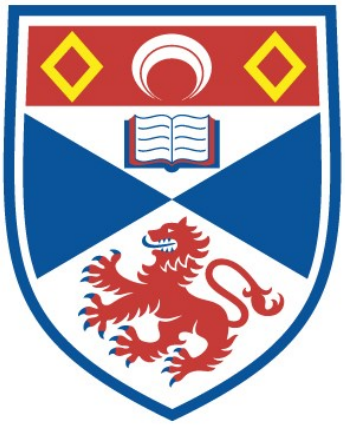
DEVELOPMENT OF A BMIDA LAROCK REACTION AND ITS APPLICATION IN TOTAL SYNTHESIS

George Edward Bell

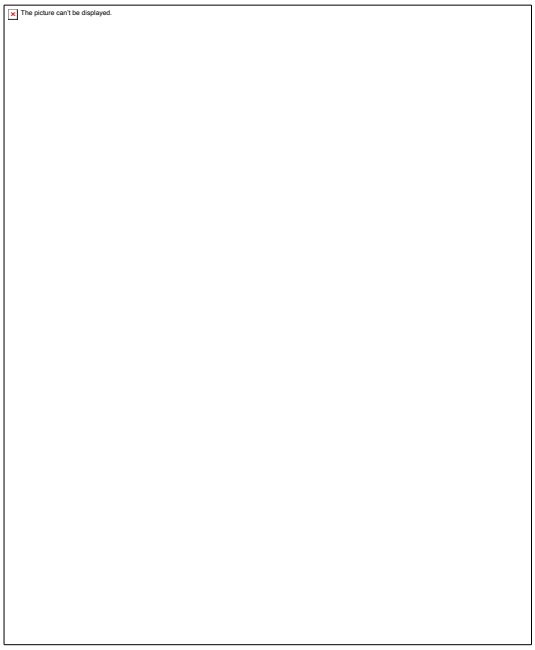
A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



2023

Development of a BMIDA Larock Reaction and its Application in Total Synthesis.

George Edward Bell



This thesis is submitted in partial fulfilment for the degree of

Doctor of Philosophy (PhD)

at the University of St Andrews

May 2022

Candidate's declaration

I, George Bell, do hereby certify that this thesis, submitted for the degree of PhD, which is approximately 43,600 words in length, has been written by me, and that it is the record of work carried out by me, or principally by myself in collaboration with others as acknowledged, and that it has not been submitted in any previous application for any degree. I confirm that any appendices included in my thesis contain only material permitted by the 'Assessment of Postgraduate Research Students' policy.

I was admitted as a research student at the University of St Andrews in January 2018.

I, George Bell, received assistance in the writing of this thesis in respect of grammar and syntax, which was provided by Jamie Fyfe, Liam McLean, Claire Young, Matthew Adams, Matthew Ashford, Kane Bastick.

I received funding from an organisation or institution and have acknowledged the funder(s) in the full text of my thesis.

Date 12/5/23 Signature of candidate

Supervisor's declaration

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of PhD in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree. I confirm that any appendices included in the thesis contain only material permitted by the 'Assessment of Postgraduate Research Students' policy.

Date 12/5/23 Signature of supervisor

Permission for publication

In submitting this thesis to the University of St Andrews we understand that we are giving permission for it to be made available for use in accordance with the regulations of the

University Library for the time being in force, subject to any copyright vested in the work not being affected thereby. We also understand, unless exempt by an award of an embargo as requested below, that the title and the abstract will be published, and that a copy of the work may be made and supplied to any bona fide library or research worker, that this thesis will be electronically accessible for personal or research use and that the library has the right to migrate this thesis into new electronic forms as required to ensure continued access to the thesis.

I, George Bell, confirm that my thesis does not contain any third-party material that requires copyright clearance.

The following is an agreed request by candidate and supervisor regarding the publication of this thesis:

Printed copy

No embargo on print copy.

Electronic copy

No embargo on electronic copy.

Date 12/5/23 Signature of candidate

Date 12/5/23 Signature of supervisor

Underpinning Research Data or Digital Outputs

Candidate's declaration

I, George Bell, understand that by declaring that I have original research data or digital outputs, I should make every effort in meeting the University's and research funders' requirements on the deposit and sharing of research data or research digital outputs.

Date 12/5/23 Signature of candidate

Permission for publication of underpinning research data or digital outputs

We understand that for any original research data or digital outputs which are deposited, we are giving permission for them to be made available for use in accordance with the requirements of the University and research funders, for the time being in force.

We also understand that the title and the description will be published, and that the underpinning research data or digital outputs will be electronically accessible for use in accordance with the license specified at the point of deposit, unless exempt by award of an embargo as requested below.

The following is an agreed request by candidate and supervisor regarding the publication of underpinning research data or digital outputs:

No embargo on underpinning research data or digital outputs.

Date 12/5/23 Signature of candidate

Date 12/5/23 Signature of supervisor

Publication list

- Synthesis of 2-BMIDA Indoles via Heteroannulation: Applications in Drug Scaffold and Natural Product Synthesis. G. E. Bell, J. W. B. Fyfe, E. M. Israel, A. M. Z. Slawin, M. Campbell, and A. J. B. Watson. *Org. Lett.* 2022, 24, 16, 3024–3027, doi.org/10.1021/acs.orglett.2c00959.

Acknowledgements

I would like to thank first and foremost my supervisor, Prof. Allan Watson, for his unending patience and help in this project and aid in overcoming difficulties both chemical and personal. Despite all the hurdles that my time at St Andrews and Strathclyde brought up, he always offered sound advice and direction.

In roughly chronological order, the OG Strathclyde Crew: Dr. Chao Xu and Dr John Molloy for their help and expertise at the start of my PhD which helped me find my feet in the lab. Dr Matt West, Dr Eilidh Sood, Dr David Cain who together formed an incredibly morale-boosting atmosphere conducive to happy and productive work and were sorely missed when they graduated. Dr Matthew 'Mash' Coles and I started our PhD on the same day and have held a special bond since. We have had countless conversations both about chemistry and whatever controversial hill he decided to die on that day. His assistance in both chemistry and matters outside the lab really kept me going when I felt I couldn't, so I thank him for that.

I would like to thank Dr Jamie Fyfe for his help on the Larock project, particularly in carrying out reactions to add to the substrate scope as well as demonstrating that these Larock products (sometimes) behaved as expected and could be further cross-coupled. I also thank Dr Liam McLean with his indispensable gym chat and car maintenance tips.

I would like to thank other postdocs, both past and present: Dr Nicola Bell (no relation), Dr Monica Gill, Dr Aitor Maestro, the click reaction Maestro, and Dr Matthew Andrews for our conversations about cars and copper and his useful skillset of, and expertise in, inorganic chemistry.

Current members of the group: Eva Israel and Jeremy Brals, with their loud music and useful French phrases/expletives, which I'm sure will serve me well should I ever feel the urge to visit France or much of Sub-Saharan Africa (the latter is more likely) and their camaraderie and jovial manner always lightened up a dark day. The Chemistry by Design dream team: Prof. John McGuff and his incredibly insightful ideas and help around organic chemistry with wisdom beyond his years, and Kane 'Mr Bombastik' Bastik with his wee feet and love of lithiation/borylation chemistry. Grumpy old man Tim Hilton and his dilapidated Volvo kept my brain ticking over with his stereochemistry issues. Marek 'Czech out this NMR' Varga, to whom I pass on the baton of alkyne BMIDA chemistry, good luck and may it serve you well.

Reece, Nikki and Callum from the CPJ group and I shared lab-space for some months and this time was great fun, with music that was much easier on the ears than in lab 336. It was interesting to work alongside people who work in a different subfield of organic chemistry and the knowledge they possessed and shared undoubtedly helped me in my area of chemistry.

I would like to thank members of the Prof. Andrew Smith group for letting me borrow the equivalent of a small nation's GDP in chemicals over the years.

Prof. Alex Slawin was always cheerful, keen to chat and have a look at my crystals and promptly returned a resolved structure, and each of these structures greatly assisted my project and will feature in this thesis and I thank her immensely for that. Thank you to Dr Tom Lebl and Dr Siobhan Smith for their help running the NMR facilities here in St Andrews and answering the many questions I had regarding the theory behind NMR.

Thank you to Dr. Matthew Campbell at GSK and GSK for the funding for my studentship. Although we never met in person and the placement at GSK was never came to fruition, it was always good to chat to you about my project over Skype and let you know how things were coming along.

Last but by no means least, I would like to thank my family. Without the support and encouragement of each of you, I would not be where I am today. Mum and dad, I am sorry I could not study somewhere closer to home so I couldn't see you as often as I would have liked. Emily and Alice, thank you for being so reassuring and supportive and believing in me when I didn't believe in myself.

Abstract

Indoles are ubiquitous in natural products and in pharmaceuticals. Methods for their synthesis range from the classic Fischer synthesis to more modern, transition metal-catalysed reactions. One such method of indole synthesis is the Larock reaction, where a 2-haloaniline (usually iodoaniline, although recently, Larock reactions using bromo- and chloro-anilines have been disclosed) reacts with an internal alkyne, in the presence of Pd catalyst and a base (a chloride additive is often beneficial) to give a 2,3-disubtituted indole. A key feature of the Larock indole synthesis is its excellent regioselectivity, if one of the groups on the alkyne is larger than the other.

Work in this thesis concerns the Larock reaction of 2-iodoanilines and borylated alkynes to form 2,3-difunctionalised indoles bearing a useful synthetic linchpin, *N*-methyliminodiacetic acid boronic ester (BMIDA), at the 2-position. The second chapter of this thesis concerns the optimisation of this so-called BMIDA Larock reaction on a model substrate. These optimised conditions would be used to create a variety of indoles bearing varied functionality about the benzenoid core of the indole and at the C-3 of the indole, all with a BMIDA group at C-2 which is amenable to Suzuki-Miyaura cross-coupling. It was found that two sets of conditions would be required depending on whether the carbon attached to the C-3 of the indole product would be sp^2 or sp^3. It was discovered that the relatively bulky BMIDA group was large enough to leverage the regioselectivity of the Larock reaction, resulting in the BMIDA group being reliably placed at the C-2 of the indole products.

The third chapter involves using this developed methodology in the total synthesis of indole alkaloids. Initially, three alkaloids were targeted, each of which were proposed to be made in just several steps from a common intermediate. However, two of these failed due to the inability to form a macrocycle in one, and unexpected reactivity during a ring-closing step in the other. The third alkaloid, Goniomitine, was successfully synthesised.

Table of contents

Abbreviations

Ac – acetyl

Ad – adamantane

AIBN – azabis-*iso*-butyronitrile

Alkyne BMIDA – Alk-1-ynyl-1-boronic acid *N*-methyliminodiacetic acid ester

atm – atmospheres of pressure

BMIDA – boron *N*-methyliminodiacetic acid ester

Boc – *tert*-butyloxycarbonyl

BuLi – butyllithium

BQ – benzoquinone

br – broad

Bz – benzoyl

CAN – cerium ammonium nitrate

Cbz – carboxybenzyl

Cy – cyclohexyl

DABCO – 1,4-diazabicyclo[2.2.2]octane

DIPEA – di-*iso*-propylethylamine

DMA – dimethylacetamide

DMF – dimethylformamide

DMP – Dess-Martin periodinane

DPPF – diphenylphosphinoferrocene

D^{t}BPF – 1,1′-bis(di-*tert*-butylphosphino)ferrocene

D^{t}BMP – 2,6-di-*tert*-butyl-4-methyl pyridine.

Et – ethyl

FIS – Fischer indole synthesis

Gluc – glucose

h – hour(s)

LDA – lithium di-*iso*-propylamide

LG – leaving group

LSD – lysergic acid diethylamide

Me – methyl

MeCN – acetonitrile

MIDA – *N*-methyliminodiacetic acid

min – minute(s)

μW – microwave(s)

n.d. – none detected

NBS – *N*-bromosuccinimide

NHC – *N*-heterocyclic carbene

NMP – *N*-methyl-2-pyrrolidinone

NSAID – non-steroidal, anti-inflammatory drug

Piv – pivalate

PPA – polyphosphoric acid

PG – protecting group

Ph – phenyl

Pr – propyl

Quant. – quantitative

r.r. – regioisomeric ratio

rt – room temperature

SAR – structure activity relationship

TBAB – tetra-*n*-butylammonium bromide

TBS – *tert*-butyldimethylsilyl

TES – triethylsilyl

Tf – trifluoromethanesulphonyl

TFA – trifluoroacetic acid

THP – tetrahydropyran

TMEDA – tetramethylethylenediamine

TMP – 2,2,6,6-tetramethylpiperidine

TMS – trimethylsilyl

TMSE – trimethylsilylethanol

Ts – tosyl

Chapter One: Development and Optimisation of a BMIDA Larock Protocol: Introduction.

Compounds in this section will be labelled 1.1, 1.2, 1.3…1.*x*

1. Introduction

1.1. Prevalence of Indoles in Nature and Pharmaceuticals

Indoles are one of the most common heterocycles encountered in nature. More than 10,000 biologically active, indole-containing compounds have been discovered, and some 200 marketed drugs contain an indole.[1]

The indole-containing amino acid tryptophan is essential in humans and is the biosynthetic precursor to many other biologically important molecules such as melatonin and serotonin (Figure 1A).[2]

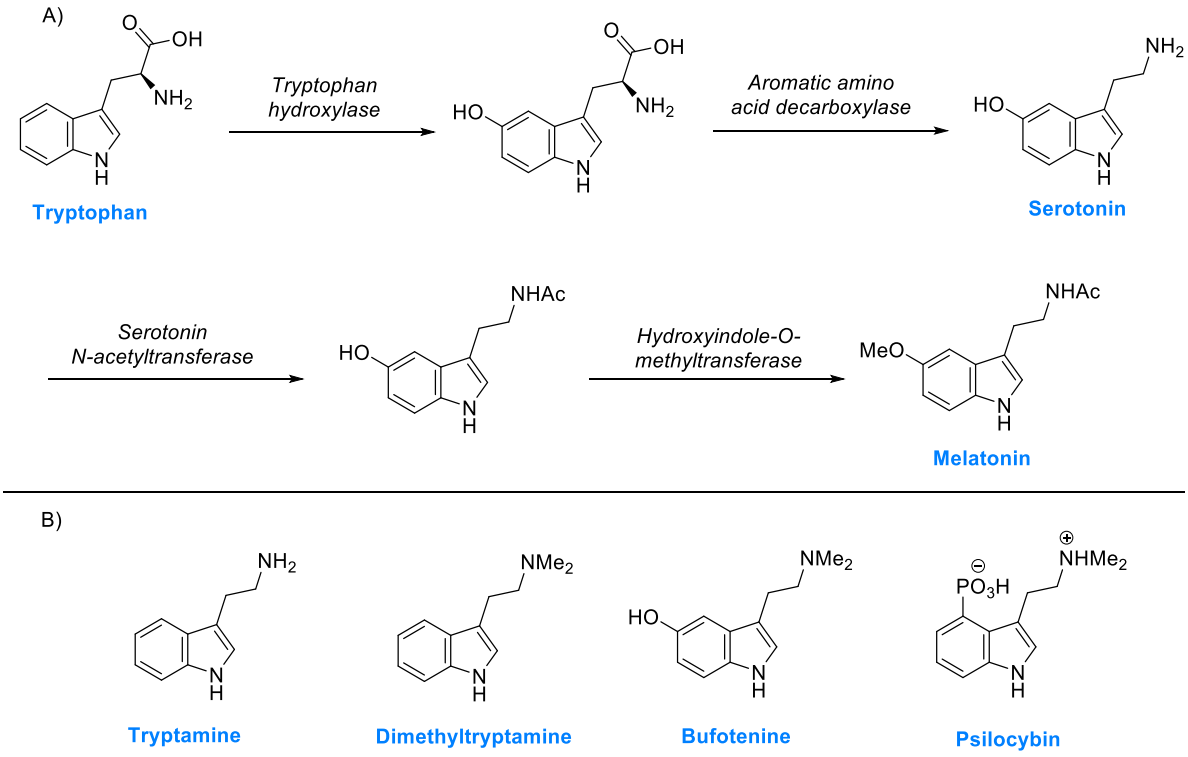


Figure 1: A) Biosynthesis of serotonin and melatonin. B) examples of simple bioactive indole alkaloids.

Melatonin plays a key role in the human circadian rhythm as well as affecting bone growth and immune system modulation,[3] and serotonin is responsible for mood, appetite and, alongside melatonin, sleep regulation.[4] Tryptamine derivatives dimethyltryptamine, bufotenine and psilocybin are well known for their psychoactive properties (Figure 1B).[5]

There are many examples of larger, more complex natural products which contain an indole and many of these have biological effects in humans, several examples are shown below (Figure 2).

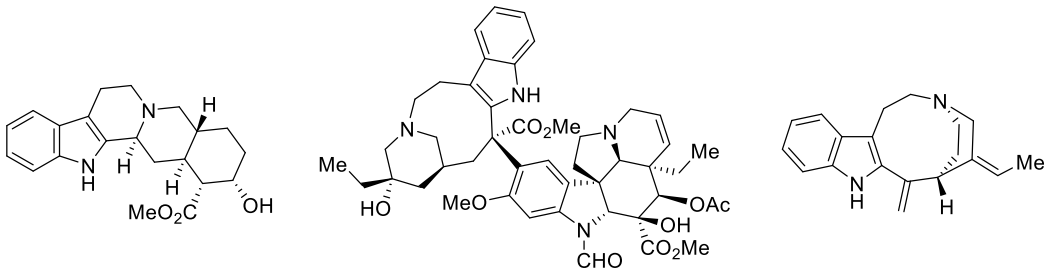
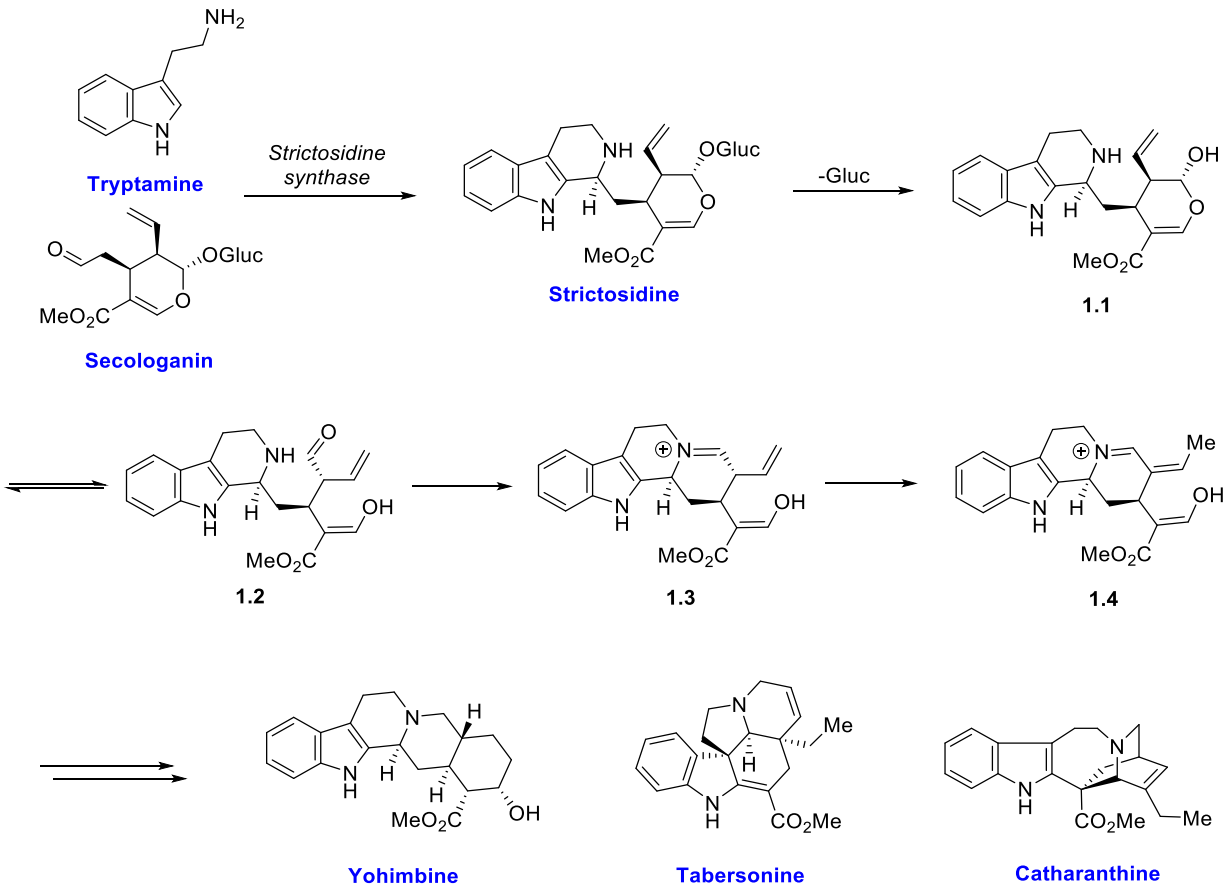


Figure 2: Complex indoles with biological effects.

Yohimbine is an indole-containing pentacycle and has been used in traditional medicine but more recently has been put forward as a potential treatment for male impotence.[6] Vincristine is used in the treatment of various cancers but is particularly effective against leukaemia and acts by inhibiting microtubule formation, ultimately preventing mitosis in cells.[7] Pericine is extracted from the bark of the tree *Aspidosperma subincanum* and has exhibited cytotoxic effects against lymphoma in mouse cells as well as human skin cancer cells *in vitro*.[8]

Complex indole alkaloids found in nature are often derived from tryptamine (and therefore tryptophan). For example, the biosynthesis of indole alkaloids yohimbine and catharanthine, and indolene tabersonine, begins with an enzyme-catalysed Pictet–Spengler reaction between tryptamine and secologanin to make strictosidine (Scheme 1).[9]



Scheme 1: Biosynthesis of indole/indolene alkaloids from tryptamine and secologanin.

Following removal of the glucose group from strictosidine to give **1.1**, the hemi-acetal can open up as the enal **1.2**. On this aldehyde, an intramolecular condensation takes place to give iminium **1.3** then double bond migration gives the more stable, conjugated **1.4**. The three alkaloids yohimbine, tabersonine and catharanthine are each derived from the common intermediate **1.4**.

In addition to natural products, indoles are present in many synthetic drugs and three of these are shown below in Figure 3.

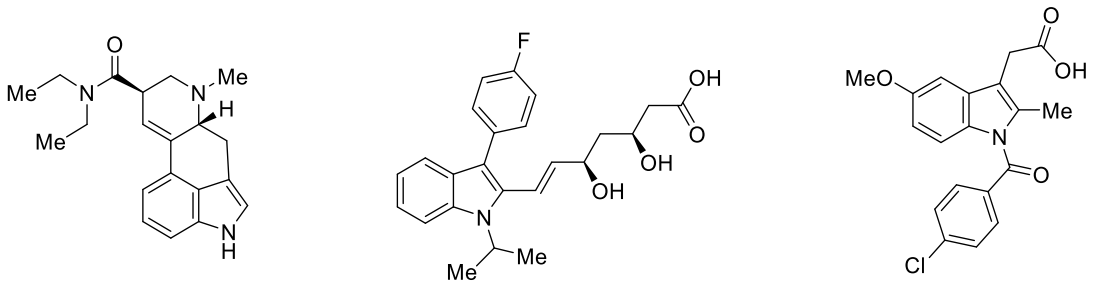


Figure 3: Synthetic drugs containing an indole.

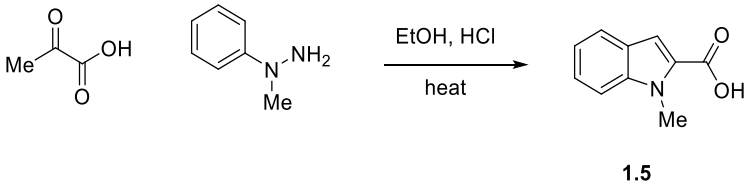
Lysergic acid diethylamide (LSD) is a hallucinogenic compound which saw brief use as an experimental clinical drug in the 1950s and 1960s and is composed of an indole-containing tetracyclic skeleton.[10] Fluvastatin inhibits the enzyme responsible for producing mevalonic acid, an early intermediate in the biosynthesis of cholesterol, ultimately resulting in a lowering of cholesterol levels in the blood.[11] Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) prescribed as a treatment for rheumatoid arthritis and works by inhibiting the production of prostaglandin, a molecule which plays a key role in the body's pain and inflammation response.[12]

The ubiquity of indoles in natural products and medicines, as well as their varied and useful effects, has driven efforts towards their synthesis for well over 100 years.[13] Outlined below are examples of indole synthesis, from the nascence of organic chemistry through to the modern day.

1.2. Synthesis and Functionalisation of Indoles

1.2.1 Fischer Indole Synthesis

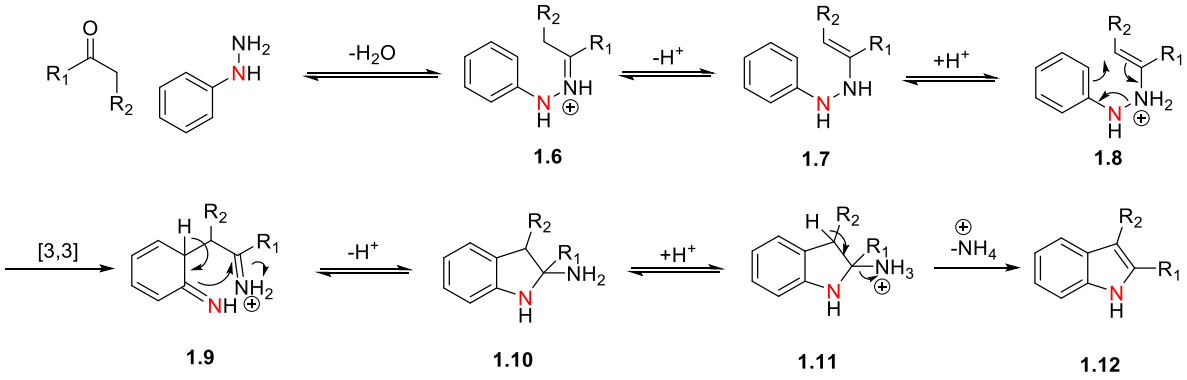
The first synthesis of an indole in a laboratory was carried out by Fischer and Jourdan in 1883 by heating pyruvic acid and 1-methyl-1-phenylhydrazine with catalytic HCl in ethanol (Scheme 2).[14] It was not until the following year that the product was identified as indole **1.5**.[15]



1.5

Scheme 2: Fischer and Jourdan's original indole synthesis.

A mechanism for this reaction was proposed in 1924 by Robert and Gertrude Robinson,[16] and their proposed mechanism was corroborated by Allen and Wilson in 1943 using heavy nitrogen labelling, where ^{15}N aniline was synthesised from ^{15}N benzamide through a Hoffman degradation.[17] This radiolabelled aniline was then converted into phenylhydrazine with the heavy nitrogen attached directly to the aromatic ring and this was present in the indole product (Scheme 3, ^{15}N is coloured red), supporting the Robinsons' earlier proposed mechanism.



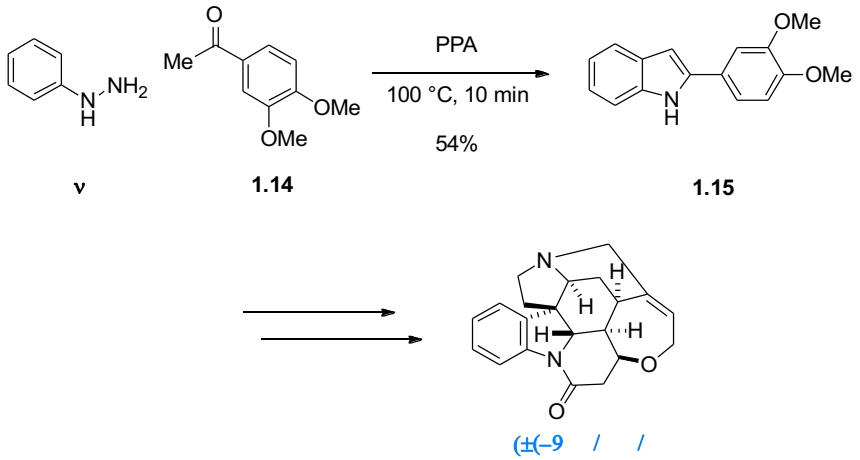
1.6 **1.7** **1.8** **1.9** **1.10** **1.11** **1.12**

Scheme 3: Mechanism for the FIS (^{15}N, as used in Allen and Wilson's mechanistic investigation, is coloured red).

The Fischer indole synthesis (FIS) begins with condensation of phenylhydrazine with a ketone to form hydrazinium **1.6** which is depronated to give enehydrazine **1.7**. Next, protonation of **1.7** to **1.8** facilitates a sigmatropic rearrangement to give dearomatised **1.9**, breaking the σ bond between the two nitrogens present in the hydrazine starting material. Rearomatisation then attack of the nascent aniline in **1.9** on the neighbouring iminium forms indolene **1.10**. Finally, elimination of ammonium across the C-2 and C-3 (**1.11**) gives indole **1.12**.

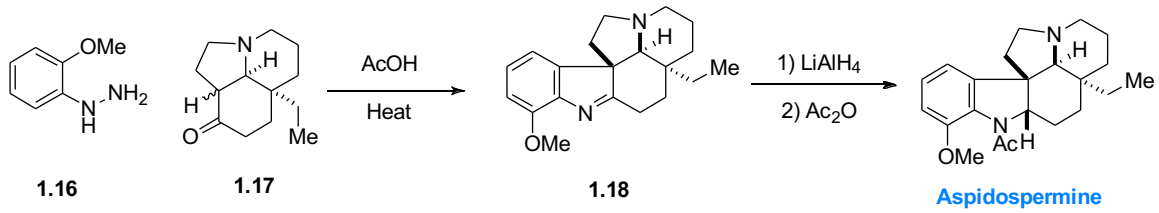
Since its inception, the FIS has seen use in both industry and academia from small scale up to 25 kg pilot-plant scale.[18] The FIS has been used in perhaps one of the most well-

renowned total syntheses: Woodward's total synthesis of strychnine published in 1954, wherein a FIS is used at an early stage between phenylhydrazine **1.13** and acetophenone **1.14** to give indole **1.15** (Scheme 4).[19] A multitude of steps were then carried out to produce strychnine.



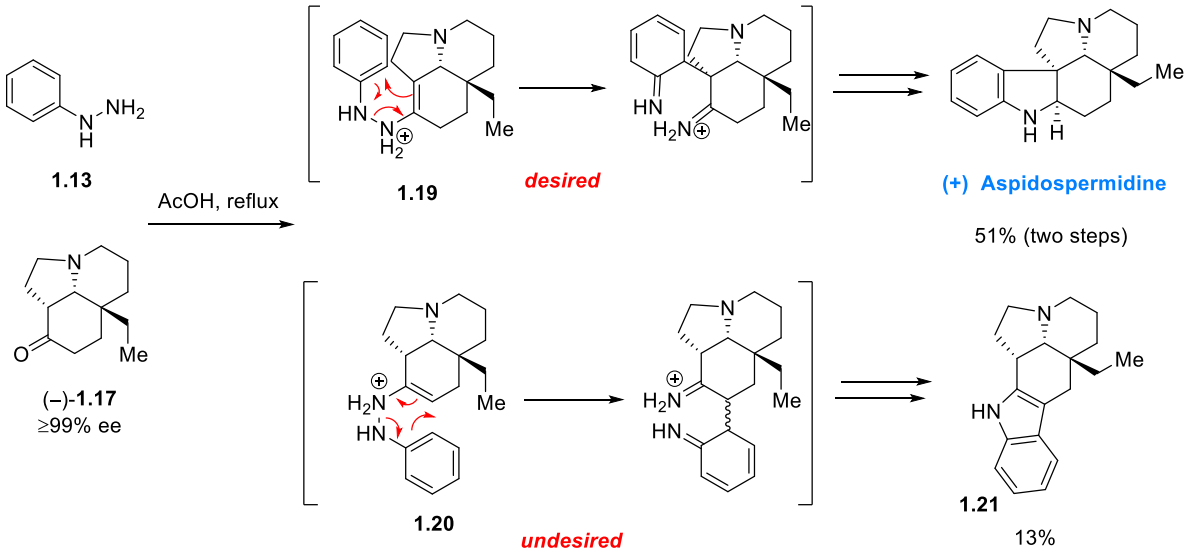
Scheme 4: FIS used in Woodward's total synthesis of Strychnine.

Stork and co-workers' racemic total synthesis of aspidospermine, published in 1963, also utilised a FIS (Scheme 5).[20] Hydrazine **1.16** was condensed with tricyclic ketone **1.17** to form the corresponding hydrazone which cyclised to form **1.18**. As the C-3 position formed is an all-carbon quaternary centre, aromatisation by loss of ammonium across C-2 and C-3 is not possible. Rather, the endocyclic nitrogen of the hemiaminal intermediate (see **1.10**) uses its lone pair to expel ammonium, forming an imine between itself and the C-2 position, giving the non-aromatic indolenine instead of the indole. Following reduction of this indolenine with $LiAlH_4$ and acetylation of the resultant indoline nitrogen, racemic aspidospermine was obtained. It is worth noting that the phenylhydrazine **1.16** bears an OMe group at one of the *ortho* positions, meaning the [3+3] cyclisation must proceed at the other *ortho* position, leading predictably to one regioisomer.



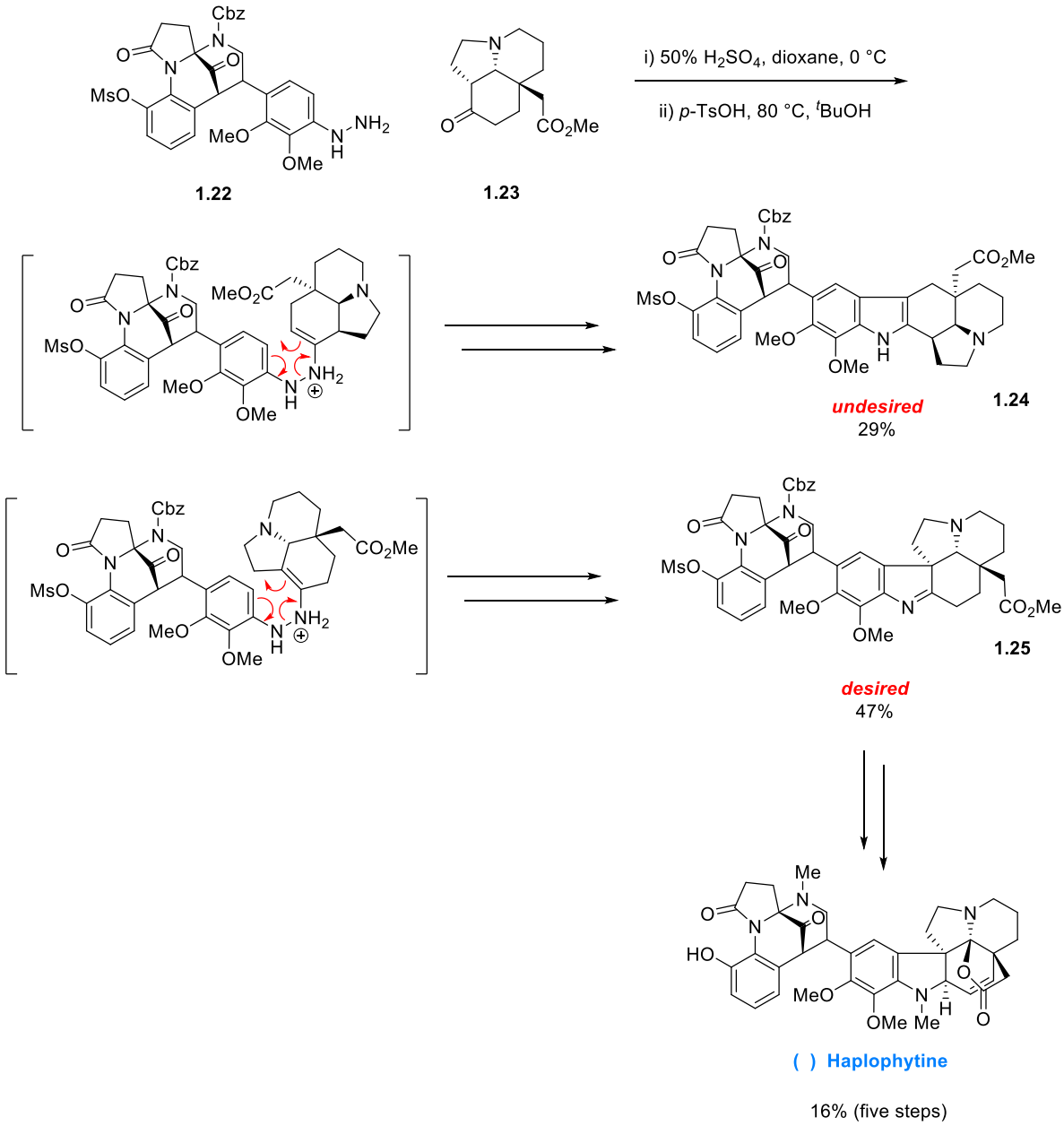
Scheme 5: FIS used in Stork's total synthesis of aspidospermine.

The structurally similar alkaloid aspidospermidine was prepared using a FIS in 2005 by Aubé and co-workers, who built on Stork's work by using chiral aminoketone (–)-**1.17**, resulting in a chiral FIS product (Scheme 6).[21] Following FIS between phenylhydrazine **1.13** and tricyclic ketone (–)–**1.17** and subsequent reduction, the alkaloid product (+)–aspidospermidine was isolated in 51% yield over these two steps. The hydrazone (and therefore hydrazinium) formed between **1.13** and (–)–**1.17** has two positions from which it can be enolised, leading to desired enehydrazine **1.19** and undesired enehydrazine **1.20**. By-product **1.21** was formed from the cyclisation of the latter in 13% yield. This regioselectivity issue is an inherent drawback of the FIS but can be obviated by using symmetrical ketone and hydrazine starting materials.



Scheme 6: FIS used in Aubé's total synthesis of (+)–aspidospermidine and the formation of impurity 1.21.

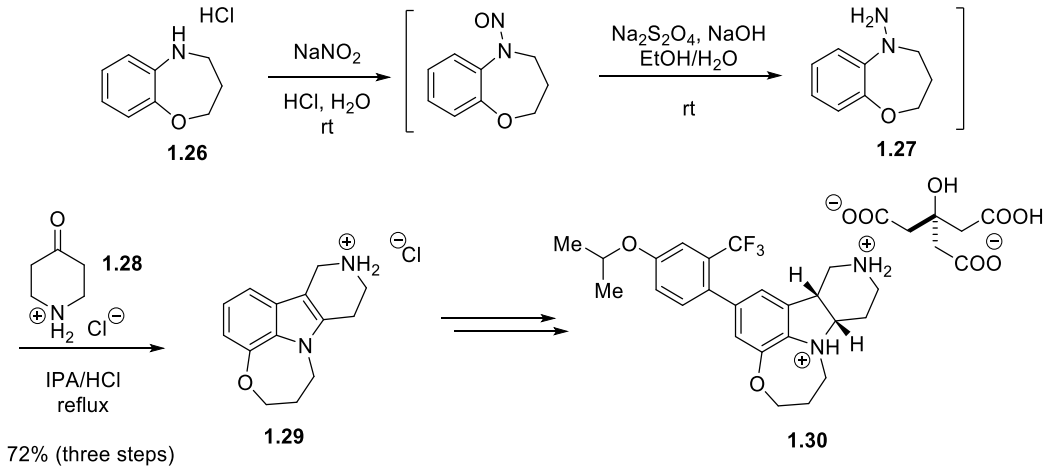
A similar regioselectivity issue was encountered in Fukuyama's total synthesis of (+)–haplophytine (Scheme 7).[22] Following condensation of hydrazine **1.22** and tricyclic ketoester **1.23**, heating with catalytic acid initially gave a combined yield of FIS products **1.24** and **1.25** of just 20%. Optimisation of reaction conditions gave increased yields of undesired indole **1.24** in 29% yield and desired indolenine **1.25** in a yield of 47%. The latter was carried through several straightforward steps to give the target haplophytine.



Scheme 7: Production of regioisomers from the FIS in Fukuyama's synthesis of (+)–haplophytine.

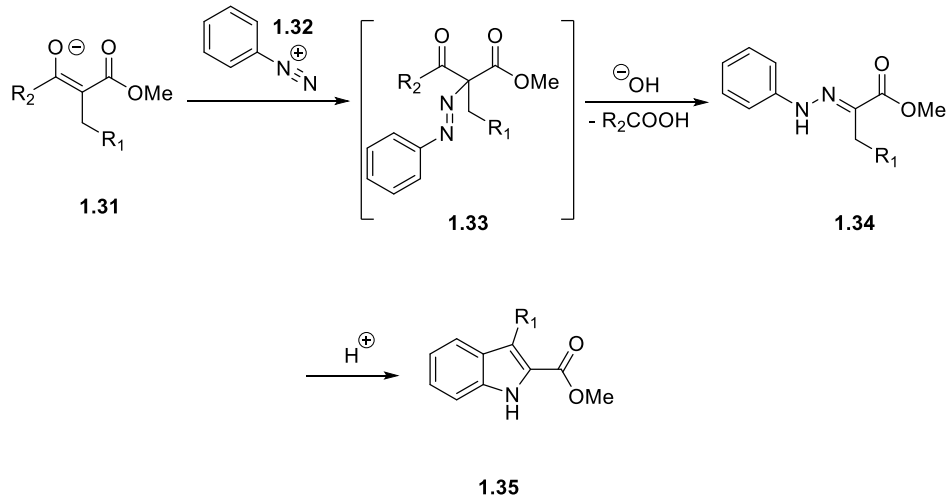
The FIS is not limited to academic laboratories and has been employed successfully on pilot plant scale, for example in the synthesis of **1.30**, a drug candidate intended to suppress appetite in patients who are obese (Scheme 8).[23] This was realised *via* a telescoped nitrosylation of amine **1.26**, followed by reduction with sodium dithionite then FIS of hydrazine **1.27** with piperidinone **1.28**. After recrystallisation, **1.29** was obtained in a yield of 72% (24.6 kg) over three steps. Following reduction to the indoline, 5-bromination and Suzuki-Miyaura cross-coupling, the drug molecule **1.30** was isolated as its citrate salt. In this example, regioselectivity of the FIS is not an issue as piperidone **1.28** is symmetrical

and the phenylhydrazine intermediate **1.27** has only one free *ortho* C-H from which it can carry out a [3+3] cyclisation.



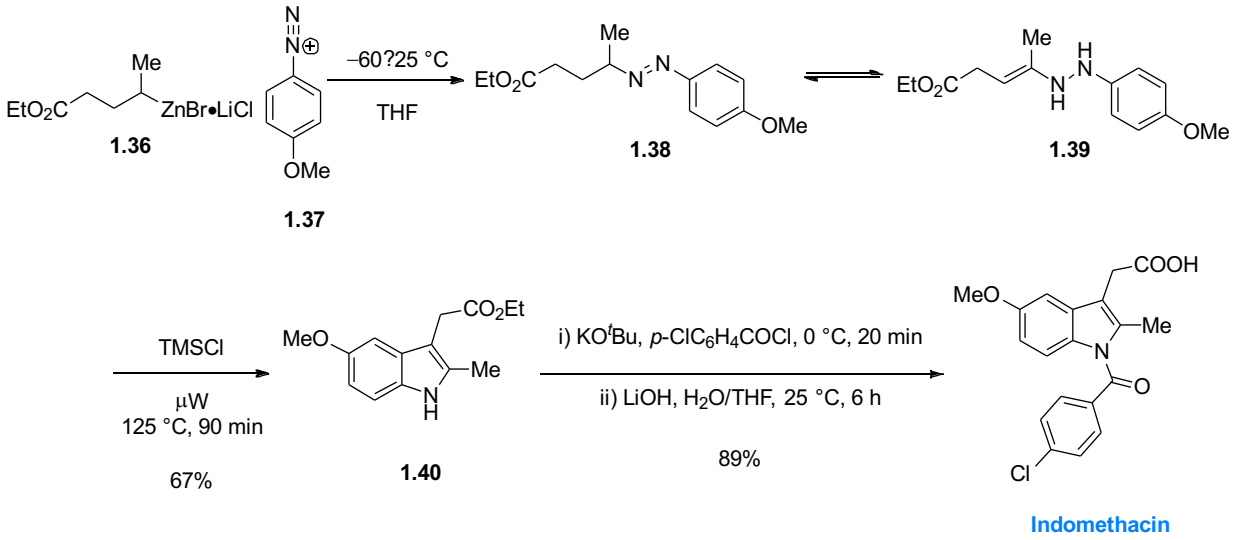
*Scheme 8: Synthesis of **1.30** using a FIS.*

Methods have also been developed to directly react a diazonium salt with carbon nucleophiles, obviating the reduction of the diazonium and the resultant hydrazine's condensation with a ketone. For instance, shortly after the publication of the seminal FIS paper, a modification was put forward by Japp and Klingemann (Scheme 9).[24] In this work, β-ketoester enolate **1.31** reacted with the diazonium salt **1.32**. The diazo product **1.33** was deacylated, giving direct access to phenylhydrazone **1.34**. Under acidic conditions, **1.34** then cyclises to make indole **1.35**.



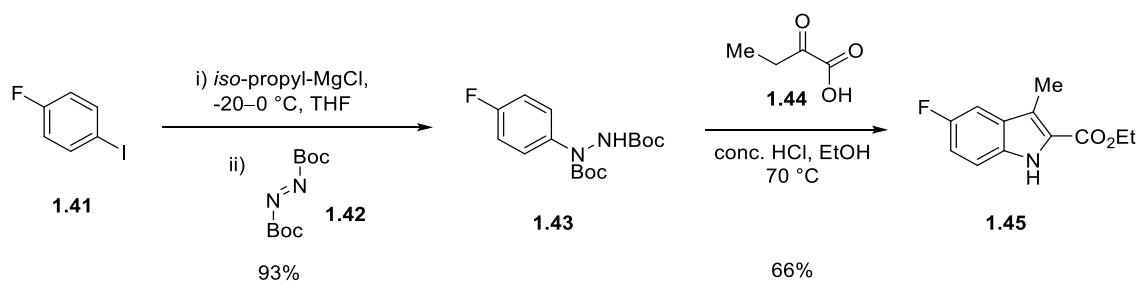
Scheme 9: Japp-Klingemann modification to the FIS.

Knochel and co-workers disclosed a procedure in 2010 wherein alkyl zinc reagents were reacted with aryldiazonium salts, again circumventing the use of hydrazines (Scheme 10).[25] Addition of alkylzinc **1.36** to the diazonium **1.37** results in azo compound **1.38**, which tautomerises to enehydrazine **1.39**. Following addition of TMSCl, the reaction mixture is heated using microwave irradiation to give indole **1.40**, which then underwent an amide coupling, followed by ester hydrolysis, to give the NSAID indomethacin. This FIS is free of regioselectivity issues as the diazonium **1.37** is 4-substituted, so the two possible regioisomers which could form are equivalent.



Scheme 10: Addition of an alkylzinc reagent to an aryldiazonium salt in the synthesis of indomethacin.

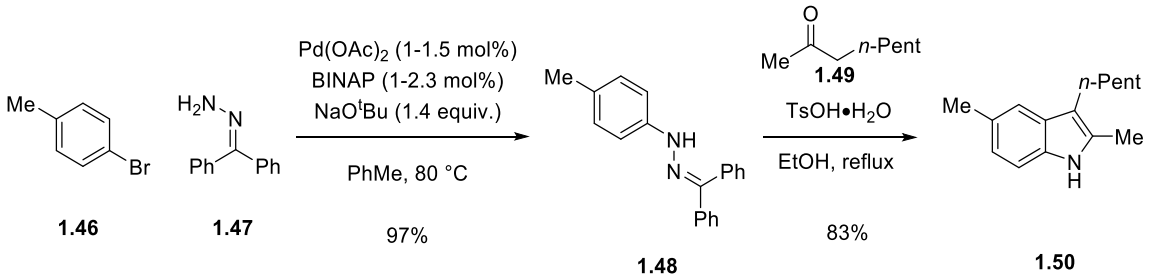
Aryl hydrazines can be directly accessed by reacting Grignard reagents, such as that formed between **1.41** and *iso*-propyl-MgCl, with di-*tert*-butyl-azodicarboxylate **1.42** to give aryl hydrazine **1.43**. Reaction of the latter under acidic conditions in the presence of ketoacid **1.44** gave concomitant Boc deprotection, condensation, and indole cyclisation to form **1.45** (Scheme 11).[26]



Scheme 11: Metalation of an aryl iodide and its addition into an azo compound followed by FIS.

The use of stoichiometric organometallic reagents limits the applicability of this reaction as the Grignard reagent will deprotonate acidic sites or attack other electrophilic functionalities, *e.g.*, carbonyl groups. To this end, several methods for producing phenylhydrazines under comparatively mild, cross-coupling conditions have been developed.

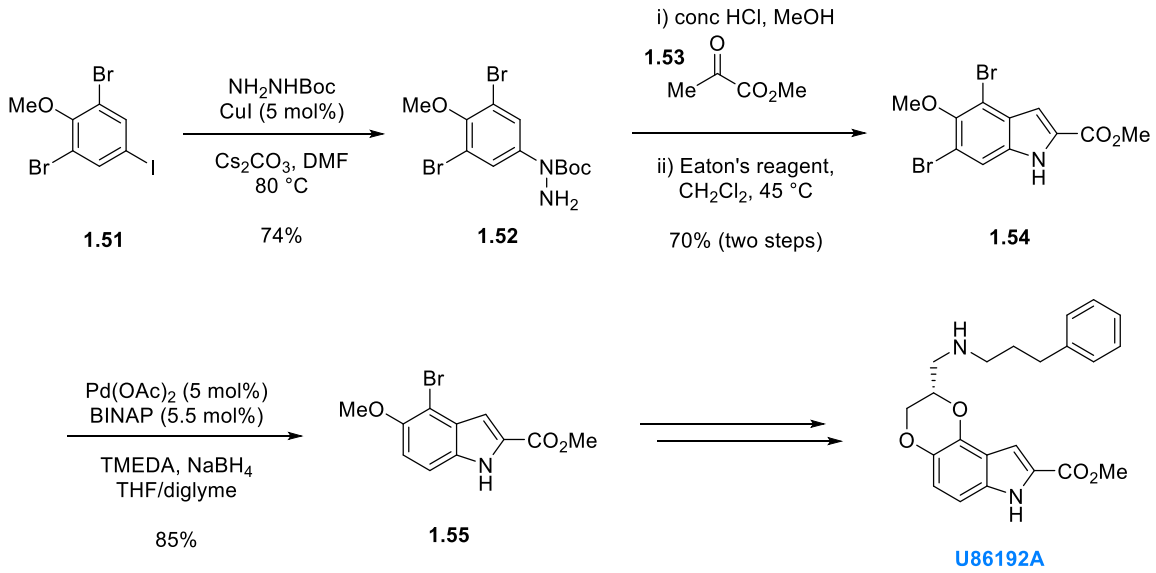
In 1998, Buchwald and co-workers published work on using Pd-catalysed C-N cross-coupling between aryl bromide **1.46** with benzophenone hydrazone **1.47** (Scheme 12).[27] The coupled benzophenone phenylhydrazone **1.48** was then exchanged with the desired ketone **1.49** (**1.48** has no α protons so cannot undergo FIS) under acidic conditions, forming the desired phenylhydrazone, which cyclises to form indole **1.50**. The use of Pd catalysis to form arylhydrazones offers a much more mild and tolerant method to access phenylhydrazines and phenylhydrazones over, for example, the method outlined in Scheme 11.



Scheme 12: Pd-catalysed coupling of aryl bromide and benzophenone hydrazone and subsequent exchange to ketone hydrazone and FIS.

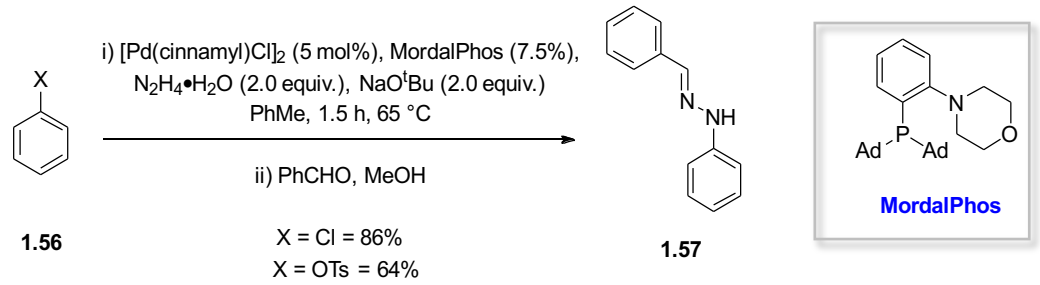
Similar work was carried out in the same lab, four years later, using Cu rather than Pd catalysis to couple *N*-Boc hydrazine to an aryl iodide **1.51** (Scheme 13).[28] The primary benefit of this process is the large difference in price and availability of Cu over Pd. *N*-Boc phenylhydrazine product **1.52** was deprotected under acidic conditions and condensed with methyl pyruvate **1.53** prior to formation of the indole **1.54** using Eaton's reagent (7.7% P_2O_5 in methanesulphonic acid). The dibromo indole is selectively monoprotodebrominated using Pd catalysis, leaving the bromide at the 4-position intact in **1.55**. This reiterates the largest drawback of the FIS: regioselectivity. In this case, a symmetrical dibromophenylhydrazine was used to sidestep any regioselectivity issues, only for one of these bromides to be removed, which increases step count and decreases yield and atom economy of the process. If the monobrominated equivalent of **1.52** were used in the FIS, there would almost certainly

be a regioisomeric mixture of products obtained. The product was further elaborated to compound U86192A which has shown promising antihypertensive properties.[29]



Scheme 13: Copper-catalysed coupling of aryl iodide with N-Boc hydrazine, subsequent indole formation, and selective protodebromination.

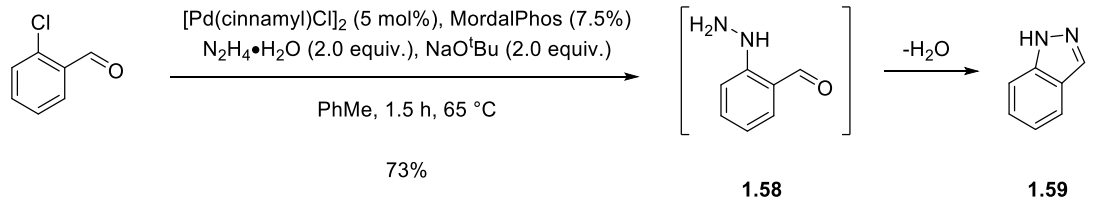
In 2010, work from Stradiotto and co-workers was published on the Pd-catalysed coupling of hydrazine hydrate with aryl chlorides and tosylates *e.g.* **1.56** (Scheme 14).[30]



Scheme 14: Pd-catalysed coupling of hydrazine hydrate with aryl chloride/tosylate and condensation with benzaldehyde. Ad = adamantyl.

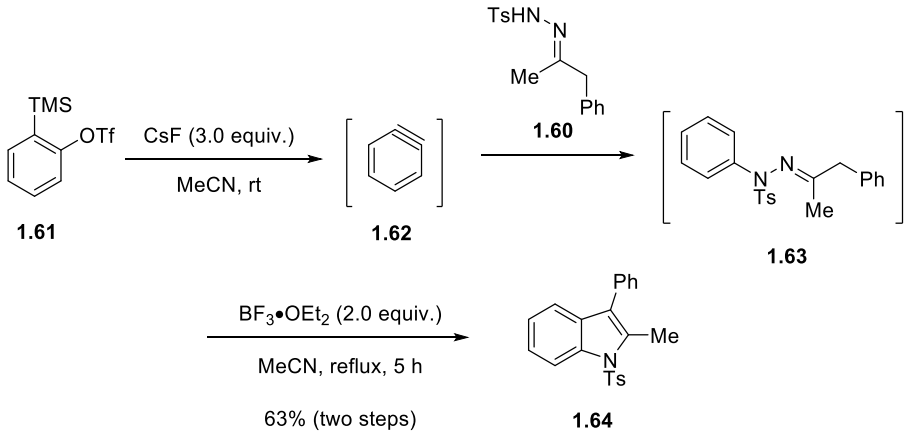
Following a ligand screen, electron-rich phosphine ligands were found to be most efficient in this transformation and MordalPhos was selected as the optimum ligand. The products were then condensed with benzaldehyde to produce phenylhydrazone **1.57** to aid in isolation and characterisation. The synthesis of indoles was not included in this work, rather, indazole **1.59** was synthesised through condensation of the phenylhydrazine **1.58** with a neighbouring aldehyde (Scheme 15). It is conceivable that the phenyl hydrazine products could be condensed with ketones/aldehydes and undergo FIS. This would increase the potential scope

of the FIS, as now aryl chlorides and aryl tosylates, the latter easily accessible from phenols, would be viable starting materials to make indoles.



Scheme 15: Pd-catalysed coupling of hydrazine hydrate with an aryl chloride and subsequent condensation to form the indazole.

Finally, phenylhydrazones can be made using benzynes as demonstrated by Greaney and coworkers in 2011 (Scheme 16).[31] Reaction of **1.60** with benzyne **1.62**, itself formed from reacting **1.61** with CsF gave phenylhydrazone product **1.63**, which underwent cyclisation in the presence of a Lewis acid to give indole **1.64**.

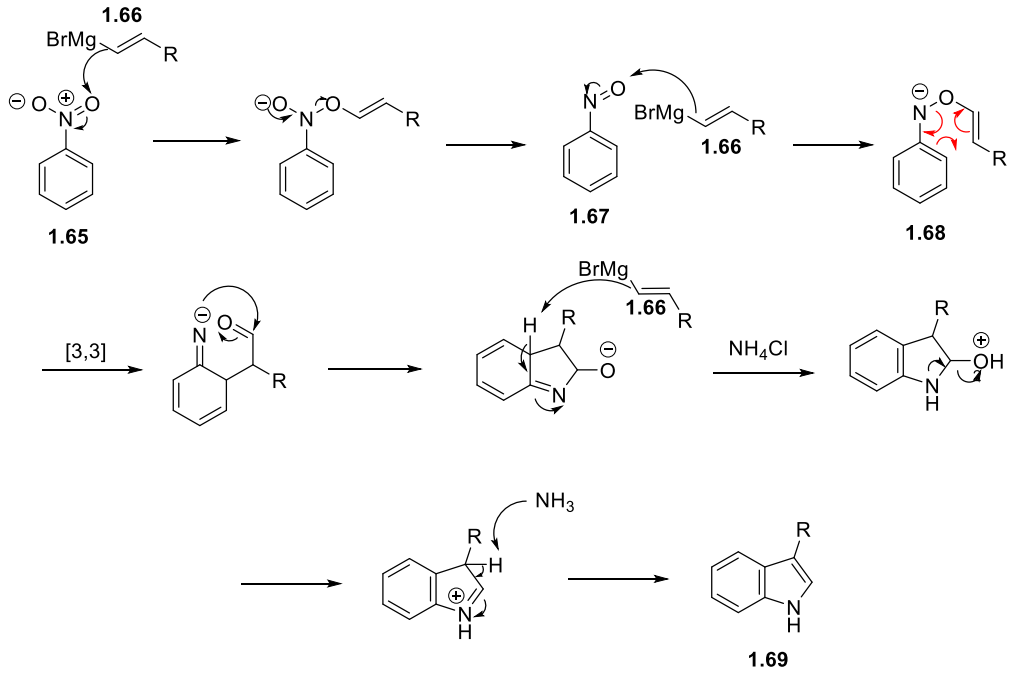


Scheme 16: Indole formation via reaction of benzyne and hydrazone and Lewis acid-mediated cyclisation.

The FIS is still in use almost 150 years since its discovery and the reaction has allowed the synthesis of a multitude of natural products and pharmaceuticals. However, regioselectivity of the reaction remains a major limitation. A multitude of other approaches to make indoles have been disclosed in the intervening years and several of these are laid out below.

1.2.2. Non-transition Metal (TM) Catalysed Methods of Indole Synthesis.

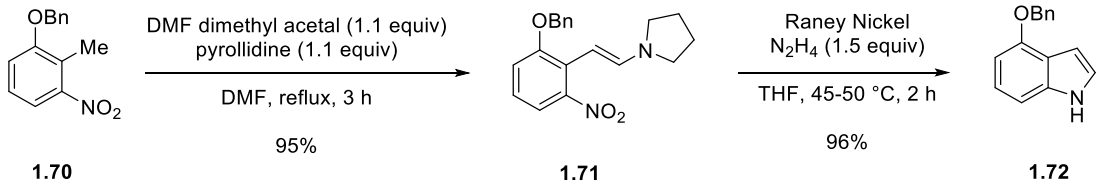
The Bartoli indole synthesis involves the reaction of a nitroarene with an excess of Grignard reagent (Scheme 17).[32]



Scheme 17: Mechanism of the Bartoli indole synthesis.

Vinyl Grignard reagent **1.66** is reacted with a nitroarene **1.65** which forms the nitroso intermediate **1.67.** Another equivalent of **1.66** adds into the nitroso group at the oxygen and the product **1.68** undergoes a Claisen rearrangement. Following cyclisation, rearomatisation of the benzene ring occurs and after elimination of water and a proton, indole **1.69** is furnished. The use of excess equivalents of Grignard reagent means that the functional group tolerance is limited to those which will not react with this strongly nucleophilic and basic class of reagents. The substitution at the C-2 or C-3 position of the indole product is dictated by the Grignard reagent used in the reaction.

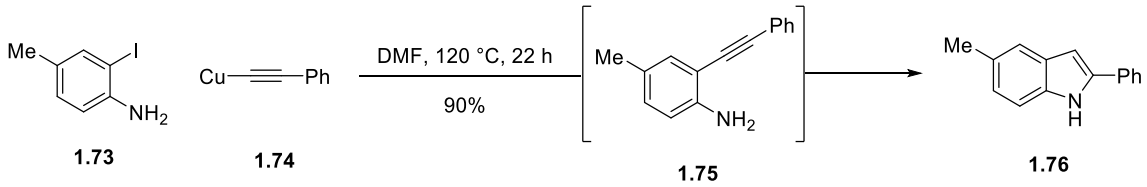
Another method is the Leimgruber-Batcho indole synthesis, an example of which is shown below in Scheme 18.[33].



Scheme 18: Leimgruber-Batcho indole synthesis.

A 2-nitro toluene **1.70** is deprotonated and condensed with DMF dimethyl acetal and, in the presence of pyrrolidine, the enamine **1.71** is formed. Following reduction of the nitro group, the nascent aniline performs an intramolecular attack on the enamine (in equilibrium with its iminium) which closes the ring. Following loss of pyrrolidinium, indole **1.72** is formed and this final step is analogous to the FIS. This method is primarily used to create indoles unsubstituted at C-2 and C-3. The reaction scope is limited to 2-nitrotoluenes, as this group is required to increase the acidity of the tolyl position significantly and the nitro group is reduced to aniline which ultimately forms the indole nitrogen. These constraints on the arrangement of atoms in the starting material means that there is predictable regiochemistry of the product.

Castro and co-workers disclosed the synthesis of C-2 substituted indoles by reaction of 2-iodoanilines, *e.g.,* **1.73**, with a cuprous acetylide, *e.g.*, **1.74** (Scheme 19).[34]

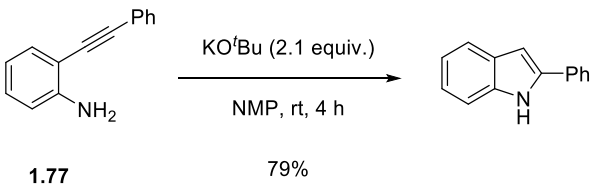


1.73 **1.74** **1.75** **1.76**

Scheme 19: Castro's indole synthesis from ortho-*iodoaniline and cuprous acetylide.*

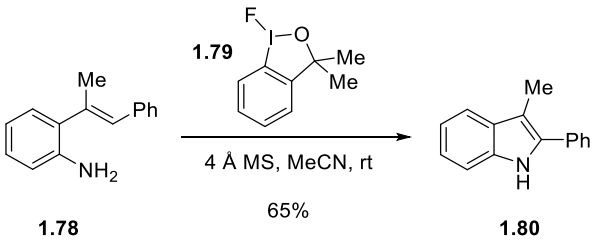
The reaction proceeds first through a Castro-Stephens reaction to produce 2-alkynyl aniline **1.75** prior to intramolecular attack from the aniline nitrogen onto the alkyne to furnish the indole **1.76**. The cyclisation step is thought to be made possible due to the Lewis-acidic action of Cu on the alkyne. This method only produces 2-substituted indoles due to the requirement of a terminal alkyne (*i.e.,* acetylide) starting material in the Castro-Stephens coupling step.

In 2000, Knochel and coworkers reported the 5-*endo-dig* cyclisation of 2-alkynyl aniline **1.77** using potassium *tert*-butoxide as base (Scheme 20).[35] This reaction is similar to previously published work carried out by Castro and co-workers (see Scheme 19), the key difference being that the alkyne at the 2-position is pre-installed and the cyclisation is achieved through deprotonation of aniline by the alkoxide base with no transition metal present. The conditions used are relatively benign, leading to indole formation in a short time, at ambient temperature in the presence of a moderately strong alkoxide base. However, this method results only in substitution at the C-2 position.



Scheme 20: Knochel's KO^{t}Bu-mediated indole synthesis. NMP = N*-methyl-2-pyrrolidinone.*

Gulder and coworkers disclosed an oxidative indole synthesis in 2018 (Scheme 21).[36] Iodane **1.79** was used as the oxidant in this reaction which furnished 2,3-disubstituted indole **1.80** from the corresponding disubstituted 2-alkenyl aniline **1.78**. However, the substrate scope is rather limited, ostensibly due to the use of oxidising iodane **1.79**.

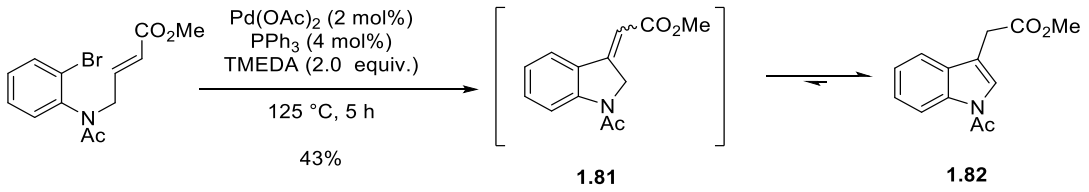


Scheme 21: Oxidative synthesis of indoles using hypervalent iodine.

1.2.3. Transition Metal-catalysed Indole Synthesis

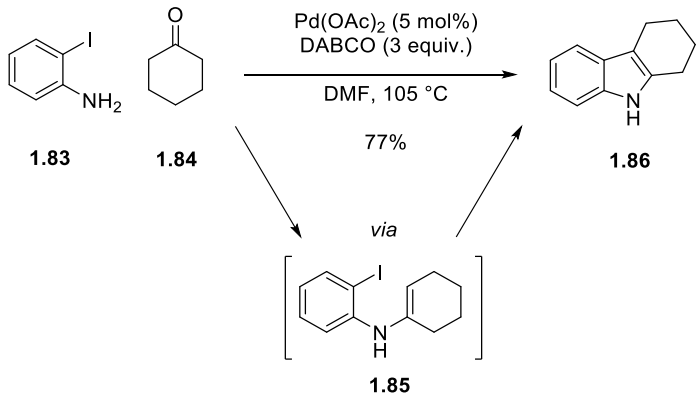
Transition metal-catalysed phenylhydrazone formation was discussed in section **1.2.1** as a method of making FIS substrates. Discussed here is the formation of indoles *via* pathways other than the FIS using TM catalysis.

In 1977, Mori and coworkers published work on the synthesis of indoles *via* an intramolecular Heck reaction (Scheme 22).[37] Following β-hydride elimination, the exocyclic alkene **1.81** is formed which tautomerises to the more stable, aromatic indole **1.82**. This method married indole synthesis with the nascent field of Pd catalysed cross-coupling. Although only 3-substituted indoles were reported, it would be possible to create 2,3-disubstituted indoles simply by changing the alkyl chain attached to the nitrogen in the starting material.



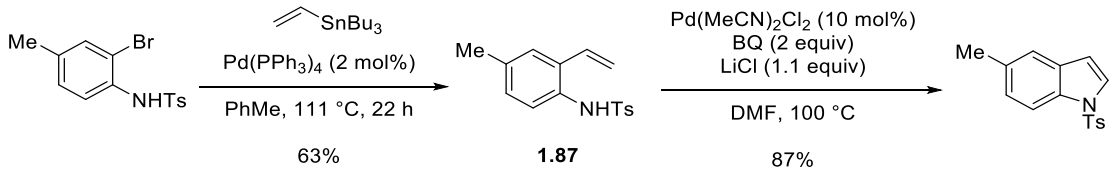
Scheme 22: Mori's synthesis of indoles via *an intramolecular Heck reaction.*

In 1997, Chen and coworkers published work on the formation of indoles through condensation of ketones with 2-iodoanilines, *e.g.*, **1.83** and **1.84**, to form the corresponding enamine **1.85**, followed by an intramolecular Heck reaction to give tetrahydrocarbazole **1.86** (Scheme 23).[38] This work is similar to Mori's earlier work (see Scheme 22) and is capable of furnishing 2,3-disubsituted indoles. A limitation of this method is regioselectivity when non-symmetrical ketones and anilines are used as two possible enamines can be formed, a problem analogous to the FIS.



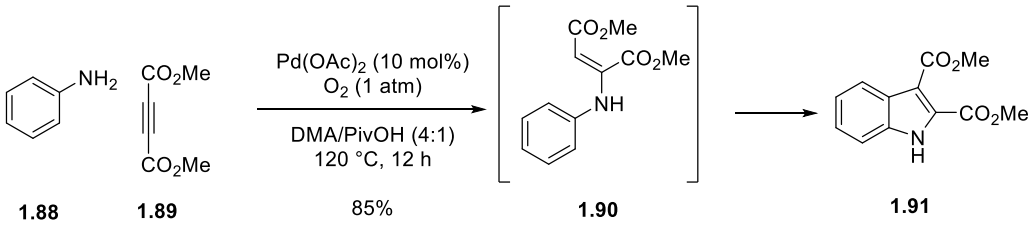
Scheme 23: Synthesis of indoles via *an enamine and intramolecular Heck reaction.*

The Stille lab developed a Pd-catalysed indole synthesis in 1988 by cyclising 2-vinylanilines, *e.g.,* **1.87**, under oxidative conditions (Scheme 24).[39] The examples given generally proceed in good yield, although they lack functionality at C-2 and C-3 of the indole product. However, this chemical space could be explored by changing the substitution of the vinyl stannane coupling partner to produce various 2-vinyl anilines.



Scheme 24: Stille's oxidative indole synthesis. BQ = benzoquinone.

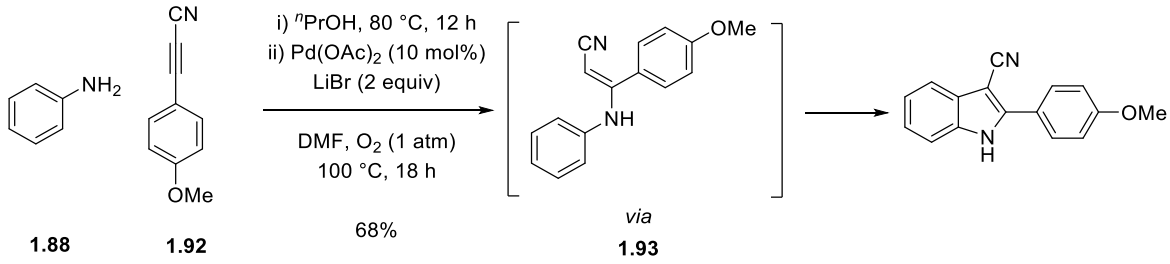
It is also possible to synthesise indoles from anilines bearing no *ortho*-functionality and alkynes under oxidative, Pd-catalysed C-H activation conditions. (Scheme 25).[40]



Scheme 25: Formation of indole from aniline and electron-deficient alkyne using C-H activation. PivOH = pivalic acid. DMA = N,N*-dimethylacetamide.*

This reaction is proposed to proceed *via* the Michael adduct (an enamine) **1.90** of aniline **1.88** and acetylenedicarboxylic acid diester **1.89**, which undergoes an oxidative C–C bond formation at the *ortho* position to give indole **1.91**. As a symmetrical alkyne is used, it results in identical substituents at C-2 and C-3 and the alkyne must be sufficiently electrophilic to be attacked by aniline.

Expanding on this, Chen and co-workers published work on the reaction between aniline **1.88** and cyanoalkyne **1.92** (Scheme 26).[41]

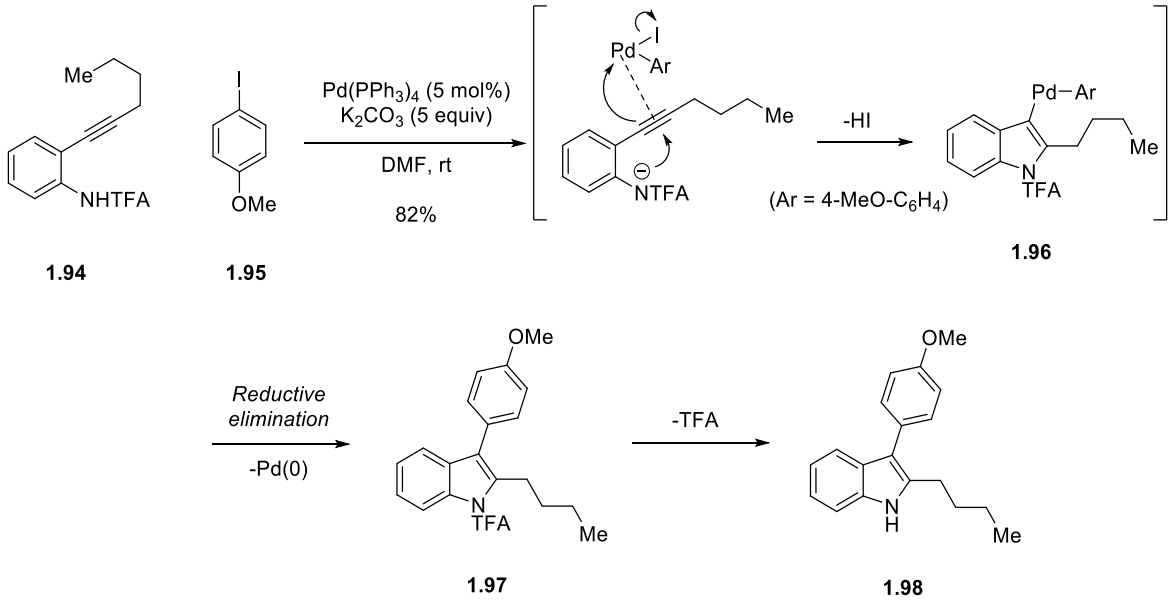


Scheme 26: Formation of indole from aniline and cyanoalkyne under oxidative conditions.

Again, the reaction is thought to proceed *via* the enamine **1.93** which is made through the Michael addition between aniline and alkyne. The indole product will invariably feature a nitrile at the C-3 position which limits the scope of the reaction. Both these oxidative methods are hampered by a regioselectivity problem: both protons *ortho* to the aniline can potentially undergo C-H activation. However, this is not a problem when one of these sites is replaced/blocked with another group or if the aniline is symmetrical.

In 1992, Cacchi and co-workers reported the synthesis of 2,3-disubstituted indoles *via* a Pd-catalysed cyclisation of an *ortho*-alkynyl aniline **1.94**.[42] A π-interaction between the Pd(II)

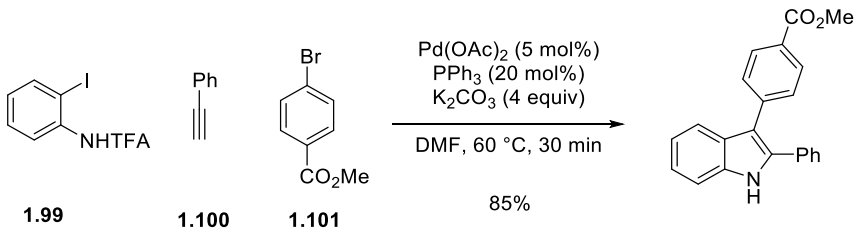
oxidative addition adduct (formed from **1.95** and Pd(0)) and the alkyne facilitates the intramolecular attack of nitrogen on the alkyne, resulting in a C-3 palladated indole **1.96** which undergoes reductive elimination to introduce the Ar group at the C-3 of the indole, giving **1.97** and regenerating the Pd(0) catalyst. Following hydrolysis of the trifluoroacetamide, 2,3-disubstituted indole **1.98** was obtained (Scheme 27).



Scheme 27: Cacchi's synthesis of 2,3-disubstituted indoles.

This work is intriguing because a multitude of indoles could conceivably be made simply by varying the aryl halide coupling partner (**1.95** in this case), allowing a small library of 2,3-disubtituted indoles to be made by reacting the same 2-alkynyl aniline with various aryl halides. Parallels can be drawn between this reaction and Castro's earlier work (see Scheme 19) in that the aniline nitrogen performs an intramolecular attack on the adjacent alkyne.[34] The resultant 3-palladated indole **1.96** introduces functionality at this position, something Castro's indole synthesis lacked the ability to do.

This work was expanded upon in 2006 with the publication of work from Boehringer-Ingelheim Pharmaceuticals.[43] Here, 2-iodoaniline **1.99** undergoes a Cu-free Sonogashira-type reaction with alkyne **1.100** prior to Cacchi-type ring closure. Again, C-3 palladation allows **1.101** to be introduced at the C-3 of the indole, resulting in a 2,3-disubstituted indole from a multicomponent reaction (Scheme 28).



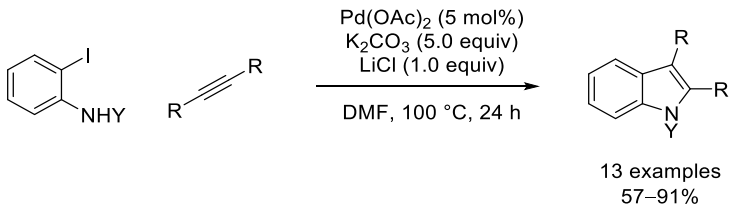
Scheme 28: Three component Sonogashira/Cacchi cascade.

This is an improvement on Cacchi's previous work as the terminal alkyne coupling partner of choice can be added to the reaction mixture from the outset, negating the need to pre-form the 2-alknyl aniline. The substituent on this alkyne ends up at C-2 of the indole product and the aryl bromide ends up at C-3. This allows for a great increase in structural complexity from simple starting materials in a single, multicomponent reaction. This method is of high synthetic utility for building up a library of indoles, which is valuable if structure-activity relationship (SAR) testing of the indole products were to be pursued. Indole formation is dependent on the Sonogashira reaction occurring between the terminal alkyne **1.100** and the aryl iodide **1.99** over the aryl bromide **1.101**. Despite this, the authors note that all three components can be present from the outset, and the undesired Sonogashira-type reaction between aryl bromide **1.101** and alkyne **1.100** does not occur in any measurable amount, likely owing to the difference in the rate of reaction of aryl iodides and bromides.[44].

Although this is a very attractive method for making 2,3-disubstituted indoles, the substituent at C-3 is limited to sp^2 electrophiles, as it must form a stable oxidative addition adduct with Pd whereas the nature of the substituent at the C-2 is dictated by the alkyne used and need not necessarily be sp^2 hybridised.

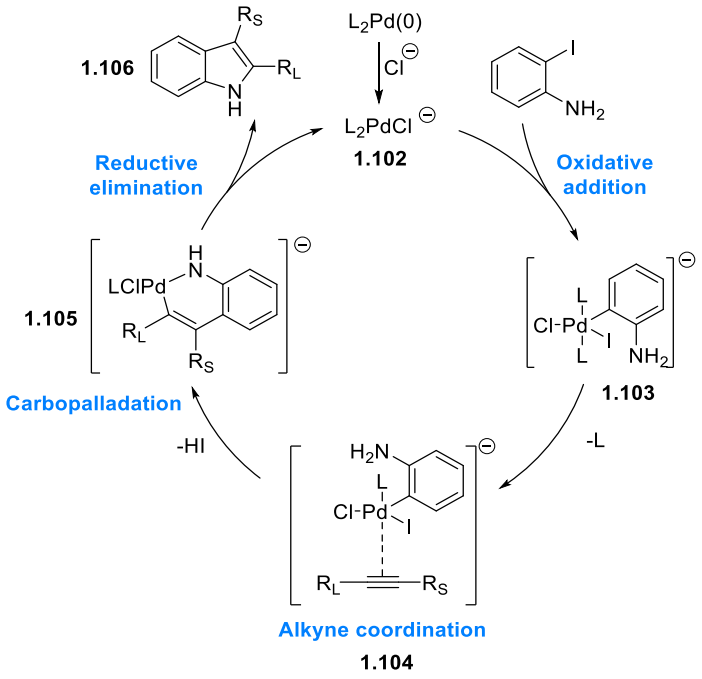
1.2.3.1. Larock Indole Synthesis

In 1991, Larock and co-workers published work on the reaction between 2-iodoanilines and internal alkynes. In the presence of a Pd catalyst, base and a chloride salt, an indole is obtained (Scheme 29).[45]



Scheme 29: Larock reaction in Larock and co-worker's 1991 publication. Y = Ac, Me, H or Ts.

The proposed catalytic cycle for this reaction is shown below in Scheme 30. The reaction is believed to begin from an anionic chloropalladium(0) species **1.102** which undergoes oxidative addition into the C-I bond to give the Pd(II) complex **1.103**. The alkyne coordinates to the Pd adduct in **1.104** prior to carbopalladation to form a 6-membered palladacyle **1.105**. Reductive elimination gives the indole **1.106** and regenerates the chloropalladium(0) complex **1.102**.



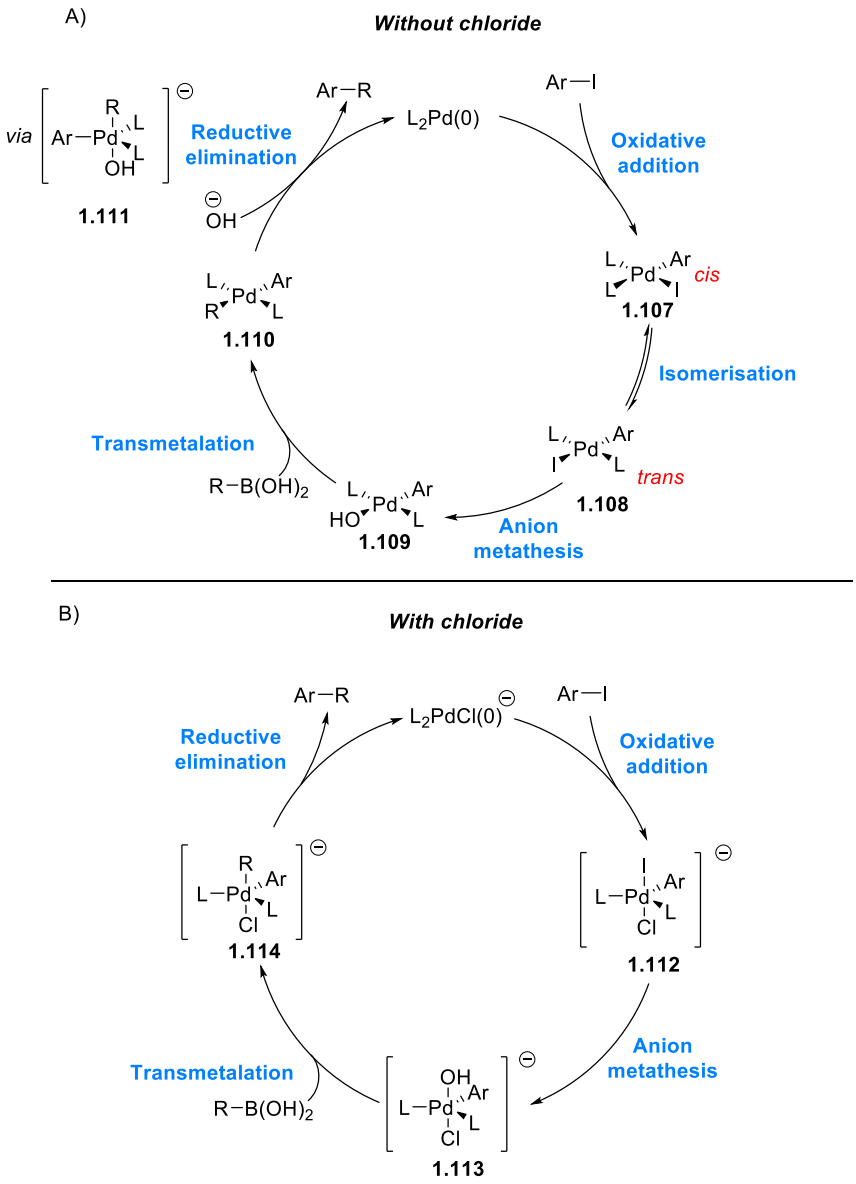
Scheme 30: Proposed Larock indole synthesis catalytic cycle. R_L = larger group, R_S = smaller group.

Chloride in this reaction is thought to make the Pd complex adopt a pentacoordinate geometry, which aids in the reductive elimination step.[46] While evidence for the role of chloride in the Larock reaction is lacking, shown below is a general catalytic cycle for a Suzuki-Miyaura cross-coupling demonstrating this effect of chloride (Scheme 31). In the

absence of exogenous chloride ions (Scheme 31A): following oxidative addition, the square planar complex **1.107** can undergo *cis*/*trans* isomerisation to the more thermodynamically stable *trans* isomer **1.108**. Following anion metathesis to **1.109** and transmetalation of the boron species to give **1.110** reductive elimination furnishes the cross-coupled product. The *trans* configuration of complex **1.110** precludes direct reductive elimination. Instead, hydroxide can coordinate to **1.110** to form transient oxopalladium species **1.111** which assumes a pentacoordinate geometry. The Ar and R groups are now closer together around the metal to allow reductive elimination to take place.[47] In the presence of chloride (Scheme 31B): the Pd(0) complex is ligated by chloride to form an anionic chloropalladium species. The oxidative addition adduct **1.112** remains ligated by chloride and adopts a pentacoordinate geometry. Anion metathesis of this complex gives **1.113** and, following transmetalation, gives **1.114**, which is capable of reductive elimination. Larock reactions rarely, if ever, require water and therefore the amount of hydroxide present in the reaction mixture will necessarily be very low. In the absence of hydroxide, chloride can instead enforce the pentacoordinate geometry of Pd to aid in reductive elimination. However, the example shown in Scheme 31 depicts a Suzuki-Miyaura reaction and the idiosyncratic action of chloride may not hold true for a Larock reaction. As carbopalladation occurs in a *syn* fashion, what will become the indole nitrogen and C-2 carbon are both bound to Pd prior to reductive elimination in a 6-membered palladacycle (see Scheme 30). This carbon and nitrogen are adjacent to one another around Pd, linked through a rigid carbon backbone, which precludes isomerisation of the palladacycle about Pd. It is therefore difficult to envision how chloride will have a beneficial effect on the reaction based on the above rationalisation of the action of chloride in the Suzuki-Miyaura reaction. The precise role of chloride in the Larock reaction remains unclear, however, many Larock reactions encountered in the literature employ chloride additives (often LiCl) with no explanation offered as to why, other than the empirical observation that it results in higher yields.

Work carried out by Jutand, Amatore and Shaik suggests that in an anionic chloropalladium complex, the chloride can push together the phosphine ligands which results in a decrease in the P-Pd-P bite angle, lowering the barrier to oxidative addition.[48] Furthermore, when the nucleophile transmatelates to the Pd centre, the chloride is displaced and the 'pushing' effect of the chloride on the phosphine ligands is lost, resulting in a larger bite angle which favours reductive elimination. The combination of both effects: lowering of the oxidative addition barrier and destabilising the complex prior to reductive elimination, reduces the energy

difference between the highest and lowest energy steps in the catalytic cycle which translates to an increase in turnover rate.



Scheme 31: Catalytic cycles of a Suzuki-Miyaura cross-coupling with and without chloride additive.

The Larock reaction generally proceeds with excellent regioselectivity which is thought to be driven by steric interactions during the alkyne coordination and subsequent carbopalladation steps. The alkyne coordinates to the Pd oxidative addition adduct in such a way that the larger of the two groups affixed on the alkyne faces away from the aryl group to minimise unfavourable steric interactions, and this group ultimately ends up at the C-2 of the indole (Figure 4).

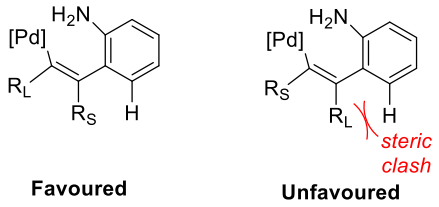
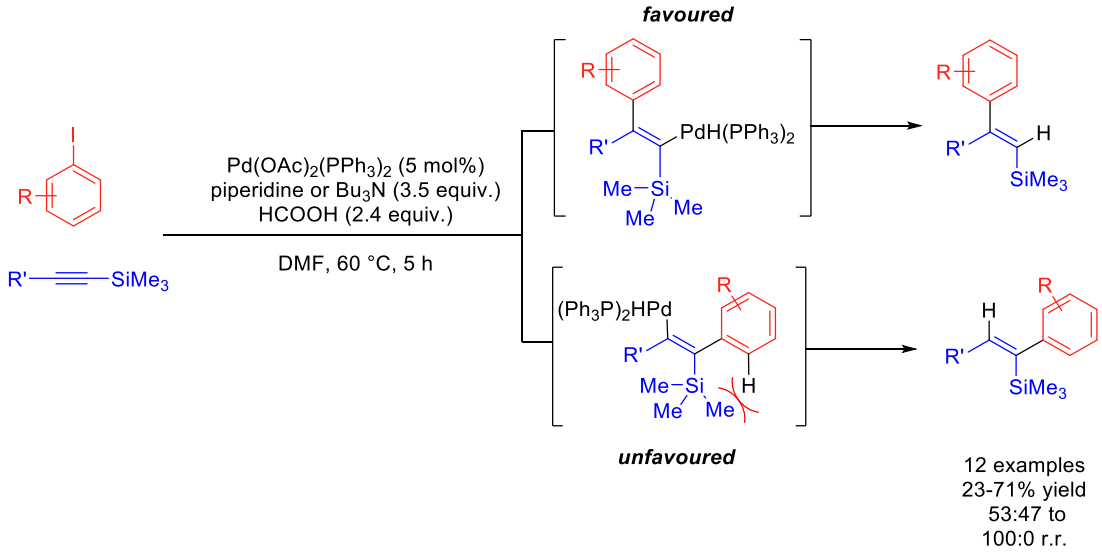


Figure 4: Theorised origin of the Larock reaction's regioselectivity. R_L = larger of the two R groups on the alkyne, R_S = smaller of the two R groups on the alkyne.

This hypothesis is based on observations made in 1986 by Cacchi and co-workers, where carbopalladation of a Pd oxidative addition adduct across a trimethylsilyl (TMS) alkyne resulted in the aromatic group being preferentially attached to the β carbon with respect to TMS and the Pd to the α carbon, which can be rationalised as the minimisation of steric interactions between the TMS and aromatic group (Scheme 32).[49] Reductive elimination of the Pd–H complex gives the trisubstituted alkene, with the silyl and aromatic group preferentially placed *E* to each other on different carbons.

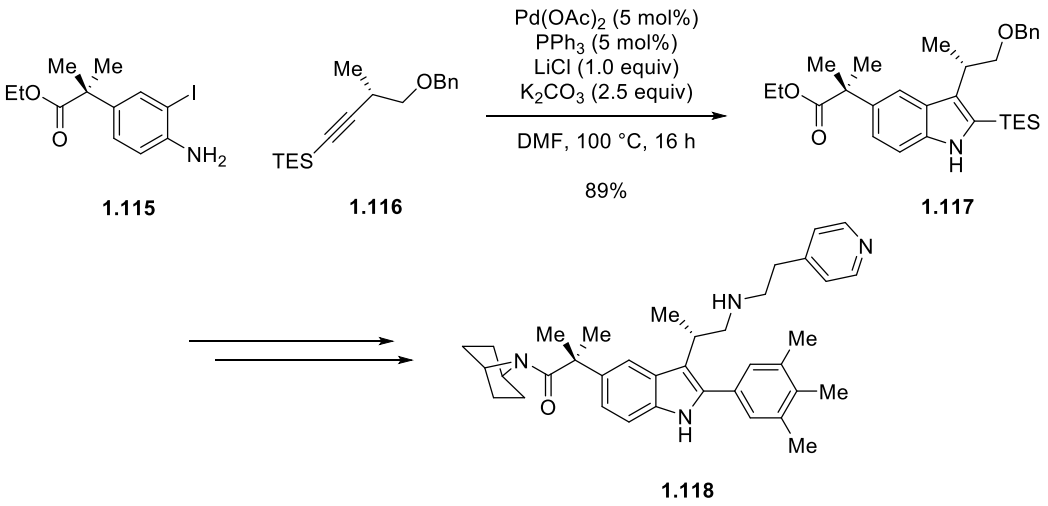


Scheme 32: Cacchi and coworker's rationale for the regioselectivity of carbopalladation of alkynes.

To take advantage of this regioselectivity, many examples of the Larock reaction use alkynes bearing bulky silyl substituents, *e.g.* triethylsilane (TES), which results in the silyl group being placed reliably at the C-2 of the indole product. The silyl group is then often removed under acidic conditions and in this sense, it can be considered as a traceless directing group.

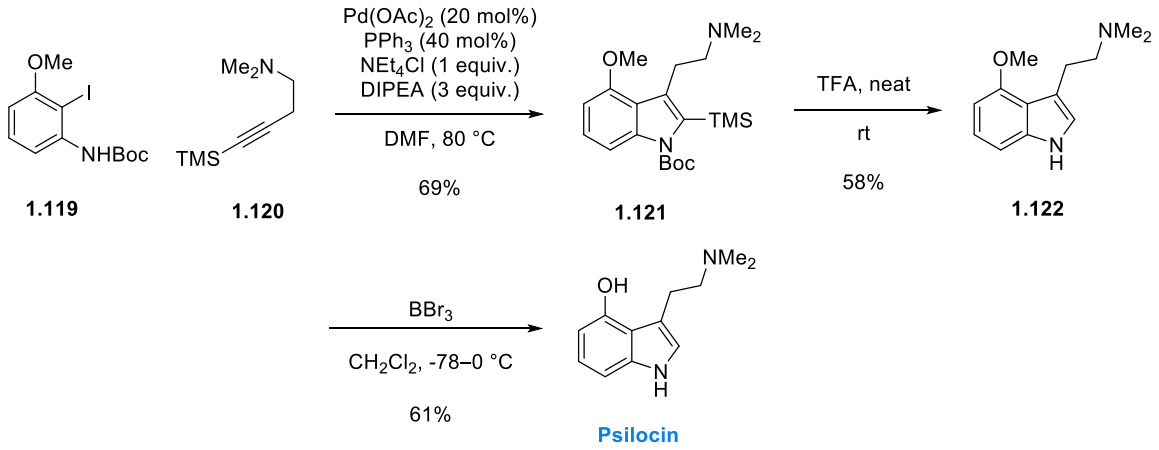
The Larock reaction has seen extensive use since its inception, a few examples of this have been outlined below.

In 2001, a Larock reaction was used in the synthesis of **1.118**, a potential candidate for the treatment of sex hormone imbalances (Scheme 33).[50] 2-Iodoaniline **1.115** was reacted with alkyne **1.116** under conditions similar to those used in Larock's original publication (see Scheme 29). The resultant indole **1.117** bore a TES group at C-2 and this compound was elaborated to the target molecule **1.118**.



Scheme 33: Larock reaction in the synthesis of a sex hormone antagonist 1.118.

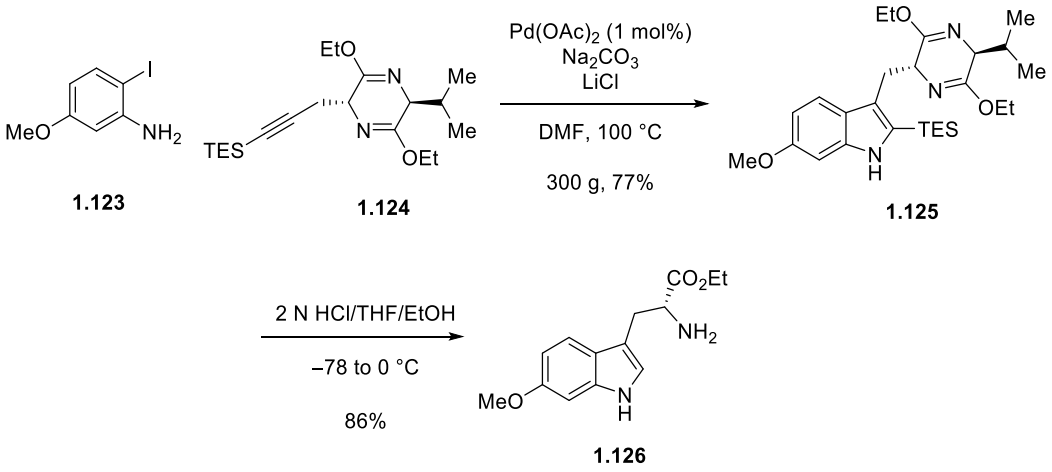
Another instance of using a silyl group to direct the regioselectivity of the Larock reaction was given in a short synthesis of psilocin, the active metabolite of psilocybin found in hallucinogenic mushrooms (Scheme 34).[51]



Scheme 34: Synthesis of psilocin using the Larock reaction. DIPEA = di-iso-*propylethylamine.*

Alkyne **1.120** and *N*-Boc protected 2-iodoaniline **1.119** were reacted together, in the presence of catalytic $Pd(OAc)_2$ with NEt_4Cl as an additive and *di-iso*-propylamine as base to give indole **1.121** in 69% yield. The use of 'standard' Larock conditions ($Pd(OAc)_2$, LiCl, K_2CO_3/K_3PO_4) gave lower conversions in this case. Treatment of **1.122** with TFA gave concomitant protodesilylation and Boc deprotection. Finally, demethylation with BBr_3 gave psilocin in 61% yield.

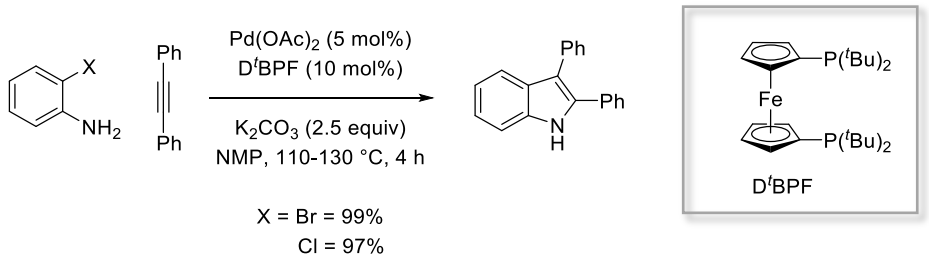
Masked tryptophan derivative **1.125** was synthesised in 77% yield on a 300 g scale from 2-iodoaniline **1.123** and TES-alkyne **1.124** (Scheme 35).[52]



Scheme 35: Synthesis of an unnatural tryptophan using a 300 g scale Larock reaction.

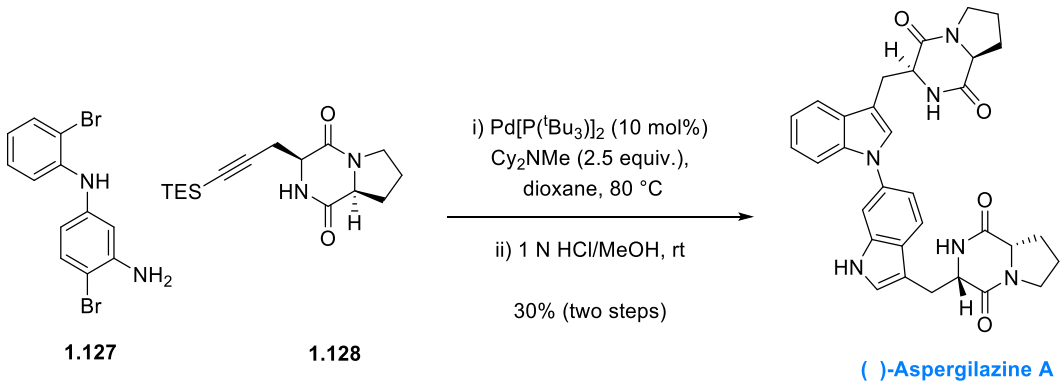
Acidic hydrolysis of **1.125** not only removes the TES group in the 2-position but also hydrolyses the Schöllkopf auxiliary to generate the unnatural amino acid **1.126**.

In 2004, a group from Boehringer-Ingelheim Pharmaceuticals published work on the Larock reaction using 2-bromo and -chloro anilines, rather than the thitherto employed 2-iodoanilines.[53] This was achieved using an electron-rich ligand, 1,1′-bis(di-*tert*-butylphosphino)ferrocene (D^{t}BPF), which increases the electron density on, and therefore nucleophilicity of, Pd; allowing the more facile insertion into the less reactive carbon-chlorine or -bromine bonds (Scheme 36).[54] The ability to use bromo- and chloro-anilines greatly increases the potential of the Larock reaction as these tend to be cheaper and more widely available than their iodo counterparts.



Scheme 36: Larock reaction on 2-chloro and -bromo anilines enabled using DtBPF.

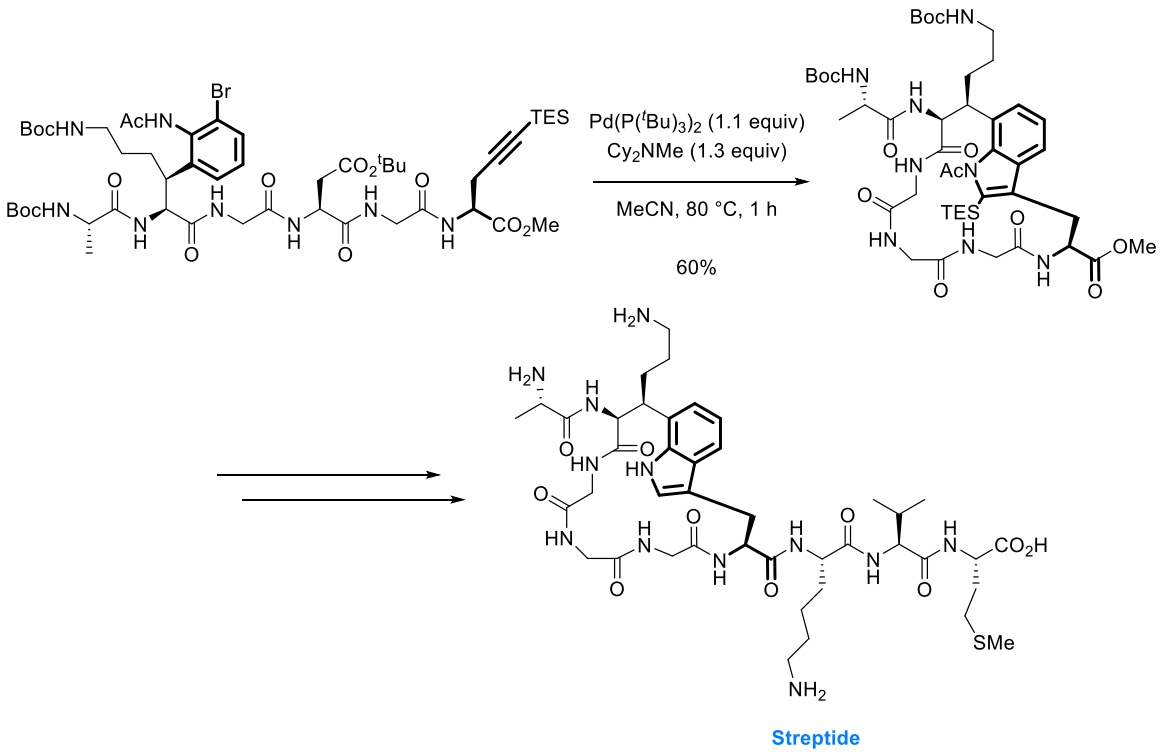
Reisman and co-workers disclosed the synthesis of (–)-aspergilazine A using a late-stage Larock reaction between bromoaniline **1.127** and TES-alkyne **1.128** (Scheme 37).[55]



Scheme 37: Synthesis of (-)–aspergilazine A by Reisman et al.

Two indoles are created in this step which requires 3 equivalents of alkyne **1.128**. The TES groups are then removed under acidic conditions to give the desired product. In contrast to many Larock examples, Pd(0) was used as the catalyst rather than a Pd(II) precatalyst and no chloride additive was employed, although no explanation was proffered as to why. Notably, this is an example of a Larock reaction on a 2-bromo aniline, rather than a 2-iodoaniline. This reaction was made feasible through the use of a strongly electron-donating ligand ($P(^tBu)_3$), analogous to the use of D^{t}BPF in the above work (see Scheme 36). Furthermore, the very sterically large $P(^tBu)_3$ is thought to form a coordinatively unsaturated monophosphine Pd complex, leaving a vacant coordination site which allows more facile alkyne coordination and carbopalladation (see Scheme 30).[56]

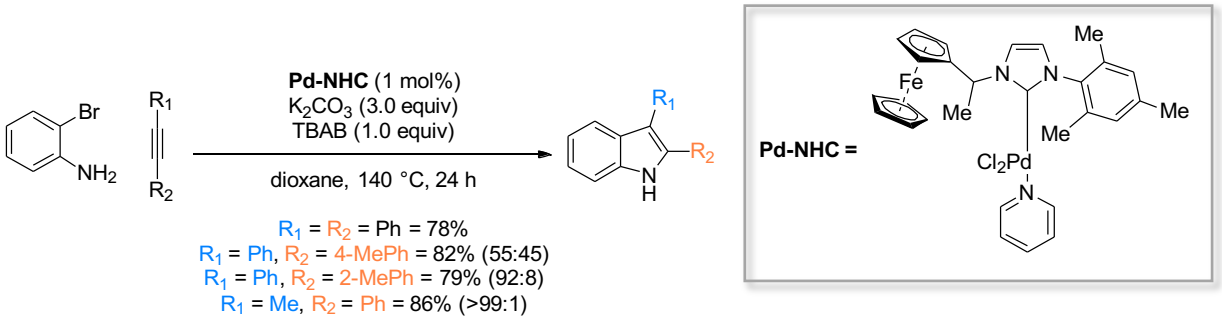
Recently, the Larock reaction has been used as a tool for macrocyclisation to form the cyclic peptide streptide, the synthesis of which allowed the structure to be correctly determined by comparing the synthetic sample with an authentic sample. (Scheme 38).[57]



Scheme 38: Larock macrocyclisation in the synthesis of streptide. Reacting components and tryptophan residue in product in bold.

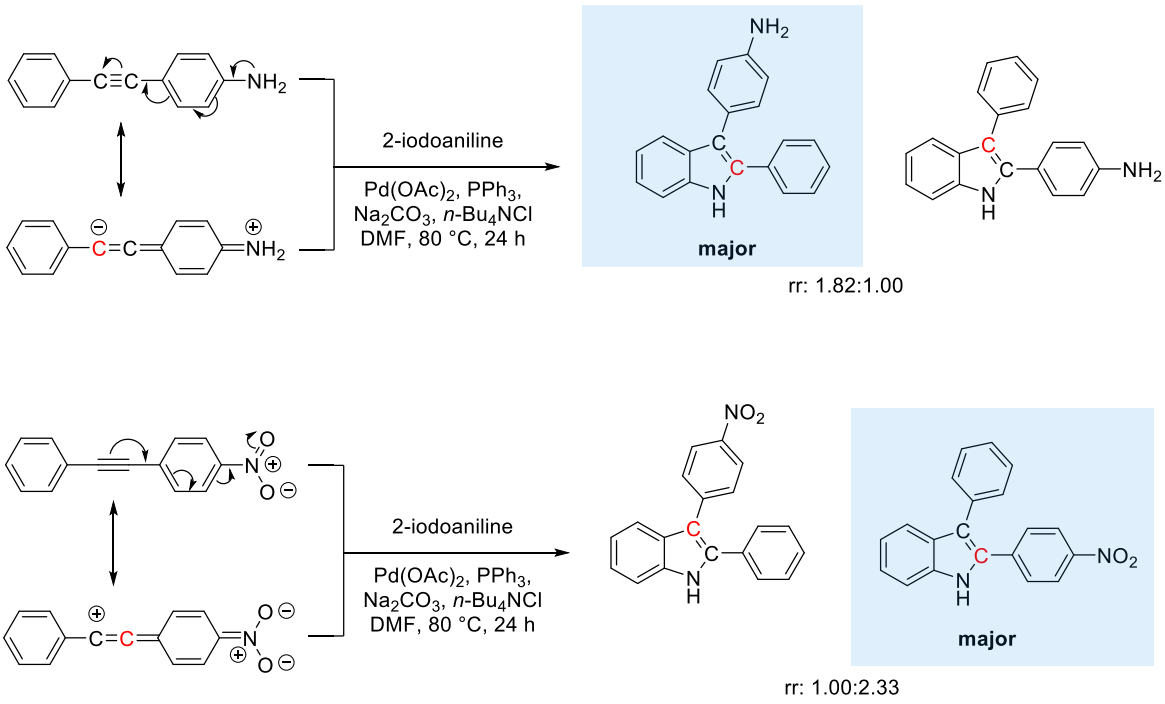
Boger and co-workers saw that streptide contained a tryptophan within the cycle and envisioned using the Larock reaction to create this residue, thereby closing the ring. Again, a bulky TES group is used to direct the regioselectivity of the reaction before being removed under acidic conditions. This represents another deviation from 'standard' Larock conditions as it uses an organic base (Cy_2NMe) and does not use a chloride additive. A superstoichiometric amount of Pd catalyst (no longer a catalyst but an expensive reagent) is required, the reason for this is not given, although it naturally indicates a problem with catalyst turnover. The variation of conditions from Larock reaction to Larock reaction could be considered a lack of generality in the reaction, which perhaps is linked to a lack of intimate understanding of the reaction and the precise role of the reagents and additives. The same lab had previously published work on using the Larock reaction to induce macrocyclisation while making indoles.[58][59] A noteworthy example of these was in the synthesis of 16-membered macrocycles; such large cycles are notoriously difficult to synthesise due to the large entropic penalty of tethering two ends of a long, flexible chain.[60] In many of these examples, however, a (super)stoichiometric amount of Pd was required.

Recently, a Larock reaction using an NHC ligand was reported (Scheme 39).[61] Bromo-anilines were reacted with various alkynes to produce indoles in generally high yields with Pd loadings as low as 1 mol%. This work also demonstrates the low regioselectivity observed in the Larock reaction when near-symmetrical alkynes are employed. Notably, when R_1 is phenyl and R_2 is 4-tolyl, there is nearly no regiodiscrimination (r.r. = 55:45) as the differentiating methyl group is too distal to have an influence over the regiodefining alkyne coordination and carbopalladation steps. When the methyl group is moved to the 2-position, it is much closer to the alkyne so exerts much more steric influence over the alkyne coordination and carbopalladation steps, giving a much higher r.r. of 92:8. When R_1 is methyl and R_2 is phenyl, essentially a single regioisomer is formed with an r.r. of >99:1, due to the much larger steric bulk of phenyl *vs.* methyl.



Scheme 39: Pd-NHC catalysed Larock reaction. Regiomeric ratios given in parentheses.

Electronics are also believed to influence the regioselectivity of the Larock reaction. Work by Chuawong and co-workers suggests that, based on the results of a Hammett analysis, that Pd migrates to the sp carbon which possesses the greater electron density during the carbopalladation step.[62] Following reductive elimination, the carbon with this greater electron density will form the C-2 of the indole, and the one with less electron density the C-3. This can be rationalised through the delocalisation of charges from or to the substituents on the phenyl ring, as shown below in Scheme 40.



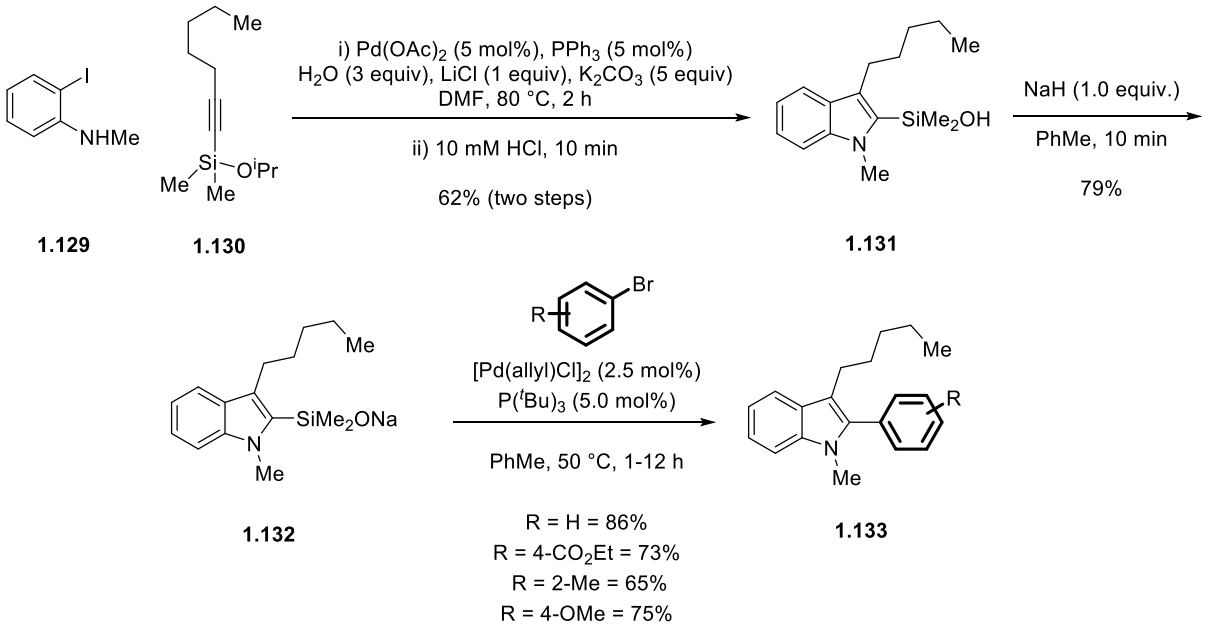
Scheme 40: Representation of electronic contributions to the regioselectivity of the Larock reaction. The carbon bearing greater electron density in the alkyne starting material is coloured red in the product.

In the case of electron-donating 4-(phenylethynyl)aniline, delocalisation of aniline's lone pair gives a resonance form where the negative charge sits on the sp carbon distal from the aniline, which gives a mixture of regioisomers favouring the product with this carbon at the C-2 of indole and the aniline is therefore placed at the C-3 of the indole. The inverse is true for electron-withdrawing 1-nitro-4-(phenylethynyl)benzene, where a resonance form leaves a positive charge on the sp carbon distal to nitrobenzene and the proximal carbon is comparatively electron-dense and therefore nitrobenzene is preferentially placed at the C-2 position. The preferred placement of the more electron-rich sp carbon at the C-2 of the indole is true in both cases. The authors made sure to minimise any steric contributions during this study by having the substituents at the *para* position in both cases.

These findings were further corroborated in a recent paper from the same group where they suggest that the electronics of the iodoaniline has little to no effect on the regiochemical product distribution of the Larock reaction and it is the electronics of the alkyne which dictate the outcome.[63] The electronics of the aniline do, however, have an impact on the rate of the reaction as electron-donating substituents were seen to retard the rate of oxidative addition, which is thought to be the rate-limiting step.

The regioselectivity of the Larock reaction is likely an interplay between steric and electronic contributions. Based on the observations seen in Scheme 39, a drastic change in r.r. results on changing R_2 = 4-Me to R_2 = 2-Me despite the difference in electronics being only negligible; both can stabilise the cation formed through delocalisation into the alkyne (see Scheme 40). Steric influences will likely therefore nullify any contributions from electronics.

Work carried out by Denmark and co-workers involved using a bulky silyl ether group to direct the regioselectivity of the Larock reaction, however, what stands out about this application is the subsequent conversion of this silyl group to the silanolate which is amenable to cross-coupling, giving access to a variety of 2-arylated indoles from a common starting material. (Scheme 41).[64]



Scheme 41: Denmark's Larock reaction to produce 2-siloxy indoles and their subsequent cross-coupling.

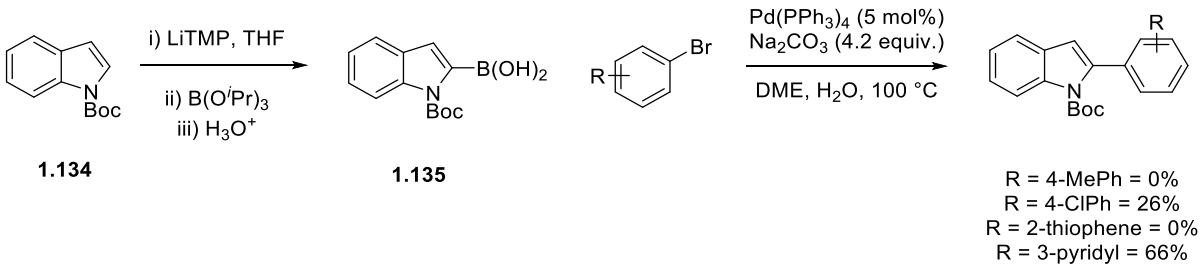
The sodium silanolate **1.132** was cross-coupled with various aryl bromides in generally good yields to give 2-arylindoles **1.133**. The retention of the silyl group as a functional handle demonstrates the potential of the Larock reaction in generating structural diversity from a common C-2 functionalised indole. The silanolate at the C-2 of the indole product can conceivably be coupled with any competent cross-coupling partner, in this instance an aryl bromide. If a large amount of 2-silanol indole, *e.g.* **1.131**, were synthesised and reacted with various aryl halides, a small library of indoles could be made. This library can be expanded greatly by varying the functionality of aniline **1.129** and alkyne **1.130** employed

in the Larock step. However, in this instance the authors highlight the difficulty in hydrolysing the silyl ether after the Larock step to give the silanol **1.131** while limiting the amount of complete desilylation under acidic conditions, so the conditions for this step must be judiciously chosen. Furthermore, the sodium salt **1.132** must be handled under an inert atmosphere in a glovebox for the subsequent cross-coupling reaction to prevent its quenching by atmospheric moisture to the silanol. Owing to these drawbacks of silanol/silanolates in a cross-coupling, a method whereby a Larock reaction can introduce a more stable functional linchpin, *e.g.,* a boronic ester, at the C-2 of an indole would be highly desirable.

The Larock indole synthesis has seen widespread use since its discovery 30 years ago in both methodology studies and total syntheses. It remains a powerful method for synthesising 2,3-disubstituted indoles under relatively mild conditions with the potential for excellent regioselectivity; the level of regioselectivity is almost entirely dependent on the size disparity between the two groups attached to the internal alkyne starting material.

1.2.4. 2-Borylation of Indoles.

2-Indolyl boronic acids can be made by deprotonation of indole using a very strong base (*e.g.* BuLi,[65] LDA[66]) then adding into a trialkyl borate followed by acidic hydrolysis to give the boronic acid. The harsh deprotonation conditions limits the scope of indoles this can be performed upon. An example of this was carried out by Johnson and coworkers (Scheme 42).[67]

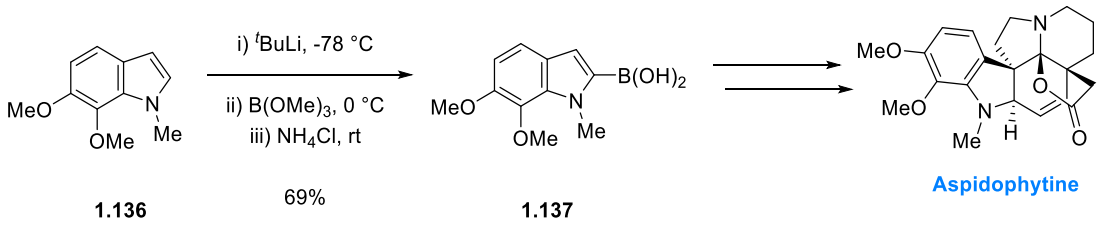


Scheme 42: Formation of indole-2-boronic acid using LiTMP. LiTMP = lithium 2,2,6,6-tetramethylpiperidide.

Indole **1.134** was deprotonated with the strong base LiTMP, quenched with tri-*iso*-propyl borate and the resultant boronic ester was hydrolysed under acidic conditions. The indole 2-

boronic acid product **1.135** was cross-coupled with various aryl halides in only moderate, if any, yields to give C-2 functionalised indoles.

In Nicolaou's asymmetric total synthesis of aspidophytine, indole **1.136** was deprotonated at C-2 using ^{t}BuLi before being quenched into trimethyl borate and hydrolysed to the boronic acid **1.137** with aqueous NH_4Cl (Scheme 43).[68]



Scheme 43: Formation of indole-2-boronic acid in the total synthesis of aspidophytine.

1.137 was isolated by "rapid" column chromatography in "semi-pure" form and had to be used in this form in the subsequent cross-coupling step, where it was used in excess. This exemplifies the instability of such indole-2-boronic acids. It would therefore be desirable to create an indole-2-boronic acid surrogate which is bench stable and stable to column chromatography as well as able to cross-couple productively in good yields.

1.3 BMIDA

The chemistry of boron is largely dictated by its p orbital. In the cases of trivalent boronic esters and acids, boron is covalently bound to one carbon atom and two oxygen atoms in a trigonal planar geometry where the boron is sp^2 hybridised and the p orbital orthogonal to these covalent bonds remains vacant (Figure 5). In the case of *N*-coordinated boronates, a nitrogen on the boronic ester backbone forms a Lewis acid-base adduct by donating its lone pair of electrons into the vacant p orbital (a dative bond), changing boron from a trivalent sp^2 atom into a tetravalent sp^3 atom (*i.e.,* from boronic ester to boronate) and this stereoelectronic change fundamentally alters the reactivity of boron. The most widely used of these *N*-coordinated boronates is the *N*-methyliminodiacetic acid (MIDA) boronic ester, hereafter referred to as BMIDA.

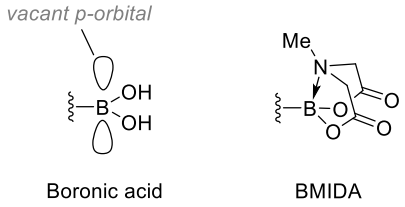
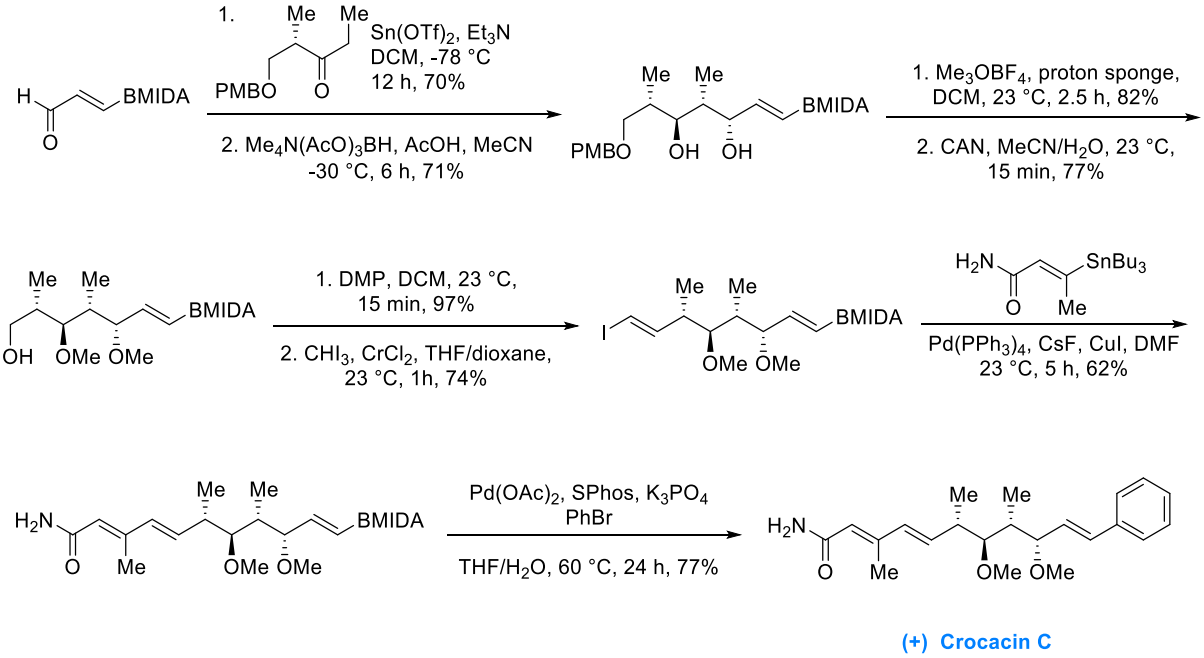


Figure 5: Structure of boronic acid and BMIDA.

BMIDAs are free-flowing (often crystalline) solids, monomeric, stable to column chromatography and are bench-stable for extended periods of time.[69] BMIDAs are also resistant to a range of chemical transformations as demonstrated by Burke and co-workers in the synthesis of (+)-crocacin C (Scheme 44).[69] In this work, the BMIDA group is retained from starting material to the final cross-coupling step, surviving an aldol reaction, methylation, borohydride reduction, two oxidations, a Takai olefination and Stille cross-coupling. It is only in the final step, where aqueous base and elevated temperatures are employed, that the BMIDA is hydrolysed to the boronic acid to cross-couple with bromobenzene in good yield.

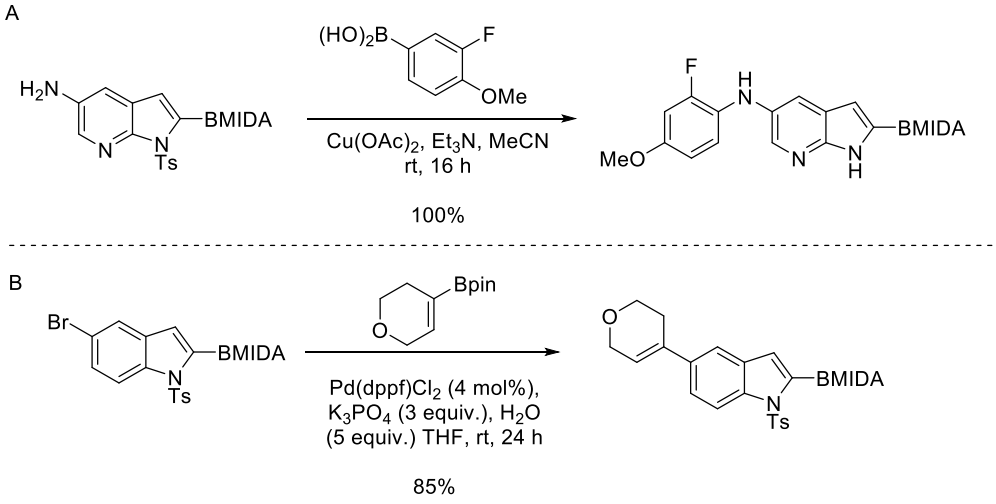


Scheme 44: Burke's synthesis of crocacin C, demonstrating the stability of BMIDA. Proton sponge = 1,8-bis(dimethylamino)naphthalene.

The authors further highlight the stability of the BMIDA group by carrying out an array of reactions on a different BMIDA-containing model substrate including an Appel iodination,

Horner-Wadsworth-Emmons olefination, Evans aldol, and reductive amination. The same group later demonstrated the stability of BMIDA esters to other Pd-catalysed cross-coupling reactions: Negishi, Sonogashira, Heck and Miyaura borylation.[70] The BMIDA group is, however, unstable to hard nucleophiles such as metal alkoxides, $LiAlH_4$, DIBAL-H and TBAF.[69] In this sense, BMIDA can be thought of as a boron protecting group.

Previous work in the Watson group has shown that 2-BMIDA indoles are also stable under Chan-Evans-Lam cross-coupling conditions (Scheme 45A) as well as Suzuki cross-coupling conditions between a B(pin) and aryl bromide (Scheme 45B).[71] In both these examples, the BMIDA at the C-2 of the indole is retained, further demonstrating the stability of BMIDAs and how they serve as an effectively orthogonal boron protecting group.

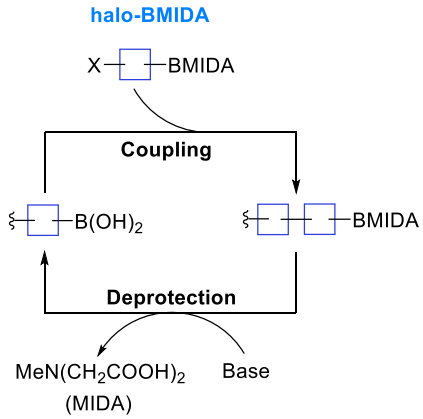


Scheme 45: A: Chan-Lam amination with retention of BMIDA, B: Suzuki-Miyaura cross-coupling with retention of BMIDA.

In order to 'deprotect' the boron in a BMIDA it must be hydrolysed; with moderately strong aqueous base, *e.g.,* K_3PO_4, complete hydrolysis is achieved on the order of several hours and when aqueous NaOH is used, complete hydrolysis is seen in minutes.[72] The boronic acid product, with its vacant, Lewis-acidic p orbital is now capable of transmetalating to, for example, Pd in a Suzuki-Miyaura reaction, as coordination between Pd hydroxide and this vacant p orbital is thought to be a key interaction in the transmetalation event.[47][73][74]

An excellent leverage of the stability of BMIDA groups, and their facile hydrolysis under basic aqueous conditions, was demonstrated again by Burke co-workers where building blocks containing both an sp^2 halide and sp^2 BMIDA (halo-BMIDA) were coupled with boronic acids in an iterative fashion, giving the homologated product bearing a BMIDA

group (Scheme 46).[75] As this BMIDA group could not cross-couple as it is, it was hydrolysed using aqueous base to give the boronic acid, which was then coupled with the halogen of another halo-BMIDA building block which can be hydrolysed and coupled again, theoretically *ad infinitum.*



Scheme 46: Representation of Burke's halo-BMIDA, coupling, deprotection, coupling method for iterative synthesis.

This idea culminated in the development of a machine which could couple, deprotect and couple again halo-BMIDA building blocks, giving automated iterative synthesis.[76] This method is analogous to the coupling, deprotection, coupling method used for the automated construction of peptides.[77]

Another useful feature of BMIDA is the so-called 'slow release' mechanism of its hydrolysis, whereby the rate of hydrolysis can be tuned so that only a small amount of a nascent, reactive boronic acid exists in the reaction mixture at any one time, with the remainder 'locked up' as the BMIDA. The small amount of boronic acid in the reaction mixture has the best chance possible to transmetalate to the catalytic amount of metal before it can protodeboronate, which is best achieved when the rate of hydrolysis is commensurate with the rate of catalytic turnover. If the rate of hydrolysis is too fast, a build-up of boronic acid in solution will allow for off-cycle degradation before the boronic acid can cross-couple fruitfully. This 'slow release' mechanism is particularly useful in the cross-coupling of unstable boronic acids. Heterocycles, particularly pyridines, with boronic acids in the 2-position are poor nucleophiles in the Suzuki-Miyaura cross-coupling as they are prone to protodeboronation.[78] This occurs fastest over a neutral pH range (4-8) where, through autoionisation of water, the pyridine is protonated and the remaining hydroxide forms a

boronate on the adjacent boronic acid, giving a zwitterionic product which fragments, resulting in protodeboronation (Figure 6).[79]

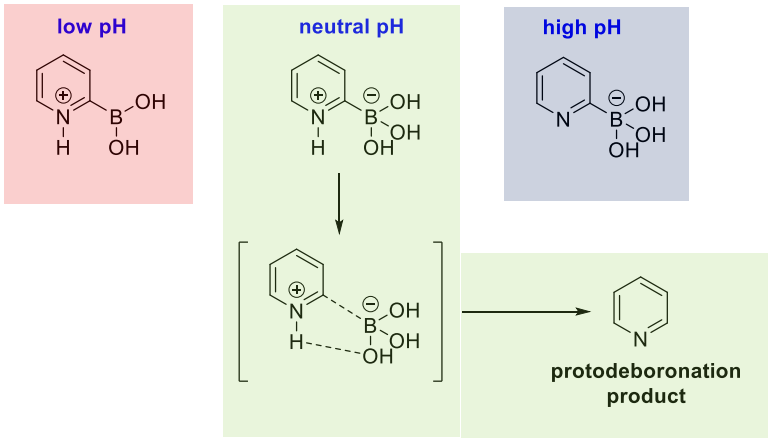
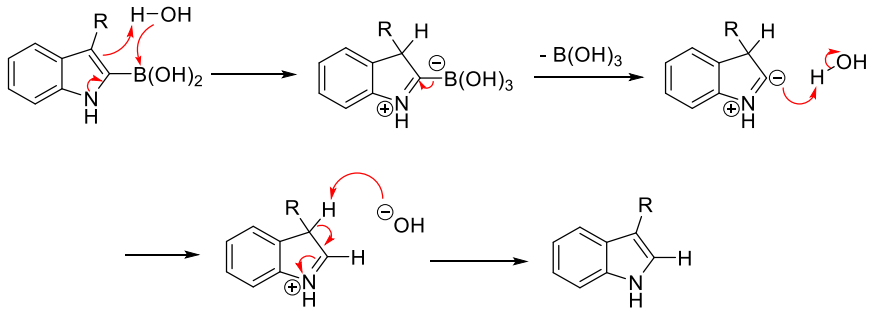


Figure 6: pH dependence on the protodeboronation of 2-pyridyl boronic acid.

At low pH, the pyridinium is formed, however the boron has little to no boronate character and conversely, at high pH, there is little to no pyridinium formation and the boron becomes the boronate. It is the formation of zwitterionic pyridinium and boronate which gives rise to protodeboronation, hence protodeboronation of 2-pyridyl boronic acids occurs fastest at neutral pH.

A conceivable method by which indole-2-boronic acids can protodeboronate is shown below (Scheme 47), this process also involves the autoionisation of water and would therefore occur fastest at neutral pH.

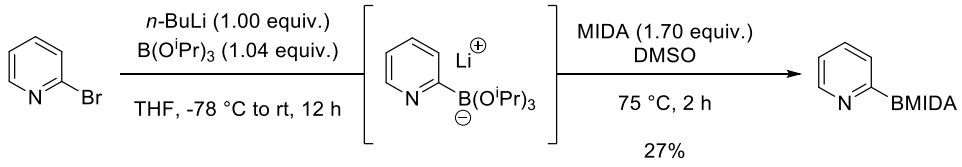


Scheme 47: a potential protodeboronation mechanism for indole-2-boronic acid.

A potential method to mitigate this process is to attach an electron-withdrawing group to the indole nitrogen, which will attenuate the nucleophilicity of the C-3 position of the indole.

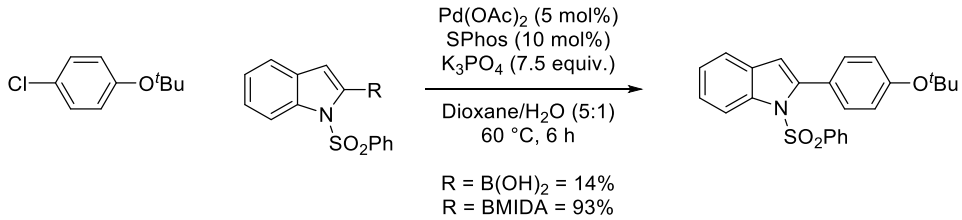
However, based on the outcome of the reactions seen in Scheme 42 and Scheme 49 this can still result in poor yields of the cross-coupled product.

In an attempt to tackle the poor cross-coupling performance of 2-heterocyclic boronic acids, Burke and co-workers formed pyridyl-2-boronic acid MIDA ester which is capable of undergoing cross-coupling reactions in high yields *i.e.,* the slow-release of unstable boronic acid circumvents the instability problem of the boronic acid.[80] The synthesis of the 2-BMIDA pyridine involved first lithium/halogen exchange of 2-bromopyridine and addition of this lithiate into tri-*iso*-propyl borate followed by ligand exchange of the boronate with MIDA to form the BMIDA (Scheme 48).[72] This synthesis is rather arduous and protracted and as it uses BuLi, there are limitations as to what substitution can be present on the pyridine, it also requires a 3-day long freeze-drying process in order to remove excess DMSO.



Scheme 48: Burke's synthesis of 2-BMIDA pyridine from 2-bromopyridine

The same lab further showed that indole-2-boronic acid MIDA ester was significantly more stable under ambient storage than the corresponding boronic acid.[72]. Importantly, the BMIDA also greatly outperformed the boronic acid in a benchmark Suzuki-Miyaura reaction (93% vs. 14%, respectively) (Scheme 49).



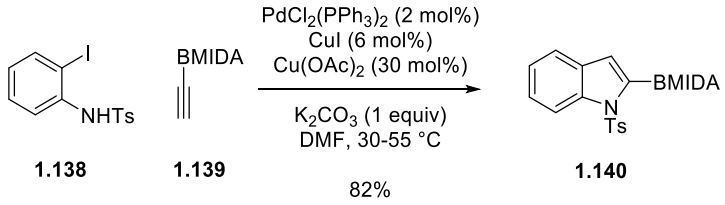
Scheme 49: Comparison of cross coupling reaction with indole-2-boronic acid vs. the MIDA ester.

Based on these observations of the useful stability of BMIDA groups and their ability to circumvent boronic acid instability in the Suzuki-Miyaura reaction, the synthesis of indoles bearing a BMIDA group at the C-2 position without first forming the boronic acid by

deprotonation using a very strong base or by lithium/halogen exchange, using BuLi, would be desirable.

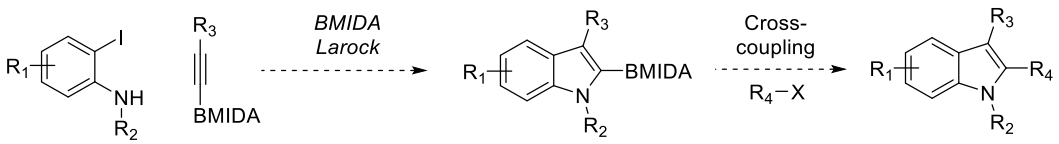
1.4. Project Aims.

Previous work in the Watson group has shown that 2-iodoaniline **1.138** can undergo a cascade Sonogashira/cyclisation reaction with acetylene BMIDA **1.139**, resulting in a Castro-type ring closure and formation of 2-BMIDA indole **1.140** (Scheme 50).[71]



Scheme 50: Synthesis of 2-BMIDA indoles by cascade Sonogashira/Cacchi-type annulation.

Toste and Sakurai have also published work on the sequential Sonogashira and cyclisation of 2-iodo-anilines and -phenols to make 2-BMIDA indoles and benzofurans, respectively.[81][82] A drawback of these methods is the inability to install functionality at the C-3 of the indole as the Sonogashira step necessitates the use of a terminal alkyne. The work in this thesis is an expansion on these ideas and concerns using a so-called 'BMIDA Larock' reaction to create a variety of indoles bearing tuneable functionality at C-3, on the indole nitrogen, at the 4,5,6,7-positions of the indole as well as a useful synthetic linchpin (BMIDA) at the C-2, amenable to cross-coupling (Scheme 51).

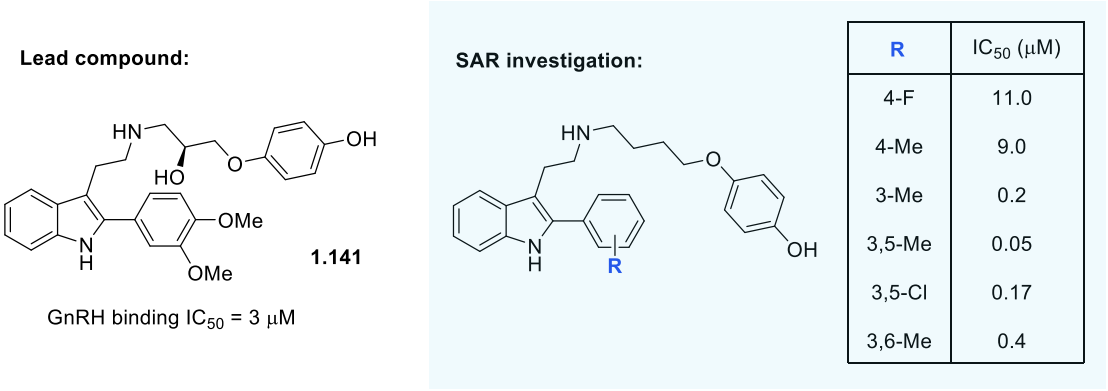


Scheme 51: Work to be carried out in this thesis.

The functionality of the indole products will be dictated by varying the alk-1-ynyl-1-boronic acid MIDA ester (hereafter referred to as 'alkyne BMIDA') and 2-iodoaniline starting materials, thus allowing a 'combinatorial' approach which, once the methodology has been optimised, will give access to a wide array of indole products by combining different

permutations of aniline and alkyne BMIDAs. Furthermore, these indole products, which are stable under ambient conditions, can be further derivatised by cross-coupling at the C-2 position which would allow even greater structural diversity to be achieved. Using such an approach is useful in, for example, synthesising drug/natural product derivatives where the synthesis is not necessarily target-driven, rather a wide spread of target-like products is desirable.

For example, Chu and co-workers found that varying the C-3 alkyl and C-2 aromatic substituents on indole gave a marked increase in potency *vs*. the lead compound **1.141** in its ability to suppress levels of sex hormones in rats (Figure 7).[83] This could lead to therapeutic use in humans as a number of endocrine disorders are caused by an excess of these hormones.

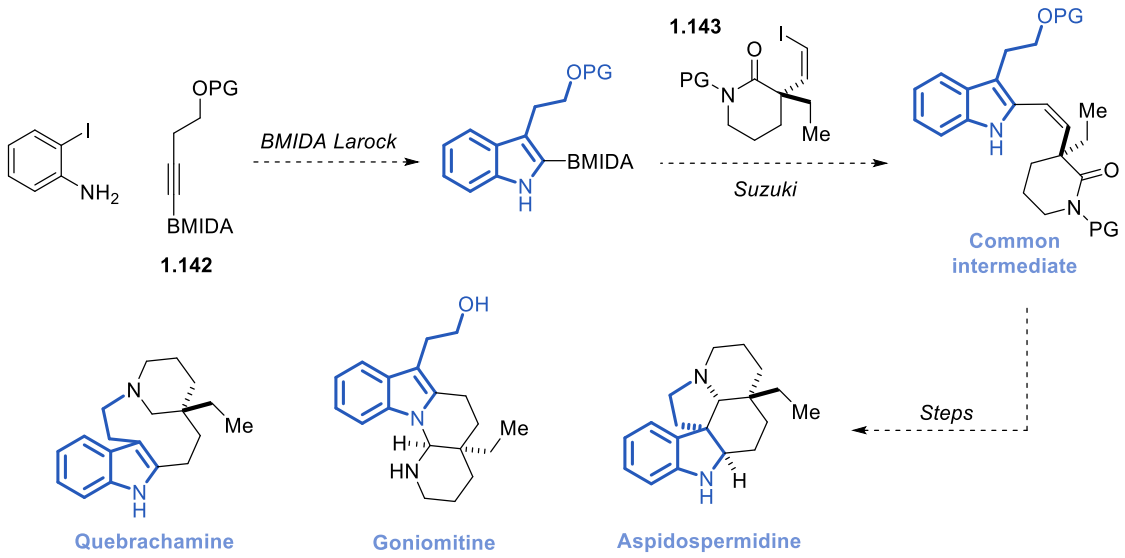


R	IC_{50} (μM)
4-F	11.0
4-Me	9.0
3-Me	0.2
3,5-Me	0.05
3,5-Cl	0.17
3,6-Me	0.4

Figure 7: SAR probing of GnRH antagonist by varying aromatic group at the C-2 position.

After probing the importance of the linker between the pendant tryptamine amine and hydroquinone ether, a linker of 4 -CH_2- units was found to be optimal. Variation of the aromatic group at the C-2 position led to a 60-fold large increase in binding affinity for the target receptor when a 3,5-dimethylphenyl group is used. Each of the compounds tested was synthesised from tryptamine, which is a convenient source of indole, however, this limits the scope for SAR as there will necessarily be no substitution around the benzenoid core whose activity could be probed. Using tryptamine will also only give products with ethylamine at the C-3 position of the indole with no straightforward method of varying this appendage. There could exist even more powerful drugs of this class which were missed due to the limitation of using tryptamine as a starting material. The BMIDA Larock protocol proposed here would allow access to, for example, this chemical space by allowing the use of substituted iodoanilines, offering bespoke substitution around the benzenoid ring, as well as C-2 and C-3 functionality dictated by the Suzuki-cross coupling electrophile and alkyne BMIDA, respectively.

Building on this, natural products containing an indole may also be synthesised using a BMIDA Larock. For example, members of the *aspidosperma* family of alkaloids can be synthesised from a common intermediate, obtained from a BMIDA Larock reaction between 2-iodoaniline and alkyne BMIDA **1.142**, followed by Suzuki cross-coupling with lactam **1.143** (Scheme 52).



Scheme 52: Synthesis of aspidosperma alkaloids from a common intermediate. PG = protecting group

As discussed at the start of this chapter and as shown in Figure 7, many indole-containing natural products are derived from tryptamine and as such lack substitution around the benzenoid core and have an ethylamine chain at the C-3 position. Using this BMIDA Larock methodology, we are no longer limited to the tryptamine skeleton and can vary the iodoaniline and alkyne BMIDA to access unnatural natural product analogues largely inaccessible through late-stage functionalisation of the parent natural product.

To summarise, the aims of this project are to:

- Develop and optimise Larock reaction conditions to synthesise a variety of C-2-BMIDA, C-3 functionalised indoles.
- Demonstrate the utility of this methodology in using it to synthesise a common intermediate, from which several natural products can be made straightforwardly.

Chapter Two: Development and Optimisation of a BMIDA Larock Protocol: Results and Discussion

Compounds in this chapter will be labelled:

Alkyne BMIDAs	1a, 1b, 1c… 1*x*
Iodoanilines	2a, 2b, 2c… 2*x*
C-3 sp^3 Indole BMIDA products	3a, 3b, 3c… 3*x*
C-3 sp^2 Indole BMIDA products	4a, 4b, 4c… 4*x*

2. Results and Discussion

2.1. Synthesis of Starting Materials

2.1.1. Alkyne BMIDA Synthesis

For this methodology project, a variety of alkyne BMIDAs would be required. Their synthesis falls into two general categories: i) addition of acetylide (either a pre-formed, commercial Grignard salt or by deprotonation of a terminal alkyne with a strong base) into trimethyl borate ($B(OMe)_3$) then ligand exchange to the MIDA ester, or ii) Sonogashira of acetylene BMIDA **1a** with an aryl halide/pseudohalide. These methods differ on whether the C-B is formed during the reaction (as in the former) or whether it is already present, and a C-C bond is formed (as in the latter). **1a** and propyne BMIDA **1b** are commercially available (Figure 8), however, higher alkyne BMIDAs are not so must be synthesised in-house. **1a** would be used as a starting material for aromatic alkyne BMIDAs (*via* Sonogashira reaction) and **1b** would be used as the workhorse substrate for the optimisation of BMIDA Larock reaction conditions.

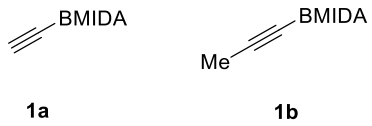
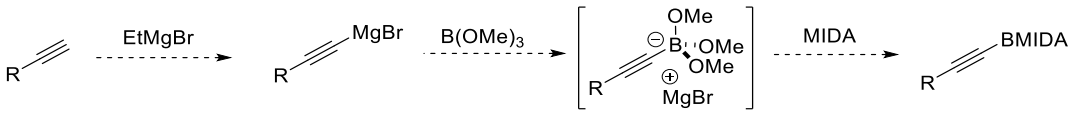


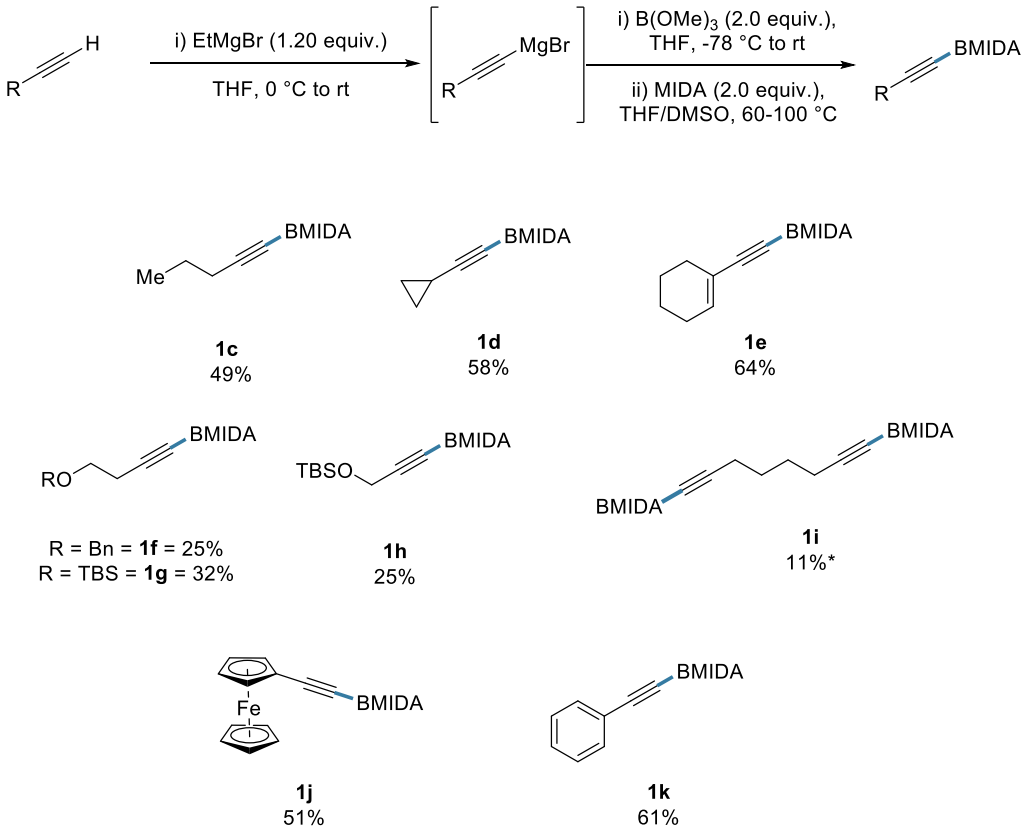
*Figure 8: acetylene BMIDA, **1a**, and propyne BMIDA, **1b**.*

Following Burke and co-workers' method,[84] commercially acetylide Grignard salts can be added into $B(OMe)_3$ to form the respective triol boronate, followed by ligand exchange with *N*-methyliminodiacetic acid to form the desired alkyne BMIDA (Scheme 53).



Scheme 53: Synthesis of acetylene and propyne BMIDAs.

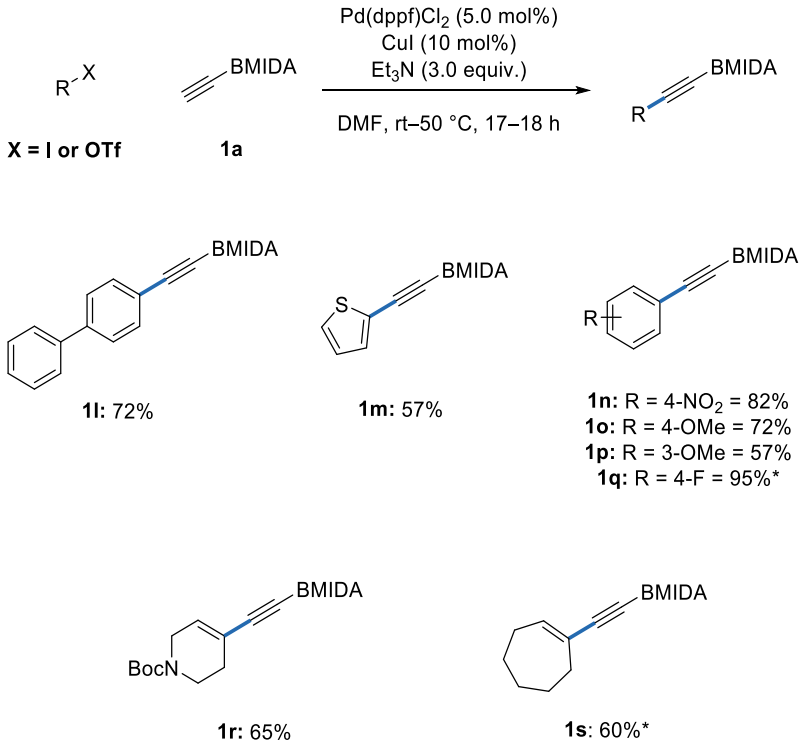
This method was used to create a number of alkyne BMIDAs in poor to moderate yields (Scheme 54).



*Scheme 54: Synthesis of alkyne BMIDAs from terminal alkynes. *i) EtMgBr (2.40 equiv.), THF, 0 °C– rt. ii) $B(OMe)_3$ (4.00 equiv.), THF, –78 °C to rt. iii) MIDA, 4.0 equiv. DMSO/THF, 60-100 °C.*

Perhaps the largest disadvantage to this literature procedure is the need for manual and prolonged addition of the trimethyl boronate suspension into MIDA in hot DMSO, under vacuum, with constant distillation of THF and nascent MeOH. This required full attention as the addition had to be carefully managed so that it did not bump out of control, the temperature did not drop significantly, and the addition funnel tap did not become clogged by the heterogeneous mixture of the boronate and other salts in THF. A modification to the procedure was made where the crude boronate was simply combined in a flask with DMSO and MIDA and concentrated on a rotary evaporator. After most of the volatiles had been removed, the remaining DMSO was then distilled by heating under high vacuum and the crude product was worked up according to the original procedure. This greatly increased operational simplicity without sacrificing yield.

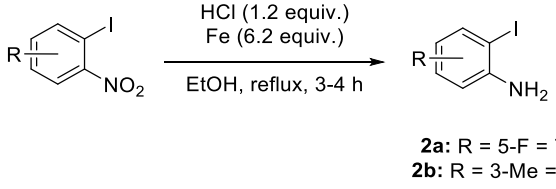
A Sonogashira reaction could also be used to create various alkyne BMIDAs from the simplest alkyne BMIDA building block **1a** (Scheme 55):



*Scheme 55: Sonogashira reactions to produce aromatic acetylene BMIDAs. *Reaction carried out by Dr Jamie Fyfe.*

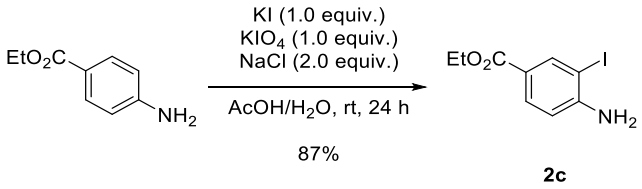
2.1.2. Iodoaniline Synthesis

Substituted 2-iodoanilines are widely available and generally inexpensive, allowing their use directly in the BMIDA Larock reaction. However, their substitution pattern is typically dictated by the electron-donating nature of aniline and substitution is therefore typically seen at the 4- or 6-positions. This somewhat limits the structural diversity that can be achieved using the BMIDA Larock protocol and therefore to access 3- or 5-substituted-2-iodoanilines, 2-iodonitrobenzenes substituted at these positions were purchased and reduced. This was achieved using a Bechamp reduction: HCl and superstoichiometric Fe powder in refluxing ethanol (Scheme 56).[85]



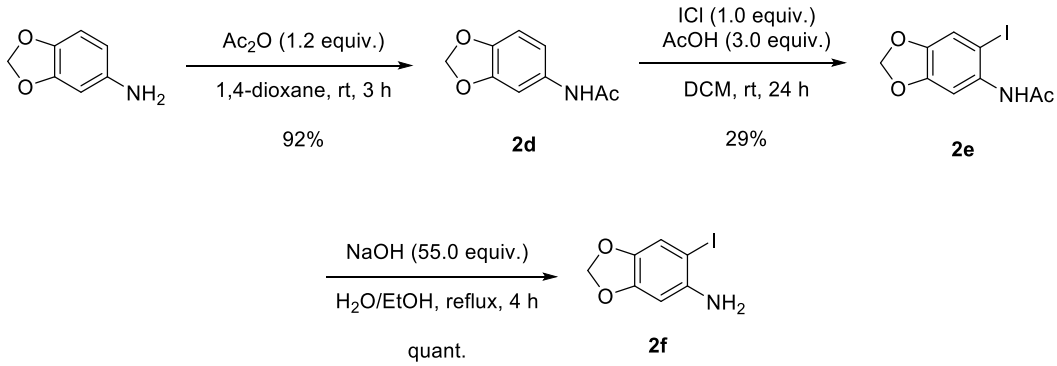
Scheme 56: Bechamp reduction of nitrobenzenes to anilines.

Anilines can be iodinated at the 2-position, for example in the synthesis of iodobenzocaine **2c**, formed from iodination of benzocaine in an acidic mixture of KI, NaCl and KIO_4 (Scheme 57).[86]



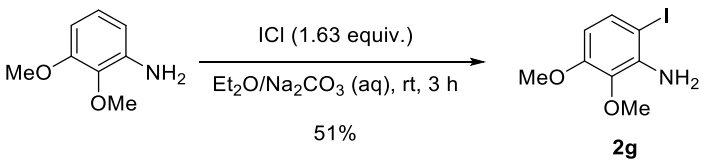
Scheme 57:Iodination of benzocaine.

3,4-Methylenedioxyaniline was iodinated using ICl, although the aniline had to be first acetylated to **2d**, perhaps to limit over-iodination on the relatively electron-rich aniline (Scheme 58). Removal of the acetate group in **2e** gave the target 2-iodoaniline **2f**.



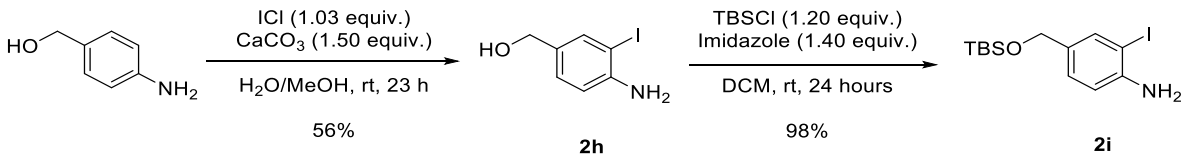
Scheme 58: Synthesis of methylenedioxyiodoaniline.

Electron-rich 2,3-dimethoxyaniline was iodinated without the need to first acetylate the aniline, giving **2g** in 51% yield.



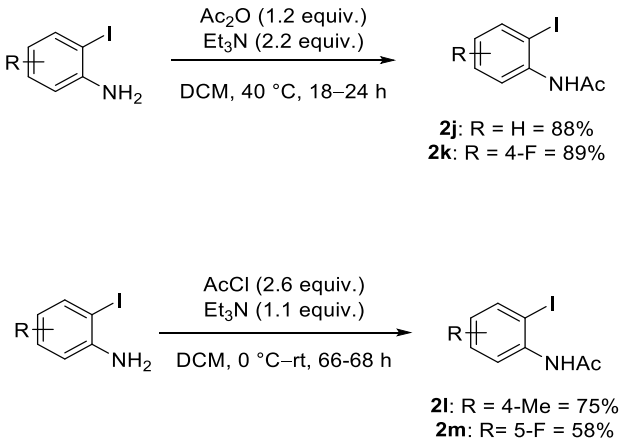
Scheme 59: Iodination of 2,3-dimethoxyaniline.

4-Aminobenzyl alcohol was also iodinated using ICl to give **2h**, followed by protection of the benzyl alcohol with a TBS group to give **2i**.



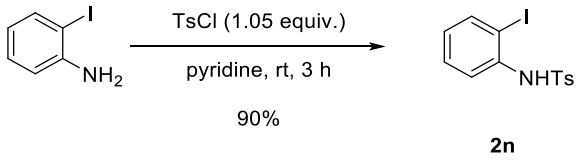
Scheme 60: Iodination and protection of aminobenzyl alcohol.

As will be discussed in the following section, it was discovered through the course of optimisation that some iodoaniline substrates required *N*-acetylation to increase the yields of the BMIDA Larock reaction in certain cases. Acetylation was carried out using either acetyl chloride or acetic anhydride (Scheme 61).



Scheme 61: Acetylation of iodoanilines.

In the same vein, 2-iodoaniline was tosylated to give **2n** (Scheme 62):

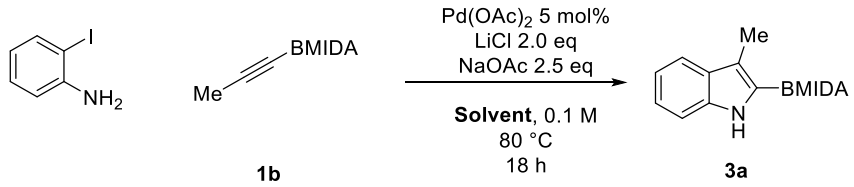


Scheme 62: Tosylation of iodoaniline.

With a selection of anilines and alkyne BMIDAs in hand, the reaction conditions were optimised to optimise the yields of BMIDA Larock products.

2.2. Reaction Optimisation Data

The simplest possible BMIDA Larock product, **3a**, was chosen as the reaction optimisation target, formed by reaction between 2-iodoaniline and propyne BMIDA **1b**. Optimisation of the Larock reaction began with an investigation of the solvent (Table 1). Dipolar aprotic solvents performed best where DMSO gave the highest conversion and DMF and NMP gave similar albeit slightly lower yields (Entries 1 to 3). MeCN is also a dipolar aprotic solvent however, this solvent only provided trace conversion to **3a** (Entry 4). The success of dipolar aprotic solvents is likely due to their ability to sufficiently solubilise inorganic salts in the reaction mixture. Furthermore, BMIDAs are strongly polarised due to the dative bond between nitrogen's lone pair and boron's vacant p-orbital, lending an almost ylidic character to the group and as a result, polar solvents are superior at solubilising BMIDAs.

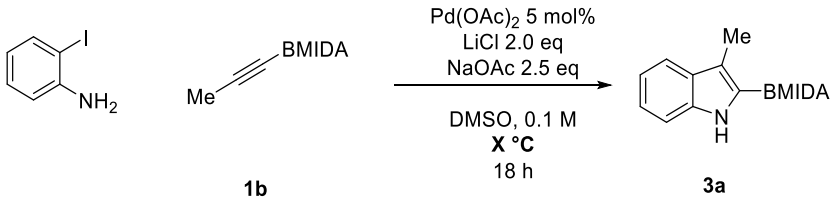


Entry	Solvent	Yield (%)[a]
1	DMF	69
2	DMSO	76
3	NMP	69
4	MeCN	<5
5	THF	0
6	Dioxane	0
7	Toluene	0
8	Sulpholane	0

Table 1: Larock reaction solvent study. [a]Yields determined using ^{1}H NMR assay with 1,4-dinitrobenzene as an internal standard.

A temperature study revealed that the reaction gave trace conversion when carried out at room temperature (Table 2, Entry 1). Raising the temperature to 40 °C gave just 5% yield and 60 °C gave the product in 42% yield (Entries 2 + 3, respectively), falling short of the conversion achieved at 80 °C (Table 1, Entry 2). At 100 °C, a decrease in yield was seen *vs.* 80 °C (Table 2, Entry 4). It is known that BMIDA esters hydrolyse under aqueous basic conditions and although best efforts were taken to exclude water from the reaction, it is likely

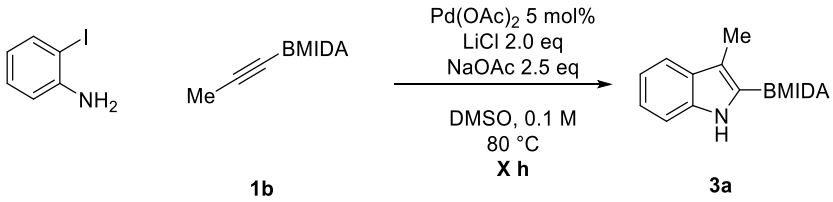
a very small amount of water is nonetheless present which hydrolyses the BMIDA group at higher temperatures in the presence of weakly basic NaOAc.[87] Every effort can be taken to exclude water, however, it is possible that the boronic acid produced by BMIDA hydrolysis can trimerise into the boronic acid anhydride, *i.e.,* boroxine, releasing water in the process.[88] The extent to which this occurs under these conditions is not clear, although it is unlikely to happen to any large extent as the concentration of boronic acid will be low at any time due to the slow release hydrolysis of BMIDA and the instability of the boronic acid.[89] There is also the possibility that free MIDA can react with cyclise with itself, forming a 6-membered anhydride, releasing an equivalent of water.



Entry	Temperature (°C)	3a (%)[a]
1	rt	Trace
2	40	5
3	60	42
4	100	50

Table 2: Larock reaction temperature study. [a]Yields determined by using ^{1}H NMR assay with 1,4-dinitrobenzene as an internal standard.

Performing the reaction at 80 °C, a time study showed that conversion reached a maximum of 72% after 8 hours (Table 3). No decrease in yield was observed after 24 hours, suggesting that the product is stable in the reaction mixture at 80 °C. It was therefore decided that the reaction would be carried out for 18 hours, as this would safely allow the reaction to achieve maximum yield without loss of product.

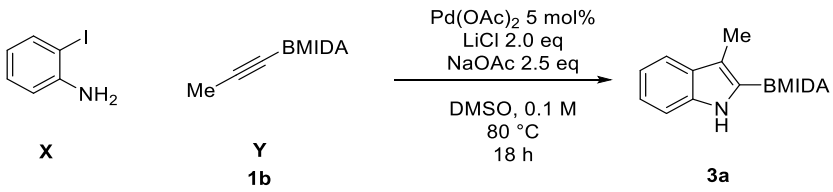


1b **3a**

Entry	Time (h)	3a (%)[a]
1	2	49
2	4	62
3	6	65
4	8	72
5	24	73

Table 3: Larock reaction time study. [a]Yields determined by using ^{1}H NMR assay with 1,4-dinitrobenzene as an internal standard.

The stoichiometry employed up to this point was 1.0 equivalent of **1b** and 1.2 equivalents of the **2e**. In many of the Larock reactions carried out during the optimisation, there would often be very little, if any, propyne BMIDA **1b** remaining. The stoichiometry of the reagents was altered in the hope that this would increase the yield, as it was possible some of the alkyne BMIDA starting material would decompose before it could react. A very minor increase in yield was observed on increasing the equivalents to 1.5 (Table 4, Entry 1). Increasing this further gave a very slight drop back down in yield (Entry 2). Reversing the stoichiometry, so 2-iodoaniline was now the limiting reagent, also showed no great variation in yield (Entries 3–5). 2-Iodoanilines are relatively cheap and widely available, whereas alkyne BMIDAs are generally not commercially available (two exceptions being **1a** and **1b**) so they must be made in-house in a rather protracted, low-yielding process; it is therefore reasonable to use the former in excess. Compounded with the fact that the indole BMIDA product and alkyne BMIDA starting material often co-elute during purification, the stoichiometry remained unaltered.

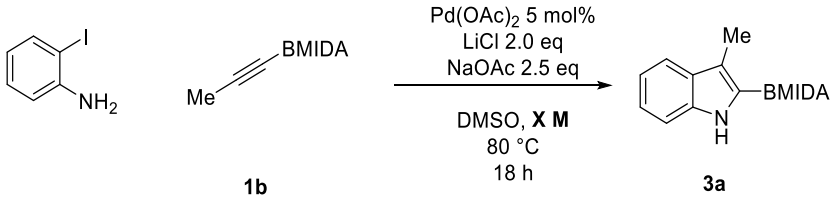


X Y 1b 3a

Entry	X:Y	3a (%)[a]
1	1.5:1.0	77
2	2.0:1.0	74
3	1.0:1.2	76
4	1.0:1.5	72
5	1.0:2.0	73

Table 4: Larock reaction stoichiometry study. [a]Yields determined by using ^{1}H NMR assay with 1,4-dinitrobenzene as an internal standard.

A concentration study was carried out and both halving and doubling the concentration gave no change in yield (Table 5, Entries 1 + 2, respectively). Increasing concentration five-fold gave a significant decrease in yield (Entry 3), likely owing to the decreased solubility of salts and BMIDA species in the concentrated reaction mixture and as such, the concentration was maintained at 0.1 M.



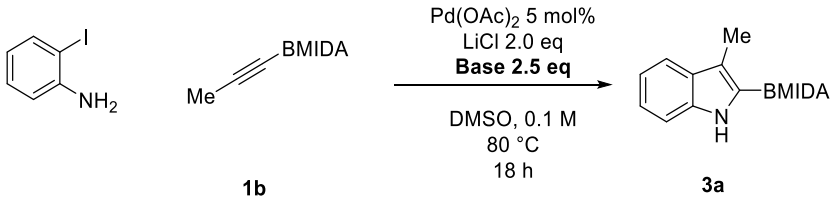
1b 3a

Entry	Concentration (M)	3a (%)[a]
1	0.05 (4.00 mL)	66
2	0.20 (1.00 mL)	67
3	0.50 (0.40 mL)	55

Table 5: Larock reaction concentration study. [a]Yields determined by using ^{1}H NMR assay with 1,4-dinitrobenzene as an internal standard.

A survey of bases showed that KOAc and LiOAc performed similarly to NaOAc (Table 6, Entries 1 + 2, respectively). K_3PO_4 gave a large decrease in yield to just 17% (Entry 3), which could be due to increased hydrolysis of the BMIDA in the presence of this comparatively strong base. K_2CO_3 is also stronger than acetate bases and this base results in

only trace conversion (Entry 4). Et_3N performed well in this reaction, giving a yield of 71% which is comparable to acetate bases (Entry 5).

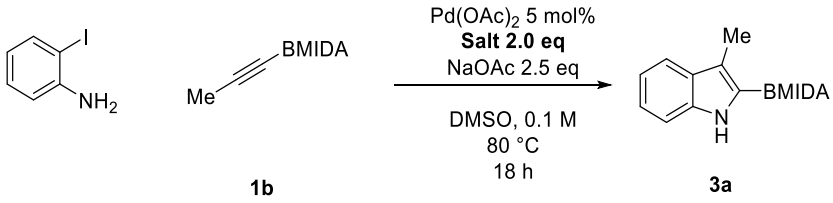


1b 3a

Entry	Base	3a (%)[a]
1	KOAc (49.1 mg)	78
2	LiOAc (33.0 mg)	77
3	K_3PO_4 (106.2 mg)	17
4	K_2CO_3 (69.1 mg)	<5
5	Et_3N (70.0 µL)	71

Table 6: Larock reaction base study. [a]Yields determined by using ^1H NMR assay with 1,4-dinitrobenzene as an internal standard.

As chloride is thought to play an important role in the catalytic cycle of the Larock reaction, namely ligating to Pd to form an anionic Pd(0) complex prior to oxidative addition (see Scheme 30),[90] various halide salts were trialled (Table 7). Both LiF and NaCl gave yields comparable to LiCl (Entries 1 + 2, respectively). TBACl (*tetra-n*-butyl ammonium chloride) exists as its hydrate and it is possible this water contributed to the hydrolysis of BMIDA in either the product or starting material, hence its low conversion (Entry 3).

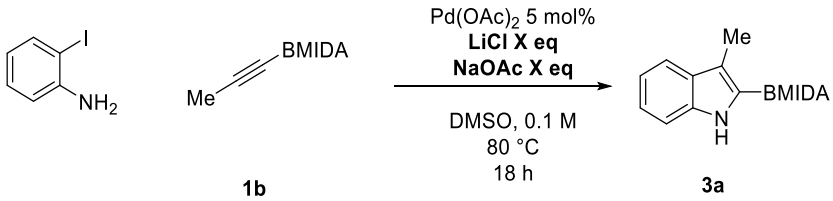


1b 3a

Entry	Salt	3a (%)[a]
1	LiF (10.4 mg)	77
2	NaCl (23.4 mg)	77
3	TBACl hydrate (111.2 mg)	56

Table 7: Larock reaction salt additive study. [a]Yields determined by using ^1H NMR assay with 1,4-dinitrobenzene as an internal standard.

The stoichiometry of halide salt:base was investigated next and the importance of base became clear, as each incremental decrease gave a drop in yield (Table 8, Entries 1–4), with 0 equivalents of base giving only 7% yield (Entry 4). Conversely, it was found that the equivalents of LiCl could be lowered, even to substoichiometric amounts, without a detriment to yield (Entries 5–7). However, removing LiCl entirely results in a sizeable decrease in yield to 66% (Entry 8). As chloride is thought to bind to Pd(0) to make chloropalladium complex, it stands to reason that only a catalytic amount of chloride is required to react with the catalytic amount of Pd present, and its entire absence results in a lower yield.

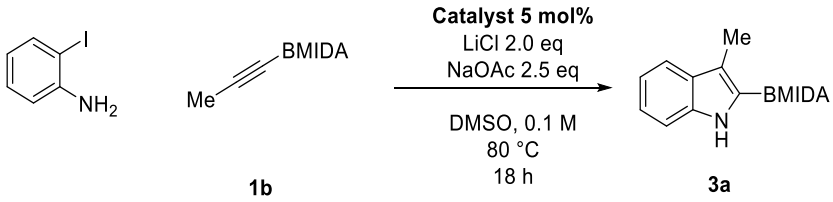


1b **3a**

Entry	LiCl:NaOAc (equiv.)	3a (%)[a]
1	2:3 (17.0: 49.2 mg)	82
2	2:1 (17.0: 16.4 mg)	79
3	2:0.5 (17.0: 8.2 mg)	45
4	2:0 (17.0 mg)	7
5	3:2.5 (25.4 mg: 41 mg)	78
6	1:2.5 (8.5 mg: 41 mg)	83
7	0.5:2.5 (4.2: 41 mg)	83
8	0:2.5 (41 mg)	66

Table 8: Larock reaction salt:base stoichiometry study. [a]Yields determined by using ^{1}H NMR assay with 1,4-dinitrobenzene as an internal standard.

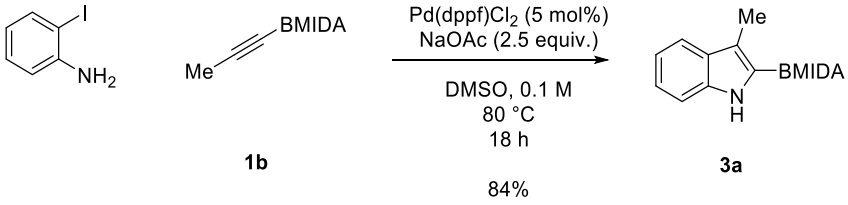
Finally, a catalyst study revealed that many Pd(II) precatalysts performed similarly well to each other (Table 9, Entries 1–4) although $Pd(PPh_3)_2Cl_2$ resulted in a lower yield (Entry 5). Use of a Pd(0) catalyst gave only minor conversion to product (Entry 6). Although the catalysts in Entries 1–4 gave similar yields, $Pd(dppf)Cl_2$ became the desired catalyst.



Entry	Catalyst	3a (%)[a]
1	$PdCl_2$ (1.8 mg)	85
2	$Pd(dppf)Cl_2$ (7.3 mg)	87
3	$[Pd(allyl)Cl]_2$ (1.8 mg)	84
4	$Pd(MeCN)_2Cl_2$ (2.6 mg)	85
5	$Pd(PPh_3)_2Cl_2$ (7.0 mg)	62
6	$Pd(PPh_3)_4$ (11.6 mg)	10

Table 9: Larock reaction catalyst study. [a]Yields determined by using ^1H NMR assay with 1,4-dinitrobenzene as an internal standard.

Based on the information obtained from these optimisation reactions, a set of ideal reaction conditions was obtained: the reaction would be carried out at 0.1 M concentration in DMSO for 18 hours. 2.5 equivalents of NaOAc would be used, along with 2.0 equivalents of LiCl and 5 mol% of $Pd(dppf)Cl_2$. The stoichiometry of reagents is 1.2 equivalents of aniline and 1.0 equivalent of alkyne BMIDA. In addition, based on the results in Table 8, it was theorised that the equivalents of LiCl could be lowered even to zero. Gratifyingly, the reaction proceeded well in the absence of LiCl and product **3a** was isolated in 84% yield using the LiCl-free optimised conditions (Scheme 63).



Scheme 63: Isolation of BMIDA Larock product using optimised conditions.

A crystal structure of **3a** was obtained to unambiguously define the regioselectivity of the reaction and indeed the C-2 BMIDA indole is formed.

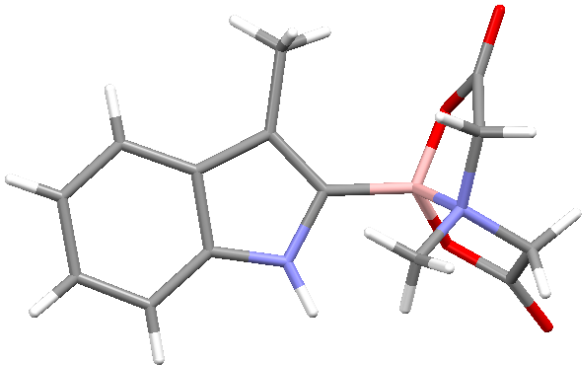
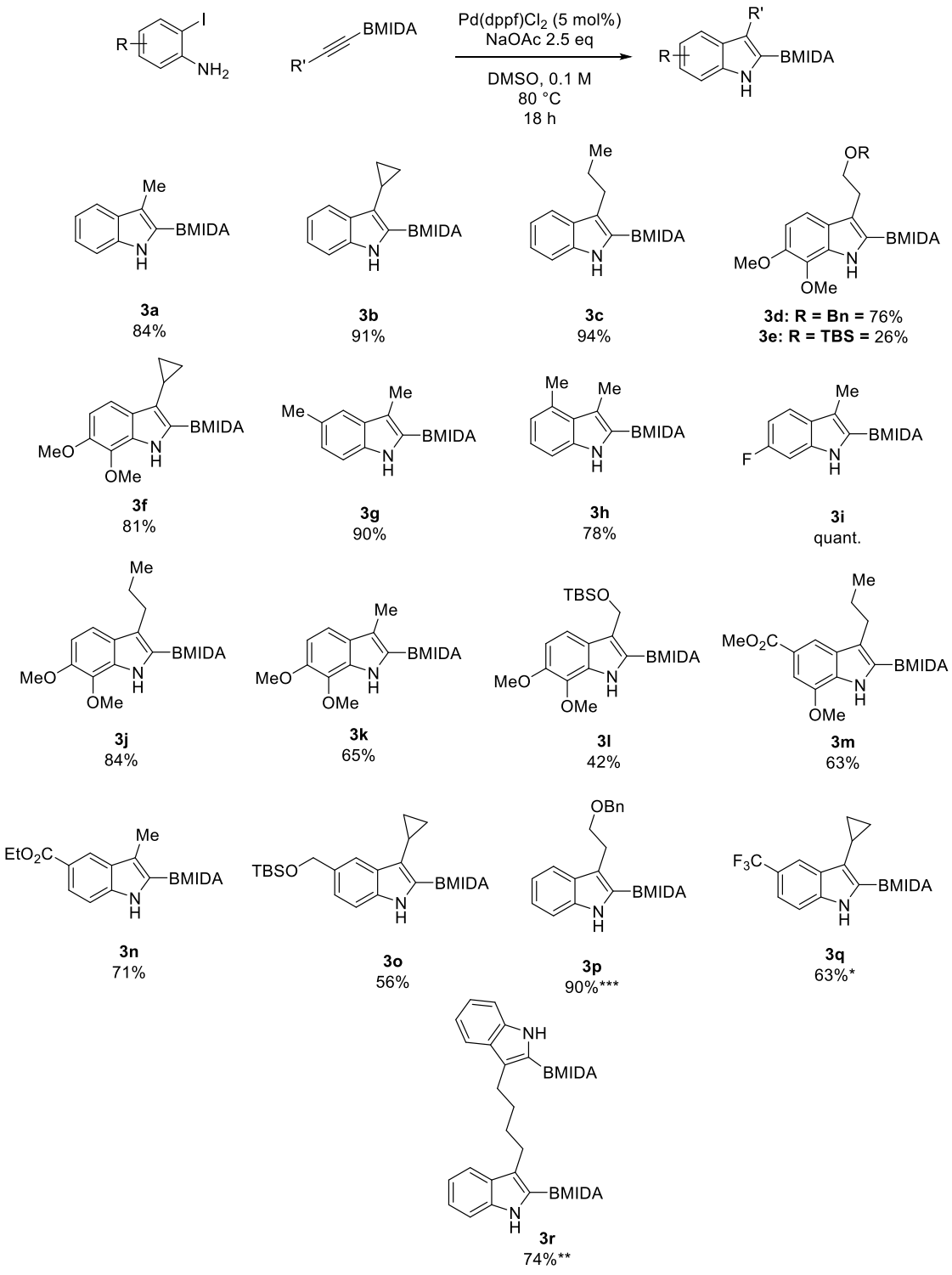


*Figure 9: Crystal structure of indole BMIDA product **3a**.*

2.3. Reaction Scope

Alkyne BMIDAs and 2-iodoanilines were reacted under the optimised reaction conditions to form 2-BMIDA indoles (Scheme 64).



*determined by ^{1}H NMR assay using dinitrobenzene as an internal standard.
**required NaOAc (5.0 equiv.), iodoaniline (2.4 equiv.) and Pd(dppf)Cl_2 (10 mol%)
*** conducted on 19.3 mmol scale

Scheme 64: Larock reaction substrate scope.

The so-called 'sp^3 BMIDA Larock' (as the alkyne BMIDA starting material bears an sp^3 carbon on one of its sp carbons and a boron on the other, resulting in an sp^3 carbon attached to the C-3 of the indole product) reactions generally proceeded in moderate to good yields. Using the parent 2-iodoaniline gave generally good yields (**3a–3c**, **3p** and **3r**). Dimethoxy aniline **2g** generally gave moderate to good yields of indole product (**3d** and **3f** and **3j**) with some exceptions giving only poor to moderate yields (**3e** and **3k** and **3l**). Based on a like-for-like comparison of alkyne BMIDAs used, the yields of these dimethoxy indoles was lower than for the unsubstituted aniline, *e.g.,* the yield of **3a** *vs*. **3k** shows a 20% drop in yield when **2g** is used as the aniline with alkyne **1b**. Only a 7% drop in yield is seen between **3c** and **3j**, both of which use **1c** as the alkyne BMIDA. Similarly, a difference in yield of 13% is seen between substrates **3b** and **3f**, indicating perhaps that electron-rich anilines gave lower yields of product which is in agreement with observations made by Chuawong and co-workers,[63] where they theorised that the rate of oxidative addition into the C-I bond of iodoanilines is lowered when electron-donating groups are present on the aniline. There are, however, a few exceptions to this idea.

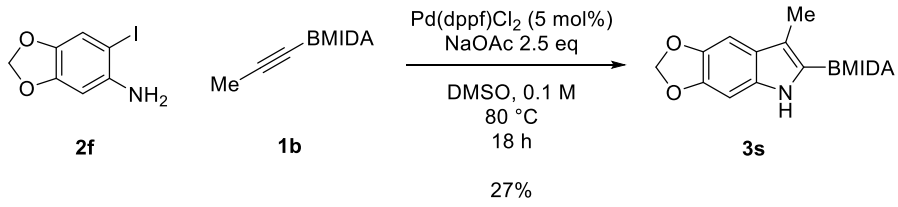
Comparing **3a** with **3n**, a 13% drop in yield is seen when the aniline starting material bears an electron-withdrawing ester group at the 4-position. Conversely, an increase in yield from 84% to 90% is seen between **3a** and **3g** when a methyl group is at the 4-position of the aniline, resulting in a more electron-rich aniline giving a higher yield of product. However, both these groups are at the 3-position with respect to the iodine so neither can have a large impact on the electronics at the carbon *ipso* to the iodine. Any electronic effect will be through much weaker inductive effects, not through delocalisation/mesomeric effects.

This motif features heavily in the substrate scope as it often gave good consumption of alkyne BMIDA. This led to the initial anecdotal observation that the reaction was accelerated by electron-rich anilines, as further evidenced by the good yields of methylated indoles **3g** and **3h**. Products **3i** and **3l** provide a good comparison of how the electronics of the aniline affect the yield, in the former a dimethoxy aniline gave 84% yield and, in the latter, replacing one of the methoxy groups with an electron-withdrawing ester at the C-5 position gave just 63% yield, both with the same alkyne BMIDA. However, there are several exceptions to this rule, for example in products **3a** and **3j** where the parent 2-iodoaniline gave better yields of indole product than the dimethoxy derivative, as was also the case between **3b** and **3e**, **3c** and **3i**, and **3d** and **3o**. These confounding results do not paint a clear picture of the influence of electronics on the reaction. Substrate **3k** was produced in low yield, which could be due

to the steric bulk of the OTBS group close to the alkyne, which could provide a barrier to alkyne coordination and carbopalladation steps.

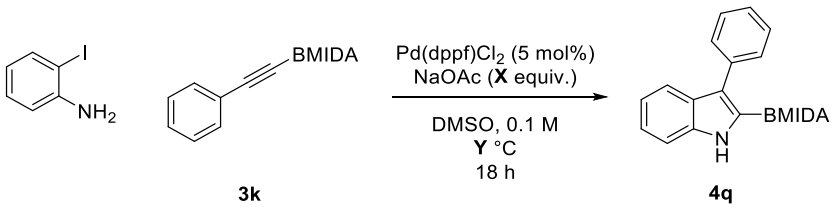
Bisindole product **3q** could be synthesised in good yield however this did require a doubling of catalyst loading. Fluorinated indole **3h** was obtained in quantitative yield. Product **3o** could successfully be made in 90% yield on 19.3 mmol scale, adding confidence that this process could be used on large scale to produce sizeable quantities of these borylated indoles.

Due to the good to moderate yields when **2g** was used as a substrate in these Larock reactions, a different electron-rich aniline, **2f**, was synthesised (see Scheme 58). Unfortunately, this substrate gave the product in only 27% yield when subjected to the optimised BMIDA Larock conditions as determined by NMR assay; clean product could not be isolated (Scheme 65).



*Scheme 65: Larock reaction of **2f** and **1b**.*

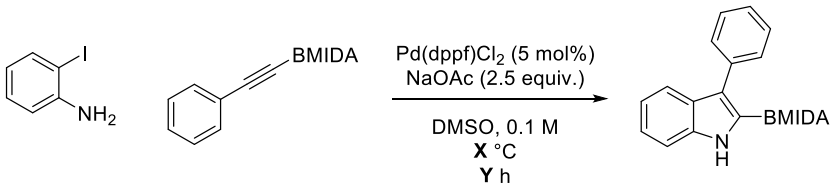
Expanding on the sp^3 BMIDA Larock, the analogous reaction to produce indoles bearing an sp^2 carbon at C-3 was carried out. The reaction between 2-iodoaniline and **1k** was carried out using the previously optimised sp^3 BMIDA Larock conditions. Unfortunately, this gave only 14% yield of the desired product (Table 10, Entry 1). Raising the temperature did offer a slight increase in yield, however, there was a significant decrease in the amount of alkyne BMIDA starting material remaining, suggesting that this could decompose at higher temperatures before it could react. Decreasing the equivalents of base did not have much of an effect on yield at 80 °C (Entries 1 and 2) or 100 °C (Entries 3 and 4). Beyond these temperatures, the effect of going from 1.2 to 2.5 equivalents of base becomes apparent, as increasing the amount of base decreases the amount of product, likely due to increased BMIDA hydrolysis (Entries 5–8).



Entry	NaOAc (eq.)	Temperature (°C)	4q (%)[a]	Remaining 3k (%)[a]
1	1.2	80	14	65
2	2.5	80	16	58
3	1.2	100	37	25
4	2.5	100	35	24
5	1.2	120	41	5
6	2.5	120	30	7
7	1.2	140	37	8
8	2.5	140	14	2

Table 10: Phenylacetylene BMIDA Larock base equivalents and temperature study. [a]Yields determined by using ^{1}H NMR assay with 1,4-dinitrobenzene as an internal standard..

Increasing both the reaction time and temperature still gave low yields of product (Table 11). Leaving the reaction for 72 hours at 80 °C shows little increase in conversion over 48 hours (Entries 2 and 1, respectively) and only a slight drop in concentrations of alkyne BMIDA starting material. At 100 °C, a yield of 39% is achieved after 48 hours however this drops down to 25% after 72 hours (Entries 3 and 4, respectively), indicating again that the product is liable to hydrolysis at these elevated temperatures. Oddly, though the amount of BMIDA starting material seems to plateau at 12% after 48 hours and does not hydrolyse further over the next 24 hours, which is at odds with the idea that prolonged reaction times increase hydrolysis of the BMIDA in the starting material and/or the product. This instead suggests that perhaps a small amount of water is present from the outset of the reaction and this is consumed as it hydrolyses the BMIDA and after this water is consumed, BMIDA hydrolysis is attenuated. It appeared that a fine balance must be struck between using temperatures high enough to allow the reaction to proceed while attenuating product and/or starting material BMIDA hydrolysis.

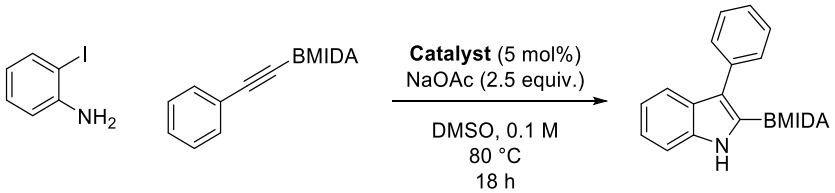


3k **4q**

Entry	Temperature (°C)	Time (h)	4q (%)[a]	Remaining 3k (%)[a]
1	80	48	23	45
2	80	72	25	38
3	100	48	39	12
4	100	72	25	12

Table 11: Phenylacetylene BMIDA Larock temperature and time study. [a] Conversion determined by ^{1}H NMR against an internal standard (1,4-dinitrobenzene).

As varying temperature, base equivalents and time did not give a significant increase in yields, a brief survey of other Pd(II) precatalysts showed that allyl Pd chloride dimer did give a small increase in yield, however it was still unsatisfactory (Table 12, Entry 2) and $PdCl_2$ and $Pd(MeCN)_2Cl_2$ gave unremarkable yields (Entries 1 + 3, respectively).



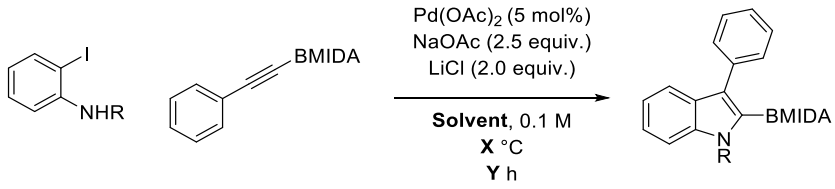
3k **4q**

Entry	Catalyst	4q (%)[a]	Remaining 3k (%)[a]
1	$PdCl_2$	34	30
2	$[Pd(allyl)Cl]_2$	47	32
3	$Pd(MeCN)_2Cl_2$	29	43

Table 12: Phenylacetylene BMIDA Larock catalyst study. [a]Yields determined by using ^{1}H NMR assay with 1,4-dinitrobenzene as an internal standard.

It appeared that the optimised sp^3 BMIDA Larock conditions formed a poor basis on which to optimise the analogous sp^2 BMIDA Larock. The pre-optimisation BMIDA Larock conditions (see Table 1) were revisited and 2-iodoaniline produced a low yield (Table 13, Entry 1). A hitherto unexplored variation was the substitution on the aniline nitrogen and it

was thought that varying this group could have an impact on the yield of the reaction. Attaching an electron-withdrawing group, *e.g.,* Ac or Ts, will reduce the Lewis basicity of the aniline nitrogen as its lone pair can now be delocalised into these groups and as nitrogen is naturally intimately involved in the Larock reaction mechanism, it was thought that altering the electronics on this nitrogen may have more of an effect on yield than other external influences *e.g.,* solvent, temperature *etc.* Employing 2-iodoacetanilide **2h** gave a decent increase in yield (Entry 2), although increasing the reaction time to 48 hours showed no increase in yield nor consumption of starting material (Entry 3). This could be indicative of catalyst poisoning, where the catalyst can only carry out a few turnovers before becoming deactivated. The reaction conditions were stringently oxygen-free, and using degassed DMF (achieved using three freeze-pump-thaw cycles of the solvent) conferred no increase in yield so it is unlikely that aerobic oxidation of Pd(0) is the source of this catalyst inactivation. The tosylated aniline **2n** showed no conversion to product (Entry 4) which is at odds with the idea of decreasing the Lewis basicity of the nitrogen increases the yield. Employing 2-iodoacetanilide in the optimised sp^3 BMIDA Larock conditions (see Scheme 63) gave just 11% yield (Entry 5).



3k

Entry	R	Solvent	Temperature (° C)	Reaction time (h)	Indole (%)[a]	Remaining 3k (%)[a]
1	H	DMF	65	24	38	44
2	Ac	DMF	65	24	55	20
3	Ac	DMF	65	48	55	20
4	Ts	DMF	65	48	n.d.	72
5	Ac	DMSO	80	18	11	52

Table 13: Phenylacetylene BMIDA Larock protecting group, solvent, temperature and time study. [a]Yields determined by using ^{1}H NMR assay with 1,4-dinitrobenzene as an internal standard.

As indicated in Table 13 Entries 2 + 3, leaving the reaction for 48 hours rather than 24 showed no decrease in yield or consumption/degradation of starting material, so the reaction

time for the substrate scope was extended to 48 hours to allow for any particularly recalcitrant substrates to react. Catalyst loading was also increased to 10 mol% $Pd(OAc)_2$ to mitigate the effects of suspected catalyst degradation, if this is indeed the cause for the low yield.

The reason for the different conditions required for sp^2 and sp^3 BMIDA Larock reactions is not completely clear. The regioselectivity for the Larock reaction is thought to arise from unfavourable steric interactions between the larger of the two groups on the alkyne and the oxidative addition adduct, which results in the larger group being distal during the carbopalladation step, ultimately giving an indole with this larger group at the C-2 position (see Scheme 30); suggesting that the reaction is sensitive to sterics. It could be that the larger substituent appended on the alkyne in an sp^2 Larock reaction increases the energy barrier for the alkyne coordination and carbopalladation steps but would favour reductive elimination to form the C-2-N bond, as this would result in a relief of steric crowding around Pd. The sp^3 Larock conditions employ $Pd(dppf)Cl_2$ as the (pre)catalyst and this phosphine ligand could simply be too large to allow facile coordination and carbopalladation with the larger sp^2 groups on the alkyne, whereas the sp^2 conditions are ligandless.

With optimal conditions found for the sp^2 BMIDA Larock, acetylated anilines were reacted with sp^2 BMIDA alkynes, alongside Dr. Jamie Fyfe. These reactions were, on the whole, lower-yielding than the sp^3 alternative (Figure 10).

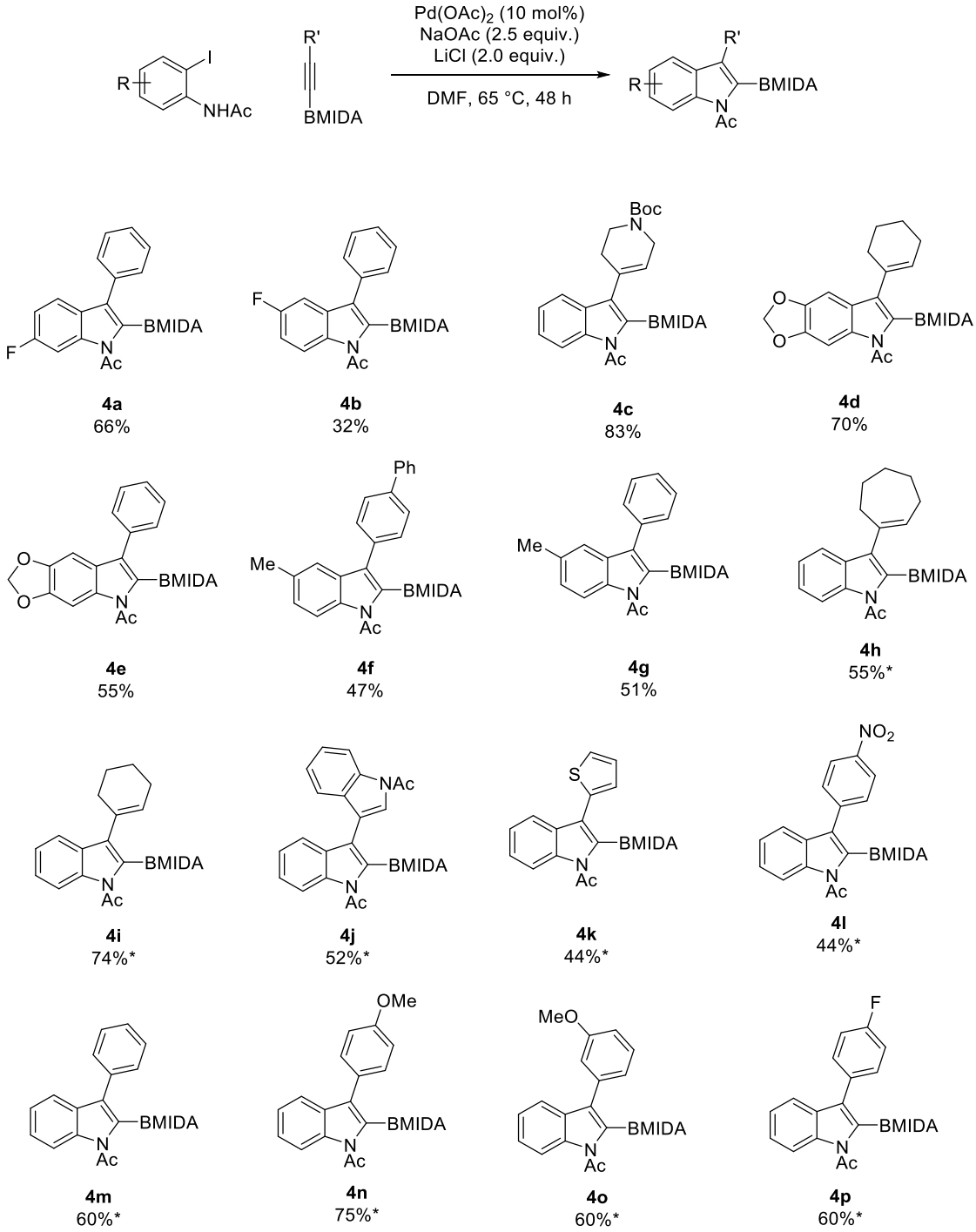


Figure 10: Substrate scope of the sp² BMIDA Larock.

Isomeric fluorinated indoles **4a** and **4b** were produced in moderate and good yields, respectively, which supports the idea that an electron-withdrawing substituent *para* to the iodine increases the yield of product, although this fluorine will only be weakly electron-

withdrawing through inductive, not mesomeric effects. The reaction of **2e** under these new conditions pleasingly gave the methylenedioxy indole in good yields (**4d** and **4e**). Indoles bearing a cyclohexene ring were made in good yield (**4d** and **4i**) and the cycloheptene version was obtained in moderate yield of 55% (**4h**). Heteroaromatic products **4j** and **4k** were obtained in moderate yields. A potential trend could be observed in substrates **4l**, **4n**, and **4o**, where the electronics of the alkyne BMIDA are electron-deficient, to electron-rich then electron neutral, respectively. The electron-rich alkyne BMIDA (4-MeO) gave the highest yield of the three at 75% (**4n**). The electron-deficient alkyne BMIDA (4-NO_2) gave the lowest yield of 44% (**4l**). Moving the methoxy group the 3-position of the aromatic ring, so it is no longer in conjugation with the alkyne gave a yield of 60% (**4o**); exactly halfway between the other two and identical to the yield obtained with 'electron-neutral' unsubstituted phenyl acetylene BMIDA **1k**.

A crystal structure of product **4m** was obtained which showed, again, unambiguously that the BMIDA group had been placed at the C-2 of the indole product and the Ph group at the C-3 (Figure 11).

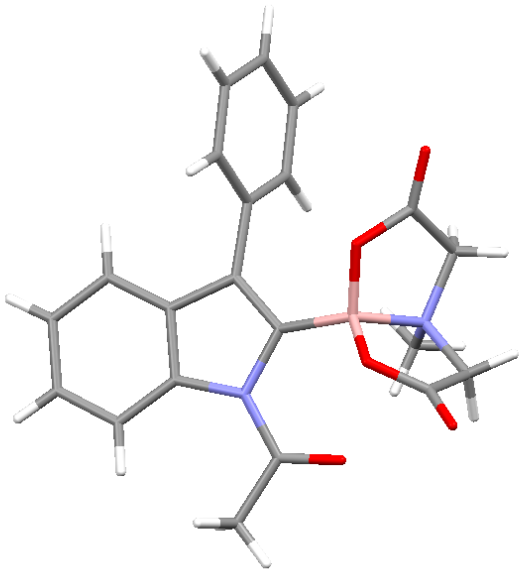


*Figure 11: X-ray crystal structure of product **4m**.*

2.4. Conclusions and Future Work

The work in this chapter has demonstrated the development and optimisation of two different BMIDA Larock conditions to produce two different classes of compounds. These products have a useful synthetic linchpin at the C-2 position and tuneable functionality at the C-3 position and substitution around the benzenoid core of the indole. For indoles bearing an alkyl group (sp^3) at the C-3, the yields were generally good to excellent with one example being quantitative. No relationship could realistically be discerned from the nature of the aniline and alkyne BMIDA starting material, as both electron-rich and electron-poor anilines gave unpredictable yields. For BMIDA Larock reactions resulting in an sp^2 carbon at the C-3 position, a different set of conditions would be required; a change in catalyst, catalyst loading, solvent, temperature, reaction time and group on the aniline nitrogen. The exact reason behind this is unknown.

The synthesis of product **3p** could be successfully scaled up to produce multigram quantities of this indole BMIDA which will be used in the following chapter in the total synthesis of natural products. Overall, sp^2 BMIDA Larock products were generally obtained in lower yields than sp^3 BMIDA Larock products, which could be due to the higher steric bulk of alkynes bearing an sp^2 group resulted in a greater barrier to alkyne coordination and carbopalladation steps.

The largest unanswered questions from this chapter are: i) why the need for different conditions in the sp^2 *vs.* sp^3 BMIDA Larock? And ii) what is the nature of the Pd species in the former reaction? The sp^2 BMIDA Larock employs $Pd(OAc)_2$ as the ligand and this is normally used with phosphine ligands as these can both ligate to the Pd, and become oxidised, in turn reducing Pd(II) to Pd(0), the latter capable of undergoing oxidative addition into a carbon-halogen bond.[91][92] However, there are no phosphine ligands present in this reaction so the exact nature of the active species of the reaction is not known, and the mechanism by which it reduces from Pd(II) to Pd(0) is not clear either. Boronic acids and esters can undergo oxidative homocoupling using Pd where reductive elimination to form the homocoupled product results in reduction of Pd(II) to Pd(0), giving the dialkyne Glaser coupling product.[93] This is, however, unlikely for two reasons: the first being that this homocoupling occurs from a peroxopalladium species, derived from the reaction of Pd with molecular oxygen and this reaction is stringently oxygen-free. The second reason is that, as it involves transmetalation, the boron needs to have a vacant p orbital, which precludes BMIDA from this pathway with its filled p orbital.

A mechanistic investigation, probing the above questions, would be of interest as a greater understanding of the mechanism of a reaction makes optimisation and troubleshooting of problems more straightforward. A better understanding may also reveal some interesting details of this reaction which could be applied more broadly to the field of transition metal catalysis and heterocycle synthesis, contributing to the body of knowledge in these areas. For example, in the case of the sp^3 BMIDA Larock conditions, it may be possible to follow the reaction by monitoring ^{31}P NMR, which is a sensitive method and can detect electronic changes on the Pd centre it is ligated to. Perhaps a difference in ^{31}P NMR shifts can be observed between a neutral Pd(0) species and an anionic chloropalladium(0) species, which may shed light on the exact nature of the active catalytic species in this reaction and the role of chloride which is so often seen employed as an additive in the Larock reaction. As the sp^2 BMIDA Larock reaction is ligandless, it cannot be observed by ^{31}P NMR, so demystifying this reaction may not be as straightforward as in the case of the sp^3 reaction. A potential pathway for this reaction could be a Pd(II)/Pd(IV) couple rather than the more conventional Pd(0)/Pd(II) couple. This would explain how the reaction can proceed in the absence of a reductant to achieve Pd(II) reduction. It has been demonstrated that acetanilides can undergo directed *ortho* C-H insertion to form a Pd(II) adduct which is then capable of further oxidative addition with a competent electrophile to give a Pd(IV) intermediate, which reductively eliminates the *ortho*-functionalised acetanilide and regenerates Pd(II).[94] However, this applies to acetanilides bearing *ortho* C-H groups, not an *ortho* iodide and the Pd(IV) oxidative addition adduct is therefore incapable of reductively eliminating HOAc. If this pathway were effective for this sp^2 BMIDA Larock, the expected product would feature an iodide at the C-7 position, untouched by the Pd(II)/Pd(IV) couple. As this product is not observed and the expected product from oxidative addition into the C-I bond is obtained, this suggests that this mechanism is not at play but does not offer a suitable alternative.

2.5. Chapter Two Experimental

Purification of Solvents & Reagents

Dry DMSO for Larock reactions was obtained by standing DMSO over activated alumina overnight before filtration then distilling over CaH_2 under vacuum and storing over activated 4 Å molecular sieves. Dry DMF for Larock reactions was obtained by stirring over 4 Å molecular sieves for 24 hours before distilling over fresh 4 Å molecular sieves under vacuum and storing over activated 4 Å molecular sieves under nitrogen. Dry THF for synthesis was obtained from a PureSolv SPS-400-5 solvent purification system. DCM, MeCN, Et_2O, EtOAc, and hexane for purification purposes were used as obtained from suppliers without further purification. Sodium acetate was flame-dried under vacuum until it melted, then was cooled to room temperature and stored in a capped vial under ambient conditions. LiCl was placed in a vacuum oven kept at 60 °C for at least 24 hours prior to use. $B(OMe)_3$ was distilled over CaH_2 and stored over activated 4 Å molecular sieves.

All other reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.

Experimental Details

Reactions were carried out using conventional glassware (preparation of intermediates) or in capped 5 or 20 mL microwave vials. Microwave vials were oven-dried (150 °C) and cooled to room temperature under vacuum and backfilled with nitrogen prior to use. Reaction mixtures were prepared in a microwave vial before being capped with a septum and purged with a threefold nitrogen/vacuum cycle. Reactions were carried out at elevated temperatures in a sand bath atop a temperature-regulated hotplate/stirrer. Cooling to 0 °C was achieved using an ice/water bath. Cooling to -78 °C was achieved using a dry ice/acetone bath.

Purification of Products

Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light and/or developed using potassium permanganate or vanillin solution. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel.

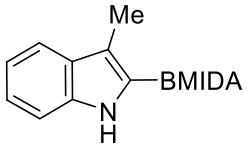
Analysis of Products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AV 400 at 400 MHz and 101 MHz, respectively, or Bruker DRX 500 at 500 MHz and 126 MHz, respectively. ^{19}F NMR spectra were obtained on a Bruker AV 400 spectrometer at 376 MHz. ^{11}B NMR spectra were obtained on a Bruker AV 300 spectrometer at 96 MHz. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.16 ppm (^{13}C), DMSO-d_6 referenced at 2.50 (^{1}H) and 39.5 (^{13}C), acetone-d_6 referenced at 2.05 (^{1}H) and 28.9 and 206.3 ppm (^{13}C) and acetonitrile-d_3 referenced at 1.94 (^{1}H) and 1.3 and 118.3 ppm (^{13}C). ^{11}B NMR spectra are referenced to $BF_3 \cdot Et_2O$. High-resolution mass spectra were obtained through analysis at the University of St Andrews. NMR conversions for optimisation studies were carried out by adding a known standard (0.05 M dinitrobenzene in DMSO-d_6) to the crude reaction mixture.

General experimental procedures

General procedure A:

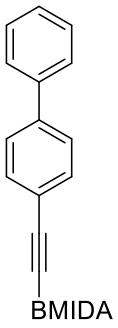
For example, synthesis of **3a**



An oven-dried 5 mL microwave vial was charged successively with Pd(dppf)Cl_2 (7.3 mg, 10 μmol, 5 mol%), **1b** (39.0 mg, 0.2 mmol, 1.0 equiv.), 2-iodoaniline (52.6 mg, 0.24 mmol, 1.2 equiv.) and NaOAc (41.0 mg, 0.5 mmol, 2.5 equiv.). The vial was capped and purged with nitrogen, then DMSO (2 mL) was added before being heated to 80 °C for 18 hours. The vial was cooled to room temperature, decapped and diluted with EtOAc (10 mL) then washed with 10% aqueous LiCl solution (2 x 5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to flash column chromatography (silica gel, 5-20% MeCN in DCM) to give the title product as an off-white solid (48 mg, 84%).

General procedure B:

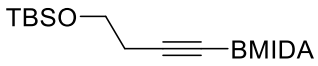
For example, synthesis of **1l**



An oven-dried 20 mL microwave vial was charged successively with CuI (19.0 mg, 0.1 mmol, 10 mol%), $Pd(dppf)Cl_2$ (36.6 mg, 50 μmol, 5 mol%) 4-iodobiphenyl (336 mg, 1.20 mmol, 1.20 equiv.) and **1a** (181 mg, 1.0 mmol, 1.0 equiv.). The vial was capped and purged with nitrogen. Et_3N (418 μL, 3.0 mmol, 3.0 equiv.) was then charged followed by DMF (5.0 mL, 0.2 M). The reaction mixture was stirred at room temperature for 18 hours before being decapped and diluted with EtOAc (50 mL) then washed with 10% aqueous LiCl solution (2 x 25 mL) before being dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to flash column chromatography (silica gel, 5-20% MeCN in DCM) to give the title product as a brown solid (241 mg, 72%).

General procedure C:

For example, synthesis of **1g**



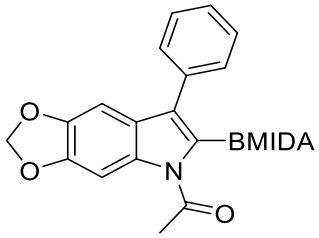
In a flame-dried 250 mL round bottom flask, (but-3-yn-1-yloxy)(tert-butyl)dimethylsilane (13.8 g, 75.0 mmol, 1.0 equiv.) was dissolved in THF (100 mL) and cooled to 0 °C. To this solution was added EtMgBr (27.4 mL, 90.0 mmol, 3.28 M in Et_2O, 1.2 equiv.) dropwise and

the resulting suspension was stirred at 0 °C for 10 minutes before the ice bath was removed and and stirring continued for a further 30 minutes.

In a separate, flame-dried 250 mL round bottom flask, $B(OMe)_3$ (16.7 mL, 150 mmol, 2.0 equiv.) was dissolved in THF (100 mL) and cooled to -78 °C. To this cold solution was added, *via* cannula, the above Grignard suspension over approximately 10 minutes. After complete addition, the reaction mixture was stirred at -78 °C for one hour before removing the dry ice/acetone bath and stirring for a further two hours. The flask was unstoppered and *N*-methyliminodiacetic acid (22.1 g, 150 mmol, 2.0 equiv.) was added followed by DMSO (75 mL). The flask was placed on a rotary evaporator with the water bath set at 60 °C to remove the majority of the volatiles. The flask contents were then distilled under high vacuum (<0.5 mbar, 80 °C) to remove remaining DMSO to leave a gum-like residue. To this was added 1:1 brine:H_2O (500 mL) and this was extracted twice with 3:2 EtOAc:acetone (500 mL). The organic layers were combined, washed with water (75 mL), dried over Na_2SO4, filtered, and concentrated *in vacuo* prior to flash column chromatography (silica gel, 0-25% MeCN in DCM) to give the title product as a white solid (8.14 g, 32%).

General procedure D:

For example, synthesis of **4e**

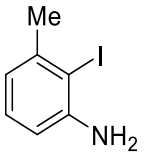


An oven-dried 5 mL microwave vial was charged successively with $Pd(OAc)_2$ (4.49 mg, 20.0 μmol, 10 mol%), (phenylethynyl)boronic acid MIDA ester (51.4 mg, 0.20 mmol, 1.00 equiv.), *N*-(6-iodobenzo[*d*][1,3]dioxol-5-yl)acetamide (73.2 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The vial was capped and purged with nitrogen, then 2 mL DMF was added and the vial was heated to 65 °C for 48 hours. The vial was then cooled to room temperature, decapped and diluted with EtOAc (10 mL). The organic layer was washed with 10% aqueous LiCl solution

(2 x 5 mL) and the organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to flash column chromatography (silica gel, 8-30% MeCN in DCM) to give the title product as a light brown solid (48 mg, 55%).

General procedure E:

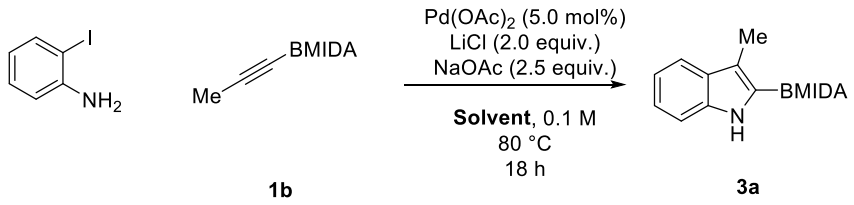
For example, synthesis of **2b**.



In a 100 mL round bottom flask, a mixture of 2-iodo-3-nitrotoluene (2.63 g, 10.0 mmol, 1.00 equiv.) and iron powder (4.05 g, 62.0 mmol, 6.20 equiv.) was stirred vigorously in EtOH (30 mL) before concentrated hydrochloric acid (0.99 mL, 12.0 mmol, 1.20 equiv.) was added. The reaction mixture was heated to reflux for 3 hours before being cooled to room temperature and diluted with EtOAc (50 mL) then filtered through a pad of celite into a separatory funnel and the cake washed with water (50 mL). The layers were mixed, split and the organic layer was dried over Na2SO4, filtered, and concentrated *in vacuo* prior to flash column chromatography (silica gel, 5-10% Et_2O in hexane) to give the title product as a light pink solid (2.12 g, 91%).

Reaction optimisation data

Larock solvent study



1b **3a**

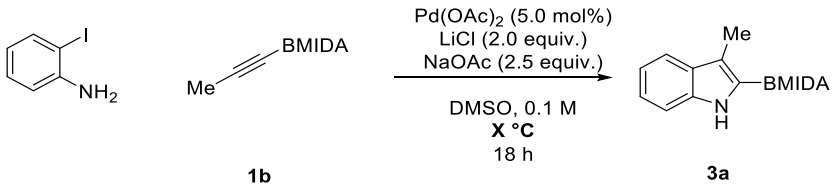
Reactions were carried out according to General Procedure A using $Pd(OAc)_2$ (2.25 mg, 10.0 μmol, 5.00 mol%), **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.), 2-iodoaniline (52.6 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The vial was capped and purged with nitrogen prior to addition of

solvent (2.00 mL, 0.10 M). The reaction was stirred at 80 °C for 18 hours, cooled to room temperature and decapped. The reaction mixture was diluted with EtOAc (10 mL) and washed with 10% aqueous LiCl solution (2 x 5 mL), the organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. 1,4-Dinitrobenzene in DMSO-d_6 (0.05 M, 1.00 mL) was added to the crude product and this was analysed by ^1H NMR to give % yield.

Entry	Solvent	3a (%)
1	DMF	69
2	THF	0
3	MeCN	<5
4	Dioxane	0
5	Toluene	0
6	Sulpholane	0
7	DMSO	76
8	NMP	69

Supplementary Table 1: Larock reaction solvent screen.

Larock temperature study

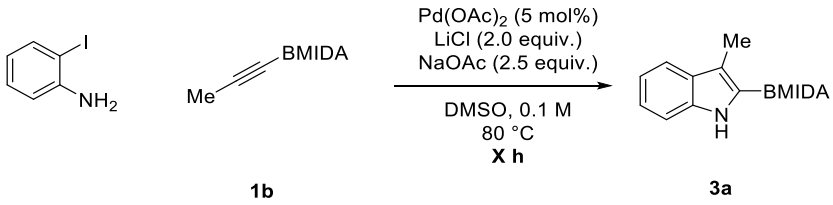


Reactions were carried out according to General Procedure A using $Pd(OAc)_2$ (2.25 mg, 10.0 μmol, 5.00 mol%), **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.), 2-iodoaniline (52.6 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The vial was capped and purged with nitrogen prior to addition of DMSO (2.00 mL, 0.10 M) The reaction was stirred at **X °C** for 18 hours, cooled to room temperature and decapped. The reaction mixture was diluted with EtOAc (10 mL) and washed with 10% aqueous LiCl solution (2 x 5 mL), the organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. 1,4-Dinitrobenzene in DMSO-d_6 (0.05 M, 1.00 mL) was added to the crude product and this was analysed by ^1H NMR to give % yield.

Entry	Temperature (°C)	3a (%)
1	rt	Trace
2	40	5
3	60	42
4	100	50

Supplementary Table 2: Larock reaction temperature screen.

Larock time study

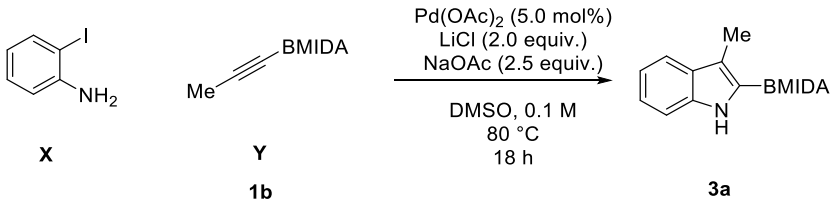


Reactions were carried out according to General Procedure A using $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 5.00 mol%), **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.), 2-iodoaniline (52.6 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The vial was capped and purged with nitrogen prior to addition of DMSO (2.00 mL, 0.10 M) The reaction was stirred at 80 °C for **X hours**, cooled to room temperature and decapped. The reaction mixture was diluted with EtOAc (10 mL) and washed with 10% aqueous LiCl solution (2 x 5 mL), the organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. 1,4-Dinitrobenzene in DMSO-d_6 (0.05 M, 1.00 mL) was added to the crude product and this was analysed by ^1H NMR to give % yield.

Entry	Time (h)	3a (%)
1	2	49
2	4	62
3	6	65
4	8	72
5	24	73

Supplementary Table 3: Larock reaction time study.

Larock stoichiometry study

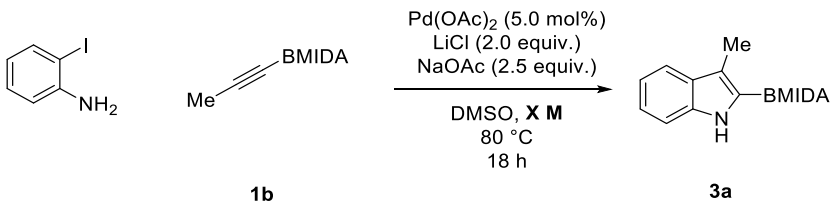


Reactions were carried out according to General Procedure A using $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 5.00 mol%), **Y *(a* mg, *b* mmol, *c* equiv.)**, **X *(d* mg, *e* mmol, *f* equiv.)**, NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The vial was capped and purged with nitrogen prior to addition of DMSO (2.00 mL, 0.10 M) The reaction was stirred at 80 °C for 18 hours, cooled to room temperature and decapped. The reaction mixture was diluted with EtOAc (10 mL) and washed with 10% aqueous LiCl solution (2 x 5 mL), the organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. 1,4-Dinitrobenzene in DMSO-d_6 (0.05 M, 1.00 mL) was added to the crude product and this was analysed by ^1H NMR to give % yield.

Entry	X:Y	3a (%)
1	1.5:1	77
2	2.0:1	74
3	1:1.2	76
4	1:1.5	72
5	1:2.0	73

Supplementary Table 4: Larock reaction stoichiometry study.

Larock concentration study



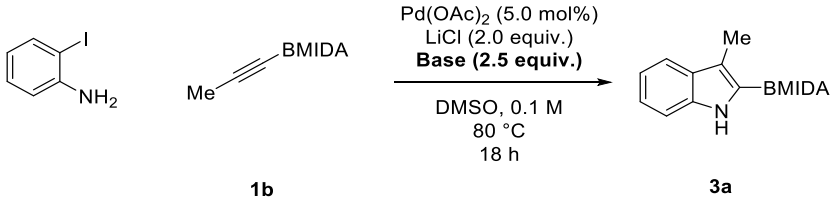
Reactions were carried out according to General Procedure A using $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 5.00 mol%), **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.), 2-iodoaniline (52.6 mg, 0.24

mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The vial was capped and purged with nitrogen prior to addition of DMSO **(X mL, X M)**. The reaction was stirred at 80 °C for 18 hours, cooled to room temperature and decapped. The reaction mixture was diluted with EtOAc (10 mL) and washed with 10% aqueous LiCl solution (2 x 5 mL), the organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. 1,4-Dinitrobenzene in DMSO-d_6 (0.05 M, 1.00 mL) was added to the crude product and this was analysed by ^{1}H NMR to give % yield.

Entry	Concentration (M)	3a (%)
1	0.05	66
2	0.10	72
3	0.20	67
4	0.50	55

Supplementary Table 5: Larock reaction concentration study.

Larock base study

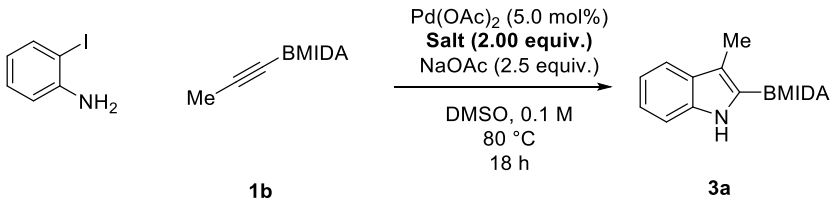


Reactions were carried out according to General Procedure A using $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 5.00 mol%), **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.), 2-iodoaniline (52.6 mg, 0.24 mmol, 1.20 equiv.), **Base (XX mg, 0.50 mmol, 2.50 equiv.)** and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The vial was capped and purged with nitrogen prior to addition of DMSO (2.00 mL, 0.10 M). The reaction was stirred at 80 °C for 18 hours, cooled to room temperature and decapped. The reaction mixture was diluted with EtOAc (10 mL) and washed with 10% aqueous LiCl solution (2 x 5 mL), the organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. 1,4-Dinitrobenzene in DMSO-d_6 (0.05 M, 1.00 mL) was added to the crude product and this was analysed by ^{1}H NMR to give % yield.

Entry	Base	3a (%)
1	KOAc (49.1 mg)	78
2	LiOAc (33.0 mg)	77
3	K_3PO_4 (106.2 mg)	17
4	K_2CO_3 (69.1 mg)	<5
5	Et_3N (70.0 µL)	71

Supplementary Table 6: Larock reaction base study.

Larock salt study



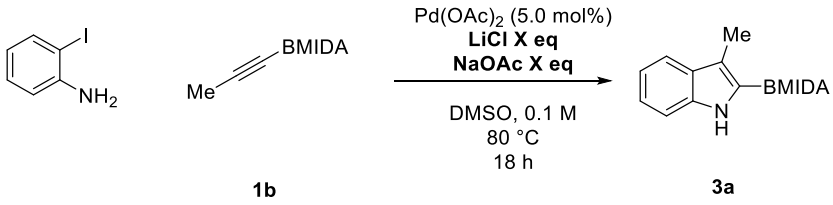
1b **3a**

Reactions were carried out according to General Procedure A using $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 5.00 mol%), **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.), 2-iodoaniline (52.6 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and **Salt (XX mg, 0.40 mmol, 2.00 equiv.).** The vial was capped and purged with nitrogen prior to addition of DMSO (2.00 mL, 0.10 M). The reaction was stirred at 80 °C for 18 hours, cooled to room temperature and decapped. The reaction mixture was diluted with EtOAc (10 mL) and washed with 10% aqueous LiCl solution (2 x 5 mL), the organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. 1,4-Dinitrobenzene in DMSO-d_6 (0.05 M, 1.00 mL) was added to the crude product and this was analysed by ^1H NMR to give % yield.

Entry	Salt	3a (%)
1	LiF (10.4 mg)	77
2	NaCl (23.4 mg)	77
3	TBACl hydrate (111.2 mg)	56

Supplementary Table 7: Larock reaction salt additive study.

Larock salts stoichiometry study



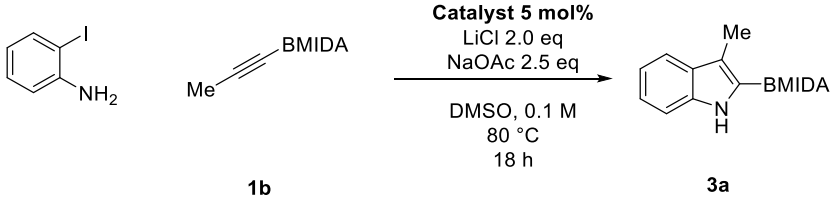
1b **3a**

Reactions were carried out according to General Procedure A using $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 5.00 mol%), **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.), 2-iodoaniline (52.6 mg, 0.24 mmol, 1.20 equiv.), **NaOAc (XX mg, XX mmol, XX equiv.)** and **LiCl (XX mg, XX mmol, XX equiv.).** The vial was capped and purged with nitrogen prior to addition of DMSO (2.00 mL, 0.10 M). The reaction was stirred at 80 °C for 18 hours, cooled to room temperature and decapped. The reaction mixture was diluted with EtOAc (10 mL) and washed with 10% aqueous LiCl solution (2 x 5 mL), the organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. 1,4-Dinitrobenzene in DMSO-d_6 (0.05 M, 1.00 mL) was added to the crude product and this was analysed by ^1H NMR to give % yield.

Entry	LiCl:NaOAc (equiv.)	3a (%)
1	2:3 (17.0: 49.2 mg)	82
2	2:1 (17.0: 16.4 mg)	79
3	2:0.5 (17.0: 8.2 mg)	45
4	2:0 (17.0 mg)	7
5	3:2.5 (25.4 mg: 41 mg)	78
6	1:2.5 (8.5 mg: 41 mg)	83
7	0.5:2.5 (4.2: 41 mg)	83
8	0:2.5 (41 mg)	66

Supplementary Table 8: Larock reaction salt:base stoichiometry study.

Larock catalyst study



1b **3a**

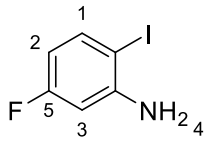
Reactions were carried out according to General Procedure A using **Catalyst (XX mg, 10.0 µmol, 5.00 mol%)**, **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.), 2-iodoaniline (52.6 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The vial was capped and purged with nitrogen prior to addition of DMSO (2.00 mL, 0.10 M). The reaction was stirred at 80 °C for 18 hours, cooled to room temperature and decapped. The reaction mixture was diluted with EtOAc (10 mL) and washed with 10% aqueous LiCl solution (2 x 5 mL), the organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. 1,4-Dinitrobenzene in DMSO-d_6 (0.05 M, 1.00 mL) was added to the crude product and this was analysed by ^1H NMR to give % yield.

Entry	Catalyst	3a (%)
1	$PdCl_2$ (1.8 mg)	85
2	$Pd(dppf)Cl_2$ (7.3 mg)	87
3	$Pd(PPh_3)_4$ (11.6 mg)	10
4	$[Pd(allyl)Cl]_2$ (1.8 mg)	84
5	$Pd(MeCN)_2Cl_2$ (2.6 mg)	85
6	$Pd(PPh_3)_2Cl_2$ (7.0 mg)	62

Supplementary Table 9: Larock reaction catalyst study.

Iodoaniline synthesis

2a



Prepared according to General procedure E using 2-iodo-5-fluoronitrobenzene (1.33 g, 5.00 mmol, 1.00 equiv.), iron powder (2.03 g, 31.0 mmol, 6.20 equiv.) and concentrated hydrochloric acid (493 µL, 12.0 mmol, 1.20 equiv.). The crude product was purified according to the General procedure (silica gel, 2-4% Et_2O in hexane) to give the title product as a light yellow solid (902 mg, 76%).

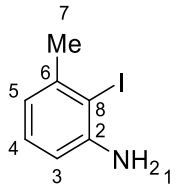
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.7, 6.2 Hz, 1H, **H3**), 6.49 (dd, *J* = 10.5, 2.8 Hz, 1H, **H1**), 6.28 (ddd, *J* = 8.7, 8.2, 2.8 Hz, 1H, **H2**), 4.21 (brs, 2H, **H4**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.03 (d, $^{1}J_{C\text{-}F}$ = 244.8 Hz), 148.12 (d, $^{3}J_{C\text{-}F}$ = 11.0 Hz), 139.68 (d, $^{3}J_{C\text{-}F}$ = 9.6 Hz), 107.23 (d, $^{2}J_{C\text{-}F}$ = 22.2 Hz), 101.55 (d, $^{2}J_{C\text{-}F}$ = 25.6 Hz), 76.98 (d, $^{4}J_{C\text{-}F}$ = 2.5 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) δ -113.4.

Spectral data in agreement with literature values.[95]

2b



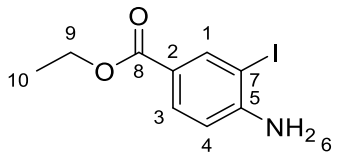
Prepared according to General procedure E using 2-iodo-3-nitrotoluene (2.63 g, 10.0 mmol, 1.00 equiv.), iron powder (4.05 g, 62.0 mmol, 6.20 equiv.) and concentrated hydrochloric acid (0.99 mL, 12.0 mmol, 1.20 equiv.). The crude product was purified according to the General procedure (silica gel, 5-10% Et_2O in hexane) to give the title product as a light pink solid (2.12 g, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (t, *J* = 7.6 Hz, 1H, **H4**), 6.68 (dd, *J* = 7.4, 1.6 Hz, 1H, **H5**), 6.61 (dd, *J* = 8.0, 1.5 Hz, 1H, **H3**), 4.12 (brs, 2H, **H1**), 2.45 (s, 3H, **H7**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1, 142.5, 128.5, 119.6, 111.9, 91.6, 29.3.

Spectral data in agreement with literature values.[96]

2c



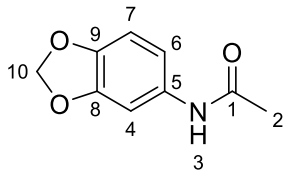
A mixture of benzocaine (826 mg, 5.00 mmol, 1.00 equiv.), KIO_4 (1.15 g, 5.00 mmol, 1.00 equiv.), NaCl (584 mg, 10.0 mmol, 2.00 equiv.) and KI (830 mg, 5.00 mmol, 1.00 equiv.) was stirred vigorously in H_2O (1.00 mL) and AcOH (9.00 mL) at room temperature for 24 hours. After this time, EtOAc (25 mL) was charged and this was washed successively with brine (10 mL), saturated aqueous $Na_2S_2O_3$ (10 mL) then saturated $NaHCO_3$ (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to flash column chromatography (silica gel, 10-30% Et_2O in hexane) to afford the title product as a white solid (1.26 g, 87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 1.9 Hz, 1H, **H1**), 7.84 (dd, *J* = 8.4, 1.9 Hz, 1H, **H3**), 6.72 (d, *J* = 8.4 Hz, 1H, **H4**), 4.54 (brs, 2H, **H6**), 4.34 (q, *J* = 7.1 Hz, 2H, **H9**), 1.38 (t, *J* = 7.1 Hz, 3H, **H10**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 150.6, 141.0, 131.2, 121.6, 113.1, 82.2, 60.7, 14.4.

Spectral data in agreement with literature values.[97]

2d



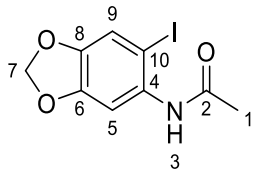
3,4-(Methylenedioxy)aniline (1.37 g, 10.0 mmol, 1.00 equiv.) was dissolved in 1,4-dioxane (14.3 mL) and cooled to 0 °C. To this was added, with stirring, acetic anhydride (1.13 mL, 12.0 mmol, 1.20 equiv.) dropwise then the reaction mixture was allowed to warm to room temperature and was stirred for 25 hours. MeOH (10 mL) was added stirred at this temperature for 10 minutes before being concentrated *in vacuo* and purified by flash column chromatography (silica gel, 20-60% EtOAc in hexane) to afford the title product as a light brown solid (1.65 g, 92%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, J = 1.9 Hz, 1H, **H4**), 7.11 (brs, 1H, **H3**), 6.77 – 6.71 (m, 2H, **H6** + **H7**), 5.95 (s, 2H, **H10**), 2.15 (s, 3H, **H2**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 147.8, 144.3, 132.0, 113.2, 108.1, 103.0, 101.3, 24.5.

Spectral data in agreement with literature values.[98]

2e



2d (1.12 g, 6.23 mmol, 1.10 equiv.) and AcOH (971 µL, 17.0 mmol, 3.00 equiv.) were dissolved in DCM (13.5 mL) and stirred at room temperature. To this was added, *via* syringe, a solution of iodine monochloride (919 mg, 5.66 mmol, 1.00 equiv.) in DCM (10 mL). After 24 hours, saturated aqueous $Na_2S_2O_5$ (10 mL) was charged and the layers were split in a separatory funnel then the aqueous layer was extracted with DCM (10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to flash column chromatography (silica gel, 20-30% EtOAc in hexane) to give the title product as white crystals (500 mg, 29%).

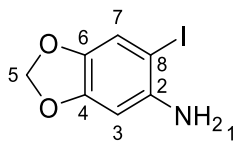
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.37 (s, 1H, **H3**), 7.38 (s, 1H, **H5**), 6.95 (s, 1H, **H9**), 6.07 (s, 2H, **H7**), 2.01 (s, 3H, **H1**).

^{13}C NMR (126 MHz, DMSO-d_6) δ 168.9 **C2**, 148.3 **C8**, 146.8 **C6**, 134.1 **C4**, 117.3 **C5**, 109.0 **C9**, 102.5 **C7**, 86.4 **C10**, 23.5 **C1**.

υ_{max} (solid): 3244, 1645, 1533, 1476, 1234 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_9H_8INNaO_3$) requires *m/z* 327.9447, found *m/z* 327.9429.

2f



2e (458 mg, 1.50 mmol, 1.00 equiv.) and NaOH (3.00 g, 75.0 mmol, 55.0 equiv.) were heated to reflux in a mixture of EtOH (61 mL) and water (14 mL) for 4 hours. The reaction mixture

was concentrated *in vacuo* to give a crude residue which was taken up in water (10 mL) and extracted with DCM (5 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title product as a beige solid (360 mg, quantitative).

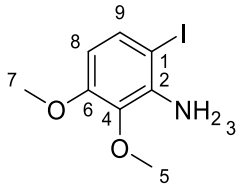
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (s, 1H, **H7**), 6.40 (s, 1H, **H3**), 5.90 (s, 2H, **H5**), 3.88 (brs, 2H, **H1**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2 **C2**, 141.6 **C4**, 141.1 **C6**, 117.2 **C7**, 101.2 **C5**, 96.8 **C3**, 70.8 **C8**.

υ_{max} (solid): 3304, 2897, 1673, 1603, 1497, 1466, 1258, 1229, 1196, 1113 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_7H_7INO_2$) requires *m/z* 263.9521, found *m/z* 263.9509.

2g



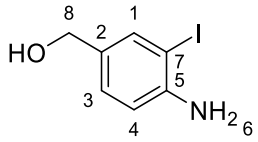
A mixture of 2,3-dimethoxyaniline (157 mg, 1.02 mmol, 1.00 equiv.) in Et_2O (6.8 mL) and saturated aqueous Na_2CO_3 (2.0 mL) was stirred vigorously in the dark at room temperature, then a solution of iodine monochloride (271 mg, 1.67 mmol, 1.63 equiv.) in Et_2O (2.0 mL) was added in one portion. The reaction mixture was stirred for three hours at room temperature before the layers were split and the organic layer washed successively with saturated aqueous NaS_2O_3 (10 mL) then saturated aqueous $NaHCO_3$ (10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to purification by flash column chromatography (silica gel, 2.5–5% acetone in hexane) to give the title product as a pale yellow oil which crystallised on standing into a pale yellow solid (146 mg, 51%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.9 Hz, 1H, **H9**), 6.21 (d, *J* = 8.9 Hz, 1H, **H8**), 4.27 (brs, 2H, **H3**), 3.85 (s, 3H, **H7**), 3.84 (s, 3H, **H5**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.1, 141.6, 135.3, 133.1, 104.2, 73.9, 59.9, 55.9.

Spectral data in agreement with literature values.[99]

2h



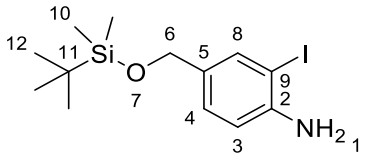
A mixture of 4-aminobenzyl alcohol (2.25 g, 18.3 mmol, 1.00 equiv.) and $CaCO_3$ (2.75 g, 27.5 mmol, 1.50 equiv.) was stirred vigorously in water (30.5 mL) and MeOH (30.5 mL) at room temperature. To this suspension was added iodine monochloride (3.06 g, 18.9 mmol, 1.03 equiv.) dropwise as a solution in MeOH (5.0 mL) and the reaction mixture was stirred at room temperature for 23 hours. Et_2O (50 mL) was then added, the layers were split and the aqueous layer was extracted once more with Et_2O (50 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to purification by flash column chromatography (silica gel, 10-30% EtOAc in hexane) to afford the title product as a brown solid (2.54 g, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.0 Hz, 1H, **H1**), 7.17 (dd, *J* = 8.2, 2.0 Hz, 1H, **H3**), 6.75 (d, *J* = 8.2 Hz, 1H, **H4**), 4.55 (s, 2H, **H8**), 4.14 (brs, 2H, **H6**). OH proton is not observed.

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.4, 138.1, 132.6, 128.8, 114.6, 83.9, 64.4.

Spectral data in agreement with literature values.[86]

2i



A solution of 4-amino-3-iodobenzyl alcohol (400 mg, 1.61 mmol, 1.00 equiv.) and imidazole (153 mg, 2.24 mmol, 1.40 equiv.) were dissolved in DCM (4.90 mL) and *tert*-butyldimethylsilyl chloride (290 mg, 1.93 mmol, 1.20 equiv.) was added in one portion. The

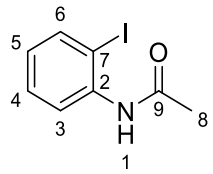
reaction mixture was stirred at room temperature for 24 hours before it was filtered, through a plug of silica and eluted with 1:1 EtOAc:hexane (100 mL). The filtrate was concentrated *in vacuo* to give the title product as a brown oil (570 mg, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 1.9 Hz, 1H, **H8**), 7.12 (dd, *J* = 8.2, 1.8 Hz, 1H, **H4**), 6.73 (d, *J* = 8.1 Hz, 1H, **H3**), 4.60 (s, 2H, **H6**), 4.06 (brs, 2H, **H1**), 0.96 (s, 9H, **H12**), 0.11 (s, 6H, **H10**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7, 137.0, 133.2, 127.8, 114.5, 84.0, 64.1, 26.0, 18.5, -5.1.

Spectral data in agreement with literature values.[86]

2j



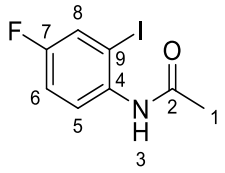
A solution of 2-iodoaniline (21.9 g, 100 mmol, 1.00 equiv.) and Et_3N (30.7 mL, 220 mmol, 2.20 equiv.) in DCM (250 mL) was cooled to 0 °C then acetic anhydride (11.3 mL, 120 mmol, 1.20 equiv.) was added. The reaction mixture was then warmed to a gentle reflux for 18 hours before being cooled to room temperature then saturated $NaHCO_3$ (200 mL) was charged and the layers were split, the aqueous layer was then extracted with DCM (2 x 100 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to purification by flash column chromatography (silica gel, 20-80% EtOAc in hexane) to afford the title product as a white solid (23.1 g, 88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 – 8.20 (m, 1H, **H3**), 7.80 (d, *J* = 7.9 Hz, 1H, **H6**), 7.44 (brs, 1H, **H1**), 7.37 (t, *J* = 7.8 Hz, 1H, **H5**), 6.87 (t, *J* = 7.7 Hz, 1H, **H4**), 2.27 (s, 3H, **H8**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 138.8, 138.2, 129.3, 126.0, 122.1, 90.0, 24.9.

Spectral data in agreement with literature values.[100]

2k



4-fluoro-2-iodoaniline (237 mg, 1.00 mmol, 1.00 equiv.) and Et_3N (307 µL, 2.20 mmol, 2.20 equiv.) were dissolved in DCM (5.0 mL) and acetic anhydride (113 µL, 1.20 mmol, 1.20 equiv.) was added dropwise. The reaction was then heated to reflux for 24 hours, cooled to room temperature and saturated $NaHCO_3$ (10 mL) was then charged. The layers were split and the aqueous layer was extracted with DCM (10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to purification by flash column chromatography (silica gel, 30-50% EtOAc in hexane) to afford the title product as a beige solid (241 mg, 89%).

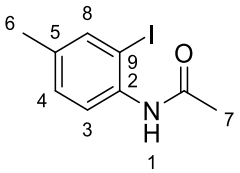
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 9.1, 5.5 Hz, 1H, **H5**), 7.52 (dd, *J* = 7.7, 2.9 Hz, 1H, **H8**), 7.33 (brs, 1H, **H3**), 7.10 (ddd, *J* = 9.1, 7.8, 2.9 Hz, 1H, **H6**), 2.26 (s, 3H, **H1**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 158.7 (d, $^1J_{C\text{-}F}$ = 248.9 Hz), 134.7 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 125.4 (d, $^2J_{C\text{-}F}$ = 24.8 Hz), 123.2 (d, $^3J_{C\text{-}F}$ = 7.9 Hz), 116.1 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 89.8 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 24.7.

^{19}F NMR (471 MHz, $CDCl_3$) δ -116.1.

Spectral data in agreement with literature values.[101]

2l



A solution of 4-methyl-2-iodoaniline (1.17 g, 5.00 mmol, 1.00 equiv.) and Et_3N (767 µL, 5.50 mmol, 1.10 equiv.) in DCM (16.7 mL) was cooled to 0 °C and acetyl chloride (945 µL, 13.0 mmol, 2.60 equiv.) was added dropwise. The ice bath was then removed and the

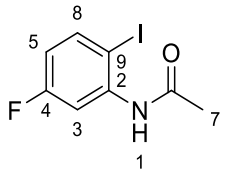
reaction mixture was allowed to stir at room temperature for 68 hours before MeOH (10 mL) was charged and allowed to stir for 10 minutes further. Water (25 mL) was then added, the layers were split and the aqueous layer was extracted with DCM (25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to purification by flash column chromatography (silica gel, 20-40% EtOAc) in hexane to give the title product as a light yellow solid (1.03 g, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 1H, **H3**), 7.63 (d, *J* = 2.0 Hz, 1H, **H8**), 7.34 (brs, 1H, **H1**), 7.17 (dd, *J* = 8.8, 1.7 Hz, 1H, **H4**), 2.30 (s, 3H, **H6**), 2.25 (s, 3H, **H7**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 139.0, 136.1, 135.7, 130.0, 122.0, 90.2, 24.8, 20.4.

Spectral data in agreement with literature values.[102]

2m



A solution of 2-fluoro-5-iodoaniline (510 mg, 2.15 mmol, 1.00 equiv.) and Et_3N (330 µL, 2.37 mmol, 1.10 equiv.) in DCM (7.2 mL) was cooled to 0 °C, and acetyl chloride (406 µL, 5.59 mmol, 2.60 equiv.) was added dropwise. The solution was then warmed to room temperature and allowed to stir for 66 hours before MeOH (10 mL) was added, followed by water (20 mL) and the layers were split and the aqueous layer washed once with DCM (20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to purification by flash column chromatography (silica gel, 10-30% EtOAc in hexane) to yield the title product as a white solid (349 mg, 58%).

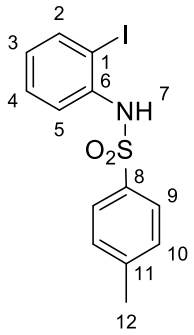
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 11.2 Hz, 1H, **H3**), 7.73 (dd, *J* = 8.8, 6.0 Hz, 1H, **H5**), 7.49 (brs, 1H, **H1**), 6.66 (ddd, *J* = 8.8, 7.6, 3.0 Hz, 1H, **H8**), 2.28 (s, 3H, **H7**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 163.3 (d, $^1J_{C\text{-}F}$ = 246.4 Hz), 139.5 (d, $^3J_{C\text{-}F}$ = 11.7 Hz), 139.1 (d, $^3J_{C\text{-}F}$ = 8.9 Hz), 113.0 (d, $^2J_{C\text{-}F}$ = 22.7 Hz), 109.2 (d, $^2J_{C\text{-}F}$ = 28.4 Hz), 81.8, 25.0.

^{19}F NMR (471 MHz, $CDCl_3$) δ -110.5.

Spectral data in agreement with literature values.[103]

2n



Tosyl chloride (0.92 g, 4.80 mmol, 1.05 equiv.) was added in one portion to a solution of 2-iodoaniline (1.00 g, 4.57 mmol, 1.00 equiv.) in pyridine (10 mL) and the reaction was stirred at room temperature for three hours. Water (20 mL) was then added and the reaction mixture was extracted with DCM (3 x 20 mL). The combined organics were then washed with aqueous $CuSO_4$ solution (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to purification by flash column chromatography (silica gel, 10-20% EtOAc in hexane) to give the title product as a light yellow solid (1.54 g, 90%).

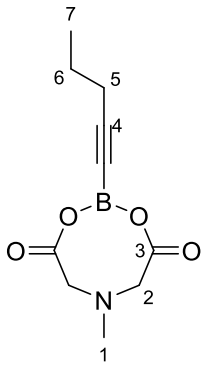
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 4H, **H2 + H5 + H9**), 7.33 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1H, **H3**), 7.26 – 7.22 (m, 2H, **H10**), 6.85 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H, **H4**), 6.82 (brs, 1H, **H7**), 2.40 (s, 3H, **H12**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3, 139.1, 137.5, 135.9, 129.7, 129.5, 127.5, 126.9, 122.5, 92.4, 21.6.

Spectral data in agreement with literature values.[104]

Alkyne BMIDA synthesis

1c



Prepared according to General Procedure C using 1-pentyne (0.99 mL, 10.0 mmol, 1.00 eq), EtMgBr (3.0 M in Et_2O, 4.00 mL, 12.0 mmol, 1.20 eq), $B(OMe)_3$ (2.23 mL, 20.0 mmol, 2.00 eq), *N*-methyliminodiacetic acid (2.95 g, 20.0 mmol, 2.00 eq). The product was purified as outlined in the General Procedure (silica gel, 10-30% MeCN in DCM) to give the title product as a white solid (1.10 g, 49%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (d, *J* = 16.8 Hz, 2H, **H2**), 3.81 (d, *J* = 16.8 Hz, 2H, **H2'**), 3.10 (s, 3H, **H1**), 2.23 (t, *J* = 7.1 Hz, 2H, **H5**), 1.56 (q, *J* = 7.2 Hz, 2H, **H6**), 0.99 (t, *J* = 7.4 Hz, 3H, **H7**).

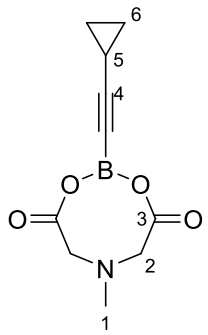
^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0 **C3**, 103.8 **C4**, 61.5 **C2**, 47.9 **C1**, 21.9 **C6**, 21.4 **C5**, 13.6 **C7**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (160 MHz, $CDCl_3$) δ 6.3.

ν_{max} (solid): 2960, 2205, 1761, 1462, 1337, 1288,1163, 1148, 1022 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{10}H_{15}BNO_4$) requires *m/z* 224.1094, found *m/z* 224.1088.

1d



Prepared according to General Procedure C using cyclopropylacetylene (2.54 mL, 30.0 mmol, 1.00 eq), EtMgBr (3.0 M in Et_2O, 12.0 mL, 36.0 mmol 1.20 eq), $B(OMe)_3$ (6.69 mL, 60.0 mmol, 2.00 eq) and *N*-methyliminodiacetic acid (8.83 g, 60.0 mmol, 2.00 equiv.). The product was purified as outlined in the General Procedure (silica gel, 10-30% MeCN in DCM) to give the title product as a white solid (3.83 g, 58%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 4.21 (d, J = 17.1 Hz, 2H, **H2**), 4.02 (d, J = 17.1 Hz, 2H, **H2'**), 2.93 (s, 3H, **H1**), 1.33 (m, 1H, **H5**), 0.78 (m, 2H, **H6**), 0.64 (m, 2H, **H6'**).

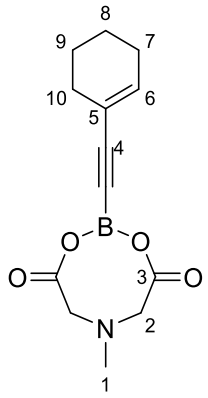
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2 **C3**, 105.0 **C4**, 61.7 **C2**, 48.1 **C1**, 8.6 **C6**, 0.2 **C5**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (160 MHz, DMSO-d_6) δ 5.8.

ν_{max} (solid): 3013, 2369, 2205, 1765, 1464, 1288, 1020 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{10}H_{12}BNaNO_4$) requires *m/z* 244.0757 found *m/z* 244.0753.

1e



Prepared according to General Procedure C using 1-ethynylcyclohexene (3.19 mL, 30.0 mmol, 1.00 eq), EtMgBr (3.0 M in Et_2O, 12.0 mL, 36.0 mmol, 1.20 eq), $B(OMe)_3$ (6.69 mL, 60.0 mmol, 2.00 eq), *N*-methyliminodiacetic acid (8.83 g, 60.0 mmol, 2.00 eq). The product was purified as outlined in the General Procedure (silica gel, 10-30% MeCN in DCM) to give the title product as a white solid (4.99 g, 64%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 6.15 – 6.10 (m, 1H, **H6**), 4.27 (d, J = 16.9 Hz, 2H, **H2**), 4.10 (d, J = 17.0 Hz, 2H, **H2'**), 3.22 (s, 3H, **H1**), 2.14-2.05 (m, 4H, **H7** + **H10**), 1.66 – 1.53 (m, 4H, **H8** + **H9**).

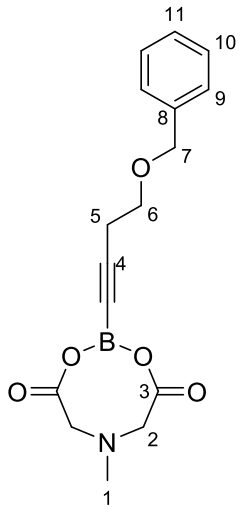
^{13}C NMR (126 MHz, Acetone-d_6) δ 167.8 **C3**, 135.3 **C6**, 120.8 **C5**, 102.0 **C4**, 61.4 **C2**, 47.5 **C1**, 28.8 **C10**, 25.2 **C7**, 22.0 **C9**, 21.3 **C8**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (160 MHz, DMSO-d_6) δ 6.4.

ν_{max} (solid): 2361, 2343, 1761, 1749, 1734, 1558, 1506, 1456 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{13}H_{16}BNaNO_4$) requires *m/z* 284.1070 found *m/z* 284.1058.

1f



Prepared according to General Procedure C using ((but-3-yn-1-yloxy)methyl)benzene (1.60 g, 10.0 mmol 1.00 equiv.), EtMgBr (2.47 M in Et_2O, 4.86 mL, 12.0 mmol, 1.20 equiv.), $B(OMe)_3$ (2.08 mL, 20.0 mmol, 2.00 equiv.) and *N*-methyliminodiacetic acid (2.94 g, 20.0

mmol, 2.00 equiv.). The reaction was purified as outlined in the General Procedure (silica gel 10-30% MeCN in DCM) to give the title product as a white solid (2.47 g, 25%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.18 (m, 5H, **H9** + **H10** + **H11**), 4.55 (s, 2H, **H7**), 3.88 (d, *J* = 16.5 Hz, 2H, **H2**), 3.70 (d, *J* = 16.5 Hz, 2H, **H2'**), 3.64 (t, *J* = 6.7 Hz, 2H, **H6**), 2.98 (s, 3H, **H1**), 2.58 (t, *J* = 6.7 Hz, 2H, **H5**).

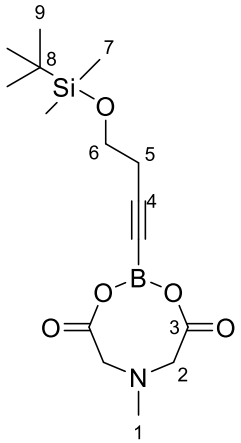
^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0 **C3**, 138.0 **C8**, 128.5 **C9**, 127.9 **C11**, 127.8 **C10**, 100.6 **C4**, 72.9 **C7**, 68.1 **C6**, 61.3 **C2**, 47.6 **C1**, 20.9 **C5**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 6.0.

υ_{max} (solid): 3017, 2866, 2208, 1763, 1462, 1331, 116, 1024 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{16}H_{18}BNNaO_5$) requires *m/z* 338.1176, found *m/z* 338.1164.

1g



Prepared according to General Procedure C using (but-3-yn-1-yloxy)(tert-butyl)dimethylsilane (13.8 g, 75.0 mmol, 1.00 equiv.), EtMgBr (3.28 M in Et_2O, 27.4 mL, 90.0 mmol, 1.20 eq), $B(OMe)_3$ (16.7 mL, 150 mmol, 2.00 eq), *N*-methyliminodiacetic acid (22.1 g, 150 mmol, 2.00 eq). The product was purified as outlined in the General Procedure (silica gel, 0-25% MeCN in DCM) to give the title product as a white solid (8.14 g, 32%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 4.25 (d, J = 16.9 Hz, 2H, **H2**), 4.05 (d, J = 16.9 Hz, 2H, **H2'**), 3.77 (t, J = 6.9 Hz, 2H, **H6**), 3.21 (s, 3H, **H1**), 2.44 (t, J = 6.9 Hz, 2H, **H5**), 0.91 (s, 9H, **H9**), 0.09 (s, 6H, **H7**).

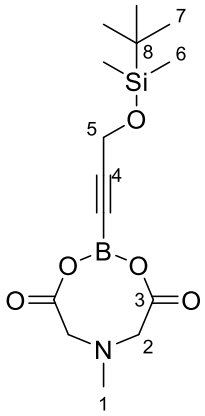
^{13}C NMR (126 MHz, Acetone-d_6) δ 167.7 **C3**, 98.7 **C4**, 61.7 **C6**, 61.3 **C2**, 47.4 **C1**, 25.4 **C9**, 23.5 **C5**, 17.9 **C8**, -6.0 **C7**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone-d_6) δ 6.0.

ν_{max} (solid): 2955, 2930, 2857, 2208, 1759, 1462, 1337, 1252, 1024 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{15}H_{26}BNNaO_5Si$) requires *m/z* 362.1571, found *m/z* 362.1560.

1h



Prepared according to General Procedure C using *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (5.11 g, 30.0 mmol 1.00 equiv.), EtMgBr (3.08 M in Et_2O, 11.7 mL, 36.0 mmol, 1.20 equiv.), $B(OMe)_3$ (6.69 mL, 60.0 mmol, 2.00 equiv.) and *N*-methyliminodiacetic acid (8.83 g, 60.0 mmol, 2.00 equiv.). The reaction was purified as outlined in the General Procedure (silica gel 10-30% MeCN in DCM) to give the title product as a white solid (2.47 g, 25%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 4.33 (s, 2H, **H5**), 4.27 (d, J = 17.2 Hz, 2H, **H2**), 4.06 (d, J = 17.1 Hz, 2H, **H2'**), 2.97 (s, 3H, **H1**), 0.87 (s, 9H, **H7**), 0.09 (s, 6H, **H6**).

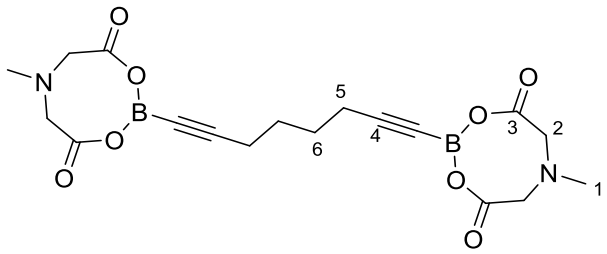
13C NMR (126 MHz, DMSO-d_6) δ 169.1 **C3**, 99.6 **C4**, 61.9 **C2**, 52.0 **C5**, 48.2 **C1**, 26.2 **C7**, 18.4 **C8**, -4.7 **C6**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 5.8.

υ_{max} (solid): 2930, 1763, 1462, 1287, 1024 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{14}H_{24}BNNaO_5Si$) requires *m/z* 348.1414, found *m/z* 348.1405.

1i



Prepared according to General Procedure C with 1,7-octadiyne (1.33 mL, 10.0 mmol, 1.00 equiv.), EtMgBr (2.85 M in Et_2O, 8.42 mL, 2.40 equiv.), $B(OMe)_3$ (4.46 mL, 40.0 mmol, 2.00 equiv.) and MIDA (5.89 g, 40.0 mmol, 4.00 equiv.). The reaction was purified as outlined in the General Procedure (silica gel 10-60% MeCN in DCM) to give the title product as a white solid (448 mg, 11%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 4.24 (d, *J* = 17.2 Hz, 4H, **H2**), 4.04 (d, *J* = 17.1 Hz, 4H, **H2'**), 2.96 (s, 6H, **H1**), 2.34 – 2.20 (m, 4H, **H5**), 1.64 – 1.51 (m, 4H, **H6**).

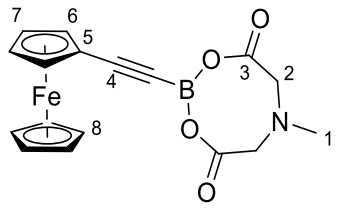
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2 **C3**, 101.8 **C4**, 61.8 **C2**, 48.2 **C1**, 27.7 **C6**, 18.7 **C5**. The carbons bearing borons are not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 6.0.

υ_{max} (solid): 1749, 1454, 1339, 1290, 1167, 1140, 1022, 1005 cm^{-1}.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{18}H_{21}B_2N_2O_8$) requires *m/z* 415.1490, found *m/z* 415.1490.

1j



Prepared according to General Procedure C using ethynlferrocene (840 mg, 4.00 mmol, 1.00 equiv.), EtMgBr (3.08 M in Et_2O, 1.56 mL, 4.80 mmol, 1.20 equiv.), $B(OMe)_3$ (892 µL, 8.00 mmol, 2.00 equiv.), *N*-methyliminodiacetic acid (1.18 g, 8.00 mmol, 2.00 equiv.). The product was purified as outlined in the General Procedure (silica gel, 5-30% MeCN in DCM) to give the title product as a brick red solid (750 mg, 51%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 4.50 (t, J = 1.9 Hz, 2H, **H6**), 4.32 – 4.26 (m, 4H, **H7+ H2**), 4.24 (s, 5H, **H8**), 4.12 (d, J = 17.1 Hz, 2H, **H2'**), 3.05 (s, 3H, **H1**).

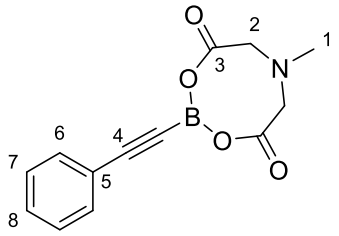
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2 **C3**, 99.1 **C4**, 71.7 **C6**, 70.2 **C8**, 69.3 **C7**, 64.8 **C5**, 62.0 **C2**, 48.4 **C1**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 6.5.

ν_{max} (solid): 2187, 1765, 1452, 1072, 1001 cm^{-1}.

HRMS: exact mass calculated for $[M]^+$ ($C_{17}H_{16}BFeNO_4$) requires *m/z* 365.0522, found *m/z* 365.0516.

1k



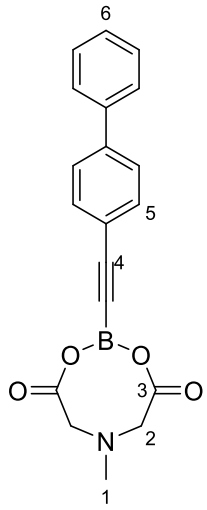
Prepared according to General Procedure C using phenylacetylene (5.11 g, 50.0 mmol, 1.00 equiv.), EtMgBr (3.28 M in Et_2O, 18.3 mL, 60.0 mmol, 1.20 eq), $B(OMe)_3$ (11.1 mL, 100 mmol, 2.00 eq), *N*-methyliminodiacetic acid (14.7 g, 100 mmol, 2.00 eq). The product was purified as outlined in the General Procedure (silica gel, 0-30% MeCN in DCM) to give the title product as a pale yellow solid (7.82 g, 61%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.53 – 7.45 (m, 2H, **H6 + H7 + H8**), 7.45 – 7.35 (m, 3H, **H6 + H7 + H8**), 4.32 (d, *J* = 17.1 Hz, 2H, **H2**), 4.15 (d, *J* = 17.2 Hz, 2H, **H2'**), 3.07 (s, 3H, **H1**).

^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2, 132.0, 129.4, 129.1, 122.9, 99.9, 62.0, 48.4. The carbon bearing boron is not observed due to quadrupolar relaxation.

Spectral data in agreement with literature values.[105]

1l



Prepared according to General Procedure B using Pd(dppf)Cl_2 (36.6 mg, 50.0 μmol, 5.00 mol%) 4-iodobiphenyl (336 mg, 1.20 mmol, 1.20 equiv.) CuI (19.0 mg, 100 μmol, 10.0 mol%), **1a** (181 mg, 1.00 mmol, 1.00 equiv.) and Et_3N (418 uL, 3.00 mmol, 3.00 equiv.). The reaction was stirred at room temperature for 18 hours then subjected to purification as outlined in the General Procedure (silica gel, 5-20% MeCN in DCM) to give the title product as a brown solid (241 mg, 72%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.73 – 7.65 (m, 4H, **Ar-H**), 7.63 – 7.57 (m, 2H, **H5**), 7.54 – 7.46 (m, 2H **Ar-H**), 7.44 – 7.37 (m, 1H, **H6**), 4.36 (d, *J* = 17.0 Hz, 2H, **H2**), 4.22 (d, *J* = 16.9 Hz, 2H, **H2'**), 3.36 (s, 3H, **H1**).

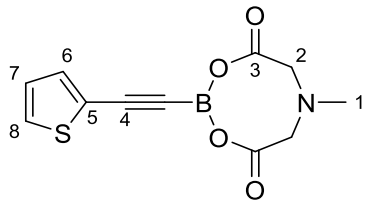
^{13}C NMR (126 MHz, Acetone-d_6) δ 167.7 **C3**, 141.1 **Ar-C**, 139.9 **Ar-C**, 132.3 **Ar-C**, 129.0 **Ar-C**, 127.8 **C5**, 126.9 **Ar-C**, 126.8 **Ar-C**, 122.1 **Ar-C**, 99.5 **C4**, 61.5 **C2**, 47.6 **C1**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone-d_6) δ 6.5.

υ_{max} (solid): 3024, 2191, 1765, 1483, 1288, 1254, 1020, 1005 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{19}H_{16}BNNaO_4$) requires *m/z* 356.1070, found *m/z* 356.1067.

1m



Prepared according to General Procedure B using $Pd(dppf)_2Cl_2$ (73.2 mg, 0.10 mmol, 5.00 mol%), **1a** (362 mg, 2.00 mmol, 1.00 eq), 2-iodothiophene (265 µL, 2.40 mmol, 1.20 eq), CuI (38.1 mg, 0.20 mmol, 10.0 mol%) and Et_3N (836 µL, 6.00 mmol, 3.00 eq). The reaction was stirred at room temperature for 18 hours then subjected to purification as outlined in the General Procedure (silica gel, 5-25% MeCN in DCM) to give the title product as a pale yellow solid (151 mg, 57%).

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.52 (dd, *J* = 5.2, 1.1 Hz, 1H, **H8**), 7.32 (dd, *J* = 3.6, 1.2 Hz, 1H, **H6**), 7.07 (dd, *J* = 5.2, 3.6 Hz, 1H, **H7**), 4.36 (d, *J* = 17.0 Hz, 2H, **H2**), 4.21 (d, *J* = 17.0 Hz, 2H, **H2'**), 3.32 (s, 3H, **H1**).

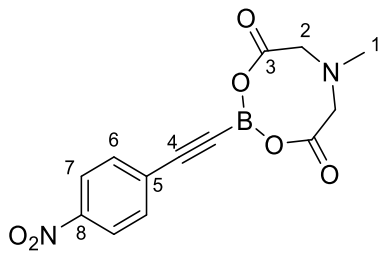
^{13}C NMR (101 MHz, Acetone-d_6) δ 167.7 **C3**, 132.8 **C6**, 127.9 **C8**, 127.2 **C7**, 122.8 **C5**, 92.3 **C4**, 61.6 **C2**, 47.4 **C1**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone-d_6) δ 6.5.

ν_{max} (solid): 3019, 2189, 1767, 1514, 1464, 1450, 1422 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{11}H_{10}BNNaO_4S$) requires *m/z* 286.0321, found *m/z* 286.0317.

1n



Prepared according to General Procedure B using $Pd(dppf)Cl_2$ (47.6 mg, 65.0 μmol, 5.00 mol%), 4-iodonitrobenzene (388 mg, 1.20 mmol, 1.20 equiv.), CuI (24.8 mg, 130 μmol, 10.0 mol%), **1a** (235 mg, 1.30 mmol, 1.00 equiv.) and Et_3N (544 uL, 3.90 mmol, 3.00 equiv.). The reaction was stirred at 50 °C for 20 hours then subjected to purification as outlined in the General Procedure (5-30% MeCN in DCM) to give the title product as a yellow solid (323 mg, 82%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29 – 8.19 (m, 2H, **H7**), 7.82 – 7.70 (m, 2H, **H6**), 4.35 (d, J = 17.2 Hz, 2H, **H2**), 4.18 (d, J = 17.1 Hz, 2H, **H2'**), 3.11 (s, 3H, **H1**).

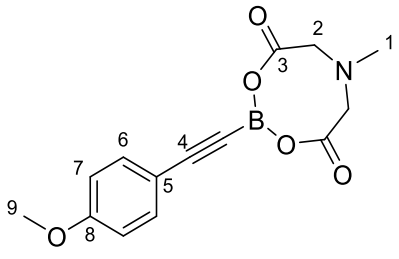
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2 **C3**, 147.5 **C8**, 133.3 **C6**, 129.5 **C3**, 124.3 **C3**, 97.9 **C3**, 62.0 **C3**, 48.4 **C3**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 6.6.

υ_{max} (solid): 2930, 2361, 1765, 1514, 1348, 1072, 1022 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{13}H_{11}BN_2NaO_6$) requires *m/z* 325.0608, found *m/z* 325.0603.

1o



Prepared according to General Procedure B using $Pd(dppf)Cl_2$ (20.2 mg, 27.6 µmol, 5.00 mol%), 4-iodoanisole (155 mg, 663 µmol, 1.20 equiv.), CuI (10.5 mg, 55.3 µmol, 10.0 mol%), **1a** (100 mg, 553 µmol, 1.00 equiv.) and Et_3N (231 uL, 1.66 mmol, 3.00 equiv.). The reaction was stirred at room temperature for 23 hours then subjected to purification as outlined in the General Procedure (5-30% MeCN in DCM) to give the title product as a light brown solid (115 mg, 72%).

^1H NMR (500 MHz, DMSO-d_6) δ 7.43 (d, J = 8.8 Hz, 2H, **H6**), 6.94 (d, J = 8.8 Hz, 2H **H7**), 4.31 (d, J = 17.1 Hz, 1H **H2**), 4.13 (d, J = 17.1 Hz, 1H **H2'**), 3.78 (s, 3H **H9**), 3.06 (s, 3H **H1**).

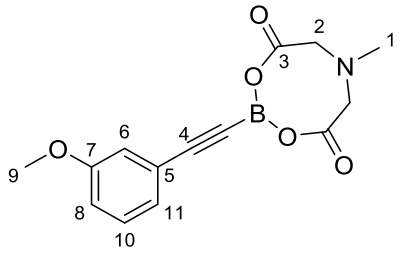
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2 **C3**, 160.0 **C8**, 133.6 **C6**, 114.8 **C5**, 114.7 **C7**, 100.1 **C4**, 61.9 **C2**, 55.7 **C9**, 48.3 **C1**.

^{11}B NMR (96 MHz, DMSO-d_6) δ 6.2.

υ_{max} (solid): 2183, 1749, 1508, 1285, 1242, 1005 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{15}BNO_5$) requires *m/z* 288.1043, found *m/z* 288.1039.

1p



Prepared according to General Procedure B using $Pd(dppf)Cl_2$ (20.2 mg, 27.6 µmol, 5.00 mol%), 3-iodoanisole (155 mg, 663 µmol, 1.20 equiv.), CuI (10.5 mg, 55.3 µmol, 10.0 mol%), **1a** (100 mg, 553 µmol, 1.00 equiv.) and Et_3N (231 µL, 1.66 mmol, 3.00 equiv.). The reaction was stirred at room temperature for 23 hours then subjected to purification as outlined in the General Procedure (5-30% MeCN in DCM) to give the title product as a white solid (90 mg, 57%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.29 (t, J = 7.9 Hz, 1H, **H10**), 7.12 – 6.92 (m, 3H, **H6** + **H8** + **H11**), 4.31 (d, J = 17.2 Hz, 2H, **H2**), 4.13 (d, J = 17.2 Hz, 2H, **H2'**), 3.75 (s, 3H, **H9**), 3.06 (s, 3H, **H1**).

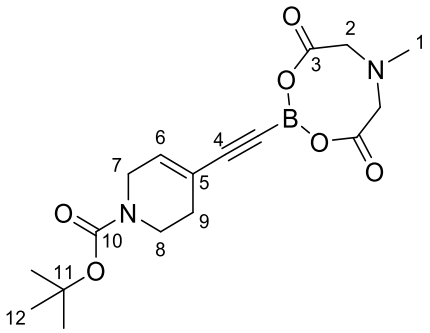
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2 **C3**, 159.6 **C7**, 130.3 **C10**, 124.4 **C11**, 123.9 **C5**, 116.8 **C6**, 115.9 **C8**, 99.8 **C4**, 62.0 **C2**, 55.7 **C9**, 48.4 **C1**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 6.6.

υ_{max} (solid): 3013, 2197, 1767, 1574, 1464, 1290, 1202, 1018 cm^{-1}.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{14}H_{13}BNO_5$) requires *m/z* 286.0892, found *m/z* 286.0891.

1r



A solution of freshly distilled hexamethyldisilizane (1.24 mL, 6.00 mmol, 1.20 equiv.) in THF (6.00 mL) was cooled to -78 °C then *n*-butyllithium (2.17 M in hexanes, 2.76 mL, 6.00 mmol, 1.20 equiv.) was added with stirring then the reaction mixture was allowed to warm to room temperature to give a solution of LiHMDS. In a separate flask, a solution of *N*-Boc-piperidin-4-one (996 mg, 5.00 mmol, 1.00 equiv.) and *N*-phenyl-bis(trifluoromethanesulfonimide) (1.96 g, 5.50 mmol, 1.10 equiv.) in THF (120 mL) was cooled to -78 °C and to this was added the above LiHMDS solution dropwise. After complete addition, the dry ice/acetone bath was removed and the reaction mass was allowed to warm to room temperature then stirred overnight at room temperature. The reaction mixture was then quenched by addition of saturated NH_4Cl (2 mL) then the mixture was concentrated *in vacuo* to a residue, then to this was added Et_2O (20 mL) and aqueous 2 M NaOH (10 mL) and this was stirred vigorously at room temperature for 15 minutes. The layers were split,

the organic layer was washed successively with 2 M NaOH (10 mL) and brine (10 mL) then the organic layer was dried over $MgSO_4$ filtered, and concentrated *in vacuo*. The vinyl triflate product was isolated in semi-pure form (silica gel, 5% EtOAc in hexane) and used in excess in the following Sonogashira reaction.

Prepared according to General Procedure B using $Pd(dppf)Cl_2$ (73.2 mg, 0.10 mmol, 5 mol%), the vinyl triflate from the previous step (795 mg, 1.20 mmol, 1.20 equiv.), CuI (38.1 mg, 0.20 mmol, 10.0 mol%), **1a** (181 mg, 1.00 mmol, 1.00 equiv.) and Et_3N (836 µL, 3.00 mmol, 3.00 equiv.). The reaction mixture was stirred at 50 °C for 16 hours then subjected to purification as outlined in the General Procedure (5-20% MeCN in DCM) followed by trituration from acetone with Et_2O to give the title product as a light yellow solid (65%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 6.12 (s, 1H, **H6**), 4.27 (d, J = 17.2 Hz, 2H, **H2**), 4.08 (d, J = 17.1 Hz, 2H, **H2'**), 3.90 (brs, 2H, **H7**), 3.43 – 3.37 (m, 1H, **H9**), 2.98 (s, 3H, **H1**), 2.20 – 2.13 (m, 2H, **H8**), 1.41 (s, 9H, **H12**).

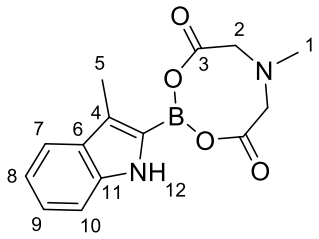
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.1 **C3**, 154.3 **C10**, 132.4 **C6**, 119.0 **C5**, 79.5 **C11**, 61.9 **C2**, 48.2 **C1**, 43.9 **C7**, 29.0 **C9**, 28.5 **C12**. **C8** is obscured beneath the NMR solvent peak. **C4** is not observed. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 7.0.

υ_{max} (solid): 2976, 2374, 2191, 1769, 1695, 1288, 1024 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{17}H_{23}BN_2NaO_6$) requires *m/z* 385.1547, found *m/z* 385.1537.

3a



Prepared according to General Procedure A using Pd(dppf)Cl_2 (7.32 mg, 10.0 μmol, 5.00 mol%), **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.), 2-iodoaniline (52.6 mg, 0.24 mmol, 1.20 equiv.) and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 5-20% MeCN in DCM) to give the title product as a tan solid (48.0 mg, 84%).

1H NMR (400 MHz, Acetone-d_6) δ 9.90 (brs, 1H, **H12**), 7.54 (ddt, J = 7.9, 1.4, 0.8 Hz, 1H, **H7**), 7.38 (dt, J = 8.1, 0.9 Hz, 1H, **H10**), 7.09 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H, **H9**), 7.00 (ddd, J = 7.9, 6.9, 1.0 Hz, 1H, **H8**), 4.40 (d, J = 17.0 Hz, 2H, **H2**), 4.17 (d, J = 17.1 Hz, 2H, **H2'**), 2.84 (s, 3H, **H1**), 2.39 (s, 3H, **H5**).

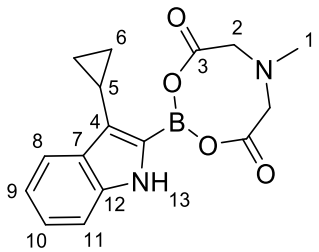
^{13}C NMR (101 MHz, Acetone-d_6) δ 168.3 **C3**, 138.1 **C11**, 129.9 **C6**, 121.5 **C9**, 118.4 **C7**, 118.1 **C8**, 117.3 **C4**, 111.1 **C10**, 61.9 **C2**, 47.1 **C1**, 9.1 **C5**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone-d_6) δ 10.7.

ν_{max} (solid): 3366, 1771, 1749, 1539, 1458, 1333, 1294, 1244, 1211, 1138, 1030 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}BN_2O_4$) requires *m/z* 287.1203, found *m/z* 287.1197.

3b



Prepared according to General Procedure A using Pd(dppf)Cl_2 (7.32 mg, 10.0 μmol, 5.00 mol%), **1d** (44.2 mg, 0.20 mmol, 1.00 equiv.), 2-iodoaniline, (52.6 mg, 0.24 mmol, 1.20 equiv.) and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 0-35% MeCN in DCM) to give the title product as a tan solid (57 mg, 91%).

^{1}H NMR (400 MHz, Acetone-d_6) δ 9.90 (brs, 1H, **H13**), 7.66 (dd, *J* = 8.1, 1.0 Hz, 1H, **H8**), 7.46 – 7.34 (m, 1H, **H11**), 7.06 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, **H10**), 6.96 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H, **H9**), 4.41 (d, *J* = 17.0 Hz, 2H, **H2**), 4.20 (d, *J* = 17.0 Hz, 2H, **H2'**), 2.89 (s, 3H, **H1**), 2.04 – 1.95 (m, 1H, **H5**), 0.98 – 0.80 (m, 4H, **H6**).

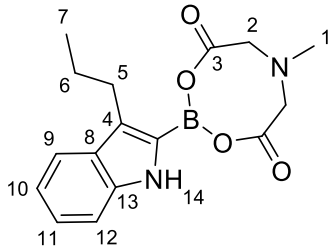
^{13}C NMR (126 MHz, Acetone-d_6) δ 168.3 **C3**, 137.8 **C12**, 128.9 **C7**, 122.7 **C4**, 121.3 **C10**, 119.4 **C8**, 118.3 **C11**, 111.4 **C9**, 62.2 **C2**, 47.2 **C1**, 7.3 **C5**, 5.8 **C6**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone-d_6) δ 10.8.

ν_{max} (solid): 1761, 1533, 1456, 1290, 1194, 1032, 1009, 858, 746 cm^{-1}.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{16}H_{16}BN_2O_4$) requires *m/z* 311.1209, found *m/z* 311.1212.

3c



Prepared according to General Procedure A using Pd(dppf)Cl$_2$ (7.32 mg, 10.0 μmol, 5.00 mol%), **1c** (44.6 mg, 0.20 mmol, 1.00 equiv.), 2-iodoaniline (52.6 mg, 0.24 mmol, 1.20 equiv.), and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 0-35% MeCN in DCM) to give the title product as a tan solid (59 mg, 94%).

^{1}H NMR (500 MHz, CD_3CN) δ 9.08 (brs, 1H, **H14**), 7.60 (dd, *J* = 8.0, 1.0 Hz, 1H, **H9**), 7.38 (dt, *J* = 8.1, 0.9 Hz, 1H, **H12**), 7.14 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, **H11**), 7.03 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H, **H10**), 4.13 (d, *J* = 17.2 Hz, 2H, **H2**), 3.95 (d, *J* = 17.2 Hz, 2H, **H2'**), 2.79 – 2.69 (m, 2H, **H5**), 2.62 (s, 3H, **H1**), 1.73 – 1.61 (m, 2H, **H6**), 0.98 (t, *J* = 7.4 Hz, 3H, **H7**).

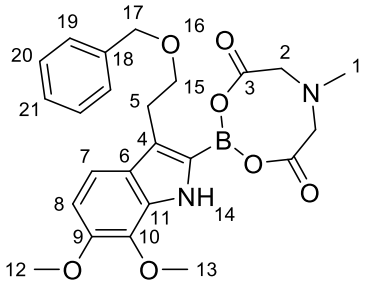
^{13}C NMR (126 MHz, CD_3CN) δ 168.4 **C3**, 138.0 **C13**, 129.1 **C8**, 123.4 **C4**, 121.9 **C11**, 118.9 **C9**, 118.4 **C10**, 111.1 **C12**, 62.0 **C2**, 47.5 **C1**, 27.3 **C5**, 25.2 **C6**, 13.7 **C7**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, CD_3CN) δ 10.7.

ν_{max} (solid): 3360, 2953, 2361, 1765, 1744, 1541, 1454, 1225, 1292, 1034, 1009 cm^{-1}.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{16}H_{18}BN_2O_4$) requires *m/z* 313.1365, found *m/z* 313.1368.

3d



Prepared according to General Procedure A using $Pd(dppf)Cl_2$ (7.32 mg, 10.0 μmol, 5.00 mol%), **1f** (63.0 mg, 0.20 mmol, 1.00 equiv.) **2g** (67.0 mg, 0.24 mmol, 1.20 equiv.) and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 5-20% MeCN in DCM) to give the title product as a light brown solid (71 mg, 76%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 9.75 (brs, 1H, **H14**), 7.34 – 7.26 (m, 5H, **H19** + **H20** + **H21**), 7.23 (d, J = 8.6 Hz, 1H, **H7**), 6.83 (d, J = 8.6 Hz, 1H, **H8**), 4.47 (s, 2H, **H17**), 4.16 (d, J = 17.0 Hz, 2H, **H2**), 4.04 (d, J = 17.0 Hz, 2H, **H2'**), 3.92 – 3.85 (m, 6H, **H12** + **H13**), 3.79 (t, J = 6.2 Hz, 2H, **H15**), 3.13 (t, J = 6.2 Hz, 2H, **H5**), 2.77 (s, 3H, **H1**).

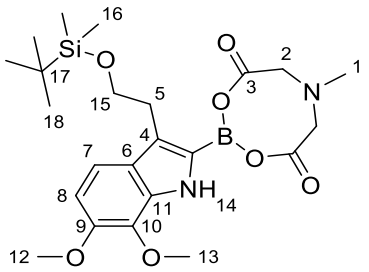
^{13}C NMR (126 MHz, Acetone-d_6) δ 168.5 **C3**, 147.3 **C9**, 138.5 **C18**, 134.8 **C10**, 132.6 **C11**, 128.3 **C19**, 128.2 **C20**, 127.6 **C21**, 126.1 **C5**, 120.3 **C4**, 113.6 **C7**, 108.0 **C8**, 72.7 **C17**, 71.0 **C15**, 62.2 **C2**, 59.9 **C12**, 57.0 **C13**, 47.2 **C1**, 25.9 **C5**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone-d_6) δ 10.7.

υ_{max} (solid): 3374, 1771, 1744, 1310, 1217, 1024 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{24}H_{27}BN_2NaO_7$) requires *m/z* 489.1809, found *m/z* 489.1802

3e



Prepared according to General Procedure A using $Pd(dppf)Cl_2$ (7.32 mg, 10.0 μmol, 5.00 mol%), **1g** (67.9 mg, 0.20 mmol, 1.00 equiv.), **2g** (67.0 mg, 0.24 mmol, 1.20 equiv.), and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 5-30% MeCN in DCM) followed by recrystallisation from EtOAc/hexane to give the title product as a beige powder (25 mg, 26%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 9.78 (brs, 1H, **H14**), 7.25 (dd, J = 8.6, 0.7 Hz, 1H, **H7**), 6.84 (d, J = 8.6 Hz, 1H, **H8**), 4.37 (d, J = 17.0 Hz, 2H, **H2**), 4.18 (d, J = 17.0 Hz, 2H, **H2'**), 3.92 – 3.83 (m, 8H, **H12** + **H13** + **H15**), 3.02 (t, J = 7.4 Hz, 2H, **H5**), 2.95 (s, 3H, **H1**), 0.89 (s, 9H, **H18**), 0.06 (s, 6H, **H16**).

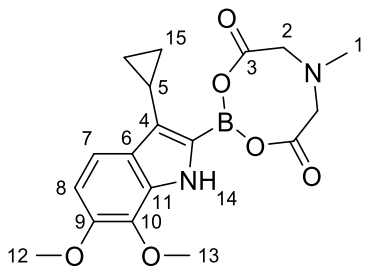
^{13}C NMR (126 MHz, Acetone-d_6) δ 168.3 **C3**, 147.3 **C9**, 134.7 **C10**, 132.6 **C11**, 126.6 **C6**, 119.8 **C4**, 113.7 **C7**, 108.0 **C8**, 64.5 **C15**, 62.1 **C2**, 59.9 **C13**, 57.0 **C12**, 47.4 **C1**, 25.6 **C18**, 18.2 **C17**, -5.9 **C16**. **C5** is obscured beneath the NMR solvent peak. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone-d_6) δ 10.7.

υ_{max} (solid): 3354, 2928, 1773, 1742, 1248, 1219, 1096, 1042, 1005 cm^{-1}.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{23}H_{34}BN_2O_7Si$) requires *m/z* 489.2234, found *m/z* 489.2230.

3f



Prepared according to General Procedure A using $Pd(dppf)Cl_2$ (7.32 mg, 10.0 μmol, 5.00 mol%), **1d** (44.2 mg, 0.20 mmol, 1.00 equiv.) **2g** (67.0 mg, 0.24 mmol, 1.20 equiv.) and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 5-30% MeCN in DCM) to afford the product as a light pink solid (60 mg, 81%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.31 (brs, 1H, **H14**), 7.21 (d, J = 8.7 Hz, 1H, **H7**), 6.75 (d, J = 8.7 Hz, 1H, **H8**), 4.35 (d, J = 17.3 Hz, 2H, **H2**), 4.07 (d, J = 17.3 Hz, 2H, **H2'**), 3.86-3.78 (m, 6H, **H12** + **H13**), 2.66 (s, 3H, **H1**), 1.89 (tt, J = 8.5, 5.4 Hz, 1H, **H5**), 0.85 – 0.63 (m, 4H, **H15**).

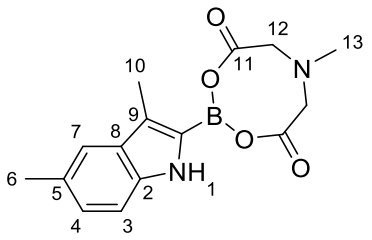
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.9 **C3**, 146.8 **C9**, 134.6 **C10**, 132.2 **C11**, 125.7 **C6**, 123.4 **C4**, 114.6 **C7**, 107.9 **C8**, 62.9 **C2**, 60.9 **C12**, 57.7 **C13**, 48.3 **C1**, 7.8 **C5**, 6.4 **C15**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 10.5.

υ_{max} (solid): 3374, 1748, 1450, 1246, 1030 cm^{-1}.

HRMS: exact mass calculated for $[M]^+$ ($C_{18}H_{21}BN_2O_6$) requires *m/z* 372.1493, found *m/z* 372.1491.

3g



Prepared according to General Procedure A using Pd(dppf)Cl_2 (7.32 mg, 10.0 μmol, 5.00 mol%), **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.) 4-amino-3-iodotoluene (55.9 mg, 0.24 mmol, 1.20 equiv.) and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 5-30% MeCN in DCM) to give the title product as a beige solid (54 mg, 90%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 9.75 (brs, 1H, **H1**), 7.34 – 7.29 (m, 1H, **H7**), 7.26 (d, *J* = 8.2, 1H, **H3**), 6.93 (dd, *J* = 8.4, 1.6 Hz, 1H, **H4**), 4.38 (d, *J* = 17.1 Hz, 2H, **H12**), 4.15 (d, *J* = 17.0 Hz, 2H, **H12'**), 2.83 (s, 3H, **H13**), 2.42 (s, 3H, **H6**), 2.35 (s, 3H , **H10**).

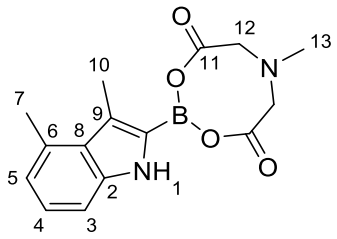
^{13}C NMR (126 MHz, Acetone-d_6) δ 168.3 **C11**, 136.5 **C2**, 130.2 **C8**, 126.8 **C5**, 123.2 **C4**, 118.0 **C7**, 116.7 **C9**, 110.8 **C3**, 61.9 **C12**, 47.1 **C13**, 20.7 **C6**, 9.1 **C10**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone-d_6) δ 10.7.

υ_{max} (solid): 3414, 2924, 1759, 1456, 1288, 1215, 1030 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{15}H_{17}BNaN_2O_4$) requires *m/z* 323.1179, found *m/z* 323.1172.

3h



Prepared according to General Procedure A using Pd(dppf)Cl_2 (7.32 mg, 10.0 μmol, 5.00 mol%), **1b** (39.0 mg, 0.2 mmol, 1.0 equiv.) **2b** (55.9 mg, 0.24 mmol, 1.20 equiv.) and NaOAc (41.0 mg, 0.50 mmol, 2.5 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 5-30% MeCN in DCM) to give the title product as a beige solid (47 mg, 78%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 9.78 (s, 1H, **H1**), 7.20 (dt, *J* = 8.2, 0.9 Hz, 1H, **H3**), 6.92 (dd, *J* = 8.2, 7.0 Hz, 1H, **H4**), 6.68 (dt, *J* = 7.0, 1.0 Hz, 1H, **H5**), 4.38 (d, *J* = 17.1 Hz, 2H,

H12), 4.16 (d, *J* = 17.1 Hz, 2H, **H12'**), 2.85 (s, 3H, **H13**), 2.70 (s, 3H, **H7**), 2.59 (s, 3H, **H10**).

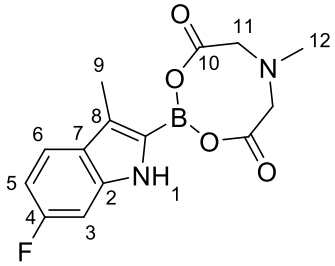
^{13}C NMR (126 MHz, Acetone-d_6) δ 168.3 **C11**, 138.6 **C2**, 130.6 **C6**, 128.2 **C8**, 121.6 **C4**, 119.9 **C5**, 118.4 **C9**, 109.4 **C3**, 62.0 **C12**, 47.1 **C13**, 20.0 **C7**, 12.2 **C10**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone-d_6) δ 10.7.

υ_{max} (solid): 3381, 2918, 1757, 1456, 1327, 1211, 1030, 993 cm^{-1}

HRMS: exact mass calculated for $[M-H]^-$ ($C_{15}H_{16}BN_2O_4$) requires *m/z* 299.1209, found *m/z* 299.1210.

3i



Prepared using General Procedure A using Pd(dppf)Cl$_2$ (7.32 mg, 10.0 μmol, 5.00 mol%), **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and **2a** (56.9 mg, 0.24 mmol, 1.20 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 5-20% MeCN in DCM) to give the title product as a light brown powder (62 mg, quantitative).

^{1}H NMR (500 MHz, Acetone-d_6) δ 10.00 (brs, 1H, **H1**), 7.51 (dd, *J* = 8.6, 5.4 Hz, 1H, **H6**), 7.09 (dd, *J* = 10.1, 2.3 Hz, 1H, **H3**), 6.82 (ddd, *J* = 9.8, 8.6, 2.3 Hz, 1H, **H5**), 4.40 (d, *J* = 17.1 Hz, 2H, **H11**), 4.18 (d, *J* = 17.2 Hz, 2H, **H11'**), 2.87 (s, 3H, **H12**), 2.37 (s, 3H, **H9**).

^{13}C NMR (126 MHz, Acetone-d_6) δ 168.3 **C10**, 160.0 (d, $^1J_{C-F}$ = 234.8 Hz) **C4**, 137.9 (d, $^3J_{C-F}$ = 12.4 Hz) **C2**, 126.8 **C7**, 119.3 (d, $^3J_{C-F}$ = 10.5 Hz) **C6**, 117.6 **C8**, 106.6 (d, $^2J_{C-F}$ = 25.0 Hz) **C5**, 96.8 (d, $^2J_{C-F}$ = 25.5 Hz) **C3**, 61.9 **C11**, 47.1 **C12**, 9.0 **C9**. The carbon bearing boron is not observed due to quadrupolar relaxation.

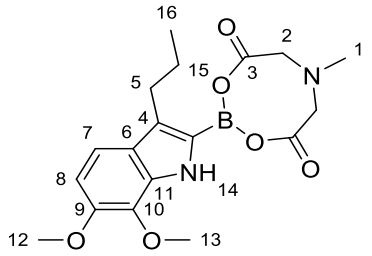
^{11}B NMR (96 MHz, Acetone-d_6) δ 10.5.

^{19}F NMR (471 MHz, Acetone-d_6) δ -123.7.

υ_{max} (solid): 1763, 1705, 1456, 1288, 1209, 1032 cm^{-1}.

HRMS: exact mass calculated for [M-H]$^-$ ($C_{14}H_{13}BFN_2O_4$) requires *m/z* 303.0958, found *m/z* 303.0959.

3j



Prepared according to General Procedure A using Pd(dppf)Cl$_2$ (7.32 mg, 10.0 μmol, 5.00 mol%), **1c** (44.6 mg, 0.20 mmol, 1.00 equiv.) **2g** (67.0 mg, 0.24 mmol, 1.20 equiv.) and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 5-30% MeCN in DCM) to give the title product as a light pink solid (63 mg, 84%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 9.69 (brs, 1H, **H14**), 7.23 (d, J = 8.6 Hz, 1H, **H7**), 6.82 (d, J = 8.6 Hz, 1H, **H8**), 4.39 (d, J = 17.1 Hz, 2H, **H2**), 4.15 (d, J = 17.1 Hz, 2H, **H2'**), 3.89 – 3.85 (m, 6H, **H12** + **H13**), 2.94 (s, 3H, **H1**) 2.79 – 2.71 (m, 2H, **H5**), 1.78 – 1.59 (m, 2H, **H15**), 0.97 (t, *J* = 7.3 Hz, 3H, **H16**).

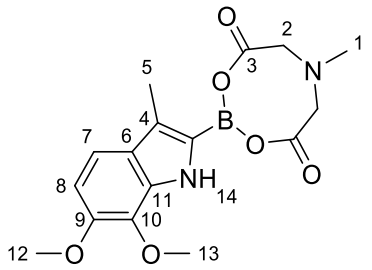
^{13}C NMR (126 MHz, Acetone-d_6) δ 168.3 **C3**, 147.2 **C9**, 134.7 **C10**, 132.6 **C11**, 126.5 **C6**, 123.9 **C4**, 113.7 **C7**, 107.9 **C8**, 62.2 **C2**, 59.8 **C13**, 57.0 **C12**, 47.5 **C1**, 27.4 **C5**, 25.3 **C15**, 13.9 **C16**. The carbon bearing boron is not observed due to quadrupolar relaxation

^{11}B NMR (96 MHz, Acetone-d_6) δ 10.6.

υ_{max} (solid): 3389, 2957, 1748, 1450, 1246, 1213, 1028, 1009 cm^{-1}.

HRMS: exact mass calculated for [M]$^+$ ($C_{18}H_{23}BN_2O_6$) requires *m/z* 374.1649, found *m/z* 374.1643.

3k



Prepared according to General Procedure A using $Pd(dppf)Cl_2$ (7.32 mg, 10.0 μmol, 5.00 mol%), **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.), **2g** (67.0 mg, 0.24 mmol, 1.20 equiv.), and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 5-30% MeCN in DCM) to give the title product as a tan solid (45 mg, 65%).

^{1}H NMR (500 MHz, Acetone- d_6) δ 9.68 (brs, 1H, **H14**), 7.19 (dd, J = 8.5, 0.7 Hz, 1H, **H7**), 6.84 (d, J = 8.6 Hz, 1H, **H8**), 4.37 (d, J = 17.1 Hz, 2H, **H2**), 4.14 (d, J = 17.1 Hz, 2H, **H2'**), 3.89-3.85(m, 6H, **H12** + **H13**), 2.91 (s, 3H, **H1**), 2.33 (s, 3H, **H5**).

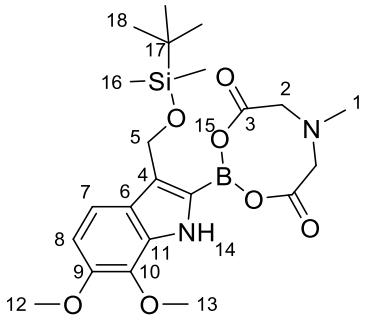
^{13}C NMR (126 MHz, Acetone- d_6) δ 168.4 **C3**, 147.4 **C9**, 134.7 **C10**, 132.4 **C11**, 127.2 **C6**, 118.1 **C4**, 113.4 **C8**, 107.9 **C7**, 62.0 **C2**, 59.8 **C12**, 57.0 **C13**, 47.3 **C1**, 9.1 **C5**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone- d_6) δ 10.7.

υ_{max} (solid): 3383, 2932, 1757, 1294, 1217, 1032, 1011 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{16}H_{19}BN_2NaO_6$) requires *m/z* 369.1234, found *m/z* 369.1228.

3l



Prepared according to General Procedure A using $Pd(dppf)Cl_2$ (7.32 mg, 10.0 μmol, 5.00 mol%), **1h** (65.0 mg, 0.20 mmol, 1.00 equiv.) **2g** (67.0 mg, 0.24 mmol, 1.20 equiv.) and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 5-30% MeCN in DCM) to give the title product as a light pink solid (40 mg, 42%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 9.98 (brs, 1H, **H14**), 7.32 (dd, J = 8.6, 0.6 Hz, 1H, **H7**), 6.89 (d, J = 8.6 Hz, 1H, **H8**), 4.96 (s, 2H, **H5**), 4.38 (d, J = 16.8 Hz, 2H, **H2**), 4.18 (d, J = 16.8 Hz, 2H, **H2'**), 3.92 – 3.86 (m, 6H, **H12** + **H13**), 2.91 (s, 3H, **H1**), 0.93 (s, 9H, **H18**), 0.17 (s, 6H, **H16**).

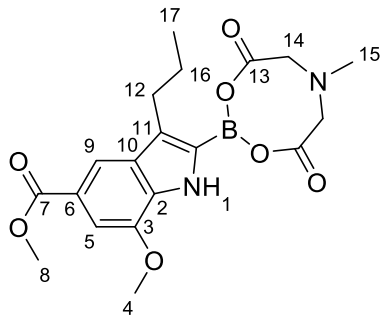
^{13}C NMR (126 MHz, Acetone-d_6) δ 168.3 **C3**, 147.3 **C9**, 134.8 **C10**, 132.1 **C11**, 125.9 **C6**, 122.1 **C4**, 113.4 **C7**, 108.6 **C8**, 62.0 **C2**, 59.9 **C13**, 57.0 **C12**, 56.3 **C5**, 47.4 **C1**, 25.6 **C18**, 18.3 **C17**, -5.9 **C16**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone-d_6) δ 10.4.

υ_{max} (solid): 3310, 2930, 1765, 1517, 1449, 1341, 1247, 1088, 1045, 999, 847 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{22}H_{33}BN_2NaO_7Si$) requires *m/z* 499.2048, found *m/z* 499.2034.

3m



Prepared using General Procedure A using $Pd(dppf)Cl_2$ (7.32 mg, 10.0 μmol, 5.00 mol%), **1c** (44.6 mg, 0.20 mmol, 1.00 equiv.), methyl 4-amino-3-iodo-5-methoxybenzoate (73.7 mg, 0.24 mmol, 1.20 equiv.) and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 10-30% MeCN in DCM) to give the title product as a light brown powder (51 mg, 63%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 10.24 (brs, 1H, **H1**), 8.01 (s, 1H, **H9**), 7.27 (d, J = 1.2 Hz, 1H, **H5**), 4.44 (d, J = 17.2 Hz, 2H, **H14**), 4.21 (d, J = 17.2 Hz, 2H, **H14'**), 3.98 (s, 3H, **H4**), 3.88 (s, 3H, **H8**), 2.98 (s, 3H, **H15**), 2.85 – 2.80 (m, 2H, **H12**), 1.76 – 1.62 (m, 2H, **H16**), 1.00 (t, J = 7.4 Hz, 3H, **H17**).

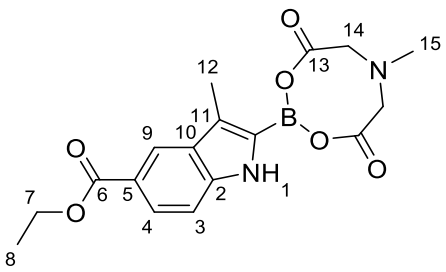
^{13}C NMR (126 MHz, Acetone-d_6) δ 168.3 **C13**, 167.5 **C7**, 145.9 **C3**, 131.2 **C2**, 129.8 **C10**, 125.6 **C11**, 121.2 **C6**, 115.3 **C9**, 101.9 **C5**, 62.4 **C14**, 54.8 **C4**, 51.0 **C8**, 47.7 **C15**, 27.3 **C12**, 25.6 **C16**, 13.8 **C17**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone-d_6) δ 10.6.

υ_{max} (solid): 2953, 1763, 1697, 1435, 1254, 1229, 1034 cm^{-1}.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{19}H_{22}BN_2O_7$) requires *m/z* 401.1526, found *m/z* 401.1525.

3n



Prepared using General Procedure A using $Pd(dppf)Cl_2$ (7.32 mg, 10.0 μmol, 5.00 mol%), **1b** (39.0 mg, 0.20 mmol, 1.00 equiv.), **2c** (52.6 mg, 0.24 mmol, 1.20 equiv.) and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Proced ure (silica gel, 5-20% MeCN in DCM) to give the title product as a light brown powder (51 mg, 71%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (brs, 1H, **H1**), 8.18 (s, 1H, **H9**), 7.70 (dd, J = 8.6, 1.6 Hz, 1H, **H4**), 7.40 (d, J = 8.5 Hz, 1H, **H3**), 4.39 (d, J = 17.3 Hz, 2H, **H14**), 4.31 (q, J = 7.1 Hz, 2H, **H7**), 4.13 (d, J = 17.3 Hz, 2H, **H14'**), 2.58 (s, 3H, **H15**), 2.32 (s, 3H, **H12**), 1.34 (t, J = 7.1 Hz, 3H, **H8**).

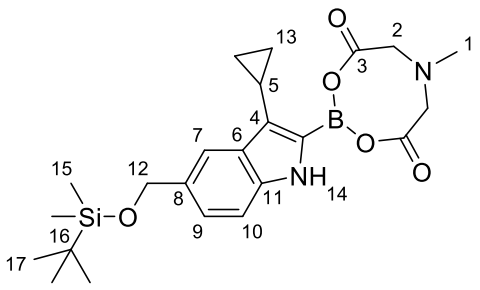
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.7 **C13**, 167.4 **C6**, 140.6 **C2**, 129.2 **C10**, 122.7 **C2**, 121.3 **C9**, 120.1 **C5**, 118.7 **C11**, 111.5 **C3**, 62.3 **C14**, 60.5 **C7**, 47.8 **C15**, 14.9 **C8**, 9.9 **C12**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 9.8.

υ_{max} (solid): 1767, 1694, 1449, 1250, 1099, 1034, 1001, 858 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{17}H_{19}BN_2NaO_6$) requires *m/z* 381.1234, found *m/z* 381.1222.

3o



Prepared using General Procedure A using $Pd(dppf)Cl_2$ (7.32 mg, 10.0 μmol, 5.00 mol%), **1d** (44.2 mg, 0.20 mmol, 1.00 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and **2i** (87.2 mg, 0.24 mmol, 1.20 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 5-30% MeCN in DCM) to give the title product as a light brown solid (51 mg, 56%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.55 (brs, 1H, **H14**), 7.51 (s, 1H, **H7**), 7.28 (d, J = 8.3 Hz, 1H, **H10**), 6.95 (d, J = 8.4 Hz, 1H, **H9**), 4.74 (s, 2H, **H12**), 4.38 (d, J = 17.3 Hz, 2H, **H2**), 4.11 (d, J = 17.3 Hz, 2H, **H2'**), 2.59 (s, 3H, **H1**), 1.91 (tt, J = 8.5, 5.4 Hz, 1H, **H5**), 0.92 (s, 9H, **H17**), 0.87 – 0.72 (m, 4H, **H13**), 0.08 (s, 6H, **H15**).

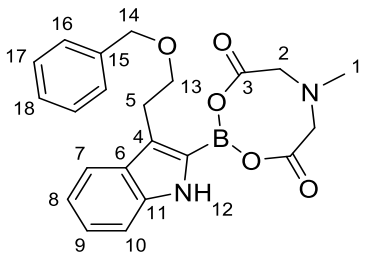
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.7 **C3**, 137.2 **C11**, 131.0 **C8**, 128.2 **C6**, 122.3 **C4**, 120.7 **C9**, 117.3 **C7**, 111.7 **C10**, 65.7 **C12**, 62.5 **C2**, 47.9 **C1**, 26.3 **C17**, 18.5 **C16**, 7.9 **C5**, 6.4 **C13**, -4.6 **C15**.

^{11}B NMR (96 MHz, DMSO-d_6) δ 11.5.

υ_{max} (solid): 2923, 2361, 1771, 1456, 1339, 1292, 1250, 1215, 1032, 835 cm^{-1}.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{23}H_{32}BN_2O_5Si$) requires *m/z* 455.2179, found *m/z* 455.2186.

3p



Prepared using General Procedure A using $Pd(dppf)Cl_2$ (707 mg, 966 µmol, 5.00 mol%), **1f** (6.09 g, 19.3 mmol, 1.00 equiv.), 2-iodoaniline (5.08 g, 23.2 mmol, 1.20 equiv.) and NaOAc (3.96 g, 48.3 mmol, 2.50 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 6-30% MeCN in DCM) to give the title product as a brown solid (7.08 g, 90%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.63 (brs, 1H, **H12**), 7.50 (d, J = 7.9 Hz, 1H, **H7**), 7.41 – 7.23 (m, 6H, **H10** + **Ph-H**), 7.06 (t, J = 7.4 Hz, 1H, **H9**), 6.94 (t, J = 7.3 Hz, 1H, **H8**), 4.44 (s, 2H, **H14**), 4.29 (d, J = 17.3 Hz, 2H, **H2**), 3.98 (d, J = 17.3 Hz, 2H, **H2'**), 3.63 (t, J = 6.7 Hz, 2H, **H13**), 3.06 (t, J = 6.7 Hz, 2H, **H5**), 2.51 (s, 3H, **H1**).

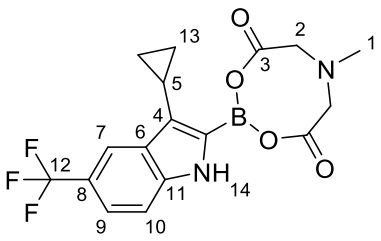
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.7 **C3**, 138.9 **C15**, 138.3 **C11**, 128.9 **C6**, 128.7 **C17**, 128.2 **C16**, 127.9 **C18**, 121.7 **C9**, 119.0 **C4**, 118.9 **C7**, 118.4 **C8**, 111.7 **C10**, 72.4 **C14**, 71.3 **C13**, 62.4 **C2**, 47.9 **C1**, 25.9 **C5**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 10.6.

υ_{max} (solid): 3352, 1769, 1746, 1234, 1221, 1038, 997, 739 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{24}BN_2O_5$) requires *m/z* 407.1778, found *m/z* 407.1767.

3q



Prepared according to General Procedure A using Pd(dppf)Cl_2 (7.32 mg, 10.0 μmol, 5.00 mol%), **1d** (44.2 mg, 0.20 mmol, 1.00 equiv.) 4-amino-3-iodobenzotrifluoride (68.9 mg, 0.24 mmol, 1.20 equiv.) and NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.). The reaction mixture was worked up according to the General Procedure then 1,4-dinitrobenzene (0.05 M, 1.00 mL) standard was added to the crude reaction mixture, and a yield was obtained using quantitative ^{1}H NMR (63%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 10.38 (brs, 1H, **H14**), 8.05 – 7.94 (m, 1H, **H7**), 7.59 (d, J = 8.5 Hz, 1H, **H10**), 7.37 (dd, J = 8.6, 1.8 Hz, 1H, **H9**), 4.45 (d, J = 17.1 Hz, 2H, **H2**), 4.24 (d, J = 17.0 Hz, 2H, **H2'**), 2.92 (s, 3H, **H1**), 2.02 (tt, J = 8.4, 5.3 Hz, 1H, **H5**), 1.03 – 0.94 (m, 2H, **H13**), 0.90 – 0.83 (m, 2H, **H13**').

^{13}C NMR (126 MHz, Acetone-d_6) δ 168.1 **C3**, 139.0 **C11**, 128.4 **C6**, 126.0 (q, $^1J_{C\text{-}F}$ = 270.4 Hz) **C12**, 123.8 **C4**, 120.1 (q, $^2J_{C\text{-}F}$ = 31.1 Hz) **C8**, 117.8 (q, $^3J_{C\text{-}F}$ = 3.3 Hz) **C9**, 116.8 (q, $^3J_{C\text{-}F}$ = 4.5 Hz) **C7**, 112.1 **C10**, 62.3 **C2**, 47.3 **C11**, 6.7 **C5**, 5.8 **C13**. The carbon bearing boron is not observed due to quadrupolar relaxation.

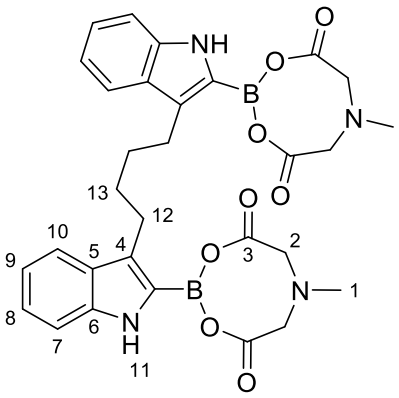
^{19}F NMR (377 MHz, Acetone-d_6) δ -60.35.

^{11}B NMR (96 MHz, Acetone-d_6) δ 10.5.

υ_{max} (solid): 1767, 1744, 1456, 1331, 1269, 1049, 1034 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ requires *m/z* 403.1053 , found *m/z* 403.1044.

3r



Prepared using General Procedure A using $Pd(dppf)Cl_2$ (14.6 mg, 20.0 μmol, 10.0 mol%), **1i** (83.2 mg, 0.20 mmol, 1.00 equiv.), NaOAc (82.0 mg, 1.00 mmol, 5.00 equiv.) and 2-iodoaniline (105 mg, 0.48 mmol, 2.40 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 5-50% MeCN in DCM) to give the title product as a brown solid (89.0 mg, 74%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 9.88 (brs, 2H, **H11**), 7.61 (dd, J = 7.9, 0.9 Hz, 2H, **H10**), 7.36 (dd, J = 8.1, 1.0 Hz, 2H, **H7**), 7.07 (ddd, J = 8.1, 6.9, 1.2 Hz, 2H, **H8**), 6.98 (ddd, J = 7.9, 6.9, 1.0 Hz, 2H, **H9**), 4.34 (d, J = 17.2 Hz, 4H, **H2**), 4.08 (d, J = 17.2 Hz, 4H, **H2'**), 2.97 – 2.88 (m, 4H, **H12**), 2.78 (s, 6H, **H1**), 1.85 – 1.74 (m, 4H, **H13**).

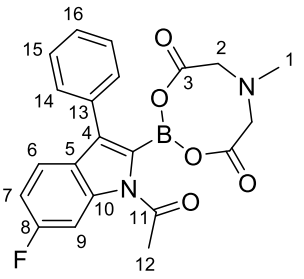
^{13}C NMR (126 MHz, Acetone-d_6) δ 168.4 **C3**, 138.3 **C6**, 129.3 **C5**, 123.7 **C4**, 121.5 **C8**, 118.9 **C10**, 118.1 **C9**, 111.1 **C7**, 62.2 **C2**, 47.5 **C1**, 33.0 **C13**, 25.1 **C12**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, Acetone-d_6) δ 10.7.

υ_{max} (solid): 1761, 1539, 1456, 1331, 1290, 1036, 858 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{30}H_{32}B_2N_4O_8$) requires *m/z* 621.2304, found *m/z* 621.2286.

4a



Prepared according to General Procedure D using $Pd(OAc)_2$ (4.49 mg, 20.0 μmol, 10.0 mol%), **1k** (51.4 mg, 0.20 mmol, 1.00 equiv.), **2m** (67.0 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 6-30% MeCN in DCM) to give the title product as a dark brown solid (48 mg, 66%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.70 (dd, J = 11.1, 2.1 Hz, 1H, **H9**), 7.45 – 7.38 (m, 2H, **H15**), 7.37 – 7.31 (m, 1H, **H16**), 7.26 (d, J = 7.4 Hz, 2H, **H14**), 7.13 (m, 2H, **H6** + **H7**), 4.53 – 4.02 (m, 4H, **H2**), 3.16 (s, 3H, **H1**), 2.86 (s, 3H, **H12**).

^{13}C NMR (126 MHz, DMSO-d_6) δ 172.3 **C11**, 170.3 **C3**, 168.3 **C3'**, 161.1 (d, $^{1}J_{C\text{-}F}$ = 238.8 Hz) **C8**, 136.8 (d, $^{3}J_{C\text{-}F}$ = 12.0 Hz) **C10**, 135.4 **C13**, 134.4 **C5**, 129.5 **C14**, 128.8 **C15**, 128.6 **C4**, 127.5 **C16**, 121.5 (d, $^{3}J_{C\text{-}F}$ = 10.4 Hz) **C6**, 111.3 (d, $^{2}J_{C\text{-}F}$ = 24.2 Hz) **C7**, 102.3 (d, $^{2}J_{C\text{-}F}$ = 28.6 Hz) **C9**, 65.2 **C2**, 50.9 **C1**, 27.4 **C12**. The carbon bearing boron is not observed due to quadrupolar relaxation.

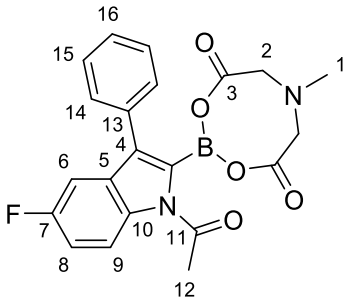
^{11}B NMR (96 MHz, DMSO-d_6) δ 11.2.

^{19}F NMR (376 MHz, DMSO-d_6) δ -116.3.

υ_{max} (solid): 1769, 1715, 1479, 1314, 1152, 1061 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{21}H_{18}BFN_2NaO_5$) requires *m/z* 431.1191, found *m/z* 431.1174.

4b



Prepared according to General Procedure D using $Pd(OAc)_2$ (4.49 mg, 20.0 μmol, 10.0 mol%), **1k** (51.4 mg, 0.20 mmol, 1.00 equiv.), **2k** (67.0 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.5 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 6-30% MeCN in DCM) to give the title product as a brown solid (26 mg, 32%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (dd, J = 9.2, 4.1 Hz, 1H, **H9**), 7.42 (m, 2H, **H15**), 7.39 – 7.30 (m, 1H, **H16**), 7.31 – 7.20 (m, 3H, **H14 + H8**), 6.82 (dd, J = 8.8, 2.7 Hz, 1H, **H6**), 4.32 (m, 4H, **H2**), 3.17 (s, 3H, **H1**), 2.87 (s, 3H, **H12**).

^{13}C NMR (126 MHz, DMSO-d_6) δ 172.1 **C11**, 170.2 **C3**, 168.3 **C3'**, 159.0 (d, $^1J_{C\text{-}F}$ = 238.2 Hz, **C7**), 135.2 **C13**, 134.3 (d, $^4J_{C\text{-}F}$ = 3.8 Hz, **C10**), 133.3 **C4**, 133.0 (d, $^3J_{C\text{-}F}$ = 9.0 Hz, **C5**), 129.5 **C14**, 128.9 **C15**, 127.6 **C16**, 116.4 (d, $^3J_{C\text{-}F}$ = 9.1 Hz, **C9**), 113.2 (d, $^2J_{C\text{-}F}$ = 25.2 Hz, **C8**), 105.2 (d, $^2J_{C\text{-}F}$ = 23.2 Hz, **C6**), 65.5 **C2**, 50.9 **C1**, 27.5 **C12**. The carbon bearing boron is not observed due to quadrupolar relaxation.

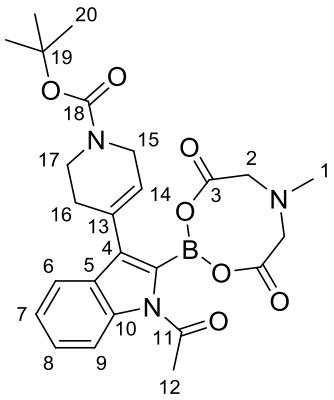
^{19}F NMR (376 MHz, DMSO-d_6) δ -120.9.

^{11}B NMR (96 MHz, DMSO-d_6) δ 9.8.

υ_{max} (solid): 1749, 1709, 1269, 1304, 1121, 1043 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{21}H_{18}BFN_2NaO_5$) requires *m/z* 431.1191, found *m/z* 431.1176.

4c



Prepared according to General Procedure D using $Pd(OAc)_2$ (4.49 mg, 20.0 µmol, 10.0 mol%), **1q** (72.4 mg, 0.20 mmol, 1.00 equiv.), **2j** (62.7 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.5 equiv.) and LiCl (17.0 mg, 0.4 mmol, 2.0 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 6-30% MeCN in DCM) to give the title product as a brown solid (82 mg, 83%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.84 – 7.75 (m, 1H, **H9**), 7.42 – 7.32 (m, 2H, **H6+8**), 7.29 – 7.21 (m, 1H, **H7**), 5.59 (brs, 1H, **H14**), 4.63 – 4.16 (m, 4H, **H2**), 4.08 – 3.94 (m, 1H, **H15**), 3.92 – 3.65 (m, 2H, **H15' + H16**), 3.64 – 3.51 (m, 1H, **H16'**), 3.01 (s, 3H, **H1**), 2.81 (s, 3H, **H12**), 2.48 – 2.35 (m, 1H, **H17**), 2.29 – 2.18 (m, 1H, **H17'**), 1.46 (s, 9H, **H20**).

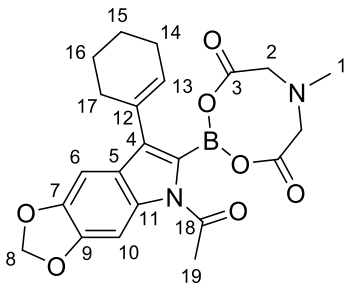
^{13}C NMR (126 MHz, DMSO-d_6) δ 171.7 **C11**, 170.3 **C3**, 169.4 **C3'**, 154.6 **C18**, 136.7 **C10**, 135.5 **C4**, 132.6 **C13**, 130.9 **C5**, 125.5 **C8**, 123.0 **C14 + C7**, 120.3 **C6**, 114.9 **C9**, 79.1 **C19**, 65.4 **C2**, 65.1 **C2'**, 50.9 **C1**, 44.0 **C15**, 30.1 **C17**, 28.6 **C20**, 27.4 **C12**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 11.0.

υ_{max} (solid): 1763, 1695, 1676, 1283, 1026 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{25}H_{31}BN_3O_7$) requires *m/z* 496.2255 , found *m/z* 496.2238.

4d



Prepared according to General Procedure D using $Pd(OAc)_2$ (4.49 mg, 20.0 μmol, 10.0 mol%), **1e** (51.4 mg, 0.20 mmol, 1.00 equiv.), **2e** (73.2 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 10-30% MeCN in DCM) to give the title product as a light brown solid (61 mg, 77%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37 (s, 1H, **H10**), 6.79 (s, 1H, **H6**), 6.06 (s, 2H, **H8**), 5.51 (brs, 1H, **H13**), 4.53 – 4.30 (m, 2H, **H2**), 4.24 – 3.96 (m, 2H, **H2'**), 2.98 (s, 3H, **H1**), 2.74 (s, 3H, **H19**), 2.19 (brs, 2H, **H14**), 2.04 (brs, 2H, **H17**), 1.81 (brs, 1H, **H16**), 1.68 (brs, 3H, **H16'+ H15**).

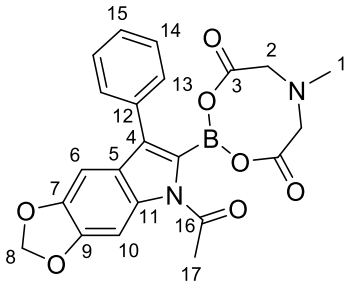
^{13}C NMR (126 MHz, DMSO-d_6) δ 171.6 **C18**, 170.3 **C3**, 169.1 **C3'**, 146.9 **C9**, 144.4 **C7**, 137.1 **C4**, 131.5 **C11**, 125.8 **C13**, 125.4 **C5**, 101.7 **C8**, 98.6 **C6**, 96.6 **C10**, 65.2 **C2**, 64.9 **C2'**, 50.9 **C1**, 29.9 **C14**, 27.2 **C19**, 25.6 **C17**, 22.5 **C16**, 21.7 **C15**. The carbon bearing boron is not observed due to quadrupolar relaxation. **C12** is not observed.

^{11}B NMR (96 MHz, DMSO-d_6) δ 11.3.

υ_{max} (solid): 1759, 1686, 1337, 1300, 1173, 1032 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{24}BN_2O_7$) requires *m/z* 439.1677, found *m/z* 439.1664.

4e



Prepared according to General Procedure D using $Pd(Oac)_2$ (4.49 mg, 20.0 μmol, 10.0 mol%), **1k** (51.4 mg, 0.20 mmol, 1.00 equiv.), **2e** (73.2 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 8-30% MeCN in DCM) to give the title product as a light brown solid (48 mg, 55%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.45 (s, 1H, **H10**), 7.43 – 7.36 (m, 2H, **H14**), 7.34 – 7.29 (m, 1H, **H15**), 7.28 – 7.19 (m, 2H, **H13**), 6.49 (s, 1H, **H6**), 6.05 (s, 2H, **H8**), 4.38 – 3.90 (m, 4H, **H2**), 3.15 (s, 3H, **H1**), 2.81 (s, 3H, **H17**).

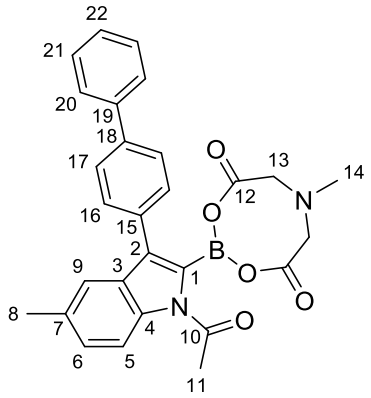
^{13}C NMR (126 MHz, DMSO-d_6) δ 172.3 **C16**, 170.1 **C3**, 168.3 **C3'**, 147.2 **C9**, 144.6 **C7**, 135.8 **C12**, 134.7 **C4**, 131.5 **C11**, 129.5 **C13**, 128.8 **C14**, 127.4 **C15**, 126.1 **C5**, 101.9 **C8**, 98.5 **C6**, 96.5 **C10**, 65.4 **C2**, 50.8 **C1**, 27.4 **C17**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 11.5.

υ_{max} (solid): 2363, 1773, 1749, 1707, 1476, 1348, 1310, 1169, 1024 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{22}H_{19}BN_2NaO_7$) requires *m/z* 457.1183 , found *m/z* 457.1178.

4f



Prepared according to General Procedure D using $Pd(Oac)_2$ (4.49 mg, 20.0 μmol, 10.0 mol%), **1l** (66.6 mg, 0.20 mmol, 1.00 equiv.), **2l** (66.0 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 6-30% MeCN in DCM) to give the title product as a light brown solid (45 mg, 47%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79 – 7.62 (m, 5H, **H5** + **H20** + **H21**), 7.51 (t, J = 7.7 Hz, 2H, **H16**), 7.47 – 7.32 (m, 3H, **H17** + **H22**), 7.23 (dd, J = 8.7, 1.8 Hz, 1H, **H6**), 7.03 (s, 1H, **H9**), 4.42 – 4.08 (m, 4H, **H13**), 3.18 (s, 3H, **H14**), 2.85 (s, 3H, **H11**), 2.35 (s, 3H, **H8**).

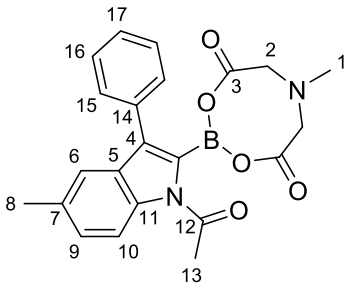
^{13}C NMR (126 MHz, DMSO-d_6) δ 172.0 **C10**, 170.3 **C12**, 168.4 **C12'**, 140.5 **C18**, 138.9 **C19**, 135.2 **C2**, 135.2 **C4**, 134.3 **C15**, 132.3 **C3**, 132.2 **C7**, 130.2 **C22**, 129.4 **C16**, 127.8 **C17**, 127.0 **C6** + **C21**, 120.1 **C9**, 114.7 **C5**, 65.7 **C13**, 65.1 **C13'**, 50.9 **C14**, 27.5 **C11**, 21.1 **C8**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 11.2.

υ_{max} (solid): 1751, 1690, 1269, 1342, 1308, 1038 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{28}H_{25}BN_2NaO_5$) requires *m/z* 503.1754, found *m/z* 503.1744.

4g



Prepared according to General Procedure D using $Pd(Oac)_2$ (4.49 mg, 20.0 μmol, 10.0 mol%), **1k** (51.4 mg, 0.20 mmol, 1.00 equiv.), **2l** (66.0 mg, 0.24 mmol, 1.20 equiv.), NaOAc (41.0 mg, 0.50 mmol, 2.50 equiv.) and LiCl (17.0 mg, 0.40 mmol, 2.00 equiv.). The reaction mixture was subjected to the purification procedure as outlined in the General Procedure (silica gel, 8-30% MeCN in DCM) to give the title product as a light brown solid (41 mg, 51%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74 (d, J = 8.6 Hz, 1H, **H10**), 7.40 (d, J = 7.7 Hz, 2H, **H16**), 7.36 – 7.29 (m, 1H, **H17**), 7.29 – 7.18 (m, 3H, **H15** + **H9**), 6.93 (s, 1H, **H6**), 4.38 – 4.03 (m, 4H, **H2**), 3.15 (s, 3H, **H1**), 2.84 (s, 3H, **H13**), 2.33 (s, 3H, **H8**).

^{13}C NMR (126 MHz, DMSO-d_6) δ 172.0 **C12**, 170.3 **C3**, 168.3 **C3'**, 135.9 **C14**, 135.1 **C11**, 134.8 **C5**, 132.3 **C4**, 132.2 **C7**, 129.5 **C15**, 128.7 **C16**, 127.3 **C17**, 126.9 **C9**, 120.1 **C6**, 114.6 **C10**, 65.6 **C2**, 65.1 **C2'**, 50.9 **C1**, 27.5 **C13**, 21.1 **C8**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, DMSO-d_6) δ 9.5.

υ_{max} (solid): 1746, 1697, 1449, 1310, 1038 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{22}H_{21}BN_2NaO_5$) requires *m/z* 427.1441 , found *m/z* 427.1432.

X-ray crystallographic data.

3a

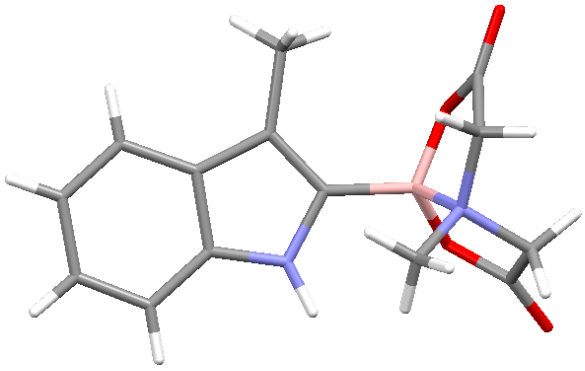


Table 1 Crystal data and structure refinement for 3a.	
Identification code	3a
Empirical formula	$C_{14}H_{15}BN_2O_4$
Formula weight	286.09
Temperature/K	125
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	8.91842(12)
b/Å	11.69930(14)
c/Å	13.55730(17)
α/°	90.0000
β/°	103.0910(14)
γ/°	90.0000
Volume/Å^3	1377.80(3)
Z	4
ρ_{calc}g/cm^3	1.379
μ/mm^{-1}	0.836
F(000)	600.0
Crystal size/mm^3	0.180 × 0.120 × 0.030
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	10.102 to 151.238
Index ranges	-11 ≤ h ≤ 11, -14 ≤ k ≤ 14, -16 ≤ l ≤ 16
Reflections collected	14684
Independent reflections	2771 [R_{int} = 0.0189, R_{sigma} = 0.0082]
Data/restraints/parameters	2771/1/196
Goodness-of-fit on F^2	1.055
Final R indexes [I>=2σ (I)]	R_1 = 0.0409, wR_2 = 0.1072
Final R indexes [all data]	R_1 = 0.0413, wR_2 = 0.1081
Largest diff. peak/hole / e Å^{-3}	0.35/-0.22

4m

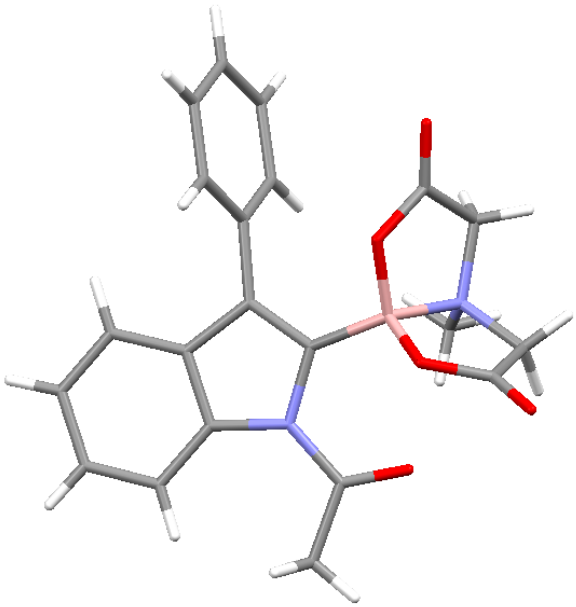


Table 1 Crystal data and structure refinement for 4m.	
Identification code	4m
Empirical formula	$C_{21}H_{19}BN_2O_5$
Formula weight	390.20
Temperature/K	173
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	14.7636(15)
b/Å	12.0831(12)
c/Å	10.7076(11)
α/°	90.0000
β/°	97.887(2)
γ/°	90.0000
Volume/Å^3	1892.1(3)
Z	4
ρ_{calc}g/cm^3	1.370
μ/mm^{-1}	0.097
F(000)	816.0
Crystal size/mm^3	0.100 × 0.100 × 0.020
Radiation	Mo Kα (λ = 0.71075)
2Θ range for data collection/°	5.562 to 50.718
Index ranges	-17 ≤ h ≤ 17, -14 ≤ k ≤ 14, -12 ≤ l ≤ 12
Reflections collected	35689
Independent reflections	3469 [R_{int} = 0.1314, R_{sigma} = 0.0503]
Data/restraints/parameters	3469/0/264
Goodness-of-fit on F^2	1.053
Final R indexes [I>=2σ (I)]	R_1 = 0.0525, wR_2 = 0.1332
Final R indexes [all data]	R_1 = 0.0590, wR_2 = 0.1415
Largest diff. peak/hole / e Å^{-3}	0.39/-0.23

Chapter 3: Efforts Toward the Total Synthesis of *Aspidosperma* Alkaloids Employing a BMIDA Larock Reaction

Compounds in the introduction section will be labelled 3.1, 3.2, 3.3…3.*x*

3. Introduction

3.1 Aspidosperma Alkaloids

Aspidosperma alkaloids are a family of monoterpene indole alkaloids comprising over 250 members.[106] These natural products are typified by their A B C D E ring system and the archetypal alkaloid, aspidospermidine, is shown below along with other members of the same family, demonstrating the similarity between their structures (Figure 12).

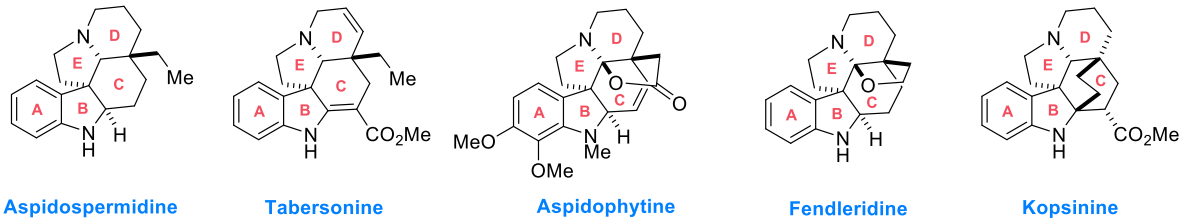
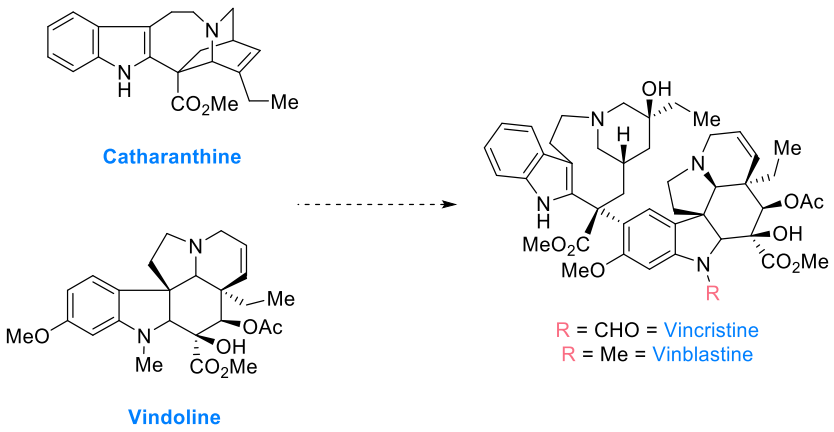


Figure 12: Five typical aspidosperma alkaloids.

Aspidosperma alkaloids have drawn interest from synthetic chemists over the decades owing to their challenging, interesting architecture, with multiple, sometimes contiguous, stereocentres and their synthesis is often used to showcase novel synthetic methodologies.[107][108][109] Furthermore, these alkaloids often possess attractive and widely varied biological properties. For example, extracts from the plant *Aspidosperma pyrifolium*, found in Brazil, were found to have modest activity against *Plasmodium falciparum*, the parasite responsible for malaria.[110] Extracts of the Madagascan periwinkle, *Catharanthus roseus,* have traditionally been brewed as a tea and drank to treat the effects of hyperglycaemia in diabetics (Scheme 66).[111] Extracts from the leaves of this periwinkle contain the bisindole alkaloids vincristine and vinblastine, themselves formed by dimerisation of monomeric indole alkaloids catharanthine and vindoline.[112]



Scheme 66: Vinblastine and vincristine are formed by dimerisation of catharanthine and vindoline.

While vinblastine and vincristine may not decrease blood sugar levels, they have seen extensive use as chemotherapeutics over the past six decades in the treatment of numerous forms of cancer.[113][114] Their mechanism of action involves binding to tubulin, preventing mitotic spindles from forming which are responsible for pulling apart the chromosomes during the metaphase of mitosis, ultimately arresting the ability of cancer cells (as well as healthy cells) to divide and proliferate.[115] Unfortunately, both vincristine and vinblastine constitute a miniscule fraction of the dried weight of the leaves of the Madagascan periwinkle (0.001–0.0003%),[116] meaning their extraction is costly, time-consuming, inefficient and results in these life-saving drugs being very expensive.

The varying and useful effects of aspidosperma alkaloids, as well as products derived therefrom, demonstrates the need for chemists to devise novel methods of making indole alkaloids and their derivatives; to supply demand for drugs as well as design new drugs based on natural product scaffolds.

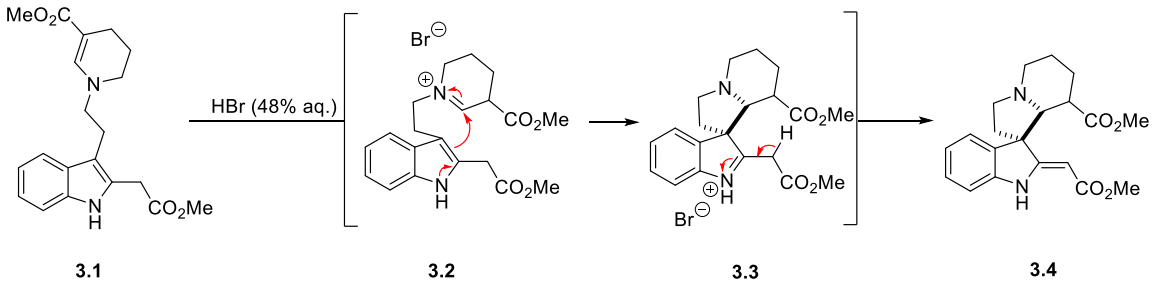
3.2 Previous Total Syntheses

There have been a multitude of total syntheses of aspidosperma alkaloids spanning a range of 60 years.[117] Shown below are some examples which highlight the different ring-closing approaches to forming members of this family.

Stork and co-workers' synthesis of aspidospermine in 1963 has already been discussed in Chapter 1 of this thesis (see Scheme 5). The crucial step in this synthesis was a FIS between

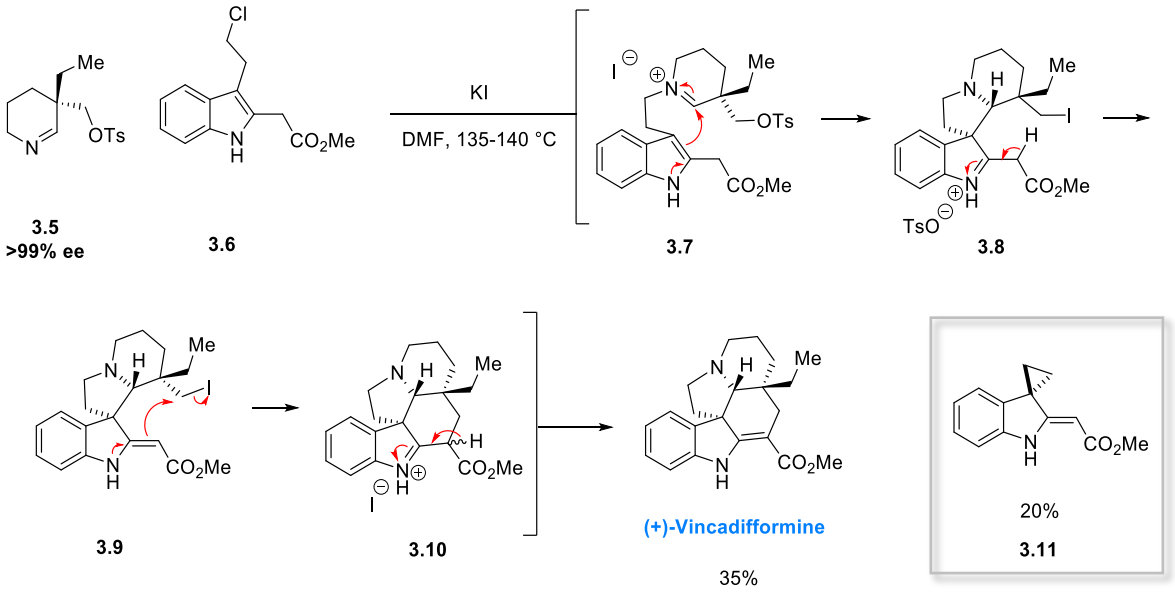
a phenylhydrazine (A ring) and tricyclic ketone (containing the C D E rings), which formed an indole (making the B ring), forming the pentacyclic skeleton of aspidospermine.

Wenkert and co-workers reported in 1968 the formation of the A B D E ring system *via* an intramolecular attack of an iminium from the C-3 of the indole, which resulted in a five-membered spirocycle at the C-3 position, in what is effectively an interrupted Pictet-Spengler reaction (Scheme 67).[118] Treatment of enamine **3.1** with aqueous acid forms the iminium **3.2**, susceptible to intramolecular nucleophilic attack. Loss of an acidic proton α to an ester group quenches the indolenium **3.3** and forms the indoline **3.4**. This method formed the A B D E rings of an aspidosperma skeleton, however, this work stops at this indoline product **3.4**.



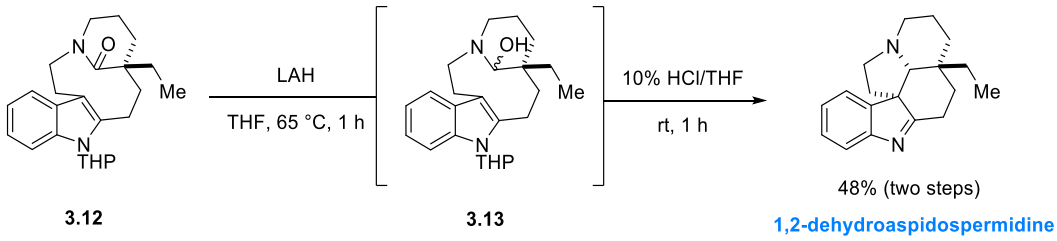
Scheme 67: Wenkert's formation of the A B D E rings.

This work was expanded upon in 2011 by Pandey and co-workers, using chiral imine **3.5**, which displaced a halide on indole **3.6**, then, following a similar sequence of events as above (Scheme 67), a cascade of ring-closing reactions gave vincadifformine.[119] This reaction employed Finkelstein conditions (excess KI), which presumably gives displacement of both the chloride on the indole **3.6** as well as the tosylate in the tetracyclic intermediate **3.7** with iodide. Quenching of the indolenium in **3.8** primes molecule **3.9** for an intramolecular attack, closing the final ring and furnishing desired pentacyclic skeleton of the product. Following quenching of the positive charge on the nitrogen through loss of an acidic proton in **3.10**, vincadifformine was obtained in 35% yield. The authors also note the formation of spirocycle **3.11** in 20% yield, formed by the intramolecular attack of the C-3 of the indole starting material **3.6** on the pendant halide (either as the chloride or the iodide).



Scheme 68: Pandey's ring-closing cascade reaction to form vincadifformine

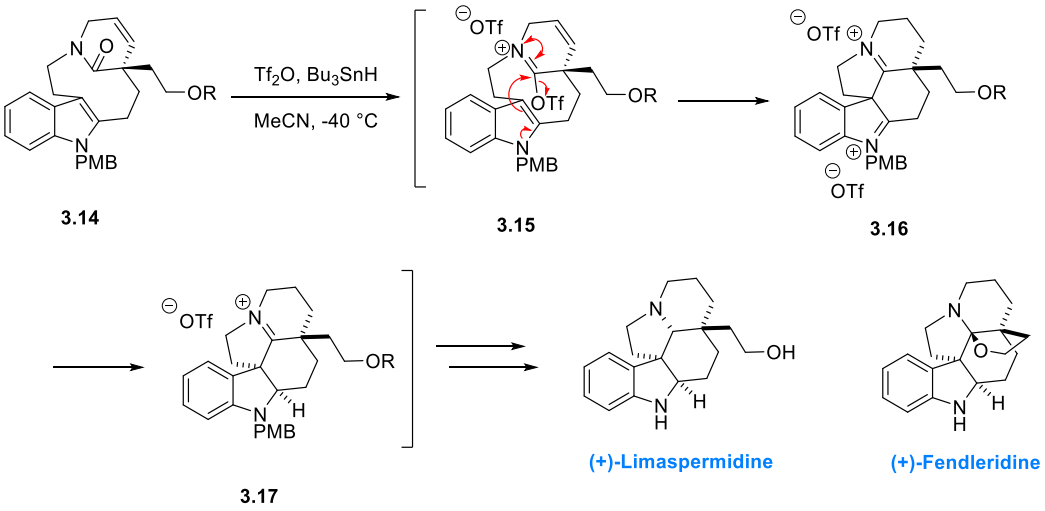
In 1981, Ban and co-workers reported the synthesis of 1,2-dehydroaspidospermidine from lactam **3.12** (Scheme 69).[120] Reduction of this lactam with LAH gave the hemiaminal **3.13**, which, on treatment with acid, formed the iminium which is receptive to nucleophilic attack from the C-3 position of the indole (the acid also gave concomitant THP deprotection of the indole nitrogen). This cyclisation forms the A B C D E ring system, typical of aspidosperma alkaloids, from a starting material with A B and D rings in place. The would-be C and E rings are part of the same large cycle, and formation of this new C-C bond splits them into the C and E rings. Following this nucleophilic attack from the indole, the indolene product is obtained.



Scheme 69: Ban's synthesis of 1,2-dehydroaspidospermidine by a ring-closing reaction. THP = tetrahydropyran

Movassaghi and White disclosed the synthesis of aspidosperma alkaloids fendleridine and limaspermidine by employing a transannular cyclisation of a compound containing the A B D ring and a large C/E ring, analogous to Ban's earlier work (Scheme 70).[121] This example

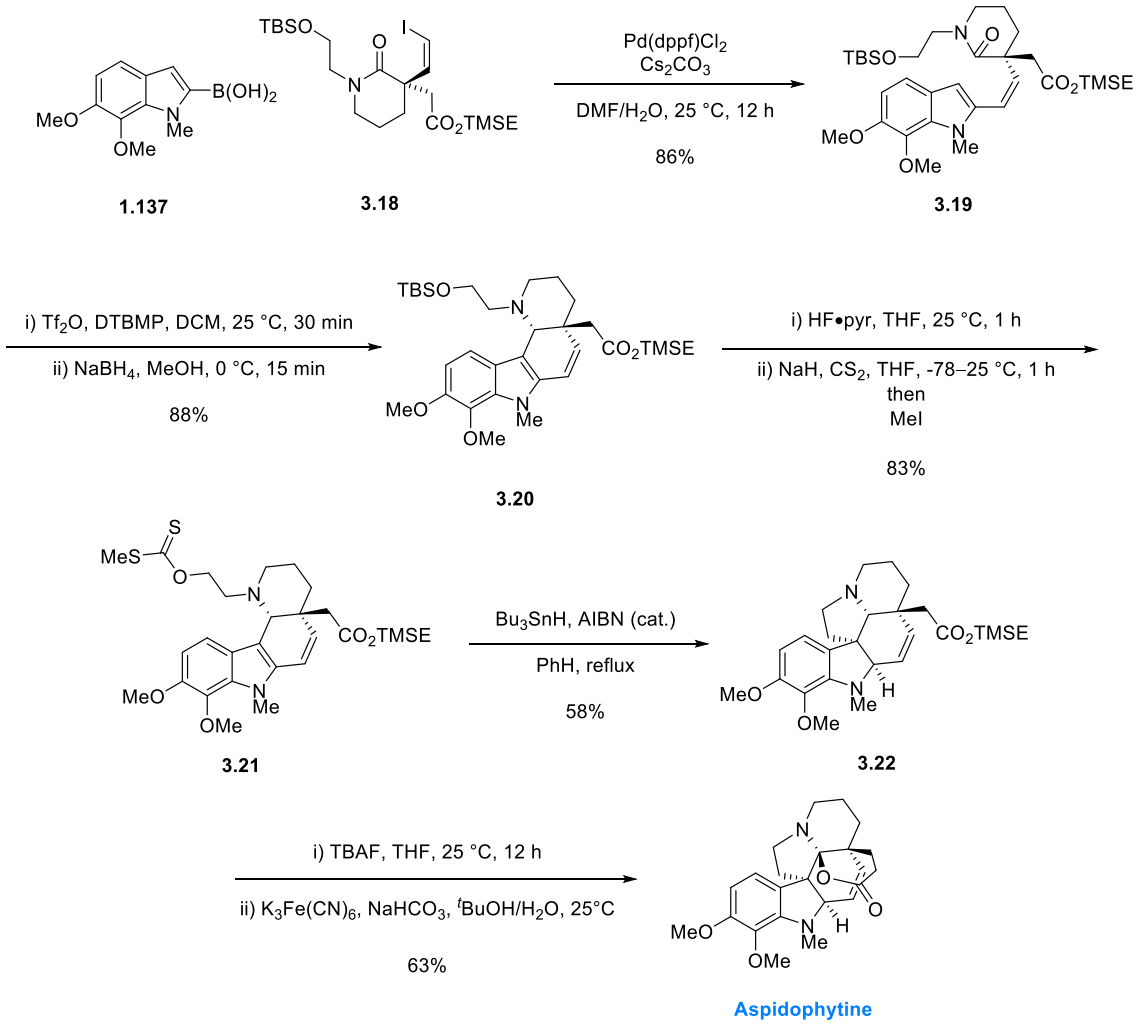
uses instead Tf_2O to convert lactam **3.14** into an imidoyl triflate **3.15** (related to a Vilsmeier functionality, with a TfO instead of a Cl) and this incredibly electrophilic functionality is attacked by the C-3 of the indole to form a quaternary centre at this C-3, giving the A B C D E aspidosperma skeleton in **3.16**, and in the presence of Bu_3SnH, the resultant indolenium was reduced to the indolene **3.17**. The resultant iminium (at the site of the former imidoyl triflate) in **3.17** was not reduced by the tin hydride, and offered the potential for divergence as it could either be reduced to the piperidine using $NaBH(OMe)_3$ to give a limaspermidine precursor, or it could be attacked by the neighbouring pendant ethanol to furnish an intermediate en route to fendleridine.



Scheme 70: Movassaghi's synthesis of aspidosperma alkaloids.

Earlier work published by Nicolaou and co-workers employed a similar Tf_2O-mediated cyclisation strategy (Scheme 71).[68] A difference between this and Movassaghi's later work is that the A B C D ring is in place in the former prior to final closure of the E ring, and the Tf_2O-mediated cyclisation results in the formation of an indole, rather than a non-aromatic indolene/indolenium. The cyclisation precursor was formed through a Suzuki cross-coupling between an indole-2-boronic acid **1.137** (formed by deprotonation of the C-2 proton with ^{t}BuLi and quenching into $B(OMe)_3$, see Scheme 43) and lactam **3.18**. Following cross-coupling to give **3.19**, the Tf_2O-mediated cyclisation was carried out, followed by reduction of the iminium and indolenium with $NaBH_4$ to give **3.20**. Formation of the E ring was achieved through a radical cyclisation of **3.21** formed by homolytic decomposition of the pendant xanthate ester, initiated by AIBN, reacting with the C-3 of the indole to give pentacyclic **3.22**. The two-methylene backbone which would ultimately form the E ring is

attached to the lactam nitrogen of the starting material. Deprotection of the ester to the acid then oxidation of the piperidine amine with Fe(III), to the corresponding iminium, allowed for attack of the pendant carboxylic acid to form the ester, producing aspidophytine.

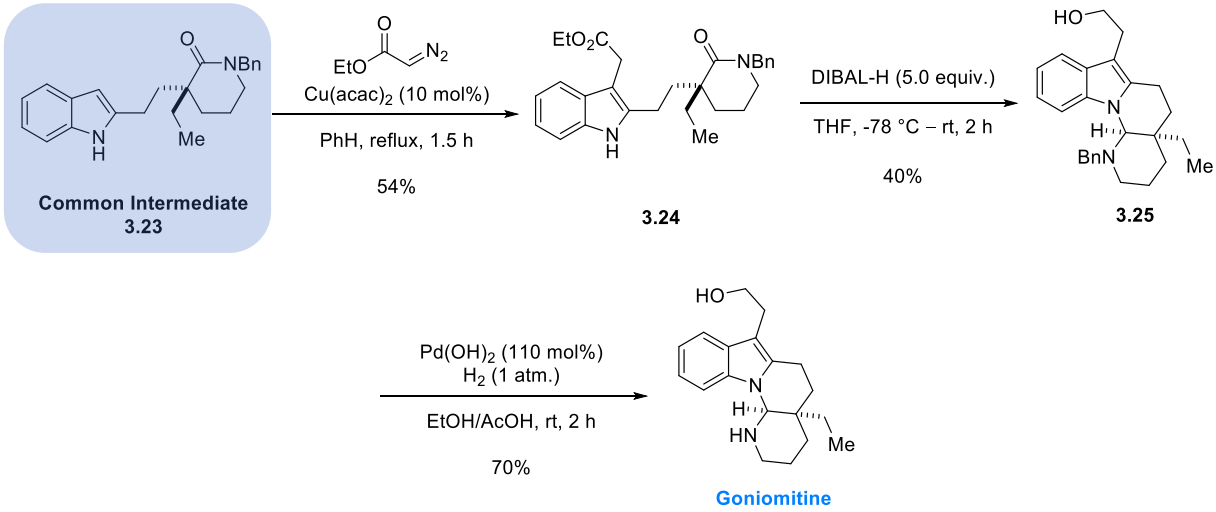


Scheme 71: Nicolaou's total synthesis of aspidophytine. TMSE = 2-trimethylsilylethanol. DTBMP (2,6-di-tert-butyl-4-methyl pyridine).

In 2018, a paper was put forward concerning the divergent syntheses of several alkaloids from a common intermediate, among them aspidospermidine, goniomitine, and quebrachamine.[122]

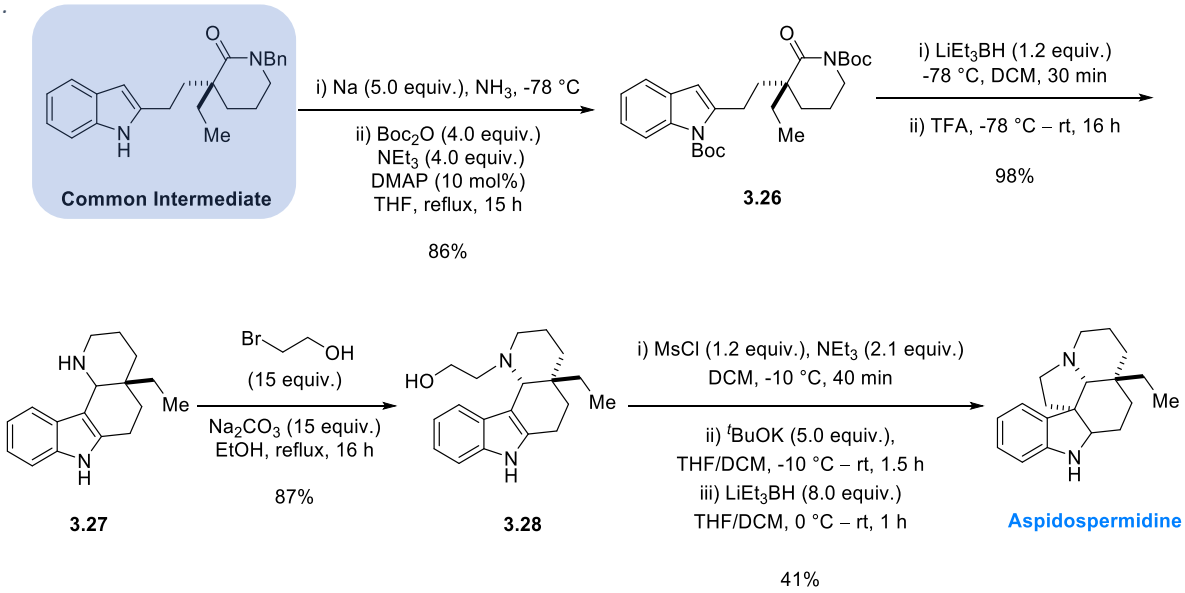
In the first of the three syntheses, the common intermediate **3.23**, valerolactam with an appended indole, was first adorned with an ethyl acetate group at the C-3 position, using ethyl diazoacetate with catalytic copper, to give **3.24** (Scheme 72). This was then treated with DIBAL-H, which led to the reduction of the lactam moiety and formation of an iminium intermediate (as well as reduction of the pendant ester). Instead, the indole nitrogen (likely

deprotonated by DIBAL-H into the much more nucleophilic anion) attacked the iminium, resulting in the tetracyclic core of goniomitine in **3.25** (see Scheme 79). Finally, debenzylation using a superstoichiometric amount of Pearlman's catalyst ($Pd(OH)_2$) with hydrogen in acidic ethanol gave the natural product goniomitine.



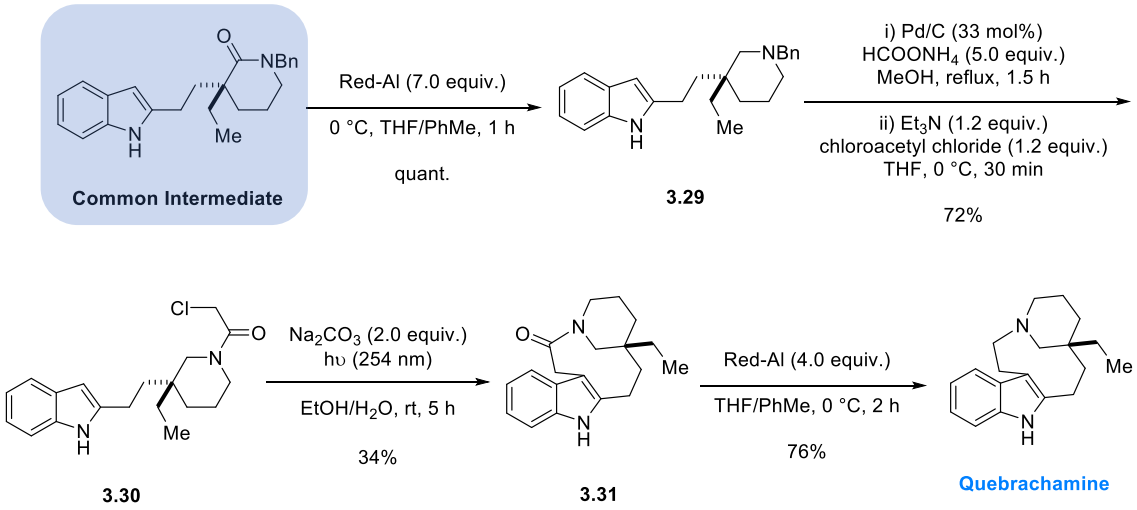
Scheme 72: Synthesis of goniomitine from the Common Intermediate.

Next, aspidospermidine was targeted and this first required Birch reduction conditions of the Common Intermediate to remove the benzyl group on the lactam, followed by Boc protection of both the lactam and indole nitrogens to yield **3.26** (Scheme 73). This modified common intermediate was treated with $LiEt_3BH$ (superhydride) which gave reduction of the lactam, analogous to the synthesis of goniomitine, however, in contrast, this iminium is attacked by the C-3 of the indole, most likely due to the indole nitrogen being Boc protected. This results in a skeleton structurally distinct to that observed in the transformation of **3.24** to **3.25**, bearing the familiar A B C D ring structure typical of aspidosperma alkaloids in **3.27**. The final E ring is formed by installation of an ethanol group on the piperidine nitrogen to give **3.28**, followed by conversion of the alcohol into a mesylate then attack from the C-3 of the indole closes the ring, and reduction with superhydride furnishes aspidospermidine.



Scheme 73: Synthesis of aspidospermidine from the Common Intermediate.

Finally, quebrachamine was synthesised by first reducing the common intermediate with Red-Al to the piperidine **3.29** then Pd/C/$HCOONH_4$ to remove the benzyl group (Scheme 74). Then, condensation of the piperidine nitrogen with α-chloroacetyl chloride gave the α-chlorinated amide **3.30**. Macrocylisation to give quebrachamine was achieved through a Witkop photocyclisation,[123] where irradiation of chloride **3.30** formed the α-radical which reacts with the C-3 of the indole. Reduction of the lactam **3.31** with Red-Al gave quebrachamine.

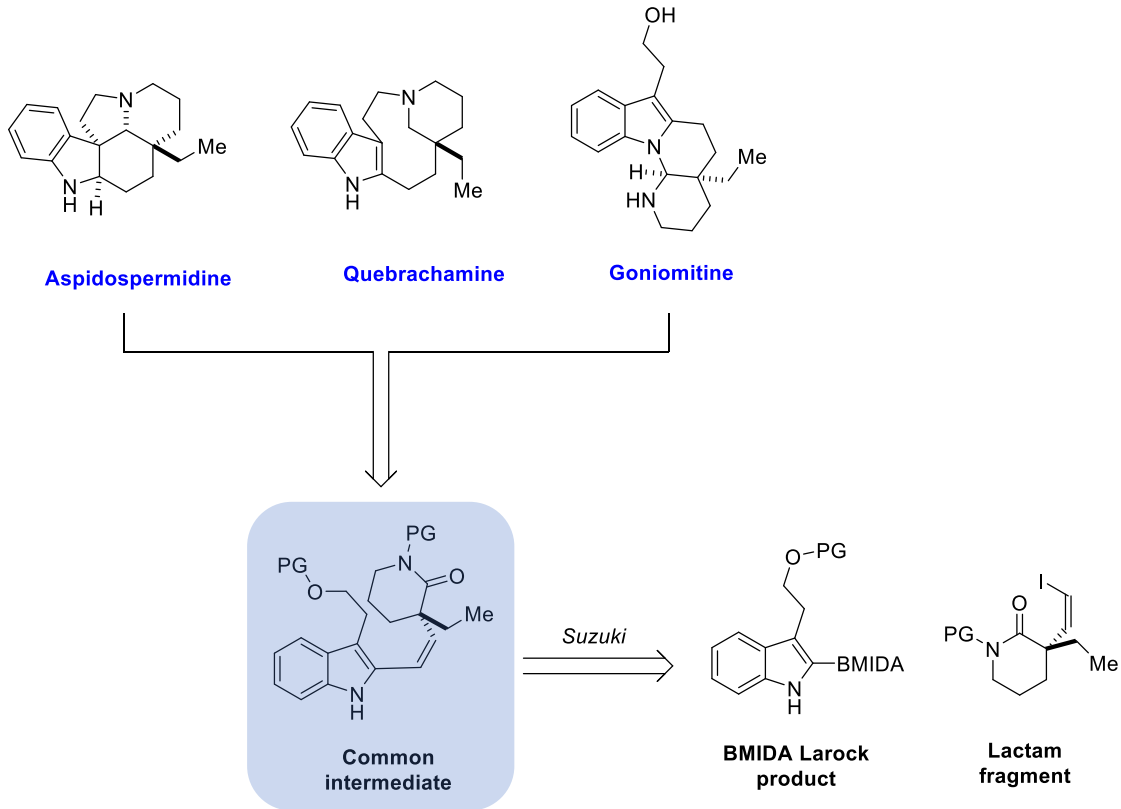


Scheme 74: Synthesis of quebrachamine from the Common Intermediate.

This final set of examples demonstrates the advantages of careful synthetic design where multiple attractive products can be obtained from a common intermediate. The evolution of the approach to total synthesis has hopefully been demonstrated where a shift from single, target-driven synthesis has developed into a more divergent approach to expedite the formation of multiple products.

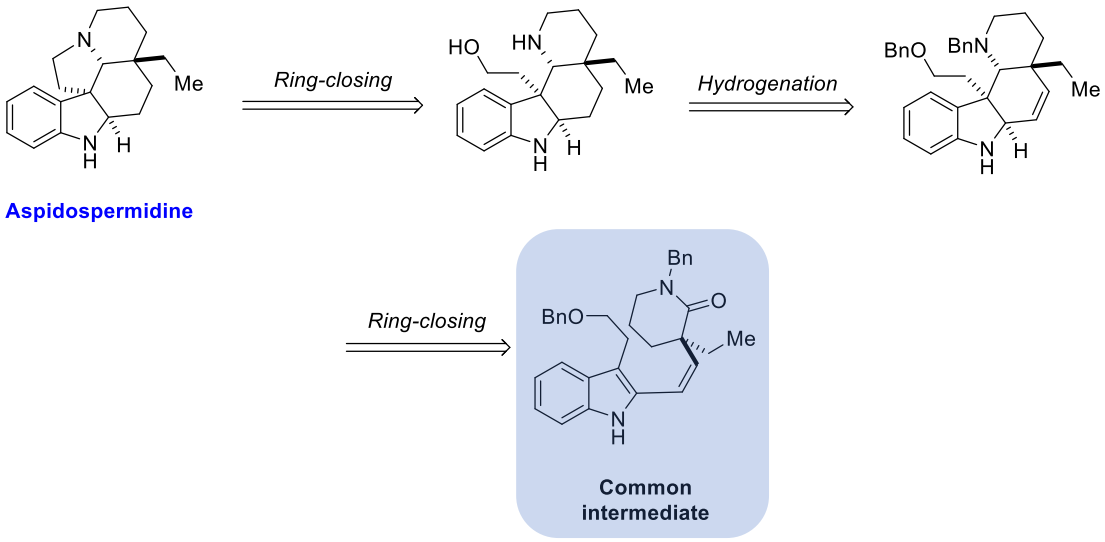
3.2. Project aims

The work in the final chapter deals with the application of the BMIDA Larock methodology in the synthesis of natural products. The alkaloids targeted for this synthesis section are: aspidospermidine, quebrachamine and goniomitine, and each could be made from a Common Intermediate (Scheme 75). Once the syntheses of these natural products have been carried out, it is hoped that derivatives of each could be made bearing bespoke functionality by varying the indole BMIDA starting material, in turn made by changing the 2-iodoanilines and alkyne BMIDAs used as starting materials (see Scheme 51).



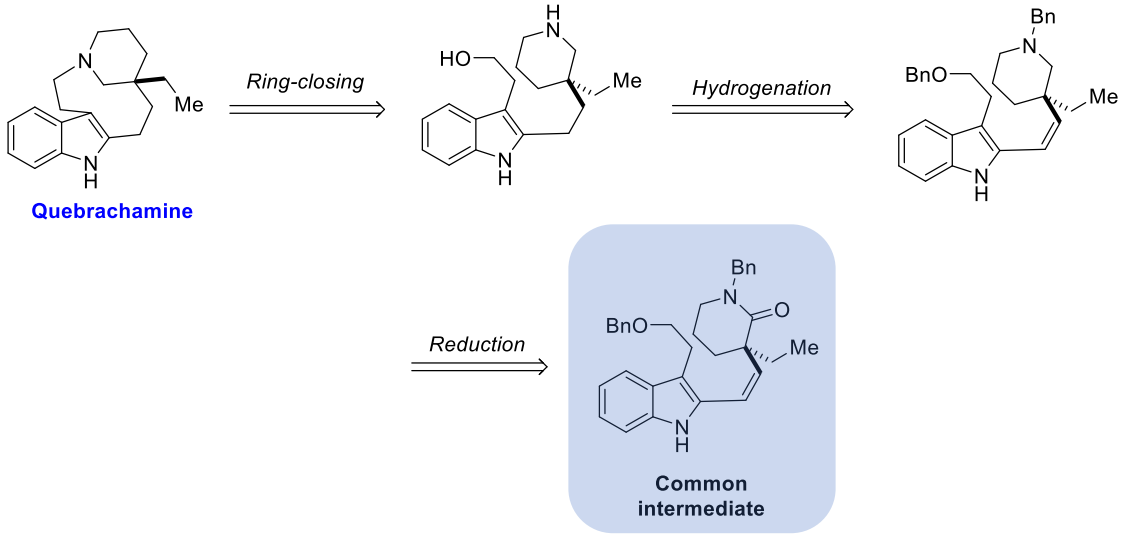
Scheme 75: Target alkaloids, showing how these can each be made from a common intermediate and how this intermediate can be made from a BMIDA Larock and Suzuki reactions. PG = protecting group.

The Common Intermediate can be synthesised by Suzuki cross-coupling of a 2-BMIDA indole, obtained through a BMIDA Larock reaction, and a lactam bearing a vinyl iodide. From the Common Intermediate, aspidospermidine could be formed in as few as three fundamental steps (Scheme 76). Ring-closing to form the ABCD ring structure of aspidospermidine can be achieved through a Vilsmeier-Haack-type reaction where the lactam of the Common Intermediate is converted into an electrophilic species (*e.g.,* imidoyl triflate) to be attacked by the nucleophilic C-3 position of the indole. This method is based on the similar cyclisation reaction carried out by Nicolaou and co-workers[68] as well as Movassaghi and White[121] (see Scheme 70 and Scheme 71, respectively). Hydrogenation should give concomitant alkene reduction and global debenzylation. The pendant alcohol could then be converted into a good leaving group (*e.g.,* OMs, OTs, I *etc*.) to allow intramolecular attack from the piperidine nitrogen, closing the E ring and furnishing aspidospermidine.



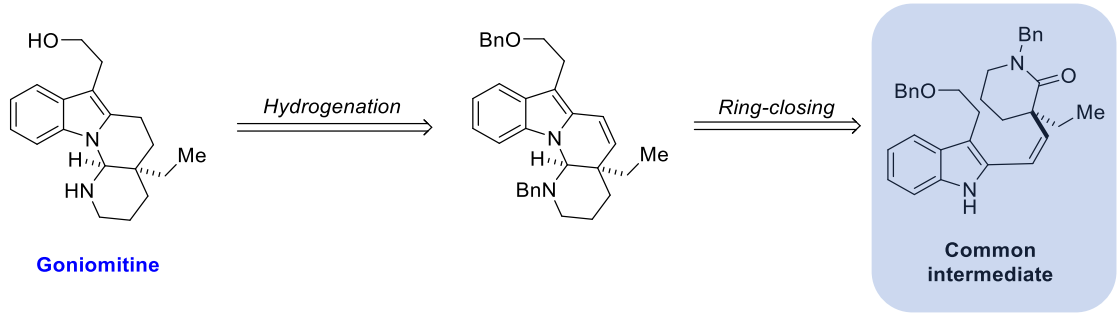
Scheme 76: Proposed retrosynthesis of aspidospermidine from the common intermediate. LG = leaving group.

Quebrachamine could also be made in as few as three steps, the first of which will be reduction of the lactam to the piperidine using *e.g.* LAH. Following this, hydrogenation will again give global deprotection and alkene reduction. Finally, conversion of the alcohol into a good leaving group (similar conditions can likely be employed to the aspidospermidine synthesis above) then macrocyclisation will furnish quebrachamine.



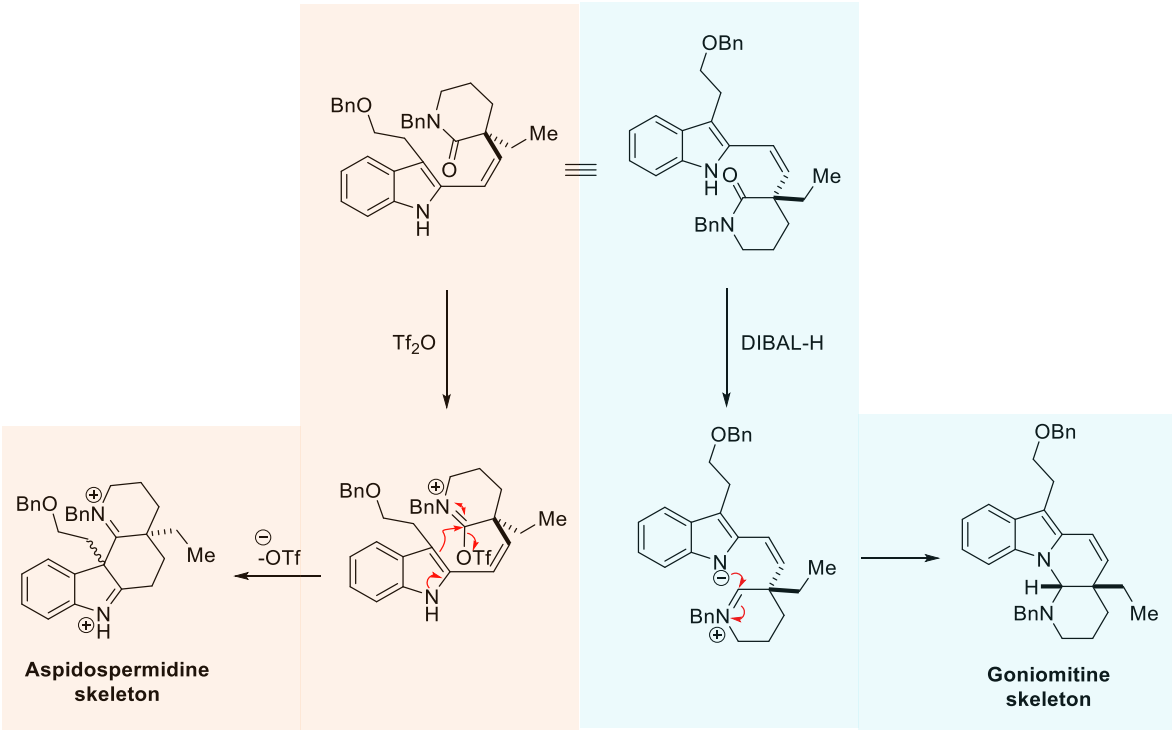
Scheme 77: Proposed retrosynthesis of quebrachamine from the common intermediate. LG = leaving group.

Formation of goniomitine also involves intramolecular nucleophilic attack at the lactam carbonyl carbon however, using DIBAL-H results in attack from the indole nitrogen instead of the C-3 position, as seen in Scheme 76. As well as the example seen in Scheme 72, similar reactivity was observed by Cheon and Park.[124] This results in a structurally distinct alkaloid from quebrachamine and aspidospermidine. Following this cyclisation, hydrogenation could give alkene reduction with accompanying debenzylation, and goniomitine could theoretically be obtained in just two steps from the Common Intermediate (Scheme 78):



Scheme 78: Proposed retrosynthesis of goniomitine from the common intermediate.

The cyclisation step in the formation of goniomitine and aspidospermidine create structurally distinct products despite arising from the same starting material, which can be visualised as shown below (Scheme 79).



Scheme 79: Scheme showing how aspidospermidine and goniomitine structures are formed from the same starting material. Counter ions omitted for clarity.

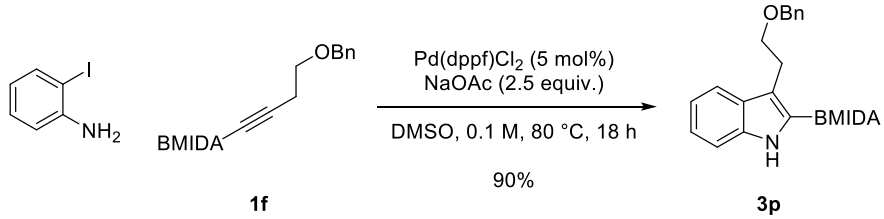
Based on the BMIDA Larock methodology developed in Chapter 2, various 2-BMIDA indoles can be synthesised which could then be elaborated to various analogues of the common intermediate, ultimately resulting in the formation of bespoke derivatives of natural products.

Chapter 4: Efforts Towards the Total Synthesis of *Aspidosperma* Alkaloids Employing a BMIDA Larock Reaction

Compounds in this section will be labelled: 5a, 5b, 5c… 5*x*.

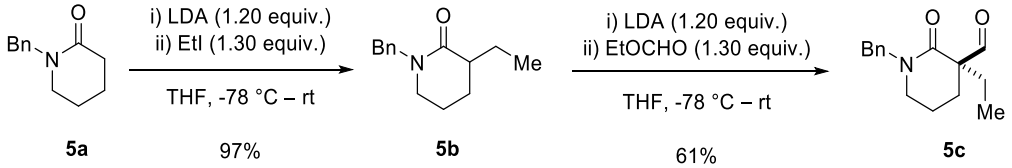
4.1. Results and Discussion

Based on the retrosynthesis shown in Scheme 75, indole BMIDA **3p** is desired as the starting material for the Common Intermediate. The pendant ethanol attached to the indole is protected with a benzyl group, which will be removed under hydrogenolysis conditions required for the necessary reduction of the double bond, streamlining the synthesis. Gratifyingly, using the optimised BMIDA Larock conditions on 2-iodoaniline and alkyne BMIDA **1f** this reaction could be scaled up to 19.3 mmol to furnish 7.08 g of **3p** in 90% yield (Scheme 80).



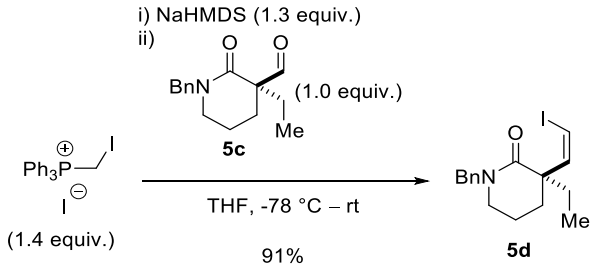
Scheme 80: BMIDA Larock reaction to produce the indole BMIDA required for the total synthesis campaign.

With sufficient amounts of the indole BMIDA fragment in hand, efforts were focused on the synthesis of its lactam coupling partner. From *N*-benzylpiperidin-2-one **5a**, formation of the enolate and reaction with ethyl iodide gave **5b** and following further enolate formation and reacting with ethyl formate, α-formyl lactam **5c** was obtained.



Scheme 81: Lactam α ethylation and formylation.

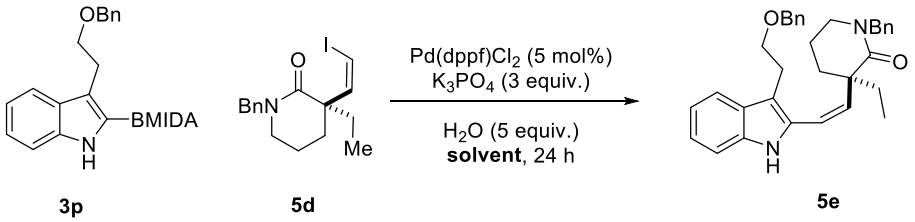
In order to convert the aldehyde into a vinyl iodide group, a Wittig reaction was carried out (specifically, this variant of the reaction to form a *Z* vinyl iodide is called a Stork-Zhao olefination).[125] Treatment of iodomethylphosphonium iodide with NaHMDS formed the ylide and to this was added a solution of the aldehyde **5c** in THF. This gave excellent yields of the vinyl iodide product **5d** and the reaction was thankfully completely *Z*-selective (Scheme 82).



Scheme 82: Stork-Zhao olefination to form the Z vinyl iodide.

The geometry of the alkene at this point is important in the synthesis of aspidospermidine and goniomitine as the cyclisation steps (Tf_2O or DIBAL-H, respectively) result in this double bond becoming part of a cyclohexene ring; impossible if the geometry is *E*. It is, however, immaterial for the synthesis of quebrachamine as a global hydrogenation will take place before the macrocyclisation is carried out.

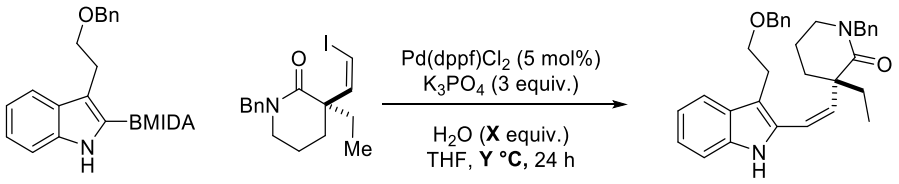
With both vinyl iodide and indole BMIDA in hand, the subsequent Suzuki cross-coupling could be optimised. Firstly, solvents were selected for and based on the optimisation of the BMIDA Larock reaction in Chapter 2, it was likely that non-polar solvents would be suboptimal for this reaction as the BMIDA starting material requires a polar solvent to sufficiently solubilise. Initial conditions were chosen based on those previously used in the Watson group in the cross-coupling of 2-BMIDA indoles.[71] DMSO gave just 15% conversion to product **5e** (Table 14, Entry 1) and DMF and MeCN gave similar, moderate, yields (Entries 2 and 3). THF was the superior solvent, giving the product in 53% yield (Entry 4).



Entry	Solvent	4e (%)
1	DMSO	15
2	DMF	37
3	MeCN	40
4	THF	53

Table 14: Suzuki reaction solvent study.

Next, temperature and equivalents of water were investigated. Oddly, increasing the equivalents of water from 5 to 10 at 65 °C gave only trace conversion (Table 15, Entry 1). At 65 °C, the yield is relatively consistent across 15 to 50 equivalents of water (Entries 2 – 5). Increasing the temperature to 80 °C shows a greater dependence on water equivalents with 5 equivalents giving just 26% (Entry 6) and 10 equivalents gave a good yield of 60% (Entry 7). However, increasing the equivalents of water beyond 10 shows a drop off in yield (Entries 8 – 10).

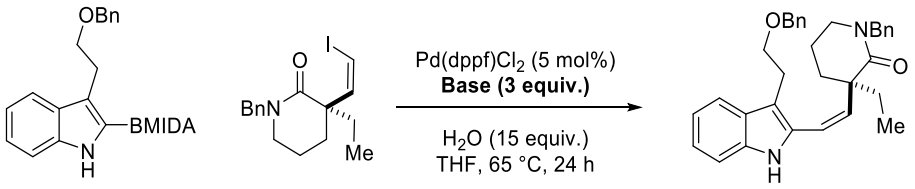


3p **5d** **5e**

Entry	T (°C)	H_2O (equiv.)	4e (%)
1	65	10	Trace
2	65	15	62
3	65	20	55
4	65	30	62
5	65	50	58
6	80	5	26
7	80	10	60
8	80	15	49
9	80	20	48
10	80	30	30

Table 15: Suzuki water equivalents and temperature study.

Next, a base screen was carried out. Despite having the same pK_a, Na_2CO_3 and K_2CO_3 gave disappointing yields of just 40% and 35%, respectively, (Table 16, Entries 1 and 4) whereas Cs_2CO_3 gave an excellent yield of 78% (Entry 2). This could be due to solubility of the base in the aqueous/organic mixture, or the cation may play a non-innocent role in the reaction, as has been seen by Amatore and co-workers.[47] NaOH gave yields comparable to Cs_2CO_3 (Entry 3) and $NaHCO_3$ gave just 26% yield (Entry 5), the low yield in the latter could be due to a retardation of BMIDA hydrolysis by this weak base.

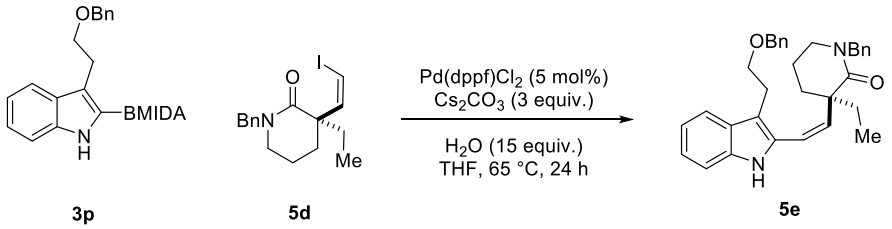


3p **5d** **5e**

Entry	Base	4e (%)
1	K_2CO_3	40
2	Cs_2CO_3	78
3	NaOH	73
4	Na_2CO_3	35
5	$NaHCO_3$	26

Table 16: Suzuki reaction base study.

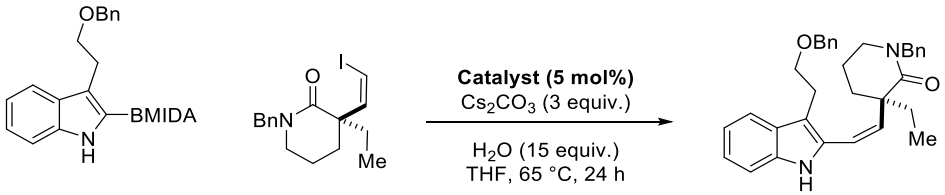
As the product **5e** and iodide **5d** would often co-elute during purification, the stoichiometry was reversed so the indole BMIDA **3p** would be in excess (the stoichiometry was hitherto 1:1.2 **3p:5d**) (Table 17). This resulted in complete consumption of the vinyl iodide when 1.2-2.0 equivalents of the indole BMIDA were used (Entries 1–4), aiding purification as in the relatively non-polar eluent used to purify the Suzuki product, the R_F of remaining indole BMIDA SM is close to zero so would sit on the baseline of the column while the product eluted. There are diminishing returns on increasing the equivalents of **3p** beyond 1.5 so this was chosen as the optimal amount. When 2.5 equivalents of the **3p** were used, the yield drops to just 35% (Entry 5), which could be due to the increased heterogeneity of the reaction mixture.



Entry	3p:4d ratio	4e (%)
1	1.2:1	79
2	1.5:1	81
3	1.8:1	82
4	2.0:1	81
5	2.5:1	35

Table 17: Suzuki reaction starting material stoichiometry study.

Finally, a screen of Pd(II) precatalysts and, where required, ligands, revealed that $Pd(PPh_3)_2Cl_2$ and $[Pd(allyl)Cl]_2$ with PPh_3 performed equally well as $Pd(dppf)Cl_2$ (Table 18, Entries 3 + 5). It was decided that $Pd(dppf)Cl_2$ would remain the catalyst of choice. $Pd(MeCN)Cl_2$ and $Pd(OAc)_2$ with PPh_3 performed slightly worse than the optimal catalyst (Entries 1 + 4) whereas $Pd(OAc)_2$ with SPhos gave a yield of just 44% (Entry 2).

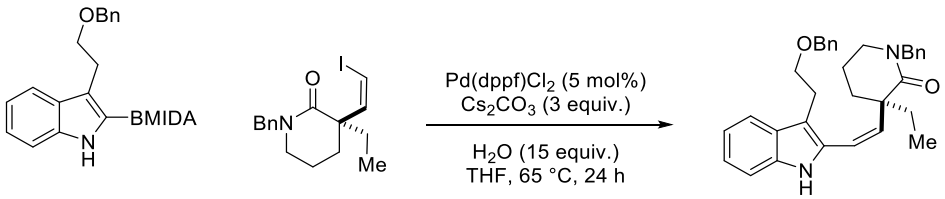


3p **5d** **5e**

Entry	Catalyst	Ligand (mol %)	4e (%)
1	$Pd(OAc)_2$	PPh_3 (10)	78
2	$Pd(OAc)_2$	SPhos (10)	44
3	$Pd(PPh_3)_2Cl_2$	-	83
4	$Pd(MeCN)_2Cl_2$	PPh_3 (10)	78
5	$[Pd(allyl)Cl]_2$	PPh_3 (10)	83

Table 18: Suzuki reaction catalyst study.

Application of the optimal Suzuki conditions gave an isolated yield of **5e** of 89% (Scheme 83).



3p **5d** **5e**

Scheme 83: Optimised Suzuki conditions.

It was found that the Suzuki product **5e** undergoes isomerisation from the *Z* isomer to the *E* isomer. This is based on evidence seen in the ^1H NMR where the freshly isolated Suzuki product **5e** contains a clean pair of alkene doublets possessing a coupling constant of 13.2 Hz (consistent with a *cis* coupling constant based on the Karplus relationship).[126] On reacquiring the ^1H NMR spectrum of the same sample, having been exposed to ambient light and room temperature over a weekend, there is complete conversion of this product to the

other isomer containing a new pair of olefinic doublets with a coupling constant of 16.7 Hz, consistent with a *trans* coupling constant (Figure 13).

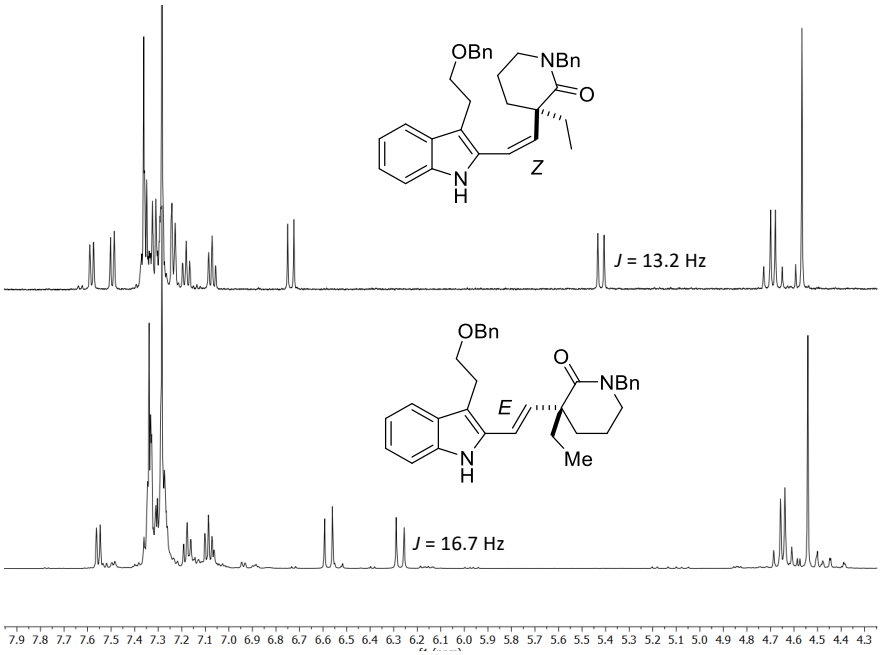
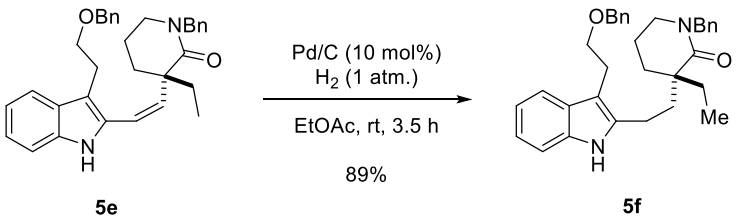


*Figure 13: [1]H NMR spectra showing isomerisation of the Suzuki product **5e** from Z to E.*

This change in geometry to the thermodynamically more stable *E* isomer would preclude cyclisation to goniomitine and aspidospermidine (see Scheme 76 and Scheme 78), but poses no problem to the synthetic route for quebrachamine (see Scheme 77). For the former two products, this would require reducing the double bond first to allow for free rotation, allowing cyclisation to take place but unfortunately adds another step count to the synthesis. It was previously hoped that the hydrogenolysis could be carried out in a single step giving alkene reduction and global debenzylation.

Reduction with Pd/C under one atmosphere of hydrogen gave alkene reduction with no debenzylation (Scheme 84).

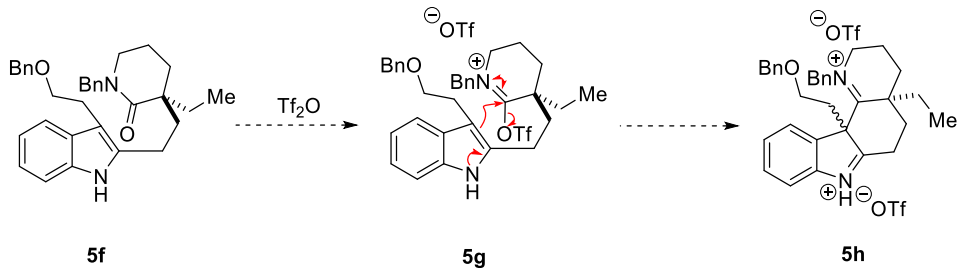


Scheme 84: reduction of the alkene.

With this slightly modified Common Intermediate **5f** in hand, the synthesis of the target alkaloids could take place.

4.1.1. Aspidospermidine Synthesis

Synthesis of aspidospermidine began from the Common Intermediate, **5f**. Based on the procedure outlined by Nicolaou and co-workers in their total synthesis of the structurally similar aspidophytine,[68] treatment of this compound with Tf_2O should convert the lactam to an imidoyl triflate **5g**, a very electrophilic species which will then be attacked by the nucleophilic C-3 position of the indole (Scheme 85).



Scheme 85: Proposed Tf_2O-mediated ring-closing reaction.

This results in the formation of two iminiums in **5h**: one at the indole nitrogen where it becomes the indolium, and an iminium at the former imidoyl triflate, where nucleophilic attack from the C-3 forms a hemiaminal which will likely rapidly collapse to an iminium triflate which can then be reduced by $NaBH_4$, as used in Nicolaou's example,[68] with excellent yield and seemingly complete diastereoselectivity. However, there are two major distinctions between the proposed synthesis and the synthesis reported by Nicolaou and co-workers: the first is in Nicolaou's example the pendant ethanol, which ultimately closes to form the E ring, is attached to the nitrogen of the lactam, meaning the C-3 of the indole is unsubstituted prior to the final ring closure. In the total synthesis proposed herein, the pendant ethanol chain is attached at the C-3 position of the indole and therefore Tf_2O-mediated cyclisation would give an all-carbon quaternary centre at this position, so a proton cannot be lost to form the indole. Shown below are the two late-stage synthetic intermediates bearing the A B C D tetracycle prior to closure of the final E ring; **5i** is an indoline, **3.20** is an indole (Figure 14).

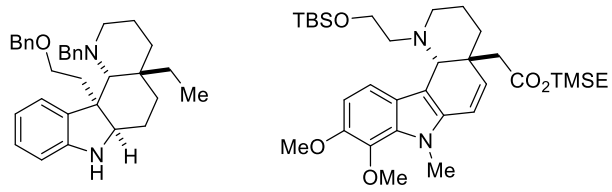
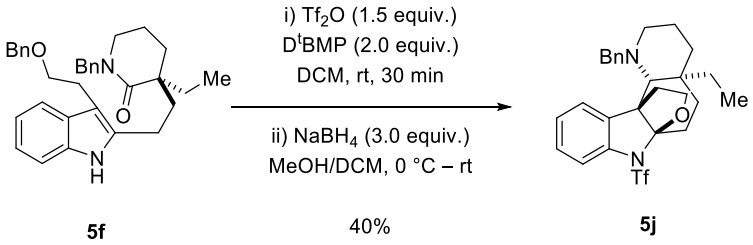


*Figure 14: Indoline **5i** and indole **3.20**, both with the A B C D ring.*

The other key difference between this proposed synthesis and the literature example is that a *Z* double bond is present between the lactam and indole whereas in this proposed synthesis, this alkene has already been reduced to sidestep any potential isomerisation issues as the undesired *E* isomer precludes cyclisation. It could be that the *Z* isomer pre-organises the imidoyl triflate close in space to the C-3 of the indole, allowing the nucleophilic attack to take place more easily, whereas if this alkene is reduced, the free rotation it enjoys means the imidoyl triflate could be too far away in space to react, and the entropy cost for the ring-closing is higher, as the free-rotating alkane has more degrees of freedom *vs.* the alkene. Similarly, Movassaghi's Tf_2O-mediated cyclisation step is also carried out between a conformationally constrained starting material (Scheme 70). Despite these foreseen potential problems, it was hoped that an analogy could be drawn between the two substrates and the ring-closing reaction would proceed to form the A B C D ring system.

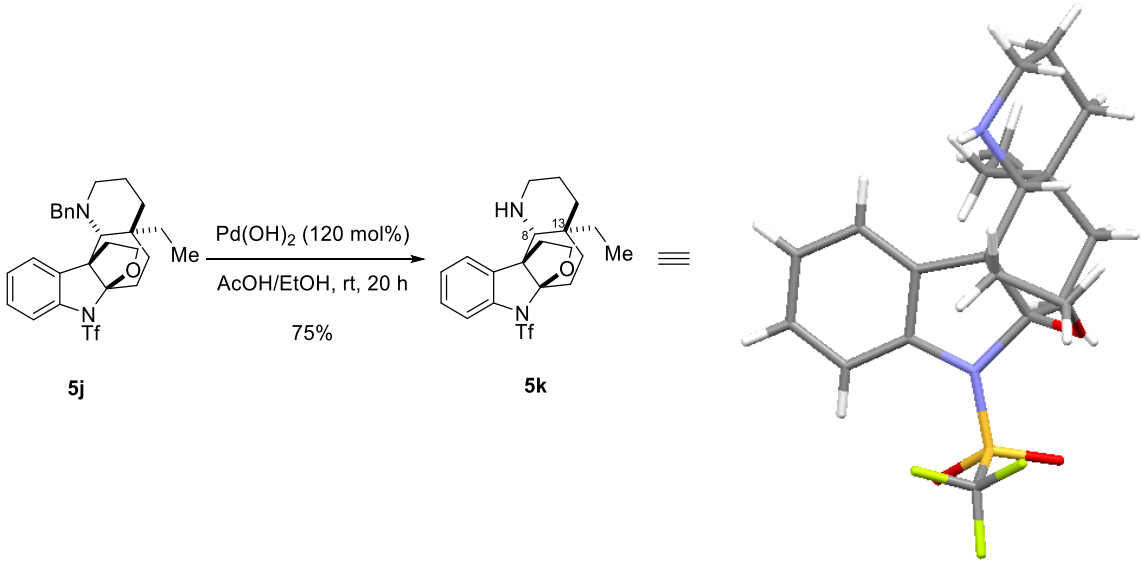
Treatment of **5f** with Tf_2O in the presence of D^{t}BMP, followed by addition of $NaBH_4$, as per the literature conditions, did indeed give consumption of starting material, however, an unexpected product **5j** was obtained (Scheme 86).



Scheme 86: Tf_2O-mediated cyclisation and an unexpected byproduct.

This product arose due to the pendant alcohol attacking the indolium following C-3 nucleophilic attack of the imidoyl triflate. Although this alcohol is protected with a benzyl group, it is possible that a small amount of the very strong TfOH acid which could be present

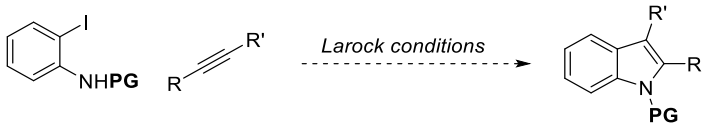
as an impurity in Tf_2O, caused this ether to hydrolyse. The now unprotected alcohol attacks the C-2 of the indolium to quench the positive charge and form the ether. Furthermore, the indole nitrogen becomes triflated to form the triflamide. Formation of this triflamide results in the net loss of TfOH, which could be responsible for the benzyl ether hydrolysis, perhaps indicating that the triflamide formation occurs first, then the resulting TfOH from this reaction goes on to hydrolyse the ether. Even if the Tf_2O is pure and free of TfOH, the formation of this triflamide results in the net loss of TfOH which is an inherent drawback of carrying out this reaction with an unprotected indole. Another difference between this substrate and the one used in Nicolaou's total synthesis of aspidophytine is that the indole in that synthesis is methylated, which will prevent the triflamide formation and therefore the release of TfOH through triflamide formation is not a concern. To unambiguously determine the structure of **5j**, it was first debenzylated to **5k** to grow a single crystal for X-ray diffraction, as a crystal of **5j** could not be grown easily. The hydride is delivered to the same face as the cyclic ether, perhaps because of coordination to the oxygen which is known to direct the reduction of 1,3-hydroxy ketones.[127] This results in the incorrect conformation at the junction of rings C + D, where the hydrogen at C-8 is *anti* to the pendant ethyl group attached to C-13, where it should be *syn*.



5j **5k**

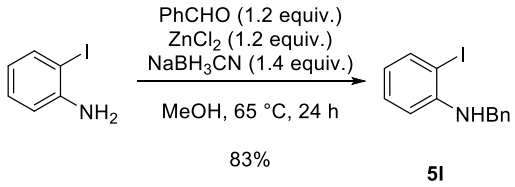
*Figure 15: Hydrogenation of **5j** and the crystal structure of product **5k**.*

One of the main benefits of the BMIDA Larock methodology is its modularity, in that if an *N*-protected 2-iodoaniline is used in the Larock reaction with an Alkyne BMIDA, the result would be an *N*-protected 2-BMIDA indole (Scheme 87).



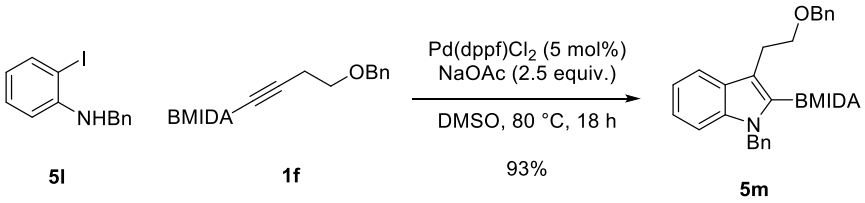
Scheme 87: General scheme for the Larock reaction where PG = protecting group.

To this end 2-iodoaniline was reacted with benzaldehyde under reductive amination conditions to give *N*-benzyl-2-iodoaniline **5l** (Scheme 88). The reason for choosing a benzyl protecting group on this indole nitrogen is that it should be cleaved with the other two benzyl groups during hydrogenolysis so should not result in an overall increase in step count.



Scheme 88: iodoaniline benzylation by reductive amination.

Gratifyingly, when **5l** was reacted under the optimised BMIDA Larock conditions with alkyne BMIDA **1f**, the doubly benzylated indole BMIDA **5m** was obtained in 93% yield.

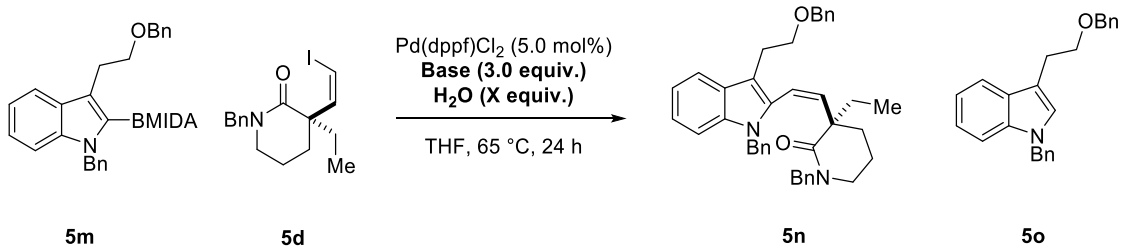


Scheme 89: BMIDA Larock reaction to produce an N*-benzyl indole product **5m**.*

Interestingly, subjecting **5m** to the previously optimised Suzuki conditions resulted in the absence of any new olefinic protons; only the peaks belonging to the vinyl iodide starting material **5d** could be seen in the crude ^{1}H NMR. There were significant amounts of the protodeboronated product **5o** detected in the reaction mixture, suggesting that rapid protodeboronation is causing this reaction to fail.

A small optimisation was carried out in the hope of finding more suitable conditions to fruitfully cross-couple **5m** to give product **5n**. This began with an investigation into the

equivalents of water and type of base used (Table 19). No product formation was observed using either Cs_2CO_3 or K_3PO_4 with a range of equivalents of water.

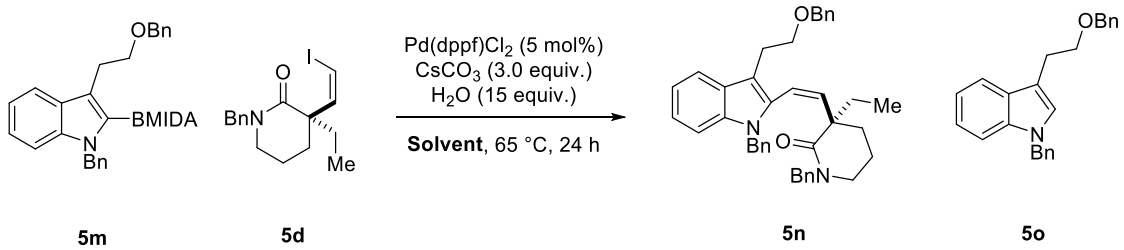


5m **5d** **5n** **5o**

Entry	Base	H_2O (equiv.)	5n(%)	5d(%)	5o(%)
1	Cs_2CO_3	5	n.d.	54	83
2	Cs_2CO_3	10	n.d.	61	61
3	K_3PO_4	5	n.d.	50	46
4	K_3PO_4	10	n.d.	55	60
5	K_3PO_4	15	n.d.	53	75

Table 19: Effect of water and base on the Suzuki reaction.

Next, the solvent was varied, and this also did not offer any conversion to product (Table 20). When DMSO was used as the solvent (Entry 2), complete degradation of the vinyl iodide starting material was observed with no formation of product.

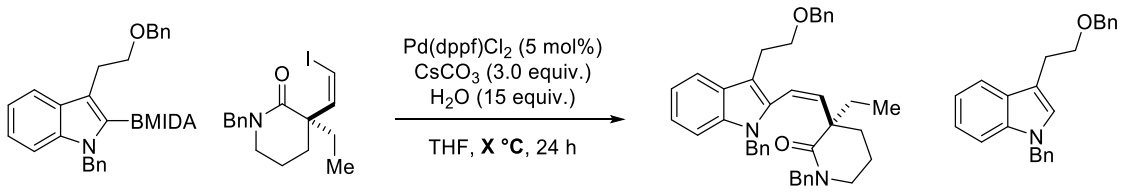


5m **5d** **5n** **5o**

Entry	Solvent	5n(%)	5d(%)	5o(%)
1	DMF	n.d.	32	52
2	DMSO	n.d.	n.d.	38
3	MeCN	n.d.	45	80
4	Acetone	n.d.	27	59
5	PhMe	n.d.	57	96

Table 20: Effect of solvent on the Suzuki reaction.

It was thought that lowering the temperature would retard the rate of protodeboronation (Table 21). With this would likely come a decrease in yield but if any product was observed, it would serve as a promising sign from which the rest of the optimisation could be based. No product was observed, however a clear temperature dependence on the level of protodeboronation was observed; as temperature increases; so too does the amount of protodeboronation.

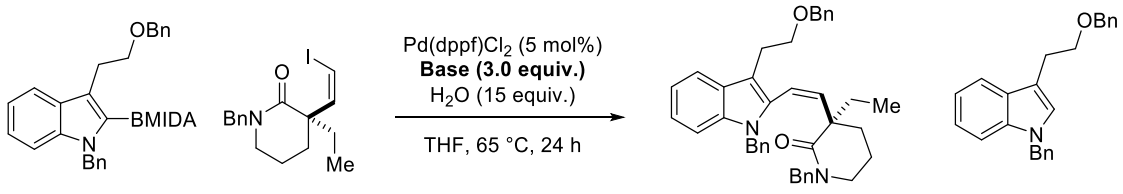


5m **5d** **5n** **5o**

Entry	Temperature (°C)	5n(%)	5d(%)	5o(%)
1	rt	n.d.	67	17
2	40	n.d.	68	42
3	50	n.d.	64	60

Table 21: Effect of temperature on the Suzuki reaction.

In a similar vein to the above lowering of reaction temperatures, weaker bases were next screened, as a weaker base would hydrolyse the BMIDA at a slower rate and therefore reduce the amount of protodeboronation (Table 22). Again, no product formation was observed and a range of levels of protodeboronation was observed.



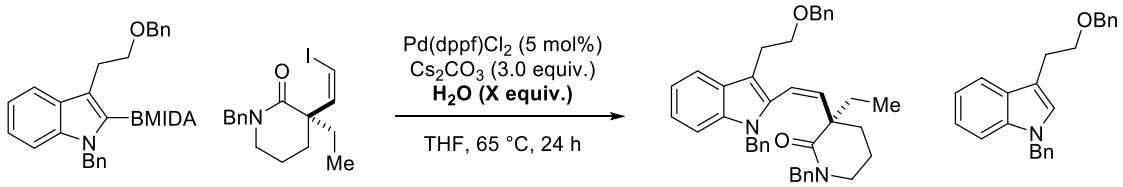
5m **5d** **5n** **5o**

Entry	Base	5n(%)	5d(%)	5o(%)

1	KF	n.d.	53	100
2	NaOAc	n.d.	62	66
3	$NaHCO_3$	n.d.	59	28
4	K_2HPO_4	n.d.	61	30

Table 22: Effect of weak bases on the Suzuki reaction.

Lowering the equivalents of water to much lower than usual, again to retard the rate of BMIDA hydrolysis, showed no product formation (Table 23).



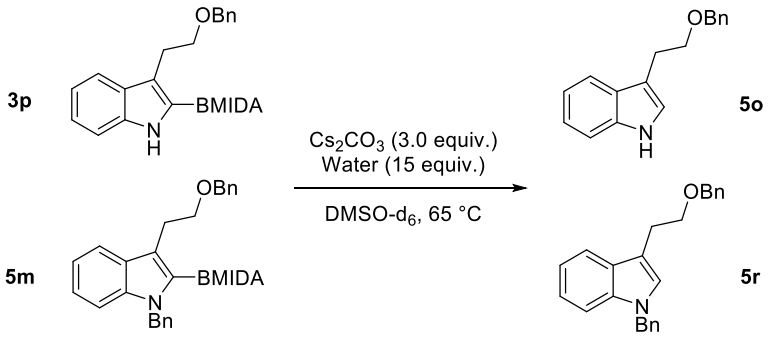
5m **5d** **5n** **5o**

Entry	H_2O (equiv.)	5n(%)	5d(%)	5o(%)
1	0	n.d.	45	83
2	1	n.d.	51	55
3	2	n.d.	54	98
4	4	n.d.	60	100

Table 23: Effects of low equivalents of water on the Suzuki reaction.

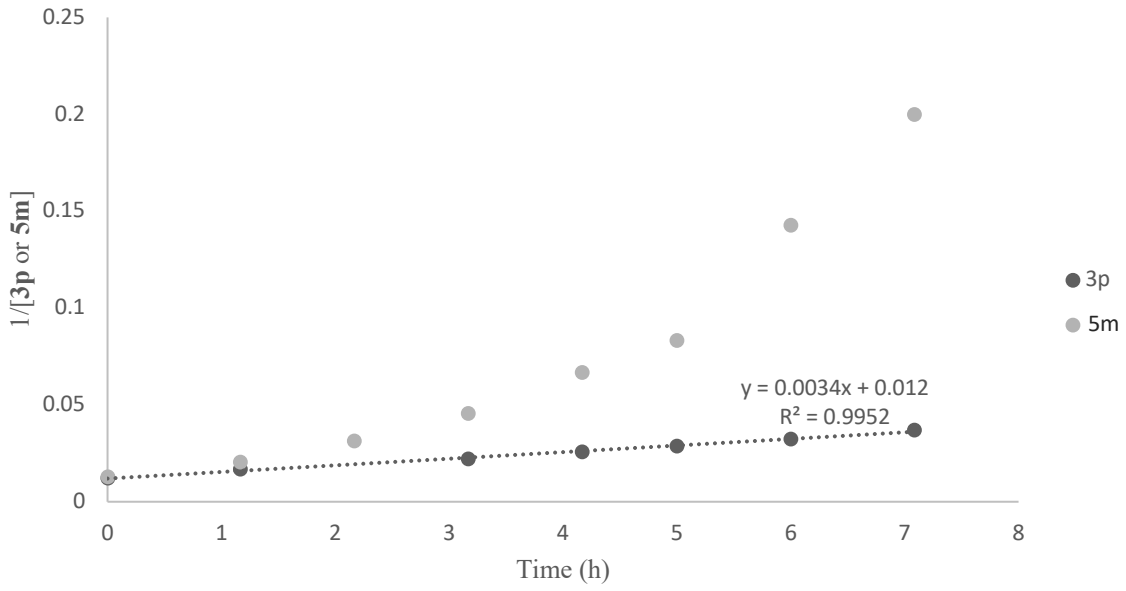
Finally, **5m** was added over 10 hours to the reaction vessel containing all the other reagents and solvent at temperature (in hopes of emulating the effect of slow-release BMIDA hydrolysis) then reacted for a further 14 hours. This sadly did not produce any new olefinic peaks and 50% **5d** and 36% **5o** was detected in the crude NMR, showing that this method did drastically decrease the amount of protodeboronation compared to the reaction where all reagents are present at the start.

An NMR experiment was carried out in hopes of elucidating this odd behaviour of **5m**'s inability to cross-couple, given that its NH analogue **3p** can cross-couple in high yield. Both **3p** and **5m** were reacted in separate NMR tubes, with naphthalene as an internal standard, and each with 15 equivalents of water, 3.0 equivalents of Cs_2CO_3 at 65 °C (Scheme 90). DMSO-d_6 was chosen as the reaction solvent, rather than the expensive THF-d_8.



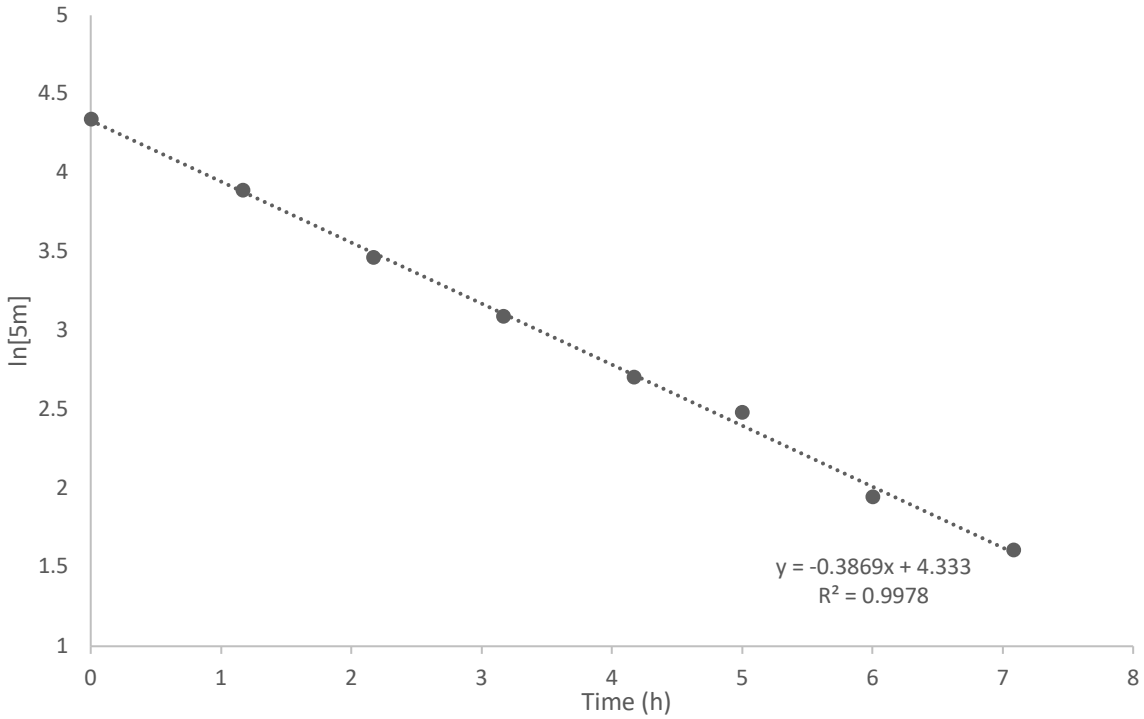
Scheme 90: NMR protodeboronation study

A plot of the inverse of the concentration of **3p** over time provides a straight line, indicative of second order kinetics (Graph 1). This can be interpreted simply as the reaction between **3p** and another reactant molecule, in this case hydroxide. This rate of protodeboronation is likely relatively slow, given the high yields of this indole in the Suzuki cross-coupling step. The same inverse concentration plot of **5m** reveals a non-linear relationship, showing that this protodeboronation likely takes place through a different mechanism to that of **3p**. Even though the gradient of **5m** is non-linear in this case, it can be seen qualitatively that the rate of protodeboronation in this indole is higher than in **3p**.



*Graph 1: Inverse of concentration over time for both **3p** and **5m**.*

Plotting the natural log of the concentration of **5m** over time reveals a straight line, indicative of first order kinetics.



*Graph 2: Natural log of concentration of **5m** over time.*

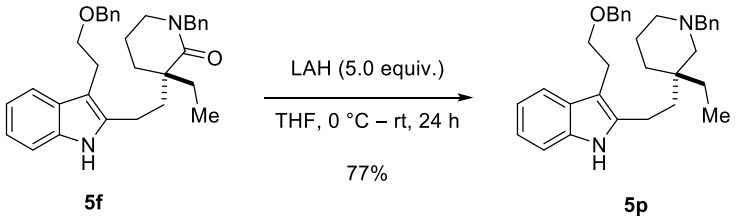
This result shows that protodeboronation of **5m** is dependent solely on the concentration of **5m** *i.e.,* protodeboronation of this substrate occurs at a certain rate irrespective of the concentration of other reactants. This agrees with data seen during the optimisation of the Suzuki cross-coupling of **5m**, where no product formation was seen despite varying reaction conditions rather widely. Based on the gradients of the slopes of Graph 1 + 2, it can be determined that the rate of protodeboronation of **5m** is 114 times faster than in **3p**.

The reason why adding a benzyl group to the indole nitrogen leads to first order kinetics in protodeboronation, where the free NH indole is second order, is unclear. Benzyl groups, as alkyl groups, are inductively donating, which would result in the indole nitrogen becoming more Lewis basic and therefore the C-3 of the indole would be more nucleophilic. Based on the mechanism in Scheme 47, a more nucleophilic C-3 would increase the basicity at this position which would increase the amount of hydroxide in solution through increased autoionisation of water, perhaps leading to accelerated BMIDA hydrolysis.

This synthesis was stopped here in the interests of time. Please see the Conclusions and Future Work section for ideas on how this synthesis could be completed.

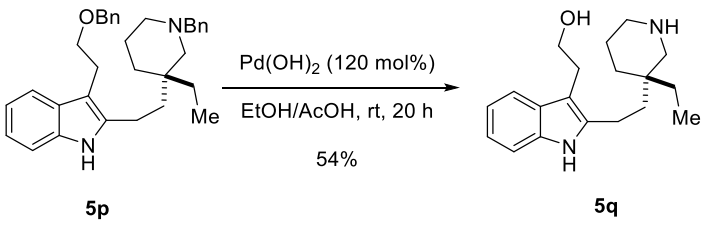
4.1.2. Quebrachamine Synthesis

The synthesis of quebrachamine began with the reduction of Common Intermediate **5f** using LAH to give piperidine **5p** in 92% yield.



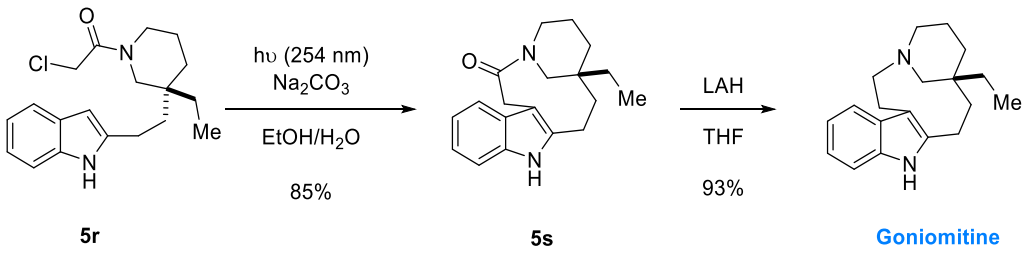
*Scheme 91: Lactam **5f** reduction to piperidine **5p**.*

To carry out the ring-closing reaction, the nitrogen and oxygen must both be debenzylated to give **5q** (Scheme 92). Removal of these groups required use of superstoichiometric $Pd(OH)_2$, which points to an issue with catalyst turnover.



Scheme 92: Global debenzylation.

With the nitrogen and oxygen now deprotected, several sets of conditions were employed to try and close the ring and form quebrachamine. These included an Appel reaction, Mitsunobu reaction and conversion of the alcohol to a mesylate, all with the aim of converting the oxygen into a good leaving group. These efforts were fruitless, however, and a search of the literature revealed that this reaction is unlikely to proceed,[128] likely due to the large entropic cost of tethering together two long, flexible chains to create a large macrocycle. The reaction could instead proceed through a Witkop cyclisation,[123] which is a radical process. However, this requires formation of an α-chloro acetamide on the piperidine nitrogen *i.e.* the two methylene linker between C-3 of the indole and piperidine is attached to the nitrogen of the latter, and this necessarily means that the C-3 of the indole must be unsubstituted; incompatible with the BMIDA Larock methodology to be used in this synthesis. Below is shown Pagenkopf's and Bajto's Witkop cyclisation of chloroacetamide **5r**, forming **5s** which was then reduced with LAH to give quebrachamine (Scheme 93).[128]

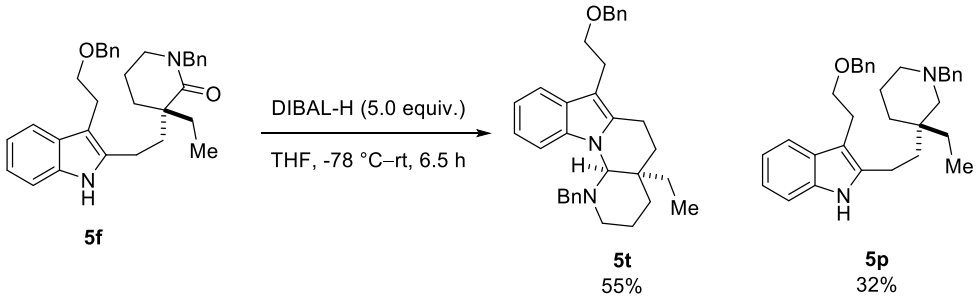


Scheme 93: Pagenkopf's and Bajto's Witkop cyclisation to make quebrachamine

Considering these previously reported failures of ring-closing by intramolecular S_N2, and the incompatibility of the Witkop pathway with the BMIDA Larock protocol, the synthesis of quebrachamine was abandoned.

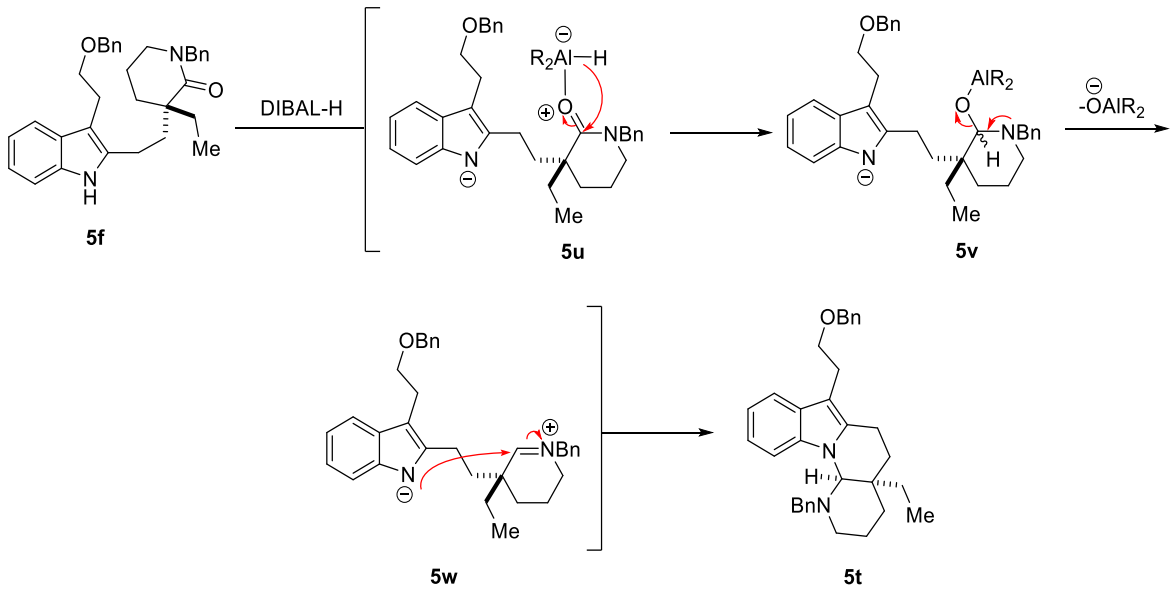
4.1.3. Goniomitine Synthesis

The synthesis of goniomitine began with the treatment of **5f** with an excess of DIBAL-H which gave concomitant deprotonation of the indole nitrogen and reduction of the lactam (Scheme 94). This resulted in formation of the desired tetracycle **5t** as well as over-reduced by-product **5p**. Fortunately, **5p** could be recycled and used in the synthesis of quebrachamine.



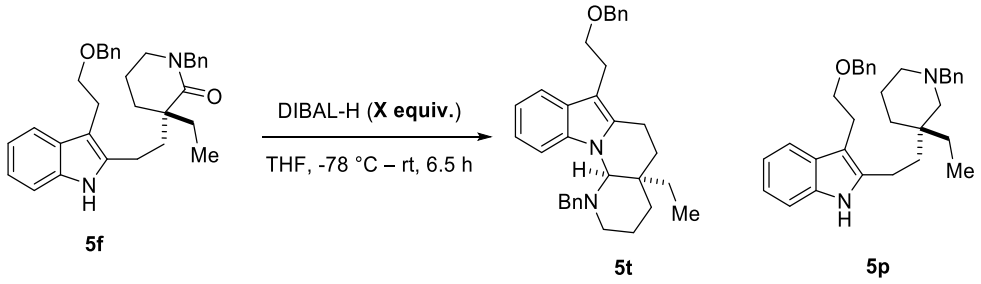
Scheme 94: DIBAL-H mediated cyclisation in making goniomitine

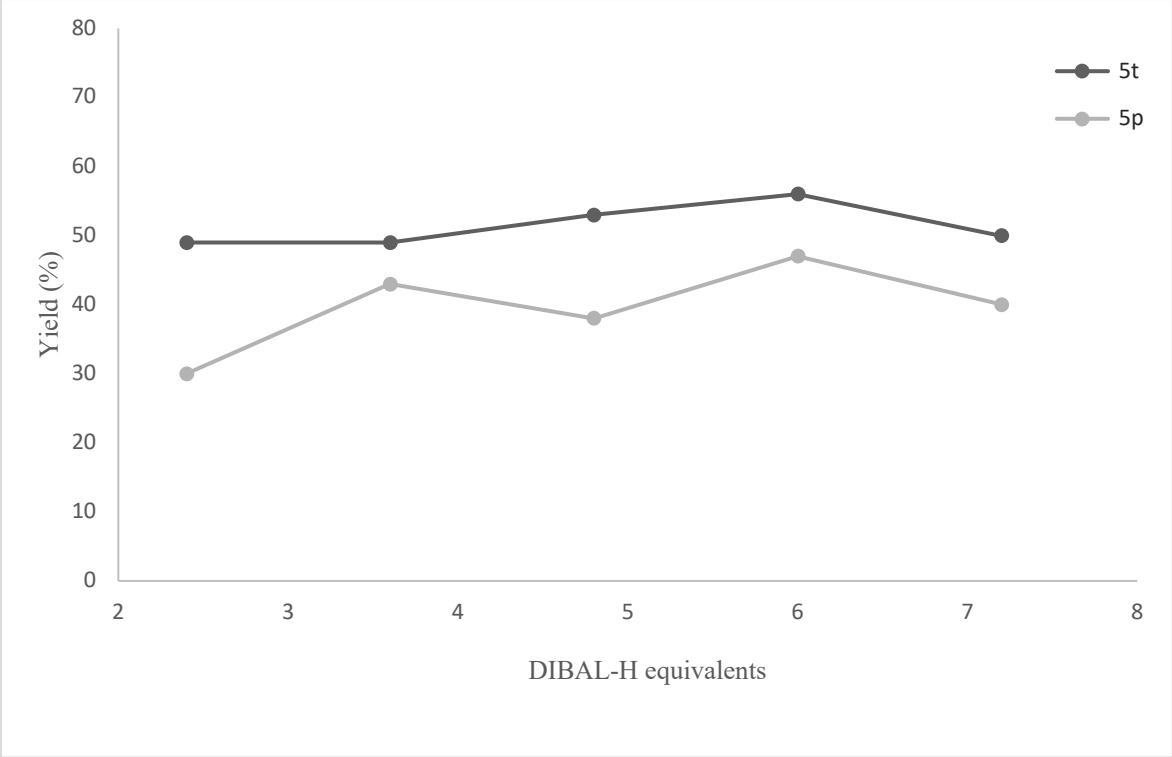
Following delivery of a single hydride from DIBAL-H to **5f**, an iminium results and it is this which is attacked by a nucleophile, and there is competition between another equivalent of DIBAL-H and the deprotonated indole nitrogen (Scheme 95). The first attack of DIBAL-H on the lactam results from coordination between the carbonyl oxygen and oxophilic aluminium in **5u** to form a hemi-aminal. After loss of an aluminium oxide species after this first reduction in **5v**, any subsequent DIBAL-H reduction does not enjoy this beneficial formation of the strong aluminium-oxygen bond. Furthermore, the attack from the indole nitrogen in **5w** is intramolecular, which is entropically much more favourable than intermolecular delivery of another hydride.



Scheme 95: Mechanism of the DIBAL-H mediated cyclisation. R = iso-*butyl*

Nonetheless, no small amount of **5p** was observed and an equivalents study was carried out to ascertain the optimal equivalents of DIBAL-H to limit the formation of this by-product.

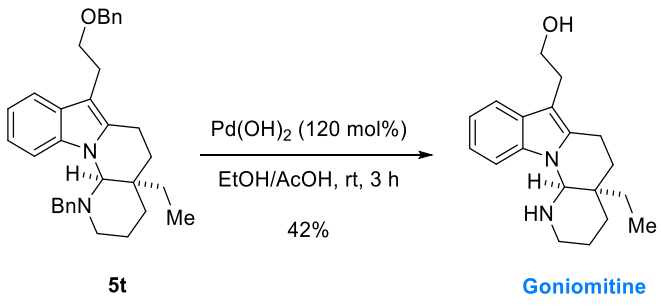




Graph 3: DIBAL-H equivalents study.

As seen in Graph 3, there does not seem to be a discernible trend between DIBAL-H equivalents and the conversions of **5t** and **5p** and as such, no change was made to the procedure. There are other factors which could favour the formation of the desired product, for example, increasing dilution should tip the balance in favour of the intramolecular attack of the indole nitrogen. Temperature, solvent and perhaps addition rate of the DIBAL-H will likely also influence the distribution of **5t** and **5p**.

Finally, with tetracyclic **5t** in hand, global debenzylation would afford the natural product. Hydrogenation in acidic ethanol with superstoichiometric $Pd(OH)_2$ gave goniomitine in 42% yield (Scheme 96).



Scheme 96: Global debenzylation to give goniomitine,

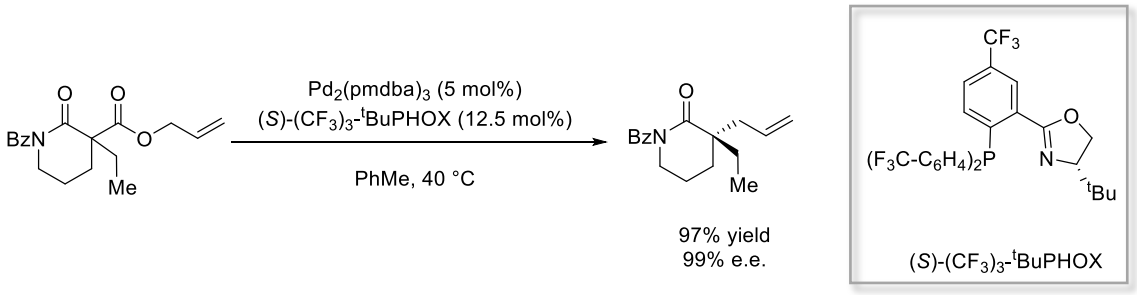
4.2. Conclusions and Future Work

In this final chapter, the BMIDA Larock reaction was employed in the synthesis of a Common Intermediate, from which three natural products could be derived in theoretically as few as two to three steps. In practice, it was found that the Suzuki cross-coupled product would isomerise requiring the addition of an extra hydrogenation step. The synthesis of aspidospermidine was not achieved due to an unexpected reaction during the critical A B C D ring formation step. It was thought that benzylating the indole nitrogen might obviate this problem however this presented its own problems as a mechanistic investigation showed that it protodeboronates rapidly under first order kinetics. The final intermediate en route to quebrachamine was reached but the final macrocylisation step would not proceed and a literature search revealed that it is unlikely to proceed from this intermediate, likely owing to the large size of the macrocycle being formed. There was a reported success in macrocyclisation using a one-electron Witkop pathway but this is not compatible with the BMIDA Larock methodology this chapter is intended to demonstrate. Goniomitine was successfully synthesised.

In terms of future work, the synthesis of aspidospermidine could likely be achieved by altering the protecting group on the indole nitrogen. As demonstrated in the synthesis of **5m**, the BMIDA Larock is modular, and by changing the protecting groups on the iodoaniline starting material, these can be carried through to the indole BMIDA product. Quebrachamine is likely unachievable if a BMIDA Larock reaction is used.

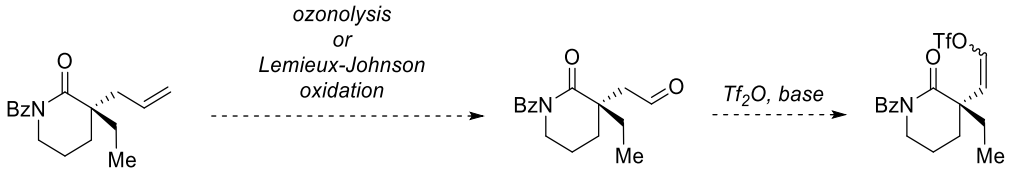
The modularity of the BMIDA Larock reaction is one of its key benefits. By varying the iodoaniline and alkyne BMIDA starting material, many different permutations of indole BMIDA products can be obtained. This allows for the formation of Common Intermediate analogues bearing bespoke functionality. These can then be carried through to the natural products, to produce novel natural product derivatives bearing functionality which would otherwise be difficult to introduce onto the natural product through late-stage functionalisation.

An obvious progression of this synthesis is to carry it out non-racemically. This asymmetry centres on the α position of the lactam, once this centre has been established, the rest of the synthesis should be diastereoselective and as this centre is quaternary, it cannot epimerise. Asymmetric formation of this quaternary centre could be achieved using the decarboxylative asymmetric allylic alkylation as developed by Stoltz and co-workers (Scheme 97).[129]



Scheme 97: Stoltz's decarboxylative asymmetric allylic alkylation of valerolactam. Bz = benzoyl

While this appears to be a very attractive method for forming this quaternary centre asymmetrically, it introduces a 3-carbon chain where a one carbon unit is required, specifically a formyl group which can then be converted into a vinyl iodide by a Stork-Zhao reaction (see Scheme 82). Alternatively, ozonolysis or Lemieux-Johnson oxidation will give an ethanal at the α-position, which could be converted into a vinyl triflate, amenable to Suzuki cross-coupling (Scheme 98).

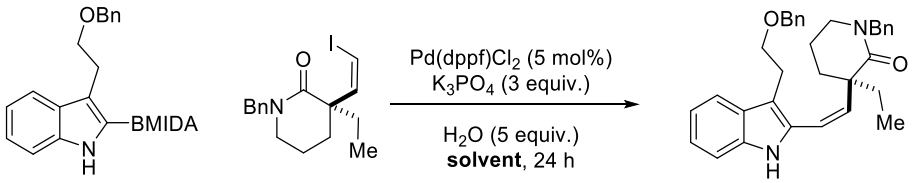


Scheme 98: proposed conversion of the allyl group to a vinyl triflate

4.3 Chapter Four Experimental

Reaction optimisation data

NH indole (3p) Suzuki solvent study



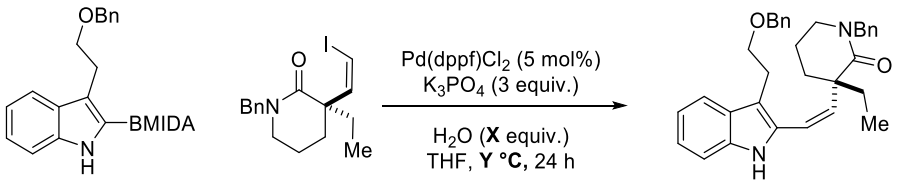
3p **5d** **5e**

In a 5 mL microwave vial, $Pd(dppf)Cl_2$ (7.31 mg, 10.0 µmol, 5.00 mol%), **5d** (74.2 mg, 0.20 mmol, 1.00 equiv.), **3p** (122 mg, 0.30 mmol, 1.50 equiv.) and Cs_2CO_3 (196 mg, 0.60 mmol, 3.00 equiv.) were charged and the vial was capped and purged with nitrogen. **Solvent (2.0 mL)** followed by water (54.3 µL, 3.00 mmol, 15.0 equiv.) were added through the septum and the reaction mixture was heated to 65 °C for 24 hours, then cooled to room temperature, decapped and diluted with brine (10 mL) and extracted with EtOAc (2 x 5 mL). 0.05 M 1,4-dinitrobenzene in MeCN (1.00 mL) was added to the organic layer, which was then concentrated and a yield was obtained by quantitative ^1H NMR.

Entry	Solvent	5e (%)
1	DMSO	15
2	DMF	37
3	MeCN	40
4	THF	53

Supplementary Table 10: Suzuki solvent study.

Suzuki water and temperature study

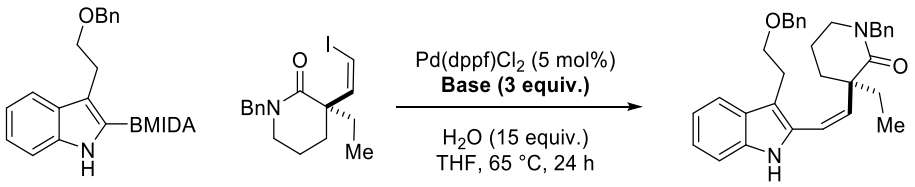


In a 5 mL microwave vial, $Pd(dppf)Cl_2$ (7.31 mg, 10.0 µmol, 5.00 mol%), **5d** (74.2 mg, 0.20 mmol, 1.00 equiv.), **3p** (122 mg, 0.30 mmol, 1.50 equiv.) and Cs_2CO_3 (196 mg, 0.60 mmol, 3.00 equiv.) were charged and the vial was capped and purged with nitrogen. THF (2.0 mL) followed by water (**XX µL, YY mmol, ZZ equiv**.) were added through the septum and the reaction mixture was heated to 65 °C for 24 hours, then cooled to room temperature, decapped and diluted with brine (10 mL) and extracted with EtOAc (2 x 5 mL). 0.05 M 1,4-dinitrobenzene in MeCN (1.00 mL) was added to the organic layer, which was then concentrated and a yield was obtained by quantitative ^1H NMR.

Entry	T (°C)	H_2O (equiv.)	5e (%)
1	65	10	Trace
2	65	15	62
3	65	20	55
4	65	30	62
5	65	50	58
6	80	5	26
7	80	10	60
8	80	15	49
9	80	20	48
10	80	30	30

Supplementary Table 11: Suzuki temperature and water equivalents study.

Suzuki base study



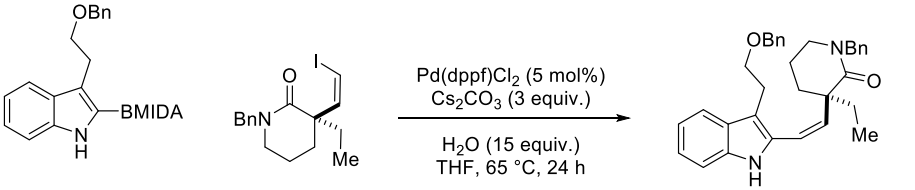
3p **5d** **5e**

In a 5 mL microwave vial, $Pd(dppf)Cl_2$ (7.31 mg, 10.0 µmol, 5.00 mol%), **4d** (74.2 mg, 0.20 mmol, 1.00 equiv.), **3p** (122 mg, 0.30 mmol, 1.50 equiv.) and **base (XX mg, YY mmol, ZZ equiv.)** were charged and the vial was capped and purged with nitrogen. THF (2.0 mL) followed by water (54.3 µL, 3.00 mmol, 15.0 equiv.) were added through the septum and the reaction mixture was heated to 65 °C for 24 hours, then cooled to room temperature, decapped and diluted with brine (10 mL) and extracted with EtOAc (2 x 5 mL). 0.05 M 1,4-dinitrobenzene in MeCN (1.00 mL) was added to the organic layer, which was then concentrated and a yield was obtained by quantitative ^1H NMR.

Entry	Base	5e (%)
1	K_2CO_3	40
2	Cs_2CO_3	78
3	NaOH	73
4	Na_2CO_3	35
5	$NaHCO_3$	26

Supplementary Table 12: Suzuki base study.

Suzuki stoichiometry study



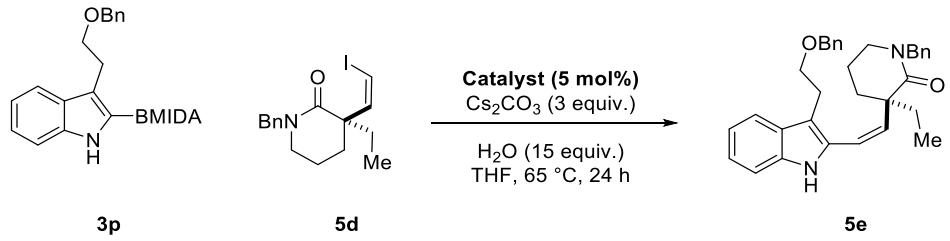
3p **5d** **5e**

In a 5 mL microwave vial, $Pd(dppf)Cl_2$ (7.31 mg, 10.0 μmol, 5.00 mol%), **5d** (**XX mg, YY mmol, ZZ equiv**.), **3p** (**XX mg, YY mmol, ZZ equiv**.) and Cs_2CO_3 (196 mg, 0.60 mmol, 3.00 equiv.) were charged and the vial was capped and purged with nitrogen. THF (2.0 mL) followed by water (54.3 μL, 3.00 mmol, 15.0 equiv.) were added through the septum and the reaction mixture was heated to 65 °C for 24 hours, then cooled to room temperature, decapped and diluted with brine (10 mL) and extracted with EtOAc (2 x 5 mL). 0.05 M 1,4-dinitrobenzene in MeCN (1.00 mL) was added to the organic layer, which was then concentrated and a yield was obtained by quantitative ^1H NMR.

Entry	3p:5d ratio	5e (%)
1	1.2:1	79
2	1.5:1	81
3	1.8:1	82
4	2.0:1	81
5	2.5:1	35

Supplementary Table 13: Suzuki starting material stoichiometry study.

Suzuki catalyst study



In a 5 mL microwave vial, **catalyst** (**XX** mg, 10.0 μmol, 5.00 mol%) (where applicable, **ligand** (**YY** mg, 20.0 μmol, 10.0 mol%)), **5d** (74.2 mg, 0.20 mmol, 1.00 equiv.), **3p** (122 mg, 0.30 mmol, 1.50 equiv.) and Cs_2CO_3 (196 mg, 0.60 mmol, 3.00 equiv.) were charged and the vial was capped and purged with nitrogen. THF (2.0 mL) followed by water (54.3 μL, 3.00 mmol, 15.0 equiv.) were added through the septum and the reaction mixture was heated to 65 °C for 24 hours, then cooled to room temperature, decapped and diluted with brine (10 mL) and extracted with EtOAc (2 x 5 mL). 0.05 M 1,4-dinitrobenzene in MeCN

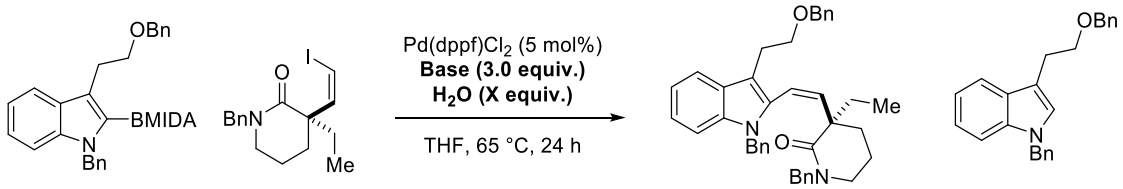
(1.00 mL) was added to the organic layer, which was then concentrated and a yield was obtained by quantitative ^{1}H NMR.

Entry	Catalyst	Ligand (mol %)	5e (%)
1	$Pd(OAc)_2$	PPh_3 (10)	78
2	$Pd(OAc)_2$	SPhos (10)	44
3	$Pd(PPh_3)_2Cl_2$	-	83
4	$Pd(MeCN)_2Cl_2$	-	78
5	$[Pd(allyl)Cl]_2$	PPh_3 (10)	83

Supplementary Table 14: Suzuki catalyst study.

NBn (4m) Suzuki optimisation

Suzuki base and water equivalents study.

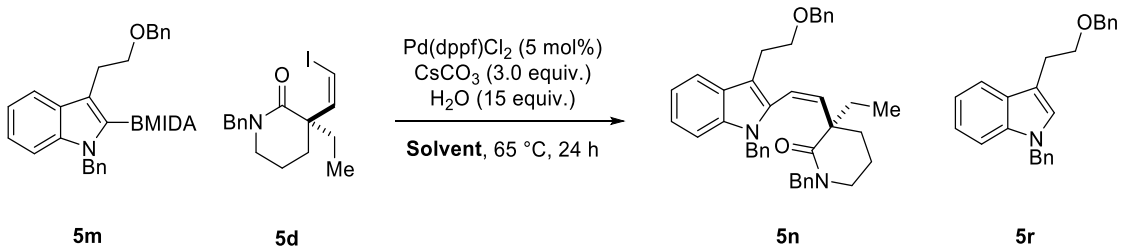


In a 5 mL microwave vial, $Pd(dppf)Cl_2$ (7.31 mg, 10.0 µmol, 5.00 mol%), **5d** (74.2 mg, 0.20 mmol, 1.00 equiv.), **5m** (150 mg, 0.30 mmol, 1.50 equiv.) and **base** (**XX** mg, 0.60 mmol, 3.00 equiv.) were charged and the vial was capped and purged with nitrogen. THF (2.0 mL) followed by water (**XX µL, YY mmol, ZZ equiv**.) were added through the septum and the reaction mixture was heated to 65 °C for 24 hours, then cooled to room temperature, decapped and diluted with brine (10 mL) and extracted with EtOAc (2 x 5 mL). 0.05 M 1,4-dinitrobenzene in MeCN (1.00 mL) was added to the organic layer, which was then concentrated and a yield was obtained by quantitative ^{1}H NMR.

Entry	Base	H_2O (equiv.)	5n (%)	5d (%)	5r (%)
1	Cs_2CO_3	5	n.d.	54	83
2	Cs_2CO_3	10	n.d.	61	61
3	K_3PO_4	5	n.d.	50	46
4	K_3PO_4	10	n.d.	55	60
5	K_3PO_4	15	n.d.	53	75

Supplementary Table 15: Suzuki base and water equivalents study.

Suzuki solvent study

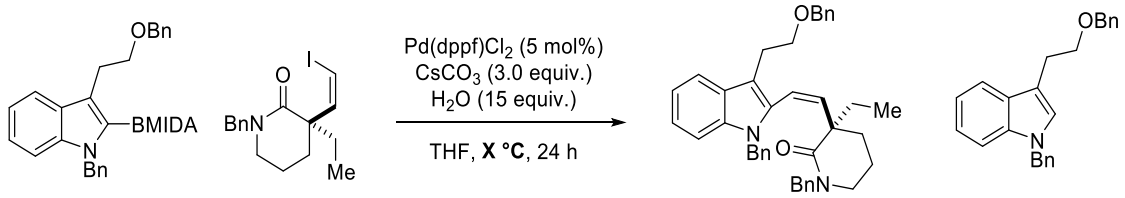


In a 5 mL microwave vial, $Pd(dppf)Cl_2$ (7.31 mg, 10.0 µmol, 5.00 mol%), **5d** (74.2 mg, 0.20 mmol, 1.00 equiv.), **5m** (150 mg, 0.30 mmol, 1.50 equiv.) and Cs_2CO_3 (196 mg, 0.60 mmol, 3.00 equiv.) were charged and the vial was capped and purged with nitrogen. **Solvent (2.0 mL)** followed by water (54.3 µL, 3.00 mmol, 15.0 equiv.) were added through the septum and the reaction mixture was heated to 65 °C for 24 hours, then cooled to room temperature, decapped and diluted with brine (10 mL) and extracted with EtOAc (2 x 5 mL). 0.05 M 1,4-dinitrobenzene in MeCN (1.00 mL) was added to the organic layer, which was then concentrated and a yield was obtained by quantitative ^1H NMR.

Entry	Solvent	5n (%)	5d (%)	5r (%)
1	DMF	n.d.	32	52
2	DMSO	n.d.	n.d.	38
3	MeCN	n.d.	45	80
4	Acetone	n.d.	27	59
5	PhMe	n.d.	57	96

Supplementary Table 16: Suzuki solvent study.

Suzuki temperature study



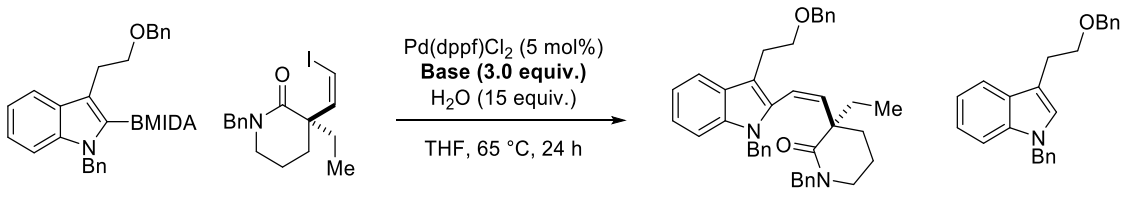
5m **5d** **5n** **5r**

In a 5 mL microwave vial, $Pd(dppf)Cl_2$ (7.31 mg, 10.0 µmol, 5.00 mol%), **5d** (74.2 mg, 0.20 mmol, 1.00 equiv.), **5m** (150 mg, 0.30 mmol, 1.50 equiv.) and Cs_2CO_3 (196 mg, 0.60 mmol, 3.00 equiv.) were charged and the vial was capped and purged with nitrogen. THF (2.0 mL) followed by water (54.3 µL, 3.00 mmol, 15.0 equiv.) were added through the septum and the reaction mixture was heated to **XX °C** for 24 hours, then cooled to room temperature, decapped and diluted with brine (10 mL) and extracted with EtOAc (2 x 5 mL). 0.05 M 1,4-dinitrobenzene in MeCN (1.00 mL) was added to the organic layer, which was then concentrated and a yield was obtained by quantitative ^1H NMR.

Entry	Temperature (°C)	5n (%)	5d (%)	5r (%)
1	rt	n.d.	67	17
2	40	n.d.	68	42
3	50	n.d.	64	60

Supplementary Table 17: Suzuki temperature study.

Suzuki base study



5m **5d** **5n** **5r**

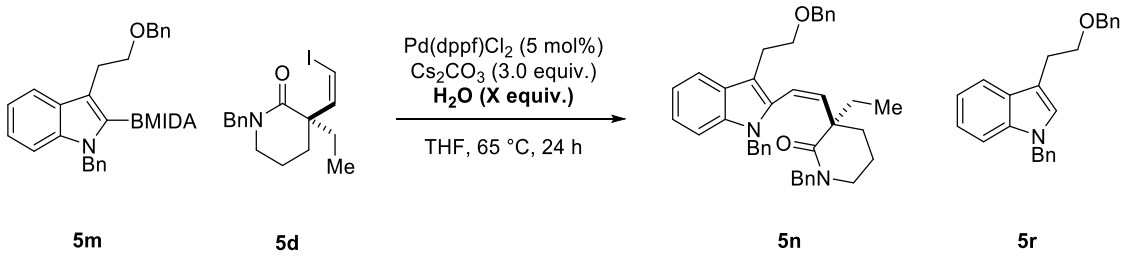
In a 5 mL microwave vial, $Pd(dppf)Cl_2$ (7.31 mg, 10.0 µmol, 5.00 mol%), **5d** (74.2 mg, 0.20 mmol, 1.00 equiv.), **5m** (150 mg, 0.30 mmol, 1.50 equiv.) and **base** (**XX** mg, 0.60 mmol, 3.00 equiv.) were charged and the vial was capped and purged with nitrogen. THF (2.0 mL) followed by water (54.3 µL, 3.00 mmol, 15.0 equiv.) were added through the septum and the reaction mixture was heated to 65 °C for 24 hours, then cooled to room temperature,

decapped and diluted with brine (10 mL) and extracted with EtOAc (2 x 5 mL). 0.05 M 1,4-dinitrobenzene in MeCN (1.00 mL) was added to the organic layer, which was then concentrated and a yield was obtained by quantitative ^{1}H NMR.

Entry	Base	5n (%)	5d (%)	5r (%)
1	KF	n.d.	53	100
2	NaOAc	n.d.	62	66
3	$NaHCO_3$	n.d.	59	28
4	K_2HPO_4	n.d.	61	30

Supplementary Table 18: Suzuki reaction weak base study.

Suzuki low water equivalents study



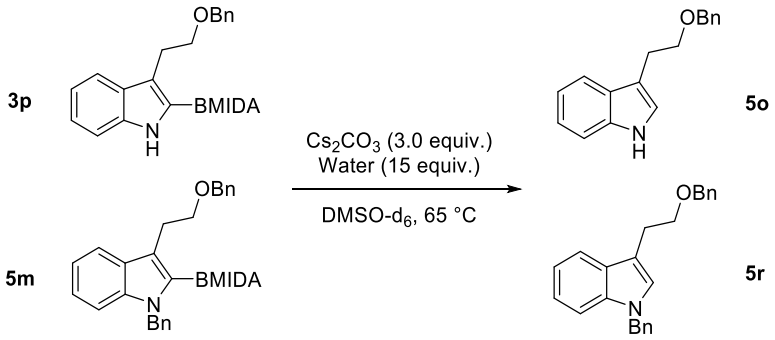
5m **5d** **5n** **5r**

In a 5 mL microwave vial, $Pd(dppf)Cl_2$ (7.31 mg, 10.0 µmol, 5.00 mol%), **5d** (74.2 mg, 0.20 mmol, 1.00 equiv.), **5m** (150 mg, 0.30 mmol, 1.50 equiv.) and Cs_2CO_3 (196 mg, 0.60 mmol, 3.00 equiv.) were charged and the vial was capped and purged with nitrogen. THF (2.0 mL) followed by water (**XX µL, YY mmol, ZZ equiv**.) were added through the septum and the reaction mixture was heated to 65 °C for 24 hours, then cooled to room temperature, decapped and diluted with brine (10 mL) and extracted with EtOAc (2 x 5 mL). 0.05 M 1,4-dinitrobenzene in MeCN (1.00 mL) was added to the organic layer, which was then concentrated and a yield was obtained by quantitative ^{1}H NMR.

Entry	H_2O (equiv.)	5n (%)	5d (%)	5r (%)
1	0	n.d.	45	83
2	1	n.d.	51	55
3	2	n.d.	54	98
4	4	n.d.	60	100

Supplementary Table 19: Suzuki low equivalents of water study.

NMR protodeboronation study

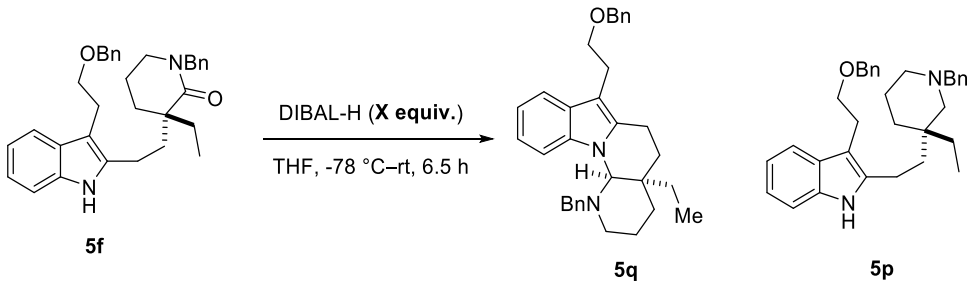


In two separate Young's NMR tubes, Cs_2CO_3 (65.2 mg, 0.20 mmol, 2.00 equiv.) was added, followed by **3p** (40.6 mg, 0.10 mmol, 1.00 equiv.) into one NMR tube then **5m** (49.6 mg, 0.10 mmol, 1.00 equiv.) was added to the other. A stock solution of naphthalene (37.5 μM, 667 μL in DMSO-d_6) and D_2O (27.1 μL, 15.0 equiv.) were added to both tubes. The NMR tubes were capped and heated to 65 °C, and ^1H NMRs were taken at intervals.

Time (min)	3p (%)	5m (%)
0	83	77
70	60	49
130	-	32
190	45	22
250	39	15
300	35	12
360	31	7
425	27	5

Supplementary Table 20: NMR protodeboronation study.

DIBAL-H equivalents study



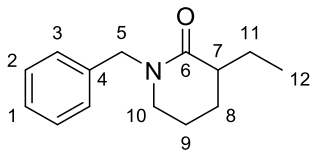
In an oven-dried 5 mL microwave vial, a solution of **5f** (16.0 mg, 32.3 μmol, 1.00 equiv.) in THF (0.81 mL) was cooled to -78 °C and **DIBAL-H** (1.2 M in THF, **XX mL, YY mmol, ZZ equiv.)** was added through the septum. After complete addition, the reaction mixture was allowed to warm to room temperature, then stirred until six and a half hours had passed since complete addition, quenched with saturated Rochelle's salt solution (5 mL) and stirred at room temperature for one hour. The reaction mixture was extracted with EtOAc (2 x 5 mL), to the combined organics was added 8.1 μM 1,4-dinitrobenzene in MeCN (1.00 mL), the organics were concentrated and a quantitative ^{1}H NMR of this crude was taken to obtain yield.

Entry	DIBAL-H (equiv.)	5q(%)	5p(%)
1	2.4	49	30
2	3.6	49	43
3	4.8	53	38
4	6.0	56	47
5	7.2	50	40

Supplementary Table 21: DIBAL-H cyclisation study.

Characterisation data

5b



In a flame-dried round-bottom flask, distilled di-*iso*-propylamine (9.95 mL, 71.0 mmol, 1.30 equiv.) was dissolved in THF (250 mL) and cooled to 0 °C. To this stirring solution was added, *via* syringe, *n*-butyllithium (2.43 M in hexanes, 27.0 mL, 65.6 mmol, 1.20 equiv.) and the solution was stirred at 0 °C for 30 minutes before a solution of 1-benzyl-2-piperidinone (10.3 g, 54.6 mmol, 1.0 equiv.) in THF (100 mL) was added, resulting in a bright yellow solution. This was stirred at 0 °C for 10 minutes before being warmed to room temperature where it was stirred for a further 30 minutes before being cooled to -78 °C. Ethyl iodide (5.71 mL, 71.0 mmol, 1.30 equiv.) was added *via* syringe over several minutes and

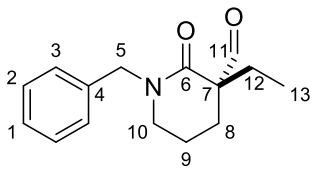
the reaction mixture was stirred at this temperature for a further 30 minutes before being warmed to room temperature and stirred for a further hour. Saturated ammonium chloride solution (100 mL) was added and the aqueous layer was extracted twice with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated prior to flash column chromatography (silica gel, 10-30% EtOAc in hexane) to give the title product as a colourless oil (11.56 g, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.09 (m, 5H, **H1 + H2 + H3**), 4.61 (d, *J* = 3.0 Hz, 2H, **H5**), 3.21 (dd, *J* = 7.3, 4.9 Hz, 2H, **H10**), 2.44 – 2.24 (m, 1H, **H7**), 2.13 – 1.91 (m, 2H, **H8 + H11**), 1.90 – 1.82 (m, 1H, **H9**), 1.78 – 1.66 (m, 1H, **H9'**), 1.66 – 1.53 (m, 2H, **H8' + H11'**), 0.99 (t, *J* = 7.5 Hz, 3H, **H12**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 137.6, 128.6, 128.0, 127.2, 50.3, 47.5, 43.0, 25.8, 24.9, 21.7, 11.5.

Spectral data in agreement with literature values.[122]

5c



An oven-dried round bottom flask was charged with THF (30 mL) and di-*iso*-propylamine (2.80 mL, 12.0 mmol, 1.20 equiv.) and the stirring solution was cooled to 0 °C and stirred for 30 minutes prior to the addition of *n*-butyllithium (2.3 M in hexanes, 5.17 mL, 11.9 mmol, 1.19 equiv.). A solution of **5b** (2.17 g, 10.0 mmol, 1.00 equiv.) in THF (20 mL) was charged *via* cannula to the LDA solution where it was stirred for one hour at 0 °C before being cooled to -78 °C. A solution of ethyl formate (1.05 mL, 13.0 mmol, 1.30 equiv.) in THF (10 mL) was charged to the enolate solution *via* syringe then the reaction mixture was warmed to room temperature and stirred overnight before being quenched with saturated ammonium chloride (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated prior to purification by flash column chromatography (silica gel, 10-20% EtOAc in hexane) to give the title product as a colourless oil (1.50 g, 61%).

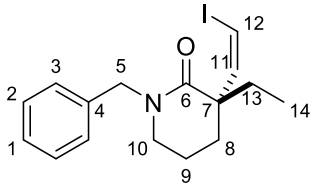
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H, **H11**), 7.67 – 7.03 (m, 5H, **H1 + H2 + H3**), 4.69 (d, *J* = 14.6 Hz, 1H, **H5**), 4.57 (d, *J* = 14.6 Hz, 1H, **H5'**), 3.32 – 3.01 (m, 2H, **H10**), 2.35 – 2.25 (m, 1H, **H12**), 2.17 – 2.02 (m, 1H, **H9**), 1.98 – 1.76 (m, 2H, **H8 + H9'**), 1.75 – 1.57 (m, 2H, **H8' + H12'**), 0.91 (t, *J* = 7.5 Hz, 3H, **H13**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.0 **C11**, 168.9 **C6**, 136.9 **C4**, 128.7 **C2**, 128.0 **C3**, 127.5 **C1**, 59.4 **C7**, 50.7 **C5**, 47.6 **C10**, 27.8 **C9**, 24.4 **C12**, 20.3 **C8**, 8.4 **C13**.

υ_{max} (neat): 2967, 2940, 1724, 1628, 1489, 1452, 1352, 1265, 1200, 1169 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}NO_2$) requires *m/z* 246.1494, found *m/z* 246.1484.

5d



A slurry of iodomethylphosphonium iodide (6.76 g, 12.8 mmol, 1.40 equiv.) in THF (57 mL) was cooled to 0 °C prior to addition of NaHMDS (0.85 M in THF, 13.9 mL, 11.8 mmol, 1.30 equiv.) dropwise *via* syringe. The deep yellow suspension was stirred at 0 °C for 10 minutes before being cooled to -78 °C and stirred for a further 30 minutes then **5c** (2.23 g, 9.11 mmol, 1.00 equiv.) was added as a solution in THF (3.5 mL) dropwise *via* syringe. The reaction mixture was stirred at -78 °C for 3 hours before being quenched with saturated ammonium chloride solution then warmed to room temperature and extracted with EtOAc (3 x 100 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated prior to purification by flash column chromatography (silica gel, 5-30% EtOAc in hexane) to give the title product as a light yellow oil (3.07 g, 91%).

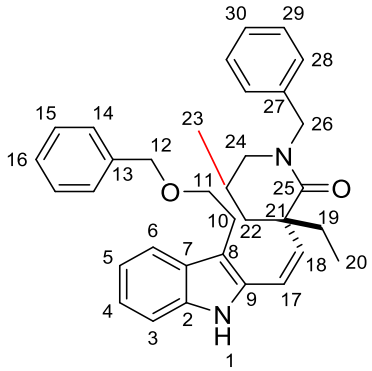
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.15 (m, 5H, **H1 + H2 + H3**), 6.72 (d, *J* = 8.4 Hz, 1H, **H11**), 6.38 (d, *J* = 8.3 Hz, 1H, **H12**), 5.05 (d, *J* = 14.5 Hz, 1H, **H5**), 4.20 (d, *J* = 14.5 Hz, 1H, **H5'**), 3.48 – 3.11 (m, 2H, **H10**), 2.49 – 2.15 (m, 1H, **H8**), 2.11 – 1.74 (m, 5H, **H13 + H9 + H8'**), 1.00 (t, *J* = 7.4 Hz, 3H, **H14**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8 **C6**, 144.3 **C11**, 137.3 **C4**, 128.5 **C2**, 128.5 **C3**, 127.3 **C1**, 78.7 **C12**, 50.8 **C5**, 50.0 **C7**, 47.5 **C10**, 31.5 **C13**, 29.1 **C8**, 19.5 **C9**, 9.0 **C14**.

υ_{max} (neat): 2936, 1632, 1487, 1294, 1194, 696 cm^{-1}.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{16}H_{20}INNaO$) requires *m/z* 392.0487, found *m/z* 392.0470.

5e



A flame-dried round bottom flask was charged successively with **5d** (1.74 g, 4.71 mmol, 1.00 equiv.), **3p** (2.87 g, 7.06 mmol, 1.50 equiv.), Cs_2CO_3 (4.61 g, 14.1 mmol, 3.00 equiv.) and $Pd(dppf)Cl_2$ (165 mg, 236 µmol, 5.00 mol%). The flask was purged with nitrogen before THF (47.1 mL) was charged followed by water (1.27 mL, 70.7 mmol, 15.0 equiv.) then the reaction mixture was stirred at 65 °C under nitrogen for 20 hours. The reaction mixture was cooled to room temperature then brine (50 mL) was added and the reaction mixture was extracted with EtOAc (3 x 50 mL), the combined organics were dried over Na_2SO_4, filtered, and concentrated prior to flash column chromatography (silica gel, 5-20% EtOAc in hexane) to give the title product as a light yellow oil (2.07 g, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) (only peaks belonging to *Z* isomer reported) δ 12.38 (s, 1H, **H1**), 7.58 (d, *J* = 7.9 Hz, 1H, **H6**), 7.49 (d, *J* = 8.2 Hz, 1H, **H3**), 7.38 – 7.25 (m, 8H, **Ph-H**), 7.25 – 7.22 (m, 2H, **Ph-H**), 7.18 (t, *J* = 8.2 Hz, 1H, **H4**), 7.07 (td, *J* = 7.5, 7.0, 1.0 Hz, 1H, **H5**), 6.74 (d, *J* = 13.2 Hz, 1H, **H17**), 5.42 (d, *J* = 13.2 Hz, 1H, **H18**), 4.78 – 4.64 (m, 2H, **H26**), 4.57 (s, 2H, **H12**), 3.69 (pd, *J* = 9.3, 6.2 Hz, 2H, **H11**), 3.35 – 3.08 (m, 4H, **H10** + **H24**), 2.17 – 1.83 (m, 6H, **H19** + **H22** + **H23**), 0.78 (t, *J* = 7.4 Hz, 3H, **H20**).

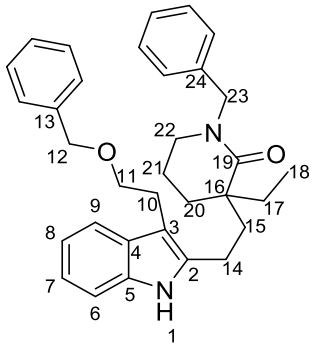
^{13}C NMR (126 MHz, $CDCl_3$) (only peaks belonging to *Z* isomer reported) δ 174.1 **C25**, 138.6 **C13**, 136.9 **C27**, 136.1 **C2**, 131.5 **C9**, 130.5 **C18** 122.0 **C17**, 118.5 **C6**, 112.3 **C3**, 111.5 **C8**, 73.0 **C12**, 71.1 **C11**, 51.2 **C26**, 47.6 **C24**, 47.3 **C21**, 33.6 **C22**, 25.3 **C10**, 19.4 **C23**, 18.7 **C19**, 8.9 **C20**. Aromatic methine carbons have not been included owing to the

convolution around the aromatic region for these signals, meaning major and minor peaks could not be discerned.

υ_{max} (neat): 3327, 2972, 2359, 1609, 1452, 1088, 1045, 737, 698 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{33}H_{37}N_2O_2$) requires *m/z* 493.2855 , found *m/z* 493.2852.

5f



5e (526 mg, 1.07 mmol, 1.00 equiv.) was dissolved in EtOAc (11 mL) and Pd/C (10 wt%, 114 mg, 0.107 mmol, 10 mol%) was added. The suspension was then stirred vigorously as it was sparged with a balloon of hydrogen then the needle was moved into the headspace and an atmosphere of hydrogen was maintained as the reaction was stirred at room temperature. After 3 hours, the reaction mixture was passed through a plug of celite and washed with copious amounts of MeOH (*ca.* 100 mL) then the filtrate was concentrated *in vacuo* prior to purification by flash column chromatography (silica gel, 10-30% EtOAc in hexane) to give the product as a light brown oil (527 mg, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H, **H1**), 7.51 (dd, *J* = 7.7, 1.2 Hz, 1H, **H9**), 7.37 – 7.23 (m, 11H, **H6 + Ph-H**), 7.12 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H, **H7**), 7.07 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H, **H8**), 4.69 (d, *J* = 14.6 Hz, 1H, **H23**), 4.59 – 4.53 (m, 3H, **H23' + H12**), 3.73 – 3.63 (m, 2H, **H11**), 3.24 (dd, *J* = 7.8, 3.9 Hz, 2H, **H22**), 3.05 (t, *J* = 7.6 Hz, 2H, **H10**), 2.91 (ddd, *J* = 14.3, 10.6, 6.5 Hz, 1H, **H14**), 2.54 (ddd, *J* = 14.5, 10.5, 4.2 Hz, 1H, **H14'**), 2.15 (ddd, *J* = 13.6, 10.6, 4.2 Hz, 1H, **H15**), 1.93 – 1.64 (m, 7H, **H15' + H17 + H20 + H21**), 0.90 (t, *J* = 7.5 Hz, 3H, **H18**).

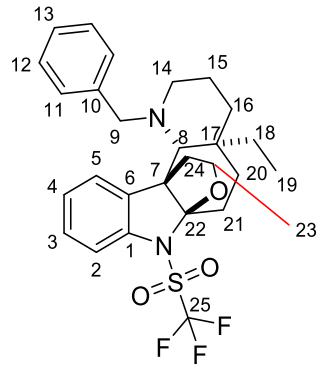
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1 **C19**, 138.6 **C13**, 137.5 **C24**, 137.4 **C2**, 135.6 **C5**, 128.7 **Ph-C**, 128.4 **C4**, 128.3 **Ph-C**, 127.9 **Ph-C**, 127.7 **Ph-C**, 127.5 **Ph-C**, 127.4 **Ph-C**,

120.9 **C7**, 118.8 **C8**, 117.9 **C9**, 110.6 **C6**, 107.2 **C3**, 73.0 **C12**, 71.0 **C11**, 50.7 **C23**, 47.8 **C22**, 45.8 **C16**, 38.3 **C15**, 31.7 **C20**, 28.9 **C21**, 25.0 **C10**, 21.6 **C14**, 19.6 **C17**, 8.5 **C18**.

υ_{max} (neat): 3277, 2936, 1609, 1452, 1096, 737, 696 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{33}H_{39}N_2O_2$) requires *m/z* 495.3012, found *m/z* 495.2997.

5j



A solution of **5f** (524 mg, 1.06 mmol, 1.00 equiv.) and 2,6-di-*tert*-butyl-4-methylpyridine (435 mg, 2.12 mmol, 2.00 equiv.) in DCM (21 mL) was stirred at room temperature and Tf_2O (268 µL, 1.59 mmol, 1.50 equiv.) was added slowly dropwise, then this solution was allowed to stir at room temperature for 30 minutes. The reaction mixture was then cooled to 0 °C before MeOH (20 mL) was added followed by portion-wise addition of $NaBH_4$ (120 mg, 3.18 mmol, 3.00 equiv.), after complete addition the reaction ice bath was removed and the effervescent solution was allowed to room temperature, stirred for a further hour then brine (20 mL) was added. The layers were split, and the aqueous layer was extracted with DCM (5 x 10 mL), the combined organics were dried over Na2SO4, filtered, and concentrated in vacuo prior to purification by flash column chromatography (silica gel, 1–10% Et_2O in hexane) to yield the title product as a white foam (223 mg, 40%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.4 Hz, 1H, **H5**), 7.50 (d, *J* = 7.5 Hz, 3H, **H2** + **H11**), 7.43 (t, *J* = 7.7 Hz, 2H, **H12**), 7.32 (t, *J* = 7.3 Hz, 1H, **H13**), 7.19 (ddd, *J* = 8.5, 7.6, 1.4 Hz, 1H, **H3**), 6.95 (t, *J* = 8.1 Hz, 1H, **H4**), 4.59 (d, *J* = 13.5 Hz, 1H, **H9**), 4.42 – 4.23 (m, 2H, **H23**), 3.36 (d, *J* = 13.6 Hz, 1H, **H9**), 3.28 – 3.15 (m, 1H, **H14**), 2.83 (ddd, *J* = 13.0, 7.4, 3.8 Hz, 1H, **H24**), 2.58 (dt, *J* = 14.5, 4.1 Hz, 1H, **H21**), 2.50 (s, 1H, **H8**), 2.20 (dt, *J* = 13.0, 9.3 Hz, 1H, **H24'**), 2.15 – 2.05 (m, 2H, **H21** + **H18**), 1.95 (td, *J* = 12.3, 3.2 Hz, 1H, **H14'**),

1.86 – 1.67 (m, 2H, **H15** + **H16**), 1.55 (dt, *J* = 14.4, 4.2 Hz, 1H, **H20**), 1.49 – 1.34 (m, 1H, **H15'**), 1.28 – 1.20 (m, 1H, **H20'**), 1.08 – 0.95 (m, 2H, **H16' + H18'**), 0.63 (t, *J* = 7.5 Hz, 3H, **H19**).

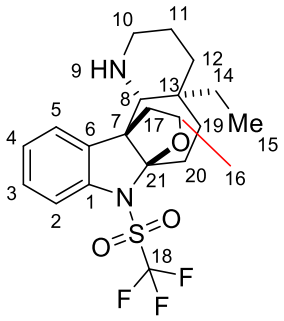
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0 **C10**, 137.3 **C1**, 133.9 **C6**, 128.8 **C12**, 128.3 **C3**, 127.3 **C5**, 127.2 **C11**, 127.0 **C13**, 124.3 **C4**, 117.2 **C22**, 114.6 **C2**, 73.3 **C8**, 68.4 **C23**, 61.3 **C9**, 56.43 **C14**, 56.40 **C7**, 43.1 **C24**, 38.3 **C17**, 35.5 **C16**, 30.1 **C20**, 28.9 **C21**, 21.5 **C15**, 20.7 **C18**, 6.7 **C19**. **C25** is not detected.

^{19}F NMR (470 MHz, $CDCl_3$) δ -76.4.

υ_{max} (neat): 3734, 2359, 1395, 1213, 1192, 669 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{27}H_{32}F_3N_2O_3S$) requires *m/z* 521.2086, found *m/z* 521.2067.

5k



5j (238 mg, 457 µmol, 1.00 equiv.) was dissolved in a mixture of EtOH (7.6 mL), AcOH (15.2 mL) and $Pd(OH)_2$ (385 mg, 549 µmol, 1.20 equiv.), then the suspension was sparged with hydrogen before the needle was moved to the headspace and an atmosphere of hydrogen was maintained as the reaction mixture was stirred vigorously at room temperature. After 20 hours, the reaction mixture was filtered through celite and the cake washed with copious MeOH (*ca.* 100 mL). The filtrate was then concentrated to a low volume, taken up in DCM (10 mL) and 1 M NaOH was carefully added until a pH of *ca.* 10 was achieved, then the layers were split and the aqueous layer was extracted with DCM (5 x 10 mL), the combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to flash column chromatography (silica gel, 20–60% EtOAc in hexane with 1% Et_3N) to afford the product as a white solid (147 mg, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.6 Hz, 1H, **H5**), 7.49 (d, *J* = 8.3 Hz, 1H, **H2**), 7.23 (t, *J* = 7.9 Hz, 1H, **H3**), 7.06 (t, *J* = 7.6 Hz, 1H, **H4**), 4.21 (q, *J* = 7.7 Hz, 1H, **H16**), 4.03 (q, *J* = 8.1 Hz, 1H, **H16'**), 3.33 (d, *J* = 10.6 Hz, 1H, **H10**), 2.78 – 2.68 (m, 1H, **H10'**), 2.66 (s, 1H, **H8**), 2.51 – 2.41 (m, 2H, **H17 + H20**), 2.30 (td, *J* = 11.6, 11.0, 5.8 Hz, 1H, **H20'**), 2.09 (dt, *J* = 13.0, 7.6 Hz, 1H, **H17'**), 1.81 (d, *J* = 13.5 Hz, 1H, **H12**), 1.73 – 1.48 (m, 5H, **H11** + **H14** + **H19**), 1.43 (d, *J* = 13.4 Hz, 1H, **H11'**), 1.24 – 1.16 (m, 1H, **H19'**), 1.02 (td, *J* = 13.5, 4.0 Hz, 1H, **H12'**), 0.64 – 0.56 (m, 4H, **H14'** + **H15**).

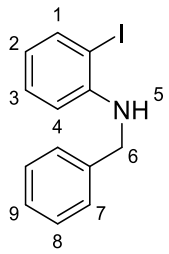
^{13}C NMR (126 MHz, $CDCl_3$) δ 138.1 **C1**, 133.6 **C6**, 128.4 **C3**, 125.9 **C5**, 124.6 **C4**, 114.4 **C2**, 113.6 **C21**, 68.6 **C8**, 68.4 **C16**, 57.4 **C7**, 49.3 **C10**, 41.4 **C17**, 35.4 **C13**, 35.2 **C12**, 30.6 **C19**, 29.7 **C20**, 22.6 **C11**, 20.3 **C14**, 7.0 **C15**. **C18** is not detected.

^{19}F NMR (470 MHz, $CDCl_3$) δ -75.6.

υ_{max} (neat): 2925, 1456, 1391, 1207, 935 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{26}F_3N_2O_3S$) requires *m/z* 431.1616, found *m/z* 431.1596.

5l



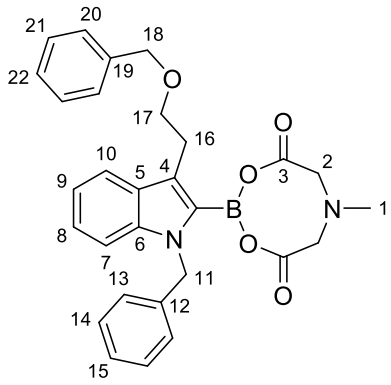
2-iodoaniline (1.10 g, 5.00 mmol, 1.00 equiv.), benzaldehyde (610 μL, 6.00 mmol, 1.20 equiv) and $ZnCl_2$ (818 mg, 6.00 mmol, 1.20 equiv.) were suspended in MeOH (50 mL) then sodium cyanoborohydride (377 mg, 6.00 mmol, 1.20 equiv.) was added before heating to reflux overnight. The reaction was then quenched by addition of 1 M NaOH, then EtOAc (*ca.* 50 mL) was added, the layers were split and the aqueous layer was extracted with EtOAc (3 x 50 mL), the combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to purification by flash column chromatography (silica gel, 2–4% Et_2O in hexane) to afford the title product as a light brown oil (1.28 g, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.9 Hz, 1H, **H1**), 7.47 – 7.31 (m, 5H, **H7** + **H8** + **H**9), 7.19 (t, *J* = 7.7 Hz, 1H, **H3**), 6.57 (d, *J* = 8.2 Hz, 1H, **H4**), 6.49 (t, *J* = 7.5 Hz, 1H, **H2**), 4.66 (brs, 1H, **H5**), 4.44 (d, *J* = 5.1 Hz, 2H, **H6**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1, 139.0, 138.7, 129.5, 128.8, 127.4, 127.2, 118.9, 111.0, 85.3, 48.4.

Spectral data in agreement with literature values.[130]

5m



An oven-dried 5 mL microwave vial was charged successively with $Pd(dppf)Cl_2$ (36.6 mg, 50.0 μmol, 5.00 mol%), **1f** (315 mg, 1.00 mmol, 1.0 equiv.), **4l** (371 mg, 1.20 mmol, 1.20 equiv.) and NaOAc (205 mg, 2.50 mmol, 2.50 equiv.). The vial was capped and purged with nitrogen, then DMSO (2.00 mL) was added before being heated to 80 °C for 18 hours. The vial was cooled to room temperature, decapped and diluted with EtOAc (10 mL) then washed with 10% aqueous LiCl solution (2 x 5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to flash column chromatography (silica gel, 0–20% MeCN in DCM) to give the title product as a tan solid (461 mg, 93%).

^{z1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.9 Hz, 1H, **H10**), 7.43 (d, *J* = 8.3 Hz, 1H, **H7**), 7.37 – 7.17 (m, 10H, **H8** + **H9** + **H14** + **H15** + **H20** + **H21** + **H22**), 7.16 – 7.09 (m, 2H, **H13**), 5.57 (brs, 2H, **H11**), 4.39 (brs, 2H, **H18**), 3.96 (t, *J* = 5.8 Hz, 2H, **H17**), 3.57 – 3.14 (m, 4H, **H2 + H16**), 1.80 (s, 3H, **H1**). **H2'** protons are not observed.

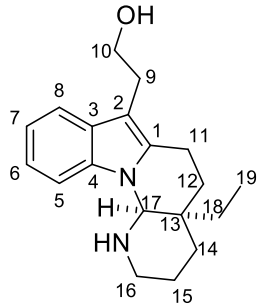
^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9 **C3**, 140.7 **C6**, 139.2 **C12**, 137.7 **C19**, 128.9 **C21**, 128.7 **C14**, 128.5 **C10**, 128.2 **C5**, 128.1 **C22**, 127.6 **C15**, 127.0 **C13**, 123.31 **C4**, 123.28 **C8**, 119.21 **C9**, 119.16 **C10**, 109.8 **C7**, 73.6 **C18**, 71.4 **C17**, 63.1 **C2**, 48.3 **C11**, 47.3 **C1**, 26.7 **C16**. The carbon bearing boron is not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz, $CDCl_3$) δ 11.0.

υ_{max} (solid): 1763, 1452, 1281, 1026, 735, 694 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{29}H_{30}BN_2O_5$) requires *m/z* 497.2248, found *m/z* 497.2234.

Goniomitine



A mixture of **5t** (73.0 mg, 0.15 mmol, 1.00 equiv.) and $Pd(OH)_2$ (20 wt.% on carbon, 128 mg, 0.18 mmol, 1.20 equiv.) in EtOH (2.5 mL) and AcOH (5.1 mL) was sparged with hydrogen before the hydrogen balloon was replaced and the needle removed from the liquid into the headspace and an atmosphere of hydrogen was maintained while stirring at room temperature. After 3 hours, the reaction mixture was filtered through a pad of celite and the cake was washed with copious amounts of MeOH (*ca.* 100 mL). The filtrate was concentrated to a small volume, taken up in DCM (20 mL) and 1 M NaOH was carefully added until a pH of *ca.* 10 was achieved. The layers were split and the aqueous layer was extracted with DCM (5 x 10 mL) then the combined organics were dried over Na_2SO_4, filtered, and concentrated prior to purification by flash column chromatography (silica gel, 2–5% MeOH in DCM) to give the title product as a light yellow residue (19.0 mg, 42%).

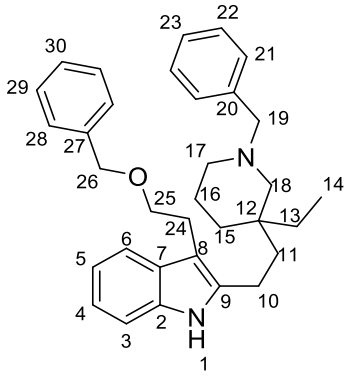
^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.7 Hz, 1H, **H8**), 7.32 (d, *J* = 7.9 Hz, 1H, **H5**), 7.19 – 7.15 (m, 1H, **H6**), 7.11 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, **H7**), 4.82 (s, 1H, **H17**), 3.85 (t, *J* = 6.4 Hz, 2H, **H10**), 3.12 – 3.04 (m, 2H, **H11 + H16**), 2.96 (td, *J* = 6.5, 3.4 Hz, 2H, **H9**), 2.90 – 2.78 (m, 2H, **H11' + H16'**), 2.53 (td, *J* = 13.1, 6.7 Hz, 1H, **H14**), 1.94 – 1.85 (m, 1H, **H12**), 1.80 – 1.68 (m, 1H, **H14'**), 1.62 (dd, *J* = 14.3, 7.4 Hz, 1H, **H18**), 1.58 – 1.47 (m, 3H, **H12' + H15**), 1.34 – 1.13 (m, 1H, **H18'**), 0.90 (t, *J* = 7.5 Hz, 3H, **H19**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.4 **C4**, 132.8 **C1**, 129.1 **C3**, 120.6 **C6**, 119.6 **C7**, 118.1 **C8**, 108.2 **C5**, 106.0 **C2**, 71.5 **C17**, 62.6 **C16**, 45.6 **C10**, 35.1 **C13**, 34.0 **C14**, 28.6 **C18**, 27.7 **C9**, 21.6 **C12**, 21.5 **C15**, 18.5 **C11**, 7.1 **C19**.

υ_{max} (solid): 3303, 2926, 2853, 1460, 1308, 1043, 737 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{27}N_2O$) requires *m/z* 299.2123, found *m/z* 299.2110.

5p



A suspension of $LiAlH_4$ (637 mg, 16.8 mmol, 5.00 equiv.) in THF (34 mL) was cooled to 0 °C and to this was charged **5f** as a solution in THF (34 mL) *via* cannula. After complete addition, the reaction mixture was warmed to room temperature and stirred for 24 hours before being cooled to 0 °C and diluted with Et_2O (20 mL). Water (0.64 mL) was slowly added, followed by 2 M NaOH (0.64 mL) then water (1.92 mL) and finally $MgSO_4$. The grey suspension was stirred at room temperature for one hour before being filtered, and the filtrate was concentrated *in vacuo* prior to flash column chromatography (silica gel, 5–20% EtOAc in hexane with 1% Et_3N) to give the product as a clear, colourless oil (1.24 g, 77%).

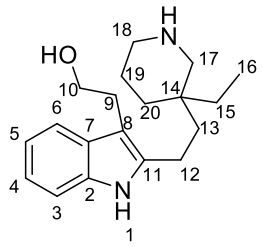
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (brs, 1H, **H1**), 7.53 (dd, *J* = 7.5, 1.4 Hz, 1H, **H6**), 7.45 – 7.23 (m, 11H, **H21** + **H22** + **H23** + **H28** + **H29** + **H30**), 7.13 (td, *J* = 7.9, 7.5, 1.4 Hz, 1H, **H4**), 7.09 (td, *J* = 7.4, 1.3 Hz, 1H, **H5**). 4.56 (s, 2H, **H26**), 3.69 (t, *J* = 7.7 Hz, 2H, **H25**), 3.48 (s, 2H, **H19**), 3.06 (t, *J* = 7.7 Hz, 2H, **H24**), 2.72 – 2.57 (m, 2H, **H10** + **H18**), 2.47 (ddd, *J* = 14.5, 11.9, 4.9 Hz, 1H, **H10'**), 2.38 – 2.19 (m, 2H, **H17** + **H18'**), 1.99 (brs, 1H, **H17'**), 1.91 – 1.79 (m, 2H, **H11**), 1.76 – 1.56 (m, 2H, **H16**), 1.55 – 1.23 (m, 4H, **H15 + H13**), 0.84 (t, *J* = 7.5 Hz, 3H, **H14**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0 **C20**, 138.6 **C27**, 137.1 **C9**, 135.3 **C2**, 129.0 **C21**, 128.7 **C7**, 128.4 **C22**, 128.2 **C29**, 127.7 **C28**, 127.5 **C23**, 127.0 **C30**, 120.9 **C4**, 119.1 **C5**, 118.0 **C6**, 110.3 **C3**, 107.3 **C8**, 73.0 **C26**, 70.9 **C25**, 63.5 **C19**, 62.2 **C17**, 54.9 **C18**, 35.9 **C12**, 34.2 **C11**, 33.9 **C13**, 28.8 **C15**, 25.1 **C24**, 21.9 **C16**, 19.8 **C10**, 7.4 **C14**.

υ_{max} (solid): 2931, 1701, 1462, 1096, 734, 696 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{33}H_{41}N_2O$) requires *m/z* 481.3219, found *m/z* 481.3197.

5q



A suspension of **5p** (1.28 g, 2.66 mmol, 1.00 equiv.) and $Pd(OH)_2$ (20 wt.% on carbon, 2.24 g, 3.20 mmol, 1.20 equiv.) in EtOH (44 mL) and AcOH (89 mL) was stirred vigorously at room temperature and sparged with hydrogen. The needle was then moved to the headspace to maintain an atmosphere of hydrogen while stirring at room temperature for 20 hours before being filtered through celite and the cake was washed with a copious amount of MeOH (*ca.* 100 mL). The filtrate was concentrated to a low volume then 1 M NaOH was added until a pH of *ca.* 10 was achieved, then this aqueous layer was extracted with DCM (5 x 50 mL), the combined organics were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* prior to purification by flash column chromatography (silica gel, 2–20% MeOH in DCM with 1% Et_3N) to give the title product as a pale yellow foam (434 mg, 54%).

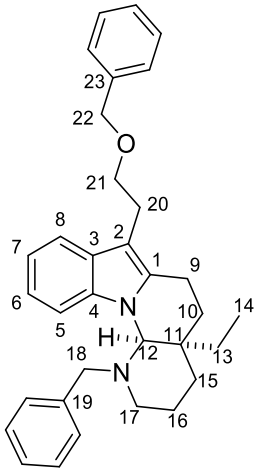
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (s, 1H, **H1**), 7.53 (d, *J* = 7.7 Hz, 1H, **H6**), 7.33 (d, *J* = 8.0 Hz, 1H, **H3**), 7.16 – 7.04 (m, 2H, **H4** + **H5**), 4.03 – 3.80 (m, 2H, **H10**), 3.18 (d, *J* = 12.0 Hz, 1H, **H18**), 3.08 – 2.93 (m, 3H, **H9** + **H17**), 2.78 – 2.54 (m, 3H, **H12** + **H18'**), 2.45 (d, *J* = 12.7 Hz, 1H, **H17'**), 2.23 – 2.17 (m, 1H, **H13**), 1.87 – 1.74 (m, 1H, **H19**), 1.67 – 1.41 (m, 4H, **H19'** + **H20** + **H13'** + **H15**), 1.36 – 1.20 (m, 2H, **H20' + H15'**), 0.91 (t, *J* = 7.5 Hz, 3H, **H16**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.3 **C11**, 135.7 **C2**, 128.3 **C7**, 121.0 **C4**, 118.9 **C5**, 117.9 **C6**, 110.7 **C3**, 106.6 **C8**, 62.7 **C10**, 51.7 **C17**, 45.3 **C18**, 34.7 **C14**, 33.5 **C20**, 27.9 **C13**, 25.1 **C9**, 24.9 **C15**, 19.9 **C19**, 19.6 **C12**, 6.9 **C16**.

υ_{max} (solid): 3248, 2930, 1560, 1462, 1043, 737 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{29}NO_2$) requires *m/z* 301.2280, found *m/z* 301.2271.

5t



A solution of **5f** (143 mg, 0.29 mmol, 1.00 equiv.) in THF (6.1 mL) was cooled to -78 °C and DIBAL-H (1.0 M in THF, 1.45 mL, 1.45 mmol, 5.0 equiv.) was added dropwise over 5 minutes. After complete addition, the reaction mixture was allowed to warm to room temperature, then stirred for a further hour, quenched with saturated Rochelle's salt solution (10 mL) and stirred overnight at room temperature. The layers were split and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated prior to flash column chromatography (silica gel, 5–40% EtOAc in hexane) to give the title product as a clear, colourless residue (76 mg, 55%).

^{1}H NMR (500 MHz $CDCl_3$) δ 7.53 – 7.48 (m, 1H, **H8**), 7.40 (d, *J* = 8.2 Hz, 1H, **H5**), 7.38 – 7.25 (m, 5H, **Ph-H**), 7.21 – 7.11 (m, 4H, **H6 + Ph-H**), 7.12 – 7.05 (m, 3H, **H7 + Ph-H**), 4.55 (s, 2H, **H22**), 4.33 (s, 1H, **H12**), 3.67 (t, *J* = 7.7 Hz, 2H, **H21**), 3.60 (d, *J* = 13.2 Hz, 1H, **H18**), 3.23 (ddd, *J* = 16.3, 9.5, 5.1 Hz, 1H, **H9**), 3.12 – 2.97 (m, 3H, **H20 + H9'**), 2.94 (d, *J* = 13.3 Hz, 3H, **H18' + H17**), 2.52 (ddd, *J* = 13.4, 9.5, 5.9 Hz, 1H, **H10**), 2.15 (td, *J* = 12.1,

2.7 Hz, 1H, **H17'**), 1.92 – 1.68 (m, 2H, **H15 + H16**), 1.56 – 1.42 (m, 3H, **H15' + H16' + H10'**), 1.04 – 0.80 (m, 2H, **H13**), 0.70 (t, *J* = 7.5 Hz, 3H, **H14**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.1 **C19**, 138.7 **C23**, 137.3 **C4**, 133.6 **C1**, 128.4 **C5**, 128.3 **Ph-C**, 127.9 **Ph-C**, 127.6 **Ph-C**, 127.4 **Ph-C**, 126.4 **Ph-C**, 120.1 **Ph-C**, 119.0 **Ph-C**, 117.9 **C8**, 108.6 **C5**, 106.3 **C2**, 76.7 **C12**, 73.0 **C22**, 70.8 **C21**, 57.5 **C18**, 52.0 **C17**, 38.5 **C11**, 33.8 **C15**, 30.7 **C13**, 25.0 **C20**, 24.0 **C10**, 21.2 **C16**, 18.2 **C9**, 7.6 **C14**.

υ_{max} (solid): 3734, 3628, 2922, 2851, 2361, 1458, 1096, 735, 696, 669 cm^{-1}.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{33}H_{39}N_2O$) requires *m/z* 479.3062, found *m/z* 479.3053.

X-ray crystallographic data.

5k

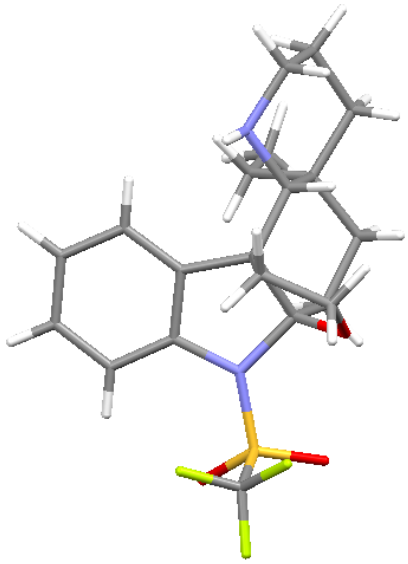


Table 1 Crystal data and structure refinement for 5k.	
Identification code	4 (2)
Empirical formula	$C_{21}H_{19}BN_2O_5$
Formula weight	390.20
Temperature/K	173
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	14.7636(15)
b/Å	12.0831(12)
c/Å	10.7076(11)
α/°	90.0000
β/°	97.887(2)
γ/°	90.0000
Volume/Å^3	1892.1(3)
Z	4
ρ_{calc}g/cm^3	1.370
μ/mm^{-1}	0.097
F(000)	816.0
Crystal size/mm^3	0.100 × 0.100 × 0.020
Radiation	Mo Kα (λ = 0.71075)
2Θ range for data collection/°	5.562 to 50.718
Index ranges	-17 ≤ h ≤ 17, -14 ≤ k ≤ 14, -12 ≤ l ≤ 12
Reflections collected	35689
Independent reflections	3469 [R_{int} = 0.1314, R_{sigma} = 0.0503]
Data/restraints/parameters	3469/0/264
Goodness-of-fit on F^2	1.053
Final R indexes [I>=2σ (I)]	R_1 = 0.0525, wR_2 = 0.1332

Final R indexes [all data]	R_1 = 0.0590, wR_2 = 0.1415
Largest diff. peak/hole / e Å^{-3}	0.39/-0.23

References

[1] S. M. Bronner, G. Y. J. Im, N. K. Garg, *Heterocycles Nat. Prod. Synth.* **2011**, 221–265.

[2] D. Zhao, Y. Yu, Y. Shen, Q. Liu, Z. Zhao, R. Sharma, R. J. Reiter, *Front. Endocrinol. (Lausanne).* **2019**, *10*, 1–16.

[3] A. Carrillo-Vico, J. M. Guerrero, P. J. Lardone, R. J. Reiter, *Endocrine* **2005**, *27*, 189–200.

[4] L. Wang, H. Erlandsen, J. Haavik, P. M. Knappskog, R. C. Stevens, *Biochemistry* **2002**, *41*, 12569–12574.

[5] C. P. Snook, *Crit. Care Toxicol.* **2016**, DOI 10.1007/978-3-319-20790-2.

[6] J. G. Susset, C. D. Tessier, J. Wincze, S. Bansal, C. Malhotra, M. G. Schwacha, *J. Urol.* **1989**, *141*, 1360–1363.

[7] I. S. Johnson, J. G. Armstrong, M. Gorman, J. P. Burnett, *Cancer Res.* **1963**, *23*, 1390–1427.

[8] J. Kobayashi, M. Sekiguchi, S. Shimamoto, H. Shigemori, H. Ishiyama, A. Ohsaki, *J. Org. Chem.* **2002**, *67*, 6449–6455.

[9] S. E. O'Connor, E. McCoy, *Recent Adv. Phytochem.* **2006**, *40*, 1–22.

[10] T. Passie, J. H. Halpern, D. O. Stichtenoth, H. M. Emrich, A. Hintzen, *CNS Neurosci. Ther.* **2008**, *14*, 295–314.

[11] O. Repič, K. Prasad, G. T. Lee, *Org. Process Res. Dev.* **2001**, *5*, 519–527.

[12] S. H. Ferreira, S. Moncada, J. R. Vane, *Nat. New Biol.* **1971**, *231*, 237–239.

[13] G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875–2911.

[14] E. Fischer, F. Jourdan, *Eur. J. Inorg. Chem.* **1883**, 2241–2245.

[15] E. Fischer, O. Hess, *Berichte der Dtsch. Chem. Gesellschaft* **1884**, *17*, 559–568.

[16] G. M. Robinson, R. Robinson, *J. Chem. Soc. Trans.* **1924**, 827–840.

[17] C. F. H. Allen, C. V Wilson, *J. Am. Chem. Soc.* **1943**, *65*, 611–612.

[18] M. Inman, C. J. Moody, *Chem. Sci.* **2013**, *4*, 29–41.

[19] R. B. Woodward, M. P. Cava, *J. Am. Chem. Soc.* **1954**, *76*, 4749–4751.

[20] G. Stork, J. E. Dolfini, *J. Am. Chem. Soc.* **1963**, *85*, 2872–2873.

[21] R. Iyengar, K. Schildknegt, M. Morton, J. Aube, *J. Org. Chem.* **2005**, *70*, 10645–10652.

[22] T. Fukuyama, H. Ueda, H. Satoh, K. Matsumoto, K. Sugimoto, H. Tokuyama, *Angew. Chem., Int. Ed.* **2009**, *48*, 7600–7603.

[23] L. A. Hobson, W. A. Nugent, S. R. Anderson, S. S. Deshmukh, *Org. Proc. Res. Dev.* **2007**, *11*, 985–995.

[24] F. R. Japp, F. Klingemann, *Berichte Der Dtsch. Chem. Gesellschaft* **1887**, *20*, 2942–2944.

[25] B. A. Haag, Z. Zhang, J. Li, P. Knochel, *Angew. Chem., Int. Ed.* **2010**, *49*, 9513–9516.

[26] M. Inman, C. J. Moody, *Chem. Comm.* **2011**, *47*, 788–790.

[27] S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *7863*, 6621–6622.

[28] J. Chae, S. L. Buchwald, *J. Org. Chem.* **2004**, *69*, 3336–3339.

[29] U. Milano, M. D. Ennis, E. Mark, W. Smith, C. F. Lawson, R. B. Mccall, *J. Med. Chem.* **1992**, *35*, 3058–3066.

[30] M. Stradiotto, R. J. Lundgren, *Angew. Chem., Int. Ed.* **2010**, *49*, 8686–8690.

[31] M. F. Greaney, D. McAusland, S. Seo, D. G. Pintori, J. Finlayson, *Org. Lett.* **2011**, *13*, 3667–3669.

[32] G. Bartoli, G. Palmieri, S. Chimiche, C. Mc, M. Bosco, R. Dalpozzo, *Tetrahedron Lett.* **1989**, *30*, 2129–2132.

[33] W. Leimgruber, *Org. Synth.* **1985**, *63*, 214.

[34] C. E. Castro, E. J. Gaughan, D. C. Owsley, *J. Org. Chem.* **1966**, *31*, 4071–4078.

[35] A. L. Rodriguez, C. Koradin, W. Dohle, P. Knochel, *Angew. Chem., Int. Ed.* **2000**, *39*, 2488–2490.

[36] A. Andries-Ulmer, C. Brunner, J. Rehbein, T. Gulder, *J. Am. Chem. Soc.* **2018**, *140*, 13034–13041.

[37] M. Mori, K. Chiba, Y. Ban, *Tetrahedron Lett.* **1977**, *18*, 1037–1040.

[38] C. Chen, D. R. Lieberman, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *J. Org. Chem.* **1997**, *2*, 2676–2677.

[39] M. E. Krolski, A. F. Renaldo, D. E. Rudisill, J. K. Stille, *J. Org. Chem.* **1988**, *53*, 1170–1176.

[40] Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui, N. Jiao, *Angew. Chem., Int. Ed.* **2009**, *48*, 4572–4576.

[41] D. Shi, Z. Guan, X. Yao, W. Shi, H. Chen, *ChemistrySelect* **2016**, *1*, 119–121.

[42] S. Cacchi, F. Marinelip, *Tetrahedron Lett.* **1992**, *33*, 3915–3918.

[43] B. Z. Lu, W. Zhao, H. Wei, M. Dufour, V. Farina, C. H. Senanayake, E. L. Street, *Org. Lett.* **2006**, *8*, 3271–3274.

[44] R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874–922.

[45] R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690.

[46] C. Amatore, A. Jutand, A. Suarez, *J. Am. Chem. Soc.* **1993**, *115*, 9531–9541.

[47] C. Amatore, A. Jutand, G. Le Duc, *Chem. - A Eur. J.* **2011**, *17*, 2492–2503.

[48] S. Kozuch, C. Amatore, A. Jutand, S. Shaik, **2005**, 2319–2330.

[49] A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron Lett.* **1986**, *27*, 6397–6400.

[50] T. F. Walsh, R. B. Toupence, F. Ujjainwalla, J. R. Young, M. T. Goulet, *Tetrahedron Lett.* **2001**, *57*, 5233–5241.

[51] N. Gathergood, P. J. Scammells, *Org. Lett.* **2003**, *5*, 921–923.

[52] X. Liu, J. R. Deschamp, J. M. Cook, *Org. Lett.* **2002**, *4*, 3339–3342.

[53] M. Shen, G. Li, B. Z. Lu, A. Hossain, F. Roschangar, V. Farina, C. H. Senanayake, *Org. Lett.* **2004**, *6*, 4129–4132.

[54] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

[55] K. V Chuang, M. E. Kie, S. E. Reisman, *Org. Lett.* **2016**, *18*, 6–9.

[56] A. F. Littke, G. C. Fu, *Angew. Chem., Int. Ed.* **1999**, *37*, 3387–3388.

[57] N. A. Isley, Y. Endo, Z. Wu, B. C. Covington, L. B. Bushin, M. R. Seyedsayamdost, D. L. Boger, *J. Am. Chem. Soc.* **2019**, *141*, 17361–17369.

[58] J. Garfunkle, F. S. Kimball, J. D. Trzupek, S. Takizawa, H. Shimamura, M. Tomishima, D. L. Boger, *J. Am. Chem. Soc.* **2009**, *131*, 16036–16038.

[59] H. Shimamura, S. P. Breazzano, J. Garfunkle, F. S. Kimball, J. D. Trzupek, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 7776–7783.

[60] S. P. Breazzano, Y. B. Poudel, D. L. Boger, *J. Am. Chem. Soc.* **2013**, 1600–1606.

[61] P. He, Y. Du, G. Liu, C. Cao, Y. Shi, J. Zhang, G. Pang, *RSC Adv.* **2013**, *3*, 18345–18350.

[62] N. Phetrak, T. Rukkijakan, J. Sirijaraensre, S. Prabpai, P. Kongsaeree, C. Klinchan, P. Chuawong, *J. Org. Chem.* **2013**, *78*, 12703–12709.

[63] K. Yiamsawat, K. P. Gable, P. Chuawong, *J. Org. Chem.* **2022**, *87*, 1218–1229.

[64] S. E. Denmark, J. D. Baird, *Tetrahedron* **2009**, *65*, 3120–3129.

[65] X. Cai, V. Snieckus, *Org. Lett.* **2004**, *6*, 2293–2295.

[66] G. Chen, H. Ren, A. Turpoff, A. Arefolov, *Bioorganic Med. Chem. Lett.* **2013**, *23*, 3942–3946.

[67] C. N. Johnson, G. Stemp, N. Anand, S. C. Stephen, T. Gallagher, *Synlett* **1998**, 1025–1027.

[68] K. C. Nicolaou, S. M. Dalby, U. Majumder, *J. Am. Chem. Soc.* **2008**, *130*, 14942–14943.

[69] E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2008**, *130*, 14084–14085.

[70] J. L. Suk, K. C. Gray, J. S. Paek, M. D. Burke, *J. Am. Chem. Soc.* **2008**, *130*, 466–468.

[71] C. P. Seath, K. L. Wilson, A. Campbell, J. M. Mowat, A. J. B. Watson, *Chem. Comm.* **2016**, *52*, 8703–8706.

[72] D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963.

[73] B. P. Carrow, J. F. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 2116–2119.

[74] A. F. Schmidt, A. A. Kurokhtina, E. V. Larina, *Russ. J. Gen. Chem.* **2011**, *81*, 1573–1574.

[75] E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717.

[76] J. Li, S. G. Ballmer, E. P. Gillis, S. Fujii, M. J. Schmidt, A. M. E. Palazzolo, J. W. Lehmann, G. F. Morehouse, M. D. Burke, *Science (80-.).* **2015**, *347*, 1221–1226.

[77] R. B. Merrifield, *Science (80-.).* **1965**, *150*, 178–184.

[78] P. A. Cox, A. G. Leach, A. D. Campbell, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2016**, *138*, 9145–9157.

[79] P. A. Cox, M. Reid, A. G. Leach, A. D. Campbell, E. J. King, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2017**, *139*, 13156–13165.

[80] G. R. Dick, E. M. Woerly, M. D. Burke, *Angew. Chem., Int. Ed.* **2012**, *51*, 2667–2672.

[81] J. M. W. Chan, G. W. Amarante, F. D. Toste, *Tetrahedron* **2011**, *67*, 4306–4312.

[82] Y. Sakurai, *Heterocycles* **2017**, *94*, 1322–1336.

[83] L. Chu, J. E. Hutchins, A. E. Weber, J. Lo, Y. Yang, K. Cheng, R. G. Smith, M. H. Fisher, M. J. Wyvratt, M. T. Goulet, *Bioorganic Med. Chem. Lett.* **2001**, *11*, 509–513.

[84] S. J. Lee, T. M. Anderson, M. D. Burke, *Angew. Chemie - Int. Ed.* **2010**, *49*, 8860–8863.

[85] A. J. Bechamp, *Ann. Chim. Phys.* **1854**, *42*.

[86] R. Weinstain, A. Sagi, N. Karton, D. Shabat, *Chem. - A Eur. J.* **2008**, *14*, 6857–6861.

[87] J. A. Gonzalez, O. M. Ogba, G. F. Morehouse, N. Rosson, K. N. Houk, A. G. Leach, P. H. Y. Cheong, M. D. Burke, G. C. Lloyd-Jones, *Nat. Chem.* **2016**, *8*, 1067–1075.

[88] A. J. J. Lennox, G. C. Lloyd-Jones, *Chem. Soc. Rev.* **2014**, *43*, 412–443.

[89] D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963.

[90] R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652–7662.

[91] C. Amatore, A. Jutand, A. Thuilliez, *Organometallics* **2001**, *20*, 3241–3249.

[92] F. Ozawa, A. Kubo, T. Hayashi, *Chem. Lett.* **1992**, *21*, 2177–2180.

[93] C. Adamo, C. Amatore, I. Ciofini, A. Jutand, H. Lakmini, *J. Am. Chem. Soc.* **2006**, *128*, 6829–6836.

[94] H. U. Rahman, J. Tremont, *J. Am. Chem. Soc.* **1984**, *106*, 5759–5760.

[95] L. V. Politanskaya, I. P. Chuikov, E. V. Tretyakov, V. D. Shteingarts, L. P. Ovchinnikova, O. D. Zakharova, G. A. Nevinsky, *J. Fluor. Chem.* **2015**, *178*, 142–153.

[96] L. Fra, A. Millán, J. A. Souto, K. Muñiz, *Angew. Chemie - Int. Ed.* **2014**, *53*, 7349–7353.

[97] A. Ikeda, M. Omote, K. Kusumoto, M. Komori, A. Tarui, K. Sato, A. Ando, *Org. Biomol. Chem.* **2016**, *14*, 2127–2133.

[98] E. Morisset, A. Chardon, J. Rouden, J. Blanchet, *European J. Org. Chem.* **2020**, *2020*, 388–392.

[99] J. M. Mejía-Oneto, A. Padwa, *Org. Lett.* **2006**, *8*, 3275–3278.

[100] Q. Wen, J. Jin, Y. Mei, P. Lu, Y. Wang, *European J. Org. Chem.* **2013**, 4032–4036.

[101] S. Kathiravan, I. A. Nicholls, *Chem. - A Eur. J.* **2017**, *23*, 7031–7036.

[102] A. Bruch, R. Fröhlich, S. Grimme, A. Studer, D. P. Curran, *J. Am. Chem. Soc.* **2011**, *133*, 16270–16276.

[103] N. Chaisan, W. Kaewsri, C. Thongsornkleeb, J. Tummatorn, S. Ruchirawat, *Tetrahedron Lett.* **2018**, *59*, 675–680.

[104] C. Leitner, T. Gaich, *Chem. Commun.* **2017**, *53*, 7451–7453.

[105] K. L. Wilson, A. R. Kennedy, J. Murray, B. Greatrex, C. Jamieson, A. J. B. Watson, *Beilstein J. Org. Chem.* **2016**, *12*, 2005–2011.

[106] J. M. Lopchuk, *Recent Advances in the Synthesis of Aspidosperma-Type Alkaloids*,

Elsevier Ltd., **2011**.

[107] J. M. Saya, E. Ruijter, R. V. A. Orru, *Chem. - A Eur. J.* **2019**, *25*, 8916–8935.

[108] S. A. Kozmin, T. Iwama, Y. Huang, V. H. Rawal, *J. Am. Chem. Soc.* **2002**, *124*, 4628–4641.

[109] Y. He, Z. Li, K. Robeyns, L. Van Meervelt, E. V. Van der Eycken, *Angew. Chemie - Int. Ed.* **2018**, *57*, 272–276.

[110] I. P. Ceravolo, C. L. Zani, F. J. B. Figueiredo, M. Kohlhoff, A. E. G. Santana, A. U. Krettli, *Malar. J.* **2018**, *17*.

[111] P. M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach*, Wiley, **2009**.

[112] H. Ishikawa, D. A. Colby, D. L. Boger, *J. Am. Chem. Soc.* **2008**, *130*, 420–421.

[113] M. E. Hodes, R. J. Rohn, I. L. H. Bond, *Cancer Res.* **1960**, *20*, 1041–1049.

[114] R. A. Bohannon, D. G. Miller, H. D. Diamond, *Cancer Res.* **1963**, *23*, 613–621.

[115] R. J. Owellen, C. A. Hartke, R. M. Dickerson, F. O. Hains, *Cancer Res.* **1976**, *36*, 1499–1502.

[116] A. Kumar, *Int. J. Med. Pharm. Sci.* **2016**, *16*, 23–30.

[117] N. Wang, X. Jiang, *Chem. Rec.* **2021**, *21*, 295–314.

[118] E. Wenkert, K. G. Dave, C. T. Gnewuch, P. W. Sprague, *J. Am. Chem. Soc.* **1968**, *90*, 5251–5256.

[119] G. Pandey, P. Kumara, *Org. Lett.* **2011**, *13*, 4672–4675.

[120] Y. Ban, K. Yoshida, J. Goto, T. Oishi, *J. Am. Chem. Soc.* **1981**, 6990–6992.

[121] K. L. White, M. Movassaghi, *J. Am. Chem. Soc.* **2016**, *138*, 11383–11389.

[122] M. V. Mijangos, L. D. Miranda, *Org. Biomol. Chem.* **2018**, *16*, 9409–9419.

[123] B. Witkop, P. Cerutti, O. Yonemitsu, *J. Am. Chem. Soc.* **1966**, *88*, 3941–3945.

[124] E. Park, C. H. Cheon, *Adv. Synth. Catal.* **2019**, *361*, 4888–4892.

[125] G. Stork, K. Zhao, *Tetrahedron* **1989**, *30*, 2173–2174.

[126] M. Karplus, *J. Chem. Phys.* **1959**, *30*, 11–15.

[127] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

[128] B. Bajtos, B. L. Pagenkopf, *European J. Org. Chem.* **2009**, 1072–1077.

[129] D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil, B. M. Stoltz, *Nat. Chem.* **2012**, *4*, 130–133.

[130] S. R. Laursen, M. T. Jensen, A. T. Lindhardt, M. F. Jacobsen, T. Skrydstrup, *European J. Org. Chem.* **2016**, *2016*, 1881–1885.