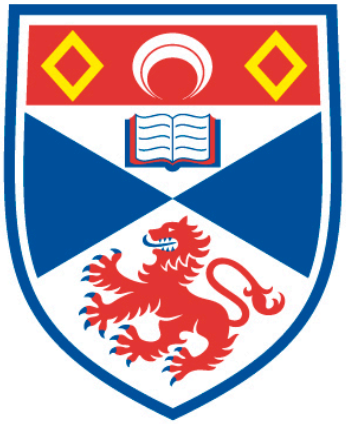
DEVELOPMENT OF CASCADE CROSS-COUPLING / DIELS–ALDER APPROACHES FOR COMPLEX MOLECULE SYNTHESIS

David Cain

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



2021

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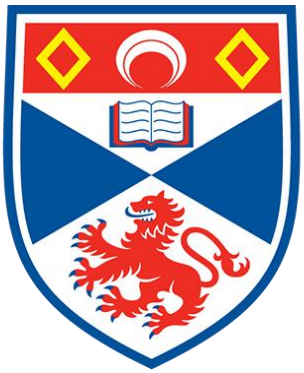

University of St Andrews

This thesis is submitted in partial fulfilment for the degree of

Doctor of Philosophy (PhD)

at the University of St Andrews

November 2020

“That is the essence of science: ask an impertinent question, and you are on your way to a pertinent answer” – Jabob Bronowski.

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Publication List

1. *"A cascade Suzuki-Miyaura/Diels-Alder protocol: exploring the bifunctional utility of vinyl Bpin:"* D. L. Cain, C. McLaughlin, J. J. Molloy, C. Carpenter-Warren, N. A. Anderson and A. J. B. Watson, *Synlett*, 2019, **30**, 787–791, doi.org/10.1055/s-0037-1611228.

Acknowledgements

All of those mentioned below have played an important role in my Ph.D and my life. I have decided to start with the academic thanks and move on to the more personal.

Dr. Allan Watson, my supervisor, I thank for giving me the opportunity to work within the Watson research group. His continued support and advice has been invaluable in improving my understanding of organic chemistry and developing me as a person. The research undertaken during my Ph.D has been both stimulating and challenging, and this has improved my confidence as a chemist.

Within our group (and now I include past and present members) I would like to thank the following;

Drs Matthew West and Eilidh Sood and John Molloy: Matthew for never-ending patience in answering questions, banter (mostly from his side), expanding my knowledge of music; Eilidh for hearing me out, sharing intriguing views on food, keeping me level headed and John, for his unique sense of humour, letting me see the iconic "Green Brigade." I also thank Callum McLaughlin for his part in the first part of my research project.

Matthew Ashford and George Bell: intimidating giants, whose hearts were always in the right place, with whom I discussed much and who kept me on my A-game.

Eva Israel and Jeremy Brals, merci beaucoup for their companionship, helping me to understand the "Things French", and for praising my DJ skills.

Post-docs Dr. Chao Xu, Dr. Jamie Fyfe and Dr. Liam McLean and also previous members of the Watson research group, for their valuable feedback during project updates, proof reading and general chemistry discussions.

I would also like to thank my industrial supervisor Dr. Niall Anderson, for his valuable feedback during our updates, and for his help in organising a potential placement at GSK that wasn't to be (thank COVID-19).

In the extended team of St Andrews, I would thank Professor Alexandra Slawin, Dr. David Cordes and Cameron Carpenter-Warren for their help in providing excellent crystallography data and Dr. Tomas Lebl and Dr. Siobhan Smith for their support with any NMR problems.

Now to the personal: I would like to give a big thanks to my parents Dr. Clive Cain and Karen Cain, for their continued support and advice during both the good and bad times, and for their limitless belief in me.

A big thank you to Dr. Stephanie Linnell as well, who as a house-mate and friend has helped keep me cheerful and in good spirits whilst living together. Her uncanny way of finding the right words at the right times never ceased /ceases to amaze me.

Last and certainly not the least, I would like to thank Heather Hayes. There are so many things that can be said, but most importantly, from the bottom of my heart I want to thank you for being there for me. It has definitely not been easy at times, with a rollercoaster-ride being an accurate description of our lives. It is safe to say you have been my rock. Your numerous bakes and exceptional cooking have helped keep me energised during these last 4 years.

Funding

This work was supported by Engineering and Physical Sciences Research Council [grant number EP/N509371/1], GlaxoSmithKlein and the University of St Andrews.

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Abstract

The Diels–Alder (DA) reaction is an important and frequently used synthetic transformation in the formation of both complex building blocks and natural products. Significant attention has being invested in its utilisation within cascade events, primarily due to its ability to form six-membered rings with numerous contiguous stereocenters in a selective manner. Its combination with cross-coupling reactions has become an evolving field in accessing novel chemical space, by circumventing the need for handling potentially reactive diene intermediates. This thesis will begin with a discussion surrounding the multiple terminologies defining multi-step reactions, and provide examples focussing in the area involving cross-coupling/Diels–Alder reactions (CCDA).

The first chapter highlights the development of a cascade Suzuki–Miyaura/Diels–Alder (SM/DA) protocol, involving vinyl Bpin, a bi-functional entity (as nucleophile in the SM, and the dienophile in DA), in facilitating the overall transformation. A discussion involving its optimization is disclosed, alongside the challenges that were encountered and how these were overcome. The optimised conditions were applied to generate a range of borylated carbocylic products of varying complexity (17 examples). In this work the effect of the organoboron subtype on Diels-Alder regioselectivity was investigated and post-synthetic modifications were carried out on a model substrate. Lastly, the potential for a complementary Heck/Diels-Alder process was also assessed.

Having developed the SM/DA methodology, its application was envisaged as a key step in the divergent synthesis of *Aspidosperma* alkaloids in the second chapter. Despite these alkaloids being synthesized numerous times, due to their challenging structural topology and beneficial biological properties, there is a lack in Structure activity relationship (SAR) studies. The SM/DA protocol allows the rapid and efficient creation of an advanced skeletal framework in a single reaction, which can then be subjected to a series of simple chemical manipulations to furnish a common intermediate from which a natural product library can be generated. The optimization of pertinent steps in the synthesis are disclosed, along with interesting observations that were encountered.

List of Abbreviations

µL	-	Microlitre
9-BBN	-	9-Borabicylco[3.3.1]nonane
Å	-	Angstrom
AcOH	-	Acetic acid
$AlCl_3$	-	Alumminium trichloride
Bpin	-	Boronic acid, pinacalato ester
BnBr	-	Benzyl bromide
Br_2	-	Bromine
CCDA	-	cross-coupling/Diels–Alder
$CHCl_3$	-	Chloroform
CH_2Cl_2	-	Dichloromethane
DACC	-	Diels–Alder/cross-coupling
DA	-	Diels–Alder
DCM	-	Dichloromethane
d.e.	-	Diastereomeric excess
DEM	-	Diethoxymethane
DMAP	-	4-Dimethylaminopyridine
DMF	-	*N*, *N*-Dimethyl formamide
DMSO	-	Dimethyl sulfoxide
Dppe	-	1,2-Bis(diphenylphosphino)ethane
d.r.	-	Diastereomeric ratio
EAS	-	Electrophilic aromatic substitution
EDG	-	Electron Donating Group
e.e.	-	Enantiomeric excess
EPSRC	-	Engineering and Physical Sciences Research Council

Equiv	-	Equivalent
EWG	-	Electron Withdrawing Group
Et_2O	-	Diethyl ether
Et_3N	-	Triethylamine
EtOH	-	Ethanol
FMO	-	Frontier Molecular Orbital
FTIR	-	Fourier Transform Infrared Specstroscopy
h	-	Hours
H_2O_2	-	Hydrogen peroxide
HDA	-	Hetero-Diels-Alder
HOMO	-	Highest Occupied Molecular Orbital
HRMS	-	High Resolution Mass Spectrometry
Hz	-	Hertz
IEDDA	-	Inverse electron-demand Diels–Alder
IMDA	-	Intramolecular Diels-Alder
IMHDA	-	Intramolecular Hetero-Diels-Alder
IR	-	Infrared
K_2CO_3	-	Potassium carbonate
K_3PO_4	-	Potassium phosphate
LA	-	Lewis Acid
LDA	-	Lithium Diisopropylamide
LUMO	-	Lowest Unoccupied Molecular Orbital
M	-	Molar
MeCN	-	Acetonitrile
mg	-	Milligrammes
MHz	-	Megahertz

MIDA - *N*-Methyliminodiacetic acid

min - Minutes

mL - Millilitres

MS - Molecular sieves

MSR - Multi-step reactions

MW - Microwave

NaH - Sodium hydride

NaOH - Sodium hydroxide

NBS - N-bromosuccinimide

NMR - Nuclear Magnetic Resonance

$Pd_2(dba)_3$ - Tris(dibenzylideneacetone)dipalladium(0)

$Pd(OAc)_2$ - Palladium (II) acetate

$Pd(OH)_2$ - Pearlman's catalyst

PG - Protecting Group

$PGF_{2\alpha}$ - Prostagladin $F_{2\alpha}$

PhMe - Toluene

Pin - Pinacol

PK - Pausan-Khand

PMB - Para-methoxybenzyl

ppm - Parts per million

PPh_3 - Triphenylphosphine

r.r. - Regiomeric ratio

r.t. - Room temperature

SAR - Structure activity relationship

SM - Suzuki–Miyaura

SM/DA - Suzuki–Miyaura / Diels–Alder

SOO - Secondary orbital overlap

SPhos - Dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphane

STAB - Sodium triacetoxyborohydride

TBSCl - *Tert*-Butyldimethylsilyl chloride

TBAHS - Tetrabutylammonium Hydrogen Sulfate

TFA - Trifluoroacetic acid

THF - Tetrahydrofuran

TLC - Thin Layer Chromatography

TS - Transition state

TsOH - Tosic acid

UV - Ultraviolet

WK - Wolf-Kishner

Wt. - Weight

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1. Chapter 1: Introduction

1.1. Multi-step reactions

Traditional chemical synthesis of organic molecules typically adopts a singular step-wise transformation approach. However, this method has obvious flaws given that for every chemical transformation performed a certain amount of waste is potentially produced, as well as increased labour demands and purification steps required etc. Therefore, there is a significant drive to develop more streamlined synthetic methods or overall approaches.

Multi-step reaction (MSR) events offer such a possibility. These are described as processes where at least two chemical transformations are performed on a particular molecule or molecules in the same reaction vessel (Figure 1).

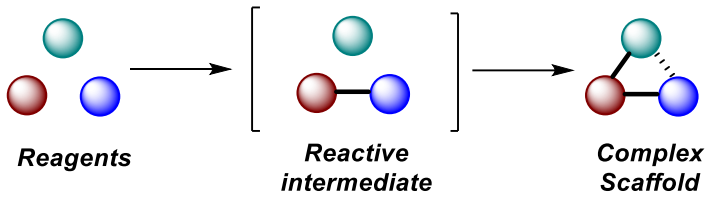
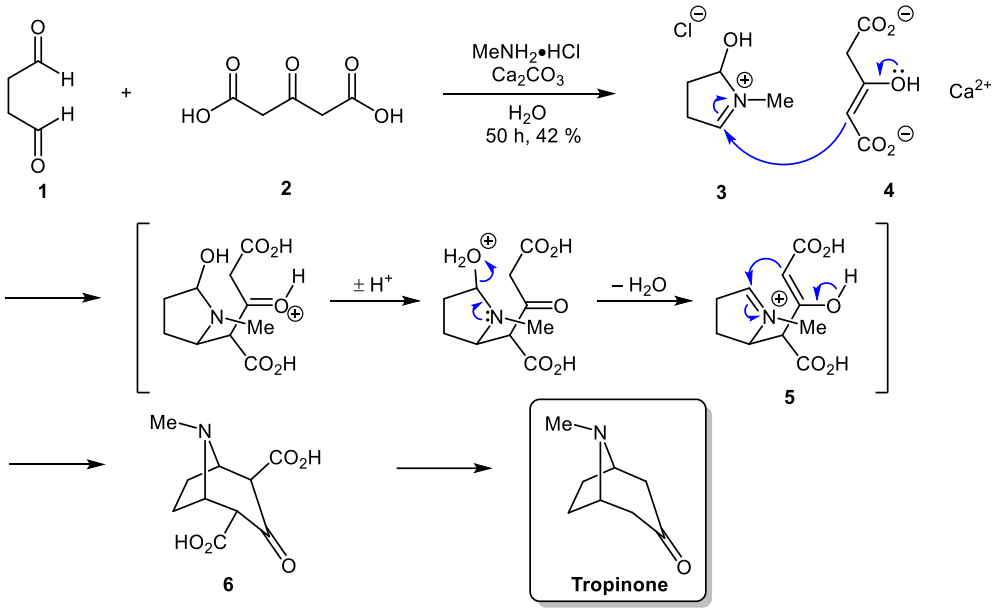


Figure 1: General scheme for an MSR event.

There are a plethora of MSRs in the literature.[1–3] This thesis will focus on particular approaches involving cross-coupling/Diels-Alder (CCDA) reactions giving an account of the work that has been conducted in this area, specifically in the development of novel methodologies and applications in total synthesis (Sections 1.6. and 1.7., respectively). Prior to this, the various terminologies associated with MSRs will be discussed in detail using relevant examples (Sections 1.2. and 1.3.) and a basis will be covered for cross-coupling and DA reactions (Sections 1.4. and 1.5.), highlighting fundamental aspects of these individual transformations.

In terms of the birth of this concept, MSRs have been around since 1917 when Robinson reported the total synthesis of tropinone (Scheme 1).[4]



Scheme 1: Robinson's total synthesis of tropinone involving a cascade reaction.

In this pioneering reaction, succindialdehyde **1**, methylamine hydrochloride, and acetone dicarboxylic acid **2** were reacted together to produce the natural product. Several fundamental transformations are involved in this synthesis: a condensation first occurs between the dialdehyde **1** and methylamine, yielding the cyclic iminium **3**; a Mannich reaction between the cyclic iminium **3** and the enol tautomer of calcium acetone dicarboxylate **4** then occurs. After a series of proton transfers and the expulsion of water, a new cyclic iminium species **5** is generated, becoming primed for the second intramolecular Mannich cyclisation to occur, resulting in the formation of intermediate **6**. Lastly two sets of decarboxylation reactions occur to afford tropinone.

MSRs are becoming increasingly more important in organic synthesis given the many benefits they offer, including: the reduction in overall step count in a total synthesis, avoiding the need to make and isolate reactive intermediates; helping to challenge and expand our repertoire of chemical transformations in terms of generating molecular complexity; and, increased atom economy, reducing not only the resources required, but the amount of chemical waste formed.[5] As a result, significant resources have been directed towards developing novel MSRs,[6] with the end goal being to push the boundaries of chemical synthetic efficiency, and, hopefully, emulate the levels nature delivers by. However, in order to fully appreciate the meaning of these types of

reactions it is necessary to explain and differentiate the various terminologies associated with this concept. In the literature, the two terms most commonly used to describe MSR events are cascade/domino and tandem reactions. The following flowchart provides a useful rational base to aid in the classification of a particular MSR, with the key questions and corresponding answers ironed out (Figure 2).[7] For example, in the instance of a catalytically driven process, if more than one catalytic mechanism is required to facilitate the MSR, then a domino/cascade catalysed process can be discounted, and the reaction is deemed a tandem catalysed transformation. The exact nature of this tandem reaction is dependent on the number of catalysts implemented and the need for a trigger to change the catalyst's mechanistic pathway. This will be further discussed in the following sub-sections (1.2.1.−1.2.3.).

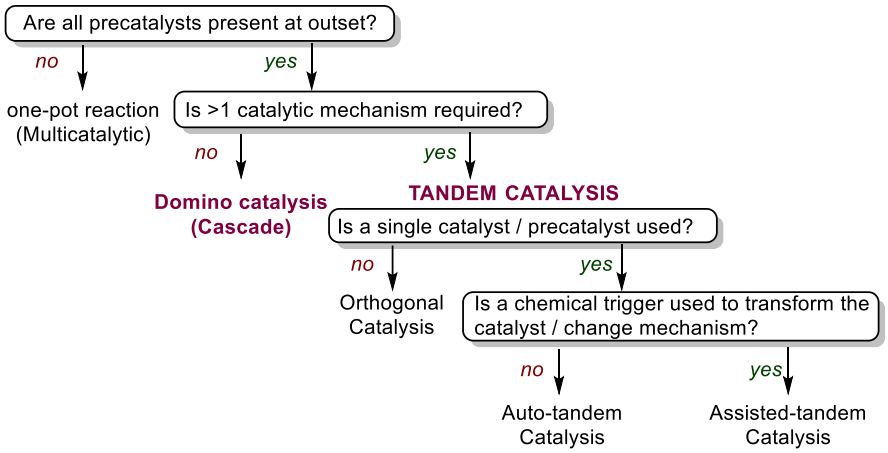
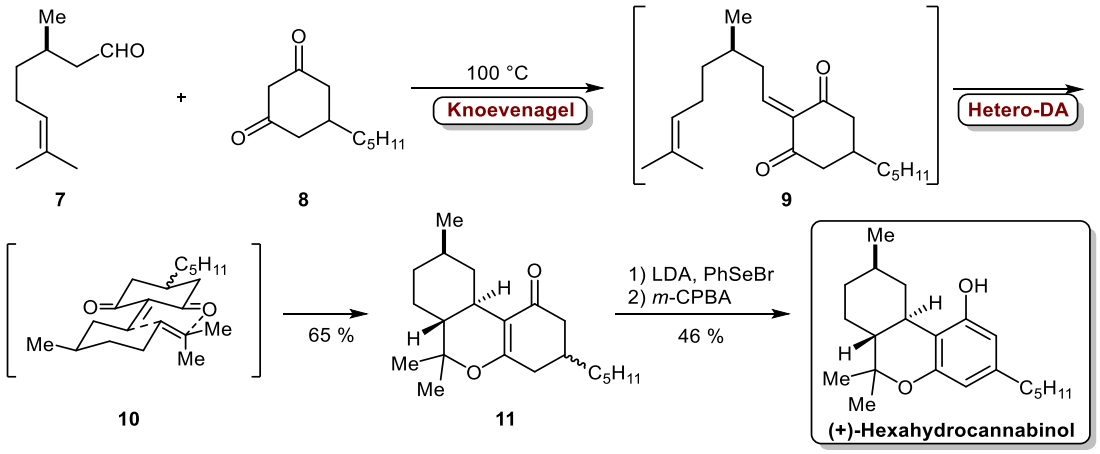


Figure 2: Flowchart for classification of one-pot reactions involving multiple-step transformations.[7]

1.2. Tandem Reactions

This class of reaction can be characterised as a reaction in which two or more new bonds are generated simultaneously, as opposed to sequentially.[8] Here multiple reactions are combined into one synthetic operation. In this instance the two or more reaction sites may or may not influence each other during the transformation. In an ideal scenario, the reaction rates for the two different transformations would be the same for optimal reaction parameters. Otherwise the likelihood of the amount of intermediate present increases, leading to greater possibilities of side reactions occurring. Hence, a "stationary state" of intermediate concentration must be achieved for a favourable outcome.[9] This phenomena was demonstrated by Tietze and co-

workers in the publication reporting the implementation of the Knoevenagel/hetero-Diels-Alder (HDA) for the synthesis of (+) or (-)-hexahydrocannabinol (Scheme 2).[10] This non-catalysed tandem reaction commences *via* a Knoevenagel condensation between aldehyde **7** and diketone **8** to generate intermediate **9**. The HDA reaction then ensues *via* transition state (TS) **10**, forming the tricyclic core structure **11** of the natural product in relatively high yield and excellent stereoselectivity. Lastly an aromatization step is carried out to form the natural product.



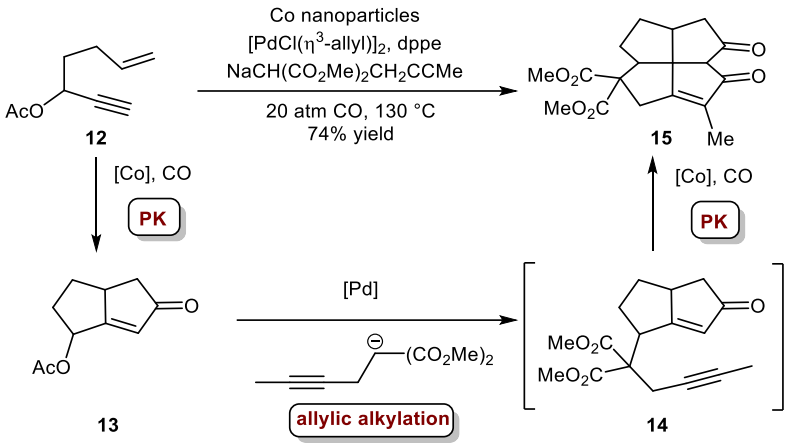
Scheme 2: Tandem Knoevenagel/HDA reaction for the synthesis of (+) or (-)-Hexahydrocannabinol.

In addition, for this class of reaction it is more likely that the multi-step reaction will proceed by a stable intermediate. As can be seen from the flowchart (Figure 2), particularly when discussing catalytically-driven processes, tandem reactions can be split into three sub-forms; orthogonal, auto-, and assisted-tandem catalysis. Each of which have their own advantages and disadvantages.

1.2.1. Orthogonal Tandem Catalysis

This sub-class is defined by two sets of functionally different catalysts working independently from the onset, hence, they do not interfere with each other's specific reactions, and equally perform two distinguishably different reactions. For example, Chung and coworkers reported the following tandem allylic alkylation – Pausan-Khand (PK) reaction (Scheme 3).[11] Initially, the starting material **12** engages with the Co catalyst in a PK cyclisation. The isolated bis-fused ring **13** then acts as the precursor for the tandem reaction in discussion. The first catalytic event is triggered

by Pd, *via* an allylic-alkylation to form intermediate **14** *in situ*, before undergoing an additional PK reaction to generate the target molecule **15**.



Scheme 3: Synthesis of fenestranes using orthogonal tandem catalysed allylic alkylation - PK reaction.

For this particular reaction set-up there are limitations: recovery of each individual catalyst is not necessarily trivial; the catalysts that are involved may not be inert to one another, leading to potential negative effects on their individual transformations; finally, perhaps the greatest limitation lies with the identification of one set of reaction conditions that proves to be ideal for both catalytic transformations.[7]

1.2.2. Auto-Tandem Catalysis

This type of process involves a single catalyst entity, which facilitates the catalysis of at least two mechanistically unique manipulations from the outset. They occur spontaneously through cooperative effects of different species in the reaction media (catalyst, substrate, additional reagents if required). Therefore, the means to trigger a change in mechanistic pathway of the overall reaction is already present within the reaction mixture. As can be seen below in Figure 3, a single catalyst participates in two distinct cycles to produce the product. Similar to orthogonal tandem catalysis, the transformations occur sequentially initially, up to the point where product A is formed and mechanism B commences, after which the cycles are operating simultaneously.

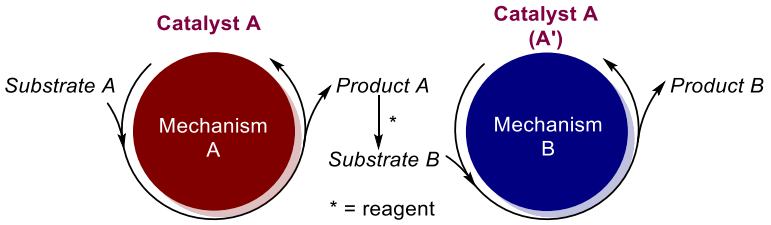
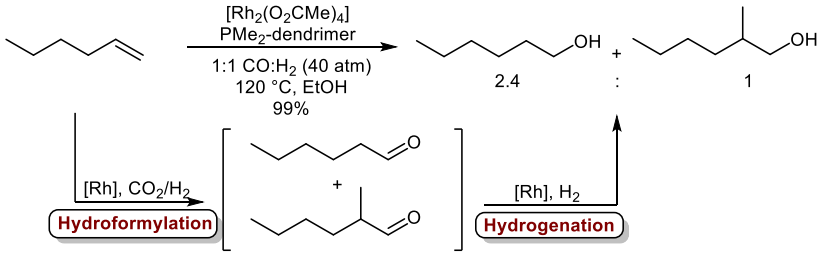


Figure 3: Diagram illustrating auto-tandem catalysis (*reagent, if required, must be present from start).[7]

A major problem associated with auto-tandem catalysis is the level of control to perform the desired transformation, as on numerous occasions side reactions are observed. This flaw becomes very apparent when working with precursors that are able to enter both catalytic cycles. Likewise to the orthogonal variant, obtaining optimal conditions for both cycles remains a challenging feat to achieve. Nevertheless, if a balance can be struck that adheres to both sets of catalytic systems; the overall process becomes unparalleled in terms of efficiency. A significant example where this balance was achieved is the "Shell oxo process",[12] a heavily used industrial operation which transforms α-olefins into the corresponding alcohols. A modified version of this process is shown below where the ruthenium complex catalyses this two-step tandem process; firstly hydroformylation occurs followed by hydrogenation (Scheme 4).[13]



Scheme 4: Auto-tandem catalysis in hydroformylation–hydrogenation of α-olefins to alcohols.

1.2.3. Assisted-Tandem Catalysis

Reactions that come under this classification have one substantial advantage over the previous two, namely the additional flexibility they possess. Being an assisted process by means of a particular trigger mechanism, this method offers greater range in capabilities and scope for application. Much like auto-tandem catalysis, here the process involves a single catalyst. This catalyst can perform a particular transformation, but is then significantly altered by a trigger mechanism, such as by the

addition of a reagent, changing its properties and in turn enabling its participation in a different catalytic cycle (Figure 4).

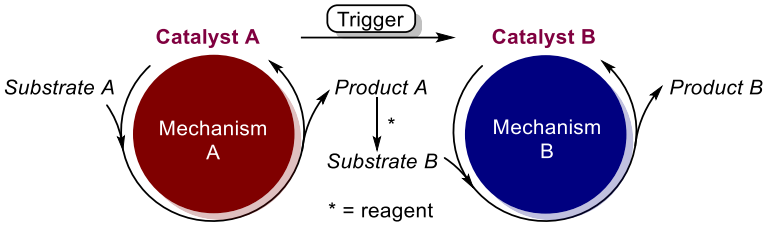
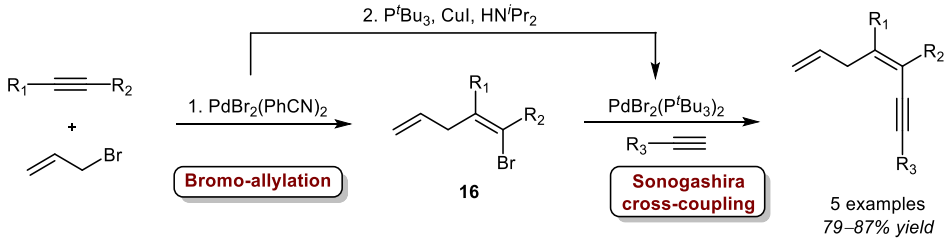


Figure 4: Schematic illustration of assisted-tandem catalysis. (*additional reagent may or may not be required).[7]

Compared to orthogonal and auto-tandem catalysis, this is no longer a simultaneous series of catalytic cycles, as the catalysts are not present at the same time during the reaction. In addition, a drawback with this type of process lies with the need to monitor the progress of the reaction, in order to ascertain when to initiate the trigger mechanism. An example involving this type of transformation has been developed below by Rawal and co-workers (Scheme 5).[14] After the initial bromo-allylation to generate intermediate **16**, tri-*tert*-butylphosphine (P^tBu_3) is added to convert the palladium dihalide species formed as a result of the first step into the catalytic species ($PdBr_2(P^tBu_3)_2$) required for the Sonogashira cross-coupling, constructing highly functionalized enynes.



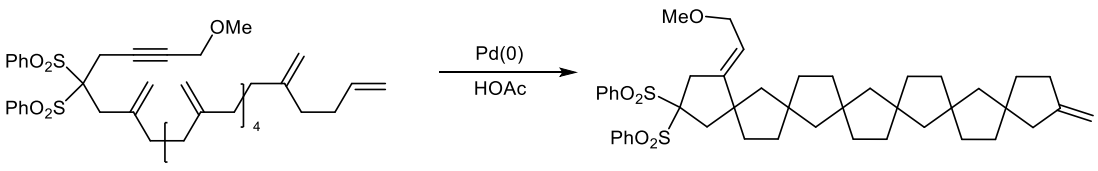
Scheme 5: Tandem Pd-catalysed bromo-allylation / Sonogashira cross-coupling.

To briefly summarize, a theme that is common to all three catalytic-tandem variations is the mitigation of intermediate isolation. Auto- and assisted-catalysis are more efficient in terms of catalyst utilization, as both only use a single catalyst. Orthogonal and auto-tandem catalysis benefit from being multi-step reactions under one set of reaction conditions; however, the drawback is that these conditions may not

be optimal for each catalytic event, which assisted-catalysis does not suffer from. Additionally, given the nature of assisted-catalysis not having two catalysts that exist at the same time, there is no cause for concern regarding the interference between catalysts influencing desired reactivity. This is not the case for orthogonal and is less so for auto-tandem catalysis.

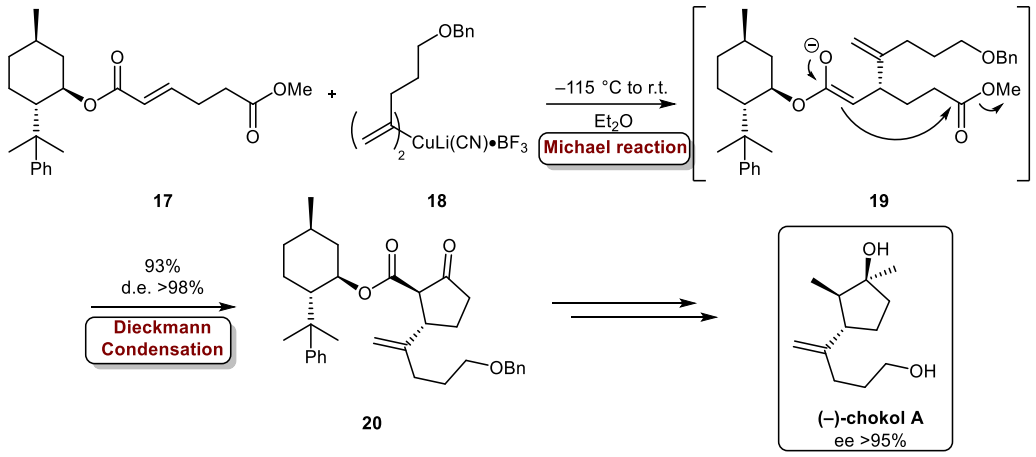
1.3. Domino Reactions & Cascade Reactions

These types of reactions involve the formation of a complex scaffold through multiple sequential transformation steps. Typically, for a reaction to be classified as either of these terms, the new bonds being formed must be a result of the same reaction conditions being applied, *i.e.* no additional reagents or catalyst were added in order to promote subsequent reactivity. In addition, the new product formed has to result from an intermediate generated *in situ*. These intermediates are often reactive species, which can pose problematic with respect to handling and isolation.[8,15] This is a key feature, because if a substrate possessed numerous functionalities and each were to react individually in the same reaction vessel, this would not be deemed a sequential reaction. Compared to tandem reactions, the intermediates being formed *in situ* are usually rapidly converted through a subsequent reaction into a more stable species.[16] If a catalyst is involved in the reaction this would also imply that the transformation proceeds *via* a single catalytic mechanism. For example, Trost reported an intriguing example involving the formation of polyspiranes *via* a Pd-catalysed cycloisomerization pathway (Scheme 6).[17] This cycloisomerization is initiated by the addition Pd-H to the acetylene functionality, propagation *via* intramolecular carbopalladation ensues up to the point when a terminating β-hydride elimination occurs yielding the polyspirane product.



Scheme 6: Intramolecular domino (cascade) catalysis in the synthesis of a polyspirane *via* Pd-catalysed cycloisomerization of a polyenyne.

Compared to tandem reactions, precursors for domino/cascade reactions tend to be of a more complex nature, with predetermined functionalities being in place to facilitate the overall transformation.[9] Out of the two definitions, domino has been portrayed as the more appropriate term to describe these types of MSRs, as was made clear by Tietze, despite 'cascades' being used more frequently.[9] A recent example involving a domino reaction is provided below (Scheme 7). In the synthesis of (–)-chokol A,[18] the key fragment **20** was constructed *via* a domino Michael addition/Dieckmann cyclization between enone **17** and the cuprate **18**. The sequence proceeds *via* intermediate **19**, which cyclises to form the desired product in high yield and diastereoselectivity.

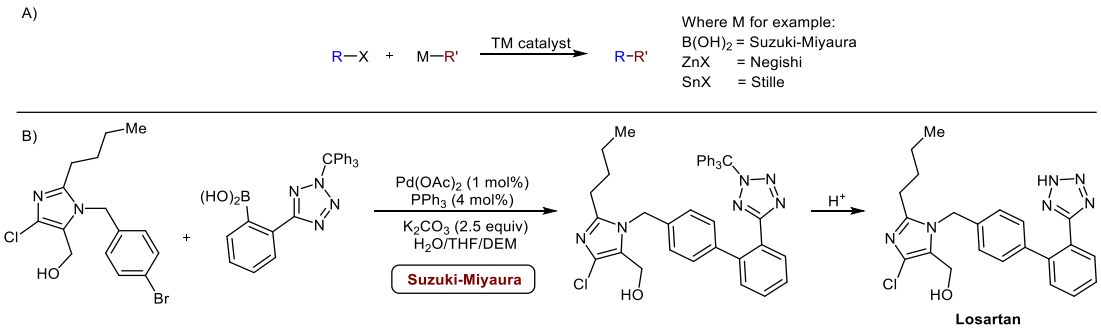


Scheme 7: Total synthesis of (–)-chokol A *via* a domino Michael/Dieckman reaction.

In addition to understanding the correct terminology, key points to consider when analysing and critiquing a particular MSR, as Tietze laid out, include the bond-forming efficiency, *i.e.* number of bonds formed in a sequence; the increase in structural complexity and its applicability in a general sense.[15] These points will be referred to when discussing the examples in Sections 1.6. and 1.7..

1.4. Cross-Coupling Reactions

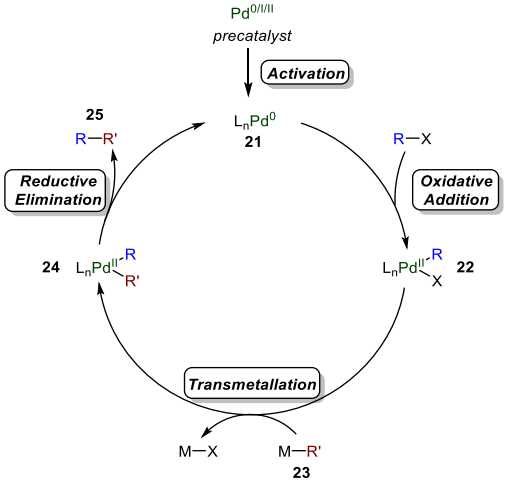
Transition metal (TM) catalysed reactions, involving the formation of carbon-carbon bond or carbon-heteroatom bonds, have become an invaluable source in organic chemistry (Scheme 8A). Cross-coupling reactions are typically metal-catalysed reactions (Pd being one of the most common choice of metal),[19] with the two reacting components involved being traditionally an sp^2-hybridized aryl halide and a nucleophile.[20] Reactions such as the Suzuki-Miyaura (SM) have become hugely popular, particularly in industry,[21,22] significantly since it was applied for the late stage-functionalization of losartan, a ground-breaking demonstration of this type of reactions capabilities (Scheme 8B).[23] In 2014, a survey on chemical reactions demonstrated the SM reaction to be the second most commonly used transformation in medicinal chemistry,[22] which in part coincided with the period for increased development of pharmaceuticals bearing more planar structures.[24] SM specifically are highly utilized synthetic manipulations given their ease of application and generally excellent tolerance/robustness of variety of functional groups.[25]



Scheme 8: A) Generic cross-coupling reaction, B) SM coupling used in losartan synthesis.

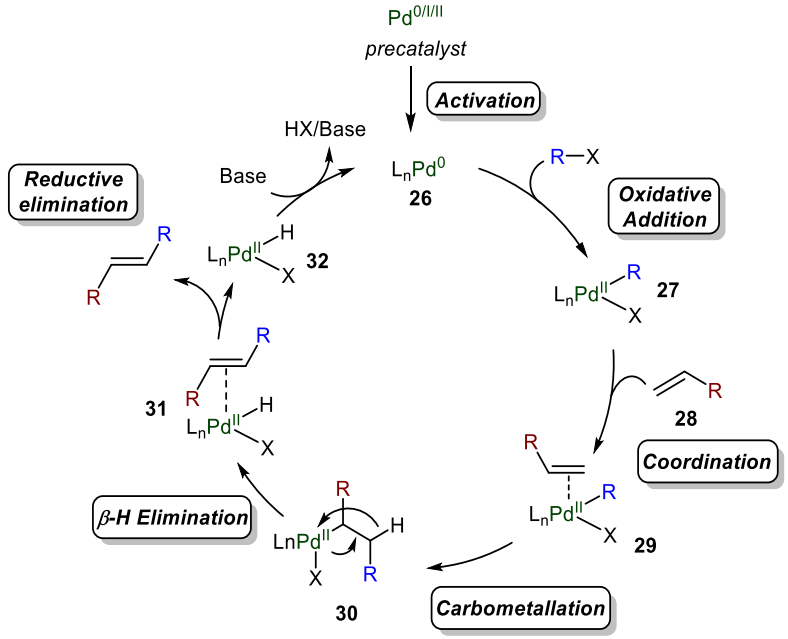
In the catalytic cycle of a Pd cat. cross-coupling reaction there are three distinct key events taking place to facilitate the transformation, each of which has seen extensive research and continues to be the focus of academic and industrial study.[26] These three mechanistic events are oxidative addition, transmetallation and reductive elimination (Scheme 9). The catalytic cycle initiates by undergoing an activation step to generate the required catalytically active species **21**, usually converting a Pd(II) to a Pd(0) species. Subsequent oxidative addition of an incoming electrophile generates a new the Pd(II) species **22**, which then partakes in a transmetallation step with an

appropriate nucleophile **23**. The resulting Pd species **24** then finally undergoes a reductive elimination step, which simultaneously forms a molecule of the cross-coupled product **25** and regenerates the catalytic species for subsequent turnovers. Although this catalytic cycle is common in most parts to all Pd metal-catalysed cross-coupling reactions (like the Stille reaction); there are subtleties that must be noted when referring to the Heck and Sonogashira reactions specifically, which will become important when discussing examples in Sections 1.6 and 1.7.



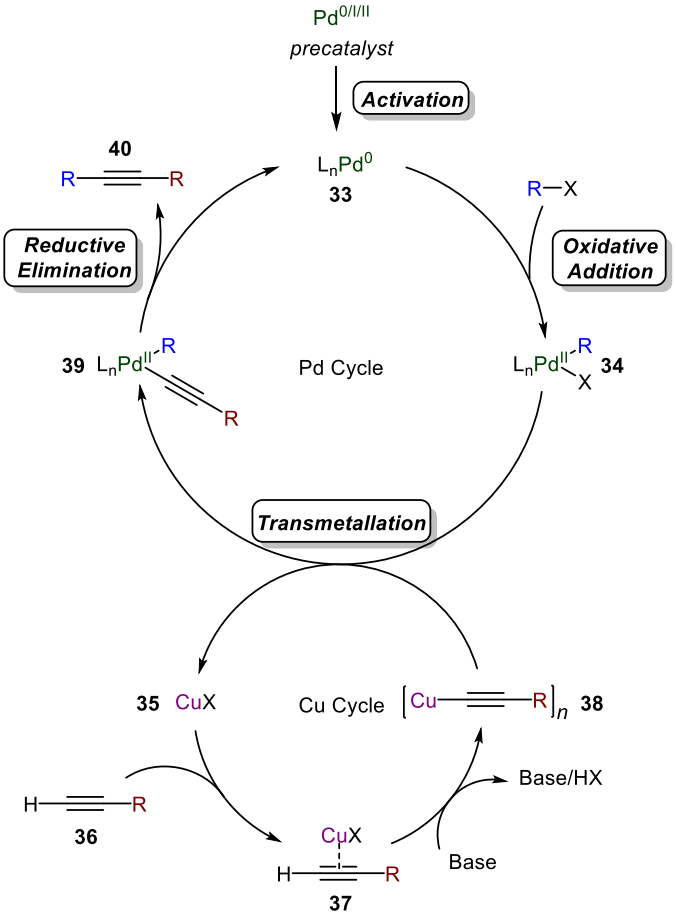
Scheme 9: General mechanism for typical Pd-catalysed cross-coupling reaction.

Starting with the Heck reaction (which couples together olefins with aryl halides), the main differences associated with this catalytic cycle compared to the above (Scheme 9), are the additional steps known as carbometallation and β-H elimination (Scheme 10).[27] After the oxidative addition of the electrophile has taken place to form the Pd(II) species **27**, this then interacts with the olefin **28** species *via* coordination (**29**). Subsequent isomerization occurs to relieve torsional strain, followed by carbometallation (or carbopalladation) forming the Pd(II) alkyl complex **30**, which then undergoes β-H elimination to form Pd(II) complex **30**. The catalytic cycle is then completed by a reductive elimination step, ejecting the *trans* exclusive cross coupled product from the cycle, followed by a base induced elimination of HX from **32**, to regenerate catalytically active species **26**.



Scheme 10: Catalytic cycle for a Heck-Mizoroki cross-coupling reaction.

The Sonogashira reaction, which enables the formation of C-C bonds between alkynes and aryl halides, also has its own unique features. Unlike in the previously discussed examples, the Sonogashira reaction employs a copper co-catalyst, which plays a key role in the transmetallation step (Scheme 11). Similarly the cycle commences by generating the catalytically active Pd(0) species **33**, which undergoes oxidative addition with the electrophile to form Pd (II) species **34**. This then reacts with the copper acetylide **38**, preformed through its own catalytic cycle, *via* transmetallation to form the Pd(II) alkyne bound complex **39**. After a cis/trans isomerization takes place, the Pd species is primed for the following reductive elimination, extruding the product **40** and regenerating the catalyst in the process and completing the cycle.

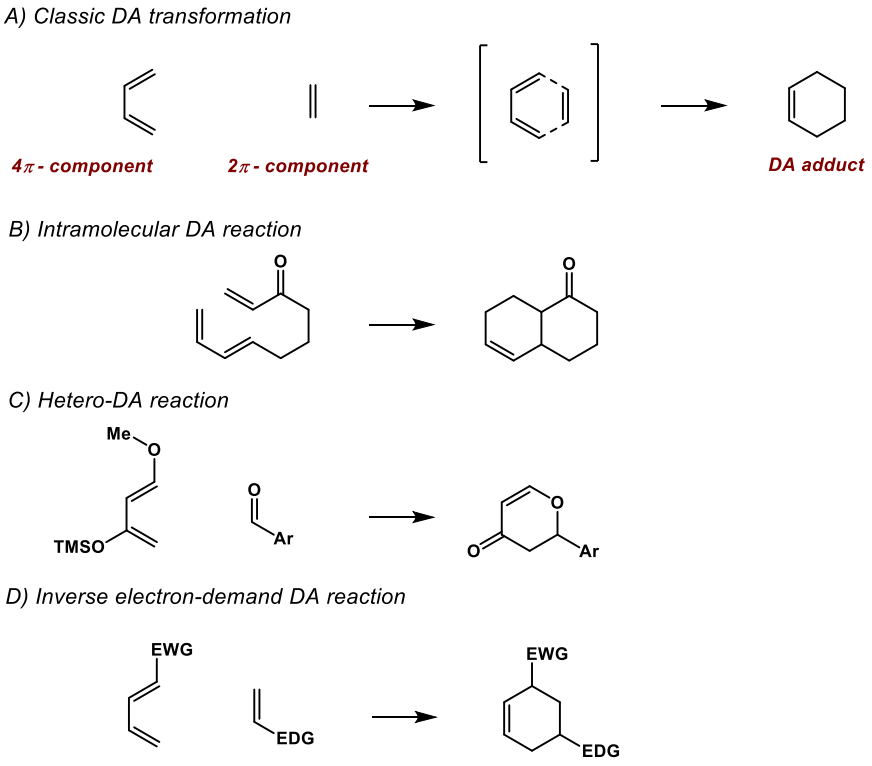


Scheme 11: Catalytic cycle for a Sonogashira cross-coupling reaction.

Our greater understanding of these mechanistic events for all cross-coupling variations has in turn directly contributed to the excellent reliability of these reactions. Furthermore, the vast improvement in utility of these reactions is owed to the continuing pursuit for the development of better catalysts through ligand design.[25] Given the high efficiencies of cross-couplings reactions it makes them a natural choice for integration and implementation in the development of novel MSRs.

1.5. Diels-Alder Reaction

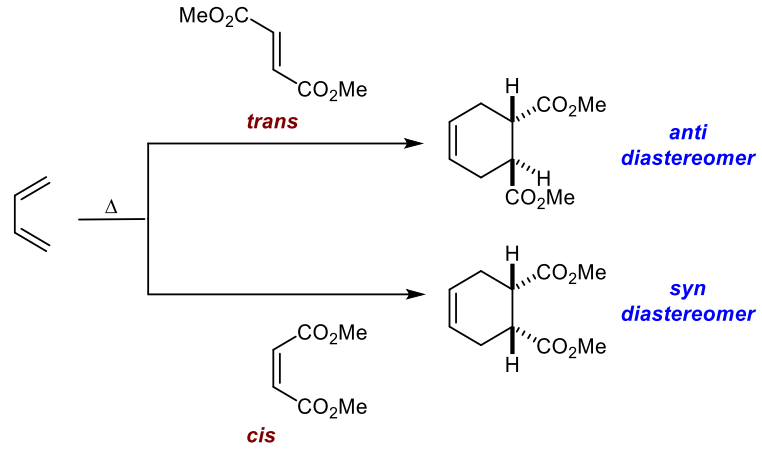
The Diels-Alder (DA) reaction is a pericyclic transformation, which proceeds *via* a [4+2] cycloaddition.[28] Since its discovery in 1928,[29] huge strides have been taken in exploring the reactivity and application of the DA reaction, particularly in MSRs.[30] The reaction involves a diene (4π component) and a dienophile (2π component) (Scheme 12A), and results in the formation of two new σ-bonds and one π-bond. When the two reacting components are part of the same molecule then this is known as an intramolecular Diels-Alder (IMDA) reaction (Scheme 12B). An additional variant of this transformation has been depicted below (Scheme 12C) involving a hetero-atom on the dienophile, yielding a HDA reaction. Examples B and C are known as normal demand DA reactions, where the diene bears electron donating groups (EDG) and the dienophile electron withdrawing groups (EWG), however, these roles can be reversed around in an inverse-electron demand DA (IEDDA) (Scheme 12D).[31]



Scheme 12: A) General scheme depicting the DA reaction; B) Intramolecular DA example; C) Hetero DA example; D) Inverse electron-demand DA reaction.

1.5.1. Mechanism

The DA reaction is typically considered to be a concerted process.[32] This results in a stereospecific reaction, meaning the existing stereochemical relationship on the reacting precursors are translated to the product, and therefore retained (Scheme 13).



Scheme 13: Pictorial representation of stereospecificity of the DA reaction.

The DA reaction proceeds *via* a single transition state (TS), and is governed by orbital symmetry overlapping correctly. The reaction proceeds *via* a [4+2] cycloaddition, which involves a suprafacial interaction of a 4π electron system (diene) and a 2π electron system (dienophile). This interaction is allowed under thermal conditions according to the Woodward-Hoffmann symmetry rules.[33] It was previously believed that the reaction proceeds *via* a two-step mechanism involving a biradical or zwitterionic intermediate.[32] Fukui was a dominant figure alongside Woodward and Hoffman in the investigation of frontier molecular orbital (FMO) theory, specifically in the prediction of reactivity by looking into the highest occupied molecular orbital (HOMO) of one species and the lowest occupied molecular orbital (LUMO) of another species in a reacting system.[34] His work, coupled with the Woodward-Hoffmann symmetry rules, allow us to predict the stereochemical outcome of thermally allowed pericylic reactions. Figure 5 illustrates the symmetric requirement of orbitals as well as the phase matching in order for the DA reaction to proceed.

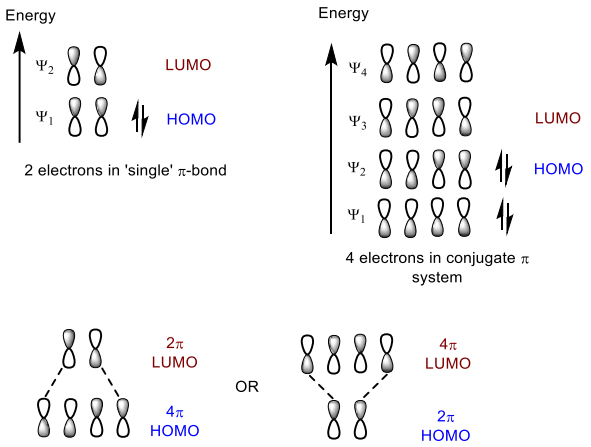


Figure 5: Displays the nodes symmetries of the orbtials in both the diene (4π-component) and dienophile (2π-component). As well as the suprafacial phase matching, regardless of which species is defined as the HOMO or LUMO.

Another important concept in FMO theory to consider is the coefficient or size of the orbitals involved in the interaction. In Figure 5, they are all of the same size, however, in most reaction cases they tend to vary. In addition to matching phases, coefficients have to match as well in order to facilitate the DA (Figure 6). Hückel's MO theory allows us calculate the size of the coefficients on each atom involved in the cycloaddition giving us an additional handle in rationalising the regioselectivity.[35]

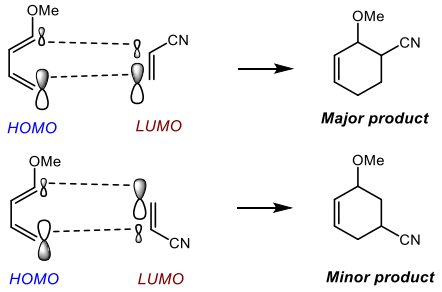


Figure 6: Displays the orbital phase match as well coefficient (size) match in a synthetic example for determining the major product outcome.

1.5.2. Reactivity

In a general consensus the DA reaction can be split into two types: normal electron demand and inverse electron demand (see Scheme 12). Figure 7 demonstrates that normal or inverse electron demand DA reactions depend on the substituents present on each reacting component. In addition, in both cases the orbitals which are

interacting with each other are always in phase (suprafacial), as this is paramount for the DA reaction to proceed.

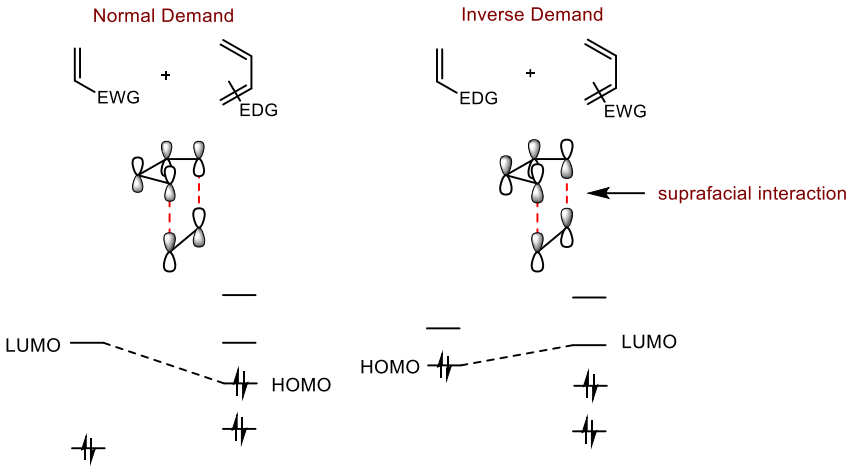


Figure 7: Displays the orbital interactions between diene and dienophile in both normal and inverse electron demand DA reaction, as well Molecular Orbitals (MO) diagrams.

Figure 7 depicts simplified versions of the DA reaction, in often significantly more complex scenarios where unsymmetrically substituted dienes/dienophiles are implemented, electronic and steric properties have to be taken into account when rationalizing the regioselective and stereoselective outcome. In terms of electronic effects the highest yielding DA reactions are typically those consisting of a large imbalance between the diene and dienophile, in order to reduce the energy gap between the interacting HOMO and LUMO. The DA reaction is also very sensitive to steric effects, due to the compact nature of the DA TS.[36] In addition, with unsymmetrical dienes/dienophiles two possible TS can form (*exo* and *endo*), each leading to different overall stereochemistry in the product.[37] The kinetic product or *endo*-adduct is formed preferentially due to the Secondary Orbital overlap (SOO) stabilising the transition state, which lowers the overall energy barrier (Figure 8).

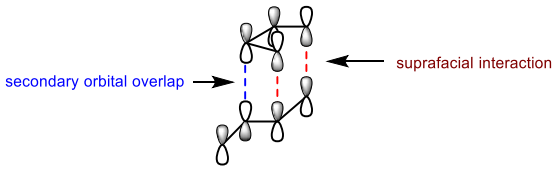


Figure 8: Picture depicted the key stabilising SOO interaction, to increase stability of *endo* TS.

This overrides any steric interaction that may prohibit the formation of the kinetic product. In contrast, due to the significantly lower steric interaction in the *exo* product, this is the thermodynamic product, and is typically seen to increase in yield at higher temperatures (Figure 9).[36,38]

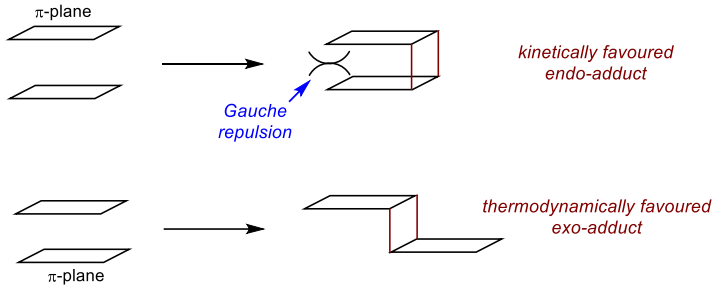
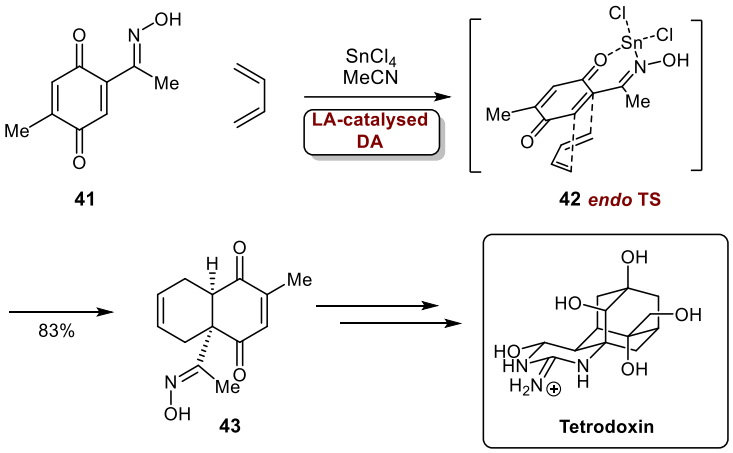


Figure 9: Differentiation in π-plane interaction, to form either the kinetic or thermodynamic DA product.

1.5.3. Regioselectivity

The regioselectivity of the DA reaction is governed by electronics, hence the introduction of a third body in the reaction, such as a Lewis acid (LA), can substantially aid in promoting the desired DA reaction to occur. A great example of the benefits in applying a LA in the DA reaction was reported in the total synthesis of tedrodotoxin by Kishi *et al* (Scheme 14).[39]



Scheme 14: Chemoseletivity obtained through LA-catalysed DA, to generate key intermediate C.

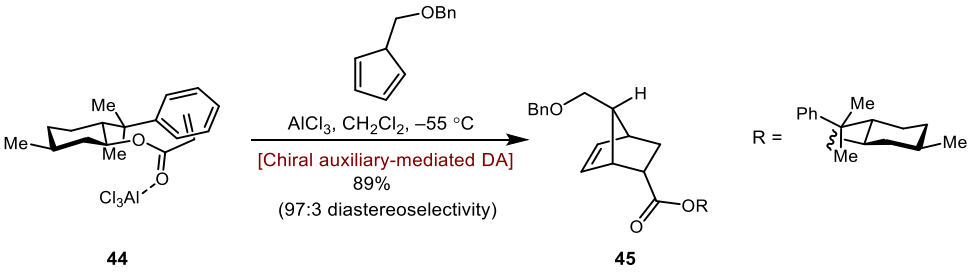
In addition to the enhanced regioselectivity, this example also demonstrates excellent chemoselectivity. The dual-complexation of the $SnCl_4$ (LA) to the dienophile in the TS **42** causes the diene to react exclusively with the olefin nearest to the oxime

substituent in **41** yielding DA adduct **43**. LA complexation causes an increase in electronegativity on the nitrogen, meaning the difference in orbital coefficients on the reacting carbons is greater (refer to Figure 6). This not only enhances the regioselectivity, but also the rate of the reaction, as the LUMO energy level of the dienophile is significantly lowered. It is worth mentioning as well that there are numerous examples where high levels of regioselectivity are observed in cases of "formal" DA reactions, especially when heteroatoms are involved.[40]

1.5.4. Asymmetry in Diels-Alder Reactions

The two most common ways for facilitating asymmetric DA transformations include the usage of either chiral auxiliaries or asymmetric catalysis (LA-catalysed, iminium-catalysed).

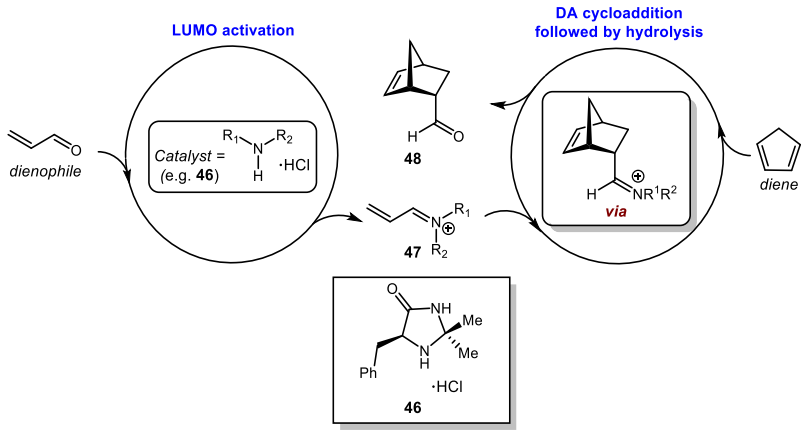
Corey and coworkers reported the total synthesis of Prostagladin $F_{2\alpha}$ ($PGF_{2\alpha}$), which effectively implemented the use of a menthol-derived auxiliary to achieve a diastereoselective DA reaction on route to the natural product (Scheme 15).[41]



Scheme 15: Chiral auxiliary used to facilitate asymmetric DA reaction.

The attachment of the homo chiral cyclohexane ring **44** induces the observed facial selectively by controlling the approach the dienophile adopts during the TS. The auxiliary's presence means that dienophile orientates itself in space, in order to reduce steric repulsion between the LA and the bulky menthol-derived phenyl ring. The favourable π-stacking interaction observed also helps in fixing the dienophiles spatial arrangement. These combined effects mean that the diene approaches from the less hindered face exclusively, explaining the observed high levels of diastereoselectivity achieved for compound **45**.

Iminium-catalysed DA reactions are another approach to achieving high enantioselectivity. This idea was first published by MacMillan's group in 2000, where they demonstrated that chiral amines can act as catalysts to facilitate the transformation between α,β-unsaturated aldehydes and various dienes enantioselectively (Scheme 16).[42]



Scheme 16: Iminium-catalysed DA reaction employing a chiral amine to achieve high *ee*.

The process is initiated by an *in situ* condensation of the chiral amine **46** with the aldehyde of the dienophile to form the iminium ion species **47**, which becomes significantly activated to then undergo the DA reaction with the diene. Once the DA adduct is formed, subsequent hydrolysis of the iminium species yields the enantio-enriched DA product **48** as well as the recovery of the chiral amine catalyst. The high levels of *ee* observed are rationalised by two main factors; firstly the selective formation of the (*E*) iminium avoiding steric repulsion between the olefin and the geminal methyl substituents in **49** and secondly the bulky benzyl group on **50** acts as a shield for the top face, so that the diene can only approach from the lower face during the cycloaddtion (Figure 10).

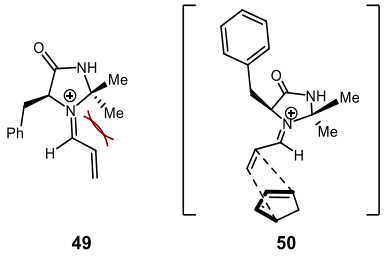


Figure 10: Summarises the two key factors that rationalise the high level of *ee* observed for the DA product.

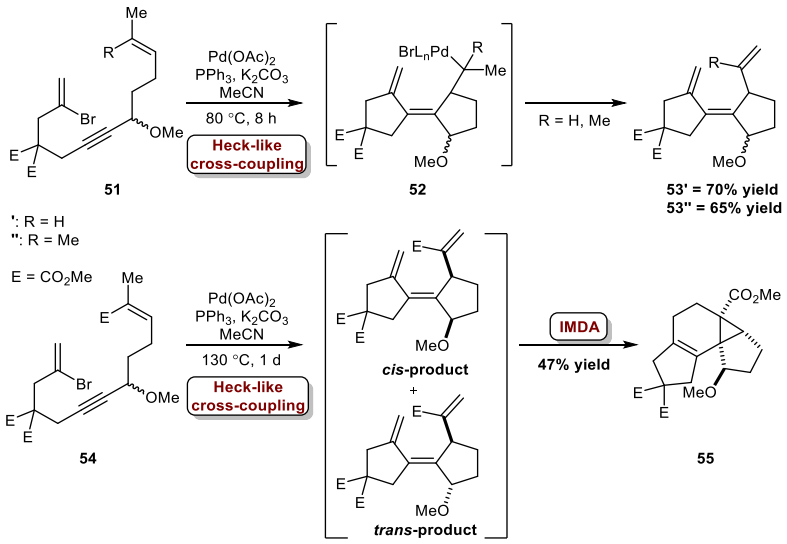
The DA reaction possesses the ability to expediently generate complex 6-membered carbon ring frameworks, unless a heteroatom(s) is also involved, with multiple contiguous stereocenters, selectively and with relative ease, making it one of the most attractive methods for the synthesis of 6-membered rings. Given its ability to form numerous bonds in a single step, with high regio- and stereo- selectivity, it is an ideal reaction for the synthesis of complex target molecules, such as terpenes, sesquiterpenes, alkaloids, and many more.[29] As such, the reactivity and application of this reaction have been thoroughly explored and documented to this point and continues to be an integral synthetic tool for organic chemists.[43] The DA reaction offers a huge amount of flexibility in reactivity, given the many parameters that have to be considered, such as electronics, sterics, choice of coupling components and additional reagents, which can be finely tuned in order to carry out a desired DA reaction.

Bringing together cross-coupling and DA reactions in MSR events would provide expedient access to novel chemical space. In the case of the DA reaction, the means are there to generate high levels of molecular complexity in a clean and predictable fashion. Additionally, while cross-coupling are constrained in the means to construct molecular complexity to the same extent as the DA reaction, their sheer robustness and reliability more than make up for this.[44] The following sections will discuss examples involving cross-coupling/Diels-Alder (CCDA) (or the reverse order) focusing firstly on methodology developments (Section 1.6) and secondly on the use of CCDA strategies towards the total synthesis of natural product targets (Section 1.7).

1.6. CCDA Reaction in Methodology

1.6.1. Heck Cross-Coupling Examples

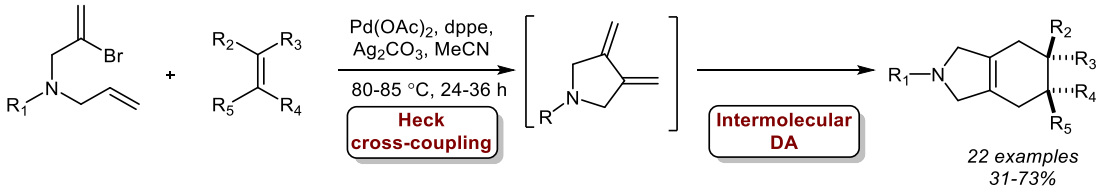
Most notable early examples of cross-coupling reactions that were combined with the DA reaction were of the Heck variation. This is due to high level of stereochemical retention the Heck coupling offers, as it gives exclusively the *trans* alkene product. De Meijere and coworkers were amongst the first to identify and utilize this type of cascade reaction for the successful generation of highly complex polycycles (Scheme 17).[45]



Scheme 17: A domino Heck/intramolecular reaction for the generation of highly complex polycycles.

Starting from the dienynes (**51'** & **51''**) they could successfully furnish the mixture of diastereomeric triene intermediates (**53'** & **53''**) under Heck like cross-coupling conditions, *via* intermediate **52**, isolating them in good yields. However, despite attempting forcing conditions on these precursors, neither underwent the subsequent intramolecular DA reaction. The flaw in these systems was found to be the unreactive nature of the dienophile. Hence, after changing the methyl substituent to the methyl ester (seen in **54**) (lower resulting LUMO), and elevating the reaction temeperature to 130 °C, they did indeed obtain the desired DA adduct **55** in reasonable yield. This simple, yet elegant sequence, rapidly generates densely functionalized scaffolds, constructing in the process four new bonds, four new rings and four contiguous centers (including two quaternaries).

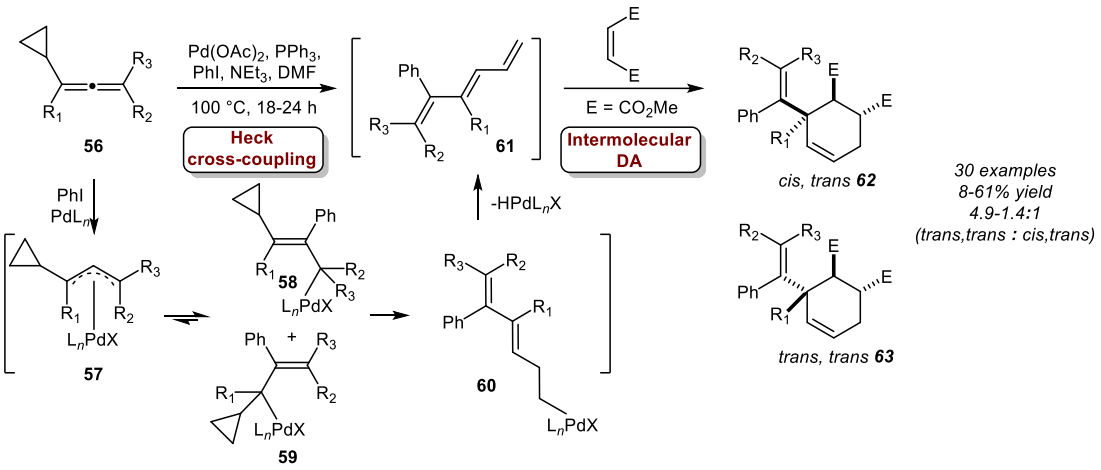
In 2001, de Meijere and co-workers published an intriguing paper on the application of domino Heck/DA reactions in the synthesis of heterobicycles,[46] taking a particular interest in how the regioselectivity and stereoselectivity of the DA step was affected based on changes to the protecting group on the nitrogen. In this work, easily accessible 2-bromo-4-aza-1,6-heptadiene precursors undergo an intramolecular Heck cross-coupling, forming the diene moiety for subsequent DA cycloaddition (Scheme 18).



Scheme 18: A domino Heck/DA reaction for the synthesis of heterobicycles.

In addition, their methodology was amenable to other precursors, including: ethers, the introduction of methyl groups for more substituted olefins, and the use of arcylamides instead allylamides. All of which proceeded with reasonable regio- and stereoselectivity, as well as yields.

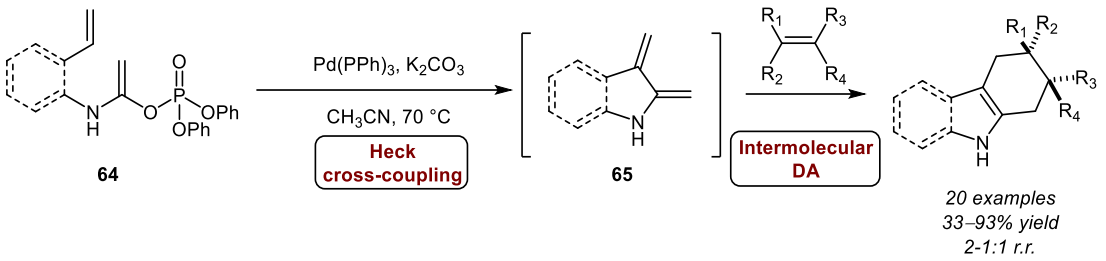
Following on from this work in 2005, de Meijere's research group reported another domino Heck/DA process, involving reactive allene species, for the formation of 4,5-disubstituted 3-alkenylcyclohexenes (Scheme 19).[47] When cyclopropylallene **56** is employed in a Heck reaction, the subsequent carbopalladated product **57** formed exists in equilibrium with the two σ-allyl complexes **58** and **59**. Whilst **58** yields undesirable side products through the addition of another cyclopropylallene motif, **59** exhibits a cyclopropylcarbinyl to homo-allyl rearrangement,[48] with the resulting intermediate **60** then undergoing a β-dehydropalladation, releasing the 1,3,5-hexatriene **61**, which can go on to react in a DA reaction with the dienophile present in the reaction mixture.



Scheme 19: Heck/DA reaction involving cyclopropylallenes to generate 4,5-disubstituted 3-alkenylcyclohexenes.

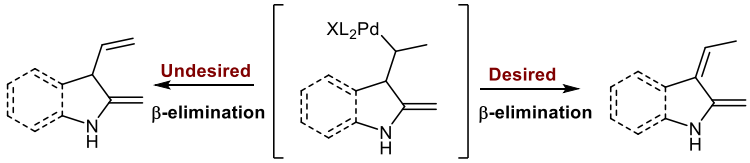
The key identification of the intrinsically more reactive nature of the allene towards carbopalladation compared to the dienophile, helped facilitate the successful discovery of this one-pot domino process. The reaction is tolerant to a variety of differently substituted allenes, with yields being moderate across the board. The authors state that this [4+2] cycloaddition proceeds in a non-concerted fashion, explaining the observed mixtures of **62**:**63** being obtained. Interestingly a preference towards the thermodynamically more stable *trans, trans* **63** product was observed, which cannot be formed in a concerted process. The sequence forms three new bonds, along with one ring and three new stereocenters.

In 2007, an intramolecular Heck/DA cycloaddition reaction for the rapid synthesis of tetrahydrocarbazole derivatives was reported by Sasaki and co-workers (Scheme 20).[49] Starting from acyclic α-phosphono enecarbamates **64**, a Pd-catalysed Heck reaction is performed to facilitate the formation of the diene intermediate **65**, which can then engage with a dienophile to form the corresponding DA adduct.



Scheme 20: Cascade intramolecular Heck/DA reaction for tetrahydrocarbazole synthesis.

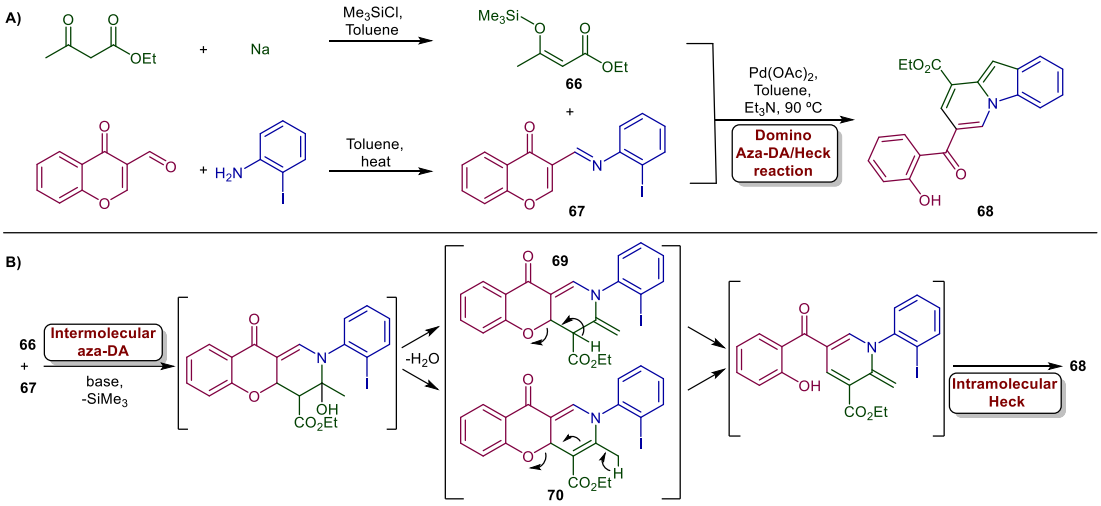
The yields were modest to very good for a broad range of substrates, and the reaction tolerated a variety of substituted tetrahydrocarbazoles and dienophiles. The regioselectivity of the DA reaction, using mono-substituted dienophiles, was consistent throughout, typically in a 2:1 ratio in favour of the 1,3- versus 1,4-regioisomer respectively. Furthermore, the scope could be expanded to accommodate non-benzofused nitrogen heterocycles as well, delivering complex motifs in comparable yields. A slight limitation of this process was if the system bore a methyl substituent on the terminal olefin, a significant depreciation in yield was observed. This was likely due to the competing modes of β-elimination occurring (Scheme 21). Overall, this methodology facilitates the formation of three new bonds, one new ring and up to three contiguous stereocenters depending on choice of starting materials.



Scheme 21: Two modes of competing β-elimination pathways.

In 2009, Ishar and co-workers reported a domino aza-DA/Heck cross-coupling reaction for the synthesis of benzoindolizines (Scheme 22A).[50] In order to circumvent the handling of the reactive precursors **66** and **67** for ensuing domino process, the authors prepared each fresh and separately prior to mixing alongside the Pd catalyst. After conducting the [4+2] cycloaddition, the intermediate undergoes a Pd-catalysed Heck cross-coupling reaction to furnish the benzoindolizines **68**. The sequence constructs three new bonds as well as two rings. The proposed mechanism behind the transformation is highlighted in Scheme 22B. The authors postulated that after forming

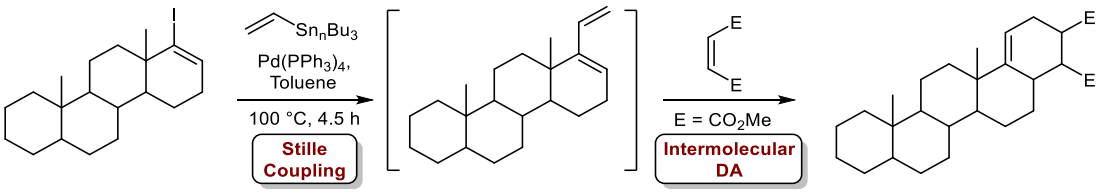
the aza-DA adduct, a base-induced hydrolysis of the silyl species is followed by elimination of water to unmask the required olefin. In principle the elimination can generate two regioisomers; either as the terminal alkene **69** or the more substituted internal alkene **70**. It is clear however, that the product isolated can only be generated through a Heck coupling with the terminal olefin. As a result, in the case of intermediate **70**, it must isomerise, breaking the C-O bond and generating the olefin required for the subsequent Heck cross-coupling. An additional driving force behind this reaction, is the aromaticity gained in the formation of the product.



Scheme 22: A) Domino aza-DA/Heck cross-coupling reaction. B) Proposed mechanism.

1.6.2. Stille Cross-Coupling Example

In 1997, Tuba and co-workers reported a tandem Stille/DA for the synthesis of pentacyclic steroids (Scheme 23).[51] Here, the goal was to provide a methodology enabling the synthesis of a carbocycle as the "E" ring fused to the rest of the steroid molecule, in order to further expand potential avenues for future biological evaluations.

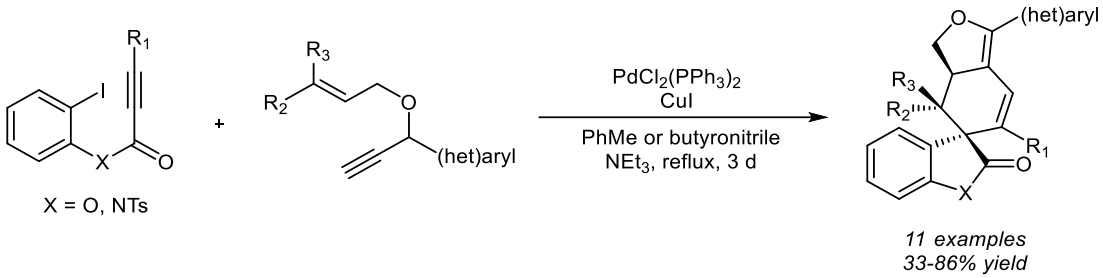


Scheme 23: Tandem Stille/DA reaction for pentacyclic steroid synthesis.

The reaction tolerated a variety of alternative dienophiles as well as different steroidal frameworks. During the sequence, three new bonds, one ring and two stereocenters are formed. The authors envisaged that this methodology could be used as a tool for late-stage functionalization of steroidal motifs in SAR studies.

1.6.3. Sonogashira Cross-Coupling Example

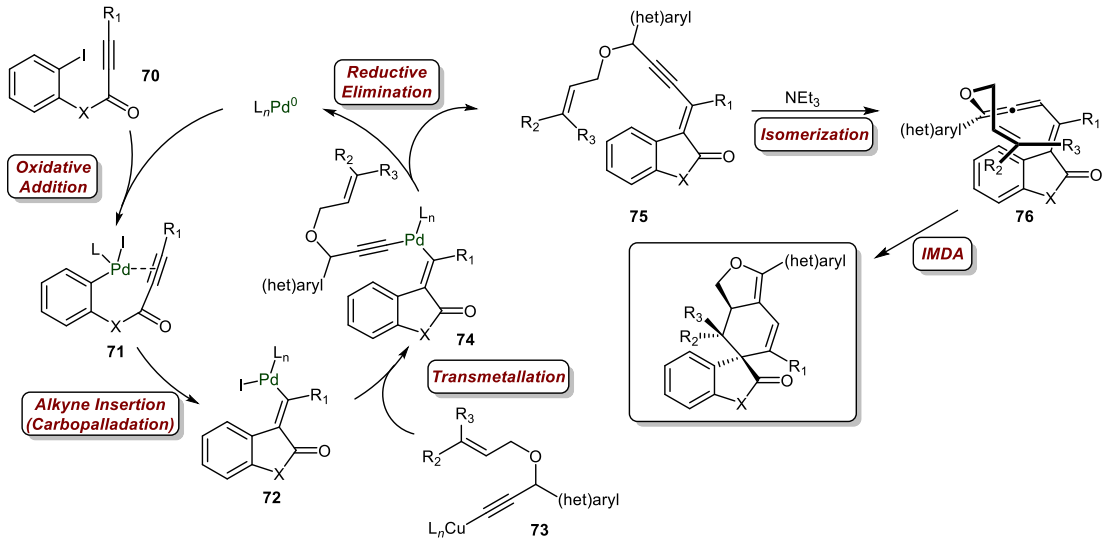
In 2005, Mueller and co-workers, developed a methodology involving a domino insertion/coupling/isomerization/DA reaction for the preparation of spirocycles (Scheme 24).[52]



Scheme 24: Domino insertion/coupling/isomerization/Diels-Alder reaction for flourescent spirocycle synthesis.

This impressive reaction generates four new bonds, three new rings and three contiguous stereocenters (two of which are quaternary centers). In addition, the reaction tolerates a variety of functional groups with yields being moderate in most cases.

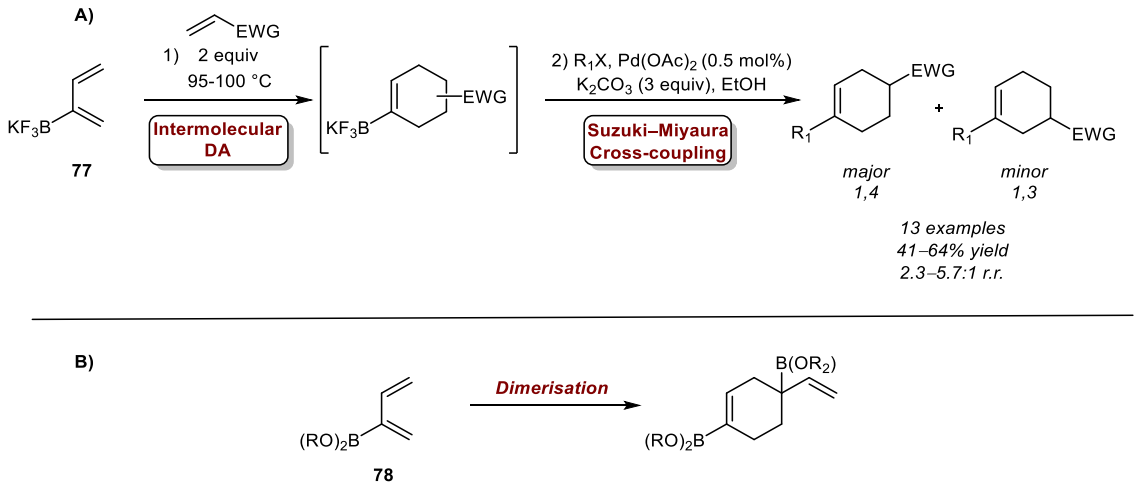
This domino sequence commences with the oxidation addition of aryl halide **70** to afford intermediate **71** (Scheme 25), which then coordinates and inserts the tethered triple bond through *syn*-carbopalladation to give species **72**. The copper acetylide **73** generated *in situ* then enters the cycle *via* transmetallation, forming Pd complex **74**. This saturated Pd complex then readily undergoes reductive elimination, ejecting compound **75** and regenerating the active catalyst. The vinylpropargyl ether then undergoes base-induced isomerization, yielding the electron-poor enallene dienophile **76**, for the subsequent IMDA cycloaddition, which was deduced to proceed *via* the *anti-exo* transition state (TS).



Scheme 25: Proposed mechanism of authors domino sequence.

1.6.4. Suzuki Cross-Coupling Examples

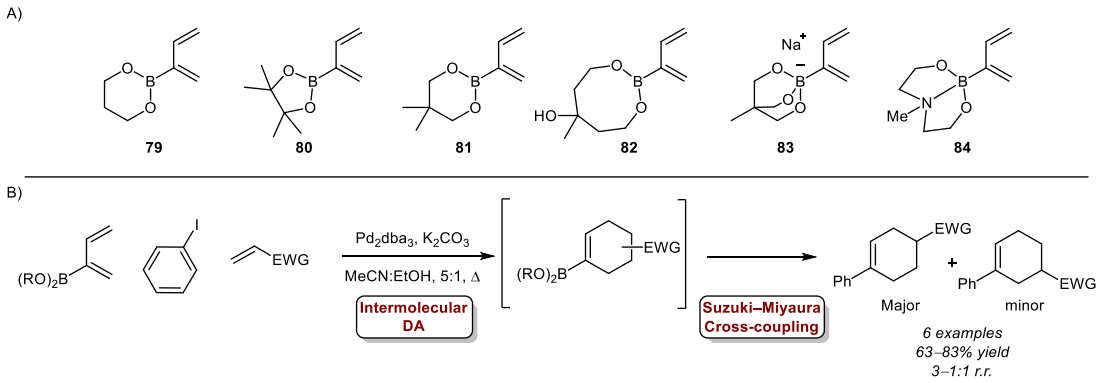
Welker and co-workers published a series of tandem DACC reactions involving different types of borylated diene motifs.[53,54] The first of these examples involved the use of 2-BF_3K-substituted 1,3-dienes **77** (Scheme 26A). Their goal was to tackle the major issue concerning the instability and ease of dimerization or homo-DA (even at room temperature) of 1,3-dienyl-2-boronates **78** (Scheme 26B),[55] and to provide an alternative route towards these useful precursors for synthetic chemists.



Scheme 26: A) Tandem DACC reaction employing 2-BF_3K-substituted 1,3-dienes. B) Dimerization issue.

The choice of using organotrifluoroboronates was based on their stability in air as well as ease of purification.[56] After isolating and studying these diene moieties, it was found that they do not undergo dimerisation, confirming them as ideal precursors. Subsequently the authors tested them in the tandem reaction, finding that the reaction tolerated phenyl halides bearing either EDG or EWG as the cross-coupling partner, giving moderate yields. In addition, the yields were typically higher when employing acrylate instead of methyl vinyl ketone (MVK) as the dienophile. Furthermore, the 1,4-regioisomer was always predominantly formed with ranges varying between 2.3–5.7:1. The reaction was also carried out in a microwave reactor with the timescale being considerably lowered, whilst maintaining similar levels of yields and selectivity.

In a follow-up publication in 2012,[54] Welker reported the synthesis of a range of different borylated dienes, bearing diol or triol ligands, and investigated their relative reactivity in a tandem DA/cross-coupling reaction (Scheme 27A&B). This research was performed in order to tackle the problem associated with the 2-BF_3K-substituted 1,3-dienes poor solubility. To ascertain first of all whether these were suitable starting materials, they carried out a dimerization (or homo-DA) test, whereby the reagents were refluxed in toluene and the amount of starting material recovered was profiled. Satisfyingly, only trace amounts of dimerization were observed, even after 24 h, enabling the authors to test their reactivity in the proposed tandem reaction.



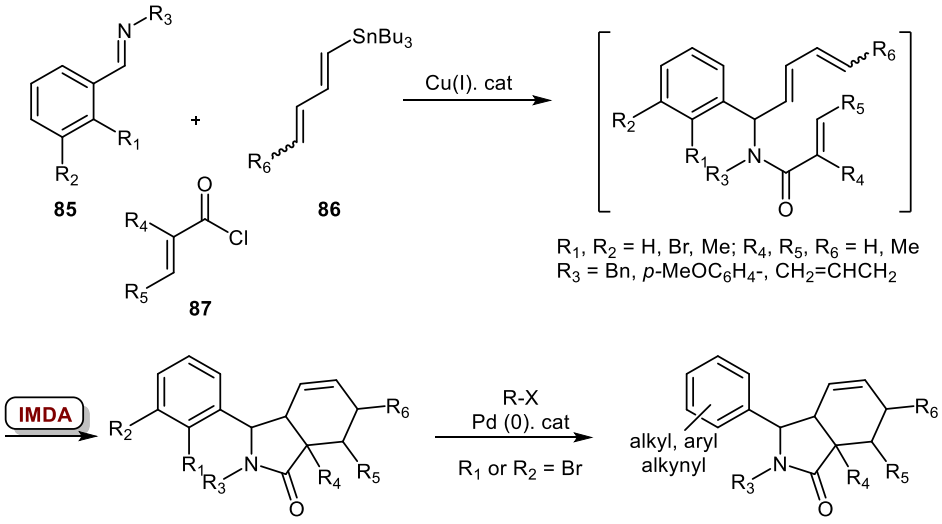
Scheme 27: A) Structures of borylated diene derivatives investigated. B) Tandem DACC reaction involving borylated dienes.

In their investigation it was found that out of the six new borylated diene reagents synthesized, four were compatible in the tandem reaction (**79**, **81**, **82** and **83**). Given

the discrepancies in reactivity between the different borylated diene species, they decided to investigate the matter further through mechanistic analysis. After conducting their NMR experiments they came to the conclusion that in the overall process the DA reaction was being catalysed by a Pd(II) species, because when dienes **79**, **81** and **82** were treated with Pd(0) under the same reaction conditions, no formation of the corresponding cycloadducts were observed. The yields in most examples were good, and the regioselectivities were fairly consistent favouring the 1,4-regioisomer. Similarly to Welker's previous methodology, this sequence also leads to the formation of three new bonds.

1.6.5. Copper-catalysed Example

Malinakova's group reported a copper-catalysed multicomponent cascade process involving imines **85**, dienylstannanes **86**, and acryloyl chlorides **87** to generate isoindolones (Scheme 28).[57] This reaction sequence allows for the formation of densely functionalized compounds, bearing up to four new stereocentres. A diverse range of substitution patterns was possible based on the large selection of building blocks to choose from.



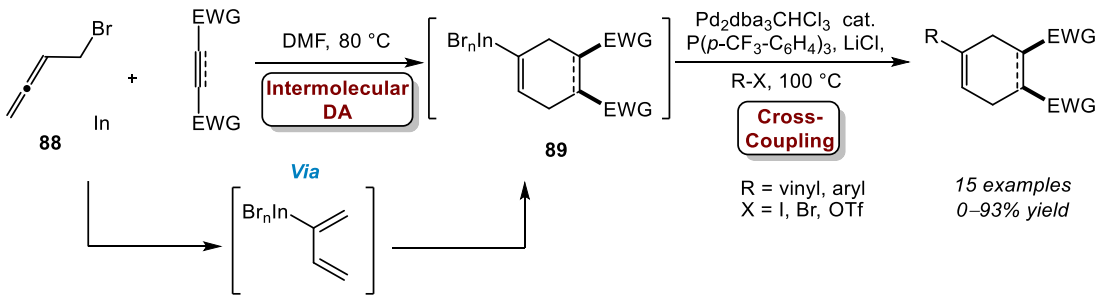
Scheme 28: Copper-catalysed multicomponent cascade process for the synthesis of hexahydro-1*H*-isoindolones.

Initially the authors sought to use Pd as the catalyst to facilitate the multicomponent coupling reaction from the amide intermediate;[58] however, low yields

were obtained. Switching the metal source to copper proved incisive, with significantly improved yields being obtained (from 20 to >70% respectively). Moving forward with the cascade process, they found the DA reaction to be relatively facile. The yields could be increased by using an excess of dienylstannane, as it was proposed the rate determining step was the transmetallation event between tin and copper. During the substrate scope exploration, a notable observation was made, namely a bromine substituent could be carried through the reaction sequence unperturbed, and be used subsequently in a series of cross-coupling reactions in post-synthetic modifications. More importantly the reaction is relatively atom economical, bar the stannane, all starting materials are incorporated into the product.

1.6.6. Additional Examples

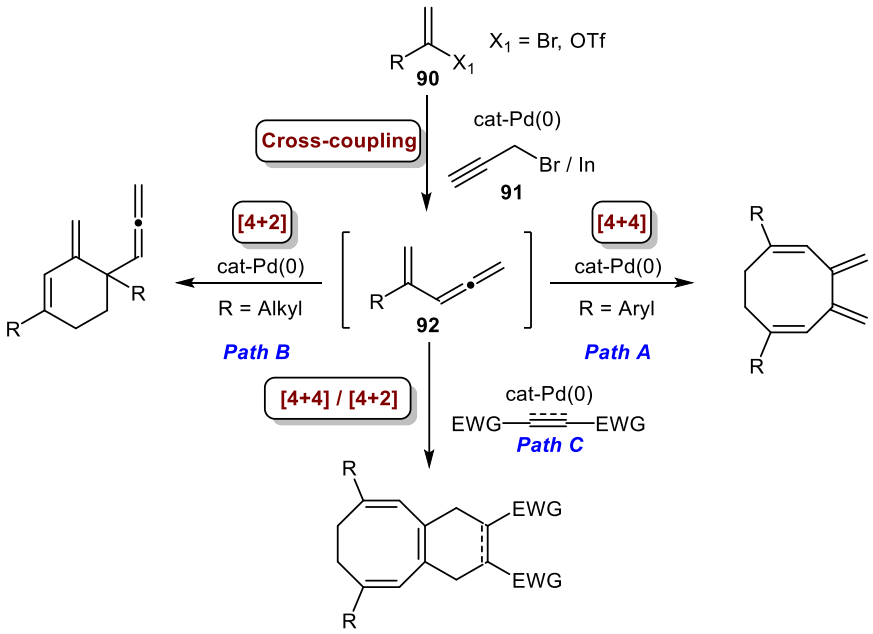
In 2010, Lee and co-workers reported a Diels-Alder/cross-coupling (DACC), reaction involving the usage of organoindium reagents (Scheme 29).[59]



Scheme 29: Tandem DACC reaction involving indium.

Here the reactive diene species is generated *in situ* by reacting allene compound **88** with indium first through a rearrangemet, which subsequently undergoes the DA reaction with a designated dienophile. This one-pot reaction was made feasible after detecting the DA adduct **89** formed *in situ*, still possessed the indium functional handle. The scope that was explored after obtaining optimized conditions was extensive, with a range of electrophiles and dienophiles being tolerated in the reaction, providing moderate to good yields for this tandem process. It should be noted that the majority of dienophiles applied in the scope were symmetrical. In spite of this, the methodology enables quick access to carbocyclic frameworks, with three new bonds being formed and up to two new stereocenters.

Kang and co-workers reported a complex methodology involving a tandem Pd-catalysed cross-coupling/cycloaddition reaction for the rapid synthesis of different sized carbocycles, as well as fused ring structures.[60] This tandem reaction commences *via* a Pd-catalysed cross-coupling reaction between the electrophilic reactant **90** and an allenylindium species **91** generated *in situ*. The resulting intermediate **92** could then go down various reaction pathways depending on the choice of reactant selected (Scheme 30). When α-bromovinyl arenes were employed, the reaction proceeded *via* a [4+4] cycloaddition producing 8-membered rings (**Path A**). Interestingly when the same reaction conditions were applied to α-bromovinyl alkanes, products resulting from a cross-coupling/[4+2] cycloaddition were obtained (**Path B**). Spurred on by these results they probed the limits of the reaction to find that five components could be assembled *via* a tandem cross-coupling/[4+4] cycloaddition/[4+2] cycloaddition (**Path C**).



Scheme 30: MSRs involving cross-coupling/[4+2], cross-coupling/[4+4] and cross-coupling/[4+4]/[4+2] examples.

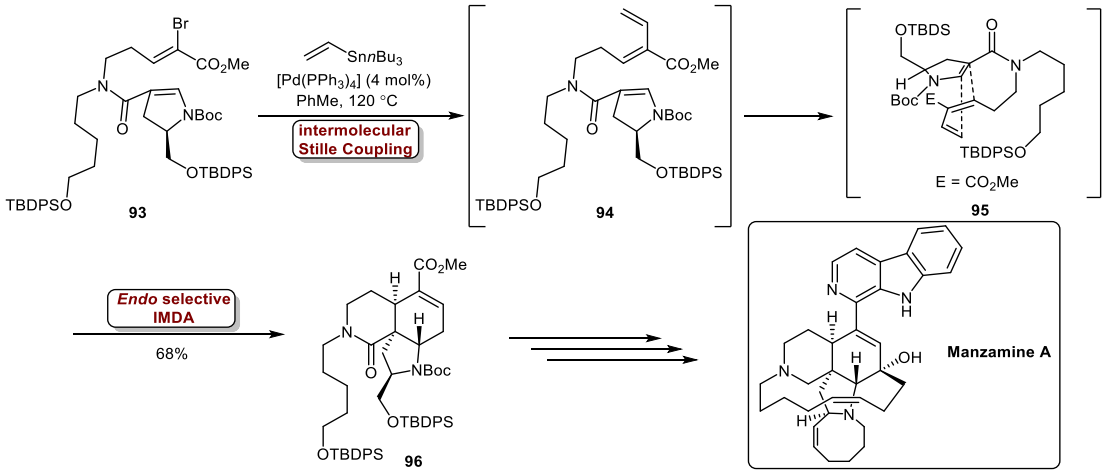
This MSR generates bicyclo[6.4.0]dodecene derivatives rapidly and efficiently with a variety of dienophiles being tolerated and in excellent yields. Unfortunately, examples involving dienophiles such as imines did not perform the corresponding [4+2] cycloaddition. During this MSR, in the case of the formation of the

Bicyclo[6.4.0]dodecene derivatives, four new bonds, two rings and in some cases up to two new stereocenters are formed.

1.7. CCDA Reactions in Total Synthesis

1.7.1. Stille Cross-Coupling Examples

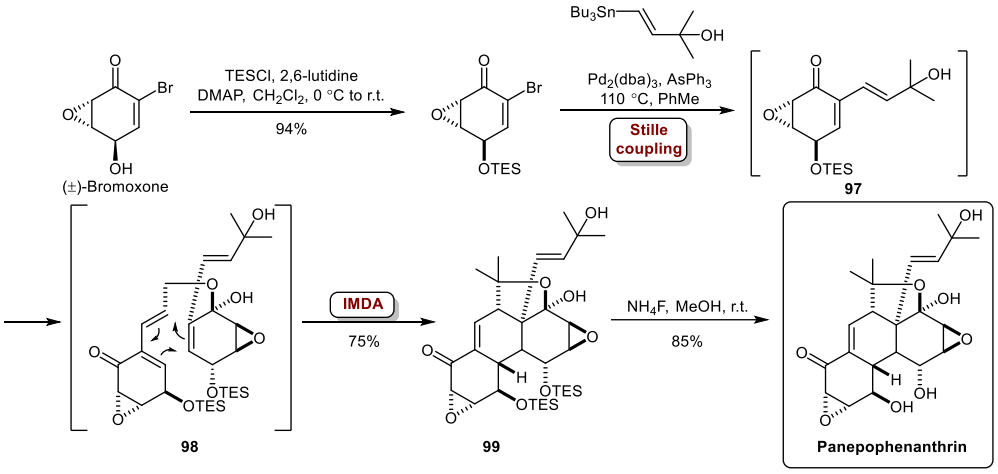
The Stille coupling reaction was found to be ideal in the formation of intermediates that can undergo a subsequent intramolecular reaction, given its robust nature. The first example was demonstrated by Martin and co-workers, in the total synthesis of manzamine A,[61] a marine sponge-derived alkaloid which exhibits antitumor properties (Scheme 31).[62]



Scheme 31: Total synthesis of manzamine A by Martin.

This domino reaction is initiated by a Pd-catalysed Stille cross-coupling reaction between the vinyl halide **93** and the vinyl organotin reagent, to generate the corresponding reactive diene moiety **94** *in situ*. This species then undergoes an *endo*-intramolecular DA reaction with the pendant dienophile *via* TS **95** to furnish the complex architectural tricyclic core **96** as a single diastereomer. Overall during this cascade reaction three new carbon bonds are formed as well as three new stereocenters, all of which having been formed stereoselectively based on the fixed stereocentre established in the starting material.

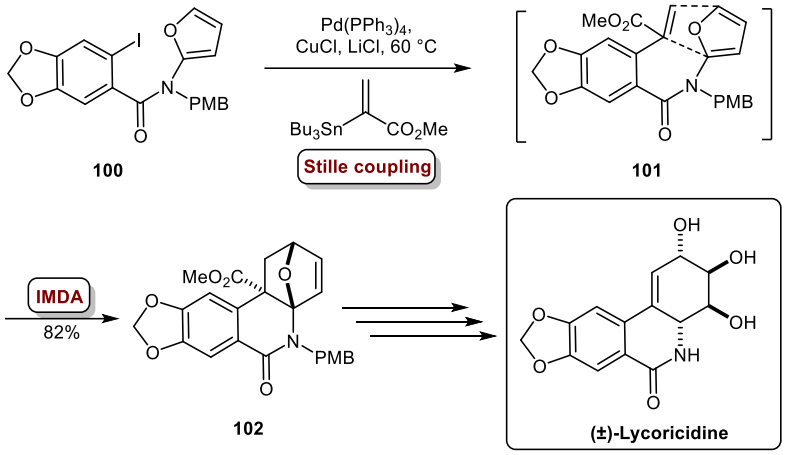
An additional example involving a Stille cross-coupling/DA tandem reaction was reported by Adlington and co-workers, in the racemic total synthesis of the dimer panepophenanthrin.[63] Incredibly, this challenging looking molecule bearing a densely funtionalized tetracyclic core was fashioned in only three steps from (±)-bromoxone (Scheme 32).



Scheme 32: Total synthesis of panepophenanthrin by Adlington.

During the tandem reaction a diene moiety **97** is formed *in situ* post cross-coupling reaction. This then reacts with an additional equivalent of itself *via* the formation of the hemiacetal **98**, bringing the diene/dienophile in close proximity of each other, promoting an intramolecular DA reaction to occur, which results in the formation of the tetracyclic scaffold **99**. Subsequent deprotection of the alcohols using ammonium flouride yields the natural product. Impressively, starting from a simple building block the tandem reaction generates eleven contiguous stereocenters, four new bonds, and two new rings.

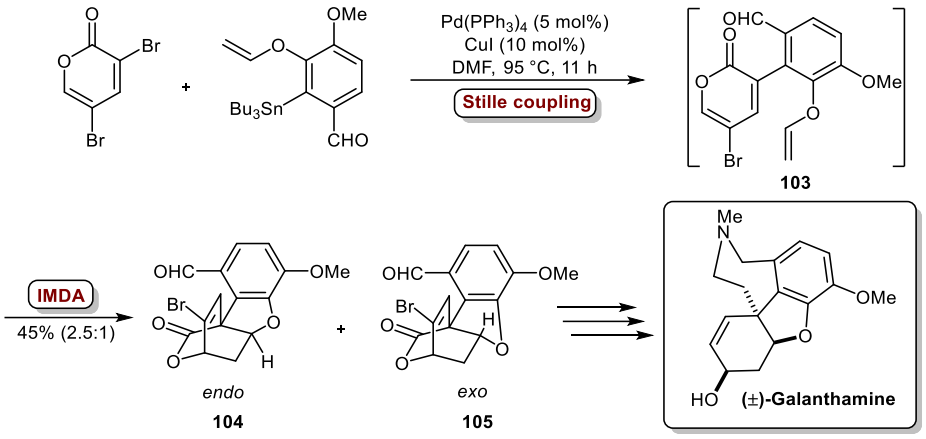
In 2006, Padwa reported the synthesis of (±)-lycoricidine, which features a cascade Stille/intramolecular DA reaction to generate the core structure (Scheme 33).[64] This novel sequence facilitates the formation of three new bonds, as well as two new rings and three new stereocenters under relatively benign conditions. This key step enabled the synthesis of the natural product to be carried out in an impressive 14 steps, with an overall yield of 12.6%.



Scheme 33: Total synthesis of (±)-lycoridine by Padwa.

During the synthesis of this natural product the DA step acts as the instigator in establishing the necessary stereochemistry for the following diasteroeselective reactions. The methyl ester on the dienophile helps to drive the DA reaction forward, by lowering the LUMO energy, as well as providing the correct functionality for a subsequent elimination step to furnish the required double bond seen in the natural product. Interestingly, having established optimized conditions for the Stille cross-coupling for aryl iodide **100**, isolation of the corresponding product **101** was not possible, with the compound undergoing spontaneous cyclisation to give DA adduct **102**.

Cho and co-workers reported the total synthesis of (±)-galanthamine in 2010,[65] which is a prescription drug used for the symptomatic treatment of senile dementia for patients with Alzheimer's disease.[66] Their synthetic route employed a tandem C3 site selective Stille/IMDA reaction as the key synthetic step (Scheme 34).

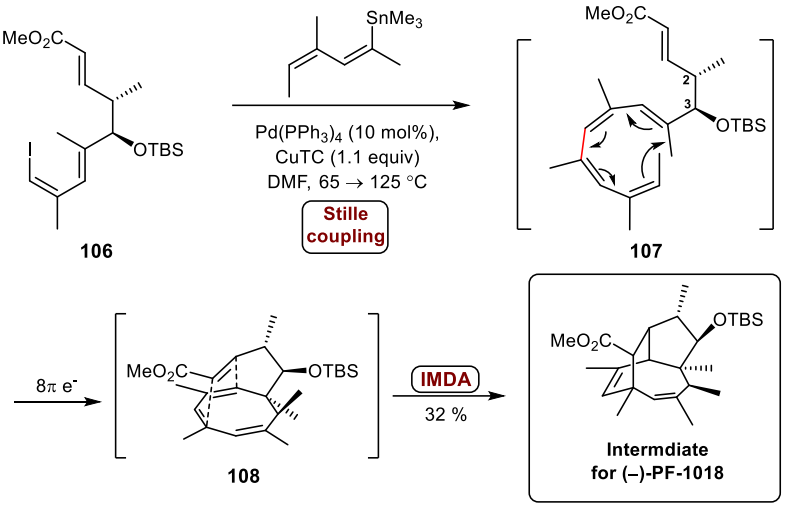


Scheme 34: Racemic total synthesis of (±) galanthamine by Cho.

During the investigation of the reaction, the authors anticipated that the intermediate **103** resulting from the Stille coupling could be isolated. However, serendipitously only the mixture of DA adducts (**104** & **105**) were obtained as a result of the reaction. When carrying out optimization studies, they found that the cascade is sensitive to the choice of solvent, temperature, and Cu co-catalyst, but not the Pd source. Furthermore, the reaction was found to be temperature sensitive, with lower temperatures promoting side product formation, and higher temperatures (110 °C) causing product degradation.

Another example was reported by Trauner's group, in their assembly of the core structure for (–)-PF-1018, a tricyclic insecticide (Scheme 35).[67] Their inspiration came from the proposed biosynthetic pathway, which proceeds *via* an abnormal DA reaction as the last step. The cascade event is triggered by a Stille cross-coupling reaction between **106** and the diene tin reagent, to produce the highly conjugated tetraene **107**. This then undergoes an 8π-electrocyclisation, forming **108**, despite the 6π-electrocyclisation normally being observed in the case of monocyclic cyclo-octatrienes.[68] With all the functionality in place, the molecule orientates itself to undergo the sequential IMDA reaction, producing the tricyclic intermediate required for the natural product in 32% yield as a single diastereomer. The authors stipulated that the stereochem of the methyl group on C2 is the defining factor behind the observed facial selectivity, and that bulky substituents on C3 help to promote DA

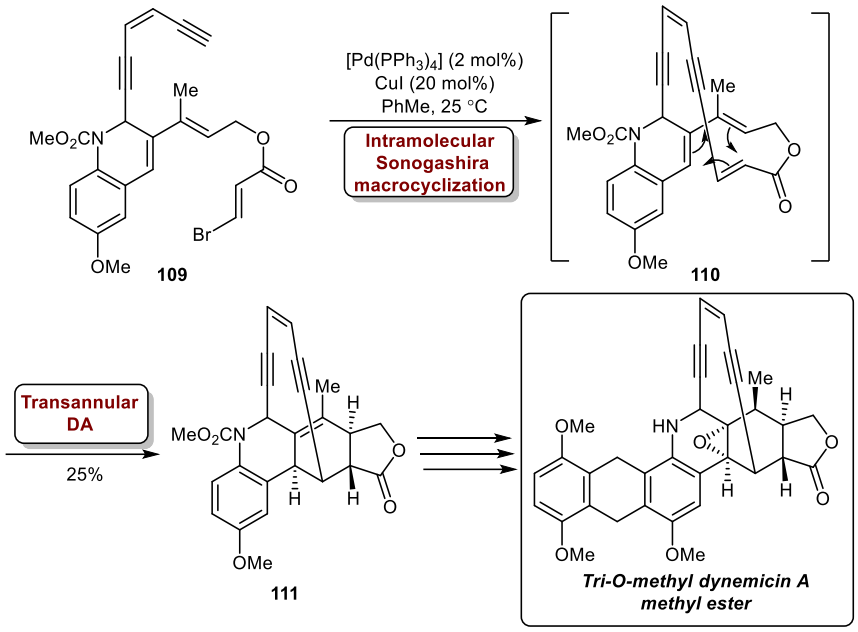
reactivity over undesired 6π-electrocyclisation. During the formation of the tricyclic core architecture, three new bonds, three rings, and eight stereocentres are formed.



Scheme 35: Trauner's cascade approach to PF-1018.

1.7.2. Sonogashira Cross-Coupling Example

Schreiber and co-workers reported a route for the total synthesis of dynemicin A,[69] a potent cytotoxin,[70] employing a Sonogashira coupling reaction to form the species required for sequential transannular DA reaction (Scheme 36).



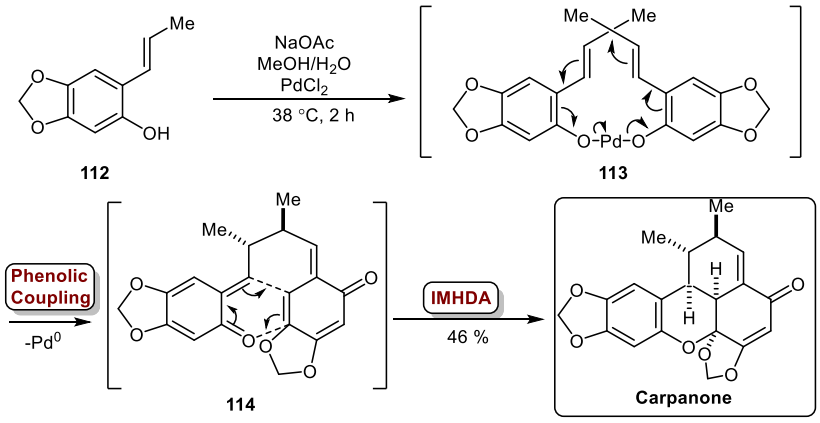
Scheme 36: Total synthesis tri-*O*-methyl dynemicin A methyl ester using a cascade Sonogashira/transannular DA reaction.

This was a serendipitous discovery as initially their intent was to generate and isolate the macrocyclic intermediate **110**; however, after the intramolecular coupling reaction of **109** finished the subsequent transannular DA reaction was observed, yielding the key fragment intermediate **111**,which could be further elaborated to form the natural product. In this example, the pentacylic intermediate was generated as a single stereoisomer. During this elegant synthetic manipulation, four bonds, three rings, and four new contiguous stereocenters are formed. Additionally, coupled with the significant increase in molecular complexity, the short (2 h) and benign (25 °C) reaction conditions make this transformation all the more impressive.

1.7.3. Phenolic Coupling Example

One of the earliest examples involving a CC type DA in a total synthesis was reported in 1971 by Chapman and co-workers, for the synthesis of Carpanone.[71] A Pd-catalysed phenolic dimerization acts as the key step of its synthesis (Scheme 37). The intermediate **113** resulting from the dimerization event of **112** was found to be short lived, with it undergoing a phenolic coupling first forming **114,** prior to being involved in an intramolecular hetero-DA reaction with the dienophile in close proximity. The cascade generates carpanone stereoselectively and in moderate yield (46%).

Impressively, in a single transformation; three bonds, two rings, and five contiguous stereocenters were formed as a result of this cascade.



Scheme 37: Total syntheis of carpanone by Chapman.

2. Chapter 2: A cascade Suzuki–Miyaura/Diels–Alder protocol: exploring the bifunctional utility of vinyl Bpin

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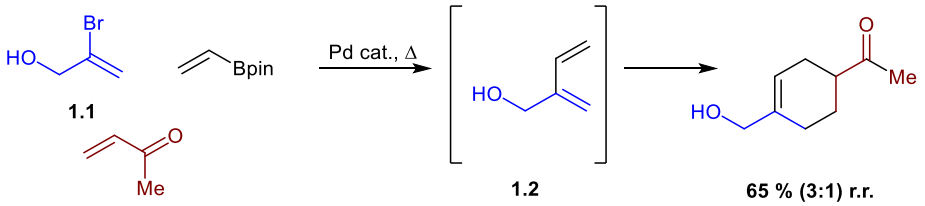
This chapter is based upon the following publication: Synlett 2019; 30(07): 787-791.[72]

Numbered compounds in Chapter 2 will be based on the following nomenclature:

Dibromo or earlier compounds	1S or 1S' respectively and so on
Vinyl halides/triflates	**1a, 2a, 3a,** *etc*
Dienes	**1b**, **2b**, **3b**, *etc*
Bpin DA adduct	**1c**, **2c**, **3c**, *etc*
Alcohol DA adducts	**1d**, **2d**, **3d**, *etc*

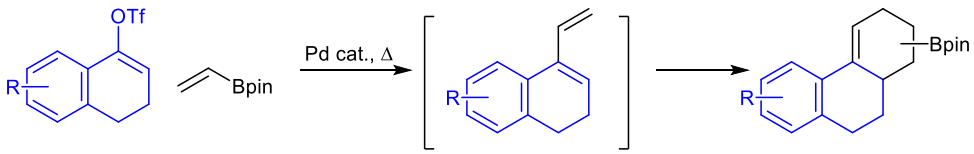
2.1. Previous work

Recent work in the Watson research group led to the successful development of a cascade Suzuki-Miyaura/Diels-Alder (SM/DA) reaction for the rapid construction of complex frameworks (Scheme 38).[73] The cascade reaction is initiated by a SM cross-coupling reaction between vinyl halide **1.1** and vinyl Bpin to generate the diene intermediate **1.2** in-situ, which then undergoes a trapping cycloaddition reaction with excess MVK, leading to the formation of a cyclic system with moderate regioselectivity. This methodology offers quick access to potentially biologically active steroid like compounds when suitable precursors and dienophiles are employed, such as *N*-Phenylmaleimide.



Scheme 38: SM/DA cascade reaction employing reactive dienophiles.

During the optimisation of the cascade reaction, a side reaction was observed leading to the formation of a minor by-product (Scheme 39). Instead of MVK acting as the dienophile during the DA step, another equivalent of vinyl Bpin reacted with the diene intermediate in its place, resulting in the formation of a carbocyclic framework bearing a Bpin moiety.

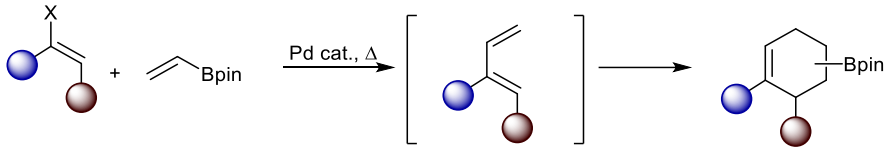


Scheme 39: By-product formed during the SM/DA cascade reaction.

2.2. Proposed work

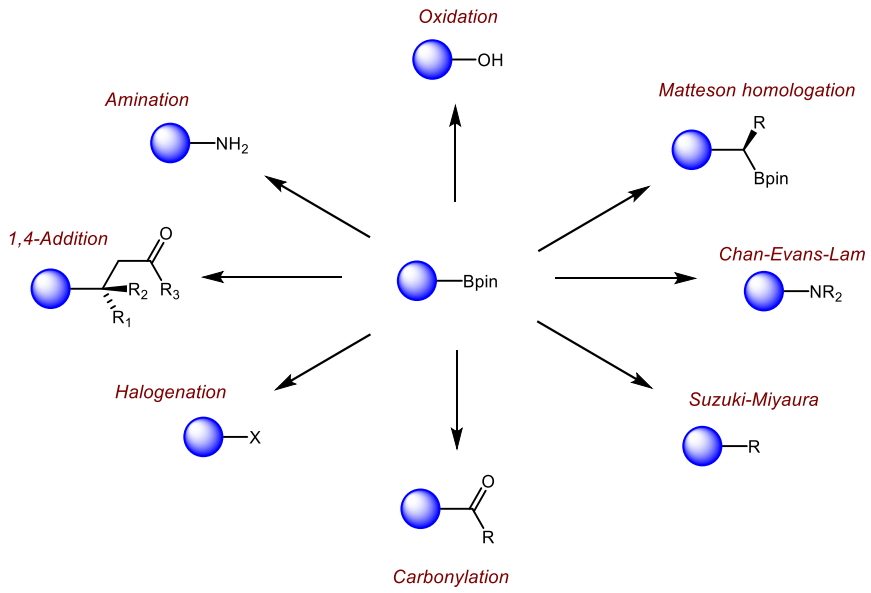
This serendipitous discovery lead to further efforts being invested into developing this cascade reaction. The bifunctional vinyl Bpin reagent has two distinct

roles in the cascade reaction; it acts as both an organoboron nucleophile for cross-coupling and as a DA dienophile. As such, a minimum of two equivalents of vinyl Bpin would be required to facilitate this cascade transformation. Merging these two reactions enables a rapid and operationally simple synthesis of functionalised borylated carbocycles (Scheme 40).



Scheme 40: Cascade SM/DA reaction

It was recognised that the DA step would be the most challenging step to optimise, given the comparatively less reactive nature of vinyl Bpin as a dienophile compared to MVK or maleic anhydride used in the previous work.[73] Taking inspiration from Welker's work,[53,54] it was envisaged that increasing the temperature could aid in overcoming this reactivity barrier and achieve the desired outcome. The fact that the methodology constructs boron bearing carbocyclic scaffolds, it permits further functionalisation to be performed at the boron functional handle, providing an additional dimension to the methodology's application (Scheme 41).[74]



Scheme 41: Potential post synthetic modifications that could be performed on the Bpin species.

2.3. Results and Discussion

2.3.1. Starting material synthesis

The cascade protocol is initiated by a SM cross-coupling reaction. Therefore, a suitable halide or pseudo-halide starting material is required to explore the transformation. It is well known that the order of reactivity going down the halogen series (Cl-, Br-, I-) increases in the SM protocol, due to the increasing rate of oxidative addition.[75] Triflates (OTf-) are typically more reactive than chloride derived substrates; however, there are numerous examples where this is proven otherwise, through changes in ligand, catalytic system, solvent medium *etc*.[76,77] The following investigations were carried out on two types of starting material motifs: 1) the tetralone-like system (**1a-7a**) and 2) the α-bromo styrene system (**8a-17a**) (Figure 11).

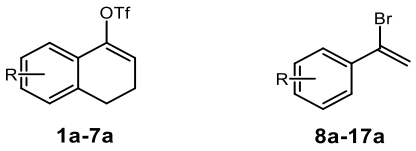


Figure 11: Systems involved during SM/DA study.

Due to the different levels of reactivity these two types of motifs exhibited in the cascade reaction, a subtle change in optimised conditions between the pair of systems will be highlighted during the optimisation discussion (Section 2.3.3.).

It was proposed that triflate **1a** would be an ideal candidate to commence the initial optimisation studies on the tetralone moieties; given its highly reactive nature and ease of accessibility (Figure 12). Furthermore, the diene generated as a result of the initial SM cross-coupling is the reactive Dane's diene (**1b**),[78] a well-known precursor for exploring DA reactivity.[79,80]

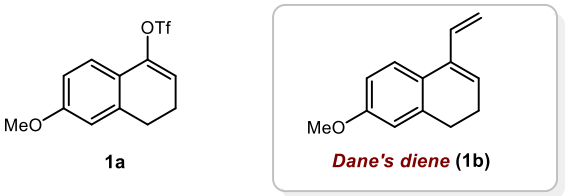
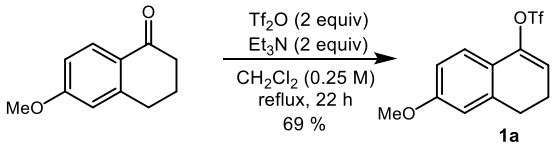


Figure 12: Starting material of choice to begin optimisation studies and Dane's diene structure.

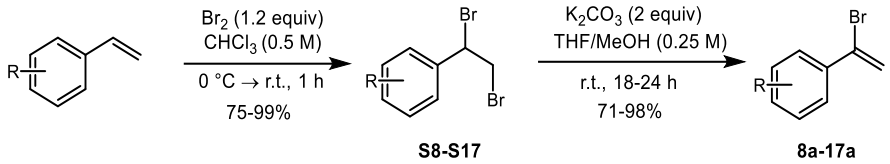
This diene's reactivity for the DA stage stems from the methoxy group present in the molecule. The electron donating nature of this substituent causes an increase in its reactivity through conjugation, as the oxygen is able to contribute its lone-pair *via* delocalisation into the extended π-system. Gaining access to the necessary precursor **1a** was straightforward by reacting 6-methoxytetralone with triflic anhydride under mildly basic conditions (Scheme 42).



Scheme 42: Enol triflate formation from corresponding tetralone.

Substrate **1a** is relatively stable and only reverts back to the starting ketone upon exposure to significant amounts of water. Exposure to silica during column chromatography also caused partial hydrolysis of this compound. In order to avoid further degradation of the product, large quantities were synthesised and stored at 4 °C.

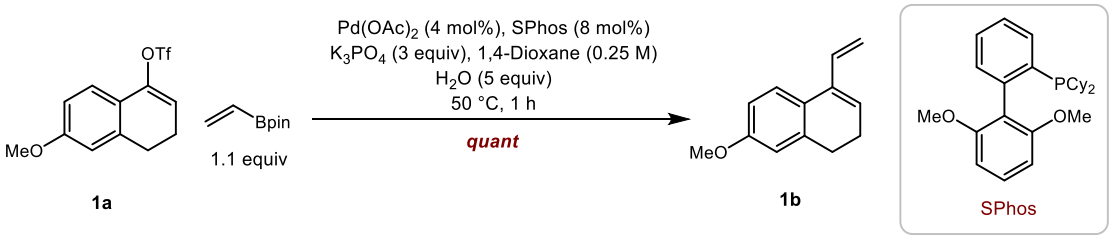
The styrenyl vinyl halides were synthesised *via* a simple two-step process from the corresponding styrene (Scheme 43). The first step involves electrophilic bromination of the alkene to afford the di-brominated species (**S8-S17**). This was then exposed to potassium carbonate in a mixed solvent medium, forming the reactive α-bromo-styrene starting materials (**8a-17a**) *via* an E2 elimination. As no undesired β-bromo styrene was observed an E1 elimination mechanism can be discounted. The exclusive formation of the desired α-bromo styrene vs β-bromo styrene is due to the substantially more acidic benzylic proton being deprotonated. Both steps typically produced the resulting product in good yields as well as high purity, avoiding the need to expose these to silica chromatography, which proved beneficial, particularly when handling the reactive α-bromo styrenes precursors.



Scheme 43: General scheme for the formation of α-bromo styrene starting materials.

2.3.2. Cascade reaction

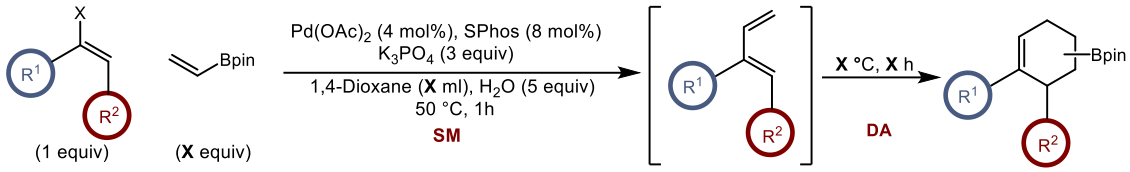
Having identified a route for forming the requisite starting materials to probe the cascade process, investigations into the DA step of this protocol were explored. In the initial optimised SM cross coupling reaction, our group identified that $Pd(OAc)_2$ and SPhos (Scheme 44) were a suitable catalyst and ligand combination for this C-C bond forming step. The ligand helps to facilitate the SM through its electronic and steric properties.[81] Firstly, aryl methoxy groups, in combination with the alkyl substituents, form an electron-rich phosphine, which can help promote the rate of oxidative addition by increasing the electron density at the palladium centre. Secondly, the bulky nature of the cyclohexyl substituents enhances the rate of reductive elimination in the catalytic cycle. A SM cross-coupling example involving the formation of a diene using this catalytic system has been provided (Scheme 44).



Scheme 44: SM reaction to form diene species.

As the SM stage of the cascade reaction has been optimised (Scheme 44),[73] it mitigated any further investigations into alterations for; the catalyst, ligand loading, water content, solvent medium, as well as base equivalents for the overall cascade reaction. 1,4-Dioxane was identified as an ideal solvent medium as it not only worked well for the SM step, but its high boiling point would prove beneficial in the optimisation of the DA stage. As a result, it left the following parameters; temperature, reaction time, concentration of reaction mixture and the equivalents of vinyl Bpin as

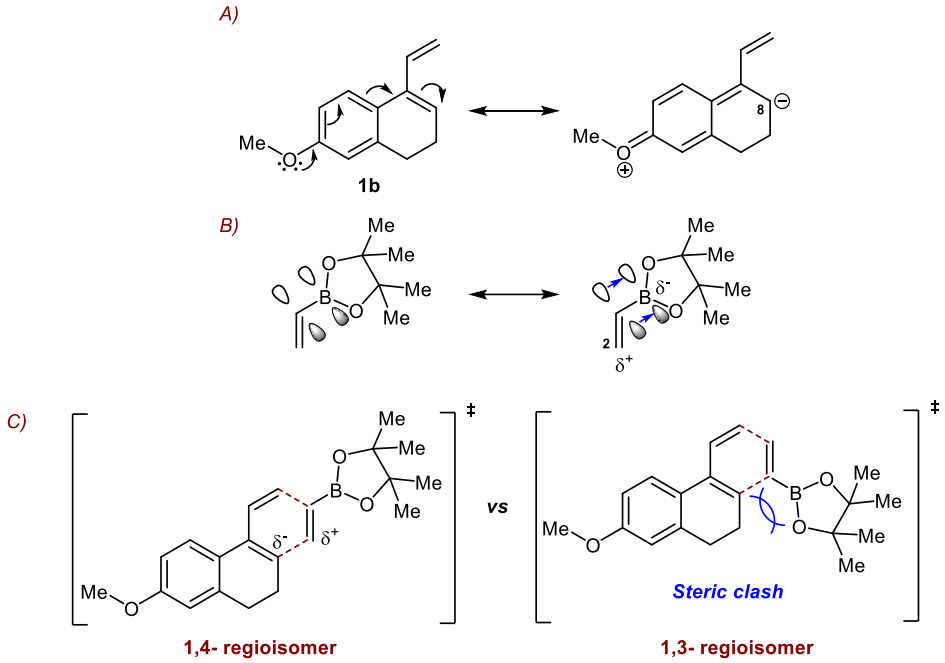
changes that could be made to optimise the DA step of the cascade reaction (Scheme 45).



Scheme 45: Proposed SM/DA reaction with "X" parameters to be studied during the optimisation of the reaction.

Theoretical DA regiochemistry rational

From a theoretical standpoint it is predicted that the 1,4-regioisomer will be formed predominately for the planned substrates to be examined, based on analysis of the electronic effects, and the results Welker and co-workers observed.[54] For example, taking a closer look at the resonance structures of both the diene **1b** and vinyl Bpin (Scheme 46A), indicates the preferred orientation each component adopts on approach during the transition state. For the diene, a partial negative charge would reside on C8, increasing its δ-negative character (Scheme 46A). Whereas, for vinyl Bpin, which can be considered as a pseudo EWG due to the boron's empty p-orbital, its inductive effect causes the terminal C2 alkene carbon to have a partially positive charge (Scheme 46B). This coupled with potentially arising steric clashes, when considering the minor 1,3-regiosiomer (Scheme 46C), rationalises the predicted outcome of this DA reaction.



Scheme 46: A) Resonance structures of Dane's diene. B) Resonance structure of vinyl Bpin. C) Resulting two TS for cycloaddition.

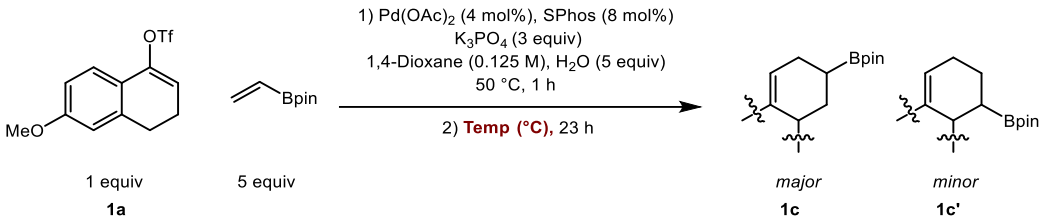
2.3.3. Optimisation

2.3.3.1. Tri-cyclic systems - Tetralones

With an understanding of the potential selectivity of the DA reaction. The first set of optimisation reactions were carried out on triflate **1a** as the benchmark system. The conversions were quantified by ^{1}H NMR through the combined integration of both alkene protons in the mixture of Bpin regioisomers measured against a known internal standard (dibenzylether with concentration 2 mL = 0.03125 mmol), which was added after the reaction mixture had been worked-up (see experimental section 2.6.1.5. and 2.6.3.1 for more information). Some degree of error has to be accounted for due to the addition of internal standard using a 2 mL syringe. The study commenced with looking into the temperature dependence of the reaction (Table 1). It is clear to see that with increasing temperature, higher conversions to the desired product **1c** were observed, with 150 °C giving the highest conversion, which was taking forward as part of the optimised conditions. This is unsurprising, as DA reactions typically require high temperatures to go to completion, particularly without the presence of a LA for example to lower the activation barrier, *i.e.*, the energy gap between the HOMO-

LUMO orbitals.[82] More interestingly, these early results already indicated a considerable preference for the formation of the 1,4-regioisomer (3:1), corroborating the theoretical discussion (*vida supra*), which was further supported by 2D NMR analysis of isolated material (see experimental Section 2.6.5)

Table 1: Temperature study.



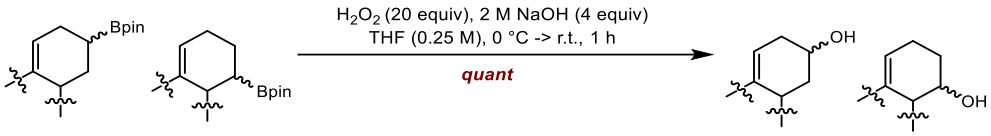
Entry	Temperature (°C)	Conversion[a] (%) (r.r.)
1	75	24 (--)
2	100	33 (--)
3	125	66 (--)
4	150	98 (3:1)
5 (0.25 M)	150	85 (3.1:1)

[a] Conversion to products determined by ^{1}H NMR analysis against a known internal standard (dibenzylether), r.r. = regiomeric ratio, determined after oxidation. (--) = unable to be determined due to impurity profile, obtained from diene intermediate alkene peaks and by-product overlapping.

An increase in concentration was also trialed (Table 1, Entry 5), which provided a slightly lower conversion, hence 0.125M was carried forward as part of the optimised conditions.

Validating these conversions values through isolation was a substantial challenge. The DA adducts bearing the Bpin functional handles were unstable on silica, readily undergoing protodeboronation. In addition, separation of the regioisomers was extremely difficult, with regioisomers consistently co-eluting during column chromatography. Furthermore, residual amounts of SPhos ligand co-eluted during isolation attempts of these compounds. In order to circumvent these isolation difficulties and corroborate regiomeric distribution of optimisation entries (seen in Table 1, Entry 4); the oxidation of the Bpin to the corresponding

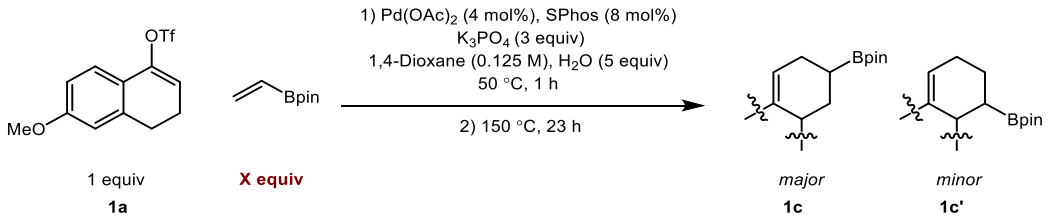
alcohol using Brown's conditions, was implemented as a separate step after the cascade reaction to obtain spectroscopically pure compounds (Scheme 47). This particular method to oxidise boron species has been known since 1959.[83] In must be noted, that attempts at obtaining regiomeric ratios prior to the oxidation step were made, however, the definitive alkene peaks were not resolved enough for accurate reporting – something which the separate oxidation step also aided with. Despite the additional oxidation step, the yields as a result of the cascade reaction remained unperturbed (Scheme 47).



Scheme 47: Oxidation of Bpin to alcohol using Brown's conditions.

The effects of varying the amount of vinyl Bpin equivalents (Table 2) was pursued to deduce the lowest amount that can be employed in the cascade process. Although the cascade reaction could be carried out with a minimum of two equivalents of vinyl Bpin (Table 2, Entry 1), reductions in vinyl Bpin loading resulted in lower conversions (Entries 1 and 2 vs Entry 3). This can be explained by organoboron degradation. Alternatively it is possible that homo-DA (see Figure 13), is becoming more prevalent, as Welker's group also observed in trace amounts (refer to Scheme 27).[54]

Table 2: Vinyl Bpin study.



Entry	Vinyl Bpin (equiv)	Conversion[a] (%) (r.r.)
1	2	62 (3.1:1)
2	3	84 (3.2:1)
3	4	93 (3.2:1)
4	5	98 (3:1)

[a] Conversion to products determined by ^{1}H NMR analysis against a known internal standard (dibenzylether), r.r. = regiomeric ratio, determined after oxidation.

The proposed side homo-DA reaction mentioned above, is be the result of two diene entities engaging with each other in a [4+2] cycloaddition (Figure 13). Theoretically, this can generate a total of four different structures. Two sets of regioisomers can arise depending on which alkene (either external (**1.3** & **1.3'**) or internal (**1.4** & **1.4'**)) of the diene acts as the dienophile component. When less equivalents of vinyl Bpin were implemented in the reaction, it is possible the formation of the side homo-DA product becomes more pronounced. Its less reactive nature compared to other classic dienophiles, such as MVK, meant that a large excess of vinyl Bpin (5 equiv) was required in order to obtain high levels of conversion.

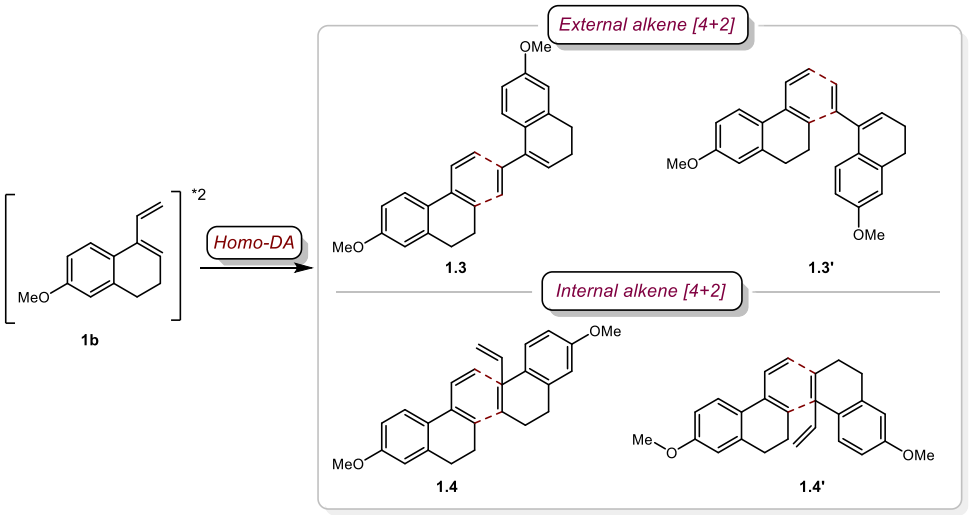
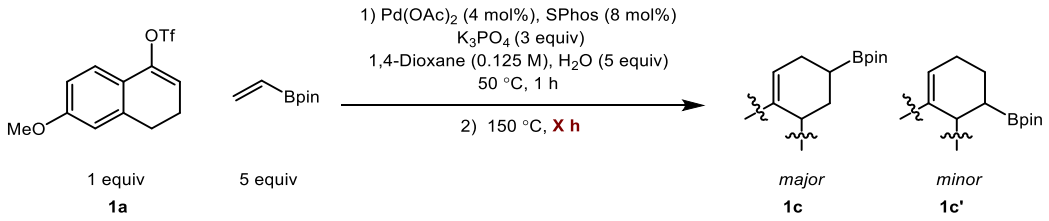


Figure 13: Proposed formation of homo-DA by-products from 1c.

A time study was performed next (Table 3), with results showing that the reaction yielded quantitative conversions after 6 h (Table 3, Entry 3). Reaction periods of less than 6 h yielded lower conversions (Entries 1 and 2). Despite this positive result,

in being able to conduct the reaction in as short as 6 h, there were reservations that these conditions would be broadly applicable to other substrates, given the nature of the reactive, electron rich, Dane's diene intermediate generated *in-situ*.

Table 3: Time study.

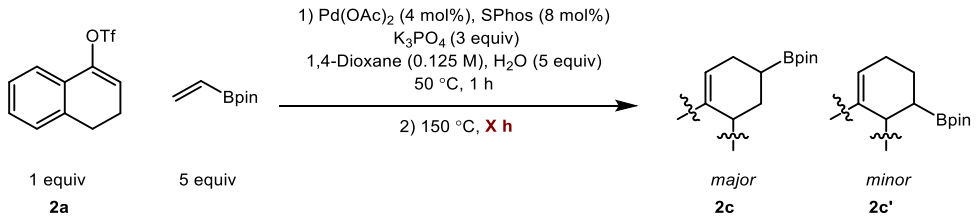


Entry	Time (h)	Conversion[a] (%) (r.r.)
1	2	64 (--)
2	4	88 (3.1:1)
3	6	99 (3.5:1)
4	23	98 (3:1)

[a] Conversion to products determined by ^{1}H NMR analysis against a known internal standard (dibenzylether), r.r. = regiomeric ratio, determined after oxidation. (--) = unable to be determined due to impurity profile, obtained from diene intermediate alkene peaks and by-product overlapping.

In order to probe this reservation, a control experiment using the des-methoxy tetralone **2a** was performed. As predicted, in this instance, after 6 h this substrate yielded a lower conversion, with similar conversion observed to the model substrate after 23 h (Table 4). Hence, as a precaution, the 23 h reaction period was carried forward as part of the optimised conditions.

Table 4: Time study (des-methoxy substrate comparison).

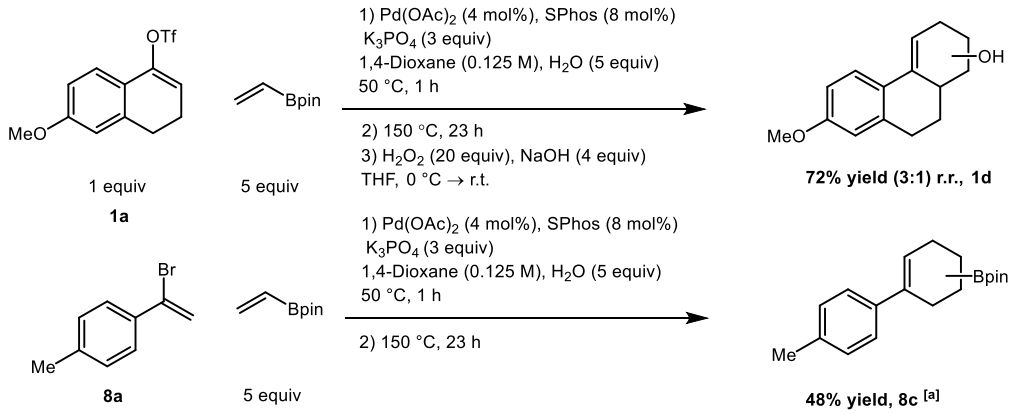


Entry	Time (h)	Conversion[a] (%) (r.r.)
1	6	88 (3.1:1)
2	23	96 (3:1.1)

[a] Conversion to products determined by ^{1}H NMR analysis against a known internal standard (dibenzylether), r.r. = regiomeric ratio.

2.3.3.2. Styrenyl systems - *α*-bromo styrenes

Initial exploration of the substrate scope for this cascade reaction was short-lived. After applying the optimised conditions on a few styrenyl substrates significantly lower yields were obtained. For example, when **8a** was exposed to the optimised conditions a reduction of more than 20% in yield was observed compared to the benchmark system (Scheme 48), when isolating **8c**. This meant the optimisation of these substrates had to be revisited.



Scheme 48: Results comparison between benchmark substrate and 8a. [a] r.r. not determined.

As discussed earlier, homo-DA was proposed to be a potential problem in this reaction, this may be even more the case when working with these styrenyl derivatives. The greater difficulty in controlling the level of side reactions for these substrates could rationalise the large drop in yield. Similar to **1b**, **8b** can also form potentially up to four different homo-DA adducts (**1.4/1.4'** & **1.5/1.5'**) (Figure 14). However, there are notable differences between the two types of systems, which may help explain the differing levels of homo-DA taking place. Firstly, the substrate the original optimisation was carried out on, yielding **1b** *in situ*, is electron-rich and thereby more reactive. Secondly, given its greater steric bulk, it rotates in space less

freely compared to the styrenyl equivalent (**8b**, Figure 14), meaning it will interact more readily with a vinyl Bpin molecule. Thirdly, the HOMO-LUMO gap is smaller in the tetralone system compared to the styrenyl one when interacting with vinyl Bpin, due to the presence of the methoxy group providing a source of electron density, increasing the negative charge character in the resonance form (Scheme 46, *vide supra*).

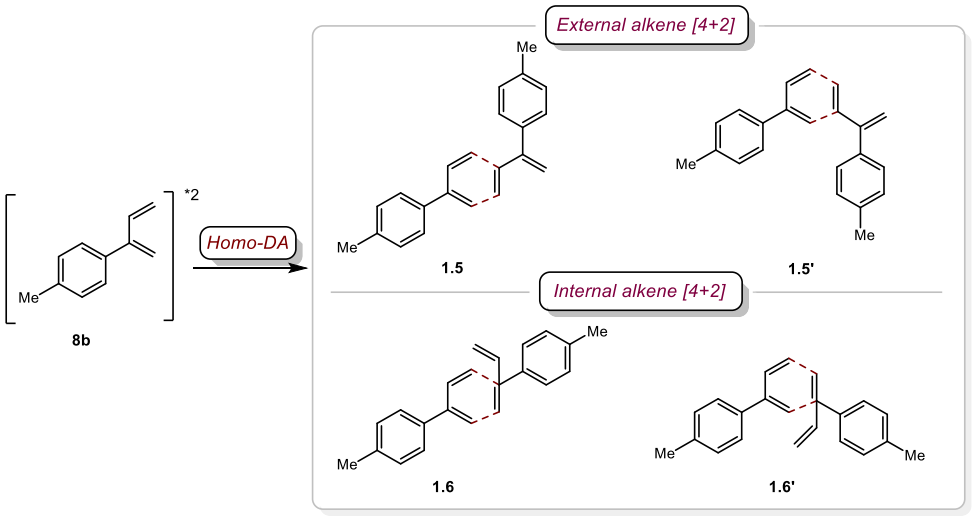


Figure 14: Proposed formation of homo-DA by-products from 8c.

An argument can also be made purely on relative size of reacting components. Looking at homo-DA TS **1.6** specifically, the dienophile's spatial size is comparable to that of a vinyl Bpin species; meaning there is little discrepancy in the transition state, reducing both the overall selectivity and the yield of the reaction (Figure 15).

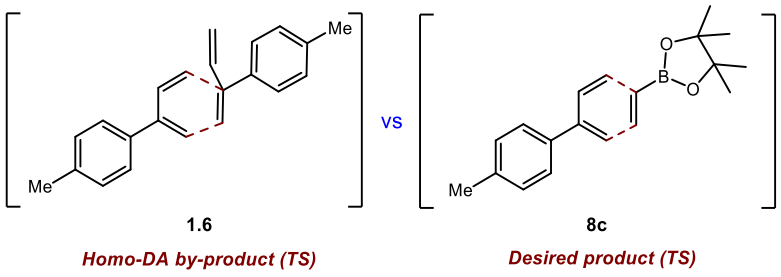


Figure 15: Competing [4+2] cycloadditions.

Furthermore, comparatively the styrenyl dienes consist of two terminal alkenes, as opposed to only one in the case of Dane's diene, where one alkene is

embedded in the six-membered ring (Figure 16). This promotes the possibility of two diene moieties engaging with one another and forming the corresponding homo-DA by-products.

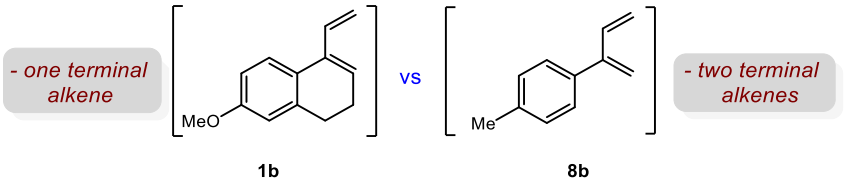


Figure 16: Difference in number of terminal alkenes.

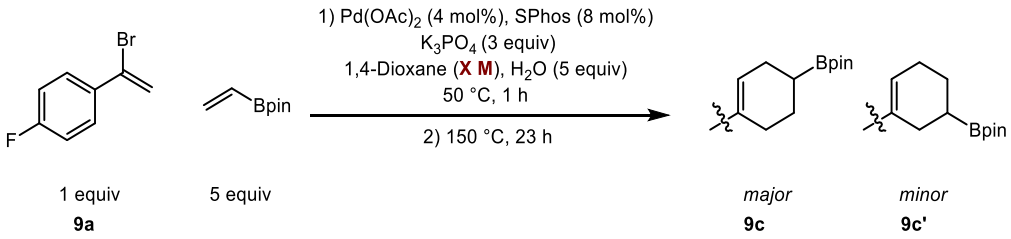
Seeking minimal change between the two sets of optimised conditions, it was envisaged that potentially increasing the amount of vinyl Bpin present within the reaction medium would suppress the formation of the by-product, by putting the stoichiometry in favour of the vinyl Bpin. Furthermore, it was reasoned equally that altering the relative concentration of the reaction mixture could aid in promoting desired product formation.

4-Methyl-α-bromo styrene (**8a**) was the chosen starting material to begin the optimisation studies for styrenyl compounds, due to the stark decrease in yield observed for this substrate compared to the benchmark tetralone substrate (refer to Scheme 48). It was hoped that potential small modifications to the conditions could increase overall conversions. However, it became apparent that the measurements of conversions, using the same internal standard as before, were inaccurate. The alkene peak of the product, used to calculate conversions, was overlapping with the alkene protons from the homo-DA by-product, meaning accurate conversions could not be reported. Alternatively, the methyl peak could have been integrated to calculate the conversion of the reaction, however, the same problem was encountered. As a result, the attention turned to ^{19}F NMR as the analysis tool for accurately measuring conversions, using 4-fluoro-α-bromo-styrene (**9a**) as the designated starting material. After having isolated and verified shift of products fluorine peaks (mixture of Bpin regioisomers), the conversions were quantified by ^{19}F NMR through the combined integration of both fluorine signals, measured against a known internal standard (triflourotoluene 30.7 µL). The internal standard was added after the reaction was

complete (see experimental sections 2.6.1.5 & 2.6.3.2. for more information). Some degree of error has to be accounted for due to the addition of internal standard using a 50 µL syringe.

Initially the effects of concentration of the reaction medium were investigated (Table 5). It was proposed that being a bimolecular system, increasing the concentration may theoretically promote the DA reaction.

Table 5: Concentration study.



Entry	Concentration (mL, M)	Conversion[a] (%) (r.r.)
1	2 mL, 0.125 M	64 (n.d.)
2	1 mL, 0.25 M	65 (n.d.)
3	0.5 mL, 0.5 M	62 (n.d.)

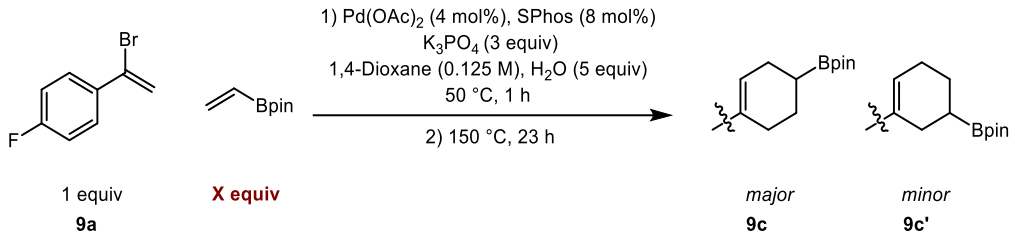
[a] Conversion to products determined by ^{19}F NMR analysis against a known internal standard (trifluorotoluene), r.r. = regiomeric ratio. n.d. = not determined.

Unfortunately, the concentration study revealed no trends. Increases or decreases in concentration levels had negligible effects on conversion. This could simply be due to the instability, as well as less reactive nature, of the diene generated *in situ*. Reactions with concentration greater than 0.5 M were not performed, as it was questionable whether all the reaction materials would be in a homogeneous solution. Hence, the concentration of 0.125 M was maintained.

The effects of increasing the vinyl Bpin content were investigated subsequently (Table 6). Pleasingly, it was found that using more equivalents in the reaction mixture caused a slight increase in conversions (Entry 1). A rise in vinyl Bpin equivalents promotes the likeliness of vinyl Bpin interacting with a diene molecule, lowering the diene's potential to react with another molecule of itself. Nevertheless,

adding even more equivalents of vinyl Bpin (Table 6, Entry 2) did not fully suppress homo-DA. Hence, it was decided to proceed with seven equivalents of vinyl Bpin as the optimised conditions for this set of compounds.

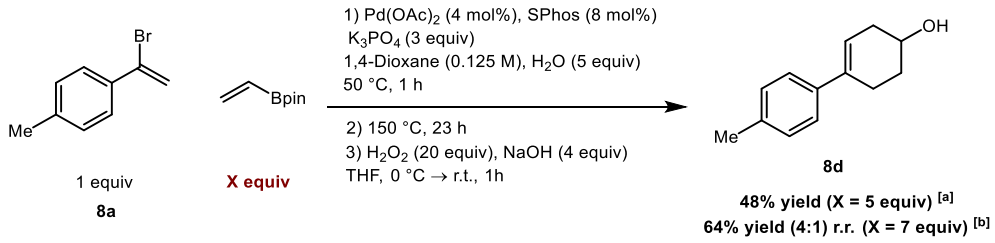
Table 6: Vinyl Bpin study.



Entry	Vinyl Bpin (equiv)	Conversion (%) (r.r.)
1	5	64 (n.d.)
2	7	71 (n.d.)
3	9	73 (n.d.)

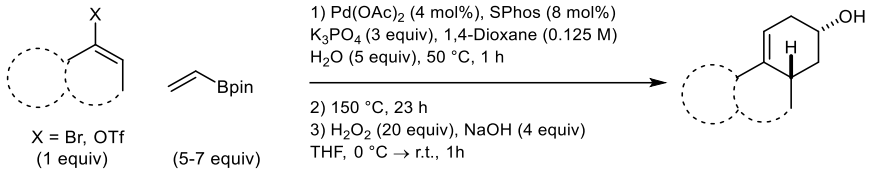
[a] Conversion to products determined by ^{19}F NMR analysis against a known internal standard (trifluorotoluene), r.r. = regiomeric ratio. n.d. = not determined.

The following scheme illustrates the improvement in yield of isolated product **8d**, providing the reassurances the studies could be taken to the next phase.



Scheme 49: Comparative isolation results for substrate 8a, with major regiosiomer displayed. [a] r.r. not determined, and isolated as Bpin mixture. [b] (n = 2), average of two experiments.

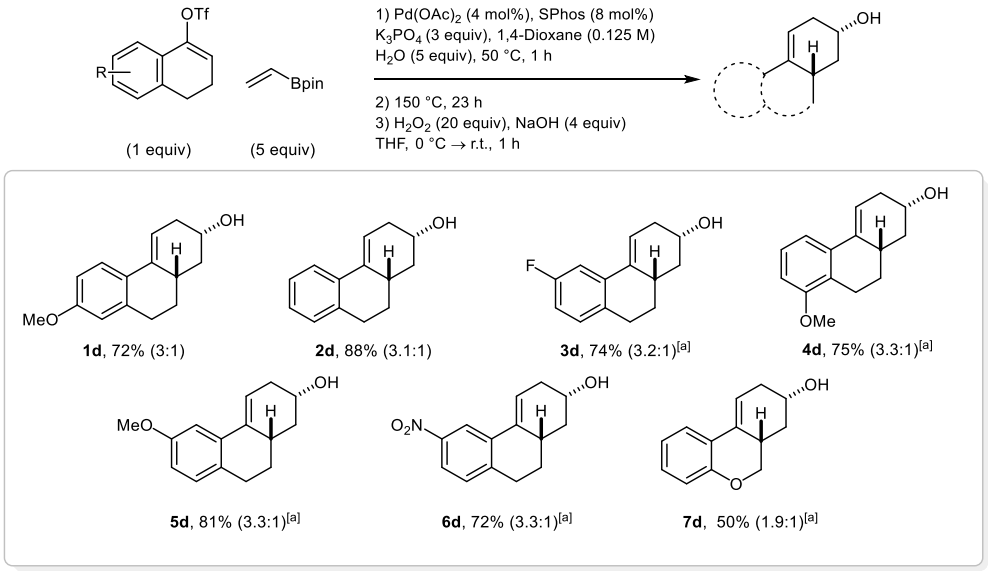
With a method now in hand to obtain data for characterisation purposes of the compounds generated and the optimised conditions for both sets of derivatives (Scheme 50), our attention turned to exploring the substrate scope of the cascade protocol.



Scheme 50: SM/DA optimised conditions for either system.

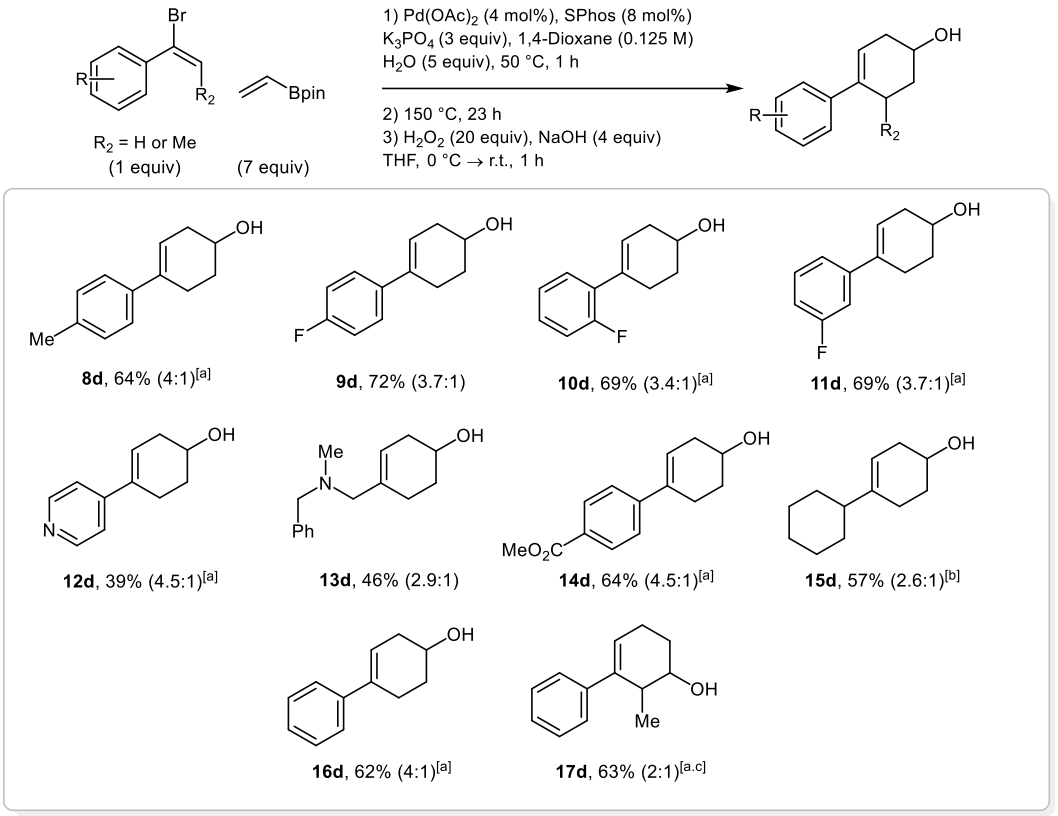
2.3.4. Substrate Scope

During the substrate exploration, a total of 17 compounds were synthesised using the developed methodology (see sections 2.6.5.1 & 2 for detailed discussion on assignment of major regioisomer for substrates **5d** and **9d** which were carried out using 2D NMR). Firstly, for the tetralone system, seven structurally different compounds were constructed (Scheme 51). The tetralone-derived scaffolds (**1d-7d**) displayed good yields in all examples, with both EDGs (**1d**, **4d**, **5d**) and EWGs (**6d**) tolerated, in addition to a chromane example (**7d**). The position and nature of the substituent on the aromatic ring had little effect on the regioselectivity of the cycloaddition, with a moderate ratio of regioisomers (*ca*. 3:1) observed throughout, which is unsurprising considering the proximity of the substituents in relation to reaction centre. In line with the highly stereoselective nature of the DA reaction, a single diastereomer was produced, which, following X-ray crystallographic analysis of a derivative, confirmed an *endo* DA adduct (see Section 2.3.6).



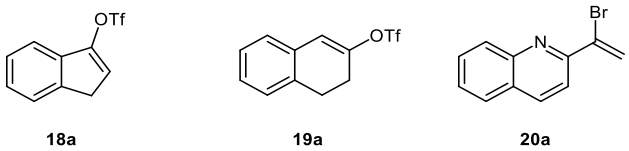
Scheme 51: Substrate scope of the cascade reaction. Major regioisomer displayed. Isolated yields of regioisomeric products. Numbers in brackets are the r.r. [a] [n = 2].

Use of styrenyl and alkenyl electrophiles allowed the formation of cyclohexenyl products (**8d-17d**) (Scheme 52). As already discussed (see Section 2.3.3.2.), due to potential homo-DA being significantly more problematic for these motifs, the yields for these substrates were consistently lower compared to their tetralone counterparts. Pleasingly, a pyridine substrate was also tolerated (**12d**) in the cascade sequence. The handling of the precursor for this substrate was particularly challenging, as it would readily decompose upon concentration, perhaps explaining the low yield. Lastly, use of β-methyl styrene resulted in the formation of the product **17d** in moderate yield. Interestingly, a change in regioselectivity was observed with this substrate, now favouring what was the minor regioisomer for all previous examples. The presence of the adjacent methyl substituent causes a significant change in the electronics of the diene. It acts as the dominant directing group for the preceding DA reaction, overriding the effects the aromatic backbone had in the other examples, explaining the preferential formation of the "1,3-regioisomer." The major regioisomer for substrate **17d** was confirmed using 2D NMR, after having performed an additional oxidation step to generate the mixture of ketones and subsequently separated.



Scheme 52: Substrate scope of the cascade reaction. Major regioisomer displayed. Isolated yields of regioisomeric products. Numbers in brackets are the r.r. [a] [n = 2]. [b] [n = 3]. [c] d.r. of both regioisomers = 2:1

There are notable substrates that are provided below, which were not compatible in the cascade methodology (Scheme 53). In the case of **18a**, the more rigid 5-membered ring is likely the reason for disallowing the formation of the DA adduct. For **19a**, the β-tetralone substrate did not successfully undergo the cross-coupling step, meaning no diene intermediate was generated. This could be due to the less stable nature of this precursor, with it rapidly reverting back to ketone under the reaction conditions. As for **20a**, the precursor was simply too reactive, readily undergoing polymerisation/decomposition upon exposure to the cascade conditions.

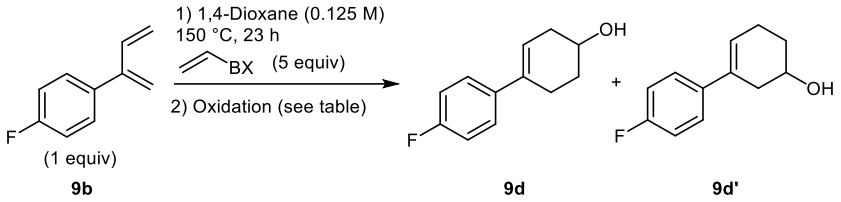


Scheme 53: Notable failed substrates.

2.3.5. Investigation of alternative vinyl boron species in DA reaction

The modest regioselectivities observed for most compounds in the substrate scope (ranging from 4.5-3:1), posed the question if the regioselectivity could be influenced or indeed enhanced through the usage of different vinyl organoboron species during the DA step of the cascade reaction. Due to the more reactive and unstable nature of the dienes generated for the tetralone systems, the styrenyl diene (**9b**) was seen as the more appropriate choice for this investigation. Under the aqueous basic conditions used for the initial SM cross-coupling of the tandem process, the vinyl Bpin could conceivably exist as its boronate derivative.[84] As a result, this species exhibits significantly different electronic properties to the parent neutral boronic ester. Since altering the electronics of the dienophile may have a direct influence on the regioselectivity of the cycloaddition, several different organoboron species were assessed (Bpin, *N*-methyliminodiacetate (MIDA), boroxine, potassium triflouroborate (BF_3K), and 1,8-diaminonaphthalenate (dan)) to determine any influence on regioselectivity (Table 7). However, no noticeable trends were observed, with all reactions producing a similar regioisomeric ratio. The cycloaddition requires significant thermal promotion and it is possible that these observations could be explained by the high temperatures required for reactivity overriding any potentially electronically induced kinetic effects contributions. This was purely a regiochemical distribution study, as a result the conversions of these reactions were not reported.

Table 7: DA regioselectivity: variation of vinyl boron species.

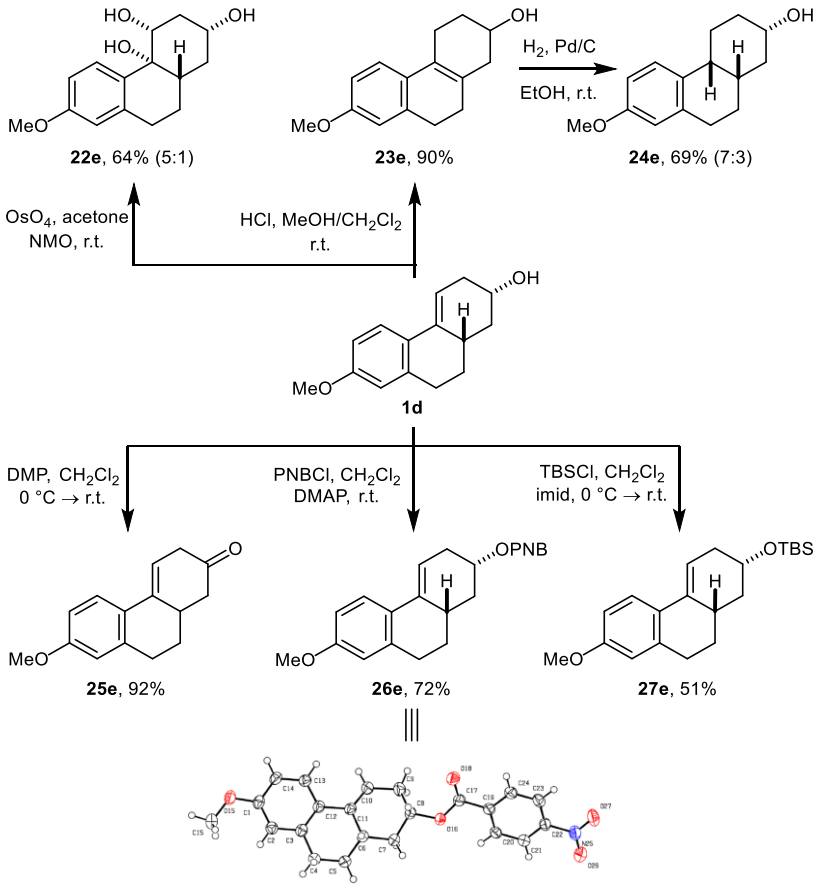


Entry	Vinyl Boron species (BX)	Ratio (9d:9d')[a]
1	Bpin	3.7:1[b]
2	BF_3K	3.5:1[c]
3	Bdan (**21S**)	3.5:1[d]
4	BMIDA	2.8:1[e]
5	Boroxine	3.6:1[b]

[a] Determined after oxidation to the corresponding alcohol. [b] Oxidation conditions: H_2O_2 (20 equiv), 2 M NaOH (4 equiv), THF, 0 °C to r.t., 1 h. [c] Oxidation conditions: Oxone® (1.1 equiv), acetone/H_2O (1:1), r.t., 2 h. [d] (i) 2 M HCl (6 equiv), THF, r.t., 23 h; (ii) H_2O_2 (20 equiv), 2 M NaOH (4 equiv), THF, 0 °C to r.t., 1 h. [e] (i) K_3PO_4 (3 equiv), H_2O (5 equiv), CPME, 80 °C, 10 min; (ii) Oxone® (2.5 equiv), CPME/H_2O (4:1), 70 °C, 1 h; dan = 1,8-diaminonaphthalenate; MIDA = *N*-methyliminodiacetate; pin = pinacolato.

2.3.6. Derivatisation of benchmark substrate

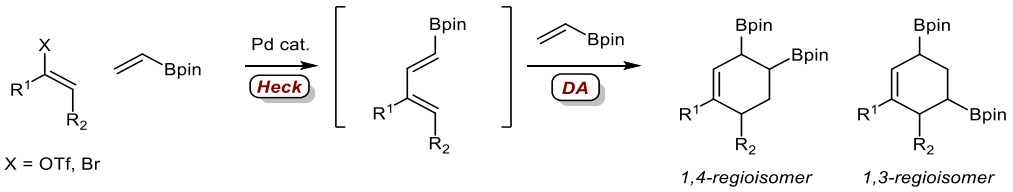
After demonstrating the potential of the methodology *via* the synthesis of a variety of compounds, and exploring the possibility for regioselectivity enhancement or changes *via* application of other vinyl boron species, a series of derivatisation reactions were carried out on the model substrate **1d** (Scheme 54). Dihydroxylation, alkene isomerisation, hydrogenation, oxidation, acylation, and alcohol protection were all shown to be feasible, giving compounds **22e**–**27e** and illustrating the potential for rapid diversification of the newly accessed carbocycles. Compound **26e** was characterised by single crystal X-ray diffraction (by Cameron-Carpenter Warren), confirming relative stereochemistry and providing evidence that the cycloaddition proceeds *via* the *endo* transition state, which is unsurprising given the presence of secondary orbital overlap the Bpin substituent provides.



Scheme 54: Illustrative synthetic modifications of benchmark susbstrate 1d. DMAP = 4-dimethylaminopyridine; DMP = Dess–Martin periodinane; imid = imidazole; NMO = *N*-methylmorpholine *N*-oxide; PNB = *para*-nitrobenzoyl chloride; TBS = *tert*-butyldimethylsilyl.

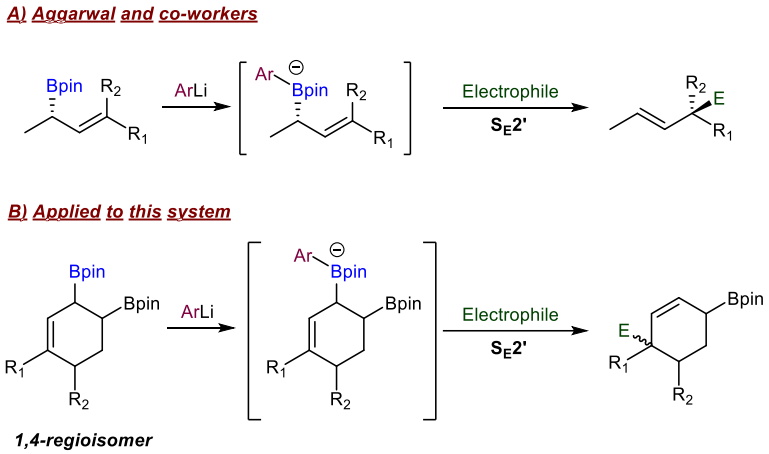
2.3.7. Complimentary Heck/Diels–Alder investigation

Through the successful development of this cascade reaction, and the expertise gathered from related work reported by the Watson group (see Section 2.1.),[73] it was considered whether vinyl Bpin could equally be implemented in a cascade Heck/DA reaction, providing potentially rapid access to carbocycles bearing two Bpin functional handles that are vicinal in the case of the 1,4-regioisomer (Scheme 55).



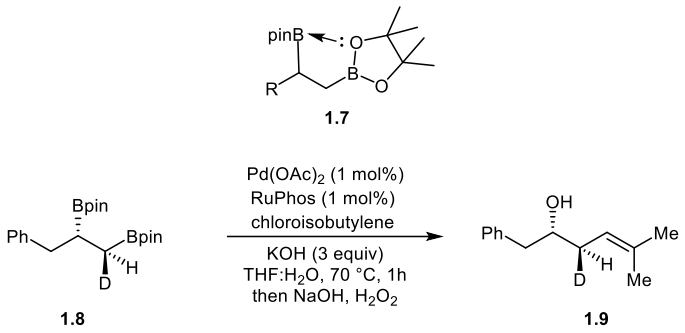
Scheme 55: Proposed cascade Heck/DA reaction.

If successful, one could perform chemoselective chemistry thereafter, by taking advantage of the intrinsically different reactivity the two boron substituents exhibit. For instance, given that one Bpin is an allyl boronate, it could be selectively further functionalised through interception of an appropriate electrophile, as shown in the work by Aggarwal (Scheme 56).[85] Furthermore, after effective application of the reaction this would generate another allylic Bpin species in our system, which could perform the same reaction once again, resulting in a potential cascade sequence.



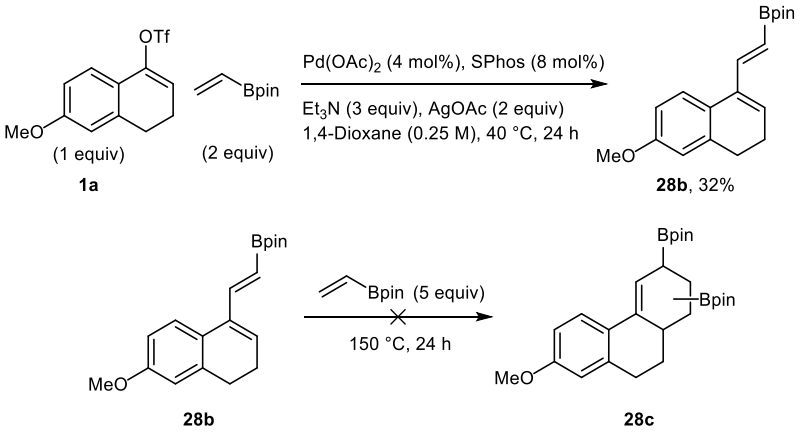
Scheme 56: A) Allyl boronates being intercepted by electrophiles, by Aggarwal. B) Its application in the discussed system.

In some examples the complementary nature of these vicinal Bpin systems, such as in a SM reaction, could also be harnessed, as demonstrated by Morken and co-workers (Scheme 57).[86] It has been well documented that cross coupling reactions involving sp^3-sp^2 centres are more challenging compared to their sp^2-sp^2 counterparts. However, the vicinal relationship between the two Bpin systems aids in overcoming this coupling reactivity, through the enhancement in rate of transmetallation. This sp^3-sp^2 cross-coupling reaction is enabled by neighbouring-group activation through internal Lewis base donation of the reacting boronate (**1.7**).



Scheme 57: Cascade diboration and cross-coupling reaction of terminal alkenes by Morken.

Initial one-pot attempts into the Heck/DA reaction proved unsuccessful, with only complex crude mixtures being obtained. No meaningful information verifying the presence of desired product or regarding the identity of potential by-products could be extrapolated from the mixtures, with polymerisation/degradation having occurred. As a result, a stepwise approach was adopted to validate this proof of concept, whereby the diene substituted Bpin (**28b**) was isolated prior to vinyl Bpin exposure for the DA step (Scheme 58).



Scheme 58: Stepwise approach for validating cascade Heck/DA reaction.

The Bpin diene intermediate **28b** was successfully isolated, albeit in low yield. Poor conversion to the diene intermediate and its instability during chromatography were believed to be reasons associated with the poor yield. Despite our best efforts, and our acquired knowledge on this DA reaction, we were unable to obtain the DA adduct **28c** upon exposing the diene **28b** to excess vinyl Bpin at elevated temperatures, with the reaction yielding a complex mixture of unknown products. This could be due

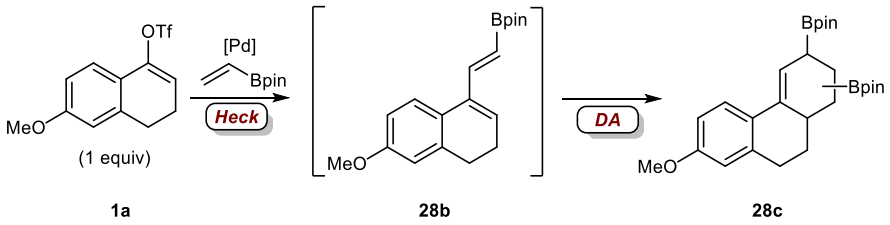
to the noted poor stability/high reactivity of intermediate **28b**, with protodeboronation likely also taking place, which is exacerbated by the requirement for high temperatures for the DA step.

2.4. Conclusion

In conclusion, a SM/DA cascade protocol has been successfully optimised for two sets of substrates (tetralone and styrenyl systems). The optimised conditions differ only in the quantity of vinyl Bpin added to the reaction mixture. The main reason for this change in reaction conditions was to overcome the proposed increased amount of homo-DA by-product being noticed for the styrenyl derivatives. This observation is rationalised by relative sterics and electronics of the dienes generated *in situ*. The substrate scope shows a good tolerance for a variety of functionalities, as well as heterocycles, with yields being modest to good in most cases. The effects of regioselectivity of the DA reaction were investigated by reacting different vinyl boron species with an isolated diene, with results displaying minimal impact. Furthermore, a set of derivatisation reactions were carried out to showcase versatility of these carbocycles being generated. Lastly, a complimentary Heck/DA reaction was pursued, by taking advantage of the "transmetallation switch"[73] to access vicinal Bpin systems. However, attempts at this thus far have proven unsuccessful.

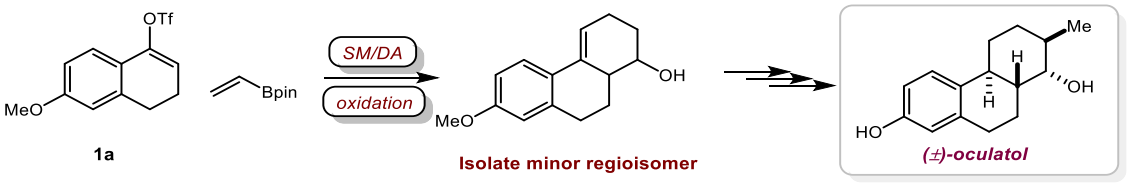
2.5. Future Work

Further investigations into probing the Heck/DA alternative will be performed, by firstly understanding the by-products that are generated. In addition, screening conditions at lower temperatures may be necessary to facilitate this transformation, as the desired vicinal Bpin products are likely highly reactive (Scheme 59).



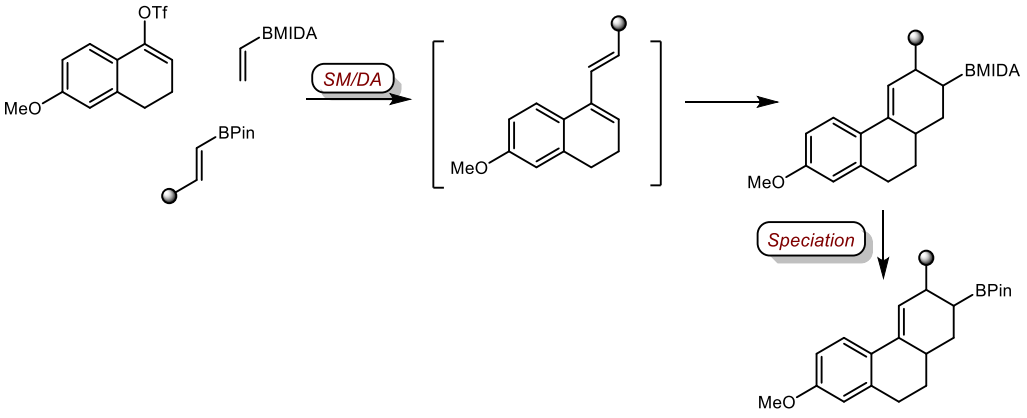
Scheme 59: Development of cascade Heck/DA reaction.

An alternative idea in the pipeline is to apply the methodology in the synthesis of natural products, for example Oculatol (Scheme 60). Here, the minor regioisomer of the benchmark substrate could be isolated and further elaborated to generate the natural product as a racemate.



Scheme 60: Proposed SM/DA cascade reaction used as key step to synthesise Oculatol.

Lastly, in the long-term a proposed three component SM/DA cascade reaction (Scheme 61) will be pursued. The idea is to take advantage of chemoselectivity that arises due to the reactivity difference between Bpin and BMIDA species in a SM reaction. This coupled with the in-depth study performed within the group regarding speciation control for these two boron species in SM reactions;[87] will help to facilitate this transformation to generate intrinsically complex structures bearing two contiguous stereocentres.



Scheme 61: Proposed scheme for a multicomponent one-pot SM/DA cascade reaction

2.6. Experimental

2.6.1. General

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[88]

2.6.1.1. Purification of solvents

All solvents used for dry reactions (PhMe, CH_2Cl_2, THF, Et_2O) were obtained from a PureSolv SPS-400-5 solvent purification system and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves under nitrogen. Dry 1,4-dioxane was obtained by distillation over $LiAlH_4$ and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves under nitrogen. EtOAc, Et_2O, MeOH, CH_2Cl_2 and petroleum ether 40–60°C for purification purposes were used as obtained from suppliers without further purification.

2.6.1.2. Drying of inorganic bases

Inorganic bases were dried in a Heraeus Vacutherm oven at 60 °C under vacuum for a minimum of 24 hours before use.

2.6.1.3. Experimental details

Reactions were carried out using conventional glassware (preparation of intermediates) or in 5 mL capped microwave vials (optimisation reactions and substrates). The glassware was oven-dried (150 °C) and cooled under vacuum before use. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature was generally 20 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer and a sand bath. Temperature quoted is a measurement of the sand bath heating block. Reactions were carried out at 0 °C using an ice bath. Reactions were carried out at –78 °C using an acetone/dry ice bath.

2.6.1.4. Purification of products

Thin layer chromatography (TLC) was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light or developed using potassium permanganate, vanillin or anisaldehyde solutions. Column chromatography was carried out using ZEOprep 60 HYD 40–63μm silica gel.

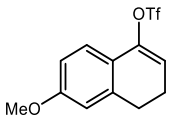
2.6.1.5. Analysis of products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine at Strathclyde University or on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory at St Andrews University. Spectra were recorded of either thin films or solids, with characteristic absorption wavenumbers (υ_{max}) reported in cm^{-1}. ^{19}F NMR spectra were obtained on either a Bruker AV 400 spectrometer at 376 MHz or Bruker AV 500 at 470 MHz. ^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AV 400 at 400 MHz and 101 MHz, or Bruker AV 500 at 500 MHz and 126 MHz. ^{11}B NMR spectra were obtained on a Bruker AV 500 at 160 MHz or Bruker AV 300 at 96 MHz. Chemical shifts are reported in ppm and coupling constants are reported in Hz: $CDCl_3$ referenced at 7.26 (^{1}H) and 77.2 ppm (^{13}C); DMSO-d_6 referenced at 2.50 (^{1}H) and 39.5 ppm (^{13}C); Acetone-d_6 referenced at 2.05 (^{1}H) and 206.26 ppm (^{13}C). Coupling constants throughout the experimental section were reported as observed in spectra without corrections. High-resolution mass spectra were obtained through analysis at the EPSRC National Mass Spectrometry Facility, University of Swansea or the University of St Andrews mass spectrometry facility. NMR conversion was obtained through addition of a known standard (solution of dibenzyl ether in MeCN (2 mL, 0.03125 M)) to the crude reaction mixture. Solvent was removed under reduced pressure and conversion against the internal standard was determined by ^{1}H NMR. For fluorine containing molecules NMR conversion was obtained through the addition of a known standard (trifluorotoluene (30.7 μL, 0.25 mmol)). After 10 min of stirring, an aliquot of the mixture was filtered through Celite® and conversion against the internal standard was determined by ^{19}F NMR. Crystallography data is available at the end of the experimental section (Table 8).

2.6.2. General experimental procedures

2.6.2.1. General Procedure A: Triflation of tetralones

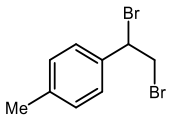
For example, the preparation of 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (**1a**)



6-Methoxy-1-tetralone (2.00 g, 11.35 mmol, 1 equiv) was weighed into an oven-dried flask. The flask was sealed and purged with N_2 before the addition of CH_2Cl_2 (45 mL, 0.25 M). The reaction was cooled to 0 °C and triflic anhydride (3.8 mL, 22.7 mmol, 2 equiv) and Et_3N (3.2 mL, 22.7 mmol, 2 equiv) were added dropwise via syringe sequentially. The reaction mixture was then heated to reflux for 22 h with stirring. After the reaction was complete, the reaction was allowed to cool to room temperature and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–5% EtOAc in petroleum ether) to afford the desired product as a yellow oil (2.41 g, 69%).

2.6.2.2. General Procedure B: Bromination of styrene derivatives

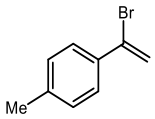
For example, the preparation of 1-(1,2-dibromoethyl)-4-methylbenzene (**8S**)



Bromine (260 µL, 5.07 mmol, 1.2 equiv) was added dropwise to a stirred solution of 4-methylstyrene (500 mg, 4.23 mmol, 1 equiv) in $CHCl_3$ (8.5 mL, 0.5 M) at 0 °C under N_2 atmosphere. After 5 min the reaction mixture was allowed to warm to room temperature and was stirred for 1 h. After the reaction was complete, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (15 mL) and diluted in CH_2Cl_2 (20 mL). The organic phase was then separated, washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure, to afford the desired product as a white solid (1.2 g, yield quant.).

2.6.2.3 General Procedure C: Elimination reaction to form SM/DA precursor.

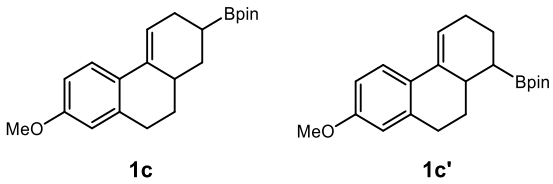
For example, the preparation of 1-(1-bromovinyl)-4-methylbenzene (**8a**)



1-(1,2-Dibromoethyl)-4-methylbenzene (300 mg, 1.08 mmol, 1 equiv) and K_2CO_3 (298 mg, 2.16 mmol, 2 equiv) were weighed into an oven-dried flask. The flask was sealed and purged N_2, before the addition of THF (2.2 mL) and methanol (2.2 mL) (1:1, 0.25 M). The reaction mixture was stirred at room temperature for 6 h. After the reaction was complete, the reaction mixture was diluted in Et_2O (20 mL) and washed with H_2O (20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired product as a pale yellow oil (209 mg, 98%), which was used immediately in subsequent reactions without further purification.

2.6.2.4. General Procedure D: SM/DA optimisation protocol for tricyclic system

For example, the preparation of **1c** & **1c'**

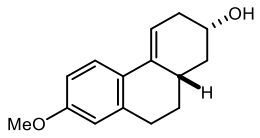


$Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **1a** (77.0 mg, 0.25 mmol, 1 equiv), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv) and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv) were weighed into an oven-dried microwave vial. The reaction vessel was then capped and purged with N_2 before the addition of 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µl, 1.25 mmol, 5 equiv). The reaction mixture was heated to 50 °C with stirring. After 1 h the temperature was increased to 150 °C, and the reaction mixture was stirred for 23 h. After the reaction was complete, the reaction mixture was allowed to cool to room temperature and was vented and de-capped. The reaction

mixture was diluted with EtOAc (20 mL) and passed through a layer of Celite®. Conversion to the desired product was measured by ^{1}H NMR against a known internal standard (dibenzyl ether).

2.6.2.5. General Procedure E: SM/DA/oxidation protocol

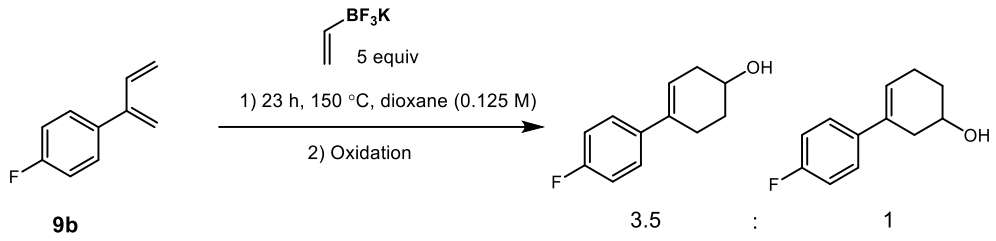
For example, the preparation of **1d**



$Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **1a** (77.0 mg, 0.25 mmol, 1 equiv), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv) and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv) were weighed into an oven-dried microwave vial. The reaction vessel was then capped and purged with N_2 before the addition of 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µl, 1.25 mmol, 5 equiv). The reaction mixture was heated to 50 °C with stirring. After 1 h the temperature was increased to 150 °C, and the reaction mixture was stirred for 23 h. After the reaction was complete, the reaction mixture was allowed to cool to room temperature and was vented and de-capped. The reaction mixture was diluted in EtOAc (20 mL) and passed through a layer of Celite®, and concentrated under reduced pressure. THF (1 mL, 0.25 M) was added to the crude residue and the solution was cooled to 0 °C before the addition of aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv) and 2 M NaOH (500 µL, 1 mmol, 4 equiv) sequentially. After 5 min the reaction mixture was allowed to warm to room temperature and was stirred for 1 h. After the reaction was complete, the mixture was quenched with $Na_2S_2O_3$ at 0 °C until effervescence ceased and was subsequently diluted in saturated aqueous NH_4Cl (25 mL). Organics were extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–60% EtOAc in petroleum ether) to afford the desired product as a yellow oil (41.3 mg, 72%, 3:1 r.r.).

2.6.2.6. General Procedure F: DA reaction with different vinyl boron species

For example, 1-(buta-1,3-dien-2-yl)-4-fluorobenzene (**9b**) DA reaction with vinyl BF_3K

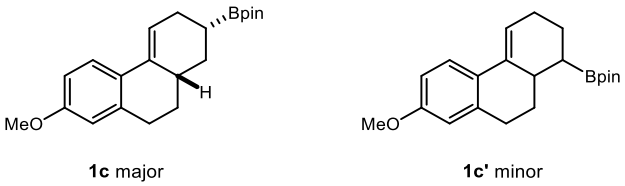


1-(Buta-1,3-dien-2-yl)-4-fluorobenzene **9b** (37.0 mg, 0.25 mmol, 1 equiv) and vinyl BF_3K (167 mg, 1.25 mmol, 5 equiv) were weighed into an oven-dried microwave vial. The vial was the capped and purged with N_2 before 1,4-dioxane (2 mL, 0.125 M) was added. The reaction mixture was then heated for 23 h at 150 °C. After the reaction was complete, the reaction mixture was left to cool to room temperature, vented and de-capped, before being concentrated under reduced pressure. The crude mixture was then exposed to oxidation conditions and subsequently worked up. Column chromatography (silica gel, 0–20% EtOAc in petroleum ether) of crude material afforded the product with regioisomer ratio of 3.5:1.

2.6.3. Reaction optimisation data

2.6.3.1. Tetralone scaffold

Conversion was determined by ^{1}H NMR analysis of olefinic peaks at 6.22 (minor) and 6.18 ppm (major) against a known internal standard (dibenzylether in MeCN where 2 mL = 0.03125 mmol). Regiomeric ratios were determined after oxidation of Bpin to the alcohol by ^{1}H NMR analysis of olefinic peaks at 6.12 (minor) and 6.04 ppm (major), as ratio could not be determined post initial Bpin DA adduct formation due to alkene protons overlapping. Oxidation was carried out according to General Procedure E.



1c major **1c'** minor

2.6.3.1.1. Temperature study (Table 1**)**

Reactions were carried out according to General Procedure D using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **1a** (77.0 mg, 0.25 mmol, 1 equiv), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction was stirred for 1 h at 50 °C and 23 h at **X** °C, before analysis by ^1H NMR analysis against a known internal standard (dibenzyl ether).

For entry 5 only: Reactions were carried out according to General Procedure D using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **1a** (77.0 mg, 0.25 mmol, 1 equiv), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (**X** mL, **X** M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction was stirred for 1 h at 50 °C and 23 h at 150 °C, before analysis by ^1H NMR analysis against a known internal standard (dibenzyl ether).

Entry	Temperature (°C)	Conversion (%) (r.r.)
1	75	24 (--)
2	100	33 (--)
3	125	66 (--)
4	150	98 (3:1)
5 (0.25 M, 1 mL)	150	85 (3.1:1)

(--) = was not able to be determined due to impurity.

2.6.3.1.2. Vinyl Bpin equivalents study (Table 2**)**

Reactions were carried out according to General Procedure D using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **1a** (77.0 mg, 0.25 mmol, 1 equiv), vinyl Bpin (**X** mg, **X** equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv).The reaction was stirred for 1 h at

50 °C and 23 h at 150 °C, before analysis by ^{1}H NMR analysis against a known internal standard (dibenzyl ether).

Entry	Vinyl Bpin (equiv)	Conversion (%) (r.r.)
1	77 mg, 2 equiv	62 (3.1:1)
2	115 mg, 3 equiv	84 (3.2:1)
3	154 mg, 4 equiv	93 (3.2:1)
4	192 mg, 5 equiv	98 (3:1)

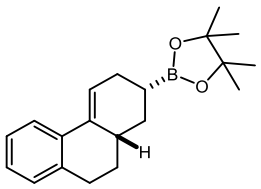
2.6.3.1.3. Time study (Table 3)

Reactions were carried out according to General Procedure D using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **1a** (77.0 mg, 0.25 mmol, 1 equiv), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction was stirred for 1 h at 50 °C and **X** h at 150 °C, before analysis by ^{1}H NMR analysis against a known internal standard (dibenzyl ether).

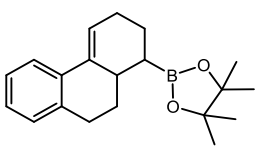
Entry	Time (h)	Conversion (%) (r.r.)
1	2	64 (n.d.)
2	4	88 (3.1:1)
3	6	99 (3.5:1)
4	23	98 (3:1)

n.d. = not determined.

2.6.3.1.4. Des-methoxy tetralone comparison experiment (Table 4)



2c major



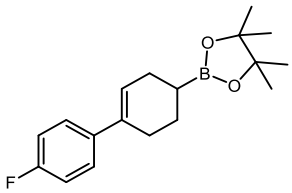
2c' minor

Reactions were carried out according to General Procedure D using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (69.5 mg, 0.25 mmol, 1 equiv), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction was stirred for 1 h at 50 °C and **X** h at 150 °C, before analysis by ^1H NMR analysis against a known internal standard (dibenzyl ether).

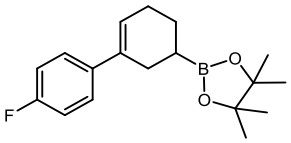
Entry	Time (h)	Conversion (%) (r.r.)
1	6	88 (3.1:1)
2	23	96 (3:1.1)

2.6.3.2. Styrenyl scaffold

Conversion was determined by ^{19}F NMR analysis of fluorine peaks at -116.91 ppm (major) and -117.01 ppm (minor) against a known internal standard (trifluorotoluene). The relaxation values of T1 for the ^{19}F nuclei of compounds **9c** and **9c'** were measured by running single experiments, changing the value of τ until a null intensity was found. This data was then used to calculate the T1 relaxation time.



9c major



9c' minor

2.6.3.2.1. Concentration study (Table 5)

Reactions were carried out according to General Procedure D using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-fluorobenzene (50.2 mg, 0.25 mmol, 1 equiv), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (**X** mL, **X** M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction was stirred for 1 h at 50 °C and 23 h at 150 °C, before analysis by ^{19}F NMR analysis against a known internal standard (trifluorotoluene).

Entry	Concentration (mL, M)	Conversion (%) (r.r.)
1	2 mL, 0.125 M	64 (n.d.)
2	1 mL, 0.25 M	65 (n.d.)
3	0.5 mL, 0.5 M	62 (n.d.)

n.d. = not determined.

2.6.3.2.2. Vinyl Bpin equivalents study (Table 6)

Reactions were carried out according to General Procedure D using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-fluorobenzene (50.2 mg, 0.25 mmol, 1 equiv), vinyl Bpin (**X** mg, **X** equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction was stirred for 1 h at 50 °C and 23 h at 150 °C before analysis by ^{19}F NMR analysis against a known internal standard (trifluorotoluene).

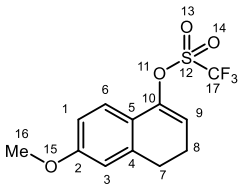
Entry	Vinyl Bpin (equiv)	Conversion (%) (r.r.)
1	192 mg, 5 equiv	64 (n.d.)
2	269 mg, 7 equiv	71 (n.d.)
3	345 mg, 9 equiv	73 (n.d.)

n.d. = not determined

2.6.4. Compound characterisation data

2.6.4.1. Preparation of intermediates

6-Methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (**1a**), starting material for compound **1d**



Prepared according to General Procedure A using 6-Methoxy-1-tetralone (2.00 g, 11.35 mmol, 1 equiv), triflic anhydride (3.8 mL, 22.7 mmol, 2 equiv), Et_3N (3.2 mL, 22.7 mmol, 2 equiv) and CH_2Cl_2 (45 mL, 0.25 M). After 22 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% EtOAc in petroleum ether) to afford the desired product as a yellow oil (2.41 g, 69%).

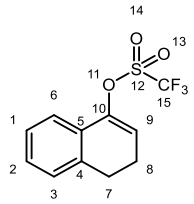
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 1H, 6), 6.77 (dd, *J* = 8.5, 2.6 Hz, 1H, 1), 6.73 (d, *J* = 2.5 Hz, 1H, 3), 5.86 (t, *J* = 4.8 Hz, 1H, 9), 3.82 (s, 3H, 16), 2.84 (t, *J* = 8.1 Hz, 2H, 7), 2.48 (td, *J* = 8.1, 4.8 Hz, 2H, 8).

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.4 (2), 146.4 (10), 138.4 (4), 122.8 (6), 121.8 (5), 118.7 (17) (d, $^1J_{CF}$ = 320.2 Hz), 114.9 (9), 114.4 (3), 111.4 (1), 55.5 (16), 27.5 (7), 22.4 (8).

^{19}F NMR (376 MHz, $CDCl_3$): δ -73.73 (s, CF_3).

Spectroscopic data were in agreement with literature values.[89]

3,4-Dihydronaphthalen-1-yl trifluoromethanesulfonate (**2a**), starting material for compound **2d**



Prepared according to General Procedure A using 1-tetralone (400 mg, 2.74 mmol, 1 equiv), triflic anhydride (920 µL, 5.47 mmol, 2 equiv), Et_3N (760 µL, 5.47 mmol, 2 equiv) and CH_2Cl_2 (6.8 mL, 0.4 M). After 3.5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% EtOAc in petroleum ether) to afford the desired product as a yellow oil (475 mg, 62%).

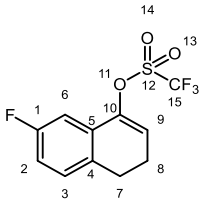
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.32 (m, 1H, 2), 7.27 (dd, *J* = 5.7, 3.3 Hz, 2H, 1, 3), 7.21 – 7.15 (m, 1H, 6), 6.02 (t, *J* = 4.8 Hz, 1H, 9), 2.88 (t, *J* = 8.2 Hz, 2H, 7), 2.52 (ddd, *J* = 9.0, 7.6, 4.8 Hz, 2H, 8).

^{13}C NMR (126 MHz, $CDCl_3$): δ 146.5 (10), 136.3 (4), 129.3 (6), 128.8 (5), 127.9 (3), 127.1 (1), 121.3 (2), 118.7 (15) (d, $^1J_{CF}$ = 320.2 Hz), 117.9 (9), 27.0 (7), 22.4 (8).

^{19}F NMR (470 MHz, $CDCl_3$): δ -73.67 (s, CF_3).

Spectroscopic data were in agreement with literature values.[90]

7-Fluoro-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (**3a**), starting material for compound **3d**



Prepared according to General Procedure A using 7-fluoro-1-tetralone (300 mg, 1.82 mmol, 1 equiv), triflic anhydride (610 µL, 3.65 mmol, 2 equiv), Et_3N (510 µL, 3.65 mmol, 2 equiv) and CH_2Cl_2 (7.3 mL, 0.25 M). After 21 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–

1% EtOAc in petroleum ether) to afford the desired product as a light yellow oil (254 mg, 46%).

υ_{max} (film): 2951, 2843,1584, 1491, 1418, 1204, 1136, 1018, 901 cm^{-1}.

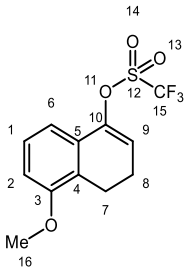
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 – 7.10 (m, 1H, 3), 7.05 (dd, *J* = 9.2, 2.6 Hz, 1H, 6), 6.95 (td, *J* = 8.4, 2.6 Hz, 1H, 2), 6.09 (td, *J* = 4.8, 0.9 Hz, 1H, 9), 2.87 – 2.80 (m, 2H, 7), 2.52 (ddd, *J* = 9.0, 7.6, 4.8 Hz, 2H, 8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.9 (1) (d, $^{1}J_{CF}$ = 244.8 Hz), 145.5 (10) (d, $^{4}J_{CF}$ = 2.5 Hz), 131.7 (4) (d, $^{4}J_{CF}$ = 3.2 Hz), 130.4 (5) (d, $^{3}J_{CF}$ = 8.1 Hz), 129.3 (3) (d, $^{3}J_{CF}$ = 8.1 Hz), 119.3 (9), 118.7 (15) (d, $^{1}J_{CF}$ = 320.4 Hz), 115.8 (2) (d, $^{2}J_{CF}$ = 21.5 Hz), 108.9 (6) (d, $^{2}J_{CF}$ = 24.7 Hz), 26.2 (7), 22.6 (8).

^{19}F NMR (470 MHz, $CDCl_3$): δ -73.56 (s, CF_3, 3F), -114.75 (s, CF, 1.5F).

HRMS: exact mass calculated for $[M\text{-}OTf]^+$ ($C_{10}H_8F$) requires *m/z* 147.0605 found *m/z* 147.0603

5-Methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (**4a**), starting material for compound **4d**



Prepared according to General Procedure A using 5-methoxy-1-tetralone (300 mg, 1.7 mmol, 1 equiv), triflic anhydride (570 µL, 3.4 mmol, 2 equiv), Et_3N (470 µL, 3.4 mmol, 2 equiv) and CH_2Cl_2 (6.8 mL, 0.25 M). After 2 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% EtOAc in petroleum ether) to afford the desired product as a light yellow oil (471 mg, 90%).

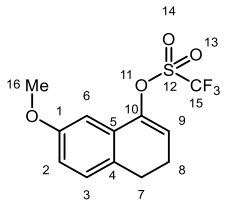
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (t, *J* = 8.0 Hz, 1H, 1), 7.00 (d, *J* = 7.8 Hz, 1H, 6), 6.88 (d, *J* = 8.3 Hz, 1H, 2), 6.01 (t, *J* = 4.8 Hz, 1H, 9), 3.84 (s, 3H, 16), 2.86 (t, *J* = 8.4 Hz, 2H, 7), 2.48 (td, *J* = 8.4, 4.8 Hz, 2H, 8).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.1 (3), 146.3 (10), 129.7 (5), 127.2 (1), 124.2 (4), 118.6 (15) (d, $^{1}J_{CF}$ = 320.3 Hz), 117.9 (9), 113.9 (6), 111.7 (2), 55.6 (16), 21.9 (7), 19.1 (8).

^{19}F NMR (471 MHz, $CDCl_3$): δ -73.70 (s, CF_3).

Spectroscopic data were in agreement with literature values.[91]

7-Methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (**5a**), starting material for compound **5d**



Prepared according to General Procedure A using 7-methoxy-1-tetralone (300 mg, 1.7 mmol, 1 equiv), triflic anhydride (570 µL, 3.4 mmol, 2 equiv), Et_3N (470 µL, 3.4 mmol, 2 equiv) and CH_2Cl_2 (6.8 mL, 0.25 M). After 1.5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 1–5% EtOAc in petroleum ether) to afford the desired product as a dark brown oil (460 mg, 88%).

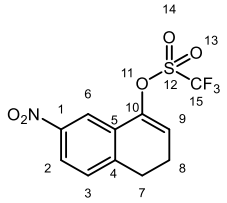
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, *J* = 8.3 Hz, 1H, 3), 6.90 (d, *J* = 2.6 Hz, 1H, 6), 6.80 (dd, *J* = 8.3, 2.6 Hz, 1H, 2), 6.03 (t, *J* = 4.8 Hz, 1H, 9), 3.81 (s, 3H, 16), 2.80 (t, *J* = 8.1 Hz, 2H, 7), 2.49 (td, *J* = 8.2, 4.8 Hz, 2H, 8).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.8 (1), 146.4 (10), 129.7 (5), 128.8 (3), 128.3 (4), 118.8 (15) (d, $^{1}J_{CF}$ = 320.4 Hz), 118.5 (9), 114.7 (2), 107.3 (6), 55.5 (16), 26.1 (7), 22.9 (8).

^{19}F NMR (376 MHz, $CDCl_3$): δ -73.68 (s, CF_3).

Spectroscopic data were in agreement with literature values.[92]

7-Nitro-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (**6a**), starting material for compound **6d**



Prepared according to General Procedure A using 7-nitro-1-tetralone (500 mg, 1.7 mmol, 1 equiv), triflic anhydride (880 µL, 3.4 mmol, 2 equiv), Et_3N (730 µL, 3.4 mmol, 2 equiv) and CH_2Cl_2 (5.1 mL, 0.25 M). After 2 h, an additional 2 equiv of both triflic anhydride and Et_3N were added at 0 °C, before being refluxed for a further 16 h. The reaction mixture was then subjected to the purification method outlined in the General Procedure (silica gel, 5–10% EtOAc in petroleum ether) to afford the desired product as a viscous yellow oil (234 mg, 27%).

υ_{max} (film): 2949, 2897, 1525, 1419, 1385, 1348, 1209, 1181, 1132, 1019, 1049 cm^{-1}.

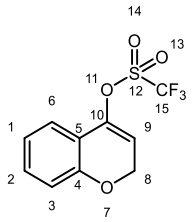
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 2.2 Hz, 1H, 6), 8.14 (dd, *J* = 8.2, 2.3 Hz, 1H, 2), 7.36 (d, *J* = 8.2 Hz, 1H, 3), 6.22 (t, *J* = 4.8 Hz, 1H, 9), 2.99 (t, *J* = 8.2 Hz, 2H, 7), 2.61 (td, *J* = 8.2, 4.8 Hz, 2H, 8).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.5 (10), 144.5 (1), 143.4 (4), 130.2 (5), 128.9 (3), 124.2 (2), 120.7 (6), 118.7 (15) (d, $^1J_{CF}$ = 320.3 Hz), 116.4 (9), 27.1 (7), 22.0 (8).

^{19}F NMR (471 MHz, $CDCl_3$): δ -73.29 (s, CF_3).

HRMS (NSI): exact mass calculated for $[M+NH_4]^+$ ($C_{11}H_{12}F_3N_2O_5S$) requires *m/z* 341.0414, found *m/z* 341.0416.

2*H*-Chromen-4-yl trifluoromethanesulfonate (**7a**), starting material for compound **7d**



Prepared according to General Procedure A using chroman-4-one (300 mg, 2.02 mmol, 1 equiv), triflic anhydride (680 µL, 4.04 mmol, 2 equiv), Et_3N (410 µL, 4.04 mmol, 2 equiv) and CH_2Cl_2 (8.1 mL, 0.25 M). After 21 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% EtOAc in petroleum ether) to afford the desired product as a light yellow oil (366 mg, 65%).

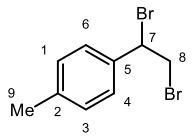
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 7.6, 1.5 Hz, 2H, 2, 6), 6.97 (td, *J* = 7.6, 1.0 Hz, 1H, 1), 6.85 (dd, *J* = 8.6, 1.0 Hz, 1H, 3), 5.76 (t, *J* = 3.9 Hz, 1H, 9), 4.99 (d, *J* = 3.9 Hz, 2H, 8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2 (4), 143.3 (10), 131.7 (2), 122.0 (6), 121.9 (1), 118.7 (15) (d, $^1J_{CF}$ = 320.6 Hz), 117.5 (5), 116.4 (9), 110.2 (3), 65.2 (8).

^{19}F NMR (376 MHz, $CDCl_3$): δ -73.47 (s, CF_3).

Spectroscopic data were in agreement with literature values.[93]

1-(1,2-Dibromoethyl)-4-methylbenzene (**8S**)



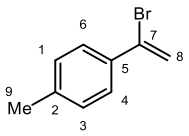
Prepared according to General Procedure B using 4-methylstyrene (500 mg, 4.23 mmol, 1 equiv), bromine (260 µL, 5.07 mmol, 1.2 equiv) and $CHCl_3$ (8.5 mL, 0.5 M). After 1 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a white solid (1.20 g, quant).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.1 Hz, 2H, 4, 6), 7.19 (d, *J* = 7.9 Hz, 2H, 1, 3), 5.14 (dd, *J* = 10.7, 5.4 Hz, 1H, 7), 4.08 (dd, *J* = 10.2, 5.4 Hz, 1H, 8'), 4.03 (t, *J* = 10.5 Hz, 1H, 8''), 2.36 (s, 3H, 9).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.4 (2), 135.8 (5), 129.7 (1, 3), 127.7 (4, 6), 51.2 (7), 35.2 (8), 21.5 (9).

Spectroscopic data were in agreement with literature values.[94]

1-(1-Bromovinyl)-4-methylbenzene (**8a**), starting material for compound **8d**



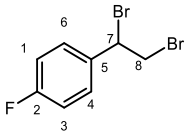
Prepared according to General Procedure C using 1-(1,2-dibromoethyl)-4-methylbenzene **8S** (300 mg, 1.08 mmol, 1 equiv) and K_2CO_3 (298 mg, 2.16 mmol, 2 equiv), THF (2.2 mL), and methanol (2.2 mL) (1:1, 0.25 M). After 6 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a colourless oil (209 mg, 98%), which was immediately used in subsequent reactions without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.3 Hz, 2H, 4, 6), 7.16 (d, *J* = 7.9 Hz, 2H, 1, 3), 6.09 (d, *J* = 2.0 Hz, 1H, 8_{cis}), 5.74 (d, *J* = 1.9 Hz, 1H, 8_{trans}), 2.38 (s, 3H, 9).

^{13}C NMR (126 MHz, $CDCl_3$): δ 139.3 (2), 135.9 (5), 131.2 (7), 129.1 (1, 3), 127.3 (4, 6), 116.9 (8), 21.3 (9).

Spectroscopic data were in agreement with literature values.[95]

1-(1,2-Dibromoethyl)-4-fluorobenzene (**9S**)



Prepared according to General Procedure B using 4-fluorostyrene (500 mg, 4.09 mmol, 1 equiv), bromine (250 µL, 4.91 mmol, 1.2 equiv) and $CHCl_3$ (8.2 mL, 0.5 M). After 1 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a white solid (986 mg, 85%).

υ_{max} (film): 3074, 3024, 1599, 1506, 1231, 1199, 1158, 1132 cm^{-1}.

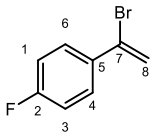
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.36 (m, 2H, 4, 6), 7.11 – 7.04 (m, 2H, 1, 3), 5.13 (dd, *J* = 11.0, 5.1 Hz, 1H, 7), 4.07 (dd, *J* = 10.3, 5.1 Hz, 1H, 8'), 3.97 (dd, *J* = 11.0, 10.3 Hz, 1H, 8'').

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.4 (2) (d, $^1J_{CF}$ = 249.2 Hz), 134.1 (5) (d, $^4J_{CF}$ = 3.5 Hz), 129.0 (4, 6) (d, $^3J_{CF}$ = 8.6 Hz), 115.4 (1, 3) (d, $^2J_{CF}$ = 21.8 Hz), 49.3 (7), 34.5 (8).

^{19}F NMR (471 MHz, $CDCl_3$): δ -111.71 (s, CF).

Spectroscopic data were in agreement with literature values.[96]

1-(1-Bromovinyl)-4-fluorobenzene (**9a**), starting material for compound **9d**



Prepared according to General Procedure C using 1-(1,2-dibromoethyl)-4-fluorobenzene **9S** (400 mg, 1.42 mmol, 1 equiv) and K_2CO_3 (392 mg, 2.84 mmol, 2 equiv), THF (2.8 mL), and methanol (2.8 mL) (1:1, 0.25 M). After 14 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a pale yellow oil (255 mg, 89%), which was immediately used in subsequent reactions without further purification.

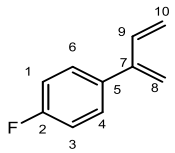
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 – 7.53 (m, 2H, 4, 6), 7.07 – 7.00 (m, 2H, 1, 3), 6.05 (d, *J* = 2.1 Hz, 1H, 8_{cis}), 5.76 (d, *J* = 2.1 Hz, 1H, 8_{trans}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.3 (2) (d, $^1J_{CF}$ = 249.8 Hz), 135.0 (5) (d, $^4J_{CF}$ = 2.8 Hz), 129.8 (7), 129.3 (4, 6) (d, $^3J_{CF}$ = 8.4 Hz), 117.8 (8), 115.3 (1, 3) (d, $^2J_{CF}$ = 21.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -112.30 (s, CF).

Spectroscopic data were in agreement with literature values.[95]

1-(Buta-1,3-dien-2-yl)-4-fluorobenzene (**9c**)



$Pd(OAc)_2$ (13.4 mg, 0.06 mmol, 4 mol%), SPhos (49.2 mg, 0.12 mmol, 8 mol%), 1-(1-bromovinyl)-4-fluorobenzene **9b** (302 mg, 1.25 mmol, 1 equiv), vinyl Bpin (243 mg, 1.57 mmol, 1.1 equiv), K_3PO_4 (953 mg, 4.5 mmol, 3 equiv), were weighed into an oven-dried flask. The reaction vessel was then purged with N_2 before the addition of 1,4-dioxane (12 mL, 0.125 M) and H_2O (135 μL, 7.5 mmol, 5 equiv). The reaction mixture was heated to 50 °C with stirring for 1 h. After the reaction was complete, the reaction mixture was left to cool to room temperature. The reaction mixture was diluted in EtOAc (20 mL), and passed through a layer of Celite®. The organic phase was washed with H_2O (2 × 20 mL) and brine (20 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 1% EtOAc in petroleum ether) to afford the desired product as a colourless oil (103 mg, 47%). Product is highly air sensitive and was used immediately in subsequent reactions.

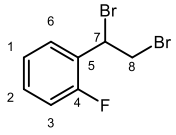
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.27 (m, 2H, 6, 4), 7.04 (ddd, *J* = 8.7, 5.8, 2.5 Hz, 2H, 1, 3), 6.61 (dd, *J* = 17.4, 10.7 Hz, 1H, 9), 5.29 (s, 1H, 8'), 5.22 (d, *J* = 10.7 Hz, 1H, 8''), 5.15 (d, *J* = 18.0 Hz, 2H, 10).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.5 (2) (d, $^1J_{CF}$ = 245.9 Hz), 147.4 (7), 138.3 (9), 135.8 (5) (d, $^4J_{CF}$ = 3.1 Hz), 130.0 (4, 6) (d, $^3J_{CF}$ = 8.1 Hz), 117.4 (8), 117.2 (10), 115.14 (1, 3) (d, *J* = 21.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -115.16 (s, CF).

Spectroscopic data were in agreement with literature values.[20]

1-(1,2-Dibromoethyl)-2-fluorobenzene (**10S**)



Prepared according to General Procedure B using 2-fluorostyrene (150 mg, 1.23 mmol, 1 equiv), bromine (75 µL, 1.47 mmol, 1.2 equiv) and $CHCl_3$ (2.5 mL, 0.5 M). After 1 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a light yellow oil (260 mg, 75%).

υ_{max} (film): 3040, 2973, 1614, 1586, 1491, 1458, 1231, 1132 cm^{-1}.

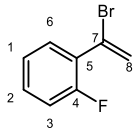
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (td, *J* = 7.6, 1.8 Hz, 1H, 6), 7.35 (dddd, *J* = 8.2, 7.2, 5.2, 1.7 Hz, 1H, 2), 7.20 (td, *J* = 7.6, 1.2 Hz, 1H, 1), 7.09 (ddd, *J* = 10.5, 8.3, 1.2 Hz, 1H, 3), 5.44 (dd, *J* = 10.9, 5.5 Hz, 1H, 7), 4.11 (t, *J* = 10.6 Hz, 1H, 8'), 4.06 (dd, *J* = 10.2, 5.5 Hz, 1H, 8'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.4 (4) (d, $^{1}J_{CF}$ = 250.1 Hz), 131.0 (6) (d, $^{3}J_{CF}$ = 8.6 Hz), 128.9 (1) (d, $^{4}J_{CF}$ = 2.9 Hz), 126.1 (5) (d, $^{2}J_{CF}$ = 12.4 Hz), 124.8 (2) (d, $^{3}J_{CF}$ = 3.7 Hz), 116.2 (3) (d, $^{2}J_{CF}$ = 21.8 Hz), 42.9 (7) (d, $^{3}J_{CF}$ = 3.3 Hz), 33.8 (8) (d, $^{4}J_{CF}$ = 2.1 Hz).

^{19}F NMR ($CDCl_3$, 376 MHz): δ -116.37 (s, CF).

Spectroscopic data were in agreement with literature values.[96]

1-(1-Bromovinyl)-2-fluorobenzene (**10a**), starting material for compound **10d**



Prepared according to General Procedure C using 1-(1,2-dibromoethyl)-2-fluorobenzene **10S** (259 mg, 0.91 mmol, 1 equiv) and K_2CO_3 (254 mg, 1.83 mmol, 2 equiv), THF (1.8 mL), and methanol (1.8 mL) (1:1, 0.25 M). After 14 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford

the desired product as a pale yellow oil (180 mg, 97%). Product is highly air sensitive and was used immediately in subsequent reactions.

υ_{max} (film): 3035, 3008, 1607, 1577, 1486, 1450, 1227, 1199, 1052 cm^{-1}.

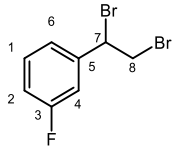
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (td, *J* = 7.7, 1.8 Hz, 1H, 6), 7.31 (tdd, *J* = 7.2, 5.0, 1.7 Hz, 1H, 2), 7.15 (td, *J* = 7.6, 1.2 Hz, 1H, 1), 7.10 – 7.04 (m, 1H, 3), 6.14 (t, *J* = 1.5 Hz, 1H, 8_{cis}), 6.03 (t, *J* = 1.5 Hz, 1H, 8_{trans}'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.3 (4) (d, $^{1}J_{CF}$ = 252.0 Hz), 131.4 (1) (d, $^{4}J_{CF}$ = 1.9 Hz), 130.7 (6) (d, $^{3}J_{CF}$ = 8.6 Hz), 129.7 (7) (d, ^{3}J = 8.6 Hz), 127.2 (5) (d, $^{2}J_{CF}$ = 12.3 Hz), 124.1 (8) (d, $^{4}J_{CF}$ = 3.7 Hz), 123.2 (2) (d, $^{3}J_{CF}$ = 6.4 Hz), 116.1 (3) (d, $^{2}J_{CF}$ = 22.4 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ -113.29 (s, CF).

Spectroscopic data were in agreement with literature values.[96]

1-(1,2-Dibromoethyl)-3-fluorobenzene (**11S**)



Prepared according to General Procedure B using 3-fluorostyrene (100 mg, 0.82 mmol, 1 equiv), bromine (50 µL, 0.98 mmol, 1.2 equiv) and $CHCl_3$ (1.6 mL, 0.5 M). After 1 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a white solid (236 mg, quant).

υ_{max} (film): 2921, 2851, 1614, 1590, 1489, 1454, 1249, 1223, 1147, 1132 cm^{-1}.

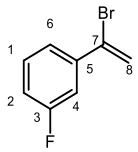
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 13.9, 7.9 Hz, 1H, 1), 7.19 (d, *J* = 7.7 Hz, 1H, 6), 7.12 (d, *J* = 9.4 Hz, 1H, 4), 7.08 – 7.02 (m, 1H, 2), 5.10 (dd, *J* = 10.9, 5.1 Hz, 1H, 7), 4.06 (dd, *J* = 10.4, 5.1 Hz, 1H, 8'), 3.97 (t, *J* = 10.7 Hz, 1H, 8'').

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.9 (3) (d, $^1J_{CF}$ = 247.4 Hz), 141.2 (5) (d, $^3J_{CF}$ = 7.3 Hz), 130.5 (1) (d, $^3J_{CF}$ = 8.1 Hz), 123.6 (6) (d, $^4J_{CF}$ = 3.3 Hz), 116.4 (2) (d, $^2J_{CF}$ = 21.1 Hz), 114.9 (4) (d, $^2J_{CF}$ = 22.4 Hz), 49.6 (7), 34.7 (8).

^{19}F NMR (376 MHz, $CDCl_3$): δ -111.86 (s, CF).

Spectroscopic data were in agreement with literature values.[96]

1-(1-Bromovinyl)-3-fluorobenzene (**11a**), starting material for compound **11d**



Prepared according to General Procedure C using 1-(1,2-dibromoethyl)-3-fluorobenzene **11S** (230 mg, 0.82 mmol, 1 equiv) and K_2CO_3 (226 mg, 1.63 mmol, 2 equiv), THF (1.7 mL), and methanol (1.7 mL) (1:1, 0.25 M). After 15 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a pale yellow oil (165 mg, quant). Product is highly air sensitive and was used immediately in subsequent reactions.

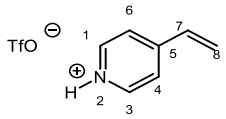
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (dt, *J* = 7.9, 1.3 Hz, 1H, 4), 7.34 – 7.29 (m, 2H, 1, 6), 7.04 (tdd, *J* = 8.2, 2.6, 1.0 Hz, 1H, 2), 6.16 (d, *J* = 2.2 Hz, 1H, 8_{cis}), 5.83 (d, *J* = 2.2 Hz, 1H, 8_{trans}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.6 (3) (d, $^1J_{CF}$ = 246.1 Hz), 140.8 (5) (d, $^3J_{CF}$ = 8.1 Hz), 129.9 (1) (d, $^3J_{CF}$ = 8.2 Hz), 129.4 (7) (d, $^4J_{CF}$ = 2.7 Hz), 123.0 (6) (d, $^4J_{CF}$ = 2.8 Hz), 118.9 (8), 116.1 (2) (d, $^2J_{CF}$ = 21.5 Hz), 114.7 (4) (d, $^4J_{CF}$ = 23.2 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ -112.90 (s, CF).

Spectroscopic data were in agreement with literature values.[98]

4-Vinylpyridinium triflate (**12S'**)



Triflic acid (300 µL, 3.42 mmol, 1.2 equiv) was added dropwise via syringe to a stirred solution of 4-vinylpyridine (300 mg, 2.85 mmol, 1 equiv) in Et_2O (6 mL, 0.5 M) at 0 °C. After 15 min, the precipitate was filtered, rinsed with diethyl ether and dried under vacuum to afford the desired product as a white solid (707 mg, 97%).

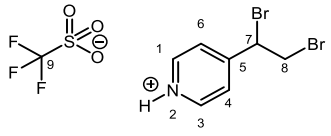
^{1}H NMR (500 MHz, DMSO-d_6): δ 8.86 (d, *J* = 6.6 Hz, 2H, 1, 3), 8.14 (d, *J* = 6.6 Hz, 2H, 4, 6), 7.01 (dd, *J* = 17.6, 10.9 Hz, 1H, 7), 6.56 (d, *J* = 17.6 Hz, 1H, 8_{trans}), 5.96 (d, *J* = 10.9 Hz, 1H, 8_{cis}). NH not observed.

^{13}C NMR (101 MHz, DMSO-d_6): δ 153.2 (5), 142.4 (1, 3), 132.9 (7), 126.8 (4, 6), 123.5 (8). CF_3 carbon not observed.

^{19}F NMR (376 MHz, DMSO-d_6): δ -77.74 (s, CF_3).

Spectroscopic data were in agreement with literature values.[99]

4-(1′,2′-Dibromoethyl)pyridinium triflate (**12S**)



Prepared according to General Procedure B using 4-vinylpyridinium triflate **12S'** (250 mg, 0.98 mmol, 1 equiv), bromine (150 µL, 2.94 mmol, 3 equiv) and $CHCl_3$ (4 mL, 0.25 M). The reaction mixture was stirred at 0 °C for 1 h followed by 1 hour at room temperature. Et_2O (10 mL) was added and the precipitate was filtered, rinsed with diethyl ether and dried under vacuum to afford the desired product as a yellow/orange solid (213 mg, 53%). Compound has low solubility.

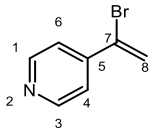
^{1}H NMR (500 MHz, DMSO-d_6): δ 8.97 (d, *J* = 6.7 Hz, 2H, 1, 3), 8.20 (d, *J* = 6.7 Hz, 2H, 4, 6), 5.79 (dd, *J* = 10.7, 5.4 Hz, 1H, 7), 4.52 (t, *J* = 10.5 Hz, 1H, 8), 4.36 (dd, *J* = 10.4, 5.4 Hz, 1H). NH not observed.

^{13}C NMR (126 MHz, DMSO-d_6): δ 143.7 (1, 3), 125.6 (4, 6), 124.0 (5), 120.7 (9) (d, $^1J_{CF}$ = 321.5 Hz), 46.0 (7), 33.2 (8).

^{19}F NMR (470 MHz, DMSO-d_6): δ -77.77 (s, CF_3).

Spectroscopic data were in agreement with literature values.[99]

4-(1-Bromovinyl)pyridine (**12a**), starting material for compound **12d**



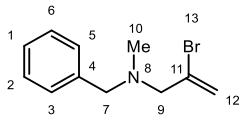
4-(1,2-Dibromoethyl)pyridine triflate **12S** (270 mg, 0.65 mmol, 1 equiv) was weighed into an oven-dried flask. The flask was sealed and purged with N_2 before the addition of MeCN (4.3 mL, 0.15 M) and cooled to 0 °C. Et_3N (450 µL, 3.25 mmol, 5 equiv) was added dropwise to the stirred solution. After 1 h, the reaction mixture was allowed to warm to room temperature and was stirred for 2 h. The reaction mixture was then concentrated under reduced pressure. To the remaining residue was added H_2O (15 mL), and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure, to afford the desired product as a red/brown oil (124 mg, quant). Product is highly air sensitive and was used immediately in subsequent reactions.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 6.1 Hz, 2H, 1, 3), 7.47 (dd, *J* = 4.6, 1.6 Hz, 2H, 4, 6), 6.36 (d, *J* = 2.4 Hz, 1H, 8_{cis}), 5.97 (d, *J* = 2.4 Hz, 1H, 8_{trans}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.3 (1, 3), 145.6 (5), 128.4 (7), 121.5 (8), 121.1 (4,6).

Spectroscopic data were in agreement with literature values.[99]

N-Benzyl-2-bromo-*N*-methylprop-2-en-1-amine (**13a**), starting material for compound **13d**



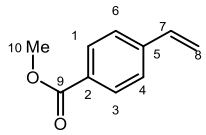
To a solution of 2,3-dibromoprop-1-ene (500 mg, 2.5 mmol, 1 equiv) in THF (8.3 mL, 0.3 M) was added *N*-methyl-1-phenylmethanamine (646 µL, 5 mmol, 2 equiv) via syringe. The reaction mixture was heated to 35 °C for 4 h. After the reaction was complete, H_2O (25 mL) was added and the organics were extracted with Et_2O (25 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography (silica gel, 20–50% EtOAc in petroleum ether) to afford the desired product as a clear oil (485 mg, 81%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (dt, *J* = 15.1, 7.2 Hz, 4H, 2, 3, 5, 6), 7.27 – 7.25 (m, 1H, 1), 5.90 (d, *J* = 1.3 Hz, 1H, 12_{cis}), 5.60 (s, 1H, 12_{trans}), 3.57 (s, 2H, 7), 3.22 (s, 2H, 9), 2.25 (s, 3H, 10).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.1 (4), 131.3 (11), 128.4 (3, 5), 127.8 (2, 6), 126.6 (1), 118.0 (12), 64.8 (9), 60.7 (7), 41.3 (10).

Spectroscopic data were in agreement with literature values.[73]

Methyl 4-vinylbenzoate (**14S'**)



Methyl-4-formylbenzoate (500 mg, 3.04 mmol, 1 equiv) and methyl triphenylphosphonium bromide (1.09 g, 3.04 mmol, 1 equiv) were weighed into an oven-dried flask. The flask was sealed and purged with N_2 before the addition of THF (15.2 mL, 0.2 M) and a solution of NaH (87.8 mg, 3.65 mmol, 1.2 equiv) in THF (7 mL). The resulting suspension was left to stir for 6 h at room temperature. After the reaction was complete, the reaction mixture was poured onto an ice/H_2O slurry (30 mL), and extracted with Et_2O (3 × 20 mL). The organic phase was collected and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was

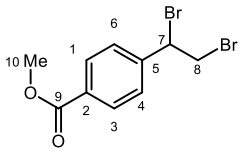
purified by column chromatography (silica gel, 0–10% EtOAc in petroleum ether) to afford the desired product as a white solid (136 mg, 27%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.4 Hz, 2H, 1, 3), 7.46 (d, *J* = 8.2 Hz, 2H, 4, 6), 6.75 (dd, *J* = 17.6, 10.9 Hz, 1H, 7), 5.86 (dd, *J* = 17.6, 0.7 Hz, 1H, 8_{trans}), 5.38 (dd, *J* = 10.9, 0.6 Hz, 1H, 8_{cis}), 3.92 (s, 3H, 10).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.0 (9), 142.1 (5), 136.2 (7), 130.1 (1, 3), 129.5 (2), 126.3 (4, 6), 116.6 (8), 52.2 (10).

Spectroscopic data were in agreement with literature values.[100]

Methyl 4-(1,2-dibromoethyl)benzoate (**14S**)



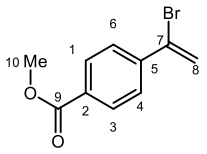
Prepared according to General Procedure B using methyl 4-vinylbenzoate **14S'** (136 mg, 0.83 mmol, 1 equiv), bromine (50 µL, 1.0 mmol, 1.2 equiv) and $CHCl_3$ (1.7 mL, 0.5 M). After 1 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a light yellow solid (269 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.5 Hz, 2H, 1, 3), 7.48 (d, *J* = 8.4 Hz, 2H, 4, 6), 5.15 (dd, *J* = 10.9, 5.2 Hz, 1H, 7), 4.08 (dd, *J* = 10.3, 5.2 Hz, 1H, 8'), 4.04 – 3.97 (m, 1H, 8''), 3.93 (s, 3H, 10).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5 (9), 143.5 (5), 131.0 (2), 130.3 (1, 3), 127.9 (4, 6), 52.4 (10), 49.5 (7), 34.5 (8).

Spectroscopic data were in agreement with literature values.[101]

Methyl 4-(1-bromovinyl)benzoate (**14a**), starting material for compound **14d**



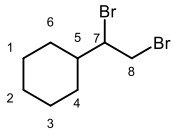
Prepared according to General Procedure C using methyl 4-(1,2-dibromoethyl)benzoate **14S** (269 mg, 0.84 mmol, 1 equiv) and K_2CO_3 (231 mg, 1.67 mmol, 2 equiv), THF (1.7 mL), and methanol (1.7 mL) (1:1, 0.25 M). After 16 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a pale yellow oil (194 mg, 96%), which was immediately used in subsequent reactions without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 – 8.00 (m, 2H, 1, 3), 7.68 – 7.64 (m, 2H, 4, 6), 6.22 (d, *J* = 2.2 Hz, 1H, 8_{cis}), 5.89 (t, *J* = 2.2 Hz, 1H, 8_{trans}), 3.93 (s, 3H, 10).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6 (9), 142.7 (5), 130.7 (7), 129.9 (2), 129.7 (1, 3), 127.4 (4, 6), 119.7 (8), 52.4 (10).

Spectroscopic data were in agreement with literature values.[102]

(1,2-Dibromoethyl)cyclohexane (**15S**)



Prepared according to General Procedure B using vinylcyclohexane (400 mg, 3.63 mmol, 1 equiv), bromine (230 µL, 4.36 mmol, 1.2 equiv) and $CHCl_3$ (7.3 mL, 0.5 M). After 1 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as colourless oil (926 mg, 94%).

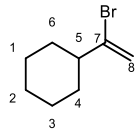
υ_{max} (film): 2924, 2853, 1449, 1437, 1227, 1161, 1132, 957, 885 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.16 (ddd, *J* = 9.0, 5.0, 3.5 Hz, 1H, 7), 3.82 (dd, *J* = 10.5, 5.2 Hz, 1H, 8'), 3.79 – 3.72 (m, 1H, 8''), 1.87 (ddt, *J* = 11.1, 7.7, 3.4 Hz, 1H, 5), 1.83 – 1.76 (m, 2H), 1.76 – 1.66 (m, 2H), 1.67 – 1.61 (m, 1H), 1.38 – 1.31 (m, 2H), 1.28 (tt, *J* = 12.7, 3.3 Hz, 1H), 1.17 (dddt, *J* = 16.4, 12.3, 8.2, 3.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 60.5 (7), 40.2 (5), 34.3 (8), 32.0, 26.7, 26.2, 26.2, 25.8.

Product mass could not be obtained by HRMS.

(1-Bromovinyl)cyclohexane (**15a**), starting material for compound **15d**



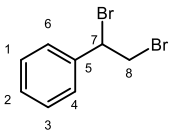
Prepared according to General Procedure C using (1,2-dibromoethyl)cyclohexane **15S** (200 mg, 0.74 mmol, 1 equiv) and K_2CO_3 (410 mg, 2.96 mmol, 4 equiv), THF (1.5 mL), and methanol (1.5 mL) (1:1, 0.25 M). After 48 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a pale yellow oil (123 mg, 88%). Product is highly air sensitive and was used immediately in subsequent reactions.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55 (dd, *J* = 1.6, 1.1 Hz, 1H, 8_{cis}), 5.37 (d, *J* = 1.8 Hz, 1H, 8_{trans}), 2.21 – 2.14 (m, 1H), 1.96 – 1.87 (m, 2H), 1.79 (dd, *J* = 8.9, 3.6 Hz, 2H), 1.73 – 1.70 (m, 1H), 1.28 (ddd, *J* = 10.2, 4.9, 2.8 Hz, 4H), 1.17 – 1.12 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.4 (7), 114.3 (8), 48.7 (5), 32.4, (2), 32.3 (4, 6), 26.1 (1,3).

Product mass could not be obtained by HRMS.

(1,2-Dibromoethyl)benzene (**16S**)



Prepared according to General Procedure B using styrene (300 mg, 2.88 mmol, 1 equiv), bromine (180 µL, 3.46 mmol, 1.2 equiv) and $CHCl_3$ (5.8 mL, 0.5 M). After 1 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a white solid (752 mg, 99%).

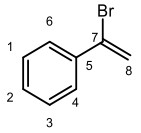
υ_{max} (film): 3063, 3029, 2975, 1497, 1456, 1432, 1199, 1134 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 – 7.32 (m, 5H, 1, 2, 3, 4, 6), 5.15 (dd, *J* = 10.6, 5.4 Hz, 1H, 7), 4.08 (dd, *J* = 10.3, 5.4 Hz, 1H, 8'), 4.03 (t, *J* = 10.5 Hz, 1H, 8'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 138.8 (5), 129.3 (2), 129.0 (1, 3), 127.8 (4, 6), 51.0 (7), 35.2 (8).

Spectroscopic data were in agreement with literature values.[16]

(1-Bromovinyl)benzene (**16a**), starting material for compound **16d**



Prepared according to General Procedure C using (1,2-dibromoethyl)benzene **16S** (400 mg, 1.51 mmol, 1 equiv) and K_2CO_3 (419 mg, 3.02 mmol, 2 equiv), THF (3 mL), and methanol (3 mL) (1:1, 0.25 M). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a pale yellow oil (254 mg, 92%), which was immediately used in subsequent reactions without further purification.

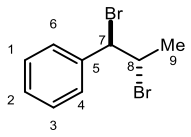
υ_{max} (film): 3059, 2923, 1698, 1681, 1597, 1448, 1279, 1194 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 – 7.59 (m, 2H, 4, 6), 7.37 – 7.32 (m, 3H, 1, 2, 3), 6.12 (d, *J* = 2.0 Hz, 1H, 8_{cis}), 5.78 (d, *J* = 2.0 Hz, 1H, 8_{trans}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.7 (5), 131.2 (7), 129.2 (2), 128.4 (1, 3), 127.5 (4, 6), 117.8 (8).

Spectroscopic data were in agreement with literature values.[17]

trans-(1,2-Dibromopropyl)benzene (**17S**)



Prepared according to General Procedure B using trans-β-methylstyrene (300 mg, 2.54 mmol, 1 equiv), bromine (160 µL, 3.05 mmol, 1.2 equiv) and $CHCl_3$ (5.1 mL, 0.5 M).

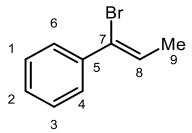
After 2 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a white solid (703 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.31 (m, 5H, 1, 2, 3, 4, 6), 5.04 (d, *J* = 10.2 Hz, 1H, 7), 4.60 (dq, *J* = 10.2, 6.5 Hz, 1H, 8), 2.05 (d, *J* = 6.5 Hz, 3H, 9).

^{13}C NMR (126 MHz, $CDCl_3$): δ 140.7 (5), 128.9 (2), 128.8 (1, 3), 127.9 (4, 6), 59.3 (7), 51.3 (8), 26.0 (9).

Spectroscopic data were in agreement with literature values.[18]

(*Z*)-(1-Bromoprop-1-en-1-yl)benzene (**17a**), starting material for compound **17d**



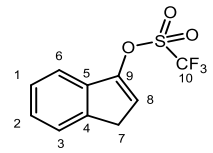
Prepared according to General Procedure C using *trans*-(1,2-dibromopropyl)benzene **17S** (300 mg, 1.08 mmol, 1 equiv) and K_2CO_3 (298 mg, 2.16 mmol, 2 equiv), THF (2.1 mL), and methanol (2.1 mL) (1:1, 0.25 M). After 15 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a pale yellow oil (151 mg, 71%), which was immediately used in subsequent reactions without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.35 (m, 4H, 1, 3, 4, 6), 7.33 – 7.29 (m, 1H, 2), 6.28 (q, *J* = 7.3 Hz, 1H, 8), 1.67 (d, *J* = 7.3 Hz, 3H, 9).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.6 (5), 129.3 (1, 3), 129.1 (2), 128.5 (8), 128.3 (4, 6), 120.7 (7), 16.6 (9).

Spectroscopic data were in agreement with literature values.[19]

1H-inden-3-yl trifluoromethanesulfonate (**18a**), starting material for failed substrate **18d**



Prepared according to General Procedure A using 2-tetralone (500 mg, 3.78 mmol, 1 equiv), triflic anhydride (1.27 mL, 7.57 mmol, 2 equiv), Et_3N (1.05 mL, 7.57 mmol, 2 equiv) and CH_2Cl_2 (15.1 mL, 0.25 M). After 13 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% EtOAc in petroleum ether) to afford the desired product as a pale yellow oil (478 mg, 48%).

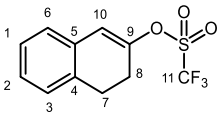
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.3 Hz, 1H, 6), 7.43 (d, *J* = 7.4 Hz, 1H, 3), 7.39 (t, *J* = 7.2 Hz, 1H, 1), 7.34 (td, *J* = 7.3, 1.1 Hz, 1H, 2), 6.38 (t, *J* = 2.3 Hz, 1H, 8), 3.49 (d, *J* = 2.2 Hz, 2H, 7).

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.5 (9), 140.7 (5), 136.1 (4), 126.5 (6), 126.4 (3), 124.0 (1), 118.2 (10) (d, *J* = 320.6 Hz), 117.7 (2), 117.6 (8), 34.3 (7).

^{19}F NMR (376 MHz, $CDCl_3$): δ -73.11 (s, CF_3).

Spectroscopic data were in agreement with literature values.[106]

3,4-dihydronaphthalen-2-yl-trifluoromethanesulfonate (**19a**), starting material for failed substrate **19d**



Prepared according to General Procedure A using 2-tetralone (300 mg, 2.05 mmol, 1 equiv), triflic anhydride (0.69 mL, 22.7 mmol, 2 equiv), Et_3N (0.57 mL, 22.7 mmol, 2 equiv) and CH_2Cl_2 (8.2 mL, 0.25 M). After 13 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% EtOAc in petroleum ether) to afford the desired product as a pale yellow oil (153 mg, 27%).

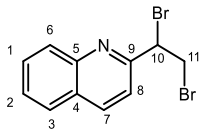
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (dd, *J* = 5.5, 2.9 Hz, 2H, 2, 6), 7.14 (dd, *J* = 5.4, 3.1 Hz, 1H, 1), 7.10 – 7.05 (m, 1H, 3), 6.48 (s, 1H, 10), 3.06 (t, *J* = 8.4 Hz, 2H, 7), 2.70 (t, *J* = 12.2, 4.6 Hz, 2H, 8).

^{13}C NMR (126 MHz, $CDCl_3$): δ 150.1 (9), 133.1 (4), 131.3 (5), 128.6 (6), 127.7 (3), 127.5 (1), 127.2 (2), 118.8 (11) (d, $^{1}J_{CF}$ = 320.6 Hz), 118.7 (10), 28.7 (8), 26.7 (7).

^{19}F NMR (471 MHz, $CDCl_3$): δ -73.54 (s, CF_3).

Spectroscopic data were in agreement with literature values.[106]

2-(1,2-dibromoethyl)quinoline (**20S**)



Prepared according to General procedure B using 2-vinylquinoline (100 mg, 0.64 mmol, 1 equiv), bromine (0.04 mL, 0.77 mmol, 1.2 equiv) and chloroform (1.3 mL, 0.5M). After 1 h, the reaction mixture was subjected to the purification outlined in general procedure C to afford the desired product as a brown solid (202.9 mg, quant). Compound was used in next step without further purification.

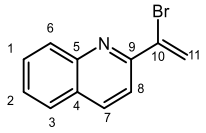
υ_{max} (film): 3055, 1597, 1506, 1429, 1142, 758, 592 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.4 Hz, 1H, 7), 8.12 (d, *J* = 8.5 Hz, 1H, 6), 7.83 (d, *J* = 8.1 Hz, 1H, 3), 7.75 (dd, *J* = 8.3, 7.0 Hz, 1H, 1), 7.58 (t, *J* = 7.5 Hz, 1H, 2), 7.50 (d, *J* = 8.5 Hz, 1H, 8), 5.42 (dd, *J* = 10.8, 4.9 Hz, 1H, 10), 4.54 (dd, *J* = 10.8, 9.9 Hz, 1H, 11'), 4.13 (dd, *J* = 9.9, 4.9 Hz, 1H, 11'').

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.9 (9), 147.8 (5), 137.5 (7), 130.2 (1), 129.8 (6), 127.9 (4), 127.7 (3), 127.4 (2), 120.3 (8), 50.6 (10), 33.0 (11).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_{10}N^{81}Br_2$) requires *m/z* 317.9134, found *m/z* 317.9130.

2-(1-bromovinyl)quinoline (**20a**), starting material for failed substrate **20d**



Prepared according to General procedure C using **20S** (202.9 mg, 0.64 mmol, 1 equiv.) and K_2CO_3 (178 mg, 1.29 mmol, 2 equiv.), THF (1.5 mL), and methanol (1.5 mL). After 24 h, the reaction mixture was subjected to the purification outlined in general procedure C, with the exception of using sat NH_4Cl during work up, to afford the desired product as a orange/brown solid (116.9 mg, 77 %). Product is air sensitive and was used immediately in subsequent reactions.

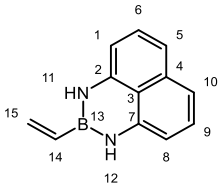
υ_{max} (film): 3059, 2922, 1593, 1501, 1080, 827, 756 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.6 Hz, 1H, 7), 8.12 (d, *J* = 8.5 Hz, 1H, 6), 7.87 (d, *J* = 8.6 Hz, 1H, 8), 7.82 (d, *J* = 8.1 Hz, 1H, 3), 7.74 (t, *J* = 7.7 Hz, 1H, 1), 7.56 (t, *J* = 7.5 Hz, 1H, 2), 6.92 (d, *J* = 1.5 Hz, 1H, 11'), 6.12 (d, *J* = 1.5 Hz, 1H, 11").

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.4 (9), 147.5 (5), 138.9 (10), 137.1 (7), 130.2 (1), 129.9 (6), 127.7 (4), 127.5 (3), 127.3 (2), 122.2 (12), 119.6 (8).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_9{}^{79}Br$) requires *m/z* 233.9913, found *m/z* 233.9913.

2-Vinyl-2,3-dihydro-1*H*-naphtho[1,8-de][1,3,2]diazaborinine (**21S**)



Vinyl Bpin (100 mg, 0.65 mmol, 1 equiv) was weighed into an oven-dried flask before the addition of MeCN (2.6 mL, 0.25 M) and $FeCl_3$ (5.3 mg, 0.03 mmol, 5 mol%) as a solution in H_2O and MeCN (1:1) via syringe. Imidazole (132 mg, 1.95 mmol, 3 equiv) and 1,8-diaminonaphthalene (103 mg, 0.65 mmol, 1 equiv) were added sequentially and the flask was placed under an argon atmosphere. The reaction mixture was left to stir for 1 h at room temperature. After the reaction was complete, the reaction mixture

was diluted in EtOAc (20 mL), and passed through a layer of Celite®. The organic phase was washed with H_2O (2 × 20 mL) and brine (20 mL). The organic phase as then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–5% EtOAc in petroleum ether) to afford the desired product as a grey/blue solid (116 mg, 92%).

υ_{max} (film): 3402, 3051, 1628, 1595, 1504, 1418, 1398, 1371, 1331, 1148, 1049 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 – 7.07 (m, 2H, 6, 9), 7.02 (d, *J* = 8.1 Hz, 2H, 5, 10), 6.33 (d, *J* = 7.3 Hz, 2H, 1, 8), 6.04 (dd, *J* = 20.7, 12.4 Hz, 1H, 14), 5.91 (dd, *J* = 17.3, 3.0 Hz, 2H, 15), 5.75 (s, 2H, 11, 12).

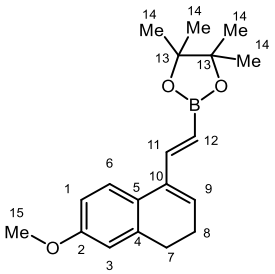
^{13}C NMR (101 MHz, $CDCl_3$): δ 141.2 (2, 7), 136.5 (4), 130.9 (15), 127.7 (6, 9), 120.0 (3), 117.8 (5, 10), 105.9 (1, 8). Carbon bearing boron not observed due to quadrupolar relaxation.

^{11}B NMR (128 MHz, $CDCl_3$): δ 28.16.

HRMS (ESI): exact mass calculated for $[M]^+$ ($C_{12}H_{11}N_2B$) requires *m/z* 194.1015, found *m/z* 194.1006.

Spectroscopic data were in agreement with literature values.[21]

(*E*)-2-(2-(6-Methoxy-3,4-dihydronaphthalen-1-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**28b**)



$Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **1a** (77.0 mg, 0.25 mmol, 1 equiv), vinyl Bpin (76.9 mg, 0.5 mmol, 2 equiv) and AgOAc (83.4 mg, 0.5 mmol, 2 equiv) were weighed into an oven-dried microwave vial. The reaction vessel

was then capped and purged with N_2 before the addition of 1,4-dioxane (1 mL, 0.25 M) and distilled Et_3N (104 µL, 0.75 mmol, 3 equiv). The reaction mixture was heated to 40 °C and with stirring for 24 h. After the reaction was complete, the reaction mixture was allowed to cool to room temperature and was vented and de-capped. The reaction mixture was diluted in EtOAc (20 mL) and passed through a layer of Celite®. The mixture was then washed with H_2O (3 × 20 mL) and separated. The combined organics were washed with brine (20 mL), before being dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–5% EtOAc in petroleum ether) to afford the desired product as a yellow oil (24.8 mg, 32%). Product is highly air sensitive and was used immediately in subsequent reactions.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.3 Hz, 1H, 6), 7.32 – 7.26 (m, 1H, 11), 6.74 – 6.69 (m, 2H, 1, 3), 6.22 (td, *J* = 4.9, 1.0 Hz, 1H, 9), 5.94 (d, *J* = 18.3 Hz, 1H, 12), 3.80 (s, 3H, 15), 2.70 (t, *J* = 7.8 Hz, 2H, 7), 2.30 (td, *J* = 7.7, 4.9 Hz, 2H, 8), 1.30 (s, 12H, 14).

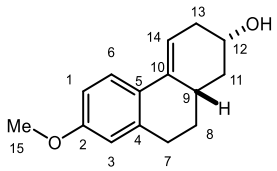
^{13}C NMR (126 MHz, $CDCl_3$): δ 158.6 (2), 148.7 (11), 138.8 (5), 136.9 (4), 127.9 (9), 126.7 (10), 125.8 (6), 113.8 (1), 110.9 (3), 83.4 (13), 55.4 (15), 28.8 (7), 25.0 (14), 23.6 (8). Carbon bearing boron not observed due to quadrupolar relaxtion.

^{11}B NMR (96 MHz, $CDCl_3$): δ 30.41.

2.6.4.2. Products from substrate scope

Following compounds will display data of the major regioisomer isolated. Both the appearance and quoted yields represent the mixture of regioisomers formed.

Compound 1d



Prepared according to General Procedure E using 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **1a** (77.0 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–60% EtOAc in petroleum ether) to afford the desired mixture of products as a yellow oil (41.3 mg, 72%, 3:1 r.r.). The major regioisomer was separated by column chromatography (c.a. 95% purity).

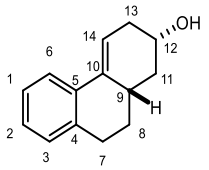
υ_{max} (film): 3364 (br), 2914, 2847, 2830, 1605, 1493, 1456, 1279, 1253, 1231, 1034 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.8 Hz, 1H, 6), 6.71 (dd, *J* = 8.8, 2.5 Hz, 1H, 1), 6.60 (d, *J* = 2.6 Hz, 1H, 3), 6.07 – 6.02 (m, 1H, 14), 4.04 – 3.95 (m, 1H, 12), 3.79 (s, 3H, 15), 2.95 – 2.75 (m, 2H, 7), 2.61 - 2.54 (m, 1H, 13'), 2.52 – 2.39 (m, 1H, 9), 2.23 – 2.10 (m, 2H, 11', 13''), 2.02 – 1.94 (m, 1H, 8'), 1.54 – 1.49 (m, 1H, 8''), 1.46 – 1.36 (m, 1H, 11'').

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7 (2), 138.0 (4), 135.7 (5), 127.1 (10), 125.1 (6), 115.5 (14), 113.4 (3), 112.9 (1), 67.7 (12), 55.4 (15), 40.7 (11), 36.7 (9), 36.1 (13), 31.2 (8), 30.5 (7).

HRMS (NSI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}O_2$) requires *m/z* 231.1380, found *m/z* 231.1378.

Compound 2d



Prepared according to General Procedure E using 3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **2a** (69.5 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01

mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (192.3 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–25% EtOAc in petroleum ether) to afford the desired mixture of products as a yellow solid (43.9 mg, 88%, 3.1:1 r.r.). The major regioisomer was separated by column chromatography (c.a. 99% purity).

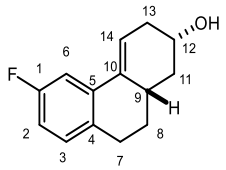
υ_{max} (film): 3364 (br), 2914, 2842, 1456, 1480, 1432, 1088, 1037, 1000 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 5.5, 3.8 Hz, 1H, 2), 7.16 – 7.11 (m, 2H, 1, 3), 7.11 – 7.06 (m, 1H, 6), 6.21 (dt, *J* = 5.2, 2.4 Hz, 1H, 14), 4.06 - 3.97 (m, 1H, 12), 3.00 – 2.78 (m, 2H, 7), 2.64 - 2.57 (m, 1H, 13'), 2.55 – 2.43 (m, 1H, 9), 2.26 – 2.12 (m, 2H, 11', 13''), 2.05 – 1.97 (m, 1H, 8'), 1.54 (dd, *J* = 12.6, 5.5 Hz, 1H, 8''), 1.43 (q, 1H, 11'').

^{13}C NMR (101 MHz, $CDCl_3$): δ 136.6 (5), 136.2 (4), 134.1 (10), 129.5 (6), 127.1 (3), 126.1 (1), 123.7 (2), 117.6 (14), 67.6 (12), 40.7 (11), 36.6 (9), 36.2 (13), 31.2 (8), 30.1 (7).

HRMS (NSI): exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}O$) requires *m/z* 201.1274, found *m/z* 201.1272.

Compound 3d



Prepared according to General Procedure E using 7-fluoro-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **3a** (74.0 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5

mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% EtOAc in petroleum ether) to afford the desired mixture of products as a pale yellow solid (40.3 mg, 74%, 3.2:1 r.r. (as an average of two experiments)). The major regioisomer was separated by column chromatography (c.a. 95% purity).

υ_{max} (film): 3347 (br), 2920, 2851, 1610, 1582, 1489, 1437, 1261, 1041 cm^{-1}.

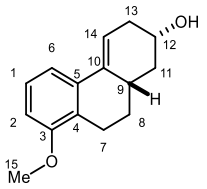
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 11.1, 2.6 Hz, 1H, 6), 7.03 (dd, *J* = 8.3, 6.2 Hz, 1H, 3), 6.83 (td, *J* = 8.3, 2.6 Hz, 1H, 2), 6.19 – 6.14 (m, 1H, 14), 4.05 – 3.96 (m, 1H, 12), 2.82 (dd, *J* = 10.4, 4.5 Hz, 2H, 7), 2.65 – 2.56 (m, 1H, 13'), 2.45 (s, 1H, 9), 2.25 – 2.18 (m, 1H, 13''), 2.19 – 2.13 (m, 1H, 11'), 2.00 (ddd, *J* = 10.8, 7.3, 3.9 Hz, 1H, 8'), 1.54 – 1.47 (m, 1H, 8''), 1.43 – 1.37 (m, 1H, 11'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.6 (1) (d, $^{1}J_{CF}$ = 242.1 Hz), 135.9 (5) ((d, $^{3}J_{CF}$ = 7.0 Hz), 135.6 (4) (d, $^{4}J_{CF}$ = 2.4 Hz), 132.2 (10) (d, $^{4}J_{CF}$ = 2.8 Hz), 130.8 (3) (d, $^{3}J_{CF}$ = 7.9 Hz), 119.0 (14), 114.1 (2) (d, $^{2}J_{CF}$ = 21.6 Hz), 109.8 (6) (d, $^{2}J_{CF}$ = 22.0 Hz), 67.4 (12), 40.6 (11), 36.3 (9), 36.1 (13), 31.1 (8), 29.5 (7).

^{19}F NMR (376 MHz, $CDCl_3$): δ -117.53 (s, CF).

HRMS (ASAP): exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}FO$) requires *m/z* 219.1182, found *m/z* 219.1185.

Compound 4d



Prepared according to General Procedure E using 5-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **4a** (77.0 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M)

and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% EtOAc in petroleum ether) to afford the desired mixture of products as a pale yellow solid (42.9 mg, 75%, 3.3:1 r.r. (as an average of two experiments)). The major regioisomer was separated by column chromatography (c.a. 96% purity).

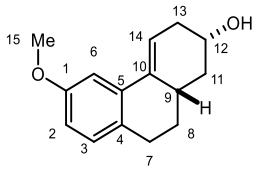
υ_{max} (film): 3353 (br), 2918, 2851, 2832, 1575, 1473, 1458, 1437, 1346, 1259, 1095, 1041 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.0 Hz, 1H, 6), 7.11 (t, *J* = 8.0 Hz, 1H, 1), 6.70 (d, *J* = 7.9 Hz, 1H, 2), 6.22 – 6.18 (m, 1H, 14), 4.04 – 3.94 (m, 1H, 12), 3.82 (s, 3H, 15), 2.99 (dd, *J* = 17.6, 3.9 Hz, 1H, 7'), 2.65 – 2.47 (m, 2H, 7'', 13'), 2.46-2.42 (m, 1H, 9), 2.36 – 2.19 (m, 1H, 13''), 2.19 – 2.13 (m, 1H, 11'), 2.10 – 2.02 (m, 1H, 8'), 1.53 – 1.47 (m, 1H, 8''), 1.44 – 1.38 (m, 1H, 11'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.5 (3), 136.4 (5), 135.4 (4), 126.2 (1), 125.8 (10), 118.0 (14), 116.1 (6), 108.1 (2), 67.6 (12), 55.5 (15), 40.8 (11), 36.2 (13), 35.9 (9), 30.7 (8), 23.5 (7).

HRMS (NSI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}O_2$) requires *m/z* 231.1380, found *m/z* 231.1381.

Compound 5d



Prepared according to General Procedure E using 7-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **5a** (77.0 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5

mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 5–20% EtOAc in petroleum ether) to afford the desired mixture of products as a pale yellow oil (46.9 mg, 81%, 3.3:1 r.r. (as an average of two experiments)). The major regioisomer was separated by column chromatography (c.a. 99% purity).

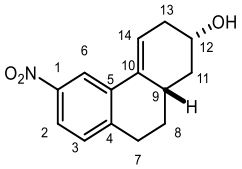
υ_{max} (film): 3332 (br), 2914, 2849, 2830, 1607, 1571, 1493, 1458, 1432, 1279, 1249, 1207, 1039 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (dd, *J* = 7.9, 2.6 Hz, 1H, 6), 7.00 (d, *J* = 8.4 Hz, 1H, 3), 6.74 (dd, *J* = 8.4, 2.6 Hz, 1H, 2), 6.22 – 6.14 (m, 1H, 14), 4.05 – 3.96 (m, 1H, 12), 3.80 (s, 3H, 15), 2.90 – 2.73 (m, 2H, 7), 2.65 – 2.56 (m, 1H, 13'), 2.46-2.42 (m, 1H, 9), 2.21 (ddt, *J* = 14.3, 6.4, 3.2 Hz, 1H, 13''), 2.19 – 2.12 (m, 1H, 11'), 2.03 – 1.93 (m, 1H, 8'), 1.51 (dd, *J* = 12.5, 5.7 Hz, 1H, 8''), 1.46 – 1.38 (m, 1H, 11'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0 (1), 136.3 (5), 135.0 (4), 130.4 (3), 129.2 (10), 117.9 (14), 113.9 (2), 108.1 (6), 67.6 (12), 55.3 (15), 40.8 (11), 36.6 (9), 36.2 (13), 31.5 (8), 29.3 (7).

HRMS (ASAP): exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}O_2$) requires *m/z* 231.1385, found *m/z* 231.1386.

Compound 6d



Prepared according to General Procedure E using 7-nitro-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate **6a** (70.8 mg, 0.22 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.0 mg, 0.008 mmol, 4 mol%), SPhos (7.2 mg, 0.016 mmol, 8 mol%), vinyl Bpin (168.2 mg, 1.1 mmol, 5 equiv), K_3PO_4 (138.9 mg, 0.66 mmol, 3 equiv), 1,4-dioxane (1.75 mL, 0.125 M) and H_2O (19.6 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 460 µL, 4.4 mmol, 20 equiv), 2 M NaOH (440 µL, 0.88 mmol, 4 equiv) and THF (880 µL).

After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 5–40% EtOAc in petroleum ether) to afford the desired mixture of products as a yellow solid (38.8 mg, 72%, 3.3:1 r.r. (as an average of two experiments)). The major regioisomer was separated by column chromatography (c.a. 89% purity).

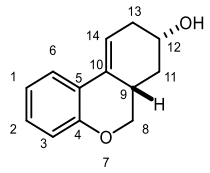
υ_{max} (film): 3349 (br), 2921, 2851, 1517, 1460, 1344, 1268, 1106, 1090, 1043 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (dd, *J* = 11.5, 2.1 Hz, 1H, 6), 7.94 (dd, *J* = 8.4, 2.0 Hz, 1H, 2), 7.22 (d, *J* = 8.4 Hz, 1H, 3), 6.40 – 6.35 (m, 1H, 14), 4.08 – 3.98 (m, 1H, 12), 3.00 – 2.90 (m, 2H, 7), 2.66 (ddd, *J* = 19.7, 12.7, 7.1 Hz, 1H, 13'), 2.55 – 2.45 (m, 1H, 9), 2.29 – 2.23 (m, 1H, 13''), 2.23 – 2.15 (m, 1H, 11'), 2.10 – 2.01 (m, 1H, 8'), 1.56 – 1.50 (m, 1H, 8''), 1.43 (dd, *J* = 12.5, 10.6 Hz, 1H, 11'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 143.8 (1), 135.6 (4), 134.6 (5), 130.4 (3), 121.3 (2), 121.2 (10), 121.0 (14), 119.1 (6), 67.2 (12), 40.2 (11), 36.1 (13), 36.1(9), 30.3 (7), 30.2 (8).

HRMS (NSI): exact mass calculated for $[M-H]^-$ ($C_{14}H_{14}O_3N$) requires *m/z* 244.0979, found *m/z* 244.0980.

Compound 7d



Prepared according to General Procedure E using 2*H*-chromen-4-yl trifluoromethanesulfonate **7a** (70.0 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 5–40% EtOAc in petroleum ether) to afford the desired

mixture of products as a white solid (25.3 mg, 50%, 1.9:1 r.r. (as an average of two experiments)). The major regioisomer was separated by column chromatography (c.a. 98% purity).

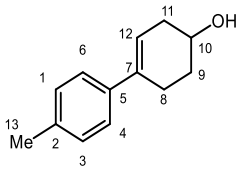
υ_{max} (film): 3351 (br), 3061, 3029, 2914, 2875, 1573, 1482, 1452, 1281, 1235, 1214, 1045 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 7.9, 1.2 Hz, 1H, 6), 7.19 – 7.06 (m, 1H, 2), 6.92 – 6.86 (m, 1H, 1), 6.83 (d, *J* = 8.2 Hz, 1H, 3), 6.14 – 6.09 (m, 1H, 14), 4.32 – 4.29 (m, 1H, 12), 4.28 (d, *J* = 4.6 Hz, 1H, 8'), 3.76 (dd, *J* = 12.1, 10.4 Hz, 1H, 8''), 2.96 (d, *J* = 2.4 Hz, 1H, 9), 2.61 (ddd, *J* = 19.2, 7.2, 3.5 Hz, 1H, 13'), 2.42 – 2.30 (m, 1H, 13''), 2.05 – 1.90 (m, 1H, 11'), 1.28 – 1.24 (m, 1H, 11'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.4 (4), 131.0 (5), 128.7 (2), 123.8 (6), 121.2 (10), 120.9 (1), 117.5 (3), 114.4 (14), 71.0 (8), 64.3 (12), 34.4 (13), 31.0 (11), 28.6 (9).

HRMS (ASAP): exact mass calculated for $[M+H]^+$ ($C_{13}H_{15}O_2$) requires *m/z* 203.1072, found *m/z* 203.1076.

Compound 8d



Prepared according to General Procedure E using 1-(1-bromovinyl)-4-methylbenzene **8a** (49.2 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (269 mg, 1.75 mmol, 7 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–20% EtOAc in petroleum ether) to afford the desired mixture of products as a white solid (30.2 mg, 64%, 4:1 r.r. (as an average of two experiments)). The major regioisomer was separated by column chromatography.

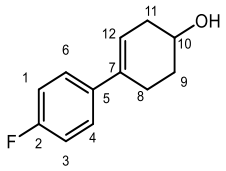
υ_{max} (film): 3304 (br), 2918, 2851, 1720, 1512, 1454, 1437, 1076, 1049 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.1 Hz, 2H, 4, 6), 7.12 (d, *J* = 8.0 Hz, 2H, 1, 3), 5.95 (s, 1H, 12), 4.08 – 4.02 (m, 1H, 10), 2.62 – 2.53 (m, 2H, 8', 11'), 2.53 – 2.46 (m, 1H, 8''), 2.33 (s, 3H, 13), 2.25 – 2.16 (m, 1H, 11''), 2.06 – 1.98 (m, 1H, 9'), 1.82 (ddd, *J* = 15.5, 8.7, 4.4 Hz, 1H, 9'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 138.9 (2), 136.7 (5), 136.3 (7), 129.1 (1, 3), 125.1 (4, 6), 120.6 (12), 66.8 (10), 35.1 (11), 31.4 (9), 25.7 (8), 21.2 (13).

HRMS (ASAP): exact mass calculated for $[M\text{-}OH]^+$ ($C_{13}H_{15}$) requires *m/z* 171.1174, found *m/z* 171.1178.

Compound 9d



Prepared according to General Procedure E using 1-(1-bromovinyl)-4-fluorobenzene **9a** (50.2 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (269 mg, 1.75 mmol, 7 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–20% EtOAc in petroleum ether) to afford the desired mixture of products as a white solid (34.9 mg, 72%, 3.7:1 r.r.). The major regioisomer was separated by column chromatography (c.a. 92% purity).

υ_{max} (film): 3232 (br), 2920, 2892, 2840, 1599, 1508, 1367, 1229, 1075, 1049 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.29 (m, 2H, 4, 6), 7.02 – 6.96 (m, 2H, 1, 3), 5.93 (t, *J* = 3.9 Hz, 1H, 12), 4.09 – 4.02 (m, 1H, 10), 2.63 – 2.53 (m, 2H, 8', 11'), 2.53

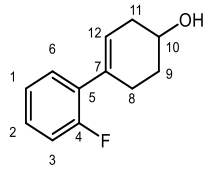
– 2.44 (m, 1H, 8’’), 2.26 – 2.16 (m, 1H, 11’’), 2.06 – 1.96 (m, 1H, 9’), 1.87 – 1.78 (m, 1H, 9’’).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.1 (2) (d, $^1J_{CF}$ = 246.0 Hz), 137.8 (5) (d, $^4J_{CF}$ = 3.2 Hz), 135.6 (7), 126.7 (4, 6) (d, $^3J_{CF}$ = 7.8 Hz), 121.4 (12), 115.1 (1, 3) (d, $^2J_{CF}$ = 21.0 Hz), 66.6 (10), 35.0 (11), 31.2 (9), 25.8 (8).

^{19}F NMR (376 MHz, $CDCl_3$): δ -116.12 (s, CF).

HRMS (EI): exact mass calculated for $[M]^+$ ($C_{12}H_{13}FO$) requires *m/z* 192.0950, found *m/z* 192.0956.

Compound 10d



Prepared according to General Procedure E using 1-(1-bromovinyl)-2-fluorobenzene **10a** (50.2 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (269 mg, 1.75 mmol, 7 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–20% EtOAc in petroleum ether) to afford the desired mixture of products as a yellow oil (33.4 mg, 69%, 3.4:1 r.r. (as an average of two experiments)). The major regioisomer was separated by column chromatography (c.a. 88% purity).

υ_{max} (film): 3319 (br), 2921, 2851, 1486, 1447, 1214, 1199, 1073, 1050 cm^{-1}.

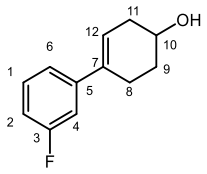
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.16 (m, 2H, 2, 6), 7.08 (td, *J* = 7.5, 1.2 Hz, 1H, 1), 7.05 – 6.98 (m, 1H, 3), 5.85 – 5.81 (m, 1H, 12), 4.12 – 4.05 (m, 1H, 10), 2.60 (dd, *J* = 8.0, 3.6 Hz, 1H, 11’), 2.56 – 2.49 (m, 2H, 8), 2.27 – 2.15 (m, 1H, 11’’), 2.00 (dtdd, *J* = 12.6, 5.5, 3.1, 1.5 Hz, 1H, 9’), 1.87 – 1.74 (m, 1H, 9’’).

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.0 (4) (d, $^1J_{CF}$ = 247.0 Hz), 133.5 (7), 130.6 (5) (d, $^2J_{CF}$ = 13.7 Hz), 129.4 (6) (d, $^3J_{CF}$ = 4.5 Hz), 128.4 (2) (d, $^3J_{CF}$ = 8.4 Hz), 125.1 (12) (d, $^4J_{CF}$ = 3.1 Hz), 124.1 (1) (d, $^4J_{CF}$ = 3.6 Hz), 115.9 (3) (d, $^2J_{CF}$ = 23.2 Hz), 66.6 (10), 35.0 (11), 31.3 (9), 26.9 (8) (d, $^4J_{CF}$ = 3.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -115.29 (s, CF).

HRMS (EI): exact mass calculated for $[M]^+$ ($C_{12}H_{13}FO$) requires *m/z* 192.0950, found *m/z* 192.0955.

Compound 11d



Prepared according to General Procedure E using 1-(1-bromovinyl)-3-fluorobenzene **11a** (50.2 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (269 mg, 1.75 mmol, 7 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–20% EtOAc in petroleum ether) to afford the desired mixture of products as a pale yellow solid (33.3 mg, 69%, 3.7:1 r.r. (as an average of two experiments)). The major regioisomer was separated by column chromatography (c.a. 91% purity).

υ_{max} (film): 3249 (br), 2918, 2905, 2834, 1580, 1489, 1428, 1259, 1073, 1063 cm^{-1}.

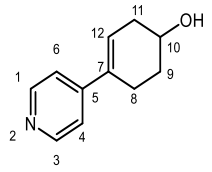
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.23 (m, 1H, 1), 7.15 (d, *J* = 7.9 Hz, 1H, 6), 7.07 (dt, *J* = 10.8, 2.0 Hz, 1H, 4), 6.92 (td, *J* = 8.3, 2.0 Hz, 1H, 2), 6.05 – 6.01 (m, 1H. 12), 4.11 – 4.01 (m, 1H, 10), 2.62 – 2.53 (m, 2H, 8', 11'), 2.49 (dtd, *J* = 17.2, 5.8, 2.9 Hz, 1H, 8''), 2.22 (ddt, *J* = 15.2, 6.5, 3.1 Hz, 1H, 11''), 2.06 – 1.96 (m, 1H, 9'), 1.83 (ddd, *J* = 15.6, 8.5, 4.4 Hz, 1H, 9'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.1 (3) (d, $^1J_{CF}$ = 244.5 Hz), 144.1 (5) (d, $^3J_{CF}$ = 7.6 Hz), 135.5 (7) (d, $^4J_{CF}$ = 1.7 Hz), 129.8 (1) (d, $^3J_{CF}$ = 8.4 Hz), 122.7 (12), 120.8 (6) (d, $^4J_{CF}$ = 2.7 Hz), 113.7 (2) (d, $^2J_{CF}$ = 21.2 Hz), 112.1 (4) (d, $^2J_{CF}$ = 21.9 Hz), 66.5 (10), 35.0 (11), 31.2 (9), 25.5 (8).

^{19}F NMR (376 MHz, $CDCl_3$): δ -113.72 (s, CF).

HRMS (EI): exact mass calculated for $[M]^+$ ($C_{12}H_{13}FO$) requires *m/z* 192.0950, found *m/z* 192.0955.

Compound 12d



Prepared according to General Procedure E using 4-(1-bromovinyl)pyridine **12a** (46.0 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (269 mg, 1.75 mmol, 7 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure, with the exception of using $NaHCO_3$ (20 mL) instead of NH_4Cl during the work-up, (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired mixture of products as a grey/brown solid (17.3 mg, 39%, 4.5:1 r.r. (as an average of two experiments)). The major regioisomer was separated by column chromatography (c.a. 99% purity).

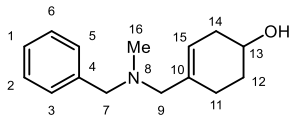
υ_{max} (film): 3293 (br), 3033, 2921, 2853, 1599, 1437, 1415, 1078, 1056 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 2H, 1, 3), 7.27 (d, *J* = 3.2 Hz, 2H, 4, 6), 6.25 (ddt, *J* = 4.9, 3.4, 1.5 Hz, 1H, 12), 4.16 – 4.04 (m, 1H, 10), 2.68 – 2.54 (m, 2H, 8', 11'), 2.54 – 2.43 (m, 1H, 8''), 2.25 (ddt, *J* = 15.3, 6.8, 3.3 Hz, 1H, 11''), 2.03 (dddd, *J* = 10.3, 8.8, 5.0, 2.4 Hz, 1H, 9'), 1.90 – 1.79 (m, 1H, 9'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 149.9 (1, 3), 148.6 (5), 134.3 (7), 125.4 (12), 119.8 (4, 6), 66.2 (10), 35.0 (11), 30.9 (9), 24.6 (8).

HRMS (NSI): exact mass calculated for $[M+H]^+$ ($C_{11}H_{14}NO$) requires *m/z* 176.1070, found *m/z* 176.1068.

Compound 13d



Prepared according to General Procedure E using *N*-benzyl-2-bromo-*N*-methylprop-2-en-1-amine **13a** (60.1 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv) 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired mixture of products as a pale yellow oil (26.9 mg, 46%, 2.9:1 r.r.). The major regioisomer was separated by column chromatography (c.a. 85% purity).

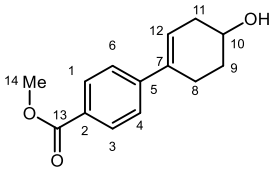
υ_{max} (film): 3321 (br), 2918, 2834, 2780, 1495, 1454, 1365, 1075, 1054, 1023 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.27 (m, 4H, 2, 3, 5, 6), 7.23 (tt, *J* = 5.7, 2.8 Hz, 1H, 1), 5.51 (s, 1H, 15), 3.99 – 3.90 (m, 1H, 13), 3.47 – 3.36 (m, 2H, 7), 2.86 (s, 2H, 9), 2.41 (dd, *J* = 31.8, 18.9 Hz, 1H, 14'), 2.29 – 2.20 (m, 1H, 11'), 2.16 (tq, *J* = 6.0, 2.4 Hz, 1H, 11''), 2.11 (s, 3H, 17), 2.08 – 1.98 (m, 1H, 14''), 1.92 – 1.84 (m, 1H, 12'), 1.64 (ddd, *J* = 12.3, 6.3, 3.3 Hz, 1H, 12'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 139.7 (4), 136.0 (10), 129.0 (3, 5), 128.3 (2, 6), 127.0 (1), 121.4 (15), 67.3 (13), 64.5 (9), 61.9 (7), 42.4 (17), 34.5 (14), 31.2 (12), 25.3 (11).

HRMS (NSI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{22}NO$) requires *m/z* 232.1696, found *m/z* 232.1696.

Compound 14d



Prepared according to General Procedure E using methyl 4-(1-bromovinyl)benzoate **14a** (60.2 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (269 mg, 1.75 mmol, 7 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–40% EtOAc in petroleum ether) to afford the desired mixture of products as a white solid (37.0 mg, 64%, 4.5:1 r.r (as an average of two experiments)). The major regioisomer was separated by column chromatography (c.a. 94% purity).

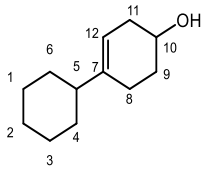
υ_{max} (film): 3397 (br), 2921, 2851, 1713, 1605, 1437, 1277, 1192, 1114 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.4 Hz, 2H, 1, 3), 7.43 (d, *J* = 8.4 Hz, 2H, 4, 6), 6.12 (s, 1H, 12), 4.12 – 4.03 (m, 1H, 10), 3.90 (s, 3H, 14), 2.60 (dt, *J* = 8.4, 6.7 Hz, 2H, 8', 11'), 2.52 (ddd, *J* = 14.4, 6.4, 4.0 Hz, 1H, 8''), 2.24 (ddd, *J* = 15.2, 6.5, 3.3 Hz, 1H, 11''), 2.02 (ddd, *J* = 7.1, 5.4, 3.3 Hz, 1H, 9'), 1.83 (ddd, *J* = 14.3, 8.6, 4.3 Hz, 1H, 9'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.2 (13), 146.2 (5), 135.8 (7), 129.8 (1, 3), 128.6 (2), 125.1 (4, 6), 123.9 (12), 66.5 (10), 52.2 (14), 35.1 (11), 31.1 (9), 25.4 (8).

HRMS (NSI): exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}O_3$) requires *m/z* 233.1172, found *m/z* 233.1173.

Compound 15d



Prepared according to General Procedure E using (1-bromovinyl)cyclohexane **15a** (47.2 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (269 mg, 1.75 mmol, 7 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% EtOAc in petroleum ether) to afford the desired mixture of products as a pale yellow oil (25.5 mg, 57%, 2.6:1 r.r. (as an average of three experiments)). The major regioisomer was separated by column chromatography (c.a. 96% purity).

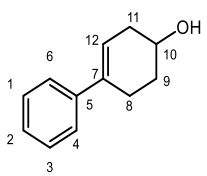
υ_{max} (film): 3336 (br), 2921, 2849, 1448, 1071, 1054 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.26 (dd, *J* = 2.8, 1.4 Hz, 1H, 12), 3.95 – 3.88 (m, 1H, 10), 2.35 (d, *J* = 16.6 Hz, 1H, 11'), 2.17 – 2.03 (m, 2H, 8), 1.99 (dd, *J* = 18.1, 5.1 Hz, 1H, 11''), 1.85 (dddt, *J* = 12.5, 5.5, 3.1, 1.9 Hz, 1H, 9'), 1.79 – 1.72 (m, 3H, 5), 1.71 – 1.65 (m, 3H), 1.62 (dq, *J* = 8.8, 2.6 Hz, 1H, 9''), 1.25 (td, *J* = 13.3, 12.4, 7.4 Hz, 2H), 1.15 (ddt, *J* = 16.2, 12.6, 3.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 143.0 (7), 115.7 (12), 67.5 (10), 45.4 (5), 34.6 (11), 32.1(4/6), 32.0(4/6), 31.5 (9), 26.9 (1/3), 26.9(1/3), 26.5 (2), 25.0 (8).

HRMS (ASAP): exact mass calculated for $[M+H]^+$ ($C_{12}H_{21}O$) requires *m/z* 181.1592, found *m/z* 181.1597.

Compound 16d



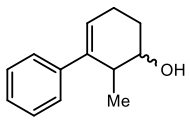
Prepared according to General Procedure E using (1-bromovinyl)benzene **16a** (45.7 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (269 mg, 1.75 mmol, 7 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–60% EtOAc in petroleum ether) to afford the desired mixture of products as a white solid (27.2 mg, 62%, 4:1 r.r. (as an average of two experiments)). The major regioisomer was separated by column chromatography (c.a. 91% purity).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.5 Hz, 2H, 4, 6), 7.31 (t, *J* = 7.6 Hz, 2H, 1, 3), 7.23 (t, *J* = 7.3 Hz, 1H, 2), 6.00 (dd, *J* = 4.5, 3.0 Hz, 1H, 12), 4.10 – 4.03 (m, 1H, 10), 2.67 – 2.48 (m, 3H, 8, 11'), 2.26 – 2.18 (m, 1H, 11''), 2.06 – 1.98 (m, 1H, 9'), 1.88 – 1.79 (m, 1H, 9'').

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.7 (5), 136.5 (7), 128.4 (1, 3), 127.0 (2), 125.2 (4, 6), 121.5 (12), 66.8 (10), 35.1 (11), 31.3 (9), 25.7 (8).

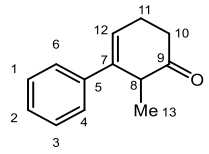
Spectroscopic data were in agreement with literature values.[91]

Compound 17d



Prepared according to General Procedure E using (*Z*)-(1-bromoprop-1-en-1-yl)benzene **17a** (49.2 mg, 0.25 mmol, 1 equiv)**,** $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (269 mg, 1.75 mmol, 7 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv) and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% EtOAc in petroleum ether) to afford the desired product

as a light yellow oil (29.7 mg, 63%, 2:1 r.r., 2:1 d.r. for both regioisomers (as an average of two experiments)). This mixture of alcohols could not be separated or characterised, and a further oxidation was necessary.



An oven-dried two necked flask under nitrogen atmosphere was charged with oxalyl chloride (0.03 mL, 0.4 mmol, 1.5 equiv) and CH_2Cl_2 (1 mL). The reaction was cooled to -78 °C. DMSO (0.05 mL, 0.08 mmol 3 equiv,) was added dropwise and the reaction mixture was stirred for 15 min. The alcohol mixture **17d/17d'** (50 mg, 0.027 mmol, 1 equiv), diluted in CH_2Cl_2 (1.6 mL) was added dropwise and the reaction was left to stir for a further 30 min. Then Et_3N (0.18 mL, 1.33 mmol, 5 equiv) was added dropwise, and the reaction mixture was left to reach room temperature over 1 h. After the reaction was complete, the reaction mixture was diluted in H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 12 mL). The organics were combined and washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–5% EtOAc in petroleum ether) to afford the desired product as a pale yellow oil (21.6 mg, 45%). The major regioisomer was separated by column chromatography (c.a. 99% purity).

υ_{max} (film): 2967, 2926, 2851, 2361, 2342, 1713, 1674, 1493, 1445, 1352, 1188 cm^{-1}.

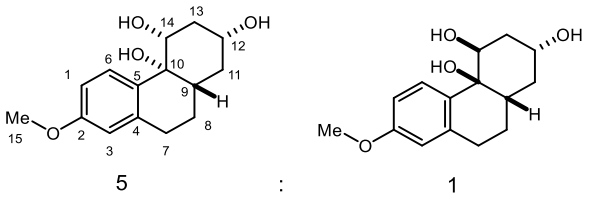
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.30 (m, 4H, 1, 3, 4, 6), 7.30 – 7.27 (m, 1H, 2), 6.08 (t, *J* = 3.9 Hz, 1H, 12), 3.40 (q, *J* = 7.3 Hz, 1H, 8), 2.73 – 2.65 (m, 1H, 10'), 2.65 – 2.57 (m, 2H, 11), 2.50 (dt, *J* = 12.7, 6.5 Hz, 1H, 10''), 1.18 (d, *J* = 7.3 Hz, 3H, 13).

^{13}C NMR (126 MHz, $CDCl_3$): δ 213.6 (9), 141.7 (5), 140.1 (7), 128.6 (1, 3), 127.5 (2), 126.2 (4, 6), 124.1 (12), 45.7 (8), 36.2 (10), 25.6 (11), 17.5 (13).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{13}H_{15}O$) requires *m/z* 187.1117, found *m/z* 187.1112.

2.6.4.3. Derivatization of major regioisomer 1d

Compound 22e



1d (16.5 mg, 0.07 mmol, 1 equiv) and 4-methylmorpholine *N*-oxide (18.7 mg, 0.16 mmol, 2.2 equiv) were weighed into an oven-dried flask before the addition of acetone (2.5 mL, 0.03 M) and OsO_4 4% in H_2O (36.4 mg, 0.006 mmol, 8 mol%). The reaction was stirred at room temperature for 4 h. After the reaction was complete, the reaction mixture was quenched with Na_2SO_3 and diluted with CH_2Cl_2 (20 mL). The organic phase was washed with aqueous 2 M HCl (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a mixture of diastereomers as a brown solid (12.2 mg, 64%). The major diastereomer was obtained through recrystalisation in CH_2Cl_2/hexane as a white solid.

Data for the major diastereomer is provided below.

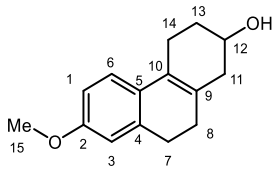
υ_{max} (film): 3408, 2930, 2851, 2361, 2342, 1609, 1506, 1456, 1271, 1246, 1061 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.6 Hz, 1H, 6), 6.80 (dd, *J* = 8.6, 2.7 Hz, 1H, 1), 6.68 (d, *J* = 2.7 Hz, 1H, 3), 4.54 (dt, *J* = 10.2, 3.6 Hz, 1H, 12), 4.50 (t, *J* = 5.4 Hz, 1H, 14), 3.79 (s, 3H, 15), 2.79 (tt, *J* = 8.1, 4.4 Hz, 1H, 9'), 2.70 (ddt, *J* = 23.3, 16.0, 3.8 Hz, 2H, 7), 2.46 (dddd, *J* = 12.8, 10.1, 5.8, 2.7 Hz, 1H, 13'), 2.08 (dd, *J* = 11.6, 8.5 Hz, 1H, 11'), 1.87 (dq, *J* = 12.1, 3.9 Hz, 1H, 8'), 1.56 – 1.52 (m, 1H, 11''), 1.48 – 1.37 (m, 2H, 8''. 13'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.3 (2), 142.7 (4), 129.1 (6), 125.0 (5), 113.4 (3), 112.9 (1), 85.0 (1), 77.9 (12), 77.8 (14), 55.4 (15), 40.4 (11), 39.9 (13), 33.4 (9), 31.2 (7), 28.7 (8).

HRMS (ESI): exact mass calculated for $[M\text{-}OH]^+$ ($C_{15}H_{19}O_3$) requires *m/z* 247.1329, found *m/z* 247.1321.

Compound 23e



1d (30.0 mg, 0.13 mmol, 1 equiv) was weighed into an oven-dried flask. The flask was sealed and purged with N_2 before the addition of CH_2Cl_2/MeOH 9:1 (3 mL, 0.04 M) and conc. HCl (250 µL, 3.12 mmol, 24 equiv). The reaction mixture was stirred at room temperature for 4 h. After the reaction was complete, the reaction mixture was poured onto saturated aqueous $NaHCO_3$ (20mL) at 0 °C and extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 5–50% EtOAc in petroleum ether) to afford the desired product as a pale yellow solid (27.1 mg, 90%).

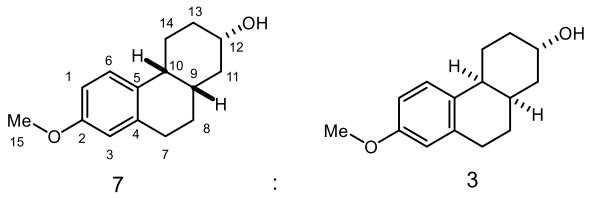
υ_{max} (film): 3364(br), 2922, 2832, 2359, 2342, 1607, 1497, 1263, 1248, 1034 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.4 Hz, 1H, 6), 6.71 (dd, *J* = 8.4, 2.8 Hz, 1H, 1), 6.68 (d, *J* = 2.7 Hz, 1H, 3), 4.07 – 4.00 (m, 1H, 12), 3.80 (s, 3H, 15), 2.80 – 2.68 (m, 2H, 8), 2.59 – 2.50 (m, 1H, 14'), 2.50 – 2.41 (m, 2H, 11', 14''), 2.25 – 2.18 (m, 1H, 11'), 2.19 – 2.12 (m, 2H, 7), 2.06 – 1.98 (m, 1H, 13'), 1.79 (dtd, *J* = 12.5, 8.8, 5.7 Hz, 1H, 13'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.1 (2), 137.1 (4), 129.1 (5), 128.7 (10), 126.0 (9), 122.8 (6), 113.6 (3), 110.9 (1), 67.2 (12), 55.4 (15), 39.8 (11), 31.4 (13), 29.0 (7), 28.7 (8), 23.6 (14).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}O_2$) requires *m/z* 231.1374, found *m/z* 231.1377.

Compound 24e



7 : 3

1d (17.3 mg, 0.07 mmol, 1 equiv) and Pd/C (8.0 mg, 10 mol%, 0.1 equiv) were weighed into an oven-dried flask. The flask was sealed and purged with N_2 before the addition of EtOH (5 mL, 0.01 M). The reaction was stirred at room temperature for 29 h under a H_2 atmosphere. After the reaction was complete, the reaction mixture was diluted in CH_2Cl_2 (20 mL), passed through a layer of Celite®, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 5–15% EtOAc in petroleum ether) to afford the desired product as a mixture of diastereomers as a colourless oil (12.0 mg, 69%). The major diastereomer was separated by column chromatography.

Data for the major diastereomer is provided below.

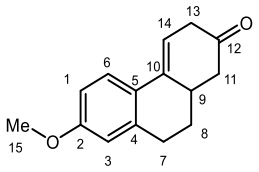
υ_{max} (film): 3348 (br), 2924, 2855, 2361, 2342, 1609, 1499, 1456, 1273, 1260, 1234, 1045 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.6 Hz, 1H, 6), 6.73 (dd, *J* = 8.6, 2.8 Hz, 1H, 1), 6.62 (d, *J* = 2.7 Hz, 1H, 3), 3.85 – 3.79 (m, 1H, 12), 3.78 (s, 3H, 15), 2.86 (dd, *J* = 17.0, 8.2 Hz, 1H, 7'), 2.81 (d, *J* = 3.9 Hz, 1H, 10), 2.71 (dt, *J* = 17.1, 5.7 Hz, 1H, 7''), 2.30 (ddd, *J* = 14.6, 7.5, 4.4 Hz, 1H, 14'), 2.07 – 2.02 (m, 1H, 9), 1.88 (dt, *J* = 8.5, 5.9 Hz, 2H, 8), 1.81 – 1.75 (m, 1H, 11'), 1.75 – 1.70 (m, 1H, 13'), 1.64 (tdd, *J* = 14.5, 4.3, 3.5 Hz, 1H, 14''), 1.43 (dt, *J* = 10.0, 8.0 Hz, 1H, 11''), 1.33 – 1.30 (m, 1H, 13'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.5 (2), 138.1 (4), 131.0 (5), 128.1 (6), 113.8 (3), 112.3 (1), 70.1 (12), 55.3 (15), 36.8 (10), 36.4 (11), 34.0 (9), 31.3 (13), 27.6 (8), 27.5 (7), 26.9 (14).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}O_2$) requires *m/z* 233.1536, found *m/z* 233.1534.

Compound 25e



1d (50.0 mg, 0.21 mmol, 1 equiv) was weighed into an oven-dried flask and CH_2Cl_2 (4.3 mL, 0.05 M) was added. The reaction was cooled to 0 °C before the portionwise addition of Dess-Martin Periodine (184 mg, 0.43 mmol, 2 equiv). The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. After the reaction was complete, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL). Organics were extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–10% EtOAc in petroleum ether) to afford the desired product as a pale red solid (45.6 mg, 92%).

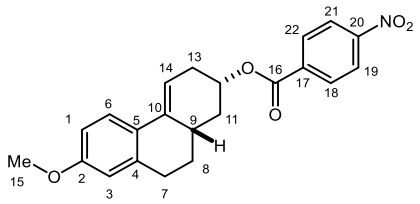
υ_{max} (film): 2922, 2851, 2835, 2359, 1713, 1605, 1495, 1279, 1233, 1040 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.8 Hz, 1H, 6), 6.76 (dd, *J* = 8.8, 2.8 Hz, 1H, 1), 6.64 (d, *J* = 2.7 Hz, 1H, 3), 6.24 (q, *J* = 3.4 Hz, 1H, 14), 3.80 (s, 3H, 15), 3.15 (dd, *J* = 4.8, 2.3 Hz, 1H, 13'), 3.05 – 2.93 (m, 1H, 13''), 2.87 – 2.80 (m, 2H, 7), 2.78 (dd, *J* = 5.0, 2.7 Hz, 1H, 9), 2.62 (dd, *J* = 14.7, 4.6 Hz, 1H, 11'), 2.39 (dd, *J* = 14.7, 12.3 Hz, 1H, 11''), 2.09 – 1.99 (m, 1H, 8'), 1.59 (qd, *J* = 12.3, 5.1 Hz, 1H, 8'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 210.6 (12), 158.9 (2), 138.6 (4), 136.4 (5), 125.8, (10) 124.8 (6), 114.2 (14), 113.3 (3), 113.1 (1), 55.4 (15), 46.4 (11), 40.7 (13), 36.8 (9), 30.7 (8), 30.4 (7).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{16}O_2Na$) requires *m/z* 251.1043, found *m/z* 251.1041.

Compound 26e



1d (24.6 mg, 0.106 mmol, 1 equiv) was weighed into an oven-dried flask and CH_2Cl_2 (3 mL, 0.03 M) was added. DMAP (29.7 mg, 0.16 mmol, 1.5 equiv) and *para*-nitrobenzoyl chloride (19.6 mg, 0.16 mmol, 1.5 equiv) were added sequentially and the reaction was placed under a N_2 atmosphere and stirred at room temperature for 12 h. After the reaction was complete, the reaction mixture was diluted in Et_2O (20 mL) and washed with H_2O (15 mL). The organic phase was then washed 1% aqueous HCl (3 mL) and 5% aqueous $NaHCO_3$ (10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–10% EtOAc in petroleum ether) to afford the desired product as a yellow solid (29.0 mg, 72%). Product was recrystallized from CH_2Cl_2/hexane for x-ray analysis.

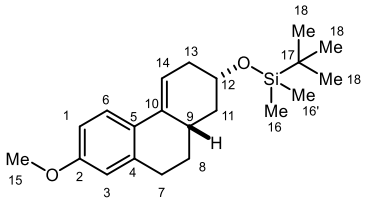
υ_{max} (film): 2922, 2853, 2361, 2342, 1717, 1607, 1526, 1499, 1271, 1248, 1117, 1101 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 – 8.28 (m, 2H, 19, 21), 8.25 – 8.21 (m, 2H, 18, 22), 7.54 (d, *J* = 8.8 Hz, 1H, 6), 6.74 (dd, *J* = 8.7, 2.8 Hz, 1H, 1), 6.62 (d, *J* = 2.7 Hz, 1H, 3), 6.09 (dt, *J* = 5.4, 2.5 Hz, 1H, 14), 5.36 – 5.29 (m, 1H, 12), 3.80 (s, 3H, 15), 2.93 (ddd, *J* = 17.7, 12.8, 5.2 Hz, 1H, 7'), 2.82 (ddd, *J* = 16.8, 5.1, 2.1 Hz, 1H, 7''), 2.79 – 2.72 (m, 1H, 13'), 2.59 (d, *J* = 13.2 Hz, 1H, 9), 2.47 (ddt, *J* = 16.9, 9.7, 3.3 Hz, 1H, 13''), 2.34 (dddd, *J* = 10.9, 5.3, 3.5, 2.0 Hz, 1H, 11'), 2.03 (dp, *J* = 10.9, 2.3 Hz, 1H, 8'), 1.66 (q, *J* = 11.7 Hz, 1H, 11''), 1.57 (qd, *J* = 12.8, 5.0 Hz, 1H, 8'') small overlap with H_2O peak observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 164.4 (16), 158.8 (2), 150.6 (2), 138.0 (4), 136.2 (17), 135.9 (5), 130.8 (18, 22), 126.7 (10), 125.1 (6), 123.64 (19, 21), 114.4 (14), 113.3 (3), 112.9 (1), 72.2 (12), 55.4 (15), 36.5 (11), 36.2 (9), 32.2 (13), 31.0 (8), 30.3 (7).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{22}H_{22}O_5N$) requires *m/z* 380.1492, found *m/z* 380.1479.

Compound 27e



1d (26.4 mg, 0.11 mmol, 1 equiv) was weighed into an oven-dried flask and CH_2Cl_2 (5 mL, 0.02 M) was added. The reaction was cooled to 0 °C before the sequential addition of TBSCl (38.0 mg, 0.25 mmol, 2.2 equiv) and imidazole (34.3 mg, 0.38 mmol, 4.4 equiv). The reaction was placed under a N_2 atmosphere and was allowed to warm to room temperature and was stirred for 22 h. After the reaction was complete, the reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL) and then extracted with CH_2Cl_2 (3 × 10 mL). The separated organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–5% EtOAc in petroleum ether) to afford the desired product as a white solid (20.0 mg, 51%).

υ_{max} (film): 2951, 2926, 2855, 2359, 2332, 1607, 1497, 1462, 1256, 1233, 1103, 1061 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.8 Hz, 1H, 6), 6.71 (dd, *J* = 8.8, 2.8 Hz, 1H, 1), 6.59 (d, *J* = 2.8 Hz, 1H, 3), 6.06 – 6.01 (m, 1H, 14), 3.99 – 3.91 (m, 1H, 12), 3.78 (s, 3H, 15), 2.88 (ddd, *J* = 17.7, 12.8, 5.2 Hz, 1H, 7'), 2.78 (ddd, *J* = 16.7, 5.1, 2.0 Hz, 1H, 7''), 2.50 – 2.37 (m, 2H, 9, 13'), 2.27 – 2.14 (m, 1H, 13''), 2.08 – 2.00 (m, 1H, 11'), 2.00 – 1.93 (m, 1H, 9, 8'), 1.52 – 1.47 (m, 1H, 8''), 1.44 (d, *J* = 11.8 Hz, 1H, 11''), 0.91 (s, 9H, 18), 0.09 (d, *J* = 2.3 Hz, 6H, 16).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5 (2), 138.0 (4), 135.5 (5), 127.2 (10), 125.0 (6), 116.2 (14), 113.3 (3), 112.8 (1), 68.3 (12), 55.3 (15), 41.0 (11), 36.8 (9), 36.7 (13), 31.2 (8), 30.5 (7), 26.1 (18), 18.4 (17), -4.4 (16), -4.5 (16').

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{21}H_{33}O_2Si$) requires *m/z* 345.2244, found *m/z* 345.2241.

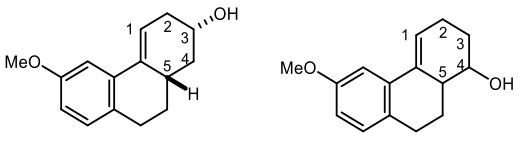
2.6.5. Structure elucidation by 2D NMR

Elucidation of major regioisomer

This section aims to elucidate regiochemistry and stereochemistry for the tetralone derived products, and regiochemistry for styrenyl derived products.

2.6.5.1 Tetralone example

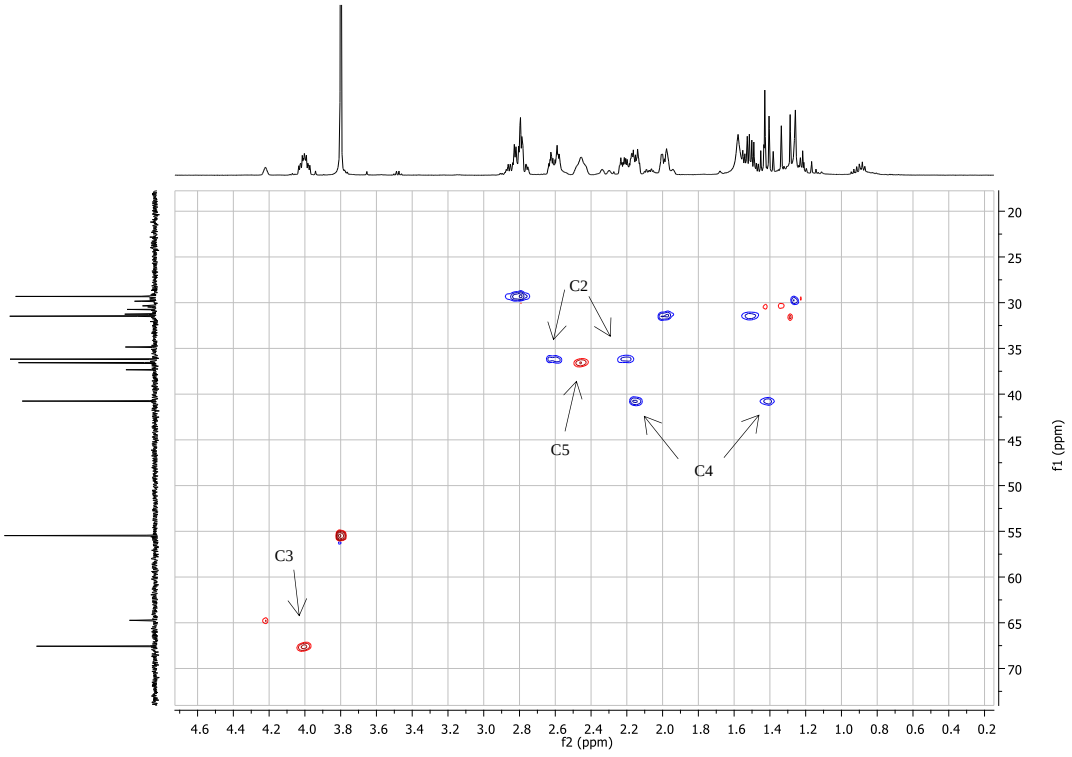
For the tetralone system compound **5d** was analysed:



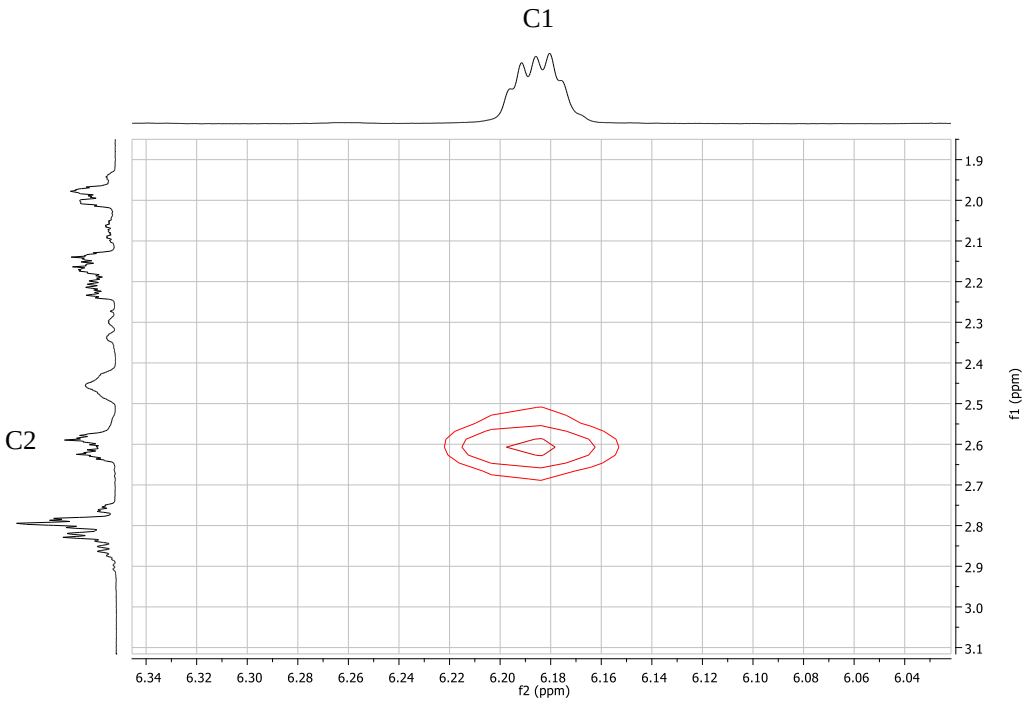
major
5d

minor
5d'

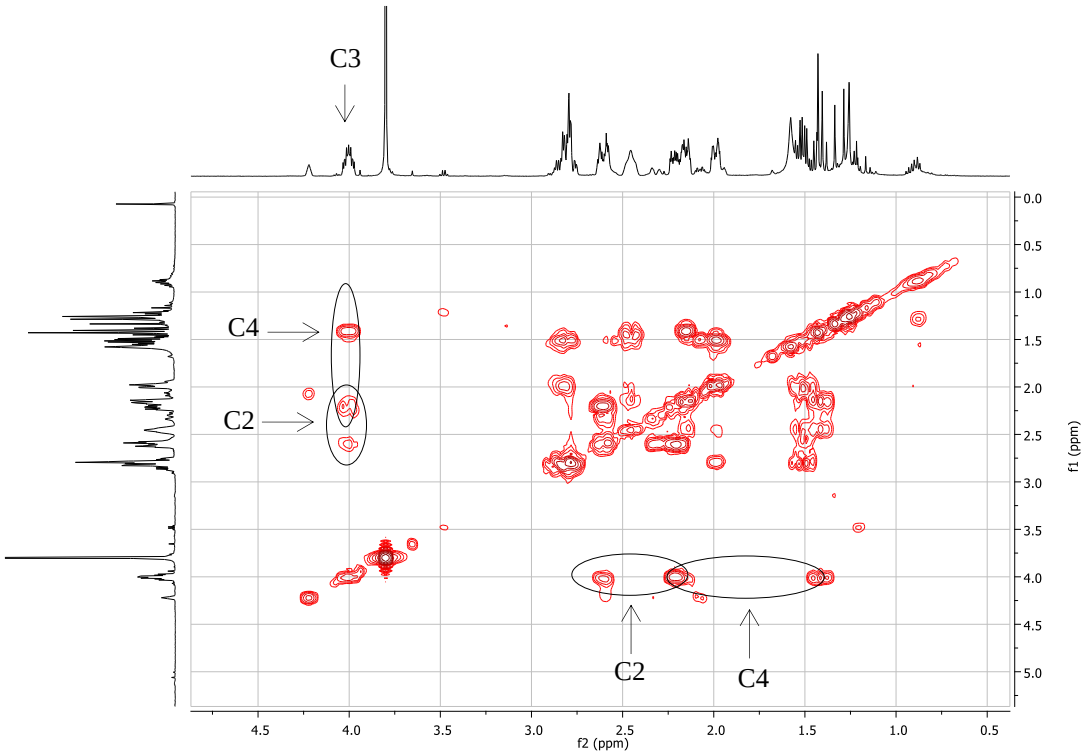
The HSQC spectrum demonstrates the presence of 2 CH groups (C3/C5) and 2 diastereotopic CH_2 groups in the aliphatic region (C2/C4).



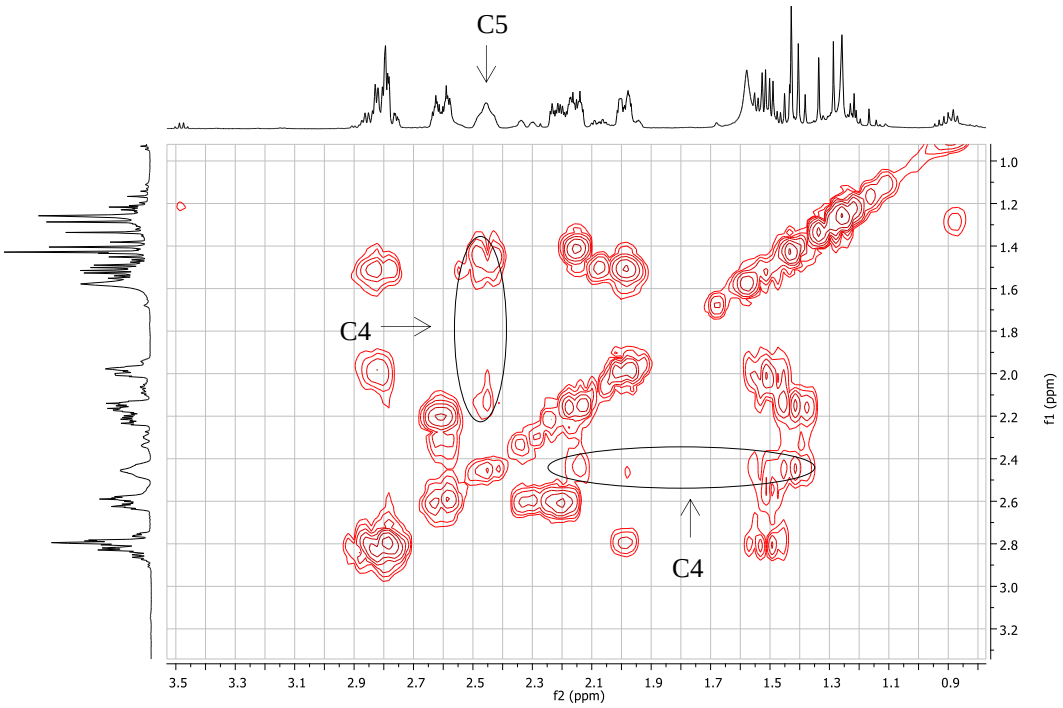
Analysis of the COSY spectrum shows a clear through bond correlation between the alkene CH (C1) and a CH_2 component (C2) showing the carbon atoms are adjacent.



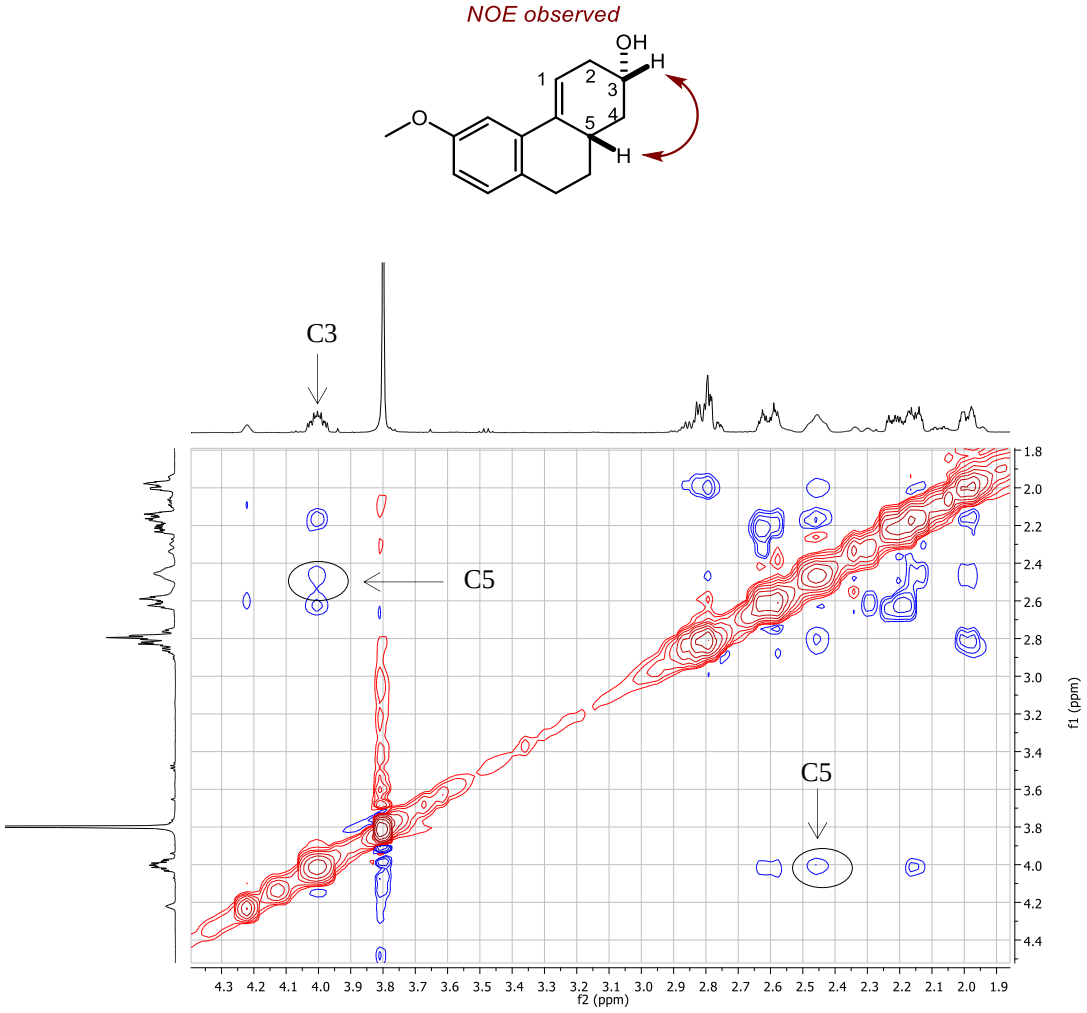
The CH (C3) also shows a clear through bond correlation with the CH_2 groups (C2, 2.59, 2.11 ppm; C4, 2.15, 1,41 ppm). In addition, there is no clear through bond correlation between CH (C3) and CH (C5) supporting formation of the major regioisomer.



It is also clear that CH_2 (C4; 2.15, 1,41 ppm) has a through bond correlation with CH (C5; 2.54 ppm).

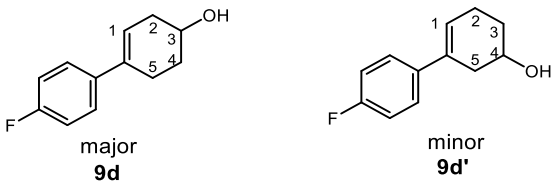


NOESY data supports formation of the *endo* product as there is a through space interaction between CH (C3; 4.00 ppm) and CH (C5; 2.45 ppm).

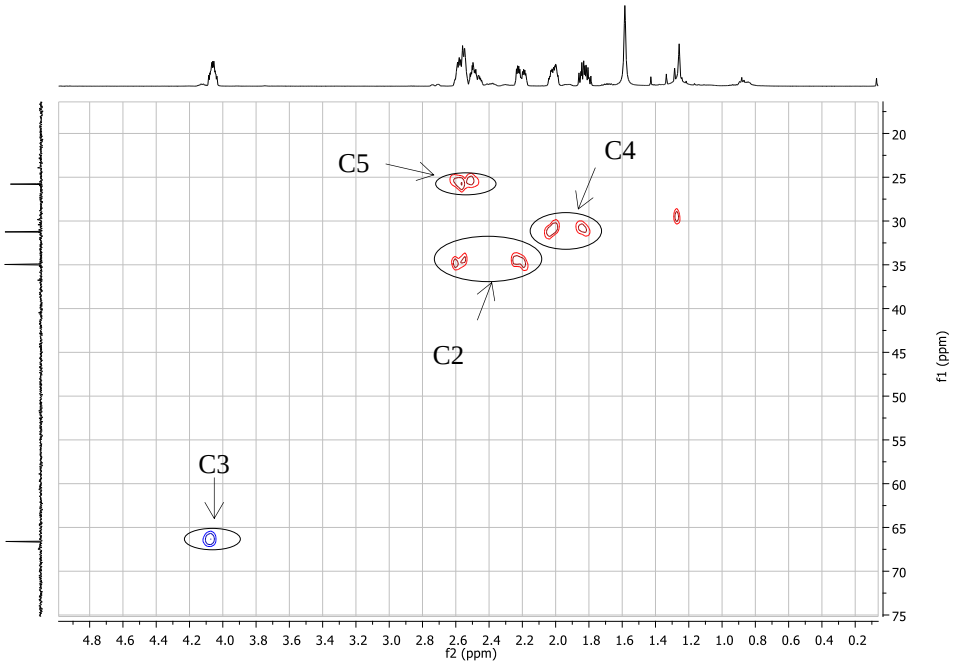


2.6.5.2 Styrenyl example

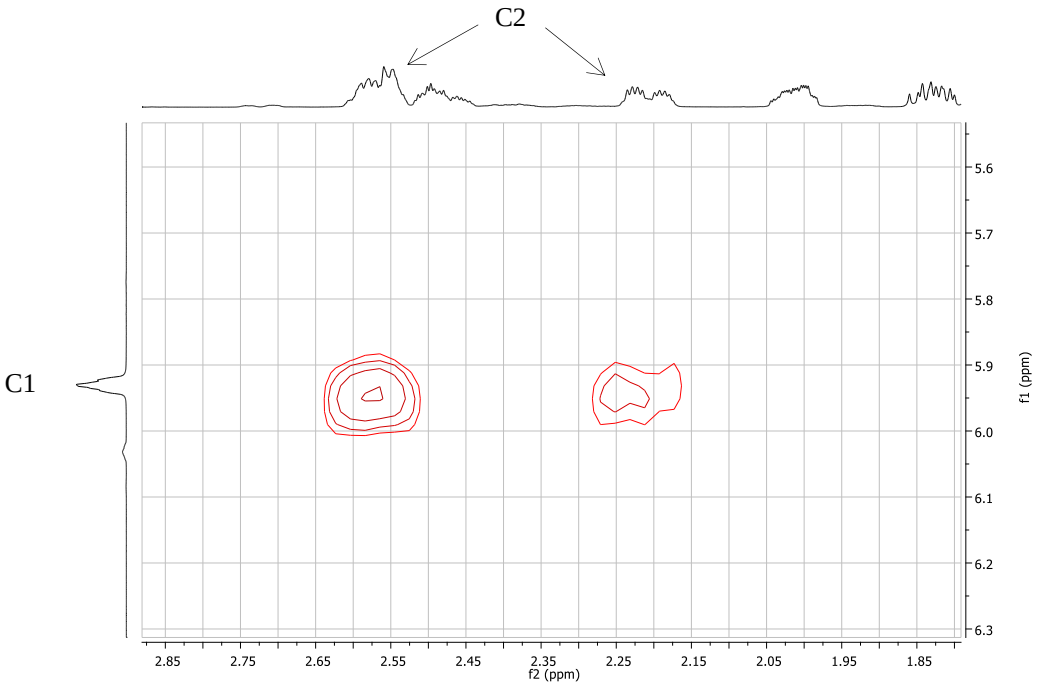
For the styrenyl system, compound **9d** was analysed:



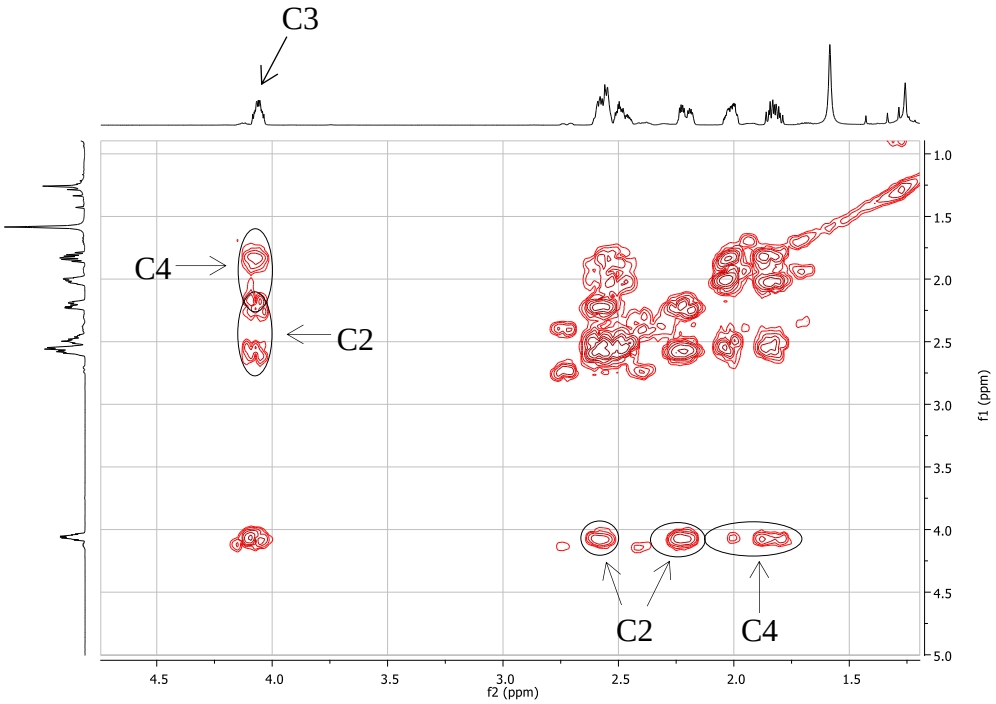
The HSQC spectrum demonstrates the presence of CH group (C3), 2 diastereotopic CH_2 groups (C2/C4) and 1 CH_2 group (C5) in the aliphatic region.



Analysis of the COSY spectrum shows a clear through bond correlation between the alkene CH (C1) and a diastereotopic CH_2 component (C2) showing the carbon atoms are adjacent.

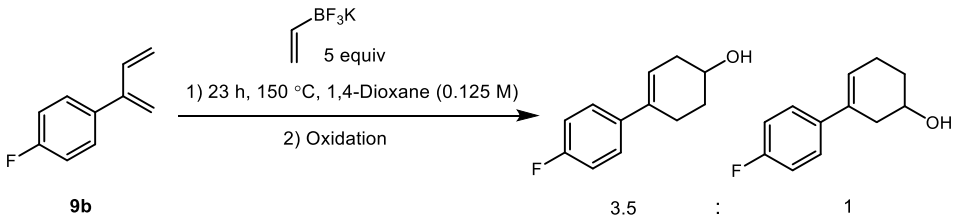


The CH (C3) also shows a clear through bond correlation with the diastereotopic CH_2 groups (C2: 2.56, 2.21 ppm; C4:1.86, 1.96 ppm). In addition, there is no clear through bond correlation between CH (C3) and CH_2 (C5: 2.48, 2.57 pp,). In summary, the characterisation of the 2D spectra supports the proposed major regioisomer structure.


C3
C4
C2
C2
C4
f1 (ppm)
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

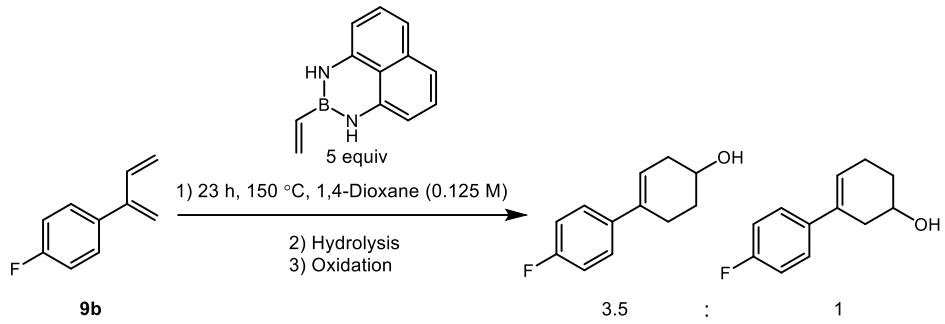
2.6.6. Investigation of various vinyl boron species in DA reaction.

Vinyl BF_3K:



Prepared according to General Procedure F using 1-(buta-1,3-dien-2-yl)-4-fluorobenzene **9b** (37.0 mg, 0.25 mmol, 1 equiv), vinyl BF_3K (167 mg, 1.25 mmol, 5 equiv) and 1,4-dioxane (2 mL, 0.125 M). After the reaction was complete, the reaction mixture was left to cool and concentrated under reduced pressure. Then the crude mixture was dissolved in acetone (1 mL) and oxone was added (84.4 mg, 0.27 mmol, 1.1 equiv) as a solution in acetone (0.25 mL) and H_2O (1.25 mL) (1:5, 0.2 M). The reaction mixture was left to stir at room temperature for 2 h. After the reaction was complete, aqueous 2 M HCl (2.5 mL) was added to quench the reaction. The reaction mixture was diluted in CH_2Cl_2 (20 mL) and washed with H_2O (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Column chromatography (silica gel, 0–20% EtOAc in petroleum ether) of crude material afforded the product with regioisomer ratio of 3.5:1.

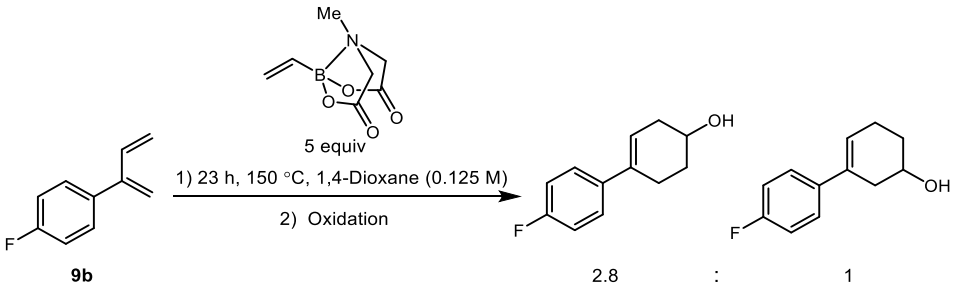
Vinyl Bdan:



Prepared according to General Procedure F using 1-(buta-1,3-dien-2-yl)-4-fluorobenzene **9b** (37.0 mg, 0.25 mmol, 1 equiv), vinyl Bdan **21S** (242 mg, 5 equiv, 1.25 mmol) and 1,4-dioxane (2 mL, 0.125 M). After the reaction was complete, the

reaction mixture was left to cool and concentrated under reduced pressure. Then the crude residue was dissolved in THF (3 mL, 0.08 M) and 2 M H_2SO_4 (750 µL, 6 equiv) was added. The reaction mixture was left to stir at room temperature for 23 h. After the reaction was complete, 2 M HCl (10 mL) was added to reaction mixture, and was subsequently extracted with Et_2O (3 × 10 mL). Organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. THF (1 mL, 0.25 M) was added to the crude residue and the solution was cooled to 0 °C before the addition of aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv) and 2 M NaOH (500 µL, 1 mmol, 4 equiv) sequentially. The reaction mixture was left to stir at room temperature for 1 h. After the reaction was complete, the reaction mixture was then subjected to the purification method outlined in the General Procedure E. Column chromatography (silica gel, 0–20% EtOAc in petroleum ether) of crude material afforded the product with regioisomer ratio of 3.5:1.

Vinyl BMIDA:

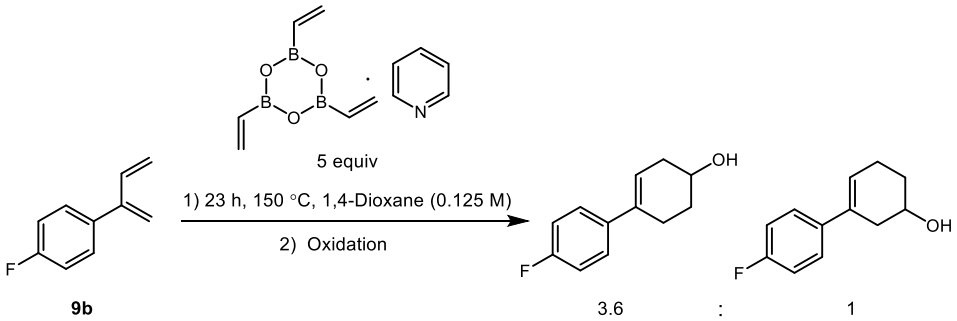


9b 2.8 : 1

Prepared according to General Procedure F using 1-(buta-1,3-dien-2-yl)-4-fluorobenzene **9b** (37.0 mg, 0.25 mmol, 1 equiv), vinyl BMIDA (228 mg, 5 equiv, 1.25 mmol) and 1,4-dioxane (2 mL, 0.125 M). After the reaction was complete, the reaction mixture was left to cool and concentrated under reduced pressure. Then to the crude residue, K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), CPME (2.5 mL, 0.1 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv) were added. The reaction mixture was heated for 10 min at 80 °C, then after being cooled, oxone (192 mg, 0.625 mmol, 2.5 equiv) as a solution in H_2O (1 mL) and CPME (0.25 mL) (4:1) was added. The reaction mixture was stirred at 70 °C for 1 h. After the reaction was complete, the reaction mixture was then diluted in saturated NH_4Cl (20 mL). Organics were extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under

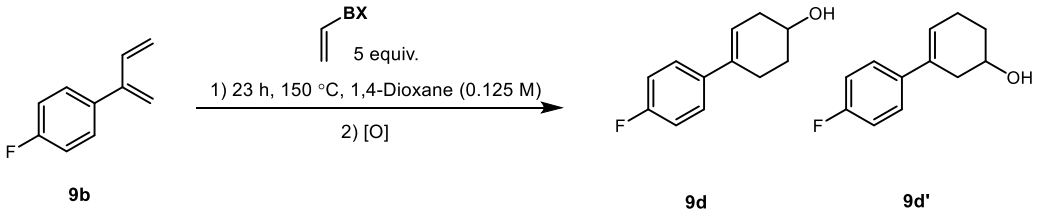
reduced pressure. Column chromatography (silica gel, 0–20% EtOAc in petroleum ether) of crude material afforded the product with regioisomer ratio of 2.8:1.

Vinyl boroxine pyridine complex:



Prepared according to General Procedure F using 1-(buta-1,3-dien-2-yl)-4-fluorobenzene **9b** (37.0 mg, 0.25 mmol, 1 equiv), Vinylboronic anhydride pyridine complex (100 mg, 5 equiv, 1.25 mmol) and 1,4-dioxane (2 mL, 0.125 M). After the reaction was complete, the reaction mixture was left to cool and concentrated under reduced pressure. Then the crude residue was subjected to the oxidation conditions and purification method outlined in the General Procedure E. Column chromatography (silica gel, 0–20% EtOAc in petroleum ether) of crude material afforded the product with regioisomer ratio of 3.6:1.

Tabulated results for DA investigation (Table 7)



Entry	Vinyl Boron species (BX)	Ratio (9d:9d')
1	Bpin	3.7:1
2	BF_3K	3.5:1
3	Bdan (**21S**)	3.5:1
4	BMIDA	2.8:1
5	Boroxine	3.6:1

2.6.7. X-ray Crystal data

X-ray diffraction data for compound **26e** were collected at 125 K using a Rigaku MM-007HF High Brilliance RA generator/confocal optics with XtaLAB P200 diffractometer [Cu Kα radiation (λ = 1.54187 Å)]. Data were collected using CrystalClear[108] and processed using CrysAlisPro.[109] The structure was solved by dual-space methods (SHELXT[110]) and refined by full-matrix least-squares against F^2 (SHELXL-2014/7[111]). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model. All calculations were performed using the Olex2[112] interface. Selected crystallographic data are presented in Table 8.

Table 8: Selected crystallographic data for compound 26e.

	26e
empirical formula	$C_{22}H_{21}NO_5$
fw	379.41
crystal description	Colourless prism
crystal size [mm^3]	0.15×0.12×0.09
space group	$P2_1/c$
a [Å]	7.87570(6)
b [Å]	11.27690(7)
c [Å]	20.63090(15)
β [°]	95.2404(7)
vol [$Å^3$]	1824.64(2)
Z	4
ρ (calc) [g/cm^3]	1.381
μ [mm^{-1}]	0.810
F(000)	800
reflections collected	21369
independent reflections (R_{int})	3718 (0.0225)
parameters, restraints	254, 0
GOF on F^2	1.058
R_1 [$I > 2\sigma(I)$]	0.0440
wR_2 (all data)	0.1266
largest diff. peak/hole [$e/Å^3$]	0.30, -0.30

3. Chapter 3: Total Synthesis of *Aspidosperma* alkaloids utilizing a cascade Suzuki–Miyaura/Diels–Alder reaction

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This work was published in Cain , D , Anderson , N , Cordes , D B , Slawin , A M Z & Watson , A J B 2022 , ' Total synthesis of (±)-aspidospermidine, (±)-aspidofractinine, (±)-limaspermidine, and (±)-vincadifformine via a cascade and common intermediate strategy ' , *The Journal of Organic Chemistry* , vol. 87 , no. 22 , pp. 15559–15563 . https://doi.org/10.1021/acs.joc.2c02099

Numbered compounds in Chapter 3 will follow the order **1f**, **2f**, **3f** *etc*

3.1. *Aspidosperma* alkaloids

The *Aspidosperma* alkaloids are a class of monoterpenoid indole alkaloid (Figure 17), which have seen a great deal of interest from both chemical and biological communities. Their intriguing, densely-fused polycyclic structures make them molecules for synthetic chemists to assemble in order to showcase newly developed methodologies.[113–119]

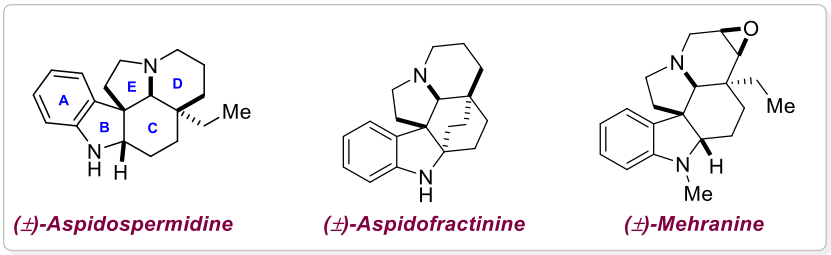


Figure 17: Example structures of selected *Aspidosperma* alkaloids.

The genus *Aspidosperma*, a flowering plant, in the Apocynaceae family, is found in the Americas, predominately between Mexico and Argentina,[120] and these natural products are known to exhibit beneficial biological properties. They have regularly been used for the treatment of cardiovascular diseases,[121] malaria, fever and other diseases in those countries.[120] Since Woodward's pioneering work in the total synthesis of Strychnine (1954),[122] a *Strychnos* type alkaloid (Figure 18), there has been a significant increase in the development of methods for the synthesis of these structurally challenging natural products. Even to this day novel synthetic strategies are being reported in the literature.[113,123–125]

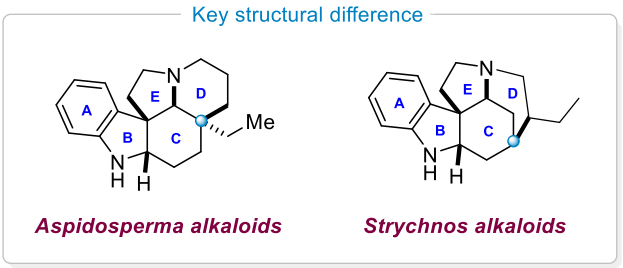
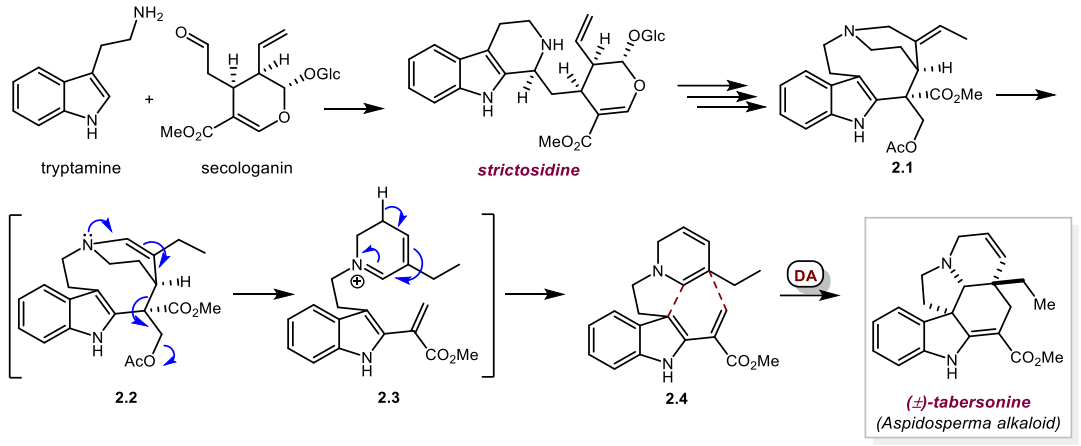


Figure 18: Key structural discrepancy between aspidosperma and stychnos type alkaloids.

The biosynthetic pathway for the construction of *Aspidosperma* alkaloids is proposed to proceed through a biocatalytic DA-type cyclisation (Scheme 62).[126]

Tryptamine and secolgonin are the key starting components in the synthesis of the *Aspidosperma* alkaloids. The first step involves an enzymatically-driven Pictet–Spengler reaction to join the two fragments together to make strictosidine, then a series of transformations occur forming intermediate **2.1**. Subsequent isomerisation of the double bond generates **2.2**, which then rearranges to yield intermediate **2.3**, resulting in the expulsion of the acetate group. A proton transfer then occurs to facilitate the formation of **2.4**. This intermediate is then primed to undergo the ensuing intramolecular [4+2] cycloaddition to form the natural product.[113]

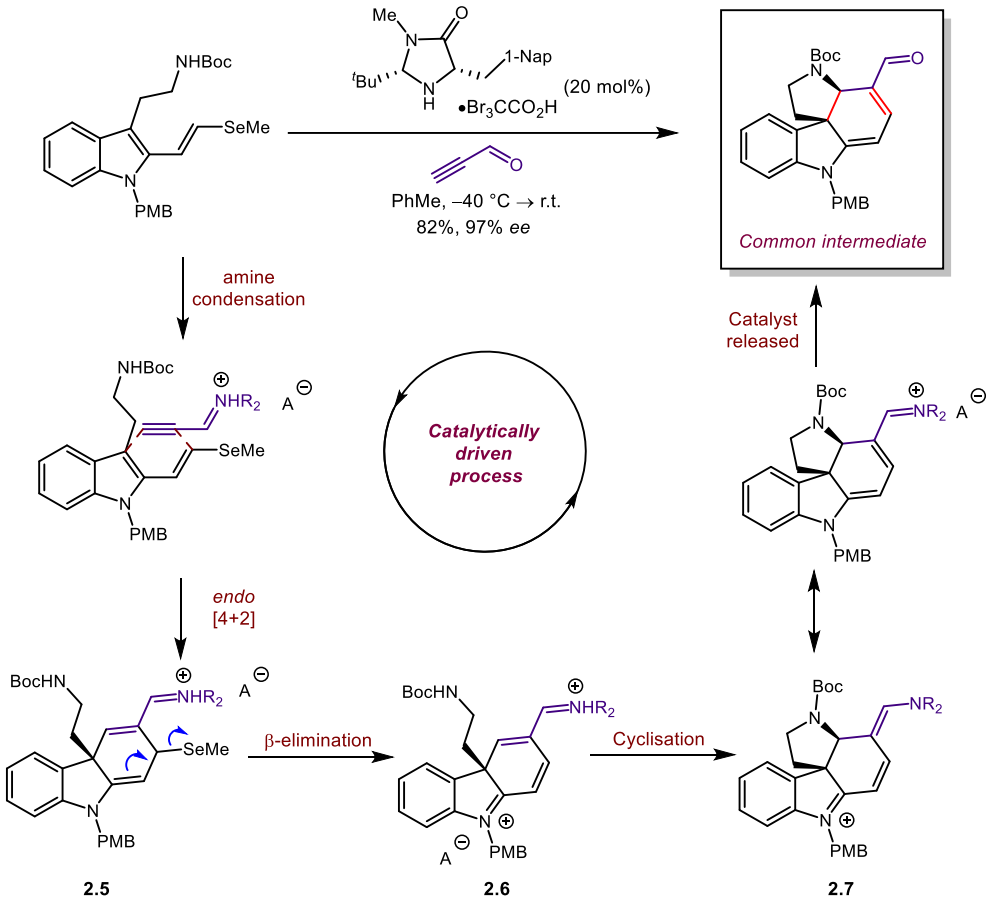


Scheme 62: Biosynthetic DA-like pathway towards *Aspidosperma* alkaloids.

3.2. Previous work

In 2011, a significant example in the literature for the synthesis of *Aspidosperma* alkaloids was reported by MacMillan and co-workers, due to its enantioselective and fast approach (9 steps).[127] In this work, they describe an asymmetric DA approach for the construction of a core intermediate fragment, from which they can access numerous structurally different alkaloids of the same family – coined "collective total synthesis". Here, they implement iminium catalysis (See section 1.5.4.) to facilitate an asymmetric DA reaction (Scheme 63), which proceeds with both excellent yield and *ee* (82% and 97%, respectively). As already discussed, the high levels of facial selectivity are due to bulky groups attached the pyrrolidine ring, which help control the approach of the dienophile in the TS, through steric effects. The incorporation of the organoselenide species into the molecule is to help enable the β-elimination step to form intermediate **2.6** from **2.5**. A 5-*exo*-*trig* heterocyclisation then transpires,

which is promoted by the presence of the pyrrolidine catalyst by activating the aldehyde, to construct the **E** ring (see Figure 17). Finally, hydrolysis of intermediate **2.7** releases the product, as well as the organocatalyst allowing further catalytic turnovers.

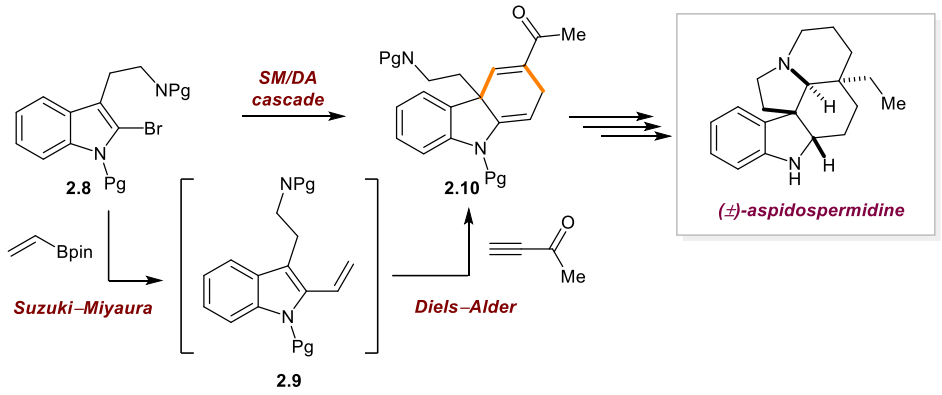


Scheme 63: Key DA step during *Aspidosperma* alkaloid synthesis by MacMillan.

Despite the impressive efficiency with which this reaction builds the core framework, there are some disadvantages to the overall process. Firstly, the utilization of propynal as the dienophile is challenging to use due to its volatility, and requires to be prepared freshly before use, making translation of these conditions to a large-scale operation potentially difficult. Secondly, the presence of the selenium group increases the toxicity of the starting material.

3.3. Proposed work

Having successfully established a SM/DA protocol for the construction of borylated carbocyclic frameworks (*vida supra)*,[72] potential applications for this work were pursued. In the literature, there have been few reports where CCDA reactions are implemented in total synthesis (see section 1.7.), especially in the case of integrating SM cross-coupling reactions. Inspired by this gap in the literature, the application of the SM/DA reaction into the total synthesis of *Aspidosperma* alkaloids commenced. It was envisaged that the core structure of these alkaloids could be rapidly assembled using the SM/DA principle (Scheme 64), with the initial target molecule in mind being (±)-aspidospermidine. Considering this natural product has over 50 different synthetic routes,[128] successful optimisation of the SM/DA reaction would render the rest of the synthesis relatively straightforward. Having synthesised the bromo-bearing indole substrate **2.8**, exposure to the SM conditions from the methodology with vinyl Bpin, would yield the pseudo diene species **2.9**. Subsequent reaction with designated dienophile 3-butyne-2-one under thermally promoted conditions would facilitate the formation of the core skeletal framework **2.10**. With the core intermediate in hand, this will then be subjected to a series of simple transformations to complete the natural product synthesis. An additional goal of this work will be to investigate the possibility of accessing a variety of alkaloids from the same family, from either the DA adduct, similar to MacMillan's work,[127] or from a more advanced intermediate in the synthesis. Ultimately, the objective of this work is to deliver the natural product as a racemate or asymmetrically, if conditions permit, in an unparalleled number of synthetic steps.



Scheme 64: Proposed application of SM/DA in total synthesis of (±)-aspidospermidine. Pg = protecting group.

3.4. Results and Discussion

3.4.1. Retrosynthetic analysis

Our intended approach for making the natural product will be through the following disconnections (Figure 19). As already mentioned, the **C** ring will be delivered through the proposed SM/DA protocol. Ring **E** will be formed in a similar fashion to the method imposed in MacMillan's synthesis, *via* an aza-Michael type mechanism. Finally, the **D** ring will be constructed through a 1,4-conjugate addition.

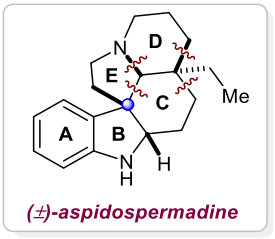
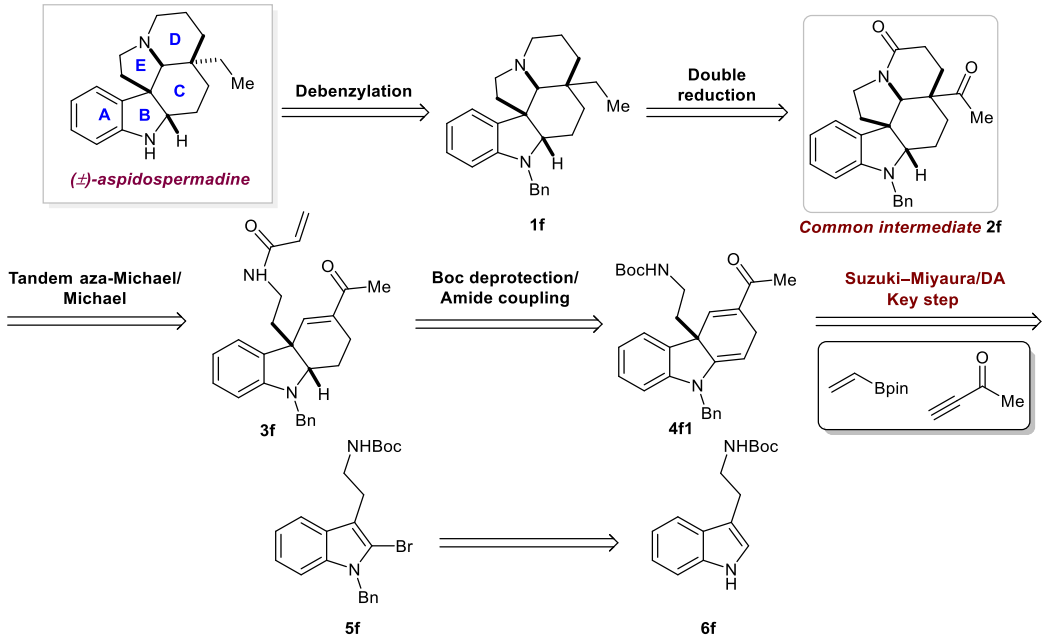


Figure 19: Disconnections for tackling the synthesis of the natural product.

Taking a closer look at the full retrosynthetic pathway (Scheme 65), it was envisaged that (±)-Aspidospermidine could be readily accessed from common intermediate **2f** through a series of reduction and deprotection steps. This planned intermediary would act as the stepping stone for accessing multiple structurally different alkaloids. Compound **2f** can be derived from **3f** via a proposed aza-Michael/Michael cascade reaction. Acrylamide **3f** can be obtained through a

deprotection/amide coupling strategy from carbamate **4f1**. For the construction of key intermediate **4f1**, indole bromide **5f**, vinyl Bpin and 3-butyne-2-one could be combined in the proposed SM/DA sequence. Finally **5f** can be synthesised from commercially available *N*-boc-tryptamine **6f**.

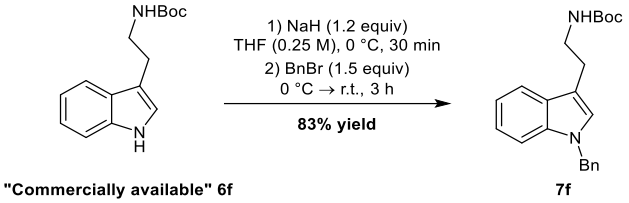


Scheme 65: Complete retrosynthesis analysis of (±)-aspidospermidine.

3.4.2. Forward Synthesis

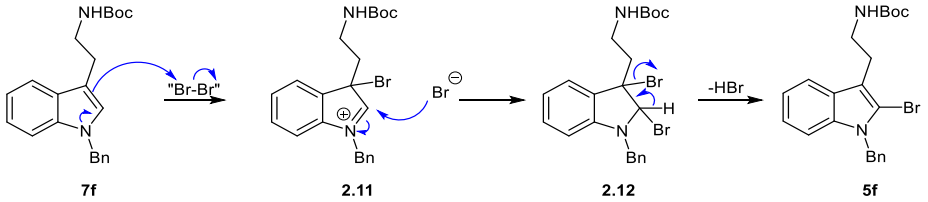
3.4.2.1. Benzyl protection and bromination

The first step of the synthesis commences with a simple benzyl protection of the indole nitrogen, which proceeded with excellent yield (Scheme 66). In contrast, the following bromination of the C-2 position of the indole did not proceed smoothly. It is well-known that the C-3 position of the indole is the most nucleophilic site, with electrophilic aromatic substitutions (EAS) selectively occurring here.[129] In spite of this, given the presence of the extended functionality on the C-3 position, a second EAS is less feasible on this location, as it would result in the loss of aromaticity. This implies that the C-2 position's reactivity would be enhanced towards an incoming bromide electrophile.



Scheme 66: Benzylation of 6f.

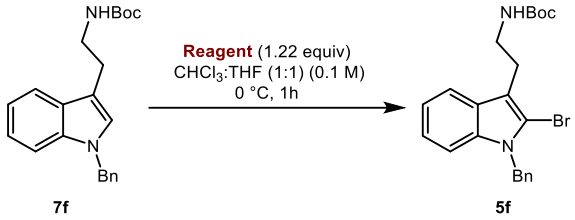
Looking at the mechanism behind this particular bromination more closely (Scheme 67), we can understand how to boost the formation of the desired product. After the initial EAS to form intermediate **2.11**, the bromide anion can then attack into the C-2 position and quench the iminium ion, forming **2.12**. Afterwards, elimination of HBr yields the desired product **5f**. It is likely that slow exposure to the brominating reagent, hence portionwise addition, will be crucial for the reaction, to avoid additional bromination of the aromatic ring occurring.



Scheme 67: Bromination mechanism.

After screening different brominating reagents, it was found that the milder ones such as NBS and pyridinium tribromide were best at facilitating this transformation (Table 9, Entries 2 & 3 respectively). The use of Br_2 produced a more complex reaction profile, with bromination likely having occurred at multiple positions on the aromatic backbone. In comparison the milder reagents provided improved selectivity for the C-2 position. In the case of pyridinium tribromide it has been reported, when in solution, exists as an equilibrium between pyridium bromide and Br_2,[130] meaning there is a controlled release of bromine during the transformation, aiding in turn the desired reaction. The reason for employing a bi-solvent system in $CHCl_3$:THF was to aid solvation of the less soluble brominating reagent (Table 9, Entry 3). Given the similar performance levels of the milder reagents, it was decided that pyridinium tribromide would be carried forward as part of the optimised system, as it had been reported in the literature of brominating similar systems to good effect.[131]

Table 9: Brominating reagent screen.

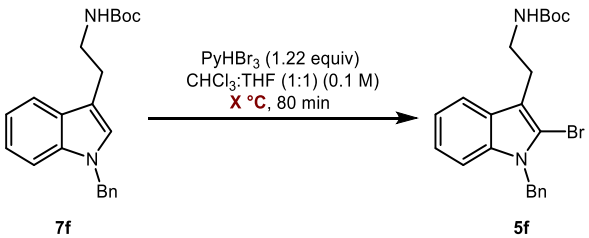


Entry	Reagent	SM[a] (%)	Conversion[a] (%)
1	Br_2	12	13
2	NBS	12	51
3	Pyridinium tribromide	5	50

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene).

Moving forward with pyridinium tribromide as the brominating agent, temperature was identified as a key parameter to improve conversions. Table 10 summarizes the results obtained from changing this variable. When the reaction was conducted at –10 °C (Table 10, Entry 1), a significant improvement in conversion was observed. Lowering the temperature further to –20°C (Table 10, Entry 2), provided an additional increase in conversion, which was confirmed through isolation. Going to even lower temperatures (Table 10, Entry 3) caused a decrease in reactivity, with some starting material being leftover. A by-product was predominantly formed under these conditions, presumably as a result of bromination occurring at the aromatic ring or potential formation of the oxaindole. The conditions in entry 2 were used moving forward.

Table 10: Bromination temperature screen.

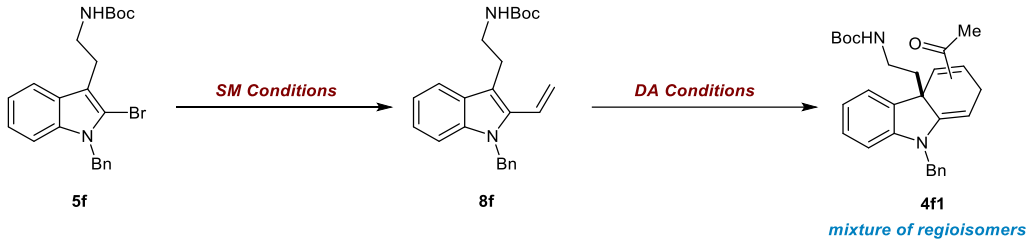


Entry	Temperature (°C)	SM (%)	Conversion[a] (%)
1	–10	5	65
2	–20	7	79 (74)
3	–40	18	10

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene). Isolated yield in brackets.

3.4.2.2. *Aspidosperma* alkaloid C ring formation

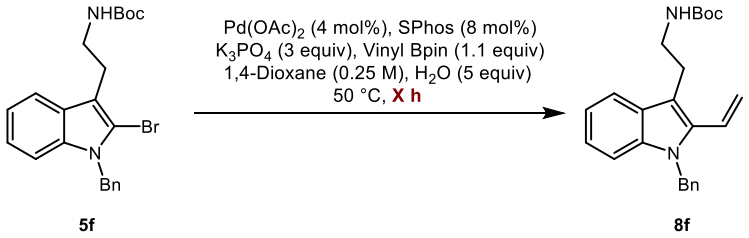
With a route now in hand to synthesise the bromo-bearing indole starting material **5f**, investigations into the cascade SM/DA reaction were launched. In order to validate this proposed reaction, a step-wise approach was adopted (Scheme 68).



Scheme 68: Two-step validation of cascade SM/DA reaction.

Starting with the SM coupling, we were pleased to see that the conditions employed in the methodology,[72] albeit with a few adjustments, namely the equivalents of vinyl Bpin employed and the solvent concentration, were transferable (Table 11, Entry 1), giving a reasonable 13% conversion. Hence, it was deemed suitable to begin the optimisation of the reaction with a time study (Table 11). The results indicated that the reaction goes to completion after 16 h (Table 11, Entry 4). One slight difficulty that was encountered during the optimisation of this step was confirming these conversion measurements through isolation; as any remaining starting material would co-elute with the product during column chromatography, therefore, complete consumption was essential moving forward. Despite the reaction going to completion in 16 h (Table 11, Entry 4), for scaling-up purposes, 24 h was carried forward as part of the optimised conditions.

Table 11: Suzuki–Miyaura cross-coupling time study.



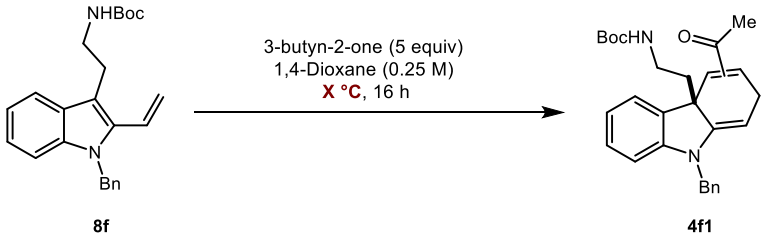
5f **8f**

Entry	Time (h)	SM (%)	Conversion[a] (%)
1	1	88	13
2	4	70	32
3	8	10	91
4	16	0	98
5	24	0	>99

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene).

Given the success of the SM reaction, the subsequent optimisation of the DA step was solely conducted in 1,4-dioxane, in order to gauge the possibility of combining the two reactions in a cascade scenario. Firstly, a temperature study was carried out to see if it could be thermally facilitated (Table 12). Compared to vinyl Bpin, the significantly more reactive nature of 3-butyn-2-one as a dienophile, provided merit for obtaining desired reactivity. Only at 125 °C was reactivity observed (Table 12, Entry 4). The resulting NMR and high res data ($[M+Na]^+$ ($C_{28}H_{32}N_2O_3Na$) requires *m/z* 467.2305, found *m/z* 467.2298) suggested that **4f1** may have been formed, with the compound isolated (albeit not clean) existing potentially as a complex mixture of diastereomers and regioisomers. Given the large temperature requirement for observing minimal reactivity, it was thought the use of a 3rd body or activator would alleviate both the reactivity and selectivity challenges.

Table 12: DA Temperature study.

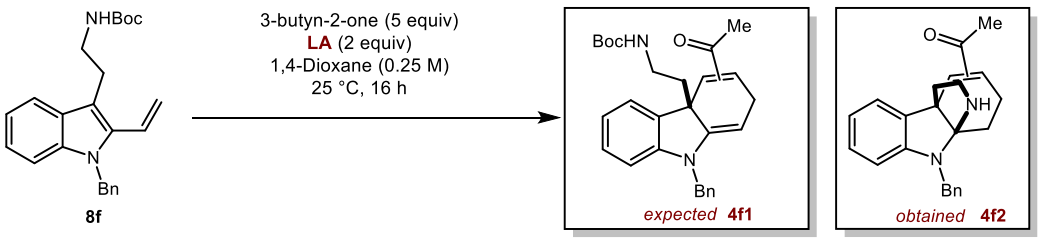


Entry	Temperature (°C)	SM (%)	Conversion[a] (%)
1	25	100	0
2	50	100	0
3	75	97	0
4	125	56	38

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene).

As suggested above, the addition of a Lewis acid or Brønsted acid (activators) to bridge the gap between the HOMO-LUMO levels was investigated next. Starting with the former, a few trial runs were conducted (Table 13). After screening a few examples, a hit was obtained using $BF_3 \bullet OEt_2$. $Cu(OTf)_2$ and $AlCl_3$ yielded some success, however, the reaction profile for both were considerably worse compared to the reaction involving $BF_3 \bullet OEt_2$. Further examination of the successful experiment revealed that a different product was formed. Similar to the mechanism described by MacMillan and co-workers,[127] the DA product had undergone a subsequent cyclisation, with the pendant amine group cyclising onto the C-2 position of the indoline (structure confirmed by 2D NMR) . In addition, an *in situ* deprotection of the Boc group had occurred.

Table 13: LA screen.

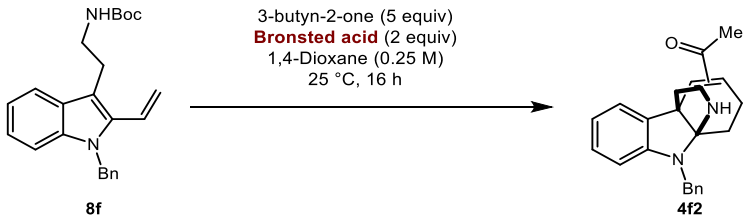


Entry	LA	SM (%)	Conversion[a] (%)
1	$Cu(OTf)_2$	<10	17[b]
2	$AlCl_3$	19	16[b]
3	$BF_3 \bullet OEt_2$	0	40[b]

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene). [b] Conversion to 4f2.

We then turned our attention towards utilizing a Brønsted acids to see how they compare (Table 14). The reaction profile using Tosic acid (TsOH) showed minimal starting material remaining after 16 hours, with ^{1}H NMR analysis giving comparable conversion to the product as observed with $BF_3 \bullet OEt_2$. In spite of this, the LA was carried forward as part of the optimised conditions to minimise potential starting material degradation, as it could be added as the final reagent during reaction preparation. The use of AcOH, a weaker acid, led to no product formation, with only unreacted starting material remaining.

Table 14: Bronsted acid screen.

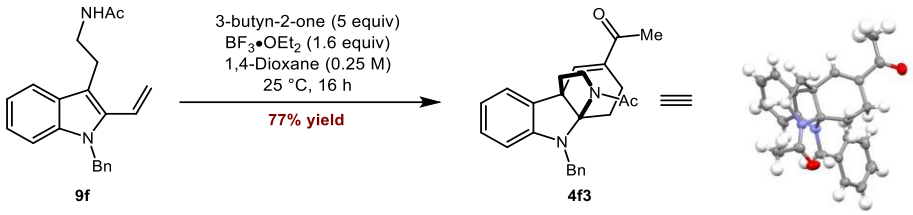


Entry	Bronsted acid	SM (%)	Conversion[a] (%)
1	TsOH	<5	33
2	AcOH	97	0

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene).

Spurred on by these results, absolute confirmation of the compound's structure was imperative moving forward to confirm which regioisomer was being formed. 2D NMR analysis proved too ambiguous in clarifying this matter, as a result the growth of crystals was attempted, with limited success. It was postulated that the attachment of an acetate group onto the free secondary amine would generate a crystalline compound. Using the same overall synthetic approach, as described up to this point,

the equivalent acetate protected indole pseudo-diene **9f** was furnished (see section 3.7.4.6. for more information). Exposure to similar set of conditions highlighted above (Table 13, Entry 3), yielded the resulting product **4f3** in 77% yield (Scheme 69). An X-ray single crystal structure of this compound was successfully obtained (solved by Dr. David Cordes), verifying which regioisomer has been generated.



Scheme 69: DA reaction with acetate protected pseudo indole diene.

Interestingly, compared to typical DA-type reactivity, one regioisomer is formed exclusively, suggesting that an asynchronous DA process may be taking place.[132,133] This implies that the DA adduct is being formed in non-concerted fashion. The selective formation of one regioisomer can be explained by the relative dipole distribution on each reacting component (Figure 20). As previously mentioned, (see Section 3.4.2.1.), the C-3 position on the indole is the most nucleophilic site, whereas for the dienophile the most electrophilic site is the terminal alkyne position. Therefore, upon approach of the dienophile during the TS, it orientates itself accordingly to maximize this interaction; which is promoted even further by the presence of the LA coordinating to the ketone functionality.

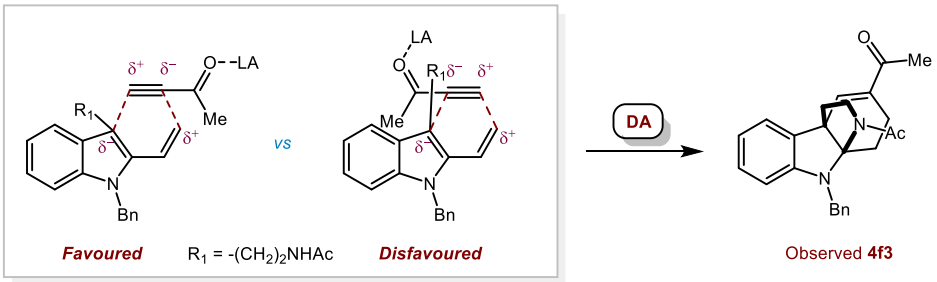
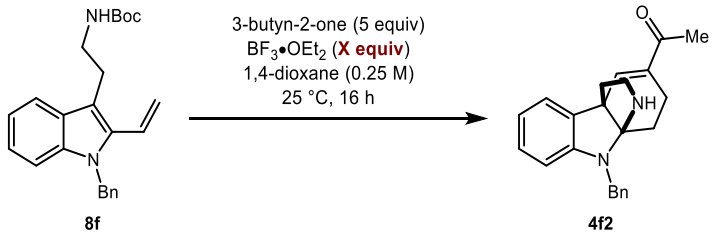


Figure 20: Dipole distribution of reacting components explaining observed selectivity.

With full elucidation of the cycloadduct's structure, optimisation of the DA step began. Given the necessity for the LA being present, the effects of its loading were investigated first (Table 15). The results demonstrated that lower loadings of LA led to reduced conversions to the desired product, *pari passu* a significant amount of unidentified by-product was formed at lower loadings as well. Increasing the LA content (Table 15, Entry 5) also led to no further increase in conversion to the DA adduct, with the reaction seemingly plateauing. In spite of this, in almost all entries, the starting material was fully consumed. This prompted the question as to where mass balance was being lost at higher loadings.

Table 15: LA loading study.



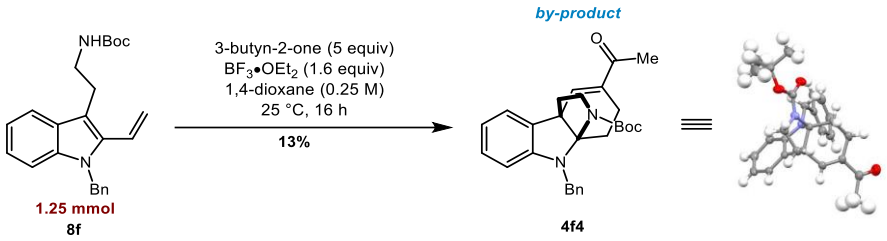
8f 4f2

Entry	$BF_3 \bullet OEt_2$ (X equiv)	SM [a] (%)	Conversion 4f2 [a] (%)	By-product [a] (%)
1	0.5	<5	<4	84
2	1	0	26	60
3	1.5	0	33	30
4	2	0	40	9
5	2.5	0	38	0
6	0.1	43	n.d	49

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene). N.d. = not determinable.

To answer the mass balance issue it was key that the by-product's structure was identified. After repeating the experiment using the conditions highlighted, on a larger scale (1.25 mmol), the by-product was isolated (13% yield) (Scheme 70). This less polar compound was in fact the same DA adduct, but with the Boc-protecting group still attached on the amine, which exists as a mixture of rotomers. A single X-ray crystal structure confirmed this (solved by Dr. David Cordes). In light of this new

information regarding the by-product structure, and that the formation of the free amine DA adduct could not be increased beyond 40%, it was decided to make the protected DA adduct (**4f4**) the target for the optimisation of this step. An additional bonus of making the boc-bearing DA adduct the subject meant that we could also accurately corroborate conversions being observed as it was more easily isolated compared to its analogue **4f2**.

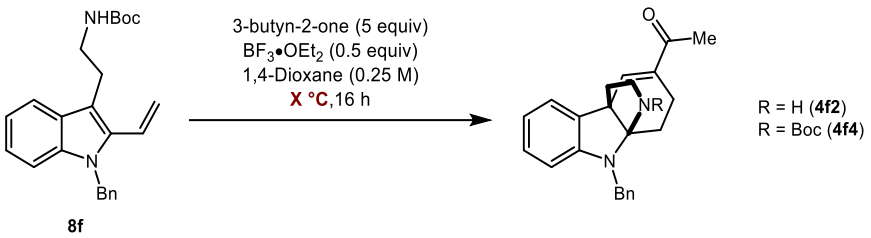


Scheme 70: Isolation of Boc-protected DA adduct.

The hypothesis as to why at higher loadings, mass balance was being lost, was presumably due to undesirable polymerisation and/or salt formation pathways. Intriguingly, the results show that the transformation can be facilitated using sub-stoichiometric quantities of LA (Table 15, entries 1 & 6); providing the possibility for exploring an asymmetric variant for the DA transformation. From a step-count perspective it would have been attractive to persist with the *in situ* Boc-deprotecting DA protocol, as this would have constructed an advanced intermediate for the overall synthesis with great efficiency. However, the substantial yield difference observed in the formation of the two sets of DA adducts was simply too great to ignore, particularly when contemplating the integration of SM step to achieve the overall cascade reaction.

Although excellent conversion had been achieved in forming **4f4** (Table 15, Entry 1), for completeness of optimising the reaction's parameters, the following point changes were investigated: temperature, concentration, time and alkyne loading. Beginning with temperature (Table 16), it can be seen that with increasing levels of applied heat, the formation of both products decreased. This can be explained by the greater extent of decomposition taking place.

Table 16: Temperature study with LA.

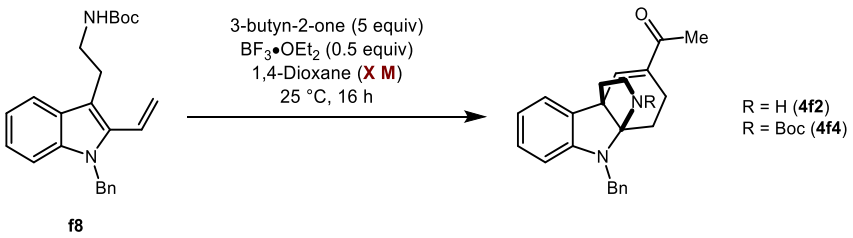


Entry	Temperature (°C)	SM [a] (%)	Conversion 4f2 [a] (%)	Conversion 4f4 [a] (%)
1	25	<5	<4	84
2	35	<1	19	71
3	50	0	18	66
4	75	0	13	55
5	100	0	6	44

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene).

A concentration study of the reaction revealed no noticeable trends (Table 17). Both higher and lower concentrations provided similar reaction profiles. Hence, conditions in Entry 1 were carried forward as part of the optimised conditions.

Table 17: Concentration study.

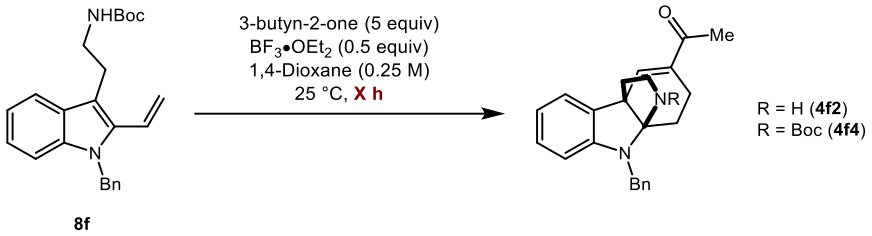


Entry	Concentration (X M)	SM [a] (%)	Conversion 4f2 [a] (%)	Conversion 4f4 [a] (%)
1	0.25	<5	<4	84
2	0.5	0	13	81
3	0.125	0	18	82

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene).

A subsequent time study revealed that the reaction went to completion after 4 h (Table 18). Even after 2 h, only a trace amount of starting material was detected. Any prolonged periods of reaction also did not cause any degradation of the products, with the reaction profiles staying relatively consistent throughout. These rapid reaction times provide further evidence that this is a "formal" DA reaction.

Table 18: Time study.



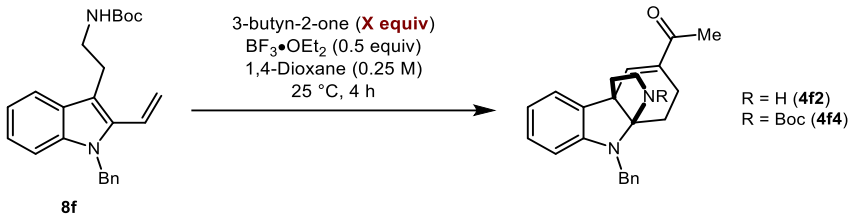
8f

Entry	Time (X h)	SM [a] (%)	Conversion 4f2 [a] (%)	Conversion 4f4 [a] (%)
1	0.5	17	7	68
2	1	9	7	77
3	2	1	12	79
4	4	0	11 (n = 2)	86 (n = 2)
5	8	0	14	86
6	16	0	<4	84
7	20	0	16	72
8	24	0	17	77
9	48	0	18	76

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene). n = 2, average of two experiments.

Lastly, the alkyne loading was studied (Table 19). The results demonstrated that the reaction could be performed effectively with a minimum of two equivalents. Although the use of one equivalent provided good conversion to the product (Table 19, Entry 1), the use of two equivalents was carried forward, to maintain the short reaction interval and ensure full consumption of starting material.

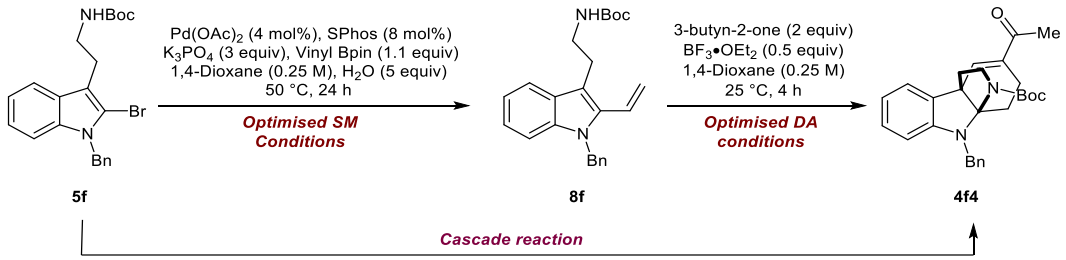
Table 19: Alkyne loading study.



Entry	Alkyne (equiv)	SM [a] (%)	Conversion 4f2 [a] (%)	Conversion 4f4 [a] (%)
1	5	0	<4	84
2	1	18	6	75
3	2	<1	10	77
4	3	<1	10	78
5	4	0	10	80

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene).

With satisfactory conditions developed for the DA step, as well as the SM step, efforts into completing the cascade protocol intensified (Scheme 71).

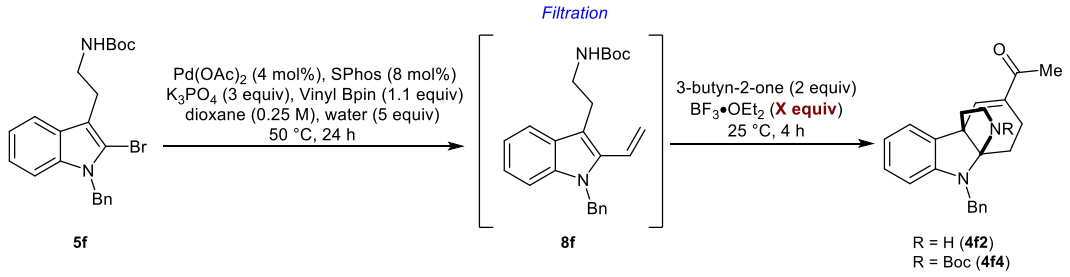


Scheme 71: Optimised conditions for seperate SM and DA steps.

Early trial experiments unfortunately provided disappointing results, although this was perhaps unsurprising. The obvious flaw within the proposed cascade reaction is the requirement for basic conditions in the SM step and acidic conditions in the DA step – which fundamentally are incompatible, when considering a concerted process. If, however, the reaction is acidified prior to the second step, this issue could be circumvented. Nevertheless, it was hypothesized that a "one-pot" reaction involving step-wise addition of reagents could be devised, with the addition of a filtration step in between to remove the excess inorganic base post-diene formation. Some degree of

success was obtained when implementing these measures (Table 20). Using the optimised conditions for each step afforded the product in 8% conversion (Table 20, Entry 1). Doubling the loading of LA during the second step, gave a slightly improved conversion, with considerably more starting material being consumed. A threshold was reached for the formation of **4f4** after going above 1.5 equiv of LA (Table 20, Entry 3). Interestingly, when a greater excess of LA was implemented (Table 20, Entry 3), although none of the desired **4f4** was formed, the conversion to **4f2** was comparable to earlier results (Table 15, Entry 4), and in some cases better (Table 20, Entries 5-7) leaving potential for future exploration. Nonetheless, the primary focus was to establish a cascade protocol to generate **4f4**, and so far there is insufficient evidence to suggest why the one-pot transformation was greatly underperforming, compared to carrying out the steps individually. A likely reason behind the low conversions, is that the base from the SM step is still present, despite filtration, resulting in the LA being quenched during the DA step. The slight increase in conversion observed, when doubling the LA content, (Table 20, Entry 2) supports this hypothesis. It is clear, however, from prior optimisation insights (Table 15, *vida supra*), that low loadings of LA are paramount to the successful formation of **4f4**.

Table 20: Cascade SM/DA trials – LA loading study.

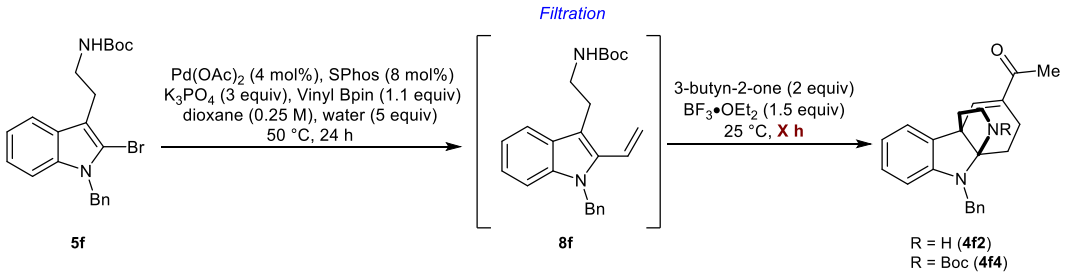


Entry	$BF_3 \bullet OEt_2$ (X µL, X equiv)	Diene 8f [a] (%)	Conversion [a] 4f2 (%)	Conversion [a] 4f4 (%)
1	0.5 equiv	65	2	8
2	1 equiv	40	12	14
3	1.5 equiv	15	32	22
4	2 equiv	8	46	6
5	2.5 equiv	0	71	0
6	3 equiv	0	68	0
7	4 equiv	0	67	0

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene).

Next it was reasoned that time may have a positive effect on the cascade sequence (Table 21). Unfortunately, any increase in reaction period led to either similar or lower conversions to **4f4**. It must be noted, that the reaction profile over longer periods also became messier with unidentified peaks in the NMR becoming visible. Therefore, the short reaction period of 4 h was carried forward. Although these results showed great promise in forming **4f2**, frustratingly the desired DA adduct formation could not be pushed beyond the 20% mark. Therefore, in the interest of completing the total synthesis and increasing the overall yield, the stepwise approach was implemented moving forward.

Table 21: Cascade SM/DA trials – Time study.

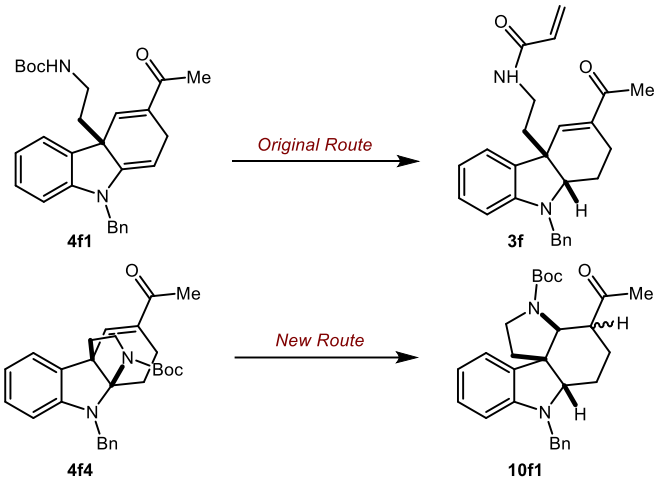


Entry	Time (h)	Diene 8f [a] (%)	Conversion [a] 4f2 (%)	Conversion [a] 4f4 (%)
1	4	15	32	22
2	16	4	8	14
3	20	16	27	12
4	24	16	32	9
5	48	10	17	7

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene).

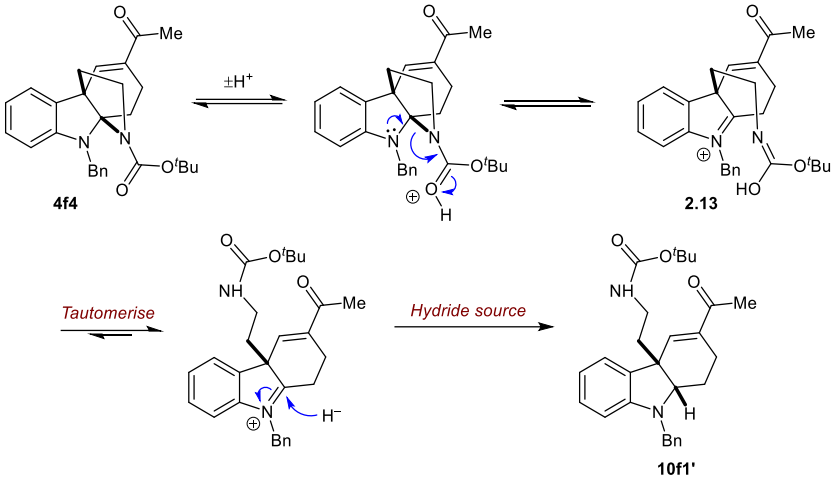
3.4.2.3. *Aspidosperma* alkaloid E ring formation

The attainment of the different DA adduct, compared to the predicted one outlined in the retrosynthetic analysis (see Section 3.4.1.) has consequently affected the next set of synthetic steps. Originally, a deprotection followed by amide coupling step was planned (refer to Scheme 65); instead a tandem ring-opening/aza-Michael transformation was now pursued (Scheme 72) to form the correctly positioned **E** ring.



Scheme 72: Proposed transformation alteration post DA step.

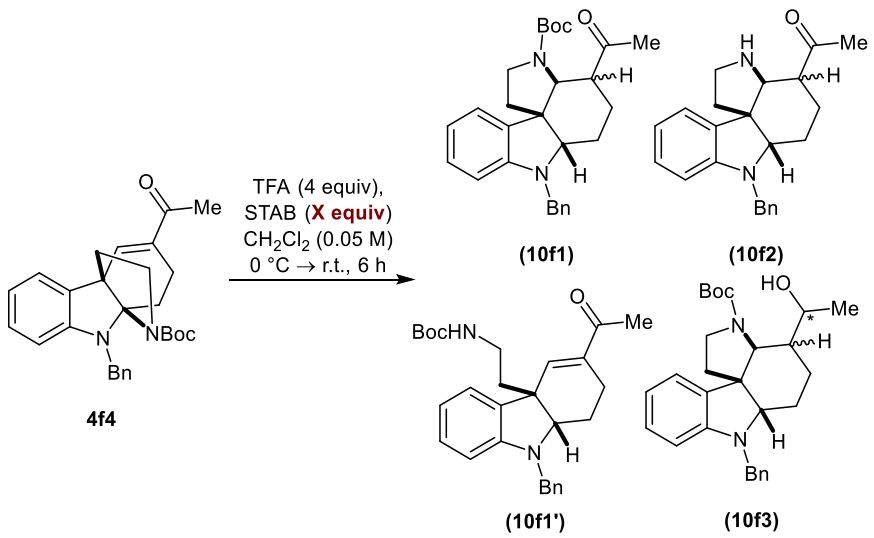
The *N*,*N*-acetal embedded in the compound, can be opened using protonation. Upon exposure to acidic conditions the carbamate functionality will be protonated, resulting in the lone pair on the indoline nitrogen pushing into the C-N bond, breaking the adjacent C-N bond and forming reversibly an iminium species (**2.13**) (Scheme 73).



Scheme 73: Proposed ring-opening mechanism.

Now, in the absence of an additional reagent, such as a reducing reagent, the formation of the iminium species would remain in equilibrium. However, in the presence of a hydride source, the iminium species will be quenched, delivering the ring-opened product (**10f1'**) in the process. Other reported synthesises for similar natural products have implemented this strategy successfully, as such we began optimising this step using analogous conditions.[134,135] Firstly, the effectiveness of sodium triacetoxyborohydride (STAB) was investigated (Table 22). Initial screening quickly identified a set of conditions for facilitating the desired reaction (Table 22, Entry 1). One equivalent smoothly generated desired intermediate **10f1** (80% yield), with small amounts of starting material leftover. Predictably, incremental increases in reducing agent (Table 22, Entries 2-4) led to a greater proportion of undesirable over reduced alcohol (**10f3**) being formed. At the same time this led to greater amounts of uncyclised product also being formed. Remarkably, despite the large excess of TFA being applied to the reaction, no trace of the Boc-cleaved product (**10f2**) was observed. Notably, in the cases where conversions were corroborated by isolation, the desired intermediate **10f1** was obtained as an inconsequential mixture of diastereomers. This is because this stereocentre alpha to the ketone would be rectified later on in the synthesis during the construction of the **D** ring in the *Aspidosperma* framework.

Table 22: STAB loading study.

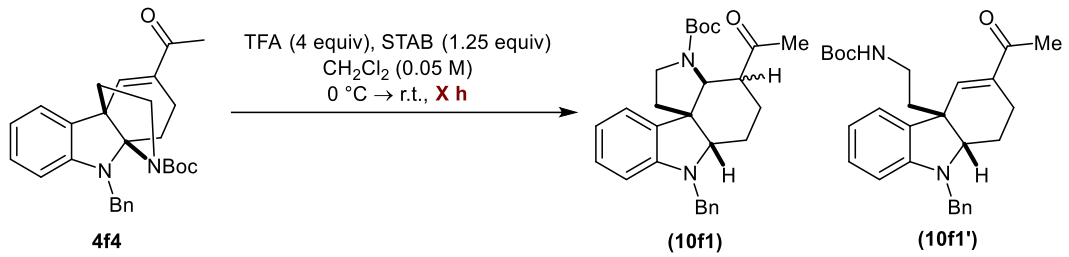


Entry	STAB (equiv)	SM [a] (%)	Conversion 10f1 [a] (%)	Conversion 10f1' [a] (%)	Conversion 10f2 [a] (%)	Conversion 10f3 [a] (%)
1	1	18	78 (80)	0	0	0
2	2	0	68	2	0	6
3	3	0	57	18	0	17
4	4	0	34	42	0	21
5	1.5	0	82	2	0	6
6	1.25	0	92 (89)	0	0	0

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene). Isolated yield in brackets. Product isolated as mixture of diastereomers, *d.r.* (~60:40).

Next, the time dependence of the reaction was examined (Table 23). Similar to the DA reaction, in this transformation the starting material is consumed in as little as 2 h, demonstrating the efficiency of the process. Nevertheless longer reaction periods were important to encourage the second aza-Michael step to occur.

Table 23: Time study.



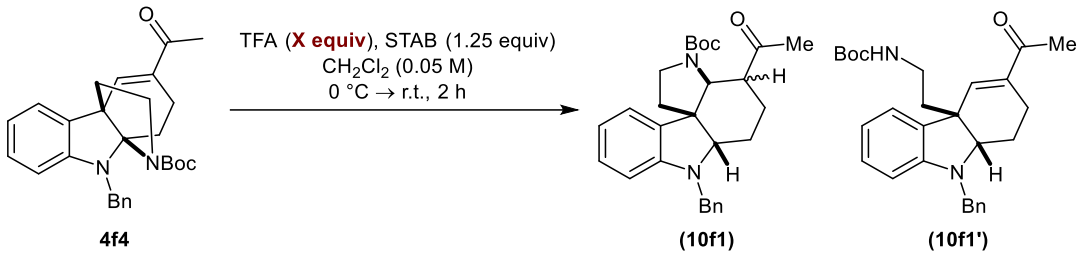
4f4 (10f1) (10f1')

Entry	Time (h)	SM [a] (%)	Conversion 10f1 [a] (%)	Conversion 10f1' [a] (%)
1	6	0	92 (89)	0
2	2	0	90	9
3	4	0	97	4

[a] Determined by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene). Isolated yield in brackets. Product isolated as mixture of diastereomers, *d.r.* (~60:40).

Lastly, the requirement for excess TFA was probed (Table 24). This study was conducted with 2 h reaction periods, with the results highlighting some interesting trends, as well as explaining its overall importance to the reaction. Decreases in the amount of TFA present led to reductions in desired product formation, whilst in turn, the amount of ring-opened but uncyclised intermediate **10f1'** grew (Table 24, Entry 3 vs 2). A control experiment in the absence of TFA showed no consumption of starting material (Table 24, Entry 5). As such, it is clear that the TFA plays two distinct roles in the reaction; firstly, during the protonation phase to generate the iminium species, and secondly, to activate the enone system, enabling the subsequent conjugate addition to take place. In spite of these results demonstrating a clearer picture on how the reaction behaves, the conditions highlighted in the time study (Table 23, Entry 1) were carried forward as part of the optimised system.

Table 24: TFA study.

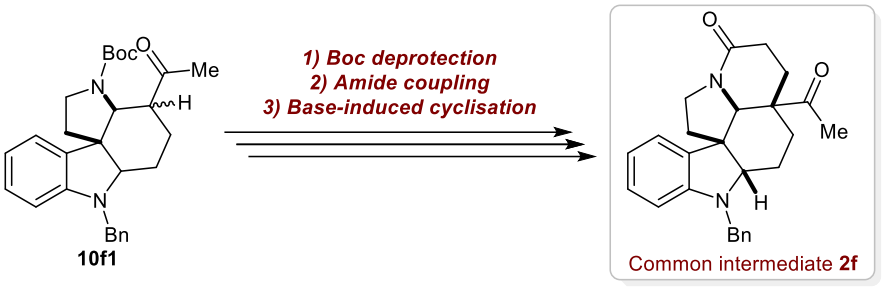


Entry	TFA (equiv)	SM [a] (%)	Conversion 10f1 [a] (%)	Conversion 10f1' [a] (%)
1	1	33	0	67
2	2	0	43	57
3	3	0	69	25
4	4	0	90	9
5	0	>99	0	0

[a] Determined by ^{1}H NMR analysis against a known internal standard (1,4-dinitrobenzene).

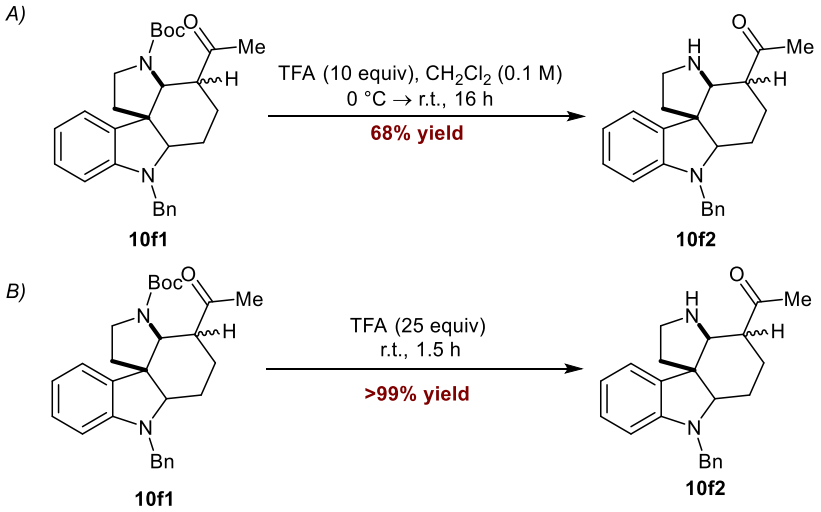
3.4.2.4. *Aspidosperma* alkaloid D ring formation

Having successfully orchestrated the formation of the **E** ring, focus turned towards developing a strategy for building the remaining **D** ring. Here, it was proposed that after installing the correct functionality on the nitrogen, a second conjugate addition would competently generate the alkaloid's common intermediate (**2f**). Ideally, a one-pot protocol was pursued for this transformation, as it was believed, given the simple chemical transformations involved, this would be feasible (Scheme 74).



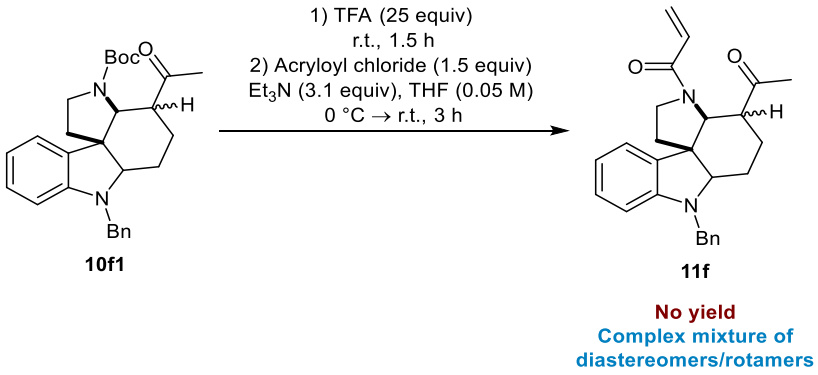
Scheme 74: Approach in furnishing the D ring.

Efforts into devising an efficient method for the initial deprotection of the Boc group commenced. Standard TFA conditions commonly employed for the removal of this carbamate group worked reasonably well (Scheme 75A). Nevertheless, being the simplest transformation in the three-step sequence, achieving maximum yield was paramount. Conceptually, it was reasoned that the steric encumbrance surrounding the protecting group, may be aiding its overall stabilization. This problem was quickly resolved by performing the reaction in neat TFA, providing the product **10f2** in quantitative yield (Scheme 75B).



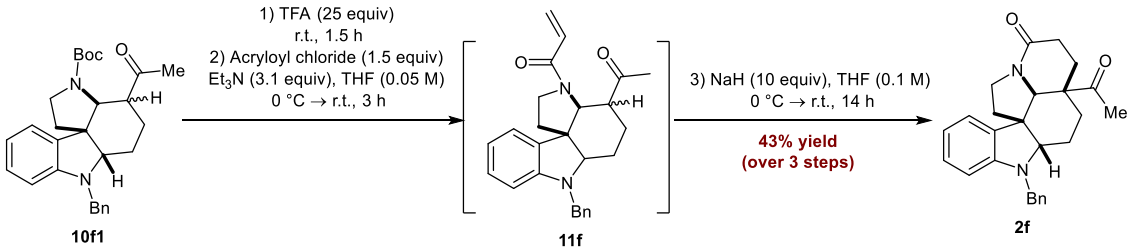
Scheme 75: Boc-deprotection step.

With a robust set of conditions in hand for the first phase of the one-pot reaction, the following amide coupling was investigated. In the final ring-closing step to form the six-membered **D** ring, a three-carbon component bearing a Michael acceptor was required. Naturally, one of the few realistic reagents that could adhere to the criteria set was acryloyl chloride. With this in mind, suitable conditions were pursued using a base that could not only form the amide bond efficiently, but also enable the final cyclisation. It was hypothesized that a large excess of base would be necessary to enact both roles. To test this theory, the crude material generated from the deprotection step, was subjected to the corresponding amide coupling conditions in a one-pot fashion, and pleasingly the crude NMR revealed that **11f** had been successfully generated (Scheme 76). No starting material was visible in the NMR, however, the complex mixture of diastereomers/rotamers could not be successfully separated to provide clean data. It was reasoned that the subsequent cyclisation step would rectify this issue by resolving the chiral centres and form a single diastereomer.



Scheme 76: One-pot boc-deprotection/amide coupling step.

As the scheme above suggests, no conjugate addition was observed. This was not unexpected, as Et_3N is not a strong enough base to generate the enolate species required to drive the reaction towards the cyclised product. As anticipated, after repeating the experiment, the crude material **11f** from the amide coupling step was subjected to a stronger base in NaH (10 equiv), causing gratifingly the desired cyclisation to occur to generate the natural products framework in a reasonable 43% yield over 3 steps (Scheme 77A). If these steps were to be amalgamated into a more efficient overall process in the future, a base suitable of enacting both steps must be implemented from the onset. With these results in hand we were pleased to move on with the remaining synthetic steps.

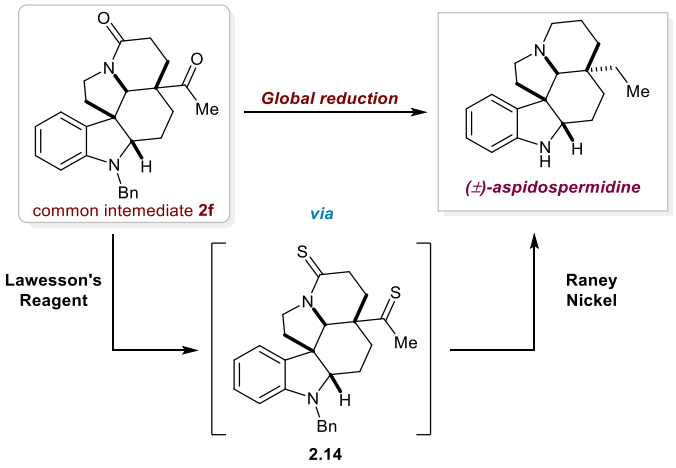


Scheme 77: "One-pot" reaction to generate common intermediate 2f from 10f1

3.4.2.5. Completing the synthesis of (±)-aspidospermidine

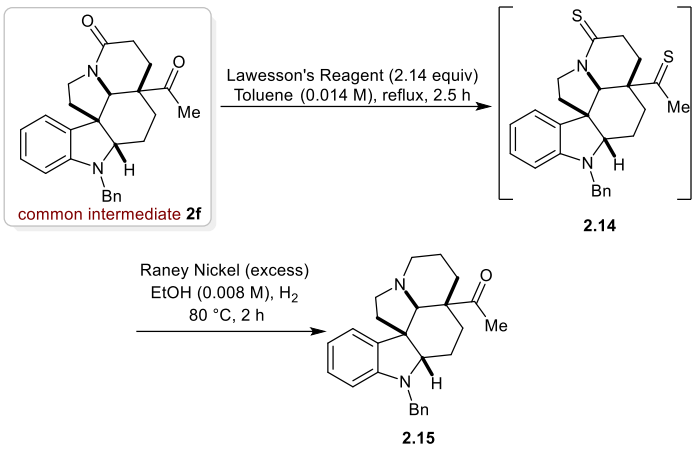
With the synthesis of the natural product nearly complete, all that remained was the removal of the excess functionality. Considering the possibility of any step-count reductions henceforth, we strived to seek a method that would allow for the joint reductions of the amide and ketone functional groups, whilst simultaneously freeing up the indole nitrogen (Scheme 78). It has been shown that this particular *N*-benzyl

group can be cleaved using Raney-Ni chemistry.[136] In addition, Raney-Ni has the ability to efficiently reduce thioamides and thioketones down to the amine and alkane, respectively. As a result, we started investigations into this combined strategy, by exploring ways of exchanging the oxygen with sulphur atoms. Lawesson's reagent has been demonstrated to be viable option in facilitating this interchange, when carrying out each one individually.[137]



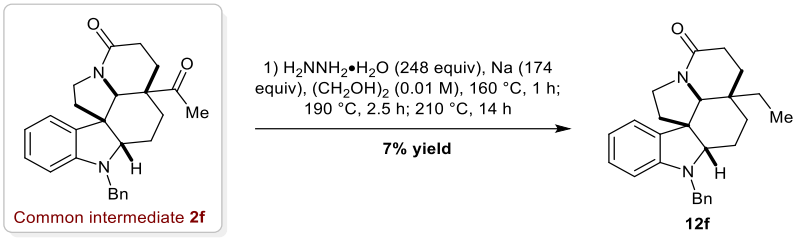
Scheme 78: Proposed endgame strategy.

Early attempts at forming the desired intermediate **2.14** proved ineffective (Scheme 79). Despite attempts, no evidence of dithionation was observed, with the exchange only successfully taking place at the amide, which was confirmed through subsequent Raney-Ni hydrogenation of intermediate **2.14** generating trace amount of compound **2.15**. It is likely that the thioketone never formed or was generated in only trace amounts, explaining the observed reactivity. Closer examination of the literature revealed that there is a significant energy barrier to overcome, to force the second thionation.[138] With focus upon successfully completing the synthesis, investigations into a more stepwise process were undertaken.



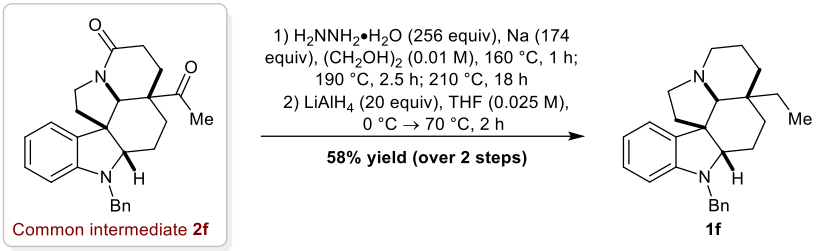
Scheme 79: Global reduction trial.

In common intermediate **2f**, the most challenging functionality to remove is the ketone, given its neopentyl position. Its remote location within the molecule and the surrounding bulk make it more difficult to access for subsequent manipulation. As such, vigorous conditions were likely needed to remove this functional group. The literature revealed that one of the few viable routes for direct ketone reduction would be to carry out a Wolff–Kishner (WK) reaction, which has been reported in other synthesis of (±)-aspidospermidine.[139] An additional benefit of this reaction is that it has the potential to reduce the amide as well, as it has been shown that when the geometrical constraints are right, i.e. twisted enough about the C–N bond, amide reduction can be achieved.[140] Pleasingly, the first trial reaction of this reduction provided the reduced compound cleanly, with no trace of starting material remaining (Scheme 80). However, the amide remained untouched. Purification of compound (**12f**) proved to be a serious struggle, as a molecule originating from ethylene glycol (the reaction solvent), co-eluted with the product during chromatography. Multiple water/brine extractions eventually cleaned the compound up to a satisfactory standard for analysis, but at the expense of reaction yield (7%).



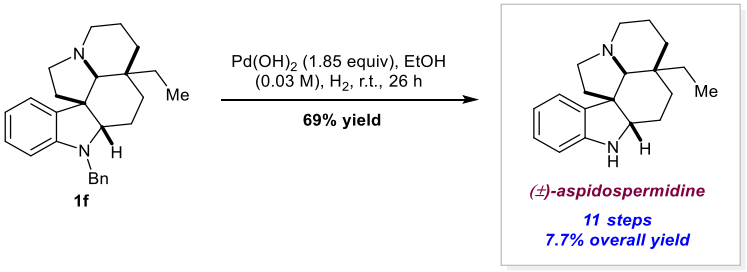
Scheme 80: WK reaction of common intermediate.

The subsequent reduction of the amide functionality was carried out with relative ease. For scaling purposes, in order to have enough material for the final debenzylation step, it was decided that the material obtained from the WK reaction would be carried through crude to the second reduction step. Gratifyingly, this worked exceptionally well, with the resulting doubly reduced complex being isolated in 58% over the two steps (Scheme 81). This large increase in yield can be explained by the more lipophilic nature of compound **1f** compared to **12f**, meaning separation from the aforementioned impurity (post WK reaction) was considerably more straightforward.



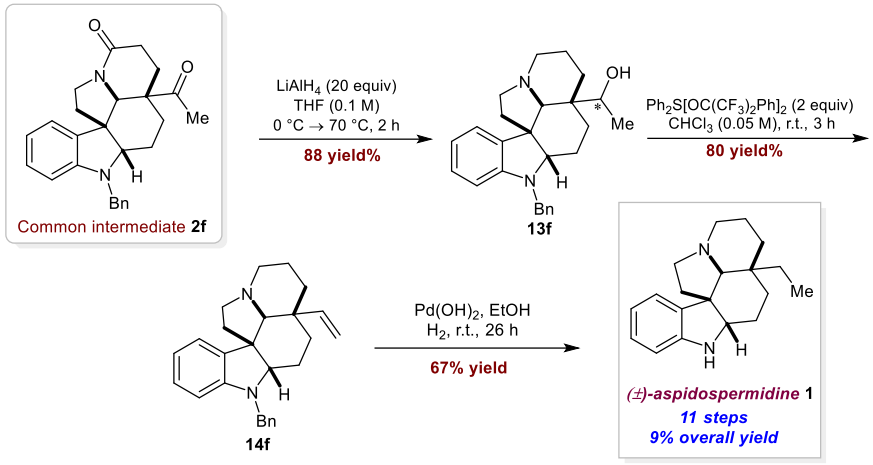
Scheme 81: Scaled-up two-step process for generating the final intermediate.

The final step of the synthesis involved a simple deprotection. Pearlman's catalyst was chosen to carry out the hydrogenation, given its enhanced reactivity towards *N/O*-debenzylation compared to other traditional catalysts like Pd/C.[141] Pleasingly, the reaction worked well, delivering racemic (±)-aspidospermidine in 69% yield. In total, 11 steps were required to synthesize the natural product from commercially available *N*-Boc tryptamine, with an overall yield of 7.7% (Scheme 82).



Scheme 82: Debenzylation step to generate (±)-aspidospermidine.

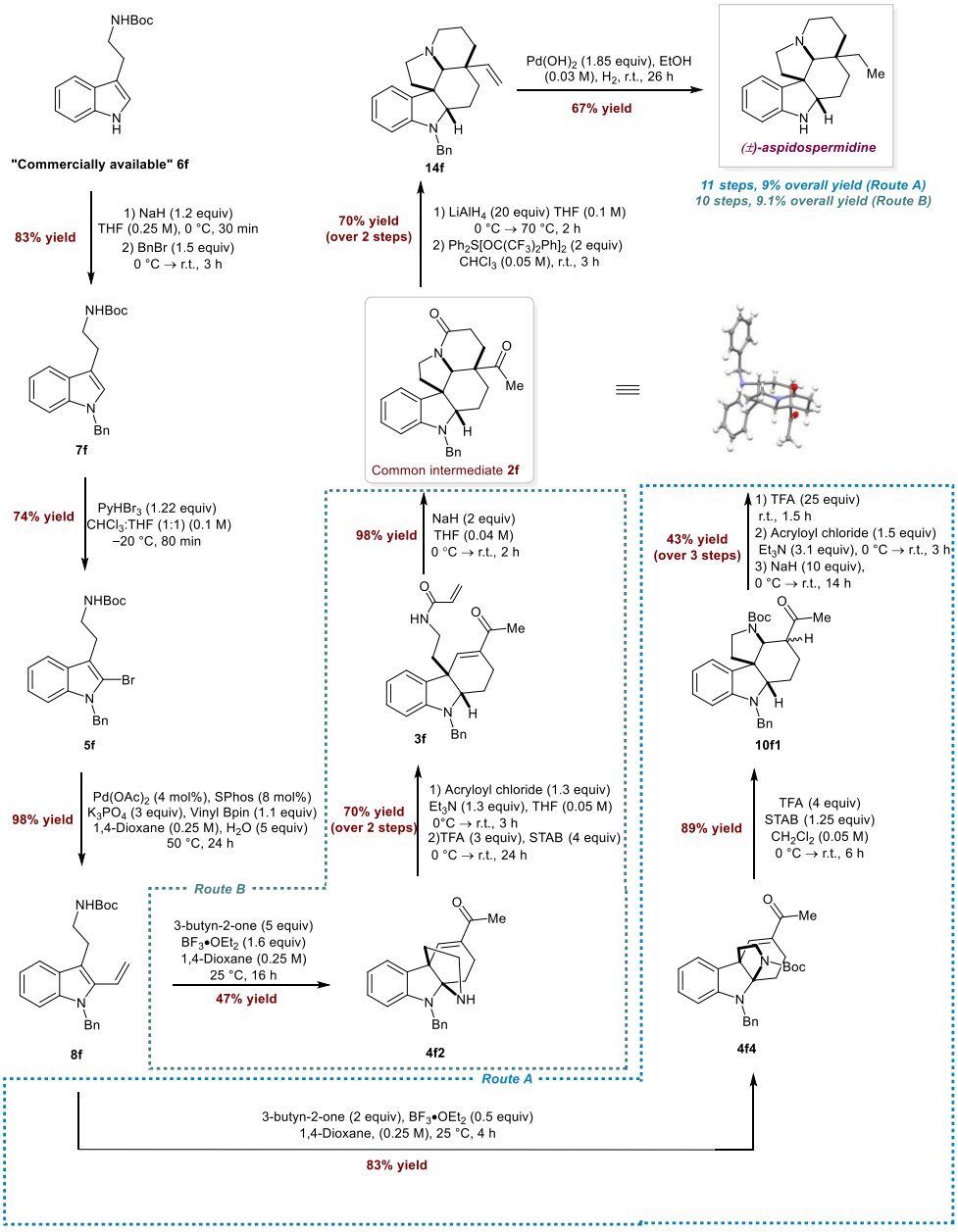
With the task complete in synthesising (±)-aspidospermidine, the overall route was scrutinised to establish its overall efficiency. Up to the common intermediate, all steps were shown to be scalable. However, the WK reaction was identified as problematic if scaled to larger quantities, particularly from a safety standpoint, hence an alternative pathway in conducting these final steps was highly desirable. A much milder set of events was hypothesised involving a reduction and elimination strategy to generate the corresponding olefin species (Scheme 83). The reduction step proceeded smoothly to furnish the corresponding alcohol **13f**, however, the resulting neopentyl alcohol was to our surprise challenging to eliminate at first. Traditional methods such as by acidic/basic means would not facilitate this transformation. Additionally, mesityl formation to enhance the alcohol's leaving capabilities followed by base exposure also failed to generate the olefin. Frustrated by these results, dehydrating reagents such as Burgess Reagent and Martin Sulfurane were tried next. Gratifyingly, the latter worked exceptionally well (80% yield). An additional bonus to this sequence of reactions, were the simpler purification measures involved compared to aforementioned ones (*vida supra*). Finally, application of Pearlman's catalyst in the joint hydrogenation of the olefin and benzyl group afforded the natural product in the same number of steps, in slightly better overall yield (9%). Compared to MacMillan's enantioselective synthesis,[127] our racemic route required two more steps, and the overall yield was considerably lower (24%). However, it can be stipulated that their synthesis commences from a more advanced building block, which is not commercially available from major suppliers.



Scheme 83: Scalable alternative final sequence of reactions.

3.4.2.6. Alternative route and comparison

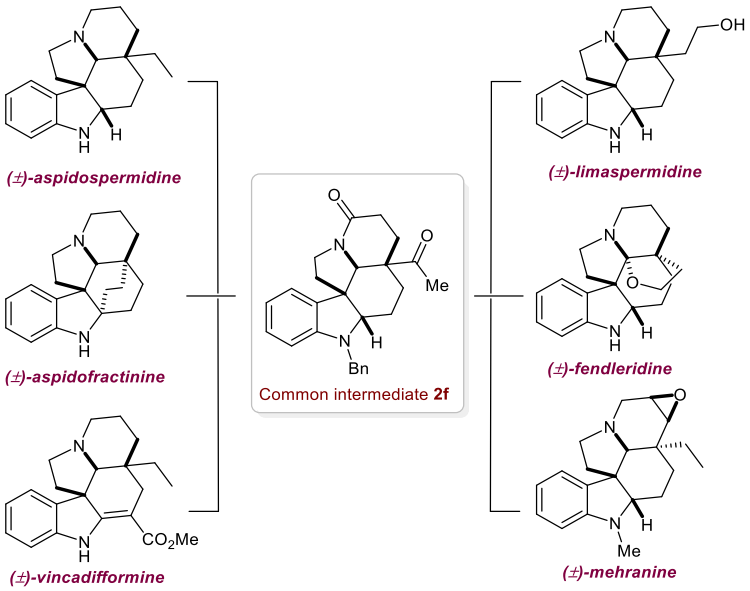
As was discussed earlier (see Section 3.4.2.2.), the ability to generate the free amine DA adduct (**4f2**), when a large excess of LA was used as in either a single transformation (Table 15) or in a "one-pot" fashion (Table 20), made us question how the subsequent synthesis would compare. Access to the common intermediate (**2f**) could be obtained with minor adjustments during the **D** and **E** ring forming parts of the synthesis highlighted in the full synthesis (Scheme 84, Route B). Using similar templates implemented during the formation of the **D** and **E** rings in the previously described route; a set of conditions were developed which enable the amide coupling and ring-opening step to be conducted in a one-pot fashion, providing **3f** in good yield (70%). Subsequent exposure to a strong base (NaH), initiated an efficient intramolecular cascade process, to construct the **E** and **D** ring. This is not a novel sequence of events, with a similar approach having been demonstrated in another synthesis of an *Aspidosperma* alkaloid.[142] An X-ray single crystal stucture of the common intermediate **2f** (solved by Prof Alexandra Slawin), provided unequivocal evidence for not only its structure, but also the relative stereochemistry of the four contiguous stereocentres. In contrast to the Boc-bearing DA adduct pathway (Scheme 84, Route A), this avenue employs fewer synthetic manipulations (10), with only seven purification steps. The overall yield is also slightly better (9.1%), and could significantly be improved once the predicaments involved during the DA step are sorted.



Scheme 84: Full synthetic route showcasing both potential routes to (±)-aspidospermidine.

3.4.3. Additional *Aspidosperma* alkaloid targets

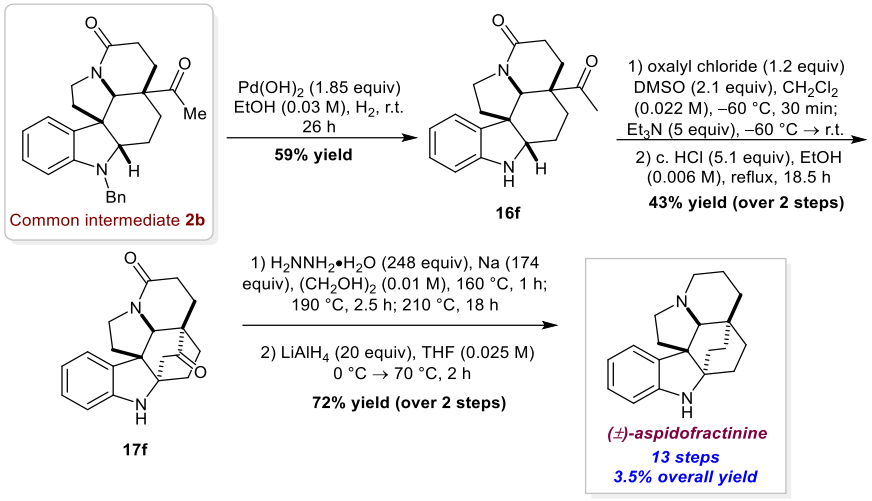
From the beginning we set out to establish an efficient route in synthesising *Aspidosperma* alkaloids, which utilises a SM/DA protocol as the key step. Furthermore, our intention was to showcase the shortest synthetic route for (±)-aspidospermidine, but so far, this remains to be achieved. Taking inspiration from MacMillan's work,[127] we laid out additional alkaloid targets to synthesise from the advanced common intermediate **2f** (Scheme 85).



Scheme 85: Additional alkaloid targets to synthesise.

3.4.3.1 Synthesis of (±)-aspidofractinine

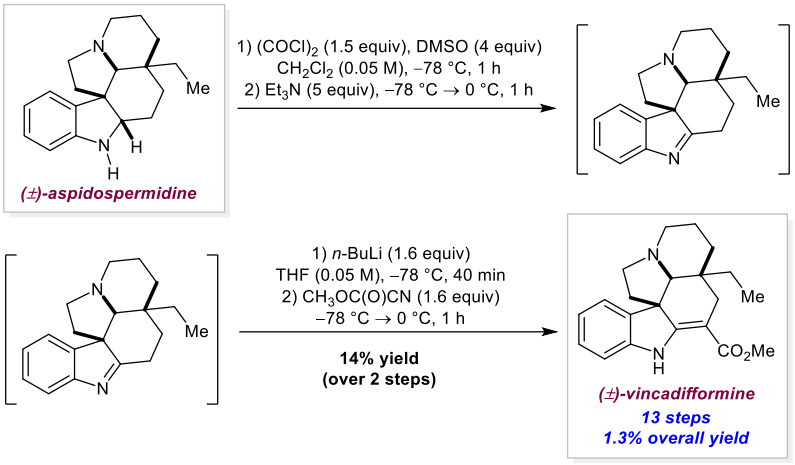
The first target was (±)-aspidofractinine, which was completed in 13 steps (Scheme 86). Changing the order in which the excess functionality is removed was imperative to finishing its synthesis. Here, the debenzylation was carried out first to give compound **16f**. This was because the ketone functionality and the free indoline nitrogen were essential for constructing the bicyclic architecture in the natural product. Employing conditions that were reported in the literature,[143] a Swern reaction oxidises the secondary amine to the imine species. After formation of the intermediate, acidic conditions cause the ketone to tautomerise to the enol, which can then cyclise onto the imine, building the bicyclic system (**17f**) in the process. Finally, the same set of reduction chemistry was carried out to generate the natural product (Dr. Tomas Lebl aided with the assignment), in 13 steps with an overall yield of 3.5%. This pales in comparison to a recent publication on the asymmetric synthesis of (–)-aspidofractinine (19% overall yield, 8 steps),[123] however, it does showcase the flexibility of our route by being able to access this natural product as well.



Scheme 86: Final steps in (±)-aspidofractinine total synthesis.

3.4.3.2 Synthesis of (±)-vincadifformine

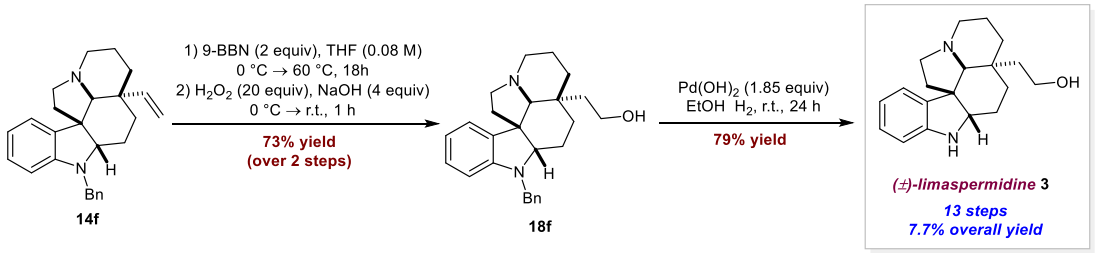
The synthesis of (±)-vicadifformine was considerably more straightforward, as it was achieved through implementation of precedent steps from (±)-aspidospermidine in 13 steps, with an overall yield of 1.3%.[127] This is again two steps longer than MacMillan's synthesis, and a comparatively lower overall yield was obtained (9%). Similar to the chemistry above (Scheme 86), an oxidation was carried out first to generate the corresponding imine intermediate (Scheme 87). This molecule is then deprotonated at the β-position using *n*-BuLi and reacted with Mander's reagent to install the requisite methyl ester. The yield for this two-step process was unremarkable at best (14%). Admittedly, this was due to an inseparable by-product arising from the initial oxidation step, believed to be a second oxidation occurring at the tertiary amine. In spite of this, the crude mixture was carried forward for the second stage. Although the reaction itself worked well, isolation of the natural product was difficult. Impurities were challenging to remove, and the compound itself was surprisingly unstable upon isolation, with gradual decomposition observed, although prior syntheses did not report the same issue.[127]



Scheme 87: Final steps in (±)-vincadifformine total synthesis.

3.4.3.3 Synthesis of (±)-limaspermidine

An additional alkaloid was successfully synthesised using the olefin species **14f** generated from **2f** (Scheme 88). In order to access this product, **14f** was exposed to a hydroboration/oxidation protocol to install the requisite alcohol functionality on the terminal position. This worked relatively well, providing the desired compound **18f** in 73% yield. A small amount of by-product accounting for ~10% of mass balance was as also isolated, which was identified as the protodeboronated product. Although not intended, this still can be viewed as productive as it would lead to (±)-aspidospermidine, offering divergence in the synthesis. Lastly, the conventional hydrogenation conditions were employed once more to finish the natural product synthesis in 13 steps, with an overall yield of 7.7%. As a comparison, recent work by Soós group, generated this natural product asymmetrically in 12 steps, and in an overall yield of 7%.[124]



Scheme 88: Final steps in (±)-limaspermidine synthesis.

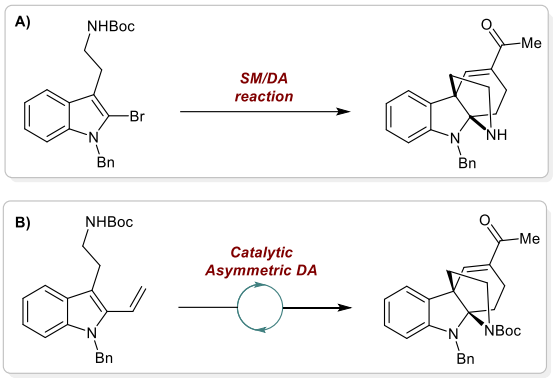
3.5. Conclusion

In summary, the total synthesis of (±)-aspidospermidine and three other alkaloids from a common intermediate was accomplished. The route up to the common intermediate has been showcased to be scalable and robust, with X-ray crystal structures obtained for key intermediates to validate regiochemistry as well as relative stereochemistry. Methods to reduce the number of steps involved post common intermediate **2f** synthesis were trialled, which were unfortunately unsuccessful. Identification of an alternative end game pathway *via* the reduction/elimination sequence enabled final steps to be deemed scalable. Despite lack of promising advancement in devising a high yielding cascade SM/DA protocol for the generation of **4f4**, individually the steps were performed in an exemplary manner. Pertinent to the DA step, with sub-stoichiometric LA loadings working well, it offers the exciting possibility of conducting this step asymmetrically which may be investigated further in the future. Moreover, several interesting tandem and one-pot reactions have been developed along the way to build the **E** and **D** rings, in order to help streamline the overall synthesis. Finally, an alternative pathway was successfully carried through to the common intermediate, employing the free amine DA adduct, which presents a more realistic opportunity in achieving success for the development of the desired "one-pot" SM/DA reaction. Overall, this efficient one-pot reaction facilitates the formation of four bonds, two cyclic rings and two contiguous stereocentres.

3.6. Future work

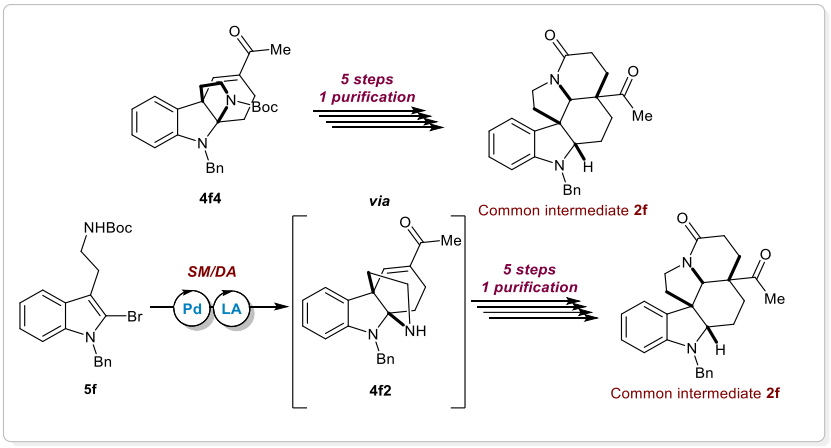
In the short-term, on top of completing the remaining set of alkaloid synthesis, as well any other easy to access targets, we aim to deliver the key SM/DA cascade reaction, with early promise being observed in the generation of the free amine DA adduct (Scheme 89A). In addition, as suggested previously, the possibility of achieving an asymmetric synthesis is plausible (Scheme 89B). The DA reaction is the stereo-defining step during the route, rendering the rest of the synthesis diastereoselective. Therefore, potential avenues that could be explored to help induce facial selectivity include: chiral LA acids bound to metal catalysts, such as phosphoric acid derivatives,

chiral auxiliaries, or even some co-chiral ligands.[144–147] It is likely that in pursuit of achieving the enantioselective DA, cryogenic temperatures may be necessary, requiring inevitable the previously optimised conditions to be readdressed. Naturally, with a successful asymmetric DA method established, the next level of exploration would be to see how it fares when combined with the Suzuki step in a one-pot fashion.



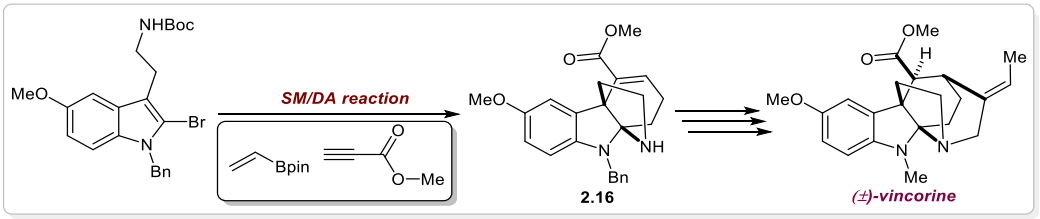
Scheme 89: A) Continued SM/DA optimisation. B) Proposed catalytic asymmetric DA.

Furthermore, exploration into a potential "one-pot" 5-step transformation is off significant interest, granting access to **2f** from **4f4** or **5f** in a rapid and efficient manner, meaning very few purification steps would be necessary for the overall synthesis of the natural product (Scheme 90). Naturally, this will require much deliberation in terms conditions that are implemented, however, as some of these steps have already been successfully amalgamated, there is genuine optimism that this complex series of events could indeed be facilitated. Before this were to be tackled, however, improvement in yields for the formation of the **D** ring first are critical, as on current standing the amide coupling step is the most problematic. As a result, this would have been one of the last pieces in the puzzle to investigate, however, due to COVID-19 and the restrictions in place, there was insufficient time to pursue this unique opportunity further.



Scheme 90: Proposed one-pot transformation to generate 2f from either 5f or 4f4.

In the long-term, we want to explore ways of influencing the regioselectivity of the DA reaction, to see if we can promote exclusive formation of the other regioisomer, and then apply the SM/DA principle in this format. On the current basis, the DA reaction yields the correct regioisomer for the synthesis of (±)-aspidospermidine; however, the additional cyclisation of the pendant amine is considered an unproductive step, with reversal of this step needed afterwards. This is not the case if (±)-vincorine were to be synthesised. Granted, a different dienophile and tryptamine derivative will need to be implemented, which will have a direct effect on the electronics and sterics governing the subsequent DA reaction (Scheme 91). If successful, we aspire to deliver the synthesis in an unprecedented number of steps from core intermediate **2.16**, providing further evidence for the potential of CCDA reactions in creating and accessing novel chemical space.



Scheme 91: Proposed total synthesis of (±)-vincorine.

3.7. Experimental

3.7.1. General

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[88]

3.7.1.1. Purification of solvents

All solvents used for dry reactions (PhMe, CH_2Cl_2, THF, Et_2O) were obtained from a PureSolv SPS-400-5 solvent purification system and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves under nitrogen. Dry 1,4-dioxane was obtained by distillation over $LiAlH_4$ and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves under nitrogen. Dry $CHCl_3$ was obtained by washing out residual amounts of EtOH with water, drying the organics with K_2CO_3 and then subsequently distilling organics over $CaCl_2$. The distilled solvent was stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves under nitrogen. The flask was then covered in aluminium foil. Dry Et_3N was obtained by distillation over CaH and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves under nitrogen. The flask was then covered in aluminium foil. EtOAc, Et_2O, MeOH, CH_2Cl_2, hexane, and petroleum ether 40–60°C for purification purposes were used as obtained from suppliers without further purification.

3.7.1.2. Drying of inorganic bases

Inorganic bases were dried in a Heraeus Vacutherm oven at 60 °C under vacuum for a minimum of 24 hours before use.

3.7.1.3. Experimental details

Reactions were carried out using conventional glassware or in 5/20 mL capped microwave vials. The glassware was oven-dried (150 °C) or flame-dried and then cooled under vacuum before use. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature was generally 20 °C. Reactions were carried out at

elevated temperatures using a temperature-regulated hotplate/stirrer and a sand bath. Temperature quoted is a measurement of the sand bath heating block. Reactions were carried out at 0 °C using an ice bath. Reactions were carried out at –78 °C / –60 °C using an acetone/dry ice bath. Reactions were carried out at –20 °C / –40 °C using an MeCN/dry ice bath.

3.7.1.4. Purification of products

Thin layer chromatography (TLC) was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light or developed using potassium permanganate, vanillin or anisaldehyde solutions. Column chromatography was carried out using ZEOprep 60 HYD 40–63μm silica gel.

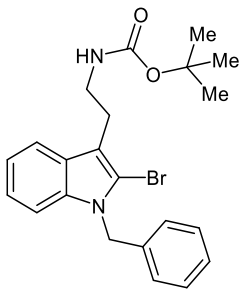
3.7.1.5. Analysis of products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory at St Andrews University. Spectra were recorded of either thin films or solids, with characteristic absorption wavenumbers (υ_{max}) reported in cm^{-1}. ^{19}F NMR spectra were obtained on either a Bruker AV 400 spectrometer at 376 MHz or Bruker AV 500 at 470 MHz. ^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AV 400 at 400 MHz and 125 MHz, Bruker AV 500 at 500 MHz and 126 MHz, or Bruker AV 700 at 700 MHz and 127 MHz. Chemical shifts are reported in ppm and coupling constants are reported in Hz: $CDCl_3$ referenced at 7.26 (^{1}H) and 77.2 ppm (^{13}C); CD_3CN referenced at 1.94 (^{1}H) and 118.26 ppm (^{13}C). Coupling constants throughout the experimental section were reported as observed in spectra without corrections. High-resolution mass spectra were obtained through analysis at the University of St Andrews mass spectrometry facility. NMR conversion was obtained through addition of a known standard (solution of 1,4-dinitrobenzene in either $CDCl_3$ or MeCN (1 mL, 0.0625 mmol)) to the crude reaction mixture, and conversion against the internal standard was determined by ^{1}H NMR. Crystallography data is available at the end of the experimental section (Table 26).

3.7.2. General Experimental Procedures

3.7.2.1. General Procedure A: C-2 Bromination

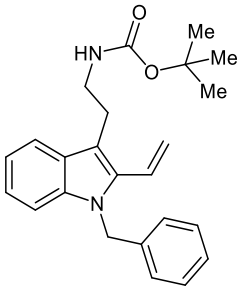
For example the preparation of *tert*-butyl (2-(1-benzyl-2-bromo-1*H*-indol-3-yl)ethyl)carbamate (**5f**)



Tert-butyl (2-(1-benzyl-1*H*-indol-3-yl)ethyl)carbamate **7f** (350 mg, 1 mmol, 1 equiv) was weighed into an oven-dried 2 necked flask and dissolved in THF:$CHCl_3$ (1:1, 10 mL. 0.1 M), before being stirred at –20 °C for 15 mins. Then pyridinium tribromide **(recrystallized)** (390 mg, 1.54 mmol, 1.22 equiv) was then added portion-wise over 1 hr at –20 °C. The reaction mixture was then let to stir for 20 min at this temperature before being quenched with sat. aqueous sodium sulphite (20 mL), and following a colour change to light yellow, sat. aqueous NaHCO3 (20 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (0–10% EtOAc in petroleum ether) to afford the desired product as a white solid (317 mg, 74%).

3.7.2.2. General Procedure B: Suzuki–Miyaura cross-coupling reaction

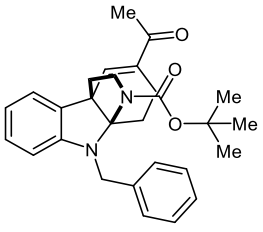
For example the preparation of *tert*-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate (**8f**)



$Pd(OAc)_2$ (17.9 mg, 0.08 mmol, 4 mol%), SPhos (65.5 mg, 0.16 mmol, 8 mol%), *tert*-butyl (2-(1-benzyl-2-bromo-1*H*-indol-3-yl)ethyl)carbamate **5f** (856 mg, 2 mmol, 1 equiv), vinyl Bpin (338 mg, 2.19 mmol, 1.1 equiv) and K_3PO_4 (1268 mg, 6 mmol, 3 equiv) were weighed into an oven-dried microwave vial (20 mL). The reaction vessel was then capped and purged with N_2 before the addition of 1,4-dioxane (8 mL, 0.25 M) and H_2O (180 µl, 10 mmol, 5 equiv). For scaling-up purposes, reaction was carried out at stated scale in a total of **five** (20 mL) microwave vials. The reaction mixture was heated to 50 °C with stirring for 24 h. After the reaction was complete the reaction mixture was left to cool to room temperature, vented and de-capped. The reaction mixture was diluted in EtOAc (200 mL), and passed through a layer of Celite® and then concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–10% EtOAc in petroleum ether 40–60°) to afford the desired product as a beige solid (3.69 g, 98%).

3.7.2.3. General Procedure C: Diels–Alder reaction

For example the preparation of *tert*-butyl 6-acetyl-9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazole-10-carboxylate (**4f4**)

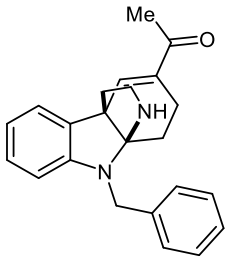


In an oven-dried MW vial (20 mL) weighed out *tert*-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate **8f** (752 mg, 2 mmol, 1 equiv). The vial was then capped and purged. 3-butyn-2-one (0.31 mL, 4 mmol, 2 equiv), 1,4-dioxane (8 mL, 0.25 M)

and $BF_3 \bullet OEt_2$ (123 µL, 1 mmol, 0.5 equiv) were then added sequentially via syringe. The reaction was then stirred at 25 °C for 4 h. After the reaction was complete the reaction mixture was vented and de-capped. The reaction mixture was then transferred to a round bottom flask using MeOH (25 mL) and subsequently concentrated. The residue was then neutralized using sat. aqueous $NaHCO_3$ (30 mL) and the organics were extracted with EtOAc (3 × 30 mL). The organics were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–10% EtOAc in hexane) to afford the desired product as a mixture of rotamers as a white solid (735 mg, 83 %).

3.7.2.3. General procedure D: One-pot Suzuki−Miyaura/Diels−Alder optimisation

For example the preparation of 1-(9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazol-6-yl)ethan-1-one (**4f2**)

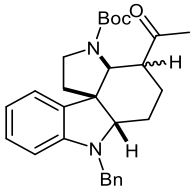


In an oven-dried MW vial (5 mL) weighed out $Pd(OAc)_2$ (2.2 mg, 0.04 mmol, 4 mol%), SPhos (8.2 mg, 0.08 mmol, 8 mol%), *tert*-butyl (2-(1-benzyl-2-bromo-1*H*-indol-3-yl)ethyl)carbamate **5f** (107 mg, 0.25 mmol, 1 equiv), vinyl Bpin (42.2 mg, 0.275 mmol, 1.1 equiv) and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The reaction vessel was then capped and purged with N_2 before the addition of 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was heated to 50 °C with stirring for 24 h. After the reaction was complete the reaction mixture was left to cool to room temperature, the vial was then vented and de-capped. The reaction mixture was diluted in EtOAc (20 mL) and passed through a layer of Celite® and then concentrated under reduced pressure.

Crude material was transferred to a 10 mL round-bottom flask and concentrated. Without purging the crude mixture, 3-butyn-2-one (39 μL, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M) and $BF_3 \bullet OEt_2$ (15 μL, 0.125 mmol, 0.5 equiv) were then added sequentially via syringe. The reaction was then stirred at 25 °C for 4 h. After the reaction was complete the reaction mixture was quenched using sat. aqueous $NaHCO_3$ (20 mL) and the organics were extracted with EtOAc (3 × 10 mL). The organics were collected, dried with Na_2SO_4, filtered, internal standard was added before being concentrated under reduced pressure. Conversion was determined by ^1H NMR.

3.7.2.4. General Procedure E: Tandem ring-opening/aza-Michael reaction

For example the preparation of *tert*-butyl 4-acetyl-7-benzyl-1,2,3a,4,5,6,6a,7-octahydro-3*H*-pyrrolo[2,3-d]carbazole-3-carboxylate (**10f1**)

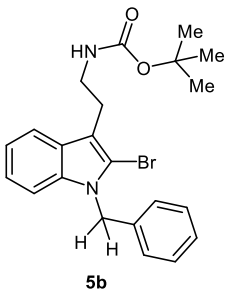


An oven-dried MW vial was charged with *tert*-butyl 6-acetyl-9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazole-10-carboxylate **4f4** (111 mg, 0.25 mmol, 1 equiv) and STAB (66.1 mg, 0.31 mmol, 1.25 equiv). The vial was then sealed and purged. Then CH_2Cl_2 (5 mL, 0.05 M) was added and the resulting suspension was cooled to 0 °C. After 15 min, TFA (76.5 μL, 1 mmol, 4 equiv) was added *via* syringe and the reaction was allowed to reach ambient temperatures. The reaction was left to stir for 6 h at room temperature. After the reaction was complete the reaction mixture was vented and de-capped. The reaction was then quenched with sat. aqueous $NaHCO_3$ (30 mL) and the organics were extracted with CH_2Cl_2 (3×25 mL). The organics were then combined, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography (silica gel, 0–40% EtOAc in hexane) to yield the product as pale yellow oil (99.3 mg, 89%) as an inconsequential mixture of diastereomers (0.62:0.38 ratio).

3.7.3. Reaction Optimisation of various steps

3.7.3.1. Bromination optimisation

Conversion was determined by ^{1}H analysis of the benzylic peak (s) at 5.41 ppm against a known internal standard (1,4-dinitrobenzene).



5b

3.7.3.1.1 Brominating reagent screen (Table 9)

Reactions were carried out according to General Procedure A using *tert*-butyl (2-(1-benzyl-1*H*-indol-3-yl)ethyl)carbamate **7f** (350 mg, 1 mmol, 1 equiv), **brominating reagent** (**xx** mg, 1.22 equiv) and THF:$CHCl_3$ (1:1, 10 mL. 0.1 M). The reaction was stirred for 1 h at 0 °C, before analysis by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	Brominating reagent (xx mg / xx µL)	SM (%)	Conversion 5f (%)
1	Br_2 (62 µL)	12	13
2	NBS (217 mg)	12	51
3	Pyridinium tribromide (390 mg)	5	50

3.1.2. Temperature study (Table 10)

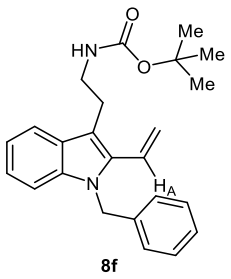
Reactions were carried out according to General Procedure A using *tert*-butyl (2-(1-benzyl-1*H*-indol-3-yl)ethyl)carbamate **7f** (350 mg, 1 mmol, 1 equiv), pyridinium tribromide **(recrystallized)** (390 mg, 1.54 mmol, 1.22 equiv) and THF:$CHCl_3$ (1:1, 10 mL. 0.1 M). The reaction was stirred for 80 min at **X** °C, before analysis by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	Temperature (°C)	Conversion 5f (%)
1	–10	65
2	–20	79(74)
3	–40	10

Isolated yield in brackets.

3.7.3.2. Suzuki–Miyaura optimisation

Conversion was determined by ^{1}H analysis of the olefin peak (dd) at 6.71 ppm against a known internal standard (1,4-dinitrobenzene).



8f

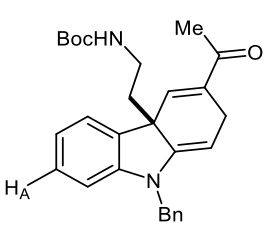
3.7.3.2.1 Time study (Table 11)

Reactions were carried out according to General Procedure B using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), *tert*-butyl (2-(1-benzyl-2-bromo-1*H*-indol-3-yl)ethyl)carbamate **5f** (107 mg, 0.25 mmol, 1 equiv), vinyl Bpin (42.2 mg, 0.27 mmol, 1.1 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction was stirred for **X** h at 50 °C, before analysis by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene).

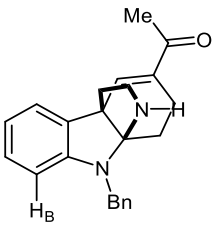
Entry	Time (h)	SM (%)	Conversion[a] (%)
1	1	88	13
2	4	70	32
3	8	10	91
4	16	0	98
5	24	0	>99

3.7.3.3. Diels–Alder optimisation

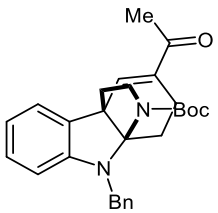
Conversion was determined by ^{1}H analysis of the aromatic proton (H_A) at 6.62 ppm (t) for product **4f1**, aromatic proton (H_B) at 6.21 ppm (d) for product **4f2** and olefin peak at 6.89 ppm (s) for product **4f4**, against a known internal standard (1,4-dinitrobenzene).



4f1



4f2



4f4

3.7.3.3.1. Temperature study (Table 12)

Reactions were carried out according to General Procedure C using *tert*-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate **8f** (94 mg, 0.25 mmol, 1 equiv), 3-butyn-2-one (98 µL, 1.25 mmol, 5 equiv) and 1,4-dioxane (1 mL, 0.25 M). The reaction was stirred for 16 h at **X** °C, before analysis by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	Temperature (°C)	SM (%)	Conversion 4f1 (%)
1	25	100	0
2	50	100	0
3	75	97	0
4	125	56	38

3.7.3.3.2. Lewis acid screen (Table 13)

Reactions were carried out according to General Procedure C using *tert*-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate **8f** (94 mg, 0.25 mmol, 1 equiv), 3-butyn-2-one (98 µL, 1.25 mmol, 5 equiv), 1,4-dioxane (1 mL, 0.25 M) and **LA** (**X** mg, 2 equiv). The reaction was stirred for 16 h at 25 °C, before analysis by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	LA (X µL/ X mg, 2 equiv)	SM (%)	Conversion 4f2 (%)
1	$Cu(OTf)_2$ (181 mg)	<10	17
2	$AlCl_3$ (66.7 mg)	19	16
3	**BF_3•OEt_2 (62 µL)**	**0**	**40**

3.7.3.3.3. Brønsted screen (Table 14)

Reactions were carried out according to General Procedure C using *tert*-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate **8f** (94 mg, 0.25 mmol, 1 equiv), 3-butyn-2-one (98 µL, 1.25 mmol, 5 equiv), 1,4-dioxane (1 mL, 0.25 M) and **Bronsted acid** (**X** mg, 2 equiv). The reaction was stirred for 16 h at 25 °C, before analysis by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	Bronsted acid (X µL/ X mg, 2 equiv)	SM (%)	Conversion 4f2 (%)
1	TsOH (181 mg)	<5	33
2	AcOH (66.7 mg)	97	0

3.7.3.3.4. Lewis Acid Loading Study (Table 15)

Reactions were carried out according to General Procedure C using *tert*-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate **8f** (94 mg, 0.25 mmol, 1 equiv), 3-butyn-2-one (98 µL, 1.25 mmol, 5 equiv), 1,4-dioxane (1 mL, 0.25 M) and $BF_3 \bullet OEt_2$ (**X** µL, **X** equiv). The reaction was stirred for 16 h at 25 °C, before analysis by ^1H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	$BF_3 \bullet OEt_2$ (X µL, X equiv)	SM (%)	Conversion 4f2 (%)	Conversion 4f4 (%)
1	**15 µL, 0.5 equiv**	**<5**	**4**	**84**
2	31 µL, 1 equiv	0	26	60
3	46 µL, 1.5 equiv	0	30	33
4	62 µL, 2 equiv	0	40	9
5	77 µL. 2.5 equiv	0	38	0
6	3 µL. 0.1 equiv	43	n.d	49

n.d. = not determinable.

3.7.3.3.5. Temperature study with Lewis acid (Table 16)

Reactions were carried out according to General Procedure C using *tert*-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate **8f** (94 mg, 0.25 mmol, 1 equiv), 3-butyn-2-one (98 µL, 1.25 mmol, 5 equiv), 1,4-dioxane (1 mL, 0.25 M) and $BF_3 \bullet OEt_2$ (15 µL, 0.125 mmol, 0.5 equiv). The reaction was stirred for 16 h at **X** °C, before analysis by ^1H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	Temperature (°C)	SM (%)	Conversion 4f2 (%)	Conversion 4f4 (%)
1	**25**	**<5**	**<4**	**84**
2	35	<1	19	71
3	50	0	18	66
4	75	0	13	55
5	100	0	6	44

3.7.3.3.6. Concentration Study (Table 17)

Reactions were carried out according to General Procedure C using *tert*-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate **8f** (94 mg, 0.25 mmol, 1 equiv), 3-butyn-2-one (98 µL, 1.25 mmol, 5 equiv), 1,4-dioxane (**X** mL, **X** M) and $BF_3 \bullet OEt_2$ (15 µL, 0.125 mmol, 0.5 equiv). The reaction was stirred for 16 h at 25 °C, before analysis by ^1H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	Concentration (X mL, X M)	SM (%)	Conversion 4f2 (%)	Conversion 4f4 (%)
1	**1 mL, 0.25 M**	<5	**<4**	**84**
2	0.5 mL, 0.5 M	0	13	81
3	2 mL, 0.125 M	0	18	82

3.7.3.3.7. Time Study (Table 18)

Reactions were carried out according to General Procedure C using *tert*-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate **8f** (94 mg, 0.25 mmol, 1 equiv), 3-butyn-2-one (98 µL, 1.25 mmol, 5 equiv), 1,4-dioxane (1 mL, 0.25 M) and $BF_3 \bullet OEt_2$ (15 µL, 0.125 mmol, 0.5 equiv). The reaction was stirred for **X** h at 25 °C, before analysis by ^1H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	Time (X h)	SM (%)	Conversion 4f2 (%)	Conversion 4f4 (%)
1	0.5	17	7	68
2	1	9	7	77
3	2	1	12	79
4	**4**	0	**11 (n = 2)**	**86 (n = 2)**
5	8	0	14	86
6	16	0	<4	84
7	20	0	16	72
8	24	0	17	77
9	48	0	18	76

n = 2, average of two experiments.

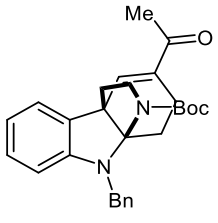
3.7.3.3.8. Alkyne Loading Study (Table 19)

Reactions were carried out according to General Procedure C using *tert*-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate **8f** (94 mg, 0.25 mmol, 1 equiv), 3-butyn-2-one (**X** µL, **X** equiv), 1,4-dioxane (1 mL, 0.25 M) and $BF_3 \bullet OEt_2$ (15 µL, 0.125 mmol, 0.5 equiv). The reaction was stirred for 4 h at 25 °C, before analysis by ^1H NMR against a known internal standard (1,4-dinitrobenzene).

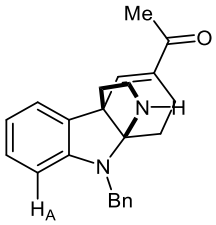
Entry	Alkyne (X µL, X equiv)	SM (%)	Conversion 4f2 (%)	Conversion 4f4 (%)
1	98 µL, 5 equiv	0	<4	84
2	19.5 µL, 1 equiv	18	18	75
3	**39 µL, 2 equiv**	<1	**10**	**78**
4	59 µL, 3 equiv	<1	10	77
5	78 µL, 4 equiv	0	10	80

3.7.3.4. One-pot SM/DA optimisation

Conversion was determined by ^1H analysis of the olefin peak at 6.89 ppm (s) for product **4f4** and aromatic proton (H_A) at 6.21 ppm (d) for product **4f2**, against a known internal standard (1,4-dinitrobenzene).



4b4



4b2

3.7.3.4.1. Lewis acid loading study (Table 20)

Reactions were carried out according to General Procedure D using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), *tert*-butyl (2-(1-benzyl-2-bromo-1*H*-indol-3-yl)ethyl)carbamate **5f** (107 mg, 0.25 mmol, 1 equiv), vinyl Bpin (42.2 mg, 0.27 mmol, 1.1 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane

(1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv); followed by 3-butyn-2-one (39 µL, 2 equiv), 1,4-dioxane (1 mL, 0.25 M) and $BF_3{\bullet}OEt_2$ (**X** µL, **X** equiv). The reaction was stirred for 4 h at 25 °C, before analysis by ^1H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	$BF_3{\bullet}OEt_2$ (X µL, X equiv)	Diene 8f (%)	Conversion 4f2 (%)	Conversion 4f4 (%)
1	15 µL, 0.5 equiv	65	2	8
2	31 µL, 1 equiv	40	12	14
3	**46 µL, 1.5 equiv**	**15**	**32**	**22**
4	62 µL, 2 equiv	8	46	6
5	77 µL, 2.5 equiv	0	71	0
6	92.5 µL, 3 equiv	0	68	0
7	123 µL, 4 equiv	0	67	0

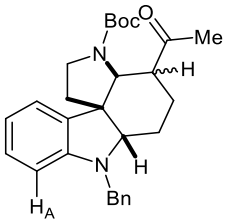
3.7.3.4.2. Time study (Table 21)

Reactions were carried out according to General Procedure D using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), *tert*-butyl (2-(1-benzyl-2-bromo-1*H*-indol-3-yl)ethyl)carbamate **5f** (107 mg, 0.25 mmol, 1 equiv), vinyl Bpin (42.2 mg, 0.27 mmol, 1.1 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv); followed by 3-butyn-2-one (39 µL, 2 equiv), 1,4-dioxane (1 mL, 0.25 M) and $BF_3{\bullet}OEt_2$ (46 µL, 1.5 equiv). The reaction was stirred for **X** h at 25 °C, before analysis by ^1H NMR against a known internal standard (1,4-dinitrobenzene).

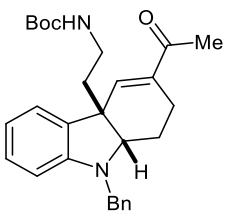
Entry	Time (h)	Diene 8f (%)	Conversion 4f2 (%)	Conversion 4f4 (%)
1	**4**	**15**	**32**	**22**
2	16	4	8	14
3	20	16	27	12
4	24	16	32	9
5	48	10	17	7

3.7.3.5. Tandem ring-opening/aza-Michael reaction optimisation

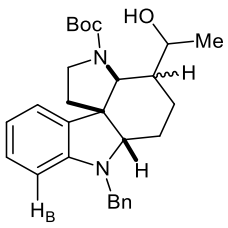
Conversion was determined by ^{1}H analysis of both diastereotopic aromatic protons (H_A) at 6.51 and 6.44 ppm (doublets) for product **10f1**, olefin peak (s) at 6.58 ppm for product **10f1'** and both diastereotopic aromatic protons (H_B) at 6.36 and 6.32 ppm (doublets) for product **10f3** against a known internal standard (1,4-dinitrobenzene).



10f1



10f1'



10f3

3.7.3.5.1. STAB loading study (Table 22)

Reactions were carried out according to General Procedure E using *tert*-butyl 6-acetyl-9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazole-10-carboxylate **4f4** (111 mg, 0.25 mmol, 1 equiv), STAB (**X** mg, **X** equiv), CH_2Cl_2 (5 mL, 0.05 M) and TFA (76.5 µL, 1 mmol, 4 equiv). The reaction was stirred for 6 h at room temperature, before analysis by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	STAB (X mg, X equiv)	SM (%)	Conversion 10f1 (%)	Conversion 10f1' (%)	Conversion 10f3 (%)
1	52.9 mg, 1 equiv	18	78 (80)	0	0
2	106 mg, 2 equiv	0	68	2	6
3	159 mg, 3 equiv	0	57	18	17
4	212 mg, 4 equiv	0	34	42	21
5	79.4 mg, 1.5 equiv	0	82	2	6
6	**66.1 mg, 1.25 equiv**	**0**	**92 (89)**	**0**	**0**

Isolation in brackets.

3.7.3.5.2. Time study (Table 23)

Reactions were carried out according to General Procedure E using *tert*-butyl 6-acetyl-9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazole-10-carboxylate **4f4** (111 mg, 0.25 mmol, 1 equiv), STAB (66.1 mg, 0.31 mmol, 1.25 equiv), CH_2Cl_2 (5 mL, 0.05 M) and TFA (76.5 µL, 1 mmol, 4 equiv). The reaction was stirred for **X** h at room temperature, before analysis by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	Time (h)	SM (%)	Conversion 10f1 (%)	Conversion 10f1' (%)
1	**6**	**0**	**92 (89)**	**0**
2	2	0	90	9
3	4	0	97	4

Isolation in brackets

3.7.3.5.3.TFA equiv study (Table 24)

Reactions were carried out according to General Procedure E using *tert*-butyl 6-acetyl-9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazole-10-carboxylate **4f4** (111 mg, 0.25 mmol, 1 equiv), STAB (66.1 mg, 0.31 mmol, 1.25 equiv), CH_2Cl_2 (5 mL, 0.05 M) and TFA (**X** µL, **X** equiv). The reaction was stirred for 2 h at room temperature, before analysis by ^1H NMR against a known internal standard (1,4-dinitrobenzene).

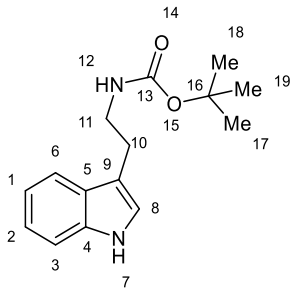
Entry	TFA (X µL, X equiv)	SM (%)	Conversion 10f1 (%)	Conversion 10f1' (%)
1	19 µL, 1 equiv	33	0	67
2	38 µL, 2 equiv	0	43	57
3	57 µL, 3 equiv	0	69	25
4	76.5 µL, 4 equiv	0	90	9
5	0 µL, 0 equiv	>99	0	0

.

3.7.4. Compound Characterisation data

3.7.4.1. Intermediates leading to (±)-aspidospermidine

Tert-butyl (2-(1*H*-indol-3-yl)ethyl)carbamate (**6f**)



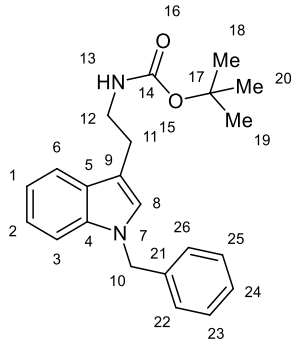
In an oven-dried flask was weighed in tryptamine (500 mg, 1 equiv, 3.13 mmol). This was then dissolved in 1,4-dioxane (5.2 mL, 0.6 M) before the addition of Et_3N (870 µL, 2 equiv, 6.26 mmol). The suspension was left to stir for 15 min at room temperature. Then Boc anhydride (750 mg, 1.1 equiv, 3.44 mmol) was added to the reaction mixture. Reaction was left to stir for 5 h at room temperature. After the reaction was complete, the mixture was concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, 5–50% EtOAc in petroleum ether 40–60°) to afford the product as light yellow oil, which solidifies upon standing (820 mg, >99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H, 7), 7.61 (dd, *J* = 7.9, 1.1 Hz, 1H, 6), 7.37 (dt, *J* = 8.1, 0.9 Hz, 1H, 3), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, 2), 7.13 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, 1), 7.03 (s, 1H), 4.62 (s, 1H, 12), 3.53 – 3.39 (m, 2H, 11), 2.96 (t, *J* = 6.8 Hz, 2H, 10), 1.44 (s, 9H, 17, 18, 19).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.1 (13), 136.5 (4), 127.5 (5), 122.3 (2), 122.2 (8), 119.5 (1), 119.0 (6), 113.3 (9), 111.3 (3), 79.3 (16), 40.9 (11), 28.6 (17, 18, 19), 25.9 (10).

Spectroscopic data were in agreement with literature values.[148]

Tert-butyl (2-(1-benzyl-1*H*-indol-3-yl)ethyl)carbamate (**7f**)



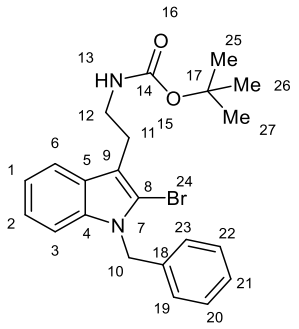
In an oven-dried flask was weighed in NaH (184 mg, 4.61 mmol, 1.2 equiv). This was then dissolved in THF (7.6 mL) and cooled to 0 °C. Then a solution of *tert*-butyl (2-(1*H*-indol-3-yl)ethyl)carbamate **6f** (1 g, 3.84 mmol, 1 equiv) in THF (7.6 mL, 0.25 M) was added slowly. The resulting suspension was left to stir for 30 min at 0 °C. Benzyl bromide (0.68 mL, 5.76 mmol, 1.5 equiv) was then added dropwise to the reaction mixture. After 5 min, the reaction was allowed to reach room temperature and stirred for 3 h. After the reaction was complete, water (20 mL) was added to quench the mixture, and the organics were extracted with EtOAc (3 × 20 mL). The organics were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, 0–10% EtOAc in petroleum ether 40–60°) to afford the product as pale yellow oil (1.11 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (dt, *J* = 7.7, 1.0 Hz, 1H, 3), 7.32 – 7.25 (m, 4H, 22, 23, 25, 26), 7.18 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, 2), 7.11 (dddd, *J* = 6.9, 5.2, 3.1, 1.1 Hz, 3H, 1, 6, 24), 6.96 (s, 1H, 8), 5.28 (s, 2H, 10), 4.59 (s, 1H, 13), 3.46 (q, *J* = 6.9 Hz, 2H, 12), 2.96 (t, *J* = 6.9 Hz, 2H, 11), 1.43 (s, 9H, 18, 19, 20).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.1 (14), 137.7 (21), 136.9 (4), 128.9 (23, 25), 128.2 (5), 127.7 (8), 126.9 (22, 26), 126.3 (24), 122.0 (2), 119.3 (1), 119.2 (6), 112.5 (9), 109.8 (3), 79.2 (17), 50.0 (10), 41.0 (12), 28.5 (18, 19, 20), 25.9 (11).

Spectroscopic data were in agreement with literature values.[149]

Tert-butyl (2-(1-benzyl-2-bromo-1*H*-indol-3-yl)ethyl)carbamate (**5f**)



Prepared according to General Procedure A using *tert*-butyl (2-(1-benzyl-1*H*-indol-3-yl)ethyl)carbamate **7f** (350 mg, 1 mmol, 1 equiv), pyridinium tribromide **(recrystallized)** (390 mg, 1.54 mmol, 1.22 equiv) and THF:$CHCl_3$ (1:1, 10 mL. 0.1 M). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–10% EtOAc in petroleum ether) to afford the desired product as a white solid (317 mg, 74%).

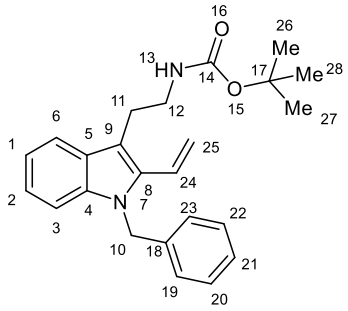
υ_{max} (film): 3429, 3350, 2974, 2928, 1695, 1506, 1497, 1452, 1363, 1331, 1159 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.5 Hz, 1H, 6), 7.31 – 7.20 (m, 4H, 19, 20, 22, 23), 7.17 – 7.10 (m, 2H, 1, 2), 7.08 (ddt, *J* = 7.3, 1.5, 0.8 Hz, 2H, 3, 21), 5.41 (s, 2H, 10), 4.59 (s, 1H, 13), 3.41 (t, *J* = 6.0 Hz, 2H, 12), 3.00 (t, *J* = 6.7 Hz, 2H, 11), 1.43 (s, 9H, 25, 26, 27).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.1 (14), 137.3 (18), 136.8 (4), 128.9 (20, 22), 127.7 (5), 127.6 (21), 126.6 (19, 23), 122.3 (2), 120.2 (1), 118.5 (6), 113.8 (8), 112.5 (9), 110.0 (3), 79.2 (17), 48.5 (10), 40.6 (12), 28.6 (25, 26, 27), 26.2 (11).

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{22}H_{25}O_2N_2{}^{79}BrNa$) requires *m/z* 451.0992, found *m/z* 451.0987.

Tert-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate (**8f**)



Prepared according to General Procedure B using $Pd(OAc)_2$ (17.9 mg, 0.08 mmol, 4 mol%), SPhos (65.5 mg, 0.16 mmol, 8 mol%), *tert*-butyl (2-(1-benzyl-2-bromo-1H-indol-3-yl)ethyl)carbamate **5f** (856 mg, 2 mmol, 1 equiv), vinyl Bpin (338 mg, 2.19 mmol, 1.1 equiv), K_3PO_4 (1268 mg, 6 mmol, 3 equiv), 1,4-dioxane (8 mL, 0.25 M) and H_2O (180 μL, 10 mmol, 5 equiv). 5 reactions were run in parallel for scaling-up purposes. After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–10% EtOAc in petroleum ether 40–60°) to afford the desired product as a beige solid (3.69 g, 98%).

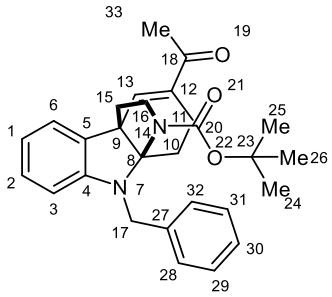
υ_{max} (film): 3350, 2976, 2931, 1694, 1504, 1496, 1452, 1366, 1263, 1248, 1165 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.8 Hz, 1H, 6), 7.28 (dd, *J* = 8.1, 6.4 Hz, 2H, 20, 22), 7.25 – 7.19 (m, 2H, 3, 21), 7.19 – 7.15 (m, 1H, 2), 7.12 (td, *J* = 7.2, 6.6, 1.4 Hz, 1H, 1), 7.05 – 7.02 (m, 2H, 19, 23), 6.71 (dd, *J* = 17.9, 11.8 Hz, 1H, 24), 5.53 (d, *J* = 17.8 Hz, 1H, 25), 5.43 (dd, *J* = 11.8, 1.2 Hz, 1H), 5.39 (s, 2H, 10), 4.63 (s, 1H, 13), 3.45 (q, *J* = 6.8 Hz, 2H, 12), 3.09 (t, *J* = 7.0 Hz, 2H, 11), 1.45 (s, 9H, 26, 27, 28).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.1 (14), 138.1 (18), 137.5 (8), 135.2 (4), 128.9 (20, 22), 128.2 (5), 127.4 (21), 126.1 (19, 23), 125.8 (24), 122.7 (2), 119.8 (1), 119.2 (6), 119.0 (25), 111.8 (9), 109.8 (3), 79.2 (17), 47.5 (10), 41.4 (12), 28.6 (26, 27, 28), 25.6 (11).

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{24}H_{28}O_2N_2Na$) requires *m/z* 399.2043, found *m/z* 399.2036.

Tert-butyl 6-acetyl-9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazole-10-carboxylate (**4f4**)



Prepared according to General Procedure C using *tert*-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate **8f** (752 mg, 2 mmol, 1 equiv), 3-butyn-2-one (0.31 mL, 4 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M) and $BF_3 \bullet OEt_2$ (123 µL, 1 mmol, 0.5 equiv). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–10% EtOAc in hexane) to afford the desired product as a mixture of rotamers as a white solid (735 mg, 83 %). Crystal was successfully grown in MeCN.

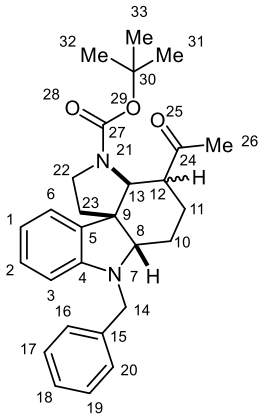
υ_{max} (film): 2974, 2930, 1690, 1670, 1485, 1366, 1161, 1130 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN, 75 °C): δ 7.32 – 7.18 (m, 6H, 6, 28, 29, 30, 31, 32), 7.00 (t, *J* = 1.5 Hz, 1H, 13), 6.96 (td, *J* = 7.7, 1.2 Hz, 1H, 2), 6.67 (td, *J* = 7.5, 0.9 Hz, 1H, 1), 6.10 (d, *J* = 7.9 Hz, 1H, 3), 4.99 (d, *J* = 16.9 Hz, 1H, 17''), 4.58 (d, *J* = 16.9 Hz, 1H, 17'), 3.64 – 3.58 (m, 1H, 16'), 3.34 (dt, *J* = 10.8, 7.1 Hz, 1H, 16''), 2.56 – 2.45 (m, 2H, 10), 2.35 (dt, *J* = 12.7, 6.4 Hz, 1H, 15''), 2.29 (s, 3H, 33), 2.25 – 2.11 (m, 3H, 11, 15'), 1.37 (s, 9H, 24, 25, 26).

^{13}C NMR (126 MHz, CD_3CN, 75 °C): δ 199.6 (18), 155.4 (20), 150.1 (4), 141.3 (27), 140.6 (13), 139.7 (12), 132.4 (5), 129.9 (2), 129.7 (29, 31), 127.9 (28, 32), 127.8 (30), 123.8 (6), 119.0 (1), 108.6 (3), 91.2 (8), 81.1 (23), 59.6 (9), 49.0 (17), 48.3 (16), 36.6 (15), 29.0 (24, 25, 26), 27.3 (10), 26.1 (33), 21.4 (11).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{28}H_{32}O_3N_2Na$) requires *m/z* 467.2305, found *m/z* 467.2309.

Tert-butyl 4-acetyl-7-benzyl-1,2,3a,4,5,6,6a,7-octahydro-3*H*-pyrrolo[2,3-d]carbazole-3-carboxylate (**10f1**)



Reaction was carried out according to General Procedure D using *tert*-butyl 6-acetyl-9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazole-10-carboxylate **4f4** (111 mg, 0.25 mmol, 1 equiv), STAB (66.1 mg, 0.31 mmol, 1.25 equiv), CH_2Cl_2 (5 mL, 0.05 M) and TFA (76.5 µL, 1 mmol, 4 equiv). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–40% EtOAc in hexane) to yield the product as yellow oil (99.3 mg, 89%) as an inconsequential inseparable mixture of diastereomers (0.62:0.38 ratio). Major diastereomer assigned in data below unless specified otherwise.

υ_{max} (film): 2972, 2361, 1686, 1603, 1391, 1364, 1167, 1126 cm^{-1}.

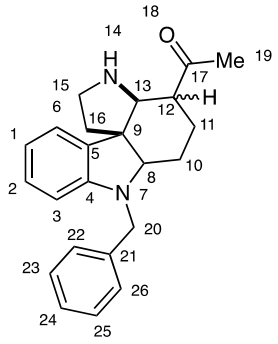
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 4H, 16, 17, 19, 20), 7.28 – 7.25 (m, 1H, 18), 7.09 – 7.03 (m, 1H, 2), 6.90 (dd, *J* = 7.4, 1.3 Hz, 0.37H, 6 minor), 6.87 (dd, *J* = 7.3, 1.3 Hz, 0.63H, 6 major), 6.72 – 6.67 (m, 1H, 1), 6.53 (d, *J* = 7.9 Hz, 0.6H, 3 major), 6.46 (d, *J* = 7.9 Hz, 0.37H, 3 minor), 4.43 (t, *J* = 17.1 Hz, 1H, 14''), 4.16 (d, *J* = 16.2 Hz, 1H, 14'), 4.07 (dt, *J* = 11.9, 9.2 Hz, 0.64H, 22'' major), 3.86 (dt, *J* = 11.8, 9.2 Hz, 0.39H, 22'' minor), 3.83 (d, *J* = 10.9 Hz, 0.38H, 13 minor), 3.59 – 3.50 (m, 2H, 13 major, 22' major), 3.46 (t, *J* = 3.0 Hz, 0.39H, 8 minor), 3.44 (t, *J* = 3.3 Hz, 0.62H, 8 major), 2.37 (ddd, *J* = 12.7, 10.9, 2.5 Hz, 0.62H, 12 major), 2.29 – 2.21 (m, 1.12H, 23' major), 2.19 (s, 1.27H, 26 minor), 2.16 (s, 1.83H, 26 major), 2.15 – 2.10 (m, 0.56H, 23'' major), 2.10 – 2.04 (m, 1H, 10''), 1.88 (qt, *J* = 13.5, 1.9 Hz, 1H, 11'),

1.59 – 1.49 (m, 2H, 10', 11"), 1.44 (s, 3.37H, 31, 32, 33 minor), 1.31 (s, 5.63H, 31, 32, 33 major).

^{13}C NMR (126 MHz, $CDCl_3$): δ 210.6, 210.2 (24), 155.0 (27), 154.5, 151.2, 151.1 (4), 138.7, 138.6 (15), 136.2 (5), 136.1, 128.7 (17, 19), 128.4, 128.3 (2), 127.5 (16, 20), 127.2, 127.2 (18), 121.8 (6), 121.7, 119.2 (1), 119.1, 108.7 (3), 80.6 (30), 79.7, 67.1, 66.8 (8), 65.0 (13), 63.5, 55.2, 52.8 (12), 52.6 (9), 51.8 (14), 51.7, 51.5, 43.8, 43.2 (22), 32.3, 31.8 (23), 31.7, 30.9 (26), 28.5, 28.3 (31, 32, 33), 27.5, 22.7, 22.4 (10), 22.1, 21.8 (11).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{28}H_{35}O_3N_2$) requires *m/z* 447.2642, found *m/z* 447.2626.

1-(7-Benzyl-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-4-yl)ethan-1-one (**10f2**),



In an oven-dried flask was weighed out *tert*-butyl 4-acetyl-7-benzyl-1,2,3a,4,5,6,6a,7-octahydro-3*H*-pyrrolo[2,3-d]carbazole-3-carboxylate **10f1** (35 mg, 0.08 mmol, 1 equiv), and was then sealed and purged. Then TFA (0.15 mL, 1.96 mmol, 25 equiv) was added and the reaction mixture was left to stir at room temperature for 1.5 h. After the reaction was complete, the mixture was quenched with sat. aqueous NaHCO3 (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). Then organics were collected, dried, filtered and concentrated under reduced pressure to yield the product as a pale brown oil (28.1 mg, >99 %), as a mixture of inconsequential diastereomers (9:1). No further purification was required. Major diastereomer assigned in data below unless specified otherwise.

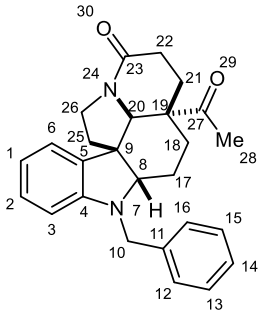
υ_{max} (film): 2930, 2868, 1705, 1603, 1479, 1348, 1028 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.29 (m, 4H, 22, 23, 25, 26), 7.30 – 7.22 (m, 1H, 24), 7.12 – 7.02 (m, 1H, 2), 6.96 (dd, *J* = 7.3, 1.3 Hz, 1H, 6), 6.74 (td, *J* = 7.4, 1.0 Hz, 1H, 1), 6.47 (dd, *J* = 7.9, 1.0 Hz, 0.88H, 3 major), 6.39 (d, *J* = 7.7 Hz, 0.12H, 3 minor), 4.40 (d, *J* = 16.3 Hz, 1H, 20''), 4.15 (d, *J* = 16.3 Hz, 1H, 20'), 3.86 (d, *J* = 2.9 Hz, 0.08H, 13 minor), 3.63 (t, *J* = 2.9 Hz, 1H, 8), 3.31 (ddd, *J* = 12.2, 9.4, 6.7 Hz, 1H, 15''), 3.19 (ddd, *J* = 12.2, 10.5, 4.6 Hz, 1H, 15'), 2.95 (d, *J* = 11.2 Hz, 0.87H, 13 major), 2.36 (td, *J* = 11.8, 2.9 Hz, 1H, 12), 2.19 (s, 3H, 19), 2.19 – 2.16 (m, 1H, 16''), 2.10 – 2.04 (m, 1H, 10'), 1.98 (ddd, *J* = 13.4, 10.5, 6.8 Hz, 1H, 16'), 1.77 – 1.66 (m, 1H, 11''), 1.64 – 1.56 (m, 2H, 10'', 11').

^{13}C NMR (126 MHz, $CDCl_3$): δ 212.0 (17), 211.2, 151.4 (4), 151.2, 139.0 (21), 138.7, 138.4 (5), 133.1, 128.7 (23, 25), 128.2, 128.0 (2), 127.5, 127.3 (22, 26), 127.1 (24), 122.0, 121.3 (6), 118.7 (1), 118.0, 108.5 (3), 107.3, 67.8 (8), 67.6, 65.3 (13), 60.0, 54.3 (9), 53.4, 52.3 (12), 51.9 (20), 50.1, 49.4, 44.6, 43.9 (15), 39.7, 34.0 (16), 29.9 (19), 28.4, 24.0, 23.2 (10), 22.8 (11), 18.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{23}H_{27}N_2O$) requires *m/z* 347.2118, found *m/z* 347.2112.

3a-Acetyl-6-benzyl-2,3,3a,3a^{1},4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazol-1-one (**2f**)



Three step reaction set-up: In an oven-dried flask was weighed out *tert*-butyl 4-acetyl-7-benzyl-1,2,3a,4,5,6,6a,7-octahydro-3*H*-pyrrolo[2,3-d]carbazole-3-carboxylate **10f1** (223 mg, 0.5 mmol, 1 equiv). The flask was then sealed and purged. Then TFA (0.96 mL, 12.5 mmol, 25 equiv) was added and the reaction mixture was

left to stir at room temperature for 1.5 h. The reaction mixture was then concentrated and azeotroped with toluene (3 × 20 mL). The resulting mixture was sealed and purged, before being dissolved in THF (10 mL, 0.05 M). Then Et_3N (0.22 mL. 1.55 mmol, 3.1 equiv) was added and the reaction mixture was cooled to 0 °C. After 15 min, acryloyl chloride (62.7 µL, 0.75 mmol, 1.5 equiv) was added dropwise. Then the reaction was left to reach room temperature and stirred for a further 3 h. After the reaction was complete, sat. aqueous $NaHCO_3$ (20 mL) was added and the organics were extracted with EtOAc (3 × 20 mL). The organics were then collected, dried with Na_2SO_4, filtered, before and subsequently concentrated under reduced pressure. The resulting crude residue was carried forward without further purification.

The crude material was dissolved in THF (5 mL, 0.1 M) and cooled to 0 °C. After 15 min, NaH (200 mg, 5 mmol, 10 equiv) was added. After 10 min, the reaction mixture was left to reach room temperature and stirred for 14 h. After the reaction was complete, the mixture was cooled to 0 °C and quenched with water (30 mL). The organics were extracted with CH_2Cl_2 (3 × 30 mL) and washed once with brine (30 mL). The organics were then collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography (silica gel, 0–50% MeCN in CH_2Cl_2) to afford the desired product as a beige solid (86.9 mg, 43%).

υ_{max} (film): 3049, 2930, 2872, 2361, 2342, 1701, 1616, 1605, 1479, 1452, 1352 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 5H, 12, 13, 14, 15, 16), 7.14 (dd, *J* = 7.4, 1.2 Hz, 1H, 6), 7.04 (td, *J* = 7.6, 1.3 Hz, 1H, 2), 6.71 (t, *J* = 7.4 Hz, 1H, 1), 6.37 (d, *J* = 7.9 Hz, 1H, 3), 4.73 (s, 1H, 20), 4.45 (d, *J* = 14.9 Hz, 1H, 10'), 4.07 (d, *J* = 14.9 Hz, 1H, 10''), 3.65 (dd, *J* = 12.6, 9.6 Hz, 1H, 26'), 3.48 (td, *J* = 11.9, 7.6 Hz, 1H, 26''), 3.14 (dd, *J* = 10.1, 5.1 Hz, 1H, 8), 2.47 (ddd, *J* = 18.2, 7.1, 2.8 Hz, 1H, 22'), 2.42 – 2.29 (m, 2H, 22'', 25'), 2.06 (s, 3H, 28), 1.97 – 1.90 (m, 1H, 21'), 1.90 – 1.86 (m, 1H, 18'), 1.82 (dtd, *J* = 13.1, 4.9, 2.7 Hz, 1H, 17'), 1.76 – 1.67 (m, 2H, 21'', 25''), 1.42 (td, *J* = 13.6, 2.8 Hz, 1H, 18''), 1.30 (ddd, *J* = 13.2, 9.9, 2.9 Hz, 1H, 17'').

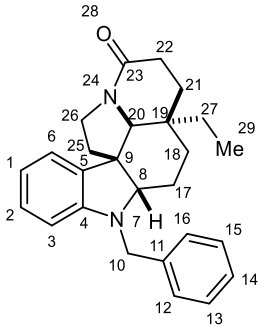
^{13}C NMR (126 MHz, $CDCl_3$): δ 208.7 (27), 168.4 (23), 150.0 (4), 138.0 (11), 129.4 (5), 128.8 (13, 15), 128.6 (2), 127.7 (12, 16), 127.5 (14), 124.3 (6), 118.1 (1), 107.3

(3), 63.9 (8), 60.4 (20), 54.3 (9), 49.9 (19), 48.6 (10), 43.2 (26), 35.5 (25), 31.1 (21), 27.9 (22), 25.3 (28), 22.5 (17), 22.2 (18).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{26}H_{29}O_2N_2$) requires *m/z* 401.2224, found *m/z* 401.2216.

3.7.4.1.1. End game route 1

6-Benzyl-3a-ethyl-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazol-1-one (**12f**)



A solution of 3a-acetyl-6-benzyl-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazol-1-one **2f** (100 mg, 0.249 mmol, 1 equiv), Na (1 g, 43.5 mmol, 174 equiv) and hydrazine monohydrate (3 mL, 61.9 mmol, 248 equiv) in ethylene glycol (25 ml, 0.01 M) in a round bottom flask was heated at 160 °C for 1 h, then the temperature was raised to 190 °C for 4 h to remove the distillable material. The remaining solution was heated at 210 °C for 14 h. The resulting mixture was poured into water (50 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with brine (5 × 30 mL) and separated. Then the organics were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography (0–5% MeOH in CH_2Cl_2) to afford the product as a colourless oil (7 mg, 7%).

υ_{max} (film): 2965, 2934, 2866, 2359, 2342, 1620, 1604, 1481, 1452, 1416, 1227 cm^{-1}.

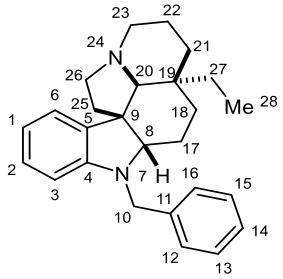
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.32 (m, 4H, 12, 13, 15, 16), 7.31 – 7.27 (m, 1H, 14), 7.08 (td, J = 7.6, 1.3 Hz, 1H, 2), 7.04 (dd, J = 7.4, 1.3 Hz, 1H, 6), 6.70 (td, J = 7.4, 1.0 Hz, 1H, 1), 6.42 (d, J = 7.8 Hz, 1H, 3), 4.46 (d, J = 14.9 Hz, 1H, 10''), 4.11

(d, J = 14.9 Hz, 1H, 10'), 3.82 (s, 1H, 20), 3.58 (dd, J = 12.5, 9.7 Hz, 1H, 26''), 3.48 (td, J = 11.9, 7.7 Hz, 1H, 26'), 3.14 (dd, J = 10.5, 5.7 Hz, 1H, 8), 2.46 – 2.24 (m, 3H, 22', 22'', 25''), 1.72 (tdd, J = 11.1, 6.5, 2.1 Hz, 2H, 17'', 21''), 1.66 – 1.53 (m, 3H, 21', 25', 27'), 1.41 – 1.28 (m, 2H, 17', 18''), 1.23 – 1.18 (m, 1H, 18'), 1.08 (dq, J = 14.6, 7.4 Hz, 1H, 27''), 0.72 (t, J = 7.5 Hz, 3H, 29).

^{13}C NMR (126 MHz, $CDCl_3$): δ 169.6 (23), 149.8 (4), 138.2 (11), 132.4 (5), 128.8 (13, 15), 128.3 (2), 127.7 (12, 16), 127.5 (14), 122.3 (6), 118.0 (1), 107.5 (3), 64.9 (20), 64.4 (8), 53.7 (9), 48.6 (10), 43.3 (26), 35.6 (25), 35.0 (19), 30.7 (21), 28.6 (27), 28.0 (22), 21.7 (18), 21.2 (17), 7.3 (29).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{26}H_{31}ON_2$) requires *m/z* 387.2431, found *m/z* 387.2425.

6-Benzyl-3a-ethyl-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazole (**1f**)



Two step synthesis: A solution of 3a-acetyl-6-benzyl-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazol-1-one **2f** (290 mg, 0.72 mmol, 1 equiv), Na (2.9 g, 126 mmol, 174 equiv) and hydrazine monohydrate (9 mL, 185 mmol, 256 equiv) in ethylene glycol (72.4 mL, 0.01 M) in a round bottom flask was heated at 160 °C for 1 h, then the temperature was raised to 190 °C for 2.5 h to remove the distillable material. The remaining solution was heated at 210 °C for 18 h. The resulting mixture was quenched with water (75 mL) and extracted with ethyl acetate (5 × 50 mL). The combined organic extracts were washed with brine (5 × 50 mL) and separated. Then the organics were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure, to give a pale yellow oil crude residue, which was carried through to the next step without further purification.

To an oven-dried flask, which was sealed and purged, a solution of crude residue in THF (29 mL, 0.025 M) was added and subsequently cooled to 0 °C. Then under a N_2 flow, $LiAlH_4$ (578 mg, 14.5 mmol, 20 equiv) was added. After 30 min the reaction mixture was heated to 70 °C for 2 h. After the reaction was complete, cooled to 0 °C and diluted with Et_2O (30 mL). Then water (0.6 mL), 15% NaOH solution (0.6 mL), water (1.8 mL) were added in intervals of 5 minutes between each. Then the mixture was left to reach room temperature. Then the organics were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography (0–40% Et_2O in petroleum ether) to afford the product as a colourless oil (156 mg, 58%).

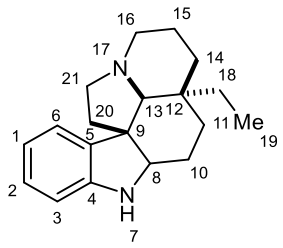
υ_{max} (film): 3063, 2927, 2859, 2778, 1603, 1479, 1452 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.30 (m, 4H, 12, 13, 15, 16), 7.29 – 7.23 (m, 1H, 14), 7.07 (dd, *J* = 7.3, 1.3 Hz, 1H, 6), 7.05 – 7.01 (m, 1H, 2), 6.66 (td, *J* = 7.4, 1.0 Hz, 1H, 1), 6.37 (d, *J* = 7.7 Hz, 1H, 3), 4.45 (d, *J* = 14.8 Hz, 1H, 10''), 4.08 (d, *J* = 14.8 Hz, 1H, 10'), 3.39 (dd, *J* = 10.9, 5.7 Hz, 1H, 8), 3.09 (td, *J* = 8.9, 2.8 Hz, 1H, 25'), 3.02 (ddt, *J* = 11.0, 4.0, 1.9 Hz, 1H, 23''), 2.35 (dt, *J* = 12.8, 8.6 Hz, 1H, 26''), 2.29 – 2.19 (m, 2H, 20, 25''), 1.95 (ddd, *J* = 12.3, 11.0, 2.9 Hz, 1H, 23'), 1.83 – 1.66 (m, 3H, 17'', 18', 22''), 1.63 – 1.47 (m, 4H, 21', 22', 26', 27''), 1.38 – 1.31 (m, 1H, 17'), 1.16 – 1.05 (m, 2H, 18'', 21''), 0.90 – 0.84 (m, 1H, 27'), 0.65 (t, *J* = 7.5 Hz, 3H, 28).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0 (4), 138.7 (11), 136.9 (5), 128.6 (13, 15), 127.9 (12, 16), 127.3 (2), 127.1 (14), 122.5 (6), 117.4 (1), 106.7 (3), 71.3 (20), 69.2 (8), 53.9 (23), 53.1 (25), 52.6 (9), 48.4 (10), 39.2 (26), 35.6 (19), 34.6 (21), 30.2 (27), 23.1 (18), 22.5 (17), 21.9 (22), 7.0 (28).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{26}H_{33}N_2$) requires *m/z* 373.2638, found *m/z* 373.2627.

(±)-Aspidospermidine



A round bottom flask was charged with Pearlman's catalyst ($Pd(OH)_2/C$, 20% wt on carbon) (544 mg, 0.77 mmol, 1.85 equiv) and 6-benzyl-3a-ethyl-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazole **1f** (156 mg, 0.42 mmol, 1 equiv). The flask was then sealed and purged. Then EtOH (14 mL, 0.03 M) was added to the flask and the reaction mixture was subsequently sparged with hydrogen gas, and the resulting suspension was stirred at room temperature for 26 h under H_2 atmosphere. After the reaction was complete, the mixture was filtered through a pad of Celite® and concentrated. The crude residue was purified by chromatography (0–10% MeOH in CH_2Cl_2) to afford the product as a colourless wax. Product was then washed with 2 M HCl (20 mL) and organics were extracted with CH_2Cl_2 (2 × 20 mL). The aqueous phase was then basified with 2 M NaOH (25 mL) and organics were extracted with CH_2Cl_2 (2 × 20 mL). Then the organics were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure, to give a colourless wax (81.9 mg, 69%).

υ_{max} (film): 3318, 3298, 2934, 2828, 1607, 1462 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (dd, *J* = 7.4, 1.3 Hz, 1H, 6), 7.01 (td, *J* = 7.6, 1.3 Hz, 1H, 2), 6.73 (td, *J* = 7.4, 1.0 Hz, 1H, 1), 6.64 (dt, *J* = 7.7, 0.8 Hz, 1H, 3), 3.51 (dd, *J* = 11.1, 6.2 Hz, 1H, 8), 3.16 – 3.09 (m, 1H, 21''), 3.06 (ddt, *J* = 10.9, 4.0, 1.8 Hz, 1H, 16''), 2.35 – 2.19 (m, 3H, 13, 20', 21'), 2.00 – 1.89 (m, 2H, 11'', 16'), 1.81 – 1.69 (m, 1H, 15''), 1.67 – 1.59 (m, 2H, 10'', 14'), 1.55 – 1.43 (m, 3H, 15', 18'', 20''), 1.42 – 1.33 (m, 1H, 10'), 1.13 (dd, *J* = 13.5, 4.6 Hz, 1H, 14''), 1.09 – 1.02 (m, 1H, 11'), 0.94 – 0.80 (m, 1H, 18'), 0.63 (t, *J* = 7.5 Hz, 3H, 19). Indoline proton not observed.

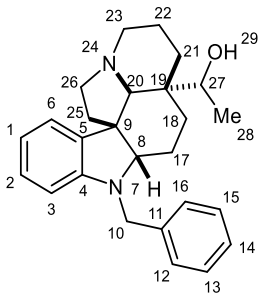
^{13}C NMR (126 MHz, $CDCl_3$): δ 149.5 (4), 135.9 (5), 127.2 (2), 123.0 (6), 119.1 (1), 110.5 (3), 71.4 (13), 65.8 (8), 54.0 (16), 53.5 (9), 53.2 (21), 39.0 (20), 35.8 (12), 34.6 (14), 30.1 (18), 28.2 (10), 23.1 (11), 21.9 (15), 7.0 (19).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{27}N_2$) requires *m/z* 283.2169, found *m/z* 283.2161.

Data in agreement with that reported in the literature.[139]

3.7.4.1.2. End game route 2

1-(6-Benzyl-2,3,4,5,5a,6,11,12-octahydro-1*H*-indolizino[8,1-cd]carbazol-3a(3a^1*H*)-yl)ethan-1-ol (**13f**),



In an oven-dried flask was weighed in 3a-acetyl-6-benzyl-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazol-1-one **f2** (676 mg, 1.69 mmol, 1 equiv) which was sealed and purged after. Then THF (17 mL, 0.1 M) was added via syringe and the mixture was subsequently cooled to 0 °C. Then under a N_2 flow, $LiAlH_4$ (1.35 g, 33.8 mmol, 20 equiv) was added. After 30 min the reaction mixture was heated to 70 °C for 2 h. After the reaction was complete, the reaction was cooled to 0 °C and diluted with Et_2O (20 mL). Then water (1.35 mL), 15% NaOH solution (1.35 mL), water (4.05 mL) were added in intervals of 5 minutes between each. Then the mixture was left to reach room temperature. Then the organics were dried with $MgSO_4$, filtered and concentrated under reduced pressure to yield the product as a beige foam solid (578 mg, 88%) as an inconsequential inseparable mixture of diastereomers (3:1 ratio). No further purification was required. Assignment below is for the major diastereomer.

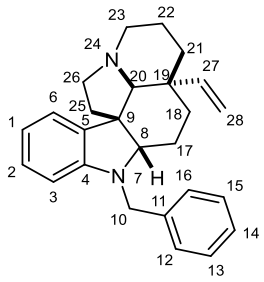
υ_{max} (film): 3379 (br), 2934, 2864, 1603, 1479, 1452, 1265, 1070 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.38 – 7.35 (m, 2H, 12, 16), 7.32 (dd, *J* = 8.3, 6.9 Hz, 2H, 13, 15), 7.27 – 7.24 (m, 1H, 14), 7.02 (td, *J* = 7.6, 1.3 Hz, 1H, 2), 6.99 (dd, *J* = 7.3, 1.3 Hz, 1H, 6), 6.64 (td, *J* = 7.4, 0.9 Hz, 1H, 1), 6.37 (d, *J* = 7.8 Hz, 1H, 3), 4.44 (d, *J* = 14.9 Hz, 1H, 10''), 4.08 (dd, *J* = 14.8, 8.7 Hz, 1H, 10'), 3.88 (p, *J* = 5.8 Hz, 1H, 27), 3.41 (dt, *J* = 10.6, 6.6 Hz, 1H, 8), 3.09 (td, *J* = 9.0, 3.1 Hz, 1H, 26''), 3.00 (ddd, *J* = 11.3, 4.1, 2.0 Hz, 1H, 23''), 2.34 – 2.30 (m, 1H, 25''), 2.29 (s, 1H, 20), 2.27 – 2.22 (m, 1H, 26'), 1.99 – 1.91 (m, 1H, 23'), 1.88 (td, *J* = 14.5, 3.7 Hz, 1H, 18'), 1.79 (ddt, *J* = 13.6, 10.2, 4.8 Hz, 1H, 17'), 1.72 – 1.68 (m, 1H, 22''), 1.62 – 1.53 (m, 2H, 22', 25'), 1.53 – 1.43 (m, 3H, 17'', 18'', 21''), 1.38 (td, *J* = 13.4, 4.7 Hz, 1H, 21'), 1.15 (d, *J* = 6.2 Hz, 3H, 28). Alcohol proton not observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 150.3 (4), 150.1, 138.6 (11), 138.6, 136.6, 135.6 (5), 128.7, 128.6 (13, 15), 127.9 (12, 16), 127.9, 127.7, 127.7 (2), 127.2, 127.2 (14), 122.3 (6), 121.5, 117.8, 117.5 (1), 106.9 (3), 106.9, 68.7 (8), 67.1 (20, 27), 66.9, 66.1, 63.0, 53.8 (23), 53.6, 53.2, 53.0 (9), 52.8 (26), 52.3, 48.6, 48.4 (10), 39.9 (19), 39.6, 39.2 (25), 39.1, 30.0, 26.6 (21), 26.0, 23.8, 22.3 (18), 22.1 (17), 21.4, 21.3 (22), 18.0 (28), 16.6.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{26}H_{33}N_2O$) requires *m/z* 389.2587, found *m/z* 389.2578.

6-Benzyl-3a-vinyl-2,3,3a,3a^{1},4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazole (**14f**)



In an oven-dried flask MW vial was weighed out 1-(6-benzyl-2,3,4,5,5a,6,11,12-octahydro-1*H*-indolizino[8,1-cd]carbazol-3a(3a^{1}*H*)-yl)ethan-1-ol **13f** (180 mg, 0.46 mmol, 1 equiv) and Martin Sulfurane (649 mg, 0.93 mmol, 2 equiv). The flask was then sealed and purged, before $CHCl_3$ (9.3 mL, 0.05 M) was added *via* syringe. The

reaction mixture was then stirred at room temperature for 3 h. After the reaction was complete, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by chromatography (silica gel, 0–10% EtOAc in hexane with 1% Et_3N additive) to afford the desired product as a pale yellow solid (138 mg, 80%).

υ_{max} (film): 2930, 2783, 2357, 1481, 1454, 905 cm^{-1}.

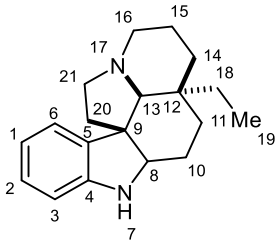
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.36 (m, 2H, 13, 15), 7.34 – 7.30 (m, 2H, 12, 16), 7.28 – 7.24 (m, 1H, 14), 7.05 (dd, *J* = 7.3, 1.3 Hz, 1H, 6), 7.02 (td, *J* = 7.6, 1.3 Hz, 1H, 2), 6.66 (td, *J* = 7.4, 1.0 Hz, 1H, 1), 6.35 (d, *J* = 7.8 Hz, 1H, 3), 5.95 – 5.79 (m, 1H, 27), 4.88 – 4.82 (m, 1H, 28''), 4.77 (d, *J* = 11.0 Hz, 1H, 28'), 4.42 (d, *J* = 14.7 Hz, 1H, 10''), 4.06 (d, *J* = 14.7 Hz, 1H, 10'), 3.39 (dd, *J* = 11.3, 5.6 Hz, 1H, 8), 3.16 – 3.07 (m, 1H, 26'), 3.03 (d, *J* = 11.0 Hz, 1H, 23''), 2.37 (d, *J* = 10.4 Hz, 2H, 20, 25''), 2.27 (q, *J* = 8.3, 7.5 Hz, 1H, 26''), 2.04 – 1.94 (m, 2H, 18', 23'), 1.77 – 1.68 (m, 2H, 17'', 22''), 1.58 – 1.39 (m, 5H, 17', 21, 22', 25'), 1.28 – 1.22 (m, 1H, 18'').

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3 (4), 145.7 (27), 138.7 (11), 135.5 (5), 128.6 (13, 15), 127.9 (12, 16), 127.4 (2), 127.1 (14), 122.9 (6), 117.4 (1), 111.5 (28), 106.8 (3), 70.5 (20), 68.7 (8), 53.7 (23), 52.9 (9), 52.7 (26), 48.5 (10), 39.1 (19), 38.2 (25), 36.6 (21), 25.3 (18), 22.8 (17), 21.9 (22).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{26}H_{31}N_2$) requires *m/z* 371.2482, found *m/z* 371.2470.

Data in agreement with that reported in the literature.[127]

(±)-Aspidospermidine



A round bottom flask was charged with Pearlman's catalyst ($Pd(OH)_2$/C, 20% wt on carbon) (175 mg, 0.25 mmol, 1.85 equiv) and 6-benzyl-3a-vinyl-

2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazole **14f** (50 mg, 0.135 mmol, 1 equiv). The flask was then sealed and purged. Then EtOH (6.75 mL, 0.02 M) was added to the flask and the reaction mixture was subsequently sparged with hydrogen gas, and the resulting suspension was stirred at room temperature for 24 h under H_2 atmosphere. After the reaction was complete, the mixture was filtered through a pad of Celite® and concentrated. The crude residue was purified by chromatography (0–10% MeOH in CH_2Cl_2) to afford the product as a light brown wax (25.7 mg, 67%).

υ_{max} (film): 3318, 3298, 2934, 2828, 1607, 1462 cm^{-1}.

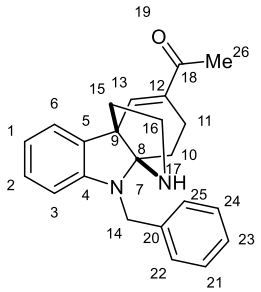
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (dd, *J* = 7.4, 1.3 Hz, 1H, 6), 7.01 (td, *J* = 7.6, 1.3 Hz, 1H, 2), 6.73 (td, *J* = 7.4, 1.0 Hz, 1H, 1), 6.64 (dt, *J* = 7.7, 0.8 Hz, 1H, 3), 3.51 (dd, *J* = 11.1, 6.2 Hz, 1H, 8), 3.16 – 3.09 (m, 1H, 21''), 3.06 (ddt, *J* = 10.9, 4.0, 1.8 Hz, 1H, 16''), 2.35 – 2.19 (m, 3H, 13, 20', 21'), 2.00 – 1.89 (m, 2H, 11'', 16'), 1.81 – 1.69 (m, 1H, 15''), 1.67 – 1.59 (m, 2H, 10'', 14'), 1.55 – 1.43 (m, 3H, 15', 18'', 20''), 1.42 – 1.33 (m, 1H, 10'), 1.13 (dd, *J* = 13.5, 4.6 Hz, 1H, 14''), 1.09 – 1.02 (m, 1H, 11'), 0.94 – 0.80 (m, 1H, 18'), 0.63 (t, *J* = 7.5 Hz, 3H, 19). Indoline proton not observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 149.5 (4), 135.9 (5), 127.2 (2), 123.0 (6), 119.1 (1), 110.5 (3), 71.4 (13), 65.8 (8), 54.0 (16), 53.5 (9), 53.2 (21), 39.0 (20), 35.8 (12), 34.6 (14), 30.1 (18), 28.2 (10), 23.1 (11), 21.9 (15), 7.0 (19).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{27}N_2$) requires *m/z* 283.2169, found *m/z* 283.2161.

3.7.4.2. Alternative route to 2f intermediates

1-(9-Benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazol-6-yl)ethan-1-one (**4f2**)



Prepared according to General Procedure C using *tert*-butyl (2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)carbamate **8f** (470 mg, 1.25 mmol, 1 equiv), 3-butyn-2-one (488 µL, 6.25 mmol, 5 equiv), 1,4-dioxane (5 mL, 0.25 M) and $BF_3 \bullet OEt_2$ (246 µL, 2 mmol, 1.6 equiv), 16 h at 25 °C. After the reaction was complete the reaction mixture the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–30% EtOAc in CH_2Cl_2) to afford the desired product as a red/brown oil (200 mg, 47%).

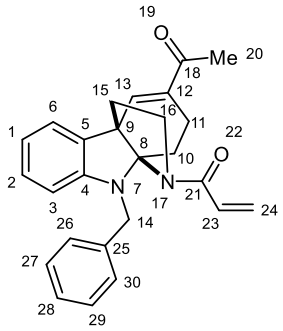
υ_{max} (film): 2928, 2870, 2357, 2342, 1667, 1601, 1489, 1354, 1069, 1030 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.29 (m, 4H, 21, 22, 24, 25), 7.27 – 7.22 (m, 1H, 23), 7.14 (dd, *J* = 7.3, 1.3 Hz, 1H, 6), 7.10 (d, *J* = 1.5 Hz, 1H, 13), 7.00 (td, *J* = 7.7, 1.3 Hz, 1H, 2), 6.68 (td, *J* = 7.4, 1.0 Hz, 1H, 1), 6.22 (dd, 1H, 3), 4.54 (d, *J* = 16.7 Hz, 1H, 14'), 4.32 (d, *J* = 16.8 Hz, 1H, 14''), 3.09 (ddd, *J* = 11.1, 7.2, 2.1 Hz, 1H, 16''), 2.85 (td, *J* = 10.8, 5.7 Hz, 1H, 16'), 2.39 (ddd, *J* = 12.0, 5.7, 2.1 Hz, 1H, 15''), 2.34 (s, 3H, 26), 2.33 – 2.27 (m, 2H, 11), 2.09 – 1.97 (m, 2H, 10', 15'), 1.73 (ddd, *J* = 13.5, 8.2, 5.4 Hz, 1H, 10''). Amine proton not observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 198.8 (18), 150.9 (4), 142.8 (13), 139.6 (20), 137.9 (12), 131.6 (5), 128.7 (2), 128.7 (22, 24), 126.9 (23), 126.8 (21, 25), 123.0 (6), 117.6 (1), 106.9 (3), 90.7 (8), 56.8 (9), 47.3 (14), 44.8 (16), 42.4 (15), 31.0 (10), 25.4 (26), 20.1 (11).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{23}H_{25}ON_2$) requires *m/z* 345.1961 , found *m/z* 345.1956.

1-(6-Acetyl-9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazol-10-yl)prop-2-en-1-one (**15f**)



To an oven-dried flask, which was sealed and purged, was added a solution of 1-(9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazol-6-yl)ethan-1-one **4f2** (84 mg, 0.24 mmol, 1 equiv) in THF (4.9 mL, 0.05 M) followed by Et_3N (44 µL, 0.32 mmol, 1.3 equiv). The resulting mixture was cooled to 0 °C. Then acryloyl chloride (26.5 µL, 0.32 mmol, 1.3 equiv) was added dropwise *via* syringe. Then reaction mixture was then left to reach ambient temperature, and stirred for 3 h. After the reaction was complete, sat. aqueous $NaHCO_3$ (20 mL) was added and the organics were extracted with EtOAc (3× 30 mL). Then the organics were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography (0–10% EtOAc in CH_2Cl_2) to afford the product as a beige yellow solid (67.5 mg, 69%). Crystal growth was successful from CH_2Cl_2/EtOAc *via* solvent diffusion.

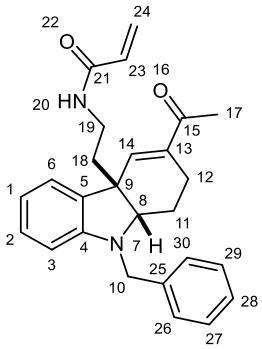
υ_{max} (film): 2965, 2928, 2874, 2359, 2342, 1667, 1651, 1605, 1485, 1416, 1223, 1072 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (t, *J* = 7.2 Hz, 2H, 6, 28), 7.16 (td, *J* = 8.0, 4.0 Hz, 4H, 26, 28, 29, 30), 7.00 (td, *J* = 7.7, 1.3 Hz, 1H, 2), 6.81 (d, *J* = 1.9 Hz, 1H, 13), 6.72 (t, *J* = 7.4 Hz, 1H, 1), 6.37 (dd, *J* = 16.7, 10.1 Hz, 1H, 23), 6.27 (dd, *J* = 16.8, 2.1 Hz, 1H, 24_{trans}), 6.14 (d, *J* = 7.8 Hz, 1H, 3), 5.65 (dd, *J* = 10.1, 2.1 Hz, 1H, 24_{cis}), 5.19 (d, *J* = 17.3 Hz, 1H, 14'), 4.74 (d, *J* = 17.4 Hz, 1H, 14''), 3.73 (ddd, *J* = 10.2, 7.7, 2.9 Hz, 1H, 16'), 3.49 (td, *J* = 9.8, 6.4 Hz, 1H, 16''), 3.36 – 3.26 (m, 1H, 15'), 2.54 (ddd, *J* = 12.4, 6.3, 2.8 Hz, 1H, 10'), 2.40 – 2.33 (m, 1H, 11'), 2.30 (s, 3H, 20), 2.25 – 2.11 (m, 3H, 10'', 15'', 11'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 198.7 (18), 165.9 (21), 149.1 (4), 139.0 (12), 139.0 (13), 138.0 (25), 130.2 (23), 129.5 (5), 129.2 (2), 128.5 (27, 29), 128.1 (23), 126.5 (28), 126.4 (25, 29), 122.3 (6), 118.2 (1), 108.8 (3), 91.4 (8), 57.0 (9), 48.1 (14), 47.6 (16), 34.7 (10), 25.7 (15), 25.7 (20), 21.0 (11).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{26}H_{27}O_2N_2$) requires *m/z* 399.2067, found *m/z* 399.2060.

N-(2-(3-acetyl-9-benzyl-1,2,9,9a-tetrahydro-4a*H*-carbazol-4a-yl)ethyl)acrylamide (**3f**)



In an oven-dried flask weighed in 1-(6-Acetyl-9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazol-10-yl)prop-2-en-1-one **15f** (67.3 mg, 0.17 mmol, 1 equiv). The reaction vessel was then sealed and purged, before THF (3.4 mL, 0.05 M) was added. The reaction mixture was then cooled to 0 °C, before TFA (39 µL, 0.51 mmol, 3 equiv) was added *via* syringe. After 30 min, under N_2 flow, STAB (143 mg, 0.68 mmol, 4 equiv) was added. Then the reaction mixture was allowed to reach room temperature and left to stir for 24 h. After the reaction was complete, sat. aqueous $NaHCO_3$ (20 mL) was added and the organics were extracted with EtOAc (3 × 20 mL). The organics were then collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography (0–2% MeOH in CH_2Cl_2) to afford the product as a pale yellow oil (49.8 mg, 74%).

One-pot approach from 4f2: To an oven-dried flask, which was sealed and purged, was added a solution of 1-(9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazol-6-yl)ethan-1-one **4f2** (141 mg, 0.41 mmol, 1 equiv) in THF (8.2 mL, 0.05 M) followed by Et_3N (74 µL, 0.53 mmol, 1.3 equiv). The resulting mixture was cooled to 0 °C.

Then acryloyl chloride (44.5 µL, 0.53 mmol, 1.3 equiv) was added dropwise *via* syringe. Then reaction mixture was then left to reach ambient temperature, and stirred for 3 h. Then the reaction mixture was cooled to 0 °C, before TFA (94 µL, 1.23 mmol, 3 equiv) was added *via* syringe. After 25 min, under N_2 flow, STAB (347 mg, 1.64 mmol, 4 equiv) was added. Then the reaction mixture was allowed to reach room temperature and left to stir for 24 h. After the reaction was complete, sat. aqueous $NaHCO_3$ (20 mL) was added and the organics were extracted with EtOAc (3 × 20 mL). The organics were then collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography (0–30% EtOAc in CH_2Cl_2) to afford the product as a pale yellow oil (114 mg, 70%).

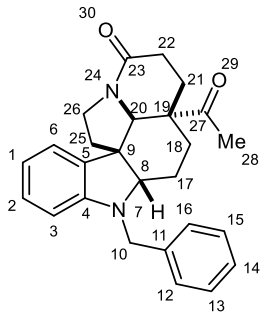
υ_{max} (film): 3281 (br), 3061, 2926, 2855, 2361, 2342, 1655, 1601, 1483, 1263, 957 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.23 (m, 5H, 26, 27, 28, 29, 30), 7.13 (dd, *J* = 7.3, 1.3 Hz, 1H, 6), 7.08 (td, *J* = 7.7, 1.3 Hz, 1H, 2), 6.73 (td, *J* = 7.4, 1.0 Hz, 1H, 1), 6.62 (d, *J* = 1.5 Hz, 1H, 14), 6.44 (d, *J* = 7.8 Hz, 1H, 3), 6.25 (dd, *J* = 16.9, 1.4 Hz, 1H, 24_{trans}), 5.99 (dd, *J* = 16.9, 10.3 Hz, 1H, 23), 5.64 (dd, *J* = 10.4, 1.4 Hz, 1H, 24_{cis}), 5.60 (d, *J* = 6.2 Hz, 1H, 20), 4.46 (d, *J* = 16.0 Hz, 1H, 10'), 4.21 (d, *J* = 16.0 Hz, 1H, 10''), 3.79 (dd, *J* = 4.7, 3.0 Hz, 1H, 8), 3.43 – 3.31 (m, 2H, 19), 2.29 (s, 3H, 17), 2.29 – 2.25 (m, 2H, 12), 2.20 – 1.99 (m, 3H, 11', 18), 1.70 (dddd, *J* = 14.3, 9.4, 6.6, 3.1 Hz, 1H, 11'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 199.1 (15), 165.6 (21), 151.4 (4), 142.8 (14), 138.6 (13), 138.3 (25), 132.0 (5), 130.7 (23), 128.9 (2), 128.8 (27, 29), 127.4 (26, 30), 127.3 (28), 126.7 (24), 123.2 (6), 118.2 (1), 108.2 (3), 66.0 (8), 50.6 (10), 47.9 (9), 38.0 (18), 36.2 (19), 25.5 (17), 22.3 (11), 18.2 (12).

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{26}H_{28}O_2N_2Na$) requires *m/z* 423.2043, found *m/z* 423.2034.

3a-Acetyl-6-benzyl-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazol-1-one (**2f**)



In an oven-dried MW vial weighed in *N*-(2-(3-acetyl-9-benzyl-1,2,9,9a-tetrahydro-4a*H*-carbazol-4a-yl)ethyl)acrylamide **3f** (15.6 mg, 0.04 mmol, 1 equiv). This was then dissolved in THF (1 mL, 0.04 M) and cooled to 0 °C. Then NaH (3.1 mg, 0.08 mmol, 2 equiv) was added. After 30 min, the reaction was left to reach room temperature and stirred for a further 1.5 h. After the reaction was complete, the mixture was washed with sat. aqueous $NaHCO_3$ (20 mL) and the organics extracted with EtOAc (3 × 20 mL). The organics were then collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield the product as a yellow solid (15.3 mg, 98%). No further purification was required. Crystal was successfully grown in MeCN.

υ_{max} (film): 3049, 2930, 2872, 2361, 2342, 1701, 1616, 1605, 1479, 1452, 1352 cm^{-1}.

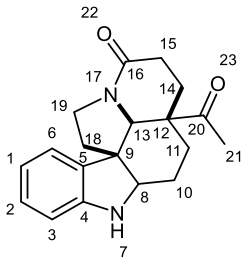
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 5H, 12, 13, 14, 15, 16), 7.14 (dd, *J* = 7.4, 1.2 Hz, 1H, 6), 7.04 (td, *J* = 7.6, 1.3 Hz, 1H, 2), 6.71 (t, *J* = 7.4 Hz, 1H, 1), 6.37 (d, *J* = 7.9 Hz, 1H, 3), 4.73 (s, 1H, 20), 4.45 (d, *J* = 14.9 Hz, 1H, 10'), 4.07 (d, *J* = 14.9 Hz, 1H, 10''), 3.65 (dd, *J* = 12.6, 9.6 Hz, 1H, 26'), 3.48 (td, *J* = 11.9, 7.6 Hz, 1H, 26''), 3.14 (dd, *J* = 10.1, 5.1 Hz, 1H, 8), 2.47 (ddd, *J* = 18.2, 7.1, 2.8 Hz, 1H, 22'), 2.42 – 2.29 (m, 2H, 22'', 25'), 2.06 (s, 3H, 28), 1.97 – 1.90 (m, 1H, 21'), 1.90 – 1.86 (m, 1H, 18'), 1.82 (dtd, *J* = 13.1, 4.9, 2.7 Hz, 1H, 17'), 1.76 – 1.67 (m, 2H, 21'', 25''), 1.42 (td, *J* = 13.6, 2.8 Hz, 1H, 18''), 1.30 (ddd, *J* = 13.2, 9.9, 2.9 Hz, 1H, 17'').

^{13}C NMR (126 MHz, $CDCl_3$): δ 208.7 (27), 168.4 (23), 150.0 (4), 138.0 (11), 129.4 (5), 128.8 (13, 15), 128.6 (2), 127.7 (12, 16), 127.5 (14), 124.3 (6), 118.1 (1), 107.3 (3), 63.9 (8), 60.4 (20), 54.3 (9), 49.9 (19), 48.6 (10), 43.2 (26), 35.5 (25), 31.1 (21), 27.9 (22), 25.3 (28), 22.5 (17), 22.2 (18).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{26}H_{29}O_2N_2$) requires *m/z* 401.2224, found *m/z* 401.2216.

3.7.4.3. Intermediates leading to (±)-aspidofractinine

3a-Acetyl-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazol-1-one (**16f**)



Pearlman's catalyst ($Pd(OH)_2/C$, 20%) (324 mg, 0.46 mmol, 1.85 equiv) and 3a-acetyl-6-benzyl-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazol-1-one **2f** (100 mg, 0.097 mmol, 1 equiv) were weighed into an oven-dried MW vial. The vial was then capped and purged. Then EtOH (8.3 ml, 0.03 M) was added to the flask and subsequently sparged with hydrogen gas, and the resulting suspension was stirred at room temperature for 26 h under H_2 atmosphere. After the reaction was complete, the mixture was filtered through a pad of Celite® and concentrated. The crude residue was purified by chromatography (0–10% MeOH in CH_2Cl_2) to afford the product as a pale yellow solid (45.9 mg, 59%).

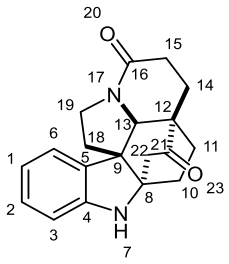
υ_{max} (film): 3302, 2936, 2887, 1701, 1620, 1464, 1416 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 7.6, 1.3 Hz, 1H, 6), 7.03 (td, *J* = 7.6, 1.3 Hz, 1H, 2), 6.77 (td, *J* = 7.5, 1.0 Hz, 1H, 1), 6.59 (d, *J* = 7.8 Hz, 1H, 3), 4.73 (s, 1H, 13), 3.68 (dd, *J* = 12.6, 9.7 Hz, 1H, 19''), 3.57 (td, *J* = 11.9, 7.6 Hz, 1H, 19'), 3.28 (dd, *J* = 10.4, 5.5 Hz, 1H, 8), 2.53 – 2.47 (m, 1H, 15'), 2.39 (ddd, *J* = 18.1, 11.1, 7.0 Hz, 1H, 15''), 2.29 (ddd, *J* = 13.2, 7.7, 1.3 Hz, 1H, 18''), 2.06 (s, 3H, 21), 1.97 – 1.84 (m, 2H, 11', 14''), 1.76 (dddt, *J* = 13.8, 10.2, 7.0, 3.0 Hz, 2H, 10', 14'), 1.67 (ddd, *J* = 13.1, 11.3, 9.7 Hz, 1H, 18'), 1.56 (td, *J* = 13.8, 2.9 Hz, 1H, 11''), 1.35 (tdd, *J* = 13.4, 10.4, 3.0 Hz, 1H, 10''). Indoline proton not observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 208.7 (20), 168.3 (16), 149.4 (4), 128.5 (5), 128.4 (2), 124.6 (6), 119.3 (1), 110.4 (3), 60.3 (13), 60.0 (8), 55.1 (9), 50.1 (12), 43.3 (19), 35.3 (18), 31.0 (14), 28.0 (10), 27.9 (15), 25.2 (21), 22.4 (11).

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{19}H_{22}N_2O_2Na$) requires *m/z* 333.1573, found *m/z* 333.1564.

2,3,11,12-Tetrahydro-1*H*,3a^1*H*,6*H*-3a,5a-ethanoindolizino[8,1-*cd*]carbazole-1,4(5*H*)-dione (**17f**)



Two step synthesis: In an oven-dried MW, capped and purged, was added CH_2Cl_2 (11.5 mL). Then the vessel was cooled to -60 °C, before oxalyl chloride (39 µL, 0.46 mmol, 1.2 equiv) was added. Then a mixture of DMSO (58 µL, 0.81 mmol, 2.1 equiv) in CH_2Cl_2 (3 mL) was added, and left to stir for 15 min. Then a mixture of 3a-acetyl-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazol-1-one **16f** (120 mg, 0.39 mmol, 1 equiv) dissolved in CH_2Cl_2 (3 mL, 0.018 M) was added *via* syringe to reaction mixture and left to stir for another 30 min at -60 °C. Then Et_3N (269 µL, 0.34 mmol, 5 equiv) was added and the reaction mixture was left to reach room temperature over 45 min. After the reaction was complete, water was added (20 mL), and the organics were extracted with CH_2Cl_2 (3 × 25 mL). The organics were then washed with brine (20 mL). Then the organics were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure, to give a pale yellow oil crude residue, which was carried through to the next step without further purification.

In a round bottom flask the crude residue was dissolved in ethanol (60 mL, 0.007 M), and c.HCl (6 mL) was added. The reaction mixture was then refluxed for 18 h. After the reaction was complete, the mixture was concentrated under reduced pressure. The mixture was then quenched with 5% Na_2CO_3 solution (100 mL) and extracted with

CH_2Cl_2 (3 × 50 mL). Then the organics were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography (0–10% MeOH in EtOAc) to afford the product as a beige solid (51.1 mg, 43%).

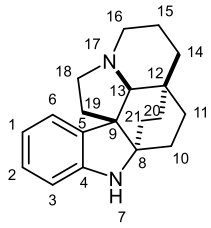
υ_{max} (film): 3294, 2934, 2897, 1726, 1612, 1601, 1460, 1449, 1410 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (t, *J* = 7.7 Hz, 1H, 2), 7.09 (d, *J* = 7.3 Hz, 1H, 6), 6.82 (t, *J* = 7.4 Hz, 1H, 1), 6.75 (d, *J* = 7.8 Hz, 1H, 3), 4.34 (dd, *J* = 11.8, 7.8 Hz, 1H, 19'), 3.80 (s, 1H, 13), 3.77 (s, 1H, 7), 3.29 (td, *J* = 12.0, 5.7 Hz, 1H, 19''), 2.71 (dd, *J* = 18.4, 3.6 Hz, 1H, 22''), 2.51 (ddd, *J* = 14.4, 8.2, 6.1 Hz, 1H, 14'), 2.42 – 2.36 (m, 2H, 15'), 2.32 (td, *J* = 12.4, 8.0 Hz, 2H, 10', 18''), 2.11 – 1.99 (m, 2H, 11'', 22'), 1.85 (ddd, *J* = 12.8, 10.9, 7.4 Hz, 1H, 10''), 1.60 (dd, *J* = 12.7, 5.7 Hz, 1H, 18'), 1.43 (dt, *J* = 14.9, 7.6 Hz, 1H, 14''), 1.37 – 1.29 (m, 1H, 11').

^{13}C NMR (126 MHz, $CDCl_3$): δ 209.6 (21), 169.4 (16), 148.9 (4), 135.3 (5), 128.7 (2), 121.7 (6), 120.5 (1), 111.8 (3), 67.0 (8), 61.1 (13), 57.7 (9), 48.0 (22), 47.9 (12), 43.8 (19), 33.8 (18), 29.6 (15), 26.8 (10), 23.7 (11), 22.0 (14).

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{19}H_{20}N_2O_2Na$) requires *m/z* 331.1417, found *m/z* 331.1417.

(±)-Aspidofractinine



Two step synthesis: A solution of 2,3,11,12-Tetrahydro-1*H*,3a^1*H*,6*H*-3a,5a-ethanoindolizino[8,1-*cd*]carbazole-1,4(5*H*)-dione **17f** (50 mg, 0.162 mmol, 1 equiv), Na (650 mg, 28.2 mmol, 174 equiv) and hydrazine monohydrate (1.95 mL, 40.2 mmol, 248 equiv) in ethylene glycol (16.2 ml, 0.01 M) was heated at 160 °C for 1 h, then the temperature was raised to 190 °C for 2 h to remove the distillable material. The remaining solution was heated at 210 °C for 18 h. The resulting mixture was quenched

with water (25 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (5 × 50 mL) and separated. Then the organics were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure, to give a pale yellow oil crude residue, which was carried through to the next step without further purification.

In an oven-dried MW vial, to a solution of crude residue above in THF (6.5 mL, 0.025 M) was added $LiAlH_4$ (129 mg, 3.24 mmol, 20 equiv) at 0 °C. After 15 min the MW was capped and heated to 70 °C for 2 h. After the reaction was complete, cooled to 0 °C and diluted with Et_2O. Then water (0.2 mL), 15% NaOH solution (0.2 mL), water (0.6 mL) were added. Then the mixture was left to reach room temperature. Then the organics were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography (0–10% MeOH in CH_2Cl_2) to afford the product as a pale yellow oil. Product was then washed with 2 M HCl (20 mL) and organics were extracted with CH_2Cl_2 (2 × 20 mL). The aqueous phase was then basified with 2 M NaOH (25 mL) and organics were extracted with CH_2Cl_2 (2 × 20 mL). Then the organics were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure, to give a yellow amorphous oil (32.9 mg, 72%).

υ_{max} (film): 3343, 2926, 2855, 1609, 1460 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.31 (d, *J* = 7.2 Hz, 1H, 6), 7.00 (td, *J* = 7.6, 1.3 Hz, 1H, 2), 6.78 (td, *J* = 7.4, 1.0 Hz, 1H, 1), 6.64 (dd, *J* = 7.8, 0.8 Hz, 1H, 3), 3.23 (q, *J* = 8.4 Hz, 1H, 18'), 3.11 (ddt, *J* = 13.5, 4.0, 1.5 Hz, 1H, 16'), 3.08 (s, 1H, 13), 3.04 (td, *J* = 9.0, 3.7 Hz, 1H, 18''), 3.02 – 2.97 (m, 1H, 16''), 2.70 (ddd, *J* = 13.8, 8.4, 3.5 Hz, 1H, 19'), 2.24 – 2.14 (m, 2H, 10', 11'), 1.85 – 1.77 (m, 2H, 15', 21''), 1.73 (td, *J* = 12.2, 11.7, 5.7 Hz, 1H, 10'), 1.65 (dt, *J* = 13.9, 8.3 Hz, 1H, 19''), 1.52 – 1.49 (m, 1H, 14'), 1.40 (ddd, *J* = 12.6, 11.3, 6.8 Hz, 1H, 20'), 1.30 – 1.24 (m, 3H, 14'', 15'', 21'), 1.23 – 1.17 (m, 2H, 11'', 20''). Indoline proton not observed.

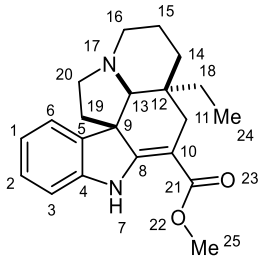
^{13}C NMR (101 MHz, $CDCl_3$): δ 150.1 (4), 140.2 (5), 126.8 (2), 122.3 (6), 119.9 (1), 110.9 (3), 69.1 (13), 64.6 (8), 57.1 (9), 50.8 (18), 47.9 (16), 36.1 (14), 35.2 (20), 34.8 (19), 31.5 (21), 31.5 (12), 29.3 (11), 26.6 (10), 17.2 (15).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{25}N_2$) requires *m/z* 281.2012, found *m/z* 281.2010.

Data in agreement with that reported in the literature.[123]

3.7.4.4. (±)-Vincadifformine synthesis

(±)-Vincadifformine



Two step synthesis: In an oven-dried flask, which was sealed and purged was added CH_2Cl_2 (2.9 mL). The mixture was then cooled to −78°C. Oxalyl chloride (37 µL, 0.43 mmol, 1.5 equiv) was then added and the reaction mixture was left to stir for 30 min. Subsequently, DMSO (83 µL, 1.16 mmol, 4 equiv) dissolved in CH_2Cl_2 (0.3 mL) was added and the reaction mixture was left to stir for another 30 min at −78°C. Then a solution of (±)-aspidospermidine (81.9 mg, 0.29 mmol, 1 equiv) in CH_2Cl_2 (2.6 mL, 0.05 M) was added dropwise to the reaction mixture and left to stir for 1 h at −78°C. Lastly, Et_3N (204 µL, 1.45 mmol, 5 equiv) was added slowly at −78°C, before the cooling bath was removed and the reaction mixture was left to reach ambient temperature over 1 h. After the reaction was complete, sat. aqueous $NaHCO_3$ (20 mL) was added and the organics were extracted CH_2Cl_2 (3 × 30 mL). The organics were then washed once with brine (20 mL). Then the organics were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure, to give a pale brown oil crude residue of dehydroaspidospermidine, which was carried through to the next step without further purification.

To an oven-dried MW, which was sealed and purged, was added a solution of the crude residue above in THF (2.9 mL, 0.1 M) under N_2 atmosphere. The mixture was then cooled to −78°C and *n*-butyl lithium (0.2 mL, 2.3 M in hexane, 0.46 mmol, 1.6 equiv) was added dropwise. The resulting mixture was stirred for 40 min at −78°C, before

methyl cyanoformate (37 µL, 0.46, 1.6 equiv) was added dropwise. The resulting mixture was stirred for 30 min at −78°C, and then allowed to warm to ambient temperature over 1 h. After the reaction was complete, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by chromatography (0–10% EtOAc in hexane) to afford the product as a colourless oil (14 mg, 14%).

υ_{max} (film): 3366, 2930, 2774, 1672, 1605, 1464, 1435, 1250, 1157, 1111 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.90 (s, 1H, 7), 7.19 (d, *J* = 7.4 Hz, 1H, 6), 7.12 (td, *J* = 7.7, 1.2 Hz, 1H, 2), 6.86 (td, *J* = 7.4, 1.0 Hz, 1H, 1), 6.79 (d, *J* = 7.7, 0.8 Hz, 1H, 3), 3.76 (s, 3H, 25), 3.15 – 3.10 (m, 1H, 20''), 2.92 (t, *J* = 7.4 Hz, 1H, 16''), 2.72 (d, *J* = 15.1 Hz, 1H, 11''), 2.59 – 2.53 (m, 1H, 16'), 2.45 (s, 1H, 13), 2.44 – 2.38 (m, 1H, 20'), 2.27 (dd, *J* = 15.1, 1.9 Hz, 1H, 11'), 2.09 – 2.01 (m, 1H, 19''), 1.89 – 1.78 (m, 2H, 14'', 15''), 1.70 (dd, *J* = 11.7, 4.6 Hz, 1H, 19'), 1.57 – 1.51 (m, 1H, 15'), 1.29 – 1.21 (m, 1H, 14'), 1.01 – 0.94 (m, 1H, 18''), 0.67 – 0.54 (m, 4H, 18', 24) (Spectra contains trace amount of EtOAc).

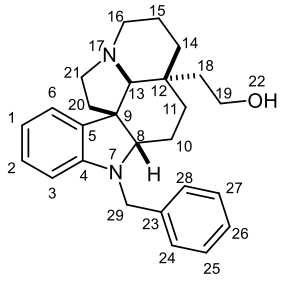
^{13}C NMR (126 MHz, $CDCl_3$): δ 169.3 (21), 167.9 (8), 143.4 (4), 138.1 (5), 127.6 (2), 121.2 (6), 120.7 (1), 109.4 (3), 92.7 (10), 72.8 (13), 55.6 (9), 51.9 (16), 51.2 (25), 50.8 (20), 45.3 (19), 38.2 (12), 33.0 (14), 29.5 (18), 25.7 (11), 22.3 (15), 7.2 (24).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{27}O_2N_2$) requires *m/z* 339.2067, found *m/z* 339.2057.

Data in agreement with that reported in the literature.[127]

3.7.4.5. Intermediates leading to (±)-limaspermidine

2-(6-Benzyl-2,3,4,5,5a,6,11,12-octahydro-1*H*-indolizino[8,1-cd]carbazol-3a(3a1*H*)-yl)ethan-1-ol (**18f**)



In an oven-dried MW vial, that has been sealed and purged, was added 6-benzyl-3a-vinyl-2,3,3a,3a^1,4,5,5a,6,11,12-decahydro-1*H*-indolizino[8,1-cd]carbazole **14f** (151 mg, 0.41 mmol, 1 equiv) dissolved in THF (3.4 mL, 0.08 M). The reaction mixture was then cooled to 0 °C. Then 9-BBN in THF (0.5M, 1.63 mL, 0.82 mmol, 2 equiv) was added slowly via syringe. Reaction mixture was then allowed to reaction room temperature, before being heated to 60 °C for 18 h. After the reaction was complete, reaction was cooled to 0 °C. After 15 min, H_2O_2 (30% w/v, 0.83 mL, 8.15 mmol, 20 equiv) and 2 M NaOH (0.82 mL, 1.63 mmol, 4 equiv) were added sequentially. Then reaction was left to reach room temperature and stirred for 1 h. After the reaction was complete, the mixture was quenched with sat. aqueous $Na_2S_2O_3$ at 0 °C until effervescence ceased and was subsequently diluted in saturated aqueous NH_4Cl (20 mL). Organics were extracted with EtOAc (3 × 20 mL), washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–30% EtOAc in hexane + 1% Et_3N additive) to afford the desired product as a beige solid (115 mg, 73%).

υ_{max} (film): 3337 (br), 2928, 2781, 2359, 1603, 1481, 1452, 1265 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.2 Hz, 2H, 24, 28), 7.32 (dd, *J* = 8.4, 6.8 Hz, 2H, 25, 27), 7.26 (dt, *J* = 14.5, 1.5 Hz, 1H, 26), 7.06 (dd, *J* = 7.3, 1.3 Hz, 1H, 6), 7.01 (td, *J* = 7.6, 1.3 Hz, 1H, 1), 6.66 (td, *J* = 7.4, 1.0 Hz, 1H, 2), 6.36 (d, *J* = 7.8 Hz, 1H, 3), 4.44 (d, *J* = 14.7 Hz, 1H, 29'), 4.08 (d, *J* = 14.7 Hz, 1H, 29''), 3.59 (td, *J* = 10.1, 5.5 Hz, 1H, 19''), 3.51 (td, *J* = 10.0, 6.2 Hz, 1H, 19'), 3.41 – 3.36 (m, 1H, 8), 3.07 (t, *J*

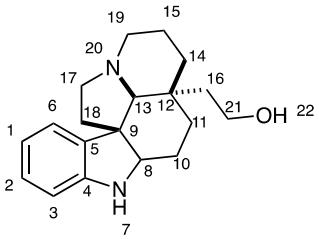
= 9.5 Hz, 1H, 21'), 3.00 (d, *J* = 10.8 Hz, 1H, 16''), 2.34 (q, *J* = 10.0 Hz, 1H, 20''), 2.29 – 2.19 (m, 2H, 13, 21''), 1.96 (t, *J* = 11.6 Hz, 1H, 16'), 1.88 (t, *J* = 13.7 Hz, 1H, 11''), 1.82 – 1.74 (m, 2H, 10', 18'), 1.74 – 1.66 (m, 1H, 15'), 1.62 (d, *J* = 13.7 Hz, 1H, 14'), 1.59 – 1.52 (m, 1H, 20'), 1.49 (d, *J* = 12.5 Hz, 1H, 15''), 1.38 (tdd, *J* = 14.0, 11.0, 3.6 Hz, 1H, 10''), 1.29 – 1.23 (m, 1H, 14''), 1.22 – 1.16 (m, 1H, 18''), 1.04 (d, *J* = 13.7 Hz, 1H, 11'). Alcohol proton not observed.

^{13}C NMR (176 MHz, $CDCl_3$): δ 150.0 (4), 138.6 (23), 136.4 (5), 128.6 (25, 27), 127.9 (24, 28), 127.5 (1), 127.2 (26), 122.4 (6), 117.6 (2), 106.9 (3), 70.8 (13), 68.8 (8), 58.7 (19), 53.8 (16), 52.9 (21), 52.6 (9), 48.5 (29), 40.7 (18), 38.9 (20), 35.5 (14), 35.4 (12), 24.3 (11), 22.6 (10), 21.8 (15).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{26}H_{33}ON_2$) requires *m/z* 389.2587, found *m/z* 389.2579.

Data in agreement with that reported in the literature.[150]

(±)-Limaspermidine



A round bottom flask was charged with 2-(6-benzyl-2,3,4,5,5a,6,11,12-octahydro-1*H*-indolizino[8,1-cd]carbazol-3a(3a1*H*)-yl)ethan-1-ol **18f** (115 mg, 0.3 mmol, 1 equiv) and Pearlman's catalyst ($Pd(OH)_2/C$, 20% wt on carbon) (384 mg, 0.55 mmol, 1.85 equiv). The flask was then sealed and purged with N_2. Then EtOH (9.9 mL, 0.03 M) was added to the flask and the reaction mixture was subsequently sparged with H_2, and the resulting suspension was stirred at room temperature for 24 h under H_2 atmosphere. After the reaction was complete, the mixture was filtered through a pad of Celite® and concentrated. The crude residue was purified by chromatography (silica gel, 0–100% EtOAc in Hexane + 1% Et_3N additive) to afford the product as a white solid (70.2 mg, 79%).

υ_{max} (film): 3310 (br), 2928, 1462, 1258, 1043, 741 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.08 (d, *J* = 7.4 Hz, 1H, 6), 7.01 (t, *J* = 7.6 Hz, 1H, 2), 6.73 (t, *J* = 7.4 Hz, 1H, 1), 6.63 (d, *J* = 7.7 Hz, 1H, 3), 3.62 (td, *J* = 10.1, 5.4 Hz, 1H, 21''), 3.52 (dp, *J* = 16.5, 6.1 Hz, 2H, 8, 21'), 3.11 (dt, *J* = 9.0, 5.5 Hz, 1H, 17''), 3.04 (d, *J* = 11.0 Hz, 1H, 19), 2.32 – 2.19 (m, 3H, 13, 17', 18''), 2.04 (td, *J* = 13.9, 3.4 Hz, 1H, 11''), 2.00 – 1.94 (m, 1H, 19), 1.75 (ddq, *J* = 18.2, 8.5, 5.3, 4.4 Hz, 2H, 15'', 16''), 1.72 – 1.67 (m, 1H, 10'), 1.64 (d, *J* = 13.7 Hz, 1H, 14'), 1.48 (dddd, *J* = 24.7, 17.5, 10.6, 3.8 Hz, 3H, 10'', 15', 18'), 1.26 (td, *J* = 13.5, 4.6 Hz, 1H, 14''), 1.18 (ddd, *J* = 14.6, 9.5, 5.7 Hz, 1H, 16'), 1.02 (dd, *J* = 13.2, 4.0 Hz, 1H, 11'). Alcohol and indoline protons not observed.

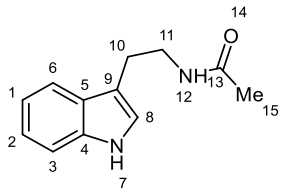
^{13}C NMR (176 MHz, $CDCl_3$): δ 149.6 (4), 135.4 (5), 127.5 (2), 122.9 (6), 119.3 (1), 110.6 (3), 70.9 (13), 65.5 (8), 58.7 (21), 53.9 (19), 53.6 (9), 53.0 (17), 40.6 (16), 38.7 (18), 35.6 (14), 35.5 (12), 28.3 (10), 24.4 (11), 21.8 (15).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{19}H_{27}N_2O$) requires *m/z* 299.2118, found *m/z* 299.2111.

Data in agreement with that reported in the literature.[124]

3.7.4.6. Additional Intermediates

N-(2-(1*H*-indol-3-yl)ethyl)acetamide (**19f**)



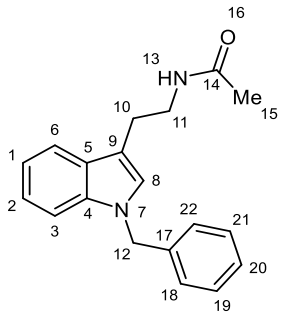
In an oven-dried flask was weighed in tryptamine (1 g, 1 equiv, 6.25 mmol). This was then dissolved in CH_2Cl_2 (20 mL, 0.3 M) before the addition of Et_3N (2 mL, 2.3 equiv, 14.4 mmol). The mixture was then cooled to 0 °C. Once cooled, AcCl (0.49 mL, 1.1 equiv, 6.86 mmol) was added dropwise over 2 min. Then reaction was left to reach room temperature and stirred for a further 23 h. After the reaction was complete, water (20 mL) was added and organics were extracted with CH_2Cl_2 (3 × 20 mL). The organics were then combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the product as a light brown oil (1.2 g, 95%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (s, 1H, 7), 7.59 (dd, *J* = 8.0, 1.1 Hz, 1H, 6), 7.37 (dd, *J* = 8.1, 1.0 Hz, 1H, 3), 7.20 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, 1), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, 2), 7.00 (d, *J* = 2.4 Hz, 1H, 8), 5.71 (s, 1H, 12), 3.58 (q, *J* = 6.5 Hz, 2H, 11), 3.02 – 2.89 (m, 2H, 10), 1.91 (s, 3H, 15).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4 (13), 136.5 (4), 127.4 (5), 122.3 (2), 122.2 (8), 119.5 (1), 118.7 (6), 112.8 (9), 111.5 (3), 40.0 (11), 25.3 (10), 23.4 (15).

Spectroscopic data were in agreement with literature values.[151]

N-(2-(1-benzyl-1*H*-indol-3-yl)ethyl)acetamide (**20f**)



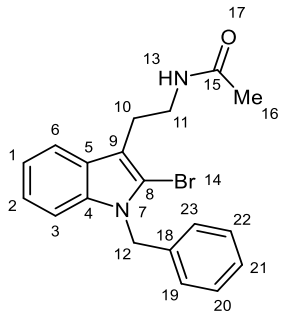
In an oven-dried flask *N*-(2-(1*H*-indol-3-yl)ethyl)acetamide **19f** (4.5 g, 22.2 mmol, 1 equiv) was weighed in and dissolved after in CH_2Cl_2 (111 mL, 0.2 M). Then TBAHS (378 mg, 1.11 mmol, 5 mol%), **crushed** NaOH (2.67 g, 66.7 mmol, 3 equiv), and BnBr (2.9 mL, 24.5 mmol, 1.1 equiv) were added. The resulting mixture was stirred at room temperature for 19 h. After the reaction was complete, the mixture was quenched with water (50 mL). Organics were then extracted with CH_2Cl_2 (3×50 mL) and separated before being washed with brine (50 mL). The organics were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, 0–80% EtOAc in petroleum ether 40–60°) to afford the product as pale yellow oil, which upon standing solidifies (4.58 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dt, *J* = 7.7, 1.0 Hz, 1H, 6), 7.34 – 7.25 (m, 4H, 18, 19, 20, 21), 7.20 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, 2), 7.17 – 7.08 (m, 3H, 1, 3, 20), 6.97 (d, *J* = 0.9 Hz, 1H, 8), 5.60 (s, 1H, 13), 5.28 (s, 2H, 12), 3.58 (td, *J* = 6.8, 5.7 Hz, 2H, 11), 2.98 (td, *J* = 6.8, 0.9 Hz, 2H, 10), 1.91 (s, 3H, 15).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.1 (14), 137.6 (17), 136.9 (4), 128.9 (19, 21), 128.1 (5), 127.8 (8), 126.9 (18, 22), 126.2 (20), 122.1 (2), 119.3 (1), 119.0 (6), 112.3 (9), 109.9 (3), 50.0 (12), 40.0 (11), 25.3 (10), 23.5 (15).

Spectroscopic data were in agreement with literature values.[152]

N-(2-(1-benzyl-2-bromo-1*H*-indol-3-yl)ethyl)acetamide (**21f**)



Prepared according to General Procedure A using *N*-(2-(1-benzyl-1*H*-indol-3-yl)ethyl)acetamide **20f** (584 mg, 2 mmol, 1 equiv), THF:$CHCl_3$ (1:1, 20 mL, 0.1 M) and Pyridinium tribromide (**not recrystallized**) (781 mg, 2 mmol, 1.1 equiv) at 0 °C. After 45 min, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–70% EtOAc in petroleum ether) to afford the desired product as a white solid (560 mg, 76%).

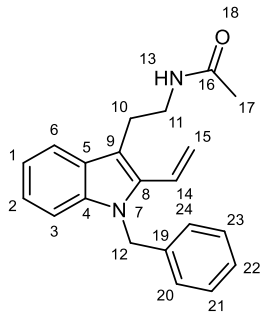
υ_{max} (film): 3285 (br), 3061, 2928, 1651, 1549, 1452, 1366, 1333, 1298, 1202, 739 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (dt, *J* = 7.8, 0.9 Hz, 1H, 6), 7.31 – 7.22 (m, 4H, 14, 15, 17, 18), 7.19 – 7.15 (m, 1H, 2), 7.13 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, 1), 7.10 – 7.04 (m, 2H, 3, 21), 5.49 (s, 1H, 13), 5.42 (s, 2H, 12), 3.56 (q, *J* = 6.4 Hz, 2H, 11), 3.02 (t, *J* = 6.6 Hz, 2H, 10), 1.91 (s, 3H, 16).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.2 (15), 137.2 (18), 136.8 (4), 128.9 (20, 22), 127.7 (21), 127.6 (5), 126.5 (19, 23), 122.5 (2), 120.3 (1), 118.3 (6), 113.7 (8), 112.5 (9), 110.1 (3), 48.5 (12), 39.6 (11), 25.5 (10), 23.6 (16).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{20}ON_2{}^{79}Br$) requires *m/z* 371.0754, found *m/z* 371.0744.

N-(2-(1-benzyl-2-vinyl-1*H*-indol-3-yl)ethyl)acetamide (**9f**)



Prepared according to General Procedure B using $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 4 mol%), SPhos (32.8 mg, 0.08 mmol, 8 mol%), *N*-(2-(1-benzyl-2-bromo-1*H*-indol-3-yl)ethyl)acetamide **21f** (371.2 mg, 1 mmol, 1 equiv), vinyl Bpin (169 mg, 1.1 mmol, 1.1 equiv), K_3PO_4 (636 mg, 3 mmol, 3 equiv), 1,4-dioxane (4 mL, 0.25 M) and H_2O (90 μL, 5 mmol, 5 equiv). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–60% EtOAc in petroleum ether 40–60°) to afford the desired product as a pale yellow solid (262 mg, 82%).

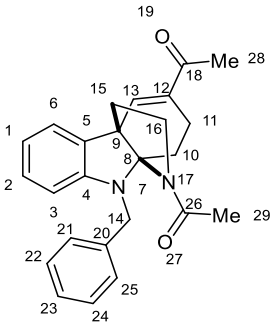
υ_{max} (film): 3285 (br), 3086, 2930, 1651, 1553, 1452, 1366, 1338, 1300, 1182 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 – 7.61 (m, 1H, 6), 7.32 – 7.22 (m, 4H, 20, 21, 23, 24), 7.21 – 7.17 (m, 1H, 1), 7.14 (ddd, *J* = 7.9, 6.7, 1.4 Hz, 1H, 2), 7.07 – 7.02 (m, 2H, 3, 22), 6.73 (dd, *J* = 17.9, 11.8 Hz, 1H, 14), 5.83 (s, 1H, 13), 5.57 (dd, *J* = 18.0, 1.2 Hz, 1H, 15), 5.45 (dd, *J* = 11.8, 1.2 Hz, 1H), 5.39 (s, 2H, 12), 3.57 (q, *J* = 6.7 Hz, 2H, 11), 3.12 (t, *J* = 7.0 Hz, 2H, 10), 1.92 (s, 3H, 17).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.3 (16), 137.9 (19), 137.4 (4), 135.1 (8), 128.8 (21, 23), 128.0 (5), 127.4 (14), 126.0 (20, 24), 125.6 (22), 122.7 (2), 119.9 (1), 118.9 (15), 118.8 (6), 111.6 (9), 109.8 (3), 47.4 (12), 40.3 (11), 24.9 (10), 23.4 (17).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{23}N_2O$) requires *m/z* 319.1805, found *m/z* 319.1798.

1,1'-(9-benzyl-7,8-dihydro-9*H*-8a,4b-(epiminoethano)carbazole-6,10-diyl)bis(ethan-1-one) (**4f3**)



Reactions were carried out according to General Procedure C using N-(2-(1-benzyl-2-vinyl-1H-indol-3-yl)ethyl)acetamide **9f** (79.5 mg, 0.25 mmol, 1 equiv), 3-butyn-2-one (98 µL, 1.25 mmol, 5 equiv), 1,4-dioxane (1 mL, 0.25 M) and BF_3OEt_2 (49 µL, 0.5 mmol, 1.6 equiv). Two 0.25 mmol scale reactions were performed in parallel. After the reaction was complete, the two reaction mixtures were combined and subjected to the purification method outlined in the General Procedure (silica gel, 0–20% EtOAc in CH_2Cl_2) to afford the product as a pale yellow solid (149 mg, 77%). Crystal growth was successful from CH_2Cl_2/Pentane *via* solvent diffusion.

υ_{max} (film): 3005, 2970, 2936, 2359, 1645, 1603, 1485, 1398, 1383, 1233, 1217 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (tt, *J* = 7.1, 1.0 Hz, 2H, 21, 25), 7.16 (qd, *J* = 6.6, 5.9, 3.2 Hz, 4H, 6, 22, 23, 24), 6.99 (td, *J* = 7.7, 1.3 Hz, 1H, 2), 6.83 (d, *J* = 1.5 Hz, 1H, 13), 6.71 (td, *J* = 7.4, 1.0 Hz, 1H, 1), 6.13 (d, *J* = 7.8 Hz, 1H, 3), 5.09 (d, *J* = 17.4 Hz, 1H, 14''), 4.75 (d, *J* = 17.4 Hz, 1H, 14'), 3.64 – 3.54 (m, 1H, 16'), 3.42 (td, *J* = 9.7, 6.4 Hz, 1H, 16''), 3.18 – 3.09 (m, 1H, 15'), 2.50 (ddd, *J* = 12.4, 6.4, 3.3 Hz, 1H, 10'), 2.35 – 2.25 (m, 3H, 11', 28), 2.24 – 2.15 (m, 3H, 10'', 11'', 15''), 1.99 (s, 3H, 29). One proton missing from CH_3 peak (C-28).

^{13}C NMR (126 MHz, $CDCl_3$): δ 198.7 (18), 170.6 (26), 149.0 (4), 139.1 (13), 139.1 (20), 138.1, 129.5 (5), 129.1 (2), 128.4 (21, 25), 126.4 (23), 126.3 (22, 24), 122.2 (3), 117.9 (1), 108.4 (6), 90.9 (8), 57.1 (9), 48.2 (16), 48.0 (14), 34.8 (10), 25.6 (28), 25.6 (15), 24.7 (29), 20.7 (11).

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{25}H_{26}O_2N_2Na$) requires *m/z* 409.1886, found *m/z* 409.1878.

3.7.5. X-ray Crystal data

X-ray diffraction data for compounds **4f3** and **2f** were collected at either 173 K (**4f4**) or 93 K (**2f**) using a Rigaku FR-X Ultrahigh Brilliance Microfocus RA generator/confocal optics with XtaLAB P200 diffractometer [Mo Kα radiation (λ = 0.71075 Å)]. Diffraction data for compound **4f4** were collected at173 K using a Rigaku MM-007HF High Brilliance RA generator/confocal optics with XtaLAB P100 diffractometer [Cu Kα radiation (λ = 1.54187 Å)]. Data for all compounds were collected using CrystalClear[108] and processed (including correction for Lorentz, polarization and absorption) using either CrystalClear[108] or CrysAlisPro.[153] Structures were solved by charge-flipping (Superflip[154]) or dual-space (SHELXT[110]) methods, and refined by full-matrix least-squares against F^2 (SHELXL-2018/3[111]). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model. All calculations were performed using the CrystalStructure[155] or Olex2[112] interface. Selected crystallographic data are presented in table 26.

Table 25: Selected crystallographic data for compounds 43f, 4f4 and 2f.

	4f3	**4f4**	**2f**
empirical formula	$C_{25}H_{26}N_2O_2$	$C_{28}H_{32}N_2O_3$	$C_{26.5}H_{28.75}N_{2.25}O_2$
fw	386.49	444.55	410.78
crystal description	Yellow prism	Colourless prism	Colourless prism
crystal size [mm^3]	0.14×0.09×0.02	0.08×0.07×0.05	0.10×0.05×0.05
space group	$P2_12_12$	$I2/a$	$P4/n$
a [Å]	9.7529(5)	18.5288(2)	20.161(3)
b [Å]	24.8852(11)	8.57002(10)	
c [Å]	8.2620(4)	30.0773(4)	10.6895(13)
α [°]			
β [°]		98.6665(12)	
γ [°]			
vol [Å]^3	2005.21(17)	4721.51(10)	4344.9(11)
Z	4	8	8
ρ (calc) [g/cm^3]	1.280	1.251	1.256
μ [mm^{-1}]	0.081	0.643	0.079
F(000)	824	1904	1756
reflections collected	26176	23893	23547
independent reflections (R_{int})	4524 (0.0677)	4286 (0.0366)	3953 (0.0268)
parameters, restraints	264, 0	303, 0	282, 0
GOF on F^2	1.036	1.048	1.074
R_1 [$I > 2\sigma(I)$]	0.0420	0.0388	0.0338
wR_2 (all data)	0.0876	0.1075	0.0870
largest diff. peak/hole [e/Å^3]	0.17, -0.18	0.25, -0.25	0.26, -0.22

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