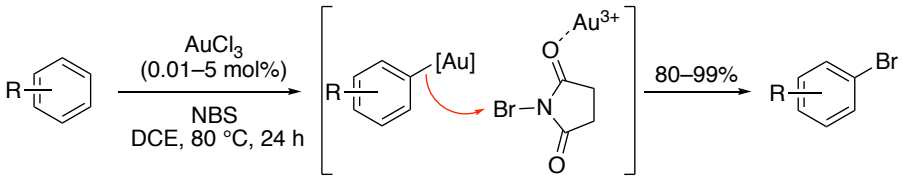
Halogenation of aryl C–H bonds is most frequently performed *via* electrophilic aromatic substitution with an electrophilic halogen source. A traditional method involves the use of elemental bromine or iodine however, this approach usually suffer from poor regiocontrol, often resulting in the formation of poly-halogenated aromatic compounds.[184–186] Alternatively, aryl halogenation reactions are frequently carried out using corrosive reagents such as thionyl halides, hydrogen bromide or iodine monochloride under harsh conditions.[187–189] Wang and co-workers reported an example of this process, that allowed regioselective bromination of anilides using hydrogen bromide, selectfluor and water as a solvent.[190] Another approach for aryl iodination involved the combination of iodide salts such as sodium iodide or ammonium iodide and oxidants such as hydrogen peroxide, sodium chlorite and hypervalent iodine(III) or iodine(V) reagents.[191–196] Despite the mild reaction conditions, the use of a strong oxidant may be incompatible with more complex aromatic substrates bearing sensitive functional groups.

N-Halosuccinimides (NXS, X = Cl, Br, I) have recently gained attention as very useful halogen sources due to their stability and ease of handling. These are significantly less reactive than other halogen sources and usually are only applicable to electron-rich arenes using forcing reaction conditions. For this reason, attention has turned to developing strategies to increase the reactivity of *N*-halosuccinimides by activation using Brønsted or Lewis acid catalysis (Scheme 46). For example, the iodination of arenes has been achieved using *N*-iodosuccimimide (NIS) in harsh acidic media such as TFA,[197,198] triflic acid[199] and recently using HFIP as a solvent.[200] In addition, the use of the boron trifluoride diethyl etherate adduct allowed for the iodination of electron deficient arenes, albeit with a mixture of regioisomers.[201] Transition metals have found great utility in activation of NXS, through co-ordination of the carbonyl functionality.[202,203] Indium(III),[204] zirconium(IV)[205] and gold(I)[206] complexes have all been used for the development of efficient aromatic halogenation procdures.



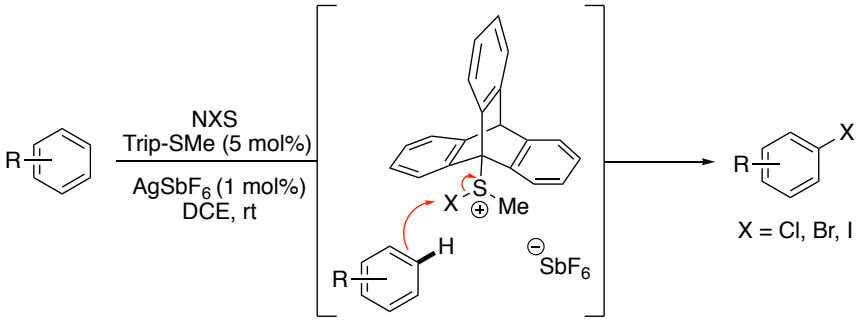
Scheme 46: Brønsted/Lewis acid-catalysed activation of NXS

In a distinct process, Wang and co-workers developed a gold(III) chloride-catalysed bromination procedure using *N*-bromosuccinimide (Scheme 47).[207] As well as Lewis acid activation of NBS, this process involved the simultaneous activation of the arene component, *via* direct metalation to form an organometallic arylgold(III) species, allowing for rapid bromination. It was then demonstrated that this Au(III)-catalysed bromination could be used in combination with the Miyaura borylation reaction, the Suzuki-Miyaura and the Sonogashira cross-coupling reactions, in a one-pot process. In addition, copper(0)-catalysed C–N bond formation was possible using the succinimide by-product generated during the halogenation step.



Scheme 47: Gold(III)-catalysed halogenation

Further to this, a number of C–H activation strategies have emerged for the halogenation of arenes using palladium(II),[208] rhodium(III),[209] ruthenium(0),[210] cobalt(III)[211] and copper(II)[212] catalysis. While these methods are highly efficient, allowing the synthesis of aryl bromides and iodides in excellent yield, they require the use of appropriate auxiliary directing groups and hence, are only effective for *ortho*-halogenation in most cases. In contrast, Miura and co-workers have used Lewis base catalysis for direct electrophilic aromatic halogenation using *N*-halosuccinimides (Scheme 48).[213] The nucleophilic sulfur atom of the triptycenyl substituted sulfide (Trip-SMe) catalyst interacts with the NXS halogenating reagent to generate a halonium complex as a hexafluoroantimony salt. This highly electrophilic halogen atom is then able to undergo electrophilic aromatic substitution with various aryl systems, including BINOL and strychnine.



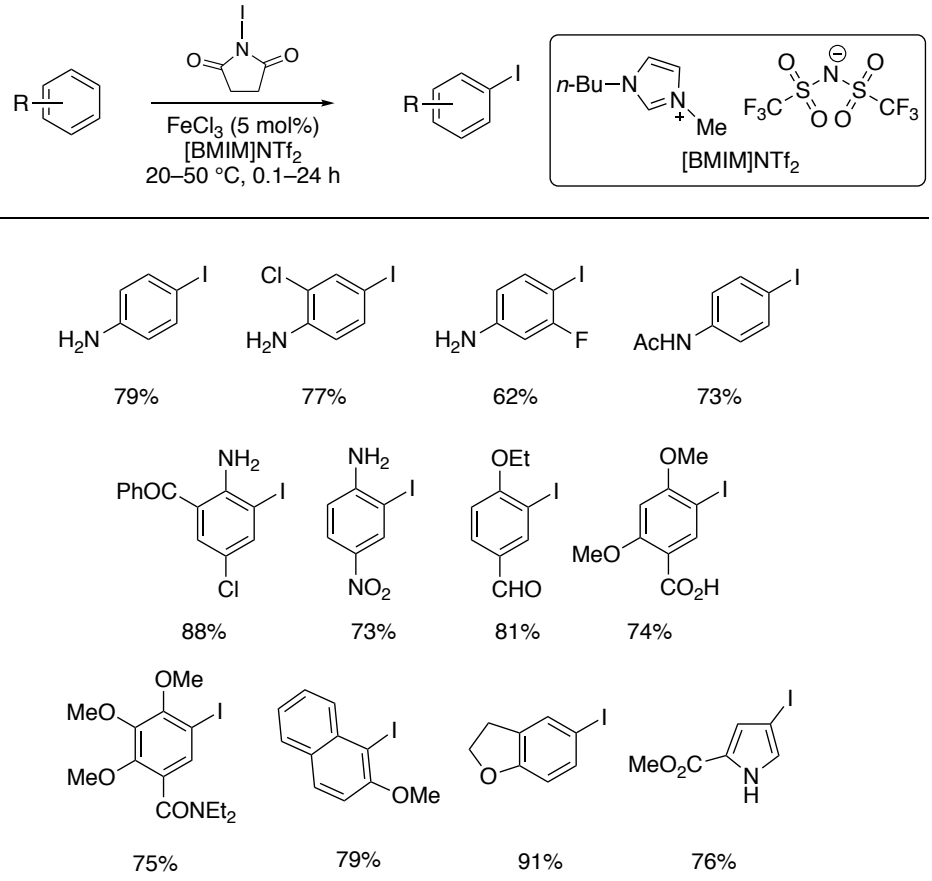
Scheme 48: Lewis base-catalysed halogenation

Other Lewis base catalysts have been reported for the halogenation of aromatic rings including disulfides,[214,215] thioureas[216] and anilines,[217] which all proceed *via* the formation of reactive halonium cation-Lewis base complexes or by formation of halo-amines.

2.1.2 Previous Work in the Sutherland Group

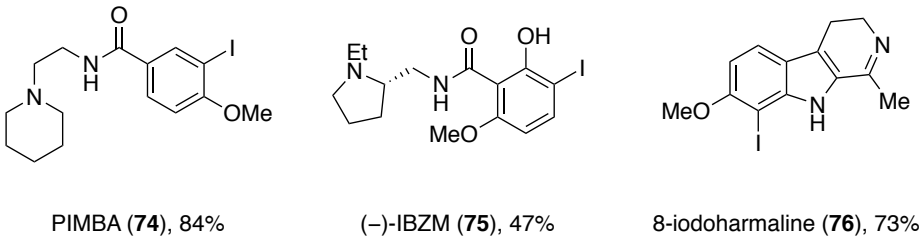
Previous work in the Sutherland group focused on the development of methodology for the mild iodination of arenes in the context of developing of novel SPECT tracers for radionuclide imaging of neurological conditions and cancer. In this regard, the group developed a nickel-catalysed Finkelstein reaction for the synthesis of aryl iodides from less reactive aryl bromides and used this in the preparation of a SPECT tracer for the imaging of human nicotinic acetylcholine receptors.[218,219] Further to this, procedures have been developed for the synthesis of aryl iodides by the substitution of (pseudo)halides such as boronates.[220,221] In addition, the group developed methodology which allowed the synthesis of stable diazonium salts from readily available anilines using a polymer-supported nitrite reagent which could undergo Sandmeyer-type reactions using [^{125}I]iodide for the preparation of radiolabelled aryl iodides.[222,223]

In 2015, the group develop a new protocol for the Lewis acid activation of NIS for rapid and regioselective aryl iodination by electrophlic aromatic substitution.[224] An activity screen of a range of transition metal Lewis acid catalysts for the iodination of anisole using NIS revealed that $FeCl_3$ was highly effective, leading to 100% conversion after 1.5 h. While this was an effective catalyst for electron rich arenes, less activated aromatic compounds required significantly higher catalytic loadings of $FeCl_3$, in some cases up to 1 equivalent. From this limited substrate scope, it became apparent that a more active form of Fe(III) was required. Metal triflimides had been shown to be powerful Lewis acids due to the highly delocalised, weakly coordinating nature of the triflimide counterion and on that basis, it was proposed that iron(III) triflimide would be a more effective Lewis acid catalyst for the activation of *N*-iodosuccinimide.[225,226] It was also shown that iron(III) triflimide could be made by the simple dissolution of $FeCl_3$ in the readily available and inexpensive ionic liquid, 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([BMIM]NTf_2).[227] Using the combination of $FeCl_3$ (5 mol%) and [BMIM]NTf_2 as a reaction solvent, led to a marked increase in rate when applied to electron deficient arenes. This process was then used with a wide range of electron rich aromatic compounds, also bearing deactivating groups, resulting in the formation of a library of aryl iodides in high yields (Scheme 49).



Scheme 49: Iron(III) triflimide-catalysed iodination substrate scope

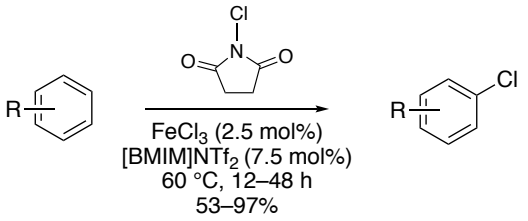
This iron(III) triflimide-catalysed procedure was used in the synthesis of pharmaceutically relevant compounds such as PIMBA (**74**), for imaging of breast cancer tumours (Figure 1).[228] Other targets synthesised were (–)-IBZM (**75**), a SPECT imaging agent and a dopamine D_2 receptor antagonist,[229] and 8-iodoharmaline (**76**), a monoamine oxidase inhibitor.[230] It should be noted that NIS is incompatible with highly nucleophilic substrates therefore, the basic nitrogen atoms in these compounds were first protected as tetrafluoroborate salts before being subjected to electrophilic aromatic substitution under these conditions.



PIMBA (**74**), 84% (–)-IBZM (**75**), 47% 8-iodoharmaline (**76**), 73%

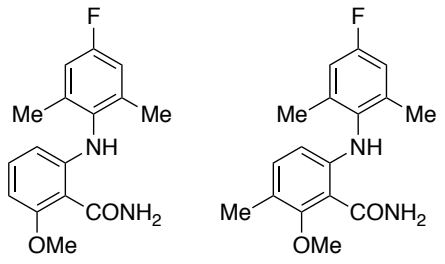
Figure 1: Utility of iron(III) triflimide-catalysed iodination

It was shown that the use of a highly charged, hard iron(III) Lewis acid led to the formation of bis-iodinated products when using particularly active aromatic compounds such as phenols. To overcome this limitation, a complementary procedure was developed using a softer silver(I) triflimide catalyst to tune the activation of NIS and supress over-iodination.[231] This methodology was extended for the radioiodination of active arenes using radiolabelled NIS, generated by the reaction of [^{125}I]iodide with *N*-chlorosuccinimide. In an extension of this method, the iron(III) triflimide was effective for the activation of NCS for the chlorination of activated arenes (Scheme 50).[232] In general, higher temperatures and longer reaction times were required which was expected due to the stronger N–Cl bond of NCS.



Scheme 50: Iron(III) triflimide-catalysed chlorination of arenes

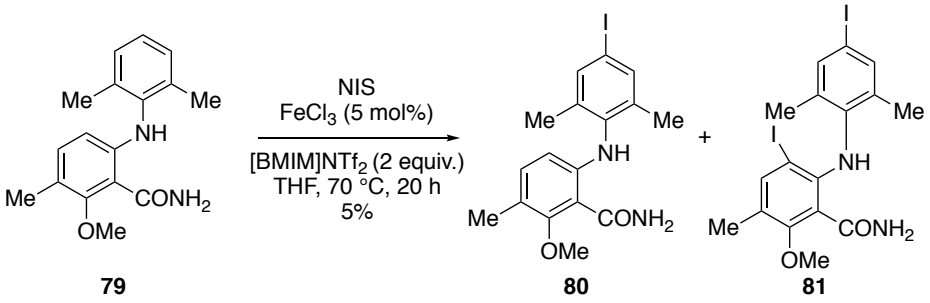
The Sutherland group is currently involved in the development of PET imaging agents that can act as antagonists of sphingosine-1-phosphate 5 ($S1P_5$) in the human brain and could be used in understanding the demylelination process, associated with neurological conditions such as multiple sclerosis. A group from Novartis reported a series of benzamide compounds which proved to be potent and selective $S1P_5$ receptor antagonists.[233] Building on this work, a previous PhD student, Tim Morgan, identified two lead compounds **77** and **78** as potential PET radiotracers for the imaging of $S1P_5$, based on their binding affinity and selectivity for $S1P_5$ as determined by their physiochemical properties (Figure 2).



77 **78**

Figure 2: Lead $S1P_5$ receptor antagonists

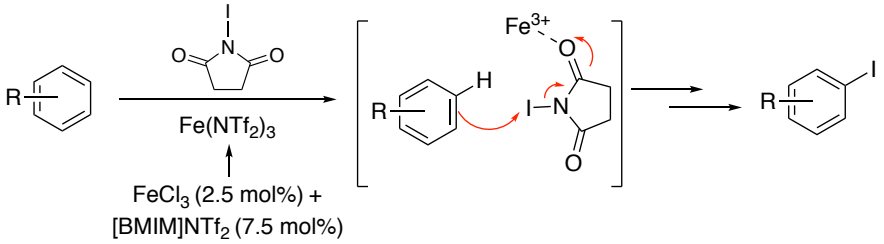
To synthesise potential precursors for the radiofluorination of benzamide **79** to give a potential PET radiotracer for $S1P_5$ imaging, a reactive iodine functional group had to be selectively installed to allow further transformations. Previous attempts to synthesise iodinated benzamide **80** with NIS and $FeCl_3$ (5 mol%) using excess quantities of $[BMIM]NTf_2$ resulted in poor selectivity, with the formation of a mixture of mono- and di-iodinated compounds, **80** and **81** (Scheme 51).[234] As a consequence of competing iodination at the C-5 position of the benzamide ring, mono-iodinated compound **80** was isolated in only 5% yield.



Scheme 51: Previous attempted iodination of benzamide 79

2.1.3 Project Aims

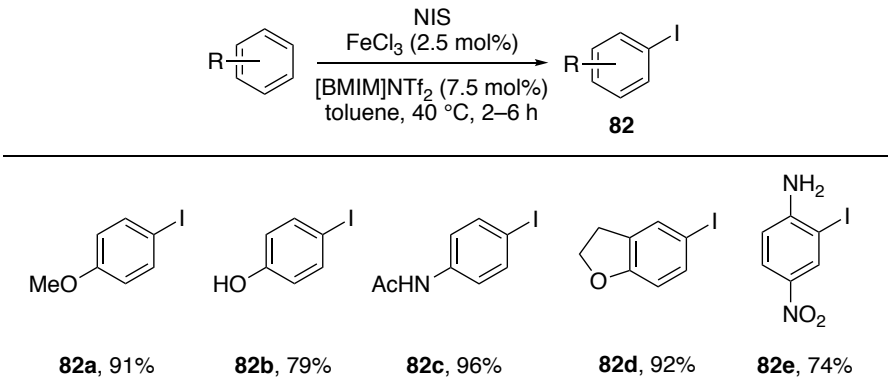
The first aim of this PhD was to build upon previous work in the group and investigate the iron(III)-catalysed electrophilic aromatic iodination of electron-rich arenes with NIS as the halogenating reagent and using $[BMIM]NTf_2$ in catalytic quantities instead of as a reaction solvent (Scheme 52). It was proposed that, using $FeCl_3$ (2.5 mol%) and $[BMIM]NTf_2$ (7.5 mol%), would allow for the formation of the highly Lewis acidic $Fe(NTf_2)_3$ catalyst which would facilitate the activation of NIS *via* coordination to the carbonyl oxygen. Another goal of this project was to use this regioselective iodination procedure to synthesise a potential precursor for the development of a PET radiotracer for the imaging of the $S1P_5$.



Scheme 52: Iron(III)-triflimide-catalysed iodination of activated arenes

2.1.4 Iron(III)-Catalysed Iodination of Arenes

The project began by using a combination of $FeCl_3$ (2.5 mol%) and [BMIM]NTf_2 (7.5 mol%) for the generation of iron(III) triflimide and subsequent activation of NIS (Scheme 53). The triflimide counterion is weakly coordinating as a consequence of the highly delocalised nature of the negative charge which results in an enhancement of the Lewis acidity of the iron(III) species, due to the increased positive charge density on the metal cation. Applying this catalytic system to anisole using toluene as a solvent resulted in full conversion to 4-iodoanisole (**82a**) in 4 h, with no formation of the *ortho*-regioisomer. This process was then applied to other electron-rich aromatic compounds such as phenol, acetanilide and 2,3-dihydrobenzofuran giving the corresponding aryl iodides **82b**–**82d** in 79–92% yield. *ortho*-Iodination of 4-nitroaniline gave aryl iodide **82e** in 74% yield.

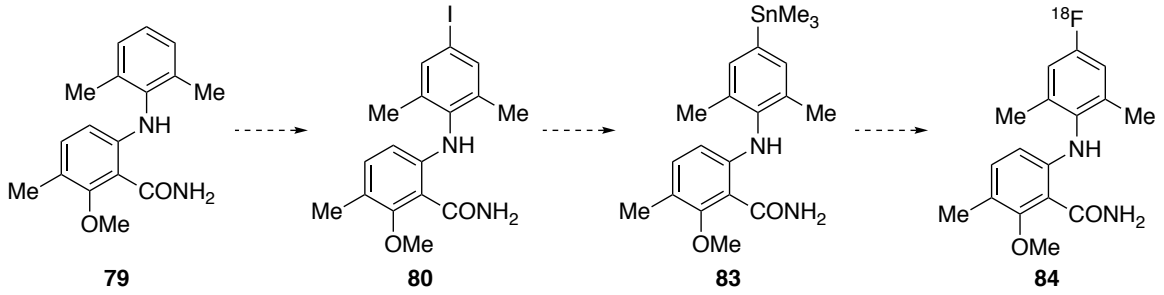


Scheme 53: Aromatic iodination using catalytic quantities of [BMIM]NTf_2

2.1.5 Application to the Synthesis of an $S1P_5$ Imaging Agent

To synthesise a potential precursor, to generate [^{18}F]-fluorinated benzamide **84**, selective electrophilic aromatic iodination of **79** could afford iodinated compound **80**, directed into the *para*-position of the upper 2,6-dimethyl substituted aniline ring (Scheme 54). It was proposed that the aryl ring bearing the amide functionality would be sufficiently deactivated as to minimise iodination at the C-5 position, *para* to the methoxy group. In addition to this, the benzamide ring is sterically shielded by the 2,6-dimethyl substituted aniline substituents, limiting access of the large iodine atom. Aryl iodide **80** could then be subjected to palladium-catalysed stannylation reaction to form aryl stannane **83**. Fluoro-destannylation with

[^{18}F]fluoride would then give compound **84**, a potential PET radiotracer for S1P$_5$ imaging.

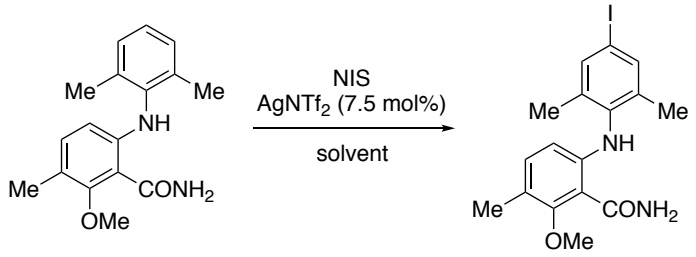


Scheme 54: Proposed route towards fluorine-18 precursor 84

As previous attempts to synthesise iodinated benzamide **80** using $FeCl_3$ (5 mol%) and [BMIM]NTf_2 (2 equiv.) led to a mixture of mono- and di-iodinated products, it was proposed that the use of the larger, less charged silver(I) Lewis acid catalyst would improve these selectivity issues, disfavouring iodination of the sterically congested benzamide ring. The initial reaction of **79** and NIS using $AgNTf_2$ in dichloromethane resulted in only 40% conversion to mono- and di-iodinated products after 22 h under reflux (Table 1, entry 1). Only the di-iodinated compound could be separated by flash column chromatography leaving an inseparable mixture of desired product **80** and starting material **79** in a 2:1 ratio. Changing the solvent to toluene allowed for the reaction to be performed at higher temperature (70 °C). The higher reaction temperature allowed the energy barrier associated with the formation of the Wheland intermediate to be overcome which led to 70% conversion after 2 h. The conversion to **80** did not improve upon heating under reflux for a subsequent 20 h and a ratio of 3:1 of **80** to **79** was obtained (entry 2). To push the reaction to completion while minimising di-iodination, 1.2 equivalents of NIS were added initially, followed by 0.3 equivalents after 4 h (entry 3). This reaction was performed at a slightly higher temperature (80 °C) over 20 h and led to 86% conversion of the starting material. After separating the di-iodinated material, this gave a 6:1 mixture of **80** and **79**. Further increasing the equivalents of NIS (2.5 equiv. in total), added to the reaction mixture in portions over 20 h, led to no change in the ratio of **80**:**79** (entry 4). It was clear that adding more than 2.0 equivalents of NIS was not resulting in an improved conversion of benzamide **79**, due to decomposition of NIS at 80 °C and an increased formation of the di-iodinated

compound. In addition, extended reaction times (>20 h) were unnecessary and were likely only leading to degradation of iodinated product **80**.

Table 1: Optimisation of the iodination reaction

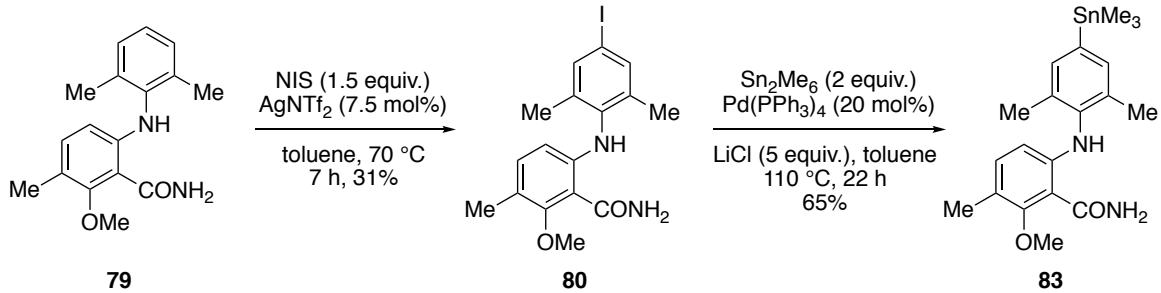


79 **80**

Entry	Solvent	NIS (equiv.)	Temperature (°C)	Time (h)	Ratio of **80**:**79**[a]
1	CH_2Cl_2	1.0	40	22	2:1
2	toluene	1.0	70	22	3:1
3	toluene	1.5	80	20	6:1
4	toluene	2.5	80	20	6:1

[a]Determined using ^{1}H NMR spectroscopy

The reaction of benzamide **79** with NIS and $AgNTf_2$ in toluene at 70 °C allowed for 85% conversion of the starting material after 7 h (Scheme 55). After separating the di-iodinated compound by flash column chromatography, starting material **79** was separated by recrystallisation, giving aryl iodide **80** in 31% yield. Next, a palladium-catalysed stannylation of aryl iodide **80** using hexamethylditin in the presence of lithium chloride was performed to give aryl stannane **83** in 65% yield. Compound **83** was unstable when exposed to silica gel due to protodestannylation therefore flash column chromatography was performed with neutral alumina.

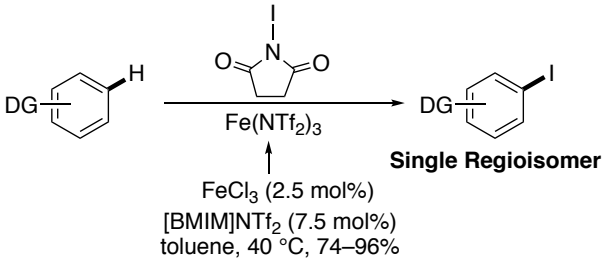


79 **80** **83**

Scheme 55: Synthesis of [^{18}F]-fluorinated benzamide precursor 83

2.1.6 Conclusions and Outlook

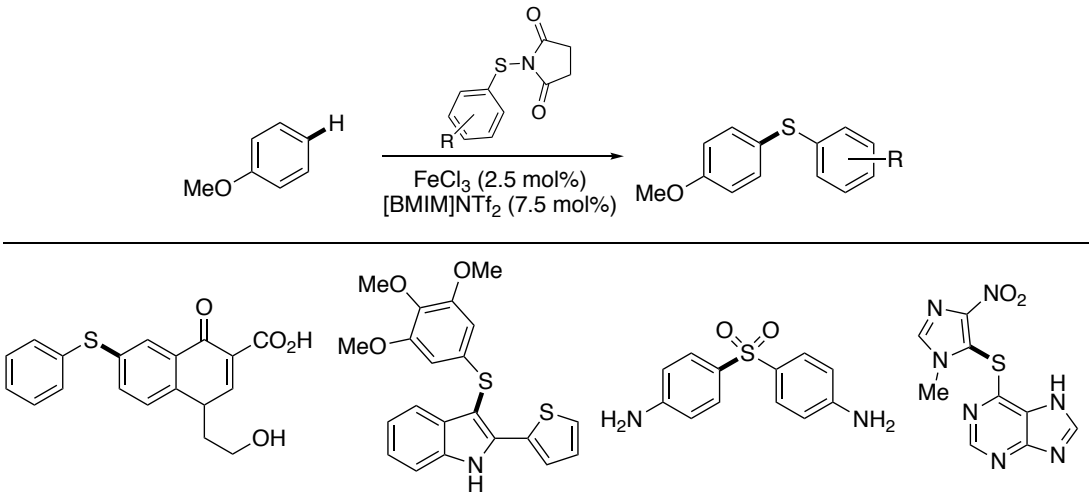
An efficient and highly regioselective procedure for the iodination of activated arenes was developed which avoided the use of [BMIM]NTf_2 as the reaction solvent (Scheme 56). The combination of $FeCl_3$ (2.5 mol%) and [BMIM]NTf_2 (7.5 mol%) allowed the generation of the highly Lewis acidic iron(III) triflimide species *in situ* which was an effective catalyst for the activation of NIS and resulted in the selective iodination of aromatic compounds such as anisole, phenol and acetanilide. The use of [BMIM]NTf_2 as a reagent in catalytic quantities, as opposed to as a reaction solvent, would ensure that this iodination procedure was compatible with further transformations during the development of one-pot processes. Despite the effectiveness of iron(III) triflimide as a Lewis acid catalyst for the activation of NIS, the use of silver(I) triflimide was required for the iodination of benzamide derivative **79**. This is due to the lower charge density of the silver(I) ion, compared to the highly charged iron(III) ion, which resulted in better overall selectivity by suppressing di-iodination. Palladium-catalysed stannylation of this iodinated benzamide gave aryl stannane **83** which is a precursor for [^{18}F]-fluorinated benzamide **84**, a potential PET radiotracer for $S1P_5$ imaging.



Scheme 56: Iron(III) triflimide-catalysed iodination of arenes

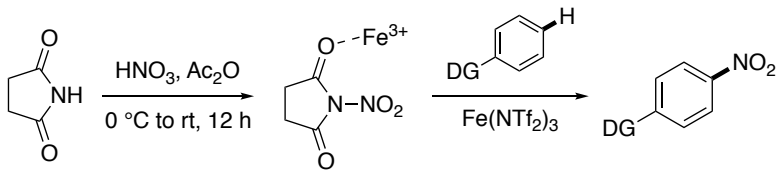
With the development of an efficient iodination procedure using NIS, it was envisioned that iron(III) triflimide could be utilised as a powerful Lewis acid for the activation of other electrophiles. For example, it is proposed that using iron(III) triflimide in conjunction with *N*-(arylthio)succinimides would lead to the formation of an electrophilic source of sulfur and allow for the synthesis of aryl thioethers (Scheme 57). Such a process could then be used for the synthesis of biologically active compounds. Currently, this transformation can only be achieved using harsh

conditions such as the reaction of electron-rich arenes and thiosuccinimides using TFA or TfOH as Lewis acid catalysts.[235,236]



Scheme 57: Proposed synthesis of thioethers

In 2020, Katayev and co-workers reported the use of bench-stable nitrosuccinimide and nitrosaccarin reagents for *ipso*-nitration of aryl boronic acids under mild conditions.[237] These nitrating reagents could be employed in the iron(III)-catalysed electrophilic aromatic substitution reaction for the selective formation of aryl C–N bonds (Scheme 58). After preparation of the nitrosuccinimide reagent using literature conditions,[238] activation using iron(III) triflimide could allow the regioselective nitration of aryl C–H bonds under mild conditions. This method would not require pre-functionalised starting materials and would avoid the use of corrosive, concentrated acids.

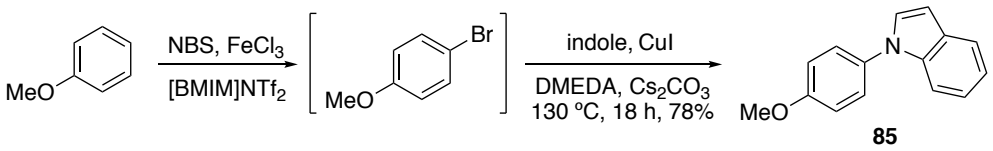


Scheme 58: Proposed aryl C–H nitration reaction

2.2 One-pot Intermolecular Amination of Aryl C–H Bonds

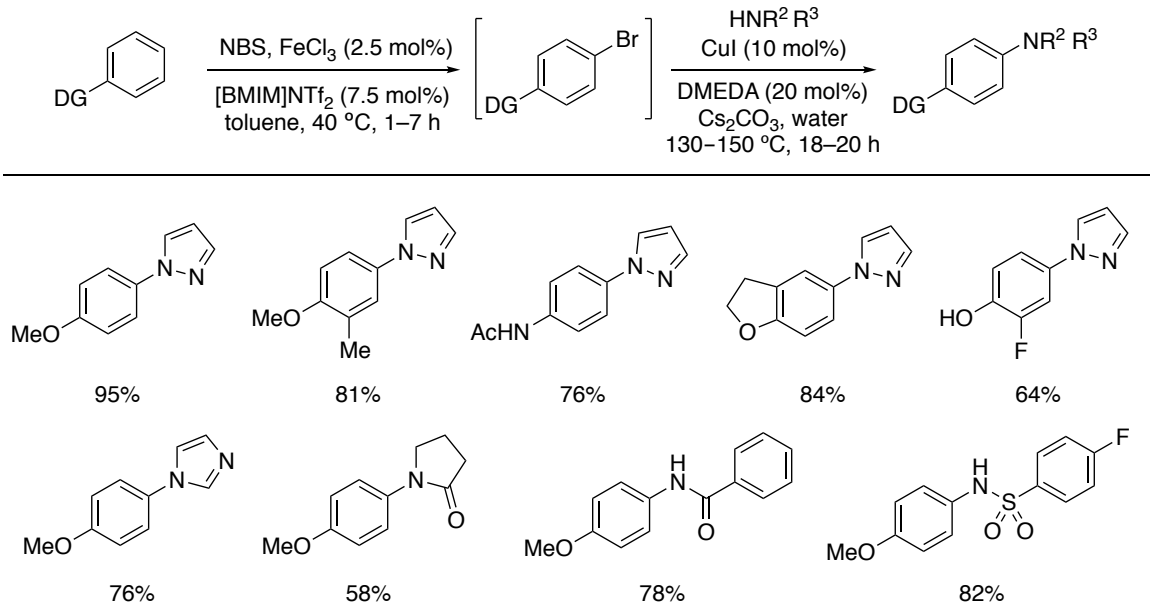
2.2.1 Previous Work in the Sutherland Group

In 2017, the group published methodology that allowed the selective amination of *para*-C–H bonds of electron-rich aromatic compounds.[239] This method used regioselective, iron(III) triflimide-catalysed bromination to activate aryl rings followed by ligand assisted, copper(I)-catalysed cross-coupling with *N*-nucleophiles in a one-pot process. As part of the optimisation of this process using anisole, it was found that while the use of the ionic liquid, [BMIM]NTf_2, as a solvent allowed for full conversion to the brominated intermediate, no amination was observed in the second step (Scheme 59). To overcome this incompatibility, a catalytic protocol was developed using iron(III) chloride (2.5 mol%) and [BMIM]NTf_2 (7.5 mol%) in toluene. This allowed for complete conversion to the brominated intermediate under mild conditions (40 °C, 4 h) and 45% conversion was then observed to the C–N coupled product in the Cu(I)-catalysed second step. It was found that the addition of water during the Ullmann coupling step allowed for dissolution of the inorganic base and facilitated better mixing of the reagents which led to near quantitative conversion to coupled product **85** and an isolated yield of 78%.



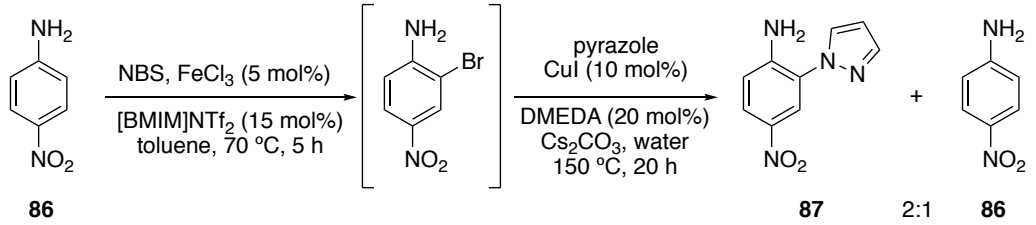
Scheme 59: One-pot, *para*-directed coupling of anisole and indole

The process was then applied to the coupling of aromatic substrates, bearing activating and deactivating groups, with a range of *N*-nucleophiles giving a small library of *para*-aminated products (Scheme 60). This process was efficient for the coupling of functional anisole, aniline, acetanilide and phenol compounds with *N*-heterocyclic nucleophiles such as pyrazole, imidazole and 2-pyrrolidinone as well as benzamides and sulfonamides.



Scheme 60: One-pot, two-step *para*-C–H amination of arenes

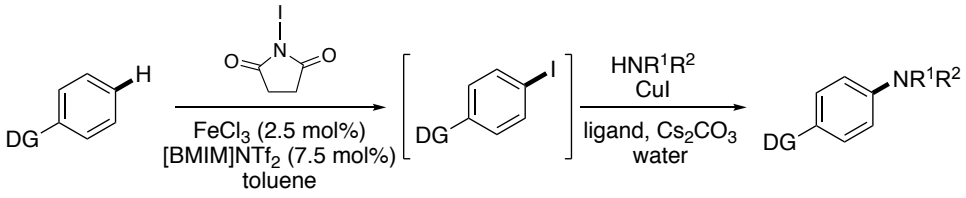
During this previous study, a limitation of the one-pot process was demonstrated with the *ortho*-bromination/*N*-arylation of 4-nitroaniline (**86**), which yielded a 2:1 mixture of the coupled product **87** and 4-nitroaniline starting material (Scheme 61). Analysis of the ^{1}H NMR spectrum of the bromination reaction mixture showed full conversion under more forcing conditions (70 °C) after 5 h. However, it was proposed that the slower *ortho*-amination process resulted in a competing reaction pathway involving protodecupration which led to the regeneration of the starting material from the brominated intermediate.



Scheme 61: Previous attempted *ortho*-amination of 4-nitroaniline (86)

2.2.2 Project Aims

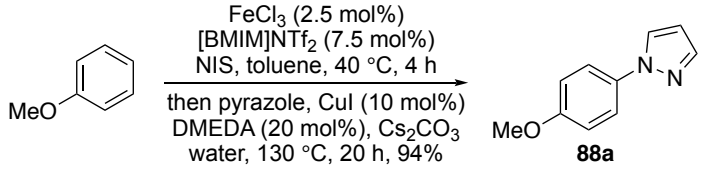
The first key objective of this project was to develop a one-pot, two-step process using the previously described iron(III) triflimide-catalysed iodination procedure (chapter 2.1) to activate aryl rings, followed by copper-catalysed cross-coupling with *N*-nucleophiles (Scheme 62). It was proposed that using aryl iodide intermediates in the one-pot process would allow for a more efficient cross-coupling reaction, owing to the lower bond dissociation energy of the carbon-iodine bond compared to the carbon-bromine bond. Another aim of this project was the application of this one-pot iodination/copper-catalysed cross-coupling process for efficient *ortho*-C–H amination when the *para*-position is blocked. This would build on previous work in the group and involve optimisation of the one-pot process to minimise protodecupration during the C–N bond forming step.



Scheme 62: Proposed one-pot *para*-iodination/amination process

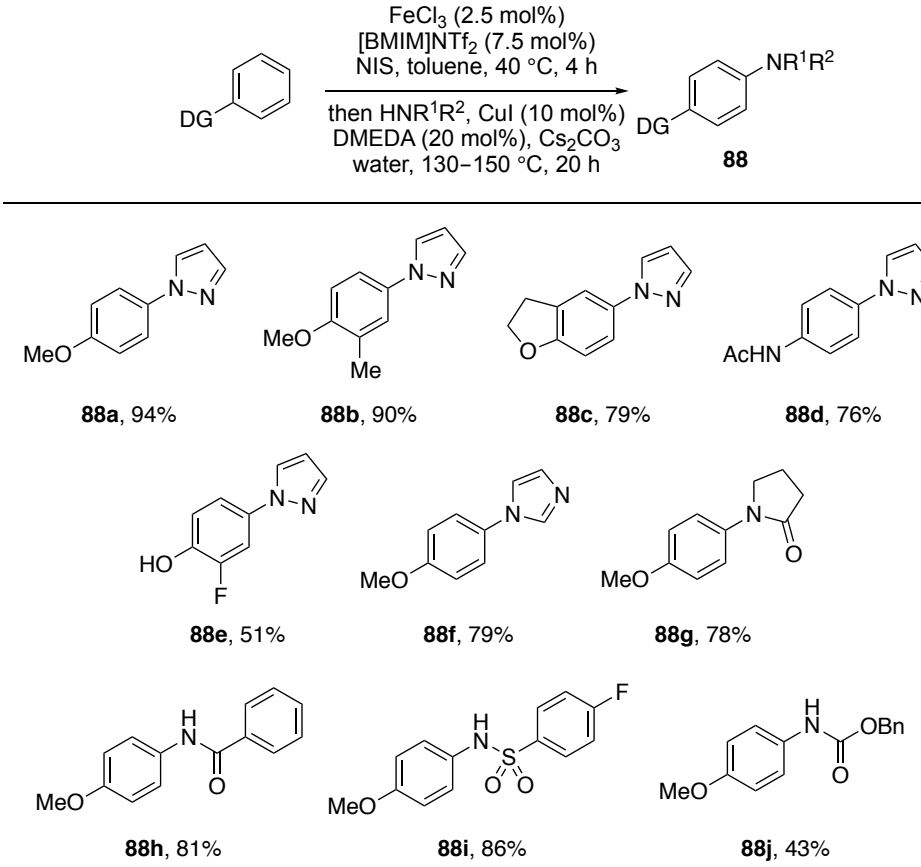
2.2.3 One-Pot *para*-Amination of Aryl C–H Bonds

The initial aim of this project was to use NIS for arene activation, then utilise the reactive C–I bond in a copper(I)-catalysed amination/amidation for the selective functionalisation of *para*-C–H bonds. The model substrates chosen to investigate this coupling were anisole and pyrazole, which gave the best results in the previous bromination protocol. Lewis acid activation of NIS using iron(III) triflimide in toluene, followed by addition of anisole resulted in full conversion to the iodinated intermediate in 4 h at 40 °C, with only the *para*-regioisomer observed (Scheme 63). In the same pot, copper-catalysed cross-coupling with pyrazole in the presence of an ancillary ligand gave coupled product **88a** in 94% yield after 20 h.



Scheme 63: *para*-Directed coupling of anisole and pyrazole

Encouraged by this result, the scope of the intermolecular copper(I)-catalysed cross-coupling reaction using aryl iodide intermediates was explored (Scheme 64). Using pyrazole as the nucleophile, the scope of the arene coupling partner was first investigated. Anisole, acetanilide and phenol derivatives were found to undergo regioselective iodination and subsequent amination, giving coupled products **88a**–**88e** in 51–94% yield. In the case of 2-fluorophenol, the low yield of **88e** can be attributed to the formation of the homo-coupled compound as a minor by-product. Using anisole, a series of *N*-nucleophiles such as imidazole, 2-pyrrolidinone, benzamide and 4-fluorobenzenesulfonamide gave coupled products **88f**–**88i** in 78–86% yield. It is worth noting that the coupling of anisole and 2-pyrrolidone was performed at a lower temperature (130 °C) than the previously developed bromination procedure (150 °C) and gave coupled product **88g** in better overall yield (78% vs 58%). Benzyl carbamate was also used as a nucleophile in the one-pot process giving Cbz protected aniline **88j** in 43% yield.



Scheme 64: One-pot, two-step *para*-C–H amination/amidation

Limitations of the one-pot process were observed when using nucleophiles such as 1,2,3-triazole, acetamide and dibenzylamine with anisole, which gave no coupled products **88k**–**88m** (Figure 3). Additionally, none of these coupled products were obtained even upon increasing the temperature (150 °C) or extending the reaction time (up to 72 h), with no conversion from 4-iodoanisole (**82a**) observed. Using *tert*-butyl carbamate gave only traces of coupled product **88n** (<10% conversion), while using phenol as a nucleophile resulted in no conversion to diaryl ether **88o**.

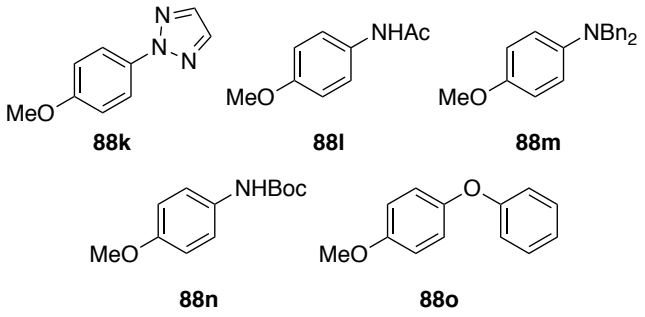
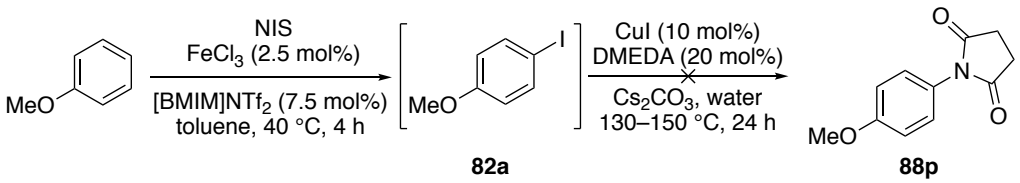


Figure 3: Limitation of the one-pot process

It was considered that succinimide, generated *in situ* during the iodination step, could be utilised as a nucleophile in the subsequent C–N bond forming step (Scheme 65). However, attempts at this resulted in no formation of coupled product **88p**, even at elevated temperature (150 °C).

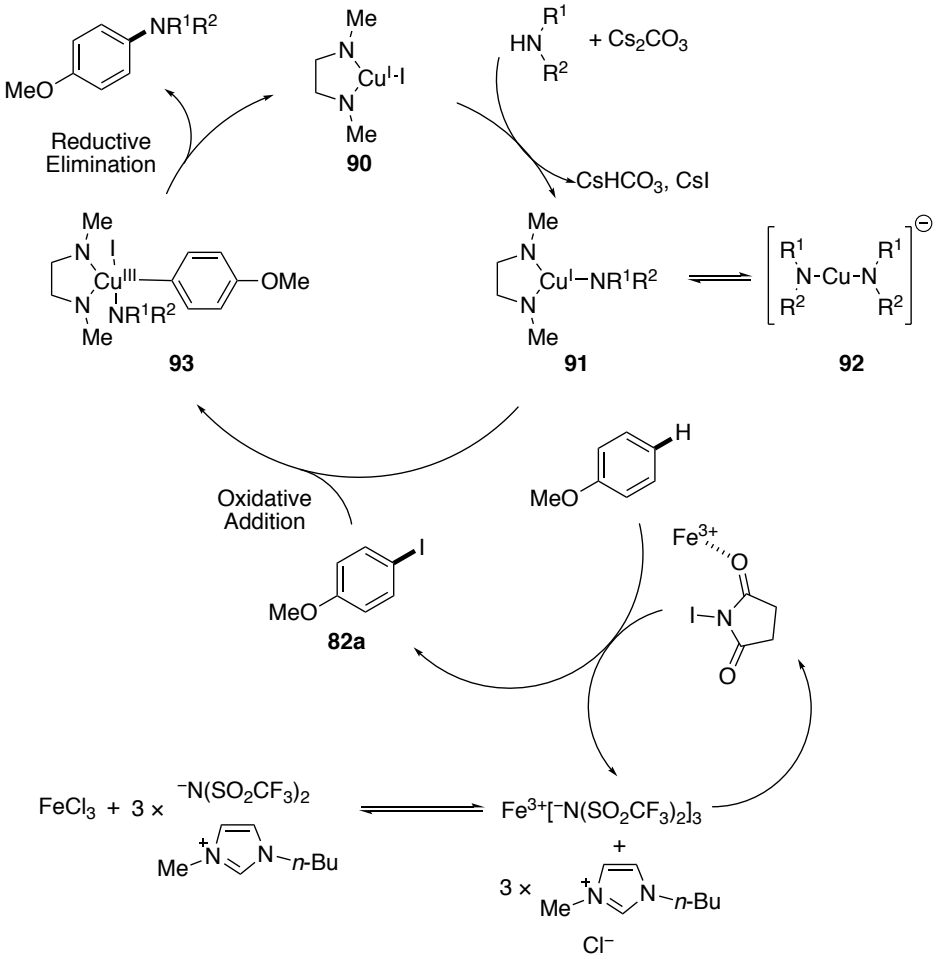


Scheme 65: Coupling of anisole and succinimide

2.2.4 Mechanism of the One-Pot Two-Step Process

A proposed mechanism for the one-pot, two-step aryl C–N bond forming process is shown in Scheme 66. As previously described, the combination of iron(III) chloride and [BMIM]NTf_2 leads to the formation of iron(III) triflimide. The highly delocalised, weakly coordinating nature of the triflimide anion results in the effective activation of NIS, promoting rapid, regioselective electrophilic aromatic substitution of anisole. In the second step, the addition of copper(I) iodide and the bidentate ligand, *N*,*N*′-dimethylethylenediamine (**89**) allows the formation of 1,2-diamine-ligated copper(I) intermediate **90**. Subsequent reaction of copper(I) intermediate **90** with the *N*-nucleophile and base generates the three-coordinate copper(I) amidated species **91**. Kinetic studies by Buchwald and Blackmond have shown that this active catalytic species is in equilibrium with the unreactive amine or amidate dimer, [Cu(I)-Nu_2] **92**, which is the major species at low 1,2-diamine ligand concentration.[240,241] The exact mechanism of haloarene activation remains unclear however it is believed to proceed either *via* oxidative addition to give neutral Cu(III) species **93**, single electron transfer (SET) to form a Cu(II) intermediate or by an iodine atom transfer (IAT) mechanism.[242–244] DFT calculations have revealed that Cu(III) intermediates are kinetically accessible *via* either concerted oxidative addition or by inner sphere electron transfer from a Cu(II) intermediate.[243,245] Reaction pathways involving aryl free radical intermediates, such as SET and IAT mechanisms, have largely been ruled out using experimental methods to detect radical intermediates.[246] Furthermore, direct evidence for the Cu(I)/Cu(III) redox cycle has been observed with isolation of stable Cu(III) complexes with macrocyclic ligands which were

characterised using X-ray crystallography.[247,248] Finally, facile reductive elimination of **93** then forms the coupled products while simultaneously regenerating the 1,2-diamine ligated copper(I) complex **90**. It is evident that the iron(III)-catalysed iodination and copper(I)-catalysed amination are highly compatible in the one-pot process.

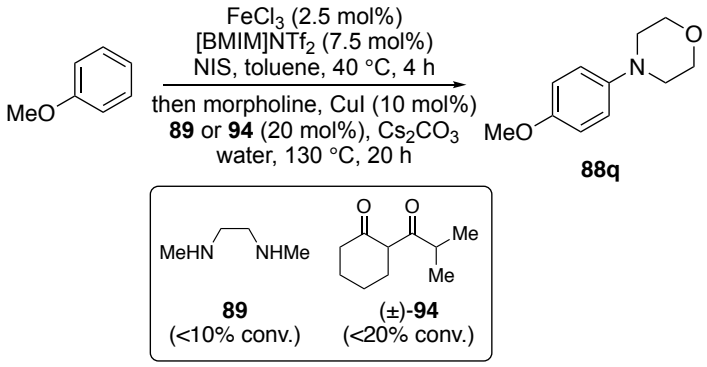


Scheme 66: Proposed mechanism for one-pot, two-step process

2.2.5 One-Pot Process Using Aliphatic Amine Nucleophiles

Using an aliphatic amine, morpholine, in the one-pot process gave low conversion (<10%) to coupled product **88q** (Scheme 67). It was though that the catalytic activity of the copper(I) species was supressed due to competitive binding of the electron-rich alkylamine nucleophile, which is present in significantly higher concentration than the diamine ligand. In an attempt to overcome this limitation, the copper ligand was changed from DMEDA (**89**) to 2-isobutyrylcyclohexanone (**94**), a 1,3-diketone ligand which has been shown to be effective in the Cu(I)-catalysed amination of

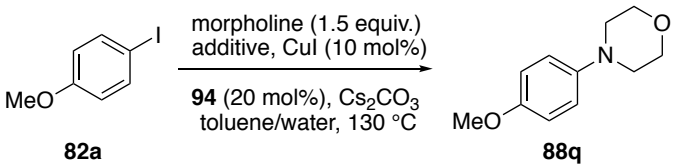
simple aryl halides using aliphatic primary amines and secondary cyclic amines.[249,250] Ligand **94** exists in a delocalised enolate form and has found utility in more difficult Goldberg-type coupling reactions.[21] Mechanistic investigations into the role of 1,3-diketonate ligated copper species have suggested that stronger binding has prevented multiple ligations of the aliphatic amine nucleophile, reducing the energy barrier for oxidative addition of the aryl iodide.[251–253] Using ligand **94** in the one-pot process resulted in only 20% conversion to coupled product **88q**. Increasing the concentration of ligand **94** (40 mol%) and changing the solvent from toluene to DMF did not result in an improvement in conversion.



Scheme 67: Coupling of anisole and morpholine

In order to investigate the poor conversion to the coupled product, the reaction of 4-iodoanisole (**82a**) and morpholine was performed as a single step. Using CuI (10 mol%) and 2-*iso*-butyrylcyclohexanone (**94**) (20 mol%), 90% conversion to coupled product **88q** was observed, which was then isolated in a 60% yield (Table 2, entry 1). *N*-Succinimide (1 equiv.), a by-product of the iodination step, was added to determine whether it played a detrimental role in the C–N coupling step (entry 2) and a conversion to the coupled product of 80% was recorded. Another experiment was performed where $FeCl_3$ and [BMIM]NTf_2 were added which resulted in 80% conversion to **88q** after 40 h (entry 3). Addition of *N*-succinimide, $FeCl_3$ and [BMIM]NTf_2 resulted in 70% conversion to **88q** after 40 h (entry 4). It was evident that the C–N coupling with morpholine proceeded in the presence of $FeCl_3$, the ionic liquid and *N*-succinimide, albeit at a slower rate.

Table 2: Coupling of 4-iodoanisole and morpholine

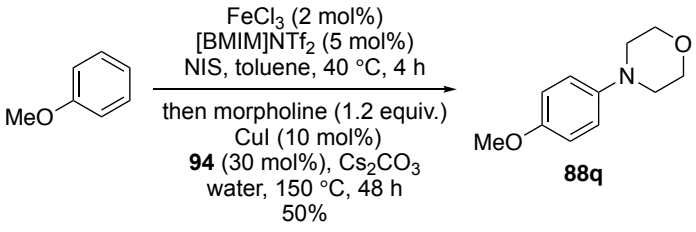


82a **88q**

Entry	Additive	Time (h)	Conversion (%)[a]
1	none	20	90
2	*N*-succinimide (1 equiv.)	40	80
3	$FeCl_3$ (2.5 mol%) and [BMIM]NTf_2 (7.5 mol%)	40	80
4	*N*-succinimide (1 equiv.), $FeCl_3$ (2.5 mol%) and [BMIM]NTf_2 (7.5 mol%)	40	70

[a]Determined using ^{1}H NMR spectroscopy.

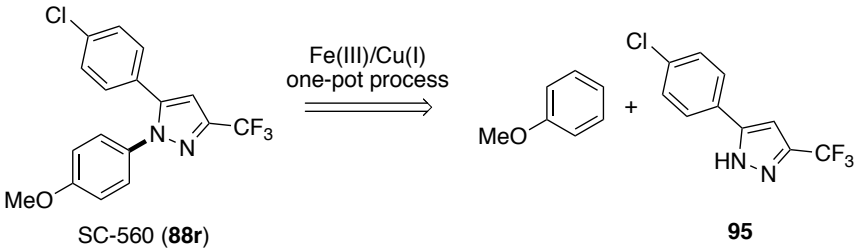
Taking this decrease of rate into account, the one-pot reaction was repeated with a lower catalytic loading of $FeCl_3$ (2 mol%) and [BMIM]NTf_2 (5 mol%), in order to reduce the interference of these reagents in the subsequent C–N coupling step (Scheme 68). In addition to lowering the concentration of reagents from the first step, the loading of the 1,3-diketone ligand was increased to 30 mol%. Also, the number of equivalents of morpholine were reduced from 1.5 to 1.2, to minimise undesired ligation to the copper(I)-catalyst. The result was 86% conversion after 48 h at 150 °C and coupled product **88q** was isolated in 50% yield.



Scheme 68: One-pot, two-step synthesis of 88q

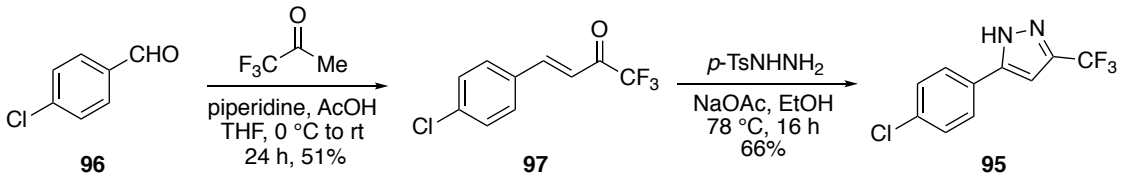
2.2.6 Synthesis of SC-560

The *N*-aryl trifluoromethylpyrazole, SC-560 (**88r**) has been shown to selectively inhibit the cyclooxygenase enzyme, COX-1, over COX-2 and hence has potential therapeutic use as an anti-inflammatory agent.[254] It was proposed that SC-560 could be synthesised by the direct functionalisation of the *para*-C–H bond of anisole followed by coupling of pyrazole **95** using the iron(III)/copper(I)-catalysed one-pot procedure (Scheme 69).



Scheme 69: Retrosynthesis of SC-560 (88r)

The α,β-unsaturated trifluoromethyl ketone **97** was synthesised from 4-chlorobenzaldehyde (**96**) using a crossed aldol condensation with 1,1,1-trifluoroacetone (Scheme 70).[255] Mechanistically, this aldol reaction proceeds *via* an enamine intermediate. A tandem cyclisation/1,5-H shift reaction between trifluoromethyl enone **97** and *p*-toluenesulfonyl hydrazide was then used to form the 3-trifluoromethylpyrazole derivative **95** in 66% yield, using the procedure of Wang and co-workers.[256] It was proposed that the use of ethanol as the solvent suppresses the formation of the diazo by-product *via* the Bamford-Stevens reaction on the intermediate hydrazone salt.

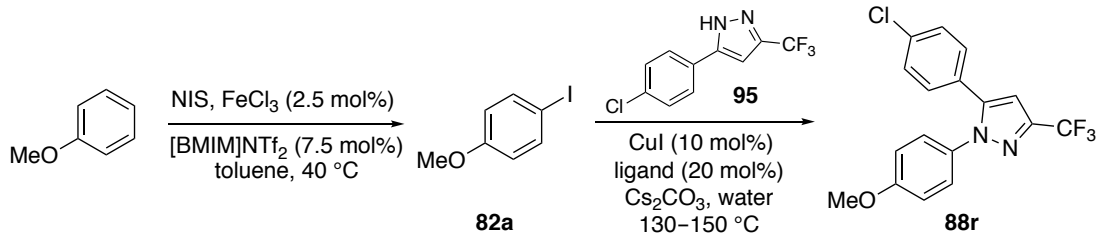


Scheme 70: Synthesis of pyrazole 95

3-Trifluoromethylpyrazole derivative **95** was then investigated as a nucleophile following iron(III) triflimide-catalysed iodination of anisole (Table 3). Using DMEDA and a reaction temperature of 130 °C for 24 h resulted in no conversion to the coupled product **88r** (entry 1). Increasing the temperature to 150 °C also gave no

conversion to **88r** after 48 h (entry 2). The coupling between aryl iodide **82a** and pyrazole **95** has previously been reported by Jamison and co-workers.[257] In their protocol, they performed the cross-coupling reaction using *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**98**) as the copper ligand in 1,4-dioxane which gave SC-560 **88r** in 70% yield. It was therefore decided to change the ligand from DMEDA (**89**) to *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**98**) and this gave **88r** in 8% yield (entry 3). Next, after forming the aryl iodide, the *N*-arylation step was performed in a mixture of toluene and 1,4-dioxane at 150 °C for 60 h, using 3 equivalents of pyrazole **95** (entry 4). These conditions resulted in the isolation of the coupled product **88r** in 23% yield. It was thought that the electron-withdrawing nature of the 3-trifluoromethyl and 5-aryl substituents led to an overall decrease in the nucleophilicity of pyrazole **95**, contributing to the inefficiency of this *N*-arylation reaction. In addition, the steric bulk of the 5-aryl substituent makes pyrazole **95** too hindered for this transformation to proceed under these conditions, either by increasing the energy required for oxidative addition or inhibiting ligation of **95** to the Cu(I)-centre. This cross-coupling reaction required harsh conditions with long reaction times (60 h), a high reaction temperature (150 °C) and used a large excess of pyrazole **88r** (3 equiv.) therefore, it was decided not to pursue any further optimisation.

Table 3: Coupling of anisole and pyrazole 95



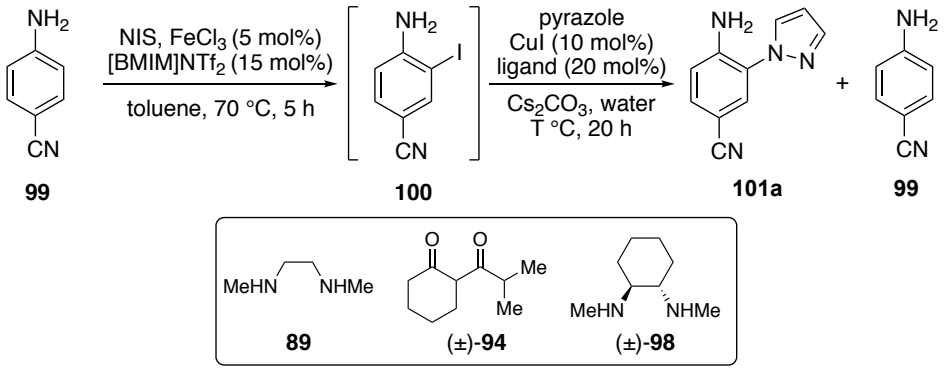
Entry	Pyrazole (equiv.)	Ligand (20 mol%)	Solvent	Temperature (°C)	Time (h)	Yield of **88r** (%)
1	1.1	**89**	toluene	130	24	n/a
2	1.1	**89**	toluene	150	48	n/a
3	1.1	**98**	toluene	150	48	8
4	3	**98**	toluene/1,4-dioxane	150	60	23

2.2.7 One-Pot *ortho*-Amination of Aryl C–H Bonds

The one-pot iron(III)-catalysed iodination and copper-catalysed C–N bond forming process was next investigated for the selective *ortho*-amination/amidation of arenes. The key objective was to improve upon the *ortho*-bromination/amination of 4-nitroaniline previously attempted in the group and completely supress the de-halogenation pathway in favour of C–N bond formation. It was proposed that this could be achieved by using NIS in the activation step. The weaker C–I bond would lower the energy requirement for oxidative addition and hence, lead to a more efficient procedure, minimising the undesired protodecupration process. This project began with the optimisation of the one-pot *ortho*-C–H amination of 4-aminobenzonitrile (**99**) with pyrazole. Iron(III) chloride (5 mol%) and [BMIM]NTf_2 (15 mol%) were used in the activation step, resulting in full conversion to *ortho*-iodide intermediate **100** in 5h at 70 °C. DMEDA ligand-assisted, copper(I)-catalysed coupling with pyrazole then gave a 3:1 mixture of coupled product **101a** and reduced compound **99** (Table 4, entry 1). Performing the cross-coupling step at a lower temperature (130 °C) improved the ratio of **101a** and **99** to 6:1, implying that protodecupration is disfavoured at lower temperatures (entry 2). To improve this process and reduce the ratio of **101a** and **99** further, alternative copper-chelating ligands were used in the second step. Diketone ligand **94**, which has previously been shown to be effective in more challenging coupling reactions by forming more stable, anionic copper intermediates, was used in the one-pot process. As diketone ligands are weaker nucleophiles than nitrogen-containing ligands, they do not tend to undergo *O*-arylation, a reaction pathway implicated in catalyst deactivation.[249,258] The use of ligand **94** did allow for the formation of coupled product **101a** but offered no improvement in the product ratio (entry 3). Studies by Buchwald and co-workers have suggested that the use of cyclic diamine ligands improves the efficiency of copper-catalysed *N*-arylation reactions by increasing the stability of the active copper-nucleophile intermediate.[15,16] On that basis, *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**98**) was used in the one-pot process which resulted in higher selectivity of 12:1 for **101a** versus **99** (entry 4). It was clear that, while the choice of copper ligand did improve the product ratio, copper-catalysed dehalogenation remained a competing reaction pathway. To prevent this, the number of equivalents of pyrazole were increased which led to complete

suppression of the reductive de-halogenation pathway, allowing for generation of only the coupled product **101a**, which was isolated in 60% yield (entry 5).

Table 4: Optimisation of the one-pot *ortho*-C–H amination

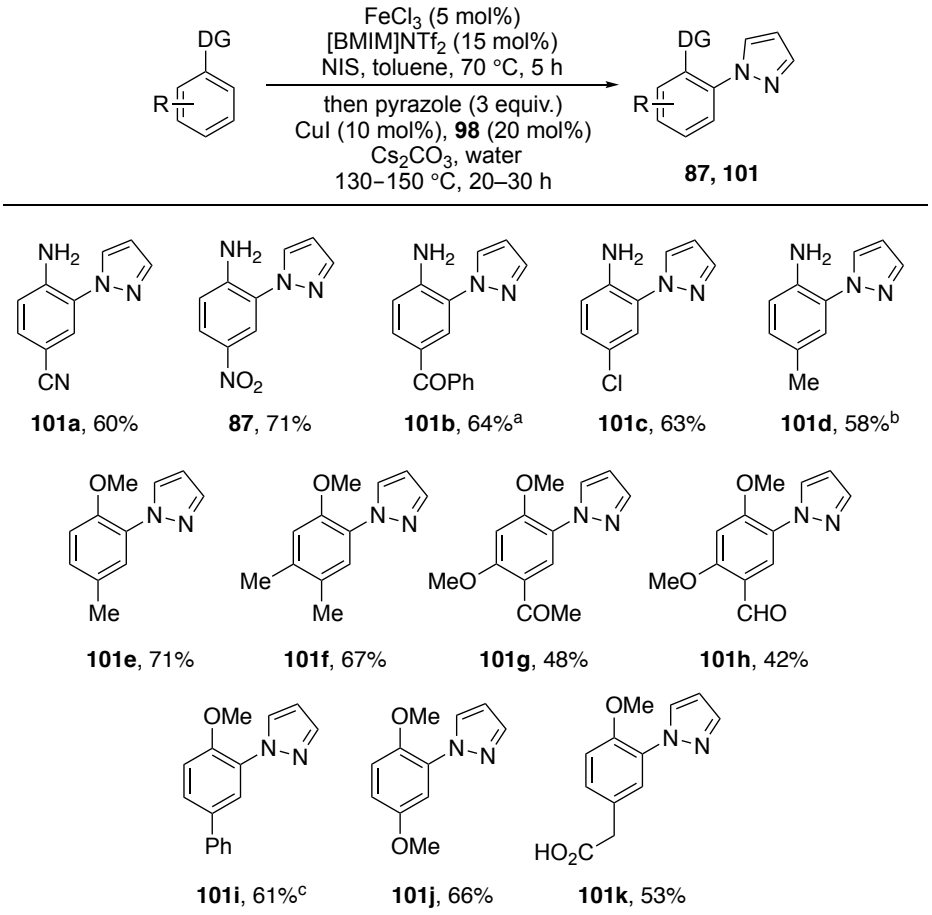


Entry	Pyrazole (equiv.)	Ligand (20 mol%)	Temp. (°C)	Ratio (**101a**:**99**)[a]
1	1.5	**89**	150	3:1
2	1.5	**89**	130	6:1
3	1.5	**94**	130	5:1
4	1.5	**98**	130	12:1
5	3	**98**	130	**101a** only

[a]Determined using ^{1}H NMR spectroscopy

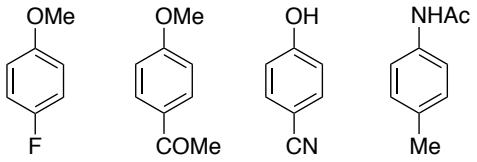
The optimised conditions were then used to evaluate the substrate scope of the one-pot *ortho*-amination of a range of activated aromatic compounds with pyrazole (Scheme 71). A variety of *para*-substituted aniline derivatives, bearing electron-withdrawing groups, were submitted to the iron(III)-catalysed iodination and copper(I)-catalysed cross-coupling with pyrazole which gave *ortho*-substituted compounds **87**, **101a**–**101d** in 58–71% yield. It is worth noting that this method allows *ortho*-amination of anilines without the requirement of a protecting group or covalent chelation-controlled directing group. Despite the use of relatively nucleophilic arenes, no intermolecular self-arylation of the aniline functional group was observed. Next, the one-pot process was extended for the *ortho*-substitution of anisole derivatives bearing multiple activating groups, which gave coupled products **101e**–**101k** in 42–71% yield. A substrate bearing a free carboxylic acid functional group was also tolerated in this process and gave coupled product **101k** in 53% yield. The use of the highly regioselective iron(III) triflimide iodination ultimately led to the formation of exclusively *ortho*-coupled products even when using electron-

rich arenes with multiple activating groups. The modest yields for some compounds (e.g. **101g** and **101h**) was due to co-elution with the excess pyrazole nucleophile during flash column chromatography, complicating the purification procedure.



Scheme 71: Scope of arene in the one-pot process; [a]Iodination step was complete after 20 h, [b]Iodination step was performed at 40 °C, [c]Pyrazole (1.5 equiv.) used.

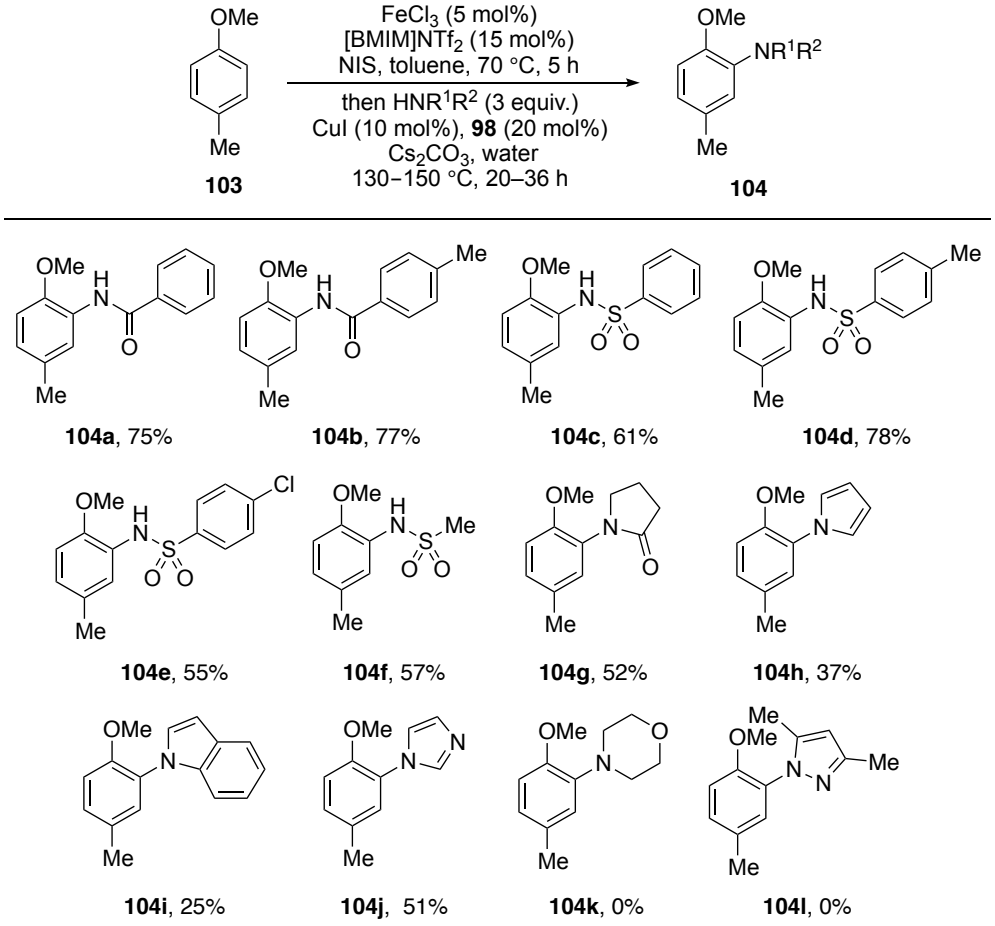
When anisole and phenol derivatives **102a**–**102d** bearing electron withdrawing groups in the *para*-position where submitted to the iron(III)-catalysed iodination step, only trace amounts of *ortho*-iodinated products were observed (Figure 4). In addition, there was no conversion to the aryl iodide when using acetanilide as a directing group. This lack of conversion is attributed to the deactivated nature of these aryl systems towards electrophilic aromatic substitution.



102a **102b** **102c** **102d**

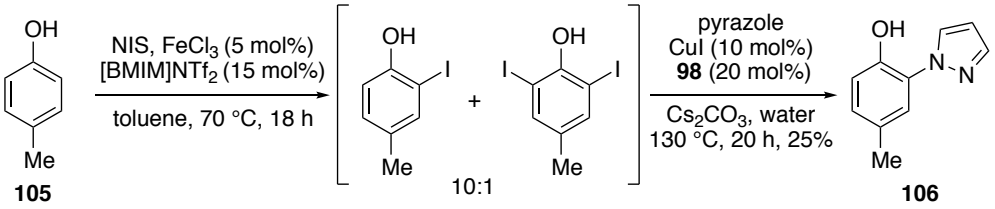
Figure 4: Limitations of one-pot process

Using the standard one-pot conditions for 4-methylanisole (**103**), a variety of *N*-nucleophiles were evaluated (Scheme 72). Applying benzamides, sulfonamides and 2-pyrrolidone as nucleophiles in the one-pot process gave the corresponding *ortho*-coupled products, **104a**–**104g** in 52–78% yield. Other *N*-heterocycles such as pyrrole, indole and imidazole required a longer reaction time (36 h) for the copper-catalysed amination step, however, this still gave the coupled products, **104h**–**104j** in 25–51% yield. Limitations were found when investigating the scope of the nucleophilic coupling partner in the one-pot process. As before, the electron-rich aliphatic amine, morpholine, was not tolerated and led to the formation of only traces of coupled product **104k**. This is likely due to the competitive binding of morpholine with the active Cu(I)-catalyst. When using the hindered *N*-heterocyclic nucleophile 3,5-dimethylpyrazole, no formation of **104l** was observed, even at 150 °C for 96 h and the addition of a further portion of copper iodide (10 mol%) and ligand **98** (20 mol%). Coupling at the *ortho*-position of 4-methylanisole (**103**) with a 5-substituted pyrazole is obviously too sterically demanding under these conditions.



Scheme 72: Scope of nucleophile in the one-pot process

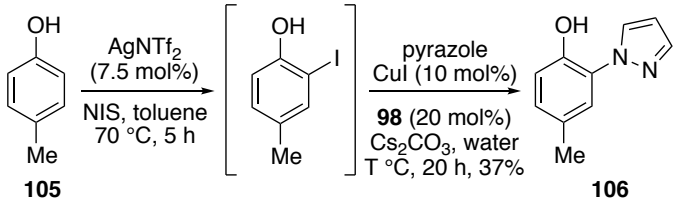
Another limitation of this method was found during the investigation of the *ortho*-substitution of phenols. For example, using *p*-cresol (**105**) as a substrate in the one-pot process yielded 25% of coupled product **106** (Scheme 73). The iodination step using iron(III) triflimide (5 mol%) was sluggish, with 55% conversion of starting material **105** after 18 h at 70 °C and a 10:1 mixture of the desired mono-iodinated and poly-iodinated compound was obtained. This mixture was then submitted to copper-catalysed cross-coupling step with pyrazole. Both the moderate conversion and poor selectivity encountered in the electrophilic aromatic substitution step account for the low yield of **106**.



Scheme 73: Coupling of *p*-cresol and pyrazole

It was previously shown the reaction of a hard, highly charged Fe(III) Lewis acid catalyst with active phenol substrates led to the formation of bis-iodinated compounds, reducing the yield of the desired mono-iodinated products.[231] For this reason, a less charged, softer Ag(I) Lewis acid catalyst was used to catalyse the iodination of *p*-cresol (**105**). Using silver(I) triflimide (7.5 mol%) to catalyse the iodination step allowed for 90% conversion to the desired mono-*ortho*-iodinated regioisomer, as determined by ^{1}H NMR spectroscopy. Subsequent copper(I)-catalysed amination with pyrazole, however, led to a 1:1 mixture of coupled product **106** and *p*-cresol (**105**) and **106** was isolated in 37% yield (Table 5, entry 1). To limit this competing reductive dehalogenation pathway, the reaction was performed using 5 equivalents of pyrazole however, this resulted in no improvement, with **106** again isolated in 37% yield (entry 2). The reaction was next performed at 150 °C and this gave a 1.4:1 ratio of coupled product **106** to *p*-cresol (**105**), with a lower isolated yield of 26%, perhaps due to decomposition of **106** (entry 3). The C–N coupling step was next attempted without the addition of water, a possible source of hydrogen atoms responsible for the protodecupration side-reaction. This resulted in a 0.8:1 mixture of **106** to **105** with the lower overall isolated yield due to the poor solubility and therefore poor mixing of reagents (entry 4). Attempts to minimise the de-halogenation and increase the isolated yield of **106** did not improve the outcome therefore, the best conditions were those of entry 1.

Table 5: One-pot *ortho*-amination of *p*-cresol

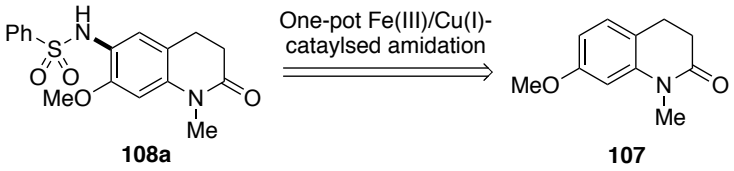


Entry	Temperature (°C)	Pyrazole (equiv.)	water	Ratio of **106**:**105**[a]	Isolated yield of **106** (%)
1	130	3	yes	1:1	37
2	130	5	yes	1:1	37
2	150	3	yes	1.4:1	26
3	130	3	no	0.8:1	15

[a]Determined by ^{1}H NMR spectroscopy.

2.2.8 Late-stage Functionalisation of 3,4-Dihydroquinolin-2-ones

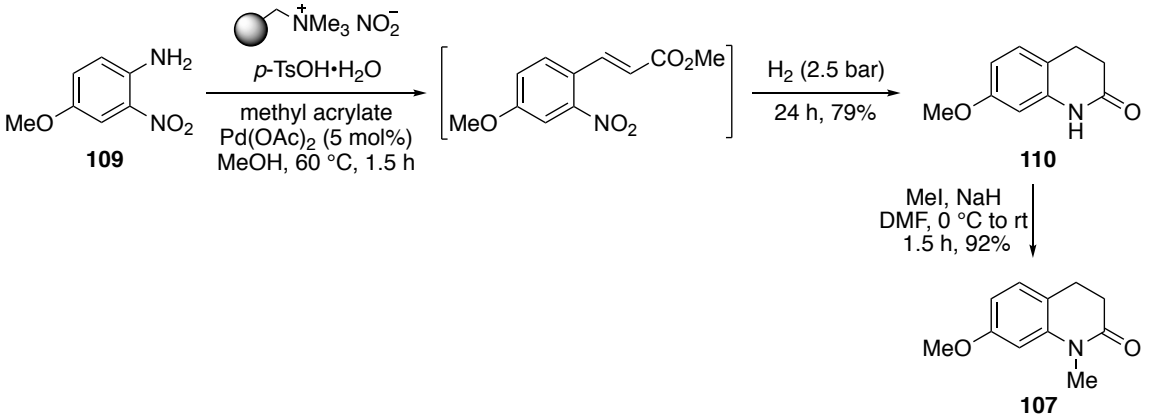
Following the examination of the scope and limitations of the one-pot intermolecular *ortho*-amination process, it was next used for the synthesis of a pharmaceutically relevant target. Palmer and co-workers have shown that 3,4-dihydroquinolin-2-ones are potential, effective small molecule inhibitors of the bromodomain tripartite motif containing protein 24 (TRIM24), which has been implicated in human cancer.[259,260] Over-expression of this particular protein is often correlated with aggressive tumour growth and poor patient prognosis.[261,262] It was proposed that the one-pot iodination and *ortho*-amidation process could be used for the rapid, selective late-stage functionalisation of *N*-methyl 3,4-dihydroquinolin-2-one **107**, allowing access to bromodomain inhibitor **108a** and a library of novel analogues (Scheme 74).



108a **107**

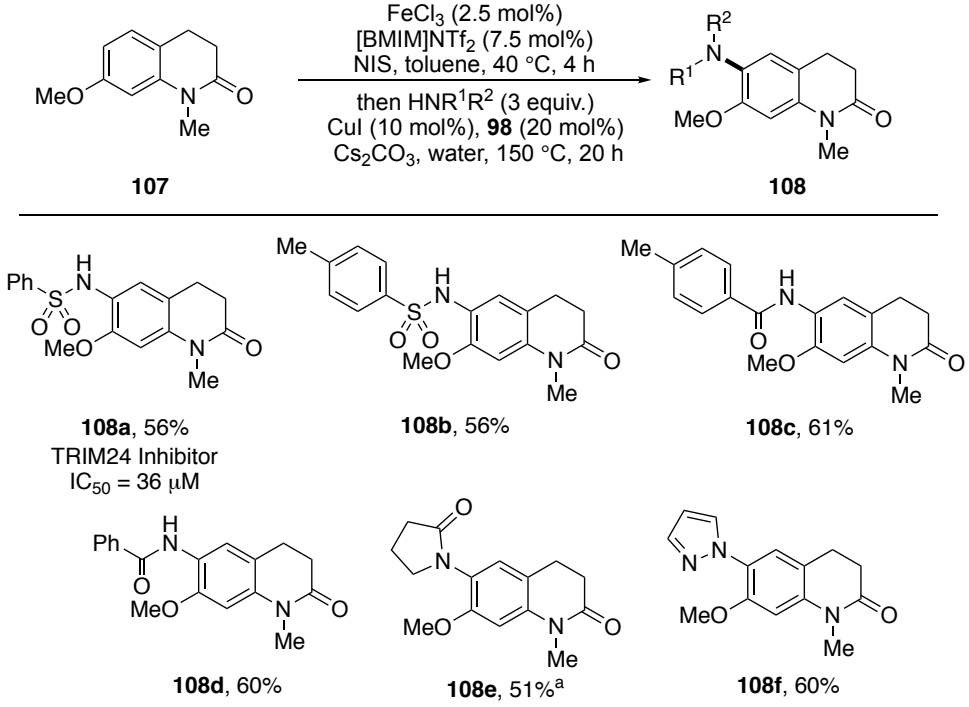
Scheme 74: Proposed synthesis of TRIM24 inhibitor 108a

Firstly, 3,4-dihydroquinolin-2-one **107** was prepared by Rochelle McGrory, an MSci project student, using a one-pot, four-step process previously developed in the group (Scheme 75).[263] This involved the conversion of 4-methoxy-2-nitroaniline (**109**) into the corresponding diazonium tosylate salt, using a resin-bound nitrite reagent. In the same-pot, this diazonium salt was then utilised during a palladium-catalysed Heck-Matsuda cross-coupling reaction with methyl acrylate. Subjecting this mixture to 2.5 bar pressure of hydrogen, while re-utilising the palladium catalyst, resulted in the reduction of both the alkene and the nitro group, which allowed for *in situ* cyclisation to form the 3,4-dihydroquinolin-2-one core. This gave 3,4-dihydroquinolin-2-one **110** in 79% yield over the four steps. Subsequent methylation using sodium hydride and methyl iodide under standard conditions, gave *N*-methyl quinolinone **107** in 92% yield.



Scheme 75: Synthesis of *N*-methyl-3,4-dihydroquinolin-2-one 107

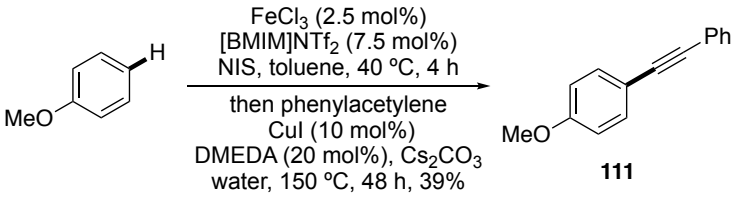
The one-pot *ortho*-amidation process was then applied to *N*-methylquinolin-2-one **107**, and the late-stage functionalisation of the C-6 position (Scheme 76). Iodination of **107** was found to proceed using lower catalyst loadings of both $FeCl_3$ (2.5 mol%) and [BMIM]NTf_2 (7.5 mol%) and was complete in 4 h. Following this, copper(I)-catalysed cross-coupling with benzenesulfonamide completed the one-pot process and gave TRIM24 inhibitor **108a** in 56% yield. This one-pot process was then used for the late-stage synthesis of novel analogues of bioactive compound **108a**. Coupling of **107** with sulfonamide and benzamide nucleophiles as well as pyrazole and 2-pyrrolidinone gave coupled products **108b**–**108f** in 51–61% yield. It should be noted that compounds **108b** and **108d**–**108f** were synthesised by Rochelle McGrory.



Scheme 76: One-pot synthesis of TRIM24 inhibitor 108a and novel analogues; [a]The second step required 72 h

2.2.9 One-Pot Iron and Copper-Catalysed Iodination and Sonogashira Cross-Coupling Reaction

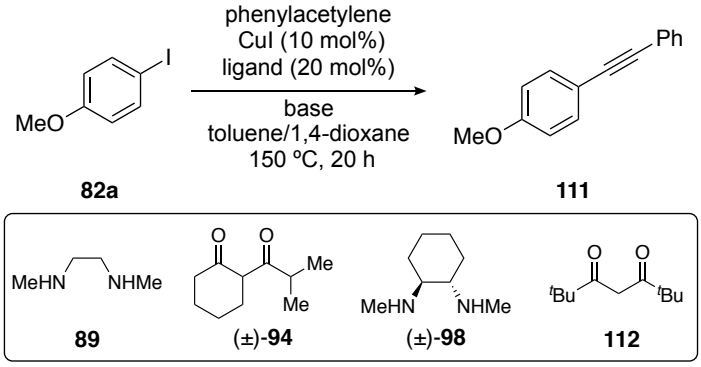
In the past decade, it has been shown that Sonogashira cross-coupling reactions can be performed under palladium-free conditions using iron[264] or copper catalysis.[265] Therefore, another aim of this project was to develop a one-pot method for the construction of C–C bonds directly from aryl C–H bonds. Initially, this was investigated using anisole and phenylacetylene as coupling partners (Scheme 77). As reported above, iron(III)-catalysed of anisole resulted in full conversion to the iodide intermediate after 4 h. Following this, coupling with phenylacetylene using CuI (10 mol%) led to 70% conversion to coupled product **111**, which was then isolated in 39% yield. A major by-product in this process was acetophenone, resulting from the hydration of the alkyne under the basic aqueous conditions. In fact, iron(III) triflimide has been shown to effectively coordinate to the π-electron rich systems, facilitating the addition of water to alkynes.[266]



Scheme 77: One-pot coupling of anisole and phenylacetylene

The reaction of 4-iodoanisole (**82a**) and phenylacetylene was performed as a single step to determine the optimal base and ligand combination. As the use of water in the reaction was resulting in hydration of the alkyne, a mixture of toluene and 1,4-dioxane was instead used. Using copper(I) iodide (10 mol%) and cesium carbonate, multiple ligands were screened including DMEDA (**89**), 2-isobutyrylcyclohexanone (**94**), *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**98**), and TMHD (**112**) (Table 6, entries 1,2,3 and 4). DMEDA (**89**) was found to be the most effective and gave 41% conversion to coupled product **111**. A change of base to potassium carbonate led to a substantial decrease in conversion, whereas the use of potassium phosphate gave comparable conversion (entries 5 and 6). The use of a soluble organic base, triethylamine, resulted in the formation of only traces of **111** (entry 7). To investigate the effect of an iron(III) catalyst on the cross-coupling of **82a** and phenylacetylene, $FeCl_3$ (2.5 mol%) was added (entry 8). This resulted in only 20% conversion to coupled product **111**. Iron(III) triflimide (2.5 mol%) was next added however this neither hindered nor improved the cross-coupling reaction (entry 9).

Table 6: Optimisation of the Sonogashira reaction



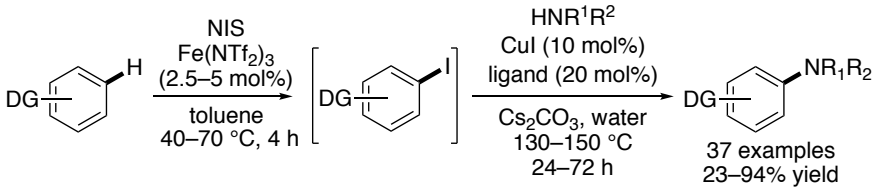
Entry	Ligand (20 mol%)	Base (2 equiv.)	Additive	Conversion (%)[a]
1	**89**	Cs_2CO_3	none	41
2	**94**	Cs_2CO_3	none	20
3	**98**	Cs_2CO_3	none	33
4	**112**	Cs_2CO_3	none	8
5	**89**	K_2CO_3	none	25
6	**89**	K_3PO_4	none	41
7	**89**	Et_3N	none	traces
8	**89**	Cs_2CO_3	$FeCl_3$ (2.5 mol%)	20
9	**89**	Cs_2CO_3	$Fe(NTf_2)_3$ (2.5 mol%)	40

[a]Determined by ^{1}H NMR spectroscopy

2.2.10 Conclusions and Outlook

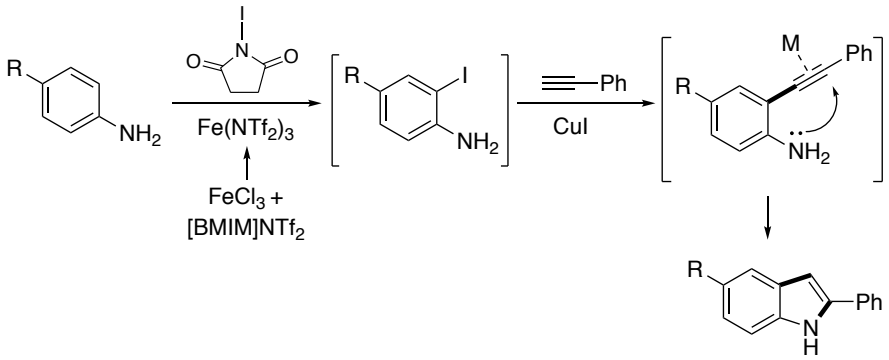
The regioselective iodination of arenes using the Lewis acid, iron(III) triflimide, was combined with a copper(I)-catalysed, ligand-assisted coupling with unactivated *N*-nucleophiles allowing for the *para*-amination of C–H bonds in a one-pot process (Scheme 78). Using this method, a small library of *para*-C–N coupled products were synthesised and, with some optimisation, allowed the coupling of electron rich morpholine with anisole. In addition, when the *para*-position was blocked, the one-pot method allowed for *ortho*-amination and amidation of aromatic compounds. This methodology was applicable to a series of anisole derivatives and permitted *ortho*-amination of anilines, without the necessity of a protecting or chelation-based directing group. The synthetic utility of this method was demonstrated by the late-

stage functionalisation of a quinoline-2-one scaffold, allowing for the synthesis of a bromodomain-containing protein inhibitor as well as a series of novel analogues.



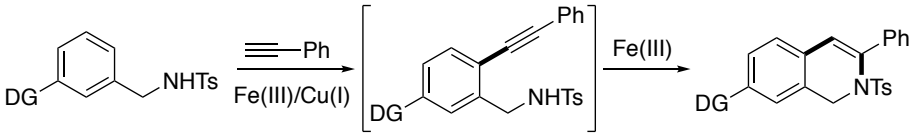
Scheme 78: Summary of the one-pot, two-step iodination/amination process

This methodology was extended to C–C bond formation, using the Fe(III)-catalysed activation, followed by Cu(I)-catalysed coupling with phenyl acetylene in a palladium-free Sonogashira-type process. After further optimisation of the one-pot iron(III)/Cu(I)-catalysed Sonogashira process, an application of this methodology is the synthesis of benzannulated heterocycles (Scheme 79). *ortho*-Iodination of anilines and subsequent C–C bond formation would then allow for cyclisation of the internal nitrogen nucleophile, facilitated by coordination of the re-utilised Fe(III) ion to the alkyne, leading to the formation of indoles in a one-pot, three-step process.



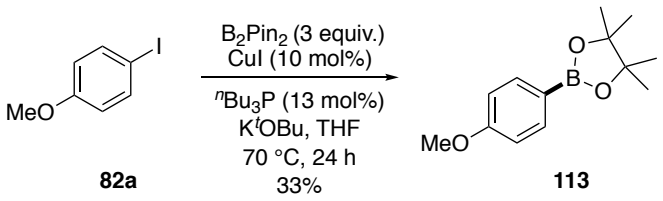
Scheme 79: Proposed one-pot, three-step synthesis of indoles

This methodology could then be applied to the synthesis of other, larger heterocyclic ring systems, such as dihydroisoquinolines (Scheme 80).



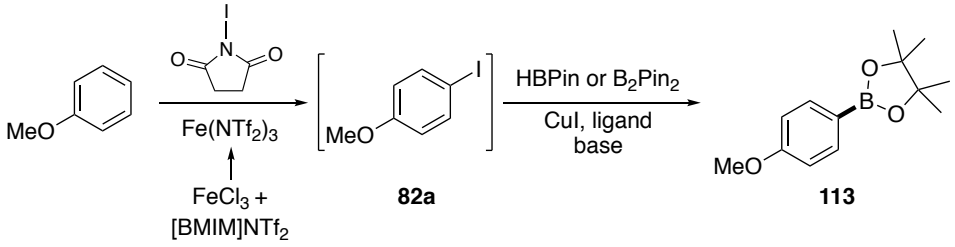
Scheme 80: Proposed one-pot, three-step synthesis of 1,2-dihydroisoquinolines

Borylation of aryl bromides has been recently demonstrated using a cooperative iron and copper-catalysed protocol, avoiding the use of palladium catalysis.[267] In addition, several methods of copper(I)-catalysed borylation of aryl halides have previously been reported.[268,269] To build on this work, it was proposed that the regioselective iron(III)-catalysed iodination could be used in combination with a Cu(I)-catalysed C–B bond formation for the one-pot borylation of C–H bonds. An initial result demonstrated the feasibility of copper-catalysed borylation using the conditions developed by Marder and co-workers with the synthesis of coupled product **113** in 33% yield (Scheme 81).[269]



Scheme 81: Copper(I)-catalysed borylation of 4-iodoanisole (82a)

It was envisioned that, after extensive optimisation, this copper-catalysed borylation would be incorporated into the one-pot process, combining with the iron(III) triflimide-catalysed iodination, for the efficient synthesis of pinacol borane-derived aryl compounds (Scheme 82).

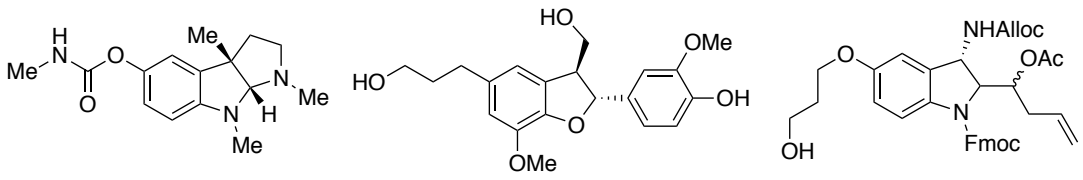


Scheme 82: One-pot C–H borylation

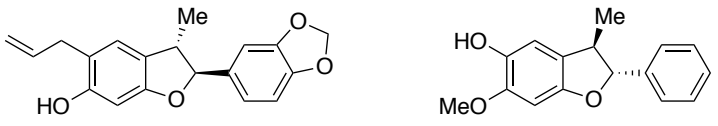
2.3 One-Pot, Two-Step Synthesis of Indolines and Dihydrobenzofurans

2.3.1 Introduction

Indoline and 2,3-dihydrobenzofuran scaffolds can be widely found in a range of natural products, pharmaceutical agents and biologically active compounds.[270,271] For example, physostigmine (**114**), a natural product from the African Calabar bean *(Physostigma venenosum*), is a potent reverse cholinesterase inhibitor which has shown promise in the treatment of Alzheimer's disease (Figure 5).[272] Another example is natural product lawsonicin (**115**), a major component in hazelnut (*Corylus avellana L.*) shell extracts, which has recently been investigated for its antioxidant effects and cytotoxic activity on human cancer cell lines.[273] In addition to this, indoline **116** was found to be the lead compound in a study of the small molecule modulation of protein-protein interactions.[274] More specifically, **116** was found to inhibit the PTK2 protein tyrosine kinase enzyme and hence, has applications in the prevention of cancer metathesis. Further examples that include these structural motifs are liliflol A (**117**), a potent COX-2 inhibitor[275] and neolignan natural product (+)-obtusafuran (**118**).



(–)-physostigmine (**114**) lawsonicin (**115**) PTK2 inhibitor **116**

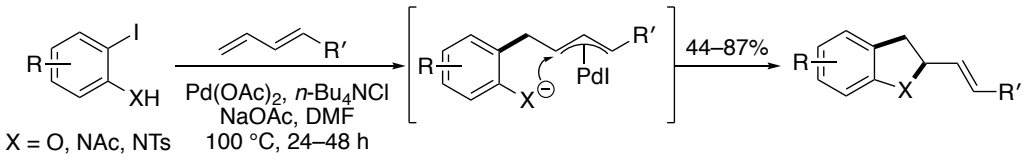


liliflol A (**117**) (+)-obtusafuran (**118**)

Figure 5: Indoline and 2,3-dihydrobenzofuran scaffold in biologically active compounds and natural products

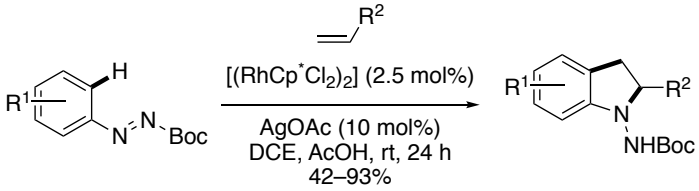
It is this prevalence in biologically important compounds that has led to considerable efforts being focused towards the discovery and development of efficient methods for the synthesis of these functional heterocycles.[276,277] Traditionally, indolines and 2,3-dihydrobenzofurans have been prepared by the alkylation of *ortho*-substituted

phenols and anilines. This approach is exemplified by Larock and co-workers who used a palladium-catalysed heteroannulation of dienes with *o*-iodoanilines and *o*-iodophenols then subsequent heterocyclisation for the synthesis of indolines and 2,3-dihydrobenzofurans (Scheme 83).[278] This method was contingent on the use of 1,3-dienes, which do not have β-hydrogen atoms, and hence, intramolecular nucleophilic attack on the π-allyl intermediate occurs instead of the formation of Heck-type products by β-hydride elimination.



Scheme 83: Larock's synthesis of indolines and 2,3-dihydrobenzofurans

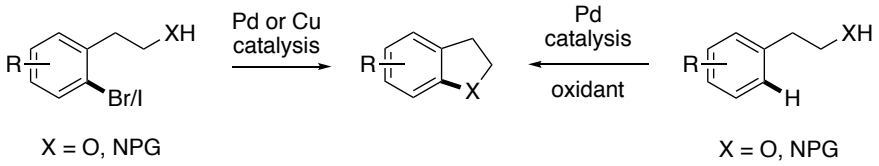
An improvement of this method was developed by Jamieson and co-workers, with the extension to terminal alkenes using a dual nickel/photoredox catalytic protocol.[279] A novel synthesis of 1-aminoindolines was reported by Glorius which employs diazenecarboxylates as directing groups in a rhodium(III)-catalysed C–H insertion followed by nucleophilic addition to alkenes (Scheme 84).[280]



Scheme 84: Glorius' synthesis of 1-aminoindolines

While these procedures offer convenient access to these heterocyclic scaffolds, they often rely on the use of highly functionalised starting materials and precious transition metal catalysts. A more general strategy for the synthesis of these heterocyclic ring systems is the Buchwald-Hartwig or Ullmann-Goldberg type aromatic C–N and C–O bond forming process of *o*-halogenated phenylethylamine and phenylethylalcohols (Scheme 85). These transition metal-catalysed approaches have found wide utility for the preparation of five- and six-membered benzofused heterocycles and have been applied in the synthesis of natural products, including Panek's total synthesis of alkaloid (+)-isatisine A.[281] Seminal

work by the Yu group presented the possibility of intramolecular cross coupling of unactivated aryl-C–H bonds with internal N–H nucleophiles.[163] The method, described in chapter 1.4, allowed for the direct synthesis of indolines from *N*-triflimide protected phenylethylamines employing a Pd(II)/Cu(I)-catalysed tandem C–H iodination/amination sequence. In the years since this work was first reported, there have been a series of improvements offered on this strategy, mainly the use of *N*-chelating groups and oxidising agents such as hypervalent iodine compounds. This strategy was highly effective for the synthesis of 5- and 6-membered nitrogen heterocycles, yet not entirely applicable to the synthesis of 2,3-dihydrobenzofurans due to the incompatibility of the oxidising conditions with primary and secondary alcohol substrates.

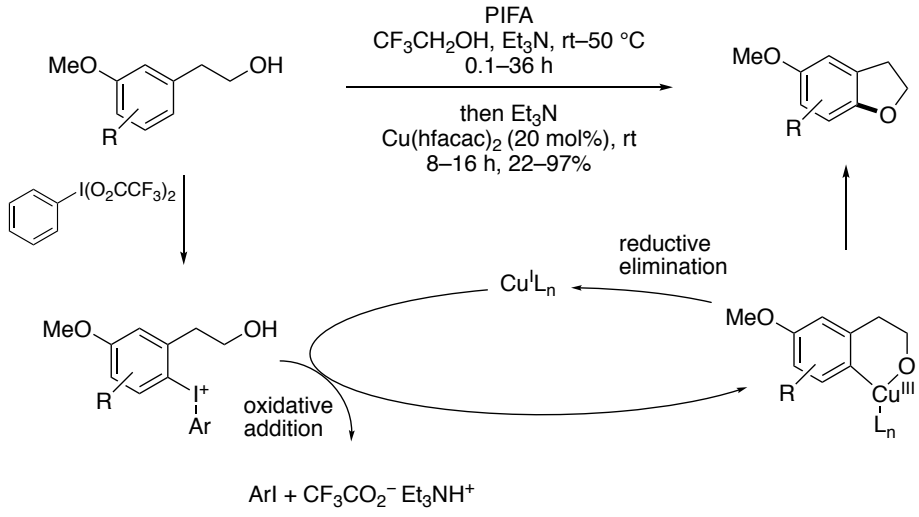


Scheme 85: Synthetic routes towards indolines and 2,3-dihydrobenzofurans

A notable exception to this was reported by Yu, using palladium-catalysed aryl C–H activation and C–O cyclisation of phenylethylalcohols for dihydrobenzofuran synthesis.[282] The success of this method was dependent on the use of tertiary alcohols, preventing the possibility of oxidation. Also, the correct choice of oxidant was critical with the most efficient being a hypervalent iodine species, diacetoxyiodobenzene. This oxidising agent allowed for the oxidation of the Pd(II) intermediate to Pd(IV) from which facile reductive elimination of the C–O bond could occur. This palladium-catalysed C–H activation/C–O cyclisation was later used in combination with a rhodium-catalysed C–H insertion for the enantioselective synthesis of *trans*-disubstituted 2,3-dihydrobenzofurans from aryldiazoacetates and protected benzyl alcohols.[283]

Zakarian and co-workers have since reported a mechanistically distinct approach for the preparation of dihydrobenzofurans involving direct, oxidative aryl C–O bond formation (Scheme 86).[284] This methodology involves the activation of phenylethylalcohols using non-symmetric diaryl-iodonium salts allowing for copper-catalysed cyclisation to occur at room temperature under very mild conditions.

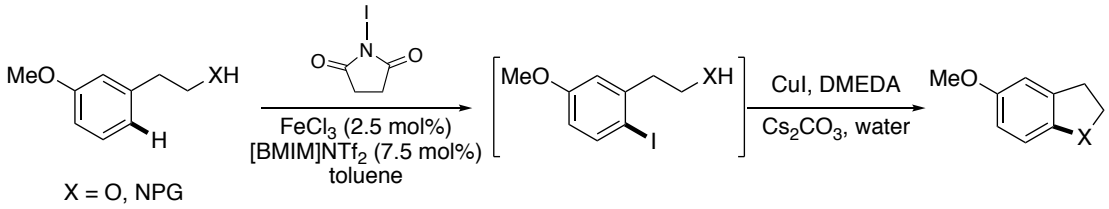
Electron rich arenes were reacted with a hypervalent iodine(III) reagent, [*bis*(trifluoroacetoxy)iodo]benzene (PIFA), which resulted in the rapid formation of a diaryl-λ^3-iodane intermediate. Subsequent exposure to a copper-catalyst results in oxidative addition of the C–I bond resulting in a Cu(III) species to which the internal oxygen nucleophile ligates. Reductive elimination then gives the 2,3-dihydrobenzofuran products, while regenerating the active Cu(I)-catalyst.



Scheme 86: Copper-catalysed synthesis of 2,3-dihydrobenzofurans reported by Zakarian

2.3.2 Project Aims

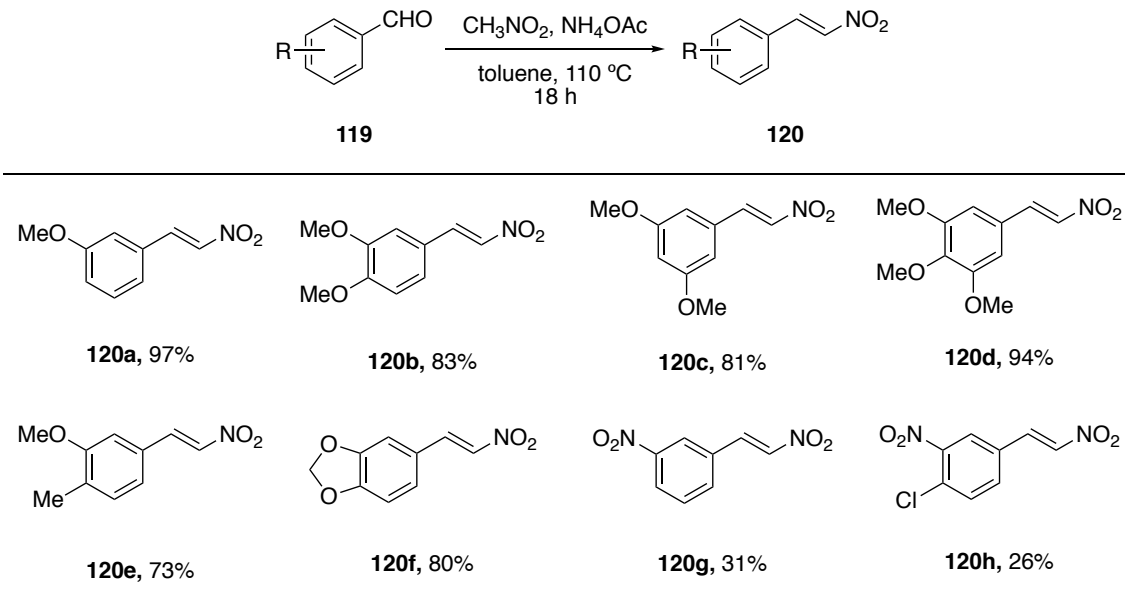
The main objective of this project was to develop a one-pot intramolecular C–N and C–O bond forming process for the synthesis of indoline and 2,3-dihydrobenzofuran heterocycles (Scheme 87). This would build upon the previously developed intermolecular C–N bond forming process (chapter 2.2) and would utilise the previously developed regioselective iron(III)-catalysed iodination for initial arene activation followed by a copper(I)-catalysed heterocyclisation with pendant nitrogen or oxygen nucleophiles. The first key objective of this project was the development of a concise, efficient synthetic route towards various *N*-protected phenylethylamines and phenylethylalcohols from readily available starting materials. These substrates would then be used in the optimisation and investigation of the scope of the one-pot process. Finally, this methodology would then be applied to the synthesis of bioactive and pharmaceutically relevant target molecules.



Scheme 87: Proposed synthesis of indolines and dihydrobenzofurans using a one-pot process

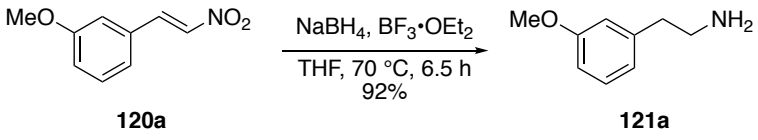
2.3.3 Synthesis of Phenylethylamines Substrates

The first stage of this project investigated a short and efficient synthesis of *N*-protected phenylethylamines from commercially available benzaldehydes (Scheme 88). Firstly, the Henry reaction was employed using nitromethane and ammonium acetate to perform a one-carbon homologation.[285] In this reaction**,** ammonium acetate is used for the deprotonation of nitromethane and the generation of a resonance stabilised nitronate species, which then undergoes an aldol reaction with the benzaldehyde. This results in the formation of a β-nitroalcohol which, under the reaction conditions, undergoes dehydration to form desired nitroalkene. This procedure was efficient when applied to electron rich benzaldehydes **119a**–**119f** and gave the corresponding nitrostyrene compounds **120a**–**120f** as exclusively *E*-isomers in 73–97% yield. Evidence for alkene *E*-selectivity was observed using ^{1}H NMR spectroscopy, with large *trans* coupling constants of 13.6 Hz for nitrostyrenes **120a**–**120f**. The use of these conditions with electron-deficient benzaldehydes **119g** and **119h** resulted in the formation of complex mixtures however, the isolation of compounds **120g** and **120h** was possible, albeit in 31% and 26% yield, respectively.



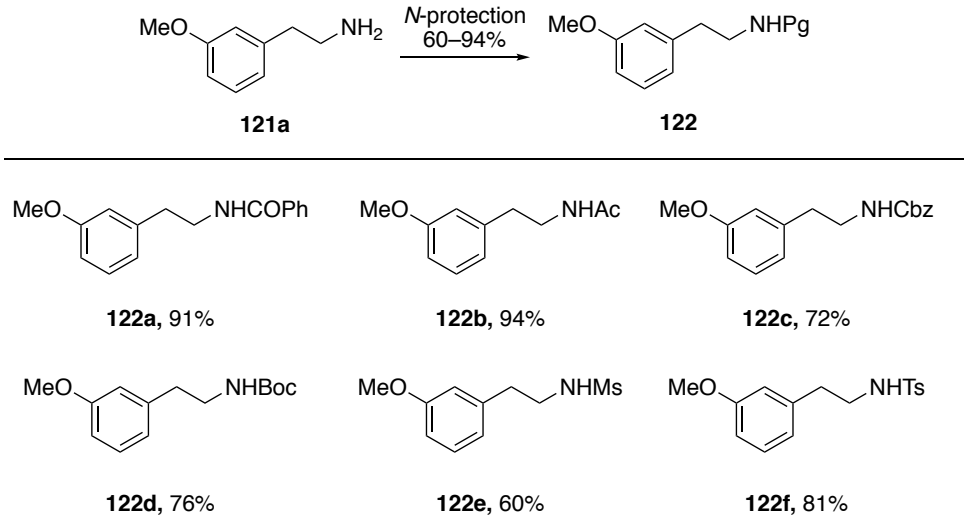
Scheme 88: Synthesis of nitrostyrenes using a nitroaldol reaction

Nitrostyrene **120a** was then submitted to hydrogenation in the presence of palladium on carbon, which was effective in reducing the olefin functionality, though was unsuccessful in reducing the resulting aliphatic nitro group to the primary amine. A new approach was therefore investigated, using the procedure of Varma and Kabalka, to reduce the vinyl nitro moiety in one-pot (Scheme 89).[286] This method involved the treatment of nitrostyrene compound **120a** with a combination of sodium borohydride and boron trifluoride diethyl etherate, generating borane-THF complex *in situ*. This resulted in the successful reduction of both the alkene and nitro group in a single step, giving 3-methoxyphenylethylamine **121a** in 92% yield.



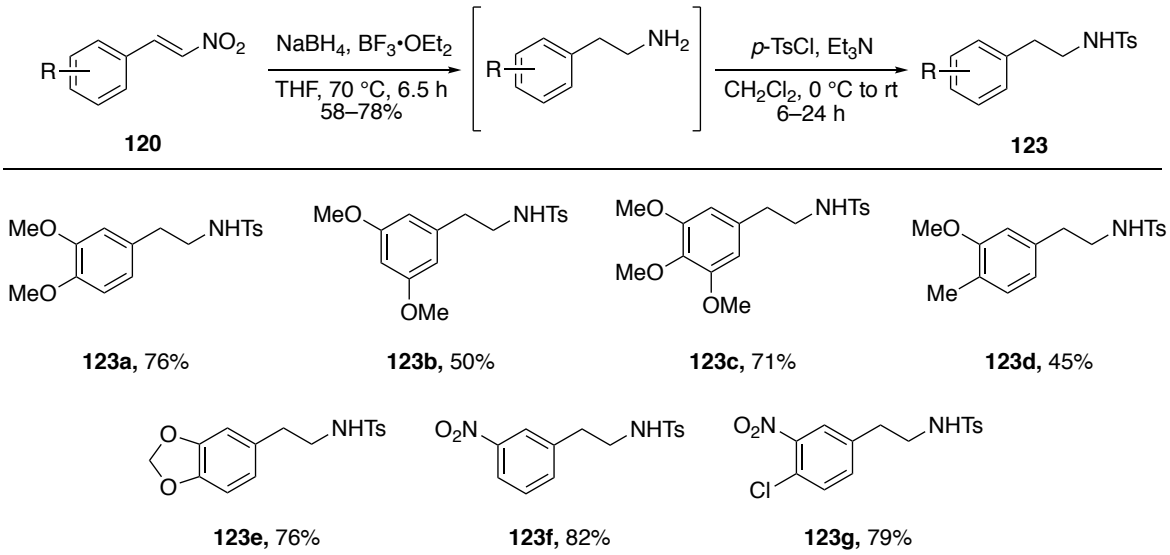
Scheme 89: Vinyl nitro reduction using the procedure of Varma and Kabalka

3-Methoxyphenylethylamine (**121a**) was then derivatised with a series of nitrogen protecting groups under standard conditions, to give a range of *N*-protected phenylethylamines **122a**–**122f** in up to 94% yield (Scheme 90).



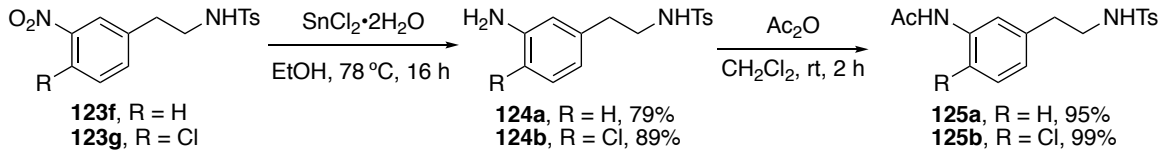
Scheme 90: *N*-Protection of 3-methoxyphenylethylamine (121a)

Having developed a strategy for reduction of the vinyl nitro group, the series of nitrostyrene compounds **120b**–**120g** were subjected to these conditions (Scheme 91). The crude phenylethylamines **121b**–**121h** were isolated by an acid-base extraction in 58–78% yield and used without purification in the next step. Interestingly, for compounds **120f** and **120g**, this method is selective for the reduction of the vinyl nitro functionality over the aromatic nitro group. Tosylation under standard conditions allowed access to a small library of *N*-tosyl protected phenylethylamine substrates **123a**–**123g** for the one-pot intramolecular C–N bond forming process.



Scheme 91: Synthesis of *N*-tosyl protected phenylethylamines 123a–123g

The aromatic nitro functionality in compounds **123f** and **123g** were reduced using tin dichloride dihydrate giving anilines **124a** and **124b** in good yields (Scheme 92). *N*-Protection of the anilines using acetic anhydride resulted in the formation of substrates **125a** and **125b** to be used in the one-pot process.



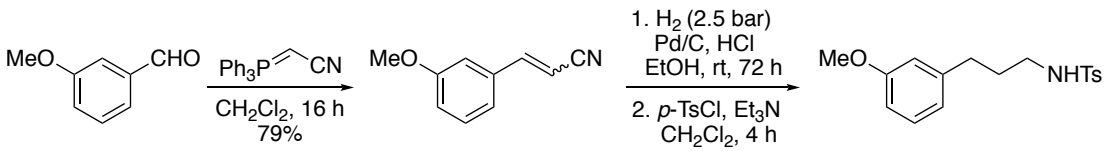
123f, R = H
123g, R = Cl

124a, R = H, 79%
124b, R = Cl, 89%

125a, R = H, 95%
125b, R = Cl, 99%

Scheme 92: Synthetic route towards *N*-tosyl protected phenylethylamines with aniline and acetamide directing groups

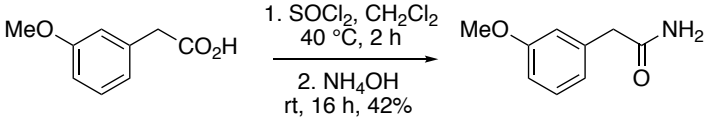
A two-carbon homologation was performed using a Wittig reaction with cyanomethylene triphenylphosphorane and *m*-anisaldehyde (**119a**) which gave vinyl nitrile compound **126** in a 79% yield as a 3:1 mixture of *E* and *Z* isomers (Scheme 93). Acrylonitrile **126** was hydrogenated at 2.5 bar of pressure, using a Parr apparatus, in the presence of palladium on charcoal and hydrochloric acid to give the aliphatic amine as a hydrochloride salt. Reaction of this ammonium salt with *p*-toluenesulfonyl chloride gave sulfonamide **127** in a 63% over the two-steps.



119a **126** **127**

Scheme 93: Synthesis of tosyl protected amine 127

Amide **129** was prepared by reaction of 3-methoxyphenylacetic acid (**128**) with thionyl chloride forming an acyl chloride intermediate *in situ* (Scheme 94). Subsequent treatment of this acid chloride with ammonium hydroxide solution resulted in the formation of 3-methoxyacetamide (**129**) in 42% yield.

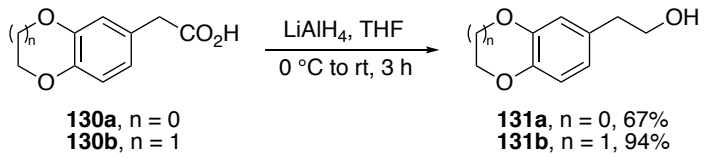


128 **129**

Scheme 94: Synthesis of amide 129

2.3.4 Synthesis of Phenylethylalcohol Substrates

A series of alcohol substrates for the one-pot procedure were either commercially available or synthesised in one step by reduction of the carboxylic acids **130a** and **130b** using lithium aluminium hydride giving alcohols **131a** and **131b** (Scheme 95).

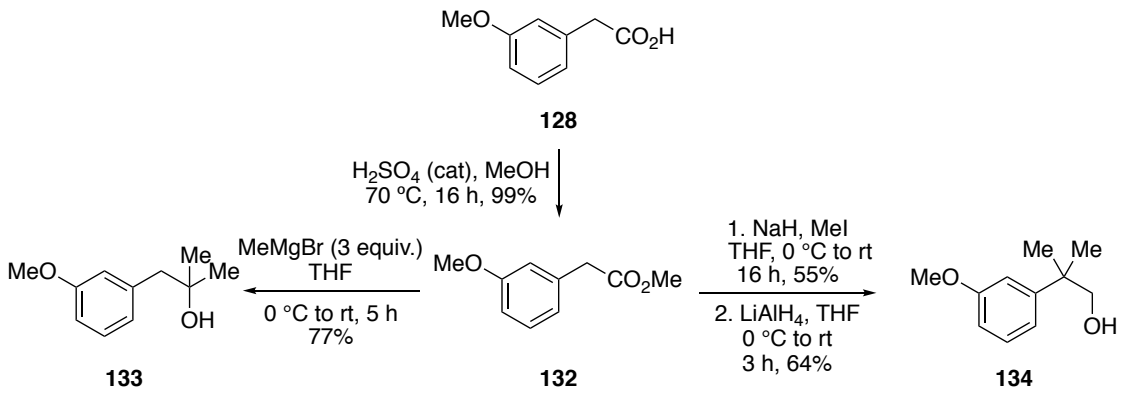


130a, n = 0
130b, n = 1

131a, n = 0, 67%
131b, n = 1, 94%

Scheme 95: Synthesis of phenylethylalcohol substrates 111a and 111b

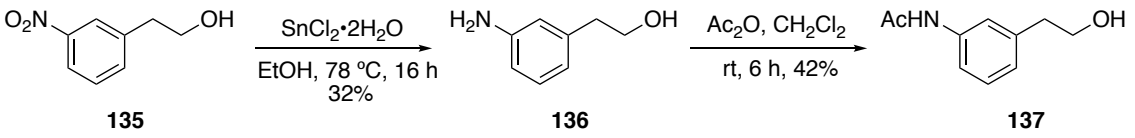
Additional substrates were prepared using 3-methoxyphenylacetic acid (**128**). This was converted to the corresponding methyl ester **132** using sulfuric acid and methanol in 99% yield (Scheme 96). This methyl ester was treated with three equivalents of methylmagnesium bromide and gave the tertiary alcohol **133** in 77% yield. Dimethylation of the α-position of methyl ester **132** using sodium hydride and methyl iodide followed by reduction gave neopentyl alcohol **134**.



133 **132** **134**

Scheme 96: Synthetic route towards tertiary alcohol 133 and neopentyl alcohol 134

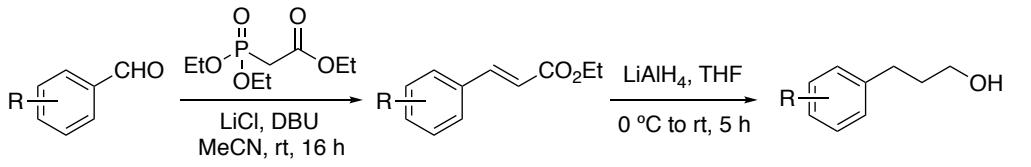
Reduction of the aromatic nitro group of phenylethylalcohol **135** using tin dichloride dihydrate gave aniline **136** in 32% yield (Scheme 97). This was then protected using acetic anhydride to give acetanilide **137** in 42% yield.



135 **136** **137**

Scheme 97: Synthesis of substituted acetanilide derivative 137

In addition to the range of phenylethylalcohols prepared, a series of longer chain alcohols were synthesised. To achieve this, a Horner-Wadsworth-Emmons reaction using Masamune-Roush conditions[287] was performed on *m*-anisaldehyde (**119a**) and 3,4,5-trimethoxybenzaldehyde (**119d**) to form the corresponding (*E*)-α,*β*-unsaturated ester **138a** and **138b**, respectively (Scheme 98). In this reaction, the mild Lewis acid, lithium chloride coordinates to the carbonyl oxygen of triethyl phosphonoacetate, increasing the acidity of the methylene hydrogens which allows the use of a relatively weak base such as DBU. This process resulted in the formation of exclusively *E*-isomers based on the large 15.9 Hz *trans* coupling constants observed in the ^{1}H NMR spectra of both compounds. Subsequent reduction of both the olefin and ester functional groups using lithium aluminium hydride gave alcohols **139a** and **139b**. The electron-rich trimethoxy-substituted aryl ring is in conjugation with the α,*β*-unsaturated ester functionality and hence, the electron density at the *β*-position is increased as a consequence. This hinders the conjugate addition of the hydride species which is reflected by the modest yield of alcohol **139b**.



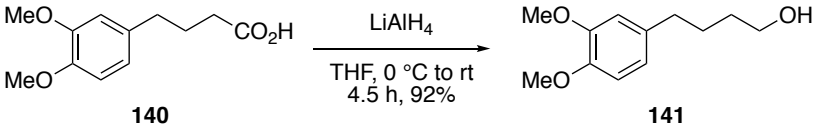
119a, 119d

138a, R = 3-OMe, 91%
138b, R = 3,4,5-OMe, 53%

139a, R = 3-OMe, 69%
139b, R = 3,4,5-OMe, 45%

Scheme 98: Synthesis of propyl alcohol derivatives 139a and 139b *via* an HWE reaction

The synthesis of a longer chain, phenylbutylalcohol **141** was synthesised in one-step by the reduction of carboxylic acid **140** using lithium aluminium hydride in 92% yield (Scheme 99).



140 **141**

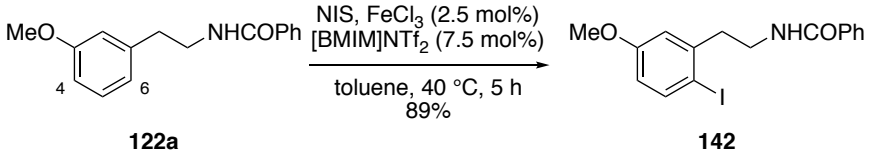
Scheme 99: Synthesis of (3,4-dimethoxyphenyl)butanol (141)

2.3.5 One-Pot Intramolecular Amination of C–H Bonds

With a library of *N*-protected phenylethylamines in hand, their application in a one-pot iodination/intramolecular amination was investigated. The initial aim was to evaluate *N*-benzoyl protected 3-methoxyphenylethylamine **122a** as a substrate for selective *para*-iodination and then investigate the potential of the resulting activated aryl intermediate to undergo an intramolecular, copper(I)-catalysed *N*-arylation. It was proposed that the *para*-directing nature of the 3-methoxy substituent would lead iodination at the C-6 position and formation of exclusively the *para*-regioisomer. However, it was also considered that iodination could occur at the C-4 position due to steric hindrance caused by the *N*-benzoyl ethylamine side chain. Therefore, it was necessary to isolate the iodinated compound and determine which regioisomer had formed.

The iodination of benzoyl protected phenylethylamine **122a** was performed using standard conditions for halogenation with *N*-iodosuccinimide, iron(III) chloride (2.5 mol%) and [BMIM]NTf_2 (7.5 mol%) (Scheme 100). After 5 hours at 40 °C, it was clear from analysis of the crude reaction mixture by ^{1}H NMR spectroscopy that there was full conversion to exclusively one regioisomer and **142** was isolated in 89% yield. Analysis of the ^{1}H NMR spectra of **142** clearly showed three resonances in the aromatic region with *ortho*- and *meta*-coupling constants, indicative of a 1,3,4-trisubstituted aromatic system. Two of these resonances were below 7 ppm, typical of aromatic hydrogen atoms that have been significantly shielded due to their proximity to the electron-rich methoxy group, entirely consistent with **142**. In addition, 2D NMR experiments were carried out, mainly heteronuclear multiple-bond correlation (HMBC) spectroscopy, to ascertain the position of the iodine atom. There was an HMBC signal between the CH_2 of the alkyl chain and the characteristically up-field shifted aromatic carbon bonded to the iodine atom. Also, there were two HMBC signals correlating with the quaternary carbon bearing the methoxy group

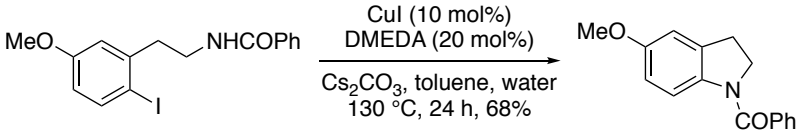
which would not be the case with C-4 *ortho*-iodination. With this evidence, it was clear that exclusively the *para*-iodinated product **142** had formed.



122a **142**

Scheme 100: Regioselective iodination of benzoyl protected phenylethylamine 122a

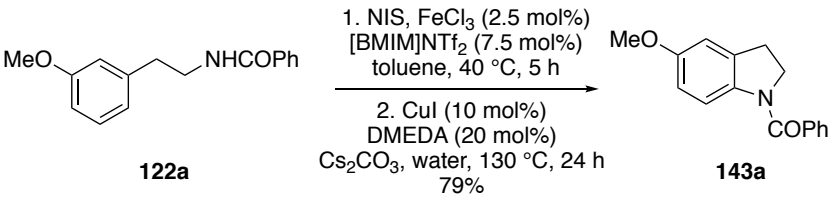
The iodinated compound **142** was subjected to the ligand assisted, copper(I)-catalysed cyclisation using copper(I) iodide (10 mol%), DMEDA (20 mol%) and cesium carbonate which resulted in the formation of indoline **143a** in 68% yield (Scheme 101).



142 **143a**

Scheme 101: Cu(I)-catalysed cyclisation of aryl iodide 142

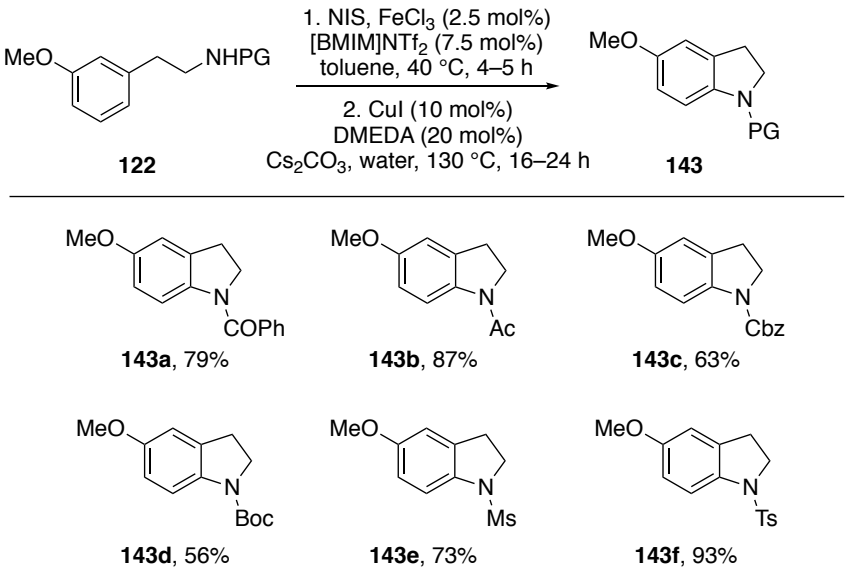
Having investigated the feasibility of the iron(III) triflimide-catalysed iodination and copper(I)-catalysed *N*-arylation as single steps, these were next combined in a one-pot procedure (Scheme 102). The regioselective iodination was followed by the intramolecular C–N bond formation to give indoline **143a** in 79% yield. It is worth noting that performing each step separately, resulted in the formation of indoline **143a** in a significantly lower overall yield (59%) than for the one-pot process. The negation of the need to purify and handle the iodinated intermediate is partly responsible for the greater yield for the one-pot process.



122a **143a**

Scheme 102: Synthesis of benzoyl protected indoline 143a in a one-pot procedure

A range of nitrogen protecting groups were examined to evaluate the most efficient nucleophile for the intramolecular Cu(I)-catalysed *N*-arylation (Scheme 103). Firstly, acetyl protected phenylethylamine **122b** was an excellent substrate for the one-pot process and gave indoline **143b** in 87% yield. A 5:1 mixture of rotamers were observed in the ^{1}H and ^{13}C NMR spectra of indoline **143b** due to restricted rotation of the amide C–N bond. Next, both *N*-Cbz and *N*-Boc carbamate nucleophiles were utilised in the one-pot procedure giving the corresponding indolines **143c** and **143d** in 63% and 56% yield, respectively. The appearance of rotamers was also observed for these two compounds however, these were resolved when the ^{1}H and ^{13}C NMR spectra were recorded at 100 °C in DMSO-d_6. The use of *N*-sulfonamide nucleophiles in the one-pot process resulted in very efficient formation of indolines **143e** and **143f** in excellent yields. In particular, the best result was obtained for the iodination and cyclisation of *N*-tosyl phenylethylamine **122f** resulting in the preparation of indoline **143f** in 93% yield.

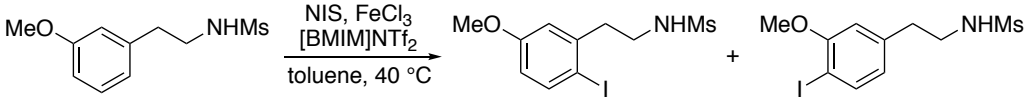


Scheme 103: One-pot iodination/cyclisation of *N*-protected 3-methoxyphenylethylamines 122a–122f

To gain some understanding of the role of catalysts and reagents in this process, some control reactions were performed with **122e**. Using $FeCl_3$ (2.5 mol%) and [BMIM]NTf_2 (7.5 mol%), generating $Fe(NTf_2)_3$ *in situ*, led to full conversion to a single regioisomer **144** in 4 h (Table 7, entry 1). It was shown that the aryl ring of *N*-mesyl protected phenylethylamine **122e** could undergo electrophilic aromatic iodination using NIS, with only [BMIM]NTf_2 as a catalyst (entry 2). This reaction was slower

overall (7 h) and resulted in a 10:1 mixture of *para*- and *ortho*-regiosisomers (**144**:**145**). Moreover, performing the aryl iodination without the use of the iron(III)-triflimide catalyst resulted in full conversion after 22 h and again gave a 10:1 mixture *of* **144**:**145** (entry 3). Thus, for rapid and highly regioselective iodination, iron(III) triflimide is required.

Table 7: Effect of iron and [BMIM]NTf_2 in the electrophilic aromatic iodination of 122e



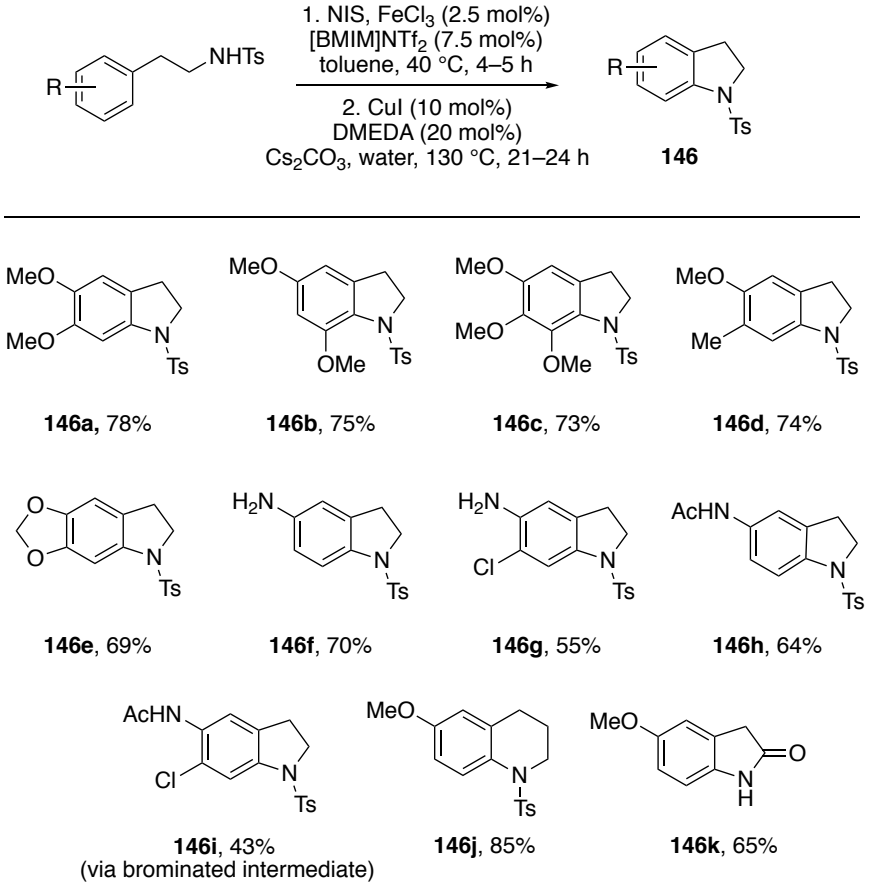
122e **144** **145**

Entry	$FeCl_3$ (mol%)	[BMIM]NTf_2 (mol%)	Time (h)	Ratio (**144**: **145**)[a]
1	2.5	7.5	4	**144** only
2	n/a	7.5	7	10:1
3	n/a	n/a	22	10:1

[a]Determined using ^{1}H NMR spectroscopy

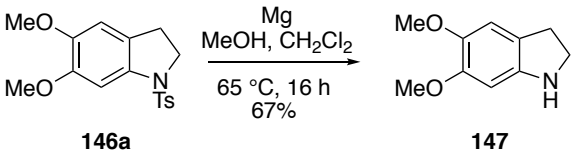
Having identified tosyl protected nitrogen as the most suitable nucleophile and developed the optimised conditions, the scope of the one-pot iodination and cyclisation process was next explored (Scheme 104). Using a range of electron-rich *N*-tosyl phenylethylamines **123a**–**123e** with strong alkoxy directing groups in the one-pot process, gave the corresponding indolines **146a**–**146e** as single regioisomers, in 69–93% yield. Next, aniline derivatives **124a** and **124b** were used in the one-pot process and gave indolines **146f** and **146h** in 70% and 55% yield, respectively. Acetanilide derivative **125a** was also a good substrate for the activation/cyclisation process and gave indoline **146h** in 64% yield. *N*-Tosyl protected phenylethylamine **125b** containing *N*-acetyl and chlorine substituents failed to undergo iodination, even at 70 °C, with only starting material being recovered. Using *N*-bromosuccinimide, full conversion to the brominated intermediate was observed at 40 °C. Completion of this one-pot process then gave indoline **146i** in 43% yield. This one-pot process was also successfully used for the synthesis of other benzannulated heterocycles. For instance, iron(III)-catalysed iodination and copper(I)-catalysed cyclisation of anisole derivative with an *N*-tosylpropylamine side chain **127** gave the 6-membered tetrahydroquinoline **146j** in

85% yield while primary amide, 3-methoxyphenylacetamide (**129**), gave oxindole **146k** in 65% yield.



Scheme 104: One-pot, two-step synthesis of *N*-heterocycles

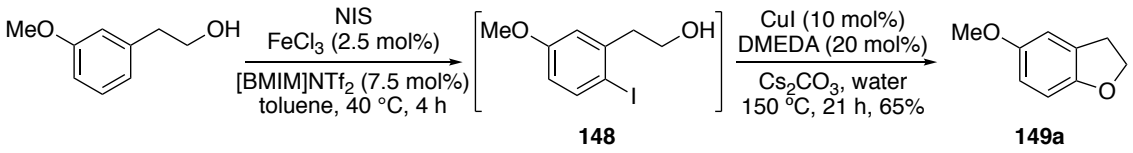
For these indolines to find use as valuable synthetic intermediates towards natural products or pharmaceutically relevant compounds, the tosyl protecting group required removal to allow further functionalisation of the nitrogen atom. This was achieved by treating the *N*-tosyl indoline **146a** with magnesium turnings resulting in the removal of the tosyl group, giving indoline **147** in 67% yield (Scheme 105).



Scheme 105: Removal of *N*-tosyl protecting group of indoline 146a

2.3.6 One-Pot Intramolecular Etherification of C–H Bonds

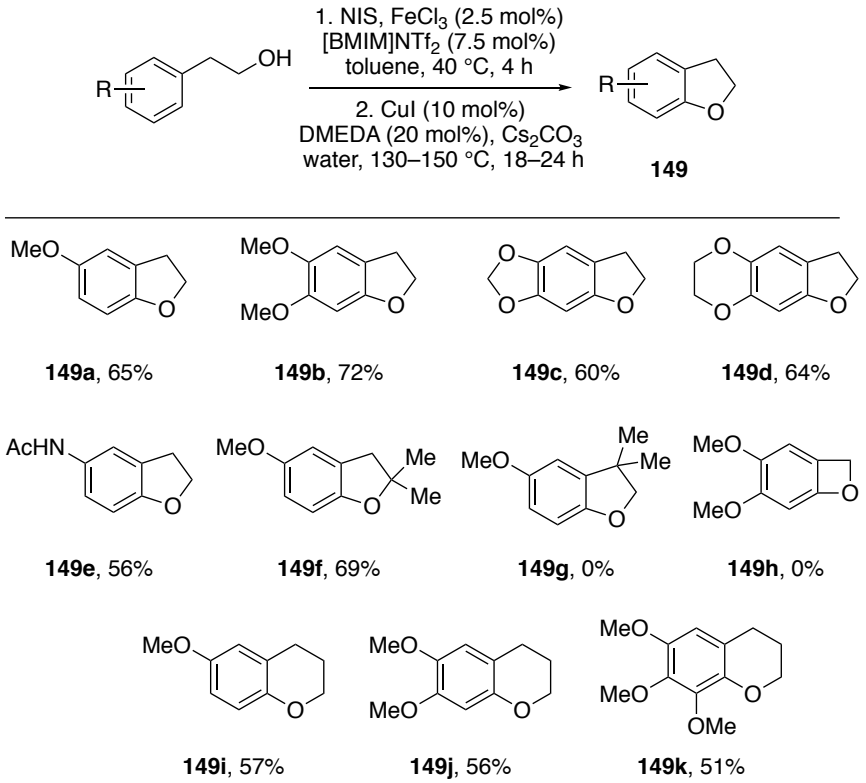
Following the successful application of the one-pot iron(III)-catalysed iodination and copper(I)-catalysed heterocyclisation for the synthesis of *N*-heterocycles, it was proposed that this process could be applied to a series of alcohol substrates for the synthesis of *O*-heterocycles. The transformation of 3-methoxyphenylethan-2′-ol to 2,3-dihydro-5-methoxybenzofuran (**149a**) was investigated using the previously developed conditions (Scheme 106). The standard conditions for iodination were used, leading to full conversion to **148** after 4 h at 40 °C. Investigation of the ^{1}H NMR spectra of the crude reaction mixture confirmed that iodination had proceeded exclusively at the position *para* to the methoxy directing group. In the second step, a slightly higher temperature (150 °C) was necessary to allow conversion to the cyclised product **149a** which was then isolated in 65% yield. This requirement for harsher conditions may be due to the fact that aliphatic alcohols are less nucleophilic than the analogous *N*-tosyl substrates.



Scheme 106: One-pot iodination/cyclisation of 3-methoxyphenylethan-2′-ol

Using these conditions, the scope of this one-pot intramolecular C–O bond forming process was next explored for the synthesis of a small library of *O*-heterocycles (Scheme 107). A range of substrates with activated aryl rings and primary and tertiary alcohol nucleophiles were successfully utilised in the process, giving 2,3-dihydrobenzofurans **149a**–**149f** in up to 72% yield. Interestingly, tertiary alcohol **133** gave the corresponding dihydrobenzofuran in 69% yield while the neopentyl alcohol **134** resulted in no cyclisation. In this case, full conversion to the iodinated intermediate was observed however the steric hindrance caused by disubstitution in the benzylic position may have prevented oxidative addition of the Cu(I)-species. This method did not allow the synthesis of highly strained 4-membered oxetane heterocycle **149h** with no conversion from the iodinated intermediate observed. Application of (3-methoxyphenyl)-propan-3′-ol to the iron(III)/copper(I)-catalysed one-pot procedure gave dihydrobenzopyran **149i** in 57% yield. Using similar propyl alcohols gave similar results and benzopyrans **149j** and **149k** were isolated in 56%

and 51% yield, respectively. The lower yields observed for the benzopyran formation was a result of a competing copper(I)-catalysed dehalogenation reaction pathway during this more difficult cyclisation.

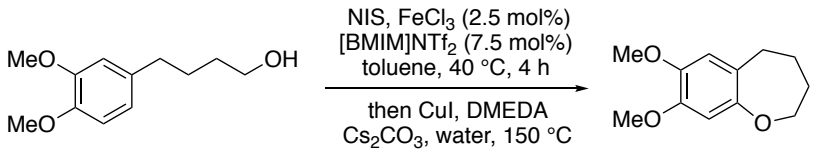


Scheme 107: One-pot, two-step synthesis of *O*-heterocycles

As this methodology was successfully applied to the synthesis of 5- and 6-membered benzofused heterocycles, it was postulated that 7-membered benzoxepine analogues could be prepared in a similar manner. Under standard conditions, (3,4-dimethoxyphenyl)butan-4′-ol (**141**) underwent regioselective iodination in 4 h at 40 °C. However, performing the second step using CuI (10 mol%) and DMEDA (20 mol%) resulted in the isolation of cyclised product **150** in only 11% yield, owing to poor conversion from the iodinated intermediate (Table 8, entry 1). A longer reaction time (48 h) resulted in the isolation of benzoxepine **150** in 19% yield (entry 2). Using *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine as a ligand and a longer reaction time (72 h) resulted in formation of trace amounts of **150** with mostly copper-catalysed de-halogenation observed (entry 3). 8-Hydroxyquinoline has been successfully employed previously as a ligand for a copper-catalysed cyclisation for 7-membered ring formation.[288] For this reason, it was used in the attempted one-pot synthesis of compound **150** (entry 4). Under these conditions, the result was full

conversion from the iodinated intermediate back to the alcohol starting material as a result of de-halogenation. As this is a difficult cyclisation process, the catalytic loadings of copper iodide and DMEDA were increased to 20 mol% and 40 mol% respectively (entry 5). After 72 h at 150 °C, from ^{1}H NMR spectroscopic analysis of the crude reaction mixture, there was a 1:1 mixture of the de-halogenated starting material **141** and the cyclised product **150** ultimately leading to the isolation of **150** in only an 8% yield. Despite the attempts, the challenging synthesis of this 7-membered ring system could not be improved beyond 19% yield.

Table 8: One-pot synthesis of 7-membered *O*-heterocycle 150



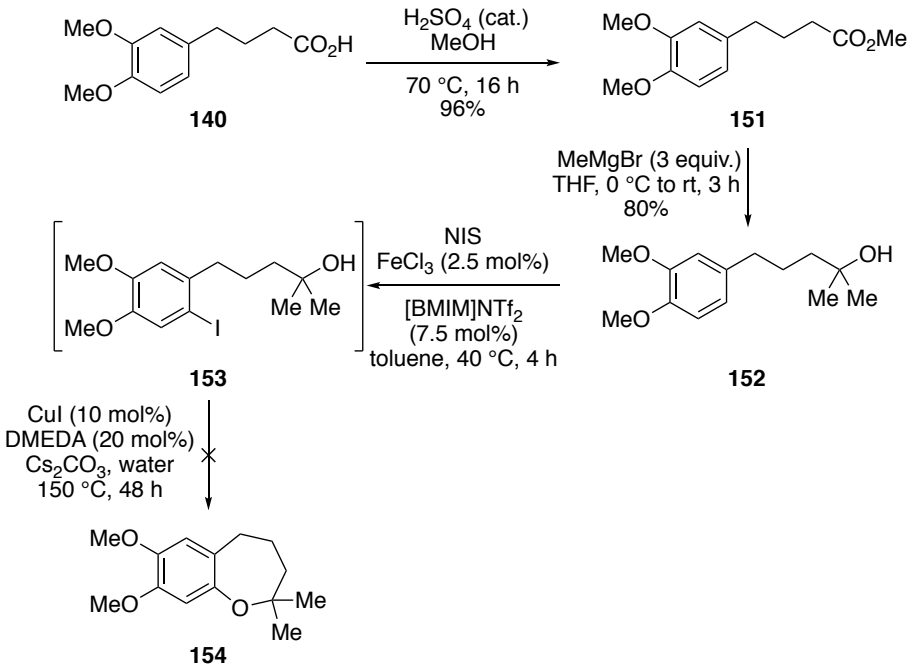
141 **150**

Entry	CuI (mol%)	Ligand	Time (h)	Yield (%)
1	10	DMEDA (20 mol%)	20	11
2	10	DMEDA (20 mol%)	48	19
3	10	*trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (20 mol%)	72	n/a
4	10	8-hydroxyquinoline (20 mol%)	72	n/a
5	20	DMEDA (40 mol%)	72	8

It is worth noting that the only previously reported synthesis of **150** was the oxidative cyclisation of (3,4-dimethoxyphenyl)butan-4′-ol (**141**) catalysed by thallium(III) trifluoroacetate, mediated by boron trifluoride.[289] This resulted in the formation of aromatic radical cations followed by intramolecular cyclisation with the internal oxygen nucleophile, giving benzoxepine **150** in a low 13.5% yield.

In an attempt to improve the efficiency of this 7-membered ring formation, the tertiary alcohol **152** was synthesised (Scheme 108). This was achieved in 77% yield over two steps from carboxylic acid **140** by first converting to methyl ester **151** then adding three equivalents of methylmagnesium bromide. The aim of using this tertiary alcohol **152** in the one-pot process was to exploit the Thorpe-Ingold effect to increase the rate of cyclisation, leading to an overall more efficient approach.

Instead, there was no conversion to benzoxepine heterocycle **154**, with only iodinated intermediate **153** being returned.



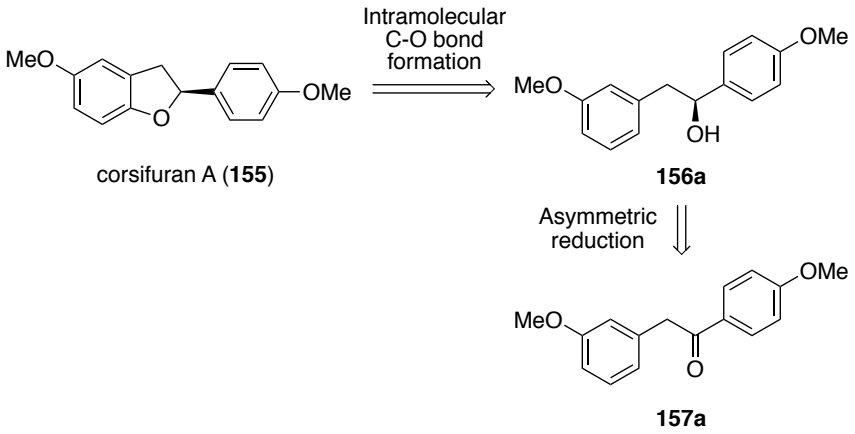
Scheme 108: Attempted synthesis of benzoxepine derivative 154

2.3.7 Synthesis of Corsifuran A

Corsifuran A (**155**), a metabolite from the Mediterranean liverwort *Corsinia coriandrina*, is an example of a natural product featuring a 2-aryl substituted 2,3-dihydrobenzofuran scaffold.[290] Jones and co-workers reported the first asymmetric synthesis of corsifuran A in 2008.[291] Their method involved a oxazaborolidine-catalysed asymmetric reduction and then subsequent Buchwald-Hartwig-type, palladium-catalysed intramolecular cross-coupling. Further to this, the Glorius group reported the synthesis of corsifuran A *via* the reduction of the unsaturated benzo[*b*]furan precursor using a ruthenium-catalysed, high-pressure (60 bar) hydrogenation mediated with *N*-heterocyclic carbene ligands.[292] Using this methodology, they were able to synthesise corsifuran A in 80% yield and 99:1 enantiomeric ratio (er).

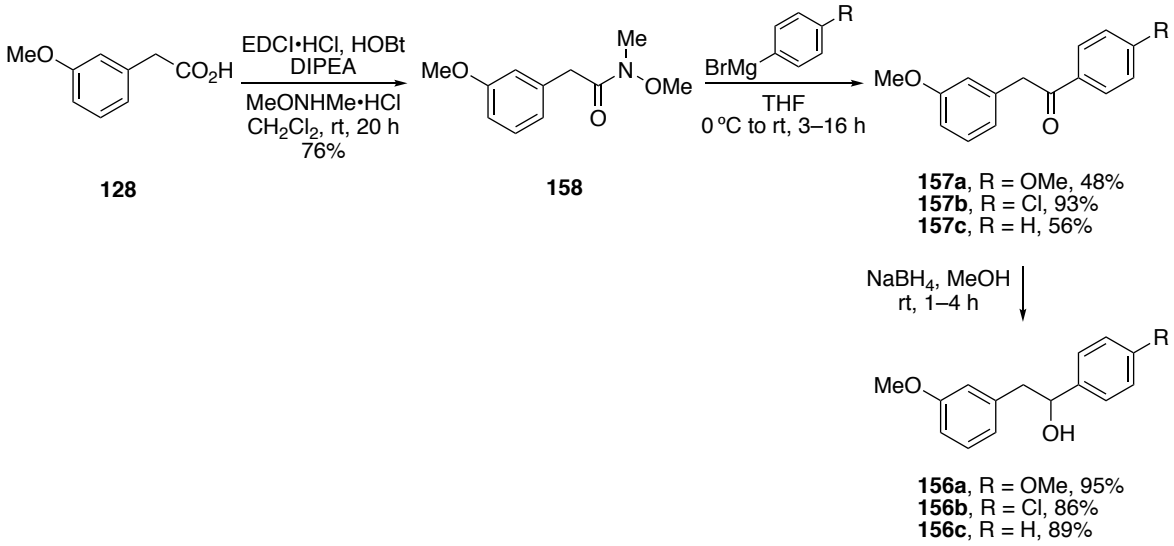
It was proposed that the iron(III)-catalysed activation and copper(I)-catalysed cyclisation would find utility in the synthesis of the dihydrobenzofuran ring system of corisfuran A in a one-pot procedure. The proposed retrosynthetic analysis is shown

in scheme 109. Synthesis of the 2-aryl 2,3-dihydrobenzofuran ring of corsifuran A could be achieved in one-pot using the iron(III)-catalysed iodination followed by copper(I)-catalysed etherification process from chiral alcohol **156a**. Alcohol **156a** could be synthesised by employing aspects of the work by Jones and co-workers to achieve the asymmetric reduction of ketone **157a** using a Corey-Bakshi-Shibata (CBS) or other oxazaborolidine catalyst.



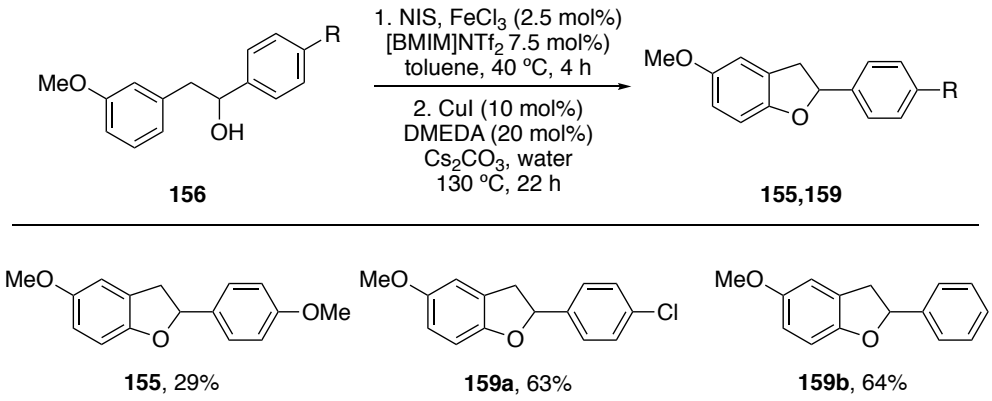
Scheme 109: Proposed retrosynthesis of (+)-corsifuran A (155)

The synthesis of racemic corsifuran A began with the preparation of Weinreb amide **158** from 3-methoxyphenylacetic acid (**128**) and *N*,*O*-dimethylhydroxylamine using EDCI and HOBt as coupling agents (Scheme 110). A Grignard addition was performed using 4-methoxyphenylmagnesium bromide, generated *in situ*, and Weinreb amide **158**, which gave the aryl ketone **157a** in 48% yield. In addition, aryl ketones **157b** and **157c** were synthesised *via* Grignard addition with the Weinreb amide **158**. Reduction of the ketone functionality with sodium borohydride gave racemic benzyl alcohols **156a**–**156c** in excellent yields.



Scheme 110: Synthesis of racemic benzylic alcohols 156a–156c

Benzylic alcohol **156a** was treated with *N*-iodosuccinimide under standard iron(III)-catalysed conditions (Scheme 111). The presence of two activated aryl rings in **156a** led to a complex mixture of products during the iodination step. The mixture was subjected to the copper(I)-catalysed C–O cross-coupling which resulted in the formation of racemic corsifuran A (**155**) in only 29% yield. It was thought that, as well as aryl iodination *para* to the methoxy group, iodination of the next most activated *ortho*-position as well as poly-iodination was resulting in a complex mixture of products. The regioselectivity was not improved by using *N*-bromosuccinimide for the activation step and again, a complex mixture of multiple compounds was obtained. Using secondary benzylic alcohols **156b** and **156c**, bearing less electron rich aromatic rings allowed for exclusive iodination *para* to the 3-methoxy group and the synthesis of 2-aryl 2,3-dihydrobenzofurans **159a** and **159b** in 64% and 63% yield, respectively.



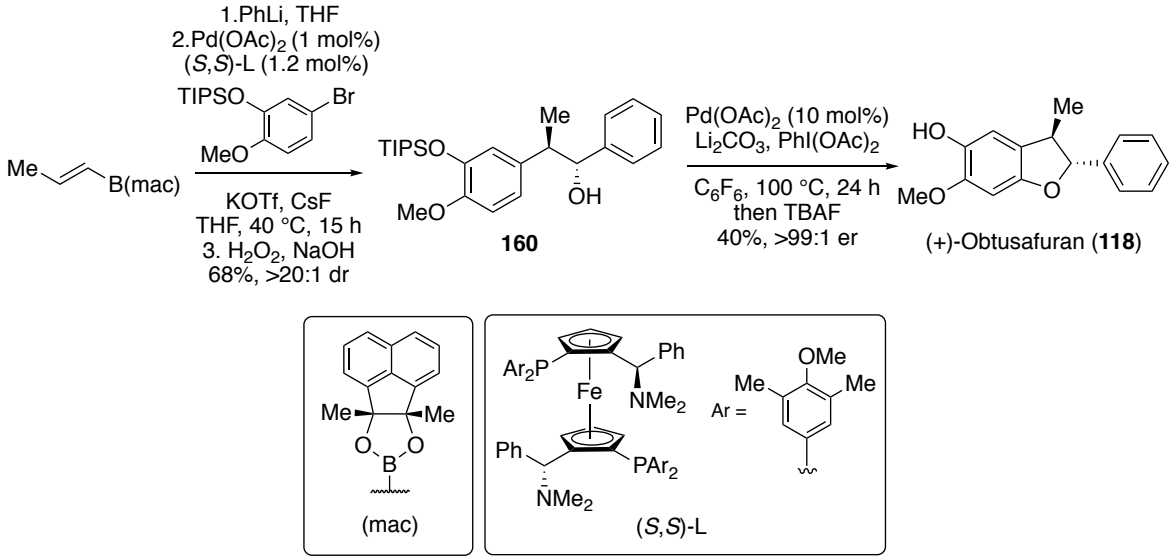
Scheme 111: One-pot synthesis of 2-aryl substituted 2,3-dihydrobenzofurans 155,159

2.3.8 Synthesis of (+)-Obtusafuran

To demonstrate the versatility and functional group tolerance of the one-pot process and further explore its application in natural product synthesis, this method was applied to the synthesis of (+)-obtusafuran (**118**), a neolignan first isolated from the heartwood of *Dalbergia retusa*[293] and more recently other *Dalbergia* species.[294–296] In a study by Frappier and co-workers, (+)-obtusafuran was able to inhibit *in vitro* growth of chloroquine-resistant strain FcB1 of *P.falciparum* with an IC_{50} value of 8.7 μM.[294] In addition to its reported antiplasmodial properties, it has been demonstrated that (+)-obtusafuran possesses potent anti-carcinogenic activity through its induction of quinone reductase, a carcinogen detoxifying enzyme.[297]

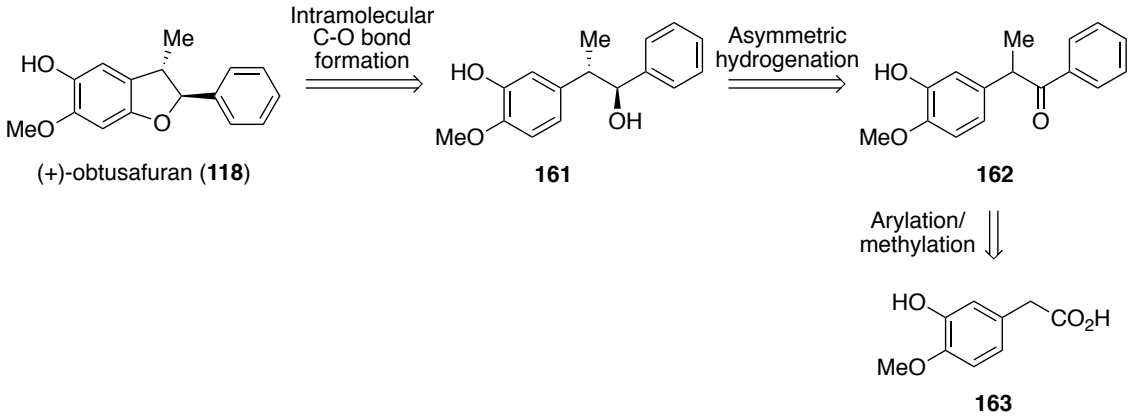
Racemic obtusafuran had previously been prepared by an acid-catalysed, thermal rearrangement of neoflavanoid obtusaquinol as reported by Manners in 1973.[298] It wasn't until 2013 that Chen and Weisel at Merck reported the first asymmetric synthesis of (+)-obtusafuran.[299] This involved the use of an enantioselective hydrogenation to produce a chiral alcohol in a dynamic kinetic resolution process. This alcohol was then subjected to a copper(I)-catalysed cross-coupling reaction to synthesise the *trans*-substituted dihydrobenzofuran core. More recently, work by Morken and co-workers demonstrated a total synthesis of (+)-obtusafuran in 27% overall yield (Scheme 112).[300] Their methodology involves a enantio- and diastereoselective conjunctive cross-coupling of β-alkenylboranate complexes with phenyl lithium and aryl bromides in the presence of methylated acenaphthoquinone (mac) ligands. This allowed for the preparation of chiral benzylic alcohol **160** in 68% yield and 20:1 dr. A palladium-catalysed oxidative cyclisation of **160** followed by

removal of the silicon protecting group afforded (+)-obtusafuran (**118**) in 40% yield and greater than 99:1 er.



Scheme 112: Morken's synthesis of (+)-obtusafuran (118)

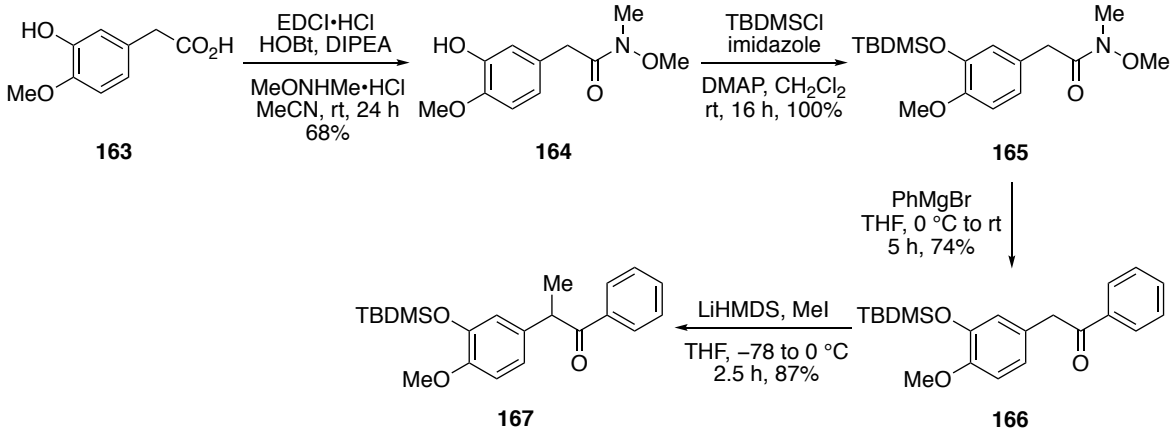
Our strategy involved using the one-pot iron(III)-catalysed iodination/copper(I)-catalysed intramolecular C–O bond formation to construct the *trans*-disubstituted furan core (Scheme 113). This required the synthesis of chiral benzylic alcohol **161** by applying a Merck-type enantioselective hydrogenation, involving a base-mediated dynamic kinetic resolution, to α-methyl phenyl ketone **162**.[301–303]



Scheme 113: Retrosyntheic analysis of (+)-obtusafuran (118)

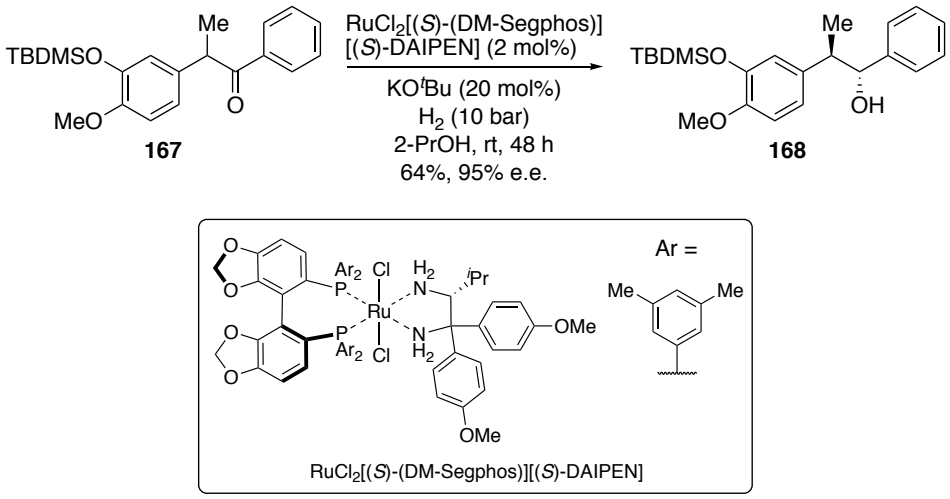
The synthesis of (+)-obtusafuran began with an amide coupling of 3-hydroxy-4-methoxyphenylacetic acid (**163**) and *N*,*O*-dimethylhydroxylamine using EDCI and HOBt which gave Weinreb amide **164** in 68% yield (Scheme 114). This was followed

by protection of the phenol as a TBDMS ether under standard conditions, giving compound **165**, in quantitative yield. Addition of phenylmagnesium bromide to Weinreb amide **165** at 0 °C gave phenyl ketone **166** in 74% yield. This was followed by α-methylation of ketone **166**, using LiHMDS and methyl iodide, which gave prochiral ketone **167** in good overall yield.



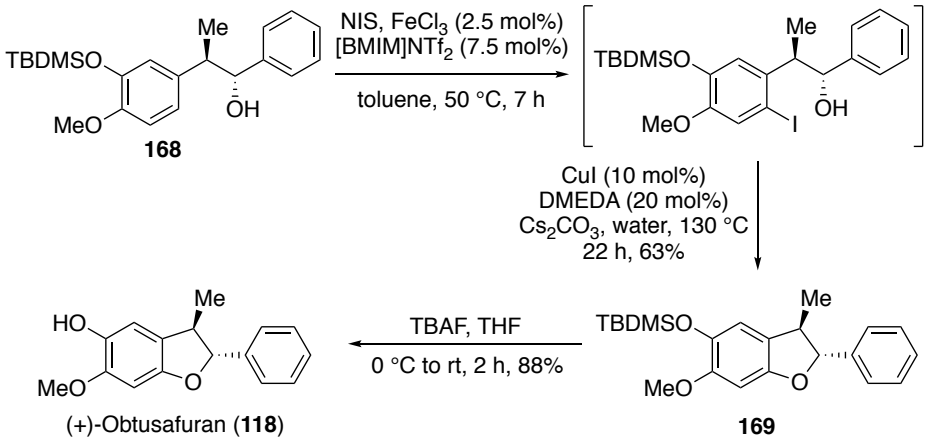
Scheme 114: Synthesis of α-methylketone 167

This key intermediate **167** was then subjected to the enantioselective hydrogenation using the commercially available Noyori-type chiral catalyst, $RuCl_2$[(*S*)-DM-Segphos][(*S*)-DAIPEN] (Scheme 115).[302–304] Potassium *tert*-butoxide is used for epimerisation of the α-position of **167**, allowing for the interconversion of enantiomers through their common enol intermediate. Initially, the hydrogenation was performed at 2.5 bar of pressure using 0.15 mol% of the Ru(II)-catalyst, however, this resulted in no conversion to chiral benzylic alcohol **168** after 48 h. Increasing the pressure to 10 bar resulted in 60% conversion to alcohol product **168** after 48 h. Finally, using 10 bar of pressure and increasing the loading of the Ru(II)-catalyst to 2 mol% gave secondary alcohol **168** as a single diastereomer, in 95% enantiomeric excess and 64% yield. The enantiomeric excess was determined using chiral HPLC, calibrated with the corresponding racemic mixture.



Scheme 115: Asymmetric hydrogenation of 167 *via* dynamic kinetic resolution

Chiral benzylic alcohol **168** was then applied in the one-pot process (Scheme 116). The iron(III)-catalysed iodination required a slightly higher temperature (50 °C) and a slightly longer reaction time (7 h) than less functionalised substrates. Again, only the *para*-regioisomer formed and no oxidation of the susceptible benzylic position was observed. Following the iodination step, standard copper(I)-catalysed conditions were used to form *trans*-disubstituted benzofuran **169** in 63% yield, in one-pot. TBAF was then used for the deprotection of the silyl ether which completed the total synthesis of (+)-obtusafuran in 16% yield over 8-steps. The spectroscopic data and optical rotation of (+)-obtusafuran (**118**) were wholly consistent with literature values, indicating no epimerisation of either stereocentre.

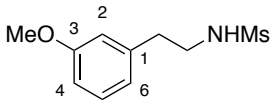


Scheme 116: Final steps of the total synthesis of (+)-obtusafuran (118)

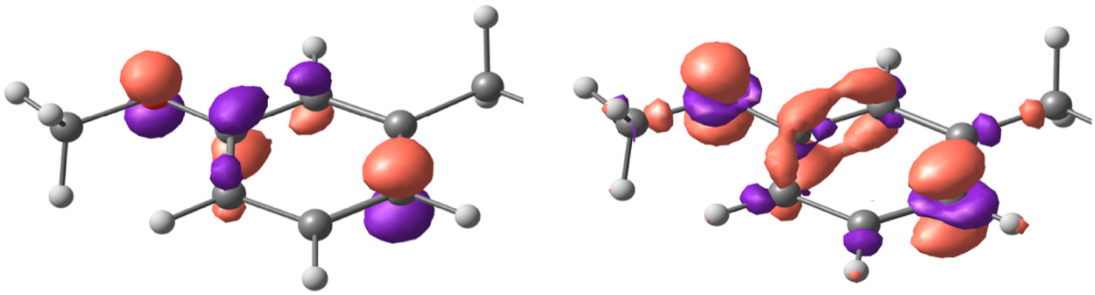
2.3.9 DFT Calculations

Iron(III)-catalysed activation of the *N*-protected phenylethylamines and phenyethylalcohols gave exclusively the *para*-iodinated regioisomers and no iodination was observed at the most sterically accessible *ortho*-position or any other activated position of the aromatic ring. To rationalise this experimental observation, DFT calculations were performed by Hans Martin Senn at the University of Glasgow. This study used the Hirshfeld partitioning scheme and electrophilic Fukui functions to assess the reactivity of different sites of *N*-mesyl protected phenylethylamine **122e** towards electrophilic attack (Table 9). The Hirshfeld charges, the difference between charge density of a free atom and the atom in a molecule, calculated for the unsubstituted aromatic carbons of **122e** showed that C-5 was the least favourable site for attack by an electrophile (entry 1). However, this method was not able differentiate between C-2, C-4 or C-6 as the most nucleophilic site. To distinguish these positions, the electrophilic Fukui functions were calculated. These functions describe the electron density distribution in a frontier molecular orbital and hence allow the prediction of the most electrophilic and nucleophilic sites of a molecule. If it is assumed that the reactivity of **122e** towards electrophilic aromatic substitution is wholly controlled by frontier molecular orbitals, then the Fukui function can be approximated by the density of the HOMO. More specifically, the condensed Fukui function contracts the Fukui functions to distinct positions (atoms) offering an estimation of the orbital coefficients on each aromatic carbon atom, using both Mulliken and Hirshfield population analysis. Using this method, the largest contribution to the HOMO was found to reside on C-6 and hence this is the most nucleophilic site (entries 2 and 3). Further analysis was performed using a “dual descriptor” Δf, which combines the separate electrophilic and nucleophilic Fukui functions into one descriptor. More positive values of Δf indicate sites for nucleophilic attack whereas more negative values show the most likely site for electrophilic attack. The Δf values calculated for phenylethylamine **122e** fully confirm the observed regioselectivity of this electrophilic aromatic iodination undertaken in this project (entry 4).

Table 9: Reactivity descriptors calculated for the aromatic carbons of methoxyphenylethylamine 122e



122e



Entry	Reactivity descriptors[a]	C-2	C-4	C-5	C-6
1	q_H/e	−0.065	−0.071	−0.042	−0.065
2	$f^-(q_H)$	0.082	0.078	0.065	0.140
3	f^-(HOMO)	13	11	6	27
4	Δf^-(HOMO)	7	4	12	−15

[a]DFT Calculations were performed using Gaussian 09 with the M06-2X exchange-correlation functional, def2-TZVP basis set and PCM solvent model for toluene

Using these computational methods, it was shown that the most nucleophilic site of the aromatic ring of **122e** is centred around C-6 as the p_z atomic orbital of this atom makes the largest contribution to the HOMO (Figure 6).

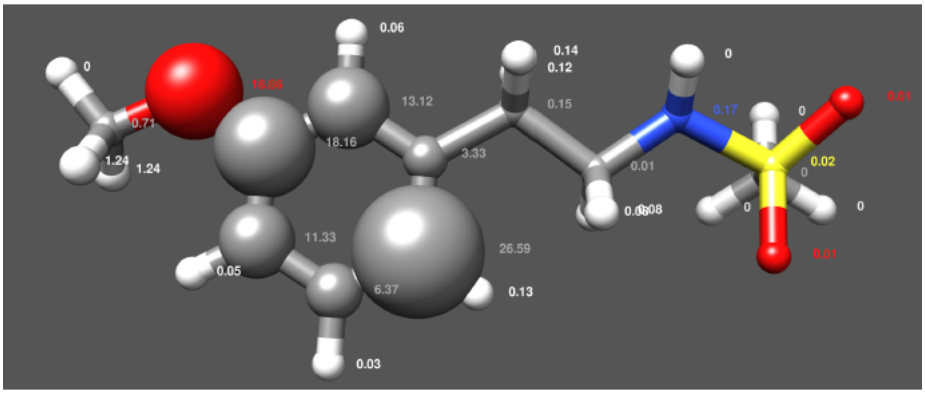
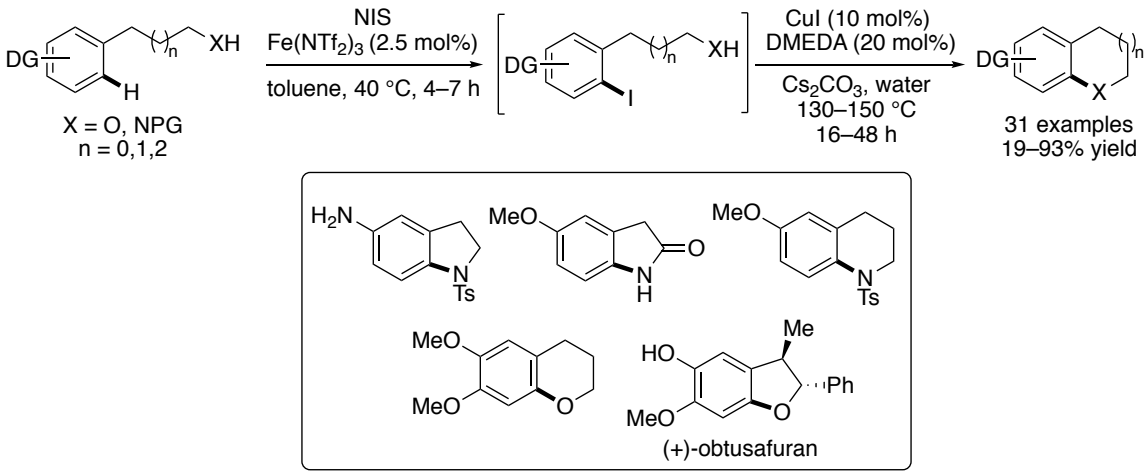


Figure 6: Fukui indices (contribution to the HOMO in %) from Mulliken population analysis

2.3.10 Conclusions

By combining the regioselective iron(III)-triflimide-catalysed iodination with a copper(I)-catalysed intramolecular C–N and C–O bond forming process, a general one-pot method for the synthesis of *N*- and *O*-heterocyclic scaffolds was developed (Scheme 117). This method uses inexpensive, readily available transition metal-catalysts and avoids pre-functionalised substrates, as is the requirement with traditional Buchwald-Hartwig and Ullmann-type intramolecular couplings. In general, this method has no issues with over-iodination and, when using primary and secondary benzylic alcohols, no oxidation was observed as may be the case with traditional palladium-catalysed methods. The use of this one-pot procedure as the key step in preparation of (+)-obtusafuran showed the general utility and applicability of this methodology for the total synthesis of natural products. Finally, DFT calculations using Fukui functions provided a molecular orbital explanation for the high levels of regioselectivity that were observed during the iron(III) triflimide-catalysed electrophilic aromatic iodination step.



Scheme 117: One-pot, two-step synthesis of functional *N*- and *O*-heterocycles

2.4 One-Pot, Two-Step Synthesis of Benzo[*b*]furans

2.4.1 Introduction

The benzo[*b*]furan ring system is a common motif found in many natural products and pharmaceutically relevant compounds. Isolated from many plant and marine sources, 2-substituted analogues in particular display interesting antimicrobial, antifungal and anti-inflammatory properties.[305–307] Frondosin B (**170**), first isolated from the marine sponge *Dysidea frondosa*, is a member of a sesquiterpene family found to be an inhibitor of interleukin-8 (IL-8) receptors (Figure 7).[308] IL-8 is largely responsible for the recruitment and accumulation of neutrophils, implicated in a wide range of autoimmune disorders such as rheumatoid arthritis therefore, receptor antagonists such as frondosin B are therapeutic lead compounds for the treatment of such inflammatory diseases.[309,310] For this reason, a number of total syntheses of **170** have been reported.[311–314] Another example of a benzo[*b*]furan with bioactivity is (−)-machaeriol B (**171**), a natural product isolated from *Machaerium multiflorum* with potent in vitro antimicrobial and antimalarial activity.[315] Vibsanol A (**172**) is a benzo[*b*]furan-type lignan natural product isolated from the bark of *Vibumum awabuki* with moderate antioxidant properties.[316,317] Another natural product containing the benzo[*b*]furan scaffold is ribisin A (**173**), which has been demonstrated to enhance nerve growth factor and hence, is potentially effective in the treatment of brain trauma and Alzheimer disease.[318,319] In addition, moracin P (**174**), part of the moracin family of natural products, has anticarcinogenic properties.[320]

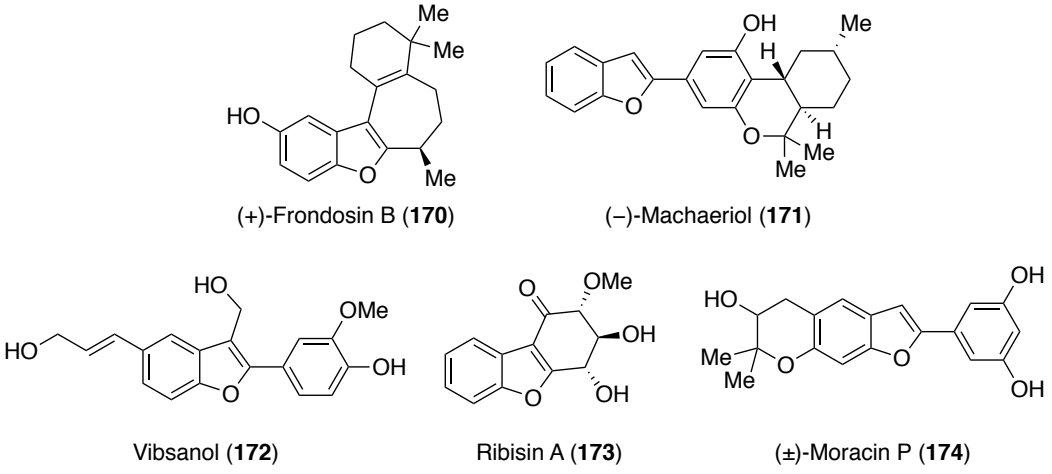
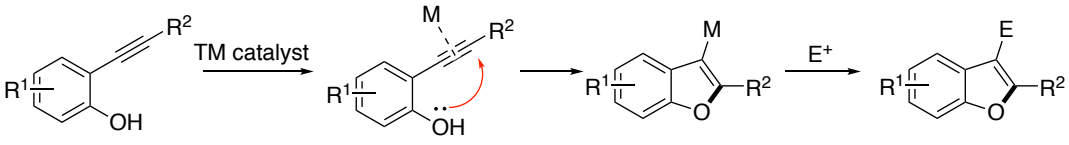


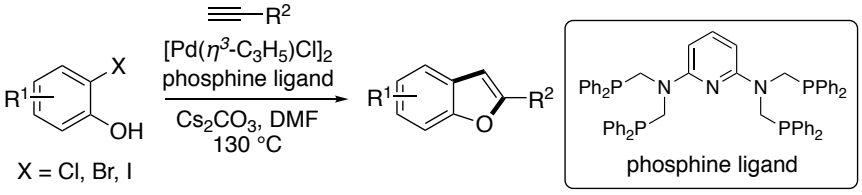
Figure 7: Benzo[*b*]furan motif in biologically active compounds

As the benzo[*b*]furan scaffold is ubiquitous in biologically active compounds, substantial efforts have been directed to new synthetic methods for their preparation.[321–323] A common approach involves the *O*-heterocyclisation of *ortho*-alkynylphenols, mediated by transition metals such as palladium,[324,325] copper,[326] zinc,[327] or indium (Scheme 118).[328] This involves π-Lewis acid activation of the alkyne functionality, allowing *5-endo-dig* cyclisation of the oxygen nucleophile. Protodemetalation or reaction with other suitable electrophiles allow for the formation of the substituted benzo[*b*]furan heterocycles.



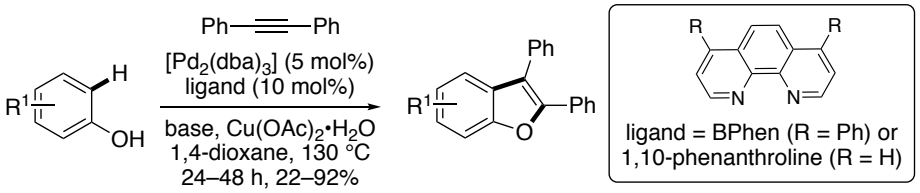
Scheme 118: *O*-Heterocyclisation of *ortho*-alkynylphenols

A variety of reliable one-pot methods have been developed for the heteroannulation of 2-halophenols and alkynes, which combine a palladium-catalysed Sonogashira coupling with an *in-situ* oxidative cyclisation.[329] This is widely applicable to a range of 2-bromo and 2-iodophenols with various unactivated alkynes, allowing for the synthesis of highly functional benzo[*b*]furans.[330–334] As well as the use of expensive palladium catalysts, it was shown that this domino Sonogashira/cyclisation-type process could also be catalysed by copper(I) iodide with parts per billion quantities of palladium or by sub-mol% quantities of Cu(II) pincer complexes.[335,336] This method has recently been expanded to include the use of less reactive but more widely available 2-chlorophenol substrates.[337–339] For example, Li and co-workers have developed a one-pot method for the synthesis of benzo[*b*]furans using a catalytic system composed of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and a pyridine-derived, tetraphosphine ligand (Scheme 119).[340] Low catalyst loadings (<0.1 mol%) were used with a wide range of halophenol substrates, including chlorophenols.



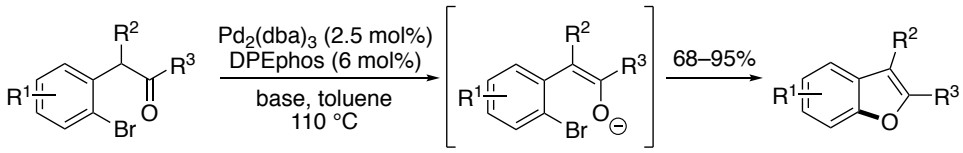
Scheme 119: Li's Pd-catalysed Sonogashira and cyclisation of 2-halophenols

A new approach to benzo[*b*]furan synthesis which has recently gained attention is the *ortho*-C–H activation/olefination or alkynylation of free phenols followed by transition metal-catalysed oxidative cyclisation.[341–344] This is typified by Sahoo and co-workers who reported a ligand-assisted, palladium-catalysed heteroannulation of phenols under basic conditions (Scheme 120).[345] This method tolerates a wide-range of unactivated, internal alkynes, allowing for selective activation and functionalisation of the *ortho*-C–H bonds of phenol substrates, followed by *O*-heterocyclisation in a one-pot process.



Scheme 120: Benzo[*b*]furan synthesis using a C–H functionalisation/cyclisation approach

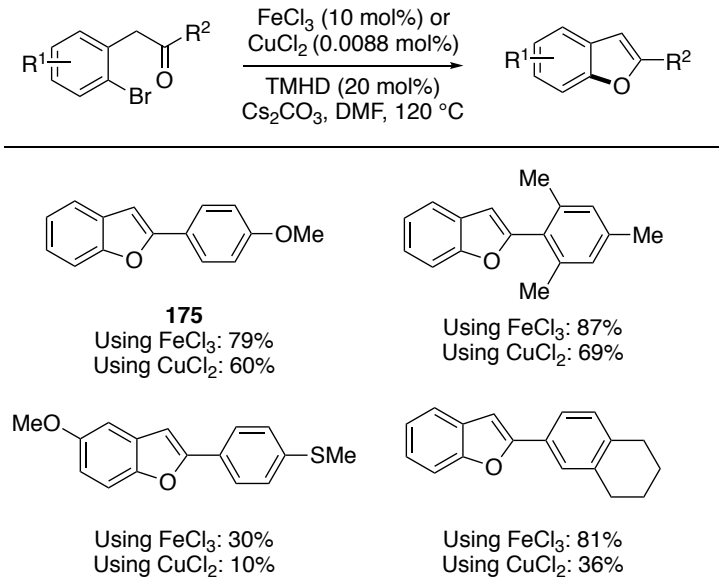
While less common, synthesis of benzo[*b*]furans by formation of the C_{7a}–O bond has been reported *via* transition metal-catalysed cyclisation of 2-haloarylketones. This approach was demonstrated by Willis and co-workers, who showed that enolates of 1-(2-bromoaryl)ketones could undergo a palladium-catalysed, ligand assisted *O*-arylation, for the synthesis of 2,3-disubstituted benzo[*b*]furans (Scheme 121).[346]



Scheme 121: Willis' Pd-catalysed intramolecular *O*-arylation of enolates

Similar reactions of 2-haloarylketones have also been described using non-precious copper(I) salts, often requiring high temperature reactions under basic conditions.[347,348] More recently, Bolm and co-workers demonstrated that iron(III) chloride could be used to catalyse this transformation (Scheme 122).[349] In their study, they examined the catalytic activity of trace metal impurities present in a commercial sample of $FeCl_3$. While the use of ultra-pure $FeCl_3$ (99.995%, 10 mol%)

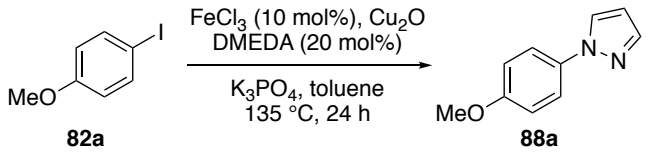
gave benzo[*b*]furan **175** in 79% yield, the use of trace amounts of $CuCl_2$ (0.0088 mol%, 344 ppm) also gave **175**, in 60% yield.



Scheme 122: Bolm's synthesis of benzo[*b*]furans using iron or copper salts

The Bolm group had previously focused on the development of cross-coupling reactions using purely iron catalysis. To this end, they studied a range of arylation reactions using aryl halides with *N*-nucleophiles, amides, phenols and thiols catalysed by a single iron salt.[350–354] The optimal results were obtained when using $FeCl_3$ (10 mol%) of 98% purity in combination with a chelating, bidentate ligand such as DMEDA or THMD (20 mol%). Following this, the group noted a correlation between the catalytic activity and the particular iron catalyst they used, where both the commercial source and purity determined the efficiency of the cross-coupling between *N*-sulfoximines and aryl iodides.[355] This phenomena was also observed by the Buchwald group at MIT, compelling Buchwald and Bolm to re-examine the coupling reactions using various sources of $FeCl_3$, with purities ranging from 98% to 99.99%.[356] For the coupling of 4-iodoanisole (**82a**) and pyrazole, the use of $FeCl_3$ with 98% purity from Merck gave coupled product **88a** in 87% yield (Scheme 123). Interestingly, using $FeCl_3$ with 98% purity from a different source (Aldrich) led to a significant reduction in the yield of **88a** (26%) while using $FeCl_3$ (99.99% purity) gave **88a** in only 9% yield. Adding a small quantity of Cu_2O (5 ppm) to the reaction mixture containing $FeCl_3$ (99.99% purity) led to compete recovery of the efficiency and **88a** was isolated in 78% yield. Provided the ligand concentration remained constant and in large excess, the reaction could be catalysed by trace quantities of Cu_2O (5 ppm)

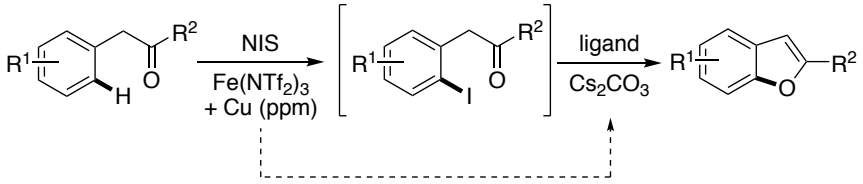
in the absence of any iron salt. This gave coupled product **88a** in 77% yield, demonstrating the very high-catalytic activity of copper salts, even when present in trace quantities. This high catalytic activity was further elucidated with additional experiments by Norrby and Bolm, showing that catalyst loadings as low as 0.001 mol% of copper(II) salts were sufficient to give coupled products in excellent yields.[357] A detailed kinetic study of the *N*-arylation of pyrazole with phenyl iodide then demonstrated the critical necessity of DMEDA in this process, a unique ligand which allows high conversion at very low concentration of metal catalyst.[358]



Scheme 123: Metal salts in cross-coupling reactions

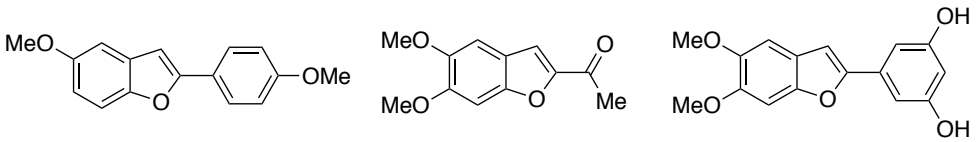
2.4.2 Project Aims

The main aim of this project was the development of a one-pot method for the synthesis of highly substituted benzo[*b*]furans from simple 1-aryl or 1-alkylketones, avoiding the need to pre-halogenate the ketone starting materials. This method was to involve a highly regioselective iron(III)-catalysed electrophilic aromatic halogenation followed by transition metal-catalysed C–O cyclisation (Scheme 124). Building on the work by Bolm and co-workers, the potential for a single iron(III) salt to catalyse both the aryl C–H halogenation step and the intramolecular *O*-arylation step in a tandem process would be investigated. In addition to this, with the knowledge that even trace quantities of copper salts are highly catalytically active, homeopathic, parts per million copper loadings of copper will be examined for the C–O cyclisation step.



Scheme 124: Proposed one-pot synthesis of benzo[*b*]furans

An important objective of this project was to establish quick and efficient synthetic routes towards 1-aryl and 1-alkylketone substrates. With this achieved, the scope of the one-pot process would examine the impact of different electronic and steric properties of the ketone substrates. The methodology would then be applied to the synthesis of natural products and biologically active compounds containing the benzo[*b*]furan unit, such as corsifuran C (**176**), the antimicrobial agent caleprunin B (**177**) and the antifungal compound moracin F (**178**) (Figure 8).

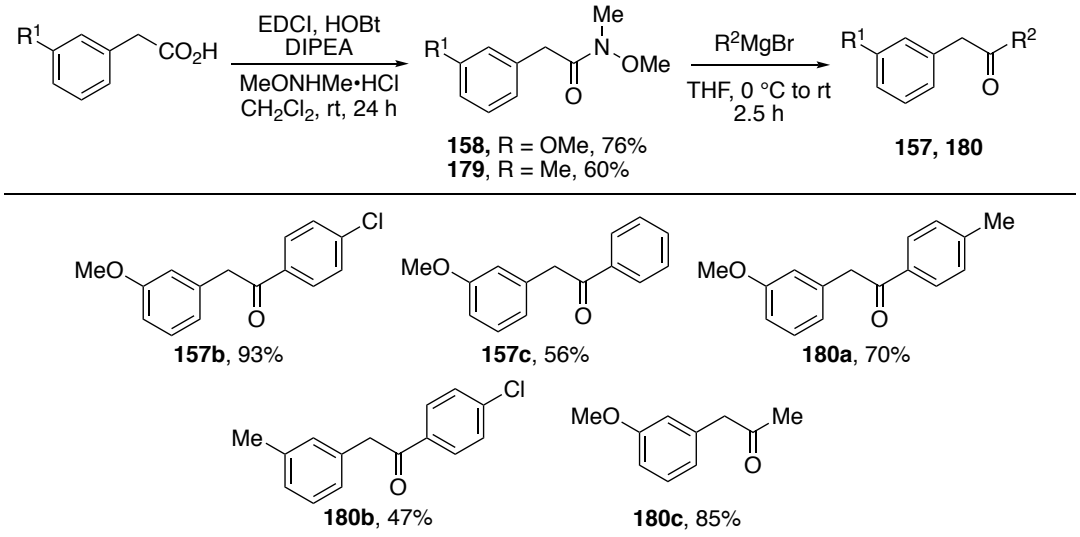


corsifuran C (**176**) caleprunin B (**177**) moracin F (**178**)

Figure 8: Biologically active benzo[*b*]furan targets

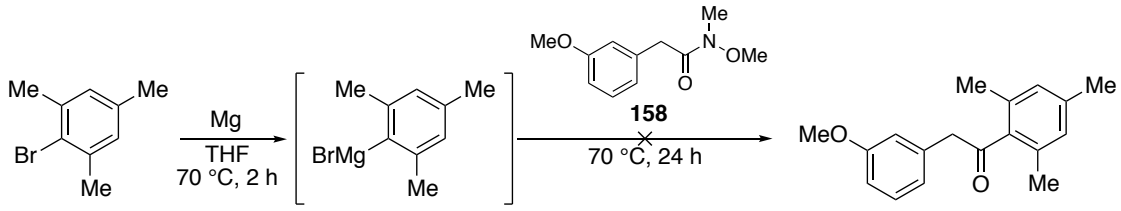
2.4.3 Synthesis of Ketone Substrates

To begin this study, a series of 1-aryl or 1-alkylketones were synthesised from commercially available starting materials. The initial approach proposed to access the required α-arylketone substrates for the one-pot process was *via* a Weinreb amide intermediate (Scheme 125).[359] For example, 3-methoxyphenylacetic acid (**128**) was converted to Weinreb amide **158** under standard amide coupling conditions, then subsequent reaction with 4-chlorophenylmagnesium bromide allowed the multigram-scale synthesis of ketone **157b** in 93%. Using other commercially available Grignard reagents and Weinreb amides **158** and **179**, this process was extended for the synthesis of a series of 1-aryl and 1-alkylketones **157c**, **180a**–**180c**.



Scheme 125: Synthesis of 1-aryl and 1-alkylketones *via* a Weinreb amide

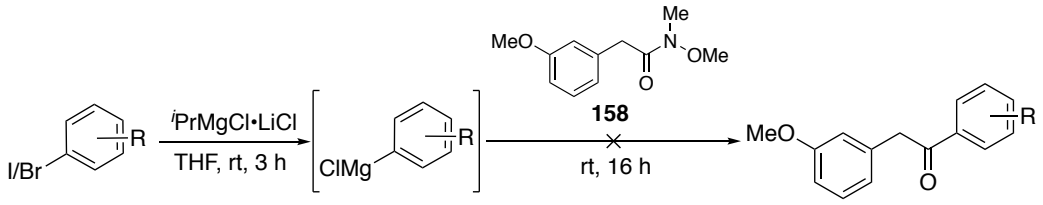
While this was an efficient and mild method for the synthesis of some aryl ketones, it was restricted by the expense and limited commercial availability of Grignard reagents. Therefore, other methods for the preparation of Grignard reagents *in situ* from widely available aryl bromides were sought. The reaction of 2-bromomesitylene with magnesium turnings resulted in the formation of 2-mesitylmagnesium bromide (Scheme 126). Addition of the magnesium reagent to Weinreb amide **158** resulted in no conversion to the aryl ketone, despite a 70 °C reaction temperature for 24 h. After work-up of the reaction mixture, the ^{1}H NMR spectra of the crude material showed a mixture of unreacted Weinreb amide **158** and mesitylene. This suggests that the steric bulk associated with *ortho*,*ortho*-methyl substituents prevented addition of the Grignard reagent.



Scheme 126: Attempted synthesis of a hindered α-aryl ketone by *in-situ* formation of a Grignard reagent

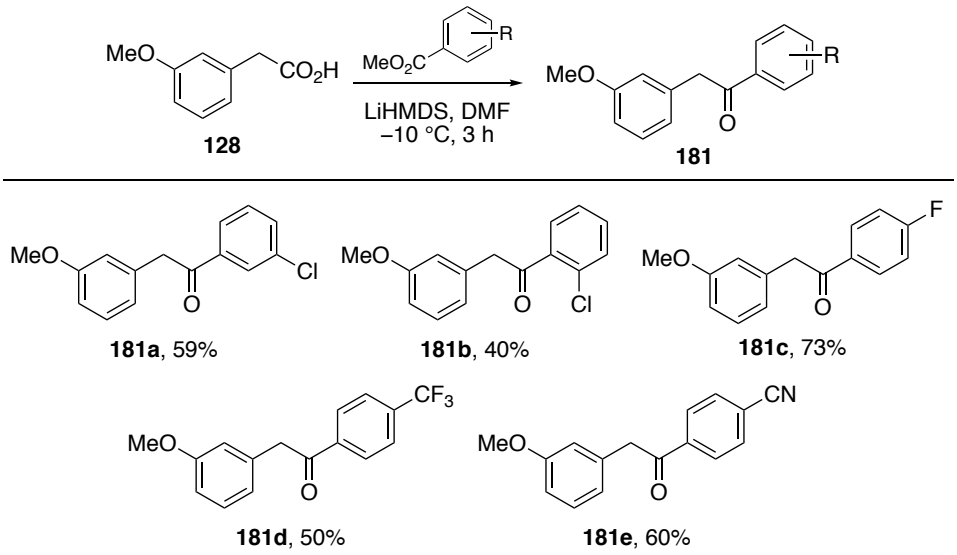
Another approach for the preparation of Grignard reagents was investigated following the work of Knochel and co-workers.[360] This involved the interaction of isopropylmagnesium chloride-lithium chloride complex, known as ‘turbo Grignard’,

with aryl halides in a magnesium-halogen exchange reaction (Scheme 127). This reaction was attempted with various electron-rich and electron-deficient aryl bromides and iodides however, in all cases only complex mixtures of unidentified by-products were observed.



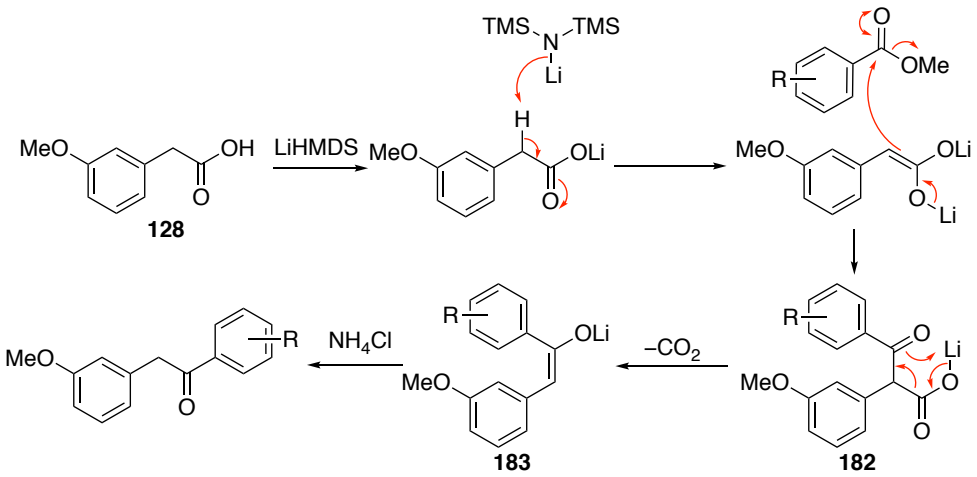
Scheme 127: Attempted synthesis of α-aryl ketones *via* magnesium-halogen exchange reactions

Alternative methods for the synthesis of α-arylketone were then investigated. Consequently, it was found that α-aryl ketones could be synthesised directly from phenylacetic acids *via* a Claisen condensation with various functionalised aryl esters (Scheme 128). This method utilised readily available starting materials and avoided the use of the expensive or unstable organometallic reagents. This method was applicable to aromatic esters, with electron-deficient substituents in the *o*-, *m*- and *p*-positions, and allowed the synthesis of a range of α-arylketones **181a**–**181e** in up to 73% yield.



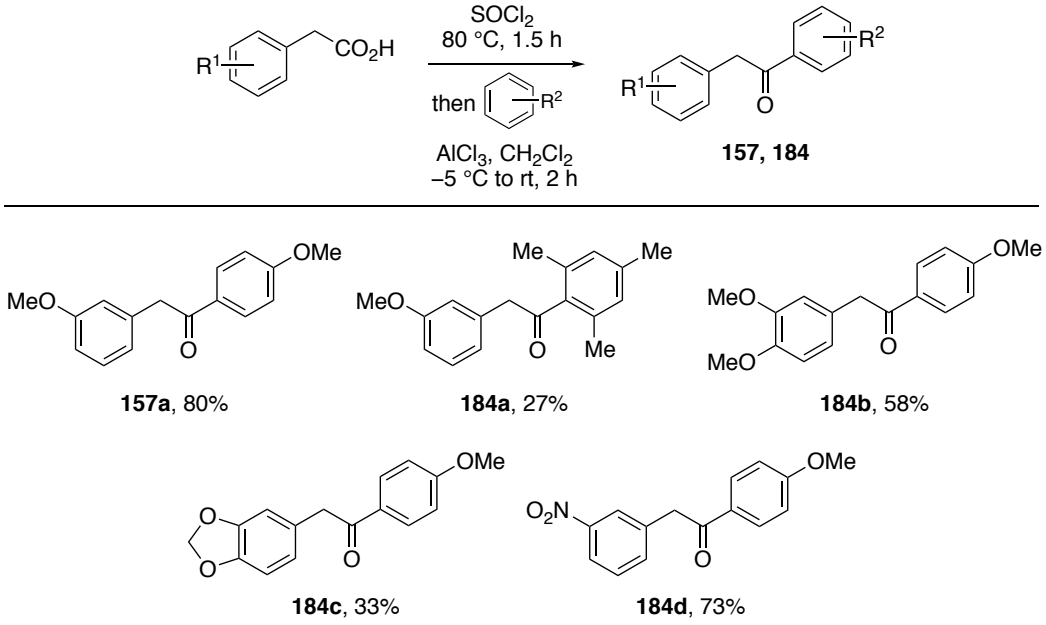
Scheme 128: Claisen condensation

The proposed mechanism for this Claisen condensation reaction is shown below (Scheme 129). Firstly, treatment of 3-methoxyphenylacetic acid (**128**) with the hindered base, LiHMDS, results in rapid removal of the most acidic carboxylic acid proton and formation of the lithium carboxylate salt. A further equivalent of LiHMDS then performs subsequent deprotonation at the α-position to give the lithium enolate, which can in turn perform nucleophilic attack of the methyl ester, resulting in the formation of 1,3-dicarbonyl intermediate **182**. This β-ketoacid lithium carboxylate salt can undergo decarboxylation, producing lithium enolate **183**. A mildly acidic work-up with ammonium chloride followed by keto-enol tautomerism affords the desired 1-arylketones.



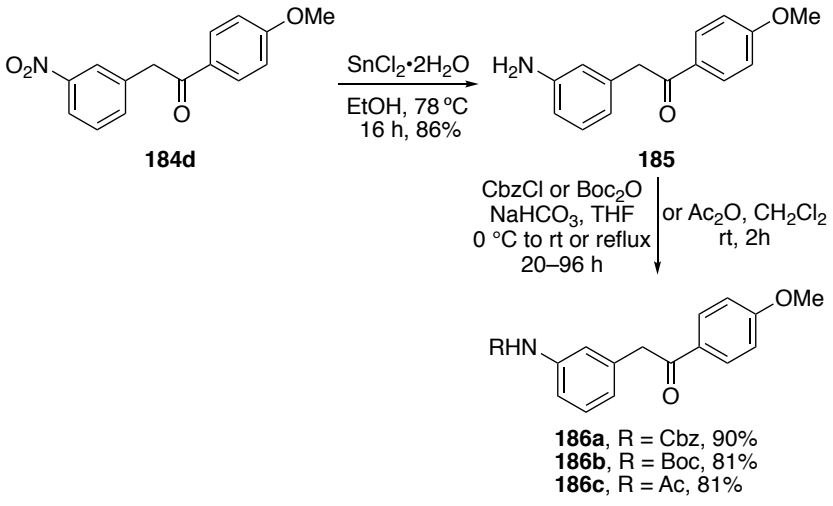
Scheme 129: Mechanism of the Claisen condensation

Friedel-Crafts acylation reactions were employed to synthesise a further small library of α-arylketones (Scheme 130). To achieve this, 3-methoxyphenylacetic acid (**128**) was converted into the corresponding acyl chloride by reaction with thionyl chloride. Subsequent electrophilic aromatic substitution with anisole using stoichiometric quantities of aluminium trichloride gave aryl ketone **157a** in 80% yield. Following this, a range of phenylacetic acid substrates were subjected to these conditions which allowed for the preparation of arylketones **184a**–**184d** using either anisole or mesitylene.



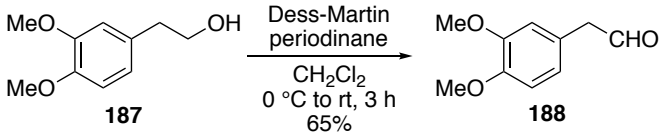
Scheme 130: Friedel-Crafts acylation

To synthesise a small library of arylketones with nitrogen directing groups attached to the α-aryl ring, the nitro group of ketone **184d** was reduced using tin(II) chloride, which gave aniline compound **165** in 86% yield (Scheme 131). The amino functionality of **185** was then protected with synthetically useful protecting groups, such as Cbz, Boc and acetamide, which gave arylketones **186a**–**186c**.



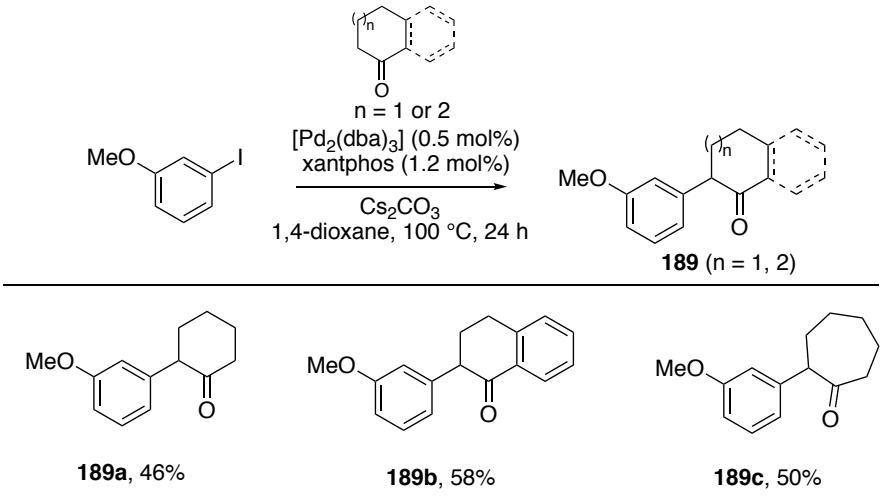
Scheme 131: Synthesis of α-arylketones with nitrogen directing groups

Aldehyde **188**, an additional substrate for the one-pot process, was synthesised by oxidation of phenylethyl alcohol **187** using Dess-Martin periodinane (Scheme 132).



Scheme 132: Oxidation of 3,4-dimethoxyphenylethyl alcohol (187)

A further series of ketone substrates were prepared *via* a palladium-catalysed α-arylation reaction using a procedure by Buchwald and co-workers (Scheme 133).[361] Under basic conditions and in the presence of $Pd_2(dba)_3$ and an electron rich phosphine ligand (xantphos), cyclohexanone, α-tetralone or cycloheptanone were reacted with 3-iodoanisole and gave α-arylated ketones **189a**–**189c** in moderate yields. The ketone starting materials were used in excess (2 equivalents) in this reaction and led to difficultly in purifying the products, which had similar retention on silica gel. This resulted in lower overall yields of the coupled products.

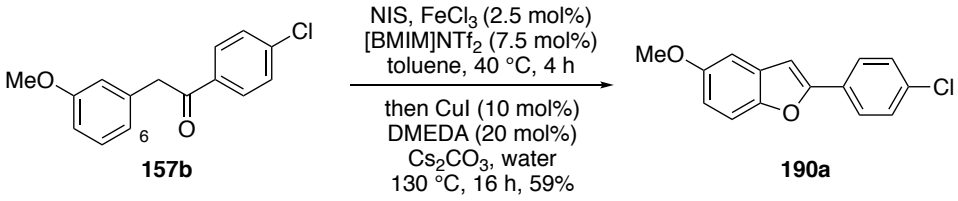


Scheme 133: Palladium-catalysed α-arylation of cyclic ketones

2.4.4 Optimisation of One-Pot Processes

Initial studies of the one-pot synthesis of benzo[*b*]furans applied iron(III)-catalysed iodination then copper(I)-cyclisation to α-arylketone **157b** (Scheme 134). Using iron(III) triflimide for the activation of NIS resulted in iodination of **157b** in 4 h at 40 °C. Despite the substantial steric effect of the *meta*-arylethanone substituent, analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed exclusive iodination at the C-6 position. The second-step of the one-pot process involved the use of copper(I) iodide (10 mol%) and DMEDA (20 mol%), which allowed the

isolation of benzo[*b*]furan **190a** in 59% yield. Using different ligands in the copper(I)-catalysed cyclisation had no discernible effect upon the efficiency or isolated yield. For example, the use of diketone ligand **94** and cyclohexanediamine ligand **98** during the second step of the one-pot process gave benzo[*b*]furan **190a** in 53% and 55% yield, respectively.

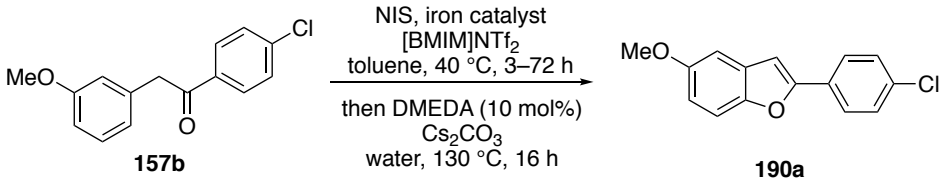


Scheme 134: Initial synthesis of benzo[*b*]furan 190a from α-arylketone 157b

Next, it was investigated whether a single iron salt could be used for both the electrophilic aromatic substitution and cyclisation steps in a tandem-catalytic, one-pot process (Table 10). Use of $FeCl_3$ (2.5 mol%) of 97% purity during the one-pot process, allowed for formation of benzo[*b*]furan **190a**, without the addition of copper(I) iodide in the second step (entry 1). A complication arose when it was discovered that all grades of commercial $FeCl_3$ contain significant amounts of metal contaminants, including sufficient levels of copper to catalyse the *O*-arylation step. For example, $FeCl_3$ with 99.9% impurity has 31.1 ppm of Cu while 99.99% $FeCl_3$ contains 24.1 ppm of Cu impurities. The levels of copper impurities specified in the batch analysis of commercial samples of $FeCl_3$ was verified using inductively coupled plasma-atomic emission spectroscopy (ICP-AES). However, this offered the prospect to develop a one-pot procedure using a single iron complex in which the residual ppm quantities of copper could be used to catalyse the cyclisation. The use of $FeCl_3$ (2.5 mol%) of 99.9% purity gave the corresponding benzo[*b*]furan **190a** in 44% yield (entry 2). Doubling the catalytic loading of $FeCl_3$ to 5 mol% resulted in a more efficient cyclisation, giving **190a** in 60% yield (entry 3). Further increasing the loading of $FeCl_3$ to 10 mol% resulted in a marginal increase in the yield of **190a** to 63% (entry 4). In contrast, a reduction of the catalyst loading to 1 mol%, resulted in a reduction in yield of **190a** to 47% (entry 5). With a purer source of $FeCl_3$ (99.99%), containing 24.1 ppm of copper impurities, benzo[*b*]furan **190a** was isolated in 65% yield (entry 6). Based on these results, the use of $FeCl_3$ (99.9% purity) at 5 mol% loading was deemed optimal for the one-pot process involving iron(III)-catalysed iodination, followed by cyclisation, catalysed by residual copper.

Ultrapure iron(III) salts were next investigated to discover whether a single iron complex (not contaminated by copper), could be used for the entire one-pot process. As ultrapure iron(III) chloride is not commercially available, alternative sources of iron were used. When iron(III) oxide (99.995% purity) was used, the iodination step was very sluggish, eventually reaching 70% conversion after 72 h at 70 °C. The subsequent cyclisation step was efficient however, giving benzo[*b*]furan **190a** in 35% yield (entry 7). Ultrapure iron(III) nitrate nonahydrate, which contains no copper impurities, in combination with [BMIM]NTf_2 was found to be an effective Lewis acid for regioselective iodination with full conversion to the iodide intermediate after 5 h at 40 °C. Using only this iron complex for the entire one-pot process gave benzo[*b*]furan **190a** in 55% yield (entry 8).

Table 10: Optimisation of the metal catalyst for the synthesis of benzo[*b*]furan 190a

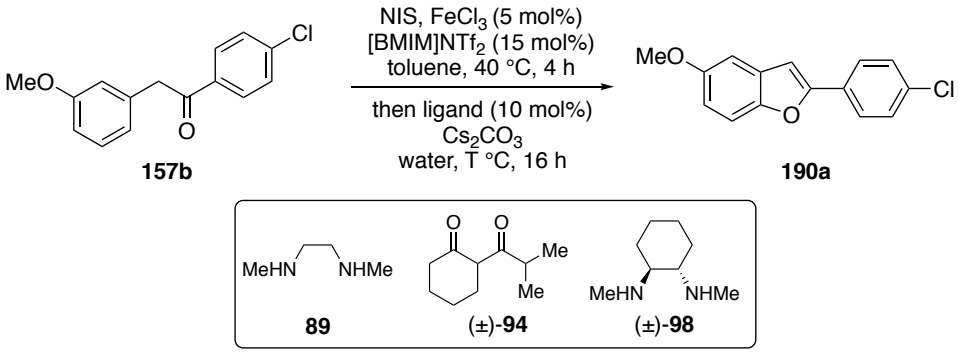


Entry	Iron Catalyst	Catalyst Loading (mol%)	Catalyst Purity (%)	Copper Impurities (ppm)	Isolated Yield (%)
1	$FeCl_3$	2.5	97	n/a	48
2	$FeCl_3$	2.5	99.9	31.1	44
3	$FeCl_3$	5	99.9	31.1	60
4	$FeCl_3$	10	99.9	31.1	63
5	$FeCl_3$	1	99.9	31.1	47
6	$FeCl_3$	5	99.99	24.1	65
7	Fe_2O_3	5	99.995	1.6	35
8	$Fe(NO_3)_3{\bullet}9H_2O$	5	99.999	ND	55

The effect of the ligand and temperature during the cyclisation step were investigated using the optimal procedure involving 5 mol% loading of $FeCl_3$ (99.9% purity) (Table 11). Using 2-isobutyrylcyclohexanone (**94**) and *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**98**) resulted in less efficient cyclisation reactions, giving benzo[*b*]furan **190a** in 24% and 44% yield, respectively (entries 1 and 2). It

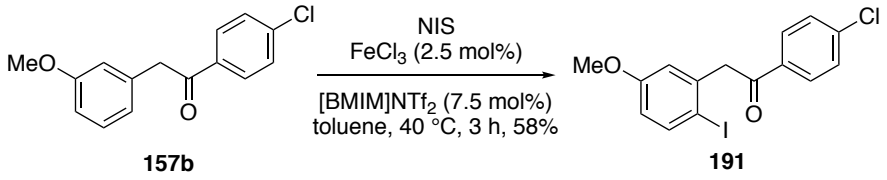
was found that no conversion to **190a** was observed in the absence of a ligand (entry 3), demonstrating that a relatively high ligand loading (10 mol%) was necessary for activity. A reduction of the cyclisation temperature led to lower conversion to benzo[*b*]furan **190a**, with yields of 35% and 13% at 110 and 90 °C, respectively, proving that a high reaction temperature was critical to overcome the energy penalty associated with oxidative addition (entries 4 and 5). Based on these results, the optimal ligand for cyclisation was DMEDA (**89**) and a reaction temperature of 130 °C.

Table 11: Optimisation of benzo[*b*]furan formation



Entry	Ligand	Temperature (°C)	Isolated Yield (%)
1	**94**	130	24
2	**98**	130	44
3	none	130	0
4	**89**	110	35
5	**89**	90	13

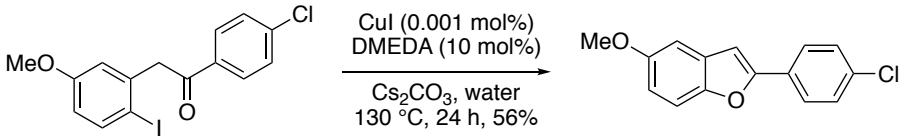
Next, the single step heterocyclisation of a 1-(2-haloaryl)ketone was performed, to verify that ppm quantities of copper could catalyse this transformation. To achieve this, aryl iodide **191** was prepared by the reaction of aryl ketone **157b** with NIS using $Fe(NTf_2)_3$ (2.5 mol%) under standard conditions (Scheme 135).



157b 191

Scheme 135: Synthesis of aryl iodide 191

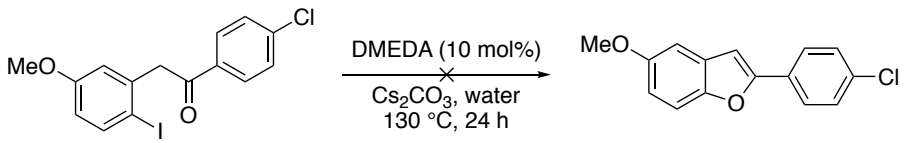
The single step cyclisation of iodide **191** was then performed using CuI (0.001 mol%), with a concentration of 14 ppm (Scheme 136). The ^{1}H NMR spectrum of the crude reaction mixture after 24 h showed 74% conversion to benzo[*b*]furan **190a**. On isolation, this gave **190a** in 56% yield.



191 190a

Scheme 136: Ultra-low loading of CuI in the synthesis of benzo[*b*]furan 190a

There was a concern that trace copper impurities may be introduced during the cyclisation step, through the addition of reagents or solvents (e.g. water), or already present from the glassware. To eliminate this possibility, a reaction was performed with aryl iodide **191** using DMEDA (10 mol%), cesium carbonate in toluene and water under standard cyclisation conditions (Scheme 137). This resulted in no conversion to **190a**. These results confirmed that *O*-arylation reaction during the one-pot processes was catalysed by ultrapure iron(III) or the associated copper impurities of the lower grade iron(III) chloride salts and not *via* the introduction of trace quantities of copper salts during the second step.

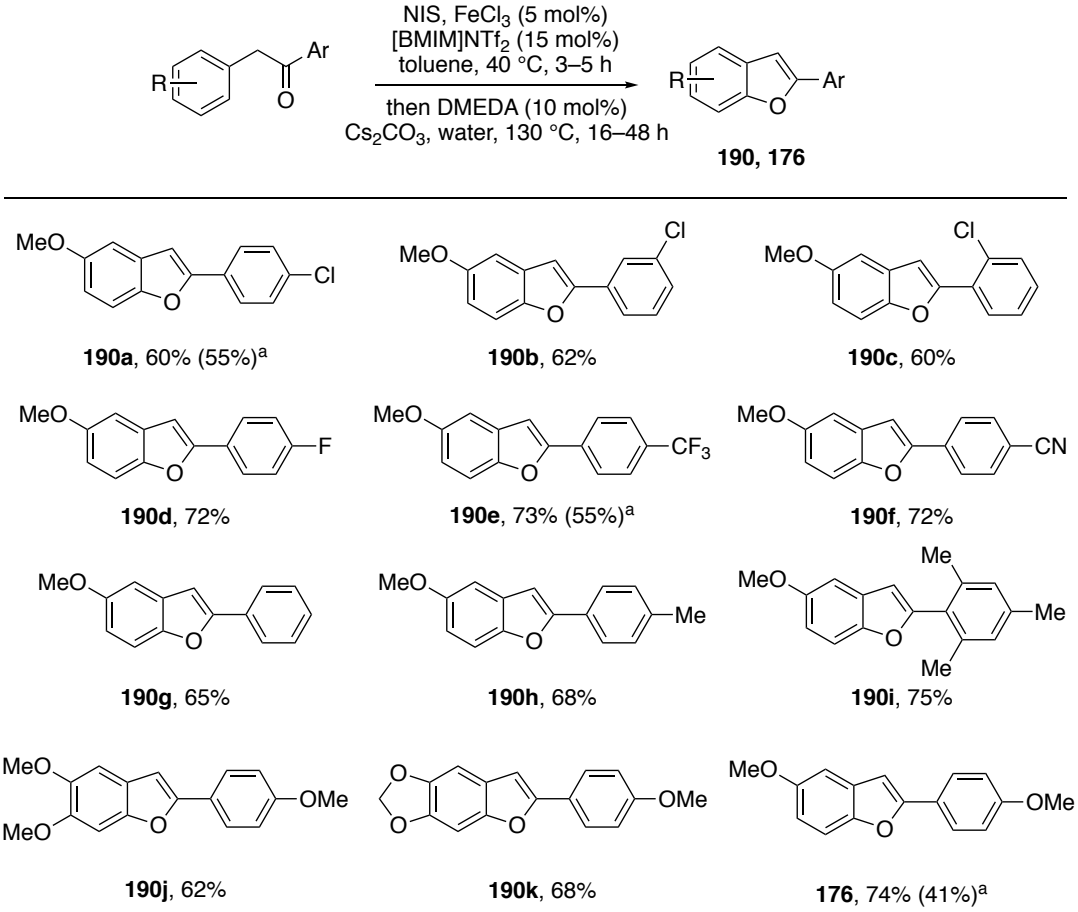


191 190a

Scheme 137: Attempted synthesis of benzo[*b*]furan 190a with no metal catalysts

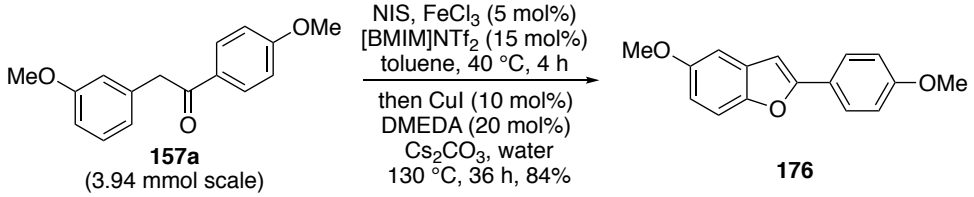
2.4.5 Substrate Scope of One-Pot Processes

The optimised one-pot process involving iron(III) chloride (5 mol%, 99.9% purity) to catalyse the iodination step and the residual copper (31.1 ppm) to catalyse the intramolecular *O*-arylation step was applied to the series of arylketones (Scheme 138). 1-Arylketone substrates with electron-deficient groups, as well as *ortho*-, *meta*- and *para*-substituents were tolerated in this process and gave benzo[*b*]furans **190a**–**190f** in 60–73% yield. Ketone substrates with electron-rich aryl groups were also efficient substrates of this process and allowed for the synthesis of benzo[*b*]furans **190g**–**190k** in 62–75% yield. Using mesityl substituted ketone **184a** in the one-pot process required a longer reaction time (48 h) during the cyclisation step, due to the steric hindrance of the two *ortho*-methyl groups. Despite the more forcing conditions, this still led to the isolation of **190i** in 75% yield. The one-pot process was also used for the efficient synthesis of corsifuran C (**176**), a stilbenoid natural product from *Corsinia coriandrina*,[290] in 74% yield from aryl ketone **157a**. The one-pot process was also performed with electron-deficient (*p*-CF_3Ph, **181d**) and electron-rich (*p*-MeOPh, **157a**) arylketone substrates using ultrapure iron(III) nitrate nonahydrate to catalyse both steps. Without the presence of trace copper impurities, benzo[*b*]furans **190e** and **176** were isolated in 55% and 41% yield, respectively.



Scheme 138: Scope of one-pot synthesis of benzo[*b*]furans using $FeCl_3$ (99.9% purity); [a]Isolated yield using $Fe(NO_3)_3$•9H2O (5 mol%)

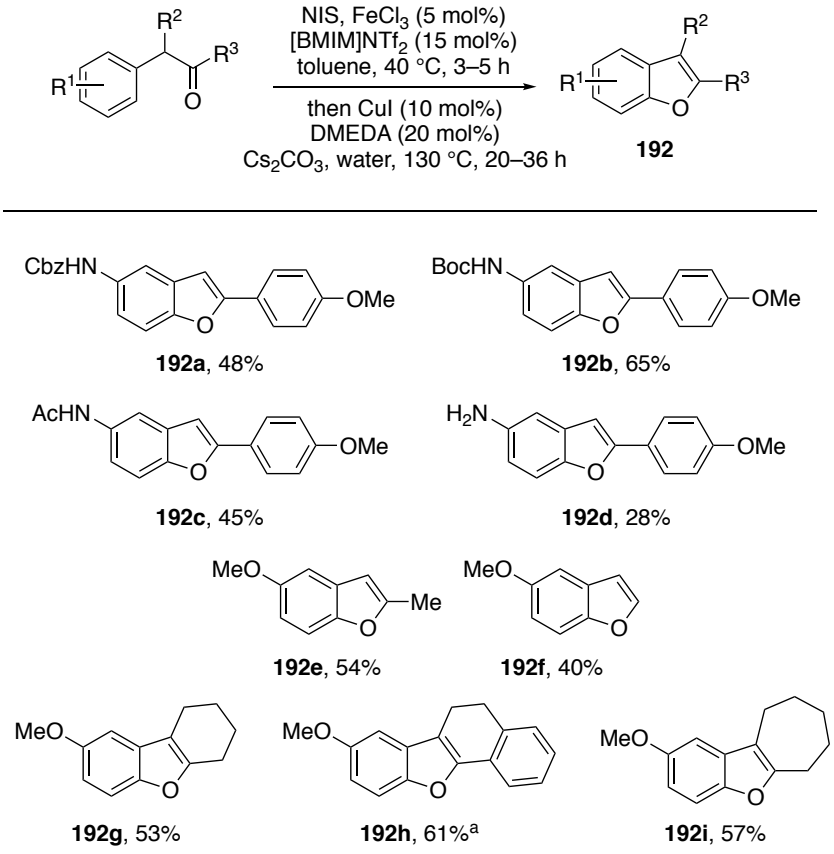
The one-pot process was next used for the gram-scale synthesis of corsifuran C (**176**) (Scheme 139). Although the use of ppm loading of copper was sufficient to catalyse the heterocyclisation step of a small-scale reaction and gave **176** in 74% yield, it was necessary to use CuI (10 mol%) to increase the efficiency of the reaction of a larger scale process. This resulted in the isolation of corsifuran C in 84% yield.



Scheme 139: Gram-scale synthesis of corsifuran C (176)

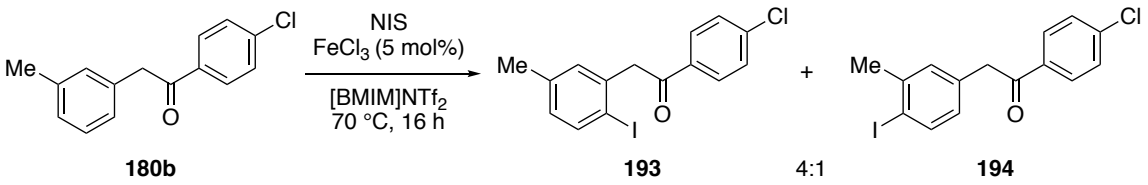
This one-pot process was then used for the more demanding synthesis of benzo[*b*]furan targets, using less reactive ketones bearing amino-substituted aryl

rings or alkyl side chains (Scheme 140). The synthesis of some of these benzo[*b*]furans were initially investigated using the one-pot process involving iron(III) chloride (5 mol%, 99.9% purity) with ppm loading of copper. However, this required longer reaction times (48–72 h) and resulted in low yields (26–32%). Consequently, the addition of copper(I) iodide during the cyclisation step was investigated for the efficient synthesis of these substrates. It was found that the use of $FeCl_3$ (97% purity) at 5 mol% loading followed by CuI at 10 mol% loading was the most efficient catalytic system for these substrates. Amino-substituted benzo[*b*]furans **192a**–**192c** bearing carbamate and acetyl protecting groups were prepared in 45–65% yield. The use of 3-amino substituted ketone **185** as a substrate gave benzo[*b*]furan **192d** in only 28% yield. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed that this was due to competing iodination at the C-4 position. 1-Methyl ketone **180c** and aldehyde **188** were also tolerated in the one-pot process and gave benzo[*b*]furans **192e** and **192f** in 54% and 40%, respectively. Cyclic ketones **189a**–**189c** were also submitted to the one-pot process and allowed for the efficient preparation of polycyclic benzo[*b*]furans **192g**–**192i** in 53–61% yield.



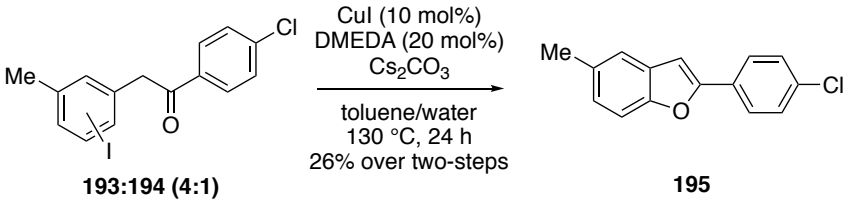
Scheme 140: Scope of the one-pot synthesis of benzo[b]furans using $FeCl_3$ (97% purity) and CuI (10 mol%); [a]Iodination step was performed at 50 °C for 6 h

It is worth noting that limitations were observed during the development of this methodology using unactivated 1-arylketones. In particular, halogenation of 3-methylphenyl substituted aryl ketone **180b** did not proceed under standard conditions, with NIS or NBS, using $FeCl_3$ (5 mol%) and [BMIM]NTf_2 (15 mol%) even at 70 °C with an extended reaction time (24 h) (Scheme 141). This substrate required the use of the ionic liquid as a solvent and harsh conditions (70 °C for 16 h), which gave an inseparable 4:1 mixture of the desired 6-iodo and undesired 4-iodo regioisomers (**193**:**194**).



Scheme 141: Iodination with a methyl directing group

After filtration through a short-pad of silica, this 4:1 mixture of regioisomers was submitted to a copper-catalysed cyclisation using CuI (10 mol%) and DMEDA (20 mol%) (Scheme 142). This led to the isolation of benzo[*b*]furan **195** in 26% yield over the two steps.



Scheme 142: Synthesis of benzo[*b*]furan 195

2.4.6 Synthesis of Biologically Active Benzo[*b*]furans

Having developed scalable, robust one-pot processes, attention shifted towards utilising this methodology for the total synthesis of a number of benzo[*b*]furan natural products. It should be noted that these one-pot processes were more efficient for the synthesis of electron-rich benzo[*b*]furans and the regioselectivity during the electrophilic aromatic substitution step was contingent on the presence of a strong methoxy or amino directing group. Fortunately, this type of benzannulated system

is widely found in pharmaceutically important compounds and natural products (Figure 9).

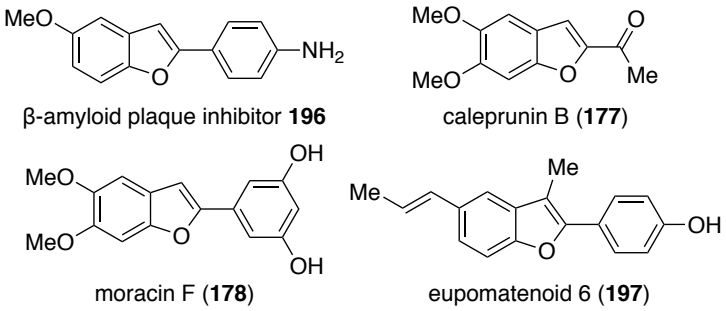
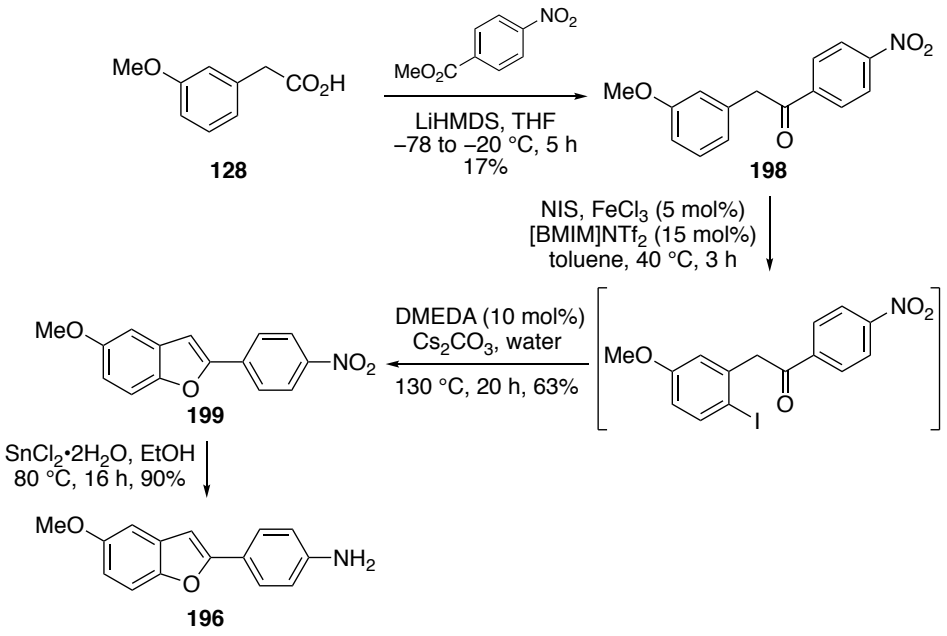


Figure 9: Bioactive benzo[*b*]furan target compounds

Compound **196** has nanomolar affinity of β-amyloid plaques and hence has potential utility as a PET tracer for patients with neurodegenerative diseases such as Alzheimer's disease.[362,363] The synthesis began with a Claisen condensation between 3-methoxyphenylacetic acid (**128**) and methyl 4-nitrobenzoate using LiHMDS and the conditions previously reported (Scheme 143). Analysis of the ^{1}H NMR spectra of the crude reaction mixture showed a complex mixture of by-products. It was believed that the lithium base can deprotonate the *ortho*-position relative to the nitro group and the resulting lithium species could react with the ester functionality, resulting in oligomerisation and other undesired side reactions. Furthermore, organolithium reagents can also attack the electrophilic nitrogen atom of the nitro group, in a similar manner to the Bartoli indole synthesis.[364] By performing the addition of reagents at −78 °C, then warming to −20 °C in THF, allowed the isolation of arylketone **198** in 17% yield. To improve this process, different bases were screened, such as *n*-BuLi and NaH, however this did not improve the reaction outcome. Following this, alternative methods were trialled for the efficient synthesis of arylketone **198**. Firstly, a Bamford-Stevens homologation of 4-nitrobenzaldehyde was attempted via the *in situ* formation of an aryldiazomethane of *m*-anisaldehyde using tosyl hydazone.[365] As well as this, a palladium-catalysed α-arylation of 4-nitroacetophenone with 3-iodoanisole was attempted. However, both reactions resulted in a complex mixture with no formation of arylketone **198** evident. It was therefore decided to proceed with arylketone **198** generated from the low yielding Claisen condensation. Treatment of **198** with NIS using iron(III) triflimide (5 mol%) resulted in full conversion to the aryl iodide intermediate in 3 h at 40 °C. Subsequent *O*-heterocyclisation, catalysed by the

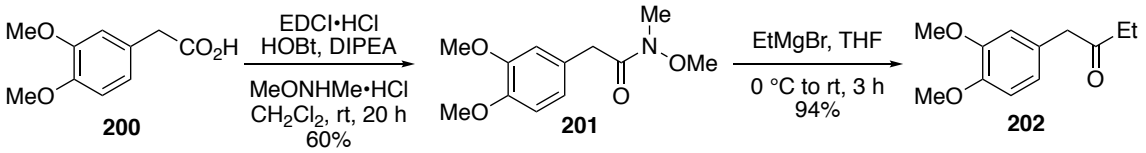
homeopathic quantities of copper residues, allowed the isolation of benzo[*b*]furan **199** in 63% overall yield. Finally, the nitro group of **199** was reduced with tin dichloride in 90% yield, which completed the total synthesis of biologically active benzo[*b*]furan **196**.



Scheme 143: Synthesis of β-amyloid plaque antagonist 196

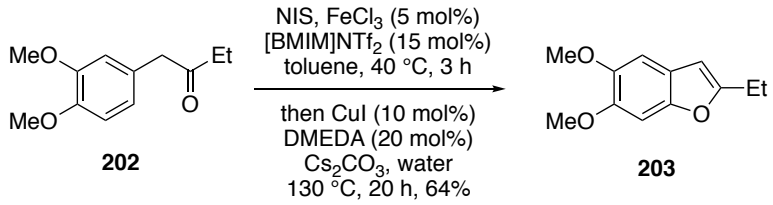
2.4.7 Total Synthesis of Caleprunin B

This methodology was then used as the key step in the total synthesis of caleprunin B (**177**), a 2-acetylbenzo[*b*]furan natural product isolated from *Eupatorium sternbergianum* and various *Calea* species.[366,367] Caleprunin B was also shown to have activity against a range of microorganisms, including several strains of *E. coli*.[368] The synthesis began with formation of Weinreb amide **201** from 3,4-dimethoxyphenylacetic acid (**200**) under standard conditions using EDCI and HOBt (Scheme 144). Weinreb amide **201** was then reacted with ethylmagnesium bromide to give ethylketone **202** in 94% yield.



Scheme 144: Preparation of ethylketone 202 using the Weinreb amide approach

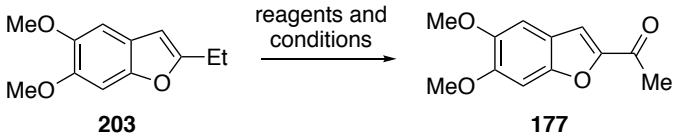
With ethylketone **202** in hand, the use of the one-pot process for the key cyclisation step was next investigated (Scheme 145). As alkylketones were previously shown to be better substrates for the one-pot process involving the addition of copper(I) iodide during the second step, this was also used for ethylketone **202**. Activation of the aryl ring using the iron(III)-catalysed iodination led to the formation of a single regioisomer in 3 h at 40 °C. Following this, the intramolecular *O*-arylation step was carried out using copper iodide (10 mol%) and DMEDA (20 mol%), which gave benzo[*b*]furan **203** in 64% yield.



Scheme 145: One-pot synthesis of benzo[*b*]furan 203

To complete the synthesis of caleprunin B, an allylic oxidation of benzo[*b*]furan **203** was required. There was very limited literature precedent for this transformation therefore a range of reagents and conditions were investigated (Table 12). Treatment of benzo[*b*]furan **203** with the $2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$ triple salt, known as Oxone®, resulted in only decomposition of the starting material (entry 1).[369] Using sodium dichromate in a mixture of concentrated acetic and sulfuric acids gave similar results, with only decomposition of **203** (entry 2).[370] The reaction of **203** with *m*-CPBA also led to a complex mixture of side-products which could not be separated or characterised (entry 3).[371] An attempt to selectively brominate, then hydrolyse, the allylic position *via* a radical halogenation using NBS and AIBN resulted in only bromination of the C-3 position of the benzo[*b*]furan ring (entry 4).[372] Selenium dioxide has previously been used in similar transformations, in particular, for the oxidation of the allylic position of pyrones.[373] When using selenium dioxide (3 equiv.), the desired product could be observed by ^{1}H NMR spectroscopy of the reaction mixture, however, this also resulted in the Riley oxidation[374] of the α-position giving a 1:1 mixture of **177** and the 1,2-dicarbonyl (entry 5).

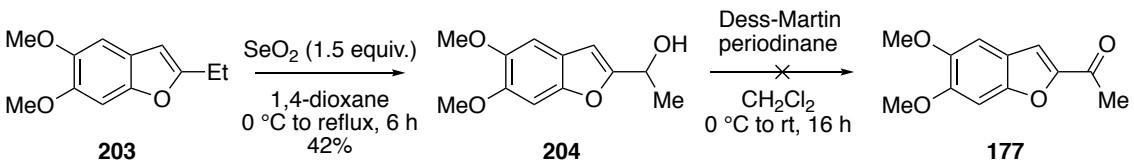
Table 12: Screened conditions for allylic oxidation



203 **177**

Entry	Reagents and conditions	Result
1	Oxone® (2.2 equiv.), KBr (0.5 equiv.), MeCN (6:1) 50 °C, 48 h	Decomposition
2	$Na_2Cr_2O_7$, AcOH, H_2SO_4, 0 °C to rt, 16 h	Decomposition
3	*m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 16 h	Decomposition
4	NBS, AIBN, $CaCO_3$, $CHCl_3$, reflux, 2 h	C-3 bromination
5	SeO_2 (3 equiv.), 1,4-dioxane, reflux, 20 h	Not purified

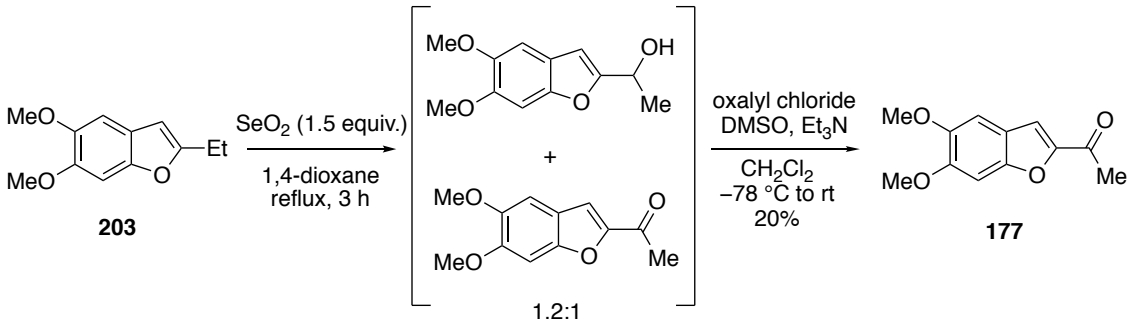
From these results, it was clear that the selenium dioxide mediated oxidation was the most promising method for this hitherto unprecedented step. To limit the undesired oxidation of the α-position of **177**, fewer equivalents of selenium dioxide (1.5 equiv.) were used, the addition of reagents was performed at 0 °C and the reaction time was reduced to 6 h (Scheme 146). More specifically, SeO_2 was added at 0 °C and then stirred at room temperature for 4 h. No conversion of the starting material was observed after this time therefore, the reaction mixture was stirred under reflux for 2 h. This allowed isolation of secondary alcohol **204** in 42% yield, with only traces of ketone **177** evident. Alcohol **204** was then treated with Dess-Martin periodinane, however, this led to the formation of a complex mixture, possibly due to undesired oxidation of the electron rich aromatic system.



203 **204** **177**

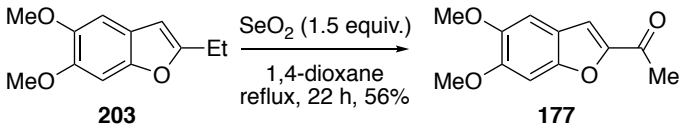
Scheme 146: Attempted synthesis of caleprunin B *via* Dess-Martin oxidation

Next, using SeO_2 but heating under reflux from the beginning resulted in complete consumption of the starting material in 3 h, giving a 1.2:1 mixture of **184** and **157** (Scheme 147). The crude mixture was submitted to a Swern oxidation conditions which gave caleprunin B (**157**) in 20% yield over the two-steps.



Scheme 147: Attempted synthesis of caleprunin B *via* Swern oxidation

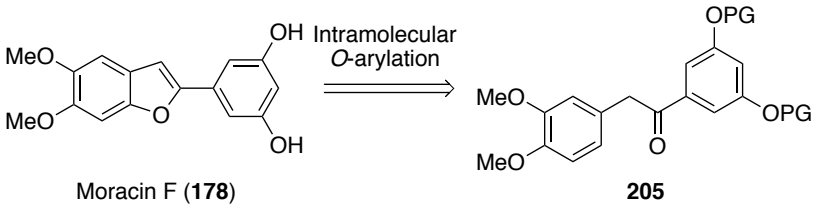
Finally, it was found that treating benzo[*b*]furan **203** with SeO_2 (1.5 equiv.) and simply extending the reaction time to 22 h under reflux, allowed for full conversion to ketone **177**, by way of intermediate alcohol **204** (Scheme 148). These conditions gave caleprunin B (**177**) in 56% yield, completing the total synthesis.



Scheme 148: Allylic oxidation of benzo[*b*]furan 203

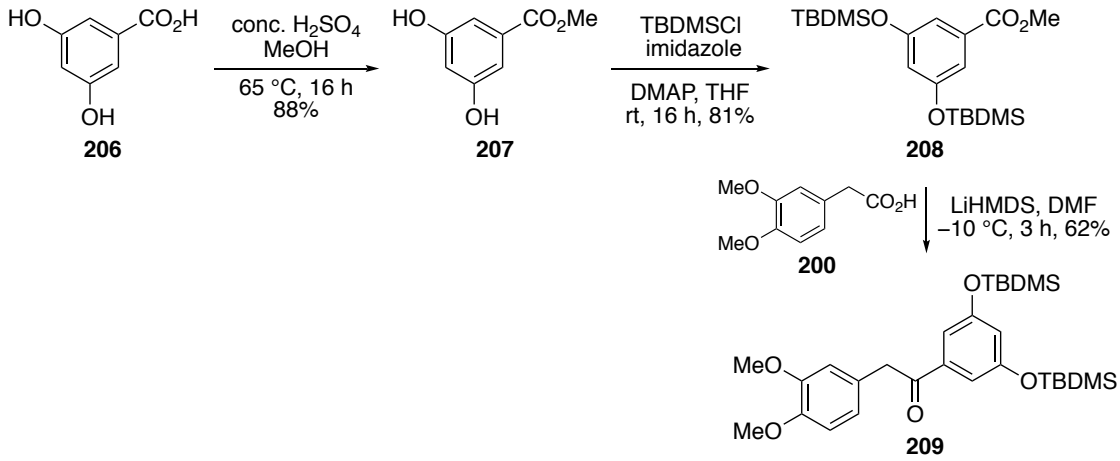
2.4.8 Total Synthesis of Moracin F

Moracin F (**178**), part of the larger family of moracin natural products, was first isolated from acetone extracts of mulberry shoots infected with *Fusarium solani* and has demonstrated promising antifungal activity.[375,376] The only known total synthesis of moracin F was reported by Jun and co-workers who developed a diversity-orientated method with four different approaches employed as key steps.[377] It was proposed that the one-pot iodination and *O*-arylation process could be applied to ketone **205**, for the rapid and efficient synthesis of moracin F (Scheme 149).



Scheme 149: Proposed synthesis of moracin F using iron- and copper-catalysed one-pot process

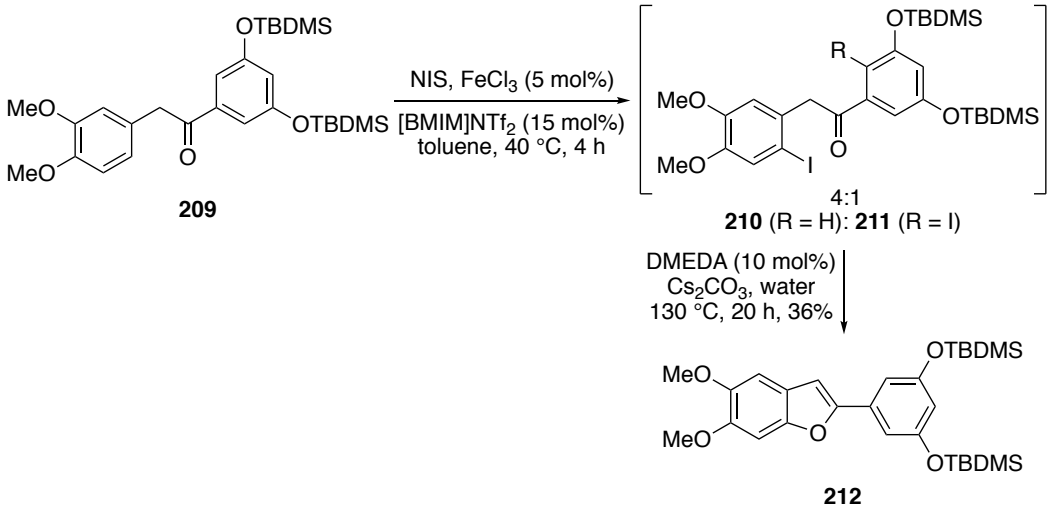
To begin this synthesis, 3,5-dihydroxyphenol (**206**) was converted to the corresponding methyl ester **207** in 88% yield using catalytic quantities of concentrated sulfuric acid in methanol under reflux (Scheme 150). The hydroxyl groups were protected using TBDMSCl under standard conditions and gave **208** in 81% yield. The Claisen condensation of ester **208** with carboxylic acid **200** using LiHMDS, gave arylketone **209** in 62% yield.



Scheme 150: Synthesis of TBDMS protected ketone 209

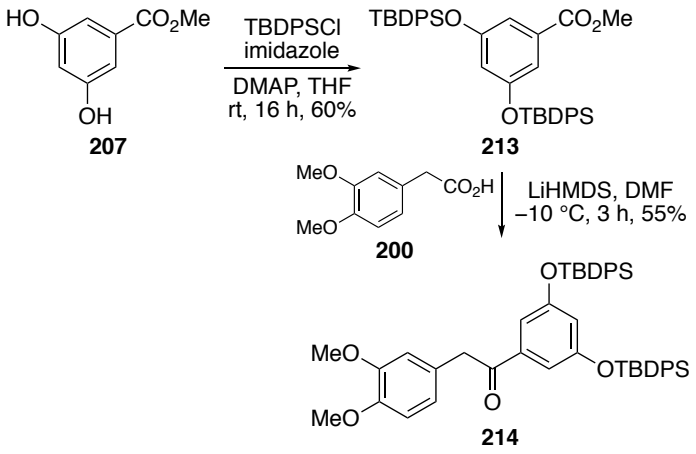
Cyclisation of arylketone **209** was then investigated using the optimal one-pot process for arylketones, specifically the use of iron(III) chloride for activation and copper residues for the cyclisation step. Initially, arylketone **209** was reacted with NIS using $Fe(NTf_2)_3$ (5 mol%) at 40 °C for 4 h (Scheme 151). Analysis of the ^1H NMR spectrum of the crude reaction mixture revealed a 4:1 ratio of desired mono-iodinated regioisomer **210** and di-iodinated material **211**. The minor component of the mixture displayed two doublets with a 2.5 Hz *meta* coupling constant, showing that iodination had occurred *para* to one of the silyl ether groups. In addition, a mass ion equal to 791, corresponding to di-iodinated compound (**211**) plus a sodium ion, was detected by electrospray mass spectrometry analysis of the crude reaction mixture. Despite the formation of two compounds, the reaction mixture was then submitted to the cross-coupling step, catalysed by the trace copper impurities present in the iron(III) catalyst. This resulted in the formation of benzo[*b*]furan **212** in only 36% yield. Alongside the selectivity issues experienced in the iodination step, the low yield was attributed to some mono-deprotection of the silyl ether. Attempts to prevent poly-iodination of ketone **209** by the reduction of the catalytic loading of

iron(III) triflimide to 2.5 mol% and a shorter reaction time of 3 h, resulted in no change to the product ratio and did not lead to an improvement in the yield of **212**.



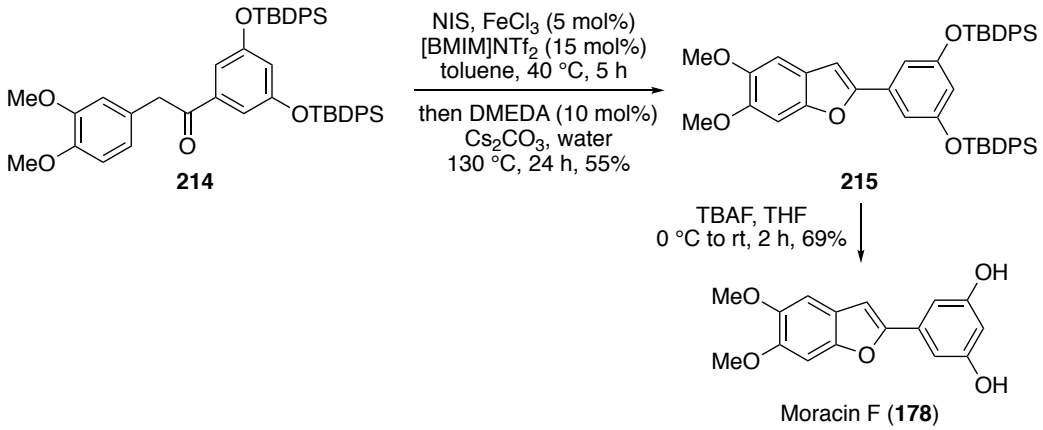
Scheme 151: Synthesis of benzo[*b*]furan 212 using TBDMS protecting groups

To overcome these selectivity and stability issues, a bulkier and less labile silyl protecting group, the TBDPS ether was used instead. To synthesise the required ketone substrate, methyl 3,5-dihydoxybenzoate (**207**) was reacted with TBDPSCl in the presence of imidazole and catalytic quantities of DMAP, which gave protected ester **213** in 60% yield (Scheme 152). A Claisen condensation between 3,4-dimethoxyphenylacetic acid (**200**) and ester **213**, followed by low temperature decarboxylation gave aryl ketone **214** in 55% yield.



Scheme 152: Synthesis of TBDPS-protected arylketone 214

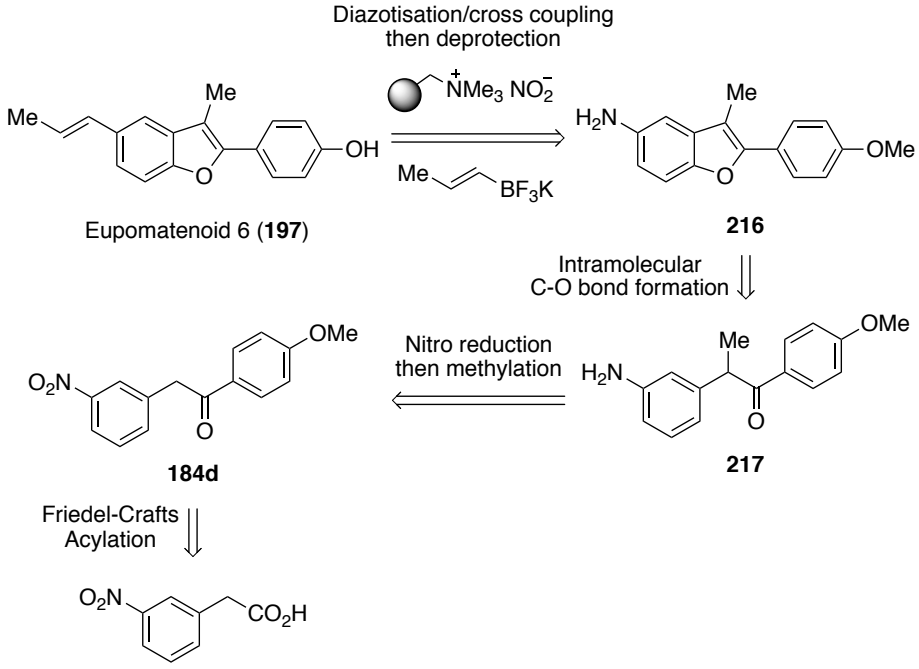
The one-pot process was then performed using arylketone **214** (Scheme 153). The iodination step was catalysed using iron(III) chloride (5 mol%, 99.9% purity) and [BMIM]NTf_2 (15 mol%), and was complete in 5 h at 40 °C. No iodination was observed of the sterically congested TBDPS-protected 3,5-disubstitued aryl ring, with reaction occurring exclusively at the C-6 position, *para* to the methoxy group. The following *O*-arylation was catalysed by the trace copper salts, assisted by DMEDA (10 mol%), and gave benzo[*b*]furan **215** in 55% yield. The total synthesis was completed with TBAF mediated removal of the silyl protecting groups, which gave moracin F (**178**) in 69% yield.



Scheme 153: Final steps in the synthesis of moracin F

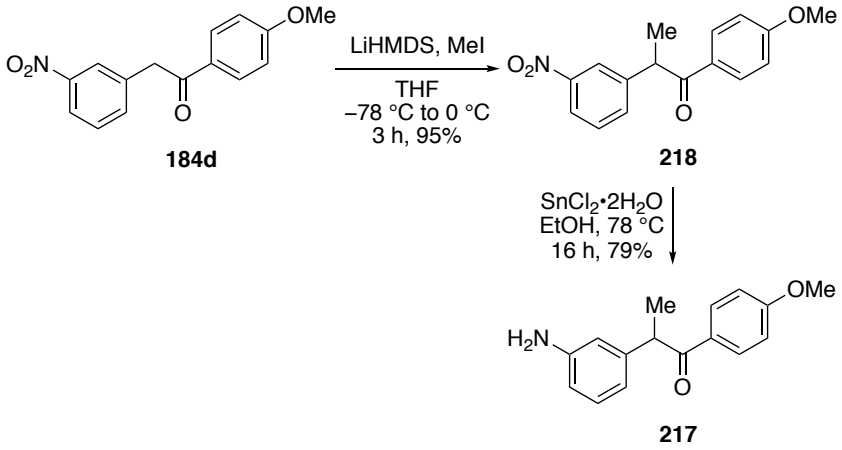
2.4.9 Attempted Synthesis of Eupomatenoid 6

The next target natural product containing the benzo[*b*]furan scaffold was eupomatenoid 6, a neolignan isolated from several plant species including *Piper decurrens*.[378,379] A previous five-step synthesis of eupomatenoid 6 used a [3,3]-sigmatropic rearrangement of an aryl oxime ether, derived from a simple aryloxyamine as the key step for the construction of the 2-arylbenzo[*b*]furan core.[380] The planned retrosynthesis of this project is shown in Scheme 154. This strategy involved the conversion of aniline **216** into the corresponding diazonium salt and then the employment of this for a cross-coupling reaction with a *trans*-propenyltrifluoroborate potassium salt. Aniline **216** could be synthesised from α-methyl phenyl ketone **217** using the one-pot iron(III)-catalysed iodination/copper(I)-catalysed intramolecular *O*-arylation, with the amino group serving as a directing group. Ketone **217** could be synthesised in two-steps from **184b** by methylation, followed by reduction of the nitro functionality.



Scheme 154: Retrosynthesis of eupomatenoid 6 (197)

Ketone **184d**, previously synthesised using a Friedel-Crafts acylation with 3-nitrophenylacetic acid and anisole, was methylated using LiHMDS and methyl iodide, which gave **218** in 95% yield (Scheme 155). Tin dichloride was then used for the chemoselective reduction of the nitro group. This gave aniline **217** in 79% yield.

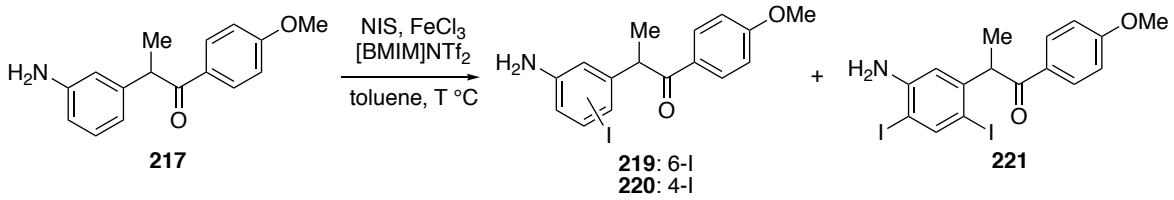


Scheme 155: Synthesis of α-methylketone 217

The key one-pot iron(III)-catalysed iodination and copper-catalysed C–O bond forming process was investigated using α-methylketone **197** (Table 13). Treatment of **217** with NIS, iron(III) chloride (5 mol%) and [BMIM]NTf_2 (15 mol%) at 40 °C resulted in the formation of the 6-iodo regioisomer, **219** and the di-iodinated

compound, **221** in a 1.3:1 ratio (entry 1). The reaction conditions were optimised to minimise di-iodination of the very active aniline ring of **217**. Reduction of the reaction temperature had no effect upon the ratio of **219** and **221** (entry 2). To slow the rate of reaction, the catalyst loading of $FeCl_3$ was reduced to 2.5 mol% however, this only led to a marginal decrease in the observed di-iodination, with **219** and **221** obtained in a 2:1 ratio (entry 3). The reaction was repeated but instead, the addition of reagents was performed at −10 °C and warmed to room temperature over 2 h. This resulted in the formation of the desired mono-regioisomer **219** and di-iodinated compound **221** in a 2.6:1 ratio (entry 4). As this aniline substrate was very active towards electrophilic aromatic substitution, the reaction was carried out without the Lewis acid catalyst. This prevented the formation of the di-iodinated compound however, the slower reaction led to the formation of a mixture of desired 6-iodo regioisomer **219** and undesired 4-regioisomer **220** in a 1.4:1 ratio (entry 5). It was clear that the Lewis acid catalyst was essential to increase the reaction rate and avoid the formation of the undesired 4-iodo regioisomer. The challenge now was to optimise the reaction conditions to achieve a reaction rate which, while not too slow, as to allow for formation of the undesired regioisomer, would not be too fast and result in the formation of di-iodinated compound **221**. In an attempt to slow the reaction, iron(III) chloride (2.5 mol%) and [BMIM]NTf_2 (7.5 mol%) were used and the reaction was stirred at −20 °C for 2 h. After this time, there was only 55% conversion of the starting material and a 10:1 ratio of desired compound **219** and di-iodinated compound **221**. The reaction was warmed to room temperature and stirred for a further 2 h. However, this led to increased formation of both the 4-iodo and di-iodinated and gave compounds **219**, **220** and **221** in 6:1:1.4 ratio (entry 6). Finally, by using $FeCl_3$ (5 mol%) and performing the reaction at −20 °C for 5 h, 75% conversion of the starting material was observed. This gave a 15:1 mixture of desired 6-iodo regioisomer **219** and the di-iodinated compound **221** (entry 7).

Table 13: Iodination of aryl ketone 217

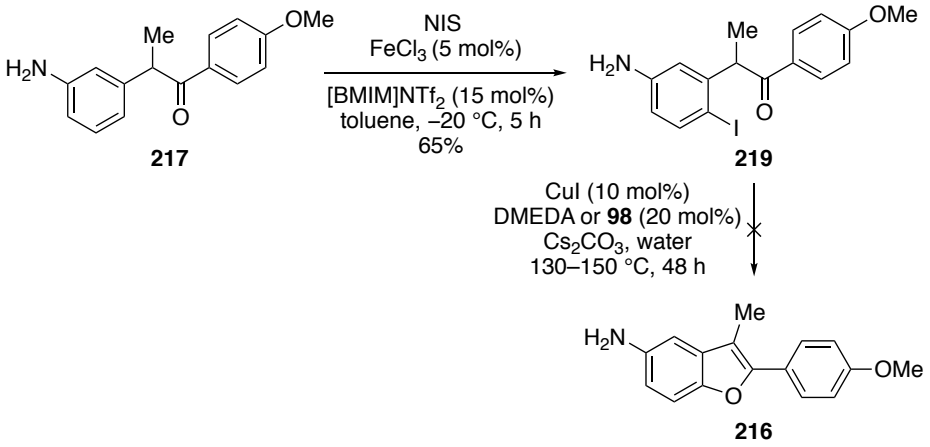


217 **219**: 6-I **220**: 4-I **221**

Entry	$FeCl_3$ (mol%)	[BMIM]NTf_2 (mol%)	Temperature (°C)	Time (h)	Ratio[a]		
					219	**220**	**221**
1	5	15	40	4	1.3	n/a	1
2	5	15	rt	2	1.3	n/a	1
3	2.5	7.5	40	2	2	n/a	1
4	2.5	7.5	−10 to rt	2	2.6	n/a	1
5	n/a	n/a	−10 to rt	16	1.4	1	n/a
6	2.5	7.5	−20 to rt	4	6	1	1.4
7	5	15	−20	5	15	n/a	1

[a]Determined using ^{1}H NMR spectroscopy

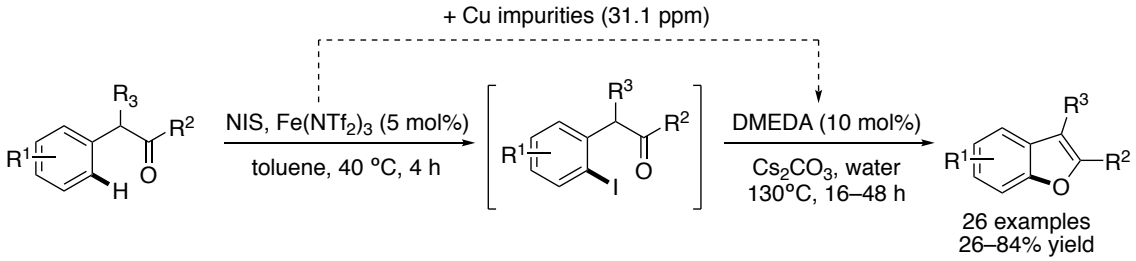
Using these optimised iodination conditions (−20 °C for 5 h), allowed the isolation of aryl iodide **219** in 65% yield (Scheme 156). Next, the cyclisation was attempted using copper at ppm loadings and DMEDA (10 mol%). However, this resulted in no conversion from the aryl iodide intermediate, even at 150 °C. Using CuI (10 mol%) and *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**98**) (20 mol%) for this more difficult cyclisation did not improve the outcome and only iodinated intermediate **219** was recovered. It was proposed that the presence of a methyl group at the α-position of arylketone **219** did not allow for the cyclisation to occur due to steric hindrance. In addition, electron donation from the *para*-amino functionality increases the electron density of the C–I bond and hence, makes oxidative addition of the Cu(I)-complex a higher energy process, hindering the cyclisation. Due to the difficulty of this cyclisation, the total synthesis of eupomatenoid 6 was not pursued any further.



Scheme 156: Attempted cyclisation of aryl iodide 219

2.4.10 Conclusions

New one-pot processes for the synthesis of benzo[*b*]furans directly from 1-aryl and 1-alkylketones were developed using non-precious, earth-abundant metals to catalyse both the C–H iodination step and then the intramolecular *O*-arylation step (Scheme 157). It was shown that both steps could be catalysed by a single iron salt, iron(III) nitrate nonahydrate, in a tandem catalytic process. It was also demonstrated that the process was more efficient when using a copper catalyst, at either ppm or 10 mol% loading, in combination with an ancillary ligand which led to the synthesis of a wide range of electron rich benzo[*b*]furan analogues. The electronic limitation for the synthesis of benzo[*b*]furans was investigated with a weakly activating methyl substituent. This substrate required harsher conditions and resulted in the formation of 4-iodo and 6-iodo regioisomers during the activation process. The *O*-cyclisation was then performed in a separate step to give the benzo[*b*]furan in 26% yield. As well as the gram-scale synthesis of corsifuran C, this methodology was then employed as the key step, for the total synthesis of several natural products including moracin F and caleprunin B.



Scheme 157: One-Pot, Two-Step Synthesis of Benzo[*b*]furans

2.5 Synthesis of 2-Substituted Benzoxazoles and Benzothiazoles

2.5.1 Introduction

Benzoxazoles and benzothiazoles are important structural motifs with a wide range of applications throughout medicinal chemistry[381–383] and material science.[384,385] 2-Substituted analogues in particular have proven to be important pharmacophores with anticancer,[386,387] antimicrobial,[388] antiviral,[389,390] antimalarial[391] and anti-inflammatory activity previously reported.[392–394] This bioactivity arises as the benzoxazole and benzothiazole scaffold may engage in a diverse range of energetically favourable, non-covalent interactions with a range of receptors and enzymes.[395] For example, the heteroatoms within the five-membered ring can act as hydrogen bond acceptors and also allow more efficient Lewis basic coordination to metal ions. Due to the extended, aromatic and planar nature of these benzannulated systems, both π-π stacking and π-cation interactions are also possible. Among the vast range of these biologically active heterocycles, Westwell and co-workers have developed a new series of 2-arylbenzothiazoles with *in vitro* antitumour properties when measured against several lung, colon and breast cancer cell lines.[386] In particular, structure activity relationship (SAR) studies revealed that benzothiazole **222**, with a 5-fluoro substituent, has remarkable antiproliferative activity, with a GI_{50} <0.1 nM for MCF-7 and MDA 468 breast cancer cell lines (Figure 10).[396] A series of novel benzoxazole and benzothiazole analogues of amodiaquine were synthesised and their antiplasmodial activity was determined.[391] Benzothiazole compound **223** was particularly effective against a chloroquine resistant *Plasmodium falciparum* W2 strain with an IC_{50} value of 11 nM and hence, has potential for the treatment of malaria. In a study by Hwang and co-workers, several benzoxazole derivatives were designed, synthesised and examined for their anti-inflammatory effects.[392] Compound **224** was shown to effectively inhibit interferon-ɣ (IFN-ɣ), a critical inflammatory cytokine protein, and mitigate an inflammatory response induced by T-cells. Hence, **224** has the potential to be used for the treatment of chronic inflammatory bowel disease.

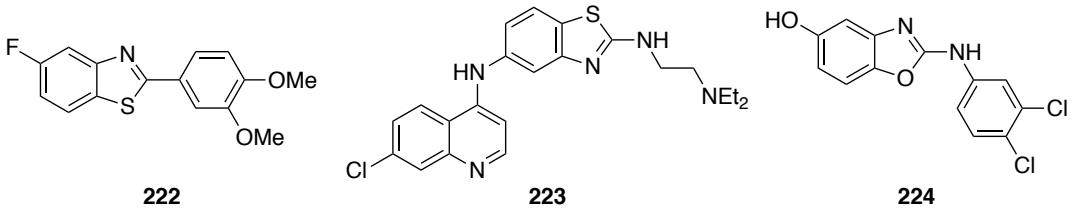
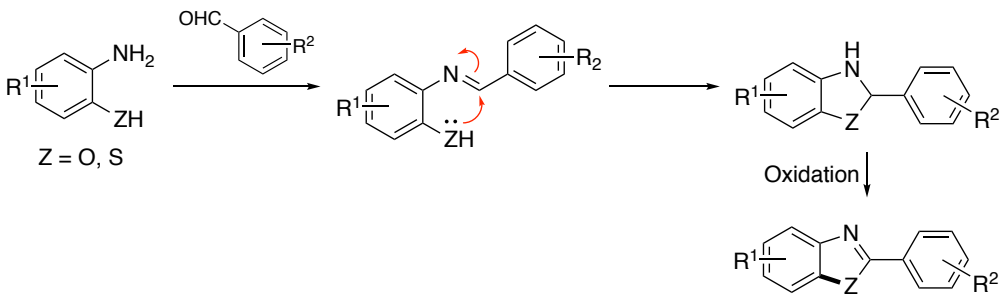


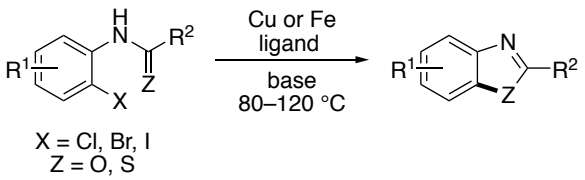
Figure 10: Biologically active benzoxazoles and benzothiazoles

Due to this biological significance, there have been numerous synthetic efforts towards the rapid and efficient preparation of these heterocyclic scaffolds.[397,398] The most common route remains cyclocondensation between 2-aminophenols/2-aminothiophenols and readily available carboxylic acids under dehydrating conditions with reagents such as polyphosphoric acid[399] and *N*,*N*-dimethylchlorosulfitemethaniminium chloride ($SOCl_2$-DMF).[400] It addition to this, it has been reported that acyl chlorides can be used in combination with Lewis acids, such as indium(III) triflate, for the synthesis of 2-substituted benzoxazoles from 2-aminophenols.[401] The use of strong mineral acids and other corrosive reagents in these processes has led to the development of alternative procedures, which employ aldehydes directly in condensation reactions with 2-aminophenols and 2-aminothiophenols (Scheme 158).[402–409] The first-step involves the formation of the phenolic or thiophenolic Schiff base, which then undergoes intramolecular nucleophilic attack and results in the formation of a benzoxazoline intermediate. This intermediate is then oxidised to the benzoxazole or benzothiazole products with a suitable oxidising agent. Protocols have been developed using strongly oxidising agents including DDQ,[402] barium manganate,[403] $PhI(OAc)_2$,[404] PCC,[405] cerium ammonium nitrate[406] or under aerobic conditions, catalysed by 4-methoxy-TEMPO.[407]



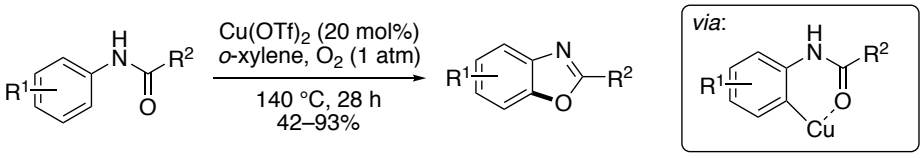
Scheme 158: Oxidative cyclisation of phenolic/thiophenolic imine intermediates

A more elegant transition metal-catalysed cross-coupling strategy has emerged for the synthesis of benzoxazoles and benzothiazoles, exploiting the C_{7a}–O/S bond disconnection. For instance, copper salts are most often used together with bidentate, chelating ligands, to catalyse intramolecular *O*- or *S*-arylation of *ortho*-haloanilides or *ortho*-halothioanilides (Scheme 159). Despite requiring elevated temperatures to overcome the energy penalty associated with oxidative addition of the carbon-halide bond, this method can produce the corresponding benzoxazoles and benzothiazoles in good yields.[410–416] Bonnamour and Bolm have shown that iron(III) chloride in combination with a diketone ligand could be used for the synthesis of benzoxazoles from *N*-haloaryl benzamides but as previously described (Chapter 2.4.1), copper impurities in the iron catalyst were most likely responsible for the observed catalytic activity.[417]



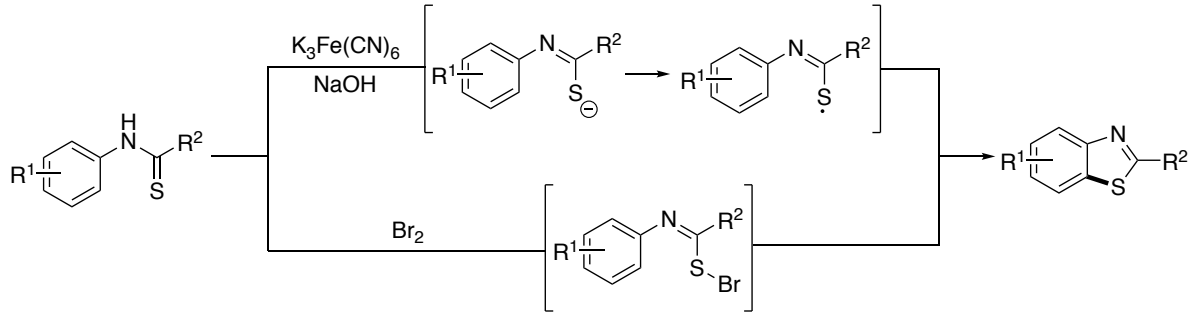
Scheme 159: Transition metal-catalysed cyclisation of 2-haloanilides and 2-halothioanilides

Influential work in the field of C–H activation was reported by the Nagasawa group in 2008 and demonstrated that benzoxazoles could be prepared directly from *N*-arylbenzamides using an oxidative, copper(II) triflate-catalysed cyclisation procedure (Scheme 160).[418,419] This methodology invokes the amide functionality of anilides to coordinate the copper catalyst and allow for activation of the *ortho*-C–H bond by directed metalation. Reductive elimination of the six-membered metallocycle then follows and can provide access to the benzoxazole scaffold in yields of up to 93%. Analogous to other copper(II)-mediated C–H functionalisation processes, molecular oxygen plays a critical role as a stoichiometric oxidant in the turnover of the catalytic cycle.[64,158] Although there is a necessity for high reaction temperatures, this highly atom economical process does not require the use of pre-functionalised halogenated starting materials and hence, avoids the production of the associated stoichiometric waste.



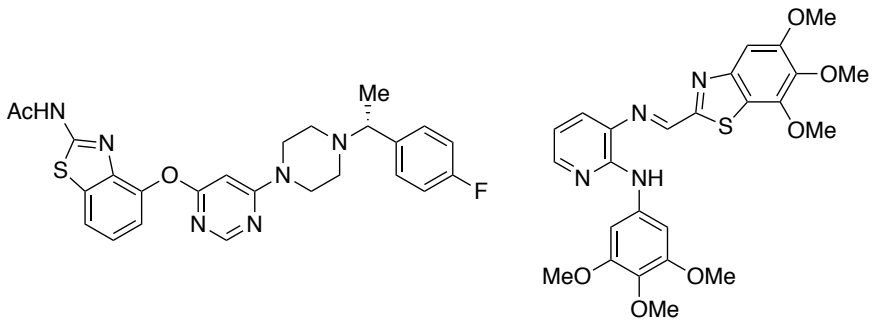
Scheme 160: Nagasawa's synthesis of benzoxazoles by C–H functionalisation

In comparison, the synthesis of benzothiazoles by oxidative cyclisation of *N*-arylthioanilides is a far more established method. First described by Jacobson in 1886, the treatment of *N*-arylthiobenzamides with potassium ferricyanide in alkaline solution was shown to result in the preparation of the corresponding benzothiazole (Scheme 161).[420] More than one hundred years later, a mechanism has been proposed by the groups of Stevens and Jackson where they indicate that potassium ferricyanide plays a role as a single electron oxidant, converting the thiolate ion to a sulfur radical which can attack the aromatic ring and form the C–S bond.[421,422] Another classical benzothiazole synthesis can be traced back to research by Hugerschoff at the turn of the 20th century.[423,424] When investigating the reaction between arylthioureas and elemental bromine in chloroform, precipitation of the cyclised 2-aminobenzothiazole heterocycle was observed. It transpired that initial activation by bromination of the sulfur atom leads to the formation of an *S*-bromide intermediate that can then undergo intermolecular electrophilic aromatic substitution. Evidence for this mechanistic pathway has since been uncovered with the observation that weakly activated or electron deficient aryl thioamides do not readily cyclise and form the benzothiazole.[425,426] In these cases, it was found that dimerisation of the starting materials occurred and thought to proceed *via* intermolecular nucleophilic attack of the *S*-bromide intermediate by the thioamide starting material.



Scheme 161: Benzothiazole synthesis by the Jacobson and Hugerschoff methods

These two simple methods have found wide applicability, particularly in medicinal chemistry for the preparation of 2-substituted benzothiazoles.[425,427–431] For example, the Hugerschoff reaction was employed in the synthesis of AMG-628 (**225**),[425] a small molecule inhibitor of the vanilloid receptor-1, while the Jacobson method has been used for the synthesis of **226**, a compound which has antimitotic properties (Figure 11).[427]



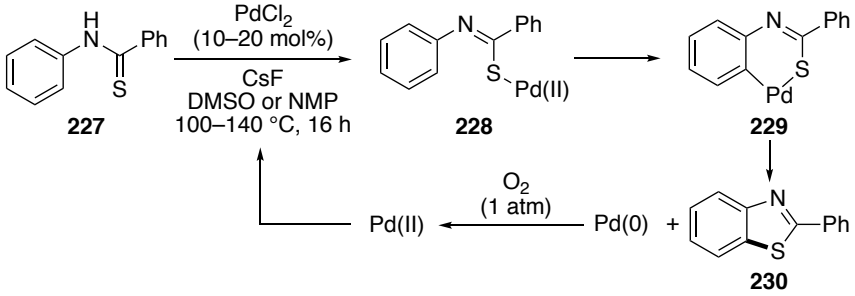
225 **226**

Figure 11: Applications of the Hugerschoff and Jacobson reactions

Since these initial findings, many similar synthetic procedures have been developed to achieve the oxidative cyclisation of *N*-arylthioanilides using reagents including the Dess-Martin periodinane,[432] NBS,[433] benzyltrimethylammonium tribromide[434] or metal species such as manganese(III) acetate.[435]

More recently, transition metal catalysts have found utility in the synthesis of benzothiazoles by efficient intramolecular C–S cross-coupling when used in combination with strong oxidants at high temperatures. The group of Doi developed an *S*-cyclisation procedure using palladium-catalysis in the presence of cesium fluoride under an oxygen atmosphere (Scheme 162).[436] The first step involves coordination of the sulfur atom of thioanilide **227** to Pd(II), leading to the formation of intermediate **228**. From this intermediate, six-membered palladacycle **229** is then formed either by σ-bond metathesis or base-assisted deprotonative metalation. The final step involves reductive elimination, whereby desired benzothiazole **230** is released and palladium(0) is generated, which is subsequently re-oxidised to Pd(II) by O_2. In general, palladium catalysis has been widely applied to achieve this oxidative C–S coupling for the synthesis of a wide range of medicinally important benzothiazoles under thermal conditions.[437–440] In a similar fashion, iron,[441] ruthenium[442] and recently nickel[443] catalysis, in conjunction with various oxidants

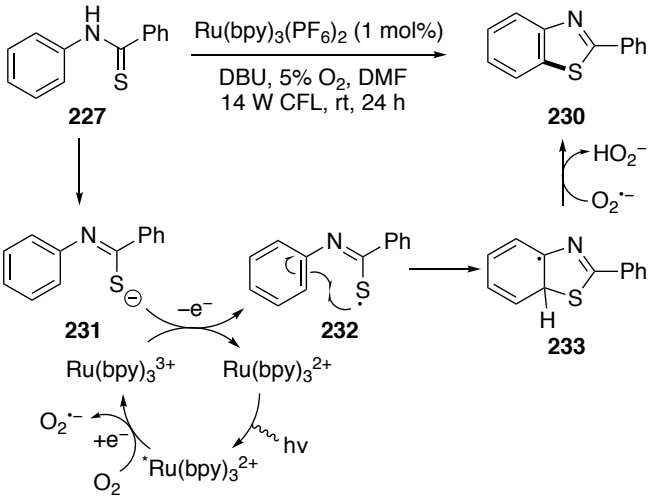
have also been utilised, allowing the transformation to be carried out at lower temperatures.



Scheme 162: Palladium-catalysed, thermal cyclisation of *N*-thioanilide 227

Related cyclisation processes under electrochemical[444,445] and organocatalytic[446] conditions have been described for the synthesis of benzothiazoles *via* C–H thiolation. Over the past decade, photoredox catalysis has developed into an extremely powerful tool, particularly in the activation and functionalisation of C–H bonds.[447] By exploiting visible light and converting it into chemical energy, reaction pathways that were previously very difficult or unattainable under thermal control can be achieved. In this regard, photoredox catalysis has been utilised in the synthesis of benzothiazoles directly from *N*-arylthiobenzamides using either transition metal[448–450] or organic photocatalysts under very mild conditions.[451,452]

One such method was reported by Li and co-workers in which they achieved room temperature C–H functionalisation of thioanilides for the synthesis of 2-substituted benzothiazoles (Scheme 163).[448] They propose that the photocatalyst, $Ru(bpy)_3^{2+}$, readily accepts a photon of visible light to generate the excited state catalyst $^{*}Ru(bpy)_3^{2+}$ which can then be oxidised by molecular oxygen, generating $Ru(bpy)_3^{3+}$ alongside the superoxide radical anion ($O_2^{\bullet-}$). Concurrently, thioanilide **227** is deprotonated with DBU to give the corresponding sulfur anion. Anion **231** is then reduced to sulfur radical species **232** through a single electron transfer by $Ru(bpy)_3^{3+}$ which regenerates the $Ru(bpy)_3^{2+}$, completing the photoredox catalytic cycle. Next, a 1,5-homolytic sulfur radical cyclisation produces aryl radical **233** while constructing the key C–S bond. Hydrogen atom transfer to the superoxide species instigates the rearomatisation of **233** and provides benzothiazole product **230** alongside the hydroperoxyl anion.

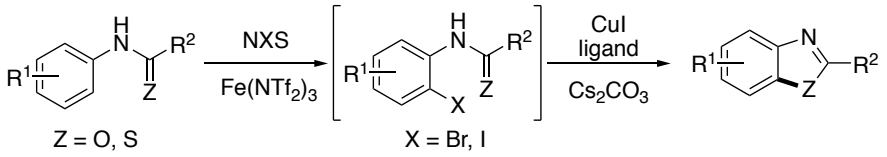


Scheme 163: Photoredox catalysis in the synthesis of benzothiazoles

In a similar process, Lang and co-workers have developed a method which utilises visible-light and TEMPO as an oxidant to promote C–H thiolation by a reverse hydrogen atom transfer (RHAT).[453] Although operating through a comparable mechanism to the above mentioned photoredox procedures *via* the generation of sulfur radicals, this method avoids the use of expensive transition metal photocatalysts and occurs under base-free conditions at room temperature.

2.5.2 Project Aims

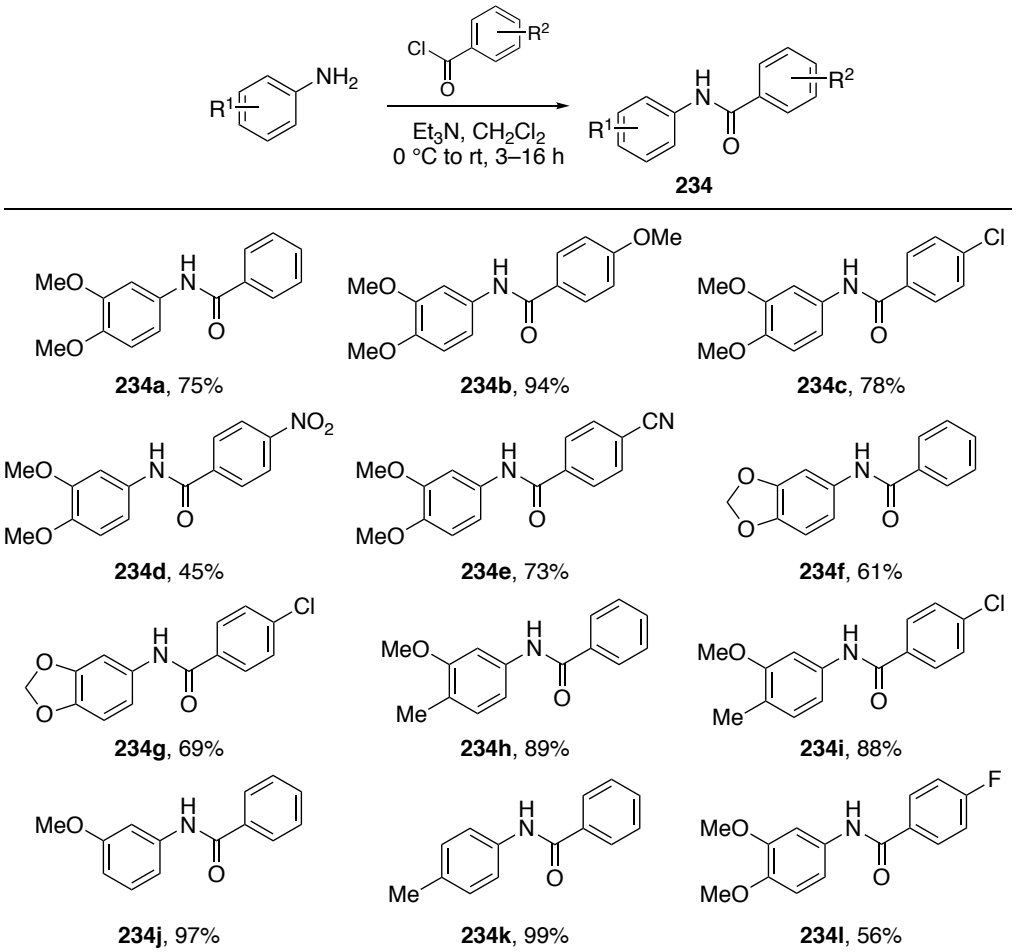
Following the successful development of one-pot processes for the synthesis of indolines, 2,3-dihydrobenzofurans and benzo[*b*]furans, the main aim of this project was the application of a similar strategy for the preparation of a wide range of 2-arylbenzoxazoles and 2-arylbenzothiazoles (Scheme 164). This one-pot method would again employ the regioselective iron(III)-catalysed halogenation, applied to a series of *N*-arylbenzamides, followed by copper(I)-catalysed *O*-heterocyclisation to allow the synthesis of a small library of 2-arylbenzoxazoles. Similarly, it was planned to apply this one-pot procedure to a series of *N*-arylthiobenzamides for the preparation of benzothiazoles through C–S bond formation. The final aim of this project was to use these new one-pot methods for the synthesis of biologically active 2-arybenzoxazoles and 2-arylbenzothiazoles.



Scheme 164: Proposed one-pot synthesis of benzoxazoles and benzothiazoles

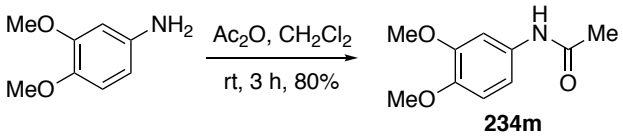
2.5.3 Synthesis of *N*-Arylbenzamide and *N*-Arylthiobenzamide Substrates

Synthetic work began with the preparation of a series of *N*-arylbenzamides by the reaction of anilines with aryl acid chlorides under standard conditions (Scheme 165). This project, particularly the synthesis of *N*-arylbenzamides and the reaction optimisation was carried out with Vincenzo Mirco Abbinante, a visiting PhD student from the University of Insurbia, Italy. It should be noted *N*-arylbenzamides **234a**, **234b** and **234k** were synthesised by Vincenzo Abbinante. This was generally a high yielding, efficient reaction and gave *N*-arybenzamides in up to 99% yield. Only 4-nitro and 4-fluoro analogues, **234d** and **234l**, were isolated in moderate yields owing to their poor solubility in dichloromethane, precipitating from solution as they formed.



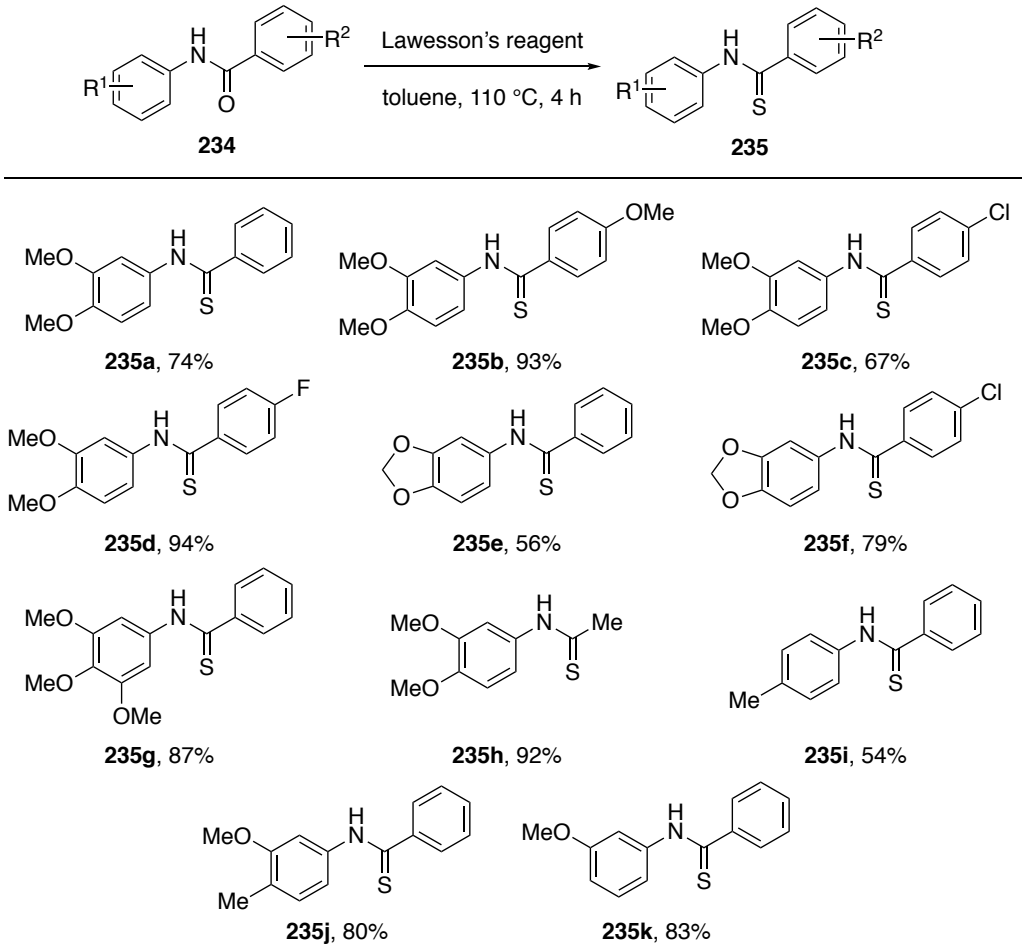
Scheme 165: Synthesis of *N*-arylbenzamides 234a–234l

Acetamide analogue **234m** was synthesised in 80% yield by reaction of 3,4-dimethoxyaniline with acetic anhydride at room temperature (Scheme 166).



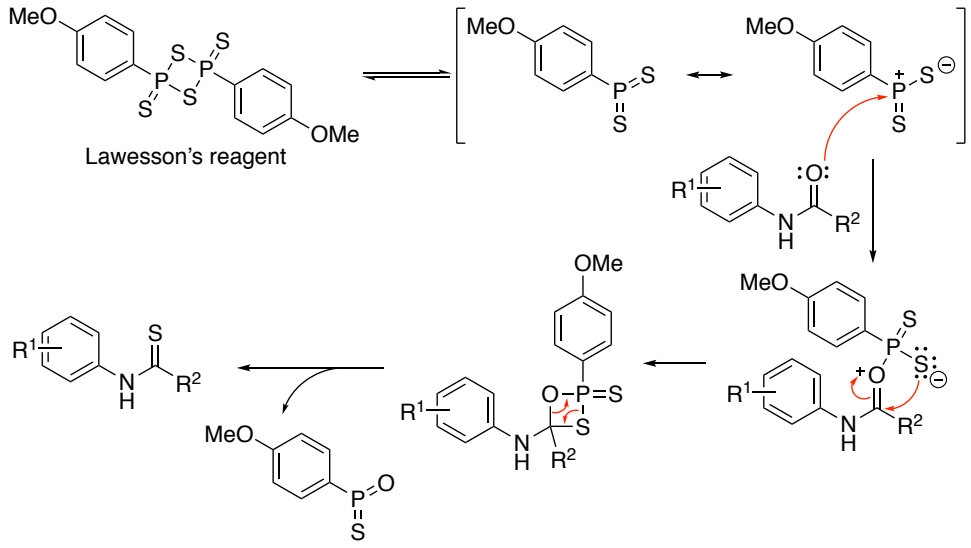
Scheme 166: Acetylation of 3,4-dimethoxyaniline

Next, a range of *N*-arylthioamides **235a**–**235k** were prepared by reaction of Lawesson's reagent with the small library of *N*-arylbenzamides (Scheme 167).[454] This thionation reaction was very efficient and gave the *N*-arylthioamides in excellent yields of up to 94%, with the exception of compound **235e** and **235i**. The more modest yields observed for these compounds can be attributed to the difficultly in separating these from by-products generated by the decomposition of Lawesson's reagent.



Scheme 167: Synthesis of thiobenzamides 235a–235k using Lawesson's reagent

The mechanism for the thionation of amides using Lawesson's reagent is shown in scheme 168.[455,456] In solution, Lawesson's reagent is in equilibrium with a more reactive dithiophosphine ylide, which reacts with the carbonyl oxygen of the amide substrate.[457] Attack of the sulfur nucleophile on the activated carbonyl carbon results in the formation of a thiaoxaphosphetane intermediate. This 4-membered ring decomposes to give the desired thioketone, thermodynamically driven by the formation of a stable P=O bond of the aryl phosphorus by-product, comparable to the Wittig reaction.

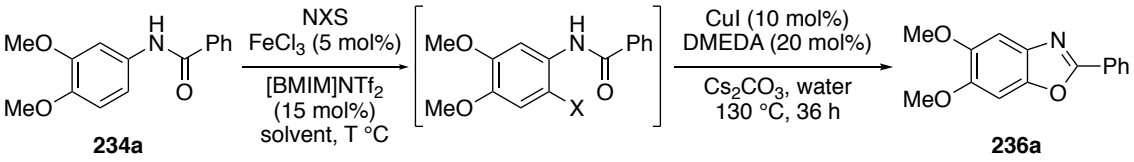


Scheme 168: Mechanism of thiolation of amides with Lawesson's reagent

2.5.4 One-Pot Synthesis of 2-Substituted Benzoxazoles

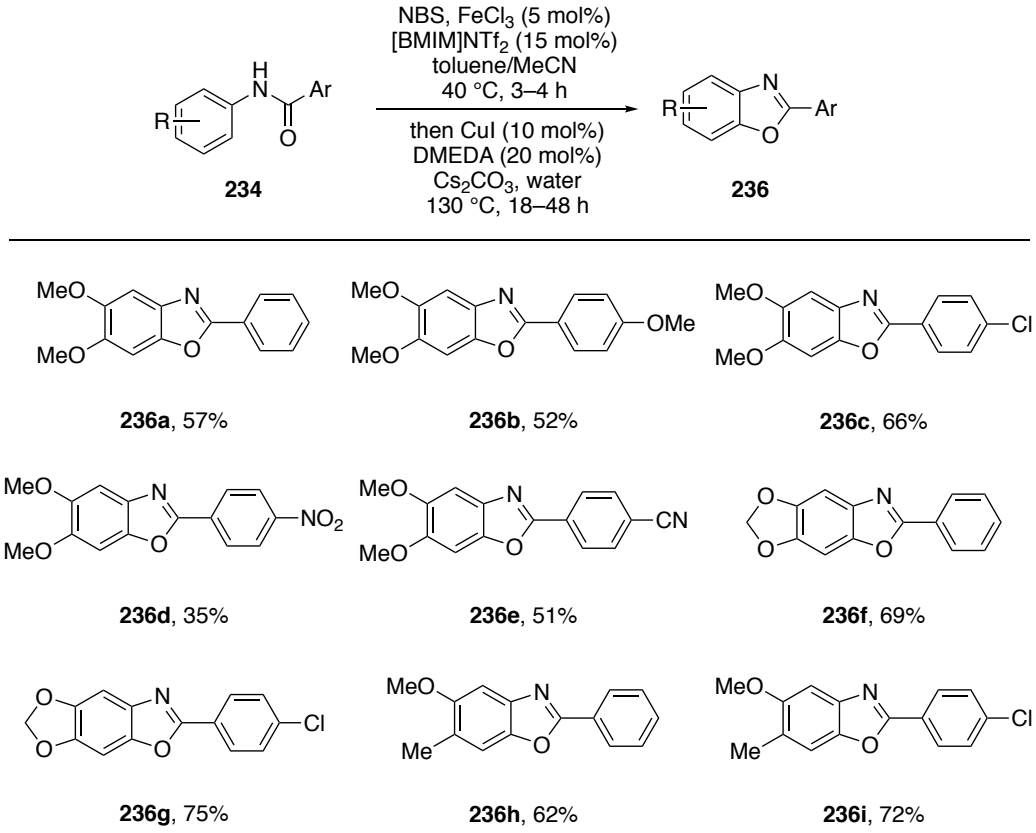
N-(3,4-Dimethoxyphenyl)benzamide (**234a**) was initially used to investigate the development of the one-pot process (Table 14). Entries 1–4 of the optimisation study were carried out by Vincenzo Abbinante. Firstly, iron(III) chloride (5 mol%) and the ionic liquid [BMIM]NTf_2 (15 mol%) were used for the activation of NIS and subsequent reaction with **234a** which resulted in a slow iodination (8 h). *O*-Cyclisation under standard conditions, using copper iodide (10 mol%) and DMEDA (20 mol%), then gave benzoxazole **236a** in 36% yield over the two-steps (entry 1). The slow reaction of benzamide **234a** with NIS was thought to be due to steric hindrance therefore, NBS, a less sterically encumbered reagent was next investigated. With NBS, halogenation was found to be faster overall and led to an improved yield of **236a** (entry 2). It was proposed that the relatively poor solubility of amide **234a** in toluene was responsible for the low isolated yield therefore, alternative solvents were sought in order to increase the efficiency of the bromination step. When using DMF, the reaction was more efficient overall, however difficulties in the isolation of final product **236a** resulted in a lower yield (entry 3). By using a mixture of toluene and THF (5:1) and an increased reaction temperature of 40 °C, led to a 51% yield over the two-steps (entry 4). The use of toluene and acetonitrile as co-solvents in a 5:1 ratio, resulted in complete conversion to the brominated intermediate. Following copper-catalysed cyclisation, benzoxazole **236a** was isolated in 57% yield (entry 5).

Table 14: Optimisation of the one-pot halogenation and *O*-cyclisation of 234a



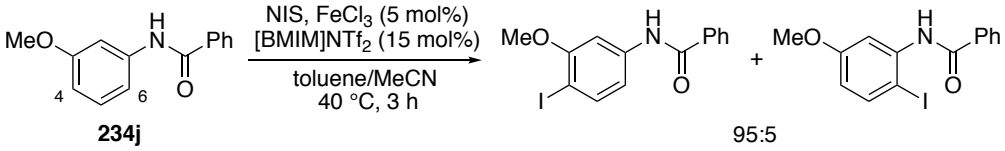
Entry	NXS	Solvent	Temp (°C)	Time (h)	Yield (%)
1	NIS	toluene	rt	8	36
2	NBS	toluene	rt	4	46
3	NBS	DMF	rt	4	40
4	NBS	toluene/THF	40	4	51
5	NBS	toluene/MeCN	40	4	57

With the optimised conditions for the bromination and *O*-cyclisation in hand, the scope of the transformation was investigated with a range of *N*-arylbenzamides **234a**–**234k** (Scheme 169). From previous chapters, it is clear that electron-rich arenes with activating groups are vital for the iron(III) triflimide-catalysed electrophilic aromatic halogenation to occur. *N*-(3,4-Dimethoxyphenyl)benzamides (**234a**–**234e**), featuring both electron-rich and electron-deficient 2-aryl systems, and *N*-(3,4-methylenedioxyphenyl)benzamide (**234f**) were investigated as substrates for the one-pot process and gave benzoxazoles **236a**–**236f** in 45–69% yield. Following this, the methodology was then applied to the synthesis of benzoxazole **236g**, a compound shown to possess potent activity as a potential upregulator of utrophin in a predictive screening assay.[399,458] Increased levels of this protein has been linked with slower disease progression in patients with Duchenne muscular dystrophy.[459,460] Starting from 4-chloro-*N*-(3,4-methylenedioxyphenyl)benzamide (**234g**), regioselective bromination followed by copper(I)-catalysed C–O cross-coupling gave **236g** in 75% yield. Benzamides **234h** and **234i**, with slightly less electron-rich aryl systems, were found to be successful substrates for the bromination/*O*-heterocyclisation process and gave 2-arylbenzoxazoles **236h** and **236i** in 62% and 72% yield, respectively.



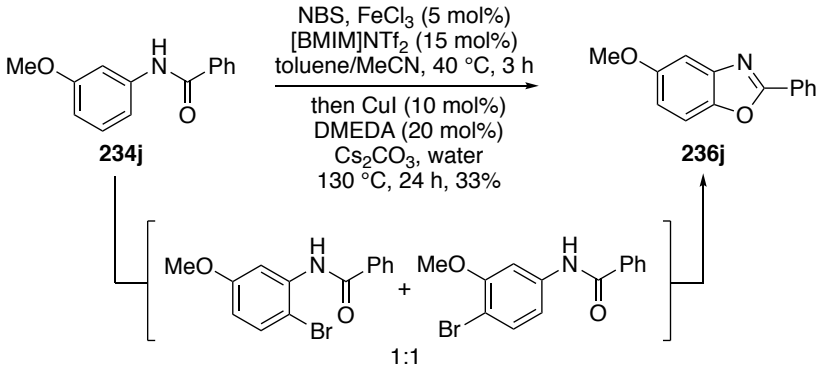
Scheme 169: Scope of the one-pot synthesis of benzoxazoles

While developing this methodology, certain limitations were discovered with some classes of *N*-arylbenzamide substrates. In the initial stages of this project, *N*-(3-methoxyphenyl)benzamide (**234j**) was reacted with NIS and iron(III) triflimide under the standard halogenation conditions (40 °C for 3 h), which led to full conversion of the starting material and a 95:5 mixture of regioisomers (Scheme 170). However, submitting this mixture to the copper(I)-catalysed *O*-cyclisation step failed to give any product. On closer inspection of the ^{1}H NMR spectra of the mixture of aryl iodide regioisomers, as well as using 2D NMR experiments, the 4-iodo regioisomer was found to be the major component. It was believed that the tethered benzamide side chain sterically shields the C-6 position and prevents access of the large iodine atom. In addition, a less significant factor which may contribute to the observed regioselectivity is the electronic directing effect exerted by the nitrogen functionality. This slightly increases the orbital coefficient at the C-4 position. Taken together, these steric and electronic factors result in almost exclusive iodination at the C-4 position.



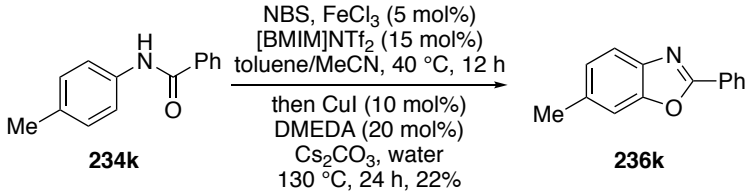
Scheme 170: Iodination of *N*-(3-methoxyphenyl)benzamide (234j)

Next, *N*-(3-methoxyphenyl)benzamide (**234j**) was instead reacted with NBS and iron(III) triflimide (Scheme 171). It was envisioned that the smaller atomic radius of the bromine atom would allow access to the hindered C-6 position and improve the regioselectivity of the halogenation step. This led to a better outcome, to an extent, with the formation of the 4- and 6-brominated regioisomers in a 1:1 ratio. This mixture was then submitted to the standard copper(I)-catalysed cyclisation which completed the one-pot process and gave benzoxazole **236j** in 33% yield.



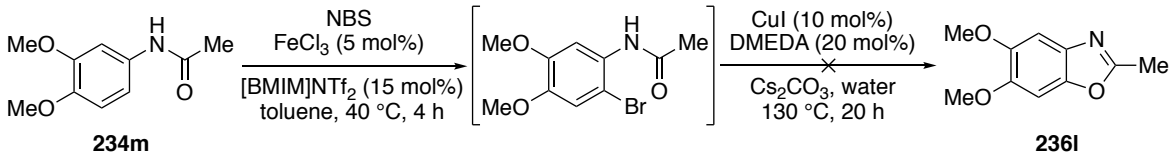
Scheme 171: Bromination and *O*-cyclisation of *N*-(3-methoxyphenyl)benzamide (234j)

Another limitation was noted, by Vincenzo Abbinante, when using *N*-(4-methylphenyl)benzamide (**234k**) as a substrate in the one-pot process (Scheme 172). As a consequence of the weakly activated aryl system, with only a mild inductive effect of the 4-methyl substituent, the electrophilic aromatic bromination step required a reaction temperature of 40 °C for 12 h. Benzoxazole **236k** was isolated in only 22% yield as a result of this extended reaction time.



Scheme 172: Synthesis of benzoxazole 236k

Alongside the synthesis of 2-arylbenoxazoles, the preparation of 2-alkyl analogues was also investigated as part of this project. The reaction of *N*-(3,4-dimethoxyphenyl)acetamide (**234m**) with NBS under the standard iron(III)-catalysed halogenation conditions resulted in full conversion to the 6-bromo regioisomer of the brominated intermediate (Scheme 173). Next, the attempted cyclisation of this brominated intermediate with copper(I) iodide and DMEDA at 130 °C for 20 h, resulted in only traces of 2-methylbenzoxazole **236l**. Instead, the ^{1}H NMR spectra of the crude material revealed almost exclusively starting material, *N*-(3,4-dimethoxyphenyl)acetamide (**234m**). This would suggest that despite oxidative addition of the aryl bromide, the acetamide functionality does not ligate to the copper metal centre, leaving protodecupration as the main reaction pathway.



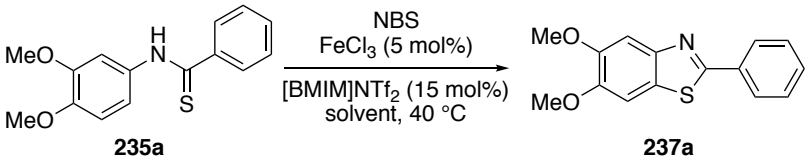
Scheme 173: Attempted synthesis of 2-alkylbenzoxazole 236l

2.5.5 Synthesis of 2-Substituted Benzothiazoles

The bromination and heterocyclisation one-pot process was next explored for the synthesis of 2-substituted benzothiazoles. Firstly, *N*-(3,4-dimethoxyphenyl)thiobenzamide (**235a**) was reacted with NBS in the presence of iron(III) triflimide using the previously developed halogenation conditions in toluene and acetonitrile (5:1) (Table 15). Investigation of the crude reaction mixture after 4 h, using ^{1}H NMR spectroscopy, revealed direct formation of benzothiazole **237a**, in contrast to the anticipated aryl ring bromination. From this, benzothiazole **237a** was then isolated in 39% yield (entry 1). Following this unexpected result, the reaction conditions were briefly optimised using iron(III) triflimide at 5 mol% loading. A

change of the reaction solvent to acetonitrile resulted in complete consumption of the starting material after 2 h at 40 °C and **237a** was obtained in 49% yield (entry 2). The optimal conditions for this *S*-cyclisation were found to be a 2 h reaction time at 40 °C in acetonitrile using a slight excess of NBS (1.1 equiv.). This allowed the synthesis of benzothiazole **237a** in 54% yield (entry 3).

Table 15: Direct synthesis of benzothiazole 237a from *N*-arylthiobenzamide 235a

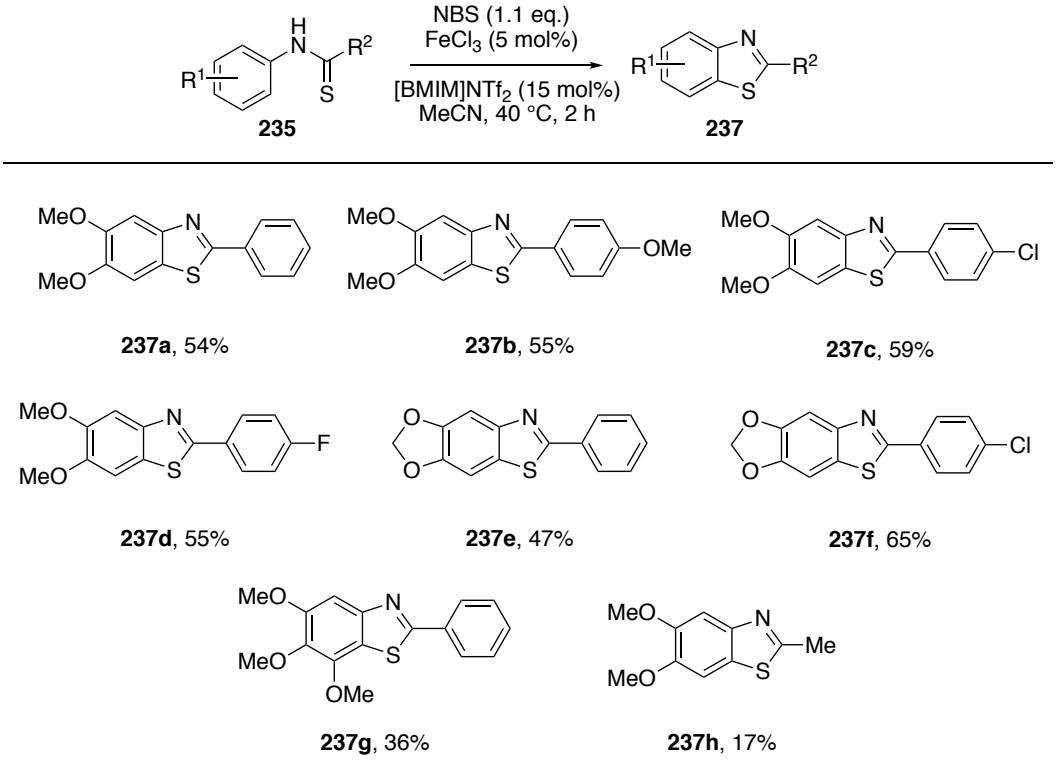


235a **237a**

Entry	NBS (equiv.)	Solvent	Temperature (°C)	Time (h)	Isolated Yield (%)
1	1.0	toluene/MeCN	40	4	39
2	1.0	MeCN	40	2	49
3	1.1	MeCN	40	2	54

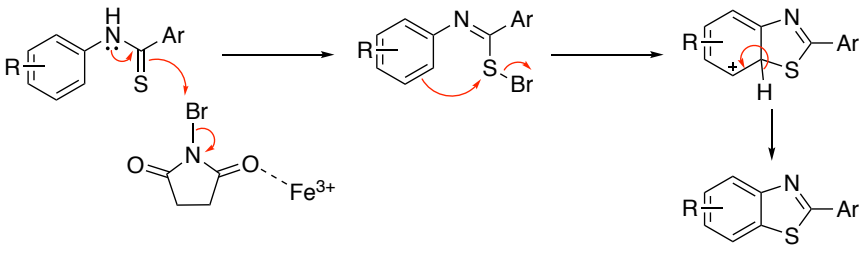
Following this short optimisation, the substrate scope of the single step transformation was investigated with a range of *N*-arylthiobenzamides **235a**–**235h** (Scheme 174). This *S*-cyclisation process gave 2-aryl-substituted benzothiazoles **237a**–**237h** in 47–65% yield. Included in this substrate scope was the synthesis of 2-(4′-fluorophenyl)-5,6-dimethoxy-1,3-benzothiazole (**237d**), a biologically active compound which binds effectively to the amyloid-beta protein and hence, is a prospective imaging agent in the diagnosis of Alzheimer's disease.[461,462] Benzothiazole **237d** was isolated in 59% yield from the single-step cyclisation of 4′-fluoro-*N*-(3,4-dimethoxyphenyl)thiobenzamide (**235d**). Several limitations were noted for this one-step *S*-cyclisation. Electron-rich trimethoxyphenyl thioamide **235g** was not an effective substrate and gave the corresponding benzothiazole **237g** in only 36% yield. As expected, the greater steric hindrance associated with the *ortho*,*ortho*-substituted aryl position of trisubstituted substrate **235g** resulted in a slower cyclisation and allowed competitive bromination of the electron-rich aromatic ring. In a similar manner, the application of thioacetamide analogue **235h** in the one-pot process gave benzothiazole in 17% yield. The low yield in this case was attributed to a less efficient cyclisation which allowed competing arene halogenation,

with a crude mixture of benzothiazole **237h** and the mono-brominated compound obtained in a 2:1 ratio.



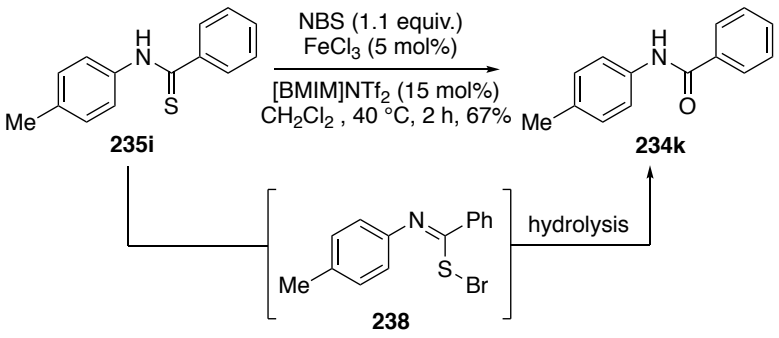
Scheme 174: Scope of the *S*-cyclisation of *N*-arylthiobenzamides

A mechanism for the benzothiazole cyclisation was proposed and is shown in scheme 175. The first step involves the *in-situ* generation of the iron(III) triflimide, which then coordinates to the carbonyl oxygen of NBS. This thiophilic iron(III)-complexed NBS species undergoes nucleophilic attack by the thioamide sulfur atom, resulting in the formation of a reactive *S*-bromide intermediate. Next, intramolecular electrophilic aromatic substitution with the pendant activated sulfur electrophile followed by re-aromatisation completes the transformation.



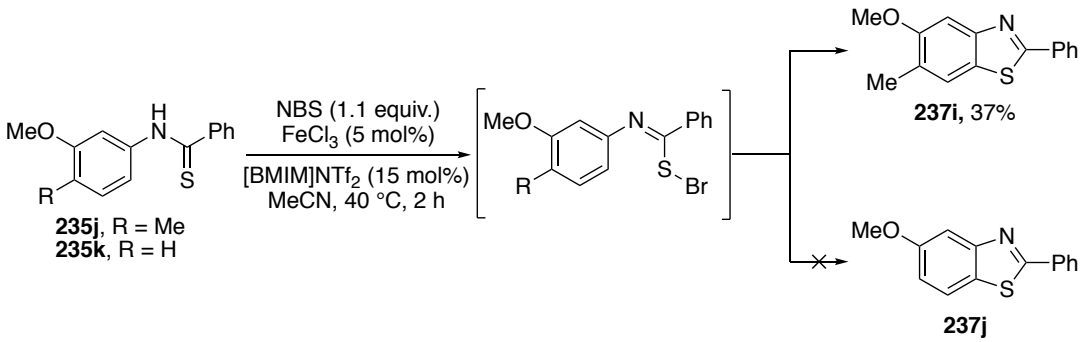
Scheme 175: Mechanism of cyclisation of *N*-arylthiobenzamides using iron(III) triflimide and NBS

Evidence for the mechanism of the *S*-cyclisation was elucidated through several experiments with less activated *N*-arylthiobenzamide substrates. Firstly, weakly-activated *N*-(4-methylphenyl)thiobenzamide **235i** was used in the single-step reaction (Scheme 176). In this instance, reaction of **235i** with the iron(III)-complexed NBS species resulted in no formation of the desired benzothiazole but instead yielded the *N*-arylbenzamide **234k** in 67% yield. This is due to the less activated aryl ring of *S*-bromide intermediate **238**, which is unable to perform intramolecular electrophilic aromatic substitution and instead, is hydrolysed upon aqueous work-up.



Scheme 176: *N*-Arylbenzamide 235i formation by hydrolysis of *S*-bromide intermediate 238

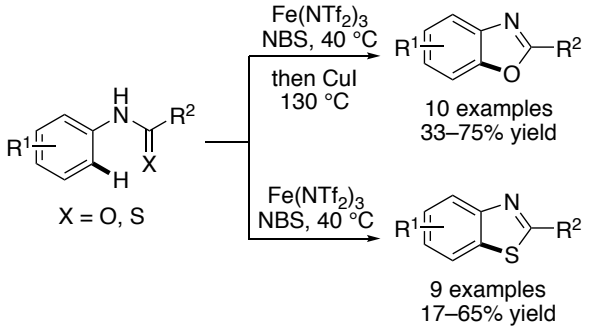
Additional evidence for this mechanism was gained with *N*-arylthiobenzamides **235j** and **235k** (Scheme 177). For example, on application of *N*-(3-methoxy-4-methylphenyl)thiobenzamide (**235j**) to the *S*-cyclisation conditions, slow electrophilic aromatic substitution led to the formation of a 4:1 mixture of benzothiazole **237i** and *N*-(3-methoxy-4-methylphenyl)benzamide (**234h**), formed through hydrolysis of the *S*-bromide intermediate. Purification of this mixture by recrystallisation then allowed for the isolation of benzothiazole **237i** in 37% yield. Furthermore, when *N*-(3-methoxyphenyl)thiobenzamide (**235k**) was used, a 2.5:1 mixture of benzothiazole **237j** and a mono-brominated compound was obtained after 2 h at 40 °C. This mixture could not be separated by flash column chromatography or recrystallisation.



Scheme 177: *S*-Cyclisation with less reactive aryl systems

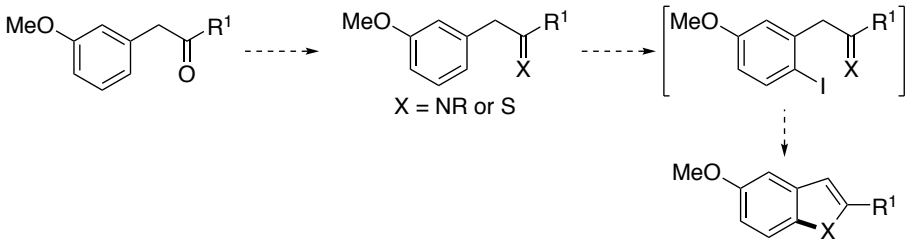
2.5.6 Conclusions and Outlook

The synthesis of 2-substituted benzoxazoles and benzothiazoles has been achieved by utilising the iron(III) triflimide-catalysed activation of NBS (Scheme 178). The first protocol involved the activation of *N*-arylbenzanilides using regioselective iron(III)-catalysed bromination followed by a copper(I)-catalysed intramolecular *O*-arylation with the benzamide side chain. The scope and limitations of the procedure were explored and allowed the synthesis of a small library of benzoxazole analogues, including a pharmaceutically relevant compound with potential therapeutic applications in the treatment of Duchenne muscular dystrophy. This one-pot, two-step synthesis of benzoxazoles is juxtaposed with the synthesis of 2-arylbenzothiazoles, which operates *via* a distinct reaction pathway under milder conditions. The reaction of *N*-arylthiobenzamides with NBS and iron(III) triflimide resulted in the isolation of the corresponding electron-rich 2-arylbenzothiazoles by direct intramolecular C–S bond formation. Control experiments indicated that this one-step *S*-cyclisation occurs *via* a reactive brominated sulfur intermediate which can undergo intramolecular electrophilic aromatic substitution, similar to the Hugerschoff reaction. Using this methodology, several functionalised benzothiazole derivatives were prepared including an antagonist of the amyloid-beta protein in patients with Alzheimer's disease.



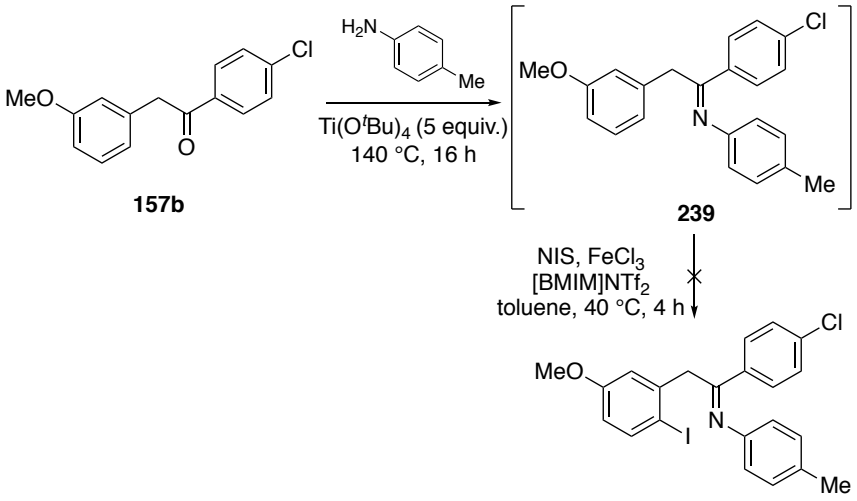
Scheme 178: Synthesis of benzoxazoles and benzothiazoles *via* distinct reaction pathways

As part of these projects, the synthesis of indoles and benzo[*b*]thiophenes from aryl imines and thioketones, respectively, using similar one-pot processes was briefly investigated (Scheme 179).



Scheme 179: Proposed synthesis of indoles and benzo[*b*]thiophenes

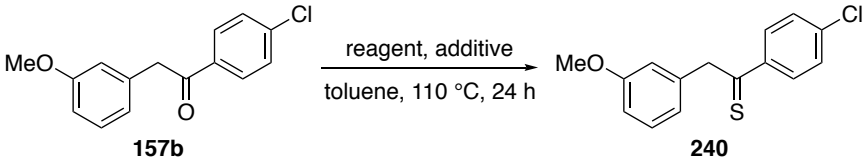
Karchava and co-workers developed a one-pot process for the synthesis of indoles directly from *ortho*-brominated α-arylketones.[463] Their reaction sequence involved a titanium mediated reaction of the ketone with various amines followed by copper-catalysed cyclisation of the resulting imine species. Our approach would incorporate this imine synthesis into the one-pot reaction and allow the synthesis of indoles directly from arylketones. In an initial attempt, imine **239** was prepared by reaction of arylketone **157b** with *p*-toluidine using titanium(IV) butoxide (Scheme 180). This imine was not compatible with the conditions used in the iodination step of the one-pot process and full conversion back to ketone **157b** was observed *via* imine hydrolysis. Future work will focus on the optimisation of this process, by the synthesis of more stable imine substrates and by screening various solvents and conditions for the iodination step. Clearly, any imine substrate will be sensitive to water therefore it will be required to perform this one-pot process under strictly anhydrous conditions.



Scheme 180: Attempted one-pot indole synthesis

The next aim was to synthesise benzo[*b*]thiophenes directly from thioketones using the one-pot process. This was not achieved due to the difficulty in accessing the α-arylthioketone starting materials. Reaction of aryl ketone **157b** with Lawesson's reagent resulted in no conversion to thioketone **240**, with only decomposition observed (Table 16, entry 1). Using 3 equivalents of Lawesson's reagent and stirring under reflux for 24 h also resulted in no conversion to thioketone **240** (entry 2). Phosphorus pentasulfide was instead used as a thionating agent however, this resulted in decomposition of the starting material, perhaps due to undesired side reactions of the anisole ring (entry 3). In general, thioketones are unstable due to the high reactivity associated with the poor orbital overlap of the C–S π-bond. As a result, thiocarbonyls have a tendency to tautomerise and then undergo spontaneous oligomerisation unless there is significant electronic stabilisation.[464] Curphey demonstrated that P_2S_5, used in combination with hexamethyldisiloxane (HMDSO), is an efficient method for the thionation of ketones.[465] It is thought that HMDSO reacts with the highly electrophilic polythiophosphate by-products, converting these to innocuous, unreactive silylated phosphates and preventing side reactions. The thionation reaction was attempted using the combination of phosphorus pentasulfide and HMDSO however, this again resulted in only decomposition of the starting material (entry 4).

Table 16: Attempted α-arylthioketone synthesis

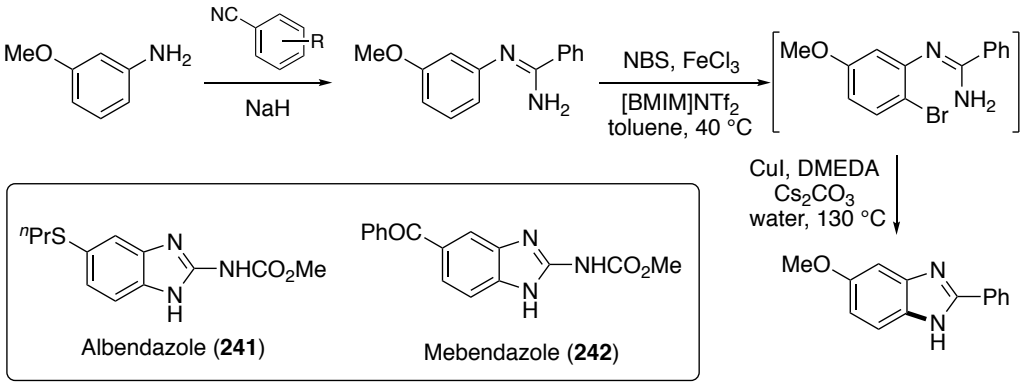


157b **240**

Entry	Reagent	Equiv.	Additive	Result
1	Lawesson's reagent	0.6	n/a	Decomposition
2	Lawesson's reagent	3	n/a	Decomposition
3	P_2S_5	2	n/a	Decomposition
4	P_2S_5	0.25	HMDSO	Decomposition

Alternative methods for the synthesis of thioketones will be explored, such as the reaction of dimethyl acetals with hydrogen sufide in the presence of zinc chloride[466] or by fragmentation of 1,3-dithiolane-derived sulfur ylides.[467,468] Future work will also investigate the synthesis of 2-arylthioketones with significant electronic aromatic stabilisation which do not undergo tautomerisation or more stable, cyclic alkylthioketones.[469]

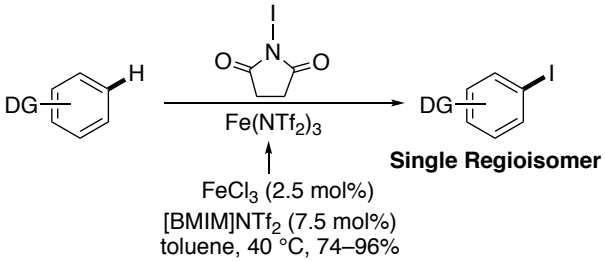
The one-pot synthesis of 2-substituted benzimidazoles directly from amidines will also be examined (Scheme 181). After the development of efficient syntheses of aryl guanidines by the reaction of anilines with benzonitriles,[470] these will then be investigated as substrates in the one-pot iron(III)-catalysed bromination and copper(I)-catalysed *O*-cyclisation. This one-pot process will be used for the preparation of a wide range of benzimidazoles, including 2-aryl, 2-alkyl and 2-amino analogues. Following this, the process will be applied to the rapid synthesis of broad spectrum anthelmintic compounds, albendazole (**241**) and mebendazole (**242**).



Scheme 181: Proposed one-pot synthesis of benzimidazoles

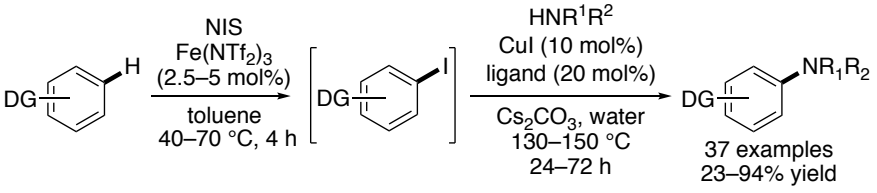
2.6 Overall Conclusions

The overall goal of this PhD was the development of novel one-pot processes for the conversion of aryl C–H bonds into aryl C–heteroatom bonds using inexpensive and earth-abundant transition metal-catalysis. This PhD began with the development of an electrophilic aromatic iodination procedure which relied upon the activation of NIS using iron(III) triflimide, generated from catalytic quantities of both iron(III) chloride and [BMIM]NTf_2 (Scheme 182). It was clear that a strong, electron-donating group on the aromatic ring was essential for both reactivity and selectivity.



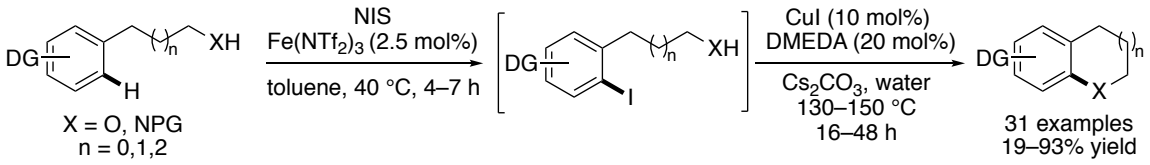
Scheme 182: Regioselective iron(III) triflimide-catalysed iodination

This regioselective, iron(III) triflimide-catalysed electrophilic aromatic substitution was then combined with an intermolecular copper(I)-catalysed, ligand-assisted *N*-arylation for the synthesis of a small library of *para*-aminated aromatic compounds in a one-pot process (Scheme 183). It was found that when the *para*-position was blocked, the *ortho*-C–H bond could selectively undergo iodination and copper(I)-catalysed cross-coupling. This one-pot process was found to be applicable to a range of unprotected anilines, anisoles and phenols bearing activating and deactivating groups in combination with a variety of nitrogen nucleophiles such as *N*-heterocycles, benzamides and sulfonamides. The synthetic utility of this one-pot, two-step method for direct amination of *ortho*-C-H bonds was exemplified with the late-stage functionalisation of 3,4-dihydroquinolin-2-ones resulting in the preparation of a TRIM24 bromodomain inhibitor and a series of novel analogues.



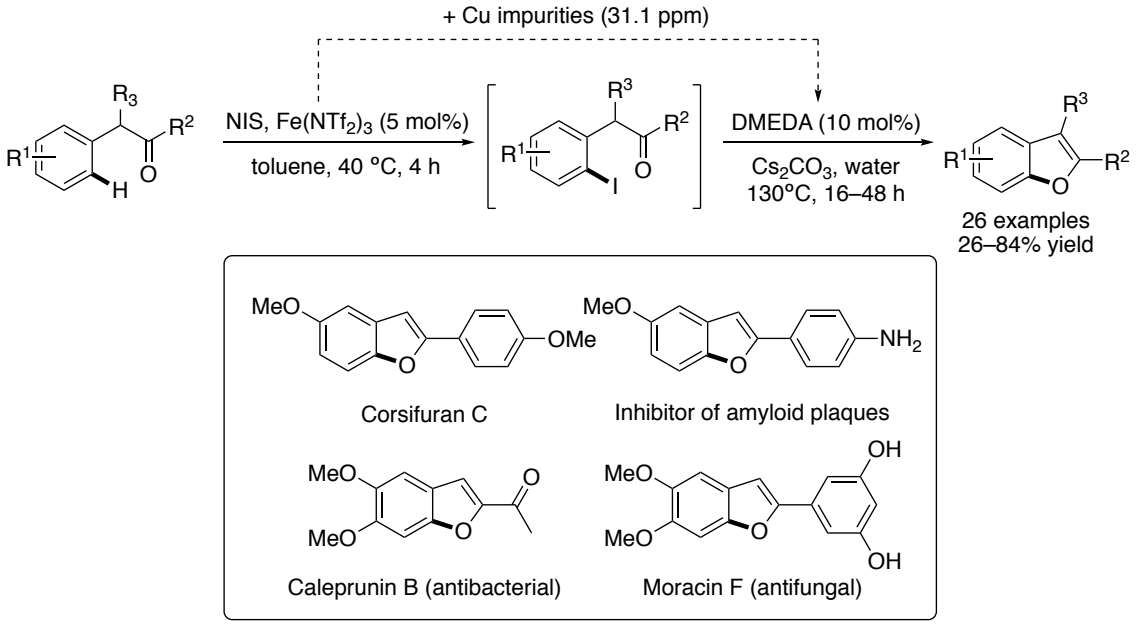
Scheme 183: One-pot, two-step intermolecular amination of C–H bonds

Another major objective of this PhD was the application of the one-pot, two-step amination procedure to the synthesis of functional heterocycles. This aim was realised when *N*-protected phenylethylamines were found to undergo regioselective iodination and intramolecular copper(I)-catalysed cross-coupling with the ethylamine side chain to give indolines in a high yielding one-pot process. Following this, it was demonstrated that this process could be used for the synthesis of a wide range of valuable heterocyclic building blocks including oxindoles, 2,3-dihydrobenzofurans as well as 6- and 7-membered analogues (Scheme 184). The synthetic utility of this methodology was demonstrated with the 8-step total synthesis of (+)-obtusafuran, where the one-pot iron- and copper-catalysed process was used as the key step for the construction of the *trans*-substituted 2,3-dihydrobenzofuran ring system. As part of this project, DFT calculations using Fukui functions revealed the molecular orbital rationale responsible for the highly regioselective iodination step.



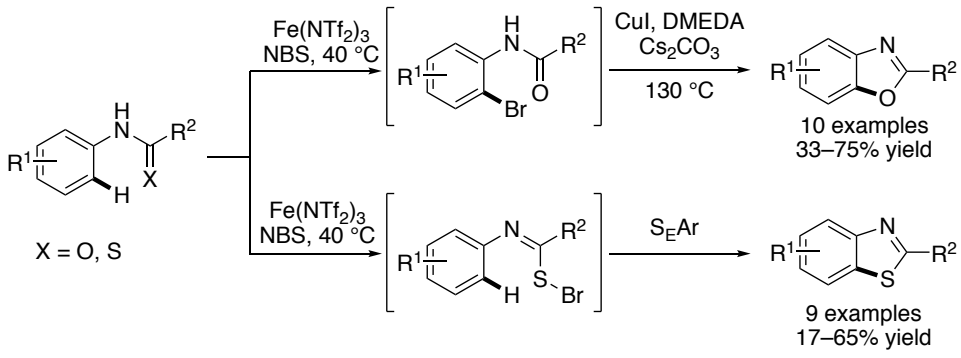
Scheme 184: One-pot, two-step synthesis of *N*- and *O*-heterocycles

In an extension of this methodology, the one-pot, two-step synthesis of benzo[*b*]furans was achieved *via* intramolecular *O*-arylation of aryl and alkyl ketones (Scheme 185). Iron(III)-catalysed electrophilic aromatic halogenation resulted in the formation of a single regioisomer of the aryl iodide intermediate which then underwent an intramolecular *O*-cyclisation of the ketone side chain without the addition of copper(I) iodide. In this project, it was shown that a single iron salt could perform both steps in a tandem catalytic process although the presence of copper salts at either ppm or 10 mol% loading was overall more effective and assisted the *O*-cyclisation step. This one-pot process was used as the key step in the preparation of a range of medicinally important benzo[*b*]furans and natural products such as corsifuran C, caleprunin B and moracin F.



Scheme 185: One-pot, two-step synthesis of benzo[*b*]furans

Finally, the one-pot synthesis of benzoxazoles was achieved by applying regioselective iron(III)-catalysed bromination to a series of *N*-arylbenzamides followed by copper(I)-catalysed *O*-cyclisation with the benzamide side chain (Scheme 186). In contrast, it was found that the application of *N*-arylthiobenzamides to the iron(III)-catalysed bromination procedure led to the direct formation of the corresponding 2-arylbenzothiazoles. This divergence in reactivity was investigated with mechanistic experiments which suggested that bromination of the Lewis basic sulfur atom occurs leading to a reactive intermediate which then undergoes electrophilic aromatic substitution resulting in intramolecular C–S bond formation. These processes were then used to prepare a small library of benzoxazoles and benzothiazoles including pharmaceutically active compounds for the potential treatment of Duchenne muscular dystrophy and Alzheimer's disease.



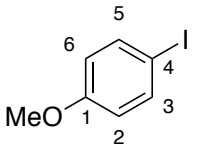
Scheme 186: Synthesis of 2-substituted benzoxazoles and benzothiazoles

3.0 Experimental

General Information

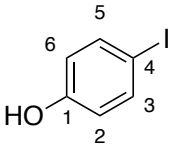
All reagents and starting materials were obtained from commercial sources and used as received. *N*-Bromosuccinimide was recrystallised from water and dried under high vacuum before use. Lithium chloride was oven-dried (140 °C) for at least 16 h before use. All reactions were performed in oven or flame dried glassware under an atmosphere of argon unless otherwise stated. All dry solvents were purified using a PureSolv 500 MD solvent purification system or by distillation. Brine refers to a saturated aqueous solution of sodium chloride. Flash column chromatography was performed using Merck Geduran silica gel 60. Merck aluminium-backed plates pre-coated with silica gel $60F_{254}$ were used for thin layer chromatography and were visualised with a UV lamp or by staining with potassium permanganate or ninhydrin. ^{1}H NMR spectra were recorded on Bruker NMR spectrometers at either 400 or 500 MHz and data are reported as follows: chemical shifts in ppm relative to tetramethylsilane (δ_H 0.00 ppm) or the residual chloroform (δ_H 7.26 ppm) as internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances). ^{13}C NMR spectra were recorded on Bruker NMR spectrometers at either 101 or 126 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane (δ_C 0.0) or residual chloroform (δ_C 77.2 ppm) internal standard, multiplicity with respect to hydrogen (deduced from DEPT experiments, C, CH, CH_2 or CH_3). Assignments are based on 2-dimensional COSY, HSQC and HMBC experiments. Infrared spectra were recorded using a Shimadzu FTIR-84005 spectrometer; wavenumbers are indicated in cm^{-1}. Mass spectra were recorded using electron impact or electrospray techniques. HRMS spectra were recorded using a dual-focusing magnetic analyser mass spectrometer. Melting points were determined on a Gallencamp melting point apparatus and are uncorrected. Where no solvent(s) are specified, the solids obtained in the procedure were melted directly without recrystallisation. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. Chiral HPLC methods were calibrated with the corresponding racemic mixtures.

4-Iodoanisole (82a)[471]



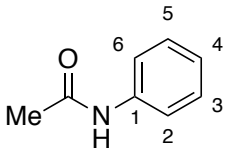
Iron(III) chloride (4.00 mg, 0.0125 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (22.0 μL, 0.0375 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-iodosuccinimide (0.225 g, 0.500 mmol) in dry toluene (1.0 mL). Anisole (0.108 mL, 1.00 mmol) was added and the mixture was heated to 40 °C for 4 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with a 1 M aqueous sodium thiosulfate solution (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with brine (40 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 4-iodoanisole (**82a**) (0.213 g, 91%) as a white solid. Mp 43–46 °C (lit.[471] 43–45 °C); δ_H (400 MHz, $CDCl_3$) 3.78 (3H, s, OCH_3), 6.65–6.72 (2H, m, 2-H and 6-H), 7.52–7.58 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 55.3 (CH_3), 82.7 (C), 116.4 (2 × CH), 138.2 (2 × CH), 159.5 (C); *m/z* (EI) 234 (M^+. 96%), 219 (35), 84 (28).

4-Iodophenol (82b)[472]



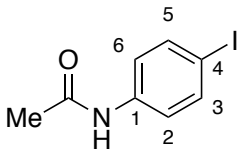
4-Iodophenol (**82b**) was synthesised as described for 4-iodoanisole (**82a**) using phenol (0.0510 g, 0.500 mmol). The reaction mixture was heated to 40 °C for 3 h. Purification by flash column chromatography (hexane/ethyl acetate, 19:1 to hexane/ethyl acetate, 9:1) gave 4-iodophenol (**82b**) (0.0867 g, 79%) as a colourless oil. Spectroscopic data were consistent with the literature.[472] δ_H (400 MHz, $CDCl_3$) 4.68 (1H, s, OH), 6.63 (2H, d, *J* 8.8 Hz, 2-H and 6-H), 7.52 (2H, d, *J* 8.8 Hz, 3-H and 5-H); δ_C (126 MHz, $CDCl_3$) 82.7 (C), 117.8 (2 × CH), 138.5 (2 × CH), 155.3 (C); *m/z* (EI) 220 (M^+. 100%), 191 (3), 127 (6), 110 (5), 93 (37), 65 (20).

_N_-Phenylacetamide[473]



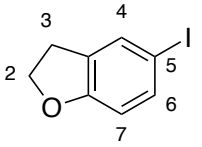
Aniline (0.978 mL, 10.7 mmol) was dissolved in dry dichloromethane (30 mL) and acetic anhydride (1.22 mL, 12.9 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was washed with saturated aqueous sodium carbonate (20 mL) and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-phenylacetamide (1.45 g, 100%) as a white solid. Mp 113–115 °C (from chloroform) (lit.[473] 114–116 °C); δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, CH_3), 7.10 (1H, t, *J* 7.6 Hz, 4-H), 7.30 (2H, t, *J* 7.6 Hz, 2-H and 6-H), 7.50 (2H, d, *J* 7.6 Hz, 3-H and 5-H), 7.62 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 24.5 (CH_3), 120.0 (CH), 124.3 (2 × CH), 129.2 (2 × CH), 137.9 (C), 168.6 (C); *m/z* (EI) 135 (M^+. 100%).

_N_-(4-Iodophenyl)acetamide (82c)[474]



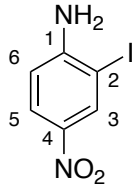
N-(4-Iodophenyl)acetamide (**82c**) was synthesised as described for 4-iodoanisole (**82a**) using *N*-phenylacetamide (0.0340 g, 0.250 mmol). The reaction mixture was heated to 50 °C for 2 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 3:2) gave *N*-(4-iodophenyl)acetamide (**82c**) (0.0623 g, 96%) as a white solid. Mp 175–177 °C (lit.[474] 172–174 °C); δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, CH_3), 7.12 (1H, br s, NH), 7.29 (2H, d, *J* 8.7 Hz, 2-H and 6-H), 7.62 (2H, d, *J* 8.7 Hz, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 24.7 (CH_3), 87.4 (C), 121.6 (2 × CH), 137.6 (C), 137.9 (2 × CH), 168.2 (C); *m/z* (EI) 261 (M^+. 100%), 219 (93), 92 (26), 65 (12).

5-Iodo-2,3-dihydrobenzofuran (82d)[475]



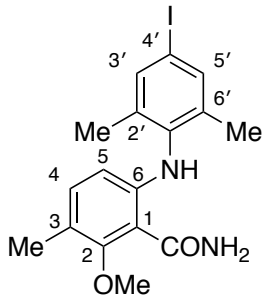
5-Iodo-2,3-dihydrobenzofuran (**82d**) was synthesised as described for 4-iodoanisole (**82a**) using 2,3-dihydrobenzofuran (0.0270 mL, 0.250 mmol). The reaction mixture was heated to 40 °C for 4 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 49:1 to 19:1) gave 5-iodo-2,3-dihydrobenzofuran (**82d**) (0.0547 g, 92%) as a white solid. Mp 61–63 °C (lit.[475] 64–65 °C); δ_H (400 MHz, $CDCl_3$) 3.20 (2H, br t, *J* 8.7 Hz, 3-H_2), 4.56 (2H, t, *J* 8.7 Hz, 2-H_2), 6.57 (1H, d, *J* 8.4 Hz, 7-H), 7.38 (1H, dd, *J* 8.4, 1.7 Hz, 6-H), 7.47 (1H, d, *J* 1.7 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 29.5 (CH_2), 71.4 (CH_2), 81.6 (C), 111.7 (CH), 130.1 (C), 133.7 (CH), 136.7 (CH), 160.0 (C); *m/z* (EI) 246 (M^+. 89%), 232 (10), 117 (20), 91 (40), 84 (39), 44 (100).

2-Iodo-4-nitroaniline (82e)[476]



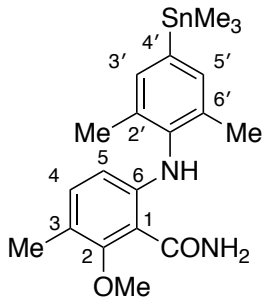
2-Iodo-4-nitroaniline (**82e**) was synthesised as described for 4-iodoanisole (**82a**) using 4-nitroaniline (0.0340 g, 0.250 mmol). The reaction mixture was heated to 40 °C for 6 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 2-iodo-4-nitroaniline (**82e**) (0.0570 g, 74%) as a white solid. Mp 99–101 °C (lit.[476] 103–104 °C); δ_H (400 MHz, $CDCl_3$) 4.83 (2H, br s, NH_2), 6.70 (1H, d, *J* 9.0 Hz, 6-H), 8.06 (1H, dd, *J* 9.0, 2.5 Hz, 5-H), 8.57 (1H, d, *J* 2.5 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 80.5 (C), 112.3 (CH), 125.7 (CH), 135.5 (CH), 139.3 (C), 152.3 (C); *m/z* (EI) 264 (M^+. 100%), 234 (38), 218 (11), 127 (5), 91 (31).

6-[(4′-Iodo-2′,6′-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (80)



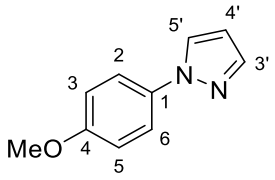
To a stirred solution suspension of *N*-iodosuccinimide (0.142 g, 0.633 mmol) and silver bis(trifluoromethanesulfonyl)imide (0.0154 g, 0.0396 mmol) in toluene (0.5 mL) was slowly added 6-[(2',6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (**79**) (0.150 g, 0.528 mmol) in dry toluene (2.0 mL). The reaction mixture was stirred at 70 °C for 5 h in the dark. A further portion of *N*-iodosuccinimide (0.0360 g, 0.158 mmol) was added and the mixture stirred at 70 °C for a subsequent 2 h. After cooling to room temperature, the reaction mixture was filtered through a short pad of Celite®, washed with ethyl acetate and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 1:1) followed by recrystallisation from acetonitrile: water (9:1) gave 6-[(4′-iodo-2′,6′-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (**80**) (0.0669 g, 31%) as a colourless crystalline solid. Mp 141–143 °C (from acetonitrile and water); ν_{max}/cm^{-1} (neat) 3447 (NH), 3202 (NH), 2934 (CH), 1645 (C=O), 1572, 1497, 1468, 1398, 1366, 1265, 1215, 1047, 851, 733; δ_H (500 MHz, $CDCl_3$) 2.13 (6H, s, 2′-CH_3 and 6′-CH_3), 2.17 (3H, s, 3-CH_3), 3.78 (3H, s, OCH_3), 5.66 (1H, br s, NH), 5.92 (1H, d, *J* 8.6 Hz, 5-H), 6.95 (1H, d, *J* 8.6 Hz, 4-H), 7.45 (2H, s, 3′-H and 5′-H), 7.92 (1H, br s, NH), 9.41 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 15.2 (CH_3), 18.0 (2 × CH_3), 61.2 (CH_3), 90.8 (C), 107.2 (C), 109.3 (CH), 118.1 (C), 135.0 (CH), 137.2 (2 × CH), 138.2 (C), 139.0 (2 × C), 148.4 (C), 158.2 (C), 170.6 (C); *m/z* (ESI) 433.0385 (MNa^+. $C_{17}H_{19}IN_2NaO_2$ requires 433.0383).

6-[(4′-(Trimethylstannyl)-2′,6′-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (83)



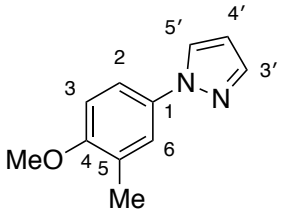
An oven-dried microwave vial was flushed with argon and charged with 6-[(4′-iodo-2′,6′-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (**80**) (0.0666 g, 0.162 mmol) in dry toluene (3.0 mL). Lithium chloride (0.0343 g, 0.810 mmol) was added and the mixture was degassed under argon, while stirring, for 0.2 h. Tetrakis(triphenylphosphine)palladium(0) (0.0374 g, 0.0324 mmol) and hexamethylditin (0.0670 mL, 0.325 mmol) were added under argon and the reaction mixture was stirred under reflux for 22 h. After cooling to room temperature, the reaction mixture was quenched by the addition of 30% aqueous potassium fluoride solution (2.0 mL) and stirred at room temperature for 0.5 h. The mixture was filtered through a short pad of Celite®, washed with ethyl acetate and concentrated *in vacuo*. Purification by neutral alumina (Brockmann grade V) flash column chromatography (hexane/diethyl ether, 1:1) gave 6-[(4′-(trimethylstannyl)-2′,6′-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (**83**) (0.0475 g, 65%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3445 (NH), 3188 (NH), 2918 (CH), 1651 (C=O), 1576, 1497, 1267, 1258, 1049, 765; δ_H (500 MHz, $CDCl_3$) 0.29 (9H, s, Sn(C*H*$_3$)$_3$), 2.16 (3H, s, 3-CH_3), 2.19 (6H, s, 2′-CH_3 and 6′-CH_3), 3.78 (3H, s, OCH_3), 5.68 (1H, br s, NH), 5.97 (1H, d, *J* 8.6 Hz, 5-H), 6.93 (1H, d, *J* 8.6 Hz, 4-H), 7.21 (2H, s, 3′-H and 5′-H), 7.92 (1H, br s, NH), 9.46 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) −9.5 (3 × CH_3), 15.2 (CH_3), 18.3 (2 × CH_3), 61.2 (CH_3), 106.9 (C), 109.5 (CH), 117.5 (C), 134.9 (CH), 135.8 (2 × CH), 136.0 (2 × C), 138.4 (C), 139.4 (C), 148.9 (C), 158.1 (C), 170.8 (C); *m/z* (ESI) 471.1056 (MNa^+. $C_{20}H_{28}N_2NaO_2Sn$ requires 471.1065).

1-(4-Methoxyphenyl)-1*H*-pyrazole (88a)[477]



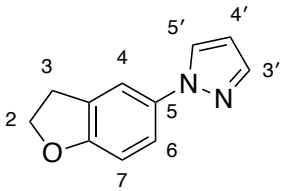
Iron(III) chloride (2.03 mg, 0.0125 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (11.0 µL, 0.0375 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-iodosuccinimide (0.113 g, 0.500 mmol) in dry toluene (0.5 mL). Anisole (0.0540 mL, 0.500 mmol) was added and the mixture was heated to 40 °C for 4 h. Upon completion of the iodination step, the reaction mixture was cooled to room temperature and pyrazole (0.0510 g, 0.750 mmol), copper(I) iodide (9.52 mg, 0.0500 mmol), cesium carbonate (0.326 g, 1.00 mmol), *N*,*N*′-dimethylethylenediamine (10.8 µL, 0.100 mmol) and water (0.4 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 22 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1 to petroleum ether/ethyl acetate, 9:1) gave 1-(4-methoxyphenyl)-1*H*-pyrazole (**88a**) (0.0821 g, 94%) as a light brown oil. Spectroscopic data were consistent with the literature.[477] δ_H (400 MHz, $CDCl_3$) 3.84 (3H, s, OCH_3), 6.44 (1H, dd, *J* 2.1, 1.5 Hz, 4-H), 6.94–7.00 (2H, m, 3′-H and 5′-H), 7.56–7.62 (2H, m, 2′-H and 6′-H), 7.69 (1H, d, *J* 1.5 Hz, ArH) 7.82 (1H, d, *J* 2.1 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 107.2 (CH), 114.5 (2 × CH), 120.8 (2 × CH), 126.8 (CH), 134.0 (C), 140.6 (CH), 158.2 (C); *m/z* (ESI) 197 (MNa^+. 100%).

1′-(4-Methoxy-5-methylphenyl)-1*H*-pyrazole (88b)



1′-(4-Methoxy-5-methylphenyl)-1*H*-pyrazole (**88b**) was synthesised as described for 1-(4-methoxyphenyl)-1*H*-pyrazole (**88a**) using 2-methylanisole (0.0620 mL, 0.500 mmol) and pyrazole (0.0510 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1′-(4-methoxy-5-methylphenyl)-1*H*-pyrazole (**88b**) (0.0859 g, 90%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2928, 1519, 1504, 1239, 1046, 909, 730; δ_H (500 MHz, $CDCl_3$) 2.28 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 6.42 (1H, t, *J* 2.0 Hz, 4-H), 6.86 (1H, d, *J* 8.7 Hz, 3′-H), 7.42 (1H, dd, *J* 8.7, 2.6 Hz, 2′-H), 7.48 (1H, d, *J* 2.6 Hz, 6′-H), 7.68 (1H, d, *J* 2.0 Hz, ArH), 7.81 (1H, d, *J* 2.0 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 16.4 (CH_3), 55.6 (CH_3), 107.0 (CH), 110.2 (CH), 117.8 (CH), 122.3 (CH), 126.8 (CH), 127.8 (C), 133.5 (C), 140.5 (CH), 156.4 (C); *m/z* (ESI) 211.0838 (MNa^+, $C_{11}H_{12}N_2NaO$ requires 211.0842).

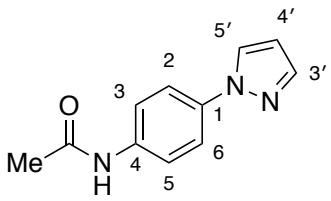
1′-(2,3-Dihydrobenzofuran-5-yl)-1*H*-pyrazole (88c)



1′-(2,3-Dihydrobenzofuran-5-yl)-1*H*-pyrazole (**88c**) was synthesised as described for 1-(4-methoxyphenyl)-1*H*-pyrazole (**88a**) using 2,3-dihydrobenzofuran (0.0570 mL, 0.500 mmol) and pyrazole (0.0510 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 150 °C for 22 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1′-(2,3-dihydrobenzofuran-5-yl)-1*H*-pyrazole (**88c**) (0.0740 g, 79%) as a yellow oil. ν_{max}/cm^{-1} (neat) 2974 (CH), 1516, 1492, 1394, 1228, 1029, 983, 942, 746; δ_H (400 MHz, $CDCl_3$) 3.25 (2H, t, *J* 8.7 Hz, 3′-H_2), 4.62 (2H, t, *J* 8.7 Hz, 2′-H_2), 6.41 (1H, t, *J*

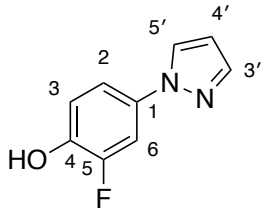
2.3 Hz, 4-H), 6.81 (1H, d, *J* 8.5 Hz, 7′-H), 7.35 (1H, dd, *J* 8.5, 2.3 Hz, 6′-H), 7.51–7.54 (1H, m, 4′-H), 7.67 (1H, d, *J* 2.1 Hz, ArH), 7.78 (1H, d, *J* 2.1 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 29.7 (CH_2), 71.7 (CH_2), 107.0 (CH), 109.3 (CH), 117.2 (CH), 119.7 (CH), 126.9 (CH), 128.3 (C), 134.1 (C), 140.4 (CH), 158.8 (C); *m/z* (ESI) 209.0682 (MNa^+. $C_{11}H_{10}N_2NaO$ requires 209.0685).

_N_-[4-(1_H_-Pyrazol-1-yl)phenyl]acetamide (88d)



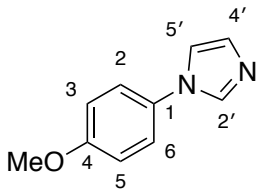
N-[4-(1*H*-Pyrazol-1′-yl)phenyl]acetamide (**88d**) was synthesised as described for 1-(4-methoxyphenyl)-1*H*-pyrazole (**88a**) using *N*-phenylacetamide (0.0680 g, 0.500 mmol) and pyrazole (0.0510 g, 0.750 mmol). The iodination step was carried out at 40 °C for 6 h and the *N*-arylation step at 130 °C for 16 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-[4-(1*H*-pyrazol-1′-yl)phenyl]acetamide (**88d**) (0.0757 g, 76%) as a brown solid. Mp 134–136 °C; ν_{max}/cm^{-1} (neat) 3304 (NH), 3062 (CH), 1667 (C=O), 1614 (C=C), 1555, 1525, 1398, 1330, 1054, 1036, 940, 826; δ_H (500 MHz, $CDCl_3$) 2.16 (3H, s, CH_3), 6.45 (1H, t, *J* 2.1 Hz, 4-H), 7.55–7.61 (4H, m, 2′-H, 3′-H, 5′-H and 6′-H), 7.70 (1H, d, *J* 2.1 Hz, ArH), 7.80 (1H, br s, NH), 7.86 (1H, d, *J* 2.1 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 24.4 (CH_3), 107.6 (CH), 119.9 (2 × CH), 120.9 (2 × CH), 127.0 (CH), 136.4 (C), 136.6 (C), 141.0 (CH), 169.0 (C); *m/z* (ESI) 224.0791 (MNa^+. $C_{11}H_{11}N_3NaO$ requires 224.0794).

5-Fluoro-1-(1*H*-pyrazol-1′-yl)phenol (88e)



2-Fluoro-4-(1*H*-pyrazol-1′-yl)phenol (**88e**) was synthesised as described for 1-(4-methoxyphenyl)-1*H*-pyrazole (**88a**) using 2-fluorophenol (0.0450 mL, 0.500 mmol) and pyrazole (0.0510 g, 0.750 mmol). The iodination step was carried out at 40 °C for 5 h and the *N*-arylation step at 130 °C for 24 h. The reaction mixture was diluted with dichloromethane (10 mL) and extracted with 1 M aqueous sodium hydroxide (20 mL). The aqueous phase was separated and then acidified with 1 M aqueous hydrochloric acid then extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 2-fluoro-4-(1*H*-pyrazol-1′-yl)phenol (**88e**) (0.0453 g, 51%) as a viscous yellow oil. ν_{max}/cm^{-1} (neat) 3123 (OH), 2970 (CH), 1526, 1516, 1401, 1288, 1248, 1186, 1039, 753; δ_H (500 MHz, $CDCl_3$) 6.45 (1H, t, *J* 2.0 Hz, 4-H), 6.49 (1H, s, OH), 7.02 (1H, t, *J* 8.9 Hz, 6′-H), 7.28 (1H, ddd, *J* 8.9, 2.5, 1.4 Hz, 5′-H), 7.44 (1H, dd, *J* 11.4, 2.5 Hz, 3′-H), 7.71 (1H, d, *J* 2.0 Hz, ArH), 7.80 (1H, d, *J* 2.0 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 107.6 (CH), 108.9 (CH, d, $^2J_{CF}$ 22.6 Hz), 116.2 (CH, d, $^3J_{CF}$ 3.3 Hz), 118.1 (CH, d, $^4J_{CF}$ 3.1 Hz), 127.7 (CH), 133.0 (C, d, $^3J_{CF}$ 8.6 Hz), 140.9 (CH), 143.2 (C, d, $^2J_{CF}$ 13.7 Hz), 151.3 (C, d, $^1J_{CF}$ 241.2 Hz); *m/z* (ESI) 177.0465 ([M–H]$^-$. $C_9H_6FN_2O$ requires 177.0470).

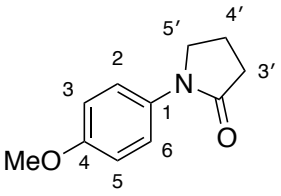
1-(4-Methoxyphenyl)-1*H*-imidazole (88f)[478]



1-(4-Methoxyphenyl)-1*H*-imidazole (**88f**) was synthesised as described for 1-(4-methoxyphenyl)-1*H*-pyrazole (**88a**) using anisole (0.0540 mL, 0.500 mmol) and

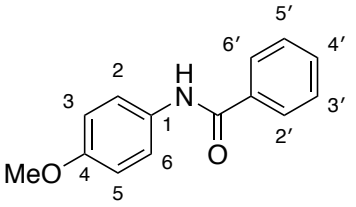
imidazole (0.0510 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 150 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1 to dichloromethane/methanol, 19:1) gave 1-(4-methoxyphenyl)-1*H*-imidazole (**88f**) (0.0685 g, 79%) as an off-white solid. Mp 60–62 °C (lit.[478] 61–63 °C); δ_H (500 MHz, $CDCl_3$) 3.79 (3H, s, OCH_3), 6.90–6.95 (2H, m, 3-H and 5-H), 7.10–7.20 (2H, m, 4′-H and 5′-H), 7.21–7.27 (2H, m, 2-H and 6-H), 7.72 (1H, br s, 2′-H); δ_C (126 MHz, $CDCl_3$) 55.6 (CH_3), 114.9 (2 × CH), 118.8 (CH), 123.1 (2 × CH), 130.1 (CH), 130.7 (C), 135.8 (CH), 158.9 (C); *m/z* (ESI) 175 (MH^+. 100%).

1-(4-Methoxyphenyl)pyrrolidin-2′-one (88g)[479]



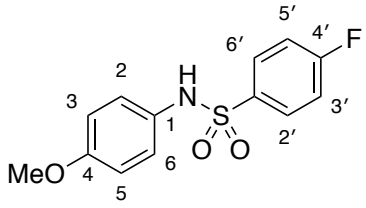
1-(4-Methoxyphenyl)pyrrolidin-2′-one (**88g**) was synthesised as described for 1-(4-methoxyphenyl)-1*H*-pyrazole (**88a**) using anisole (0.0540 mL, 0.500 mmol) and pyrrolidin-2-one (0.0570 mL, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1 to methanol/dichloromethane, 49:1) gave 1-(4-methoxyphenyl)pyrrolidin-2′-one (**88g**) (0.0772 g, 78%) as an off-white solid. Mp 112–114 °C (lit.[479] 113–114 °C); δ_H (500 MHz, $CDCl_3$) 2.14 (2H, quin., *J* 7.9 Hz, 4′-H_2), 2.58 (2H, t, *J* 7.9 Hz, 3′-H_2), 3.79 (3H, s, OMe), 3.81 (2H, t, *J* 7.9 Hz, 5′-H_2), 6.86–6.92 (2H, m, 3-H and 5-H), 7.46–7.51 (2H, m, 2-H and 6-H); δ_C (126 MHz, $CDCl_3$) 18.0 (CH_2), 32.5 (CH_2), 49.2 (CH_2), 55.5 (CH_3), 114.0 (2 × CH), 121.8 (2 × CH), 132.6 (C), 156.6 (C), 173.9 (C); *m/z* (ESI) 214 (MNa^+. 100%).

_N_-(4-Methoxyphenyl)benzamide (88h)[480]



N-(4-Methoxyphenyl)benzamide (**88h**) was synthesised as described for 1-(4-methoxyphenyl)-1*H*-pyrazole (**88a**) using anisole (0.0540 mL, 0.500 mmol) and benzamide (0.0909 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave *N*-(4-methoxyphenyl)benzamide (**88h**) (0.0920 g, 81%) as a white solid. Mp 152–154 °C (lit.[480] 149–152 °C); δ_H (500 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 6.87–6.93 (2H, m, 3-H and 5-H), 7.44–7.56 (5H, m, 2-H, 6-H and 3 × ArH), 7.80 (1H, br s, NH), 7.83–7.88 (2H, m, 2 × ArH); δ_C (126 MHz, $CDCl_3$) 55.5 (CH_3), 114.3 (2 × CH), 122.1 (2 × CH), 127.0 (2 × CH), 128.7 (2 × CH), 131.0 (C), 131.7 (CH), 135.1 (C), 156.7 (C), 165.6 (C); *m/z* (ESI) 250 (MNa^+. 100%).

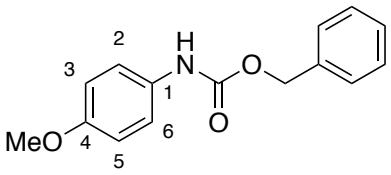
4′-Fluoro-*N*-(4-methoxyphenyl)benzenesulfonamide (88i)



4′-Fluoro-*N*-(4-methoxyphenyl)benzenesulfonamide (**88i**) was synthesised as described for 1-(4-methoxyphenyl)-1*H*-pyrazole (**88a**) using anisole (0.0540 mL, 0.500 mmol) and 4-fluorobenzenesulfonamide (0.131 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 4′-fluoro-*N*-(4-methoxyphenyl)benzenesulfonamide (**88i**) (0.120 g, 86%) as a white solid. Mp 102–104 °C; ν_{max}/cm^{-1} (neat) 3262 (NH), 2937 (CH), 1592 (C=C), 1508, 1495, 1247, 1241, 1165, 1153, 1090, 837, 754; δ_H (500 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 6.74–6.79 (3H, m, 3-H, 5-H and NH), 6.95–7.00 (2H, m,

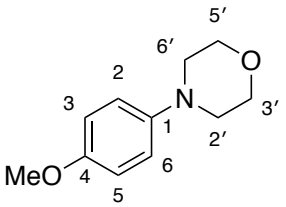
2-H and 6-H), 7.06–7.12 (2H, m, 3′-H and 5′-H), 7.69–7.74 (2H, m, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 55.4 (CH_3), 114.5 (2 × CH), 116.2 (2 × CH, d, $^2J_{CF}$ 22.6 Hz), 125.7 (2 × CH), 128.5 (C), 130.1 (2 × CH, d, $^3J_{CF}$ 9.4 Hz), 134.9 (C, d, $^4J_{CF}$ 3.2 Hz), 158.2 (C), 165.2 (C, d, $^1J_{CF}$ 255.1 Hz); *m/z* (ESI) 304.0405 (MNa^+. $C_{13}H_{12}FNNaO_3S$ requires 304.0414).

Benzyl *N*-(4-Methoxyphenyl)carbamate (88j)[481]



Benzyl *N*-(4-methoxyphenyl)carbamate (**88j**) was synthesised as described for 1-(4-methoxyphenyl)-1*H*-pyrazole (**88a**) using anisole (0.0540 mL, 0.500 mmol) and benzyl carbamate (0.113 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (petroleum ether/diethyl ether, 1:1) gave benzyl *N*-(4-methoxyphenyl)carbamate (**88j**) (0.0550 g, 43%) as a white solid. Mp 95–97 °C (lit.[481] 98 °C); δ_H (400 MHz, $CDCl_3$) 3.78 (3H, s, OCH_3), 5.19 (2H, s, OCH_2Ph), 6.53 (1H, br s, NH), 6.85 (2H, d, *J* 8.6 Hz, 3-H and 5-H), 7.24–7.43 (7H, m, 2-H, 6-H and Ph); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 67.0 (CH_2), 114.3 (2 × CH), 120.8 (C), 128.2 (2 × CH), 128.3 (2 × CH), 128.6 (2 × CH), 130.8 (CH), 136.2 (C), 153.6 (C), 156.1 (C); *m/z* (ESI) 280.0928 (MNa^+. $C_{15}H_{15}NNaO_3$ requires 280.0950).

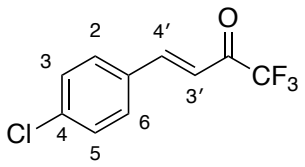
1′-(4-Methoxyphenyl)morpholine (88q)[482]



Iron(III) chloride (1.60 mg, 0.0100 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (7.00 µL, 0.0250 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-iodosuccinimide (0.113 g, 0.500 mmol) in dry toluene (0.5 mL). Anisole (0.0540 mL,

0.500 mmol) was added and the mixture was heated to 40 °C for 4 h. Upon completion of the iodination step, the reaction mixture was cooled to room temperature and copper(I) iodide (9.52 mg, 0.0500 mmol), cesium carbonate (0.326 g, 1.00 mmol), 2-isobutyrylcyclohexanone (0.0253 mL, 0.150 mmol) and water (0.4 mL) were added under argon. The resulting mixture was stirred at room temperature for 0.1 h then morpholine (0.0520 mL, 0.600 mmol) was added. The reaction mixture was degassed under argon for 0.1 h and then heated to 150 °C for 48 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 1′-(4-methoxyphenyl)morpholine (**88q**) (0.0480 g, 50%) as a light brown oil. Spectroscopic data were consistent with the literature.[482] δ_H (400 MHz, $CDCl_3$) 3.06 (4H, t, *J* 4.3 Hz, 3-H_2 and 5-H_2), 3.77 (3H, s, OCH_3), 3.86 (4H, t, *J* 4.3 Hz, 2-H_2 and 6-H_2), 6.85 (2H, d, *J* 8.6 Hz, 3-H and 5-H), 6.89 (2H, d, *J* 8.6 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 50.9 (2 × CH_2), 55.6 (CH_3), 67.1 (2 × CH_2), 114.5 (2 × CH), 117.8 (2 × CH), 145.7 (C), 154.0(C); *m/z* (EI) 193 (M^+. 100%).

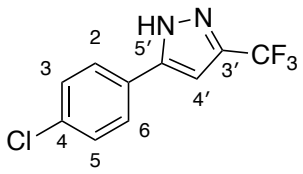
(*E*)-4′-(4-Chlorophenyl)-1′,1′,1′-trifluorobut-3′-en-2′-one (97)[483]



To a stirred solution of 4-chlorobenzaldehyde (**96**) (0.702 g, 5.00 mmol), acetic acid (0.430 mL, 7.50 mmol) and piperidine (0.500 mL, 5.00 mmol) in tetrahydrofuran (20 mL) was added 1,1,1-trifluoroacetone (1.80 mL, 20.0 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h before being warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (15 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/dichloromethane, 9:1) gave (*E*)-4′-(4-chlorophenyl)-1′,1′,1′-trifluorobut-3′-en-2′-one (**97**) (0.599 g, 51%) as a white solid. Mp 38–40°C (lit.[483] 42–

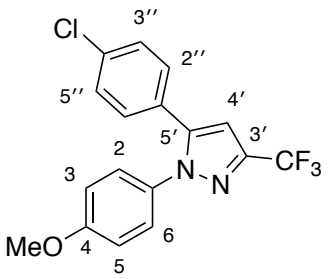
45°C); δ_H (400 MHz, $CDCl_3$) 6.98 (1H, d, *J* 15.6 Hz, 3′-H), 7.41 (2H, d, *J* 7.9 Hz, 3-H and 5-H), 7.56 (2H, d, *J* 7.9 Hz, 2-H and 6-H), 7.89 (1H, d, *J* 15.6 Hz, 4′-H); δ_C (101 MHz, $CDCl_3$) 116.3 (C, q, $^1J_{CF}$ 290.0 Hz), 117.1 (CH), 129.6 (2 × CH), 130.3 (2 × CH), 131.8 (C), 138.5 (C), 148.5 (CH), 179.8 (C, q, $^2J_{CF}$ 36.0 Hz); *m/z* (ESI) 257 (MNa^+. 100%).

5′-(4-Chlorophenyl)-3′-(trifluoromethyl)-1*H*-pyrazole (95)[256]



A solution of (*E*)-4′-(4-chlorophenyl)-1′,1′,1′-trifluorobut-3′-en-2′-one (**97**) (0.425 g, 1.82 mmol), *p*-tosylhydrazide (0.372 g, 2.00 mmol) and sodium acetate (0.164 g, 2.00 mmol) in ethanol (20 mL) was stirred under reflux for 16 h. The reaction mixture was filtered and the solvent was removed *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 5′-(4-chlorophenyl)-3′-(trifluoromethyl)-1*H*-pyrazole (**95**) (0.296 g, 66%) as a white solid. Mp 149–151 °C (lit.[256] 150–153 °C); δ_H (400 MHz, $CDCl_3$) 6.79 (1H, s, 4′-H), 7.45 (2H, d, *J* 8.4 Hz, 2-H and 6-H), 7.51 (2H, d, *J* 8.4 Hz, 3-H and 5-H), 10.78 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 101.3 (CH), 120.9 (C, q, $^1J_{CF}$ 263.0 Hz), 126.3 (C), 126.9 (2 × CH), 129.5 (2 × CH), 135.6 (C), 143.4 (C, q, $^2J_{CF}$ 38.0 Hz), 144.4 (C); *m/z* (ESI) 247 (MH^+. 100%).

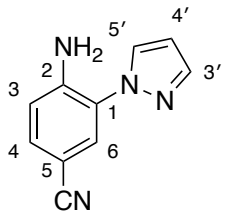
5′-(4′′-Chlorophenyl)-1′-(4-methoxyphenyl)-3′-(trifluoromethyl)-1*H*-pyrazole (88r)[257]



Iron(III) chloride (0.800 mg, 0.00500 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (4.36 μL, 0.0150 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-

iodosuccinimide (0.0450 g, 0.200 mmol) in dry toluene (0.2 mL). Anisole (0.0220 mL, 0.200 mmol) was added and the mixture was heated to 40 °C for 4 h. Upon completion of the iodination step, the reaction mixture was cooled to room temperature and copper(I) iodide (3.80 mg, 0.0200 mmol), cesium carbonate (0.130 g, 0.400 mmol) and *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (6.40 μL, 0.0400 mmol) were added under argon. 5′-(4-Chlorophenyl)-3′-(trifluoromethyl)-1*H*-pyrazole (**95**) (0.140 g, 0.600 mmol) in dry 1,4-dioxane (1.2 mL) was added, the reaction mixture was degassed under argon for 0.2 h and then heated to 150 °C for 60 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate, filtered through a short pad of silica and concentrated *in vacuo*. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 1′-(4-methoxyphenyl)-3′-(trifluoromethyl)-5′-(4″-chlorophenyl)-1*H*-pyrazole (**88r**) (0.0160 g, 23%) as a colourless oil. Spectroscopic data were consistent with the literature.[257] δ_H (500 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.73 (1H, s, 4′-H), 6.88 (2H, d, *J* 9.2 Hz, 3-H and 5-H), 7.15 (2H, d, *J* 8.9 Hz, 2″-H and 6″-H), 7.21 (2H, d, *J* 9.2 Hz, 2-H and 6-H), 7.30 (2H, d, *J* 8.9 Hz, 3″-H and 5″-H); δ_C (126 MHz, $CDCl_3$) 55.6 (CH_3), 105.3 (CH), 114.4 (2 × CH), 121.2 (C, q, $^1J_{CF}$ 270.1 Hz), 126.9 (2 × CH), 127.7 (C), 129.0 (2 × CH), 130.0 (2 × CH), 132.1 (C), 135.1 (C), 143.0 (C, q, $^2J_{CF}$ 37.4 Hz), 143.4 (C), 159.7 (C); *m/z* (ESI) 375 (MNa^+. 100%).

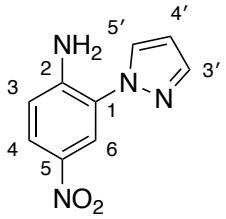
N-(2-Amino-5-cyanophenyl)-1*H*-pyrazole (101a)[484]



Iron(III) chloride (4.03 mg, 0.0250 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (22.0 μL, 0.0750 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-iodosuccinimide (0.112 g, 0.500 mmol) in toluene (0.5 mL). 4-Aminobenzonitrile (**99**) (0.0590 g, 0.500 mmol) was added and the mixture was stirred at 70 °C for 5 h. Upon the completion of the iodination step, the reaction mixture was cooled to room temperature and pyrazole (0.102 g, 1.50 mmol), copper(I) iodide (9.52 mg, 0.0500 mmol), cesium carbonate (0.326 g, 1.00 mmol), *trans*-*N*,*N*′-dimethylcyclohexane-

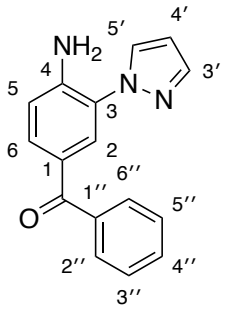
1,2-diamine (16.0 μL, 0.100 mmol) and water (0.25 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) (0.0550 g, 60%) as a colourless oil. Spectroscopic data were consistent with the literature.[484] δ_H (500 MHz, $CDCl_3$) 5.45 (2H, br s, NH_2), 6.50 (1H, t, *J* 2.2 Hz, 4′-H), 6.81 (1H, d, *J* 8.4 Hz, 3-H), 7.39 (1H, dd, *J* 8.4, 1.9 Hz, 4-H), 7.47 (1H, d, *J* 1.9 Hz, 6-H), 7.75 (1H, d, *J* 2.2 Hz, ArH), 7.77 (1H, d, *J* 2.2 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 99.7 (C), 107.2 (CH), 117.0 (CH), 119.2 (C), 125.5 (C), 127.3 (CH), 129.7 (CH), 132.2 (CH), 141.2 (CH), 145.0 (C); *m/z* (ESI) 207 (MNa^+. 100%).

_N_-(2-Amino-5-nitrophenyl)-1_H_-pyrazole (87)



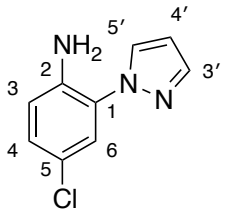
N-(2-Amino-5-nitrophenyl)-1*H*-pyrazole (**87**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-nitroaniline (**86**) (0.0700 g, 0.500 mmol) and pyrazole (0.102 g, 1.50 mmol). The iodination step was carried out at 70 °C for 5 h and the *N*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave *N*-(2-amino-5-nitrophenyl)-1*H*-pyrazole (**87**) (0.0730 g, 71%) as a yellow crystalline solid. Mp 137–139 °C (from ethanol); ν_{max}/cm^{-1} (neat) 3319 (NH), 3080 (CH), 1633, 1614, 1527 (C=C), 1494, 1333, 1316, 707; δ_H (500 MHz, $CDCl_3$) 5.84 (2H, br s, NH_2), 6.52 (1H, t, *J* 2.0 Hz, 4′-H), 6.80 (1H, d, *J* 8.9 Hz, 3-H), 7.78 (1H, d, *J* 2.0 Hz, ArH), 7.86 (1H, d, *J* 2.0 Hz, ArH), 8.05 (1H, dd, *J* 8.9, 2.5 Hz, 4-H), 8.17 (1H, d, *J* 2.5 Hz, 6-H); δ_C (126 MHz, $CDCl_3$) 107.4 (CH), 115.8 (CH), 119.4 (CH), 124.2 (C), 124.4 (CH), 129.8 (CH), 138.1 (C), 141.2 (CH), 146.8 (C); *m/z* (EI) 204.0654 (M^+. $C_9H_8N_4O_2$ requires 204.0647), 174 (20%), 159 (19), 149 (20), 131 (15), 83 (100), 77 (23), 69 (28), 57 (46).

3-Pyrazol-1′-yl-4-aminobenzophenone (101b)



3-Pyrazol-1′-yl-4-aminobenzophenone (**101b**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-aminobenzophenone (0.0986 g, 0.500 mmol) and pyrazole (0.102 g, 1.50 mmol). The iodination step was carried out at 70 °C for 20 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (dichloromethane/petroleum ether, 9:1 to dichloromethane/petroleum ether, 4:1) gave 3-pyrazol-1′-yl-4-aminobenzophenone (**101b**) (0.0760 g, 64%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3360 (NH), 1611 (C=O), 1518, 1396, 1269, 1148; δ_H (500 MHz, $CDCl_3$) 5.44 (2H, br s, NH_2), 6.47 (1H, t, *J* 2.2 Hz, 4′-H), 6.82 (1H, d, *J* 8.4 Hz, 5-H), 7.44–7.50 (2H, m, 3″-H and 5″-H), 7.56 (1H, tt, *J* 7.4, 1.3 Hz, 4″-H), 7.65 (1H, dd, *J* 8.4, 1.9 Hz, 6-H), 7.72–7.77 (3H, m, 2-H, 2″-H and 6″-H), 7.79 (1H, d, *J* 2.2 Hz, ArH), 7.81 (1H, d, *J* 2.2 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 106.8 (CH), 115.9 (CH), 125.3 (C), 126.1 (CH), 126.9 (C), 128.3 (2 × CH), 129.5 (2 × CH), 129.9 (CH), 131.5 (CH), 131.7 (CH), 138.4 (C), 140.8 (CH), 145.3 (C), 194.6 (C); *m/z* (ESI) 286.0944 (MNa^+. $C_{16}H_{13}N_3NaO$ requires 286.0951).

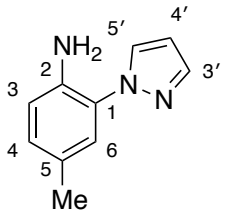
***N*-(2-Amino-5-chlorophenyl)-1*H*-pyrazole (101c)**[484]



N-(2-Amino-5-chlorophenyl)-1*H*-pyrazole (**101c**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-chloroaniline (0.0640 g, 0.500 mmol) and pyrazole (0.102 g, 1.50 mmol). The iodination step was carried out at 70 °C for 5 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash

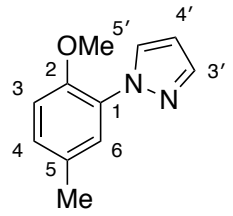
column chromatography (dichloromethane) gave *N*-(2-amino-5-chlorophenyl)-1*H*-pyrazole (**101c**) (0.0610 g, 63%) as a brown oil. Spectroscopic data were consistent with the literature.[484] δ_H (500 MHz, $CDCl_3$) 4.75 (2H, br s, NH_2), 6.44 (1H, t, *J* 2.2 Hz, 4′-H), 6.74 (1H, d, *J* 8.5 Hz, 3-H), 7.08 (1H, dd, *J* 8.5, 2.4 Hz, 4-H), 7.18 (1H, d, *J* 2.4 Hz, 6-H), 7.70 (1H, d, *J* 2.2 Hz, ArH), 7.73 (1H, d, *J* 2.2 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 106.8 (CH), 118.2 (CH), 122.2 (C), 123.7 (CH), 126.8 (C), 128.2 (CH), 129.8 (CH), 139.7 (C), 140.9 (CH); *m/z* (ESI) 216 (MNa^+. 100%).

***N*-(2-Amino-5-methylphenyl)-1*H*-pyrazole (101d)**[484]



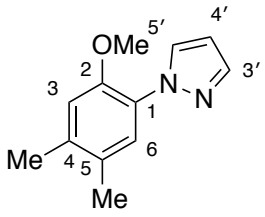
N-(2-Amino-5-methylphenyl)-1*H*-pyrazole (**101d**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-methylaniline (0.0540 g, 0.500 mmol) and pyrazole (0.102 g, 1.50 mmol). The iodination step was carried out at 40 °C for 5 h and the *N*-arylation step at 130 °C for 21 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-(2-amino-5-methylphenyl)-1*H*-pyrazole (**101d**) (0.0510 g, 58%) as an orange oil. Spectroscopic data were consistent with the literature.[484] δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, 5-CH_3), 4.48 (2H, br s, NH_2), 6.42 (1H, t, *J* 2.1 Hz, 4′-H), 6.74 (1H, d, *J* 8.1 Hz, 3-H), 6.96 (1H, dd, *J* 8.1, 1.3 Hz, 4-H), 7.00 (1H, d, *J* 1.3 Hz, 6-H), 7.70 (1H, d, *J* 2.1 Hz, ArH), 7.73 (1H, d, *J* 2.1 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 20.3 (CH_3), 106.3 (CH), 117.4 (CH), 124.7 (CH), 126.6 (C), 127.6 (C), 129.1 (CH), 129.8 (CH), 138.5 (C), 140.5 (CH); *m/z* (ESI) 174 (MNa^+. 100%).

***N*-(2-Methoxy-5-methylphenyl)-1*H*-pyrazole (101e)**



N-(2-Methoxy-5-methylphenyl)-1*H*-pyrazole (**101e**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-methylanisole (**103**) (0.0630 mL, 0.500 mmol) and pyrazole (0.102 g, 1.50 mmol). The iodination step was carried out at 70 °C for 20 h and the *N*-arylation step at 130 °C for 21 h. Purification by flash column chromatography (hexane/diethyl ether, 4:1) gave *N*-(2-methoxy-5-methylphenyl)-1*H*-pyrazole (**101e**) (0.0670 g, 71%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2936 (CH), 1524 (C=C), 1504, 1462, 1283, 1242, 1036, 804, 744; δ_H (400 MHz, $CDCl_3$) 2.33 (3H, br s, 5-CH_3), 3.83 (3H, s, OCH_3), 6.41 (1H, dd, *J* 2.4, 1.9 Hz, 4′-H), 6.92 (1H, d, *J* 8.4 Hz, 3-H), 7.05–7.10 (1H, m, 4-H), 7.55 (1H, d, *J* 2.3 Hz, 6-H), 7.69 (1H, dd, *J* 2.4, 0.4 Hz, ArH), 8.03 (1H, dd, *J* 1.9, 0.4 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 20.4 (CH_3), 56.1 (CH_3), 106.1 (CH), 112.3 (CH), 125.6 (CH), 128.3 (CH), 129.4 (C), 130.8 (C), 131.5 (CH), 139.9 (CH), 149.1 (C); *m/z* (EI) 188.0942 (M^+. $C_{11}H_{12}N_2O$ requires 188.0950), 159 (55%), 144 (34).

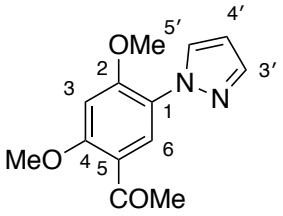
***N*-(2-Methoxy-4,5-dimethylphenyl)-1*H*-pyrazole (101f)**



N-(2-Methoxy-4,5-dimethylphenyl)-1*H*-pyrazole (**101f**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 3,4-dimethylanisole (0.0700 mL, 0.500 mmol) and pyrazole (0.102 g, 1.50 mmol). The iodination step was carried out at 70 °C for 5 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 9:1) gave *N*-(2-methoxy-4,5-dimethylphenyl)-1*H*-pyrazole (**101f**) (0.0680 g, 67%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2932 (CH), 1520, 1466, 1396, 1242, 1188, 1034,

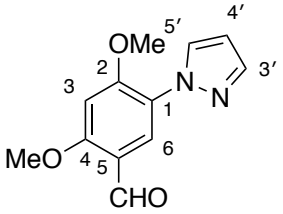
748; δ_H (400 MHz, $CDCl_3$) 2.23 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 6.39 (1H, dd, *J* 2.3, 1.7 Hz, 4′-H), 6.81 (1H, s, 3-H), 7.47 (1H, s, 6-H), 7.67 (1H, d, *J* 1.7 Hz, ArH), 7.97 (1H, d, *J* 2.3 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 18.7 (CH_3), 19.9 (CH_3), 56.1 (CH_3), 105.9 (CH), 113.9 (CH), 126.1 (CH), 127.2 (C), 129.2 (C), 131.4 (CH), 136.4 (C), 139.7 (CH), 149.1 (C); *m/z* (ESI) 225.0994 (MNa^+. $C_{12}H_{14}N_2NaO$ requires 225.0998).

N-(5-Acetyl-2,4-dimethoxyphenyl)-1*H*-pyrazole (101g)



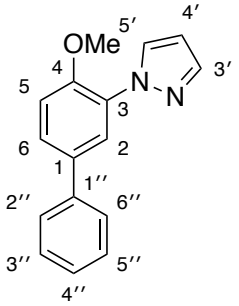
N-(5-Acetyl-2,4-dimethoxyphenyl)-1*H*-pyrazole (**101g**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 2,4-dimethoxyacetophenone (0.0900 g, 0.500 mmol) and pyrazole (0.102 g, 1.50 mmol). The iodination step was carried out at 70 °C for 5 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) followed by trituration with diethyl ether gave *N*-(5-acetyl-2,4-dimethoxyphenyl)-1*H*-pyrazole (**101g**) (0.0590 g, 48%) as a white solid. Mp 122–124 °C (Et_2O); ν_{max}/cm^{-1} (neat) 2931 (CH), 1659 (C=O), 1605, 1520, 1265, 1227, 1026, 741; δ_H (500 MHz, $CDCl_3$) 2.60 (3H, s, COMe), 3.93 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 6.41 (1H, dd, *J* 2.3, 1.8 Hz, 4′-H), 6.57 (1H, s, 3-H), 7.69 (1H, d, *J* 1.8 Hz, ArH), 7.78 (1H, d, *J* 2.3 Hz, ArH), 8.08 (1H, s, 6-H); δ_C (126 MHz, $CDCl_3$) 31.7 (CH_3), 56.0 (CH_3), 56.2 (CH_3), 95.8 (CH), 106.1 (CH), 120.6 (C), 123.4 (C), 128.8 (CH), 131.3 (CH), 140.2 (CH), 156.7 (C), 159.9 (C), 196.8 (C); *m/z* (ESI) 269.0889 (MNa^+. $C_{13}H_{14}N_2NaO_3$ requires 269.0897).

_N_-(5-Formyl-2,4-dimethoxyphenyl)-1_H_-pyrazole (101h)



_N_-(5-Formyl-2,4-dimethoxyphenyl)-1_H_-pyrazole (**101h**) was synthesised as described for _N_-(2-amino-5-cyanophenyl)-1_H_-pyrazole (**101a**) using 2,4-dimethoxybenzaldehyde (0.0830 g, 0.500 mmol) and pyrazole (0.0510 g, 0.750 mmol). The iodination step was carried out at 70 °C for 5 h and the _N_-arylation step at 130 °C for 30 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave _N_-(5-formyl-2,4-dimethoxyphenyl)-1_H_-pyrazole (**101h**) (0.0470 g, 42%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2937 (CH), 1664 (C=O), 1614 (C=C), 1523, 1478, 1332, 1277, 1209, 1152, 1038, 1020, 818; δ_H (400 MHz, $CDCl_3$) 3.95 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 6.41 (1H, dd, _J_ 2.3, 1.8 Hz, 4′-H), 6.56 (1H, s, 3-H), 7.69 (1H, d, _J_ 1.8 Hz, ArH), 7.80 (1H, d, _J_ 2.3 Hz, ArH), 8.08 (1H, s, 5-H), 10.3 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 56.1 (CH_3), 56.3 (CH_3), 95.5 (CH), 106.3 (CH), 118.3 (C), 123.8 (C), 126.6 (CH), 131.3 (CH), 140.3 (CH), 158.3 (C), 162.5 (C), 187.5 (CH); _m/z_ (EI) 232.0855 (M^+. $C_{12}H_{12}N_2O_3$ requires 232.0848), 188 (22%), 73 (28).

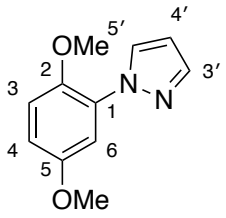
3-Pyrazol-1′-yl-4-methoxybiphenyl (101i)



3-Pyrazol-1′-yl-4-methoxybiphenyl (**101i**) was synthesised as described for _N_-(2-amino-5-cyanophenyl)-1_H_-pyrazole (**101a**) using 4-methoxybiphenyl (0.0920 g, 0.500 mmol) and pyrazole (0.0510 g, 0.750 mmol). The iodination step was carried out at 70 °C for 8 h and the _N_-arylation step at 130 °C for 26 h. Purification by flash

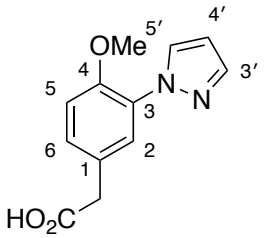
column chromatography (hexane/diethyl ether, 7:3) gave 3-pyrazol-1′-yl-4-methoxybiphenyl (**101i**) (0.0770 g, 61%) as a white solid. Mp 52–54 °C; ν_{max}/cm^{-1} (neat) 2940 (CH), 1528 (C=C), 1489, 1404, 1281, 1250, 1018, 756; δ_H (500 MHz, $CDCl_3$) 3.92 (3H, s, OCH_3), 6.45 (1H, dd, *J* 2.3, 1.8 Hz, 4′-H), 7.11 (1H, d, *J* 8.6 Hz, 5-H), 7.32 (1H, tt, *J* 7.4, 1.2 Hz, 4″-H), 7.38–7.44 (2H, m, 3″-H and 5″-H), 7.52 (1H, dd, *J* 8.6, 2.4 Hz, 6-H), 7.58–7.63 (2H, m, 2″-H and 6″-H), 7.73 (1H, d, *J* 1.8 Hz, ArH), 7.99 (1H, d, *J* 2.4 Hz, 2-H), 8.08 (1H, d, *J* 2.3 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 56.1 (CH_3), 106.3 (CH), 112.7 (CH), 123.9 (CH), 126.3 (CH), 126.8 (2 × CH), 127.1 (CH), 128.8 (2 × CH), 129.9 (C), 131.6 (CH), 134.5 (C), 139.8 (C), 140.2 (CH), 150.7 (C); *m/z* (ESI) 273.0992 (MNa^+. $C_{16}H_{14}N_2NaO$ requires 273.0998).

N-(2,5-Dimethoxyphenyl)-1*H*-pyrazole (101j)



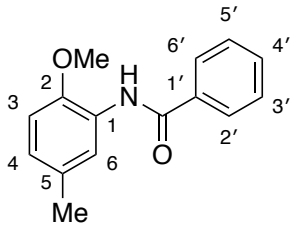
N-(2,5-Dimethoxyphenyl)-1*H*-pyrazole (**101j**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 1,4-dimethoxybenzene (0.0690 g, 0.500 mmol) and pyrazole (0.102 g, 1.50 mmol). The iodination step was carried out at 70 °C for 5 h and the *N*-arylation step at 150 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave *N*-(2,5-dimethoxyphenyl)-1*H*-pyrazole (**101j**) (0.0670 g, 66%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2940 (CH), 1597, 1520, 1504, 1211, 1042, 748; δ_H (400 MHz, $CDCl_3$) 3.82 (6H, br s, 2 × OCH_3), 6.42 (1H, dd, *J* 2.4, 1.9 Hz, 4′-H), 6.83 (1H, dd, *J* 9.0, 3.1 Hz, 4-H), 6.98 (1H, d, *J* 9.0 Hz, 3-H), 7.36 (1H, d, *J* 3.1 Hz, 6-H), 7.70 (1H, d, *J* 1.9 Hz, ArH), 8.10 (1H, d, *J* 2.4 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 55.9 (CH_3), 56.7 (CH_3), 106.3 (CH), 110.0 (CH), 113.6 (CH), 114.0 (CH), 130.2 (C), 131.6 (CH), 140.1 (CH), 145.1 (C), 154.1 (C); *m/z* (ESI) 227.0785 (MNa^+. $C_{11}H_{12}N_2NaO_2$ requires 227.0791).

2″-(4-Methoxy-3-pyrazol-1′-ylphenyl)acetic acid (101k)



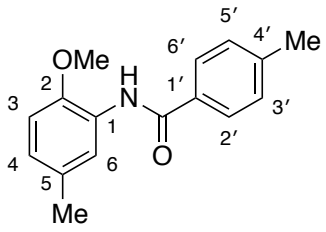
2″-(4-Methoxy-3-pyrazol-1′-ylphenyl)acetic acid (**101k**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-methoxyphenylacetic acid (0.0830 g, 0.500 mmol) and pyrazole (0.102 g, 1.50 mmol). The iodination step was carried out at 70 °C for 4 h and the *N*-arylation step at 150 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and extracted with 1 M aqueous sodium hydroxide solution (10 mL). The aqueous layer was separated and acidified with 1 M aqueous hydrochloric acid and extracted into dichloromethane (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Trituration with hexane gave 2″-(4-methoxy-3-pyrazol-1′-ylphenyl)acetic acid (**101k**) (0.0621 g, 53%) as a white crystalline solid. Mp 94–96 °C (from hexane); ν_{max}/cm^{-1} (neat) 2940 (CH), 1713 (C=O), 1526 (C=C), 1462, 1410, 1287, 1248, 1180, 1152, 1022, 760; δ_H (400 MHz, $CDCl_3$) 3.62 (2H, s, CH_2), 3.86 (3H, s, OCH_3), 6.42 (1H, dd, *J* 2.3, 1.8 Hz, 4′-H), 6.99 (1H, d, *J* 8.5 Hz, 5-H), 7.21 (1H, dd, *J* 8.5, 2.1 Hz, 6-H), 7.67 (1H, d, *J* 2.1 Hz, 2-H), 7.73 (1H, d, *J* 1.8 Hz, ArH), 8.02 (1H, d, *J* 2.3 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 40.1 (CH_2), 56.0 (CH_3), 106.3 (CH), 112.4 (CH), 126.4 (CH), 126.9 (C), 129.1 (CH), 129.2 (C), 131.9 (CH), 139.9 (CH), 150.2 (C), 175.5 (C); *m/z* (ESI) 255.0738 (MNa^+. $C_{12}H_{12}N_2NaO_3$ requires 255.0740).

***N*-(2-Methoxy-5-methylphenyl)benzamide (104a)**[485]



N-(2-Methoxy-5-methylphenyl)benzamide (**104a**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-methylanisole (**103**) (0.0630 mL, 0.500 mmol) and benzamide (0.182 g, 1.50 mmol). The iodination step was carried out at 70 °C for 7 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 4:1) gave *N*-(2-methoxy-5-methylphenyl)benzamide (**104a**) (0.0910 g, 75%) as a colourless oil. Spectroscopic data were consistent with the literature.[485] δ_H (500 MHz, $CDCl_3$) 2.33 (3H, s, 5-CH_3), 3.87 (3H, s, OCH_3), 6.78 (1H, d, *J* 8.3 Hz, 3-H), 6.86 (1H, dd, *J* 8.3 Hz, 2.1 Hz, 4-H), 7.44–7.55 (3H, m, 3′-H, 4′-H and 5′-H), 7.86–7.90 (2H, m, 2′-H and 6′-H), 8.38 (1H, d, *J* 2.1 Hz, 6-H), 8.52 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 21.0 (CH_3), 55.9 (CH_3), 109.8 (CH), 120.5 (CH), 124.1 (CH), 127.0 (2 × CH), 127.5 (C), 128.7 (2 × CH), 130.6 (C), 131.6 (CH), 135.3 (C), 146.1 (C), 165.1 (C); *m/z* (ESI) 264 (MNa^+. 100%).

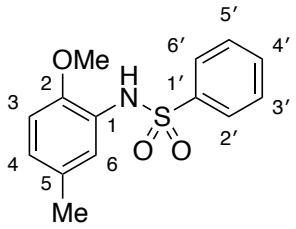
***N*-(2-Methoxy-5-methylphenyl)-4′-methylbenzamide (104b)**



N-(2-Methoxy-5-methylphenyl)-4′-methylbenzamide (**104b**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-methylanisole (**103**) (0.0630 mL, 0.500 mmol) and *p*-toluamide (0.203 g, 1.50 mmol). The iodination step was carried out at 70 °C for 5 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 4:1) gave *N*-(2-methoxy-5-methylphenyl)-4′-methylbenzamide (**104b**) (0.0980 g, 77%) as a white solid. Mp 56–58 °C; ν_{max}/cm^{-1} (neat) 3429 (NH), 2920 (CH), 1670

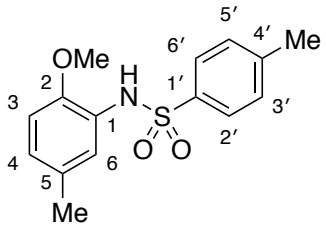
(C=O), 1530 (C=C), 1477, 1423, 1248, 1223, 1138, 1030, 799; δ_H (500 MHz, $CDCl_3$) 2.33 (3H, s, 5-CH_3), 2.41 (3H, s, 4′-CH_3), 3.87 (3H, s, OCH_3), 6.78 (1H, d, *J* 8.2 Hz, 3-H), 6.85 (1H, dd, *J* 8.2, 2.0 Hz, 4-H), 7.27 (2H, d, *J* 8.1 Hz, 3′-H and 5′-H), 7.78 (2H, d, *J* 8.1 Hz, 2′-H and 6′-H), 8.38 (1H, d, *J* 2.0 Hz, 6-H), 8.50 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 21.0 (CH_3), 21.5 (CH_3), 55.9 (CH_3), 109.8 (CH), 120.4 (CH), 123.9 (CH), 127.0 (2 × CH), 127.6 (C), 129.4 (2 × CH), 130.6 (C), 132.5 (C), 142.1 (C), 146.1 (C), 165.1 (C); *m/z* (ESI) 278.1146 (MNa^+. $C_{16}H_{17}NNaO_2$ requires 278.1151).

_N_-(2-Methoxy-5-methylphenyl)benzenesulfonamide (104c)



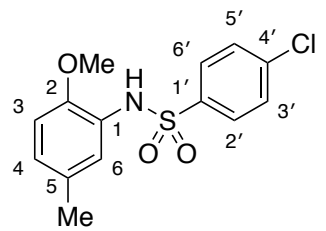
N-(2-Methoxy-5-methylphenyl)benzenesulfonamide (**104c**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-methylanisole (**103**) (0.0630 mL, 0.500 mmol) and benzene sulfonamide (0.236 g, 1.50 mmol). The iodination step was carried out at 70 °C for 7 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 1:1) gave *N*-(2-methoxy-5-methylphenyl)benzenesulfonamide (**104c**) (0.0840 g, 61%) as a white solid. Mp 134–136 °C; ν_{max}/cm^{-1} (neat) 3011 (CH), 1506, 1389, 1327, 1256, 1165, 1090, 1030, 907, 727; δ_H (400 MHz, $CDCl_3$) 2.25 (3H, s, 5-CH_3), 3.54 (3H, s, OCH_3), 6.59 (1H, d, *J* 8.3 Hz, 3-H), 6.82 (1H, dd, *J* 8.3, 1.6 Hz, 4-H), 6.98 (1H, br s, NH), 7.34 (1H, d, *J* 1.6 Hz, 6-H), 7.36–7.43 (2H, m, 3′-H and 5′-H), 7.48 (1H, t, *J* 7.4 Hz, 4′-H), 7.71–7.77 (2H, m, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 20.7 (CH_3), 55.7 (CH_3), 110.5 (CH), 122.4 (CH), 125.4 (C), 125.9 (CH), 127.2 (2 × CH), 128.7 (2 × CH), 130.6 (C), 132.8 (CH), 139.2 (C), 147.7 (C); *m/z* (ESI) 300.0653 (MNa^+. $C_{14}H_{15}NNaO_3S$ requires 300.0665).

***N*-(2-Methoxy-5-methylphenyl)-4′-methylbenzenesulfonamide (104d)**



N-(2-Methoxy-5-methylphenyl)-4′-methylbenzenesulfonamide (**104d**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-methylanisole (**103**) (0.0630 mL, 0.500 mmol) and *p*-toluenesulfonamide (0.257 g, 1.50 mmol). The iodination step was carried out at 70 °C for 7 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 1:1) gave *N*-(2-methoxy-5-methylphenyl)-4′-methylbenzenesulfonamide (**104d**) (0.113 g, 78%) as a white solid. Mp 68–70 °C; ν_{max}/cm^{-1} (neat) 3400 (NH), 2936 (CH), 1595 (C=C), 1508, 1389, 1330, 1252, 1163, 1123, 1090, 808; δ_H (400 MHz, $CDCl_3$) 2.25 (3H, s, 4′-CH_3), 2.35 (3H, s, 5-CH_3), 3.58 (3H, s, OCH_3), 6.60 (1H, d, *J* 8.4 Hz, 3-H), 6.81 (1H, dd, *J* 8.4, 2.1 Hz, 4-H), 6.95 (1H, br s, NH), 7.18 (2H, d, *J* 8.2 Hz, 3′-H and 5′-H), 7.34 (1H, d, *J* 2.1 Hz, 6-H), 7.63 (2H, d, *J* 8.2 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 20.8 (CH_3), 21.5 (CH_3), 55.7 (CH_3), 110.5 (CH), 121.8 (CH), 125.6 (CH), 125.7 (C), 127.2 (2 × CH), 129.3 (2 × CH), 130.6 (C), 136.4 (C), 143.5 (C), 147.5 (C); *m/z* (ESI) 314.0809 (MNa^+. $C_{15}H_{17}NNaO_3S$ requires 314.0821).

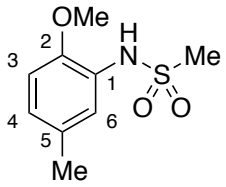
***N*-(2-Methoxy-5-methylphenyl)-4′-chlorobenzenesulfonamide (104e)**



N-(2-Methoxy-5-methylphenyl)-4′-chlorobenzenesulfonamide (**104e**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-methylanisole (**103**) (0.0630 mL, 0.500 mmol) and *p*-chlorobenzenesulfonamide (0.288 g, 1.50 mmol). The iodination step was carried out at 70 °C for 5 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography

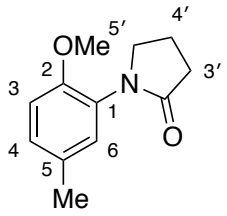
(hexane/diethyl ether, 1:1) gave *N*-(2-methoxy-5-methylphenyl)-4′-chlorobenzenesulfonamide (**104e**) (0.0890 g, 55%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3273 (NH), 2932 (CH), 1585 (C=C), 1508, 1335, 1252, 1165, 1123, 1086, 752; δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, 5-CH_3), 3.58 (3H, s, OCH_3), 6.61 (1H, d, *J* 8.3 Hz, 3-H), 6.85 (1H, dd, *J* 8.3, 2.0 Hz, 4-H), 6.97 (1H, br s, NH), 7.32–7.38 (3H, m, 6-H, 3′-H and 5′-H), 7.67 (2H, d, *J* 8.9 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 20.7 (CH_3), 55.7 (CH_3), 110.5 (CH), 122.6 (CH), 125.0 (C), 126.3 (CH), 128.7 (2 × CH), 129.0 (2 × CH), 130.7 (C), 137.8 (C), 139.2 (C), 147.8 (C); *m/z* (ESI) 334.0265 (MNa^+. $C_{14}H_{14}{}^{35}ClNNaO_3S$ requires 334.0275).

N-(2-Methoxy-5-methylphenyl)methanesulfonamide (104f)



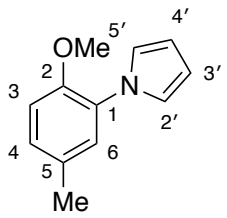
N-(2-Methoxy-5-methylphenyl)methanesulfonamide (**104f**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-methylanisole (**103**) (0.0630 mL, 0.500 mmol) and methanesulfonamide (0.143 g, 1.50 mmol). The iodination step was carried out at 70 °C for 5 h and the *N*-arylation step at 150 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-(2-methoxy-5-methylphenyl)methanesulfonamide (**104f**) (0.0610 g, 57%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3267 (NH), 2934 (CH), 1508 (C=C), 1387, 1323, 1252, 1161, 1121, 1028, 970, 760; δ_H (500 MHz, $CDCl_3$) 2.30 (3H, s, 5-CH_3), 2.94 (3H, s, SO_2CH_3), 3.85 (3H, s, OCH_3), 6.74 (1H, br s, NH), 6.80 (1H, d, *J* 8.3 Hz, 3-H), 6.92 (1H, dd, *J* 8.3, 1.9 Hz, 4-H), 7.33 (1H, d, *J* 1.9 Hz, 6-H); δ_C (126 MHz, $CDCl_3$) 20.8 (CH_3), 39.0 (CH_3), 55.9 (CH_3), 110.6 (CH), 121.7 (CH), 125.7 (C), 125.9 (CH), 131.0 (C), 147.5 (C); *m/z* (ESI) 238.0502 (MNa^+. $C_9H_{13}NNaO_3S$ requires 238.0508).

***N*-(2-Methoxy-5-methylphenyl)pyrrolidin-2′-one (104g)**[486]



N-(2-Methoxy-5-methylphenyl)pyrrolidin-2′-one (**104g**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1H-pyrazole (**101a**) using 4-methylanisole (**103**) (0.0630 mL, 0.500 mmol) and pyrrolidin-2-one (0.114 mL, 1.50 mmol). The iodination step was carried out at 70 °C for 5 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (ethyl acetate) gave *N*-(2-methoxy-5-methylphenyl)pyrrolidin-2′-one (**104g**) (0.0530 g, 52%) as a colourless oil. Spectroscopic data were consistent with the literature.[486] δ_H (500 MHz, $CDCl_3$) 2.12–2.20 (2H, m, 4′-H_2), 2.28 (3H, s, 5-CH_3), 2.54 (2H, t, *J* 7.8 Hz, 3′-H_2) 3.73 (2H, t, *J* 7.0 Hz, 5′-H_2), 3.79 (3H, s, OCH_3), 6.84 (1H, d, *J* 8.9 Hz, 3-H), 7.04–7.07 (2H, m, 4-H and 6-H); δ_C (126 MHz, $CDCl_3$) 18.9 (CH_2), 20.4 (CH_3), 31.2 (CH_2), 50.0 (CH_2), 55.8 (CH_3), 112.1 (CH), 126.9 (C), 129.1 (CH), 129.2 (CH), 130.4 (C), 152.7 (C), 175.2 (C); m/z (ESI) 228 (MNa^+. 100%).

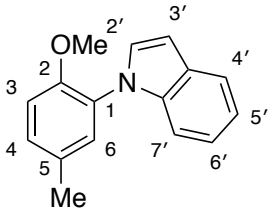
***N*-(2-Methoxy-5-methylphenyl)pyrrole (104h)**



N-(2-Methoxy-5-methylphenyl)pyrrole (**104h**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-methylanisole (**103**) (0.0630 mL, 0.500 mmol) and pyrrole (0.104 mL, 1.50 mmol). The iodination step was carried out at 70 °C for 5 h and the *N*-arylation step at 150 °C for 36 h. Purification by flash column chromatography (hexane/diethyl ether, 9:1) gave *N*-(2-methoxy-5-methylphenyl)pyrrole (**104h**) (0.0350 g, 37%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2931 (CH), 1512 (C=C), 1483, 1327, 1242, 1070, 1024, 723; δ_H (400 MHz, $CDCl_3$) 2.32 (3H, s, 5-CH_3), 3.79 (3H, s, OCH_3), 6.30 (2H, t, *J* 2.2 Hz, 3′-H and 4′-H), 6.91

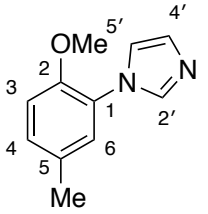
(1H, d, *J* 8.2 Hz, 3-H), 6.97 (2H, t, *J* 2.2 Hz, 2′-H and 5′-H), 7.05 (1H, dd, *J* 8.2, 2.1 Hz, 4-H), 7.10 (1H, d, *J* 2.1 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 20.4 (CH_3), 56.0 (CH_3), 108.7 (2 × CH), 112.4 (CH), 122.0 (2 × CH), 126.4 (CH), 127.7 (CH), 130.0 (C), 130.5 (C), 150.6 (C); *m/z* (ESI) 210.0892 (MNa^+. $C_{12}H_{13}NNaO$ requires 210.0889).

1-(2-Methoxy-5-methylphenyl)-1*H*-indole (104i)



1-(2-Methoxy-5-methylphenyl)-1*H*-indole (**104i**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-methylanisole (**103**) (0.0630 mL, 0.500 mmol) and indole (0.0879 g, 0.750 mmol). The iodination step was carried out at 70 °C for 20 h and the *N*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (hexane/dichloromethane, 9:1) gave 1-(2-methoxy-5-methylphenyl)-1*H*-indole (**104i**) (0.0303 g, 25%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2928 (CH), 1514 (C=C), 1462, 1254, 741; δ_H (500 MHz, $CDCl_3$) 2.34 (3H, s, 5-CH_3), 3.72 (3H, s, OCH_3), 6.63 (1H, dd, *J* 3.2, 0.7 Hz, 3′-H), 6.97 (1H, d, *J* 8.2 Hz, 3-H), 7.10–7.24 (5H, m, 6-H, 4′-H, 5′-H, 6′-H and 7′-H), 7.26 (1H, d, *J* 3.2 Hz, 2′-H), 7.66 (1H, dd, *J* 8.2, 1.2 Hz, 4-H); δ_C (126 MHz, $CDCl_3$) 20.4 (CH_3), 55.9 (CH_3), 102.4 (CH), 110.9 (CH), 112.5 (CH), 119.8 (CH), 120.7 (CH), 121.8 (CH), 127.9 (C), 128.5 (C), 128.6 (CH), 128.8 (CH), 129.3 (CH), 130.4 (C), 136.8 (C), 152.3 (C); *m/z* (ESI) 260.1040 (MNa^+. $C_{16}H_{15}NNaO$ requires 260.1046).

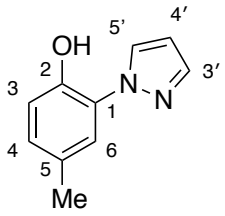
***N*-(2-Methoxy-5-methylphenyl)imidazole (104j)**[487]



N-(2-Methoxy-5-methylphenyl)imidazole (**104j**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using 4-methylanisole (**103**) (0.0630

mL, 0.500 mmol) and imidazole (0.102 g, 1.50 mmol). The iodination step was carried out at 70 °C for 5 h and the *N*-arylation step at 150 °C for 36 h. Purification by flash column chromatography (ethyl acetate/methanol, 9:1) gave *N*-(2-methoxy-5-methylphenyl)imidazole (**104j**) (0.0490 g, 51%) as a colourless oil. Spectroscopic data were consistent with the literature.[487] δ_H (500 MHz, $CDCl_3$) 2.33 (3H, s, 5-CH_3), 3.80 (3H, s, OCH_3), 6.94 (1H, d, *J* 8.4 Hz, 3-H), 7.09 (1H, d, *J* 1.8 Hz, 6-H), 7.14 (1H, dd, *J* 8.4, 1.8 Hz, 4-H), 7.15–7.24 (2H, m, 5′-H and 4′-H), 7.79 (1H, br s, 2′-H); δ_C (126 MHz, $CDCl_3$) 20.4 (CH_3), 55.9 (CH_3), 112.4 (CH), 120.3 (CH), 126.1 (CH), 126.2 (C), 128.7 (CH), 129.2 (CH), 130.7 (C), 137.8 (CH), 150.4 (C); *m/z* (ESI) 189 (MH^+. 100%).

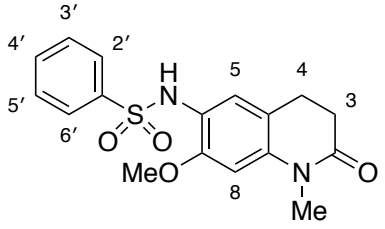
_N_-(2-Hydroxy-5-methylphenyl)-1_H_-pyrazole (106)



An oven-dried microwave vial was flushed with argon and charged with *N*-iodosuccinimide (0.113 g, 0.500 mmol) and dry toluene (3.0 mL). To this suspension was added silver bis(trifluoromethanesulfonyl)imide (0.0150 g, 0.0375 mmol) and *p*-cresol (**105**) (0.0530 mL, 0.500 mmol). The reaction mixture was stirred at 40 °C for 5 h in the dark. The reaction mixture was cooled to room temperature and pyrazole (0.102 g, 1.50 mmol), copper(I) iodide (9.52 mg, 0.0500 mmol), cesium carbonate (0.326 g, 1.00 mmol), *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (16.0 µL, 0.100 mmol) and water (0.5 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 24 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL), washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/diethyl ether, 4:1) gave *N*-(2-hydroxy-5-methylphenyl)-1*H*-pyrazole (**106**) (0.0315 g, 37%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3036 (OH), 2920 (CH), 1518 (C=C), 1333, 1279, 1250, 750; δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, 5-CH_3), 6.49 (1H, dd, *J* 2.4, 2.1 Hz, 4′-H), 6.95–7.01 (2H,

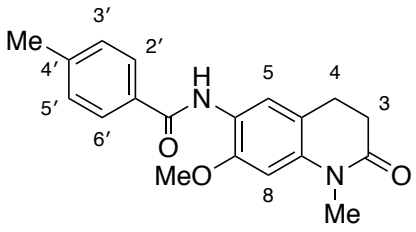
m, 3-H and 4-H), 7.18 (1H, br s, 6-H), 7.72 (1H, d, *J* 2.1 Hz, ArH), 7.99 (1H, d, *J* 2.4 Hz, ArH), 11.11 (1H, s, OH); δ_C (101 MHz, $CDCl_3$) 20.6 (CH_3), 106.7 (CH), 118.3 (CH), 118.7 (CH), 124.5 (C), 126.6 (CH), 128.2 (CH), 128.9 (C), 138.9 (CH), 147.0 (C); *m/z* (ESI) 197.0684 (MNa^+. $C_{10}H_{10}N_2NaO$ requires 197.0685).

_N_-Methyl-6-benzenesulfonamide-7-methoxy-3,4-dihydro-1H-quinolin-2-one (108a)



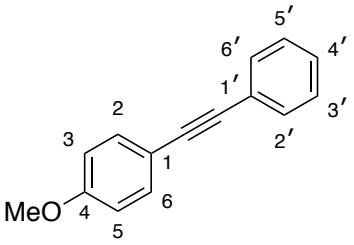
N-Methyl-6-benzenesulfonamide-7-methoxy-3,4-dihydro-1*H*-quinolin-2-one (**108a**) was synthesised as described for *N*-(2-amino-5-cyanophenyl)-1*H*-pyrazole (**101a**) using *N*-methyl-7-methoxy-3,4-dihydro-1*H*-quinolin-2-one (**107**) (0.0500 g, 0.262 mmol) and benzenesulfonamide (0.122 g, 0.780 mmol), iron(III) chloride (1.01 mg, 0.00625 mmol) and [BMIM]NTf_2 (6.00 μL, 0.0196 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 150 °C for 20 h. Purification by flash column chromatography (ethyl acetate/hexane, 7:3) gave *N*-methyl-6-benzenesulfonamide-7-methoxy-3,4-dihydro-1*H*-quinolin-2-one (**108a**) (0.0510 g, 56%) as a white solid. Mp 185–188 °C; ν_{max}/cm^{-1} (neat) 3252 (NH), 2967 (CH), 1665 (C=O), 1616, 1518, 1332, 1171, 1146, 1115, 1092, 1061, 934, 763; δ_H (400 MHz, $CDCl_3$) 2.61 (2H, dd, *J* 9.2, 6.8 Hz, 4-H_2), 2.83 (2H, dd, *J* 7.6, 6.8 Hz, 3-H_2), 3.29 (3H, s, NCH_3), 3.55 (3H, s, OCH_3), 6.33 (1H, s, 8-H), 6.76 (1H, br s, NH), 7.35 (1H, s, 5-H), 7.39–7.44 (2H, m, 3′-H and 5′-H), 7.52 (1H, tt, *J* 7.2, 1.2 Hz, 4′-H), 7.70–7.74 (2H, m, 2′-H and 6′-H); δ_c (101 MHz, $CDCl_3$) 24.6 (CH_2), 29.6 (CH_3), 31.8 (CH_2), 55.8 (CH_3), 98.7 (CH), 118.6 (C), 120.0 (C), 122.5 (CH), 127.2 (2 × CH), 128.7 (2 × CH), 132.8 (CH), 138.8 (C), 139.3 (C), 149.8 (C), 170.4 (C); *m/z* (ESI) 369.0873 (MNa^+. $C_{17}H_{18}N_2NaO_4S$ requires 369.0879).

_N_-Methyl-6-(4′-methylbenzamide)-7-methoxy-3,4-dihydro-1_H_-quinolin-2-one (108c)



_N_-Methyl-6-(4′-methylbenzamide)-7-methoxy-3,4-dihydro-1_H_-quinolin-2-one (**108c**) was synthesised as described for _N_-methyl-6-benzenesulfonamide-7-methoxy-3,4-dihydro-1_H_-quinolin-2-one (**108a**) using _N_-methyl-7-methoxy-3,4-dihydro-1_H_-quinolin-2-one (**107**) (0.0500 g, 0.262 mmol) and _p_-toluamide (0.106 g, 0.783 mmol). The iodination step was carried out at 40 °C for 4 h and the _N_-arylation step at 150 °C for 20 h. Purification by flash column chromatography (dichloromethane/diethyl ether, 3:2) gave _N_-methyl-6-(4′-methylbenzamide)-7-methoxy-3,4-dihydro-1_H_-quinolin-2-one (**108c**) (0.0520 g, 61%) as a white solid. Mp 164–166 °C; ν_{max}/cm^{-1} (neat) 3428 (NH), 2955 (CH), 1663 (C=O), 1614, 1533, 1472, 1427, 1350, 1265, 1244, 1206, 1126, 1061, 745; δ_H (500 MHz, $CDCl_3$) 2.43 (3H, s, 4′-CH_3), 2.62–2.66 (2H, m, 4-H_2), 2.86–2.90 (2H, m, 3-H_2), 3.37 (3H, s, NCH_3), 3.94 (3H, s, OCH_3), 6.56 (1H, s, 8-H), 7.29 (2H, d, _J_ 8.2 Hz, 3′-H and 5′-H), 7.78 (2H, d, _J_ 8.2 Hz, 2′-H and 6′-H), 8.36 (1H, s, 5-H), 8.39 (1H, br s, NH); δ_c (126 MHz, $CDCl_3$) 21.5 (CH_3), 24.9 (CH_2), 29.6 (CH_3), 32.0 (CH_2), 56.2 (CH_3), 98.3 (CH), 118.3 (C), 119.4 (CH), 122.7 (C), 127.0 (2 × CH), 129.4 (2 × CH), 132.3 (C), 136.6 (C), 142.3 (C), 147.6 (C), 165.1 (C), 170.5 (C); _m/z_ (ESI) 347.1364 (MNa^+. $C_{19}H_{20}N_2NaO_3$ requires 347.1366).

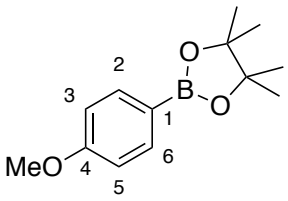
4-(Phenylethynyl)anisole (111)[488]



Iron(III) chloride (2.03 mg, 0.0125 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (11.0 μL, 0.0375 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of _N_-

iodosuccinimide (0.113 g, 0.500 mmol) in toluene (1.0 mL). Anisole (0.0540 mL, 0.500 mmol) was then added and the mixture was stirred at 40 °C for 4 h. Upon the completion of the iodination, phenylacetylene (0.110 mL, 1.00 mmol), copper(I) iodide (9.52 mg, 0.0500 mmol), cesium carbonate (0.325 g, 1.00 mmol), *N*,*N*′-dimethylethylenediamine (10.8 μL, 0.100 mmol) and water (0.5 mL) were added. The reaction mixture was degassed under argon for 0.1 h then heated to 150 °C for 48 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL), washed with a 10% sodium thiosulfate solution (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane, 9:1) gave 4-(phenylethynyl)anisole (**111**) (0.0410 g, 39%) as a brown solid. Mp 61–63 °C (lit.[488] 57–59 °C); δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 6.87 (2H, d, *J* 8.9 Hz, 3-H and 5-H), 7.29–7.36 (3H, m, 3′-H, 4′-H and 5′-H), 7.47 (1H, d, *J* 8.9 Hz, 2-H and 6-H), 7.49–7.54 (2H, m, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 55.3 (CH_3), 88.1 (C), 89.4 (C), 114.0 (CH), 115.4 (C), 123.6 (C), 128.0 (2 × CH), 128.3 (2 × CH), 131.5 (2 × CH), 133.1 (2 × CH), 159.6 (C); *m/z* (ESI) 231 (MNa^+. 100%).

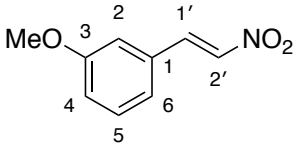
2′-(4-Methoxyphenyl)-4′,4′,5′,5′-tetramethyl-1′,3′,2′-dioxaborolane (113)[269]



An oven-dried microwave vial was flushed with argon and charged with bis(pinacolato)diboron (0.191 g, 0.750 mmol), 4-iodoanisole (0.0585 g, 0.250 mmol), copper(I) iodide (0.00476 g, 0.0250 mmol) and dry tetrahydrofuran (2.0 mL). *n*-Tributylphosphine (0.00800 mL, 0.0325 mmol) was added followed by potassium *tert*-butoxide (0.0840 g, 0.750 mmol) under argon. The mixture was degassed under argon for 0.1 h and the reaction mixture was stirred at 70 °C for 20 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate, filtered through a short-pad of Celite® then concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 9:1) gave 2′-(4-methoxyphenyl)-4′,4′,5′,5′-tetramethyl-1′,3′,2′-dioxaborolane (**113**) (0.0192 g, 33%) as a colourless oil. Spectroscopic data were consistent with the literature.[269] δ_H (400

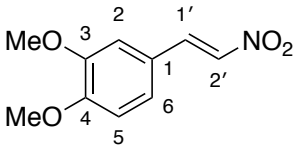
MHz, $CDCl_3$) 1.33 (12 H, s, 4 × CH_3), 3.82 (3H, s, OCH_3), 6.89 (2H, d, *J* 8.7 Hz, 3-H and 5-H), 7.75 (2H, d, *J* 8.7 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 24.9 (4 × CH_3), 55.1 (CH_3), 83.5 (C), 113.3 (2 × CH), 136.5 (2 × CH), 162.2 (C); *m/z* (ESI) 257 (MNa^+. 100%).

3-Methoxy-1-[(*E*)-2′-nitrovinyl]benzene (120a)[489]



To a solution of *m*-anisaldehyde (**119a**) (0.890 mL, 7.30 mmol) in toluene (30 mL) was added nitromethane (2.00 mL, 37.0 mmol) and ammonium acetate (0.560 g, 7.30 mmol). The resulting solution was heated under reflux for 18 h. The reaction mixture was washed with water (2 × 30 mL), followed by brine (2 × 30 mL). Purification by flash column chromatography (dichloromethane) gave 3-methoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120a**) (1.21 g, 97%) as a yellow solid. Mp 91–92 °C (lit.[489] 92–94 °C); δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 7.02–7.08 (2H, m, 2-H and 6-H), 7.14 (1H, d, *J* 7.6 Hz, 4-H), 7.37 (1H, t, *J* 7.6 Hz, 5-H), 7.57 (1H, d, *J* 13.6 Hz, 2′-H), 7.97 (1H, d, *J* 13.6 Hz, 1′-H); δ_C (101 MHz, $CDCl_3$) 55.4 (CH_3), 114.0 (CH), 118.0 (CH), 121.7 (CH), 130.4 (CH), 131.4 (C), 137.4 (CH), 139.0 (CH), 160.2 (C); *m/z* (EI) 179 (M^+. 100%), 136 (82), 135 (72), 84 (86), 77 (50).

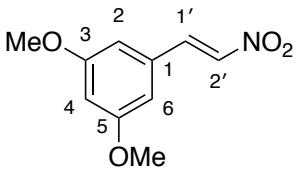
3,4-Dimethoxy-1-[(*E*)-2′-nitrovinyl]benzene (120b)[490]



3,4-Dimethoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120b**) was synthesised as described for 3-methoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120a**) using 3,4-dimethoxybenzaldehyde (**119b**) (1.00 g, 6.00 mmol). Purification by flash column chromatography (dichloromethane) gave 3,4-dimethoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120b**) (1.04 g, 83%) as a yellow solid. Mp 134–136 °C (lit.[490] 135–137 °C); δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.91 (1H, d, *J* 8.3 Hz, 5-H), 7.01 (1H, d, *J* 1.7 Hz, 2-H), 7.18 (1H, dd, *J* 8.3, 1.7 Hz, 6-H), 7.53 (1H, d, *J* 13.6 Hz, 2′-H), 7.96

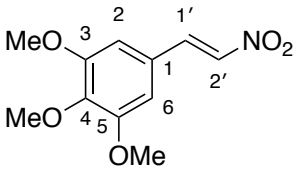
(1H, d, *J* 13.6 Hz, 1′-H); δ_C (101 MHz, $CDCl_3$) 56.0 (CH_3), 56.1 (CH_3), 110.3 (CH), 111.4 (CH), 122.8 (C), 124.6 (CH), 135.2 (CH), 139.3 (CH), 149.6 (C), 152.9 (C); *m/z* (ESI) 232 (MNa^+. 100%).

3,5-Dimethoxy-1-[(*E*)-2′-nitrovinyl]benzene (120c)[491]



3,5-Dimethoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120c**) was synthesised as described for 3-methoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120a**) using 3,5-dimethoxybenzaldehyde (**119c**) (0.350 g, 2.10 mmol). The residue was recrystallised from diethyl ether which gave 3,5-dimethoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120c**) (0.357 g, 81%) as a yellow crystalline solid. Mp 81–83 °C (from diethyl ether) (lit.[491] 78 °C); δ_H (400 MHz, $CDCl_3$) 3.83 (6H, s, 2 × OCH_3), 6.59 (1H, t, *J* 2.2 Hz, 4-H), 6.66 (2H, d, *J* 2.2 Hz, 2-H and 6-H), 7.54 (1H, d, *J* 13.6 Hz, 2′-H), 7.92 (1H, d, *J* 13.6 Hz, 1′-H); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 55.6 (CH_3), 102.8 (CH), 104.2 (CH), 107.0 (CH), 107.6 (CH), 133.4 (CH), 139.2 (C), 160.7 (C), 161.3 (C); *m/z* (EI) 209 (M^+. 100%), 189 (48), 165 (90), 135 (34), 84 (100).

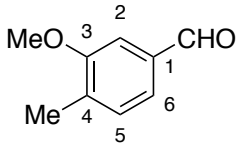
1-[(*E*)-2′-Nitrovinyl]-3,4,5-Trimethoxybenzene (120d)[490]



1-[(*E*)-2′-Nitrovinyl]-3,4,5-trimethoxybenzene (**120d**) was synthesised as described for 3-methoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120a**) using 3,4,5-trimethoxybenzaldehyde (**119d**) (1.00 g, 5.10 mmol). The residue was recrystallised from hexane, which gave 1-[(*E*)-2′-nitrovinyl]-3,4,5-trimethoxybenzene (**120d**) (1.14 g, 94%) as a yellow crystalline solid. Mp 119–121 °C (from hexane) (lit.[490] 122–124 °C); δ_H (400 MHz, $CDCl_3$) 3.91 (6H, s, 2 × OCH_3), 3.92 (3H, s, OCH_3), 6.76 (2H, s, 2-H and 6-H), 7.52 (1H, d, *J* 13.6 Hz, 2′-H), 7.94 (1H, d, *J* 13.6 Hz, 1′-H); δ_C (101 MHz, $CDCl_3$) 56.3 (2 × CH_3), 61.1 (CH_3), 106.5 (2 × CH), 125.3 (C), 136.4 (CH),

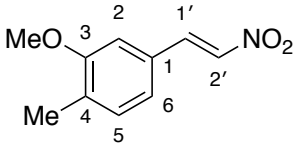
139.3 (CH), 141.8 (C), 153.7 (2 × C); *m/z* (ESI) 262 (MNa^+. 100%).

3-Methoxy-4-methylbenzaldehyde (**119e**)[492]



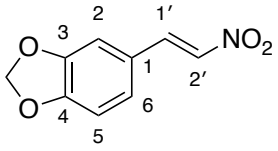
To a stirred solution of lithium aluminium hydride (0.425 g, 11.1 mmol) in dry tetrahydrofuran (20 mL) was added a solution of methyl 3-methoxy-4-methylbenzoate (1.00 g, 5.55 mmol) in dry tetrahydrofuran (10 mL) dropwise at 0 °C. The resulting suspension was warmed to room temperature and stirred for 4 h after which, the solution was cooled to 0 °C and diluted with tetrahydrofuran (20 mL). Water (0.5 mL) was added slowly followed by 15% aqueous sodium hydroxide solution (0.5 mL) and water (1.5 mL). The resulting solution was warmed to room temperature, magnesium sulfate (0.50 g) was added and stirred for 0.5 h. The suspension was filtered and the filtrate was concentrated *in vacuo* to give 3-methoxy-4-methylbenzyl alcohol (0.767 g, 91%) as a colourless oil which was used without further purification. To a stirred solution of 3-methoxy-4-methylbenzyl alcohol (0.737 g, 4.85 mmol) in chloroform (25 mL) was added manganese dioxide (4.22 g, 48.5 mmol). The resulting suspension was stirred at room temperature for 18 h. The crude reaction mixture was filtered through Celite® and concentrated *in vacuo* to give 3-methoxy-4-methylbenzaldehyde (**119e**) (0.621 g, 75%) as a white solid. Mp 34–36 °C (lit.[492] 39–41 °C); δ_H (400 MHz, $CDCl_3$) 2.29 (3H, s, 4-CH_3), 3.90 (3H, s, OCH_3), 7.29 (1H, d, *J* 7.5 Hz, 5-H), 7.34 (1H, d, *J* 1.4 Hz, 2-H), 7.36 (1H, dd, *J* 7.5, 1.4 Hz, 6-H), 9.93 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 16.9 (CH_3), 55.5 (CH_3), 107.9 (CH), 124.5 (CH), 130.9 (C), 134.9 (CH), 135.9 (C), 158.3 (C), 192.0 (CH); *m/z* (EI) 150 (M^+. 100%), 121 (19), 91 (28), 84 (21).

3-Methoxy-4-methyl-1-[(*E*)-2′-nitrovinyl]benzene (120e)



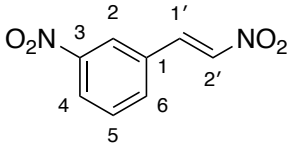
3-Methoxy-4-methyl-1-[(*E*)-2′-nitrovinyl]benzene (**120e**) was synthesised as described for 3-methoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120a**) using 3-methoxy-4-methylbenzaldehyde (**119e**) (0.624 g, 4.16 mmol). The residue was recrystallised from hexane which gave 3-methoxy-4-methyl-1-[(*E*)-2′-nitrovinyl]benzene (**120e**) (0.585 g, 73%) as a yellow solid. Mp 142–143 °C (from hexane); ν_{max}/cm^{-1} (neat) 3119, 2945 (CH), 1629, 1602 (C=C), 1573, 1494, 1414, 1343, 1328, 1248, 1159, 1035, 976, 814; δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, 4-CH_3), 3.87 (3H, s, OCH_3), 6.92 (1H, s, 2-H), 7.06 (1H, d, *J* 7.6 Hz, 6-H), 7.19 (1H, d, *J* 7.6 Hz, 5-H), 7.57 (1H, d, *J* 13.6 Hz, 2′-H), 7.97 (1H, d, *J* 13.6 Hz, 1′-H); δ_C (101 MHz, $CDCl_3$) 16.6 (CH_3), 55.4 (CH_3), 109.3 (CH), 122.2 (CH), 128.8 (C), 131.4 (CH), 132.4 (C), 136.3 (CH), 139.6 (CH), 158.3 (C); *m/z* (ESI) 216.0626 (MNa^+. $C_{10}H_{11}NNaO_3$ requires 216.0631).

3,4-Methylenedioxy-1-[(*E*)-2′-nitrovinyl]benzene (120f)[493]



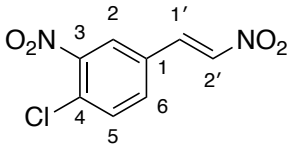
3,4-Methylenedioxy-1-[(*E*)-2′-nitrovinyl]benzene (**120f**) was synthesised as described for 3-methoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120a**) using piperonal (**119f**) (1.00 g, 6.66 mmol). The residue was recrystallised from hexane which gave 3,4-methylenedioxy-1-[(*E*)-2′-nitrovinyl]benzene (**120f**) (1.03 g, 80%) as a yellow solid. Mp 142–143 °C (from hexane) (lit.[493] 148 °C); δ_H (400 MHz, $CDCl_3$) 6.06 (2H, s, OCH_2O), 6.87 (1H, d, *J* 8.0 Hz, 5-H), 7.00 (1H, d, *J* 1.8 Hz, 2-H), 7.08 (1H, dd, *J* 8.0, 1.8 Hz, 6-H), 7.47 (1H, d, *J* 13.6 Hz, 2′-H), 7.92 (1H, d, *J* 13.6 Hz, 1′-H); δ_C (101 MHz, $CDCl_3$) 102.1 (CH_2), 107.0 (CH), 109.1 (CH), 124.2 (CH), 126.6 (CH), 135.5 (C), 139.1 (CH), 148.8 (C), 151.4 (C); *m/z* (EI) 193 (M^+. 100%), 146 (100), 89 (65), 84 (51), 63 (44).

3-Nitro-1-[(*E*)-2′-nitrovinyl]benzene (120g)[494]



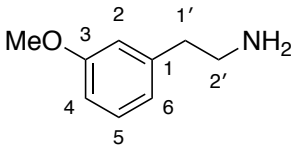
3-Nitro-1-[(*E*)-2′-nitrovinyl]benzene (**120g**) was synthesised as described for 3-methoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120a**) using 3-nitrobenzaldehyde (**119g**) (1.00 g, 6.62 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 3-nitro-1-[(*E*)-2′-nitrovinyl]benzene (**120g**) (0.406 g, 31%) as a yellow solid. Mp 119–121 °C (lit.[494] 125–126 °C); δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* 13.7 Hz, 2′-H), 7.69 (1H, t, *J* 8.0 Hz, 5-H), 7.88 (1H, dt, *J* 8.0, 1.6 Hz, 6-H), 8.05 (1H, d, *J* 13.7 Hz, 1′-H), 8.35 (1H, dt, *J* 8.0, 1.6 Hz, 4-H), 8.43 (1H, t, *J* 1.6 Hz, 2-H); δ_C (101 MHz, $CDCl_3$) 123.5 (CH), 126.2 (CH), 130.6 (CH), 131.9 (C), 134.4 (CH), 136.2 (CH), 139.3 (CH), 148.9 (C); *m/z* (EI) 194 (M^+. 100%), 147 (48), 118 (38), 102 (100), 84 (82), 76 (36).

4-Chloro-3-nitro-1-[(*E*)-2′-nitrovinyl]benzene (120h)



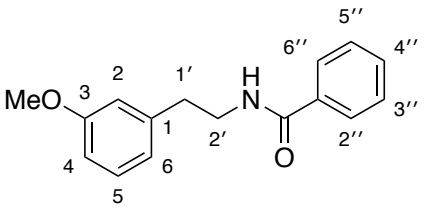
4-Chloro-3-nitro-1-[(*E*)-2′-nitrovinyl]benzene (**120h**) was synthesised as described for 3-methoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120a**) using 4-chloro-3-nitrobenzaldehyde (**119h**) (2.00 g, 10.8 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 4-chloro-3-nitro-1-[(*E*)-2′-nitrovinyl]benzene (**120h**) (0.620 g, 26%) as a yellow solid. Mp 142–143 °C; ν_{max}/cm^{-1} (neat) 3109, 2945 (CH), 2361, 1605 (C=C), 1540, 1342, 1049, 833; δ_H (400 MHz, $CDCl_3$) 7.61 (1H, d, *J* 13.7 Hz, 2′-H), 7.66–7.72 (2H, m, 5-H and 6-H), 7.96 (1H, d, *J* 13.7 Hz, 1′-H), 8.06 (1H, d, *J* 1.2 Hz, 2-H); δ_C (101 MHz, $CDCl_3$) 125.6 (CH), 130.1 (C), 130.4 (C), 132.6 (CH), 133.2 (CH), 133.8 (C), 135.1 (CH), 139.4 (CH); *m/z* (EI) 227.9929 (M^+. $C_8H_5{}^{35}ClN_2O_4$ requires 227.9938), 181 (100%), 152 (38), 136 (95), 115 (38), 101 (48), 89 (41), 75 (54).

1′-(3-Methoxyphenyl)ethyl-2′-amine (121a)[495]



To a suspension of sodium borohydride (0.180 g, 4.80 mmol) in dry tetrahydrofuran (10 mL) was added boron trifluoride diethyl etherate (0.750 mL, 6.00 mmol) dropwise at 0 °C and the contents were stirred at room temperature for 0.25 h. A solution of 3-methoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120a**) in tetrahydrofuran (3.0 mL) was added dropwise into the reaction mixture which was then heated under reflux for 6.5 h. After cooling to room temperature, the reaction was quenched by the slow addition of ice water (12 mL). The reaction mixture was acidified with 1 M aqueous hydrochloric acid (12 mL) and heated to 85 °C for 2 h. The reaction mixture was cooled to room temperature, washed with dichloromethane (2 × 10 mL), then 1 M aqueous sodium hydroxide was added until basic (ca. pH 12). The aqueous layer was extracted with dichloromethane (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give 1′-(3-methoxyphenyl)ethyl-2′-amine (**121a**) (0.137 g, 92%) as a yellow oil which was used without further purification. Spectroscopic data were consistent with the literature.[495] δ_H (400 MHz, $CDCl_3$) 1.99 (2H, br s, NH_2), 2.72 (2H, t, *J* 6.8 Hz, 1′-H_2), 2.96 (2H, t, *J* 6.8 Hz, 2′-H_2), 3.78 (3H, s, OCH_3), 6.73–6.80 (3H, m, 2-H, 4-H and 6-H), 7.21 (1H, t, *J* 7.6 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 39.0 (CH_2), 43.0 (CH_2), 55.2 (CH_3), 111.6 (CH), 114.6 (CH), 121.2 (CH), 129.5 (CH), 140.9 (C), 159.8 (C); *m/z* (ESI) 152 (MH^+. 100%).

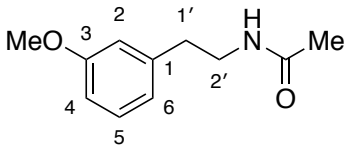
***N*-[(3-Methoxyphenyl)ethyl]benzamide (122a)**[496]



1′-(3-Methoxyphenyl)ethyl-2′-amine (**121a**) (0.0500 g, 0.331 mmol) was dissolved in dry dichloromethane (5.0 mL) and triethylamine (0.0700 mL, 0.500 mmol) was added. The reaction mixture was cooled to 0 °C and benzoyl chloride (0.0390 mL,

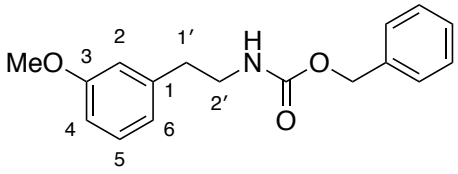
0.331 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h, warmed to room temperature and stirred for 20 h. The reaction mixture was diluted with dichloromethane (10 mL), washed with 1 M aqueous hydrochloric acid (10 mL) then brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-[(3-methoxyphenyl)ethyl]benzamide (**122a**) (0.0765 g, 91% yield) as a white solid. Mp 64–66 °C (lit.[496] 65–66 °C); δ_H (400 MHz, $CDCl_3$) 2.91 (2H, t, *J* 6.9 Hz, 1′-H_2), 3.71 (2H, q, *J* 6.9 Hz, 2′-H_2), 3.78 (3H, s, OCH_3), 6.24 (1H, br s, NH), 6.76–6.84 (3H, m, 2-H, 4-H and 6-H), 7.20–7.26 (1H, m, 5-H), 7.36–7.42 (2H, m, 3″-H and 5″-H), 7.44–7.50 (1H, m, 4″-H), 7.67–7.72 (2H, m, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 35.8 (CH_2), 41.1 (CH_2), 55.2 (CH_3), 112.1 (CH), 114.4 (CH), 121.1 (CH), 126.8 (2 × CH), 128.6 (2 × CH), 129.7 (CH), 131.4 (CH), 134.7 (C), 140.5 (C), 159.9 (C), 167.5 (C); *m/z* (EI) 255 (M^+. 25%), 134 (100), 105 (62), 77 (25).

_N_-[(3-Methoxyphenyl)ethyl]acetamide (122b)[497]



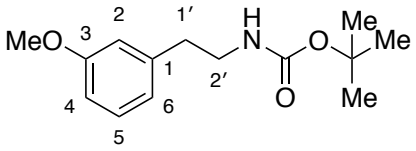
1′-(3-Methoxyphenyl)ethyl-2′-amine (**121a**) (0.0500 g, 0.331 mmol) was dissolved in dry dichloromethane (10 mL) and acetic anhydride (0.0380 mL, 0.400 mmol) was added while stirring. The reaction mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with dichloromethane (15 mL), washed with 1 M aqueous sodium carbonate (15 mL), then brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give *N*-[(3-methoxyphenyl)ethyl]acetamide (**122b**) (0.0600 g, 94%) as a yellow oil which was used without further purification. Spectroscopic data were consistent with the literature.[497] δ_H (400 MHz, $CDCl_3$) 1.94 (3H, s, CH_3CO), 2.79 (2H, t, *J* 6.8 Hz, 1′-H_2), 3.51 (2H, q, *J* 6.8 Hz, 2′-H_2), 3.80 (3H, s, OCH_3), 5.44 (1H, br s, NH), 6.72–6.82 (3H, m, 2-H, 4-H and 6-H), 7.23 (1H, t, *J* 7.9 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 23.4 (CH_3), 35.7 (CH_2), 40.5 (CH_2), 50.2 (CH_3), 111.9 (CH), 114.5 (CH), 121.1 (CH), 129.7 (CH), 140.5 (C), 159.9 (C), 170.0 (C); *m/z* (ESI) 216 (MNa^+. 100%).

Benzyl *N*-[(3-methoxyphenyl)ethyl]carbamate (122c)[498]



1′-(3-Methoxyphenyl)ethyl-2′-amine (**121a**) (0.100 g, 0.660 mmol) was dissolved in dry dichloromethane (10 mL) and triethylamine (0.142 mL, 1.00 mmol) was added while stirring. The reaction mixture was cooled to 0 °C and benzyl chloroformate (0.114 mL, 0.800 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h, warmed to room temperature and stirred for 5 h. The reaction mixture was diluted with dichloromethane (15 mL), washed with 1 M aqueous hydrochloric acid (15 mL), then brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave benzyl *N*-[(3-methoxyphenyl)ethyl]carbamate (**122c**) (0.134 g, 72%) as a colourless oil. Spectroscopic data were consistent with the literature.[498] δ_H (400 MHz, $CDCl_3$) 2.79 (2H, t, *J* 6.6 Hz, 1′-H_2), 3.45 (2H, q, *J* 6.6 Hz, 2′-H_2), 3.78 (3H, s, OCH_3), 4.76 (1H, br s, NH), 5.09 (2H, s, OCH_2), 6.69–6.81 (3H, m, 2-H, 4-H and 6-H), 7.21 (1H, t, *J* 7.9 Hz, 5-H), 7.28–7.38 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 36.1 (CH_2), 42.1 (CH_2), 55.2 (CH_3), 66.7 (CH_2), 111.9 (CH), 114.5 (CH), 121.1 (CH), 128.1 (2 × CH), 128.5 (2 × CH), 128.6 (CH), 129.6 (CH), 136.6 (C), 140.3 (C), 156.3 (C), 159.8 (C); *m/z* (ESI) 308 (MNa^+. 100%).

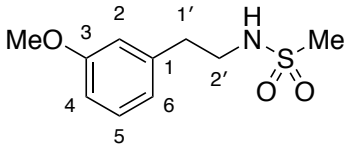
***tert*-Butyl-*N*-[(3-methoxyphenyl)ethyl]carbamate (122d)**[499]



1′-(3-Methoxyphenyl)ethyl-2′-amine (**121a**) (0.200 g, 1.32 mmol) was dissolved in dry dichloromethane (10 mL) and triethylamine (0.370 mL, 2.64 mmol) was added with stirring. Di-*tert*-butyl dicarbonate (0.870 g, 3.97 mmol) was added and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (petroleum ether/ethyl acetate, 4:1) to give *tert*-butyl-*N*-[(3-

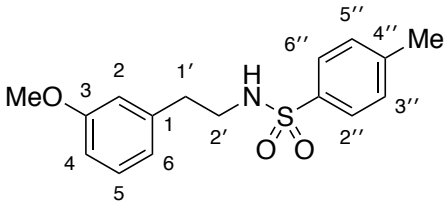
methoxyphenyl)ethyl]carbamate (**122d**) (0.253 g, 76%) as a yellow oil. Spectroscopic data were consistent with the literature.[499] δ_H (400 MHz, $CHCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 2.77 (2H, t, *J* 6.9 Hz, 1′-H_2), 3.38 (2H, q, *J* 6.9 Hz, 2′-H_2), 3.80 (3H, s, OCH_3), 4.55 (1H, br s, NH), 6.72–6.89 (3H, m, 2-H, 4-H and 6-H), 7.22 (1H, t, *J* 7.9 Hz, 5-H); δ_C (101 MHz, $CHCl_3$) 28.4 (3 × CH_3), 36.3 (CH_2), 41.7 (CH_2), 55.2 (CH_3), 80.5 (C), 111.8 (CH), 114.5 (CH), 121.1 (CH), 129.6 (CH), 140.6 (C), 155.9 (C), 159.8 (C); *m/z* (EI) 251 (M^+. 12%), 195 (32), 134 (100), 121 (48), 91 (24).

N-[(3-Methoxyphenyl)ethyl]methanesulfonamide (122e)



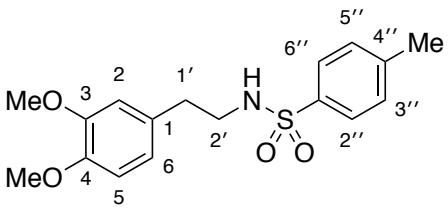
1′-(3-Methoxyphenyl)ethyl-2′-amine (**121a**) (0.198 g, 1.32 mmol) was dissolved in dry dichloromethane (10 mL) and triethylamine (0.370 mL, 2.64 mmol) was added with stirring. The reaction mixture was cooled to 0 °C and methanesulfonyl chloride (0.120 mL, 1.59 mmol) was added. The reaction mixture was stirred at 0 °C for 0.5 h, warmed to room temperature and stirred for 4 h. The reaction mixture was diluted with dichloromethane (15 mL), washed with 1 M aqueous hydrochloric acid (15 mL), brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave *N*-[(3-methoxyphenyl)ethyl]methanesulfonamide (**122e**) (0.184 g, 60%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3287 (NH), 2936 (CH), 1586 (C=C), 1489, 1312, 1258, 1146, 783; δ_H (500 MHz, $CDCl_3$) 2.82–2.87 (5H, m, SO_2CH_3 and 1′-H_2), 3.39 (2H, q, *J* 6.4 Hz, 2′-H_2), 3.80 (3H, s, OCH_3), 4.44 (1H, br s, NH), 6.74–6.81 (3H, m, 2-H, 4-H and 6-H), 7.24 (1H, t, *J* 7.9 Hz, 5-H); δ_C (126 MHz, $CDCl_3$) 36.5 (CH_2), 40.3 (CH_3), 44.3 (CH_2), 55.2 (CH_3), 112.2 (CH), 114.7 (CH), 121.1 (CH), 129.9 (CH), 139.4 (C), 159.9 (C); *m/z* (EI) 229.0780 (M^+. $C_{10}H_{15}NO_3S$ requires 229.0773), 134 (100%), 122 (76), 108 (62), 91 (25).

***N*-[(3-Methoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (122f)**[500]



1′-(3-Methoxyphenyl)ethyl-2′-amine (**121a**) (0.200 g, 1.32 mmol) was dissolved in dry dichloromethane (10 mL) and triethylamine (0.280 mL, 1.98 mmol) was added with stirring. The reaction mixture was cooled to 0 °C and *p*-toluenesulfonyl chloride (0.302 g, 1.58 mmol) was added. The reaction mixture was stirred at 0 °C for 0.5 h, warmed to room temperature and stirred for 6 h. The reaction mixture was diluted with dichloromethane (15 mL), washed with 1 M aqueous hydrochloric acid (15 mL), brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave *N*-[(1-methoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (**122f**) (0.327 g, 81%) as a yellow oil. Spectroscopic data were consistent with the literature.[500] δ_H (400 MHz, $CDCl_3$) 2.45 (3H, s, 4″-CH_3), 2.75 (2H, t, *J* 6.9 Hz, 1′-H_2), 3.23 (2H, q, *J* 6.9 Hz, 2′-H_2), 3.79 (3H, s, OCH_3), 4.54 (1H, br s, NH), 6.63 (1H, br s, 2-H), 6.69 (1H, br d, *J* 7.9 Hz, 4-H), 6.78 (1H, dd, *J* 7.9, 2.5 Hz, 6-H), 7.20 (1H, t, *J* 7.9 Hz, 5-H), 7.31 (2H, d, *J* 8.2 Hz, 3″-H and 5″-H), 7.71 (2H, d, *J* 8.2 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 35.8 (CH_2), 44.1 (CH_2), 55.1 (CH_3), 112.1 (CH), 114.4 (CH), 121.0 (CH), 127.1 (2 × CH), 129.7 (2 × CH), 129.8 (CH), 136.9 (C), 139.2 (C), 143.4 (C), 159.9 (C); *m/z* (ESI) 328 (MNa^+. 100%).

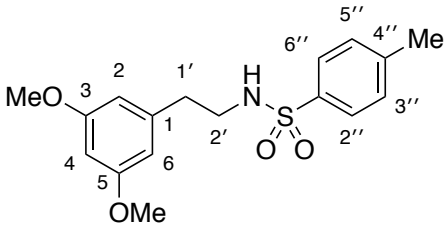
***N*-[(3,4-Dimethoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (123a)**[501]



To a suspension of sodium borohydride (0.817 g, 21.6 mmol) in dry tetrahydrofuran (50 mL) was added boron trifluoride diethyl etherate (3.37 mL, 27.3 mmol) dropwise at 0 °C and the mixture was stirred at room temperature for 0.25 h. A solution of 3,4-

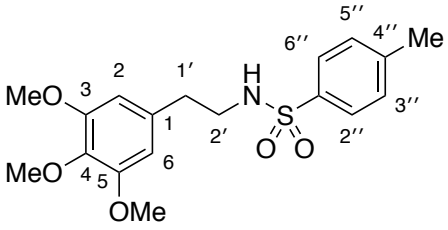
dimethoxy-1-[(*E*)-2′-nitrovinyl]benzene (**120b**) (0.950 g, 4.55 mmol) in tetrahydrofuran (15 mL) was added dropwise into the reaction mixture which was then heated under reflux for 6.5 h. After cooling to room temperature, the reaction was quenched by the slow addition of ice water (30 mL). The reaction mixture was acidified with 1 M aqueous hydrochloric acid (30 mL) and heated to 85 °C for 2 h. The reaction mixture was cooled to room temperature, washed with dichloromethane (2 × 40 mL), then 1 M aqueous sodium hydroxide was added until basic (ca. pH 12). The aqueous layer was extracted with dichloromethane (3 × 40 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give 1′-(3,4-dimethoxyphenyl)ethyl-2′-amine (**121b**) (0.582 g, 71%) as a yellow oil which was used without further purification. 1′-(3,4-Dimethoxyphenyl)ethyl-2′-amine (**121b**) (0.509 g, 2.81 mmol) was dissolved in dry dichloromethane (20 mL) and triethylamine (0.588 mL, 4.22 mmol) was added while stirring. The reaction mixture was cooled to 0 °C and *p*-toluenesulfonyl chloride (0.643 g, 3.37 mmol) was added. The reaction mixture was stirred at 0 °C for 0.5 h, warmed to room temperature and stirred for 6 h. The reaction mixture was diluted with dichloromethane (30 mL), washed with 1 M aqueous hydrochloric acid (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-[(3,4-dimethoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (**123a**) (0.716 g, 76%) as a yellow oil. Spectroscopic data were consistent with the literature.[501] δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s, 4″-CH_3), 2.71 (2H, t, *J* 6.8 Hz, 1′-H_2), 3.19 (2H, q, *J* 6.8 Hz, 2′-H_2), 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.31 (1H, t, *J* 6.8 Hz, NH), 6.55 (1H, d, *J* 2.0 Hz, 2-H), 6.62 (1H, dd, *J* 8.1, 2.0 Hz, 6-H), 6.76 (1H, d, *J* 8.1 Hz, 5-H), 7.28 (2H, d, *J* 8.2 Hz, 3″-H and 5″-H), 7.67 (2H, d, *J* 8.2 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 35.3 (CH_2), 44.3 (CH_2), 55.8 (CH_3), 56.0 (CH_3), 111.5 (CH), 111.8 (CH), 120.8 (CH), 127.1 (2 × CH), 129.7 (2 × CH), 130.1 (C), 136.9 (C), 143.4 (C), 148.0 (C), 149.2 (C); *m/z* (EI) 335 (M^+. 60%), 184 (17), 164 (38), 151 (100), 107 (17), 91 (48).

_N_-[(3,5-Dimethoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (123b)[502]



_N_-[(3,5-Dimethoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (**123b**) was synthesised as described for _N_-[(3,4-dimethoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (**123a**) using 3,5-dimethoxy-1-[(_E_)-2′-nitrovinyl]benzene (**120c**). Reduction of 3,5-dimethoxy-1-[(_E_)-2′-nitrovinyl]benzene (**120c**) (0.330 g, 1.58 mmol) using sodium borohydride (0.285 g, 7.51 mmol) and boron trifluoride diethyl etherate (1.17 mL, 9.48 mmol) gave 1′-(3,5-dimethoxyphenyl)ethyl-2′-amine (**121c**) (0.165 g, 58%) which was used without further purification. The _N_-protection step was carried out at room temperature for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave _N_-[(3,5-dimethoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (**123b**) (0.114 g, 50% yield) as a colourless oil. Spectroscopic data were consistent with the literature.[502] δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s, 4″-CH_3), 2.69 (2H, t, _J_ 6.9 Hz, 1′-H_2), 3.19 (2H, q, _J_ 6.9 Hz, 2′-H_2), 3.74 (6H, s, 2 × OCH_3), 4.48 (1H, t, _J_ 6.9 Hz, NH), 6.21 (2H, d, _J_ 2.2 Hz, 2-H and 6-H), 6.31 (1H, t, _J_ 2.2 Hz, 4-H), 7.27 (2H, d, _J_ 8.2 Hz, 3″-H and 5″-H), 7.68 (2H, d, _J_ 8.2 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 36.0 (CH_2), 44.0 (CH_2), 55.3 (2 × CH_3), 98.7 (CH), 106.7 (2 × CH), 127.1 (2 × CH), 129.7 (2 × CH), 136.9 (C), 140.0 (C), 143.4 (C), 161.1 (2 × C); _m/z_ (ESI) 358 (MNa^+. 100%).

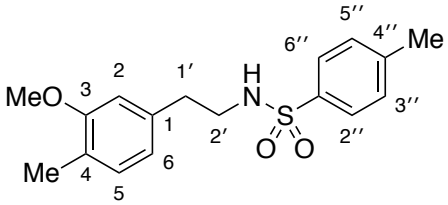
4″-Methyl-_N_-[(3,4,5-trimethoxyphenyl)ethyl]benzenesulfonamide (123c)[503]



4″-Methyl-_N_-[(3,4,5-trimethoxyphenyl)ethyl]benzenesulfonamide (**123c**) was synthesised as described for _N_-[(3,4-dimethoxyphenyl)ethyl]-4″-

methylbenzenesulfonamide (**123a**) using 1-[(*E*)-2′-nitrovinyl]-3,4,5-trimethoxybenzene (**120d**). Reduction of 1-[(*E*)-2′-nitrovinyl]-3,4,5-trimethoxybenzene (**120d**) (1.09 g, 4.56 mmol) using sodium borohydride (0.821 g, 21.7 mmol) and boron trifluoride diethyl etherate (3.90 mL, 27.4 mmol) gave 1′-(3,4,5-trimethoxyphenyl)ethyl-2′-amine (**121d**) (0.748 g, 78%) which was used without further purification. The *N*-protection step was carried out at room temperature for 6 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 3:2) gave 4″-methyl-*N*-[(3,4,5-trimethoxyphenyl)ethyl]benzenesulfonamide (**123c**) (0.903 g, 71%) as a yellow oil. Spectroscopic data were consistent with the literature.[503] δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s, 4″-CH_3), 2.71 (2H, t, *J* 6.8 Hz, 1′-H_2), 3.21 (2H, q, *J* 6.8 Hz, 2′-H_2), 3.80 (6H, s, 2 × OCH_3), 3.81 (3H, s, OCH_3), 4.48 (1H, t, *J* 6.8 Hz, NH), 6.28 (2H, s, 2-H and 6-H), 7.28 (2H, d, *J* 8.3 Hz, 3″-H and 5″-H), 7.69 (2H, d, *J* 8.3 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 36.1 (CH_2), 44.2 (CH_2), 56.1 (2 × CH_3), 60.8 (CH_3), 105.7 (2 × CH), 127.1 (2 × CH), 129.7 (2 × CH), 133.3 (C), 136.9 (C), 137.0 (C), 143.5 (C), 153.4 (2 × C); *m/z* (ESI) 388 (MNa^+. 100%).

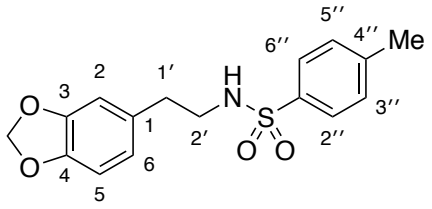
N-[(3-Methoxy-4-methylphenyl)ethyl]-4″-methylbenzenesulfonamide (123d)



N-[(3-Methoxy-4-methylphenyl)ethyl]-4″-methylbenzenesulfonamide (**123d**) was synthesised as described for *N*-[(3,4-dimethoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (**123a**) using 3-methoxy-4-methyl-1-[(*E*)-2′-nitrovinyl]benzene (**120e**). Reduction of 3-methoxy-4-methyl-1-[(*E*)-2′-nitrovinyl]benzene (**120e**) (0.585 g, 3.03 mmol) using sodium borohydride (0.757 g, 20.5 mmol) and boron trifluoride diethyl etherate (3.42 mL, 26.5 mmol) gave 1′-(3-methoxy-4-methylphenyl)ethyl-2′-amine (**121e**) (0.356 g, 71%) which was used without further purification. The *N*-protection step was carried out at room temperature for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave *N*-[(3-methoxy-4-methylphenyl)ethyl]-4″-methylbenzenesulfonamide (**123d**) (0.278 g, 45% yield) as a yellow oil. ν_{max}/cm^{-1}

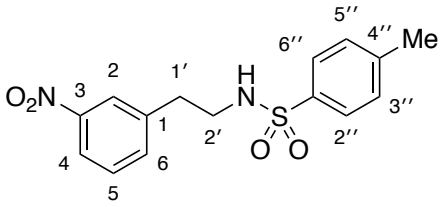
(neat) 3264 (NH), 2924 (CH), 1586 (C=C), 1512, 1464, 1414, 1323, 1256, 1155, 1094, 814; δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, 4-CH_3), 2.42 (3H, s, 4″-CH_3), 2.72 (2H, t, *J* 6.8 Hz, 1′-H_2), 3.20 (2H, q, *J* 6.8, Hz, 2′-H_2), 3.76 (3H, s, OCH_3), 4.34 (1H, t, *J* 6.8 Hz, NH), 6.51 (1H, d, *J* 1.4 Hz, 2-H), 6.51 (1H, dd, *J* 7.5, 1.4 Hz, 6-H), 7.01 (1H, d, *J* 7.5 Hz, 5-H), 7.27 (2H, d, *J* 8.2 Hz, 3″-H and 5″-H), 7.67 (2H, d, *J* 8.2 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 15.8 (CH_3), 21.5 (CH_3), 35.7 (CH_2), 44.2 (CH_2), 55.2 (CH_3), 110.4 (CH), 120.4 (CH), 125.2 (C), 127.1 (2 × CH), 129.7 (2 × CH), 130.8 (CH), 136.3 (C), 137.0 (C), 143.4 (C), 158.0 (C); *m/z* (ESI) 342.1125 (MNa^+. $C_{17}H_{21}NNaO_3S$ requires 342.1134).

4″-Methyl-*N*-[(3,4-methylenedioxyphenyl)ethyl]benzenesulfonamide (123e)[504]



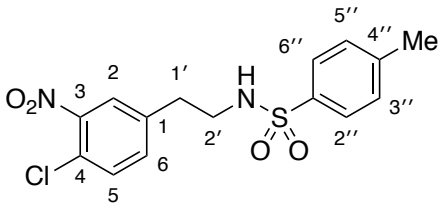
4″-Methyl-*N*-[(3,4-methylenedioxyphenyl)ethyl]benzenesulfonamide (**123e**) was synthesised as described for *N*-[(3,4-dimethoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (**123a**) using 3,4-methylenedioxy-1-[(*E*)-2′-nitrovinyl]benzene (**120f**). Reduction of 3,4-methylenedioxy-1-[(*E*)-2′-nitrovinyl]benzene (**120f**) (1.03 g, 5.32 mmol) using sodium borohydride (0.957 g, 25.3 mmol) and boron trifluoride diethyl etherate (3.90 mL, 31.9 mmol) gave 1′-(3,4-methylenedioxyphenyl)ethyl-2′-amine (**121f**) (0.587 g, 66%) which was used without further purification. The *N*-protection step was carried out at room temperature for 6 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 4″-methyl-*N*-[(3,4-methylenedioxyphenyl)ethyl]benzenesulfonamide (**123e**) (0.679 g, 76% yield) as a white solid. Mp 86–88 °C (lit.[504] 89–90 °C); δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, 4″-CH_3), 2.67 (2H, t, *J* 6.8 Hz, 1′-H_2), 3.16 (2H, q, *J* 6.8 Hz, 2′-H_2), 4.34 (1H, br s, NH), 5.92 (2H, s, OCH_2O), 6.49–6.54 (2H, m, 2-H and 5-H), 6.70 (1H, dd, *J* 7.1, 1.3 Hz, 6-H), 7.29 (2H, d, *J* 8.4 Hz, 3″-H and 5″-H), 7.69 (2H, d, *J* 8.4 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 35.5 (CH_2), 44.3 (CH_2), 101.0 (CH_2), 108.5 (CH), 109.0 (CH), 121.8 (CH), 127.1 (2 × CH), 129.7 (2 × CH), 131.3 (C), 137.0 (C), 143.5 (C), 146.5 (C), 147.9 (C); *m/z* (ESI) 342 (MNa^+. 100%).

4″-Methyl-*N*-[(3-nitrophenyl)ethyl]benzenesulfonamide (123f)



4″-Methyl-*N*-[(3-nitrophenyl)ethyl]benzenesulfonamide (**123f**) was synthesised as described for *N*-[(3,4-dimethoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (**123a**) using 3-nitro-1-[(*E*)-2′-nitrovinyl]benzene (**120g**). Reduction of 3-nitro-1-[(*E*)-2′-nitrovinyl]benzene (**120g**) (0.281 g, 1.45 mmol) using sodium borohydride (0.363 g, 9.78 mmol) and boron trifluoride diethyl etherate (1.59 mL, 12.3 mmol) gave 1′-(3-nitrophenyl)ethyl-2′-amine (**121g**) (0.186 g, 77%) which was used without further purification. The *N*-protection step was carried out at room temperature for 6 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave 4″-methyl-*N*-[(3-nitrophenyl)ethyl]benzenesulfonamide (**123f**) (0.142 g, 82%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3285 (NH), 1597 (C=C), 1526, 1348, 1325, 1155, 1094, 814; δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s, 4″-CH_3), 2.88 (2H, t, *J* 7.0 Hz, 1′-H_2), 3.25 (2H, q, *J* 7.0 Hz, 2′-H_2), 5.03 (1H, br s, NH), 7.27 (2H, d, *J* 7.9 Hz, 3″-H and 5″-H), 7.42 (1H, t, *J* 7.8 Hz, 5-H), 7.47 (1H, dt, *J* 7.8, 1.5 Hz, 6-H), 7.68 (2H, d, *J* 7.9 Hz, 2″-H and 6″-H), 7.90 (1H, t, *J* 1.5 Hz, 2-H), 8.03 (1H, dt, *J* 7.8, 1.5 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 35.5 (CH_2), 43.8 (CH_2), 121.8 (CH), 123.6 (CH), 127.0 (2 × CH), 129.5 (CH), 129.8 (2 × CH), 135.2 (CH), 136.7 (C), 140.0 (C), 143.7 (C), 148.3 (C); *m/z* (ESI) 343.0712 (MNa^+. $C_{15}H_{16}N_2NaO_4S$ requires 343.0723).

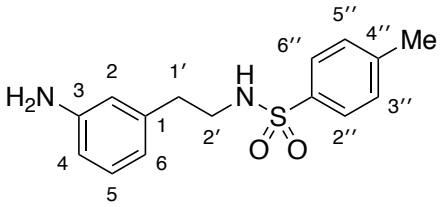
***N*-[(4-Chloro-3-nitrophenyl)ethyl]-4″-methylbenzenesulfonamide (123g)**



N-[(4-Chloro-3-nitrophenyl)ethyl]-4″-methylbenzenesulfonamide (**123g**) was synthesised as described for *N*-[(3,4-dimethoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (**123a**) using 4-chloro-3-nitro-1-[(*E*)-2′-

nitrovinyl]benzene (**120h**). Reduction of 4-chloro-3-nitro-1-[(*E*)-2′-nitrovinyl]benzene (**120h**) (0.255 g, 1.12 mmol) using sodium borohydride (0.280 g, 7.55 mmol) and boron trifluoride diethyl etherate (1.23 mL, 9.52 mmol) gave 1′-(4-chloro-3-nitrophenyl)ethyl-2′-amine (**121h**) (0.174 g, 78%) which was used without further purification. The *N*-protection step was carried out at room temperature for 6 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-[(4-chloro-3-nitrophenyl)ethyl]-4″-methylbenzenesulfonamide (**123g**) (0.238 g, 79% yield) as a yellow soild. Mp 84–86 °C; ν_{max}/cm^{-1} (neat) 3271 (NH), 2922 (CH), 2361, 1532, 1327, 1157, 1088, 810; δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, 4″-CH_3), 2.82 (2H, t, *J* 6.8 Hz, 1′-H_2), 3.22 (2H, q, *J* 6.8 Hz, 2′-H_2), 5.13 (1H, t, *J* 6.8 Hz, NH), 7.24–7.30 (3H, m, 6-H, 3″-H and 5″-H), 7.38 (1H, d, *J* 8.2 Hz, 5-H), 7.55 (1H, d, *J* 2.0 Hz, 2-H), 7.65 (2H, d, *J* 8.2 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 21.6 (CH_3), 34.9 (CH_2), 43.6 (CH_2), 125.2 (C), 125.8 (CH), 127.0 (2 × CH), 129.8 (2 × CH), 131.9 (CH), 133.8 (CH), 136.5 (C), 138.6 (C), 143.9 (C), 147.7 (C); *m/z* (ESI) 377.0326 (MNa^+. $C_{15}H_{15}{}^{35}ClN_2NaO_4S$ requires 377.0333).

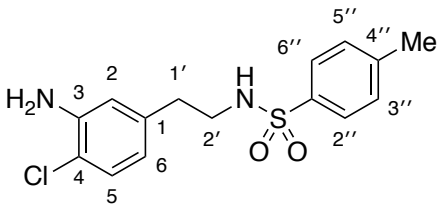
N-[(3-Aminophenyl)ethyl]-4″-methylbenzenesulfonamide (124a)



To a stirred solution of 4″-methyl-*N*-[(3-nitrophenyl)ethyl]benzenesulfonamide (**123f**) (0.142 g, 0.443 mmol) in ethanol (20 mL) was added tin dichloride dihydrate (0.758 g, 3.36 mmol) and the resulting solution was heated under reflux for 18 h. After cooling to room temperature, the reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (20 mL) and extracted with dichloromethane (4 × 50 mL). The combined extracts were washed with brine (2 × 200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave *N*-[(3-aminophenyl)ethyl]-4″-methylbenzenesulfonamide (**124a**) (0.102 g, 79%) as a white solid. Mp 80–82 °C; ν_{max}/cm^{-1} (neat) 3268 (NH), 2922 (CH), 1601 (C=C), 1495, 1460, 1319, 1153, 1093, 814; δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s, 4″-CH_3), 2.66 (2H, t, *J* 6.8 Hz, 1′-H_2), 3.17 (2H, q, *J* 6.8 Hz, 2′-H_2), 3.62 (2H, br s, NH_2), 4.38 (1H, br s,

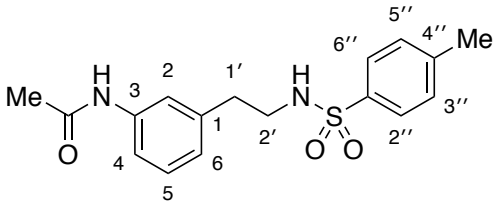
NH), 6.39 (1H, t, *J* 1.7 Hz, 2-H), 6.42–6.48 (1H, m, 4-H), 6.53 (1H, dd, *J* 7.6, 1.7 Hz, 6-H), 7.04 (1H, t, *J* 7.6 Hz, 5-H), 7.29 (2H, d, *J* 7.9 Hz, 3″-H and 5″-H), 7.69 (2H, d, *J* 7.9 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 35.7 (CH_2), 44.1 (CH_2), 113.6 (CH), 115.3 (CH), 118.8 (CH), 127.1 (2 × CH), 129.7 (2 × CH), 129.8 (CH), 137.0 (C), 138.8 (C), 143.4 (C), 146.8 (C); *m/z* (ESI) 313.0984 (MNa^+. $C_{15}H_{18}N_2NaO_2S$ requires 313.0981).

N-[(3-Amino-4-chlorophenyl)ethyl]-4″-methylbenzenesulfonamide (124b)



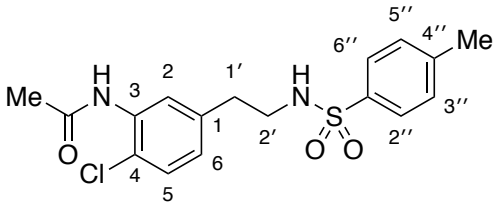
N-[(3-Amino-4-chlorophenyl)ethyl]-4″-methylbenzenesulfonamide (**124b**) was synthesised as described for *N*-[(3-aminophenyl)ethyl]-4″-methylbenzenesulfonamide (**124a**) using 4″-methyl-*N*-[(3-nitro-4-chlorophenyl)ethyl]benzenesulfonamide (**123g**) (0.278 g, 0.790 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-[(3-amino-4-chlorophenyl)ethyl]-4″-methylbenzenesulfonamide (**124b**) (0.226 g, 89%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3372 (NH), 3279 (NH), 2924 (CH), 2361, 1620 (C=C), 1497, 1435, 1319, 1156, 1088, 810; δ_H (400 MHz, $CDCl_3$) 2.41 (3H, s, 4″-CH_3), 2.62 (2H, t, *J* 6.8 Hz, 1′-H_2), 3.13 (2H, q, *J* 6.8 Hz, 2′-H_2), 4.00 (2H, br s, NH_2), 4.88 (1H, t, *J* 6.8 Hz, NH), 6.36 (1H, dd, *J* 8.1, 2.0 Hz, 6-H), 6.49 (1H, d, *J* 2.0 Hz, 2-H), 7.06 (1H, d, *J* 8.1 Hz, 5-H), 7.26 (2H, d, *J* 8.3 Hz, 3″-H and 5″-H), 7.67 (2H, d, *J* 8.3 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 21.6 (CH_3), 35.3 (CH_2), 44.0 (CH_2), 116.1 (CH), 117.7 (C), 119.2 (CH), 127.1 (2 × CH), 129.6 (CH), 129.7 (2 × CH), 136.8 (C), 137.5 (C), 143.0 (C), 143.5 (C); *m/z* (ESI) 347.0582 (MNa^+. $C_{15}H_{17}{}^{35}ClN_2NaO_2S$ requires 347.0591).

***N*-[(3-Acetamidophenyl)ethyl]-4″-methylbenzenesulfonamide (125a)**



Acetic anhydride (0.110 mL, 1.17 mmol) was added to a stirred solution of *N*-[(3-aminophenyl)ethyl]-4″-methylbenzenesulfonamide (**124a**) (0.225 g, 0.780 mmol) in dry dichloromethane (10 mL) and stirred at room temperature for 16 h. The reaction mixture was washed with saturated sodium carbonate (15 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 3:7) gave *N*-[(3-acetamidophenyl)ethyl]-4″-methylbenzenesulfonamide (**125a**) (0.245 g, 95%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3282 (NH), 2921 (CH), 1669 (C=O), 1613 (C=C), 1595, 1549, 1489, 1440, 1319, 1153, 1094, 814; δ_H (400 MHz, $CDCl_3$) 2.14 (3H, s, CH_3CO), 2.42 (3H, s, 4″-CH_3), 2.72 (2H, t, *J* 6.8 Hz, 1′-H_2), 3.18 (2H, q, *J* 6.8 Hz, 2′-H_2), 4.69 (1H, t, *J* 6.8 Hz, NH), 6.81 (1H, d, *J* 7.5 Hz, 4-H), 7.20 (1H, t, *J* 7.5 Hz, 5-H), 7.25–7.30 (3H, m, 2-H, 3″-H and 5″-H), 7.39 (1H, d, *J* 7.5 Hz, 6-H), 7.46 (1H, br s, NH), 7.69 (2H, d, *J* 7.9 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 24.6 (CH_3), 35.8 (CH_2), 44.1 (CH_2), 118.3 (CH), 120.2 (CH), 124.5 (CH), 127.1 (2 × CH), 129.3 (CH), 129.8 (2 × CH), 136.8 (C), 138.3 (C), 138.8 (C), 143.5 (C), 168.6 (C); *m/z* (ESI) 355.1080 (MNa^+. $C_{17}H_{20}N_2NaO_3S$ requires 355.1087).

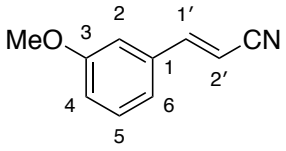
***N*-[(3-Acetamido-4-chlorophenyl)ethyl]-4″-methylbenzenesulfonamide (125b)**



N-[(3-Acetamido-4-chlorophenyl)ethyl]-4″-methylbenzenesulfonamide (**125b**) was synthesised as described for *N*-[(3-acetamidophenyl)ethyl]-4″-methylbenzenesulfonamide (**125a**) using *N*-[(3-amino-4-chlorophenyl)ethyl]-4″-methylbenzenesulfonamide (**124b**) (0.109 g, 0.340 mmol). Purification by flash

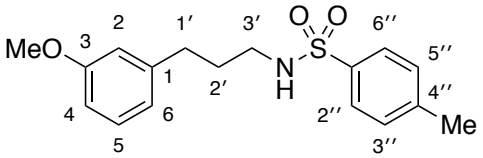
column chromatography (petroleum ether/ethyl acetate, 1:1) gave *N*-[(3-acetamido-4-chlorophenyl)ethyl]-4″-methylbenzenesulfonamide (**125b**) (0.121 g, 99%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3279 (NH), 2932 (CH), 2361, 1674 (C=O), 1582, 1528, 1427, 1319, 1157, 1096; δ_H (400 MHz, $CDCl_3$) 2.22 (3H, s, CH_3CO), 2.42 (3H, s, 4″-CH_3), 2.72 (2H, t, *J* 6.9 Hz, 1′-H_2), 3.19 (2H, q, *J* 6.9 Hz, 2′-H_2), 4.73 (1H, t, *J* 6.9 Hz, NH), 6.78 (1H, dd, *J* 8.2, 1.7 Hz, 6-H), 7.23 (1H, d, *J* 8.2 Hz, 5-H), 7.27 (2H, d, *J* 8.2 Hz, 3″-H and 5″-H), 7.59 (1H, br s, 2-H), 7.69 (2H, d, *J* 8.2 Hz, 2″-H and 6″-H), 8.11 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 24.9 (CH_3), 35.6 (CH_2), 44.0 (CH_2), 121.0 (C), 121.8 (CH), 125.1 (CH), 127.1 (2 × CH), 129.0 (CH), 129.7 (2 × CH), 134.6 (C), 136.9 (C), 137.9 (C), 143.4 (C), 168.4 (C); *m/z* (ESI) 389.0685 (MNa^+. $C_{17}H_{19}{}^{35}ClN_2NaO_3S$ requires 389.0697).

1′-(3-Methoxyphenyl)acrylonitrile (126)[505]



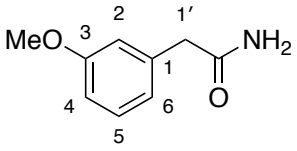
To a solution of *m*-anisaldehyde (**119a**) (1.79 mL, 14.7 mmol) in dry dichloromethane (25 mL) was added cyanomethylene triphenylphosphorane (4.88 g, 16.2 mmol) and the resulting mixture was stirred at room temperature for 16 h. After this time, the reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 9:1) to give 1′-(3-methoxyphenyl)acrylonitrile (**126**) (3:1 ratio of *E* to *Z* isomers) (1.81 g, 79%) as a colourless oil. Spectroscopic data is reported for the major *E* isomer. Spectroscopic data were consistent with the literature.[505] δ_H (400 MHz, $CDCl_3$) 3.84 (3H, s, OCH_3), 5.87 (1H, t, *J* 16.6 Hz, 2′-H), 6.93–7.05 (3H, m, 3 × ArH), 7.30–7.43 (2H, m, ArH and 1′-H); δ_C (101 MHz, $CDCl_3$) 55.4 (CH_3), 96.7 (CH), 112.5 (CH), 116.9 (CH), 117.1 (C), 120.0 (CH), 130.2 (CH), 134.8 (C), 150.5 (CH), 160.0 (C); *m/z* (EI) 159 (M^+. 100%), 116 (20), 89 (20).

***N*-[(3-Methoxyphenyl)propyl]-4″-methylbenzenesulfonamide (127)**[506]



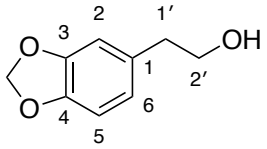
To a solution of 1′-(3-methoxyphenyl)acrylonitrile (**126**) (1.00 mL, 6.29 mmol) in ethanol (25 mL) was added 37% aqueous hydrochloric acid (3 mL) and 10% palladium on charcoal (0.073 g). The reaction mixture was hydrogenated at 2.5 bar for 72 h. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. The crude hydrochloride salt was dissolved in dichloromethane (25 mL) and triethylamine (0.700 mL, 5.00 mmol) was added. *p*-Toluenesulfonyl chloride (0.572 g, 3.00 mmol) was added at 0 °C and the resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane (20 mL) and washed with 1 M aqueous hydrochloric acid (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-[(3-methoxyphenyl)propyl]-4″-methylbenzenesulfonamide (**127**) (0.499 g, 63% over two-steps) as a colourless oil. Spectroscopic data were consistent with the literature.[506] δ_H (400 MHz, $CDCl_3$) 1.70–1.80 (2H, m, 2′-H_2), 2.40 (3H, s, 4″-CH_3), 2.56 (2H, t, *J* 7.7 Hz, 1′-H_2), 2.94 (2H, q, *J* 6.7 Hz, 3′-H_2), 3.75 (3H, s, OCH_3), 5.04 (1H, t, *J* 6.7 Hz, NH), 6.62–6.68 (2H, m, 2-H and 4-H), 6.70 (1H, ddd, *J* 8.0, 2.5, 0.8 Hz, 6-H), 7.14 (1H, t, *J* 8.0 Hz, 5-H), 7.28 (2H, d, *J* 8.3 Hz, 3″-H and 5″-H), 7.74 (2H, d, *J* 8.3 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 31.0 (CH_2), 32.8 (CH_2), 42.6 (CH_2), 55.2 (CH_3), 111.5 (CH), 114.1 (CH), 120.8 (CH), 127.1 (2 × CH), 129.4 (CH), 129.8 (2 × CH), 137.0 (C), 142.7 (C), 143.4 (C), 159.7 (C); *m/z* (ESI) 342 (MNa^+. 100%).

3-Methoxyphenylacetamide (129)[507]



To a stirred solution of 3-methoxyphenylacetic acid (**128**) (0.500 g, 3.00 mmol) in dry dichloromethane (15 mL) was added thionyl chloride (2.63 mL, 63.0 mmol) at 0 °C. The reaction mixture was heated under reflux for 2.5 h after which the solvent was removed *in vacuo*. The residue was dissolved in tetrahydrofuran (20 mL) and 25% aqueous ammonium hydroxide (4 mL) was added slowly at 0 °C. The reaction mixture was then stirred at room temperature for 16 h. The mixture was concentrated *in vacuo* and water (15 mL) was added. The solution was heated for 0.5 h. The suspension was cooled to 0 °C and the resulting white powder was collected by vacuum filtration and washed with ice-water to give 3-methoxyphenylacetamide (**129**) (0.209 g, 42%) as a colourless crystalline solid. Mp 139–141 °C (from water) (lit.[507] 137–139 °C); δ_H (400 MHz, $CDCl_3$) 3.56 (2H, s, 1′-H_2), 3.81 (3H, s, OCH_3), 5.41 (1H, br s, NH), 5.52 (1H, br s, NH), 6.80–6.88 (3H, m, 3 × ArH), 7.28 (1H, t, *J* 7.8 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 43.4 (CH_2), 55.2 (CH_3), 113.0 (CH), 115.0 (CH), 121.6 (CH), 130.1 (CH), 136.3 (C), 160.1 (C), 173.2 (C); *m/z* (ESI) 188 (MNa^+. 100%).

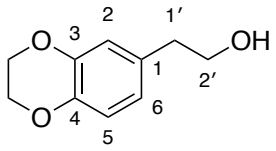
(3,4-Methylenedioxy)phenethan-2′-ol (131a)[508]



To a stirred suspension of lithium aluminium hydride (0.211 g, 5.55 mmol) in dry tetrahydrofuran (15 mL) was added 3,4-(methylenedioxy)phenylacetic acid (**130a**) (0.500 g, 2.78 mmol) in tetrahydrofuran (5 mL) dropwise under a constant stream of argon at 0 °C. The suspension was stirred at room temperature for 5 h, cooled to 0 °C and quenched with water (0.20 mL). To this solution was added 15% aqueous sodium hydroxide (0.20 mL), followed by water (0.60 mL). Magnesium sulfate was added and the suspension was stirred for 0.5 h, filtered, then concentrated *in vacuo*.

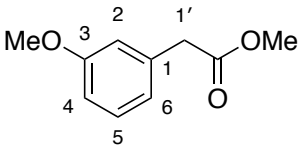
Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave (3,4-methylenedioxy)phenethan-2′-ol (**131a**) (0.308 g, 67%) as a colourless oil. Spectroscopic data were consistent with the literature.[508] δ_H (400 MHz, $CDCl_3$) 1.50 (1H, br s, OH), 2.78 (2H, t, *J* 6.6 Hz, 1′-H_2), 3.79 (2H, br s, 2′-H_2), 5.93 (2H, s, OCH_2O), 6.67 (1H, dd, *J* 7.9, 1.6 Hz, 6-H), 6.72 (1H, d, *J* 1.6 Hz, 2-H), 6.75 (1H, d, *J* 7.9 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 38.9 (CH_2), 63.7 (CH_2), 100.9 (CH_2), 108.3 (CH), 109.3 (CH), 121.9 (CH), 132.2 (C), 146.2 (C), 147.8 (C); *m/z* (EI) 166 (M^+. 30%), 135 (100).

1′-(Dihydro-3,4-benzodioxinyl)ethan-2′-ol (131b)[509]



1′-(Dihydro-3,4-benzodioxinyl)ethan-2′-ol (**131b**) was synthesised as described for (3,4-methylenedioxy)phenethan-2′-ol (**131a**) using 1,4-benzodioxane-6-acetic acid (**130b**) (0.487 g, 2.51 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave 1′-(dihydro-3,4-benzodioxinyl)ethan-2′-ol (**131b**) (0.425 g, 94%) as a colourless oil. Spectroscopic data were consistent with the literature.[509] δ_H (400 MHz, $CDCl_3$) 1.78 (1H, br s, OH), 2.74 (2H, t, *J* 6.5 Hz, 1′-H_2), 3.78 (2H, br s, 2′-H_2), 4.22 (4H, s, OCH_2CH_2O), 6.68 (1H, dd, *J* 8.2, 2.0 Hz, 6-H), 6.73 (1H, d, *J* 2.0 Hz, 2-H), 6.79 (1H, d, *J* 8.2 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 38.4 (CH_2), 63.6 (CH_2), 64.3 (CH_2), 64.4 (CH_2), 117.3 (CH), 117.6 (CH), 121.9 (CH), 131.7 (C), 142.1 (C), 143.4 (C); *m/z* (ESI) 203 (MNa^+. 100%).

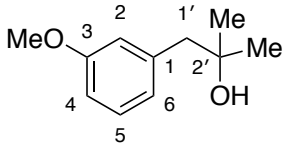
Methyl (3-methoxyphenyl)acetate (132)[510]



To a stirred solution of 3-methoxyphenylacetic acid (**128**) (2.00 g, 12.0 mmol) in methanol (20 mL) was added a few drops of concentrated sulfuric acid. The resulting mixture was heated under reflux for 16 h. The methanol was removed *in vacuo* and the residue was diluted with dichloromethane (50 mL). The solution was washed

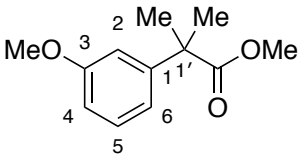
with water (4 × 50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated to give methyl (3-methoxyphenyl)acetate (**132**) (2.12 g, 99%) as a colourless oil. Spectroscopic data were consistent with the literature.[510] δ_H (400 MHz, $CDCl_3$) 3.59 (2H, s, 1′-H_2), 3.67 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 6.76–6.88 (3H, m, 2-H, 4-H and 6-H), 7.21 (1H, t, *J* 7.8 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 41.2 (CH_2), 52.0 (CH_3), 55.2 (CH_3), 112.6 (CH), 114.9 (CH), 121.6 (CH), 129.6 (CH), 135.4 (C), 159.8 (C), 171.9 (C); *m/z* (ESI) 203 (MNa^+. 100%).

2′,2′-Dimethyl-1′-(3-methoxyphenyl)ethan-2′-ol (133)



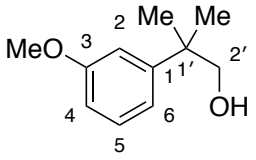
Methylmagnesium bromide (2.20 mL, 6.50 mmol; 3.0 M in diethyl ether) was added dropwise to a 0 °C solution of methyl (3-methoxyphenyl)acetate (**132**) (0.390 g, 2.17 mmol) in dry tetrahydrofuran (20 mL). The yellow solution was warmed to room temperature and stirred for 5 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (30 mL) and diluted with diethyl ether (30 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 2′,2′-dimethyl-1′-(3-methoxyphenyl)ethan-2′-ol (**133**) (0.301 g, 77%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3426 (OH), 2969 (CH), 1601 (C=C), 1489, 1261, 1153, 1047; δ_H (400 MHz, $CDCl_3$) 1.23 (6H, s, 2 × 2′-CH_3), 2.74 (2H, s, 1′-H_2), 3.79 (3H, s, OCH_3), 6.75–6.81 (3H, m, 2-H, 4-H and 6-H), 7.21 (1H, t, *J* 7.9 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 29.2 (2 × CH_3), 49.8 (CH_2), 55.2 (CH_3), 70.7 (C), 111.8 (CH), 116.3 (CH), 122.9 (CH), 129.2 (CH), 139.4 (C), 159.5 (C); *m/z* (ESI) 203.1044 (MNa^+. $C_{11}H_{16}NaO_2$ requires 203.1043).

Methyl 1′,1′-dimethyl-(3-methoxyphenyl)acetate[511]



To a stirred solution of methyl (3-methoxyphenyl)acetate (**132**) (1.10 g, 6.07 mmol) in dry tetrahydrofuran (30 mL) was added sodium hydride (60 % in mineral oil, 0.701 g, 29.2 mmol) at 0 °C. The suspension was stirred at 0 °C for 1 h, then methyl iodide (1.14 mL, 18.2 mmol) was added. The reaction mixture was warmed to room temperature, then stirred for 16 h. The reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with 1 M aqueous sodium thiosulfate solution (50 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated to give methyl 1′,1′-dimethyl-(3-methoxyphenyl)acetate (0.639 g, 55%) as a colourless oil.[511] δ_H (400 MHz, $CDCl_3$) 1.56 (6H, s, 2 × 1′-CH_3), 3.64 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 6.77 (1H, ddd, *J* 7.9, 2.2, 0.8 Hz, 4-H), 6.88 (1H, t, *J* 2.2 Hz, 2-H), 6.91 (1H, ddd, *J* 7.9, 2.2, 0.8 Hz, 6-H), 7.25 (1H, t, *J* 7.9 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 26.5 (2 × CH_3), 46.5 (C), 52.2 (CH_3), 55.2 (CH_3), 111.5 (CH), 112.1 (CH), 118.1 (CH), 129.4 (CH), 146.3 (C), 159.6 (C), 177.1 (C); *m/z* (ESI) 231 (MNa^+. 100%).

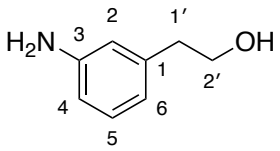
1′,1′-Dimethyl-1′-(3-methoxyphenyl)ethan-2′-ol (134)[512]



1′,1′-Dimethyl-1′-(3-methoxyphenyl)ethan-2′-ol (**134**) was synthesised as described for (3,4-methylenedioxy)phenethan-2′-ol (**131a**) using 1′,1′-dimethyl-(3-methoxyphenyl)acetate (0.640 g, 3.08 mmol). The reaction was quenched after 3 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 1′,1′-dimethyl-1′-(3-methoxyphenyl)ethan-2′-ol (**134**) (0.352 g, 64%) as a colourless oil. Spectroscopic data were consistent with the literature.[512] δ_H (400 MHz, $CDCl_3$) 1.29–1.34 (7H, m, 2 × 1′-CH_3 and OH), 3.59 (2H, d, *J* 6.2 Hz, 2′-H_2), 3.81 (3H, s, OCH_3), 6.76 (1H, ddd, *J* 8.0, 2.4, 0.7 Hz, 4-H), 6.93 (1H, t, *J* 2.4 Hz, 2-

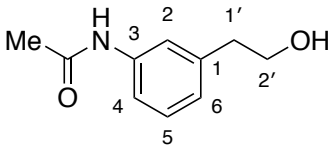
H), 6.97 (1H, ddd, *J* 8.0, 2.4, 0.7 Hz, 6-H), 7.26 (1H, t, *J* 8.0 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 25.4 (2 × CH_3), 40.2 (C), 55.2 (CH_3), 73.1 (CH_2), 110.8 (CH), 113.0 (CH), 118.7 (CH), 129.4 (CH), 148.2 (C), 159.7 (C); *m/z* (ESI) 203 (MNa^+. 100%).

1′-(3-Aminophenyl)ethan-2′-ol (136)[513]



To a stirred solution of 1′-(3-nitrophenyl)ethan-2′-ol (**135**) (0.350 g, 2.09 mmol) in ethanol (25 mL) was added tin dichloride dihydrate (2.40 g, 10.5 mmol) and the resulting solution was heated under reflux for 18 h. After cooling to room temperature, the reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (20 mL) and extracted with dichloromethane (5 × 50 mL). The combined extracts were washed with brine (2 × 200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 3:7) gave 1′-(3-aminophenyl)ethan-2′-ol (**136**) (0.090 g, 32%) as a colourless oil. Spectroscopic data were consistent with the literature.[513] δ_H (400 MHz, $CDCl_3$) 1.54 (1H, br s, OH), 2.78 (2H, t, *J* 6.5 Hz, 1′-H_2), 3.64 (2H, br s, NH_2), 3.83 (2H, t, *J* 6.5 Hz, 2′-H_2), 6.54–6.58 (2H, m, 2 × ArH), 6.60–6.65 (1H, m, ArH), 7.07–7.13 (1H, m, ArH); δ_C (101 MHz, $CDCl_3$) 39.2 (CH_2), 63.6 (CH_2), 113.3 (CH), 115.7 (CH), 119.2 (CH), 129.6 (CH), 139.7 (C), 146.6 (C); *m/z* (EI) 137 (M^+. 70%), 106 (100), 84 (38), 78 (37), 63 (42).

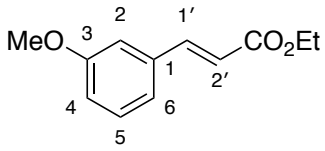
1′-(3-Acetamidophenyl)ethan-2′-ol (**137**)



Acetic anhydride (0.085 mL, 0.900 mmol) was added to a stirred solution of 1′-(3-aminophenyl)ethan-2′-ol (**136**) (0.082 g, 0.600 mmol) in dichloromethane (10 mL) and stirred for 24 h at room temperature. The reaction mixture was washed with aqueous saturated sodium carbonate (15 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from diethyl ether

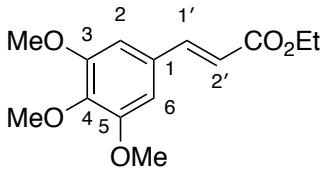
gave 1′-(3-acetamidophenyl)ethan-2′-ol (**137**) (0.042 g, 42%) as a white crystalline solid. Mp 102–104 °C (from diethyl ether); ν_{max}/cm^{-1} (neat) 3294 (NH), 2924 (CH), 1667 (C=O), 1612 (C=C), 1551, 1489, 1435, 1319, 1041, 787; δ_H (400 MHz, $CDCl_3$) 1.67 (1H, br s, OH), 2.16 (3H, s, CH_3CO), 2.84 (2H, t, *J* 6.6 Hz, 1′-H_2), 3.85 (2H, t, *J* 6.6 Hz, 2′-H_2), 6.95–7.00 (1H, m, ArH), 7.23–7.45 (4H, m, 3 × ArH and NH); δ_C (101 MHz, $CDCl_3$) 24.6 (CH_3), 39.1 (CH_2), 63.5 (CH_2), 118.1 (CH), 120.5 (CH), 125.0 (CH), 129.2 (CH), 138.1 (C), 139.6 (C), 168.4 (C); *m/z* (ESI) 202.0838 (MNa^+. $C_{10}H_{13}NNaO_2$ requires 202.0838).

Ethyl (*E*)-1′-(3-methoxyphenyl)acrylate (138a)[514]



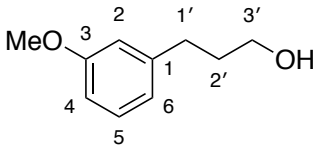
A solution of lithium chloride (0.310 g, 7.30 mmol), triethyl phosphonoacetate (1.45 mL, 7.30 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (1.09 mL, 7.30 mmol) in dry acetonitrile (30 mL) was stirred for 0.5 h. *m*-Anisaldehyde (**119a**) (0.890 mL, 7.30 mmol) was added and the solution was stirred at room temperature for 18 h. The reaction mixture was quenched with brine (30 mL), concentrated and the residue was extracted with diethyl ether (5 × 50 mL). The combined ethereal extracts were dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave ethyl (*E*)-1′-(3-methoxyphenyl)acrylate (**138a**) (1.36 g, 91%) as a colourless oil. Spectroscopic data were consistent with the literature.[514] δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 3.82 (3H, s, OCH_3), 4.26 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 6.42 (1H, d, *J* 15.9 Hz, 2′-H), 6.91 (1H, ddd, *J* 8.1, 2.5, 0.8 Hz, 4-H), 7.04 (1H, t, *J* 2.5 Hz, 2-H), 7.10 (1H, br d, *J* 8.1 Hz, 6-H), 7.29 (1H, t, *J* 8.1 Hz, 5-H), 7.64 (1H, d, *J* 15.9 Hz, 1′-H); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 55.3 (CH_3), 60.5 (CH_2), 112.9 (CH), 116.1 (CH), 118.6 (CH), 120.7 (CH), 129.9 (CH), 135.8 (C), 144.5 (CH), 159.9 (C), 166.9 (C); *m/z* (ESI) 207 (MH^+. 100%).

Ethyl (*E*)-1′-(3,4,5-trimethoxyphenyl)acrylate (138b)[515]



Ethyl (*E*)-1′-(3,4,5-trimethoxyphenyl)acrylate (**138b**) was synthesised as described for ethyl (*E*)-1′-(3-methoxyphenyl)acrylate (**138a**) using 3,4,5-trimethoxybenzaldehyde (**119d**) (1.00 g, 5.10 mmol). The resulting off-white solid was recrystallised from hot hexane which gave ethyl (*E*)-1′-(3,4,5-trimethoxyphenyl)acrylate (**138b**) (0.713 g, 53%) as a colourless crystalline solid. Mp 50–52 °C (from hexane) (lit.[515] 53–55 °C); δ_H (500 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 3.88 (3H, s, 4-OCH_3), 3.89 (6H, s, 2 × OCH_3), 4.26 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 6.35 (1H, d, *J* 15.9 Hz, 2′-H), 6.76 (2H, s, 2-H and 6-H), 7.60 (1H, d, *J* 15.9 Hz, 1′-H); δ_C (126 MHz, $CDCl_3$) 14.3 (CH_3), 56.1 (2 × CH_3), 60.5 (CH_2), 61.0 (CH_3), 105.2 (2 × CH), 117.5 (CH), 130.0 (C), 140.1 (C), 144.5 (CH), 153.4 (2 × C), 166.9 (C); *m/z* (ESI) 289 (MH^+. 100%).

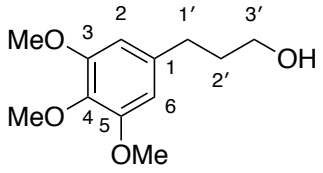
1′-(3-Methoxyphenyl)propan-3′-ol (139a)[516]



To a stirred suspension of lithium aluminium hydride (0.150 g, 3.94 mmol) in dry tetrahydrofuran (10 mL) was added ethyl (*E*)-1′-(3-methoxyphenyl)acrylate (**138a**) (0.325 g, 1.58 mmol) in tetrahydrofuran (10 mL) dropwise under a constant stream of argon at 0 °C. The suspension was stirred at room temperature for 5 h, then cooled to 0 °C and quenched with a saturated aqueous solution of potassium sodium tartrate (20 mL) and stirred overnight. The suspension was extracted with diethyl ether (5 × 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 1′-(3-methoxyphenyl)propan-3′-ol (**139a**) (0.179 g, 69%) as a colourless oil. Spectroscopic data were consistent with the literature.[516] δ_H (400 MHz, $CDCl_3$) 1.85–1.94 (2H, m, 2′-H_2), 2.69 (2H, t, *J* 7.9 Hz, 1′-H_2), 3.68

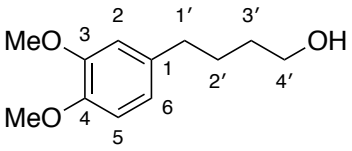
(2H, t, *J* 6.5 Hz, 3′-H_2), 3.80 (3H, s, OCH_3), 6.72–6.77 (2H, m, 2 × ArH), 6.78–6.82 (1H, m, ArH), 7.21 (1H, t, *J* 7.6 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 32.1 (CH_2), 34.1 (CH_2), 55.1 (CH_3), 62.3 (CH_2), 111.1 (CH), 114.2 (CH), 120.8 (CH), 129.4 (CH), 143.5 (C), 159.7 (C); *m/z* (ESI) 189 (MNa^+. 100%).

1′-(3,4,5-Trimethoxyphenyl)propan-3′-ol (139b)[517]



1′-(3,4,5-Trimethoxyphenyl)propan-3′-ol (**139b**) was synthesised as described for 1′-(3-methoxyphenyl)propan-3′-ol (**139a**) using ethyl (*E*)-1′-(3,4,5-trimethoxyphenyl)acrylate (**138b**) (0.596 g, 2.24 mmol). The suspension was stirred at room temperature for 5 h, cooled to 0 °C and quenched with water (0.25 mL). To this solution was added 15% aqueous sodium hydroxide (0.25 mL), followed by water (0.75 mL). Magnesium sulfate was added and the suspension was stirred for 0.5 h, filtered and concentrated *in vacuo*. Purification by flash column chromatography (ethyl acetate/petroleum ether, 3:2) gave 1′-(3,4,5-trimethoxyphenyl)propan-3′-ol (**139b**) (0.228 g, 45%) as a colourless oil. Spectroscopic data were consistent with the literature.[517] δ_H (400 MHz, $CDCl_3$) 1.42 (1H, br s, OH), 1.85–1.95 (2H, m, 2′-H_2), 2.63–2.69 (2H, m, 1′-H_2), 3.68 (2H, t, *J* 6.5 Hz, 3′-H_2), 3.83 (3H, s, OCH_3), 3.85 (6H, s, 2 × OCH_3), 6.42 (2H, s, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 32.6 (CH_2), 34.3 (CH_2), 56.1 (2 × CH_3), 60.9 (CH_3), 62.3 (CH_2), 105.3 (2 × CH), 136.1 (C), 137.7 (C), 153.2 (2 × C); *m/z* (ESI) 249 (MNa^+. 100%).

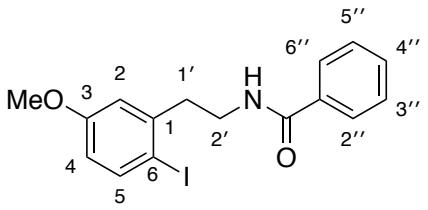
1′-(3,4-Dimethoxyphenyl)butan-4′-ol (141)[518]



1′-(3,4-Dimethoxyphenyl)butan-4′-ol (**141**) was synthesised as described for (3,4-methylenedioxy)phenethan-2′-ol (**131a**) using 3,4-dimethoxyphenylbutyric acid (**140**) (0.500 g, 2.23 mmol). The reaction was quenched after 4.5 h. Purification by

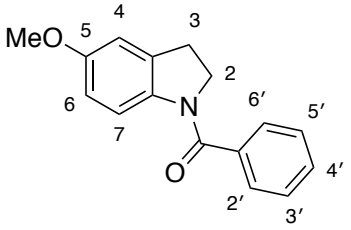
flash column chromatography (dichloromethane/ethyl acetate, 4:1) gave 1′-(3,4-dimethoxyphenyl)butan-4′-ol (**141**) (0.429 g, 92%) as a colourless oil. Spectroscopic data were consistent with the literature.[518] δ_H (500 MHz, $CDCl_3$) 1.31 (1H, br s, OH), 1.57–1.73 (4H, m, 2′-H_2 and 3′-H_2), 2.59 (2H, t, *J* 7.9 Hz, 1′-H_2), 3.66 (2H, t, *J* 6.4 Hz, 4′-H_2), 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.70–6.74 (2H, m, 2-H and 6-H), 6.78 (1H, d, *J* 8.1 Hz, 5-H); δ_C (126 MHz, $CDCl_3$) 27.3 (CH_2), 32.3 (CH_2), 35.3 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 62.8 (CH_2), 111.2 (CH), 111.7 (CH), 120.2 (CH), 135.0 (C), 147.1 (C), 148.8 (C); *m/z* (ESI) 233 (MNa^+. 100%).

6-Iodo-*N*-[(3-methoxyphenyl)ethyl]benzamide (142)



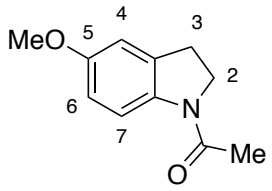
6-Iodo-*N*-[(3-methoxyphenyl)ethyl]benzamide (**142**) was synthesised as described for 4-iodoanisole (**82a**) using *N*-[(3-methoxyphenyl)ethyl]benzamide (**122a**) (0.0500 g, 0.200 mmol). The reaction mixture was stirred at 40 °C for 5 h. After cooling to room temperature, the solvent was removed *in vacuo* and the crude residue was filtered through a short-pad of silica, eluting with ethyl acetate. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 6-iodo-*N*-[(3-methoxyphenyl)ethyl]benzamide (**142**) (0.0663 g, 89%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3310 (NH), 2910 (CH), 1638 (C=O), 1595 (C=C), 1537, 1467, 1410, 1352, 1294, 1236, 1190, 1057, 802; δ_H (400 MHz, $CDCl_3$) 3.04 (2H, t, *J* 7.0 Hz, 1′-H_2), 3.66–3.75 (5H, m, 2′-H_2 and OCH_3), 6.37 (1H, br s, NH), 6.54 (1H, dd, *J* 8.7, 3.0 Hz, 4-H), 6.82 (1H, d, *J* 3.0 Hz, 2-H), 7.36–7.50 (3H, m, 3″-H, 4″-H and 5″-H), 7.67 (1H, d, *J* 8.7 Hz, 5-H), 7.71–7.76 (2H, m, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 40.1 (CH_2), 40.2 (CH_2), 55.4 (CH_3), 89.0 (C), 114.8 (CH), 115.7 (CH), 126.9 (2 × CH), 128.6 (2 × CH) 131.5 (CH), 134.5 (C), 140.0 (CH), 142.7 (C), 160.2 (C), 167.7 (C); *m/z* (EI) 381.0223 (M^+. $C_{16}H_{16}INO_2$ requires 381.0226), 260 (46%), 254 (100), 253 (12), 105 (85), 77 (36).

1-Benzoyl-5-methoxyindoline (143a)



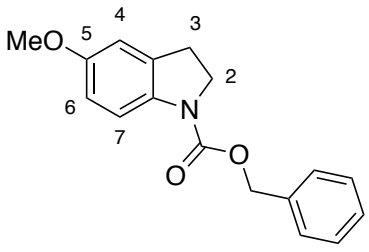
Iron(III) chloride (0.550 mg, 3.40 μmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (3.00 μL, 10.2 μmol) and stirred for 0.5 h at room temperature and then added to a solution of *N*-iodosuccinimide (0.0306 g, 0.136 mmol) in toluene (1.0 mL). *N*-[(3-Methoxyphenyl)ethyl]benzamide (**122a**) (0.0348 g, 0.136 mmol) was then added and the mixture was stirred at 40 °C for 5 h. Upon completion of the iodination step, the reaction mixture was cooled to room temperature and copper(I) iodide (3.00 mg, 14.0 μmol), cesium carbonate (0.0886 g, 0.272 mmol), *N*,*N*′-dimethylethylenediamine (3.00 μL, 27.2 μmol) and water (0.25 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 24 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 1-benzoyl-5-methoxyindoline (**143a**) (0.0271 g, 79%) as a brown solid. Mp 102–104 °C; ν_{max}/cm^{-1} (neat) 2922 (CH), 1624 (C=O), 1595 (C=O), 1487, 1400, 1294, 1140, 1026, 833; δ_H (500 MHz, DMSO-d_6, 100 °C) 3.08 (2H, t, *J* 8.2 Hz, 3-H_2), 3.76 (3H, s, OCH_3), 4.00 (2H, t, *J* 8.2 Hz, 2-H_2), 6.71 (1H, dd, *J* 8.7, 2.4 Hz, 6-H), 6.88 (1H, d, *J* 2.4 Hz, 4-H), 7.46–7.62 (6H, m, 6 × ArH); δ_C (126 MHz, DMSO-d_6, 100 °C) 28.4 (CH_2), 50.8 (CH_2), 56.1 (CH_3), 111.6 (CH), 112.6 (CH), 117.4 (CH), 127.3 (2 × CH), 128.8 (2 × CH) 130.2 (CH), 134.7 (C), 137.0 (C), 137.9 (C), 156.8 (C), 167.9 (C); *m/z* (EI) 253.1114 (M^+. $C_{16}H_{15}NO_2$ requires 253.1103), 148 (18%), 105 (100), 77 (30).

1-Acetyl-5-methoxyindoline (143b)[519]



1-Acetyl-5-methoxyindoline (**143b**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using *N*-[(3-methoxyphenyl)ethyl]acetamide (**122b**) (0.0490 g, 0.250 mmol). The iodination step was carried out at 40 °C for 5 h and the *N*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave 1-acetyl-5-methoxyindoline (**143b**) (0.0420 g, 87%) as a colourless oil. Spectroscopic data were consistent with the literature.[519] NMR spectra showed a 5:1 mixture of rotamers. Only signals for the major rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, CH_3CO), 3.17 (2H, t, *J* 8.4 Hz, 3-H_2), 3.78 (3H, s, OCH_3), 4.04 (2H, t, *J* 8.4 Hz, 2-H_2), 6.68–6.76 (2H, m, 4-H and 6-H), 8.12 (1H, d, *J* 8.6 Hz, 7-H); δ_C (101 MHz, $CDCl_3$) 24.0 (CH_3), 28.2 (CH_2), 48.9 (CH_2), 55.6 (CH_3), 110.9 (CH), 111.9 (CH), 117.5 (CH), 132.7 (C), 136.7 (C), 156.2 (C), 167.9 (C); *m/z* (EI) 191 (M^+. 80%), 149 (60), 134 (100).

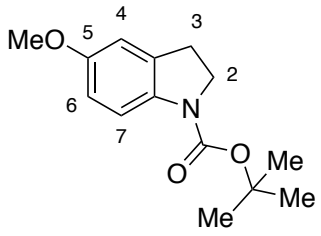
1-(Benzyloxycarbonyl)-5-methoxyindoline (143c)



1-(Benzyloxycarbonyl)-5-methoxyindoline (**143c**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using benzyl *N*-[(3-methoxyphenyl)ethyl]carbamate (**122c**) (0.0480 g, 0.170 mmol). The iodination step was carried out at 40 °C for 5 h and the *N*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 1-(benzyloxycarbonyl)-5-methoxyindoline (**143c**) (0.0302 g, 63%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2953 (CH), 1701 (C=O), 1493, 1406, 1325, 1263, 1132, 1024, 756; δ_H (500 MHz, DMSO-d_6, 100 °C) 3.09 (2H, t, *J* 8.6 Hz, 3-H_2), 3.74

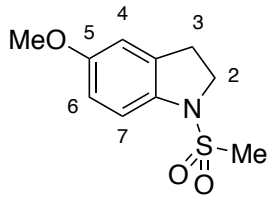
(3H, s, OCH_3), 4.01 (2H, t, *J* 8.6 Hz, 2-H_2), 5.25 (2H, s, OCH_2Ph), 6.72 (1H, dd, *J* 8.7, 2.6 Hz, 6-H), 6.84 (1H, d, *J* 2.6 Hz, 4-H), 7.31–7.45 (5H, m, Ph), 7.56 (1H, d, *J* 8.7 Hz, 7-H); δ_C (126 MHz, DMSO-d_6, 100 °C) 27.7 (CH_2), 48.0 (CH_2), 56.2 (CH_3), 66.8 (CH_2), 112.0 (CH), 112.9 (CH), 115.2 (CH), 128.1 (2 × CH), 128.3 (CH), 128.8 (2 × CH), 133.4 (C), 136.3 (C), 137.3 (C), 152.9 (C), 156.2 (C); *m/z* (ESI) 306.1095 (MNa^+. $C_{17}H_{17}NNaO_3$ requires 306.1101).

1-(*tert*-Butoxycarbonyl)-5-methoxyindoline (143d)[520]



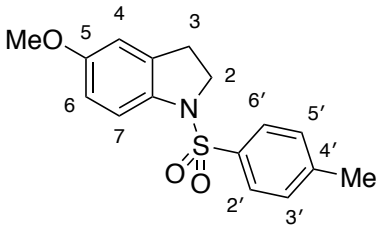
1-(*tert*-Butoxycarbonyl)-5-methoxyindoline (**143d**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using *tert*-butyl-*N*-[(3-methoxyphenyl)ethyl]carbamate (**122d**) (0.0630 g, 0.250 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 16 h. Purification by flash column chromatography (petroleum ether/diethyl ether, 9:1) gave 1-(*tert*-butoxycarbonyl)-5-methoxyindoline (**143d**) (0.0349 g, 56%) as a white solid. Mp 84–86 °C (lit.[520] Mp 87–89 °C); δ_H (500 MHz, DMSO-d_6, 100 °C) 1.53 (9H, s, $C(CH_3)_3$), 3.04 (2H, t, *J* 8.6 Hz, 3-H_2), 3.73 (3H, s, OCH_3), 3.91 (2H, *J* 8.6 Hz, 2-H_2), 6.71 (1H, dd, *J* 8.7, 2.5 Hz, 6-H), 6.81 (1H, d, *J* 2.5 Hz, 4-H), 7.50 (1H, d, *J* 8.7 Hz, 7-H); δ_C (126 MHz, DMSO-d_6, 100 °C) 27.5 (CH_2), 28.7 (3 × CH_3), 48.1 (CH_2), 56.2 (CH_3), 80.4 (C), 111.9 (CH), 112.8 (CH), 115.1 (CH), 133.3 (C), 136.6 (C), 152.3 (C), 155.8 (C); *m/z* (EI) 249 (M^+. 15%), 193 (100), 149 (28), 134 (62), 84 (30).

1-(Methanesulfonyl)-5-methoxyindoline (143e)



1-(Methanesulfonyl)-5-methoxyindoline (**143e**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using *N*-[(3-methoxyphenyl)ethyl]methanesulfonamide (**122e**) (0.0570 g, 0.250 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave 1-(methanesulfonyl)-5-methoxyindoline (**143e**) (0.0410 g, 73%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2932 (CH), 1489, 1343, 1157, 1030, 818; δ_H (400 MHz, $CDCl_3$) 2.81 (3H, s, SO_2CH_3), 3.12 (2H, t, *J* 8.5 Hz, 3-H_2), 3.78 (3H, s, OCH_3), 3.97 (2H, t, *J* 8.5 Hz, 2-H_2), 6.72 (1H, dd, *J* 8.8, 2.5 Hz, 6-H), 6.79 (1H, d, *J* 2.5 Hz, 4-H), 7.32 (2H, d, *J* 8.8 Hz, 7-H); δ_C (101 MHz, $CDCl_3$) 28.4 (CH_2), 33.9 (CH_3), 50.7 (CH_2), 55.7 (CH_3), 111.6 (CH), 112.8 (CH), 115.1 (CH), 133.1 (C), 135.4 (C), 156.8 (C); *m/z* (EI) 227.0617 (M^+. $C_{10}H_{13}NO_3S$ requires 227.0616), 148 (100%), 133 (69), 117 (38), 77 (33).

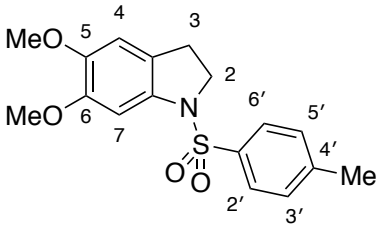
5-Methoxy-1-(4′-methylbenzenesulfonyl)indoline (143f)



5-Methoxy-1-(4′-methylbenzenesulfonyl)indoline (**143f**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using *N*-[(3-methoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (**122f**) (0.0765 g, 0.250 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 5-methoxy-1-(4′-methylbenzenesulfonyl)indoline (**143f**) (0.0703 g, 93%) as a yellow oil. ν_{max}/cm^{-1} (neat) 2943 (CH), 1597 (C=C),

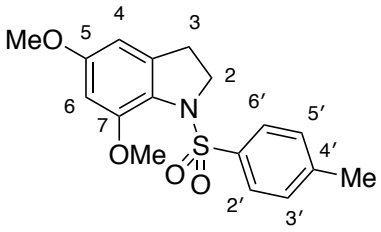
1485, 1350, 1163, 1032, 814; δ_H (400 MHz, $CDCl_3$) 2.39 (3H, s, 4′-CH_3), 2.77 (2H, t, *J* 8.2 Hz, 3-H_2), 3.77 (3H, s, OCH_3), 3.92 (2H, t, *J* 8.2 Hz, 2-H_2), 6.64 (1H, d, *J* 2.5 Hz, 4-H), 6.75 (1H, dd, *J* 8.8, 2.5 Hz, 6-H), 7.22 (2H, d, *J* 8.2 Hz, 3′-H and 5′-H), 7.58 (1H, d, *J* 8.8 Hz, 7-H), 7.63 (2H, d, *J* 8.2 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 28.3 (CH_2), 50.4 (CH_2), 55.6 (CH_3), 111.0 (CH), 112.6 (CH), 116.7 (CH), 127.4 (2 × CH), 129.6 (2 × CH), 133.9 (C), 134.0 (C), 135.5 (C), 143.9 (C), 156.9 (C); *m/z* (ESI) 326.0810 (MNa^+. $C_{16}H_{17}NNaO_3S$ requires 326.0821).

5,6-Dimethoxy-1-(4′-methylbenzenesulfonyl)indoline (146a)



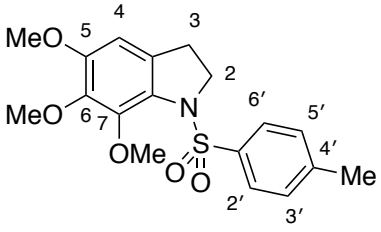
5,6-Dimethoxy-1-(4′-methylbenzenesulfonyl)indoline (**146a**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using *N*-[(3,4-dimethoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (**123a**) (0.0840 g, 0.250 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 21 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 5,6-dimethoxy-1-(4′-methylbenzenesulfonyl)indoline (**146a**) (0.0654 g, 78%) as a white solid. Mp 116–118 °C; ν_{max}/cm^{-1} (neat) 2955 (CH), 1597 (C=C), 1505, 1456, 1348, 1211, 1159, 1089, 814; δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s, 4′-CH_3), 2.70 (2H, t, *J* 8.2 Hz, 3-H_2), 3.80 (3H, s, OCH_3), 3.90 (,), 3.94 (3H, s, OCH_3), 6.60 (1H, s, 4-H), 7.20 (2H, d, *J* 8.7 Hz, 3′-H and 5′-H), 7.32 (1H, s, 7-H), 7.59 (2H, d, *J* 8.7 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 28.1 (CH_2), 50.7 (CH_2), 56.3 (CH_3), 56.3 (CH_3), 101.2 (CH), 108.2 (CH), 123.6 (C), 127.4 (2 × CH), 129.6 (2 × CH), 133.9 (C), 135.4 (C), 143.9 (C), 146.4 (C), 148.7 (C); *m/z* (ESI) 356.0918 (MNa^+. $C_{17}H_{19}NNaO_4S$ requires 356.0927).

5,7-Dimethoxy-1-(4′-methylbenzenesulfonyl)indoline (146b)



5,7-Dimethoxy-1-(4′-methylbenzenesulfonyl)indoline (**146b**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using *N*-[(3,5-dimethoxyphenyl)ethyl]-4″-methylbenzenesulfonamide (**123b**) (0.0820 g, 0.250 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 21 h. Purification by flash column chromatography (dichloromethane/diethyl ether, 19:1) gave 5,7-dimethoxy-1-(4′-methylbenzenesulfonyl)indoline (**146b**) (0.0610 g, 75%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2361 (CH), 1558 (C=C), 1350, 1165, 813; δ_H (400 MHz, $CDCl_3$) 2.32 (2H, t, *J* 7.4 Hz, 3-H_2), 2.40 (3H, s, 4′-CH_3), 3.77 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.02 (2H, t, *J* 7.4 Hz, 2-H_2), 6.25 (1H, d, *J* 2.2 Hz, 6-H), 6.38 (1H, d, *J* 2.2 Hz, 4-H), 7.19 (2H, d, *J* 8.6 Hz, 3′-H and 5′-H), 7.54 (2H, d, *J* 8.6 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 21.6 (CH_3), 29.9 (CH_2), 53.1 (CH_2), 55.6 (CH_3), 56.2 (CH_3), 99.1 (CH), 101.7 (CH), 124.5 (C), 127.7 (2 × CH), 129.3 (2 × CH), 135.6 (C), 139.6 (C), 143.6 (C), 152.9 (C), 152.6 (C); *m/z* (ESI) 356.0917 (MNa^+. $C_{17}H_{19}NNaO_4S$ requires 356.0927).

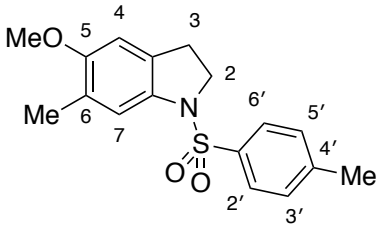
1-(4′-Methylbenzenesulfonyl)-5,6,7-trimethoxyindoline (146c)



1-(4′-Methylbenzenesulfonyl)-5,6,7-trimethoxyindoline (**146c**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 4′-methyl-*N*-[(3,4,5-trimethoxyphenyl)ethyl]benzenesulfonamide (**123c**) (0.0920 g, 0.250 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (petroleum ether/ethyl

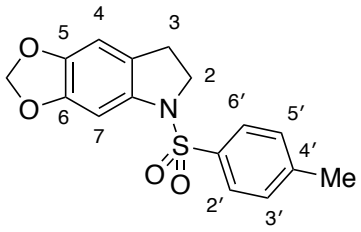
acetate, 7:3) gave 1-(4′-methylbenzenesulfonyl)-5,6,7-trimethoxyindoline (**146c**) (0.0668 g, 73%) as a white solid. Mp 126–128 °C; ν_{max}/cm^{-1} (neat) 2940 (CH), 1597 (C=C), 1470, 1418, 1350, 1236, 1163, 1125, 1067, 816; δ_H (400 MHz, $CDCl_3$) 2.30 (2H, t, *J* 7.6 Hz, 3-H_2), 2.40 (3H, s, 4′-CH_3), 3.80 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.02 (2H, t, *J* 7.6 Hz, 2-H_2), 6.38 (1H, s, 4-H), 7.18 (2H, d, *J* 8.3 Hz, 3′-H and 5′-H), 7.53 (2H, d, *J* 8.3 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 21.6 (CH_3), 29.6 (CH_2), 53.1 (CH_2), 56.3 (CH_3), 60.3 (CH_3), 61.2 (CH_3), 102.9 (CH), 127.6 (C), 127.7 (2 × CH), 129.3 (2 × CH), 132.5 (C), 135.5 (C), 141.5 (C), 143.7 (C), 146.9 (C), 152.4 (C); *m/z* (ESI) 386.1022 (MNa^+. $C_{18}H_{21}NNaO_5S$ requires 386.1033).

5-Methoxy-6-methyl-1-(4′-methylbenzenesulfonyl)indoline (146d)



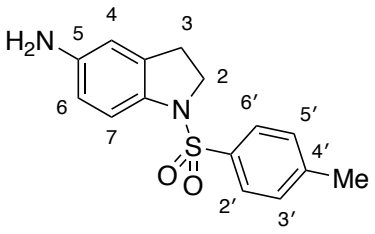
5-Methoxy-6-methyl-1-(4′-methylbenzenesulfonyl)indoline (**146d**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using *N*-[(3-methoxy-4-methylphenyl)ethyl]-4″-methylbenzenesulfonamide (**123d**) (0.0580 g, 0.180 mmol). The iodination step was carried out at 40 °C for 5 h and the *N*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (hexane/ethyl acetate, 7:3) gave 5-methoxy-6-methyl-1-(4′-methylbenzenesulfonyl)indoline (**146d**) (0.0424 g, 74%) as a colourless oil; ν_{max}/cm^{-1} (neat) 2947 (CH), 1597 (C=C), 1497, 1350, 1157, 1088, 1026, 810; δ_H (400 MHz, $CDCl_3$) 2.23 (3H, s, 6-CH_3), 2.36 (3H, s, 4′-CH_3), 2.71 (2H, t, *J* 8.2 Hz, 3-H_2), 3.75 (3H, s, OCH_3), 3.88 (2H, t, *J* 8.2 Hz, 2-H_2), 6.55 (1H, s, 4-H), 7.19 (2H, d, *J* 8.1 Hz, 3′-H and 5′-H), 7.46 (1H, s, 7-H), 7.59 (2H, d, *J* 8.1 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 16.7 (CH_3), 21.5 (CH_3), 28.3 (CH_2), 50.4 (CH_2), 55.6 (CH_3), 107.0 (CH), 118.3 (CH), 126.0 (C), 127.4 (2 × CH), 129.6 (2 × CH), 130.6 (C), 134.0 (C), 134.8 (C), 143.8 (C), 155.0 (C); *m/z* (ESI) 340.0970 (MNa^+. $C_{17}H_{19}NNaO_3S$ requires 340.0978).

1-(4′-Methylbenzenesulfonyl)-(5,6-methylenedioxy)indoline (146e)



1-(4′-Methylbenzenesulfonyl)-(5,6-methylenedioxy)indoline (**146e**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 4″-methyl-*N*-[(3,4-methylenedioxyphenyl)ethyl]benzenesulfonamide (**123e**) (0.0780 g, 0.250 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 21 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 1-(4′-methylbenzenesulfonyl)-(5,6-methylenedioxy)indoline (**146e**) (0.0534 g, 69%) as a white solid. Mp 139–141 °C; ν_{max}/cm^{-1} (neat) 2955 (CH), 1597 (C=C), 1476, 1454, 1352, 1306, 1163, 1038, 937; δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, 4′-CH_3), 2.66 (2H, t, *J* 8.2 Hz, 3-H_2), 3.90 (2H, t, *J* 8.2 Hz, 2-H_2), 5.94 (2H, s, OCH_2O), 6.51 (1H, s, 4-H), 7.22 (2H, d, *J* 8.3 Hz, 3′-H and 5′-H), 7.24 (1H, s, 7-H), 7.62 (2H, d, *J* 8.3 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 28.0 (CH_2), 50.9 (CH_2), 99.0 (CH), 101.4 (CH_2), 105.2 (CH), 124.7 (C), 127.4 (2 × CH), 129.6 (2 × CH), 134.0 (C), 136.0 (C), 144.0 (C), 144.6 (C), 147.2 (C); *m/z* (ESI) 340.0603 (MNa^+. $C_{16}H_{15}NNaO_4S$ requires 340.0614).

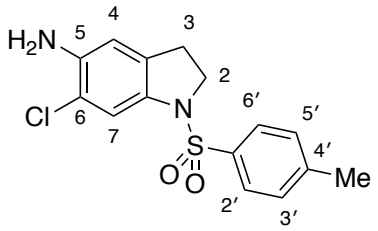
5-Amino-1-(4′-methylbenzenesulfonyl)indoline (146f)



5-Amino-1-(4′-methylbenzenesulfonyl)indoline (**146f**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using *N*-[(3-aminophenyl)ethyl]-4″-methylbenzenesulfonamide (**124a**) (0.0798 g, 0.280 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 21 h. Purification by flash column chromatography (hexane/ethyl acetate, 1:1) gave 5-amino-1-(4′-methylbenzenesulfonyl)indoline (**146f**) (0.0550 g, 70%) as a colourless oil. ν_{max}/cm^{-1}

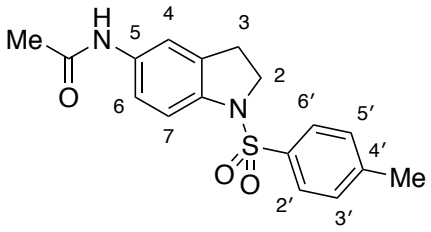
(neat) 3475 (NH), 3365 (NH), 1624, 1597 (C=C), 1488, 1343, 1161, 1091, 814; δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, 4′-CH_3), 2.64 (2H, t, *J* 8.2 Hz, 3-H_2), 3.53 (2H, br s, NH_2), 3.86 (2H, t, *J* 8.2 Hz, 2-H_2), 6.41 (1H, d, *J* 2.3 Hz, 4-H), 6.53 (1H, dd, *J* 8.5, 2.3 Hz, 6-H), 7.19 (2H, d, *J* 8.1 Hz, 3′-H and 5′-H), 7.45 (1H, d, *J* 8.5 Hz, 7-H), 7.58 (2H, d, *J* 8.1 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 28.3 (CH_2), 50.3 (CH_2), 111.9 (CH), 114.3 (CH), 117.3 (CH), 127.4 (2 × CH), 129.5 (2 × CH), 133.9 (C), 134.0 (2 × C), 143.4 (C), 143.7 (C); *m/z* (ESI) 311.0826 (MNa^+. $C_{15}H_{16}N_2NaO_2S$ requires 311.0825).

5-Amino-6-chloro-1-(4′-methylbenzenesulfonyl)indoline (146g)



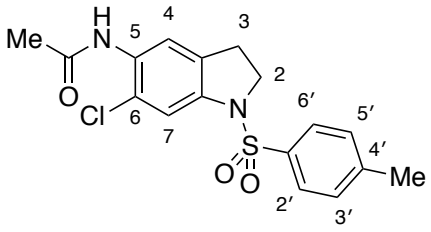
5-Amino-6-chloro-1-(4′-methylbenzenesulfonyl)indoline (**146g**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using *N*-[(3-amino-4-chlorophenyl)ethyl]-4″-methylbenzenesulfonamide (**124b**) (0.0590 g, 0.180 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (hexane/ethyl acetate, 1:1) gave 5-amino-6-chloro-1-(4′-methylbenzenesulfonyl)indoline (**146g**) (0.0320 g, 55%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3472 (NH), 3372 (NH), 2924 (CH), 2361, 1620, 1597 (C=C), 1481, 1342, 1159, 1088, 810; δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, 4′-CH_3), 2.66 (2H, t, *J* 8.2 Hz, 3-H_2), 3.71–3.96 (4H, m, 2-H_2 and NH_2), 6.49 (1H, s, 4-H), 7.22 (2H, d, *J* 8.2 Hz, 3′-H and 5′-H), 7.58 (1H, s, 7-H), 7.61 (2H, d, *J* 8.2 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 28.0 (CH_2), 50.3 (CH_2), 112.1 (CH), 117.0 (CH), 118.1 (C), 127.4 (2 × CH), 129.7 (2 × CH), 132.4 (C), 133.7 (C), 134.2 (C), 139.7 (C), 144.0 (C); *m/z* (ESI) 345.0422 (MNa^+. $C_{15}H_{15}{}^{35}ClN_2NaO_2S$ requires 345.0435).

5-Acetamido-1-(4′-methylbenzenesulfonyl)indoline (146h)



5-Acetamido-1-(4′-methylbenzenesulfonyl)indoline (**146h**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using *N*-[(3-acetamidophenyl)ethyl]-4″-methylbenzenesulfonamide (**125a**) (0.148 g, 0.450 mmol) in tolunene (1.0 mL) and acetonitrile (0.2 mL). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 21 h. Purification by flash column chromatography (hexane/ethyl acetate, 7:3) gave 5-acetamido-1-(4′-methylbenzenesulfonyl)indoline (**146h**) (0.0940 g, 64%) as a white solid. Mp 168–170 °C; ν_{max}/cm^{-1} (neat) 3320 (NH), 2924 (CH), 1675 (C=O), 1546 (C=C), 1487, 1351, 1163, 1091, 815; δ_H (400 MHz, $CDCl_3$) 2.13 (3H, s, CH_3CO), 2.37 (3H, s, 4′-CH_3), 2.83 (2H, t, *J* 8.1 Hz, 3-H_2), 3.89 (2H, t, *J* 8.1 Hz, 2-H_2), 7.05 (1H, dd, *J* 8.3, 1.6 Hz, 6-H), 7.21 (2H, d, *J* 7.7 Hz, 3′-H and 5′-H), 7.24 (1H, br s, NH), 7.49 (1H, br s, 4-H), 7.54 (1H, d, *J* 8.3 Hz, 7-H), 7.62 (2H, d, *J* 7.7 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 24.4 (CH_3), 28.1 (CH_2), 50.2 (CH_2), 115.4 (CH), 117.6 (CH), 119.3 (CH), 127.3 (2 × CH), 129.7 (2 × CH), 133.0 (C), 133.7 (C), 134.2 (C), 138.4 (C), 144.2 (C), 168.3 (C); *m/z* (ESI) 353.0925 (MNa^+. $C_{17}H_{18}N_2NaO_3S$ requires 353.0930).

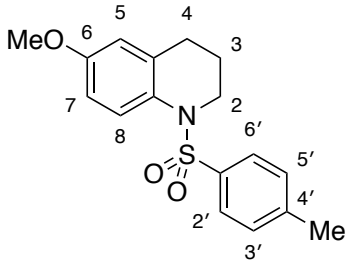
5-Acetamido-6-chloro-1-(4′-methylbenzenesulfonyl)indoline (146i)



5-Acetamido-6-chloro-1-(4′-methylbenzenesulfonyl)indoline (**146i**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using *N*-[(3-acetamido-4-chlorophenyl)ethyl]-4″-methylbenzenesulfonamide (**125b**) (0.0420 g, 0.110 mmol) and *N*-bromosuccinimide (0.0200 g, 0.110 mmol). The bromination step was carried

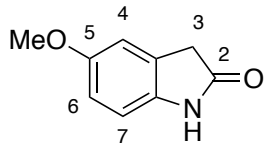
out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 21 h. Purification by flash column chromatography (hexane/ethyl acetate, 2:3) gave 5-acetamido-6-chloro-1-(4′-methylbenzenesulfonyl)indoline (**146i**) (0.0170 g, 43%) as a white solid. Mp 138–140 °C; ν_{max}/cm^{-1} (neat) 3350 (NH), 2925 (CH), 1653 (C=O), 1356, 1162; δ_H (400 MHz, $CDCl_3$) 2.21 (3H, s, CH_3CO), 2.39 (3H, s, 4′-CH_3), 2.85 (2H, t, *J* 8.4 Hz, 3-H_2), 3.90 (2H, t, *J* 8.4 Hz, 2-H_2), 7.25 (2H, d, *J* 8.5 Hz, 3′-H and 5′-H), 7.49 (1H, s, 4-H), 7.65 (2H, d, *J* 8.5 Hz, 2′-H and 6′-H), 7.68 (1H, s, 7-H), 8.05 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 21.5 (CH_3), 24.7 (CH_3), 27.9 (CH_2), 50.3 (CH_2), 115.4 (CH), 118.4 (CH), 121.9 (C), 127.3 (2 × CH), 129.8 (2 × CH), 130.5 (C), 131.6 (C), 133.6 (C), 138.6 (C), 144.4 (C), 168.2 (C); *m/z* (ESI) 387.0527 (MNa^+. $C_{17}H_{17}{}^{35}ClN_2NaO_3S$ requires 387.0541).

6-Methoxy-1-(4′-methylbenzenesulfonyl)-2,3,4-tetrahydroquinoline (146j)



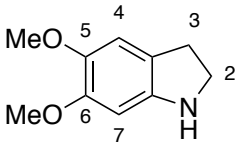
6-Methoxy-1-(4′-methylbenzenesulfonyl)-2,3,4-tetrahydroquinoline (**146j**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using *N*-[(1-methoxyphenyl)propyl]-4″-methylbenzenesulfonamide (**127**) (0.0840 g, 0.260 mmol). The iodination step was carried out at 40 °C for 5 h and the *N*-arylation step at 130 °C for 23 h. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave 6-methoxy-1-(4′-methylbenzenesulfonyl)-2,3,4-tetrahydroquinoline (**146j**) (0.0710 g, 85%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2943 (CH), 1609, 1597 (C=C), 1493, 1339, 1162, 1090, 812; δ_H (400 MHz, $CDCl_3$) 1.51–1.59 (2H, m, 3-H_2), 2.33 (2H, t, *J* 6.8 Hz, 4-H_2), 2.38 (3H, s, 4′-CH_3), 3.73–3.77 (2H, m, 2-H_2), 3.78 (3H, s, OCH_3), 6.52 (1H, d, *J* 2.8 Hz, 5-H), 6.75 (1H, dd, *J* 9.0, 2.8 Hz, 7-H), 7.18 (2H, d, *J* 8.3 Hz, 3′-H and 5′-H), 7.42 (2H, d, *J* 8.3 Hz, 2′-H and 6′-H), 7.70 (1H, d, *J* 9.0 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 21.3 (CH_2), 21.5 (CH_3), 26.6 (CH_2), 46.4 (CH_2), 55.4 (CH_3), 112.1 (CH), 113.7 (CH), 127.0 (CH), 127.2 (2 × CH), 129.5 (2 × CH), 129.9 (C), 132.7 (C), 136.7 (C), 143.4 (C), 157.0 (C); *m/z* (ESI) 340.0965 (MNa^+. $C_{17}H_{19}NNaO_3S$ requires 340.0978).

5-Methoxyindolin-2-one (146k)[521]



5-Methoxyindolin-2-one (**146k**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 3-methoxyphenylacetamide (**129**) (0.0420 g, 0.250 mmol). The iodination step was carried out at 40 °C for 5 h and the *N*-arylation step at 130 °C for 21 h. Purification by flash column chromatography (hexane/ethyl acetate, 1:1) gave 5-methoxyindolin-2-one (**146k**) (0.0269 g, 65%) as a white solid. Mp 128–130 °C (lit.[521] 132–134 °C); δ_H (400 MHz, $CDCl_3$) 3.53 (2H, s, 3-H_2), 3.78 (3H, s, OCH_3), 6.75 (1H, dd, *J* 8.5, 2.4 Hz, 6-H), 6.79 (2H, d, *J* 8.5 Hz, 7-H), 6.85 (1H, br s, 4-H), 8.53 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 36.7 (CH_2), 55.8 (CH_3), 110.0 (CH), 111.8 (CH), 112.5 (CH), 126.7 (C), 135.9 (C), 155.7 (C), 177.5 (C); *m/z* (ESI) 186 (MNa^+. 100%).

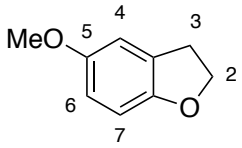
5,6-dimethoxyindoline (147)[522]



5,6-Dimethoxy-1-(4′-methylbenzenesulfonyl)indoline (**146a**) (0.0500 g, 0.150 mmol) was dissolved in methanol (10 mL) and dichloromethane (1.0 mL) and magnesium turnings (0.109 g, 4.50 mmol) were added under argon. The reaction mixture was stirred under reflux for 16 h. The reaction mixture was cooled to 0 °C, 1 M aqueous hydrochloric acid solution (10 mL) was added dropwise and the solution was washed with ethyl acetate (10 mL). The aqueous layer was separated and neutralised with 1 M aqueous sodium hydroxide (10 mL) and extracted into dichloromethane (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave 5,6-dimethoxyindoline (**147**) (0.0181 g, 67%) as yellow oil. Spectroscopic data were consistent with the literature.[522] δ_H (400 MHz, $CDCl_3$) 2.98 (2H, t, *J* 8.2 Hz, 3-H_2), 3.34 (1H, br s, NH), 3.53 (2H, t, *J* 8.2 Hz, 2-H_2), 3.81 (3H, s, OCH_3), 3.82 (3H, s,

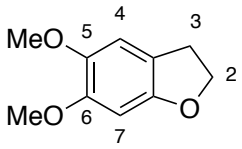
OCH_3), 6.35 (1H, s, 7-H), 6.76 (1H, s, 4-H); δ_C (101 MHz, $CDCl_3$) 30.1 (CH_2), 48.0 (CH_2), 56.1 (CH_3), 57.1 (CH_3), 96.2 (CH), 110.1 (CH), 120.4 (C), 142.7 (C), 145.3 (C), 148.9 (C); *m/z* (ESI) 202 (MNa^+. 100%).

2,3-Dihydro-5-methoxybenzofuran (149a)[284]



2,3-Dihydro-5-methoxybenzofuran (**149a**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 3-methoxyphenylethan-2′-ol (0.0710 mL, 0.500 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 150 °C for 21 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 2,3-dihydro-5-methoxybenzofuran (**149a**) (0.0460 g, 65%) as a colourless oil. Spectroscopic data were consistent with the literature.[284] δ_H (400 MHz, $CDCl_3$) 3.17 (2H, t, *J* 8.6 Hz, 3-H_2), 3.75 (3H, s, OCH_3), 4.53 (2H, t, *J* 8.6 Hz, 2-H_2), 6.64 (1H, dd, *J* 8.6, 2.6 Hz, 6-H), 6.68 (1H, d, *J* 8.6 Hz, 7-H), 6.78 (1H, d, *J* 2.6 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 30.3 (CH_2), 56.1 (CH_3), 71.3 (CH_2), 109.1 (CH), 111.4 (CH), 112.8 (CH), 128.0 (C), 154.1 (C), 154.2 (C); *m/z* (ESI) 173 (MNa^+. 100%).

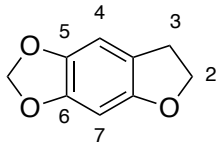
2,3-Dihydro-5,6-dimethoxybenzofuran (149b)



2,3-Dihydro-5,6-dimethoxybenzofuran (**149b**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 3,4-dimethoxyphenylethan-2′-ol (0.0910 g, 0.500 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 21 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 2,3-dihydro-5,6-dimethoxybenzofuran (**149b**) (0.0650 g, 72%) as a white solid. Mp 58–60 °C; ν_{max}/cm^{-1} (neat) 2940 (CH), 1614, 1502, 1446, 1304, 1208, 1186, 1169, 1095, 1003, 828; δ_H (400 MHz, $CDCl_3$) 3.15 (2H, t, *J* 8.7 Hz, 3-H_2), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.54 (2H, t, *J* 8.7 Hz, 2-H_2),

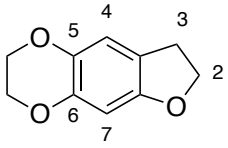
6.45 (1H, s, 7-H), 6.78 (1H, s, 4-H); δ_C (101 MHz, $CDCl_3$) 30.0 (CH_2), 56.1 (CH_3), 57.0 (CH_3), 71.7 (CH_2), 94.9 (CH), 109.3 (CH), 116.6 (C), 143.2 (C), 149.2 (C), 154.3 (C); *m/z* (ESI) 203.0679 (MNa^+. $C_{10}H_{12}NaO_3$ requires 203.0679).

2,3-Dihydro-5,6-methylenedioxybenzofuran (149c)



2,3-Dihydro-5,6-methylenedixoybenzofuran (**149c**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using (3,4-methylenedioxy)phenethan-2′-ol (**131a**) (0.0830 g, 0.500 mmol). The iodination step was carried out at 40 °C for 5 h and the *O*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 2,3-dihydro-5,6-methylenedixoybenzofuran (**149c**) (0.0520 g, 63%) as a white solid. Mp 54–56 °C; ν_{max}/cm^{-1} (neat) 2893 (CH), 2361, 1620 (C=C), 1474, 1296, 1142, 1034, 941; δ_H (400 MHz, $CDCl_3$) 3.10 (2H, t, *J* 8.7 Hz, 3-H_2), 4.54 (2H, t, *J* 8.7 Hz, 2-H_2), 5.87 (2H, s, OCH_2O), 6.37 (1H, s, 7-H), 6.65 (1H, s, 4-H); δ_C (101 MHz, $CDCl_3$) 30.0 (CH_2), 72.0 (CH_2), 93.0 (CH), 101.1 (CH_2), 105.0 (CH), 117.7 (C), 141.4 (C), 147.1 (C), 154.6 (C); *m/z* (EI) 164.0469 (M^+. $C_9H_8O_3$ requires 164.0473), 133 (18%), 84 (48), 78 (20).

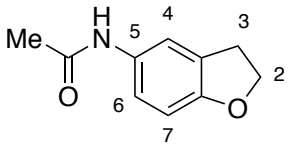
2,3-Dihydro-5,6-ethylenedioxybenzofuran (149d)



2,3-Dihydro-5,6-ethylenedioxybenzofuran (**149d**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 1′-(dihydro-3,4-benzodioxinyl)ethan-2′-ol (**131b**) (0.106 g, 0.590 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 2,3-dihydro-5,6-ethylenedioxybenzofuran (**149d**) (0.0618 g, 60%) as a white solid. Mp 64–66 °C; ν_{max}/cm^{-1} (neat) 2992 (CH), 1607 (C=C), 1486, 1327, 1185, 1060, 931; δ_H (400 MHz,

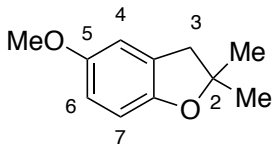
$CDCl_3$) 3.10 (2H, t, *J* 8.3 Hz, 3-H_2), 4.15–4.23 (4H, m, OCH_2CH_2O), 4.50 (2H, t, *J* 8.3 Hz, 2-H_2), 6.34 (1H, s, 7-H), 6.70 (1H, s, 4-H); δ_C (101 MHz, $CDCl_3$) 29.6 (CH_2), 64.1 (CH_2), 64.5 (CH_2), 71.6 (CH_2), 98.4 (CH), 113.2 (CH), 119.2 (C), 137.3 (C), 142.8 (C), 154.3 (C); *m/z* (EI) 178.0625 (M^+. $C_{10}H_{10}O_3$ requires 178.0630), 122 (92%), 69 (25).

5-Acetamido-2,3-dihydrobenzofuran (149e)[523]



5-Acetamido-2,3-dihydrobenzofuran (**149e**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 1′-(3-acetamidophenyl)ethan-2′-ol (**137**) (0.0270 g, 0.150 mmol) in toluene (1.0 mL) and acetonitrile (0.2 mL). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave 5-acetamido-2,3-dihydrobenzofuran (**149e**) (0.0140 g, 56%) as a white solid. Mp 94–96 °C (lit.[523] 93–95 °C); δ_H (400 MHz, $CDCl_3$) 2.12 (3H, s, CH_3CO), 3.17 (2H, t, *J* 8.4 Hz, 3-H_2), 4.54 (2H, t, *J* 8.4 Hz, 2-H_2), 6.69 (1H, d, *J* 8.5 Hz, 7-H), 7.00 (1H, dd, *J* 8.5, 2.2 Hz, 6-H) 7.44–7.49 (2H, m, 4-H and NH); δ_C (101 MHz, $CDCl_3$) 24.2 (CH_3), 29.9 (CH_2), 71.5 (CH_2), 109.0 (CH), 118.6 (CH), 120.7 (CH), 127.6 (C), 130.8 (C), 157.0 (C), 168.6 (C); *m/z* (ESI) 200 (MNa^+. 100%).

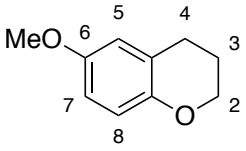
2,3-Dihydro-2,2-dimethyl-5-methoxybenzofuran (149f)[284]



2,3-Dihydro-2,2-dimethyl-5-methoxybenzofuran (**149f**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 2′,2′-dimethyl-1′-(3-methoxyphenyl)ethan-2′-ol (**133**) (0.120 g, 0.670 mmol). The iodination step was carried out at 40 °C for 5 h and the *O*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (petroleum ether/diethyl ether, 19:1) gave 2,3-dihydro-2,2-dimethyl-5-methoxybenzofuran (**149f**) (0.0821 g, 69%) as a colourless

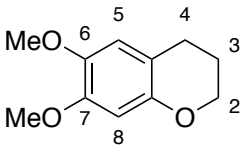
oil. Spectroscopic data were consistent with the literature.[284] δ_H (400 MHz, $CDCl_3$) 1.45 (6H, s, 2 × 2-CH_3), 2.98 (2H, s, 3-H_2), 3.74 (3H, s, OCH_3), 6.60–6.67 (2H, m, 4-H and 6-H), 6.71–6.75 (1H, m, 7-H); δ_C (101 MHz, $CDCl_3$) 28.1 (2 × CH_3), 43.3 (CH_2), 56.0 (CH_3), 86.5 (C), 109.3 (CH), 111.6 (CH), 112.8 (CH), 128.1 (C), 153.1 (C), 153.8 (C); *m/z* (ESI) 201 (MNa^+. 100%).

2,3-Dihydro-6-methoxy-1-benzopyran (149i)[284]



2,3-Dihydro-6-methoxybenzopyran (**149i**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 1′-(3-methoxyphenyl)propan-3′-ol (**139a**) (0.0830 g, 0.500 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 150 °C for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave 2,3-dihydro-6-methoxy-1-benzopyran (**149i**) (0.0460 g, 57%) as a colourless oil. Spectroscopic data were consistent with the literature.[284] δ_H (400 MHz, $CDCl_3$) 1.94–2.02 (2H, m, 3-H_2), 2.77 (2H, t, *J* 6.5 Hz, 4-H_2), 3.74 (3H, s, OCH_3), 4.13 (2H, t, *J* 5.2 Hz, 2-H_2), 6.58 (1H, d, *J* 2.9 Hz, 5-H), 6.66 (1H, dd, *J* 8.8, 2.9 Hz, 7-H), 6.71 (1H, d, *J* 8.8 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 22.5 (CH_2), 25.2 (CH_2), 55.7 (CH_3), 66.3 (CH_2), 113.3 (CH), 114.4 (CH), 117.2 (CH), 122.7 (C), 149.0 (C), 153.2 (C); *m/z* (EI) 164 (M^+. 100%), 149 (42), 136 (22), 108 (14), 84 (28), 77 (11).

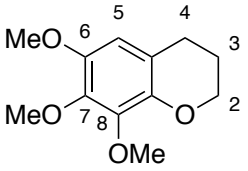
2,3-Dihydro-6,7-dimethoxy-1-benzopyran (149j)[524]



2,3-Dihydro-6,7-dimethoxybenzopyran (**149j**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 1′-(3,4-dimethoxyphenyl)propan-3′-ol (0.0490 g, 0.250 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 150 °C for 22 h. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave 2,3-dihydro-6,7-dimethoxy-1-benzopyran (**149j**)

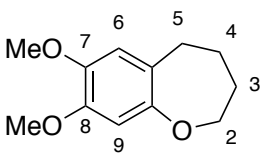
(0.0273 g, 56%) as a colourless oil. Spectroscopic data were consistent with the literature.[524] δ_H (500 MHz, $CDCl_3$) 1.95–2.02 (2H, m, 3-H_2), 2.70 (2H, t, *J* 6.6 Hz, 4-H_2), 3.81 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.10–4.14 (2H, m, 2-H_2), 6.38 (1H, s, 8-H), 6.53 (1H, s, 5-H); δ_C (126 MHz, $CDCl_3$) 22.6 (CH_2), 24.3 (CH_2), 55.9 (CH_3), 56.5 (CH_3), 66.3 (CH_2), 100.9 (CH), 112.6 (C), 112.7 (CH), 143.0 (C), 148.3 (C), 148.7 (C); *m/z* (EI) 194 (M^+. 100%), 179 (86), 149 (25), 123 (15), 57 (25).

2,3-Dihydro-6,7,8-trimethoxy-1-benzopyran (149k)



2,3-Dihydro-6,7-trimethoxy-1-benzopyran (**149k**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 1′-(3,4,5-trimethoxyphenyl)propan-3′-ol (**139b**) (0.0570 g, 0.250 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 150 °C for 22 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 2,3-dihydro-6,7,8-trimethoxy-1-benzopyran (**149k**) (0.0290 g, 51%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2932 (CH), 1489, 1462, 1420, 1277, 1219, 1126, 1099, 1072, 1011; δ_H (400 MHz, $CDCl_3$) 1.95–2.03 (2H, m, 3-H_2), 2.73 (2H, t, *J* 6.5 Hz, 4-H_2), 3.79 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.16–4.21 (2H, m, 2-H_2), 6.34 (1H, s, 5-H); δ_C (101 MHz, $CDCl_3$) 22.4 (CH_2), 24.8 (CH_2), 56.4 (CH_3), 61.1 (CH_3), 61.3 (CH_3), 66.4 (CH_2), 107.5 (CH), 117.1 (C), 141.4 (C), 142.3 (C), 142.6 (C), 146.6 (C); *m/z* (ESI) 247.0932 (MNa^+. $C_{12}H_{16}NaO_4$ requires 247.0941).

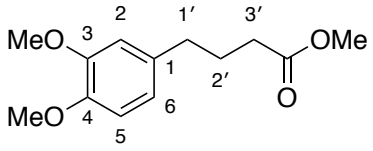
2,3,4,5-Dihydro-7,8-dimethoxy-1-benzoxepin (150)[289]



2,3,4,5-Dihydro-7,8-dimethoxy-1-benzoxepin (**150**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 1′-(3,4-dimethoxyphenyl)butan-4′-ol (**141**) (0.111 g, 0.528 mmol). The iodination step was carried out at 40 °C for 4 h

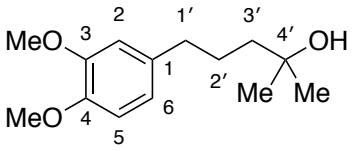
and the *O*-arylation step at 150 °C for 48 h. Purification by flash column chromatography (hexane/diethyl ether, 7:3) gave 2,3,4,5-dihydro-7,8-dimethoxy-1-benzoxepin (**150**) (0.0210 g, 19%) as a colourless oil. Spectroscopic data were consistent with the literature.[289] δ_H (400 MHz, $CDCl_3$) 1.66–1.74 (2H, m, 4-H_2), 1.91–1.98 (2H, m, 3-H_2), 2.72–2.76 (2H, m, 5-H_2), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.94–3.99 (2H, m, 2-H_2), 6.59 (1H, s, 9-H), 6.62 (1H, s, 6-H); δ_C (101 MHz, $CDCl_3$) 26.6 (CH_2), 32.7 (CH_2), 34.1 (CH_2), 56.0 (CH_3), 56.3 (CH_3), 73.8 (CH_2), 105.6 (CH), 113.3 (CH), 126.6 (C), 144.4 (C), 147.4 (C), 154.0 (C); *m/z* (EI) 208 (M^+. 100%), 193 (45).

Methyl 1′-(3,4-dimethoxyphenyl)butanoate (151)[525]



Methyl 1′-(3,4-dimethoxyphenyl)butanoate (**151**) was synthesised as described methyl (3-methoxyphenyl)acetate (**132**) using 3,4-dimethoxyphenylbutyric acid (**140**) (0.700 g, 3.12 mmol). This gave methyl 1′-(3,4-dimethoxyphenyl)butanoate (**151**) (0.715 g, 96%) as a yellow oil. Spectroscopic data were consistent with the literature.[525] δ_H (500 MHz, $CDCl_3$) 1.93 (2H, quin. *J* 7.5 Hz, 3′-H_2), 2.32 (2H, t, *J* 7.5 Hz, 2′-H_2), 2.59 (2H, t, *J* 7.5 Hz, 4′-H_2), 3.66 (3H, s, COO*CH*$_3$), 3.84 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.68–6.73 (2H, m, 2-H and 6-H), 6.78 (1H, d, *J* 8.7 Hz, 5-H); δ_C (126 MHz, $CDCl_3$) 26.7 (CH_2), 33.3 (CH_2), 34.7 (CH_2), 51.5 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 111.3 (CH), 111.8 (CH), 120.3 (CH), 134.0 (C), 147.3 (C), 148.9 (C), 174.0 (C); *m/z* (ESI) 261 (MNa^+. 100%).

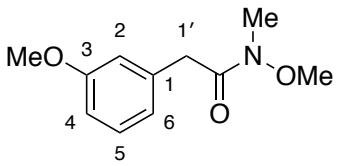
1′-(3,4-Dimethoxyphenyl)-5′-methylpentan-5-ol (152)



To a stirred solution of methyl 1′-(3,4-dimethoxyphenyl)butanoate (**151**) (0.715 g, 3.00 mmol) in dry tetrahydrofuran (25 mL) was added methylmagnesium bromide (9.00 mL, 9.00 mmol; 1.0 M in dibutyl ether) dropwise at 0 °C. The reaction mixture

was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (30 mL) at 0 °C and extracted with diethyl ether (4 × 40 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 1:1) gave 1′-(3,4-dimethoxyphenyl)-5′-methylpentan-5-ol (**152**) (0.569 g, 80%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3418 (OH), 2940 (CH), 1589, 1512, 1458, 1258, 1234, 1142, 1026, 810, 764; δ_H (500 MHz, $CDCl_3$) 1.20 (6H, s, 2 × CH_3), 1.29 (1H, br s, OH), 1.47–1.53 (2H, m, 2′-H_2), 1.63–1.72 (2H, m, 3′-H_2), 2.56 (2H, t, *J* 7.7 Hz, 4′-H_2), 3.84 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.70–6.74 (2H, m, 2-H and 6-H), 6.78 (1H, d, *J* 8.6 Hz, 5-H); δ_C (126 MHz, $CDCl_3$) 26.4 (CH_2), 29.3 (2 × CH_3), 35.9 (CH_2), 43.5 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 70.9 (C), 111.3 (CH), 111.8 (CH), 120.2 (CH), 135.1 (C), 147.2 (C), 148.8 (C); *m/z* (ESI) 261.1452 (MNa^+. $C_{14}H_{22}NaO_3$ requires 261.1461).

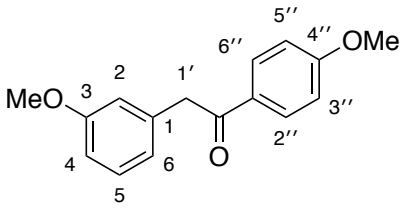
N-Methoxy-1′-(3-methoxyphenyl)-*N*-methylacetamide (158)[526]



To a solution of 3-methoxyphenylacetic acid (**128**) (2.00 g, 12.0 mmol) in dichloromethane (100 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.31 g, 12.0 mmol), 1-hydroxybenzotriazole hydrate (1.79 g, 13.2 mmol), *N*,*O*-dimethyhydroxylamine hydrochloride (1.17 g, 12.0 mmol) and *N*,*N*-diisopropylethylamine (8.60 mL, 48.2 mmol). The mixture was stirred at room temperature for 20 h. Water (100 mL) was added and the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were washed with 1 M aqueous hydrochloric acid (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave *N*-methoxy-1′-(3-methoxyphenyl)-*N*-methylacetamide (**158**) (1.91 g, 76%) as a yellow oil. Spectroscopic data were consistent with the literature.[526] δ_H (400 MHz, $CDCl_3$) 3.19 (3H, s, *N*-CH_3), 3.60 (3H, s, OCH_3), 3.74 (2H, s, 1′-H_2), 3.79 (3H, s, OCH_3), 6.79 (1H, dd, *J* 8.0, 2.6 Hz, 4-H), 6.83–6.92 (2H, m, 2-H and 6-H), 7.23 (1H,

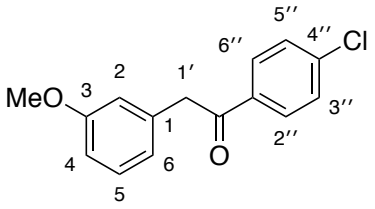
t, *J* 8.0 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 32.2 (CH_3), 39.4 (CH_2), 55.2 (CH_3), 61.3 (CH_3), 112.4 (CH), 114.8 (CH), 121.7 (CH), 129.4 (CH), 136.4 (C), 159.7 (C), 172.3 (C); *m/z* (ESI) 232 (MNa^+. 100%).

1′-(3-Methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (157a)[291]



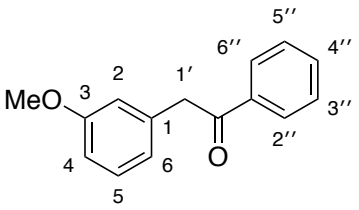
An oven-dried three-neck flask was flushed with argon and charged with magnesium turnings (0.0700 g, 2.30 mmol), a crystal of iodine and dry tetrahydrofuran (12 mL). 4-Bromoanisole (0.290 mL, 2.30 mmol) was added and the solution was heated under reflux for 1 h. This solution was then transferred *via* cannula to a solution of *N*-methoxy-1′-(3-methoxyphenyl)-*N*-methylacetamide (**158**) (0.400 g, 1.91 mmol) in dry tetrahydrofuran (15 mL). The resulting suspension was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated ammonium chloride solution (30 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1 to petroleum ether/ethyl acetate, 1:1) gave 1′-(3-methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**157a**) (0.192 g, 45%) as a yellow oil. Spectroscopic data were consistent with the literature.[291] δ_H (400 MHz, $CDCl_3$) 3.77 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.19 (2H, s, 1′-H_2), 6.78 (1H, dd, *J* 8.0, 2.4 Hz, 4-H), 6.80–6.83 (1H, m, 2-H), 6.85–6.88 (1H, m, 6-H), 6.91 (2H, d, *J* 9.0 Hz, 3″-H and 5″-H), 7.22 (1H, t, *J* 8.0 Hz, 5-H), 7.99 (2H, d, *J* 9.0 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 45.4 (CH_2), 55.2 (CH_3), 55.5 (CH_3), 112.3 (CH), 113.8 (2 × CH), 115.0 (CH), 121.8 (CH), 129.6 (CH), 131.0 (2 × CH), 136.5 (2 × C), 159.8 (C), 163.5 (C), 196.1 (C); *m/z* (ESI) 279 (MNa^+. 100%).

1′-(3-Methoxyphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (157b)



An oven-dried two-neck flask was flushed with argon and charged with *N*-methoxy-1′-(3-methoxyphenyl)-*N*-methylacetamide (**158**) (1.91 g, 9.12 mmol) in dry tetrahydrofuran (80 mL). 4-Chlorophenylmagnesium bromide (13.7 mL, 13.7 mmol; 1.0 M in 2-methyltetrahydrofuran) was added dropwise at 0 °C and the solution was warmed to room temperature and stirred for 2.5 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (80 mL) at 0 °C and extracted with diethyl ether (4 × 100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 9:1) gave 1′-(3-methoxyphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**157b**) (2.21 g, 93%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2940 (CH), 2361, 1682 (C=O), 1589 (C=C), 1489, 1265, 1157, 1088, 1049, 772; δ_H (400 MHz, $CDCl_3$) 3.78 (3H, s, OCH_3), 4.22 (2H, s, 1′-H_2), 6.78–6.85 (3H, m, 2-H, 4-H and 6-H), 7.24 (1H, t, *J* 7.6 Hz, 5-H), 7.42 (2H, d, *J* 8.6 Hz, 3″-H and 5″-H), 7.94 (2H, d, *J* 8.6 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 45.6 (CH_2), 55.2 (CH_3), 112.5 (CH), 115.1 (CH), 121.7 (CH), 129.0 (2 × CH), 129.8 (CH), 130.1 (2 × CH), 134.8 (C), 135.6 (C), 139.6 (C), 159.9 (C), 196.3 (C); *m/z* (ESI) 283.0500 (MNa^+. $C_{15}H_{13}{}^{35}ClNaO_2$ requires 283.0496).

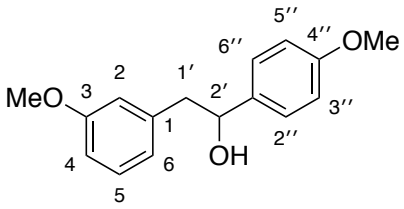
1′-(3-Methoxyphenyl)-2′-phenylethan-2′-one (157c)[527]



1′-(3-Methoxyphenyl)-2′-phenylethan-2′-one (**157c**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**157b**) using *N*-methoxy-1′-(3-methoxyphenyl)-*N*-methylacetamide (**158**) (0.349 g, 1.67 mmol) and

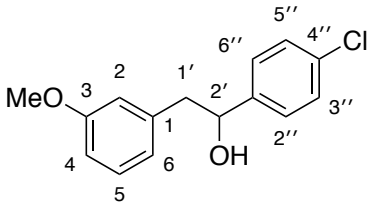
phenylmagnesium bromide (1.84 mL, 1.84 mmol; 1.0 M in tetrahydrofuran). Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1′-(3-methoxyphenyl)-2′-phenylethan-2′-one (**157c**) (0.210 g, 56%) as a colourless oil. Spectroscopic data were consistent with the literature.[527] δ_H (400 MHz, $CDCl_3$) 3.78 (3H, s, OCH_3), 4.25 (2H, s, 1′-H_2), 6.78–6.83 (2H, m, 2-H and 6-H), 6.86 (1H, br d, *J* 7.6 Hz, 4-H), 7.24 (1H, t, *J* 7.6 Hz, 5-H), 7.45 (2H, t, *J* 7.8 Hz, 3″-H and 5″-H), 7.55 (1H, t, *J* 7.8 Hz, 4″-H), 8.01 (2H, d, *J* 7.8 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 45.6 (CH_2), 55.2 (CH_3), 112.4 (CH), 115.1 (CH), 121.8 (CH), 128.6 (4 × CH), 129.7 (CH), 133.2 (CH), 136.0 (C), 136.6 (C), 159.8 (C), 197.5 (C); *m/z* (ESI) 249 (MNa^+. 100%).

1′-(3-methoxyphenyl)-2′-(4″-Methoxyphenyl)ethan-2′-ol (156a)[291]



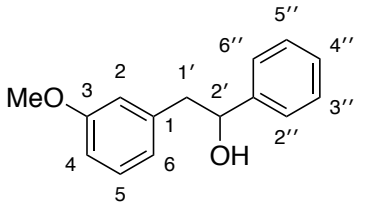
To a stirred solution of 1′-(3-methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**157a**) (0.530 g, 2.07 mmol) in methanol (15 mL) was added sodium borohydride (0.196 g, 5.17 mmol). The resulting suspension was stirred at room temperature for 4 h after which time the reaction was quenched with water (15 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with water (2 × 60 mL), brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give 1′-(3-methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-ol (**156a**) (0.508 g, 95%) as a colourless oil. Spectroscopic data were consistent with the literature.[291] δ_H (400 MHz, $CDCl_3$) 1.97 (1H, br s, OH), 2.94 (1H, dd, *J* 13.5, 8.0 Hz, 1′-*H*H), 2.99 (1H, dd, *J* 13.5, 5.6 Hz, 1′-H*H*), 3.76 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.84 (1H, ddd, *J* 8.0, 5.6, 2.7 Hz, 2′-H), 6.70–6.73 (1H, m, 2-H), 6.75–6.80 (2H, m, 4-H and 6-H), 6.87 (2H, d, *J* 8.7 Hz, 3″-H and 5″-H), 7.21 (1H, t, *J* 7.9 Hz, 5-H), 7.27 (2H, d, *J* 8.7 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 46.1 (CH_2), 55.2 (CH_3), 55.3 (CH_3), 74.9 (CH), 112.1 (CH), 113.8 (2 × CH), 115.1 (CH), 121.9 (CH), 127.2 (2 × CH), 129.5 (CH), 136.0 (C), 139.8 (C), 159.1 (C), 159.7 (C); *m/z* (ESI) 281 (MNa^+. 100%).

2′-(4″-Chlorophenyl)-1′-(3-methoxyphenyl)ethan-2′-ol (156b)



The reaction was carried out as described for 1′-(3-methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-ol (**156a**) using 2′-(4″-chlorophenyl)-1′-(3-methoxyphenyl)ethan-2′-one (**157b**) (0.243 g, 0.930 mmol), except that the reaction mixture was stirred at room temperature for 2 h. This gave 2′-(4″-chlorophenyl)-1′-(3-methoxyphenyl)ethan-2′-ol (**156b**) (0.210 g, 86%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3402 (OH), 2940 (CH), 2361, 1597 (C=C), 1489, 1258, 1157, 1088, 1049, 833, 779; δ_H (400 MHz, $CDCl_3$) 1.98 (1H, d, *J* 2.9 Hz, OH), 2.91 (1H, dd, *J* 13.7, 8.5 Hz, 1′-*H*H), 2.99 (1H, dd, *J* 13.7, 5.0 Hz, 1′-H*H*), 3.78 (3H, s, OCH_3), 4.88 (1H, ddd, *J* 8.5, 5.0, 2.9 Hz, 2′-H), 6.71 (1H, t, *J* 2.0 Hz, 2-H), 6.74–6.82 (2H, m, 4-H and 6-H), 7.22 (1H, t, *J* 8.0 Hz, 5-H), 7.27 (2H, d, *J* 8.8 Hz, 2″-H and 6″-H), 7.32 (2H, d, *J* 8.8 Hz, 3″-H and 5″-H); δ_C (101 MHz, $CDCl_3$) 46.2 (CH_2), 55.2 (CH_3), 74.5 (CH), 112.2 (CH), 115.1 (CH), 121.8 (CH), 127.3 (2 × CH), 128.5 (2 × CH), 129.6 (CH), 133.2 (C), 139.1 (C), 142.2 (C), 159.8 (C); *m/z* (ESI) 285.0646 (MNa^+. $C_{15}H_{15}{}^{35}ClNaO_2$ requires 285.0653).

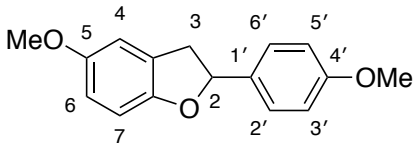
1′-(3-Methoxyphenyl)-2′-phenylethan-2′-ol (156c)[528]



The reaction was carried out as described for 1′-(3-methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-ol (**156a**) using 1′-(3-methoxyphenyl)-2′-phenylethan-2-one (**157c**) (0.188 g, 0.830 mmol), except that the reaction mixture was stirred at room temperature for 1 h. This gave 1′-(3-methoxyphenyl)-2′-phenylethan-2′-ol (**156c**) (0.169 g, 89%) as a colourless oil. Spectroscopic data were consistent with the literature.[528] δ_H (400 MHz, $CDCl_3$) 1.97 (1H, d, *J* 3.0 Hz, OH), 2.96 (1H, dd, *J*

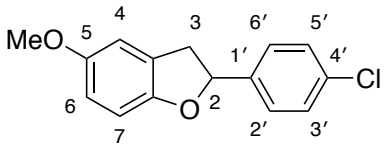
13.7, 8.4 Hz, 1′-*H*H), 3.03 (1H, dd, *J* 13.7, 5.0 Hz, 1′-H*H*), 3.77 (3H, s, OCH_3), 4.89 (1H, ddd, *J* 8.4, 5.0, 3.0 Hz, 2′-H), 6.71–6.74 (1H, m, 2-H), 6.76–6.83 (2H, m, 4-H and 6-H), 7.22 (1H, t, *J* 7.9 Hz, 5-H), 7.26–7.40 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 46.2 (CH_2), 55.2 (CH_3), 75.2 (CH), 112.2 (CH), 115.1 (CH), 121.8 (CH), 125.9 (2 × CH), 127.6 (CH), 128.4 (2 × CH), 129.5 (CH), 139.6 (C), 143.8 (C), 159.7 (C); *m/z* (ESI) 251 (MNa^+. 100%).

2,3-Dihydro-2-(4′-methoxyphenyl)-5-methoxybenzofuran (155)[291]



2,3-Dihydro-2-(4′-methoxyphenyl)-5-methoxybenzofuran (**155**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 1′-(3-methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-ol (**156a**) (0.0500 g, 0.190 mmol). The iodination step was carried out at 40 °C for 5 h and the *O*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave 2,3-dihydro-2-(4′-methoxyphenyl)-5-methoxybenzofuran (**155**) (0.0130 g, 29%) as a colourless oil. Spectroscopic data were consistent with the literature.[291] δ_H (400 MHz, $CDCl_3$) 3.19 (1H, dd, *J* 15.7, 8.3 Hz, 3-*H*H), 3.55 (1H, dd, *J* 15.7, 9.0 Hz, 3-H*H*), 3.77 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.68 (1H, dd, *J* 9.0, 8.3 Hz, 2-H), 6.65–6.84 (3H, m, 4-H, 6-H and 7-H), 6.89 (2H, d, *J* 8.7 Hz, 3′-H and 5′-H), 7.33 (2H, d, *J* 8.7 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 38.7 (CH_2), 55.3 (CH_3), 56.1 (CH_3), 84.2 (CH), 109.2 (CH), 111.2 (CH), 113.0 (CH), 114.0 (2 × CH), 127.3 (2 × CH), 127.7 (C), 133.9 (C), 153.7 (C), 154.2 (C), 159.5 (C); *m/z* (ESI) 279 (MNa^+. 100%).

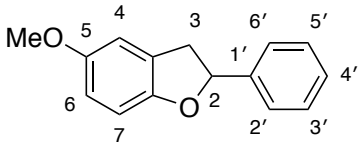
2-(4′-Chlorophenyl)-2,3-dihydro-5-methoxybenzofuran (159a)[529]



2-(4′-Chlorophenyl)-2,3-dihydro-5-methoxybenzofuran (**159a**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 2′-(4″-chlorophenyl)-1′-(3-methoxyphenyl)ethan-2′-ol (**156b**) (0.154 g, 0.590 mmol). The iodination step was

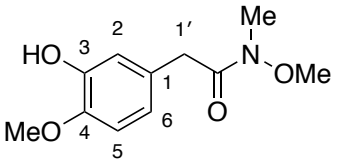
carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 2-(4′-chlorophenyl)-2,3-dihydro-5-methoxybenzofuran (**159a**) (0.0958 g, 63%) as a white solid. Mp 58–60 °C (lit.[529] 60–61 °C); δ_H (400 MHz, $CDCl_3$) 3.13 (1H, dd, *J* 15.7, 8.0 Hz, 3-*H*H), 3.60 (1H, dd, *J* 15.7, 9.4 Hz, 3-H*H*), 3.76 (3H, s, OCH_3), 5.70 (1H, dd, *J* 9.4, 8.0 Hz, 1-H), 6.70 (1H, dd, *J* 8.7, 2.6 Hz, 6-H), 6.74–6.80 (2H, m, 4-H and 7-H), 7.33 (4H, br s, 2′-H, 3′-H, 5′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 38.9 (CH_2), 56.0 (CH_3), 83.4 (CH), 109.3 (CH), 111.2 (CH), 113.1 (CH), 127.1 (2 × CH), 127.1 (C), 128.8 (2 × CH), 133.7 (C), 140.6 (C), 153.6 (C), 154.4 (C); *m/z* (ESI) 283 (MNa^+. 100%).

2,3-Dihydro-5-methoxy-2-phenylbenzofuran (159b)[284]



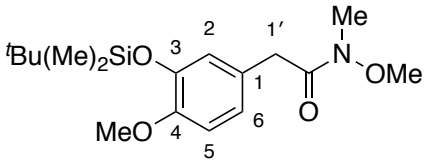
2,3-Dihydro-5-methoxy-2-phenylbenzofuran (**159b**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using 1′-(3-methoxyphenyl)-2′-phenylethan-2′-ol (**156c**) (0.0840 g, 0.370 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 2,3-dihydro-5-methoxy-2-phenylbenzofuran (**159b**) (0.0530 g, 64%) as a colourless oil. Spectroscopic data were consistent with the literature.[284] δ_H (400 MHz, $CDCl_3$) 3.18 (1H, dd, *J* 15.7, 8.2 Hz, 3-*H*H), 3.59 (1H, dd, *J* 15.7, 9.4 Hz, 3-H*H*), 3.76 (3H, s, OCH_3), 5.72 (1H, dd, *J* 9.4, 8.2 Hz, 2-H), 6.69 (1H, dd, *J* 8.7, 2.6 Hz, 6-H), 6.74–6.80 (2H, m, 4-H and 7-H), 7.26–7.43 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 38.9 (CH_2), 56.1 (CH_3), 84.3 (CH), 109.2 (CH), 111.2 (CH), 113.1 (CH), 125.8 (2 × CH), 127.5 (C), 128.0 (CH), 128.7 (2 × CH), 142.1 (C), 153.8 (C), 154.3 (C); *m/z* (ESI) 249 (MNa^+. 100%).

1′-(3-Hydroxy-4-methoxyphenyl)-*N*-methoxy-*N*-methylacetamide (164)



The reaction was carried out as described for *N*-methoxy-1′-(3-methoxyphenyl)-*N*-methylacetamide (**158**) using 3-hydroxy-4-methoxyphenylacetic acid (**163**) (1.00 g, 5.49 mmol), except that the solvent used was acetonitrile (30 mL). Purification by flash column chromatography (petroleum ether/ ethyl acetate, 3:7) gave 1′-(3-hydroxy-4-methoxyphenyl)-*N*-methoxy-*N*-methylacetamide (**164**) (0.831 g, 68%) as a white solid. Mp 62–64 °C; ν_{max}/cm^{-1} (neat) 3323 (OH), 2939 (CH), 1642 (C=O), 1590, 1511, 1440, 1271, 1131, 1006, 761; δ_H (400 MHz, $CDCl_3$) 3.18 (3H, s, *N*-CH_3), 3.61 (3H, s, *N*-OCH_3), 3.67 (2H, s, 1′-H_2), 3.85 (3H, s, OCH_3), 5.85 (1H, s, OH), 6.73–6.82 (2H, m, 5-H and 6-H), 6.87 (1H, d, *J* 1.3 Hz, 2-H); δ_C (101 MHz, $CDCl_3$) 32.3 (CH_3), 38.7 (CH_2), 56.0 (CH_3), 61.3 (CH_3), 110.8 (CH and C), 115.7 (CH), 120.7 (CH), 128.1 (C), 145.6 (C), 172.7 (C); *m/z* (ESI) 248.0889 (MNa^+. $C_{11}H_{15}NNaO_4$ requires 248.0893).

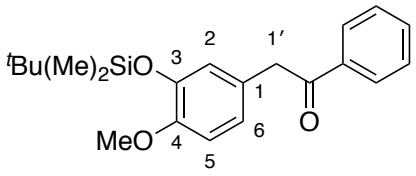
1′-(3-*tert*-Butyldimethylsilyloxy-4-methoxyphenyl)-*N*-methoxy-*N*-methylacetamide (165)



To a solution of 1′-(3-hydroxy-4-methoxyphenyl)-*N*-methoxy-*N*-methylacetamide (**164**) (1.23 g, 5.46 mmol) and imidazole (0.744 g, 10.9 mmol) in dry dichloromethane (40 mL) was added *tert*-butyldimethylsilyl chloride (0.99 g, 6.56 mmol) portionwise. 4-Dimethylaminopyridine (0.070 g, 0.55 mmol) was added and the resulting suspension was stirred at room temperature for 16 h. The reaction was quenched with water (30 mL) and the mixture was extracted with dichloromethane (4 × 50 mL). The combined organic extracts were washed with aqueous sodium hydrogen carbonate (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl

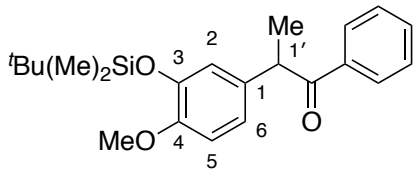
acetate, 4:1) gave 1′-(3-*tert*-butyldimethylsilyloxy-4-methoxyphenyl)-*N*-methoxy-*N*-methylacetamide (**165**) (1.87 g, 100%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2932 (CH), 1663 (C=O), 1512, 1271, 1136, 988, 839; δ_H (400 MHz, $CDCl_3$) 0.15 (6H, s, $Si(CH_3)_2$), 0.99 (9H, s, $SiC(CH_3)_3$), 3.18 (3H, s, *N*-CH_3), 3.58 (3H, s, *N*-OCH_3), 3.65 (2H, s, 1′-H_2), 3.78 (3H, s, OCH_3), 6.78 (1H, d, *J* 8.2 Hz, 5-H), 6.80 (1H, d, *J* 2.0 Hz, 2-H), 6.83 (1H, dd, *J* 8.2, 2.0 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) −4.6 (2 × CH_3), 18.4 (C), 25.8 (3 × CH_3), 32.8 (CH_3), 38.8 (CH_2), 55.6 (CH_3), 61.3 (CH_3), 112.2 (CH), 122.1 (CH), 122.3 (CH), 127.5 (C), 144.9 (C), 149.9 (C), 172.7 (C); *m/z* (ESI) 362.1745 (MNa^+. $C_{17}H_{29}NNaO_4Si$ requires 362.1758).

1′-(3-*tert*-Butyldimethylsilyloxy-4-methoxyphenyl)-2′-phenylethan-2′-one (166)



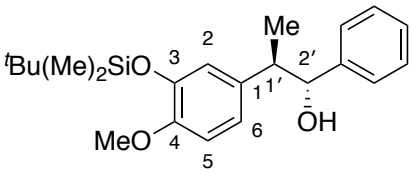
1′-(3-*tert*-Butyldimethylsilyloxy-4-methoxyphenyl)-2′-phenylethan-2′-one (**166**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**157b**) using 1′-(3-*tert*-butyldimethylsilyloxy-4-methoxyphenyl)-*N*-methoxy-*N*-methylacetamide (**165**) (1.71 g, 5.03 mmol) and phenylmagnesium bromide (7.54 mL, 7.54 mmol; 1.0 M in tetrahydrofuran), except the reaction mixture was stirred for 5 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 1′-(3-*tert*-butyldimethylsilyloxy-4-methoxyphenyl)-2′-phenylethan-2′-one (**166**) (1.32 g, 74%) as a white solid. Mp 60–62 °C; ν_{max}/cm^{-1} (neat) 2930 (CH), 1680 (C=O), 1510, 1271, 1136, 984, 839; δ_H (500 MHz, $CDCl_3$) 0.12 (6H, s, $Si(CH_3)_2$), 0.97 (9H, s, $SiC(CH_3)_3$), 3.77 (3H, s, OCH_3), 4.16 (2H, s, 1′-H_2), 6.76 (1H, d, *J* 1.4 Hz, 2H), 6.77–6.82 (2H, m, 5-H and 6-H), 7.40–7.46 (2H, m, 3″-H and 5″-H), 7.50–7.55 (1H, m, 4″-H), 7.94–8.01 (2H, m, 2″-H and 6″-H); δ_C (126 MHz, $CDCl_3$) −4.6 (2 × CH_3), 18.4 (C), 25.7 (3 × CH_3), 45.0 (CH_2), 55.5 (CH_3), 112.4 (CH), 122.2 (CH), 122.5 (CH), 127.0 (C), 128.6 (2 × CH), 128.7 (2 × CH), 133.0 (CH), 136.7 (C), 145.1 (C), 149.9 (C), 197.9 (C); *m/z* (ESI) 379.1686 (MNa^+. $C_{21}H_{28}NaO_3Si$ requires 379.1700).

1′-(3-*tert*-Butyldimethylsilyloxy-4-methoxyphenyl)-1′-methyl-2′-phenylethan-2′-one (167)



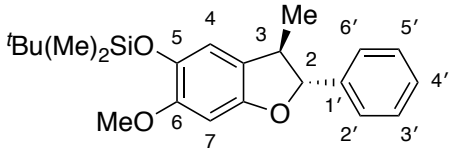
An oven dried three-neck flask was flushed with argon and charged with 1′-(3-*tert*-butyldimethylsilyloxy-4-methoxyphenyl)-2′-phenylethan-2′-one (**166**) (1.32 g, 3.69 mmol) in dry tetrahydrofuran (30 mL). To this solution was added lithium bis(trimethylsilyl)amide (4.06 mL, 4.06 mmol; 1.0 M in tetrahydrofuran) dropwise at –78 °C. The reaction mixture was stirred at –78 °C for 0.5 h before methyl iodide (0.690 mL, 11.1 mmol) was added dropwise. The resulting solution was stirred for 1 h at –78 °C, then slowly warmed to 0 °C and stirred for a further 1 h. A saturated solution of ammonium chloride (30 mL) was added at 0 °C and the solution was extracted with diethyl ether (3 × 50 mL). The combined ethereal extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1′-(3-*tert*-butyldimethylsilyloxy-4-methoxyphenyl)-1′-methyl-2′-phenylethan-2′-one (**167**) (1.19 g, 87%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2930 (CH), 1684 (C=O), 1506, 1275, 1138, 970, 837; δ_H (400 MHz, $CDCl_3$) 0.09 (6H, s, Si(CH_3)$_2$), 0.96 (9H, s, SiC(CH_3)$_3$), 1.48 (3H, d, *J* 6.8 Hz, 1′-CH_3), 3.73 (3H, s, OCH_3), 4.53 (2H, q, *J* 6.8 Hz, 1′-H), 6.74 (1H, d, *J* 8.5 Hz, 5-H), 6.75 (1H, d, *J* 2.0 Hz, 2-H), 6.79 (1H, dd, *J* 8.5, 2.0 Hz, 6-H), 7.32–7.39 (2H, m, 3″-H and 5″-H), 7.42–7.48 (1H, m, 4″-H), 7.89–7.94 (2H, m, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) −4.6 (2 × CH_3), 18.5 (C), 19.3 (CH_3), 25.7 (3 × CH_3), 47.3 (CH), 55.5 (CH_3), 112.6 (CH), 120.7 (CH), 120.8 (CH), 128.4 (2 × CH), 128.8 (2 × CH), 132.6 (CH), 134.1 (C), 136.6 (C), 145.3 (C), 149.9 (C), 200.4 (C); *m/z* (ESI) 393.1848 (MNa$^+$. $C_{22}H_{30}NaO_3Si$ requires 393.1856).

(1′*R*,2′*R*)-1′-(3-*tert*-Butyldimethylsilyloxy-4-methoxyphenyl)-1′-methyl-2′-phenylethan-2′-ol (168)



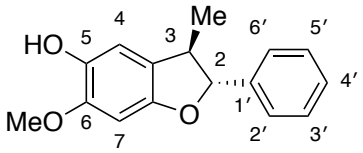
To an oven-dried conical flask was added potassium *tert*-butoxide (0.0182 g, 0.162 mmol) and ˙dichloro[(*S*)-(–)-5,5′-bis[di-(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole][(2*S*-(+)-1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine]ruthenium(II) (0.0200 g, 0.0162 mmol). Freshly distilled 2-propanol (1.0 mL) was added and the resulting yellow solution was stirred at room temperature for 2 h under a constant stream of argon. 1′-(3-*tert*-Butyldimethylsilyloxy-4-methoxyphenyl)-1′-methyl-2′-phenylethan-2′-one (**167**) (0.300 g, 0.810 mmol) in 2-propanol (2.0 mL) was added to the conical flask containing the catalyst solution and hydrogenated at 10 bar for 48 h. The reaction mixture was treated with activated carbon and stirred for 1 h. The mixture was filtered through Celite® and concentrated *in vacuo*. Purification by flash column chromatography (hexane/diethyl ether, 7:3) gave (1′*R*,2′*R*)-1′-(3-*tert*-butyldimethylsilyloxy-4-methoxyphenyl)-1′-methyl-2′-phenylethan-2′-ol (**168**) (0.192 g, 64%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3454 (OH), 2929 (CH), 1508, 1275, 1139, 962, 836; $[\alpha]_D^{23}$ +34.4 (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.15 (6H, s, $Si(CH_3)_2$), 1.00 (9H, s, $SiC(CH_3)_3$), 1.03 (3H, d, *J* 7.2 Hz, 1′-CH_3), 1.90 (1H, d, *J* 1.4 Hz, OH), 2.89 (1H, dq, *J* 8.6, 7.2 Hz, 1′-H), 3.80 (3H, s, OCH_3), 4.55 (1H, dd, *J* 8.6, 1.4 Hz, 2′-H), 6.73–6.77 (1H, m, 2-H), 6.80–6.84 (2H, m, 5-H and 6-H), 7.24–7.36 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) −4.5 (2 × CH_3), 18.3 (CH_3), 18.5 (C), 25.8 (3 × CH_3), 47.5 (CH), 55.6 (CH_3), 79.7 (CH), 112.2 (CH), 120.6 (CH), 121.2 (CH), 127.0 (2 × CH), 127.7 (CH), 128.2 (2 × CH), 135.6 (C), 142.5 (C), 145.2 (C), 149.9 (C); m/z (ESI) 395.2023 (MNa+. $C_{22}H_{32}NaO_3Si$ requires 395.2013). Enantiomeric excess was determined by HPLC analysis, using a chiralpak AD-H column (hexane:*i*-propanol 98:2, flow rate 1.0 mL min^{-1}); t_{minor} = 10.65 min, t_{major} = 14.55 min, er = 2.5:97.5.

(2*R*,3*R*)-5-(*tert*-Butyldimethylsilyloxy)-2,3-dihydro-6-methoxy-3-methyl-2-phenylbenzofuran (169)



(2*R*,3*R*)-5-(*tert*-Butyldimethylsilyloxy)-2,3-dihydro-6-methoxy-3-methyl-2-phenylbenzofuran (**169**) was synthesised as described for 1-benzoyl-5-methoxyindoline (**143a**) using (1′*R*,2′*R*)-1′-(3-*tert*-butyldimethylsilyloxy-4-methoxyphenyl)-1′-methyl-2′-phenylethan-2′-ol (**168**) (0.0600 g, 0.160 mmol). The iodination step was carried out at 50 °C for 7 h and the *O*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave (2*R*,3*R*)-5-(*tert*-butyldimethylsilyloxy)-2,3-dihydro-6-methoxy-3-methyl-2-phenylbenzofuran (**169**) (0.0378 g, 63%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2929 (CH), 1493, 1449, 1215, 1188, 1169, 904, 837; $[\alpha]_D^{20}$ +23.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.14 (3H, s, Si(CH_3)), 0.14 (3H, s, Si(CH_3)), 1.00 (9H, s, SiC(CH_3)$_3$), 1.37 (3H, d, *J* 6.7 Hz, 3-CH_3), 3.36 (1H, dq, *J* 8.9, 6.7 Hz, 3-H), 3.77 (3H, s, OCH_3), 5.11 (1H, d, *J* 8.9, 2-H), 6.46 (1H, s, 7-H), 6.61 (1H, s, 4-H), 7.27–7.45 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) −4.7 (CH_3), −4.6 (CH_3), 18.4 (CH_3), 18.5 (C), 25.8 (3 × CH_3), 45.6 (CH), 55.7 (CH_3), 92.9 (CH), 95.0 (CH), 115.7 (CH), 122.4 (C), 126.1 (2 × CH), 128.1 (CH), 128.6 (2 × CH), 139.0 (C), 141.1 (C), 150.8 (C), 153.6 (C); *m/z* (EI) 370.1955 (M^+. $C_{22}H_{30}O_3Si$ requires 370.1964), 313 (48%), 298 (100), 91 (36), 73 (40).

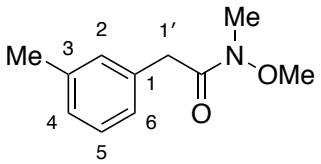
(2*R*,3*R*)-2,3-Dihydro-5-hydroxyl-6-methoxy-3-methyl-2-phenylbenzofuran, (+)-obtusafuran (118)[299]



To a stirred solution of (2*R*,3*R*)-5-(*tert*-butyldimethylsilyloxy)-2,3-dihydro-6-methoxy-3-methyl-2-phenylbenzofuran (**169**) (0.0380 g, 0.100 mmol) in dry tetrahydrofuran (10 mL) was added tetrabutylammonium fluoride solution (0.150

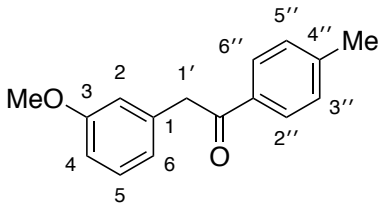
mL, 0.150 mmol; 1.0 M in tetrahydrofuran) at 0 °C. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was diluted with diethyl ether (10 mL), washed with water (2 × 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (hexane/diethyl ether, 7:3) gave (2*R*,3*R*)-2,3-dihydro-5-hydroxyl-6-methoxy-3-methyl-2-phenylbenzofuran (**118**) (0.0230 g, 88%) as a white solid. Mp 108–110 °C (lit.[299] Mp 111–113 °C); $[\alpha]_D^{23}$ +48.2 (*c* 0.5, MeOH), lit.[299] $[\alpha]_D^{25}$ +50.0 (*c* 0.33, MeOH); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.9 Hz, 3-CH_3), 3.38 (1H, dq, *J* 8.6, 6.9 Hz, 3-H), 3.87 (3H, s, OCH_3), 5.11 (1H, d, *J* 8.6 Hz, 2-H), 5.24 (1H, s, OH), 6.50 (1H, s, 7-H), 6.72 (1H, s, 4-H), 7.29–7.44 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 18.4 (CH_3), 45.7 (CH), 56.2 (CH_3), 92.8 (CH), 94.2 (CH), 109.5 (CH), 122.9 (C), 126.0 (2 × CH), 128.1 (CH), 128.6 (2 × CH), 139.9 (C), 141.0 (C), 146.2 (C), 152.4 (C); *m/z* (EI) 256 (M^+. 100%), 239 (11), 165 (12), 91 (10).

_N_-Methoxy-1′-(3-methylphenyl)-_N_-methylacetamide (179)[530]



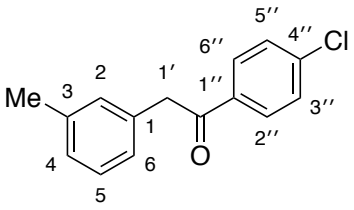
N-Methoxy-1′-(3-methylphenyl)-*N*-methylacetamide (**179**) was synthesised as described for *N*-methoxy-1′-(3-methylphenyl)-*N*-methylacetamide (**158**) using 3-methylphenylacetic acid (0.500 g, 3.33 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-methoxy-1′-(3-methylphenyl)-*N*-methylacetamide (**179**) (0.411 g, 64%) as a colourless oil. Spectroscopic data were consistent with the literature.[530] δ_H (500 MHz, $CDCl_3$) 2.32 (3H, s, 3-CH_3), 3.17 (3H, s, *N*-CH_3), 3.58 (3H, s, OCH_3), 3.72 (2H, s, 1′-H_2), 7.04 (1H, d, *J* 7.6 Hz, 4-H), 7.07 (1H, d, *J* 7.6 Hz, 6-H), 7.11 (1H, br s, 2-H), 7.19 (1H, t, *J* 7.6 Hz, 5-H); δ_C (126 MHz, $CDCl_3$) 21.4 (CH_3), 32.2 (CH_3), 39.3 (CH_2), 61.2 (CH_3), 126.3 (CH), 127.5 (CH), 128.3 (CH), 130.0 (CH), 134.8 (C), 138.0 (C), 172.5 (C); *m/z* (ESI) 216 (MNa^+. 100%).

1′-(3-Methoxyphenyl)-2′-(4″-methylphenyl)ethan-2′-one (180a)[531]



1′-(3-Methoxyphenyl)-2′-(4″-methylphenyl)ethan-2′-one (**180a**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**157b**) using *N*-methoxy-1′-(3-methoxyphenyl)-*N*-methylacetamide (**158**) (0.0950 g, 0.450 mmol) and 4-methylphenylmagnesium bromide (2.70 mL, 1.35 mmol; 0.5 M in diethyl ether). Purification by flash column chromatography (hexane/diethyl ether, 4:1) gave 1′-(3-methoxyphenyl)-2′-(4″-methylphenyl)ethan-2′-one (**180a**) (0.0760 g, 70%) as a colourless oil. Spectroscopic data were consistent with the literature.[531] δ_H (500 MHz, $CDCl_3$) 2.39 (3H, s, 4″-CH_3), 3.77 (3H, s, OCH_3), 4.22 (2H, s, 1′-H_2), 6.78 (1H, dd, *J* 7.9, 2.5 Hz, 6-H), 6.81 (1H, br s, 2-H), 6.85 (1H, br d, *J* 7.9 Hz, 4-H), 7.22 (1H, t, *J* 7.9 Hz, 5-H), 7.24 (2H, d, *J* 8.3 Hz, 3″-H and 5″-H), 7.90 (2H, d, *J* 8.3 Hz, 2″-H and 6″-H); δ_C (126 MHz, $CDCl_3$) 21.7 (CH_3), 45.5 (CH_2), 55.2 (CH_3), 112.4 (CH), 115.1 (CH), 121.8 (CH), 128.8 (2 × CH), 129.3 (2 × CH), 129.6 (CH), 134.1 (C), 136.3 (C), 144.0 (C), 159.8 (C), 197.2 (C); *m/z* (ESI) 263 (MNa^+. 100%).

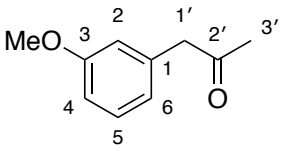
1′-(3-Methylphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (180b)



1′-(3-Methylphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**180b**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**157b**) using *N*-methoxy-1′-(3-methylphenyl)-*N*-methylacetamide (**179**) (0.294 g, 1.52 mmol) and 4-chlorophenylmagnesium bromide (1.83 mL, 1.83 mmol; 1.0 M in 2-methyltetrahydrofuran). Purification by flash column chromatography (hexane/diethyl ether, 9:1) gave 1′-(3-methylphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**180b**) (0.173 g, 47%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2920 (CH), 1678

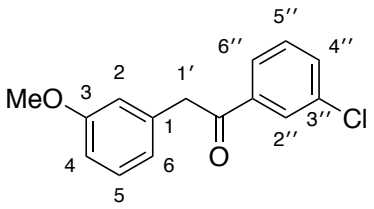
(C=O), 1587, 1398, 1271, 1206, 1090, 1011, 988, 762; δ_H (500 MHz, $CDCl_3$) 2.32 (3H, s, 3-CH_3), 4.20 (2H, s, 1′-H_2), 7.02–7.08 (3H, m, 2-H, 4-H and 6-H), 7.21 (1H, t, *J* 7.6 Hz, 5-H), 7.41 (2H, d, *J* 8.6 Hz, 3″-H and 5″-H), 7.93 (2H, d, *J* 8.6 Hz, 2″-H and 6″-H); δ_C (126 MHz, $CDCl_3$) 21.4 (CH_3), 45.5 (CH_2), 126.4 (CH), 127.8 (CH), 128.6 (CH), 128.9 (2 × CH), 130.1 (3 × CH), 134.1 (C), 134.9 (C), 138.4 (C), 139.6 (C), 196.5 (C); *m/z* (ESI) 267.0542 (MNa^+. $C_{15}H_{13}{}^{35}ClNaO$ requires 267.0547).

1′-(3-Methoxyphenyl)propan-2′-one (180c)[532]



1′-(3-Methoxyphenyl)propan-2′-one (**180c**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**157b**) using *N*-methoxy-1′-(3-methoxyphenyl)-*N*-methylacetamide (**158**) (0.300 g, 1.43 mmol) and methylmagnesium bromide (2.15 mL, 2.15 mmol; 1.0 M in dibutyl ether). Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 1′-(3-methoxyphenyl)propan-2′-one (**180c**) (0.200 g, 85%) as a yellow oil. Spectroscopic data were consistent with the literature.[532] δ_H (400 MHz, $CDCl_3$) 2.15 (3H, s, 3′-H_3), 3.66 (2H, s, 1′-H_2), 3.80 (3H, s, OCH_3), 6.74 (1H, t, *J* 2.0 Hz, 2-H), 6.77–6.84 (2H, m, 4-H and 6-H), 7.25 (1H, t, *J* 7.9 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 29.2 (CH_3), 51.1 (CH_2), 55.2 (CH_3), 112.6 (CH), 115.1 (CH), 121.8 (CH), 129.8 (CH), 135.7 (C), 159.9 (C), 206.3 (C); *m/z* (ESI) 187 (MNa^+. 100%).

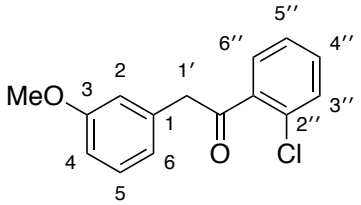
1′-(3-Methoxyphenyl)-2′-(3″-chlorophenyl)ethan-2′-one (181a)



An oven-dried two-neck flask was flushed with argon and charged with 3-methoxyphenylacetic acid (**128**) (0.300 g, 1.81 mmol), methyl 3-chlorobenzoate (0.252 mL, 1.81 mmol) and anhydrous *N*,*N*-dimethylformamide (6 mL). The solution

was cooled to –10 °C and lithium bis(trimethylsilyl)amide (7.22 mL, 7.22 mmol; 1.0 M in tetrahydrofuran) was added dropwise. The resulting reaction mixture was stirred at –10 °C for 3 h. A saturated aqueous solution of ammonium chloride (10 mL) was added and the solution was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (4 × 100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/diethyl ether, 9:1) gave 1′-(3-methoxyphenyl)-2′-(3″-chlorophenyl)ethan-2′-one (**181a**) (0.278 g, 59%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2938 (CH), 1682 (C=O), 1584, 1491, 1258, 1204, 1152, 1042, 781, 758, 709, 691, 679; δ_H (400 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 4.20 (2H, s, 1′-H_2), 6.77–6.85 (3H, m, 2-H, 4-H and 6-H), 7.20–7.26 (1H, m, 5-H), 7.36 (1H, t, *J* 7.9 Hz, 5″-H), 7.48 (1H, ddd, *J* 7.9, 2.0, 1.2 Hz, 4″-H), 7.85 (1H, dt, *J* 7.9, 1.2 Hz, 6″-H), 7.96 (1H, br t, *J* 2.0 Hz, 2″-H); δ_C (101 MHz, $CDCl_3$) 45.6 (CH_2), 55.1 (CH_3), 112.5 (CH), 115.1 (CH), 121.7 (CH), 126.7 (CH), 128.6 (CH), 129.7 (CH), 130.0 (CH), 133.1 (CH), 134.9 (C), 135.4 (C), 138.1 (C), 159.8 (C), 196.1 (C); *m/z* (ESI) 283.0490 (MNa^+. $C_{15}H_{13}{}^{35}ClNaO_2$ requires 283.0496).

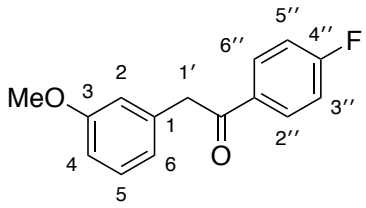
1′-(3-Methoxyphenyl)-2′-(2″-chlorophenyl)ethan-2′-one (181b)



1′-(3-Methoxyphenyl)-2′-(2″-chlorophenyl)ethan-2′-one (**181b**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(3″-chlorophenyl)ethan-2′-one (**181a**) using 3-methoxyphenylacetic acid (**128**) (0.100 g, 0.600 mmol) and methyl 2-chlorobenzoate (0.102 g, 0.600 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 9:1) gave 1′-(3-methoxyphenyl)-2′-(2″-chlorophenyl)ethan-2′-one (**181b**) (0.0620 g, 40%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2941 (CH), 1697 (C=O), 1585, 1491, 1433, 1258, 1152, 1060, 772, 756; δ_H (500 MHz, $CDCl_3$) 3.77 (3H, s, OCH_3), 4.22 (2H, s, 1′-H_2), 6.76–6.83 (3H, m, 2-H, 4-H and 6-H), 7.21 (1H, t, *J* 7.8 Hz, 5-H), 7.26 (1H, td, *J* 7.5, 1.3 Hz, 5″-H), 7.33–7.42 (3H, m, 3″-H, 4″-H and 6″-H); δ_C (126 MHz, $CDCl_3$) 49.6 (CH_2), 55.2 (CH_3), 112.7 (CH), 115.2 (CH), 122.0 (CH), 126.9 (CH), 129.1 (CH), 129.6 (CH), 130.4

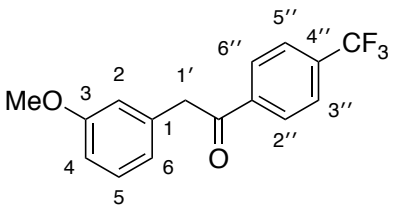
(CH), 130.8 (C), 131.6 (CH), 135.0 (C), 139.2 (C), 159.7 (C), 200.8 (C); *m/z* (ESI) 283.0501 (MNa^+. $C_{15}H_{13}{}^{35}ClNaO_2$ requires 283.0496).

1′-(3-Methoxyphenyl)-2′-(4″-fluorophenyl)ethan-2′-one (181c)[533]



1′-(3-Methoxyphenyl)-2′-(4″-fluorophenyl)ethan-2′-one (**181c**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(3″-chlorophenyl)ethan-2′-one (**181a**) using 3-methoxyphenylacetic acid (**128**) (0.500 g, 3.01 mmol) and methyl 4-fluorobenzoate (0.464 g, 3.01 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 9:1) gave 1′-(3-methoxyphenyl)-2′-(4″-fluorophenyl)ethan-2′-one (**181c**) (0.540 g, 73%) as a colourless oil. Spectroscopic data were consistent with the literature.[533] δ_H (400 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 4.20 (2H, s, 1′-H_2), 6.76–6.86 (3H, m, 2-H, 4-H and 6-H), 7.09 (2H, t, *J* 8.7 Hz, 3″-H and 5″-H), 7.22 (1H, td, *J* 7.6, 0.9 Hz, 5-H), 8.01 (2H, dd, *J* 8.7, 5.5 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 45.6 (CH_2), 55.2 (CH_3), 112.4 (CH), 115.1 (CH), 115.1 (2 × CH, d, $^2J_{CF}$ 21.8 Hz), 121.7 (CH), 129.8 (CH), 131.3 (2 × CH, d, $^3J_{CF}$ 9.2 Hz), 133.0 (C, d, $^4J_{CF}$ 3.0 Hz), 135.9 (C), 159.9 (C), 165.8 (C, d, $^1J_{CF}$ 255.7 Hz), 195.9 (C); *m/z* (ESI) 267 (MNa^+. 100%).

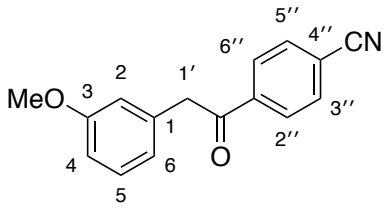
1′-(3-Methoxyphenyl)-2′-(4″-trifluoromethylphenyl)ethan-2′-one (181d)



1′-(3-Methoxyphenyl)-2′-(4″-trifluoromethylphenyl)ethan-2′-one (**181d**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(3″-chlorophenyl)ethan-2′-one (**181a**) using 3-methoxyphenylacetic acid (**128**) (0.300 g, 1.81 mmol) and methyl 4-trifluoromethylbenzoate (0.291 mL, 1.81 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 1′-(3-

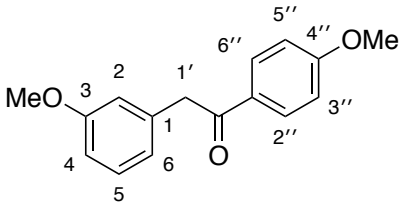
methoxyphenyl)-2′-(4″-trifluoromethylphenyl)ethan-2′-one (**181d**) (0.266 g, 50%) as a white solid. Mp 32–34 °C; ν_{max}/cm^{-1} (neat) 2941 (CH), 1688 (C=O), 1585, 1491, 1410, 1321, 1263, 1165, 1125, 1109, 1065, 1015, 1001, 993, 766; δ_H (400 MHz, $CDCl_3$) 3.78 (3H, s, OCH_3), 4.27 (2H, s, 1′-H_2), 6.78–6.86 (3H, m, 2-H, 4-H and 6-H), 7.24 (1H, dd, *J* 9.0, 7.5 Hz, 5-H), 7.70 (2H, d, *J* 7.9 Hz, 3″-H and 5″-H), 8.09 (2H, d, *J* 7.9 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 45.9 (CH_2), 55.2 (CH_3), 112.5 (CH), 115.2 (CH), 121.7 (CH), 123.6 (C, q, $^1J_{CF}$ 274.6 Hz), 125.7 (2 × CH, q, $^3J_{CF}$ 3.8 Hz), 129.0 (2 × CH), 129.9 (CH), 134.4 (C, q, $^2J_{CF}$ 32.8 Hz), 135.3 (C), 139.2 (C), 159.9 (C), 196.5 (C); *m/z* (ESI) 317.0747 (MNa^+. $C_{16}H_{13}F_3NaO_2$ requires 317.0760).

1′-(3-Methoxyphenyl)-2′-(4″-cyanophenyl)ethan-2′-one (181e)



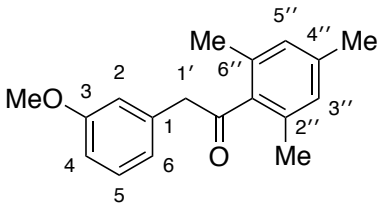
1′-(3-Methoxyphenyl)-2′-(4″-cyanophenyl)ethan-2′-one (**181e**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(3″-chlorophenyl)ethan-2′-one (**181a**) using 3-methoxyphenylacetic acid (**128**) (0.300 g, 1.81 mmol) and methyl 4-cyanobenzoate (0.292 g, 1.81 mmol). Purification by flash column chromatography (dichloromethane) gave 1′-(3-methoxyphenyl)-2′-(4″-cyanophenyl)ethan-2′-one (**181e**) (0.274 g, 60%) as a white solid. Mp 96–98 °C; ν_{max}/cm^{-1} (neat) 2968 (CH), 2224 (CN), 1699 (C=O), 1584, 1489, 1329, 1261, 1209, 1157, 1047, 887, 833, 764; δ_H (400 MHz, $CDCl_3$) 3.78 (3H, s, OCH_3), 4.26 (2H, s, 1′-H_2), 6.76–6.84 (3H, m, 2-H, 4-H and 6-H), 7.25 (1H, t, *J* 7.8 Hz, 5-H), 7.74 (2H, d, *J* 8.2 Hz, 3″-H and 5″-H), 8.07 (2H, d, *J* 8.2 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 45.9 (CH_2), 55.2 (CH_3), 112.6 (CH), 115.2 (CH), 116.4 (C), 117.9 (C), 121.6 (CH), 129.0 (2 × CH), 129.9 (CH), 132.5 (2 × CH), 134.9 (C), 139.5 (C), 160.0 (C), 196.1 (C); *m/z* (ESI) 274.0840 (MNa^+. $C_{16}H_{13}NNaO_2$ requires 274.0838).

1′-(3-Methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (157a)[291]



3-Methoxyphenylacetic acid (**128**) (1.00 g, 6.02 mmol) was dissolved in thionyl chloride (5.20 mL, 72.2 mmol) and heated under reflux for 1 h. After cooling to room temperature, the excess thionyl chloride was removed *in vacuo.* The crude residue was dissolved in dry dichloromethane (25 mL) and anisole (0.650 mL, 6.02 mmol) was added. The solution was cooled to −5 °C and aluminium trichloride (0.803 g, 6.02 mmol) was slowly added. The reaction mixture was stirred at −5 °C for 0.5 h, warmed to room temperature and stirred for 1.5 h. After this time, the reaction mixture was quenched by the slow addition of ice-cold water (20 mL) and the aqueous layer was extracted with dichloromethane (4 × 50 mL). The combined organic extracts were washed with 1 M aqueous hydrochloric acid (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 1′-(3-methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**157a**) (1.24 g, 80%) as a yellow oil. Characterisation data previously reported for 1′-(3-methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**157a**).

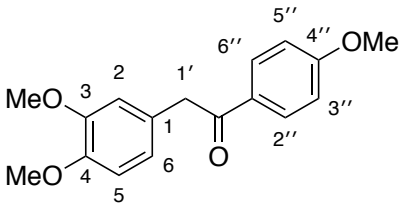
1′-(3-Methoxyphenyl)-2′-(2″,4″,6″-trimethylphenyl)ethan-2′-one (184a)



3-Methoxyphenylacetic acid (**128**) (0.500 g, 3.01 mmol) was dissolved in thionyl chloride (2.60 mL, 36.3 mmol) and heated under reflux for 1 h. After cooling to room temperature, the excess thionyl chloride was removed *in vacuo.* The crude residue was dissolved in dry dichloromethane (20 mL) and mesitylene (0.505 mL, 3.61 mmol) was added. The solution was cooled to −5 °C and aluminium trichloride

(0.482 g, 3.61 mmol) was slowly added. The reaction mixture was stirred at −5 °C for 0.5 h, warmed to room temperature and stirred for 1.5 h. After this time, the reaction mixture was quenched by the slow addition of ice-cold water (20 mL) and the aqueous layer was extracted with dichloromethane (4 × 30 mL). The combined organic extracts were washed with 1 M aqueous hydrochloric acid (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 1′-(3-methoxyphenyl)-2′-(2″,4″,6″-trimethylphenyl)ethan-2′-one (**184a**) (0.220 g, 27%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2922 (CH), 1695 (C=O), 1599, 1489, 1258, 1150, 770; δ_H (400 MHz, $CDCl_3$) 2.13 (6H, s, 2″-CH_3 and 6″-CH_3), 2.28 (3H, s, 4″-CH_3), 3.77 (3H, s, OCH_3), 3.96 (2H, s, 1'-H_2), 6.74–6.76 (1H, m, 2-H), 6.77–6.84 (4H, m, 4-H, 6-H, 3″-H and 5″-H), 7.22 (1H, t, *J* 7.9 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 19.2 (2 × CH_3), 21.1 (CH_3), 51.8 (CH_2), 55.2 (CH_3), 112.6 (CH), 115.5 (CH), 122.3 (CH), 128.5 (2 × CH), 129.5 (CH), 132.8 (2 × C), 134.7 (C), 138.5 (C), 139.1 (C), 159.7 (C), 207.4 (C); *m/z* (ESI) 291.1344 (MNa^+. $C_{18}H_{20}NaO_2$ requires 291.1356).

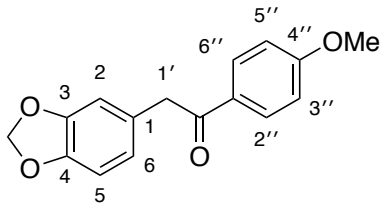
1′-(3,4-Dimethoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (184b)[534]



1′-(3,4-Dimethoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**184b**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(2″,4″,6″-trimethylphenyl)ethan-2′-one (**184a**) using 3,4-dimethoxyphenylacetic acid (**200**) (0.500 g, 2.55 mmol) and anisole (0.280 mL, 2.55 mmol). The crude residue was filtered through a short pad of silica eluting with ethyl acetate to give a brown solid. Purification by recrystallisation from hexane gave 1′-(3,4-dimethoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**184b**) (0.425 g, 58%) as a yellow solid. Spectroscopic data were consistent with the literature.[534] Mp 135–137 °C (from hexane); δ_H (400 MHz, $CDCl_3$) 3.84–3.86 (9H, m, 3 × OCH_3), 4.17 (2H, s, 1′-H_2), 6.78–6.82 (3H, m, 2-H, 5-H and 6-H), 6.93 (2H, d, *J* 9.0 Hz, 3″-H and 5″-H), 7.99 (2H, d, *J* 9.0 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 44.9 (CH_2), 55.5 (CH_3), 55.9 (CH_3), 55.9 (CH_3), 111.4 (CH), 112.6 (CH), 113.8 (2 × CH), 121.5 (CH), 127.5 (C), 129.7 (C), 130.9 (2

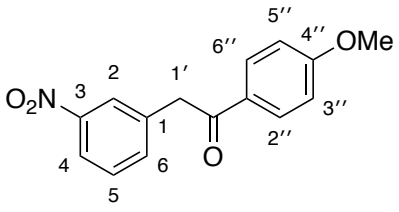
× CH), 148.0 (C), 149.1 (C), 163.5 (C), 196.4 (C); *m/z* (ESI) 309 (MNa^+. 100%).

1′-(3,4-Methylenedioxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (184c)[527]



1′-(3,4-Methylenedioxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**184c**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(2″,4″,6″-trimethylphenyl)ethan-2′-one (**184a**) using 3,4-methylenedioxyphenylacetic acid (**130a**) (0.500 g, 2.78 mmol) and anisole (0.360 mL, 3.34 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 1′-(3,4-methylenedioxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**184c**) (0.247 g, 33%) as a white solid. Mp 96–98 °C (lit.[527] 100–102 °C); δ_H (500 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 4.13 (2H, 1′-CH_2), 5.92 (2H, s, OCH_2O), 6.70 (1H, dd, *J* 8.0, 1.8 Hz, 6-H), 6.73–6.77 (2H, m, 2-H and 5-H), 6.92 (2H, d, *J* 9.0 Hz, 3″-H and 5″-H), 7.98 (2H, d, *J* 9.0 Hz, 2″-H and 6″-H); δ_C (126 MHz, $CDCl_3$) 44.8 (CH_2), 55.5 (CH_3), 101.0 (CH_2), 108.4 (CH), 109.8 (CH), 113.8 (2 × CH), 122.4 (CH), 128.5 (C), 129.6 (C), 130.9 (2 × CH), 146.5 (C), 147.8 (C), 163.5 (C), 196.2 (C); *m/z* (ESI) 293 (MNa^+. 100%).

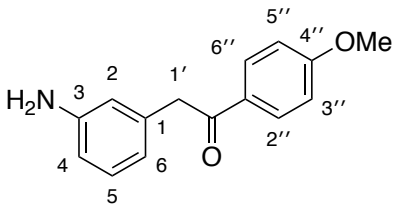
1′-(3-Nitrophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (184d)[535]



1′-(3-Nitrophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**184d**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(2″,4″,6″-trimethylphenyl)ethan-2′-one (**184a**) using 3-nitrophenylacetic acid (0.500 g, 2.76 mmol) and anisole (0.330 mL, 3.04 mmol). The reaction mixture was stirred at –5 °C for 0.5 h, warmed to room temperature and stirred for 3 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 1′-(3-nitrophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**184d**) (0.544 g, 73%) as a white solid. Spectroscopic

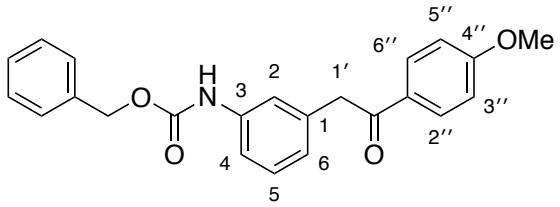
data were consistent with the literature.[535] Mp 66–68 °C; δ_H (400 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 4.36 (2H, s, 1′-H_2), 6.96 (2H, d, *J* 9.0 Hz, 3″-H and 5″-H), 7.50 (1H, td, *J* 7.6, 1.0 Hz, 5-H), 7.60 (1H, br d, *J* 7.6 Hz, 6-H), 8.00 (2H, d, *J* 9.0 Hz, 2″-H and 6″-H), 8.09–8.15 (2H, m, 2-H and 4-H); δ_C (101 MHz, $CDCl_3$) 44.3 (CH_2), 55.6 (CH_3), 114.0 (2 × CH), 122.0 (CH), 124.7 (CH), 129.2 (C), 129.3 (CH), 130.8 (2 × CH), 136.0 (CH), 136.8 (C), 148.3 (C), 164.0 (C), 194.6 (C); *m/z* (ESI) 294 (MNa^+. 100%).

1′-(3-Aminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (185)



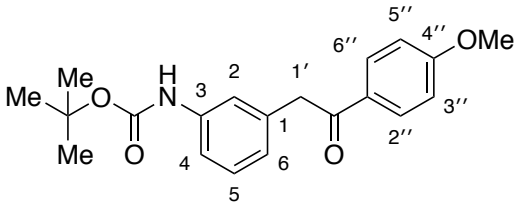
To a stirred solution of 1′-(3-nitrophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**184d**) (0.777 g, 2.86 mmol) in ethanol (40 mL) was added tin dichloride dihydrate (3.23 g, 14.2 mmol) and the resulting mixture was stirred under reflux for 16 h. After cooling to room temperature, sodium bicarbonate (40 mL) was added and the suspension was stirred for 0.1 h. The suspension was diluted with ethyl acetate (60 mL), filtered through Celite® and concentrated *in vacuo*. The crude residue was dissolved in ethyl acetate (50 mL) and washed with water (50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (dichloromethane/diethyl ether 19:1) gave 1′-(3-aminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**185**) (0.596 g, 86%) as a beige solid. Mp 112–114 °C; ν_{max}/cm^{-1} (neat) 3350 (NH), 2950 (CH), 1667 (C=O), 1601, 1258, 1217, 995, 837, 766; δ_H (500 MHz, $CDCl_3$) 3.62 (2H, br s, NH_2), 3.85 (3H, s, OCH_3), 4.12 (2H, s, 1′-H_2), 6.55 (1H, br dd, *J* 7.8, 2.0 Hz, 4-H), 6.59 (1H, br t, *J* 2.0 Hz, 2-H), 6.66 (1H, br d, *J* 7.8 Hz, 6-H), 6.91 (2H, d, *J* 8.9 Hz, 3″-H and 5″-H), 7.09 (1H, t, *J* 7.8 Hz, 5-H), 7.98 (2H, d, *J* 8.9 Hz, 2″-H and 6″-H); δ_C (126 MHz, $CDCl_3$) 45.4 (CH_2), 55.5 (CH_3), 113.7 (CH), 113.8 (2 × CH), 115.9 (CH), 119.6 (CH), 129.6 (CH), 129.7 (C), 131.0 (2 × CH), 136.2 (C), 146.7 (C), 163.5 (C), 196.4 (C); *m/z* (ESI) 264.0985 (MNa^+. $C_{15}H_{15}NNaO_2$ requires 264.0995).

1′-(3-Benzyloxycarbonylaminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (186a)



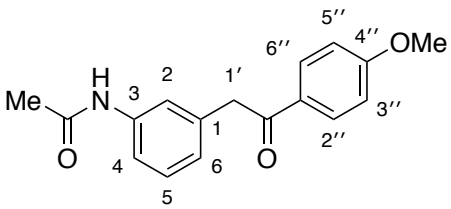
To a stirred solution of 1′-(3-aminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**185**) (0.0500 g, 0.210 mmol) in tetrahydrofuran (10 mL) was added sodium bicarbonate (0.0350 g, 0.420 mmol). The resulting suspension was cooled to 0 °C and benzyl chloroformate (0.0360 mL, 0.250 mmol) was slowly added. The reaction mixture was warmed to room temperature and stirred for 20 h. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 1′-(3-benzyloxycarbonylaminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**186a**) (0.0700 g, 90%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3323 (NH), 2936 (CH), 1730 (C=O), 1668 (C=O), 1595, 1493, 1443, 1258, 1211, 1167, 1061, 1028, 764, 696; δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 4.19 (2H, s, 1′-H_2), 5.17 (2H, s, CH_2O), 6.74 (1H, br s, NH), 6.91 (2H, d, *J* 9.0 Hz, 3″-H and 5″-H), 6.95 (1H, br d, *J* 7.6 Hz, 6-H), 7.23 (1H, t, *J* 7.6 Hz, 5-H), 7.26–7.41 (7H, m, 2-H, 4-H and Ph), 7.97 (2H, d, *J* 9.0 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 45.2 (CH_2), 55.5 (CH_3), 67.0 (CH_2), 113.8 (2 × CH), 117.2 (CH), 119.6 (CH), 124.5 (CH), 128.2 (2 × CH), 128.3 (CH), 128.6 (2 × CH), 129.3 (CH), 129.5 (C), 130.9 (2 × CH), 136.0 (C), 136.1 (C), 138.1 (C), 153.3 (C), 163.6 (C), 196.0 (C); *m/z* (ESI) 398.1353 (MNa^+. $C_{23}H_{21}NNaO_4$ requires 398.1363).

1′-(3-*N*-[*tert*-Butyloxycarbonyl]aminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (186b)



To a stirred solution of 1′-(3-aminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**185**) (0.0500 g, 0.210 mmol) in tetrahydrofuran (10 mL) was added sodium bicarbonate (0.0350 g, 0.420 mmol). The resulting suspension was cooled to 0 °C and di-*tert*-butyl dicarbonate (0.0570 mL, 0.250 mmol) was slowly added. The reaction mixture was warmed to room temperature then stirred under reflux for 96 h. After cooling to room temperature, the solvent was removed *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 1′-(3-*N*-[*tert*-butyloxycarbonyl]aminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**186b**) (0.0570 g, 81%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3333 (NH), 2976 (CH), 1724 (C=O), 1672 (C=O), 1599, 1539, 1315, 1260, 1236, 1159; δ_H (500 MHz, $CDCl_3$) 1.50 (9H, s, C(CH_3)$_3$), 3.86 (3H, s, OCH_3), 4.19 (2H, s, 1′-H_2), 6.48 (1H, br s, NH), 6.88–6.96 (3H, m, 6-H, 3″-H and 5″-H), 7.19–7.33 (3H, m, 2-H, 4-H and 5-H), 7.98 (2H, d, *J* 8.9 Hz, 2″-H and 6″-H); δ_C (126 MHz, $CDCl_3$) 28.3 (3 × CH_3), 45.2 (CH_2), 55.5 (CH_3), 80.5 (C), 113.8 (2 × CH), 117.0 (CH), 119.4 (CH), 124.0 (CH), 129.2 (CH), 129.6 (C), 131.0 (2 × CH), 135.9 (C), 138.7 (C), 152.7 (C), 163.5 (C), 196.1 (C); *m/z* (ESI) 364.1513 (MNa^+. $C_{20}H_{23}NNaO_4$ requires 364.1519).

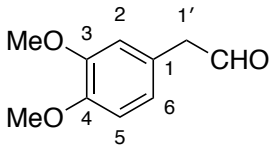
1′-(3-Acetamidophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (186c)



To a stirred solution of 1′-(3-aminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**185**) (0.150 g, 0.622 mmol) in dichloromethane (20 mL) was added acetic anhydride (0.0880 mL, 0.932 mmol) and the resulting solution was stirred at room temperature

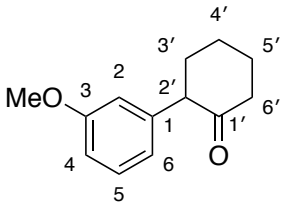
for 2 h. The reaction mixture was diluted with dichloromethane (20 mL) then washed with 1 M aqueous sodium carbonate (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification by flash column chromatography (ethyl acetate/ petroleum ether, 3:2) gave 1′-(3-acetamidophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**186c**) (0.142 g, 81%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3321 (NH), 2936, 1667 (C=O), 1597, 1553, 1317, 1260, 1171; δ_H (400 MHz, $CDCl_3$) 2.11 (3H, s, NHCOCH_3), 3.86 (3H, s, OCH_3), 4.21 (2H, s, 1′-H_2), 6.94 (2H, d, *J* 8.9 Hz, 3″-H and 5″-H), 6.99 (1H, br d, *J* 7.8 Hz, 4-H), 7.24 (1H, t, *J* 7.8 Hz, 5-H), 7.33–7.43 (3H, m, 2-H, 6-H and NH), 7.99 (2H, d, *J* 8.9 Hz, 2″-H and 6″-H); δ_C (126 MHz, $CDCl_3$) 24.6 (CH_3), 45.1 (CH_2), 55.5 (CH_3), 113.9 (2 × CH), 118.4 (CH), 120.8 (CH), 125.3 (CH), 129.2 (CH), 129.5 (C), 130.9 (2 × CH), 135.7 (C), 138.3 (C), 163.7 (C), 168.3 (C), 196.3 (C); *m/z* (ESI) 306.1093 (MNa^+. $C_{17}H_{17}NNaO_3$ requires 306.1101).

3,4-Dimethoxyphenylacetaldehyde (188)[536]



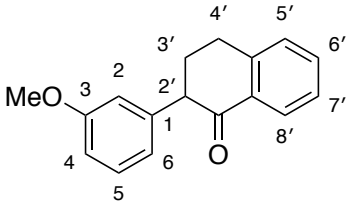
To a stirred solution of 1′-(3,4-dimethoxyphenyl)ethanol (**187**) (0.150 g, 0.823 mmol) in dry dichloromethane (10 mL) at 0 °C was slowly added Dess-Martin periodinane (0.419 g, 0.988 mmol). The reaction mixture was warmed to room temperature and stirred for 3 h. A saturated aqueous solution of sodium thiosulfate (5 mL) and a saturated aqueous solution of sodium bicarbonate (5 mL) were added and the mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with brine (60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave 3,4-dimethoxyphenylacetaldehyde (**188**) (0.0960 g, 65%) as a colourless oil. Spectroscopic data were consistent with the literature.[536] δ_H (400 MHz, $CDCl_3$) 3.62 (2H, d, *J* 2.4 Hz, 1′-H_2), 3.87 (6H, s, 2 × OCH_3), 6.71 (1H, d, *J* 2.0 Hz, 2-H), 6.76 (1H, dd, *J* 8.0, 2.0 Hz, 6-H), 6.86 (1H, d, *J* 8.0 Hz, 5-H), 9.72 (1H, t, *J* 2.4 Hz, CHO); δ_C (101 MHz, $CDCl_3$) 50.1 (CH_2), 55.9 (CH_3), 55.9 (CH_3), 111.6 (CH), 112.6 (CH), 121.9 (CH), 124.1 (C), 148.4 (C), 149.3 (C), 199.5 (CH); *m/z* (EI) 180 (M^+. 82%), 151 (100), 107 (48), 91 (24), 65 (28).

2′-(3-Methoxyphenyl)cyclohexanone (189a)[537]



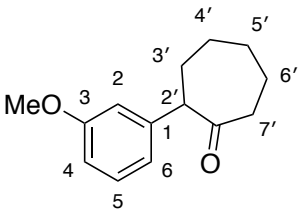
An oven-dried microwave vial was flushed with argon and charged with tris(dibenzylideneacetone)dipalladium (0.00920 g, 0.0100 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.0140 g, 0.0240 mmol), cesium carbonate (1.43 g, 4.40 mmol) and anhydrous 1,4-dioxane (4.0 mL). Cyclohexanone (0.415 mL, 4.00 mmol) and 3-iodoanisole (0.238 mL, 2.00 mmol) were added to this suspension under argon and the resulting reaction mixture was stirred at 80 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with diethyl ether (30 mL), washed with water (30 mL) and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 2′-(3-methoxyphenyl)cyclohexanone (**189a**) (0.188 g, 46%) as a colourless oil. Spectroscopic data were consistent with the literature.[537] δ_H (500 MHz, $CDCl_3$) 1.75–1.88 (2H, m, 5′-H_2), 1.95–2.17 (3H, m, 3'-*H*H and 4′-H_2), 2.23–2.31 (1H, m, 3′-H*H*), 2.40–2.53 (2H, m, 6′-H_2), 3.58 (1H, dd, *J* 12.1, 5.5 Hz, 2′-H), 3.79 (3H, s, OCH_3), 6.69 (1H, t, *J* 2.4 Hz, 2-H), 6.73 (1H, br d, *J* 7.9 Hz, 6-H), 6.80 (1H, dd, *J* 7.9, 2.4 Hz, 4-H), 7.24 (1H, t, *J* 7.9 Hz, 5-H); δ_C (126 MHz, $CDCl_3$) 25.2 (CH_2), 27.8 (CH_2), 34.9 (CH_2), 42.2 (CH_2), 55.1 (CH_3), 57.4 (CH), 112.1 (CH), 114.5 (CH), 120.9 (CH), 129.3 (CH), 140.3 (C), 159.6 (C), 210.2 (C); *m/z* (ESI) 227 (MNa^+. 100%).

2′-(3-Methoxyphenyl)-3′,4′-dihydronaphthalen-1′(2*H*)-one (189b)[538]



2′-(3-Methoxyphenyl)-3′,4′-dihydronaphthalen-1′(2*H*)-one (**189b**) was synthesised as described for 2′-(3-methoxyphenyl)cyclohexanone (**189a**) using 3-iodoanisole (0.238 mL, 2.00 mmol), α-tetralone (0.320 mL, 2.40 mmol), tris(dibenzylideneacetone)dipalladium (0.00920 g, 0.0100 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.0140 g, 0.0240 mmol), cesium carbonate (1.43 g, 4.40 mmol) in anhydrous 1,4-dioxane (3.0 mL). The reaction mixture was stirred at 100 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 19:1 to hexane/diethyl ether, 9:1) gave 2′-(3-methoxyphenyl)-3′,4′-dihydronaphthalen-1′(2*H*)-one (**189b**) (0.292 g, 58%) as a brown solid. Spectroscopic data were consistent with the literature.[538] Mp 70–72 °C; δ_H (500 MHz, $CDCl_3$) 2.40–2.49 (2H, m, 3′-H_2), 3.01–3.15 (2H, m, 4′-H_2), 3.76–3.80 (4H, m, 2′-H and OCH_3), 6.74 (1H, t, *J* 2.5 Hz, 2-H), 6.78 (1H, br d, *J* 7.5 Hz, 6-H), 6.81 (1H, dd, *J* 8.3, 2.5 Hz, 4-H), 7.24–7.30 (2H, m, 5-H and 5′-H), 7.34 (1H, t, *J* 7.6 Hz, 7′-H), 7.50 (1H, td, *J* 7.6, 1.2 Hz, 6′-H), 8.10 (1H, dd, *J* 7.6, 1.2 Hz, 8′-H); δ_C (126 MHz, $CDCl_3$) 28.7 (CH_2), 31.1 (CH_2), 54.4 (CH), 55.2 (CH_3), 112.2 (CH), 114.5 (CH), 120.8 (CH), 126.8 (CH), 127.8 (CH), 128.8 (CH), 129.5 (CH), 132.8 (C), 133.4 (CH), 141.2 (C), 144.0 (C), 159.7 (C), 198.0 (C); *m/z* (ESI) 275 (MNa^+. 100%).

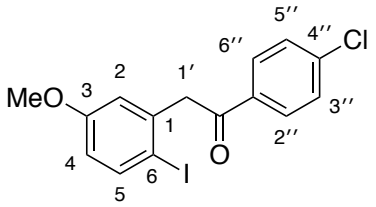
2′-(3-Methoxyphenyl)cycloheptanone (189c)



2′-(3-Methoxyphenyl)cycloheptanone (**189c**) was synthesised as described for 2′-(3-methoxyphenyl)cyclohexanone (**189a**) using 3-iodoanisole (0.238 mL, 2.00 mmol), cycloheptanone (0.473 mL, 4.00 mmol),

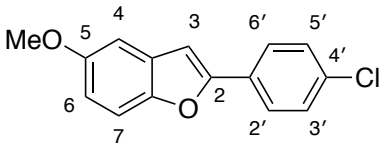
tris(dibenzylideneacetone)dipalladium (0.00920 g, 0.0100 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.0140 g, 0.0240 mmol), cesium carbonate (1.43 g, 4.40 mmol) in anhydrous 1,4-dioxane (4.0 mL). Purification by flash column chromatography (hexane/diethyl ether, 19:1 to hexane/diethyl ether, 9:1) gave 2′-(3-methoxyphenyl)cycloheptanone (**189c**) (0.218 g, 50%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2928 (CH), 1699 (C=O), 1597, 1584, 1452, 1260, 1146, 1045, 770, 694; δ_H (500 MHz, $CDCl_3$) 1.38–1.50 (2H, m, 5′-H_2), 1.57–1.67 (1H, m, 6′-*H*H), 1.86–2.17 (5H, m, 3′-H_2, 4′-H_2 and 6′-H*H*), 2.47–2.54 (1H, m, 7′-*H*H), 2.68 (1H, td, *J* 13.0, 3.2 Hz, 7′-H*H*), 3.67 (1H, dd, *J* 11.5, 4.2 Hz, 2′-H), 3.78 (3H, s, OCH_3), 6.76–6.79 (2H, m, 2-H and 4-H), 6.81 (1H, br d, *J* 7.7 Hz, 6-H), 7.22 (1H, dd, *J* 8.8, 7.7 Hz, 5-H); δ_C (126 MHz, $CDCl_3$) 25.4 (CH_2), 28.5 (CH_2), 30.0 (CH_2), 31.8 (CH_2), 42.7 (CH_2), 55.2 (CH_3), 58.8 (CH), 112.1 (CH), 113.9 (CH), 120.1 (CH), 129.4 (CH), 141.9 (C), 159.7 (C), 213.3 (C); *m/z* (ESI) 241.1190 (MNa^+. $C_{14}H_{18}NaO_2$ requires 241.1199).

1′-(3-Methoxy-6-iodophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (191)



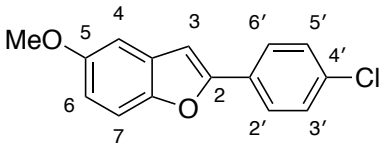
1′-(3-methoxy-6-iodophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**191**) was synthesised as described for 4-iodoanisole (**82a**) using 1′-(3-Methoxyphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**157b**) (0.300 g, 1.15 mmol) in toluene (1.5 mL). The reaction mixture was stirred at 40 °C for 3 h. Purification by flash column chromatography (hexane/diethyl ether, 9:1) gave 1′-(3-methoxy-6-iodophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**191**) (0.257 g, 58%) as a yellow oil. ν_{max}/cm^{-1} (neat) 2957 (CH), 1686 (C=O), 1587, 1568, 1466, 1398, 1296, 1277, 1250, 1238, 1209, 1090, 1009, 993, 812; δ_H (500 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 4.37 (2H, s, 1′-H_2), 6.59 (1H, dd, *J* 8.8, 3.0 Hz, 4-H), 6.80 (1H, d, *J* 3.0 Hz, 2-H), 7.46 (2H, d, *J* 8.6 Hz, 3″-H and 5″-H), 7.72 (1H, d *J* 8.8 Hz, 5-H), 7.98 (2H, d, *J* 8.6 Hz, 2″-H and 6″-H); δ_C (126 MHz, $CDCl_3$) 50.5 (CH_2), 55.4 (CH_3), 89.8 (C), 115.0 (CH), 116.9 (CH), 129.1 (2 × CH), 129.8 (2 × CH), 135.0 (C), 139.2 (C), 139.8 (C), 139.9 (CH), 160.0 (C), 195.2 (C); *m/z* (ESI) 408.9459 (MNa^+. $C_{15}H_{12}{}^{35}ClINaO_2$ requires 408.9463).

Method A: Synthesis of 2-(4′-chlorophenyl)-5-methoxybenzo[*b*]furan (190a) using iron(III) chloride (99.9%)



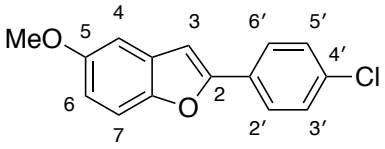
Iron(III) chloride (2.10 mg, 0.0130 mmol, 99.9% purity) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (11.0 µL, 0.0390 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-iodosuccinimide (0.0600 g, 0.260 mmol) in toluene (0.5 mL). 1′-(3-Methoxyphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**157b**) (0.0670 g, 0.260 mmol) in toluene (0.5 mL) was then added and the mixture was stirred at 40 °C for 3 h. Upon completion of the iodination step, the reaction mixture was cooled to room temperature, diluted with toluene (1.0 mL) and cesium carbonate (0.170 g, 0.520 mmol), *N*,*N*′-dimethylethylenediamine (3.00 µL, 0.0260 mmol) and water (0.5 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 16 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine (30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 2-(4′-chlorophenyl)-5-methoxybenzo[*b*]furan (**190a**) (0.0400 g, 60%) as a white solid. Mp 108–110 °C; ν_{max}/cm^{-1} (neat) 2965 (CH), 1613, 1599, 1471, 1271, 833, 800; δ_H (500 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 6.89 (1H, dd, *J* 8.9, 2.6 Hz, 6-H), 6.92 (1H, d, *J* 0.9 Hz, 3-H), 7.01 (1H, br d, *J* 2.6 Hz, 4-H), 7.35–7.42 (3H, m, 7-H, 3′-H and 5′-H), 7.74 (2H, d, *J* 8.5 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 55.9 (CH_3), 101.9 (CH), 103.3 (CH), 111.6 (CH), 113.3 (CH), 126.0 (2 × CH), 129.0 (2 × CH), 129.1 (C), 129.6 (C), 134.2 (C), 150.0 (C), 155.5 (C), 156.2 (C); *m/z* (EI) 258.0440 (M^+. $C_{15}H_{11}{}^{35}ClO_2$ requires 258.0448), 215 (12%), 152 (42).

Method B: Synthesis of 2-(4′-chlorophenyl)-5-methoxybenzo[*b*]furan (190a) using iron(III) nitrate nonahydrate (99.999%)



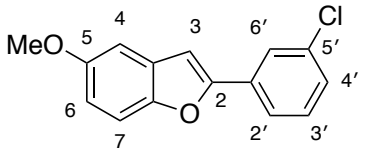
Iron(III) nitrate nonahydrate (2.40 mg, 0.0100 mmol, 99.999% purity) was suspended in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (8.70 µL, 0.0300 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-iodosuccinimide (0.0450 g, 0.200 mmol) in toluene (0.5 mL). 1′-(3-Methoxyphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**157b**) (0.0521 g, 0.200 mmol) in toluene (0.5 mL) was then added and the mixture was stirred at 40 °C for 5 h. Upon completion of the iodination step, the reaction mixture was cooled to room temperature, diluted with toluene (1.0 mL) and cesium carbonate (0.170 g, 0.520 mmol), *N*,*N*′-dimethylethylenediamine (3.00 µL, 0.0260 mmol) and water (0.5 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 22 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine (30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 2-(4′-chlorophenyl)-5-methoxybenzo[*b*]furan (**190a**) (0.0278 g, 54%) as a white solid. Characterisation data as previously reported for 2-(4′-chlorophenyl)-5-methoxybenzo[*b*]furan (**190a**).

Synthesis of 2-(4′-chlorophenyl)-5-methoxybenzo[*b*]furan (190a) from 1′-(3-methoxy-6-iodophenyl)-2′-(4″-chlorophenyl)ethan-2′-one (191) using copper(I) iodide (ppm loading)



To a solution of 1′-(3-methoxy-6-iodophenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**191**) (0.0771 g, 0.200 mmol) in toluene (1.0 mL) was added cesium carbonate (0.130 g, 0.400 mmol), *N*,*N*′-dimethylethylenediamine (2.15 µL, 0.0200 mmol) and water (0.4 mL). Copper(I) iodide (0.0038 mg, 0.001 mol%, 14 ppm) in acetonitrile (10 µL) was added (stock solution prepared by dissolving 3.80 mg of copper(I) iodide in 10 mL of acetonitrile). The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 24 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine (30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 19:1) gave 2-(4′-chlorophenyl)-5-methoxybenzo[*b*]furan (**190a**) (0.0289 g, 56%) as a white solid. Characterisation data as previously reported for 2-(4′-chlorophenyl)-5-methoxybenzo[*b*]furan (**190a**).

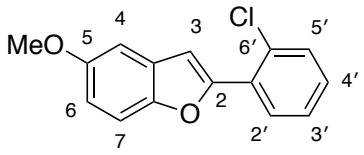
2-(3′-Chlorophenyl)-5-methoxybenzo[*b*]furan (190b)



2-(3′-Chlorophenyl)-5-methoxybenzo[*b*]furan (**190b**) was synthesised according to method A using 1′-(3-methoxyphenyl)-2′-(3″-chlorophenyl)ethan-2′-one (**181a**) (0.0500 g, 0.190 mmol). The iodination step was carried out at 40 °C for 3 h and the *O*-arylation at 130 °C for 36 h. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 2-(3′-chlorophenyl)-5-methoxybenzo[*b*]furan

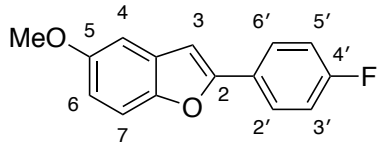
(**190b**) (0.0310 g, 62%) as a white solid. Mp 80–82 °C; ν_{max}/cm^{-1} (neat) 2932 (CH), 1599, 1470, 1215, 1205, 1148, 1034, 837, 802, 785, 737; δ_H (400 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 6.91 (1H, dd, *J* 8.8, 2.6 Hz, 6-H), 6.98 (1H, d, *J* 0.7 Hz, 3-H), 7.04 (1H, br d, *J* 2.6 Hz, 4-H), 7.31 (1H, ddd, *J* 8.0, 1.9, 1.3 Hz, 4′-H), 7.36 (1H, dd, *J* 8.0, 7.7 Hz, 5′-H), 7.41 (1H, d, *J* 8.8 Hz, 7-H), 7.70 (1H, dt, *J* 7.7, 1.3 Hz, 6′-H), 7.83 (1H, br t, *J* 1.9 Hz, 2′-H); δ_C (101 MHz, $CDCl_3$) 55.9 (CH_3), 102.5 (CH), 103.4 (CH), 111.7 (CH), 113.6 (CH), 122.9 (CH), 124.8 (CH), 128.4 (CH), 129.5 (C), 130.0 (CH), 132.2 (C), 134.8 (C), 150.0 (C), 155.1 (C), 156.2 (C); *m/z* (EI) 258.0450 (M^+. $C_{15}H_{11}{}^{35}ClO_2$ requires 258.0448), 215 (12%), 152 (28).

2-(2′-Chlorophenyl)-5-methoxybenzo[*b*]furan (190c)



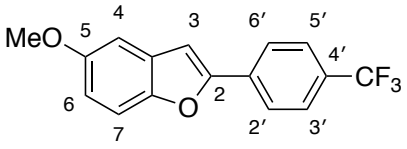
2-(2′-Chlorophenyl)-5-methoxybenzo[*b*]furan (**190c**) was synthesised according to method A using 1′-(3-methoxyphenyl)-2′-(2″-chlorophenyl)ethan-2′-one (**181b**) (0.0523 g, 0.200 mmol). The iodination step was carried out at 40 °C for 3 h and the *O*-arylation at 130 °C for 24 h. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 2-(2′-chlorophenyl)-5-methoxybenzo[*b*]furan (**190c**) (0.0311 g, 60%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2934 (CH), 1614, 1466, 1213, 1207, 1184, 1148, 1030, 1018, 835, 799, 752, 733; δ_H (500 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 6.93 (1H, dd, *J* 8.9, 2.6 Hz, 6-H), 7.08 (1H, br d, *J* 2.6 Hz, 4-H), 7.26 (1H, td, *J* 7.8, 1.6 Hz, 4′-H), 7.36 (1H, td, *J* 7.8, 1.2 Hz, 5′-H), 7.40 (1H, d, *J* 8.9 Hz, 7-H), 7.46 (1H, d, *J* 0.6 Hz, 3-H), 7.48 (1H, dd, *J* 7.8, 1.2 Hz, 3′-H), 8.02 (1H, dd, *J* 7.8, 1.6 Hz, 6′-H); δ_C (126 MHz, $CDCl_3$) 55.9 (CH_3), 103.6 (CH), 107.6 (CH), 111.6 (CH), 113.9 (CH), 127.0 (CH), 128.9 (CH), 129.0 (CH), 129.0 (C), 129.6 (C), 130.9 (CH), 131.2 (C), 149.2 (C), 152.7 (C), 156.1 (C); *m/z* (ESI) 281.0333 (MNa^+. $C_{15}H_{11}{}^{35}ClNaO_2$ requires 281.0340).

2-(4′-Fluorophenyl)-5-methoxybenzo[*b*]furan (190d)[539]



2-(4′-Fluorophenyl)-5-methoxybenzo[*b*]furan (**190d**) was synthesised according to method A using 1′-(3-methoxyphenyl)-2′-(4″-fluorophenyl)ethan-2′-one (**181c**) (0.0610 g, 0.250 mmol). The iodination step was carried out at 40 °C for 3 h and the *O*-arylation at 130 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 9:1) gave 2-(4′-fluorophenyl)-5-methoxybenzo[*b*]furan (**190d**) (0.0440 g, 72%) as a white solid. Spectroscopic data were consistent with the literature.[539] Mp 98–100 °C; δ_H (500 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.85 (1H, d, *J* 0.7 Hz, 3-H), 6.87 (1H, dd, *J* 8.9, 2.6 Hz, 6-H), 7.00 (1H, br d, *J* 2.6 Hz, 4-H), 7.10 (2H, t, *J* 8.8 Hz, 3′-H and 5′-H), 7.37 (1H, d, *J* 8.9 Hz, 7-H), 7.78 (2H, dd, *J* 8.8, 5.4 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 55.9 (CH_3), 101.2 (CH), 103.3 (CH), 111.6 (CH), 113.0 (CH), 115.8 (2 × CH, d, $^2J_{CF}$ 22.0 Hz), 126.7 (2 × CH, d, $^3J_{CF}$ 8.1 Hz), 126.9 (C, d, $^4J_{CF}$ 3.2 Hz), 129.8 (C), 149.9 (C), 155.8 (C), 156.1 (C), 162.9 (C, d, $^1J_{CF}$ 248.0 Hz); *m/z* (EI) 242 (M^+. 100%), 198 (15), 172 (15), 170 (15).

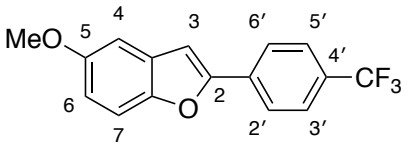
2-(4′-Trifluoromethylphenyl)-5-methoxybenzo[*b*]furan (190e)



2-(4′-Trifluoromethylphenyl)-5-methoxybenzo[*b*]furan (**190e**) was synthesised according to method A using 1′-(3-methoxyphenyl)-2′-(4″-trifluoromethylphenyl)ethan-2′-one (**181d**) (0.0500 g, 0.170 mmol). The iodination step was carried out at 40 °C for 3 h and the *O*-arylation step at 130 °C for 36 h. Purification by flash column chromatography (hexane/diethyl ether, 9:1) gave 2-(4′-trifluoromethylphenyl)-5-methoxybenzo[*b*]furan (**190e**) (0.0364 g, 73%) as a white solid. Mp 126–128 °C; ν_{max}/cm^{-1} (neat) 2938 (CH), 1618, 1477, 1333, 1171, 1134, 1117, 1109, 1072, 1026, 1012, 839, 804; δ_H (400 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 6.93 (1H, dd, *J* 9.0, 2.7 Hz, 6-H), 7.03–7.06 (2H, m, 3-H and 4-H), 7.42 (1H, d, *J* 9.0 Hz, 7-H), 7.67 (2H, d, *J* 8.2 Hz, 3′-H and 5′-H), 7.91 (2H, d, *J* 8.2 Hz, 2′-H and 6′-H);

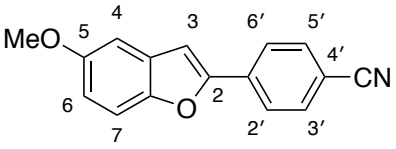
δ_C (101 MHz, $CDCl_3$) 55.9 (CH_3), 103.4 (CH), 103.4 (CH), 111.9 (CH), 114.1 (CH), 124.1 (C, q, $^1J_{CF}$ 272.0 Hz), 124.9 (2 × CH), 125.8 (2 × CH, q, $^3J_{CF}$ 3.9 Hz), 129.4 (C), 130.0 (C, q, $^2J_{CF}$ 32.5 Hz), 133.8 (C), 150.2 (C), 154.9 (C), 156.3 (C); *m/z* (EI) 292.0708 (M^+. $C_{16}H_{11}F_3O_2$ requires 292.0711), 248 (18%), 201 (17), 154 (20).

2-(4′-Trifluoromethylphenyl)-5-methoxybenzo[*b*]furan (190e)



2-(4′-Trifluoromethylphenyl)-5-methoxybenzo[*b*]furan (**190e**) was synthesised according to method B using 1′-(3-methoxyphenyl)-2′-(4″-trifluoromethylphenyl)ethan-2′-one (**181d**) (0.0588 g, 0.200 mmol). The iodination step was carried out at 70 °C for 24 h and the *O*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (petroleum ether/diethyl ether, 9:1) gave 2-(4′-trifluoromethylphenyl)-5-methoxybenzo[*b*]furan (**190e**) (0.0319 g, 55%) as a white solid. Characterisation data as previously reported for 2-(4′-trifluoromethylphenyl)-5-methoxybenzo[*b*]furan (**190e**).

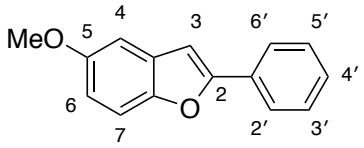
2-(4′-Cyanophenyl)-5-methoxybenzo[*b*]furan (190f)



2-(4′-Cyanophenyl)-5-methoxybenzo[*b*]furan (**190f**) was synthesised according to method A using 1′-(3-methoxyphenyl)-2′-(4″-cyanophenyl)ethan-2′-one (**181e**) (0.0520 g, 0.210 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 36 h. Purification by flash column chromatography (petroleum ether/dichloromethane, 1:1) gave 2-(4′-cyanophenyl)-5-methoxybenzo[*b*]furan (**190f**) (0.0370 g, 72%) as a white solid. Mp 144–146 °C; ν_{max}/cm^{-1} (neat) 2945 (CH), 2220 (CN), 1608, 1472, 1227, 1196, 1144, 1030, 914, 799, 748; δ_H (400 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 6.95 (1H, dd, *J* 8.9, 2.5 Hz, 6-H), 7.05 (1H, d, *J* 2.5 Hz, 4-H), 7.09 (1H, s, 3-H), 7.42 (1H, d, *J* 8.9 Hz, 7-H), 7.69 (2H, d, *J* 8.4 Hz, 3′-H and 5′-H), 7.89 (2H, d, *J* 8.4 Hz, 2′-H and 6′-H); δ_C (101 MHz,

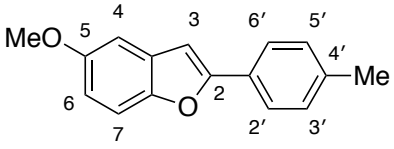
$CDCl_3$) 55.9 (CH_3), 103.5 (CH), 104.5 (CH), 111.4 (C), 111.9 (CH), 114.7 (CH), 118.8 (C), 125.0 (2 × CH), 129.2 (C), 132.6 (2 × CH), 134.5 (C), 150.3 (C), 154.3 (C), 156.4 (C); *m/z* (ESI) 272.0673 (MNa^+. $C_{16}H_{11}NNaO_2$ requires 272.0682).

2-Phenyl-5-methoxybenzo[*b*]furan (190g)[540]



2-Phenyl-5-methoxybenzo[*b*]furan (**190g**) was synthesised according to method A using 1′-(3-methoxyphenyl)-2′-phenylethan-2′-one (**157c**) (0.0480 g, 0.212 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 2-phenyl-5-methoxybenzo[*b*]furan (**190g**) (0.0310 g, 65%) as a white solid. Mp 125–127 °C (lit.[540] 128–130 °C); δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 6.88 (1H, dd, *J* 8.9, 2.6 Hz, 6-H), 6.96 (1H, d, *J* 0.7 Hz, 3-H), 7.04 (1H, br d, *J* 2.6 Hz, 4-H), 7.34 (1H, tt, *J* 7.4, 1.2 Hz, 4′-H), 7.38–7.48 (3H, m, 7-H, 3′-H and 5′-H), 7.81–7.87 (2H, m, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 55.9 (CH_3), 101.5 (CH), 103.3 (CH), 111.6 (CH), 113.0 (CH), 124.8 (2 × CH), 128.5 (CH), 128.8 (2 × CH), 129.8 (C), 130.5 (C), 149.9 (C), 156.1 (C), 156.7 (C); *m/z* (EI) 224 (M^+. 100%), 181 (18), 153 (16), 152 (20).

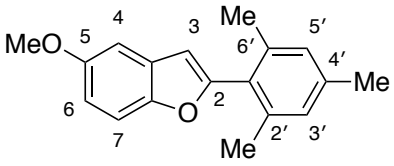
2-(4′-Methylphenyl)-5-methoxybenzo[*b*]furan (190h)[349]



2-(4′-Methylphenyl)-5-methoxybenzo[*b*]furan (**190h**) was synthesised according to method A using 1′-(3-methoxyphenyl)-2′-(4″-methylphenyl)ethan-2′-one (**180a**) (0.0550 g, 0.229 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 2-(4′-methylphenyl)-5-methoxybenzo[*b*]furan (**190h**) (0.0370 g, 68%) as a white solid. Mp 119–121 °C (lit.[349] 123–124 °C); δ_H (500 MHz, $CDCl_3$) 2.38 (3H, s, 4′-CH_3), 3.83 (3H, s, OCH_3), 6.86 (1H, dd, *J* 8.9, 2.6

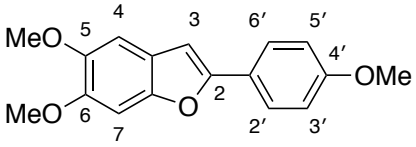
Hz, 6-H), 6.88 (1H, d, *J* 0.6 Hz, 3-H), 7.01 (1H, br d, *J* 2.6 Hz, 4-H), 7.23 (2H, d, *J* 8.1 Hz, 3′-H and 5′-H), 7.38 (1H, d, *J* 8.9 Hz, 7-H), 7.71 (2H, d, *J* 8.1 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 21.4 (CH_3), 55.9 (CH_3), 100.8 (CH), 103.3 (CH), 111.5 (CH), 112.7 (CH), 124.8 (2 × CH), 127.8 (C), 129.5 (2 × CH), 129.9 (C), 138.6 (C), 149.8 (C), 156.1 (C), 157.0 (C); *m/z* (ESI) 261 (MNa^+. 100%).

2-(2′,4′,6′-Trimethylphenyl)-5-methoxybenzo[*b*]furan (190i)[349]



2-(2′,4′,6′-Trimethylphenyl)-5-methoxybenzo[*b*]furan (**190i**) was synthesised according to method A using 1′-(3-methoxyphenyl)-2′-(2″,4″,6″-trimethylphenyl)ethan-2′-one (**184a**) (0.0670 g, 0.250 mmol). The iodination step was carried out at 40 °C for 3 h and the *O*-arylation step at 130 °C for 48 h. Purification by flash column chromatography (petroleum ether/diethyl ether, 19:1) gave 2-(2′,4′,6′-trimethylphenyl)-5-methoxybenzo[*b*]furan (**190i**) (0.0513 g, 75%) as a colourless oil. Spectroscopic data were consistent with the literature.[349] δ_H (400 MHz, $CDCl_3$) 2.22 (6H, s, 2′-CH_3 and 6′-CH_3), 2.33 (3H, s, 4′-CH_3), 3.86 (3H, s, OCH_3), 6.57 (1H, d, *J* 0.7 Hz, 3-H), 6.88 (1H, dd, *J* 8.8, 2.5 Hz, 6-H), 6.95 (2H, s, 3′-H and 5′-H), 7.07 (1H, br d, *J* 2.5 Hz, 4-H), 7.38 (1H, d, *J* 8.8 Hz, 7-H); δ_C (101 MHz, $CDCl_3$) 20.5 (2 × CH_3), 21.2 (CH_3), 56.0 (CH_3), 103.2 (CH), 106.2 (CH), 111.6 (CH), 112.3 (CH), 127.8 (C), 128.3 (2 × CH), 129.4 (C), 138.3 (2 × C), 139.0 (C), 149.7 (C), 155.9 (C), 155.9 (C); *m/z* (ESI) 289 (MNa^+. 100%).

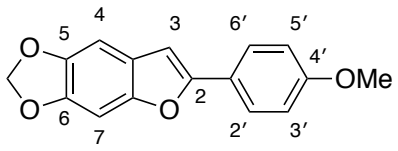
2-(4′-Methoxyphenyl)-5,6-dimethoxybenzo[*b*]furan (190j)



2-(4′-Methoxyphenyl)-5,6-dimethoxybenzo[*b*]furan (**190j**) was synthesised according to method A except 1′-(3,4-dimethoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**184b**) (0.0810 g, 0.280 mmol) was added to the

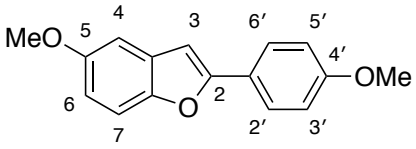
reaction mixture as a solution in toluene (1.0 mL) and acetonitrile (0.1 mL). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (dichloromethane) gave 2-(4′-methoxyphenyl)-5,6-dimethoxybenzo[*b*]furan (**190j**) (0.0492 g, 62%) as a white solid. Mp 142–144 °C; ν_{max}/cm^{-1} (neat) 2940 (CH), 1612, 1481, 1466, 1319, 1250, 1204, 1126, 1026, 1003, 918, 833, 795, 733; δ_H (500 MHz, $CDCl_3$) 3.84 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 6.78 (1H, s, 3-H), 6.95 (2H, d, *J* 8.9 Hz, 3′-H and 5′-H), 6.99 (1H, s, 7-H), 7.08 (1H, s, 4-H), 7.72 (2H, d, *J* 8.9 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 55.3 (CH_3), 56.3 (CH_3), 56.4 (CH_3), 95.3 (CH), 99.8 (CH), 102.1 (CH), 114.2 (2 × CH), 121.4 (C), 123.7 (C), 125.8 (2 × CH), 146.6 (C), 147.6 (C), 149.4 (C), 155.3 (C), 159.5 (C); *m/z* (ESI) 307.0946 (MNa^+. $C_{17}H_{16}NaO_4$ requires 307.0941).

2-(4′-Methoxyphenyl)-5,6-(methylenedioxy)benzo[*b*]furan (190k)



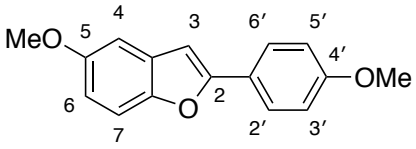
2-(4′-Methoxyphenyl)-5,6-(methylenedioxy)benzo[*b*]furan (**190k**) was synthesised according to method A except 1′-(3,4-methylenedioxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**184c**) (0.0670 g, 0.250 mmol) was added to the reaction mixture as a solution of toluene (1.0 mL) and acetonitrile (0.1 mL). The iodination step was carried out at 40 °C for 3 h and the *O*-arylation step at 130 °C for 36 h. Purification by recrystallisation from chloroform:methanol, 1:1, gave 2-(4′-methoxyphenyl)-5,6-(methylenedioxy)benzo[*b*]furan (**190k**) (0.0450 g, 68%) as a white crystalline solid. Mp 156–158 °C (from chloroform and methanol); ν_{max}/cm^{-1} (neat) 2901 (CH), 1460, 1323, 1250, 1175, 1144, 1038, 1022, 943, 829, 799; δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 5.98 (2H, s, OCH_2O), 6.77 (1H, s, 3-H), 6.92 (1H, s, 7-H), 6.95 (2H, d, *J* 8.9 Hz, 3′-H and 5′-H), 7.00 (1H, s, 4-H), 7.70 (2H, d, *J* 8.9 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 55.4 (CH_3), 93.5 (CH), 99.1 (CH), 100.2 (CH), 101.2 (CH_2), 114.2 (2 × CH), 122.7 (C), 123.6 (C), 125.8 (2 × CH), 144.5 (C), 145.7 (C), 149.9 (C), 155.7 (C), 159.6 (C); *m/z* (EI) 268.0733 (M^+. $C_{16}H_{12}O_4$ requires 268.0736), 253 (59%), 226 (8), 139 (8),133 (10).

2-(4′-Methoxyphenyl)-5-methoxybenzo[*b*]furan (176)[541]



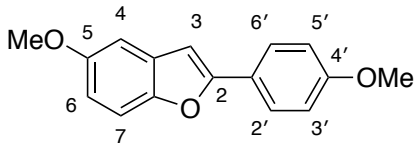
2-(4′-Methoxyphenyl)-5-methoxybenzo[*b*]furan (**176**) was synthesised according to method A using 1′-(3-methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**157a**) (0.0640 g, 0.250 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 36 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 2-(4′-methoxyphenyl)-5-methoxybenzo[*b*]furan (**176**) (0.0470 g, 74%) as a yellow solid. Mp 159–162 °C (lit.[541] 163–165 °C); δ_H (400 MHz, $CDCl_3$) 3.84 (6H, s, OCH_3), 6.81 (1H, s, 3-H), 6.84 (1H, dd, *J* 8.9, 2.5 Hz, 6-H), 6.96 (2H, d, *J* 8.5 Hz, 3′-H and 5′-H), 7.01 (1H, d, *J* 2.5 Hz, 4-H), 7.37 (1H, d, *J* 8.9 Hz, 7-H), 7.76 (2H, d, *J* 8.5 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 55.4 (CH_3), 55.9 (CH_3), 99.9 (CH), 103.2 (CH), 111.4 (CH), 112.3 (CH), 114.2 (2 × CH), 123.4 (C), 126.3 (2 × CH), 130.1 (C), 149.7 (C), 156.0 (C), 156.9 (C), 160.0 (C); *m/z* (EI) 254 (M^+. 100%), 239 (55), 211 (16), 148 (11).

2-(4′-Methoxyphenyl)-5-methoxybenzo[*b*]furan (176)[541]



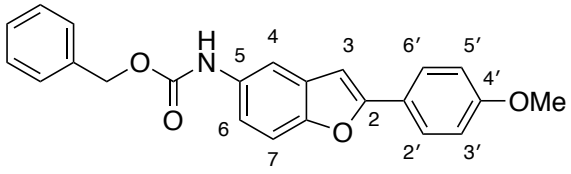
2-(4′-Methoxyphenyl)-5-methoxybenzo[*b*]furan (**176**) was synthesised according to method B using 1′-(3-methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**157a**) (0.0513 g, 0.200 mmol).The iodination step was carried out at 70 °C for 24 h and the *O*-arylation step at 130 °C for 36 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 2-(4′-methoxyphenyl)-5-methoxybenzo[*b*]furan (**176**) (0.0208 g, 41%) as a yellow solid. Characterisation data as previously reported for 2-(4′-methoxyphenyl)-5-methoxybenzo[*b*]furan (**176**).

Gram-Scale Synthesis of 2-(4′-Methoxyphenyl)-5-methoxybenzo[*b*]furan (176)[541]



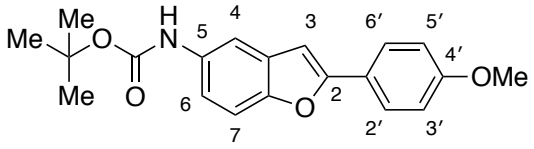
Iron(III) chloride (0.0319 g, 0.197 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (0.172 mL, 0.591 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-iodosuccinimide (0.886 g, 3.94 mmol) in toluene (5.0 mL). 1′-(3-Methoxyphenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**157a**) (1.01 g, 3.94 mmol) was added and the reaction mixture was stirred at 40 °C for 4 h. Upon completion of the iodination step, the reaction mixture was cooled to room temperature and copper(I) iodide (0.0750 g, 0.394 mmol), *N*,*N*′-dimethylethylenediamine (0.0850 mL, 0.788 mmol), cesium carbonate (2.57 g, 7.88 mmol) and water (3.0 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 36 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with 1 M aqueous sodium thiosulfate solution (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with brine (60 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1 to petroleum ether/ethyl acetate, 4:1) gave 2-(4′-methoxyphenyl)-5-methoxybenzo[*b*]furan (**176**) (0.844 g, 84%) as a yellow solid. Characterisation data as previously reported for 2-(4′-methoxyphenyl)-5-methoxybenzo[*b*]furan (**176**).

Method C: Synthesis of 2-(4′-Methoxyphenyl)-5-*N*-(benzyloxycarbonyl)aminobenzo[*b*]furan (192a) using Iron(III) Chloride (97%) and Copper(I) Iodide (10 mol%)



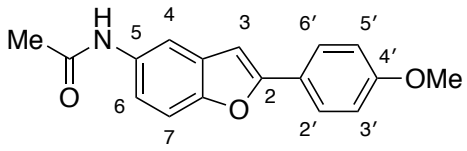
Iron(III) chloride (1.71 mg, 0.211 mmol, 97% purity) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (9.20 μL, 0.0320 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-iodosuccinimide (0.0474 g, 0.211 mmol) in toluene (0.5 mL). 1′-(3-Benzyloxycarbonylaminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**186a**) (0.0791 g, 0.211 mmol) in toluene (0.5 mL) was then added and the mixture was stirred at 40 °C for 5 h. Upon completion of the iodination step, the reaction mixture was cooled to room temperature, diluted with toluene (1.0 mL) and cesium carbonate (0.138 g, 0.422 mmol), copper(I) iodide (4.02 mg, 0.0211 mmol), *N*,*N*′-dimethylethylenediamine (4.50 μL, 0.0422 mmol) and water (0.6 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 22 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine (30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 2-(4′-methoxyphenyl)-5-*N*-(benzyloxycarbonyl)aminobenzo[*b*]furan (**192a**) (0.0379 g, 48%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3401 (NH), 3319, 2930 (CH), 1732 (C=O), 1705, 1612, 1539, 1506, 1256, 1229, 1204, 1042, 835, 797, 739; δ_H (400 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 5.22 (2H, s, CH_2O), 6.70 (1H, br s, 4-H), 6.82 (1H, d, *J* 0.7 Hz, 3-H), 6.97 (2H, d, *J* 8.9 Hz, 3′-H and 5′-H), 7.11 (1H, dd, *J* 8.7, 2.2 Hz, 6-H), 7.31–7.46 (6H, m, 7-H and Ph), 7.69 (1H, br s, NH), 7.77 (2H, d, *J* 8.9 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 55.4 (CH_3), 67.0 (CH_2), 99.8 (CH), 111.0 (2 × CH), 114.3 (2 × CH), 116.0 (CH), 123.2 (C), 126.5 (2 × CH), 128.3 (3 × CH), 128.6 (2 × CH), 128.9 (CH), 130.0 (C), 133.0 (C), 136.2 (C), 151.5 (C), 153.8 (C), 157.1 (C), 160.1 (C); *m/z* (ESI) 396.1199 (MNa^+. $C_{23}H_{19}NNaO_4$ requires 396.1206).

2-(4′-Methoxyphenyl)-5-*N*-(*tert*-butyloxycarbonyl)aminobenzo[*b*]furan (192b)



2-(4′-Methoxyphenyl)-5-*N*-(*tert*-butyloxycarbonyl)aminobenzo[*b*]furan (**192b**) was synthesised according to method C using 1′-(3-*N*-(*tert*-butyloxycarbonyl)aminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**186b**) (0.0518 g, 0.150 mmol) in toluene (1.6 mL) and acetonitrile (0.4 mL). The iodination step was carried out at 40 °C for 5 h and the *O*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (petroleum ether/dichloromethane, 1:1) gave 2-(4′-methoxyphenyl)-5-*N*-(*tert*-butyloxycarbonyl)aminobenzo[*b*]furan (**192b**) (0.0335 g, 65%) as a white solid. Mp 104–106 °C; ν_{max}/cm^{-1} (neat) 3416 (NH), 2976 (CH), 1721 (C=O), 1526, 1504, 1342, 1252, 1161, 1040, 841, 818, 793; δ_H (500 MHz, $CDCl_3$) 1.53 (9H, s, C(CH_3)$_3$), 3.84 (3H, s, OCH_3), 6.53 (1H, br s, 4-H), 6.79 (1H, s, 3-H), 6.95 (2H, d, *J* 8.8 Hz, 3′-H and 5′-H), 7.08 (1H, dd, *J* 8.7, 2.0 Hz, 6-H), 7.37 (1H, d, *J* 8.7 Hz, 7-H), 7.67 (1H, br s, NH), 7.76 (2H, d, *J* 8.8 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 28.4 (3 × CH_3), 55.4 (CH_3), 80.3 (C), 99.8 (CH), 110.8 (CH), 110.9 (CH), 114.2 (2 × CH), 116.0 (CH), 123.3 (C), 126.4 (2 × CH), 130.0 (C), 133.6 (C), 151.2 (C), 153.3 (C), 156.9 (C), 160.0 (C); *m/z* (ESI) 362.1357 (MNa^+. $C_{20}H_{21}NNaO_4$ requires 362.1363).

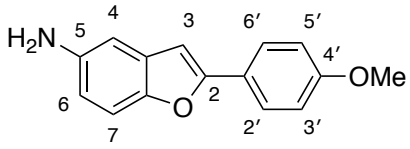
2-(4′-Methoxyphenyl)-5-acetamidobenzo[*b*]furan (192c)



2-(4′-Methoxyphenyl)-5-acetamidobenzo[*b*]furan (**192c**) was synthesised according to method C using 1′-(3-acetamidophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**186c**) (0.0680 g, 0.240 mmol) in toluene (2.0 mL) and acetonitrile (0.2 mL). The iodination step was carried out at 40 °C at 5 h and the *O*-arylation step at 130 °C for 36 h. Purification by flash column chromatography (dichloromethane/diethyl ether, 9:1), followed by recrystallisation from hot ethanol gave 2-(4′-methoxyphenyl)-5-acetamidobenzo[*b*]furan (**192c**) (0.0306 g, 45%) as a white crystalline solid. Mp

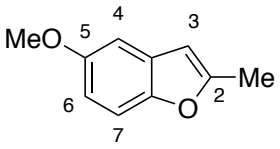
138–140 °C (from ethanol); ν_{max}/cm^{-1} (neat) 1641 (C=O), 1612, 1477, 1254, 1042, 829, 795; δ_H (500 MHz, DMSO-d$_6$) 2.06 (3H, s, NHCOC*H*$_3$), 3.82 (3H, s, OCH$_3$), 7.07 (2H, d, *J* 8.8 Hz, 3′-H and 5′-H), 7.25 (1H, s, 3-H), 7.34 (1H, dt, *J* 8.8, 2.1 Hz, 6-H), 7.50 (1H, d, *J* 8.8 Hz, 7-H), 7.83 (2H, d, *J* 8.8 Hz, 2′-H and 6′-H), 7.97 (1H, t, *J* 2.1 Hz, 4-H), 9.94 (1H, br s, NH); δ_C (126 MHz, DMSO-d$_6$) 24.4 (CH$_3$), 55.8 (CH$_3$), 100.9 (CH), 111.2 (CH), 115.0 (2 × CH), 116.6 (CH), 116.8 (CH), 122.9 (C), 126.7 (2 × CH), 129.6 (C), 135.5 (C), 150.7 (C), 156.4 (C), 160.3 (C), 168.5 (C); *m/z* (ESI) 304.0936 (MNa$^+$. $C_{17}H_{15}NNaO_3$ requires 304.0944).

2-(4′-Methoxyphenyl)-5-aminobenzo[*b*]furan (192d)



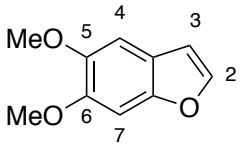
2-(4′-Methoxyphenyl)-5-aminobenzo[*b*]furan (**192d**) was synthesised according to method C using 1′-(3-aminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**185**) (0.0750 g, 0.310 mmol) in toluene (2.0 mL) and acetonitrile (0.2 mL). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (dichloromethane) gave 2-(4′-methoxyphenyl)-5-aminobenzo[*b*]furan (**192d**) (0.0210 g, 28%) as an orange oil. ν_{max}/cm^{-1} (neat) 3350 (NH), 1611, 1506, 1477, 1454, 1252, 1177, 1040, 1022, 916, 833, 797; δ_H (400 MHz, CDCl$_3$) 3.58 (2H, br s, NH$_2$), 3.85 (3H, s, OCH$_3$), 6.63 (1H, dd, *J* 8.6, 2.4 Hz, 6-H), 6.73 (1H, br s, 3-H), 6.83 (1H, d, *J* 2.4 Hz, 4-H), 6.96 (2H, d, *J* 9.0 Hz, 3′-H and 5′-H), 7.27 (1H, d, *J* 8.6 Hz, 7-H), 7.75 (2H, d, *J* 9.0 Hz, 2′-H and 6′-H); δ_C (101 MHz, CDCl$_3$) 55.4 (CH$_3$), 99.4 (CH), 105.6 (CH), 111.2 (CH), 113.0 (CH), 114.2 (2 × CH), 123.6 (C), 126.3 (2 × CH), 130.3 (C), 142.1 (C), 149.4 (C), 156.5 (C), 159.9 (C); *m/z* (ESI) 240.1012 (MH$^+$. $C_{15}H_{14}NO_2$ requires 240.1019).

2-Methyl-5-methoxybenzo[b]furan (192e)[344]



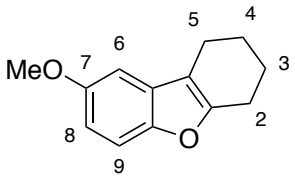
2-Methyl-5-methoxybenzo[b]furan (**192e**) was synthesised according to method C using 1′-(3-methoxyphenyl)propan-2′-one (**180c**) (0.0792 g, 0.480 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 2-methyl-5-methoxybenzo[*b*]furan (**192e**) (0.0423 g, 54%) as a colourless oil. Spectroscopic data were consistent with the literature.[344] δ_H (400 MHz, $CDCl_3$) 2.41 (3H, d, *J* 1.0 Hz, 2-CH_3), 3.81 (3H, s, OCH_3), 6.29 (1H, quin., *J* 1.0 Hz, 3-H), 6.78 (1H, dd, *J* 8.9, 2.6 Hz, 6-H), 6.93 (1H, br d, *J* 2.6 Hz, 4-H), 7.27 (1H, d, *J* 8.9 Hz, 7-H); δ_C (101 MHz, $CDCl_3$) 14.2 (CH_3), 55.9 (CH_3), 102.8 (CH), 103.1 (CH), 111.0 (CH), 111.3 (CH), 129.8 (C), 149.7 (C), 155.8 (C), 156.3 (C); *m/z* (ESI) 185 (MNa^+. 100%).

5,6-Dimethoxybenzo[*b*]furan (192f)[542]



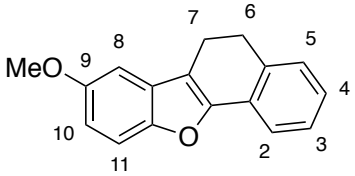
5,6-Dimethoxybenzo[*b*]furan (**192f**) was synthesised according to method C using 3,4-dimethoxyphenylacetaldehyde (**188**) (0.0680 g, 0.377 mmol). The iodination step was carried out at 40 °C for 3 h and the *O*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (hexane/diethyl ether, 9:1) gave 5,6-dimethoxybenzo[*b*]furan (**192f**) (0.0270 g, 40%) as a colourless oil. Spectroscopic data were consistent with the literature.[542] δ_H (500 MHz, $CDCl_3$) 3.91 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.67 (1H, dd, *J* 2.1, 0.8 Hz, 3-H), 7.03 (1H, s, 7-H), 7.06 (1H, br s, 4-H), 7.52 (1H, d, *J* 2.1 Hz, 2-H); δ_C (126 MHz, $CDCl_3$) 56.2 (CH_3), 56.4 (CH_3), 95.4 (CH), 102.4 (CH), 106.5 (CH), 119.1 (C), 144.0 (CH), 146.6 (C), 148.0 (C), 149.7 (C); *m/z* (ESI) 201 (MNa^+. 100%).

8-Methoxy-2,3,4,5-tetrahydrocyclohexabenzo[*b*]furan (192g)[543]



8-Methoxy-2,3,4,5-tetrahydrocyclohexabenzo[*b*]furan (**192g**) was synthesised according to method C using 2′-(3-methoxyphenyl)cyclohexanone (**189a**) (0.0598 g, 0.290 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 8-methoxy-2,3,4,5-tetrahydrocyclohexabenzo[*b*]furan (**192g**) (0.0314 g, 53%) as a colourless oil. Spectroscopic data were consistent with the literature.[543] δ_H (400 MHz, $CDCl_3$) 1.80–1.96 (4H, m, 3-H_2 and 4-H_2), 2.55–2.62 (2H, m, 2-H_2 or 5-H_2), 2.68–2.74 (2H, m, 2-H_2 or 5-H_2), 3.84 (3H, s, OCH_3), 6.78 (1H, dd, *J* 8.8, 2.6 Hz, 8-H), 6.87 (1H, d, *J* 2.6 Hz, 6-H), 7.27 (1H, d, *J* 8.8 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 20.5 (CH_2), 22.7 (CH_2), 23.0 (CH_2), 23.6 (CH_2), 56.0 (CH_3), 101.6 (CH), 111.0 (CH), 111.1 (CH), 113.0 (C), 129.4 (C), 149.2 (C), 155.0 (C), 155.7 (C); *m/z* (ESI) 225 (MNa^+. 100%).

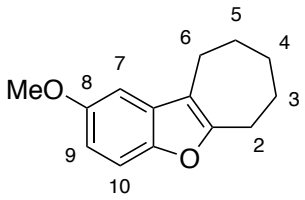
9-Methoxy-6,7-dihydronaphthobenzo[b]furan (192h)



9-Methoxy-6,7-dihydronaphthobenzo[b]furan (**192h**) was synthesised according to method C using 2′-(3-methoxyphenyl)-3′,4′-dihydronaphthalen-1′(2*H*)-one (**189b**) (0.0630 g, 0.250 mmol). The iodination step was carried out at 50 °C for 6 h and the *O*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 9-methoxy-6,7-dihydronaphthobenzo[*b*]furan (**192h**) (0.0382 g, 61%) as a white solid. Mp 185–188 °C; ν_{max}/cm^{-1} (neat) 2934 (CH), 1611, 1477, 1456, 1433, 1229, 1196, 1177, 1140, 1084, 1026, 797, 760; δ_H (500 MHz, $CDCl_3$) 2.91 (2H, dd, *J* 8.0, 7.5 Hz, 7-H_2), 3.08 (2H, dd, *J* 8.0, 7.5 Hz, 6-H_2), 3.85 (3H, s, OCH_3), 6.85 (1H, dd, *J* 8.9, 2.7 Hz, 10-H), 6.93 (1H, d, *J* 2.7 Hz, 8-

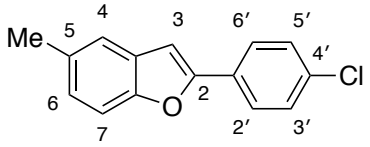
H), 7.18 (1H, td, *J* 7.5, 1.0 Hz, 4-H), 7.20–7.24 (1H, m, 5-H), 7.27 (1H, br t, *J* 7.5 Hz, 3-H), 7.38 (1H, d, *J* 8.9 Hz, 11-H), 7.62 (1H, br d, *J* 7.5 Hz, 2-H); δ_C (126 MHz, $CDCl_3$) 19.4 (CH_2), 28.7 (CH_2), 56.0 (CH_3), 101.9 (CH), 111.8 (CH), 112.5 (CH), 114.2 (C), 120.5 (CH), 126.9 (CH), 127.6 (CH), 127.9 (C), 128.0 (CH), 128.8 (C), 136.0 (C), 150.3 (C), 152.7 (C), 156.1 (C); *m/z* (ESI) 273.0887 (MNa^+. $C_{17}H_{14}NaO_2$ requires 273.0886).

8-Methoxy-2,3,4,5-tetrahydrocycloheptabenzo[*b*]furan (192i)



8-Methoxy-2,3,4,5-tetrahydrocycloheptabenzo[*b*]furan (**192i**) was synthesised according to method C using 2′-(3-methoxyphenyl)cycloheptanone (**189c**) (0.0639 g, 0.290 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 36 h. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 8-methoxy-2,3,4,5-tetrahydrocycloheptabenzo[*b*]furan (**192i**) (0.0362 g, 57%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2922 (CH), 1612, 1476, 1454, 1204, 1032, 800; δ_H (500 MHz, $CDCl_3$) 1.73–1.88 (6H, m, 3-H_2, 4-H_2 and 5-H_2), 2.65 (2H, dd, *J* 6.1, 5.5 Hz, 2-H_2 or 6-H_2), 2.89 (2H, dd, *J* 6.1, 5.5 Hz, 2-H_2 or 6-H_2), 3.83 (3H, s, OCH_3), 6.77 (1H, dd, *J* 8.8, 2.6 Hz, 9-H), 6.86 (1H, d, *J* 2.6 Hz, 7-H), 7.23 (1H, d, *J* 8.8 Hz, 10-H); δ_C (126 MHz, $CDCl_3$) 23.3 (CH_2), 26.3 (CH_2), 28.2 (CH_2), 29.2 (CH_2), 30.6 (CH_2), 56.0 (CH_3), 101.4 (CH), 110.8 (CH), 111.0 (CH), 116.0 (C), 131.0 (C), 148.2 (C), 155.6 (C), 157.4 (C); *m/z* (ESI) 239.1033 (MNa^+. $C_{14}H_{16}NaO_2$ requires 239.1043).

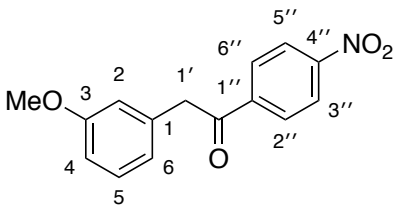
2-(4′-Chlorophenyl)-5-methylbenzo[*b*]furan (195)[544]



N-Iodosuccinimide (0.0439 g, 0.195 mmol) and iron(III) chloride (1.59 mg, 0.00980 mmol) were dissolved in [BMIM]NTf_2 (0.3 mL) and stirred at room temperature for 0.5 h. 1′-(3-Methylphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**180b**) (0.0478 g, 0.195 mmol) in [BMIM]NTf_2 (0.2 mL) was added to this suspension and the reaction mixture was heated to 70 °C for 16 h. After cooling to room temperature, the reaction mixture was extracted into hexane/ethyl acetate, 19:1 (3 × 20 mL). The combined organic extracts were washed with 1 M aqueous sodium thiosulfate (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* The crude residue was passed through a flash column, eluting with hexane/ethyl acetate, 19:1, which gave 1′-(3-methyl-6-iodophenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**193**) and 1′-(3-methyl-4-iodophenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**194**) in a 4:1 mixture (0.0398 g). This mixture was used without further purification in the next step. The 4:1 mixture of 1′-(3-methyl-6-iodophenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**193**) and 1′-(3-methyl-4-iodophenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**194**) (0.0398 g, 0.0900 mmol) was dissolved in toluene (1.0 mL) and copper iodide (1.30 mg, 0.00670 mmol), cesium carbonate (0.0437 g, 0.134 mmol), *N*,*N*′-dimethylethylenediamine (1.40 µL, 0.0134 mmol) and water (0.4 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 24 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine (30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane, 9:1), followed by recrystallisation from hot acetonitrile gave 2-(4′-chlorophenyl)-5-methylbenzo[*b*]furan (**195**) (0.0103 g, 26% over two steps) as a colourless crystalline solid. Mp 183–185 °C (from acetonitrile) (lit.[544] Mp 185–187 °C); δ_H (500 MHz, $CDCl_3$) 2.44 (3H, s, 5-CH_3), 6.93 (1H, s, 3-H), 7.10 (1H, dd, *J* 8.4, 1.5 Hz, 6-H), 7.36 (1H, br s, 4-H), 7.37–7.43 (3H, m, 7-H, 3′-H and 5′-H), 7.77 (2H, d, *J* 8.6 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 21.3 (CH_3), 101.5 (CH),

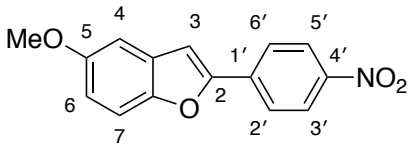
110.7 (CH), 120.8 (CH), 125.9 (CH), 126.1 (2 × CH), 129.0 (2 × CH), 129.1 (C), 129.2 (C), 132.5 (C), 134.2 (C), 153.4 (C), 154.8 (C); *m/z* (EI) 242 (M^+. 100%), 179 (45), 178 (65), 89 (28).

1′-(3-Methoxyphenyl)-2′-(4″-nitrophenyl)ethan-2′-one (198)



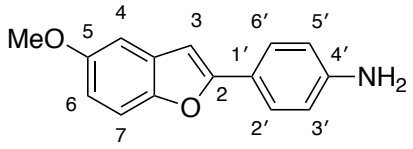
An oven-dried 2-neck flask was flushed with argon and charged with 3-methoxyphenylacetic acid (**128**) (0.500 g, 3.00 mmol), methyl 4-nitrobenzoate (0.544 g, 3.00 mmol) and dry tetrahydrofuran (15 mL). The solution was cooled to –78 °C and lithium bis(trimethylsilyl)amide (12.0 mL, 12.0 mmol; 1.0 M in tetrahydrofuran) was added dropwise. The resulting reaction mixture was stirred at –78 °C for 3 h and then warmed to –20 °C with stirring for 2 h. A saturated aqueous solution of ammonium chloride (25 mL) was added at –20 °C and the solution was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 1′-(3-methoxyphenyl)-2′-(4″-nitrophenyl)ethan-2′-one (**198**) (0.136 g, 17%) as a yellow oil. ν_{max}/cm^{-1} (neat) 2940 (CH), 1690 (C=O), 1601, 1522 (NO), 1491, 1346 (NO), 1317, 1261, 1049, 854, 746; δ_H (400 MHz, $CDCl_3$) 3.78 (3H, s, OCH_3), 4.29 (2H, s, 1′-H_2), 6.77–6.86 (3H, m, 2-H, 4-H and 6-H), 7.25 (1H, t, *J* 7.8 Hz, 5-H), 8.13 (2H, d, *J* 9.0 Hz, 2″-H and 6″-H), 8.28 (2H, d, *J* 9.0 Hz, 3″-H and 5″-H); δ_C (101 MHz, $CDCl_3$) 46.1 (CH_2), 55.2 (CH_3), 112.6 (CH), 115.2 (CH), 121.6 (CH), 123.9 (2 × CH), 129.6 (2 × CH), 130.0 (CH), 134.8 (C), 140.9 (C), 150.3 (C), 160.0 (C), 195.9 (C); *m/z* (ESI) 294.0747 (MNa^+. $C_{15}H_{13}NNaO_4$ requires 294.0737).

2-(4′-Nitrophenyl)-5-methoxybenzo[*b*]furan (199)[363]



2-(4′-Nitrophenyl)-5-methoxybenzo[*b*]furan (**199**) was synthesised according to method A using 1′-(3-methoxyphenyl)-2′-(4″-nitrophenyl)ethan-2′-one (**198**) (0.0610 g, 0.225 mmol). The iodination step was carried out at 40 °C for 3 h and the *O*-arylation at 130 °C for 20 h. Purification by flash column chromatography (petroleum ether/dichloromethane, 1:1) gave 2-(4′-nitrophenyl)-5-methoxybenzo[*b*]furan (**199**) (0.0380 g, 63%) as a yellow solid. Spectroscopic data were consistent with the literature.[363] Mp 178–180 °C; δ_H (500 MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 6.98 (1H, dd, *J* 9.0, 2.6 Hz, 6-H), 7.07 (1H, d, *J* 2.6 Hz, 4-H), 7.17 (1H, s, 3-H), 7.44 (1H, d, *J* 9.0 Hz, 7-H), 7.97 (2H, d, *J* 8.9 Hz, 2′-H and 6′-H), 8.29 (2H, d, *J* 8.9 Hz, 3′-H and 5′-H); δ_C (126 MHz, $CDCl_3$) 55.9 (CH_3), 103.5 (CH), 105.2 (CH), 112.0 (CH), 115.0 (CH), 124.3 (2 × CH), 125.1 (2 × CH), 129.2 (C), 136.3 (C), 147.2 (C), 150.6 (C), 154.0 (C), 156.4 (C); *m/z* (ESI) 292 (MNa^+. 100%).

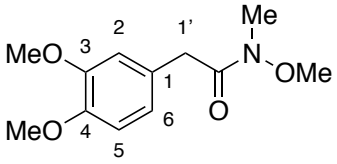
2-(4′-Aminophenyl)-5-methoxybenzo[*b*]furan (196)[363]



To a stirred solution of 2-(4′-nitrophenyl)-5-methoxybenzo[*b*]furan (**199**) (0.0320 g, 0.108 mmol) in ethanol (5 mL) was added tin dichloride dihydrate (0.122 g, 0.540 mmol) and the resulting mixture was stirred under reflux for 16 h. After cooling to room temperature, sodium bicarbonate (6 mL) was added and the suspension was stirred for 0.1 h. The suspension was diluted with ethyl acetate (20 mL), filtered through Celite® and concentrated *in vacuo*. The crude residue was dissolved in ethyl acetate (20 mL) and washed with water (25 mL) and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/dichloromethane, 1:1) gave 2-(4′-aminophenyl)-5-methoxybenzo[*b*]furan (**196**) (0.0256 g, 90%) as a yellow solid.

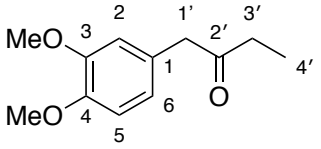
Spectroscopic data were consistent with the literature.[363] Mp 148–150 °C; δ_H (500 MHz, $CDCl_3$) 3.83 (2H, br s, NH_2), 3.85 (3H, s, OCH_3), 6.73 (2H, d, *J* 8.5 Hz, 3′-H and 5′-H), 6.75 (1H, br s, 3-H), 6.81 (1H, dd, *J* 8.8, 2.6 Hz, 6-H), 7.00 (1H, d, *J* 2.6 Hz, 4-H), 7.35 (1H, d, *J* 8.8 Hz, 7-H), 7.64 (2H, d, *J* 8.5 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 55.9 (CH_3), 98.8 (CH), 103.1 (CH), 111.2 (CH), 111.8 (CH), 115.0 (2 × CH), 121.1 (C), 126.3 (2 × CH), 130.2 (C), 146.9 (C), 149.6 (C), 155.9 (C), 157.5 (C); *m/z* (ESI) 240 (MH^+. 100%).

_N_-Methoxy-1′-(3,4-dimethoxyphenyl)-_N_-methylacetamide (201)



N-Methoxy-1′-(3,4-dimethoxyphenyl)-*N*-methylacetamide (**201**) was synthesised as described for *N*-methoxy-1′-(3-methoxyphenyl)-*N*-methylacetamide (**158**) using 3,4-dimethoxyphenylacetic acid (**200**) (1.00 g, 5.10 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave *N*-methoxy-1′-(3,4-dimethoxyphenyl)-*N*-methylacetamide (**201**) (0.730 g, 60%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2938 (CH), 1655 (C=O), 1514, 1260, 1236, 1153, 1140, 1026, 1005, 787; δ_H (500 MHz, $CDCl_3$) 3.20 (3H, s, *N*-CH_3), 3.63 (3H, s, OCH_3), 3.71 (2H, s, 1′-H_2), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.82 (2H, br s, 2-H and 5-H), 6.86 (1H, br s, 6-H); δ_C (126 MHz, $CDCl_3$) 32.3 (CH_3), 38.9 (CH_2), 55.9 (CH_3), 55.9 (CH_3), 61.3 (CH_3), 111.2 (CH), 112.5 (CH), 121.4 (CH), 127.4 (C), 147.9 (C), 148.9 (C), 172.7 (C); *m/z* (ESI) 262.1049 (MNa^+. $C_{12}H_{17}NNaO_4$ requires 262.1050).

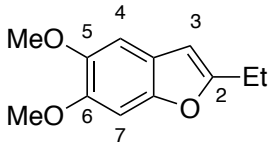
1′-(3,4-Dimethoxyphenyl)butan-2′-one (202)[545]



1′-(3,4-Dimethoxyphenyl)butan-2′-one (**202**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(4″-chlorophenyl)ethan-2′-one (**157b**) using *N*-methoxy-1′-(3,4-dimethoxyphenyl)-*N*-methylacetamide (**201**) (0.700 g, 2.93 mmol) and

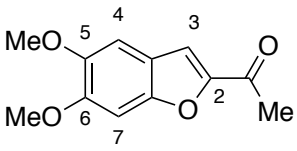
ethylmagnesium bromide (4.40 mL, 4.40 mmol; 1.0 M in tetrahydrofuran). Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave 1′-(3,4-dimethoxyphenyl)butan-2′-one (**202**) (0.575 g, 94%) as a colourless oil. Spectroscopic data were consistent with the literature.[545] δ_H (500 MHz, $CDCl_3$) 1.03 (3H, t, *J* 7.3 Hz, 4′-H_3), 2.48 (2H, q, *J* 7.3 Hz, 3′-H_2), 3.62 (2H, s, 1′-H_2), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.72 (1H, d, *J* 1.9 Hz, 2-H), 6.75 (1H, dd, *J* 8.2, 1.9 Hz, 6-H), 6.83 (1H, d, *J* 8.2 Hz, 5-H); δ_C (126 MHz, $CDCl_3$) 7.81 (CH_3), 35.0 (CH_2), 49.4 (CH_2), 55.9 (CH_3), 55.9 (CH_3), 111.4 (CH), 112.4 (CH), 121.5 (CH), 127.0 (C), 148.1 (C), 149.1 (C), 209.4 (C); *m/z* (ESI) 231 (MNa^+. 100%).

2-Ethyl-5,6-dimethoxybenzo[b]furan (203)



2-Ethyl-5,6-dimethoxybenzo[b]furan (**203**) was synthesised according to method C using 1′-(3,4-dimethoxyphenyl)butan-2′-one (**202**) (0.100 g, 0.480 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 9:1) gave 2-ethyl-5-methoxybenzo[*b*]furan (**203**) (0.0630 g, 64%) as a yellow oil. ν_{max}/cm^{-1} (neat) 2940 (CH), 1622, 1487, 1319, 1209, 1192, 1115; δ_H (500 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.6 Hz, 2-CH_2CH_3), 2.75 (2H, q, *J* 7.6 Hz, 2-CH_2CH_3), 3.90 (6H, br s, 2 × OCH_3), 6.26 (1H, br s, 3-H), 6.94 (1H, s, 7-H), 7.00 (1H, s, 4-H); δ_C (126 MHz, $CDCl_3$) 12.1 (CH_3), 21.8 (CH_2), 56.3 (CH_3), 56.5 (CH_3), 95.3 (CH), 100.9 (CH), 102.1 (CH), 120.7 (C), 146.2 (C), 147.0 (C), 149.1 (C), 160.0 (C); *m/z* (ESI) 229.0832 (MNa^+. $C_{12}H_{14}NaO_3$ requires 229.0835).

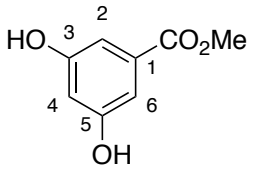
2-Acetyl-5,6-dimethoxybenzo[b]furan, caleprunin B (177)[546]



To a stirred solution of 2-ethyl-5-methoxybenzo[*b*]furan (**203**) (0.0400 g, 0.190 mmol) in anhydrous 1,4-dioxane (12 mL) was added selenium dioxide (0.0320 g,

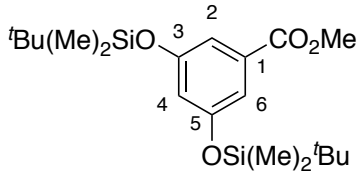
0.290 mmol) and the resulting mixture was heated under reflux for 22 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification by flash column chromatography (dichloromethane) gave 2-acetyl-5,6-dimethoxybenzo[b]furan (**177**) (0.0238 g, 56%) as a yellow oil. Spectroscopic data were consistent with the literature.[546] δ_H (500 MHz, $CDCl_3$) 2.56 (3H, s, 2-$COCH_3$), 3.93 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 7.04 (1H, s, 7-H), 7.06 (1H, s, 4-H), 7.42 (1H, s, 3-H); δ_C (126 MHz, $CDCl_3$) 26.2 (CH_3), 56.3 (CH_3), 56.3 (CH_3), 95.1 (CH), 102.8 (CH), 113.8 (CH), 119.1 (C), 147.8 (C), 151.4 (C), 151.7 (C), 152.4 (C), 187.6 (C); *m/z* (ESI) 243 (MNa^+. 100%).

Methyl 3,4-dihydroxybenzoate (207)[547]



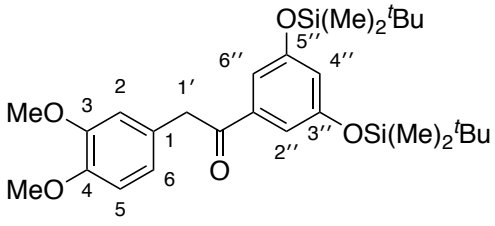
To a stirred solution of 3,5-dihydroxybenzoic acid (**206**) (2.00 g, 13.0 mmol) in methanol (40 mL) were added a few drops of concentrated sulfuric acid and the resulting mixture was stirred under reflux for 16 h. After cooling to room temperature, the methanol was removed *in vacuo* and the residue was dissolved in dichloromethane (50 mL). The solution was washed with water (4 × 50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* and gave methyl 3,4-dihydroxybenzoate (**207**) (1.92 g, 88%) as a beige solid. Mp 161–163 °C (lit.[547] 164–165 °C); δ_H (500 MHz, DMSO-d_6) 3.80 (3H, s, OCH_3), 6.46 (1H, t, *J* 2.3 Hz, 4-H), 6.84 (2H, d, *J* 2.3 Hz, 2-H and 6-H), 9.64 (2H, s, OH); δ_C (126 MHz, DMSO-d_6) 52.4 (CH_3), 107.6 (2 × CH), 107.6 (CH), 131.8 (C), 159.0 (2 × C), 166.7 (C); *m/z* (ESI) 191 (MNa^+. 100%).

Methyl 3,5-bis(*tert*-butyldimethylsilyloxy)benzoate (208)[548]



Methyl 3,4-dihydroxybenzoate (**207**) (1.00 g, 5.95 mmol) was dissolved in dry tetrahydrofuran (60 mL) and *tert*-butyldimethylsilyl chloride (2.25 g, 14.9 mmol), imidazole (1.22 g, 17.9 mmol) and 4-dimethylaminopyridine (0.0730 g, 0.595 mmol) were added. The resulting reaction mixture was stirred at room temperature for 16 h. Water (50 mL) was added and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with saturated sodium hydrogen carbonate (150 mL), brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave methyl 3,5-bis(*tert*-butyldimethylsilyloxy)benzoate (**208**) (1.90 g, 81%) as a colourless oil. Spectroscopic data were consistent with the literature.[548] δ_H (500 MHz, $CDCl_3$) 0.21 (12H, s, 2 × $Si(CH_3)_2$), 0.98 (18H, s, 2 × $Si(CH_3)_3$), 3.88 (3H, s, OCH_3), 6.52 (1H, t, *J* 2.3 Hz, 4-H), 7.12 (2H, d, *J* 2.3 Hz, 2-H and 6-H); δ_C (126 MHz, $CDCl_3$) −4.4 (4 × CH_3), 18.2 (2 × C), 25.7 (6 × CH_3), 52.1 (CH_3), 114.6 (2 × CH), 116.8 (CH), 131.9 (C), 156.5 (2 × C), 166.8 (C); *m/z* (ESI) 419 (MNa^+. 100%).

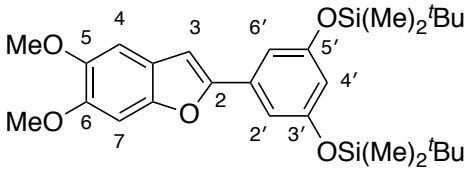
1′-(3,4-Dimethoxyphenyl)-2′-(3″,5″-bis[*tert*-butyldimethylsilyloxy]phenyl)ethan-2′-one (209)



1′-(3,4-Dimethoxyphenyl)-2′-(3″,5″-bis[*tert*-butyldimethylsilyloxy]phenyl)ethan-2′-one (**209**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(3″-chlorophenyl)ethan-2′-one (**181a**) using 3,4-dimethoxyphenylacetic acid (**200**) (0.500 g, 2.55 mmol) and methyl 3,5-bis(*tert*-butyldimethylsilyloxy)benzoate (**208**) (1.01 g, 2.55 mmol). Purification by flash column chromatography (hexane/diethyl

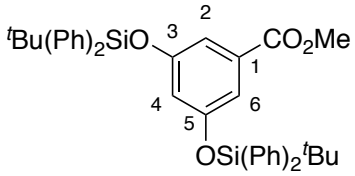
ether, 4:1) gave 1′-(3,4-dimethoxyphenyl)-2′-(3″,5″-bis[*tert*-butyldimethylsilyloxy]phenyl)ethan-2′-one (**209**) (0.821 g, 62%) as a yellow oil. ν_{max}/cm^{-1} (neat) 2930 (CH), 1682 (C=O), 1585, 1437, 1335, 1260, 1236, 1163, 1028, 829, 781; δ_H (500 MHz, $CDCl_3$) 0.19 (12H, s, 2 × Si(CH_3)$_2$), 0.97 (18H, s, 2 × SiC(CH_3)$_3$), 3.85 (6H, br s, 2 × OCH_3), 4.14 (2H, s, 1′-H_2), 6.52 (1H, t, *J* 2.2 Hz, 4″-H), 6.75–6.85 (3H, m, 2-H, 5-H and 6-H), 7.07 (2H, d, *J* 2.2 Hz, 2″-H and 6″-H); δ_C (126 MHz, $CDCl_3$) −4.4 (4 × CH_3), 18.2 (2 × C), 25.6 (6 × CH_3), 45.4 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 111.4 (CH), 112.5 (CH), 113.6 (2 × CH), 117.0 (CH), 121.5 (CH), 127.1 (C), 138.4 (C), 148.0 (C), 149.1 (C), 156.8 (2 × C), 197.4 (C); *m/z* (ESI) 539.2617 (MNa$^+$. $C_{28}H_{44}NaO_5Si_2$ requires 539.2619).

2-(3′,5′-Bis[*tert*-butyldimethylsilyloxy]phenyl)-5,6-dimethoxybenzo[*b*]furan (212)



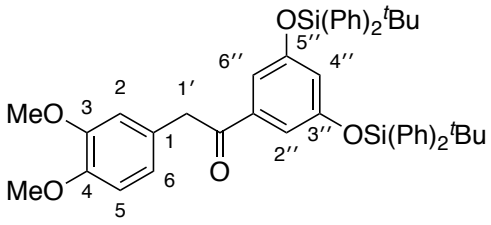
2-(3′,5′-Bis[*tert*-butyldimethylsilyloxy]phenyl)-5,6-dimethoxybenzo[*b*]furan (**212**) was synthesised according to method A using 1′-(3,4-dimethoxyphenyl)-2′-(3″,5″-bis[*tert*-butyldimethylsilyloxy])ethan-2′-one (**209**) (0.0690 g, 0.130 mmol). The iodination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 4:1) gave 2-(3′,5′-bis[*tert*-butyldimethylsilyloxy]phenyl)-5,6-dimethoxybenzo[*b*]furan (**212**) (0.0261 g, 36%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2930 (CH), 1589, 1435, 1342, 1163, 1028, 907, 829, 781; δ_H (500 MHz, $CDCl_3$) 0.24 (12H, s, 2 × Si(CH_3)), 1.01 (18H, s, 2 × SiC(CH_3)$_3$), 3.93 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.30 (1H, t, *J* 2.2 Hz, 4′-H), 6.86 (1H, br s, 3-H), 6.91 (2H, d, *J* 2.2 Hz, 2′-H and 6′-H), 7.00 (1H, s, 7-H), 7.10 (1H, s, 4-H); δ_C (126 MHz, $CDCl_3$) −4.3 (4 × CH_3), 18.3 (2 × C), 25.7 (6 × CH_3), 56.3 (CH_3), 56.4 (CH_3), 95.3 (CH), 101.7 (CH), 102.1 (CH), 109.6 (2 × CH), 111.9 (CH), 121.0 (C), 132.3 (C), 146.6 (C), 148.1 (C), 149.6 (C), 154.9 (C), 156.9 (2 × C); *m/z* (ESI) 537.2441 (MNa$^+$. $C_{28}H_{42}NaO_5Si_2$ requires 537.2463).

Methyl 3,5-bis(*tert*-butyldiphenylsilyloxy)benzoate (213)



Methyl 3,5-bis(*tert*-butyldiphenylsilyloxy)benzoate (**213**) was synthesised as described for methyl 3,5-bis(*tert*-butyldimethylsilyloxy)benzoate (**208**) using methyl 3,4-dihydroxybenzoate (**207**) (0.500 g, 2.97 mmol), *tert*-butyldiphenylsilyl chloride (1.93 mL, 7.43 mmol), imidazole (0.606 g, 8.91 mmol) and 4-dimethylaminopyridine (0.036 g, 0.297 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 9:1) gave a colourless oil. Further purification by flash column chromatography (hexane/dichloromethane, 1:1) gave methyl 3,5-bis(*tert*-butyldiphenylsilyloxy)benzoate (**213**) (1.14 g, 60%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2932 (CH), 1724 (C=O), 1587, 1427, 1339, 1169, 1107, 1034, 1015, 822, 756, 741, 698; δ_H (500 MHz, $CDCl_3$) 0.98 (18H, s, 2 × $SiC(CH_3)_3$), 3.76 (3H, s, OCH_3), 6.27 (1H, t, *J* 2.3 Hz, 4-H), 7.04 (2H, d, *J* 2.3 Hz, 2-H and 6-H), 7.25 (8H, t, *J* 7.5 Hz, ArH), 7.36 (4H, t, *J* 7.5 Hz, ArH), 7.49 (8H, d, *J* 7.5 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 19.4 (2 × C), 26.5 (6 × CH_3), 52.0 (CH_3), 114.3 (2 × CH), 116.0 (CH), 127.7 (8 × CH), 129.8 (4 × CH), 131.5 (C), 132.3 (4 × C), 135.4 (8 × CH), 156.1 (2 × C), 166.7 (C); *m/z* (ESI) 667.2648 (MNa^+. $C_{40}H_{44}NaO_4Si_2$ requires 667.2670).

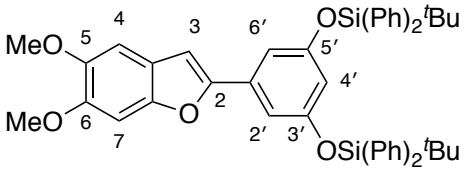
1′-(3,4-Dimethoxyphenyl)-2′-(3″,5″-bis[*tert*-butyldiphenylsilyloxy]phenyl)ethan-2′-one (214)



1′-(3,4-Dimethoxyphenyl)-2′-(3″,5″-bis[*tert*-butyldiphenylsilyloxy]phenyl)ethan-2′-one (**214**) was synthesised as described for 1′-(3-methoxyphenyl)-2′-(3″-chlorophenyl)ethan-2′-one (**181a**) using 3,4-dimethoxyphenylacetic acid (**200**) (0.184 g, 0.940 mmol) and methyl 3,5-bis(*tert*-butyldiphenylsilyloxy)benzoate (0.606

g, 0.940 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 7:3) gave a yellow oil. Further purification by flash column chromatography (hexane/diethyl ether, 4:1) gave 1′-(3,4-dimethoxyphenyl)-2′-(3″,5″-bis[*tert*-butyldiphenylsilyloxy]phenyl)ethan-2′-one (**214**) (0.397 g, 55%) as a yellow foam. ν_{max}/cm^{-1} (neat) 2932 (CH), 1682 (C=O), 1584, 1439, 1427, 1333, 1261, 1167, 1113, 1028, 822, 737, 698; δ_H (500 MHz, $CDCl_3$) 1.01 (18H, s, 2 × $SiC(CH_3)_3$), 3.71 (2H, s, 1′-H_2), 3.77 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.37 (1H, t, *J* 2.2 Hz, 4″-H), 6.43 (1H, dd, *J* 8.2, 1.9 Hz, 6-H), 6.57 (1H, d, *J* 1.9 Hz, 2-H), 6.65 (1H, d, *J* 8.2 Hz, 5-H), 6.92 (2H, d, *J* 2.2 Hz, 2″-H and 6″-H), 7.26–7.31 (8H, m, ArH), 7.38 (4H, t, *J* 7.4 Hz, ArH), 7.52–7.56 (8H, m, ArH); δ_C (126 MHz, $CDCl_3$) 19.4 (2 × C), 26.5 (6 × CH_3), 44.9 (CH_2), 55.7 (CH_3), 55.8 (CH_3), 111.2 (CH), 112.2 (CH), 113.3 (2 × CH), 116.4 (CH), 121.5 (CH), 126.9 (C), 127.7 (8 × CH), 129.9 (4 × CH), 132.4 (4 × C), 135.4 (8 × CH), 137.9 (C), 147.8 (C), 148.9 (C), 156.4 (2 × C), 197.2 (C); *m/z* (ESI) 787.3222 (MNa^+. $C_{48}H_{52}NaO_5Si_2$ requires 787.3245).

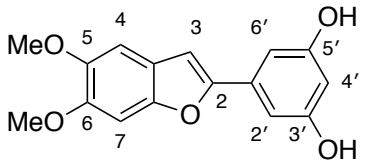
2-(3′,5′-Bis[*tert*-butyldiphenylsilyloxy]phenyl)-5,6-dimethoxybenzo[*b*]furan (215)



2-(3′,5′-Bis[*tert*-butyldiphenylsilyloxy]phenyl)-5,6-dimethoxybenzo[*b*]furan (**215**) was synthesised according to method A using 1′-(3,4-dimethoxyphenyl)-2′-(3″,5″-bis[*tert*-butyldiphenylsilyloxy])ethan-2′-one (**214**) (0.0820 g, 0.110 mmol). The iodination step was carried out at 40 °C for 5 h and the *O*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave 2-(3′,5′-bis[*tert*-butyldiphenylsilyloxy]phenyl)-5,6-dimethoxybenzo[*b*]furan (**215**) (0.0450 g, 55%) as a yellow oil. ν_{max}/cm^{-1} (neat) 2932 (CH), 1589, 1427, 1169, 1113, 907, 700; δ_H (500 MHz, $CDCl_3$) 1.02 (18H, s, 2 × $SiC(CH_3)_3$), 3.91 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 6.09 (1H, t, *J* 2.2 Hz, 4′-H), 6.51 (1H, s, 3-H), 6.81 (2H, d, *J* 2.2 Hz, 2′-H and 6′-H), 6.92 (1H, s, 7-H), 7.01 (1H, s, 4-H), 7.28 (8H, t, *J* 7.6 Hz, ArH), 7.38 (4H, tt, *J* 7.6, 1.3 Hz, ArH), 7.54–7.60 (8H, m, ArH); δ_C (126 MHz, $CDCl_3$) 19.5 (2 × C), 26.6 (6 × CH_3), 56.3 (CH_3), 56.4 (CH_3), 95.3 (CH), 101.5 (CH), 102.1 (CH), 109.2 (2 × CH), 111.3 (CH), 121.0 (C), 127.7 (8 × CH), 129.8 (4 × CH), 131.9

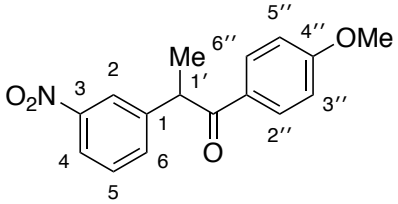
(C), 132.7 (4 × C), 135.4 (8 × CH), 146.6 (C), 148.0 (C), 149.5 (C), 154.8 (C), 156.5 (2 × C); *m/z* (ESI) 785.3087 (MNa^+. $C_{48}H_{50}NaO_5Si_2$ requires 785.3089).

2-(3′,5′-Dihydroxyphenyl)-5,6-dimethoxybenzo[*b*]furan, moracin F (178)[377]



To a stirred solution of 2-(3′,5′-bis[*tert*-butyldiphenylsilyloxy]phenyl)-5,6-dimethoxybenzo[*b*]furan (**215**) (0.0330 g, 0.0430 mmol) in dry tetrahydrofuran (4.0 mL) was added tetrabutylammonium fluoride solution (0.110 mL, 0.108 mmol; 1.0 M in tetrahydrofuran) at 0 °C. The resulting solution was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave 2-(3′,5′-dihydroxyphenyl)-5,6-dimethoxybenzo[*b*]furan (**178**) (0.00850 g, 69%) as a white solid. Mp 180–182 °C (lit.[377] Mp 186–188 °C); δ_H (400 MHz, CD_3OD) 3.86 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.25 (1H, t, *J* 2.2 Hz, 4′-H), 6.76 (2H, d, *J* 2.2 Hz, 2′-H and 6′-H), 6.93 (1H, br s, 3-H), 7.10 (1H, s, 7-H), 7.17 (1H, br s, 4-H); δ_C (101 MHz, CD_3OD) 55.5 (CH_3), 55.7 (CH_3), 95.3 (CH), 101.1 (CH), 102.2 (CH), 102.5 (2 × CH), 102.9 (CH), 121.4 (C), 132.4 (C), 146.8 (C), 148.3 (C), 149.6 (C), 155.3 (C), 158.6 (2 × C); *m/z* (ESI) 309 (MNa^+. 100%).

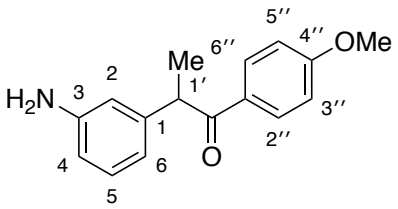
1′-(3-Nitrophenyl)-1′-methyl-2′-(4″-methoxyphenyl)ethan-2′-one (218)



To a stirred solution of 1′-(3-nitrophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**184d**) (0.455 g, 1.68 mmol) in dry tetrahydrofuran (20 mL) was added lithium bis(trimethylsilyl)amide (1.85 mL, 1.85 mmol; 1.0 M in tetrahydrofuran) dropwise at

–78 °C. The reaction mixture was stirred at –78 °C for 0.5 h before methyl iodide (0.313 mL, 5.03 mmol) was added dropwise. The resulting solution was stirred for 1 h at –78 °C, then slowly warmed to 0 °C and stirred for a further 1 h. A saturated solution of ammonium chloride (20 mL) was added at 0 °C and the solution was extracted with diethyl ether (4 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 1′-(3-nitrophenyl)-1′-methyl-2′-(4″-methoxyphenyl)ethan-2′-one (**218**) (0.454 g, 95%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2934 (CH), 1672 (C=O), 1599, 1528 1510, 1348, 1254, 1221, 1171; δ_H (500 MHz, $CDCl_3$) 1.58 (3H, d, *J* 6.9 Hz, 1′-CH_3), 3.84 (3H, s, OCH_3), 4.80 (1H, q, J 6.9 Hz, 1′-H), 6.91 (2H, d, *J* 9.1 Hz, 3″-H and 5″-H), 7.47 (1H, t, *J* 8.1 Hz, 5-H), 7.64 (1H, br dt, *J* 8.1, 1.0 Hz, 6-H), 7.95 (2H, d, *J* 9.1 Hz, 2″-H and 6″-H), 8.08 (1H, ddd, *J* 8.1, 2.2, 1.0 Hz, 4-H), 8.20 (1H, t, *J* 2.2 Hz, 2-H); δ_C (126 MHz, $CDCl_3$) 19.5 (CH_3), 46.7 (CH), 55.5 (CH_3), 114.0 (2 × CH), 122.0 (CH), 123.0 (CH), 128.8 (C), 129.8 (CH), 131.0 (2 × CH), 133.9 (CH), 143.7 (C), 148.6 (C), 163.7 (C), 197.8 (C); *m/z* (ESI) 308.0882 (MNa^+. $C_{16}H_{15}NNaO_4$ requires 308.0893).

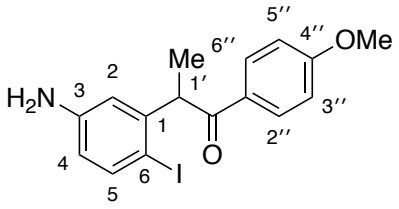
1′-(3-Aminophenyl)-1′-methyl-2′-(4″-methoxyphenyl)ethan-2′-one (217)



1′-(3-Aminophenyl)-1′-methyl-2′-(4″-methoxyphenyl)ethan-2′-one (**217**) was synthesised as described for 1′-(3-aminophenyl)-2′-(4″-methoxyphenyl)ethan-2′-one (**185**) using 1′-(3-nitrophenyl)-1′-methyl-2′-(4″-methoxyphenyl)ethan-2′-one (**218**) (0.440 g, 1.54 mmol) and tin dichloride dihydrate (1.74 g, 7.72 mmol) in ethanol (25 mL). The reaction mixture was stirred under reflux for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 1′-(3-aminophenyl)-1′-methyl-2′-(4″-methoxyphenyl)ethan-2′-one (**217**) (0.311 g, 79%) as a brown oil. ν_{max}/cm^{-1} (neat) 3453 (NH), 3368 (NH), 2932 (CH), 1668 (C=O), 1597, 1574, 1246, 1219, 1173, 961, 845; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* 6.9 Hz, 1′-CH_3), 3.55 (2H, br s, NH_2), 3.81 (3H, s, OCH_3), 4.52 (1H, q, *J* 6.9 Hz, 1′-H), 6.52

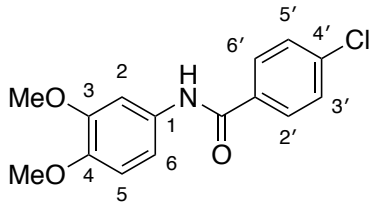
(1H, ddd, *J* 7.9, 2.4, 1.0 Hz, 4-H), 6.59 (1H, t, *J* 2.4 Hz, 2-H), 6.69 (1H, br dd, *J* 7.9, 2.4 Hz, 6-H), 6.85 (2H, d, *J* 9.0 Hz, 3″-H and 5″-H), 7.07 (1H, t, *J* 7.9 Hz, 5-H), 7.94 (2H, d, *J* 9.0 Hz, 2″-H and 6″-H); δ_C (101 MHz, $CDCl_3$) 19.4 (CH_3), 47.6 (CH), 55.4 (CH_3), 113.6 (2 × CH), 113.8 (CH), 114.2 (CH), 118.3 (CH), 129.6 (C), 129.8 (CH), 131.1 (2 × CH), 143.2 (C), 146.6 (C), 163.2 (C), 198.9 (C); *m/z* (ESI) 278.1141 (MNa^+. $C_{16}H_{17}NNaO_2$ requires 278.1151).

1′-(3-Amino-6-iodophenyl)-1′-methyl-2′-(4″-methoxyphenyl)ethan-2′-one (219)



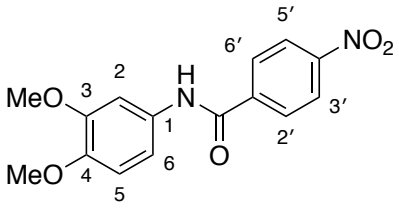
Iron(III) chloride (0.440 mg, 0.00270 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (2.30 μL, 0.00800 mmol) and stirred at room temperature for 0.5 h and then added to a stirred solution of 1′-(3-aminophenyl)-1′-methyl-2′-(4″-methoxyphenyl)ethan-2′-one (**217**) (0.0136 g, 0.0530 mmol) in toluene (1.0 mL). This solution was cooled to –20 °C and *N*-iodosuccinimide (0.0120 g, 0.0530 mmol) was slowly added. The resulting reaction mixture was stirred at –20 °C for 5 h. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine (30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 1′-(3-amino-6-iodophenyl)-1′-methyl-2′-(4″-methoxyphenyl)ethan-2′-one (**219**) (0.0133 g, 65%) as yellow oil. ν_{max}/cm^{-1} (neat) 3474 (NH), 3366 (NH), 2930 (CH), 1670 (C=O), 1597, 1470, 1261, 1242, 1169; δ_H (500 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.8 Hz, 1′-CH_3), 3.60 (2H, br s, NH_2), 3.82 (3H, s, OCH_3), 4.77 (1H, q, *J* 6.8 Hz, 1′-H), 6.27 (1H, dd, *J* 8.5, 2.8 Hz, 4-H), 6.43 (1H, d, *J* 2.8 Hz, 2-H), 6.87 (2H, d, *J* 9.0 Hz, 3″-H and 5″-H), 7.57 (1H, d, *J* 8.5 Hz, 5-H), 7.90 (2H, d, *J* 9.0 Hz, 2″-H and 6″-H); δ_C (126 MHz, $CDCl_3$) 18.0 (CH_3), 51.8 (CH), 55.4 (CH_3), 85.7 (C), 113.7 (2 × CH), 114.3 (CH), 116.0 (CH), 129.1 (C), 131.1 (2 × CH), 140.3 (CH), 145.3 (C), 147.3 (C), 163.3 (C), 198.8 (C); *m/z* (ESI) 404.0121 (MNa^+. $C_{16}H_{16}INNaO_2$ requires 404.0118).

4′-Chloro-*N*-(3,4-dimethoxyphenyl)benzamide (234c)



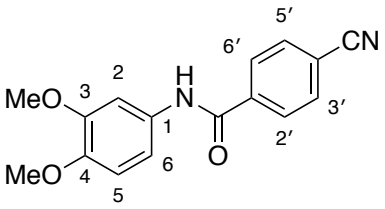
4-Chlorobenzoic acid (0.399 g, 2.55 mmol) was dissolved in thionyl chloride (4.0 mL) and the mixture was stirred under reflux for 1.5 h. After cooling to room temperature, the excess thionyl chloride was removed *in vacuo*. The resulting oil was dissolved in dry dichloromethane (10 mL) and the solution was cooled to 0 °C. 3,4-Dimethoxyaniline (0.300 g, 1.96 mmol) and triethylamine (0.355 mL, 2.55 mmol) were added and the reaction mixture was stirred at 0 °C for 0.5 h, warmed to room temperature and stirred for 3 h. The reaction mixture was diluted with dichloromethane (20 mL) and washed with water (30 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with 1 M aqueous hydrochloric acid (60 mL), brine (60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 4′-chloro-*N*-(3,4-dimethoxyphenyl)benzamide (**234c**) (0.434 g, 78%) as a white solid. Mp 116–117 °C; ν_{max}/cm^{-1} (neat) 3337 (NH), 2936 (CH), 1645 (C=O), 1605 (C=C), 1510, 1487, 1464, 1450, 1406, 1260, 1231, 1026, 1015, 750; δ_H (500 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.82 (1H, d, *J* 8.6 Hz, 5-H), 7.00 (1H, dd, *J* 8.6, 2.3 Hz, 6-H), 7.39–7.44 (3H, m, 2-H, 3′-H and 5′-H), 7.79 (2H, d, *J* 8.5 Hz, 2′-H and 6′-H), 7.95 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 55.9 (CH_3), 56.1 (CH_3), 105.3 (CH), 111.3 (CH), 112.5 (CH), 128.4 (2 × CH), 129.0 (2 × CH), 131.3 (C), 133.3 (C), 138.0 (C), 146.2 (C), 149.1 (C), 164.7 (C); *m/z* (ESI) 314.0561 (MNa^+. $C_{15}H_{14}{}^{35}ClNNaO_3$ requires 314.0554).

4′-Nitro-*N*-(3,4-dimethoxyphenyl)benzamide (234d)[549]



To a stirred solution of 3,4-dimethoxyaniline (0.500 g, 3.26 mmol) in dichloromethane (20 mL) was added triethylamine (0.546 mL, 3.94 mmol). The resulting solution was cooled to 0 °C and 4-nitrobenzoyl chloride (0.727 g, 3.92 mmol) was slowly added. The reaction mixture was stirred at 0 °C for 0.5 h, warmed to room temperature and stirred for 16 h. The resulting precipitate was collected, washed with dichloromethane (10 mL), 1 M aqueous hydrochloric acid (10 mL) and water (10 mL) then dried under high vacuum. This gave 4′-nitro-*N*-(3,4-dimethoxyphenyl)benzamide (**234d**) (0.446 g, 45%) as a yellow crystalline solid. Spectroscopic data were consistent with the literature.[549] Mp 171–174 °C (from chloroform); δ_H (500 MHz, DMSO-d_6) 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 6.96 (1H, d, *J* 8.7 Hz, 5-H), 7.35 (1H, dd, *J* 8.7, 1.5 Hz, 6-H), 7.46 (1H, d, *J* 1.5 Hz, 2-H), 8.18 (2H, d, *J* 8.6 Hz, 2′-H and 6′-H), 8.37 (2H, d, *J* 8.6 Hz, 3′-H and 5′-H), 10.42 (1H, br s, NH); δ_C (126 MHz, DMSO-d_6) 55.9 (CH_3), 56.2 (CH_3), 106.0 (CH), 112.3 (CH), 113.0 (CH), 124.0 (2 × CH), 129.5 (2 × CH), 132.6 (C), 141.2 (C), 146.0 (C), 148.9 (C), 149.5 (C), 163.8 (C); *m/z* (ESI) 325 (MNa^+. 100%).

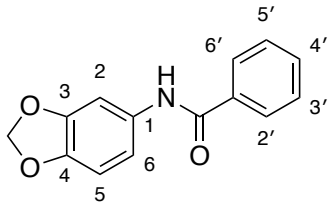
4′-Cyano-*N*-(3,4-dimethoxyphenyl)benzamide (234e)



4′-Cyano-*N*-(3,4-dimethoxyphenyl)benzamide (**234e**) was synthesised as described for 4′-chloro-*N*-(3,4-dimethoxyphenyl)benzamide (**234c**) using 3,4-dimethoxyaniline (0.300 g, 1.96 mmol), 4-cyanobenzoic acid (0.375 g, 2.55 mmol), thionyl chloride (4.0 mL) and triethylamine (0.356 mL, 2.55 mmol). Purification by flash column chromatography (dichloromethane/ethyl acetate, 19:1) gave 4′-cyano-*N*-(3,4-

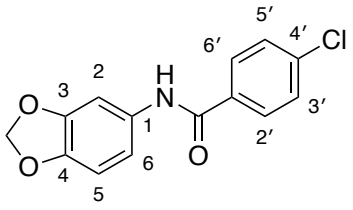
dimethoxyphenyl)benzamide (**234e**) (0.402 g, 73%) as a yellow solid. Mp 183–185 °C; ν_{max}/cm^{-1} (neat) 3329 (NH), 2837 (CH), 2232 (CN), 1649 (C=O), 1510, 1464, 1450, 1260, 1233, 1202, 1136, 1024, 752; δ_H (400 MHz, $CDCl_3$) 3.86 (6H, s, 2 × OCH_3), 6.83 (1H, d, *J* 8.5 Hz, 5-H), 7.02 (1H, d, *J* 8.5 Hz, 6-H), 7.41 (1H, s, 2-H), 7.73 (2H, d, *J* 7.7 Hz, 2′-H and 6′-H), 7.95 (2H, d, *J* 7.7 Hz, 3′-H and 5′-H), 8.01 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 56.0 (CH_3), 56.1 (CH_3), 105.3 (CH), 111.3 (CH), 112.6 (CH), 115.2 (C), 118.0 (C), 127.7 (2 × CH), 130.9 (C), 132.6 (2 × CH), 138.9 (C), 146.5 (C), 149.1 (C), 163.9 (C); *m/z* (ESI) 305.0889 (MNa^+. $C_{16}H_{14}N_2NaO_3$ requires 305.0897).

N-(3,4-Methylenedioxyphenyl)benzamide (234f)[550]



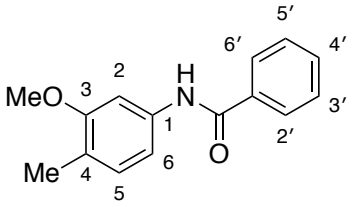
N-(3,4-Methylenedioxyphenyl)thiobenzamide (**234f**) was synthesised as described for 4′-nitro-*N*-(3,4-dimethoxyphenyl)benzamide (**234d**) using 3,4-methylenedioxyaniline (0.200 g, 1.46 mmol), benzoyl chloride (0.203 mL, 1.75 mmol) and triethylamine (0.244 mL, 1.75 mmol). The reaction mixture was diluted with dichloromethane (30 mL) and washed with water (50 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with 1 M aqueous hydrochloric acid (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification by flash column chromatography (petroleum ether/dichloromethane, 9:1) gave *N*-(3,4-methylenedioxyphenyl)benzamide (**234f**) (0.213 g, 61%) as a white solid. Mp 133–135 °C (from chloroform) (lit.[550] 137–140 °C); δ_H (500 MHz, $CDCl_3$) 5.97 (2H, s, OCH_2O), 6.77 (1H, d, *J* 8.3 Hz, 5-H), 6.90 (1H, dd, *J* 8.3, 2.1 Hz, 6-H), 7.35 (1H, br s, 2-H), 7.44–7.49 (2H, m, 3′-H and 5′-H), 7.51–7.56 (1H, m, 4′-H), 7.80 (1H, br s, NH), 7.84 (2H, d, *J* 7.5 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 101.3 (CH_2), 103.2 (CH), 108.1 (CH), 113.6 (CH), 127.0 (2 × CH), 128.8 (2 × CH), 131.8 (CH), 132.1 (C), 134.9 (C), 144.5 (C), 147.9 (C), 165.7 (C); *m/z* (ESI) 264 (MNa^+. 100%).

4′-Chloro-*N*-(3,4-methylenedioxyphenyl)benzamide (234g)



4′-Chloro-*N*-(3,4-methylenedioxyphenyl)benzamide (**234g**) was synthesised as described for 4′-chloro-*N*-(3,4-dimethoxyphenyl)benzamide (**234c**) using 3,4-methylenedioxyaniline (0.500 g, 3.65 mmol), 4-chlorobenzoic acid (0.742 g, 4.74 mmol), thionyl chloride (7.0 mL) and triethylamine (0.660 mL, 4.74 mmol). The reaction mixture was stirred at room temperature for 16 h. The crude residue was filtered through a short pad of silica, eluting with ethyl acetate, which gave 4′-chloro-*N*-(3,4-methylenedioxyphenyl)benzamide (**234g**) (0.695 g, 69%) as a brown solid. Mp 185–187 °C; ν_{max}/cm^{-1} (neat) 3300 (NH), 1645 (C=O), 1503, 1491, 1246, 1192, 1038, 810; δ_H (500 MHz, DMSO-d_6) 6.02 (2H, s, OCH_2O), 6.90 (1H, d, *J* 8.4 Hz, 5-H), 7.19 (1H, dd, *J* 8.4, 2.0 Hz, 6-H), 7.43 (1H, d, *J* 2.0 Hz, 2-H), 7.60 (2H, d, *J* 8.5 Hz, 3′-H and 5′-H), 7.97 (2H, d, *J* 8.5 Hz, 2′-H and 6′-H), 10.22 (1H, br s, NH); δ_C (126 MHz, DMSO-d_6) 101.5 (CH_2), 103.0 (CH), 108.4 (CH), 113.9 (CH), 128.9 (2 × CH), 130.0 (2 × CH), 133.7 (C), 134.1 (C), 136.8 (C), 143.8 (C), 147.5 (C), 164.6 (C); *m/z* (ESI) 298.0239 (MNa^+. $C_{14}H_{10}{}^{35}ClNNaO_3$ requires 298.0241).

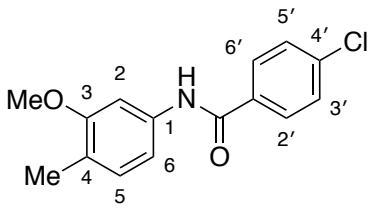
***N*-(3-Methoxy-4-methylphenyl)benzamide (234h)**[551]



N-(3-Methoxy-4-methylphenyl)benzamide (**234h**) was synthesised as described for *N*-(3,4-methylenedioxyphenyl)benzamide (**234f**) using 3-methoxy-4-methylaniline (0.100 g, 0.730 mmol), benzoyl chloride (0.102 mL, 0.870 mmol) and triethylamine (0.121 mL, 0.870 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 3 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave *N*-(3-methoxy-4-methylphenyl)benzamide

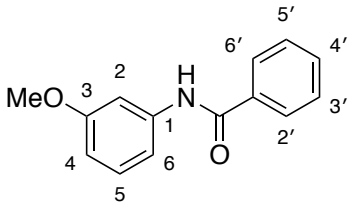
(**234h**) (0.156 g, 89%) as a white solid. Mp 126–128 °C (lit.[551] 130–131 °C); δ_H (400 MHz, $CDCl_3$) 2.19 (3H, s, 4-CH_3), 3.84 (3H, s, OCH_3), 6.89 (1H, dd, *J* 8.0, 2.0 Hz, 6-H), 7.07 (1H, d, *J* 8.0 Hz, 5-H), 7.42–7.57 (4H, m, 2-H, 3′-H, 4'-H and 5′-H), 7.83–7.88 (2H, m, 2′-H and 6′-H), 7.90 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 15.8 (CH_3), 55.4 (CH_3), 103.1 (CH), 111.6 (CH), 122.9 (C), 127.0 (2 × CH), 128.8 (2 × CH), 130.5 (CH), 131.8 (CH), 135.1 (C), 136.9 (C), 158.0 (C), 165.7 (C); *m/z* (ESI) 264 (MNa^+. 100%).

4′-Chloro-*N*-(3-methoxy-4-methylphenyl)benzamide (234i)



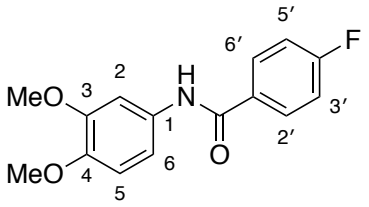
4′-Chloro-*N*-(3-methoxy-4-methylphenyl)benzamide (**234i**) was synthesised as described for 4′-chloro-*N*-(3,4-dimethoxyphenyl)benzamide (**234c**) using 3-methoxy-4-methylaniline (0.100 g, 0.730 mmol), 4-chlorobenzoic acid (0.148 g, 0.948 mmol), thionyl chloride (2.0 mL) and triethylamine (0.132 mL, 0.948 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 4′-chloro-*N*-(3-methoxy-4-methylphenyl)benzamide (**234i**) (0.176 g, 88%) as a white solid. Mp 160–162 °C; ν_{max}/cm^{-1} (neat) 3296, 2918 (CH), 1641 (C=O), 1599 (C=C), 1528, 1510, 1404, 1261, 1134, 843; δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, 4-CH_3), 3.85 (3H, s, OCH_3), 6.87 (1H, dd, *J* 8.0, 2.1 Hz, 6-H), 7.08 (1H, d, *J* 8.0 Hz, 5-H), 7.42–7.48 (3H, m, 2-H, 3′-H and 5′-H), 7.75–7.82 (3H, m, NH, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 15.8 (CH_3), 55.4 (CH_3), 103.1 (CH), 111.6 (CH), 123.2 (C), 128.4 (2 × CH), 129.1 (2 × CH), 130.5 (CH), 133.4 (C), 136.6 (C), 138.1 (C), 158.0 (C), 164.6 (C); *m/z* (ESI) 298.0602 (MNa^+. $C_{15}H_{14}{}^{35}ClNNaO_2$ requires 298.0605).

***N*-(3-Methoxyphenyl)benzamide (234j)**[552]



N-(3-Methoxyphenyl)benzamide (**234j**) was synthesised as described for *N*-(3,4-methylenedioxyphenyl)benzamide (**234f**) using 3-methoxyaniline (0.500 g, 4.06 mmol), benzoyl chloride (0.566 mL, 4.87 mmol) and triethylamine (0.677 mL, 4.87 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature for 3 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave *N*-(3-methoxyphenyl)benzamide (**234j**) (0.891 g, 97%) as a white solid. Mp 109–111 °C (lit.[552] 112–114°C); δ_H (500 MHz, $CDCl_3$) 3.80 (3H, s, OCH_3), 6.70 (1H, ddd, *J* 8.2, 2.4, 1.0 Hz, 6-H), 7.11 (1H, br dd, *J* 8.2, 2.4 Hz, 4-H), 7.24 (1H, t, *J* 8.2 Hz, 5-H), 7.42–7.48 (3H, m, 2-H, 3′-H and 5′-H), 7.50–7.55 (1H, m, 4′-H), 7.82–7.87 (2H, m, 2′-H and 6′-H), 7.97 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 55.3 (CH_3), 105.8 (CH), 110.5 (CH), 112.3 (CH), 127.0 (2 × CH), 128.8 (2 × CH), 129.7 (CH), 131.8 (CH), 135.0 (C), 139.2 (C), 160.2 (C), 165.8 (C); *m/z* (ESI) 250 (MNa^+. 100%).

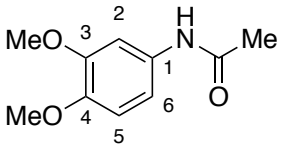
4′-Fluoro-*N*-(3,4-dimethoxyphenyl)benzamide (234l)



4′-Fluoro-*N*-(3,4-dimethoxyphenyl)benzamide (**234l**) was synthesised as described for 4′-chloro-*N*-(3,4-dimethoxyphenyl)benzamide (**234c**) using 3,4-dimethoxyaniline (0.300 g, 1.96 mmol), 4-fluorobenzoic acid (0.357 g, 2.55 mmol), thionyl chloride (4.0 mL) and triethylamine (0.356 mL, 2.55 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave 4′-fluoro-*N*-(3,4-dimethoxyphenyl)benzamide (**234l**) (0.304 g, 56%) as a white solid. Mp 153–155

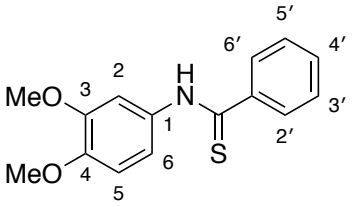
°C; ν_{max}/cm^{-1} (neat) 3292 (NH), 2839 (CH), 1638 (C=O), 1601 (C=C), 1508, 1449, 1416, 1229, 1140, 1024, 843; δ_H (500 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.82 (1H, d, *J* 8.6 Hz, 5-H), 7.00 (1H, dd, *J* 8.6, 2.4 Hz, 6-H), 7.12 (2H, t, *J* 8.6 Hz, 3′-H and 5′-H), 7.42 (1H, d, *J* 2.4 Hz, 2-H), 7.83–7.90 (2H, m, 2′-H and 5′-H), 7.95 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 55.9 (CH_3), 56.1 (CH_3), 105.3 (CH), 111.3 (CH), 112.5 (CH), 115.8 (2 × CH, d, $^2J_{CF}$ 21.8 Hz), 129.3 (2 × CH, d, $^3J_{CF}$ 9.0 Hz), 131.1 (C, d, $^4J_{CF}$ 3.1 Hz), 131.4 (C), 146.2 (C), 149.1 (C), 164.7 (C), 164.8 (C, d, $^1J_{CF}$ 253.5 Hz); *m/z* (ESI) 298.0848 (MNa^+. $C_{15}H_{14}FNNaO_3$ requires 298.0850).

_N_-(3,4-Dimethoxyphenyl)acetamide (234m)[553]



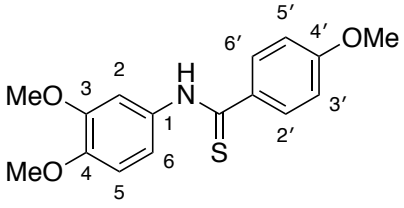
To a stirred solution of 3,4-dimethoxyaniline (1.00 g, 6.53 mmol) in dichloromethane (40 mL) was added acetic anhydride (0.930 mL, 9.80 mmol). The resulting reaction mixture was stirred at room temperature for 3 h. A saturated aqueous solution of sodium bicarbonate (30 mL) was added, the layers separated and the aqueous layer was extracted with dichloromethane (2 × 40 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (ethyl acetate/petroleum ether, 7:3) gave *N*-(3-methoxyphenyl)acetamide (**234m**) (1.02 g, 80%) as a pink solid. Mp 127–129 °C (lit.[553] 130–131 °C); δ_H (500 MHz, $CDCl_3$) 2.15 (3H, s, NHCOCH_3), 3.85 (6H, s, 2 × OCH_3), 6.79 (1H, d, *J* 8.6 Hz, 5-H), 6.87 (1H, dd, *J* 8.6, 2.4 Hz, 6-H), 7.30 (1H, dd, *J* 2.4 Hz, 2-H), 7.45 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 24.4 (CH_3), 55.9 (CH_3), 56.1 (CH_3), 105.1 (CH), 111.3 (CH), 112.0 (CH), 131.6 (C), 145.9 (C), 149.0 (C), 168.4 (C); *m/z* (EI) 195 (M^+. 100%), 153 (38), 138 (100), 110 (24).

***N*-(3,4-Dimethoxyphenyl)thiobenzamide (235a)**



To a stirred suspension of *N*-(3,4-dimethoxyphenyl)benzamide (**234a**) (0.100 g, 0.340 mmol) in dry toluene (15 mL) was added Lawesson's reagent (0.081 g, 0.200 mmol) and the resulting reaction mixture was stirred under reflux for 4 h. After cooling to room temperature, the solvent was removed *in vacuo* and the crude residue was dissolved in ethyl acetate (20 mL). The organic layer was washed with water (3 × 20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-(3,4-dimethoxyphenyl)thiobenzamide (**235a**) (0.0790 g, 74%) as a yellow solid. Mp 150–152 °C; ν_{max}/cm^{-1} (neat) 3289 (NH), 2961 (CH), 1601, 1510, 1447, 1263, 1231, 1132, 1024, 750, 692; δ_H (500 MHz, $CDCl_3$) 3.90 (6H, s, 2 × OCH_3), 6.90 (1H, d, *J* 8.6 Hz, 5-H), 7.15 (1H, dd, *J* 8.6, 2.3 Hz, 6-H), 7.43 (2H, t, *J* 7.4 Hz, 3′-H and 5′-H), 7.48–7.52 (1H, m, 4′-H), 7.59 (1H, br s, 2-H), 7.85 (2H, d, *J* 7.4 Hz, 2′-H and 6′-H), 8.98 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 56.1 (CH_3), 56.1 (CH_3), 107.9 (CH), 111.0 (CH), 116.0 (CH), 126.7 (2 × CH), 128.7 (2 × CH), 131.2 (CH), 132.4 (C), 143.2 (C), 147.7 (C), 148.9 (C), 198.0 (C); *m/z* (ESI) 296.0715 (MNa^+. $C_{15}H_{15}NNaO_2S$ requires 296.0716).

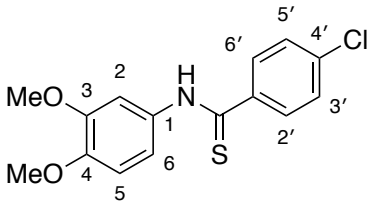
4′-Methoxy-*N*-(3,4-dimethoxyphenyl)thiobenzamide (235b)[554]



4′-Methoxy-*N*-(3,4-dimethoxyphenyl)thiobenzamide (**235b**) was synthesised as described for *N*-(3,4-dimethoxyphenyl)thiobenzamide (**235a**) using 4′-methoxy-*N*-(3,4-dimethoxyphenyl)benzamide (**234b**) (0.250 g, 0.870 mmol). Purification by flash column chromatography (dichloromethane) gave 4′-methoxy-*N*-(3,4-

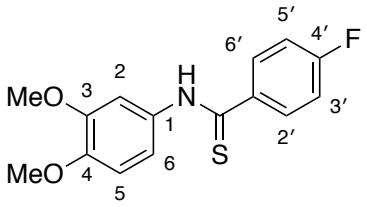
dimethoxyphenyl)thiobenzamide (**235b**) (0.244 g, 93%) as a yellow solid. Spectroscopic data were consistent with the literature.[554] Mp 155–157 °C; δ_H (500 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.91 (1H, d, *J* 7.8 Hz, 5-H), 6.94 (2H, d, *J* 8.2 Hz, 3′-H and 5′-H), 7.13 (1H, d, *J* 7.8 Hz, 6-H), 7.54 (1H, s, 2-H), 7.88 (2H, d, *J* 8.2 Hz, 2′-H and 6′-H), 8.96 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 55.5 (CH_3), 56.0 (2 × CH_3), 108.3 (CH), 111.0 (2 × CH), 113.8 (CH), 116.3 (CH), 128.6 (2 × CH), 132.6 (C), 135.3 (C), 147.6 (C), 148.9 (C), 162.3 (C), 197.1 (C); *m/z* (ESI) 326 (MNa^+. 100%).

4′-Chloro-*N*-(3,4-dimethoxyphenyl)thiobenzamide (235c)



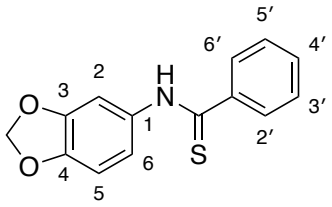
4′-Chloro-*N*-(3,4-dimethoxyphenyl)thiobenzamide (**235c**) was synthesised as described for *N*-(3,4-dimethoxyphenyl)thiobenzamide (**235a**) using 4′-chloro-*N*-(3,4-dimethoxyphenyl)benzamide (**234c**) (0.200 g, 0.690 mmol). Purification by flash column chromatography (hexane/diethyl ether, 1:1) gave 4′-chloro-*N*-(3,4-dimethoxyphenyl)thiobenzamide (**235c**) (0.141 g, 67%) as a yellow solid. Mp 159–161 °C; ν_{max}/cm^{-1} (neat) 3186 (NH), 2837 (CH), 1601, 1522, 1263, 1236, 1227, 1163, 1134, 1090, 1028, 1003, 833; δ_H (500 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.89 (1H, d, *J* 8.6 Hz, 5-H), 7.13 (1H, dd, *J* 8.6, 2.2 Hz, 6-H), 7.39 (2H, d, *J* 8.5 Hz, 3′-H and 5′-H), 7.53 (1H, d, *J* 2.2 Hz, 2-H), 7.78 (2H, d, *J* 8.5 Hz, 2′-H and 6′-H), 8.98 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 56.0 (CH_3), 56.1 (CH_3), 107.9 (CH), 111.0 (CH), 116.1 (CH), 128.0 (2 × CH), 128.8 (2 × CH), 132.2 (C), 137.5 (C), 141.3 (C), 147.8 (C), 148.9 (C), 196.4 (C); *m/z* (ESI) 330.0322 (MNa^+. $C_{15}H_{14}{}^{35}ClNNaO_2S$ requires 330.0326).

4′-Fluoro-*N*-(3,4-dimethoxyphenyl)thiobenzamide (235d)



4′-Fluoro-*N*-(3,4-dimethoxyphenyl)thiobenzamide (**235d**) was synthesised as described for *N*-(3,4-dimethoxyphenyl)thiobenzamide (**235a**) using 4′-fluoro-*N*-(3,4-dimethoxyphenyl)benzamide (**234l**) (0.269 g, 0.977 mmol) in toluene (30 mL) and tetrahydrofuran (10 mL). Purification by flash column chromatography (dichloromethane) gave 4′-fluoro-*N*-(3,4-dimethoxyphenyl)thiobenzamide (**235d**) (0.261 g, 94%) as a yellow solid. Mp 132–134 °C; ν_{max}/cm^{-1} (neat) 3289 (NH), 2936 (CH), 1599, 1464, 1261, 1227, 1157, 1132, 1022, 1001, 839, 723; δ_H (500 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.87 (1H, d, *J* 8.6 Hz, 5-H), 7.08 (2H, t, *J* 8.5 Hz, 3′-H and 5′-H), 7.12 (1H, dd, *J* 8.6, 2.2 Hz, 6-H), 7.49 (1H, d, *J* 2.2 Hz, 2-H), 7.80–7.88 (2H, m, 2′-H and 6′-H), 9.05 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 56.0 (CH_3), 56.0 (CH_3), 108.0 (CH), 110.9 (CH), 115.5 (2 × CH, d, $^2J_{CF}$ 21.8 Hz), 116.2 (CH), 129.0 (2 × CH, d, $^3J_{CF}$ 8.9 Hz), 132.3 (C), 139.1 (C, d, $^4J_{CF}$ 2.7 Hz), 147.7 (C), 148.9 (C), 164.5 (C, d, $^1J_{CF}$ 253.2 Hz), 196.5 (C); *m/z* (ESI) 314.0617 (MNa^+. $C_{15}H_{14}FNNaO_2S$ requires 314.0621).

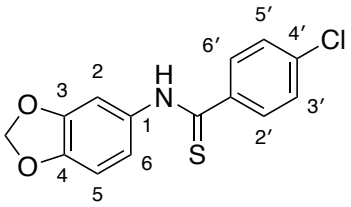
***N*-(3,4-Methylenedioxyphenyl)thiobenzamide (235e)**



N-(3,4-Methylenedioxyphenyl)thiobenzamide (**235e**) was synthesised as described for *N*-(3,4-dimethoxyphenyl)thiobenzamide (**235a**) using *N*-(3,4-methylenedioxyphenyl)benzamide (**234f**) (0.0975 g, 0.404 mmol) in toluene (20 mL) and tetrahydrofuran (2.0 mL). The crude residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 4:1) to give a yellow oil. Further purification by flash column chromatography (hexane/dichloromethane, 1:1) gave

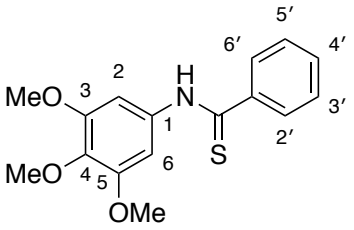
N-(3,4-methylenedioxyphenyl)thiobenzamide (**235e**) (0.0586 g, 56%) as a yellow crystalline solid. Mp 127–129 °C; ν_{max}/cm^{-1} (neat) 3204 (NH), 2893 (CH), 1501, 1485, 1447, 1346, 1248, 1227, 1190, 1036, 922, 731, 692; δ_H (500 MHz, $CDCl_3$) 6.01 (2H, s, OCH_2O), 6.83 (1H, d, *J* 8.3 Hz, 5-H), 6.99 (1H, dd, *J* 8.3, 1.8 Hz, 6-H), 7.37 (1H, d, *J* 1.8 Hz, 2-H), 7.42 (2H, t, *J* 7.4 Hz, 3′-H and 5′-H), 7.49 (1H, t, *J* 7.4 Hz, 4′-H), 7.82 (2H, d, *J* 7.4 Hz, 2′-H and 6′-H), 8.93 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 101.7 (CH_2), 106.1 (CH), 108.2 (CH), 117.7 (CH), 126.7 (2 × CH), 128.6 (2 × CH), 131.3 (CH), 133.1 (C), 142.8 (C), 146.4 (C), 147.8 (C), 198.6 (C); *m/z* (ESI) 280.0402 (MNa^+. $C_{14}H_{11}NNaO_2S$ requires 280.0403).

4′-Chloro-*N*-(3,4-methylenedioxyphenyl)thiobenzamide (235f)



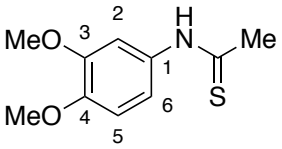
4′-Chloro-*N*-(3,4-methylenedioxyphenyl)thiobenzamide (**235f**) was synthesised as described for *N*-(3,4-dimethoxyphenyl)thiobenzamide (**235a**) using 4′-chloro-*N*-(3,4-methylenedioxyphenyl)benzamide (**234g**) (0.250 g, 0.907 mmol). Purification by flash column chromatography (dichloromethane/hexane, 3:2) gave 4′-chloro-*N*-(3,4-methylenedioxyphenyl)thiobenzamide (**235f**) (0.208 g, 79%) as a yellow solid. Mp 173–175 °C; ν_{max}/cm^{-1} (neat) 3167 (NH), 1587, 1504, 1489, 1400, 1256, 1227, 1088, 993, 837; δ_H (500 MHz, $CDCl_3$) 6.02 (2H, s, OCH_2O), 6.85 (1H, d, *J* 8.3 Hz, 5-H), 6.99 (1H, dd, *J* 8.3 Hz, 6-H), 7.36 (1H, s, 2-H), 7.40 (2H, d, *J* 8.5 Hz, 3′-H and 5′-H), 7.79 (2H, d, *J* 8.5 Hz, 2′-H and 6′-H), 8.86 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 101.8 (CH_2), 106.0 (CH), 108.2 (CH), 117.8 (CH), 128.1 (2 × CH), 128.8 (2 × CH), 132.9 (C), 137.6 (C), 141.0 (C), 146.5 (C), 147.9 (C), 197.0 (C); *m/z* (ESI) 314.0015 (MNa^+. $C_{14}H_{10}{}^{35}ClNNaO_2S$ requires 314.0013).

***N*-(3,4,5-Trimethoxyphenyl)thiobenzamide (235g)**



N-(3,4,5-Trimethoxyphenyl)thiobenzamide (**235g**) was synthesised as described for *N*-(3,4-dimethoxyphenyl)thiobenzamide (**235a**) using *N*-(3,4,5-trimethoxyphenyl)benzamide (0.300 g, 1.04 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 1:1) gave *N*-(3,4,5-trimethoxyphenyl)thiobenzamide (**235g**) (0.274 g, 87%) as a yellow solid. Mp 103–105 °C; ν_{max}/cm^{-1} (neat) 3202 (NH), 2936 (CH), 1597, 1499, 1447, 1329, 1233, 1117, 1003, 943; δ_H (500 MHz, $CDCl_3$) 3.84 (6H, s, 2 × OCH_3), 3.85 (3H, s, OCH_3), 7.15 (2H, s, 2-H and 6-H), 7.42 (2H, t, *J* 7.4 Hz, 3′-H and 5′-H), 7.50 (1H, t, *J* 7.4 Hz, 4′-H), 7.83 (2H, d, *J* 7.4 Hz, 2′-H and 6′-H), 9.13 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 56.2 (CH_3), 61.0 (2 × CH_3), 101.1 (2 × CH), 126.7 (2 × CH), 128.6 (2 × CH), 131.2 (CH), 135.0 (C), 136.4 (C), 143.3 (C), 153.2 (2 × C), 197.9 (C); *m/z* (ESI) 326.0816 (MNa^+. $C_{16}H_{17}NNaO_3S$ requires 326.0821*).*

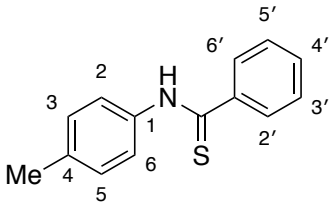
***N*-(3,4-Dimethoxyphenyl)thioacetamide (235h)**



N-(3,4-Dimethoxyphenyl)thioacetamide (**235h**) was synthesised as described for *N*-(3,4-dimethoxyphenyl)thiobenzamide (**235a**) using *N*-(3-methoxyphenyl)acetamide (**234m**) (0.200 g, 1.02 mmol). Purification by flash column chromatography (dichloromethane to dichloromethane/ethyl acetate, 9:1) gave *N*-(3,4-dimethoxyphenyl)thioacetamide (**235h**) (0.198 g, 92%) as a yellow solid. Mp 111–112 °C; ν_{max}/cm^{-1} (neat) 3285 (NH), 2934 (CH), 1603, 1512, 1462, 1375, 1261, 1234, 1171, 1132 (C=S), 1022. NMR spectra showed a 10:1 mixture of rotamers. Only signals for the major rotamer are recorded. δ_H (400 MHz, DMSO-d_6) 2.58 (3H, s, NHCSCH_3), 3.73 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 6.96 (1H, d, *J* 8.7 Hz, 5-H),

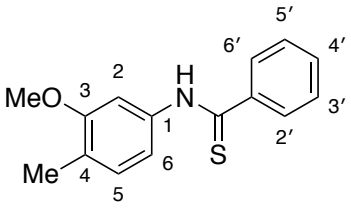
7.31 (1H, dd, *J* 8.7, 2.4 Hz, 6-H), 7.57 (1H, d, *J* 2.4 Hz, 2-H), 11.47 (1H, br s, NH); δ_C (101 MHz, DMSO-d_6) 35.5 (CH_3), 56.0 (CH_3), 56.1 (CH_3), 108.2 (CH), 111.8 (CH), 115.7 (CH), 133.5 (C), 147.1 (C), 148.5 (C), 198.4 (C); *m/z* (ESI) 234.0559 (MNa^+. $C_{10}H_{13}NNaO_2S$ requires 234.0559).

_N_-(4-Methylphenyl)thiobenzamide (235i)[555]



N-(4-Methylphenyl)thiobenzamide (**235i**) was synthesised as described for *N*-(3,4-dimethoxyphenyl)thiobenzamide (**235a**) using *N*-(4-methylphenyl)benzamide (**234k**) (0.500 g, 2.37 mmol). Purification by flash column chromatography (petroleum ether/dichloromethane, 1:1) gave *N*-(4-methylphenyl)thiobenzamide (**235i**) (0.293 g, 54%) as a yellow solid. Mp 116–118 °C (lit.[555] 116–117 °C); δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, 4-CH_3), 7.23–7.27 (2H, m, 3-H and 5-H), 7.40–7.55 (3H, m, 3′-H, 4′-H and 5′-H), 7.63 (2H, d, *J* 8.1 Hz, 2-H and 6-H), 7.85 (2H, d, *J* 7.4 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 21.2 (CH_3), 123.8 (2 × CH), 126.7 (2 × CH), 128.7 (2 × CH), 129.7 (2 × CH), 131.2 (CH), 136.5 (C), 137.1 (C), 143.2 (C), 198.4 (C); *m/z* (ESI) 250 (MNa^+. 100%).

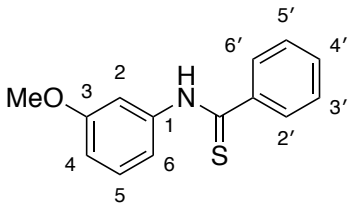
_N_-(3-Methoxy-4-methylphenyl)thiobenzamide (235j)



N-(3-Methoxy-4-methylphenyl)thiobenzamide (**235j**) was synthesised as described for *N*-(3,4-dimethoxyphenyl)thiobenzamide (**235a**) using *N*-(3-methoxy-4-methylphenyl)benzamide (**234h**) (0.297 g, 1.23 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave *N*-(3-methoxy-4-methylphenyl)thiobenzamide (**235j**) (0.253 g, 80%) as a yellow solid. Mp 135–137 °C ν_{max}/cm^{-1} (neat) 3215 (NH), 2957 (CH), 1599, 1508, 1447, 1358, 1263, 1159,

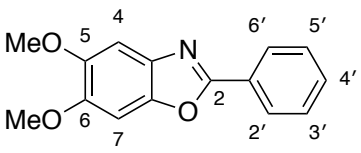
1128, 1038, 1005, 692; δ_H (500 MHz, $CDCl_3$) 2.23 (3H, s, 4-CH_3), 3.85 (3H, s, OCH_3), 7.03 (1H, d, *J* 7.8 Hz, 6-H), 7.16 (1H, d, *J* 7.8 Hz, 5-H), 7.43 (2H, t, *J* 7.5 Hz, 3′-H and 5′-H), 7.47–7.52 (1H, m, 4′-H), 7.63 (1H, s, 2-H), 7.84 (2H, d, *J* 7.5 Hz, 2′-H and 6′-H), 9.00 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 16.1 (CH_3), 55.5 (CH_3), 105.9 (CH), 115.1 (CH), 125.7 (C), 126.6 (2 × CH), 128.7 (2 × CH), 130.5 (CH), 131.2 (CH), 137.9 (C), 143.4 (C), 157.8 (C), 197.9 (C); *m/z* (ESI) 280.0763 (MNa^+. $C_{15}H_{15}NNaOS$ requires 280.0767).

_N_-(3-Methoxyphenyl)thiobenzamide (235k)[555]



N-(3-Methoxyphenyl)thiobenzamide (**235k**) was synthesised as described for *N*-(3,4-dimethoxyphenyl)thiobenzamide (**235a**) using *N*-(3-methoxyphenyl)benzamide (**234j**) (0.864 g, 3.80 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave a yellow oil. Further purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave *N*-(3-methoxyphenyl)thiobenzamide (**235k**) (0.764 g, 83%) as a yellow solid. Mp 75–77 °C (lit.[555] 79–80 °C); δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.84 (1H, d, *J* 6.9 Hz, 4-H), 7.16–7.54 (5H, m, Ph), 7.63 (1H, br s, 2-H), 7.75–7.88 (2H, m, 5-H and 6-H), 9.00 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 109.0 (CH), 112.8 (CH), 115.6 (2 × CH), 126.7 (CH), 128.7 (CH), 129.8 (2 × CH), 131.3 (CH), 140.2 (C), 143.4 (C), 160.1 (C), 198.3 (C); *m/z* (ESI) 266 (MNa^+. 100%).

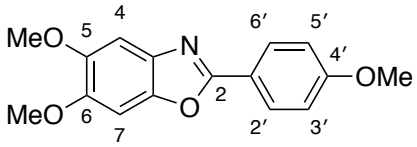
2-Phenyl-5,6-dimethoxy-1,3-benzoxazole (236a)[556]



Iron(III) chloride (1.62 mg, 0.0100 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (8.70 μL, 0.0300 mmol) and

stirred for 0.5 h at room temperature and then added to a suspension of *N*-bromosuccinimide (0.0360 g, 0.200 mmol) in toluene (0.5 mL). *N*-(3,4-dimethoxyphenyl)benzamide (**234a**) (0.0510 g, 0.200 mmol) in toluene (0.5 mL) and acetonitrile (0.2 mL) was then added and the mixture was stirred at 40 °C for 4 h. Upon completion of the bromination step, the reaction mixture was cooled to room temperature, diluted with toluene (1.0 mL) and cesium carbonate (0.130 g, 0.400 mmol), copper(I) iodide (3.80 mg, 0.0200 mmol), *N*,*N*′-dimethylethylenediamine (4.30 μL, 0.0400 mmol) and water (0.4 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 18 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine (30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate 7:3) gave 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (**236a**) (0.0286 g, 57%) as a white solid. Mp 109–112 °C (lit.[556] 114–115 °C); δ_H (400 MHz, $CDCl_3$) 3.95 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 7.13 (1H, s, 7-H), 7.25 (1H, s, 4-H), 7.48–7.52 (3H, m, 3′-H, 4′-H and 5′-H), 8.16–8.20 (2H, m, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 56.5 (CH_3), 56.5 (CH_3), 94.4 (CH), 101.8 (CH), 127.0 (2 × CH), 127.5 (C), 128.9 (2 × CH), 130.9 (CH), 135.0 (C), 145.2 (C), 147.8 (C), 148.4 (C), 162.3 (C); *m/z* (ESI) 278 (MNa^+. 100%).

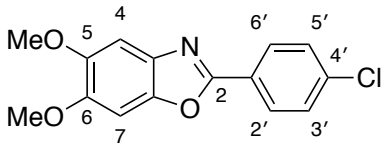
2-(4′-Methoxyphenyl)-5,6-dimethoxy-1,3-benzoxazole (236b)



2-(4′-Methoxyphenyl)-5,6-dimethoxy-1,3-benzoxazole (**236b**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (**236a**) using 4′-methoxy-*N*-(3,4-dimethoxyphenyl)benzamide (**234b**) (0.0574 g, 0.200 mmol) in toluene (1.0 mL) and acetonitrile (0.4 mL). The bromination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 48 h. Purification by flash column chromatography (hexane/ethyl acetate 4:1) gave 2-(4′-methoxyphenyl)-5,6-dimethoxy-1,3-benzoxazole (**236b**) (0.0297 g, 52%) as a light yellow solid. Mp 118–

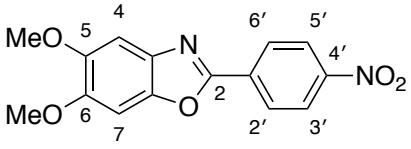
120 °C; ν_{max}/cm^{-1} (neat) 2928 (CH), 1605, 1481, 1250, 1219, 1128, 1057, 1018, 837; δ_H (500 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 7.01 (2H, d, *J* 8.9 Hz, 3′-H and 5′-H), 7.11 (1H, s, 7-H), 7.23 (1H, s, 4-H), 8.11 (2H, d, *J* 8.9 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 55.4 (CH_3), 56.4 (CH_3), 56.5 (CH_3), 94.3 (CH), 101.6 (CH), 114.3 (2 × CH), 120.1 (C), 128.7 (2 × CH), 135.0 (C), 145.0 (C), 147.6 (C), 148.0 (C), 161.8 (C), 162.4 (C); *m/z* (ESI) 308.0883 (MNa^+. $C_{16}H_{15}NNaO_4$ requires 308.0893).

2-(4′-Chlorophenyl)-5,6-dimethoxy-1,3-benzoxazole (236c)



2-(4′-Chlorophenyl)-5,6-dimethoxy-1,3-benzoxazole (**236c**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (**236a**) using 4′-chloro-*N*-(3,4-dimethoxyphenyl)benzamide (**234c**) (0.0582 g, 0.200 mmol) in toluene (1.0 mL) and acetonitrile (0.2 mL). The bromination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 48 h. Purification by flash column chromatography (hexane/ethyl acetate 7:3) gave 2-(4′-chlorophenyl)-5,6-dimethoxy-1,3-benzoxazole (**236c**) (0.0382 g, 66%) as a light yellow solid. Mp 160–161 °C; ν_{max}/cm^{-1} (neat) 2928 (CH), 1481, 1159, 1134, 1007, 883, 824; δ_H (500 MHz, $CDCl_3$) 3.95 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 7.11 (1H, s, 7-H), 7.23 (1H, s, 4-H), 7.46 (2H, d, *J* 8.7 Hz, 3′-H and 5′-H), 8.09 (2H, d, *J* 8.7 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 56.4 (CH_3), 56.5 (CH_3), 94.2 (CH), 101.7 (CH), 126.0 (C), 128.2 (2 × CH), 129.2 (2 × CH), 134.8 (C), 137.0 (C), 145.2 (C), 147.9 (C), 148.6 (C), 161.2 (C); *m/z* (ESI) 312.0391 (MNa^+. $C_{15}H_{12}{}^{35}ClNNaO_3$ requires 312.0398).

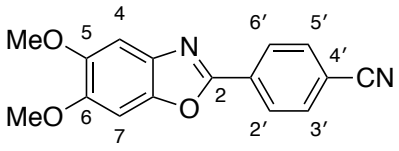
2-(4′-Nitrophenyl)-5,6-dimethoxy-1,3-benzoxazole (236d)



2-(4′-Nitrophenyl)-5,6-dimethoxy-1,3-benzoxazole (**236d**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (**236a**) using 4′-nitro-*N*-(3,4-

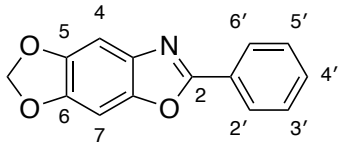
dimethoxyphenyl)benzamide (**234d**) (0.0605 g, 0.200 mmol) in toluene (2.0 mL) and acetonitrile (0.5 mL). The bromination step was carried out at 40 °C for 3 h and the *O*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (hexane/dichloromethane 4:1 to dichloromethane/ethyl acetate, 9:1) gave 2-(4′-nitrophenyl)-5,6-dimethoxy-1,3-benzoxazole (**236d**) (0.0209 g, 35%) as a yellow solid. Mp 210–212 °C; ν_{max}/cm^{-1} (neat) 2935 (CH), 1611, 1599, 1516, 1489, 1477, 1346, 1323, 1294, 1275, 1192, 1134, 1003, 856, 700; δ_H (400 MHz, $CDCl_3$) 3.90 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 7.09 (1H, s, 7-H), 7.20 (1H, s, 4-H), 8.24–8.32 (4H, m, 2′-H, 3′-H, 5′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 56.5 (CH_3), 56.6 (CH_3), 94.2 (CH), 101.8 (CH), 124.3 (2 × CH), 127.6 (2 × CH), 133.1 (C), 135.0 (C), 145.7 (C), 148.4 (C), 148.9 (C), 149.6 (C), 159.8 (C); *m/z* (ESI) 323.0633 (MNa^+. $C_{15}H_{12}N_2NaO_5$ requires 323.0638).

2-(4′-Cyanophenyl)-5,6-dimethoxy-1,3-benzoxazole (236e)



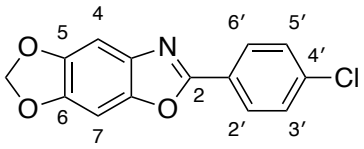
2-(4′-Cyanophenyl)-5,6-dimethoxy-1,3-benzoxazole (**236e**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (**236a**) using 4′-cyano-*N*-(3,4-dimethoxyphenyl)benzamide (**234e**) (0.0565 g, 0.200 mmol) in toluene (1.0 mL) and acetonitrile (1.0 mL). The bromination step was carried out at 40 °C for 4 h and the *O*-arylation step at 130 °C for 48 h. Purification by flash column chromatography (dichloromethane/ethyl acetate 19:1) gave 2-(4′-cyanophenyl)-5,6-dimethoxy-1,3-benzoxazole (**236e**) (0.0286 g, 51%) as a white solid. Mp 247–248 °C; ν_{max}/cm^{-1} (neat) 2968 (CH), 2220 (CN), 1481, 1329, 1273, 1192, 1161, 1134, 1003, 887, 839; δ_H (400 MHz, $CDCl_3$) 3.96 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 7.14 (1H, s, 7-H), 7.26 (1H, s, 4-H), 7.78 (2H, d, *J* 8.4 Hz, 3′-H and 5′-H), 8.26 (2H, d, *J* 8.4 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 56.5 (CH_3), 56.5 (CH_3), 94.2 (CH), 101.8 (CH), 113.9 (C), 118.3 (C), 127.2 (2 × CH), 131.4 (C), 132.7 (2 × CH), 134.9 (C), 145.5 (C), 148.3 (C), 149.4 (C), 160.1 (C); *m/z* (EI) 280.0860 (M^+. $C_{16}H_{12}N_2O_3$ requires 280.0848), 265 (62%), 237 (28), 130 (17), 109 (36), 81 (16).

2-Phenyl-5,6-methylenedioxy-1,3-benzoxazole (236f)[557]



2-Phenyl-5,6-methylenedioxy-1,3-benzoxazole (**236f**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (**236a**) using *N*-(3,4-methylenedioxyphenyl)benzamide (**234f**) (0.0513 g, 0.213 mmol) in toluene (1.6 mL) and tetrahydrofuran (0.4 mL). The bromination step was carried out at 40 °C for 3 h and the *O*-arylation step at 130 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 2-phenyl-5,6-methylenedioxy-1,3-benzoxazole (**236f**) (0.0351 g, 69%) as a white solid. Mp 142–143 °C; (lit.[557] 147–148 °C); δ_H (500 MHz, $CDCl_3$) 6.03 (2H, s, OCH_2O), 7.06 (1H, s, 7-H), 7.17 (1H, s, 4-H), 7.46–7.52 (3H, m, 3′-H, 4′-H and 5′-H), 8.12–8.18 (2H, m, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 92.6 (CH), 99.5 (CH), 101.7 (CH_2), 126.9 (2 × CH), 127.4 (C), 128.9 (2 × CH), 130.9 (CH), 136.1 (C), 145.7 (C), 145.8 (C), 146.4 (C), 162.6 (C); *m/z* (ESI) 262 (MNa^+. 100%).

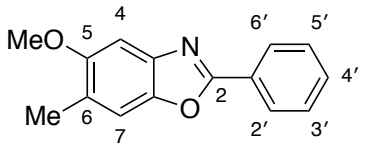
2-(4′-Chlorophenyl)-5,6-methylenedioxy-1,3-benzoxazole (236g)[458]



2-(4′-Chlorophenyl)-5,6-methylenedioxy-1,3-benzoxazole (**236g**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (**236a**) using 4′-chloro-*N*-(3,4-methylenedioxyphenyl)benzamide (**234g**) (0.0550 g, 0.200 mmol) in toluene (1.0 mL) and acetonitrile (1.0 mL). The bromination step was carried out at 40 °C for 3 h and the *O*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (dichloromethane/hexane, 7:3) gave 2-(4′-chlorophenyl)-5,6-methylenedioxy-1,3-benzoxazole (**236g**) (0.0412 g, 75%) as a white solid. Spectroscopic data were consistent with the literature.[458] Mp 252–254 °C; δ_H (500 MHz, DMSO-d_6) 6.13 (2H, s, OCH_2O), 7.36 (1H, s, 7-H), 7.49 (1H, s, 4-H), 7.65 (2H, d, *J* 8.6 Hz, 3′-H and 5′-H), 8.10 (2H, d, *J* 8.6 Hz, 2′-H and 6′-H); δ_C (126 MHz, DMSO-d_6) 93.5 (CH_2), 99.7 (CH), 102.4 (CH), 126.0 (C), 128.7 (2 × CH), 129.9 (2 ×

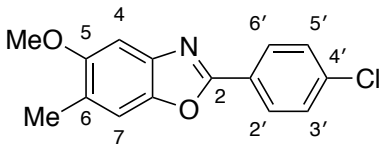
CH), 135.8 (C), 136.4 (C), 145.9 (C), 146.1 (C), 146.9 (C), 161.2 (C); *m/z* (EI) 273 (M^+. 100%).

2-Phenyl-5-methoxy-6-methyl-1,3-benzoxazole (236h)[558]



2-Phenyl-5-methoxy-6-methyl-1,3-benzoxazole (**236h**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (**236a**) using *N*-(3-methoxy-4-methylphenyl)benzamide (**234h**) (0.0680 g, 0.280 mmol) in toluene (1.8 mL) and acetonitrile (0.2 mL). The bromination step was carried out at 40 °C for 3 h and the *O*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (hexane/ethyl acetate 9:1) gave 2-phenyl-5-methoxy-6-methyl-1,3-benzoxazole (**236h**) (0.0416 g, 62%) as a white solid. Spectroscopic data were consistent with the literature.[558] Mp 137–138 °C; δ_H (500 MHz, $CDCl_3$) 2.34 (3H, s, 6-CH_3), 3.89 (3H, s, OCH_3), 7.18 (1H, s, 4-H), 7.33 (1H, s, 7-H), 7.47–7.53 (3H, m, 3′-H, 4′-H and 5′-H), 8.17–8.24 (2H, m, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 17.2 (CH_3), 55.8 (CH_3), 100.4 (CH), 111.6 (CH), 125.3 (C), 127.3 (2 × CH), 127.5 (C), 128.9 (2 × CH), 131.1 (CH), 140.7 (C), 145.0 (C), 155.7 (C), 162.7 (C); *m/z* (ESI) 262 (MNa^+. 100%).

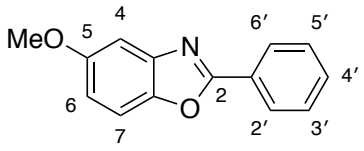
2-(4′-Chlorophenyl)-5-methoxy-6-methyl-1,3-benzoxazole (236i)



2-(4′-Chlorophenyl)-5-methoxy-6-methyl-1,3-benzoxazole (**236i**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (**236a**) using 4′-chloro-*N*-(3-methoxy-4-methylphenyl)benzamide (**234i**) (0.0700 g, 0.250 mmol) in toluene (2.5 mL) and tetrahydrofuran (1.0 mL). The bromination step was carried out at 40 °C for 3 h and the *O*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 2-(4′-chlorophenyl)-5-methoxy-6-methyl-1,3-benzoxazole (**236i**) (0.0502 g, 72%) as a white solid. Mp 141–143 °C; ν_{max}/cm^{-1} (neat) 2926 (CH), 1597, 1468, 1402, 1271, 1196, 1155, 1057, 826; δ_H

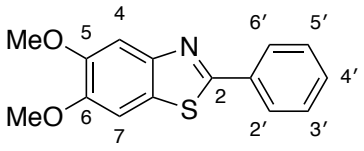
(400 MHz, $CDCl_3$) 2.33 (3H, s, 6-CH_3), 3.88 (3H, s, OCH_3), 7.15 (1H, s, 4-H), 7.30 (1H, s, 7-H), 7.44 (2H, d, *J* 8.8 Hz, 3′-H and 5′-H), 8.10 (2H, d, *J* 8.8 Hz, 2′-H and 6′-H); δ_C (101 MHz, $CDCl_3$) 17.2 (CH_3), 55.8 (CH_3), 100.4 (CH), 111.5 (CH), 125.7 (C), 126.0 (C), 128.5 (2 × CH), 129.2 (2 × CH), 137.2 (C), 140.6 (C), 145.0 (C), 155.8 (C), 161.7 (C); *m/z* (ESI) 296.0443 (MNa^+. $C_{15}H_{12}{}^{35}ClNNaO_2$ requires 296.0449).

2-Phenyl-5-methoxy-1,3-benzoxazole (236j)[557]



2-Phenyl-5-methoxy-1,3-benzoxazole (**236j**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (**236a**) using *N*-(3-methoxyphenyl)benzamide (**234j**) (0.0460 g, 0.200 mmol). The bromination step was carried out at 40 °C for 3 h and the *O*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (hexane/diethyl ether, 4:1) gave 2-phenyl-5-methoxy-1,3-benzoxazole (**236j**) (0.0150 g, 33%) as a white solid. Mp 75–77 °C (lit.[557] 79–80 °C); δ_H (500 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 6.95 (1H, dd, *J* 9.0, 2.6 Hz, 6-H), 7.27 (1H, d, *J* 2.6 Hz, 4-H), 7.46 (1H, d, *J* 9.0 Hz, 7-H), 7.49–7.55 (3H, m, 3′-H, 4′-H and 5′-H), 8.20–8.26 (2H, m, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 56.0 (CH_3), 102.9 (CH), 110.7 (CH), 113.7 (CH), 127.3 (C), 127.5 (2 × CH), 128.9 (2 × CH), 131.4 (CH), 143.0 (C), 145.4 (C), 157.4 (C), 163.8 (C); *m/z* (ESI) 248 (MNa^+. 100%).

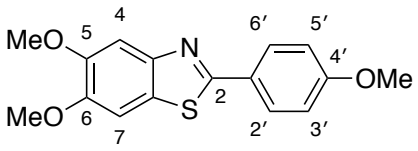
2-Phenyl-5,6-dimethoxy-1,3-benzothiazole (237a)[559]



Iron(III) chloride (2.20 mg, 0.0138 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (12.0 μL, 0.0412 mmol) and stirred for 0.5 h at room temperature and then added to a solution of *N*-bromosuccinimide (0.0538 g, 0.302 mmol) in acetonitrile (1.0 mL). *N*-(3,4-Dimethoxyphenyl)thiobenzamide (**235a**) (0.0751 g, 0.275 mmol) in acetonitrile (2.0

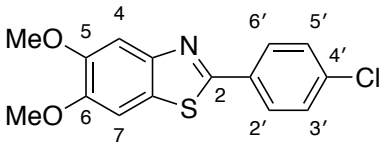
mL) was then added and the mixture was stirred at 40 °C for 2 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with 1 M aqueous sodium thiosulfate solution (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 9:1 to 4:1) then recrystallisation from hot acetonitrile gave 2-phenyl-5,6-dimethoxy-1,3-benzothiazole (**237a**) (0.0402 g, 54%) as a yellow crystalline solid. Mp 123–125 °C (from acetonitrile) (lit.[559] 127–129 °C); δ_H (500 MHz, $CDCl_3$) 3.97 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 7.31 (1H, s, 7-H), 7.43–7.50 (3H, m, 3′-H, 4′-H and 5′-H), 7.56 (1H, s, 4-H), 8.01–8.05 (2H, m, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 56.1 (CH_3), 56.3 (CH_3), 102.5 (CH), 104.8 (CH), 127.0 (2 × CH), 127.1 (C), 129.0 (2 × CH), 130.4 (CH), 133.8 (C), 148.5 (C), 148.6 (C), 149.5 (C), 166.3 (C); *m/z* (ESI) 272 (MH^+. 100%).

2-(4′-Methoxyphenyl)-5,6-dimethoxy-1,3-benzothiazole (237b)[554]



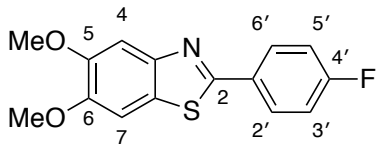
2-(4′-Methoxyphenyl)-5,6-dimethoxy-1,3-benzothiazole (**237b**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzothiazole (**237a**) using 4′-methoxy-*N*-(3,4-dimethoxyphenyl)thiobenzamide (**235b**) (0.0607 g, 0.200 mmol) in acetonitrile (2.6 mL) and dichloromethane (0.4 mL). The yellow precipitate was collected, washed with aqueous 1 M sodium thiosulfate solution (5 mL) and water (10 mL). Recrystallisation from hot acetonitrile gave 2-(4′-methoxyphenyl)-5,6-dimethoxy-1,3-benzothiazole (**237b**) (0.0330 g, 55%) as a yellow crystalline solid. Mp 163–165 °C (from acetonitrile) (lit.[554] 159–160 °C); δ_H (500 MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.98 (2H, d, *J* 8.9 Hz, 3′-H and 5′-H), 7.28 (1H, s, 7-H), 7.52 (1H, s, 4-H), 7.97 (2H, d, *J* 8.9 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 55.4 (CH_3), 56.1 (CH_3), 56.3 (CH_3), 102.6 (CH), 104.6 (CH), 114.3 (2 × CH), 126.7 (C), 126.7 (C), 128.5 (2 × CH), 148.3 (C), 148.6 (C), 149.4 (C), 161.5 (C), 166.2 (C); *m/z* (EI) 301 (M^+. 100%), 286 (30), 258 (16), 215 (12), 151 (9), 125 (7), 82 (8).

2-(4′-Chlorophenyl)-5,6-dimethoxy-1,3-benzothiazole (237c)



2-(4′-Chlorophenyl)-5,6-dimethoxy-1,3-benzothiazole (**237c**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzothiazole (**237a**) using 4′-chloro-*N*-(3,4-dimethoxyphenyl)thiobenzamide (**235c**) (0.0363 g, 0.120 mmol) in acetonitrile (2.0 mL) and dichloromethane (0.2 mL). Purification by flash column chromatography (hexane/ethyl acetate, 7:3), followed by recrystallisation from hot acetonitrile gave 2-(4′-chlorophenyl)-5,6-dimethoxy-1,3-benzothiazole (**237c**) (0.0214 g, 59%) as a white crystalline solid. Mp 194–196 °C (from acetonitrile); ν_{max}/cm^{-1} (neat) 2959 (CH), 1510, 1466, 1433, 1290, 1244, 1221, 1161, 1001, 835; δ_H (500 MHz, $CDCl_3$) 3.97 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 7.29 (1H, s, 7-H), 7.44 (2H, d, *J* 8.5 Hz, 3′-H and 5′-H), 7.53 (1H, s, 4-H), 7.95 (2H, d, *J* 8.5 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 56.1 (CH_3), 56.3 (CH_3), 102.4 (CH), 104.7 (CH), 127.1 (C), 128.2 (2 × CH), 129.2 (2 × CH), 132.4 (C), 136.4 (C), 148.5 (C), 148.8 (C), 149.6 (C), 164.7 (C); *m/z* (ESI) 328.0158 (MNa^+. $C_{15}H_{12}{}^{35}ClNNaO_2S$ requires 328.0169).

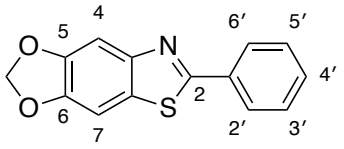
2-(4′-Fluorophenyl)-5,6-dimethoxy-1,3-benzothiazole (237d)



2-(4′-Fluorophenyl)-5,6-dimethoxy-1,3-benzothiazole (**237d**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzothiazole (**237a**) using 4′-fluoro-*N*-(3,4-dimethoxyphenyl)thiobenzamide (**235d**) (0.0583 g, 0.200 mmol). Purification by flash column chromatography (dichloromethane/hexane, 9:3 to dichloromethane), followed by recrystallisation from hot acetonitrile gave 2-(4′-fluorophenyl)-5,6-dimethoxy-1,3-benzothiazole (**237d**) (0.0317 g, 55%) as a white crystalline solid. Mp 146–148 °C (from acetonitrile); ν_{max}/cm^{-1} (neat) 2936 (CH), 1520, 1468, 1435, 1285, 1219, 1155, 999, 837; δ_H (500 MHz, $CDCl_3$) 3.98 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 7.16 (2H, t, *J* 8.6 Hz, 3′-H and 5′-H), 7.30 (1H, s, 7-H), 7.54 (1H, s, 4-H), 7.98–8.05 (2H, m, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 56.1 (CH_3), 56.4 (CH_3), 102.5 (CH),

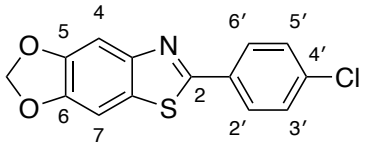
104.7 (CH), 116.1 (2 × CH, d, $^{2}J_{CF}$ 22.2 Hz), 127.1 (C), 128.9 (2 × CH, d, $^{3}J_{CF}$ 8.8 Hz), 130.2 (C, d, $^{4}J_{CF}$ 3.4 Hz), 148.5 (C), 148.7 (C), 149.6 (C), 164.1 (C, d, $^{1}J_{CF}$ 252.0 Hz), 165.0 (C); *m/z* (ESI) 312.0461 (MNa^{+}. $C_{15}H_{12}FNNaO_2S$ requires 312.0465).

2-Phenyl-5,6-methylenedioxy-1,3-benzothiazole (237e)



2-Phenyl-5,6-methylenedioxy-1,3-benzothiazole (**237e**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzothiazole (**237a**) using *N*-(3,4-methylenedioxyphenyl)thiobenzamide (**235e**) (0.0315 g, 0.122 mmol). Purification by flash column chromatography (hexane/diethyl ether, 9:1) gave 2-phenyl-5,6-methylenedioxy-1,3-benzothiazole (**237e**) (0.0148 g, 47%) as a white solid. Mp 160–161 °C; ν_{max}/cm^{-1} (neat) 2924 (CH), 1456, 1441, 1279, 1190, 1043, 945, 876, 833, 756; δ_H (500 MHz, $CDCl_3$) 5.98 (2H, s, OCH_2O), 7.17 (1H, s, 7-H), 7.36–7.42 (4H, m, 4-H, 3′-H, 4′-H and 5′-H), 7.91–7.95 (2H, m, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 100.2 (CH), 101.8 (CH_2), 102.7 (CH), 127.0 (2 × CH), 128.3 (C), 129.0 (2 × CH), 130.4 (CH), 133.8 (C), 146.9 (C), 148.0 (C), 149.3 (C), 166.4 (C); *m/z* (ESI) 256.0428 (MH^{+}. $C_{14}H_{10}NO_2S$ requires 256.0427).

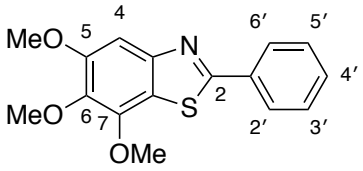
2-(4′-Chlorophenyl)-5,6-methylenedioxy-1,3-benzothiazole (237f)



2-(4′-Chlorophenyl)-5,6-methylenedioxy-1,3-benzothiazole (**237f**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzothiazole (**237a**) using 4′-chloro-*N*-(3,4-methylenedioxyphenyl)thiobenzamide (**235f**) (0.0425 g, 0.146 mmol) in acetonitrile (2.0 mL) and dichloromethane (0.5 mL). Purification by flash column chromatography (dichloromethane/hexane, 7:3) gave 2-(4′-chlorophenyl)-5,6-methylenedioxy-1,3-benzothiazole (**237f**) (0.0274 g, 65%) as a white solid. Mp 220–222 °C; ν_{max}/cm^{-1} (neat) 2897 (CH), 1506, 1456, 1285, 1090, 941, 878, 833, 824;

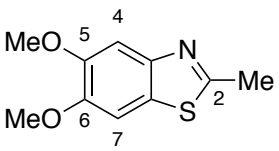
δ_H (500 MHz, $CDCl_3$) 6.07 (2H, s, OCH_2O), 7.25 (1H, s, 7-H), 7.44 (2H, d, *J* 8.6 Hz, 3′-H and 5′-H), 7.46 (1H, s, 4-H), 7.94 (2H, d, *J* 8.6 Hz, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 100.2 (CH), 101.9 (CH_2), 102.7 (CH), 128.1 (2 × CH), 128.3 (C), 129.2 (2 × CH), 132.3 (C), 136.4 (C), 147.1 (C), 148.2 (C), 149.2 (C), 164.9 (C); *m/z* (ESI) 311.9851 (MNa^+. $C_{14}H_8{}^{35}ClNNaO_2S$ requires 311.9856).

2-Phenyl-5,6,7-trimethoxy-1,3-benzothiazole (237g)[559]



2-Phenyl-5,6,7-trimethoxy-1,3-benzothiazole (**237g**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzothiazole (**237a**) using *N*-(3,4,5-trimethoxyphenyl)thiobenzamide (**235g**) (0.0440 g, 0.145 mmol). Purification by flash column chromatography (dichloromethane/hexane, 7:3 to 9:1) gave 2-phenyl-5,6,7-trimethoxy-1,3-benzothiazole (**237g**) (0.0156 g, 36%) as a white solid. Mp 65–67 °C (lit.[559] 61–63 °C); δ_H (500 MHz, $CDCl_3$) 3.94 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.11 (3H, s, OCH_3), 7.36 (1H, s, 4-H), 7.45–7.51 (3H, m, 3′-H, 4′-H and 5′-H), 8.02–8.07 (2H, m, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 56.3 (CH_3), 60.6 (CH_3), 61.5 (CH_3), 100.8 (CH), 120.3 (C), 127.2 (2 × CH), 129.0 (2 × CH), 130.7 (CH), 133.7 (C), 139.8 (C), 146.8 (C), 150.5 (C), 154.0 (C), 168.0 (C); *m/z* (ESI) 324 (MNa^+. 100%).

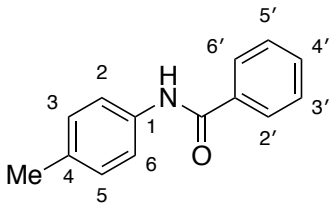
2-Methyl-5,6-dimethoxy-1,3-benzothiazole (237h)



2-Methyl-5,6-dimethoxy-1,3-benzothiazole (**237h**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzothiazole (**237a**) using *N*-(3,4-dimethoxyphenyl)thioacetamide (**235h**) (0.0423 g, 0.200 mmol). Purification by flash column chromatography (dichloromethane/ethyl acetate, 9:1) gave 2-methyl-5,6-dimethoxy-1,3-benzothiazole (**237h**) (0.00710 g, 17%) as a light yellow oil. ν_{max}/cm^{-1}

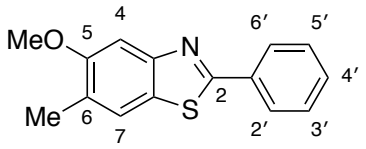
(neat) 2938 (CH), 1479, 1464, 1285, 1223, 1200, 1159, 1061, 831; δ_H (500 MHz, $CDCl_3$) 2.79 (3H, s, 2-CH_3), 3.94 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 7.24 (1H, s, 7-H), 7.44 (1H, s, 4-H); δ_C (126 MHz, $CDCl_3$) 19.9 (CH_3), 56.1 (CH_3), 56.3 (CH_3), 102.5 (CH), 104.3 (CH), 127.2 (C), 147.6 (C), 148.1 (C), 149.1 (C), 165.0 (C); *m/z* (ESI) 210.0587 (MH^+. $C_{10}H_{12}NO_2S$ requires 210.0583).

_N_-(4-methylphenyl)benzamide (234k)



Iron(III) chloride (0.810 mg, 0.00500 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (4.40 μL, 0.0150 mmol) and stirred for 0.5 h at room temperature and then added to a solution of *N*-bromosuccinimide (0.0178 g, 0.100 mmol) in dichloromethane (1.0 mL). *N*-(4-methylphenyl)thiobenzamide (**235i**) (0.0227 g, 0.100 mmol) in dichloromethane (2.0 mL) was then added and the mixture was stirred at 40 °C for 2 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with 1 M aqueous sodium thiosulfate solution (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was filtered through a short pad of silica, eluting with petroleum ether/ethyl acetate, 7:3, to give *N*-(4-methylphenyl)benzamide (**235i**) (0.0140 g, 67%) as a white solid. Mp 154–156 °C (lit. 155–156 °C); δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, 4-CH_3), 7.17 (2H, d, J 8.0 Hz, 3-H and 5-H), 7.44–7.60 (5H, m, Ph), 7.80 (1H, br s, NH), 7.86 (2H, d, J 8.0 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 20.9 (CH_3), 120.5 (2 × CH), 127.1 (2 × CH), 128.6 (2 × CH), 129.5 (2 × CH), 131.6 (CH), 134.1 (C), 135.0 (C), 135.4 (C), 165.9 (C); *m/z* (ESI) 234 (MNa^+. 100%).

2-Phenyl-5-methoxy-6-methyl-1,3-benzothiazole (237i)



2-Phenyl-5-methoxy-6-methyl-1,3-benzothiazole (**237i**) was synthesised as described for 2-phenyl-5,6-dimethoxy-1,3-benzothiazole (**237a**) using *N*-(3-methoxy-4-methylphenyl)thiobenzamide (**235j**) (0.0646 g, 0.250 mmol). Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave 2-phenyl-5-methoxy-6-methyl-1,3-benzothiazole (**237i**) (0.0238 g, 37%) as a yellow solid. Mp 156–157 °C; ν_{max}/cm^{-1} (neat) 3001, 2970 (CH), 1456, 1445, 1279, 1244, 1186, 1150, 1063, 1007, 997, 826, 760, 687; δ_H (500 MHz, $CDCl_3$) 2.34 (3H, s, 6-CH_3), 3.93 (3H, s, OCH_3), 7.44–7.50 (3H, m, 3′-H, 4′-H and 5′-H), 7.51 (1H, s, 4-H), 7.60 (1H, s, 7-H), 8.03–8.08 (2H, m, 2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 16.9 (CH_3), 55.6 (CH_3), 103.4 (CH), 121.9 (CH), 126.4 (C), 126.4 (C), 127.2 (2 × CH), 129.0 (2 × CH), 130.6 (CH), 133.9 (C), 153.7 (C), 157.5 (C), 167.7 (C); *m/z* (ESI) 256.0788 (MH^+. $C_{15}H_{14}NOS$ requires 256.0791).

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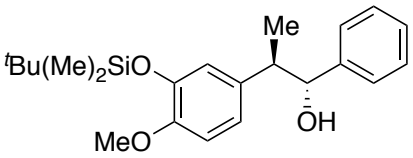
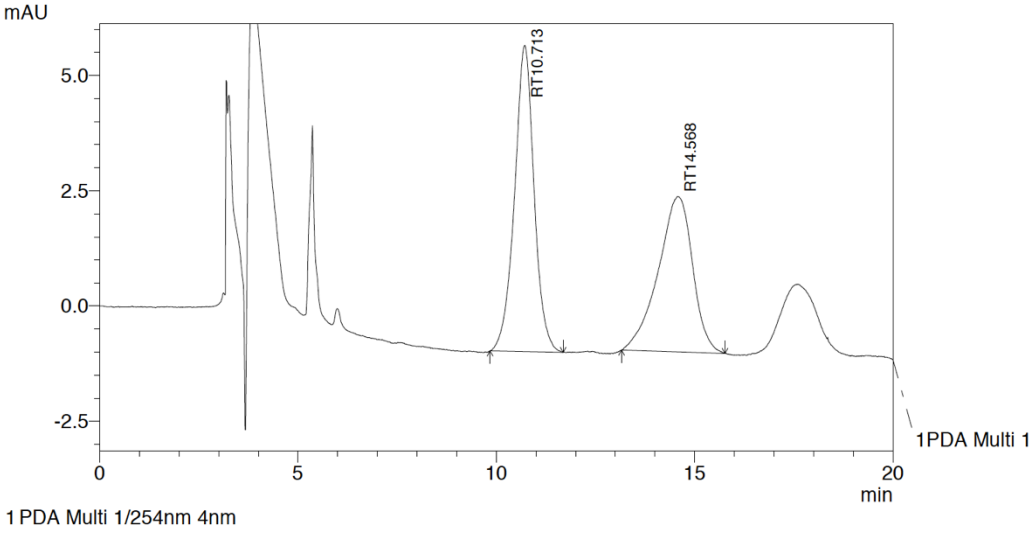
Appendix: Chiral and Racemic HPLC Traces for (1′*R*,2′*R*)-1′-(3-*tert*-Butyldimethylsilyloxy-4-methoxyphenyl)-1′-methyl-2′-phenylethan-2′-ol (168)

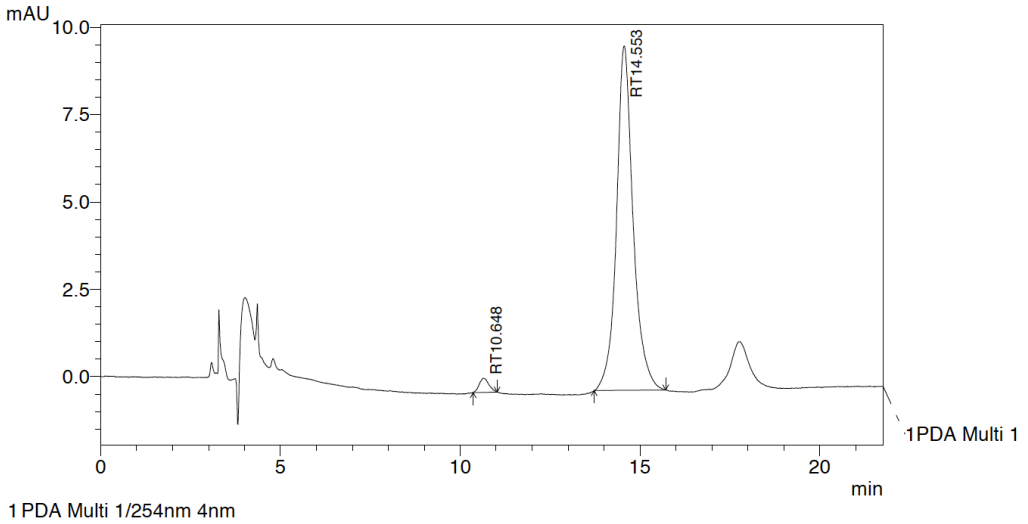


Racemate:



Peak	Retention Time	Area (uAUmin × 100)	Area %
1	10.713	228262	52.877
2	14.568	203425	47.123

Enantioselective:



Peak	Retention Time	Area (uAUmin × 100)	Area %
1	10.648	7580	2.330
2	14.553	317714	97.670