Synthesis of multi-heteroaromatic compounds by platinum-catalysed nucleophilic addition to allenes

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Preface

The research in this thesis is, to the best of my knowledge, original and my own work except where due reference has been made.

Parts of this thesis will be used in the following publication, for which the manuscript is in preparation;

L. Cooper, J. M. Alonso, L. Eagling, H. Newson, S. Herath, C. Thompson, A. Lister, C. Howsham, B. Cox and M. P. Muñoz, *Chem. Eur. J.*, **2017**.

Lisa Cooper

November 2017

Dedicated to

Simon John Cooper 16.01.1967 – 09.02.2012

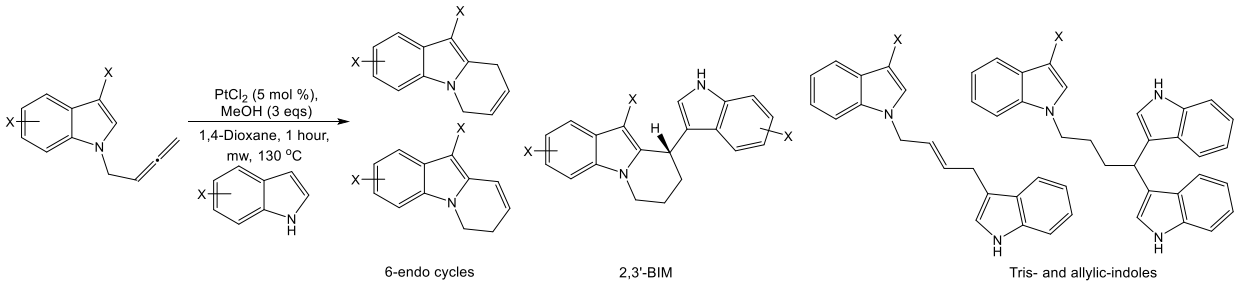
Kunbi Ajibade 30.11.1990 – 04.02.2012

I miss you both every day.

Abstract

This thesis describes the extensive investigation into the platinum-catalysed double addition of nucleophiles to allenes and in particular, our efforts towards the synthesis of 2,3'-bis-indolyl methanes (BIMs), which are important compounds with potential biologically important properties. The first chapter will describe the background of both inter- and intramolecular addition reactions to allenes with a range of different nucleophiles and array of metal catalysts. The latter part of this chapter will focus on the two synthetic strategies for BIM formation, firstly, the classical approach involving the Friedel-Crafts reaction between indoles and carbonyl compounds using protic or Lewis acid catalysis and secondly, the more recent methods involving the use of transition metal catalysis for the addition of indoles to π-bonds such as alkynes, allenes and cyclopropene *via* direct double hydroarylation.

The first part of the results and discussion chapter describes the attempts to expand the scope of the inter-intermolecular addition reaction of heteroatom and heteroaromatic nucleophiles to a model allene, generating a range of bis-substituted products. Despite an extensive investigation of both nucleophiles (e.g. imidazole, pyrazole, thiophenol and aniline) and the reaction conditions (e.g. incorporation of silver salts for chloride abstraction and gold catalysis), we could not extend the method efficiently enough for the formation of these compounds. Therefore, the second part of this chapter focuses on the successful intra-intermolecular platinum-catalysed addition reaction of an external indole to an indolyl allene with subsequent formation of 6-endo cycles, 2,3'-BIMs or tris- and allylic derivatives.



This section describes the optimisation of the reaction conditions to favour the formation of the desired 2,3'-BIM, an investigation to determine the effect that substituents on either the indolyl allene or the external indole has on the overall formation of the 2,3'-BIM and the 6-endo cycles, and a detailed mechanistic investigation to determine the overall mechanism of the reaction. A trend was found with EDG favouring the formation of the desired 2,3'-BIM and the EWG favouring the formation of the 6-endo cycles or the tris- and allylic derivatives. The mechanistic investigation revealed that the 6-endo cycles are intermediates in the formation of the 2,3'-BIM, with a platinum carbene complex as the key intermediate between the three products.

Acknowledgements

First, I would like to thank my supervisor Dr María Paz Muñoz-Herranz for her constant help and support throughout both my masters and PhD. I will be forever thankful to you for the opportunity to work in your group, for constantly believing in me, for helping me build my confidence over the years and for being a great supervisor as well as a friend. I would also like to thank Prof. Andrew Cammidge for his support and guidance as my secondary supervisor.

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I am extremely grateful for the friends and family that have supported me throughout my time at university, without them I would not have had as much fun as I have. So firstly, I must give a very special thank you to my dearest friend Emma Ainsworth who has been a constant support all the way through my undergraduate and post-graduate research, she has inspired me and helped me so much over the years. How you have stuck around I do not know, but I want you to know that for all those late nights in the library, the motivational talks and just generally being there when I have needed you I will never be able to thank you enough but please know that I am eternally grateful. I would also like to thank, Elizabeth Elliott, Teala Leeder, Michelle Woods and Jenny Lovell for being understanding, supportive and for always making me laugh, you truly are some of the best friends I could ask for.

My biggest thank you goes to my family, the constant lifeline I have whenever and wherever. You've been the best support I could ask for with everything that I do and continue to do and without that I would not be where I am today. I am thankful for all the memories that you have given me and for distracting me when I have needed it! I love each and every one of you more than I could ever express.

My love and extreme gratefulness goes to Alick, you truly are incredible and one of the smartest people I know. You have put up with the good and bad times, the late nights and listening to stuff you have no clue about. You have made this journey easier by just being there, so thank you for making me smile, laugh and carry on and I cannot wait to start our next chapter together.

Finally, I dedicate this thesis to those who cannot see me finish this in person. To my Dad, my idol, the man who was there when ever and where ever, you supported me no matter what. It's been incredibly hard without you, but I have done this for you, we all miss you every day! And to two very dear friends Kunbi Ajibade and Sarah Delf, you left us all too soon, this thesis is for the both of you, you could not be here to finish your own, but know that your hearts and memories helped to finish this work and the work of others who knew you.

Table of Contents

Abbreviations

Ar = Aromatic

BIM = Bis-indolylmethane

Biphep = 2,2′-Bis(diphenylphosphino)-1,1′-biphenyl

Bn = Benzyl

Bs = Broad singlet

Bt = Broad triplet

n-BuLi = *n*-Butyl Lithium

^{13}C = Carbon NMR

^{0}C = Celcius

CAAC = Cyclic (alkyl)(amino) carbene

CAN = Ceric Ammonium Nitrate

cm^{-1} = Inverse centimetres (Units for wavenumber)

D = Deuterium

Dppf = 1,1' – Bis(diphenylphosphino)ferrocene

DCM = Dichloromethane

Eqs. = Equivalents

Et = Ethyl

EDG = Electron Donating Group

EWG = Electron Withdrawing Group

FTMS = Fourier Transform Mass Spectrometry

g = Gram(s)

^{1}H = Proton NMR

Hr = Hour(s)

H_{Ar} = Aromatic Proton

HRMS = High Resolution Mass Spectrometry

Hz = Hertz

IR – Infrared Spectroscopy

M = Metal

Me = Methyl

mg = Milligrams

Min = Minute

mL = milliliters

Mol = Mole(s)

mmol = Millimole(s)

M.p. = Melting Point

MS = Mass Spectroscopy

MW = Microwave

M/Z = Mass to charge ratio

NBS = N-Bromosuccinamide

NHC = *N*-Heterocyclic carbene ligands

NMR = Nuclear Magnetic Resonance

NOE = Nuclear Overhauser Effect

NSI = Nano Spray Ionisation

Nuc = Nucleophile

OAc = Acetate

OTf = Triflate

Pet = Petroleum Ether

Ph = Phenyl

Ppm = Parts Per Million

i-Pr = Iso-propyl

Rbf = Round bottomed flask

rt = Room temperature

Sat. = Saturated

Sol. = Solution

T = Temperature

TBAF = Tetra-*n*-butylammonium fluoride

Temp = Temperature

THF = Tetrahydrofuran

TLC = Thin Layer Chromatography

Vol = Volume

δ = Chemical Shift

µl = Microliter

J = Coupling Constant

λ = Wavelength

Chapter 1.0 Introduction

1.0 History of allenes

Over the past few decades, allenes have gone from being regarded as chemical curiosities to being well known structures in organic synthesis, natural products and pharmaceuticals. The earliest citing regarding the structure of allenes was reported in 1875 by the first Nobel laureate in chemistry, J. H. van't Hoff when he predicted its correct but unusual stereochemistry.[1] But, it was not until 1887 that Burton and Pechmann were able to synthesise the first allene, 'glutinic acid' **1**, (**Figure 1**)[2] whilst trying to prove the non-existence of these highly unstable molecules. It was the absence of analytical instrumentation at the time which made it difficult to confirm the exact structure of the allene and to distinguish it from its corresponding alkyne.[3] It was this, coupled with the idea that they were unstable that delayed the progress in this area of chemistry. Therefore, it was not until advances in structural investigation tools emerged that Jones and co-workers in 1954 were able to confirm the structure of the first allene 'glutinic acid' **1**.[4]

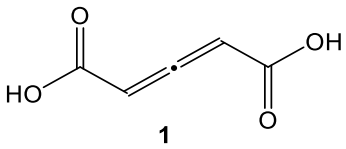


Figure 1. Structure of the first synthesised allene, glutinic acid.

After the initial identification of allenes, chemists were proposing the existence of allenic natural products, however due to the lack of analytical tools they were incorrectly characterising these compounds. For example, in 1924 Staudinger and Ruzicka published their characterisation of pyrothrolone **2**[5] (**Figure 2**) to contain a terminal allene, however upon further spectroscopic investigation it was found to contain a conjugated diene **3** (**Figure 2**).[6]

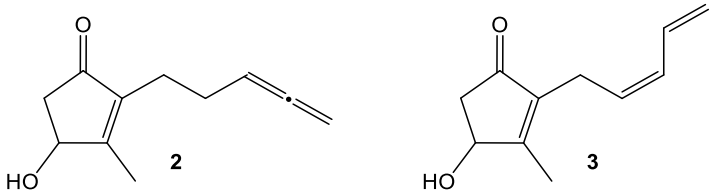


Figure 2. Incorrect structure of pyrothrolone **2** containing an allene moiety and the correctly characterised structure of pyrothrolone **3** containing a conjugated diene moiety.

Allene chemistry has thrived since the discovery of allenic natural products and scientists have reported the existence of allenes in over 150 natural products. The first known example was mycomycin **4** (**Figure 3**) isolated in 1952 by Celmer and Solomons,[7] which is an optically active allene known for its anti-biotic properties.

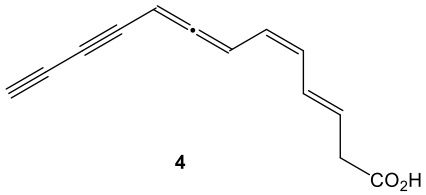


Figure 3. Structure of the first naturally occurring allenes mycomycin **4.**

Other examples of allenes from natural products and also as pharmaceutical agents include the grasshopper ketone **5** (**Figure 4**), isolated in 1968 from the flightless grasshopper *Romalea Microptera,*[8] (*R*)-cytallene **6** and (*R*)-adenallene **7** (**Figure 4**) which are inhibitors of HIV and Hepatitis B replication.[9]

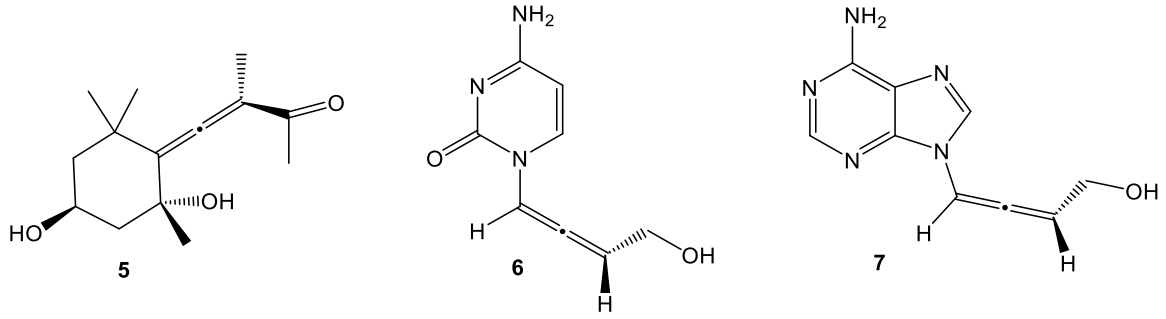


Figure 4. Structures of naturally occruing allene; grasshopper ketone **5** and structures of pharmaceutical agents (*R*)-cytallene **6** and (*R*)-adenallene **7**.

The importance of allenes in natural products with biological activity and their growing interest in organic synthesis, organometallic chemistry, pharmaceutical and industrial applications has led to an increase in the number of pathways for their synthesis.[1,10] The use of allenes as building blocks in organic chemistry is because of their unique structures, which allow them to exhibit high levels of chemo-, regio- and stereo-selectivity in numerous transformations,[11] which will be discussed in examples found within this thesis.

1.1. Structure of allenes

Since their first identification, chemists have been fascinated with the unique structure of allenes because they contain a cumulated diene function, which makes them highly reactive in comparison to alkenes and alkynes. Allene is the parent compound of the cumulene family, which contains 3 (or more for cumulenes) carbon atoms in two cumulated double bonds. The central carbon of allene is sp hybridised and the two terminal carbons are sp^2 hybridised, with the two π –bonds being orthogonal to each other and therefore not conjugated (**Figure 5**).

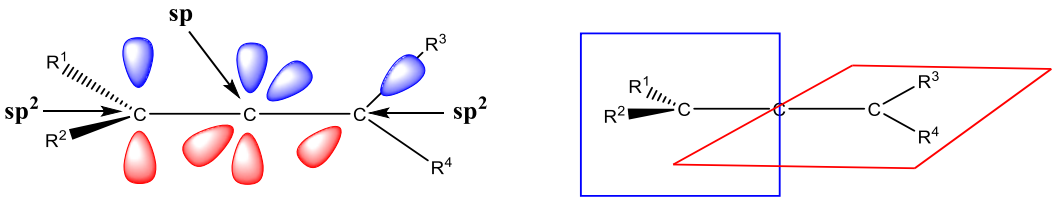


Figure 5. Diagram to show the two orthogonal π orbitals found in allenes

The resulting allenic structure has an angle of 180° with the four substituents arranged in an elongated tetrahedral conformation.[12] They have a C_2 axis through the three linear carbons and two perpendicular C_2 axes through the central sp carbon. It is the orientation of these π-orbitals and the substitution on the two sp^2 carbons that give allenes axial chirality and optical properties. The relevance of allenes for use in stereoselective synthesis or in processes that require stereocontrol has resulted in an increase in procedures to synthesise chiral allenes.[10a,13, 14] Allenes can be described as either 'asymmetric' when they lack all elements of symmetry or 'dissymmetric' when they contain a C_2 proper axis of rotation (**Figure 6**).[14]

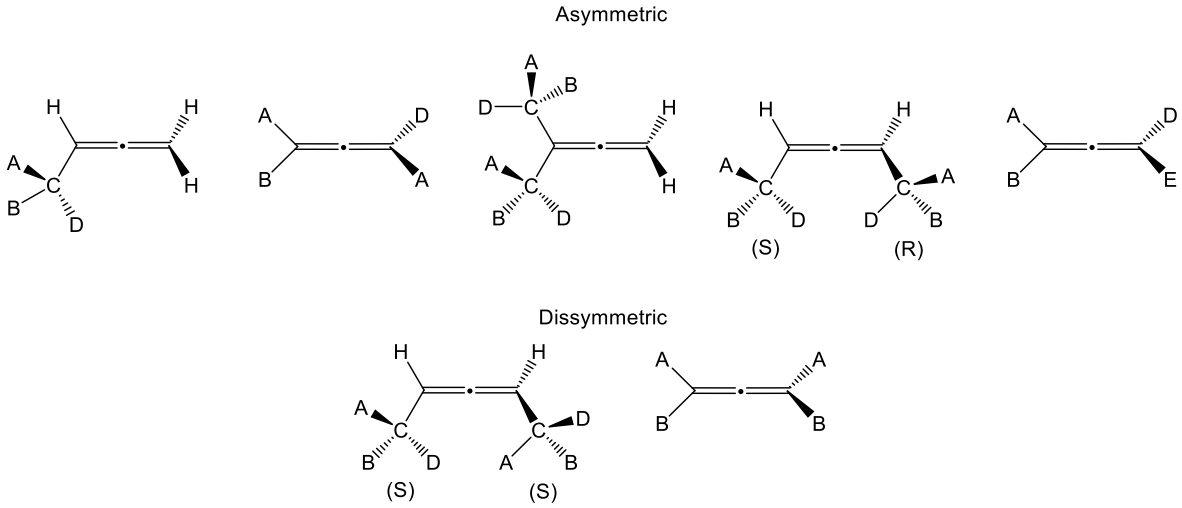


Figure 6. Structures to show the asymmetric (no symmetry element) allenes and the dissymmetric (contain C_2 proper axis of rotation) allenes.

Chiral allenes either asymmetric or dissymmetric can exist as two enantiomeric forms and we can assign the absolute configuration *R* (clockwise) or *S* (counter-clockwise) to these enantiomers using the method by Cahn, Ingold and Prelog.[15] The configuration is assigned by looking down the C_2 axis of the molecule and placing the substituent with the highest atomic number from the vertical position at the top (position **1, Figure 7**). Then the substituent with the highest atomic number in the horizontal axis takes precedence (position **3**, **Figure 7**), with the example in **Figure 7** showing the (*S*)-configuration.

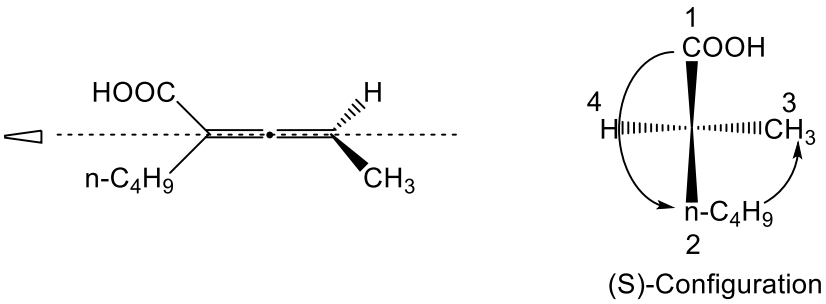


Figure 7. Assignment of absolute configuration using Cahn, Ingold and Prelog method.

The similarity of the allene structure to those of alkenes and alkynes means it is essential to be able to identify the allenic functionality using analytical techniques. Ultraviolet-visible spectroscopy is not a common technique for characterising allenes because the two orthogonal π–bonds lack conjugation, therefore allenes cannot absorb light above 200 nm. However, Infrared (IR) and Nuclear Magnetic Resonance (NMR) spectroscopy are good techniques for identifying their key features and characterising allenes.

IR spectroscopy is an ideal tool for quickly identifying the allenic moiety in a compound. It allows for the identification of the C=C=C feature, with an asymmetric stretching adsorption band observed around 1950 cm^{-1} (usually between 1900 and 2000 cm^{-1}), although if the allene is symmetrically substituted then it does not exhibit this characteristic adsorption.[16] But, IR does not give detailed information about the substituents on the allene, which is why we use ^{1}H-NMR. The four equivalent protons of the parent allene give a signal around 4.55 ppm. However if the allene becomes substituted with either methyl or ethyl groups, then a slight ppm shift down-field for the allenic protons attached to the substituted carbon is observed (H_b in **Figure 8**).[15] These allenic protons appear in a higher field than ethylenic protons which indicates that the sp-carbon and its non-conjugated π-orbitals exert a longer-range anisotropic contribution to the shielding of the terminal protons.[17]

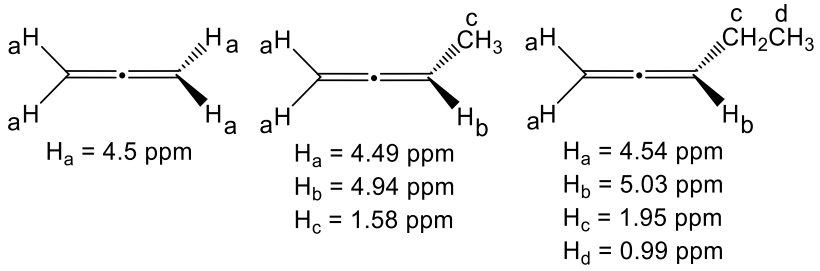


Figure 8. Unsubstituted and substituted allenes with their respective chemical shifts to show that substituted allenes give a downfield shift.

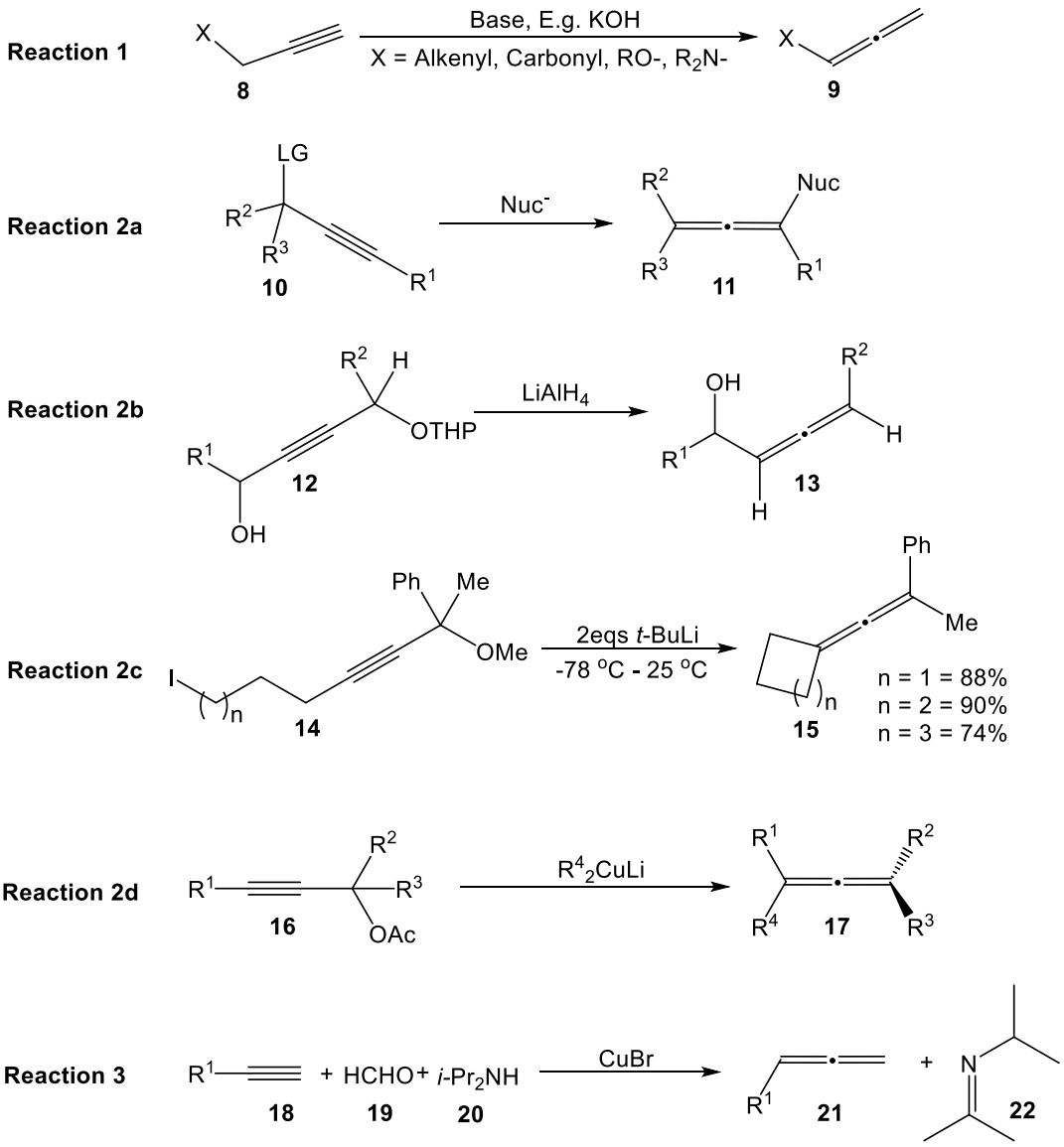
Another key importance to identifying allenes using ^{1}H NMR is the exceptionally large coupling constant that is observed between H_a and H_b, which is reported to be between 6.5 and 7 Hz. This is a J^4 coupling which is normally too small to detect, but is detectable in allenic structures because they have σ-π interactions between the C-H bond and the double bond furthest away. This has been supported by theoretical studies.[1] Alongside the ^{1}H NMR data, we can also use ^{13}C NMR to identify allenes because of their central sp carbon which gives an extremely down-field chemical shift of around 200-210 ppm and substituting the allene with alkyl groups causes a slight up-field shift of this central carbon atom.[16]

1.2. Synthesis of allenes

Over the past few decades, synthetic routes for allene synthesis using readily available starting materials and simple and effective conditions have been explored. With a rapid growth in publications for their synthesis, we have seen routes developed to form a range of mono-, di-, tri- and tetra-substituted allenes.[1,10,13] Although various starting materials can be used for allene synthesis, the most commonly reported syntheses use alkynes, with examples including the isomerization of alkynes using a strong base e.g. KOH and high temperatures to deprotonate the propargylic C-H bond to form the cumulated π bond (Reaction **1, Scheme 1**);[18] the metal-mediated S_N2' nucleophilic substitution reaction of propargyl compounds (Reaction **2a**, **Scheme 1**) and the Crabbé homologation of alkynes using paraformaldehyde to incorporate the extra carbon (Reaction **3**, **Scheme 1**)

The S_N2' route uses a range of different metals to mediate the reaction and examples include:

- Aluminium mediated synthesis, a reliable method for direct H addition on propargylic ethers, halides or alcohols using aluminium hydrides, such as $LiAlH_4$ and DIBAL-H (Reaction **2b**, **Scheme 1**).[19]
- Lithium, zinc and magnesium mediated synthesis (Reaction **2c**, **Scheme 1**).[19]
- And copper mediated synthesis, this is the most common method for allene synthesis which was first reported in 1968 by P. Rona and P. Crabbé,[20] it is one of the most versatile procedures because it can be used to make a range of different allenes as well as achieving chirality transfer (Reaction **2d**, **Scheme 1**).[19]

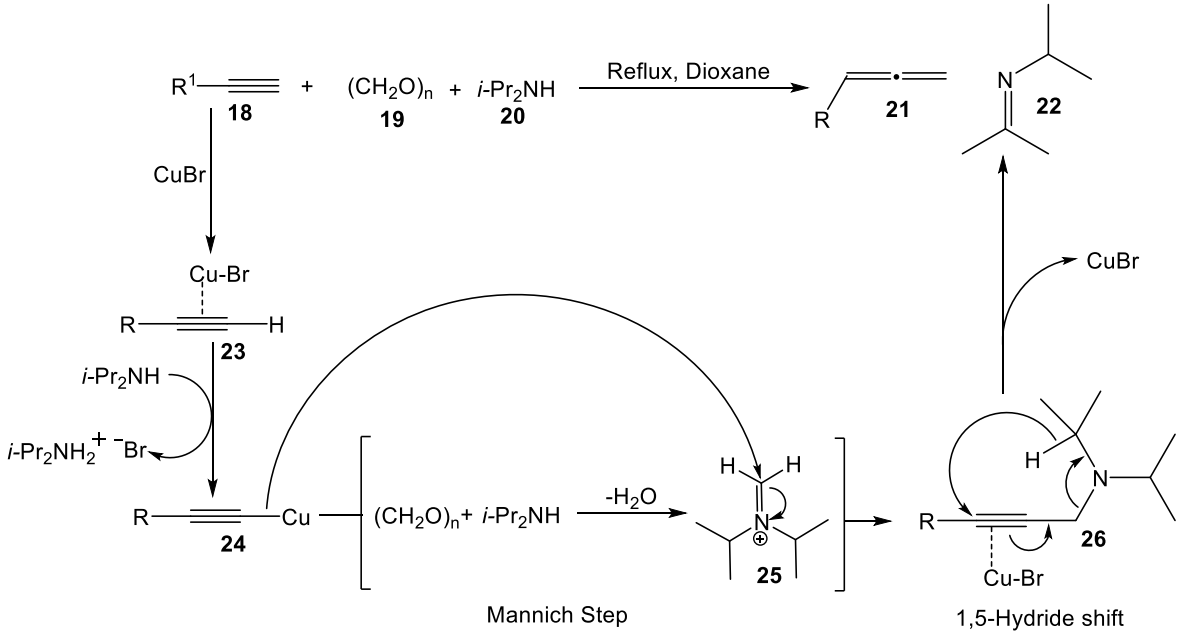


Scheme 1. Methods for allene synthesis: isomerisation of alkynes (reaction **1**); metal-mediated S_N2' reactions using aluminium hydrides (**2b**), lithium (**2c**), organo-cuprates (**2d**) and the Crabbè homologation (**3**).

The examples in reactions 2, give rise to a range of substituted allenes that can possess axial chirality. However, within this thesis it is mainly mono- and di-substituted allenes that are used and these are synthesised using the Crabbé homologation method (Reaction 3, **Scheme 1**).[21] The Crabbé homologation is readily used because of its simplicity, flexibility, effectiveness and use of low cost reagents and starting materials. Crabbé and co-workers first discovered this reaction in 1979 whilst trying to synthesise the non-natural steroid dinordrin.[22]

It was a failed Mannich reaction which gave them the allenyl-steroid after a one-step homologation of the acetylenic derivative using formaldehyde, *N,N*-diisopropylamine and copper (I) bromide refluxing in dioxane.[21] Experimental and theoretical calculations support the Crabbé homologation reaction occurring *via* a two-step mechanism.[23,24,25,26]

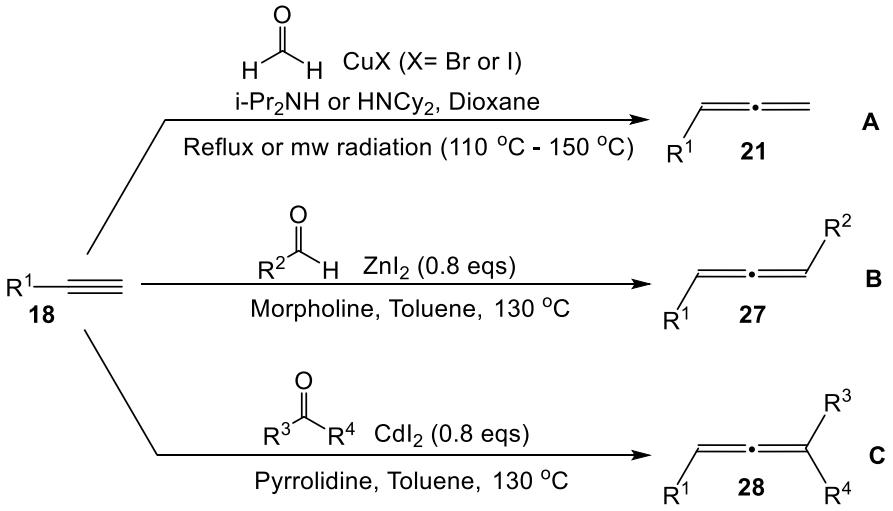
The first step involves the formation of an iminium salt **25** *via* a Mannich type reaction between formaldehyde 1**9** and the amine **20**. The terminal alkyne **24** is activated by complexation with copper that allows it to undergo an addition reaction to the iminium salt **25** to form a propargylamine intermediate **26**. The α-proton to the nitrogen on this intermediate undergoes a 1,5-sigmatropic rearrangement *via* an S_N2' type mechanism to form the corresponding allene **21** with elimination of the imine species **22** (**Scheme 2**).



Scheme 2. The proposed mechanism for Crabbé homologation of terminal alkynes using paraformaldehyde **19**, copper(I) bromide and diisopropylamine **20**.

The original Crabbé homologation conditions described above only allow for the formation of mono-substituted allenes, this major limitation has led chemists to explore the scope and efficiency of this synthetic route. Groups such as Ma's[27] and Nakamura's[25] have explored the effect of copper salts (CuBr *vs* CuI), amines (N,N-diisopropylamine *vs* N,N-dicyclohexylamine) and also microwave irradiation *vs* reflux on the synthesis of mono-substituted allenes. They found that simple variations in these conditions could lead to higher yields, shorter reaction times and toleration of a wider range of substituents (Reaction **A**, **Scheme 3**). However, these conditions are limited to paraformaldehyde, with no allene formation occurring with either aldehydes or ketones.

So, the Ma group in 2009 [28] developed a procedure that uses the cost-effective ZnI_2 and morpholine to produce a range of 1,3-disubstituted allenes from aromatic/aliphatic aldehydes and terminal alkynes (Reaction **B**, **Scheme 3**). In 2013, the Ma group also published results for the synthesis of tri-substituted allenes using CdI_2 and pyrrolidine in a one pot reaction of the terminal alkyne and the corresponding ketone (Reaction **C**, **Scheme 3**).[29]



Scheme 3. Modified Crabbé homologation reactions to form mono-, di- and tri-substituted allenes.

The modified Crabbé homologation using CuBr, iPr_2NH, HCHO and dioxane under microwave irradiation at 150 °C is used for the synthesis of numerous substituted allenes and the ease of these reactions makes it ideal for the synthesis of starting material allenes within this thesis.

1.3. Metal coordination chemistry of allenes

The metal-catalysed addition of heteroatom nucleophiles to unsaturated molecules such as alkenes, alkynes and allenes is a well-established area of organic chemistry.[30] It is a very useful method for the formation of different cyclic heteroatom-containing products by intramolecular nucleophilic addition and a range of different acyclic products from the intermolecular nucleophilic addition.

Depending on the carbon of the allenic system where the addition occurs, several products can be obtained, e.g. allyl derivatives by addition to terminal carbons; vinyl derivatives to the central carbon, or double addition products to the terminal carbon with saturation of the second double bond (**Figure 9**).

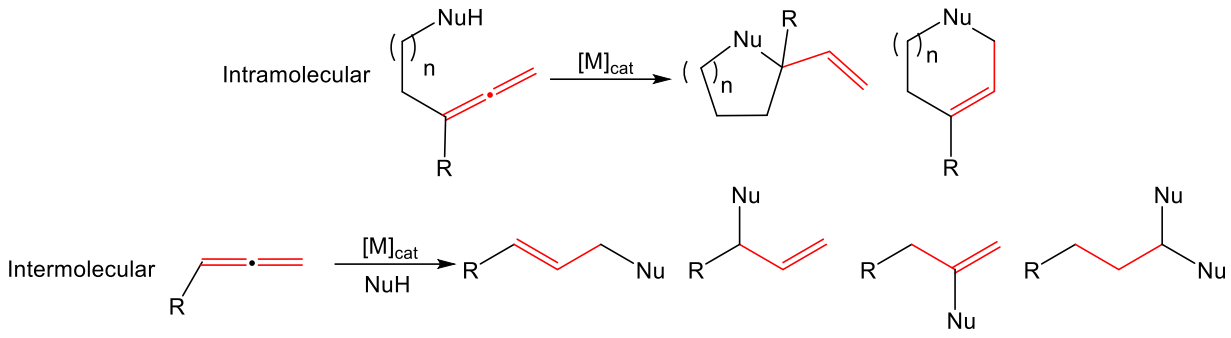


Figure 9. Possible products from both the intra- and intermolecular addition of heteroatom nucleophiles to allenes.

The successful nucleophilic addition occurs when metals such as Pt and Au (Au(III) and cationic Au(I)) act as 'soft' Lewis acids and activate the 'soft' electrophilic π-system of the unsaturated molecule.[31] The metal coordination to alkenes and alkynes occurs *via* ŋ² mode only.

The metal-alkene interaction is described by both the donor and acceptor ability of alkenes; the donor interaction results from the donation of electron-density from the π orbital of the alkene to vacant d-orbital of the metal (**A**, **Figure 10**). As well as the acceptor interaction resulting from the flow of electron-density from the metals d-orbital into the π* orbital of the alkene (**B**, **Figure 10**). These two interactions involve both carbons of the alkene and result in bond-lengthening and change of angle in the C=C bond.

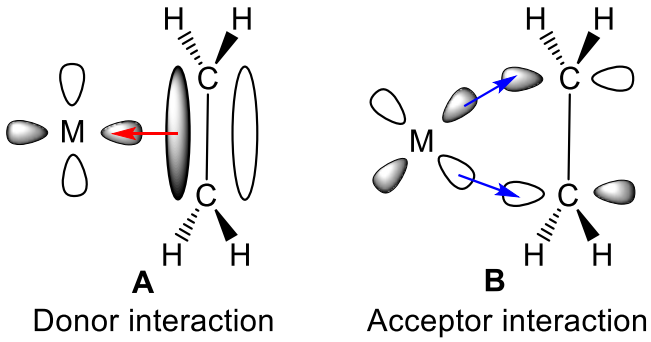


Figure 10. Metal-alkene coordination, highlighting the donor and acceptor abilities of the C=C bond.

But the metal coordination to allenes is more complex due to its unique structure with two consecutive double bonds. Two types of coordination with metals have been proposed. The common ŋ² mode, similar to that observed for alkenes (**Figure 11**), where the metal coordinates to one or the other of the two C=C bonds **29** (**Figure 11**), this depends on the electronic properties of the ligands and the substituents on the allene, with the metal shifting towards either the central carbon **30** (**Figure 11**) or one of the terminal carbons of the allene **31** (**Figure 11**).

The second coordination type is the η^1 mode, which involves the direct coordination of the metal to the central carbon of the allene and can be described by three types of structures; the σ-allylic cation 3**2**, a zwitterionic carbene **33** and a η^1-coordinated bent allene **34** (**Figure 11**).[32] The coordination mode of metals to allenes is important to explain the reactivity of these systems and also to determine the stereochemical outcome of transformations involving axial-to-centre chirality transfer, where the stereochemical information is maintained in **29** and **34**, but is lost in **32** and **33** because the three carbons and their substituents are positioned in the same plane.[33]

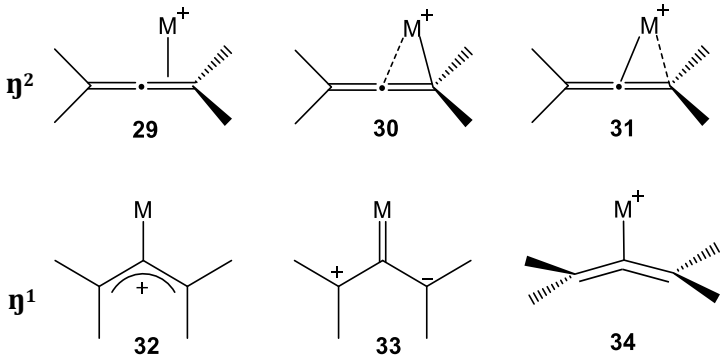


Figure 11. Possible modes of metal-allene coordination.

The metal coordination to allenes is shown to be more complex than that for alkenes and alkynes, this is also true for the selectivity of allenes. Alkenes and alkynes both possess stereo- (*cis*- or *trans*-addition to form stereoisomers) and regioselectivity (to provide constitutional isomers), with alkynes also possessing chemoselectivity (single or double addition), these issues also arise in allenes. But, because of their two orthogonal π-systems they also have positional selectivity issues (**Figure 12**), because of the challenge of addition towards a specific double bond.[34]

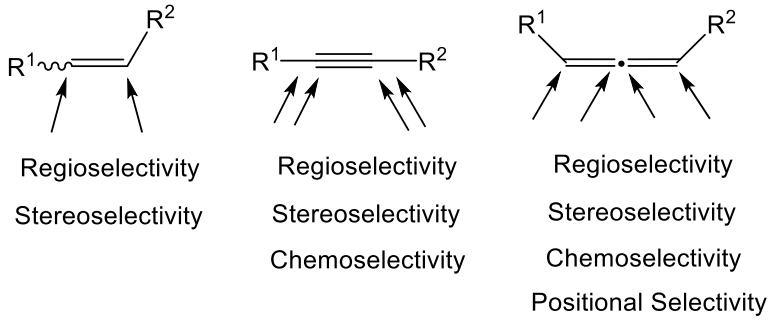


Figure 12. The selectivity problems that arise in alkenes, alkynes and allenes.

The ability for transition metals such as Au and Pt to coordinate to unsaturated molecules has shown an exceptional growth in their transformations to functionalised cyclic and acyclic compounds. The next two sections of this thesis will look at the development of this area of chemistry using metal catalysis, in particular, Au and Pt, for both inter- and intramolecular addition of heteroatom and heteroaromatic nucleophiles to allenes.

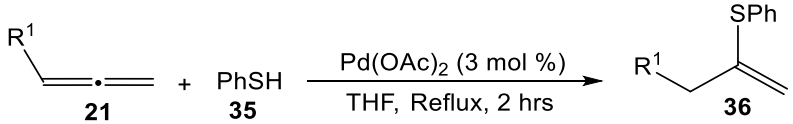
1.4. Metal catalysed intermolecular hydrofunctionalisation of allenes

Intermolecular hydrofunctionalisation of allenes has grown over recent years with the addition of either carbon-based nucleophiles e.g. indoles, pyrroles and arenes or heteroatom nucleophiles e.g. sulphur, nitrogen and oxygen, across the unsaturated carbon-double bond to give a range of allylic derivatives. There is great scope in these types of reactions with different complexities and properties of the products being achieved depending on the type of metal catalyst and nucleophile applied. This has resulted in numerous reports for the hydrofunctionalisation of allenes with a variety of different metals such as Pd, Ru, Rh, Au (Au(III) and cationic Au(I)) and Pt(II).[35] However, as it is more relevant for this thesis, this introduction will mainly summarise the use of Au, Pt catalysis and some relevant examples of Pd catalysis for the intermolecular addition of sulphur, nitrogen, oxygen and carbon-based nucleophiles to allenes.

1.4.a. Metal-catalysed intermolecular hydrothiolation of allenes

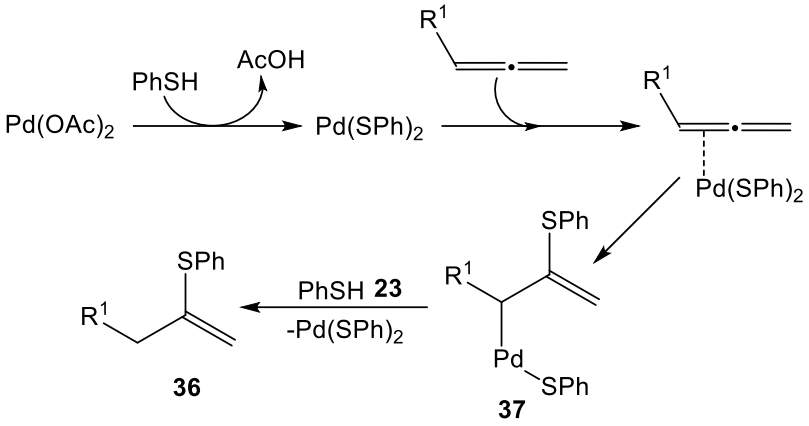
The metal-catalysed addition of sulphur nucleophiles to allenes to form allylic products is rare. This is partly due to sulphurs high affinity to transition metals,[36] therefore this process has been reported to a lesser extent than that of hydroalkoxylation and hydroamination. In fact, only a few examples of hydrothiolation using Au and Pd catalysis as well as In(III)[37] catalysis have been reported, where interestingly and in contrast to all the other heteroatom nucleophiles, the sulphur nucleophiles add regioselectivity to the central carbon of the allene.

In 1996, Ogawa[38] and co-workers reported the regioselective formation of terminal vinylic sulphide products **36** (**Scheme 4**) *via* the palladium acetate catalysed addition of benzenethiol **35** (**Scheme 4**) to the central carbon of allenes **21**.



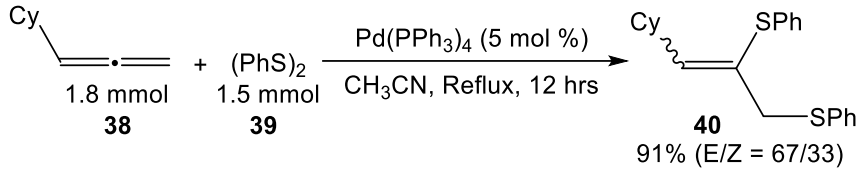
Scheme 4. Palladium acetate catalysed hydrothiolation of allenes using benzenethiol.

The first step of the mechanism proposes ligand exchange of the acetoxyl groups of the catalyst with PhS to form the active $Pd(SPh)_2$ catalyst which coordinates with the allene at the internal C=C bond. Subsequent *syn*-thio-palladation occurs forming the σ-allyl-palladium intermediate **37**, which undergoes immediate quenching by PhSH to form the vinylic sulphide product **36** with catalyst regeneration (**Scheme 5**).



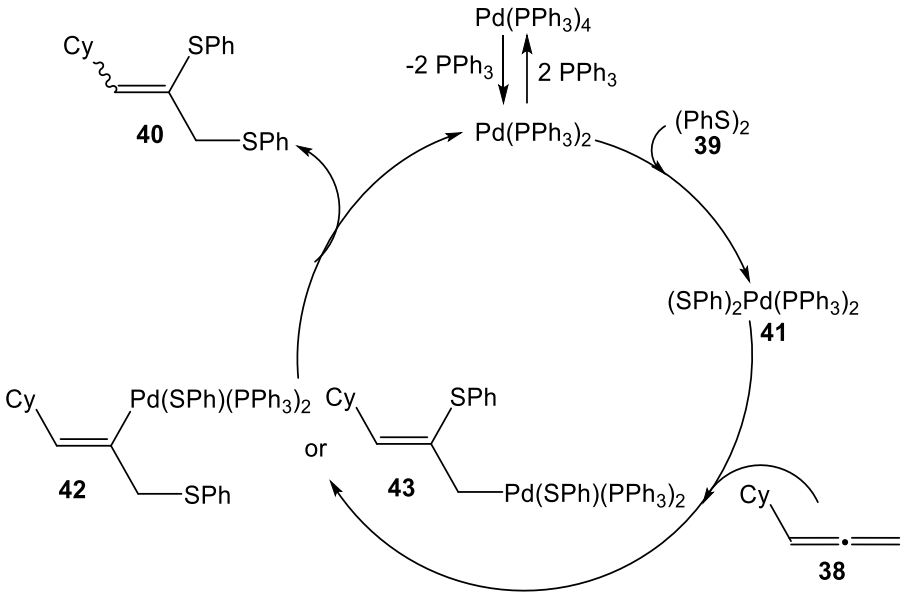
Scheme 5. Mechanism for the palladium acetate catalysed hydrothiolation of allenes using benzenethiol.

Later in 2007[39] the same group reported their results for the bisthiolation of allenes with diphenyl disulphide **38** in the presence of palladium-phosphine catalyst $Pd(PPh_3)_4$ with subsequent formation of the bisthiol species **40** (**Scheme 6**).



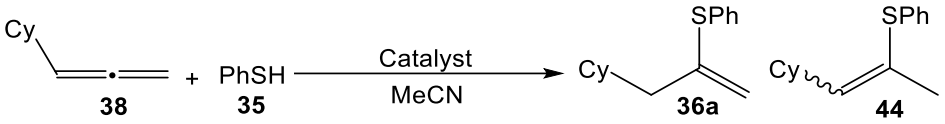
Scheme 6. Palladium-phosphine catalysed bis-thiolation of cyclohexylallene using diphenyl disulphide nucleophile.

The proposed mechanism for this reaction involves the oxidative addition of diphenyl disulphide **39** to the Pd(0) complex $Pd(PPh_3)_2$ to generate the active catalyst **41**. The catalyst coordinates to the allene allowing thiopalladation of the allene at the terminal or central carbon forming either a vinylpalladium intermediate **42** or a σ-allylpalladium intermediate **43**. Finally, reductive elimination occurs forming the bisthiol product **40** with regeneration of the catalyst (**Scheme 7**).[39]



Scheme 7. Catalytic cycle for the palladium-catalysed bisthiolation reaction of cyclohexyallene.

In 2009[40] the same conditions were used for the addition of benzenethiol to cyclohexylallene with regioselective formation of the vinylic sulphide (**36a** in **scheme 8**) in good yield. Regioselectivity of the reaction could be controlled using different catalysts $Pd(PPh_3)_4$ or $Pt(PPh_3)_4$ for the formation of the two different regioisomers (**Scheme 8**).

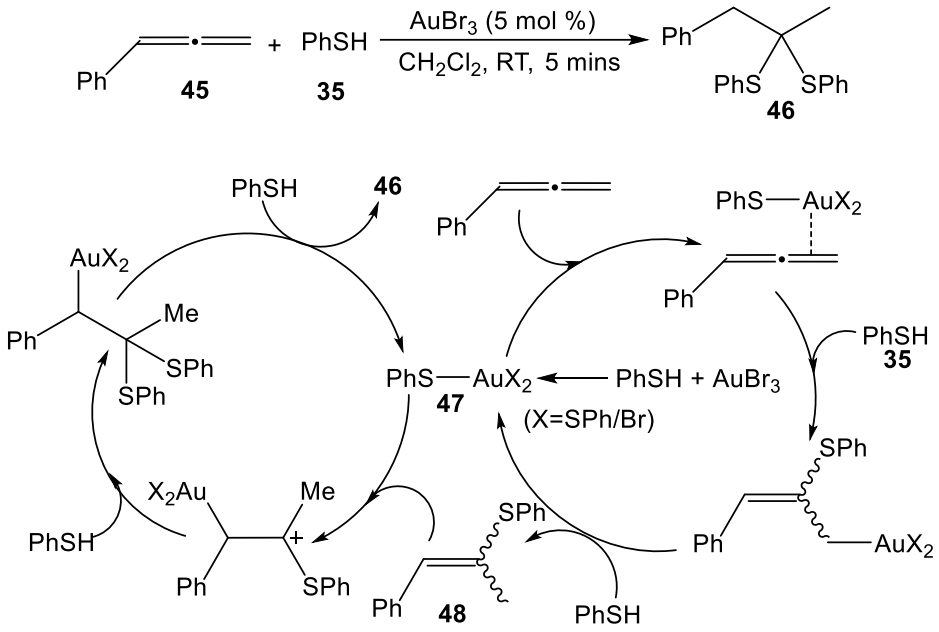


Catalyst (mol %)	36a	44
$Pd(PPh_3)_4$ (5) *	82	0
$Pt(PPh_3)_4$ (3) **	3	58

* = 12 hours reflux ** = 40 °C, 36 hrs

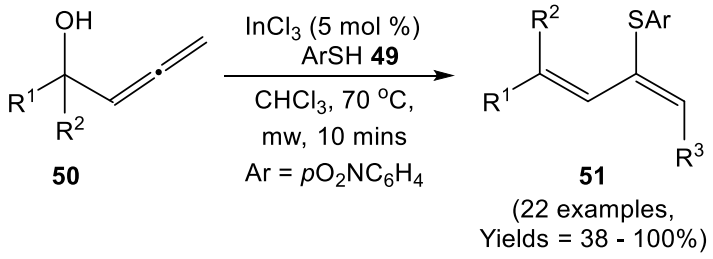
Scheme 8. Reaction scheme and results for controlling the regioselectivity of the hydrothiolation reaction.

In 2010, the group of Yamamoto[36a] published their findings for allene hydrothiolation using gold catalysis as a continuation from investigations into hydroalkoxylation [41] and hydroamination.[42] Successful double addition of an aryl-sulphur nucleophile thiophenol **35**, to the central sp-carbon of mono-aryl allenes **45** was achieved using $AuBr_3$ with resulting formation of the dithioacetal species **46** (**Scheme 9**). A double catalytic cycle (**Scheme 9**) was proposed and proceeds with the *in-situ* formation of the active catalyst **47** *via* ligand exchange. This coordinates to the allene activating it towards intermolecular nucleophilic addition with subsequent formation of the important electron-rich vinyl sulfide intermediate **48**, a second nucleophilic addition occurs at the stable carbocation forming the final compound after protonation **46** (**Scheme 9**).



Scheme 9. Reaction scheme and proposed catalytic cycle for gold-catalysed hydrothiolation of allenes.

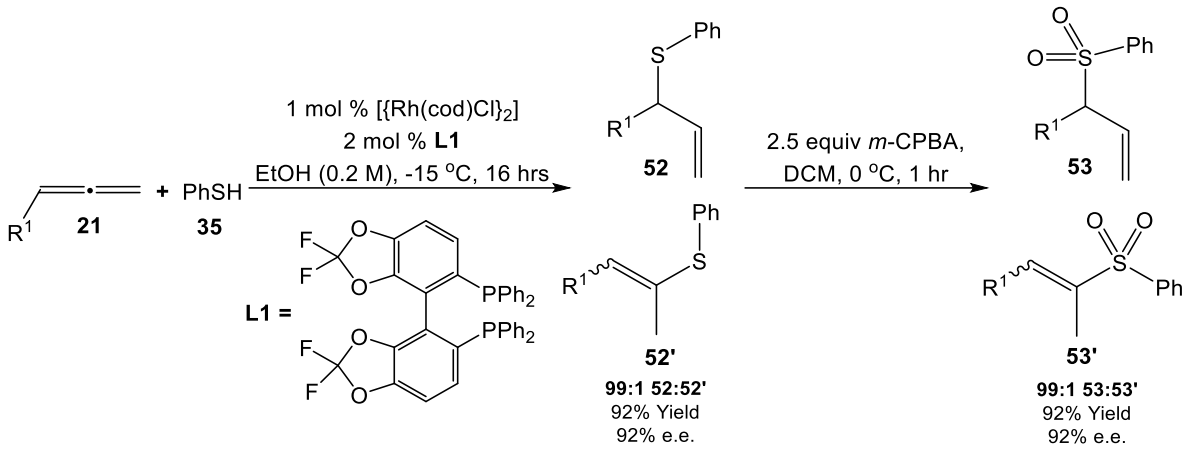
Recently, in 2015 Lee *et al*[37] found that the soft Lewis acid $InCl_3$ was far superior than Au(I) for catalysing the dehydrative thiolation of allenols. This reaction involves the intermolecular formal S_N2' addition of the subsequent thiol **49** to the allenol **50** to form a range of functionalised dienes **51** (**Scheme 10**).



Scheme 10. $InCl_3$-catalysed dehydrative thiolation of allenols.

The reaction works well with a range of substituted allenols, including those containing heterocycles and alkynes, as well as working well with a range of different thiol nucleophiles where electron-withdrawing substituents on the thiophenol gave better results than strongly electron-donating ones. The superior performance of In(III) over Au(I) in the reaction was suggested to be due to the better stability of the diene products **51** in the presence of In(III) *vs* Au(I).

These examples highlight the relative ease at which the thiol nucleophiles can add to the central carbon of the allene and shows that the addition of the thiol to terminal carbon of the allene is rare. However, recently in 2015 Pritzius and Breit[43] published their results for the rhodium-catalysed hydrothiolation of terminal allenes with thiophenol **35** for the subsequent formation of branched allylic thioethers **52** and their corresponding sulfones **53** (**Scheme 11**).



Scheme 11. Reaction procedure for the rhodium-catalysed hydrothiolation of allenes with thiophenol.

The reaction was reported to work well with a range of thiols and allenes, with high regio- and enantioselectivities of the allylic thioethers as well as obtaining enantiomerically pure forms of the sulfones after oxidation of the thioether with *m*-CPBA.[43]

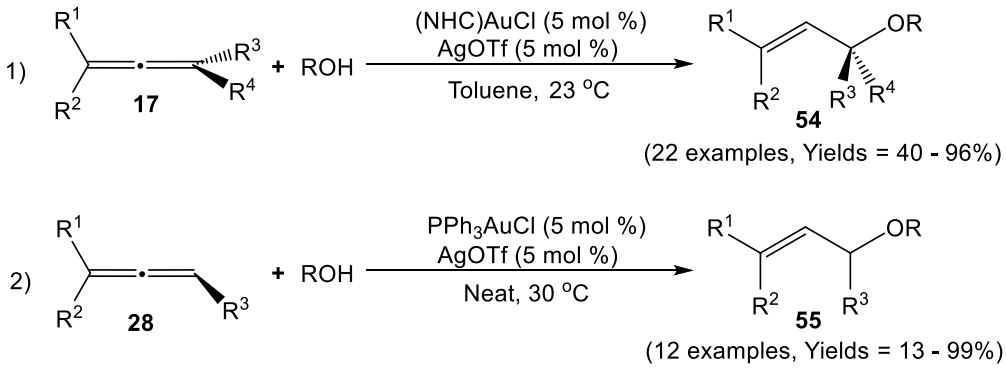
1.4.b. Metal-catalysed intermolecular hydroalkoxylation of allenes

Inter- or intramolecular addition of oxygen nucleophiles to allenes is known as hydroalkoxylation and involves the addition of alcohols across unsaturated C=C bonds with the formation of various allylic alcohols, ethers and oxygen containing heterocycles. The intramolecular addition has been more reported than that of the intermolecular addition, which has proven to be a challenging reaction. However, the development of new and more efficient transition metal complexes has shown a growth in the number of reports of metal catalysed intermolecular hydroalkoxylation. Although our focus is on the gold and platinum catalysed reactions, it is important to highlight that this reaction has great potential with other transition metals allowing the formation of different allyl, vinyl ethers and acetal products. For example, Pd, Ir, Rh and Ru catalysed hydroalkoxylation reactions of allenes have been discussed in detail in the review by Muñoz.[44]

Over the years, several groups have developed transformations of allenes using gold catalysis to form both alkyl primary-allylic ethers and alkyl tert-allylic ethers, which are important structures found in natural products and used as building blocks in organic synthesis.[45] The group of Widenhoefer[45] identified that this reaction was sensitive to the nature of ligands and counterions. Therefore, screening of these led the group to report the first regio- and stereoselective synthesis of *(E)*-alkyl allylic ethers **54** using Au(I)-*N*-heterocyclic carbene (NHC) complexes with AgOTf in toluene (Reaction 1, **Scheme 12**).

The reaction works for di-, tri- and tetra-substituted allenes and a range of primary and secondary alcohols, with the alcohols adding to the less hindered or more electron rich terminus of the allene. Alongside this report, the group of Yamamoto[41] reported that $Ph_3PAu(I)$ cationic complexes could also be used for the successful hydroalkoxylation of allenes with good yields.

This reaction also works well with 1,1- and 1,3-substituted allenes as well as a range of different alcohols. It follows a similar pattern to the reaction with Au(I)-NHC complexes with alcohol addition at the terminal, less hindered carbon of the allene giving the corresponding *E*-allylic ether **55** (Reaction 2, **Scheme 12**).

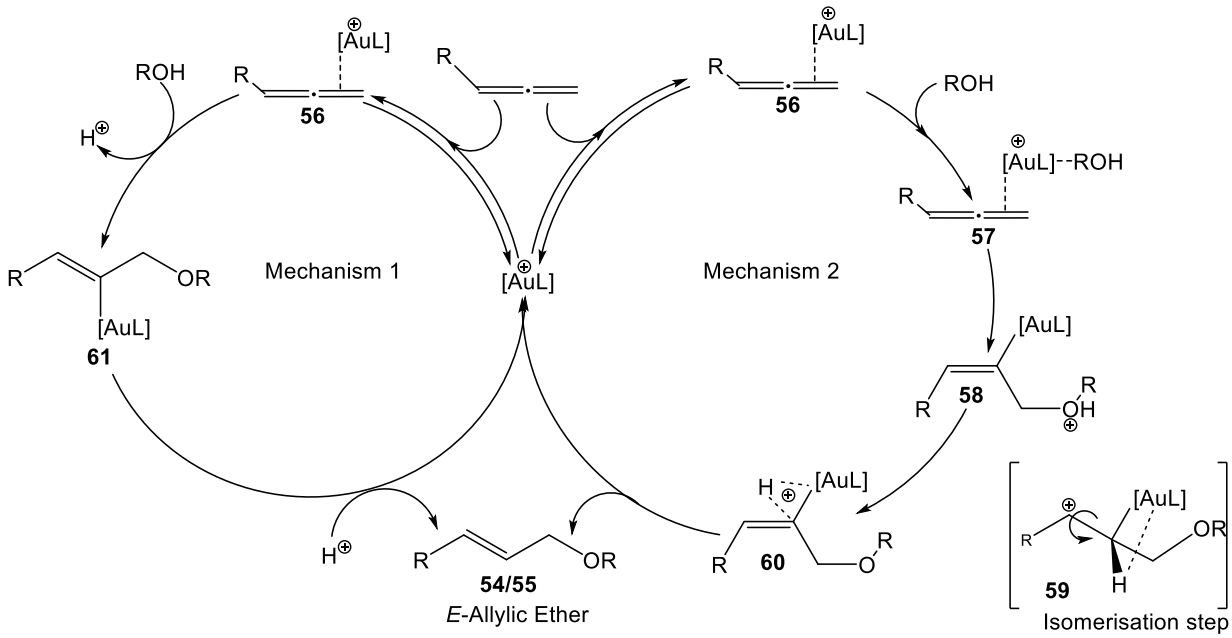


Scheme 12. Reaction schemes for hydroalkoxylation using Au(I)-NHC complexes and Au(I)-PPh_3 complexes respectively.

Widenhoefer *et al.*[45] proposed that the reaction occurs through an outer-sphere mechanism with the Au acting as a π-acid to activate the terminal C=C bond of the allene. Nucleophilic addition at the less hindered sp^2 carbon from the opposite face of the metal forms the corresponding allylic ether **54** (Mechanism 1, **Scheme 13**).

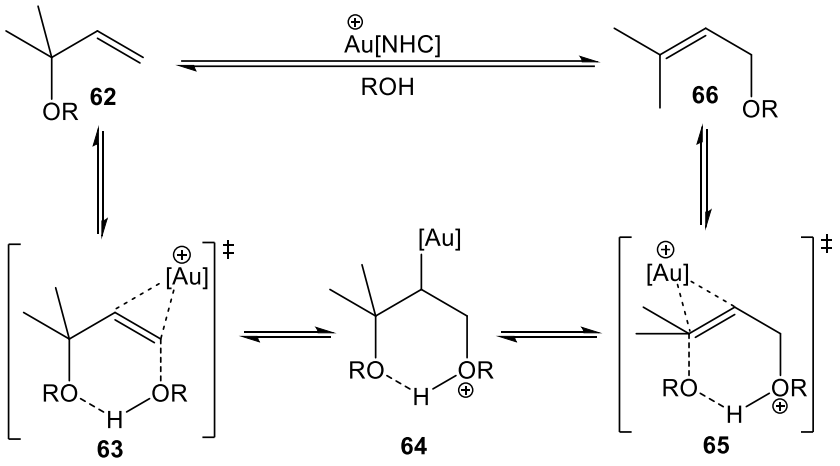
Whereas, the group of Yamamoto[41] proposed that the alcohol nucleophile adds through an inner-sphere mechanism. They suggested that the gold coordinates to the allene for activation, the nucleophile is then coordinated to the gold forming a tri-coordinate complex **57,** with transfer of the alcohol to the terminal carbon of the allene intramolecularly to form the *Z*-vinyl-gold complex **58.** *E*-Allylic ethers **54/55** are obtained in both cases.

Yamamoto suggested the *E*-isomer is obtained after isomerisation around the C-C bond of the *Z*-vinyl-gold complex **58** (Mechanism 2, **Scheme 13**).



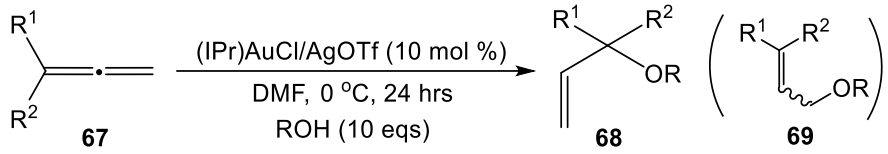
Scheme 13. Reaction mechanisms proposed by Widenhoefer (**Mechanism 1**) and Yamamoto (**Mechanism 2**) for the hydroalkoxylation of allenes.

In 2009, Paton and Maseras [46] carried out DFT studies on the mechanism of the Au(I) hydroalkoxylation. They proposed that the alcohol addition to the allene is the rate-limiting step and proceeds *via* an outer-sphere mechanism where the alcohol can attack either of the sp^2 carbons irreversibly from the opposite face of the coordinated catalyst. Their calculations found that the product from attack at the least hindered carbon, experimentally obtained, was thermodynamically more stable than the product from attack at the more hindered carbon. However, this product was calculated to be the kinetic product. This led them to propose that the primary/secondary-allylic ethers are formed by gold-catalysed isomerisation of the kinetic products, the tert-allylic ether, *via* a cyclic six-membered ring intermediate (**Scheme 14**).



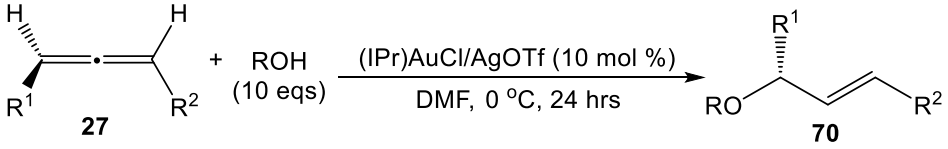
Scheme 14. Proposed mechanism for the interconversion of the kinetically stable tert-allyic ether to the thermodynamically stable primary-allylic ether.

The use of Au(I) catalysis for the hydroalkoxylation of allenes to form *tert*-allylic ethers has not been readily reported. In fact, one of the first reports for the synthesis of *tert*-allylic ethers involved the use of toxic mercury (II) salts.[47] However, in 2008 the group of Lee[48] reported high regioselectivity for *tert*-allylic ethers *vs* primary-allylic ethers upon excess alcohol addition to cyclopropenes using Au(I) catalysis.Moreover, in 2010 they provided experimental evidence for the gold-catalysed isomerisation of *tert*-allylic ethers to primary-allylic ethers as proposed by DFT calculations (**Scheme 14**) and found that using Au(I)-NHC complexes in DMF with an excess of alcohol retarded this isomerisation process and high regioselectivity for the *tert*-allylic ether **68** product was achieved (99:1, **68:69**, **Scheme 15**).[49]



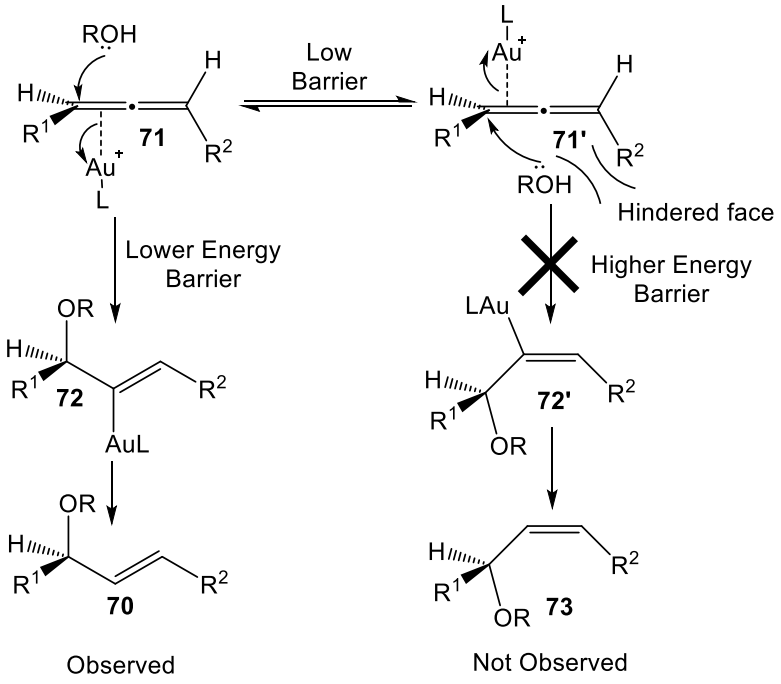
Scheme 15. Reaction scheme for Au(I)-catalysed hydroalkoxylation for the synthesis of *tert*-allylic ethers.

More recently, in 2016 Lee *et al.*[50] reported their results for the successful Au(I)-catalysed intermolecular hydroalkoxylation of enantiopure 1,3-disubsituted allenes (**Scheme 16**). These reactions have been previously reported with poor chirality transfer due to rapid racemisation of the allene.[41,45] However, they found that using their previously published reaction conditions they could obtain the allylic ether with a high degree of chirality transfer.



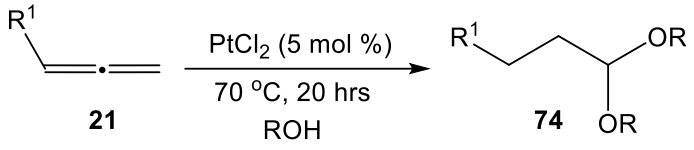
Scheme 16. Reaction scheme for Au(I)-catalysed hydroalkoxylation of 1,3-disubstituted allenes.

They reported the reaction to work well with a range of alcohol nucleophiles and a variety of substituted 1,3-disubstituted allenes, where functional groups play an important role in achieving excellent regioselectivities. The reaction is reported to also be highly stereoselective in terms of *E/Z* products, with *E* selectivity occurring, the group proposed reasoning for this selectivity (**Scheme 17**). Au can coordinate to either face of the allene activating it towards the nucleophilic addition, this occurs *anti* to the Au. The nucleophilic addition to complex **71** will occur with a lower energy barrier because it has less steric hinderance, giving intermediate **72**, which undergoes protodeauration to form the *E*-allylic ether **70**.



Scheme 17. Proposal for the *E*-selectivity of Au(I)-catalysed hydroalkoxylation of 1,3-disubstituted allenes.

The use of Pt catalysis for dihydroalkoxylation has been far less reported than that of Au(I), with only one reported example by Muñoz *et al.* in 2010.[51] They observed the double addition of alcohol nucleophiles to the terminal carbon of allenes with complete saturation of the internal C=C bond to form the corresponding aliphatic acetal species **74** (**Scheme 18**). This contrasts with the Au(I)-catalysed reaction where only single addition is observed.

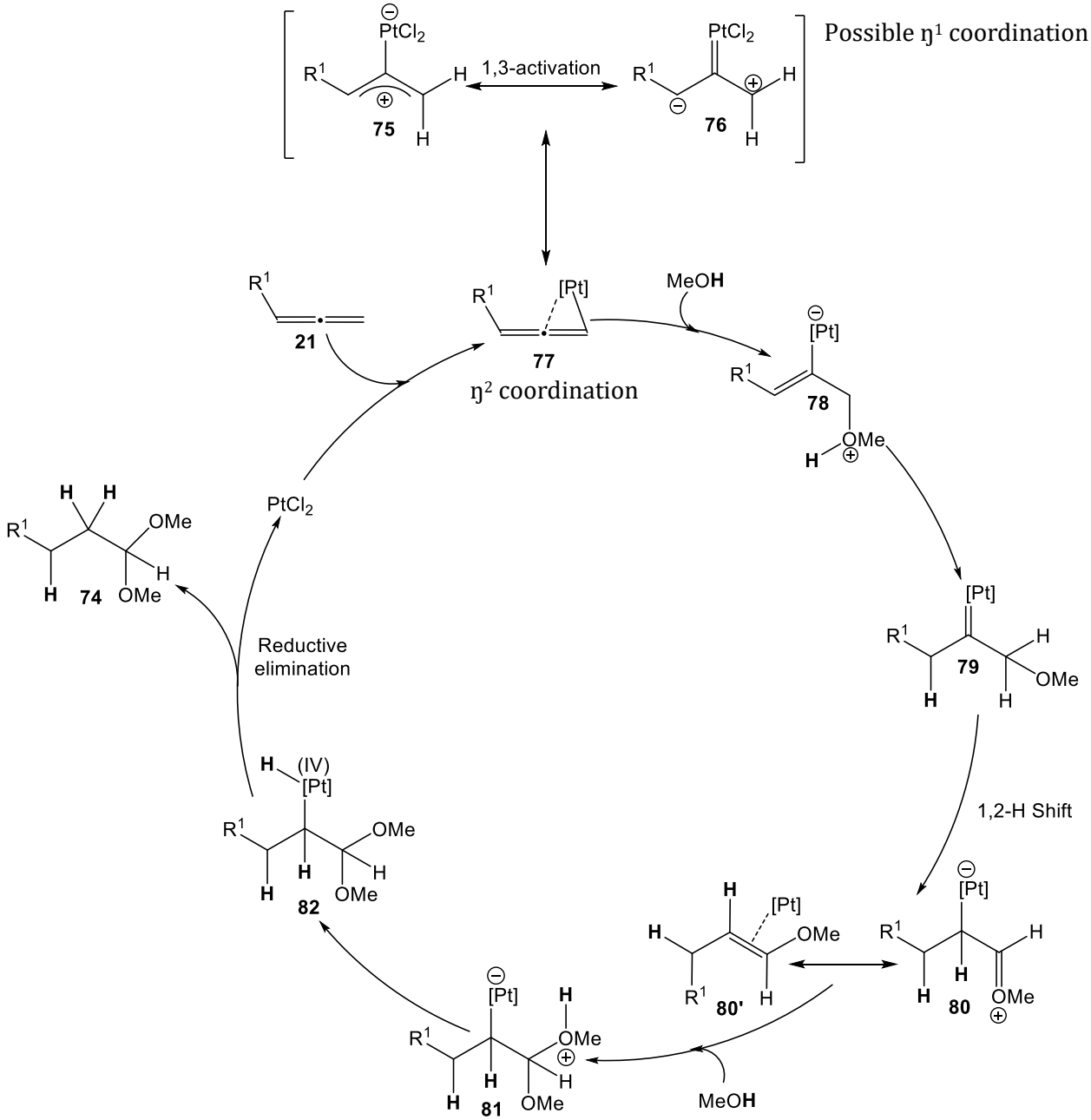


Scheme 18. Reaction scheme for Pt(II)-catalysed dihydroalkoxylation reaction for the synthesis of aliphatic acetals.

The reaction is reported to only work with mono-substituted allenes and a range of different alcohols. The proposed mechanism begins with the coordination of platinum to the allene, this has recently been supported by a new NMR technique called spin saturation transfer difference (SSTD) which has been developed by the group.[52]

This technique allowed them to study the dynamic behaviour of the Pt-allene complex in solution, and has shown that the platinum is coordinated to the less substituted allene in an η^2 fashion in the ground state, allowing for addition of the alcohol nucleophile to the terminal carbon of the allene. Instead of protonolysis as seen in the gold-catalysed reaction, this step is followed by protonation of the internal carbon of the allene, assisted by an extra molecule of methanol to form the platinum-carbene intermediate **79** which undergoes a 1,2-H shift to give intermediates **80/80'.**

This has been identified by DFT calculations as a resting state on the catalytic cycle and is observed as an enol ether activated by the platinum and ready for the second addition of alcohol to form intermediate **81**.[53] Protonation of the platinum centre and reductive elimination occur with formation of the aliphatic acetal species **74** (**Scheme 19**). A full mechanistic study has been carried out by our group and more details will be discussed in relation with the mechanisms proposed in this thesis within the corresponding section of the results and discussion chapter.



Scheme 19. Proposed mechanism for the Pt(II)-catalysed dihydroalkoxylation of allenes to form aliphatic acetals.

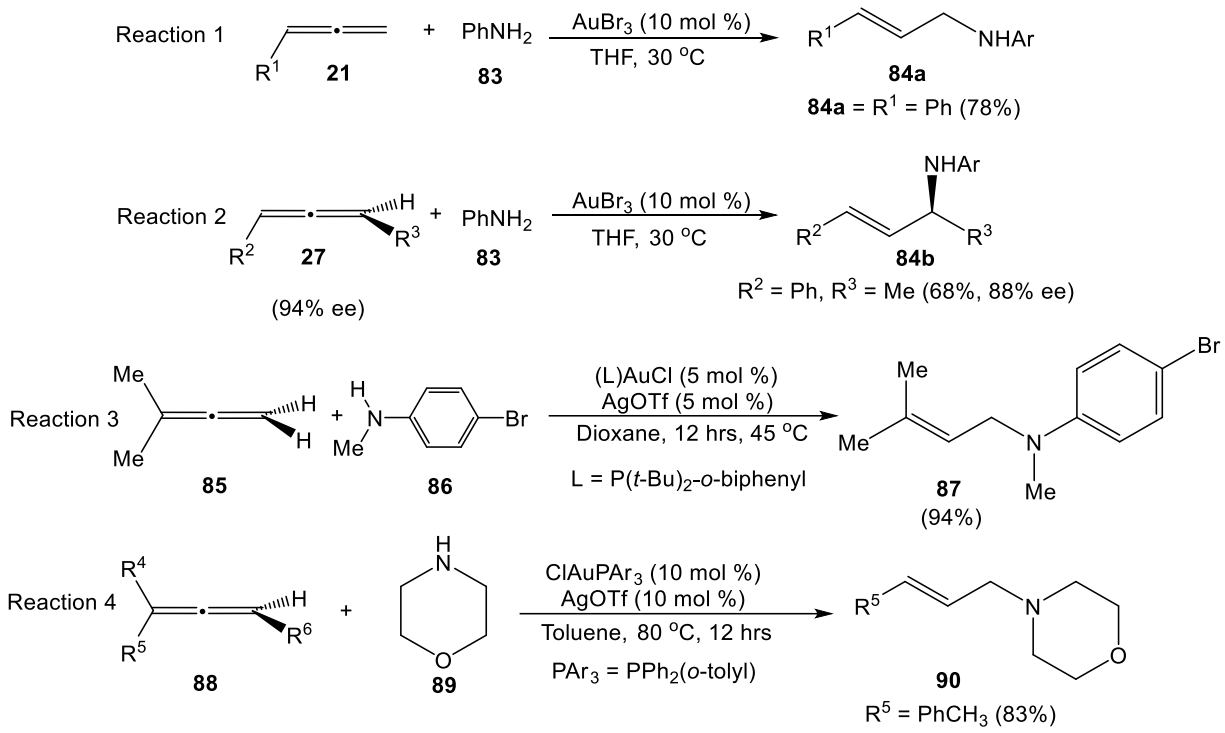
1.4.c. Metal-catalysed intermolecular hydroamination of allenes

Acyclic and heterocyclic nitrogen containing compounds are important components of many naturally occurring and biologically active molecules as well as being useful building blocks for organic synthesis. Therefore, effective and atom-economical processes for the synthesis of functionalised amine derivatives have been published over recent years with hydroamination receiving considerable interest.

Of interest to this thesis is the metal-catalysed hydroamination of allenes, which can occur *via* intra-[54] or intermolecular processes, with a wide range of different catalysts being used for the intermolecular process. For example, group IV metals,[55] Zr and Ti, which catalyse the formation of imines and Pd(II)[56,57] and Rh[58,59] complexes which catalyse the formation of allylic amines, as well as Au(I), Au(III) and Pt(II)[60] which will be discussed in more detail.

Nishina and Yamamoto were the first group to report the use of Au(III)[42a] catalysis for the hydroamination of allenes using aryl amines. The reaction uses $AuBr_3$ to catalyse the addition of aniline **83** (Reaction 1 and 2, **Scheme 20**) to non-chiral **21** and chiral **27** allenes at ambient temperature giving good to high yields of the corresponding allylic amines **84a** and **84b** (Reaction 1 and 2, **Scheme 20**). This reaction is reported to work well with mono-substituted aryl- and alkyl allenes as well as 1,3-disubstituted allenes in which transfer of chirality is observed to give enatiomerically enriched *E*-allylic amines **84b** with high ee. Mechanistic insight into the reaction suggests that it proceeds similarly to mechanism 2, **scheme 13**, where an aniline-gold complex like **57** forms and coordinates to the less hindered face of the allene . The *E*-alllyic amine is proposed to form *via* isomerisation between *Z* and *E* vinyl gold intermediates.[61] These factors solve the four selectivity problems positional-, chemo-, regio- and stereo-selectivity of substituted allenes, which are described in section 1.4.[34]

The addition of aryl amines to allenes has also been studied by other groups and in 2010 the group of Widenhoefer[62] reported their Au(I)-NHC catalysed hydroamination reaction for the successful addition of primary and *N*-alkyl anilines to mono-substituted and 1,1- and 1,3-disubstituted allenes. For example, the addition of 4-bromo-*N*-methylaniline **86** to 3-methyl-1,2-butadiene **85** using Au(I) catalysis to give the corresponding *N*-Methyl-*N*-prenylaniline **87** as a single regioisomer showing the reaction to have good diastereoselectivity as well as excellent regioselectivity (Reaction 3, **Scheme 20**). The group propose that the reaction can proceed either by an inner-sphere (Mechanism 1, **Scheme 13**) or an outer-sphere mechanism (Mechanism 2, **Scheme 13**) because there was not enough data to decide between the two. However, since then, mechanistic studies using gold catalysis have identified that the outer-sphere mechanism is most likely to be correct.[67,69]

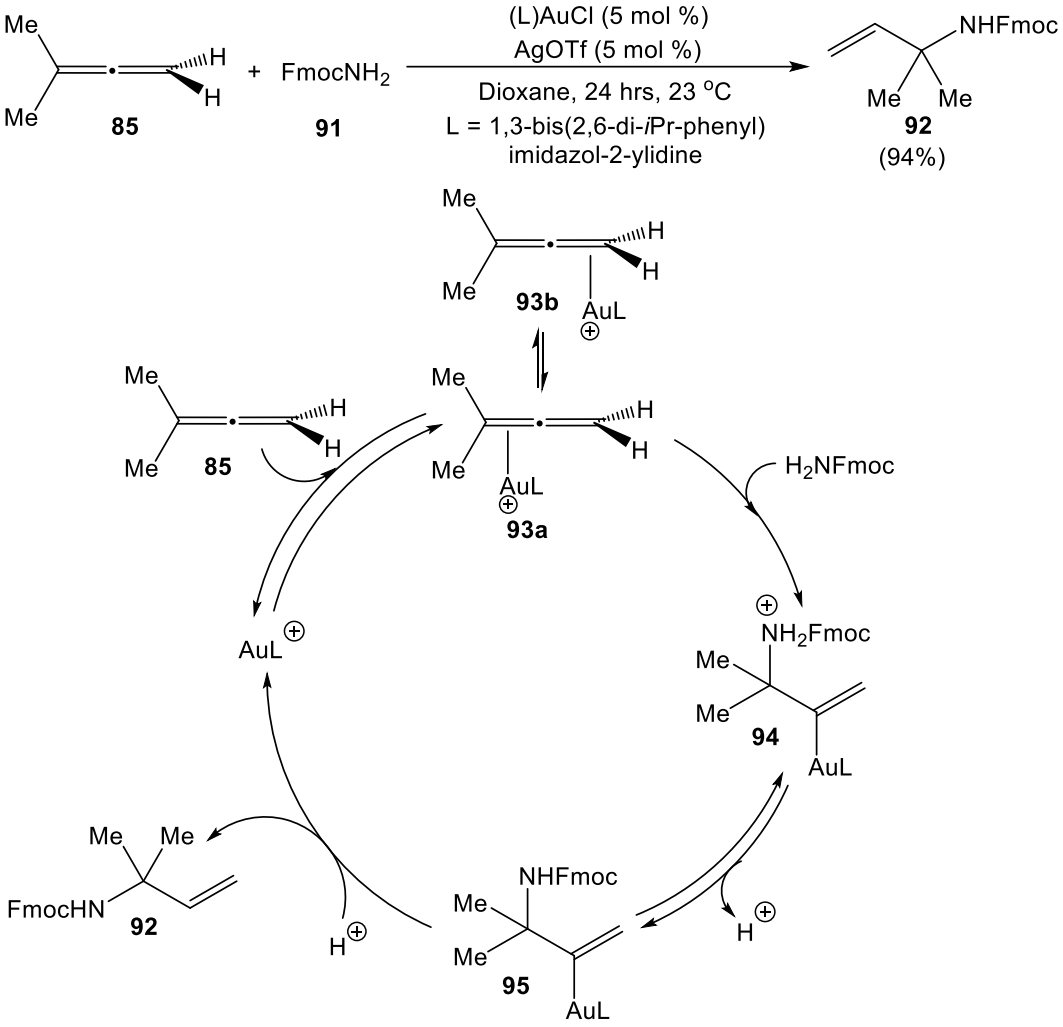


Scheme 20. Reaction schemes for Au(III) and Au(I) catalysed hydroamination of non-chiral and chiral allenes to form allylic amines.

Alongside the addition of aryl amines, the group of Yamamoto[42b] also published their results for the Au(I)-catalysed reaction involving the addition of aliphatic nitrogen nucleophiles, morpholine **89** (Reaction 4, **Scheme 20**), to allenes **88** using Au(I)-phosphine systems to form a range of different allylic amines **90** depending on the substituents. Studies of this reaction found that the Au(I)-phosphine system combined with a silver source as well as variations on the steric environment around the gold centre enhances the intermolecular addition of the nitrogen nucleophile. This enables the reaction to work with less reactive nucleophiles and increases the yield of the corresponding allylic amine.

Hydroamination reactions involving the addition of the nitrogen nucleophile to the more substituted carbon of the allene to form N-tertiary allylic amines has not received as much attention. However, in 2008, the group of Widenhoefer[63] reported their results for the Au(I)-NHC catalysed addition of *N*-unsubstituted carbamates to allenes forming a range of *N*-tertiary allylic amines. The reaction was reported to work well with 1,1- and 1,3-disubstituted, tri-substituted and tetra-substituted allenes. For example, the addition of 9-fluorenylmethyl carbamate **91** (**Scheme 21**) to 3-methyl-1,2-butadiene **85** (**Scheme 21**) using Au(I)-catalysis to form the corresponding *N*-tertiary allylic carbamate **92** (**Scheme 21**).

The group proposed an outersphere addition of the carbamate to the gold π-allene complex **93a,** which is in a rapid and reversible interconversion with **93b**,[64] forming the vinyl-gold complex **94,** this complex loses a proton to form **95** which then undergoes protonolysis to release the *N*-tertiary allylic amine **92** (**Scheme 21**).

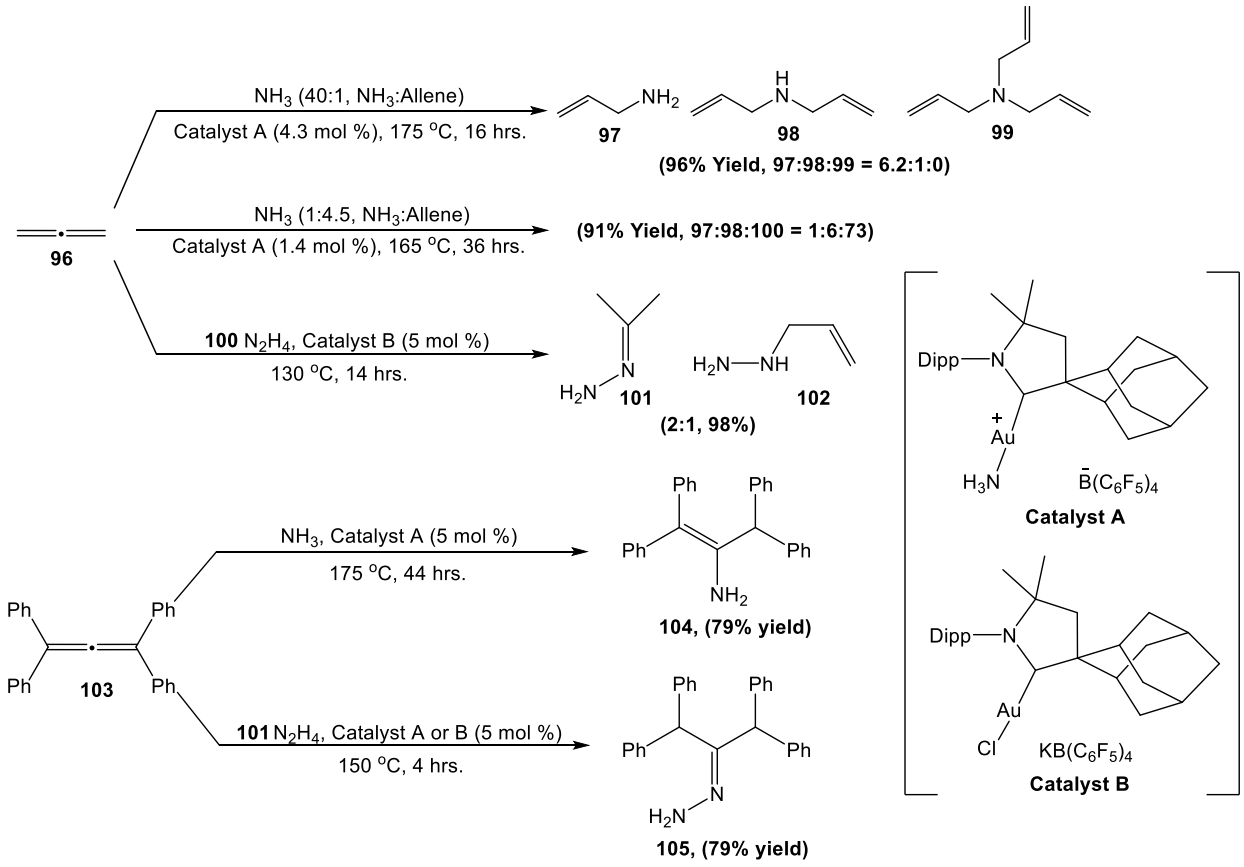


Scheme 21. Reaction scheme and proposed mechanism for Au(I)-catalysed hydroamination using *N*-unsubstituted carbamates to form *N*-tertiary allylic amines.

Addition of the larger nitrogen nucleophiles to allenes has been well reported with gold catalysis, however the addition of smaller nitrogen nucleophiles such as ammonia and hydrazine has not received as much attention, probably because of their selectivity problems and the ability for them to form Werner complexes, which deactivate the catalyst.[65] It was the group of Bertrand that explored the addition of both ammonia[66] and hydrazine[67] nucleophiles to allenes using Au(I)-CAAC complexes to form a range of structures with addition of these nucleophiles to either the terminal carbon of allene or the central carbon of the allene. The group identified that the addition reaction would only proceed if the gold centre of the catalyst is coordinated to a CAAC ligand and is rendered cationic by chloride abstraction.

Bertrand reported that NH_3 addition occurs at the terminal carbon of the allene for mono-, di- and tri-substituted allenes, forming a mixture of mono-, di- and tri-substituted amines, with selectivity being controlled by variation of the NH_3:allene ratio. For example, 40:1 (NH_3:allene) gives selectivity for the mono-allylic amine **97**, whereas 1:4.5 (NH_3:allene) gives selectivity for the tri-substituted amine **99** (**Scheme 22**).

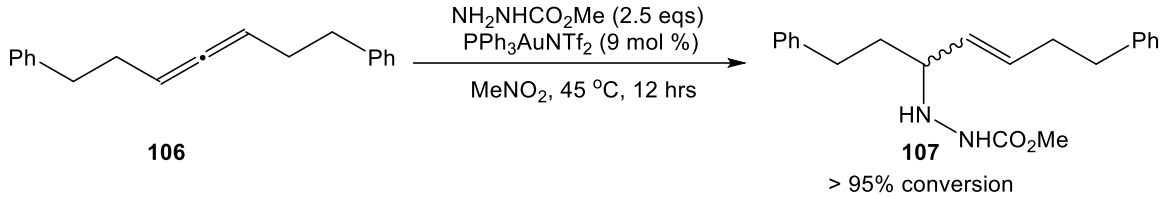
However, addition of hydrazine, N_2H_4 **100**, to allene **96** occurs at the central and terminal carbon of the allene forming a mixture of imine and allylhydrazine respectively. For example, the addition of N_2H_4 **100** to 1,2-propadiene **96** gives a 2:1 mixture of hydrazone **101** and allylhydrazine **102** (**Scheme 22**) with high yield.



Scheme 22. Reaction schemes for the addition of ammonia and hydrazine to allenes using Au(I)-CAAC complexes to yield allylic amines and imines.

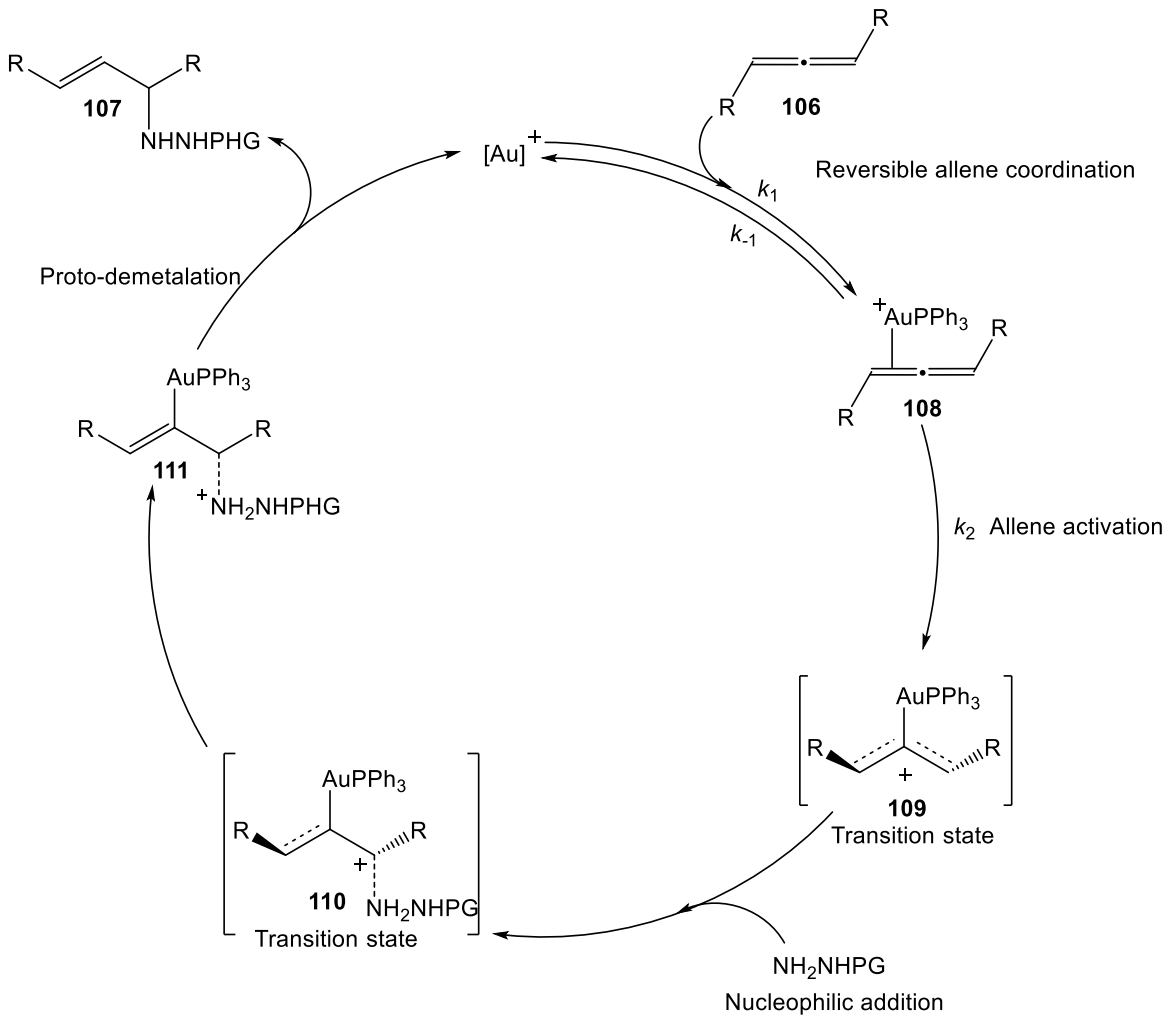
Bertrand[65] also reported that addition of both ammonia and hydrazine to allenes works well with tetra substituted allenes, e.g. tetra-phenyl-1,2-propadiene **103**, where steric factors affect the regioselectivity of the reaction resulting in the selective formation of the mono-hydroamination product **104** from NH_3 addition at the central carbon of the allene and the selective formation of hydrazone **105** (**Scheme 22**) from the addition of hydrazine at the central carbon of the allene with high yields.

In 2010,[68] the Toste group reported their results from the full mechanistic investigation into the hydroamination of allenes with carbazate nucleophiles. They achieved this by investigating the reaction of methyl carbazate with the symmetrical allene 1,7-diphenylhepta-3,4-diene **106** in the presence the Au(I) catalyst, $Ph_3PAuNTf_2$, with subsequent formation of the allyl derivative **107** (**Scheme 23**).



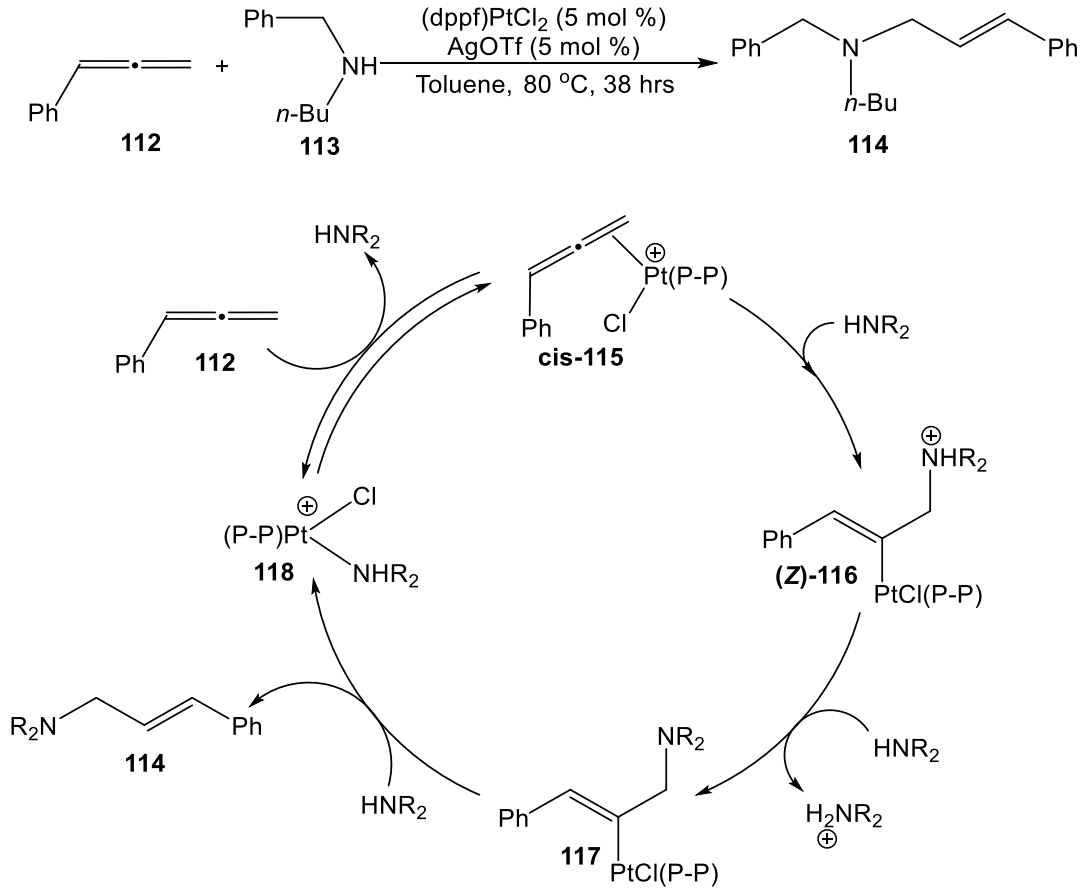
Scheme 23. Reaction scheme for hydroamination of di-substituted allene with methyl carbazate forming the corresponding allylic carbazate.

The group investigated the mechanism of this transformation to determine the role of each reagent in the catalytic cycle and the composition of the rate-limiting transition state. They carried out kinetic analysis, DFT calculations, NMR experiments, chirality transfer and Hammett analysis to establish that the reaction is first order with respect to Au and the allene, and zero order with respect to the nucleophile. They determined that the gold-allene complex is rapidly exchanging between the two diasteromeric faces of the C_2 symmetric allene. Their findings led them to propose an outer-sphere mechanism where the activation of the Au(I) catalyst to form the corresponding η^1-bent allene-gold complex **109** is the rate-limiting transition state and the nucleophilic addition occurs afterwards (**Scheme 24**).[67,69]



Scheme 24. Proposed outer-sphere mechanism for the hydroamination of symmetrical allene 1,7-diphenylhepta-3,4-diene in the presence of Au(I) catalyst $Ph_3PAuNTf_2$.

It is clear to see that the hydroamination of allenes using Au(I) and Au(III) complexes has received a lot of attention over the years with a range of different allylic amines being formed. However, the use of platinum catalysis has received far less attention with only one reported example by Toups and Widenhoefer in 2010.[60] They reported the use of Pt(II)-catalysts for the addition of secondary alkylamines to mono-substituted allenes to selectively form *E*-allylic amines in good to high yields. Based on work by Panunzi *et al.*,[70] the group suggested the use of neutral mono(phosphine) complexes, however these led to low yields and poor selectivities leaving the group to explore the use of cationic platinum bis(phosphine) complexes and their relevant phosphine bite angles. This led them to the $(dppf)PtCl_2$ catalyst which allowed the reaction to occur with several different mono-substituted allenes forming the corresponding allylic amines in good yields. For example, the addition of benzyl *n*-butyl amine **113** to phenylallene **112** in toluene at 80 ^{0}C for 38 hours gave the corresponding *E*-allylic amine **114** (**Scheme 25**) in a >50:1 *E/Z* ratio.



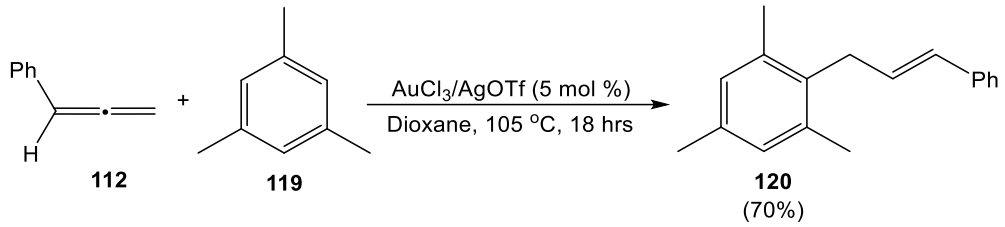
Scheme 25. Reaction scheme and proposed mechanism for the Pt(II)-catalysed hydroamination of allenes with secondary alkylamines.

The group proposed a mechanism that involves the formation of a platinum π-allene complex[71] **115,** achieved after initial chloride abstraction using AgOTF to form the cationic Pt-Amine complex **118**, followed by displacement of HNR_2 by the free allene**.** Outer-sphere addition of the amine to **115** forms the vinyl-platinum complex *Z*-**116**, which undergoes protonation with free amine, followed by an intermolecular protonolysis of the Pt-C bond to release the allylic amine **114** with regeneration of the cationic platinum amine complex **118** (**Scheme 25**).

1.4.d. Metal catalysed intermolecular hydroarylation of allenes

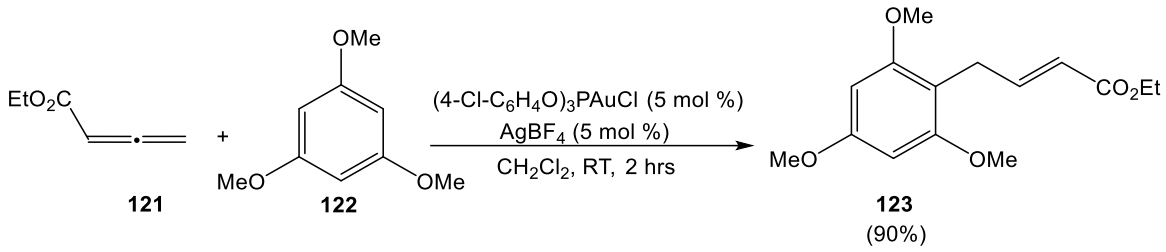
Metal-catalysed hydroarylation is an atom-economical process for the functionalisation of arenes, generating a variety of useful aromatic compounds with potential biological activities *via* the addition of aromatic C-H bonds across C-C multiple bonds. Reports for intermolecular hydroarylation have only recently flourished in comparison to the intra-molecular process. Most intermolecular hydroarylation examples reported are carried out with gold catalysis, with the first reported example by Skouta and Li in 2008.[72] They used Au(III) catalysis as a mixture of $AuCl_3$/AgOTf for the addition of electron-rich arenes, like mesitylene **119**, with allenes, such as 3-phenylpropa-1,2-diene **112**, to form the corresponding *E*-allylic arene product **120** in high yield (**Scheme 26**).

The reaction is reported to work well with a range of substituted arenes, however when highly-electron rich indoles were tested, the reaction did not proceed.



Scheme 26. Reaction scheme for Au(III)-catalysed hydroarylation of allene **115**.

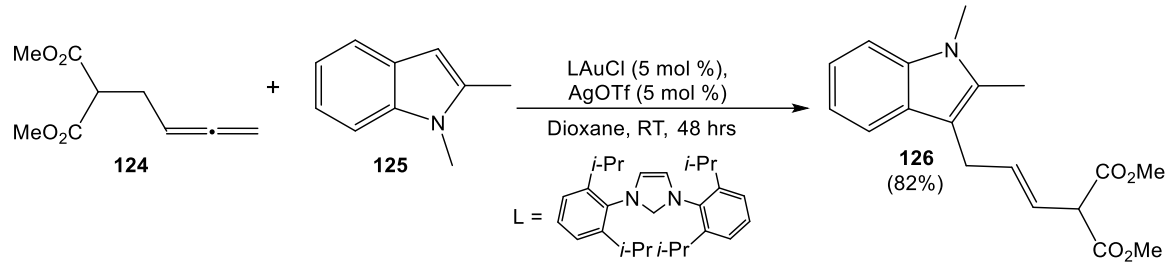
The group of Gagné[73] proposed a similar reaction with the addition of methoxy substituted arenes to unhindered monosubstituted allenes to form *E*-allylic products using a catalytic amount of (4-Cl-C_6H_4-O)$_3$PAuCl/$AgBF_4$. For example, the addition of 1,3,5-trimethoxybenzene **122** to ethyl 2,3-butadienoate **121** to form the corresponding allylic product **123** in a 90% yield (**Scheme 27**). The reaction with indoles, pyrroles and furans was again unsuccessful.



Scheme 27. Reaction scheme for Au(I)-catalysed hydroarylation of allene.

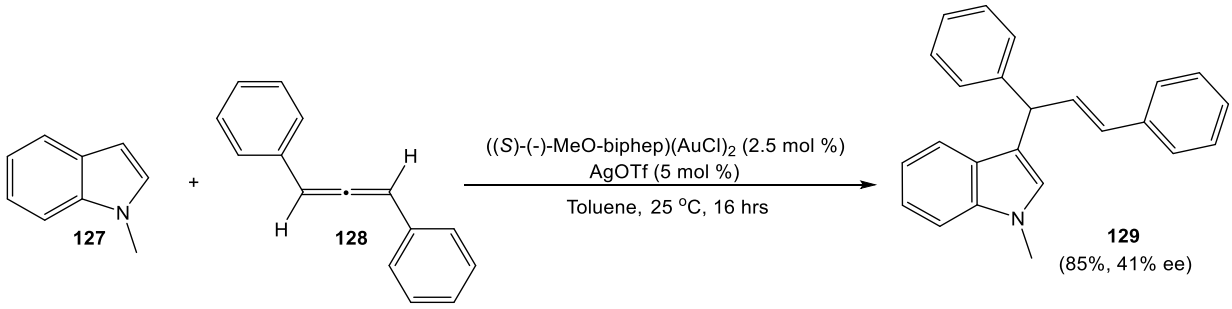
Although the above examples do not extend to highly electron rich indoles, pyrroles and furans, there are examples where gold catalysis has been successfully used to synthesise 3-allylic indoles. In 2009, the group of Widenhoefer[74] reported the use of Au(I)-NHC complexes for the addition of *N*-Me, NH and 2 and 5 substituted indoles to mono-, 1,3- and tetra-substituted allenes. For example, the addition of 1,2-dimethylindole **125** to dimethyl 2,3-butadienylmalonate **124** catalysed by a 1:1 mixture of LAuCl and AgOTf to form the corresponding 3-allylic indole **126** product as a single regio- and stereoisomer (**Scheme 28**).

The group proposed that the mechanism will most likely mirror that of the hydroalkoxylation and hydroamination reactions, *via* an outer-sphere attack, although they report that the hydroarylation process with differentially substituted allene displays lower regioselectivity in comparison.



Scheme 28. Reaction scheme for Au(I)-NHC catalysed hydroarylation of allene with indole.

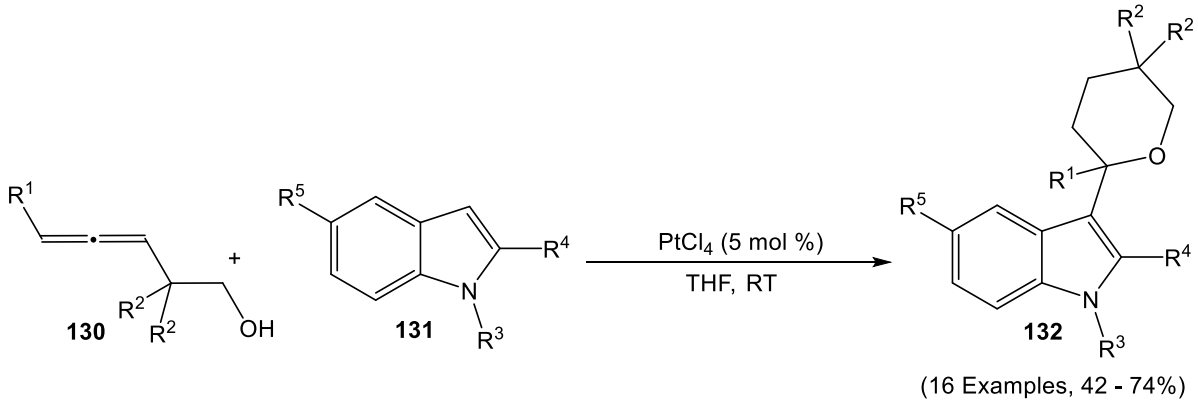
Che and co-workers[75] were the first group to report the enantioselective hydroarylation reaction of racemic allenes with indoles, using a 1:2 mixture of *(S)*-(-)-MeO-biphep$(AuCl)_2$ and AgOTf as the catalytic system to synthesise the corresponding 3-allyl indoles with moderate enantioselectivity. For example, the reaction of N-methylindole **127** with 1,3-diphenylallene **128** using the catalytic mixture gives the corresponding 3-alkylated indole **129** in an 85% yield with 41% *ee* (**Scheme 29**).



Scheme 29. Reaction scheme for Au(I)-catalysed enantioselective hydroarylation of racemic allenes with indole.

The reaction was reported to work well with a range of 1,3-diaryl allenes, giving good yields and moderate enantioselectivities, with higher enatioselectivity and yields being achieved when the *para* position of the aryl moiety contained an electron withdrawing group. The group carried out DFT calculations, which revealed that the free indole undergoes intermolecular addition to the Au-allene intermediate and this addition contributes to the enatioselectivity of the reaction.

Although gold has been readily reported for hydroarylation of allenes, other metals have been used for this type of reaction. For example, in 2012 Suresh and Swamy[76] reported a new route for the formation of indolo[2,3-*c*]pyrane-1-ones *via* palladium catalysed reaction of allenes with indole-2-carboxylic acid derivatives, with comparison of Ar-I reactivity and C-H functionalisation. In addition, platinum catalysis has been reported for the successful hydroarylation of allenes. For example, Ma *et al.*[77] in 2009 reported the highly regioselective $PtCl_4$ catalysed reaction of substituted indoles **131** with β-allenols **130**. This allowed formation of the indole derivatives bearing a 6-memebered ether rings at position 3 **132** in moderate isolated yields (**Scheme 31**).

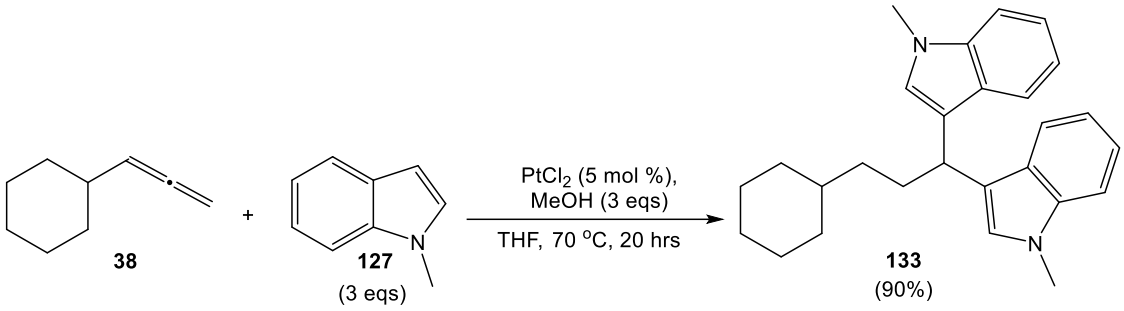


Scheme 31. $PtCl_4$-catalysed reaction of β-allenols with indoles, affording indole derivatives bearing 6-memebered ether rings **132**.

This reaction has been reported to work well with a range of *N*-unprotected indoles as well as ones bearing substituents in position 5, however, when *N*-protected indoles are used the isolated yields are lower.

The group also carried out deuterium-labelled experiments to determine the mechanism of the reaction and found that addition of the allenol to the activated indole occurs first, followed by the cyclisation to form the desired product.[76]

The use of platinum for the hydroarylation of allenes with indoles has also been reported by the Muñoz group in 2012.[78] This is the only reported platinum example for the double addition of indole to the allene, and it is based on their previously published work for the dihydroalkoxylation reaction.[55] They reported the same reaction conditions for the successful incorporation of indole and substituted indoles onto allenes, with subsequent formation of 3,3'-bis-indolylmethane (BIM). For example, the $PtCl_2$ catalysed reaction of cyclohexylallene **38** with N-methylindole **127** gives the corresponding 3,3'-BIM **133** in a 90% yield (**Scheme 32**).

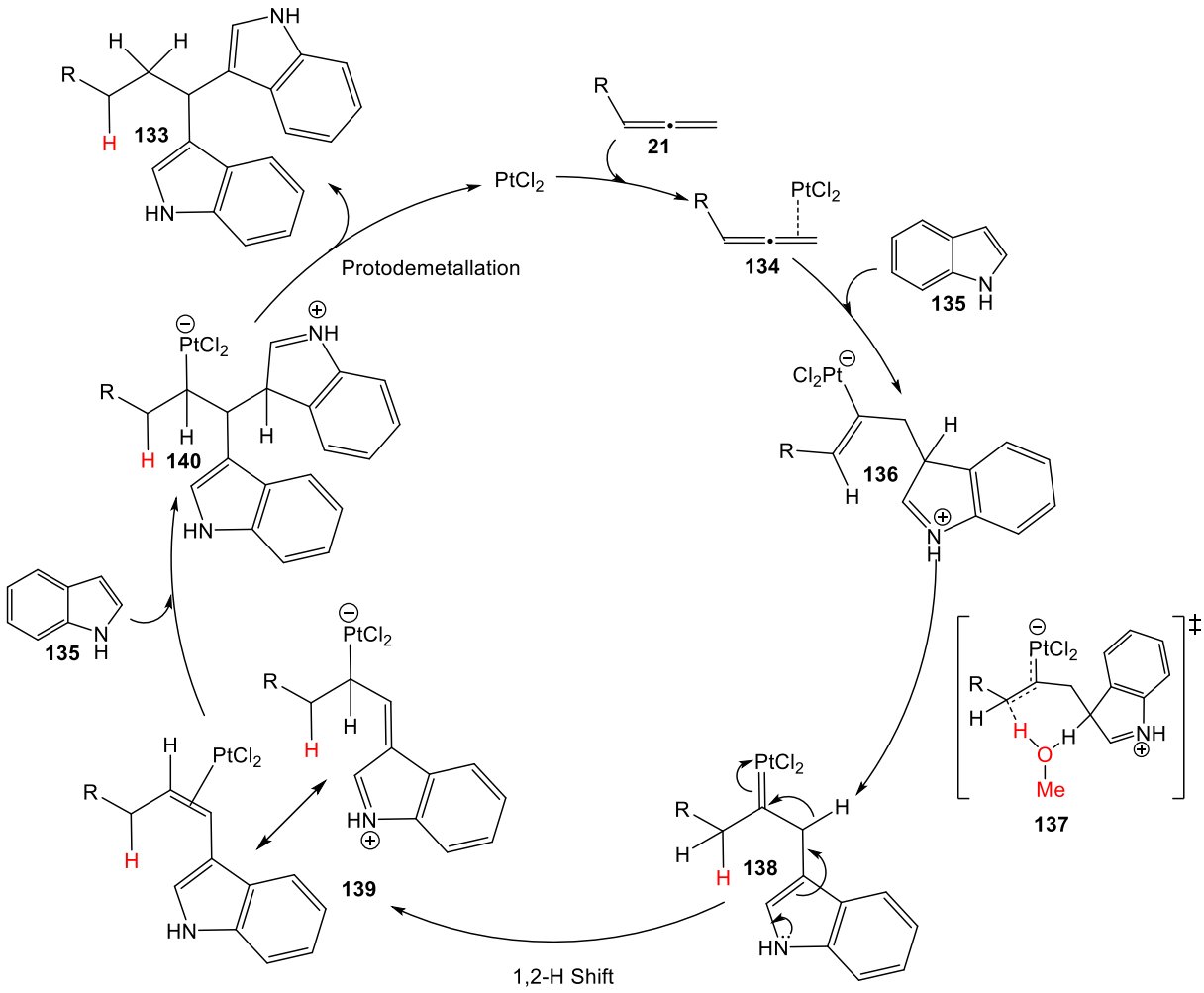


Scheme 32. Reaction scheme for Pt(II)-catalysed hydroarylation of allene with substituted indoles.

This platinum catalysed reaction is different to the gold catalysed reaction, where we observe the formation of 3-allylic indoles *via* single indole addition. Here, the platinum catalysed reaction mirrors that of the dihydroalkoxylation process with the addition of two molecules of indole to the terminal, less hindered carbon of the allene with complete saturation of the internal bond to give the corresponding BIM. These BIMs are key products from the work carried out in this thesis; they are biologically active molecules and will be discussed in detail later in the thesis.

The group found that methanol is a key additive for the reaction with an increase in yield observed when 3eqs of methanol were added. This has been investigated in more depth in relation to the mechanism of formation of acetals described in **scheme 33**. Mechanistic studies ruled out the formation of acetal species as an intermediate for the bisindolylation and instead they propose that the platinum coordinates to the allene in an η^2 fashion allowing the addition of the first indole molecule giving the vinyl-Pt intermediate **136,** which is analogous to the gold reaction. Again, instead of protodemetallation to form the allylic derivative, protonation of the internal carbon to form the carbene **138** is observed.

This step is likely to be where the methanol plays its role by acting as proton shuttle to aid the exchange of protons *via* the transition state **137**. Following this, a 1,2-H shift occurs forming intermediate **139** where a 2nd indole unit adds to form the final intermediate **140**. Finally, protonation of the platinum alongside reductive elimination occurs to form the 3,3'-BIM **133 (Scheme 33**).



Scheme 33. Proposed mechanism for the double indole addition to allenes catalysed by $PtCl_2$.

Other nitrogen containing aromatic nucleophiles such as pyrazole and imidazole have been reported for their successful addition to allenes with the formation of allylic branched alkaloid derivatives. These were reported by Breit *et al.*[79] using Rh catalysis with a variety of different ligands, the addition of pyrazole and imidazole to allenes has been explored in this thesis and will be discussed in the results and discussion section.

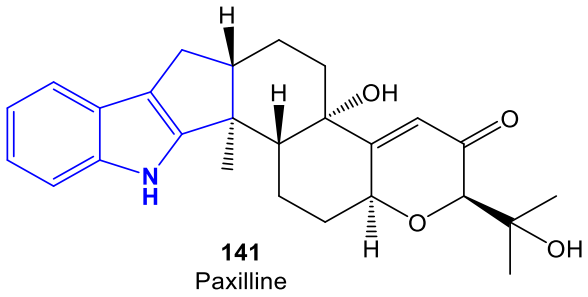
1.5. Metal catalysed intramolecular addition of indoles to allenes.

As mentioned earlier, metal-catalysed intramolecular nucleophilic addition to allenes is a broad area of chemistry with a range of metals such as Ru, Pd, Rh, Au and Pt catalysing the addition of nitrogen[80], oxygen[81], sulphur[82] and carbon[83] based nucleophiles. These reactions are synthetic routes to a variety of different heterocyclic compounds of importance to both chemical synthesis and pharmaceuticals because of their diverse properties.

Metal-catalysed intramolecular addition of indoles to allenes is significant to this thesis, in particular, the cyclisation of indoles tethered with allenes in either the C3, C2 or N position. This is a relatively new area with only a few examples for each position having been reported in the last decade. However, it has become a particularly important area because of the biological and physical applications of the resulting heterocyclic compounds containing a carbazole unit. These are key molecular motifs found in a variety of natural products, for example the Murraya trees, which are grown in southern Asia, as well as being present in many mono- and polymeric materials.[84]

1.5.a. Metal catalysed intramolecular reaction of C3 substituted indolyl allenes

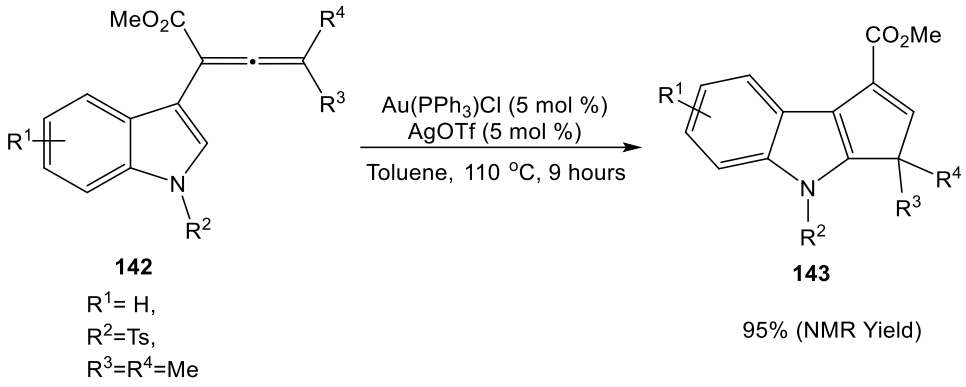
The first example involving the cyclisation of 3-allenylindole derivatives was reported in 2012 by Ma *et al.*[85] when they developed an Au(I)-catalysed method for the formation of dihydrocyclopenta[*b*] indole derivatives. These cyclopenta[*b*] indole units are found in a wide range of indole alkaloids, such as paxilline **141** (**Figure 13**) which is used as a selective blocker of high conductance calcium-activated potassium channels.[86]



141
Paxilline

Figure 13. Structure of paxilline highlighting the cyclopenta[*b*] indole unit in blue.

The group established that an electron-withdrawing group on the allene is essential for the transformation to proceed as it selectively activates the two C=C bonds of the allene moiety allowing for C2-H functionalisation of the indole unit. Optimisation of conditions found that the $Ph_3PAuCl/AgOTf$ catalytic system was the best for catalysing the cyclisation of indole-allenoate **142** forming the corresponding dihydrocyclopenta[*b*] indole **143** (**Scheme 34**).



142

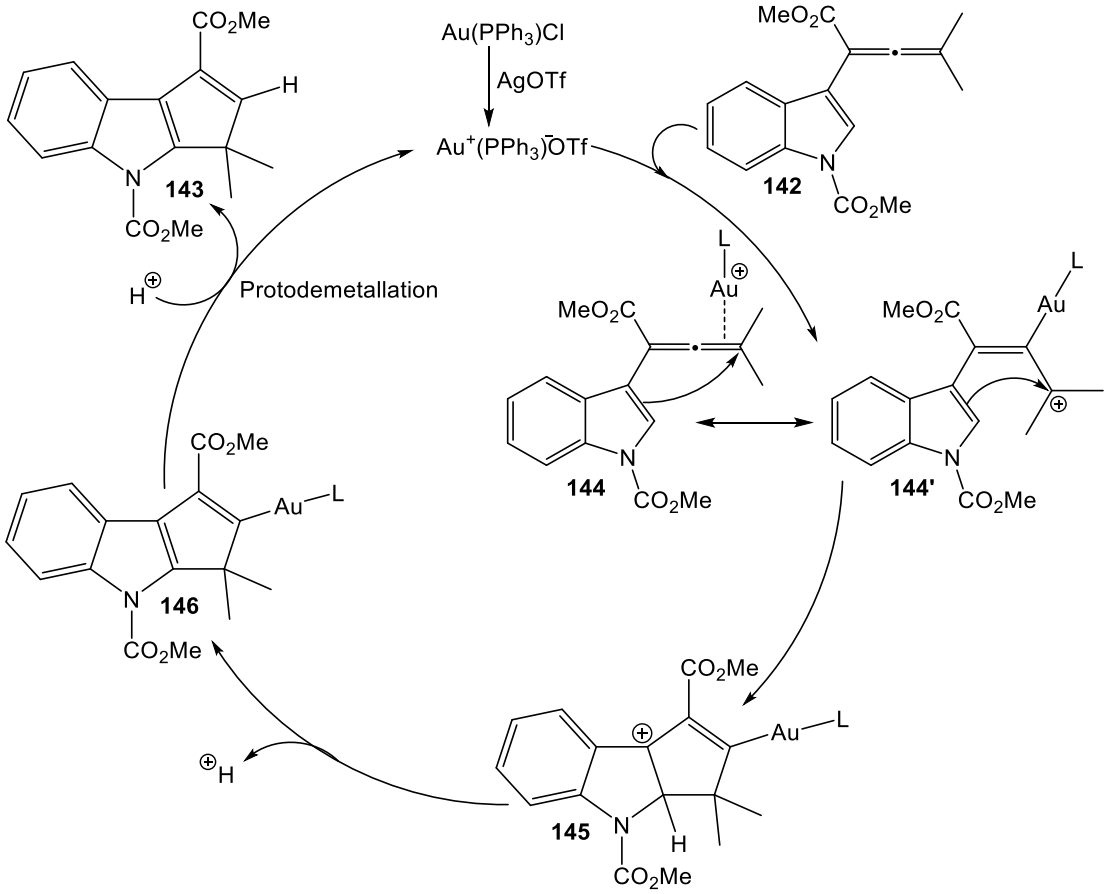
R^1= H,
R^2=Ts,
R^3=R^4=Me

143

95% (NMR Yield)

Scheme 34. Reaction scheme for Au(I)-catalysed cycloaddition of indole-allenoates with formation of corresponding dihydrocyclopenta[*b*] indole **143**.

Various substituted indolylallenes were investigated and reported to work well with alkyl, alkoxy or halide groups on the indole unit (R^1), different protecting groups (R^2) Ts, Bz, SO_2Ph, CO_2Ph or CO_2Me as well as with different alkyl or cycloalkyl groups at R^3 and R^4, giving the corresponding products in excellent yields. The proposed mechanism involves the coordination of the cationic gold species to the allene, activating it towards attack by the C2 of the indole with formation of the vinyl gold intermediate **144**. Deprotonative aromatisation of intermediate **144** followed by demetallation generates dihydrocyclopenta[*b*] indole **143** *via* intermediate **146,** with regeneration of the cationic gold catalyst (**Scheme 35**).



Scheme 35. Proposed mechanism for the Au(I)-catalysed cycloaddition of indole-allenoate.

A similar method for the formation of these dihydrocyclopenta[*b*] indole **143** (**Scheme 34**) has been reported by Wang *et al.*[87] *via* in situ formation of the 3-allenyl indole **142** from the 3-alkenylation of indole in the presence of triflic acid.

In 2013 Sanz *et al.*[88] reported their results on the Au(I)-catalysed cycloisomerisation of 3-allenylmethylindoles, containing one carbon more between indole and allene, for the synthesis of 4,9-dihydro-1H-carbazoles. This is the first efficient methodology using gold catalysis for the synthesis of 4,9-dihydro-1H-carbazoles despite their importance in natural products such as dihydrotubingensins A (**147**) and B (**148**) (**Figure 14**).[87,89]

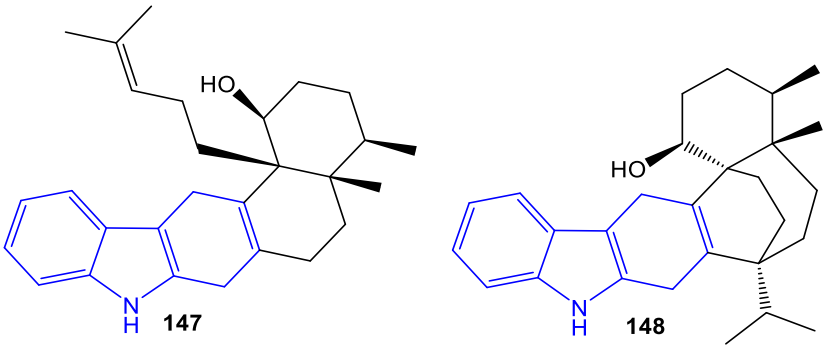
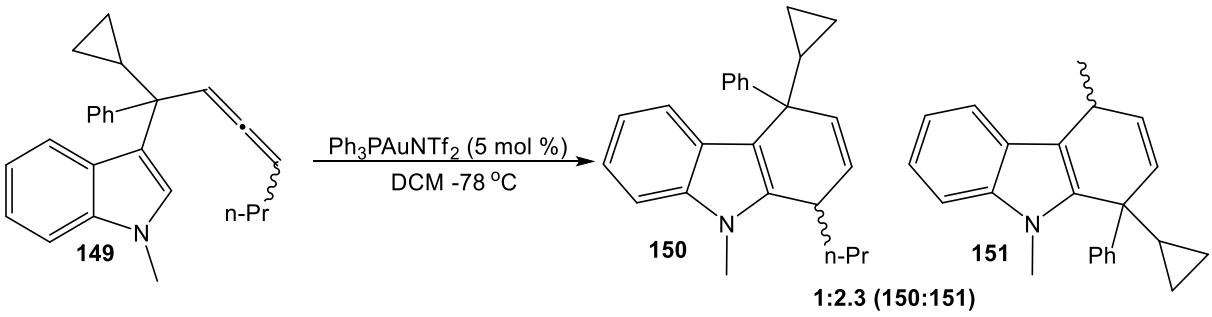


Figure 14. Natural product dihydrotubingensins A and B containing the 4,9-dihydro-1H-carbazole unit.

Initial reactions carried out by the group identified that cycloisomerisation of di-substituted allene derivatives yielded a mixture of carbazole regioisomers, for example the reaction of 3-(1-cyclopropyl-1-phenylhepta-2,3-dien-1-yl)-1-methly-1H-indole **149**, using $Ph_3PAuNTf_2$ as the catalyst at -78 ^{0}C yielded a mixture of regioisomers **150** and **151** in a ratio of 1:2.3 (**Scheme 36**). However, after extensive screening of catalytic systems and solvents, they established that appropriate combination of catalyst and solvent could alter the regioselectivity of the reaction due to the formal alkyl migration involved in the formation of compound **151** as explained by the proposed mechanism in **scheme 37**.

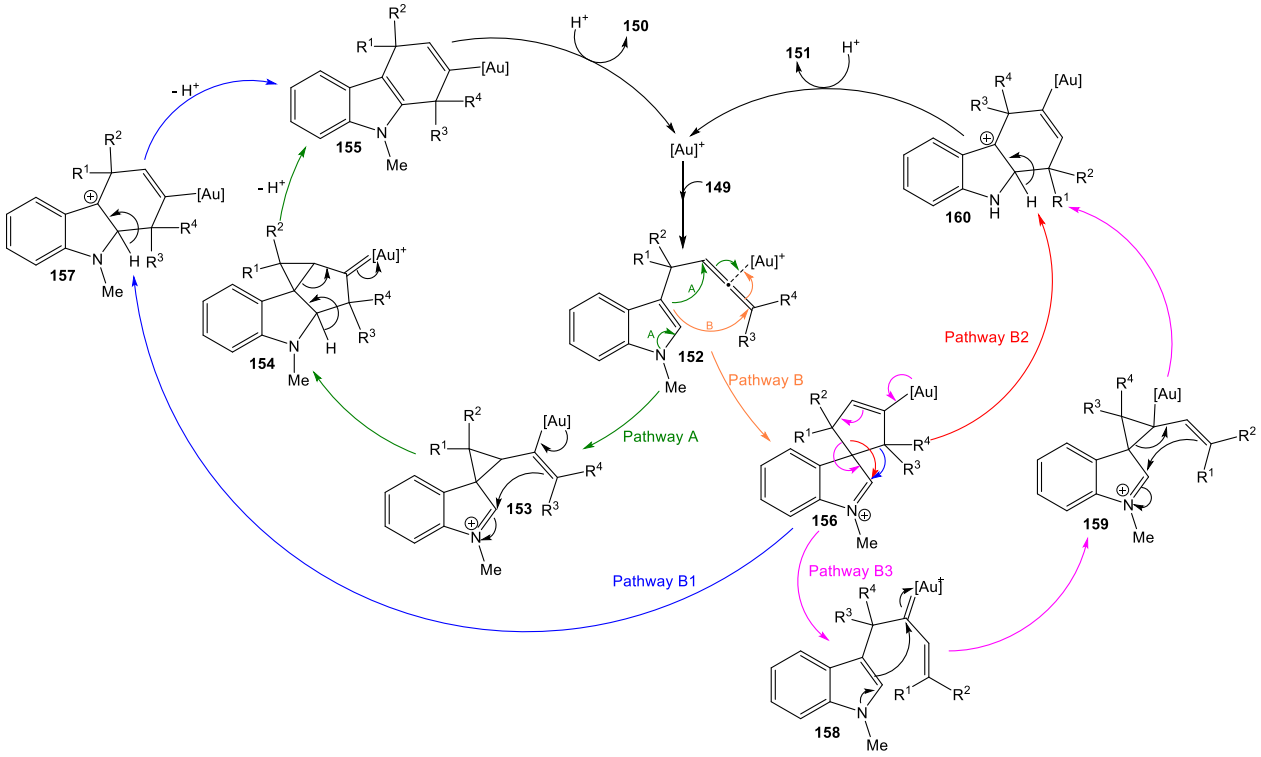


Scheme 36. Au(I)-catalysed cycloisomerisation of di-subsituted indolyl allene using method B.

Selective formation of both dihydrocarbazole isomers **150** and **151** could be achieved *via* the proposed methods A and B. Method A uses a combination of $(PhO)_3PAuCl/AgOTf$ in toluene to selectively produce **150**, whereas method B uses PPh_3AuNTf_2 in DCM to selectively produce **151.**

After a comprehensive study into the influence of substituents on the starting substrate, it was revealed that allenylindoles with di- or tri-substituted allene moieties regioselectively react to form the expected regioisomer **150** in good yields. Whereas, the unexpected regioisomer **151** is isolated from allenylmethylindoles with a quaternary centre at the allylic carbon using method B if the terminal carbon of the allene is unsubstituted or mono-substituted with a bulky alkyl group. The group have proposed a mechanism which suggests that the formation of **150** and **151** could occur *via* two pathways A and B.

Firstly, the allene is activated by coordination of the gold catalyst allowing for the intramolecular addition of indole at the more nucleophilic position C3 generating either spirocycle **153** or **156**. In pathway A, spirocycle **153** evolves *via* a 5-exo cyclisation to give the gold carbenoid **154**. Rearomatisation of this triggers the ring opening of the cyclopropane ring forming the vinyl gold intermediate **155,** which undergoes demetallation to yield product **150** (**Scheme 37**).

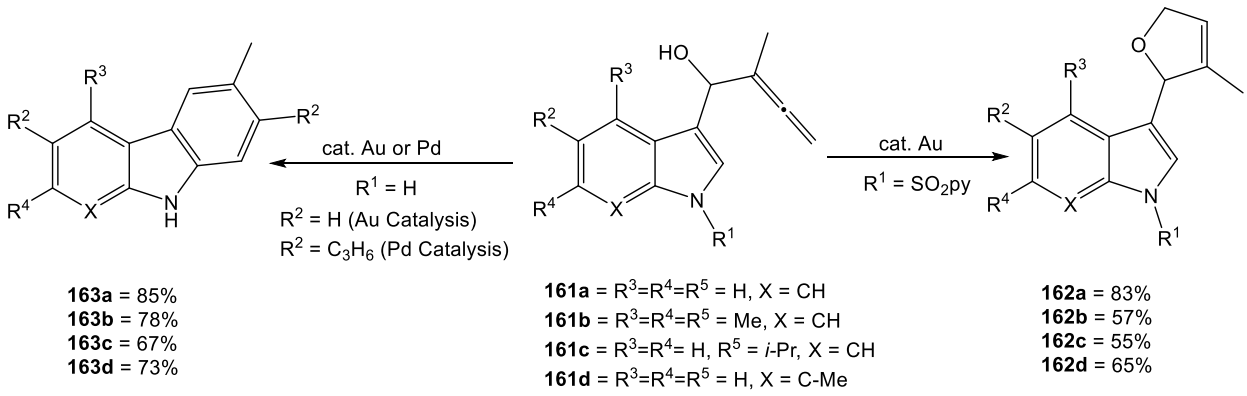


Scheme 37. Proposed mechanism for the cycloisomerisation of 3-allenylmethylindoles via various pathways to generate the two regioisomers **150** and **151**.

Pathway B generates spirocycle **156,** this intermediate can evolve in 3 different ways; pathway B1 involves the ring opening to intermediates **157** and **155** to give the corresponding product **150**. The two other pathways to form regioisomer **151,** involve a 1,2-alkyl shift of the carbon containing R^1 and R^2 through either pathway B2 with subsequent protodemetallation of the cationic gold intermediate **160**, or the step-wise pathway B3, which involves the formation of the gold carbenoid species **158** which undergoes cyclisation, ring opening and protodemetallation to afford the final regioisomer **151** (**Scheme 37**). The group have obtained some evidence for the viability for pathways A and B3.

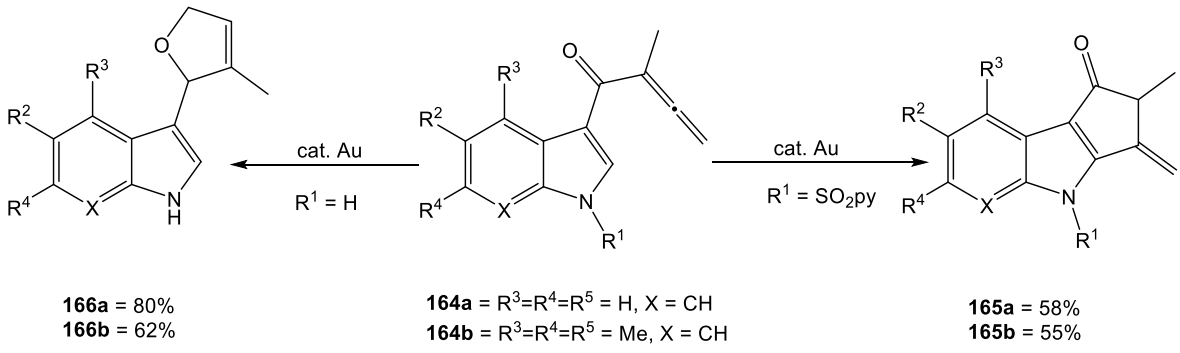
Another example using C3 functionalised indolyl allenes was reported by Alcaide *et al.*[90] in 2013, when they reported the metal-catalysed carbocyclisation and oxycyclisation of C3-tethered α-allenols **161** and α-allenones **164**. They observed different cyclisation in the presence or absence of a protecting group on the nitrogen atom.

For example, they established that the Au-catalysed reaction of substituted *α*-allenol **161** would give either oxycyclisation in the presence of the *N*-(2-pyridyl)sulfonyl protecting group yielding compound **162** or in the absence of a protecting group benzannulations would occur to yield compound **163**. They also reported the carbocyclisation-functionalisation of **161** would occur when the allene reacts with an allyl bromide in the presence of Pd-catalyst forming further functionalised benzannulations **163** (**Scheme 38**).



Scheme 38. Reaction scheme for the gold and palladium oxy- and carbo-cyclisation of C3-tethered-α-allenols **161**.

The Au-catalysed reaction of C3-tethered-allenones was also reported to give two types of cyclisation when a protecting group was present. For example, the substituted C3-tethered-allenone bearing the *N*-(2-pyridyl)sulfonyl protecting group could undergo carbocyclisation to give the cyclopentaindolone compounds **165** as the major product and the furyl-indole derivatives **166** as the minor compounds (**Scheme 39**). However, when no protecting group is present on the nitrogen atom only the furyl-indole **166** is formed via the respective oxycyclisation (**Scheme 39**).

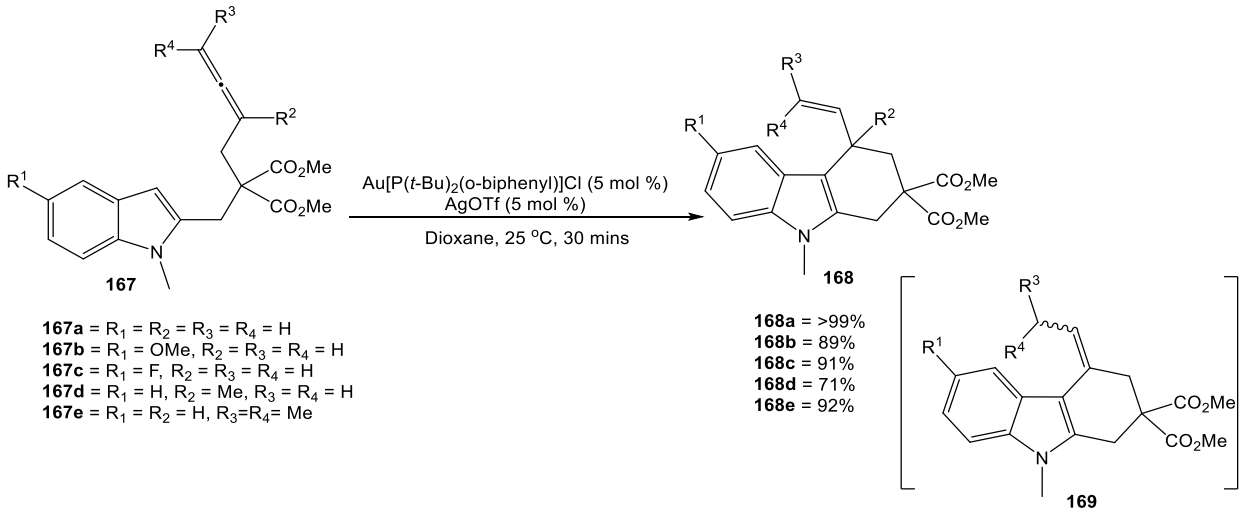


Scheme 39. Reaction scheme for the gold catalysed oxy- and carbo-cyclisation of C3-tethered-α-allenones **173**.

1.5.b. Metal catalysed intramolecular reaction of C2 substituted indolyl allenes

There are very few reported examples for the reaction of these C2 substituted indolyl allenes, with the earliest reported example by Widenhoefer *et al.* in 2006[91] and 2007,[92] with the use of gold-phosphine and bis(gold)phosphine complexes for the synthesis of carbazole derivatives. Their first report highlighted the use of the Au[P(t-Bu)$_2$(o-biphenyl)]Cl and AgOTf catalytic system for the 6-exo-hydroarylation of the internal double bond of 2-allenyl indoles **167a** with selective formation of carbazole derivatives **168** (**Scheme 40**). Other catalytic systems were found to be either inactive (e.g. Ag(I) and Pd(II)) or displaying poor selectivity (e.g. AuCl/AgOTf) for hydroarylation with selective formation of isomer **169** over **168** (**Scheme 40**).

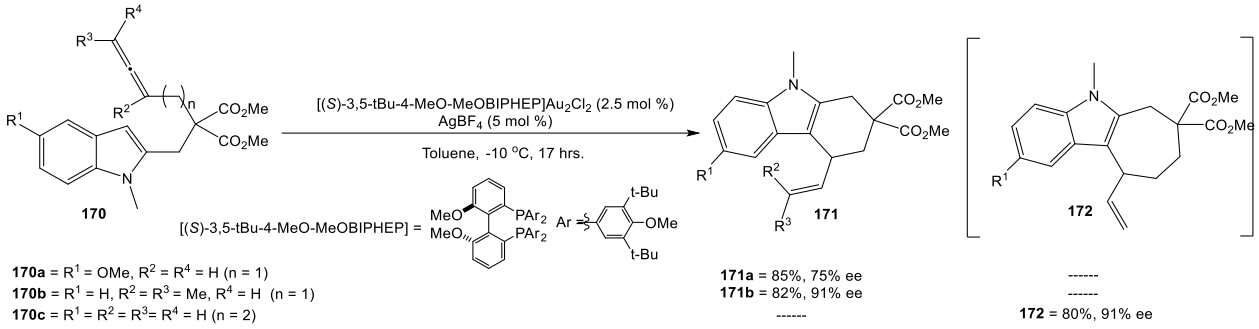
The optimised conditions were found to selectively form carbazole derivatives **168** from a range of allenyl indoles possessing either an electron-donating **167b** or electron-withdrawing **167c** group on the indole as well as with substituents on the internal **167d** or terminal **167e** carbon of the allenyl moiety (**Scheme 40**). It was also established that axially chiral allenyl indoles could transfer their chirality from the allene to the newly formed stereogenic carbon centre upon cyclisation with selective formation of the *E*-alkene.



Scheme 40. Au(I)-catalysed reaction for the intramolecular cyclisation of C2- indolyl allene for formation of tricyclic derivatives.

Widenhoefer *et al.*[91] then reported their extension of this work to establish an enantioselective intramolecular reaction with the use of chiral bis(gold)phosphine catalysts. After screening of catalysts the group found that the [(*S*)-3,5-*t*Bu-4-MeO-MeOBIPHEP]Au$_2$Cl$_2$ and AgBF$_4$ (1:2) catalytic system could catalyse the cyclisation of 2-(4,5-hexadienyl) indole **170** with formation of 4-vinyltetrahydrocarbazole **171** with high ee (**Scheme 41**). Further screening found that using toluene at low temperature with a longer reaction time resulted in better enatioselectivity.

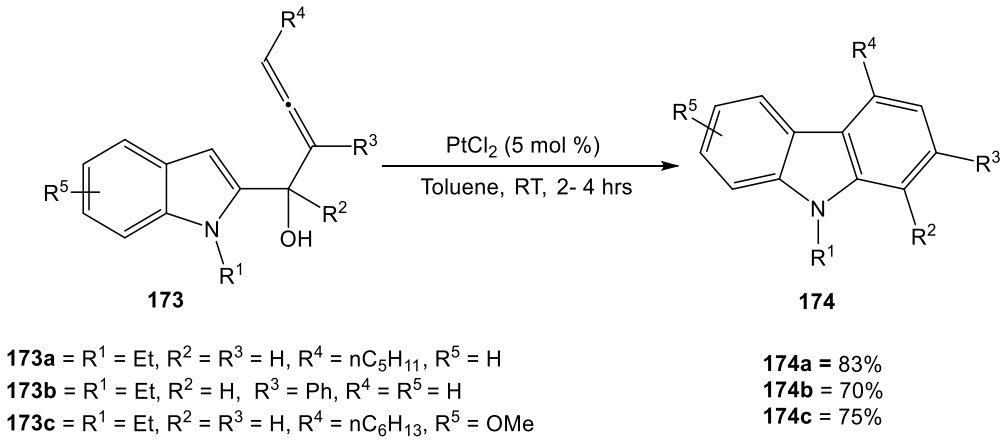
For example, the reaction of **170** in MeOH at rt for 3 hours yields **171** with 63% ee, whereas the reaction of **170** in toluene at -10 ^{o}C for 17 hours yields **171** with 91% ee (**Scheme 41**).



Scheme 41. Bis(Au)phosphine catalysed cyclisation of 2-allenyl indoles for the formation of functionalised tricyclic derivatives.

The reaction was found to work well with substituted indolyl allenes **170a** giving good yields and selectivity of the desired 4-vinyltetrahydrocarbazole derivatives **171a**, however better enatioselectivity and higher yields were achieved when the terminal carbon of the allene was substituted **170b**. Also, when the 2-(5,6-heptadienyl) indole **170c** was used resulting in 80% of the 7-exo-trig cyclised product **172** with 91% ee (**Scheme 41**).

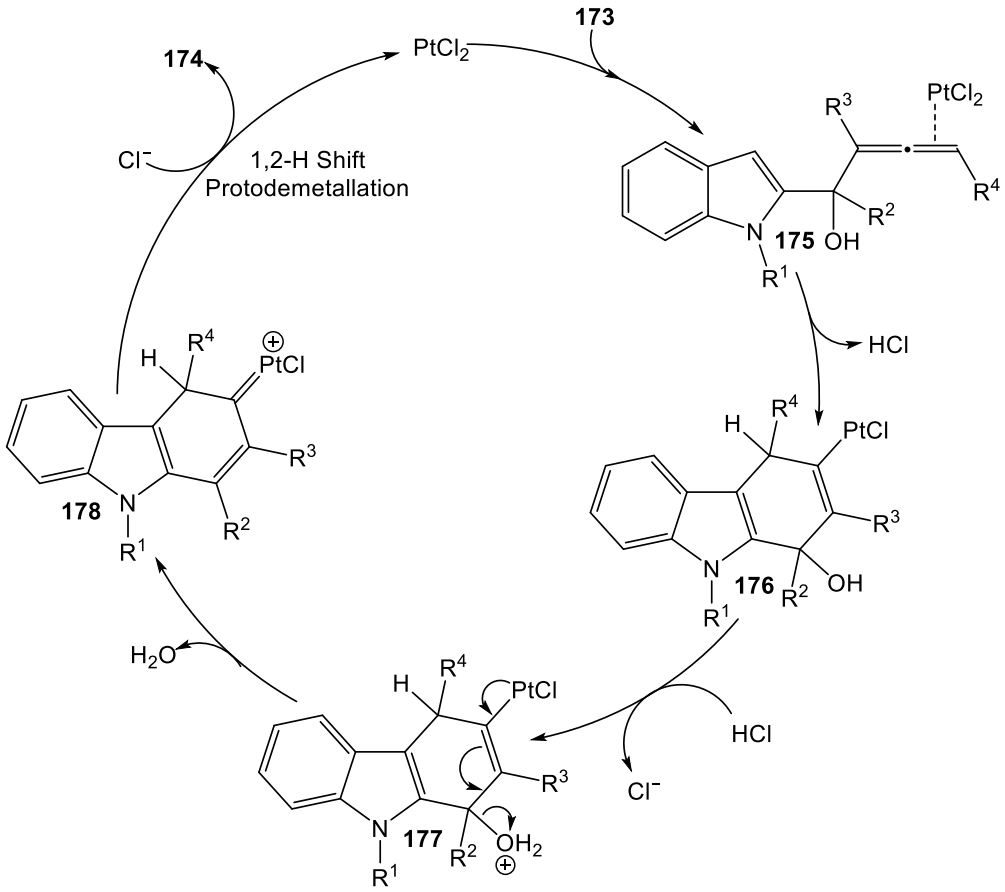
In 2009,[93] the group of Ma reported their mild and efficient method for the synthesis of substituted carbazoles **174** *via* $PtCl_2$-catalysed cyclisation of 1-(indol-2-yl)-2,3-allenols **173** (**Scheme 42**). A variety of substituted carbazoles could be afforded in high yields using the optimised conditions with substitution on the allenic moiety **173a/173b** as well as substituted indoles **173c** (**Scheme 42**).



Scheme 42. $PtCl_2$-catalysed cyclisation of 1-(indol-2-yl)-2,3-allenols with formation of substituted carbazoles.

The proposed mechanism for this reaction involves the coordination of $PtCl_2$ to the allene moiety activating it towards nucleophilic addition by the C3 of the indole with subsequent formation of intermediate **176**.

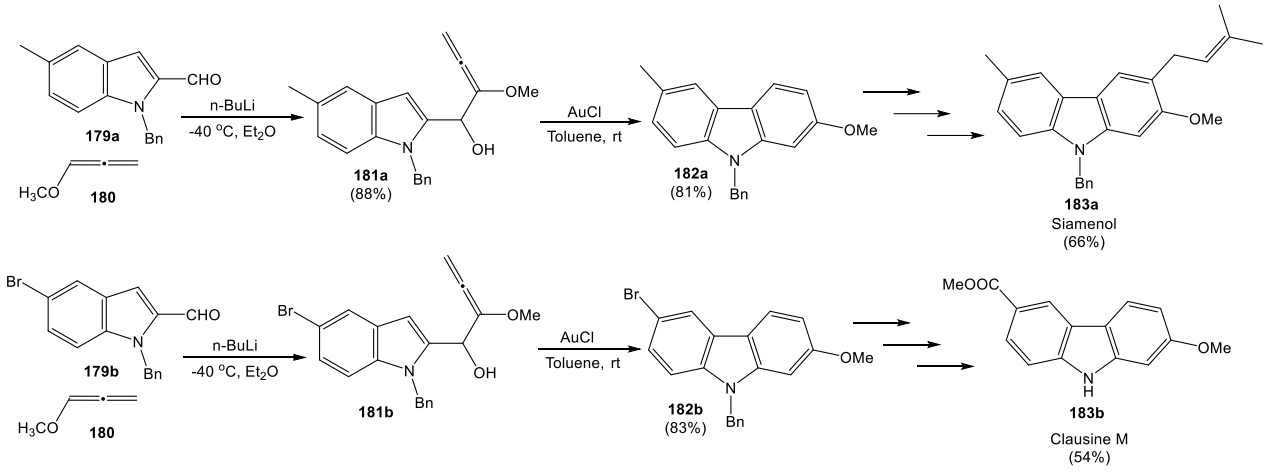
Protonation of the hydroxyl group on **176** allows for the elimination of H_2O from intermediate **177**, which forms the cyclic platinum carbene intermediate **178**. 1,2-H shift on intermediate **178** and demetallation gives the final product **174** with regeneration of $PtCl_2$ (**Scheme 43**). This mechanism has been supported by further mechanistic investigations reported by the same group,[94] where they confirmed that the reaction proceeds through the metal carbene intermediate **178**.



Scheme 43. Proposed mechanism for $PtCl_2$ catalysed cyclisation of 1-(indol-2-yl)-2,3-allenols.

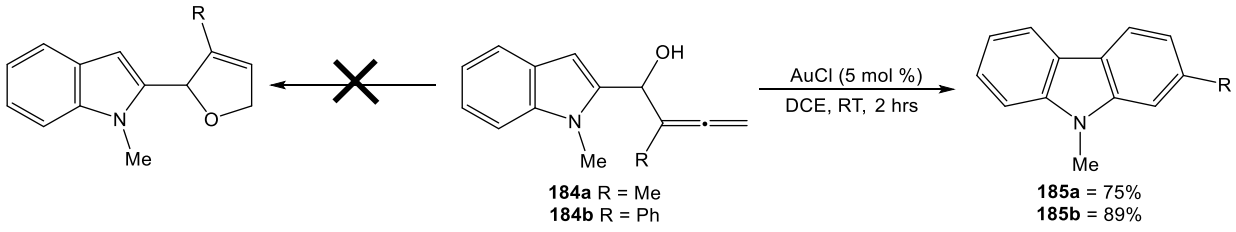
Alongside the $PtCl_2$ work, Ma *et al.*[95] also reported the synthesis of carbazoles using Au(I) catalysis. This was an extension of the $PtCl_2$ reaction to incorporate functionalities on the carbazoles with further derivatization for the formation of naturally occurring carbazole alkaloids such as Siamenol **183a** and Clausine M **183b**. Firstly, the group established a method for the synthesis of the indolyl allenols containing methoxy groups, using readily available methoxypropadiene and appropriate indole. The corresponding 2,3-allenol **181a/b**, then undergoes successful cyclisation to form the desired substituted carbazole **182a/b** (**Scheme 44**). The carbazole at this stage can undergo a series of functional group transformations to reach the desired naturally occurring carbazole alkaloid.

In 2013 the same group reported further application of this method for the synthesis of more naturally occurring carbazoles: isomukonidine, glycosinine and clausine V.[96]



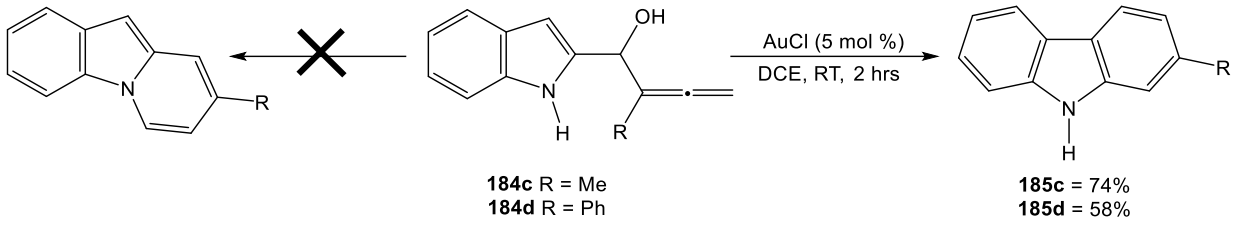
Scheme 44. Au(I)-catalysed cyclisation of substituted 2,3-allenols with formation of functionalised carbazoles as precursors to naturally occurring carbazole alkaloids siamenol **183a** and clausine M **183b**.

In 2011, Alcaide *et al.*[97] published their simple and efficient method for carbazole formation using indole-tethered allenols with Au(I) and Pd(II) catalysis. The diverse reactive sites of indole-tethered allenols could lead to either C, N or O cyclisation and specific catalytic systems are required to control which type of cyclisation occurs. They reported that AuCl was found to be the ideal catalytic system to enable this cyclisation control and observed that AuCl carbocyclisation of allenol **184a** gives selective formation of the corresponding carbazole **185a**, with no oxy-cyclisation occurring (**Scheme 45**). The high stability of the 6-membered carbocycle makes the 6-endo carbocyclisation thermodynamically more favoured than the faster 5-endo cyclisation reaction to form the furan.



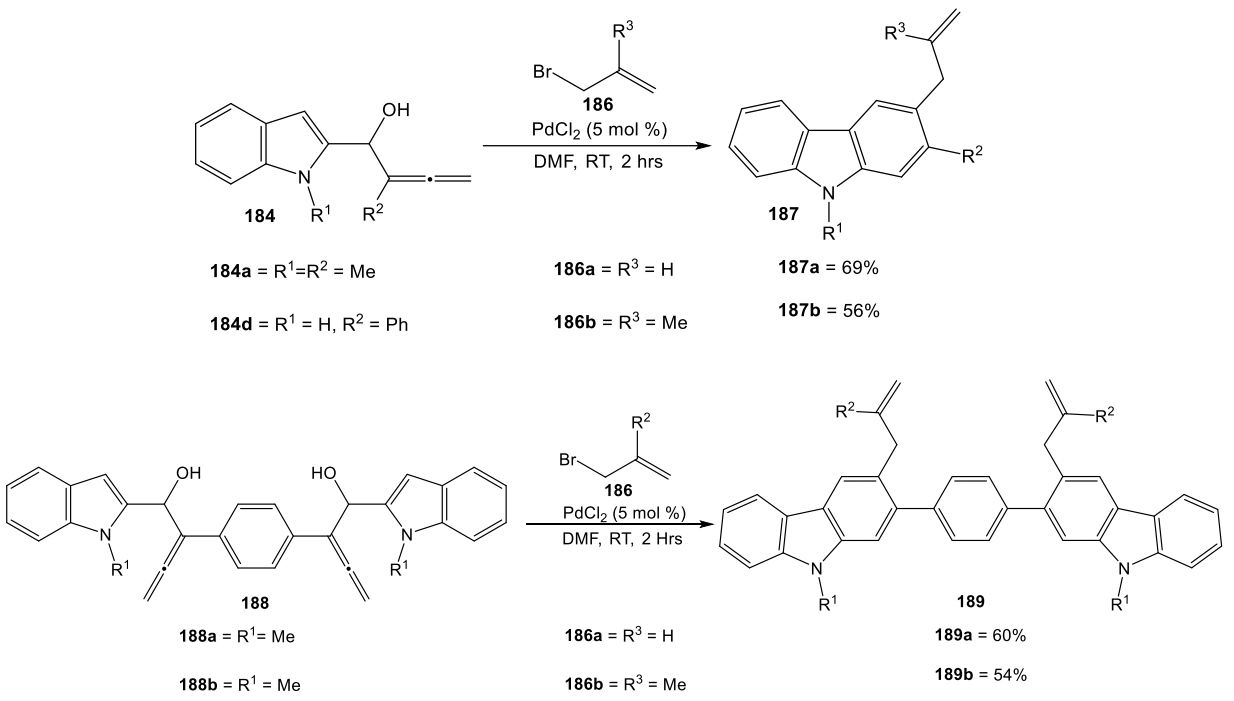
Scheme 45. Au(I)-catalysed cyclisation of indole-tethered allenols with selective carbocyclisation *vs* oxy-cyclisation with formation of functionalised carbazoles **185a and 185b.**

They also reported that unsubstituted *N*-indole-tethered allenols **184c/d** undergo selective carbocyclisation to form the corresponding carbazole **185c/d** as opposed to the proposed *N*-cyclisation that could occur to form the pyrido[1,2-α]indole derivative (**Scheme 46**). The proposed mechanism for this reaction is analogous to that proposed for the $PtCl_2$ cyclisation reaction (**Scheme 43**).



Scheme 46. Au(I)-catalysed cyclisation of indole-tethered allenols with selective carbocyclisation *vs N*-cyclisation with formation of functionalised carbazoles **185b**.

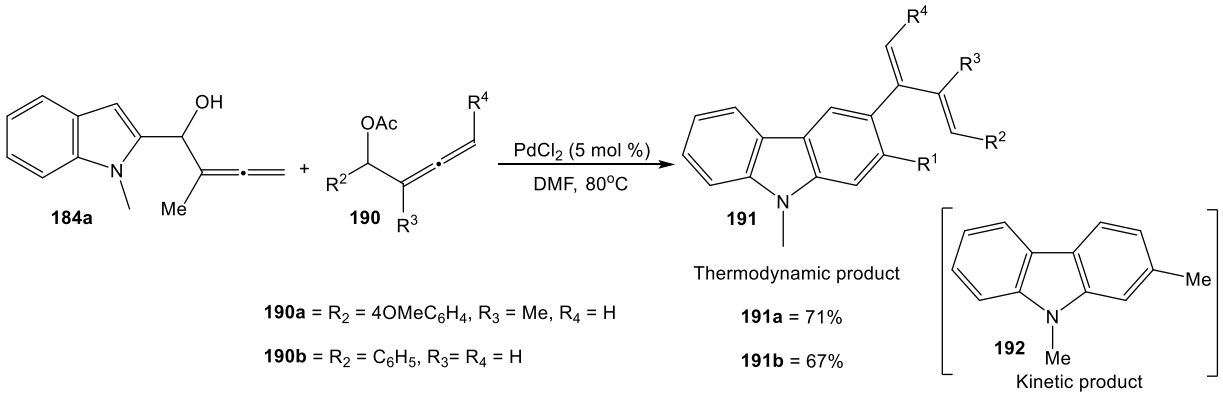
Aclaide *et al.*[96a] also reported the synthesis of functionalised carbazoles **187a/b** via the Pd-catalysed cyclisative coupling reaction of indole-tethered allenols **184** with allyl bromide **186** (**Scheme 47**). This reaction was reported to work well with a range of allenol and allyl bromide derivatives, giving relatively good yields of the corresponding carbazoles **187**. Dimers have a higher affinity for biological targets, therefore the group tested the reactivity of bis(indole-tethered allenols) **188** under the Pd conditions and achieved successful synthesis of dimeric carbazole derivatives **189** (**Scheme 47**).



Scheme 47. Pd-catalysed cyclisative coupling reaction of indole-tethered allenols **184** and **188** with allyl bromide **186**.

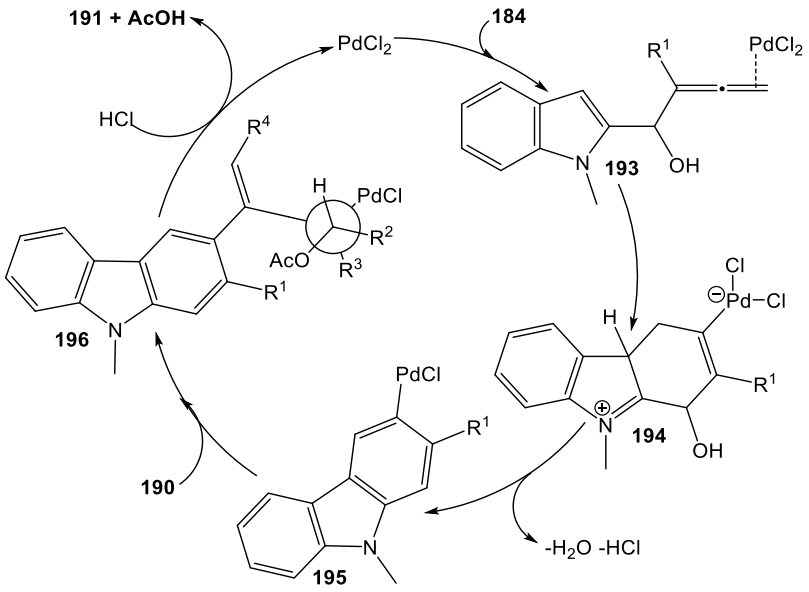
This successful carbocyclisation-coupling reaction between allenols and allyl bromides led Alcaide's group[98] to explore a similar sequence between indole-tethered allenols and *α*-allenic esters for the preparation of carbazoles. Initial reactions were carried out using $PdCl_2$ conditions for the reaction of indole-tethered allenols **184** with α-allenic acetate **190**, however only the carbazole **192** was isolated because of carbocyclisation without the cross-coupling.

But, the group established that heating the reaction to 80 ^{0}C gave successful carbocyclisation-cross-coupling to give the desired carbazole **191** (**Scheme 48**). This highlights that carbazole **192** is the kinetic product whereas carbazole **191** is the thermodynamic product. The reaction works well for a diverse range of allenic esters and allenols, giving the corresponding carbazoles as single isomers with *E*-selectivity in the newly formed C=C bond with high yields (**Scheme 48**).



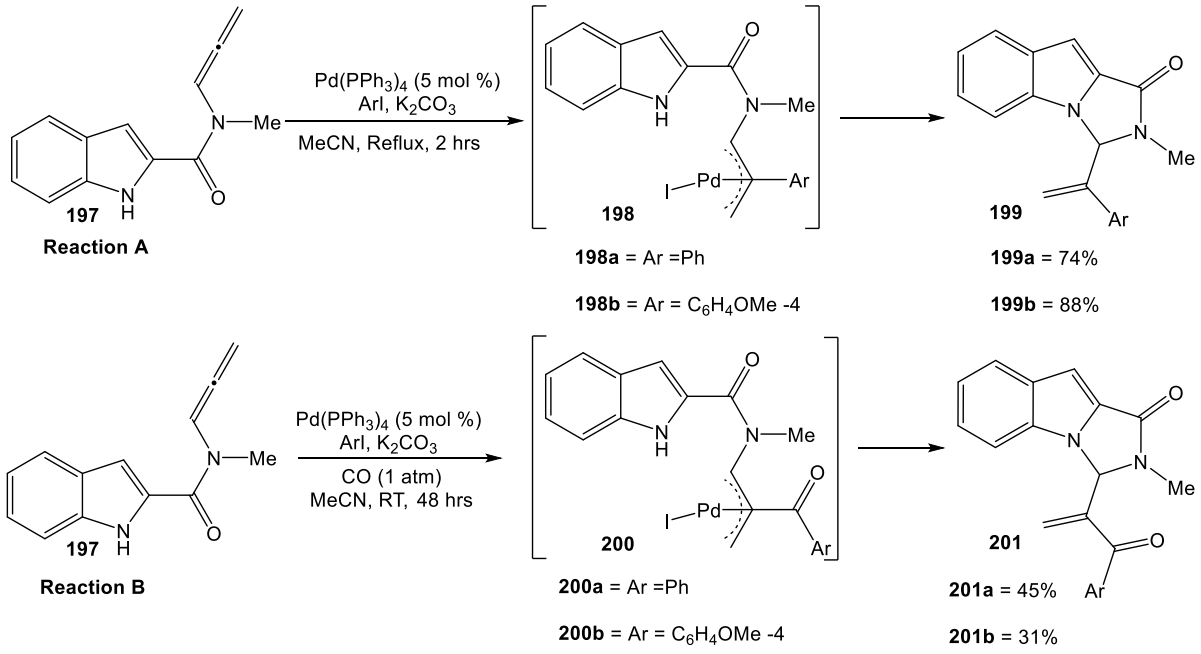
Scheme 48. Pd-catalysed cyclisative-cross-coupling reaction of indole-tethered allenols **184** with allenic esters **190**.

The group proposed a mechanism for this reaction involving the coordination of $PdCl_2$ to the allene moiety activating it towards 6-endo-trig carbocyclisation with formation of intermediate **194**. Aryl palladium intermediate **195** is formed after HCl loss and dehydration of **194.** The palladacarbazole **195** then couples with **190** regioselectively at the central carbon of allene, generating species **196**. A trans-β-deacetoxypalladation of **196** generates the highly stereoselective carbazole **191** with regeneration of the Pd(II) catalyst (**Scheme 49**).



Scheme 49. Proposed mechanism for Pd-catalysed cyclisative-cross-coupling reaction of indole-tethered allenols with allenic esters.

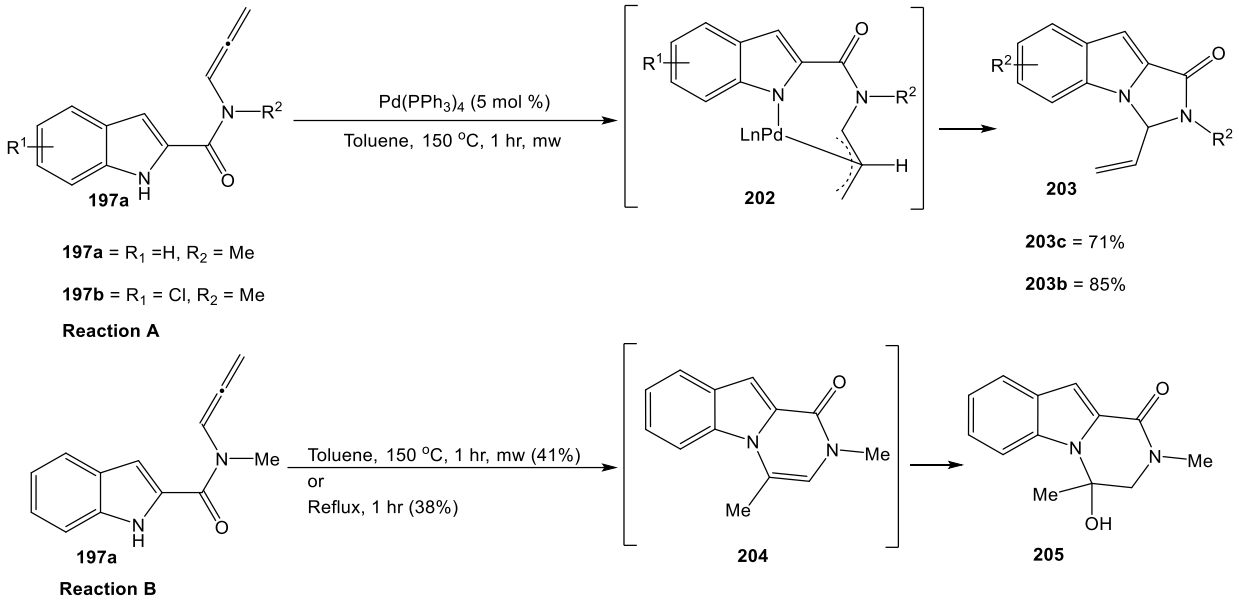
A further example of cyclisation of C2 allenic indoles is that by Becalli *et al.*[99] who reported the use of Pd(II) catalysis for the intramolecular carboamination and hydroamination of indole-2-carboxylic acid allenamides, leading to a variety of vinyl-substituted imidazo-[1,5-*a*] indole derivatives. Unlike the previous reactions, which involve the cyclisation at the C3 position of the indole, these two reactions undergo cyclisation at the nitrogen of the indole. The carboamination of allenamide **197** involves the formation of a π-allyl palladium(II) complex **198** which is generated by the insertion of an aryl Pd(II) iodide species on the allene. Selective trapping of the π-allyl palladium(II) complex at the internal carbon of the allene by the nitrogen on the indole generates the α-styryl-imidazo[1,5-*a*] indole derivative **199** (**Scheme 50**, Reaction A). Results show the reaction to work well with different allyl iodides with good yields, but also the reaction was explored using carbonylative conditions. Using a CO atmosphere, the reaction followed the same pathway with generation of imidazo-[1,5-*a*] indole products bearing an enone moiety **201** (**Scheme 50**, Reaction B), this reaction also worked with different aryl iodides however the yields were lower.



Scheme 50. Pd-catalysed carboamination of allenamides with formation of vinyl-substituted imidazo-[1,5-*a*] indole derivatives.

In the absence of an external aryl iodide, the Pd-cataylsed hydroamination reaction proceeds via a π-allyl Pd(II) complex **202**, generated by insertion of the N-Pd(II) species on the allene moiety, with subsequent cyclisation forming the vinyl-substituted imidazo-[1,5-*a*] indole derivative **203a/b** (**Scheme 51**, Reaction A). This 5-exo-allylic hydroamination reaction requires the use of microwave irradiation to achieve the desired product, without microwave irradiation degradation occurs.

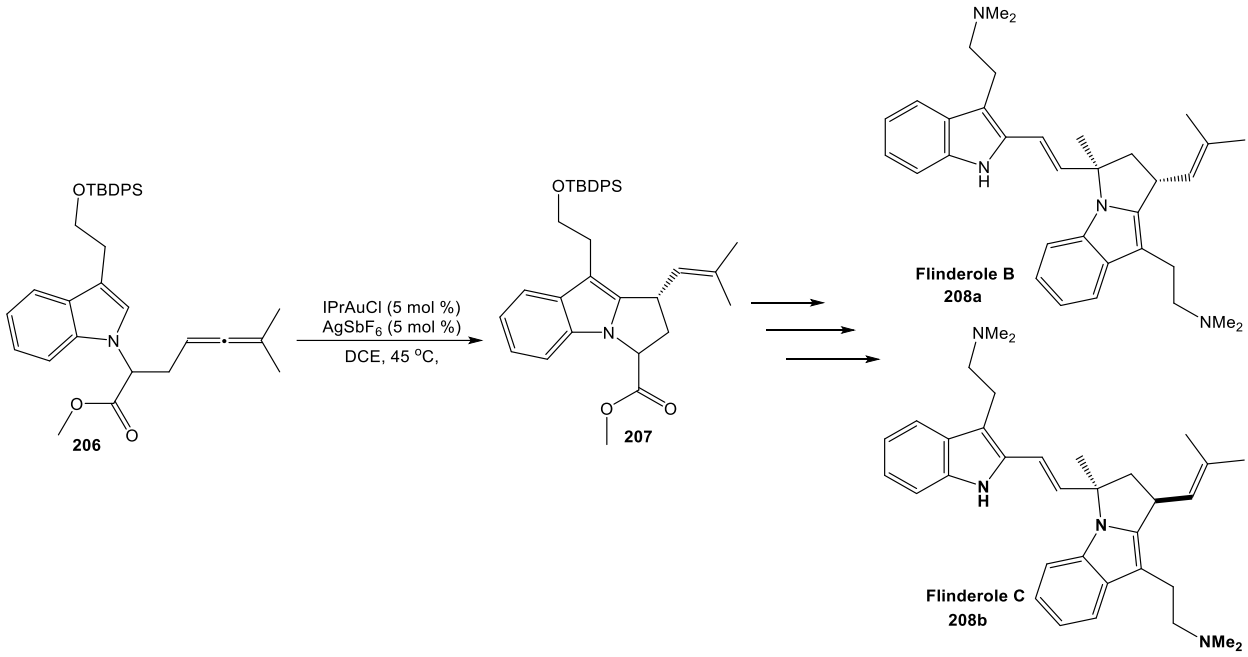
Also, without palladium present, product **203** is not formed, instead formation of the hydroxy-substituted pyrazino[1,2-a]indole species **205** is observed as a result of water addition to intermediate **204** (**Scheme 51**, Reaction B). The 5-exo-allylic hydroamination reaction works well with a range of indole allenamides substituted on the phenyl ring as well as the nitrogen.



Scheme 51. Pd(II)-catalysed hydroamination of allenamides with formation of vinyl-substituted imidazo-[1,5-*a*] indole derivatives using microwave conditions.

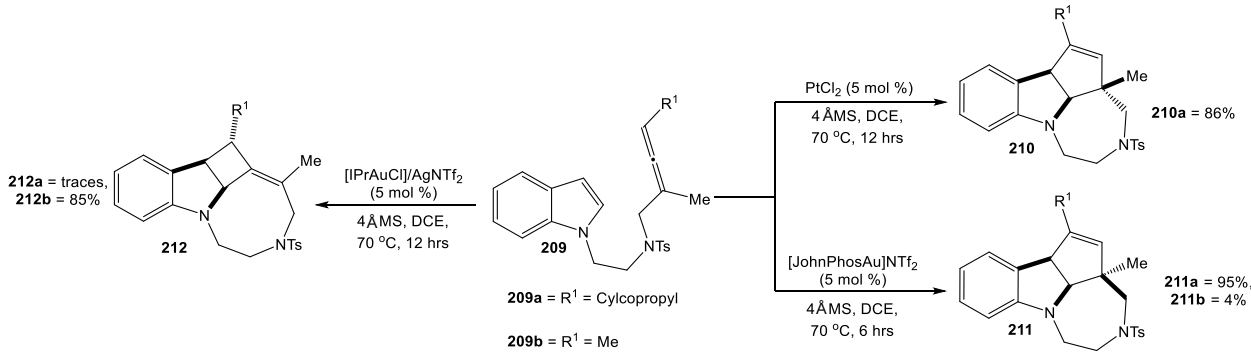
1.5.c. Metal catalysed intramolecular reaction of N-substituted indolyl allenes

There are only a few reported examples for the intramolecular reaction of *N*-tethered indolyl allenes with Au(I) and Pt(II) catalysis. Allenes have multiple reactive sites, therefore ring sizes can vary depending on the catalytic system and conditions used to control the chemo-, regio- and stereo-selectivity of the reaction.[11,34] In 2011, Zeldin and Toste [100] carried out a retrosynthetic analysis of the antimalarial bisindole alkaloids, flinderole B **208a** and C **208b**, where they proposed the pyrrolidine rings to be synthesised by Au(I)-catalysed hydroarylation of an *N*-tethered indolyl-allene through the C2 position of the indole. They reported the successful cyclisation of indolyl-allene **206** using the NHC-catalyst, $IPrAuSbF_6$, to yield 91% of the corresponding pyrrolidine **207**, further manipulation of this intermediate completed the total synthesis of flinderole B **208a** and C **208b** (**Scheme 52**).



Scheme 52. Au-catalysed cyclisation of *N*-tethered indolyl allene for the formation of flinderoles B **208a** and C **208b**.

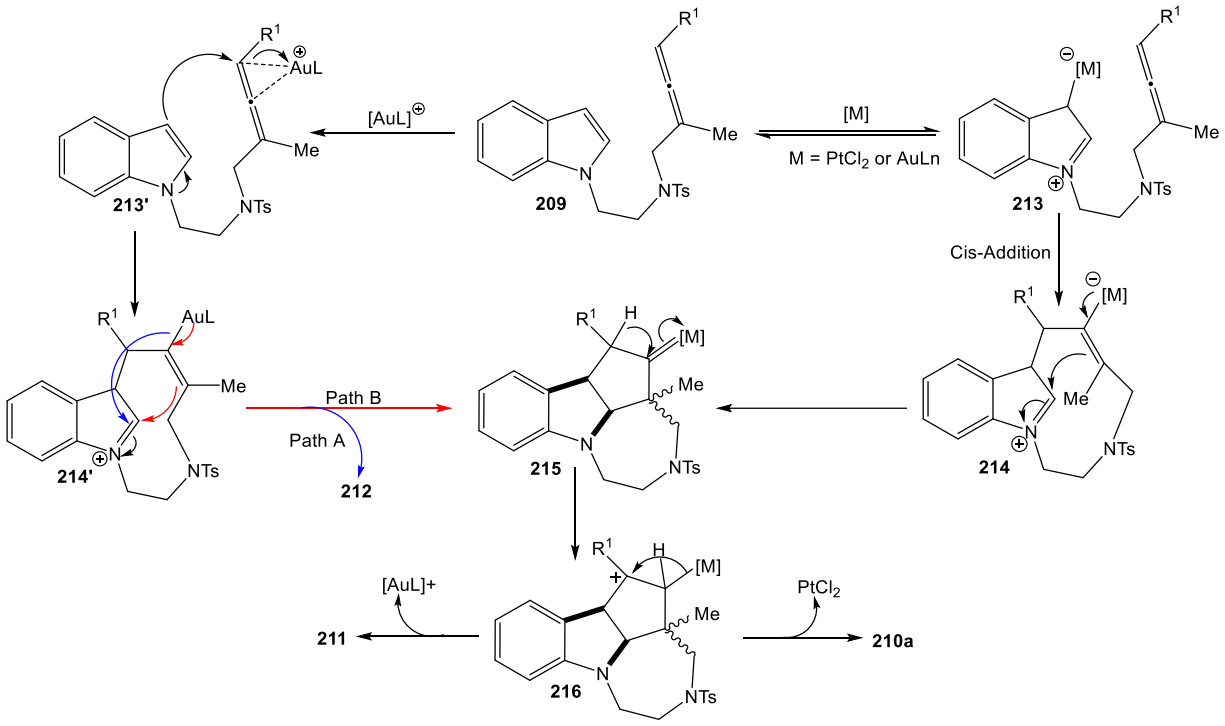
Recently, Mei *et al.*[101] reported their results for the catalyst-dependent stereo-divergent and regioselective synthesis of indole fused tricyclic systems through the cycloaddition reactions of indolyl allenes. The group were able to control the formal [3+2] and [2+2] cycloadditions of indolyl allenes by use of Pt(II) and Au(I) catalysis. They reported that $PtCl_2$ would catalyse the formal [3+2] cycloaddition of indolyl allene **209a** with formation of the cycloadduct **210**, however the [JohnPhosAuCl]/$AgNTf_2$ catalytic system with the same allene will lead to formation of the epimer cycloadduct **211** (**Scheme 53**). Screening also found that the [2+2] cycloadduct **212** could be isolated as the major product when indolyl allene **209b** was utilised (**Scheme 53**).



Scheme 53. Synthesis of indole fused tricyclic compounds via Pt and Au-catalysed reaction of indolyl allenes.

These reactions were found to work well with a range of substituted indolyl allenes with substituents on the indole ring and allene giving the corresponding products in good to high yields. The [3+2] cycloaddition reactions also worked with longer carbon tethers giving the corresponding 8 membered ring in good yields.

Deuterium and control reactions have led to proposed mechanisms for the Pt(II) and Au(I) catalysed reactions. For the $PtCl_2$ catalysed reaction, formation of the intermediate **213** is achieved by reversible C-3 metallation of indole, this intermediate can undergo successful *cis*-addition forming intermediate **214**. Ring closure of intermediate **214** forms metal-carebene intermediate **215**, which undergoes 1,2-H migration followed by demetallation of intermediate **216** to yield product **210a** (**Scheme 54**).

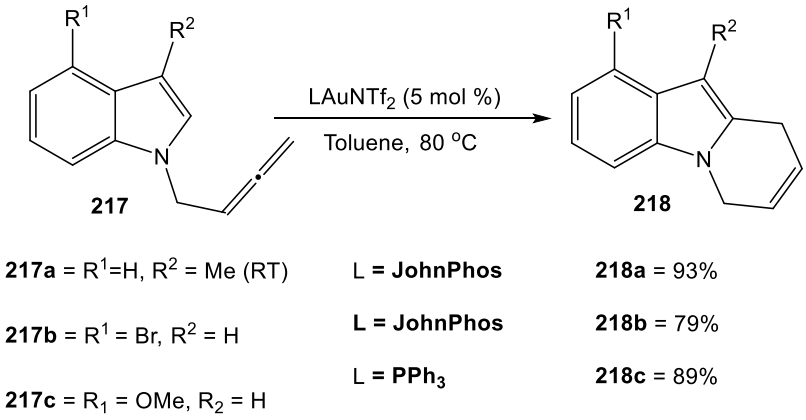


Scheme 54. Proposed mechanism for the Pt and Au catalysed cycloaddition reactions of *N*-tethered indolyl allenes.

The [3+2] cycloaddition with gold can also go *via* intermediate **213**, however the direct coordination of Au to the allene is the more dominant process, therefore intermediate **213'** is formed. Intramolecular nucleophilic addition of indole to the Au-activated allene forms the vinyl gold intermediate **214'**. This intermediate can then form either product **212** or **211**, product **212** is formed by trapping the iminium intermediate through nucleophilic attack of the C-Au bond (**Scheme 54**, Path A). Whereas product **211** is formed by tandem cyclisation, 1,2-H shift and an elimination process *via* the metal-carbene intermediate **215** and intermediate **216** (**Scheme 54**, Path B).

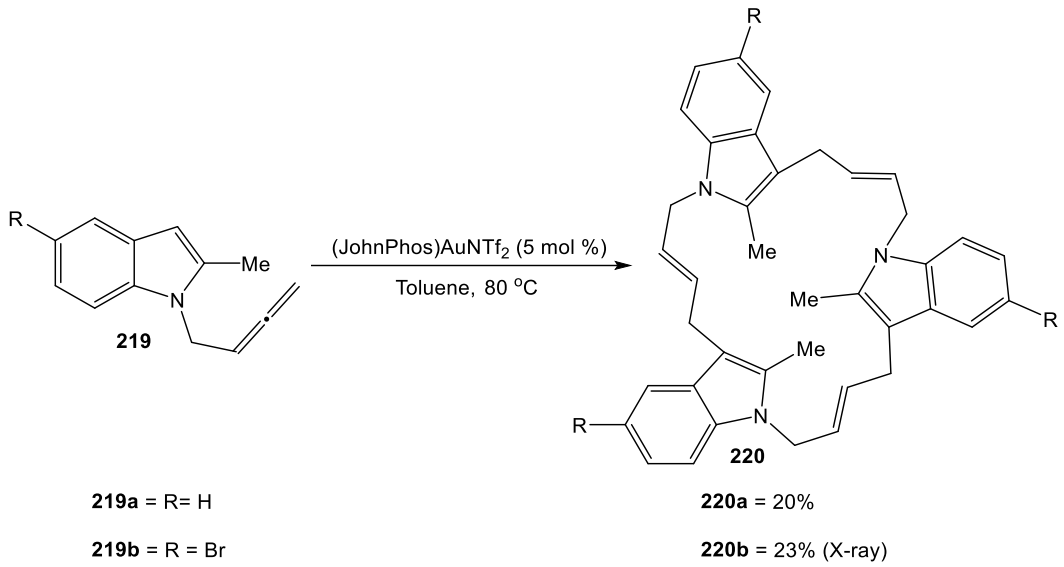
The two proposed mechanisms highlight that the stereoselective formation of products **210a** and **211** is likely to occur because of the different *E* and *Z* configurations of intermediates **214** and **214'**.

In 2010, Barluenga *et al.* [102] reported their results for the Au(I)-catalysed 6-endo cycloisomerisation of *N*-tethered indolyl allenes, as a new process for the formation of pyrido[1,2-*a*]-1*H*-indole derivatives. The reaction of 2,3-butadienyl-1*H*-indole **217** was found to undergo successful cycloisomerisation with both [JohnPhosAuCl]/$AgNTf_2$ and $Ph_3PAuNTf_2$ catalytic systems with formation of 6,9-dihydro-pyrido[1,2-*a*]-1*H*-indole derivatives **218** (**Scheme 55**). The scope of the reaction shows that the cycloisomerisation has a broad functional group tolerance, including towards strong and weak activating and deactivating groups (**Scheme 55**).



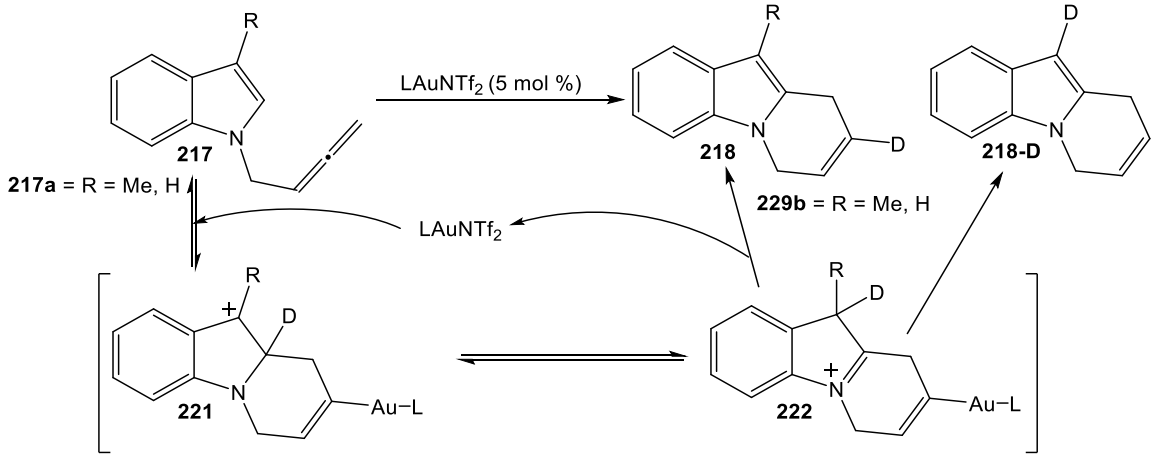
Scheme 55. Au(I)-catalysed 6-endo cycloisomerisation reaction of N-tethered indolyl allenes.

Functionalisation of the indole at position C3 favours the cycloisomerisation reaction at position C2. However, if position C2 is blocked, then the more competitive intermolecular activation of C3 will occur. This was validated by investigating the reaction with C2 substituted indolyl allenes **219** (**Scheme 56**). Carefully controlling the time and concentration of the reaction allows for cyclotrimerisation with formation of macrocyclic compounds **220** (**Scheme 56**).



Scheme 56. Au(I)-catalysed cyclotrimerisation of C2-subsituted N-tethered indolyl allenes.

Based on deuterium incorporation patterns, Barluenga proposed a mechanism for the formation of the 6,9-dihydro-pyrido[1,2-*a*]-1*H*-indole derivatives. Initially a π-complex is formed by coordination of cationic Au(I) to the allene, cyclisation of this gives intermediate **221** with a positively charged C3 position. Stabilisation by the lone pair of the nitrogen would afford cationic intermediate **222**, which would aromatise to form products **218** (**Scheme 57**).



Scheme 57. Mechanism for Au(I)-catalysed 6-endo cycloisomerisation reaction of N-tethered indolyl allenes.

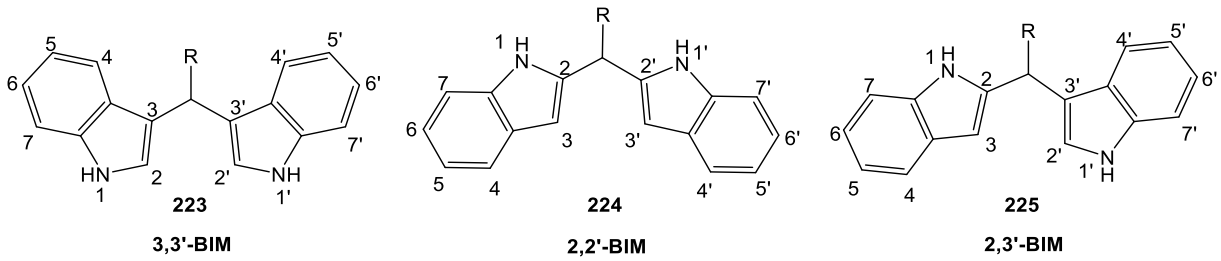
This Au(I)-catalysed 6-endo cycloisomerisation of 2,3-butadienyl-1*H*-indole derivatives is highly important to the work carried out in this thesis. It has allowed us to understand the relationship of Au(I) and Pt(II) catalysis with respect to 2,3-butadienyl-1*H*-indole derivatives and the effect that these catalytic systems have on the products of cycloisomerisation, this will be discussed further in chapter 2.

1.6. Bis-indolylmethanes (BIMs)

Indoles and their derivatives, in particular bis-indolylmethanes, are an important class of heterocyclic compounds. These biologically active compounds have received a lot of attention over the years in both chemical and pharmaceutical industries because of their diverse properties.[103] BIMs are known to exhibit a wide spectrum of biological activities and are found in a range of natural products and pharmaceutical agents. The structure, properties, uses and synthesis of these compounds will be described in this section to highlight their importance and relationship to the work carried out in this thesis.

1.6.a. Structure and properties

Bis-indolylmethanes are compounds which contain two indolyl moieties connected to the same carbon atom, examples of which include 3,3'-BIMs **223**, 2,2'-BIMs **224** and 2,3'-BIMs **225** (**Scheme 58**), where the number indicates the position at which each indole is linked.[104]



Scheme 58. Structures to show the linking between indoles 3,3'-, 2,2' and 2,3' –BIMs.

Indoles are most reactive at position 3, therefore synthesis of 3,3'-BIMs is the most commonly reported example. However, if position 3 is occupied, then synthesis of 2,2'-BIMs is also possible. The synthesis of 2,3'-BIMs is far more complicated because of the reactivity at position 3 of the indole which takes precedence over position 2.[105] Therefore there are fewer reports for their synthesis even though they are of high importance because of the broad spectrum of interesting biological and pharmacological properties. These 2,3'-BIMs form the basis of this thesis and will be discussed in further detail.

Bis-indolylmethanes and their derivatives are known to be present in a range of natural products and are found in bioactive metabolites of marine and terrestrial origin.[106] These molecules are generally isolated from a range of marine and terrestrial sources such as sponges, tunicates and parasitic bacteria.[107] Over the years many different BIM derivatives have been identified with a range of biological activities associated with them, such as antibacterial, antibiotic, antimicrobial, antifungal, and anti-inflammatory properties.[89,108]

BIMs, such as 3,3'-diindolylmethane **223a** (**Figure 15**), have been shown to exhibit inhibitory effects on cancer cells growth and induce apoptosis.[7] This has been readily reported for the inhibition of human prostate cancer cells[109,110] and human breast cancer cells[111] as well as others.[93] The importance of BIMs has also been reported for the naturally occurring example Vibrindole A **223b** (**Figure 15**), which is reported to be useful for the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome.[112]

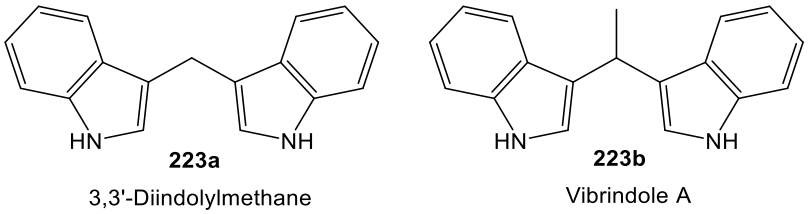
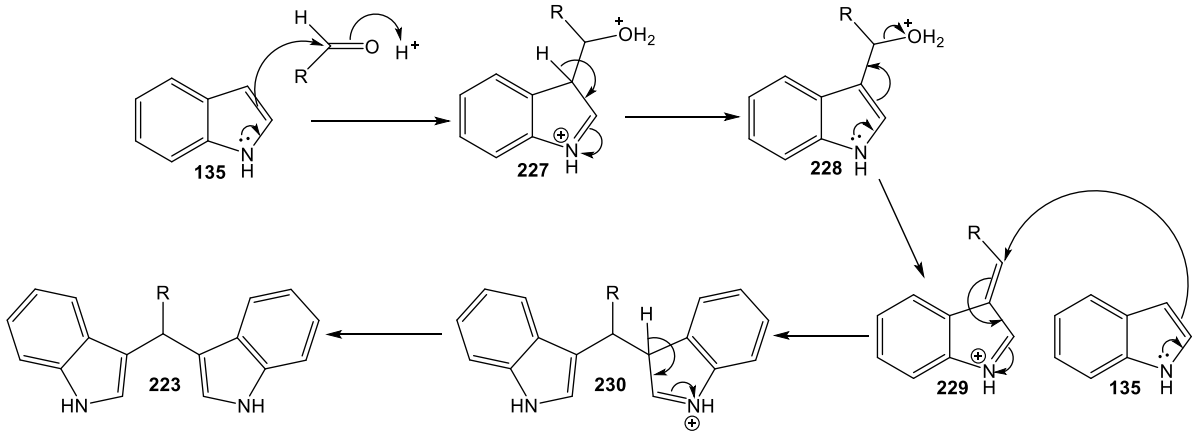


Figure 15. Structures for 3,3'-Diindolylmethane (**234a**) and Vibrindole A (**234b**).

The importance of these BIM structures has resulted in a wide range of synthetic routes being developed, these involve the more classic methods utilising protic and Lewis acid catalysis as well as the more modern methods using transition metal catalysis.

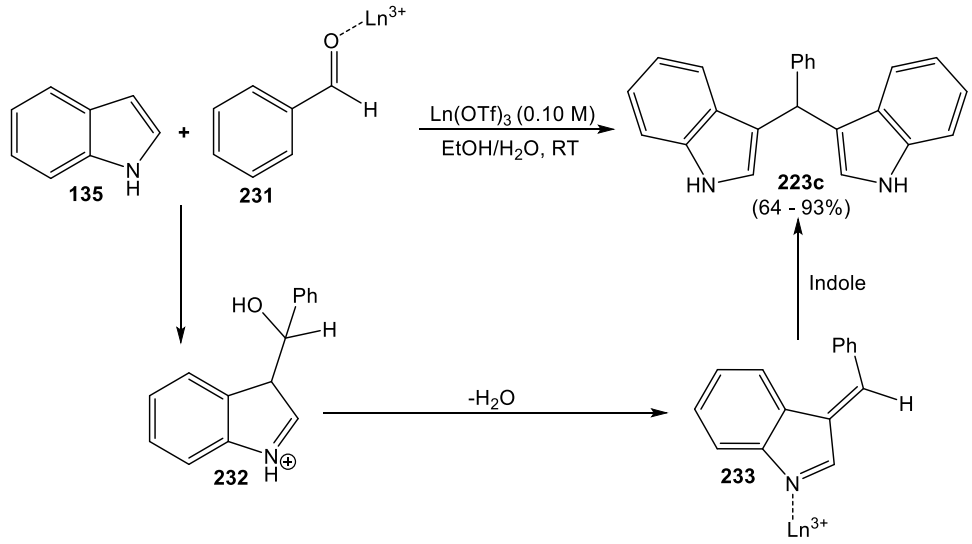
1.6.b. Classic methods for synthesis

Friedel-Crafts reaction between indoles and carbonyl compounds using protic or Lewis acid catalysis has been widely studied for the synthesis of bis-indolylmethanes (**Scheme 59**), however only a few interesting examples have been described here to briefly highlight this area.



Scheme 59. General scheme for the synthesis of bis-indolylmethanes *via* the Friedel-Crafts reaction between indoles and carbonyl compounds.

In 1996, Chen *et al.*[113] described the use of lanthanide catalysts for the reaction of indoles with aldehydes and ketones. They demonstrated that various lanthanide triflates are mild and effective catalysts for the reaction of indole **135** with various aldehydes and ketones, e.g. benzaldehyde **231**, giving the corresponding BIM **223c** in high yields. They were able to extend this reaction to various substituted indoles as well as a range of aromatic and aliphatic aldehydes and ketones. The group proposed a mechanism as seen in **scheme 60** which involves the activation of the carbonyl group **231** by the lanthanide to allow for electrophilic substitution at C3 on the indole **135**, similar to that observed for protic acid catalysis (**Scheme 59**)**.** Loss of water generates the intermediate **233**, which is then activated by the lanthanide allowing for attack at the second indole molecule to form the final BIM product **223c**.



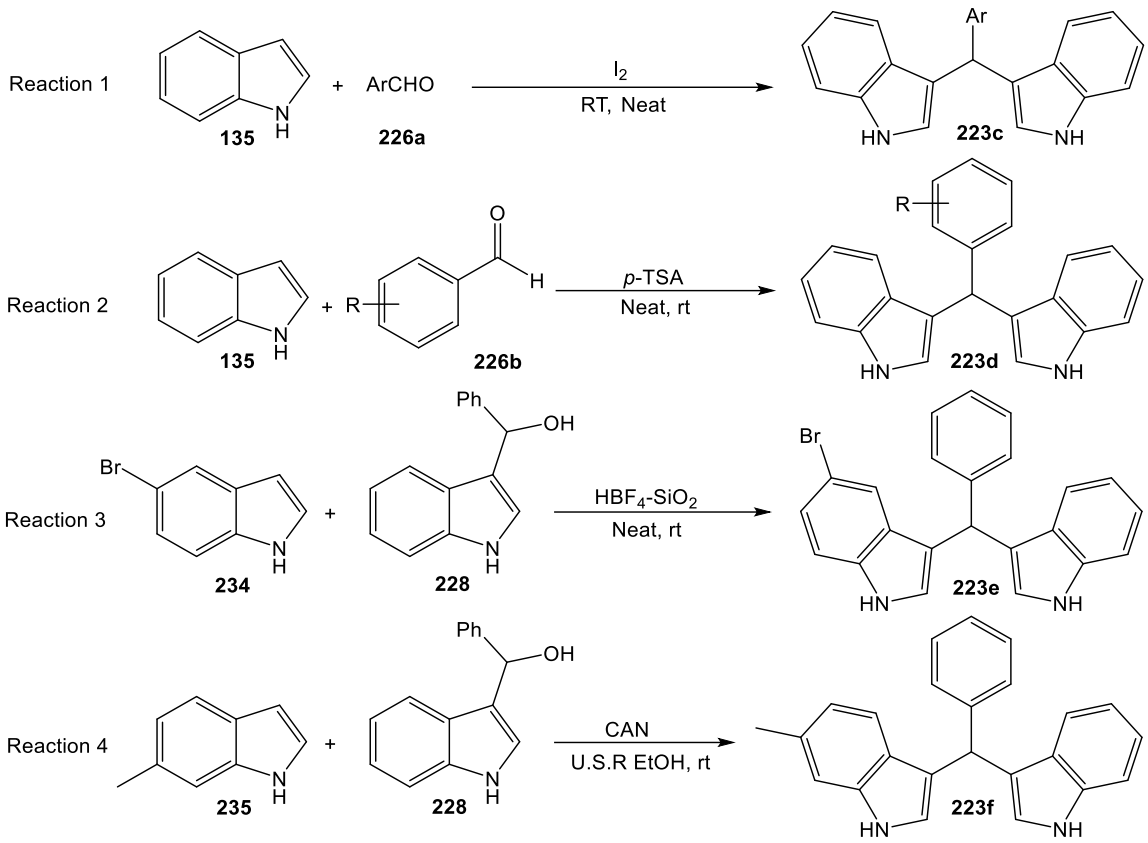
Scheme 60. The lanthanide triflate bis-indolylation reaction and mechanism.

Despite the mild and effective nature of both the catalyst and conditions, numerous groups began reporting methods that used inexpensive, facile and efficient catalysts as well as solvent-free conditions. Several groups have achieved solvent-free conditions by grinding solid reagents together yielding a viscous liquid melt phase,[114] which after a period of time gives the crude product, this is known as the grindstone method.[115] An example of this reaction includes the work by Loh *et al.*[113] which uses iodine as a mild Lewis acid, it is a highly efficient catalyst because of its ability to activate both the carbonyl group and the indole, promoting the reaction which follows a similar mechanism to that in **scheme 60**. This reaction exhibits short reaction times of <10 mins and solvent free conditions for the synthesis of a range of different BIMs with very good yields (Reaction 1, **Scheme 61**). The group of Pasha[116] were also able to achieve BIM formation using protic acids in solvent free conditions in ten minutes and found the reaction to work well with a range of aldehydes and ketones (Reaction 2, **Scheme 61**).

These examples and the majority of other BIM formation methods work for the synthesis of symmetrical BIMs, whereas the group of Bandgar *et al.*[117] were able to adapt their reaction to give a range of both symmetrical and unsymmetrical BIMS. They achieved this using solvent free conditions with fluoroboric acid adsorbed on silica, HBF_4-SiO_2, as the catalyst, and using one indole already substituted in position 3 with a group ready to form a vinyl indole which is a key intermediate in the reaction with the second indole.

The reaction was shown to be simple, inexpensive and the catalyst can be recycled, it was also shown to work well with a range of aldehydes and ketones, although it was found that aldehydes reacted faster than ketones.

The reaction was extended to a range of substituted indoles forming the corresponding unsymmetrical BIMs e.g. the reaction of 5-bromoindole **234** with 1H-indol-3-yl(phenyl)methanol **228** to give the corresponding unsymmetrical BIM **223e** in an 89% yield (Reaction 3, **Scheme 61**). The group of Wang [118] were also able to successfully form unsymmetrical BIMs in a similar approach. Their reaction was carried out with the cheap and non-toxic catalyst, ceric ammonium nirate (CAN) with ultrasonic radiation (U.S.R.) to give a fast and efficient route to a wide range of unsymmetrical BIMs with high yields, however they were not achieved using solvent free conditions. e.g. reaction of 6-methylindole **235** with 1H-indol-3-yl(phenyl)methanol **228** to yield the corresponding BIM in 96% yield (Reaction 4, **Scheme 61**).



Scheme 61. Schemes for the solvent-free BIM formation utilising various catalysts.

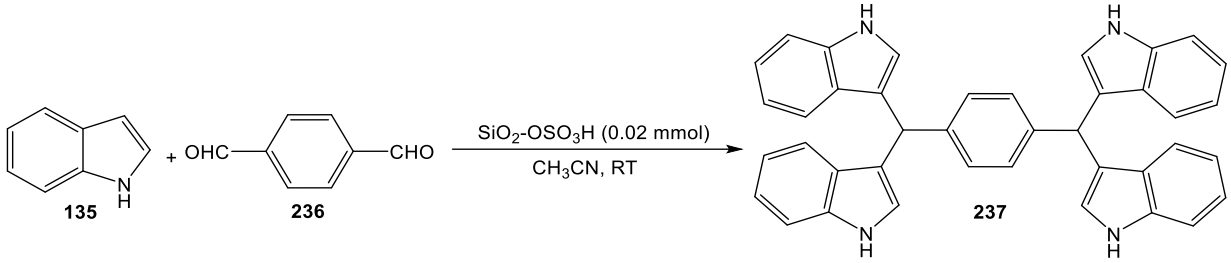
Other examples of Lewis acid catalysed reactions require different conditions and can require the use of high catalyst loadings to achieve the successful BIM formation, e.g. the sulfamic acid catalysed reaction by Wang and Li,[119] which requires methanol as the solvent and 50 mol % of the mildly acidic, non-volatile, odourless and stable acid catalyst to synthesise a range of substituted BIMs with high yields.

The group of Bandgar[120] successfully synthesised BIMs using molecular iodine, however this required the use of acetonitrile and 20 mol % catalyst loading. Although this reaction works well with a range of unsubstituted aromatic, aliphatic and α, β-unsaturated aldehydes as well as aliphatic, alicyclic and aromatic ketones, giving excellent yields, the conditions are not as favoured as those previously mentioned by Loh.[113]

Some of these high catalyst loadings are needed because Lewis acids can be deactivated or decomposed due to trapping by nitrogen containing reactants and therefore more than stoichiometric amounts of the Lewis acid are required. However, Yadav *et al.*[121] identified that lithium perchlorate could be used in catalytic amounts, as a 5 M ether solution of lithium perchlorate or as a 10 mol % of $LiClO_4$ in acetonitrile for the highly efficient synthesis of the BIMs using neutral reaction and work-up conditions.

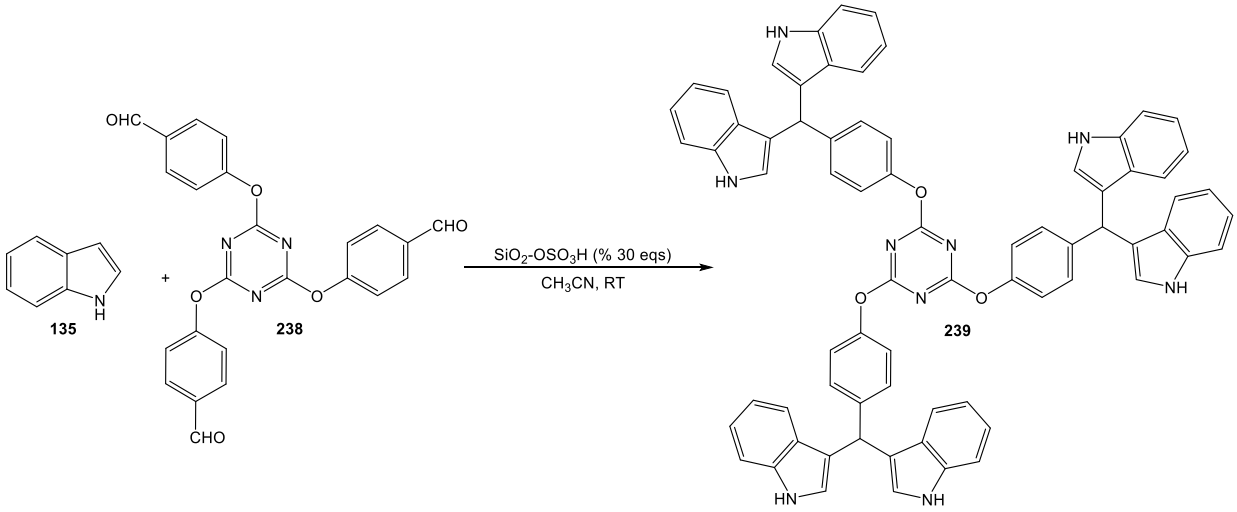
Also, Kamble *et al.*[122] were able to use the reusable, selective, simple, non-corrosive and low-cost perchlorate catalyst, $HClO_4$-SiO_2, in methanol with extremely low loading of 0.01 mmol to give very short reaction times and excellent yields.

An interesting example was reported in 2008 by Kolvari *et al.*[123] using bis- or tris-aldehydes for the synthesis of di- and tri-(bis(indolyl)methanes). They used silica sulphuric acid (SSA) synthesised from silica gel and chlorosulphonic acid as the protic catalyst for the reaction of terephthaldialdehyde **236** with indole **135** to form the corresponding di-bisindolyl derivative **237** (**Scheme 62**).



Scheme 62. Scheme for the synthesis of di-bisindolyl methanes **237** using SSA catalysis.

The group also found that the reaction worked well with tri-aldehydes to give the corresponding tri-bisindolylmethane as new materials under mild and heterogeneous reaction conditions using SSA, e.g. reaction of indole **135** with tripodal **238** to give the corresponding tri-bisindolylmethane **239** (**Scheme 63**).



Scheme 63. Scheme for the synthesis of tri-bisindolyl methanes using SSA catalysis.

The reactions outlined here and the many others that have also been published[124] show how broad the more conventional method for BIM formation is. The various groups have worked rapidly over the years to generate a wide range of methods with a variety of protic and Lewis acids to generate a range of 3,3'-BIMS in high yields and low reaction times.

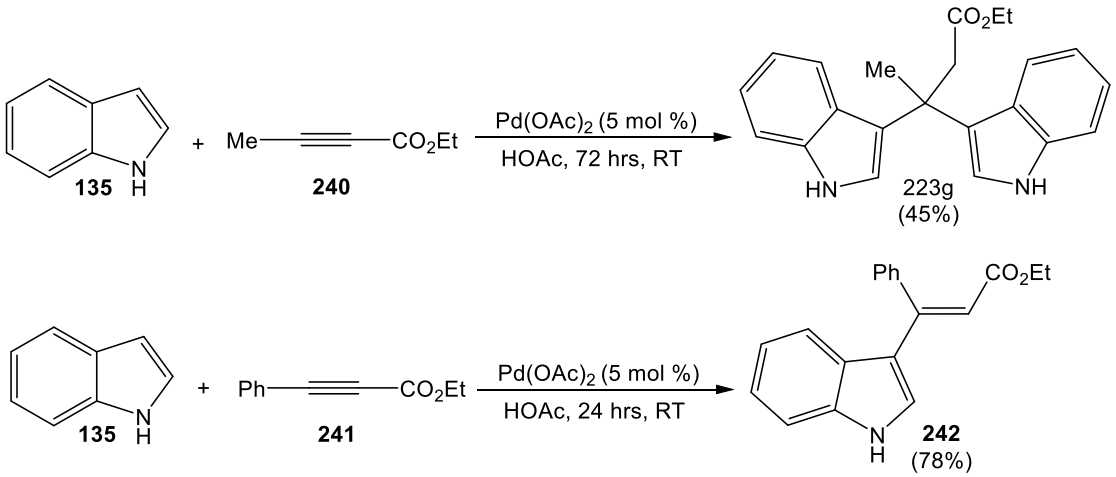
However, it may seem that their solvent free and use of low costing but efficient catalysts may only be useful for the synthesis of 3,3'-BIMs with a general approach to symmetrical examples. Whereas, the more challenging compounds such as unsymmetrical BIMs and also 2,3'-BIMs are of increasing interest and therefore transition metal catalysed reactions for BIM formation have been developed.

1.6.c. Transition metal-catalysed methods for synthesis

Although almost all the procedures for BIM formation described in literature are based on the more classic method, there are methods which have been developed over the past couple of decades which utilise transition metal catalysis. These reactions involve the addition of indoles to π-bonds such as alkynes, allenes and to cyclopropene *via* direct double hydroarylation, which can occur step wise through a vinyl indole intermediate.[125] This section will summarise these methods with a variety of transition metal catalysts.

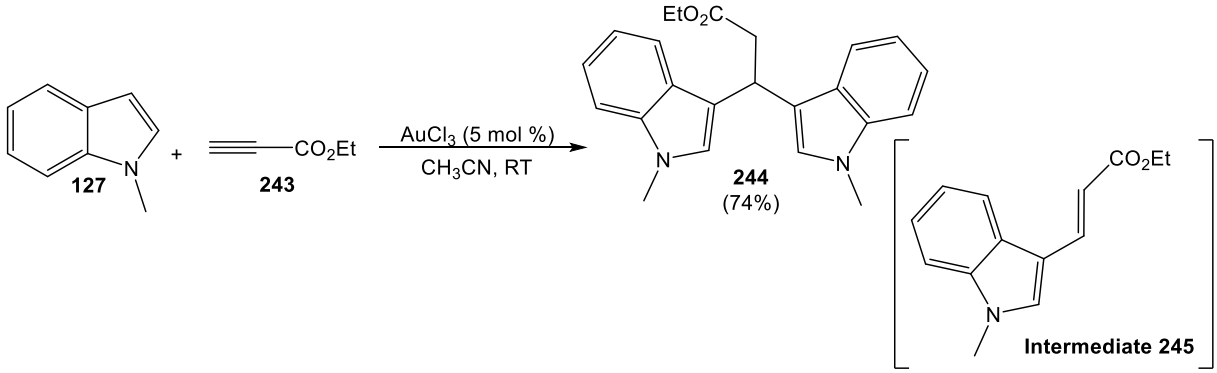
One of the earliest reports for metal catalysed BIM formation was by Fujiwara *et al.* in 2000,[126] who reported their results for palladium catalysed BIM formation. The group reported that $Pd(OAc)_2$ in acetic acid could catalyse the addition of indoles and pyrroles to alkynoates with selective formation of either *cis*-heteroarylalkenes or di-aryl products being achieved.

This was dependant on the substituents on the alkynoates and the solvent used and they found that small R groups such as Me on alkynoates **240** in acetic acid favoured di-addition products **223g,** whereas bulky R groups such as Ph **241** favour the formation of mono-addition products **242** (**Scheme 64**). Bis-indolyl products were formed by further addition of indole to the arylalkenes/vinylindole intermediates in acetic acid, they also reported that in dichloromethane they could control the reaction to stop at the mono-addition product, even when small substituents were present.



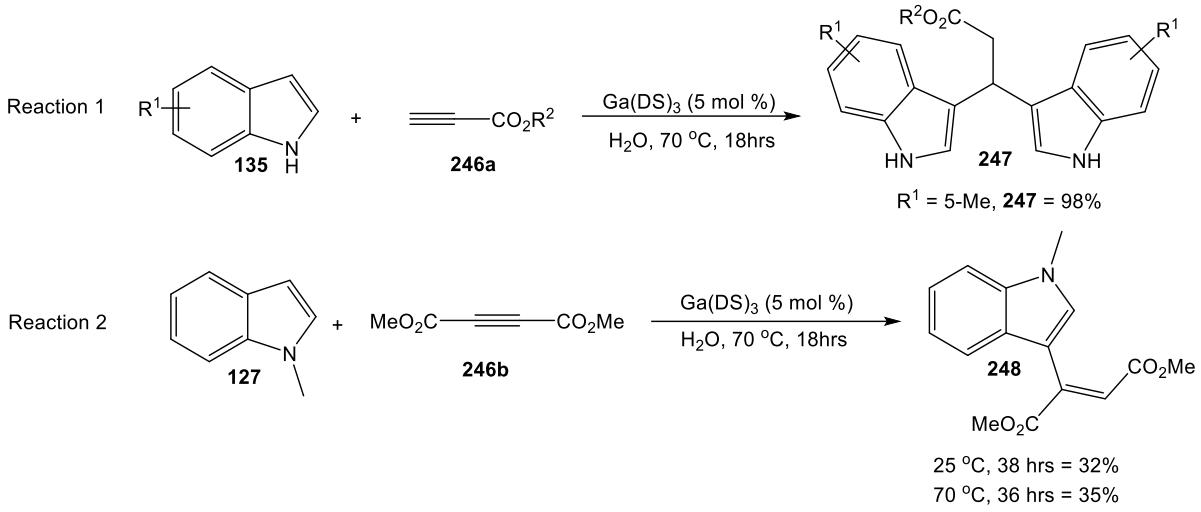
Scheme 64. $Pd(OAc)_2$ catalysed addition of indoles to alkynoates with selective formation of BIMs or *cis*-heteroarylalkenes.

The most reported methods for BIM formation using transition metal catalysis involves the use of Au(I) and Au(III) catalysis for the addition of indoles to alkynes and one example involving the addition to cyclopropenes. The earliest reported example by He *et al.*[127] in 2005 involves Au(III) catalysed addition of heterocycles such as indoles, furans and benzofuran to olefins and alkynes. The group found that using $AuCl_3$ as the catalyst gave successful addition of two *N*-methyl indole **127** units to ethyl propiolate **243** with the subsequent formation of the bis-indolyl product **244** in a 74% yield (**Scheme 65**). They proposed that the reaction occurs *via* an α,β-unsaturated ester intermediate **245** which is reactive at the β position allowing for the second indole addition to occur.



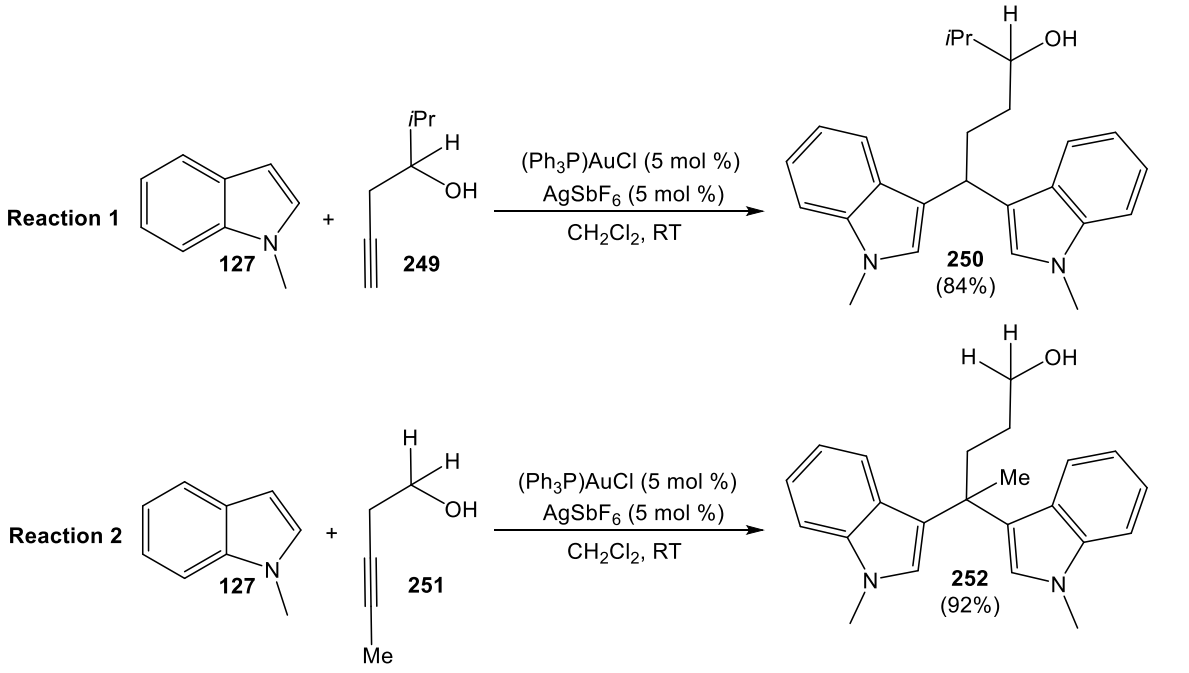
Scheme 65. $AuCl_3$ catalysed reaction of N-methylindole with ethyl propiolate to give the corresponding BIM product.

Recently, Zhang *et al.*[128] also published their results for the reaction of various substituted indoles with ethyl propiolate. However, instead of using gold catalysis, the group found they could achieve high yields of around 99% when using gallium dodecyl sulphate, $Ga(DS)_3$, in water making this a great candidate for green chemistry. For example, the reaction of 5-methyl indole with methyl propiolate gave the corresponding bisindolyl propanoate **247** in 98% yield (Reaction 1, **Scheme 66**). The reaction is reported to work well with a range of substituted indoles, however, when disubstituted alkynes were explored reactivity changed. With mono-hydroarylation occurring when *N*-methyl indole **127** was reacted with the disubsituted alkyne dimethyl acetylenedicarboxylate **246b** forming compound **248** (Reaction 2**, Scheme 66**).



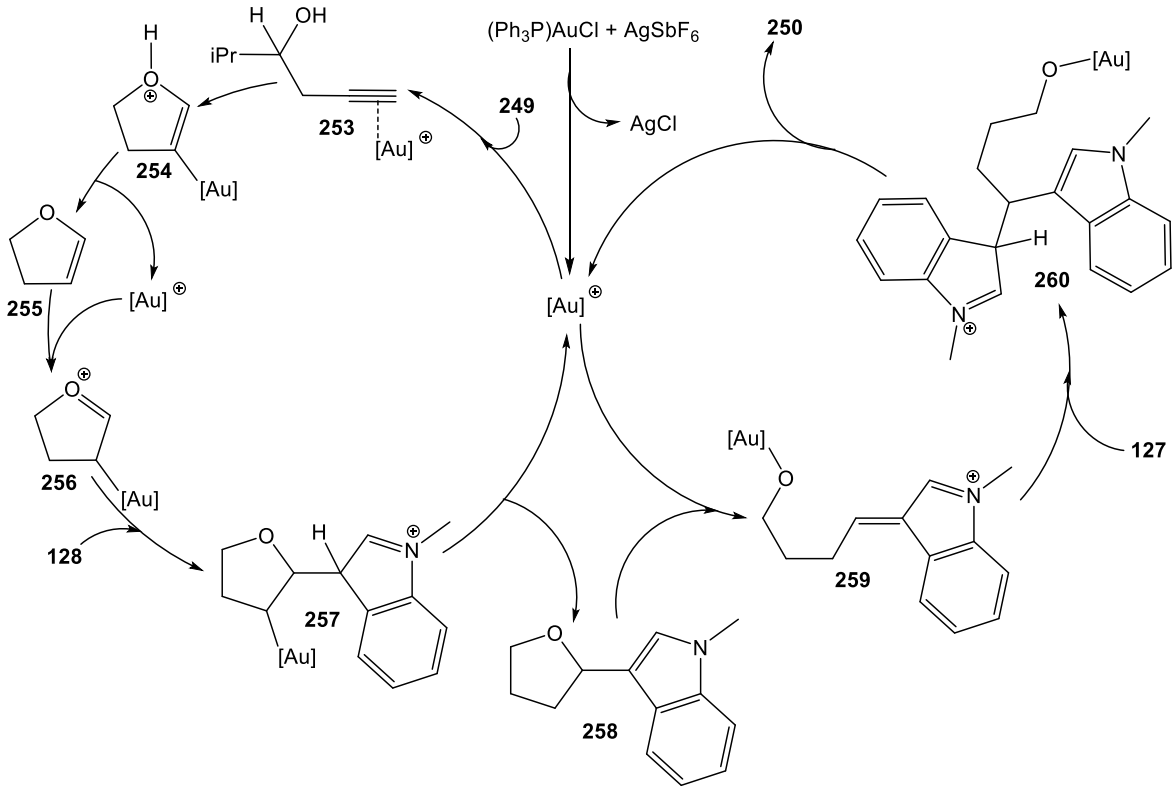
Scheme 66. $AuCl_3$ catalysed reaction of *N*-methylindole with ethyl propiolate to give the corresponding BIM product.

Other Au(I) catalysed reactions include an example by Barluenga *et al.* in 2009[129] who reported the successful double addition of *N*-methyl indole **127** to butynol derivatives. The group found that Ph_3PAuCl (5 mol %) and $AgSbF_6$ (5 mol %) could catalyse the site-selective addition of *N*-methyl indole to both terminal (Reaction 1, **Scheme 67**) and internal alkynes (Reaction 2, **Scheme 67**). The reaction with terminal alkynes **249** gives addition at the terminal carbon and works well with a range of 3-butyn-1-ol derivatives to give the single regioisomer of the corresponding BIM product **250**. When applied to internal alkynes, homopropargylic alcohols **251**, the addition occurs at the carbon distal to the free hydroxyl group, with the successful formation of the single regioisomer 3,3'-BIM **252** product with high yields.



Scheme 67. Au(I)-catalysed reaction of *N*-methylindole with terminal and internal alkynes giving the corresponding BIM product.

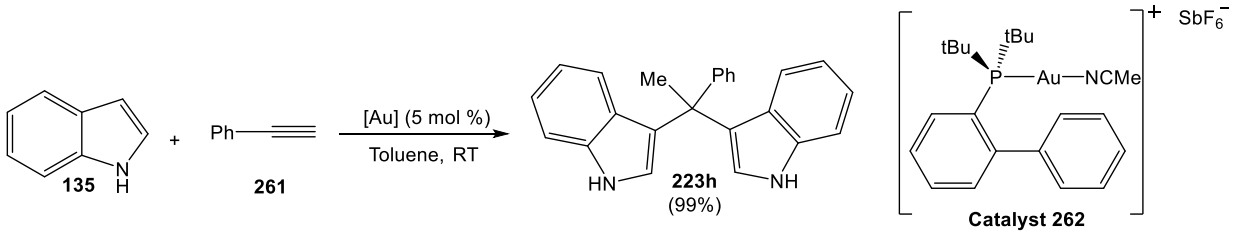
The group proposed the mechanism in **scheme 68**, which involves the formation of the reactive gold complex that coordinates to the triple bond of the alkynol **249** giving intermediate **253**. Intramolecular addition of the hydroxyl group to the terminal carbon of the alkyne gives intermediate **254**, which undergoes protodemetallation to give the enol ether **255**. The catalyst coordinates to **255** generating the oxonium intermediate **266** to which indole **127** adds forming **257**. Aromatization and protodemetallation affords the tetrahydrofurane intermediate **258** (analogous to compounds obtained by Cheng *et al*.).[130] The gold complex coordinates to the oxygen to give ring opening, forming intermediate **259**. Addition of the second indole to **259** occurs, followed by re-aromatisation and protodemetallation to obtain the final product **250** with regeneration of the catalytic species (**Scheme 68**).



Scheme 68. Mechanism for Au(I)-catalysed reaction of *N*-methylindole **127** with terminal alkyne **249** giving the corresponding BIM product **250**.

Another Au(I)-catalysed reaction involving the addition of indoles to terminal alkynes was reported by Echavarren *et al.* in 2007.[131] The reaction uses the Au(I) catalyst **262** (**Scheme 69**) to catalyse the addition to the alkynes with the formation of the corresponding BIM as a single regioisomer.

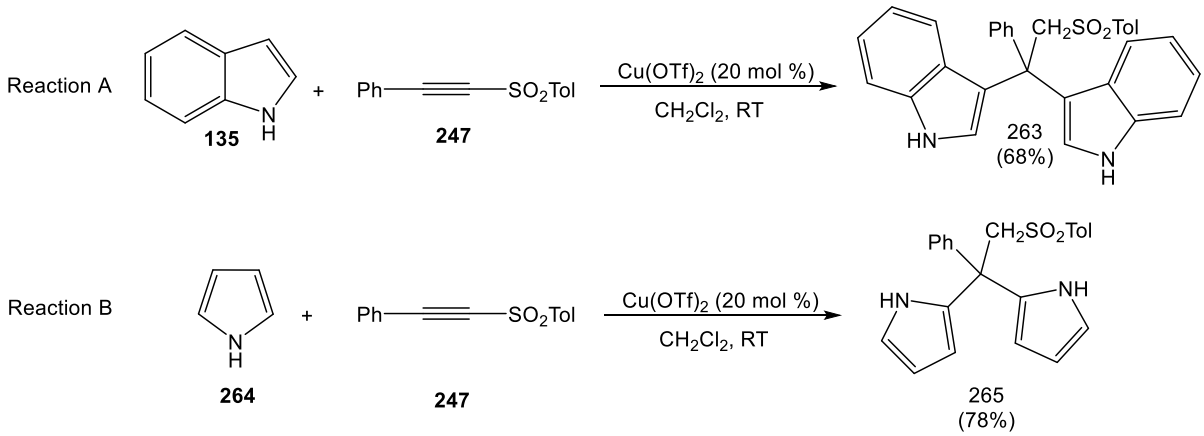
The reaction is reported to work well with a range of substituted indoles and substituents on the aryl group giving the products in relatively high yields, as well as working with pyrroles. e.g. Indole **135** addition to phenylacetylene **261** with formation of the corresponding BIM **223h** in 99% yield (**Scheme 69**).



Scheme 69. Reaction scheme for Au(I)-catalysed addition of indole to terminal alkynes with high yields.

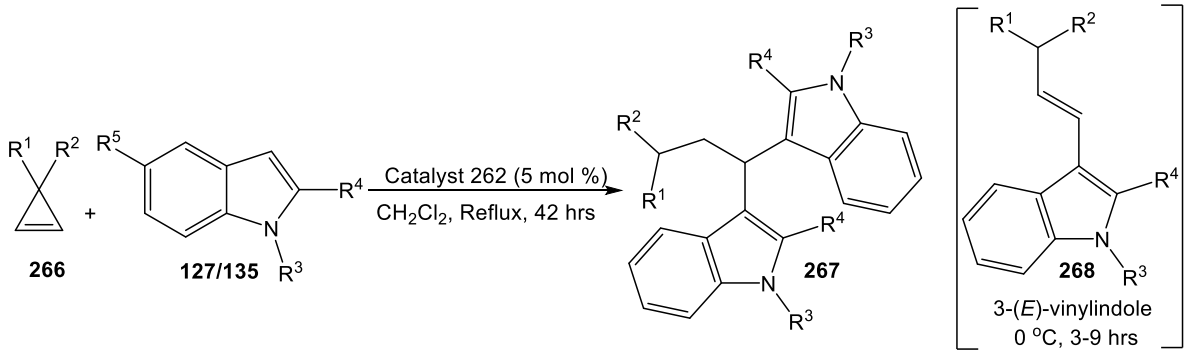
In 2009, Zhang *et al*.[132] reported their results for the synthesis of sulfonyl-containing BIMs *via* the double Michael addition reaction of indole with acetylenic sulfone **247** under $Cu(OTf)_2$ catalysis. The reaction was also reported to work with pyrrole to form the corresponding bis(pyrrolyl)alkane derivative **265** which is another biologically and physiologically active molecule generally formed *via* condensation of carbonyl reagents and pyrrole.[133]

Both reactions involving indole and pyrrole were reported to proceed in the presence of 20 mol % $Cu(OTf)_2$, with other Lewis acid catalysts showing no catalytic capability for the reaction. The reaction involving indoles and acetlylenic sulfones could proceed with a variety of substituted and unsubstituted derivatives to achieve a range of different sulfonyl-containing BIM derivatives **263** (Reaction A, **Scheme 70**). However, the reaction of pyrrole **264** with the acetylenic sulfone **247** was only expanded in the presence of substituted sulfones to achieve the bis(pyrrolyl)alkane derivative **265** (Reaction A, **Scheme 70**), with substituted pyrroles not achieving the desired product.



Scheme 70. Reaction scheme for the $Cu(OTf)_2$-catalysed reaction for the synthesis of sulfonyl-containing bis-indolyl alkanes and bis-pyrrolyl alkanes.

A novel approach to BIMs using Au(I) catalysed indole addition to cyclopropenes was reported by Lee *et al.* in 2012.[134] During their studies they found that catalyst **262** (**Scheme 69**) could selectively form the 3-(*E*)-vinylindoles or BIM products from indole addition to the 3,3-disubstituted cyclopropane **266**, depending on the reaction conditions. They established that at 0 ^{o}C for 3 hours they could selectively form the 3-(*E*)-vinylindoles **268**, whereas at reflux for 42 hours the BIM **267** was selectively formed. e.g. reaction of cyclopropene **266** with indole **127/135** results in the corresponding BIM product in 76% yield (>99:1, 280d:281d) (**Scheme 71**).



266a = R^1= Me, R^2 = $(CH_2)_2$Ph, **135** = R^3 = R^4 = R^5 = H — **267a** = 69% — **268a** = 81%

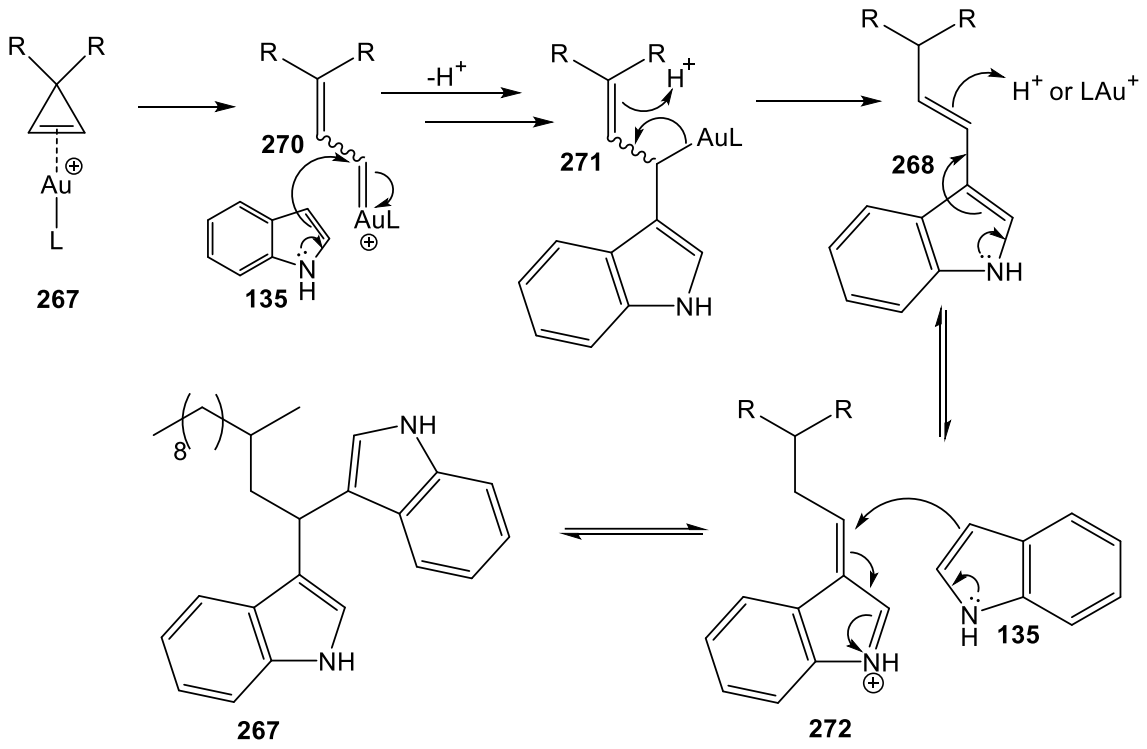
266b = R^1 = Me, R^2 = $(CH_2)_8$Me, **127** = R^3 = Me, R^4 = R^5 = H — **267b** = 71% — **268b** = 91%

266c = R^1 = Me, R^2 = Bn, **135** = R^3 = R^4 = R^5 = H — **267c** = 61% — **268c** = 73%

266d = R^1 = Me, R^2 = $(CH_2)_8$Me, **135** = R^3 = R^4 = R^5 = H — **267d:268d** = >99:1, = 76%

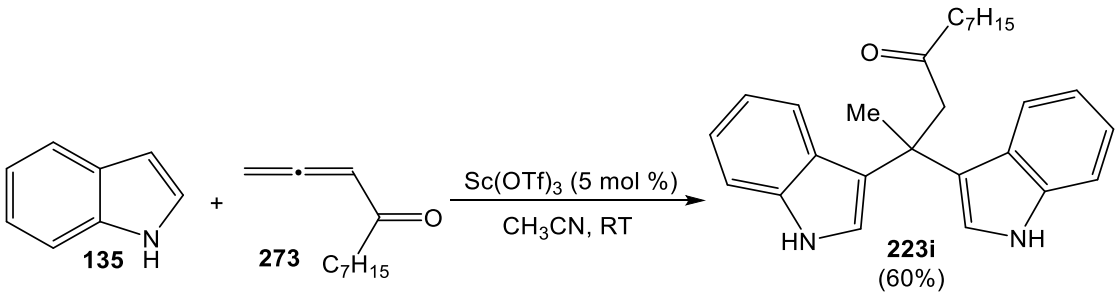
Scheme 71. Reaction scheme for Au(I)-catalysed addition of indole to 3,3-disubstituted cyclopropenes.

This selective formation is supported by their proposed mechanism where it is shown that 3-(*E*)-vinylindoles **268** are intermediates in the formation of **267**. The mechanism begins with the Au-catalysed ring opening of cyclopropene to form the carbene/cationic intermediate **270** followed by indole addition to give intermediate **271** which undergoes protonation/deauration to form the 3-(*E*)-vinylindole product **268.** Optimised conditions will either stop the reaction at this point, or activation of **268** by Au(I) or H^+ would allow the addition of the second indole molecule with formation of product **267** (**Scheme 72**).



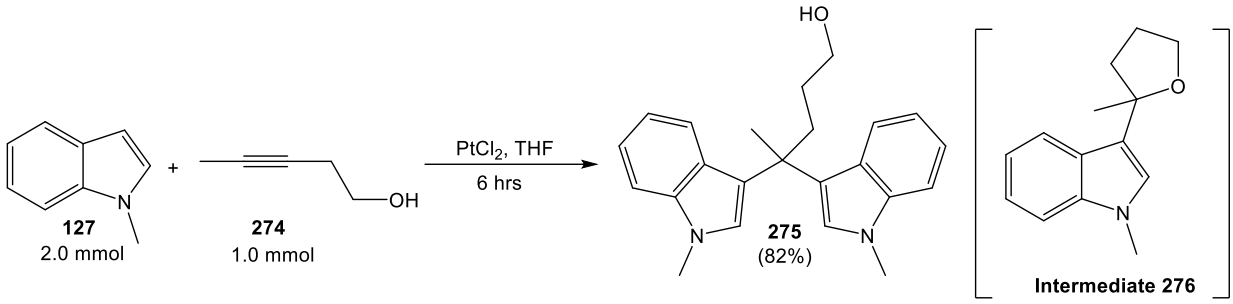
Scheme 72. Proposed mechanism for the formation of BIM from cyclopropene *via* the 3-(*E*)-vinylindole product **281**.

Another example in which vinyl indole derivatives have been identified as intermediates in the formation of bis-indolyl products is that by Ma and Yu in 2005.[135] They reported the use of triflate salts, in particular $Sc(OTf)_3$, for the addition of indoles to 1,2-allenic ketones, producing both *β*-indolyl-*α,β*-unsaturated (*E*)-enones and *β,β*-bis-indolyl ketones. The conditions for the mono-addition reaction were extended to examine the double indole addition and the group found that a variation in ratio of the indole to ketone with slightly longer reaction times gave the successful double addition with bis-indolyl ketones formed in good to high yields. e.g. reaction of indole **135** with allenic ketone **273** gives the successful formation of the *β,β*-bis-indolyl ketone **223i** in 60% yield (**Scheme 73**). The group also demonstrated the stepwise double addition by reacting the vinyl indole derivative with indole to obtain the corresponding bis-indolyl ketone product in relatively good yields.



Scheme 73. $Sc(OTf)_3$-catalysed addition of indoles to 1,2-allenic ketones for the formation of *β,β*-bisindolyl ketone derivatives.

Of importance to this thesis is the synthesis of BIMs using platinum catalysis, there are only a couple of examples to date, one of which is by Cheng *et al.*[129] They published their results for the multistep addition of indoles to alkynyl alcohols **274** using $PtCl_2$ with the formation of 3-substituted five-membered tetrahydrofuran compounds **276**, as well as six-membered tetrahydro-2H-pyran indole derivatives. It was reported that longer chain alkynyl alcohols underwent double addition of indole with the formation of the corresponding BIM product **275**. This led the group to identify that a 2:1 ratio of indole:alkynyl alcohol would give the corresponding bis-indolylmethane product with good yields (**Scheme 74**). As with the other examples (see **Scheme 71**) this reaction was found to proceed *via* 3-substituted indole intermediate **276** (**Scheme 74**).



Scheme 74. $PtCl_2$ catalysed addition of indoles to alkynyl alcohols.

Another platinum catalysed example is the bis-indolylation of allenes that has already been discussed in section 1.4.d for the metal catalysed hydroarylation of allenes. This reaction was carried out by the Muñoz group in 2012[77] and involves the addition of two molecules of indole to the terminal, less hindered carbon of the allene with complete saturation of the internal bond forming the corresponding 3,3'-BIM products in moderate yields. The reaction scheme and mechanism can be seen in **schemes 32** and **33** respectively.

1.6.d. Properties and synthesis of 2,3'-BIMs

Most of the previously described examples give rise to the more common 3,3'-BIM derivatives, however the research carried out for this thesis involves the formation of the less common 2,3'-BIMs. Although less common, they have been reported for their existence in natural products, examples of which include malassezin[136] **277** (**Scheme 75**), which is the first alkaloid described from cultures of lipophilic *Malassezia* yeast. Bengacarboline[137] **278** (**Figure 16**), a marine alkaloid extracted from Fijian ascidian *Didemnum* sp. which exhibits interesting inhibitory activity of topoisomerase II with cytotoxicity towards a wide range of tumor cell lines in vitro. Also, yuehchukene[138] **279** an indole alkaloid which is isolated from the roots of the tropical evergreen plant *Murraya paniculata* as well as other *Murraya* plant species. This compound has shown interesting anti-implantation activity in rats and has been regarded as a potential fertility regulating agent.

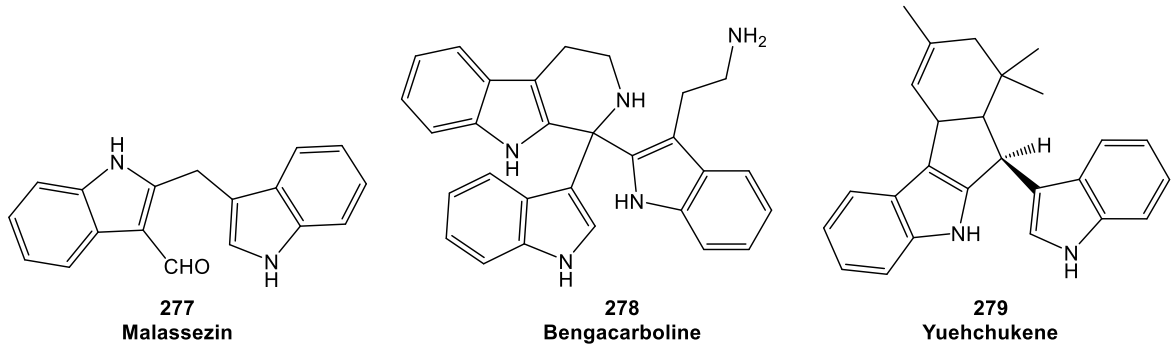


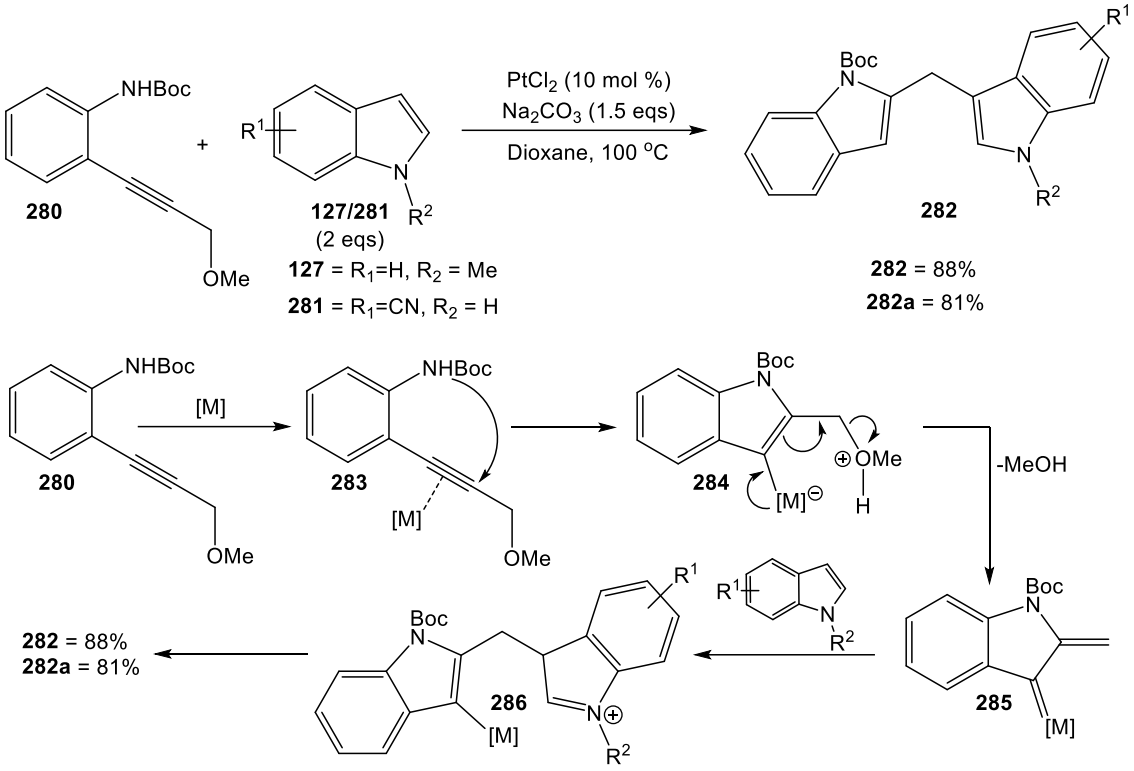
Figure 16. Examples of 2,3'-BIMs in natural products.

These three examples possess the 2,3' connectivity, however they all have different structural connectivity with different groups connecting the two indole units, this allows them to have different properties and different biological activity. This makes them of high interest to chemists and therefore allows exploration into new routes of their synthesis.

As mentioned previously, these compounds are harder to synthesise because of the favoured addition at the 3 position of indoles rather than position 2, and there are only a couple of reported examples using transition metal catalysis for their synthesis. Both examples report the use of $PtCl_2$ catalysis for the addition of indoles to alkynes and allenes, the example which utilises alkynes was reported in 2013 by Tang *et al*.[139]

The group reported the synthesis of 2,3'-BIMs through a Pt catalysed indole annulation/arylation cascade reaction, where a metal carbene intermediate is generated from annulation of propargylic ethers which can then be trapped with indoles generating the desired 2,3'-BIM.

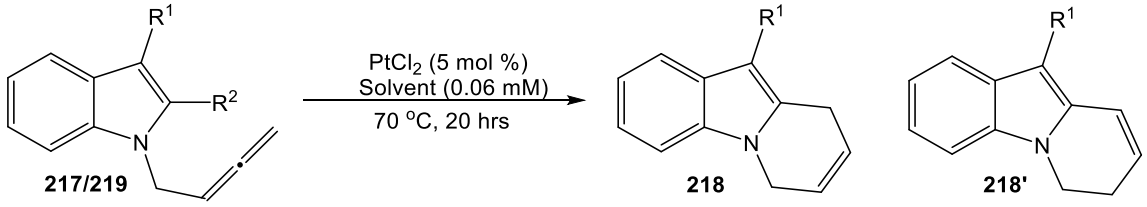
Although the reaction was found to work with both Rh and Pt catalysis, higher yields were achieved with Pt and therefore catalytic amounts of $PtCl_2$ were used as the optimised conditions. The reaction is reported to work well with a range of substituted indoles, with electron-donating groups as well as halogen substituents giving relatively high yields. For example, the reaction of *N*-methylindole **127** and 4-cyanoindole **281** with propargylic ether **280** gives the corresponding 2,3'-BIMs **282** and **282a** in 88% and 81% yield respectively (**Scheme 75**).



Scheme 75. Reaction scheme and mechanism for $PtCl_2$ catalysed annulation/arylation cascade reaction for synthesis of 2,3'-BIMs

The reaction is also reported to work well with a range of substituted anilines as well as with *N*-methylpyrrole giving the indole-pyrrole cross product in relatively good yield. The proposed mechanism for the reaction can be seen in **scheme 75** and involves the coordination of the metal catalyst to the propargylic ether **280** that initiates the 5-endo-cyclisation of the metal complex **283** generating intermediate **284**. Methanol elimination produces the metal carbene intermediate **285** which is then trapped by an indole unit to form the adduct **286**, which after protonation and re-aromatisation gives the final 2,3'-BIM products **282** and **282a**.

The second reported $PtCl_2$ catalysed reaction for 2,3'-BIM formation forms the basis for this thesis, this example was first reported by the Muñoz group in 2012[66] as an example of their bis-indolylation reaction. The group reported that $PtCl_2$ could catalyse the intramolecular reaction of *N*-(2,3-butadienyl) indole derivatives **217/219** (**Scheme 76**), however instead of observing only one 6-endo cyclised product like with Au catalysis reported by Barluenga,[101] they observed two isomers of the 6-endo cyclised product which differ in position of the double bond **218** and **218'** (**Scheme 76**). These were isolated as inseparable mixtures with differing ratios depending on the solvent used.



217a = R^1 = Me, R^2 = H

217d = R^1 = R^2 = H

219a = R^1 = H, R^2 = Me

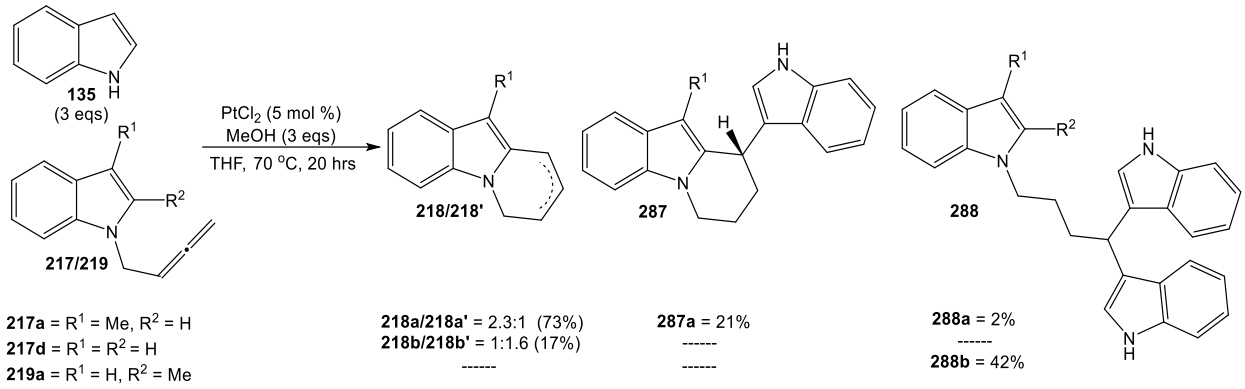
THF = **218a/218a'** = 1.2:1 (65%)
MeOH = **218a/218a'** = 2.6:1 (83%)

THF = **218b/218b'** = 1.4:1 (30%)
MeOH = **218b** = (9%)
THF (0.2 mM) + MeOH (3 eqs) = **218b/218b'** = 1:1.6 (31%)

THF = No Reaction
MeOH = No Reaction

Scheme 76. Pt-catalysed 6-endo cyclisation of *N*-(2,3-butadienyl) indole derivatives with various solvents.

This observation led the group to explore the possibility of an intra-intermolecular bis-indolylation reaction, therefore they reacted *N*-(2,3-butadienyl) indole derivatives in the presence of free indole under the platinum conditions and observed a mixture of products. Having no substituents in position 2 and 3 of the indolyl allene gave only the two isomeric 6-endo cycles, whereas having a methyl group present in position 3 led to a mixture of 3 products; the 6-endo cycles **218** and **218'** (73%), the tris-indole product **288** (2%) and the desired intra-intermolecular product **287** in 21% yield (**Scheme 77**). They also reported that having a methyl group in position 2 formed only the tris-indole product because the C2 position was blocked for 6-endo cyclisation.



Scheme 77. Platinum-catalysed reaction of *N*-(2,3-butadienyl) indole derivatives with free indole for formation of 2,3'-BIMs.

This is a novel approach to unique 2,3'-BIMs, these molecules are structurally different to those found in natural products with the connectivity occurring through the nitrogen of the indolyl allene. The availability of the 'free' indole means it could undergo further reaction or functionalisation to increase the molecules potential for biological activity.

1.7. Aims and Objectives

The first aim of this project was to further investigate the bis-indolyation reaction already reported by the Muñoz group by incorporating two different substituted indole units to synthesise unsymmetrical cross-BIM products, which could have interesting properties. Also, the same reaction conditions were used to investigate the incorporation of different nucleophiles onto allenes, such as pyrrole, imidazole, indazole, benzimidazole and pyrazole as well as others. These sets of reactions were investigated with a wide range of reaction conditions which will be described in the results and discussion section.

The main focus of this project has been to further develop the previously published work for synthesis of 2,3'-BIMs by using a range of substituted *N*-(2,3-butadienyl) indole derivatives as well as a range of substituted indoles to investigate the effect on the formation of the desired 2,3'-BIM. We aimed to highlight the effect that substituents had on the overall reaction with respect to both electron-donating and electron-withdrawing groups, also the overall reaction mechanism was investigated by identifying the intra- and intermolecular processes using deuterium, NMR spectroscopy and time progress studies.

Chapter 2.0

Results and Discussion

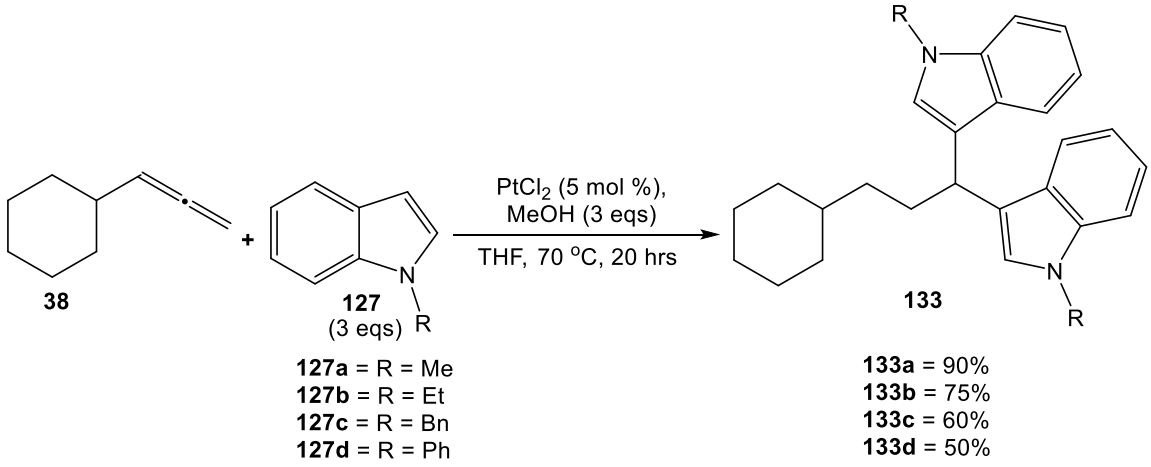
This chapter will outline the development of both the platinum-catalysed inter-intermolecular and intra-intermolecular bis-indolylation reaction of allenes, which were first introduced by the Muñoz group in 2012[77] and have been discussed in the introduction (Section 1.4, **scheme 32** and section 1.6, **scheme 77** respectively).

The first section of this chapter will discuss the results obtained from the extension of the inter-intermolecular addition reaction with different nucleophiles, as well as the results obtained from investigating the addition of two different nucleophiles to the same allene. The following sections will focus on the intra-intermolecular reaction, which make up most of the present thesis. This reaction has gained a lot of interest because of its ability to form the interesting 2,3'-BIM compounds.[104-111] In collaboration with Novartis and project students Helen Newson, Louise Eagling and Sachini Herath, we have been able to optimise conditions and investigate the reaction with respect to various substituted indoles to selectively form 2,3'-BIMs. Alongside this, an extensive mechanistic investigation has been carried out to propose the overall mechanism of the reaction and will be discussed in detail in section 2.4.

2.1. Inter-intermolecular addition reaction

2.1.1. Varying nucleophiles

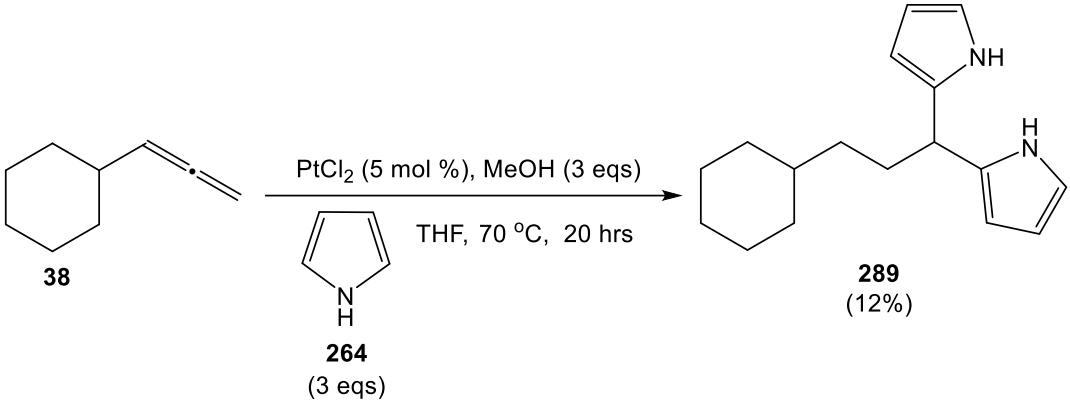
Platinum-catalysed bis-indolylation of cyclohexylallene **38** was first reported by Muñoz *et al.*[77] with *N*-substituted indoles **127** forming the corresponding 3,3'-BIMs **133** bearing the same indole unit (**Scheme 78**).



Scheme 78. Platinum-catalysed bis-indolyation reaction with *N*-substituted indoles **127**.

The group, also established that the reaction was not limited to addition of indoles and reported the double addition of pyrrole **264** to cyclohexylallene **38** forming the bis-pyrrole compound **289** (**Scheme 79**).

Pyrrole rings show different reactivity to that of indole and therefore these bis-pyrrole products have a 2,2' connectivity. This makes them interesting compounds because of their role in the synthesis of porphyrins, polypyrrolic compounds and macrocycles such as haemoglobin and vitamin B12.[140141140] Their synthesis has been readily reported as the condensation reaction of pyrrole with ketones in the presence of catalytic TFA, as well as a range of other methods.[140]

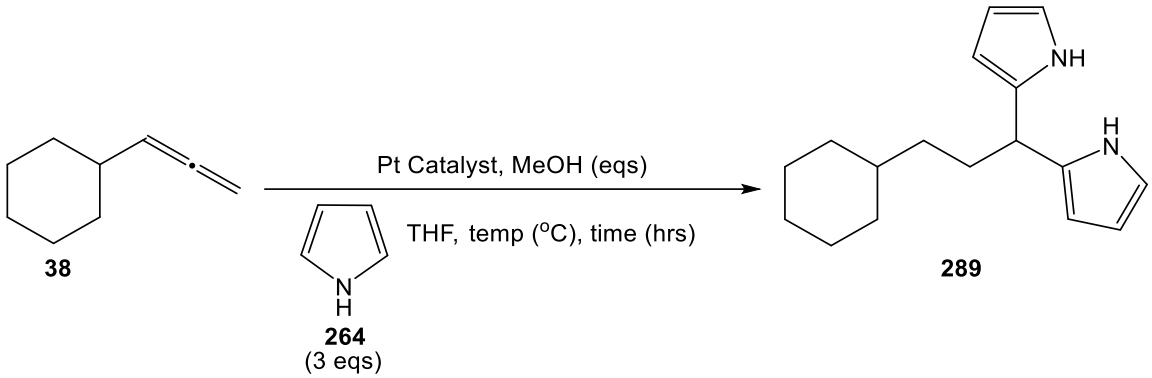


Scheme 79. Platinum-catalysed reaction for addition of pyrrole **264** to cyclohexylallene **38**.

In the work reported by Muñoz *et al.*[78] a conversion to the bis-pyrrole molecule **289** was observed in relatively low yield (12%). Considering the potential importance of these bis-pyrrole molecules, optimizing the reaction conditions to increase the yield of the desired product is highly important and was one of the first objectives of this thesis.

Pyrrole is sensitive to light, air and moisture. Consequently, pyrrole requires fresh distillation under inert atmosphere to be employed as a nucleophile in this reaction. Entry 1 (**Table 1**) compared with entry 6 (**Table 1**) shows that distilling the pyrrole directly before use improves the reaction and increases the yield to 20%. The use of silver salts as halide abstractors for the generation of more reactive metal cationic complexes has been readily reported and depending on the size and electronic properties, the counterions can provide strong or weak interactions to the metal centre therefore enhancing the catalytic activity.[142] Therefore, our reaction was explored in the presence of the silver salt AgOTf to determine if the cationic platinum complex could increase the formation of the desired product. However, using $PtCl_2(MeCN)_2$/AgOTf did not show any improvement in the reaction, achieving only traces of the product after 72 hours (Entry 5, **Table 1**). Entry 7 (**Table 1**) highlights that the presence of methanol promotes the formation of the bis-pyrrole product **289**, and its exact role and functionality will be discussed in the mechanistic investigation (**Scheme 150**, Page 174). In addition, microwave irradiation can promote the formation of the bis-pyrrole product, but in low yield (Entry 9, **Table 1**).

$PtCl_2$ as the catalyst, MeOH, distilled pyrrole in THF at 70 ^oC were found to be the best reaction conditions to promote the double addition of pyrrole to cyclohexylallene **38**, however due to polymerisation of the pyrrole and decomposition of the allene after prolonged reaction times, the yield could not be further improved (Entry 8, **Table 1**).



Scheme 80. Screening of platinum catalysts, solvent, time and temp for bis-pyrrole reaction.

Entry	Pyrrole (eqs)	Catalyst (5 mol %)	Halide abstractor (10 mol %)	MeOH (eqs)	Temp (^oC)	Time (hrs)	Result
1	3[a]	$PtCl_2$	N/A	3	rt - 70	30	**38**[c]
2	3[a]	$PtCl_2$	N/A	3	rt	25	**38**[c]
3	3[a]	$PtCl_2(MeCN)_2$	AgOTf	0	70	16	**38** (major), **289** (traces)[c]
4	3[a]	$PtCl_2(MeCN)_2$	AgOTf	3	rt	24	**38** (major), **289** (traces)[c]
5	3[b]	$PtCl_2(MeCN)_2$	AgOTf	3	70	72	**38** (major), **289** (traces)[c]
6	3[b]	$PtCl_2$	N/A	3	70	48	**289** (20%)[d]
7	3[b]	$PtCl_2$	N/A	0	70	48	Ratio of 1:0.15 for **38**:**289**
8	3[b]	$PtCl_2$	N/A	3	70	72	**289** (31%)[d]
9	3[b]	$PtCl_2$	N/A	3	70[e]	8.5	**289** (16%)[d]

[a] Pyrrole not distilled directly before use, [b] Pyrrole distilled directly before use (under N_2), [c] Results obtained qualitatively from crude NMRs, [d] Isolated product, [e] Carried out under mw irradiation.

Table 1. Results obtained during optimisation of bis-pyrrole reaction.

The partially successful addition of pyrrole to allenes led us to investigate the reaction with other nucleophiles with different heteroatoms present, including; N, S, O and C. This could expand the scope of the reaction, giving access to a wide range of compounds with a variety of properties which could have potential biological importance as well as being useful precursors in further organic synthesis.[143,144]

Firstly, we explored the reaction of cyclohexylallene **38** with other nitrogen-containing heteroaromatic nucleophiles, with initial experiments being carried out with commercially available imidazole **290** (**Figure 17**). This aromatic heterocycle is present in a range of alkaloid natural products and biological building blocks such as histidine **291** and histamine **292** (**Figure 17**).[144]

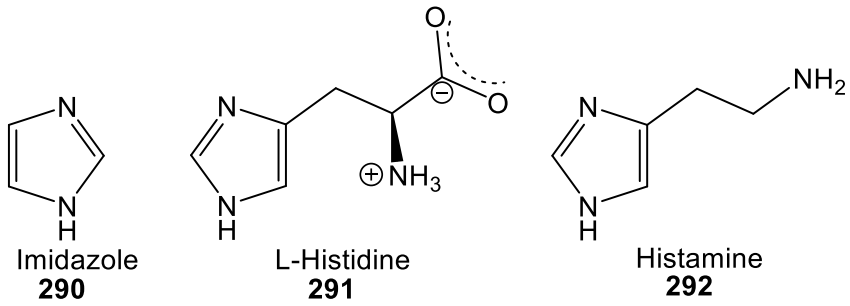
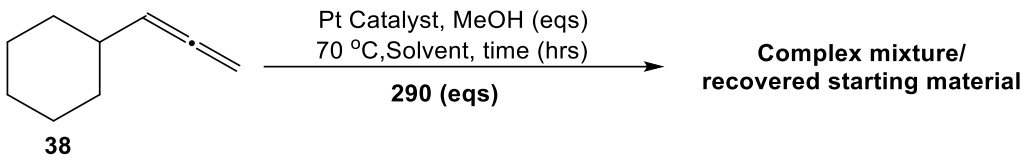


Figure 17. Structure of imidazole **290** and its presence of biological building blocks histidine **291** and histamine **292**.

Initial reactions were carried out with the same conditions reported for the bis-indolylation reaction catalysed by $PtCl_2$ and using cyclohexylallene as the model substrate (**Scheme 77**). However, using these conditions no nucleophilic addition to cyclohexylallene **38** was observed and only starting material was recovered after 20 hours (Entry 1, **Table 2**). Cationic platinum complexes were also tested by employing different silver salts ($AgNTf_2$, AgOTf and $AgSbF_6$) as halide abstractors, but despite using various cationic platinum complexes, different solvents and reaction times, the expected reaction did not occur and starting material was recovered in most cases (Entries 2 – 6, **Table 2**).



Scheme 81. Screening of platinum catalysts, solvent, time and temp for bis-imidazole reaction.

Entry	Catalyst (5 mol %)	Halide abstractor (10 mol %)	Solvent	MeOH (eqs)	Time (hrs)	Result [a]
1	$PtCl_2$	-	THF	3	20	**38**
2	$PtCl_2(MeCN)_2$	$AgNTf_2$	THF	3	20 – 48	**38**
3	$PtCl_2(MeCN)_2$	AgOTf	THF	0	20 – 48	Complex mixture.
4	$PtCl_2(MeCN)_2$	AgOTf	Dioxane	0	20	**38**
5	$PtCl_2(MeCN)_2$	$AgSbF_6$	THF	3	20	**38**
6	$PtCl_4$	$AgNTf_2$	THF	0	20	**38**

[a] Results obtained qualitatively from crude NMRs

Table 2. Reaction conditions explored for the platinum-catalysed reactions of imidazole **290** with cyclohexylallene **38**.

Nitrogen-containing heteroaromatic nucleophiles pyrazole **293**, indazole **294** and benzimidazole **295** (**Figure 18**) were also used as nucleophiles to investigate their reactivity for the inter-intermolecular addition to allenes. These heteroaromatic nucleophiles have been reported for their addition to allenes in the presence of rhodium catalysts, with subsequent formation of the allylic derivative as described by Breit *et al*.[79] and they are also found to be important structural components of natural products and drugs.[14]

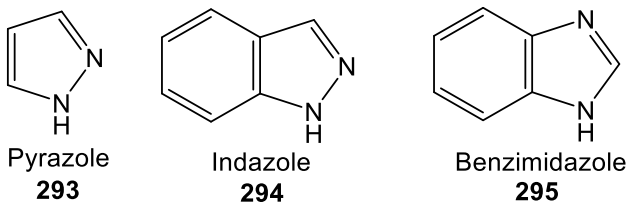
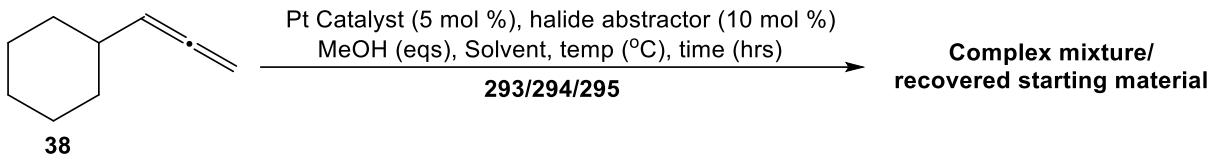


Figure 18. Structures of pyrazole **293**, indazole **294** and benzimidazole **295**.

Again, initial reactions were carried out with standard platinum conditions and cyclohexylallene, however, no incorporation of the nucleophile to the allene was observed and only starting material was recovered in all cases (entries 1-3, **table 3**).



Scheme 82. Screening of platinum catalysts, solvent, time and temp for pyrazole **293**, indazole **294** and benzimidazole **295** addition to cyclohexylallene **38**.

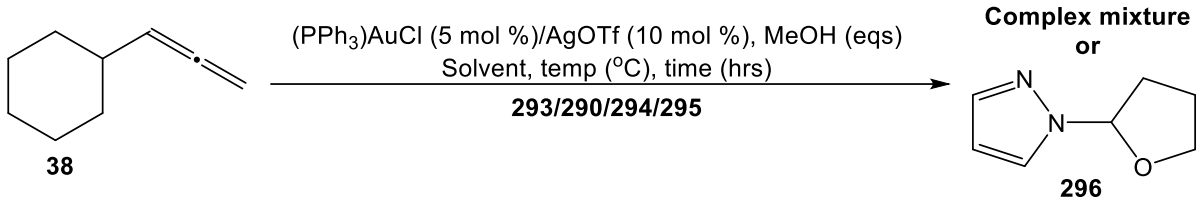
Entry	Nucleophile (3 eqs)	Catalyst	Halide abstractor (10 mol %)	Solvent	MeOH (eqs)	Temp (°C)	Time (hrs)	Result [a]
1	**293**	$PtCl_2$	-	THF	3	70	20	**38**
2	**294**	$PtCl_2$	-	THF	3	70	20	Complex mixture
3	**295**	$PtCl_2$	-	THF	3	70	20	Complex mixture
4	**293**	$PtCl_2(MeCN)_2$	$AgNTf_2$	THF	3	70	24	**38**
5	**293**	$PtCl_2(MeCN)_2$	AgOTf	THF	0	70	24	**38**
6	**293**	$PtCl_2(MeCN)_2$	AgOTf	1,4-Dioxane	0	70	24	Complex mixture
7	**293**	$PtCl_2(MeCN)_2$	$AgSbF_6$	THF	0	70	24	**38**
8	**293**	$PtCl_4$	$AgNTf_2$	THF	0	70	24	**38**
9	**294**	$PtCl_2(MeCN)_2$	AgOTf	THF	3	70	56	**38**
10	**294**	$PtCl_2(MeCN)_2$	AgOTf	1,4-Dioxane	0	80[b]	2	Complex mixture
11	**295**	$PtCl_2(MeCN)_2$	AgOTf	THF	3	70	56	**38**
12	**295**	$PtCl_2(MeCN)_2$	AgOTf	DCM	3	50	20	**38**
13	**295**	$PtCl_2(MeCN)_2$	AgOTf	DCM	0	55	18	**38**

[a] Results obtained qualitatively from crude NMRs, [b] Carried out under mw irradiation.

Table 3. Reaction conditions explored for the platinum catalysed reactions of pyrazole **293**, indazole **294** and benzimidazole **295** with cyclohexylallene **38**.

As with imidazole, these nucleophiles were explored using the cationic platinum complexes such as $PtCl_2(MeCN)_2$/AgOTf, with different solvents (THF, DCM and 1,4-dioxane), time and temperature (Entries 4 – 13, **table 3**). Several reactions were also carried out in the absence of methanol to establish if this had an effect, but overall, the reactions did not occur and gave either complex mixtures or recovered starting material.

As described in the introduction, gold can catalyse the addition of nucleophiles to allenes with formation of the allylic derivatives (Section 1.4.c., **Scheme 14**).[42a,59-67] Therefore we were interested to know if gold would catalyse the addition of these *N*-containing nucleophiles to cyclohexylallene **38**. Reactions were carried out with commercially available triphenylphosphine gold(I) chloride and AgOTf as halide abstractor to generate the cationic gold complex. Several reactions were carried out with different solvents, THF and DCM for varying lengths of time (**table 4**), but even with this catalytic system in place we could not get the addition of the nucleophile to the allene. Interestingly, the pyrazole-THF complex **296** was isolated in low yield in the reaction carried out with pyrazole in THF (Entry 1, **Table 4**). This molecule arises from the *N*-alkylation of the azole with THF, which has been previously reported to occur *via* a radical mechanism with metal catalysis such as Fe[145] and Cu.[146146] Its structure was confirmed by comparison of NMR data with reported data.[147] The reaction has been reported to work with other azoles (imidazole **290**, indazole **294** and benzimidazole **295**)[146] to generate a range of *N*-alkylated azoles which are common structures in medicinally important products, but we did not observe the formation of those analogues in our reaction conditions.



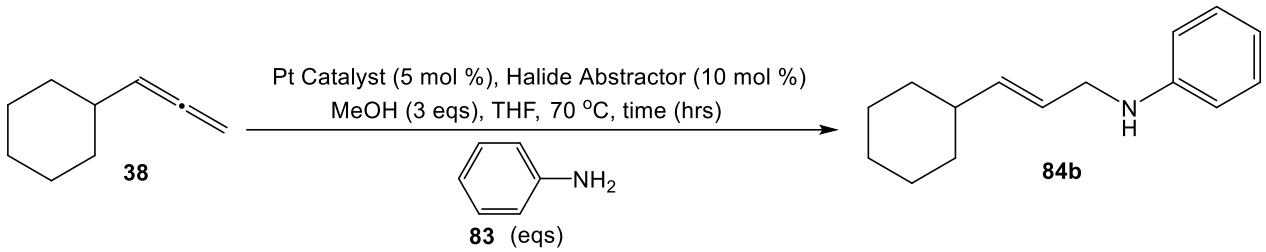
Scheme 83. Screening of solvent, time and temp for gold catalysed reaction of pyrazole **293**, imidazole **290**, indazole **294** and benzimidazole **295** addition to cyclohexylallene **38**.

Entry	Nucleophile (3 eqs)	Solvent	MeOH (eqs)	Temp (°C)	Time (hrs)	Result[a]
1	**293**	THF	3	70	30	Observed **38** and isolated **296** (8%)
2	**293**	1,4-Dioxane	0	RT-70	48	Complex mixture
3	**293**	THF	0	70	24	Complex mixture
4	**290**	THF	3	70	30	**38**
5	**290**	DCM	3	RT	48	Complex mixture
6	**294**	THF	0	70	24	Complex mixture
7	**295**	THF	3	70	24	Complex mixture

[a] Results obtained qualitatively from crude NMRs

Table 4. Reaction conditions explored for the gold-catalysed reactions of pyrazole **293**, imidazole **290**, indazole **294** and benzimidazole **295** with cyclohexylallene **38**.

Several reactions were carried out with aniline **83**, a cheap and readily available aromatic amine which can undergo gold-catalysed single addition to allenes with formation of the corresponding allylic amine (refer to section 1.4.c in introduction).[59-67] Therefore, we were interested to know if aniline under standard platinum conditions would undergo double addition to cyclohexylallene **38**. However, after 20 hours a complex mixture was obtained with traces of starting material observed (entry 1, **table 5**). To further explore this reaction and based on previously published work by Widenhoefer and Toups[59] who used cationic platinum complexes with phosphines to synthesise *E*-allylic amines from mono-substituted allenes, we investigated the reaction with cationic platinum complexes with a few silver salts as halide abstractors. Silver salt abstractors were employed in place of phosphine ligands as these were observed to inhibit the reaction. It was interesting to see that with 3 eqs of aniline (entry 2, **table 5**) we only recovered starting material, however with 1.5 eqs (entry 3, **table 5**) we obtain the allylic amine **84b** in 15% after 3-4 hrs. The time was extended for this reaction but we did not observe the addition of the second aniline unit.



Scheme 84. Screening of solvent, time and temp for platinum catalysed addition of aniline **83** to cyclohexylallene **38**.

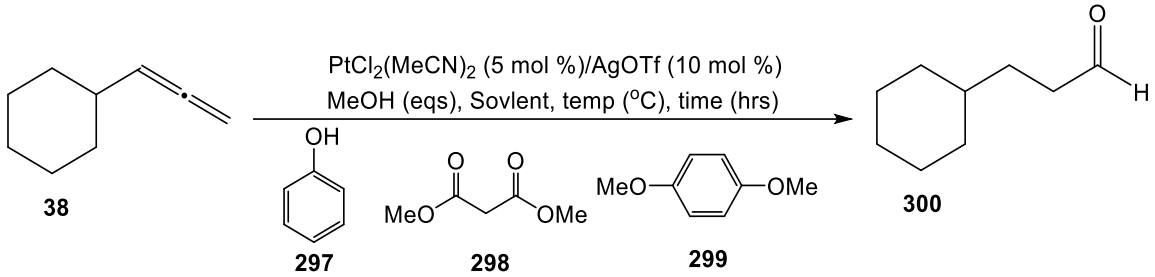
Entry	Nucleophile	Pt Catalyst	Halide abstractor (10 mol %)	Time (hrs)	Result
1	**83** (3 eqs)	$PtCl_2$	-	20	Complex mixture/**38**[a]
2	**83** (3 eqs)	$PtCl_2(MeCN)_2$	AgOTf	18	Complex mixture/**38**[a]
3	**83** (1.5 eqs)	$PtCl_2(MeCN)_2$	AgOTf	3-4	**84b** (15%)[b]
4	3,5-dimethoxy aniline (3 eqs)	$PtCl_2(MeCN)_2$	AgOTf	24	Complex mixture[a]

[a] Results obtained qualitatively from crude NMRs, [b] Isolated product.

Table 5. Reaction conditions explored for the platinum catalysed reaction of aniline **83** with cyclohexylallene **38**.

The successful dihydroalkoxylation reaction which was also reported by Muñoz *et al.*[51] in 2010 (refer to section 1.4.b in introduction) highlights the successful addition of oxygen nucleophiles to allenes. Trying to extend this methodology, phenol **297** was explored as the nucleophile with the same catalytic system, however, instead of observing the double addition of the nucleophile, aldehyde **300** was isolated (entry 1, **table 6**). This aldehyde could come from hydrolysis of the corresponding acetal formed in the reaction (PhO- or MeO-), or more likely from the double addition of water present in the reagents or the solvent. To minimize the formation of this aldehyde **300**, reactions were carried out with molecular sieves and in the absence of methanol, but only starting material was recovered (entry 2, **table 6**). Microwave irradiation was also utilised to increase the rate of the reaction and minimize aldehyde formation, but after 8 hours the reaction gave a complex mixture and traces of the aldehyde were observed (entry 3, **table 6**).

The aldehyde **300** was also observed when reactions were carried out with carbon-based nucleophile, electron-rich aromatic 1,4-dimethoxybenzene **299** even in the absence of methanol (entries 6 and 7, **table 6**). Finally, the carbon-based nucleophile dimethyl malonate **298** in the presence of a base was reacted with cyclohexylallene **38** using the platinum cationic complex, but despite the activation, there was no reaction and only starting material **38** was recovered (entries 4 and 5, **table 6**).



Scheme 85. Screening of solvent, time and temp for catatonic platinum-catalysed addition of oxygen containing nucleophiles to cyclohexylallene **38**.

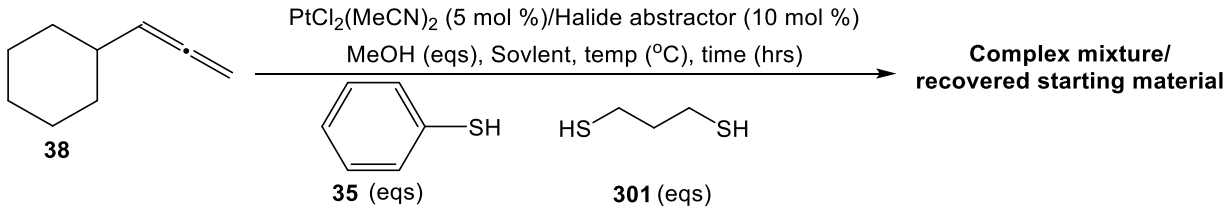
Entry	Nucleophile (3 eqs)	Solvent	Temp (^{O}C)	Time (hrs)	Result
1	**297**	THF/ Methanol	70	20	**300** (47%)[b]
2	**297**	THF/ Molecular sieves	70	20	**38**[a]
3	**297**	1,4-Dioxane	100[c]	8	Complex mixture[a]
4	**298** (3 eqs) / K_2CO_3 (10 mol %)	THF	70	3-4	**38**[a]
5	**298** /NaH (1:1)	THF	70	20	**38**
6	**299**	THF	70	20	**300** (20%)[b]
7	**299**	THF/ Molecular sieves	70	20	Complex mixture[a]

[a] Results obtained qualitatively from crude NMRs, [b] Isolated product, [c] Carried out under mw irradiation.

Table 6. Reaction conditions explored for the platinum-catalysed reactions of oxygen containing nucleophiles with cyclohexylallene **38**.

Several reactions were also carried out with sulphur containing nucleophiles, thiophenol **35** and 1,3-propanedithiol **301**, that have been shown to add to allenes with the use of palladium and gold catalysis (refer to section 1.4.a in introduction).[36-40] Using the standard platinum conditions as well as the platinum cationic complexes with different silver salts and varying the solvent, time and temperature, the addition of the sulphur nucleophiles did not occur (**table 7**).

Sulphur is known to have a high affinity to transition metals[36] and is considered harmful to some reactions, this could be the reasoning for the poor reactivity and the complex unidentifiable signals.



Scheme 86. Screening of platinum catalysts, solvent, time and temp for addition of sulphur containing nucleophiles to cyclohexylallene **38**.

Entry	Nucleophile (3 eqs)	Pt catalyst	Halide abstractor (10 mol %)	Solvent	MeOH (eqs)	Temp (^{o}C)	Time (hrs)	Result [a]
1	**35**	$PtCl_2$	-	THF	3	70	23	Complex mixture
2	**35**	$PtCl_2(MeCN)_2$	AgOTf	THF	0	70	20	**38**
3	**35**	$PtCl_2(MeCN)_2$	$AgSbF_6$	THF	0	70	6-7	**38**
4	**35**/NaH (1:1)	$PtCl_2(MeCN)_2$	AgOTf	THF	0	RT-50	20	Complex mixture
5	**301**	$PtCl_2(MeCN)_2$	AgOTf	THF	0	70	20	**38**
6	**301** (1.5 eqs)	$PtCl_2(MeCN)_2$	AgOTf	1,4-Dioxane	0	100[b]	2	**38**

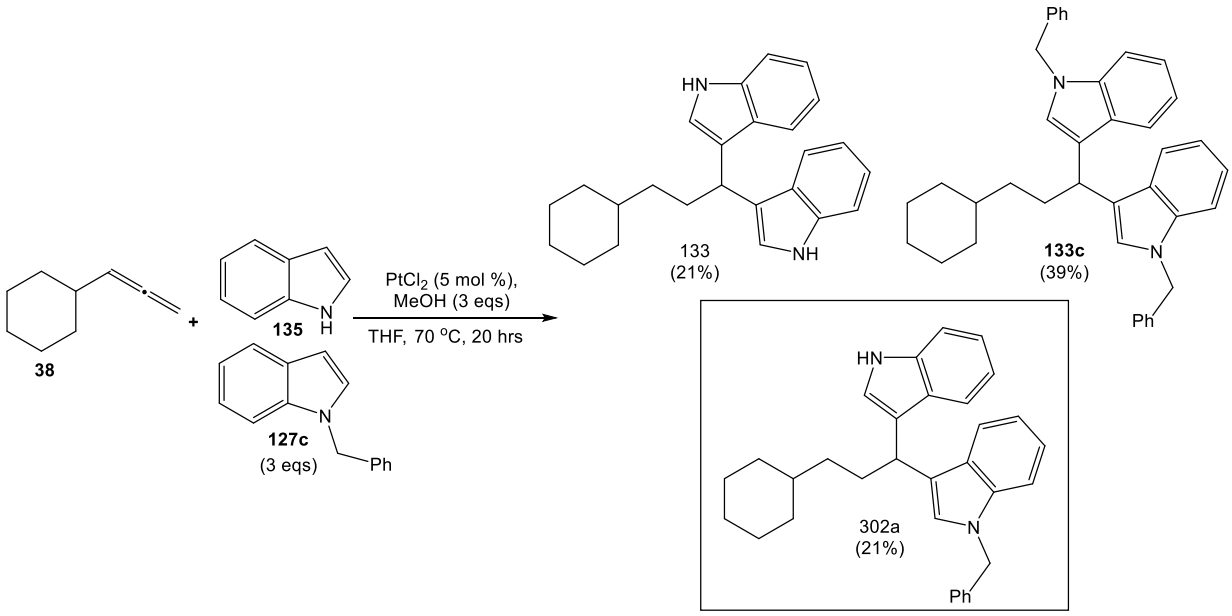
[a] Results obtained qualitatively from crude NMRs, [b] Carried out under mw irradiation.

Table 7. Reaction conditions explored for the platinum-catalysed reactions of sulphur containing nucleophiles with cyclohexylallene **38**.

After extensive exploration of the reaction conditions and nucleophiles led to no successful double addition to cyclohexylallene **38** as previously hoped, it was therefore decided to leave this investigation and focus our attention on the successful addition of indoles and pyrroles.

2.1.2. Optimisation for formation of cross-products

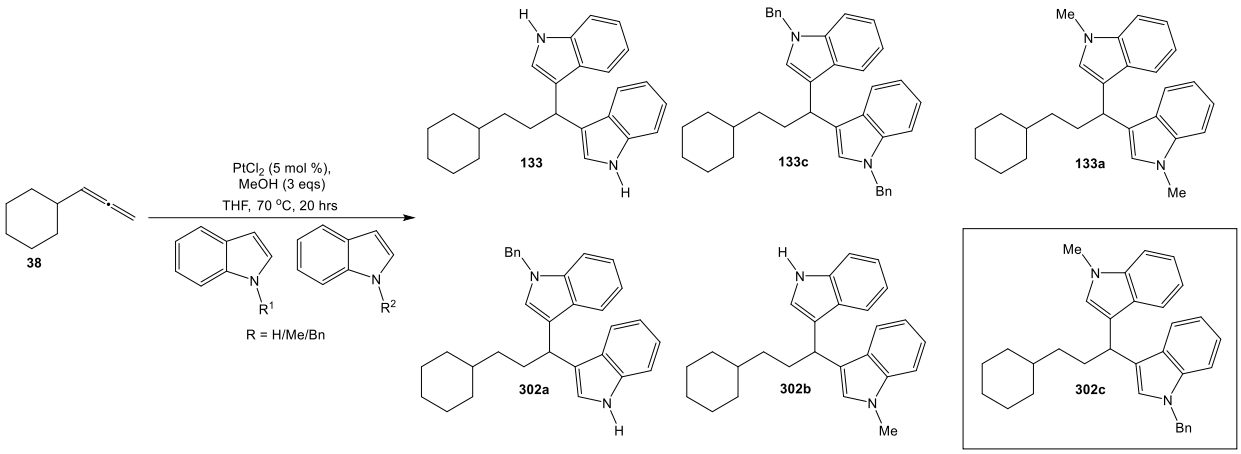
It was reported by Muñoz *et al.*[77] that the bis-indolylation reaction was not limited to the addition of the same indole and the cross-product **302**, bearing a new chiral centre, could be synthesised by addition of indole **135** and benzylindole **127c** to the same allene moiety (**Scheme 87**), although the addition of the same indole is also observed.



Scheme 87. Reaction of addition of two different indoles **135 and 127c** to cyclohexylallene **38**.

The potential utility of this reaction is increased by formation of these chiral cross-products, which could be used for functionalisation or as precursors to biologically important molecules. Therefore, modifying reaction conditions to favour their formation is important. Alongside this we were also interested to know if two different nucleophiles could be added to the same allene and investigated the addition of both indole and pyrrole in the same reaction.

Initial reactions were carried out with indole **135** and methyl indole **127a** (entry 1, **table 8**), as well as indole **135** and benzylindole **127c** (entry 2, **table 8**) under the standard bis-indolyation conditions to support the formation of the cross-products. These reactions gave rise to the cross-product **302**, with the NH-NMe **302b** as well as NH-NBn **302a** being formed. The non-cross products NMe-NMe **133a** and NBn-NBn **133c** were also achieved, however it was interesting to note that NH-NH **133** product was not formed in either case (**Scheme 88**, **table 8**).



Scheme 88. Shows the reaction for addition of two different indoles to cyclohexylallene **38**.

Entry	R^1 (eqs)	R^2 (eqs)	% Yield (**133**)	% Yield (**133a**)	% Yield (**133c**)	% Yield (**302a**)	% Yield (**302b**)	% Yield (**302c**)
1	H (3)	Me (3)	0	13[a]	-	-	32[a]	-
2	H (3)	CH_2Ph (3)	0	-	11[a]	30[a]	-	-
3	H (1)	Me (3)	0	39[a]	-	-	25[a]	-
4	H (0.5)	Me (0.5)	0	29 with respect to indole (**135**)[a]	-	-	25 with respect to indole (**135/127**)[a]	-
5	H (0.5)	CH_2Ph (0.5)	0	-	18[a]	0	-	-
6	Me (1)	CH_2Ph (1)	-	17[b]	24[b]	-	-	27[b]
7	Me (0.75)	CH_2Ph (0.75)	-	29[b]	24[b]	-	-	29[b]
8	Me (0.5)	CH_2Ph (0.5)	-	41[b]	19[b]	-	-	32[b]

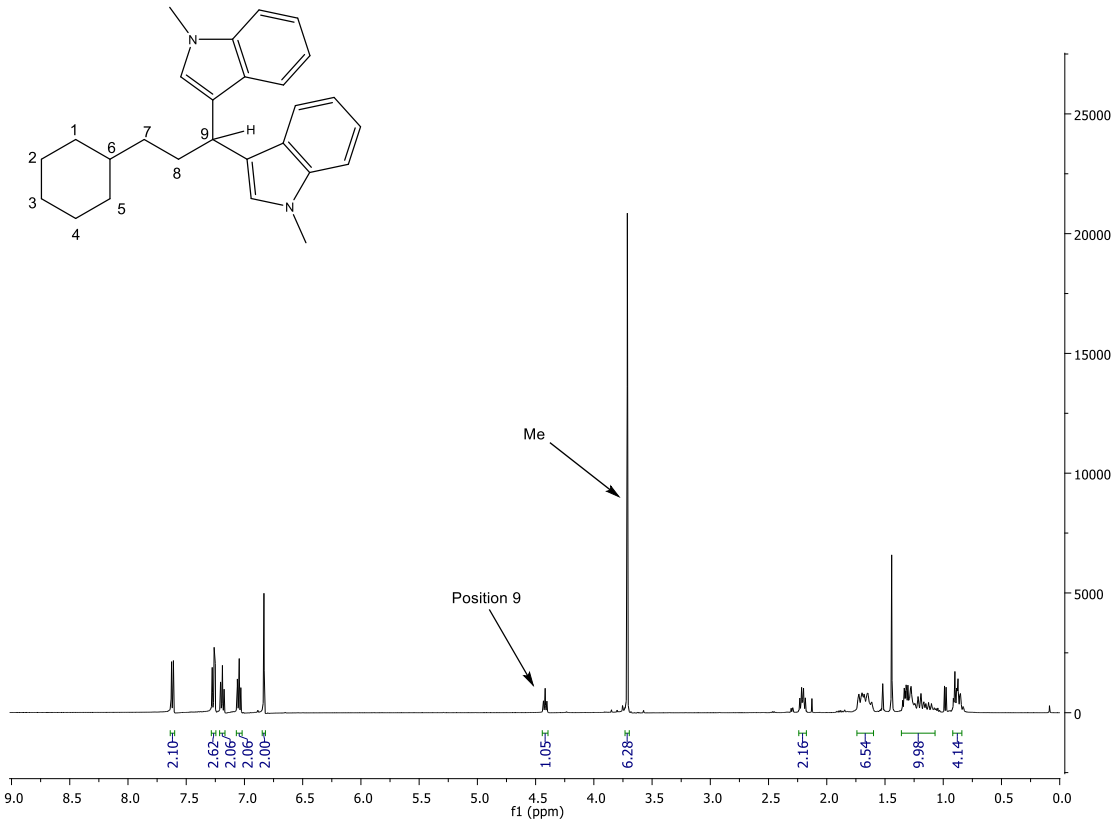
[a] Isolated Products. [b] Inseparable mixture, yields calculated from NMR integrals.

Table 8. Reaction conditions explored for the platinum-catalysed reactions of two different indoles with cyclohexylallene **38**.

This reaction works well under the $PtCl_2$ optimised conditions and changing the solvent and temperature (e.g. 1,4-dioxane at 130 ^{0}C) did not give the desired products. Therefore, to optimise the reaction to form solely the cross-product, the equivalents of substituted indoles were investigated.

Carrying out the reaction with N-Me and N-Bn indoles could give rise to three products; NMe/NMe **133a**, NBn/NBn **133c** and the cross product NBn/NMe **302c** (**Scheme 88**).

As mentioned, different ratios of indoles were utilised. From the calculated yields, it is observed that the reaction with 0.5 eqs of NBn and NMe indoles gives the best overall yield, with highest conversion to the cross-product **302c** (entry 8, **table 8**). However, all three examples show a similar ratio of products, with the cross-product **302** observed as the major compound in the reactions with 1:1 and 0.75:0.75 ratio of indoles. This reaction shows promise for the formation of these unique chiral products, however the poor separation was very time consuming and problematic. Although TLC showed only one main spot, upon purification by column chromatography, ^{1}H-NMR spectra highlighted that all three products were present, meaning that they are all eluted from the column at the same time due to similar polarities. The characteristic triplet peak at ~4.4 ppm is from the proton at position 9 (**Figure 19**), this can be seen for both the NMe/NMe **133a** structure and the NBn/NBn **133c** structure (**Figure 19**) and can be used to identify the cross-product NBn/NMe (**Figure 20**).



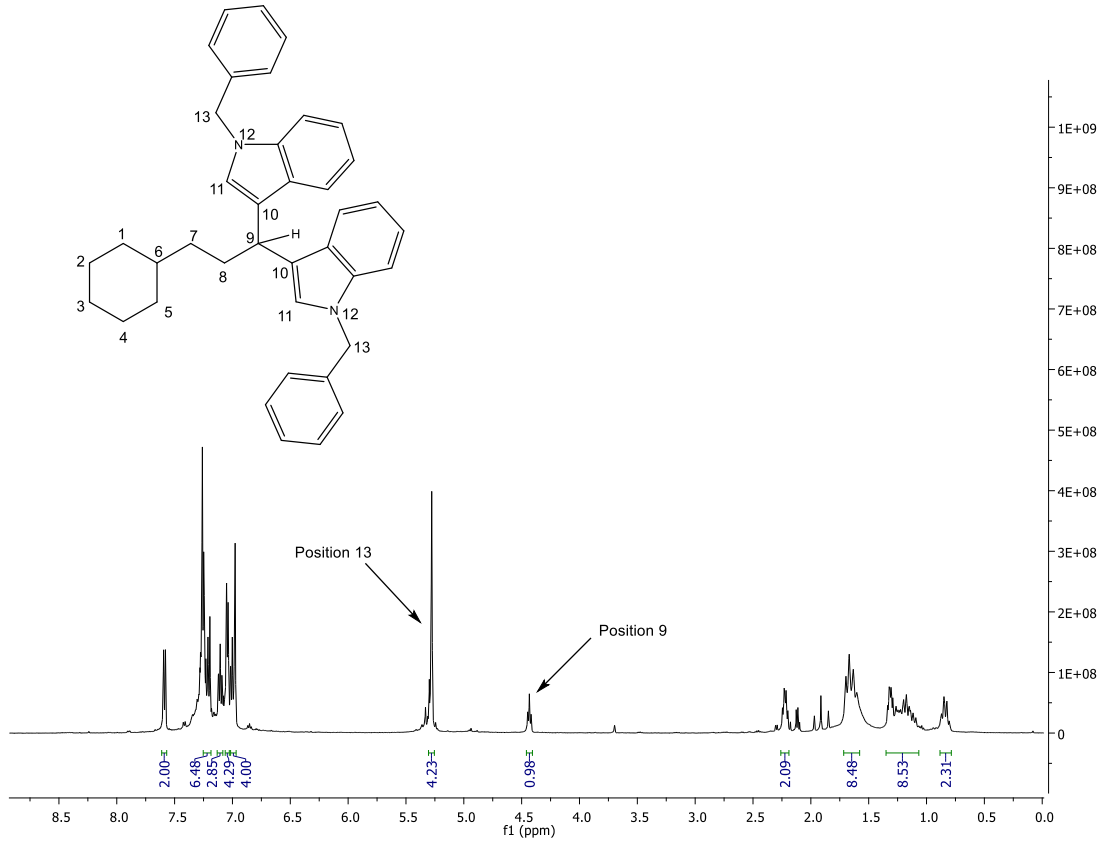


Figure 19. ^{1}H NMRs showing the characteristic peak at ~4.4 ppm for position 9 of the two BIMs **133a** and **133c**.

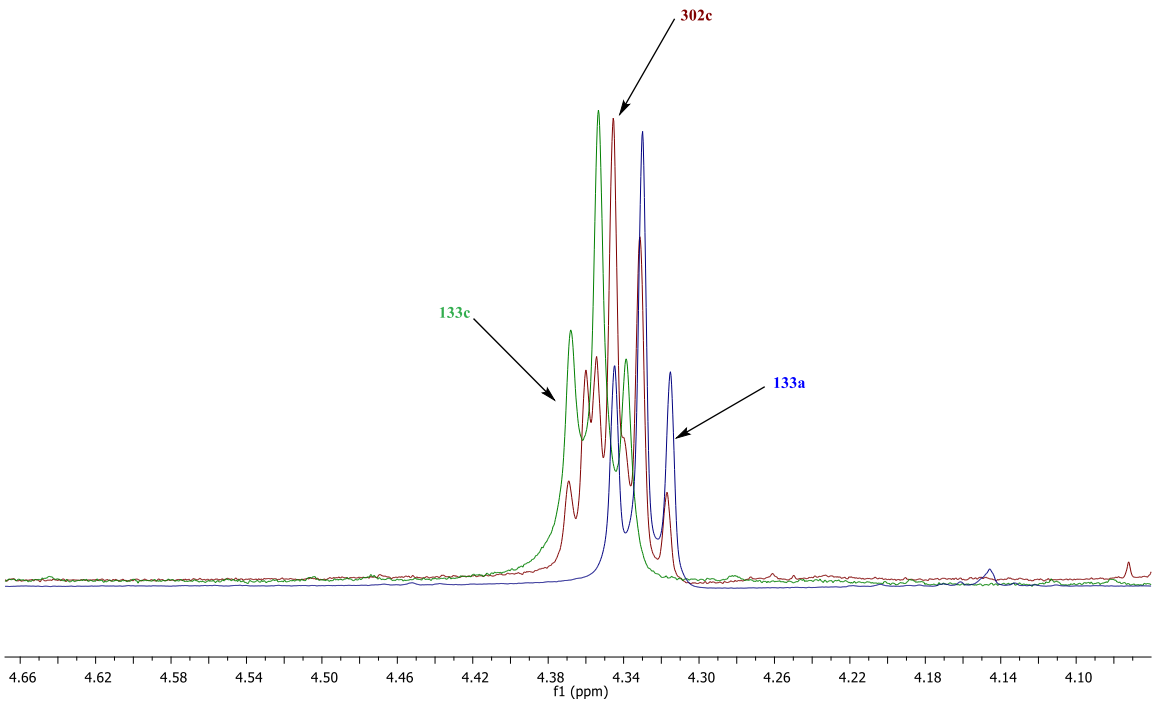


Figure 20. ^{1}H NMR highlighting peaks at ~4.4 ppm showing the presence of three products **133a** and **133c** and **302c**.

Despite all three products significantly overlapping, we could calculate yields from the combined mass and the integral ratio of the three compounds in the ^{1}H-NMR spectra, using the signals corresponding to position 2 of the three different products. These were separated enough for us to carry out the analysis (**Figure 21**).

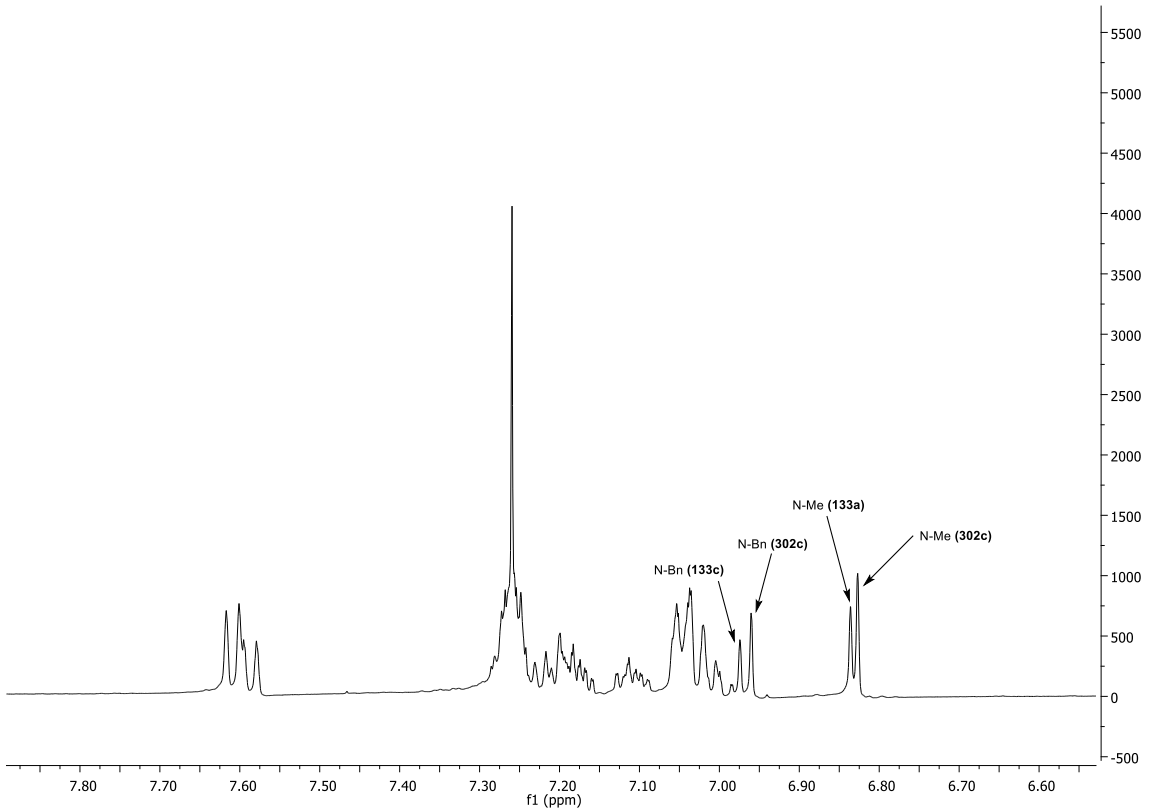
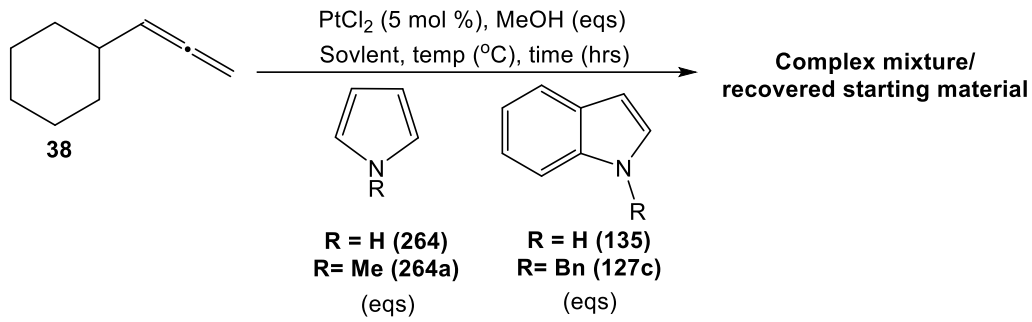


Figure 21. ^{1}H NMR highlighting peaks at ~6.8 – 7.0 ppm for the protons at position 2 of the three products used to calculate yields.

The successful double pyrrole addition to allenes and the combination of two different indoles to the same allene led us to explore the reaction of pyrrole and indole with the same allene to determine if we could get cross-products. If successful, this would open a new area for exploration with the potential biological importance of the structures and the ability to further functionalise them.

Initial reactions using the conditions reported by Muñoz *et al.*[77] (**Scheme 78**) were carried out with 3:3 equivalents of indole:pyrrole (entries 1 and 2, **table 9**) at different reaction times. However, after 48 hours there was no presence of the desired product and only starting material was recovered. The 1:1 ratio of indole:pyrrole was then investigated using the standard conditions (entries 3-4, **table 9**), even with long reaction times the reaction did not seem to occur and complex mixtures containing starting material were recovered.

Entries 8 and 9 (**table 9**) show that microwave irradiation has no effect on the overall reaction with starting material being recovered after 2.5 hours. Using the substituted benzylindole **127c** with pyrrole **264**, 1:1, (entry 10, **table 9**) a complex mixture was obtained and there was no evidence of indole addition to the allene. The use of pyrrole **264** and methyl-pyrrole **264a** as the two nucleophiles resulted in complex mixtures with no addition being observed (entries 11 – 12, **table 9**).



Scheme 89. Screening of reaction conditions for addition of pyrrole **264** and indole **135/127c** to cyclohexylallene **38**.

Entry	Indole/pyrrole (eqs)	Pyrrole (eqs)	Solvent	MeOH (eqs)	Temp (°C)	Time (Hrs)	Results [a]
1	**135** (3)	**264** (3)	THF	3	70	24	Complex mixture/**38**
2	**135** (3)	**264** (3)	THF	3	70	48	Complex mixture/**38**
3	**135** (1)	**264** (1)	THF	3	70	20	**38**
4	**135** (1)	**264** (1)	THF	3	70	24	**38**
5	**135** (1)	**264** (1)	THF	3	70	4 days	Complex mixture/**38**
6	**135** (1)	**264** (1)	THF	0	70	24	**38**
7	**135** (1)	**264** (1)	THF	3	RT	24	Complex mixture
8	**135** (1)	**264** (1)	THF	3	70[b]	2.5	**38**
9	**135** (1)	**264** (1)	1,4-Dioxane	0	100[b]	1	Complex mixture/**38**
10	**127c** (1)	**264** (1)	THF	3	70	72	Complex mixture/**38**
11	**264a** (3)	**264** (3)	THF	3	70	22	Complex mixture/**38**
12	**264a** (3)	**264** (3)	THF	0	70	24	Complex mixture
13	**264a** (1)	**264** (1)	THF	3	70	24	Complex mixture

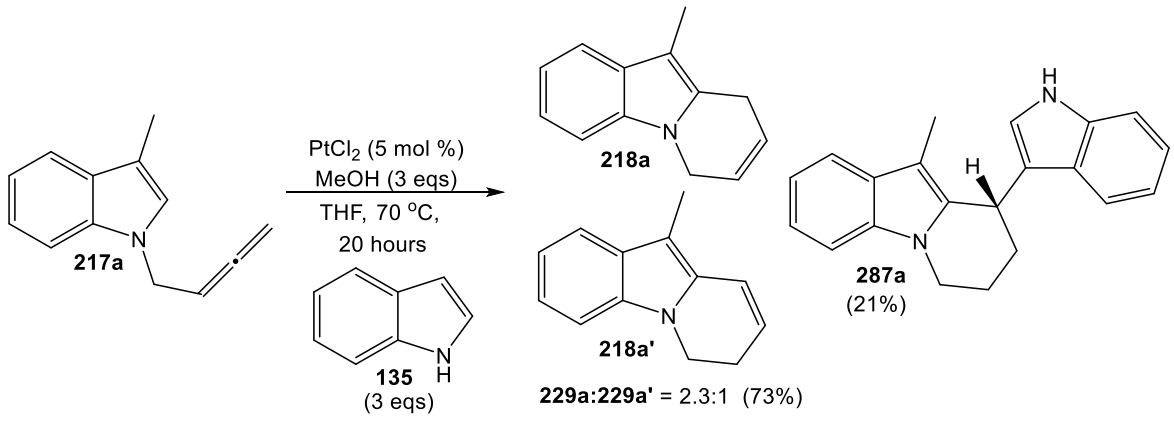
[a] Results obtained qualitatively from crude NMRs, [b] Carried out under mw irradiation.

Table 9. Reaction conditions explored for the platinum-catalysed reactions of indole and pyrrole derivatives with cyclohexylallene **38**.

These results highlight the difficulty of adapting this platinum catalysed reaction to incorporate different nucleophiles. It has also shown that the incorporation of two different nucleophiles onto the same allene cannot be successfully achieved. However, the addition of two different indoles to the same allene to produce the desired chiral cross-products has been achieved but the difficulty arises in analysis to determine if we have only one product or a mixture of more than one. These issues and the time frame of the thesis led us to explore a related pathway for the addition of two different nucleophiles to allenes, which was being explored within the group. It involved the extensive analysis of the intra-intermolecular addition of indoles to indolyl allenes using platinum catalysis to form substituted 2,3'-BIMs.

2.2 Intra-intermolecular addition reaction

As described in the introduction (refer to section 1.6.c.),[77] the intra-intermolecular reaction involves the reaction of an external indole **135** with 3-methyl-*N*-(2,3-butadienyl)indole **217a** to obtain the desired 2,3'-BIM **287a** (**Scheme 90**). The presence of the methyl group in C3 of the indolylallene was found to be essential for the formation of compound **287a** in 21% isolated yield. However, the two 6-endo cycles **218a/218a'** were also formed in a 71% isolated yield under the reported reaction conditions. The 6-endo cyclisation has been described in section 1.6.c where the difference between Au and Pt catalysis was discussed with the single cycle **218a** being formed with Au and the two cycles **218a/218a'** being formed with Pt, more details with respect to their synthesis will be discussed in the mechanistic investigation section 2.3.



Scheme 90. Intra-intermolecular reaction of indole **135** and 3-methyl-*N*-(2,3-butadienyl)indole **217a**.

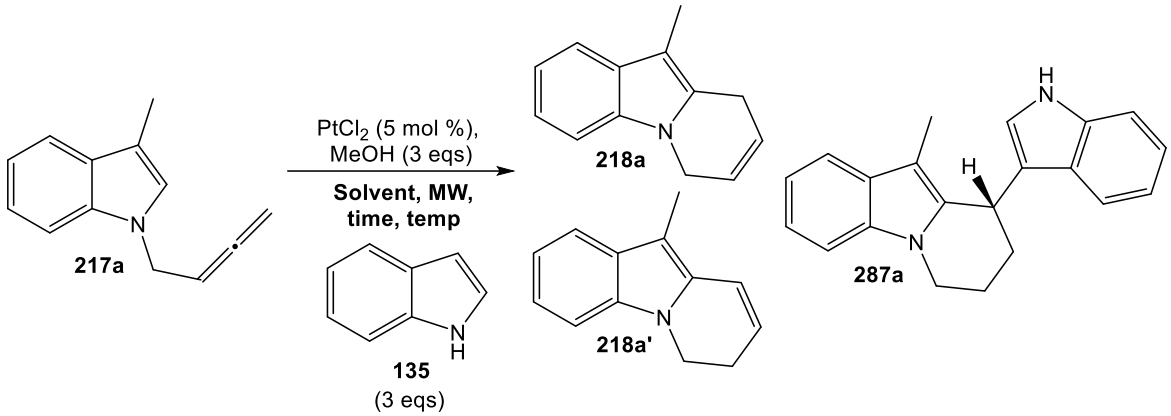
This section will first outline the screening and optimisation of reaction conditions achieved to selectively form compound **287a**. It will then describe the results achieved from investigating the reaction with various substituted indolyl allenes and external indoles as well as investigating the effect of chain length linking the allene to nitrogen. Finally, a detailed mechanistic study will outline how the reaction proceeds and the intermediates and factors that influence the overall reaction.

2.2.1. Optimisation of reaction conditions

Screening of solvent, time, temperature, concentration and equivalents of platinum, indole and methanol were carried out for the reaction of 3-methyl-*N*-(2,3-butadienyl)indole **217a** with external indole **135** to optimise the conditions for selective formation of compound **287a** (**Scheme 90**). These reactions were carried out by project student Helen Newson as part of her year in Industry placement at Novartis in their industry research lab using LC-MS ELSD (Evaporative Light Scattering Detector) traces for detecting the different components of the reactions.

Reported reactions by Muñoz *et al.*[78] were carried out at 70 ^{0}C using thermal heating in an oil bath. However, it was established that using microwave irradiation decreased the reaction time dramatically from 20 hours to 1-2 hours as well as increasing both the selectivity and yield of product **287a**. The efficiency of microwave irradiation has increased its popularity for organic synthesis over the years because of its dielectric heating and real-time monitoring of temperature and pressure which has increased yields, reduced reaction time, reduced side-product formation and can change the selectivity of reactions.[148147]

Microwave irradiation was therefore used for all further screening. Screening of solvent and temperature were carried out with THF, 1,4-dioxane, CPME (cyclopentylmethyl ether) and 2-methyl-THF (**Table 10**). Their different boiling points allowed various temperatures and times to be explored. **Table 10** shows the results obtained and identifies that 1,4-dioxane heated at 130 ^{0}C for 1 hour gives the best conversion to desired compound **287a** (77% from LCMS and 61% isolated, entry 3, **table 10**).



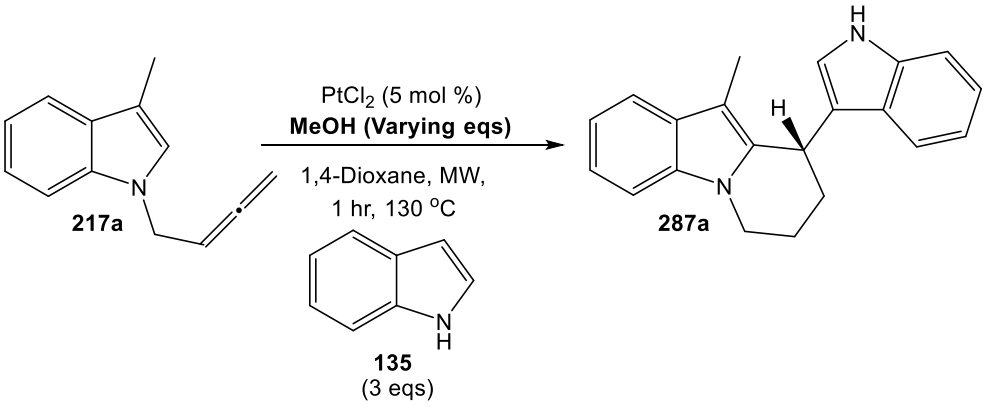
Scheme 91. Screening of conditions for the intra-intermolecular reaction of indole **135** and 3-methyl-*N*-(2,3-butadienyl)indole **217a**.

Entry	Solvent	Temp (^{0}C)	Time (mins)	% of **218a/218a'**[a]	% of **287a**[a]
1	THF	100	180	0	33
2	THF	130	30	0	37
3	1,4-dioxane	130	60	5	61
4	1,4-dioxane	150	15	0	47
5	CPME	180	20	5	39
6	2-Methyl THF	150	15	0	5

[a] Isolated product. All results in table carried out by project student Helen Newson.

Table 10. Results obtained after screening of conditions for the intra-intermolecular reaction of indole **135** and 3-methyl-*N*-(2,3-butadienyl)indole **217a**.

With the successful identification that microwave irradiation with 1,4-dioxane at 130 ^{0}C at 1 hour gives the best results (Entry 3, **Table 10**), variations in equivalents of platinum, indole and methanol were then explored. $PtCl_2$ is a relatively expensive catalyst and although results are high with 10 mol %, it is cheaper and similar reactivity is achieved when 5 mol % is used. The role of methanol was not completely understood at the time, but it had shown to be important for the selective formation of **287a**, therefore varying the equivalents of methanol was carried out. **Table 11** shows the reaction requires an excess of methanol, with the best results achieved with 3 or more equivalents as already reported.



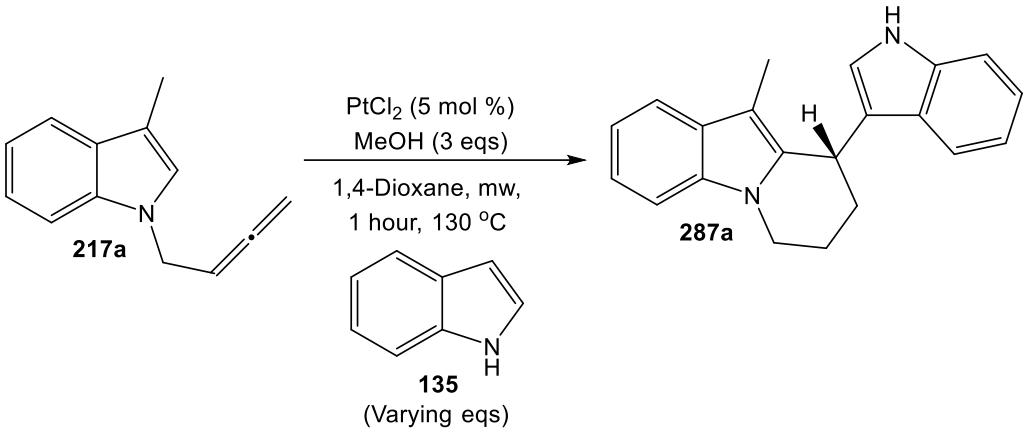
Scheme 92. Screening eqs of MeOH for the intra-intermolecular reaction of indole **135** and 3-methyl-N-(2,3-butadienyl)indole **217a**.

Entry	Equivalents of MeOH	% conversion of **287a**[a]
1	1	92
2	2.5	95
3	3	100
4	3.5	100
5	4	100

[a]Determined by LCMS ELDS traces. All results in table carried out by project student Helen Newson.

Table 11. Shows the effect the number of equivalents of methanol has on the % conversion for compound **287a.**

The equivalent of indole to allene was also investigated and **table 12** shows that using 1, 3 or 4 equivalents gives 100% conversion to product **287a**, however, the results were more reproducible with 3 equivalents therefore this was the chosen amount for the overall reaction.



Scheme 93. Screening eqs of indole **135** for the intra-intermolecular reaction of indole **135** and 3-methyl-*N*-(2,3-butadienyl)indole **217a**.

Entry	Equivalents of indole **135**	% conversion of **287a**[a]
1	1	100
2	1.5	91
3	2	91
4	2 .5	90
5	3	100
6	4	100
7	4.5	96
8	5	85

[a]Determined by LCMS ELDS traces. All results in table carried out by project student Helen Newson.

Table 12. Shows the effect the number of equivalents of indole **135** has on the % conversion for compound **287a.**.

The optimised conditions were found to be microwave irradiation at 130 ^{o}C for 1 hour with 5 mol % $PtCl_2$, 3 eqs indole, 3 eqs of methanol and 1,4-dioxane (0.2 M). These newly optimised conditions were able to give an isolated yield of 71% for compound **287a**. It is also important to state that the reaction requires dry 1,4-dioxane as the solvent, because reactions carried out with wet 1,4-dioxane resulted in the preferential formation of the cyclised products **218a/218a'** (**Table 13**).

Entry	Dioxane	Methanol	% yield of **218a/218a'**	% yield of **287a**
1	Wet	Wet	58% (not isolated)	0
2	Dry	Wet	5	61
3	Dry	Dry	Traces	71

All results in table carried out by project student Helen Newson.

Table 13. Shows the effect that wet and dry 1,4-dioxane has on the selectivity of the reaction.

2.2.2. Substituent effect on the reaction

It has already been observed that the presence of a methyl group in position 3 of the indolyl allene **217a** promotes the formation of the desired 2,3'-BIM **287a**. Therefore, we were interested to further investigate the scope of the reaction by varying the substituents in position 5 of the indolyl allene. In particular, we were interested in the electronics of the reaction, thus reactions were carried out with both electron-donating, OMe and Me and electron-withdrawing Br, Cl and CN groups to determine the effect on the selectivity of the reaction.

The indole framework is widely represented in natural and medicinal compounds and these substituted indole nuclei can be identified. The 5-methoxyindole nucleus is present in several core structures, for example it is found in melatonin **303** and 5-methoxy-3-acetic acid **304** (**Figure 22**), which are developed in vertebrate pineal glands. Melatonin exhibits antioxidant, immunomodulatory and antitumor activities and 5-methoxy-3-acetic acid **304** has been shown to exhibit antifungal and antibacterial activity making them bio-medically and agriculturally important.[149] It is also a core structure in many tubulin polymerisation inhibitors such as 2-aroylindoles **305** (**Figure 22**) which are highly active against tumours, including one's resistant to paclitaxel.[150]

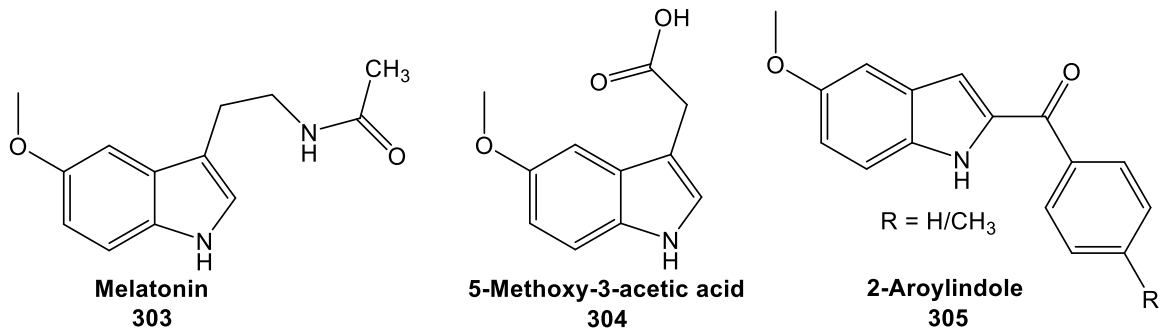


Figure 22. Shows the naturally occurring 5-methoxyindole derivatives.

Halogen-containing compounds are found in terrestrial organisms, for example there are numerous bromoindole alkaloid derivatives which have been isolated from a range of marine sponges.[146] In particular, the 5-bromindole nucleus has been identified in the structure of aplicyanins A-F **306** (**Figure 23**), which are isolated from marine tunicate apilidium cyaneum and reported to exhibit cytotoxic and antimitotic activity.[151] Less reported or observed are the chloroindole derivatives, however they have been reported in terrestrial plants. Such as the growth hormone 4-chloroindole-3-acetic acid **307** (**Figure 23**), which is found in peas and broad beans of the Vicieae tribe.[152]

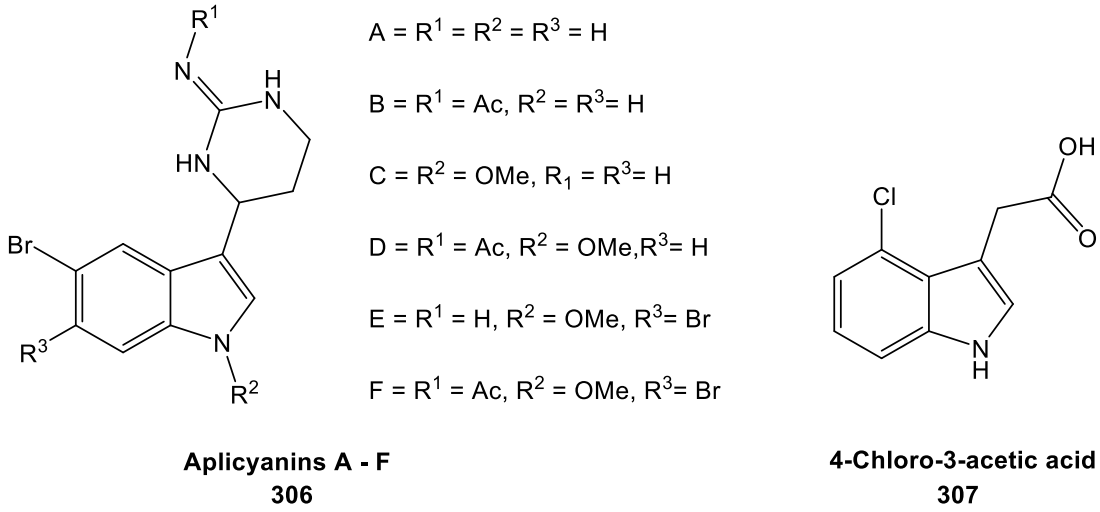


Figure 23. Shows the naturally occurring bromo- and chloro-indole derivatives.

Indoleacetonitrile derivatives **308** (**Figure 24**) have also been reported to play an essential role in plant growth after being identified in a range of Cruciferae, where they inhibit the seedling-growth of light-grown cabbage, Brassoca olearea.[153]

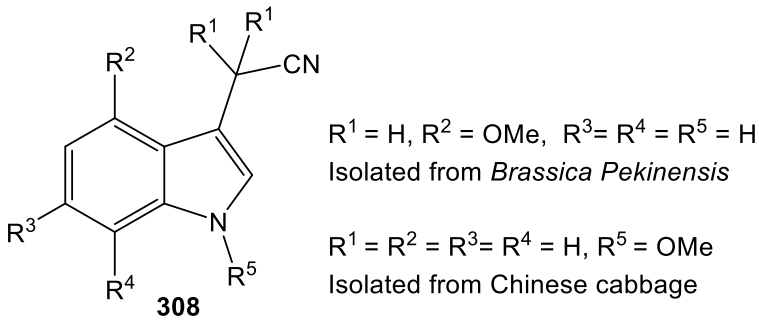
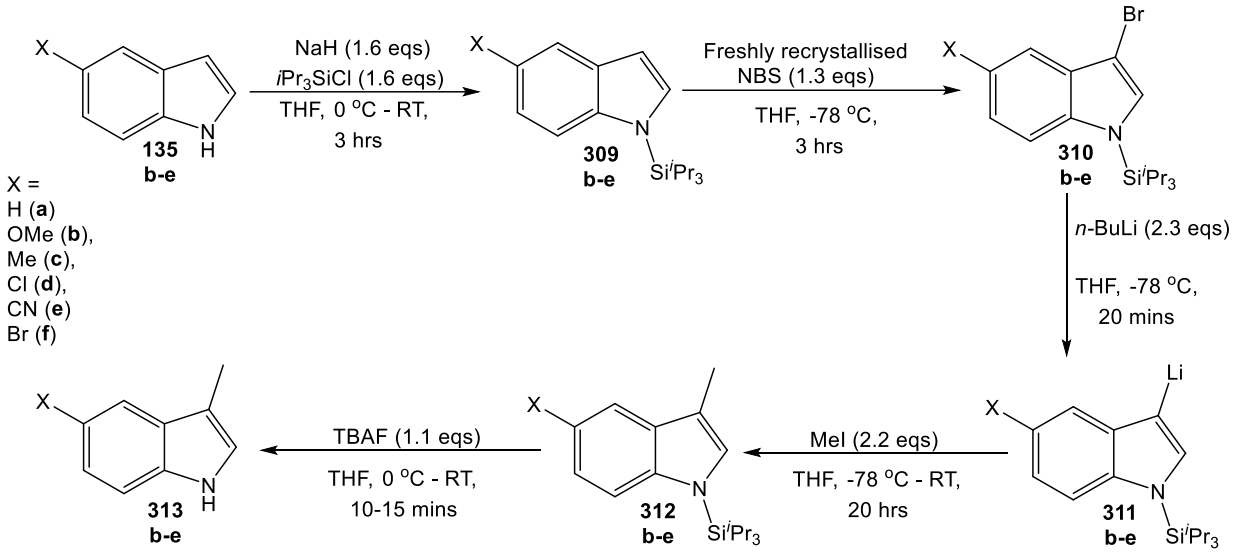


Figure 24. Shows the naturally occurring indoleacetonitrile derivatives.

As well as the mechanistic information that can be obtained by analysing the effect of the electronic properties of the starting materials, the significance of these substituted indole nuclei in naturally occurring products makes them ideal candidates for expanding the scope of this reaction with the formation of substituted 2,3'-BIMs which might have enhanced potential for biological activity.

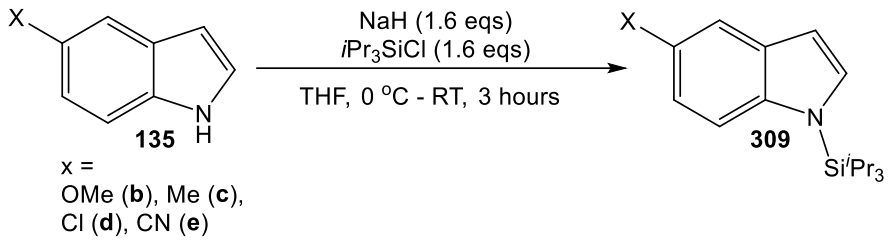
2.2.2.a. Varying substituents at position 5 of indolyl allene

Except for 5-bromo-3-methyl indole, all the other 5-substituted-3-methylindoles **313** were not commercially available and therefore were synthesised from their corresponding commercially available 5-substituted indole. The regioselective synthesis of the C3-methyl derivatives was achieved *via* a step-wise procedure adapted from that proposed by Amat *et al.*,[154] followed by *N*-propargylation and Crabbé homologation[20-26] to form the corresponding 5-substituted-3-methylindolyl allene **217**. This section will outline the procedures carried out for each step as seen in **scheme 94** and the results obtained.



Scheme 94. The step-wise procedure for the synthesis of 5-substituted-3-methylindoles **313**.

The first step involves the triisopropylsilyl protection of the nitrogen atom of indole. This bulky protecting group prevents reactivity at the nitrogen atom and provides regioselectivity to the other steps. This straightforward step gives near quantitative yields for all examples (**table 14**), with flash chromatography carried out before use in the next step.

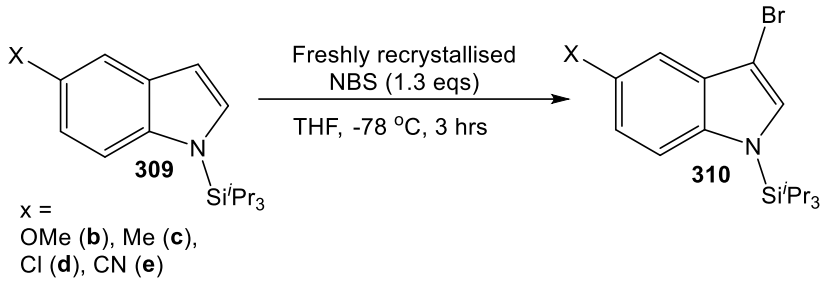


Scheme 95. *N*-protection of 5-substituted indole **135a-d** with triisopropylsilylchloride.

Entry	Substituent	**309** (%)
1	OMe	99
2	Me	90
3	Cl	98
4	CN	97

Table 14. Results from the *N*-protection of 5-substituted indole **135b-e** with triisopropylsilylchloride.

Although Amat *et al.* [154] carried out their protection and bromination in a one-pot step, we found that higher yields were achieved when two steps were employed. The reactivity of indole allows for selective bromination at position 3. At first, this step proved problematic with low yields and decomposition occurring, but we found that using freshly recrystallized NBS at -78 ^{0}C in the dark for 3 hours reduced the chance of any side reactions occurring, which improved yields and minimized decomposition (**Table 15**). Also, yields were improved when the reaction was quenched with water and extracted with Et_2O, instead of using the pyrrole and *n*-hexane conditions as reported by Amat *et al*.[154]

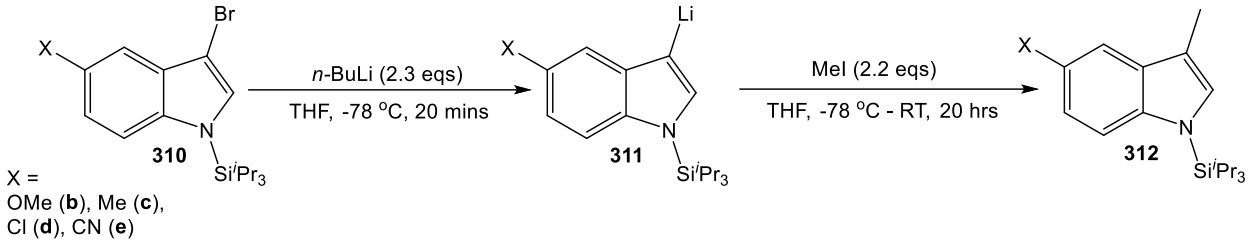


Scheme 96. Selective bromination of *N*-protected 5-substituted indole **309b-e** with NBS.

Entry	Substituent	**310** (%)
1	OMe	57
2	Me	65
3	Cl	64
4	CN	48

Table 15. Results for the formation of indole **310** *via* bromination of indole **309b-e** with NBS.

The next one-pot step involves the methylation of position 3 producing compound **312**. This involves first generating the 3-lithioindole **311** derivative *via* halogen-lithium exchange using *n*-BuLi at -78 ^{0}C (**Scheme 97**). The presence of the bulky triisopropylsilyl protecting group prevents the undesired migration of the lithium atom from position 3 to 2, due to its steric restraints.[154] 20 minutes after the addition of the *n*-BuLi (maximum), MeI is added to the solution and warmed to room temperature for 20 hours. Quenching the reaction with NH_4Cl and extracting with Et_2O isolates **312** in near quantitative yields with no further purification required (**Table 16**).



Scheme 97. One-pot step for methylation at position 3 *via* halogen-lithium exchange.

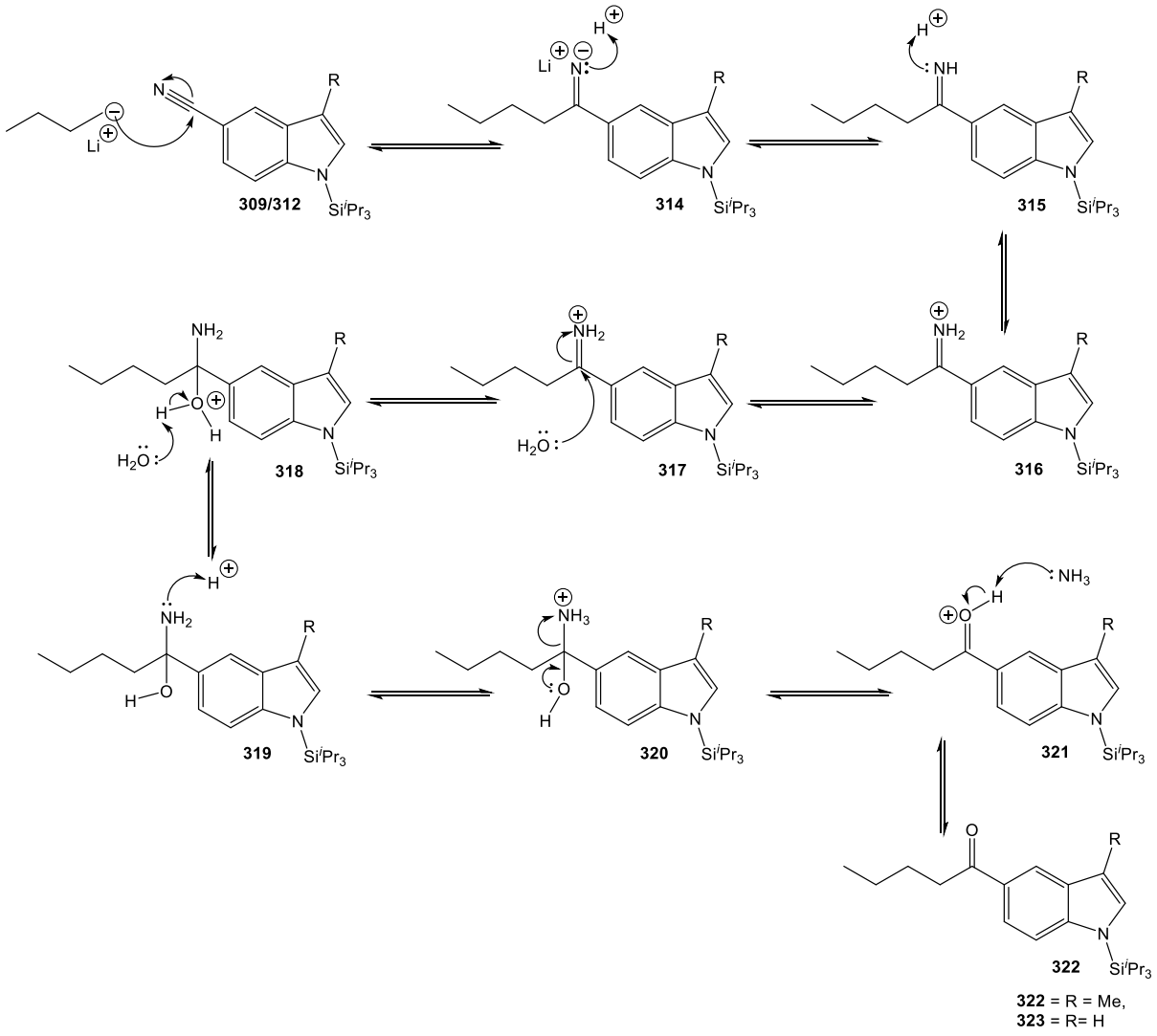
Entry	Substitutent	**312** (%)
1	OMe	96
2	Me	99
3	Cl	98
4	CN	96

Table 16. Results for the formation of indole **312** *via* methylation of indole **310** with *n*-BuLi and MeI.

Despite the high yields obtained, there were several important factors that had to be taken into account to achieve these. For example, the equivalents of *n*-BuLi were found to have an important effect, with only 33% of **312** and 66% of starting material **310** being obtained when 1 eq of *n*-BuLi was utilised. It was also established that *t*-BuLi was ineffective for this reaction with only starting material **310** being isolated. Another factor was the time delay between the *n*-BuLi addition and MeI addition, when the delay was longer than 20 minutes, traces of the unsubstituted derivative **309** were observed, therefore, the delay was found to be best around 15 minutes.

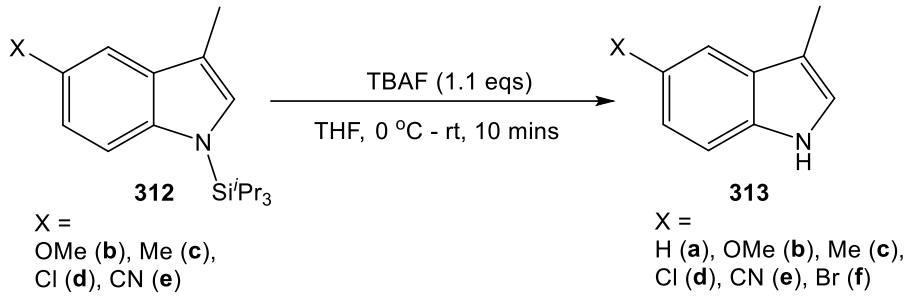
The length of time left between *n*-BuLi addition and MeI addition was also found to be important for the reaction involving the 5-cyanoindole derivative. It was observed that instead of halogen-lithium exchange, the nucleophilic addition of *n*-BuLi occurred preferably at the nitrile group if longer times were left between the two additions.

In those cases, this addition generated the corresponding imine salt complex **314** (**Scheme 98**), which upon acidic work-up with NH_4Cl generated the corresponding ketones **322/323**with either methyl or proton present in position 3 resulting from the successful and unsuccessful methylation (**Scheme 98).** The ketone derivatives were not detected until the final step when Crabbé homologation was carried out, therefore yields were not obtained. However, the corresponding indolylallenes were used in the platinum reaction with external indole, but no cyclisation or BIM formation were achieved, therefore they were not synthesised again.



Scheme 98. Mechanism for the nucleophilic addition of *n*-BuLi to nitrile group forming the corresponding ketone derivatives **322**.

Following successful methylation, the crude products were then deprotected using tetra-*n*-butyl ammonium fluoride (TBAF). Its source of fluorine is the driving force for this step with the formation of the strong Si-F bond. The deprotection takes less than 10 minutes and is followed by a vigorous work-up and column chromatography to remove the ammonium salt and isolate the 5-substituted-3-methyl indoles **313** in relatively good yields (**Table 17**).



312

X =
OMe (**b**), Me (**c**),
Cl (**d**), CN (**e**)

313

X =
H (**a**), OMe (**b**), Me (**c**),
Cl (**d**), CN (**e**), Br (**f**)

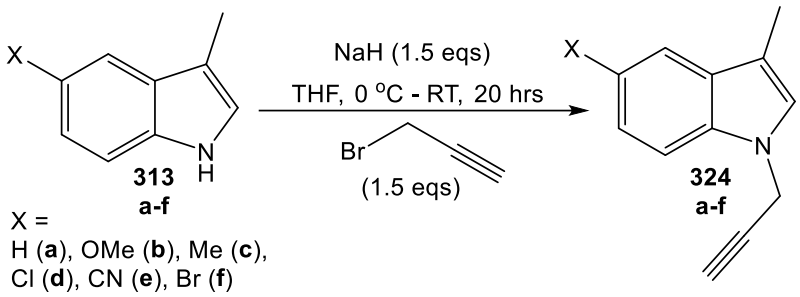
Scheme 99. Deprotection of **312** with TBAF to form **313**.

Entry	Substituent	**313** (%)
1	OMe	59
2	Me	68
3	Cl	48
4	CN	62

Table 17. Results for the formation of indole **313** *via* deprotection of indole **312** with TBAF.

The final two steps of the procedure involve firstly the propargylation of the nitrogen, followed by the Crabbé homologation[20-26] of the acetylenic precursor. These reactions were carried out for all the substituted indoles bearing the methyl group in position 3.

The propargylation of indole occurs *via* an S_N2 mechanism and worked well for all examples, giving the desired products in good yields (**Table 18**).

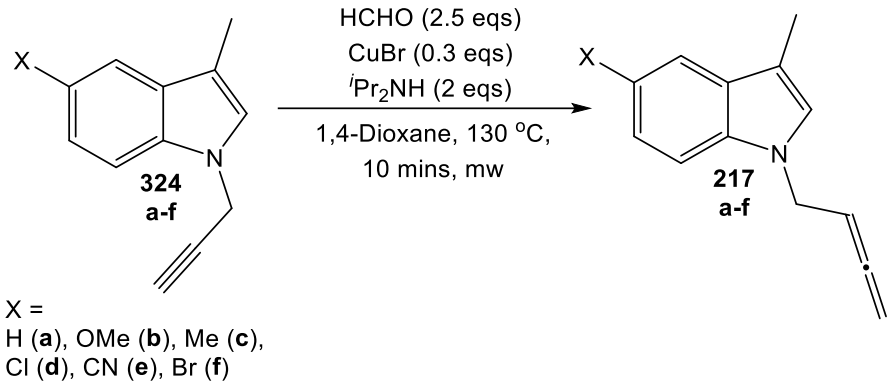


Scheme 100. Propargylation of **313** with sodium hydride and propargyl bromide to form **324**.

Entry	Substituent	**324** (%)
1	OMe	57
2	Me	30
3	Cl	59
4	CN	65
5	Br	51
6	H	84

Table 18. Results for the formation of indole **324** *via* propargylation of indole **313** with sodium hydride and propargyl bromide.

The final step involves the homologation of the acetylenic derivative **324** to the corresponding allene **217a-f** (**Scheme 101**) using a modified version of the Crabbé homologation, a procedure which has been explained in detail in the introduction (**Section 1.2**).[20-26] It is a fast and effective procedure involving microwave irradiation for 10 minutes at 150 °C using formaldehyde, *N,N*-diisopropylamine and copper(I) bromide in 1,4-dioxane. After column chromatography to remove the copper salts and by-products of the reaction, the desired indolyl allenes **217a-f** were isolated in relatively high yields (**Table 19**).

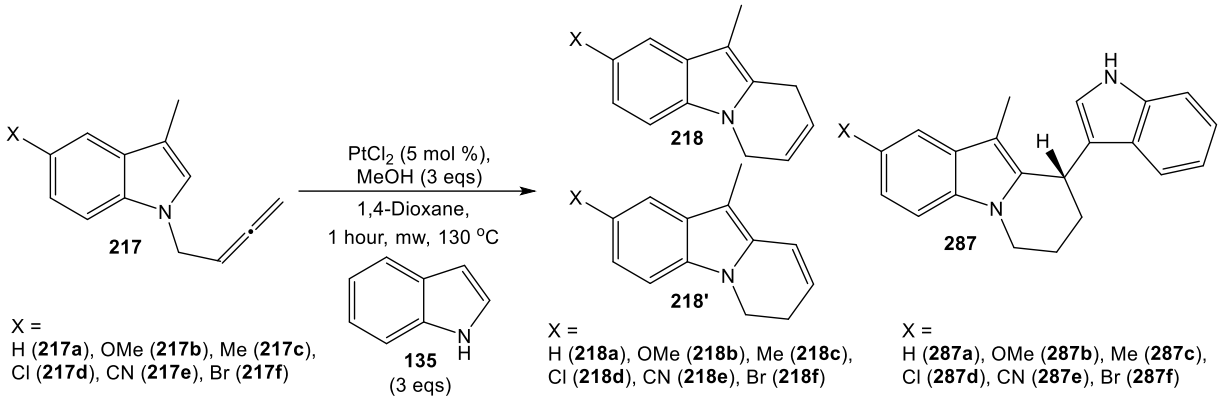


Scheme 101. Homologation of **324** using microwave irradiation to form **217**.

Entry	Substituent	**217** (%)
1	OMe	60
2	Me	60
3	Cl	70
4	CN	70
5	Br	87
6	H	74

Table 19. Results for the formation of 5-subsituted, 3-methyl indolyl allene **217 a-f** *via* homologation of acetylenic indole **324 a-f** using microwave irradiation.

With the optimised platinum conditions achieved and desired 5-substituted-3-methylindolyl allenes **217a-f** synthesised, the scope of the reaction was explored with respect to the substituents.



Scheme 102. Platinum-catalysed reaction of 5-substituted indolyl allene **217**.

Entry	Indolyl Allene	% **218/218'** (Ratio)	% **287**
1	**217a**	5 (1:0.3)	61
2	**217b**[a]	0	48
3	**217c**	0	21
4	**217d**	35 (0.8 :1)	0
5	**217e**[b]	47 (0.78:1)	0
6	**283f**	53 (1:0.95)	20

[a] Result obtained by Sachini Herath. [b] Result obtained by Helen Newson.

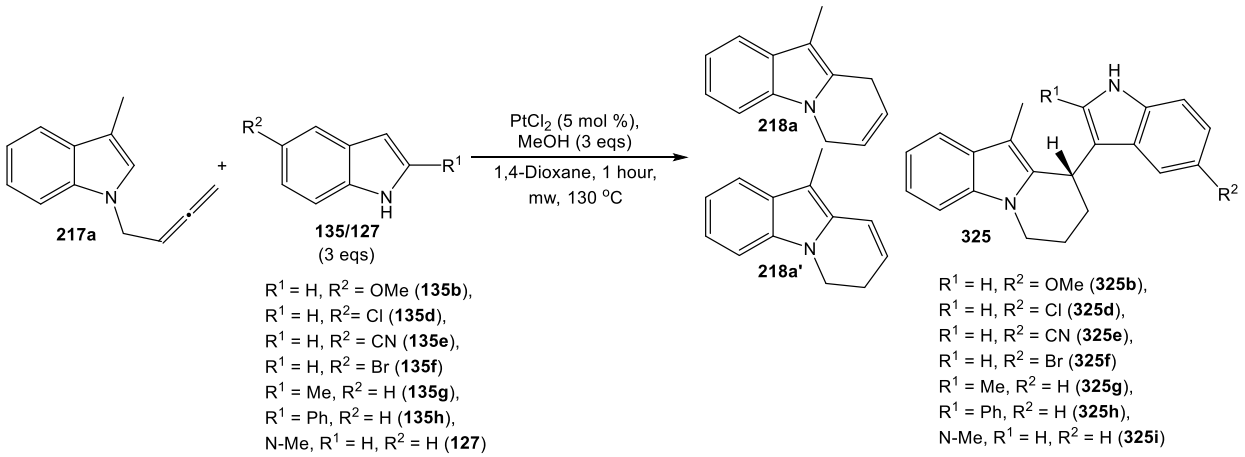
Table 20. Results from the investigation of substituent effect on the optimised platinum reaction.

Analysis of results from **table 20** highlights a trend for the selective formation of **218/218'** or **287** depending on the nature of the substituent in position 5. It was found, that if position 5 was substituted with an electron-donating group, then the desired 2,3'-BIM **287** was preferentially formed (Entries 1 and 2, **Table 20**). Poor yield for compound **287c** was obtained because of poor separation from the indole *via* column chromatography. Whereas, when position 5 contains an electron-withdrawing group the reaction is more selective for the formation of the 6-endo cyclised products **218/218'** in an almost 1:1 ratio (Entries 3–5, **Table 20**). Therefore, it has been established that formation of 2,3'-BIM **287** can be achieved preferentially when an electron-donating group is present in position 5, reasoning for this pattern will be discussed in further detail within the mechanistic investigation section (Section 2.3).

2.2.2.b Varying substituents on the external indole

Further to investigating the reaction with substituents on the aromatic ring of the indolyl allene **217**, the reaction was also investigated with different substituents present on the external indole. Therefore, reactions were carried out with both electron-donating, 5-OMe, 2-Me and 2-Ph and electron-withdrawing 5-Br, 5-Cl and 5-CN groups to determine the effect on the selectivity of the reaction.

The presence of these indole nuclei in natural products have already been discussed in section 2.2.2.[149-152] These external indoles **135a-f** are commercially available and only 3-methylindolylallene **217a** was synthesised as described in section 2.2.2.a. These reactions were carried out in collaboration with project students Louise Eagling and Sachini Herath. These reactions were carried out using the optimised platinum conditions (**Scheme 103**), under an inert atmosphere and all products were obtained after purification by column chromatography.



Scheme 103. Platinum-catalysed reaction 3-methylindolyl allene **217a** with substituted external indoles **135/127**.

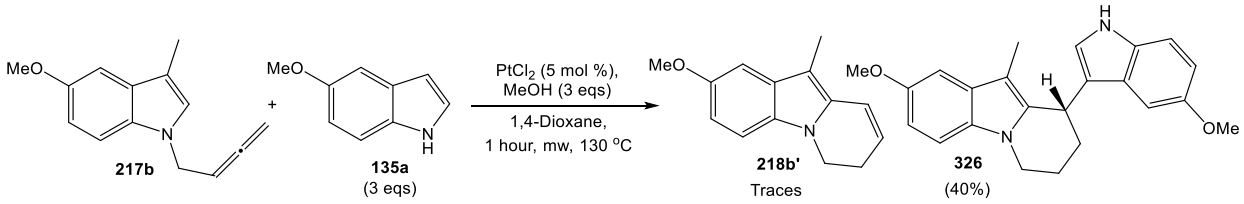
Entry	External Indole	% **218a/218a'** (Ratio)	% **325**
1	**135b**	17 (0.35:1)	37
2	**135d**[a]	74 (**218'** only)	Traces
3	**135e**[a]	74 (**218'** only)	15[b]
4	**135f**	33 (**218'** only)	Traces
5	**135g**	19 (0.2:1)	46
6	**135h**[a]	Traces	35
7	**127**	44 (**218'** only)	22

[a] Dimer product either observed in crude or traces isolated from the reaction mixture (4-10%). [b] Yield calculated from NMR. Entries 2, 3 and 4 were carried out by Louise Eagling and Sachini Herath.

Table 21. Results from the investigation of substituent effect on the external indole **286** for the optimised platinum reaction.

A similar trend to that shown for the various substituents in position 5 of the indolyl allene is observed, where the indoles bearing an electron-donating group (**Table 21**, Entries 1, 5 and 6) favour the formation of the desired 2,3'-BIM **325,** whereas an electron-withdrawing group (**Table 21**, Entries 2, 3 and 4) favours the formation of the 6-endo cyclisation products **218a**/**218a'**. Interestingly, we only observe the formation of the conjugated 6-endo cycle **218'** when electron-withdrawing groups are present, but a mixture of the two observed with electron-donating.

The selectivity of these reactions is not as predominant, with both the 6-endo cycles **218/218'** and the 2,3'-BIM **325** being observed in all cases. The substituent effect was also investigated with *N*-methyl indole **127** as the external indole, this was found to give both cycle **218'** and the corresponding 2,3'-BIM **325g** in a 2:1 ratio. Furthermore, we wanted to investigate the effect of substituents on both the external indole and the 3-methylindolyl allene, therefore an example with 5-methoxy-3-methyl indolyl allene **217b** and 5-methoxyindole **135a** was carried out (**Scheme 104**), with formation of the 2,3'-BIM **326** as the major product with 40% yield and only traces of the cycle **218b'** being observed. This helps to support the idea that 2,3'-BIMs formation is favoured in the presence of electron-donating substituents in both partners.



Scheme 104. Platinum catalysed reaction of 5-methoxy-3-methylindolyl allene **217b** with 5-methoxyindole **135a**.

The 2,3'-BIM structures have a very distinctive ^{1}H NMR spectra, with a characteristic triplet at ~4.6 ppm for the proton at position *d* and the diastereotopic protons at ~3.9 and 4.3 ppm for the CH_2 at position *a* in **figure 25**. The diastereotopic protons for positions b and c are less characteristic because of their overlap with methyl groups in the region of 2 ppm.

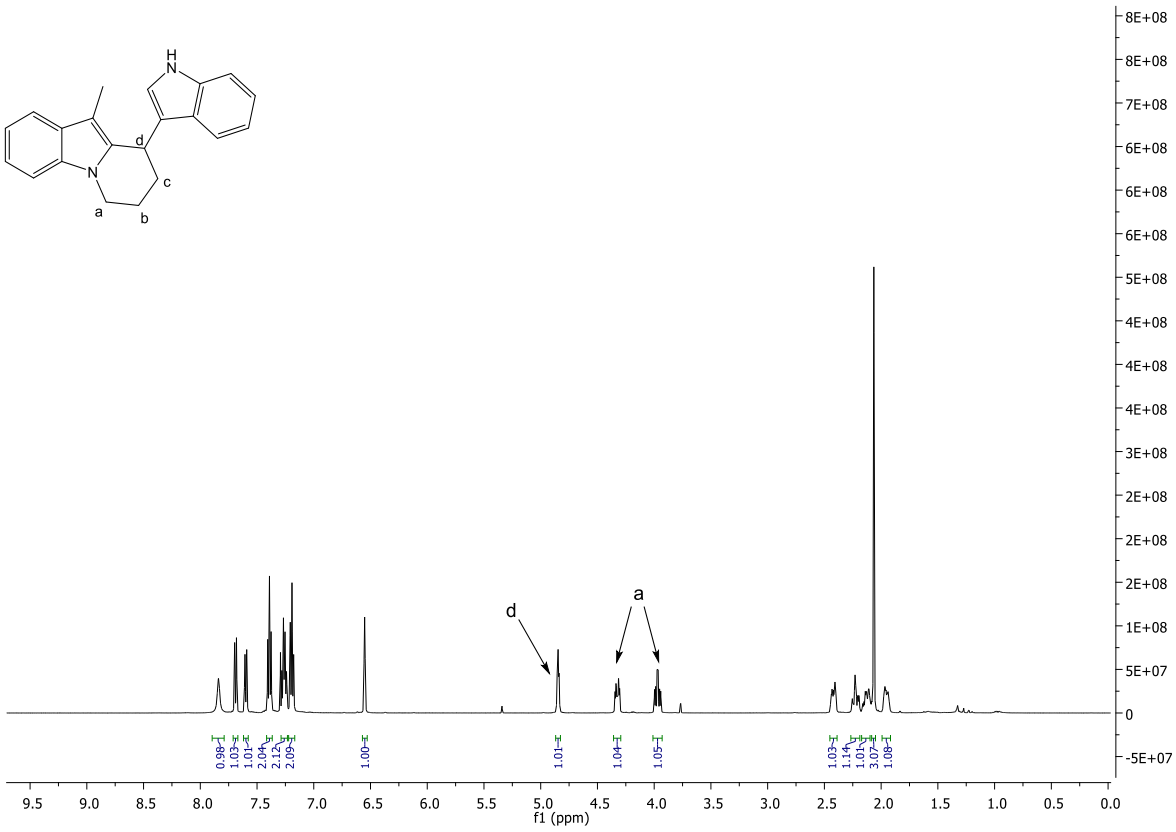


Figure 25. ^{1}H NMR showing the characteristic chemical shifts for structure **287**.

However, characterisation of compound **325** containing the Ph group at position 2 of the external indole showed shifts in the characteristic signals suggesting there is a different environment around the proton in this derivative. The diastereotopic protons were observed at a higher chemical shift of ~4.6 and 4.2 whereas the triplet was observed at a lower chemical shift of around 4.0 ppm (**Figure 26**).

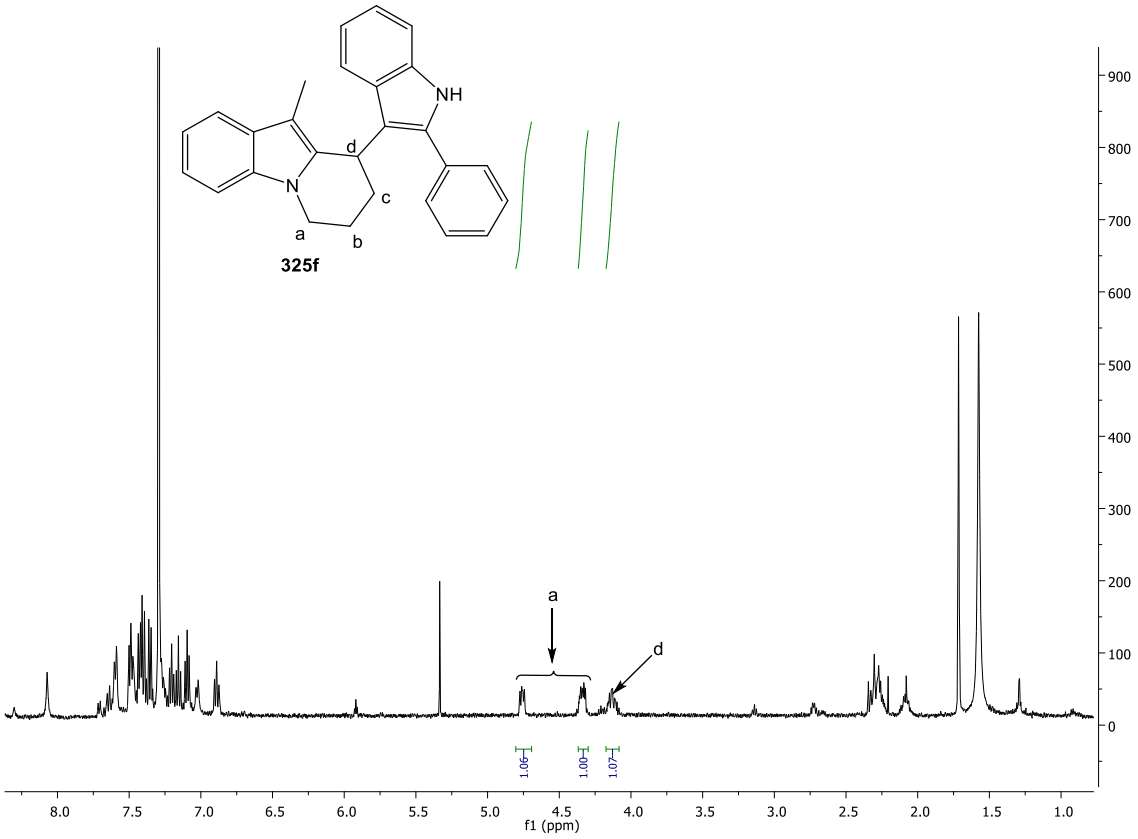


Figure 26. ^{1}H NMR showing the change in chemical shifts for structure **325**.

Further analysis of the NOESY (**Figure 27**) of this structure shows interaction between the protons at position *a* with the aromatic protons on the indole from the indolylallene and interaction of proton *d* with the *ortho*-aromatic protons of the Ph group. This suggests that the external indole is twisted with the phenyl ring on the same side of proton *d* due to sterics and therefore explaining the difference in chemical shifts, maybe due to the anisotropic effects of the aromatic ring on that proton.

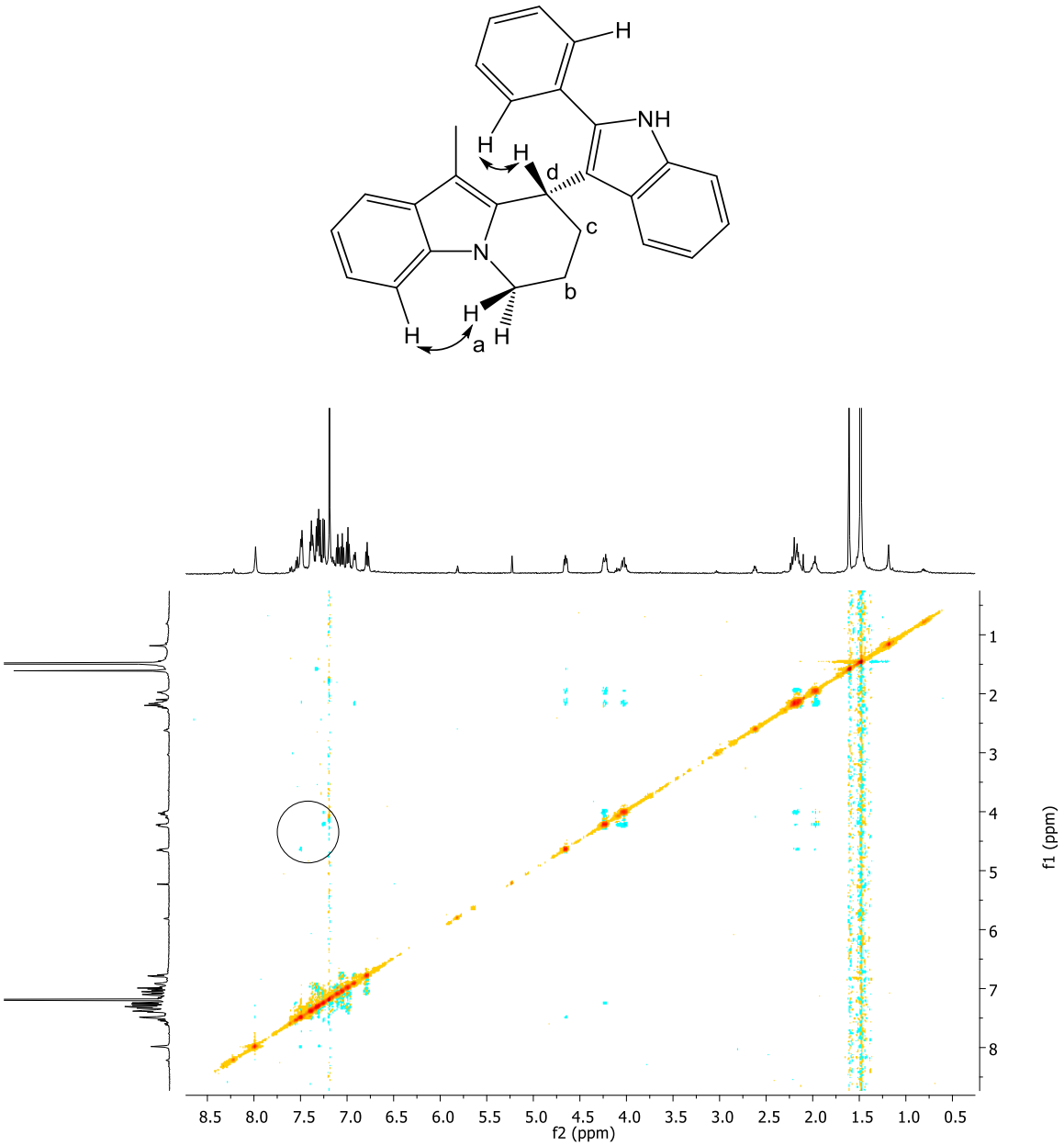


Figure 27. Structure and NOESY NMR highlighting the interaction between protons at *a* and *d* with Ph group.

Although we achieved successful 6-endo cyclisation and intra-intermolecular addition when various substituted external indoles were incorporated, there were a few reactions (5-Cl, 5-CN and 2-Ph) where small amounts (4-10%, **Table 21**) of an unexpected dimeric compound **327** were isolated. Full characterisation of the isolated compound by proton, carbon, HSQC and HMBC NMR and HRMS has allowed us to suggest that unexpected dimerization of the indolyl allene partially occurred with the following structure being suggested (**Figure 28**).

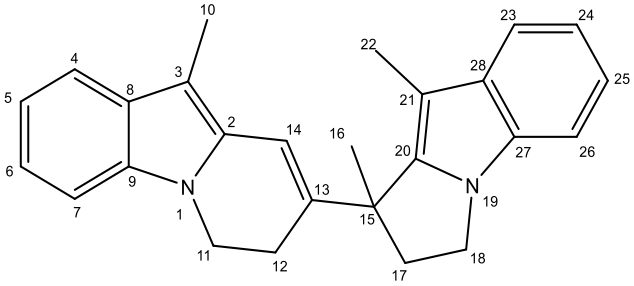


Figure 28. Structure of unexpected compound **327**, occurring from dimerization of two indolyl allene units.

Firstly, we identified the presence of 3 methyl groups, two of which correspond to those in position 3 of the starting indolyl allene (**Figure 29**), suggesting the presence of two indolyl units, this was supported by the presence of double aromatic protons of the indole (**Figure 30**).

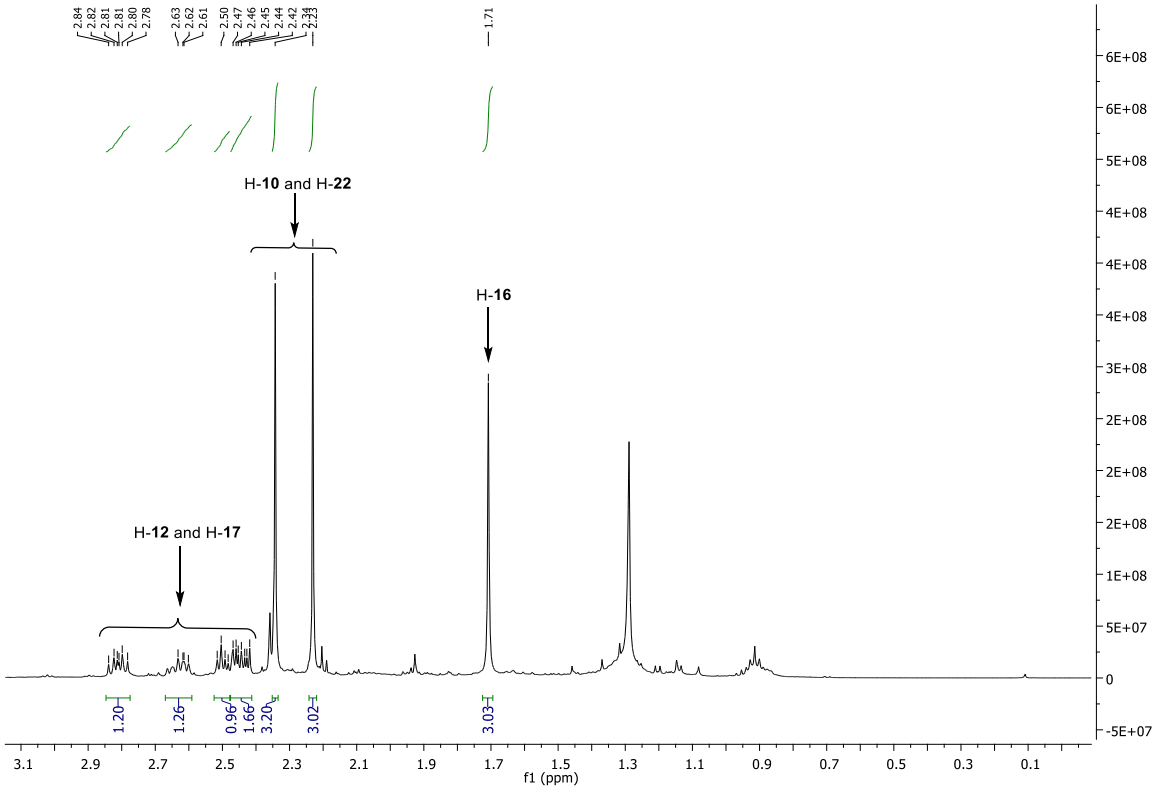


Figure 29. ^{1}H-NMR expansion showing the methyl groups of the dimerised structure.

A singlet present at 6.68 ppm was identified as the proton at position 14 (**Figure 30**). This suggested that an endocyclic double bond in a 6-membered ring was present, however a second 6-membered cycle did not seem to be present. In fact, we identified a quaternary chiral centre from the carbon NMR which along with analysis of both the HSQC and HMBC allowed us to suggest a 5-membered ring with a methyl group at the chiral centre (**Figure 31**).

There were in fact two sets of diastereotopic protons at 4 ppm suggesting two sets of N-CH_2 groups (**Figure 30**), two other sets of diastereotopic protons were identified around 2.6 – 2.2 ppm (**Figure 29**), which would correspond to the CH_2s at position 12 and 17, confirming the chiral centre.

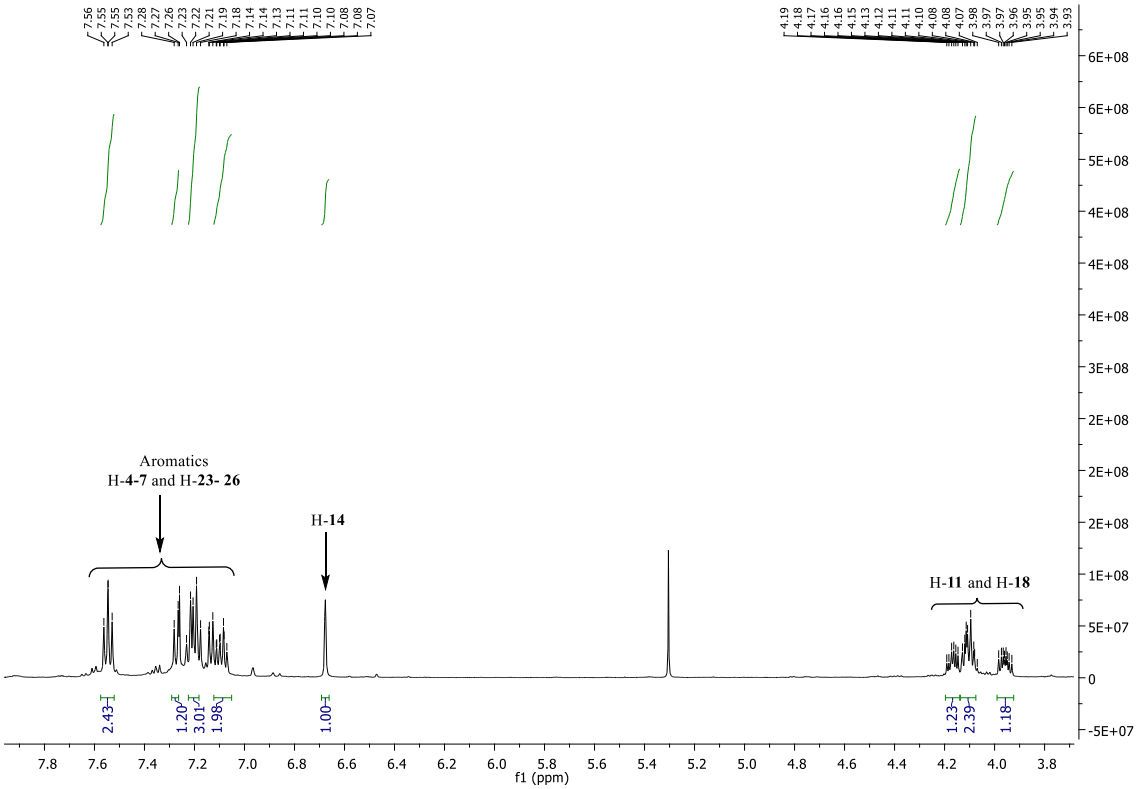


Figure 30. ^{1}H-NMR expansion showing the diastereotopic protons of the dimerised structure.

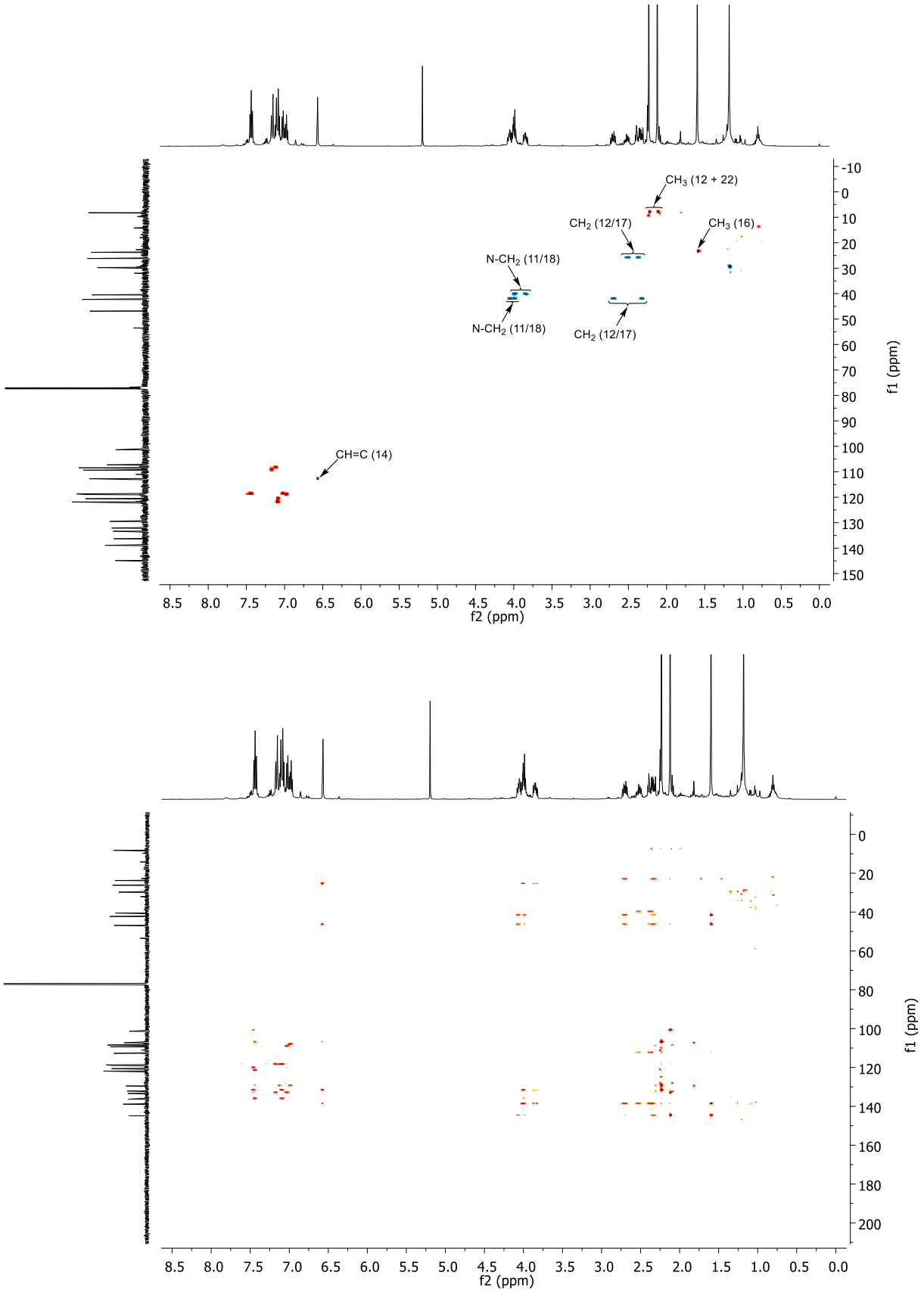


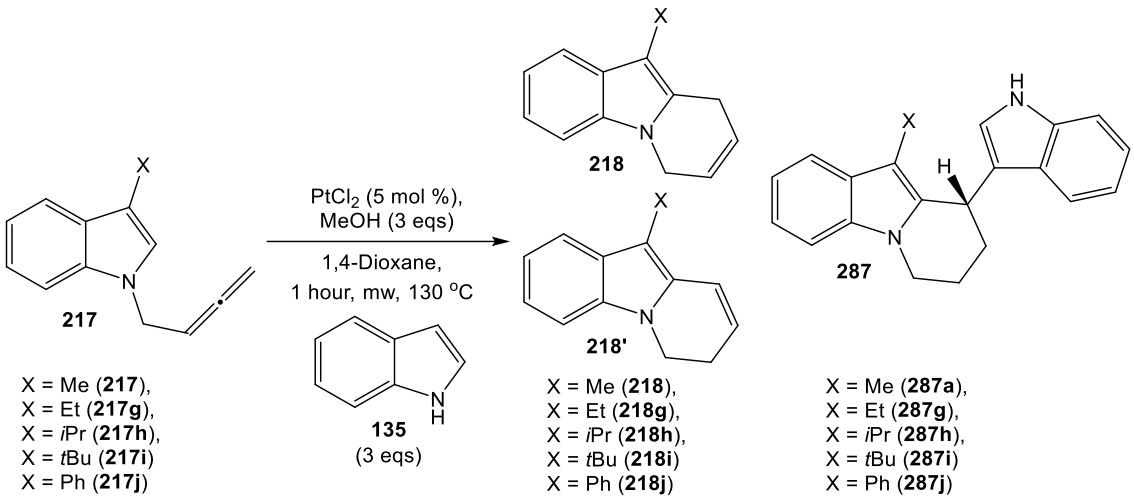
Figure 31. HSQC and HMBC NMRs showing the corresponding connectivity in dimer 327.

This suggested dimerization was also supported by HRMS where the molecular ion M+1 was identified with a mass of 367, while the M+1 of the 6-endo cyclisation product was found to be 184.

2.2.2.c Varying substituents at position 3 of indolyl allene

To further understand the effect that substitution had on the selectivity of this platinum-catalysed bis-indolylation reaction, investigations were carried out with various substituents in position 3 of the indolyl allene **217 g-j** (**Scheme 105** and **106**). These reactions were carried out by project student Louise Eagling during her time at Novartis, all the starting materials were either commercially available or synthesised on site. These reactions were carried out using the optimised platinum conditions (**Scheme 105** and **106**), under an inert atmosphere and all products were obtained after purification using column chromatography.

Interestingly, the electronics and sterics of the different groups tested have a dramatic effect on the selectivity and products of the reactions. **Table 22** shows the results from the reaction with alkyl substituents, moderate electron-donating groups by inductive effect, where we observe the formation of both the conjugated 6-endo cycle **329'** and the 2,3'-BIM **330**. However, the selectivity for **218g-j'** *vs* **287g-j** is dependent on the size of the substituent in position 3, where if position 3 bears a methyl group formation of **287** is favoured (Entry 1, **Table 22**), whereas when the *t*-Bu group is present (Entry 4, **Table 22**) **218'** is preferentially formed, possibly because of the steric restraints of the bulky substituent.



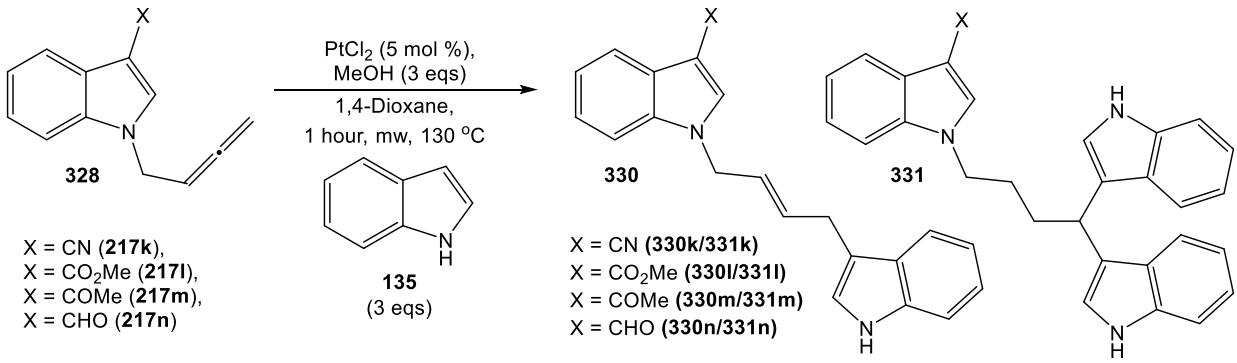
Scheme 105. Platinum-catalysed reaction of alkyl 3-substituted indolyl allenes **217g-j** with indole **135**.

Entry	X	% **329**/**329'** (%)	**287** (%)
1	**217**	5 (1:0.3) (**218**:**218'**)	61
2	**217g**	Traces (**218g'** only)	41
3	**217h**	27 (**218h'** only)	7
4	**217i**	25 (**218i'** only)	19
5	**217j**	Traces (**218j'** only)	11

*All results in table obtained by Louise Eagling and fully characterised by Lisa Cooper.

Table 22. Results from the investigation of alkyl substituents in position 3 of indolyl allene **217.**

The most surprising results were obtained with the electron-withdrawing groups in position 3 where a switch in reactivity was observed, with the formation of the allylic **330 k-n** (**Table 23**) and the tris-indole **331k-n** (**Table 23**) derivatives as the only products of the reaction (**Scheme 106**). These two compounds arise from the addition of the external indole to the terminal carbon of the allene, which is favoured because the electron-withdrawing group removes electron density from position 2 therefore making the 6-endo cyclisation unfavourable and encouraging the nucleophilic addition of the indole to the allene as in the previously reported reactions with platinum and gold. Interestingly, the greater the electron-withdrawing properties of the substituent, the better the selectivity for the tris-indole product **331**, e.g. CN vs CHO (entries 1 and 4, **Table 23**).



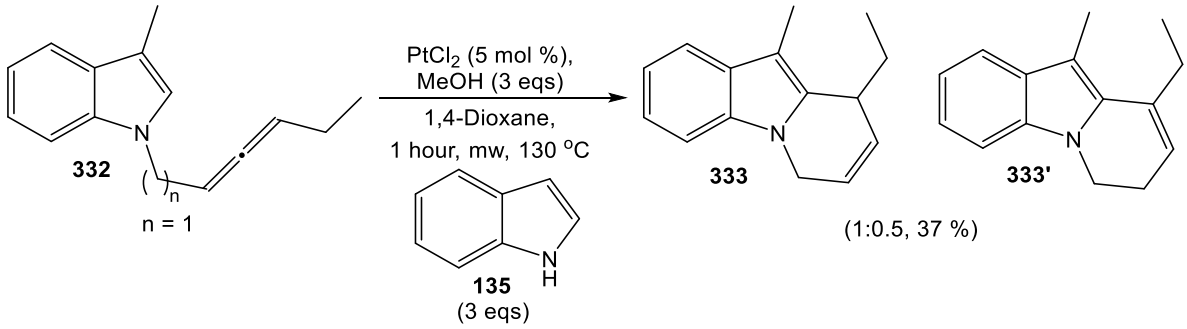
Scheme 106. Platinum-catalysed reaction of electron-withdrawing 3-substituted indolyl allenes **217** with indole **135**.

Entry	X	**330**(%)	**331**(%)
1	**217k**	15	41
2	**217l**	13	32
3	**217m**	11	23
4	**217n**	5	5

Table 23. Results from the investigation of electron-withdrawing substituents in position 3 of indolyl allene **217.**

The electronics of the substituents on both the indolyl allene and external indole have shown that selectivity can be controlled by incorporation of either an electron-donating or an electron-withdrawing group. We have established that an electron-withdrawing group present on the indolyl allene in either position 3 or 5 favours the 6-endo cyclisation or gives rise to the formation the allylic **330 k-n** and tris-indole **331 k-n** products, with little or no formation of the desired 2,3'-BIM products. Whereas incorporating an electron-donating group onto the indolyl allene in position 5 or on the external indole selectively forms the desired 2,3'-BIM. However, bulky substituents in position 3 of the indolyl allene reverse the selectivity and favours the formation of the 6-endo cycle.

Another example involving varying substituents on the indolyl allene were explored when an ethyl chain was incorporated onto the terminal carbon of the 3-methylindolyl allene to investigate the effect of this on the overall platinum reaction. This new allene **332** was synthesised *via* Crabbé homologation with propanal instead of para-formaldehyde. The allene was reacted under standard platinum conditions with indole **135** to achieve the 6-endo cyclised products **333** and **333'** (**Scheme 107**). Formation of the desired 2,3'-BIM product was not achieved, possibly due to the steric hindrance of the ethyl group in position *d* of the cyclised product (**Scheme 107**).



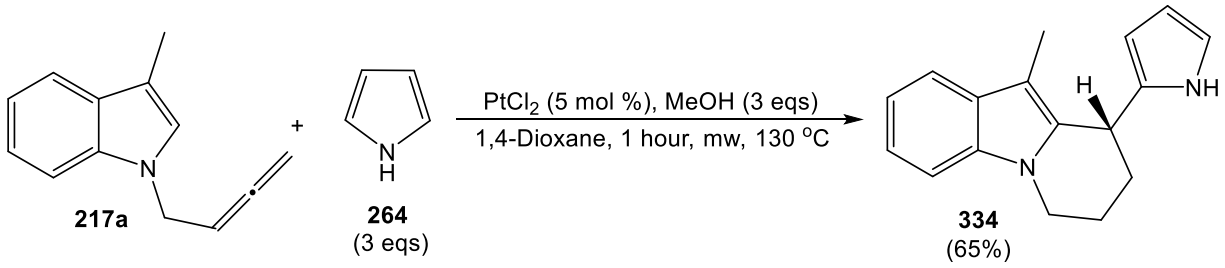
Scheme 107. Platinum-catalysed reaction of ethyl substituted indolyl allene **332** with external indole **135**.

As well as adding chains to the terminal carbon of the allene, several reactions were carried out to extend the chain connecting the nitrogen to the allene, this was explored *via* various methods to incorporate n=0, n=2 and n=3 derivatives. However, reactions to form these derivatives proved tricky, also decomposition and isomerisation were found to be an issue and no results were achieved.

2.2.3. Intra-intermolecular addition reaction with other nucleophiles

It was established during the inter-intermolecular reaction that pyrrole could successfully add to allenes with formation of the bis-pyrrole product **289** (**Scheme 79**). Therefore, this intra-intermolecular platinum reaction was extended to incorporate pyrrole as both the external and internal nucleophile.

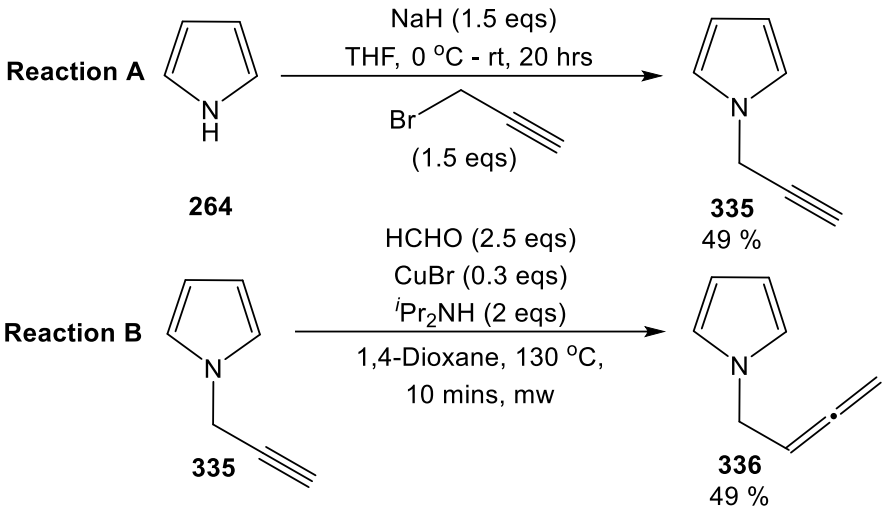
Freshly distilled pyrrole **264** was reacted with 3-methyl-*N*-(2,3-butadienyl)indole **217a** under standard platinum microwave irradiation conditions and the indole–pyrrole cross product **334** was isolated after purification by column chromatography (**Scheme 108**) in a 65% yield, with no formation of the 6-endo cycles.



Scheme 108. Platinum-catalysed reaction of pyrrole **264** with 3-methyl-*N*-(2,3-butadienyl)indole **217a**.

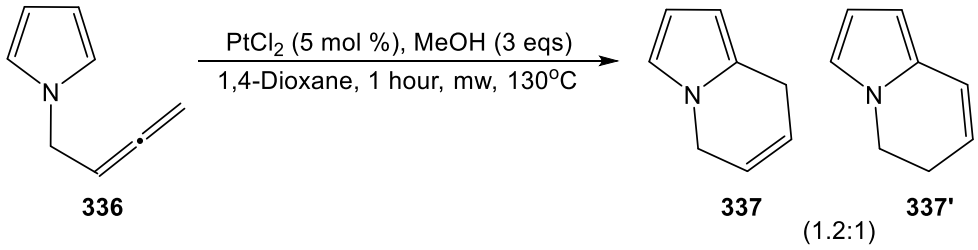
This unique structure contains two different heteroaromatic substituents, which increases the potential for biological and pharmaceutical importance. The importance of pyrroles in natural products and their biological importance led us to explore whether this reaction would work with pyrrolyl allenes, synthesis of which would follow that proposed in **scheme 94**.

Successful propargylation of freshly distilled pyrrole **264** using propargyl bromide yielded compound **335** in 49% yield (**Reaction A, Scheme 109**), this then underwent successful Crabbé homologation to also yield 49% of the desired pyrrolyl allene **336** (**Reaction B, Scheme 109**).



Scheme 109. Propargylation and Crabbè homologation of freshly distilled pyrrole **264**.

The platinum-catalysed reaction was carried out for this pyrrolyl allene **336** under microwave irradiation in the absence of external nucleophiles (**Scheme 110**). The crude from the ^{1}H-NMR showed the presence of the 6-endo cycles **337/337'** (**Figure 32**) in a ratio of 1.2:1 (**337**:**337'**), however, these compounds could not be isolated due to decomposition during column chromatography.



Scheme 110. Platinum-catalysed cyclisation of pyrrolyl allene **337**.

The pyrrolyl allene **336** was also reacted under optimised conditions as before with the external indole **135**. However, analysis of the crude ^{1}H NMR after 1 hour showed only formation of the two cycles above which were not isolated.

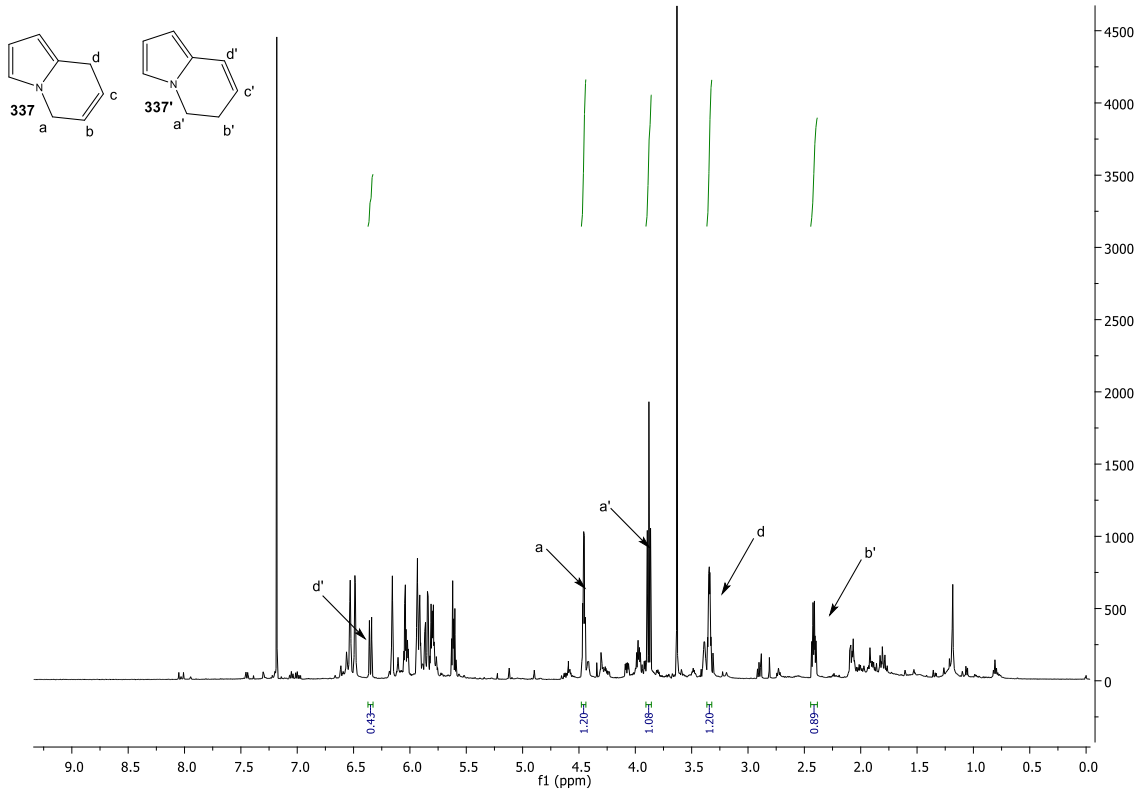
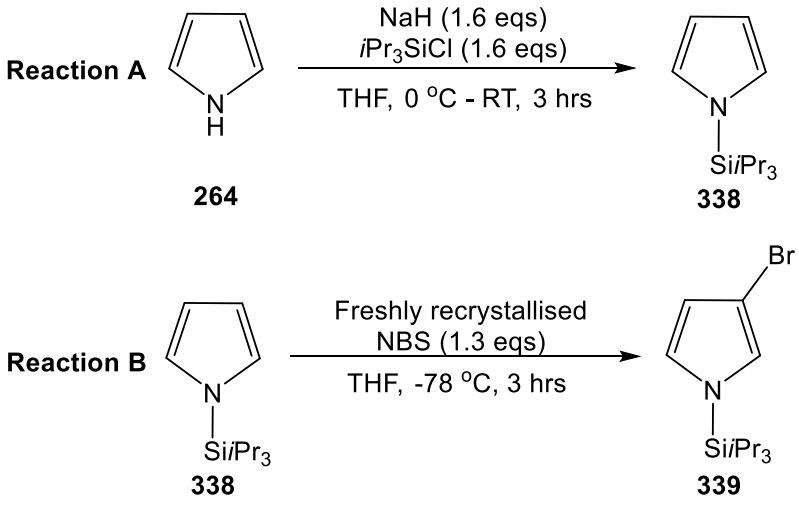


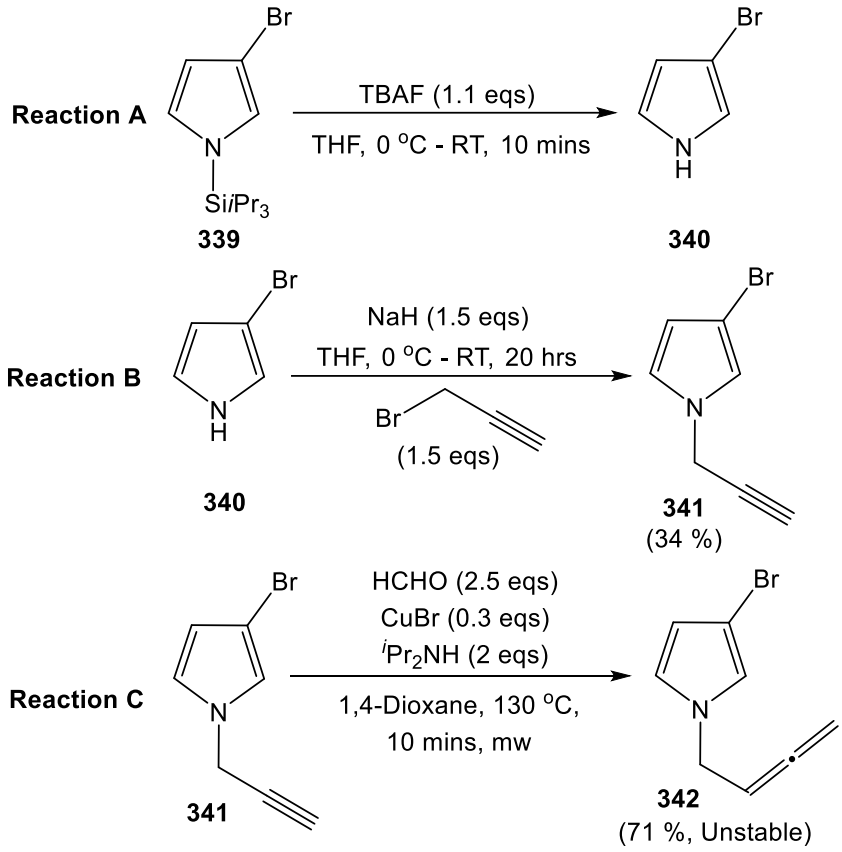
Figure 32. Crude ^{1}H-NMRs showing the presence of cycles **337** and **337'** before decomposition in column.

We know from the synthesis of 2,3'-BIMs that the methyl group has an important effect on the reaction. Therefore, we were interested to investigate this with the pyrrole. Using the route from **Scheme 77**, successful silyl protection of freshly distilled pyrrole was achieved (**Reaction A, Scheme 111**) with 98% yield and bromination in position 3 of pyrrole was also achieved with 58% yield (**Reaction A, Scheme 111**).



Scheme 111. Protection and subsequent bromination of freshly distilled pyrrole **264**.

However, when methylation using *n*-BuLi was attempted, a complex mixture was obtained resulting from the methylation in various positions of the pyrrole. The brominated derivative **339** was instead deprotected using TBAF in 94% yield (**Reaction A, Scheme 112**), but after exposure to air for less than 10 minutes, the unprotected derivative **340** decomposed. Both propargylation and Crabbé homologation were attempted for the freshly prepared 3-bromopyrrole derivative **340** (**Reaction B and C**, **Scheme 112**), however due to poor stability these compounds decomposed within 24 hours and therefore no platinum reactions could be carried out.



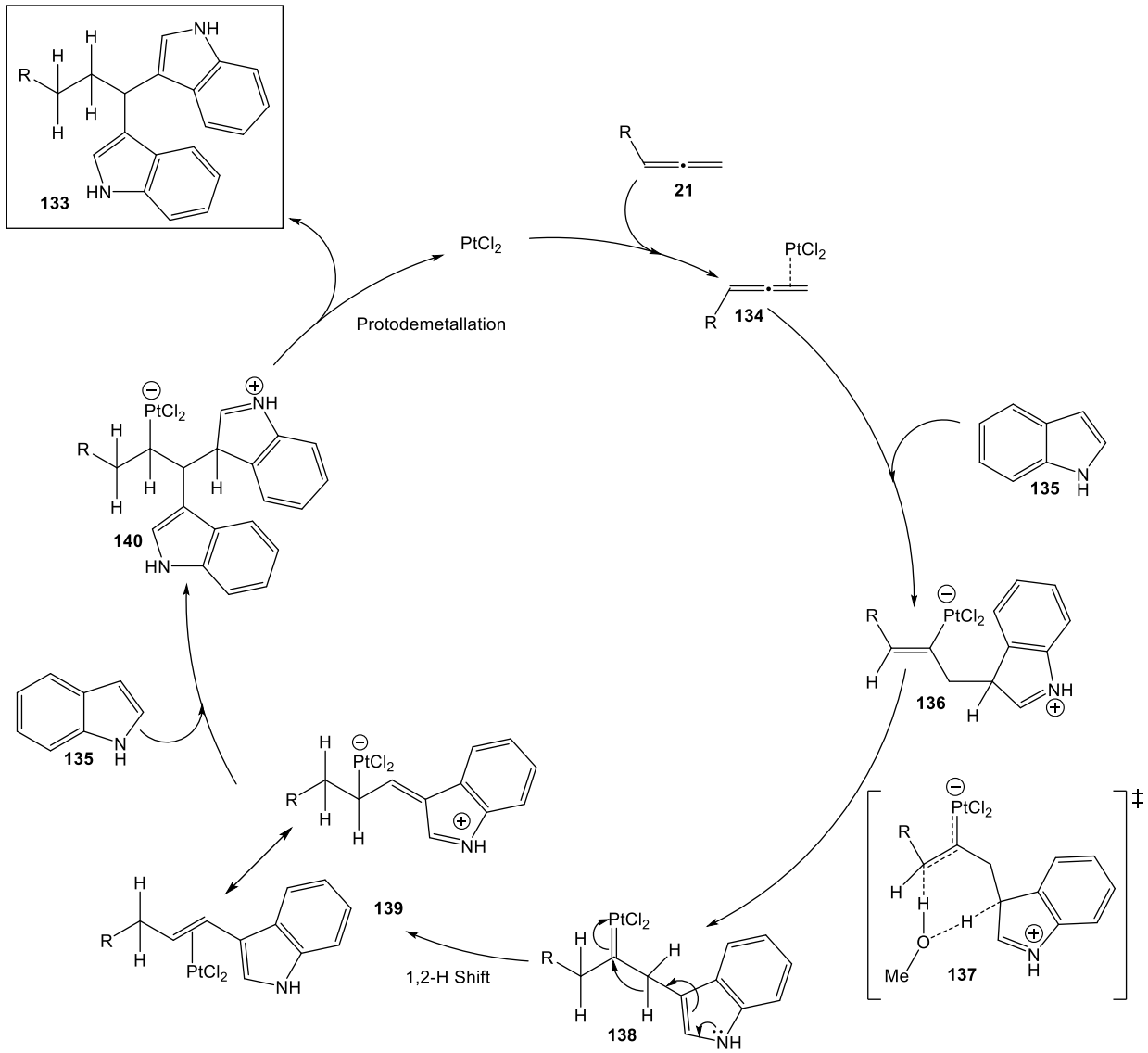
Scheme 112. Deprotection, propargylation and homologation of 3-bromopyrrole derivatives.

The quick decomposition of these products put a time restraint on this work and was therefore not continued, however because of the potential for this reaction to proceed and the available scope, further investigation is currently being carried out within our research group.

2.3. Mechanistic Investigation

Having established that we could favour the formation of the desired 2,3'-BIM by modifying the substituents on the indolyl allene, it was important to understand the mechanism of the reaction and the factors which could affect it.

Preliminary mechanisms for both the dihydroalkoxylation (**Scheme 19**, section 1.4.b.) and bis-indolylation (**Scheme 113** as seen in **Scheme 33**, section 1.4.d.) reactions involving the inter-intermolecular addition have been proposed by Muñoz *et al*.[77, 51] A more detailed mechanistic study on this reaction is being carried out in the group and some of the results have contributed to the understanding of the reaction under study in this thesis.

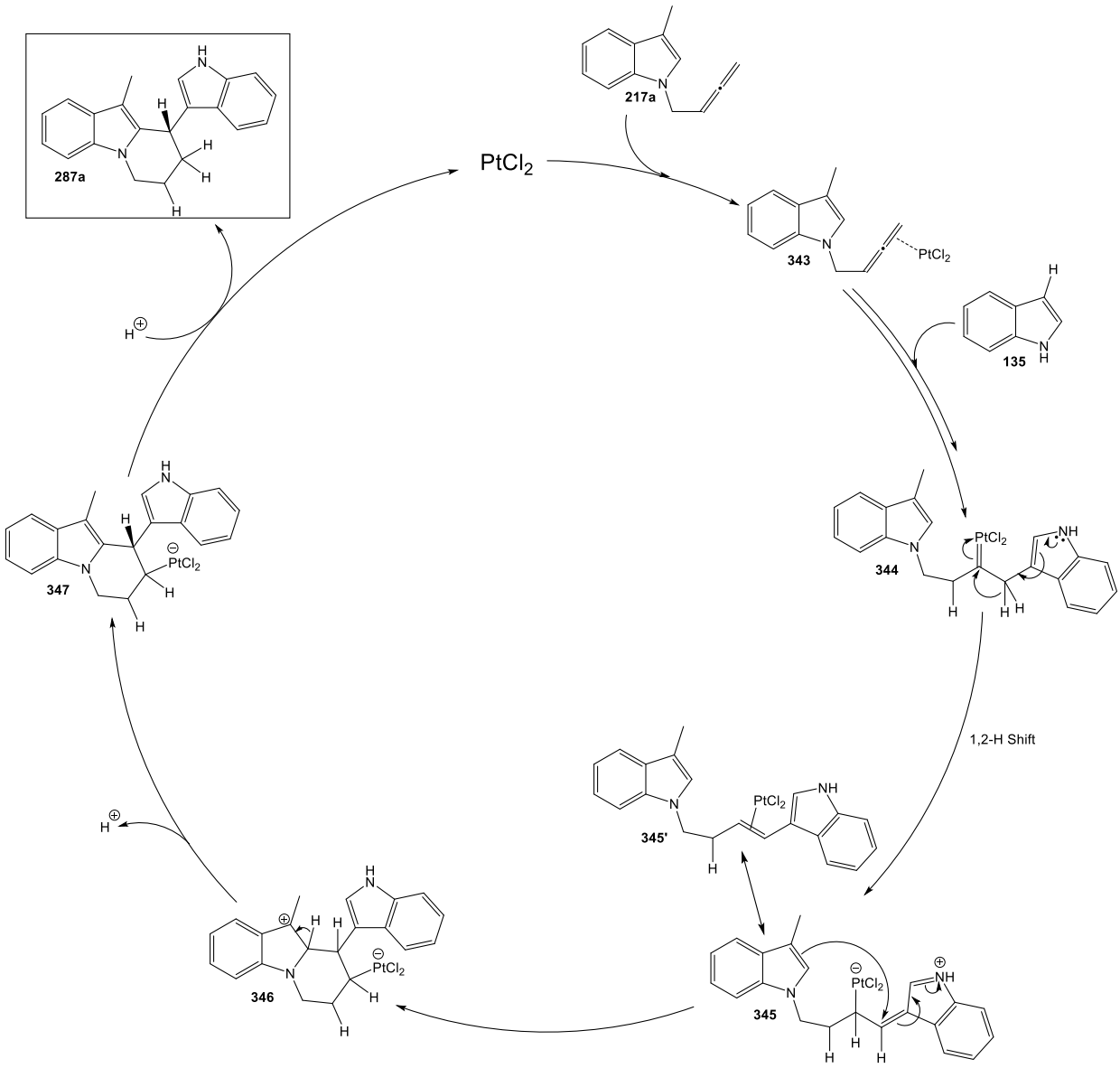


Scheme 113. Simplified proposed mechanism for the platinum-catalysed bis-indolylation of allenes.

This mechanism is proposed to proceed *via* the intermolecular addition of indole **135** to the terminal carbon of the allene **21** to form a vinyl platinum intermediate **136**. Instead of protodemetallation to give allyl indoles, this intermediate is protonated in the internal carbon of the double bond. DFT calculations carried out for the analogous dihydroalkoxylation reaction support the theory that the methanol is acting as a proton shuttle, aiding the movement of protons to generate the platinum carbene intermediate **138**.

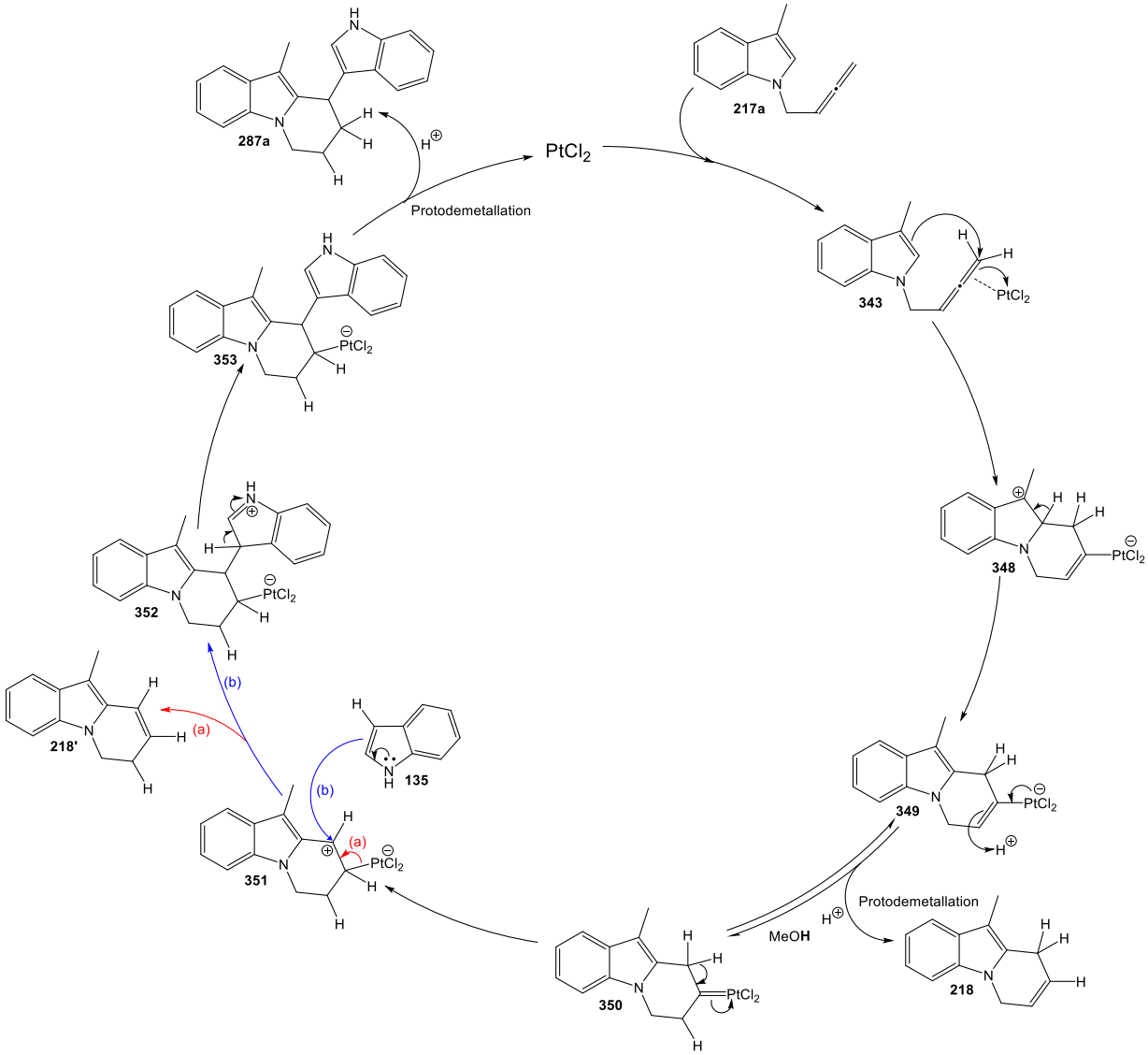
A 1,2-H shift gives intermediate **139**, which can also be seen as a resonance form of a vinyl indole with the platinum coordinated to the double bond. The analogous enol ether has been detected in the reaction with alcohols, and DFT calculations suggest that it is a resting state of the catalytic cycle, which is also in accordance with previously reported synthesis of BIMs under acidic conditions as mentioned in the introduction.[112-118] This intermediate allows for the addition of the second indole, and protodemetallation, possibly *via* protonation of the platinum centre and reductive elimination, forming the final product **133**.

A similar mechanism was originally proposed for the formation of the 2,3'-BIM structures with two possibilities, one being *via* the inter-intramolecular pathway (**Scheme 114**), which was adopted from that of the inter-intermolecular addition mechanism (**Scheme 113**).



Scheme 114. Proposed mechanism for the inter-intramolecular pathway for the formation of 2,3'-BIMs **287a**.

However, in most of the reactions we observe and isolate the 6-endo cycles **218/218'** (**Scheme 90**) as a mixture of isomers, which led us to propose a second mechanism (**Scheme 115**) that involved first the intramolecular addition to form these 6-endo cycles **218/218'**, followed by the intermolecular addition of the external indole **135** to form the desired 2,3'-BIM **287a**.



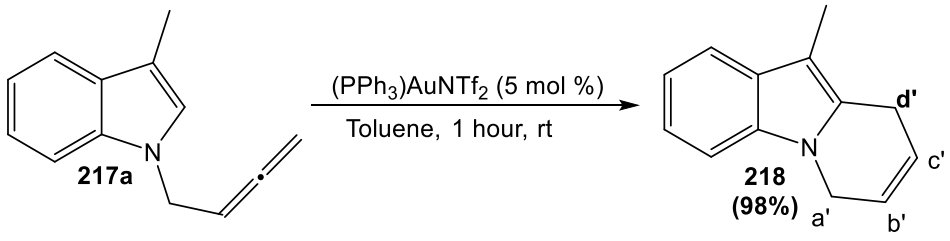
Scheme 115. Proposed mechanism for the intra-intermolecular pathway for the formation of 2,3'-BIMs **287a**.

The uncertainty between these two pathways and whether there was competition between the two was the driving force for investigating the reaction mechanism. Therefore, analysis of the 6-endo cycles **218/218'** as possible intermediates in the formation of the 2,3'-BIMs **287** was carried out alongside deuterium and carbon labelling experiments. Several NMR reactions and other supporting reactions were also carried out and are outlined below. Thorough analysis of the results has led us to propose an overall mechanism for the formation of both the 6-endo cycles **218/218'** and the 2,3'-BIMs **287** (**Scheme 149**, Section 2.4, Page 174) as well as an explanation for the effect of electronics on the overall reaction.

2.3.1. Intermediate studies

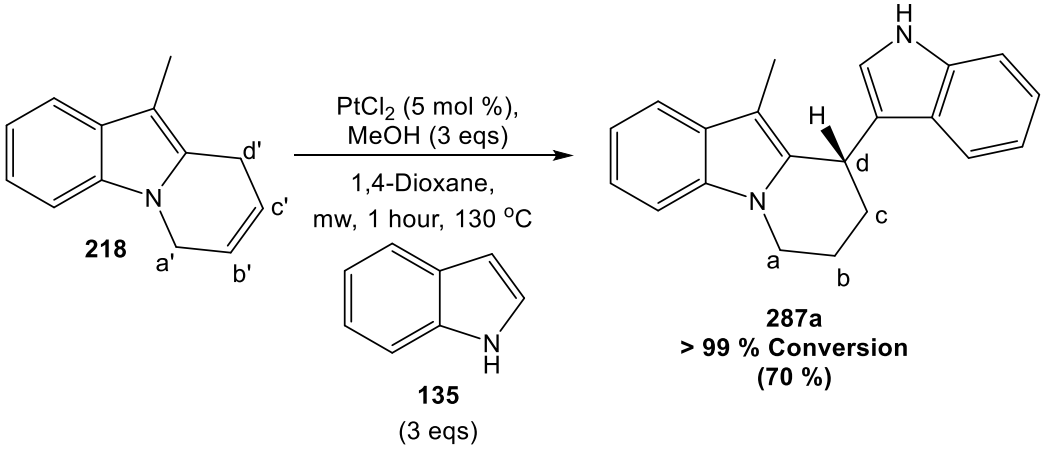
Analysis of the products from the various reactions highlight that the 6-endo cycles are likely to be intermediates of the reaction. Therefore, reactions were carried out to understand how they can interconvert between the non-conjugated cycle **218** and the conjugated cycle **218'**, as well as their ability to react with the external indole to form the desired 2,3'-BIM **287**.

As discussed in the introduction (**Scheme 55**, section 1.5.C.), Barluenga[101] reported the synthesis of the non-conjugated cycle **218** *via* gold-catalysed cyclisation of 3-methyl-*N*-(2,3-butadienyl)indole **217a**. Therefore, cycle **218** was synthesised with >99% conversion in a 98% isolated yield (**Scheme 116**) and was used as the basis of these intermediate studies.



Scheme 116. Gold-catalysed cyclisation of 3-methyl-*N*-(2,3-butadienyl)indole **217a**.

Isolated cycle **218** was reacted with an external indole **135** using the optimised platinum conditions under microwave irradiation to determine its reactivity for the formation of the 2,3'-BIM **287**. After 1 hour, a crude NMR was obtained which showed >99% conversion of cycle **218** to the desired 2,3'-BIM **287a** with no detected isomer **218'** (**Figure 33**). Column chromatography isolated compound **287a** in a 70% yield (**Scheme 117**).



Scheme 117. Platinum-catalysed reaction of cycle **218** with external indole **135**.

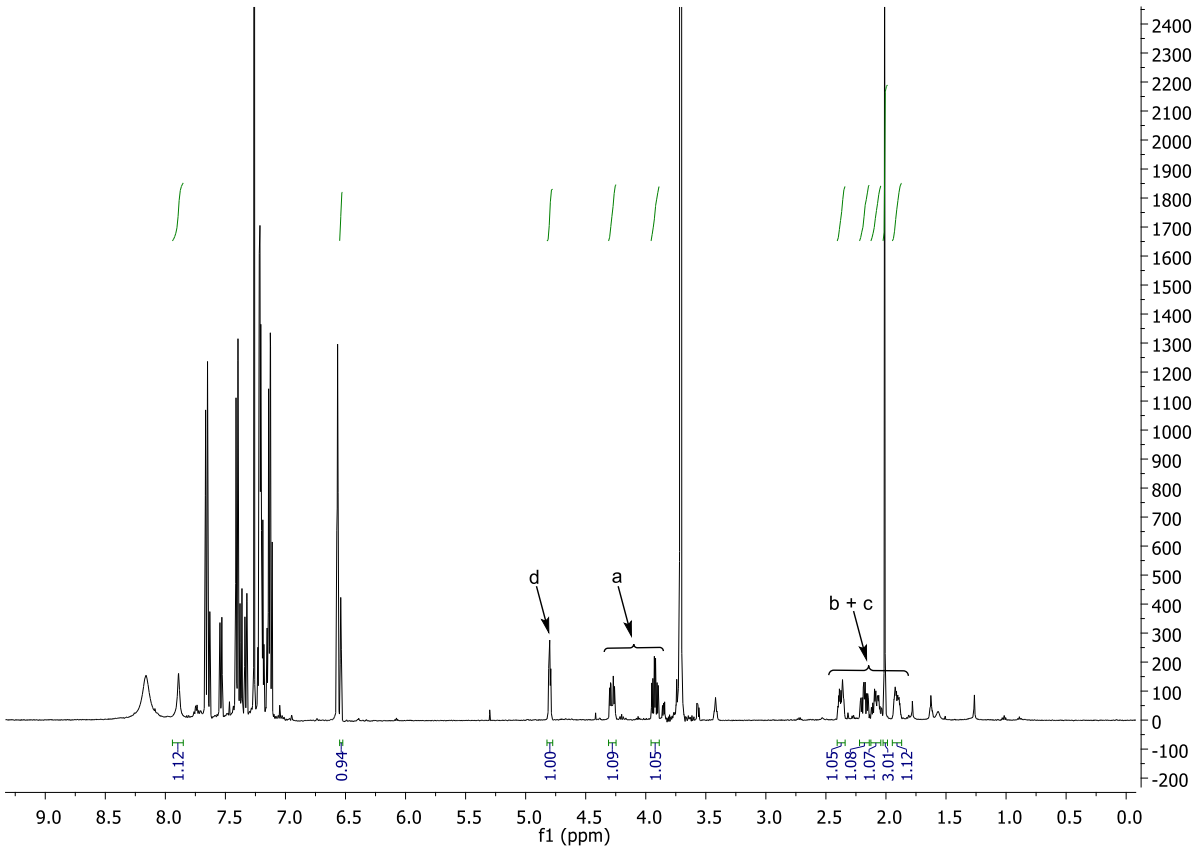
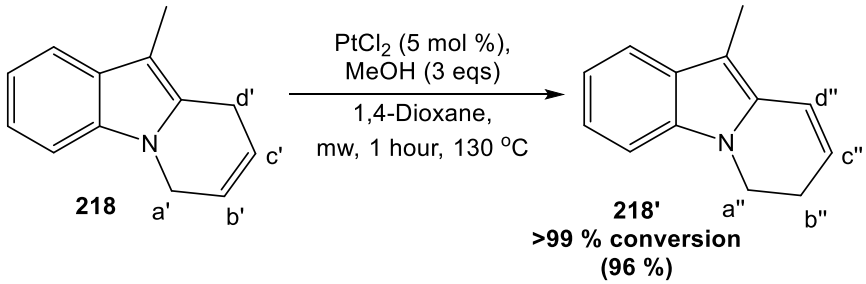


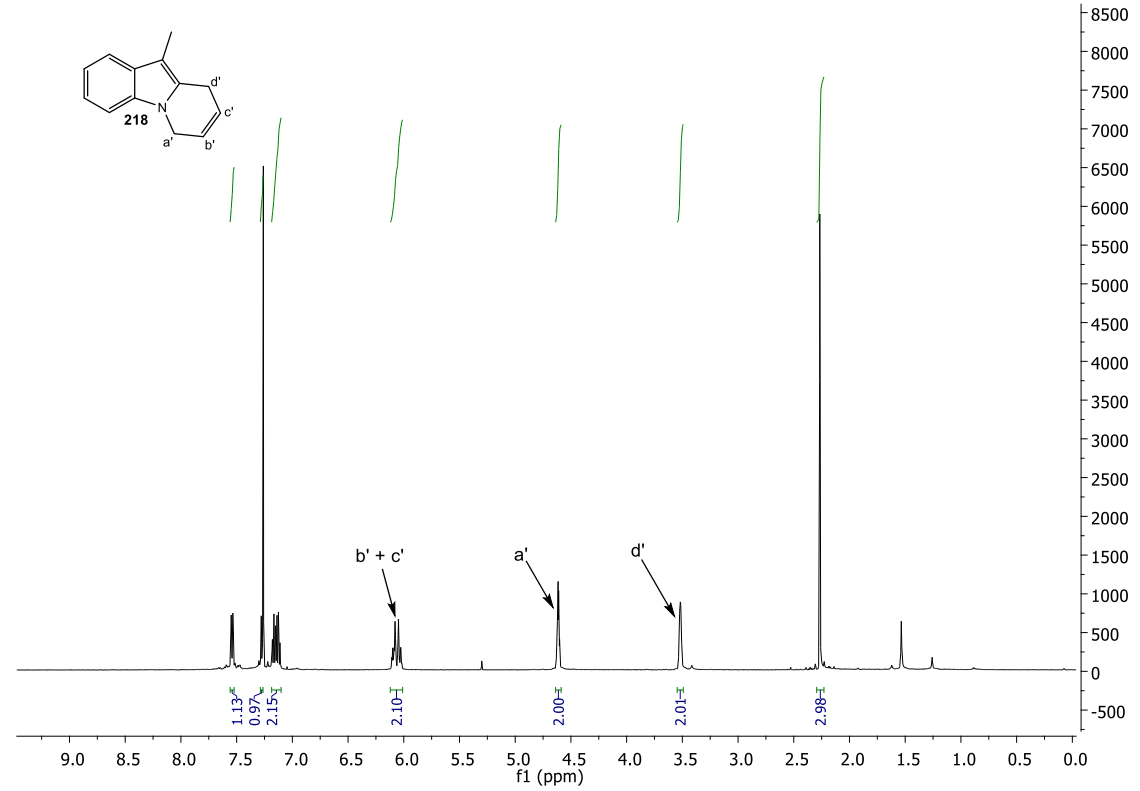
Figure 33. Crude ^{1}H-NMR for the platinum-catalysed reaction of cycle **218** with external indole **135** with complete conversion to 2,3'-BIM **287a**.

To test if isomerisation occurs between **218** and **218'** before reacting with the external indole, the non-conjugated cycle **218** was reacted under platinum conditions using microwave irradiation without the external indole. After 1 hour, the crude NMR showed complete conversion of cycle **218** to **218'** (**Figure 34**) with an isolated yield of 96% (**Scheme 118**).



Scheme 118. Platinum-catalysed isomerisation of cycle **218** to cycle **218'.**

a)



b)

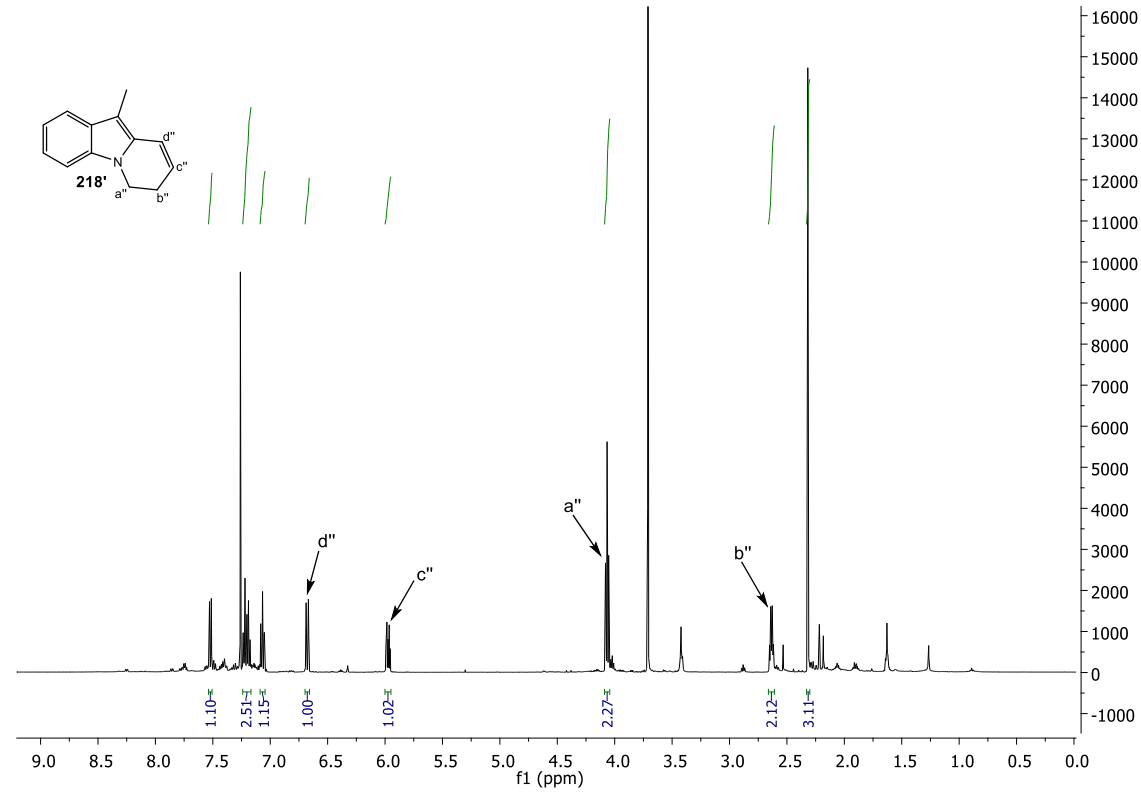


Figure 34. ^{1}H-NMRs of (a) pure cycle **218** and (b) crude of isomerisation reaction to **218'** using platinum conditions.

This isomerisation was also carried out without methanol present, interestingly when no methanol is present we do not see >99% conversion of cycle **218** to **218'**, instead we observe a mixture of the two isomers with a ratio of 0.7:1 (**218:218'**) (**Figure 35**). This highlights the importance of the methanol for the isomerisation of these two cycles, which we will discuss later in the mechanism.

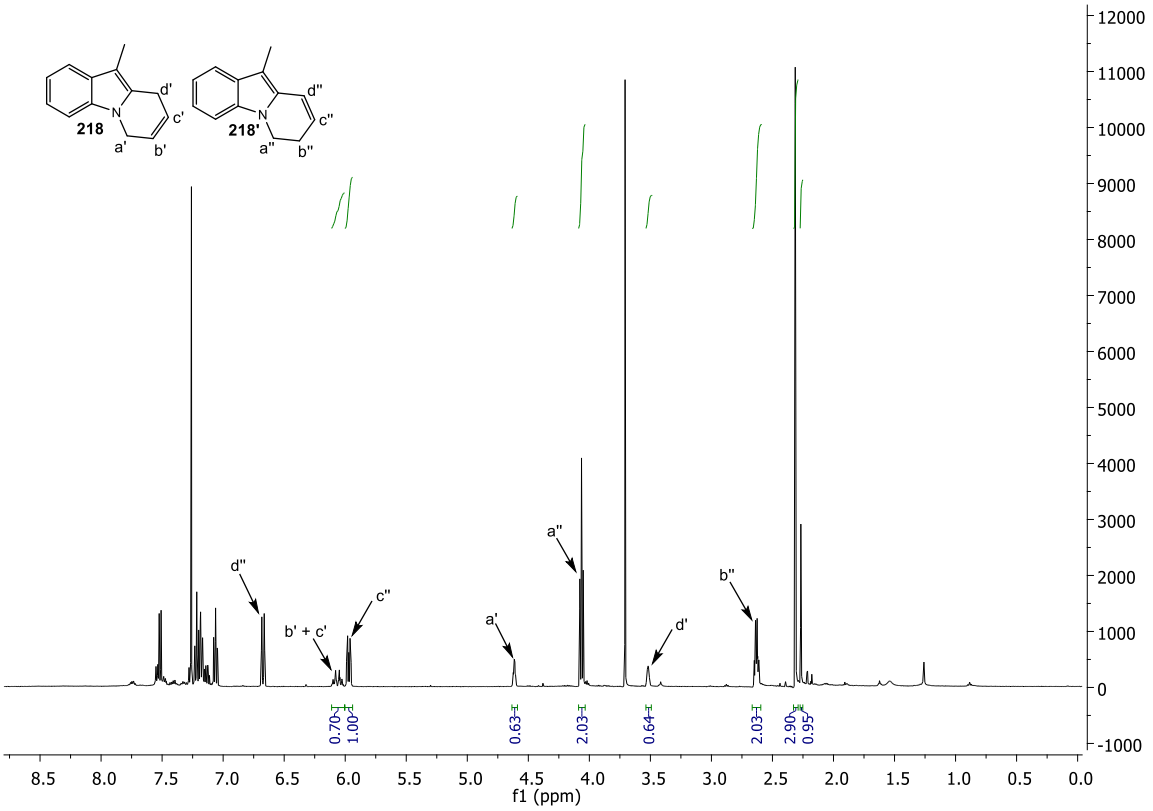
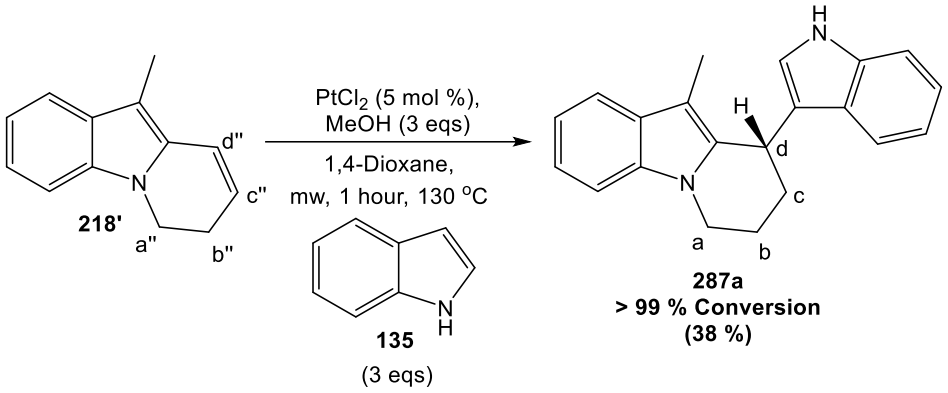


Figure 35. Crude ^{1}H-NMR for the isomerisation of **218** to **218'** with no methanol present.

To ensure that the conjugated 6-endo cycle **218'** does in fact go to the 2,3'-BIM **287**, we investigated the reaction of isolated cycle **218'** with the external indole **135** under the standard platinum conditions (**Scheme 119**). Analysis of the crude ^{1}H-NMR after 1 hour shows >99% conversion of cycle **218'** to the desired 2,3'-BIM **287** (**Figure 36**) which was isolated in a 38% yield (poor separation by column chromatography). This therefore supports the theory that cyclisation occurs first, followed by isomerisation between **218** and **218'** with subsequent intermolecular addition of the external indole.



Scheme 119. Platinum catalysed reaction of cycle **218'** with external indole **135** with complete conversion to 2,3'-BIM **287a**.

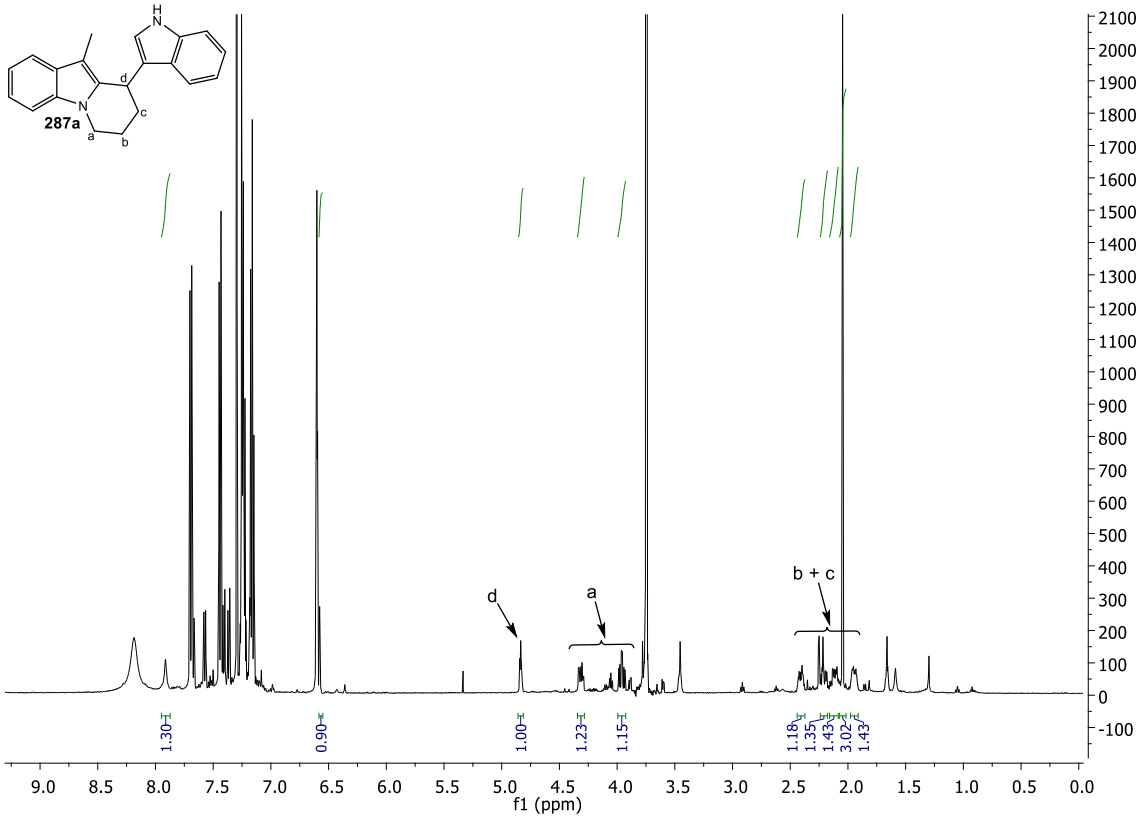
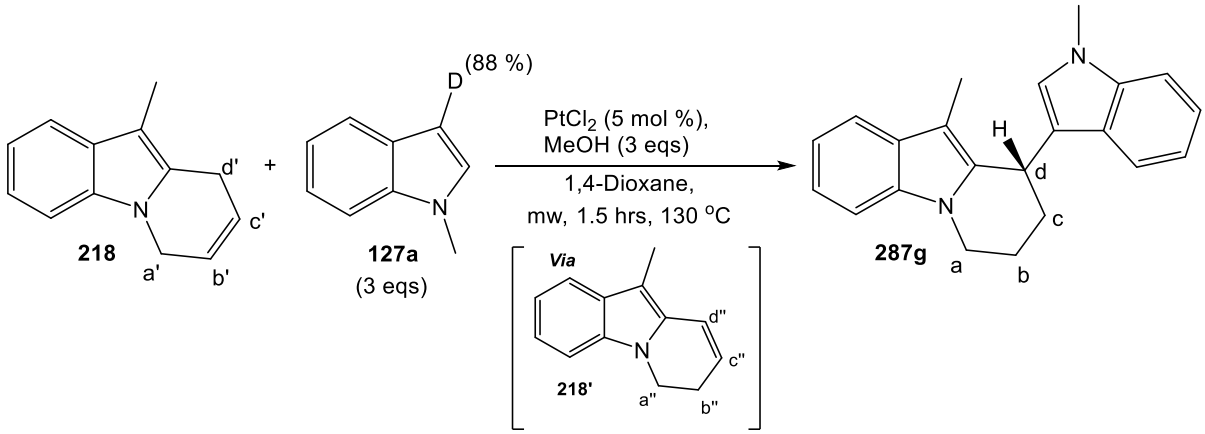


Figure 36. Crude NMR of the reaction of cycle **218'** with external indole **135** for the formation of the 2,3'-BIM **287a**.

To further support the intramolecular addition with isomerisation from cycle **218** to **218'** followed by the intermolecular addition of the external indole, the platinum catalysed microwave irradiation reaction was carried out with the non-conjugated 6-endo cycle **218** and external *N*-methyl indole **127a** with deuterium incorporated into position 3 of the indole (**Scheme 120**). Dimethylsulfone was used as a reference to allow us to take samples of the reaction mixture every 10 minutes over a 90-minute period to follow the progress of the reaction and to generate a reaction profile for the consumption of cycle **218**, formation and consumption of cycle **218'** as well as the overall formation of the 2,3'-BIM **287g**.



Scheme 120. Platinum-catalysed reaction of cycle **218** with external deuterated *N*-methyl indole **127a** with complete conversion to 2,3'-BIM **287g** *via* cycle **218'**.

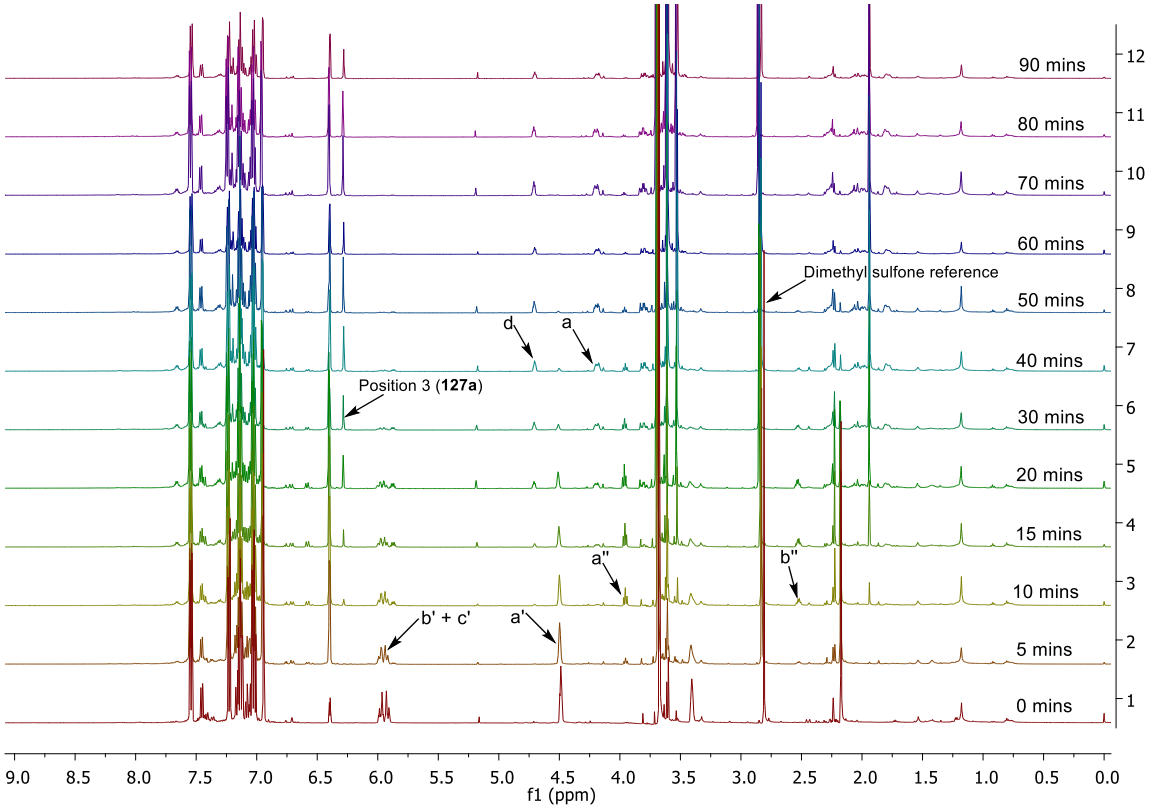


Figure 37. ^{1}H-NMR profile for the reaction of cycle **218** with deuterated *N*-methyl indole **127a**.

Calculations from the NMR integrals for positions *a*, *a'* and *a''* with respect to the internal reference allowed us to plot the concentration of the products over time (**Figure 38**), giving a clear picture of the reaction profile. It shows that the non-conjugated cycle **218** isomerizes to the conjugated cycle **218'** within the first 20 minutes. Also noted is that as soon as isomerisation to cycle **218'** begins, so does the formation of compound **287g**, although at a slower rate. At 20 minutes, cycle **218'** is shown to decrease in concentration as the concentration of compound **287g** continues to increase up to a concentration of 0.186 M and once both cycles **218/218'** are consumed the reaction is complete.

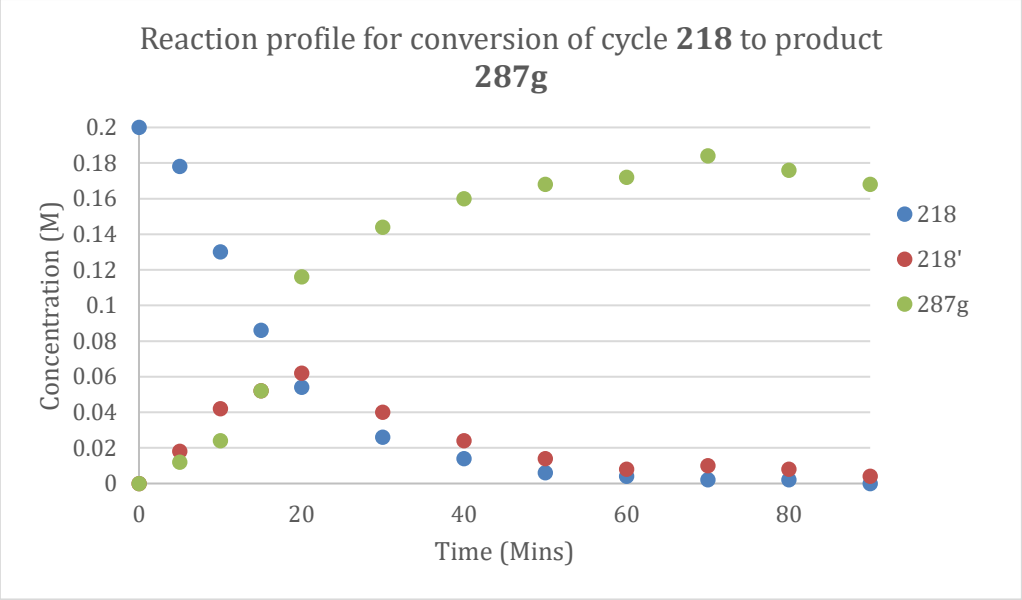
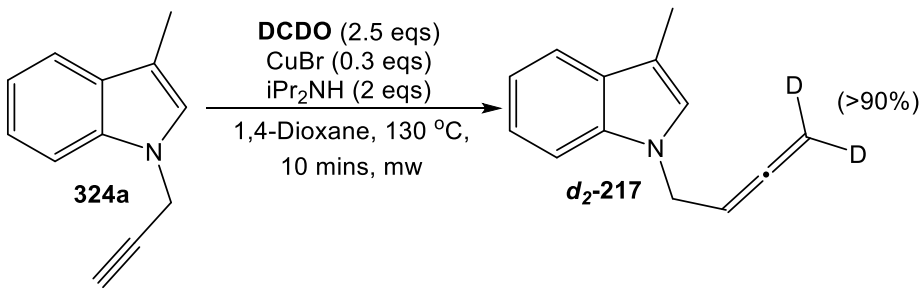


Figure 38. Reaction profile showing the consumption of cycle **218**, formation and consumption of cycle **218'** with subsequent formation of 2,3'-BIM **287g**.

The reaction was carried out with deuterated *N*-methyl indole **127a** with 88% deuterium incorporation at the beginning of the reaction, but after 5 minutes we observed a loss of deuterium in position 3. Overall we observe a deuterium loss in the external indole of 41% from position 3 and analysis of the NMRs shows that deuterium is incorporated into cycle **218'** at position *d''* within the first 10 minutes. Analysis also shows that deuterium incorporation occurs at position *d* of compound **287g** within 10 minutes, with 31% being incorporated in the final compound.

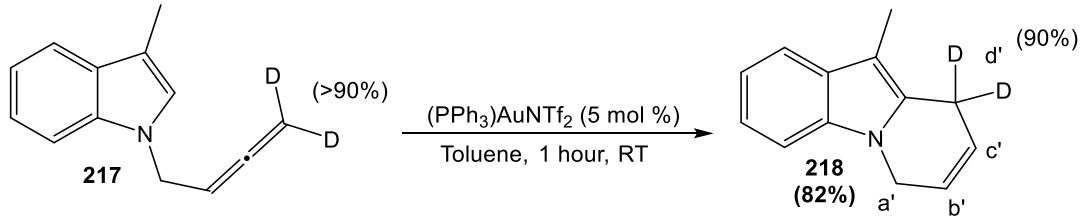
To further support these reactions and their findings, similar reactions were carried out with deuterated 3-methyl-*N*-(2,3-butadien-1-yl) indole **217**. This deuterated 3-methyl-*N*-(2,3-butadienyl)indole **217** was synthesised *via* Crabbé homologation of 3-methyl-1-(2-propyn-1-yl)-1H-indole **324a** with deuterated paraformaldehyde (**Scheme 121**) This reaction gives compound ***d*$_2$-217** with an average yield of 70% with >90% D incorporation at the terminal carbon of the allene.



Scheme 121. Crabbé homologation for the formation of deuterated 3-methyl-*N*-(2,3-butadienyl)indole ***d*$_2$-217**.

Initial platinum reactions with non-purified allene resulted in complex mixtures, due to an unknown impurity that hindered the formation of the cycles and BIM products. However, after several purifications *via* column chromatography the cyclisation and subsequent intermolecular addition was successful which allowed us to identify the deuterium incorporation patterns.

Firstly, 3-methyl-*N*-(2,3-butadienyl)indole **217** was reacted using Au catalysis to form the non-conjugated cycle **218** in an 82% yield (**Scheme 122**), with around 90% deuterium incorporation at position *d'* (**Figure 39**) as expected because the terminal protons would not transfer during this 6-endo cyclisation step.



Scheme 122. Gold-catalysed cyclisation of deuterated 3-methyl-*N*-(2,3-butadienyl) indole ***d*₂-217** with retention of deuterium.

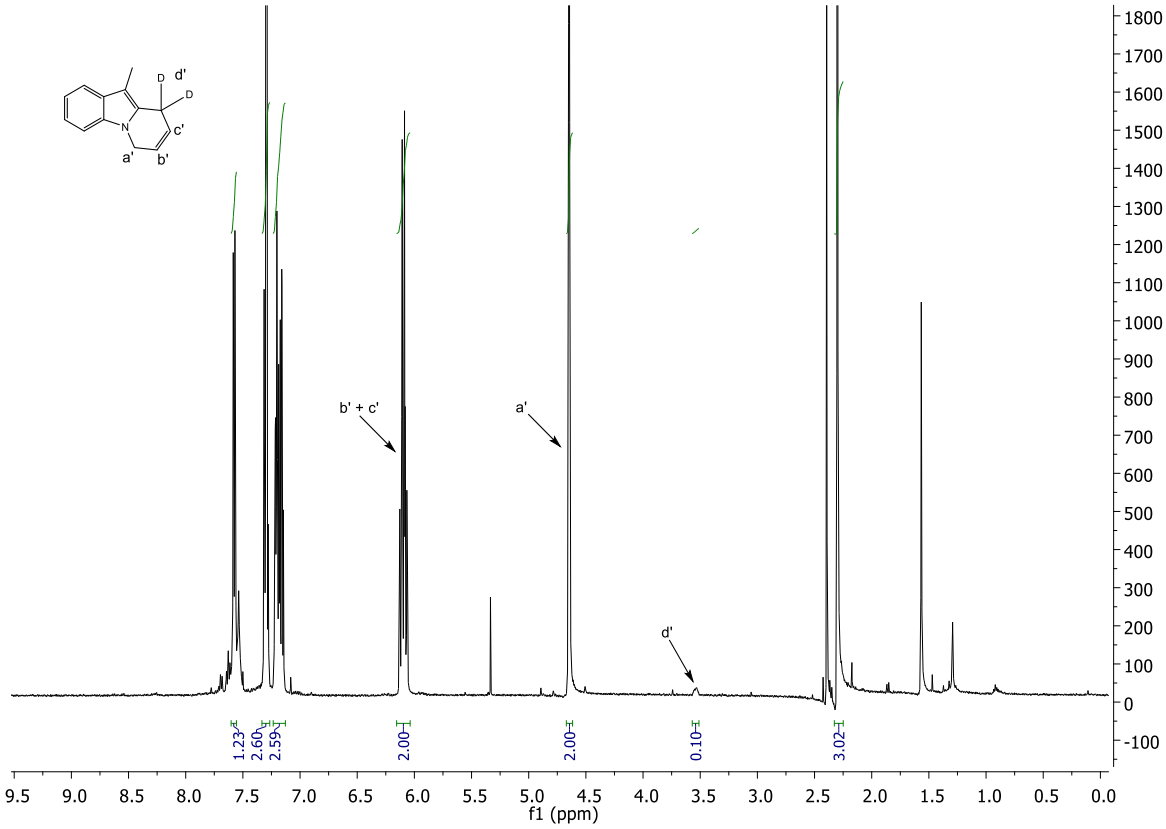
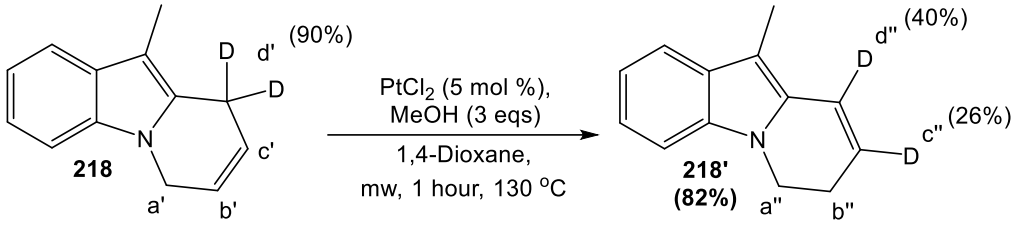


Figure 39. ^{1}H-NMR highlighting deuterium incorporation in position *d'* of compound **218.**

To further study the isomerisation of cycle **218** to cycle **218'**, cycle **218** was subjected to platinum conditions without the external indole. Successful isomerisation occurred with >99% conversion to cycle **218'** with an isolated yield of 82% (**Scheme 123**).



Scheme 123. Platinum-catalysed isomerisation of cycle **218** to cycle **218'**.

Analysis of the ^{1}H NMR identified that deuterium was incorporated into positions *c''* and *d''* in 26 and 40% respectively (**Figure 40**). The involvement of protons from position *d'* in the isomerisation process is clear from the deuterium incorporation in *c''*. However, some deuterium loss is observed overall in the process (~ 20%).

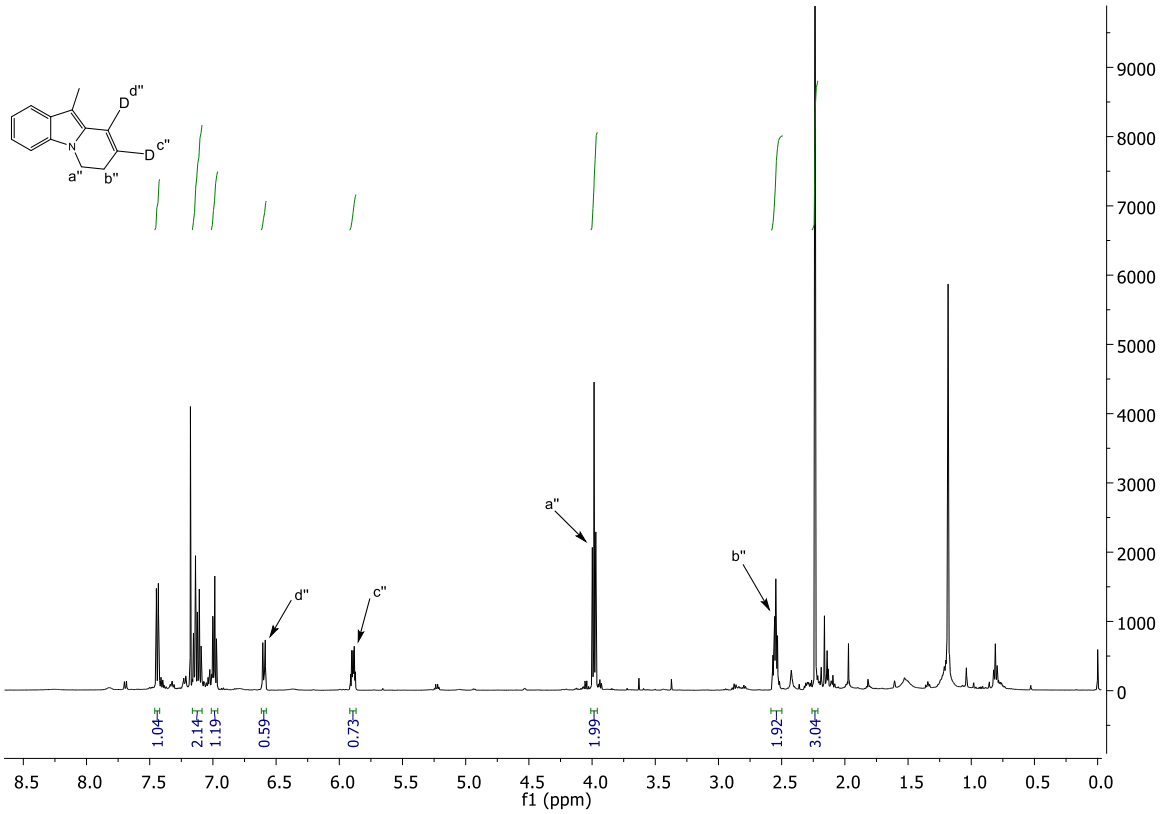
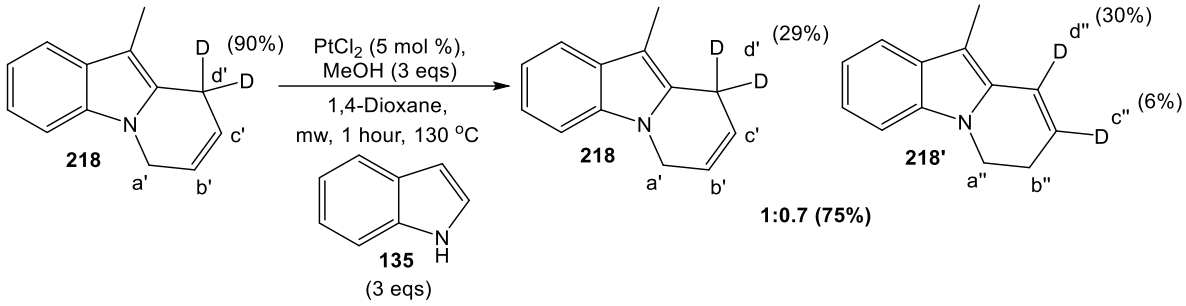


Figure 40. ^{1}H NMR highlighting deuterium incorporation in position *c''* and *d''* of compound **218'** as a result of isomerisation.

To establish the movement of these protons during the intermolecular addition of the external indole, both deuterated cycles **218** and **218'** were subject to platinum conditions with the external indole **135** present.

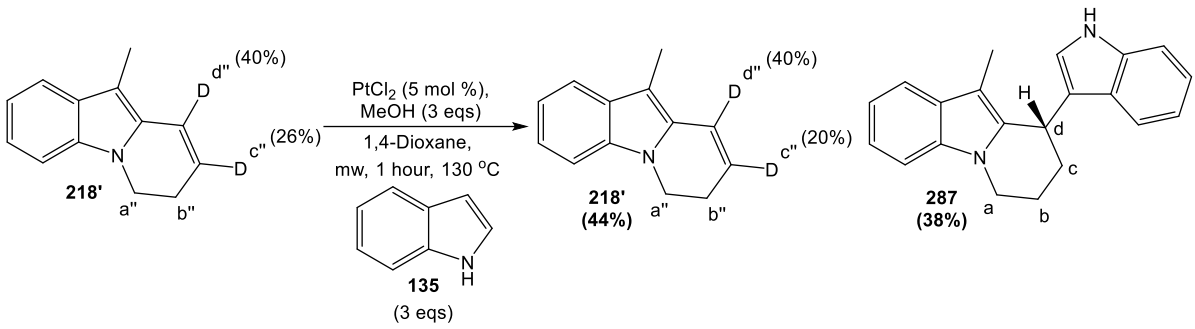
Interestingly, when cycle **218** was subject to these conditions only traces of the desired 2,3'-BIM **287** were identified in the crude ^{1}H NMR and only cycles **218** and **218'** were isolated from the reaction mixture in a 75% yield (**Scheme 124**).



Scheme 124. Platinum-catalysed reaction of cycle **218** with external indole **135**.

Analysis of these two cycles found that they were in a mixture with a ratio of 1:0.7 (**218:218'**) and that cycle **218** had 29% deuterium incorporation at position *d'* and cycle **218'** had deuterium in the expected *c''* and *d''* positions with 6 and 30% respectively. Also, analysis of the crude ^{1}H NMR showed 12% deuterium incorporation at position 3 of the unreacted external indole **135**.

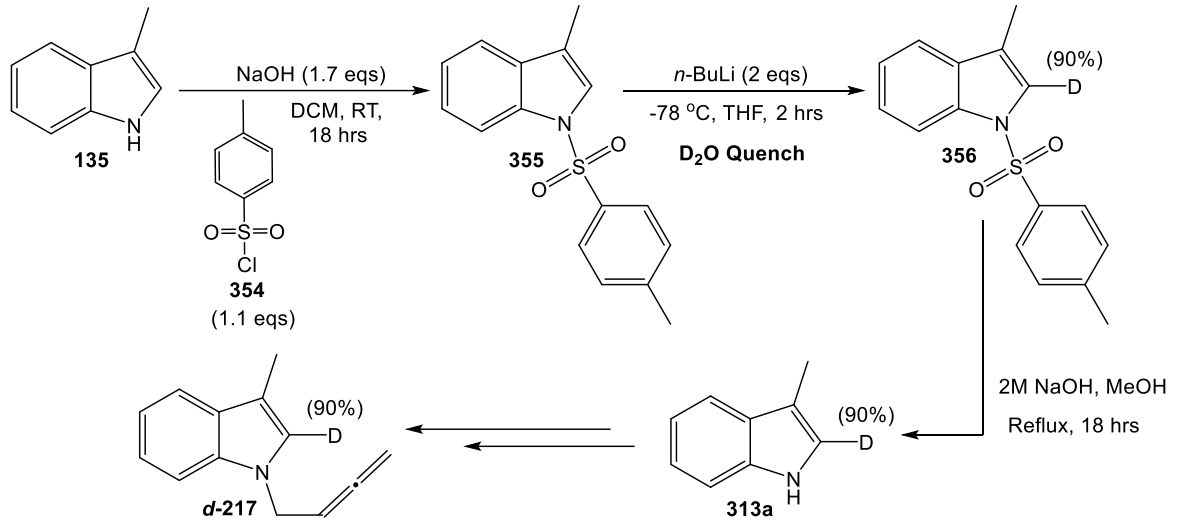
When cycle **218'** obtained from the reaction in **scheme 123** was subject to the platinum conditions with the external indole **114**, cycle **218'** and product **287** were isolated in 44 and 38% yields respectively (**Scheme 125**).



Scheme 125. Platinum-catalysed reaction of cycle **218'** with external indole **135**.

Analysis of cycle **218'** by NMR shows deuterium retention in position *d''* and partial loss in *c''*, whereas analysis of compound **287** by both ^{1}H NMR and HSQC NMR indicates that no deuterium has been incorporated into the final compound, which was surprising because we would expect deuterium to be maintained at least in position *c*. These losses and inefficient deuterium transfers suggest a complex exchange of protons in the reaction media that will be discussed later in more depth.

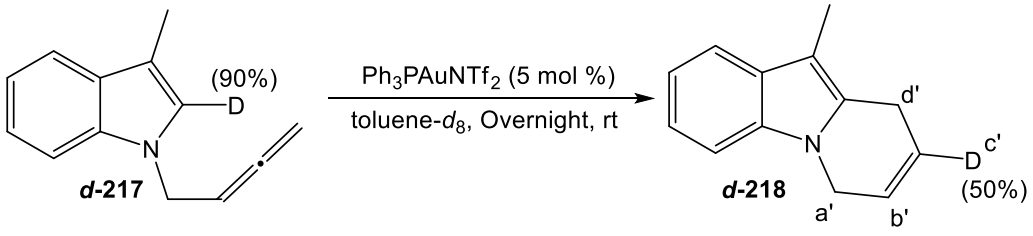
Further reactions were carried out with deuterium incorporated at position 2 of 3-methyl-*N*-(2,3-butadienyl)indole ***d*-217**, this was achieved by following a similar route to the one proposed by Katritzky *et al.*[155] (**Scheme 126**).



Scheme 126. Route for the synthesis of 3-methyl-2-deuterio-1-(2,3-butadien-1-yl) indole **217**.

The first step involves the protection of 3-methyl indole **135** with *p*-toluene sulphonamide **354** using a previously published method.[156] Deuteration of compound **355** was achieved using *n*-BuLi at -78 ^{0}C for 2 hours and quenching the reaction with D_2O, resulting in 90% deuterium incorporation at position 2 of compound **356**. Refluxing with methanol and 2M NaOH gave successful deprotection to compound **313a** with retention of deuterium. The final two steps involve propargylation and Crabbé homologation as previously described (**Schemes 100** and **101**) with compound 3-methyl-2-deuterio-1-(2,3-butadien-1-yl) indole ***d*-217** being obtained with 90% deuterium incorporation.

Using this substrate, we carried out the stepwise formation of the cycles and subsequent intermolecular indole addition. Therefore, 3-methyl-2-deuterio-1-(2,3-butadien-1-yl) indole ***d*-217** was reacted under gold conditions **(Scheme 127)** to give the desired non-conjugated cycle **218**.



Scheme 127. Gold(I)-catalysed cyclisation of 3-methyl-2-deuterio-1-(2,3-butadien-1-yl) indole ***d*-217.**

Analysis of the crude ^{1}H NMR integrals showed the incorporation of 50% deuterium at position *c'* (**Figure 41**), which suggests that the proton from position 2 of the indolyl allene **217** is directly involved in the cyclisation step by protonation of the central carbon of the allene.

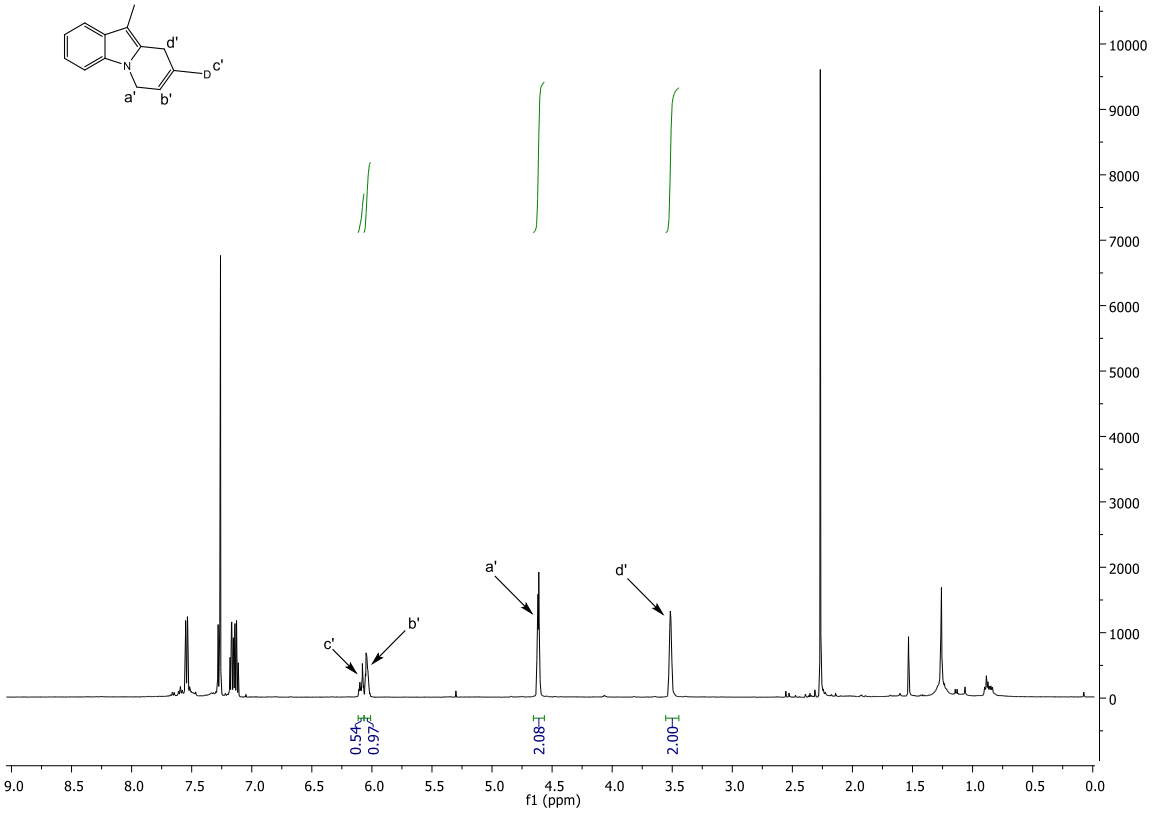
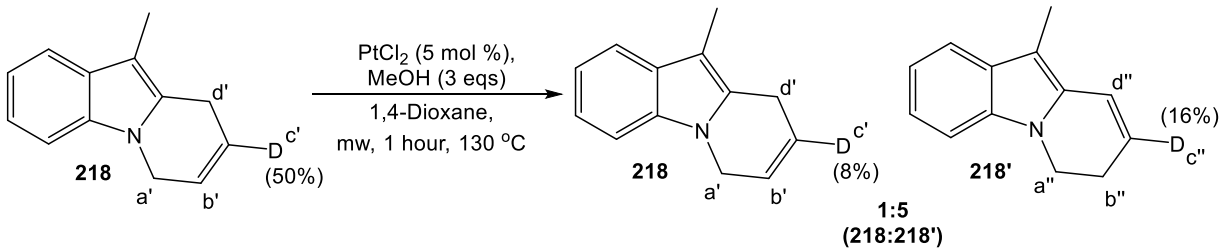


Figure 41. ^{1}H NMR showing the deuterium incorporation at position *c'* of compound *d*-**218**.

Isomerisation of deuterated cycle **218** was carried out under platinum conditions with no external indole, however 100% conversion was not achieved and cycles **218** and **218'** were obtained in a ratio of 1:5 (**218:218'**) (**Scheme 128**).

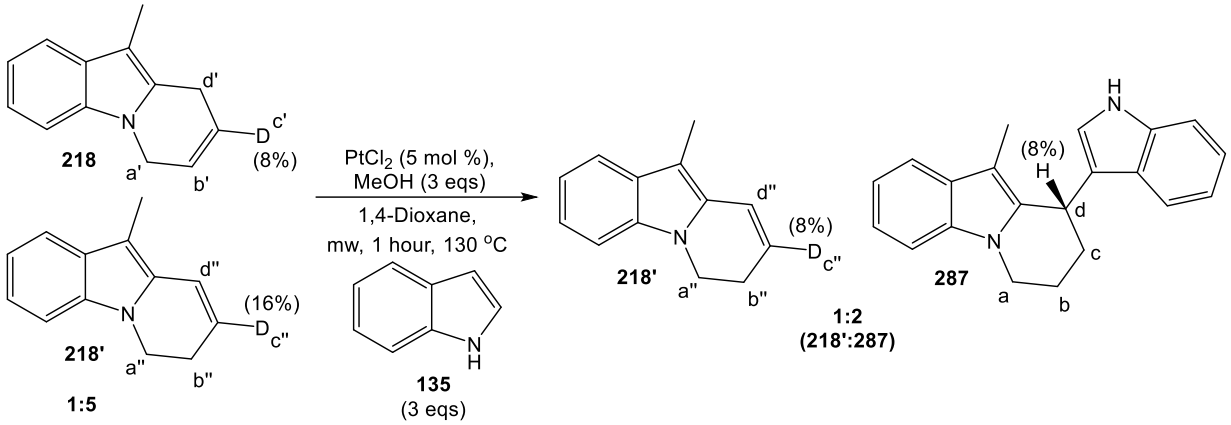


Scheme 128. Platinum catalysed isomerisation of cycle **218** to **218'**.

The crude ^{1}H NMR shows deuterium incorporation at position *c* of both cycles, with cycle **218** containing 8% and cycle **218'** containing 16%.

A loss of deuterium is observed; however we do not observe deuterium incorporation in position *d''* of cycle **218'** which would suggest that isomerisation from **218** to **218'** is not directly affected by the proton at position c'.

Finally, these two deuterated isomers were reacted with external indole **135** using standard platinum conditions, this resulted in the formation of the 2,3'-BIM **287** and cycle **218'** was retained (**Scheme 129**).



Scheme 129. Platinum-catalysed reaction of cycles **218** and **218'** with indole **135**.

Analysis of the crude ^{1}H NMR showed a ratio of 1:2 (**218':287**) and 8% deuterium incorporation was observed at position *c''* of **218'** and at position *d* of compound **287**.

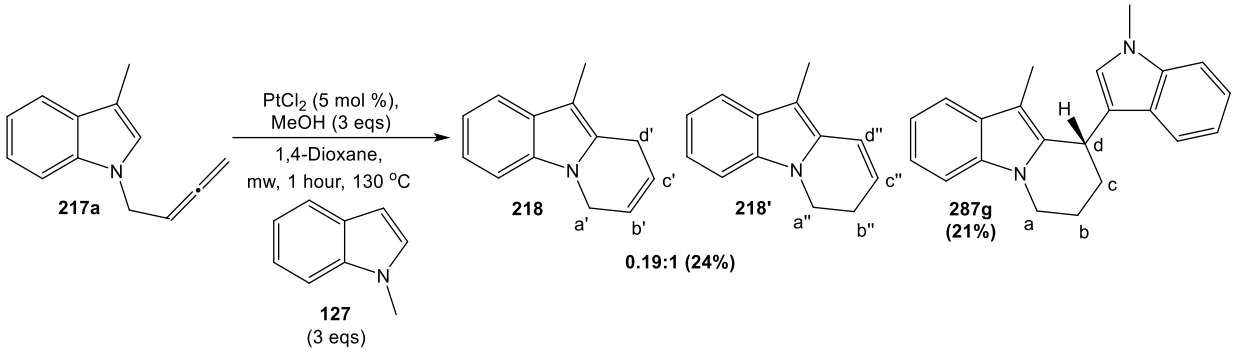
From these reactions, we can confidently propose that the reaction proceeds *via* the intramolecular addition with isomerisation followed by the intermolecular addition of the external indole. We have highlighted that the absence of methanol slows/inhibits the isomerisation between cycle **218** and **218'** which we have explored in other reactions. To further support these findings a range of different deuterium labelling experiments were carried out.

2.3.2. Deuterium labelling experiments

To fully understand the mechanism of the reaction, we must understand the movement of the protons during the reaction, therefore deuterium was incorporated into various positions of the starting allene, the external indole and in the additives of the reaction. This allowed us to explore the reaction under a variety of conditions.

Firstly, a control reaction of 3-methyl-*N*-(2,3-butadienyl)indole **217a** with *N*-methyl indole **127** was carried out with no deuterium present under standard platinum conditions (**Scheme 130**).

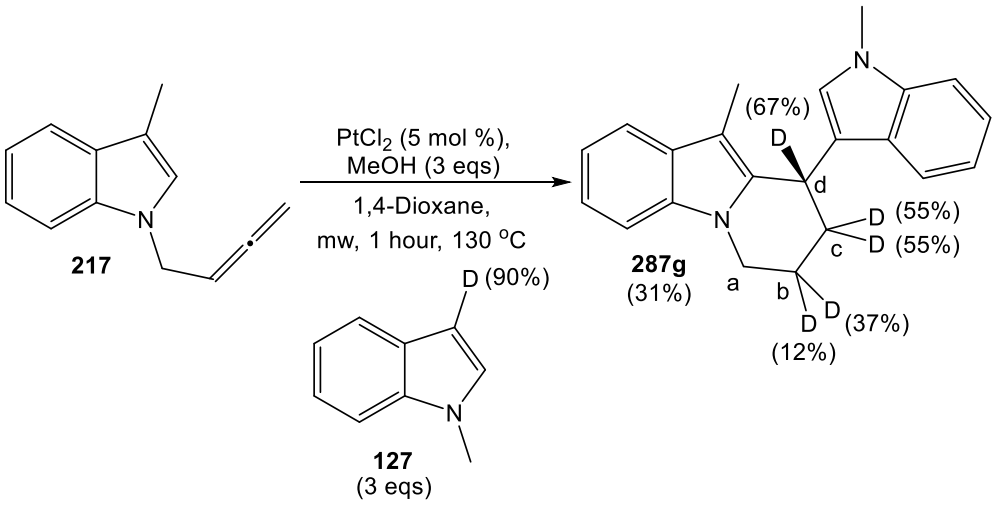
The two 6-endo cycles **218** and **218'** in a 24% yield with a ratio of 0.19:1 (**218:218'**) and 21% of compound **287g** were both isolated (similar result obtained for this reaction seen in table 21, entry 7).



Scheme 130. Control reaction for comparison with deuterium incorporation reactions.

This control reaction was carried out to ensure consistent results and to compare the deuterated products with the non-deuterated products and to establish where and how much deuterium is incorporated. The first set of reactions was carried out with deuterium incorporated into position 3 of the external N-methyl indole **127**. Three reactions were carried out to explore the effect of the methanol on the reaction with either normal methanol, deuterated methanol or no methanol being present.

Scheme 131 shows the reaction of 3-methyl-*N*-(2,3-butadienyl)indole **217** with the deuterated *N*-methyl indole **127** under the standard platinum conditions. Interestingly, this reaction gave traces of the 6-endo cycles **218/218'** which could not be isolated, however 2,3'-BIM **287g** was isolated in 31% yield and the deuterium incorporation pattern was studied.



Scheme 131. Platinum-catalysed reaction with deuterated *N*-methyl indole **127a** and methanol.

Analysis of the ^{1}H NMR of the purified **287g** in **figure 42** shows deuterium incorporation in positions *b* to *d*. This was established by comparing the spectrum of the deuterated product with the non-deuterated example. This involved analysing the disappearance of signals and change in multiplicity at those positions, by measuring the integrals in relation to the signal of the proton at 6.25 ppm corresponding to one proton at C2 of the *N*-methyl indole.

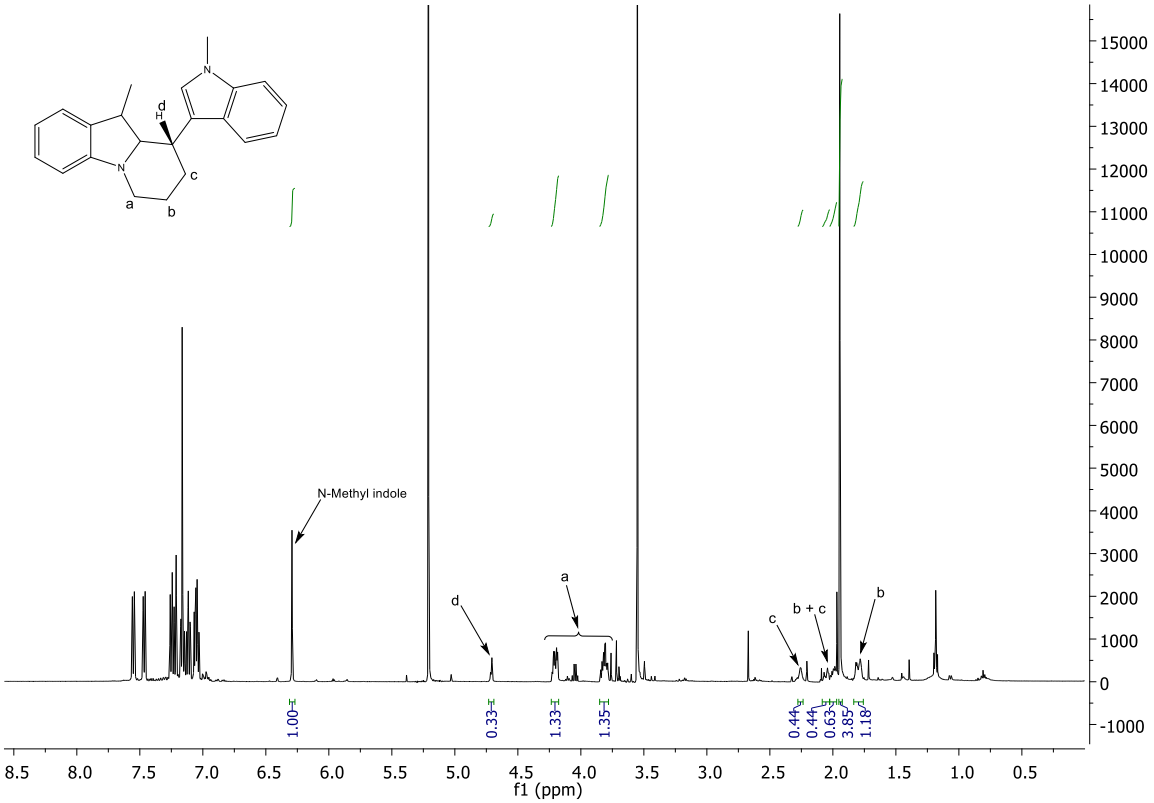


Figure 42. ^{1}H NMR spectra highlighting deuterium incorporation for compound **287g** obtained from reaction in **scheme 132**.

From this we know that position *a* is unaffected in the reaction, whereas positions *b* to *d* have significantly lower integrals, which supports deuterium incorporation. Interestingly, both diastereotopic positions of methylenes *b* and *c* showed some degree of deuterium incorporation. These are also supported by analysis of the HSQC (**Figure 43**) where we observe a mixture of CH_2 (blue spots) and CHD (red spots, shifted to the top right of the blue signals due to the kinetic isotope effect), the intensity of these two signals are in proportion to the calculated % D incorporation. It was surprising to detect the highest degree of deuteration in position *d* as this would not fit with any deuteration pattern predicted following the proposed mechanism in **scheme 115**.

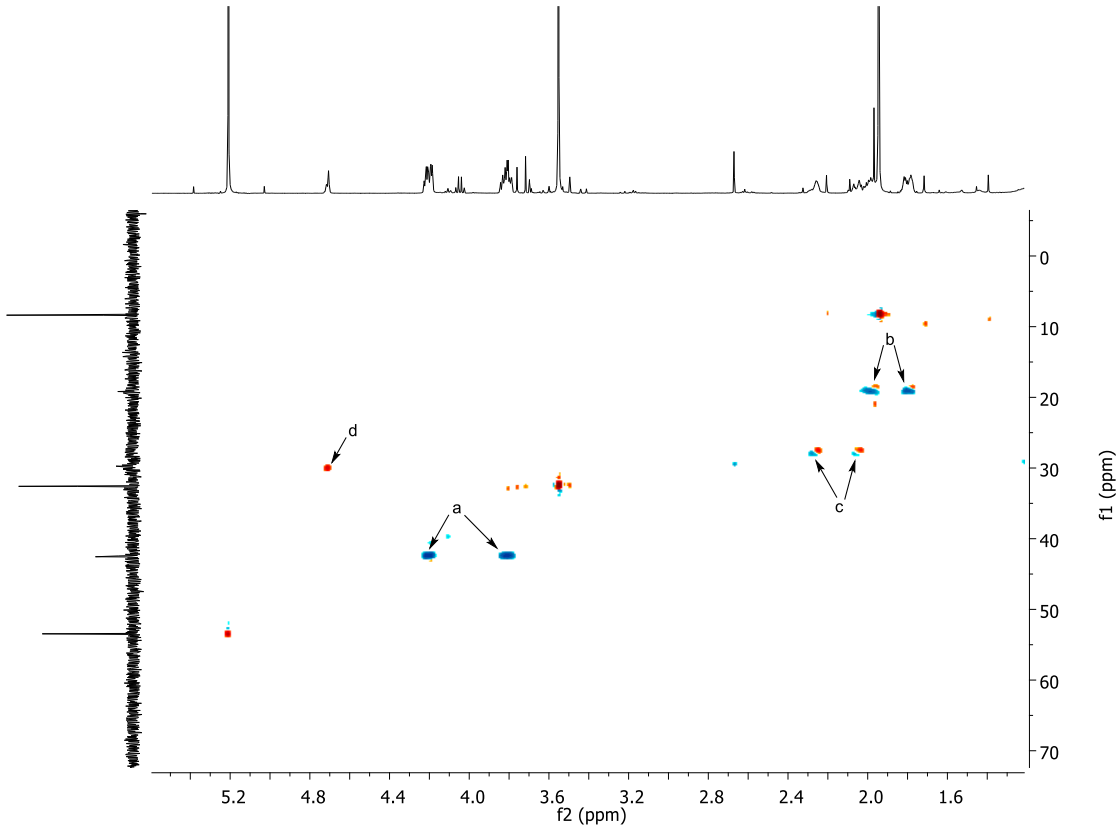


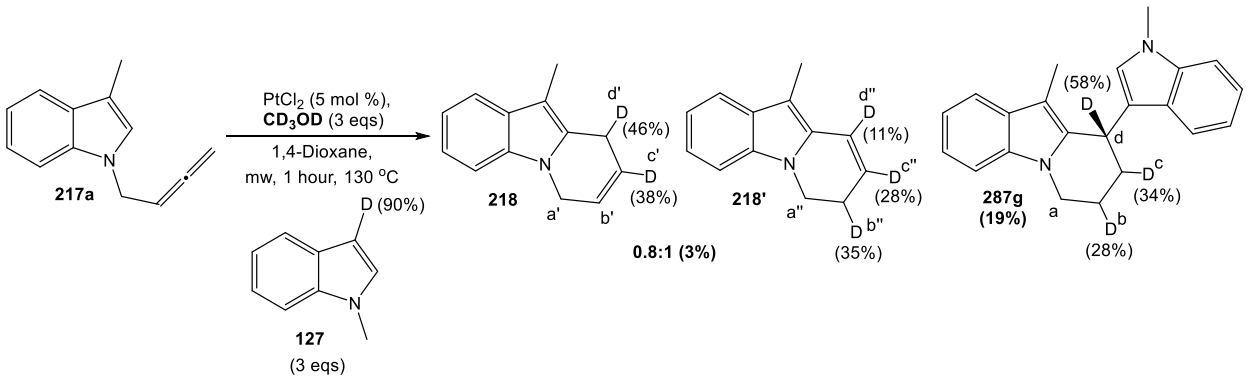
Figure 43. HSQC NMR for compound **287g**, showing clearly the deuterium incorporation at positons *b* and *c*.

The incorporation of deuterium can be represented as a % from the integral values of these positions and are shown in **table 24**. The deuterium incorporation of position 3 of the recovered external indole after the reaction was investigated and highlights that 28% of deuterium has been lost during the reaction (90% D in position 3 before reaction, 62% after).

Position	Integral	Deuterium incorporation (%)
b	0.63 and 0.88	37 and 12
c	0.44 and 0.44	55 and 55
d	0.33	67
C3 of *N*-Methyl indole	0.38	62

Table 24. Percentage of deuterium incorporated into positions *b* to *d* of compound **287g** and in position 3 of external indole **127a**.

Scheme 132 shows the second reaction with deuterated *N*-methyl indole **127a** as the external indole, but this time deuterated methanol was used in the reaction. Despite the low yield (3%), cycles **218/218'** were successfully isolated allowing for identification of deuterium incorporation. Compound **287g** was also isolated with a yield of 19% for which deuterium incorporation was also identified.



Scheme 132. Platinum-catalysed reaction with deuterated *N*-methyl indole **127** and deuterated methanol.

Cycles **218/218'** were observed as mixture with a ratio of 0.8:1 (**218:218'**) and analysis of the crude ^{1}H NMR for these two cycles identifies deuterium incorporation in positions *c'* and *d'* for cycle **218** (**Figure 44**) and in positions *b''*, *c''* and *d''* for cycle **218'** (**Figure 44**). The incorporation of deuterium for both cycles **218** and **218'** can be represented as a % from the integral values of these positions and are shown in **table 25**.

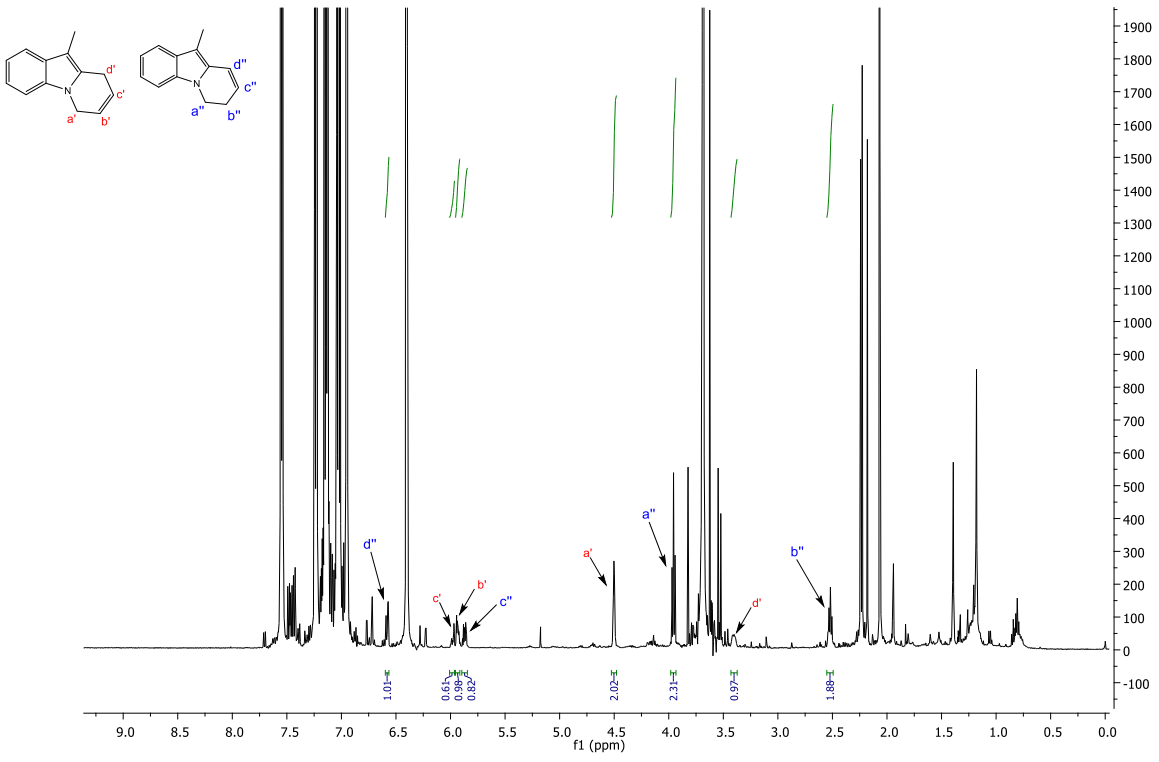


Figure 44. Crude ^{1}H NMR highlighting the deuterium incorporation for cycles **218** and **218'**.

The incorporation of deuterium for both cycles **218** and **218'** can be represented as a % from the integral values of these positions and are shown in **table 25**.

Proton	Integral	Deuterium incorporation (%)
Cycle **218**		
a'	2	0
b'	1	0
c'	0.62	38
d'	1.04	46
Cycle **218'**		
a''	2	0
b''	1.65	35
c''	0.72	28
d''	0.89	11

Table 25. Percentage of deuterium incorporated in cycles **218** and **218'**.

Isolation of product **287g** also allowed us to determine the deuterium incorporation when deuterated methanol was used. **Figure 45** shows the ^{1}H NMR, where deuterium is incorporated into positions *b*, *c* and *d*. This deuterium incorporation was also supported by analysis of the HSQC (**Figure 46**) and the values for deuterium incorporation in these positions of compound **287g** can be seen in **table 26**. Also highlighted is the loss of deuterium from position 3 of the external N-methyl indole **127a** which started with 90% D in position 3 and after reaction contained 55% giving a deuterium loss of 35%.

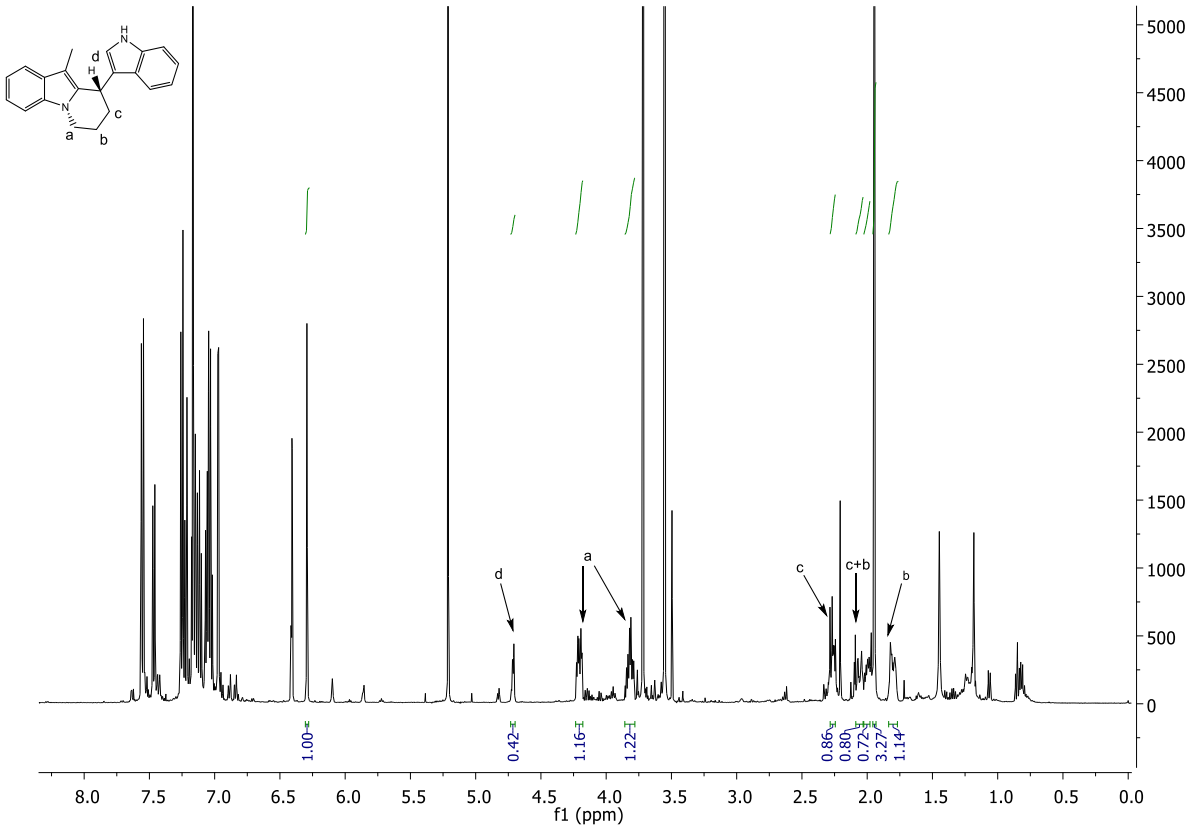


Figure 45. ^{1}H NMR for compound **287g**, highlighting the deuterium incorporation.

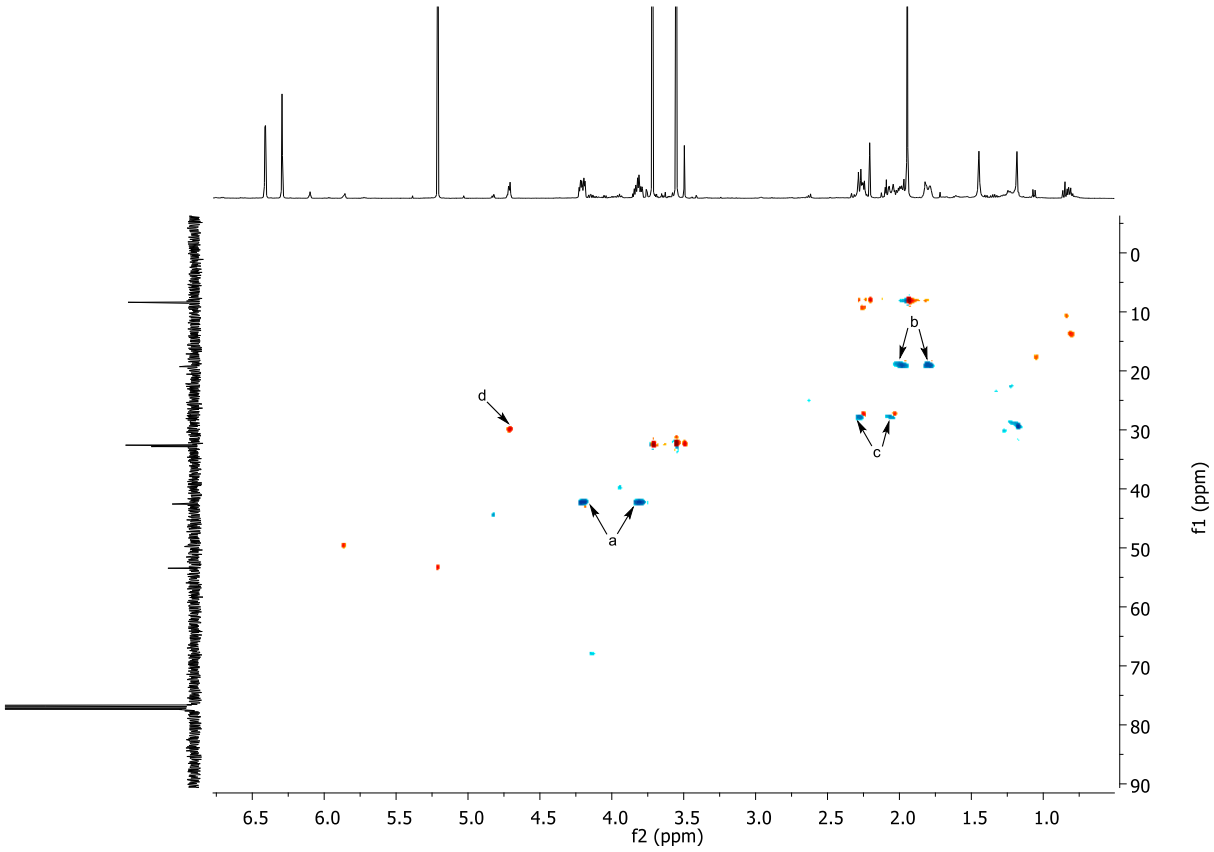


Figure 46. HSQC NMR for compound **287g**, highlighting the deuterium incorporation.

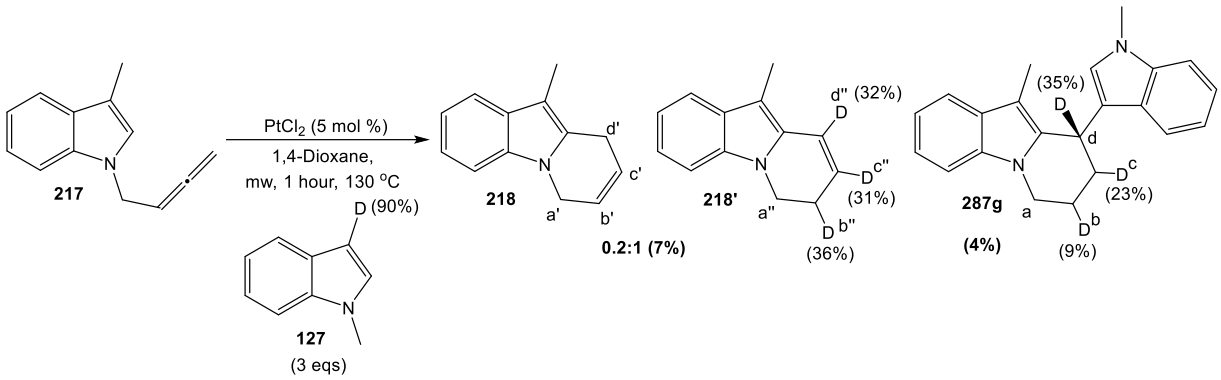
Proton	Integral	Deuterium incorporation (%)
b	1.14 and 0.72	0 and 28[a]
c	0.86 and 0.80	14 and 20[a]
d	0.42	58
3 – N-Methyl indole	0.45	55

[a] Integrals for protons b and c were difficult to measure, therefore deuterium incorporation is approximate.

Table 26. Percentage of deuterium incorporated in compound **287g** and in position 3 of external N-methyl indole **127a**.

The final example with deuterated external *N*-methyl indole **127** was carried out with platinum conditions but no methanol present (**Scheme 133**). The low isolated yield obtained for both 6-endo cycles and the 2,3'-BIM could be partly due to the poor separation *via* column chromatography, but also it could be due to the presence of deuterium or the absence of the methanol. We observe lower yields in several reactions where deuterated compounds are present, this could be a kinetic isotope effect, where the presence of the deuterium analogue may slow down the reaction which would in turn give lower yields when the same reaction time is used. The absence of methanol could lower the yields because of its important role as a proton shuttle, which will be discussed in more detail within the mechanistic study section.

Cycles **218** and **218'** were isolated with a yield of 7%, however in a ratio of 0.2:1 (**218:218'**) which means that only deuterium incorporation in cycle **218'** could be identified by ^{1}H NMR. Compound **287g** was isolated with a yield of 4% and deuterium incorporation was identified.



Scheme 133. Platinum catalysed reaction with deuterated N-methyl indole **127a** and deuterated methanol.

Analysis of the ^{1}H NMR for cycle **218'** shows deuterium incorporation in positions *b''*, *c''* and *d''*, however the % incorporation is much lower than that observed for the previous reactions (**Table 27**).

Proton	Integral	Deuterium incorporation (%)
a''	2	0
b''	1.64	36
c''	0.69	31
d''	0.68	32

Table 27. Percentage of deuterium incorporated in cycle **218'** when no methanol is present.

The ^{1}H NMR for compound **287g** shows that deuterium is incorporated into the same positions as observed before, *b*, *c* and *d*. However, the % of deuterium incorporation is also lower than previously observed (**Table 28**), this has also been supported by the appearance of both CH_2s and CHD in the HSQC.

Table 28 also shows the deuterium incorporation in the external *N*-Methyl indole **127** after the reaction, started with 90% D incorporation and after reaction only 27% D incorporation resulting in a deuterium loss of 63%.

Proton	Integral	Deuterium incorporation (%)
b	1.31 and 0.91	0 and 9
c	1.34 and 0.77	0 and 23
d	0.65	35
3-*N*-Methyl indole	0.73	27

Table 28. Percentage of deuterium incorporated in compound **287g** when no methanol is present.

The above reactions have allowed us to interpret the deuterium incorporation pattern from the use of deuterium in the external indole, it has shown that deuterium can be incorporated into positions *b*, *c* and *d* for all three products (**Figure 47**). Deuterium incorporation in positions *b* and c will be explained later in our proposed mechanism, however the unexpectedly high incorporation of deuterium into position *d* of compound **287g** was difficult to explain by the proposed mechanism at this stage.

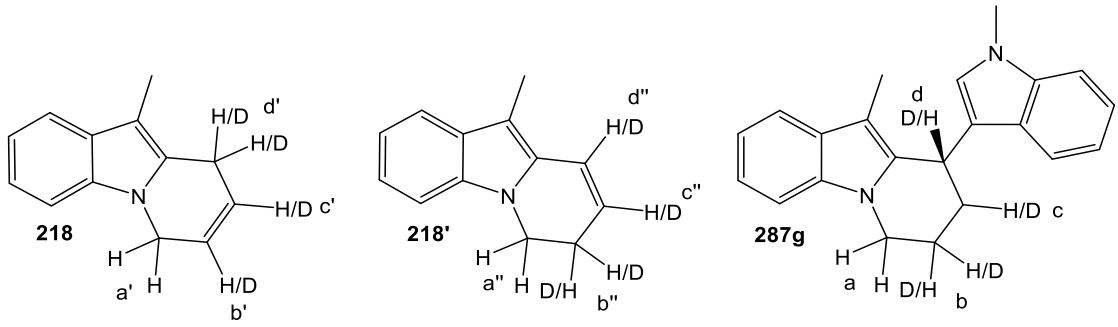


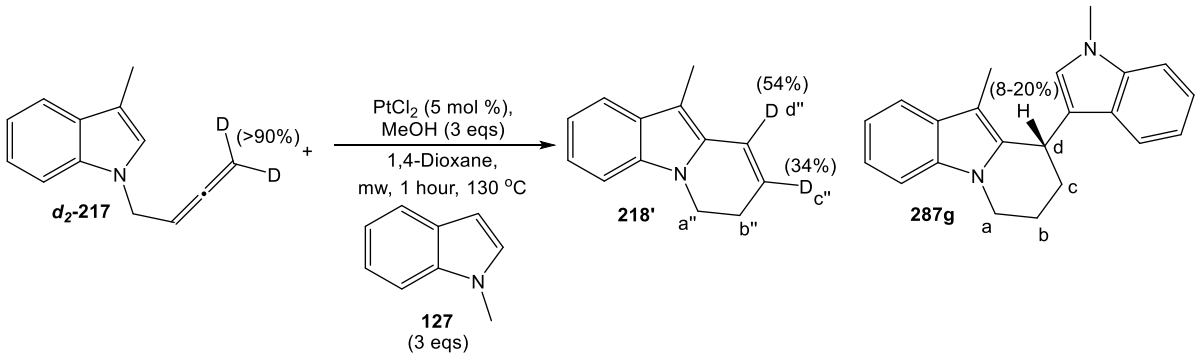
Figure 47. Shows the deuterium pattern in all three compounds **218**, **218'** and **287g**.

We also notice that deuterium incorporation varies when different sources of methanol are present. Interestingly when no methanol is present, we observe low deuterium incorporation and low yields of both the cycles **218**/**218'** and compound **287g**. This supports further our theory that methanol aids the isomerization and subsequent intermolecular addition of the external indole.

The loss of deuterium incorporation from position 3 of the external *N*-methyl indole **127a** suggests that the deuterium is being washed into the reaction mixture, this would explain the difference in deuterium incorporation and therefore means that we cannot make a proposal for the mechanism based on these reactions alone.

Therefore, further deuterium reactions were carried out with deuterated 3-methyl-*N*-(2,3-butadienyl)indole ***d*$_2$-217** under platinum conditions with either non-deuterated *N*-methylindole **127** or deuterated *N*-methyl indole **127**. These were also investigated with variations in the methanol, with either normal methanol, deuterated methanol or no methanol being present.

Firstly, 3-methyl-*N*-(2,3-butadienyl)indole ***d*$_2$-217** was reacted with *N*-methyl indole **127** using standard platinum and methanol conditions (**Scheme 134**) with formation of the conjugated 6-endo cycle **218'** and the 2,3'-BIM **287g**.



Scheme 134. Platinum-catalysed reaction of 3-methyl-*N*-(2,3-butadienyl) indole **217** with N-methyl indole **127** and methanol present.

The crude ^{1}H NMR for this reaction indicates a 1:1 ratio of **218'**:**287g**, however separation of these two compounds from excess of indole proved difficult, therefore yields were determined from analysis of ^{1}H NMRs of their mixed fractions, giving 12% for **218'** and 31% for **287g**. Further analysis of the crude ^{1}H NMR indicates deuterium incorporation of around 20% for compound **287g** in position *d*, however, after column chromatography fractions containing compound **287g** showed position d to only contain around 8% deuterium (**Figure 48**). This loss of deuterium could be due to proton exchange at this position within the mildly acidic column medium, this will be discussed in further detail later.

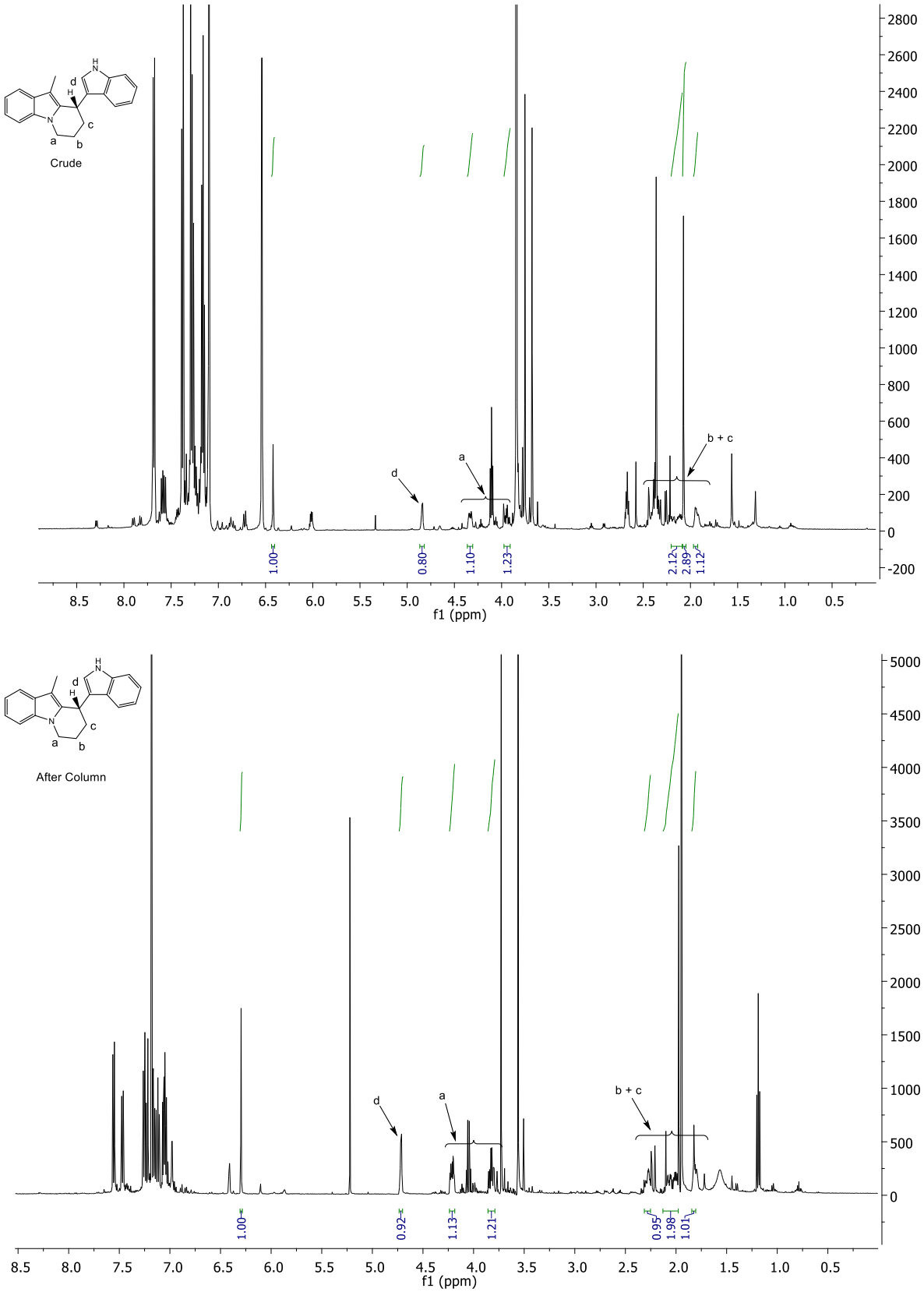
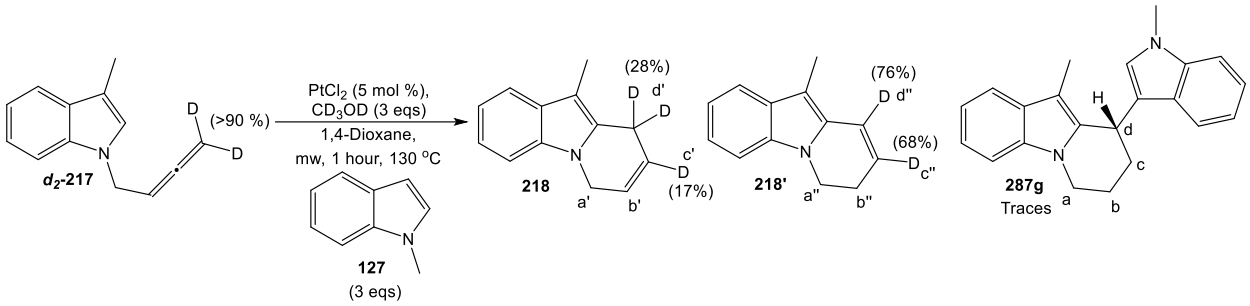


Figure 48. ^{1}H NMRs showing the difference in deuterium incorporation at position d of compound **287g** before and after column chromatography.

Deuterium analysis for cycle **218'** could only be carried out with the crude ^{1}H NMR, where deuterium incorporation of 34 and 54% is observed in positions *c''* and *d''* respectively. Another interesting finding for these reactions is that deuterium can be incorporated into position 3 of the external *N*-methyl indole **127**, this occurs through proton exchange with the deuterium present in the reaction mixture. For this particular reaction, the deuterium incorporation gain analysed for the external indole identified from the crude ^{1}H NMR is 24%.

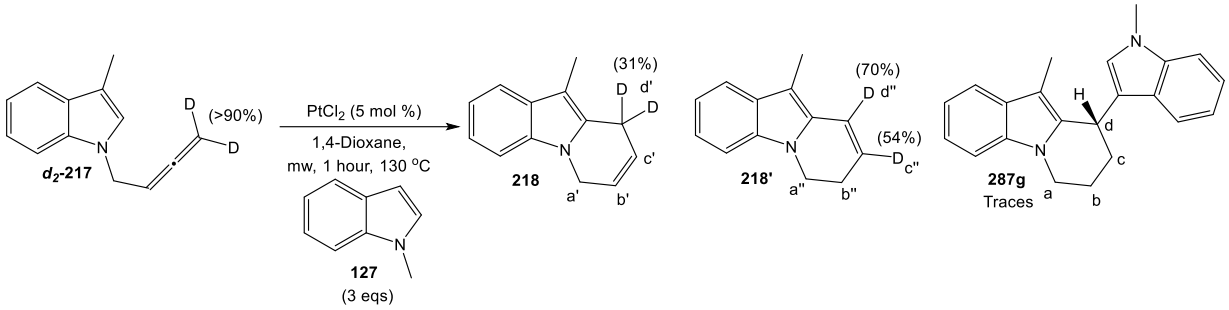
Next, 3-methyl-*N*-(2,3-butadienyl)indole ***d*$_2$-217** was reacted with *N*-methyl indole **127** under platinum conditions, but with deuterated methanol present to observe any changes in deuterium incorporation (**Scheme 135**).



Scheme 135. Platinum-catalysed reaction of 3-methyl-*N*-(2,3-butadienyl) indole **217** with *N*-methyl indole **127** and deuterated methanol.

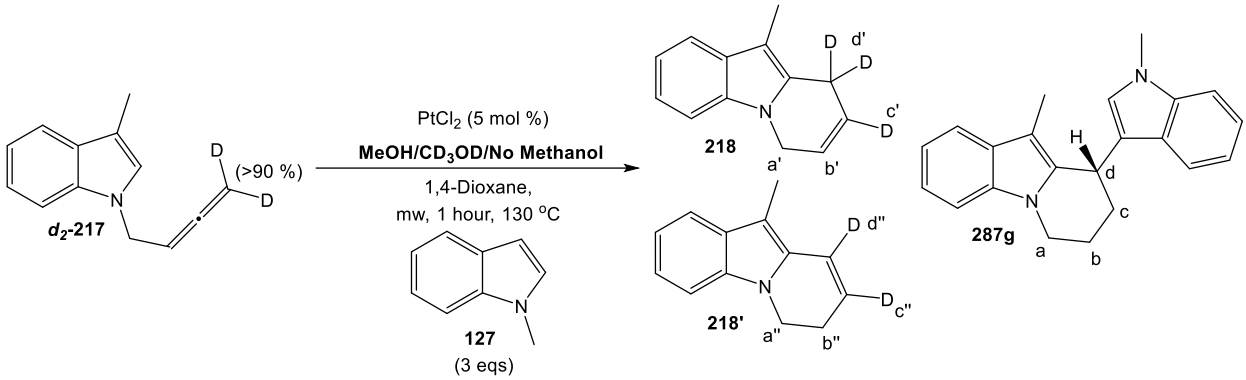
From the crude ^{1}H NMR it is clear to see that only traces of the 2,3-BIM **287g** were present and the two cycles **218** and **218'** were formed however in a ratio of 1.1:1 (**218:218'**). This poor conversion of **218** to **218'** and therefore low yield of compound **287g** can be put down to the presence of deuterated methanol, which could slow/inhibit this isomerisation step, as will be discussed in further detail later. Further analysis of the crude ^{1}H NMR identified that deuterium is incorporated into both cycles **218** and **218'**, with 17 and 28% in positions *c'* and *d'* for cycle **218** and 68 and 76% for positions *c''* and *d''* for cycle **218'**. And the external *N*-methyl indole **127** has 42% deuterium incorporation gain at position 3.

The third reaction involving 3-methyl-*N*-(2,3-butadienyl)indole ***d*$_2$-217** and *N*-methyl indole **127** was carried out in the absence of methanol (**Scheme 136**), this gave similar results to those seen when deuterated methanol was present.



Scheme 136. Platinum-catalysed reaction of 3-methyl-*N*-(2,3-butadienyl) indole **217** with *N*-methyl indole **127** with no methanol present.

The crude ^{1}H NMR highlights that only traces of compound **287g** were present and cycles **218** and **218'** were formed in a ratio of 2:1 (**218:218'**), the absence of the methanol is likely to be the cause of this poor conversion and subsequent formation of compound **287g**. Analysis identified that 31% deuterium is incorporated into cycle **218** at position *d'* and 54 and 70% incorporation occurs at positions *c''* and *d''* for cycle **218'**. The external *N*-methyl indole **127** is observed to have 20% deuterium incorporation gain at position 3, which is consistent with the amount of available deuterium in the reaction mixture. **Table 29** summarises the deuterium incorporations for the reactions of deuterated 3-methyl-*N*-(2,3-butadienyl)indole ***d*$_2$-217** with the non-deuterated *N*-methyl indole **127a** with various sources of methanol (**Scheme 137**).

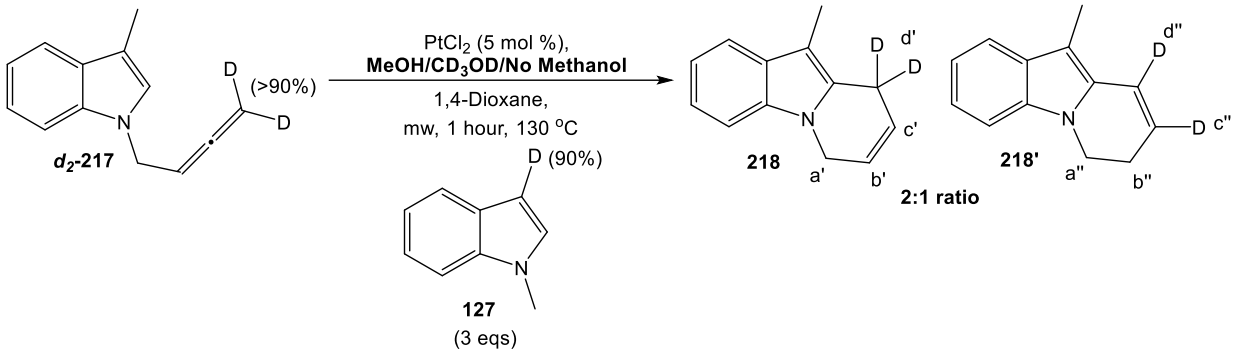


Scheme 137. Platinum-catalysed reaction of 3-methyl-*N*-(2,3-butadienyl) indole ***d*₂-217** with *N*-methyl indole **127a** with different methanol sources.

Source	**218** (D%)	**218'** (D%)	**287g** (D%)	**127** D% gain
MeOH	-	b'' = 0	b = 0	24
	-	c'' = 34	c = 0	
	-	d'' = 54	d = 8-20	
CD_3OD	b' = 0	b'' = 0	-	42
	c' = 17	c'' = 68	-	
	d' = 28	d'' = 76	-	
No MeOH	b' = 0	b'' = 0	-	20
	c' = 0	c'' = 54	-	
	d' = 31	d'' = 70	-	

Table 29. Summary of Platinum-catalysed reaction of 3-methyl-*N*-(2,3-butadienyl) indole ***d*₂-217** with N-methyl indole **127** with different methanol sources.

As mentioned previously, reactions with deuterated 3-methyl-*N*-(2,3-butadienyl)indole ***d*₂-217** were also carried out in the presence of deuterated *N*-methyl indole **127** and different methanol sources (**Scheme 138**). As analysed from their crude ^{1}H NMRs all of these reactions were unsuccessful in forming the 2,3'-BIM **287g** and only cycles **218** and **218'** were observed in a 2:1 (**218:218'**) ratio.



Scheme 138. Pt catalysed reaction of deuterated 3-methyl-N-(2,3-butadienyl) indole **217** with deuterated N-methyl indole **127** with different sources of methanol.

Deuterium incorporation was analysed using the crude ^{1}H NMRs for each reaction, for the examples with CD_3OD and no methanol, we observe deuterium incorporation at positions *c'* and *d'* for cycle **218** whereas with normal methanol, we only observe incorporation at position *d'*. **Table 30** shows the deuterium incorporations for cycle **218** at positions *c'* and *d'*, with similar values achieved for each example.

Source of methanol	Position	Deuterium incorporation (%)
MeOH	c'	0
	d'	48
CD_3OD	c'	44
	d'	52
No MeOH	c'	25
	d'	55

Table 30. Deuterium incorporation values at positions *c'* and *d'* of cycle **218**.

The deuterium incorporation pattern for cycle **218'** is similar for each example, with deuterium being present in both position *c''* and *d''* (**Table 31**).

Source of methanol	Position	Deuterium incorporation (%)
MeOH	b''	0
	c''	65
	d''	69
CD_3OD	b''	10
	c''	74
	d''	77
No MeOH	b''	15
	c''	66
	d''	68

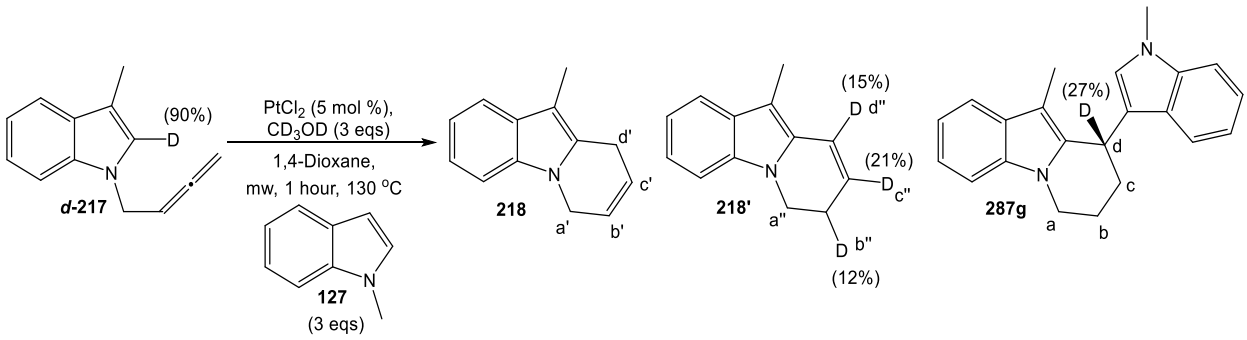
Table 31. Deuterium incorporation values at positions *c''* and *d''* of cycle **218'**.

Comparison of the reaction with non-deuterated external *N*-methyl indole **127** with the reactions with the deuterated *N*-methyl indole **127**, shows that the external indole only influences the deuterium incorporation of cycle **218** as a higher % of deuterium is incorporated into position *d'* for these reactions. The deuterium incorporation of the deuterated external indole **127** can be monitored for these reactions, the starting indole contained 90% D in position 3 for all the examples and **table 32** shows the deuterium incorporation values after reaction.

	Deuterium loss (%)
MeOH	47
CD_3OD	20
No MeOH	31

Table 32. Deuterium incorporation at position 3 of deuterated *N*-methyl indole **127** after reaction.

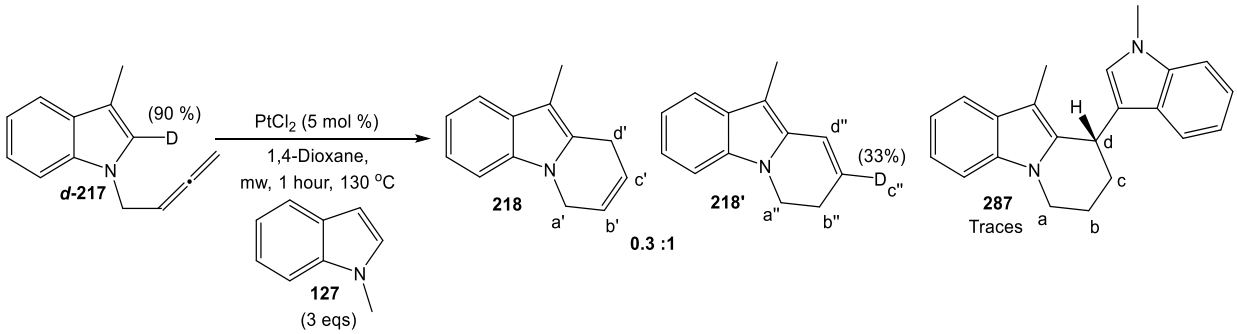
Finally, the deuterated indolyl allene ***d*-217** was used in the platinum reaction with external *N*-methyl indole **127**, these reactions were carried out with either methanol, deuterated methanol or no methanol present. The reaction carried out with methanol resulted in a complex mixture with no identification of the desired products. However, the reactions with deuterated and no methanol gave similar results with the formation of both cycles **218/218'** and 2,3'-BIM **287g**. Analysis of the crude ^{1}H NMR shows the ratio of products for the deuterated reaction to be 0.3:1:0.4 (**218:218':287g**) (**Scheme 139**).



Scheme 139. Platinum-catalysed reaction of 3-methyl-2-deuterio-1-(2,3-butadien-1-yl) indole ***d*-217** with indole **127** with methanol present.

The deuterium incorporation for these compounds were difficult to obtain, however, it was established that cycle **218'** has deuterium incorporation at positions *b''*, *c''* and *d''* in 12, 21 and 15% respectively. The 2,3'-BIM **287g** has 27% deuterium incorporation at position *d*.

The reaction with no methanol present produced both cycles **218** and **218'** in a ratio of 0.3:1 (**218:218'**) as well as traces of the 2,3'-BIM **287g** (**Scheme 140**). Analysis of the crude ^{1}H NMR for deuterium incorporation proved difficult, however 33% deuterium was found to be incorporated into position *c''* of compound **218'**.



Scheme 140. Platinum-catalysed reaction of 3-methyl-2-deuterio-1-(2,3-butadien-1-yl) indole ***d*-217** with indole **127** with no methanol present.

Table 33 shows a summary of deuterium incorporation of products **218'** and **287g** after reaction of 3-methyl-2-deuterio-1-(2,3-butadien-1-yl) indole ***d*-217** with external indole **127** with deuterated methanol and no methanol, as well as the deuterium gain at position 3 of the external indole **127**.

	218' (%)	**287g** (%)	**127** deuterium gain (%)
CD_3OD	b'' = 12	b = 0	32
	c'' = 21	c = 0	
	d'' = 15	d = 27	
No MeOH	b'' = 0	-	13
	c'' = 33	-	
	d'' = 0	-	

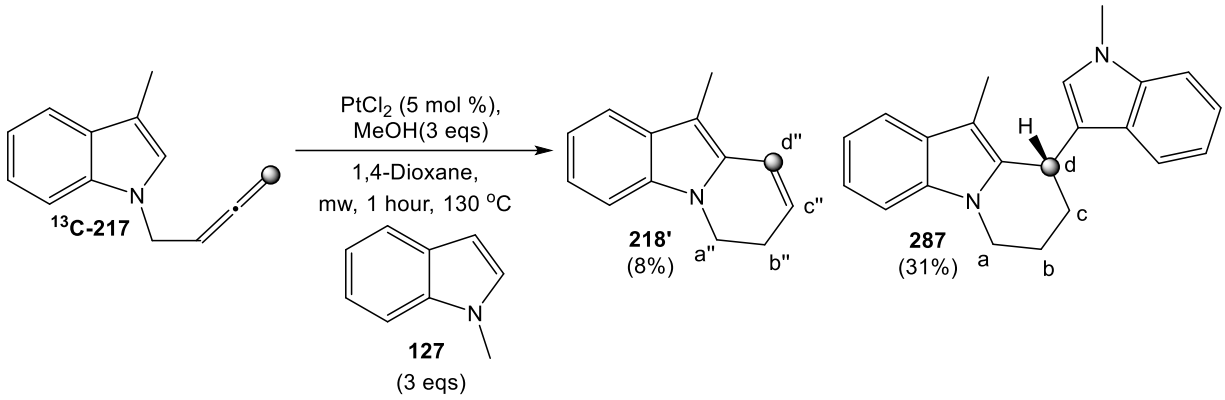
Table 33. Summary of deuterium incorporation in compounds **218'**, **287g** and **127** after reaction shown in **scheme 141**.

Overall, these deuterium experiments have shown us that the formation of the non-conjugated cycle **218** occurs first with deuterium incorporation observed at position *d'*, the subsequent isomerisation from cycle **218** to **218'** involves the transfer of proton/deuterium to position *c'*. However, when isomerisation from cycle **218** to **218'** occurs with non-deuterated *N*-methylindole **127**, the deuterium incorporation at position *c'* to *c''* remains which suggests this proton is not directly involved in the isomerisation step. It has also highlighted the importance of methanol in the reaction to aid the successful isomerisation of cycles **218** to **218'**, because the presence of CD_3OD or absence of MeOH slows down/hinders this isomerisation step. Poor isomerisation therefore disfavours the intermolecular addition of the external indole, resulting in lower yields of the 2,3'-BIM **287**. Before we propose an overall mechanism for the reaction, there are several other mechanistic studies which were carried out, including some ^{13}C labelled experiments and investigation into the exchange of indoles in the final product.

2.3.3. ^{13}C labelled experiments

Several reactions were carried out with ^{13}C-labelled 3-methyl-*N*-(2,3-butadienyl)indole **217**, with the ^{13}C in the terminal carbon of the allene, achieved *via* Crabbé homologation with ^{13}C-paraformaldehyde (99% ^{13}C). This was to allow us to further understand the mechanism of the reaction, but also to investigate the higher than expected deuterium incorporation at position *d* of the 2,3'-BIM. The differences in deuterium incorporation at this position before and after column chromatography suggest that there may be proton exchange *via* an out-of-cycle equilibrium either acid or platinum catalysed.

An initial control reaction was carried out with ^{13}C-labelled 3-methyl-*N*-(2,3-butadienyl)indole **217** and *N*-methyl indole **127** under the standard platinum conditions (**Scheme 141**). The ^{1}H NMR obtained for the 2,3'-BIM **287** confirms presence of ^{13}C at position *d* by observed splitting of the signal into a doublet with a $J_{^{13}C-^{1}H}$ of 129.3 Hz (**Figure 49**).



Scheme 141. Platinum-catalysed control reaction of ^{13}C labelled 3-methyl-N-(2,3-butadienyl)indole **217**.

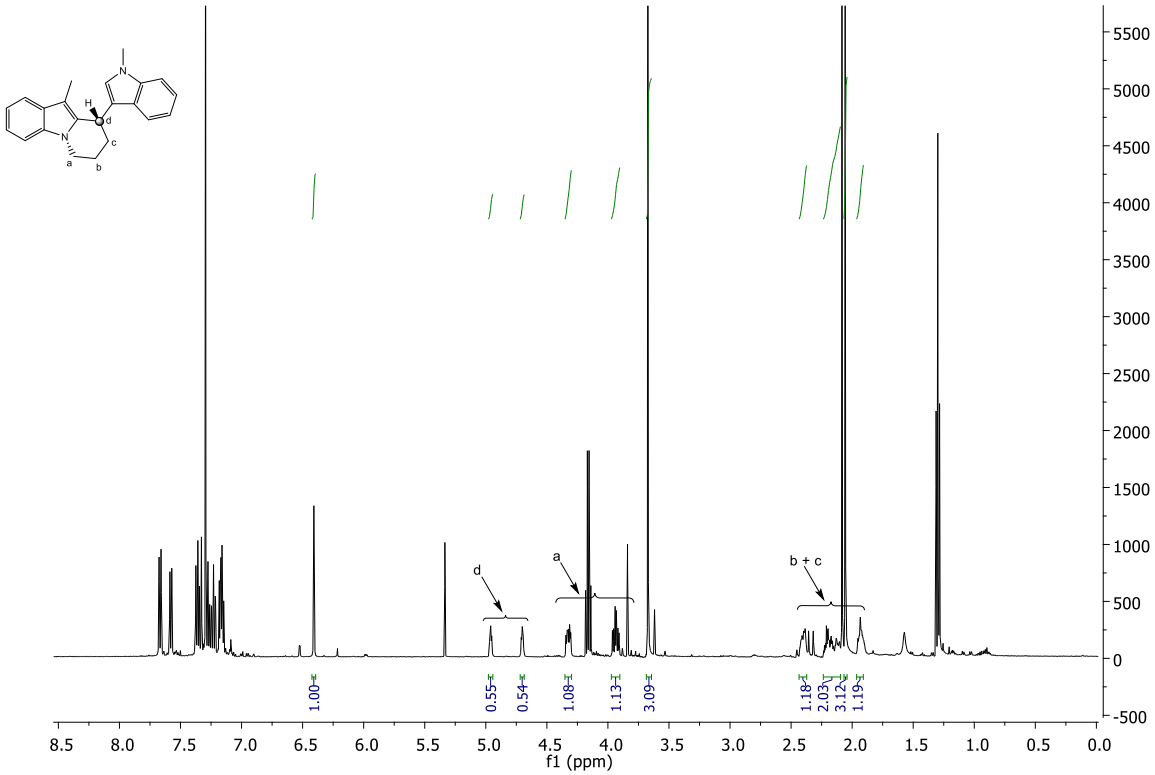
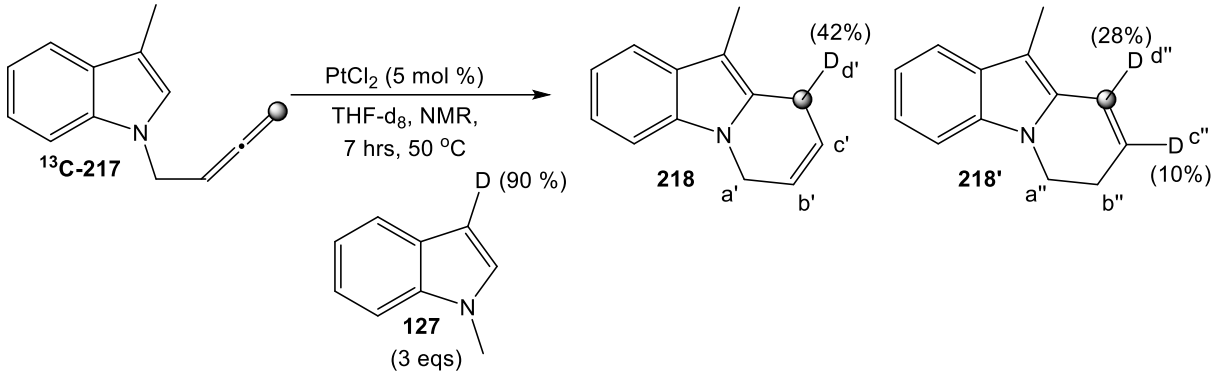


Figure 49. ^{1}H NMR showing the splitting of the signal at position *d* due to ^{13}C-^{1}H coupling in compound **287**.

To obtain more information about the deuterium incorporation at position *d* of the 2,3-BIM **287**, the platinum-catalysed reaction was carried out with the ^{13}C-labeled allene in the presence of deuterated external indole **127** and monitored periodically by both ^{1}H and ^{13}C NMR.

The reaction conditions were modified to be compatible with the spectrometer; deuterated THF was chosen as THF has been shown to give successful formation of the desired 2,3'-BIM. The temperature of the NMR machine and the boiling point of the solvent cannot reach the 130 ^{0}C used in the microwave, therefore reactions were carried out at 50 ^{0}C for an extended period.

The first NMR reaction carried out with ^{13}C-labelled 3-methyl-*N*-(2,3-butadienyl)indole **217** used platinum catalysis with deuterated *N*-methylindole **127**, in the absence of methanol (**Scheme 142**).



Scheme 142. Platinum-catalysed NMR reaction of ^{13}C-labelled 3-methyl-*N*-(2,3-butadienyl)indole **217** with deuterated *N*-methyl indole **127** in the absence of methanol.

The reaction was monitored periodically every 10 minutes by ^{1}H and ^{13}C NMR for the first hour and then every 30 minutes for a further 6 hours. Analysis of all the NMRs showed that the starting material **217** was consumed within the first hour with cycles **218** and **218'** forming within the first 10 minutes. The two cycles formed at the same time, however cycle **218** was the major product with a 2:1 ratio (**218:218'**) being achieved after 40 minutes (**Figure 50**), this remained constant for the further 6 hours and no 2,3'-BIM **287** was formed. As mentioned earlier, the isotopically labelled analogues could be causing a kinetic isotope effect which would result in slower formation of the two cycles **218/218'** and therefore the formation of the 2,3'-BIM would be unlikely in the same time frame. But also, the low temperature of 50 ^{0}C and the absence of methanol could have a significant contribution to the formation of the 2,3'-BIM.

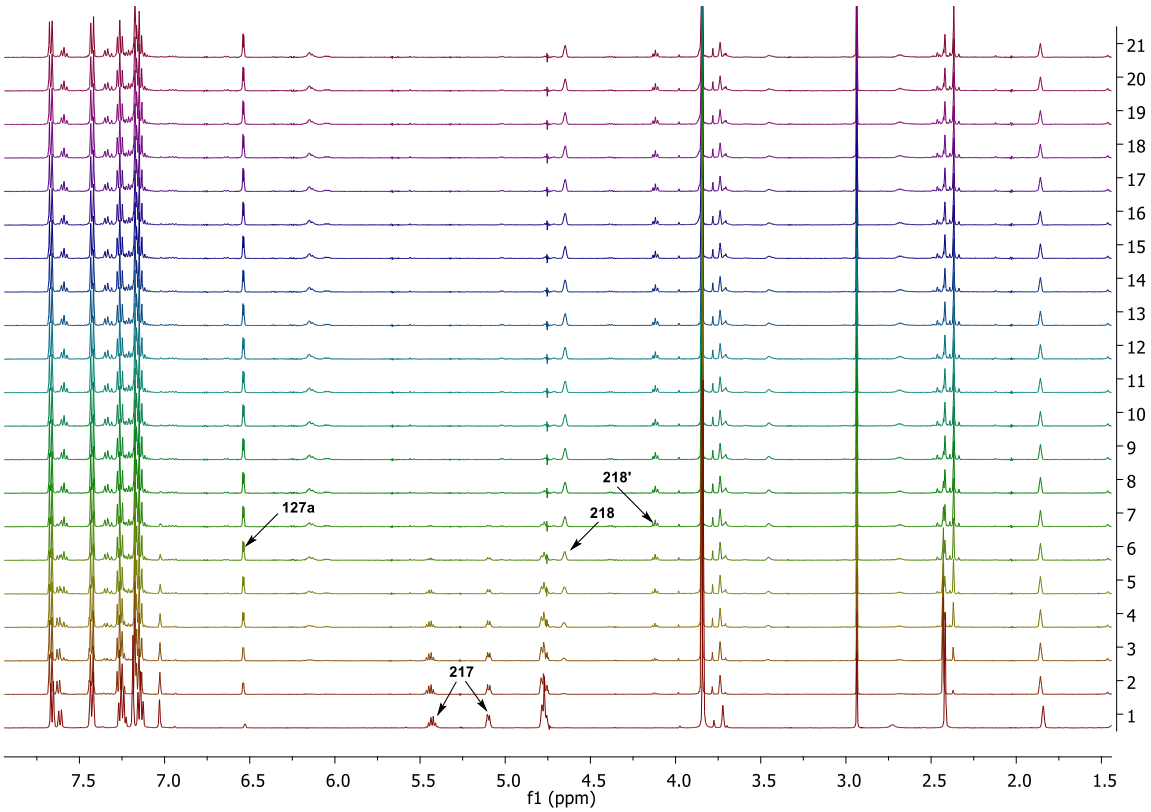


Figure 50. ^{1}H NMR showing the reaction progress for the ^{13}C reaction in **scheme 142**.

Further analysis of the final ^{1}H NMR obtained allows us to determine how much deuterium was incorporated into the cycles and at position 3 of the external indole. For the non-conjugated cycle **218** it was calculated that 42% deuterium is incorporated into position *d* whereas, the conjugated cycle **218'** has 10% deuterium in position *c''* and 28% in position *d''*. The presence of the ^{13}C at position *d'/d''* allowed us to follow the reaction by ^{13}C NMR and monitor the deuterium incorporation at this position with time. For example, the ^{13}C NMR signal for position *d'* in **218** appears around 22 ppm.

The deuterium incorporation in that position could be identified by the appearance of a triplet at ~0.3 ppm to the right of the singlet, corresponding to the CHD in that position (**Figure 51**). Interestingly, the ratio triplet to singlet seems to increase with time in the first 40 min, which would suggest scramble of deuterium in that position once the cycle has been formed. Besides, the *N*-methyl indole **127** started with 90% deuterium incorporation at position 3, but after reaction is calculated to have 50% deuterium incorporation, which results in a 40% deuterium loss.

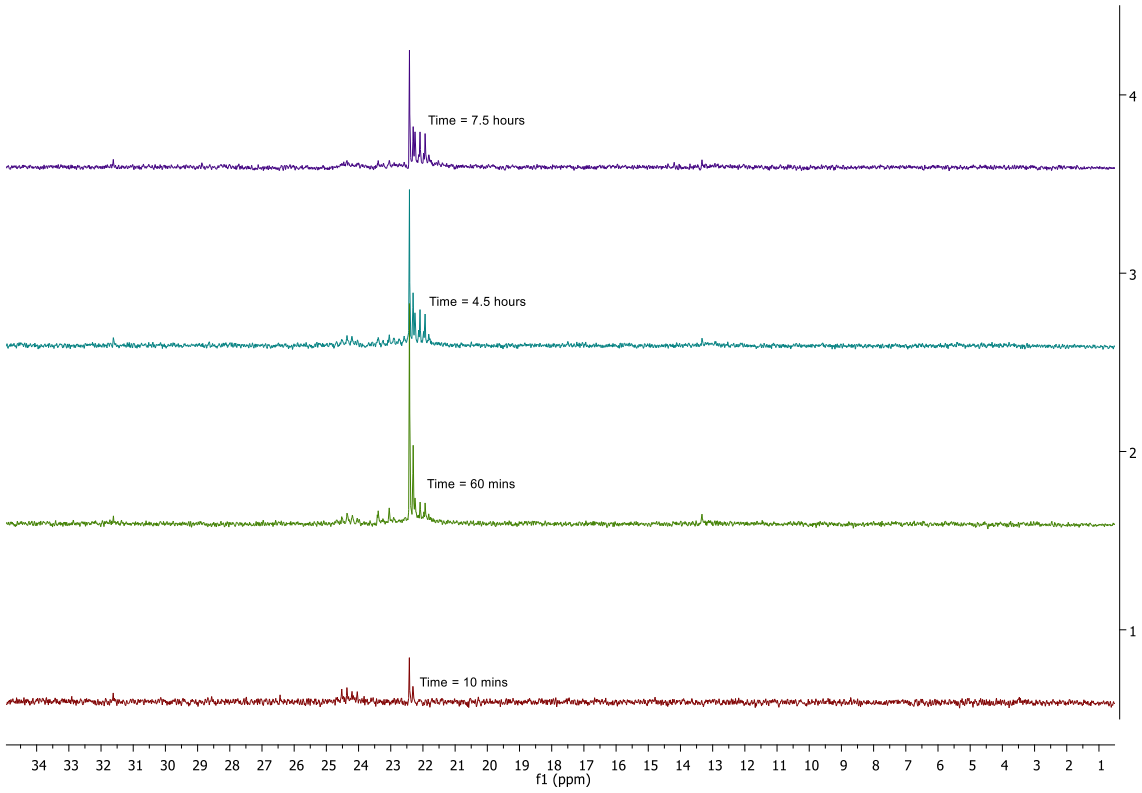
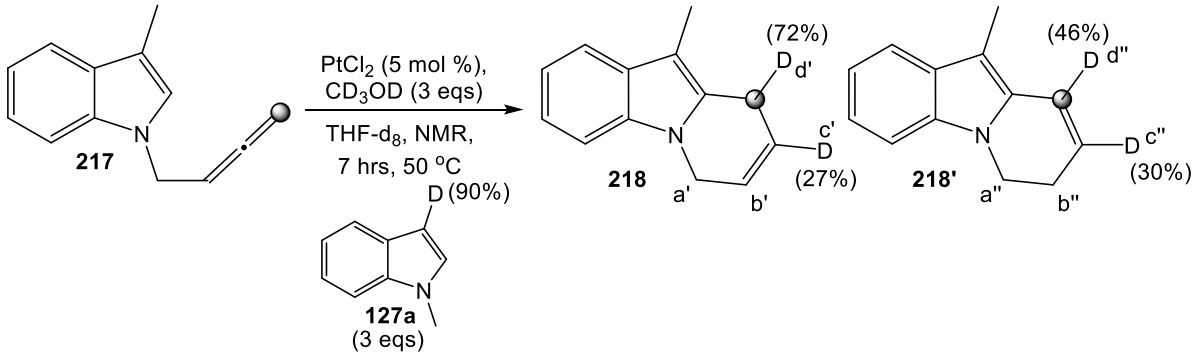


Figure 51. ^{13}C NMR showing the splitting of the carbon signal for position d' when deuterium incorporation occurs.

The same NMR reaction was carried out as above, but with deuterated methanol present to understand if it was in fact the absence of methanol or the low temperature that inhibited the formation of the desired BIM product (**Scheme 143**).

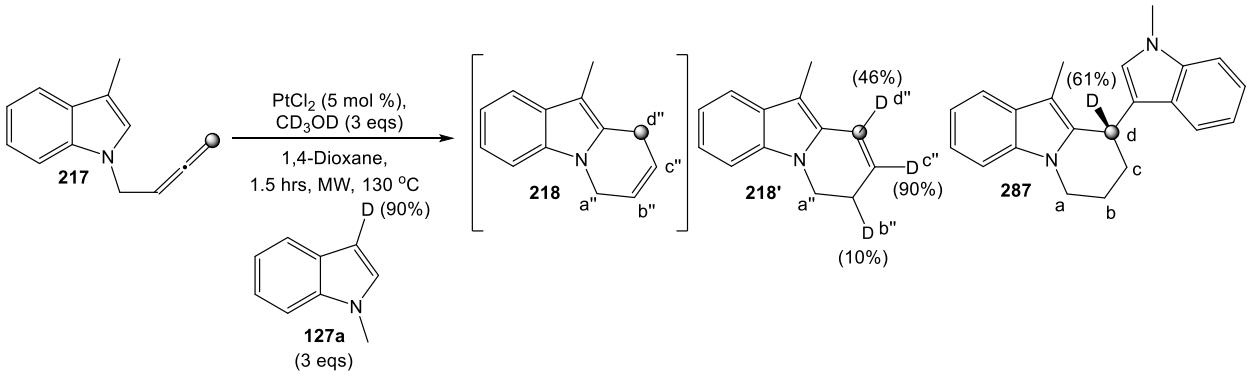


Scheme 143. Platinum-catalysed NMR reaction of ^{13}C-labelled 3-methyl-*N*-(2,3-butadienyl)indole **217** with deuterated *N*-methyl indole **127a** in the presence of deuterated methanol.

The ^{1}H and ^{13}C NMRs were obtained periodically in the same manner as before and analysis of these showed the same reaction pattern, with only cycles **218** and **218'** being formed and no formation of 2,3'-BIM **287**.

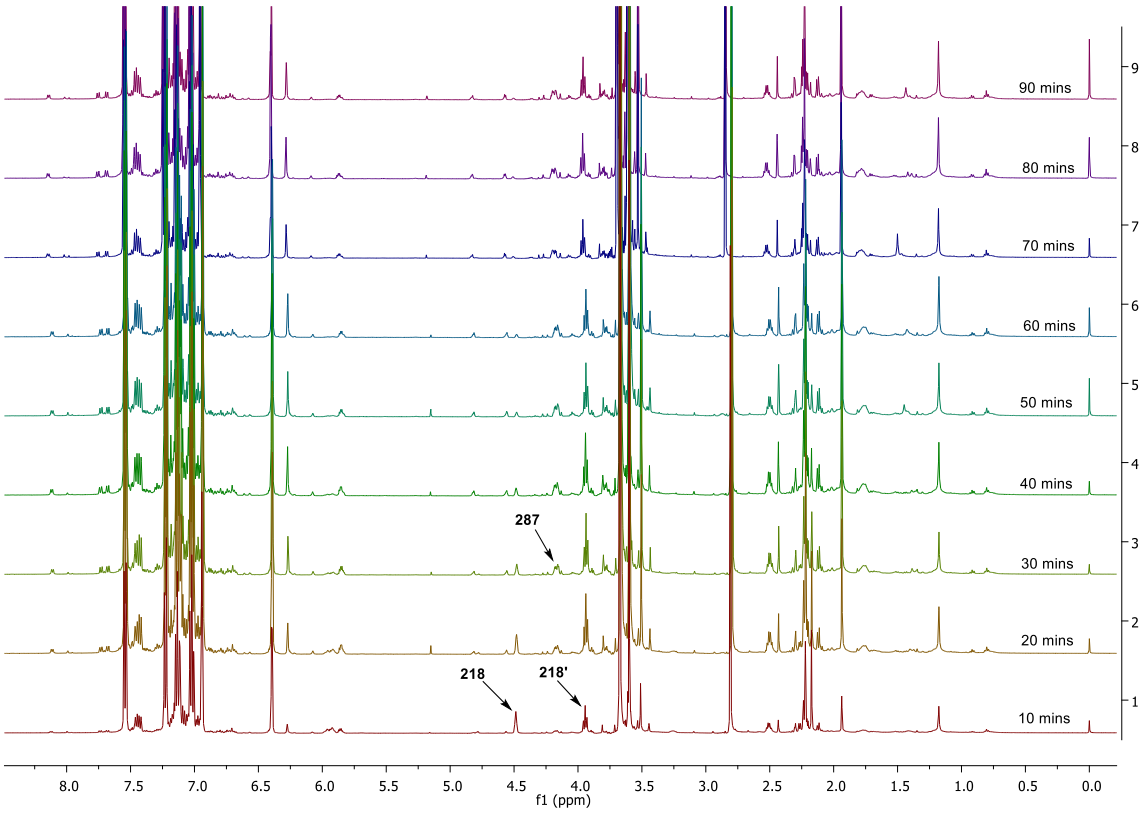
After 7 hours, the two cycles were observed in a 2:1 ratio (**218:218'**), with deuterium incorporation at positions *c'* and *d'* of cycle **218** in 27 and 72% respectively and positions *c''* and *d''* for cycle **218'** in 30 and 46% respectively. The deuterium incorporation at position 3 of the external indole **127a** was found to be 61%, therefore loss of only 29% deuterium, this low deuterium loss and the higher deuterium incorporation values would be expected because of the presence of deuterated methanol.

These results indicate that the low temperature of 50 ^{0}C does not allow for the formation of the desired 2,3'-BIM **287**, even in the presence of methanol. The same reaction mixture analysed in the spectrometer, was then heated to 130 ^{0}C in an oil bath, and after 1 hour traces of the 2,3'-BIM **287** were observed, supporting the finding that the reaction does not proceed as effectively at 50 ^{0}C. Therefore, ^{13}C-labelled 3-methyl-*N*-(2,3-butadienyl)indole **217** was reacted with deuterated *N*-methyl indole **127a** under mw irradiation in the presence of deuterated methanol under normal optimised platinum conditions with dimethyl sulfone as an internal reference (**Scheme 144**).



Scheme 144. Platinum-catalysed microwave reaction of ^{13}C-labelled 3-methyl-*N*-(2,3-butadienyl)indole **217** with deuterated *N*-methyl indole **127a** in the presence of deuterated methanol.

This reaction was monitored by ^{1}H and ^{13}C NMR over a 90-minute period, with samples taken every 10 minutes. Analysis of the ^{1}H NMR spectra showed that the starting allene **217** was consumed within the first 10 minutes with the subsequent formation of cycles **218** and **218'**. Cycle **218** forms at the same rate as cycle **218'** in the first 10 min. Then, as cycle **218** is consumed, the concentration of **218'** increases. The formation of compound **287** is observed within the first 10 minutes although in very low concentrations, but as **218** converts to **218'** we observe a slow increase in **287**. After 1 hour, compound **287** reaches a plateau with a slight decrease in the concentration of cycle **218'** (**Figure 52**).



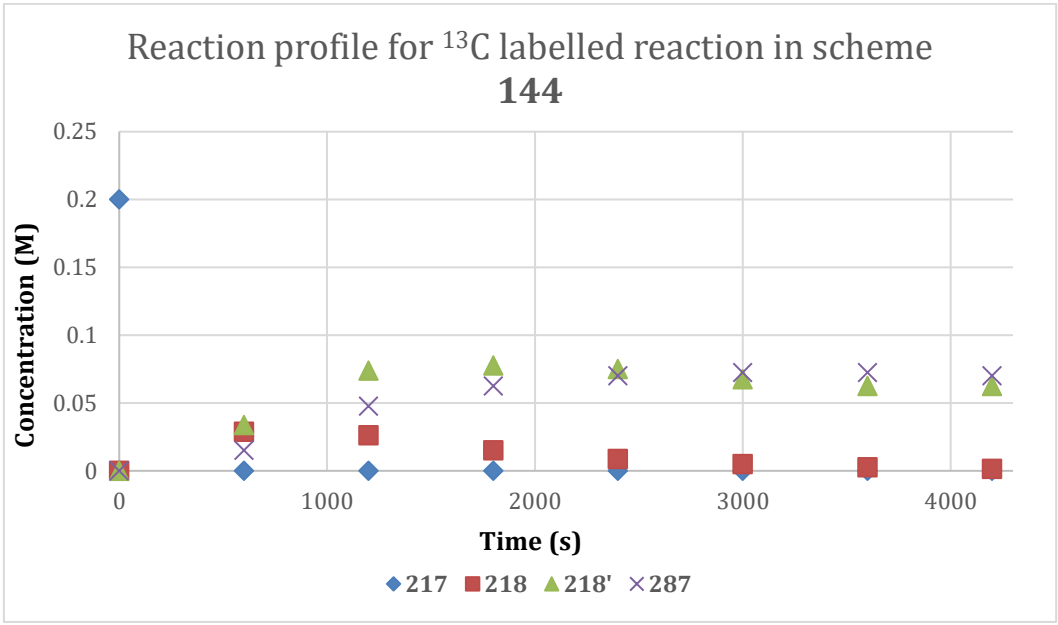
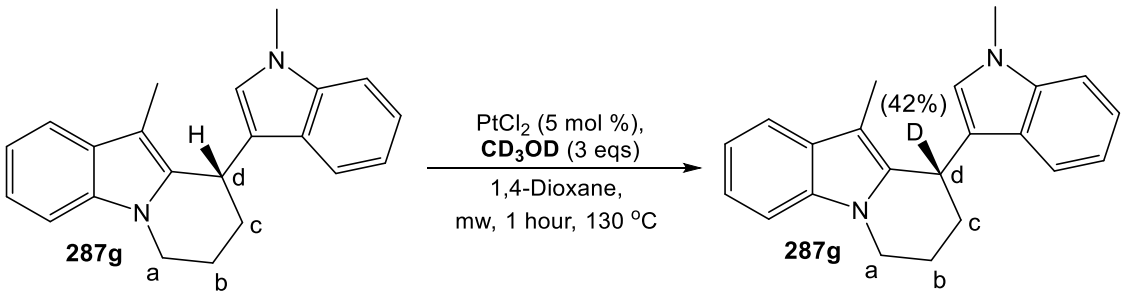


Figure 52. Reaction profile and ^{1}H NMR showing the reaction progress for the ^{13}C labelled reaction in **scheme 144**.

The ratio of cycle **218'** to product **287** was found to be 1.5:1 (**218':287**) at the end of the reaction with maximum concentration of compound **287** (0.083 M) after 1 hour and at 90 minutes, suggesting that the optimum time is 1 hour for reaction.

The slow conversion to compound **287** could be due to the presence of the deuterated methanol instead of normal methanol, where complete conversion to product **287** is observed. Cycle **218'** was found to contain deuterium in positions *b''*, *c''* and *d''* with 10, 90 and 46% respectively. Also, this reaction profile shows that the concentration of 2,3'-BIM is dependent on the formation of cycle **218'** and its subsequent reaction with the external indole, because as cycle **218'** forms we observe 2,3'-BIM formation, but without consumption of cycle **218'** we do not observe any further formation of BIM **287**.

As mentioned, the deuterium incorporation at position d of the 2,3'-BIM **287** was higher than expected in most cases, with variations occurring during purification which suggested an out-of-cycle equilibrium. Therefore, to determine if this was the case we reacted the isolated 2,3'-BIM **287g** under platinum conditions in the presence of deuterated methanol and in the absence of indole (**Scheme 145**).



Scheme 145. Platinum-catalysed reaction to highlight deuterium exchange at position *d* of compound **287g** in the presence of deuterated methanol.

Comparison of the two NMRs before (**Figure 53**) and after (**Figure 54**) the reaction confirms the presence of deuterium at position *d*, supporting the idea of an out-of-cycle equilibrium. The ^{1}H NMR shows 42% deuterium incorporation at position *d*, this supports our theory that this position can suffer deuterium scramble through proton exchange with deuterium present in the reaction mixture after the product has been formed as well as during the catalytic cycle.

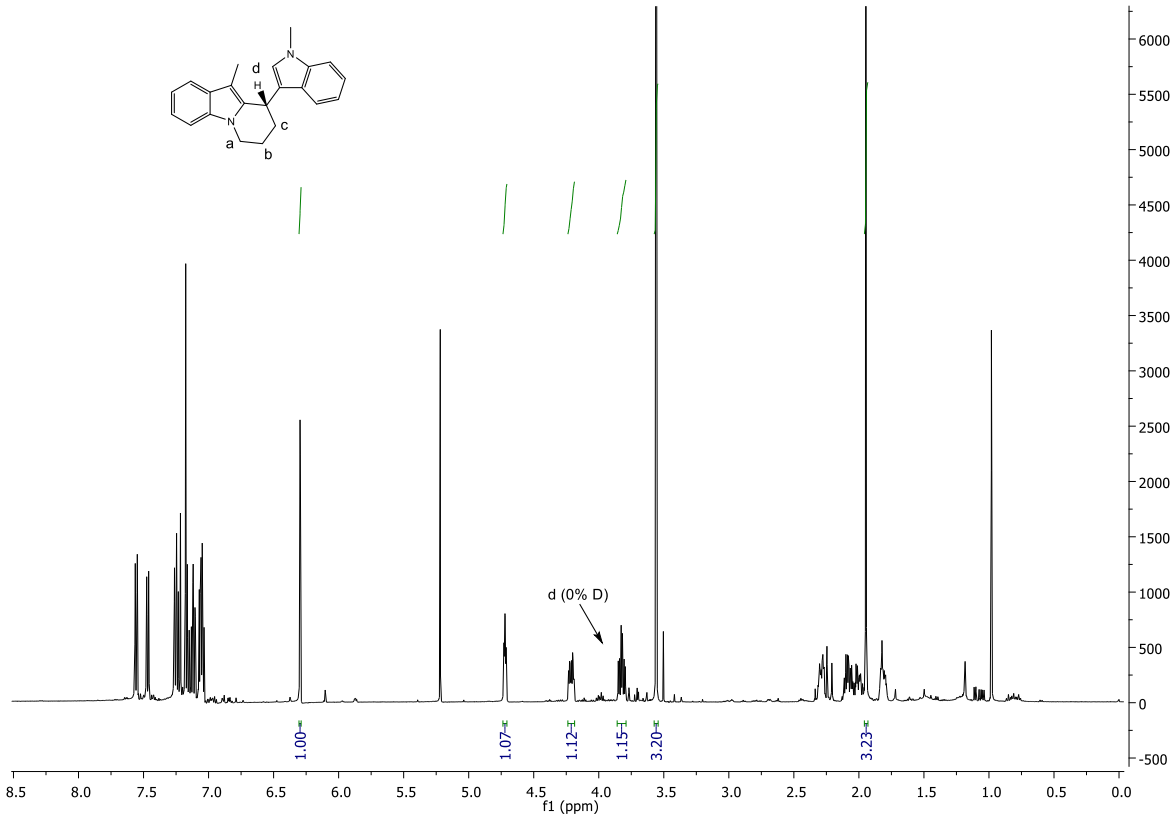


Figure 53. [1]H NMR showing the absence of deuterium at position d of **287g** before the reaction shown in **scheme 145.**

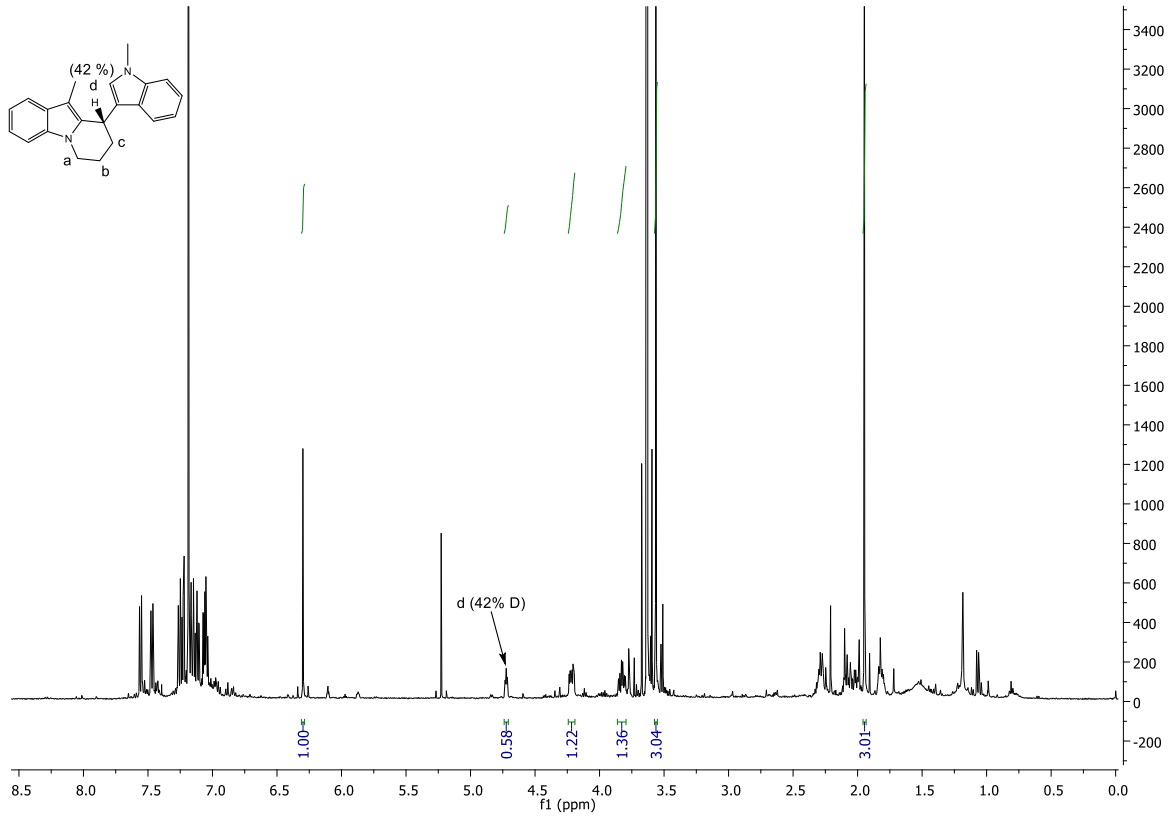


Figure 54. [1]H NMR showing the presence of 42% deuterium at position d of **287g** after the reaction shown in **scheme 145**.

However, despite this reaction supporting the out-of-cycle proton exchange, analysis of the carbon NMRs for the carbon labelled experiment in **scheme 145** showed that the deuteration in position *d* was observed from the beginning of the reaction. **Figure 55** shows the expansion of the ^{13}C NMR spectra showing position d of the 2,3'-BIM during the reaction in **scheme 135**, with the spectra of the pure non-deuterated **^{13}C-287g** analogue at the top for comparison. It clearly shows the presence of the triplet corresponding to the CD from the beginning of the reaction. These interesting results would suggest that an out-of-cycle proton exchange is occurring as supported by the reaction in **scheme 145**, but this is not the main pathway, with the protonation and deuterium scrabbling occurring within the cycle, which will be discussed with the mechanism.

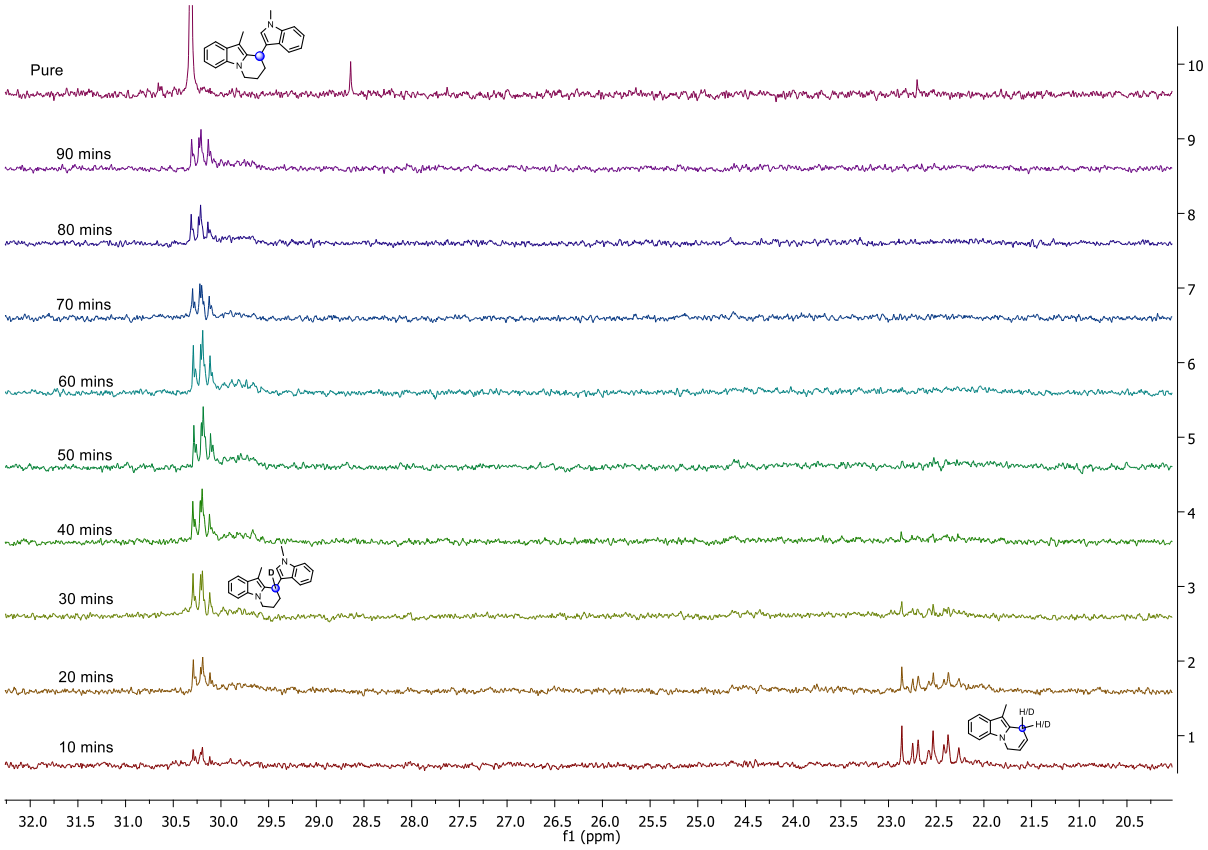


Figure 55. ^{13}C NMRs showing the deuterium incorporation with time at ^{13}C-labelled position *d* of compound **287**.

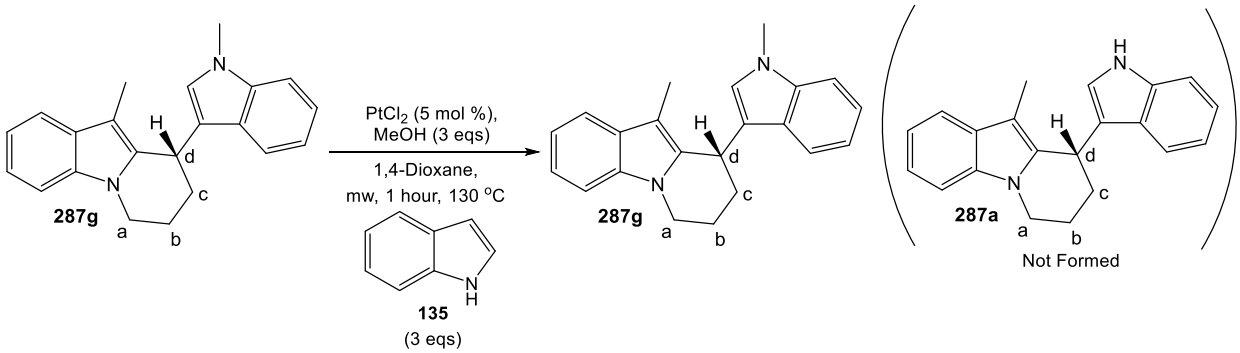
These labelling experiments further support the findings that the non-conjugated cycle **218** forms first, with isomerisation to the conjugated cycle **218'**, with methanol being important for this isomerisation step to occur. Subsequent formation of the desired 2,3'-BIM **287** occurs and again, higher yields are achieved when methanol is present. It has also highlighted the importance of the temperature for the reaction, with no formation of the desired 2,3'-BIM being formed when carried out at 50 ^{o}C, but heating to 130 ^{o}C formation of 2,3'-BIM is observed.

These ^{13}C labelled experiments have allowed us to follow the deuterium incorporation during the reaction by analysis of the CH to CD ratio of the carbon labelled positions. It has shown that the deuterium incorporation of the cycles occurs as part of the catalytic cycle *via* various proton exchanges. However, the deuterium incorporation at position d of the final 2,3'-BIM **287** can also occur *via* an out-of-cycle equilibrium with either acid or platinum catalysis.

2.3.4. Other studies to support proposed mechanism

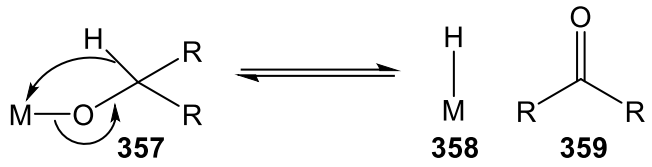
Further to these reactions, several others were carried out to help support the mechanistic investigation, including investigating the stability of the final 2,3'-BIM product **287** in the presence of a different external indole. Also, reactions were carried out in the presence of TEMPO to determine if platinum-hydride species are involved in our reaction.

As observed during the study of the 6-endo cycle as intermediates in the reaction, it is clear that the two cycles can be isolated and returned back to the catalytic cycle to react with an external indole to form the desired 2,3'-BIM **287**. This suggests that platinum could re-coordinate to the double bond of the cycles **218/218'** in a reversible process. With this in mind, we were interested to know if the final step for the formation of compound **287g** from compound **218'** was reversible. Therefore, we reacted the N-Me substituted 2,3'-BIM **287g** with the external indole **135** under the platinum conditions to determine if we could get indole exchange. This would involve the 2,3'-BIM going back into the catalytic cycle to give the platinum-coordinated vinyl indole **218'**, which would then exchange the indole to give a mixture of the two 2,3'-BIMs **287a** and **287g** (**Scheme 146**). However, after 1 hour of mw irradiation, the ^{1}H NMR spectrum of the crude showed only starting material **287g** and the excess indole **135** with no traces or formation of the other 2,3'-BIM **287a**. This therefore supports that the final step of this reaction is not reversible.



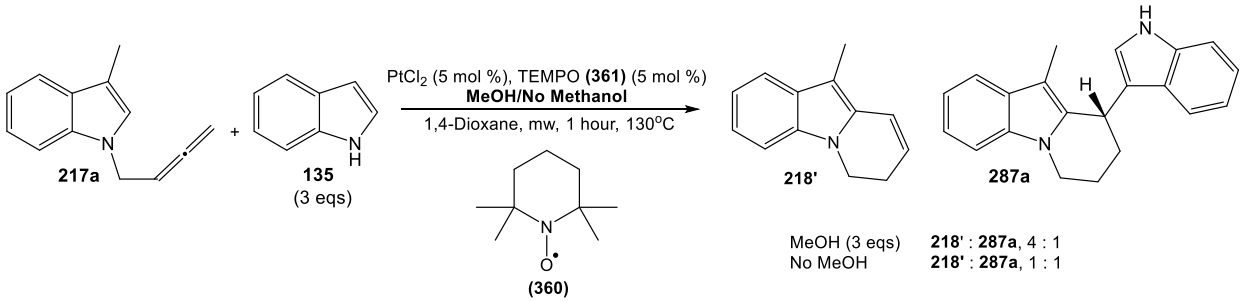
Scheme 146. Platinum-catalysed reaction to monitor indole exchange for compound **287g**.

The formation of platinum-hydrides (Pt-H) have been reported for reactions with platinum complexes and alcohols.[157] They are reported to occur *via* β-H elimination of a metal-alkoxy complex **357** with the formation of the subsequent metal-hydride **358** and carbonyl compound **359** (**Scheme 147**).[157b] These reports could explain the important role of methanol in our reaction, with its potential to aid the formation of Pt-H species in the first step with involvement in several other steps of the catalytic cycle.



Scheme 147. β-H elimination for the formation of metal-hydride species **358**.

The idea that Pt-H species could be involved in our reaction mechanism was investigated by incorporating TEMPO **360** as a Pt-H trap, which has been shown to effectively trap Pd-H species by interfering/hindering in the steps in which they are involved.[158] Our investigation was carried out with 3-methyl-*N*-(2,3-butadienyl)indole **217a** with external indole **135** in the presence of TEMPO **360** and either methanol or no methanol under optimised platinum conditions (**Scheme 148**).



Scheme 148. Platinum-catalysed reaction with TEMPO **376** present to investigate the involvement of Pt-H species.

Analysis of the ^{1}H NMR spectra of the crude for these two reactions showed that formation of product **218'** and **287a** were present as a 4:1 ratio in the reaction with methanol (**Figure 56**). Whereas, the formation of both products **218'** and **287a** were present in a 1:1 ratio (**218':287a**) in the reaction with no methanol present (**Figure 57**). The different results obtained with and without methanol in the presence of TEMPO, and in comparison, with the model reaction suggest that indeed Pt-H might be involved at different points of the catalytic cycle. The fact that formation of the BIM **287a** is more inhibited in the presence of methanol with TEMPO present could point to Pt-H species being involved in the final demetallation step and not as an active catalyst in the mechanism, this will be discussed in more detail in the next section with regards to the proposed mechanism.

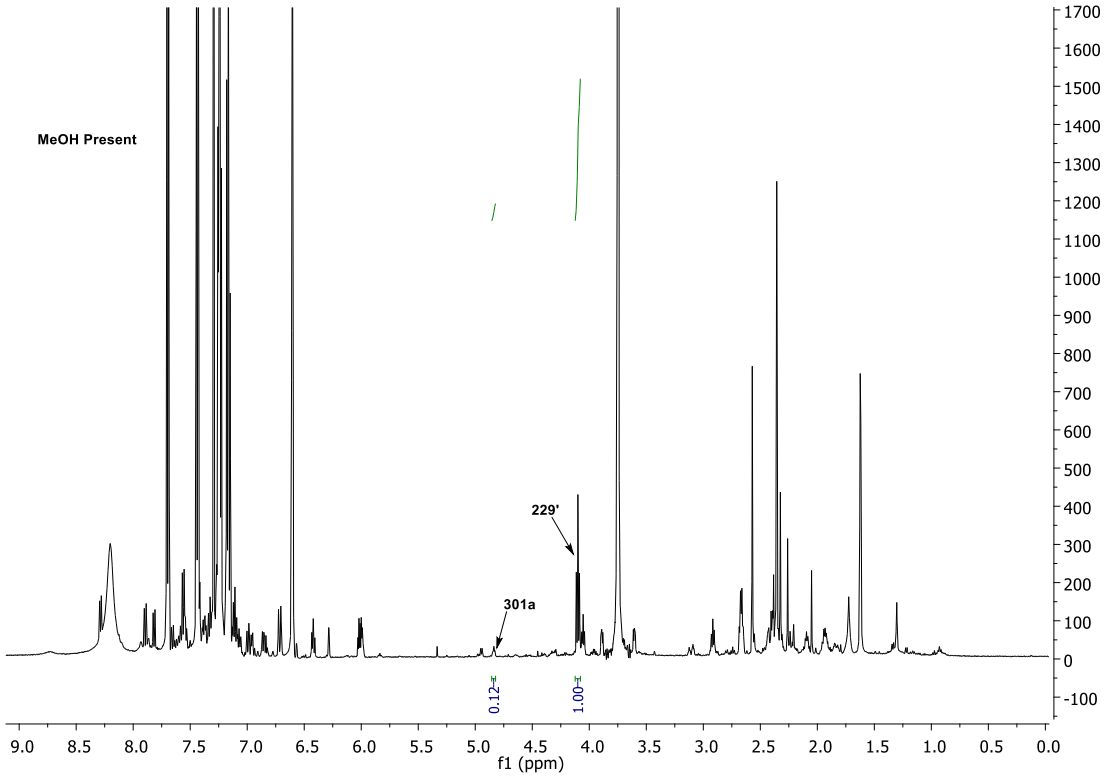


Figure 56. ^{1}H NMR spectra showing the ratio of **218'** to **287a** for the crude reaction with TEMPO and methanol as shown in **scheme 148.**

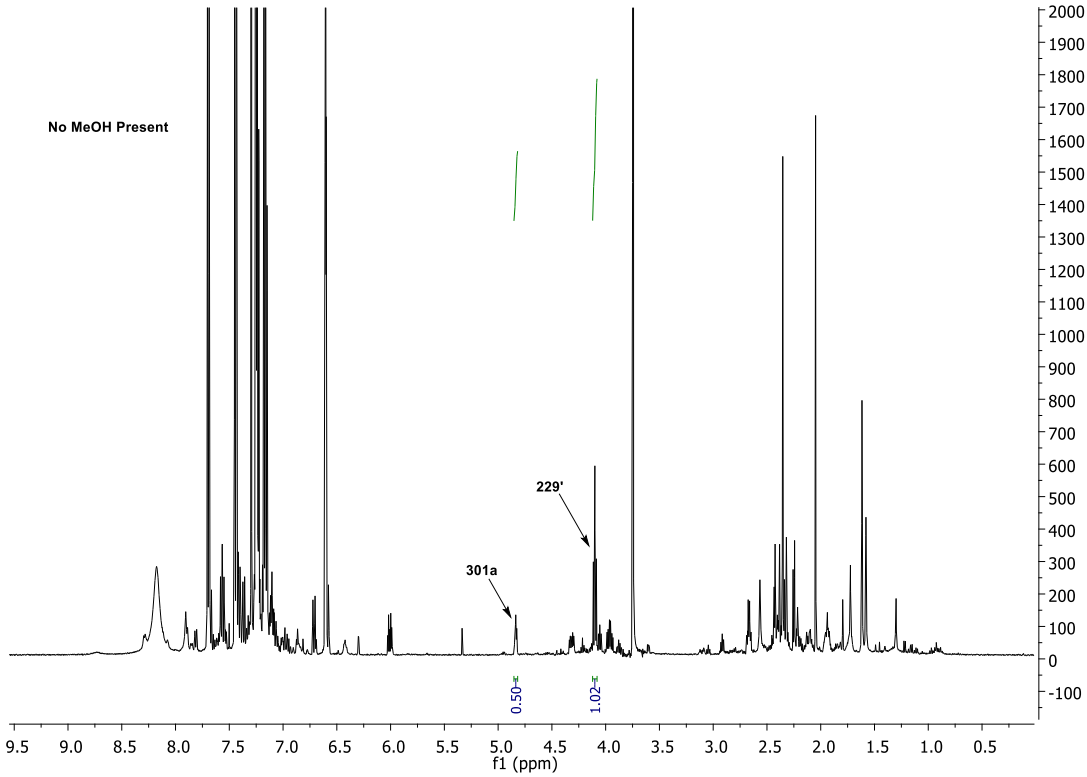
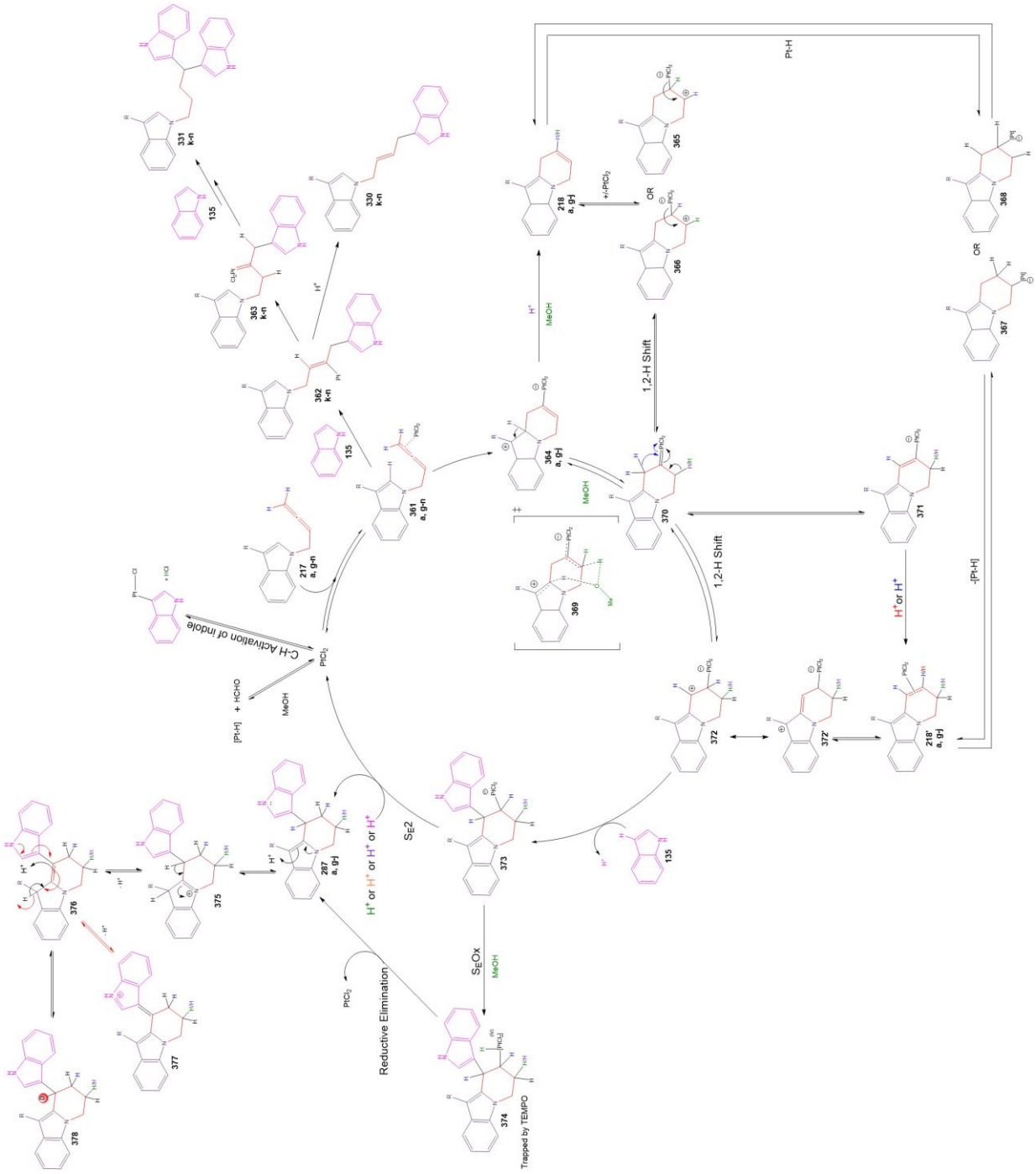


Figure 57. ^{1}H NMR spectra showing the ratio of **218'** to **287a** for the crude reaction with TEMPO and no methanol as shown in **scheme 148.**

2.4. Proposed Mechanism

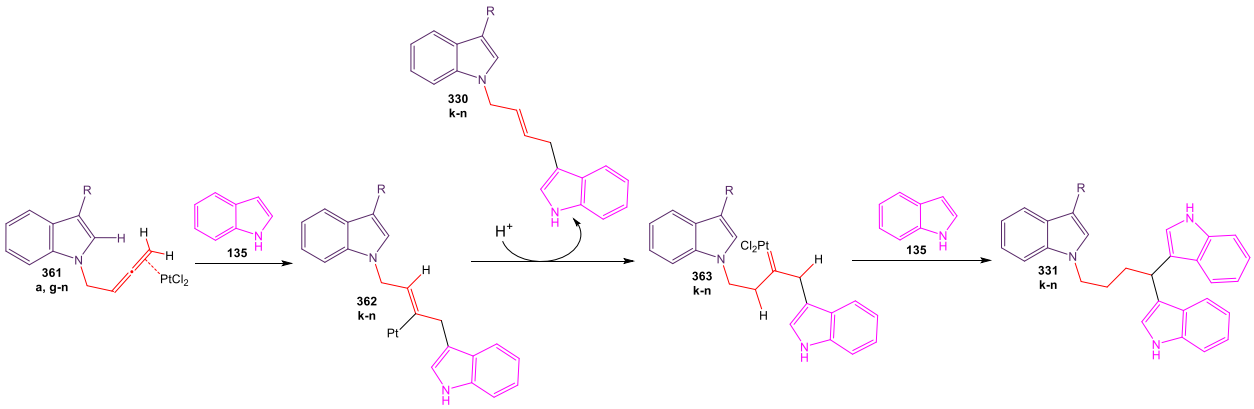
Finally, after collecting all the data from the various experiments in the mechanistic study, a proposal for the mechanism of the reaction has been developed (**Scheme 149**). It considers all the different aspects and some supporting work carried out within our group on the dihydroalkoxylation reaction.[159]



Scheme 149. Proposed mechanism for the 6-endo cyclisation and subsequent intermolecular indole addition to form 2,3'-BIMs.

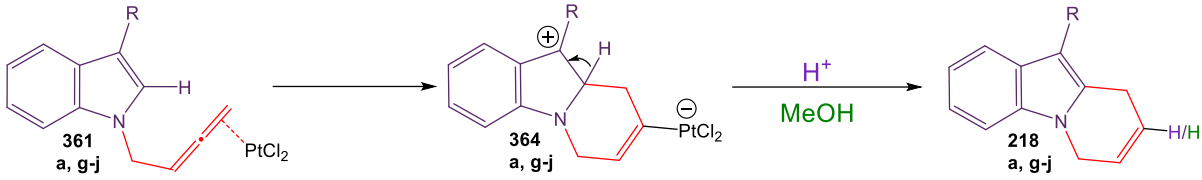
Our proposal starts with the platinum coordination to the indolyl allene **217** in an η^2 mode to give complex **361a-h**. This has been supported by work carried out on platinum-allene complexes by our group using a new NMR technique called spin saturation transfer difference (SSTD).[52]

At this stage, the electronic properties of the group present in position 3 of the internal and the external indole play an important role as to which route is taken. As discussed earlier, if position 3 of the indolyl allene contains an electron-withdrawing group then intermolecular addition of either one or two indole units forming the corresponding allylic **330k-n** or tris-indole product **331k-n** would be the preferred pathway. This occurs *via* addition to the terminal carbon of the allene with formation of the vinyl platinum and protodemetalation to give the allyl indole **330k-n**, or protonation on the internal carbon to form the platinum carbene intermediate **363k-n** as observed with the inter-intermolecular bis-indolylation reaction.[64] Subsequent attack of the second indole followed by protodemetalation of the Pt-C_{sp3} bond (*via* Pt-H or directly) would result in the tris-indole product **331k-n** (**Scheme 150**).



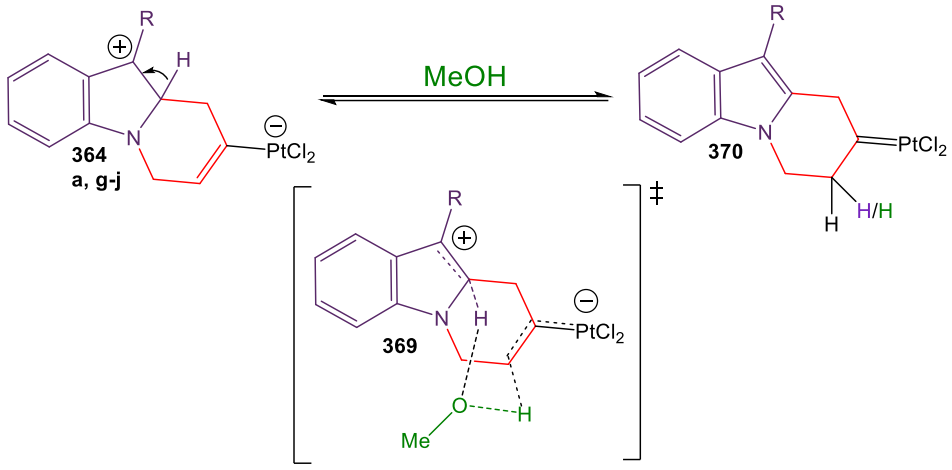
Scheme 150. Proposed mechanism for the formation of the allylic **330k-n** and tris-indole **331k-n** products when position 3 of indolyl allene **217** contains a EWG.

However, when position 3 of indolyl allene **217** contains an alkyl mild electron-donating group, then complex **361a, g-j** undergoes 6-endo cyclisation with formation of the intermediate **364a, g-j**. At this stage, protodemetalation could explain the formation of the non-conjugated cyclic allyl indole **218a, g-j,** analogous to that proposed by Barluenga *et al.*[101] for the gold catalysed cyclisation (**Scheme 151**). The proton used for this step could be the one lost from position 2 of the indolyl allene to regain aromatisation (purple), or from the MeOH present in the reaction media (green).



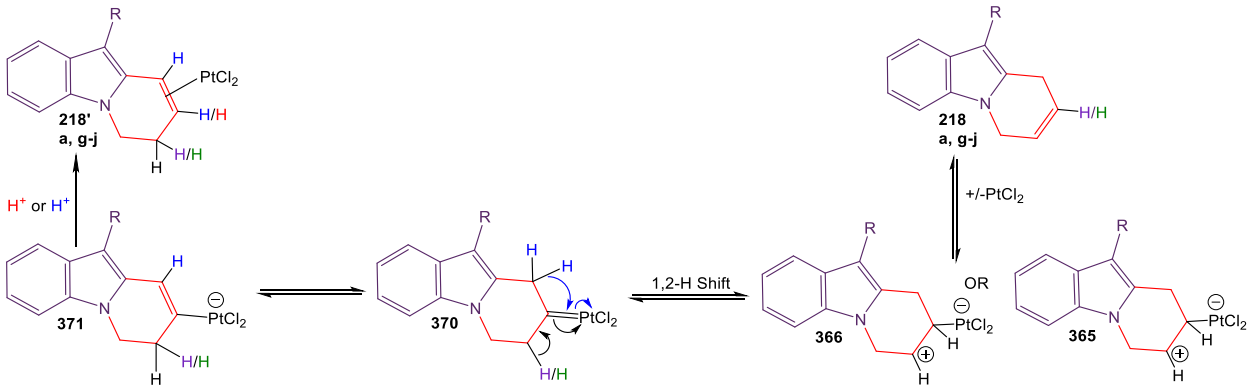
Scheme 151. Proposed mechanism for the formation of the 6-endo cycle **218a, g-j** from intermediates **361** and **364** when indolyl allene **217** contains an EDG.

To explain the isomerisation of **218** to **218'**, we propose that a platinum-carbene complex **370** is generated from complex **364** by protonation of the internal carbon of the vinyl platinum aided by the methanol. The methanol acts as a proton shuttle *via* the proposed transition state **369**, analogous to the one located for the alkoxycyclisation by DFT calculations (**Scheme 152**).



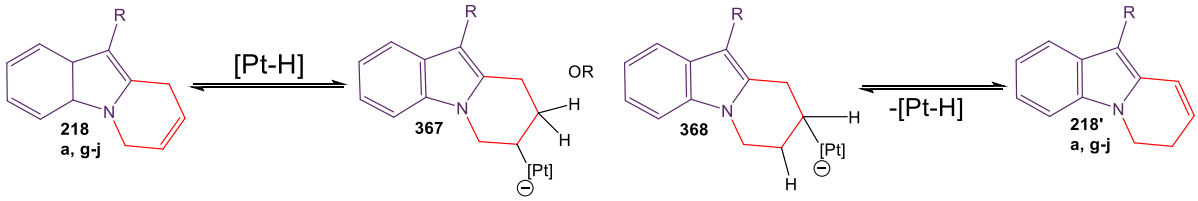
Scheme 152. Proposed role of methanol as a proton shuttle to aid the formation of platinum-carbene complex **370**.

Loss of one of the protons in position *d* (blue) in this platinum-carbene **370** would form intermediate **371**, which can undergo protodemetalation (with any proton source in the media) to form the conjugated cycle **218'** (**Scheme 153**). Our studies involving the cycles as intermediates in the reaction have highlighted that the non-conjugated cycle **218** can be returned to the platinum reaction without the external indole with successful isomerisation to **218'** achieved. Therefore, it is likely that platinum can re-coordinate and add to the cycle to generate intermediate **365/366** which will be in equilibrium with the carbene. (**Scheme 153**). A similar isomerisation has been proposed by Gagné *et al.*[160] for the isolatable cationic Pt-alkenyl species involved in enyne cycloisomerisation.



Scheme 153. Proposed route for the isomerisation of cycle **218** to **218'**.

Involvement of Pt-H in this isomerisation cannot be completely ruled out. If Pt-H were the only responsible species for the isomerisation, the reaction with TEMPO should have given only or preferentially isomer **218** (**Scheme 154**). However, in the experiments with TEMPO in the presence of MeOH, complete isomerisation of **218** to **218'** was observed, supporting the mechanism in **Scheme 154** as the main pathway for isomerisation.

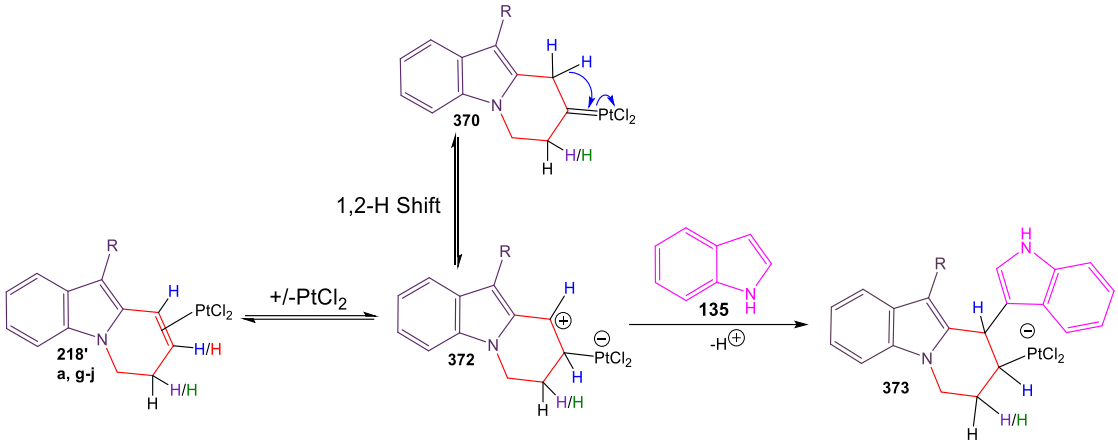


Scheme 154. Proposed route for the isomerisation of cycle **218** to **218'** *via* Pt-H.

Coordination and insertion of platinum to cycle **218'** would give intermediate **372**, which can also come from 1,2-H shift in platinum-carbene **372**. According to DFT calculations performed in the alkoxylation reaction, these Pt-coordinated **218'** and **372** can be seen as resonance structures and are the resting state of the catalytic cycle (enol ethers have been observed in the platinum-catalysed dialkoxylation of allenes). This intermediate is ready to undergo intermolecular nucleophilic addition by the external indole to form the platinum-complex **373** (**Scheme 155**).

It is important to highlight here the equilibrium between the two possible vinyl platinum intermediates via the platinum-carbene as the key steps in the catalytic cycle and to explain the deuterium scramble in all position in the three products. It is at this point that we suggest the ability for position *d* to be deuterated, the rapid exchange of protons *via* the carbene intermediate **370** and the equilibrium back and forth to vinyl platinum **371**, would introduce deuterium at position *d*. The subsequent 1,2-H shift from the carbene **370** to the intermediate **372** would occur with deuterium still present in both position *d* and position *c*.

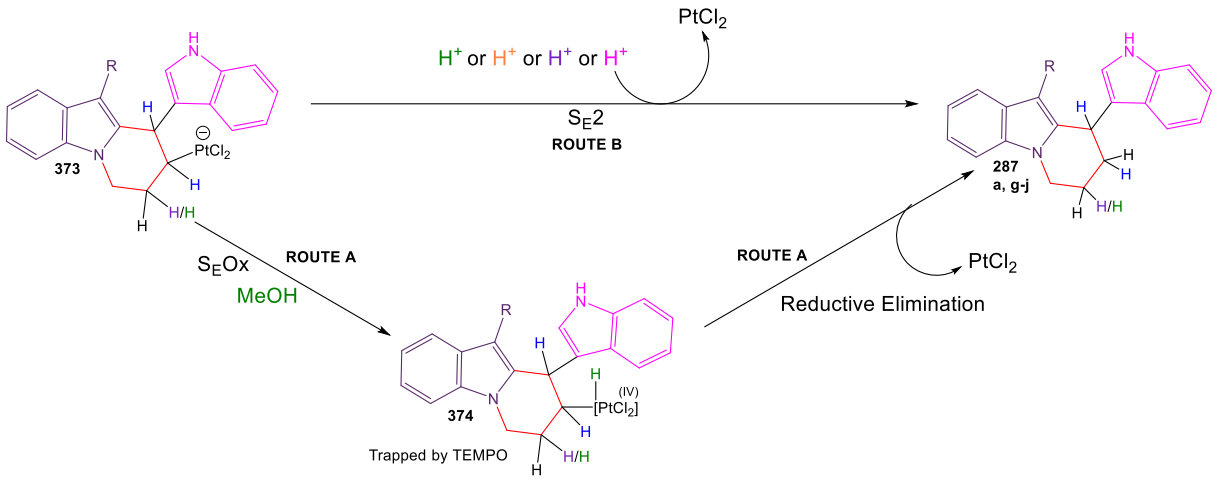
The addition of the indole would give the final 2,3'-BIM with deuterium incorporation, therefore supporting our theory that the deuteration at position d of compound **287** can come from both the catalytic cycle as well as the out-of-cycle equilibrium in **scheme 157**.



Scheme 155. Proposed route conversion of cycle **218'** to the platinum-complex **373** after addition of the external indole **135**.

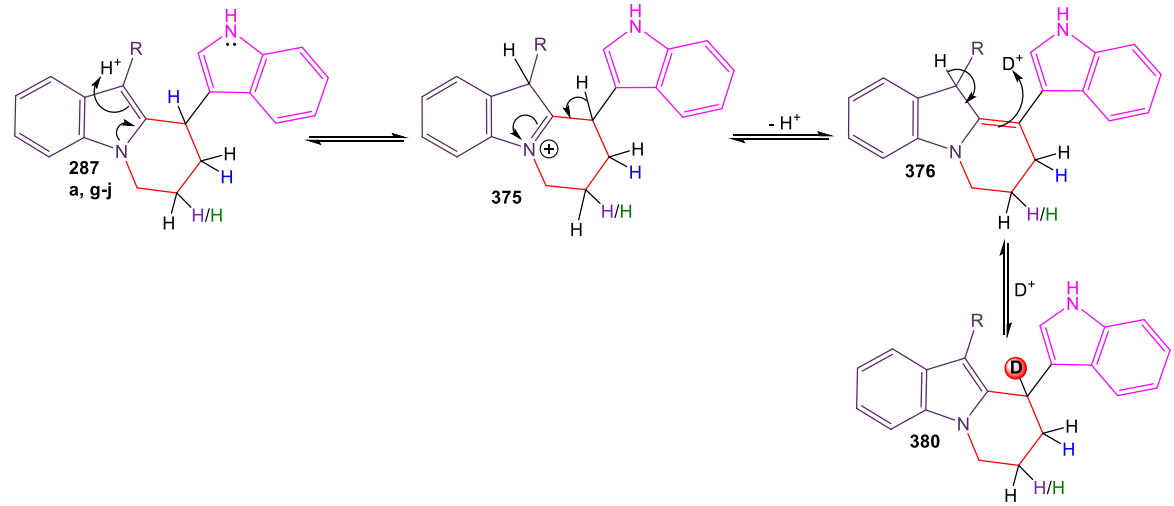
The final demetalation step is proposed to occur irreversibly *via* 1 of 2 pathways depending on the presence or absence of methanol. This was proposed based on results obtained from reactions carried out with TEMPO present, where it was observed that when methanol was present cycle **218'** was found to be the major product and only traces of the 2,3'-BIM **287** were observed. This suggested that the final step could be occurring *via* the formation of Pt(IV)-H species **374** by protonation of the platinum centre *via* S_EOx mechanism (Route A, **Scheme 156**), which then undergoes reductive elimination to form compound **287**. The poor conversion to 2,3'-BIM **287** would suggest that TEMPO was trapping/inhibiting this step. However, when no methanol was present the Pt-H species cannot be generated efficiently and although protonation of the metallic centre could occur from other protons present in the media, conventional protodemetallation could also occur *via* S_E2 mechanism (Route B, **Scheme 156**).[161]

This final demetallation step is a proposal based on our TEMPO reactions, but also from results obtained from work carried out on the mechanistic investigation of the dihydroalkoxylation reaction[64] within our group, where DFT calculations are being carried out, which could support our proposed mechanism for 2,3'-BIM **287** formation.



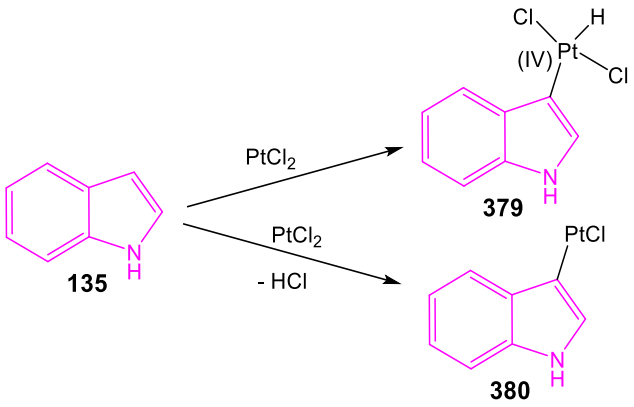
Scheme 156. Proposed demetalation of platinum-complex **373** *via* route A or B for formation of compound **287**.

The final section of the mechanism proposes the out-of-cycle equilibrium for incorporation of deuterium at position *d* of the final 2,3'-BIM compound **287** after its formation. This could be aided by the platinum complex, or just an acid-catalysed equilibrium between different species where the proton in that position can be exchanged as shown in **Scheme 157**.



Scheme 157. Proposed route for deuterium incorporation at position *d* of compound **287**.

Finally, to explain the loss or gain of deuterium in position 3 of the external indoles during the reaction, platinum-catalysed C-H activation of the indole to give Pt(II)-complexes with the loss of HCl or Pt(IV)-H intermediates, unproductive compounds in our catalytic cycle, could be proposed (**Scheme 158**).[76] The DCl formed from deuterated analogous would explain the deuterium scramble in the different products when the only source of deuterium is the external indole.



Scheme 158. Mechanism to show the loss or gain of deuterium at position 3 of the external indole **135**.

Although the overall proposed mechanism in **scheme 149** is complex, we believe it to be a good representation for the process of the reaction based on our mechanistic investigation reactions and supporting work carried out within our group.

2.5 Conclusion

This thesis highlights the work that has been carried out to explore and further expand both the inter-intermolecular and the intra-intermolecular reactions. The work has shown that the inter-intermolecular addition could not be adapted to incorporate different heteroatom nucleophiles. However, we have shown that the incorporation of pyrrole can be successfully achieved when freshly distilled pyrrole is utilised. We have also been able to show the partial success for the incorporation of two differentially substituted indoles to the same allene, however we were unable to successfully isolate the desired chiral cross 3,3'-BIM.

Despite the inter-intermolecular reaction not being successfully expanded, we have been successful with the intra-intermolecular reaction. We have successfully shown that the electronics of functional groups on either the indolyl allene or the external indole have an important role on the selectivity of the reaction. With electron-donating groups favouring the formation of the 2,3'-BIM **287**, whereas electron-withdrawing groups are shown to favour the formation of the 6-endo cycles **218**/**218'**.

The overall mechanism of the reaction was explored in detail and a mechanism has been proposed to suggest a pathway for the formation of the desired 2,3'-BIM **287** from cycles **218** and **218'**. Our proposed mechanism (**Scheme 149**) shows the successful isomerisation between the 6-endo cycles **218**/**218'** and the important role that methanol plays, it has also highlighted the potential importance of Pt-H species in the final demetalation step.

2.5 Future Work

To expand on some of the sections in this thesis, it would be of interest to further explore the reactions with pyrrole, to provide a successful route for the formation and isolation of the pyrrole 6-endo products. It would also be interesting to investigate other substituted pyrrole derivatives, to determine if they could undergo the cyclisation or if decomposition is still an issue.

If time was available, investigation of the longer chain indolyl allenes would be of interest, to determine a route for the formation of these derivatives and explore their potential for the cyclisation and inter-molecular addition. Currently, within the Muñoz group work is being carried out to explore the formation of indolyl allenes with allenes in positions 2 or 3 of the indole. These compounds could then be explored with the platinum reaction to observe potential formation of new bis-indolylmethanes.

Chapter 3.0 Experimental

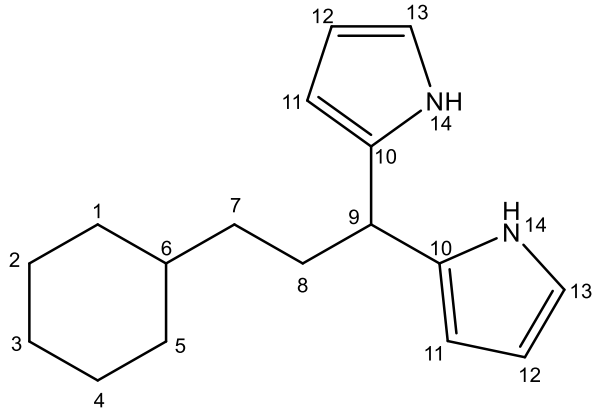
General experiment details

All reagents were purchased from commercial sources and used without further purification, unless otherwise stated. Solvents were distilled under nitrogen atmosphere and used on the same day. All reactions were carried out under nitrogen atmosphere and in the absence of moisture, unless otherwise stated. Reactions using microwave irradiation were carried out in Biotage Initiator+ Microwave system. Reactions were monitored using Thin Layer Chromatography (TLC) using 0.2 mm thick silica gel plates 60F-254 (5735 Merck) with a mobile phase of petroleum ether and ethyl acetate, with visualization by illumination using UV light (λ = 254 nm) or staining with either potassium permanganate or phosphomolybdic acid solution in EtOH. Purification techniques were carried out using column chromatography using silica gel from Sigma-Aldrich 60 Å, 230 – 400 mesh particle size as a stationary phase. Weights were accurately weighed using a Denver Instrument SI-234. NMR spectra were recorded on a Bruker Ascend™ 500 spectrometer at 500 MHz for ^{1}H NMR and 126 MHz for ^{13}C NMR with $CDCl_3$ solvent. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants values (*J*) are given in Hertz (Hz), and are approximated to the nearest 0.1 Hz. ^{13}C NMR was recorded using broad-band proton decoupling. Abbreviations used in NMR analyses are as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublet of doublets, dq = doublet of quartets, qd = quartet of doublets and m = multiplet. High Resolution Mass Spectrometry were performed by EPSRC National Mass Spectrometry Service Centre, Swansea, with the technique stated. Infrared was obtained using a Perkin Elmer System 400 FT-IR spectrophotometer, with solid samples run as thin films of their solution in DCM and liquids run neat.

Compounds obtained from inter-intermolecular nucleophilic addition reactions

Platinum catalyzed addition of pyrrole to cyclohexylallene

Platinum (II) chloride (16 mg, 0.062 mmol) and pyrrole (256 µl, 3.69 mmol) were added to an oven dried schlenk under N_2 and dissolved in 6 mL THF (0.2 M). Commercially available cyclohexylallene (179 µl, 1.23 mmol) and methanol (149 µl, 3.69 mmol) were added, and the reaction was heated at 70 ^{o}C for 72 hours. The reaction was cooled to rt and filtered through celite washing with DCM. **Compound 289** was obtained after column chromatography using Pet Ether/EtOAc (20:1), 97.1 mg, 0.38 mmol 31% as a brown oil.



Compound 289

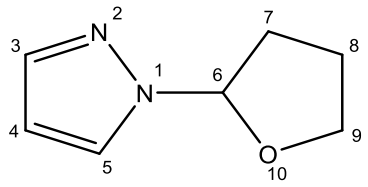
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 2H, H-***14***), 6.65-6.64 (m, 2H, H-***11*** or H-***12***), 6.15 – 6.13 (m, 2H, H-***11*** or H-***12***), 6.07 – 6.06 (m, 2H, H-***13***), 3.96 – 3.93 (t, *J* = 7.6 Hz, 1H, H-***9***), 1.98 – 0.83 (m, 15H, H- ***1-8***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 133.70 (C-***10***), 116.89 (C-***13***), 108.09 (C-***11***), 105.29 (C-***12***), 37.99 (C-***9***), 37.67 (C-***6***), 33.35, 32.00, 30.94, 26.68, 26.40.

Characterization supported by published data.[78]

Gold catalyzed addition of pyrazole to cyclohexylallene

Chloro(triphenylphosphine) gold(I) (10 mg, 0.021 mmol), silver triflate (11 mg, 0.041 mmol) and pyrazole (84 mg, 1.23 mmol) were added to an oven dried schlenk under N_2 and dissolved in 2 mL THF (0.2 M). Commercially available cyclohexylallene (60 µl, 0.41 mmol) and dry methanol (49 µl, 1.23 mmol) were added, and the reaction was heated at 70 ^{0}C for 30 hours. The reaction was cooled to rt and filtered through celite washing with DCM. **Compound 296** was obtained after column chromatography using Pet Ether/ Et_2O (5:1), 14.2 mg, 0.1 mmol, 8% as a brown oil.



Compound 296

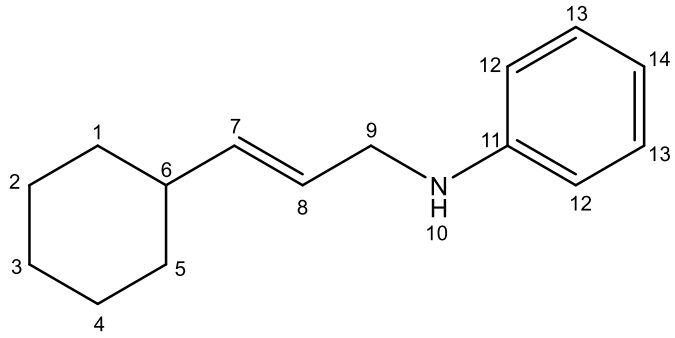
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.48 (m, 2H, H-***3*** + H-***5***), 6.20 – 6.19 (m, 1H, H-***6***), 5.94 – 5.92 (m, 1H, H-***4***), 4.07 – 4.03 (m, 1H, H-***9***), 3.94 – 3.89 (m, H-***9***), 2.57 – 1.95 (m, 4H, H-***7*** and H-***8***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.92 (C-***3***), 128.02 (C-***5***), 105.66 (C-***4***), 90.03 (C-***6***), 69.21 (C-***9***), 31.73 (C-***7***), 24.44 (C-***8***).

Characterization supported by published data.[162]

Platinum catalyzed addition of aniline to cyclohexylallene

Bis (acetonitrile) Platinum dichloride (4.4 mg, 0.0125 mmol) silver triflate (6.4 mg, 0.025 mmol) and aniline (35 mg, 0.375 mmol) were added to an oven dried schlenk under N_2 and dissolved in 1.2mL THF (0.2 M). Commercially available cyclohexylallene (36 µl, 0.25 mmol) was added, and the reaction was heated at 70 ^{0}C for 20 hours. The reaction was cooled to rt and filtered through celite washing with DCM. **Compound 84b** was obtained using preparative TLC with Pet Ether/ Et_2O (10:1), 7.9 mg, 0.037 mmol, 15% as a brown oil.



Compound 84b

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.14 (m, 2H, ***Ar***), 6.72 – 6.67 (m, 1H, ***Ar***), 6.65 – 6.60 (m, 2H, ***Ar***), 5.66 (dd, *J* = 15.5, 6.6 Hz, 1H, H-***7*** or ***8***), 5.53 (dtd, *J* = 15.5, 5.9, 1.1 Hz, 1H, H-***7*** or ***8***), 3.69 (d, *J* = 5.9 Hz, 2H, H-***9***), 2.02 – 1.91 (m, 1H, H-***6***), 1.76 – 1.61 (m, 6H, H-***1-5***), 1.32 – 1.17 (m, 4H, H-***1-5***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.31 (C-***11***), 139.29 (CH, C-***7***), 129.18 (CH, C-***13***), 124.19 (CH, C-***8***), 117.36 (CH, C-***14***), 113.01 (CH, C-***12***), 46.28 (CH_2, C-***9***), 40.46 (CH, C-***6***), 32.89 (CH, C-***1*** and ***5***), 26.17 (CH, C-***3***), 26.03 (CH, C-***2*** and ***4***).

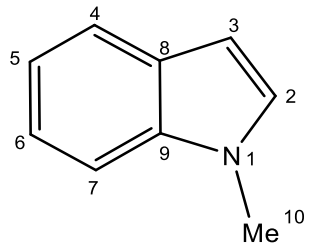
Characterization supported by published data.[163]

General procedure for alkylation of indole

Indole (1 eq) was added to a vacuum dried round bottomed flask under N_2 and dissolved in acetone (0.28 M). KOH (5 eqs) was added and reaction mixture stirred vigorously for 30 minutes. The reaction was cooled to 0 ^{0}C and the corresponding alkylation reagent, MeI or BnCl (2 eqs) was added dropwise. The reaction was stirred overnight at rt and the resulting mixture was quenched with H_2O and extracted with Et_2O. The organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuum. Final products were purified by column chromatography using Pet Ether/EtOAc as the eluent.

Synthesis of 1-methyl-1-H-indole[164]

Synthesized from indole (2 g, 17.1 mmol), KOH (4.8 g, 85.4 mmol), MeI (2.2 mL, 34.1 mmol), and 60 mL of acetone. **Compound 127a** obtained after column chromatography, Pet Ether/EtOAc, 20:1, 818.3 mg, 6.3 mmol, 73% as a yellow oil.



Compound 127a

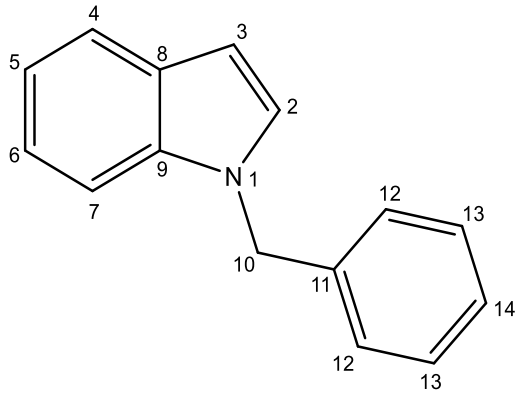
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.9 Hz, 1H, H-***4***), 7.35 (d, *J* = 8.2 Hz, 1H, H-***7***), 7.26 – 7.22 (m, 1H, H-***5***), 7.15 – 7.10 (m, 1H, H-***6***), 7.07 (d, *J* = 2.9 Hz, 1H, H-***2***), 6.50 (d, *J* = 2.9 Hz, 1H, H-***3***), 3.81 (s, 3H, H-***10***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.7 (C-***9***), 128.8 (C-***8***), 128.5 (CH, C-***2***), 121.5 (CH, C-***5***), 120.9 (CH, C-***4***), 119.3 (CH, C-***6***), 109.2 (CH, C-***7***), 100.9 (CH, C-***3***), 32.8 (CH_3, C-***10***).

Characterization consistent with reported data.[164a]

Synthesis of 1-benzyl-1-H-indole[165]

Synthesized from indole (2 g, 17.1 mmol), KOH (4.8 g, 85.3 mmol), BnCl (3.9 mL, 34.1 mmol) and 60 mL of acetone. **Compound 127d** obtained after column chromatography, Pet Ether/EtOAc, 20:1, and recrystallization with hexane, 2731.6 mg, 13.1 mmol, 77% as a white solid.



Compound 127d

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.68 (m, 1H, H-***4***), 7.36 – 7.30 (m, 4H, H-***14***, H-***12*** and H-***7***), 7.23 – 7.19 (m, 1H, H-***6***), 7.19 – 7.13 (m, 4H, H-***13***, H-***2*** and H-***5***), 6.60 (d, *J* = 3.1 Hz, 1H, H-***3***), 5.37 (s, 2H, H-***10***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.7 (C-***11***), 136.4 (C-***9***), 128.9 (CH, C-***14***), 128.8 (C-***8***), 128.3 (CH, C-***13***), 127.6 (CH, C-***12***), 126.8 (CH, C-***2***) 121.7 (CH, C-***6***), 121.1 (CH, C-***4***), 119.5 (CH, C-***5***), 109.7 (CH, C-***7***), 101.7 (CH, C-***3***), 50.1 (CH_2, C-***10***).

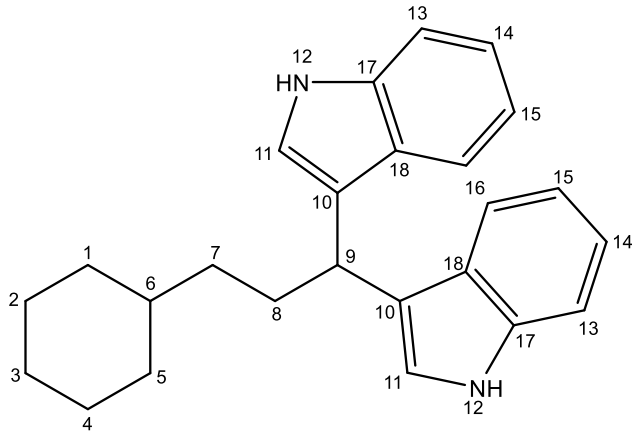
Characterization consistent with reported data.[164b]

General procedure for platinum catalyzed bis-indolylation of cyclohexylallene

Platinum (II) chloride (5 mol %) and the corresponding indole or indoles (varying eqs as specified in table 8 of chapter 2) were added to an oven dried schlenk under N_2 and dissolved in THF (0.2 M). Commercially available cyclohexylallene (1 eq) and methanol (3 eqs) were added, and the reaction was heated at 70 ^{o}C for 20 hours. The reaction was cooled to rt and filtered through celite washing with DCM. The solvent was evaporated under vacuum and the final compounds were purified by column chromatography using Pet Ether/ EtOAc (as specified).

Characterization of products

Synthesised from cyclohexyallene (119 µl, 0.82 mmol), $PtCl_2$ (11 mg, 0.04 mmol), indole (288 mg, 2.46 mmol), methanol (100 µl, 2.46 mmol) and 4 mL THF. **Compound 133** obtained after column chromatography using pet ether/EtOAc (10:1) 183.3 mg, 0.51 mmol, 61% as an orange oil. (Mixture of product and excess indole, mass and yield calculated from ^{1}H NMR by analysis of total weighted mass and ratio of both product and excess indole by comparison of integrals for both compounds).

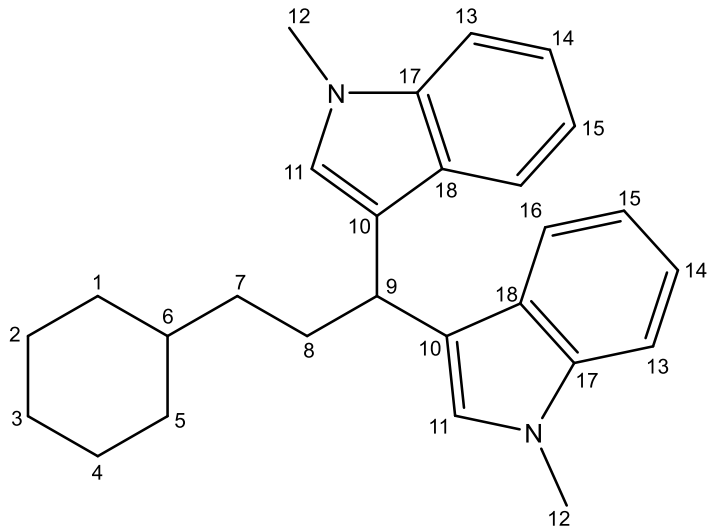


Compound 133

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 2H, H-***12***), 7.52 (d, *J* = 8.0 Hz, 2H, H-***13***), 7.26 (d, *J* = 8.0 Hz, 2H, H-***16***), 7.05 (t, *J* = 0.9 Hz, 2H, H-***14***), 6.96 (ddd, *J* = 8.0, 7.3, 0.9 Hz, 2H, H-***15***), 6.91 (d, *J* = 2.2 Hz, 2H, H-***11***), 4.35 (t, *J* = 7.3 Hz, 1H, H-***9***), 2.19 – 2.12 (m, 2H, H-***8***), 1.66 – 1.58 (m, 4H, H-***1+5***), 1.28 – 1.12 (m, 7H, H-***2+4, 3+6***), 0.83 – 0.73 (m, 2H, H-***7***).

Data consistent with published data.[78]

Synthesized from cyclohexyallene (119 µl, 0.82 mmol), $PtCl_2$ (11 mg, 0.04 mmol), 1-methyl-1-H-indole (318 mg, 2.46 mmol), methanol (100 µl, 2.46 mmol) and 3.2 mL THF. **Compound 133a** obtained after column chromatography using pet ether/EtOAc, 10:1, 230.5 mg, 0.6 mmol, 74% as an orange oil.



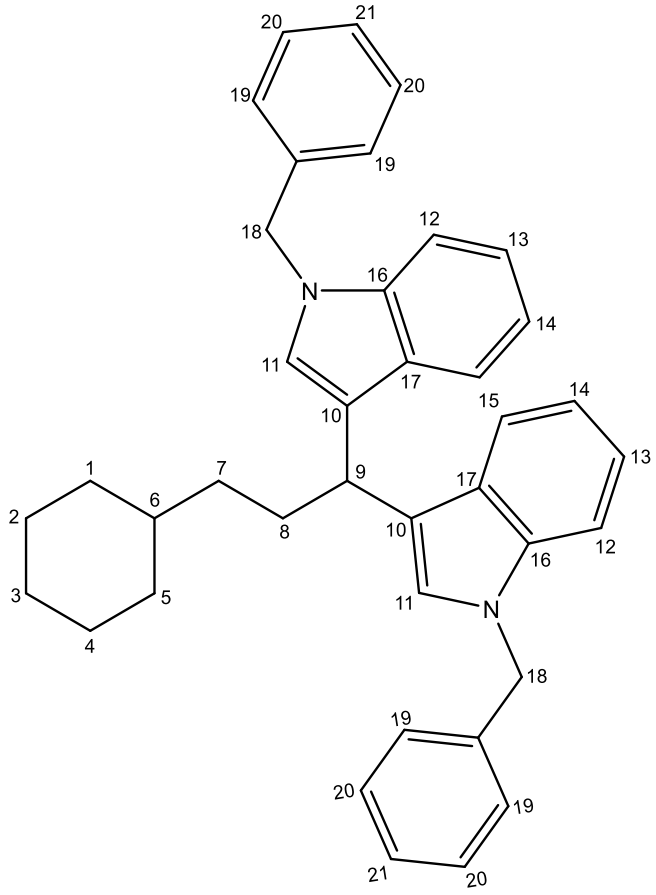
Compound 133a

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 2H, H-***13***), 7.17 (d, *J* = 8.2 Hz, 2H, H-***16***), 7.09 (t, *J* = 7.6 Hz, 2H, H-***14***), 6.95 (t, *J* = 7.5 Hz, 2H, H-***15***), 6.73 (s, 2H, H-***11***), 4.33 (t, *J* = 7.4 Hz, 1H, H-***9***), 3.60 (d, *J* = 0.5 Hz, 6H, H-***12***), 2.15 – 2.09 (m, 2H, H-***8***), 1.62 – 1.54 (m, 4H, H-***1+5***), 1.26 – 1.15 (m, 4H, H-***2+4***), 1.14 – 0.99 (m, 3H, H-***3+6***), 0.86 – 0.73 (m, 2H, H-***7***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.29 (C), 127.60 (C), 126.18 (CH, C-***11***), 121.23 (CH, C-***14***), 119.77 (CH, C-***15***), 119.38 (C), 118.40 (CH, C-***16***), 109.08 (CH, C-***13***), 38.02 (CH, C-***9***), 36.25 (CH_2, C-***7*** and C-***8***), 34.27 (CH, C-***6***), 33.75 (CH_2, C-***1*** or C-***5***), 33.47 (CH_2, C-***1*** or C-***5***), 32.66 (CH_3, C-***12***), 26.96 (CH_2, C-***4*** or C-***2***), 26.79 (CH_2, C-***4*** or C-***2***), 26.50 (CH_2, C-***3***).

Data consistent with published data.[78]

Synthesized from cyclohexyallene (60 µl, 0.41 mmol), $PtCl_2$ (6 mg, 0.02 mmol), 1-H-indole (144 mg, 1.23 mmol), 1-benzyl-1-H-indole (256 mg, 1.26 mmol), methanol (49 µl, 1.23 mmol) and 2 mL THF. **Compounds 133c** and **302a** obtained after column chromatography using pet ether/EtOAc, 20:1, 61.4 mg, 0.11 mmol, 28% as a brown oil (**133c**) and 49.3 mg, 0.11 mmol, 27% as an orange oil (**302a**).

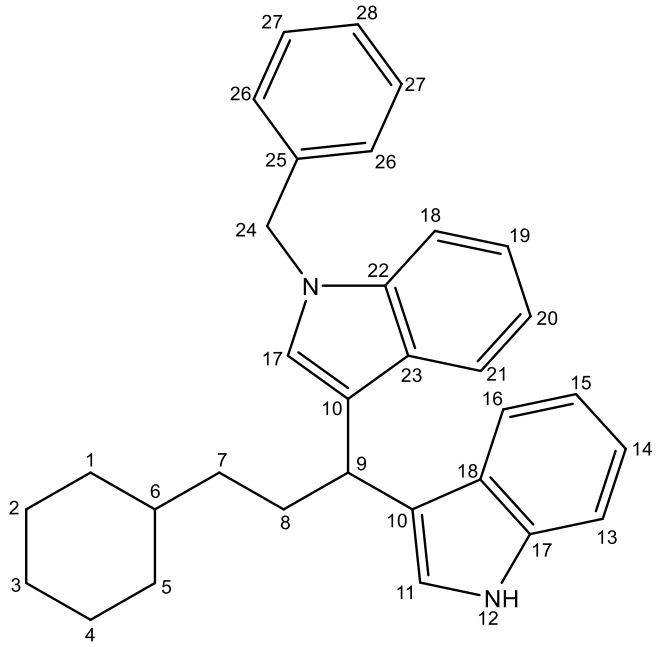


Compound 63

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.9 Hz, 2H, H-***15***), 7.18-6.90 (m, 21H, ***H-12,13,14,19,20,21***), 6.90 (s, 2H, H-***11***), 5.21 (s, 4H, H-***18***), 4.35 (t, *J* = 7.4 Hz, 1H, H-***9***), 2.18 – 2.11 (m, 2H, H-***8***), 1.64 – 1.53 (m, 6H, H-***2-4***), 1.27 – 1.20 (m, 2H, H-***7***), 1.19 – 1.14 (m, 1H, H-***6***), 1.13 – 1.00 (m, 2H, H-***5***), 0.81 – 0.71 (m, 2H, H-***1***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.07 (C), 137.01 (C), 128.67 (CH, **Ar**), 127.37 (CH, **Ar**), 126.53 (CH, **Ar**), 125.74 (CH=C, C-***11***), 121.42 (CH, **Ar**), 119.99 (CH, **Ar**), 119.76 (C), 118.63 (CH, **Ar**), 109.57 (CH, **Ar**), 49.80 (CH_2, C-***18***), 37.85 (CH, C-***6***), 36.11 (CH_2, C-***7*** and C-***8***), 34.45 (CH, C-***9***), 33.47 (CH_2, C-***1*** or C-***5***), 33.07 (CH_2, C-***1*** or C-***5***), 26.76 (CH_2, C-***2*** and C-***4***), 26.44 (CH_2, C-***3***).

Data consistent with published data.[78]



Compound 64

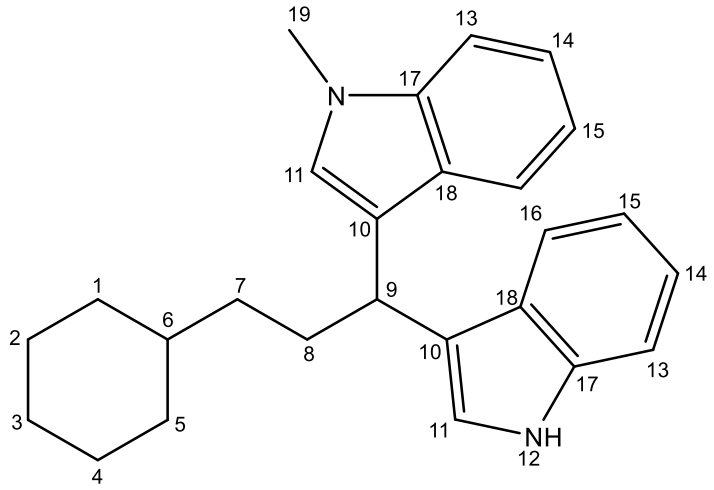
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H, H-***12***), 7.51 (dd, *J* = 7.9, 2.8 Hz, 2H, H-***13***), 7.26 (d, *J* = 8.1 Hz, 1H, H-***17***), 7.19 – 6.90 (m, 13H, H-***Ar***), 6.88 (s, H, H-***11***), 5.20 (s, 2H, H-***24***), 4.36 (t, *J* = 7.4 Hz, 1H, H-***9***), 2.18 – 2.11 (m, 2H, H-***8***), 1.62 – 1.54 (m, 4H, H-***1+5***), 1.26 – 1.09 (m, 7H, H-***2+4, 3+6***), 0.79 – 0.74 (m, 2H, H-***7***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.05 (C), 128.66 (C), 127.38 (C-***Ar***), 126.52 (C-***Ar***), 125.76 (C-***Ar***), 121.69, 121.45, 121.33(C-***Ar***), 119.89 (C-***Ar***), 119.77(C-***Ar***), 118.68 (C-***Ar***), 111.00 (C-***Ar***), 109.59 (C-***Ar***), 49.81 (CH_2, C-***19***), 37.90 (CH, C-***6***), 36.13 (CH_2, C-***1*** or C-***5***), 34.41 (CH, C-***9***), 33.49 (CH_2, C-***7***), 33.44 (CH_2, C-***1*** or C-***5***), 33.13 (CH_2, C-***8***), 26.75 (CH_2, C-***4*** and C-***2***), 26.45 (CH_2, C-***3***).

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calc. for $C_{32}H_{34}N_2$ $[M+H]^+$ 447.2795: Found: 447.2793.

Synthesized from cyclohexyallene (119 µl, 0.82 mmol), $PtCl_2$ (11 mg, 0.04 mmol), indole (288 mg, 2.46 mmol), 1-methyl-1-H-indole (322 mg, 2.46 mmol), methanol (100 µl, 2.46 mmol) and 4 mL THF. Compounds **133a** and **302b** obtained after column chromatography using pet ether/EtOAc, 20:1, 42.2 mg, 0.11 mmol, 13% as a brown oil and 81.3 mg, 0.22 mmol, 27% as an orange oil respectively.

Characterisation consistent with that for compound **133a**.

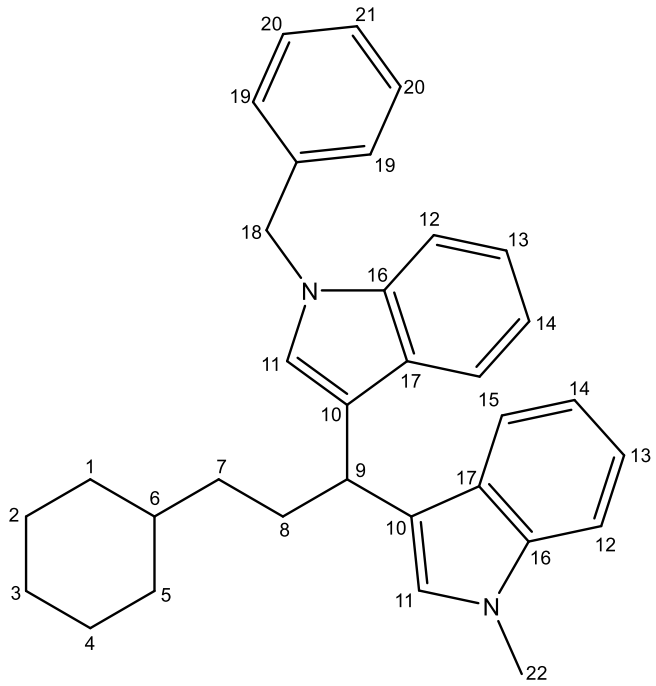


Compound 302b

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H, H-***12***), 7.64 (dd, *J* = 7.9, 3.2 Hz, 2H, H-***13***), 7.40 – 7.30 (m, 2H, H-***16***), 7.20 (dt, *J* = 14.5, 7.4 Hz, 2H, H-***15***), 7.10 – 7.05 (m, 2H, H-***14***), 7.04 (s, 1H, H-11 (**NMe**)), 6.86 (s, 1H, H-***11*** (**NH**)), 4.46 (t, *J* = 7.3 Hz, 1H, H-***9***), 3.75 (s, 3H, H-***19***), 2.29 – 2.22 (m, 2H, H-***8***), 1.74 – 1.66 (m, 4H, H-***1+5***), 1.40 – 1.28 (m, 4H, H-***2+4***), 1.26 – 1.15 (m, 3H. H-***3+6***), 0.95 – 0.84 (m, 2H, H-***7***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.29 (C), 136.61 (C), 126.21 (CH, C-***11***), 121.23 (CH, C-***11***), 119.72 (CH, **Ar**), 119.19 (C), 119.00 (CH, **Ar**), 111.01 (CH, **Ar**), 109.10 (CH, **Ar**), 37.99 (CH, C-***6***), 36.20 (CH_2, C-***1*** and C-***5***), 34.33 (CH, C-***9***), 33.48 (CH_2, C-***8*** or C-***7***), 33.45 (CH_2, C-***8*** or C-***7***), 32.66 (CH_3, C-***19***), 26.77 (CH_2, C-***2*** and C-***4***), 26.48 (CH_2, C-***3***).

Synthesized from cyclohexyallene (60 µl, 0.41 mmol), $PtCl_2$ (5.6 mg, 0.02 mmol), 1-methyl-1-H-indole (54 mg, 0.41 mmol), 1-benzyl-1-H-indole (85 mg, 0.41 mmol), methanol (49 µl, 1.23 mmol) and 2 mL THF. **Compound 302c** obtained after column chromatography using pet ether/EtOAc, 20:1, 133.5 mg, 0.29 mmol, 71% as a brown oil.

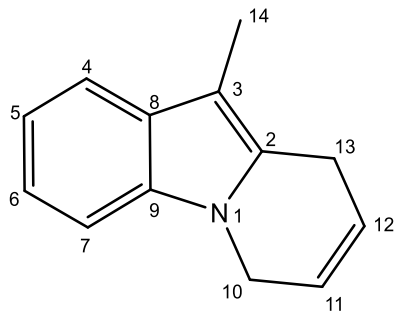


Compound 302c

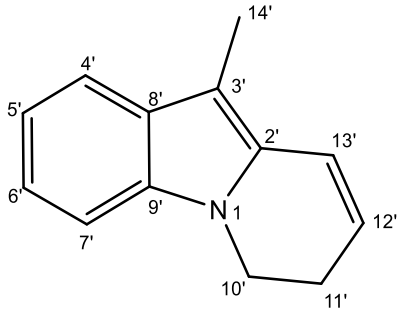
Characteristic peaks, shown in **figure 19 and 20** of results and discussion.

Platinum catalyzed reaction of 1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with indole

$PtCl_2$ (5.45 mg, 0.02 mmol) and indole (144 mg, 1.23 mmol) were added to a microwave vial, capped and flushed with N_2. The solids were dissolved in 2 mL dry 1,4-dioxane (0.2 M) and 1-(2, 3-butadien-1-yl)-3-methyl-1H-indole (75 mg, 0.41 mmol) dissolved in dry 1,4-dioxane was added. Dry methanol (50 µl, 1.23 mmol) was added and the vial heated under microwave irradiation at 130 ^{0}C for 1 hour. Compounds **218a** and **218a'** (inseparable mixture of isomers) and compound **287a** obtained after column chromatography, Pet Ether/EtOAc, 50:1 then 20:1, 4 mg, mmol, 5% as an orange/yellow solid and 76 mg, mmol, 61% as a green/yellow oil respectively.



Compound 218a

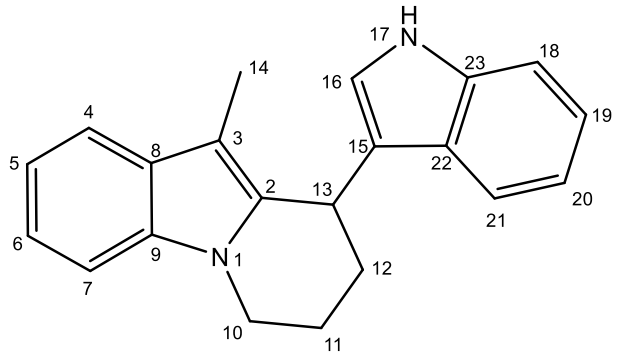


Compound 218a'

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H, H-***7+7'***), 7.21– 6.92 (m, 6H, H-***4-6*** and ***4'-6'***), 6.59 (dt, *J* = 9.9, 1.8 Hz, 1H, H-***13'***), 6.04 – 5.93 (m, 2H, H-***11*** and H-***12***), 5.92 – 5.86 (m, 1H, H-***12'***), 4.53 (ddd, *J* = 6.7, 4.4, 2.7 Hz, 2H, H-***10***), 3.98 (t, *J* = 6.9 Hz, 2H, H-***10'***), 3.47 – 3.41 (m, 2H, H-***13***), 2.58 – 2.52 (m, 2H, H-***11'***) 2.24 (s, 3H, H-***14'***), 2.19 (s, 3H, H-***14***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.74 (C-**9'**), 135.3 (C-**9**), 131.6 (C-**2'**), 129.2 (C-**2**), 129.2 (C-**8'**), 128.5 (C-**8**), 122.9 (CH, C-***12'***), 122.1 (CH, C-***11*** or ***12***), 121.9 (CH, C-***4-6*** or ***4'-6'***), 120.5 (CH, C-***11*** or ***12***), 120.3 (CH, C-***4-6*** or C-***4'-6'***), 119.2 (CH, C-***4-6*** or C-***4'-6'***), 118.9 (CH, C-***4-6*** or C-***4'-6'***), 118.8 (CH, C-***7*** or C-***7'***), 118.5 (CH, C-***13'***), 117.8 (CH, C-***7*** or C-***7'***), 108.5 (CH, C-***4-6*** and C-***4'-6'***), 108.4 (CH, C-***4-6*** and C-***4'-6'***), 107.5 (C-***3'***), 104.5 (C-***3***) 41.8 (CH_2, C-***10***), 39.8 (CH_2, C-***10'***), 24.4 (CH_2, C-***11'***), 22.8 (CH_2, C-***13***), 8.3 (CH_3, C-***14***), 8.1 (CH_3, C-***14'***)

Spectra consistent with previously published data.[165]



Compound 287a

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H, H-***17***), 7.66 (d, *J* = 7.9 Hz, 1H, H-***4***), 7.57 (d, *J* = 7.8 Hz, 1H, H-***7***), 7.36 (t, *J* = 7.4 Hz, 2H, H-***5*** + H-***6***), 7.23 (m, 2H, H-***19***+ H-***20***), 7.16 (t, *J* = 7.5 Hz, 2H, H-***18*** + H-***21***), 6.52 (s, 1H, H-***16***), 4.81 (t, *J* = 4.3 Hz, 1H, H-***13***), 4.34 – 4.25 (m, 1H, H-***10***), 3.94 (td, *J* = 11.1, 4.8 Hz, 1H, H-***10***), 2.44 – 2.35 (m, 1H, H-***12***), 2.24 – 2.15 (m, 1H, H-***12***), 2.15 – 2.06 (m, 1H, H-***11***), 2.03 (s, 3H, H-***14***), 1.97 – 1.88 (m, 1H, H-***11***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.70 (C-***2***), 135.88 (C-***9***), 134.87 (C-***23***), 128.74 (C-***8***), 126.22 (C-***22***), 123.28 (CH, C-***16***), 121.94 (CH, C-***19/20***), 120.29 (CH, C-***19/20***), 119.34 (CH, C-***18/21***), 118.98 (CH, C-***4***), 118.78 (C-***3***), 118.05 (CH, C-***7***), 111.36 (CH, C-***5/6***), 108.65 (CH, C-***5/6***), 105.96 (C-***15***), 42.58 (CH_2, C-***10***), 30.42 (CH, C-***13***), 28.17 (CH_2, C-***12***), 19.56 (CH_2, C-***11***), 8.36 (CH, CH_3, C-***14***).

M.P. 151-158 ^{o}C

Spectra consistent with previously published data.[78]

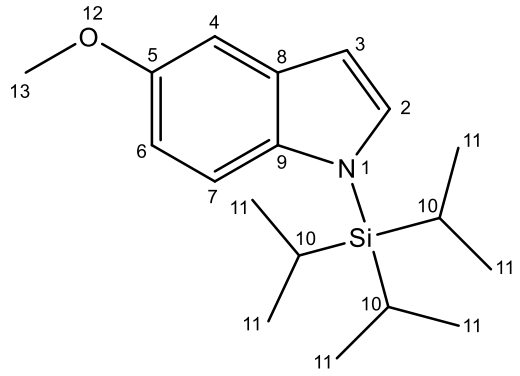
General procedure for triisopropyl silyl protection of substituted indoles

NaH (1.6 eqs) was added to a vacuum dried round bottomed flask under N_2, dissolved in dry THF (0.3 M) and stirred at 0 ^{o}C. The corresponding commercially available substituted indole under N_2 was dissolved in dry THF and added drop wise to the NaH suspension. The mixture was stirred for 30 mins, then at 0 ^{o}C, *i*Pr_3SiCl (1.6 eqs) was added drop wise. The reaction was stirred at rt for 3 hours. The reaction was quenched with methanol and water at 0 ^{o}C and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuum. Final products were purified by column chromatography using Pet Ether/EtOAc as the eluent.

Characterisation of products

5-methoxy-1-(triisopropylsilyl)-1H-indole

Synthesized from 5-methoxyindole (1000 mg, 6.8 mmol), NaH (435 mg, 11 mmol), *i*Pr_3SiCl (2.4 mL, 11 mmol) and 23 mL dry THF. Compound **309b** was obtained after column chromatography, Pet Ether/EtOAc, 50:1 then 20:1, 2062 mg, 6.8 mmol, 99% as an orange oil.



Compound 309b

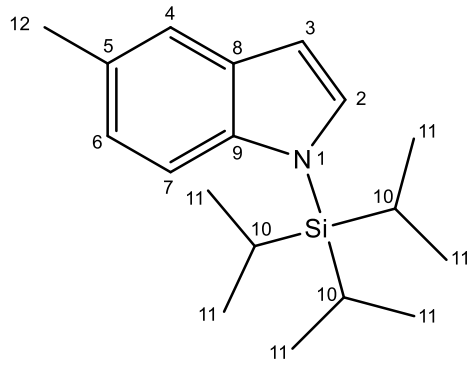
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.9 Hz, 1H, H-***7***), 7.26 (d, *J* = 3.1 Hz, 1H, H-***2***), 7.13 (d, *J* = 2.4 Hz, 1H, H-***4***), 6.83 (dd, *J* = 8.9, 2.4 Hz, 1H, H-***6***), 6.58 (d, *J* = 3.1 Hz, 1H, H-***3***), 3.88 (s, 3H, H-***13***), 1.68 (heptet, *J* = 7.5 Hz, 3H, H-***10***), 1.17 (d, *J* = 7.5 Hz, 18H, H-***11***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.06 (C-***5***), 135.76 (C-***9***), 131.96 (CH, C-***2***), 126.76 (C-***8***), 114.52 (CH, C-***4***), 111.36 (CH, C-***6***), 104.55 (CH, C-***3***), 102.26 (CH, C-***7***), 55.68 (CH, O-CH_3, C-***13***), 18.11 (CH, CH_3, C-***11***), 12.81 (CH, C-***10***).

Characterization consistent with reported data.[166]

5-methyl-1-(triisopropylsilyl)-1H-indole

Synthesized from 5-methylindole (1034 mg, 7.9 mmol), NaH (496 mg, 12.4 mmol), *i*Pr_3SiCl (2.6 mL, 12.2 mmol) and 25 mL dry THF. Compound **309c** was obtained after column chromatograph, Pet Ether/EtOAc, 30:1, 20:1, 2048 mg, 7.3 mmol, 90% as a clear oil.



Compound 309c

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.41 (m, 1H, H-***4***), 7.40 (d, *J* = 8.5 Hz, 1H, H-***7***), 7.21 (d, *J* = 3.2 Hz, 1H, H-***2***), 6.97 (dd, *J* = 8.5, 1.7 Hz, 1H, H-***6***), 6.54 (dd, *J* = 3.2, 0.8 Hz, 1H, H-***3***), 2.44 (s, 3H, H-***12***), 1.69 (heptet, *J* = 7.5 Hz, 3H, H-***10***), 1.14 (d, *J* = 7.5 Hz, 18H, H-***11***).

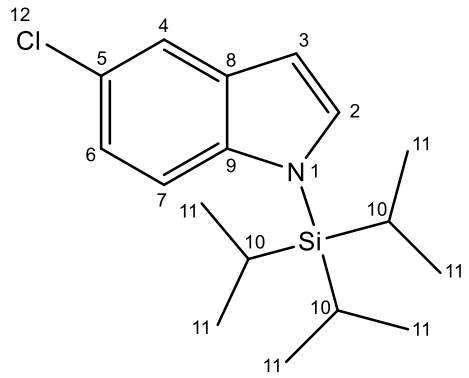
^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1 (C-***5***), 131.7 (C-***9***), 131.3 (CH, C-***2***), 128.9 (C-***8***), 122.9 (CH, C-***6***), 120.3 (CH, C-***4***), 113.5 (CH, C-***7***), 104.2 (CH, C-***3***), 21.3 (CH_3, C-***12***), 18.2 (CH_3, C-***11***), 12.8 (CH, CH, C-***10***).

ν_{max}/cm^{-1}: 2946 (s, C-H), 2868 (s, C-H), 1619m (Ar, C=C), 1471 (vs, CH_3), 1464 (vs, CH_3), 888 (s, Si-C).

HRMS ASAP (Solid): Calculated for $C_{18}H_{29}NSiH$ $(M+H)^+$: 288.2149. Found: 288.2148.

5-Chloro-1-(triisopropylsilyl)-1H-indole

Synthesized from 5-chloroindole (1770 mg, 11.2 mmol), NaH (718 mg, 18 mmol), *i*Pr_3SiCl (3.9 mL, 18 mmol) and 37 mL dry THF. Compound **309d** was obtained after column chromatograph, Pet Ether, 3363.7 mg, 11 mmol, 98% as a clear oil.



Compound 309d

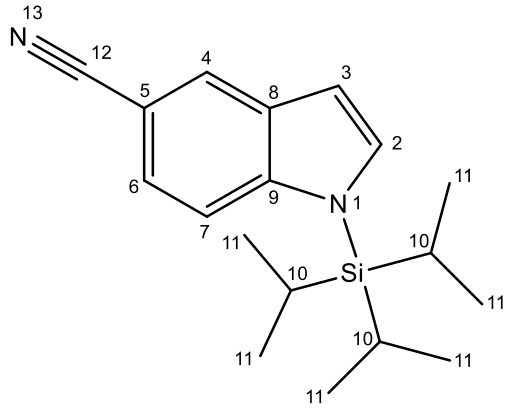
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 2.2 Hz, 1H, H-***4***), 7.40 (d, *J* = 8.8 Hz, 1H, H-***7***), 7.26 (d, *J* = 3.5 Hz, 1H, H-***2***), 7.09 (dd, *J* = 8.8, 2.2 Hz, 1H, H-***6***), 6.56 (dd, *J* = 3.5, 0.8 Hz, 1H, H-***3***), 1.68 (heptet, *J* = 7.5 Hz, 3H, H-***10***), 1.13 (d, *J* = 7.5 Hz, 18H, H-***11***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2 (C-***9***), 132.6 (CH, C-***2***), 132.6 (C-***5***) 125.4 (C-***8***), 121.6 (CH, C-***6***), 119.9 (CH, C-***4***), 114.7 (CH, C-***7***), 104.4 (CH, C-***3***), 18.1 (CH, CH_3, C-***11***), 12.8 (CH, C-***10***).

Characterization consistent with reported data.[166]

5-Cyano-1-(triisopropylsilyl)-1H-indole

Synthesized from 5-cyanoindole (1500 mg, 10.6 mmol), NaH (675 mg, 16.8 mmol), *i*Pr_3SiCl (3.6 mL, 16.8 mmol) and 35 mL dry THF. Compound **309e** was obtained after column chromatography, Pet Ether/EtOAc, 50:1 then 20:1, 3051.1 mg, 3.2 mmol, 97% as a yellow oil.



Compound 309e

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.7 Hz, 1H, H-***4***), 7.58 (d, *J* = 8.7 Hz, 1H, H-***7***), 7.41 (dd, *J* = 8.7, 1.7 Hz, 1H, H-***6***), 7.39 (d, *J* = 3.3 Hz, 1H, H-***2***), 6.73 (dd, 3.3, 0.8 Hz, 1H, H-***3***), 1.73 heptet, *J* = 7.5 Hz, 3H, H-***10***), 1.17 (d, *J* = 7.5 Hz, 18H, H-***11***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7 (C-***5***), 133.4 (CH, C-***2***), 131.3 (C-***9***), 125.9 (CH, C-***4***), 124.4 (CH, C-***6***), 120.76 (C≡N, C-***12***), 114.5 (CH, C-***7***), 105.4 (CH, C-***3***), 102.76 (C-***8***), 18.0 (CH_3, C-***11***), 12.8 (CH, C-***10***).

ν_{max}/cm^{-1}: 2949 – 2868 (s, C-H), 2221 (s, C≡N), 1608 (w, C=C), 1461 (C-H methyl), 1291 (s, C-N).

HRMS ASAP (Solid): Calc. for $C_{18}H_{26}N_2Si$ $[M+H]^+$ 299.1948: Found: 299.1944

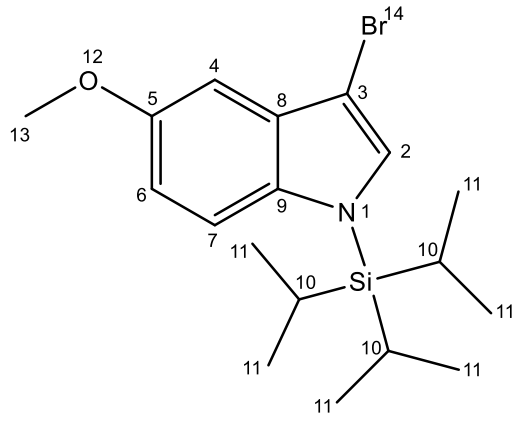
General procedure for bromination of position of triisopropyl silyl protected substituted indoles

Freshly recrystallized NBS (1.3 eqs) was added to a 2 necked round bottom flask under N_2 atmosphere, dissolved in dry THF (0.2 M) and cooled to -78 ^{0}C. The silyl protected indole (1 eq) under N_2 was dissolved in dry THF and slowly added to the NBS solution. The reaction was stirred at -78 ^{0}C for 3 hours and then quenched with water to form a precipitate. The reaction mixture was extracted with Et_2O, the organic layers were dried using $MgSO_4$, filtered and concentrated in vacuum. Final products were purified by column chromatography using Pet Ether/EtOAc as the eluent.

Characterisation of products:

3-Bromo-5-methoxy-1-(triisopropylsilyl)-1H-indole

Synthesized from 5-methoxy-1-(triisopropylsilyl)-1H-indole (2000 mg, 6.59 mmol), NBS (1290 mg, 7.25 mmol) and 33 mL dry THF. **Compound 310b** obtained after column chromatography, Pet Ether/EtOAc, 30:1, 1438.9 mg, 3.76 mmol, 57%.



Compound 310b

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 9.0 Hz, 1H, H-***7***), 7.20 (s, 1H, H-***2***), 6.98 (d, *J* = 2.6 Hz, 1H, H-***4***), 6.84 (d, *J* = 9.0, 2.6 Hz, 1 H, H-***6***), 3.89 (s, 3H, H-***13***), 1.65 (heptet, *J* = 7.5 Hz, 3 H, H-***10***), 1.13 (d, *J* = 7.5 Hz, 18 H, H-***11***)

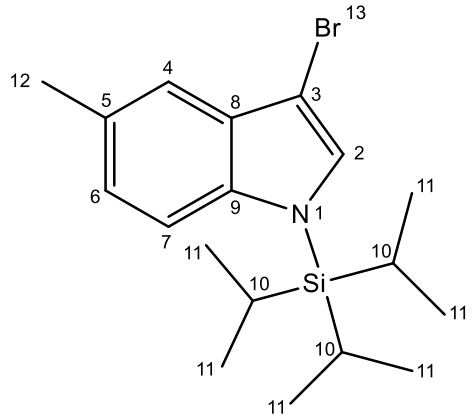
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9 (C-***5***), 135.0 (C-***9***), 130.6 (C-***8***), 130.5(CH, C-***2***), 115.1 (CH, C-***7***), 113.1 (CH, C-***6***), 100.4 (CH, C-***4***), 93.3 (C-Br, C-***3***), 55.8 (CH_3, C-***13***), 18.2 (CH_3, C-***11***), 12.9 (CH, C-***10***).

ν_{max}/cm^{-1}: 2949 – 2868 (s, C-H), 1620 (w, C=C), 1479 (C-H methyl), 1446-1434 (m, Ar C=C), 1212 – 1168 (s, C-N), 830 (m, C=C-H). HRMS:

HRMS ASAP (Solid): Calculated for $C_{18}H_{28}{}^{79}BrNOSi$ $[M+H]^+$ 382.1203: Found: 382.1202. Calculated for $C_{18}H_{28}{}^{81}BrNOSi$ $[M+H]^+$ 384.1185: Found: 384.1183.

3-Bromo-5-methyl-1-(triisopropylsilyl)-1H-indole

Synthesized from 5-methyl-1-(triisopropylsilyl)-1H-indole (1016 mg, 3.5 mmol), NBS (818 mg, 4.6 mmol) and 17 mL dry THF. **Compound** 3**10c** obtained after column chromatography, Pet/EtOAc (40:1, 20:1), 836 mg, 2.3 mmol, 65% as a clear oil.



Compound 310c

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 1H, H-***4***) 7.36 (d, *J* = 8.5 Hz, 1H, H-***7***), 7.20 (d, *J*= 1.2 Hz, 1H, H-***2***), 7.02 (d, *J* = 8.5 Hz, 1H, H-***6***), 2.47 (s, 3H, H-***12***), 1.67 (heptet, *J* = 7.5 Hz, 3H, H-***10***), 1.14 (d, *J* = 7.5 Hz, 18H, H-***11***).

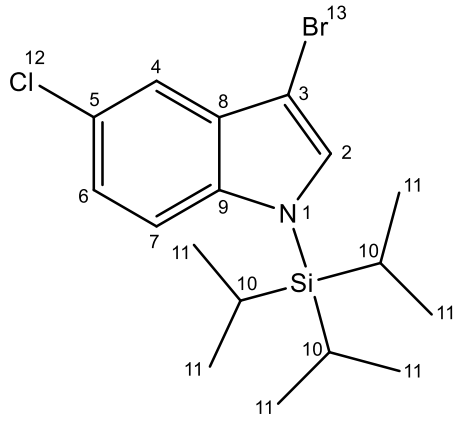
^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4 (C-***5***), 130.2 (C-***9***), 130.0 (C-***8***), 129.8 (CH, C-***2***), 124.1 (CH, C-***6***), 118.7 (CH, C-***7***), 113.8 (CH, C-***4***), 93.1 (C-Br, C-***3***), 21.3 (CH_3, C-***12***), 18.1 (CH_3, C-***11***), 12.8 (CH, C-***10***).

ν_{max}/cm^{-1}: 2948 (vs, C-H), 2869 (s, C-H), 1466 (s, CH_3), 1165 (vs, Ar-Br), 883 (s, Si-C).

HRMS ASAP (Solid): Calculated for $C_{18}H_{28}{}^{79}BrNSi$ $(M+H)^+$: 366.1244. Found: 366.1253. Calculated for $C_{18}H_{28}{}^{81}BrNSi$ $(M+H)^+$: 368.1249. Found: 368.1234.

3-Bromo-5-Chloro-1-(triisopropylsilyl)-1H-indole

Synthesized from 5-chloro-1-(triisopropylsilyl)-1H-indole (3360 mg, 11 mmol), NBS (2142 mg, 12 mmol) and 55 mL dry THF. **Compound 310d** obtained after column chromatography, Pet/EtOAc (10:1), 2744.2 mg, 7 mmol, 64% as a yellow oil.



Compound 310d

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J*= 2.1 Hz, 1H, H-***4***), 7.38 (d, *J* = 8.8 Hz, 1H, H-***7***), 7.25 (s, 1H, H-***2***), 7.14 (dd, *J* = 8.8, 2.1 Hz, 1H, H-***6***), 1.65 (heptet, *J* = 7.5 Hz, 3H, H-***10***), 1.13 (d, *J* = 7.5 Hz, 18H, H-***11***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6 (C-***9***), 131.2 (CH, C-***2***), 126.5 (C-***8***), 122.9 (CH, C-***6***), 118.7 (CH, C-***4***), 115.1 (CH, C-***7***), 92.9 (C-Br, C-***3***), 17.9 (CH_3, C-***11***), 12.8 (CH, C-***10***).

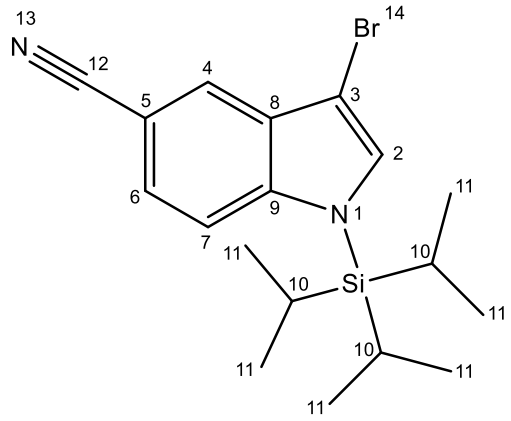
C-5 not seen in carbon NMR, low intensity.

ν_{max}/cm^{-1}: 2949 – 2869 (s, C-H), 1437 (C-H methyl), 1146 – 1127 (C-H), 784 (s, C-Cl).

HRMS ASAP (Solid): Calc. for $C_{17}H_{25}{}^{79}Br^{35}ClNSi$ $[M+H]^+$: 386.0698. Found: 386.0653.

3-Bromo-5-Cyano-1-(triisopropylsilyl)-1H-indole

Synthesized from 5-cyano-1-(triisopropylsilyl)-1H-indole (2000 mg, 6.7 mmol), NBS (1311 mg, 7.4 mmol) and 34 mL dry THF. **Compound 310e** obtained after column chromatography, Pet Ether/EtOAc, 40:1, 10:1, 1226.2 mg, 3.25 mmol, 48% as a brown oil.



Compound 310e

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 1.5 Hz, 1H, H-***4***), 7.53 (d, *J* = 8.7 Hz, 1H, H-***7***), 7.43 (dd, *J* = 8.7, 1.5 Hz, 1H, H-***6***), 7.34 (s, 1H, H-***2***), 1.67 (heptet, *J* = 7.5 Hz, 3H, H-***10***), 1.14 (d, *J* = 7.5 Hz, 18H, H-***11***)

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1 (C-***9***), 132.1 (CH, C-***2***), 125.37 (CH, C-***6***), 124.76 (CH, C-***4***), 120.10 (C-***8***), 114.9 (CH, C-***7***), 103.9 (C-***5***), 94.1 (C-Br, C-***3***), 17.9 (CH_3, C-***11***), 12.8 (CH, C-***10***).

ν_{max}/cm^{-1}: 2949 – 2869 (s, C-H), 2222 (s, C≡N), 1610 (w, C=C), 1457 (C-H methyl), 1299 (s, C-N).

HRMS (ASAP) Solid: Calculated for $C_{18}H_{25}{}^{79}BrN_2Si$ $[M+H]^+$ 377.1053: Found: 377.1049. Calculated for $C_{18}H_{25}{}^{81}BrN_2Si$ $[M+H]^+$ 379.1034: Found: 379.1030.

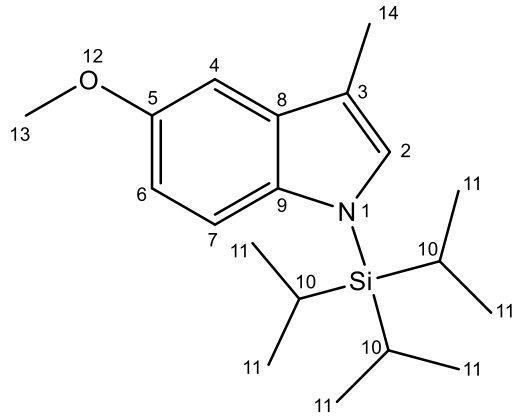
General procedure for methylation of position of bromo-1-triisopropyl silyl substituted indoles

3-Bromo-1-triisopropyl substituted indole (1 eq) was added to a 2 necked round bottomed flask under N_2 atmosphere, dissolved in dry THF (0.14 M) and cooled to -78 ^{0}C. *n*-BuLi (2.3 eqs) was added drop wise to the solution. After 20 minutes, MeI (2.7 eqs) was added and the reaction was warmed to rt and stirred for 20 hours. The reaction was quenched with saturated NH_4Cl solution at 0 ^{0}C and extracted with Et_2O. The organic layers were dried with $MgSO_4$, filtered and concentrated in vacuum. Final products were purified by column chromatography using Pet Ether/EtOAc as the eluent.

Characterisation of products:

5-Methoxy-3methyl-1-(triisopropylsilyl)-1H-indole

Synthesized from 5-methoxy-3-bromo-1-(triisopropylsilyl)-1H-indole (1200 mg, 3.14 mmol), *n*-BuLi (2.88 mL, 7.22 mmol), MeI (528 µL, 8.48 mmol) and 23 mL dry THF. **Compound 312b** obtained after concentrating in vacuum 959.6 mg, 3.0 mmol, 96% as a brown oil and used without further purification.



Compound 312b

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.9 Hz, 1H, H-***7***), 6.98 (d, *J* = 2.5 Hz, 1H, H-***4***), 6.98 (d, *J* = 0.8 Hz, 1H, H-***2***), 6.79 (dd, *J* = 8.9, 2.5 Hz, 1H, H-***6***), 3.87 (s, 3H, H-***13***), 2.29 (d, *J* = 0.8 Hz, 3H, H-***14***), 1.65 (heptet, *J* = 7.5 Hz, 3H, H-***10***), 1.13 (d, *J* = 7.5 Hz, 18H, H-***11***).

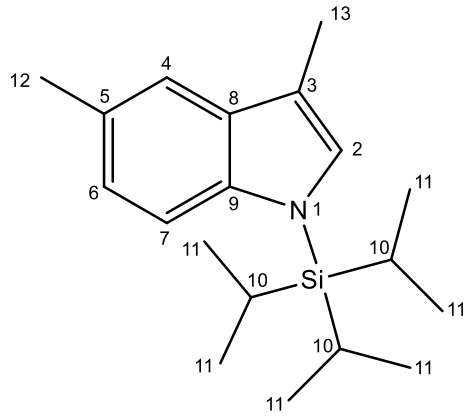
^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8 (C-***5***), 136.2 (C-***9***), 132.3 (C-***8***), 129.3 (CH, C-***2***), 114.5 (CH, C-***7***), 113.1 (C-***3***), 111.0 (CH, C-***6***), 100.5 (CH, C-***4***), 55.8 (O-CH_3, C-***13***), 18.2 (CH_3, C-***11***), 12.8 (CH, C-***10***), 9.86 (CH_3, C-***14***).

ν_{max}/cm^{-1}: 2947 – 2868 (s, C-H), 1616 – 1584 (w, C=C), 1480 (C-H methyl), 1454 – 1444 (m, Ar C=C), 1228 – 1208 (s, C-N), 1147 – 649 (m, C=C-H).

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calc. for $C_{19}H_{31}NOSi$ $[M+H]^+$ 318.2247: Found: 318.2248.

5-methyl-3-Methyl-1-(triisopropylsilyl)-1H-indole

Synthesized from 5-methyl-3-bromo-1-(triisopropylsilyl)-1H-indole (783 mg, 2.1 mmol), *n*-BuLi (2 mL, 4.9 mmol), MeI (360 µL, 5.8 mmol) and 15 mL dry THF. **Compound 312c** was obtained after work up and drying in vacuum, 628 mg, 2.1 mmol, 99% as a brown solid and used without further purification.



Compound 312c

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H, H-***6*** and H-***7***), 7.00 – 6.93 (m, 2H, H-***4*** and H-***2***), 2.46 (s, 3H, H-***12***), 2.30 (d, *J* = 1.1 Hz, 3H, H-***13***), 1.67 (heptet, *J* = 7.5 Hz, 3H, H-***10***), 1.14 (d, *J* = 7.5 Hz, 18H, H-***11***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5 (C-***9***), 132.1 (C-***5***), 128.6 (CH, C-***4*** or C-***2***), 128.3 (C-***8***), 122.7 (CH, C-***4*** or C-***2***), 118.5 (CH, C-***6*** or C-***7***), 113.5 (CH, C-***6*** or C-***7***), 112.9 (C-***3***), 21.4 (CH_3, C-***12***), 18.2 (CH, C-***11***), 12.8 (CH_3, C-***10***), 9.8 (CH_3, C-***13***).

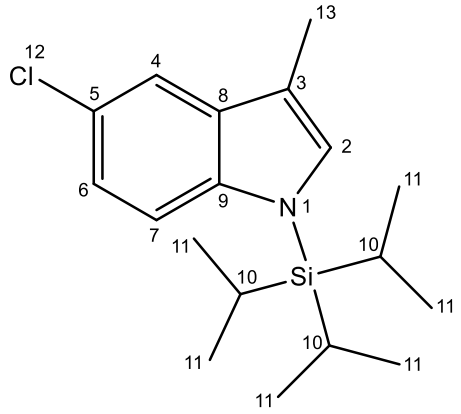
V_{max}/cm^{-1}: 2947 (vs, C-H), 2868 (vs, C-H), 1452 (s, CH_3), 883 (s, Si-C).

HRMS (ASAP) Solid: Calc. for $C_{19}H_{31}NSi$ $[M+H]^+$: 302.2297. Found: 302.2291.

M.P. 51 °C

5-Chloro-3-methyl-1-(triisopropylsilyl)-1H-indole

Synthesized from 5-chloro-3-bromo-1-(triisopropylsilyl)-1H-indole (2740 mg, 7.1 mmol), *n*-BuLi (7.7 mL, 19.2 mmol), MeI (1 mL, 16.4 mmol) and dry THF (51 mL). **Compound 312d** was obtained after work up and drying in vacuum, 2386 mg, 7.4 mmol and used without further purification.



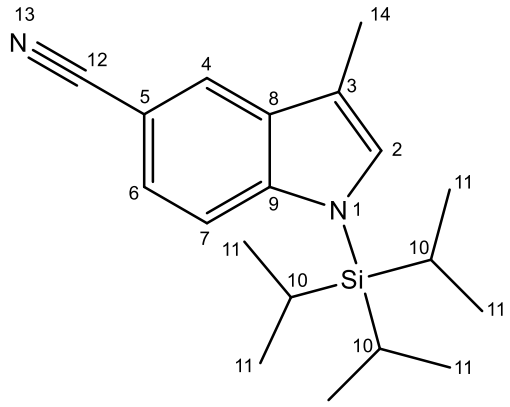
Compound 312d

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.2 Hz, 1H, H-***4***), 7.35 (d, *J* = 8.8 Hz, 1H, H-***7***), 7.08 (dd, *J* = 8.8, 2.2 Hz, 1H, H-***6***), 7.01 (d, *J* = 0.9 Hz, 1H, H-***2***), 2.28 (d, *J* = 0.9 Hz, 3H, H-***13***), 1.65 (heptet, *J* = 7.5 Hz, 3H, H-***10***), 1.13 (d, *J* = 7.5 Hz, 18H, H-***11***).

Full characterization not obtained due to deprotection being carried out immediately.

5-Cyano-3methyl-1-(triisopropylsilyl)-1H-indole

Synthesized from 5-cyano-3-bromo-1-(triisopropylsilyl)-1H-indole (600 mg, 1.6 mmol), *n*-BuLi (0.96 mL, 2.4 mmol), MeI (269 µL, 4.32 mmol) and 12 mL dry THF. **Compound 312e** was obtained after concentrating in vacuum 477.2 mg, 1.5 mmol, 96% as an orange oil and used without further purification.



Compound 312e

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 1.5 Hz, 1H, H-***4***), 7.48 (dd, *J* = 8.6, 0.5 Hz, 1H, H-***7***), 7.37 (dd, *J* = 8.6, 1.5 Hz, 1H, H-***6***), 7.10 (d, *J* = 1.1 Hz, 1H, H-***2***), 2.32 (d, *J* = 1.1 Hz, 3H, H-***14***), 1.67 (heptet, *J* = 7.5 Hz, 3H, H-***10***), 1.13 (d, *J* = 7.5 Hz, 18H, H-***11***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.17 (C-***9***), 131.7 (C-***8***), 130.6 (CH, C-***2***), 124.3 (CH, C-***6***), 124.2 (CH, C-***4***), 120.9 (CH, C-***7***), 114.4 (C≡N, C-***12***), 114.26 (C-***3***), 102.18 (C-***5***), 18.0 (CH_3, C-***11***), 12.7 (CH, C-***10***), 9.5 (CH_3, C-***14***).

ν_{max}/cm^{-1}: 2948 – 2868 (s, C-H), 2220 (s, C≡N), 1610 (w, C=C), 1457 (C-H methyl), 1320 (s, C-N).

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calc. for $C_{19}H_{32}N_3Si$ $[M+NH_4]^+$: 330.2360. Found: 330.2360.

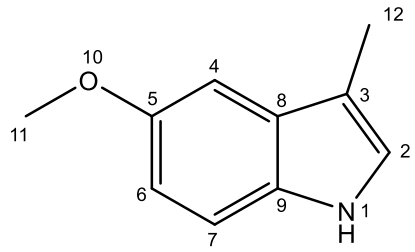
General procedure for deprotection of 3-methyl-1-triisopropyl silyl substituted indoles

TBAF (1.1 eqs) was added to a round-bottomed flask under N_2 atmosphere, dissolved in dry THF (0.14 M) and cooled to 0 ^{0}C . 3-methyl-1-triisopropylsilyl substituted indole (1 eq) was dissolved in dry THF and added to the solution of TBAF. The reaction was warmed to rt and stirred for 10-15 minutes. The reaction was quenched with a saturated $NaHCO_3$ solution at 0 ^{0}C and extracted with Et_2O. The organic layers were dried with $MgSO_4$, filtered and concentrated in vacuum. Final products were purified by column chromatography using Pet Ether/EtOAc as the eluent.

Characterisation of products

5-Methoxy-3-methyl-1H-indole

Synthesized from 5-methoxy-3-methyl-1-(triisopropylsilyl)-1H-indole (850 mg, 2.7 mmol), TBAF (769 mg, 3 mmol) and 11 mL of dry THF. **Compound 313b** was obtained after column chromatography Pet Ether/EtOAc 20:1, 256 mg, 1.6 mmol, 59% as an orange oil.



Compound 313b

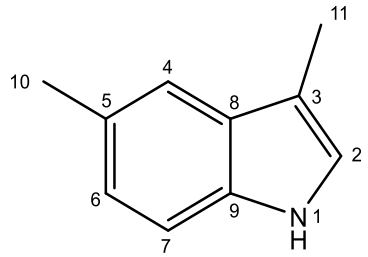
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H, H-***1***), 7.24 (d, *J* = 8.7 Hz, 1H, H-***7***), 7.02 (d, *J* = 2.5 Hz, 1H, H-***4***), 6.96 (s, 1H, H-***2***), 6.86 (dd, *J* = 8.7, 2.5 Hz, 1H, H-***6***), 3.88 (s, 3H, H-***11***), 2.31 (d, *J* = 1.0 Hz, 3H, H-***12***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9 (C-***5***), 131.4 (C Ar, C-***9***), 128.7 (CH, C-***8***), 122.4 (CH, C-***2***), 112.1 (CH, C-***6***), 111.7 (CH, C-***7***), 111.5 (C-***3***, 100.7 (CH, C-***4***), 55.9 (CH_3, C-***11***), 9.7 (CH_3, C-***12***).

Characterization consistent with reported data.[167]

5-Methyl-3-methyl-1H-indole:

Synthesized from 5-methyl-3-methyl-1-(triisopropylsilyl)-1H-indole (520 mg, 1.7 mmol), TBAF (514 mg, 2.0 mmol) and 12 mL of dry THF. **Compound 313c** was obtained after column chromatography Pet Ether/EtOAc, 40:1 to 10:1, 169 mg, 1.2 mmol, 68% as a brown oil.



Compound 313c

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H, H-***1***), 7.36 (s, 1H, H-***4***), 7.24 (d, *J* = 8.3 Hz, 1H, H-***7***), 7.01 (d, *J* = 8.3 Hz, 1H, H-***6***), 6.93 (s, 1H, H-***2***), 2.47 (s, 3H, H-***10***), 2.31 (d, *J* = 1.0 Hz, 3H, H-***11***).

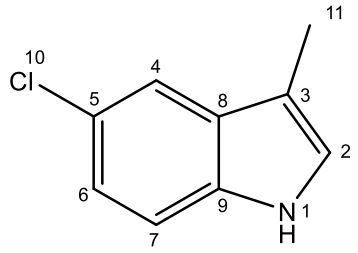
^{13}C NMR (126 MHz, $CDCl_3$) δ 134.58 (C-***5***), 128.51 (C-***9***), 128.33 (C-***8***), 123.45 (CH, C-***6***), 121.73 (CH, C-***2***), 118.51 (CH, C-***4***), 111.24 (C-***3***), 110.60 (CH, C-***7***), 21.51 (CH_3, C-***10***), 9.69 (CH_3, C-***11***).

ν_{max}/cm^{-1}: 3412 (b, N-H), 2920 (s, C-H), 2858 (m, C-H), 1456 (m, CH_3).

HRMS ASAP (DCM): Calculated for $C_{10}H_{11}N$ $[M+1]^+$: 144.0809. Found: 144.0813.

5-Chloro-3-methyl-1H-indole

Synthesized from 5-chloro-3-methyl-1-(triisopropylsilyl)-1H-indole (2386.9 mg, 7.41 mmol), TBAF (2129 mg, 8.2 mmol) and 30 mL of dry THF. **Compound 313d** was obtained by column chromatography Pet Ether/EtOAc, 30:1 to 10:1, 594 mg, 3.5 mmol, 48% as an orange oil.



Compound 313d

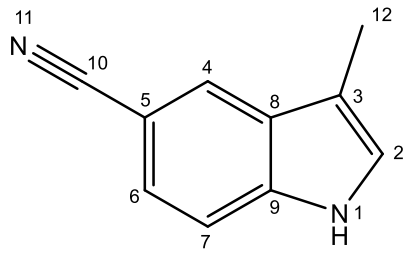
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (bs, 1H, H-***1***), 7.54 (d, *J* = 2.0 Hz, 1H, H-***4***), 7.25 (d, *J* = 8.5 Hz, 1H, H-***7***), 7.14 (dd, *J* = 8.5, 2.0 Hz, 1H, H-***6***), 6.99 (d, *J* = 1.0 Hz, 1H, H-***2***), 2.30 (d, *J* = 1.0 Hz, 3H, H-***11***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.6 (C-***9***), 129.5 (C-***5***), 124.9 (C-***8***), 122.9 (CH, C-***2***), 122.2 (CH, C-***6***), 118.4 (CH, C-***4***), 111.9 (CH, C-***7***), 111.6 (C-***3***), 9.6 (CH_3, C-***11***).

Characterization consistent with reported data.[167]

5-Cyano-3-methyl-1H-indole

Synthesized from 5-cyano-3-methyl-1-(triisopropylsilyl)-1H-indole (840 mg, 2.69 mmol), TBAF (772 mg, 3 mmol) and 11 mL of dry THF. Compound **313e** was obtained by column chromatography Pet Ether/EtOAc (20:1), 259.2 mg, 1.7 mmol, 62% as an orange oil.



Compound 313e

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H, H-***1***), 7.93 (d, *J* = 1.5 Hz, 1H, H-***4***), 7.42 (dd, *J* = 8.4, 1.5 Hz, 1H, H-***6***), 7.39 (dd, *J* = 8.4, 0.7 Hz, 1H, H-***7***), 7.09 (dd, *J* = 2.2, 1.1 Hz, 1H, H-***2***), 2.34 (dd, *J* = 1.1 Hz, 3H, H-***12***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9 (C-***9***), 128.2 (C-***8***), 124.9 (CH, C-***7***), 124.7 (CH, C-***4***), 123.6 (CH, C-***2***), 120.9 (C-***10***), 112.8 (C-***3***), 111.8 (CH, C-***6***), 102.3 (C-***5***), 9.5 (CH_3, C-***12***).

ν_{max}/cm^{-1}: 3335.3 (b, N-H), 2918(m, C-H), 2218 (s, C≡N), 1621 (w, C=C), 1457 (C-H methyl), 1320 (s, C-N).

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calculated for $C_{10}H_8N_2$ $[M+H]^+$: 157.0757. Found: 157.0760.

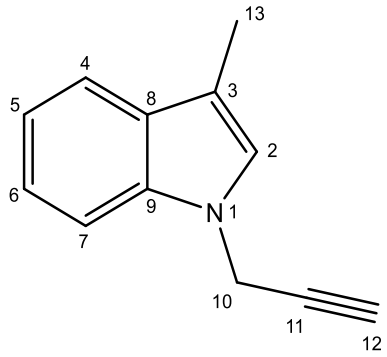
General procedure for propargylation of 3-methyl-1-H substituted indoles

NaH (1.6 eqs) was added to a vacuum dried 2 necked round bottomed flask under N_2 atmosphere and suspended in dry THF or DMF (0.2 M), as specified. The suspension was cooled to 0 ^{0}C and the desired substituted indole (1 eq) dissolved in dry THF or DMF was slowly added. The mixture was stirred for 20 minutes and warmed to rt, then propargyl bromide (or the corresponding alkyl bromide) (1.5 eqs) was added. The reaction was stirred at rt overnight, then quenched with water and extracted with Et_2O. The organic layers were dried using $MgSO_4$, filtered and concentrated in vacuum. Final products were purified by column chromatography using Pet Ether/EtOAc as the eluent.

Characterisation of products

3-Methyl-1-(2-propyn-1-yl)-1H-indole

Synthesized from 3-methyl-1H-indole (2000 mg, 12.07 mmol), NaH (772 mg, 19.31 mmol), propargyl bromide (2.5 mL, 18.11 mmol) and 60 mL of dry THF. **Compound 324a** obtained after column chromatography, Pet/EtOAc, (20:1), 1716.9 mg, 10.12 mmol, 84% as an orange liquid.



Compound 324a

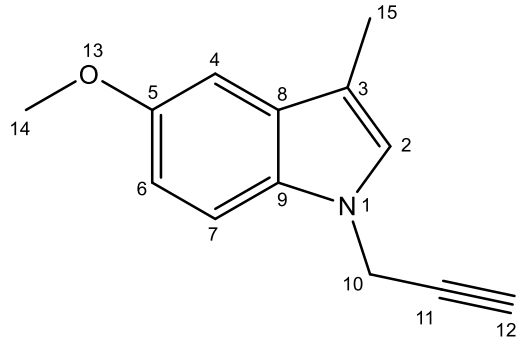
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H, H-***4***), 7.37 (d, *J* = 8.2 Hz, 1H, H-***7***), 7.27 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H, H-***6***), 7.16 (ddd, *J* = 7.9, 7.1, 1.1 Hz, 1H, H-***5***), 6.99 (d, *J* = 1.1 Hz, 1H, H-***2***), 4.83 (d, *J* = 2.5 Hz, 2H, H-***10***), 2.38 (t, *J* = 2.5 Hz, 1H, H-***12***), 2.35 (s, 3H, H-***13***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2 (C-***9***), 129.2 (C-***8***), 124.9 (CH, C-***2***), 121.9 (CH, C-***6***), 119.2 (CH, C-***4*** or ***5***), 119.2 (CH, C-***4*** or ***5***), 111.5 (C-***3***), 109.2 (CH, C-***7***), 78.2 (C-***11***), 73.1 (CH, C-***12***), 35.5 (N-CH_2, C-***10***), 9.6 (CH_3, C-***13***).

Characterization consistent with reported data.[168]

5-Methoxy-3-methyl-1-(2-propyn-1-yl)-1H-indole

Synthesized from 5-methoxy-3-methyl-1H-indole (259 mg, 1.6 mmol), NaH (103 mg, 2.6 mmol), propargyl bromide (331 µl, 2.4 mmol) and 8 mL of dry THF. **Compound 324b** obtained after column chromatography Pet Ether/EtOAc 30:1, 180.5 mg, 0.91 mmol, 57% as a yellow oil.



Compound 324b

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.8 Hz, 1H, H-***7***), 6.93 (d, *J* = 2.4 Hz, 1H, H-***4***), 6.87 (d, *J* = 0.9 Hz, 1H, H-***2***), 6.83 (dd, *J* = 8.8, 2.4 Hz, 1H, H-***6***), 4.71 (d, *J* = 2.5 Hz, 2H, H-***10***), 3.80 (s, 3H, H-***14***), 2.28 (t, *J* = 2.5 Hz, 1H, H-***12***), 2.22 (d, *J* = 0.9 Hz, 3H, H-***15***).

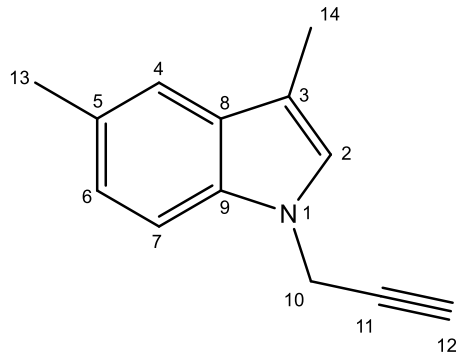
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0 (C-***5***), 131.5 (C-***9***), 129.6 (CH, C-***2***), 125.7 (C-***8***), 112.1 (CH, C-***6***), 110.9 (CH, C-***7***), 109.9 (C-***3***), 101.2 (CH, C-***4***), 78.2 (CH, C-***12***), 73.1 (C-***11***), 55.9 (C-***14***), 35.7 (N-CH_2, C-***10***), 9.6 (CH_3, C-***15***).

ν_{max}/cm^{-1}: 3283 (s, C≡C-H), 2924 – 2855 (m, C-H), 2190 (w, C≡C), 1620 – 1582(w, C=C), 1488 (s, C-H methyl), 1337 (m, Ar C-H), 1228 (s, C-N).

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calculated for $C_{13}H_{13}NO$ $[M+H]^+$ 200.1070: Found: 200.1070.

5-Methyl-3-methyl-1-(2-propyn-1-yl)-1H-indole

Synthesized from 5-methyl-3-methyl-1H-indole (167 mg, 1.2 mmol), NaH (60 mg, 1.5 mmol), propargyl bromide (152 µl, 1.7 mmol) and 2 mL of dry THF. Compound **324c** obtained after column chromatography, Pet Ether/EtOAc, 30:1 and 10:1, 64 mg, 0.35 mmol, 30% as a brown oil.



Compound 324c

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 1H, H-***4***), 7.12 (d, *J* = 8.3 Hz, 1H, H-***7***), 6.96 (d, *J* = 8.3 Hz, 1H, H-***6***), 6.79 (s, 1H, H-***2***), 4.63 (d, *J* = 1.4 Hz, 2H, H-***10***), 2.37 (s, 3H, H-***13***), 2.23 – 2.21 (m, 1H, H-***12***), 2.20 (s, 3H, H-***14***).

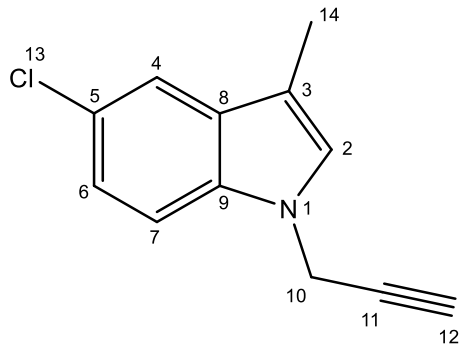
^{13}C NMR (126 MHz, $CDCl_3$) δ 134.00 (C), 125.10 (CH, C-***2***), 123.53 (ArCH), 119.05 (ArCH), 113.86 (C) 111.03 (C), 108.98 (ArCH), 106.85 (C), 73.10 (C≡C, C-***11***), 69.57 (C≡CH, C-***12***), 35.66 (CH_2, C-***10***), 21.58 (CH_3, C-***13***), 9.71 (CH_3, C-***14***).

ν_{max}/cm^{-1}: 3288 (s, -C≡C-H), 2917 (s, C-H), 2859m (C-H), 1489 (s, CH_3).

HRMS ASAP (Solid): Calculated for $C_{13}H_{13}N$ $[M+H]^+$: 184.1126. Found: 184.1130.

5-Chloro-3-methyl-1-(2-propyn-1-yl)-1H-indole

Synthesized from 4-methyl-3-methyl-1H-indole (550 mg, 3.3 mmol), NaH (213 mg, 5.3 mmol), propargyl bromide (686 µl, 4.9 mmol) and 17 mL of dry THF. **Compound 324d** obtained after column chromatography, Pet Ether/EtOAc (10:1), 400.2 mg, 1.9 mmol, 59% as a yellow oil.



Compound 324d

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.0 Hz, 1H, H-***4***), 7.27 (d, *J* = 8.3 Hz, 1H, H-***7***), 7.18 (dd, *J* = 8.3, 2.0 Hz, 1H, H-***6***), 6.98 (d, *J* = 1.0 Hz, 1H, H-***2***), 4.79 (d, *J* = 2.5 Hz, 2H, H-***10***), 2.38 (t, *J* = 2.5 Hz, 1H, H-***12***), 2.21 (s, 3H, H-***14***).

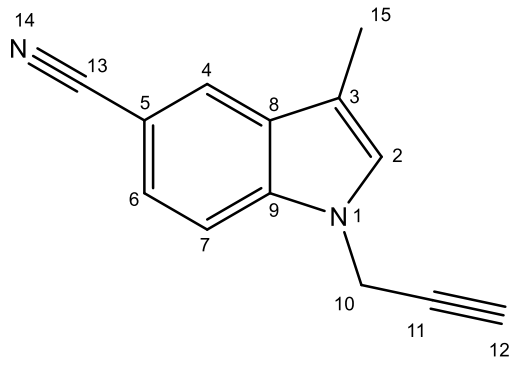
^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5 (C-***9***), 130.3 (C-***5***), 126.3 (CH, C-***2***), 125.1 (C-***8***), 122.1 (CH, C-***6***), 118.8 (CH, C-***4***), 111.2 (CH, C-***7***), 110.2 (C-***3***), 77.7 (C-***11***), 73.5 (CH, C-***12***), 35.7 (N-CH_2, C-***10***), 9.5 (CH_3, C-***14***).

ν_{max}/cm^{-1}: 3295.9 (s, C≡C-H), 2922.5 (C-H), 1468.8 (C-H, methyl), 1340.2 (s, C-N).

HRMS ASAP (Solid): Calculated for $C_{12}H_{10}{}^{35}ClN$ $[M+H]^+$: 204.0575. Found: 204.0575.

5-Cyano-3-methyl-1-(2-propyn-1-yl)-1H-indole

Synthesized from 4-methyl-3-methyl-1H-indole (255 mg, 1.6 mmol), NaH (104 mg, 2.6 mmol), propargyl bromide (337 µl, 2.5 mmol) and 8.2 mL of dry THF. **Compound 324e** obtained after column chromatography Pet Ether/EtOAc (30:1), 204.9 mg, 1.1 mmol, 65% as an orange oil.



Compound 324e

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 1.5, 0.6 Hz, 1H, H-***4***), 7.47 (dd, *J* = 8.5, 1.5 Hz, 1H, H-***6***), 7.40 (dd, *J* = 8.5, 0.6 Hz, 1H, H-***7***), 7.09 (d, *J* = 1.0 Hz, 1H, H-***2***), 4.85 (d, *J* = 2.6 Hz, 2H, H-***10***), 2.42 (t, *J* = 2.6 Hz, 1H, H-***12***), 2.33 (d, *J* = 1.0 Hz, 3H, H-***15***).

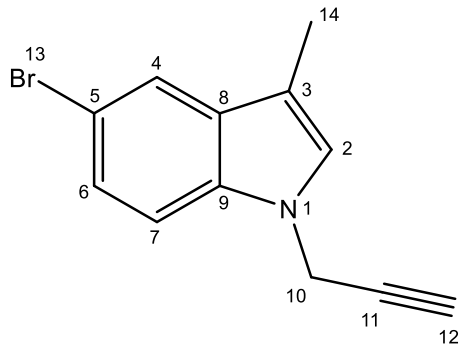
^{13}C NMR (126 MHz, $CDCl_3$) δ 129.09 (C-***9***), 127.05 (CH, C-***2***), 124.86 (CH, C-***4*** and C-***6***), 120.79 (C-***8***), 112.55 (C-***5***), 110.04 (CH, C-***7***), 102.4 (C-***3***), 101.6 (C-***13***), 100.2 (CH, C-***12***), 74.0 (C-***11***), 35.8 (N-CH_2, C-***10***), 9.4 (CH_3, C-***15***).

ν_{max}/cm^{-1}: 3288.2 (s, C≡C-H), 2948 – 2868 (s, C-H), 2218.2 (s, C≡N), 2123.1 (w, C≡C), 1616 (w, C=C), 1481 (C-H methyl), 1320 (s, C-N).

HRMS ASAP (Solid): Calculated for $C_{13}H_{10}N_2$ $[M+H]^+$ 195.0920: Found: 195.0922.

5-Bromo-3-methyl-1-(2-propyn-1-yl)-1H-indole

Synthesized from 5-bromo-3-methyl-1H-indole (1.09 g, 5.22 mmol), NaH (313 mg, 7.83 mmol), propargyl bromide (0.87 ml, 7.83 mmol) and 40.0 mL of dry THF. **Compound 324f** obtained after column chromatography Pet Ether/EtOAc, 25:2, 668 mg, 2.69 mmol, 51% as a brown oil.



Compound 324f

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H, H-***4***), 7.38 (d, *J* = 8.5 Hz, 1H, H-***7***), 7.28 (d, *J* = 8.5 Hz, 1H, H-***6***), 7.00 (s, 1H, H-***2***), 4.80 (s, 2H, H-***10***), 2.44 (s, 1H, H-***12***), 2.34 (s, 3H, H-***3***).

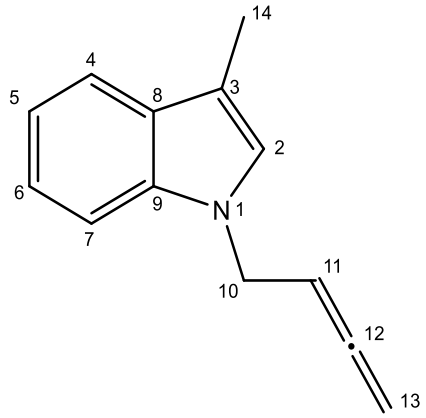
No carbon obtained as sample used directly in the Crabbè homologation.

General procedure for Crabbè homologation[20] of 3-methyl-N-propargyl substituted indoles

Paraformaldehyde (2.5 eqs) and CuBr (0.3 eqs) were added to a microwave vial, sealed and flushed with N_2. The corresponding substituted N-propargyl indole (1 eq) dissolved in dry 1,4-dioxane (0.25 M) under N_2 was added to the microwave vial followed by the drop wise addition of *i*Pr_2NH (2 eqs). The reaction was heated at 150 ^{0}C using microwave irradiation for 10 minutes. The reaction was filtered through celite, washed with DCM and concentrated in vacuum. Final products were purified by column chromatography using Pet Ether/EtOAc as the eluent.

1-(2, 3-Butadien-1-yl)-3-methyl-1H-indole

Synthesized from 3-methyl-1H-indole (850 mg, 5.02 mmol), paraformaldehyde (377 mg, 12.55 mmol), CuBr (216 mg, 1.51 mmol), *i*Pr_2NH (1.4 mL, 10.04 mmol) and 25 mL of dry 1,4-Dioxane. **Compound 217a** obtained after column chromatography, Pet Ether/EtOAc, (10:1), 679.9 mg, 3.71 mmol, 74% as an orange liquid.



Compound 217a

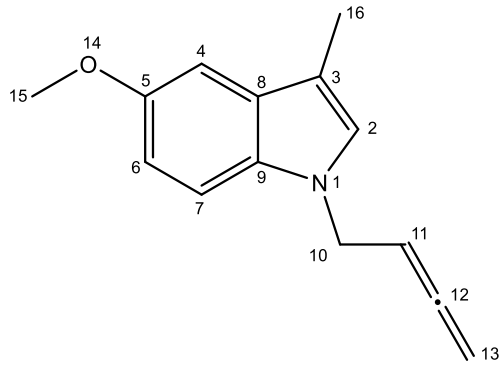
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 1H, H-***4***), 7.33 (d, *J* = 8.2 Hz, 1H, H-***7***), 7.21 (dd, *J* = 8.2, 7.1 Hz, 1H, H-***6***), 7.12 (d, *J* = 7.9, 7.1 Hz, 1H, H-***5***), 6.90 (d, *J* = 0.9 Hz, 1H, H-***2***), 5.33 – 5.27 (m, 1H, H-***11***), 4.85 (dt, *J* = 6.7, 2.7 Hz, 2H, H-***13***), 4.68 (dt, *J* = 6.7, 2.7 Hz, 2H, H-***10***), 2.33 (d, *J* = 0.9 Hz, 3H, H-***14***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.95 (C, C=C=C, C-***12***), 136.32 (C-***9***), 129.06 (C-***8***), 125.16 (CH, C-***2***), 121.50 (CH, C-***6***), 119.07 (CH, C-***5***), 118.76 (CH, C-***4***), 110.71 (C-***3***), 109.45 (CH, C-***7***), 87.62 (CH, CH=C=C, C-***11***), 76.82 (CH_2, CH_2=C=C, C-***13***), 45.18 (N-CH_2, C-***10***), 9.62 (CH_3, C-***14***).

Characterization consistent with reported data.[165]

5-Methoxy-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole

Synthesized from 5-methoxy-3-methyl-1-(2-propyn-1-yl)-1H-indole (180.5 mg, 0.91 mmol), paraformaldehyde (68 mg, 2.26 mmol), CuBr (39 mg, 0.27 mmol), *i*Pr_2NH (255 µl, 1.82 mmol) and 4.5 mL of dry 1,4-dioxane. **Compound 217b** obtained after column chromatography, Pet Ether/EtOAc, 50:1, 142 mg, 0.66 mmol, 60% as a brown oil.



Compound 217b

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.8 Hz, 1H, H-***7***), 7.00 (d, *J* = 2.4 Hz, 1H, H-***4***), 6.86 (m, H-***6*** + H-***2***), 5.28 (p, *J* = 6.7 Hz, 1H, H-***11***), 4.83 (dt, *J* = 6.7, 2.7 Hz, 2H, H-***13***), 4.63 (dt, *J* = 6.7, 2.7 Hz, 2H, H-***10***), 3.87 (s, 3H, H-***15***), 2.29 (d, *J* = 1.0 Hz, 3H, H-***16***).

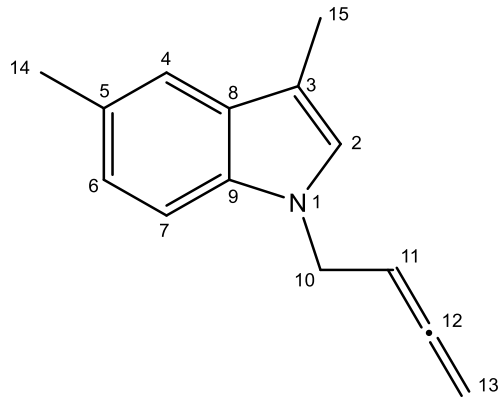
^{13}C NMR (126 MHz, $CDCl_3$) δ 208.9 (C=***C***=C, C-***12***), 153.8 (C-***5***), 131.7 (C-***9***), 129.3 (CH, C-***2***), 125.9 (C-**8**), 111.7 (CH, C-***6***), 110.3 (CH, C-***7***), 110.2 (C-***3***), 100.9 (CH, C-***4***), 87.7 (CH, CH=C=C, C-***11***), 76.6 (CH_2, CH_2=C=C, C-***13***), 55.9 (CH_3, C-***15***), 45.4 (N-CH_2, C-***10***), 9.66 (CH_3, C-***16***).

ν_{max}/cm^{-1}: 2990 – 2857 (m, C-H), 1956 (w, (C=C)=C-H), 1619 (w, C=C), 1489 (s, C-H methyl), 1456 (m, C=C), 1228 (s, C-N), 849 (w, (C=C)=CH_2).

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calc. for $C_{14}H_{15}NO$ $[M+H]^+$: 214.1226. Found: 214.1227.

5-Methyl-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole

Synthesized from 5-methyl-3-methyl-1-(2-propyn-1-yl)-1H-indole (62 mg, 0.3 mmol), paraformaldehyde (27 mg, 0.9 mmol), CuBr (15 mg, 0.1 mmol), *i*Pr_2NH (94 µL, 0.7 mmol) and 1.5 mL of dry 1,4-dioxane. **Compound 217c** obtained after column chromatography with Pet Ether, 46 mg, 0.2 mmol, 60% as a yellow/brown oil.



Compound 217c

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.35 (m, 1H, H-***4***), 7.22 (d, *J* = 8.3 Hz, 1H, H-***7***), 7.04 (dd, *J* = 8.3, 1.1 Hz, 1H, H-***6***), 6.86 (d, *J* = 1.1 Hz, 1H, H-***2***), 5.29 (p, *J* = 6.7 Hz, 1H, H-***11***), 4.84 (dt, *J* = 6.7, 2.7 Hz, 2H, H-***13***), 4.65 (dt, *J* = 6.7, 2.7 Hz, 2H, H-***10***), 2.48 (s, 3H, H-***14***), 2.31 (d, *J* = 1.1 Hz, 3H, H-***15***).

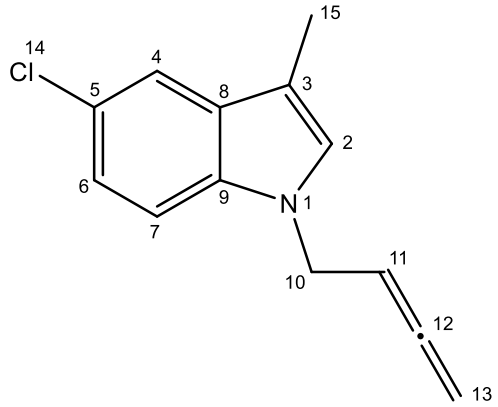
^{13}C NMR (126 MHz, $CDCl_3$) δ 208.91 (C=C=C, C-***12***), 134.73 (C-***9***), 129.27 (C-***5***), 127.97 (CH, C-***2***), 125.27 (C-***8***), 123.08 (CH, C-***6***), 118.77 (CH, C-***4***), 110.14 (C-***3***), 109.16 (CH, C-***7***), 87.68 (CH, CH=C=C, C-***11***), 76.73 (CH_2, CH_2=C=C, C-***13***), 45.22 (N-CH_2, C-***10***), 21.47 (CH_3, C-***14***), 9.60 (CH_3, C-***15***).

ν_{max}/cm^{-1}: 2923 (s, C-H), 2861 (m-C-H), 1956 (w, (C=C)=C-H), 1489 (s, C-H methyl), 1458 (m, C=C), 1353, m, Ar C-H), 1302 (s, C-N), 848 (w, (C=C)=CH_2).

HRMS ASAP (DCM): Calc. for $C_{14}H_{15}N$ $[M+H]^+$: 198.1283. Found: 198.1286.

5-Chloro-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole

Synthesized from 5-chloro-3-methyl-1-(2-propyn-1-yl)-1H-indole (400 mg, 1.9 mmol), paraformaldehyde (147 mg, 4.9 mmol), CuBr (84 mg, 0.6 mmol), *i*Pr_2NH (549 µl, 3.9 mmol) and 9.8 mL of dry 1,4-dioxane. **Compound 217d** obtained after column chromatography, Pet Ether/EtOAc, 20:1, 296.5 mg, 1.4 mmol, 70% as an orange oil.



Compound 217d

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.0 Hz, 1H, H-***4***), 7.22 (d, *J* = 8.7 Hz, 1H, H-***7***), 7.14 (dd, *J* = 8.7, 2.0 Hz, 1H, H-***6***), 6.91 (d, *J* = 1.0 Hz, 1H, H-***2***), 5.27 (p, *J* = 6.7 Hz, 1H, H-***11***), 4.84 (dt, *J* = 6.7, 2.7 Hz, 2H, H-***13***), 4.64 (dt, 6.7, 2.7 Hz, 2H, H-***10***), 2.28 (d, *J* = 1.0 Hz, 3H, H-***15***).

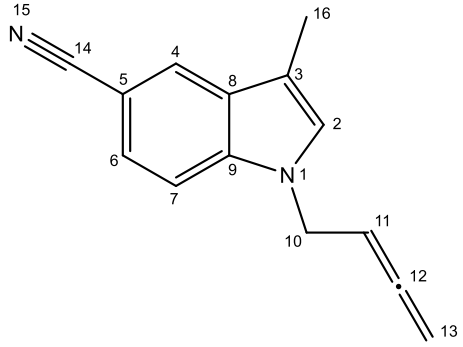
^{13}C NMR (126 MHz, $CDCl_3$) δ 208.9 (C=C=C, C-***12***), 134.7 (C-***9***), 130.1 (C-***5***), 126.6 (CH, C-***2***), 124.6 (C-***8***), 121.7 (CH, C-***6***), 118.6 (CH, C-***4***), 110.5 (C-***3***), 110.4 (CH, C-***7***), 87.4 (CH, CH=C=C, C-***11***), 77.1 (CH_2, CH_2=C=C, C-***13***), 45.3 (N-CH_2, C-***10***), 9.5 (CH_3, C-***15***).

ν_{max}/cm^{-1}: 2924 (s, C-H), 2855 (m, C-H), 1957 (w, (C=C)=C-H), 1614 (w, C=C), 1470 (s, C-H methyl), 1357 (m, Ar C-H), 849 (w, (C=C)=CH_2).

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calc. for $C_{13}H_{12}N^{35}Cl$ $[M+H]^+$: 218.0737. Found: 218.0733.

5-Cyano-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole

Synthesized from 5-cyano-3-methyl-1-(2-propyn-1-yl)-1H-indole (200 mg, 1.0 mmol), paraformaldehyde (77 mg, 2.55 mmol), CuBr (44 mg, 0.31 mmol), *i*Pr_2NH (286 µl, 2.04 mmol) and 5.1 mL of dry 1,4-dioxane. **Compound 217e** obtained after column chromatography, Pet Ether/EtOAc, (10:1), 149 mg, 0.7 mmol, 70% as an orange oil.



Compound 217e

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 1.4 Hz, 1H, H-***4***), 7.42 (dd, *J* = 8.5, 1.4 Hz, 1H, H-***6***), 7.34 (d, *J* = 8.5 Hz, 1H, H-***7***), 7.00 (d, *J* = 0.9 Hz, 1H, H-***2***), 5.28 (p, *J* = 6.6 Hz, 1H, H-***11***), 4.85 (dt, *J* = 6.5, 2.8 Hz, 2H, H-***13***), 4.68 (dt, *J* = 6.5, 2.8 Hz, 2H, H-***10***), 2.32 (d, *J* = 0.9 Hz, 3H, H-***16***).

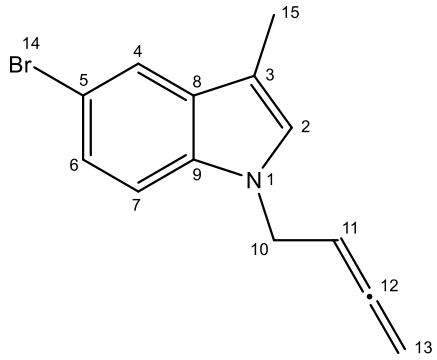
^{13}C NMR (126 MHz, $CDCl_3$) δ 208.9 (C=C=C, C-***12***), 137.8 (C-***9***), 128.9 (C-***8***), 127.4 (CH, C-***2***), 124.8 (CH, C-***4***), 124.5 (CH, C-***6***), 121.0 (C-***3***), 111.9 (C-***14***), 110.3 (CH, C-***7***), 101.8 (C-***5***), 87.0 (CH, CH=C=C, C-***11***), 77.5 (CH_2, CH_2=C=C, C-***13***), 45.3 (N-CH_2, C-***10***), 9.4 (CH_3, C-***16***).

ν_{max}/cm^{-1}: 2923 – 2857 (s, C-H), 2218.2 (s, C≡N), 1956 (w, (C=C)=C-H), 1614 (w, C=C), 1482 (s, C-H methyl), 850.6 (w, (C=C)=CH_2).

HRMS (FTMS + p NSI) (DCM)/MeOH + NH_4OAc): Calc. for $C_{14}H_{12}N_2$ $[M+H]^+$: 209.1079. Found: 209.1081.

5-Bromo-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole

Synthesized from 5-bromo-3-methyl-1-(2-propyn-1-yl)-1H-indole (668 mg, 2.69 mmol), paraformaldehyde (201 mg, 6.72 mmol), CuBr (115 mg, 0.81 mmol), *i*Pr_2NH (0.76 mL, 5.38 mmol) and 11 mL of dry 1,4-dioxane. **Compound 217f** obtained after column chromatography with Pet Ether, 617 mg, 2.35 mmol, 87% as yellow/brown oil.



Compound 217f

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H, H-***4***), 7.21 (d, *J* = 8.5 Hz, 1H, H-***7***), 7.10 (d, *J* = 8.5 Hz, 1H, H-***6***), 6.80 (s, 1H, H-***2***), 5.18 (p, *J* = 6.7 Hz, 1H, H***11***), 4.81-4.69 (m, 2H, H-***13***), 4.55 (dt, *J* = 6.7, 2.6 Hz, 2H, H-***10***), 2.19 (s, 3H, H-***15***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.93 (C, C=C=C, C-***12***), 134.9 (C-9), 130.78 (C-8), 126.4 (CH, C-***4*** or ***6***), 124.3 (CH, C-***4*** or ***6***), 121.7 (CH, C-***7***), 112.2 (C-3), 110.9 (CH, C-***2***), 110.4 (C-5), 87.4 (CH, C-***11***), 77.1 (CH_2, C-***13***), 45.3 (N-CH_2, C-***10***), 9.5 (CH_3, C-***15***).

ν_{max}/cm^{-1}: 2966 (m, =C-H), 2929 (s, C-H), 2857 (m, C-H), 1958 (w, (C=C)=C-H), 1743 (w, C=C), 1456 (m, C=C), 1357 (m, Ar-H), 1267 (s, C-N). 859 (w, (C=C)=CH_2).

HRMS Calculated for $C_{13}H_{12}{}^{79}BrN$ (M^++H): 262.0026. Found: 262.0049.

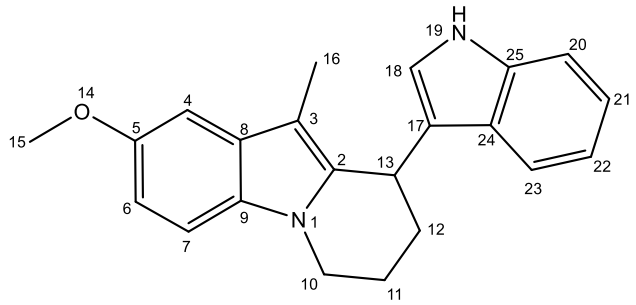
General procedure for platinum catalysed reaction of indolyl allene with external nucleophile

$PtCl_2$ (5 mol %) and the appropriate indole (3 eqs) were added to a microwave vial, capped and flushed with N_2. The solids were dissolved in dry 1,4-dioxane (0.2 M) and the appropriate indolyl allene (1 eq) dissolved in dry 1,4-dioxane was added. Dry methanol (3 eqs) was added and the vial heated under microwave irradiation at 130 ^{0}C for 1 hour. The resulting reaction mixture was filtered through celite and washed with DCM. Final products purified by column chromatography using Pet Ether/EtOAc.

Characterisation of products

Reaction of 5-methoxy-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with indole

Synthesized from 5-methoxy-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole (60 mg, 0.28 mmol), dry methanol (34 µl, 0.84 mmol), indole (98 mg, 0.84 mmol), $PtCl_2$ (3.7 mg, 0.014 mmol) in 1.4 mL of dry 1,4-dioxane. **Compound 287b** obtained after column chromatography, Pet/EtOAc, (20:1), 44.1 mg, 0.13 mmol, 48% as a fluorescent yellow solid.



Compound 287b

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H, H-***19***), 7.63 (d, *J* = 8.2 Hz, 1H, H-***7***), 7.37 (d, *J* = 8.2 Hz, 1H, H-***20***), 7.23-7.19 (m, 2H, H-***21+22***), 7.16-7.11 (m, 1H, H-***6***), 6.98 (d, *J* = 2.4 Hz, 1H, H-***4***), 6.85 (dd, *J* = 8.2, 2.4 Hz, 1H, H-***23***), 6.56 (d, *J* = 1.6 Hz, 1H, H-***18***), 4.77 (t, *J* = 4.3 Hz, 1H, H-***13***), 4.26-4.2 (m, 1H, H-***10***), 3.91-3.86 (m, 1H, H-***10***), 3.88 (s, 3H, H-***15***), 2.35 – 2.32 (m, 1H, H-***12***), 2.20 – 2.12 (m, 1H, H-***12***), 2.11-2.05 (m, 1H, H-***11***), 1.97 (s, 3H, H-***16***), 1.93-1.86 (m, 1H, H-***11***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.96 (C-***5***), 136.69 (C-***2***), 135.63 (C-***9***), 131.27 (C-***8***), 128.93 (C-***25***), 126.22 (C-***24***), 123.23 (CH, C-***18***), 121.94 (CH, C-***21/22***), 119.33 (CH, C-***6***), 118.97 (CH, C-***7***), 118.85 (C-***3***), 111.31 (CH, C-***20***), 110.10 (CH, C-***23***), 109.26 (CH, C-***21/22***), 105.58 (C-***17***), 100.31 (CH, C-***4***), 56.08 (CH_3, OMe, C-***15***), 42.61 (CH_2, C-***10***), 30.40 (CH, C-***13***), 28.07 (CH_2, C-***12***), 19.55 (CH_2, C-***11***), 8.38 (CH_3 – C-***16***).

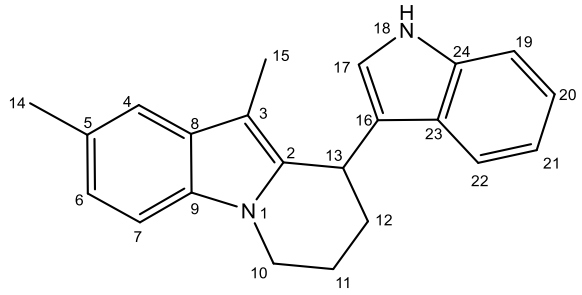
ν_{max}/cm^{-1}: 3410 (s, NH), 3053, 2942 – 2830 (m, C-H), 1618 – 1578 (w, C=C), 1484 (s, C-H methyl), 1456 (m, C-C in ring), 1227 (s, C-N).

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calc. for $C_{22}H_{22}N_2O$ $[M+H]^+$ 331.1805: Found: 331.1805.

M.P. 189-192 ^{0}C.

Reaction of 5-methyl-1-(2,3-butadien-1-yl)-3-methyl-1H-indole with indole

Synthesized from 5-methyl-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole (45 mg, 0.23 mmol), dry methanol (3.1 µl, 0.68 mmol), indole (80 mg, 0.68 mmol), $PtCl_2$ (3 mg, 0.011 mmol) in 1.14 mL of dry 1,4-dioxane (0.2 M). **Compound 287c** obtained after column chromatography, Pet Ether/Et_2O (20:1) 15.1 mg, 0.05 mmol, 21% (Isolated 10.1 mg, 0.03 mmol, 15% after prep TLC Pet Ether/Et_2O (30:1)) as a yellow oil.



Compound 287c

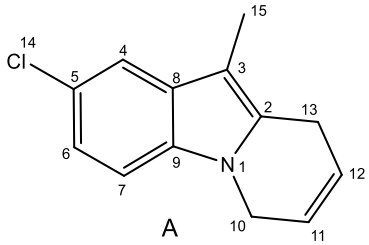
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H, H-***18***), 7.64 (d, *J* = 8.1 Hz, 1H, H-***Ar***), 7.36 (d, *J* = 8.1 Hz, 1H, H-***Ar***), 7.32 (d, *J* = 0.7 Hz, 1H, H-***Ar***), 7.24 – 7.18 (m, 2H, H-***Ar***), 7.16 – 7.11 (m, 1H, H-***Ar***), 7.02 (dd, *J* = 8.1, 1.4 Hz, 1H, H-***Ar***), 6.53 (dd, *J* = 2.3, 0.7 Hz, 1H, H-***17***), 4.78 (t, *J* = 4.3 Hz, 1H, H-***13***), 4.25 (ddd, *J* = 11.2, 4.9, 3.5 Hz, 1H, H-***10***), 3.89 (td, *J* = 11.2, 4.9 Hz, 1H, H-***10***), 2.49 (s, 3H, H-***14***), 2.39 – 2.33 (m, 1H, H-***12***), 2.21 – 2.12 (m, 1H, H-***12***), 2.11 – 2.01 (m, 1H, H-***11***), 1.98 (s, 3H, H-***15***), 1.92 – 1.85 (m, 1H, H-***11***).

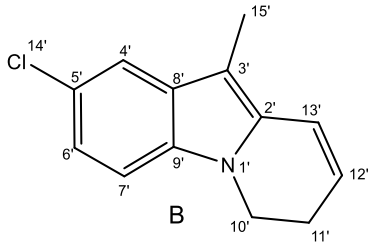
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.69 (C-***2***), 134.9 (C-***9***), 134.3 (C-***24***), 128.9 (C-***5***), 128.1 (C-***8***), 126.2 (C-***23***), 123.3 (CH, C-***17***), 121.9 (CH Ar) 121.8 (CH Ar), 119.8 (C-***3***), 119.3 (CH Ar), 118.9 (CH Ar), 117.8 (CH Ar), 111.3 (CH Ar), 108.3 (CH Ar), 105.4 (C-***16***), 42.6 (CH_2, C-***10***), 30.4 (CH, C-***13***), 28.1 (CH_2, C-***12***), 21.6 (CH_3, C-***14***), 19.6 (CH_2, C-***11***), 8.3 (CH_3, C-***15***).

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calculated for $C_{22}H_{22}N$ (M^++H): 315.1856 found: 315.1858.

Reaction of 5-chloro-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with indole

Synthesized from 5-chloro-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole (100 mg, 0.46 mmol), dry methanol (56 µl, 1.38 mmol), indole (161 mg, 1.38 mmol), $PtCl_2$ (6.1 mg, 0.023 mmol) in 3 mL of dry 1,4-dioxane (0.15 M). Compounds **218d** and **218d'** (inseparable mixture of isomers in a ratio of 0.8:1) obtained after column chromatography, Pet Ether/EtOAc, 20:1, 35.2 mg, 0.16 mmol, 35% as a brown oil.





Compound 218d **Compound 218d'**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.0 Hz, 2H, H-***7*** and ***7'***), 7.39 (t, *J* = 1.3 Hz, 2H, H-***4*** and ***4'***), 7.04 (d, *J* = 1.3 Hz, 2H, H-***6*** and ***6'***), 6.59 – 6.56 (m, 1H, H-***13'***), 6.04 – 5.90 (m, 3H, H-**11** and **12** and H-***12'***), 4.53 – 4.48 (m, 2H, H-***10***), 3.96 (t, *J* = 6.9 Hz, 2H, H-***10'***),3.45 – 3.41 (m, 2H, H-***13***), 2.59 – 2.54 (m, 2H, H-***11'***), 2.19 (s, 3H, H-***15'***), 2.14 (s, 3H, H-***15***).

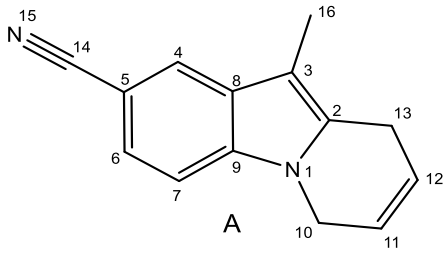
^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1 (C-***9*** or ***9'***), 132.7 (C-***2*** or ***2'***), 130.8 (C-***5*** or ***5'***), 130.2 (C-***5*** or ***5'***), 124.9 (C-***8*** or ***8'***), 124.5 (C-***8*** or ***8'***), 123.69 (CH, C-***12'***), 122.03 (CH, C-***6*** or ***6'***), 121.89 (CH, C-***11*** or ***12***), 120.41 (CH, C-***11*** or ***12***), 118.37 (CH, C-***13'*** and **7** *or* ***7'***), 117.35 (CH, C-***4*** or ***4'***), 109.41 (CH, C-***7*** or ***7'***), 109.33 (CH, C-***6*** or ***6'***), 107.10 (C-***3 or 3'***), 41.85 (CH_2, C-***10***), 39.89 (CH_2, C-***10'***), 24.33 (CH_2, C-***11'***), 22.83 (CH_2, C-***13***), 8.19 (CH_3, C-***15***), 8.04 (CH_3, C-***15'***).

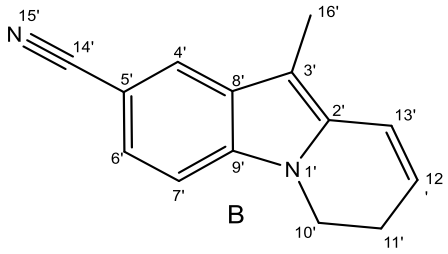
ν_{max}/cm^{-1}: 2967 (m, =C-H), 2924 (s, C-H), 2857 (m, C-H), 1699 (m, C=C), 1459 (m, C-C in ring) 1351 (w, Ar-H), 1204 (w, C-N).

HRMS (ASAP) Solid**:** Calculated for $C_{13}H_{12}{}^{35}ClN$ (M^++H): 218.0739. Found: 218.0737.

Reaction of 5-cyano-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with indole

Synthesized from 5-cyano-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole (70 mg, 0.34 mmol), dry methanol (42 µl, 1.02 mmol), indole (119 mg, 1.02 mmol), $PtCl_2$ (4.5 mg, 0.02 mmol) in 2.5 mL of dry 1,4-dioxane (0.14 M). Compounds **218e** and **218e'** (Inseparable mixture of isomers in a ratio of 0.78:1) obtained after column chromatography, Pet Ether/EtOAc, 10:1, 32.9 mg, 0.16 mmol, 47% as a brown oil.





Compound 218e **Compound 218e'**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92-7.85 (m, 2H; H-***4*** and H-***4'***), 7.46-7.41 (m, 2H; H-***6*** and H-***6'***), 7.33 (d, *J* = 8.5 Hz, 1H; H-***7*** and ***7'***), 7.27 (d, *J* = 8.5 Hz, 1H, H-***7*** and ***7'***), 6.73-6.69 (m, 1H; H-***13'***), 6.13-6.09 (m, 1H, H-***11+12*** and H-***12'***), 4.69-4.64 (m, 2H, H-***10***), 4.13 (t, *J* = 7.0 Hz, 2H, H-***10'***), 3.56 (m, 2H; H-***13***), 2.70 (ddd, *J* = 9.7, 6.7, 3.3 Hz, 2H, H-***11'***), 2.34 (s, 3H, H-***16'***), 2.29 (s, 3H, H-***16***).

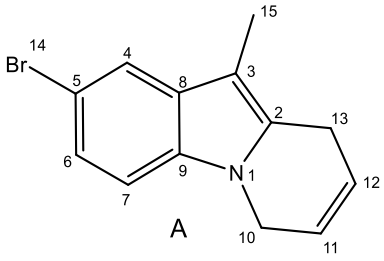
^{13}C NMR (126 MHz, $CDCl_3$) δ 124.95 (CH, C-***6/6'***), 124.73 (CH, CH=C, C-***11/12/12'***), 124.19 (CH, C-***4/4'***), 123.38 (CH, C-***6/6'***), 123.33 (CH, C-***4/4'***), 121.92 (CH, CH=C, C-***11/12/12'***), 120.01 (CH, CH=C, C-***11/12/12'***), 118.08 (CH, CH=C, C-***13'***), 109.20(CH, C-***7/7'***), 109.01 (CH, C-***7/7'***), 41.96 (CH_2, C-***10***), 39.89 (CH_2, C-***10'***), 24.16 (CH_2, C-***11'***), 22.78 (CH_2, C-***13***), 14.22, 8.14 (CH_3, C-***16***), 7.97 (CH_3, C-***16'***).

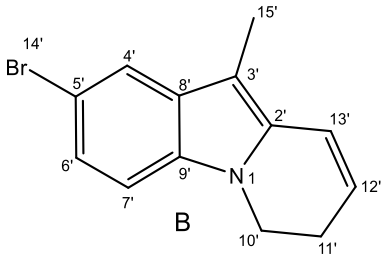
Low intensity, therefore quaternary carbons not detected.

HRMS (ASAP) Solid: Calculated for $C_{14}H_{12}N_2$ (M^++H): 209.1082. Found: 209.1079.

Reaction of 5-bromo-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with indole

Synthesized from 5-bromo-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole (100 mg, 0.38 mmol), $PtCl_2$ (5 mg, 0.02 mmol), indole (133 mg, 1.14 mmol) and dry methanol (50 µl, 1.14 mmol) in 1.9 mL of dry 1,4-dioxane. Compounds **218f** and **218f'** (inseparable mixture of isomers) and compound **287f** obtained after column chromatography, Pet Ether/EtOAc, 40:1 then 15:1, 50 mg, 0.19 mmol, 51% as an orange oil and 9 mg, 0.02 mmol, 6% as a brown oil respectively (with wet methanol). Also, same column elution obtained compounds **218f** and **218f'** (inseparable mixture of isomers) 53 mg, 0.2 mmol, 53% and 30 mg, 0.08 mmol, 20% as a brown oil respectively **287f** (with dry methanol).



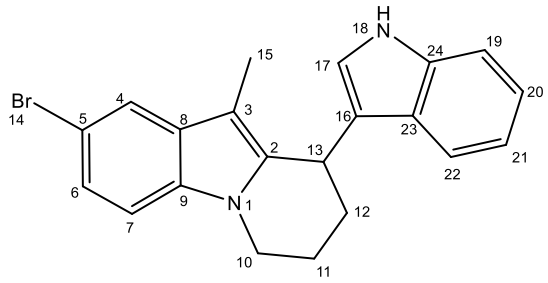


Compound 218f **Compound 218f'**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 1.7 Hz, 1H, H-***4***), 7.53 (d, *J* = 1.8 Hz, 1H, H-***4'***), 7.21 – 7.11 (m, 2H, H-***6*** and H-***7***), 7.00 (m, 2H, H-***6'*** and H-***7'***), 6.56 (d, *J* = 9.9 Hz, 1H, H-***12***), 6.02 – 5.95 (m, 1H, H-***11***), 5.92 (m, 2H, H-***13'*** and H-***12'***), 4.46 (s, 2H, H-***11'***), 3.97 – 3.88 (m, 2H, H-***13***), 3.40 (s, 2H, H-***10'***), 2.59 – 2.47 (m, 2H, H-***10***), 2.17 (s, 3H, H-***15***), 2.12 (s, 3H, H-***15'***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.36 (C-***9*** or ***9'***), 133.99 (C-***9*** or ***9'***), 132.57 (C-***2*** or ***2'***), 130.85 (C-***2*** or ***2'***), 130.66 (C – ***8*** or ***8'***), 130.18 (C – ***8*** or ***8'***), 124.57 (CH, C-***4***), 123.76 (CH, C-***4'***), 122.89 (CH, C-***6***), 121.90 (CH, C-***7***), 121.36 (CH, C-***6'***), 120.39 (CH, C-***7'***), 120.29 (CH, C-***12***), 118.24 (CH, C-***11***), 112.52 (C-***5*** or ***5'***), 112.00 (C-***5*** or ***5'***), 109.89 (CH, C-***13'***), 107.02 (C-***3*** or ***3'***), 104.31 (C-***3*** or ***3'***), 41.83 (CH_2, C-***11'***), 39.86 (CH_2, C-***13***), 30.95 (CH, C-***12'***), 24.31 (CH_2, C-***10'***), 22.80 (CH_2, C-***10***), 8.19 (CH_3, H-***15***), 8.04 (CH_3, H-***15'***).

ν_{max}/cm^{-1}: 2967 (m, =C-H), 2924 (s, C-H), 2857 (m, C-H), 1699 (m, C=C), 1459 (m, C-C in ring) 1351 (w, Ar-H), 1204 (w, C-N).



Compound 287f

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H; H-***18***), 7.65 - 7.60 (d, *J* = 1.8 Hz, 1H, H-***7***), 7.57 (d, *J* = 8.0 Hz, 1H, H-***4***), 7.39 - 7.32 (m, 1H, H-***6***), 7.23 - 7.14 (m, 4H, H-***22***, H-***20***, H-***19*** and H-***21***), 6.51 - 6.48 (m, 1H, H-***17***), 4.75 (t, *J* = 4.4 Hz, 1H, H-***13***), 4.26 - 4.17 (m, 1H, H-***10***), 3.88 (td, *J* = 11.1, 4.9 Hz, 1H, H-***10***), 2.38 - 2.31 (m, 2H; H-***11*** and H-***12***), 2.03 (s, 3H,H-***15***), 1.92 (d, *J* = 9.4 Hz, 2H, H-***12*** and H-***11***).

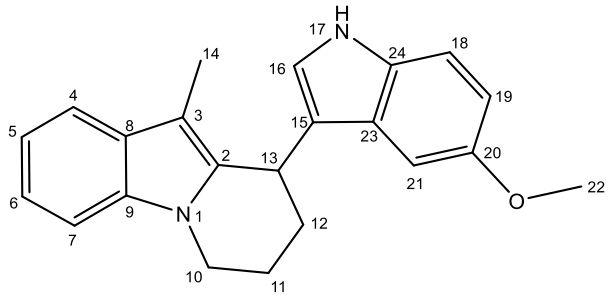
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.70 (C-***9***), 136.21 (C-***24***), 134.48 (C-***2***), 130.41 (C-***8***), 126.12 (C-***23***), 123.00 (CH, C-***17***), 122.92 (CH, C-***22/21/20/19***), 122.06 (CH, C-***22/21/20/19***), 120.63 (CH, C-***4***), 119.43 (CH, C-***7***), 118.91 (CH, C-***22/21/20/19***), 118.45 (C-***5***), 112.31 (C-***3***), 111.38 (CH, C-***6***), 110.04 (CH, C-***22/21/20/19***), 105.81 (C-***16***), 42.65 (CH_2, C-*10*), 30.45 (CH, C-***13***), 28.00 (CH_2, C-***11***), 19.45 (CH_2, C-***12***), 8.24 (CH_3, C-***15***).

ν_{max}/cm^{-1}: 3383 (m, br, N-H), 2957 (m, =C-H), 2924 (s, C-H), 2854 (m, C-H), 1713 (s, C=C), 1461 (s, Ar-H), 1366 (m, C-N).

HRMS – (FTMS + p NSI) ((MeOH)/ MeOH + NH_4OAc): Calc. for $C_{21}H_{19}{}^{79}BrN_2$ (M^++H): 379.0804. Found: 379.0807. Calc. for $C_{21}H_{19}{}^{81}BrN_2$ $[M+H]^+$: 381.0784. Found: 381.0786.

Reaction of 1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with 5-methoxy indole

Synthesized from 1-(2,3-butadien-1-yl)-3-methyl-1H-indole (100 mg, 0.55 mmol), $PtCl_2$ (7.2 mg, 0.027 mmol), 5-methoxy indole (247 mg, 1.65 mmol), methanol (66 µL, 1.65 mmol) and 3.5 mL (0.15 M) of dry 1,4-dioxane. Compounds **218a** and **218a'** (an inseparable mixture with a ratio of 0.35:1) and compound **325a** obtained after column chromatography, Pet Ether/EtOAc, (20:1), 16.5 mg, 0.09 mmol, 17% as an orange/yellow oil and 66.5 mg, 0.2 mmol, 37% as a yellow liquid respectively.



Compound 325a

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H; H-***17***), 7.45 (d, *J* = 7.9 Hz, 1H; H-***7***), 7.22 (d, *J* = 7.9 Hz, 1H; H-***4***), 7.13 – 7.08 (m, 2H; H-***5*** & H-***18***), 7.07 – 7.01 (m, 1H; H-***6***), 6.89 (d, *J* = 2.4 Hz, 1H; H-***21***), 6.76 (dd, *J* = 8.6, 2.4 Hz, 1H; H-***19***), 6.35 (d, *J* = 2.3 Hz, 1H; H-***16***), 4.67 – 4.61 (m, 1H; H-***13***), 4.16 (ddd, *J* = 11.2, 5.0, 3.2 Hz, 1H; H-***10***), 3.79 (td, *J* = 11.2, 5.0 Hz, 1H; H-***10***), 3.72 (s, 3H; H-***22***), 2.27-1.95 (m, 3H; 2H-***12*** & H-***11***), 1.92 (s, 3H; H-***14***), 1.85 – 1.73 (m, 1H; H-***11***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.19 (C-***20***), 136.19 (C-***9***), 135.20 (C-***24***), 132.13 (C), 129.05 (C-***8***), 126.93 (C-***23***), 124.42 (CH, C-***16***), 120.63 (CH, C-***5***), 119.30 (CH, C-***6***), 118.71 (C-***3***), 118.37 (CH, H-***7***), 112.36 (CH, C-***18***), 112.18 (CH, C-***19***), 108.98 (CH, C-***4***), 106.28 (C-***15***), 101.31 (CH, C-***21***), 56.29 (CH_3, C-***22***), 42.88 (N-CH_2, C-***10***), 30.62 (CH, C-***13***), 28.38 (CH_2, C-***12***), 19.80 (CH_2, C-***11***), 8.69 (CH_3, C-***14***).

HRMS (FTMS + p NSI) (DCM/ MeOH + NH_4OAc): Calc. for $C_{22}H_{22}N_2O$ $[M+H]^+$ 331.1805: Found: 331.1805.

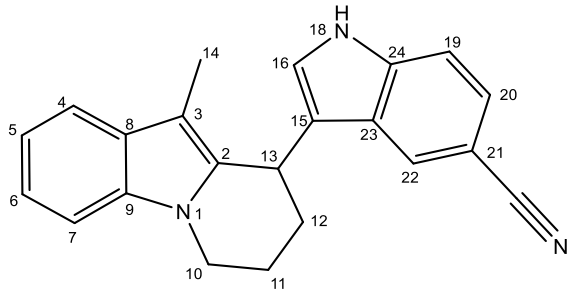
Reaction of 1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with 5-Cl-1H-indole

Synthesized from 1-(2,3-butadien-1-yl)-3-methyl-1H-indole (100 mg, 0.55 mmol), $PtCl_2$ (7.2 mg, 0.0275 mmol), 5-chloro-1H-indole (249 mg, 1.65 mmol), dry methanol (67 µL, 1.65 mmol) and 2.75 mL of dry 1,4-dioxane. Compounds **218a** and **218a'** (inseparable mixture with a ratio of 1:1) obtained after column chromatography, Pet Ether/EtOAc, 20:1, 73.6 mg, 0.40 mmol, 74% as an orange/yellow oil.

Characterization consistent with that for compound **218a** and **218a'**.

Reaction of 1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with 5-CN-1H-indole

Synthesized from 1-(2,3-butadien-1-yl)-3-methyl-1H-indole (100 mg, 0.55 mmol), $PtCl_2$ (7.2 mg, 0.0275 mmol), 5-cyano-1H-indole (235 mg, 1.65 mmol), methanol (67 µL, 1.65 mmol) and 2.75 mL of dry 1,4-dioxane. Compounds **218a'** and **325c** obtained after column chromatography, Pet Ether/EtOAc, (20:1), 73.6 mg, 0.40 mmol, 74% as an orange/yellow oil and 25.4 mg, 0.078 mmol, 15% as a brown oil respectively (NMR value).



Compound 325c

Not Isolated, identified by triplet proton for position 13 at ~4.8 ppm, also protons for position 10 at ~ 4.3 and 4.0 ppm.

* Results obtained by Sachini Herath and Louise Eagling.

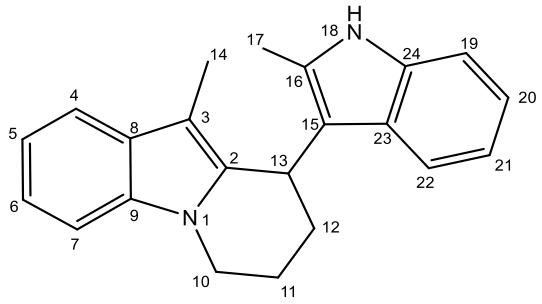
Reaction of 1-(2, 3-Butadien-1-yl)-3-methyl-1H-indole with 5-Br-1H-indole

Synthesized from 1-(2,3-butadien-1-yl)-3-methyl-1H-indole (100 mg, 0.55 mmol), $PtCl_2$ (7.2 mg, 0.0275 mmol), 5-bromo-1H-indole (323 mg, 1.65 mmol), dry methanol (67 µL, 1.65 mmol) and 2.75 mL of dry 1,4-dioxane. Compounds **218a** and **218a'** (inseparable mixture with a ratio of 0.14:1) obtained after column chromatography, Pet Ether/EtOAc, 20:1, 32.9 mg, 0.18 mmol, 33% as an orange oil.

Characterization consistent with that for compound **218a** and **218a'**.

Reaction of 1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with 2-methyl-1H-indol

Synthesized from 1-(2,3-butadien-1-yl)-3-methyl-1H-indole (100 mg, 0.55 mmol), $PtCl_2$ (7.2 mg, 0.028 mmol), 2-methyl-1H-indole (220 mg, 1.65 mmol), dry methanol (66 µL, 1.65 mmol) and 3.5 mL (0.15 M) of dry 1,4-dioxane. Compounds **218a** and **218a'** (an inseparable mixture with a ratio of 0.2:1) and **325e** obtained after column chromatography, Pet Ether/EtOAc, (10:1), 19 mg, 0.10 mmol, 19% as an orange/yellow oil and 79 mg, 0.25 mmol, 46% as a brown oil respectively.



Compound 325e

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H; H-***18***), 7.49 (d, *J* = 8.0 Hz, 1H; H-***7***), 7.36 (d, *J* = 8.0 Hz, 1H; H-***4***), 7.27 (d, *J* = 8.0 Hz, 1H; H-***19***), 7.20 (ddd, *J* = 8.0, 7.1, 1.2 Hz, 1H; H-***5***), 7.17 – 7.06 (m, 3H; H-***22***, H-***6***, H-***20***), 6.95 (t, *J* = 7.4 Hz, 1H; H-***21***), 4.67 (t, *J* = 5.8 Hz, 1H; H-***13***), 4.28 – 4.11 (m, 2H; H-***10***), 2.23 – 1.95 (m, 7H; H-***14***, H-***12***, H-***11***), 1.83 (s, 3H, H-***17***).

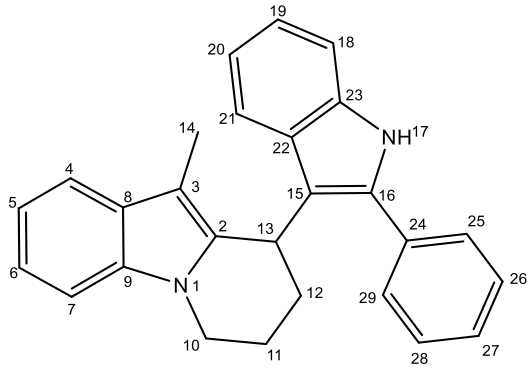
^{13}C NMR (126 MHz, $CDCl_3$) δ 135.49 (C-***16***), 135.08 (C-***2***), 134.12 (C-***8***), 131.06 (C-***24***), 128.77 (C-***15***), 127.97 (C-***8***), 120.88 (C-***23***), 120.21 (CH, C-***5***), 119.19 (CH, C-***21***), 118.83 (CH, C-***6***), 118.33 (CH, C-***22***), 117.99 (CH, C-***7***), 113.70 (C-***3***), 110.13 (CH, C-***19***), 108.52 (CH, C-***4***), 42.57 (N-CH_2, C-***10***), 30.83 (CH, C-***13***), 29.71 (CH_2, C-***11***), 21.61 (CH_2, C-***12***), 11.77 (CH_3, C-***14***), 8.16 (CH_3, C-***17***).

HRMS (FTMS + p NSI) (DCM/ MeOH + NH_4OAc): Calc. for $C_{22}H_{22}N_2$ $[M+H]^+$: 315.1783. Found: 315.1856.

* Results obtained by Sachini Herath.

Reaction of 1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with 2-Ph-1H-indole

Synthesized from 1-(2,3-butadien-1-yl)-3-methyl-1H-indole (100 mg, 0.55 mmol), $PtCl_2$ (7.2 mg, 0.028 mmol), 2-phenyl-1H-indole (319 mg, 1.65 mmol), dry methanol (67 µL, 1.65 mmol) and 2.75 mL (0.2 M) of dry 1,4-dioxane. Compound **325f** obtained after column chromatography, Pet Ether/EtOAc, (20:1), 77 mg, 0.21 mmol, 35% as a red/brown oil.



Compound 325f

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H, H-***17***), 7.45 (d, *J* = 7.9 Hz, 2H, Ar), 7.37 (d, *J* = 7.3 Hz, 2H, Ar), 7.13 (d, *J* = 7.3 Hz, 2H, Ar), 7.06 (s, 1H, Ar), 7.03 – 7.00 (m, 2H, Ar), 6.90 – 6.86 (m, 1H, Ar), 6.81 (d, *J* = 7.8 Hz, 1H, Ar), 6.70 – 6.65 (m, 1H, Ar), 4.54 (dd, *J* = 9.2, 5.8 Hz, 1H, H-***13***), 4.11 (dd, *J* = 10.2, 5.3 Hz, 1H, H-***10***), 3.91 (td, *J* = 11.0, 4.3 Hz, 1H, H-***10***), 2.13 – 1.99 (m, 3H, H-***12*** + H-***11***), 1.91 – 1.80 (m, 1H, H-***11***), 1.50 (s, 3H, H-***14***).

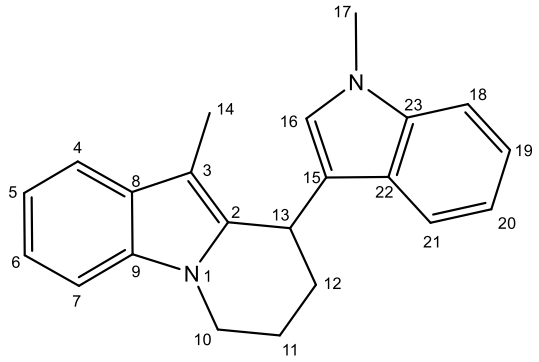
^{13}C NMR (126 MHz, $CDCl_3$) δ 137.91, 136.85, 135.52, 135.48, 134.49, 134.19, 133.27, 132.41, 129.29, 129.06, 128.91, 128.50, 127.93, 127.74, 127.70, 125.19, 122.38, 122.11, 120.69, 120.30, 120.21, 119.57, 118.71, 117.93, 115.62, 110.93, 110.75, 108.42, 106.78, 42.52 (CH_2, C-***10***), 32.22 (CH, C-***13***), 30.54 (CH_2, C-***11/12***), 23.09 (CH_2, C-***11/12***), 8.36 (CH_3, C-***14***).

HRMS (FTMS) Calculated for $C_{27}H_{24}N_2H$ (M+1): 377.2012. Found: 377.2011.

* Results obtained by Sachini Herath and Louise Eagling.

Reaction of 1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with N-methyl indole

Synthesized from 1-(2, 3-butadien-1-yl)-3-methyl-1H-indole (100 mg, 0.55 mmol), dry methanol (67 µl, 1.65 mmol), N-methyl indole (216 mg, 1.65 mmol), $PtCl_2$ (7.2 mg, 0.0275 mmol) in 2.75 mL of dry 1,4-dioxane. Compounds **218a'** and **325g** obtained after column chromatography, Pet Ether/EtOAc, (30:1), 88.3 mg, 0.48 mmol, 44% as a yellow oil and 76.6 mg, 0.24 mmol, 22% as a brown oil respectively.



Compound 325g

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.9 Hz, 1H, H-***4***), 7.47 (d, *J* = 7.7 Hz, 1H, H-***18***), 7.24 (dd, *J* = 14.9, 8.1 Hz, 2H, H-***7***+H-***21***), 7.17 – 7.09 (m, 2H, H-***5***+H-***19***), 7.08 – 7.03 (m, 2H, H-***6***+H-***20***), 6.30 (s, 1H, H-***16***), 4.72 (t, *J* = 4.1 Hz, 1H, H-***13***), 4.21 (ddd, *J* = 11.2, 4.9, 3.1 Hz, 1H, H-***10***), 3.82 (td, *J* = 11.2, 4.8 Hz, 1H, H-***10***), 3.56 (s, 3H, H-***17***), 2.32 – 2.26 (m, 1H, H-***12***), 2.12 – 2.06 (m, 1H, H-***12***), 2.06 – 1.98 (m, 1H, H-***11***), 1.95 (s, 3H, H-***14***), 1.84 – 1.78 (m, 1H, H-***11***).

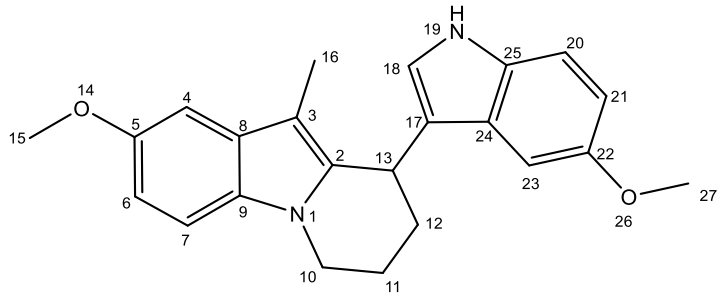
^{13}C NMR (126 MHz, $CDCl_3$) δ 137.4 (C-***2***), 135.9 (C-***9***), 135.07 (C-***23***), 128.7 (C-***8***), 128.12 (CH, C-***16***), 126.6 (C-***22***), 121.4 (CH, C-***6/20***), 120.2 (CH, C-***6/20***), 119.0 (CH, C-***4***), 118.9 (CH, C-***5/19***), 118.7 (CH, C-***5/19***), 118.0 (CH, C-***18***), 117.1 (C-***3***), 109.4 (CH, C-***7/21***), 108.7 (CH, C-***7/21***), 105.9 (C-***15***), 42.6 (CH_2, C-***10***), 32.6 (CH_3, C-***17***), 30.2 (CH, C-***13***), 28.2 (CH_2, C-***12***), 19.4 (CH_2, C-***11***), 8.4 (CH_3, C-***14***).

ν_{max}/cm^{-1}: 3410 (s, NH), 3053, 2942 – 2830 (m, C-H), 1618 – 1578 (w, C=C), 1484 (s, C-H methyl), 1456 (m, C-C in ring), 1227 (s, C-N).

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calc. for $C_{22}H_{22}N_2$ $[M+H]^+$ 315.4320: Found: 315.4220.

Reaction of 5-Methoxy-1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with 5-methoxy indole

Synthesized from 5-methoxy-1-(2,3-butadien-1-yl)-3-methyl-1H-indole (71 mg, 0.33 mmol), $PtCl_2$ (4.4 mg, 0.016 mmol), 5-methoxy-1H-indole (132 mg, 0.89 mmol), dry methanol (36 µL, 0.89 mmol) and 1.7 mL of dry 1,4-dioxane. Compound **326** obtained after column chromatography, Pet Ether/EtOAc, 20:1, 43.6 mg, 0.12 mmol, 40% as an orange/brown solid.



Compound 326

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H, H-***19***), 7.22 (m, 2H, H-***7*** + H-***20***), 6.98 (t, *J* = 2 Hz, 2H, H-***4*** + H-***23***), 6.85 (m, 2H, H-***6*** + H-***21***), 6.54 (d, *J* = 2 Hz, 1H, H-***18***), 4.73 (t, *J* = 4.3 Hz, 1H, H-***13***), 4.24 (ddd, *J* = 11.0, 4.9, 3.1 Hz, 1H, H-***10***), 3.87 (m, 4H, H-***10*** + H-***15***), 3.82 (s, 3H, H-***27***), 2.32 (m, 1H, H–***12***), 2.11-2.05 (m, 2H, H-***12*** + H-***11***),1.99 (s, 3H, H-***16***), 1.90 (m, 1H, H-***11***).

^{13}C NMR (500 MHz, $CDCl_3$) δ 153.99, 153.88 (C-***5*** and C-***22***), 135.68, 131.80, 131.29, 128.95, 126.63, 124.07 (CH, C-***18***), 118.46 (CH, C-***4***), 112.01 (CH, C-***7*** or C-***20***), 111.87 (CH, C-***6*** or C-***21***), 110.15 (CH, C-***6*** or C-***21***), 109.30 (CH, C-***7*** or C-***20***), 105.61, 100.97 (CH, C-***23*** or C-***4***), 100.34 (CH, C-***23*** or C-***4***), 56.11 (CH_3, C-***15***), 55.96 (CH_3, C-***27***), 42.61 (CH_2, C-***10***), 30.32 (CH, C-***13***), 28.00 (CH_2, C-***12***), 19.48 (CH_2, C-***11***), 8.41 (CH_3, C-***16***).

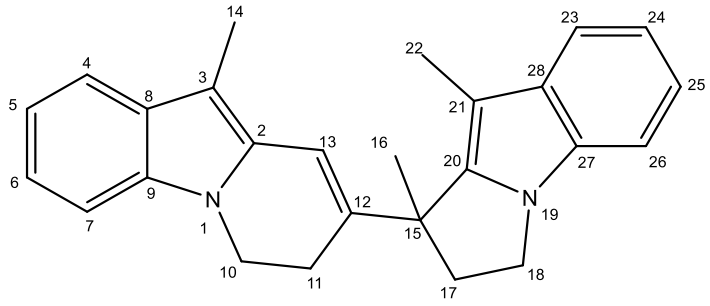
ν_{max}/cm^{-1}: 3410 (s, NH), 3053, 2942 – 2830 (m, C-H), 1618 – 1578 (w, C=C), 1484 (s, C-H methyl), 1456 (m, C-C in ring), 1227 (s, C-N).

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calc. for $C_{23}H_{24}N_2O_2$ $[M+H]^+$ 360.1910: Found: 361.1911.

M.P. = 180-182 ^oC.

‘Unknown compound’ 327a

Compound **327a** isolated from platinum reactions when substituted external indoles were present.



Compound 327a

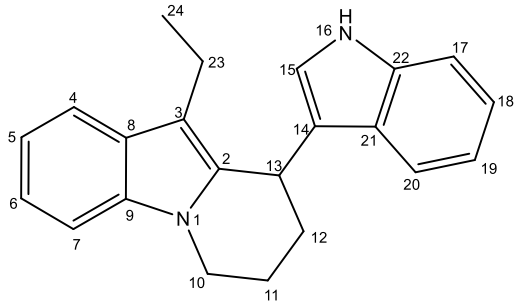
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.04 (m, 8H, H-***4-7*** + H-***23-26***), 6.65 (s, 1H, H-***13***), 4.18 – 3.92 (m, 4H, H-***10*** and H-***18***), 2.83 – 2.41 (m, 4H, H-***11*** and H-***17***), 2.32 (s, 3H, H-***22***), 2.20 (s, 3H, H-***14***), 1.69 (s, 3H, H-***16***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.96 (C_q), 138.98 (C_q), 136.39 (C_q), 133.44 (C_q), 132.19 (C_q), 131.77 (C_q), 129.58 (C_q), 121.95 (C-***Ar***), 120.67 (C-***Ar***), 119.03 (C-***Ar***), 118.84 (C-***Ar***), 118.77 (C-***Ar***), 118.74 (C-***Ar***), 112.82 (C-***13***), 109.45 (C-***Ar***), 108.52 (C-***Ar***), 107.37 (C_q), 101.45 (C_q), 46.98 (C_q), 42.36(C-***11***, C-***17***, C-***10*** or C-***18***), 40.60 (C-***10*** or C-***18***), 26.31 (C-***11*** or C-***17***), 23.87 (C-***16***), 8.42 (C-***22***), 8.31 (C-***14***).

HRMS ASAP (Solid): Calc. for $C_{26}H_{27}N_2$ $[M+H]^+$ 367.2096: Found: 367.2174.

Reaction of 1-(2,3-butadien-1-yl)-3-ethyl-1H-indole with indole

Synthesized from 1-(2,3-butadien-1-yl)-3-ethyl-1H-indole (109.3 mg, 0.55 mmol), $PtCl_2$ (7.4 mg, 0.03 mmol), indole (194.7 mg, 1.66 mmol), methanol (0.074mL, 1.66 mmol) and 2.77 mL of dry 1,4-dioxane. Compound **287g** obtained after column chromatography using pet ether/EtOAc, 20:1, 71.7 mg, 0.23 mmol, 41% as a brown oil.



Compound 287g

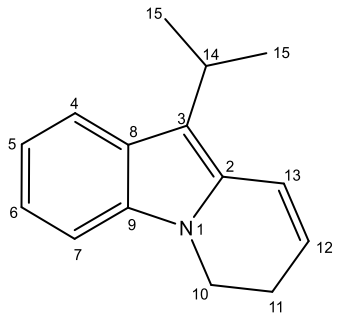
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H, H***16***), 7.67 (d, *J* = 7.8 Hz, 1H, H-***4***), 7.62 (d, *J* = 7.8 Hz, 1H, H-***7***), 7.41 (d, *J* = 8.1 Hz, 1H, H-***17***), 7.37 (d, *J* = 8.1 Hz, 1H, H-***20***), 7.27 – 7.20(m, 2H, H-***5***+H-***6***), 7.19 – 7.13 (m, 2H, H-***18*** + H-***19***), 6.60 (dd, *J* = 2.3, 0.7 Hz, 1H, H-***15***), 4.86 (t, *J* = 3.7 Hz, 1H, H-***13***), 4.33 (ddd, *J* = 11.2, 5.0, 2.9 Hz, 1H, H-***10***), 3.94 (ddd, *J* = 11.2, 4.8 Hz, 1H, H-***10***), 2.55 (q, *J* = 7.5 Hz, 2H, H-***23***), 2.44 – 2.38 (m, 1H, H-***12***), 2.24 – 2.15 (m, 1H, H-***12***), 2.15 – 2.07 (m, 1H, H-***11***), 1.97 – 1.89 (m, 1H, H-***11***), 1.06 (t, *J* = 7.5 Hz, 3H, H-***24***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.64, 136.10 (C-***22***), 134.38 (C-***2***), 127.90, 123.39 (CH, C-***15***), 121.93 (CH, C-***5***/C-***6***), 120.21 (CH, C-***5***/C-***6***), 119.36 (CH, C-***18***/C-***19***), 119.31, 118.97 (CH, C-***18***/C-***19***), 118.89 (CH, C-***4***), 118.41 (CH, C-***7***), 112.56, 111.33 (CH, C-***17***), 108.76 (CH, C-***20***), 42.58 (N-CH_2, C-***10***), 30.21 (CH, C-***13***), 28.04 (CH_2, C-***11***), 19.30 (CH_2, C-***12***), 17.27 (CH_2, C-***23***), 14.94 (CH_2, C-***24***).

HRMS – (FTMS + p APCI, ASAP) (MeOH) Calc. for $C_{22}H_{21}N_2$ $[M-H]^+$: 313.1699. Found: 313.1699. Calc. for $C_{22}H_{23}N_2$ $[M+H]^+$: 315.1856. Found: 315.1856.

Reaction of 1-(2,3-butadien-1-yl)-3-isopropyl-1H-indole with indole

Synthesized from 1-(2,3-butadien-1-yl)-3-isopropyl-1H-indole (167.1 mg, 0.791 mmol), $PtCl_2$ (10.52 mg, 0.040 mmol), indole (278 mg, 2.372 mmol), methanol (0.096 mL, 2.372 mmol) and 3.95 mL of dry 1,4-dioxane. Compounds **218h'** and **287h** obtained after ISCO column chromatography using 2 x 12g silica gel Redisep columns eluting with a gradient of *i*-hexane to 5% ethyl acetate using the instrument's default settings to yield 45.3 mg, 0.215 mmol, 27% as a brown oil and 18.8 mg, 0.057 mmol, 7% as a brown oil respectively.



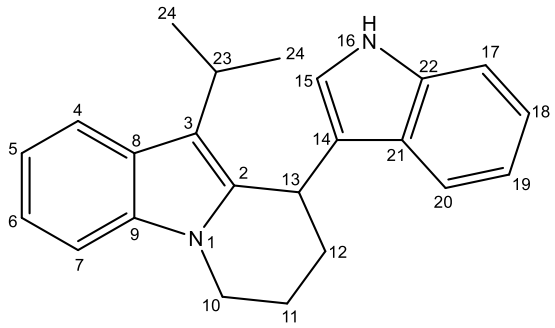
Compound 218h'

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 1H, H-***4***), 7.14 (d, *J* = 8.2 Hz, 1H, H-***7***), 7.08 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H, H-***5***), 6.95 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H, H-***6***), 6.64 (dt, *J* = 10.0, 1.8 Hz, 1H, H-***13***), 5.87 (dt, *J* = 10.0, 4.5 Hz, 1H, H-***12***), 3.97 (t, *J* = 6.9 Hz, 2H, H-***10***), 3.21 (heptet, *J* = 7.1 Hz, 1H, H-***14***), 2.56 – 2.50 (m, 2H, H-***11***), 1.35 (d, *J* = 7.1 Hz, 6H, H-***15***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.01, 130.13 (C-***2***), 127.06, 122.94 (CH, C-***12***), 121.69 (CH, C-***5***), 120.29 (CH, C-***4***), 118.96 (CH, C-***6***), 118.66 (CH, C-***13***), 108.67 (CH, C-***7***), 39.71 (CH_2, C-***10***), 25.64 (CH, C-***14***), 24.29 (CH_2, C-***11***), 23.59 (CH_3, C-***15***).

HRMS – (FTMS + p APCI) (DCM): Calc. for $C_{15}H_{16}N$ $[M+H]^+$: 210.1277. Found: 210.1280.

* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.



Compound 287h

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H, H-***16***), 7.66 (d, *J* = 7.9 Hz, 1H, H-***4***), 7.58 (d, *J* = 7.8 Hz, 1H, H-***7***), 7.29 (d, *J* = 8.1 Hz, 1H, H-***17***), 7.25 (d, *J* = 8.1 Hz, 1H, H-***20***), 7.16 – 7.12 (m, 1H, H-***5***), 7.12 – 7.09 (m, 1H, H-***6***), 7.09 – 7.06 (m, 1H, H-***18***), 7.04 – 7.00 (m, 1H, H-***19***), 6.43 (dd, *J* = 2.3, 0.8 Hz, 1H, H-***15***), 4.79 (dd, *J* = 5.0, 2.7 Hz, 1H, H-***13***), 4.22 (ddd, *J* = 11. 5, 5.4, 1.5 Hz, 1H, H-***10***), 3.78 (td, *J* = 11.5, 4.9 Hz, 1H, H-***10***), 2.88 (heptet, *J* = 7.1 Hz, 1H, H-***23***), 2.33 – 2.27 (m, 1H, H-***12***), 2.09 – 2.03 (m, 1H, H-***12***), 2.02 – 1.91 (m, 1H, H-***11***), 1.82 – 1.75 (m, 1H, H-***11***), 1.25 (d, *J* = 7.1 Hz, 3H, H-***24***), 1.07 (d, *J* = 7.0 Hz, 3H, H-***24***).

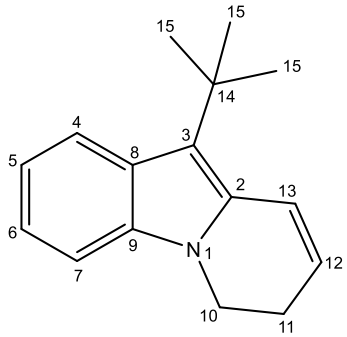
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.67 (C-***9***), 136.53 (C-***22***), 133.51 (C-**2**), 126.50 (C-***8***), 126.11 (C-***8***), 123.55 (CH, C-***15***), 121.94 (CH, C-***5***), 120.09 (CH, C-***4***), 119.96 (CH, C-***6***), 119.49 (C-***3***), 119.38 (CH, C-***18***), 118.90 (CH, C-***7***), 118.62 (CH, C-***19***), 116.49 (C-***14***), 111.35 (CH, C-***17***), 108.97 (CH, C-***20***), 42.53 (N-CH_2, C-***10***), 30.11 (CH, C-***13***), 27.77 (CH_2, C-***11***), 25.57 (CH, C-***23***), 23.33 (CH_3, C-***24***), 22.33 (CH_3, C-***24***), 18.88 (CH_2, C-***12***).

HRMS – (FTMS + p NSI) ((MeOH) / MeOH + NH_4OAc): Calc. for $C_{23}H_{25}N_2$ $[M+H]^+$: 329.2012. Found: 329.2016.

* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.

Reaction of 1-(2,3-butadien-1-yl)-3-(2-methyl-2-propanyl)-1H-indole with indole

Synthesized from 1-(2,3-butadien-1-yl)-3-(2-methyl-2-propanyl)-1H-indole (60 mg, 0.26 mmol), $PtCl_2$ (3.5 mg, 0.013 mmol), indole (91 mg, 0.78 mmol), methanol (0.030 mL, 0.78 mmol) and 1.3 mL of dry 1,4-dioxane. Compounds **218i** and **287i** obtained after column chromatography using pet ether/EtOAc/DCM, 14:1:1, 14 mg, 0.062 mmol, 25% as a bright yellow oil and 15 mg, 0.044 mmol, 19% as a dark yellow oil respectively.



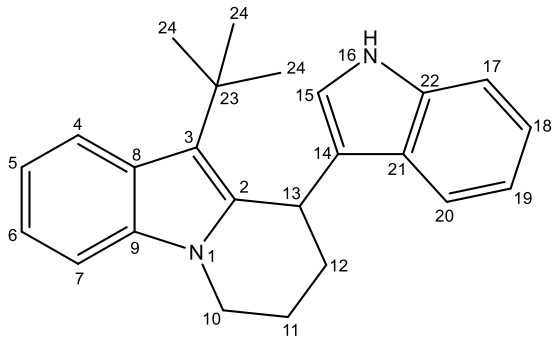
Compound 218i

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.78 (dd, *J*=8.2, 1.1, 1H, **Ar**), 7.15 (d, *J*=8.2, 1H, **Ar**), 7.08 (ddd, *J*=8.2, 7.0, 1.1, 1H, **Ar**), 7.01 – 6.92 (m, 2H, **Ar** and H-***13***), 5.88 (dt, *J*=10.4, 4.5, 1H, H-***12***), 3.97 (t, *J*=6.9, 2H, H-***10***), 2.49 (tdd, *J*=6.7, 4.5, 1.8, 2H, H-***11***), 1.49 (s, 9H, H-***15***).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 137.13 (C-***9***), 129.95 (C-***2***), 127.33 (C-***3***), 123.43 (C-***8***), 122.38 (C-***12***), 121.71 (C-***5***), 121.62 (C-***4***), 118.54 (C-***6***), 108.73 (C-***13***), 100.10 (C-***7***), 39.91 (C-***10***), 34.20 (C-***14***), 32.57 (C-***15***), 24.04 (C-***11***).

HRMS – (FTMS + p APCI, ASAP) (MeOH) Calc. for $C_{16}H_{20}N$ $[M+H]^+$: 226.1590. Found: 226.1586.

* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.



Compound 287i

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.89 (dt, *J*=8.1, 0.9, 1H, **Ar**), 7.65 (d, *J*=7.7, 1H, **Ar**), 7.36 (dt, *J*=8.1, 0.9, 1H, **Ar**), 7.31 (dt, *J*=8.2, 0.9, 1H, **Ar**), 7.24 – 7.14 (m, 3H, **Ar**), 7.10 (ddd, *J*=8.2, 7.0, 1.2, 1H, **Ar**), 6.38 (dd, *J*=2.4, 1.0, 1H, H-***15***), 5.37 – 5.08 (m, 1H, H-***13***), 4.35 (dd, *J*=11.7, 6.0, 1H, H-***10***), 3.83 (ddd, *J*=12.5, 11.6, 5.3, 1H, H-***10***), 2.43 – 2.35 (m, 1H, H-***12***), 2.13 (tdd, *J*=13.0, 4.6, 2.6, 1H, H-***12***), 2.01 (dddt, *J*=16.3, 13.3, 8.8, 2.6, 1H, H-***11***), 1.84 – 1.72 (m, 1H, H-***11***), 1.40 (s, 9H, H-***24***).

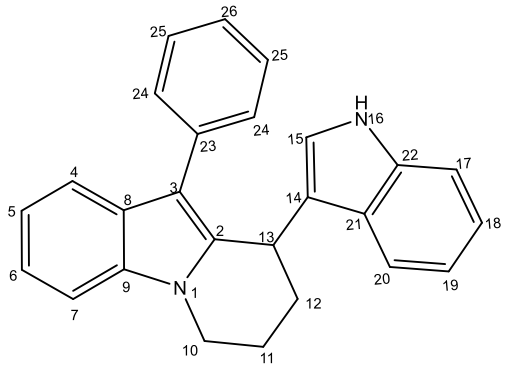
^{13}C NMR (126 MHz, $CDCl_3$) δ = 136.98 (C), 136.78 (C), 133.56 (C), 127.29 (C), 125.79 (C), 124.29 (C), 122.05 (CH, C-***15***), 121.97 (CH, C-***Ar***), 121.00 (C), 120.24 (CH, C-***Ar***), 119.49 (CH, C-***Ar***), 118.93 (CH, C-***Ar***), 118.57 (CH, C-***Ar***), 118.30 (C), 111.41 (CH, C-***Ar***), 109.03 (CH, C-***Ar***), 43.07 (N-CH_2, C-***10***), 33.93 (C, C-***23***), 31.79 (CH, C-***13***), 31.46 (3 x CH_3, C-***24***), 27.53 (CH_2, C-***11***), 18.18 (CH_2, C-***12***).

HRMS – (FTMS + p APCI, ASAP) (MeOH) Calc. for $C_{24}H_{25}N_2$ $[M-H]^+$: 341.2012. Found: 343.2008. Calc. for $C_{24}H_{27}N_2$ $[M+H]^+$: 343.2169. Found: 343.2167.

* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.

Reaction of 1-(2,3-butadien-1-yl)-3-phenyl-1H-indole with indole

Synthesized from 1-(2,3-butadien-1-yl)-3-phenyl-1H-indole (233 mg, 0.950 mmol), $PtCl_2$ (13 mg, 0.047 mmol), indole (334 mg, 2.85 mmol), methanol (0.115 mL, 2.85 mmol) and 4.75 mL of dry 1,4-dioxane. Compounds **218j/218j'** and **287j** obtained after ISCO column chromatography using an 12g silica gel Redisep column eluting with a gradient of i-hexane to 2.5% ethyl acetate using the instrument's default settings, traces (<5%) of **218j/218j'** as a 1:1 inseparable mixture and 39.1 mg, 0.108 mmol, 11% as a brown oil respectively.



Compound 287j

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s,1H, H-***16***), 7.82 (d, *J* = 7.8 Hz, 1H, H-***17***), 7.62 (d, *J* = 8.2 Hz, 1H, H-***20***), 7.42 – 7.38 (m, 4H, H-***25***), 7.31 – 7.28 (m, 1H, H-***26***), 7.27 – 7.20 (m, 4H, H-***4*** +H-***7***), 7.18 – 7.12 (m, 2H, H-18 + H-***19***), 6.63 (d, *J* = 1.6 Hz, 1H, H-***15***), 4.92 (t, *J* = 3.7 Hz, 1H, H-***13***), 4.45 (ddd, *J* = 11.6, 5.8, 1.9 Hz, 1H, H-***10***), 3.98 (td, *J* = 11.6, 5.5 Hz, 1H, H-***10***), 2.47 – 2.41 (m, 1H, H-***12***), 2.24 – 2.17 (m, 1H, H-***12***), 2.17 – 2.09 (m, 1H, H-***11***), 1.99 – 1.92 (m, 1H, H-***11***).

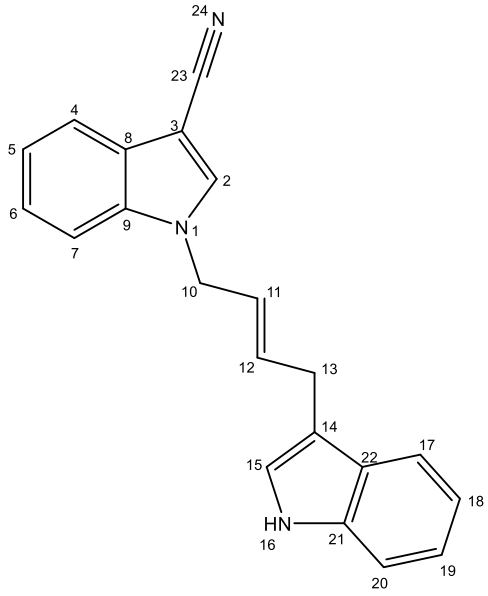
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.79 (C-***9***), 136.69 (C-***22***), 136.26 (C-***2***), 135.40 (C-***23***), 128.77 (C-***Ar***), 128.28 (C-***Ar***), 127.41 (C-***Ar***), 125.67 (C-***Ar***), 125.29 (C-***Ar***), 123.29 (C-***Ar***), 123.97 (CH, CH=C, C-***15***), 121.98 (C-***Ar***), 121.07 (C-***Ar***), 120.20 (C-***Ar***), 119.73 (C-***Ar***), 119.40 (C-***Ar***), 119.34 (CH, C-***17***), 119.10 (CH, C-***20***), 112.41 (C-***26***), 111.30 (CH, C-***25***), 109.20, (CH, C-***24***), 42.88 (N-CH_2, C-***10***), 30.69 (CH, C-***13***), 27.38 (CH_2, C-***11***), 18.44 (CH_2, C-***12***).

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calc. for $C_{26}H_{23}N_2$ $[M+H]^+$ 363.1856: Found: 363.1857.

* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.

Reaction of 1-(2,3-butadien-1-yl)-3-carbonitrile-1H-indole with indole

Synthesized from 1-(2,3-butadien-1-yl)-3-carbonitrile-1H-indole (140.2 mg, 0.722 mmol), $PtCl_2$ (9.60 mg, 0.036 mmol), indole (254 mg, 2.165 mmol), methanol (0.088 mL, 2.165 mmol) and 3.61 mL of dry 1,4-dioxane. Compounds **330k** and **331k** obtained after ISCO column chromatography using a 12g silica gel Redisep column eluting with a gradient of i-hexane to 40% ethyl acetate using the instrument's default settings to yield 33 mg, 0.106 mmol, 15% as a brown oil and 128 mg, 0299 mmol, 41% as a brown oil respectively.



Compound 330k

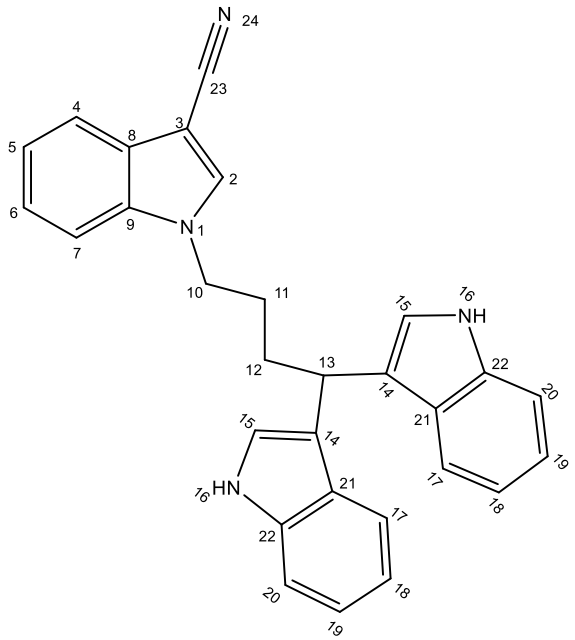
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H, H-***16***), 7.69 (m, 1H, H-***4***), 7.52 (s, 1H, H-***2***), 7.45 (dd, *J* = 7.9, 0.9 Hz, 1H, H-***7***), 7.35 – 7.28 (m, 2H, H-***17***+ H-***20***), 7.23 (dtd, *J* = 14.2, 7.1, 1.3 Hz, 2H, H-***5***+ H-***6***), 7.13 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H, H-***18***), 7.04 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H, H-***19***), 6.87 (d, *J* = 2.3 Hz, 1H, H-***15***), 5.91 (dtt, *J* = 15.4, 6.2, 1.4 Hz, 1H, H-***12***), 5.65 (dtt, *J* = 15.4, 6.1, 1.6 Hz, 1H, H-***11***), 4.65 (dd, *J* = 6.2, 1.2 Hz, 2H, H-***10***), 3.47 (d, *J* = 6.1, 1.2 Hz, 2H, H-***13***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.05 (CH, CH=C, C-***11***), 134.46 (CH, C-***2***), 123.96 (CH, CH=C, C-***12***), 123.77 (CH, C-***5***/C-***6)***, 122.20 (CH, C-***5***/C-***6***), 122.24 (CH, C-***18***), 121.75 (CH, CH=C, C-***15***), 119.91 (CH, C-***4***), 119.46 (CH, C-***19***), 119.16 (CH, C-***17***), 119.19 (CH, C-***20***), 110.90 (CH, C-***7***), 48.77 (CH_2, C-***10***), 28.05 (CH_2, CH_2, C-***13***).

Low intensity, therefore quaternary carbons not detected.

HRMS (FTMS + p NSI) ((DCM) / MeOH + NH_4OAc): Calc. for $C_{21}H_{13}N_3$ $[M+H]^+$: 312.1495. Found: 312.1498.

* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.



Compound 331k

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 2H, H-***16***), 7.67 – 7.63 (m, 1H, H-***2***), 7.42 (d, *J* = 8.0 Hz, 2H, H-***17***), 7.23 (d, *J* = 8.1 Hz, 2H, H-***20***), 7.19 – 7.12 (m, 2H, H-***4*** + H-***7***), 7.09 – 7.04 (m, 2H, H-***18***), 6.97 – 6.91 (m, 2H, H-***19***), 6.77 (d, *J* = 2.2 Hz, 2H, H-***15***), 4.38 (t, *J* = 7.5 Hz, 1H, H-***13***), 3.98 (t, *J* = 7.1 Hz, 2H, H-***10***), 2.13 (dt, *J* = 15.4, 7.6 Hz, 2H, H-***12***), 1.87 (dt, *J* = 15.7, 7.4 Hz, 2H, H-***11***)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.60 (C-***9***), 135.36 (C-***22***), 134.70, 127.91 (C-***8***), 126.81 (C-***21***), 123.69 (CH, C-***4*** +C-***7***), 122.03 (CH, C-***4*** and C-***7*** and C-***18***), 121.45 (CH, CH=C, C-***15***), 119.91 (CH, C-***2***), 119.28 (CH, C-***17***), 119.25 (CH, C-***19***), 111.30 (CH, C-***20***), 110.62 (CH, C-***4*** +C-***7***), 47.19 (N-CH_2, C-***10***), 33.77 (CH, C-***13***), 32.59 (CH_2, C-***12***), 28.41 (CH_2, C-***11***).

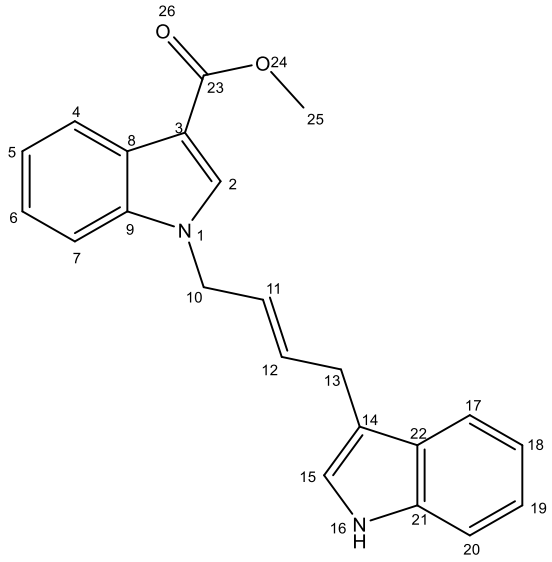
Low intensity, therefore not all quaternary carbons detected.

HRMS – (FTMS + p NSI) ((MeOH) / MeOH + NH_4OAc): Calc. for $C_{29}H_{25}N_4$ $[M+H]^+$: 429.2074. Found: 429.2080.

* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.

Reaction of 1-(2,3-butadien-1-yl)-3-carboxylate-1H-indole with indole

Synthesized from 1-(2,3-butadien-1-yl)-3-carboxylate-1H-indole (210.1 mg, 0.924 mmol), $PtCl_2$ (12 mg, 0.046 mmol), indole (325 mg, 2.77 mmol), methanol (0.112 mL, 2.77 mmol) and 4.75 mL of dry 1,4-dioxane. Compounds **330l** and **331l** obtained after ISCO column chromatography using a 12g silica gel Redisep column eluting with a gradient of *i*-hexane to 100% ethyl acetate using the instrument's default settings to yield 39.7 mg, 0.115 mmol, 13% as a brown oil and 136.9 mg, 0.297 mmol, 32% as a brown oil respectively.



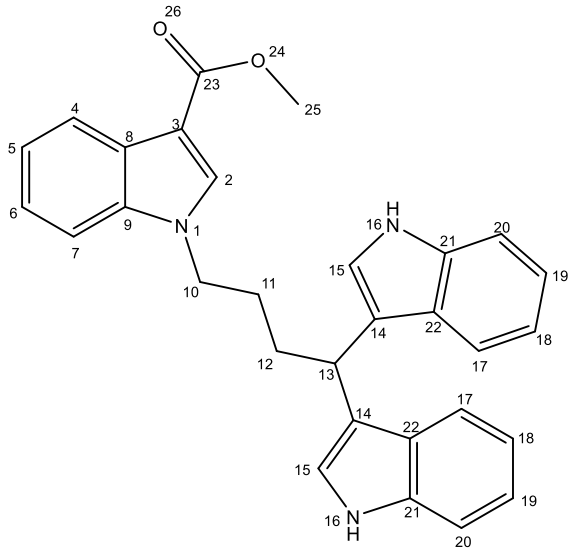
Compound 330l

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (m, 1H, H-***4***), 7.96 (s, 1H, H-***16***), 7.74 (s, 1H, H-***2***), 7.45 (m, 1H, H-***17***), 7.28 (m, 1H, H-***7***), 7.26 (d, *J* = 8.1 Hz, 1H, H-***20***), 7.20 – 7.17 (m, 2H, H-***5*** + H-***6***), 7.13 – 7.08 (m, 1H, H-***19***), 7.04 – 6.99 (m, 1H, H-***18***), 6.82 (d, *J* = 2.2 Hz, 1H, H-***15***), 5.86 (dtt, *J* = 15.3, 6.3, 1.2 Hz, 1H, H-***12***), 5.64 (dtt, *J* = 15.2, 6.1, 1.5 Hz, 1H, H-***11***), 4.61 (dd, *J* = 6.1, 1.0 Hz, 2H, H-***10***), 3.43 (dd, *J* = 6.4, Hz, 2H, H-***13***), 3.82 (s, 3H, H-***25***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6 (C-***23***), 136.6 (C-***9***), 136.4 (C-***21***), 134.3 (CH, C-***11***), 134.15 (CH, C-***2***), 127.2 (C-***8***), 126.8 (C-***22***), 124.5(CH, C-***12***), 122.7 (CH, C-***5*** or C-***6***), 122.1 (CH, C-***19***), 121.9 (CH, C-***5*** or C -***6***), 121.9 (CH, CHC, C-***15***), 121.7 (CH, C-***4***), 119.4 (CH, C-***18***), 118.9 (CH, C-***17***), 113.7 (C-***14***), 111.22 (CH, C-***20***), 110.3 (CH, C-***7***), 107.1 (C-***3***), 51.0 (CH_3, C-***25***) , 48.7 (N-CH_2 C-***10***), 28.2 (CH_2, C-***13***).

HRMS – (FTMS + p NSI) ((MeOH) / MeOH + NH_4OAc): Calc. for $C_{22}H_{21}N_2O_2$ $[M+H]^+$: 345.1598. Found: 345.1601.

* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.



Compound 331l

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 4.9, 3.8 Hz, 1H, H-***4***), 7.81 (s, 2H, H-***16***), 7.63 (s, 1H, H-***2***), 7.41 (d, *J* = 8.0 Hz, 2H, H-***17***), 7.19 (d, *J* = 8.1 Hz, 2H, H-***20***), 7.16 – 7.14 (m, 1H, H-***7***), 7.12 – 7.10 (m, 2H, H-***5*** + H-***6***), 7.07 – 7.03 (m, 2H, H-***19***), 6.94 – 6.90 (m, 2H, H-***18***), 6.69 (d, *J* = 2.2 Hz, 2H, H-***15***), 4.35 (t, *J* = 7.5 Hz, 1H, H-***13***), 3.97 (t, *J* = 7.1 Hz, 2H, H-***10***), 3.81 (s, 3H, H-***25***), 2.10 (m, 2H, H-***12***), 1.86 (m, 2H, H-***11***).

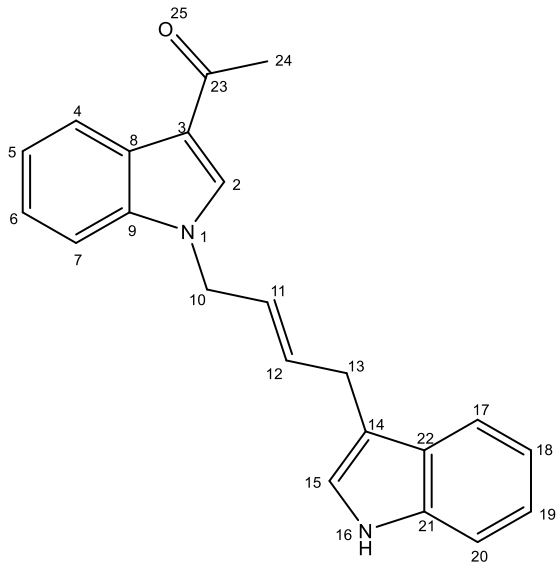
^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7 (C-***23***), 136.59 (C-***9***), 136.54 (C-***21***), 134.38 (CH, C-***2***), 126.87 (C-***8***), 126.71 (C-***22***), 122.67 (CH, C-***4***), 121.91 (CH, C-***19***), 121.84 (CH, C-***7***), 121.74 (CH, C-***5*** or C-***6***), 121.52(CH, C-***15***), 119.39 (CH, C-***17***), 119.18 (CH, C-***18***), 111.25 (CH, C-***20***), 110.15 (CH, C-***5*** or C-***6***), 106.76 (C-***3***), 51.02 (CH_3, C-***25***), 46.99 (CH_2, C-***10***), 33.72 (CH_2, C-***13***), 32.65 (CH_2, C-***12***), 28.38 (CH_2, C-***11***).

HRMS – (FTMS + p NSI) ((MeOH) / MeOH + NH_4OAc): Calc. for $C_{30}H_{27}N_3O_2Na$ $[M+Na]^+$: 484.1995. Found: 484.1989.

* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.

Reaction of 1-(2,3-butadien-1-yl)-3-ethanoate-1H-indole with indole

Synthesized from 1-(2,3-butadien-1-yl)-3-ethanoate-1H-indole (213.3 mg, 1.010 mmol), $PtCl_2$ (13 mg, 0.05 mmol), indole (335 mg, 3.03 mmol), methanol (0.123 mL, 3.03 mmol) and 4.75 mL of dry 1,4-dioxane. Compounds **330m** and **331m** obtained after ISCO column chromatography using a 12g silica gel Redisep column eluting with a gradient of i-hexane to 100% ethyl acetate using the instrument's default settings to yield 36.4 mg, 0.111 mmol, 11% as a brown oil and 103.4 mg, 0.232 mmol, 23% as a brown oil respectively.



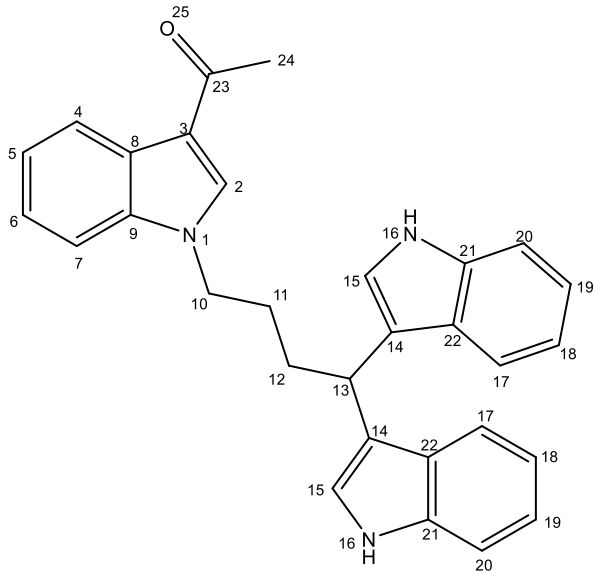
Compound 330m

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (m, 1H, H-***4***), 7.96 (s, 1H, H-***16***), 7.64 (s, 1H, H-***2***), 7.47 (m, 1H, H-***17***), 7.29 (m, 1H, H-***6*** + H-***7***), 7.23 – 7.19 (m, 2H, H-5+ H-***20***), 7.15 – 7.10 (m, 1H, H-***19***), 7.03 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1H, H-***18***), 6.87 (d, *J* = 2.2 Hz, 1H, H-***15***), 5.92 (dtt, *J* = 15.3, 6.3, 1.3 Hz, 1H, H-***12***), 5.69 (dtt, *J* = 15.3, 6.1, 1.5 Hz, 1H, H-***11***), 4.65 (dd, *J* = 6.1, Hz, 2H, H-***10***), 3.47 (d, *J* = 6.3, Hz, 2H, H-***13***), 2.41 (s, 3H, H-***24***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 193.15 (C-***23***), 136.89 (C-***9***), 136.45 (C-***21***), 134.70 (CH, C-***12***), 134.60 (CH, C-***2***), 127.22 (C-***8***), 126.47 (C-***22***), 124.32 (CH, C-***11***), 122.63 (CH, C-***5*** + C-***20***), 122.59 (CH, C-***4***), 122.20 (CH, C-***19***), 121.84 (CH, CH=C, C-***15***), 119.46 (CH, C-***18***), 118.89 (CH, C-***17***), 117.14 (C-***3***), 113.63 (C-***14***), 111.26 (CH, C-***6*** or C-***7***), 110.09 (CH, C-***6*** or C-***7***), 48.70 (N-CH_2, C-***10***), 28.22 (CH_2, C-***13***), 27.62 (CH_3, C-***24***).

HRMS – (FTMS + p NSI) ((MeOH) / MeOH + NH_4OAc): Calc. for $C_{30}H_{28}N_3O$ $[M+H]^+$: 446.2227. Found: 446.2226.

* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.



Compound 331m

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (m, 1H, H-***4***), 7.94 (s, 1H, H-***16***), 7.63 (s, 1H, H-***2***), 7.55 (d, *J* = 8.1 Hz, 2H, H-***17***), 7.37 (d, *J* = 8.1 Hz, 2H, H-***20***), 7.32 (dd, *J* = 5.9, 2.1 Hz, 1H, H-***7***), 7.28 – 7.25 (m, 2H, H-***5*** + H-***6***), 7.22 – 7.17 (m, 2H, H-***19***), 7.09 – 7.04 (m, 2H, H-***18***), 6.90 (d, *J* = 2.2 Hz, 2H, H-***15***), 4.53 (t, *J* = 7.5 Hz, 1H, H-***13***), 4.17 (t, *J* = 7.1 Hz, 2H, H-***10***), 2.49 (s, 3H, H-***24***), 2.30 (m, 2H, H-***12***), 2.12 - 2.04 (m, 2H, H-***11***).

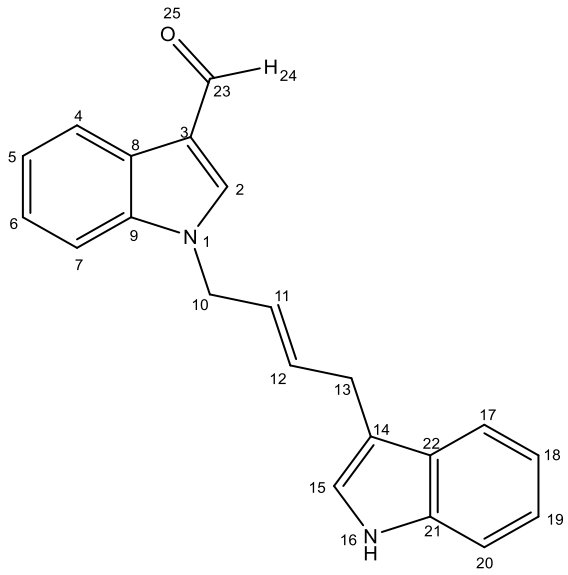
^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2 (C-***23***), 136.84 (C-***9***), 136.61 (C-***21***), 134.99 (CH, C-***2***), 126.85 (C-***8***), 126.37 (C-***22***), 122.61 (CH, C-***4***), 121.95 (CH, C-***19***), 121.54 (CH, C-***15***), 119.37 (CH, C-***17***), 119.20 (CH, C-***18***), 111.30 (CH, C-***20***), 109.98 (CH, C-***7***), 47.04 (N-CH_2, C-***10***), 33.78 (CH_2, C-***13***), 32.67 (CH_2, C-***12***), 28.41 (CH_2, C-***11***), 27.63 (CH_3, C-***24***).

HRMS – (FTMS + p NSI) ((MeOH) / MeOH + NH_4OAc): Calc. for $C_{22}H_{21}N_2O$ $[M+H]^+$: 329.1648. Found: 329.1652.

* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.

Reaction of 1-(2,3-butadien-1-yl)-3-formyl-1H-indole with indole

Synthesized from 1-(2,3-butadien-1-yl)-3-formyl-1H-indole (44.5 mg, 0.226 mmol), $PtCl_2$ (3.00 mg, 0.011 mmol), indole (79 mg, 0.677 mmol), methanol (0.027 mL, 0.677 mmol) and 1.1 mL of dry 1,4-dioxane. Compounds **330n** and **331n** obtained after ISCO column chromatography using a 12g silica gel Redisep columns eluting with a gradient of i-hexane to 40% ethyl acetate using the instrument's default settings to yield 3.6 mg, 0.011 mmol, 5% as a brown oil and 4.6 mg, 0.011 mmol, 5% as a brown oil respectively.



Compound 330n

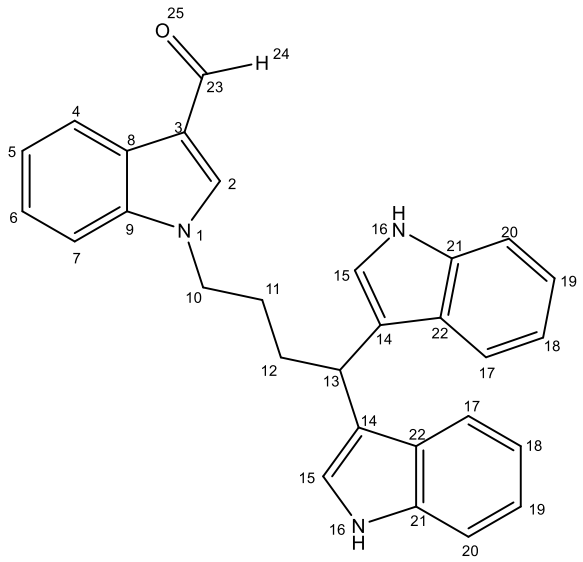
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.0 (s, 1H, H-***24***), 8.34 (dd, *J* = 5.9, 3.0 Hz, 1H, H-***4***), 8.04 (s, 1H, H-***16***), 7.74 (s, 1H, H-***2***), 7.58 (d, *J* = 7.9 Hz, 1H, H-***17***), 7.44 – 7.38 (m, 2H, H-***7*** + H-***20***), 7.35 (dd, *J* = 6.2, 3.0 Hz, 2H, H-***5*** + H-***6***), 7.24 (t, *J* = 7.5 Hz, 1H, H-***19***), 7.14 (t, *J* = 7.5 Hz, 1H, H-***18***), 6.99 (d, *J* = 1.5 Hz, 1H, H-***15***), 6.05 (dt, *J* = 13.8, 6.2 Hz, 1H, H-***11***), 5.80 (dt, *J* = 13.8, 6.2 Hz, 1H, H-***12***), 4.78 (d, *J* = 6.2 Hz, 2H, H-***10***), 3.59 (d, *J* = 6.2 Hz, 2H, H-***13***).

^{13}C NMR (126 MHz, $CDCl_3$) 184.59 (C-***23***), 140.19, 138.06 (CH, C-***2***), 135.11 (CH, C-***11***), 124 (CH, C-***5***/C-***6***), 123.95 (CH, C-***12***), 122.97 (CH, C-***5*** or C-***6***), 122.26 (CH, C-***4***), 121.82 (CH, C-***19***), 121.79 (CH, C-***15***), 119.48 (CH, C-***18***), 119.23 (C-***3***), 118.91 (CH, C-***17***), 111.25 (CH, C-***7*** or C-***20***), 110.32 (CH, C-***7*** or C-***20***), 48.87 (CH_2, N-CH_2 C-***10***), 28.22 (CH_2, C-***13***), 27.97.

Low intensity, therefore quaternary carbons not detected.

HRMS – (FTMS + p NSI) ((MeOH)/ MeOH + NH_4OAc): Calc. for $C_{21}H_{18}N_2ONa$ $[M+Na]^+$: 337.1311. Found: 337.1315.

* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.



Compound 331n

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1H, H-***24***), 8.33 (d, *J* = 6.9, 1.3 Hz, 1H, H-***4***), 7.94 (s, 2H, H-***16***), 7.58 (s, 1H, H-***2***), 7.55 (d, *J* = 7.9 Hz, 1H, H-***17***), 7.37 (d, *J* = 8.2 Hz, 1H, H-***20***), 7.35 – 7.30 (m, 2H, H-***5***+H-***6***), 7.27 (dd, *J* = 8.4, 6.9 Hz, 1H, H-***7***), 7.20 (ddd, *J* = 8.1, 7.0 Hz, 2H, H-***19***), 7.06 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 2H, H-***18***), 6.92 (d, *J* = 2.2 Hz, 2H, H-***15***), 4.54 (t, *J* = 7.5 Hz, 1H, H-***13***), 4.19 (t, *J* = 7.1 Hz, 2H, H-***10***), 2.31 (m, 2H, H-***12***), 2.09 (m, 2H, H-***11***).

^{13}C NMR (126 MHz, $CDCl_3$) 138.35 (CH, ***Ar***), 123.72 (CH, ***Ar***), 123.01 (CH, ***Ar***), 122.18 (CH, ***Ar***), 122.10 (CH, ***Ar***), 121.47 (CH, ***Ar***), 119.42 (CH, ***Ar***), 119.34 (CH, ***Ar***), 111.41 (CH, ***Ar***), 110.07 (CH, ***Ar***), 47.44 (CH_2, C-***10***), 33.94 (CH, C-***13***), 32.58 (CH_2, C-***12***), 28.50 (CH_2, C-***11***).

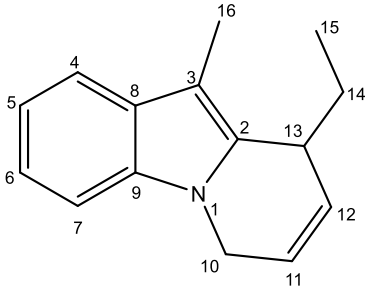
Low intensity, therefore quaternary carbons not detected.

HRMS – (FTMS + p NSI) ((MeOH)/ MeOH + NH_4OAc): Calc. for $C_{29}H_{26}N_3O$ $[M+H]^+$: 432.2070. Found: 432.2070.

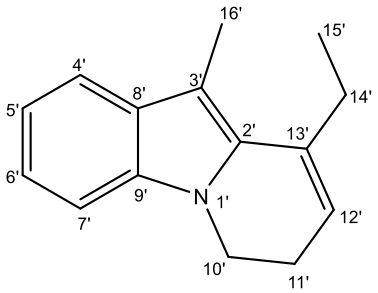
* Results obtained by Louise Eagling, with full characterisation completed by Lisa Cooper.

Reaction of 1-(hexa-4,5-dien-1-yl)-3-methyl-1H-indole with indole

Synthesized from 1-(hexa-4,5-dien-1-yl)-3-methyl-1H-indole (330 mg, 1.5 mmol), $PtCl_2$ (20 mg, 0.075 mmol), indole (550 mg, 4.7 mmol), dry methanol (190 µL, 4.7 mmol) and 10 mL of dry 1,4-dioxane. Compounds **333** and **333'** obtained after column chromatography, Hexan/EtOAc, 10:1, as an inseparable mixture 0.1:1 (**333:333'**), 165 mg, 0.78 mmol, 52% as a brown oil.



Compound 333



Compound 333'

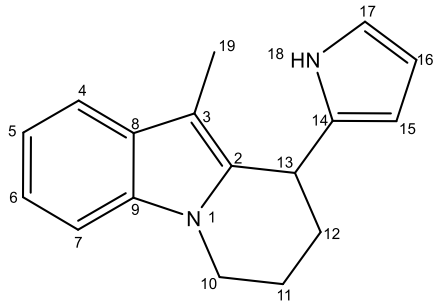
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.57 (dt, *J* = 7.8, 0.9, 1H, H-***4***), 7.29 – 7.18 (m, 2H, H-***5*** + H-***6***), 7.09 (ddd, *J* = 8.0, 6.6, 1.4, 1H, H-***7***), 5.77 (tt, *J* = 4.8, 1.4 Hz, 1H, H-***12'***), 4.04 (t, *J* = 7.0, 2H, H-***10'***), 2.67 (m, 2H, H-***11'***), 2.59 – 2.52 (m, 2H, H-***14'***), 2.51 (s, 3H, H-***16'***), 1.23 (t, *J* = 7.0, 3H, H-***15'***).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 136.04 (C), 135.50 (C), 131.83 (C), 129.56 (C), 122.02 (CH, C-***12'***), 119.29 (CH, ***Ar***), 118.77 (CH, ***Ar***), 118.71 (CH, ***Ar***), 108.44 (CH, ***Ar***, 106.71 (C), 39.92 (CH_2, C-***10'***), 26.79 (CH_2, C-***11'***), 24.45 (CH_2, C-***14'***), 13.87 (CH_3, C-***15'***), 10.35 (CH_3, C-***16'***).

HRMS – (FTMS + p APCI, ASAP) (MeOH) Calc. for $C_{15}H_{18}N$ $[M+H]^+$: 212.1434. Found: 212.1429.

Reaction of 1-(2, 3-butadien-1-yl)-3-methyl-1H-indole with pyrrole

Synthesized from 1-(2,3-butadien-1-yl)-3-methyl-1H-indole (100 mg, 0.55 mmol), $PtCl_2$ (7.2 mg, 0.0275 mmol), pyrrole (111 mg, 1.65 mmol), dry methanol (67 µL, 1.65 mmol) and 2.75 mL of dry 1,4-dioxane. Compound **334** obtained after column chromatography, Pet Ether/EtOAc, 20:1, 89.8 mg, 0.36 mmol, 65% as a brown oil.



Compound 334

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (bs, 1H, H-***18***), 7.59 (d, *J* = 7.8 Hz, 1H, H-***4***), 7.32 (d, *J* = 8.1 Hz, 1H, H-***7***), 7.24 (m, 1H, H-***6***), 7.18 (m, 1H, H-***5***), 6.58 (dd, *J* = 4.0, 2.6 Hz, 1H, H-***17***), 6.22 (dd, *J* = 5.8, 2.6 Hz, 1H, H-***16***), 6.04 (m, 1H, H-***15***), 4.55 (t, *J* = 4.5 Hz, 1H, H-***13***), 4.20 (dt, *J* = 11.2, 4.7 Hz, 1H, H-***10***), 3.91 (m, 1H, H-***10***), 2.26 (m, 1H, H-***12***), 2.18 (m, 1H, H-***12***), 2.14 (s, 3H, H-***19***), 2.08 (m, 1H, H-***11***), 2.00 (m, 1H, H-***11***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2 (C-***3***), 133.5 (C-***2***), 132.9 (C-***4***), 128.6 (C-***9***), 121.0 (CH, C-***6***), 119.3 (CH, C-***5***), 118.3 (CH, C-***4***), 116.0 (CH, CH=C, C-***17***), 108.9 (CH, C-***7***), 108.8 (CH, C-***16***), 104.7 (CH, CH=C, C-***15***), 42.5 (N-CH_2, C-***10***), 32.2 (CH, C-***13***), 29.5 (CH_2, C-***12***), 20.0 (CH_2, C-***11***), 8.25 (CH_3, C-***19***).

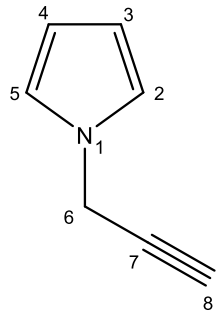
ν_{max}/cm^{-1}: 3407 (m, br, N-H), 2930 (s, C-H), 2860 (m, C-H), 1695, 1667, 1462, 1360 (m, C-N), 739.

HRMS: Calculated for $C_{17}H_{18}N_2$ $[M+H]^+$: 251.1545. Found: 251.1543.

Synthesis of substituted pyrroles

Synthesis of 1-(2-propyn-1-yl)-1H-pyrrole

NaH (300 mg, 7.5 mmol) was added to a vacuum dried 2 necked round bottomed flask under N_2 atmosphere and dissolved in 100 mL dry DMF (0.05 M). The flask was wrapped with foil and cooled to 0 ^{0}C , then freshly distilled pyrrole (387 µL, 5 mmol) was added and the reaction mixture stirred for 20 minutes. Propargyl bromide (80% in toluene, 1.4 mL, 10 mmol) was added and the mixture warmed to rt and stirred overnight. The reaction was quenched with methanol and water, then extracted with Et_2O. The organic layers were dried using $MgSO_4$, filtered and concentrated in vacuum. **Compound 335** obtained after column chromatography, Pet Ether/EtOAc, 20:1, 257.6 mg, 2.45 mmol, 49% as a brown oil.



Compound 335

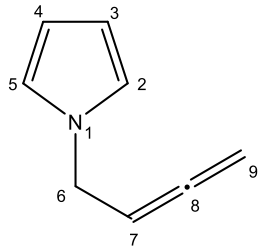
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (t, *J* = 2.1 Hz, 2H, H-***2+5***), 6.20 (t, *J* = 2.1 Hz, 2H, H-***3+4***), 4.69 (d, *J* = 2.6 Hz, 2H, H-***6***), 2.43 (t, *J* = 2.6 Hz, 1H, H-***8***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 120.46 (CH, C-***2+5***), 108.94 (CH, C-***3+4***), 78.10 (C-***7***), 73.62 (CH, C-***8***), 38.62 (CH_2, C-***6***).

Characterization consistent with reported data.[169]

Synthesis of 1-(2,3-butadien-1-yl)-1H-pyrrole

Paraformaldehyde (178 mg, 5.95 mmol) and CuBr (101 mg, 0.70 mmol) were added to a microwave vial, sealed and flushed with N_2. 1-(2-Propyn-1-yl)-1H-pyrrole (250 mg, 2.34 mmol) was dissolved in 11.7 mL of dry 1,4-dioxane (0.2 M) under N_2 and added to the microwave vial, followed by the dropwise addition of *i*Pr_2NH (656 µL, 4.68 mmol). The reaction was heated at 150 ^{O}C using microwave radiation for 10 minutes. The resulting reaction mixture was filtered through celite, washed with DCM and concentrated in vacuum. Compound **336** was obtained after column chromatography, Pet Ether, 135.9 mg, 1.14 mmol, 49% as an orange oil.



Compound 336

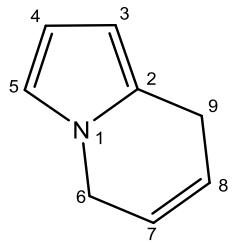
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (t, *J* = 2.1 Hz, 2H, H-***2+5***), 6.17 (t, *J* = 2.1 Hz, 2H, H-***3+4***), 5.33 (p, *J* = 6.8 Hz, 1H, H-***7***), 4.85 (dt, *J* = 6.8, 2.7 Hz, 2H, H-***6***), 4.49 (dt, *J* = 6.8, 2.7 Hz, 2H, H-***9***).

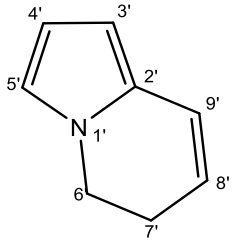
^{13}C NMR (126 MHz, $CDCl_3$) δ 208.99 (C, C-***8***), 120.45 (CH, C-***2+5***), 108.36 (CH, C-***3+4***), 88.14 (CH, C-***7***), 76.78 (CH_2, C-***9***), 48.40 (CH_2, C-***6***).

HRMS (GC/MS EI+): Calc. for C_8H_9N: 119.0735. Found: 119.0730.

Platinum catalysed 6-endo cyclisation of 1-(2,3-butadien-1-yl)-1H-pyrrole

Platinum (II) Chloride (5.6 mg, 0.021 mmol) and 1-(2,3-butadien-1-yl)-1H-pyrrole (50 mg, 0.42 mmol) were added to a microwave vial, capped and flushed with N_2 and dissolved in 3 mL 1,4-dioxane (0.14 M). Dry methanol (51 µL, 1.26 mmol) was added and the vial heated under microwave irradiation at 130 ^{0}C for 1 hour. The resulting reaction mixture was filtered through celite and washed with DCM. **Compounds 337** and **337'** were identified and characterized using the crude NMR as decomposition occurred during column chromatography.

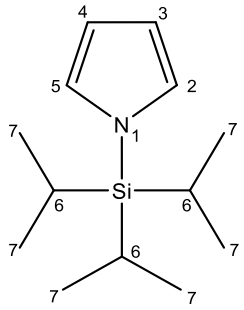




Compound 337 **Compound 337'**

Synthesis of N-triisopropylsilyl pyrrole

NaH (1311 mg, 33 mmol) was added to a vacuum dried 2 necked round bottomed flask under N_2, dissolved in 43 mL dry THF (0.7 M) and cooled to 0 ^{0}C. Freshly distilled pyrrole (2100 mg, 31.3 mmol) was added dropwise to the suspension and stirred at 0 ^{0}C for 15 minutes. After this time *i*Pr_3SiCl (6.4 mL, 29.8 mmol) was added drop wise and the reaction was stirred at rt for 2 hours. The reaction mixture was quenched with methanol and water at 0 ^{0}C and extracted with Et_2O. The organic layers were dried using $MgSO_4$, filtered and concentrated in vacuum. **Compound 338** was obtained, 6874.2 mg, 30.8 mmol, 98% as a colorless oil and used without any further purification.



Compound 338

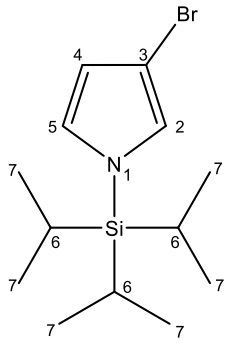
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 – 6.79 (m, 2H, H-***2+5***), 6.34 – 6.31 (m, 2H, H-***3+4***), 1.51 – 1.41 (heptet, *J* = 7.5 Hz, 3H, H-***6***), 1.10 (d, *J* = 7.5 Hz, 18H, H-***7***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 124.1 (CH, C-***2+5***), 110.1 (CH, C-***3+4***), 17.9 (CH_3, C-***7***), 11.8 (CH, C-***6***).

Characterization consistent with reported data.[170]

Synthesis of 3-bromo-1-(triisopropylsilyl)-1H-indole

Freshly recrystallized NBS (1.3 eqs) was added to a 2 neck round-bottom flask wrapped in foil and under N_2 atmosphere. 124 mL of dry THF (0.45 M) was added, the mixture was cooled down to -78 ^{0}C and N-triisopropylsilyl pyrrole (1250 mg, 56 mmol) was added. The reaction was stirred at -78 ^{0}C for 8 hours and then quenched with water to form a precipitate. The reaction mixture was extracted with Et_2O, the organic layers were dried using $MgSO_4$, filtered and concentrated in vacuum. **Compound 339** was obtained after column chromatography using Pet Ether/EtOAc, 10:1, 9855.8 mg, 32.5 mmol, 58% as a brown oil.



Compound 339

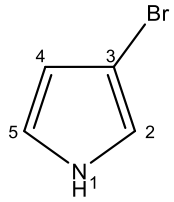
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 – 6.61 (m, 1H, H-***2***), 6.57 (t, *J* = 2.7 Hz, 1H, H-***5***), 6.19 (dd, *J* = 2.7, 1.3 Hz, 1H, H-***4***), 1.32 (heptet, *J* = 7.5 Hz, 3H, H-***6***), 0.99 (d, *J* = 7.5 Hz, 18H, H-***7***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 124.7 (CH, C-***5***), 123.7(C-***3***), 123.3 (CH, C-***2***), 113.1 (CH, C-***4***), 17.7 (CH_3, C-***7***), 11.6 (CH, C-***6***).

Characterization consistent with reported data.[170]

Synthesis of 3-bromo-1H-pyrrole

TBAF (2590 mg, 9.9 mmol) was added to a round-bottomed flask under N_2 atmosphere, dissolved in 9.9 mL dry THF (1 M) and cooled to 0 ^{0}C . 3-Bromo-1-(triisopropylsilyl)-1H-pyrrole (3000 mg, 9.9 mmol) was dissolved in THF and added to the solution of TBAF. The reaction was warmed to rt and stirred for 5 minutes. The reaction was quenched with saturated $NaHCO_3$ solution at 0 ^{0}C and extracted with Et_2O. The organic layers were dried with $MgSO_4$, filtered and concentrated in vacuum. Compound **340** was obtained after column chromatography using Pet Ether/EtOAc, 10:1, 1350 mg, 9.31 mmol, 94% as a colorless oil.



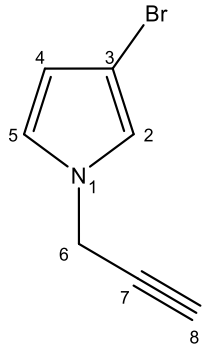
Compound 340

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H, H-***1***), 6.82 (m, 1H, H-***2***), 6.74 (m, 1H, H-***5***), 6.27 (m, 1H, H-***4***).

No Carbon obtained, proton NMR obtained before compound decomposed. (Also, the product from this reaction was used immediately in the propargylation reaction)

Synthesis of 3-bromo-1-(2-propyn-1-yl)-1H-pyrrole

NaH (353 mg, 8.8 mmol) was added to a vacuum dried 2 necked round bottomed flask under N_2 atmosphere and dissolved in 28 mL dry THF (0.2 M). The flask was wrapped with foil and cooled to 0 ^{0}C , then 3-bromo-1H-pyrrole (800 mg, 5.5 mmol) was added and stirred for 20 minutes. Propargyl bromide (80% in toluene, 1.14 mL, 8.3 mmol) was added, warmed to rt and stirred for 2 hours. The reaction was quenched with methanol and water then extracted with Et_2O. The organic layers were dried using $MgSO_4$, filtered and concentrated in vacuum. **Compound 341** was obtained after column chromatography, Pet Ether/EtOAc, 20:1, 320.2 mg, 1.7 mmol, 34% as a brown oil.



Compound 341

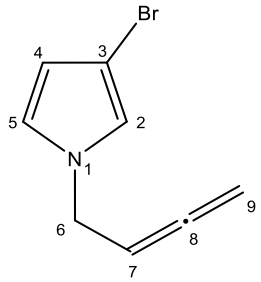
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 – 6.68 (m, 1H, H-***2***), 6.60 (t, *J* = 2.8 Hz, 1H, H-***5***), 6.10 (dd, *J* = 2.8, 1.7 Hz, 1H, H-***4***), 4.55 (d, *J* = 2.6 Hz, 2H, H-***6***), 2.39 (t, *J* = 2.6 Hz, 1H, H-***8***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 121.08 (CH, C-***5***), 120.05 (CH, C-***2***), 111.63 (CH, C-***4***), 96.1 (C-***7***), 74.38 (CH, C-***8***), 39.10 (CH_2, C-***6***).

IR and MS not obtained due to decomposition.

Synthesis of 3-bromo-1-(2,3-butadien-1-yl)-1H-pyrrole

Paraformaldehyde (82 mg, 2.72 mmol) and CuBr (47 mg, 0.33 mmol) were added to a microwave vial, sealed and flushed with N_2. 3-Bromo-1-(2-propyn-1-yl)-1H-pyrrole (200 mg, 1.09 mmol) was dissolved in 5.5 mL of dry 1,4-dioxane (0.2 M) under N_2 and added to the microwave vial, followed by the dropwise addition of *i*Pr_2NH (305 µL, 2.17 mmol). The reaction was heated at 150 ^0C using microwave irradiation for 10 minutes. Compound **342** was obtained after column chromatography, Pet Ether, 152.6 mg, 0.77 mmol, 71% as an orange oil.



Compound 342

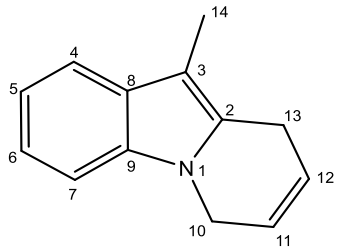
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (t, *J* = 1.9 Hz, 1H, H-***2***), 6.51 (t, *J* = 2.6 Hz, 1H, H-***5***), 6.08 – 6.05 (m, 1H, H-***4***), 5.21 (p, *J* = 6.4 Hz, 1H, H-***7***), 4.80 (td, *J* = 6.4, 2.6 Hz, 2H, H-***9***), 4.35 (dt, *J* = 6.4, 2.6 Hz, 2H, H-***6***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.15 (C, C-***8***), 121.09 (CH, C-***5***), 120.06 (CH, C-***2***), 111.03 (CH, C-***4***), 95.48 (C-***3***), 87.58 (CH, C-***7***), 77.11 (CH_2, C-***9***), 48.90 (CH_2, C-***6***).

IR and MS not obtained due to decomposition.

Gold catalysed 6-endo cyclisation of indolyl allene[5]

[Bis(trifluromethanesulfonyl)imidate](triphenylphosphine)gold(I) (22 mg, 0.0275 mmol) and 1-(2, 3-butadien-1-yl)-3-methyl-1H-indole (100 mg, 0.55 mmol) were added to a microwave vial, capped and flushed with N_2. The solids were dissolved in 14 mL toluene (0.04 M) and stirred at rt for 1 hour. The resulting reaction mixture was filtered through celite and washed with DCM. **Compound 218a** was isolated after concentration in vacuum, 98 mg, 0.54 mmol, 98% as a brown oil.



Compound 218a

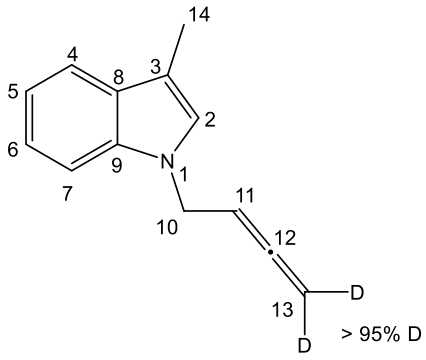
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H, H-***7***), 7.21– 7.19 (m, 1H, H-***4***), 7.12 – 7.02 (m, 2H, H-***5*** + H-***6***), 6.05 – 5.94 (m, 2H, H-***11*** + H-***12***), 4.57 – 4.52 (m, 2H, H-10), 3.48 – 3.42 (m, 2H, H-***13***), 2.19 (s, 3H, H-***14***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 122.08 (C-***12***), 120.52 (C-***11***), 120.24 (C-***Ar***), 119.14 (C-***Ar***), 117.74 (C-***Ar***), 108.48 (C-***Ar***), 41.82 (C-***10***), 22.81 (C-***13***), 8.28 (C-***14***).

Spectra consistent with previously published data.[5]

Procedure for synthesis of deuterated indolyl allene

Deuterated paraformaldehyde (98% D, 280 mg, 8.75 mmol), CuBr (150 mg, 1.05 mmol) and 3-methyl-1-(2-propyn-1-yl)-1H-indole (592 mg, 3.5 mmol) were added to a microwave vial, sealed and flushed with N_2. *i*Pr_2NH (2 eqs) was added drop wise and the reaction was heated at 150 ^{0}C using microwave irradiation for 10 minutes. The reaction was filtered through celite, washed with DCM and concentrated in vacuum. Compound ***d_2*-217** was obtained after column chromatography, Pet Ether/EtOAc, 20:1, 462.4 mg, 2.5 mmol, 71% as a yellow oil with >99% D incorporation.



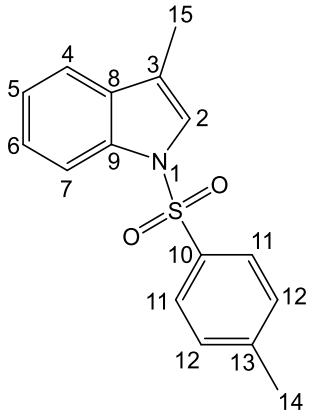
Compound *d*$_2$-217

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 1H, H-***4***), 7.32 (d, *J* = 8.2 Hz, 1H, H-***7***), 7.21 (t, *J* = 7.6 Hz, 1H, H-***6***), 7.11 (t, *J* = 7.4 Hz, 1H, H-***5***), 6.90 (s, 1H, H-***2***), 5.29 (t, *J* = 6.8 Hz, 1H, H-***11***), 4.68 (d, *J* = 6.8 Hz, 2H, H-***10***), 2.24 (s, 3H, H-***14***).

Synthesis of 1-(2,3-butadien-1-yl)-3-methyl-2-deuterio-1H-indole from 3-methyl-1H-indole[155]

Procedure for synthesis of 3-methyl-1-tosyl-1H-indole

NaOH (267 mg, 6.7 mmol) was dissolved in DCM (15 mL, 0.25 M) under N_2 atmosphere, 3-methylindole (500 mg, 3.82 mmol) was added and the reaction mixture was stirred for 30 minutes. A solution of p-toluenesulfonylchloride (798 mg, 4.2 mmol) was added and the reaction was stirred for 18 hours at rt. The reaction was stopped and filtered, the filtrate was concentrated in vacuum. **Compound 355** was obtained after column chromatography, Pet Ether/EtOAc (20:1), 811.7 mg, 2.8 mmol, 75% as a white solid.



Compound 355

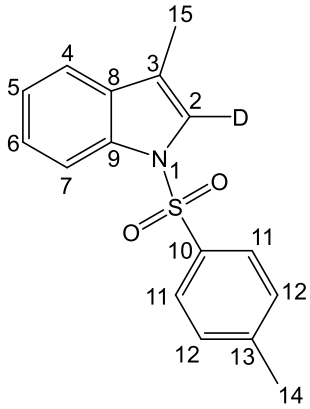
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 1H, H-***4***), 7.74 (d, *J* = 8.2 Hz, 2H, H-***11***), 7.45 (m, 1H, H-***7***), 7.33 – 7.28 (m, 2H, H-***2*** + H-***6***), 7.26 – 7.21 (m, 1H, H-***5***), 7.19 (d, *J* = 8.2 Hz, 2H, H-***12***), 2.33 (s, 3H, H-***14***), 2.24 (d, *J* = 1.2 Hz, 3H, H-***15***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 129.8 (CH, C-***11***), 126.7 (CH, C-***12***), 124.5-123.0 (CH=C and CH-Ar, C-***2*** and C-***5***), 122.9 (CH, C-***6***), 119.3 (CH, C-***4***), 113.6 (CH, C-***7***), 21.4 (CH_3, C-***14***), 9.5 (CH_3, C-***15***).

Low intensity, therefore quaternary carbons not detected. Spectra consistent with previously published data.[156]

Procedure for synthesis of 3-methyl-2-deuterio-1-tosyl-1H-indole

3-Methyl-1-tosyl-1H-indole (811.7 mg, 2.8 mmol) was dissolved in 11.4 mL of dry THF under N_2 and cooled to -78 ^{0}C. *n*-BuLi (2.25 ml, 5.64 mmol) was added drop wise to the solution and the reaction mixture was stirred at rt for 2 hours. The reaction was re-cooled to -78 ^{0}C, quenched with D_2O and warmed to rt. Et_2O followed by anhydrous K_2CO_3 were added. The solid precipitate was filtered off and the filtrate evaporated under pressure. **Compound 356** was obtained 634.9 mg, 2.2 mmol, 78% as a yellow solid with ~90% D incorporation.



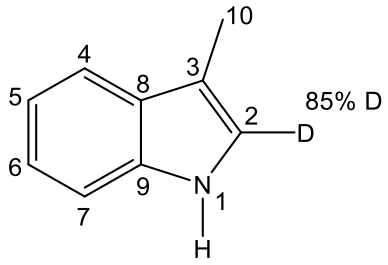
Compound 55

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 1H, H-***4***), 7.74 (d, *J* = 8.6 Hz, 1H, H-***11***), 7.45 (d, *J* = 7.7 Hz, 1H, H-***7***), 7.33 – 7.28 (m, 1H, H-***6***), 7.25 – 7.21 (m, 2H, H-***11***), 7.21 – 7.18 (m, 2H, H-***12***), 6.97 (s, 0.1H, ***d-2***), 2.33 (s, *J* = 6.3 Hz, 3H, H-***14***), 2.24 (s, 3H, H-***15***).

Only ^{1}H NMR obtained due to deprotection being carried out immediately.

Procedure for synthesis of 3-methyl-2-deuterio-1H-indole

Phenylsulphonyl-[2-^{2}H]-3-methylindole (634.9 mg, 2.2 mmol) was added to a round bottomed flask. Methanol (8.5 mL) was added followed by 2M NaOH (2.3 mL) solution and the mixture was heated at reflux under nitrogen. The reaction did not go to completion, but deprotection was observed by NMR to be around 50%. The reaction mixture was cooled down, poured into water (10 mL) and extracted with Et_2O. The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuum, **compound 313a** was obtained, 96.9 mg, 0.7 mmol, 45% as a pale yellow solid with 85% deuterium incorporation. This compound was used in the next step without further purification.



Compound 313a

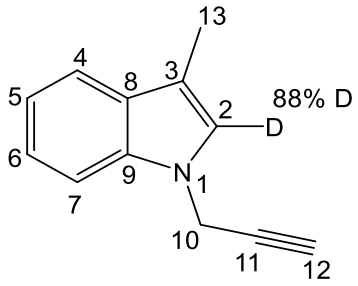
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H, H-***1***), 7.62 (dd, *J* = 7.9, 0.6 Hz, 1H, H-***4***), 7.39 (d, *J* = 8.1 Hz, 1H, H-***7***), 7.23 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H, H-***6***), 7.16 (td, *J* = 7.6, 1.0 Hz, 1H, H-***5***), 7.01 (d, *J* = 1.0 Hz, 0.15H, H-***2,*** H^2), 2.38 (s, 3H, H-***10***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 121.88 (CH, C-***6***), 119.12 (CH, C-***5***), 118.84 (CH, C-***4***), 110.93 (CH, C-***7***), 9.66 (CH_3, C-***10***).

Low intensity, therefore quaternary carbons not detected.

Procedure for synthesis of 3-methyl-2-deuterio-1-(2-propyn-1-yl)-1H-indole

Sodium hydride (41 mg, 1.03 mmol) added to round bottomed flask under N_2 and dissolved in 11 mL THF. The reaction was cooled to 0 ^{0}C and a solution of 2-deuterio-3-methyl-1H-indole (271.4 mg 0.65 mmol) in THF was added and stirred for 30 minutes at 0 ^{0}C. Propargyl bromide (145 mg, 0.98 mmol) was slowly added and the reaction warmed to rt, after 2 hours the reaction was quenched with $NaHCO_3$ and worked up with Et_2O and water. Compound obtained after column chromatography, Hex:EtOAc, 20:1 to give 53 mg, 0.3 mmol, 48% as a yellow oil with 88% deuterium incorporation at position 2.



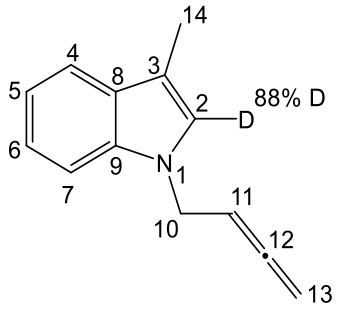
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60-7.57 (m, 1H, H-***4***), 7.36 (d, *J* = 8.2 Hz, 1H, H-***7***), 7.25 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, H-***6***), 7.13 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H, H-***5***), 6.98 (d, *J* = 1.0 Hz, 0.12 H, H-***2***, H^2), 4.83 (d, *J* = 2.5 Hz, 2H, H-***10***), 2.37 (t, *J* = 2.5 Hz, 1H, H-***12***), 2.34 (s, 3H, H-***13***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 121.82 (CH, C-***5***), 119.19 (CH, C-***6*** and C-***7***), 109.12 (CH, C-***4***), 73.10 (CH, C-***12***), 35.46 (CH_2, C-***10***), 9.55 (CH_3, C-***13***).

Low intensity, therefore quaternary carbons not detected.

Procedure for synthesis of 3-methyl-2-deuterio-1-(2,3-butadien-1-yl)-1H-indole

Paraformaldehyde (33 mg, 1.09 mmol), CuBr (19 mg, 0.132 mmol) and 3-methyl-1-(2-propyn-1-yl)-1H-indole (74 mg, 0.44 mmol) were added to a microwave vial, sealed, flushed with N_2 and dissolved in 2.2 mL dioxane. *i*Pr_2NH (123 µl, 0.88 mmol) was added drop wise and the reaction was heated at 150 ^{0}C using microwave irradiation for 10 minutes. The reaction was filtered through celite, washed with DCM and concentrated in vacuum. **Compound *d*-217** was obtained after column chromatography using Pet Ether/EtOAc, 70:1, 55.1 mg, 0.3 mmol, 68% as a yellow oil with 88% deuterium incorporation.



Compound *d*-217

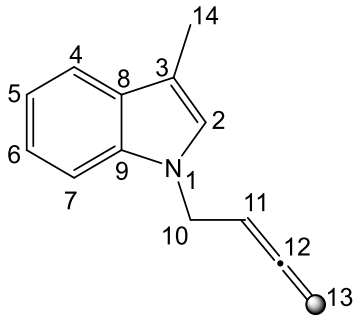
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 1H, H-***4***), 7.33 (d, *J* = 8.2 Hz, 1H, H-***7***), 7.21 (t, *J* = 7.6 Hz, 1H, H-***6***), 7.12 (t, *J* = 7.4 Hz, 1H, H-***5***), 6.90 (s, 0.12H, H-***2***), 5.33 – 5.27 (m, 1H, H-***11***), 4.85 (dt, *J* = 6.6, 2.6 Hz, 2H, H-***10***), 4.68 (dt, *J* = 6.6, 2.6 Hz, 2H, H-***13***), 2.33 (d, *J* = 2.2 Hz, 3H, H-***14***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 121.47 (CH, C-***6***), 119.04 (CH, C-***5***), 118.74 (CH, C-***4***), 109.43(CH, C-***7***), 87.59 (CH, CH=C=C, C-***11***), 67.11 (CH_2, CH_2=C=C, C-***13***), 45.14 (N-CH_2, C-***10***), 9.57 (CH_3, C-***14***).

Low intensity, therefore quaternary carbons not detected.

Procedure for synthesis of ^{13}C-labelled 3-methyl-1-(2,3-butadien-1-yl)-1H-indole

^{13}C Paraformaldehyde (99% atom) (229 mg, 7.38 mmol), CuBr (127 mg, 0.885 mmol) and 3-methyl-1-(2-propyn-1-yl)-1H-indole (500 mg, 2.95 mmol) were added to a microwave vial, sealed, flushed with N_2 and dissolved in 14.75 mL dioxane. *i*Pr_2NH (827 µl, 5.9 mmol) was added drop wise and the reaction was heated at 150 ^{0}C using microwave irradiation for 10 minutes. The reaction was filtered through celite, washed with DCM and concentrated in vacuum. **Compound ^{13}C-217** was obtained after column chromatography using Pet Ether/EtOAc, 30:1, 428.7 mg, 2.32 mmol, 79% as a yellow oil.



Compound ^{13}C-217

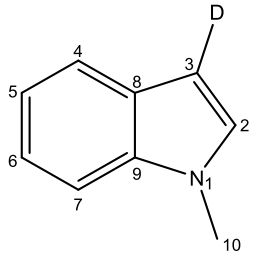
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dt, *J* = 7.9, 1.0 Hz, 1H, H-***4***), 7.34 (dt, *J* = 8.2, 0.9, Hz, 1H, H-***7***), 7.23 (ddd, *J* = 8.2, 7.0, 1.2Hz, 1H, H-***5***), 7.13 (ddd, *J* = 7.9, 7.0, 1.0 Hz, H-***6***), 6.91 (d, *J* = 1.0 Hz, 1H, H-***2***), 5.39 – 5.18 (m, 1H, H-***11***), 4.87 (ddt, $J_{C\text{-}H}$ = 168.73 Hz, $J_{H\text{-}H}$ = 6.6, 2.7 Hz, 2H, H-***13***), 4.70 – 4.68 (m, 2H, H-***10***), 2.35 (d, *J* = 1.0 Hz, 3H, H-***14***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 76.92 ($^{13}CH_2$, C-***13***).

Procedure for synthesis of 1-methyl-(3-2H)-1H-indole

All glassware for this experiment was prewashed with deuterium oxide and dried to minimize proton exchange during the reaction.

To a pre-washed round bottomed flask was added 1-methylindole (1220 mg, 9.3 mmol), 2.5 mL D_2O was added, the reaction mixture was heated to 80 ^{0}C and left for 18 hours. The reaction mixture was worked up with DCM and D_2O. Product obtained after concentrating in vacuum, to yield 1093 mg, 8.27 mmol, 89% of compound 60 with 90% D incorporation.



Compound 60

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.67 (m, 1H, H-***4***), 7.38 (d, *J* = 8.2 Hz, 1H, H-***7***), 7.30 – 7.26 (m, 1H, H-***5***), 7.17 (m, 1H, H-***6***), 7.10 (s, 1H, H-***2***), 6.55 (d, *J* = 3.1 Hz, 0.1H, H^2-***3***), 3.85 (s, 3H, H-***10***).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.7 (C-***9***), 128.8 (C-***8***), 128.5 (CH, C-***2***), 121.5 (CH, C-***5***), 120.9 (CH, C-***4***), 119.3 (CH, C-***6***), 109.2 (CH, C-***7***), 32.8 (CH_3, C-***10***).

Spectra consistent with previously published data.[171]

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