Synthesis of Novel Polyfunctional 3D Scaffolds for Drug Discovery

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The candidate confirms that the work submitted is his own and that appropriate credit has been given where reference has been made to the work of others.

Acknowledgements

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Finally, I want to give a special thanks to my parents, family and all my friends for the unwavering support they have all given me throughout my PhD. I couldn't have got this far without you all!

Abstract

Lead-oriented synthesis (LOS) is a synthetic concept that aims to efficiently prepare libraries of diverse three-dimensional compounds that possess the ideal properties for biological screening. This thesis discusses the preparation of two libraries of structurally and shape diverse molecular scaffolds that can then undergo subsequent decoration and target lead-like chemical space. Additionally, a library of structurally diverse chemical probes was prepared through a highly efficient high throughput synthetic approach. Computational tools were used to then retrospectively analyse the scaffold libraries to determine their shape/structural diversity and their effectiveness to target lead-like chemical space.

Chapter 1 discusses the ideal properties that fragments, leads and drugs should ideally possess; the overall drug discovery process and examples of modern synthetic approaches for the preparation of fragment-like and lead-like screening compounds.

Chapter 2 discusses a bottom-up branching synthetic approach for the synthesis of 17 shape diverse molecular scaffolds. This approach involved the preparation of cyclisation precursors that contained several reaction handles within their core structure. A toolkit of cyclisation reaction was then developed to cyclise the reaction handles together and generate the final library of shape and structurally diverse molecular scaffolds that could be used to target lead-like chemical space.

Chapter 3 discusses a ‘stitching’ annulation strategy for the synthesis of 37 shape and structurally diverse molecular scaffolds. This approach involved *syn*-selective C-H arylation of cyclic/bicyclic amines to provide a set of arylated intermediates. A second toolkit of cyclisations was used to then generate a second library of diverse scaffolds.

Chapter 4 discusses a highly efficient high throughput approach for the preparation of 23 diverse chemical probes. Rhodium-catalysed carbenoid chemistry was used in a reaction array to provide the library of diverse chemical probes. Four of these chemical probes possessed low micromolar antiparasitic activity against *T. brucei*.

Chapter 5 compares the three synthetic approaches in terms of their efficiency, shape/structural diversity and the ability for the scaffolds to access lead-like space.

List of Abbreviations

δ	chemical shift
λ	wavelength
Ac	acetyl
ADS	activity directed synthesis
Ar	aryl
B/C/P	build-couple-pair
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
Bz	benzoyl
Cbz	carboxybenzyl
*c*logP	logarithm of the partition coefficient (fragment-based prediction)
CNS	central nervous system
COSY	correlation spectroscopy
CPBA	*m*-chloroperbenzoic acid
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet
Da	Daltons
DCM	dichloromethane
DEPT	distortionless enhancement through polarisation transfer
dr	diastereomeric ratio
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DOS	diversity-oriented synthesis
DPEPhos	bis[(2-diphenylphosphino)phenyl] ether

DPPA	diphenylphosphoryl azide
E	entgegen
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
e.g.	exempli gratia
EI	electron impact
ESI	electrospray ionisation
eq	equivalents
er	enantiomeric ratio
Et	ethyl
FBDD	fragment-based drug discovery
FDA	US Food and Drug Administration
Fsp^3	fraction of sp^3 hybridised carbons
GSK	GlaxoSmithKline
h	hours
HAC	heavy atom count
HMBC	heteronuclear multiple bond connectivity
HMDS	hexamethyldisilazane
HMQC	heteronuclear multiple quantum coherance
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence
HTS	high-throughput screening
Hz	hertz
i	*iso*
IR	infrared
J	coupling constant
LLAMA	lead-likeness and molecular analysis
LCMS	liquid chromatography mass spectrometry
LOS	lead-oriented synthesis

m	*meta*
m	milli
M	molar
mol%	mole percent
m.p.	melting point
Me	methyl
MIC	minimum inhibitory concentration
Ms	mesyl
min	minutes
mw	molecular weight
NBS	*N*-bromosuccinimide
NME	new molecular entities
NMR	nuclear magnetic resonance
No.	number
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ns	nitrophenysulfonyl
o	*ortho*
NR	no reaction
p	*para*
Ph	phenyl
PG	protecting group
PMI	principal moment of inertia
PMP	*para* methoxyphenyl
ppm	parts per million
Pr	propyl
py	pyridine, pyridyl
q	quartet
R	rectus
RCM	ring-closing metathesis

R_f	retention factor
RO5	rule of five
rt	room temperature
s	singlet
s	secondary
S	sinister
S. aureus	*Staphylococcus aureus*
S_N	nucleophilic substitution
t	time
t	triplet
t	*tert* (tertiary-)
T	temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
T. brucei	*Trypanosoma brucei brucei*
TBS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydroperoxide
TDG	transient directing group
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
TSA	toluenesulfonic acid
US	United States of America
vs	versus
wrt	with respect to
Z	zusammen

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1 Introduction

1.1 Challenges facing the pharmaceutical industry

It was revealed in 2010 that the pharmaceutical industry was the largest investor in UK research and development (£4.5 billion) as well as contributing a whole £17 billion to the country's exports.[1] However, the challenges that face this industry are numerous. A few examples of these include the ever increasingly expensive and lengthy procedures to prepare possible new drug molecules[2], the loss of income from expiring patents, a healthcare system that is becoming more cost constrained and tighter industry regulations.[3–5] A major challenge is that the cost of drug discovery and developing new drugs has increased rapidly each year, combined with the approximately 12-15 year process before any successful drug candidates can enter the market.[5,6] Perhaps one of the greatest challenges facing the industry in recent years is the high attrition rate of potential drug candidates in clinical trials, causing a major stumbling block for an efficient drug discovery development programme.[2] For all these reasons, it should be no surprise that increasing the efficiency in drug discovery has been identified as the major challenge for chemists to solve for the future.[2] The 96% attrition rate that is reported in the preliminary stages of drug discovery clinical trials has now been associated with poorly defined physical properties of the lead molecule, from which the drug candidates in the trial are derived.[2]

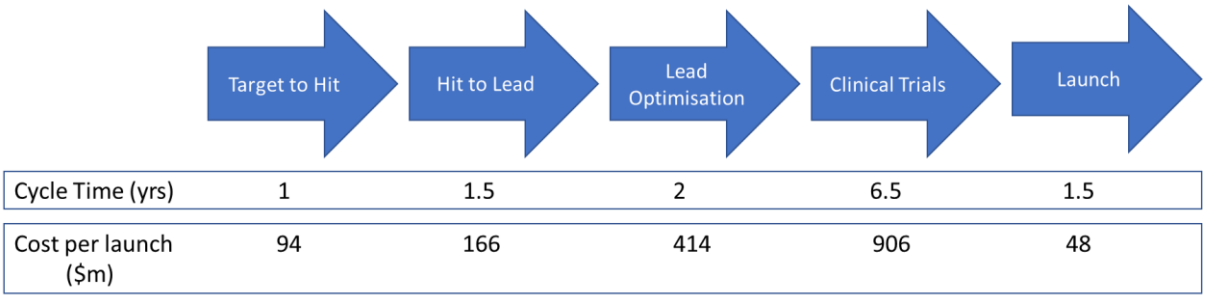
1.2 Overview of the Drug Discovery Process

The primary objective of the drug discovery process is to identify and develop new drug compounds that are safe, reliable, effective and meet the criteria for medical treatments where the drug is required.[7] The use of bioactive small molecules as drug candidates has been one of the main ways in which we currently treat diseases. As an example, in 2019 the US Food and Drug Administration (FDA) approved 48 new molecular entities (NME) and around 70% of these were small molecules.[8]

Figure 1 outlines the variety of stages within a typical drug discovery programme. Firstly, a target is identified that can be associated with the disease.[9,10] This target is usually a protein that is active in the pathway of the disease. Once identified, this can then be validated by a range of chemical and biological techniques.[7] For example, high-throughput screening (HTS) of a large and diverse chemical library can be performed to try and discover any compound that interacts with the desired target.[11] If one of the compounds in the library is found to interact by binding or inhibiting the target in any way this is called a "hit". A hit is a primary active compound with biological relevance to its target and is a small molecule with non-promiscuous binding behaviour, which exceeds a certain threshold value in a given assay.[12] From this, the most promising hits are then developed into "leads" through a process called "hit-to-lead" and is an early stage in the drug development process (Figure 1).[12] These leads can then be refined during a lead optimisation process which can improve the selectivity, potency and safety of the compound by improving the ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of the lead compound.[13] Further testing can also be undertaken to better understand and optimise the candidate's biological properties.[13] After this step is complete, the final compound is first subject to *in vivo* and *in vitro* cell based studies, in order to determine the biological mechanism of action towards the desired target.[14] Finally, the potential drug candidate can be taken forward in the development programme, where more safety, toxicology and metabolism studies are then conducted.[15] At this point the drug candidate must perform well in clinical trials to finally get the approval to enter the drug market.[7,16] Brown *et al.* have recently highlighted which strategies are most commonly employed to identify suitable drug candidates.[17] It was found that the most frequent lead generation strategy was to design drugs based on previously known compounds (43%) or through random HTS (29%).[17] An alternative method for small molecule drug discovery highlighted is to instead screen fragments (FBDD) and this is discussed further in Section 1.2.4.[17,18]

This entire process is very costly (~£1-2 billion for each drug including failed campaigns), time consuming and prone to failure due to the uncertainty in predicting toxicological and pharmacological effects in humans, as well as poor bioavailability, pharmacokinetic properties and other unforeseen consequences during trials.[2,19] The high attrition rates seen in phase II (66% of compounds) and phase III (33% of

compounds) of clinical trials also shows the need to improve the molecular properties of these screening compounds in order to try and increase the success rate at these stages of the drug discovery process.[2]



Cycle Time (yrs)	1	1.5	2	6.5	1.5
Cost per launch ($m)	94	166	414	906	48

Figure 1: The steps involved in a typical drug discovery programme including general timescales and costs associated with each step. Cost per launch includes the cost of any failed programmes. Image adapted from Paul *et al*.[2]

It is now understood that the highest chance of a small molecule drug candidate being successful is when its physicochemical properties lie within a certain range (Section 1.2.3).[19] Properties such as molecular weight and lipophilicity have been shown to have a significant effect on the drug's ability to progress through the discovery pipeline. Therefore, if these desired properties can be targeted at an early stage in the drug discovery process, then lead compounds can be developed without these undesirable, problematic properties which can improve the overall efficiency of drug discovery. It should be noted that monitoring the physicochemical properties of candidates in early phases of drug discovery may reduce the number of efficacy and safety related failures suffered.[20] Thus, any candidates that give unsuitable results can then be dropped from the programme at this stage, therefore helping to decrease the number of overall failures.[21] It has been shown during this analysis, that the pharmacokinetic properties of the candidates are intrinsic to the molecule, which means that these pharmacokinetic properties should also be optimised in the lead molecules to increase the chances of success at this stage of the drug discovery process.[22]

1.2.1 The role of synthesis in drug discovery programmes

During the preliminary stages of drug discovery, such as hit-to-lead and lead optimisation, the process is very much dependent on synthetic pathways where the compounds are delivered for high-throughput screening. The focus has recently been to develop and prepare small molecule libraries for the lead generation process, which are called arrays.[23] A study has shown however that of the many reactions used to prepare these arrays, around 80% of them fell into only five reaction classes.[24] These were amide formation, palladium-catalysed couplings, aromatic nucleophilic substitution, reductive aminations and protecting group chemistry.[24] It's also been highlighted that there has been only 2 new reactions that are routinely used within drug discovery added to the medicinal chemist's toolbox of reactions over the past four decades (Buchwald-Hartwig and Suzuki reactions), with no new reactions added in the last 10-20 years.[25] Additionally, most of the compounds prepared in medicinal chemistry have not been particularly shape diverse, with the majority of these compounds being shown to primarily lie in the 'flatland' area of chemical space.[26,27] Therefore, many of these compounds possess a low fraction of sp^3 hybridized carbons (Fsp^3) and generally only contain a small number of stereocentres within their structures. This can be an issue, as there is evidence to suggest that the introduction of more stereocentres in these compounds can lead to the lowering of attrition rates in drug candidates, therefore candidates with more stereocentres are beginning to become more desirable for drug discovery.[26,28] It has been highlighted that increasing the complexity of drug candidates by varying their chirality and shape can lead to a higher success for a compound's transition from the early stages of drug discovery all the way through clinical trials and eventually to market.[26,27] Saturated molecules have also been shown to have higher aqueous solubility and lower lipophilicity compared to their unsaturated counterparts, which are both very important physical properties in order for success in the drug discovery process.[26] The overall complexity and saturation of a 3D molecule can be assessed by evaluating the fraction of sp^3 hybridized carbons (Fsp^3) in the molecule, where more complex 3D compounds will generally have a higher Fsp^3 count. There have also been studies that have suggested more complex 3D compounds can have more desirable aqueous solubility than highly

sp^2-rich molecules, due to increased solvation and poorer solid state crystal lattice packing.[26,29,30]

Due to these reasons previously described and the limited toolkit routinely used by medicinal chemists, there only seems to be a small area of chemical space explored during drug discovery at the moment.[31,32] For example, 50% of all known compounds are based on only 0.25% of all the known small molecular scaffolds available at present.[32] Reymond *et al.* also enumerated the chemical universe of ring systems and they found that all current known structures only account for 1.4% of the possible chemically feasible ring systems.[33] The industry's focus on this small number of specific reaction types has allowed the generation of a high percentage of screening compounds that are sp^2-rich and have a fairly 2D molecular geometry (for example through biaryl couplings and amide bond formations).[34] This has now led to the realisation that a key aspect of improving drug discovery programmes is to increase the overall shape diversity of the compounds prepared and to enable a larger area of chemical space to be explored by medicinal chemists.

To illustrate the traditional focus of the pharmaceutical industry in the preparation of screening compounds, one can examine their 3D structure by using a normalised principal moment of inertia (PMI) plot. A PMI plot represents the 3D geometry of a compound using a 2D ternary plot. The three vertexes of the plot represent the three extremes in molecular geometry. The left-hand vertex is labelled as *rod-like* and describes the molecular geometry of compounds such as a sp-hybridised 2,4,6-octatriyne. The bottom vertex is labelled as *disk-like* and represents the molecular geometry of compounds such as benzene. Finally, the right-hand vertex is labelled *sphere-like* and is represented by adamantane to describe the molecular geometry of compounds in this section of the plot. Compounds can be plotted as a function of these three geometric extremes to allow for the assessment of their 3D shape.

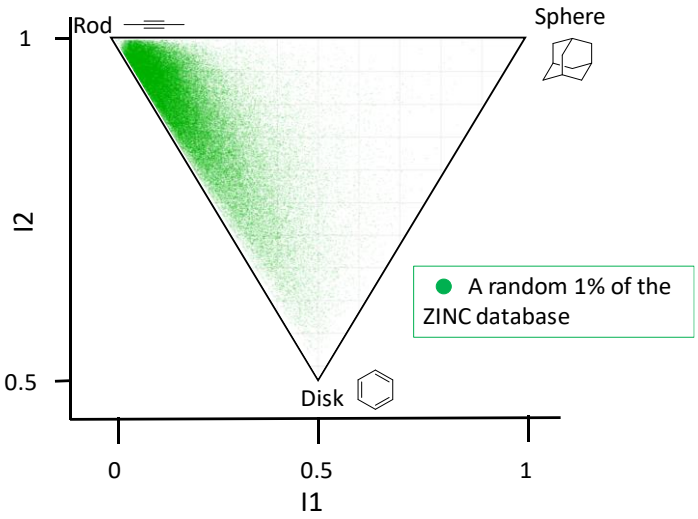


Figure 2: A PMI plot of 90911 virtual compounds as a 1% random sample taken from the ZINC database of commercially available compounds. The compounds, shown as green dots, are plotted as a function of their rod-like, disk-like and sphere like properties.[35]

Figure 2 above outlines a PMI plot that was produced for a random 1% (90911 compounds) of compounds from the ZINC database, showing the molecular shape of each of the compounds highlighted.[35] The ZINC database consists of commercially available compounds for virtual screening, where over 35 million compounds can be purchased.[36] This PMI plot provides evidence for the lack of 3D shape diversity in current screening libraries, therefore giving increased importance to produce molecular scaffolds with more 3D character and complexity to better explore 3D chemical space.

1.2.2 Characteristics of drug-like molecules

The properties of drug-like compounds can refer to the physical, absorption, toxicity and metabolic properties of a molecule.[37] Chemists have been wanting to develop some criteria for assessing how drug-like a compound is by looking at some of its physical and chemical properties, such as lipophilicity (logP), molecular weight and total polar surface area. In 1997, Lipinski released his “rule of five” paper that aimed to summarise compounds by these physiochemical properties to determine their drug

likeness and therefore attempt to increase their bioavailability.[21] These criteria also allowed chemists to target drug-like chemical space by giving a guide of properties that the compounds they synthesise should ideally possess.[21] These properties are summarised below in Table 1 along with the ideal values for corresponding lead-like (Section 1.2.3)[19] and fragment-like molecules (Section 1.2.4).[38]

Physicochemical Properties	Ideal value – Drug like	Ideal value – Lead like	Ideal value – Fragment like
Molecular Weight	≤500	250 ≤ Mw ≤ 350 Da	140 ≤ Mw ≤ 230 Da
Lipophilicity	≤5	-1 ≤ *c*logP ≤3	0 ≤ *c*logP ≤ 2
H-bond donors	≤5	≤3	≤3
H-bond acceptors	≤10	≤3	≤3

Table 1: The typical parameters for drug-like, lead-like and fragment-like compounds. Adapted from Lipinski *et al.*, Churcher *et al*. and Jhoti *et al.*[19,21,38]

Possibly the most important of these parameters is the logP value, which indicates the lipophilicity of the compound. The higher the logP value, the more lipophilic the compound is, meaning the less likely it will dissolve in aqueous environments. This can lead to several issues arising, such as problems with transport in the body.[39] It has also been found that there is a link between logP and problems associated with promiscuous and off target binding, which can increase toxicological effects and reduced the safety of the drug candidate.[39] The other parameters such as molecular weight and number of hydrogen bond donors/acceptors are also vitally important, but these characteristics seem to be correlated with logP. As previously described (Section 1.2.1), recently the discovery has been made that the three-dimensional shape of a compound can make a dramatic difference in the solubility properties that the compound may possess.[28] More specifically, it had been found that a higher fraction of sp^3-hybridised carbons (Fsp^3) contained in the compound can increase the solubility properties over flatter molecules around the same size. It has also been found that these compounds have higher success rates in clinical trials than their flatter counterparts.[26] Similar studies have also determined that having greater than three aromatic rings in the compound can increase the likelihood of failure.[28]

1.2.3 Characteristics of lead-like molecules

In order to design compounds to be in drug-like space, we must prepare a range of lead molecules that have properties which include having the lipophilicity and molecular weight at a lower value, so that when these leads are optimised into suitable drug-like compounds, they are able to have the correct physiochemical properties as previously described (Section 1.2.2).[22] This is because during optimisation the molecular weight, lipophilicity and molecular complexity of the compounds will increase, so the lead-like molecules prepared should allow for this shift in physiochemical properties during the optimisation process. Churcher *et al.* defined a lead-like region of chemical space as an area where compounds had the optimum properties, where any shift of physiochemical properties during drug optimisation would give compounds in Lipinski's area of drug-like chemical space (Figure 3).[19] Their definition of the properties that lead-like molecules should exhibit is summarised in Table 1.

Churcher e*t al.* found that after the complete analysis of almost 5 million commercially available compounds, 97.4% of these fail in at least one of the lead-likeness properties described in Table 1.[19] A similar study in 2010 performed by Shivanyuk and co-workers looked into the lead-likeness of a library of 7.9 million compounds, where a more relaxed definition of lead-like properties was used in this case ($200 < \text{molecular weight (Da)} < 460$, $-4 < c\log P < 4.2$, rotating bonds ≤ 10, polar surface area ≤ 170).[40] This study consisted of analysing these 7.9 million commercially available compounds from 29 suppliers, where 5.2 million structures in this library were identified as unique. These compounds were then subjected to assessments of their physical and biological properties where it was found that only 16% of them had potential to be leads under these broader lead-like parameters.[40] These studies argued that there is a need to provide more reliable and robust methodologies of synthesising diverse molecules that have lead-like properties. The diagram below (Figure 3) shows the steady increase in logP associated with the optimisation process from lead-like space to drug-like space. It is this increase in logP that makes the reliable synthesis of lead-like compounds an important attribute in the exploration of chemical space and drug discovery. Lead-oriented synthesis (LOS) is a concept to develop such methodologies to systematically prepare a diverse range of lead-like compounds to help solve the problem Churcher

et al. has reported and enable lead-like compounds to be reliably produced. This however is still a significant ongoing challenge in chemistry at present.[19] LOS is discussed in more detail in Section 1.3.2

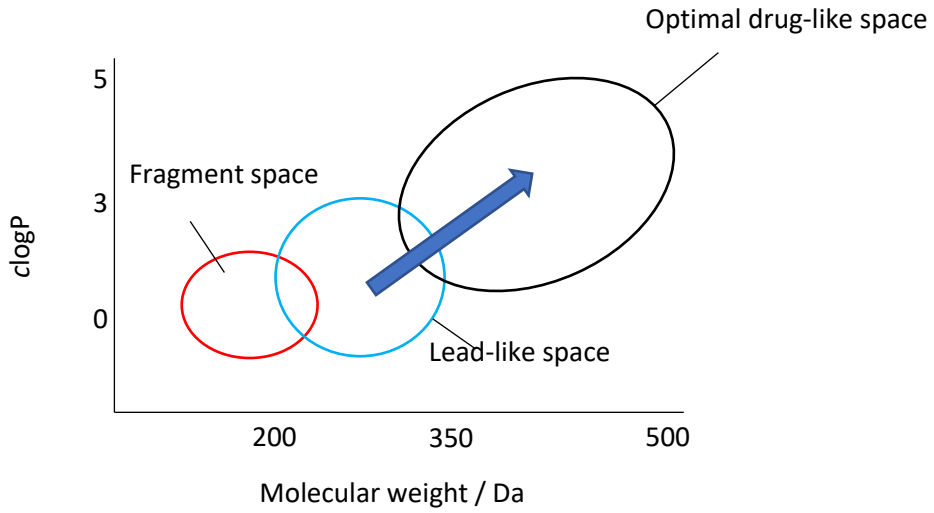


Figure 3: A diagram that shows the areas of fragment space, lead-like space and drug-like space. Adapted from Churcher *et al.*[19]

1.2.4 Fragment-based Drug Discovery (FBDD)

High-throughput screenings (HTS) have traditionally needed a large library of compounds to be synthesised and screened for suitable hits to be easily identified. This obviously can cause associated costs and time spent to increase dramatically before suitable compounds are identified as hits. A complementary method frequently used to find leads called Fragment-based drug discovery (FBDD) is now established as an alternative useful method within drug discovery programmes.[41] The major advantage of this method is the screening of a large range of small fragments, which represents a much higher proportion of the chemical space available in comparison to screening a library containing higher molecular weight molecules.[18] It has also been found that there tends to be more hits associated with these fragment screening programmes than with traditional HTS.[42] Therefore, a smaller library of compounds is needed to achieve the same amount of hits, leading to lower associated costs and a

smaller timescale of development.[41] A disadvantage of FBDD is that usually high quality structural data is required to determine the binding of the fragment to a target. This is normally achieved through the use of X-ray crystallography and NMR spectroscopy to determine binding.[41] Another potential drawback with this method is that the binding affinity for fragments is much lower than that for drug-like molecules. This means conventional HTS assays to determine activity cannot be applied when using FBDD. The solubility of fragments must also be very high as sometimes high concentrations of fragment is needed in order to detect weakly bound fragments to their target, which can limit the application of some compounds in the fragment library.[41]

Once a fragment hit has been correctly identified, it can be grown into a drug molecule by adding linkages to the fragment that enables binding to happen at other sites on the target, leading to a greater binding affinity.[43] Ligand efficiency (LE) is a useful support tool in the evaluation of fragments during FBDD. Ligand efficiency is the binding free energy of the molecule per atom in the fragment.[44] This value is an effective parameter to allow the comparison of binding efficiencies of compounds with different molecular weights. This is a more effective tool in FBDD than absolute potency due to the weaker binding affinities often observed with fragment screens. The first FDA approved drug discovered by FBDD was Vemurafenib (PLX4720) **1** which is a kinase inhibitor.[45] The initial fragment (shown in Figure 4) was identified by Tsai *et al.* after screening a library of over 20,000 fragments.[46] Derivatisation of this fragment led to the discovery of the drug molecule and was found to be active for B-Raf^{V600E} kinase, which is the most common oncogenic kinase.[46] An IC_{50} of 13 nM was determined for Vemurafenib **1** when targeting the B- Raf^{V600E} kinase.[46] It was also shown that Vemurafenib **1** had quite remarkable selectivity for the B- Raf^{V600E} kinase when screened against over 70 different kinases.[46]

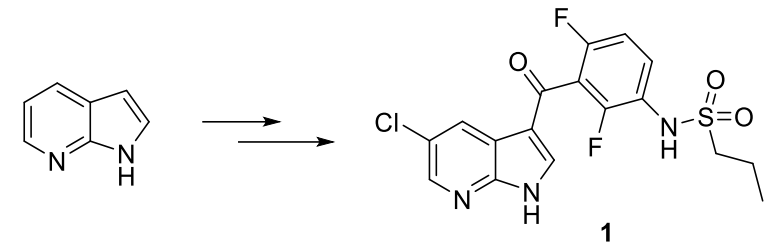


Figure 4: The initial fragment hit and the kinase inhibitor Vemurafenib (PLX4720) **1** this becomes after derivatisation. Adapted from Tsai *et al.*[46]

1.3 Synthesis of diverse screening libraries

As previously discussed, the ability to efficiently synthesise diverse libraries of compounds, that can also effectively explore large areas of chemical space, has been a well-known problem among chemists.[31] This problem is now being addressed with the development of a range of synthetic techniques to help more and more diverse libraries of lead/drug-like molecules to be prepared effectively. This should help ensure many more diverse screening libraries can be efficiently prepared in the future, therefore helping to improve the overall drug discovery process.

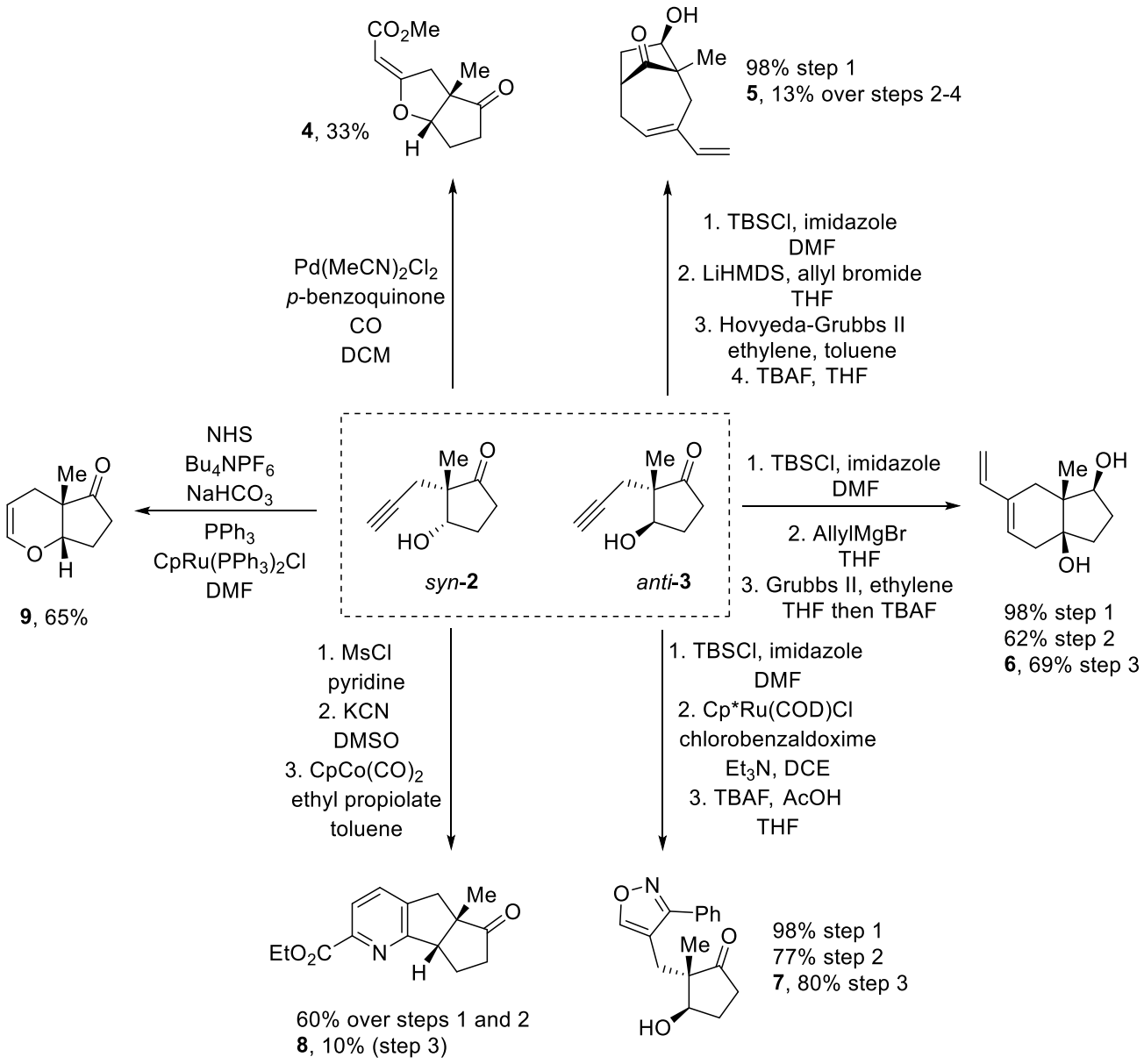
1.3.1 Synthesis of diverse screening libraries

Diversity-oriented synthesis is an approach that helps to prepare a diverse library of compounds that explore various regions of chemical space.[47] It leads to efficient preparation of diverse scaffold libraries, which can be arranged into the following diversity descriptors.[47,48] The first is appendage diversity where it is the substituents on the scaffold that are varied to increase the diversity. The second is stereochemical diversity which uses a range of stereochemical reactions to give the maximum number of possible stereoisomers. Finally, there is skeletal diversity which is where the scaffold of the small molecules is varied in each case. There are many different methods in DOS that allow skeletal diversity in scaffold libraries.[48] Three of these

approaches to explore chemical space with DOS are branching pathways, folding pathways and oligomer-based approaches. Build-couple-pair (B/C/P) is another well-established DOS approach, however B/C/P is a more generalised approach that can also be an intrinsic part of branching and folding DOS approaches.[49] The B/C/P approach first involves synthesising chiral building blocks that can then be coupled together to provide large stereochemical diversity. Finally, these coupled intermediates can then undergo intramolecular cyclisation which can then account for increased skeletal diversity of the final compounds.

1.3.1.1 Branching Pathways

The use of branching pathways is one of the more commonly used methods within DOS programmes. Branching pathways involve preparing a substrate that has many different reactive functional groups attached to it, and by using a reaction toolkit, these reaction handles can then be cyclised and made to react with each other in several ways to give a diverse range of scaffolds all from one substrate. Spring *et al.* recently reported the synthesis of a complex natural product inspired small molecule library where a DOS branching pathway was successfully utilised (Scheme 1).[50] This efficient and strategic synthetic strategy enabled the preparation of 38 complex small molecule fragments that were all based around two key building block intermediates.[50] These two intermediates **2** and **3** could be cyclised using a variety of reaction conditions to generate a library of novel, three-dimensional fragments that all incorporate numerous positions in their structure for further growth and fragment elaboration. The key intermediates were prepared *via* alkylation of commercially available substituted cyclopentadiones. Subsequent reduction with sodium borohydride gave the key common intermediates **2** and **3** as *syn*- and *anti*-diastereomers.[50] These common intermediate building blocks could then be elaborated and cyclised under a variety of reaction conditions to generate the final library of 38 novel, diverse 3D fragments (Scheme 1).

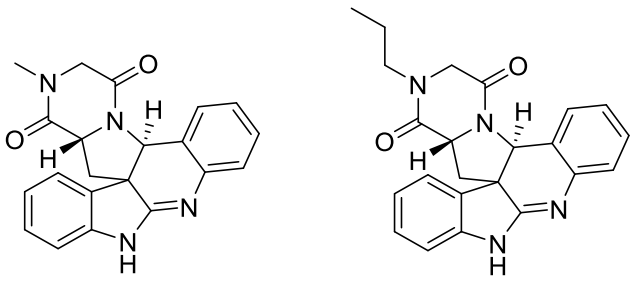


Scheme 1: The DOS branching synthetic strategy employed for the preparation of 38 natural product inspired fragments. A limited selection of reactions has been highlighted to demonstrate an overview for this synthetic approach. Adapted from Spring *et al.*[50]

Computational analysis of the final fragment library allowed for the assessment of the predicted physicochemical properties of the library as well as its shape diversity. This analysis found that the library adheres to the fragment 'rule of 3' guidelines as the mean molecular weight was calculated to be 208 Daltons (less than ideal value of 230 Daltons) and a logP calculated to be 1.37 (less than the ideal value of 3).[38,51] A PMI

plot was also generated to analyse the shape diversity of the fragment library. This PMI plot showed the fragments to be widely dispersed, with 92% of the library being outside of the ‘flatland’ zone where many fragments and screening compounds are traditionally found (Section 1.2.1).[26,50]

Sen *et al.* have also recently developed a DOS branching pathway in order to prepare a natural product inspired molecular library (Scheme 2).[52] They were able to use this DOS approach to successfully synthesise a library of 22 compounds based on the following natural products: perophoramidine, spirotryprostatin, harmicin and tryprostatin A and B. This was achieved by preparing a central tetrahydro-β-carboline core **12** *via* a Pictet-Spengler reaction between *R*-tryptophan and substituted *o*-nitrobenzaldehydes.[52] These could then undergo various different reactions to give the final library of natural product-like compounds (Scheme 2).[52] Phenotypic screening of this library found two molecules **10** and **11** that selectively inhibit MCF7 breast cancer cells with IC_{50} values of ~5 μM potency in both cases (Figure 5).[52]

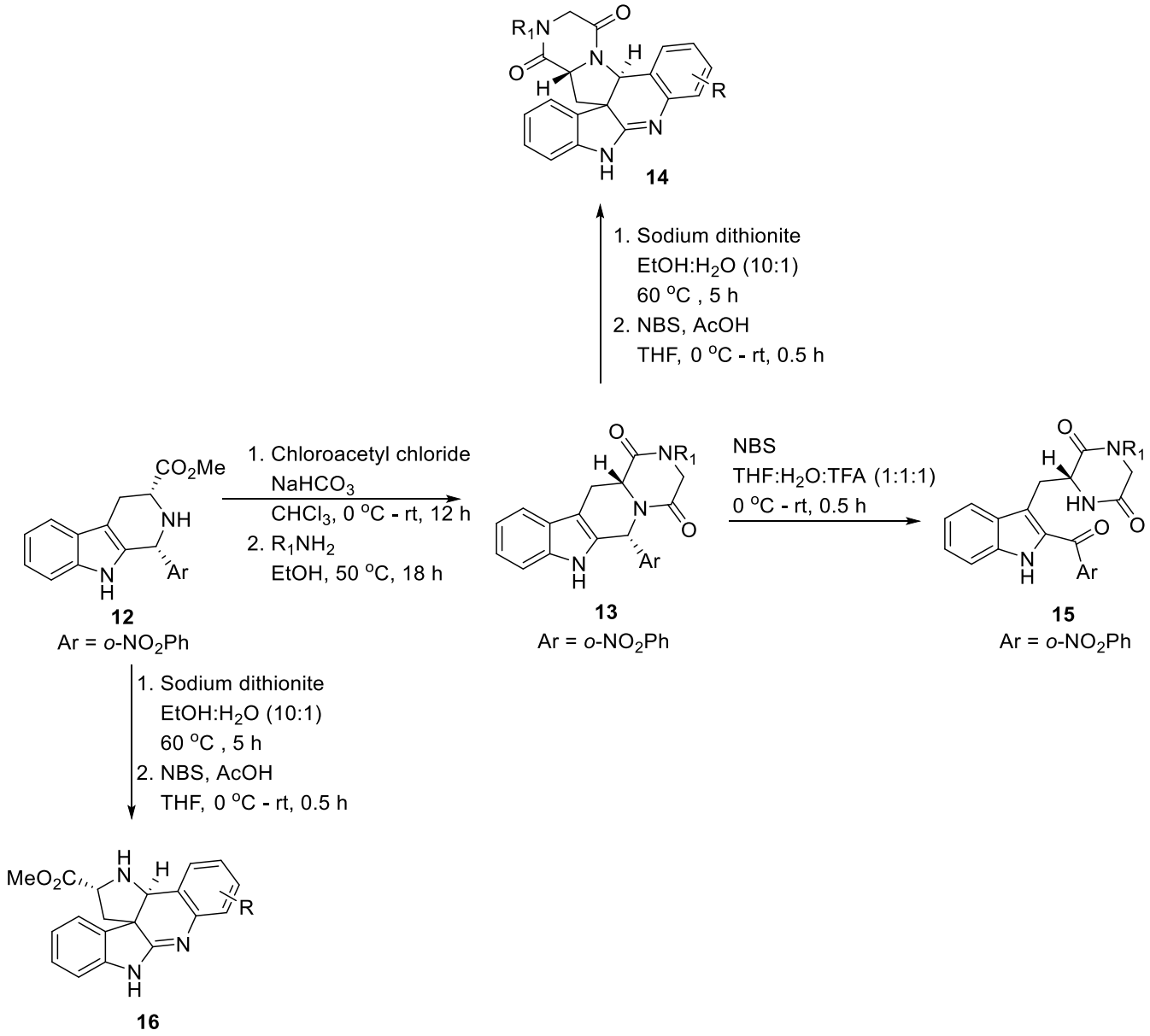


10
IC_{50} = 5.01 μM

11
IC_{50} = 5.33 μM

Figure 5: The compounds identified in the molecular natural product-like library that displayed bioactivity towards MCF7 breast cancer cells. Adapted from Sen *et al.*[52]

Sodium dithionite aryl nitro reduction of **12** and **13** followed by an intramolecular oxidative ring rearrangement mediated by NBS facilitated the preparation of scaffolds **14** and **16**. Finally an NBS-mediated ring opening of intermediate **13** gave the ring cleaved scaffold product **15** (Scheme 2).



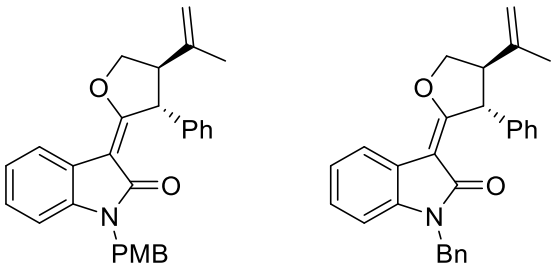
Scheme 2: The synthetic strategy employed to prepare a diverse library of natural product-like scaffolds using the branching diversity-oriented synthesis pathway. Adapted from Sen *et al.*[52]

Many other successful DOS branching pathway methodologies are reported throughout the literature. These include another report by Spring *et al.* who developed a branching pathway to efficiently prepare a range of structurally diverse scaffolds using diazo compounds as a starting material.[53] Other branching pathways reported include the use of *N*-allyl amino propargylic alcohols[54] and building blocks derived from the Petasis reaction.[55]

1.3.1.2 Folding Pathways

Folding pathways are different to branching pathways in DOS as diversity is ensured through changing the building blocks used rather than continually changing the reagent/reaction conditions.[56] For example, cyclic or acyclic starting materials could be used to increase diversity as well as changing the reactive functional groups or by changing the distances between each of them.

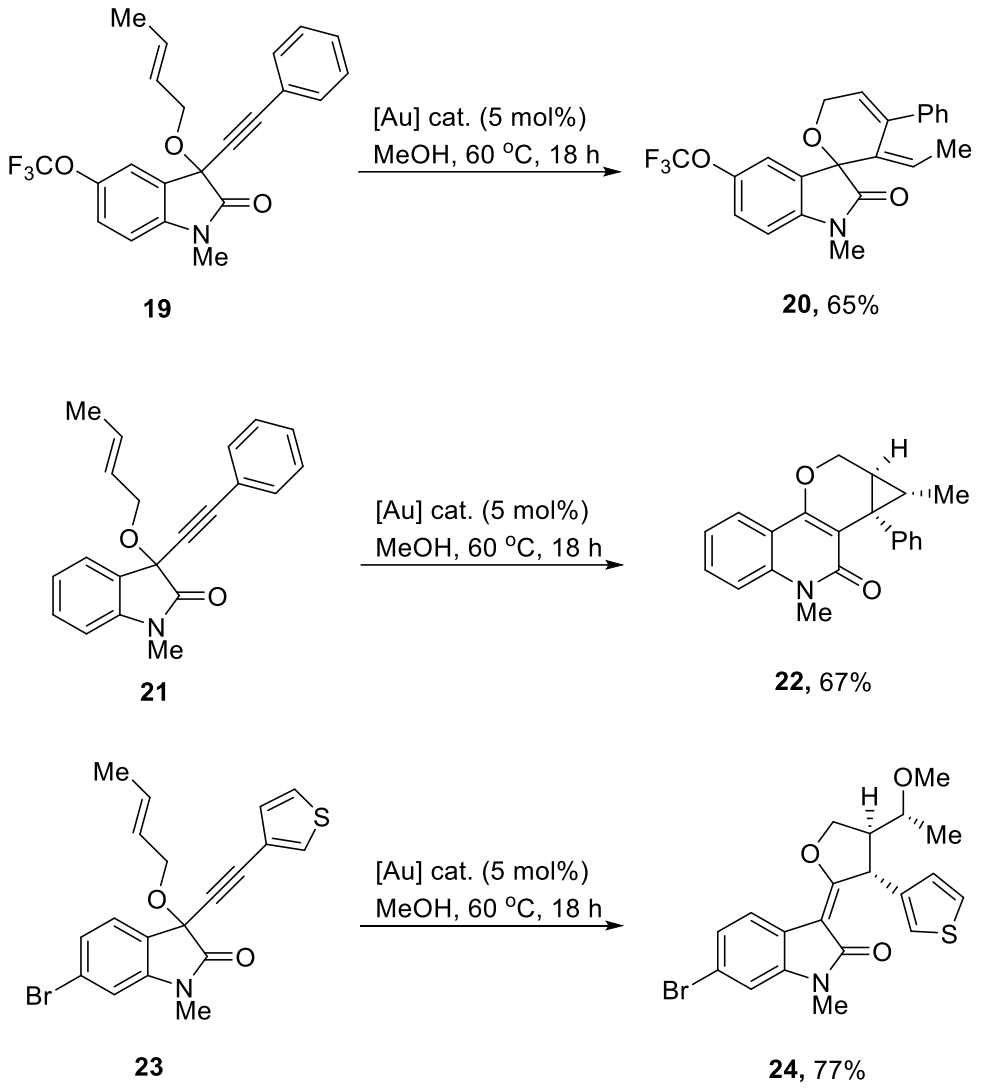
Waldmann *et al.* aimed to generate a skeletally diverse library of compounds by using gold(I)-mediated cycloisomerisation reactions of cyclisation precursor molecules (Scheme 3).[57] This catalytic divergent pathway enabled them to prepare a library of 36 compounds including spirooxindoles and quinolones.[57] This was achieved by preparing a selection of cyclisation precursor molecules that could then undergo gold(I)-mediated cyclisation.[57] The reaction conditions were optimised by varying the ligand used to allow optimisation of reaction conditions regardless of the starting material used. Exploration of any bioactivity in their compound library led to the discovery of structurally novel selective inhibitors of the Hh and Wnt signalling pathways.[57] Several of the oxindole compounds in the library showed IC_{50} values in the low micromolar range, with the two most potent compounds **17** and **18** highlighted below (Figure 6).



17
IC_{50} = 2.8 μM

18
IC_{50} = 3.1 μM

Figure 6: The compounds identified in the molecular library that displayed the most potent bioactivity towards inhibiting the Hh and Wnt signalling pathways. The ligand on the Au(I) catalyst was varied to allow optimisation of reaction conditions to give the diverse range of products observed. Adapted from Waldmann *et al.*[57]



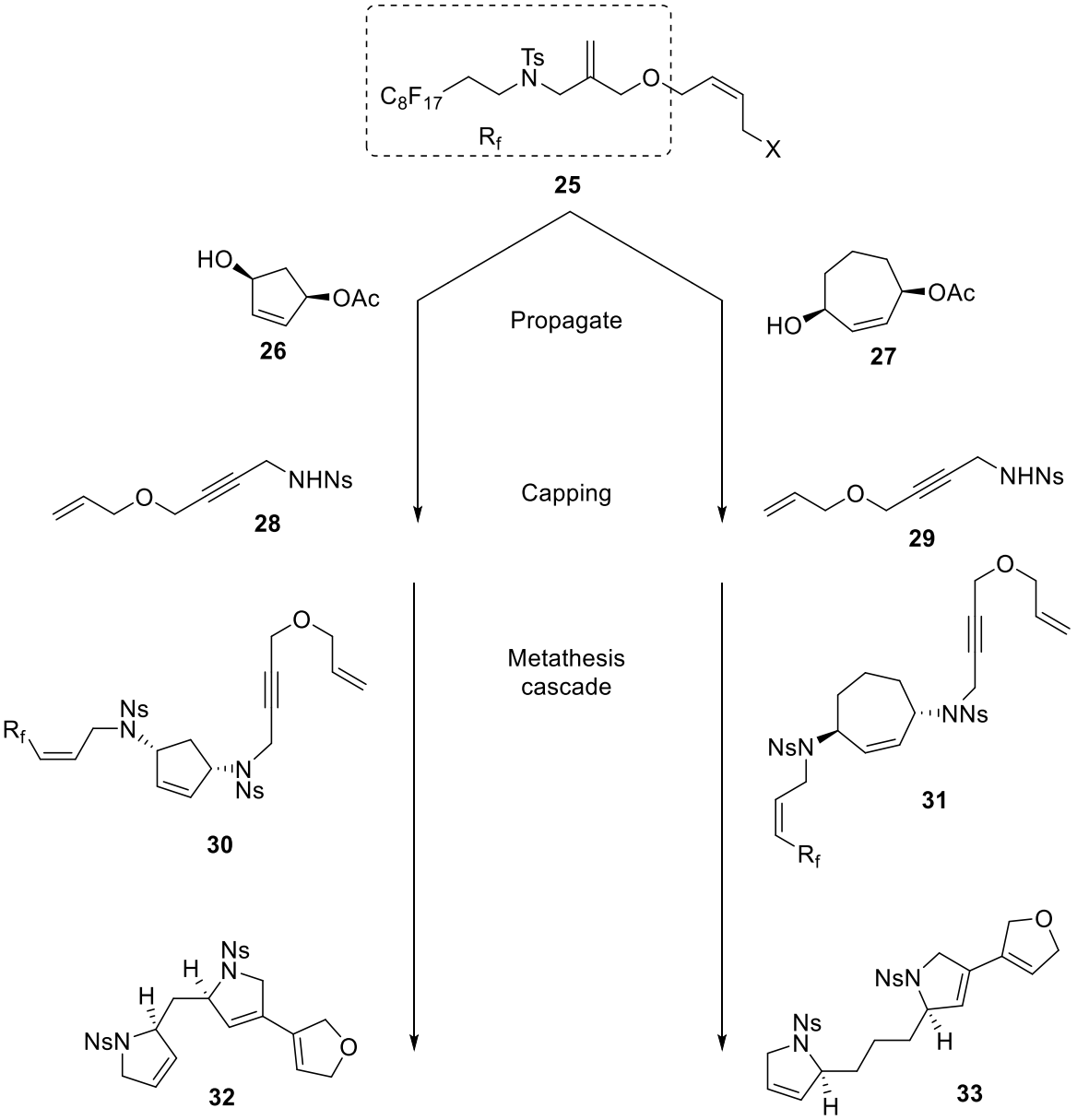
Scheme 3: Selected examples of the folding DOS pathway employed by Waldmann *et al.* Adapted from work done by Waldmann *et al.*[57]

There are other DOS folding pathways reported in the literature, which involve building blocks being cyclised by Rh(II) catalysed tandem cyclisation-cycloadditions[47], three-component coupling reactions[58] and ring closing metathesis cascade chemistry.[59] A recent example by Chen *et al.* demonstrated a folding DOS approach by employing a one-pot Groebke–Blackburn–Bienaymé multicomponent reaction to generate a library of 15 fused ring imidazopyridine scaffolds, where one of these scaffolds was shown to possess low micromolar activity towards human prostate cancer cell DU-145 proliferation.[60]

1.3.1.3 Oligomer-based approaches

An oligomer-based approach attempts to combine elements from both folding and branching pathways so that diverse scaffold libraries can be efficiently generated. The starting material in this approach is usually bound on to a tag or polymeric support and immobilised. At this point the substrate undergoes coupling reactions to increase the size and complexity of the bound species. Then the substrate can be released from its bound support, where many cyclisations can occur between reactive groups on the substrate. This in turn leads to a diverse library of products.

This type of synthetic strategy has been used by the Nelson group to create diverse scaffold libraries with remarkable success (Scheme 4).[61] By using various oligomer bound starting materials, they were able to add a variety of building blocks *via* propagation and capping steps. These diverse intermediate oligomers could then undergo alkene metathesis upon cyclisation of the intermediates, followed by cleavage from the oligomer tag, giving the diverse library of cyclised compounds. The Nelson group found that after varying the position of the alkene bonds in the substrate, it was possible to generate 84 molecular scaffolds with various ring sizes and diversity, where 65% were found to be novel scaffolds.[61] This clearly demonstrated that oligomer-based approaches in DOS could be used to systematically explore chemical space as intended.



Scheme 4: An example of the oligomer-based approach in DOS where the initial substrate is bound to a fluorous linker and extended before its release. R_f = Fluorous tag. Adapted from work by Nelson *et al.*[61]

An advantage of this method is the use of the fluorous tag (R_f) as this linker allows quick purification of any intermediate and final compounds *via* simple fluorous solid-phase extraction.[61] A major challenge in DOS is finding and developing reaction toolkits that tolerate a variety of functional groups.[62] Since ideally this should be achieved in as few steps as possible, the use of protecting groups is avoided wherever possible.

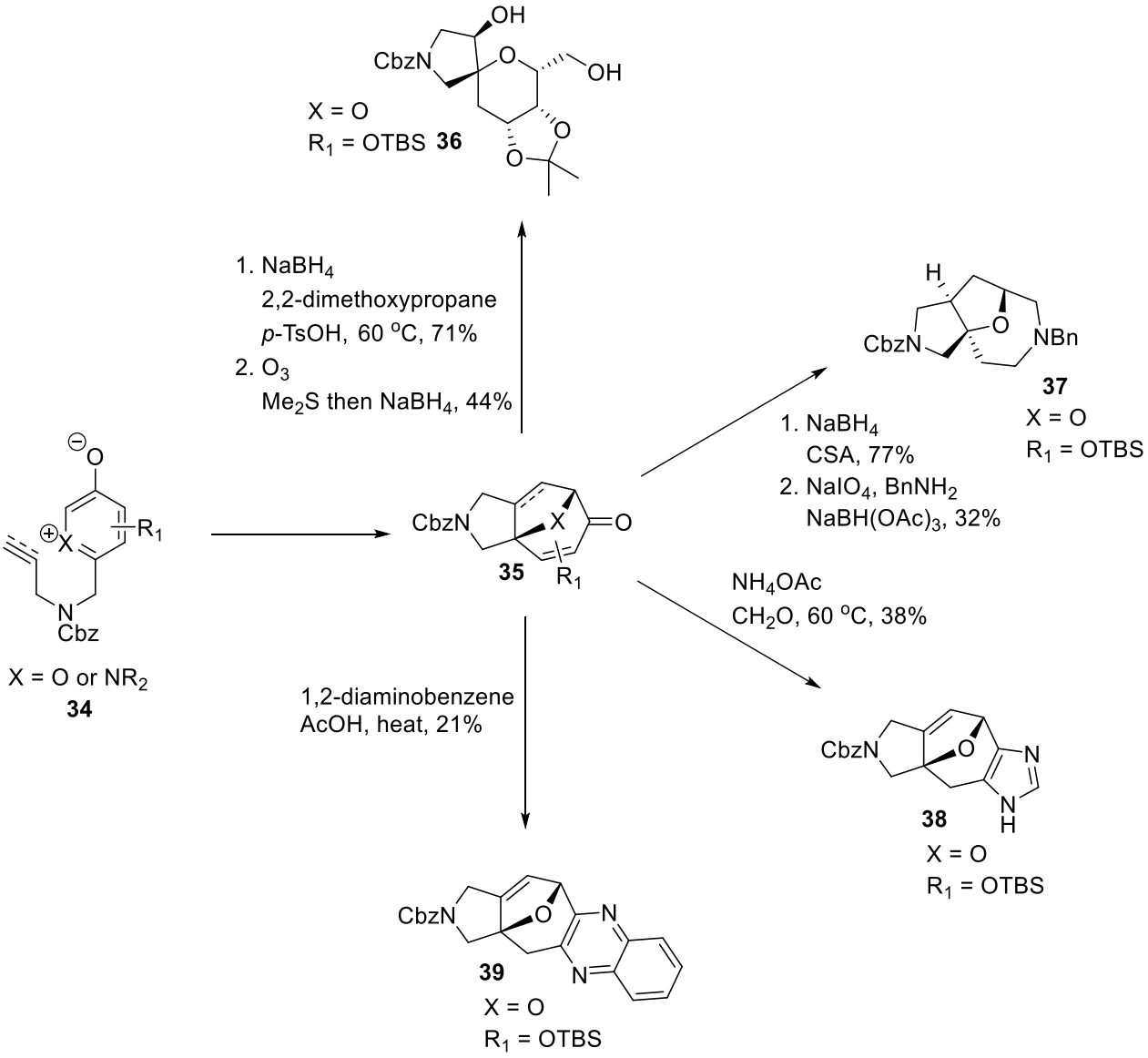
1.3.2 Lead-oriented Synthesis (LOS)

The concept of Lead-oriented synthesis (LOS) was developed to try and increase the number of synthetic methodologies to prepare diverse compounds which lie in lead-like chemical space (Section 1.2.3). Importance was placed on the synthetic efficiency, compatibility with polar functional groups and trying to avoid undesirable logP values in the compounds prepared.[19] LOS can be evaluated by the diversity of the compounds prepared and molecular properties of the relevant derivative compounds. The help of readily available computational tools can also allow many synthetic approaches to be evaluated and prioritised to ensure the compound library stays in lead-like chemical space as intended. Computational software such as LLAMA (Lead-Likeness And Molecular Analysis) can be freely accessed and used to monitor the lead-like synthesis of compound libraries to better ensure the compounds within these libraries can be used to effectively target lead like space as designed.[63] The LOS strategies to be discussed includes both “top-down” and “bottom-up” approaches for the preparation of diverse scaffold libraries that lend themselves to diversification by capping groups to give lead-like screening compounds.

1.3.2.1 Lead-oriented synthesis – The “top-down” approach

Work recently undertaken as a collaboration between the Marsden and Nelson groups includes the development of a “top-down” LOS strategy that was successfully able to prepare a library of 26 diverse sp^3-rich natural product-like scaffolds (Scheme 5).[64] This was achieved by initially preparing bridged scaffold intermediates using intramolecular [5 + 2] cyclisation reactions. These bridged intermediates **35** were then able to be transformed into the corresponding scaffolds *via* a toolkit of reactions. These included ring cleavage, ring expansion, annulation and functional group modification reactions, yielding the diverse sp^3-rich scaffold library.[64] It was found that the ring cleavage pathway was the most challenging pathway to obtain final scaffolds with just three scaffolds being successful prepared using this approach. This compares with the ring expansion and annulation-based approaches which yielded a total of seven final scaffolds, with the rest of the scaffolds resulting from functional group modification. This approach contrasts with DOS strategies in which building blocks are

synthesised and reacted together to give intermediate compounds that can then be cyclised to yield alternative scaffolds. The work undertaken was able to efficiently synthesise a variety of sp^3-rich diverse scaffolds with good diastereoselectivity in most cases, including spirocycles and scaffolds containing bridged linkages. The branching nature of this approach also enabled the high numbers of diverse scaffolds to be prepared in the most efficient and least time-consuming manner possible.



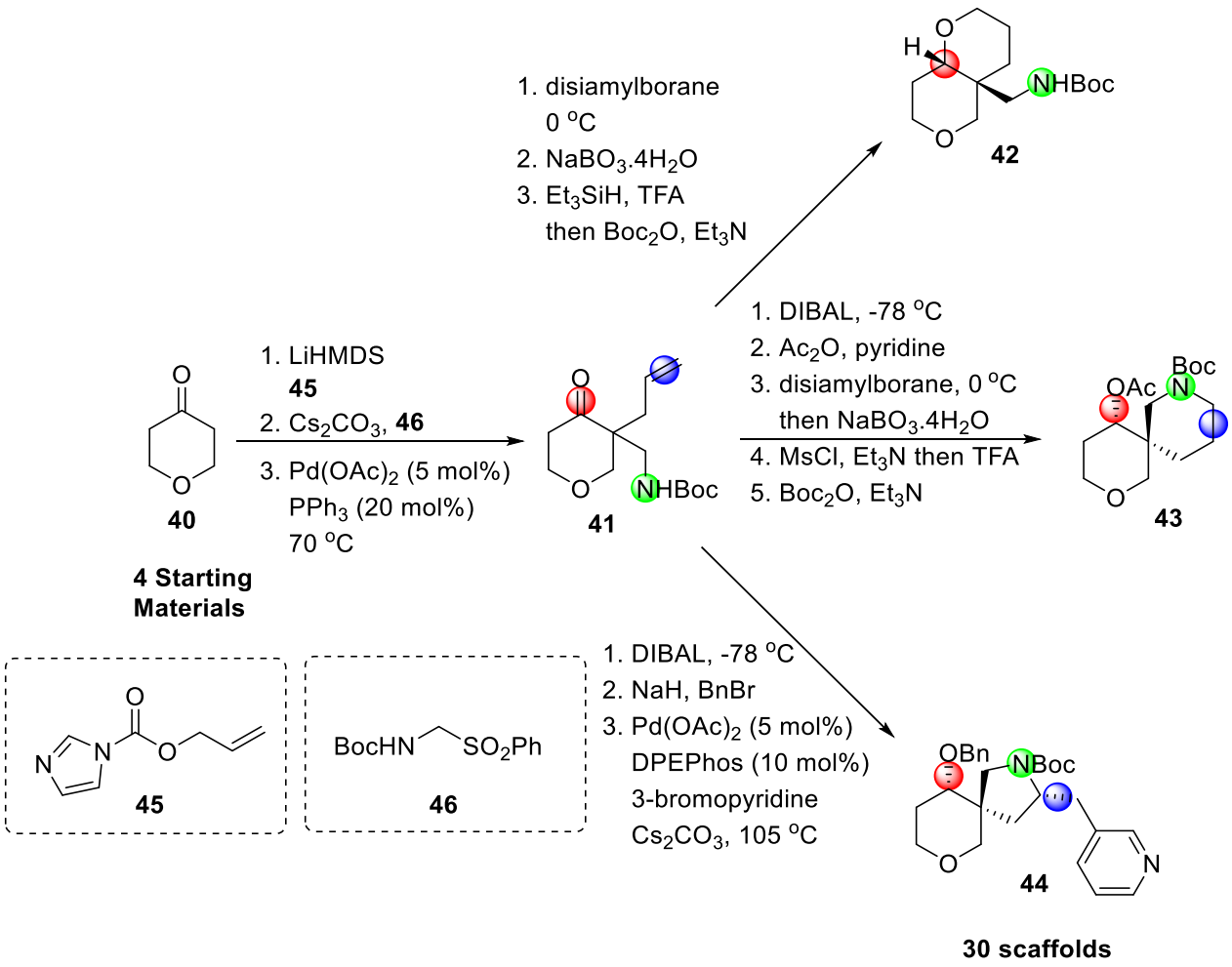
Scheme 5: Overview of the "top-down" LOS approach to generate a library of 26 natural product-like scaffolds that lie in lead-like chemical space. Adapted from work done by Marsden and Nelson *et al.*[64]

To begin the assessment of any biological relevance, a fragment library was prepared based around the final scaffolds made *via* this LOS synthetic approach with contained 52 racemic fragments based on 23 of the scaffolds.[64] This gave a highly shape diverse fragment set that had good exploration of chemical space. This library was screened against three different protein targets (ATAD2, BRD1 and JMJD2D) which wave been shown to have biological relevance with different cancers including leukaemia.[65,66] From this screen, 17 initial hits were identified across all three protein targets, which demonstrated that the natural product related frameworks in the final scaffold library prepared can allow for new biologically relevant chemical space to be realised.[64]

1.3.2.2 Lead-oriented Synthesis – The "bottom-up" approach

A "bottom-up" approach in LOS involves the preparation of small building blocks that can be joined together, built up and then cyclised to give the corresponding scaffolds. This approach combined both the build-couple-pair (Section 1.3.1) and branching pathway approaches (Section 1.3.1.1) by first preparing a common intermediate containing various functional group handles that can then undergo cyclisation leading to the library of final products. An excellent example of a bottom-up approach in LOS was recently reported by the Nelson group where they were able to successfully prepare a diverse library of 30 scaffolds that were suitable for CNS drug discovery.[67] This was achieved by preparing cyclisation precursor compounds containing 3-4 different reaction handles that could then be cyclised, using a robust reaction toolkit that they had developed in the process, to generate the final compound library.[67]

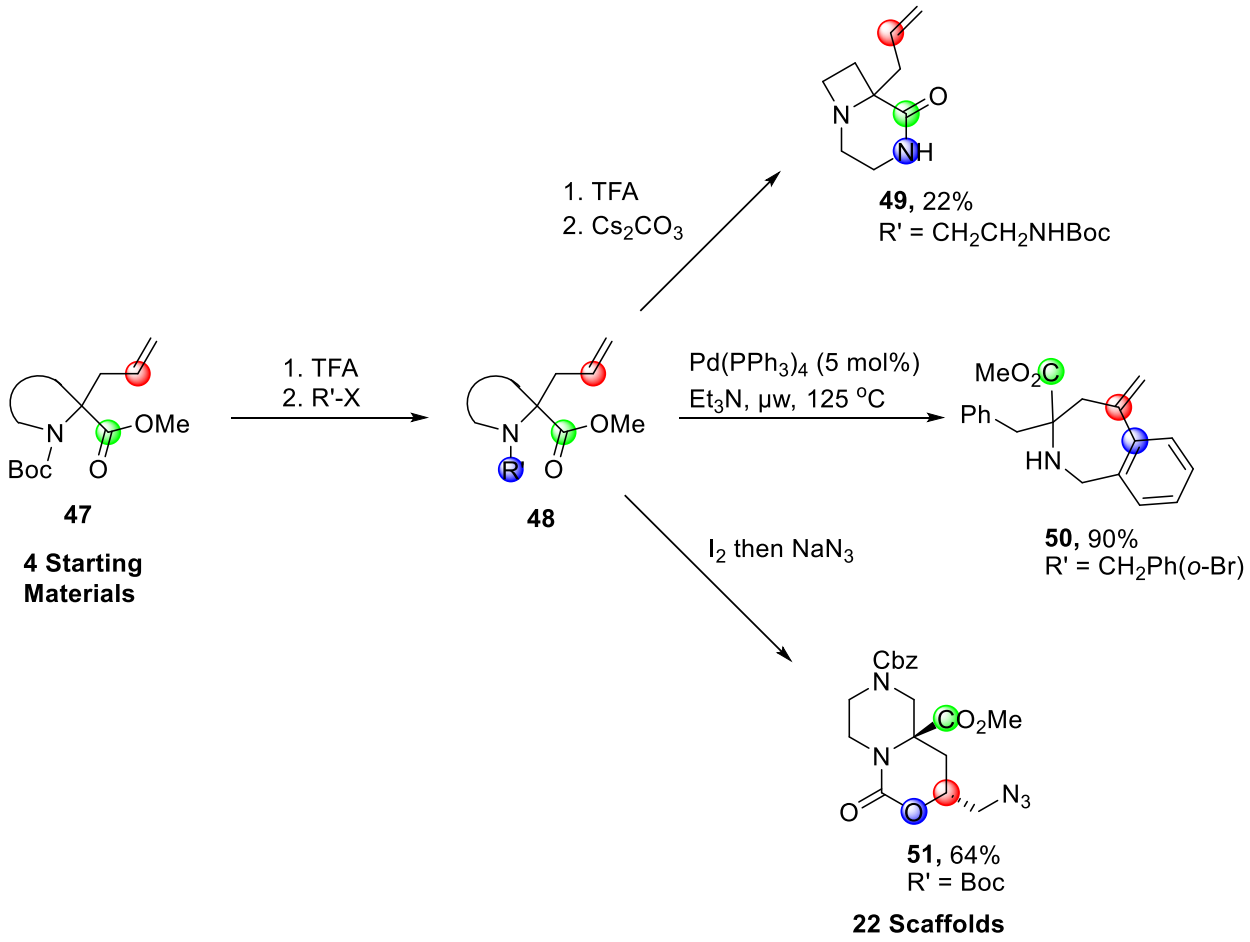
The cyclisation precursor compounds were prepared *via* the reaction of a lithium enolate **40** with a carbonyl imidazole species **45** to give the corresponding ketoester. The reaction of this species with an α-NHBoc sulfone, followed by palladium-catalysed decarboxylative allylation gave the desired cyclisation precursor **41** with good yields reported in each step (Scheme 6).[67] From these precursor compounds prepared, a variety of diverse scaffolds could then be synthesised. The scaffold diversity included fused, bridged and spirocyclic ring systems and all could be prepared from just one of the precursor compounds.[67] A selection of final scaffolds from this diverse library that was generated from this synthetic strategy is outlined below (Scheme 6).



Scheme 6: Overview of the range of scaffolds that were prepared *via* this "bottom-up" LOS approach. Adapted from work done by Nelson *et al.*[67]

Another bottom up approach developed within the Nelson and Marsden groups involved the preparation of small α-amino acid-derived polyfunctionalised cyclisation precursors that were then used to generate a library of 22 diverse lead-like scaffolds (Scheme 7).[68] These polyfunctional precursors were subject to a toolkit of 6 connective cyclisation reactions which allowed the preparation of 22 diverse 3D scaffolds in a short number of synthetic steps. This diverse scaffold library was analysed using LLAMA by decorating the final scaffolds to generate a virtual compound library to check whether these final scaffolds could target lead-like chemical space as required.[63,68] This analysis indicated that the virtual library did indeed target the broad regions of lead-like space (c.f. Table 1) and followed the rules for lead-likeness as 66% of this virtual library conformed to these set rules. This compares to the ZINC database, where only 23% of the 9 million compounds conform to the area of lead-like

space, with most compounds lying well outside of this area of lead-like chemical space. The shape diversity and scaffold novelty were also analysed, and it was confirmed that the final scaffold library was shape diverse and novel as designed.



Scheme 7: Overview of the bottom-up synthetic approach employed to generate 22 diverse lead-like scaffolds from only 4 α-amino acid-derived starting materials. Adapted from work done by Marsden and Nelson *et al.*[68]

Other bottom-up LOS approaches reported in the literature include work by Ryabukhin and co-workers in 2014, where they were successfully able to synthesise a library of 132 diverse lead-like scaffolds using a one-pot Castagnoli condensation reaction in good yield and with high diasteroselectivity.[69] Another example includes the use of a LOS folding pathway by Dixon *et al.* where they utilised a nitro-Mannich-lactamisation cascade to prepare diverse pyrrolidinones.[70]

1.4 Project aims and outlines

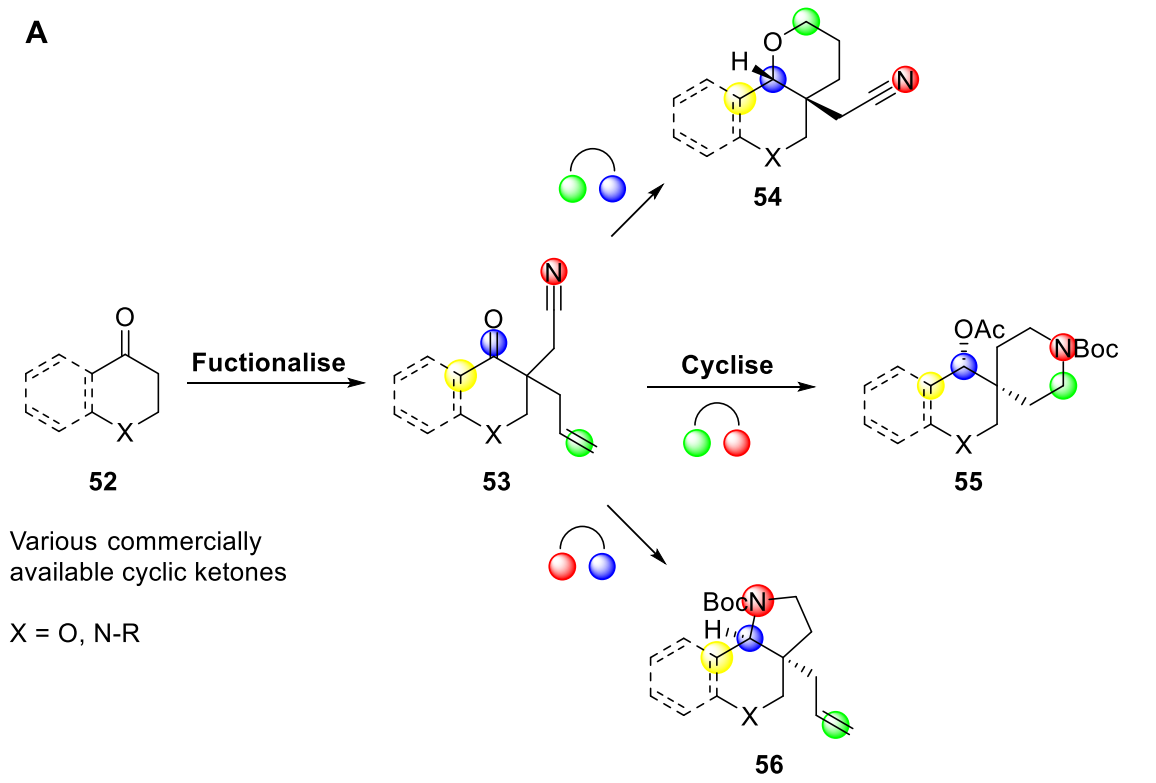
The overall aim of this project is to develop multiple unified synthetic approaches for the efficient preparation of sp^3-rich diverse scaffold libraries that upon decoration, can generate numerous compounds that can target lead-like chemical space. To achieve this goal, bottom-up synthetic approaches will be designed and employed, which encompass both B/C/P and branching strategies, in order to generate different libraries of novel, highly three-dimensional scaffolds to effectively target lead-like chemical space. Finally, a high throughput connective synthetic approach will be used to prepare a library of diverse chemical probes. This high throughput approach can then be compared to the previous bottom-up synthetic approaches in terms of efficiency and structural/shape diversity. There are five main objectives within this project to achieve these goals:

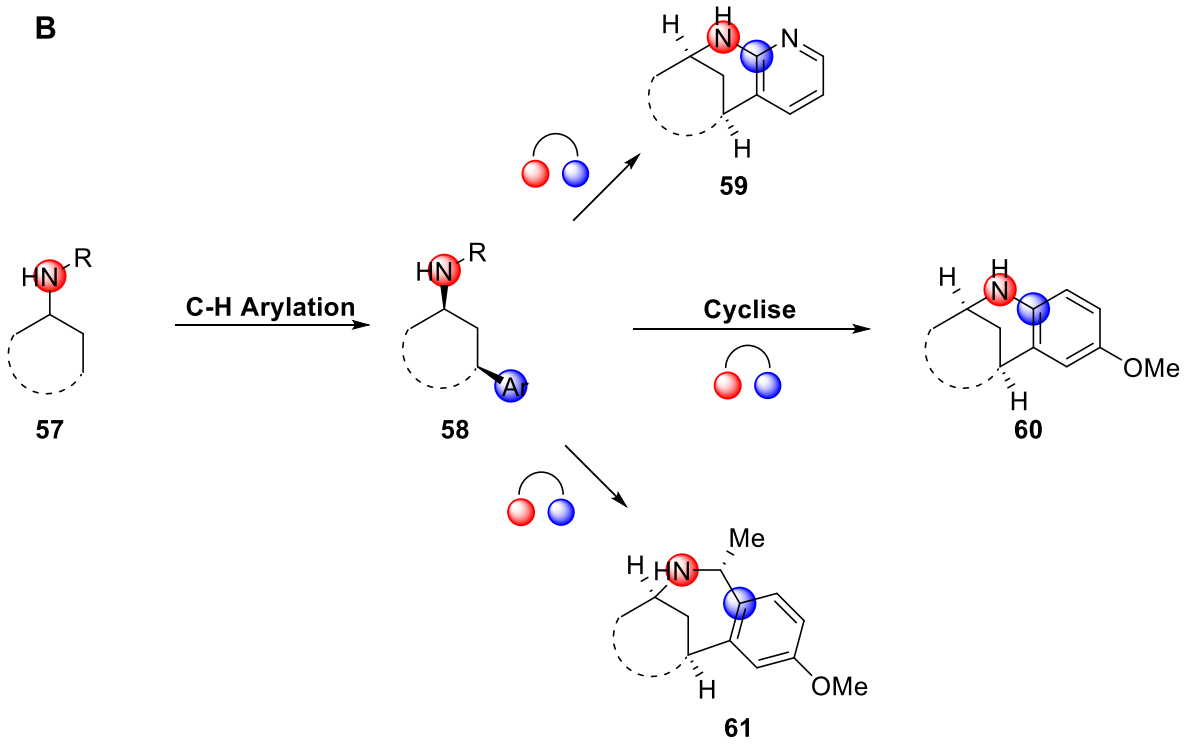
Objective one – Synthesis of cyclisation precursors:

The first objective involves the preparation of various cyclisation precursor compounds that each contain multiple functional group handles that can then allow many cyclisation reactions to generate libraries of lead-like final scaffolds. Ideally, these precursors should be synthesised in high yield, with a short number of synthetic steps and a degree of modularity to allow multiple precursors to be generated using the same overall approach.

Objective two – Develop toolkit of cyclisation reactions:

With these precursors in hand, a novel toolkit of cyclisation reactions can be developed to enable intramolecular cyclisations to occur and generate the libraries of final 3D scaffolds. These cyclisations should ideally be applicable to as many precursor compounds as possible to allow for a highly modular efficient overall synthetic strategy for scaffold library generation.





Scheme 8: A general overview of the unified, modular synthetic pathways proposed in order to prepare a library of diverse sp^3-rich diverse lead-like scaffolds using bottom-up LOS approaches. These strategies involve the different cyclisation precursor compounds containing different reaction handles (coloured circles) that can then be cyclised to give a final scaffold library in a short number of synthetic steps.

Objective three – Synthesis of scaffold library *via* intramolecular cyclisations:

The cyclisation precursors can then be cyclised using the toolkit of cyclisation reactions already developed in order to prepare a variety of novel and shape diverse scaffold libraries. The final scaffolds will be designed to incorporate approximately 1-3 points of diversification which can allow further growth along different reaction vectors. Decoration of these scaffolds would then able these scaffold libraries to target lead-like chemical space as intended (Scheme 8).

Objective four – Synthesis of diverse chemical probe library *via* a high throughput connective approach:

The final synthetic strategy investigated will involve the synthesis of structurally diverse chemical probes. This will be achieved through the use of small-scale reaction arrays *via* a high throughput connective approach. Careful design of the substrates and co-substrates employed, as well as the use of promiscuous chemistry in the reaction array, should allow for a structurally diverse selection of intermolecular products to be formed within each reaction well. Purification of the intermolecular products will then provide a diverse library of chemical probes. This high throughput synthetic approach can then be compared to the previous bottom-up synthetic strategies in terms of efficiency and product diversity.

Objective five – Computational analysis of scaffold and chemical probe libraries:

The final objective is to utilise computational tools to analyse the diverse scaffold and chemical probe libraries in terms of their molecular properties, overall structural diversity and shape diversity. Firstly, analysis of the scaffold libraries will attempt to verify that each of the scaffolds prepared can be used to target lead-like chemical space effectively and also possess significant shape and structural diversity as initially intended. To achieve this goal, computational tools such as LLAMA (Lead-Likeness And Molecular Analysis) will be used in order to assess the lead-likeness, scaffold novelty and three-dimensionality of the compounds within each library, to ensure the aims of this project have been met.[63] LLAMA allows the generation of a virtual library

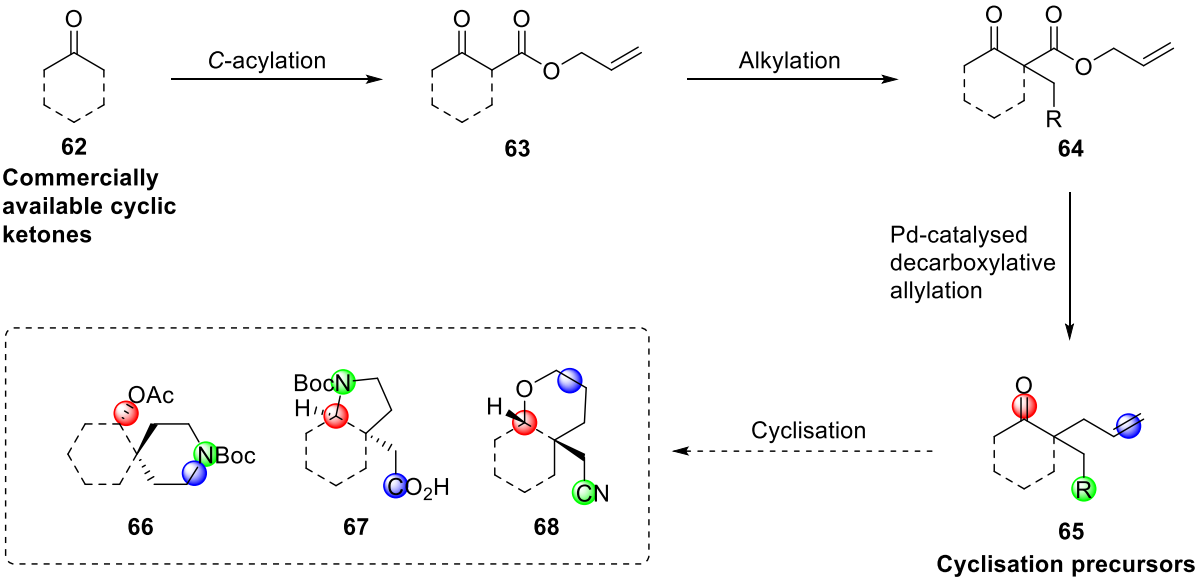
of screening compounds through decoration of the scaffold libraries using common medicinal chemistry capping groups.[63] Analysis of these virtual screening libraries can ensure that each of the scaffolds prepared during this project are indeed both shape and structurally diverse and have the ability to target lead-like chemical space effectively. LLAMA can also be used to assess both the molecular properties and shape diversity of the chemical probe library. Finally, other computational tools, such as Waldmann's hierarchical scaffold tree analysis, can also be used to analyse the structural diversity of each scaffold library and chemical probe library.[71] This tool allows for comparison between frameworks of compounds within the libraries by removing rings until a selection of parental monocyclic ring systems are found.[71] Therefore, this tool can be very useful in determining the structural diversity within each library of compounds.

2 Synthesis of a diverse lead-like scaffold library through a ‘bottom-up’ B/C/P branching synthetic approach

2.1 Identification of a unified LOS approach based around alkylation and Pd-catalysed connective reactions

The synthetic strategy envisaged to prepare a library of diverse sp^3-rich scaffolds first depended on successfully making cyclisation precursor compounds that contained several functional groups, which can then act as reaction handles for subsequent intramolecular cyclisations to occur. It would then be possible to induce cyclisation of these precursor compounds in a variety of ways by harnessing a toolkit of cyclisation reactions, to give a diverse range of novel scaffold products as desired. The final scaffolds should also ideally contain several points of diversification incorporated into their structure, as decoration at these points will allow further growth of the scaffolds along different reaction vectors to target lead-like chemical space as required.

It was decided that the best approach to achieve this aim was to utilise and modify a previously successful ‘bottom-up’ B/C/P LOS strategy developed within the Nelson group.[67] This new adapted approach would start with the preparation of keto-ester building blocks **63** from commercially available cyclic ketone starting materials **62** that could then be regioselectively functionalised *via* alkylation chemistry with various electrophiles. These quaternary allyl ester intermediates **64** could then undergo a palladium-catalysed decarboxylative allylation reaction to give the cyclisation precursors **65** as desired.[72] These precursors would then contain up to four different functional groups, including alkene, ketone and amine groups that can act as reaction handles for subsequent intramolecular cyclisation. Therefore, this synthetic approach should allow for the preparation of novel sp^3-rich, structurally diverse molecular scaffolds, that upon decoration, can target lead-like chemical space (Scheme 9).



Scheme 9: An overview of the general synthetic strategy to prepare cyclisation precursors *via* C-acylation of cyclic ketone starting materials **62** followed by alkylation and subsequent Pd-catalysed decarboxylative allylation chemistry. These cyclisation precursors can then yield a novel, highly sp^3-rich, diverse scaffold library through intramolecular cyclisations between the reaction handles present in the precursors (coloured circles).

It has been previously demonstrated that these connective reactions can yield cyclisation precursor compounds **65** with this generic structure and that these connective reactions can work well with different ring sizes and with rings containing different heteroatoms (Figure 7).[73,74] These compounds have also been made successfully as both racemates and single enantiomer derivatives *via* the use of chiral PHOX ligands during the Pd-catalysed decarboxylative allylation step.[67,73,74] This suggests that the scope for this pathway to prepare cyclisation precursors with this overall generic structure may be extended to allow a larger range of structurally diverse precursors to be made. This would therefore allow the preparation of multiple cyclisation precursors that: are structurally diverse, contain numerous reaction handles for subsequent cyclisations and can be prepared in a short number of synthetic steps. Thus, this strategy should enable the efficient and modular synthesis of multiple cyclisation precursors that can then be cyclised between the different reaction handles to generate a library of novel, highly shape diverse scaffolds that can target lead-like chemical space as required.

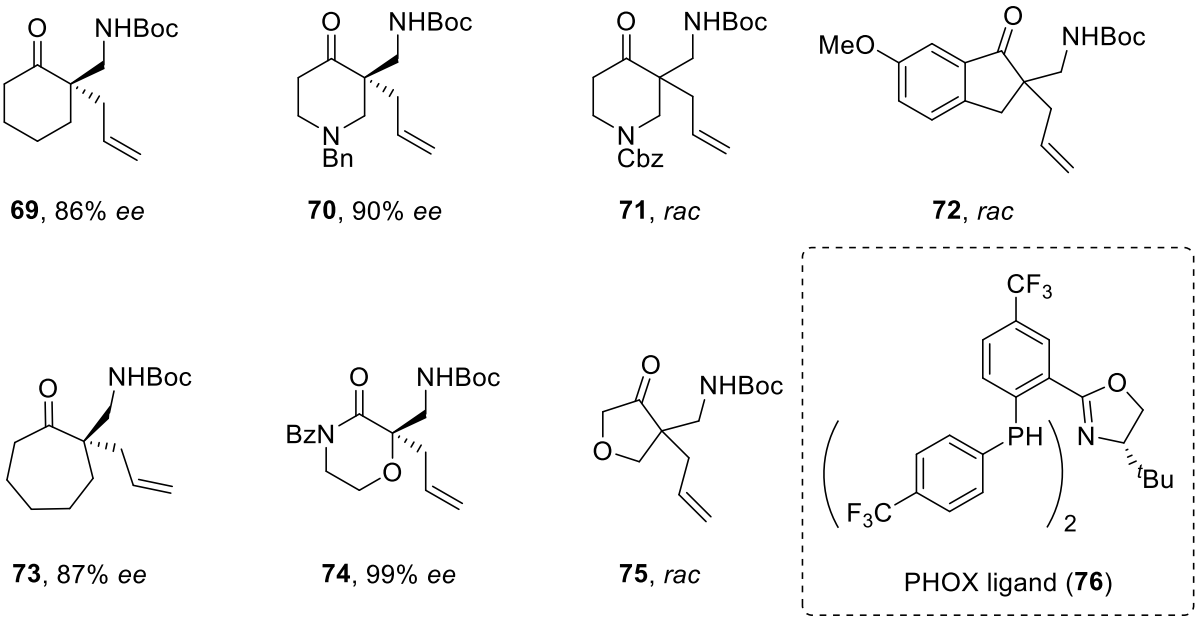
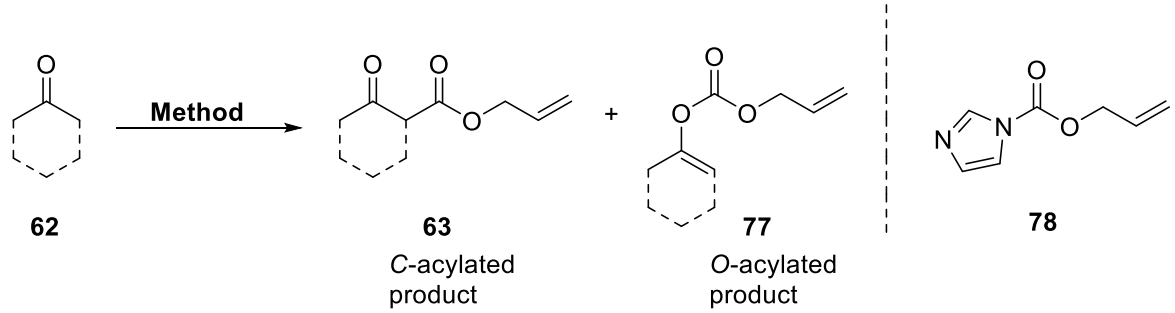


Figure 7: A general outline of the literature precedent which shows the synthetic scope for the preparation of cyclisation precursor compounds with this desired generic core structure. These types of compounds have also been synthesised enantioselectivity and as the corresponding racemates[67]. The *ee* values corresponds to the Pd-catalysed decarboxylative allylation reaction step (5 mol% $Pd_2(dba)_3$, 12.5 mol% PHOX ligand, toluene, rt).[73]

2.2 Synthesis of cyclisation precursor compounds

2.2.1 Preparation of *C*-acylation building blocks

Before any cyclisation reactions could be attempted, the initial cyclisation precursors containing all the reactive handles needed for cyclisation had to be prepared. The first step of this process was to prepare the keto-ester building blocks **63** from a variety of commercially available cyclic ketone starting materials (Table 2). This was achieved by using the base LiHMDS to generate the lithium enolate, which was then able to react with an electrophile to give the desired allyl ester products.[67] Two different allyl ester-containing electrophiles were used (allyl chloroformate and **78**) and these were initially screened with the tetrahydropyran-4-one (THP) cyclic ketone **62a**. This was done to determine which electrophile gave the better selectivity between *C*- and *O*-acylation and also which gave the highest yield of the desired *C*-acylated allyl-ester building block **63** rather than *O*-acylated product **77**.



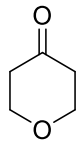
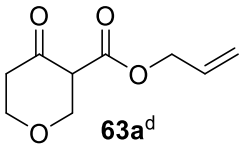
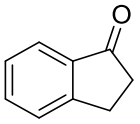
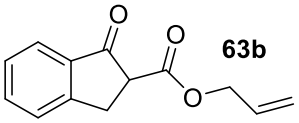
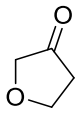
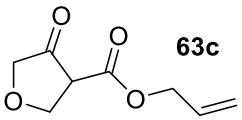
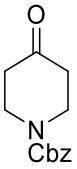
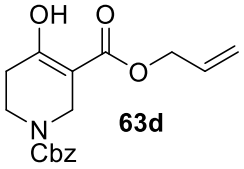
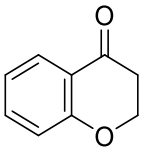
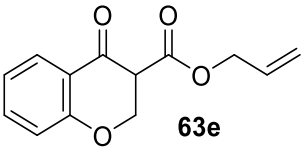
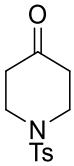
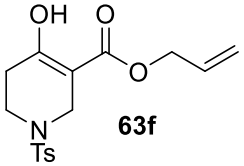
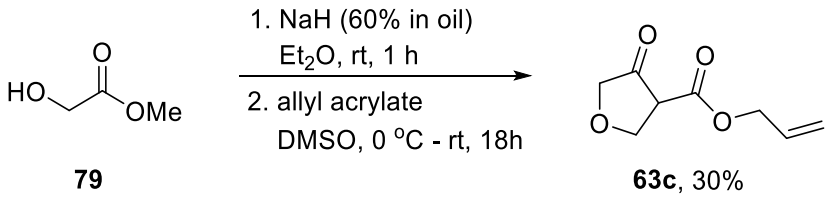
Entry	Cyclic Ketone	Method[a]	Product	*C*-:*O*-Acylation[b]	Yield[c]
1a **1b**	 **62a**	A **B**	 **63a**[d]	>95:<5 **87:13**	35% **57%**
2	 **62b**	**B**	 **63b**	**>95:<5**	**53%**
3	 **62c**	**B**	 **63c**	-	-[e]
4	 **62d**	**B**	 **63d**	**>95:<5**	**67%**
5	 **62e**	**B**	 **63e**	-	-[e]
6	 **62f**	**B**	 **63f**	**>95:<5**	**64%**

Table 2: The optimisation and synthesis of allyl ester building blocks **63**. [a]**Method: A:** LiHMDS, **78**, toluene, -78 °C; **B:** LiHMDS, allyl chloroformate, toluene, 0 °C - rt. [b]*C*-:*O*-acylation ratio determined by 400 MHz ^{1}H NMR spectroscopic analysis of the crude product mixture. [c]Isolated yield after purification. [d]Observed as a 25:75 *keto*:*enol* tautomer mixture by 400 MHz ^{1}H NMR spectroscopy. [e]Observed as a complex mixture.

Electrophile **78** was chosen for this initial screen as it has been shown previously on similar substrates that a soft electrophile such as **78** can increase the control over *C*-:*O*-acylation to therefore give a better overall yield of the desired *C*-acylated keto-ester product.[67,75] It was found that electrophile **78** did selectively provide the desired *C*-acylated allyl-ester **63a** but only in a moderate 35% yield (Table 2, Entry 1a). This compared to the corresponding reaction with allyl chloroformate which gave a crude product *C*-:*O*-acylation ratio of 87:13 but with a much higher 57% isolated yield of pure *C*-acylated allyl-ester **63a** (Table 2, Entry 1b). It was therefore decided to continue the substrate scope using allyl chloroformate as the electrophile of choice, due to the higher yield of the desired *C*-acylated product outweighing the slightly higher *C*-acylation selectivity given with electrophile **78**. It was found that this acylation reaction was not completely reproducible for every cyclic ketone, with both the chromone **62e** and ketone **62c** giving a complex mixture of products from this reaction (Table 2, Entries 3 and 5). However, allyl-ester building blocks **63b, 63d** and **63f** were all successfully prepared in good yields *via* this method, with excellent *C*-acylation selectivity observed in all these cases (Table 2, Entries 2,4 and 6).

The unsuccessful synthesis of allyl ester **63c** by this method meant that the synthesis of this building block was achieved using alternative literature conditions from methyl glycolate **79** and with allyl acrylate as the electrophile (Scheme 10).[67,76] This reaction proceeded *via* a Michael addition followed by an intramolecular Dieckmann condensation to give allyl-ester **63c** as desired in 30% yield.

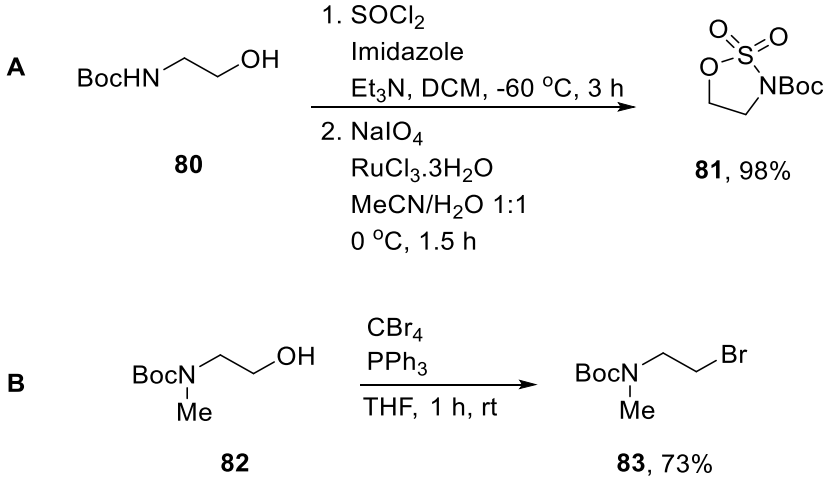


79 **63c**, 30%

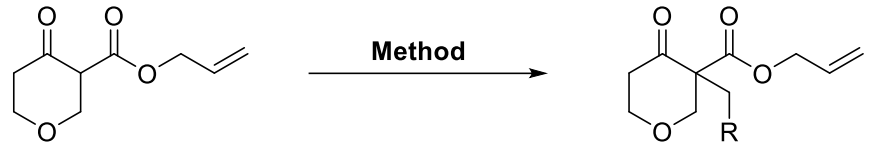
Scheme 10: The alternative method to synthesise allyl-ester building block **63c** from methyl glycolate **79** and allyl acrylate.[67,76]

2.2.2 Preparation of quaternary allyl ester building blocks *via* alkylation

With allyl ester building blocks **63** in hand, these were then taken onto the next step of the synthesis in order to prepare the cyclisation precursor compounds. The keto-ester motif in these intermediates facilitated a regioselective alkylation which can provide quaternary allyl ester products from this reaction. This therefore allows the addition of another reaction handle to the final cyclisation precursors, which can enable a wider variety of subsequent intramolecular cyclisations to occur and provide the final library of shape diverse scaffolds. It was initially decided to introduce an *N*-Boc ethylamino group to allyl-esters **63** so that this reaction handle would be present in the final cyclisation precursor compounds. A variety of different electrophiles were initially tested with THP allyl-ester **63a**, including common alkylating reagents such as benzyl bromide. This was done in order to determine which electrophiles would be the best reagents to take forward in the synthesis of the final cyclisation precursors (Table 3). The cyclic sulfamidate **81** (Scheme 11, Panel A) and aminobromide **83** (Scheme 11, Panel B) electrophiles were first prepared *via* known literature methods with excellent yields observed in both cases.[77,78]



Scheme 11: Synthesis of cyclic sulfamidate **81** (Panel A) and aminobromide **83** (Panel B) for their use in the initial electrophile screen in order to prepare the corresponding quaternary allyl ester intermediates.[77,78]



63a

Allyl-ester building blocks

84

Quaternary allyl ester derivatives

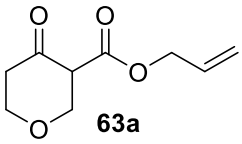
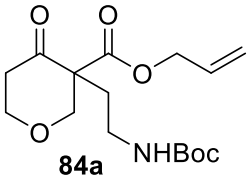
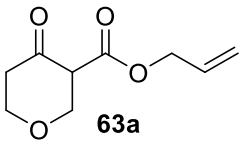
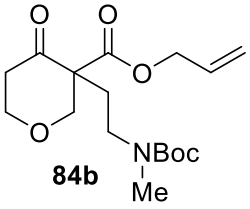
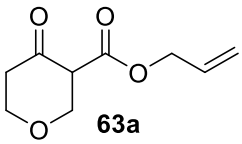
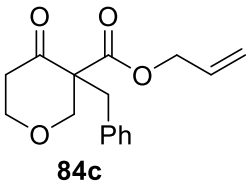
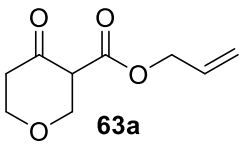
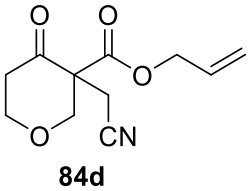
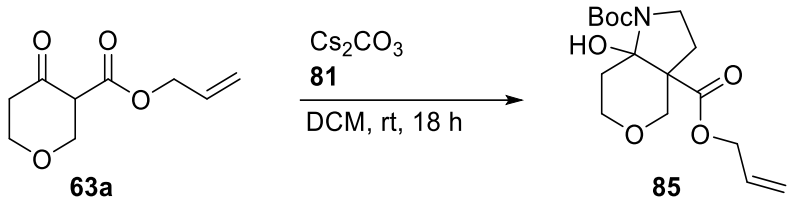
Entry	Allyl ester	Method[a]	Quaternary allyl ester	Yield[b]
1	 **63a**	A	 **84a** NHBoc	-[c]
2a	 **63a**	B	 **84b** NBoc, Me	-[d]
2b		C		-[d]
2c		D		-[d]
3	 **63a**	**E**	 **84c** Ph	**50%**
4a	 **63a**	F (1.2 eq.)	 **84d** CN	50%
4b		**F (1.5 eq.)**		**65%**
4c		F (2.2 eq.)		55%

Table 3: The reaction of various electrophiles with allyl-ester **63a** to prepare the corresponding quaternary allyl ester derivatives. [a]**Method: A:** Cs_2CO_3, **81**, DCM, 18 h; **B:** K_2CO_3, **83**, acetone, 70 °C, 18 h; **C:** NaH (60% in oil), **83**, THF, rt, 18 h; **D:** Cs_2CO_3, **83**, TBAI, THF, rt, 18 h; **E:** K_2CO_3, benzyl bromide, acetone, 70 °C, 2 h; **F:** NaH (60% in oil), bromoacetonitrile (x eq.), THF, 18 h. [b]Isolated yield after purification. [c]Desired product not isolated but reaction gave hemiacetal **85** selectively (Scheme 12). [d]No reaction was observed by TLC and LCMS.

The screening of electrophiles with allyl-ester **63a** found that only benzyl bromide and bromoacetonitrile gave the desired quaternary allyl ester products **84c** and **84d** (Table

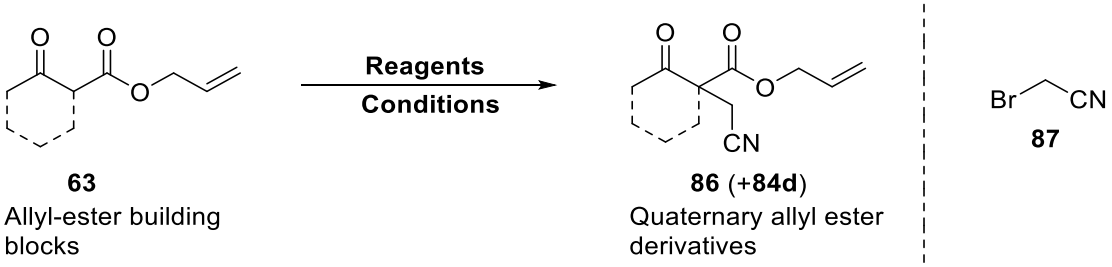
3, Entries 3-4). The cyclic sulfamidate electrophile **81** did not give the desired quaternary ally ester compound but instead selectively gave the fused ring hemiaminal **85** as the only alkylated product from this reaction (Scheme 12). Hemiaminal **85** was then subjected to the decarboxylative allylation conditions (c.f. Table 4), but this only yielded unreacted starting material. This unfortunately made this electrophile not desirable in our proposed synthetic route, as the keto-ester motif is likely required to stabilise the resulting anion that is formed during the reaction mechanism.[79]



Scheme 12: The selective formation of fused-ring hemiaminal **85** from the reaction of allyl-ester **63a** with cyclic sulfamidate **81**.

The aminobromide electrophile **83** failed to give any desired alkylated product under any of the reaction conditions attempted, with only allyl-ester starting material observed from each of these reaction attempts (Table 3, Entries 2a-c). Changing the base, solvent and temperature also did not seem to allow the desired alkylation to take place with this electrophile. Bromoacetonitrile was shown to provide the highest yield when 1.5 equivalents were used during a brief optimisation stage (Table 3, Entry 4b).

From these initial results, it was decided that only the products from the alkylation with benzyl bromide and bromoacetonitrile (**84c** and **84d**) should be taken forward to the final synthetic step for preparing the set of cyclisation precursors. The alkylation of allyl-esters **63a** with bromoacetonitrile was a promising result as this enabled a nitrile motif to be successfully incorporated into quaternary allyl ester intermediates. Nitriles can act as masked amine reaction handles, as subsequent nitrile reduction at a later stage in the synthesis would reveal the desired ethylamine reaction handle for a range of intramolecular cyclisations to then take place. The alkylation reaction of keto-esters with bromoacetonitrile was then investigated to generate a library of quaternary allyl ester intermediates **86** based around different cyclic ketone starting materials (Table 4).



63
Allyl-ester building blocks

86 (+**84d**)
Quaternary allyl ester derivatives

87

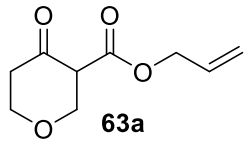
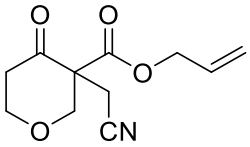
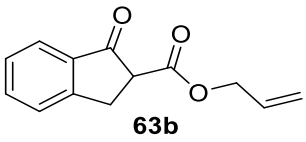
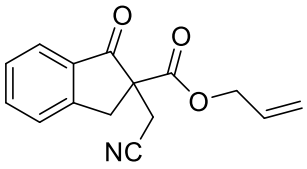
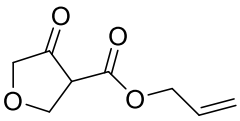
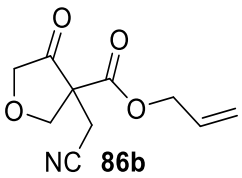
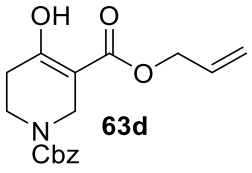
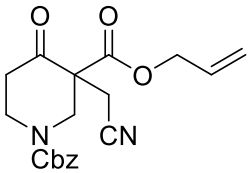
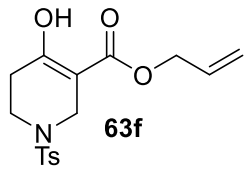
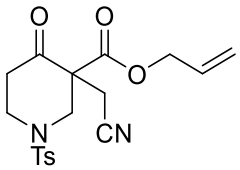
Entry	Allyl-ester	Reagents and Conditions	Quaternary allyl ester	Yield[a]
1	 **63a**	**87, NaH, THF, rt, 18 h**	 **84d**	**65%**
2	 **63b**	**87, NaH, THF, rt, 18 h**	 **86a**	**75%**
3a **3b** **3c**	 **63c**	87, NaH, THF, rt, 18 h 87, NaH, THF, rt, 3 h 87, Cs_2CO_3, THF, rt, 18 h	 **86b**	-[b] -[b] -[b]
4	 **63d**	**87, NaH, THF, rt, 18 h**	 **86c**	**64%**
5	 **63f**	**87, NaH, THF, rt, 18 h**	 **86d**	**65%**

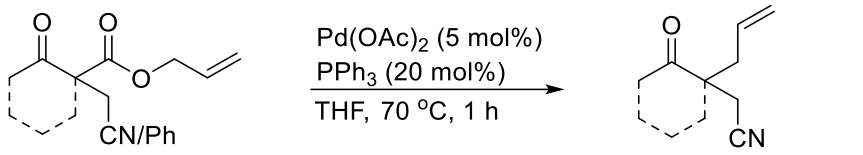
Table 4: The reaction of allyl-ester building blocks **63** with bromoacetonitrile (**87**) to prepare the corresponding quaternary allyl ester derivatives **86** (+**84d**). [a]Isolated yield after purification. [b]Complex mixture of products determined by TLC, LCMS and analysis of the crude material by 400 MHz ^{1}H NMR spectroscopy.

The alkylation of allyl-esters **63** with bromoacetonitrile was found to be generally reproducible throughout the library of allyl-ester building blocks, apart from with allyl-ester **63c**, where a complex mixture of crude products was observed under all reaction conditions that were tested (Table 4, Entries 3a-c). The corresponding quaternary allyl esters **84d**, **86a** and **86c-d** were all isolated in good yields (64-75%) after purification (Table 4, Entries 1-2 and 4-5). These compounds were then ready to be taken forward to the final reaction step for the preparation of the cyclisation precursors.

2.2.3 Preparation of cyclisation precursors *via* Pd-catalysed decarboxylative allylation

With the quaternary allyl ester intermediates **86** now in hand, the ester groups were removed by a palladium-catalysed decarboxylative allylation reaction to give the final cyclisation precursor compounds **88** ready for any subsequent intramolecular cyclisation reactions (Table 5). It was decided to prepare the cyclisation precursor compounds as racemates using PPh_3 as the ligand. This was mainly due to the high expense of the chiral PHOX ligand, which is needed to perform this decarboxylative allylation on gram scale with high enantioselectivity.[73] The high expense of this chiral PHOX ligand is likely because it is derived from an unnatural amino acid. The reaction was therefore performed with 5 mol% $Pd(OAc)_2$ catalyst, 20 mol% PPh_3 ligand in THF at 70 ^oC for 1 h.[67,72] The reaction was found to be very reproducible over all of the quaternary allyl ester derivatives prepared giving the corresponding cyclisation precursors **88a-e** in good yields ranging from 69-84% (Table 5, Entries 1-5).

This final reaction step allowed the generation of five final cyclisation precursor compounds that contained up to four different reaction handles for subsequent cyclisation reactions to take place. These functionalised precursors could now be employed to prepare a library of structurally diverse, sp^3-rich scaffolds with multiple points of diversification to enable the compounds to target lead-like chemical space as originally designed.



86 (+**84c-d**)
Quaternary allyl ester derivatives

88
Cyclisation precursor compounds

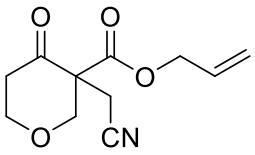
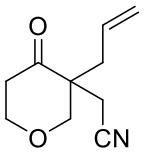
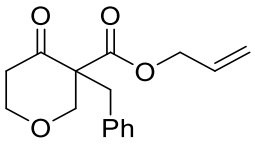
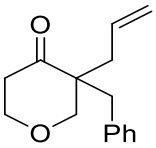
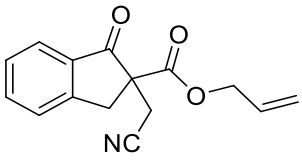
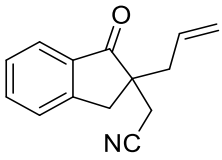
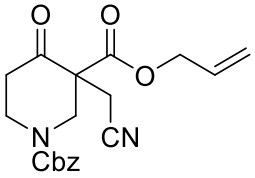
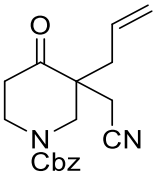
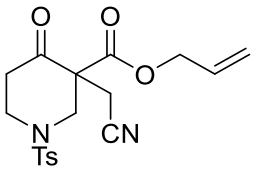
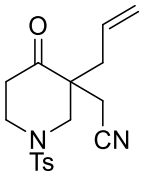
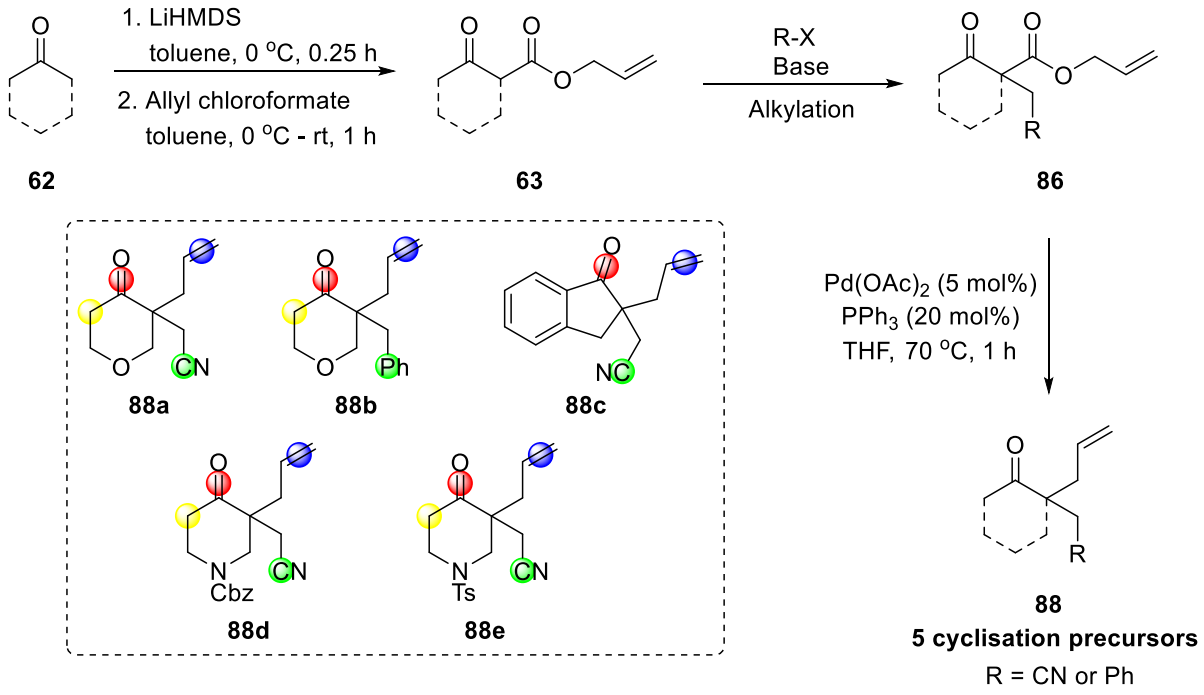
Entry	Quaternary allyl ester	Cyclisation precursor	[a]Yield
1	 **84d**	 **88a**	**75%**
2	 **84c**	 **88b**	**77%**
3	 **86a**	 **88c**	**84%**
4	 **86c**	 **88d**	**69%**
5	 **86d**	 **88e**	**71%**

Table 5: Pd-catalysed decarboxylative allylation of quaternary allyl esters **86** (+**84c-d**) to generate the library of five successful cyclisation precursors **88**. [a]Isolated yield of purified cyclisation precursor compound.

2.2.4 Summary of cyclisation precursor synthesis

To summarise, a three-step synthetic pathway, first involving *C*-acylation, then regioselective alkylation followed by Pd-catalysed decarboxylative allylation allowed for the successful preparation of five cyclisation precursor compounds, with good yields observed throughout each of the three synthetic steps (Scheme 13). The five cyclisation precursors prepared all contain up to four reaction handles, including ketone, alkene and nitrile (masked amine) functional groups to allow for the subsequent synthesis of diverse scaffolds *via* a wide range of intramolecular cyclisation reactions (Section 2.3).



Scheme 13: Overview of the synthesis of five cyclisation precursors **88a-e** *via* *C*-acylation, alkylation and Pd-catalysed decarboxylative allylation chemistry. Reaction handles are indicated with different coloured circles.

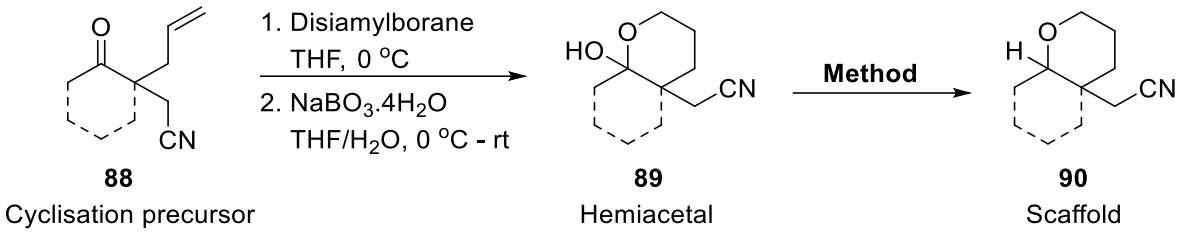
2.3 Synthesis of structurally diverse 3D scaffold library

With the synthesis of the cyclisation precursor compounds now complete, an investigation into the scope of subsequent intramolecular cyclisation reactions could

now begin. The cyclisation precursors could undergo various cyclisations between the different reaction handles incorporated in their structure to prepare numerous final scaffold compounds. Cyclisation precursors **88** could undergo cyclisation between the ketone and terminal alkene or NHBoc (after nitrile reduction) functional groups to prepare fused-ring scaffolds, or could instead cyclise between the NHBoc and terminal alkene groups to prepare the corresponding spirocyclic derivatives. All of the cyclisation precursors prepared have closely related structures, meaning cyclisation reaction that are successful with one of these precursors, may also be successful with the other precursor compounds, using identical or slightly modified reaction conditions. This should give a modular synthetic approach, where cyclisations are tolerated by many different precursor compounds, which can then lead to the subsequent generation of the diverse sp^3-rich scaffold library as desired.

2.3.1 Cyclisation between ketone and alkene reaction handles

The first cyclisation reactions to be tested involved reacting between the ketone and alkene reaction handles present in the precursor compounds. The first transformation attempted was hydroboration-oxidation of the terminal alkene to give the corresponding terminal alcohol. This could then cyclise *via* nucleophilic attack into the ketone to generate a hemiacetal intermediate that can subsequently be reduced to prepare the final fused ring scaffolds. The cyclisation precursors **88** were first treated with disiamylborane in THF followed by oxidation with $NaBO_3 \bullet 4H_2O$ as these conditions were known to be successful with similar substrates.[67,80] Subsequent reduction of the hemiacetal intermediates **89** under either Brønsted or Lewis acidic conditions then gave the desired cyclised scaffolds **90** (Table 6). This pathway was first tested on cyclisation precursor **88a** with the hemiacetal intermediate **89a** being successfully isolated in 70% yield as a single diastereomer. However, the relative configuration of this intermediate was unable to be determined due to broad and overlapping key peaks in the 400 MHz ^1H NMR spectrum. This hemiacetal intermediate was then successfully reduced with Et_3SiH in TFA to give scaffold **90a** as a single diastereomer in 80% yield (Table 6, Entry 1).[67] The reaction pathway was then repeated with three other cyclisation precursors to determine the reaction reproducibility over the precursors prepared.



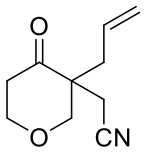
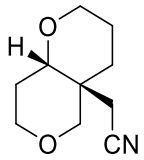
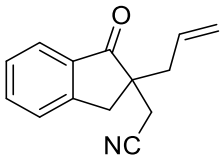
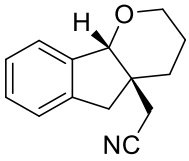
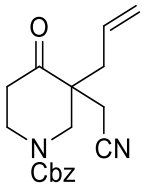
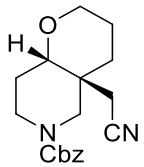
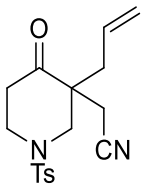
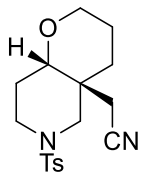
Entry	Cyclisation precursor	Scaffold	[a]Method	[b]Yield 89 (*dr*)[c]	[d]Yield 90 (*dr*)[c]
1	 **88a**	 **90a**	**A**	**70% (>95:<5)**	**80% (>95:<5)**
2	 **88c**	 **90b**	**B**	**-[e]**	**68%[f] (>95:<5)**
3	 **88d**	 **90c**	A	-[e]	-[g]
4a **4b**	 **88e**	 **90d**	A B	-[e] -[e]	-[g] -[g]

Table 6: The hydroboration-oxidation reaction of cyclisation precursors **88** to give hemiacetal intermediates **89** that were then subject to reduction to give scaffolds **90**. [a]**Method: A:** Et_3SiH, TFA, DCM, rt; **B:** Et_3SiH, BF_3•Et_2O, DCM, -78 °C - rt. [b]Isolated yield of purified hemiacetal intermediate. [c]Determined by 400 MHz ^1H NMR spectroscopic analysis of purified compound. [d]Isolated yield of purified scaffold. [e]Hemiacetal intermediate not isolated due to telescoped reaction procedure. [f]Isolated yield calculated over two steps due to telescoped procedure. [g]Complex mixture of products observed.

The reactions were also telescoped through to the final scaffold compounds with the hemiacetal intermediates not isolated. It was found that only the indanone precursor **88c** was tolerant of this reaction pathway, where the reduction with Et_3SiH and BF_3•Et_2O gave scaffold gave scaffold **90b** as a single diastereomer in 68% yield over the two reaction steps (Table 6, Entry 2). The reduction conditions were changed in this case due to previous precedent of reduction with BF_3•Et_2O on similar substrates.[67,81] The *N*-Cbz and *N*-Ts piperidinone precursors **88d** and **88e** were not tolerant of these reaction conditions and no desired cyclised product could be isolated in either case (Table 6, Entries 3-4). With scaffolds **90a** and **90b** in hand, the relative configurations of both scaffolds were established. Analysis of the ^1H NMR spectra (400 MHz) showed that protons on the tertiary carbon in each scaffold were either a singlet (**90b**) or small apparent triplet with *J* 3.7 Hz (**90a**). Therefore, there should not be a vicinal proton in a *trans* di-axial position with respect to this proton, as in that case a much larger coupling constant would be expected. Thus, this evidence suggests the scaffolds have *cis* ring fusion. Inspection of key nOe enhancements from NOESY (500 MHz) supported *cis* ring fusion as nOe enhancements were observed between the tertiary carbon proton and protons on the cyanomethyl side chain (Figure 8, Panel A). If the scaffolds had a *trans* ring fusion, then these nOe enhancements would not be observed. The formation of the observed *cis*-fused ring configuration can be explained by selective hydride delivery to the oxocarbenium ion intermediate. The triethylsilane reductant will preferentially attack the less hindered convex face of the molecule, which exists in a bowl-like conformation, therefore leading to the observed *cis* stereochemical outcome (Figure 8, Panel B).

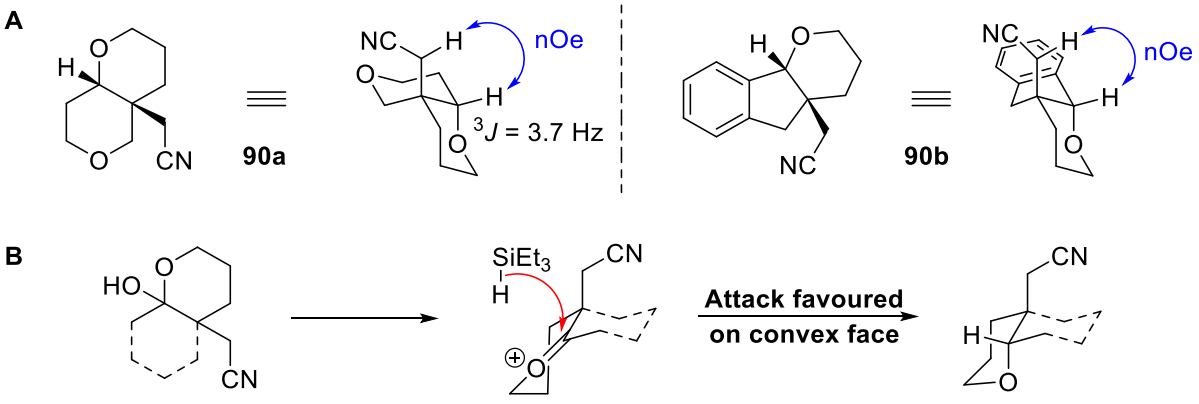
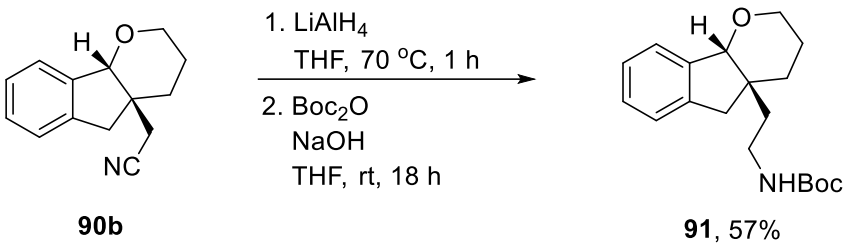


Figure 8: Determination of the relative configuration in scaffolds **90a** and **90b**. **Panel A:** Key nOe enhancements from NOESY spectra for each scaffold. **Panel B:** Proposed rationale for *cis*-fused ring stereochemistry observed.

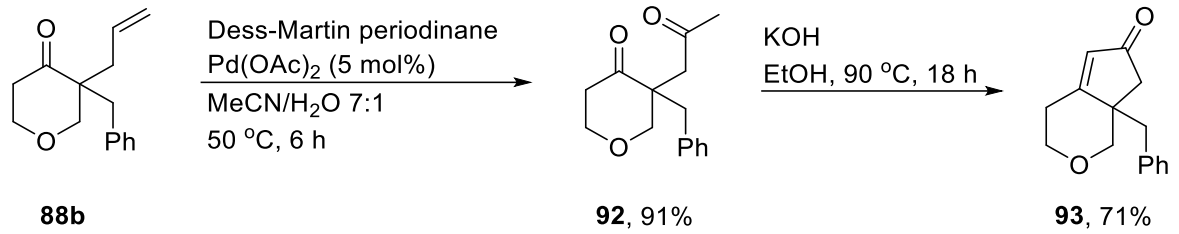
With the relative configuration of the scaffolds now confirmed, the nitrile functional group on indanone-based scaffold **90b** was reduced to give the corresponding *N*-Boc amine derivative **91** (Scheme 14). This reaction was performed to confirm that the nitrile groups on these fused ring scaffolds can be unmasked *via* reduction to give an amine as a point of diversification for subsequent scaffold decoration. Treatment of **90b** with $LiAlH_4$ in THF followed by Boc protection to ease purification gave the desired Boc-protected amine **91** in 57% yield. This success demonstrated that the nitrile groups on scaffolds **90a-b** prepared through this hydroboration-oxidation chemistry can be unmasked to give a point of diversification to allow further scaffold growth and decoration as designed.



90b **91**, 57%

Scheme 14: Reduction of the nitrile functional group in scaffold **91** to give the corresponding NHBoc derivative **90b**.

Attention now turned to investigating other intramolecular cyclisation reactions that could take place between the ketone and alkene reaction handles in the set of cyclisation precursors prepared. A synthetic pathway was first proposed which involved a Wacker oxidation of the terminal alkene groups to give the corresponding methyl ketone product.[82] This intermediate could then undergo an intramolecular aldol condensation to give the final cyclised product. This synthetic pathway was initially tested on cyclisation precursor **88b** to determine whether this pathway can access the cyclised scaffold product as intended. Wacker oxidation of precursor **88b** with 5 mol% $Pd(OAc)_2$ and Dess-Martin periodinane proceeded very cleanly to give the corresponding methyl ketone intermediate **92** in an excellent 91% yield.[82] This intermediate was then able to cyclise *via* an intramolecular aldol condensation to give the fused ring enone **93** in 71% yield (Scheme 15).



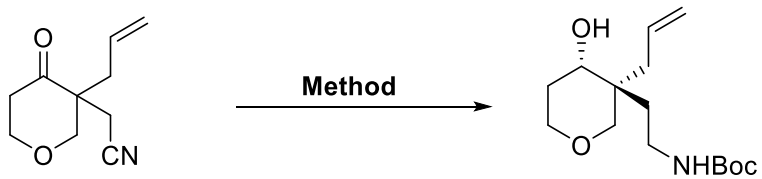
88b **92**, 91% **93**, 71%

Scheme 15: A possible cyclisation pathway that utilises a Wacker oxidation followed by an intramolecular aldol condensation to give the corresponding cyclised enone product **93**.

After the apparent success of this cyclisation method with precursor **88b**, Luche reduction of the enone to give the corresponding allyl alcohol was attempted in order to provide a point of diversification for subsequent scaffold decoration.[83] Unfortunately, this reaction was unsuccessful with **93** and gave a complex mixture of undetermined products as observed by TLC and analysis of the crude material by 400 MHz ^{1}H NMR spectroscopy. The Wacker oxidation/aldol condensation pathway was therefore attempted instead with THP-based cyclisation precursor **88a** to determine whether the reaction conditions in this pathway can tolerate the nitrile functionality, as reduction of the nitrile group in the final enone derivative could reveal an alternative position for scaffold decoration. Disappointingly, the Wacker oxidation was unsuccessful in the presence of the nitrile group with mainly starting material recovered from this reaction attempt. This led to the decision to deprioritise this reaction pathway and to instead focus on investigating alternative cyclisations with the more functionalised precursors (**88a** and **88c-e**), to build up the toolbox of cyclisation reactions and enable more final scaffolds to be prepared.

In order to access a wider range of structurally diverse scaffolds, it was decided that reduction of the ketone to the corresponding alcohol could enable more cyclisations to take place between this reaction handle and the terminal alkene. It would also be advantageous to develop a reduction that will reduce both the ketone and the nitrile groups in a stereoselective manner under identical reaction conditions, as this would also unmask the amine reaction handle needed for subsequent cyclisations to occur. It has been shown previously that aluminium-based reducing agents can stereoselectivity reduce the ketone on similar compounds, as well as being able to reduce nitriles to the corresponding primary amines.[67,73] Therefore, it was decided that

DIBAL-H and $LiAlH_4$ would be employed as reducing agents in an initial reaction screen with cyclisation precursor **88a** (Table 7). As it is possible for the DIBAL-H reduction of nitrile groups to yield the aldehyde product instead of the amine, the reaction was attempted with various DIBAL-H equivalents in order to determine how much reagent was needed to give the desired ketone and nitrile reduced product **94a** in the highest possible yield and with the best stereoselectivity. Following this reduction, the resulting amine was *N*-Boc protected to ease purification as well as providing amine protection for any subsequent cyclisation reactions.



88a
Cyclisation precursor

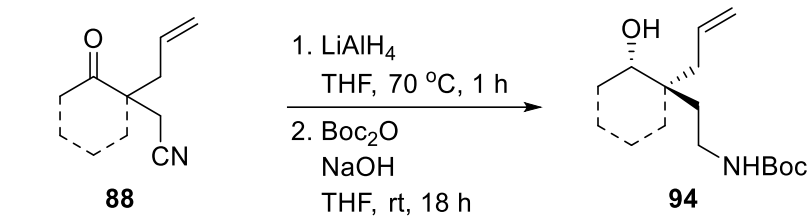
94a
Reduced derivative

Entry	[a]Method	Number of DIBAL-H equivalents	Number of $LiAlH_4$ equivalents	[b]Yield (*dr*)[c]
1	A	4.0 eq.	-	40%[d] (80:20)
2	A	4.5 eq.	-	41%[d] (81:19)
3	A	7.0 eq.	-	56% (81:19)
4	**B**	**-**	**4.5 eq.**	**62% (84:16)**

Table 7: Optimisation studies for the reduction of cyclisation precursor **88a** with various equivalents of DIBAL-H or $LiAlH_4$ to give the reduced derivative **94a**. [a]**Method: A:** DIBAL-H, DCM, -78 °C, 1 h then Boc_2O, Et_2N, DCM, rt, 18 h; **B:** $LiAlH_4$, THF, 70 °C, 1h, then Boc_2O, NaOH, THF, rt, 18 h. [b]Isolated yield of purified reduced derivative. [c]Determined by 400 MHz ^1H NMR spectroscopic analysis of purified compound. [d]Product collected as a mixture with other reduced side products.

From the initial screen of reaction conditions with compound **88a**, it was determined that at least 7 equivalents of the DIBAL-H reducing agent were needed to get the desired ketone and nitrile reduced derivative **94a** instead of a mixture of alternatively reduced products. Reduced derivative **94a** was isolated in 56% yield with good diastereoselectivity observed (*dr* 81:19) using the DIBAL reducing agent (Table 7, Entry 3). However, it was found that $LiAlH_4$ reduction provided the desired product **94a**

at an improved 63% yield with better diastereoselectivity (*dr* 84:16) then for the corresponding DIBAL-H reduction (Table 7, Entry 4). Therefore, it was decided that the $LiAlH_4$ reducing conditions would be employed in order to prepare the reduced derivatives **94** from the set of cyclisation precursors **88** due to these conditions giving a cleaner reaction with good diastereoselectivity and higher yield observed (Table 8).



88 Cyclisation precursor — **94** Reduced derivative

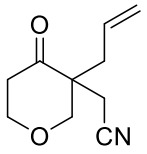
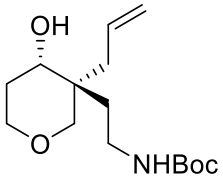
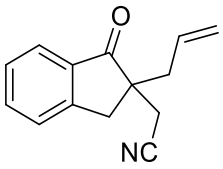
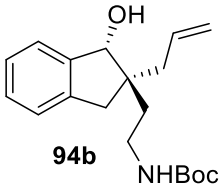
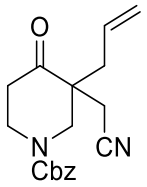
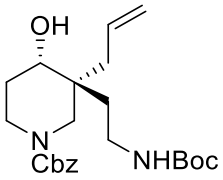
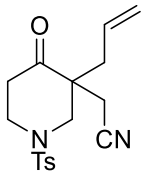
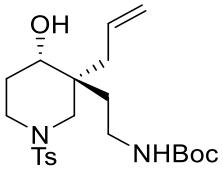
Entry	Cyclisation precursor	Reduced derivative	[a]Yield (*dr*)[b]
1	 **88a**	 **94a**	**62% (84:16)**
2	 **88c**	 **94b**	**65% (80:20)**
3	 **88d**	 **94c**	-[c]
4	 **88e**	 **94d**	**67% (80:20)**

Table 8: Reduction of cyclisation precursors **88** with $LiAlH_4$ to give the corresponding reduced derivatives **94**. [a]Isolated yield of the purified reduced derivatives. [b]Determined by 400 or 500 MHz ^{1}H NMR spectroscopic analysis of purified compound. [c]Complex mixture of products observed due to decomposition of *N*-Cbz under reaction conditions.

These reduction conditions were found to be reproducible throughout most of the cyclisation precursors, with only the *N*-Cbz piperidinone precursor **88d** failing to give any desired product. This was likely due to the decomposition of the *N*-Cbz protecting group leading to the complex mixture of products observed (Table 8, Entry 3). The other three precursors (**88a, 88c** and **88e**) all gave the corresponding reduced products **94** in good consistent yields (62-67%) with similar diastereoselectivity observed (*dr* 80:20-84:16) throughout the successful precursors (Table 8, Entries 1-2 and Entry 4).

The relative configuration of these reduced derivatives **94** was determined though 400 or 500 MHz ^{1}H NMR spectroscopy, NOESY and *via* analogy with related compounds prepared through similar aluminium-based reductions.[67,73] Inspection of the coupling constants in compounds **94a** and **94d** for proton 4-H shows high couplings of *J* 11.4 Hz and 9.7 Hz, which suggests there is a vicinal proton in the *trans* position leading to the *trans*-diaxial couplings observed. The NOESY of compound **94a** and benzyl derivative **116b** also showed key nOe interactions between proton 4-H and protons in the *N*-Boc ethylamine side chain (Figure 9, Panel A). This information suggests an *anti*-configuration between the alcohol and the *N*-Boc ethylamine side chain. If the relative configuration was *syn* then these nOe interactions would not be observed and the 4-H coupling constants would be much lower as there would be no *trans* vicinal proton. The stereochemistry of **94d** was also determined by analogy with compound **94a** and carbocyclic analogues prepared using similar reduction chemistry.[67,73] The apparent diastereoselective nature of this reaction can be explained by possible steric effects. Reduction of the ketone would first occur by the hydride attacking the ketone past the smaller cyanomethyl side chain. Subsequent reduction of the nitrile followed by *N*-Boc protection of the resulting amine would therefore provide the observed *anti* stereochemistry between the resulting alcohol and *N*-Boc ethylamine side chain (Figure 9, Panel B).

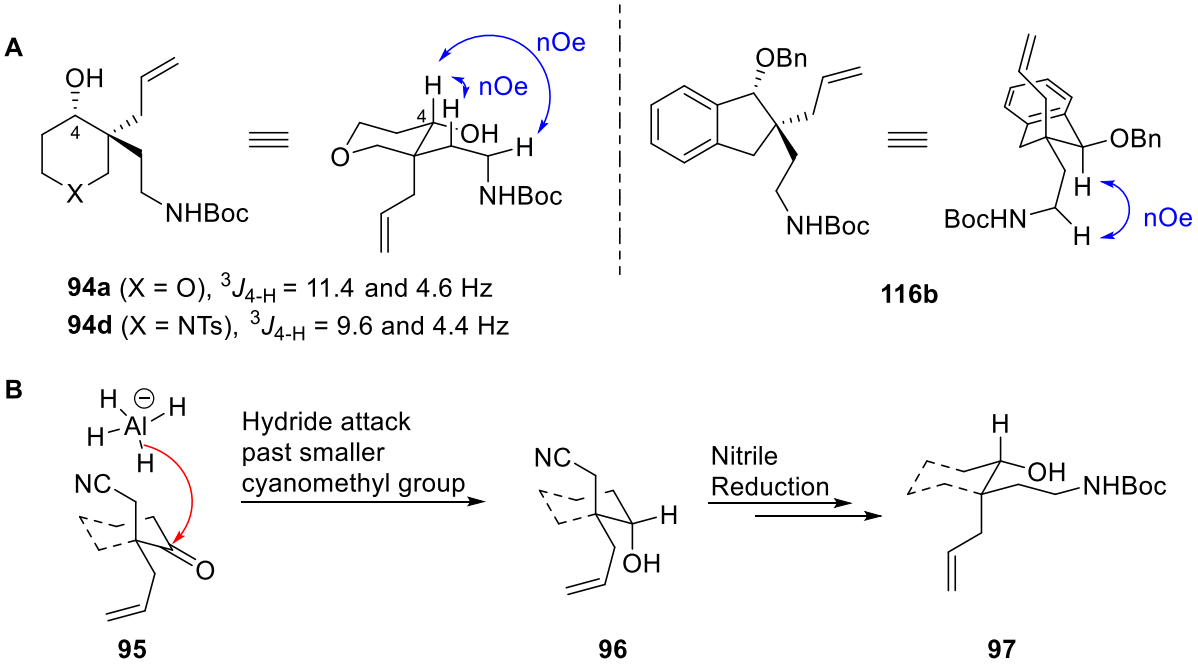
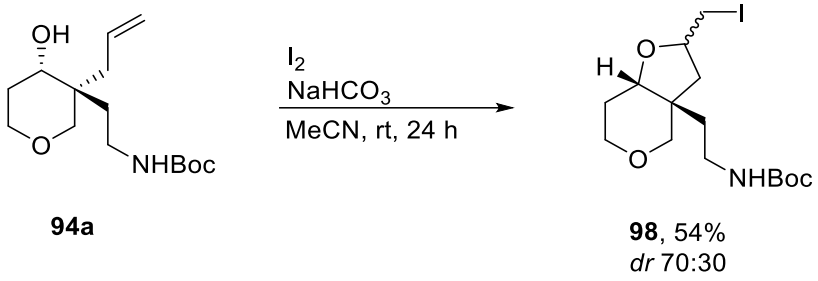


Figure 9: Determination of the relative configuration of reduced derivatives **94**. **Panel A:** Key nOe enhancements of the NOESY for derivatives **94a** and benzylated derivative **116b**. **Panel B:** Proposed rationale for *anti*-stereochemistry observed between alcohol and *N*-Boc ethylamine motifs.

With the reduced derivatives **94** now in hand, they could now be used for subsequent cyclisation reactions with the terminal alkene motif. It has been shown previously that iodocyclisation can allow cyclisation to occur between the alcohol and alkene reaction handles to prepare the corresponding fused-ring iodinated derivatives.[67,84] This reaction was first attempted with cyclisation precursor **94a** by reacting this compound with I_2 and $NaHCO_3$ in acetonitrile, which gave the fused-ring iodocyclised product **98** in 54% yield (Scheme 16). The reaction was found to be not very diastereoselective with this substrate giving compound **98** as a mixture of inseparable diastereomers (*dr* 70:30 by ^{1}H NMR) where the major diastereoisomer was not identified. Due to the relatively poor diastereoselectivity that was observed for this cyclisation with precursor **94a**, it was decided that this iodocyclisation pathway would not be repeated with the other precursor compounds. This was mainly because the poor diastereoselectivity of this reaction gave mixtures of inseparable diastereomers are not ideal for a final scaffold compound.



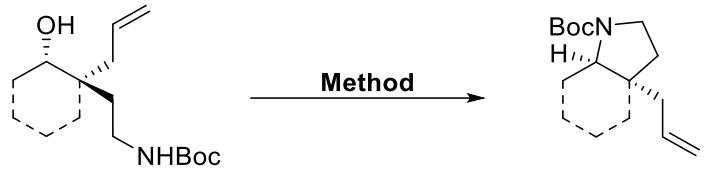
94a

98, 54%
dr 70:30

Scheme 16: Synthesis of fused-ring compound **98** *via* an iodocyclisation of alcohol **94a** to give the iodocyclised product as an inseparable mixture of diastereomers (*dr* 70:30).

2.3.2 Cyclisation between ketone and *N*-Boc amine reaction handles

The next cyclisation reactions to be investigated were cyclisations between the ketone and *N*-Boc amine reaction handles. As the secondary alcohols **94** could be prepared in good diastereoselectivity and have the *N*-Boc amine handle already unmasked *via* nitrile reduction, it was determined these reduced intermediates would be good substrates to begin the investigation into this cyclisation pathway. It was identified that these intermediates could provide two alternative pathways for the preparation of fused-ring pyrrolidine scaffolds after intramolecular cyclisation (Table 9). The secondary alcohol could first be reoxidised to the ketone which would allow cyclisation to occur between this ketone and *N*-Boc amine motifs to yield a hemiaminal intermediate. This hemiaminal could then be reduced to prepare the desired fused-ring pyrrolidines. Alternatively, the alcohol could be transformed into a suitable leaving group, for example *via* mesylation, which could then undergo S_N2-like intramolecular cyclisation with the *N*-Boc amine as the nucleophile to also yield the desired fused-ring pyrrolidines.[85] These two reaction pathways were first attempted with cyclisation precursor **94a** to determine which route was the most promising to then repeat with the other precursors **94b** and **94d**. Treatment of **94a** with Dess-Martin periodinane in DCM followed by hemiaminal reduction with Et_3SiH and TFA in DCM with subsequent Boc-reprotection of the amine gave pyrrolidine **99a** in 24% yield (Table 9, Entry 1a).[86]



94 Reduced derivatives

99 Fused-ring pyrrolidines

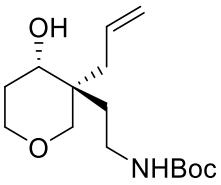
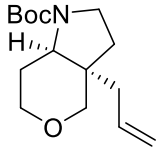
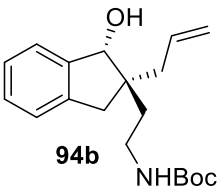
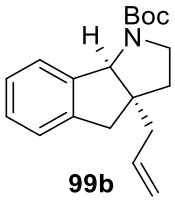
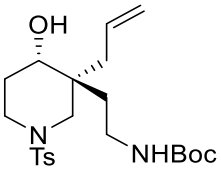
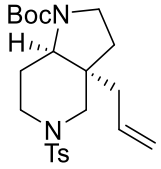
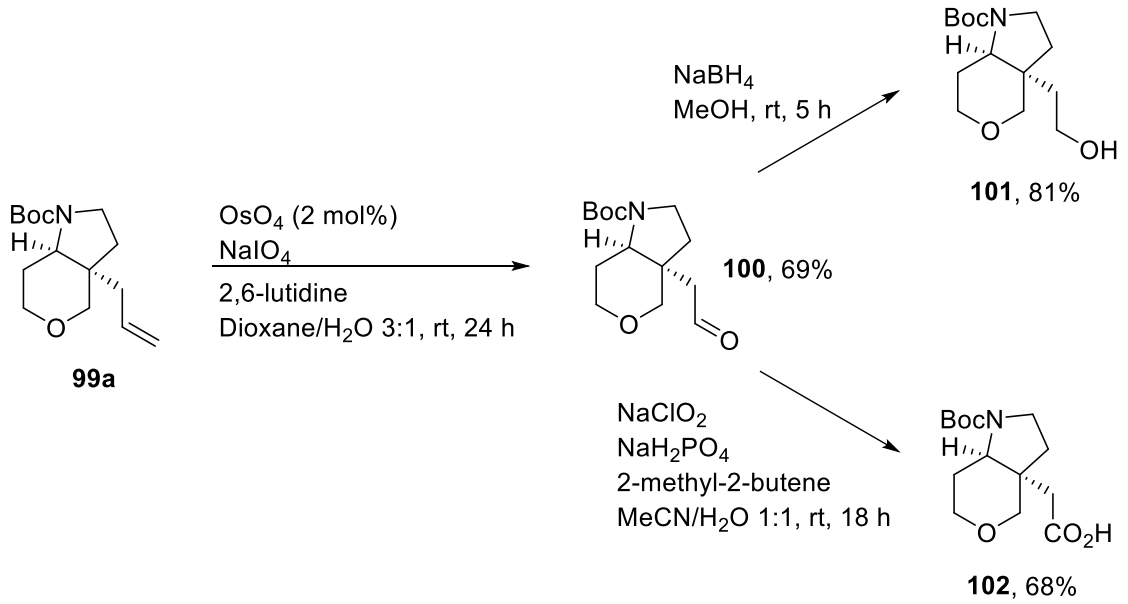
Entry	Reduced derivatives	[a]Method	Fused-ring pyrrolidines	[b]Yield (*dr*)[c]
1a **1b**	 **94a**	A **B**	 **99a**	24% (>95:<5) **43% (>95:<5)**
2	 **94b**	**B**	 **99b**	**68% (>95:<5)**
3	 **94d**	B	 **99c**	-[d]

Table 9: Cyclisation of precursors **94** to give fused-ring pyrrolidines **99** *via* either oxidation/hemiaminal reduction or S_N2-like intramolecular cyclisation pathways. [a]**Method: A:** (i) Dess-Martin periodinane, DCM, rt, 24 h; (ii) Et_3SiH, TFA, DCM, rt, 18 h then Boc_2O, Et_3N, DCM, rt, 18 h; **B:** (i) MsCl, Et_3N, DCM, rt, 18 h then TFA, DCM, rt, 5 h; (ii) Et_3N, DCM, rt, 18h then Boc_2O, DCM, rt, 18 h. [b]Isolated yield of purified pyrrolidines calculated over all reaction steps performed. [c]Determined by 400 or 500 MHz ^1H NMR spectroscopic analysis of purified compound. [d]Complex mixture of products observed.

Alternatively, reacting precursor **94a** with MsCl in DCM to generate the corresponding mesylate followed by deprotection of the *N*-Boc ethylamine group with TFA in DCM induced intramolecular S_N2 cyclisation, where subsequent Boc-reprotection of the secondary amine gave the same pyrrolidine compound **99a** in a higher 43% yield (Table 9, Entry 1b).[85] This result led to the decision to use the S_N2-like cyclisation pathway on the other cyclisation precursors due to the higher overall yield obtained

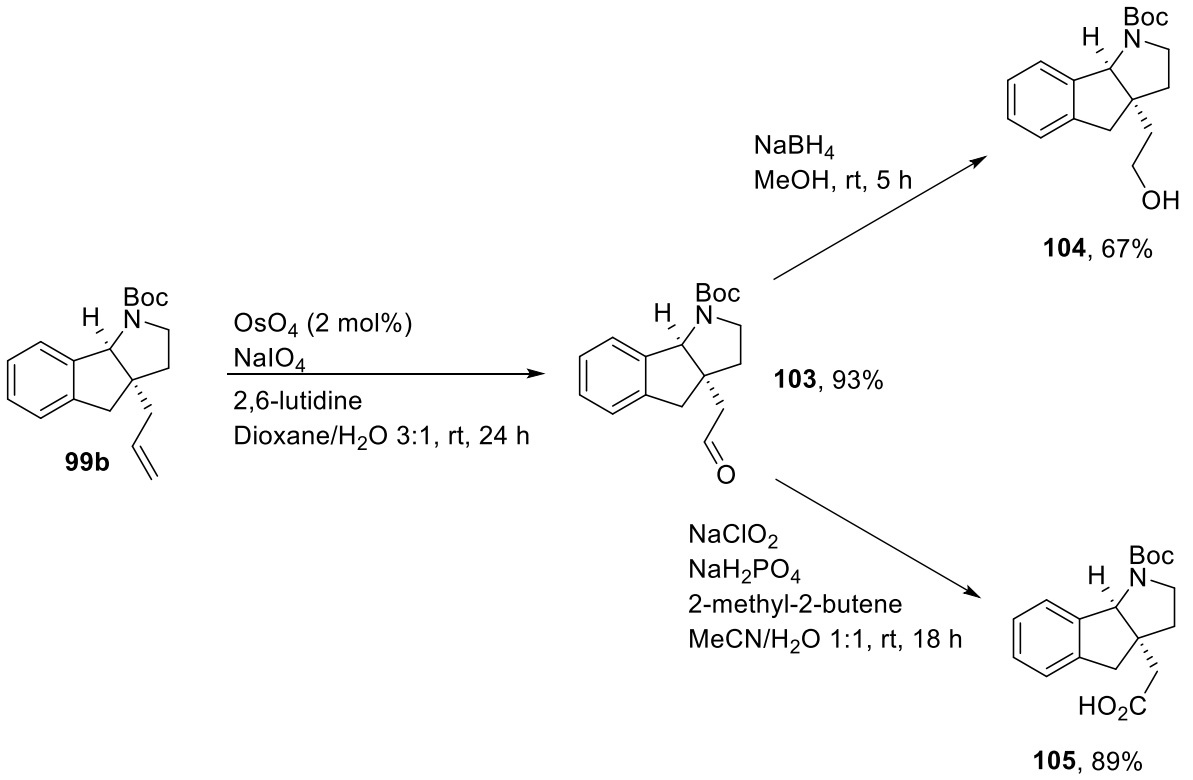
and an easier final purification step. It was found that this cyclisation was only reproducible with indanone precursor **94b**, where the corresponding pyrrolidine compound **99b** was isolated in 68% yield (Table 9, Entry 2). The two pyrrolidines prepared *via* this method were isolated as single diastereomers as the minor diastereomers from the alcohol starting materials **94a-b** (*dr* 80:20-84:16) were removed during the final purification step in each case.

After the success of this cyclisation, it was decided that ideally the final pyrrolidine scaffolds should possess at least two points of diversification for scaffold decoration. This would make the final pyrrolidine scaffolds more desirable as it would allow for scaffold decoration and growth along different reaction vectors, therefore targeting a wider, more diverse region of chemical space. Therefore, manipulation of the terminal alkene in pyrrolidines **99** would enable an additional point of diversification to be introduced as desired. Three alternative functional handles were identified for preparation at this position in each of the pyrrolidines. The handles chosen were aldehyde, alcohol and carboxylic acid functional groups as these groups lend themselves to further diversification through alkylation, reductive amination and amide coupling chemistry (Scheme 17).



Scheme 17: Synthesis of three final pyrrolidine scaffolds from intermediate **99a** *via* Lemieux-Johnson oxidative cleavage (**100**), aldehyde reduction (**101**) and Pinnick oxidation (**102**).

The transformation of the terminal alkene to the aldehyde was achieved *via* Lemieux-Johnson oxidative cleavage of the alkene to give the corresponding aldehyde **100** in 69% yield.[87] The successful transformation of the alkene of the aldehyde functional group then enabled the corresponding alcohol **101** to be prepared by $NaBH_4$ reduction in 81% yield. Finally, the carboxylic acid analogue **102** was successfully synthesised through performing a Pinnick oxidation ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, MeCN/H_2O 3:1, rt) on aldehyde **100** using standard literature conditions, giving the desired final scaffold **102** in 68% yield.[88,89] With three final scaffolds successfully being prepared through this chemistry, the reaction pathway was repeated with indanone-based pyrrolidine intermediate **99b** in order to demonstrate reaction reproducibility with alternate intermediates and to add more compounds to the final scaffold library (Scheme 18).



Scheme 18: Synthesis of three final pyrrolidine scaffolds from indanone-based intermediate **99b** *via* Lemieux-Johnson oxidative cleavage (**103**), aldehyde reduction (**104**) and Pinnick oxidation (**105**).

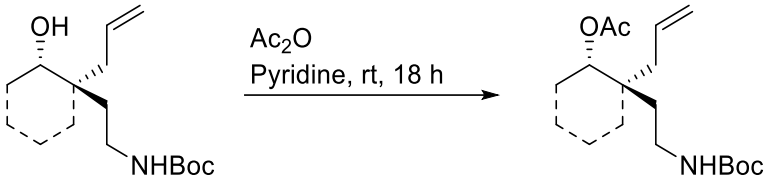
As with the THP-based intermediate **99a** before, the terminal alkene on **99b** was manipulated by performing a Lemieux-Johnson oxidative cleavage to give the

corresponding aldehyde **103** in an excellent 93% yield.[87] This aldehyde intermediate could then be either reduced to give the alcohol derivative or oxidised to give the corresponding carboxylic acid derivative. The reduction of aldehyde intermediate **103** with $NaBH_4$ gave the corresponding alcohol scaffold **104** in 67% yield. The carboxylic acid derivative **105** was then able to be prepared *via* Pinnick oxidation of aldehyde **103** in an excellent 89% yield, under identical reaction conditions that were used previously for the preparation of THP-based analogue **102**.[88,89]

This reaction pathway proved to be a successful route for the synthesis of six fused-ring pyrrolidine scaffolds, based off two of the cyclisation precursors prepared. The manipulation of the terminal alkene in intermediates **99a-b** allowed for the synthesis of final scaffolds that contained two points of diversification in their structure for subsequent scaffold decoration to target lead-like chemical space as originally designed.

2.3.3 Cyclisation between *N*-Boc amine and terminal alkene reaction handles

The next cyclisations to be investigated were cyclisations between the *N*-Boc amine and terminal alkene reaction handles as this cyclisation would provide spirocyclic compounds, therefore adding to the overall structural diversity of the final scaffold library. As with the cyclisations previously discussed (Section 2.3.2), secondary alcohols **94** could be prepared in good diastereoselectivity and have the *N*-Boc amine handle already unmasked *via* nitrile reduction. Therefore, it was determined these reduced intermediates would be good substrates to begin the investigation into this cyclisation pathway. In order to avoid any unwanted side reactions, the secondary alcohols were first acetyl protected (Table 10). This protecting group was chosen as it is an orthogonal protecting group to the *N*-Boc amine. Therefore, this would allow selective deprotection of either the *O*-acetyl (K_2CO_3, MeOH) or *N*-Boc (TFA, DCM) groups in the final scaffolds to allow selective decoration at either the alcohol or amine points of diversification. Secondary alcohol intermediates **94** were treated with Ac_2O in pyridine to prepare the acetyl protected derivatives **106** (Table 10).[67,90] The reactions proceeded cleanly in good yield (81-90%) to give the corresponding *O*-acetyl protected products **106** as desired (Table 10, Entries 1-3).



94
Alcohol

106
Acetyl protected derivative

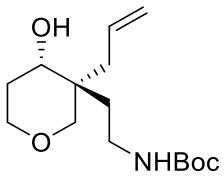
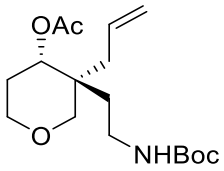
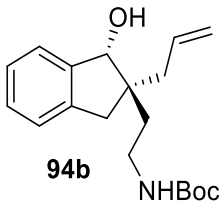
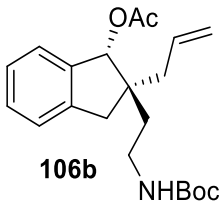
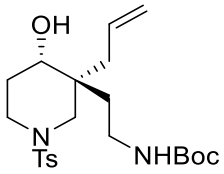
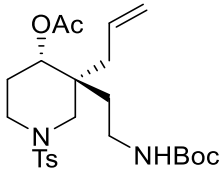
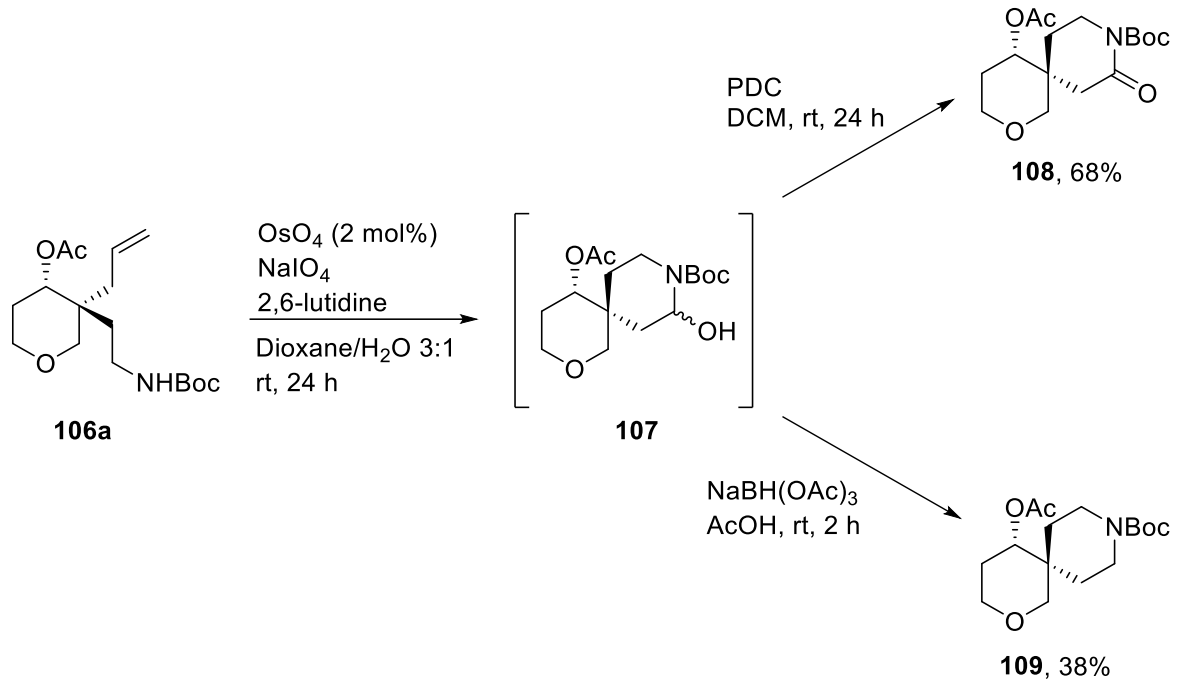
Entry	Alcohol	Acetyl protected derivative	Yield
1	 **94a**	 **106a**	**90%[a]**
2	 **94b**	 **106b**	**82%[a]**
3	 **94d**	 **106c**	**81%[b]**

Table 10: Acetyl protection of secondary alcohols **94** to prepare to acetyl protected derivatives **106**. [a]Isolated yield of purified acetyl protected derivatives. [b]Yield of acetyl protected derivative calculated after work up during a telescoped reaction pathway in the synthesis of enecarbamate **115**.

The acetyl protected derivatives **106** were isolated as single diastereomers due to the minor diastereomer taken through from the alcohol starting materials being removed during final purification.

With the acetyl protected alcohols now in hand, the investigation into cyclisation between the *N*-Boc amine and ketone groups to prepare the corresponding spirocycles could now begin. Acetyl protected intermediate **106a** was first subject to

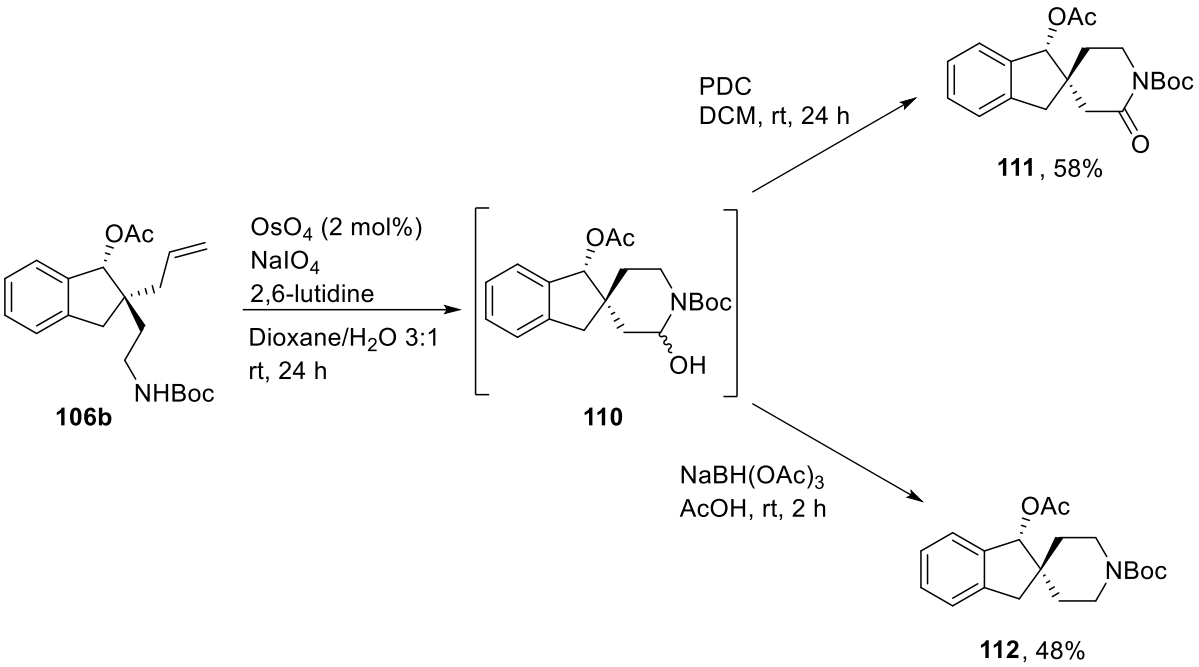
Lemieux-Johnson oxidative cleavage of the terminal alkene by treatment with 2 mol% OsO_4 and $NaIO_4$ to give the corresponding aldehyde.[87] This subsequently induced a cyclisation between the *N*-Boc ethyl side chain and the aldehyde to provide the corresponding hemiaminal **107** as a mixture of diastereomers (*dr* approx. 50:50). This hemiaminal intermediate was then either oxidised with PDC to give the spirocyclic lactam **108** or reduced with $NaBH(OAc)_3$ in acetic acid to give the corresponding spirocyclic *N*-Boc amine **109** (Scheme 19).[67,91,92] Acetic acid was chosen as the acid of choice to form the *N*-Boc iminium intermediate as a mild acid was needed to avoid unwanted *N*-Boc deprotection during the reaction. Spirocyclic lactam **108** was obtained in 68% yield after a telescoped procedure from acetyl derivative **106a**. The spirocyclic *N*-Boc amine scaffold **109** was isolated in 38% yield after another telescoped procedure from acetyl derivative **106a**.



Scheme 19: Synthesis of spirocyclic scaffolds **108** and **109** *via* Lemieux-Johnson oxidative cleavage of starting material **106a** followed by hemiaminal oxidation or reduction.

After the success of this cyclisation pathway with acetyl intermediate **106a**, the same telescoped reaction pathway was performed with the indanone-based acetyl compound **106b** in order to add more spirocyclic compounds to the final scaffold

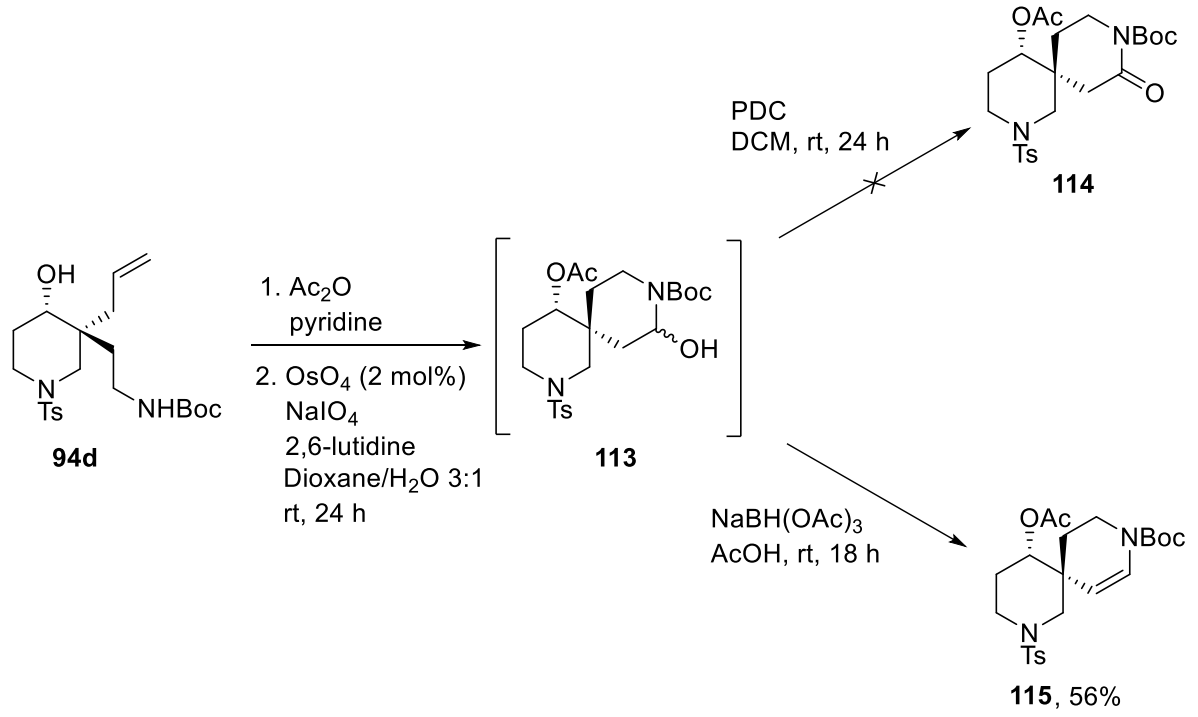
library. Treatment of **106b** with 2 mol% OsO_4 and $NaIO_4$ gave the hemiaminal intermediate **110** (*dr* approx. 50:50) that was then oxidised with PDC in DCM to give the corresponding spirocyclic lactam **111** in 58% yield (Scheme 20).[87,91] Reduction of hemiaminal intermediate **110** with $NaBH(OAc)_3$ in acetic acid provided spirocyclic *N*-Boc amine **112** in 48% yield (Scheme 20).[92]



Scheme 20: Synthetic route to prepare spirocyclic scaffolds **111** and **112** *via* the Lemieux-Johnson oxidative cleavage pathway followed by either oxidation or reduction.

This reaction pathway was also attempted with *N*-Ts alcohol **94d** *via* a telescoped reaction procedure to give the desired spirocyclic scaffold products. Acetylation of the alcohol derivative **94d** gave the *O*-acetyl protected derivative which was then used directly in the subsequent cyclisation reaction. The acetylated intermediate was then subject to Lemieux-Johnson oxidative cleavage to give the hemiaminal intermediate **113** as a mixture of diasteromers.[87] Hemiaminal **113** could then either undergo oxidation or reduction as previously employed when preparing the THP and indanone based spirocyclic scaffolds (Scheme 21). Unfortunately, the telescoped reaction pathway *via* PDC hemiaminal oxidation to give the spirocyclic lactam **114** was unsuccessful and a complex mixture of unidentified products were isolated. However,

reduction of the hemiaminal intermediate **113** with $NaBH(OAc)_3$ in the presence of acetic acid surprisingly gave the spirocyclic *N*-Boc enecarbamate scaffold **115** in 56% yield instead of the desired spirocyclic *N*-Boc amine, as observed previously with acetylated derivatives **106a** and **106b**.

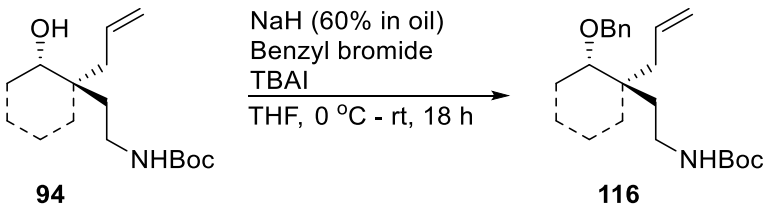


Scheme 21: The attempted synthesis of spirocyclic lactam **114** from alcohol **94d** and the synthesis of spirocyclic enecarbamate scaffold **115** from alcohol derivative **94d**.

Surprisingly, only enecarbamate **115** was observed after the $NaBH(OAc)_3$ reduction step and the expected spirocyclic amine product was not observed. This enecarbamate product was also not observed with either of the previous two precursors. One possible explanation for the observation of the enecarbamate product could be due to an acid-mediated elimination of the hemiaminal hydroxyl group, leading to selective formation of the enecarbamate product **115** instead of the expected spirocyclic amine. However, it is still not clear why this occurred preferentially with the piperidinone precursor and not the other two precursors previously employed.

The final cyclisation attempted between the *N*-Boc amine and ketone motifs was a Pd-catalysed aminoarylation reaction to prepare the corresponding spirocyclic scaffolds.

However, due to the basic nature of this chemistry, it was decided to change the acetyl protecting group on the alcohol intermediates **94** to a more base stable protecting group. It has been shown previously that the benzyl protecting group was the most successful when this chemistry was employed on similar substrates.[67] Therefore, the *O*-Bn protected derivatives **116** were first prepared by treating alcohols **94** with NaH, benzyl bromide and TBAI in THF (Table 11).[93]



94 Alcohol

116 *O*-Bn derivative

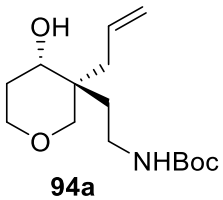
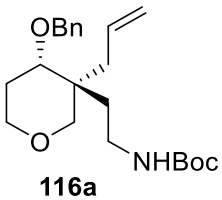
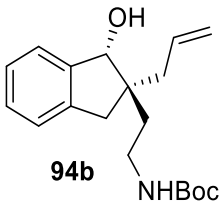
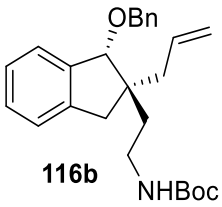
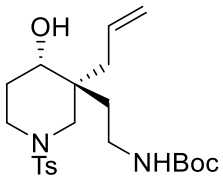
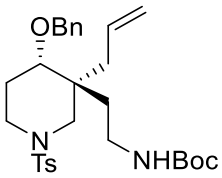
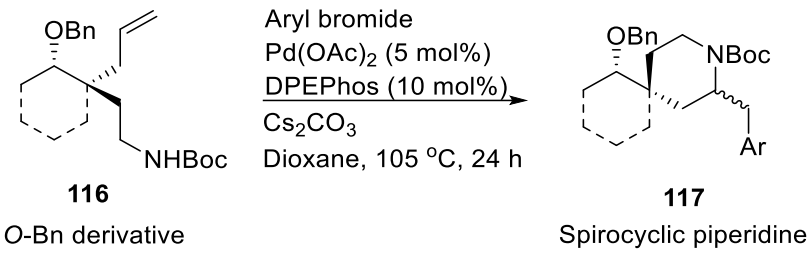
Entry	Alcohol	*O*-Bn derivative	Yield[a]
1	 **94a**	 **116a**	**71%**
2	 **94b**	 **116b**	**75%**
3	 **94d**	 **116c**	-[b]

Table 11: Benzyl protection of alcohols **94** to give the corresponding *O*-Bn derivatives **116** for the subsequent investigation into aminoarylation chemistry. [a]Isolated yield of purified *O*-Bn derivative. [b]Observed complex mixture.

It was found that the benzyl protection of alcohols **94** was successful with compounds **94a** and **94b** providing their *O*-Bn derivatives **116a** and **116b** in 71% and 75% yields

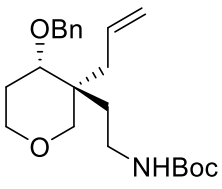
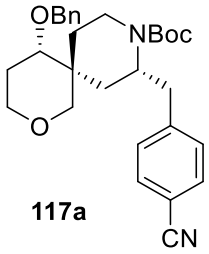
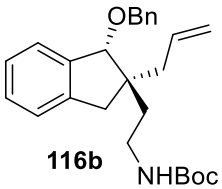
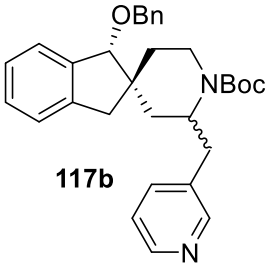
respectively. Unfortunately, the attempted benzyl protection of alcohol **94d** failed to yield any of the desired product, with only a mixture of starting material and degradation products observed by TLC, LCMS and analysis of the crude material by 400 MHz ^{1}H NMR spectroscopy.

With *O*-benzylated derivatives **116** now in hand, the investigation into aminoarylation cyclisation chemistry could now begin. Previous work into this chemistry has shown these reactions to be robust in the preparation of pyrrolidine-based spirocycles, however, there is little evidence in the current literature where this chemistry has been used to prepare the corresponding piperidine derivatives.[67,94] Nevertheless, benzyl protected derivatives **116** were treated with various aryl bromides, 5 mol% $Pd(OAc)_2$, 10 mol% DPEPhos ligand and Cs_2CO_3 in 1,4-dioxane at 105 ^{o}C for 24 h to give the corresponding spirocyclic piperidine scaffolds **117** (Table 12).[94]



116
O-Bn derivative

117
Spirocyclic piperidine

Entry	*O*-Bn derivative	Aryl bromide	Spirocyclic piperidine	[a]Yield (*dr*)[b]
1	 **116a**	**4-bromobenzonitrile**	 **117a**	**62% (80:20)**
2	 **116b**	**3-bromopyridine**	 **117b**	**40% (65:35)**

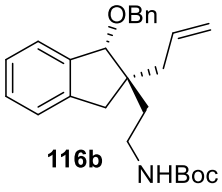
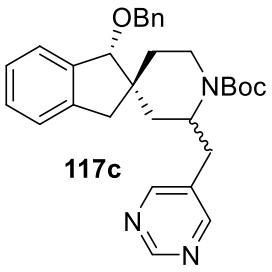
3		**5-bromopyrimidine**		**30% (65:35)**

Table 12: The formation of spirocyclic piperidine scaffolds **117** through aminoarylation chemistry with different aryl bromides employed. [a]Isolated yield of spirocyclic piperidine scaffold. Determined by 400 or 500 MHz ^{1}H NMR spectroscopic analysis of purified compound.

It was found that this aminoarylation cyclisation was successful with all the *O*-Bn derivatives, where the corresponding spirocyclic piperidine scaffolds could be isolated in 30-62% yield. However, it was determined that this aminoarylation reaction was not very diastereoselective with these substrates, as the piperidine scaffolds **117** could only be isolated as a mixture of diastereomers. All the crude products had a crude *dr* 65:35 but only with scaffold **117a** could the diastereomers be separated enough to give an improved *dr* 80:20 after purification by column chromatography. Due to the poor diastereoselectivity and difficult separation of the diastereomers obtained, it was decided to not investigate the reaction further with more aryl bromides. As scaffold **117a** could be obtained as mainly a single diastereomer, the relative configuration of the new chiral centre was investigated through NOESY (500 MHz) analysis of the corresponding ^{1}H NMR spectrum (Figure 10). There was an nOe interaction observed between protons 1-H_A and 8-H which suggested that this new chiral centre at position 8 has the opposite relative stereochemistry (*S**) to the stereocentre at position 5 (*R**) in scaffold **117a**. If these two stereocentres had the same relative stereochemistry, then this nOe interaction would not be observed between protons 1-H_A and 8-H.

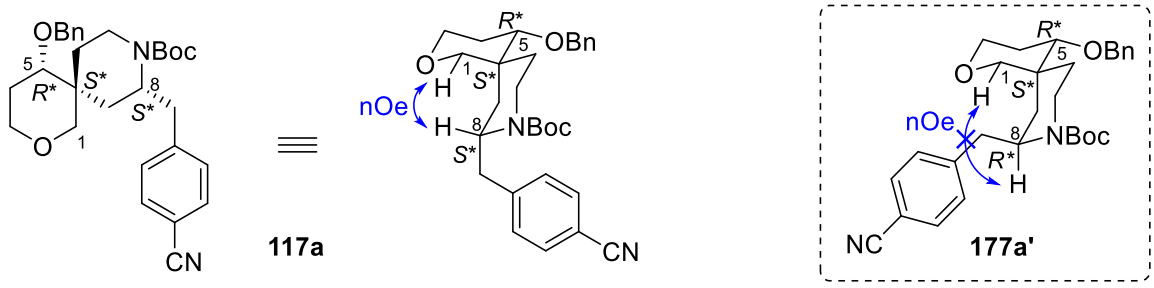
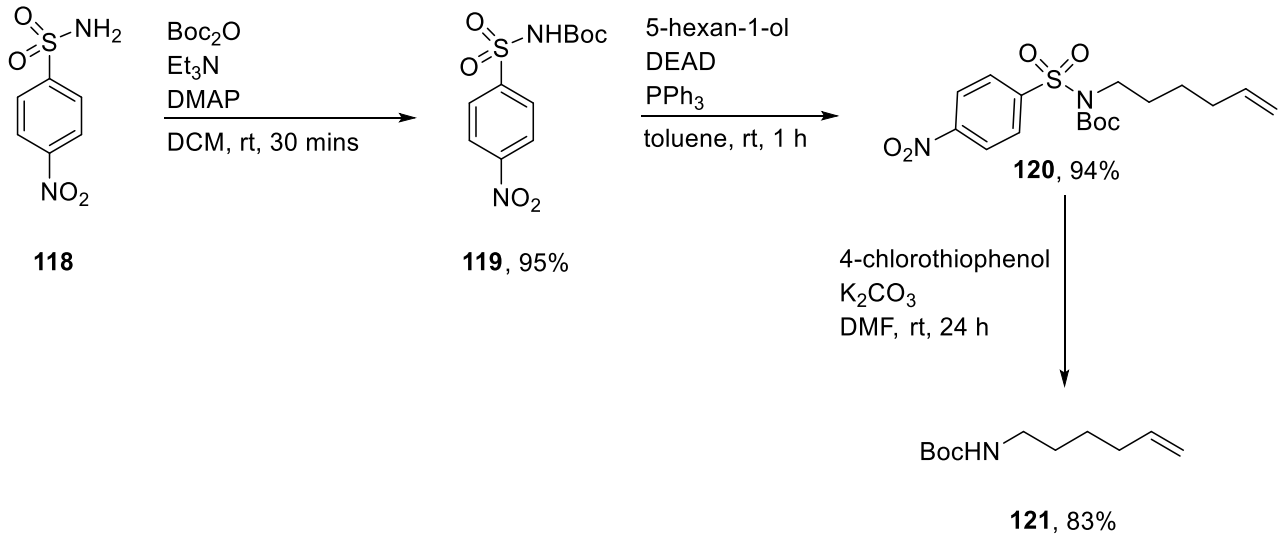


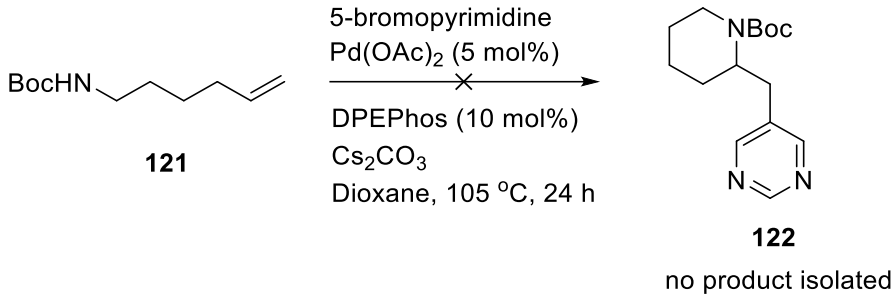
Figure 10: Determination of the relative stereochemistry in spirocyclic scaffold **117a** where a key nOe enhancement in the NOESY for scaffold **117a** was observed.

Given the limited literature precedent for the cyclisation of *N*-Boc-pentenylamines *via* aminoarylation cyclisation chemistry, we envisaged that the success of this cyclisation may be, in part, due to the Thorpe–Ingold effect.[95] To investigate this further, we decided to prepare open-chain analogue **121** to test identical aminoarylation cyclisation conditions on this compound to determine if cyclisation would occur without any substituents on the carbon chain. The open chain compound **121** was first prepared by initially *N*-Boc protecting starting material **118** (95% yield), followed by a Mitsunobu reaction with 5-hexan-1-ol to give the *N*-Boc-*N*-Ns derivative **120** in 94% yield.[96] Subsequent *N*-nosyl deprotection with 4-chlorothiophenol and K_2CO_3 in DMF gave the desired open chain analogue **121** in 83% yield (Scheme 22).[97]



Scheme 22: Synthesis of open-chain compound **121** *via* Mitsunobu reaction with 5-hexan-1-ol and subsequent *N*-Ns deprotection.

The aminoarylation reaction was then performed on open chain compound **121** with 5-bromopyrimidine as the aryl bromide. It was determined that after the reaction was left for 24 hours no cyclisation was observed, with only starting material **121** and 5-bromopyrimidine being recovered (Scheme 23).



Scheme 23: Failed aminoarylation reaction with open chain starting material **121** and 5-bromopyrimidine, which gave no observed cyclised product **122**.

The failure of this aminoarylation with the open chain substrate **121** indicated that the Thorpe-Ingold effect may play a significant role in allowing cyclisations to prepare *N*-Boc piperidines **117** using this aminoarylation cyclisation chemistry.

2.3.4 Summary of diverse scaffold library prepared

A modular unified synthetic approach enabled the successful preparation of a structurally diverse scaffold library containing 17 final scaffolds from three different cyclisation precursor compounds (Figures 11 and 12). The final scaffolds prepared contained both spirocyclic and fused ring systems, which demonstrated the overall success in the preparation of sp^3-rich and structurally diverse compounds as designed. Each scaffold also contained several points of diversification which can enable subsequent scaffold decoration in order to target lead-like chemical space as designed. This unified approach first involved the synthesis of a range of cyclisation precursor compounds that contained multiple reaction handles in their structure. These handles were reacted together *via* intramolecular cyclisations in order to prepare the final library of diverse scaffolds. This toolkit of cyclisation reactions was first employed on THP cyclisation precursor **88a** to successfully prepare 8 scaffolds.

The most promising cyclisations were then attempted on precursors **88c** and **88e** to prepare an additional 9 scaffolds to add to the final library. Therefore, the toolkit of intramolecular cyclisation reactions developed during this unified synthetic approach were found to be generally reproduceable on the cyclisation precursors prepared, which enabled the efficient generation this shape and structurally diverse scaffold library to target lead-like chemical space.

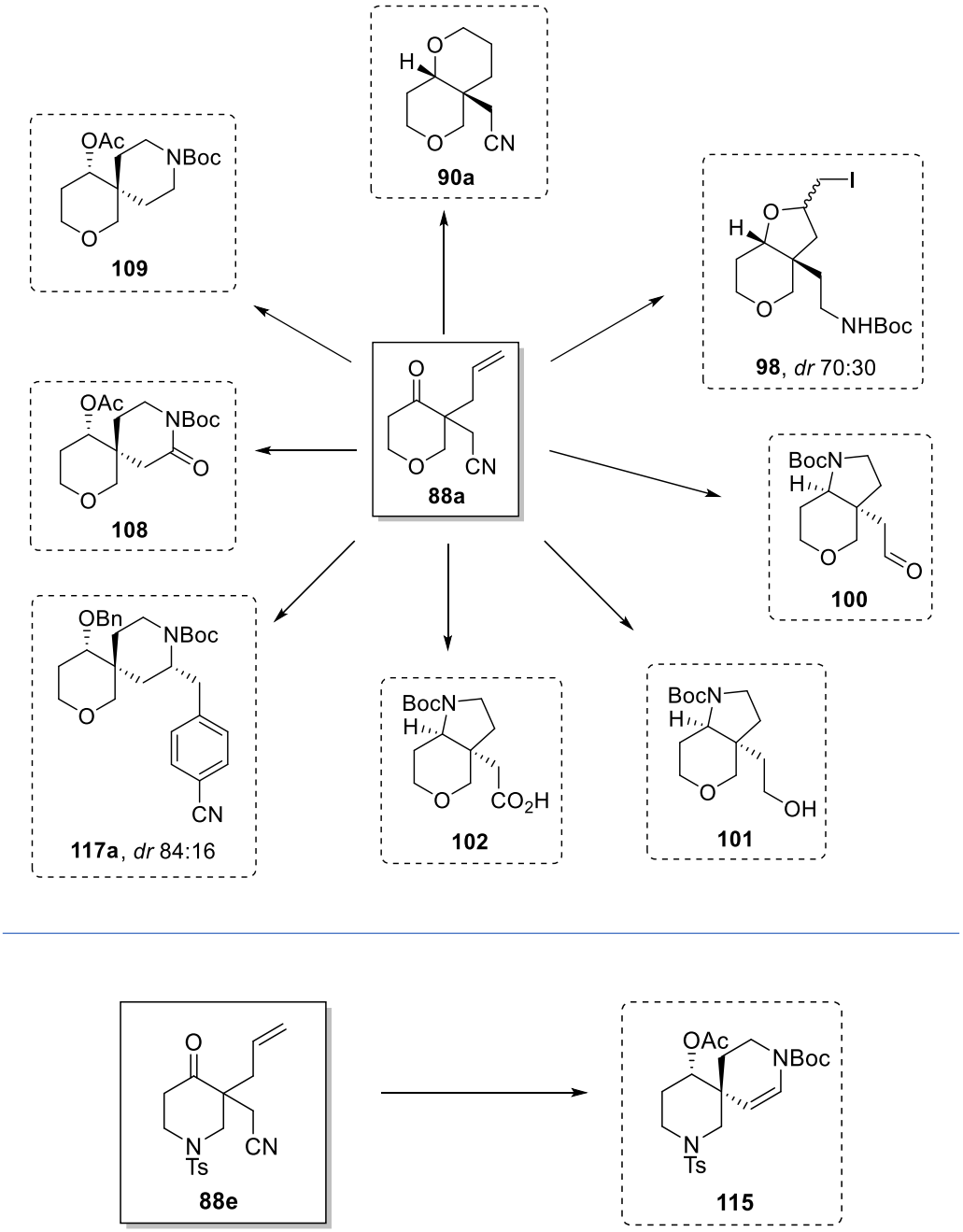


Figure 11: Overview of **t**he nine final scaffolds that were synthesised from THP cyclisation precursor **88a** and *N*-Ts piperidinone precursor **88e** through this synthetic approach.

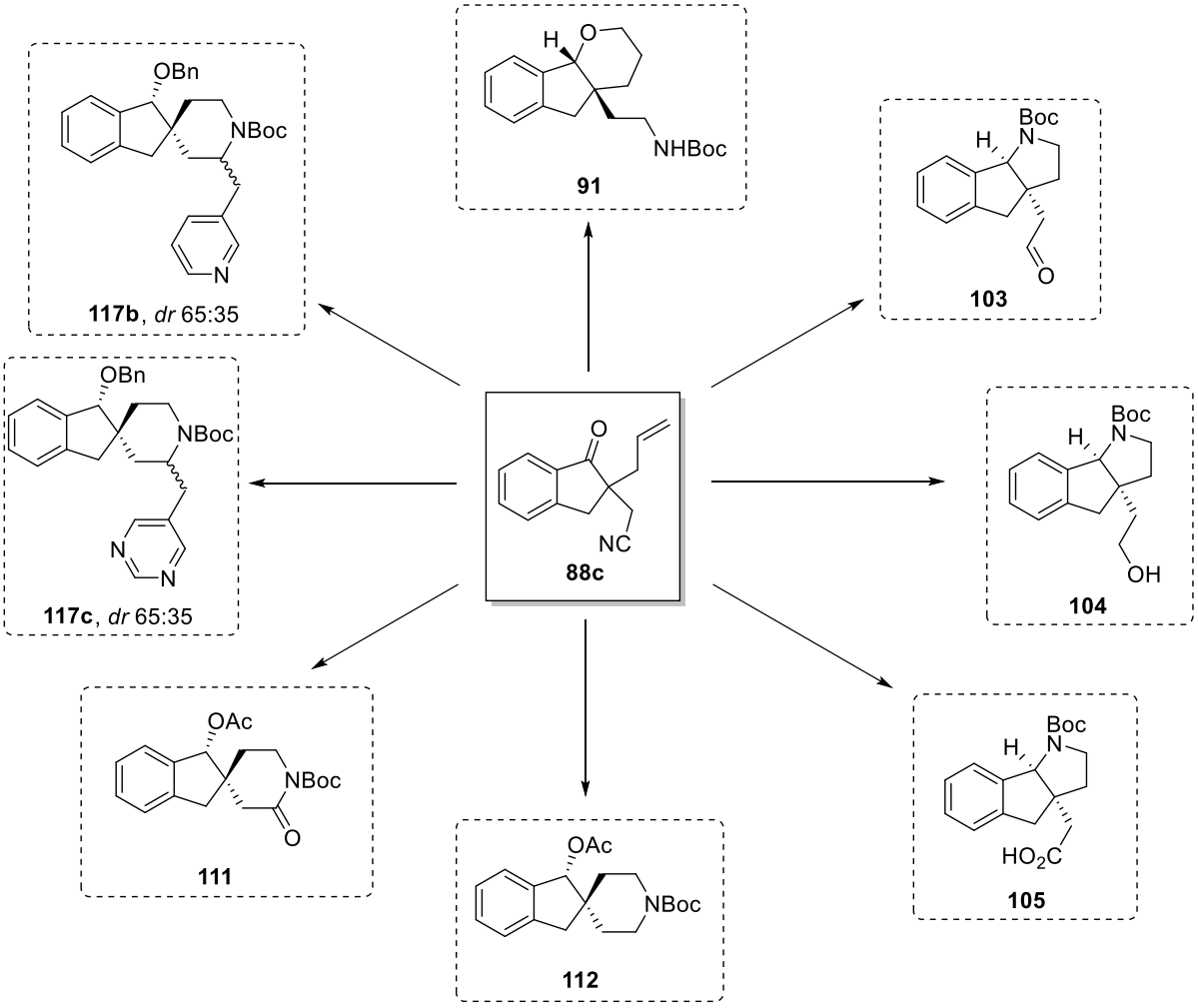


Figure 12: Overview of the final eight scaffolds prepared though this synthetic approach that are derived from indanone-based precursor **88c**

2.4 Computational analysis of first scaffold library

The final scaffolds prepared were analysed using a variety of computational methods to assess the overall novelty, shape diversity and molecular properties of the scaffold library to determine whether these scaffolds can target lead-like chemical space as intended. The molecular properties and shape diversity of the final library of 17 scaffolds were first analysed using LLAMA (Lead-Likeness And Molecular Analysis). This is a computational tool which can analyse virtual libraries of compounds that are derived from specific scaffolds.[63] Analysis of the undecorated scaffold library showed that many of these compounds had molecular properties that were appropriate for

application as fragments in fragment-based lead discovery (*e.g.* 140 < *MW* < 230 and 0 < *c*logP < 2) as many compounds were found to sit in fragment-like chemical space (Figure 13).[98] Secondly, none of the Murcko frameworks[99] of the scaffolds were found as substructures in a random 2% sample of the ZINC database of commercially-available compounds.[100] Furthermore, analysis of the PMI plot generated for the undecorated library provided an excellent visual representation for the shape diversity of the scaffold library. This PMI plot showed clearly that the scaffold library had significant shape diversity as designed, with many of the scaffolds prepared moving away from the rod-disk axis into more three-dimensional areas of chemical space.

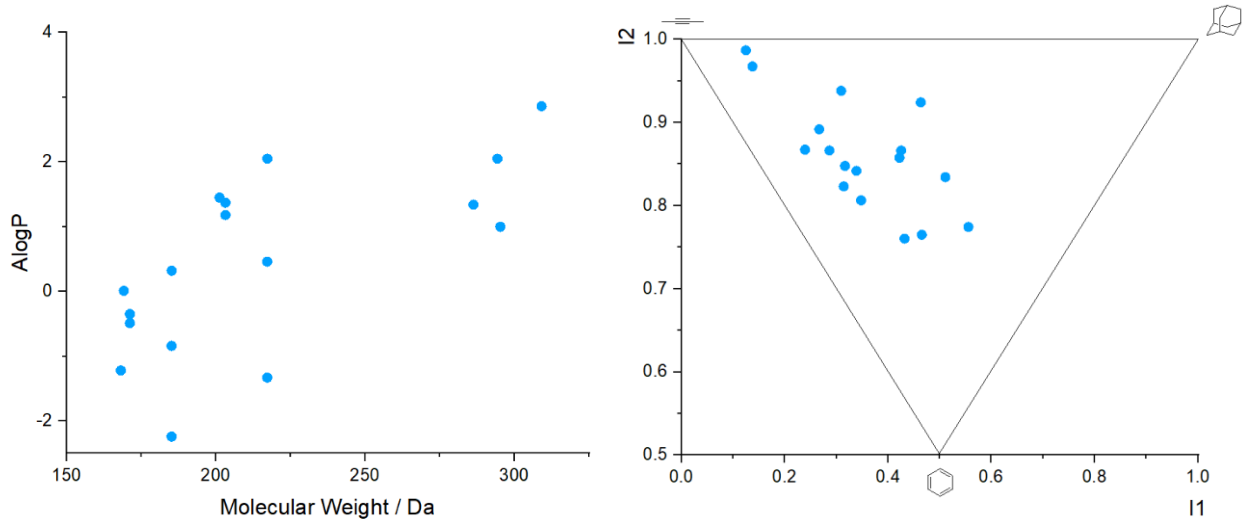


Figure 13: Computational analysis of the undecorated scaffold library using LLAMA in order to assess the chemical space and shape diversity of the scaffold library prepared.

Decoration of the scaffolds using a selection of medicinally relevant capping groups was also performed to assess whether the scaffolds can successfully target lead-like chemical space as required (Figure 14). The scaffolds were decorated only once through one of the available points of diversification incorporated into each of the molecules. Firstly, the lead-likeness of the virtual scaffold library was analysed, and it was found that approximately 60% of the decorated scaffolds did lie in lead-like chemical space. Secondly, a PMI plot of the decorated scaffolds was generated, which confirmed that many of these virtual lead-like compounds also showed significant shape diversity. The fraction of sp^3-hybridised carbons (Fsp^3) in the virtual decorated scaffold library was also analysed. This parameter was analysed as it has been shown

that compounds with more Fsp^3 character correlated strongly with success in drug discovery, which has led to the recent drive for the efficient preparation of more sp^3-rich screening compounds (Section 1.2.2).[26] The mean Fsp^3 of the decorated scaffold library was found to be 0.58 which shows significantly higher Fsp^3 in comparison with a random 1% sample from the ZINC database (0.33). Therefore, this highlighted the apparent success of this unified B/C/P synthetic approach in preparing decorated scaffold libraries with higher Fsp^3 than many commercially available compounds.

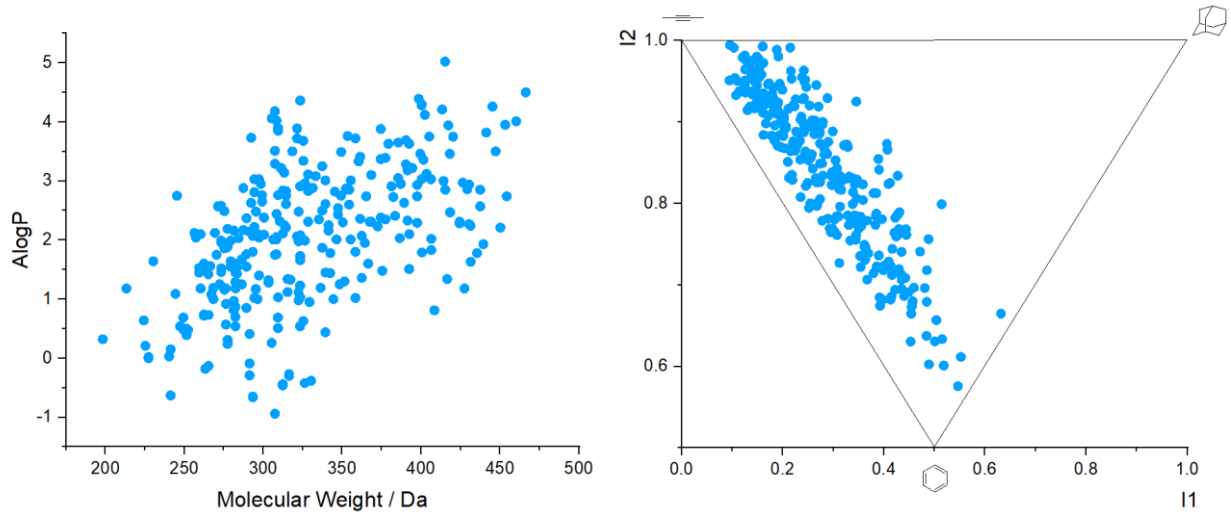


Figure 14: Computational analysis of a virtual scaffold library after decoration with one capping group to investigate the lead-likeness and molecular shape diversity of this virtual library.

Finally, the skeletal diversity and relationship between each of the scaffolds in the final library were investigated be construction of a hierarchical 'scaffold tree' originally developed by Waldmann and co-workers.[71] This analysis involves deconstruction of the scaffolds through iterative removal of rings until a final set of parental frameworks are obtained. The rules used to determine the priority of ring removal at each iteration step typically involve the removal of peripheral rings while the more central and complex rings are retained. The scaffold tree analysis of the 17 scaffolds prepared found that they were based around eleven different frameworks at the graph-node-bond level. These could then be taken back to give five different parental monocyclic ring systems (Figure 15). Additionally, the graph-node-bond frameworks for scaffolds **109** and **112** were found to be sub-frameworks of the graph-node-bond frameworks corresponding to scaffolds **117a** and **117b-c** respectively.

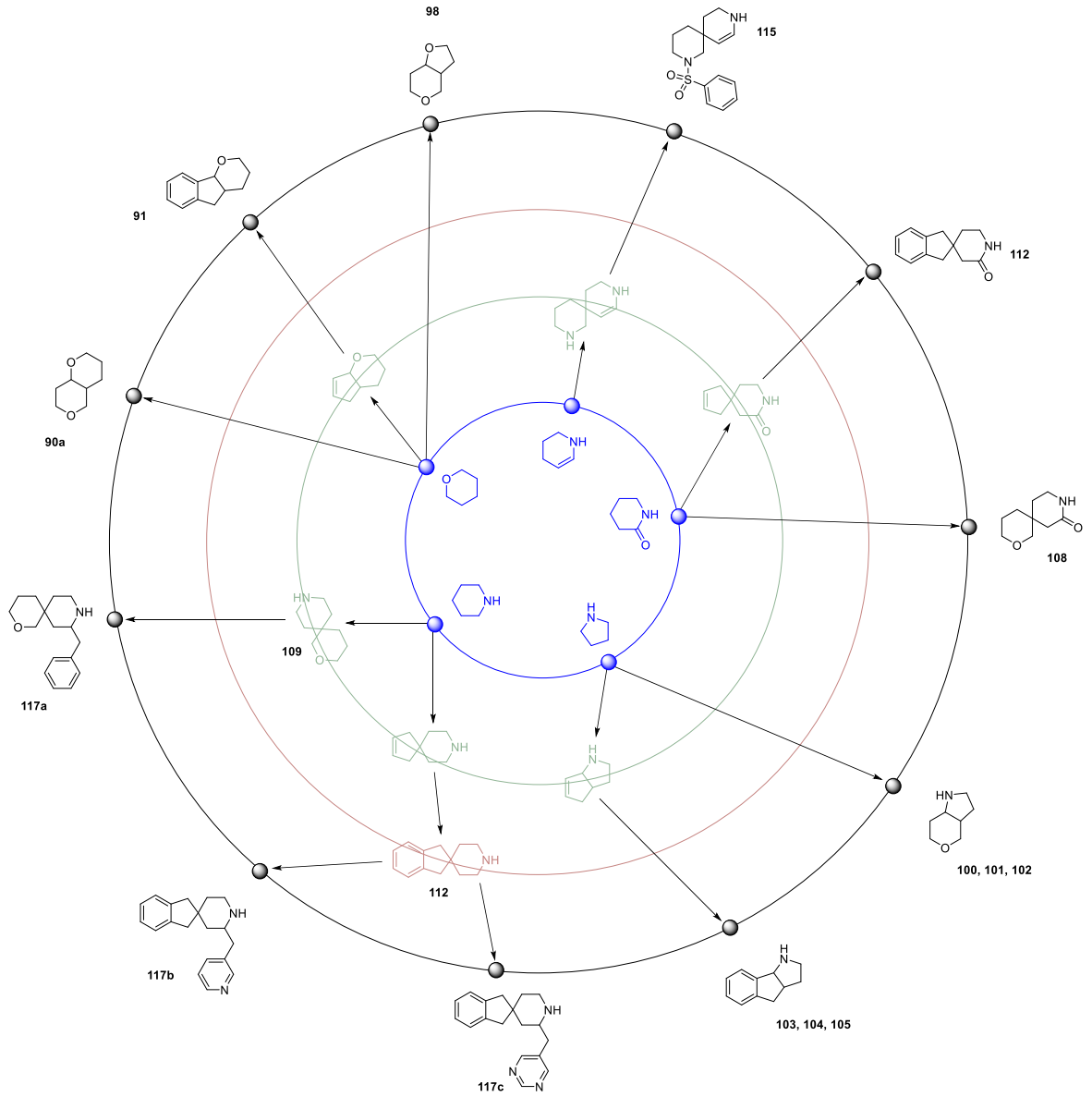


Figure 15: The hierarchical scaffold tree analysis of the final diverse scaffold library. The 17 final scaffolds were based on eleven different frameworks at the graph-node-bond level (black) that could be stripped back to give five parental monocyclic frameworks (blue). The final scaffolds from which the frameworks are derived are indicated.

This analysis indicated that the library is sufficiently skeletally diverse as many of the final scaffolds are based around different monocyclic parental frameworks. This result also highlights the overall success of this unified approach for the synthesis of diverse scaffolds, as even though the majority of the final scaffolds were prepared from only two cyclisation precursors, the five parental monocyclic frameworks highlighted in this analysis indicated that skeletal diversity can also be introduced successfully *via* the toolkit of cyclisation reactions that was employed on these cyclisation precursors.

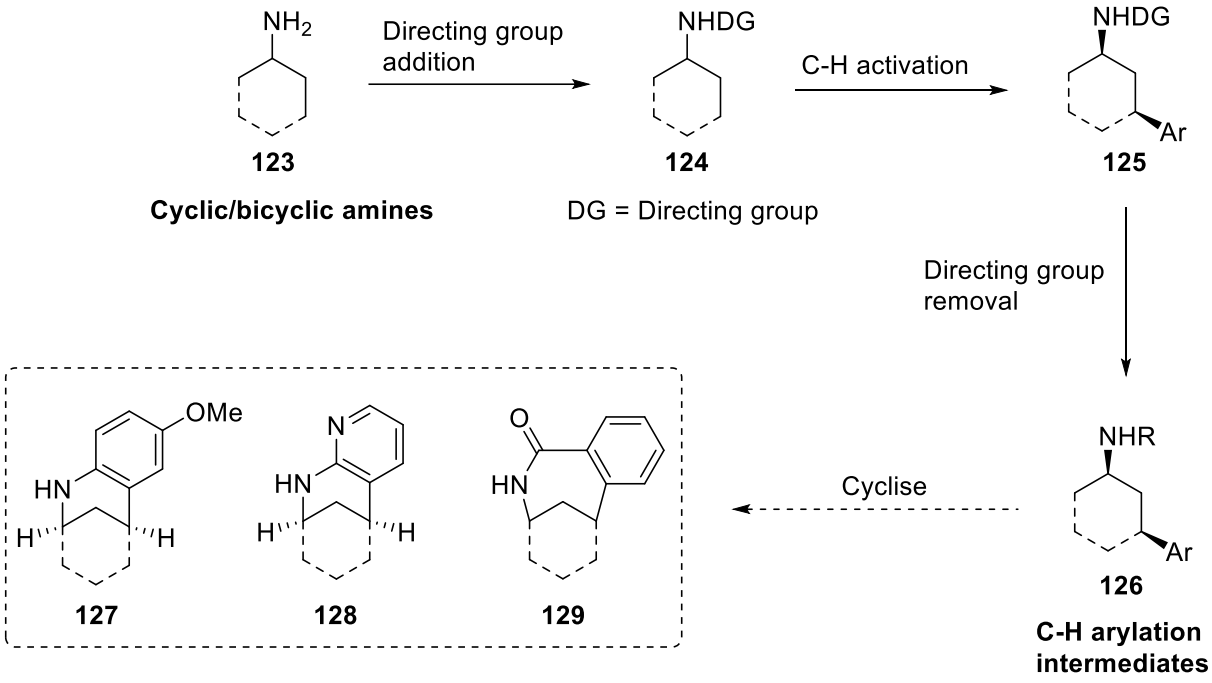
3 Synthesis of a polycyclic scaffold library through complexity-generating ‘stitching’ annulations

3.1 Design of synthetic approach for synthesis of a second diverse 3D scaffold library

After the success of the first unified synthetic approach for diverse scaffold generation (Chapter 2), a second modular synthetic strategy was designed to allow for the preparation of another structurally diverse, sp^3-rich scaffold library. One disadvantage of the first synthetic approach was that in most cases, many synthetic steps were needed to prepare each of the final scaffold compounds from their corresponding precursors. Therefore, in this second library, it was decided that a major priority would be to design a strategy that would prepare final scaffold compounds in a similar modular approach but can also be prepared in a shorter number of overall synthetic steps. In order to achieve this aim, it was decided to utilise alternative chemistry from what was employed for the first scaffold library to limit the number of synthetic steps needed to synthesise each final scaffold. Thus, a new approach for the synthesis of cyclisation precursors, as well as a new toolkit of cyclisation reactions would need to be developed to allow for efficient scaffold generation, whilst keeping the high shape and structural diversity in the final scaffold library. As with before, it was envisaged that this synthetic approach should ideally provide a structurally and shape diverse set of scaffolds that contain several points of diversification in their core structure. Subsequent decoration along different reaction vectors can therefore allow these scaffolds to target lead-like chemical space as required.

It was decided that a complexity-generation ‘stitching’ annulation approach using palladium catalysed C-H activation chemistry could be utilised to prepare the variety of cyclisation precursor compounds needed for subsequent cyclisation. Recent literature precedent shows that this chemistry can be used to perform site specific C-H arylation of cyclic/bicyclic amines to provide the corresponding *cis*-configured C-H arylated products in a short number of synthetic steps.[101–103] Therefore, this chemistry could be utilised to prepare a set of C-H arylated intermediates containing amine and aryl reaction handles that can then be cyclised together to provide the library of diverse scaffolds as desired. This new approach would begin *via* site specific

diastereoselective C-H arylation of a variety of cyclic and bicyclic amine starting materials to provide the corresponding arylated intermediates **126**. The C-H activation step uses directing groups bound to the amine functional group to allow for the stereoselective aryl addition at a specific position in the amine starting materials. After C-H arylation has taken place, this directing group would then have to be removed to provide the amine reaction handle required for any subsequent cyclisations. A novel toolkit of cyclisation reactions would then be developed and utilised on these arylated intermediates to allow intramolecular cyclisations between the amine and aryl reaction handles to occur (Scheme 24). This would then provide a modular synthetic approach for the synthesis of highly sp^3-rich diverse scaffolds to target lead-like chemical space.



Scheme 24: The general overview of the synthetic approach for the preparation of a second library of novel, diverse sp^3-rich scaffolds to target lead-like chemical space. This approach involves site specific C-H activation of cyclic/bicyclic amine starting materials **123** followed by subsequent intramolecular cyclisation to provide the library of final scaffolds.

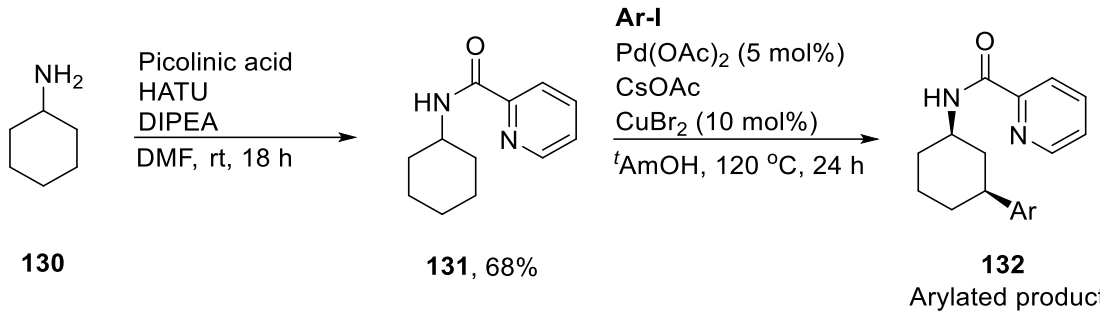
3.2 Synthesis of C-H arylated intermediates

3.2.1 Investigation and optimisation of C-H functionalisation conditions

Palladium-catalysed C-H activation reactions are commonly seen as an excellent strategy for C-C bond formation in modern organic synthesis.[101–103] However, site selectivity of a particular C-H bond can be a challenge in C-H activation reactions. For this reason, directing groups containing between 1-2 Lewis basic groups are often used to selectively activate the desired C-H bond in the molecule to provide the desired regioselective control through the formation of palladacyclic intermediates.[104–106] These C-H activation arylation reactions also allow control of stereochemistry as usually only one possible diastereomer can form to give the *cis*-arylated product, due to the formation of the palladacyclic intermediates previously discussed.

3.2.1.1 C-H activation with auxiliary picolinamide directing group

To begin the synthesis of the C-H arylated cyclisation precursors, an investigation into different C-H activation conditions was first employed. The first reaction conditions investigated were C-H activation using picolinamide directing groups covalently bound to the amine starting material. This investigation involved attaching the picolinamide group to the cyclic amine starting material, through amide coupling, to act as the directing group for subsequent C-H activation. Cyclohexylamine was chosen to be the cyclic amine of choice as the first starting material, due to the ease of its availability and low cost of purchase. Firstly, the picolinamide directing group was added to the cyclohexylamine starting material *via* HATU mediated amide bond formation with picolinic acid with a 68% yield observed.[107] Many previous reported Pd-catalysed C-H activation reactions required stoichiometric quantities of silver salts in order for the reaction to proceed which can be undesirable. This is due to loss of reaction efficiency as well as leading to purification issues, especially on a larger scale. Recently, Sheppard and co-workers demonstrated C-H arylation reactions on a range of bicyclic amine starting materials and instead employed CsOAc as a base/halide scavenger and $CuBr_2$ as an additive to broad success.[107] We initially decided to use these silver-free, picolinamide directing group C-H activation conditions to selectively arylate at the C-3 position of cyclohexylamine (Table 13).



130 **131**, 68% **132** Arylated products

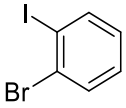
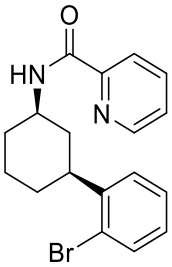
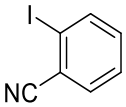
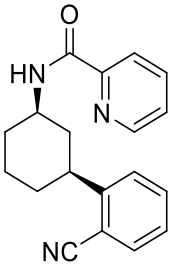
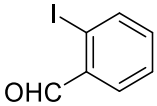
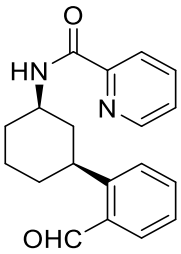
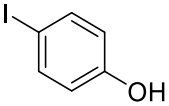
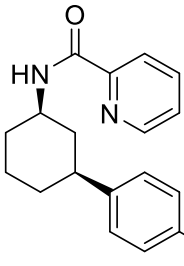
Entry	Aryl iodide	Arylated product	[a]Yield (*dr*)[b]
1		 **132a**	Trace[c]
2		 **132b**	Trace[c]
3		 **132c**	-[d]
4		 **132d**	**18% (>95:<5)**

Table 13: C-H activation of cyclohexylamine using silver-free picolinamide directing group conditions to prepare the corresponding C-H arylated products **132**. [a]Isolated yield after purification. [b]Determined by 500 MHz ^{1}H NMR spectroscopic analysis of purified compound. [c]Trace product observed by LCMS and analysis of crude material by 500 MHz ^{1}H NMR spectroscopy. [d]No reaction occurred with only starting material observed by TLC and LCMS.

The aryl iodides were initially chosen to have different *ortho*-functionality present in their structure, as this could allow for subsequent cyclisation reactions to take place to generate the desired diverse sp^3-rich scaffold library. Any isolated compounds were obtained as the mono-arylated derivatives with no di-arylation being observed in any case.[108,109] Unfortunately, the *ortho*-substituted substrates (*ortho*-bromo, *ortho*-formyl and *ortho*-nitrile containing aryl iodides) were not tolerated under these conditions. Only trace amounts of the desired C-H arylated products, as well as mainly unreacted starting material could be observed from these reactions (Table 13, Entry 1-3). Surprisingly, 4-iodophenol was tolerated to give the corresponding arylated product **132d** albeit in only 18% yield (Table 13, Entry 4). This result is of note as there are very limited examples where unprotected hydroxyl groups are tolerated under metal-catalysed C-H activation conditions. This isolated C-H arylated product **132d** was collected as a single *cis* diastereomer due to the mechanism in which these C-H activation reactions proceed (Figure 16). The relative configuration of **132d** was also confirmed through analysis of the relevant coupling constants (see Figure 18).

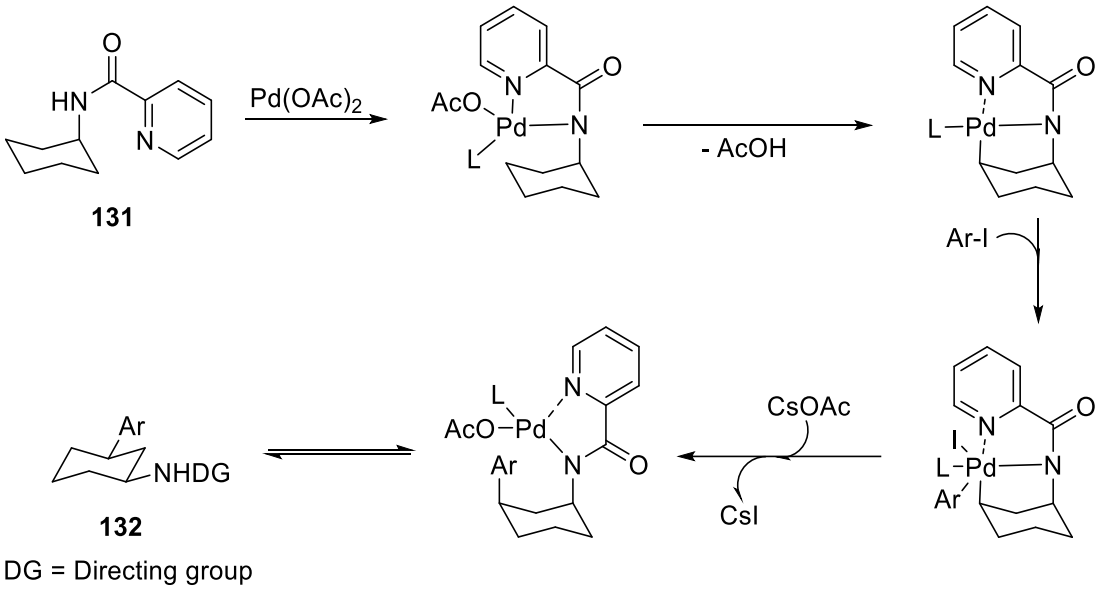


Figure 16: The reaction mechanism for picolinamide directed C-H activation of cyclohexylamine with aryl iodides to provide the corresponding arylated products solely as the *cis* diastereomer.

These results gave the initial indication that substitution at the *ortho* position of the aryl iodides can have a large influence over whether the reaction can proceed or not. This substitution at the *ortho* position of the aryl iodides may disrupt the formation of the necessary palladacyclic intermediates due to steric effects, therefore leading to the lower reactivity observed with these substrates.

3.2.1.2 C-H activation with transient directing group

After the mixed success observed with the picolinamide directing group chemistry with cyclohexylamine, it was decided to continue the investigation with an alternative directing group strategy to perform the C-H arylations. Yu *et al.* have recently reported the use of a transient directing groups (TDG) in order to selectively perform C-H arylations on cyclic and acyclic amine substrates at the γ-position.[110] The use of transient directing group chemistry would also streamline the synthesis of the C-H arylated cyclisation precursors, as it eliminates the directing group addition and removes reaction steps from the synthesis. These reaction conditions also only require a catalytic amount of directing group aldehyde to be present. The transient directing group can bond to the desired substrate for C-H activation, then once this is achieved, it can subsequently dissociate reversibly to leave the C-H arylated product as the free amine (Figure 17).

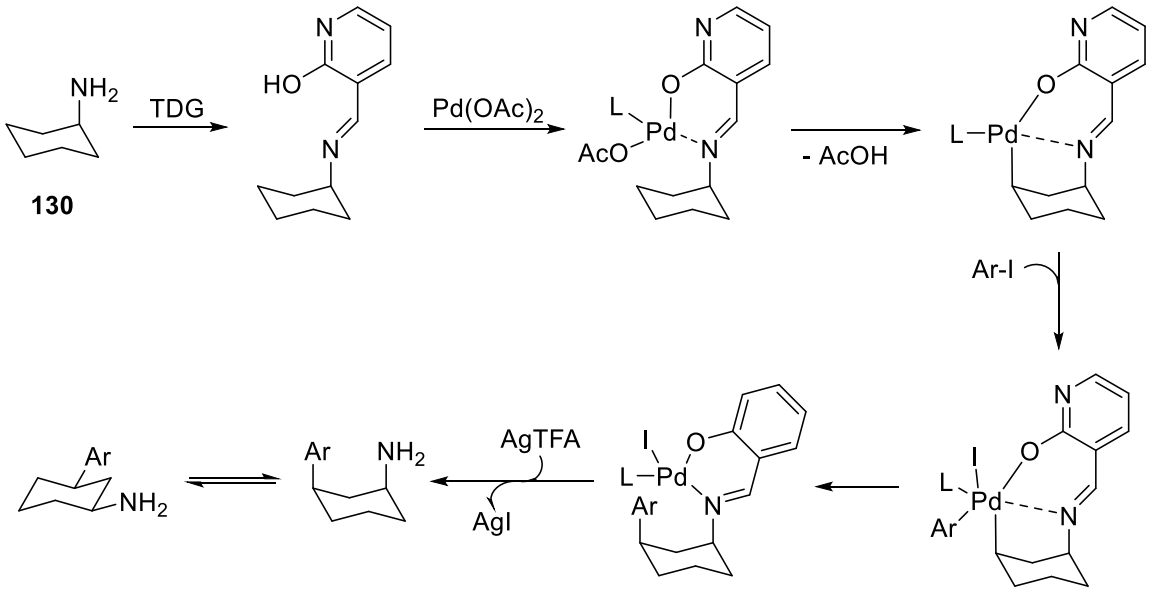
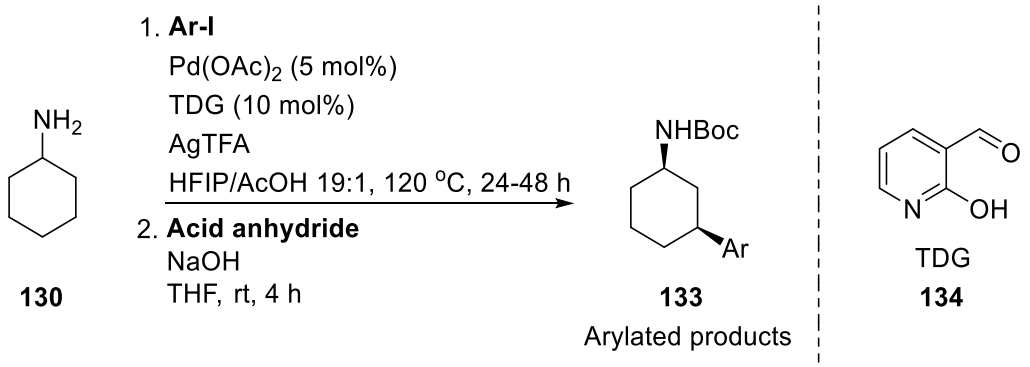
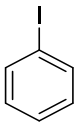
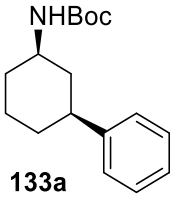
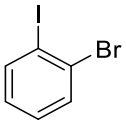
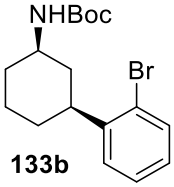
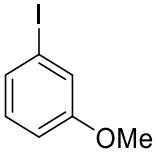
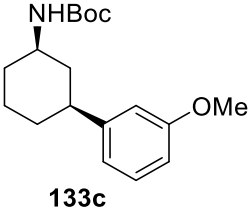
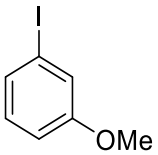
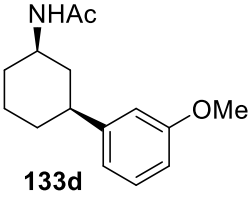


Figure 17: The reaction mechanism for C-H activation of cyclohexylamine **130** using transient directing group conditions to give the corresponding *cis*-configured arylated products.

It was decided that the transient directing group chemistry reported by Yu *et al.* looked desirable for the synthesis of the library of C-H arylated cyclisation precursors. Thus, these conditions were chosen to attempt C-H arylation reactions initially with cyclohexylamine. A substrate scope was performed with various aryl iodides in order to address the feasibility of this approach for C-H arylation. C-H arylation was attempted with seven different aryl iodides, which included different substitution patterns and various *ortho*-functionality to aid in subsequent cyclisations (Table 14).



Entry	Aryl iodide	Acid anhydride	Arylated product	[a]Yield (*dr*)[b]
1		**Boc_2O**	 **133a**	**61% (>95:<5)**
2		**Boc_2O**	 **133b**	**57% (>95:<5)**
3		**Boc_2O**	 **133c**	**93% (>95:<5)**
4		**Ac_2O**	 **133d**	**74% (>95:<5)**

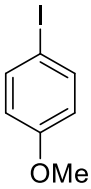
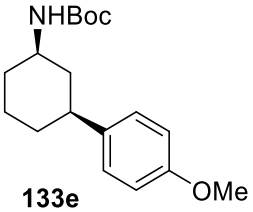
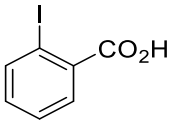
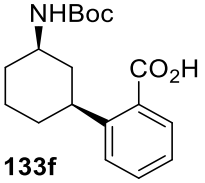
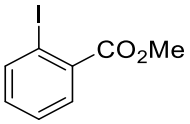
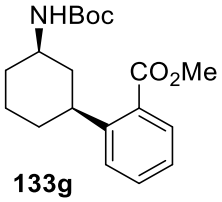
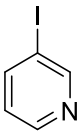
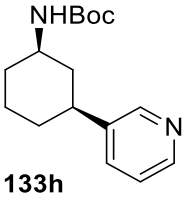
5		**Boc_2O**	 **133e**	**38% (>95:<5)**
6		Boc_2O	 **133f**	-[c]
7		**Boc_2O**	 **133g**	**19% (>95:<5)**
8		Boc_2O	 **133h**	-[c]

Table 14: C-H arylation substrate scope with cyclohexylamine using the transient directing group conditions reported by Yu *et al.*[110] [a]Isolated yield after purification. [b]Determined by 500 MHz ^{1}H NMR spectroscopic analysis of purified compound. [c]No reaction occurred with only unreacted starting material and aryl iodide observed by TLC and LCMS.

Subsequent *N*-Boc or *N*-acetyl protection of the resulting free amine was performed during this one-pot process in order to ease purification of the C-H arylated products, as well as providing amine protection for subsequent cyclisations during scaffold synthesis. This substrate scope proved to be predominantly successful as it was shown that all substitution patterns could be tolerated on the aryl iodide species to give the corresponding mono-arylated C-H arylated products **133**. Moderate to excellent yields (38-93%) were observed for those substrates that best tolerated these C-H activation conditions (Table 14, Entries 1-4), whilst the lower yields corresponded to aryl iodides that contained substitution in the *ortho*-position (Table 14, Entries 6-7). As mentioned previously, this steric effect perhaps inhibits the formation of the palladacyclic intermediate species during the catalytic cycle, corresponding to lower yields of the desired arylated product isolated at the end of the reaction.[110] The 3-

iodopyridine substrate (Table 14, Entry 8) was not tolerated under these reaction conditions as only unreacted starting material and aryl iodide were isolated from this reaction attempt. The C-H arylated products were again isolated only as the *cis* diastereomer. This relative configuration was confirmed by analysis of coupling constants in the 500 MHz ^{1}H NMR spectra for all the cyclohexylamine derived C-H arylated products isolated. This analysis showed *J* ~12 Hz for protons 1-H and 3-H in the C-H arylated products isolated. The large *J* ~12 Hz coupling constants correlated with vicinal *trans*-diaxial coupling to adjacent protons on the cyclohexylamine ring. This suggests both the NHR and aryl substituents are positioned equatorially with both protons 1-H and 3-H being positioned axially to allow for the observed large *trans*-diaxial coupling constants (Figure 18).

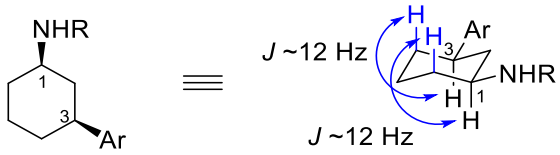
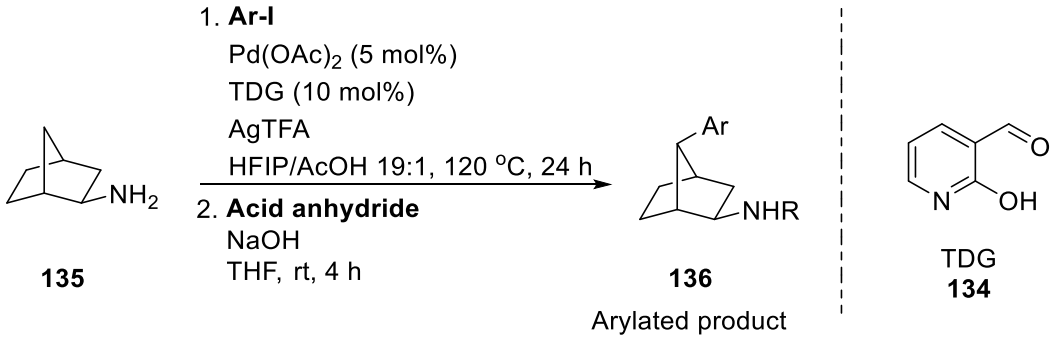


Figure 18: Confirmation of the relative configuration of the cyclohexylamine C-H arylated products by inspection and analysis of diagnostic coupling constants.

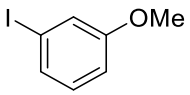
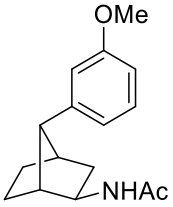
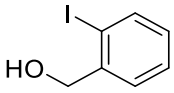
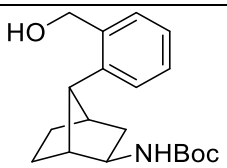
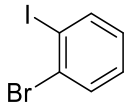
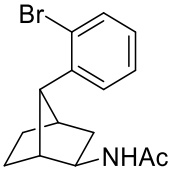
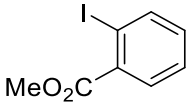
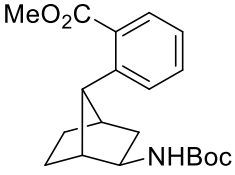
3.2.2 C-H activation of *exo*-2-aminonorbornane

After the success of C-H activation chemistry with cyclohexylamine under transient directing group conditions, it was decided to continue the synthesis of C-H arylated cyclisation precursors by attempting C-H activation on bicyclic amine starting materials. *Exo*-2-aminonorbornane (**135**) was chosen due to its commercial availability and previous literature precedent for C-H activation chemistry using picolinamide directing group chemistry.[107] However, it was decided to employ the transient directing group C-H activation conditions because if successful, it would provide highly three-dimensional C-H arylated cyclisation precursors all in a one-pot procedure without requiring additional reaction steps to add or remove a directing group. As with the C-H activation of cyclohexylamine, *exo*-2-aminonorbornane (**135**) was reacted with various aryl iodides using 5 mol% $Pd(OAc)_2$ catalyst, 10 mol% TDG and AgTFA in

HFIP–AcOH 19:1 at 120 °C for 24 h. Subsequent protection of the resulting free amine gave the corresponding arylated products **136** (Table 15). The aryl iodides were chosen to contain useful functionality in order to provide the corresponding arylated cyclisation precursors **136** with various reaction handles that would enable subsequent cyclisations to yield a range of diverse cyclised scaffolds.



135 **136** Arylated product TDG **134**

Entry	Aryl iodide	Acid anhydride	Arylated product	[a]Yield (*dr*)[b]
1		**Ac_2O**	 **136a**	**70% (>95:<5)**
2		**Boc_2O**	 **136b**	**30% (>95:<5)**
3		Ac_2O	 **136c**	-[c]
4		**Boc_2O**	 **136d**	**56%[d] (>95:<5)**

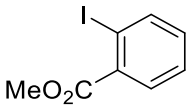
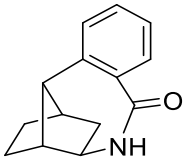
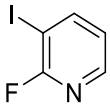
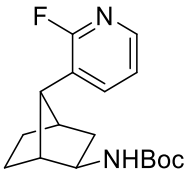
5		-[e]	 **136e**	**60%[f] (>95:<5)**
6		Boc_2O	 **136f**	-[c]

Table 15: C-H activation of *exo*-2-aminonorbornane under transient directing group conditions to provide the corresponding C-H arylation derivatives **136**. [a]Isolated yield after purification. [b]Determined by 500 MHz ^{1}H NMR spectroscopic analysis of purified compound. [c]No reaction occurred with only unreacted starting material and aryl iodide observed by TLC and LCMS. [d]Isolated as an inseparable 1:1 mixture of *N*-Boc arylated product **135d** and cyclised product **136e** by 500 MHz ^{1}H NMR spectroscopy. [e]No acid anhydride added to the reaction mixture. [f]Isolated yield after one-pot C-H arylation/cyclisation cascade where the reaction mixture was instead stirred for 18 h after basification with NaOH to give cyclised scaffold **136e**.

It was found that many of the aryl iodide substrates were tolerated under these reaction conditions and gave the corresponding arylated derivatives **136** as single diastereomers in a moderate to excellent yields, where C-H arylation selectively occurred on the one-carbon bridge. 3-iodoanisole and 2-iodobenzyl alcohol were successfully employed to prepare the arylated derivatives **136a-b** in 70% and 30% yields respectively (Table 15, Entries 1-2). The heteroaromatic aryl iodide 2-fluoro-3-iodopyridine was found to not tolerate these reaction conditions with no reaction being observed in this case (Table 15, Entry 6). Similarly, 2-bromoiodobenzene was also found to not tolerate these reaction conditions, possible due to the *ortho* bromine functionality interfering with the formation of the palladacyclic intermediates required for C-H activation to take place (Table 15, Entry 3). Interestingly, C-H activation was found to be successful with methyl 2-iodobenzoate, however, after following standard C-H activation and subsequent *N*-Boc protection, a 1:1 mixture of the expected C-H arylation product **136d** and cyclised scaffold **136e** was observed (Table 15, Entry 4). This result implied that basifying the reaction mixture with NaOH during amine protection caused some material to cyclise to the corresponding lactam scaffold **136e** rather than undergoing *N*-Boc protection to give the expected arylated product **136d**. It was therefore decided to attempt a one-pot reaction procedure to prepare lactam

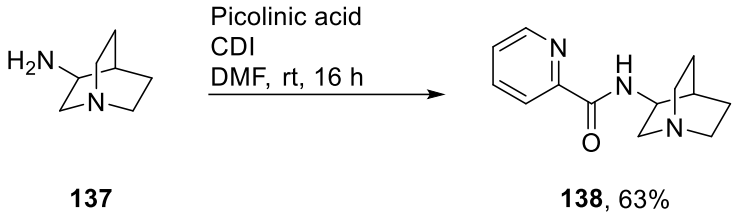
scaffold **136e** in just two reaction steps with only a single purification. This was achieved by first performing the standard transient directing group C-H activation of *exo*-2-aminonorbornane with methyl-2-iodobenzoate to give the arylated intermediate *in situ*. The reaction mixture was then basified with NaOH and allowed to stir at room temperature for a further 18 h. It was found that this one-pot procedure did indeed allow the preparation of lactam scaffold **136e** in 60% yield without the need to isolate any C-H arylated intermediate (Table 15, Entry 5). Thus, C-H activation of *exo*-2-aminonorbornane under transient directing group conditions was found to be predominately successful for the preparation arylated cyclisation precursors, as well as allowing for the synthesis of lactam scaffold **136e** through a one-pot procedure to provide the first cyclic scaffold to enter the final scaffold library.

3.2.3 C-H activation of 3-aminoquinuclidine

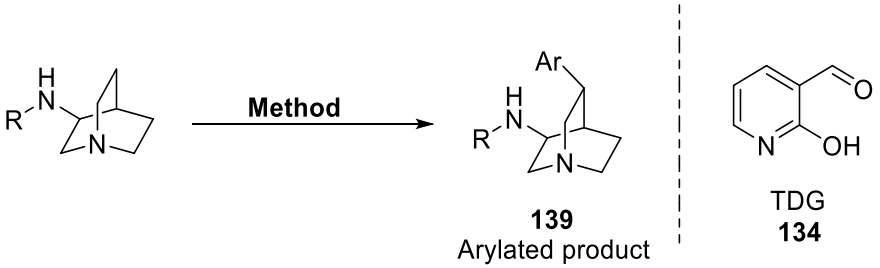
After the success of the C-H activation chemistry with cyclohexylamine and *exo*-2-aminonorbornane, it was decided to continue this investigation with cyclic/bicyclic amine starting materials that contained more heteroatoms within their core structure. This would allow for the synthesis of arylated cyclisation precursors and subsequent cyclised scaffolds with more desirable physicochemical properties, as the additional heteroatoms can lower the overall lipophilicity and incorporate additional points of diversification within the core scaffold structure. This would therefore allow decoration of the final scaffolds along different reaction vectors to target a wider region of lead-like chemical space.

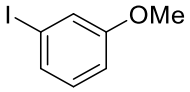
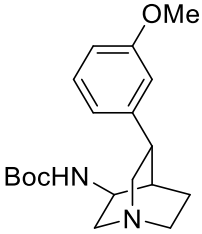
In 2018, Maulide and co-workers demonstrated that a small number of site-selective C-H arylations could be performed on bicyclic amine 3-aminoquinuclidine (**137**) on the two carbon bridge.[111] Therefore, it was decided to perform a substrate scope with various aryl iodides in order to determine if C-H activation of 3-aminoquinuclidine could provide a range of arylated cyclisation precursors as desired (Table 16). As with *exo*-2-aminonorbornane (Section 2.2.2), the chosen set of aryl iodides contained useful functionality to provide the corresponding arylated cyclisation precursors **139** with reaction handles to allow for subsequent cyclisations. Both the picolinamide and transient directing group C-H activation conditions were utilised to determine which

set of conditions gave the most reproducible results across the set of aryl iodides. For the picolinamide directing group reaction conditions, an amide coupling was first performed between 3-aminoquinuclidine **137** and picolinic acid with CDI gave the corresponding picolinamide **138** in 63% yield (Scheme 25).[111] This purified picolinamide substrate **138** was used for the picolinamide directing group C-H activation chemistry, whereas 3-aminoquinuclidine **137** was the starting material for the corresponding transient directing group conditions.



Scheme 25: The amide coupling of 3-aminoquinuclidine **137** with the picolinic acid to give the corresponding picolinamide **138**.



Entry	Aryl iodide	[a]Method	Product	[b]Yield (*dr*)[c]
1		A	 **139a**	-[d]

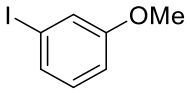
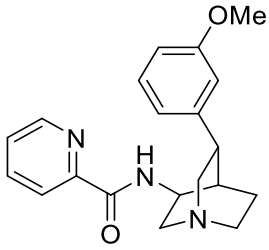
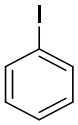
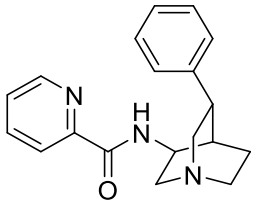
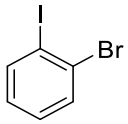
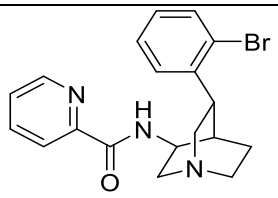
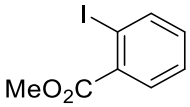
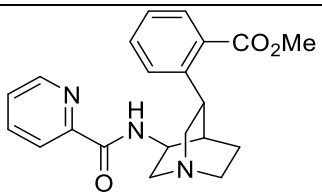
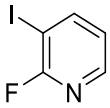
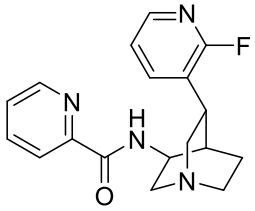
2a **2b**		**B** **C**	 **139b**	**28% (>95:<5)** **71% (>95:<5)**
3		**B**	 **139c**	**24% (>95:<5)**
4		B C	 **139d**	Trace[e] Trace[e]
5		C	 **139e**	-[d]
6		C	 **139f**	-[d]

Table 16: C-H activation of 3-aminoquinuclidine to give the corresponding arylated cyclisation precursors **139**. [a]**Method: A:** ArI, $Pd(OAc)_2$ (5 mol%), TDG (10 mol%), AgTFA, HFIP–AcOH 19:1, 120 °C, 24 h; **B:** (i) Picolinic acid, CDI, DMF, rt, 16 h, 63% (ii) ArI, $Pd(OAc)_2$ (5 mol%), Ag_2CO_3, PivOH, DMF, 100 °C, 24 h; **C:** (i) Picolinic acid, CDI, DMF, rt, 16 h, 63% (ii) ArI, $Pd(OAc)_2$ (15 mol%), Ag_2CO_3, PivOH, DMF, 100 °C, 24 h; [b]Isolated yield of C-H activation products (step ii) after purification. [c]Determined by 500 MHz ^{1}H NMR spectroscopic analysis of purified compound. [d]No reaction occurred with only unreacted starting material and aryl iodide observed. [e]Product only observed by LCMS but was not able to be isolated.

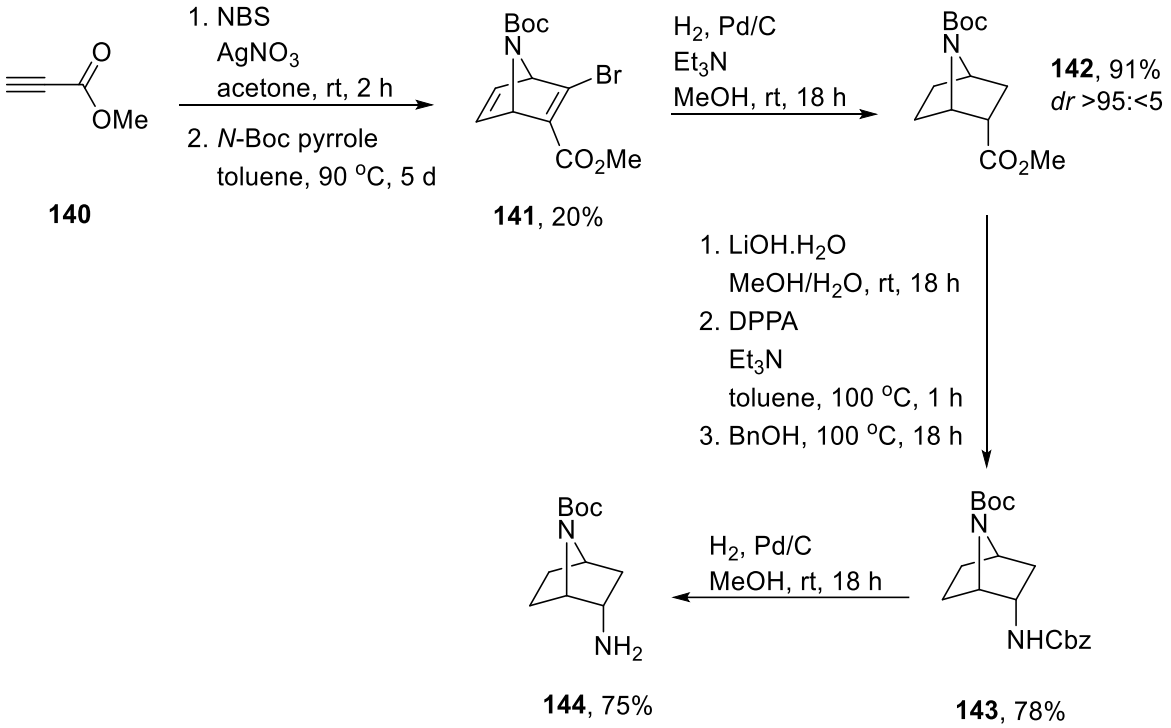
It was found that C-H activation using transient directing group chemistry did not provide the corresponding arylated products **139**, possibly due to the basic nitrogen

lone pair in 3-aminoquinuclidine **137** interfering with the formation of the required palladacyclic species (Table 16, Entry 1). However, C-H activation through picolinamide directing group conditions was able to provide the desired arylated products for a couple of the aryl iodides employed in this substrate scope (Table 16, Entries 2-3). Subsequent C-H arylation of picolinamide **138** was found to be successful only with the aryl iodides 3-iodoanisole and iodobenzene, yielding the corresponding arylated derivatives **139b-c** as single diastereomers. It was found that a catalyst loading of 15 mol% $Pd(OAc)_2$ gave the higher yields with these successful substrates (Table 16, Entry 2b), whereas a lower catalyst loading of 5 mol% $Pd(OAc)_2$ significantly lowered the isolated yield of arylated product (Table 16, Entries 2a and 3). Aryl iodides containing any *ortho* functionality were found to not be tolerated under these reaction conditions, possibly due to problems with the *ortho* substitution pattern disrupting the palladacyclic intermediate formation as described previously (Table 16, Entries 4-5). It was also shown that the heteroaromatic aryl iodide 2-fluoro-3-iodopyridine was again not tolerated with only unreacted starting material observed through analysis of the crude reaction mixture by TLC, LCMS and 500 MHz ^{1}H NMR spectroscopy (Table 16, Entry 6). Therefore, C-H activation of 3-aminoquinuclidine was only able to provide two arylated products **139b-c** using picolinamide directing group conditions, as transient directing group chemistry was found to not be tolerated with this substrate.

3.2.4 C-H activation of *N*-Boc-2-amino-7-azabicyclo[2.2.1]heptane

As it was found that only a limited number of arylated cyclisation precursors could be prepared from 3-aminoquinuclidine, it was decided to continue the investigation into C-H activation of bicyclic amines containing heteroatoms in their core structure. This would hopefully achieve the goal of preparing a larger number of more desirable arylated cyclisation precursors for subsequent scaffold synthesis through intramolecular cyclisation. The diastereoselective synthesis of bicyclic amine *endo*-*N*-Boc-2-amino-7-azabicyclo[2.2.1]heptane **144** has been reported in the literature and has been synthesised *via* a Diels-Alder cycloaddition between *N*-Boc pyrrole and methyl-3-bromopropiolate (Scheme 26).[112,113] Therefore, synthesis of bicyclic amine **144** began with this cycloaddition between *N*-Boc pyrrole and methyl 3-bromopropiolate, with the cycloaddition intermediate **141** being isolated in 20% yield.

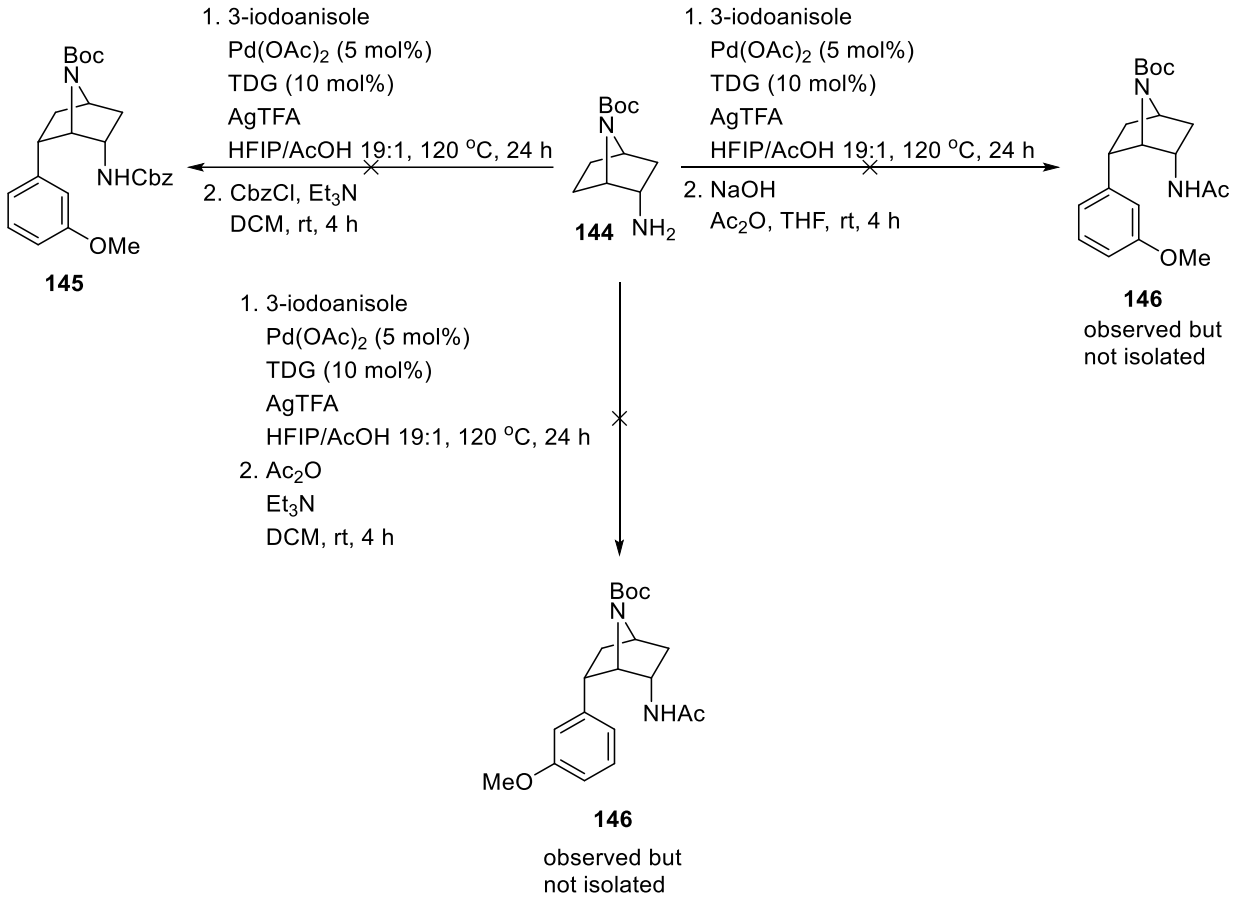
This intermediate **141** was then subject to hydrogenation in the presence of triethylamine to give the reduced intermediate **142** as a single diastereomer (*dr* >95:<5) in 91% yield.[114] Ester hydrolysis of intermediate **142** followed by Curtius rearrangement provided the corresponding isocyanate, which was then trapped with benzyl alcohol to give the *N*-Cbz carbamate derivative **143** in 78% yield.[113] The final synthetic step involved removal of the *N*-Cbz protection *via* hydrogenation to give the desired *endo* free amine bicyclic starting material **144** in 75% yield.[113]



Scheme 26: The synthetic pathway outlining the preparation of bicyclic compound **144** *via* Diels-Alder cycloaddition of *N*-Boc pyrrole.[112–114]

With the bicyclic amine starting material *N*-Boc-2-amino-7-azabicyclo[2.2.1]heptane **144** now in hand, subsequent C-H activation reactions were then attempted with 3-iodoanisole as the aryl iodide in order to determine whether bicyclic amine **144** could provide the corresponding arylated cyclisation precursors as desired. It was found that C-H activation under transient directing group conditions was observed but only with poor conversion by analysis of the crude material with LCMS and 500 MHz ^{1}H NMR spectroscopy. Subsequent amine protection of the small amount of arylated product

observed with either CbzCl or Ac_2O failed to yield any of the desired arylated cyclisation precursors **145** and **146** from this chemistry (Scheme 27). Therefore, it was decided to deprioritise C-H activation of bicyclic amine **144** due to the relatively long synthetic route to prepare this starting material as well as the initial poor results from the C-H activations attempted with 3-iodoanisole.

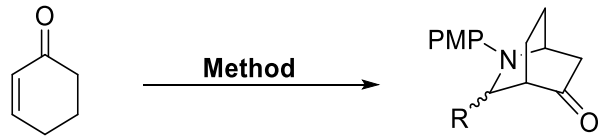


Scheme 27: The reaction schemes outlining the attempted C-H arylation and subsequent *N*-protection of bicyclic starting material **144**.

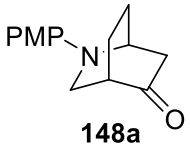
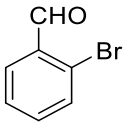
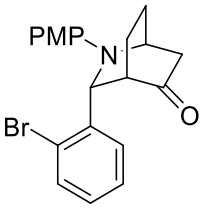
3.2.5 Synthesis of arylated cyclisation precursors derived from substituted 2-azabicyclo[2.2.2]octan-5-one

After the unsuccessful investigation into the C-H activation of bicyclic amine **146**, the synthesis of arylated cyclisation precursors continued by further investigating the

scope of C-H activation of heteroatom containing bicyclic amines. The one step synthesis of 2-azabicyclo[2.2.2]octan-5-one cores though proline catalysed aza-Diels-Alder cycloadditions of cyclohexanone (**147**) with various aldehydes has been widely reported in the literature.[115,116] The heteroatom containing bicyclic ketones could then undergo reductive amination at the ketone to provide the free amine functional group to allow for subsequent C-H activation. This synthetic approach can be used to prepare substrates already containing various aryl group functionality, as well as providing bicyclic ketones for subsequent investigations into C-H functionalisation Thus, a variety of *N*-PMP protected bicyclic ketones **148** was prepared through this aza-Diels-Alder cycloaddition between *p*-anisidine, cyclohexanone and a variety of aldehydes catalysed using 30 mol% proline (Table 17). For simplicity, it was decided to prepare the corresponding bicyclic ketones **148** as racemates. Therefore *rac*-proline was used as the organocatalyst instead of (*S*)-proline, commonly used for these cycloadditions, in order to achieve this aim.



147 Bicyclic ketone **148**

Entry	Aldehyde	[a]Method	Bicyclic ketone	[b]Yield (*dr*)[c]
1		**A**	 **148a**	**41% (>95:<5)**
2		**B**	 **148b**	**53% (>95:<5)[d]**

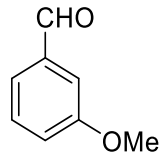
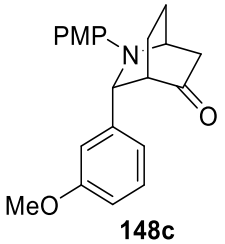
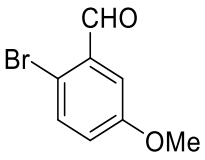
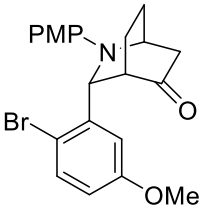
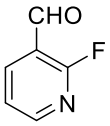
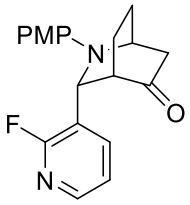
3		**B**	 **148c**	**41% (90:10)[d]**
4		B	 **148d**	-[e]
5		B	 **148e**	-[e]

Table 17: The proline catalysed aza-Diels-Alder cycloaddition between *p*-anisidine, cyclohexanone and various aldehydes to prepare the corresponding *N*-PMP protected bicyclic ketones **148**. [a]**Method: A:** Aldehyde, *p*-anisidine, cyclohexanone, *rac*-proline (30 mol%), DMSO, 50 ^{o}C, 24 h; **B:** Aldehyde, *p*-anisidine, cyclohexanone, *rac*-proline (30 mol%), MeCN–H_2O 9:1, 35 ^{o}C, 3 days. [b]Isolated yield of purified compound. [c]Determined by 500 MHz ^{1}H NMR spectroscopic analysis of purified compound. [d]Diastereomeric ratio of the product after purification, where *dr* 80:20 of the crude material was determined by 500 MHz ^{1}H NMR spectroscopy. [e]Complex mixture of products observed.

This aza-Diels-Alder chemistry was found to be relatively substrate dependent as only three cyclic ketones **148a-c** were successfully prepared through this synthetic pathway (Table 17, Entries 1-3). The reaction was shown to be relatively diastereoselective, with *dr* 80:20 observed for the crude reaction material of aryl substituted bicyclic ketones **148b-c** by 500 MHz ^{1}H NMR spectroscopy (Table 17, Entries 2-3). It was found that bicyclic ketone **148b** could be isolated as a single diastereomer after purification and bicyclic ketone **148c** allowed some separation of the diastereomers during purification to give an improved *dr* 90:10 of the purified compound (Table 17, Entries 2-3). Unfortunately, the aza-Diels-Alder cycloaddition with 2-bromo-5-methoxybenzaldehyde and 2-fluoro-3-formylpyridine were shown to not be successful under these reaction conditions as a complex mixture of products were observed from these reactions (Table 17, Entries 4-5).

The relative configuration of cyclic ketones **148b-c** was determined though analysis of key nOe interactions identified from the corresponding NOESY spectra (500 MHz). The observation of key nOe interactions between protons 3-H and 8-H_A as well as between aryl 6-H and 6-H_A supported *endo* product formation (Figure 19). These nOe interactions would not be observed if the *exo* product had been isolated, therefore the relative configuration of cyclic ketones **148b-c** was determined to be the *endo* cycloadduct.

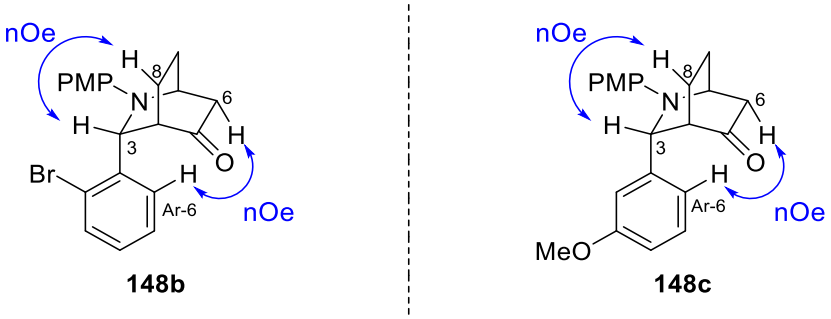
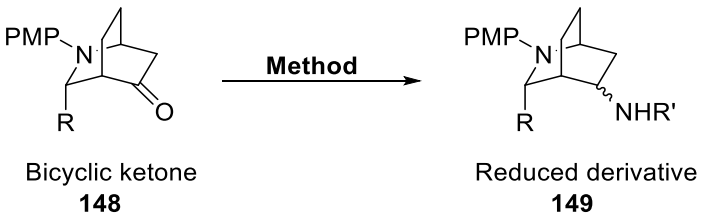


Figure 19: Determination of the relative configuration of bicyclic ketones **148b-c** through observation of key nOe interactions from the corresponding NOESY spectra (500 MHz).

With bicyclic ketones **148** now in hand, reductive amination of the ketone was then performed to prepare the desired amine functional group required for either C-H activation of compound **149a** or subsequent intramolecular cyclisations with compounds **149b-c**. Treatment of bicyclic ketones **148** with either ammonium acetate or saturated methanolic ammonia with Ti(^{i}OPr)$_4$ in MeOH, followed by imine reduction with either Na(CN)BH_3 or $NaBH_4$ then subsequent amine protection allowed the preparation of reduced derivatives **149** (Table 18).[64,117]



Bicyclic ketone **148** | Reduced derivative **149**

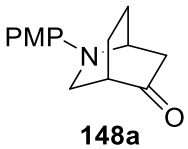
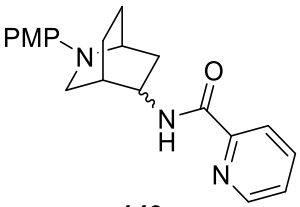
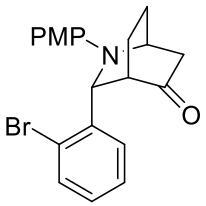
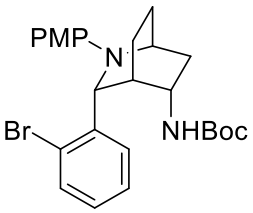
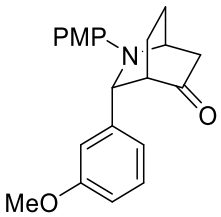
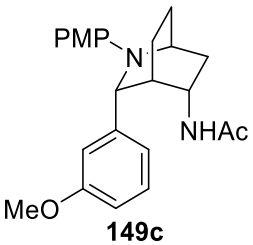
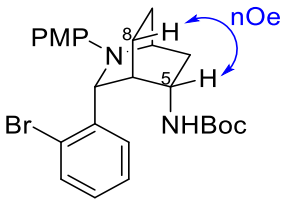
Entry	Bicyclic ketone	[a]Method	Reduced derivative	[b]Yield (*dr*)[c]
1	 **148a**	**A**	 **149a**	**44% (60:40)**
2	 **148b**	**B**	 **149b**	**25% (74:26)**
3	 **148c**	**C**	 **149c**	**54% (>95:<5)**

Table 18: Reductive amination of bicyclic ketones **148** to provide the corresponding reduced derivatives **149**. [a]**Method: A:** NH_4OAc, $Na(CN)BH_3$, MeOH, rt, 18 h then picolinic acid, CDI, DMF, rt, 18 h; **B:** sat. NH_3/MeOH, $Ti(O^iPr)_4$, $NaBH_4$, rt, 20 h then Boc_2O, NaOH, THF, rt, 4 h; **C:** sat. NH_3/MeOH, $Ti(O^iPr)_4$, $NaBH_4$, rt, 20 h then Ac_2O, NaOH, THF, rt, 4 h. [b]Isolated yield of purified compound. [c]Determined by 500 MHz ^1H NMR spectroscopic analysis of purified compound.

It was found that reductive amination of bicyclic ketones **148b-c** followed by subsequent amine protection gave the arylated cyclisation precursors **149b** and **149c** in 25% and 54% yield respectively (Table 18, Entries 2-3). Arylated precursor **149c** was isolated as a single diastereomer, whereas precursor **149b** gave an inseparable 74:26 mixture of diastereomers by analysis of the 500 MHz ^1H NMR spectrum for the purified compound.

The relative configuration of the major diastereomer of precursor **149b** was determined by analysis of a key nOe interaction in the NOESY spectrum (500 MHz). Inspection of the NOESY spectrum found a nOe interaction between protons 4-H and 8a-H, which indicated the *syn* relative stereochemistry between the protected amine and aryl substituent (Figure 20). This observed stereochemical outcome is likely due to the hydride attack of the iminium intermediate from the less hindered top face of the molecule to give the expected *syn*-stereochemistry observed. The relative

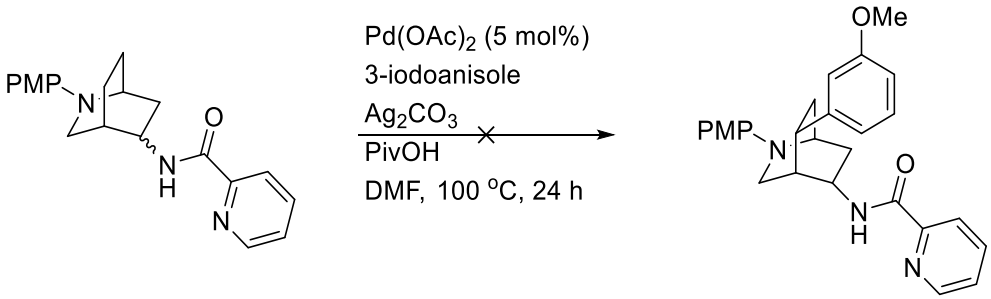
configuration of **149c** was determined by analogy with the major diastereomer of compound **149b**.



149b

Figure 20: Determination of the relative configuration of the major diastereomer of precursor **149b** through observation of key nOe interactions from the corresponding NOESY spectra (500 MHz).

Bicyclic ketone **148a** was able to undergo reductive amination and subsequent amide bond formation to prepare picolinamide **149a** in 44% yield an isolated as an inseparable 60:40 mixture of diastereomers (Table 18, Entry 1). This substrate was then treated with the standard picolinamide directing group C-H activation conditions in order to investigate whether this substrate can also provide arylated cyclisation precursors for subsequent cyclisation reactions. Treatment of this mixture of picolinamide diastereomers **149a** with 5 mol% $Pd(OAc)_2$, 3-iodoanisole, Ag_2CO_3 and pivalic acid in DMF at 100 ^oC for 24 h gave no desired arylated product with only unreacted starting material being observed (Scheme 28).



149a **150**

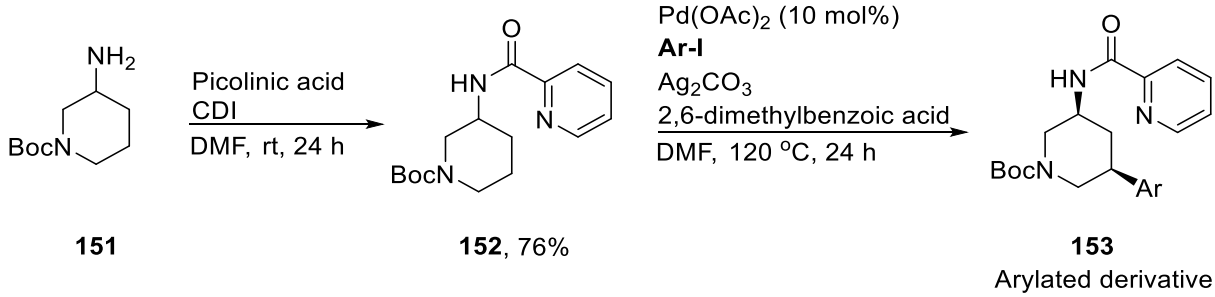
Scheme 28: The attempted C-H activation of picolinamide **149a** with 3-iodoanosole under picolinamide directing group conditions.

As this attempted C-H activation was unsuccessful and due to the poor diastereoselectivity of the reductive amination, it was decided to deprioritise this investigation into C-H activation of this substrate. The arylated cyclisation precursors **149b-c** made *via* the cycloaddition chemistry were added to the final set of cyclisation precursors to be utilised in subsequent cyclisation chemistry for the generation of the final scaffold library.

3.2.6 C-H activation of *N*-Boc-3-aminopiperidine

It has been reported in the literature that C-H activation reactions with *N*-Boc-3-aminopiperidine (**151**) have been shown to be previously successful with this substrate.[118] Therefore, it was decided to continue the investigation into C-H activation of heteroatom containing starting materials with this substrate in order to prepare more arylated cyclisation precursors for subsequent scaffold generation.[118] Identical picolinamide reaction conditions to this literature precedent were utilised to expand the known substrate scope. The same set of aryl iodides that contained the required functionality to allow subsequent intramolecular cyclisations for scaffold generation were used to prepare the desired C-H arylated derivatives.

Treatment of *N*-Boc-3-aminopiperidine **151** with picolinic acid and CDI in DMF at rt for 24 hours gave the corresponding picolinamide **152** in 76% yield. This intermediate was then treated with a variety of aryl iodides, 10 mol% $Pd(OAc)_2$, Ag_2CO_3 and 2,6-dimethylbenzoic acid in DMF at 120 ^oC for 24 h to provide the desired arylated derivatives **153** (Table 19).[118]



151 **152**, 76% **153** Arylated derivative

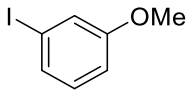
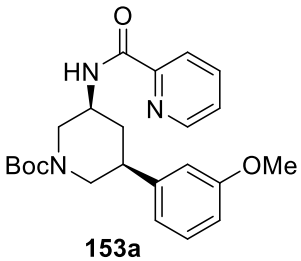
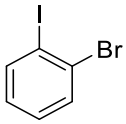
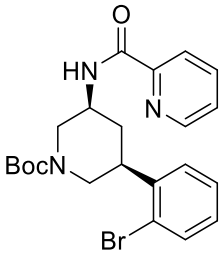
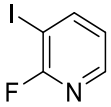
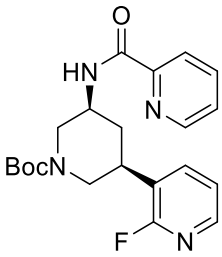
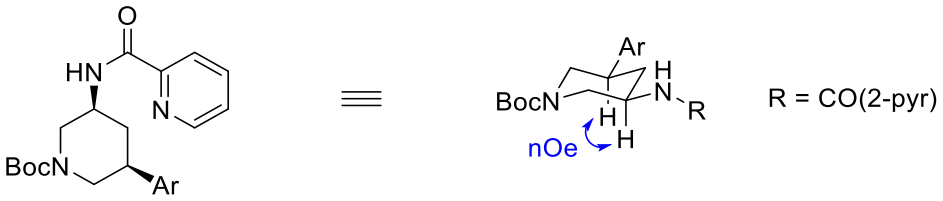
Entry	Aryl Iodide	Arylated derivative	[a]Yield (*dr*)[b]
1		 **153a**	**61% (>95:<5)**
2		 **153b**	-[c]
3		 **153c**	**78% (>95:<5)**

Table 19: C-H activation of *N*-Boc-3-aminopiperidine **151** with a variety of aryl iodides under picolinamide directing group conditions to prepare the corresponding arylated derivatives **153**. [a]Isolated yield of purified compound. [b]Determined by 500 MHz ^{1}H NMR spectroscopic analysis of purified compound. [c]No reaction observed by TLC and LCMS.

These reaction conditions were found to be successful with aryl iodides 3-iodoanisole and 2-fluoro-3-iodopyridine as these gave their corresponding arylated derivatives **153a** and **153c** as single diastereomers in 61% and 78% yields (Table 19, Entries 1 and 3). Unfortunately, 2-bromoiodobenzene was not tolerated under these reaction conditions, likely due to similar issues discussed previously with substitution at the *ortho* position affecting the C-H activation mechanism (Table 19, Entry 2). For this reason, other *ortho*-functionalised aryl iodides were not employed in this substrate scope, with only arylated derivatives **153a** and **153c** being taken forward for subsequent cyclisations to allow the preparation of the final diverse scaffold library. Confirmation of the expected *cis* relative stereochemistry was determined by analysis of key nOe interactions from the corresponding NOESY spectra (500 MHz). There

were nOe interactions observed between protons 3-H and 5-H in the NOESY spectra for both arylated derivatives **153a** and **153c** (Figure 21). These interactions would not be observed if the relative stereochemistry was *trans*, therefore this analysis confirmed the relative stereochemistry to be *cis*.

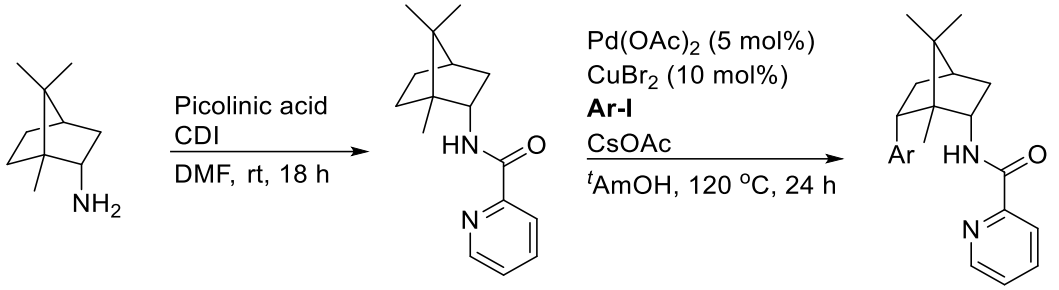


153

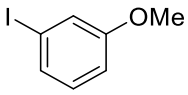
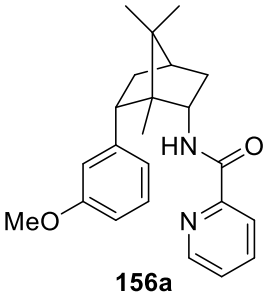
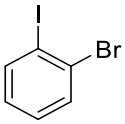
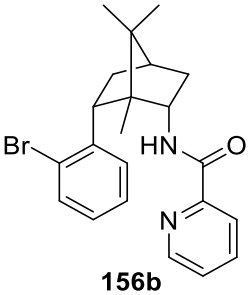
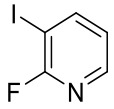
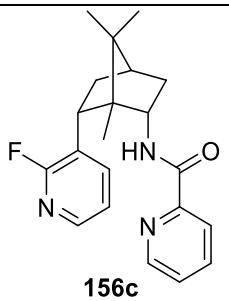
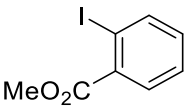
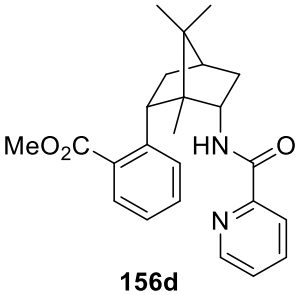
Figure 21: Confirmation of the *cis* relative stereochemistry for arylated derivatives **153** through analysis of key nOe interactions from the NOESY spectra.

3.2.7 C-H activation of bornylamine

After the mixed success with the C-H activation of heteroatom containing amine starting materials, it was decided to continue the preparation of arylated cyclisation precursors using starting materials with good previous literature precedent for C-H activation reactions. Sheppard and co-workers have recently reported the successful palladium catalysed C-H activation of bicyclic amine bornylamine (**154**) with a limited number of aryl iodide substrates, using the silver free reaction conditions previously discussed for the C-H activation of cyclohexylamine (Section 3.2.1.1).[107] The bornylamine starting material was first coupled with picolinic acid with CDI to prepare picolinamide **155** in 90% yield. C-H activation under silver free conditions of picolinamide **155** with the same set of functionalised aryl iodides previously discussed gave the corresponding arylated derivatives **156** (Table 20).



154 **155**, 90% **156**
Arylated derivative

Entry	Aryl iodide	Arylated derivative	[a]Yield (*dr*)[b]
1		 **156a**	**50% (>95:<5)**
2		 **156b**	-[c]
3		 **156c**	**42% (>95:<5)**
4		 **156d**	**53% (>95:<5)**

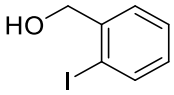
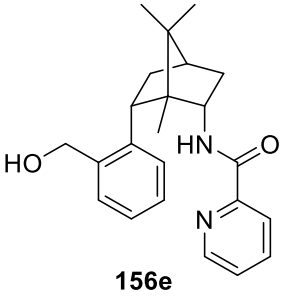
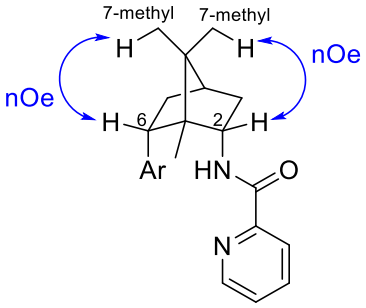
5		 **156e**	-[c]

Table 20: C-H activation of bornylamine with various functionalised aryl iodides to give the corresponding arylated derivatives **156**. [a]Isolated yield of purified compound. [b]Determined by 500 MHz ^{1}H NMR spectroscopic analysis of purified compound. [c]No reaction observed by TLC and LCMS.

The C-H activation reaction conditions employed were found to be more widely tolerated over the set of aryl iodides used than what was previously observed with the heteroatom containing starting materials. The reaction with 3-iodoanisole was observed to be successful and gave arylated derivative **156a** in 50% yield (Table 20, Entry 1). Some *ortho* functionality was tolerated as both methyl-2-iodobenzoate and heteroaromatic aryl iodide 2-fluoro-3-iodopyridine gave their corresponding arylated derivatives **156c-d** in 42% and 53% yields respectively (Table 20, Entries 3-4). Unfortunately, 2-bromoiodobenzene and 2-iodobenzyl alcohol were found to not be tolerated under these reaction conditions as no reaction was observed with either substrate (Table 20, Entries 2 and 5). As expected, all isolated arylated derivatives prepared through this chemistry were isolated as single diastereomers. Confirmation of the expected *cis* stereochemistry was determined through analysis of key nOe interactions from the corresponding NOESY spectra (500 MHz). This analysis found nOe interactions between protons 2-H and 7-methyl as well between 6-H and 7-methyl (Figure 22). The observation of these nOe interactions indicated that these arylated derivatives did possess the expected *cis* stereochemistry as these nOe interactions would not be observed in the *trans* product.

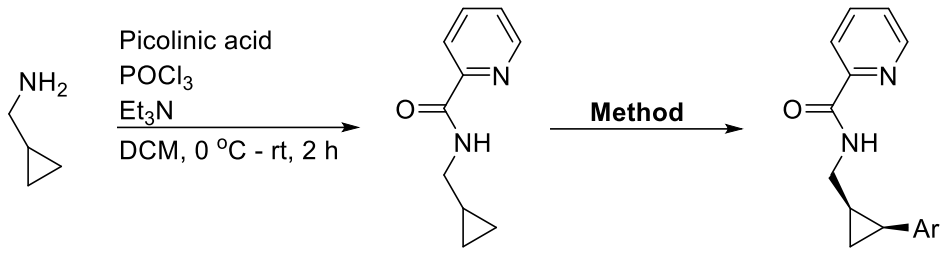


156

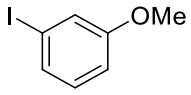
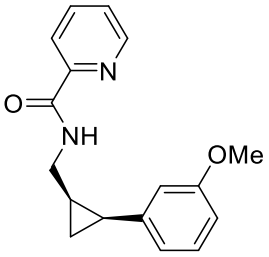
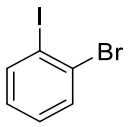
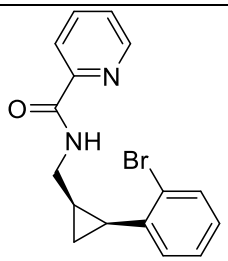
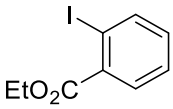
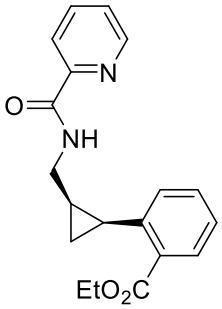
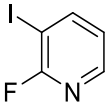
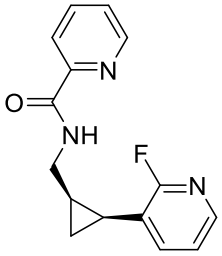
Figure 22: Confirmation of the relative configuration of arylated derivatives **156** prepared though picolinamide directed silver free C-H activation of bornylamine.

3.2.8 C-H activation on cyclopropylmethylamine ring system

With the relative success of C-H activation on the cyclic/bicyclic amines utilised this far, it was decided to investigate C-H activation of a cyclic amine starting material with a smaller ring size. Reducing the ring size of the amine starting material can add skeletal diversity to the arylated cyclisation precursors and therefore ultimately increasing the diversity of the final scaffold library. Charette and co-workers reported the site selective C-H activation of cyclopropylmethylamine **157** using picolinamide directing group conditions.[108] Therefore, it was decided to harness these C-H activation conditions in order to expand the substrate scope of this chemistry with the same set of functionalised aryl iodides as before to prepare the corresponding arylated derivatives **159**. Treatment of picolinic acid and cyclopropylmethylamine **157** with $POCl_3$ and Et_3N in DCM at rt for 2 h gave the corresponding picolinamide **158** in 71% yield.[119] This was then reacted with 5 mol% $Pd(OAc)_2$, varying equivalents of aryl iodides, pivalic acid and K_2CO_3 in toluene at 130 ^oC for 18 h to give the desired arylated derivatives **159** (Table 21).[108]



157 **158**, 71% **159**
Arylated derivative

Entry	Aryl iodide	[a]Method	Arylated derivative	[b]Yield (*dr*)[c]
1a **1b**		A **B**	 **159a**	-[d] **68% (>95:<5)**
2		B	 **159b**	-[e]
3		**B**	 **159c**	**40% (>95:<5)**
4		**B**	 **159d**	**50% (>95:<5)**

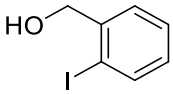
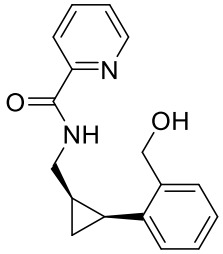
5		B	 **159e**	-[e]

Table 21: C-H activation of cyclopropylmethylamine to give the corresponding arylated derivatives **159**. [a]**Method: A:** Ar-I (2.2 eq.), $Pd(OAc)_2$ (5 mol%), PivOH, K_2CO_3, toluene, 130 ^oC, 18 h; **B:** Ar-I (1.1 eq.), $Pd(OAc)_2$ (5 mol%), PivOH, K_2CO_3, toluene, 130 ^oC, 18 h. [b]Isolated yield of purified compound. [c]Determined by 500 MHz ^1H NMR spectroscopic analysis of purified compound. [d]Inspection of 500 MHz ^1H NMR spectrum showed an inseparable 1:0.8 mixture of mono- and di-arylated products where the di-arylated product had a *dr* approx. 50:50 by ^1H NMR. [e]No reaction observed by TLC and LCMS.

This C-H activation chemistry was found to have mixed success with the set of aryl iodides used, with three out of the five desired arylated derivatives **159** being successfully prepared. It was found that if this reaction used 2.2 equivalents of 3-iodoanisole, it actually gave an inseparable 1:0.8 mixture of mono- and di-arylated product, where the diarylated product was observed to be a mixture of diastereomers (*dr* approx. 50:50) by inspection of the 500 MHz ^1H NMR spectrum (Table 21 Entry 1a). However, this issue was easily solved by reducing the number of equivalents of 3-iodoanisole used in the reaction. Arylated derivative **159a** could be isolated in 68% yield as a single diastereomer if only 1.1 equivalents of 3-iodoanisole was used instead (Table 21, Entry 1b). C-H activation with the *ortho*-functionalised aryl iodides was successful with both ethyl-2-iodobenzoate and heteroaromatic aryl iodide 2-fluoro-3-iodopyridine to give the corresponding arylated derivatives **159c-d** as single diastereomers in 40% and 50% yield respectively (Table 21, Entries 3-4). It was shown that both 2-bromoiodobenzene and 2-iodobenyl alcohol were not tolerated under these reaction conditions as no reaction was observed in either case. (Table 21, Entries 2 and 5).

The relative configuration of arylated derivatives **159** was confirmed by analysis of key nOe interaction in the corresponding NOESY spectra (500 MHz). Inspection of each of the NOESY spectra showed key nOe interactions between protons 1-H and 2-H as well as interactions between cyclopropylmethyl 1-H_2 and the aryl group (Figure 23). The observation of these key nOe enhancements indicated the relative configuration

of derivatives **159** to be *cis* as these interactions would not be observed in the alternative *trans* product.

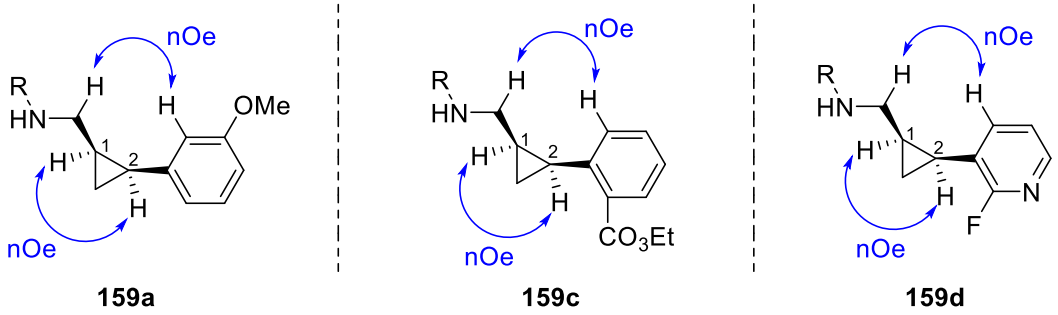
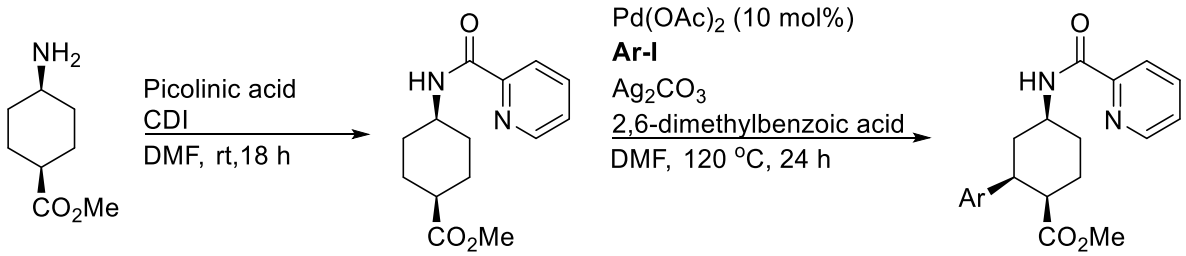


Figure 23: Determination of the relative configuration of arylated derivatives **159** by analysis of key nOe enhancements in the corresponding NOESY spectra (500 MHz).

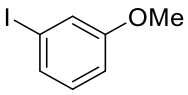
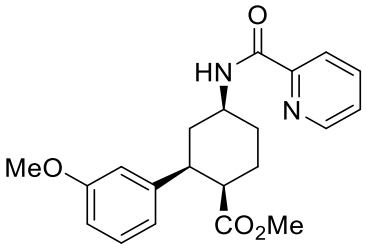
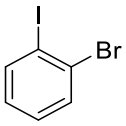
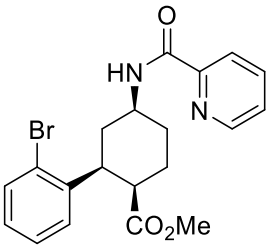
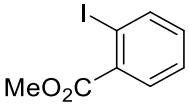
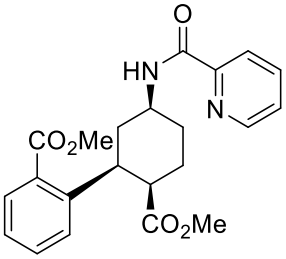
3.2.9 C-H activation of 1,4-*cis*-disubstituted cyclohexylamines

To complete the investigation into the preparation of arylated derivatives through C-H activation chemistry, it was decided to attempt C-H activation reactions on a 1,4-*cis*-disubstituted cyclohexylamine **160**. This was due to the previous success in preparing arylated derivatives from cyclohexylamine-based starting materials (Section 3.2.1). The advantage of utilising disubstituted amine starting materials is that another point of diversification can be added to the core structure of the final cyclised scaffolds, therefore enabling these scaffolds to be selectively decorated along different reaction vectors, thus allowing these scaffolds to better target lead-like chemical space. *Cis*-4-aminocyclohexanecarboxylic acid methyl ester **160** was chosen to be the 1,4-disubstituted cyclohexylamine starting material used in this investigation, as the ester functional group can allow final scaffold decoration through well-known chemistry such as amide coupling reactions. As there is currently not any literature precedent for C-H arylation on this exact substrate, it was decided to use picolinamide directing group conditions as it has been shown through this investigation that these conditions are generally less substrate dependant than the transient directing group conditions. 1,4-*cis* disubstituted cyclohexylamine **160** was first treated with picolinic acid and CDI in DMF at rt for 18 h to give the corresponding picolinamide **161** in 91% yield. This

substrate was then treated with 10 mol% $Pd(OAc)_2$, various aryl iodides, Ag_2CO_3 and 2,6-dimethylbenzoic acid in DMF at 120 °C for 24 h to prepare the desired arylated derivatives **162** (Table 22).[118]



160 **161**, 91% **162** Arylated derivative

Entry	Aryl iodide	Arylated derivative	[a]Yield (*dr*)[b]
1		 **162a**	**87% (>95:<5)**
2		 **162b**	-[c]
3		 **162c**	-[c]

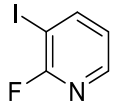
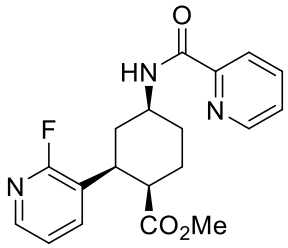
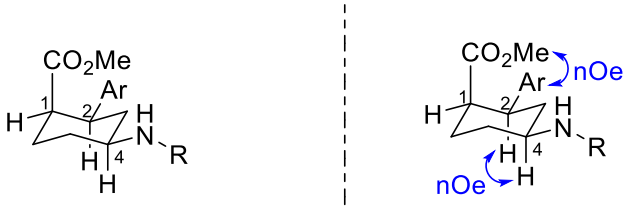
4		 **162d**	**39% (>95:<5)**

Table 22: C-H activation of 1,4-*cis*-disubstituted cyclohexylamine **160** to provide the corresponding arylated derivatives **162**. [a]Isolated yield of purified compound. [b]Determined by 500 MHz ^{1}H NMR spectroscopic analysis of purified compound. [c]No reaction observed by TLC and LCMS.

It was again found that aryl iodides containing the larger *ortho*-functionality were not tolerated under these reaction conditions, with no reaction being observed in both cases (Table 22, Entries 2-3). 3-iodoanisole was found to tolerate these reaction conditions very well, providing the corresponding arylated derivative **162a** in an excellent 87% yield as a single diastereomer (Table 22, Entry 1). It was also shown that the heteroaromatic aryl iodide 2-fluoro-3-iodopyridine was also tolerated, providing the corresponding arylated derivative **162d** in 39% yield, also as a single diastereomer (Table 22, Entry 4).

The relative configuration of arylated derivatives **162** was confirmed through analysis of key coupling constants from the 500 MHz ^{1}H NMR spectra as well as through key nOe enhancements from inspection of the corresponding NOESY spectra (500 MHz). Analysis of the ^{1}H NMR spectra showed *J* 13.1 and 12.4 Hz for protons 2-H and 4-H in the C-H arylated products isolated (Figure 24). These large coupling constants correlated with vicinal diaxial coupling to adjacent protons on the cyclohexylamine ring. This suggests both the NHR and aryl substituents are positioned equatorially with both protons 2-H and 4-H being positioned axially to allow for the large diaxial coupling constants observed. Inspection of the NOESY spectra also showed key nOe enhancements between protons 2-H and 4-H as well as between the ester CO_2Me and the aryl group (Figure 24). The observation of these large coupling constants and nOe interactions indicated the relative configuration of **162** to be *cis* as expected.



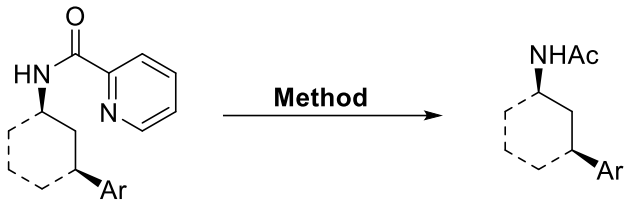
2-H: dt, *J* = 13.1 and 3.8 Hz
4-H: tdt, *J* = 12.4, 8.4 and 4.1 Hz

162

Figure 24: Determination of the relative configuration of arylated derivatives **162** by analysis of key coupling constants and nOe enhancements.

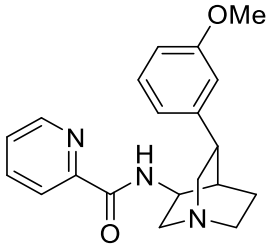
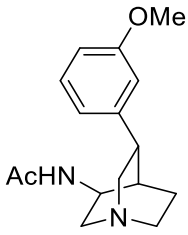
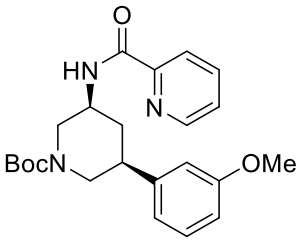
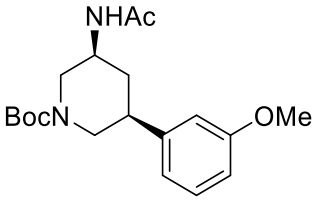
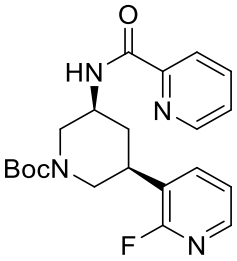
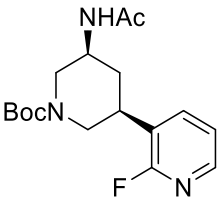
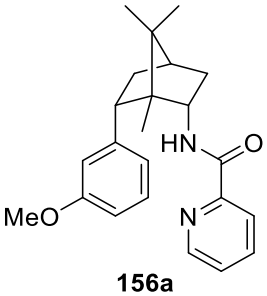
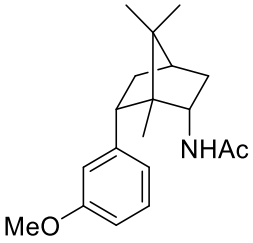
3.3 Removal of picolinamide directing group

The final step for the preparation of the library of arylated cyclisation precursors was to remove the picolinamide directing group from all the arylated derivatives prepared through picolinamide directing group C-H activation chemistry. Removal of this directing group can be achieved through either amide hydrolysis or reduction to give the free amine. Cleavage though hydrolysis was achieved by treatment of the arylated derivatives with NaOH in ^{i}PrOH at 85 ^{o}C for 18 h to provide the free amine intermediates.[118] Alternatively, reductive cleavage of the picolinamide directing group was achieved using chemistry reported by Spring and co-workers, where treatment of the arylated derivatives with Zn/HCl in THF at rt for up to 18 h provided the free amine derivatives.[120] These free amine derivatives were then acetyl protected to ease purification, providing the desired *N*-Ac arylated cyclisation precursors required for subsequent scaffold synthesis *via* intramolecular cyclisation chemistry (Table 23).



Picolinamide

163
Cyclisation precursor

Entry	Picolinamide	[a]Method	Cyclisation precursor	[b]Yield
1	 **139b**	**A**	 **163a**	**74%**
2	 **153a**	**B**	 **163b**	**54%**
3a **3b**	 **153c**	A B	 **163c**	-[c] -[c]
4	 **156a**	**A**	 **163d**	**79%**

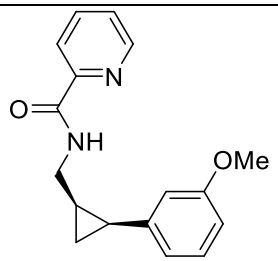
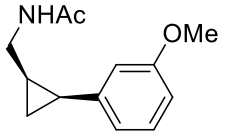
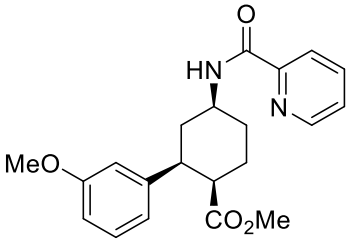
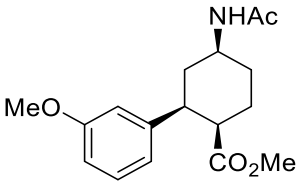
5	 **159a**	**C**	 **163e**	**60%**
6	 **162a**	**D**	 **163f**	**54%**

Table 23: Removal of the picolinamide directing group to prepare the corresponding cyclisation precursors **163**. [a]**Method: A:** Zn/HCl, THF, rt, o/n then Ac_2O, NaOH, THF, rt, 1-4 h; **B:** NaOH, ^{i}PrOH, 85 ^{o}C, 18 h then Ac_2O, NaOH, THF, rt, 4 h; **C:** Zn/HCl, THF, rt, 3 h then Ac_2O, NaOH, THF, rt, 18 h; **D:** Zn/HCl, THF, rt, 2 h then Ac_2O, Et_3N, DCM, rt, 18 h. [b]Isolated yield of purified compound. [c]Complex mixture of products observed.

It should be noted that many of the picolinamides containing heteroaromatic and *ortho*-ester aryl groups were not subject to directing group cleavage at this stage. This was because it was postulated that removal of the directing group in these substrates may induce intramolecular cyclisations to provide the corresponding cyclised scaffolds in a one-pot reaction (Section 3.5). Therefore, only picolinamides where directing group removal would not likely induce any cyclisations were investigated at this stage to provide the *N*-Ac cyclisation precursors **163**. The reductive cleavage conditions were found to be reproducible across most the picolinamides to provide the corresponding cyclisation precursors in 54-79% yield (Table 23, Entries 1 and 4-6). Directing group removal through amide bond hydrolysis was performed on picolinamides **153a** and **153c** due to the close literature precedent for picolinamide removal on related substrates.[118] Directing group removal was successful performed with **153a** to provide cyclisation precursor **163b** in 54% yield (Table 23, Entry 2). Unfortunately, attempts to cleave the directing group on picolinamide **153c** was unsuccessful, where only a complex mixture of undetermined products was observed (Table 23, Entry 3).

3.4 Summary of arylated cyclisation precursors prepared

To summarise, C-H activation chemistry has been utilised to provide a library of 20 arylated cyclisation precursor compounds that were prepared from 7 different cyclic/bicyclic amine starting materials (Figure 25). These cyclisation precursors all contained protected amine and functionalised aryl reaction handles which can allow subsequent intramolecular cyclisations to provide a library of structurally diverse cyclised scaffolds to target lead-like chemical space.

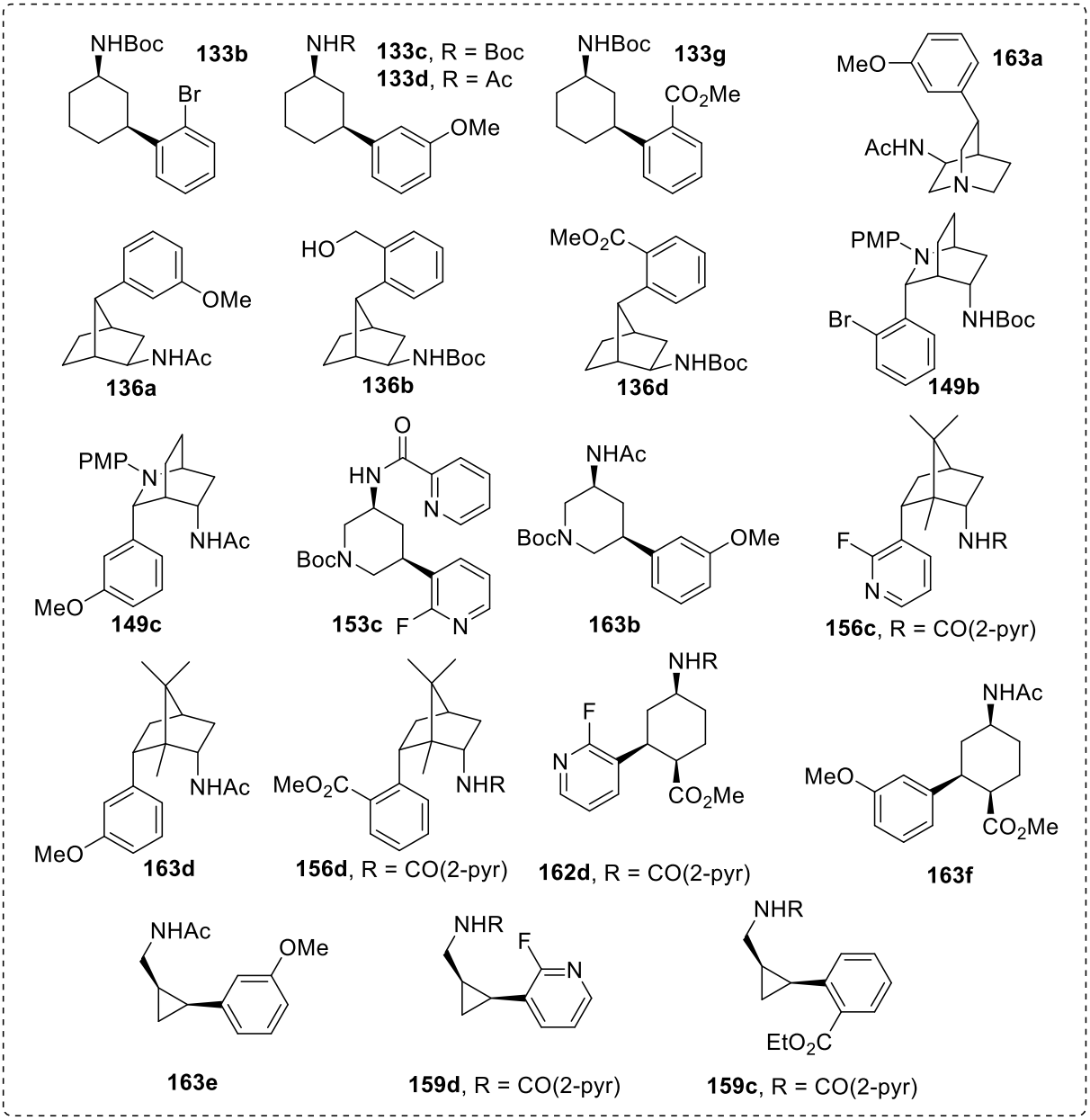


Figure 25: The 20 arylated cyclisation precursors prepared through C-H activation of cyclic/bicyclic amines.

It was found that 7 cyclisation precursors were successfully prepared using transient directing group chemistry, whereas 11 of the precursors had been prepared through picolinamide directing group chemistry. The remaining 2 cyclisation precursors were prepared through cycloaddition and subsequent reductive amination (Figure 26).

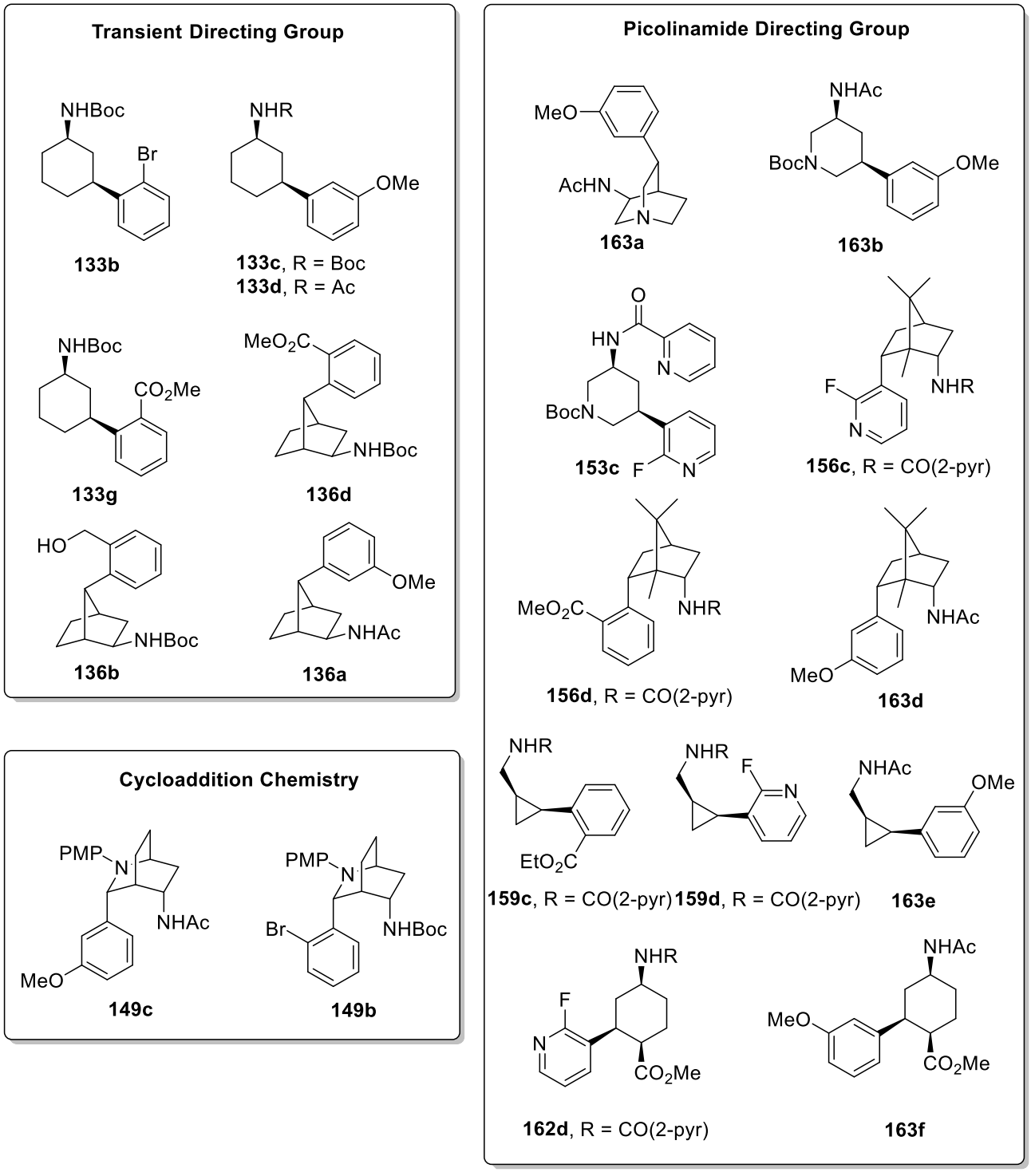


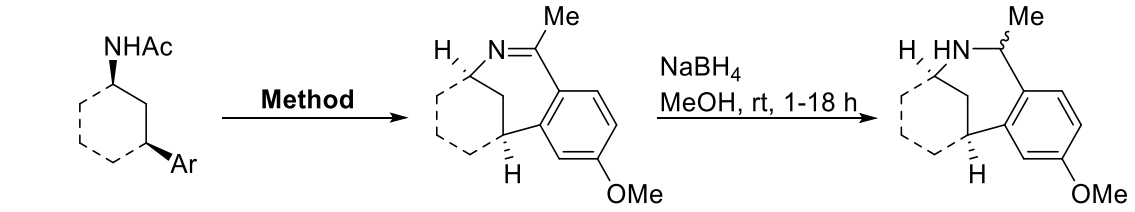
Figure 26: An outline of the different synthetic pathways used to prepare the 20 arylated cyclisation precursors.

3.5 Synthesis of diverse scaffold library through intramolecular cyclisations

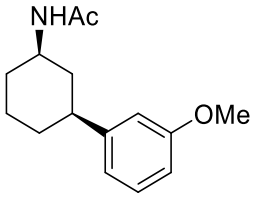
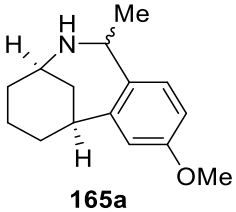
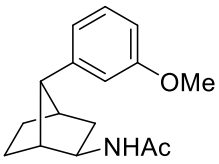
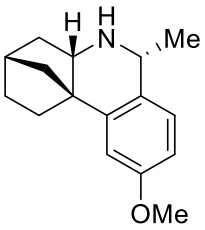
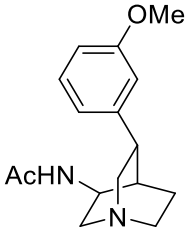
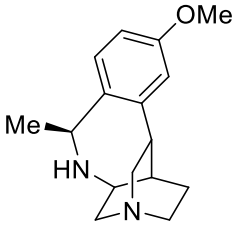
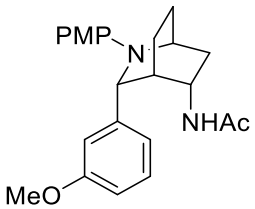
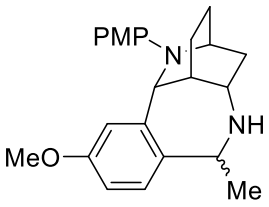
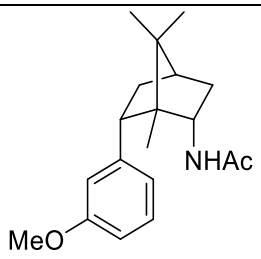
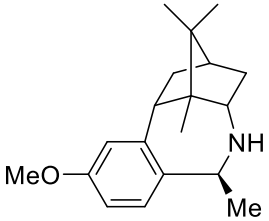
With the synthesis of the library of arylated cyclisation precursors now complete, an investigation into the scope of subsequent intramolecular cyclisations could now commence. This library of arylated cyclisation precursors contained amine and functionalised aryl reaction handles that can be reacted together to give a library of structurally diverse, sp^3-rich cyclised scaffolds to target lead-like chemical space as desired. As the same set of functionalised aryl iodides were used during C-H activation, many of these cyclisation precursors contain the same functionalised aryl reaction handles but with differing core structures. Therefore, a toolkit of cyclisation reactions can be developed and applied to the cyclisation precursors with matching functionalised aryl reaction handles to allow the efficient and modular preparation of a library of diverse scaffolds.

3.5.1 Preparation of scaffolds by Bischler-Napieralski cyclisation

The first cyclisation reaction to be tested involved utilising the Bischler-Napieralski reaction in order to prepare the corresponding cyclised scaffolds **165**.[121] During the synthesis of the arylated cyclisation precursors, many of these compounds were designed to have the amine reaction handle protected as an acetamide. This protecting group was chosen as it provides the amide functional group required for this intramolecular Bischler-Napieralski cyclisation to take place. This initial cyclisation was attempted with cyclisation precursors that contained *meta*-methoxy aryl groups in their structure, as this provides the electron rich aromatic group required for this cyclisation to take place. Treatment of the cyclisation precursors with $POCl_3$ in MeCN at 100 ^oC was found to be the most tolerated reaction conditions that always gave the corresponding cyclised imine derivatives **164** in the best yields.[122] These imine intermediates **164** were then reduced with $NaBH_4$ in MeOH to provide the desired cyclised scaffolds **165** (Table 24). As with all the cyclised scaffolds prepared this far, several points of diversification in these final scaffolds can then allow subsequent scaffold decoration along different reaction vectors to enable these scaffolds target lead-like chemical space as required.



Cyclisation precursor | **164** Cyclised imine | **165** Scaffold

Entry	Cyclisation precursor	Scaffold	[a]Method	[b]Yield 164	[c]Yield 165 (*dr*)[d]
1a **1b** **1c**	 **133d**	 **165a**	A B C	-[e] -[e] -[e]	-[f] -[f] -[f]
2	 **136a**	 **165b**	**C**	**33%**	**74%** **(>95:<5)**
3	 **163a**	 **165c**	**C**	**-[g]**	**54%** **(84:16)**
4	 **149c**	 **165d**	C	-[e]	-[f]
5	 **163d**	 **165e**	**C**	**-[g]**	**62%** **(>95:<5)**

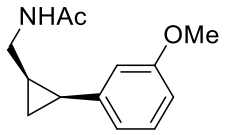
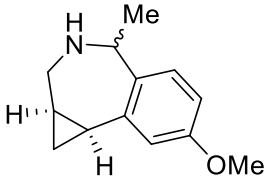
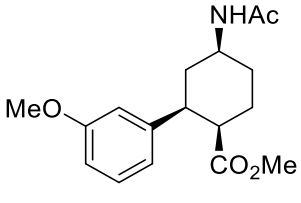
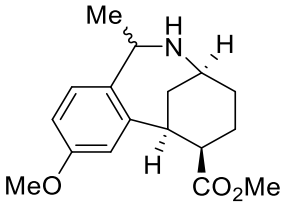
6	 **163e**	 **165f**	C	-[e]	-[f]
7	 **163f**	 **165g**	C	-[e]	-[f]

Table 24: Bischler-Napieralski cyclisation of *meta*-methoxy aryl containing cyclisation precursors to prepare the corresponding cyclised scaffolds **165**. [a]**Method: A:** PCl_5, $CHCl_3$, rt; **B:** $POCl_3$, toluene, 100 ^oC; **C:** $POCl_3$, MeCN, 100 ^oC. [b]Isolated yield of pure cyclised imine intermediate. [c]Isolated yield of pure cyclised scaffold. [d]Determined by 500 MHz ^1H NMR spectroscopic analysis of purified compound. [e]Complex mixture of products observed. [f]Reduction not performed. [g]Cyclised imine not isolated due to telescoped reaction procedure.

This intramolecular Bischler-Napieralski cyclisation was found to only be tolerated with bicyclic cyclisation precursors **136a**, **163a** and **163d** to provide the corresponding cyclised scaffolds **165b-c** and **165e** as a single regioisomer. The reaction was found to work well with the quinuclidine based cyclisation precursor **163a**, where a telescoped reaction procedure over the two synthetic steps gave cyclised scaffold **165c** in 54% yield as an 84:16 mixture of diastereomers after purification (Table 24, Entry 3). The cyclisation reaction was also tolerated with the bornylamine based precursor **163d**, where the telescoped procedure gave the corresponding cyclised scaffold **165e** in 62% yield as a single diastereomer (Table 24, Entry 5). Interestingly, it was found that Bischler-Napieralski cyclisation of bicyclic cyclisation precursor **136a** did not give the expected cyclised product as observed with the other successful substrates. Instead, it was found that a rearrangement had occurred to provide an alternate fused ring cyclised intermediate **164b** in 33% yield. Subsequent reduction of this imine intermediate provided the fused ring cyclised scaffold **165b** in 74% yield as a single diastereomer (Table 24, Entry 2). Unfortunately, the cyclisation reaction conditions were not tolerated with the remainder of the cyclisation precursors, with only a complex mixture of unknown products being observed after the Bischler-Napieralski cyclisation step in all cases (Table 24, Entries 1, 4 and 6-7). This observation is likely due to conformational effects as both the aryl and acetamide

functional groups would need to adopt an energetically unfavourable diaxial conformation for the Bischler-Napieralski cyclisation to proceed. However, this is not the case in the bicyclic acetamide substrates, where both the aryl and acetamide functional groups are held close together in space, likely aiding the cyclisation to occur. Therefore, it was found that this cyclisation pathway was predominantly a good method for cyclisation on the bicyclic substrates to provide the desired final scaffolds.

The rearrangement observed with bicyclic cyclisation precursor **136a** to provide fused ring scaffold **164b** was an unexpected result. It was found that scaffold **164b** was the only observed cyclised product from this reaction, with none of the expected cyclised imine being observed. A mechanism for this rearrangement was proposed to try and understand why a rearrangement was favourable with this substrate under these reaction conditions (Figure 27).

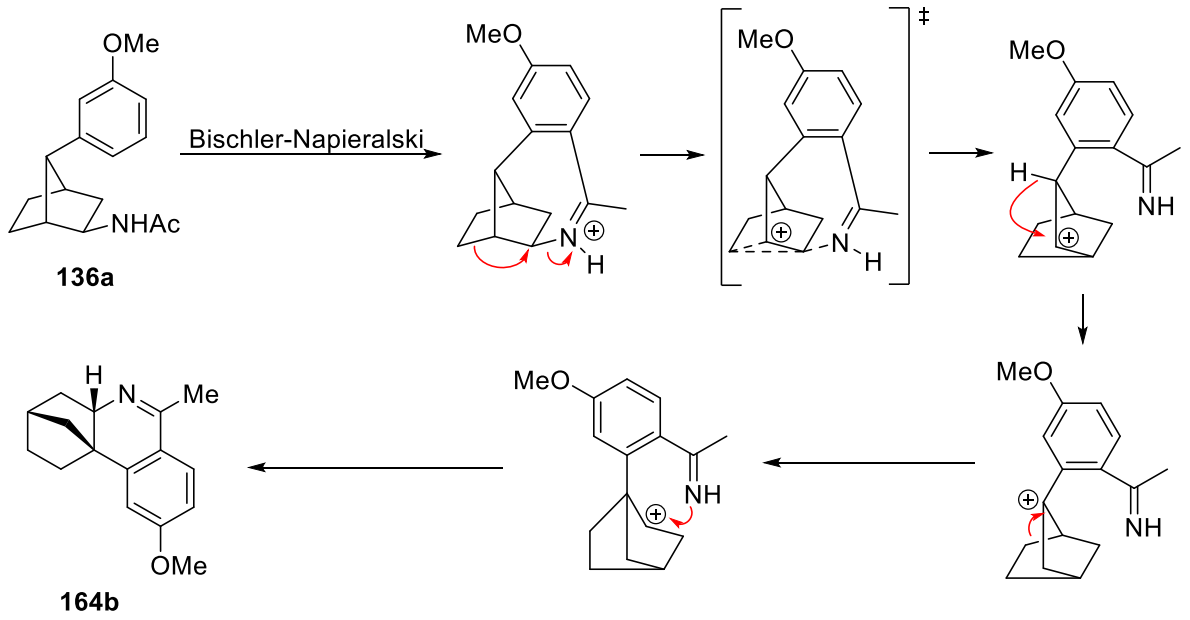


Figure 27: The proposed mechanism for the observed rearrangement to provide scaffold **165b** after the Bischler-Napieralski cyclisation and subsequent imine reduction of intermediate **164b**.

From the proposed mechanism, it is believed that the initial Bischler-Napieralski cyclisation first provides the expected cyclised imine. This imine intermediate can be protonated, which then provides a good leaving group for subsequent Wagner-

Meerwein rearrangement to occur.[123] This initial rearrangement is then believed to initiate the resulting fragmentation of the cyclised product and allows a cationic rearrangement cascade through hydride shifts and alkyl migrations to provide the fused ring imine intermediate **164b** observed. Subsequent imine reduction can then provide scaffold **165b**. The driving force for this rearrangement is likely due to the relief of ring strain in the 7-membered ring imine after the initial Bischler-Napieralski cyclisation. The relief of this ring strain gives a less strained six membered fused ring scaffold structure observed in scaffold **165b**.

The relative configurations of the three cyclised scaffolds **165b-c** and **165e** was determined through analysis of key nOe interaction observed in the corresponding NOESY spectra (500 MHz). This analysis showed key nOe enhancements between each of the highlighted protons and therefore indicated the relative configurations in each of the final scaffolds (Figure 28). The high diastereoselectivity of this reduction is likely due to the bowl-like conformations of each of the cyclised imine intermediates leading to selective hydride attack from the less hindered face of the imine.

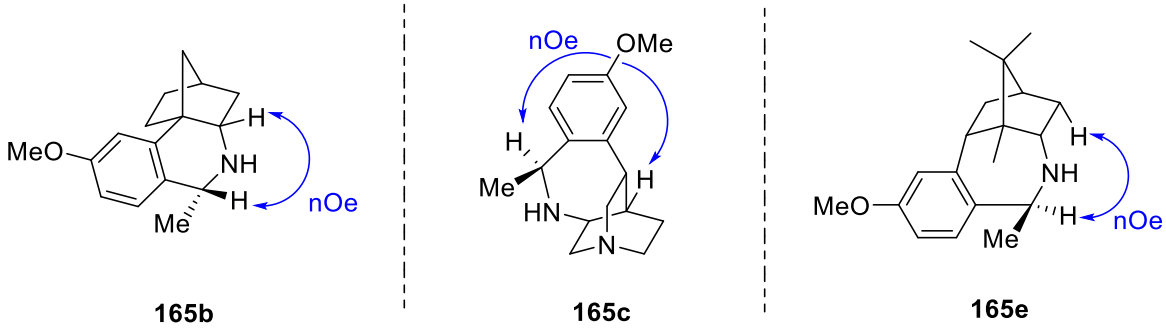
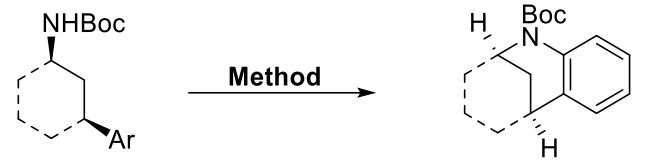


Figure 28: Determination of the relative configuration of cyclised scaffolds **165** through analysis of key nOe interactions in the corresponding NOESY spectra (500 MHz).

3.5.2 Preparation of scaffolds through Buchwald-Hartwig amination

The next cyclisation to be investigated was an intramolecular Buchwald-Hartwig amination between the protected amine reaction handle and corresponding aryl group. The cyclisation precursors chosen for this investigation contained aryl groups with either *ortho* bromo or *meta* methoxy functionality. The *meta*-methoxy based precursors were chosen as regioselective bromination of these substrates would

provide the *ortho* bromine functionality then required for subsequent intramolecular Buchwald-Hartwig cyclisation. This cyclisation was initially attempted with the *ortho*-bromine based cyclisation precursors, under both palladium and copper catalysed reaction pathways, in order to optimise the reaction conditions and to provide the desired cyclised derivatives **166** (Table 25).[124–126]



Cyclisation precursor

166
Cyclised derivative

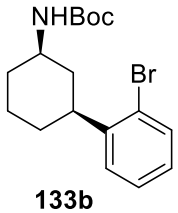
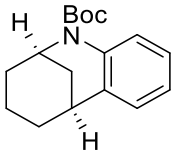
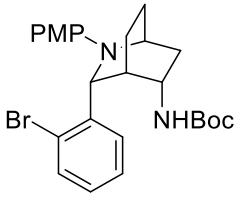
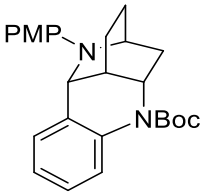
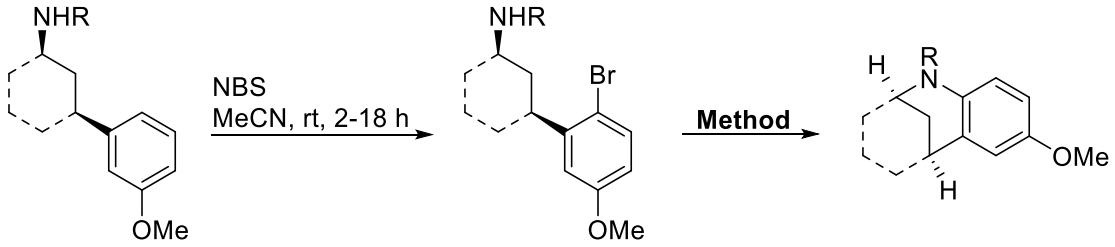
Entry	Cyclisation precursor	[a]Method	Cyclised derivative	[b]Yield
1a **1b** **1c**	 **133b**	A B **C**	 **166a**	-[c] Trace[d] **40%**
2a **2b**	 **149b**	C **D**	 **166b**	Trace[d] **32%**

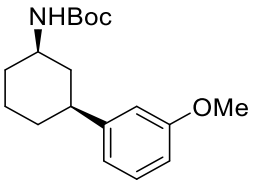
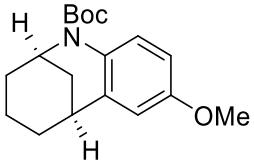
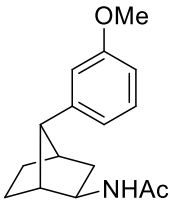
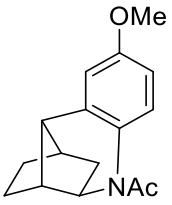
Table 25: The intramolecular Buchwald-Hartwig cyclisation reactions on *ortho*-bromine based cyclisation precursors to provide the corresponding cyclised derivatives **166**. [a]**Method: A:** CuI (5 mol%), DMEDA (20 mol%), K_2CO_3, toluene, 100 °C; **B:** TFA, DCM, rt then $Pd_2(dba)_3$ (2 mol%), *rac*-BINAP (4 mol%), NaO^{t}Bu, toluene, 85 °C; **C:** $Pd(OAc)_2$ (5 mol%), *rac*-BINAP (7.5 mol%), Cs_2CO_3, toluene, 100 °C; **D:** $Pd(OAc)_2$ (5 mol%), *rac*-BINAP (7.5 mol%), NaO^{t}Bu, toluene, 100 °C. [c]No reaction observed. [d]Trace amount of product observed by analysis of crude material by TLC, LCMS and 500 MHz ^{1}H NMR spectroscopy.

It was found that palladium catalysed Buchwald-Hartwig amination of precursors **133b** and **149b** using *rac*-BINAP as the ligand enabled formation of the desired cyclised derivatives **166**. It was noted that cyclised derivative **166a** was able to be isolated in 40% yield when Cs_2CO_3 was employed as the base under these reaction conditions (Table 25, Entry 1c). However, when these reaction conditions were repeated with precursor **149b**, it was found that these reaction conditions only provided a trace

amount of the desired cyclised derivative **166b** (Table 25, Entry 2a). Fortunately, it was discovered that changing the base from Cs_2CO_3 to NaO^{t}Bu was able to give the desired cyclised derivative **166b** in a moderate 32% yield (Table 25, Entry 2b). After the successful cyclisation of the *ortho*-brominated cyclisation precursors, the investigation into scaffold synthesis *via* intramolecular Buchwald-Hartwig cyclisations continued with the *meta*-methoxy derived cyclisation precursors. Regioselective bromination of the *meta*-methoxy aryl group by treatment of these precursors with NBS in MeCN at room temperature provided the corresponding brominated intermediates **167**.[127] These intermediates were then subject to the same palladium catalysed Buchwald-Hartwig cyclisation conditions previously employed with the *ortho*-bromine based cyclisation precursors to prepare the desired cyclised derivatives **166** (Table 26).



Cyclisation precursor | **167** Brominated intermediate | **166** Cyclised derivative

Entry	Cyclisation precursor	[a]Method	Cyclised derivative	[b]Yield 167	[b]Yield 166
1	 **133c**	A	 **166c**	79%	62%
2	 **136a**	A	 **166d**	89%	85%

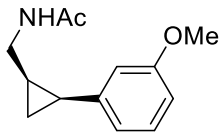
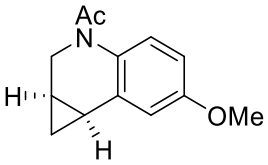
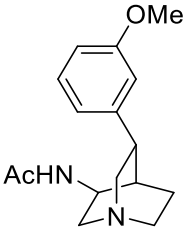
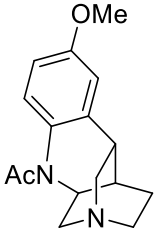
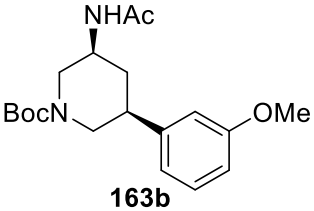
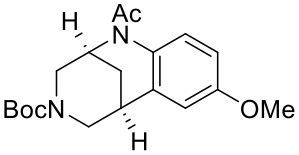
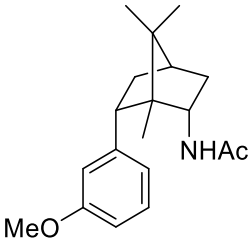
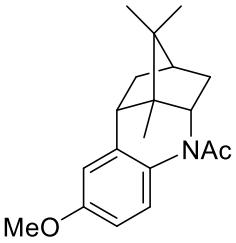
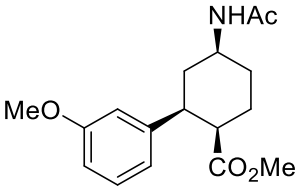
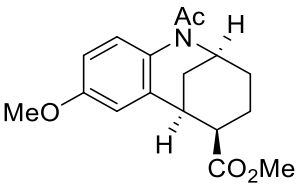
3a **3b**	 **163e**	A **B**	 **166e**	-[c] **-[c]**	-[d] **41%[e]**
4	 **163a**	**A**	 **166f**	**-[c]**	**41%[e]**
5a **5b**	 **163b**	A B	 **166g**	-[c] -[c]	-[d] -[d]
6a **6b**	 **163d**	A **B**	 **166h**	-[c] **-[c]**	-[d] **47%[e]**
7a **7b**	 **163f**	**A** B	 **166i**	**-[c]** -[c]	**43%[e]** -[d]

Table 26: Intramolecular Buchwald-Hartwig cyclisation of *meta*-methoxy based cyclisation precursors to give the corresponding cyclised derivatives **166**. [a]**Method: A:** $Pd(OAc)_2$ (5 mol%), *rac*-BINAP (7.5 mol%), Cs_2CO_3, toluene, 100 °C; **B:** $Pd(OAc)_2$ (5 mol%), *rac*-BINAP (7.5 mol%), NaO^{t}Bu, toluene, 100 °C. [b]Isolated yield of purified product. [c]Brominated intermediate not isolated due to telescoped reaction procedure. [d]No reaction was observed. [e]Isolated yield of telescoped procedure over two steps.

The reaction conditions for this cyclisation was found to be tolerated by many of the cyclisation precursors, where it was found that changing the base between Cs_2CO_3 and NaO^{t}Bu allowed this cyclisation to provide the desired cyclised product from most of the starting materials used in this investigation. A stepwise procedure was used for cyclisation precursors **133c** and **136a**, where the corresponding brominated intermediates **167a-b** were isolated in 79% and 89% yields respectively (Table 26,

Entries 1-2). Brominated derivative **167b** was crystallised and its structure was determined using single crystal X-ray crystallography (Figure 29). The X-ray crystal structure obtained from this analysis was able to confirm the regioselectivity of the aryl bromination reaction, as well as confirming the relative configuration of the compound after the C-H arylation reaction step (Section 3.2.2).

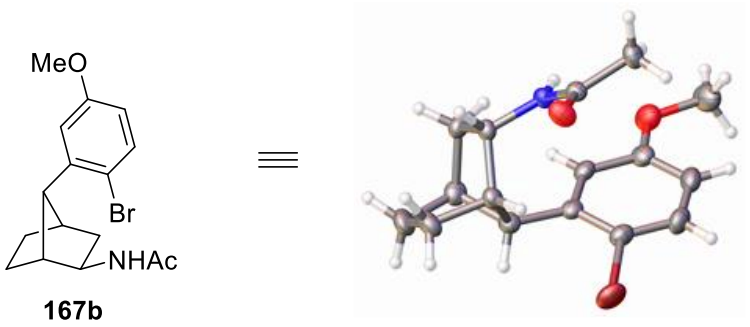
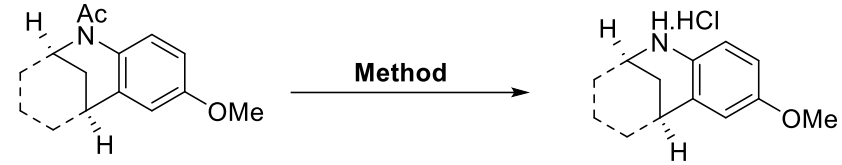


Figure 29: The X-ray crystal structure of brominated intermediate **167b** that confirmed the regiochemistry of the bromination step and the relative configuration of the C-H arylation reaction (Section 3.2.2).

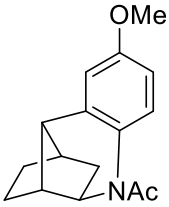
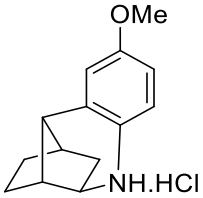
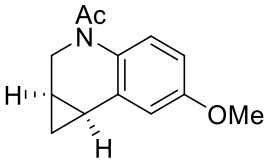
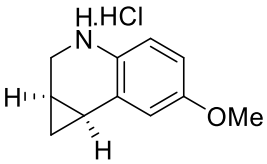
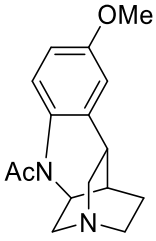
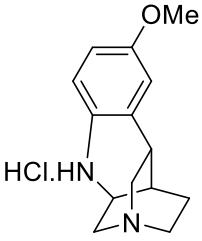
These intermediates then were successfully cyclised to provide the cyclised derivatives **166c-d** in 62% and 85% yields (Table 26, Entries 1-2). Cyclisation precursors **163a** and **163f** were subject to a telescoped reaction procedure, where Buchwald-Hartwig cyclisation using Cs_2CO_3 as the base was found to provide the desired cyclised derivatives **166f** and **166i** in 41% and 43% yields (Table 26, Entries 4 and 7). A similar telescoped reaction procedure was used with cyclisation precursors **163e** and **163d**, where it was found that changing the base from Cs_2CO_3 to NaO^tBu allowed cyclisation to take place to provide the corresponding cyclised derivatives **166e** and **166h** in moderate 41% and 47% yields respectively (Table 26, Entries 3 and 6). Cyclisation precursor **163b** was found to be the only starting material where no cyclised derivative could be formed under both sets of cyclisation conditions (Table 26, Entry 5). Therefore, this cyclisation pathway was found to be generally reproducible over many of the starting materials employed and allowed the formation of the desired cyclised scaffolds in a short number of synthetic steps.

With cyclised derivatives **166** now in hand, deprotection of the *N*-acetyl points of diversification was then undertaken, in order to ensure that this protecting group strategy can allow for selective deprotection as designed. This would then give the desired unprotected amine point of diversification required to allow these final scaffolds to undergo subsequent decorations and therefore begin to target lead-like chemical space. Treatment of the *N*-acetyl cyclised derivatives **166** with a 1:1 mixture of either 37% HCl–EtOH or 37% HCl–MeOH at 80 °C for 18 h provided the corresponding deacetylated scaffolds **168** as the HCl salts (Table 27).[128]



166
Cyclised derivative

168
Deprotected scaffold

Entry	Cyclised derivative	[a]Method	Deprotected scaffold	[b]Yield
1	 **166d**	**A**	 **168a**	**94%**
2	 **166e**	A	 **168b**	-[c]
3	 **166f**	**A**	 **168c**	**89%**

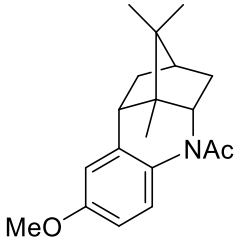
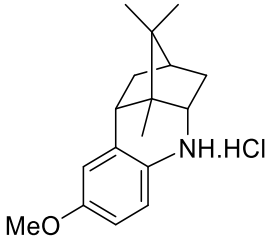
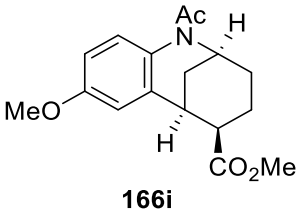
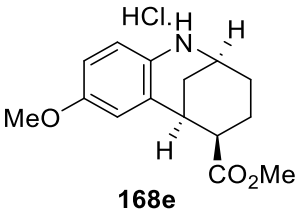
4	 **166h**	**A**	 **168d**	**67%**
5	 **166i**	B	 **168e**	-[c]

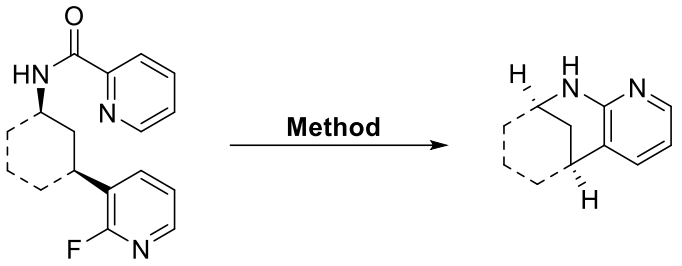
Table 27: Deacetylation of cyclised derivatives **166** to provide the corresponding deprotected scaffolds **168**. [a]**Method: A:** 37% HCl–EtOH 1:1, 80 °C; **B:** 37% HCl–MeOH 1:1, 80 °C. [b]Isolated yield of purified product. [c]Complex mixture of products observed by TLC, LCMS and ^{1}H NMR of the crude material.

This deacetylation reaction was found to be successful across three of the acetylated cyclised derivatives **166d**, **166f** and **166h** to provide the corresponding deprotected scaffolds **169a, 168c** and **168d** as HCl salts with good yields (67%-94%) observed throughout. Unfortunately, deacetylation of cyclised derivatives **166e** and **166i** was found to be unsuccessful under the reaction conditions employed. Therefore, only the cyclised derivatives that were stable under these strong acidic reaction conditions were able to be deacetylated with this chemistry.

3.5.3 Preparation of scaffolds through S_NAr cyclisation

The next cyclisation to be investigated was utilising S_NAr chemistry to cyclise between the amine and aryl reaction handles to prepare the corresponding cyclised scaffolds. This cyclisation was tested out on cyclisation precursors that contained the 2-fluoropyridine heteroaromatic motif. This is because these precursors have the functionality required in order for S_NAr cyclisation to occur between the amine and this aryl group, therefore providing a range of cyclised scaffolds containing a heteroaromatic group in their structure. The cyclisation precursors first had the picolinamide directing group removed by reductive cleavage with Zn/HCl to provide

the amine intermediates.[120] These intermediates could then undergo subsequent S_NAr cyclisation to provide the corresponding cyclised scaffolds (Table 28).



Cyclisation precursor

169
Scaffold

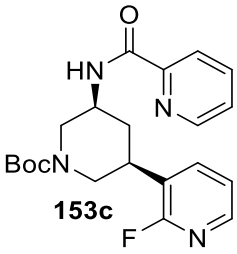
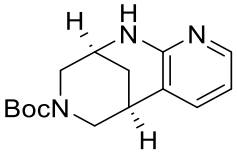
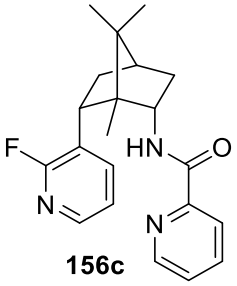
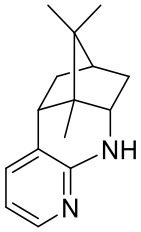
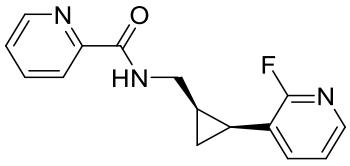
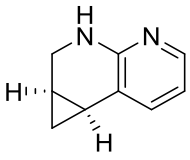
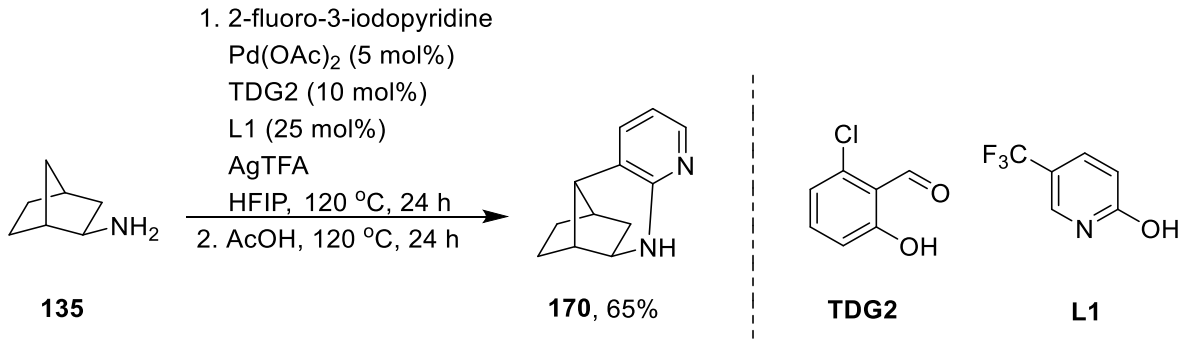
Entry	Cyclisation precursor	[a]Method	Scaffold	[b]Yield
1a **1b**	 **153c**	A B	 **169a**	-[c] -[c]
2	 **156c**	**A**	 **169b**	**55%**
3a **3b**	 **159d**	A C	 **169c**	-[c] -[c]

Table 28: S_NAr cyclisation of cyclisation precursors containing the 2-fluoropyridine heteroaromatic group to provide the corresponding cyclised scaffolds **169**. [a]**Method: A:** Zn/HCl, THF, rt; **B:** Zn/HCl, THF, rt then K_2CO_2, DMSO, 100 °C; **C:** Zn/HCl, THF, rt then K_2CO_3, MeCN, rt. [b]Isolated yield of purified product. [c]Complex mixture observed.

It was found that only bicyclic cyclisation precursor **156c** could undergo S_NAr cyclisation under the reaction conditions used in this investigation. Precursor **156c** was found to provide the corresponding cyclised scaffold **169b** in 55% yield under the acidic picolinamide cleavage conditions (Table 28, Entry 2). Unfortunately, cyclisation precursors **153c** and **159d** were not able to provide the corresponding cyclised

scaffolds under either the acidic or basic cyclisation conditions attempted (Table 28, Entries 1 and 3).

Yu and co-workers had recently reported in 2018 a modified set of reaction conditions that now enabled heteroaromatic groups to be tolerated under transient directing group conditions in C-H activation reactions.[109] These revised conditions involved a different transient directing group (TDG2) to what was used previously and a ligand (L1) in order to allow heteroaromatic rings to be tolerated in C-H activation.[109] As only one cyclised scaffold was able to be prepared *via* this S_NAr cyclisation chemistry (Table 28), it was decided to utilise these modified C-H activation conditions to prepare cyclised scaffold **170** in a one-pot procedure from *exo*-2-aminonorbornane. Treatment of *exo*-2-aminonorbornane with 2-fluoro-3-iodopyridine, 5 mol% $Pd(OAc)_2$, 10 mol% TDG2, 25 mol% L1 and AgTFA in HFIP at 120 °C for 24 h, followed by the addition of AcOH and subsequent reaction at 120 °C for 24 h provided the desired cyclised scaffold **170** in 65% yield (Scheme 29).[109] These revised C-H arylation conditions are believed to tolerate heteroaromatic groups as they now prevent the formation of many unwanted palladium complexes that end up poisoning the palladium catalyst.[109]



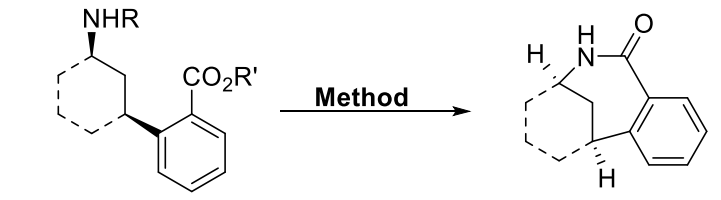
Scheme 29: One-pot C-H activation S_NAr cyclisation cascade used to prepare cyclised scaffold **170** from *exo*-2-aminonorbornane **135**.

This one-pot C-H activation cyclisation cascade reaction enabled another cyclised scaffold to be prepared using similar S_NAr cyclisation chemistry. Therefore, it was found that only two final scaffolds could be prepared from their corresponding cyclisation precursors through this S_NAr cyclisation strategy.

The major limitation of this cyclisation method was found to be the difficulty of synthesising the C-H arylated starting materials *via* transient directing group chemistry. This meant that picolinamide directing group chemistry was ultimately needed, which led to the difficulty of removing the picolinamide directing group in the presence of another heteroaromatic group. This was determined to be one of the major causes of reaction failure when attempting this S_NAr cyclisation approach.

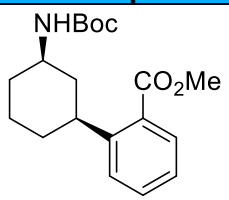
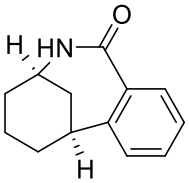
3.5.4 Preparation of scaffolds through lactamisation

During the synthesis of the cyclisation precursors, it was found that C-H activation of *exo*-2-aminonorbornane under transient directing group conditions with methyl-2-iodobenzoate could undergo cyclisation when basified to provide lactam scaffold **136e** in a one-pot procedure (Section 3.2.2). Therefore, the synthesis of lactam scaffolds was investigated using the cyclisation precursors containing *ortho* ester functionality. The cyclisation precursors were first converted into the free amine intermediates by either *N*-Boc deprotection or picolinamide directing group cleavage.[120] Basification of the reaction mixture would then initiate cyclisation to occur between the amine and *ortho* ester functional groups to provide the corresponding lactam scaffolds **171** (Table 29).[129]



Cyclisation precursor

171
Lactam scaffold

Entry	Cyclisation precursor	[a]Method	Amide scaffold	[b]Yield
1	 **133g**	**A**	 **171a**	-[c]

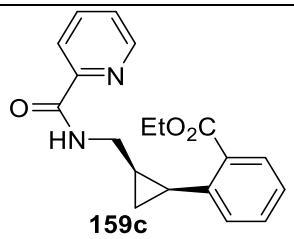
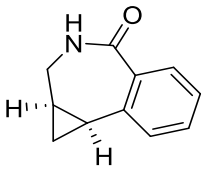
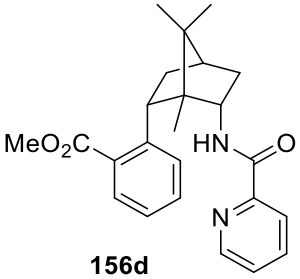
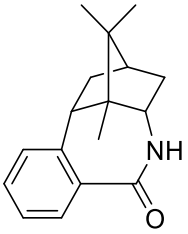
2	 **159c**	**B**	 **171b**	**57%**
3	 **156d**	**B**	 **171c**	**71%**

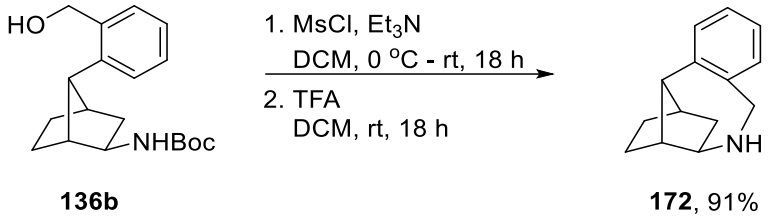
Table 29: Synthesis of lactam scaffolds **171** from their corresponding cyclisation precursors through amide bond forming reactions. [a]**Method: A:** TFA, DCM, rt then NaOH, THF, rt; **B:** Zn/HCl, THF, rt then NaOH, THF, rt. [b]Isolated yield of purified product. [c]Desired product not observed.

These cyclisation reaction conditions were found to be tolerated with cyclisation precursors **159c** and **156d** as their corresponding lactam scaffolds **171b-c** were able to be successfully prepared in 57% and 71% yields respectively (Table 29, Entries 2-3). Cyclisation precursor **133g** was found to not cyclise under these reaction conditions, with only *N*-Boc deprotection being observed by analysis of the crude material by TLC and LCMS (Table 29, Entry 1). This is likely due to the energetically unfavourable diaxial conformation that this substrate would need to adopt to allow this cyclisation to take place. Therefore, it was found that only two more cyclised scaffolds were able be prepared *via* this cyclisation pathway, which gave three lactam scaffolds to add to the final diverse sp^3-rich scaffold library. This cyclisation approach was found to work best with the bicyclic substrates and for the synthesis of fused-ring scaffolds. The limitation of this approach was the apparent difficulty in synthesising the *ortho* ester C-H arylated intermediates. This meant only a small number of lactamisations could be carried out to give three final scaffolds made through this cyclisation pathway.

3.5.5 Preparation of scaffolds through S_N2-like cyclisation chemistry

The final successful cyclisation to be investigated involved utilising S_N2-like cyclisation chemistry with cyclisation precursor **136b**. The benzyl alcohol functional group present

in precursor **136b** was found to be the only cyclisation precursor where this functionality was able to be successfully installed through the C-H activation pathway. Therefore, this cyclisation was only investigated with this cyclisation precursor **136b**. The alcohol group could be transformed into a good leaving group through mesylation, where subsequent *N*-Boc deprotection could provide the desired cyclised amine final scaffold **172**. Treatment of cyclisation precursor **136b** with MsCl and Et_3N in DCM followed by *N*-Boc deprotection using TFA in DCM provided the corresponding cyclised amine scaffold **172** in 91% yield as the TFA salt (Scheme 30).[67,130]



136b **172**, 91%

Scheme 30: The reaction conditions used to perform the S_N2 cyclisation reaction of cyclisation precursor **136b** to give cyclised amine scaffold **172** as the TFA salt.

3.5.6 Summary of final library of diverse scaffolds prepared

This modular synthetic approach was able to successfully provide a library containing 37 structurally diverse, sp^3-rich cyclised scaffolds from seven cyclic or bicyclic amine starting materials (Figure 30). These 37 scaffolds incorporated both the 17 cyclised scaffolds and the 20 arylated intermediates prepared through the C-H arylation chemistry. These 20 arylated intermediate compounds were included in the final scaffold count, as these compounds were found to still be novel, shape/structurally diverse and could also be decorated in order to access lead-like chemical space. It was found that this ‘stitching’ annulation approach was highly efficient, as these 37 scaffolds could be prepared in a very small number of synthetic steps (1.46 synthetic steps per scaffold). The scaffolds prepared through this approach contained both bridged and fused ring systems, which demonstrated the successful preparation of structurally and shape diverse compounds using this synthetic approach as desired. The cyclised scaffolds prepared in this approach contained several points of

diversification in their structure, in order for subsequent decoration reactions to allow the scaffolds to target lead-like chemical space as designed. This synthetic approach first involved the synthesis of a library of 20 arylated cyclisation precursor compounds from seven cyclic and bicyclic amine starting materials using various C-H activation chemistry. These precursors contained amine and functionalised aryl reaction handles in their structure to allow for subsequent intramolecular cyclisations to take place. With the cyclisation precursors in hand, the second phase of this synthetic approach involved the development of a toolkit of cyclisation reactions. This cyclisation toolkit was then successfully utilised by enabling intramolecular cyclisation reactions to prepare the corresponding library of 17 diverse cyclised scaffolds in a short number of overall synthetic steps.

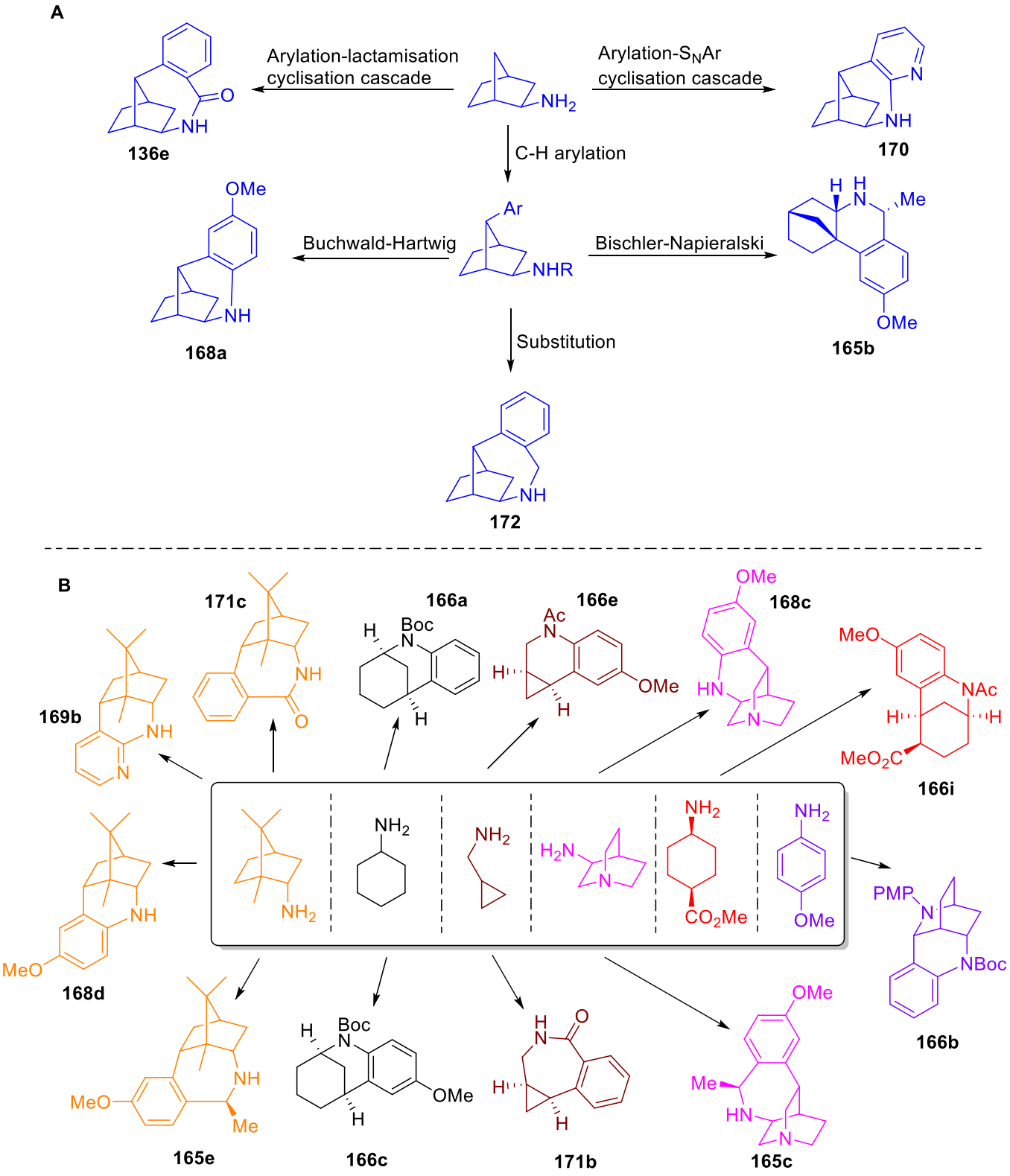


Figure 30: A summary of the 17 diverse cyclised scaffolds prepared through this modular synthetic approach. **Panel A:** Overview of the 5 cyclisation pathways used to prepare scaffolds from *exo*-2-aminonorbornane. **Panel B:** A summary of the remaining 12 final scaffolds, where the colours depict which cyclised scaffolds are derived from their corresponding amine starting material.

3.5.7 Computational analysis of second scaffold library

This library of final scaffolds prepared was analysed using the same computational methods employed for the analysis of the first scaffold library (Section 2.4). This was performed in order to assess the overall novelty, molecular properties and shape and structural diversity of the scaffolds in this library to ascertain whether these scaffolds are able to target lead-like chemical space as intended.

It was decided to assess the properties of both the unprotected final cyclised scaffolds and the unprotected arylated cyclisation precursors, as these cyclisation precursors also contained several points of diversification to enable these compounds to act as scaffolds to also target lead-like chemical space. The molecular properties and shape diversity of this library of 37 compounds were first analysed using LLAMA.[63] Similar to the first scaffold library, this analysis showed that many of these scaffolds were appropriate for application as fragments in fragment based-lead discovery (*e.g.* 140 < *MW* < 230 and 0 < *c*logP < 2), as many of the undecorated compounds were found to lie in the top end of fragment-like chemical space (Figure 31).[98] Further analysis of the PMI plot generated for these scaffolds showed the excellent shape diversity of this scaffold library, with many of the compounds moving away from the 'flatland' areas of the PMI plot (rod-disk axis) towards more three-dimensional areas of chemical space as designed. Furthermore, it was determined that none of the Murcko frameworks for any of the 17 cyclised scaffolds were found to be substructures in a random 2% sample of the ZINC database of commercially-available compounds.[99,100] Furthermore, most of the arylated cyclisation precursor compounds in this library also gave zero substructure matches in the random 2% ZINC database sample. Also, it was found that only the Murcko assemblies derived from the seven cyclohexylamine and cyclopropyl based cyclisation precursors gave any substructure matches (18-32 hits) in this random 2% sample. This analysis therefore demonstrated the high diversity and novelty associated with the compounds within this second scaffold library.

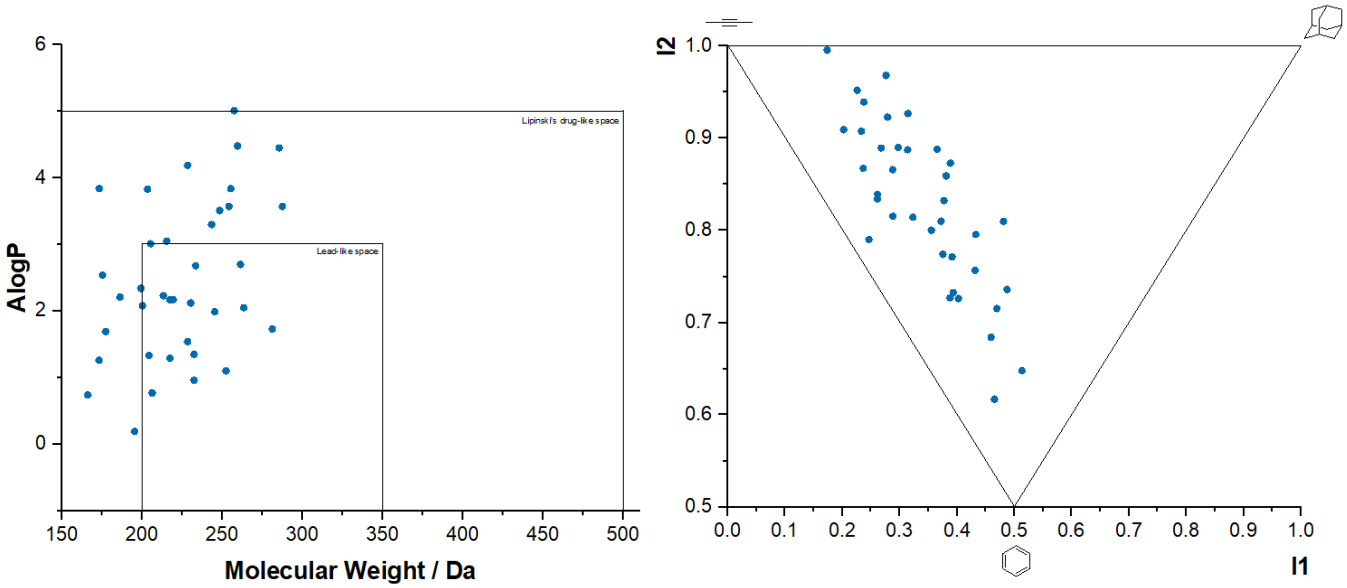


Figure 31: Computational analysis of the undecorated scaffold library using LLAMA in order to assess the chemical space and shape diversity of the scaffold library prepared.

In order to determine whether these scaffolds can effectively target lead-like chemical space as intended, decoration using a selection of medicinally relevant capping groups was performed to provide a virtual library of decorated compounds (Figure 32). The scaffolds were decorated only once through one of the available points of diversification incorporated into each of the molecules. Firstly, the lead-likeness of the virtual library was analysed, and it was found that approximately 50% of the decorated scaffolds lie within lead-like chemical space. Secondly, analysis of the PMI plot generated for this virtual library showed significant shape diversity, with many of the decorated compounds moving away from the rod-disk axis to lie in more three-dimensional areas of chemical space. The fraction of sp^3-hybridised carbons (Fsp^3) in the virtual decorated scaffold library was also analysed to assess the overall shape diversity. The mean Fsp^3 of the decorated virtual library was found to be 0.49 which shows higher Fsp^3 in comparison with a random 1% sample from the ZINC database (0.33). Therefore, this highlights the apparent success of this synthetic approach to prepare a decorated scaffold library with significant shape diversity and a higher mean Fsp^3 than in many commercially available compounds.

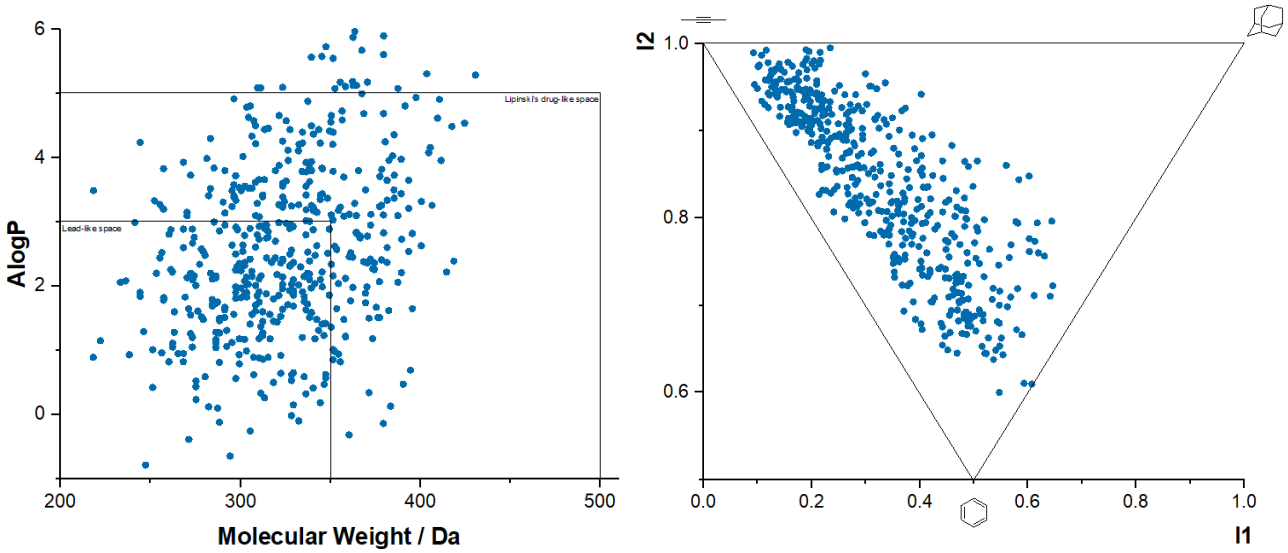


Figure 32: Computational analysis of the virtual scaffold library after decoration with one capping group to investigate the lead-likeness and molecular shape diversity of this virtual library.

The skeletal diversity of this scaffold library was then analysed through a hierarchical scaffold tree developed by Waldmann and co-workers.[71] Similarly to the corresponding analysis of the first scaffold library, this procedure involved the iterative removal of rings by following a defined set of priority rules until a final parental ring system is obtained.[71] This scaffold tree analysis found that the 37 scaffolds prepared in this library (which were based around 26 different frameworks at the graph-node-bond level) were based on eight different monocyclic parental ring systems (Figure 33).

Subsequent inspection of the scaffold tree clearly shows the high skeletal diversity within this second scaffold library due to the large number of parental frameworks from which the final scaffolds are derived. This result also highlights the overall success of this modular synthetic approach for the preparation of highly shape and structurally diverse scaffolds to effectively target lead-like chemical space as designed. Additionally, the small number of synthetic steps required to prepare each of the final scaffolds also demonstrates the high synthetic efficiency for preparing a large number of final scaffolds that are also largely diverse in both shape and structure.

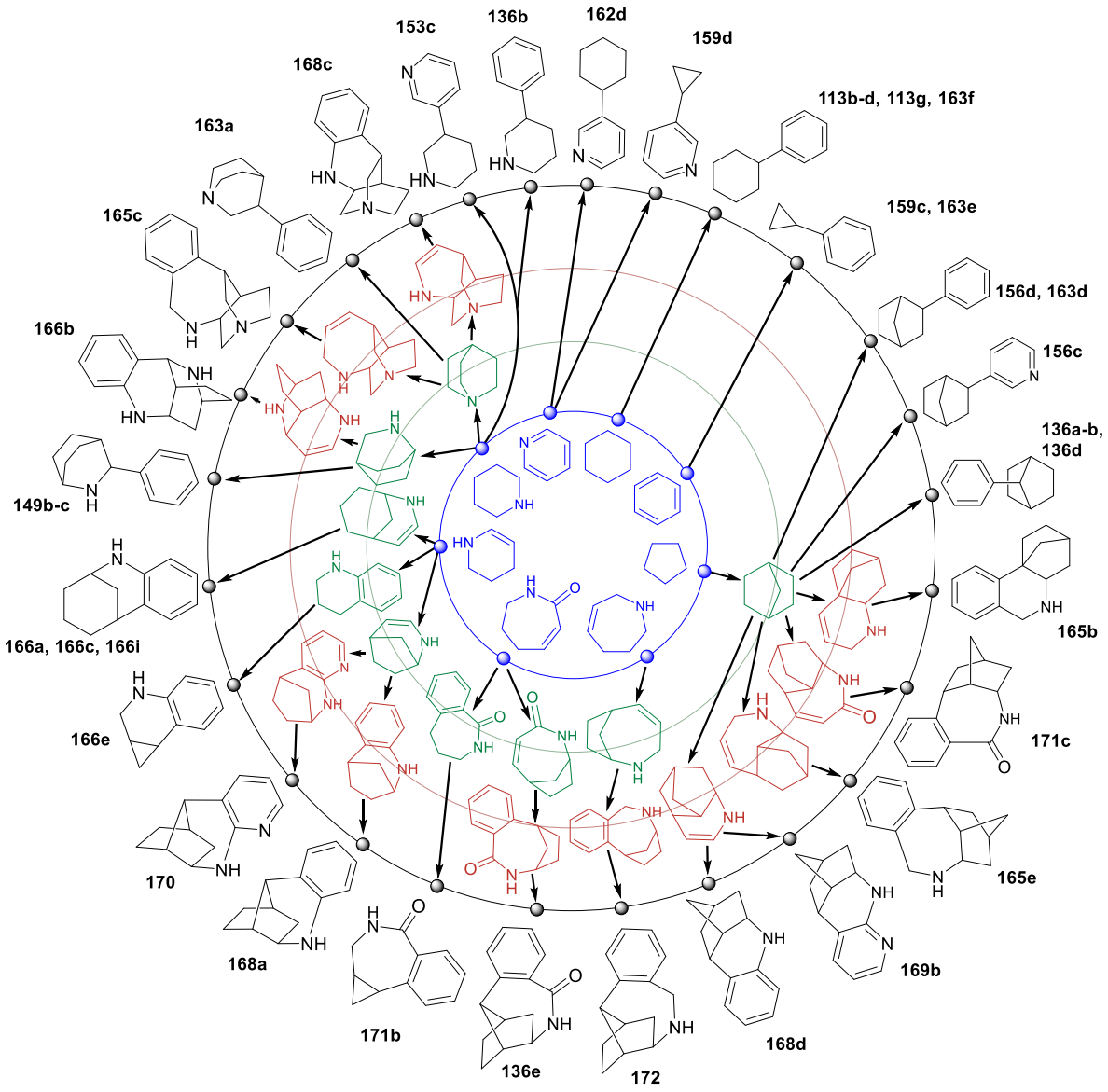


Figure 33: The hierarchical scaffold tree analysis of the final diverse scaffold library. The 37 final scaffolds (17 cyclised and 20 arylated intermediates), based on 26 different frameworks at the graph-node-bond level (black), were shown to be based around eight different monocyclic parental frameworks (blue).

4 Connective high throughput synthesis of a diverse library of chemical probes

Following on from the success of the first two ‘bottom up’ synthetic strategies for the synthesis of diverse molecular scaffold libraries (Chapter 2 and Chapter 3), it was decided that a third and final synthetic approach would be designed for the synthesis of a diverse library of chemical probes. This third approach was designed to contrast with the previous two approaches by incorporating a one-pot convergent synthetic strategy utilising high throughput chemistry. This high throughput approach would therefore allow for the rapid generation of chemical probes in an efficient manner. The initial aim of this approach was to utilise metal-catalysed carbenoid chemistry within reaction arrays. This would allow for efficient screening of various substrate, co-substrate and catalyst combinations to enable the identification of the best reaction combination for each substrate pair in a highly efficient manner. At this point, only the most promising reaction wells would be purified to give a final library of diverse chemical probes. Metal-catalysed carbenoid chemistry was chosen as the reaction of choice for the reaction array, as this chemistry is well known to provide a diverse selection of products (see Figure 34, Section 4.1.1) depending on the functional groups contained within the reaction substrates (e.g. through C-H insertion, O-H insertion, N-H insertion, cyclopropanation, ylide formation and rearrangement).[131–133] Additionally, varying the catalyst and ligands can also provide significant diversity of reaction products as different catalysts can give each of the intermolecular products in different ratios.

4.1 Use of metal-catalysed carbenoid chemistry in bioactive molecular discovery

4.1.1 General overview of metal carbenoid reactivity

It was envisaged that metal-catalysed carbenoid chemistry could be employed for the synthesis of a diverse library of chemical probes, as the Nelson group has already

previously demonstrated that this chemistry can be successfully used within a high-throughput approach to prepare a range of bioactive small molecules with significant structural diversity.[134–136] Metal-catalysed carbenoid reactions are ideal for a high throughput synthetic approach as they can undergo many different reactions depending on the functional groups present in the co-substrates. Some of the common reactions that metal carbenoids (which are derived from the corresponding α-diazo ester/amides **173**) can undergo include but are not limited to: C-H insertion to give new alkane chains (**174**),[137] O-H insertion to give ethers (**175**),[138] N-H insertion to give secondary/tertiary amines (**176**),[139] S-H insertion to provide sulfides (**177**),[140] cyclopropanation with alkenes (**178**)[141] and reaction with nitriles to give oxazoles (**179**) (Figure 34).[142]

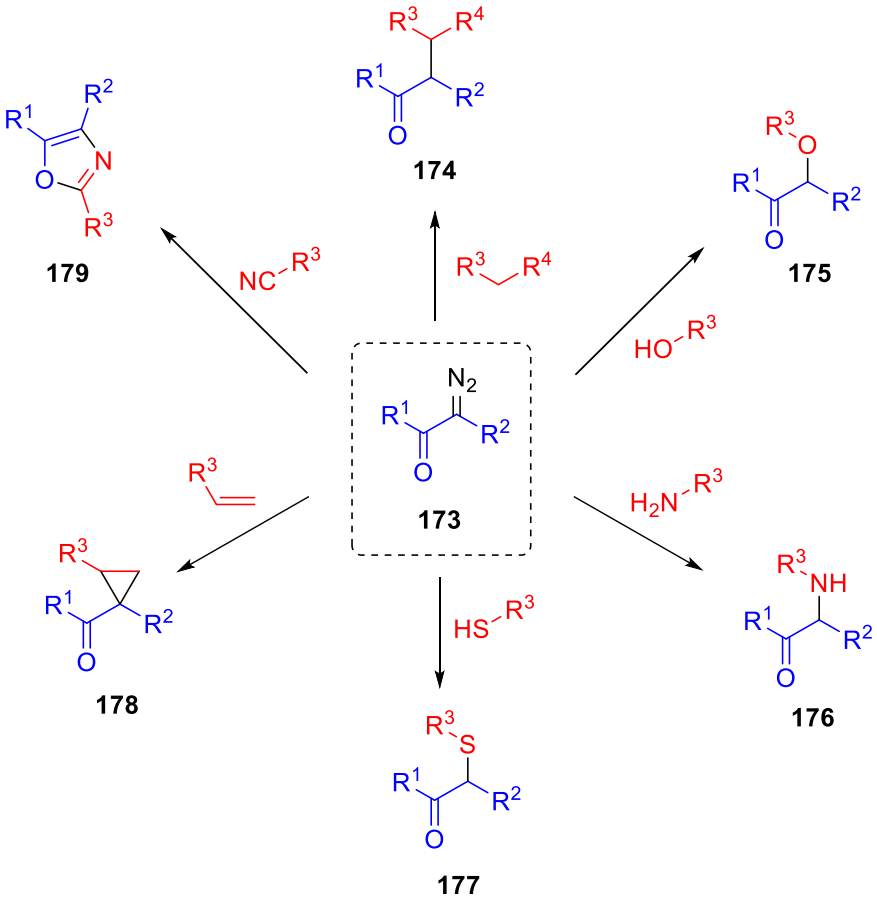
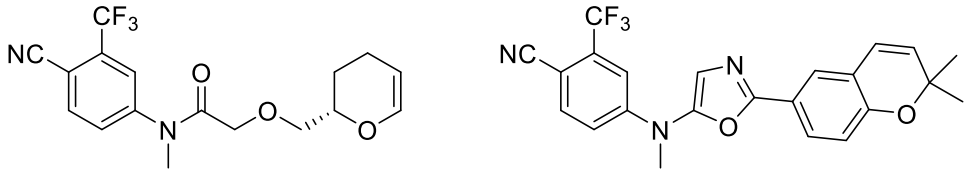


Figure 34: An overview of the potential reactions of metal carbenoids (derived from the corresponding diazo) to yield diverse scaffolds from the same starting material. Functional groups derived from the diazo starting material (blue) and co-substrate (red) are indicated.

This reactivity can occur with a metal carbenoid and a co-substrate to give intermolecular products, and where a co-substrate is not present, metal carbenoids can react with themselves to provide alternative intramolecular products.[143] It has also been shown that changing the catalyst can lead to dramatic changes in the reactivity of the metal carbenoid, providing different major products depending on the catalyst employed.[144] The promiscuous reactivity of metal carbenoids makes this ideal chemistry for the high throughput synthesis of chemical probes, as many different products are possible in each reaction well. Therefore, by carefully choosing a selection of substrates, co-substrates and catalysts, a wide range of chemical space can be investigated in an efficient manner by varying each of these parameters in a reaction array. This should then lead to a diverse range of products being prepared from the reaction array, therefore providing a library of chemical probes with significant structural diversity.

4.1.2 Previous applications of high throughput metal-catalysed carbenoid chemistry in bioactive molecular discovery

A successful high throughput synthetic strategy was previously used to discover two novel androgen agonists with metal-catalysed carbenoid chemistry using an activity directed synthesis approach (ADS).[135] In this approach, a selection of 4 diazo amides were first reacted with 10 co-substrates and 6 different catalysts in two solvents. This gave an array of 192 reactions in total that were performed in 96-well plate format. These reaction wells were then directly screened for biological activity against the androgen receptor and two of the reaction wells showed promising activity at this stage. From these two initial hits, two more subsequent diverse reaction arrays were designed and performed one after the other. These diverse reaction arrays aided the discovery of two novel small molecule Androgen agonists **180** and **181**, where each compound displayed submicromolar activity (Figure 35).[135] It was also notable that agonists **180** and **181** were in two different compound series, which was only possible in a single experiment because of the diversity of rhodium-catalysed carbenoid chemistry.

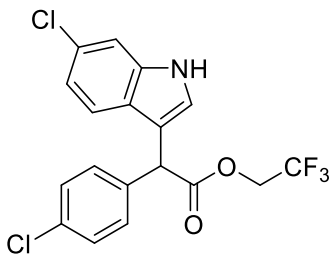


180, EC_{50} = 860 ± 40 nM
(prepared through O-H insertion)

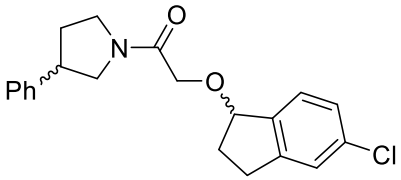
181, EC_{50} = 730 ± 30 nM
(prepared through oxazole formation)

Figure 35: Two androgen agonists (**180** and **181**) with submicromolar activity identified using an ADS approach involving successive diverse reaction arrays with metal-catalysed carbenoid chemistry.[135]

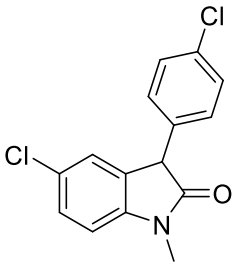
A second recently successful high throughput synthetic strategy was employed for the discovery of novel inhibitors of the p53/*h*DM2 protein-protein interaction, which again utilised metal-catalysed carbenoid chemistry using an ADS approach.[136] Initially, the first reaction array involved a selection of 7 diazo substrates (including both diazo esters and diazo amides), 10 co-substrates and 2 catalysts. These substrates were then reacted together in 96-well plate format to give a total of 154 different reactions. From this first reaction array, 6 different reaction mixtures were shown to have promising activity against the p53/*h*DM2 protein-protein interaction. A second reaction array was then designed based off the six hits discovered in this first round. The design of this second round involved 6 diazo substrates, 16 co-substrates, and two different catalysts, comprising a total of 196 different reaction combinations. Subsequent screening of these reactions found 6 additional reaction combinations that displayed promising biological activity. These reaction combinations were then scaled up 50-fold and purified to isolate the active component in each case. This high throughput approach was therefore able to identify six novel small molecule inhibitors of the p53/*h*DM2 protein-protein interaction **182**-**187**, displaying micromolar activity in each case (Figure 36).[136] Notably, the six inhibitors identified were found to be in five distinct compound series.



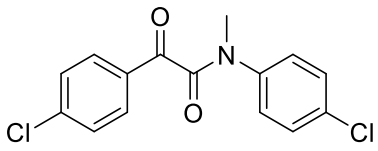
182, IC_{50} = 3.4 ± 0.4 μM
(prepared through C-H insertion)



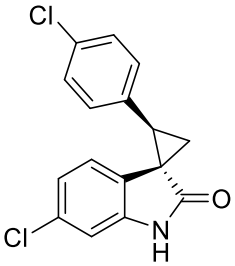
183, IC_{50} = 15 ± 0.1 μM
(prepared through O-H insertion)



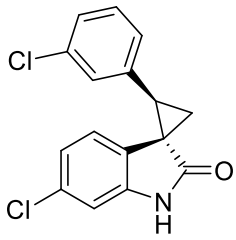
184, IC_{50} = 130 ± 26 μM
(prepared through C-H insertion)



185, IC_{50} = 65.8 ± 0.5 μM
(prepared through O-H insertion then oxidation)



186, IC_{50} = 15.8 ± 0.4 μM
(prepared through cyclopropanation)



187, IC_{50} = 48.4 ± 28.3 μM
(prepared through cyclopropanation)

Figure 36: The six novel small molecule inhibitors of the p53/hDM2 protein-protein interaction (**182-187**) discovered through an ADS high throughput synthetic approach with metal-catalysed carbenoid chemistry.[136]

4.2 Design of diverse reaction array

4.2.1 Sulfonyl fluorides as chemical probe warheads

Chemical probes are selective small molecules that can modulate a protein's function and can allow the user to delve into mechanistic and phenotypic questions about its molecular target within cell-based or animal studies.[145] The use of chemical probes has increasingly played an important part within chemical biology, as they can be used to verify new therapeutic molecular targets.[145] Chemical probes that also bear an electrophilic warhead can also be particularly valuable for target identification because that can form a covalent linkage to the targets.

For this high throughput approach, the sulfonyl fluoride warhead was chosen for this chemical probe library as they have been shown to possess the ideal properties

needed for a suitable covalent chemical probe warhead.[146] Sulfonyl fluorides have been shown to be excellent warheads for small molecule chemical probes. This is due to the sulfonyl fluoride warheads containing appropriate electrophilicity, whilst still possessing good aqueous stability that is needed for biological experimentation.[146] Moreover, sulfonyl fluorides, unlike sulfonyl chlorides, are more resistant to reduction as they possess significantly better thermodynamic stability than their sulfonyl chloride counterparts.[146,147] Also, unlike other common chemical probe warheads, such as acrylamides, the sulfonyl fluoride warhead can capture a wider range of nucleophilic protein amino acid residues then just cysteine, therefore making this warhead a more versatile alternative.[146] For example, the other reactive amino acids sulfonyl fluoride warheads can capture include cysteine, histidine, lysine, serine, threonine and tyrosine residues.[146]

4.2.2 Design and synthesis of diazo substrates that contain the sulfonyl fluoride warhead

In order for this high throughput approach to be able to widely explore chemical space in an efficient manner, both the diazo substrates and co-substrates needed to be carefully designed to allow for the possibility of reactions to occur at multiple different sites, therefore enabling a diverse range of products to be produced. In addition, parameters such as molecular weight, lipophilicity, heavy atom count (HAC), diversity of aromatic rings and commercial availability were all considered during the design of the reaction array to achieve maximum diversity of any potential products.

Initially, α-diazo amides were chosen as the first substrates for the array, as the use and general reactivity of α-diazo amides are still relatively underrepresented within the literature, in comparison with α-diazo esters for example. This, therefore, provides some additional novelty with the reactions being performed in the high-throughput array, whilst also allowing the array to access wider areas of chemical space. The general structure of the α-diazo amide substrates to be used in the array was designed to involve an aryl sulfonyl fluoride group (blue) to act as the warhead for the final chemical probes, a diazo amide functional group (black) to act as the site of reactivity and a variety of different ring systems on the amide (red) (Figure 37).

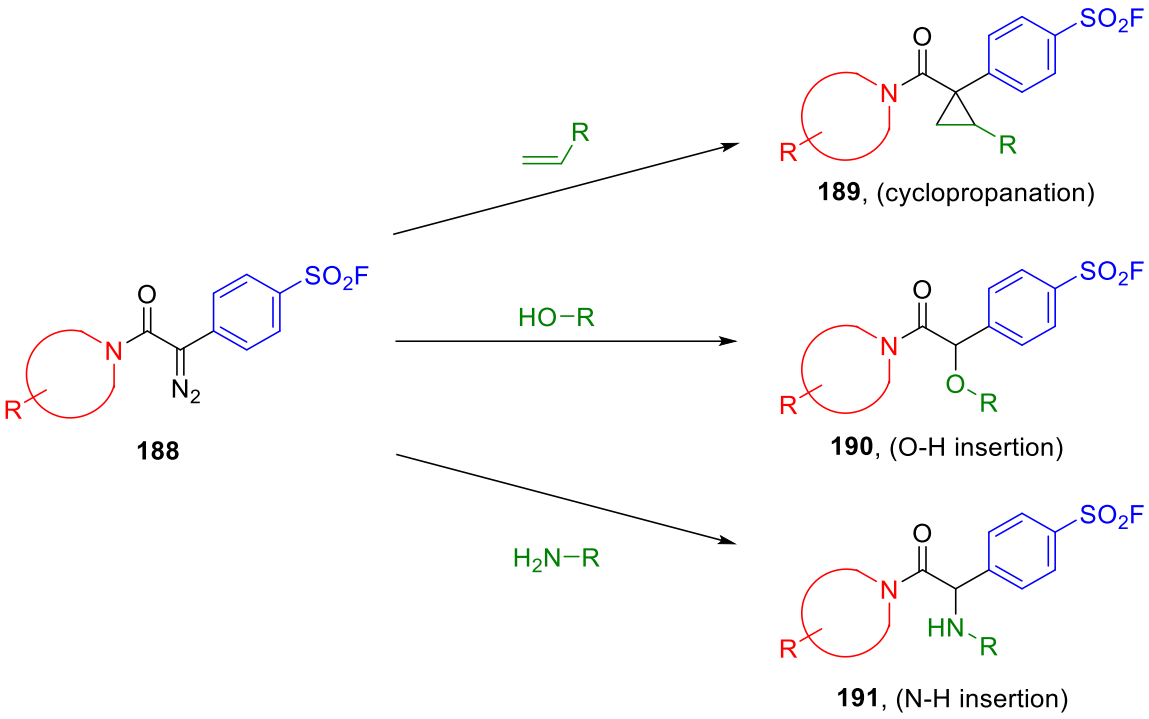
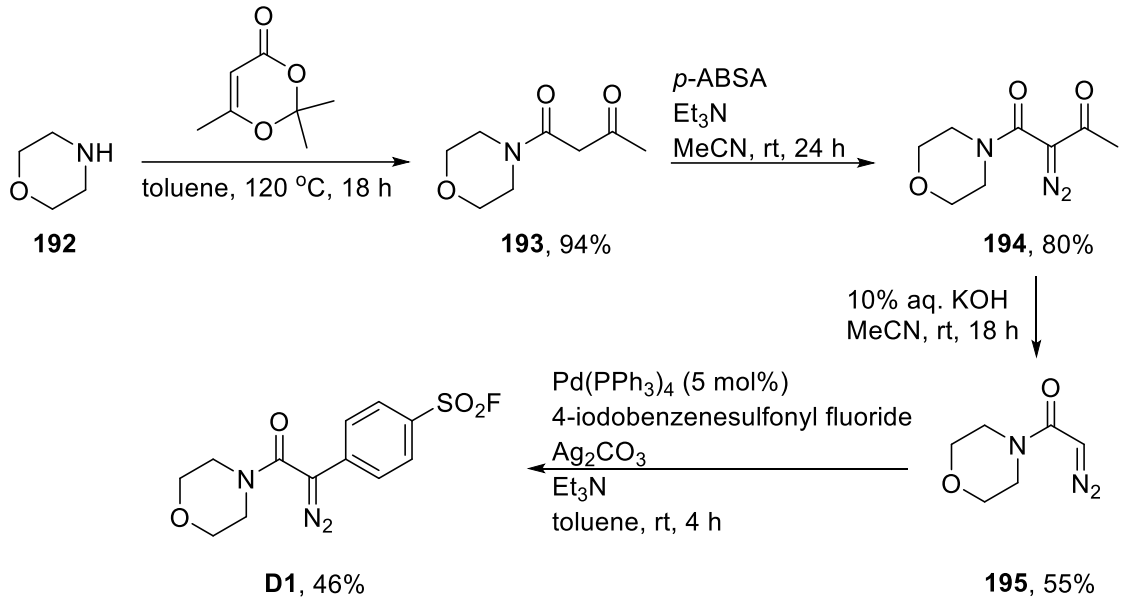


Figure 37: The general structure of the α-diazo amide substrates (**188**) to be used in the diverse reaction array. These substrates were designed to include an aryl sulfonyl fluoride warhead (blue), diazo functional group (black) and cyclic systems on the amide (red) in their structure. Examples of possible products from the array are indicated.

4.2.3 Synthesis of diazo substrates

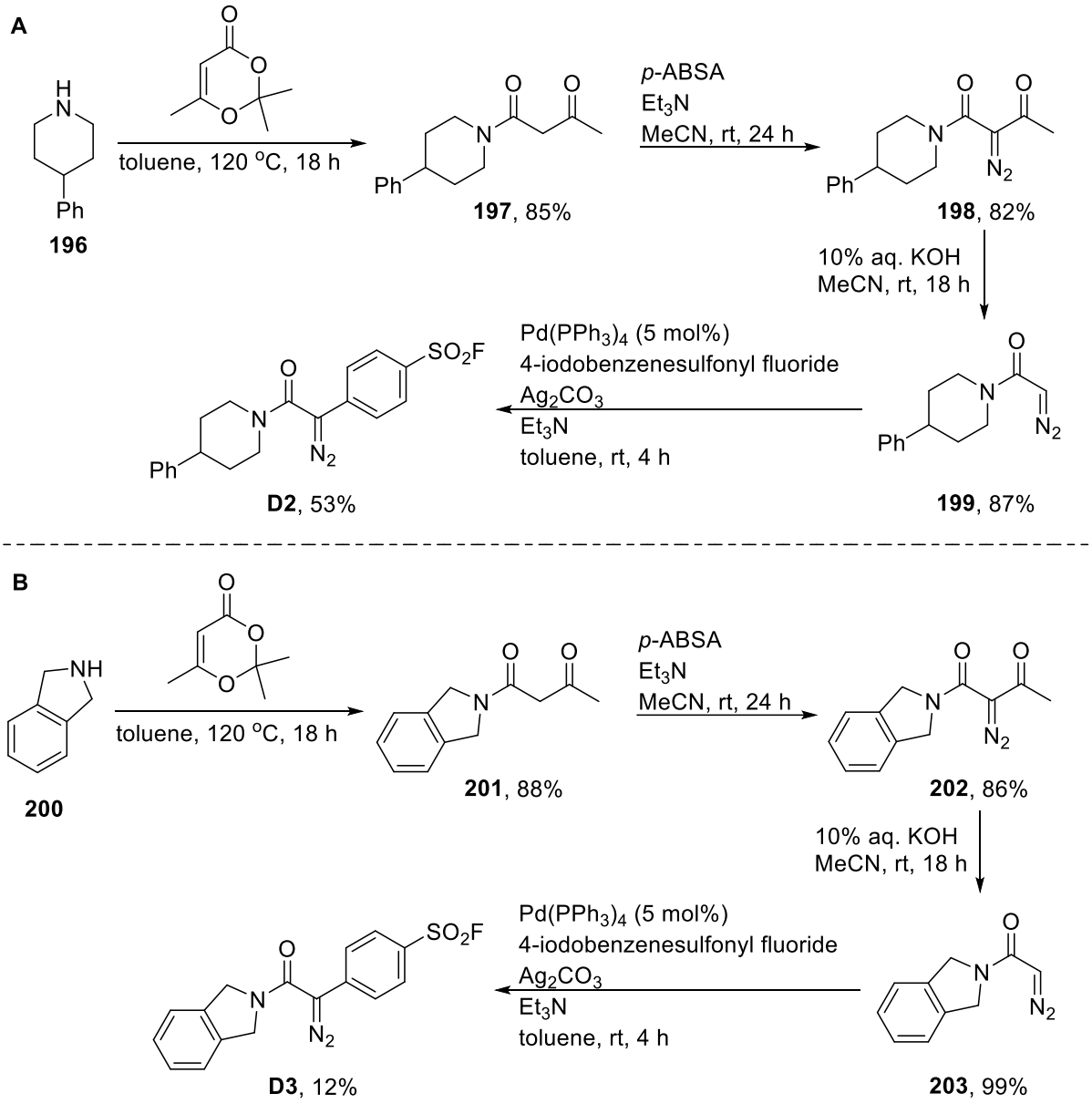
The synthetic pathway for the preparation of the α-diazo amide substrates needed for the reaction array was first developed during the successful synthesis of diazo substrate **D1**, which was derived from morpholine as the amine starting material (Scheme 31).

To prepare diazo **D1**, morpholine (**192**) was first reacted with diketene acetone adduct (2,2,6-trimethyl-4*H*-1,3-dioxin-4-one) in toluene at 120 °C to provide the corresponding 1,3-dicarbonyl derivative **193** in a 94% yield.[148] Subsequent diazo transfer by treatment of **193** with *p*-ABSA and Et_3N in acetonitrile provided diazo **194** in 80% yield.[148] Then, treatment of **194** with 10% aqueous KOH in MeCN induced deacetylation to take place and provide diazo **195** (55% yield), which then underwent a diazo-aryl cross coupling with 4-iodobenzenesulfonyl fluoride upon treatment with 5 mol% $Pd(PPh_3)_4$, Ag_2CO_3 and Et_3N in toluene to access the first α-diazo amide substrate **D1** in 46% yield.[149]



Scheme 31: The synthetic pathway for the synthesis of α-diazo amide substrates developed during the synthesis of diazo substrate **D1**.

The same synthetic route was then used to prepare a further two α-diazo amide substrates **D2** and **D3**, derived from the amine starting materials 4-phenylpiperidine (**196**) and isoindoline (**200**) respectively (Scheme 32). Treatment of both 4-phenylpiperidine and isoindoline with diketene acetone adduct (2,2,6-trimethyl-4*H*-1,3-dioxin-4-one) provided the corresponding 1,3-dicarbonyl derivatives **197** and **201** both in excellent 85% yield and 88% yield respectivelly.[148] Subsequent diazo transfer of **197** and **201** with *p*-ABSA and Et_3N in MeCN gave diazos **198** and **202** in 82% yield and 86% yield.[148] Deacetylation of **198** and **202** after treatment with 10% aqueous KOH in MeCN provided diazos **199** and **203** in 87% and 97% yields respectivelly.[148] Finally, diazos **199** and **203** then underwent diazo-aryl cross couplings with 4-iodobenzenesulfonyl fluoride upon treatment with 5 mol% $Pd(PPh_3)_4$, Ag_2CO_3 and Et_3N in toluene at room temperature to give the final two α-diazo amide substrates **D2** (53% yield) and **D3** (12% yield) ready for the reaction array.[149]



Scheme 32: The synthesis of α-diazo amide substrates **D2** (Panel A) and **D3** (Panel B) following the same synthetic pathway used to prepare diazo substrate **D1**.

4.2.4 Rationale for the selection of co-substrates

As the main driving force for this high-throughput reaction array was structural/reaction diversity, a number of factors needed to be considered during the selection process of the co-substrates. The primary factors in the choice of co-substates included: overall structural diversity of each co-substrate, the presence of a wide range of potential sites for reaction with a metal carbenoid, molecular weight/HAC, availability within the

Nelson group inventory and examples of previous successful reactivity with metal carbenoids.

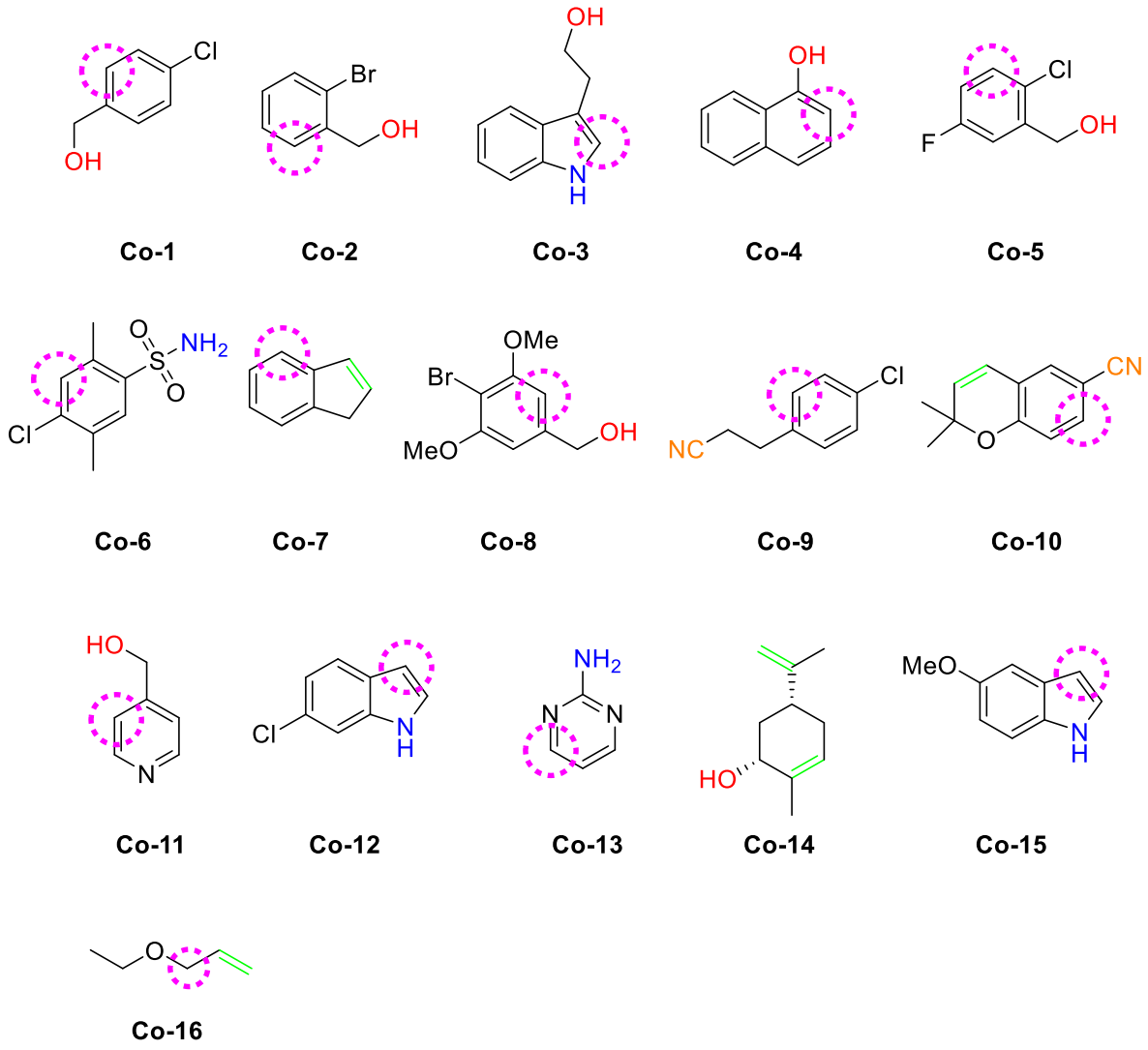


Figure 38: An overview of the library of sixteen co-substrates chosen for the reaction array. The modes of reactivity with a metal carbenoid are indicated as follows: O-H insertion (red), N-H insertion (blue), C-H insertion (purple), cyclopropanation (green) and oxazole formation (orange).

Due to the already relatively large nature of the diazo substrates (313 ≤ *Mw* ≤ 387), it was decided that the HAC for co-substrate selection would be limited to compounds with HAC ≤ 15, in order for the final chemical probes to not become too large in terms of molecular weight. In terms of reactivity, it was decided that the library of co-

substrates should contain compounds that are able to react with metal carbenoids in a number of different ways (e.g. through O-H insertion, cyclopropanation, oxazole formation etc) and the majority of the co-substrates should include at least 2 potential sites of reactivity to ensure maximum diversity of the intermolecular compounds prepared. Availability with the Nelson inventory, as well as examples of the co-substrate already showing successful reactivity with metal carbenoid chemistry, were also important factors considered to help ensure that a large proportion of reactions within the array would produce intermolecular products.

At this point, the Nelson group inventory was filtered, taking into account the parameters outlined above, and a total of 16 co-substates were found to fit this predetermined selection criteria. Therefore, these 16 co-substrates were chosen to be used in the reaction array (Figure 38). As per design, these 16 co-substrates all contained at least 2 possible sites for reaction with a metal carbenoid. Some examples of the possible sites for reactivity within this library of co-substrates includes: the OH groups within co-substrates **Co-1**, **Co-2**, **Co-3**, **Co-4**, **Co-5**, **Co-8**, **Co-11** and **Co-14** where O-H insertion is possible; the NH groups within co-substrates **Co-3**, **Co-6**, **Co-12**, **C-13** and **C-15** where N-H insertions are possible; alkenes present in co-substrates **Co-7**, **Co-10**, **Co-14** and **Co-16** where cyclopropanation is possible; the nitrile groups within co-substrates **Co-9** and **Co-10** where oxazole formation is possible. Finally, C-H insertion is possible in all 16 co-substrates, either on the aryl or alkyl C-H bonds present (Figure 38).

Lastly, it was decided that the three diazo substrates and 16 co-substrates would be reacted in the reaction array with three different rhodium-based catalysts. The three catalysts chosen for the array were $Rh_2(piv)_4$, $Rh_2(pfb)_4$ and $Rh_2(cap)_4$. These catalysts were chosen as previous studies within the Nelson group have demonstrated that the reactivity of each catalyst can vary with co-substrates containing multiple sites for reactivity, which can then lead to different major intermolecular products being formed depending on which catalyst was used.[136] Therefore, in total, three diazo substrates, 16 co-substrates and three rhodium catalysts were selected to perform the reaction array (Figure 39).

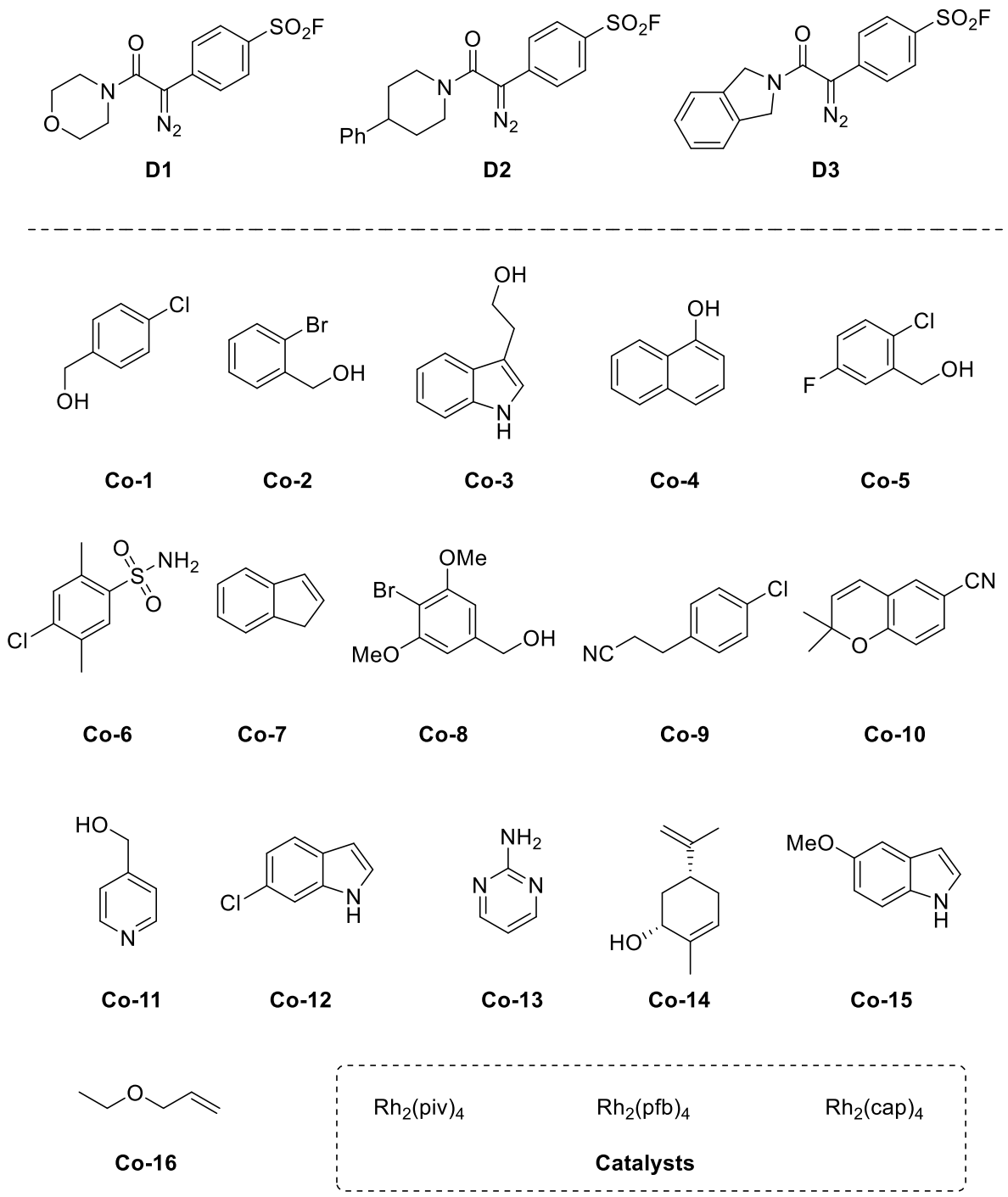


Figure 39: An overview of the diazo substrates (**D1** - **D3**), co-substrates (**Co-1** - **Co-3**) and three catalysts chosen to be used in the reaction array for the efficient synthesis of a diverse chemical probe library.

4.3 Execution of the rhodium-catalysed diverse reaction array

To begin the reaction array, stock solutions of the diazo substrates co-substrates and catalysts were first prepared by dissolving these compounds in a specific amount of DCM to give a set concentration of each substrate (1.25 M for diazo substrates, 6.25 M for co-substrates and 1 mM for each catalyst), where the majority of the compounds were found to be soluble at these concentrations. In the cases where solubility was an issue at the desired concentration, additional solvent was added to prepare a less concentrated stock solution. In the few cases where the compound was found to still not dissolve completely, these compounds were stirred prior to addition and added to the 96-well reaction plates as a suspension to ensure even loading.

The reaction array was then prepared as follows: to a custom-made PTFE reaction block, each containing 96 borosilicate glass vials, the diazo substrates (1.25 M in DCM) were added and the solvent left to evaporate. Then, the co-substrates (6.25 M in DCM) were added and the solvent left to evaporate. Finally, the appropriate catalysts were then added (1 mM in DCM) to give the final concentration of each reaction vial to be 100 mM in 200 µL of solvent, where the diazo substrate was the limiting reagent. Additionally, the final concentration of the co-substrates was 500 mM per reaction vial and the final concentration of the catalysts was 1 mM per reaction vial. Each reaction vial was then capped and left to react at room temperature without any stirring for a total of 48 hours. The array was designed to be performed over three different PTFE reaction blocks, where each reaction block contained all the reaction combinations between each diazo, co-substrate and one of the catalysts (Figure 40). This meant that, in total, the reaction array contained 144 different reaction combinations from the three diazo substrates (**D1**-**D3**), 16 co-substrates (**Co-1**-**Co-16**) and three catalysts ($Rh_2(piv)_4$, $Rh_2(pfb)_4$ and $Rh_2(cap)_4$).

Reaction plate layout

	1	2	3	4	5	6	7	8	9	10	11	12
A	**D1Co1**	**D1Co2**	**D1Co3**	**D1Co4**	**D1Co5**	**D1Co6**	**D1Co7**	**D1Co8**	**D1Co9**	**D1Co10**	**D1Co11**	**D1Co12**
B	**D1Co13**	**D1Co14**	**D1Co15**	**D1Co16**								
C	**D2Co1**	**D2Co2**	**D2Co3**	**D2Co4**	**D2Co5**	**D2Co6**	**D2Co7**	**D2Co8**	**D2Co9**	**D2Co10**	**D2Co11**	**D2Co12**
D	**D2Co13**	**D2Co14**	**D2Co15**	**D2Co16**								
E	**D3Co1**	**D3Co2**	**D3Co3**	**D3Co4**	**D3Co5**	**D3Co6**	**D3Co7**	**D3Co8**	**D3Co9**	**D3Co10**	**D3Co11**	**D3Co12**
F	**D3Co13**	**D3Co14**	**D3Co15**	**D3Co16**								
G												
H												

Figure 40: An overview of the reaction layout used to perform the reaction array. This plate layout was used over three PTFE reaction blocks in the array, where each reaction block also contained one of the three catalysts Rh_2(piv), Rh_2(pfb)$_4$ or Rh_2(cap)$_4$. This gave the reaction array 144 different reaction combinations in total.

4.4 Analysis of reaction outcomes from the diverse reaction array

Once the reaction array was complete, the reaction solvent (DCM) was evaporated and the resulting residues redissolved in DMSO (200 µL) to make 100 mM stock solutions of each reaction mixture. The reaction mixtures were then transferred out of the three PTFE reaction blocks into three standard 96-well plates following the same plate layout highlighted above in Figure 40. Analysis of the reaction mixtures began by first transferring 5 µL of each of the 100 mM reaction mixtures into three additional 96-well plates. These 5 µL reaction mixture samples were then diluted with DMSO to give 20 mM solutions of each reaction mixture ready for subsequent HPLC analysis. The samples were than analysed by HPLC in order to determine which reaction combinations from the array produced any desired intermolecular product (Figure 41). Quantitative HPLC analysis was able to be performed using ELS detection in order to quantify the yield of the desired intermolecular product from any of the successful reaction combinations within the array.[150]

Catalyst 1 – $Rh_2(piv)_4$

	Co1	Co2	Co3	Co4	Co5	Co6	Co7	Co8	Co9	Co10	Co11	Co12	Co13	Co14	Co15	Co16
D1	8	10	7	2	10	7	-	10	-	-	-	8[a]	9	-	15[a]	-
D2	10	11	11[a]	2	13	12	12	13	-	-	-	-	12	8	19[a]	-
D3	5	14	-	9	5	7	-	4	-	-	-	2	9	-	5[a]	-

Catalyst 2 – $Rh_2(pfb)_4$

	Co1	Co2	Co3	Co4	Co5	Co6	Co7	Co8	Co9	Co10	Co11	Co12	Co13	Co14	Co15	Co16
D1	12	9	16	8	13	6	-	11	-	-	-	14[a]	-	6	24[a]	-
D2	18	13	18	13	17	5	7	14	-	-	-	17[a]	-	12	17[a]	-
D3	3	8	9	8	3	5	-	9	-	-	-	5[a]	-	2	2	-

Catalyst 3 – $Rh_2(cap)_4$

	Co1	Co2	Co3	Co4	Co5	Co6	Co7	Co8	Co9	Co10	Co11	Co12	Co13	Co14	Co15	Co16
D1	16	14	10[a]	4	12	9	4	14	-	-	-	3	-	6	10	-
D2	10	19	14[a]	10	20	13	2	18	-	-	-	4	-	15	15	-
D3	3	4	7	10	4	2	5	6	-	-	-	3[a]	-	4	10[a]	-

Figure 41: Analysis of the diverse reaction array through analytical HPLC with ELS detection. Key: green = ≥10% yield, yellow = 0 < yield < 10 %, red = no intermolecular product observed. Yields for each reaction combination (as determined by ELS quantification) are indicated. Reaction combinations highlighted in a **bold** box were selected for subsequent purification and product isolation. [a]Multiple intermolecular products observed by analytical HPLC.

Analysis of these results found a large number of intermolecular products were prepared during the reaction array a variety of different yields (2-24%) as determined by ELS quantification.[150] It was found that the co-substrates containing nitrile groups (**Co-9** and **Co-10**), as well as the allyl ether co-substrate (**Co-16**) failed to yield any intermolecular product with any of the diazo substrates or catalyst combinations. Generally, co-substrates containing alcohol functional groups (**Co-1**, **Co-2**, **Co-3**, **Co-4**, **Co-5**, **Co-8** and **Co-14**) gave intermolecular products across all three diazos and catalyst combinations. The exception to this observation was heteroaromatic alcohol **Co-11** which failed to give any intermolecular product across all reaction combinations. It was also observed that indole co-substrates (**Co-3**, **Co-12** and **Co-15**) generally were successful in giving intermolecular product across most reaction combinations. Interestingly, these three indole co-substrates were shown by analytical

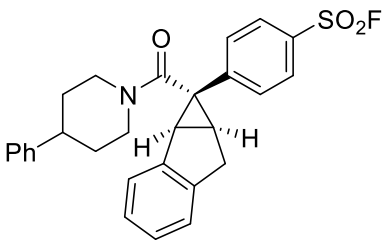
HPLC to have formed multiple intermolecular products in some reaction combinations (D1Co12Piv, D1/D3Co15Piv, D2Co3Piv, D1/D2/D3Co12Pfb, D1/D2Co15Pfb, D1/D2Co3Cap, D3Co12cap and D3Co15Cap), which in some cases were dependent on the diazo substrate and catalyst employed. It was also found that sulfonamide co-substrate **Co-6** gave intermolecular product across all reaction combinations. Indene (**Co-7**) and $Rh_2(cap)_4$ was found to provide intermolecular product with all three diazo substrates; however, indene with $Rh_2(piv)_4$ and $Rh_2(pfb)_4$ was only shown to give intermolecular product with diazo **D2** and was unsuccessful with diazos **D1** and **D3**. Another interesting result was that 2-aminopyrimidine co-substrate **Co-13** only ever gave intermolecular product with catalyst $Rh_2(piv)_4$ and was shown to be unsuccessful for the other two catalysts employed in the array.

In terms of the diazo substrates, the HPLC analysis found that generally diazo **D2** provided intermolecular products in the highest yields across the range of co-substrates. This compares with diazo substrate **D3**, which was found to give much lower yield of intermolecular product than the other two diazo substrates by ELS quantification. This was maybe due to diazo **D3** being a potentially poor diazo substrate for intermolecular carbenoid chemistry, as diazo **D3** possesses a benzylic C-H bond that could instead undergo intramolecular C-H insertion with the rhodium carbenoid to provide the corresponding beta lactam product. Lastly, $Rh_2(cap)_4$ was shown to be the catalyst that generally provided the highest yields of intermolecular product across the successful reaction combinations.

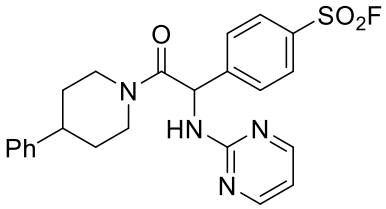
However, it was found that the rhodium-catalysed carbenoid chemistry employed in this reaction array never gave a high yield of intermolecular product between the diazos and co-substrates, with a highest yield of 24% determined by the HPLC analysis with ELS quantification (D1Co15Pfb). Nevertheless, it was found that 45 reaction combinations over the entire reaction array gave a yield of at least 10%, which equates to approximately at least 1 mg of intermolecular product in each case, which was determined to be plenty of product for any subsequent biological screening. At this point, combinations of diazo and co-substrate with the highest yields (as determined by ELS quantification) were selected for subsequent product purification. In total, 18 reaction combinations were selected to isolate the corresponding intermolecular products (Figure 41, **bold** boxes).

4.5 Isolation of intermolecular products from diverse reaction array

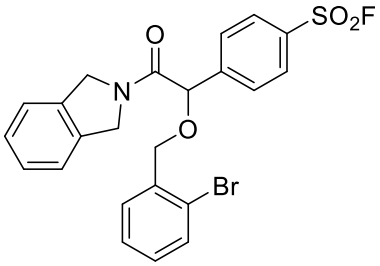
The 18 selected reaction combinations were then purified by preparative HPLC, where only compounds that corresponded to the expected intermolecular mass from each reaction combination were collected. A total of 23 different intermolecular products were isolated from the 18 different reaction combinations (Figure 42). It was found that reaction combinations that contained co-substrates with benzyl alcohol functional groups (D3Co2Piv, D1Co5Pfb, D1Co1Cap, D1Co2Cap, D1Co8Cap, D2Co2Cap, D2Co5Cap and D2Co8Cap) all gave an O-H insertion product as the only intermolecular product (**206, 209, 213-217, 219**) from the reaction in 11-14% yields. Interestingly, the reaction mixture D2Co14Cap, which contained alcohol co-substrate **Co-14**, only gave the O-H insertion product **220** as a 51:49 mixture of diastereomers in 10% yield, where no other intermolecular products from either cyclopropanation or C-H insertion were isolated. On the other hand, reaction combinations containing naphthalene co-substate **Co-4** gave either solely the O-H insertion product **212** (D2Co4Pfb) in 11% yield or a 51:49 mixture of inseparable regioisomers **223a-b** (D3Co4Cap) from both O-H insertion and C-H insertion at the C-2 position in 5% yield overall. The reaction combination containing indene co-substrate **Co-7** (D2Co7Piv) was found to only give the cyclopropanation intermolecular product **204** in 13% yield, which was isolated as a single diastereomer. With sulfonamide co-substate **Co-6**, N-H insertion into the sulfonamide N-H bond gave the observed intermolecular product **218** in 10% yield from the corresponding reaction combination D2Co6Cap. Furthermore, it was found that reaction combinations that involved tryptophol co-substrate **Co-3** (D1Co3Pfb and D2Co3Pfb) provided a mixture of N-H insertion (**207** and **210**) in 13-15% yield or O-H insertion product (**208** and **211**) in 1% yield, where N-H insertion was found to be the major product. Similarly, reaction combinations containing indole **Co-15** (D2Co15Cap and D1Co15Piv) also gave a mixture of products, this time either from N-H insertion (**222** and **225**) in 1-8% yield or C(3)-H insertion (**221** and **224**) in 6-11% yield. Finally, it was found that reaction combination D2Co13Piv, which involved aminopyrimidine co-substrate **Co-13**, provided the corresponding heteroaromatic N-H insertion product **205** in 12% yield.



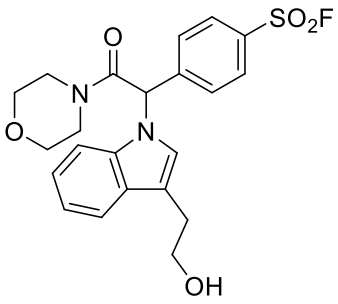
204, 13%, *dr* >95:<5
from D2/Co-7 with $Rh_2(piv)_4$



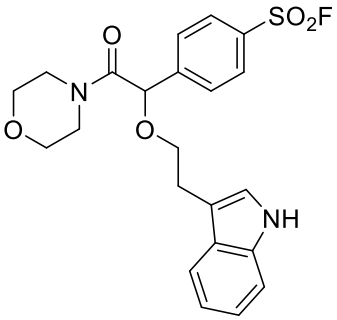
205, 12%
from D2/Co-13 with $Rh_2(piv)_4$



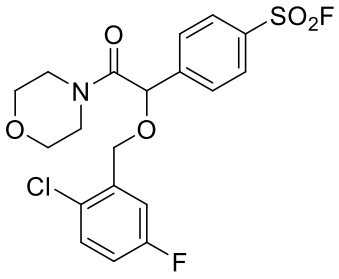
206, 13%
from D3/Co-2 with $Rh_2(piv)_4$



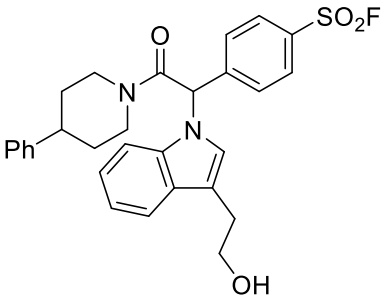
207, 15%
from D1/Co-3 with $Rh_2(pfb)_4$



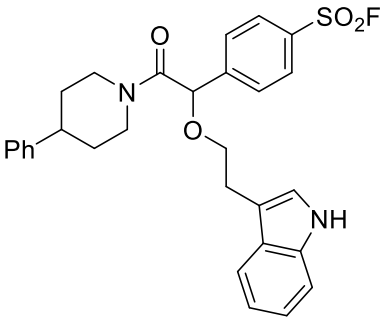
208, 1%
from D1/Co-3 with $Rh_2(pfb)_4$



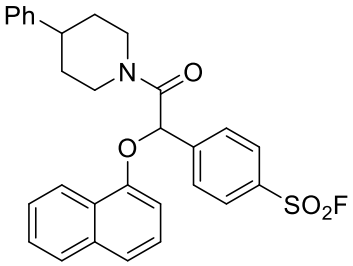
209, 11%
from D1/Co-5 with $Rh_2(pfb)_4$



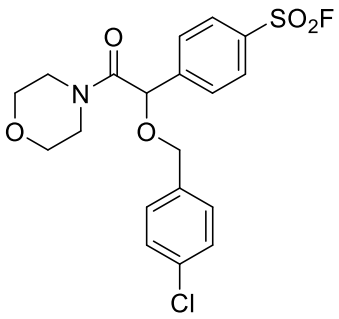
210, 13%
from D2/Co-3 with $Rh_2(pfb)_4$



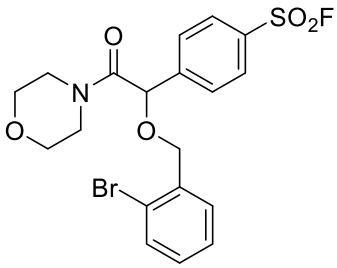
211, 1%
from D2/Co-3 with $Rh_2(pfb)_4$



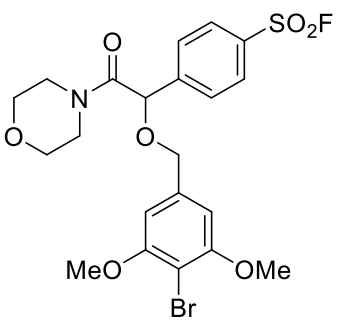
212, 11%
from D2/Co-4 with $Rh_2(pfb)_4$



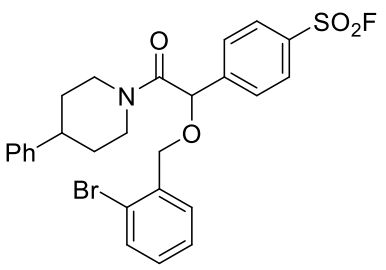
213, 14%
from D1/Co-1 with $Rh_2(cap)_4$



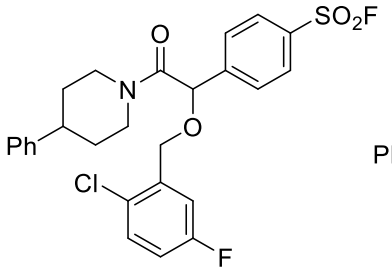
214, 12%
from D1/Co-2 with $Rh_2(cap)_4$



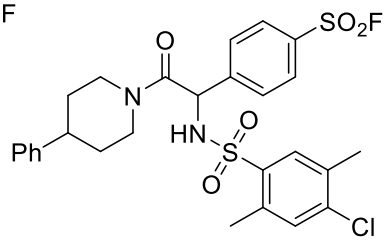
215, 12%
from D1/Co-8 with $Rh_2(cap)_4$



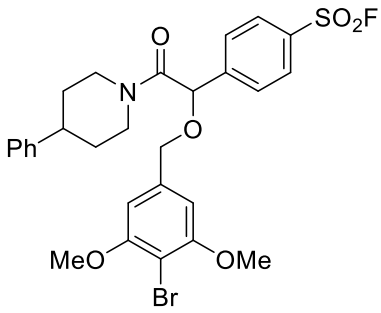
216, 14%
from D2/Co-2 with $Rh_2(cap)_4$



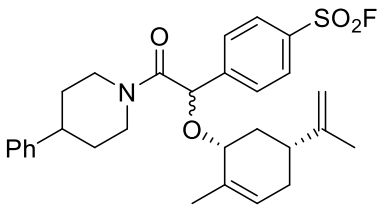
217, 14%
from D2/Co-5 with $Rh_2(cap)_4$



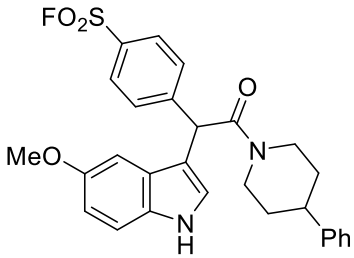
218, 10%
from D2/Co-6 with $Rh_2(cap)_4$



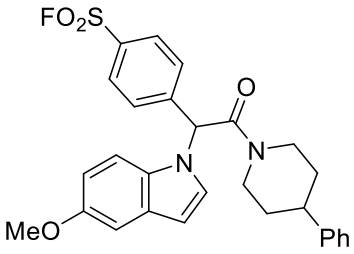
219, 13%
from D2/Co-8 with $Rh_2(cap)_4$



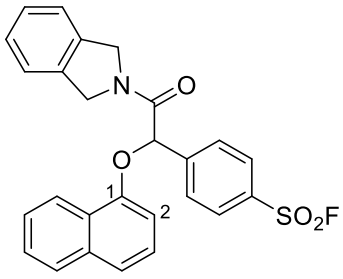
220, 10%, *dr* 51:49
from D2/Co-14 with $Rh_2(cap)_4$



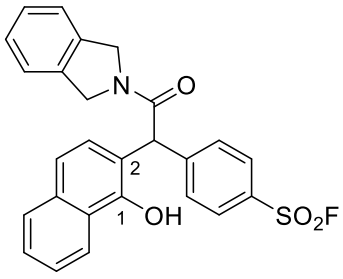
221, 11%
from D2/Co-15 with $Rh_2(cap)_4$



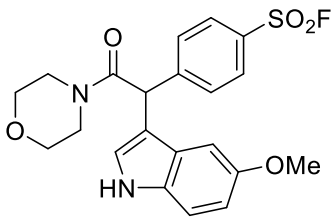
222, 1%
from D2/Co-15 with $Rh_2(cap)_4$



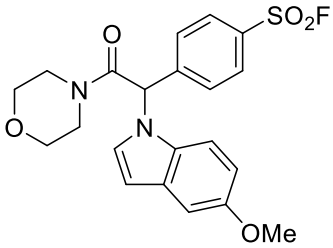
223a, 5%[a]
from D3/Co-4 with $Rh_2(cap)_4$



223b, 5%[a]
from D3/Co-4 with $Rh_2(cap)_4$



224, 6%
from D1/Co-15 with $Rh_2(piv)_4$



225, 8%
from D1/Co-15 with $Rh_2(piv)_4$

Figure 42: The 23 intermolecular products isolated from the 18 selected reaction combinations by preparative HPLC. The isolated yield of each intermolecular product after preparative HPLC purification is indicated. [a]Isolated as a 51:49 (**223a**:**223b**) mixture of regioisomers where the indicated isolated yield is total yield of both regioisomers.

4.6 Determination of the structures of isolated intermolecular products

The final structures of the 23 intermolecular products isolated from the array were determined by analysis of the corresponding 2D NMR spectra for each of the compounds, mainly through the observation of key HMBC, COSY and NOESY interactions. The structure of compounds where O-H insertion had occurred onto a benzyl alcohol co-substrate (**206, 209, 213-217, 219**) were confirmed by a key HMBC interaction observed between proton 1-H and benzyl C-1 (Figure 43).

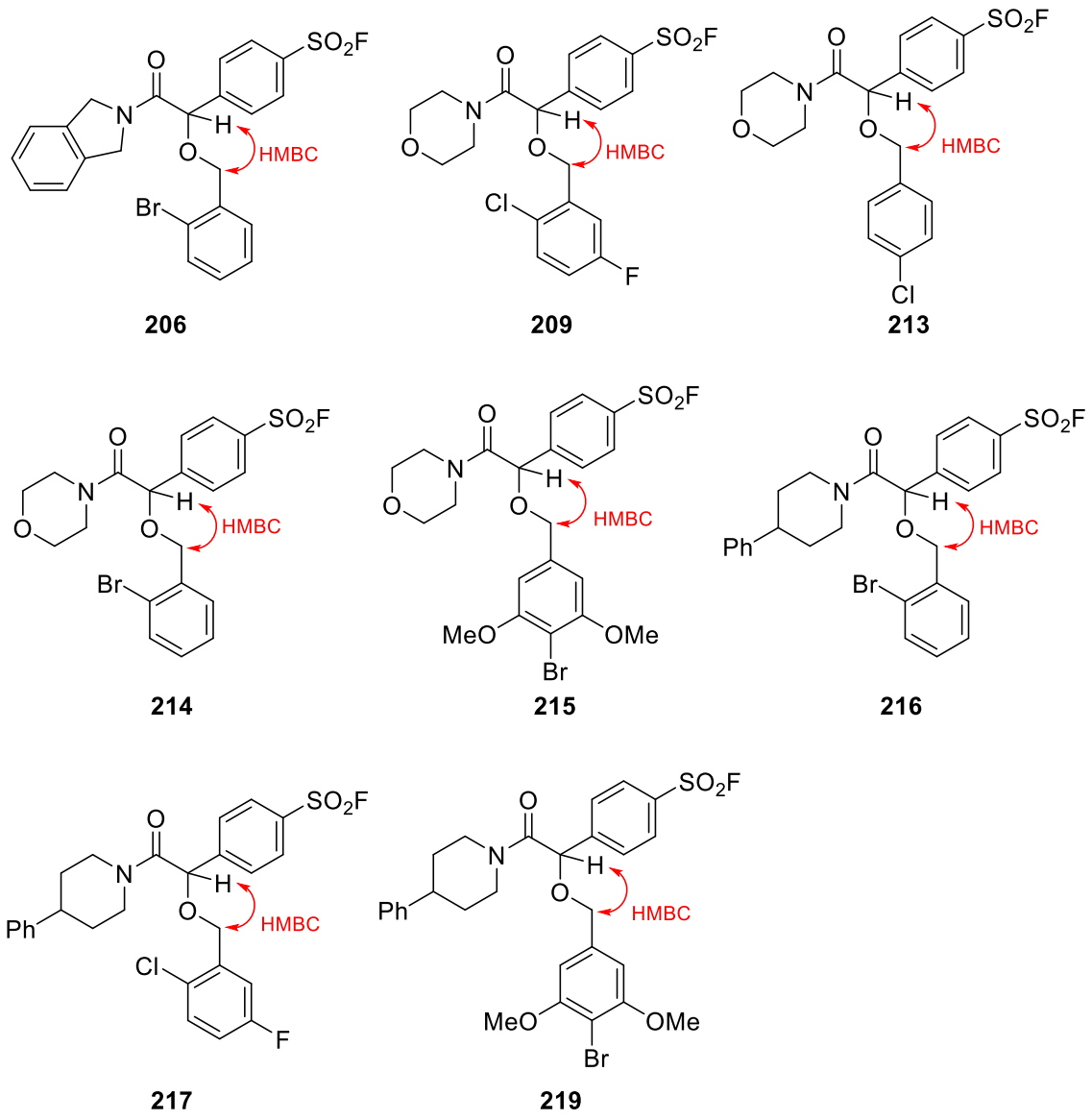


Figure 43: An overview of the key HMBC interactions that confirmed compounds **206, 209, 213-217** and **219** were prepared through O-H into the corresponding benzyl alcohol co-substrates.

Next, the structure of compounds where O-H insertion had occurred to give products **212**, **220** and **223a** were also confirmed through a key HMBC interaction (Figure 44). Unfortunately, confirmation of the structures of the remaining O-H insertion products **208** and **211** could not be determined through analysis of HMBC spectra, as only poor quality HMBC spectra could be obtained due to the small quantity of material isolated in these cases (approx. 0.1 mg). Therefore, the structure of **208** and **211** were determined by analogy with the other O-H insertion products isolated.

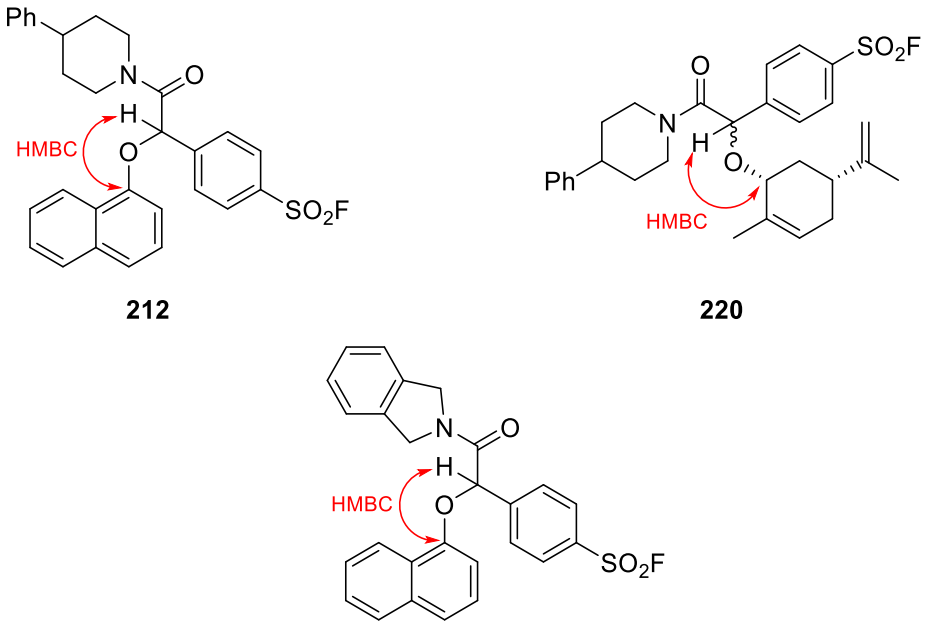


Figure 44: Determination of the structure of intermolecular products **212**, **220** and **223a** through observation of a key HMBC interaction.

The structures of compounds which had undergone N-H insertion (**205, 207, 210, 218, 222** and **225**) were also confirmed through observations of key 2D NMR interactions in the corresponding HMBC and COSY spectra (Figure 45). In the products that had undergone N-H insertion into an indole N-H, an HMBC interaction between proton 1-H and indolyl C-2 was observed, along with the loss of any NH peaks in the ^{1}H NMR spectra. Where N-H insertion had occurred into sulfonamide **Co-6** and aminopyrimidine **Co-13** to give products **218** and **205**, coupling between the N-H

proton and proton 1-H was observed on the corresponding COSY spectra, as well as only one N-H peak being observed instead of NH_2 peaks on the corresponding ^1H NMR spectra.

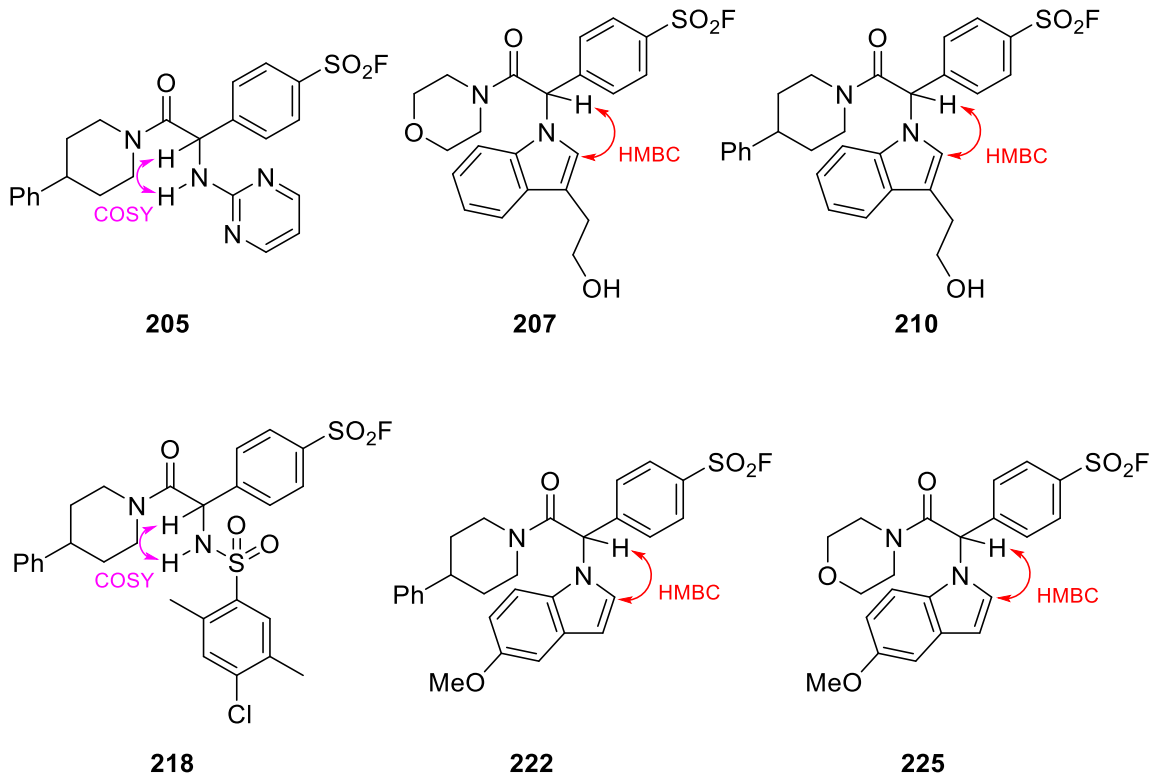


Figure 45: Overview of the key HMBC interactions and couplings observed by COSY in compounds **205, 207, 210, 218, 222** and **225** that were prepared through N-H insertions.

Lastly, the structures of products prepared by either cyclopropanation (**204**) or C-H insertion (**221** and **224**) were also confirmed by observation of key HMBC interactions. Compound **204** showed a key HMBC interaction between indenyl 6-H_2 and quaternary carbon C-1 which suggested cyclopropanation had taken place (Figure 46). The relative configuration of **204** was then determined through inspection of the corresponding NOESY spectrum, where a key nOe enhancement was observed between aryl 3,5-H and indenyl 6-H_A (Figure 46). Compounds **221** and **224** were found to have been prepared *via* C(3)-H insertion into the indole co-substrate **Co-15**. This was determined by observation of a HMBC interaction between proton 1-H and indolyl

C-2 (Figure 46). Determination of the structures of **221** and **224** was also aided by the presence of the indole N-H (ruling out N-H insertion) as well of no observation of the indolyl 3-H proton in the ^{1}H NMR spectra. Finally, it was determined that the other regioisomer in product **223b** was C(2)-H insertion into the naphthyl ring. This was determined by observation of a HMBC interaction between proton 1-H and napthanenyl C-1 (Figure 46).

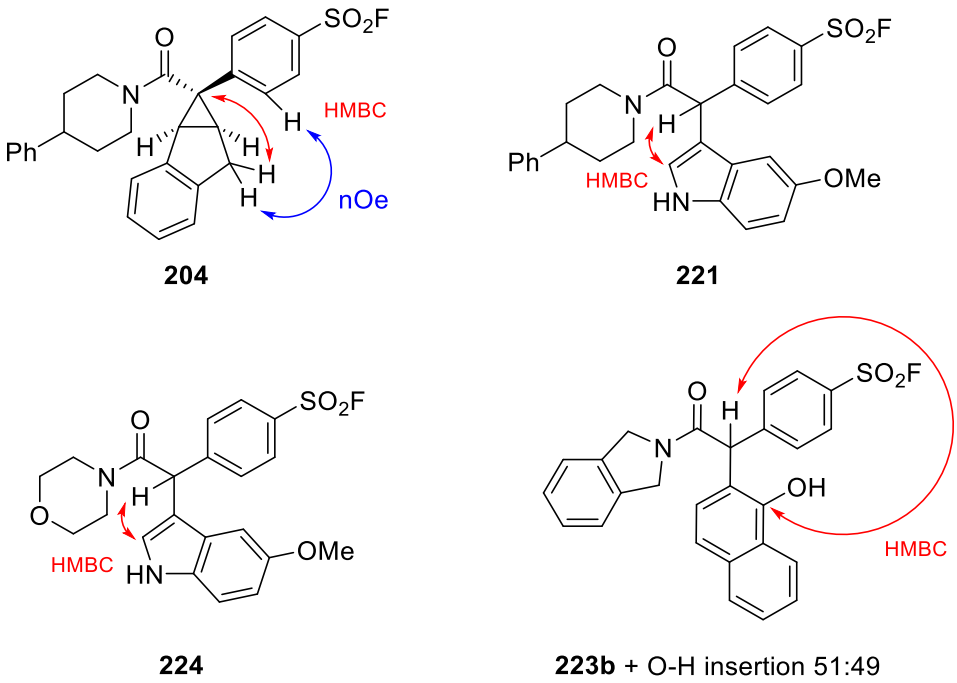


Figure 46: Overview of the key HMBC interactions and nOe enhancements in compounds **204, 221, 224** and **223b** that were prepared through either cyclopropanation or C-H insertions.

4.7 Analysis of the chemical probe library prepared *via* the diverse reaction array

In total, this high throughput connective approach enabled a library of 23 different chemical probes to be prepared in a highly efficient manner. Analysis of the library began by investigating the relatively low yield of intermolecular product that was isolated from each of the 18 best reaction combinations (major products 8-15% yield and minor products 1-6% yield). It was thought that mass balance of these reactions

were low, as potentially other common side reactions were also occurring in the reaction wells of the reaction array. For example, intramolecular C-H insertions (**226**), reaction of the carbenoid with residual water (**227**), dimerisation of the carbenoid (**228**) and loss of molecular nitrogen from the diazo substrates (**229**) (Figure 47).

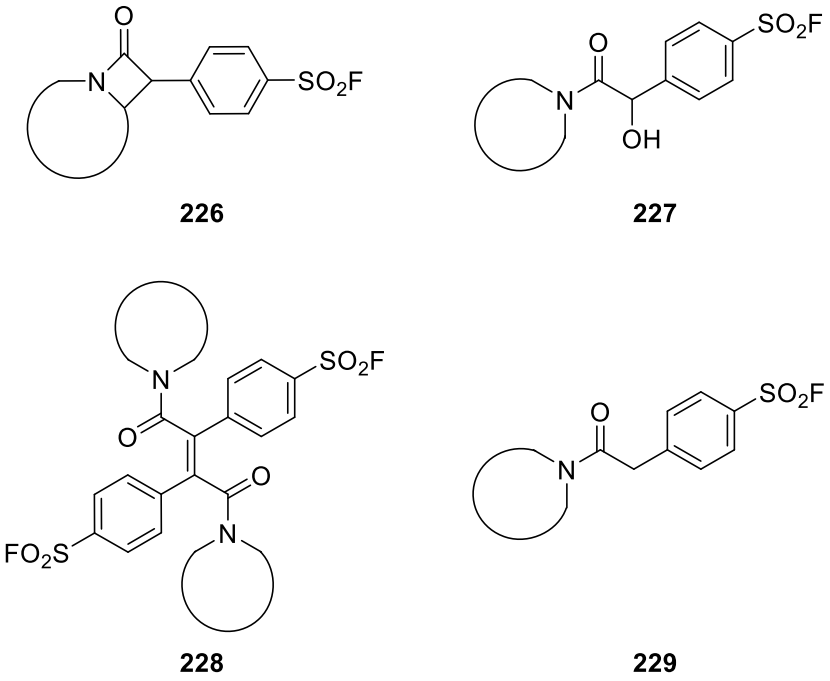


Figure 47: An overview of the general structures of possible by-products that could be generated in the reaction array. These include intramolecular C-H insertion (**226**), reaction of the carbenoid with residual water (**227**), dimerisation of the carbenoid (**228**) and loss of molecular nitrogen from the diazo substrates (**229**).

Analysis of the eighteen selected reaction wells by analytical HPLC found that the intermolecular products were the major products in each of these reaction wells (Figure 48). It was found that 17 out of the 18 reaction combinations analysed did show a small amount (< 10 %) of α-hydroxy amide product **227**, which likely arises due to reaction of the rhodium carbenoid with residual water present in the reaction wells (Figure 48). This is likely because the reaction array was not performed under a strict anhydrous or air free environment, therefore O-H insertion into any residual water was possible.

Reaction Well	Intermolecular	Intramolecular	Reaction with water	Dimer	Diazo – N_2
D2Co7piv	✓	✗	✓	✗	✗
D2Co13piv	✓	✗	✓	✗	✓
D3Co2piv	✓	✗	✓	✗	✓
D1Co3pfb	✓	✗	✗	✗	✗
D1Co5pfb	✓	✗	✓	✗	✗
D2Co3pfb	✓	✗	✓	✗	✗
D2Co4pfb	✓	✗	✓	✗	✗
D1Co1cap	✓	✗	✓	✗	✗
D1Co2cap	✓	✗	✓	✗	✗
D1Co8cap	✓	✗	✓	✗	✗
D2Co2cap	✓	✗	✓	✗	✗
D2Co5cap	✓	✗	✓	✗	✗
D2Co6cap	✓	✗	✓	✗	✗
D2Co8cap	✓	✗	✓	✗	✗
D2Co14cap	✓	✗	✓	✗	✗
D2Co15cap	✓	✗	✓	✗	✗
D3Co4cap	✓	✗	✓	✗	✗
D1Co15piv	✓	✗	✓	✗	✗

Figure 48: An overview of the different reaction products observed by analytic HPLC from the 18 reaction combinations that were chosen for subsequent product isolation. Green tick = ≥10% yield; Yellow tick = 1-10% yield and Red cross = No product observed.

Furthermore, in two of the reaction combinations (D2Co13Piv and D3Co2Piv) a small amount (< 10%) of by-product **229** was observed, where there had been loss of molecular nitrogen from the diazo substrate. There was also no observation of any intramolecular products (**226**) or dimerisation products (**228**) by the HPLC analysis. Therefore, the origin of the low yields of intermolecular products was determined to not be due to the prevalence of any of the aforementioned side reactions occurring in the reaction wells. It is possible that the low yields observed could be due to either the

presence of unreacted diazo starting material or formation of another unknown side products that both could not be observed through the HPLC analysis. It's also possible that the sulfonyl fluoride warhead may undergo some degradation under the reaction conditions to provide alternative products that also could not be observed through the HPLC analysis.

Additionally, this library of 23 chemical probes was analysed using the same computational methods employed for the analysis of both the first scaffold library (Section 2.4) and the second scaffold library (Section 3.6). This analysis assessed the overall novelty, molecular properties and the shape/structural diversity of the chemical probe library. These results could then be used to ascertain whether this high throughput connective approach was able to provide a diverse range of chemical probes that can occupy a wide range of chemical space. The molecular properties and shape diversity of the 23 compounds were first analysed using LLAMA (Figure 49).[63]

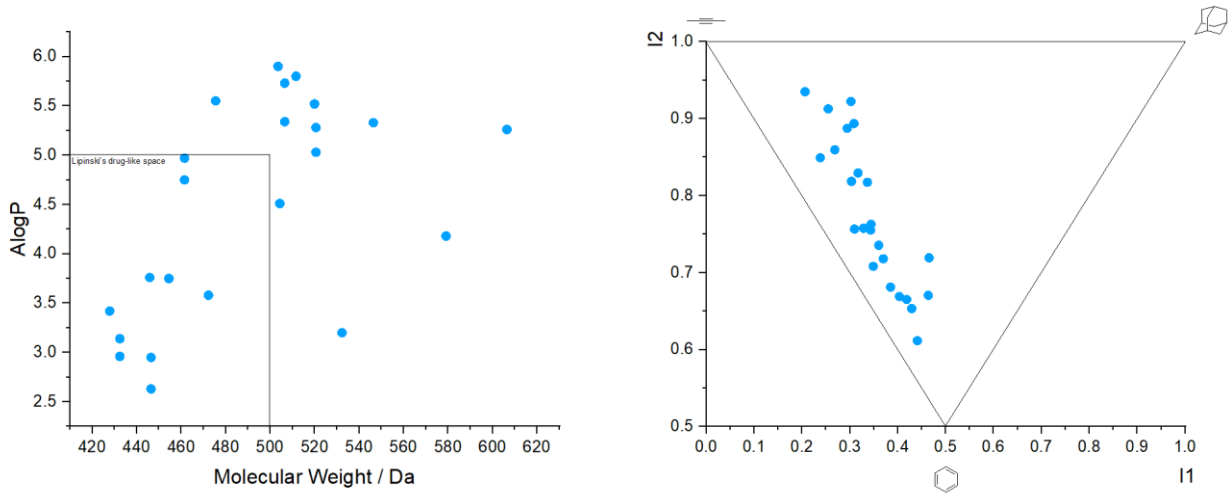


Figure 49: Computational analysis of the chemical probe library using LLAMA in order to assess the chemical space and shape diversity of the library of 23 chemical probes prepared.

This analysis found that just over half of the probes prepared lie outside of Lipinski's area of drug-like chemical space, mainly due to their large molecular weights. The remaining probes were found to lie at the top end of Lipinski's area of drug-like space, as these probes were slightly smaller in terms of molecular weight and were deemed to be a bit less lipophilic. These findings were not too surprising, as generally, the diazo that gave the highest amount of intermolecular product in the reaction array with

most co-substrates was diazo **D2**, which was the largest of the diazo substrates in the reaction array in terms of molecular weight. Next, the shape diversity of the chemical probe library was assessed by construction of a PMI plot (Figure 49).[63] Analysis of this PMI plot found that whilst a few of the chemical probes did lie in the 'flatland' areas of chemical space (along the rod-disk axis), many of the probes were beginning to gradually move away from this flatland area of chemical space into more three-dimensional areas of the PMI plot. Furthermore, it was determined that none of the Murcko frameworks for any of the 23 chemical probes were found to be substructures in a random 2% sample of the ZINC database of commercially available compounds.[99,100] This analysis therefore demonstrated a high level of novelty associated with the compounds within this chemical probe library.

Additionally, inspection of the 23 compounds prepared through this high throughput approach showed there was significant structural diversity within this library of compounds, due to the variety of different connectivity patterns within the chemical probes prepared. This variety of connectivity patterns arises from the diverse reactivity between the diazo substrates and co-substrates in the reaction array. This library of chemical probes included connectivity between the diazos and co-substrates arising from O-H insertions, heteroaromatic N-H insertion, sulfonamide N-H insertion, C-H insertions and cyclopropanation. This diverse range of reactivity therefore provided the corresponding chemical probe library with the diverse connectivity patterns observed.

In terms of reaction novelty, the heteroaromatic N-H insertion is a relatively rare reaction mode for metal carbenoids and has only previously been reported with aminopyridines and diazo-esters, usually with copper catalysts.[151] Furthermore, the sulfonamide N-H insertion is also a rare reaction mode, where all previously reported cases involve either free carbenes or metal carbenoids derived from diazo esters.[152,153] In addition to this, the skeletal diversity of this scaffold library was also analysed through construction of a hierarchical scaffold tree, originally developed by Waldmann and co-workers.[71] As demonstrated previously (Section 2.4 and Section 3.6), this procedure involved the iterative removal of rings by following a defined set of priority rules until a final selection parental ring system are obtained.[71] Construction of this scaffold tree found that the sixteen frameworks at the graph-node-bond level,

corresponding to the 23 chemical probes prepared in this library, were based five different parental monocyclic ring systems (Figure 50).

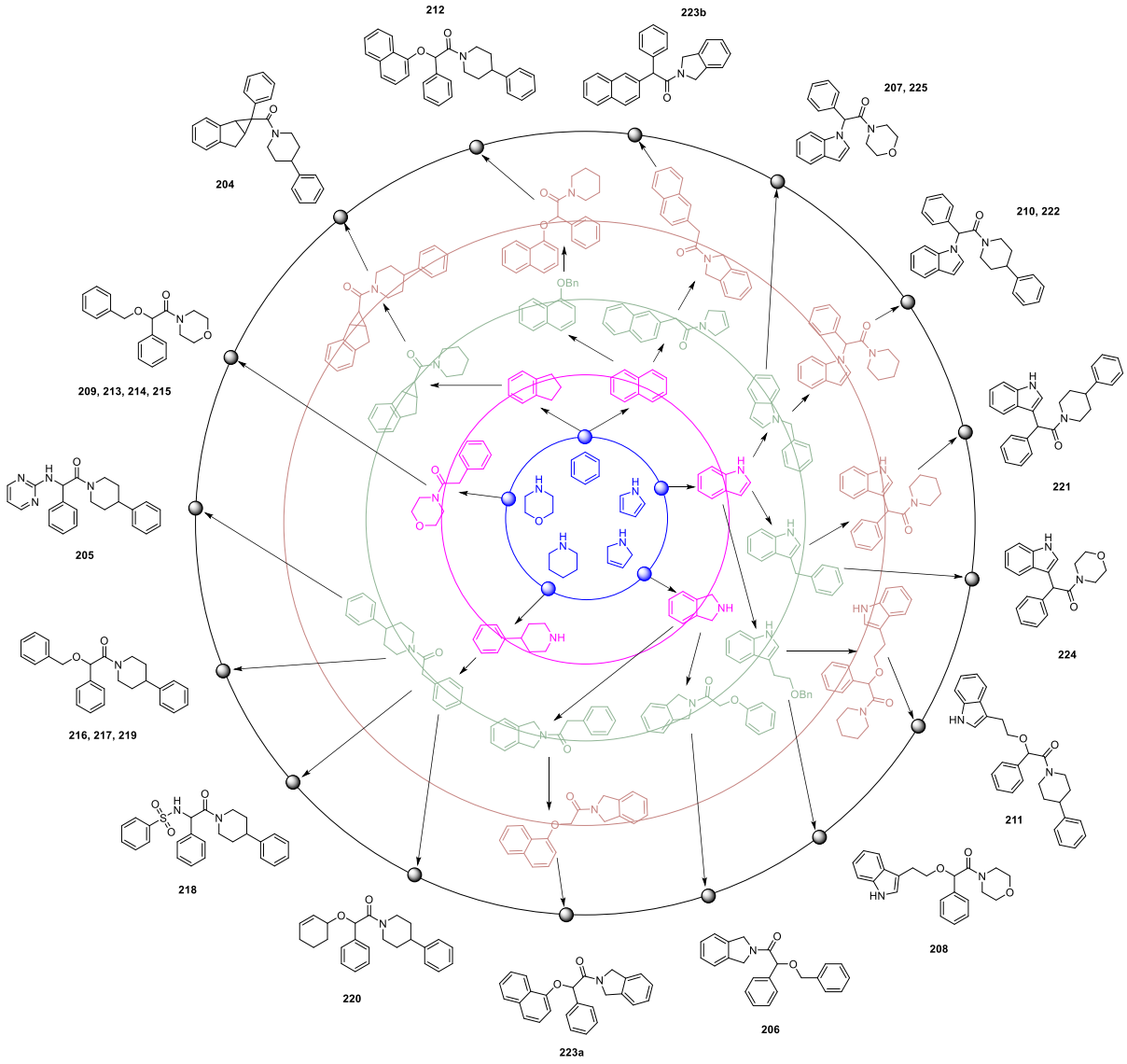


Figure 50: The hierarchical scaffold tree analysis of the final library of 23 chemical probes prepared through this high throughput connective approach. The 23 chemical probes were based on 16 different frameworks at the graph-node-bond level (black) that were shown to be related hierarchically to five different parental monocyclic frameworks (blue). The corresponding chemical probes relating to each of the frameworks are numbered accordingly.

Inspection of the scaffold tree found that there was significant skeletal diversity within this library of chemical probes. This was because the set of parental monocyclic

frameworks that this library was derived from contained more ring structures that the number of diazo substrates in the reaction array. This demonstrated that the rhodium-catalysed carbenoid chemistry used in this high throughput connective approach was able to increase the skeletal diversity of the intermolecular products prepared and that the diversity of the products was not solely reliant on the number of diazo substrates employed within the reaction array.

4.8 Biological evaluation of diverse chemical probe library

4.8.1 Minimum inhibitory concentration (MIC) determination of chemical probes against *S. aureus* strain SH1000

The first biological evaluation undertaken with the chemical probe library involved an investigation to assess whether these compounds could possess any significant antibacterial activity. To achieve this, the 23 chemical probes were screened against *S. aureus* strain SH100[154] in order to determine the minimum inhibitory concentration (MIC) for each of the compounds.

The screening of the chemical probe library against *S. aureus* strain SH1000 was performed by Abbie Leggott at the University of Leeds. The MIC values for the 23 chemical probes were determined by broth microdilution against *S. aureus* strain SH1000 with Mueller Hinton Broth (MHB-II) as the media according to CLSI guidelines.[155] Firstly, a 2-fold dilution series of the chemical probes in DMSO was prepared, ranging from 10.0–0.625 mM. Each dilution was transferred into a 96-well format at a final volume of 10 µL, then 90 µL of water was added to each well to give stock concentrations of 1.00–0.0625 mM (10% DMSO in water). The stock solutions were then diluted to give a final volume of 10 µL, then 90 µL of the standardised culture was added to each well to give final product concentrations of 100–6.35 µM (1% DMSO in MHB-II). Plates were incubated for 16 hours at 37 ^{o}C and the minimum inhibitory concentration (MIC) was determined visually as the lowest concentration at which growth was inhibited (Table 30).

Chemical Probe	MIC / μM (*S. aureus* – SH1000)
204	> 100
205	> 100
206	> 100
207	> 100
208	> 100
209	> 100
210	> 100
211	> 100
212	> 100
213	> 100
214	> 100
215	> 100
216	> 100
217	> 100
218	> 100
219	> 100
220	> 100
221	> 100
222	> 100
223a-b	> 100
224	> 100
225	> 100

Table 30: The minimum inhibitory concentration (MIC) values determined for each of the chemical probes when screened against *S. aureus* strain SH1000. Penicillin G was used as a positive control in all experiments.

Unfortunately, it was found that none of the 23 chemical probes showed any significant antibacterial activity against *S. aureus* strain SH1000, with MIC values of >100 μM determined for all of the compounds tested. Therefore, it was determined that the 23 chemical probes prepared through this high throughput approach did not possess any significant antibacterial activity against *S. aureus* strain SH1000.

4.8.2. Determination of antiparasitic activity for chemical probe library against *Trypanosoma brucei*

The second biological evaluation undertaken with the chemical probe library involved an investigation to determine if any of the chemical probes could possess any significant antiparasitic activity. To achieve this, the library of 23 chemical probes were screened against *Trypanosoma brucei* (*T. brucei*) to determine the EC_{50} values for each of the compounds. *T. brucei* is a parasite that is responsible for African sleeping sickness in 36 different countries within sub-Saharan Africa, leading to around 70,000 deaths each year.[156] It is transmitted between mammalian hosts by the tsetse fly.[156]

The screening of the chemical probe library against *T. brucei* was performed William Mosedale at the University of St Andrews. The EC_{50} values for each of the probes was determined by incubating the *T. brucei* cells with each chemical probe at various concentrations (usually 50.0 – 2.11 μM) for 66 hours in 96 well plates. Resazurin sodium salt (in PBS) was then added and the *T. brucei* and probe mixtures were incubated for a further 6 hours (for a total assay duration of 72 hours). Plates were then read on a plate reader using excitation/emission 560/590 nm in order to determine accurate EC_{50} values for each probe. These values were used to determine if any of the probes possessed any significant antiparasitic activity (Table 31).

Analysis from the raw data from the plate reader found that the activity of the probes against *T. brucei* ranged from very mild activity (estimated EC_{50} values of 50.0 – 12.5 μM) to more significant antiparasitic activity (estimated EC_{50} values of 12.5 – 6.25 μM). The four most active chemical probes **217**, **218**, **220** and **221** (determined from analysis of the raw data from the plate reader) were then re-screened against *T. brucei* under the same assay conditions and their corresponding dose response curves were plotted to provide accurate EC_{50} values for these four most active compounds (Figure 51). It was found that these four chemical probes (**217**, **218**, **220** and **221**) possessed low micromolar antiparasitic activity against *T. brucei*. The highest activity was found with compound **218**, which was found to have an EC_{50} value of 6.81 ± 0.07 μM. The next most active probes were compound **217** and **220**, which were found to have EC_{50} values of 9.38 ± 0.06 μM and 9.26 ± 0.06 μM respectively. Finally, compound **221** was found to have activity of 11.9 ± 0.2 μM (Figure 52).

Chemical Probe	EC_{50} / μM (*T. brucei*)
204	25.0 – 12.5
205	50.0 – 25.0
206	25.0 – 12.5
207	50.0 – 25.0
208	50.0 – 25.0
209	50.0 – 25.0
210	25.0 – 12.5
211	50.0 – 25.0
212	25.0 – 12.5
213	50.0 – 25.0
214	50.0 – 25.0
215	50.0 – 25.0
216	25.0 – 12.5
217	**12.5 – 6.25**
218	**12.5 – 6.25**
219	50.0 – 25.0
220	**12.5 – 6.25**
221	**25.0 – 12.5**
222	50.0 – 25.0
223a-b	25.0 – 12.5
224	50.0 – 25.0
225	50.0 – 25.0

Table 31: The estimated EC_{50} ranges for the chemical probe library. These values were determined by analysis of the raw data from the plate reader after screening the 23 chemical probes against *T. brucei* to assess antiparasitic activity.

It was found that all four of the most active chemical probes (**217**, **218**, **220** and **221**) were based around diazo substrate **D2**, as all four of these chemical probes contained the 4-phenyl piperidine motif in their core structures. Interestingly, it was found that these active compounds had core structures with different connectivity patterns. For

example, compounds **217** and **220** had been prepared through O-H insertion into either a benzylic alcohol (**217**) or secondary alcohol (**220**) co-substrate. Additionally, compound **218** had been prepared through sulfonamide N-H insertion and compound **221** was prepared through indole C(3)-H insertion. Therefore, it could be shown that low micromolar antiparasitic activity could be achieved with varying connectivity patterns within the core structures of the chemical probes.

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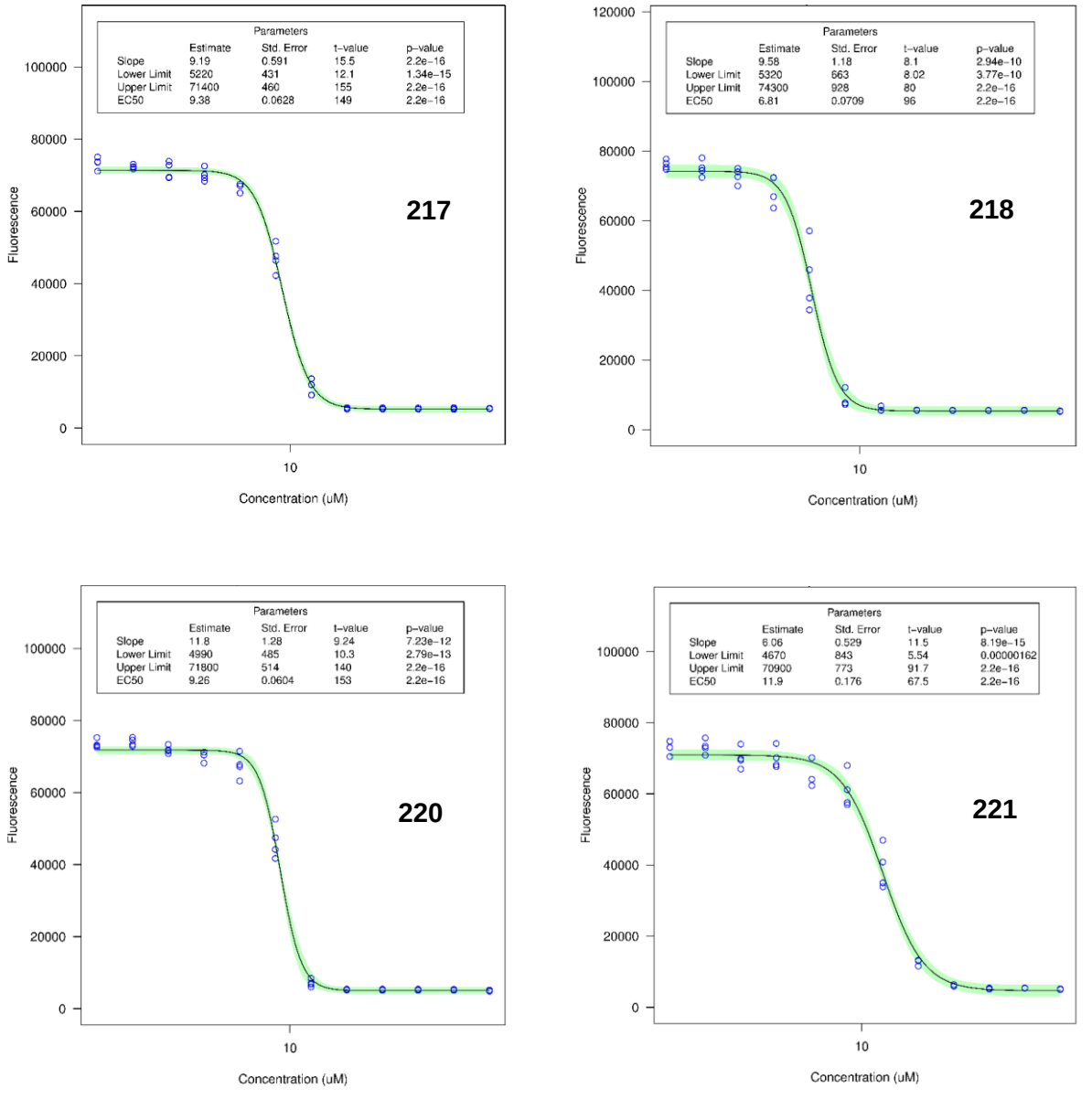


Figure 51: The dose response curves for the most active chemical probes **217**, **218**, **220** and **221** used to determine the EC_{50} values for these probes against *T. brucei*.

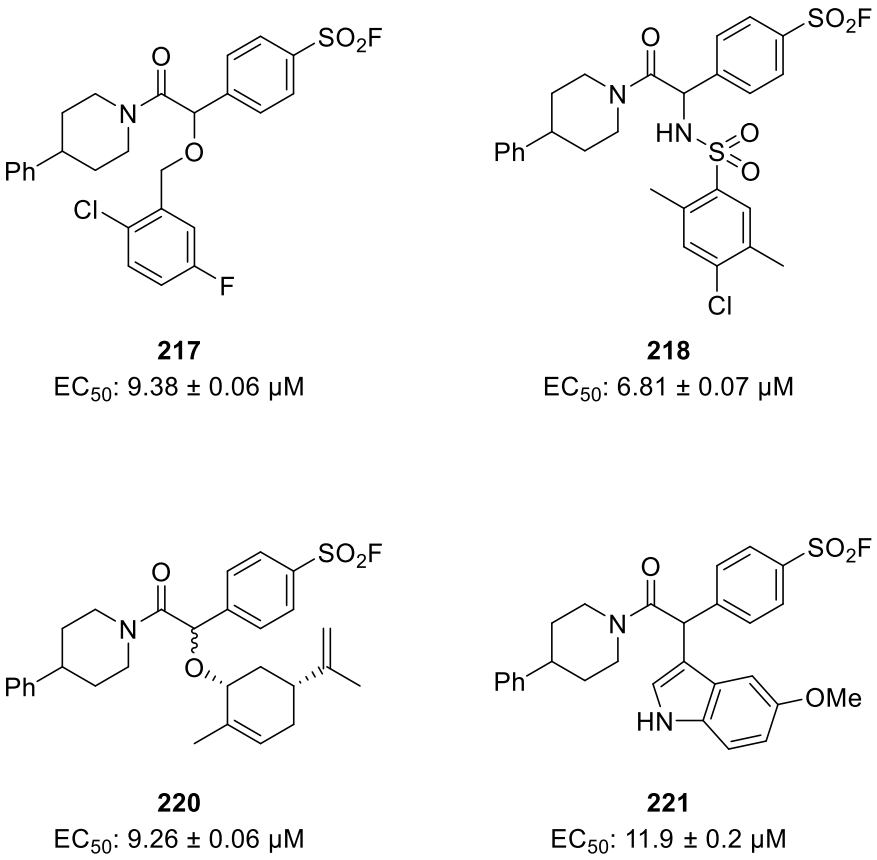


Figure 52: An overview of the four most active chemical probes that were found to possess low micromolar antiparasitic activity against *T. brucei*.

To conclude this section of work, an efficient high throughput synthetic approach was successfully able to prepare a library of 23 structurally diverse chemical probes. Subsequent biological evaluation of these probes found that they did not possess significant antibacterial activity when screened against *S. aureus* strain SH1000. However, four of the chemical probes were found to have low micromolar antiparasitic activity when screened against *T. brucei*. These four chemical probes were found to all be based around diazo substrate **D2**. However, they were also found to have three different connectivity patterns in their core structures and be prepared from four different co-substrates in the original reaction array.

5 Summary/comparison between synthetic approaches employed for the synthesis of diverse small molecules

In total, three different synthetic strategies have been successfully developed for the synthesis of diverse molecular scaffolds and chemical probes. Firstly, a bottom-up build-couple-pair (B/C/P) strategy (Chapter 2) was developed that enabled a total of 17 diverse molecular scaffolds to be prepared in total. This approach first involved the synthesis of three cyclisation precursors from commercially available cyclic ketone starting materials, where these cyclisation precursors contained several reaction handles within their structure. A toolkit of cyclisation reaction was developed to allow cyclisation to take place between these reaction handles to provide the first library of shape and structurally diverse final scaffolds.

Secondly, another bottom-up synthetic approach was developed for the preparation of a second diverse scaffold library that involved complexity generating ‘stitching’ annulations (Chapter 3). This approach utilised *syn*-selective amine directed C-H arylation chemistry of cyclic/bicyclic amine starting materials to provide 20 arylated intermediates in a diastereoselective manner. Another toolkit of cyclisation reactions was then developed to allow for cyclisation between the aryl and amine functional groups and provide a library of 17 highly three-dimensional cyclised scaffolds in total.

Finally, a high throughput strategy was used to prepare a library of 23 diverse chemical probes (Chapter 4). This approach involved the use of rhodium-catalysed carbenoid chemistry in a reaction array. This enabled a set of three diazo substrates, 16 co-substrates and three catalysts to be reacted together in 144 different reaction combinations. Reaction combinations that gave the highest yields of intermolecular products were then directly purified by preparative HPLC to provide the library of 23 diverse chemical probes in a highly efficient manner, with each of the 23 chemical probes being products from 18 of the 48 diazo and co-substrate combinations.

These three different approaches for the synthesis of diverse small molecules were then compared in order to determine which strategy was able to prepare compounds that best fulfilled the initial aims of the project. In other words, which strategy provided the most shape and structurally diverse compounds that could best target lead-like chemical space in the most efficient manner. To begin with, four key parameters were

compared between the three synthetic strategies to help draw this conclusion (Table 32). These parameters are: the total number of scaffolds/probes prepared, number of synthetic steps per scaffold, mean Fsp^3 value of the scaffold/probe library and the percentage of decorated scaffolds that occupy lead-like chemical space after being decorated once.

	Total Scaffolds/Probes Prepared	Synthetic Steps per Scaffold/Probe[b]	Mean Fsp^3 of library[c]	% of Decorated Scaffolds within Lead-Like Chemical Space
B/C/P Approach (Chapter 2)	17	2.18	0.70	60%[d]
'Stitching' Annulation Approach (Chapter 3)	37[a]	1.46	0.55	50%[d]
High Throughput Approach (Chapter 4)	23	1.17	0.28	-[e]

Table 32: Comparison between the three synthetic approaches employed for the synthesis of diverse small molecules with four key parameters highlighted. [a]These 37 compounds include the 17 cyclised scaffolds and the 20 arylated intermediates prepared through this approach. [b]Calculated as the total number of synthetic steps required to prepare all the scaffolds divided by the total number of scaffolds/probes prepared. [c]Mean Fsp^3 of the undecorated libraries. [d]Analysis of virtual lead-like library after scaffolds were decorated once with the standard range of capping groups present in LLAMA.[63] [e]Not considered for chemical probe library.

It was found that the 'stitching' annulation approach was able to prepare the highest number of scaffolds in total with a high degree of efficiency. The most efficient strategy was the high throughput approach which gave 23 distinct chemical probes in only 1.17 steps per scaffold, which includes the synthetic steps needed to prepare each of the diazo substrates for the reaction array. Additionally, the high throughput approach allows the 18 reactions between the diazo substrates and the co-substrates to be achieved in parallel, which is something that cannot be achieved at the same degree with the other two approaches. However, this approach was also found to give the least shape diverse set of final compounds, which was be determined by comparison of the corresponding PMI plots, as well as the chemical probe library having the lowest mean Fsp^3 value (0.28). In contrast, the B/C/P approach was found to give the most

shape diverse set of scaffolds (mean Fsp^3 value of 0.70) as well as the highest proportion of scaffolds that could target lead-like chemical space (60%) after being decorated once with the standard range of capping groups present within LLAMA.[63] However, this approach also delivered the lowest number of scaffolds in total and provided these scaffolds with the lowest efficiency (2.18 synthetic steps per scaffold) out of the three synthetic approaches used. Therefore, it can be deduced that whilst increasing the efficiency of the synthetic approach can provide more scaffolds/probes in a more time and cost-effective manner, it can become more challenging to control the overall diversity of the compounds being prepared.

The parameters assessed in Table 32 (as well as taking into account the molecular properties, PMI plots and scaffold trees for each of the scaffold/probe libraries previously discussed for each of the approaches) were then used to generate five distinct descriptors to aid the comparison of each synthetic approach. These descriptors are: overall efficiency, shape diversity, structural diversity, ability to access lead-like chemical space and scaffold/probe novelty for each synthetic approach (Table 33). These descriptors range from 'poor' to 'excellent' after considering all the available analysis for each synthetic approach.

	Efficiency	**Shape Diversity**	**Structural Diversity**	**Ability to Access Lead-Like Chemical Space**	**Novelty**
B/C/P Approach (Chapter 2)	Moderate	Good	Good	Excellent	Excellent
'Stitching' Annulation Approach (Chapter 3)	Good	Excellent	Excellent	Good	Excellent
High Throughput Approach (Chapter 4)	Excellent	Moderate	Good	-[a]	Excellent

Table 33: Comparison of five key parameters in the three synthetic approaches developed for the synthesis of diverse small molecules. [a]Not considered for chemical probe library.

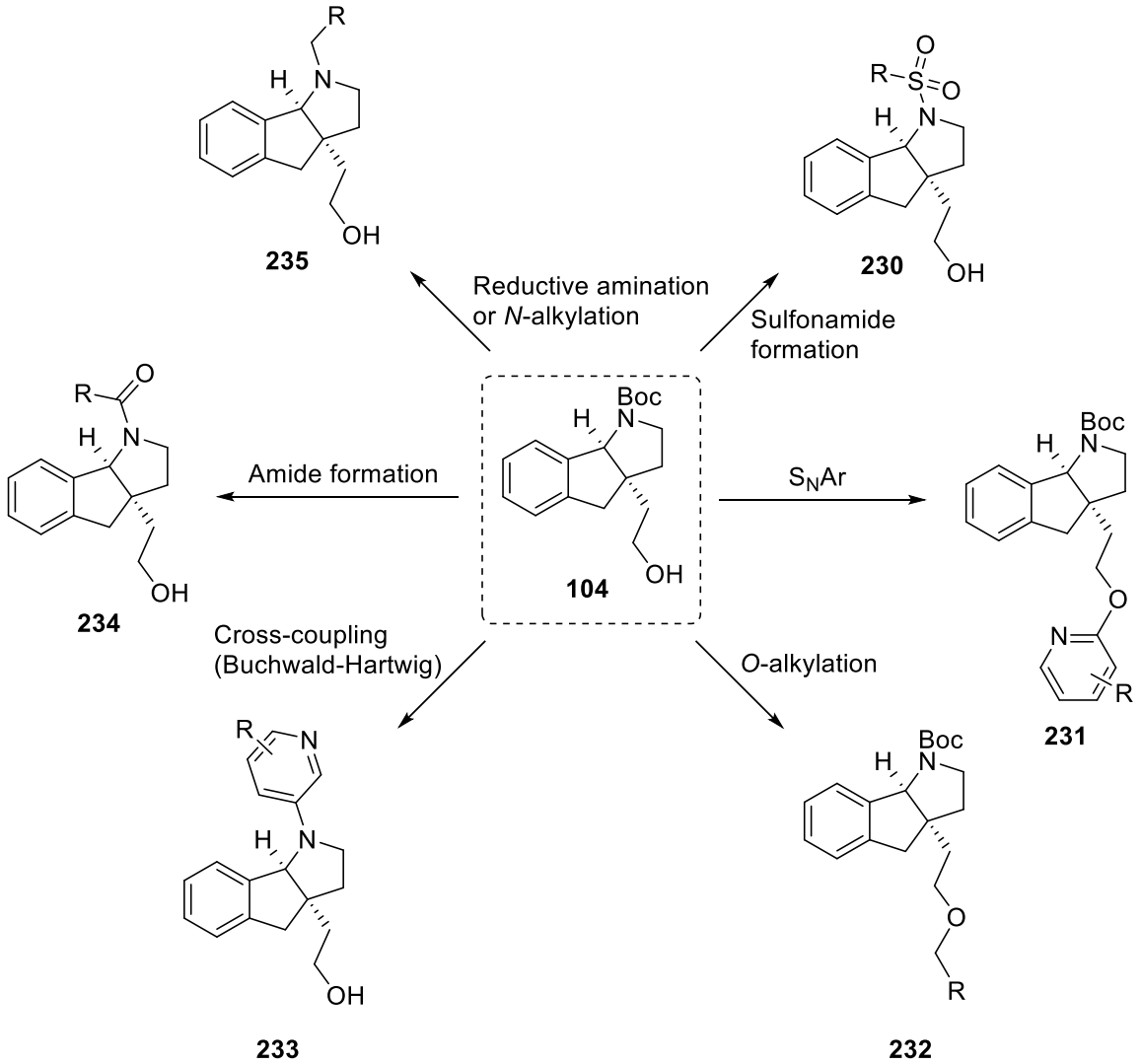
It was concluded that after taking into consideration all the available analysis, the high throughput approach was indeed the most efficient synthetic approach, with good structural diversity also observed, but this approach could only provide moderate shape diversity of probes within its final library. This limitation is mainly due to the rhodium-catalysed carbenoid chemistry only allowing new bonds to be formed at the same position in the diazo substrates, as well as subsequent cyclisation reactions being very difficult to achieve within this high throughput approach. It was also found that all three synthetic approaches were able to provide compound libraries with excellent novelty. Whilst the B/C/P approach was the least efficient out of the three approaches employed, it was determined that this approach did still possess moderate efficiency, as 2.18 synthetic steps per scaffold is still a considerably low value for this library of 17 scaffolds. This B/C/P approach also gave good structural diversity and allowed the greatest proportion of any decorated scaffolds to access lead-like chemical space. Finally, the ‘stitching’ annulation approach provided scaffolds that possessed excellent shape and structural diversity with good efficiency. Therefore, this approach was able to balance out both the synthetic efficiency and scaffold diversity, by providing a highly concise approach that still allowed for control over stereochemistry to give the three-dimensional scaffolds prepared through this approach.

To conclude, whilst high throughput approaches can allow for the fast exploration of chemical space in a time and cost-effective manner, it can become increasingly challenging to prepare significantly shape and structurally diverse compounds in high throughput. Therefore, if the diversity of the final compounds is of significant priority, the ‘stitching’ annulation approach can be seen as the ideal synthetic ‘middle ground’ as this approach was able to produce a high number of structurally and shape diverse scaffolds whilst still possessing high overall synthetic efficiency.

5.1 Future work

The three different synthetic approaches that were developed have successfully demonstrated that a wide range of diverse small molecular scaffolds/probes can be prepared in a highly efficient manner and also have the ability to explore a wide area of chemical space effectively. However, for these scaffolds to effectively target lead-

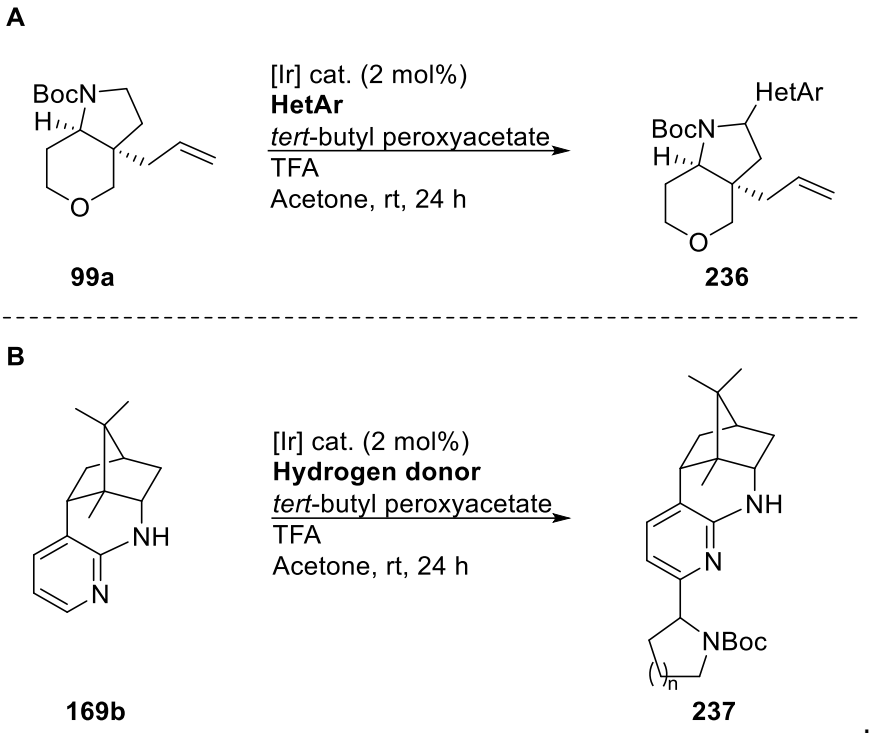
like chemical space as originally intended, they still would need to be decorated with a selection of medicinally relevant capping groups to provide a library of lead-like screening compounds. Therefore, any future work involving these scaffolds would first entail selecting a set of suitable capping groups for scaffold decoration, followed by decoration of the scaffold libraries at the points of diversification within each scaffold (e.g. amine, alcohol, carboxylic acid etc.). This would therefore enable these scaffolds to rapidly provide a library of lead-like screening compounds for any subsequent biological evaluation (Scheme 33).



Scheme 33: An overview of potential decorations (with scaffold **104** as an example) at the points of diversification within the scaffolds to rapidly access a large library of lead-like compounds suitable for subsequent screening.

Suitable reactions to achieve this would include reductive aminations with a selection of ketones and aldehydes to allow for decoration at any amines present in the scaffolds. Additionally, these amines could undergo alkylation chemistry with a variety of different alkylating agents, sulfonamide formation with a range of sulfonyl chlorides and amide formation with a set of suitable carboxylic acids. Moreover, any alcohol or amine points of diversification within the scaffolds could also under S_NAr chemistry or cross couplings (such as Buchwald-Hartwig aminations)[124] with a selection of aromatic and heteroaromatic capping groups to generate the corresponding decorated compounds. These decorated compounds would then make up a shape and structurally diverse lead-like screening library that could then undergo subsequent high throughput screening.

Some additional further work could also entail decorating the scaffolds through C-H activation chemistry, such as utilising photoredox catalysis, to allow these scaffolds to be decorated at more 'non-traditional' points of diversification. This would increase the potential value of these scaffolds as they could then be decorated across additional reaction vectors to target lead-like chemical space even more effectively. Recent developments in the field of photoredox catalysis could enable regioselective decoration at a specific C-H bond within the scaffolds. For example, a photoredox mediated Minisci reaction, developed by Wang *et. al*, could allow for selective scaffold decoration through α-arylation chemistry next to any *N*-Boc functional groups present in the scaffolds (Scheme 34, Panel A).[157] This could allow for these scaffolds to be decorated with a large selection of aromatic and heteroaromatic capping groups to rapidly generate a large and diverse lead-like compound library for subsequent high throughput screening. Additionally, the same reaction conditions could be used to decorate any scaffolds that contain heteroaromatic groups within their structure (Scheme 34, Panel B). These scaffolds could be decorated at the 2- or 4-position of the heteroaromatic ring using identical Minisci photoredox conditions, however this time varying the hydrogen donor utilised in the reaction. Examples of suitable hydrogen donors include saturated *N*-heterocycles such as substituted *N*-Boc pyrrolidines and *N*-Boc piperidines. Therefore, scaffold decoration by either varying the heteroaromatic group or by varying the hydrogen donors would allow for a large library of lead-like screening compounds to be prepared from the scaffold library in a time efficient manner.



Scheme 34: An overview of scaffold decorations utilising photoredox catalysis to enable decorations to take place at more 'non-traditional' points of diversification through C-H activation chemistry.

One final piece of work would then involve the biological evaluation of any decorated lead-like compounds prepared. Any of the decorated compounds derived from the B/C/P and 'stitching' annulation approaches would be suitable substrates for both high throughput biological target-based screening as well as phenotypic screening. An example of a useful phenotypic screen would be a cell painting assay.[158] The cell painting assay involves staining various cellular features with up to six different dyes in a single well.[158] Subsequent automatic image analysis can then identify hundreds of different parameters which can then be used to identify the phenotypic profile of the cell.[158] This can be used to identify the modes of action for new compounds. Additionally, most of the undecorated scaffolds from the B/C/P and 'stitching' annulation approaches could also be appropriate compounds for screening as fragments, for example within fragment-based drug discovery. These potential fragments could be assessed for any promising activity by utilising high throughput fragment-based screening at LifeArc. Therefore, subsequent screening of the undecorated scaffolds, as well as any decorated lead-like compounds, would then

provide the necessary biological data to ascertain whether the scaffolds prepared through these synthetic approaches can also access novel biologically relevant chemical space in an effective manner.

6 Experimental

6.1 General experimental

Commercially available starting materials were obtained from Sigma−Aldrich, Fluorochem and Alfa Aesar. All non-aqueous reactions were performed under nitrogen atmosphere unless otherwise stated. Water-sensitive reactions were performed in anhydrous solvents in oven-dried glassware cooled under nitrogen before use. Anhydrous dichloromethane (DCM), anhydrous tetrahydrofuran (THF), anhydrous toluene, anhydrous diethyl ether, anhydrous ethanol, anhydrous methanol and anhydrous acetonitrile were obtained from a PureSolv MD5 Purification System. All other solvents used were of chromatography or analytical grade. An IKA RV 10 rotary evaporator was used to remove the solvents under reduced pressure.

Thin layer chromatography (TLC) was performed using aluminium backed silica (Merck silica gel 60 F254) plates obtained from Merck. Ultraviolet lamp (λ_{max} = 254 nm) and $KMnO_4$ were used for visualisation. Flash column chromatography was performed using silica gel 60 (35-70 µm particles) supplied by Merck.

Analytical LC-MS was performed using an Ultimate3000 HPLC instrument with a UV diode array detector and an MS detector Bruker Amazon Speeds with electrospray ionisation run positive and negative switching mode. The system used a Phenomenex Kinetex C18 2.1 × 50 mm 2.6 micron column and two solvent systems: MeCN/H_2O + 0.1% Formic acid or MeCN/H_2O. Preparative HPLC was performed using a Water (2767) instrument with a Water SQ detector 2. The system used an XBridge C18 19.0 × 100 mm 5 micron OBD column. The general preparation method used a solvent system of MeCN/H_2O (5−95%) + 0.1% Formic acid.

A Bruker MaXis Impact spectrometer with electrospray (ES) ionisation source was used for high-resolution mass spectrometry (HRMS). A Bruker Alpha-P ATR FR-IR spectrometer was used to analyse the infrared spectra. Optical rotation measurements were performed at the sodium D-line (589 nm) on a Schmidt and Haensch H532. They are given in 10^{-1} deg cm^2 g^{-1}.

Proton (^{1}H) and carbon (^{13}C) NMR data was collected on a Bruker 300 (AV3 NMR spectrometer operating at 7.05 T and equipped with a 5 mm BBO probe), 400 (AV3HD NMR spectrometer operating at 9.4 T and equipped with a 5 mm BBO probe) and 500 (AV-NEO NMR spectrometer operating at 11.7 T and equipped with a 5 mm DCH cryoprobe) MHz spectrometer. Fluorine (^{19}F) NMR data was collected on a Bruker 500 (AV-NEO NMR spectrometer operating at 11.7 T and equipped with 5mm TBO (^{1}H/^{19}F/BB) and TXI (^{1}H/^{13}C/^{15}N) probes) MHz spectrometer. Data was collected at 298 K unless otherwise stated. Chemical shifts (δ) are given in parts per million (ppm) and they are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and splitting patterns are reported in an abbreviated manner: app. (apparent), s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), sept (septet), m (multiplet), br (broad). Assignments were made using COSY, DEPT, HSQC, HMBC and NOESY experiments. Abbreviations: TDG = 2-hydroxynicotinaldehyde (CAS 36404-89-4); TDG2 = 2-chloro-6-hydroxybenzaldehyde (CAS 18362-30-6); L1 = 2-hydroxy-5-trifluoromethylpyridine (CAS 33252-63-0).

6.2 General procedures

General Procedure A (Acylation with allyl chloroformate)

LiHMDS (2.20 eq of a 1.0 M solution in toluene) was added to a solution of the carbonyl derivative (1.00 eq) in the specified amount of toluene at 0 °C. After stirring for 15 min, allyl chloroformate (1.20 eq) was added and the reaction mixture was allowed to warm to rt and stirred for 1.5 h. Then, a saturated aqueous solution of NH_4Cl (3 mL per 1.00 mmol of the carbonyl derivative) was added, the mixture was stirred for 15 min, the phases were separated and the aqueous phase was extracted with EtOAc (3 × (1 mL per 1.00 mmol of the carbonyl derivative)). The organic phases were combined, washed with brine (2 mL per 1.00 mmol of the carbonyl derivative), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure B (Alkylation with bromoacetonitrile)

The allyl ester derivative (1.00 eq) was dissolved in THF (0.16 M) where NaH (1.50 eq, 60% dispersion in oil) was added portionwise at rt. The reaction mixture was stirred for 1 h then bromoacetonitrile (2.20 eq) in THF (0.88 M) was added dropwise at rt. The reaction mixture was stirred for 18 h at rt. An extra equivalent of bromoacetonitrile was added after 24 h if the reaction had not reached completion by TLC, then left to stir at rt for an extra 24 h. Then, any solids were filtered off and the filtrate evaporated under reduced pressure to give a crude material.

General Procedure C (Pd-catalysed decarboxylative allylation)

According to a procedure,[72] PPh_3 (20 mol%) and $Pd(OAc)_2$ (5 mol%) were added to a solution of the quaternary allyl ester derivative (1.00 eq) in THF (0.10 M) and the reaction mixture was stirred for 1 h at 70 °C. Then, the solution was allowed to cool to rt, filtered through celite and concentrated under reduced pressure to give a crude material.

General Procedure D (Hydroboration-oxidation of terminal alkenes)

By modification of an existing procedure,[80] 2-methyl-2-butene (7.50 eq) was added dropwise to BH_3•THF (3.50 eq of a 1.0 M solution in THF) at 0 °C. The mixture was stirred for 2 h at 0 °C. Then, a solution of the ketone derivative (1.00 eq) in THF (0.35 M) at 0 °C was added dropwise. The reaction mixture was stirred for 45 min at 0 °C and subsequently it was stirred for 1 h at rt. Then, $NaBO_3$•$4H_2O$ (7.50 eq) and water (3 mL per 1.00 mmol of the cyclisation precursor) were added. After stirring the mixture vigorously for 18 h at rt, EtOAc (3 mL per 1.00 mmol of the cyclisation precursor) was added, the phases were separated and the aqueous phase was extracted with EtOAc (3 × (3 mL per 1.00 mmol of the cyclisation precursor)). Then, the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure E (Hemiacetal reduction)

Trifluoroacetic acid (20.0 eq) and Et_3SiH (1.50 eq) were added to a solution of the hemiacetal derivative (1.00 eq) in DCM (0.1 M) at rt. The reaction mixture was stirred for 18 h at rt. A saturated aqueous solution of $NaHCO_3$ (10 mL per 1.00 mmol of the hemiacetal derivative) was added, the phases were separated and the aqueous phase was extracted with DCM (3 × (4 mL per 1.00 mmol of the hemiacetal derivative)). Then, the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure F ($LiAlH_4$ reduction)

Lithium aluminium hydride (4.50 eq, 1.0 M solution in THF) was added dropwise to a solution of ketone derivative (1.00 eq) in THF (1.2 M) at rt. The reaction mixture was then stirred at reflux temperature for 1 h. Then 2M NaOH was added dropwise to the solution at room temperature until effervescence ceased, at which point Boc_2O (2.20 eq) was added and the mixture stirred at room temperature for 18 h. The reaction mixture was filtered to remove any solids and the phases were then separated. The aqueous phase then extracted with EtOAc (3 x (3 ml per mmol of cyclisation

precursor). The organic phases were then combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure to a crude material.

General Procedure G (Alcohol acetylation)

Pyridine (31.0 eq) was added to a solution of the alcohol derivative (1.00 eq) in Ac_2O (26.4 eq) at rt. Then, the reaction mixture was stirred for 18 h at rt and the solvent was then removed under reduced pressure. The crude material was dissolved in DCM (3 mL per 1.00 mmol of the alcohol derivative) and an aqueous solution of 10% $CuSO_4$ (3 mL per 1.00 mmol of the alcohol derivative) was added. After stirring the mixture for 5 min at rt, the phases were separated and the aqueous phase was extracted with DCM (3 × (2 mL per 1.00 mmol of the alcohol derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the acetate derivative.

General Procedure H (Piperidine synthesis *via* alkene oxidative cleavage)

To a solution of acetate derivative (1.00 eq) in 1,4-dioxane–water 3:1 (0.1 M) were added 2,6-lutidine (2.00 eq), OsO_4 (2 mol%, 2.5 wt% solution in ^{t}BuOH) and $NaIO_4$ (4.00 eq) at rt. The reaction mixture was stirred at rt for 24 h. Then water (7 ml per mmol of acetate derivative) and DCM (7 ml per mmol of acetate derivative) were added and the phases separated. The aqueous layer was extracted with DCM (3 x (9 ml per mmol of acetate derivative)), organic layers combined, washed with brine (7 ml per mmol of acetate derivative), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the intermediate hemiaminal species. This hemiaminal intermediate (1.00 eq) was dissolved in AcOH (10 ml per mmol of hemiaminal intermediate) and $NaBH(OAc)_3$ (7.00 eq wrt hemiaminal intermediate), was added at rt. The reaction mixture was stirred at rt for 2 h. Then a saturated solution of $NaHCO_3$ (35 ml per mmol of hemiaminal intermediate) and DCM (30 ml per mmol of hemiaminal intermediate) were added sequentially. The mixture was stirred for 30 mins and the phases were separated. The aqueous phase was extracted with DCM (3 x (14 ml per mmol of hemiaminal intermediate) and the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure I (Lactam synthesis via alkene oxidative cleavage)

To a solution of acetate derivative (1.00 eq) in 1,4-dioxane–water 3:1 (0.1 M) were added 2,6-lutidine (2.00 eq), OsO_4 (2 mol%, 2.5 wt% solution in ^tBuOH) and $NaIO_4$ (4.00 eq) at rt. The reaction mixture was stirred at rt for 24 h. Then water (7 ml per mmol of acetate derivative) and DCM (7 ml per mmol of acetate derivative) were added and the phases separated. The aqueous layer was extracted with DCM (3 x (9 ml per mmol of acetate derivative)), organic layers combined, washed with brine (7 ml per mmol of acetate derivative), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the intermediate hemiaminal species. This hemiaminal intermediate (1.00 eq) was dissolved in DCM (12 ml per mmol of hemiaminal intermediate) and PDC (2.00 eq wrt hemiaminal intermediate) and celite were added sequentially at rt. The reaction was left to stir for 24 h at rt. At this point, the reaction mixture was filtered through celite and concentrated under reduced pressure to give a crude material.

General Procedure J (Alcohol benzylation)

NaH (1.10 eq, 60% dispersion in oil) was added to a mixture of alcohol derivative (1.00 eq), TBAI (20 mol%) and benzyl bromide (1.20 eq) in THF (0.18 M) at 0 ^oC. The solution was then stirred at rt for 18 h until completion of the reaction was shown by TLC. A saturated aqueous solution of $NaHCO_3$ (6 ml per mmol of alcohol derivative) was added, phases separated and the aqueous phase extracted with EtOAc (3 x (6 ml per mmol of alcohol derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure K (Aminoarylation)

The benzyl ether derivative (1.00 eq), $Pd(OAc)_2$ (5 mol%), DPEPhos (10 mol%) and Cs_2CO_3 (2.50 eq) were dissolved in 1,4-dioxane (0.10 M) at rt. Then the arylbromide (1.40 eq) was added and the mixture heated at 105 ^oC for 24 h. The reaction mixture was filtered through celite and then concentrated under reduced pressure to give a crude material.

General Procedure L (Fused-ring pyrrolidine synthesis *via* substitution)

The alcohol derivative (1.00 eq), Et_3N (2.00 eq) and MsCl (1.20 eq) were dissolved in DCM (0.11 M) at 0 ^oC. The reaction mixture was then stirred at rt for 18 h. A saturated solution of $NaHCO_3$ (4 ml per mmol of alcohol derivative) was added and the phases were separated. The aqueous phase was extracted with DCM (3 x (4 ml per mmol of alcohol derivative)), organic phases combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the mesylate intermediate. This was then dissolved in DCM (0.10 M) at rt and TFA (40.0 eq) was added dropwise at rt and then stirred for 5 h also at rt. The solvent and TFA were removed under reduced pressure and the resulting product was dissolved in DCM (0.10 M). Et_3N (22.0 eq) was added dropwise at rt and the resulting solution stirred for 18 h at rt. Then Boc_2O (2.00 eq) was added and the reaction mixture stirred for a further 18 h at rt. A saturated solution of $NaHCO_3$ (4 ml per mmol of alcohol derivative) was added, phases separated and the aqueous phase extracted with DCM (3 x (5 ml per mmol of alcohol derivative). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product.

General Procedure M (Alkene oxidative cleavage)

According to a procedure,[87] to a solution of fused-ring pyrrolidine derivative (1.00 eq) in 1,4-dioxane–water 3:1 (0.11 M) were added 2,6-lutidine (2.00 eq), OsO_4 (2 mol%, 2.5 wt% solution in ^{t}BuOH) and $NaIO_4$ (4.00 eq) at rt. The reaction mixture was stirred at rt for 24 h. Then water (7 ml per mmol of alkene derivative) and DCM (10 ml per mmol of alkene derivative) were added and the phases separated. The aqueous layer was extracted with DCM (3 x (7 ml per mmol of alkene derivative)), organic layers combined, dried (Na_2SO_4) and concentrated under reduced pressure to give the crude material.

General Procedure N (Aldehyde reduction)

The aldehyde derivative (1.00 eq) was dissolved in MeOH (0.1 M) and $NaBH_4$ (1.50 eq) was added at rt. The reaction mixture was stirred or a further 5 h then a saturated

aqueous solution of NH_4Cl (20 ml per mmol of aldehyde derivative) and DCM (20 ml per mmol of aldehyde derivative) were added to the solution. The phases were separated and the aqueous phase was extracted with DCM (3 x (10 ml per mmol of aldehyde derivative)). The organic phases were combined and washed with water (20 ml per mmol of aldehyde derivative) and brine (20 ml per mmol of aldehyde derivative). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the alcohol product.

General Procedure O (Pinnick oxidation)

By modification of an existing procedure,[88] a solution of aldehyde derivative (1.00 eq) in MeCN (0.15 M) was added 2-methyl-2-butene (13.0 eq) at rt. Then a solution of $NaClO_2$ (4.00 eq) and NaH_2PO_4 (5.00 eq) in H_2O (0.15 M) was added dropwise at rt. The reaction mixture was left to stir overnight at rt. The mixture was diluted with a saturated aqueous solution of NH_4Cl (10 ml per mmol of aldehyde derivative) and then extracted with EtOAc (3 x (13 ml per mmol of aldehyde derivative)). The organic layers were combined, washed with brine (13 ml per mmol of aldehyde derivative), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure P (Iodocyclisation)

By modification of an existing procedure,[63] the alcohol derivative (1.00 eq), I_2 (2.00 eq) and $NaHCO_3$ (2.00 eq) were dissolved in MeCN (0.16 M) at rt. The reaction mixture was then stirred at rt for 24 h or until TLC showed completion of the reaction. The solution was quenched with aqueous saturated sodium thiosulphate solution (3 ml per mmol of alcohol derivative) and diluted with EtOAc (3 ml per mmol of alcohol derivative). The phases were then separated and the aqueous phase extracted with EtOAc (3 x (6 ml per mmol of alcohol derivative)). The organic layers were then combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude material.

General Procedure Q (TDG C-H arylation with subsequent *N*-Boc protection)

$Pd(OAc)_2$ (5 mol%), 2-hydroxynicotinaldehyde (10 mol%), aryl iodide (2.00 eq) and AgTFA (2.00 eq) were added to HFIP–AcOH 19:1 (0.25 M). Then amine derivative (1.00 eq) and H_2O (10.0 eq) were added and the reaction mixture allowed to stir at rt for 10 mins. The reaction mixture was then stirred at 120 ^oC for 24 h. The dark brown suspension was allowed to cool to rt and filtered through celite, with the celite being subsequently washed with THF (3 x (3 ml per mmol of amine derivative)). The filtrate was concentrated under reduced pressure and the resulting residue was dissolved in THF (0.25 M). 1M HCl (4 ml per mmol of amine derivative) was added and the light brown suspension was left to stir for 1 h at rt. The mixture was basified with 2M NaOH and Boc_2O (3.00 eq) was added with the reaction mixture then being left to stir for 4 h at rt. EtOAc (10 ml per mmol of amine derivative) was added and the layers were separated. The organic layer was passed through a plug of silica, then the aqueous layer was extracted with EtOAc (3 x (4 ml per mmol of amine derivative)). The organic layers were then combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General procedure R (TDG C-H arylation with subsequent *N*-Acetyl protection)

$Pd(OAc)_2$ (5 mol%), 2-hydroxynicotinaldehyde (10 mol%), aryl iodide (2.00 eq) and AgTFA (2.00 eq) were added to HFIP–AcOH 19:1 (0.50 M). Then amine derivative (1.00 eq) and H_2O (10.0 eq) were added and the reaction mixture allowed to stir at rt for 10 mins. The reaction mixture was then stirred at 120 ^oC for 24 h. The dark brown suspension was allowed to cool to rt and filtered through celite, with the celite being subsequently washed with THF (3 x (3 ml per mmol of amine derivative)). The filtrate was concentrated under reduced pressure and the resulting residue was dissolved in THF (0.25 M). 1M HCl (4 ml per mmol of amine derivative) was added and the light brown suspension was left to stir for 1 h at rt. The mixture was basified with 2M NaOH and Ac_2O (3.00 eq) was added with the reaction mixture then being left to stir for 4 h at rt. EtOAc (10 ml per mmol of amine derivative) was added and the layers were separated. The organic layer was passed through a plug of silica, then the aqueous layer was extracted with EtOAc (3 x (4 ml per mmol of amine derivative)). The organic

layers were then combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General procedure S (Amide coupling with CDI)

Picolinic acid (1.10 eq) was dissolved in DMF (0.40 M) and CDI (1.10 eq) was subsequently added portionwise. The mixture was then allowed to stir at rt for 90 mins. Amine derivative (1.00 eq) was added and the mixture stirred at rt for a further 16-24 h. Water (1 ml per mmol of amine derivative) was added followed by 5M NaOH solution (2 ml per mmol of amine derivative). The mixture was then extracted with DCM (3 x (2 ml per mmol of amine derivative)), organic layers combined, washed with water (5 x (2 ml per mmol of amine derivative)), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General procedure T (C-H arylation with picolinamide directing group 1)

Picolinamide derivative (1.00 eq) was added to a pressure vial covered with aluminium foil at rt. Then Ag_2CO_3 (1.10 eq), 2,6-dimethylbenzoic acid (0.25 eq), $Pd(OAc)_2$ (10 mol%) and aryl iodide (6.00 or 8.00 eq) were added sequentially. The vial was then flushed with nitrogen, sealed with a screw-cap, a minimal amount of DMF added to enable suitable stirring and then heated to 120 °C for 24 h. Upon cooling to rt, the reaction mixture was filtered through a pad of celite, eluting with DCM. The filtrate was then concentrated under reduced pressure to give a crude material.

General procedure U (C-H arylation with picolinamide directing group 2)

A tube was charged with picolinamide derivative (1.00 eq), $CuBr_2$ (10 mol%), $Pd(OAc)_2$ (5 mol%), CsOAc (4.00 eq), ^{t}AmOH (1.00 M) and aryl iodide (4.00 eq). The tube was sealed and heated at 120 ^{o}C for 24 h. The reaction mixture was allowed to cool to rt, filtered through celite (eluting with EtOAc) then the filtrate was concentrated under reduced pressure to give a crude material.

General procedure V (C-H arylation with picolinamide directing group 3)

To a pressure vial was added picolinamide derivative (1.00 eq), PivOH (0.30 eq), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2.00 eq), aryl iodide (1.10 eq) and toluene (0.60 M). The mixture was stirred at 130 ^oC for 18 h. The reaction mixture was cooled to rt then filtered through celite, eluting with EtOAc and MeOH. The filtrate was concentrated under reduced pressure to give a crude material.

General procedure W - (implementation of reaction array)

By modification of an existing procedure,[136] the reaction arrays were carried out in a 96-well plate (8 × 12) custom made out of PTFE in borosilicate glass vials (vial volume = 750 µL, vial dimensions = 8 × 30 mm, CV-2100-0830 Chemglass). Diazo substrates were typically dissolved in DCM to give 1.25 M stock solutions. Co-substrates were dissolved in DCM to give 6.25 M stock solutions. The stock solutions of the catalysts were prepared that were 1.00 mM in DCM. Then, 16 µL of the appropriate diazo substrate stock solution was added to the appropriate wells and the solvent was evaporated. Then, 16 µL of the appropriate co-substrate stock solution was added to the appropriate wells and evaporated. This was followed by the addition of 200 µL of the catalyst stock solution. Lastly, each of the reaction wells in the plate was capped. The final volume of the reaction mixture was 200 µL; with final concentrations of catalyst (1 mM), substrate (100 mM) and co-substrate (500 mM). The wells were left to react at rt, without any stirring, for 48 h and the crude mixtures were concentrated under pressure overnight to remove any residual DCM. The wells were re-dissolved in 200 µL of DMSO to give a total product concentration of 100 mM and transferred to a 96-well plate ready for subsequent analysis and purification.

Evaluating antibacterial activity of isolated compounds from α-diazo amide reaction array

Minimum inhibitory concentration (MIC) values for selected compounds were determined by broth microdilution against *S. aureus* strain SH1000[154] according to CLSI guidelines.[155] A 2-fold dilution series of the isolated compounds in DMSO was

prepared, ranging from 10.0–0.625 mM. Each dilution was transferred into a 96-well format at a final volume of 10 µL and 90 µL of water was added to each well to give stock concentrations of 1.00–0.0625 mM (10% DMSO in water). Stock solutions were diluted to a final volume of 10 µL and 90 µL of the standardised culture was added to each well to give final product concentrations of 100–6.35 µM (1% DMSO in MHB-II). Plates were incubated for 16 h at 37 ºC (Inkubator 1000, Heidolph) and the minimum inhibitory concentration (MIC) was determined visually as the lowest concentration at which growth was inhibited.

General Procedure for Phenotypic *Trypanosoma brucei* Cell Culture

a. *Trypanosoma brucei brucei* culture

Trypanosoma brucei brucei (*T. b. brucei*) bloodstream form strain 427 were grown at 37 ºC, in HMI-11 media in vented flasks in an atmosphere containing 5% CO_2. The cells were passaged by transferring into fresh media as to not exceed a cell density of 2 x 106 cells/mL.

b. Cryogenic Storage of *Trypanosoma brucei brucei*

T. b. brucei (5 mL) at confluent density (2 x 106 cells/mL) was centrifuged at 800 xg for 5 minutes. The supernatant is removed, and cells resuspended in fresh media to a density of around 2 x 107 cells/mL. A sterile solution of 60% glycerol in water was added to the cell suspension to give a final concentration of 10% glycerol. The cell suspension was transferred to a cryovial, into a Mr Frosty (ThermoFisher Scientific Cat No. 5100-0001) containing isopropan-1-ol, which was then surrounded with dry ice and left for 24 hours. Cryovials were then stored at -170 ºC in the liquid nitrogen vapour phase for long term storage.

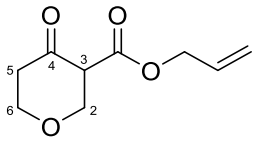
Cells are revived from cryogenic storage by first removing them from liquid nitrogen onto ice for 15 minutes. The cells are then allowed to warm to room temperature in a culture hood. Once defrosted, the cells can be transferred into a non-vented 25 mL cell culture flask with fresh medium (9.4 mL) and left to grow in a 37 ºC shaking incubator.

c. Standard *Trypanosoma brucei brucei* Resazurin Cell Viability Assay

Cell viability assays carried out in 96 well plates with 200 µL of culture per well. Cells are seeded at 5 x 103 cells/mL and incubated with drug for 66 hours (in the same conditions as culturing). The plate included wells containing the positive control pentamidine (100 nM) and the negative control of 0.5% DMSO. After 66 hours, 10 µL of 1.1 mg/mL Resazurin sodium salt (in PBS) is added and incubated for a further 6 hours (for a total assay duration of 72 hours). Plates are then read on a plate reader using excitation/emission 560/590 nm.

6.3 Experimental data

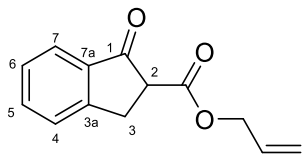
Prop-2-en-1-yl 4-oxooxane-3-carboxylate (63a)



Prepared according to General procedure A, tetrahydro-4*H*-pyran-4-one (4.00 mL, 43.4 mmol) and LiHMDS (95.4 mL, 95.4 mmol, 1.0 M solution in toluene) gave a crude material. The crude material was then purified by flash column chromatography, eluting with EtOAc−hexane 5:95 to yield the allyl ester derivative **63a**[67] (4.55 g, 57%, *keto:enol* 25:75 by ^{1}H NMR in $CDCl_3$) as a colourless oil. R_f 0.68 (50:50 petrol−EtOAc). Compound existed as mixture of keto and enol tautomers. ν_{max}/cm^{-1}: 3424, 2948, 1740, 1728, 1660, 1384, 1174, 1126, 1079; δ_H (300 MHz, $CDCl_3$): 11.75 (1H, s, OH^{enol}), 5.91 (2H, ddt, *J* 17.1, 10.3 and 5.7 Hz, propenyl 2-H), 5.34 (1H, app. dq, *J* 17.1 and 1.4 Hz, propenyl 3-H_{trans}^{keto}), 5.31 (1H, app. dq *J* 17.1 and 1.4 Hz, propenyl 3-H_{trans}^{enol}), 5.27 (1H, dd *J* 10.3 and 1.4 Hz, propenyl 3-H_{cis}^{keto}), 5.25 (1H, app. dq *J* 10.3 and 1.4 Hz, propenyl 3-H_{cis}^{enol}), 4.66 (4H, dt, *J* 5.7 and 1.4 Hz, propenyl 1-H_2), 4.29 (2H, app. t, *J* 1.7 Hz, 2-H_2^{enol}), 4.23 (1H, dd, *J* 11.6 and 7.1 Hz, 2-H_A^{keto}), 4.11 (1H, dd, *J* 11.6 and 5.1 Hz, 2-H_B^{keto}), 4.05-3.92 (2H, m, 6-H_2^{keto}), 3.85 (2H, t, *J* 5.7 Hz,

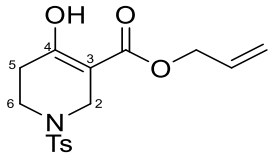
6-H_2^{enol}), 3.50 (1H, app. ddd, *J* 6.1, 5.1 and 1.4 Hz, 3-H^{keto}), 2.68 (1H, ddd, *J* 14.4, 6.0 and 5.1 Hz, 5-H_A^{keto}), 2.55 (1H, dddd, *J* 14.4, 7.1, 5.7 and 1.4 Hz, 5-H_B^{keto}), 2.39 (2H, tt, *J* 5.7 and 1.7 Hz, 5-H_2^{enol}); δ_C (100 MHz, $CDCl_3$): 201.3 (C-4^{keto}), 169.8 (carboxylate C=O^{enol}), 169.3 (C-4^{enol}), 167.5 (carboxylate C=O^{keto}), 131.9 (propenyl C-2^{enol}), 131.4 (propenyl C-2^{keto}), 118.9 (propenyl C-3^{keto}), 118.3 (propenyl C-3^{enol}), 97.3 (C-3^{enol}), 69.7 (C-2^{keto}), 68.2 (C-6^{keto}), 66.1 (propenyl C-1^{keto}), 64.9 (propenyl C-1^{enol}), 63.9 (C-6^{enol}), 63.0 (C-2^{enol}), 57.8 (C-3^{keto}), 42.1 (C-5^{keto}), 28.8 (C-5^{enol}); HRMS found MNa^+ 207.0618. $C_9H_{12}O_4$ requires *MNa*, 207.0628.

Prop-2-en-1-yl 1-oxo-2,3-dihydroindene-2-carboxylate (63b)



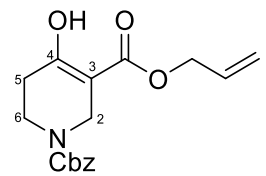
Prepared according to General procedure A, 1-indanone (4.00 g, 30.3 mmol) and LiHMDS (66.7 ml, 66.7 mmol, 1.0 M solution in toluene) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give the *allyl ester derivative* ***63b*** (3.47 g, 53%) as a red-yellow oil. R_f 0.57 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 3077, 2945, 1739, 1708, 1592, 1571, 1463, 1413, 1314, 1287, 1252, 1204, 1185, 1150, 1019; δ_H (300 MHz, $CDCl_3$): 7.77 (1H, d, *J* 7.7 Hz, 7-H), 7.62 (1H, td, *J* 7.7 and 1.2 Hz, 5-H), 7.50 (1H, d, *J* 7.7 Hz, 4-H), 7.39 (1H, t, *J* 7.7 Hz, 6-H), 5.93 (1H, ddt, *J* 17.1, 10.5 and 5.8 Hz, propenyl 2-H), 5.36 (1H, app. dq, *J* 17.1 and 1.5 Hz, propenyl 3-H_{trans}), 5.25 (1H, app. dq, *J* 10.5 and 1.5 Hz, propenyl 3-H_{cis}), 4.69 (2H, dt, *J* 5.8 and 1.5 Hz, propenyl 1-H_2), 3.75 (1H, dd, *J* 8.3 and 4.1 Hz, 2-H), 3.56 (1H, dd, *J* 16.4 and 4.1 Hz, 3-H_A), 3.38 (1H, dd, *J* 16.4 and 8.3 Hz, 3-H_B); δ_C (100 MHz, $CDCl_3$): 199.4 (C-1), 168.9 (carboxylate C=O), 153.6 (C-3a), 135.5 (C-5), 135.4 (C-7a), 131.7 (propenyl C-2), 127.9 (C-6), 126.7 (C-4), 124.8 (C-7), 118.7 (propenyl C-3), 66.3 (propenyl C-1), 55.4 (C-2), 30.4 (C-3); HRMS found MNa^+ 239.0685. $C_{13}H_{12}O_3$ requires *MNa*, 239.0679.

Prop-2-en-1-yl 4-hydroxy-1-(4-methylbenzenesulfonyl)-5,6-dihydro-2*H*-pyridine-3-carboxylate (63f)



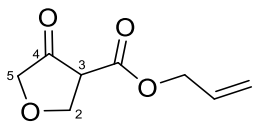
Prepared according to General procedure A, 1-tosyl-4-piperidinone (4.00 g, 15.7 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 10:90 to give the *allyl ester derivative* ***63f*** (3.41 g, 64%, >95% *enol* by ^{1}H NMR) as a colourless oil. R_f 0.38 (EtOAc–hexane 25:75). ν_{max}/cm^{-1}: 3436, 3032, 2928, 2864, 1665, 1624, 1450, 1398, 1343, 1299, 1225, 1159, 1090, 1007; δ_H (400 MHz, $CDCl_3$): 11.92 (1H, s, OH), 7.68 (2H, d, *J* 8.3 Hz, benzenesulfonyl 2,6-H), 7.32 (2H, d, *J* 8.3 Hz, benzenesulfonyl 3,5-H), 5.92 (1H, ddt, *J* 17.2, 10.4 and 5.7 Hz, propenyl 2-H), 5.31 (1H, app. dq, *J* 17.2 and 1.5 Hz, propenyl 3-H_{trans}), 5.27 (1H, app. dq, *J* 10.4 and 1.5 Hz, propenyl 3-H_{cis}), 4.66 (2H, app. dt, *J* 5.7 and 1.5 Hz, propenyl 1-H_2), 3.78 (2H, s, 2-H_2), 3.26 (2H, t, *J* 5.9 Hz, 6-H_2), 2.48-2.40 (5H, m, 5-H_2 and benzenesulfonyl CH_3); δ_C (100 MHz, $CDCl_3$): 169.9 (carboxylate C=O), 169.8 (C-4), 144.0 (benzenesulfonyl C-4), 133.6 (benzenesulfonyl C-1), 131.8 (propenyl C-2), 129.9 (benzenesulfonyl C_2-3,5), 127.7 (benzenesulfonyl C_2-2,6), 118.9 (propenyl C-3), 95.0 (C-3), 65.4 (propenyl C-1), 42.4 (C-2), 42.3 (C-6), 29.1 (C-5), 21.6 (benzenesulfonyl CH_3); HRMS found MNa^+ 360.0882. $C_{16}H_{19}NO_5S$ requires *MNa*, 360.0876. Compound existed only as *enol* tautomer.

1-Benzyl 3-prop-2-en-1-yl 4-hydroxy-1,2,5,6-tetrahydropyridine-1,3-dicarboxylate (63d)



Prepared according to General procedure A, 1-(benzyloxycarbonyl)-4-piperidinone (4.00 g, 17.2 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 10:90 to give the allyl ester derivative **63d**[67] (3.67 g, 67%, >95% enol by ^{1}H NMR) as a colourless oil. R_f 0.41 (EtOAc–hexane 20:80). δ_H (400 MHz, $CDCl_3$): 11.98 (1H, br. s, OH), 7.43-7.28 (5H, m, phenyl), 5.94 (1H, ddt, *J* 17.1, 10.8 and 5.6 Hz, propenyl 2-H), 5.33 (1H, app. d, *J* 17.1 Hz, propenyl 3-H_{trans}), 5.25 (1H, dd, *J* 10.8 and 1.2 Hz, propenyl 3-H_{cis}), 5.17 (2H, s, arylmethyl 1-H_2), 4.67 (2H, app. dt, *J* 5.6 and 1.2 Hz, propenyl 1-H_2), 4.18 (2H, s, 2-H_2), 3.65 (2H, t, *J* 5.9 Hz, 6-H_2), 2.39 (2H, app. br. s, 5-H_2); δ_C (100 MHz, $CDCl_3$): 170.2 (carboxylate C=O), 167.5 (C-4), 155.1 (Cbz C=O), 136.7 (phenyl C-1), 131.9 (propenyl C-2), 128.6 (phenyl C_2-3,5), 128.2 (phenyl C_2-2,6), 128.0 (phenyl C-4), 118.6 (propenyl C-3), 95.9 (C-3), 67.4 (arylmethyl C-1), 65.2 (propenyl C-1), 40.6 (C-2), 40.0 (C-6), 29.0 (C-5). All data consistent with known literature values.[67]

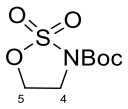
Prop-2-en-1-yl 4-oxooxolane-3-carboxylate (63c)



Prepared according to known literature procedure. Methyl glycolate (5.00 g, 55.5 mmol) was added dropwise to a suspension of NaH (2.90 g, 61.1 mmol, 60% in mineral oil) in Et_2O (100 ml) at rt. After allowing the mixture to stir for 1 h, the solvent was removed under reduced pressure and the crude material was dissolved in DMSO (100 ml). Allyl acrylate (7.25 ml, 61.1 mmol) was added dropwise at 0 ^oC and the reaction mixture was allowed to warm to rt and left to stir overnight. Then 1M HCl (50 ml) and Et_2O (100 ml) were added sequentially and the solution allowed to stir for a further 30 mins. Water (50 ml) was then added and the phases separated. The aqueous phase was extracted with Et_2O (3 x 70 ml), organic layers combined, washed with brine (70 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude material. This was then purified *via* column chromatography, eluting EtOAc–

hexane 10:90 → 20:80 to give the allyl ester derivative **63c**[67] (2.78 g, 30%) as a colourless oil. R_f 0.37 (EtOAc–hexane 30:70). δ_H (500 MHz, $CDCl_3$): 5.89 (1H, ddt, *J* 17.2, 10.5 and 5.7 Hz, propenyl 2-H), 5.34 (1H, app. dq, *J* 17.2 and 1.5 Hz, propenyl 3-H_{trans}), 5.26 (1H, app. dq, *J* 10.5 and 1.5 Hz, propenyl 3-H_{cis}), 4.70-4.61 (2H, m, propenyl 1-H_2), 4.52-4.41 (2H, m, 2-H_2), 4.03 (1H, d, *J* 17.1 Hz, 5-H_A), 3.95 (1H, d, *J* 17.1 Hz, 5-H_B), 3.53 (1H, t, *J* 8.3 Hz, 3-H); δ_C (125 MHz, $CDCl_3$): 207.3 (C-4), 166.3 (carboxylate C=O), 131.4 (propenyl C-2), 119.1 (propenyl C-3), 70.8 (C-5), 69.5 (C-2), 66.5 (propenyl C-1), 53.4 (C-3). All data is consistent with known literature values.[67]

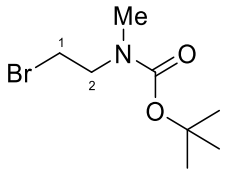
tert-butyl 1,2,3-oxathiazolidine-3-carboxylate-2,2-dioxide (81)



N-Boc-ethanolamine (3.00 g, 18.6 mmol) in DCM (10 ml) was added dropwise to a stirred solution of $SOCl_2$ (1.50 ml, 20.5 mmol), Et_3N (5.70 ml, 40.9 mmol) and imidazole (5.07 g, 74.4 mmol) in DCM (91 ml) at −60 °C and the resulting solution was stirred at −60 °C for 3 hours until completion was indicated by TLC. The reaction mixture was warmed to room temperature, quenched by addition of water (50 ml), phases separated, organic phase washed with brine (20 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude cyclic sulfamidite. The crude cyclic sulfamidite was dissolved in MeCN (70 ml) and cooled to 0 °C. $NaIO_4$ (6.20g, 28.0 mmol), $RuCl_3{\cdot}3H_2O$ (20.0 mg, 0.10 mol%) and water (70 ml) were added sequentially, with the resulting solution was stirred at 0 °C until completion was indicated by TLC. The cold reaction mixture was diluted with water (70 ml), warmed to room temperature and extracted with Et_2O (3 x 30 ml). The organic layers were combined, washed with brine (20 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give cyclic sulfamidate **81**[77] (4.06 g, 98%) as a white powder. δ_H (300 MHz, $CDCl_3$): 4.63 (2H, t, *J* 6.5 Hz, 5-H_2), 4.06 (2H, t, *J* 6.5 Hz, 4-H_2), 1.57 (9H, s, ^{t}Bu); δ_C

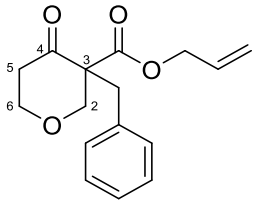
(100 MHz, $CDCl_3$): 148.7 (C=O), 85.6 (C_1 ^{t}Bu), 65.5 (C-5), 45.3 (C-4), 27.9 (C_3 ^{t}Bu). All data consistent with known literature values.[77]

2-[*N*-(*tert*-butyloxycarbonyl)-*N*-methylamino]bromoethane (83)



To a solution of *N*-Boc-*N*-methylethanolamine (4.00 g, 22.9 mmol) in THF (90 ml) were added CBr_4 (11.4 g, 34.3 mmol) and PPh_3 (9.00 g, 34.3 mmol). The mixture was subsequently stirred at room temperature for 1 h. After filtration and washing the filter cake with THF (2 x 10 ml), the filtrate was evaporated under reduced pressure and purified *via* column chromatography, eluting EtOAc−hexane 10:90 to give alkyl bromide **83**[78] (3.98 g, 73%) as a colourless oil. δ_H (300 MHz, $CDCl_3$): 3.60 (2H, app. q, *J* 6.8 Hz, 2-H_2), 3.45 (2H, t, *J* 6.8 Hz, 1-H_2), 2.92 (3H, s, NMe), 1.46 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$): 158.9 (Boc C=O), 79.9 (^{t}Bu C_1), 50.7 (C-2), 31.1 (NMe), 29.2 (C-1), 28.4 (^{t}Bu C_3). All data consistent with known literature values.[78]

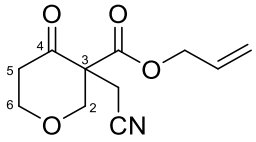
3-prop-2-en-1-yl 3-benzyl-4-oxooxane-1,3-dicarboxylate (84c)



Prepared according to an adapted General procedure B, the allyl ester derivative **63a** (3.00 g, 16.2 mmol), K_2CO_3 (8.90 g, 64.8 mmol) and benzyl bromide (3.86 ml, 32.4 mmol) were stirred in acetone (0.26 M) at 70 ^{o}C for 2 h and this gave a crude material.

This was then purified *via* column chromatography, eluting EtOAc−hexane 20:80 to give the *quaternary allyl ester derivative* ***84c*** (2.22 g, 50%) as a colourless oil. R_f 0.66 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3064, 3030, 2858, 1714, 1649, 1496, 1215, 1168, 1116; δ_H (300 MHz, $CDCl_3$): 7.34-7.16 (5H, m, phenyl), 5.81 (1H, ddt, *J* 16.2, 10.7 and 5.9 Hz, propenyl 2-H), 5.34-5.21 (2H, m, propenyl 3-H_2), 4.57 (2H, app. dt, *J* 5.9 and 1.4 Hz, propenyl 1-H_2), 4.50 (1H, d, *J* 11.7 Hz, 2-H_A), 4.27-4.16 (1H, m, 6-H_A), 3.75 (1H, td, *J* 11.1 and 3.4 Hz, 6-H_B), 3.50 (1H, d, *J* 11.7 Hz, 2-H_B), 3.32 (1H, d, *J* 14.1 Hz, arylmethyl 1-H_A), 2.96 (1H, d, *J* 14.1 Hz, arylmethyl 1-H_B), 2.84 (1H, ddd, *J* 14.3, 10.9 and 6.3 Hz, 5-H_A), 2.55 (1H, dt, *J* 14.3 and 3.4 Hz, 5-H_B); δ_C (100 MHz, $CDCl_3$): 202.8 (C-4), 169.4 (carboxylate C=O), 135.4 (phenyl C-1), 131.2 (propenyl C-2), 130.4 (phenyl C_2-2,6), 128.3 (phenyl C_2-3,5), 127.0 (phenyl C-4), 119.1 (propenyl C-3), 74.0 (C-2), 68.7 (C-6), 66.1 (propenyl C-1), 63.9 (C-3), 41.7 (C-5), 36.1 (arylmethyl C-1); HMRS found MNa$^+$ 297.1107. $C_{16}H_{18}O_4$ requires *MNa*, 297.1097.

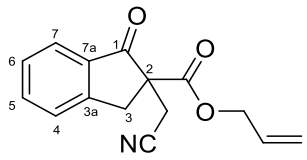
Prop-2-en-1-yl 3-(cyanomethyl)-4-oxooxane-3-carboxylate (84d)



Prepared according to General procedure B, the allyl ester derivative **63a** (2.50 g, 13.5 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc−hexane 25:75 to give the *quaternary allyl ester derivative* ***84d*** (1.95 g, 65%) as a pale-yellow oil. R_f 0.59 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2965, 2929, 2848, 2240, 1719, 1650, 1496, 1427, 1254, 1176, 1099; δ_H (300 MHz, $CDCl_3$): 5.92 (1H, ddt, *J* 17.1, 10.6 and 5.8 Hz, propenyl 2-H), 5.38 (1H, app. dq, *J* 17.1 and 1.4 Hz, propenyl 3-H_{trans}), 5.31 (1H, app. dq, *J* 10.6 and 1.4 Hz, propenyl 3-H_{cis}), 4.75-4.70 (2H, m, propenyl 1-H_2), 4.64 (1H, app. dd, *J* 11.7 and 1.4 Hz, 2-H_A), 4.33-4.24 (1H, m, 6-H_A), 3.77 (1H, td, *J* 11.5 and 3.4 Hz, 6-H_B), 3.66 (1H, d, *J* 11.7 Hz, 2-H_B), 2.99 (1H, ddd, *J* 15.0, 11.5 and 7.4 Hz, 5-H_A), 2.83 (1H, d, *J* 16.9 Hz, cyanomethyl 1-H_A), 2.73 (1H, d, *J* 16.9 Hz, cyanomethyl 1-H_B), 2.56 (1H, dt, *J* 15.0, and 3.4 Hz, 5-H_B); δ_C (100 MHz,

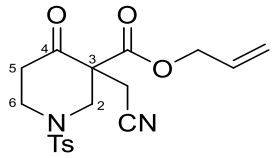
$CDCl_3$): 200.1 (C-4), 168.0 (carboxylate C=O), 130.6 (propenyl C-2), 120.0 (propenyl C-3), 115.5 (CN), 73.5 (C-2), 68.7 (C-6), 67.3 (propenyl C-1), 59.2 (C-3), 40.8 (C-5), 19.0 (cyanomethyl C-1). HMRS found MNa^+ 246.0728. $C_{11}H_{13}NO_4$ requires *MNa*, 246.0737.

Prop-2-en-1-yl 2-(cyanomethyl)-1-oxo-3*H*-indene-2-carboxylate (86a)



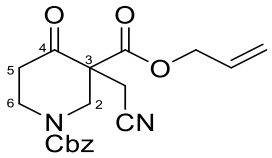
Prepared according to General procedure B, the allyl ester derivative **63b** (3.50 g, 16.2 mmol) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give the *quaternary allyl ester derivative* ***86a*** (3.10 g, 75%) as a yellow oil. R_f 0.41 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 2942, 2248, 1738, 1709, 1606, 1589, 1465, 1435, 1415, 1360, 1233, 1212, 1183, 1155, 1066; δ_H (400 MHz, $CDCl_3$): 7.82 (1H, d, *J* 7.7 Hz, 7-H), 7.70 (1H, td, *J* 7.7 and 1.1 Hz, 5-H), 7.55 (1H, d, *J* 7.7 Hz, 4-H), 7.46 (1H, app. t, *J* 7.7 Hz, 6-H), 5.80 (1H, ddt, *J* 17.6, 10.2 and 5.6 Hz, propenyl 2-H), 5.22-5.15 (2H, m, propenyl 3-H_2), 4.62 (2H, app. dt, *J* 5.6 and 1.4 Hz, propenyl 1-H_2), 3.81 (1H, d, *J* 17.5 Hz, 3-H_A), 3.34 (1H, d, *J* 17.5 Hz, 3-H_B), 3.23 (1H, d, *J* 16.9 Hz, cyanomethyl 1-H_A), 2.86 (1H, d, *J* 16.9 Hz, cyanomethyl 1-H_B); δ_C (100 MHz, $CDCl_3$): 199.0 (C-1), 168.6 (carboxylate C=O), 152.6 (C-3a), 136.5 (C-5), 134.1 (C-7a), 131.0 (propenyl C-2), 128.6 (C-6), 126.7 (C-4), 125.6 (C-7), 119.1 (propenyl C-3), 116.8 (CN), 67.0 (propenyl C-1), 57.2 (C-2), 37.2 (C-3), 22.7 (cyanomethyl C-1); HRMS found MNa^+ 278.0798. $C_{15}H_{13}NO_3$ requires *MNa*, 278.0788.

Prop-2-en-1-yl 3-(cyanomethyl)-1-(4-methylbenzenesulfonyl)-4-oxopiperidine-3-carboxylate (86d)



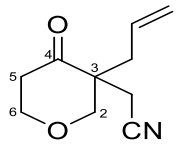
Prepared according to General procedure B, the allyl ester derivative **63f** (4.10 g, 12.5 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give the *quaternary allyl ester derivative* ***86d*** (3.06 g, 65%) as a colourless oil. R_f 0.15 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 2935, 2856, 2249, 1723, 1650, 1494, 1450, 1361, 1341, 1290, 1208, 1119, 1091; δ_H (400 MHz, $CDCl_3$): 7.66 (2H, d, *J* 8.2 Hz, benzenesulfonyl 2,6-H), 7.35 (2H, d, *J* 8.2 Hz, benzenesulfonyl 3,5-H), 5.94 (1H, ddt, *J* 16.6, 10.5 and 6.0 Hz, propenyl 2-H), 5.39 (1H, app. dq, *J* 16.6 and 1.4 Hz, propenyl 3-H_{trans}), 5.32 (1H, app. dq, *J* 10.5 and 1.4 Hz, propenyl 3-H_{cis}), 4.73 (2H, app. dt, *J* 6.0 and 1.4 Hz, propenyl 1-H_2), 4.42 (1H, app. dd, *J* 12.2 and 2.6 Hz, 2-H_A), 3.99-3.92 (1H, m, 6-H_A), 3.04 (1H, ddd, *J* 15.1, 11.7 and 7.1 Hz, 5-H_A), 2.90 (1H, d, *J* 16.9 Hz, cyanomethyl 1-H_A), 2.85-2.77 (2H, m, 2-H_B and 6-H_B), 2.73 (1H, d, *J* 16.9 Hz, cyanomethyl 1-H_B), 2.58 (1H, dt, *J* 15.1 and 3.3 Hz, 5-H_B), 2.44 (3H, s, benzenesulfonyl CH_3); δ_C (100 MHz, $CDCl_3$): 199.9 (C-4), 167.5 (carboxylate C=O), 144.7 (benzenesulfonyl C-4), 133.0 (benzenesulfonyl C-1), 130.7 (propenyl C-2), 130.3 (benzenesulfonyl C_2-3,5), 127.6 (benzenesulfonyl C_2-2,6), 120.4 (propenyl C-3), 115.5 (CN), 67.8 (propenyl C-1), 58.1 (C-3), 52.6 (C-2), 46.3 (C-6), 39.2 (C-5), 21.7 (benzenesulfonyl CH_3), 20.2 (cyanomethyl C-1); HRMS found MNa^+ 399.0991. $C_{18}H_{20}N_2O_5S$ requires *MNa*, 399.0985.

1-benzyl 3-prop-2-en-1-yl 3-(cyanomethyl)-4-oxopiperidine-1,3-dicarboxylate (86c)



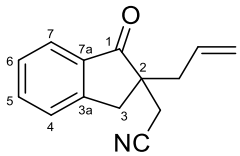
Prepared according to General procedure B, the allyl ester derivative **63d** (1.30 g, 4.10 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 30:70 to give the *quaternary allyl ester derivative* ***86c*** (0.93 g, 64%) as a yellow oil. R_f 0.34 (EtOAc–hexane 40:60). ν_{max}/cm^{-1}: 3032, 2944, 2249, 1697, 1429, 1365, 1227, 1126, 1057; δ_H (500 MHz, $CDCl_3$, unresolved peaks due to rotamers): 7.40-7.32 (5H, m, phenyl), 5.80 (1H, app. br. s, propenyl 2-H), 5.34-5.24 (2H, m, propenyl 3-H_2), 5.17 (2H, s, arylmethyl 1-H_2), 4.88-4.80 (1H, m, 2-H_A), 4.65-4.35 (3H, m, propenyl 1-H_2 and 6-H_A), 3.38-3.32 (2H, m, 2-H_B and 6-H_B), 3.01-2.82 (2H, m, 5-H_A and cyanomethyl 1-H_A), 2.78 (1H, d, *J* 16.9 Hz, cyanomethyl 1-H_B), 2.56 (1H, app. d, 15.1 Hz, 5-H_B); δ_C (125 MHz, $CDCl_3$, rotamers): 207.4 (C-4^{rotA}), 201.0 (C-4^{rotB}), 171.3 (carboxylate C=O^{rotA}), 167.5 (carboxylate C=O^{rotB}), 155.2 (Cbz C=O^{rotA}), 154.9 (Cbz C=O^{rotB}), 136.4 (phenyl C-1^{rotA}), 136.1 (phenyl C-1^{rotB}), 130.5 (propenyl C-2), 128.8 (phenyl C_2-3,5), 128.5 (phenyl C_2-2,6), 128.3 (phenyl C-4^{rotA}), 128.2 (phenyl C-4^{rotB}), 120.4 (propenyl C-3), 115.9 (CN), 68.2 (arylmethyl C-1), 67.8 (propenyl C-1^{rotA}), 67.6 (propenyl C-1^{rotB}), 58.1 (C-3), 50.3 (C-2), 43.6 (C-6^{rotA}), 43.3 (C-6^{rotB}), 41.2 (C-5^{rotA}), 39.5 (C-5^{rotB}), 20.2 (cyanomethyl C-1); HRMS found MNa^+ 379.1267. $C_{19}H_{20}N_2O_5$ requires *MNa*, 379.1264.

2-[4-oxo-3-(prop-2-en-1-yl)oxan-3-yl]acetonitrile (88a)



Prepared according to General procedure C, the quaternary allyl ester derivative **84d** (1.20 g, 5.38 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc−hexane 20:80 to give the *ketone derivative* ***88a*** (0.72 g, 75%) as a light brown oil. R_f 0.63 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3080, 2965, 2850, 2245, 1711, 1640, 1470, 1366, 1213, 1126, 1058; δ_H (300 MHz, $CDCl_3$): 5.54 (1H, ddt, *J* 17.6, 10.4 and 7.3 Hz, propenyl 2-H), 5.28-5.14 (2H, m, propenyl 3-H_2), 4.34-4.20 (1H, m, 6-H_A), 4.04 (1H, app. dd, *J* 11.6 and 1.3 Hz, 2-H_A), 3.75 (1H, td, *J* 11.4 and 3.4 Hz, 6-H_B), 3.60 (1H, d, *J* 11.6 Hz, 2-H_B), 2.90-2.74 (2H, m, propenyl 1-H_2), 2.58 (1H, d, *J* 17.2 Hz, cyanomethyl 1-H_A) 2.54-2.36 (3H, m, cyanomethyl 1-H_B and 5-H_2); δ_C (100 MHz, $CDCl_3$): 206.2 (C-4), 130.3 (propenyl C-2), 120.9 (propenyl C-3), 116.7 (CN), 74.6 (C-2), 68.7 (C-6), 51.9 (C-3), 39.6 (C-5), 37.8 (propenyl C-1), 19.7 (cyanomethyl C-1). HMRS found MH^+ 180.1017. $C_{10}H_{13}NO_2$ requires *MH*, 180.1019.

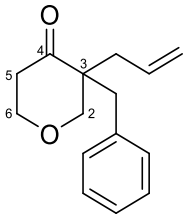
2-[1-oxo-2-(prop-2-en-1-yl)-3*H*-inden-2-yl]acetonitrile (88c)



Prepared according to General procedure C, the quaternary allyl ester derivative **86a** (5.00 g, 19.6 mmol) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 15:85 to give the *ketone derivative* ***88c*** (3.48 g, 84%) as a yellow oil. R_f 0.45 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 2921, 2246, 1709,

1608, 1512, 1465, 1415, 1282, 1209, 1187, 1111, 1072; δ_H (400 MHz, $CDCl_3$): 7.78 (1H, d, *J* 7.7 Hz, 7-H), 7.65 (1H, td, *J* 7.7 and 1.1 Hz, 5-H), 7.48 (1H, d, *J* 7.7 Hz, 4-H), 7.42 (1H, t, *J* 7.7 Hz, 6-H), 5.58 (1H, ddt, *J* 16.9, 10.2 and 6.2 Hz, propenyl 2-H), 5.17 (1H, dd, *J* 16.9 and 1.4 Hz, propenyl 3-H_{trans}), 5.11-5.05 (1H, m, propenyl 3-H_{cis}), 3.25 (1H, d, *J* 17.4 Hz, 3-H_A), 3.19 (1H, d, *J* 17.4 Hz, 3-H_B), 2.70 (1H, d, *J* 16.8 Hz, cyanomethyl 1-H_A), 2.57 (1H, d, *J* 16.8 Hz, cyanomethyl 1-H_B), 2.51 (1H, dd, *J* 13.7 and 6.2 Hz, propenyl 1-H_B), 2.44 (1H, dd, *J* 13.7 and 7.8 Hz, propenyl 1-H_B); δ_C (100 MHz, $CDCl_3$): 206.2 (C-1), 151.9 (C-3a), 136.0 (C-5), 135.2 (C-7a), 131.5 (propenyl C-2), 128.3 (C-6), 126.8 (C-4), 124.8 (C-7), 120.5 (propenyl C-3), 117.4 (CN), 49.9 (C-2), 41.4 (propenyl C-1), 37.3 (C-3), 24.9 (cyanomethyl C-1); HRMS found MNa^+ 234.0897. $C_{14}H_{13}NO$ requires *MNa*, 234.0889.

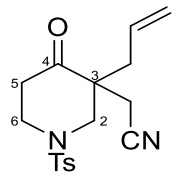
3-benzyl-3-(prop-2-en-1-yl)oxan-4-one (88b)



Prepared according to General procedure C, the quaternary allyl ester derivative **84c** (1.00 g, 3.65 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc−hexane 20:80 to give the *ketone derivative* ***88b*** (0.65 g, 77%) as a yellow-brown oil. R_f 0.78 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3064, 2951, 1717, 1524, 1454, 1400, 1171; δ_H (300 MHz, $CDCl_3$): 7.32-7.21 (3H, m, phenyl 3,4,5-H), 7.13 (2H, dd, *J* 6.9 and 1.8 Hz, phenyl 2,6-H), 5.74 (1H, ddt, *J* 17.6, 10.4 and 7.3 Hz, propenyl 2-H), 5.16-5.05 (2H, m, propenyl 3-H_2), 4.05-3.87 (2H, m, 6-H_2), 3.70 (1H, d, *J* 11.8 Hz, 2-H_A), 3.64 (1H, d, *J* 11.8 Hz, 2-H_B), 3.02 (1H, d, *J* 14.0 Hz, arylmethyl 1-H_A), 2.96 (1H, d, *J* 14.0, arylmethyl 1-H_B), 2.70-2.51 (2H, m, 5-H_2), 2.06 (2H, app. d, *J* 7.3 Hz, propenyl 1-H_2); δ_C (100 MHz, $CDCl_3$): 209.4 (C-4), 136.4 (phenyl C-1), 134.0 (propenyl C-2), 133.0 (phenyl C_2-3,5), 128.3 (phenyl C_2-2,6), 126.7 (phenyl C-4), 118.7 (propenyl C-3), 74.6 (C-2), 68.3 (C-6), 54.2 (C-3), 40.1 (arylmethyl

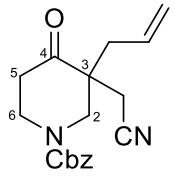
C-1), 38.5 (C-5), 36.9 (propenyl C-1); HMRS found MH^+ 231.1371. $C_{15}H_{18}O_2$ requires *MH*, 231.1380.

2-[1-(4-methylbenzenesulfonyl)-4-oxo-3-(prop-2-en-1-yl)piperidin-3-yl]acetonitrile (88e)



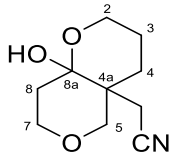
Prepared according to General procedure C, the quaternary allyl ester derivative **86d** (1.10 g, 3.00 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 15:85 to give the *ketone derivative* ***88e*** (0.70 g, 71%) as a colourless oil. R_f 0.26 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 2927, 2856, 2246, 1717, 1493, 1468, 1362, 1213, 1163, 1091, 1042; δ_H (400 MHz, $CDCl_3$): 7.66 (2H, d, *J* 8.3 Hz, benzenesulfonyl 2,6-H), 7.36 (2H, d, *J* 8.3 Hz, benzenesulfonyl 3,5-H), 5.57 (1H, ddt, *J* 17.2, 10.0 and 7.5 Hz, propenyl 2-H), 5.26 (1H, app. dq, *J* 17.2 and 1.3 Hz, propenyl 3-H_{trans}), 5.25-5.21 (1H, m, propenyl 3-H_{cis}), 4.06-3.99 (1H, m, 6-H_A), 3.87 (1H, app. dd, *J* 12.1 and 2.7 Hz, 2-H_A), 2.88-2.72 (2H, m, 6-H_B and propenyl 1-H_A), 2.67 (1H, d, *J* 12.1 Hz, 2-H_B), 2.64-2.56 (1H, m, propenyl 1-H_B), 2.55 (1H, d, *J* 16.9 Hz, cyanomethyl 1-H_A), 2.51-2.42 (6H, m, cyanomethyl 1-H_B, 5-H_2 and benzenesulfonyl CH_3); δ_C (100 MHz, $CDCl_3$): 205.6 (C-4), 144.6 (benzenesulfonyl C-4), 133.0 (benzenesulfonyl C-1), 130.3 (benzenesulfonyl C_2-3,5), 129.7 (propenyl C-2), 127.6 (benzenesulfonyl C_2-2,6), 121.8 (propenyl C-3), 116.7 (CN), 53.4 (C-2), 51.0 (C-3), 46.5 (C-6), 38.4 (propenyl C-1), 37.9 (C-5), 21.7 (benzenesulfonyl CH_3), 21.1 (cyanomethyl C-1); HRMS found MNa^+ 355.1089. $C_{17}H_{20}N_2O_3S$ requires *MNa*, 355.1087.

Benzyl 3-(cyanomethyl)-4-oxo-3-(prop-2-en-1-yl)piperidine-1-carboxylate (88d)



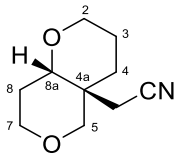
Prepared according to General procedure C, the quaternary allyl ester derivative **86c** (1.50 g, 4.21 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give the *ketone derivative* ***88d*** (0.90 g, 69%, *rotamers* 53:47 by ^{1}H NMR) as a colourless oil. R_f 0.36 (EtOAc–hexane 40:60). ν_{max}/cm^{-1}: 3033, 2916, 2245, 1694, 1430, 1226, 1122, 1079; δ_H (500 MHz, $CDCl_3$): 7.40-7.32 (10H, m, phenyl), 5.60-5.41 (2H, m, propenyl 2-H), 5.24-5.13 (8H, m, propenyl 3-H_2 and arylmethyl 1-H_2), 4.44 (1H, app. br. s, 6-H_A^{min}), 4.39-4.25 (2H, m, 2-H_A), 3.94-3.78 (1H, m, 6-H_A^{maj}), 3.58-3.47 (1H, m, 6-H_B^{maj}), 3.33-3.25 (1H, app. br. s, 6-H_B^{min}) 3.20 (2H, app. d, *J* 13.6 Hz, 2-H_B), 2.73-2.63 (2H, m, propenyl 1-H_A), 2.54-2.35 (10H, m, propenyl 1-H_B, cyanomethyl 1-H_2 and 5-H_2); δ_C (125 MHz, $CDCl_3$): 206.9 (C-4), 155.3 (Cbz C=O^{maj}), 155.2 (Cbz C=O^{min}), 136.5 (phenyl C-1^{min}), 136.1 (phenyl C-1^{maj}), 130.0 (propenyl C-2), 128.8 (phenyl C_2-3,5^{maj}), 128.7 (phenyl C_2-3,5^{min}), 128.6 (phenyl C_2-2,6^{maj}), 128.4 (phenyl C_2-2,6^{maj}), 128.2 (phenyl C-4^{min}), 128.1 (phenyl C-4^{maj}), 121.3 (propenyl C-3), 116.9 (CN), 68.1 (arylmethyl C-1^{maj}), 67.7 (arylmethyl C-1^{min}), 51.1 (C-2), 47.2 (C-3), 43.9 (C-6^{min}), 42.5 (C-6^{maj}), 38.3 (propenyl C-1), 38.1 (C-5), 21.0 (cyanomethyl C-1); HRMS found MNa$^+$ 335.1359. $C_{18}H_{20}N_2O_3$ requires *MNa*, 335.1366.

2-{8a-hydroxy-hexahydropyrano[4,3-*b*]pyran-4a-yl}acetonitrile (89a)



Prepared according to General procedure D, the ketone derivative **88a** (0.20 g, 1.12 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc−hexane 40:60 to give the *hemiacetal derivative* ***89a*** (0.15 g, 70%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil that solidified to a white solid upon drying. R_f 0.40 (50:50 EtOAc−hexane). ν_{max}/cm^{-1}: 3404, 2957, 2887, 2254, 1470, 1289, 1158, 1065; δ_H (400 MHz, $CDCl_3$): 4.02 (1H, td, *J* 11.7 and 3.0 Hz, 2-H_A), 3.88 (1H, app. dd, *J* 11.9 and 1.7 Hz, 5-H_A), 3.84 (1H, app. tt, *J* 5.5 and 1.2 Hz, 7-H_A), 3.75-3.57 (3H, m, 7-H_B, 2-H_B and 5-H_B), 2.87 (1H, d, *J* 16.7, cyanomethyl 1-H_A), 2.62 (1H, app. dd, *J* 16.7 and 1.7 Hz, cyanomethyl 1-H_B), 2.05-1.75 (3H, m, 8-H_A and 3-H_2), 1.65 (1H, app. d, *J* 13.5 Hz, 8-H_B), 1.60-1.44 (2H, m, 4-H_2); δ_C (100 MHz, $CDCl_3$): 118.0 (CN), 94.6 (C-8a), 69.6 (C-5), 65.9 (C-7), 60.4 (C-2), 39.3 (C-4a), 36.5 (C-8), 25.6 (C-4), 22.6 (C-3), 21.3 (cyanomethyl C-1); HMRS found MNa^+ 220.0945. $C_{10}H_{15}NO_3$ requires *MNa*, 220.0944.

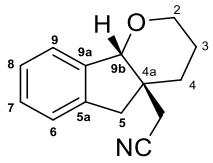
2-[(4a*R,8a*R**)-hexahydro-*2H*-pyrano[4,3-*b*]pyran-4a-yl]acetonitrile (90a)**



Prepared according to General procedure E, the hemiacetal derivative **89a** (0.10 g, 0.51 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc−hexane 35:65 to give the *fused-ring ether derivative* ***90a*** (73.0 mg, 80%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.31 (35:65 EtOAc−hexane). ν_{max}/cm^{-1}: 2966, 2929, 2848, 2238, 1470, 1335, 1256, 1100; δ_H (400 MHz, $CDCl_3$): 4.02 (1H, app. dd, *J* 11.4 and 4.0 Hz, 2-H_A), 3.97 (1H, d, *J* 11.7 Hz, 5-H_A), 3.74-3.62 (2H, m, 7-H_2), 3.53 (1H, app. t, *J* 3.7 Hz, 8a-H), 3.43 (1H, td, *J* 11.4 and 2.5 Hz, 2-H_B), 3.28 (1H, d, *J* 11.7 Hz, 5-H_B), 2.61 (1H, d, *J* 16.9 Hz, cyanomethyl 1-H_A), 2.52 (1H, d, *J* 16.9 Hz, cyanomethyl 1-H_B), 1.96-1.87 (1H, m, 8-H_A), 1.85-1.72 (1H, m, 3-H_A), 1.66-1.55 (3H, m, 8-H_B and 4-H_2), 1.48 (1H, app. dt, *J* 13.5 and 2.1 Hz, 3-H_B); δ_C (100 MHz, $CDCl_3$):

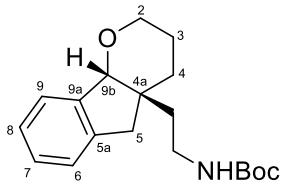
117.3 (CN), 74.7 (C-8a), 68.2 (C-5), 67.8 (C-2), 63.3 (C-7), 35.0 (C-4a), 30.2 (C-3), 28.08 (C-8), 25.1 (cyanomethyl C-1), 22.2 (C-4); HMRS found MNa^+ 204.0994. $C_{10}H_{15}NO_2$ requires *MNa*, 204.0995. The relative configuration was determined using NOESY (500 MHz, $CDCl_3$), nOe observed between 8a-H and cyanomethyl 1-H_A, 8a-H and cyanomethyl 1-H_B.

2-[(4a*R,9b*R**)-2*H*,3*H*,4*H*,5*H*,9b*H*-indeno[1,2-*b*]pyran-4a-yl]acetonitrile (90b)**



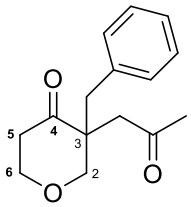
Prepared according to General procedure D, the ketone derivative **88c** (2.34 g, 11.1 mmol) gave a crude hemiacetal intermediate. Then Et_3SiH (16.0 eq) was added dropwise to a solution of the crude hemiacetal derivative (1.00 eq) in DCM (16 mM) at rt. The mixture was cooled to –78 °C and BF_3•Et_2O (4.00 eq) was added dropwise. After stirring the reaction mixture at –78 °C for 2 h, it was allowed to warm to rt and stirred overnight. The solvent was removed under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give the *fused-ring ether derivative* ***90b*** (1.61 g, 68%, *dr* >95:<5 by ^{1}H NMR) as a colourless solid. R_f 0.19 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3023, 2946, 2876, 2240, 1460, 1444, 1337, 1296, 1248, 1190, 1121, 1020; δ_H (400 MHz, MeOD): 7.40-7.35 (1H, m, 9-H), 7.27-7.18 (3H, m, 6-H, 7-H and 8-H), 4.83 (1H, s, 9b-H), 3.55 (2H, app. t, *J* 6.3 Hz, 2-H_2), 3.00 (1H, d, *J* 16.0 Hz, 5-H_A), 2.80 (1H, d, *J* 16.0 Hz, 5-H_B), 2.54 (2H, app. s, cyanomethyl 1-H_2), 1.80-1.65 (2H, m, 4-H_2), 1.64-1.45 (2H, m, 3-H_2); δ_C (100 MHz, MeOD): 144.9 (C-9a), 141.8 (C-5a), 129.6 (C-7), 128.1 (C-8), 126.0 (C_2-6,9), 119.6 (CN), 81.4 (C-9b), 63.5 (C-2), 49.9 (C-4a), 41.6 (C-5), 30.1 (C-4), 28.8 (C-3), 25.7 (cyanomethyl C-1); HRMS found MH^+ 214.1231. $C_{14}H_{15}NO$ requires *MH*, 214.1226. The relative configuration was determined using NOESY (500 MHz, $CDCl_3$), nOe observed between 9b-H and cyanomethyl 1-H_2.

tert-butyl _N_-{2-[(4a_R_*,9b_R_*)-2_H_,3_H_,4_H_,5_H_,9b_H_-indeno[1,2-_b_]pyran-4a-yl]ethyl}carbamate (91)



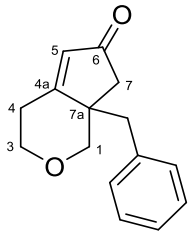
Prepared according to General procedure F, the fused-ring ether derivative **90b** (1.10 g, 5.20 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–cyclohexane 25:75 to give the *protected amine derivative* ***91*** (0.93 g, 57%) as a pale-yellow oil. R_f 0.31 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 3401, 2977, 2933, 1688, 1514, 1458, 1393, 1367, 1277, 1251, 1157, 1100, 1040; δ_H (500 MHz, $CDCl_3$): 7.36-7.30 (1H, m, 9-H), 7.23-7.11 (3H, m, 6-H, 7-H and 8-H), 4.89 (1H, s, 9b-H), 4.74 (1H, br. s, NH), 4.00 (2H, app. t, *J* 6.1 Hz, 2-H_2), 3.24-3.14 (2H, m, ethylcarbamate 2-H_2), 2.84 (1H, d, *J* 16.0 Hz, 5-H_A), 2.65 (1H, d, *J* 16.0 Hz, 5-H_B), 1.77-1.54 (5H, 4-H_2, ethylcarbamate 1-H_2 and 3-H_A), 1.46 (10H, app. s, 3-H_B and ^{t}Bu); δ_C (125 MHz, $CDCl_3$): 153.7 (C=O), 144.4 (C-9a), 141.0 (C-5a), 128.5 (C-7), 127.0 (C-8), 125.0 (C-9), 124.3 (C-6), 82.1 (C-9b), 82.0 (C_1 ^{t}Bu), 67.7 (C-2), 49.4 (C-4a), 41.8 (C-5), 38.0 (ethylcarbamate C-2), 28.6 (C-4), 27.9 (C_3 ^{t}Bu), 27.5 (C-3), 24.2 (ethylcarbamate C-1); HRMS found MH$^+$ 318.2060. $C_{19}H_{27}NO_3$ requires *MH*, 318.2064.

3-benzyl-3-(2-oxopropyl)oxan-4-one (92)



Prepared according to an adapted procedure[82], to a stirred solution of ketone derivative **88b** (0.60 g, 2.60 mmol) in MeCN (18 ml) and H_2O (3 ml) were added $Pd(OAc)_2$ (30.0 mg, 5 mol%) and Dess-Martin periodinane (1.33 g, 3.13 mmol) at room temperature. The reaction was warmed to 50 ^oC and stirred for 6 h. The mixture was then extracted with EtOAc (3 x 20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc−hexane 15:85 to give the *methyl ketone derivative* ***92*** (0.58 g, 91%) as a yellow oil. R_f 0.39 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2943, 2831, 1748, 1667, 1496, 1370, 1289, 1223, 1142, 1025; δ_H (300 MHz, $CDCl_3$): 7.35-7.15 (3H, m, phenyl 3,4,5-H), 7.11 (2H, m, phenyl 2,6-H), 4.27-4.16 (1H, m, 6-H_A), 3.96 (1H, td, *J* 11.1 and 3.7 Hz, 6-H_B), 3.80 (1H, d, *J* 11.6 Hz, 2-H_A), 3.74 (1H, d, *J* 11.6 Hz, 2-H_B), 3.08 (1H, d, *J* 13.4 Hz, arylmethyl 1-H_A), 2.99 (1H, d, *J* 18.6 Hz, oxopropyl 1-H_A), 2.88-2.71 (2H, m, arylmethyl 1-H_B and 5-H_A), 2.47 (1H, ddd, *J* 9.8, 5.4 and 3.1 Hz, 5-H_B), 2.17 (1H, d, *J* 18.6 Hz, oxopropyl 1-H_B), 2.06 (3H, s, oxopropyl 3-H_3); δ_C (100 MHz, $CDCl_3$): 209.4 (oxopropyl C-2), 206.2 (C-4), 135.8 (phenyl C-1), 130.6 (phenyl C_2-2,6), 128.4 (phenyl C_2-3,5), 127.0 (phenyl C-4), 72.2 (C-2), 67.8 (C-6), 52.4 (C-3), 45.4 (oxopropyl C-1), 40.4 (arylmethyl C-1), 39.2 (C-5), 30.6 (oxopropyl C-3). HMRS found MNa^+ 269.1141. $C_{15}H_{18}O_3$ requires *MNa*, 269.1148.

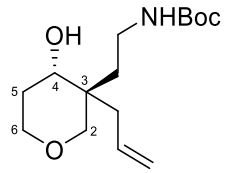
7a-benzyl-1*H*,3*H*,4*H*,7*H*-cyclopenta[*c*]pyran-6-one (93)



Methyl ketone derivative **92** (0.60 g, 2.40 mmol) was dissolved in EtOH (15 ml) and 10% aq. KOH solution (approx. 3 ml) was added until the solution turned a light brown colour. This was then stirred and heated at reflux temperature for 18 h. Brine (20 ml) was then added to the solution, the phases were separated and the aqueous phase

extracted with Et_2O (3 x 10 ml). The organic layers were then combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc−hexane 30:70 to give the *cyclised enone derivative* ***93*** (0.39 g, 71%) as a white solid. R_f 0.45 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3051, 2985, 1748, 1496, 1408, 1290, 1108, 1080; δ_H (300 MHz, $CDCl_3$): 7.32-7.20 (3H, m, phenyl 3,4,5-H), 7.14 (2H, d, *J* 7.1 Hz, phenyl 2,6-H), 5.89 (1H, d, *J* 1.5 Hz, 5-H), 4.36 (1H, app. dd, *J* 10.9 and 6.7 Hz, 3-H_A), 4.10 (1H, d, *J* 11.1 Hz, 1-H_A), 3.50 (1H, m, 3-H_B), 3.20-3.13 (2H, m, 1-H_B and arylmethyl 1-H_A), 2.93 (1H, d, *J* 13.4 Hz, arylmethyl 1-H_B), 2.68 (2H, app. dd, *J* 13.9 and 2.3 Hz, 4-H_2), 2.44 (1H, d, *J* 18.7 Hz, 7-H_A), 1.78 (1H, d, *J* 18.7 Hz, 7-H_B); δ_C (100 MHz, $CDCl_3$): 206.1 (C-6), 181.5 (C-4a), 136.9 (phenyl C-1), 130.2 (phenyl C_2-2,6), 128.4 (phenyl C_2-3,5), 128.2 (C-5), 126.9 (phenyl C-4), 76.6 (C-1), 69.2 (C-3), 48.9 (C-7a), 42.9 (C-7), 40.2 (arylmethyl C-1), 29.7 (C-4). HMRS found MNa^+ 251.1054. $C_{15}H_{16}O_2$ requires *MNa*, 251.1043.

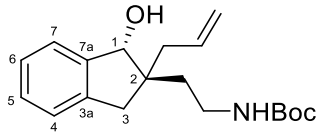
tert-butyl _N_-{2-[(_3R*_,_4R*_)-4-hydroxy-3-(prop-2-en-1-yl)oxan-3-yl]ethyl}carbamate (94a)



Prepared according to General procedure F, the ketone derivative **88a** (1.30 g, 7.30 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc−hexane 25:75 → 60:40 to give the *alcohol derivative* ***64a*** (1.24 g, 62%, *dr* 84:16 by ^1H NMR) as a colourless viscous oil. R_f 0.48 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3415, 3074, 2952, 2853, 1712, 1521, 1446, 1366, 1249, 1163, 1084; δ_H (400 MHz, $CDCl_3$): 5.87 (1H, ddt, *J* 17.4, 10.1 and 7.5 Hz, propenyl 2-H), 5.19-5.08 (2H, m, propenyl 3-H_2), 4.77 (1H, br. s, NH), 3.92 (1H, dt, *J* 11.3 and 4.8 Hz, 6-H_A), 3.76-3.70 (1H, m, 4-H), 3.58 (1H, d, *J* 11.7 Hz, 2-H_A), 3.51-3.44 (1H, m, 6-H_B), 3.30-

3.14 (2H, m, ethylcarbamate 2-H_2), 3.05 (1H, d, *J* 11.7 Hz, 2-H_B), 2.27 (2H, app. d, *J* 7.5 Hz, propenyl 1-H_2), 1.93 (1H, br. s, OH), 1.83-1.69 (2H, m, 5-H_2), 1.64-1.55 (1H, m, ethylcarbamate 1-H_A), 1.43 (10H, app. s, ^{t}Bu and ethylcarbamate 1-H_B); δ_C (100 MHz, $CDCl_3$): 156.3 (Boc C=O), 134.2 (propenyl C-2), 118.5 (propenyl C-3), 79.9 (^{t}Bu C_1), 72.4 (C-4), 71.9 (C-2), 66.1 (C-6), 41.1 (C-3), 33.9 (ethylcarbamate C-2), 32.9 (propenyl C-1), 30.9 (C-5), 29.8 (ethylcarbamate C-1), 28.6 (^{t}Bu C_3); HMRS found MNa^+ 308.1841. $C_{15}H_{27}NO_4$ requires *MNa*, 308.1832. The relative configuration was determined using NOESY (500 MHz, $CDCl_3$). nOe observed between 4-H and ethylcarbamate 1-H_A and between 4-H and ethylcarbamate 1-H_B.

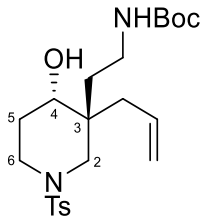
tert-butyl *N*-{3-[(1*R**,2*R**)-1-hydroxy-2-(prop-2-en-1-yl)-1,3-dihydroinden-2-yl]ethyl}carbamate (94b)



Prepared according to General procedure F, the ketone derivative **88c** (1.50 g, 7.10 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 15:85 to give the *alcohol derivative* ***94b*** (1.48 g, 65%, *dr* 80:20 by ^{1}H NMR) as a brown-yellow oil. R_f 0.51 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 3341, 2976, 2929, 1685, 1513, 1458, 1392, 1366, 1247, 1166, 1019; δ_H (400 MHz, $CDCl_3$): 7.40-7.32 (1H, m, 7-H), 7.25-7.16 (3H, m, 4-H, 5-H and 6-H), 5.81 (1H, ddt, *J* 17.0, 10.0 and 6.9 Hz, propenyl 2-H), 5.10-5.02 (2H, m, propenyl 3-H_2), 4.94 (1H, d, *J* 7.7 Hz, 1-H), 4.75 (1H, s, NH), 3.29-3.19 (2H, m, ethylcarbamate 2-H_2), 2.92 (1H, d, *J* 16.0 Hz, 3-H_A), 2.64 (1H, d, *J* 16.0 Hz, 3-H_B), 2.37 (1H, dd, *J* 14.2 and 6.9 Hz, propenyl 1-H_A), 2.21-2.08 (2H, m, propenyl 1-H_B and OH), 1.85-1.65 (2H, m, ethylcarbamate 1-H_2), 1.44 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$): 156.2 (Boc C=O), 144.4 (C-7a), 140.8 (C-3a), 135.5 (propenyl C-2), 128.5 (C-6), 127.0 (C-5), 125.0 (C-4), 124.1 (C-7), 117.8 (propenyl C-3), 82.5 (C-1), 81.6 (^{t}Bu C_1), 49.9 (C-2), 41.5 (C-3), 38.2 (ethylcarbamate C-2), 37.3 (ethylcarbamate C-1), 36.1 (propenyl C-1), 28.6 (^{t}Bu C_3); HRMS found MH^+

318.2059. $C_{19}H_{27}NO_3$ required *MH*, 318.2064. The relative configuration was determined using NOESY (500 MHz, $CDCl_3$) on benzylated derivative **116b**. nOe observed on benzylated derivative **116b** between 1-H and ethylcarbamate 2-H_2.

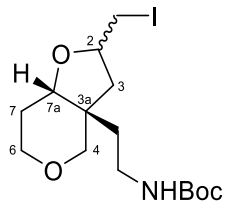
tert-butyl _N_-{2-[(3_R_*,4_R_*)-4-hydroxy-1-(4-methylbenzenesulfonyl)-3-(prop-2-en-1-yl)piperidin-3-yl]ethyl}carbamate (94d)



Prepared according to General procedure F, the ketone derivative **88e** (1.30 g, 3.92 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 30:70 to give *the alcohol derivative* ***94d*** (1.16 g, 67%, *dr* 80:20 by ^{1}H NMR) as a colourless oil. R_f 0.18 (EtOAc–hexane 40:60). ν_{max}/cm^{-1}: 3396, 2975, 2874, 1685, 1597, 1509, 1456, 1393, 1340, 1248, 1162, 1087; δ_H (500 MHz, $CDCl_3$): 7.62 (2H, d, *J* 8.3 Hz, benzenesulfonyl 2,6-H), 7.32 (2H, d, *J* 8.3 Hz, benzenesulfonyl 3,5-H), 5.89 (1H, ddt, *J* 17.0, 9.7 and 7.1 Hz, propenyl 2-H), 5.23-5.10 (2H, m, propenyl 3-H_2), 4.72 (1H, br. s, NH), 3.55 (1H, dd, *J* 9.6 and 4.4 Hz, 4-H), 3.34-3.22 (1H, m, ethylcarbamate 2-H_A), 3.20-3.08 (2H, m, ethylcarbamate 2-H_B and 6-H_A), 2.99-2.91 (1H, m, 6-H_B), 2.88 (1H, d, *J* 11.5 Hz, 2-H_A), 2.59 (1H, d, *J* 11.5 Hz, 2-H_B), 2.43 (3H, s, benzenesulfonyl CH_3), 2.31-2.22 (1H, m, propenyl 1-H_A), 2.19 (1H, dd, *J* 12.7 and 7.1 Hz, propenyl 1-H_B), 2.04 (1H, br. s, OH), 1.99-1.91 (1H, m, 5-H_A), 1.81-1.75 (1H, m, 5-H_B), 1.73-1.66 (1H, m, ethylcarbamate 1-H_A), 1.56-1.49 (1H, m, ethylcarbamate 1-H_B), 1.43 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$): 156.1 (Boc C=O), 143.6 (benzenesulfonyl C-4), 133.3 (propenyl C-2), 133.2 (benzenesulfonyl C-1), 129.7 (benzenesulfonyl C_2-3,5), 127.6 (benzenesulfonyl C_2-2,6), 119.0 (propenyl C-3), 79.4 (^{t}Bu C_1), 70.8 (C-4), 50.1 (C-2), 43.1 (C-6), 40.6 (C-3), 35.6 (ethylcarbamate C-2), 34.3 (propenyl C-1), 33.5 (ethylcarbamate C-1), 29.1 (C-5), 28.4 (^{t}Bu C_3), 21.5

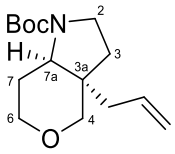
(benzenesulfonyl CH_3); HRMS found MH^+ 439.2256. $C_{22}H_{34}N_2O_5S$ requires *MH*, 439.2261. The relative configuration was determined *via* analogy with compounds **94a** and **94b**.

tert-butyl _N_-{2-[(3a_R_*,7a_S_*)-2-(iodomethyl)-hexahydrofuro[3,2-c]pyran-3a-yl]ethyl}carbamate (98)



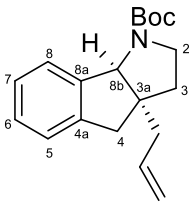
Prepared according to General procedure P, the alcohol derivative **94a** (0.90 g, 3.16 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 20:80 to give the *alkyl iodide derivative* ***98*** (0.72 g, 54%, *dr* 70:30 by ^{1}H NMR) as a colourless oil. R_f 0.26 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3350, 2970, 2862, 1694, 1513, 1364, 1165, 1021; δ_H (400 MHz, $CDCl_3$): 4.62 (2H, br. s, NH), 4.27 (1H, app. sept, *J* 7.0 Hz, 2-H^{maj}), 4.19-3.96 (2H, m, 2-H^{min} and 7a-H^{maj}), 3.92 (1H, app. t, *J* 3.0 Hz, 7a-H^{min}), 3.78-3.67 (2H, m, 6-H$_A$), 3.65 (1H, d, *J* 11.7 Hz, 4-H$_A^{min}$), 3.55 (1H, d, *J* 11.7 Hz, 4-H$_A^{maj}$), 3.39 (1H, d, *J* 11.7 Hz, 4-H$_B^{maj}$), 3.36-3.31 (1H, m, 4-H$_B^{min}$), 3.30-3.10 (10H, m, 6-H$_B$, ethylcarbamate 2-H$_2$ and iodomethyl 1-H$_2$), 2.25 (1H, dd, *J* 12.5 and 6.3 Hz, 3-H$_A^{min}$), 2.03-1.76 (7H, m, 3-H$_A^{maj}$, ethylcarbamate 1-H$_2$ and 7-H$_A$), 1.59-1.48 (2H, m, 7-H$_B$), 1.47 (18H, s, ^{t}Bu), 1.34 (1H, dd, *J* 12.5 and 6.5, 3-H$_B^{maj}$), 1.26 (1H, dd, *J* 12.5 and 6.3 Hz, 3-H$_B^{min}$); δ_C (100 MHz, $CDCl_3$): 156.0 (Boc C=O), 83.3 (C-7a^{min}) 80.2 (C-7a^{maj}), 79.5 (^{t}Bu C$_1^{maj}$), 79.3 (^{t}Bu C$_1^{min}$), 77.4 (C-2), 73.3 (C-6^{min}), 70.6 (C-4^{maj}), 69.3 (C-4^{min}), 64.0 (C-6^{maj}), 45.3 (C-3a^{maj}), 43.9 (C-3a^{min}), 42.9 (C-3^{maj}), 41.4 (C-3^{min}), 40.1 (C-7^{maj}), 39.1 (C-7^{min}), 37.3 (ethylcarbamate C-2^{maj}), 36.8 (ethylcarbamate C-2^{min}), 28.6 (^{t}Bu C$_3$), 26.5 (ethylcarbamate C-1^{maj}), 26.3 (ethylcarbamate C-1^{min}), 10.3 (iodomethyl C-1^{min}), 9.24 (iodomethyl C-1^{maj}); HRMS found MNa^+ 434.0811. $C_{15}H_{26}INO_4$ requires *MNa*, 434.0799.

tert-butyl (3a*R,7a*S**)-3a-(prop-2-en-1-yl)-hexahydropyrano[4,3-*b*]pyrrole-1-carboxylate (99a)**



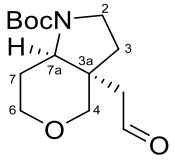
Prepared according to General procedure L, the alcohol derivative **94a** (1.15 g, 4.04 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give the *fused-ring pyrrolidine derivative* ***99a*** (0.48 g, 43%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.21 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 2973, 2853, 1688, 1454, 1401, 1364, 1248, 1162, 1134, 1096; δ_H (500 MHz, MeOD): 5.86 (1H, ddt, *J* 17.7, 10.2 and 7.5 Hz, propenyl 2-H), 5.21-5.12 (2H, m, propenyl 3-H_2), 3.85 (1H, app. br. s, 6-H_A), 3.73-3.63 (2H, m, 4-H_A and 7a-H), 3.54 (1H, d, *J* 12.0 Hz, 4-H_B), 3.51-3.39 (3H, m, 6-H_B and 2-H_2), 2.17 (3H, app. d, *J* 7.5 Hz propenyl 1-H_2 and 3-H_A), 2.02 (1H, dq, *J* 14.1 and 3.1 Hz, 7-H_A), 1.78-1.68 (2H, m, 7-H_B and 3-H_B), 1.53 (9H, s, ^{t}Bu); δ_C (100 MHz, MeOD): 156.4 (Boc C=O), 134.5 (propenyl C-2), 119.0 (propenyl C-3), 80.8 (^{t}Bu C_1), 72.2 (C-4), 66.6 (C-6), 59.6 (C-7a), 45.0 (C-2), 44.5 (C-3a), 41.2 (propenyl C-1), 30.1 (C-7), 29.7 (C-3), 28.8 (^{t}Bu C_3); HRMS found MNa^+ 290.1730. $C_{15}H_{25}NO_3$ requires *MNa*, 290.1727.

tert-butyl (3a*R,8b*S**)-3a-(prop-2-en-1-yl)-2*H*,3*H*,4*H*,8b*H*-indeno[1,2-*b*]pyrrole-1-carboxylate (99b)**



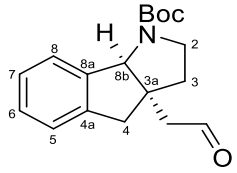
Prepared according to General procedure L, the alcohol derivative **94b** (1.80 g, 5.68 mmol) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give the *fused-ring pyrrolidine derivative* ***99b*** (1.16 g, 68%, *rotamers* 58:42 by ^{1}H NMR) as a pale-yellow oil. R_f 0.30 (5:95 EtOAc–hexane). ν_{max}/cm^{-1}: 2975, 2854, 1687, 1454, 1400, 1369, 1247, 1234, 1163, 1137, 1094; δ_H (400 MHz, $CDCl_3$): 7.68 (1H, d, *J* 6.4 Hz, 8-H^{min}), 7.52 (1H, d, *J* 6.4 Hz, 8-H^{maj}), 7.24-7.10 (6H, m, 5-H, 6-H and 7-H), 5.90-5.76 (2H, m, propenyl 2-H), 5.17-5.07 (4H, m, propenyl 3-H$_2$), 5.02 (1H, s, 8b-H^{min}), 4.91 (1H, s, 8b-H^{maj}), 3.59 (1H, dt, *J* 16.6 and 8.3 Hz, 2-H$_A$^{maj}), 3.99 (1H, app. dd, *J* 16.6 and 8.3 Hz, 2-H$_A$^{min}), 3.35-3.25 (2H, m, 2-H$_B$), 2.94 (1H, d, *J* 16.3 Hz, 4-H$_A$^{min}), 2.92 (1H, d, *J* 16.3 Hz, 4-H$_A$^{maj}), 2.81 (2H, d, *J* 16.3 Hz, 4-H$_B$), 2.38 (4H, app. d, *J* 7.2 Hz, propenyl 1-H$_2$), 1.92 (2H, ddd, *J* 11.7, 7.4 and 4.0 Hz, 3-H$_A$), 1.78-1.66 (2H, m, 3-H$_B$), 1.53 (18H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$): 155.2 (Boc C=O^{min}), 154.8 (Boc C=O^{maj}), 144.2 (C-8a^{min}), 143.7 (C-8a^{maj}), 141.4 (C-4a^{maj}), 141.2 (C-4a^{min}), 134.9 (propenyl C-2^{min}), 134.7 (propenyl C-2^{maj}), 128.0 (C-6^{maj}), 127.9 (C-6^{min}), 127.0 (C-8^{min}), 126.9 (C-8^{maj}), 125.9 (C-7), 125.3 (C-5^{maj}), 124.9 (C-5^{min}), 118.1 (propenyl C-3), 79.8 (C$_1$ ^{t}Bu^{min}), 79.2 (C$_1$ ^{t}Bu^{maj}), 70.7 (C-8b), 53.6 (C-3a^{maj}), 52.5 (C-3a^{min}), 45.8 (C-2^{min}), 45.5 (C-2^{maj}), 41.9 (propenyl C-1^{min}), 41.8 (propenyl C-1^{maj}), 41.4 (C-4^{min}), 41.2 (C-4^{maj}), 34.9 (C-3^{min}), 34.1 (C-3^{maj}), 28.8 (^{t}Bu C$_3$^{maj}), 28.6 (^{t}Bu C$_3$^{min}); HRMS found MNa$^+$ 322.1781. $C_{19}H_{25}NO_2$ requires *MNa*, 322.1778. The relative configuration was confirmed through NOESY (500 MHz, $CDCl_3$). nOe observed between 8b-H and propenyl 1-H$_2$.

tert-butyl (3a*R,7a*S**)-3a-(2-oxoethyl)-hexahydropyrano[4,3-*b*]pyrrole-1-carboxylate (100)**



Prepared according to General procedure M, the fused-ring pyrrolidine derivative **99a** (90 mg, 0.34 mmol) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 35:65 to give the *aldehyde derivative* ***100*** (63.0 mg, 69%) as a colourless oil. R_f 0.34 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2972, 2850, 1719, 1690, 1401, 1366, 1324, 1254, 1165, 1131, 1098; δ_H (400 MHz, $CDCl_3$): 9.70 (1H, t, *J* 2.0 Hz, oxoethyl 2-H), 3.77 (2H, app. br. s, 4-H_A and 6-H_A), 3.69 (1H, dd, *J* 8.7 and 6.1 Hz, 7a-H), 3.59 (1H, d, *J* 12.2 Hz, 4-H_B), 3.49-3.37 (3H, m, 2-H_2 and 6-H_B), 2.51 (2H, d, *J* 2.0 Hz, oxoethyl 1-H_2), 2.29-2.12 (1H, m, 3-H_A), 2.00-1.93 (1H, m, 7-H_A), 1.85-1.77 (1H, m, 3-H_B), 1.68-1.59 (1H, m, 7-H_B), 1.46 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$): 202.7 (oxoethyl C-2), 156.5 (Boc C=O), 80.9 (^{t}Bu C_1), 72.6 (C-4), 66.5 (C-6), 60.5 (C-7a), 45.2 (oxoethyl C-1), 44.6 (C-3a), 43.4 (C-2), 30.3 (C-7), 29.4 (C-3), 28.8 (^{t}Bu C_3); HRMS found MNa^+ 292.1520. $C_{14}H_{23}NO_4$ requires *MNa*, 292.1519.

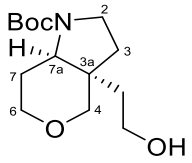
tert-butyl-(3a*R,8b*S**)-3a-(2-oxoethyl)-2*H*,3*H*,4*H*,8b*H*-indeno[1,2-*b*]pyrrole-1-carboxylate (103)**



Prepared according to General procedure M, the fused-ring pyrrolidine derivative **94b** (1.10 g, 3.70 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 20:80 to give the *aldehyde derivative* ***103*** (1.04 g, 93%, *rotamers* 52:48 by ^{1}H NMR) as a white solid. R_f 0.44 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 2972, 2923, 2852, 1718, 1680, 1460, 1394, 1345, 1297, 1217, 1114, 1082; δ_H (400 MHz, $CDCl_3$): 9.85 (2H, t, *J* 1.8 Hz, oxoethyl 2-H), 7.67 (1H, d, *J* 6.5 Hz, 8-H^{min}), 7.53 (1H, d, *J* 6.5 Hz, 8-H^{maj}), 7.25-7.14 (6H, m, 5-H, 6-H and 7-H), 5.11 (1H, s, 8b-H^{min}), 4.99 (1H, s, 8b-H^{maj}), 3.65-3.56 (1H, m, 2-H_A^{maj}), 3.55-3.46 (1H, m, 2-H_A^{min}), 3.35 (2H, ddd, *J* 11.3, 8.2 and 4.4 Hz, 2-H_B), 3.11 (2H, d, *J* 16.2 Hz, 4-H_A), 2.98 (2H, d, *J* 16.2 Hz, 4-H_B), 2.83 (2H, app. d, *J* 17.3, oxoethyl 1-H_A), 2.75 (2H, app. d, *J*

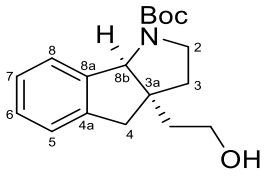
17.3 Hz, oxoethyl 1-H_B), 1.98 (2H, ddd, *J* 11.3, 7.4 and 4.4 Hz, 3-H_A), 1.94-1.83 (2H, m, 3-H_B), 1.57 (9H, s, ^{t}Bu^{maj}), 1.49 (9H, s, ^{t}Bu^{min}); δ_C (100 MHz, $CDCl_3$): 201.1 (oxoethyl C-2^{min}), 200.9 (oxoethyl C-2^{maj}), 155.1 (Boc C=O^{min}), 154.6 (Boc C=O^{maj}), 143.2 (C-8a^{min}), 142.7 (C-8a^{maj}), 140.9 (C-4a^{maj}), 140.6 (C-4a^{min}), 128.4 (C-6^{maj}), 128.3 (C-6^{min}), 127.4 (C-8^{min}), 127.2 (C-8^{maj}), 126.9 (C-7^{min}), 126.0 (C-7^{maj}), 125.4 (C-5^{maj}), 125.1 (C-5^{min}), 80.2 (C_1 ^{t}Bu^{maj}), 79.7 (C_1 ^{t}Bu^{min}), 71.4 (C-8b^{min}), 71.3 (C-8b^{maj}), 51.1 (C-3a^{maj}), 51.0 (oxoethyl C-1^{min}), 50.8 (oxoethyl C-1^{maj}), 50.0 (C-3a^{min}), 45.7 (C-2^{min}), 45.4 (C-2^{maj}), 41.9 (C-4^{min}), 41.6 (C-4^{maj}), 35.4 (C-3^{min}), 34.6 (C-3^{maj}), 28.8 (C_3 ^{t}Bu^{maj}), 28.6 (C_3 ^{t}Bu^{min}); HRMS found MNa^+ 324.1571. $C_{18}H_{23}NO_3$ requires *MNa*, 324.1570.

tert-butyl (3a*R,7a*S**)-3a-(2-hydroxyethyl)-hexahydropyrano[4,3-*b*]pyrrole-1-carboxylate (101)**



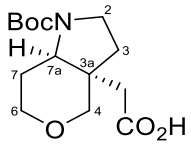
Prepared according to General procedure N, the aldehyde derivative **100** (60 mg, 0.22 mmol) gave the *alcohol derivative* ***101*** (48.0 mg, 81%) as a colourless oil. R_f 0.16 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3431, 2931, 2856, 1668, 1402, 1365, 1240, 1162, 1128, 1097; δ_H (400 MHz, MeOD, peak broadening due to unresolved rotamers): 3.82-3.66 (2H, m, 4-H_A and 6-H_A), 3.62 (2H, t, *J* 7.0 Hz, hydroxyethyl 2-H_2), 3.57-3.48 (2H, m, 4-H_B and 7a-H), 3.47-3.34 (3H, m, 6-H_B and 2-H_2), 2.12 (1H, app. br. d, *J* 7.0 Hz, 3-H_A), 2.01-1.89 (1H, m, 7-H_A), 1.77-1.66 (2H, m, 3-H_B and 7-H_B), 1.60 (2H, t, *J* 7.0 Hz, hydroxyethyl 1-H_2), 1.46 (9H, s, ^{t}Bu); δ_C (100 MHz, MeOD): 156.5 (Boc C=O), 81.0 (^{t}Bu C_1), 72.5 (C-4), 66.5 (C-6), 60.5 (C-7a), 58.8 (hydroxyethyl C-2), 45.2 (C-2), 43.9 (C-3a), 39.2 (hydroxyethyl C-1), 30.3 (C-7), 29.5 (C-3), 28.8 (^{t}Bu C_3); HRMS found MNa^+ 294.1684. $C_{14}H_{25}NO_4$ requires *MNa*, 294.1678

tert-butyl (3a_R_*,8b_S_*)-3a-(2-hydroxyethyl)-2_H_,3_H_,4_H_,8b_H_-indeno[1,2-_b_]pyrrole-1-carboxylate (104)



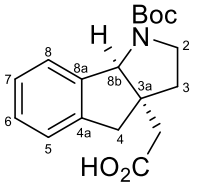
Prepared according to General procedure N, the aldehyde derivative **103** (0.75 g, 2.50 mmol) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give the *alcohol derivative* ***104*** (0.51 g, 67%, *rotamers* 44:56 by ^{1}H NMR) as a colourless oil that solidified on standing to give a colourless solid. R_f 0.23 (30:70 EtOAc–hexane). ν_{max}/cm^{-1}: 3414, 2973, 2928, 1687, 1477, 1390, 1365, 1295, 1165, 1119, 1050; δ_H (400 MHz, $CDCl_3$): 7.65 (1H, d, *J* 6.5 Hz, 8-H^{min}), 7.52 (1H, d, *J* 6.5 Hz, 8-H^{maj}), 7.24-7.08 (6H, m, 5-H, 6-H and 7-H), 5.01 (1H, s, 8b-H^{min}), 4.91 (1H, s, 8b-H^{maj}), 3.94 (2H, t, *J* 7.0 Hz, hydroxyethyl 2-H$_2^{min}$), 3.76 (2H, t, *J* 7.0 Hz, hydroxyethyl 2-H$_2^{maj}$), 3.65-3.54 (1H, m, 2-H$_A^{maj}$), 3.54-3.45 (1H, m, 2-H$_A^{min}$), 3.32 (2H, ddd, *J* 11.3, 8.2 and 4.3 Hz, 2-H$_B$), 2.96 (1H, d, *J* 16.1 Hz, 4-H$_A^{min}$), 2.94 (1H, d, *J* 16.1 Hz, 4-H$_A^{maj}$), 2.86 (1H, d, *J* 16.1 Hz, 4-H$_B^{maj}$), 2.84 (1H, d, *J* 16.1 Hz, 4-H$_B^{min}$), 2.01-1.84 (6H, m, hydroxyethyl 1-H$_2$ and 3-H$_A$), 1.79-1.66 (2H, m, 3-H$_B$), 1.57 (9H, s, ^{t}Bu^{maj}), 1.50 (9H, s, ^{t}Bu^{min}); δ_C (100 MHz, $CDCl_3$): 155.2 (Boc C=O^{min}), 154.7 (Boc C=O^{maj}), 143.9 (C-8a^{min}), 143.4 (C-8a^{maj}), 141.5 (C-4a^{maj}), 141.2 (C-4a^{min}), 128.0 (C-6^{maj}), 127.9 (C-6^{min}), 127.0 (C-8^{min}), 126.8 (C-8^{maj}), 126.6 (C-7^{min}), 125.8 (C-7^{maj}), 125.2 (C-5^{maj}), 124.9 (C-5^{min}), 79.9 (^{t}Bu C$_1^{maj}$), 79.3 (^{t}Bu C$_1^{min}$), 71.5 (C-8b^{maj}), 71.2 (C-8b^{min}), 60.9 (hydroxyethyl C-2^{min}), 59.8 (hydroxyethyl C-2^{maj}), 52.4 (C-3a^{maj}), 51.3 (C-3a^{min}), 45.8 (C-2^{min}), 45.5 (C-2^{maj}), 41.4 (C-4^{maj}), 41.3 (C-4^{min}), 39.8 (hydroxyethyl C-1^{maj}), 38.4 (hydroxyethyl C-1^{min}), 35.0 (C-3^{min}), 34.1 (C-3^{maj}), 28.7 (^{t}Bu C$_3^{maj}$), 28.5 (^{t}Bu C$_3^{min}$); HRMS found MNa$^+$ 326.1730. $C_{18}H_{25}NO_3$ requires *MNa*, 326.1727.

[(3a*R,7a*S**)-1-(*tert*-butoxycarbonyl)-hexahydropyrano[4,3-*b*]pyrrol-3a-yl]acetic acid (102)**



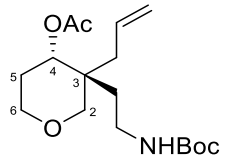
Prepared according to General procedure O, the aldehyde derivative **100** (0.20 g, 0.74 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 → DCM–EtOH–NH_4OH 50:8:1 to give the *carboxylic acid derivative* ***102*** (0.14 g, 68%) as a colourless solid. R_f 0.15 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3130, 2951, 2861, 1725, 1401, 1323, 1148, 1013; δ_H (400 MHz, MeOD, peak broadening due to unresolved rotamers): 3.89-3.77 (2H, m, 4-H_A and 6-H_A), 3.72 (1H, app. br. s, 7a-H), 3.64 (1H, d, *J* 12.1 Hz, 4-H_B), 3.52-3.38 (3H, m, 6-H_B and 2-H_2), 2.33 (2H, s, C$H_2$$CO_2H$), 2.02-1.92 (1H, m, 3-$H_A$), 1.91-1.78 (1H, m, 3-$H_B$), 1.46 (9H, s, ^{t}Bu), 1.35-1.24 (2H, m, 7-H_2); δ_C (100 MHz, MeOD): 174.5 (carboxylic acid C=O), 156.5 (Boc C=O), 81.0 (^{t}Bu C_1), 71.9 (C-4), 66.5 (C-6), 59.7 (C-7a), 44.5 (C-2), 43.8 (C-3a), 40.5 (*C*$H_2$$CO_2H$), 30.1 (C-7), 29.5 (C-3), 28.8 (^{t}Bu C_3); HRMS found MNa^+ 308.1468. $C_{14}H_{23}NO_5$ requires *MNa*, 308.1468.

[(3a*R,8b*S**)-1-(*tert*-butoxycarbonyl)-2*H*,3*H*,4*H*,8b*H*-indeno[1,2-*b*]pyrrol-3a-yl]acetic acid (105)**



Prepared according to General procedure O, the aldehyde derivative **103** (0.11 g, 0.37 mmol) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give the *carboxylic acid derivative* ***105*** (104 mg, 89%, *rotamers* 43:57 by ^{1}H NMR) as a pale-yellow oil. R_f 0.28 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 2977, 2931, 1687, 1392, 1366, 1349, 1287, 1249, 1164, 1024; δ_H (500 MHz, $CDCl_3$): 7.65 (1H, d, *J* 6.8 Hz, 8-H^{min}), 7.51 (1H, d, *J* 6.8 Hz, 8-H^{maj}), 7.27-7.12 (6H, m, 5-H, 6-H and 7-H), 5.13 (1H, s, 8b-H^{min}), 5.04 (1H, s, 8b-H^{maj}), 3.64-3.57 (1H, m, 2-H$_A^{min}$), 3.55-3.48 (1H, m, 2-H$_A^{maj}$), 3.36 (2H, ddd, *J* 13.0, 7.2 and 3.5 Hz, 2-H$_B$), 3.10-3.02 (4H, m, acetic acid 1-H$_2$), 2.72 (2H, d, *J* 15.5, 4-H$_A$), 2.68 (1H, d, *J* 15.5 Hz, 4-H$_B^{maj}$), 2.66 (1H, d, *J* 15.5 Hz, 4-H$_B^{min}$), 2.09 (2H, ddd, *J* 13.0. 7.2 and 3.5 Hz, 3-H$_A$), 1.86 (2H, app. tt, *J* 13.0 and 8.9 Hz, 3-H$_B$); 1.57 (9H, s, ^{t}Bu^{maj}), 1.48 (9H, s, ^{t}Bu^{min}); δ_C (125 MHz, $CDCl_3$): 177.0 (carboxylic acid C=O), 155.4 (Boc C=O^{min}), 155.0 (Boc C=O^{maj}), 143.5 (C-8a^{min}), 143.0 (C-8a^{maj}), 141.0 (C-4a^{maj}), 140.8 (C-4a^{min}), 128.4 (C-6^{maj}), 128.2 (C-6^{min}), 127.3 (C-8^{min}), 127.2 (C-8^{maj}), 126.8 (C-7^{min}), 125.9 (C-7^{maj}), 125.4 (C-5^{maj}), 125.1 (C-5^{min}), 80.3 (^{t}Bu C$_1^{maj}$), 79.8 (^{t}Bu C$_1^{min}$), 71.3 (C-8b), 51.7 (C-3a^{maj}), 50.6 (C-3a^{min}), 45.7 (C-2^{min}), 45.4 (C-2^{maj}), 41.7 (acetic acid C-1^{min}), 41.6 (acetic acid C-1^{maj}), 41.1 (C-4^{maj}), 41.0 (C-4^{min}), 35.1 (C-3^{min}), 34.3 (C-3^{maj}), 28.8 (^{t}Bu C$_3^{maj}$), 28.7 (^{t}Bu C$_3^{min}$); HRMS found MH$^+$ 318.1701. $C_{18}H_{23}NO_4$ requires *MH*, 318.1700.

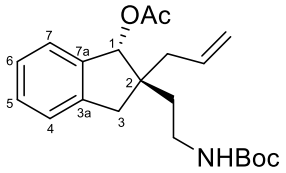
(3*R,4*R**)-3-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-3-(prop-2-en-1-yl)oxan-4-yl acetate (106a)**



Prepared according to General procedure G, the alcohol derivative **94a** (0.81 g, 2.84 mmol) gave the *acetate derivative* ***106a*** (0.84 g, 90%) as a colourless oil. R_f 0.40 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3350, 2972, 2860, 1739, 1709, 1516, 1454, 1366, 1235, 1166, 1087; δ_H (400 MHz, $CDCl_3$): 5.85-5.71 (1H, m, propenyl 2-H), 5.12-5.05

(2H, m, propenyl 3-H_2), 4.88-4.82 (1H, m, 4-H), 4.50 (1H, br. s, NH), 3.81-3.73 (1H, m, 6-H_A), 3.65-3.57 (1H, m, 6-H_B), 3.57 (1H, d, *J* 11.8 Hz, 2-H_A), 3.28 (1H, d, *J* 11.8 Hz, 2-H_B), 3.16 (2H, app. br. s, ethylcarbamate 2-H_2), 2.17 (2H, d, *J* 7.2 Hz, propenyl 1-H_2), 2.08 (3H, s, acetyl), 1.97-1.86 (1H, m, 5-H_A), 1.75-1.67 (1H, m, 5-H_B), 1.63-1.51 (2H, m, ethylcarbamate 1-H_2), 1.44 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$): 170.4 (acetyl C=O), 155.9 (Boc C=O), 133.0 (propenyl C-2), 118.8 (propenyl C-3), 79.4 (^{t}Bu C_1), 73.2 (C-4), 71.5 (C-2), 65.0 (C-6), 39.4 (C-3), 35.8 (ethylcarbamate C-2), 34.3 (propenyl C-1), 32.8 (ethylcarbamate C-1), 28.6 (^{t}Bu C_3), 27.4 (C-5), 21.4 (acetyl CH_3); HRMS found MNa^+ 350.1948. $C_{17}H_{29}NO_5$ requires *MNa*, 350.1938.

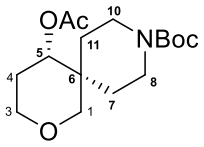
(1*R,2*R**)-2-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-2-(prop-2-en-1-yl)-1,3-dihydroinden-1-yl acetate (106b)**



Prepared according to General procedure G, the alcohol derivative **94b** (1.10 g, 3.47 mmol) gave the *acetate derivative **106b*** *(*1.02 g, 82%) as a pale-yellow oil. R_f 0.55 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 3362, 2976, 2929, 1733, 1693, 1512, 1479, 1453, 1391, 1367, 1303, 1234, 1167, 1018; δ_H (400 MHz, $CDCl_3$): 7.36-7.29 (1H, m, 7-H), 7.27-7.16 (3H, m, 4-H, 5-H and 6-H), 5.99 (1H, s, 1-H), 5.80 (1H, ddt, *J* 17.3, 11.6 and 7.2 Hz, propenyl 2-H), 5.10 (1H, dd, *J* 17.3 Hz and 1.4 Hz, propenyl 3-H_{trans}), 5.04 (1H, dd, *J* 11.6 and 1.4 Hz, propenyl 3-H_{cis}), 4.41 (1H, br. s, NH), 3.20-3.05 (2H, m, ethylcarbamate 2-H_2), 2.98 (1H, d, *J* 16.0 Hz, 3-H_A), 2.77 (1H, d, *J* 16.0 Hz, 3-H_B), 2.38 (1H, dd, *J* 14.2 and 7.2 Hz, propenyl 1-H_A), 2.27 (1H, dd, *J* 14.2 and 7.2, propenyl 1-H_B), 2.08 (3H, s, acetyl), 1.85-1.67 (1H, m, ethylcarbamate 1-H_A), 1.68-1.59 (1H, m, ethylcarbamate 1-H_B), 1.41 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$): 170.9 (acetyl C=O), 155.9 (Boc C=O), 142.7 (C-7a), 140.8 (C-3a), 134.8 (propenyl C-2), 129.2 (C-6), 127.0 (C-5), 126.0 (C-7), 125.0 (C-4), 118.0 (propenyl C-3), 82.2 (C-1), 79.3 (^{t}Bu C_1), 48.1

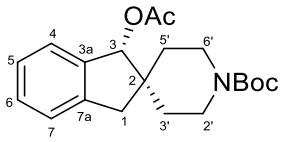
(C-2), 42.0 (C-3), 37.8 (propenyl C-1), 37.2 (ethylcarbamate C-1), 36.9 (ethylcarbamate C-2), 28.6 (^{t}Bu C_3), 21.3 (acetyl CH_3); HRMS found MNa^+ 382.1997. $C_{21}H_{29}NO_4$ requires *MNa*, 382.1989.

tert-butyl (5*R,6*R**)-5-(acetyloxy)-2-oxa-9-azaspiro[5.5]undecane-9-carboxylate (109)**



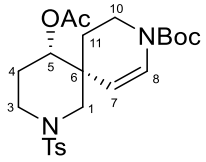
Prepared according to General procedure H, the acetate derivative **106a** (0.50 g, 1.53 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give *spirocyclic piperidine derivative* ***109*** (0.18 g, 38%) as a colourless oil that solidified to a colourless solid upon drying. R_f 0.60 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2974, 2845, 2812, 1710, 1685, 1486, 1405, 1335, 1252, 1127, 1028; δ_H (500 MHz, MeOD): 4.81 (1H, dd, *J* 7.3 and 3.4 Hz, 5-H), 3.85 (1H, d, *J* 11.9 Hz, 1-H_A), 3.80 (1H, ddd, *J* 11.3, 7.3 and 3.9 Hz, 3-H_A), 3.73-3.60 (3H, m, 3-H_B, 8-H_A and 10-H_A), 3.39 (1H, d, *J* 11.9, 1-H_B), 3.11 (2H, app. br. s, 8-H_B and 10-H_B), 2.07 (3H, s, acetyl), 1.91 (1H, tdd, *J* 11.2, 7.3 and 3.4 Hz, 4-H_A), 1.69 (1H, dtd, *J* 11.2, 7.3 and 3.9 Hz, 4-H_B), 1.65-1.57 (2H, m, 7-H_A and 11-H_A), 1.54-1.47 (2H, m, 7-H_B and 11-H_B), 1.45 (9H, s, ^{t}Bu); δ_C (100 MHz, MeOD): 172.0 (acetyl C=O), 156.5 (Boc C=O), 81.0 (^{t}Bu C_1), 75.2 (C-5), 71.2 (C-1), 66.0 (C-3), 40.3 (C_2-8,10), 36.9 (C-6), 31.4 (C_2-7,11), 28.7 (^{t}Bu C_3), 28.1 (C-4), 21.0 (acetyl CH_3); HRMS found MNa^+ 336.1788. $C_{16}H_{27}NO_5$ requires *MNa*, 336.1781.

tert-butyl (2_R_*,3_R_*)-3-(acetyloxy)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (112)



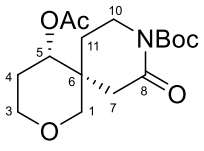
Prepared according to General procedure H, the acetate derivative **106b** (1.00 g, 2.79 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 10:90 to give the *spirocyclic piperidine derivative* ***112*** (0.46 g, 48%) as a colourless oil. R_f 0.53 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 2974, 2930, 2851, 1732, 1687, 1479, 1421, 1365, 1230, 1148, 1100, 1064; δ_H (400 MHz, MeOD): 7.33 (1H, d, *J* 7.5 Hz, 4-H), 7.31-7.22 (2H, m, 5-H and 7-H), 7.19 (1H, app. td, *J* 7.1 and 2.1 Hz, 6-H), 5.90 (1H, s, 3-H), 3.70 (2H, app. tt, *J* 14.0 and 4.8 Hz, 2'-H_A and 6'-H_A), 3.30-3.18 (2H, m, 2'-H_B and 6'-H_B), 3.01 (1H, d, *J* 15.9 Hz, 1-H_A), 2.87 (1H, d, *J* 15.9 Hz, 1-H_B), 2.05 (3H, s, acetyl), 1.75 (1H, ddd, *J* 14.0, 9.9 and 4.8 Hz, 3'-H_A or 5'-H_A), 1.65-1.57 (1H, m, 3'-H_B or 5'-H_B), 1.54 (1H, ddd, *J* 13.9, 9.9 and 4.1, 3'-H_A or 5'-H_A), 1.46 (10H, app. s, 3'-H_B or 5'-H_B and ^{t}Bu); δ_C (100 MHz, MeOD): 172.5 (acetyl C=O), 156.5 (Boc C=O), 144.0 (C-3a), 141.3 (C-7a), 130.2 (C-7), 127.9 (C-6), 127.2 (C-4), 126.3 (C-5), 84.0 (C-3), 81.1 (^{t}Bu C_1), 46.4 (C-2), 42.1 (C_2-2',6'), 41.6 (C-1), 35.5 (C_A-3',5'), 31.8 (C_B-3',5'), 28.7 (^{t}Bu C_3), 20.9 (acetyl CH_3); HRMS found MNa^+ 368.1835. $C_{20}H_{27}NO_4$ requires *MNa* 368.1832.

tert-butyl (5_R_*,6_S_*)-5-(acetyloxy)-2-(4-methylbenzenesulfonyl)-2,9-diazaspiro[5.5]undec-7-ene-9-carboxylate (115)



Prepared according to a telescoped reaction using General procedure G and H, the alcohol derivative **94d** (0.95 g, 2.17 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give the *enecarbamate derivative* ***115*** (0.56 g, 56%, *rotamers* 51:49 by ^{1}H NMR) as a brown oil. R_f 0.18 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2967, 2869, 1739, 1699, 1649, 1507, 1455, 1411, 1366, 1308, 1236, 1161, 1038; δ_H (400 MHz, $CDCl_3$): 7.63 (2H, d, *J* 8.3 Hz, benzenesulfonyl 2,6-H^{maj}), 7.62 (2H, d, *J* 8.3 Hz, benzenesulfonyl 2,6-H^{min}) 7.33 (4H, d, *J* 8.3 Hz, benzenesulfonyl 3,5-H), 6.94 (1H, d, *J* 8.3 Hz, 8-H^{min}), 6.82 (1H, d, *J* 8.3 Hz, 8-H^{maj}), 4.70 (1H, app. br. s, 7-H^{maj}), 4.64-4.53 (3H, m, 7-H^{min} and 5-H), 3.74 (2H, dt, *J* 13.4 and 4.8 Hz, 3-H$_A$), 3.44-3.26 (4H, m, 3-H$_B$ and 10-H$_A$), 3.21 (1H, d, *J* 11.7 Hz, 1-H$_A^{maj}$), 3.04 (1H, d, *J* 11.7 Hz, 1-H$_A^{min}$), 2.86 (1H, d, *J* 11.7 Hz, 1-H$_B^{min}$), 2.76 (1H, d, *J* 11.7 Hz, 1-H$_B^{maj}$), 2.70-2.57 (2H, m, 10-H$_B$), 2.43 (6H, s, benzenesulfonyl CH_3), 2.04-1.94 (8H, m, acetyl and 4-H$_A$), 1.86-1.71 (4H, m, 4-H$_B$ and 11-H$_A$), 1.66-1.54 (2H, m, 11-H$_B$), 1.47 (18H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$): 170.1 (acetyl C=O), 152.0 (Boc C=O), 143.7 (benzenesulfonyl C-4), 133.9 (benzenesulfonyl C-1), 129.9 (benzenesulfonyl C_2-3,5), 128.0 (C-8^{min}), 127.8 (C-8^{maj}), 127.6 (benzenesulfonyl C_2-2,6), 104.6 (C-7^{min}), 104.2 (C-7^{maj}), 81.3 (^{t}Bu C_1), 74.0 (C-5^{maj}), 73.4 (C-5^{min}), 52.2 (C-6), 51.1 (C-1^{maj}), 50.0 (C-1^{min}), 41.9 (C-10^{maj}), 41.5 (C-10^{min}), 38.5 (C-3^{min}), 37.6 (C-3^{maj}), 28.9 (C-4), 28.4 (^{t}Bu C_3), 26.5 (C-11), 21.7 (benzenesulfonyl CH_3), 21.2 (acetyl CH_3); HRMS found MNa$^+$ 487.1877. $C_{23}H_{32}N_2O_6S$ requires *MNa*, 487.1873.

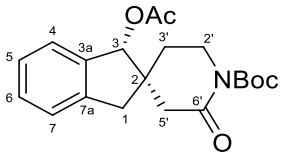
tert-butyl (5*R,6*R**)-5-(acetyloxy)-8-oxo-2-oxa-9-azaspiro[5.5]undecane-9-carboxylate (108)**



Prepared according to General procedure I, the acetate derivative **106a** (0.50 g, 1.53 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 40:60 to give the *spirocyclic lactam derivative* ***108*** (0.34 g,

68%) as a colourless oil. R_f 0.31 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2975, 2862, 1770, 1712, 1665, 1454, 1367, 1321, 1233, 1145, 1090; δ_H (500 MHz, $CDCl_3$, peak broadening due to unresolved rotamers): 4.77 (1H, dd, *J* 8.9 and 4.3 Hz, 5-H), 3.85 (1H, dt, *J* 11.7 and 4.9 Hz, 3-H_A), 3.79-3.71 (1H, m, 10-H_A), 3.69-3.65 (1H, m, 10-H_B), 3.62 (1H, d, *J* 11.9 Hz, 1-H_A), 3.52 (1H, ddd, *J* 11.7, 9.3 and 3.3 Hz, 3-H_B), 3.25 (1H, d, *J* 11.9, 1-H_B), 2.63 (1H, d, *J* 16.2 Hz, 7-H_A), 2.50 (1H, d, *J* 16.2, 7-H_B), 2.05 (3H, s, acetyl), 1.90-1.82 (1H, m, 4-H_A), 1.79-1.69 (2H, m, 4-H_B and 11-H_A), 1.66-1.58 (1H, m, 11-H_B), 1.50 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$): 170.4 (C-8), 170.0 (acetyl C=O), 151.9 (Boc C=O), 83.3 (^{t}Bu C_1), 75.0 (C-5), 73.3 (C-1), 65.5 (C-3), 42.1 (C-10), 38.2 (C-7), 37.5 (C-6), 29.8 (C-11), 28.1 (^{t}Bu C_3), 27.5 (C-4), 21.1 (acetyl CH_3); HRMS found MH^+ 328.1751. $C_{16}H_{25}NO_6$ requires *MH*, 328.1755.

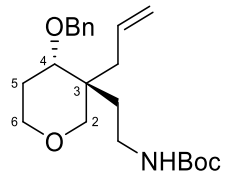
tert-butyl (2*R**,3*R**)-3-(acetyloxy)-6'-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (111)



Prepared according to General procedure I, the acetate derivative **106b** (1.00 g, 2.79 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 10:90 to give the *spirocyclic lactam derivative* ***111*** (0.58 g, 58%, *rotamers* 52:48 by ^{1}H NMR) as a colourless oil. R_f 0.67 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 2975, 2932, 1736, 1703, 1646, 1478, 1437, 1409, 1352, 1233, 1168, 1130, 1019; δ_H (500 MHz, $CDCl_3$): 7.41 (1H, d, *J* 7.6 Hz, 4-H^{min}), 7.33-7.19 (7H, m, 4-H^{maj}, 5-H, 6-H and 7-H), 6.04 (1H, s, 3-H^{maj}), 5.81 (1H, s, 3-H^{min}), 3.79 (1H, dt, *J* 13.0 and 5.4 Hz, 2'-H_A^{maj}), 3.75-3.65 (3H, m, 2'-H_A^{min} and 2'-H_B), 3.11 (1H, d, *J* 15.6 Hz, 1-H_A^{min}), 2.98 (1H, d, *J* 15.6 Hz, 1-H_A^{maj}), 2.88 (1H, d, *J* 15.6 Hz, 1-H_B^{maj}), 2.75 (2H, app. t, *J* 15.1 Hz, 1-H_B^{min} and 5'-H_A^{min}), 2.54-2.35 (3H, m, 5'-H_A^{maj} and 5'-H_B), 2.10 (3H, s, acetyl^{maj}), 2.07 (3H, s, acetyl^{min}), 2.05-1.86 (4H, m, 3'-H_2), 1.54 (9H, s, ^{t}Bu^{min}), 1.53 (9H, s, ^{t}Bu^{maj}); δ_C (125 MHz, $CDCl_3$): 171.0 (amide C=O^{maj}), 170.7 (amide C=O^{min}), 170.2 (acetyl C=O^{maj}), 169.5 (acetyl C=O^{min}), 152.7 (Boc C=O^{min}), 152.6 (Boc C=O^{maj}),

142.0 (C-3a^{min}), 140.8 (C-3a^{maj}), 139.7 (C-7a^{maj}), 139.6 (C-7a^{min}), 129.7 (C-6^{min}), 129.3 (C-6^{maj}), 127.4 (C-7), 126.8 (C-4^{min}), 125.8 (C-4^{maj}), 125.4 (C-5^{min}), 125.2 (C-5^{maj}), 83.4 (^{t}Bu C$_1$^{min}), 83.3 (^{t}Bu C$_1$^{maj}), 82.1 (C-3), 46.2 (C-2^{maj}), 45.8 (C-2^{min}), 45.1 (C-5'^{maj}), 43.9 (C-5'^{min}), 43.7 (C-2'^{maj}), 42.6 (C-2'^{min}), 41.6 (C-1^{min}), 41.5 (C-1^{maj}), 32.3 (C-3'), 28.2 (^{t}Bu C$_3$), 21.2 (acetyl CH$_3$^{min}), 21.1 (acetyl CH$_3$^{maj}); HRMS found MNa$^+$ 382.1612. $C_{20}H_{25}NO_5$ requires *MNa*, 382.1625.

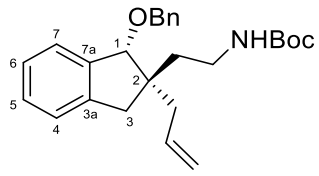
tert-butyl _N_-{2-[(3_R_*,4_R_*)-4-(benzyloxy)-3-(prop-2-en-1-yl)oxan-3-yl]ethyl}carbamate (116a)



Prepared according to General procedure J, the alcohol derivative **94a** (0.50 g, 1.76 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 20:80 to give the *benzyl ether derivative* ***116a*** (0.45 g, 71%) as a colourless oil. R_f 0.53 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3350, 3067, 2974, 2860, 1709, 1513, 1454, 1391, 1365, 1250, 1171, 1093; δ_H (400 MHz, $CDCl_3$): 7.39-7.26 (5H, m, phenyl), 5.80 (1H, ddt, *J* 12.8, 10.1 and 5.0 Hz, propenyl 2-H), 5.14-5.03 (2H, m, propenyl 3-H$_2$), 4.63 (1H, d, *J* 11.6 Hz, arylmethyl 1-H$_A$), 5.42 (1H, br. s, NH), 4.40 (1H, d, *J* 11.6 Hz, arylmethyl 1-H$_B$), 3.94-3.84 (1H, m, 6-H$_A$), 3.61 (1H, d, *J* 11.6, 2-H$_A$), 3.52 (1H, app. td, *J* 7.5 and 4.0 Hz, 4-H), 3.47-3.39 (1H, m, 6-H$_B$), 3.29-3.01 (3H, m, 2-H$_B$ and ethylcarbamate 2-H$_2$), 2.38-2.13 (2H, m, propenyl 1-H$_2$), 1.98-1.86 (1H, m, 5-H$_A$), 1.76 (1H, dtd, *J* 11.6, 7.5 and 4.0 Hz, 5-H$_B$), 1.67-1.50 (2H, m, ethylcarbamate 1-H$_2$), 1.42 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$): 155.8 (Boc C=O), 138.7 (phenyl C-1), 133.9 (propenyl C-2), 128.4 (phenyl C$_2$-3,5), 127.5 (phenyl C-4), 127.4 (phenyl C$_2$-2,6), 118.2 (propenyl C-3), 78.3 (^{t}Bu C$_1$), 77.2 (C-4), 71.6 (C-2), 70.4 (arylmethyl C-1), 65.2 (C-6), 40.6 (C-3), 36.1 (ethylcarbamate C-2), 34.0 (propenyl C-

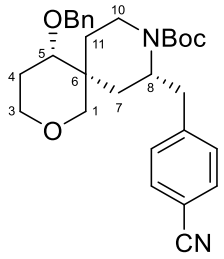
1), 33.2 (ethylcarbamate C-1), 28.5 (^{t}Bu C_3), 26.1 (C-5). HRMS found MNa^+ 398.2296. $C_{22}H_{33}NO_4$ requires *MNa*, 398.2301.

tert-butyl _N_-{2-[(1_R_*,2_R_*)-1-(benzyloxy)-2-(prop-2-en-1-yl)-1,3-dihydroinden-2-yl]ethyl}carbamate (116b)



Prepared according to General procedure J, the alcohol derivative **94b** (0.90 g, 2.84 mmol) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 10:90 to give the *benzyl ether derivative* ***116b*** (0.87 g, 75%) as a pale-yellow oil. R_f 0.31 (EtOAc–hexane 10:90). ν_{max}/cm^{-1}: 3360, 3027, 2975, 2929, 1697, 1505, 1454, 1365, 1248, 1067; δ_H (400 MHz, $CDCl_3$): 7.37-6.79 (9H, m, 4-H, 5-H, 6-H, 7-H and phenyl), 5.80 (1H, ddt, *J* 17.2, 10.1 and 7.4 Hz, propenyl 2-H), 5.02 (1H, app. dq, *J* 17.2 and 1.8 Hz, propenyl 3-H^{trans}), 4.97 (1H, app. dq, *J* 10.1 and 1.8 Hz, propenyl 3-H^{cis}), 4.62 (1H, d, *J* 11.7 Hz, arylmethyl 1-H_A), 4.53 (1H, d, *J* 11.7 Hz, arylmethyl 1-H_B), 4.44 (1H, s, 1-H), 4.23 (1H, br. s, NH), 3.02-2.92 (2H, m, ethylcarbamate 2-H_2), 2.89 (1H, d, *J* 15.8 Hz, 3-H_A), 2.57 (1H, d, *J* 15.8 Hz, 3-H_B), 2.45 (1H, dd, *J* 14.1 and 7.4 Hz, propenyl 1-H_A), 2.27 (1H, dd, *J* 14.1 and 7.4 Hz, propenyl 1-H_B), 1.55-1.41 (2H, m, ethylcarbamate 1-H_2), 1.32 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$): 155.9 (Boc C=O), 142.7 (C-7a), 142.3 (C-3a), 138.8 (phenyl C-1), 135.9 (propenyl C-2), 128.6 (C-5), 128.5 (phenyl C_2-3,5), 127.7 (phenyl C_2-2,6), 127.6 (C-4), 126.3 (phenyl C-4), 125.5 (C-6), 125.4 (C-7), 117.4 (propenyl C-3), 87.6 (C-1), 79.2 (^{t}Bu C_1), 71.5 (arylmethyl C-1), 49.8 (C-2), 41.7 (C-3), 37.6 (propenyl C-1), 37.1 (ethylcarbamate C_2-1,2), 28.6 (^{t}Bu C_3); HRMS found MH^+ 408.2538. $C_{26}H_{33}NO_3$ requires *MH*, 408.2533.

tert-butyl (5*R,6*S**,8*S**)-5-(benzyloxy)-8-[(4-cyanophenyl)methyl]-2-oxa-9-azaspiro[5.5]undecane-9-carboxylate (117a)**

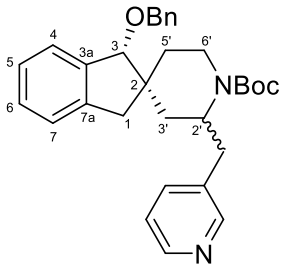


Prepared according to General procedure K, the benzyl ether derivative **116a** (0.25 g, 0.69 mmol) gave a crude material (*dr* 65:35 by ^{1}H NMR). This was then purified *via* column chromatography, eluting EtOAc–hexane 10:90→50:50 to give the *piperidine derivative* ***117a*** (0.21 g, 62%, *dr* 80:20, *rotamers* 55:45 by ^{1}H NMR) as a yellow oil. R_f 0.27 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2978, 2886, 2847, 2227, 1682, 1453, 1410, 1246, 1158, 1088; δ_H (500 MHz, $CDCl_3$): 7.59 (4H, m, cyanophenyl 3,5-H), 7.39-7.32 (14H, m, phenyl and cyanophenyl 2,6-H), 4.65 (1H, d, *J* 11.6 Hz, phenylmethyl 1-H_A^{maj}), 4.57 (1H, d, *J* 11.6 Hz, phenylmethyl 1-H_A^{min}), 4.36 (1H, d, *J* 11.6 Hz, phenylmethyl 1-H_B^{maj}), 4.31 (1H, d, *J* 11.6 Hz, phenylmethyl 1-H_B^{min}), 4.22 (1H, app. p, *J* 6.8 Hz, 8-H^{min}), 4.09 (1H, m, 8-H^{maj}), 3.99-3.90 (2H, m, 3-H_A), 3.89-3.77 (2H, m, 10-H_A), 3.75 (2H, d, *J* 11.5 Hz, 1-H_A), 3.62-3.56 (2H, m, 3-H_B), 3.54 (1H, d, *J* 11.5 Hz, 1-H_B^{maj}), 3.47-3.38 (3H, m, 10-H_B and 1-H_B^{min}), 3.20 (1H, dd, *J* 9.0 and 3.9 Hz, 5-H^{min}), 3.15-3.10 (1H, m, 5-H^{maj}), 3.27-2.87 (4H, m, 10-H_B and cyanophenylmethyl 1-H_A), 2.81-2.76 (1H, m, cyanophenylmethyl 1-H_B^{maj}), 2.70 (1H, dd, *J* 13.1 and 7.8 Hz, cyanophenylmethyl 1-H_B^{min}), 1.88-1.76 (4H, m, 4-H_A and 11-H_A), 1.73-1.63 (4H, m, 4-H_B and 11-H_B), 1.61-1.54 (4H, m, 7-H_2), 1.38 (9H, s, ^{t}Bu^{maj}), 1.37 (9H, s, ^{t}Bu^{min}); δ_C (125 MHz, $CDCl_3$): 156.0 (Boc C=O^{min}), 154.9 (Boc C=O^{maj}), 144.9 (cyanophenyl C-1^{min}), 144.6 (cyanophenyl C-1^{maj}), 138.6 (phenyl C-1), 132.2 (cyanophenyl C_2-3,5^{maj}), 132.2 (cyanophenyl C_2-3,5^{min}), 130.5 (cyanophenyl C_2-2,6^{min}), 130.3 (cyanophenyl C_2-2,6^{maj}), 128.6 (phenyl C_2-3,5), 127.9 (phenyl C_2-2,6^{maj}) 127.8 (phenyl C_2-2,6^{min}), 127.6 (phenyl C-4^{maj}), 127.5 (phenyl C-4^{min}), 119.2 (CN), 111.1 (cyanophenyl C-4), 80.7 (^{t}Bu C_1), 79.8 (C-5), 72.5 (C-1), 71.7 (phenylmethyl C-1^{maj}), 71.1 (phenylmethyl C-1^{min}),

64.4 (C-3), 50.9 (C-8), 41.4 (cyanophenylmethyl C-1^{maj}), 41.0 (cyanophenylmethyl C-1^{min}), 37.3 (C-6), 36.9 (C-10), 30.6 (C-11), 29.8 (C-7), 28.6 (^{t}Bu C_3), 25.4 (C-4); HRMS found MNa^+ 499.2561. $C_{29}H_{36}N_2O_4$ requires *MNa*, 499.2567. The relative configuration was determined through NOESY (600 MHz, MeOD). nOe observed between 8-H and 1-H_A.

tert-butyl (2*R,3*R**,2'*R**)-3-(benzyloxy)-2'-(pyridin-3-ylmethyl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (117b')**

tert-butyl (2*R,3*R**,2'*S**)-3-(benzyloxy)-2'-(pyridin-3-ylmethyl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (117b'')**

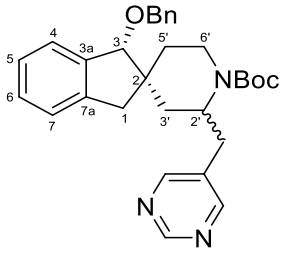


Prepared according to General procedure K, the benzyl ether derivative **116b** (0.25 g, 0.62 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 40:60 to give the *piperidine derivative* ***117b*** (120 mg, 40%, *dr* 65:35 and *rotamers* 40:60 by ^{1}H NMR) as a colourless oil. R_f 0.27 (EtOAc–hexane 40:60). ν_{max}/cm^{-1}: 2975, 2929, 2871, 1683, 1415, 1391, 1320, 1274, 1159, 1066, 1027; δ_H (500 MHz, $CDCl_3$, major diastereomer): 8.35-8.30 (2H, m, pyridinyl 2-H), 8.29-8.24 (2H, m, pyridinyl 6-H), 7.35-6.95 (22H, m, phenyl, 4-H, 5-H, 6-H, 7-H, pyridinyl 4-H and pyridinyl 5-H), 4.65-4.25 (8H, m, arylmethyl 1-H_2, 2'-H and 3-H), 3.03 (1H, d, *J* 15.0 Hz, 1-H_A^{min}), 3.02 (1H, d, *J* 15.0 Hz, 1-H_A^{maj}), 2.95-2.60 (5H, m, 6'-H_2 and 1-H_B^{min}), 2.31 (1H, d, *J* 15.0 Hz, 1-H_B^{maj}), 2.19 (2H, dd, *J* 13.9 and 2.9 Hz, 3'-H_A), 1.94 (2H, dd, *J* 14.3 and 6.3 Hz, pyridinylmethyl 1-H_A), 1.90-1.85 (2H, m, pyridinylmethyl 1-H_B), 1.68 (2H, dd, *J* 13.9 and 6.4 Hz, 3'-H_B), 1.32-1.25 (4H, m, 5'-H_2), 1.12 (9H, s, ^{t}Bu^{min}), 1.08 (9H, s, ^{t}Bu^{maj}); δ_C (125 MHz, $CDCl_3$, major diastereomer): 154.9 (Boc C=O^{min}), 154.6

(Boc C=O^{maj}), 150.5 (pyridinyl C-2^{min}), 150.4 (pyridinyl C-2^{maj}), 147.6 (pyridinyl C-6^{maj}), 147.3 (pyridinyl C-6^{min}), 144.2 (C-3a^{min}), 143.0 (C-3a^{maj}), 141.5 (C-7a^{maj}), 140.9 (C-7a^{min}), 138.7 (pyridinyl C-3^{min}), 138.4 (pyridinyl C-3^{maj}), 137.0 (pyridinyl C-4^{maj}), 136.9 (pyridinyl C-4^{min}), 135.3 (phenyl C-1^{maj}), 135.0 (phenyl C-1^{min}), 128.9 (C-6^{maj}), 128.8 (C-6^{min}), 128.6 (C-4^{maj}), 128.5 (C-4^{min}), 128.4 (phenyl C_2-3,5), 128.1 (phenyl C-4), 127.7 (phenyl C_2-2,6^{maj}), 127.6 (phenyl C_2-2,6^{min}), 126.6 (C-5), 125.7 (C-7), 123.5 (pyridinyl C-5^{min}), 123.3 (pyridinyl C-5^{maj}), 90.9 (C-3^{min}), 85.6 (C-3^{maj}), 79.6 (^{t}Bu C_1^{maj}), 79.5 (^{t}Bu C_1^{min}), 70.2 (arylmethyl C-1^{min}), 69.8 (arylmethyl C-1^{maj}), 52.3 (C-2'), 46.6 (C-1), 45.9 (C-2^{maj}), 45.4 (C-2^{min}), 36.6 (C-6'^{maj}), 36.5 (C-6'^{min}), 34.6 (C-5'), 34.1 (pyridinylmethyl C-1), 32.8 (C-3'), 28.3 (^{t}Bu C_3); HRMS found MNa^+ 507.2612. $C_{31}H_{36}N_2O_3$ requires *MNa*, 507.2618.

tert-butyl (2*R,3*R**,2'*R**)-3-(benzyloxy)-2'-(pyrimidin-5-ylmethyl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (117c')**

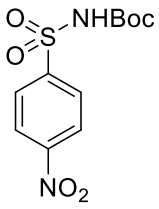
tert-butyl (2*R,3*R**,2'*S**)-3-(benzyloxy)-2'-(pyrimidin-5-ylmethyl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (117c'')**



Prepare according to General procedure K, the benzyl ether derivative **116b** (0.30 g, 0.74 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 10:90 → EtOAc to give the *piperidine derivative* ***117c*** (105 mg, 30%, *dr* 65:35 and *rotamers* 48:52 by ^{1}H NMR) as a colourless oil. R_f 0.31 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2974, 2929, 2869, 1687, 1561, 1551, 1478, 1410, 1365, 1271, 1066; δ_H (400 MHz, $CDCl_3$, major diastereomer): 9.14 (1H, s, pyrimidinyl 2-H^{min}), 9.10 (1H, s, pyrimidinyl 2-H^{maj}), 8.62-8.38 (4H, m, pyrimidinyl 4,6-H), 7.47-7.16 (18H,

m, phenyl, 4-H, 5-H, 6-H and 7-H), 4.65-4.45 (5H, m, arylmethyl 1-H_2 and 3-H^{min}), 4.20 (1H, s, 3-H^{maj}), 4.10-3.90 (2H, m, 2'-H), 3.17 (2H, d, *J* 15.3 Hz, 1-H_A), 3.10-2.72 (5H, m, 1-H_B^{maj} and 6'-H_2), 2.47 (1H, d, *J* 15.3 Hz, 1-H_B^{min}), 2.35 (2H, dd, *J* 14.0 and 2.8 Hz, 3'-H_A), 2.13 (2H, dd, *J* 14.3 and 6.4 Hz, pyrimidinylmethyl 1-H_A), 2.08-2.00 (2H, m, pyrimidinylmethyl 1-H_B), 1.85 (2H, dd, *J* 14.0 and 6.4 Hz, 3'-H_B), 1.53-1.37 (4H, m, 5'-H_2), 1.27 (9H, s, ^{t}Bu^{min}), 1.23 (9H, s, ^{t}Bu^{maj}); δ_C (100 MHz, $CDCl_3$, major diastereomer): 157.9 (Boc C=O^{min}), 157.5 (pyrimidinyl C_2-4,6), 157.4 (Boc C=O^{maj}), 157.1 (pyrimidinyl C-2^{maj}), 156.9 (pyrimidinyl C-2^{min}), 154.5 (pyrimidinyl C-5), 144.0 (C-3a^{min}), 142.9 (C-3a^{maj}), 141.3 (C-7a^{maj}), 140.8 (C-7a^{min}), 138.6 (phenyl C-1^{min}), 138.3 (phenyl C-1^{maj}), 129.1 (C-6^{maj}), 128.9 (C-6^{min}), 128.7 (C-4), 128.4 (phenyl C_2-3,5^{maj}), 128.2 (phenyl C_2-3,5^{min}), 127.7 (phenyl C_2-2,6^{maj}), 127.6 (phenyl C_2-2,6^{min}), 126.7 (phenyl C-4), 126.3 (C-5^{maj}), 126.0 (C-5^{min}), 125.9 (C-7^{min}), 125.8 (C-7^{maj}), 90.9 (C-3^{min}) 85.4 (C-3^{maj}), 80.0 (^{t}Bu C_1^{min}), 79.9 (^{t}Bu C_1^{maj}), 70.3 (arylmethyl C-1^{min}), 69.8 (arylmethyl C-1^{maj}), 52.0 (C-2'), 46.6 (C-1), 45.9 (C-2^{maj}), 45.5 (C-2^{min}), 36.2 (C-6'), 34.6 (C-5'), 34.1 (pyrimidinylmethyl C-1), 33.0 (C-3'), 28.4 (^{t}Bu C_3^{min}), 28.3 (^{t}Bu C_3^{maj}); HRMS found MH^+ 486.2752. $C_{30}H_{35}N_3O_3$ requires *MH*, 486.2751.

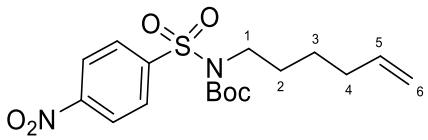
N-Boc-*p*-nitrobenzenesulfonamide (119)



To a solution of 4-nitrobenzenesulfonamide (4.16 g, 20.6 mmol) in DCM (60 ml) were added Et_3N (4.30 ml, 30.8 mmol), Boc_2O (5.38 g, 24.8 mmol) and DMAP (252 mg, 2.06 mmol) at room temperature under nitrogen. After 30 mins, the reaction mixture was poured into a solution of 1 M HCl (50 ml) and the aqueous layer was extracted with diethyl ether (4 x 30 ml). The combined organic extracts were washed with brine (30 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. Purification of this crude material by trituration (Et_2O–hexane 40:60)

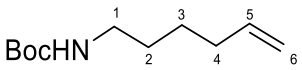
gave compound **119**[159] (5.93 g, 95%) as a white powder. R_f 0.83 (EtOAc). δ_H (400 MHz, $CDCl_3$): 8.40 (2H, d, *J* 8.9 Hz, aryl 3,5-H), 8.24 (2H, d, *J* 8.9 Hz, aryl 2,6-H), 7.49 (1H, br. s, NH), 1.41 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$): 150.8 (Boc C=O), 148.7 (aryl C-4), 144.4 (aryl C-1), 129.9 (aryl C_2-2,6), 124.3 (aryl C_2-3,5), 85.3 (^{t}Bu C_1), 28.0 (^{t}Bu C_3). All data is consistent with known literature values.[159]

tert-butyl _N_-(hex-5-en-1-yl)-_N_-(4-nitrobenzenesulfonyl)carbamate (120)



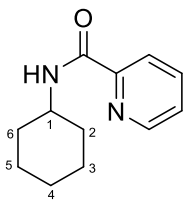
N-Boc-*p*-nitrobenzenesulfonamide **119** (5.90 g, 19.5 mmol) was dissolved in toluene (60 ml) at rt. Then 5-hexan-1-ol (4.66 ml, 38.9 mmol) and PPh_3 (10.2 g, 38.9 mmol) were added and the resulting solution allowed to stir for 5 mins at rt. DEAD (6.10 ml, 38.9 mmol) was then added dropwise and the reaction mixture allowed to stir at rt for 1 h. The mixture was concentrated under reduced pressure to give the crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 10:90 to give the *sulfonamide derivative* ***120*** (7.08 g, 94%) as a pale-yellow oil. R_f 0.41 (EtOAc–hexane 10:90). ν_{max}/cm^{-1}: 2980, 2935, 1727, 1532, 1349, 1305, 1285, 1150, 1086; δ_H (400 MHz, $CDCl_3$): 8.36 (2H, d, *J* 8.9 Hz, aryl 3,5-H), 8.10 (2H, d, *J* 8.9 Hz, aryl 2,6-H), 5.81 (1H, ddt, *J* 16.9, 10.2 and 7.1 Hz, hexenyl 5-H), 5.04 (1H, app. dq, *J* 16.9 and 1.6 Hz, hexenyl 6-H_{trans}), 4.98 (1H, app. dq, *J* 10.2 and 1.6 Hz, hexenyl 6-H_{cis}), 3.84 (2H, t, *J* 7.6 Hz, hexenyl 1-H_2), 2.12 (2H, q, *J* 7.1 Hz, hexenyl 4-H_2), 1.77 (2H, pent, *J* 7.1 Hz, hexenyl 2-H_2), 1.46 (2H, pent, *J* 7.1 Hz, hexenyl 3-H_2), 1.36 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$): 150.6 (Boc C=O), 150.4 (aryl C-4), 146.0 (aryl C-1), 138.3 (hexenyl C-5), 129.4 (aryl C_2-2,6), 124.0 (aryl C_2-3,5), 115.2 (hexenyl C-6), 85.2 (^{t}Bu C_1), 47.6 (hexenyl C-1), 33.3 (hexenyl C-4), 29.8 (hexenyl C-2), 28.0 (^{t}Bu C_3), 26.0 (hexenyl C-3); HRMS found MNa^+ 407.1243. $C_{17}H_{24}N_2O_6S$ requires *MNa*, 407.1245.

***tert*-butyl *N*-(hex-5-en-1-yl)carbamate (121)**



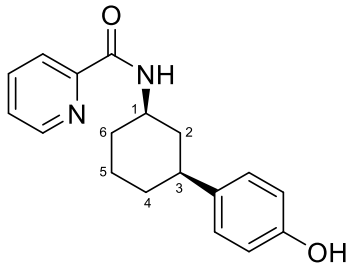
Sulfonamide derivative **120** (1.38 g, 3.60 mmol) and K_2CO_3 (0.75 g, 5.40 mmol) were dissolved in DMF (35 ml) at rt. Then 4-chlorothiophenol (0.78 g, 5.40 mmol) was added and the reaction mixture allowed to stir at rt for 24 h. Then, a saturated solution of $NaHCO_3$ (30 ml) was added and the mixture was extracted with EtOAc (3 x 20 ml). The combined organic extracts were washed sequentially with water (30 ml) and brine (30 ml), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give the alkene derivative **121**[160] (0.59 g, 83%) as a colourless oil. R_f 0.33 (EtOAc–hexane 10:90). δ_H (400 MHz, $CDCl_3$): 5.77 (1H, ddt, *J* 17.0, 10.2 and 6.7 Hz, hexenyl 5-H), 4.98 (1H, app. dq, *J* 17.0 and 1.6 Hz, hexenyl 6-H_{trans}), 4.92 (1H, app. dq, *J* 10.2 and 1.6 Hz, hexenyl 6-H_{cis}), 4.56 (1H, br. s, NH), 3.13-3.05 (2H, m, hexenyl 1-H_2), 2.04 (2H, q, *J* 7.0 Hz, hexenyl 4-H_2), 1.50-1.36 (13H, m, hexenyl 2-H_2, hexenyl 3-H_2 and ^{t}Bu); δ_C (100 MHz, $CDCl_3$): 156.1 (Boc C=O), 138.6 (hexenyl C-5), 114.8 (hexenyl C-6), 79.1 (^{t}Bu C_1), 40.5 (hexenyl C-1), 33.4 (hexenyl C-4), 29.6 (hexenyl C-2), 29.6 (^{t}Bu C_3), 26.1 (hexenyl C-3). All data is consistent with known literature values.[160]

***N*-cyclohexylpyridine-2-carboxamide (131)**



DIPEA (4.18 ml, 24 mmol) was added dropwise to a solution of cyclohexylamine (2.00 g, 20.0 mmol), picolinic acid (2.95 g, 24.0 mmol) and HATU (9.26 g, 24.0 mmol) in DMF (100 ml) at rt. The resulting solution was stirred at rt for 18 h. A saturated aqueous solution of LiCl (150 ml) was added and the aqueous phase extracted with EtOAc (3 x 50 ml). The organic layers were combined, washed sequentially with water (100 ml) and brine (100 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 30:70 to give picolinamide derivative **131**[107] (2.78 g, 68%) as a white crystalline solid. R_f 0.67 (EtOAc–hexane 50:50). δ_H (500 MHz, $CDCl_3$): 8.42 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.09 (1H, dt, *J* 7.8 and 1.0 Hz, pyridinyl 3-H), 7.90 (1H, br. d, *J* 6.9 Hz, NH), 7.71 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.29 (1H, ddd, *J* 7.8. 4.8 and 1.0 Hz, pyridinyl 5-H), 3.91-3.82 (1H, m, cyclohexyl 1-H), 1.93-1.87 (2H, m, cyclohexyl 2-H_A and 6-H_A), 1.65 (2H, app. dt, *J* 13.3 and 3.8 Hz, cyclohexyl 2-H_B and 6-H_B), 1.55-1.49 (1H, m, cyclohexyl 4-H_A), 1.37-1.04 (5H, m, cyclohexyl 4-H_B, 3-H_2 and 5-H_2); δ_C (125 MHz, $CDCl_3$): 163.1 (C=O), 150.1 (pyridinyl C-2), 147.8 (pyridinyl C-6), 137.1 (pyridinyl C-4), 125.8 (pyridinyl C-5), 122.0 (pyridinyl C-3), 48.0 (cyclohexyl C-1), 32.9 (cyclohexyl C_2-2,6), 25.4 (cyclohexyl C-4), 24.7 (cyclohexyl C_2-3,5). All data is consistent with known literature values.[107]

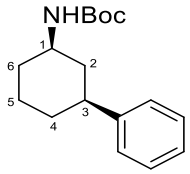
N-[(1*R**,3*S**)-3-(4-hydroxyphenyl)cyclohexyl]pyridine-2-carboxamide (132d)



Prepared according to General procedure U, picolinamide derivative **131** (0.50 g, 2.45 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give *arylated derivative* ***132d*** (124 mg, 18%, *dr* >95:<5 by ^1H NMR) as a white solid. R_f 0.21 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3293, 2927,

2853, 1651, 1529, 1514, 1447, 1434, 1369, 1214, 1171, 1088; δ_H (500 MHz, $CDCl_3$): 8.53 (1H, ddd, *J* 4.7, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.21 (1H, dt, *J* 7.7 and 1.0 Hz, pyridinyl 3-H), 7.98 (1H, br. d, *J* 8.4 Hz, NH), 7.84 (1H, td, *J* 7.7 and 1.7 Hz, pyridinyl 4-H), 7.42 (1H, ddd, *J* 7.7, 4.8 and 1.0 Hz, pyridinyl 5-H), 7.04 (2H, d, *J* 8.5 Hz, phenyl 2,6-H), 6.76 (2H, d, *J* 8.5 Hz, phenyl 3,5-H), 5.49 (1H, br. s, OH), 4.15-4.06 (1H, m, cyclohexyl 1-H), 2.64 (1H, tt, *J* 12.2 and 3.3 Hz, cyclohexyl 3-H), 2.27-2.21 (1H, m, cyclohexyl 2-H_A), 2.15-2.09 (1H, m, cyclohexyl 6-H_A), 1.98-1.91 (1H, m, cyclohexyl 5-H_A), 1.88 (1H, app. d, *J* 12.9 Hz, cyclohexyl 4-H_A), 1.60-1.51 (1H, m, cyclohexyl 5-H_B), 1.40-1.29 (3H, m, cyclohexyl 2-H_B, cyclohexyl 6-H_B and cyclohexyl 4-H_B); δ_C (125 MHz, $CDCl_3$): 163.6 (C=O), 154.2 (phenyl C-4), 150.1 (pyridinyl C-2), 148.1 (pyridinyl C-6), 138.5 (phenyl C-1), 137.6 (pyridinyl C-4), 127.9 (phenyl C_2-2,6), 126.3 (pyridinyl C-5), 122.5 (pyridinyl C-3), 115.3 (phenyl C_2-3,5), 49.1 (cyclohexyl C-1), 42.4 (cyclohexyl C-3), 41.2 (cyclohexyl C-2), 33.6 (cyclohexyl C-4), 32.9 (cyclohexyl C-6), 25.3 (cyclohexyl C-5); HRMS found MH^+ 297.1594. $C_{18}H_{20}N_2O_2$ requires *MH*, 297.1598.

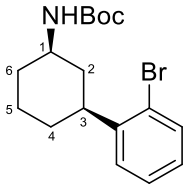
tert-butyl _N_-[(1_R_*,3_S_*)-3-phenylcyclohexyl]carbamate (133a)



Prepared according to an adapted General procedure Q, cyclohexylamine (1.00 g, 10.1 mmol), iodobenzene (4.10 g, 20.2 mmol) and Boc_2O (8.80 g, 40.4 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 10:90 to give arylated derivative **133a**[110] (1.69 g, 61%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.35 (EtOAc–hexane 20:80). δ_H (500 MHz, $CDCl_3$): 7.31-7.26 (2H, m, phenyl 2,6-H), 7.22-7.15 (3H, m, phenyl 3,4,5-H), 4.52 (1H, br. s, NH), 3.66-3.54 (1H, m, 1-H), 2.63 (1H, tt, *J* 12.3 and 3.5 Hz, 3-H), 2.23-2.17 (1H, m, 2-H_A), 2.08-2.02 (1H, m, 6-H_A), 1.95-1.83 (2H, m, 4-H_A and 5-H_A), 1.55-1.41 (10H, m, 5-H_B and ^{t}Bu),

1.35 (1H, qd, *J* 12.6 and 3.5 Hz, 4-H_B), 1.24 (1H, q, *J* 12.1 Hz, 2-H_B), 1.11 (1H, qd, *J* 12.6 and 3.5 Hz, 6-H_B); δ_C (125 MHz, $CDCl_3$): 155.2 (Boc C=O), 146.3 (phenyl C-1), 128.4 (phenyl C_2-2,6), 126.8 (phenyl C_2-3,5), 126.1 (phenyl C-4), 79.1 (^{t}Bu C_1), 50.1 (C-1), 43.3 (C-3), 41.5 (C-2), 33.2 (C_2-4,6), 28.5 (^{t}Bu C_3), 25.3 (C-5). All data is consistent with known literature values.[110]

tert-butyl _N_-[(1_R_*,3_S_*)-3-(2-bromophenyl)cyclohexyl]carbamate (133b)



Prepared according to General procedure Q, cyclohexylamine (0.50 g, 5.00 mmol) and 2-bromoiodobenzene (2.83 g, 10.0 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give arylated derivative **133b**[110] (1.00 g, 57%, *dr* >95:<5 by ^{1}H NMR) an off-white solid. R_f 0.50 (EtOAc–hexane 20:80). δ_H (500 MHz, $CDCl_3$): 7.53 (1H, dd, *J* 8.0 and 0.8 Hz, phenyl 3-H), 7.28-7.23 (1H, m, phenyl 5-H), 7.20 (1H, dd, *J* 8.0 and 1.7 Hz, phenyl 6-H), 7.03 (1H, td, *J* 8.0 and 1.7 Hz, phenyl 4-H), 4.45 (1H, br. s, NH), 3.69-3.50 (1H, m, 1-H), 3.10 (1H, t, *J* 11.6 Hz, 3-H), 2.24-2.15 (1H, m, 2-H_A), 2.08 (1H, d, *J* 12.0 Hz, 6-H_A), 1.92-1.83 (2H, m, 4-H_A and 5-H_A), 1.53 (1H, app. qt, *J* 13.2 and 3.2 Hz, 5-H_B), 1.44 (9H, s, ^{t}Bu), 1.32-1.17 (2H, m, 2-H_B and 4-H_B), 1.11 (1H, qd, *J* 12.6 and 3.8 Hz, 6-H_B); δ_C (125 MHz, $CDCl_3$): 155.2 (Boc C=O), 144.8 (phenyl C-1), 133.1 (phenyl C-3), 127.7 (phenyl C-4), 127.6 (phenyl C-5), 127.3 (phenyl C-6), 124.6 (phenyl C-2), 79.3 (^{t}Bu C_1), 50.0 (C-1), 42.0 (C-3), 39.9 (C-2), 33.4 (C-6), 32.3 (C-4), 28.6 (^{t}Bu C_3), 25.2 (C-5). All data is consistent with known literature values.[110]

tert-butyl _N_-[(1_R_*,3_S_*)-3-(3-methoxyphenyl)cyclohexyl]carbamate (133c)

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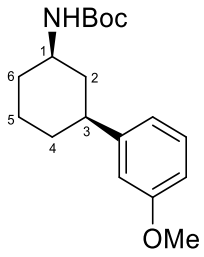
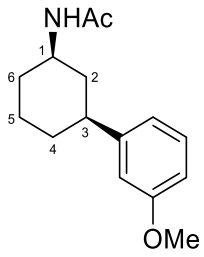


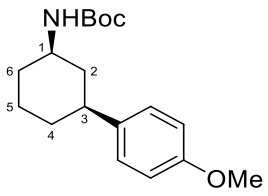
Prepared according to General procedure Q, cyclohexylamine (0.50 g, 5.00 mmol) and 3-iodoanisole (1.17 g, 10.0 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give *arylated derivative* ***133c*** (1.43 g, 93%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.48 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 3345, 2975, 2929, 2855, 1687, 1584, 1494, 1390, 1266, 1241, 1159, 1049; δ_H (500 MHz, $CDCl_3$): 7.23-7.18 (1H, m, phenyl 5-H), 6.79 (1H, dt, *J* 7.7 and 1.2 Hz, phenyl 6-H), 6.75-6.71 (2H, m, phenyl 2-H and phenyl 4-H), 4.43 (1H, br. s, NH), 3.79 (3H, s, OMe), 3.64-3.54 (1H, m, 1-H), 2.61 (1H, tt, *J* 12.2 and 3.1 Hz, 3-H), 2.19 (1H, d, *J* 12.2 Hz, 2-H$_A$), 2.08-2.01 (1H, m, 6-H$_A$), 1.93-1.80 (2H, m, 5-H$_A$ and 4-H$_A$), 1.54-1.39 (10H, m, ^{t}Bu and 5-H$_B$), 1.33 (1H, qd, *J* 12.4 and 3.2 Hz, 4-H$_B$), 1.22 (1H, app. q, *J* 12.2 Hz, 2-H$_B$), 1.09 (1H, qd, *J* 12.4 and 3.4 Hz, 6-H$_B$); δ_C (125 MHz, $CDCl_3$): 159.8 (phenyl C-3), 155.3 (Boc C=O), 148.2 (phenyl C-1), 129.4 (phenyl C-5), 119.3 (phenyl C-6), 112.9 (phenyl C-2), 111.4 (phenyl C-4), 79.3 (^{t}Bu C_1), 55.3 (OMe), 50.1 (C-1), 43.4 (C-3), 41.5 (C-2), 33.4 (C-6), 33.2 (C-4), 28.6 (^{t}Bu C_3), 25.3 (C-5); HRMS found MNa$^+$ 328.1876. $C_{18}H_{27}NO_3$ requires *MNa*, 328.1883.

_N_-[(1_R_*,3_S_*)-3-(3-methoxyphenyl)cyclohexyl]acetamide (133d)



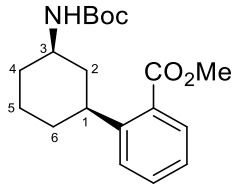
Prepared according to General procedure R, cyclohexylamine (0.50 g, 5.00 mmol) and 3-iodoanisole (1.19 ml, 10.0 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give *arylated derivative* ***133d*** (0.91 g, 74%, *dr* >95:<5 by ^{1}H NMR) a light brown solid. R_f 0.17 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3287, 2930, 2852, 1637, 1552, 1447, 1370, 1271, 1043; δ_H (500 MHz, $CDCl_3$): 7.19 (1H, t, *J* 8.1 Hz, phenyl 5-H), 6.77 (1H, d, *J* 7.7 Hz, phenyl 6-H), 6.74-6.69 (2H, m, phenyl 2-H and phenyl 4-H), 5.55 (1H, br. d, *J* 7.4 Hz, NH), 3.90 (1H, tdt, *J* 12.0, 8.1 and 3.9 Hz, 1-H), 3.77 (3H, s, OMe), 2.62 (1H, tt, *J* 12.1 and 3.1 Hz, 3-H), 2.18-2.12 (1H, m, 2-H_A), 2.07-1.99 (1H, m, 6-H_A), 1.94 (3H, s, acetyl), 1.72-1.65 (2H, m, 4-H_A and 5-H_A), 1.64-1.56 (1H, m, 5-H_B), 1.37-1.30 (1H, m, 4-H_B), 1.23 (1H, q, *J* 12.0 Hz, 2-H_B), 1.14-1.08 (1H, m, 6-H_B); δ_C (125 MHz, $CDCl_3$): 169.2 (acetyl C=O), 159.7 (phenyl C-3), 148.0 (phenyl C-1), 129.4 (phenyl C-5), 119.2 (phenyl C-6), 112.8 (phenyl C-2), 111.3 (phenyl C-4), 55.3 (OMe), 48.8 (C-1), 43.2 (C-3), 41.0 (C-2), 33.3 (C-4), 33.1 (C-6), 25.0 (C-5), 23.6 (acetyl CH_3); HRMS found MNa^+ 270.1471. $C_{15}H_{21}NO_2$ requires *MNa*, 270.1465.

***tert*-butyl _N_-[(1_R_*,3_S_*)-3-(4-methoxyphenyl)cyclohexyl]carbamate (133e)**



Prepared according to General procedure Q, cyclohexylamine (0.50 g, 5.00 mmol) and 4-iodoanisole (2.23 g, 10.0 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give *arylated derivative* ***133e*** (0.57 g, 38%, *dr* >95:<5 by ^{1}H NMR) an off-white solid. R_f 0.40 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 3368, 2977, 2923, 1680, 1512, 1249, 1235, 1170, 1036; δ_H (500 MHz, $CDCl_3$): 7.10 (2H, d, *J* 8.6 Hz, phenyl 2,6-H), 6.83 (2H, d, *J* 8.6 Hz, phenyl 3,5-H), 4.43 (1H, br. s, NH), 3.78 (3H, s, OMe), 3.62-3.51 (1H, m, 1-H), 2.57 (1H, tt, *J* 12.2 and 2.9 Hz, 3-H), 2.17 (1H, app. d, *J* 12.2 Hz, 2-H$_A$), 2.07-2.00 (1H, m, 6-H$_A$), 1.91-1.80 (2H, m, 4-H$_A$ and 5-H$_A$), 1.53-1.38 (10H, m, 5-H$_B$ and ^{t}Bu), 1.30 (1H, qd, *J* 12.7 and 3.4 Hz, 4-H$_B$), 1.18 (1H, app. q, *J* 12.2 Hz, 2-H$_B$), 1.08 (1H, qd, *J* 12.5 and 3.8 Hz, 6-H$_B$); δ_C (125 MHz, $CDCl_3$): 158.0 (phenyl C-4), 155.3 (Boc C=O), 138.7 (phenyl C-1), 127.7 (phenyl C$_2$-2,6), 113.9 (phenyl C$_2$-3,5), 79.2 (^{t}Bu C$_1$), 55.4 (OMe), 50.2 (C-1), 42.5 (C-3), 41.8 (C-2), 33.5 (C-4), 33.3 (C-6), 28.6 (^{t}Bu C$_3$), 25.3 (C-5); HRMS found MNa$^+$ 328.1893. $C_{18}H_{27}NO_3$ requires *MNa*, 328.1883.

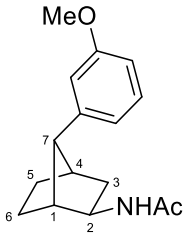
methyl 2-[(1*R,3*S**)-3-[(*tert*-butoxycarbonyl)amino]cyclohexyl]benzoate (133g)**



Prepared according to General procedure Q, cyclohexylamine (0.50 g, 5.00 mmol) and methyl-2-iodobenzoate (1.52 ml, 10.0 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give *arylated derivative* ***133g*** (316 mg, 19%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.21 (EtOAc–hexane 10:90). ν_{max}/cm^{-1}: 3351, 2977, 2936, 2851, 1722, 1677, 1486, 1239, 1169, 1071; δ_H (500 MHz, $CDCl_3$): 7.74 (1H, d, *J* 7.4 Hz, phenyl 3-H), 7.43 (1H, t, *J* 7.4 Hz, phenyl 4-H), 7.34 (1H, d, *J* 7.4 Hz, phenyl 6-H), 7.22 (1H, t, *J* 7.4 Hz, phenyl 5-H), 4.42 (1H, br. s, NH), 3.92 (3H, s, CO_2Me), 3.64-3.52 (1H, m, cyclohexyl 3-H), 3.44 (1H, app. t, *J* 11.7 Hz, cyclohexyl 1-H), 2.18-2.12 (1H, m, cyclohexyl 2-H$_A$), 2.07 (1H, app. br. d,

J 11.8 Hz, cyclohexyl 4-H_A), 1.91-1.81 (2H, m, cyclohexyl 5-H_A and cyclohexyl 6-H_A), 1.58-1.50 (1H, m, cyclohexyl 5-H_B), 1.43 (9H, s, ^{t}Bu), 1.36-1.23 (2H, m, cyclohexyl 2-H_B and cyclohexyl 6-H_B), 1.12 (1H, qd, *J* 12.8 and 4.3 Hz, cyclohexyl 4-H_B); δ_C (125 MHz, $CDCl_3$): 168.7 (ester C=O), 155.2 (Boc C=O), 147.0 (phenyl C-1), 131.8 (phenyl C-4), 130.2 (phenyl C-3), 130.0 (phenyl C-2), 126.8 (phenyl C-6), 125.9 (phenyl C-5), 79.2 (^{t}Bu C_1), 52.2 (CO_2Me), 50.2 (cyclohexyl C-3), 41.0 (cyclohexyl C-1), 39.0 (cyclohexyl C-2), 33.7 (cyclohexyl C-6), 33.5 (cyclohexyl C-4), 28.6 (^{t}Bu C_3), 25.4 (cyclohexyl C-5); HRMS found MH^+ 334.2011. $C_{19}H_{27}NO_4$ requires *MH*, 334.2013.

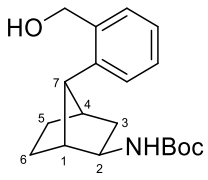
_N_-[(1_R_*,2_R_*,4_R_*,7_R_*)-7-(3-methoxyphenyl)bicyclo[2.2.1]heptan-2-yl]acetamide (136a)



Prepared according to General procedure Q, *exo*-2-aminonorbornane (0.50 g, 4.50 mmol) and 3-iodoanisole (1.07 ml, 9.00 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give *arylated derivative* ***136a*** (0.81 g, 70%, *dr* >95:<5 by ^{1}H NMR) as an off-white solid. R_f 0.14 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3271, 2961, 2897, 2870, 1637, 1555, 1433, 1294, 1044; δ_H (500 MHz, $CDCl_3$): 7.22 (1H, t, *J* 7.9 Hz, phenyl 5-H), 6.88 (1H, app. d, *J* 7.6 Hz, phenyl 6-H), 6.84-6.82 (1H, m, phenyl 2-H), 6.73 (1H, dd, *J* 8.2 and 2.6 Hz, phenyl 4-H), 4.56 (1H, br. d, *J* 7.2 Hz, NH), 3.83 (1H, td, *J* 8.5 and 4.0 Hz, 2-H), 3.77 (3H, s, OMe), 2.95 (1H, app. s, 7-H), 2.70 (1H, t, *J* 4.0 Hz, 4-H), 2.66 (1H, d, *J* 4.4 Hz, 1-H), 1.85 (1H, dd, *J* 13.4 and 8.5 Hz, 3-H_A), 1.75 (1H, tt, *J* 11.7 and 4.4 Hz, 6-H_A), 1.70-1.61 (1H, m, 5-H_A), 1.55-1.46 (4H, m, 3-H_B and acetyl), 1.40-1.34 (1H, m, 6-H_B), 1.29-1.22 (1H, m, 5-H_B); δ_C (125 MHz, $CDCl_3$): 168.6 (acetyl C=O), 159.8 (phenyl C-3), 142.3 (phenyl C-1), 129.5 (phenyl C-5), 120.7 (phenyl C-6), 114.3 (phenyl C-2), 111.2

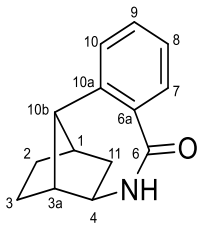
(phenyl C-4), 55.2 (OMe), 53.2 (C-2), 52.8 (C-7), 46.7 (C-1), 37.9 (C-3), 37.6 (C-4), 28.6 (C-5), 27.8 (C-6), 23.3 (acetyl CH_3); HRMS found MH^+ 260.1644. $C_{16}H_{21}NO_2$ requires *MH*, 260.1645.

tert-butyl _N_-[(1_R_*,2_R_*,4_R_*,7_R_*)-7-[2-(hydroxymethyl)phenyl]bicyclo[2.2.1]heptan-2-yl]carbamate (136b)



Prepared according to General procedure Q, *exo*-2-aminonorbornane (0.50 g, 4.50 mmol) and 2-iodobenzyl alcohol (2.10 g, 9.00 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give *arylated derivative* ***136b*** (0.42 g, 30%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.36 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 3485, 3433, 2962, 2869, 1693, 1504, 1451, 1346, 1275, 1007; δ_H (500 MHz, $CDCl_3$): 7.46 (1H, app br. d, *J* 4.1 Hz, phenyl 6-H), 7.27-7.18 (3H, m, phenyl 3-H, phenyl 4-H and phenyl 5-H), 4.75-4.64 (2H, m, hydroxymethyl 1-H_2), 3.57-3.46 (2H, m, 2-H and NH), 2.94 (1H, app. s, 7-H), 2.72-2.62 (3H, m, 1-H, 4-H and OH), 1.87 (1H, dd, *J* 13.7 and 8.0 Hz, 3-H_A), 1.82-1.72 (2H, m, 3-H_B and 6-H_A), 1.69-1.61 (1H, m, 5-H_A), 1.39-1.18 (11H, m, 5-H_B, 6-H_B and ^{t}Bu); δ_C (125 MHz, $CDCl_3$): 155.2 (Boc C=O), 140.1 (phenyl C-2), 138.0 (phenyl C-1), 128.4 (phenyl C-6), 127.6 (phenyl C-5), 127.4 (phenyl C-3), 126.6 (phenyl C-4), 78.7 (^{t}Bu C_1), 62.5 (hydroxymethyl C-1), 54.9 (C-2), 50.9 (C-7), 47.0 (C-1), 38.3 (C-4), 38.2 (C-3), 28.6 (C-5), 28.3 (^{t}Bu C_3), 27.6 (C-6); HRMS found MNa^+ 340.1885. $C_{19}H_{27}NO_3$ requires *MNa*, 340.1883.

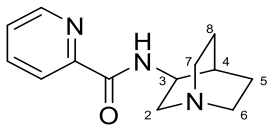
(1*R,3a*R**,4*R**,10b*S**)-2,3,3a,4,5,10b-hexahydro-1,4-methanobenzo[*c*]cyclopenta[*e*]azepin-6(1*H*)-one (136e)**



$Pd(OAc)_2$ (51.0 mg, 5 mol%), 2-hydroxynicotinaldehyde (55.0 mg, 10 mol%), methyl-2-iodobenzoate (1.32 ml, 9.00 mmol) and AgTFA (1.99 g, 9.00 mmol) were added to HFIP–AcOH 19:1 (10 ml). Then *exo*-2-aminonorbornane (0.50 g, 4.50 mmol) and H_2O (0.90 ml) were added sequentially and the reaction mixture allowed to stir at rt for 10 mins. The reaction mixture was then stirred at 120 ^oC for 24 h. The dark brown suspension was allowed to cool to rt and filtered through celite, with the celite being washed with THF (3 x 15 ml). The filtrate was concentrated under reduced pressure and the resulting residue was dissolved in THF (20 ml). 1M HCl (20 ml) was added and the light brown suspension was left to stir for 1 h at rt. The mixture was basified with 2M NaOH and left to stir for 18 h at rt. EtOAc (50 ml) was added and the layers were separated. The organic layer was passed through a plug of silica, then the aqueous layer was extracted with EtOAc (3 x 20 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 35:65 to give *lactam derivative* ***136e*** (0.58 g, 60%) as a white solid. R_f 0.21 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 3170, 3055, 2947, 2870, 1639, 1445, 1343, 1251, 1131; δ_H (500 MHz, $CDCl_3$): 8.35 (1H, br. d, *J* 7.2 Hz, NH), 8.30 (1H, d, *J* 8.0 Hz, 7-H), 7.35 (1H, td, *J* 7.8 and 1.2 Hz, 9-H), 7.27-7.21 (2H, m, 8-H and 10-H), 3.30-3.24 (1H, m, 4-H), 2.98 (1H, app. s, 10b-H), 2.37 (1H, d, *J* 3.9 Hz, 3a-H), 2.32 (1H, br. t, *J* 4.0 Hz, 1-H), 1.81-1.61 (4H, m, 11-H_2 and 2-H_2), 1.37-1.30 (1H, m, 3-H_A), 1.22-1.14 (1H, m, 3-H_B); δ_C (125 MHz, $CDCl_3$): 169.2 (C-6), 141.0 (C-10a), 132.0 (C-7), 131.6 (C-6a), 131.1 (C_2-9,10), 125.9 (C-8), 57.4 (C-10b), 54.7 (C-4), 48.1 (C-1), 43.1 (C-3a),

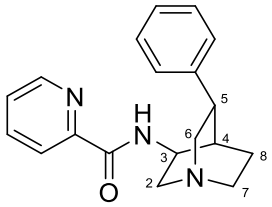
38.0 (C-11), 27.7 (C-2), 27.4 (C-3); HRMS found MNa^+ 236.1050. $C_{14}H_{15}NO$ requires *MNa*, 236.1046.

_N_-[(1_R_*,3_R_*,4_R_*)-1-azabicyclo[2.2.2]octan-3-yl]pyridine-2-carboxamide (138)



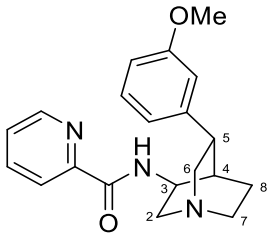
Prepared according to General procedure S, 3-aminoquinuclidine dihydrochloride (5.00 g, 25.1 mmol) gave a crude material. This was further purified by stirring in MTBE (60 ml) for 2 h and any solids were subsequently filtered off. The filtrate was concentrated under reduced pressure to give picolinamide derivative **138**[111] (3.67 g, 63%) as a colourless oil. R_f 0.45 (DCM–MeOH 90:10). δ_H (500 MHz, $CDCl_3$): 8.56 (1H, d, *J* 4.7 Hz, pyridinyl 6-H), 8.26 (1H, br. d, *J* 5.7 Hz, NH), 8.19 (1H, d, *J* 7.8 Hz, pyridinyl 3-H), 7.85 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.43 (1H, ddd, *J* 7.8, 4.7 and 1.2 Hz, pyridinyl 5-H), 4.20-4.14 (1H, m, 3-H), 3.44 (1H, ddd, *J* 14.2, 9.5 and 2.3 Hz, 2-H_A), 3.02-2.95 (1H, m, 6-H_A), 2.95-2.80 (3H, m, 6-H_B and 7-H_2), 2.68 (1H, ddd, *J* 14.2, 4.9 and 2.1 Hz, 2-H_B), 2.07-2.03 (1H, m, 4-H), 1.86-1.80 (1H, m, 5-H_A), 1.76-1.69 (2H, m, 8-H_2), 1.57-1.48 (1H, m, 5-H_B); δ_C (125 MHz, $CDCl_3$): 164.3 (C=O), 150.0 (pyridinyl C-2), 148.2 (pyridinyl C-6), 137.6 (pyridinyl C-4), 126.3 (pyridinyl C-5), 122.3 (pyridinyl C-3), 56.2 (C-2), 47.7 (C-6), 46.9 (C-7) 46.6 (C-3), 26.0 (C-8), 25.9 (C-4), 20.4 (C-5). All data is consistent with known literature values.[111]

***N*-[(1*R**,3*R**,4*S**,5*S**)-5-phenyl-1-azabicyclo[2.2.2]octan-3-yl]pyridine-2-carboxamide (139c)**



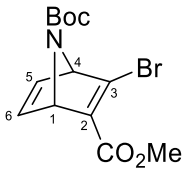
To a solution of picolinamide derivative **138** (0.50 g, 2.16 mmol) and iodobenzene (0.72 ml, 6.49 mmol) in DMF (10 ml) were added pivalic acid (221 mg, 2.16 mmol), $Pd(OAc)_2$ (24.2 mg, 5 mol%) and Ag_2CO_3 (656 mg, 2.38 mmol). The resulting mixture was stirred and heated at 100 ^oC for 24 h. Then 5M NaOH (20 ml) was added and the resulting solution extracted with DCM (3 x 30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting DCM–sat. MeOH/NH_3 95:5 to give arylated derivative **139c**[111] (159 mg, 24%, *dr* >95:<5 by ^1H NMR) as a white solid. R_f 0.25 (DCM–sat. MeOH/NH_3 95:5). δ_H (500 MHz, $CDCl_3$): 8.13 (1H, d, *J* 4.7 Hz, pyridine 6-H), 7.93 (1H, d, *J* 7.8 Hz, pyridine 3-H), 7.73-7.64 (2H, m, pyridine 4-H and NH), 7.35 (2H, d, *J* 8.1 Hz, phenyl 2,6-H), 7.27-7.20 (3H, m, phenyl 3,5-H and pyridine 5-H), 7.10 (1H, t, *J* 7.3 Hz, phenyl 4-H), 4.16 (1H, ddd, *J* 12.0, 8.2 and 3.5 Hz, 3-H), 3.50 (1H, dd, *J* 13.7 and 7.7 Hz, 6-H_A), 3.47-3.35 (2H, m, 6-H_B and 2-H_A), 3.12 (1H, t, *J* 8.7 Hz, 5-H), 2.95-2.84 (2H, m, 7-H_2), 2.79-2.74 (1H, m, 2-H_B), 2.57 (1H, dt, *J* 5.7 and 3.0 Hz, 4-H), 1.93-1.78 (2H, m, 8-H_2) δ_C (125 MHz, $CDCl_3$): 163.7 (C=O), 149.6 (pyridine C-2), 147.5 (pyridine C-6), 143.2 (phenyl C-1), 137.0 (pyridine C-4), 129.0 (phenyl C_2-3,5), 127.1 (phenyl C_2-2,6), 126.0 (phenyl C-4), 125.8 (pyridine C-5), 121.7 (pyridine C-3), 57.0 (C-2), 52.0 (C-6), 46.8 (C-3), 46.3 (C-7), 38.2 (C-5), 32.7 (C-4), 28.9 (C-8). All data is consistent with known literature values.[111]

_N_-[(1_R_*,3_R_*,4_S_*,5_S_*)-5-(3-methoxyphenyl)-1-azabicyclo[2.2.2]octan-3-yl]pyridine-2-carboxamide (139b)



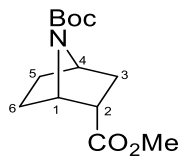
To a solution of picolinamide derivative **138** (0.50 g, 2.16 mmol) and 3-iodoanisole (0.77 ml, 6.49 mmol) in DMF (10 ml) were added pivalic acid (242 mg, 2.38 mmol), $Pd(OAc)_2$ (73.0 mg, 15 mol%) and Ag_2CO_3 (657 mg, 2.38 mmol). The resulting mixture was stirred and heated at 100 ^oC for 24 h. Then 5M NaOH (20 ml) was added and the resulting solution extracted with DCM (3 x 30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting DCM–sat. NH_3/MeOH 95:5 to give *arylated derivative* ***139b*** (0.52 g, 71%, *dr* >95:<5 by ^1H NMR) as a dark yellow oil. R_f 0.29 (DCM–sat. NH_3/MeOH 95:5). ν_{max}/cm^{-1}: 3343, 2938, 2872, 1658, 1590, 1515, 1461, 1434, 1319, 1252, 1157, 1040; δ_H (500 MHz, $CDCl_3$): 8.19 (1H, ddd, *J* 4.7, 1.7 and 0.9 Hz, pyridinyl 6-H), 7.96 (1H, dt, *J* 7.8 and 1.2 Hz, pyridinyl 3-H), 7.81 (1H, br. d, *J* 7.9 Hz, NH), 7.70 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.27 (1H, ddd, *J* 7.8, 4.7 and 1.2 Hz, pyridinyl 5-H), 7.18 (1H, t, *J* 7.7 Hz, phenyl 5-H), 6.94 (1H, dd, *J* 7.7 and 0.7 Hz, phenyl 6-H), 6.90 (1H, app. s, phenyl 2-H), 6.65 (1H, dd, *J* 7.7 and 2.5 Hz, phenyl 4-H), 4.20-4.14 (1H, m, 3-H), 3.72 (3H, s, OMe), 3.52-3.36 (3H, m, 2-H_A and 6-H_2), 3.10 (1H, t, *J* 8.7 Hz, 5-H), 2.94-2.86 (2H, m, 7-H_2), 2.78 (1H, dd, *J* 14.1 and 4.6 Hz, 2-H_B), 2.56 (1H, dt, *J* 5.7 and 3.0 Hz, 4-H), 1.93-1.77 (2H, m, 8-H_2); δ_C (125 MHz, $CDCl_3$): 163.7 (C=O), 160.2 (phenyl C-3), 149.6 (pyridinyl C-2), 147.5 (pyridinyl C-6), 144.9 (phenyl C-1), 137.0 (pyridinyl C-4), 130.0 (phenyl C-5), 125.8 (pyridinyl C-5), 121.7 (pyridinyl C-3), 119.6 (phenyl C-6), 112.7 (phenyl C-2), 111.4 (phenyl C-4), 57.0 (C-2), 55.2 (OMe), 52.0 (C-6), 46.7 (C-3), 46.2 (C-7), 38.3 (C-5), 32.7 (C-4), 28.8 (C-8); HRMS found MH^+ 338.1879. $C_{20}H_{23}N_3O_2$ requires *MH*, 338.1863.

tert-butyl 2-methyl (1*R,4*S**)-3-bromo-7-azabicyclo[2.2.1]hepta-2,5-diene-2,7-dicarboxylate (141)**



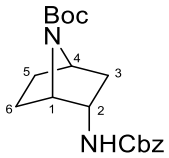
Methyl propiolate (2.00 g, 23.8 mmol) in acetone was added NBS (4.89 g, 27.4 mmol) and $AgNO_3$ (0.40 g, 2.38 mmol) and the reaction was left to stir for 2 h at rt. Water (100 ml) was added and the mixture extracted with DCM (3 x 80 ml). The combined organic layers were combined, washed sequentially with a saturated aqueous solution of $NaHCO_3$ (20 ml) and brine (20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude intermediate. This was then dissolved in toluene (10 ml) and *N*-Boc pyrrole (8.00 g, 48.0 mmol) was added and the resulting reaction mixture heated at 90 ^oC for 5 days. The mixture was concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 10:90 to give the bicyclic alkene derivative **141**[112] (1.49 g, 20%) as a bright yellow oil. R_f 0.31 (EtOAc–hexane 10:90). δ_H (500 MHz, $CDCl_3$): 7.16-7.02 (2H, m, 5-H and 6-H), 5.47 (1H, app. s, 1-H), 5.11 (1H, app. br. s, 4-H), 3.78 (3H, s, OMe), 1.40 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$): 162.8 (ester C=O), 154.2 (carbamate C=O), 148.0 (C-3), 144.1 (C-2), 141.5 (C-6), 140.5 (C-5), 81.7 (^{t}Bu C_1), 75.1 (C-4), 68.5 (C-1), 52.0 (OMe), 28.2 (^{t}Bu C_3). All data is consistent with known literature values.[112]

tert-butyl 2-methyl (1*R,2*R**,4*S**)-7-azabicyclo[2.2.1]heptane-2,7-dicarboxylate (142)**



Bicyclic alkene derivative **141** (1.40 g, 4.26 mmol) was dissolved in MeOH (30 ml) at rt. Et_3N (1.19 ml, 8.52 mmol) and Pd/C (43.0 mg, 10 wt%) were added sequentially. The black suspension was then left to stir for 18 h at rt under H_2 atmosphere. The reaction mixture was then filtered through celite and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give methyl ester derivative **142**[113] (0.98 g, 91%, *dr* >95:<5 by ^{1}H NMR) as a pale-yellow oil. R_f 0.35 (EtOAc–hexane 10:90). δ_H (500 MHz, $CDCl_3$): 4.36 (1H, app. br. s, 1-H), 4.19 (1H, app. br. s, 4-H), 3.68 (3H, s, OMe), 3.05-2.98 (1H, m, 2-H), 1.99-1.90 (1H, m, 3-H_A), 1.83 (1H, dd, *J* 12.4 and 4.9 Hz, 3-H_B), 1.79-1.72 (1H, m, 5-H_A), 1.72-1.63 (1H, m, 6-H_A), 1.47-1.43 (2H, m, 5-H_B and 6-H_B), 1.42 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$): 173.3 (ester C=O), 155.5 (carbamate C=O), 80.0 (^{t}Bu C_1), 58.4 (C-1), 57.3 (C-4), 52.0 (OMe), 46.4 (C-2), 32.5 (C-3), 29.2 (C-5), 28.4 (^{t}Bu C_3), 25.6 (C-6). All data is consistent with known literature values.[113]

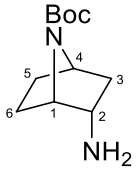
tert-butyl (1*R,2*R**,4*S**)-2-(benzyloxycarbonylamino)-7-azabicyclo[2.2.1]heptane-7-carboxylate (143)**



Methyl ester derivative **142** (3.00 g, 11.8 mmol) was added to MeOH–H_2O 1:1 (150 ml) and LiOH.H_2O (0.55 g, 13.0 mmol) was added at rt. The reaction mixture was stirred at rt for 18 h then carefully adjusted to pH 3 with 5M HCl and extracted with $CHCl_3$ (3 x 50 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude carboxylic acid intermediate. This was then dissolved in toluene (50 ml) and Et_3N (2.06 ml, 14.8 mmol) and DPPA (3.00 ml, 14.1 mmol) were added sequentially. The resulting reaction mixture was heated at 100 ^{o}C for 1 h. BnOH (2.44 ml, 23.6 mmol) was added and the reaction mixture heated at 100 ^{o}C for a further 18 h. Once the reaction was complete, the

reaction mixture was concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting petrol–Et_2O 50:50 to give carbamate derivative **143**[113] (3.16 g, 78%) as a pale-yellow oil. R_f 0.20 (petrol–Et_2O 50:50). δ_H (500 MHz, $CDCl_3$): 7.38-7.32 (5H, m, phenyl), 5.12 (1H, d, *J* 11.8 Hz, arylmethyl 1-H_A), 5.07 (1H, d, *J* 11.8 Hz, arylmethyl 1-H_B), 4.80 (1H, br. d, *J* 4.8 Hz, NH), 4.36 (1H, app. br. s, 1-H), 4.17 (1H, app. br, s, 4-H), 4.13-4.05 (1H, m, 2-H), 2.40-2.31 (1H, m, 3-H_A), 1.85-1.73 (2H, m, 5-H_2), 1.73-1.63 (1H, m, 6-H_A), 1.44 (9H, s, ^{t}Bu), 1.40-1.34 (1H, m, 6-H_B), 0.89 (1H, dd, *J* 12.7 and 4.3 Hz, 3-H_B); δ_C (125 MHz, $CDCl_3$): 156.1 (Cbz C=O), 155.5 (Boc C=O), 136.4 (phenyl C-1), 128.7 (phenyl C_2-3,5), 128.4 (phenyl C-4), 128.3 (phenyl C_2-2,6), 80.0 (^{t}Bu C_1), 67.0 (arylmethyl C-1), 58.8 (C-1), 56.5 (C-4), 51.8 (C-2), 37.6 (C-3), 29.8 (C-6), 28.4 (^{t}Bu C_3), 22.2 (C-5). All data is consistent with known literature values.[113]

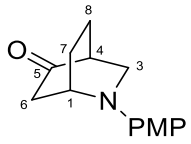
tert-butyl (1*R,2*R**,4*S**)-2-amino-7-azabicyclo[2.2.1]heptane-7-carboxylate (144)**



Carbamate derivative **143** (530 mg, 1.54 mmol) was dissolved in MeOH (10 ml) then Pd/C (53.0 mg, 10 wt%) was added and the suspension stirred under H_2 atmosphere for 18 h. The suspension was then filtered through celite and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting DCM–MeOH/NH_3 95:5 to give amine derivative **144**[113] (243 mg, 75%) as a colourless oil. R_f 0.21 (DCM–MeOH 90:10). δ_H (500 MHz, $CDCl_3$): 4.10 (1H, app. br. s, 4-H), 4.00 (1H, app. br. s, 1-H), 3.49-3.44 (1H, m, 2-H), 2.26-2.19 (1H, m, 3-H_A), 2.01 (1H, ddd, *J* 12.2, 9.2 and 4.2 Hz, 6-H_A), 1.82-1.72 (1H, m, 5-H_A), 1.68-1.59 (1H, m, 6-H_B), 1.50 (2H, br. s, NH_2), 1.43 (10H, s, 5-H_B and ^{t}Bu), 0.81 (1H, dd, *J* 12.3 and 4.6 Hz, 3-H_B); δ_C (125 MHz, $CDCl_3$): 155.8 (Boc C=O), 79.6 (^{t}Bu C_1), 60.8

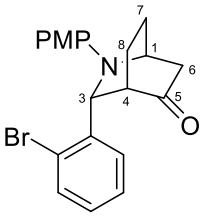
(C-1), 57.5 (C-4), 52.5 (C-2), 40.0 (C-3), 30.2 (C-5), 28.4 (^{t}Bu C_3), 21.0 (C-6). All data is consistent with known literature values.[113]

(1*R,4*R**)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-one (148a)**



p-anisidine (4.06 g, 33.0 mmol), *rac*-proline (1.04 g, 30 mol%), 2-cyclohexenone (5.76 g, 60.0 mmol) and formaldehyde (2.24 ml, 30.0 mmol, 37% solution in H_2O) were dissolved in DMSO (50 ml) at rt. The reaction mixture was then stirred at 50 ^{o}C for 24 h. The mixture was allowed to cool to rt, diluted with water and extracted with EtOAc (3 x 30 ml). The combined organic layers were washed with water (5 x 50 ml) then brine (20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 15:85 to give bicyclic ketone derivative **148a**[115] (2.84 g, 41%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.29 (EtOAc–hexane 20:80). δ_H (500 MHz, $CDCl_3$): 6.86 (2H, d, *J* 9.1 Hz, phenyl 3,5-H), 6.64 (2H, d, *J* 9.1 Hz, phenyl 2,6-H), 4.23-4.19 (1H, m, 1-H), 3.76 (3H, s, OMe), 3.64 (1H, app. dt, *J* 9.9 and 2.5 Hz, 3-H_A), 3.47 (1H, dd, *J* 9.9 and 1.9 Hz, 3-H_B), 2.67 (1H, app. dt, *J* 18.6 and 3.1 Hz, 6-H_A), 2.61 (1H app. p, *J* 2.8 Hz, 4-H), 2.41 (1H, dd, *J* 18.6 and 1.7 Hz, 6-H_B), 2.21-2.13 (1H, m, 7-H_A), 2.05-1.92 (2H, m, 8-H_2), 1.85-1.77 (1H, m, 7-H_B); δ_C (125 MHz, $CDCl_3$): 214.0 (C-5), 151.6 (phenyl C-4), 143.0 (phenyl C-1), 115.2 (phenyl C_2-3,5), 113.0 (phenyl C_2-2,6), 55.9 (OMe), 50.8 (C-3), 48.3 (C-1), 45.1 (C-6), 44.4 (C-4), 25.2 (C-7), 22.3 (C-8). All data is consistent with known literature values.[115]

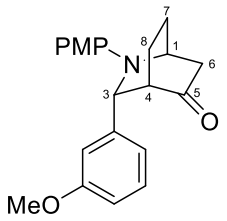
(1*R,3*S**,4*R**)-3-(2-bromophenyl)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-one (148b)**



p-anisidine (2.00 g, 16.2 mmol), *rac*-proline (0.19 g, 30 mol%), 2-cyclohexenone (1.56 ml, 16.2 mmol) and 2-bromobenzaldehyde (1.00 g, 5.41 mmol) were dissolved in MeCN–H_2O 9:1 (15 ml) at rt. The reaction mixture was then stirred at 35 ^oC for 3 days. The mixture was filtered through celite, eluting with EtOAc. The filtrate was diluted with EtOAc (20 ml) and subsequently washed with water (2 x 40 ml). The aqueous washings were then back extracted with EtOAc (3 x 30 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material (*dr* 80:20 by ^1H NMR). This was then purified *via* column chromatography, eluting EtOAc–hexane 15:85 to give *bicyclic ketone derivative* ***148b*** (1.08 g, 53%, *dr* >95:<5 by ^1H NMR) as a yellow oil. R_f 0.30 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 3062, 2934, 2868, 2832, 1732, 1508, 1460, 1440, 1293, 1240, 1180, 1110, 1083; δ_H (500 MHz, $CDCl_3$): 7.56 (1H, dd, *J* 7.9 and 1.1 Hz, bromophenyl 3-H), 7.35 (1H, dd, *J* 7.9 and 1.7 Hz, bromophenyl 6-H), 7.20 (1H, td, *J* 7.9 and 1.1 Hz, bromophenyl 5-H), 7.10 (1H, td, *J* 7.9 and 1.7 Hz, bromophenyl 4-H), 6.76 (2H, d, *J* 9.2 Hz, methoxyphenyl 3,5-H), 6.56 (2H, d, *J* 9.2 Hz, methoxyphenyl 2,6-H), 4.90 (1H, d, *J* 1.8 Hz, 3-H), 4.48-4.44 (1H, m, 1-H), 3.71 (3H, s, OMe), 2.88-2.81 (2H, m, 4-H and 6-H_A), 2.51 (1H, dd, *J* 18.8 and 2.2 Hz, 6-H_B), 2.24-2.17 (2H, m, 7-H_A and 8-H_A), 2.03-1.97 (1H, m, 8-H_B), 1.82-1.77 (1H, m, 7-H_B); δ_C (125 MHz, $CDCl_3$): 212.1 (C-5), 152.6 (methoxyphenyl C-4), 141.9 (methoxyphenyl C-1), 140.2 (bromophenyl C-1), 133.5 (bromophenyl C-3), 129.3 (bromophenyl C-4), 128.2 (bromophenyl C-5), 128.0 (bromophenyl C-6), 122.3 (bromophenyl C-2), 115.4 (methoxyphenyl C_2-2,6), 114.9 (methoxyphenyl C_2-3,5), 65.2 (C-3), 55.7 (OMe), 50.6 (C-1), 49.4 (C-4), 46.1 (C-6), 22.7 (C-7), 22.3 (C-8); HRMS found MH^+ 388.0730. $C_{20}H_{20}BrNO_2$ requires *MH*, 388.0730. The relative

configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 3-H and 8-H_A and bromophenyl 6-H and 6-H_A.

(1*R,3*S**,4*R**)-3-(3-methoxyphenyl)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-one (148c)**

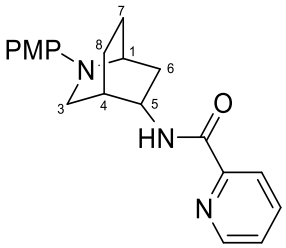


p-anisidine (2.72 g, 22.1 mmol), *rac*-proline (0.26 g, 30 mol%), 2-cyclohexenone (2.14 ml, 22.1 mmol) and 3-methoxybenzaldehyde (1.00 g, 7.40 mmol) were dissolved in MeCN–H_2O 9:1 (15 ml) at rt. The reaction mixture was then stirred at 35 ^oC for 3 days. The mixture was then filtered through celite eluting with EtOAc. The filtrate was diluted with EtOAc (20 ml) and subsequently washed with water (2 x 40 ml). The aqueous washing were then back extracted with EtOAc (3 x 30 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material (*dr* 80:20 by ^1H NMR). This was then purified *via* column chromatography, eluting EtOAc–hexane 10:90 to give *bicyclic ketone derivative* ***148c*** (1.02 g, 41%, *dr* 90:10 by ^1H NMR) as a yellow oil. R_f 0.29 (EtOAc–hexane 20:80). δ_H (500 MHz, $CDCl_3$): 7.29 (1H, t, *J* 7.9 Hz, methyoxyphenyl 5-H), 7.03-6.98 (2H, m, methoxyphenyl 2-H and 6-H), 6.83 (1H, dd, *J* 7.9 and 2.1 Hz, methoxyphenyl 4-H), 6.74 (2H, d, *J* 9.2 Hz, paramethoxyphenyl 3,5-H), 6.56 (2H, d, *J* 9.2 Hz, paramethoxyphenyl 2,6-H), 4.66 (1H, d, *J* 1.9 Hz, 3-H), 4.44-4.40 (1H, m, 1-H), 3.80 (3H, s, OMe), 3.70 (3H, s, OMe), 2.75 (1H, app. dt, *J* 18.7 and 3.1 Hz, 6-H_A), 2.66 (1H, app. q, *J* 2.9 Hz, 4-H), 2.37 (1H, dd, *J* 18.7 and 1.8 Hz, 6-H_B), 2.31-2.22 (1H, m, 7-H_A), 1.92-1.84 (1H, m, 7-H_B), 1.81-1.73 (1H, m, 8-H_A), 1.67-1.58 (1H, m, 8-H_B); δ_C (125 MHz, $CDCl_3$): 214.0 (C-5), 160.3 (methoxyphenyl C-3), 152.2 (paramethoxyphenyl C-4), 142.9 (methoxyphenyl C-1), 142.5 (paramethoxyphenyl C-1), 129.9 (methoxyphenyl C-5), 118.9 (methoxyphenyl

C-6), 115.0 (paramethoxyphenyl C_2-3,5), 114.5 (paramethoxyphenyl C_2-2,6), 112.7 (methoxyphenyl C-4). 112.2 (methoxyphenyl C-2), 62.9 (C-3), 55.8 (OMe), 55.3 (OMe), 51.1 (C-4), 49.0 (C-1), 42.0 (C-6), 26.5 (C-7), 16.5 (C-8); HRMS found MH^+ 338.1749. $C_{21}H_{23}NO_3$ requires *MH*, 338.1751. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between methoxyphenyl 6-H and 6-H_A.

***N*-[(1*R**,4*R**,5*R**)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-yl]pyridine-2-carboxamide (149a')**

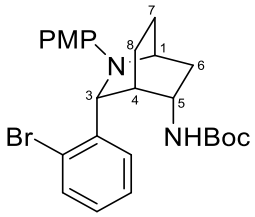
***N*-[(1*R**,4*R**,5*S**)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-yl]pyridine-2-carboxamide (149a'')**



Bicyclic ketone derivative **148a** (1.25 g, 5.41 mmol) was dissolved in MeOH (25 ml) and ammonium acetate (4.17 g, 54.1 mmol) was added followed by $Na(CN)BH_3$ (0.68 g, 10.8 mmol) and the reaction mixture left to stir for 18 h at rt. 1M NaOH (20 ml) was added and the mixture was then extracted with EtOAc (3 x 30 ml). The organic layers were combined, washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. Picolinic acid (0.73 g, 5.95 mmol) and CDI (0.98 g, 5.95 mmol) were then dissolved in DMF (25 ml) and left to stir for 1 h at rt. Then the crude amine intermediate in DMF (10 ml) was added and the resulting solution allowed to stir for a further 18 h at rt. Water (20 ml) and 1M NaOH (20 ml) was added and the mixture was then extracted with DCM (3 x 30 ml). The organic layers were combined, washed with water (5 x 30 ml), dried ($MgSO_4$), filtered

and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 20:80 to give *picolinamide derivative* ***149a*** (0.80 g, 44%, *dr* 60:40 by ^{1}H NMR, *rotamers* 51:49 by ^{1}H NMR) as a colourless oil. R_f 0.25 (EtOAc–hexane 25:75). ν_{max}/cm^{-1}: 3378, 2931, 2858, 2830, 1668, 1506, 1479, 1432, 1236, 1179, 1038; δ_H (500 MHz, $CDCl_3$, major rotamers reported): 8.58-8.54 (1H, m, pyridinyl 6-H^{min}), 8.50 (1H, ddd, *J* 4.8, 1.6 and 0.9 Hz, pyridinyl 6-H^{maj}), 8.21-8.16 (3H, m, pyridinyl 3-H and NH^{maj}), 8.03 (1H, br. d, *J* 9.5 Hz, NH^{min}), 7.89-7.80 (2H, m, pyridinyl 4-H), 7.47-7.39 (2H, m, pyridinyl 5-H), 6.87 (2H, d, *J* 9.1 Hz, methoxyphenyl 3,5-H^{maj}), 6.73 (2H, d, *J* 8.9 Hz, methoxyphenyl 3,5-H^{min}), 6.66 (2H, d, *J* 9.1 Hz, methoxyphenyl 2,6-H^{maj}), 6.55 (2H, d, *J* 8.9 Hz, methoxyphenyl 2,6-H^{min}), 4.41-4.34 (1H, m, 5-H^{maj}), 3.97-3.89 (1H, m, 5-H^{min}), 3.88-3.85 (2H, app. p, *J* 2.7 Hz, 1-H), 3.77 (3H, s, OMe^{maj}), 3.72 (3H, s, OMe^{min}), 3.60 (1H, app. dt, *J* 10.1 and 2.3 Hz, 3-H$_A$^{maj}), 3.23 (1H, dd, *J* 13.1 and 3.7 Hz, 3-H$_A$^{min}), 3.21-3.17 (1H, m, 3-H$_B$^{maj}), 2.99 (1H, dd, *J* 13.1 and 6.5 Hz, 3-H$_B$^{min}), 2.64-2.56 (1H, m, 6-H$_A$^{min}), 2.35 (1H, ddd, *J* 13.4, 10.5 and 2.5 Hz, 6-H$_A$^{maj}), 2.28 (1H, app. dd, *J* 5.5 and 2.8 Hz, 4-H^{min}), 2.24 (1H, app. dd, *J* 5.5 and 2.8 Hz, 4-H^{maj}), 2.08-2.03 (1H, m, 7-H$_A$^{min}), 1.99-1.90 (1H, m, 7-H$_A$^{min}), 1.86-1.53 (6H, m, 6-H$_B$, 7-H$_B$ and 8-H$_A$), 1.44-1.23 (2H, m, 8-H$_B$); δ_C (125 MHz, $CDCl_3$, major rotamers reported): 164.1 (C=O^{maj}), 164.0 (C=O^{min}), 151.7 (methoxyphenyl C-4^{min}), 151.0 (methoxyphenyl C-4^{maj}), 149.9 (pyridinyl C-2^{min}), 149.5 (pyridinyl C-2^{maj}), 148.2 (pyridinyl C-3^{maj}), 148.1 (pyridinyl C-3^{min}), 143.6 (methoxyphenyl C-1^{maj}), 143.1 (methoxyphenyl C-1^{min}), 137.6 (pyridinyl C-4^{min}), 137.4 (pyridinyl C-4^{maj}), 126.4 (pyridinyl C-5^{min}), 126.3 (pyridinyl C-5^{maj}), 122.5 (pyridinyl C-3^{min}), 122.2 (pyridinyl C-3^{maj}), 115.1 (methoxyphenyl C$_2$-3,5^{maj}), 114.9 (methoxyphenyl C$_2$-3,5^{min}), 114.1 (methoxyphenyl C$_2$-2,6^{min}), 112.6 (methoxyphenyl C$_2$-2,6^{maj}), 56.0 (OMe^{maj}), 55.9 (OMe^{min}), 48.0 (C-3^{maj}), 47.8 (C-3^{min}), 46.6 (C-5^{min}), 45.8 (C-5^{maj}), 45.0 (C-1^{maj}), 43.9 (C-1^{min}), 35.9 (C-6^{maj}), 35.3 (C-6^{min}), 31.6 (C-4^{maj}), 30.2 (C-4^{min}), 25.6, (C-7^{min}), 25.4 (C-7^{maj}), 24.8 (C-8^{min}), 23.6 (C-8^{maj}); HRMS found MH$^+$ 338.1866. $C_{20}H_{23}N_3O_2$ requires *MH*, 338.1863.

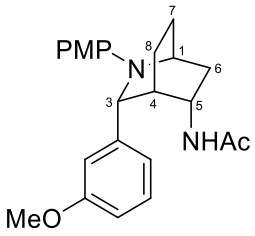
tert-butyl _N_-[(1_R_*,3_S_*,4_S_*,5_R_*)-3-(2-bromophenyl)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-yl]carbamate (149b)



Bicyclic ketone **148b** (1.02 g, 2.64 mmol) was dissolved in sat. NH_3/MeOH (50 ml) and Ti(O^iPr)$_4$ (1.59 ml, 5.27 mmol) was added at rt. The solution was allowed to stir for 18 h at rt, then cooled to 0 ^oC and $NaBH_4$ (150 mg, 3.96 mmol) was added portionwise. The resulting reaction mixture was left to stir at rt for 2 h. The mixture was concentrated under reduced pressure and the resulting residue was dissolved in EtOAc (30 ml) and brine (30 ml) was added with vigorous stirring. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. This intermediate was dissolved in THF (20 ml) and the solution was basified with 2M NaOH. Then Boc_2O (1.73 g, 7.92 mmol) was added and the resulting mixture was allowed to stir at rt for 4 h. Water (20 ml) was added and the mixture was then extracted with EtOAc (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 10:90 to give *carbamate derivative* ***149b*** (311 mg, 25%, *dr* 74:26 by ^1H NMR) as a colourless oil. R_f 0.54 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 3285, 2937, 2865, 1694, 1510, 1346, 1270, 1225, 1190, 1081; δ_H (500 MHz, $CDCl_3$): 7.64-7.57 (3H, m, bromophenyl 3-H and bromophenyl 6-H^{maj}), 7.57-7.51 (1H, m, bromophenyl 6-H^{min}), 7.29 (1H, td, *J* 7.6 and 1.0 Hz, bromophenyl 5-H^{maj}), 7.23 (1H, td, *J* 7.6 and 1.0 Hz, bromophenyl 5-H^{min}), 7.14 (1H, td, *J* 7.6 and 1.6 Hz, bromophenyl 4-H^{maj}), 7.11 (1H, td, *J* 7.6 and 1.6 Hz, bromophenyl 4-H^{min}), 6.76-6.70 (4H, m, methoxyphenyl 3,5-H), 6.51-6.43 (4H, m, methoxyphenyl 2,6-H), 4.71 (2H, d, *J* 6.2 Hz, NH), 4.56 (2H, d, *J* 2.2 Hz, 3-H), 4.08-4.04 (1H, m, 1-H^{maj}), 4.01-3.97 (1H, m, 1-H^{min}), 3.80-3.73 (2H, m, 5-H), 3.71 (3H, s,

OMe^{maj}), 3.70 (3H, s, OMe^{min}), 2.95-2.91 (2H, m, 4-H), 2.42-2.35 (1H, m, 6-$H_A{}^{maj}$), 2.24-2.16 (1H, m, 6-$H_A{}^{min}$), 2.12-2.03 (2H, m, 7-H_A), 1.82-1.70 (6H, m, 6-H_B and 8-H_2), 1.60-1.54 (2H, m, 7-H_B, overlap with residual water peak), 1.45 (9H, s, ^{t}Bu^{min}), 1.26 (9H, s, ^{t}Bu^{maj}); δ_C (125 MHz, $CDCl_3$): 155.5 (Boc C=O^{min}), 154.9 (Boc C=O^{maj}), 151.9 (methoxyphenyl C-4^{min}), 151.7 (methoxyphenyl C-4^{maj}), 142.8 (methoxyphenyl C-1^{maj}), 142.2 (methoxyphenyl C-1^{min}), 140.5 (bromophenyl C-1), 134.2 (bromophenyl C-3^{maj}), 133.3 (bromophenyl C-3^{min}), 129.0 (bromophenyl C-4^{min}), 128.7 (bromophenyl C-4^{maj}), 128.5 (bromophenyl C-6), 127.9 (bromophenyl C-5^{maj}), 127.5 (bromophenyl C-5^{min}), 122.1 (bromophenyl C-2), 114.8 (methoxyphenyl C_2-3,5^{maj}), 114.7 (methoxyphenyl C_2-3,5^{min}), 113.9 (methoxyphenyl C_2-2,6), 78.7 (C_1 ^{t}Bu), 65.4 (C-3), 55.7 (OMe^{maj}), 55.6 (OMe^{min}), 48.3 (C-5^{min}), 47.5 (C-5^{maj}), 46.8 (C-1^{min}), 46.2 (C-1^{maj}), 36.6 (C-6), 35.2 (C-4), 28.5 (C_3 ^{t}Bu^{min}), 28.2 (C_3 ^{t}Bu^{maj}), 26.0 (C-8^{min}), 25.7 (C-8^{maj}), 22.6 (C-7^{min}), 21.9 (C-7^{maj}); HRMS found MH^+ 489.1583. $C_{25}H_{31}BrN_2O_3$ requires *MH*, 489.1570. The relative configuration of the major diastereomer was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 5-H and 8-H_A.

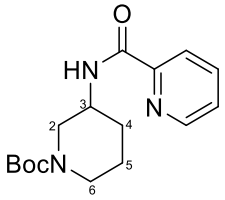
_N_-[(1_R_*,3_S_*,4_S_*,5_R_*)-3-(3-methoxyphenyl)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-yl]acetamide (149c)



Bicyclic ketone derivative **148c** (0.59 g, 1.45 mmol) was dissolved in sat. NH_3/MeOH (20 ml) and $Ti(O^iPr)_4$ (0.86 ml, 2.90 mmol) was added at rt. The solution was allowed to stir for 18 h at rt, then cooled to 0 ^{o}C and $NaBH_4$ (83.0 mg, 2.18 mmol) was added portionwise. The resulting reaction mixture was left to stir at rt for 2 h. The mixture was concentrated under reduced pressure and the resulting residue was dissolved in EtOAc (30 ml) and brine (30 ml) was added with vigorous stirring. The phases were

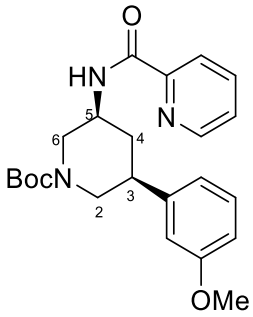
separated and the aqueous phase was then extracted with EtOAc (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. This intermediate as dissolved in THF (20 ml) and the solution was basified with 2M aq. NaOH. Then Ac_2O (0.43 ml, 4.53 mmol) was added and the resulting mixture was allowed to stir at rt for 4 h. Water (20 ml) was added and the mixture was then extracted with EtOAc (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 50:50 → 70:30 to give the *acetamide derivative* ***149c*** (297 mg, 54%, *dr* >95:<5 by ^{1}H NMR) as an off-white solid. R_f 0.26 (EtOAc–hexane 70:30). ν_{max}/cm^{-1}: 3275, 2959, 2924, 1575, 1508, 1463, 1409, 1365, 1259, 1183, 1022; δ_H (500 MHz, $CDCl_3$): 7.24 (1H, t, *J* 7.9 Hz, methoxyphenyl 5-H), 6.93 (1H, app. d, *J* 7.9 Hz, methoxyphenyl 6-H), 6.90 (1H, app. s, methoxyphenyl 2-H), 6.79-6.73 (3H, m, methoxyphenyl 4-H and paramethoxyphenyl 3,5-H), 6.54 (2H, d, *J* 9.2 Hz, paramethoxyphenyl 2,6-H), 5.44 (1H, br. d, *J* 7.1 Hz, NH), 4.42 (1H, app. s, 3-H), 4.27 (1H, ddd, *J* 10.7, 7.1 and 4.3 Hz, 5-H), 4.01-3.97 (1H, m, 1-H), 3.77 (3H, s, OMe), 3.71 (3H, s, OMe), 2.30-2.26 (1H, m, 4-H), 2.19-2.13 (1H, m, 6-H_A), 2.03-1.96 (1H, m, 7-H_A), 1.95 (3H, s, acetyl), 1.71-1.58 (2H, m, 6-H_B and 7-H_B), 1.53-1.44 (1H, m, 8-H_A), 1.44-1.35 (1H, m, 8-H_B); δ_C (125 MHz, $CDCl_3$): 170.0 (acetyl C=O), 160.0 (methoxyphenyl C-3), 151.6 (paramethoxyphenyl C-4), 144.9 (methoxyphenyl C-1), 143.1 (paramethoxyphenyl C-1), 129.6 (methoxyphenyl C-5), 118.7 (methoxyphenyl C-6), 114.9 (paramethoxyphenyl C_2-3,6), 114.0 (paramethoxyphenyl C_2-2,6), 112.2 (methoxyphenyl C-4), 111.9 (methoxyphenyl C-2), 60.9 (C-3), 55.8 (OMe), 55.3 (OMe), 47.3 (C-5), 45.7 (C-1), 38.5 (C-4), 32.2 (C-6), 26.2 (C-7), 23.6 (acetyl CH_3), 18.2 (C-8); HRMS found MH^+ 381.2179. $C_{23}H_{28}N_2O_3$ requires *MH*, 381.2173. The relative configuration was determined *via* analogy with the stereochemistry observed in carbamate derivative **149b**.

tert-butyl 3-(pyridine-2-amido)piperidine-1-carboxylate (152)



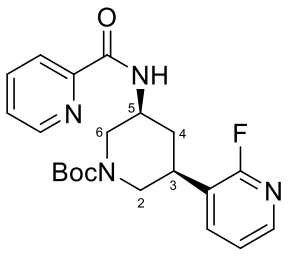
Prepared according to General procedure S, *tert*-butyl 3-aminopiperidine-1-carboxylate (1.00 g, 5.00 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 20:80 to give the picolinamide derivative **152**[118] (1.16 g, 76%) as a colourless oil that solidified on standing to give a white solid. R_f 0.10 (EtOAc–hexane 25:75). δ_H (500 MHz, $CDCl_3$): 8.51 (1H, d, *J* 4.3 Hz, pyridinyl 6-H), 8.18 (2H, app. d, *J* 7.8 Hz, pyridinyl 3-H and NH), 7.83 (1H, td, *J* 7.8 and 1.5 Hz, pyridinyl 4-H), 7.41 (1H, dd, *J* 6.7 and 4.3 Hz, pyridinyl 5-H), 4.17-4.07 (1H, m, 3-H), 3.70-3.60 (1H, m, 2-H_A), 3.53-3.35 (3H, m, 2-H_B and 6-H_2), 1.92 (1H, td, *J* 9.4 and 5.1 Hz, 4-H_A), 1.79-1.70 (2H, m, 4-H_B and 5-H_A), 1.62-1.54 (1H, m, 5-H_B), 1.42 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$): 163.8 (amide C=O), 155.1 (Boc C=O), 149.9 (pyridinyl C-2), 148.1 (pyridinyl C-6), 137.4 (pyridinyl C-4), 126.3 (pyridinyl C-5), 122.2 (pyridinyl C-3), 80.0 (C_1 ^{t}Bu), 48.8 (C-2), 45.3 (C-3), 43.8 (C-6), 30.0 (C-4), 28.5 (C_3 ^{t}Bu), 22.5 (C-5). All data is consistent with known literature values.[118]

tert-butyl (3*R,5*R**)-3-(3-methoxyphenyl)-5-(pyridine-2-amido)piperidine-1-carboxylate (153a)**



Prepared according to General procedure T, picolinamide derivative **152** (0.50 g, 1.64 mmol) and 3-iodoanisole (1.17 ml, 9.84 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 30:70 to give the arylated derivative **153a**[118] (0.41 g, 61%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.45 (EtOAc–hexane 50:50). δ_H (500 MHz, $CDCl_3$): 8.53 (1H, ddd, *J* 4.7, 1.5 and 0.8 Hz, pyridinyl 6-H), 8.19 (1H, d, *J* 7.8 Hz, pyridinyl 3-H), 7.97 (1H, br. d, *J* 8.5 Hz, NH), 7.85 (1H, td, *J* 7.8 and 1.5 Hz, pyridinyl 4-H), 7.43 (1H, ddd, *J* 7.5, 4.7 and 1.0 Hz, pyridinyl 5-H) 7.23 (1H, t, *J* 7.8 Hz, phenyl 5-H), 6.83 (1H, d, *J* 7.8 Hz, phenyl 6-H), 6.80-6.75 (2H, m, phenyl 2-H and phenyl 4-H), 4.45 (1H, app. br. s, 2-H_A), 4.37-4.25 (1H, app. br. s, 6-H_A), 4.23-4.14 (1H, m, 5-H), 3.79 (3H, s, OMe), 2.88 (1H, app. t, *J* 11.5 Hz, 3-H), 2.75-2.61 (2H, m, 2-H_B and 6-H_B), 2.39 (1H, app. d, *J* 12.1 Hz, 4-H_A), 1.68 (1H, app. q, 12.1 Hz, 4-H_B), 1.48 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$): 163.8 (amide C=O), 159.9 (phenyl C-3), 154.7 (Boc C=O), 149.8 (pyridinyl C-2), 148.1 (pyridinyl C-6), 143.7 (phenyl C-1), 137.6 (pyridinyl C-4), 129.7 (phenyl C-5), 126.4 (pyridinyl C-5), 122.4 (pyridinyl C-3), 119.5 (phenyl C-6), 113.1 (phenyl C-2), 112.3 (phenyl C-4), 80.3 (C_1 ^{t}Bu), 55.3 (OMe), 49.6 (C-6), 48.8 (C-2), 46.2 (C-5), 41.4 (C-3), 38.6 (C-4), 28.6 (C_3 ^{t}Bu). The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 3-H and 5-H. All data is consistent with known literature values.[118]

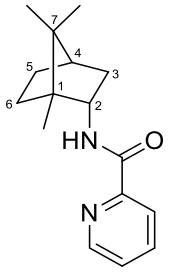
tert-butyl (3*R,5*R**)-3-(2-fluoropyridin-3-yl)-5-(pyridine-2-amido)piperidine-1-carboxylate (153c)**



Prepared according to an adapted General procedure T, picolinamide derivative **152** (0.50 g, 1.64 mmol) and 2-fluoro-3-iodopyridine (2.92 g, 13.1 mmol) gave a crude

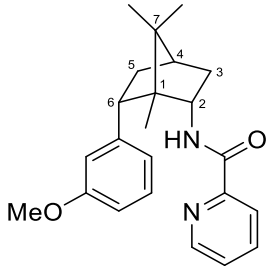
material. This was then purified *via* column chromatography, eluting EtOAc–hexane 40:60 to give the *arylated derivative* ***153c*** (0.51 g, 78%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.20 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3382, 3070, 2991, 2877, 1690, 1660, 1591, 1571, 1516, 1458, 1420, 1254, 1230, 1156, 1144, 1043; δ_H (500 MHz, $CDCl_3$): 8.53 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.20 (1H, dt, *J* 7.6 and 1.2 Hz, pyridinyl 3-H), 8.11 (1H, dt, *J* 3.3 and 1.2 Hz, fluoropyridinyl 6-H), 7.99 (1H, br. d, *J* 8.2 Hz, NH), 7.86 (1H, td, *J* 7.6 and 1.7 Hz, pyridinyl 4-H), 7.65 (1H, ddd, *J* 9.3, 7.5 and 1.7 Hz, fluoropyridinyl 4-H), 7.44 (1H, ddd, *J* 7.6, 4.8 and 1.2 Hz, pyridinyl 5-H), 7.16, (1H, ddd, *J* 6.9, 4.9 and 1.7 Hz, fluoropyridinyl 5-H), 4.55-4.40 (1H, m, 6-H_A), 4.37-4.25 (1H, m, 2-H_A), 4.24-4.15 (1H, m, 5-H), 3.09 (1H, tt, *J* 11.9 and 3.6 Hz, 3-H), 2.87-2.77 (1H, m, 2-H_B), 2.73 (1H, t, *J* 11.1 Hz, 6-H_B), 2.39 (1H, d, *J* 11.8 Hz, 4-H_A), 1.81 (1H, q, *J* 11.8 Hz, 4-H_B), 1.49 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$): 163.9 (amide C=O), 161.8 (d, *J* 240.1 Hz, fluoropyridinyl C-2), 154.6 (Boc C=O), 149.7 (pyridinyl C-2), 148.1 (pyridinyl C-6), 146.1 (d, *J* 15.3 Hz, fluoropyridinyl C-6), 139.2 (fluoropyridinyl C-4), 137.7 (pyridinyl C-4), 126.5 (pyridinyl C-5), 123.7 (d, *J* 29.4 Hz, fluoropyridinyl C-3), 122.5 (pyridinyl C-3), 121.8 (d, *J* 4.0 Hz, fluoropyridinyl C-5), 80.6 (C_1 ^{t}Bu), 48.8 (C-2 and C-6), 46.0 (C-5), 36.6 (C-4), 36.3 (C-3), 28.5 (C_3 ^{t}Bu); δ_F (470 MHz, $CDCl_3$): -69.6 (pyridinyl CF); HRMS found MNa^+ 423.1805. $C_{21}H_{25}FN_4O_3$ requires *MNa*, 423.1803. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 3-H and 5-H.

_N_-[(1_R_,2_S_,4_R_)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]pyridine-2-carboxamide (155)



Prepared according to General procedure S, (*R*)-bornylamine (400 mg, 2.61 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 40:60 to give the picolinamide derivative **155**[107] (604 mg, 90%) as a white solid. R_f 0.41 (EtOAc–hexane 40:60). δ_H (500 MHz, $CDCl_3$): 8.48 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.11 (2H, app. br. d, *J* 7.7 Hz, pyridinyl 3-H and NH), 7.75 (1H, td, *J* 7.7 and 0.9 Hz, pyridinyl 4-H), 7.33 (1H, dd, *J* 7.0 and 4.8 Hz, pyridinyl 5-H), 4.40-4.33 (1H, m, 2-H), 2.38-2.30 (1H, m, 3-H_A), 1.73 (1H, ddd, *J* 16.0, 8.1 and 3.8 Hz, 6-H_A), 1.67-1.59 (2H, m, 4-H and 5-H_A), 1.39-1.31 (1H, m, 5-H_B), 1.27-1.20 (1H, m, 6-H_B), 0.95-0.88 (4H, m, 3-H_B and methyl), 0.82 (3H, s, methyl), 0.80 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 164.1 (C=O), 150.1 (pyridinyl C-1), 147.9 (pyridinyl C-6), 137.2 (pyridinyl C-4), 125.9 (pyridinyl C-5), 122.1 (pyridinyl C-3), 53.7 (C-2), 49.8 (C-7), 48.2 (C-1), 45.0 (C-4), 37.5 (C-3), 28.4 (C-6), 28.1 (C-5), 19.8 (methyl), 18.7 (methyl), 13.7 (methyl). All data is consistent with known literature values.[107]

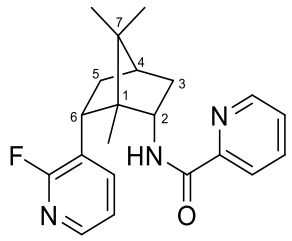
_N_-[(1_R_,2_S_,4_R_,6_S_)-6-(3-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]pyridine-2-carboxamide (156a)



Prepared according to General procedure U, picolinamide derivative **155** (400 mg, 1.55 mmol) and 3-iodoanisole (0.76 ml, 6.20 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give arylated derivative **156a**[107] (276 mg, 50%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.23 (EtOAc–hexane 30:70). δ_H (500 MHz, $CDCl_3$): 8.23 (1H, d, *J* 4.4 Hz, pyridinyl 6-H), 7.95 (1H, d, *J* 7.8 Hz, pyridinyl 3-H), 7.85 (1H, br. d, *J* 8.9 Hz, NH), 7.69 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.28-7.25 (1H, m, pyridinyl 5-H), 7.22 (1H, t, *J* 7.9 Hz,

methoxyphenyl 5-H), 7.02 (1H, s, methoxyphenyl 2-H), 7.00 (1H, d, *J* 7.9 Hz, methoxyphenyl 6-H), 6.75 (1H, dd, *J* 7.9 and 2.3 Hz, methoxyphenyl 4-H), 4.57-4.50 (1H, m, 2-H), 3.78 (3H, s, OMe), 3.32 (1H, dd, *J* 11.6 and 5.4 Hz, 6-H), 2.59-2.51 (1H, m, 3-H_A), 2.30-2.22 (1H, m, 5-H_A), 2.03 (1H, dd, *J* 13.3 and 5.4 Hz, 5-H_B), 1.93 (1H, t, *J* 4.6 Hz, 4-H), 1.29 (1H, dd, *J* 13.3 and 5.9 Hz, 3-H_B), 1.10 (3H, s, methyl), 1.09 (3H, s, methyl), 1.07 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 164.5 (C=O), 160.3 (methoxyphenyl C-3), 150.1 (pyridinyl C-1), 147.3 (pyridinyl C-6), 143.9 (methoxyphenyl C-1), 136.9 (pyridinyl C-4), 129.9 (methoxyphenyl C-5), 125.6 (pyridinyl C-5), 121.8 (pyridinyl C-3 and methoxyphenyl C-6), 114.2 (methoxyphenyl C-2), 111.6 (methoxyphenyl C-4), 55.2 (OMe), 54.4 (C-2 and C-1), 51.2 (C-7), 47.9 (C-6), 43.7 (C-4), 37.2 (C-3), 32.9 (C-5), 20.3 (methyl), 20.0 (methyl), 13.9 (methyl). All data is consistent with known literature values.[107]

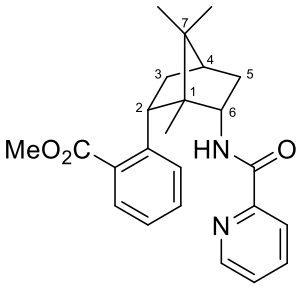
_N_-[(1_R_,2_S_,4_R_,6_R_)-6-(2-fluoropyridin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]pyridine-2-carboxamide (156c)



Prepared according to General procedure U, picolinamide derivative **155** (200 mg, 0.78 mmol) and 2-fluoro-3-iodopyridine (691 mg, 3.10 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 35:65 to give *arylated derivative* ***156c*** (118 mg, 42%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.17 (EtOAc–hexane 40:60). [α_D^{20}] +2.50 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3387, 3057, 2957, 1676, 1595, 1570, 1517, 1461, 1398, 1345, 1279, 1241, 1163, 1070; δ_H (500 MHz, $CDCl_3$): 8.23 (1H, d, *J* 4.5 Hz, pyridinyl 6-H), 8.06 (1H, d, *J* 4.8 Hz, fluoropyridinyl 6-H), 8.03 (1H, t, *J* 7.9 Hz, fluoropyridinyl 4-H), 7.98 (1H, d, *J* 7.8 Hz, pyridinyl 3-H), 7.72 (1H, td, *J* 7.8 and 1.6 Hz, pyridinyl 4-H), 7.69 (1H, br. s, NH), 7.30 (1H, ddd, *J*

7.8, 4.5 and 0.8 Hz, pyridinyl 5-H), 7.22-7.18 (1H, m, fluoropyridinyl 5-H), 4.53-4.47 (1H, m, 2-H), 3.57 (1H, dd, *J* 11.8 and 5.6 Hz, 6-H), 2.66-2.58 (1H, m, 3-H_A), 2.29 (1H, tt, *J* 12.9 and 3.7 Hz, 5-H_A), 2.00-1.93 (2H, m, 5-H_B and 4-H), 1.36 (1H, dd, *J* 13.5 and 6.0 Hz, 3-H_B), 1.12 (3H, s, methyl), 1.11 (3H, s, methyl), 1.06 (3H, d, *J* 4.0 Hz, methyl); δ_C (125 MHz, $CDCl_3$): 164.3 (C=O), 162.5 (d, *J* 239.4 Hz, fluoropyridinyl C-2), 149.6 (pyridinyl C-2), 147.4 (pyridinyl C-6), 144.8 (d, *J* 15.2 Hz, fluoropyridinyl C-6), 141.2 (d, *J* 5.0 Hz, fluoropyridinyl C-4), 137.2 (pyridinyl C-4), 125.9 (pyridinyl C-5), 124.8 (d, *J* 29.0 Hz, fluoropyridinyl C-3), 122.1 (d, *J* 4.1 Hz, fluoropyridinyl 5-H), 121.9 (pyridinyl C-3), 55.5 (C-1), 54.9 (C-2), 51.4 (C-7), 43.8 (C-4), 41.2 (C-6), 36.9 (C-3), 33.2 (C-5), 20.3 (methyl), 19.9 (methyl), 13.5 (methyl); δ_F (470 MHz, $CDCl_3$): -66.3 (pyridinyl CF); HRMS found MH^+ 354.1993. $C_{21}H_{24}FN_3O$ requires *MH*, 354.1976. The configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 2-H and 7-methyl and nOe observed between 6-H and 7-methyl (500 MHz, $CDCl_3$).

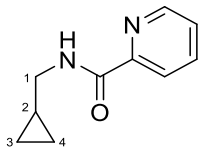
methyl 2-[(1*R*,2*S*,4*R*,6*S*)-6-(pyridine-2-carboxyamidyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]benzoate (156d)



Prepared according to General procedure U, picolinamide derivative **155** (200 mg, 0.78 mmol) and methyl 2-bromobenzoate (670 mg, 3.10 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 30:60 to give the *arylated ester derivative* ***156d*** (160 mg, 53%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.29 (EtOAc–hexane 40:60). [α_D^{20}] +16.2 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3364, 2948, 1713, 1663, 1595, 1569, 1508, 1437, 1428, 1395, 1385, 1255, 1210, 1128, 1040; δ_H (500 MHz, $CDCl_3$): 8.22 (1H, ddd, *J* 4.1, 1.7 and 1.0 Hz, pyridinyl 6-H),

7.95 (1H, dt, *J* 7.8 and 1.0 Hz, pyridinyl 3-H), 7.87 (1H, d, *J* 7.7 Hz, phenyl 6-H), 7.70 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.67 (1H, br. s, NH), 7.63 (1H, dd, J 7.7 and 1.5 Hz, phenyl 3-H), 7.55 (1H, td, *J* 7.7 and 1.5 Hz, phenyl 5-H), 7.30-7.27 (1H, m, phenyl 4-H), 7.27-7.24 (1H, m, pyridinyl 5-H), 4.65 (1H, dd, *J* 11.8 and 5.7 Hz, 2-H), 4.48 (1H, app. dddd, *J* 11.2, 9.2, 6.3 and 1.7 Hz, 6-H), 3.84 (3H, s, CO_2Me), 2.58 (1H, app. dddd, *J* 13.5, 11.2, 4.6 and 3.3 Hz, 5-H_A), 2.35 (1H, tt, *J* 13.1 and 3.8 Hz, 3-H_A), 2.03 (1H, dd, *J* 13.1 and 5.7 Hz, 3-H_B), 1.97 (1H, t, *J* 4.6 Hz, 4-H), 1.39 (1H, dd, *J* 13.5 and 6.3 Hz, 5-H_B), 1.13 (3H, s, methyl), 1.08 (3H, s, methyl), 0.83 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 170.1 (C=O ester), 164.5 (C=O amide), 149.9 (pyridinyl C-2), 147.3 (pyridinyl C-6), 142.4 (phenyl C-1), 137.0 (pyridinyl C-4), 133.4 (phenyl C-2), 132.3 (phenyl C-5), 130.6 (phenyl C-3), 129.5 (phenyl C-6), 125.7 (pyridinyl C-5), 125.6 (phenyl C-4), 121.9 (pyridinyl C-3), 55.8 (C-1), 55.2 (C-6), 52.1 (CO_2Me), 51.4 (C-7), 44.0 (C-4), 41.1 (C-2), 36.7 (C-5), 33.9 (C-3), 20.4 (methyl), 20.1 (methyl), 12.6 (methyl); HRMS found MH^+ 393.2182. $C_{24}H_{28}N_2O_3$ requires *MH*, 393.2173. The configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 2-H and 7-methyl and nOe observed between 6-H and 7-methyl (500 MHz, $CDCl_3$).

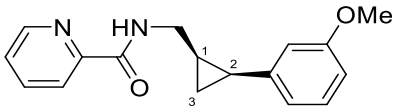
_N_-(cyclopropylmethyl)pyridine-2-carboxamide (158)



A mixture of picolinic acid (2.08 g, 16.9 mmol), cyclopropanemethylamine (1.00 g, 14.1 mmol) and Et_3N (3.92 ml, 28.2 mmol) were dissolved in DCM (20 ml). $POCl_3$ (2.63 ml, 28.2 mmol) was added dropwise at 0 ^oC then the reaction mixture was stirred at rt for 2 h. DCM (20 ml) and 1M NaOH (30 ml) were added at 0 ^oC, then the phases were separated and the aqueous phase extracted with DCM (3 x 30 ml). The organic phases were combined, washed with water (20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column

chromatography, eluting EtOAc–hexane 20:80 to give the picolinamide derivative **158**[108] (1.75 g, 71%) as a white solid. R_f 0.30 (EtOAc–hexane 30:70). δ_H (500 MHz, $CDCl_3$): 8.57 (1H, dd, *J* 4.7 and 0.7 Hz, pyridinyl 6-H), 8.21 (1H, d, *J* 7.8 Hz, pyridinyl 3-H), 8.13 (1H, br. s, NH), 7.85 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.42 (1H, ddd, *J* 7.2, 4.7 and 0.7 Hz, pyridinyl 5-H), 3.35 (2H, app. t, *J* 6.8 Hz, cyclopropylmethyl 1-H_2), 1.13-1.04 (1H, m, cyclopropylmethyl 2-H), 0.59-0.54 (2H, m, cyclopropylmethyl 3-H_A and cyclopropylmethyl 4-H_A), 0.34-0.26 (2H, m, cyclopropylmethyl 3-H_B and cyclopropylmethyl 4-H_B); δ_C (125 MHz, $CDCl_3$): 164.3 (C=O), 150.3 (pyridinyl C-2), 148.2 (pyridinyl C-6), 137.5 (pyridinyl C-4), 126.2 (pyridinyl C-5), 122.4 (pyridinyl C-3), 44.4 (cyclopropylmethyl C-1), 10.9 (cyclopropylmethyl C-2), 3.7 (cyclopropylmethyl C-3 and cyclopropylmethyl C-4). All data is consistent with known literature values.[108]

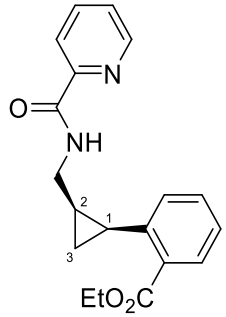
N-{[(1*R**,2*S**)-2-(3-methoxyphenyl)cyclopropyl]methyl}pyridine-2-carboxamide (159a)



Prepared according to General procedure V, picolinamide derivative **158** (200 mg, 1.14 mmol) and 3-iodoanisole (0.15 ml, 1.25 mmol) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 20:80 to give the *arylated derivative* ***159a*** (220 mg, 68%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.27 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 3354, 3008, 2936, 1659, 1519, 1431, 1238, 1160, 1044; δ_H (500 MHz, $CDCl_3$): 8.53 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.15 (1H, dt, *J* 7.8 and 1.2 Hz, pyridinyl 3-H), 7.96 (1H, br. s, NH), 7.82 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.40 (1H, ddd, *J* 7.8, 4.8 and 1.2 Hz, pyridinyl 5-H), 7.22 (1H, t, *J* 7.9 Hz, methoxyphenyl 5-H), 6.89-6.84 (2H, m, methoxyphenyl 6-H and methoxyphenyl 2-H), 6.76 (1H, dd, *J* 7.9 and 2.5 Hz, methoxyphenyl 4-H), 3.81 (3H, s, OMe), 3.44-3.37 (1H, m, cyclopropylmethyl 1-H_A), 3.05-2.98 (1H, m, cyclopropylmethyl 1-H_B), 2.29 (1H, td, *J* 8.3 and 6.3 Hz, 2-H), 1.55-1.47 (1H, m, 1-H), 1.07 (1H, td, *J* 8.3 and 5.4 Hz, 3-H_A), 0.94 (1H, dd, *J* 11.4 and 5.4 Hz, 3-H_B); δ_C (125 MHz, $CDCl_3$): 164.2 (C=O),

159.8 (methoxyphenyl C-3), 150.2 (pyridinyl C-2), 148.1 (pyridinyl C-6), 139.9 (methoxyphenyl C-1), 137.4 (pyridinyl C-4), 129.4 (methoxyphenyl C-5), 126.1 (pyridinyl C-5), 122.3 (pyridinyl C-3), 121.5 (methoxyphenyl C-6), 114.8 (methoxyphenyl C-2), 112.2 (methoxyphenyl C-4), 55.3 (OMe), 39.6 (cyclopropylmethyl C-1), 21.0 (C-2), 18.4 (C-1), 8.6 (C-3); HRMS found MNa^+ 305.1269. $C_{17}H_{18}N_2O_2$ requires *MNa*, 305.1260. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 1-H and 2-H and nOe observed between cyclopropylmethyl 1-H_2 and methoxyphenyl 2-H (500 MHz, $CDCl_3$).

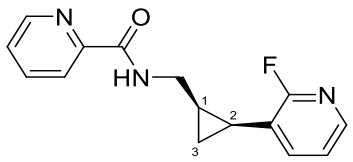
ethyl 2-[(1*R,2*S**)-2-{[(pyridine-2-carbonyl)amino]methyl}cyclopropyl]benzoate (159c)**



Prepared according to General procedure V, picolinamide derivative **158** (200 mg, 1.14 mmol) and ethyl-2-iodobenzoate (345 mg, 1.25 mmol) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 30:70 to give *arylated ester derivative* ***159c*** (146 mg, 40%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.23 (EtOAc–hexane 40:60). ν_{max}/cm^{-1}: 3382, 2981, 1712, 1669, 1519, 1488, 1449, 1291, 1253, 1132, 1076; δ_H (500 MHz, $CDCl_3$): 8.51 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.10 (1H, dt, *J* 7.8 and 1.0 Hz, pyridinyl 3-H), 8.07 (1H, br. s, NH), 7.92 (1H, dd, *J* 7.7 and 1.4 Hz, phenyl 6-H), 7.79 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.44 (1H, td, *J* 7.6 and 1.4 Hz, phenyl 4-H), 7.38 (1H, ddd, *J* 7.8, 4.8 and 1.0 Hz, pyridinyl 5-H), 7.31-7.26 (2H, m, phenyl 3-H and phenyl 5-H), 4.39 (2H, qd, *J* 7.1 and 1.4 Hz, ethyl 1-H_2), 3.34 (1H, dt, *J* 14.0 and 6.5 Hz, cyclopropylmethyl 1-H_A), 2.85 (1H, ddd, *J* 14.0, 8.3 and 4.4 Hz, cyclopropylmethyl 1-H_B), 2.69 (1H, dd, *J* 15.4 and 8.3 Hz,

cyclopropyl 1-H), 1.67-1.59 (1H, m, cyclopropyl 2-H), 1.38 (3H, t, *J* 7.1 Hz, ethyl 2-H_3), 1.17 (1H, td, *J* 8.3 and 5.5 Hz, cyclopropyl 3-H_A), 1.04 (1H, dd, *J* 11.9 and 5.5 Hz, cyclopropyl 3-H_B); δ_C (125 MHz, $CDCl_3$): 167.9 (C=O ester), 164.3 (C=O amide), 150.3 (pyridinyl C-2), 148.1 (pyridinyl C-6), 139.4 (phenyl C-2), 137.3 (pyridinyl C-4), 132.0 (phenyl C-4), 131.9 (phenyl C-1), 131.0 (phenyl C-6), 129.9 (phenyl C-5), 126.6 (phenyl C-3), 126.0 (pyridinyl C-5), 122.3 (pyridinyl C-3), 61.1 (ethyl C-1), 40.1 (cyclopropylmethyl C-1), 21.5 (cyclopropyl C-1), 18.9 (cyclopropyl C-2), 14.4 (ethyl C-2), 9.2 (cyclopropyl C-3); HRMS found MH^+ 325.1542. $C_{19}H_{20}N_2O_3$ requires *MH*, 325.1547. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between cyclopropyl 1-H and cyclopropyl 2-H and nOe observed between cyclopropylmethyl 1-H_2 and phenyl 3-H (500 MHz, $CDCl_3$).

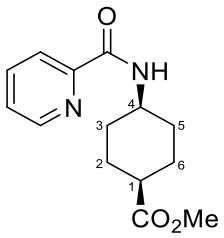
N-{[(1*R**,2*S**)-2-(2-fluoropyridin-3-yl)cyclopropyl]methyl}pyridine-2-carboxamide (159d)



Prepared according to General procedure V, picolinamide derivative **158** (200 mg, 1.14 mmol) and 2-fluoro-3-iodopyridine (279 mg, 1.25 mmol) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give the *arylated derivative* ***159d*** (156 mg, 50%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.29 (EtOAc–hexane 60:40). ν_{max}/cm^{-1}: 3387, 3012, 2923, 1669, 1570, 1523, 1463, 1432, 1335, 1243, 1044; δ_H (500 MHz, $CDCl_3$): 8.56 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.12 (1H, dt, *J* 7.7 and 1.2 Hz, pyridinyl 3-H), 8.09-8.04 (2H, m, fluoropyridinyl 6-H and NH), 7.82 (1H, td, *J* 7.7 and 1.7 Hz, pyridinyl 4-H), 7.63-7.58 (1H, m, fluoropyridinyl 4-H), 7.41 (1H, ddd, *J* 7.7, 4.8 and 1.2 Hz, pyridinyl 5-H), 7.17-7.12 (1H, m, fluoropyridinyl 5-H), 3.38-3.27 (1H, m, cyclopropylmethyl 1-H_A), 3.04 (1H, ddd, *J* 14.1, 7.6 and 5.0 Hz, cyclopropylmethyl 1-H_B), 2.26 (1H, dd, *J* 15.0 and 8.3 Hz, 2-H), 1.71-1.58 (1H, m, 1-H), 1.21 (1H, td, *J* 8.3 and 5.8 Hz, 3-H_A), 0.98 (1H, app. q, *J*

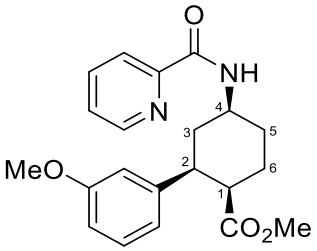
5.8 Hz, 3-H_B); δ_C (125 MHz, $CDCl_3$): 164.4 (C=O), 163.5 (d, *J* 239.2 Hz, fluoropyridinyl C-2), 149.9 (pyridinyl C-2), 148.3 (pyridinyl C-6), 145.5 (d, *J* 14.6 Hz, fluoropyridinyl 6-H), 140.6 (d, *J* 5.1 Hz, fluoropyridinyl C-4), 137.4 (pyridinyl C-4), 126.3 (pyridinyl C-5), 122.3 (pyridinyl C-3), 121.4 (d, *J* 4.2 Hz, fluoropyridinyl C-5), 120.9 (d, *J* 30.3 Hz, fluoropyridinyl C-3), 39.4 (cyclopropylmethyl C-1), 18.3 (C-1), 15.1 (C-2), 8.3 (C-3); δ_F (470 MHz, $CDCl_3$): - 70.1 (pyridinyl CF); HRMS found MH^+ 272.1192. $C_{15}H_{14}FN_3O$ requires *MH*, 272.1194. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 1-H and 2-H and nOe observed between cyclopropylmethyl 1-H_2 and fluoropyridinyl 4-H (500 MHz, $CDCl_3$).

methyl (1*R,4*R**)-4-[(pyridine-2-carbonyl)amino]cyclohexane-1-carboxylate (161)**



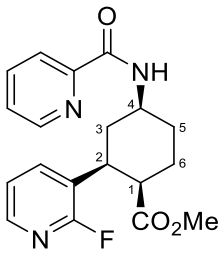
Prepared according to an adapted General procedure S, *cis*-4-amino-cyclohexanecarboxylic acid methyl ester hydrochloride (1.00 g, 5.18 mmol) followed by addition of a saturated aqueous solution of $NaHCO_3$ instead of 5M NaOH gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 30:70 to give picolinamide derivative **161**[161] (1.24 g, 91%) as a colourless oil. R_f 0.20 (EtOAc–hexane 40:60). δ_H (500 MHz, $CDCl_3$): 8.54 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.18 (1H, dt, *J* 7.7 and 1.2 Hz, pyridinyl 3-H), 8.12 (1H, br. d, *J* 6.6 Hz, NH), 7.83 (1H, td, *J* 7.7 and 1.7 Hz, pyridinyl 4-H), 7.41 (1H, ddd, *J* 7.7, 4.8 and 1.2 Hz, pyridinyl 5-H), 4.18-4.11 (1H, m, 4-H), 3.70 (1H, s, CO_2Me), 2.56-2.50 (1H, m, 1-H), 2.02-1.93 (2H, m, 2-H_A and 6-H_A), 1.85-1.69 (6H, m, 2-H_B, 6-H_B, 3-H_2 and 5-H_2); δ_C (125 MHz, $CDCl_3$): 175.7 (C=O ester), 163.6 (C=O amide), 150.2 (pyridinyl C-2), 148.2 (pyridinyl C-6), 137.4 (pyridinyl C-4), 126.2 (pyridinyl C-5), 122.2 (pyridinyl C-3), 51.8 (CO_2Me), 45.9 (C-4), 40.4 (C-1), 29.6 (C_2-3,5), 25.2 (C_2-2,6). All data is consistent with known literature values.[161]

methyl (1*R,2*S**,4*S**)-4-[(pyridine-2-carbonyl)amino]-2-(3-methoxyphenyl)cyclohexane-1-carboxylate (162a)**



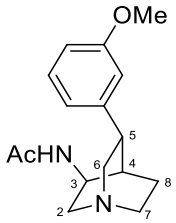
Prepared according to General procedure T, picolinamide derivative **161** (200 mg, 0.76 mmol) and 3-iodoanisole (0.55 ml, 4.58 mmol) gave a crude material. This was then purified *via* column chromatography eluting with EtOAc–hexane 25:75 to give *arylated derivative* ***162a*** (243 mg, 87%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.22 (EtOAc–hexane 40:60). ν_{max}/cm^{-1}: 3377, 2944, 2864, 1726, 1669, 1585, 1516, 1433, 1239, 1158; δ_H (500 MHz, $CDCl_3$): 8.56 (1H, d, *J* 4.8 Hz, pyridinyl 6-H), 8.20 (1H, d, *J* 7.7 Hz, pyridinyl 3-H), 8.11 (1H, br. d, *J* 8.4 Hz, NH), 7.84 (1H, td, *J* 7.7 and 1.5 Hz, pyridinyl 4-H), 7.42 (1H, dd, *J* 7.7 and 4.8 Hz, pyridinyl 5-H), 7.19 (1H, t, *J* 7.7 Hz, methoxyphenyl 5-H), 6.80 (1H, d, *J* 7.7 Hz, methoxyphenyl 6-H), 6.78-6.72 (2H, m, methoxyphenyl 2-H and methoxyphenyl 4-H), 4.17 (1H, tdt, *J* 12.2, 8.4 and 4.1 Hz, 4-H), 3.78 (3H, s, OMe), 3.45 (3H, s, CO_2Me), 3.05-2.96 (2H, m, 1-H and 2-H), 2.47 (1H, app. q, *J* 12.2 Hz, 3-H_A), 2.17-2.11 (2H, m, 3-H_B and 5-H_A), 2.03-1.81 (3H, m, 5-H_B and 6-H_2); δ_C (125 MHz, $CDCl_3$): 174.3 (C=O ester), 163.6 (C=O amide), 159.7 (methoxyphenyl C-3), 150.2 (pyridinyl C-2), 148.2 (pyridinyl C-6), 144.6 (methoxyphenyl C-1), 137.5 (pyridinyl C-4), 129.3 (methoxyphenyl C-5), 126.2 (pyridinyl C-5), 122.4 (pyridinyl C-3), 119.8 (methoxyphenyl C-6), 113.3 (methoxyphenyl C-2), 112.1 (methoxyphenyl C-4), 55.3 (OMe), 51.2 (CO_2Me), 48.5 (C-4), 44.8 (C-1), 44.0 (C-2), 32.6 (C-3), 28.2 (C-6), 28.0 (C-5); HRMS found MH^+ 369.1818. $C_{21}H_{24}N_2O_4$ requires *MH*, 369.1809. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between CO_2Me and methoxyphenyl 2-H and nOe observed between 2-H and 4-H (500 MHz, $CDCl_3$).

methyl (1*R,2*S**,4*S**)-2-(2-fluoropyridin-3-yl)-4-[(pyridine-2-carbonyl)amino]cyclohexane-1-carboxylate (162d)**



Prepared according to General procedure T, picolinamide derivative **161** (200 mg, 0.76 mmol) and 2-fluoro-3-iodopyridine (1.02 g, 4.58 mmol) gave a crude material. This was then purified *via* column chromatography eluting with EtOAc–hexane 40:60 to give the *arylated derivative* ***162d*** (105 mg, 39%, *dr* >95:<5 by ^{1}H NMR) as a pale-yellow solid. R_f 0.13 (EtOAc–hexane 40:60). ν_{max}/cm^{-1}: 3386, 2845, 1733, 1670, 1520, 1205; δ_H (500 MHz, $CDCl_3$): 8.57 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.20 (1H, dt, *J* 7.8 and 1.2 Hz, pyridinyl 3-H), 8.10 (1H, br. d, *J* 8.4 Hz, NH), 8.07 (1H, dt, *J* 4.7 and 1.5 Hz, fluoropyridinyl 6-H), 7.86 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.73-7.68 (1H, m, fluoropyridinyl 4-H), 7.44 (1H, ddd, *J* 7.8, 4.8 and 1.2 Hz, pyridinyl 5-H), 7.15-7.11 (1H, m, fluoropyridinyl 5-H), 4.19 (1H, tdt, *J* 12.4, 8.4 and 4.1 Hz, 4-H), 3.45 (3H, s, CO_2Me), 3.29 (1H, dt, *J* 13.1 and 3.8 Hz, 2-H), 3.16-3.13 (1H, m, 1-H), 2.46 (1H, q, *J* 12.2 Hz, 3-H_A), 2.23 (1H, dq, *J* 14.0 and 6.1 Hz, 6-H_A), 2.16-2.11 (1H, m, 3-H_B), 2.07-2.01 (1H, m, 5-H_A), 2.01-1.93 (1H, m, 6-H_B), 1.74 (1H, qd, *J* 12.7 and 4.1 Hz, 5-H_B); δ_C (125 MHz, $CDCl_3$): 173.7 (C=O ester), 163.7 (C=O amide), 161.5 (d, *J* 238.1 Hz, fluoropyridinyl C-2), 150.1 (pyridinyl C-2), 148.2 (pyridinyl C-6), 145.6 (d, *J* 15.1 Hz, fluoropyridinyl C-6), 139.4 (d, *J* 5.2 Hz, fluoropyridinyl C-4), 137.6 (pyridinyl C-4), 126.4 (pyridinyl C-5), 124.8 (d, *J* 29.0 Hz, fluoropyridinyl C-3), 122.4 (pyridinyl C-3), 121.4 (d, *J* 4.1 Hz, fluoropyridinyl C-5), 51.3 (CO_2Me), 48.4 (C-4), 42.2 (C-1), 36.6 (d, *J* 2.5 Hz, C-2), 31.7 (C-3), 28.2 (C-5), 28.0 (C-6); δ_F (470 MHz, $CDCl_3$): -72.5 (pyridinyl CF) HRMS found MH$^+$ 358.1573. $C_{19}H_{20}FN_3O_3$ requires *MH*, 358.1561. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between CO_2Me and fluoropyridinyl 4-H and nOe observed between 2-H and 4-H (500 MHz, $CDCl_3$).

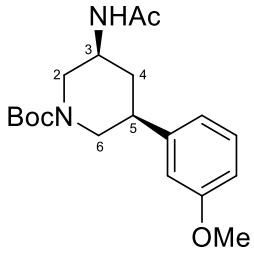
_N_-[(1_R_*,3_R_*,4_S_*,5_S_*)-5-(3-methoxyphenyl)-1-azabicyclo[2.2.2]octan-3-yl]acetamide (163a)



Arylated derivative **139b** (0.52 g, 1.54 mmol) was suspended in water (40 ml) to which HCl (5 ml, 37%) was added slowly with stirring. The reaction mixture was stirred for 5 mins at rt then zinc powder (1.50 g, 23.1 mmol) was added slowly. The reaction mixture was left to stir at rt for 18 h. Then DCM (70 ml) and 5M NaOH (100 ml) were added slowly at 0 ^{o}C. The mixture was filtered through celite, with the celite pad being subsequently washed with water (30 ml) and DCM (30 ml). The combined filtrate was extracted with DCM (3 x 50 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. This amine intermediate (0.35 g, 1.51 mmol) was dissolved in THF (20 ml) then NaOH (60.0 mg, 1.51 mmol) in water (5 ml) was added at rt. Ac_2O (0.18 ml, 1.89 mmol) was added and the reaction mixture stirred at rt for a further 1 h. 5M NaOH was added to basify the solution to pH 13. This solution was then extracted with DCM (3 x 40 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting DCM–sat. NH_3/MeOH 95:5 to give *acetamide derivative* ***163a*** (306 mg, 74%) as a colourless oil. R_f 0.52 (DCM–sat. NH_3/MeOH 90:10). ν_{max}/cm^{-1}: 3291, 3068, 2937, 2870, 2835, 1644, 1546, 1433, 1257, 1043; δ_H (500 MHz, $CDCl_3$): 7.30 (1H, t, *J* 8.0 Hz, phenyl 5-H), 6.96 (1H, dd, *J* 8.0 and 0.7 Hz, phenyl 6-H), 6.88 (1H, s, phenyl 2-H), 6.78 (1H, dd, *J* 8.0 and 2.5 Hz, phenyl 4-H), 5.06 (1H, br. d, *J* 7.2 Hz, NH), 3.98-3.91 (1H, m, 3-H), 3.81 (3H, s, OMe), 3.44-3.25 (3H, m, 2-H_A and 6-H_2), 3.05 (1H, t, *J* 8.6 Hz, 5-H), 2.91-2.77 (2H, m, 7-H_2), 2.57 (1H, ddd, *J* 14.2, 4.9 and 2.1 Hz, 2-H_B), 2.44-2.41 (1H, m, 4-H), 1.87-1.78 (1H, m, 8-H_A), 1.77-1.69 (1H, m, 8-H_B), 1.42 (3H, s, acetyl); δ_C (125 MHz, $CDCl_3$): 169.4 (acetyl C=O), 160.3 (phenyl C-3), 145.7 (phenyl

C-1), 130.0 (phenyl C-5), 119.0 (phenyl C-6), 113.5 (phenyl C-2), 111.5 (phenyl C-4), 56.7 (C-2), 55.4 (OMe), 51.8 (C-6), 46.9 (C-3), 46.2 (C-7), 38.2 (C-5), 32.7 (C-4), 28.6 (C-8), 23.0 (acetyl CH_3); HRMS found MH^+ 275.1762. $C_{16}H_{22}N_2O_2$ requires *MH*, 275.1754.

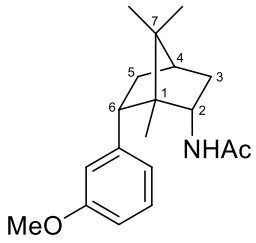
tert-butyl (3*R,5*R**)-3-acetamido-5-(3-methoxyphenyl)piperidine-1-carboxylate (163b)**



Arylated derivative **153a** (0.51 g, 1.24 mmol) was dissolved in ^{i}PrOH (15 ml) and NaOH (496 mg, 12.4 mmol) was added at rt. The reaction mixture was stirred and heated at 85 ^{o}C for 18 h. Water (20 ml) was added and the mixture was then extracted with DCM (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. This was dissolved in THF (20 ml) and the solution was subsequently basified with 2M NaOH. Ac_2O (0.43 ml, 3.72 mmol) was added and the reaction mixture was allowed to stir at rt for a further 4 h. Water (20 ml) was added and the resulting mixture was extracted with DCM (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 50:50 → 70:30 to give the *acetamide derivative* ***163b*** (233 mg, 54%) as a colourless oil that solidified to a white solid upon drying. R_f 0.17 (EtOAc–hexane 70:30). ν_{max}/cm^{-1}: 3532, 3089, 2976, 2936, 1690, 1651, 1601, 1569, 1495, 1426, 1392, 1367, 1287, 1251, 1148, 1036; δ_H (500 MHz, $CDCl_3$): 7.23 (1H, t, *J* 7.9 Hz, phenyl 5-H), 6.82-6.74 (3H, m, phenyl 2-H, phenyl 4-H and phenyl 6-H), 5.26 (1H, br. d, *J* 7.8 Hz, NH), 4.33 (1H, app. d, *J* 10.5 Hz, 2-H_A), 4.25 (1H, app. br. s, 6-H_A), 3.98 (1H, m, 3-H), 3.80 (3H, s, OMe), 2.80 (1H, app. t, *J* 11.6 Hz, 5-H), 2.68 (1H, app. br. s, 6-H_B), 2.49 (1H, app. t, *J* 11.6 Hz, 2-H_B), 2.28 (1H, app. d, *J* 10.8

Hz, 4-H_A), 1.97 (3H, s, acetyl), 1.47 (10H, app. s, 4-H_B and ^{t}Bu); δ_C (125 MHz, $CDCl_3$): 169.5 (C=O acetyl), 159.9 (phenyl C-3), 154.7 (Boc C=O), 146.7 (phenyl C-1), 129.8 (phenyl C-5), 119.4 (phenyl C-6), 113.2 (phenyl C-2), 112.2 (phenyl C-4), 80.3 (C_1 ^{t}Bu), 55.4 (OMe), 49.5 (C-2 and C-6), 46.2 (C-3), 41.3 (C-5), 38.6 (C-4), 28.6 (C_3 ^{t}Bu), 23.6 (acetyl CH_3); HRMS found MNa^+ 371.1945. $C_{19}H_{28}N_2O_4$ requires *MNa*, 371.1941.

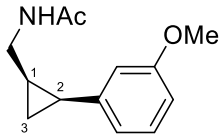
_N_-[(1_R_,2_S_,4_R_,6_S_)-6-(3-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]acetamide (163d)



Water (7.6 ml) and HCl (1.9 ml, 37%) were added to a solution of arylated derivative **156a** (276 mg, 0.76 mmol) in THF (7.6 ml) and the solution was stirred at rt for 5 mins. Zinc dust (741 mg, 11.4 mmol) was then added portionwise over 30 mins and the resulting suspension was stirred at rt for 18 h. The reaction mixture was filtered through celite (eluting with DCM) and then saturated aqueous $NaHCO_3$ (20 ml) was added to the filtrate. The phases were separated and the aqueous phase was extracted with DCM (3 x 20 ml). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. This intermediate was dissolved in THF (10 ml) and the solution was then basified with 2M NaOH. Ac_2O (0.22 ml, 2.28 mmol) was added to this solution and the reaction mixture was then stirred at rt for 4 h. Water (20 ml) was added and the mixture was then extracted with DCM (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give the *acetamide derivative* ***163d*** (181 mg, 79%) as a colourless oil. R_f 0.42 (EtOAc–hexane 80:20). [α_D^{20}] +30.2 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3425, 2951, 1661, 1598, 1580, 1518,

1490, 1457, 1378, 1267, 1150, 1041; δ_H (500 MHz, $CDCl_3$): 7.31 (1H, t, *J* 8.0 Hz, methoxyphenyl 5-H), 7.04 (1H, d, *J* 7.4 Hz, methoxyphenyl 6-H), 6.94 (1H, s, methoxyphenyl 2-H), 6.81 (1H, dd, *J* 8.0 and 2.4 Hz, methoxyphenyl 4-H), 5.24 (1H, br. d, *J* 8.3 Hz, NH), 4.28-4.21 (1H, m, 2-H), 3.82 (3H, s, OMe), 3.26 (1H, dd, *J* 11.5 and 5.1 Hz, 6-H), 2.48-2.39 (1H, m, 3-H_A), 2.24-2.15 (1H, td, *J* 13.2 and 4.0 Hz, 5-H_A), 1.96 (1H, dd, *J* 13.2 and 5.8 Hz, 5-H_B), 1.87 (1H, t, *J* 4.7 Hz, 4-H), 1.35 (3H, s, acetyl), 1.07 (1H, dd, *J* 13.4 and 5.8 Hz, 3-H_B), 1.04 (3H, s, methyl) 1.01 (6H, s, dimethyl); δ_C (125 MHz, $CDCl_3$): 169.6 (C=O), 160.1 (methoxyphenyl C-3), 144.8 (methoxyphenyl C-1), 129.8 (methoxyphenyl C-5), 122.2 (methoxyphenyl C-6), 115.4 (methoxyphenyl C-2), 111.6 (methoxyphenyl C-4), 55.4 (OMe), 54.4 (C-2), 54.2 (C-1), 50.9 (C-7), 47.7 (C-6), 43.7 (C-4), 37.1 (C-3), 32.3 (C-5), 23.1 (acetyl), 20.2 (methyl), 19.9 (methyl), 13.9 (methyl); HRMS found MH^+ 302.2119. $C_{19}H_{27}NO_2$ requires *MH*, 302.2115.

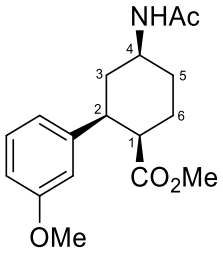
_N_-{[(1_R_*,2_S_*)-2-(3-methoxyphenyl)cyclopropyl]methyl}acetamide (163e)



Water (7.8 ml) and HCl (1.79 ml, 37%) were added to a solution of arylated derivative **159a** (200 mg, 0.71 mmol) in THF (10 ml). The solution was stirred for 5 mins at rt then zinc (689 mg, 10.6 mmol) was added portionwise and the resulting suspension left to stir at rt for 3 h. The mixture was filtered through celite (eluting with DCM) and saturated aqueous $NaHCO_3$ (40 ml) was added to the filtrate. The phases were separated and the aqueous phase extracted with DCM (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. This intermediate was dissolved in THF (10 ml), basified with 2M NaOH, then Ac_2O (0.20 ml, 2.13 mmol) was added and the resulting solution stirred at rt for 18 h. Water (20 ml) was added and the mixture was extracted with DCM (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified

via column chromatography, eluting EtOAc–hexane 90:10 to give *acetamide derivative* ***163e*** (94.0 mg, 60%) as a colourless oil. R_f 0.26 (EtOAc–hexane 90:10). ν_{max}/cm^{-1}: 3282, 3070, 2932, 1648, 1580, 1545, 1434, 1370, 1271, 1253, 1150, 1042; δ_H (500 MHz, $CDCl_3$): 7.20 (1H, t, *J* 7.7 Hz, phenyl 5-H), 6.83-6.79 (1H, m, phenyl 6-H), 6.77-6.72 (2H, m, phenyl 2-H and phenyl 4-H), 5.27 (1H, br. s, NH), 3.80 (3H, s, OMe), 3.22 (1H, dt, *J* 13.7 and 6.7 Hz, cyclopropylmethyl 1-H_A), 2.84-2.78 (1H, m, cyclopropylmethyl 1-H_B), 2.22 (1H, td, *J* 8.6 and 6.3 Hz, 2-H), 1.87 (3H, s, acetyl), 1.43-1.35 (1H, m, 1-H), 1.02 (1H, td, *J* 8.6 and 5.4 Hz, 3-H_A), 0.84 (1H, dd, *J* 11.4 and 5.4 Hz, 3-H_B); δ_C (125 MHz, $CDCl_3$): 169.9 (C=O), 159.8 (phenyl C-3), 140.0 (phenyl C-1), 129.5 (phenyl C-5), 121.3 (phenyl C-6), 114.9 (phenyl C-2), 111.6 (phenyl C-4), 55.3 (OMe), 39.7 (cyclopropylmethyl C-1), 23.4 (acetyl), 20.8 (C-2), 18.5 (C-1), 8.6 (C-3); HRMS found MNa^+ 242.1146. $C_{13}H_{17}NO_2$ requires *MNa*, 242.1151.

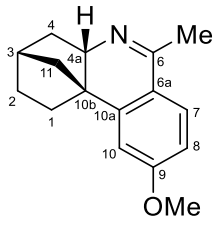
methyl (1*R,2*S**,4*S**)-4-acetamido-2-(3-methoxyphenyl)cyclohexane-1-carboxylate (163f)**



Water (7.40 ml) was added to arylated derivative **162a** (240 mg, 0.65 mmol) in THF (7.40 ml) then HCl (1.64 ml, 37%) was added and the solution stirred for 5 mins at rt. Then zinc powder (636 mg, 9.78 mmol) was added portionwise and the resulting suspension allowed to stir at rt for a further 2 h. The reaction mixture was filtered through celite (eluting with EtOAc) then saturated aqueous $NaHCO_3$ (20 ml) was added to the filtrate. The phases were separated and the aqueous phase extracted with EtOAc (3 x 30 ml). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. This was dissolved in DCM (20 ml) then Et_3N (0.91 ml, 6.50 mmol) and Ac_2O (0.61 ml, 6.50 mmol) were added sequentially. The reaction mixture was then stirred at rt for 18 h

then saturated aqueous NH_4Cl (20 ml) was added to the reaction mixture. The phases were separated and the aqueous phase extracted with DCM (3 x 30 ml). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 75:25 → 100% EtOAc to give *acetamide derivative* ***163f*** (108 mg, 54%) as a colourless oil. R_f 0.24 (EtOAc). ν_{max}/cm^{-1}: 3277, 2935, 2836, 1728, 1651, 1527, 1434, 1293, 1166; δ_H (500 MHz, $CDCl_3$): 7.19 (1H, t, *J* 7.8 Hz, phenyl 5-H), 6.78-6.72 (3H, m, phenyl 2-H, phenyl 4-H and phenyl 6-H), 5.44 (1H, br. d, *J* 8.1 Hz, NH), 4.10-3.91 (1H, m, 4-H), 3.78 (3H, s, OMe), 3.43 (3H, s, CO_2Me), 2.96-2.91 (2H, m, 1-H and 2-H), 2.27 (1H, app. q, *J* 12.2 Hz, 3-H_A), 2.09-2.01 (2H, m, 3-H_B and 5-H_A), 1.98 (3H, s, acetyl), 1.92-1.86 (1H, m, 6-H_A), 1.83 (1H, dt, *J* 13.5 and 4.1 Hz, 6-H_B), 1.71-1.60 (1H, m, 5-H_B); δ_C (125 MHz, $CDCl_3$): 174.4 (C=O ester), 169.3 (C=O amide), 159.7 (phenyl C-3), 144.5 (phenyl C-1), 129.3 (phenyl C-5), 119.7 (phenyl C-6), 113.3 (phenyl C-2), 112.0 (phenyl C-4), 55.3 (OMe), 51.2 (CO_2Me), 48.5 (C-4), 44.7 (C-1), 44.0 (C-2), 32.7 (C-3), 28.0 (C-6), 27.9 (C-5), 23.8 (acetyl CH_3); HRMS found MH^+ 306.1700. $C_{17}H_{23}NO_4$ requires *MH*, 306.1700.

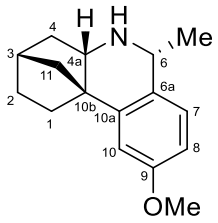
(3*R,4a*R**,10b*S**)-9-methoxy-6-methyl-2,3,4,4a-tetrahydro-1H-3,10b-methanophenanthridine (164b)**



Arylated derivative **133d** (100 mg, 0.39 mmol) was dissolved in MeCN (5 ml) at rt. $POCl_3$ (0.28 ml, 3.09 mmol) was added to the solution dropwise over 5 mins. The resulting solution was then stirred and heated at 100 ^oC for 4 h. The reaction mixture was allowed to cool to rt and the volatiles removed under reduced pressure. DCM (20 ml) and water (20 ml) were added to the residue and this solution was then basified to pH 12 with 2M NaOH. This was then extracted with DCM (4 x 20 ml), organic layers

combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting DCM–MeOH 95:5 to give the *cyclised imine derivative* ***164b*** (31.0 mg, 33%, *dr* >95:<5 by ^1H NMR) as a colourless oil. R_f 0.15 (DCM–MeOH 95:5). δ_H (500 MHz, $CDCl_3$): 7.57 (1H, d, *J* 8.6 Hz, 7-H), 7.05 (1H, d, *J* 2.4 Hz, 10-H), 6.80 (1H, dd, *J* 8.6 and 2.4 Hz, 8-H), 3.86 (3H, s, OMe), 3.46 (1H, app. br. s, 4a-H), 2.45 (3H, s, methyl), 2.33 (1H, app. br. t, *J* 3.9 Hz, 3-H), 2.26 (1H, td, *J* 12.3 and 4.1 Hz, 1-H_A), 2.21-2.14 (1H, m, 4-H_A), 2.09-2.03 (1H, m, 4-H_B), 1.83-1.75 (1H, m, 2-H_A), 1.58 (1H, app. d, *J* 9.5 Hz, 11-H_A), 1.40-1.33 (1H, m, 2-H_B), 1.30-1.24 (1H, m, 1-H_B), 1.22 (1H, app. d, *J* 9.5 Hz, 11-H_B); δ_C (125 MHz, $CDCl_3$): 162.4 (C-9), 161.3 (C-6), 142.8 (C-10a), 129.1 (C-6a), 121.2 (C-7), 111.3 (C-8), 111.0 (C-10), 62.6 (C-4a), 55.6 (OMe), 46.3 (C-10b), 44.2 (C-11), 41.7 (C-4), 35.6 (C-3), 31.7 (C-1), 29.4 (C-2), 23.0 (methyl CH_3); HRMS found MH^+ 242.1557. $C_{16}H_{19}NO$ requires *MH*, 242.1539.

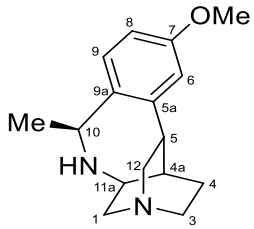
(3*R,4a*R**,6*S**,10b*S**)-9-methoxy-6-methyl-2,3,4,4a,5,6-hexahydro-1*H*-3,10b-methanophenanthridine (165b)**



Cyclised imine derivative **164b** (30.0 mg, 0.12 mmol) was dissolved in MeOH (2 ml) and $NaBH_4$ (9.00 mg, 0.24 mmol) was added at rt. The reaction mixture was left to stir at rt for 18 h. 1M HCl (5 ml) was added to quench the reaction and 2M NaOH to basify the reaction mixture to pH 12. This solution was subsequently extracted with DCM (4 x 10 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *amine derivative* ***165b*** (21.0 mg, 74%, *dr* >95:<5 by ^1H NMR) as a colourless oil. R_f 0.63 (DCM–MeOH 80:20). δ_H (500 MHz, $CDCl_3$); 7.13 (1H, d, *J* 8.6 Hz, 7-H), 6.90 (1H, d, *J* 2.7 Hz, 10-H), 6.71 (1H, dd, *J* 8.6 and 2.7 Hz, 8-

H), 3.99 (1H, q, *J* 6.6 Hz, 6-H), 3.80 (3H, s, OMe), 2.91 (1H, dd, *J* 7.8 and 4.0 Hz, 4a-H), 2.29 (1H, app. br. t, *J* 4.0 Hz, 3-H), 2.01-1.88 (2H, m, 4-H_A and 1-H_A), 1.86-1.78 (1H, m, 2-H_A), 1.63 (1H, dd, *J* 10.0 and 1.6 Hz, 11-H_A), 1.52 (1H, dd, *J* 10.0 and 1.6 Hz, 11-H_B), 1.45 (3H, d, *J* 6.6 Hz, methyl), 1.41-1.24 (4H, m, 4-H_B, 1-H_B, 2-H_B and NH); δ_C (125 MHz, $CDCl_3$): 158.1 (C-9), 140.6 (C-10a), 134.1 (C-6a), 125.9 (C-7), 112.6 (C-10), 111.3 (C-8), 60.8 (C-4a), 55.4 (OMe), 52.4 (C-6), 48.9 (C-10b), 44.8 (C-11), 40.8 (C-4), 36.8 (C-3), 35.2 (C-1), 30.3 (C-2), 21.8 (methyl CH_3); HRMS found MH^+ 244.1708. $C_{16}H_{21}NO$ requires *MH*, 244.1696. The relative configuration was determined through NOESY (500 MHz, $CDCl_2$). nOe interaction observed between 4a-H and 6-H.

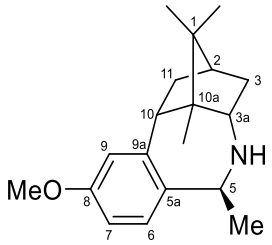
(2*R,4a*S**,5*S**,10*R**,11a*S**)-7-methoxy-10-methyl-1,3,4,4a,5,10,11,11a-octahydro-2,5-methanobenzo[*e*]pyrido[3,4-*b*]azepine (165c)**



Acetamide derivative **163a** (221 mg, 0.81 mmol) was dissolved in MeCN (10 ml) and $POCl_3$ (0.76 ml, 8.10 mmol) was added dropwise at rt. The reaction mixture was stirred and heated to 100 ^oC for 18 h. The reaction mixture was cooled to rt and all volatiles removed under reduced pressure. This residue was dissolved in DCM (10 ml), then water (5 ml) and 5M NaOH were added to basify the reaction mixture. This was then extracted with DCM (3 x 50 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude imine intermediate. This crude intermediate (140 mg, 0.55 mmol) was dissolved in MeOH (5 ml) and $NaBH_4$ (42.0 mg, 1.10 mmol) was added at rt. The resulting solution was allowed to stir at rt for 1 h. Then 1M HCl (15 ml) was added to quench the reaction, followed by 2M NaOH to basify the solution to pH 12. Then this mixture was extracted with DCM (3 x 30 ml),

organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material (*dr* 68:32 by ^1H NMR). This was then purified *via* column chromatography, eluting DCM–sat. NH_3/MeOH 95:5 → 90:10 to give the *cyclised amine derivative* ***165c*** (112 mg, 54%, *dr* 84:16 by ^1H NMR) as a colourless oil. R_f 0.25 (DCM–sat. NH_3/MeOH 95:5). ν_{max}/cm^{-1}: 3251, 2947, 2909, 2783, 1602, 1502, 1238, 1038; δ_H (500 MHz, $CDCl_3$): 7.13 (1H, d, *J* 8.6 Hz, 9-H), 6.69-6.62 (2H, m, 6-H and 8-H), 4.19 (1H, q, *J* 6.7 Hz, 10-H), 3.78 (3H, s, OMe), 3.39-3.25 (2H, m, 11a-H and 12-H_A), 3.06-2.80 (5H, m, 12-H_B, 5-H, 1-H_A and 3-H_2), 2.63 (1H, d, *J* 13.8 Hz, 1-H_B), 2.55 (1H, t, *J* 4.5 Hz, 4a-H), 1.76-1.56 (3H, m, 4-H_2 and NH), 1.50 (3H, d, *J* 6.7 Hz, methyl); δ_C (125 MHz, $CDCl_3$): 157.8 (C-7), 144.5 (C-5a), 138.3 (C-9a), 126.8 (C-9), 116.4 (C-6), 110.3 (C-8), 57.3 (C-1), 55.9 (C-12), 55.4 (OMe), 52.0 (C-11a), 49.9 (C-10), 46.6 (C-3), 42.7 (C-5), 29.2 (C-4a), 24.4 (C-4), 22.4 (methyl CH_3); HRMS found MH^+ 259.1808. $C_{16}H_{22}N_2O$ requires *MH*, 259.1805. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 10-H and 4a-H (500 MHz, $CDCl_3$).

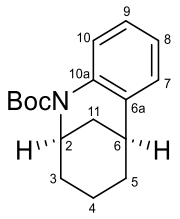
(2*R*,3a*S*,5*S*,10*S*,10a*R*)-8-methoxy-1,1,5,10a-tetramethyl-1,2,3,3a,4,5,10,10a-octahydro-2,10-methanobenzo[*e*]cyclopenta[*b*]azepine (165e)



Acetamide derivative **163d** (80.0 mg, 0.27 mmol) was dissolved in MeCN (4 ml) and $POCl_3$ (0.25 ml, 2.70 mmol) was added dropwise at rt. The resulting solution was stirred and heated at 100 ^oC for 2 h. The reaction mixture was cooled to rt and then all the volatiles were removed under reduced pressure. The residue was dissolved in DCM (10 ml) then water (5 ml) and 5M NaOH was added to basify the solution. This was then extracted with DCM (3 x 20 ml), organic layers combined, dried ($MgSO_4$),

filtered and concentrated under reduced pressure to give the crude imine intermediate. This intermediate was dissolved in MeOH (4 ml) and $NaBH_4$ (21.0 mg, 0.54 mmol) was added at rt. The solution was allowed to stir for 2 h then 1M HCl (5 ml) was added to quench the reaction. This solution was basified with 5M NaOH then extracted with DCM (3 x 20 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–MeOH 95:5 to give the *cyclised amine derivative* ***165e*** (47.0 mg, 62%, *dr* >95:<5 by ^1H NMR) as a fine white solid. R_f 0.10 (EtOAc–MeOH 95:5). [α_D^{20}] +39.7 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3332, 2944, 2833, 1606, 1580, 1506, 1461, 1282, 1239, 1147, 1089; δ_H (500 MHz, $CDCl_3$): 7.16 (1H, d, *J* 9.2 Hz, 6-H), 6.70-6.65 (2H, m, 7-H and 9-H), 4.42 (1H, q, *J* 6.5 Hz, 5-H), 3.78 (3H, s, OMe), 3.48 (1H, d, *J* 9.7 Hz, 3a-H), 2.98 (1H, dd, *J* 10.6 and 7.9 Hz, 10-H), 2.35-2.07 (3H, m, 3-H_A, 11-H_A and NH), 1.82 (1H, t, *J* 4.1 Hz, 2-H), 1.72-1.62 (2H, m, 3-H_B and 11-H_B), 1.50 (3H, d, *J* 6.5 Hz, 5-methyl), 1.00 (3H, s, methyl), 0.94 (3H, s, methyl), 0.66 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 157.9 (C-8), 142.9 (C-9a), 138.4 (C-5a), 125.4 (C-6), 119.4 (C-9), 110.1 (C-7), 63.6 (C-3a), 55.3 (OMe), 52.5 (C-10), 49.2 (C-10a), 48.4 (C-1), 45.1 (C-5), 43.3 (C-2), 33.5 (C-3), 32.1 (C-11), 21.6 (methyl C-5), 19.9 (methyl), 19.8 (methyl), 13.0 (methyl); HRMS found MH^+ 286.2171. $C_{19}H_{27}NO$ requires *MH*, 286.2165. The configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 5-H and 3-H_B (500 MHz, $CDCl_3$).

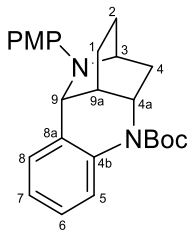
tert-butyl (2*R**,6*S**)-3,4,5,6-tetrahydro-2,6-methanobenzo[*b*]azocine-1(2*H*)-carboxylate (166a)



Arylated derivative **133b** (100 mg, 0.30 mmol), $Pd(OAc)_2$ (4.00 mg, 5 mol%) and *rac*-BINAP (14.0 mg, 7.5 mol%) were added to toluene (5 ml) and heated until all solids

had dissolved. Cs_2CO_3 (194 mg, 0.60 mmol) was then added and the resulting suspension stirred and heated at 100 ^oC for 24 h. The reaction mixture was cooled to rt then filtered through a small plug of silica (washed with EtOAc). The filtrate was concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 2:98 to give *cyclised bridged derivative* ***166a*** (33.0 mg, 40%) as a colourless oil. R_f 0.57 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 2973, 2930, 2852, 1705, 1488, 1454, 1366, 1318, 1277, 1254, 1160, 1130; δ_H (500 MHz, $CDCl_3$): 8.32 (1H, d, *J* 8.5 Hz, 10-H), 7.15 (1H, ddd, *J* 8.5, 7.5 and 1.8 Hz, 9-H), 7.03 (1H, dd, *J* 7.5 and 1.8 Hz, 7-H), 6.91 (1H, td, *J* 7.5 and 1.0 Hz, 8-H), 4.60-4.56 (1H, m, 2-H), 3.00-2.95 (1H, m, 6-H), 2.09-2.02 (1H, m, 3-H_A), 1.92-1.84 (2H, m, 11-H_2), 1.76 (2H, dt, *J* 10.6 and 3.5 Hz, 5-H_2), 1.55 (9H, s, ^{t}Bu), 1.54-1.50 (1H, m, 3-H_B), 1.45-1.39 (1H, m, 4-H_A), 1.31-1.22 (1H, m, 4-H_B); δ_C (125 MHz, $CDCl_3$): 153.9 (Boc C=O), 140.2 (C-10a), 131.3 (C-6a), 128.6 (C-7), 126.5 (C-9), 121.7 (C-8), 120.3 (C-10), 80.8 (^{t}Bu C_1), 50.3 (C-2), 34.5 (C-6), 33.9 (C-5), 32.1 (C-3), 30.2 (C-11), 28.6 (^{t}Bu C_3), 17.6 (C-4); HRMS found MNa^+ 296.1619. $C_{17}H_{23}NO_2$ requires *MNa*, 296.1621.

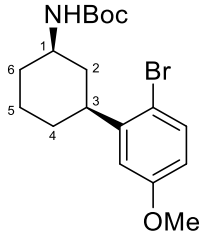
tert-butyl (3*R,4a*R**,9*S**,9a*S**)-11-(4-methoxyphenyl)-2,3,4,4a,9,9a-hexahydro-3,9-epiminoacridine-10(1*H*)-carboxylate (166b)**



$Pd(OAc)_2$ (4.00 mg, 5 mol%), *rac*-BINAP (16.0 mg, 7.5 mol%) and NaO^{t}Bu (63.0 mg, 0.66 mmol) were added to a solution of carbamate derivative **149b** (160 mg, 0.33 mmol) in toluene (10 ml) at rt. The reaction mixture was then stirred and heated at 100 ^oC for 24 h, allowed to cool to rt and then filtered through celite. The filtrate was concentrated under reduced pressure to give a crude material. This was then purified

via column chromatography, eluting EtOAc–hexane 5:95 to give the *cyclised carbamate derivative* ***166b*** (45.0 mg, 32%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.58 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 2990, 2934, 2858, 1692, 1509, 1328, 1273, 1192, 1078; δ_H (500 MHz, $CDCl_3$): 7.97 (1H, d, *J* 8.4 Hz, 5-H), 7.38 (1H, dd, *J* 7.6 and 1.3 Hz, 8-H), 7.21-7.17 (1H, m, 6-H), 7.00 (2H, d, *J* 9.1 Hz, methoxyphenyl 2,6-H), 6.95 (1H, td, *J* 7.6 and 0.9 Hz, 7-H), 6.84 (2H, d, *J* 9.1 Hz, methoxyphenyl 3,5-H), 4.65-4.59 (1H, m, 3-H), 4.54 (1H, d, *J* 2.3 Hz, 9-H), 3.77 (3H, s, OMe), 3.69-3.64 (1H, m, 4a-H), 2.27 (1H, ddd, *J* 13.9, 9.9 and 2.6 Hz, 4-H_A), 2.00-1.92 (2H, m, 9a-H and 2-H_A), 1.87 (1H, ddd, *J* 13.9, 6.5 and 3.4 Hz, 4-H_B), 1.83-1.69 (2H, m, 2-H_B and 1-H_A), 1.57 (9H, s, ^{t}Bu), 1.45-1.36 (1H, m, 1-H_B); δ_C (125 MHz, $CDCl_3$): 153.5 (Boc C=O), 152.2 (methoxyphenyl C-4), 143.5 (methoxyphenyl C-1), 135.9 (C-4b), 131.5 (C-8a), 128.5 (C-8), 127.6 (C-6), 123.2 (C-5), 122.6 (C-7), 116.4 (methoxyphenyl C_2-2,6), 114.9 (methoxyphenyl C_2-3,5), 81.4 (C_1 ^{t}Bu), 55.9 (OMe), 55.3 (C-9), 48.8 (C-3), 46.5 (C-4a), 36.9 (C-4), 30.9 (C-9a), 28.6 (C_3 ^{t}Bu), 21.3 (C-2), 21.2 (C-1); HRMS found MH$^+$ 407.2338. $C_{25}H_{30}N_2O_3$ requires *MH*, 407.2329. Confirmation of the relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 1-H_B and 4a-H.

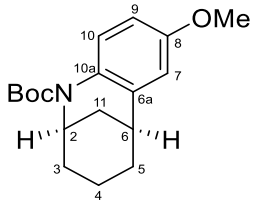
tert-butyl _N_-[(1_R_*,3_S_*)-3-(2-bromo-5-methoxyphenyl)cyclohexyl]carbamate (167a)



Arylated derivative **133c** (100 mg, 0.33 mmol) was dissolved in MeCN (5 ml) then NBS (64.0 mg, 0.36 mmol) was added to the solution at rt. The resulting solution was stirred overnight for 18 h at rt. The solvent was then removed under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–

hexane 5:95 to give the *brominated derivative* ***167a*** (101 mg, 79%) as a white solid. R_f 0.50 (EtOAc–hexane 20:80). δ_H (500 MHz, $CDCl_3$): 7.40 (1H, d, *J* 8.7 Hz, phenyl 3-H), 6.75 (1H, d, *J* 3.0 Hz, phenyl 6-H), 6.60 (1H, dd, *J* 8.7 and 3.0 Hz, phenyl 4-H), 4.48 (1H, br. s, NH), 3.75 (3H, s, OMe), 3.66-3.50 (1H, m, 1-H), 3.02 (1H, tt, *J* 11.9 and 2.9 Hz, 3-H), 2.17 (1H, app. d, *J* 11.9 Hz, 2-H_A), 2.06 (1H, app. d, *J* 11.9 Hz, 6-H_A), 1.91-1.82 (2H, m, 4-H_A and 5-H_A), 1.51 (1H, qt, *J* 13.2 and 3.0 Hz, 5-H_B), 1.43 (9H, s, ^{t}Bu), 1.28-1.14 (2H, m, 2-H_B and 4-H_B), 1.09 (1H, qd, *J* 12.7 and 3.6 Hz, 6-H_B); δ_C (125 MHz, $CDCl_3$): 159.2 (phenyl C-5), 155.2 (Boc C=O), 145.8 (phenyl C-1), 133.4 (phenyl C-3), 114.9 (phenyl C-2), 113.7 (phenyl C-6), 112.6 (phenyl C-4), 79.2 (^{t}Bu C_1), 55.5 (OMe), 49.9 (C-1), 42.1 (C-3), 39.8 (C-2), 33.3 (C-6), 32.2 (C-4), 28.5 (^{t}Bu C_3), 25.1 (C-5); HRMS found MNa^+ 406.0984. $C_{18}H_{26}BrNO_3$ requires *MNa*, 406.0988.

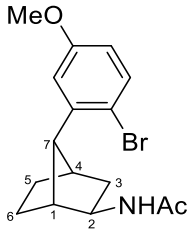
tert-butyl (2*R,6*S**)-8-methoxy-3,4,5,6-tetrahydro-2,6-methanobenzo[*b*]azocine-1(2H)-carboxylate (166c)**



Brominated derivative **167a** (95.0 mg, 0.25 mmol), $Pd(OAc)_2$ (3.00 mg, 5 mol%) and *rac*-BINAP (12.0 mg, 7.5 mol%) were added to toluene (5 ml) and heated until all solids had dissolved. Cs_2CO_3 (163 mg, 0.50 mmol) was then added and the resulting suspension stirred and heated at 100 ^{o}C for 24 h. The reaction mixture was cooled to rt then filtered through a small plug of silica (washed with EtOAc). The filtrate was concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give *cyclised bridged derivative* ***166c*** (46.0 mg, 62%) as a colourless oil. R_f 0.62 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 2973, 2930, 2852, 1695, 1494, 1325, 1245, 1163, 1048; δ_H (500 MHz, $CDCl_3$): 8.27 (1H, d, *J* 9.2 Hz, 10-H), 6.72 (1H, dd, *J* 9.2 and 3.1 Hz, 9-H), 6.59 (1H,

d, *J* 3.1 Hz, 7-H), 4.56 (1H, br. t, *J* 3.1 Hz, 2-H), 3.77 (3H, s, OMe), 2.96-2.92 (1H, m, 6-H), 2.05 (1H app. d, *J* 13.4 Hz, 3-H_A), 1.87 (2H, app. t, *J* 2.6 Hz, 11-H_2), 1.78-1.72 (2H, m, 5-H_2), 1.54 (9H, s, ^{t}Bu), 1.50 (1H, ddd, *J* 13.4, 4.7 and 2.8 Hz, 3-H_B), 1.45-1.37 (1H, m, 4-H_A), 1.33-1.20 (1H, m, 4-H_B); δ_C (125 MHz, $CDCl_3$): 154.2 (C-8), 153.8 (Boc C=O), 133.7 (C-10a), 132.8 (C-6a), 121.5 (C-10), 113.6 (C-7), 111.7 (C-9), 80.6 (^{t}Bu C_1), 55.5 (OMe), 50.0 (C-2), 34.7 (C-6), 33.9 (C-5), 32.1 (C-3), 30.3 (C-11), 28.6 (^{t}Bu C_3), 17.7 (C-4); HRMS found MNa^+ 326.1728. $C_{18}H_{25}NO_3$ requires *MNa*, 326.1727.

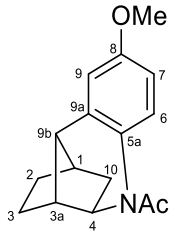
_N_-[(1_R_*,2_R_*,4_R_*,7_R_*)-7-(2-bromo-5-methoxyphenyl)bicyclo[2.2.1]heptan-2-yl]acetamide (167b)



Arylated derivative **136a** (100 mg, 0.39 mmol) was dissolved in MeCN (5 ml) at rt. Then NBS (76.0 mg, 0.43 mmol) was added at rt. The resulting solution was stirred at rt for 18 h and then concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give the *brominated derivative* ***167b*** (118 mg, 89%) as a white powder. R_f 0.20 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3303, 2952, 2906, 2868, 1639, 1533, 1463, 1287, 1175; δ_H (500 MHz, $CDCl_3$); 7.46 (1H, d, *J* 8.7 Hz, phenyl 3-H), 6.90 (1H, d, *J* 2.5 Hz, phenyl 6-H), 6.64 (1H, dd, *J* 8.7 and 2.5 Hz, phenyl 4-H), 4.48 (1H, br. d, *J* 5.4 Hz, NH), 3.82 (1H, td, *J* 8.1 and 2.9 Hz, 2-H), 3.77 (3H, s, OMe), 3.08 (1H, d, *J* 4.3 Hz, 1-H), 2.88 (1H, app. s, 7-H), 2.64 (1H, br. t, *J* 3.9 Hz, 4-H), 1.99-1.91 (1H, m, 3-H_A), 1.89-1.80 (2H, m, 3-H_B and 6-H_A), 1.72-1.64 (1H, m, 5-H_A), 1.48 (3H, s, acetyl), 1.41-1.32 (1H, m, 6-H_B), 1.30-1.22 (1H, m, 5-H_B); δ_C (125 MHz, $CDCl_3$): 168.7 (acetyl C=O), 158.9 (phenyl C-5), 141.4 (phenyl C-1), 134.2 (phenyl C-3), 116.2 (phenyl C-6), 115.8

(phenyl C-2), 112.5 (phenyl C-4), 55.6 (OMe), 54.1 (C-7), 53.3 (C-2), 46.4 (C-1), 38.8 (C-3), 38.2 (C-4), 28.9 (C-5), 27.4 (C-6), 23.2 (acetyl CH_3); HRMS found MH^+ 338.0748. $C_{16}H_{20}BrNO_2$ requires *MH*, 338.0750.

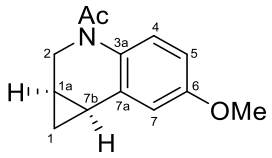
1-[(1*R,3a*R**,4*R**,9b*S**)-8-methoxy-1,2,3,3a,4,9b-hexahydro-5*H*-1,4-methanocyclopenta[*c*]quinoline-5-yl]ethan-1-one (166d)**



Brominated derivative **167b** (110 mg, 0.33 mmol) was dissolved in toluene (10 ml) and $Pd(OAc)_2$ (3.71 mg, 5 mol%), *rac*-BINAP (15.0 mg, 7.5 mol%) and Cs_2CO_3 (215 mg, 0.66 mmol) were added sequentially at rt. The reaction mixture was then stirred at 100 ^oC for 24 h. The reaction mixture was allowed to cool to rt and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 20:80→50:50 to give *cyclised acetamide derivative* ***166d*** (71.0 mg, 85%, *rotamers* 60:40 by ^1H NMR) as a white solid. R_f 0.54 (EtOAc–hexane 50:50). δ_H (500 MHz, $CDCl_3$, broad peaks due to unresolved rotamers); 8.10 (1H, app. br. s, 6-H^{maj}), 6.95 (1H, app. br. s, 6-H^{min}), 6.71 (2H, app. d, *J* 8.8 Hz, 7-H), 6.65 (2H, app. br. s, 9-H), 5.11 (1H, app. br. s, 4-H^{min}), 4.19-4.01 (1H, m, 4-H^{maj}), 3.77 (6H, s, OMe), 2.71 (2H, app. s, 9b-H), 2.44-2.34 (2H, m, 3a-H), 2.28 (6H, s, acetyl), 2.19 (2H, app. br. s, 1-H), 1.84 (2H, app. br. s, 2-H_A), 1.62 (4H, app. br. s, 10-H_A and 3-H_A), 1.49 (2H, app. br. s, 3-H_B), 1.32 (2H, app. br. s, 2-H_B), 1.31-1.20 (2H, m, 10-H_B); δ_C (125 MHz, $CDCl_3$): 169.7 (acetyl C=O^{min}), 168.5 (acetyl C=O^{maj}), 156.3 (C-8^{min}), 155.7 (C-8^{maj}), 134.3 (C-$9a^{min}$), 132.4 (C-$9a^{maj}$), 130.2 (C-$5a^{min}$), 129.4 (C-$5a^{maj}$), 124.8 (C-6^{maj}), 124.4 (C-6^{min}), 113.9 (C-9), 111.5 (C-7), 60.5 (C-4^{maj}), 59.7 (C-4^{min}), 55.5 (OMe), 50.8 (C-9b), 46.5 (C-3a), 40.1 (C-1^{min}), 39.1 (C-

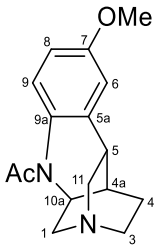
1^{maj}), 34.5 (C-3^{maj}), 32.8 (C-3^{min}), 29.2 (C-10), 25.1 (C-2), 24.5 (acetyl CH_3); HRMS found MNa^+ 280.1312. $C_{16}H_{19}NO_2$ requires *MNa*, 280.1308.

1-[(1a*R,7b*S**)-6-methoxy-1,1a,2,7b-tetrahydro-3*H*-cyclopropa[*c*]quinolin-3-yl]ethan-1-one (166e)**



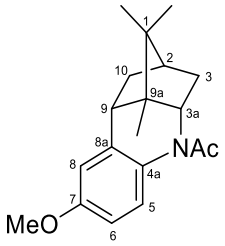
Acetamide derivative **163e** (95.0 mg, 0.43 mmol) was dissolved in MeCN (5 ml) then NBS (85.0 mg, 0.47 mmol) was added and the resulting solution stirred at rt for 4 h. The volatiles were removed under reduced pressure to give the crude brominated intermediate. This was then dissolved in toluene (2 ml) then added to a pressure vial. Then $Pd(OAc)_2$ (5.00 mg, 5 mol%), *rac*-BINAP (20.0 mg, 7.5 mol%) and NaO^tBu (83.0 mg, 0.86 mmol) were added sequentially, the pressure vial sealed then stirred at 100 ^oC for 18 h. The reaction mixture was cooled to rt then filtered through celite (eluting with DCM). The filtrate was concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give the *cyclised acetamide derivative* ***166e*** (38.0 mg, 41%) as a colourless oil. R_f 0.31 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3004, 2920, 2836, 1651, 1502, 1385, 1265, 1215, 1139; δ_H (500 MHz, $CDCl_3$): 6.93 (1H, d, *J* 8.7 Hz, 4-H), 6.87 (1H, d, *J* 2.7 Hz, 7-H), 6.68 (1H, dd, *J* 8.7 and 2.7 Hz, 5-H), 5.04 (1H, d, *J* 12.5 Hz, 2-H_A), 3.81 (3H, s, OMe), 2.68 (1H, d, *J* 12.5 Hz, 2-H_B), 2.12 (3H, s, acetyl), 1.93 (1H, td, *J* 8.4 and 4.5 Hz, 7b-H), 1.84-1.78 (1H, m, 1a-H), 1.01 (1H, td, *J* 8.4 and 5.6 Hz, 1-H_A), 0.61 (1H, dd, *J* 10.0 and 5.0 Hz, 1-H_B); δ_C (125 MHz, $CDCl_3$): 170.5 (C=O), 157.6 (C-6), 135.3 (C-3a), 129.4 (C-7a), 126.1 (C-4), 113.8 (C-7), 110.8 (C-5), 55.6 (OMe), 38.4 (C-2), 22.5 (acetyl CH_3), 18.4 (C-1a), 15.2 (C-7b), 9.0 (C-1); HRMS found MH^+ 218.1172. $C_{13}H_{15}NO_2$ requires *MH*, 218.1176.

1-[(2*R,4a*S**,5*S**,10a*R**)-7-methoxy-1,3,4,4a,5,10a-hexahydro-10*H*-2,5-methanobenzo[*b*][1,7]naphthridin-10-yl]ethan-1-one (166f)**



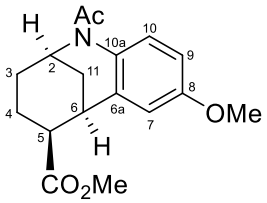
Acetamide derivative **163a** (100 mg, 0.36 mmol) was dissolved in MeCN (5 ml) and NBS (65.0 mg, 0.36 mmol) was added. The reaction mixture was left to stir at rt for 18 h. The solvent was removed under reduced pressure to give the crude *p*-bromo intermediate. This crude intermediate (82.0 mg, 0.23 mmol) was dissolved in toluene (5 ml) and $Pd(OAc)_2$ (3.00 mg, 5 mol%), *rac*-BINAP (11.0 mg, 7.5 mol%) and Cs_2CO_3 (152 mg, 0.47 mmol) were added sequentially. The reaction mixture was heated at 100 ^oC for 24 h then allowed to cool to rt. The resulting mixture was filtered through celite and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting DCM–sat. NH_3/MeOH 95:5 to give the *cyclised acetamide derivative* ***166f*** (40.0 mg, 41%) as a pale-yellow oil. R_f 0.61 (DCM–sat. NH_3/MeOH 90:10). ν_{max}/cm^{-1}: 2934, 2871, 1634, 1494, 1243, 1038; δ_H (500 MHz, $CDCl_3$): 6.76 (1H, dd, *J* 9.0 and 2.0 Hz, 8-H), 6.60 (1H, d, *J* 2.0 Hz, 6-H), 3.79 (3H, s, OMe), 3.37-3.26 (2H, m, 1-H_A and 11-H_A), 2.94-2.85 (2H, m, 5-H and 3-H_A), 2.78-2.70 (1H, m, 3-H_B), 2.60 (1H, d, *J* 13.3 Hz, 1-H_B), 2.47-2.42 (1H, m, 11-H_B), 2.33 (3H, s, acetyl), 1.91 (1H, app. s, 4a-H), 1.84-1.72 (2H, m, 4-H_2); δ_C (125 MHz, $CDCl_3$): 170.0 (C=O), 156.8 (C-7), 135.6 (C-9a), 127.5 (C-5a), 125.3 (C-9), 113.3 (C-6), 112.2 (C-8), 57.0 (C-1), 55.6 (OMe), 53.1 (C-11), 46.3 (C-3), 34.6 (C-5), 26.2 (C-4a), 24.8 (acetyl CH_3), 23.0 (C-4); HRMS found MH^+ 273.1606. $C_{16}H_{20}N_2O_2$ requires *MH*, 273.1598. 9-H and 10a-H not observed by ^1H NMR and C-10a not observed by ^{13}C NMR due to unresolved rotamers causing extensive peak broadening of these peaks.

1-[(2*R*,3a*S*,9*R*,9a*R*)-7-methoxy-1,1,9a-trimethyl-1,2,3,3a,9,9a-hexahydro-4*H*-2,9-methanocyclopenta[*b*]quinilin-4-yl]ethan-1-one (166h)



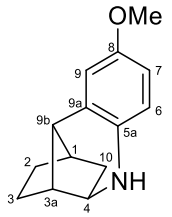
NBS (59 mg, 0.33 mmol) was added to a solution of acetamide derivative **163d** (91.0 mg, 0.30 mmol) in MeCN (5 ml) at rt and stirred at rt for 4 h. The reaction mixture was concentrated under reduced pressure to give the crude *p*-bromo intermediate. This intermediate was dissolved in toluene (5 ml) and $Pd(OAc)_2$ (3.00 mg, 5 mol%), *rac*-BINAP (14.0 mg, 7.5 mol%) and NaO^{t}Bu (57.6 mg, 0.60 mmol) were then added sequentially at rt. The reaction mixture was then stirred at 100 ^{o}C for 24 h, cooled to rt and filtered through celite (eluting with DCM). The filtrate was then concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 20:80 to give the *cyclised acetamide derivative* ***166h*** (42.0 mg, 47%) as a colourless oil. R_f 0.55 (EtOAc–hexane 50:50). [α_D^{20}] +2.00 (c 0.01, MeOH); ν_{max}/cm^{-1}: 2949, 2878, 1652, 1500, 1462, 1369, 1301, 1273, 1240, 1145, 1110, 1048; δ_H (500 MHz, $CDCl_3$): 6.72 (1H, dd, *J* 9.0 and 2.9 Hz, 6-H), 6.64 (1H, d, *J* 2.9 Hz, 8-H), 3.78 (3H, s, OMe), 2.87 (1H, dt, *J* 9.3 and 2.4 Hz, 9-H), 2.45-2.33 (2H, m, 3-H$_A$ and 10-H$_A$), 2.32 (3H, s, acetyl), 1.65 (1H, t, *J* 4.2 Hz, 2-H), 1.02 (3H, s, methyl), 1.00-0.93 (5H, m, 3-H$_B$, 10-H$_B$ and methyl), 0.77 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 171.1 (C=O), 156.3 (C-7), 133.6 (C-4a), 126.7 (C-8a), 124.9 (C-5), 114.3 (C-8), 111.6 (C-6), 56.4 (C-3a), 55.5 (OMe), 48.9 (C-9a), 45.2 (C-1), 42.9 (C-2), 42.4 (C-9), 40.8 (C-3 and C-10), 24.6 (acetyl CH_3), 19.7 (methyl), 18.9 (methyl), 12.4 (methyl); HRMS found MNa^+ 322.1777. $C_{19}H_{25}NO_2$ requires *MNa*, 322.1778. 5-H and 3a-H are not observed by ^{1}H NMR (500 MHz, $CDCl_3$).

methyl (2*R,5*S**,6*R**)-1-acetyl-8-methoxy-1,2,3,4,5,6-hexahydro-2,6-methano-1-benzazocine-5-carboxylate (166i)**



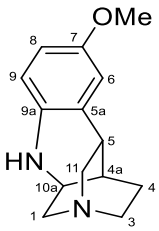
Acetamide derivative **163f** (81.0 mg, 0.27 mmol) was dissolved in MeCN (5 ml) then NBS (52.0 mg, 0.29 mmol) was added and the reaction mixture left to stir at rt for 18 h. The volatiles were removed under reduced pressure to give the crude brominated intermediate. This was then dissolved in toluene (2 ml) and added to a pressure vial. Then $Pd(OAc)_2$ (3.00 mg, 5 mol%), *rac*-BINAP (13.0 mg, 7.5 mol%) and Cs_2CO_3 (176 mg, 0.54 mmol) were added sequentially and the resulting reaction mixture stirred at 100 ^oC for 24 h. The reaction mixture was allowed to cool to room temperature, filtered through celite (eluting with DCM) and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give the *cyclised acetamide derivative* ***166i*** (35.0 mg, 43%) as a colourless oil. R_f 0.58 (EtOAc). ν_{max}/cm^{-1}: 2993, 2835, 1730, 1649, 1493, 1434, 1305, 1264, 1176, 1049; δ_H (500 MHz, $CDCl_3$): 6.73 (1H, dd, *J* 9.2 and 3.0 Hz, 9-H), 6.52 (1H, d, *J* 3.0 Hz, 7-H), 4.59 (1H, app. br. s, 2-H), 3.74 (3H, s, OMe), 3.69 (3H, s, CO_2Me), 3.50 (1H, d, *J* 2.8 Hz, 6-H), 2.73 (1H, dt, *J* 12.8 and 3.6 Hz, 5-H), 2.35 (3H, s, acetyl), 2.15 (1H, br. d, *J* 13.5 Hz, 3-H_A), 1.99 (2H, app. s, 11-H_2), 1.76-1.70 (1H, m, 4-H_A), 1.60 (1H, app. t, *J* 13.5 Hz, 3-H_B), 1.38 (1H, qd, *J* 13.7 and 4.0 Hz, 4-H_B); δ_C (125 MHz, $CDCl_3$): 173.7 (C=O ester), 170.7 (C=O amide), 155.1 (C-8), 133.2 (C-10a), 129.7 (C-10), 123.1 (C-6a), 114.1 (C-7), 112.6 (C-9), 55.5 (OMe), 51.7 (CO_2Me), 49.1 (C-2), 48.2 (C-5), 36.7 (C-6), 31.3 (C-11), 31.0 (C-3), 25.1 (acetyl CH_3), 19.5 (C-4); HRMS found MH^+ 304.1544. $C_{17}H_{21}NO_4$ requires *MH*, 304.1543. 10-H is not observed by ^1H NMR (500 MHz, $CDCl_3$).

(1*R,3a*R**,4*R**,9b*S**)-8-methoxy-1,2,3,3a,4,9b-hexahydro-5*H*-1,4-methanocyclopenta[*c*]quinoline (168a)**



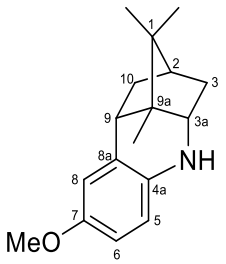
Cyclised acetamide derivative **166d** (70.0 mg, 0.27 mmol) was dissolved in EtOH–HCl 1:1 (10 ml) and stirred at 80 ^{o}C for 18 h. The reaction mixture was allowed to cool to rt and concentrated under reduced pressure to give the *aniline derivative* ***168a*** (64.0 mg, 94%) as a white powder. R_f 0.84 (DCM–MeOH 90:10). ν_{max}/cm^{-1}: 3483, 3434, 2961, 2868, 1504, 1446, 1268, 1034; δ_H (500 MHz, MeOD); 7.19 (1H, d, *J* 8.5 Hz, 6-H), 6.97-6.92 (2H, m, 7-H and 9-H), 3.94-3.91 (1H, m, 4-H), 3.83 (3H, s, OMe), 2.97 (1H, app. s, 9b-H), 2.53 (2H, app. d, *J* 3.9 Hz, 3a-H and 1-H), 2.03-1.94 (1H, m, 2-H_A), 1.86-1.77 (1H, m, 3-H_A), 1.77-1.72 (2H, m, 10-H_2), 1.50-1.39 (2H, m, 2-H_B and 3-H_B); δ_C (125 MHz, MeOD): 161.6 (C-8), 136.8 (C-9a), 125.3 (C-6), 120.2 (C-5a), 116.2 (C-9), 115.0 (C-7), 57.6 (C-4), 56.2 (OMe), 49.5 (C-9b), 46.7 (C-3a), 40.8 (C-1), 32.0 (C-10), 30.4 (C-3), 24.8 (C-2); HRMS found MH$^+$ 216.1394. $C_{14}H_{17}NO$ requires *MH*, 216.1383. The product was isolated as the corresponding HCl salt.

(2*R,4a*S**,5*S**,10a*R**)-7-methoxy-3,4,4a,5,10,10a-hexahydro-1*H*-2,5-methanobenzo[*b*][1,7]naphthridine (168c)**



Cyclised acetamide derivative **166f** (40.0 mg, 0.15 mmol) was dissolved in 1:1 HCl–EtOH (10 ml) and stirred at 80 ^{o}C for 18 h. The reaction mixture was allowed to cool to rt then concentrated under reduced pressure to give the *amine derivative* ***168c*** (36.0 mg, 89%) as an off-white solid. R_f 0.37 (DCM–sat. NH_3/MeOH 90:10). ν_{max}/cm^{-1}: 3151, 3052, 1595, 1238, 1016; δ_H (500 MHz, MeOD): 7.33 (1H, d, *J* 8.7 Hz, 9-H), 7.08 (1H, d, *J* 8.7 Hz, 8-H), 7.05 (1H, s, 6-H), 4.56-4.48 (1H, m, 10a-H), 4.00-3.93 (1H, m, 1-H_A), 3.86 (4H, app. s, OMe and 11-H_A), 3.64-3.58 (1H, m, 5-H), 3.52-3.44 (1H, m, 3-H_A), 3.40-3.32 (2H, m, 1-H_B and 3-H_B), 3.27 (1H, d, *J* 12.3 Hz, 11-H_B), 2.64 (1H, app. s, 4a-H), 2.34-2.24 (2H, m, 4-H_2); δ_C (125 MHz, MeOD): 162.1 (C-7), 136.6 (C-9a), 126.1 (C-9), 119.9 (C-5a), 117.2 (C-8), 115.8 (C-6), 56.4 (OMe), 54.7 (C-11), 48.8 (C-1), 47.0 (C-3), 46.8 (C-10a), 30.6 (C-5), 23.9 (C-4a), 20.3 (C-4); HRMS found MH$^+$ 231.1495. $C_{14}H_{18}N_2O$ requires *MH*, 231.1492. The product was isolated as the HCl salt.

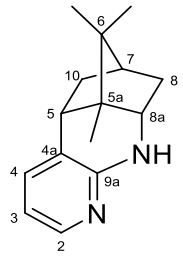
(2*R*,3a*S*,9*R*,9a*R*)-7-methoxy-1,1,9a-trimethyl-1,2,3,3a,9,9a-hexahydro-1*H*-2,9-methanocyclopenta[*b*]quiniline (168d)



Cyclised acetamide derivative **166h** (40.0 mg, 0.13 mmol) was dissolved in 1:1 HCl–EtOH (10 ml) and stirred at 80 ^{o}C for 18 h. The reaction mixture was allowed to cool to rt then concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–MeOH 95:5 to give the *amine derivative* ***168d*** (21.0 mg, 67%) as an off-white solid. R_f 0.67 (EtOAc–MeOH 90:10). [α_D^{20}] +6.00 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3339, 2918, 2850, 1504, 1462, 1256, 1072; δ_H (500 MHz, $CDCl_3$): 6.66-6.60 (2H, m, 5-H and 8-H), 6.51 (1H, d, *J* 8.3 Hz, 6-H), 3.74

(3H, s, OMe), 3.50-3.43 (1H, m, 3a-H), 2.78 (1H, dt, *J* 9.0 and 2.8 Hz, 9-H), 2.45-2.38 (1H, m, 10-H_A), 2.31-2.23 (1H, m, 3-H_A), 1.52 (1H, t, *J* 4.3 Hz. 2-H), 1.24 (1H, br. s, NH), 1.04-0.95 (5H, m, 10-H_B, 3-H_B and methyl), 0.93 (3H, s, methyl), 0.73 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 151.7 (C-7), 143.7 (C-4a), 124.9 (C-8a), 115.3 (C-8), 114.3 (C-6), 113.2 (C-5), 55.9 (OMe), 55.8 (C-3a), 48.9 (C-9a), 42.8 (C-1), 41.7 (C-9), 41.3 (C-2), 40.0 (C-10), 38.8 (C-3), 19.8 (methyl), 19.2 (methyl), 12.8 (methyl); HRMS found MH^+ 258.1867. $C_{17}H_{23}NO$ requires *MH*, 258.1852. The product was isolated as the HCl salt.

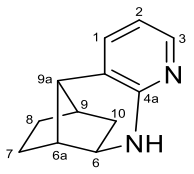
(5*R*,5a*R*,7*R*,8a*S*)-5a,6,6-trimethyl-5a,6,7,8,8a,9-hexahydro-5*H*-5,7-methanocyclopenta[*b*][1,8]naphthyridine (169b)



Water (3.5 ml) and HCl (0.78 ml, 37%) were added to a solution of arylated derivative **156c** (110 mg, 0.31 mmol) in THF (15 ml) at rt. The solution was stirred at rt for 5 mins then zinc powder (304 mg, 4.67 mmol) was added portionwise over 30 mins. The resulting suspension was stirred at rt for 18 h. The reaction mixture was filtered through celite (eluting with EtOAc) and saturated aqueous $NaHCO_3$ solution (10 ml) was added to the filtrate. This was then extracted with DCM (3 x 20 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc to give the *fused-ring pyridine derivative* ***169b*** (40.0 mg, 55%) as a white solid. R_f 0.26 (EtOAc). $[\alpha_D^{20}]$ +34.8 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3329, 2948, 2928, 2871, 1602, 1537, 1456, 1389, 1323, 1289, 1162, 1077; δ_H (500 MHz, $CDCl_3$): 7.86 (1H, dd, *J* 5.1 and 1.0 Hz, 2-H), 7.27-7.23 (1H, m, 4-H, overlaps with residual chloroform peak), 6.52 (1H, dd, *J* 6.8 and 5.1 Hz, 3-H), 5.80 (1H, br. s, NH), 3.63-3.56 (1H, m, 8a-H), 2.83 (1H, dt, *J* 8.6

and 3.3 Hz, 5-H), 2.45 (1H, tt, *J* 12.3 and 3.8 Hz, 10-H_A), 2.40-2.33 (1H, m, 8-H_A), 1.56 (1H, t, *J* 4.3 Hz, 7-H), 1.00 (3H, s, methyl), 0.99-0.93 (5H, m, 10-H_B, 8-H_B and methyl), 0.72 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 151.7 (C-9a), 144.3 (C-2), 137.7 (C-4), 120.2 (C-4a), 112.4 (C-3), 55.7 (C-8a), 48.9 (C-5a), 42.8 (C-6), 41.3 (C-5), 41.0 (C-7), 39.7 (C-8), 39.3 (C-10), 19.6 (methyl), 19.3 (methyl), 12.7 (methyl); HRMS found MH^+ 229.1705. $C_{15}H_{20}N_2$ requires *MH*, 229.1699.

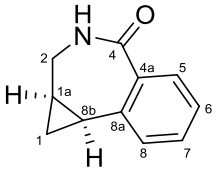
(6*R,6a*R**,9*R**,9a*S**)-6,6a,7,8,9,9a-hexahydro-5*H*-6,9-methanocyclopenta[*c*][1,8]naphthyridine (170)**



$Pd(OAc)_2$ (51.0 mg, 5 mol%), TDG2 (70.0 mg, 10 mol%), L1 (183 mg, 25 mol%), 2-fluoro-3-iodopyridine (2.00 g, 9.00 mmol) and AgTFA (2.00 g, 9.00 mmol) were dissolved in HFIP (10 ml) at rt. Then *exo*-2-aminonorboranane (0.50 g, 4.50 mmol) and H_2O (0.90 ml) were added and the resulting mixture allowed to stir at rt for 10 mins. Then the mixture has stirred at 120 ^oC for 24 h. AcOH (1 ml) was added and the reaction mixture left to stir for a further 24 h at 120 ^oC. The mixture was cooled to rt, filtered through celite (washed with MeOH–$CHCl_3$ 1:4) and the filtrate concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc to give the fused-ring pyridine derivative **170**[109] (0.55 g, 65%) as a light brown oil. R_f 0.19 (EtOAc). δ_H (500 MHz, $CDCl_3$): 7.49 (1H, dd, *J* 6.4 and 1.4 Hz, 3-H), 7.42 (1H, dd, *J* 7.1 and 1.4 Hz, 1-H), 6.54 (1H, app. t, *J* 6.7 Hz, 2-H), 3.65 (1H, app. d, *J* 6.2 Hz, 6-H), 2.71 (1H, br. t, *J* 4.1 Hz, 9a-H), 2.65 (1H, br. t, *J* 1.2 Hz, 6a-H), 2.19 (1H, app. d, *J* 5.0 Hz, 9-H), 1.94-1.86 (1H, m, 8-H_A), 1.86-1.80 (1H, m, 10-H_A), 1.69-1.59 (2H, m, 10-H_B and 7-H_A), 1.42 (1H, ddd, *J* 13.4, 9.1 and 6.3 Hz, 8-H_B), 1.28-1.24 (1H, m, 7-H_B); δ_C (125 MHz, $CDCl_3$): 152.7 (C-4a), 139.4 (C-1), 133.8

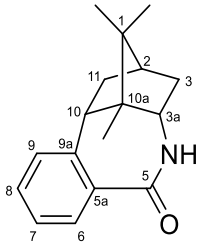
(C-3), 126.3 (C-9b), 110.9 (C-2), 54.5 (C-6), 49.2 (C-6a), 48.5 (C-9a), 40.0 (C-10), 36.6 (C-9), 29.9 (C-7), 23.4 (C-8). All data is consistent with known literature values.[109]

(1a*R,8b*S**)-1a,2,3,8b-tetrahydrocyclopropa[*d*][2]benzazepin-4(1*H*)-one (171b)**



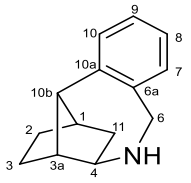
Water (4.73 ml) and HCl (1.08 ml, 37%) were added to a solution of arylated ester derivative **159c** (140 mg, 0.43 mmol) in THF (15 ml). The reaction mixture was stirred at rt for 5 mins then zinc powder (419 mg, 6.45 mmol) was added portionwise over 30 mins. The resulting suspension was stirred at rt for 2 h. The reaction mixture was filtered through celite (eluting with THF) then the filtrate was basified with 5M NaOH solution and the resulting solution allowed to stir at rt for a further 18 h. This was then extracted with DCM (3 x 30 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 90:10 to give *lactam derivative* ***171b*** (42.0 mg, 57%) as a white solid. R_f 0.36 (EtOAc). ν_{max}/cm^{-1}: 3272, 2995, 2850, 1643, 1598, 1455, 1359, 1153, 1023; δ_H (500 MHz, $CDCl_3$): 7.75 (1H, dd, *J* 7.8 and 1.1 Hz, 5-H), 7.45-7.38 (2H, m, 7-H and 8-H), 7.30 (1H, td, *J* 7.8 and 1.5 Hz, 6-H), 6.39 (1H, br. s, NH), 3.58 (1H, ddd, *J* 14.9, 6.3 and 4.5 Hz, 2-H_A), 2.92-2.81 (1H, m, 2-H_B), 2.13 (1H, td, *J* 8.7 and 5.3 Hz, 8b-H), 1.79-1.70 (1H, m, 1a-H), 1.11 (1H, ddd, *J* 8.7, 7.9 and 5.3 Hz, 1-H_A), 0.78-0.70 (1H, m, 1-H_B); δ_C (125 MHz, $CDCl_3$): 172.4 (C=O), 138.5 (C-8a), 133.2 (C-4a), 132.0 (C-7), 131.1 (C-8), 130.6 (C-5), 126.8 (C-6), 43.5 (C-2), 21.3 (C-1a), 18.3 (C-8b), 11.1 (C-1); HRMS found MH^+ 174.0907. $C_{11}H_{11}NO$ requires *MH*, 174.0913.

(2*R*,3a*S*,10*S*,10a*R*)-1,1,10a-trimethyl-2,3,3a,4,10,10a-hexahydro-2,10-methanobenzo[*e*]cyclopenta[*b*]azepin-5(1*H*)-one (171c)



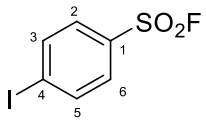
Water (4.3 ml) and HCl (0.96 ml, 37%) were added to a solution of arylated ester derivative **156d** (150 mg, 0.38 mmol) in THF (15 ml). The reaction mixture was stirred at rt for 5 mins then zinc powder (373 mg, 5.74 mmol) was added portionwise over 30 mins. The resulting suspension was stirred at rt for 18 h. The reaction mixture was filtered through celite (eluting with THF) then the filtrate was basified with 5M NaOH solution and the resulting solution allowed to stir at rt for a further 18 h. This was then extracted with DCM (3 x 30 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 40:60 to give the *lactam derivative* ***171c*** (69.0 mg, 71%) as a white solid. R_f 0.46 (EtOAc–hexane 70:30). $[\alpha_D^{20}]$ +17.7 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3283, 3050, 2950, 2875, 1645, 1452, 1392, 1372, 1353, 1259, 1208, 1161, 1129, 1029; δ_H (500 MHz, $CDCl_3$): 8.51 (1H, dd, *J* 8.1 and 1.6 Hz, 6-H), 7.41 (1H, td, *J* 7.7 and 1.6 Hz, 8-H), 7.30 (1H, ddd, *J* 8.1, 7.7 and 1.4 Hz, 7-H), 7.18 (1H, dd, *J* 7.7 and 1.4 Hz, 9-H), 6.44 (1H, br. d, *J* 5.7 Hz, NH), 3.71-3.65 (1H, m, 3a-H), 3.48 (1H, ddd, *J* 12.6, 6.2 and 2.6 Hz, 10-H), 2.53 (1H, tt, *J* 12.6 and 4.0 Hz, 11-H_A), 2.45-2.38 (1H, m, 3-H_A), 1.73 (1H, t, *J* 4.7 Hz, 2-H), 1.19 (1H, dd, *J* 13.0 and 5.6 Hz, 3-H_B), 1.14 (1H, dd, *J* 12.6 and 6.2 Hz, 11-H_B), 1.09 (3H, s, methyl), 0.99 (3H, s, methyl), 0.91 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 167.9 (C=O), 143.8 (C-9a), 133.7 (C-6), 132.4 (C-9), 132.1 (C-8), 128.8 (C-5a), 126.1 (C-7), 59.0 (C-3a), 51.5 (C-10), 50.4 (C-10a), 47.8 (C-1), 41.3 (C-2), 40.9 (C-11), 39.5 (C-3), 20.0 (methyl), 19.9 (methyl), 13.1 (methyl); HRMS found MH^+ 256.1692. $C_{17}H_{21}NO$ requires *MH*, 256.1696.

(1*R,3a*R**,4*R**,10b*S**)-1,2,3,3a,4,5,6,10b-octahydro-1,4-methanobenzo[*c*]cyclopenta[*e*]azepine (172)**



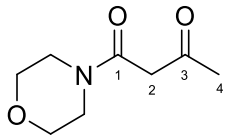
Arylated derivative **136b** (310 mg, 0.98 mmol), Et_3N (0.27 ml, 1.96 mmol) and MsCl (0.09 ml, 1.17 mmol) were dissolved in DCM (10 ml) at 0 °C. The reaction mixture was then stirred at rt for 18 h. A saturated solution of $NaHCO_3$ (10 ml) was added and the phases separated. The aqueous phase was extracted with DCM (3 x 10 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the mesylate intermediate. This intermediate was then dissolved in DCM (10 ml) and TFA (3 ml) was added dropwise at rt and the reaction mixture left to stir for 18 h at rt. The TFA and solvent were removed under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc → MeOH–EtOAc 10:90 to give the *cyclised amine derivative* ***172*** (279 mg, 91%) as a colourless hygroscopic solid. R_f 0.08 (EtOAc). ν_{max}/cm^{-1}: 3400, 3254, 2976, 2884, 1669, 1513, 1472, 1398, 1179, 1132; δ_H (500 MHz, $CDCl_3$): 7.43 (1H, app. d, *J* 7.3 Hz, 10-H), 7.34-7.27 (3H, m, 7-H, 8-H and 9-H), 4.80 (1H, d, *J* 11.8 Hz, 6-H_A), 4.62 (1H, d, *J* 11.8 Hz, 6-H_B), 3.28-3.22 (2H, m, 4-H and 10b-H), 2.98 (1H, d, *J* 4.3 Hz, 3a-H), 2.84 (1H, br t. *J* 4.1 Hz, 1-H), 2.19 (1H, dd, *J* 14.7 and 2.8 Hz, 11-H_A), 2.05-1.93 (2H, m, 11-H_B and 3-H_A), 1.81-1.71 (1H, m, 3-H_B), 1.39-1.28 (2H, m, 2-H_2); δ_C (125 MHz, $CDCl_3$): 162.4 (q, *J* 35.2 Hz, TFA C=O), 137.4 (C-10a), 136.7 (C-6a), 132.4 (C-10), 129.9 (C-7), 128.6 (C-9), 128.1 (C-8), 116.5 (q, *J* 290.7 Hz, TFA CF_3), 55.6 (C-4), 50.4 (C-10b), 45.5 (C-3a), 44.2 (C-6), 38.7 (C-1), 35.8 (C-11), 28.3 (C-3), 27.7 (C-2); HRMS found MH^+ 200.1428. $C_{14}H_{17}N$ required *MH*, 200.1434. The product was isolated as the corresponding TFA salt.

4-iodobenzenesulfonyl fluoride (S1)



4-iodobenzenesulfonyl chloride (1.00 g, 3.33 mmol) was dissolved in MeCN (3.33 ml) then a solution of KHF_2 (515 mg, 6.66 mmol) in water (1.67 ml) was added and the resulting biphasic mixture stirred at rt for 18 h. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 30 ml). The organic phases were combined, washed with sat. aq. $NaHCO_3$ (20 ml) and brine (20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give sulfonyl fluoride derivative **S1**[162] (721 mg, 76%) as a white solid. R_f 0.50 (EtOAc–hexane 10:90). δ_H (500 MHz, $CDCl_3$): 8.01 (2H, d, *J* 8.4 Hz, 3-H and 5-H), 7.71 (2H, d, *J* 8.4 Hz, 2-H and 6-H); δ_C (125 MHz, $CDCl_3$): 139.2 (C_2-3,5), 132.8 (d, *J* 25.6 Hz, C-1), 129.6 (C_2-2,6), 104.2 (C-4); δ_F (470 MHz, $CDCl_3$): 66.2 (SO_2F). All data is consistent with known literature values.[162]

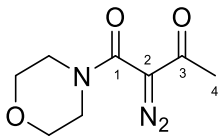
1-(morpholin-4-yl)butane-1,3-dione (193)



Morpholine (1.00 g, 11.5 mmol) was dissolved in toluene (100 ml) then 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (2.30 ml, 17.3 mmol) was added dropwise over 5 mins and the resulting solution was stirred at rt for 15 mins. The reaction mixture was stirred at 120 ^oC for a further 18 h then concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 50:50 → EtOAc to give 1,3-dicarbonyl derivative **193**[148] (1.85 g, 94%, *keto:enol* 85:15 by ^1H NMR) as a pale-yellow oil. R_f 0.17 (EtOAc). δ_H (500 MHz, $CDCl_3$): 14.55 (1H, s, OH^{enol}),

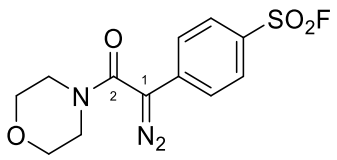
5.06 (1H, s, 2-H^{enol}), 3.64-3.60 (8H, m, morpholinyl 2,6-H_2), 3.59-3.56 (4H, m, morpholinyl 3-H_2 or morpholinyl 5-H_2), 3.51 (2H, s, 2-H_2^{keto}), 3.38-3.34 (4H, m, morpholinyl 3-H_2 or morpholinyl 5-H_2), 2.22 (3H, s, 4-H_3^{keto}), 1.90 (3H, s, 4-H_3^{enol}); δ_C (125 MHz, $CDCl_3$): 202.2 (C-3^{keto}), 175.5 (C-3^{enol}), 170.8 (C-1^{enol}), 165.0 (C-1^{keto}), 86.2 (C-2^{enol}), 66.7 (morpholinyl C_A-2,6), 66.6 (morpholinyl C_B-2,6), 49.8 (C-2^{keto}), 46.8 (morpholinyl C_A-3,5), 42.2 (morpholinyl C_B-3,5) 30.3 (C-4^{keto}), 22.0 (C-4^{enol}). All data is consistent with known literature values.[148]

2-diazo-1-(morpholin-4-yl)butane-1,3-dione (194)



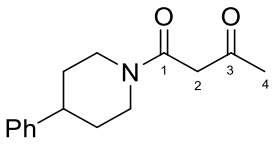
1,3-dicarbonyl derivative **193** (1.85 g, 10.8 mmol) and *p*-ABSA (2.86 g, 11.9 mmol) were dissolved in MeCN (40 ml) then Et_3N (1.66 ml, 11.9 mmol) was added at rt. The resulting solution was at rt for 24 h then filtered through celite (eluting with EtOAc) to remove any solids. The filtrate was concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 → EtOAc to give the diazo derivative **194**[148] (1.71 g, 80%) as a yellow oil. R_f 0.26 (EtOAc). δ_H (500 MHz, $CDCl_3$): 3.72-3.68 (4H, m, morpholinyl 2,6-H_2), 3.53-3.45 (4H, m, morpholinyl 3,5-H_2), 2.30 (3H, s, 4-H_3); δ_C (125 MHz, $CDCl_3$): 188.0 (C-3), 160.4 (C-1), 74.7 (C-2), 66.8 (morpholinyl C_2-2,6), 46.1 (morpholinyl C_2-3,5), 27.2 (C-4). All data is consistent with known literature values.[148]

4-[1-diazo-2-(morpholin-4-yl)-2-oxoethyl]benzene-1-sulfonyl fluoride (D1)



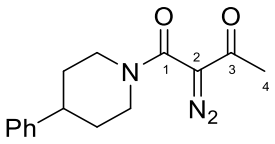
Diazo derivative **194** (1.70 g, 8.63 mmol) was dissolved in MeCN (20 ml) then 10% aq. KOH (20 ml) was added and the resulting solution allowed to stir at rt for 18 h. EtOAc (50 ml) was added and the phases then separated. The aqueous phase was extracted with EtOAc (3 x 30 ml), organic phases combined, washed with sat. aq. ammonium chloride (40 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the deacetylate diazo intermediate (736 mg, 55%) as a yellow oil. This intermediate (736 mg, 4.74 mmol) was then dissolved in toluene (20 ml) and $Pd(PPh_3)_4$ (274 mg, 5 mol%), Ag_2CO_3 (654 mg, 2.37 mmol), 4-iodobenzenesulfonyl fluoride (1.76 g, 6.12 mmol) and Et_3N (0.85 ml, 6.12 mmol) were added and the resulting mixture allowed to stir at rt for 4 h. The mixture was filtered through celite (eluting with EtOAc) and the filtrate concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 70:30 to give the *sulfonyl fluoride diazo derivative* ***D1*** (0.68 g, 46%) as a bright yellow oil that solidified upon drying to give a yellow solid. R_f 0.40 (EtOAc–hexane 70:30). ν_{max}/cm^{-1}: 2983, 2922, 2860, 2072, 1639, 1586, 1460, 1212, 1193; δ_H (500 MHz, $CDCl_3$): 7.96 (2H, d, *J* 8.8 Hz, aryl 2,6-H), 7.44 (2H, d, *J* 8.8 Hz, aryl 3,5-H), 3.75-3.70 (4H, m, morpholinyl 2,6-H_2), 3.55-3.52 (4H, m, morpholinyl 3,5-H_2); δ_C (125 MHz, $CDCl_3$): 163.2 (C-2), 136.9 (aryl C-4), 129.4 (aryl C_2-2,6), 128.9 (d, *J* 25.1 Hz, aryl C-1), 123.7 (aryl C_2-3,5), 66.7 (morpholinyl C_2-2,6), 46.2 (morpholinyl C_2-3,5); δ_F (470 MHz, $CDCl_3$): 66.7 (SO_2F); HRMS found MNa^+ 336.0422. $C_{12}H_{12}FN_3O_4S$ requires *MNa*, 336.0425. C-1 not observed by ^{13}C NMR (125 MHz).

1-(4-phenylpiperidin-1-yl)butane-1,3-dione (197)



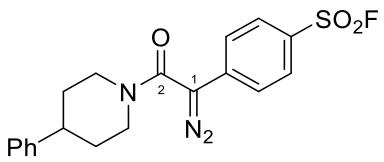
4-phenylpiperidine (3.00 g, 18.6 mmol) was dissolved in toluene (200 ml) then 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (3.72 ml, 28.0 mmol) was added dropwise over 5 mins and the resulting solution was stirred at rt for 15 mins. The reaction mixture was stirred at 120 ^{o}C for a further 18 h then concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give *1,3-dicarbonyl derivative* ***197*** (3.86 g, 85%, *keto:enol* 83:17 by ^{1}H NMR) as a yellow oil. R_f 0.38 (EtOAc). ν_{max}/cm^{-1}: 3002, 2920, 2855, 1718, 1630, 1491, 1389, 1268, 1226, 1007; δ_H (500 MHz, $CDCl_3$): 15.00 (1H, s, OH^{enol}), 7.34 (4H, t, *J* 7.5 Hz, phenyl 3,5-H), 7.27-7.20 (6H, m, phenyl 2,6-H and phenyl 4-H), 5.27 (1H, s, 2-H^{enol}), 4.83-4.77 (2H, m, piperidinyl 2-H_A or piperidinyl 6-H_A), 3.88-3.82 (2H, m, piperidinyl 2-H_A or piperidinyl 6-H_A), 3.64 (2H, s, 2-H_2^{keto}), 3.19 (2H, app. td, *J* 13.2 and 2.4 Hz, piperidinyl 2-H_B or piperidinyl 6-H_B), 2.82-2.74 (2H, m, piperidinyl 4-H), 2.71 (2H, app. td, *J* 13.2 and 2.6 Hz, piperidinyl 2-H_B or piperidinyl 6-H_B), 2.32 (3H, s, 4-H_3^{keto}), 2.00 (3H, s, 4-H_3^{enol}), 1.96-1.90 (4H, m, piperidinyl 3,5-H_A), 1.68 (4H, app. pd, *J* 12.8 and 4.2 Hz, piperidinyl 3,5-H_B); δ_C (125 MHz, $CDCl_3$): 202.3 (C-3^{keto}), 175.0 (C-3^{enol}), 170.3 (C-1^{enol}), 164.7 (C-1^{keto}), 144.8 (phenyl C-1), 128.4 (phenyl C_2-3,5), 126.6 (phenyl C_2-2,6), 126.4 (phenyl C-4), 86.3 (C-2^{enol}), 49.9 (C-2^{keto}), 46.9 (piperidinyl C_A-2,6), 42.34 (piperidinyl C_B-2,6), 42.32 (piperidinyl C-4), 33.4 (piperidinyl C_A-3,5), 32.6 (piperidinyl C_B-3,5), 30.1 (C-4^{keto}), 21.9 (C-4^{enol}); HRMS found MH^+ 246.1483. $C_{15}H_{19}NO_2$ requires *MH*, 246.1489.

2-diazo-1-(4-phenylpiperidin-1-yl)butane-1,3-dione (198)



1,3-dicarbonyl derivative **197** (3.86 g, 15.6 mmol) and *p*-ABSA (4.15 g, 17.3 mmol) were dissolved in MeCN (80 ml) then Et_3N (2.41 ml, 17.3 mmol) was added at rt. The resulting solution was at rt for 24 h then filtered through celite (eluting with EtOAc) to remove any solids. The filtrate was concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 30:70 to give the *diazo derivative* ***198*** (3.46 g, 82%) as a yellow oil. R_f 0.63 (EtOAc). ν_{max}/cm^{-1}: 3027, 2920, 2855, 2071, 1718, 1630, 1492, 1358, 1268, 1155, 1068; δ_H (500 MHz, $CDCl_3$): 7.34-7.30 (2H, m, phenyl 3,5-H), 7.25-7.20 (3H, m, phenyl 2,6-H and phenyl 4-H), 4.14 (2H, app. br. s, piperidinyl 2,6-H_A), 3.04 (2H, app. t, *J* 12.7 Hz, piperidinyl 2,6-H_B), 2.78 (1H, tt, *J* 12.2 and 3.6 Hz, piperidinyl 4-H), 2.36 (3H, s, 4-H_3), 1.97-1.91 (2H, m, piperidinyl 3,5-H_A), 1.74 (2H, qd, *J* 12.7 and 4.1 Hz, piperidinyl 3,5-H_B); δ_C (125 MHz, $CDCl_3$): 160.4 (C-1), 145.0 (phenyl C-1), 128.8 (phenyl C_2-3,5), 126.9 (phenyl C_2-2,6), 126.8 (phenyl C-4), 46.5 (piperidinyl C_2-2,6), 42.8 (piperidinyl C-4), 33.3 (piperidinyl C_2-3,5), 27.3 (C-4); HRMS found MNa^+ 294.1212. $C_{15}H_{17}N_3O_2$ requires *MNa*, 294.1213. C-2 and C-3 not observed by ^{13}C NMR (125 MHz).

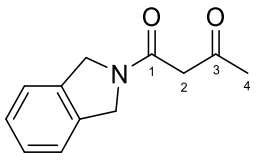
4-[1-diazo-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl]benzene-1-sulfonyl fluoride (D2)



Diazo derivative **198** (3.40 g, 12.5 mmol) was dissolved in MeCN (40 ml) then 10% aq. KOH (40 ml) was added and the resulting solution allowed to stir at rt for 18 h.

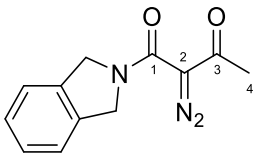
EtOAc (80 ml) was added and the phases then separated. The aqueous phase was extracted with EtOAc (3 x 40 ml), organic phases combined, washed with sat. aq. ammonium chloride (40 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the deacetylate diazo intermediate (2.53 g, 87%) as a yellow oil. This intermediate (2.53 g, 10.9 mmol) was then dissolved in toluene (50 ml) and $Pd(PPh_3)_4$ (485 mg, 5 mol%), Ag_2CO_3 (1.16 g, 4.20 mmol), 4-iodobenzenesulfonyl fluoride (2.40 g, 8.39 mmol) and Et_3N (1.52 ml, 10.9 mmol) were added and the resulting mixture allowed to stir at rt for 4 h. The mixture was filtered through celite (eluting with EtOAc) and the filtrate concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 20:80 to give the *sulfonyl fluoride diazo derivative* ***D2*** (1.72 g, 53%) as a yellow-orange solid. R_f 0.66 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3060, 2953, 2876, 2069, 1627, 1455, 1396, 1367, 1296, 1264, 1158, 1068; δ_H (500 MHz, $CDCl_3$): 7.96 (2H, d, *J* 8.8 Hz, aryl 2,6-H), 7.46 (2H, d, *J* 8.8 Hz, aryl 3,5-H), 7.36-7.30 (2H, m, phenyl 3,5-H), 7.26-7.19 (3H, m, phenyl 2,6-H and phenyl 4-H), 4.20 (2H, app. br. d, *J* 13.2 Hz, piperidinyl 2,6-H_A), 3.06 (2H, td, *J* 13.2 and 2.4 Hz, piperidinyl 2,6-H_B), 2.80 (1H, tt, *J* 12.1 and 3.5 Hz, piperidinyl 4-H), 1.97 (2H, app. br. d, *J* 13.9 Hz, piperidinyl 3,5-H_A), 1.71 (2H, app. qd, *J* 12.8 and 4.1 Hz, piperidinyl 3,5-H_B); δ_C (125 MHz, $CDCl_3$): 162.9 (oxoethyl C-2), 144.7 (phenyl C-1), 137.4 (aryl C-4), 129.3 (aryl C_2-2,6), 128.8 (phenyl C_2-3,5), 128.6 (d, *J* 24.9 Hz, aryl C-1), 126.9 (phenyl C-4), 126.8 (phenyl C_2-2,6), 123.6 (aryl C_2-3,5), 63.5 (oxoethyl C-1), 46.6 (piperidinyl C_2-2,6), 42.7 (piperidinyl C-4), 33.3 (piperidinyl C_2-3,5); δ_F (470 MHz, $CDCl_3$): 66.8 (SO_2F); HRMS found MH^+ 388.1115. $C_{19}H_{18}FN_3O_3S$ requires *MH*, 388.1126.

1-(2,3-dihydro-1*H*-isoindol-2-yl)butane-1,3-dione (201)



Isoindoline (1.00 g, 8.40 mmol) was dissolved in toluene (80 ml) then 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (1.67 ml, 12.6 mmol) was added dropwise over 5 mins and the resulting solution was stirred at rt for 15 mins. The reaction mixture was stirred at 120 ^{o}C for a further 18 h then concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 50:50 → EtOAc to give *1,3-dicarbonyl derivative* ***201*** (1.51 g, 88%, *keto:enol* 75:25 by ^{1}H NMR) as a dark brown solid. R_f 0.38 (EtOAc). ν_{max}/cm^{-1}: 3030, 2908, 2866, 1712, 1632, 1455, 1355, 1224, 1161; δ_H (500 MHz, $CDCl_3$): 14.58 (1H, s, OH^{enol}), 7.35-7.19 (8H, m, isoindolyl 4,5,6,7-H), 5.10 (1H, s, 2-H^{enol}), 4.81 (4H, s, isoindolyl 1,3-H$_2^{keto}$), 4.74 (4H, s, isoindolyl 1,3-H$_2^{enol}$), 3.60 (2H, s, 2-H$_2^{keto}$), 2.34 (3H, s, 4-H$_3^{keto}$), 1.99 (3H, s, 4-H$_3^{enol}$); δ_C (125 MHz, $CDCl_3$): 202.2 (C-3^{keto}), 175.0 (C-3^{enol}), 170.7 (C-1^{enol}), 165.4 (C-1^{keto}), 136.3 (isoindolyl C$_A$-3a,7a^{enol}), 136.1 (isoindolyl C$_A$-3a,7a^{keto}), 136.0 (isoindolyl C$_B$-3a,7a^{enol}), 135.8 (isoindolyl C$_B$-3a,7a^{keto}), 128.0 (isoindolyl C$_A$-5,6^{keto}), 127.9 (isoindolyl C$_A$-5,6^{enol}), 127.7 (isoindolyl C$_{\mathbf{B}}$-5,6^{keto}), 127.6 (isoindolyl C$_B$-5,6^{enol}), 123.1 (isoindolyl C$_2$-4,7^{keto}), 122.7 (isoindolyl C$_2$-4,7^{enol}), 88.5 (C-2^{enol}), 53.1 (isoindolyl C$_A$-1,3^{keto}), 52.4 (isoindolyl C$_B$-1,3^{keto}), 52.2 (isoindolyl C$_A$-1,3^{enol}), 51.4 (isoindolyl C$_B$-1,3^{enol}), 51.1 (C-2^{keto}), 30.5 (C-4^{keto}), 21.9 (C-4^{enol}); HRMS found MNa^{+} 226.0852. $C_{12}H_{13}NO_2$ requires *MNa*, 226.0838.

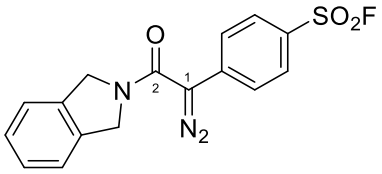
2-diazo-1-(2,3-dihydro-1*H*-isoindol-2-yl)butane-1,3-dione (202)



1,3-dicarbonyl derivative **201** (1.50 g, 7.39 mmol) and *p*-ABSA (1.95 g, 8.13 mmol) were dissolved in MeCN (40 ml) then Et_3N (1.13 ml, 8.13 mmol) was added at rt. The resulting solution was at rt for 24 h then filtered through celite (eluting with EtOAc) to remove any solids. The filtrate was concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–

hexane 30:70 to give the *diazo derivative* ***202*** (1.46 g, 86%) as a pale-yellow oil. R_f 0.62 (EtOAc). ν_{max}/cm^{-1}: 3033, 2930, 2866, 2094, 1650, 1612, 1400, 1355, 1232, 1088; δ_H (400 MHz, $CDCl_3$): 7.31-7.20 (4H, m, isoindolyl 4,5,6,7-H), 4.84 (4H, s, isoindolyl 1,3-H_2), 2.40 (3H, s, 4-H_3); δ_C (100 MHz, $CDCl_3$): 190.0 (C-3), 159.9 (C-1), 153.7 (isoindolyl C_2-3a,7a), 127.9 (isoindolyl C_2-5,6), 122.7 (isoindolyl C_2-4,7), 73.7 (C-2), 53.3 (isoindolyl C_2-1,3), 27.9 (C-4); HRMS found MNa^+ 252.0748. $C_{12}H_{11}N_3O_2$ requires *MNa*, 252.0743.

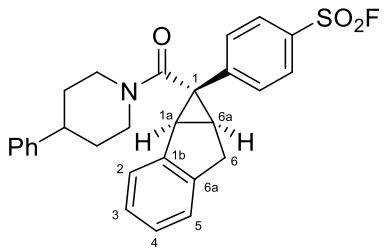
4-[1-diazo-2-(2,3-dihydro-1*H*-isoindol-2-yl)-2-oxoethyl]benzene-1-sulfonyl fluoride (D3)



Diazo derivative **202** (1.40 g, 6.11 mmol) was dissolved in MeCN (20 ml) then 10% aq. KOH (20 ml) was added and the resulting solution allowed to stir at rt for 18 h. EtOAc (40 ml) was added and the phases then separated. The aqueous phase was extracted with EtOAc (3 x 30 ml), organic phases combined, washed with sat. aq. ammonium chloride (40 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the deacetylate diazo intermediate (1.15 g, 99%) as a yellow oil. This intermediate (1.15 g, 6.05 mmol) was then dissolved in toluene (30 ml) and $Pd(PPh_3)_4$ (269 mg, 5 mol%), Ag_2CO_3 (643 mg, 2.33 mmol), 4-iodobenzenesulfonyl fluoride (1.33 g, 4.66 mmol) and Et_3N (0.84 ml, 6.05 mmol) were added and the resulting mixture allowed to stir at rt for 4 h. The mixture was filtered through celite (eluting with EtOAc) and the filtrate concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 15:85 to give the *sulfonyl fluoride diazo derivative* ***D3*** (0.26 g, 12%) as a yellow solid. R_f 0.19 (EtOAc–hexane 15:85). ν_{max}/cm^{-1}: 3047, 2857, 2074, 1625, 1585, 1393, 1230, 1210, 1184; δ_H (500 MHz, $CDCl_3$): 7.98 (2H, d, *J* 8.8 Hz, aryl 2,6-H), 7.60 (2H, d, *J* 8.8 Hz, aryl 3,5-

H), 7.36-7.28 (4H, m, isoindolyl 4,5,6,7-H), 4.91 (4H, s, isoindolyl 1,3-H_2); δ_C (125 MHz, $CDCl_3$): 161.9 (oxoethyl C-2), 136.7 (aryl C-4), 135.7 (isoindolyl C_2-3a,7a), 129.3 (aryl C_2-2,6), 129.0 (d, *J* 25.0 Hz, aryl C-1), 128.2 (isoindolyl C_2-5,6), 124.3 (aryl C_2-3,5), 122.9 (isoindolyl C_2-4,7), 63.5 (oxoethyl C-1), 53.6 (isoindolyl C_2-1,3); δ_F (470 MHz, $CDCl_3$): 66.7 (SO_2F); HRMS found MNa^+ 368.0470. $C_{16}H_{12}FN_3O_3S$ requires *MNa*, 368.0476.

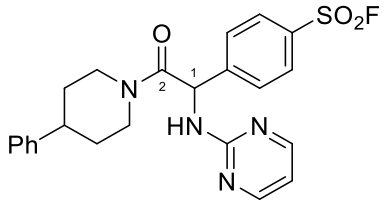
4-[(1*R,1a*S**,6a*S**)-1-(4-phenylpiperidine-1-carbonyl)-1*H*,1a*H*,6*H*,6a*H*-cyclopropa[*a*]inden-1-yl]benzene-1-sulfonyl fluoride (204)**



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D2** (100 mM), co-substrate **Co-7** (500 mM) and $Rh_2(piv)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *cyclopropane derivative* ***204*** (1.20 mg, 13%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.49 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2924, 2854, 1634, 1432, 1409, 1236, 1213, 1100; δ_H (500 MHz, $CDCl_3$, some peak broadening due to unresolved rotamers): 7.68 (2H, d, *J* 8.6 Hz, aryl 2,6-H), 7.50-7.44 (1H, m, indenyl 2-H), 7.35-7.23 (4H, m, aryl 3,5-H and phenyl 3,5-H), 7.23-7.16 (2H, m, phenyl 4-H and indenyl 3-H), 7.18-6.90 (3H, m, phenyl 2,6-H and indenyl 4-H), 6.85 (1H, d, *J* 7.5 Hz, indenyl 5-H), 4.70-4.55 (2H, m, piperidinyl 2,6-H_A), 3.30-3.22 (2H, m, indenyl 1a-H and indenyl 6-H_A), 2.96 (1H, app. t, *J* 6.8 Hz, indenyl 6a-H), 2.90-2.60 (3H, m, piperidinyl 2,6-H_B and piperidinyl 4-H), 2.49 (1H, d, *J* 17.9 Hz, indenyl 6-H_B), 2.08-1.50 (4H, br. m, piperidinyl 3,5-H_2); δ_C (125 MHz, $CDCl_3$): 169.0 (C=O), 144.8 (aryl C-4 and phenyl C-1), 143.4 (indenyl C-5a), 141.0 (indenyl C-1b), 131.8 (aryl C_2-3,5), 131.0 (d, *J* 24.6 Hz, aryl C-1), 128.8 (phenyl C_2-3,5), 128.0

(aryl C_2-2,6), 127.4 (indenyl C-4), 127.0 (indenyl C-3), 126.8 (phenyl C-4), 126.7 (phenyl C_2-2,6), 125.2 (indenyl C-5), 124.5 (indenyl C-2), 42.6 (piperidinyl C-4), 40.1 (C-1), 37.1 (indenyl C-1a), 32.9 (indenyl C-6), 32.8 (piperidinyl C_2-3,5), 29.6 (indenyl C-6a); δ_F (470 MHz, $CDCl_3$): 65.9 (SO_2F); HRMS found MH^+ 476.1683. $C_{28}H_{26}FNO_3S$ requires *MH*, 476.1690. Piperidinyl C_2-2,6 not observed by ^{13}C NMR (125 MHz). The relative configuration was determined though NOESY (500 MHz). nOe observed between indenyl 6-H_B and aryl 3,5-H and nOe observed between indenyl 1a-H and indenyl 6a-H.

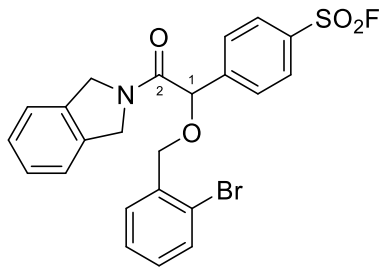
4-[2-oxo-2-(4-phenylpiperidin-1-yl)-1-[(pyrimidin-2-yl)amino]ethyl]benzene-1-sulfonyl fluoride (205)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D2** (100 mM), co-substrate **Co-13** (500 mM) and $Rh_2(piv)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *aminopyrimidine derivative* ***205*** (1.10 mg, 12%, *rotamers* 52:48 by ^1H NMR) as a colourless oil. R_f 0.10 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3225, 3030, 2924, 2854, 1639, 1581, 1507, 1447, 1210, 1098; δ_H (500 MHz, $CDCl_3$): 8.27 (4H, t, *J* 4.7 Hz, pyrimidinyl 4,6-H), 8.02 (2H, d, *J* 8.3 Hz, aryl 2,6-H^{min}), 7.98 (2H, d, *J* 8.3 Hz, aryl 2,6-H^{maj}), 7.89 (2H, d, *J* 8.3 Hz, aryl 3,5-H^{min}), 7.81 (2H, d, *J* 8.3 Hz, aryl 3,5-H^{maj}), 7.31 (2H, t, *J* 7.5 Hz, phenyl 3,5-H^{maj}), 7.28-7.15 (6H, m, phenyl 3,5-H^{min}, phenyl 2,6-H^{maj} and phenyl 4-H), 6.97 (2H, d, *J* 7.5 Hz, phenyl 2,6-H^{min}), 6.85 (1H, d, *J* 7.5 Hz, NH^{min}), 6.82 (1H, d, *J* 6.8 Hz, NH^{maj}), 6.58 (2H, app. q, *J* 4.7 Hz, pyrimidinyl 5-H), 6.13 (2H, app. t, *J* 7.5 Hz, 1-H), 4.81 (2H, app. d, *J* 13.1 Hz, piperidinyl 2-H_A or piperidinyl 6-H_A) 4.07 (2H, app. t, *J* 13.1 Hz, piperidinyl 2-H_A or piperidinyl 6-H_A), 3.22 (2H, app. t, *J* 12.0 Hz, piperidinyl 2-H_B^{min} or

piperidinyl 6-H_B^{min}), 2.90 (2H, app. t, *J* 12.0 Hz, piperidinyl 2-H_B^{min} or piperidinyl 6-H_B^{min}), 2.80-2.64 (4H, m, piperidinyl 2,6-H_B^{maj} and piperidinyl 4-H), 1.96-1.64 (6H, m, piperidinyl 3,5-H_A and piperidinyl 3,5-H_B^{min}), 1.42 (2H, qd, *J* 12.7 and 4.1 Hz, piperidinyl 3-H_B^{maj} or piperidinyl 5-H_B^{maj}), 0.71 (2H, qd, *J* 12.7 and 4.1 Hz, piperidinyl 3-H_B^{maj} or piperidinyl 5-H_B^{maj}); δ_C (125 MHz, $CDCl_3$): 167.5 (C-2^{maj}), 167.4 (C-2^{min}), 160.7 (pyrimidinyl C-2^{min}), 160.6 (pyrimidinyl C-2^{maj}), 158.2 (pyrimidinyl C_2-4,6), 147.5 (phenyl C-1^{min}), 147.0 (phenyl C-1^{maj}), 144.7 (aryl C-4^{min}), 144.4 (aryl C-4^{maj}), 132.6 (d, *J* 24.9 Hz, aryl C-1), 129.6 (aryl C_2-3,5^{min}), 129.4 (aryl C_2-3,5^{maj}), 129.1 (phenyl C_2-3,5^{min}), 129.0 (phenyl C_2-3,5^{maj}), 128.8 (aryl C_2-2,6), 126.9 (phenyl C-4), 126.8 (phenyl C_2-2,6^{maj}), 126.6 (phenyl C_2-2,6^{min}), 111.9 (pyrimidinyl C-5^{min}), 111.8 (pyrimidinyl C-5^{maj}), 54.8 (C-1^{maj}), 54.7 (C-1^{min}), 46.5 (piperidinyl C_A-2,6^{maj}), 46.2 (piperidinyl C_B-2,6^{maj}), 43.7 (piperidinyl C_A-2,6^{min}), 43.6 (piperidinyl C_B-2,6^{min}), 42.7 (piperidinyl C-4^{maj}), 42.3 (piperidinyl C-4^{min}), 33.9 (piperidinyl C_A-3,5^{maj}), 32.9 (piperidinyl C_B-3,5^{maj}), 32.8 (piperidinyl C_A-3,5^{min}), 32.7 (piperidinyl C_B-3,5^{min}); δ_F (470 MHz, $CDCl_3$): 66.2 (SO_2F^{min}), 66.0 (SO_2F^{maj}); HRMS found MH^+ 455.1552. $C_{23}H_{23}FN_4O_3S$ requires *MH*, 455.1548.

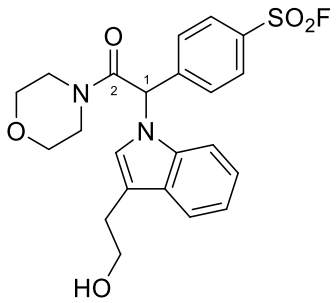
4-{1-[(2-bromophenyl)methoxy]-2-(2,3-dihydro-1*H*-isoindol-2-yl)-2-oxoethyl}benzene-1-sulfonyl fluoride (206)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D3** (100 mM), co-substrate **Co-2** (500 mM) and $Rh_2(piv)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *ether derivative* ***206*** (1.30 mg, 13%) as a colourless oil. R_f 0.63 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2920,

2874, 1650, 1412, 1213, 1096; δ_H (500 MHz, $CDCl_3$): 8.30 (2H, d, *J* 8.6 Hz, aryl 2,6-H), 7.85 (2H, d, *J* 8.6 Hz, aryl 3,5-H), 7.58 (1H, dd, *J* 7.6 and 1.1 Hz, bromophenyl 3-H), 7.52 (1H, dd, *J* 7.6 and 1.5 Hz, bromophenyl 6-H), 7.35 (1H, td, *J* 7.6 and 1.1 Hz, bromophenyl 5-H), 7.29-7.24 (3H, m, isoindolyl 5,6-H and isolindolyl 4-H or isolindolyl 7-H), 7.21 (1H, td, *J* 7.6 and 1.5 Hz, bromophenyl 4-H), 7.16 (1H, d, *J* 6.8 Hz, isoindolyl 4-H or isoindolyl 7-H), 5.39 (1H, s, 1-H), 4.92 (2H, d, *J* 15.2 Hz, isoindolyl 1,3-H_A), 4.87-4.80 (2H, m, bromophenylmethoxy 1-H_A and isoindolyl 1-H_B or isoindolyl 3-H_B), 4.76 (1H, d, *J* 12.2 Hz, bromophenylmethoxy 1-H_B), 4.58 (1H, d, *J* 15.2 Hz, isoindolyl 1-H_B or isoindolyl 3-H_B); δ_C (125 MHz, $CDCl_3$): 167.8 (C-2), 144.4 (aryl C-4), 136.2 (isoindolyl C_A-3a,7a), 136.0 (isoindolyl C_B-3a,7a), 135.3 (bromophenyl C-1), 133.1 (bromophenyl C-3), 133.0 (d, *J* 24.9 Hz, aryl C-1), 130.2 (bromophenyl C-6), 130.1 (bromophenyl C-4), 129.0 (aryl C_2-2,6), 128.1 (aryl C_2-3,5), 127.8 (bromophenyl C-5 and isoindolyl C_2-5,6), 123.6 (bromophenyl C-2), 123.0 (isoindolyl C_A-4,7), 122.7 (isoindolyl C_B-4,7), 81.1 (C-1), 72.0 (bromophenylmethoxy C-1), 53.5 (isoindolyl C_A-1,3), 51.9 (isoindolyl C_B-1,3); δ_F (470 MHz, $CDCl_3$): 66.1 (SO_2F); HRMS found MH^+ 504.0267. $C_{23}H_{19}BrFNO_4S$ requires *MH*, 504.0275.

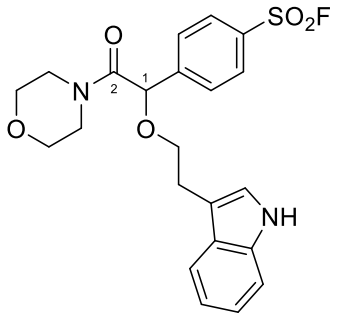
4-{1-[3-(2-hydroxyethyl)-1*H*-indol-1-yl]-2-(morpholin-4-yl)-2-oxoethyl}benzene-1-sulfonyl fluoride (207)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D1** (100 mM), co-substrate **Co-3** (500 mM) and $Rh_2(pfb)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 35:65 → 60:40 → 95:5 MeCN–H_2O to give the *indole derivative* ***207***

(1.30 mg, 15%) as a colourless oil. R_f 0.05 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3433, 2925, 2858, 1651, 1459, 1410, 1213, 1115, 1035; δ_H (500 MHz, $CDCl_3$): 7.96 (2H, d, *J* 8.5 Hz, aryl 2,6-H), 7.69-7.67 (1H, m, indolyl 4-H), 7.31 (2H, d, *J* 8.5 Hz, aryl 3,5-H), 7.24-7.14 (3H, m, indolyl 5,6,7-H), 7.09 (1H, s, indolyl 2-H), 6.40 (1H, s, 1-H), 3.94 (2H, t, *J* 6.0 Hz, hydroxyethyl 2-H_2), 3.90-3.84 (1H, m, morpholinyl 3-H_A or morpholinyl 5-H_A), 3.78-3.71 (1H, m, morpholinyl 2-H_A or morpholinyl 6-H_A), 3.68-3.55 (2H, m, morpholinyl 3,5-H_B and morpholinyl 2,6-H_B), 3.48 (1H, ddd, *J* 11.4, 6.0 and 2.9 Hz, morpholinyl 2-H_A or morpholinyl 6-H_A), 3.42-3.34 (1H, m, morpholinyl 3-H_A or morpholinyl 5-H_B), 3.27-3.17 (2H, m, morpholinyl 2,6-H_B and morpholinyl 3,5-H_B), 3.06 (2H, t, *J* 6.0 Hz, hydroxyethyl 1-H_2), 1.45 (1H, br. s, OH); δ_C (125 MHz, $CDCl_3$): 165.8 (C-2), 145.0 (aryl C-4), 136.1 (indolyl C-7a), 133.0 (d, *J* 25.0 Hz, aryl C-1), 128.93 (aryl C_2-2,6), 128.88 (aryl C_2-3,5), 128.7 (indolyl C-3a), 124.3 (indolyl C-2), 123.3 (indolyl C-6), 120.8 (indolyl C-5), 120.0 (indolyl C-4), 114.4 (indolyl C-3), 108.9 (indolyl C-7), 66.9 (morpholinyl C_A-2,6), 66.3 (morpholinyl C_B-2,6), 62.8 (hydroxyethyl C-2), 59.7 (C-1), 46.4 (morpholinyl C_A-3,5), 43.3 (morpholinyl C_B-3,5), 28.8 (hydroxyethyl C-1); δ_F (470 MHz, $CDCl_3$): 66.0 (SO_2F); HRMS found MH^+ 447.1381. $C_{22}H_{23}FN_2O_5S$ requires *MH*, 447.1384.

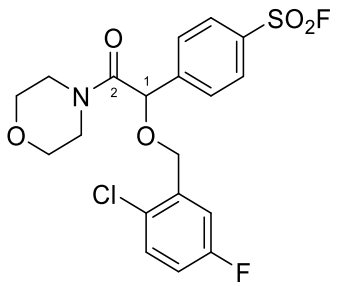
4-{1-[2-(1*H*-indol-3-yl)ethoxy]-2-(morpholin-4-yl)-2-oxoethyl}benzene-1-sulfonyl fluoride (208)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D1** (100 mM), co-substrate **Co-3** (500 mM) and $Rh_2(pfb)_4$ (1 mM) gave a

crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 35:65 → 60:40 → 95:5 MeCN–H_2O to give the *indole derivative* ***208*** (0.10 mg, 1%) as a colourless oil. R_f 0.10 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3432, 2921, 2855, 1651, 1459, 1412, 1213, 1114, 1036; δ_H (500 MHz, $CDCl_3$): 8.03 (1H, br. s, NH), 7.96 (2H, d, *J* 8.6 Hz, aryl 2,6-H), 7.65-7.59 (3H, m, aryl 3,5-H and indolyl 4-H), 7.39 (1H, dt, *J* 8.2 and 0.9 Hz, indolyl 7-H), 7.24-7.20 (1H, m, indolyl 6-H), 7.13 (1H, ddd, *J* 8.2, 7.0 and 1.0 Hz, indolyl 5-H), 7.08 (1H, d, *J* 2.3 Hz, indolyl 2-H), 5.25 (1H, s, 1-H), 3.98 (1H, dt, *J* 8.9 and 6.7 Hz, ethoxyindolyl 2-H_A), 3.91 (1H, dt, *J* 8.9 and 6.1 Hz, ethoxyindolyl 2-H_B), 3.59-3.43 (4H, m, morpholinyl 2-H_2 or morpholinyl 6-H_2 and morpholinyl 3-H_2 or morpholinyl 5-H_2), 3.31-2.94 (6H, m, morpholinyl 2-H_2 or morpholinyl 6-H_2, morpholinyl 3-H_2 or morpholinyl 5-H_2 and ethoxyindolyl 1-H_2); δ_C (125 MHz, $CDCl_3$): 167.7 (C-2), 145.3 (aryl C-4), 136.2 (indolyl C-7a), 128.8 (aryl C_2-2,6), 127.0 (aryl C_2-3,5), 122.4 (indolyl C-6), 122.2 (indolyl C-2), 120.7 (indolyl C-3a), 119.6 (indolyl C-5), 118.8 (indolyl C-4), 112.8 (indolyl C-3), 111.4 (indolyl C-7), 83.0 (C-1), 71.4 (ethoxyindolyl C-2), 66.8 (morpholinyl C_A-2,6), 66.2 (morpholinyl C_B-2,6), 45.4 (morpholinyl C_A-3,5), 42.8 (morpholinyl C_B-3,5), 26.0 (ethoxyindolyl C-1); δ_F (470 MHz, $CDCl_3$): 66.1 (SO_2F); HRMS found MNa^+ 469.1204. $C_{22}H_{23}FN_2O_5S$ requires *MNa*, 469.1204. Aryl C-1 not observed by ^{13}C NMR.

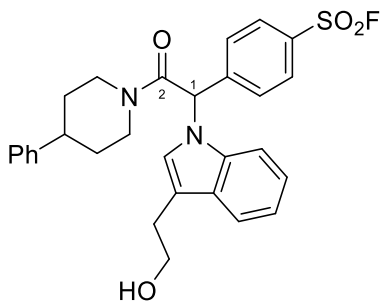
4-{1-[(2-chloro-5-fluorophenyl)methoxy]-2-(morpholin-4-yl)-2-oxoethyl}benzene-1-sulfonyl fluoride (209)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D1** (100 mM), co-substrate **Co-5** (500 mM) and $Rh_2(pfb)_4$ (1 mM) gave a

crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 35:65 → 60:40 → 95:5 MeCN–H_2O to give the *ether derivative* ***209*** (1.00 mg, 11%) as a colourless oil. R_f 0.34 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2964, 2925, 2857, 1650, 1412, 1301, 1213, 1115; δ_H (500 MHz, $CDCl_3$): 8.05 (2H, d, *J* 8.6 Hz, aryl 2,6-H), 7.75 (2H, d, *J* 8.6 Hz, aryl 3,5-H), 7.37 (1H, dd, *J* 8.8 and 5.0 Hz, chlorophenyl 3-H), 7.23 (1H, dd, *J* 8.8 and 3.0 Hz, chlorophenyl 6-H), 7.04-7.00 (1H, m, chlorophenyl 4-H), 5.41 (1H, s, 1-H), 4.81 (1H, d, *J* 12.7 Hz, chlorophenylmethoxy 1-H_A), 4.73 (1H, d, *J* 12.7 Hz, chlorophenylmethoxy 1-H_B), 3.69-3.60 (4H, m, morpholinyl 2-H_2 or morpholinyl 6-H_2 and morpholinyl 3-H_2 or morpholinyl 5-H_2), 3.59-3.51 (1H, m, morpholinyl 3-H_A or morpholinyl 5-H_A), 3.49-3.42 (1H, m, morpholinyl 2-H_A or morpholinyl 6-H_A), 3.40-3.29 (2H, m, morpholinyl 3-H_B or morpholinyl 5-H_B and morpholinyl 2-H_B or morpholinyl 6-H_B); δ_C (125 MHz, $CDCl_3$): 167.2 (C-2), 161.6 (d, *J* 247.4 Hz, chlorophenyl C-5), 144.7 (aryl C-4), 136.4 (d, *J* 7.5 Hz, chlorophenyl C-1), 133.1 (d, *J* 25.1 Hz, aryl C-1), 131.1 (d, *J* 8.2 Hz, chlorophenyl C-3), 129.1 (aryl C_2-2,6), 127.9 (d, *J* 3.3 Hz, chlorophenyl C-2), 127.3 (aryl C_2-3,5), 116.7 (d, *J* 22.8 Hz, chlorophenyl C-4), 116.4 (d, *J* 24.1 Hz, chlorophenyl C-6), 82.3 (C-1), 69.5 (chlorophenylmethoxy C-1), 66.9 (morpholinyl C_A-2,6), 66.5 (morpholinyl C_B-2,6), 45.9 (morpholinyl C_A-3,5), 43.1 (morpholinyl C_B-3,5); δ_F (470 MHz, $CDCl_3$): 66.1 (SO_2F), -114.1 (chlorophenyl CF); HRMS found MNa^+ 468.0457. $C_{19}H_{18}ClF_2NO_5S$ requires *MNa*, 468.0454.

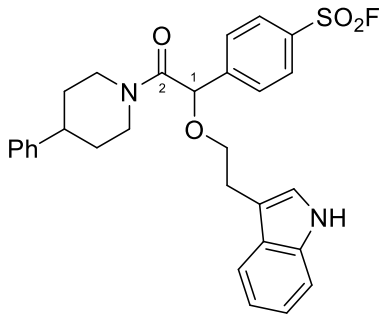
4-{1-[3-(2-hydroxyethyl)-1*H*-indol-1-yl]-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl}benzene-1-sulfonyl fluoride (210)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D2** (100 mM), co-substrate **Co-3** (500 mM) and $Rh_2(pfb)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *indole derivative* ***210*** (1.40 mg, 13%, *rotamers* 38:62 by ^1H NMR) as a colourless oil. R_f 0.16 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3434, 3060, 2924, 2856, 1645, 1458, 1410, 1212, 1099; δ_H (500 MHz, $CDCl_3$): 7.98 (2H, d, *J* 8.6 Hz, aryl 2,6-H^{min}), 7.95 (2H, d, *J* 8.6 Hz, aryl 2,6-H^{maj}), 7.69-7.66 (2H, m, indolyl 4-H), 7.37 (2H, d, *J* 8.6 Hz, aryl 3,5-H^{min}), 7.34-7.30 (4H, m, aryl 3,5-H^{maj} and phenyl 4-H), 7-26-7.14 (14H, m, phenyl 2,6-H^{min}, phenyl 3,5-H, indolyl 2,5,6,7-H), 6.96-6.93 (2H, m, phenyl 2,6-H^{maj}), 6.51 (1H, s, 1-H^{min}), 6.50 (1H, s, 1-H^{maj}), 4.89-4.78 (2H, m, piperidinyl 2-H_A or piperidinyl 6-H_A), 3.93 (4H, q, *J* 6.6 Hz, hydroxyethyl 2-H_2), 3.86-3.76 (2H, m, piperidinyl 2-H_A or piperidinyl 6-H_A), 3.18 (1H, td, *J* 13.1 and 2.6 Hz, piperidinyl 2-H_B^{maj} or piperidinyl 6-H_B^{maj}), 3.09-3.03 (4H, m, hydroxyethyl 1-H_2), 2.99-2.93 (1H, m, piperidinyl 2-H_B^{min} or piperidinyl 6-H_B^{min}), 2.86-2.60 (4H, m, piperidinyl 2-H_B or piperidinyl 6-H_B and piperidinyl 4-H), 2.03-1.97 (1H, m, piperidinyl 3-H_A^{min} or piperidinyl 5-H_A^{min}), 1.93-1.88 (2H, m, piperidinyl 3-H_B or piperidinyl 5-H_B), 1.71 (1H, qd, *J* 12.8 and 4.2 Hz, piperidinyl 3-H_A^{maj} or piperidinyl 5-H_A^{maj}), 1.55-1.45 (5H, m, piperidinyl 3-H_A or piperidinyl 5-H_A, piperidinyl 3-H_B or piperidinyl 5-H_B and piperidinyl 3,5-H_B^{min}), 1.42 (2H, s, OH), 0.76 (1H, qd, *J* 12.8 and 4.2 Hz, piperidinyl 3-H_B^{maj} or piperidinyl 5-H_B^{maj}); δ_C (125 MHz, $CDCl_3$): 165.7 (C-2^{min}), 165.4 (C-2^{maj}), 145.5 (phenyl C-1^{maj}), 145.3 (phenyl C-1^{min}), 144.6 (aryl C-4^{maj}), 144.5 (aryl C-4^{min}), 136.3 (indolyl C-$7a^{min}$), 136.2 (indolyl C-$7a^{maj}$), 133.0 (d, *J* 25.1 Hz, aryl C-1^{min}), 132.8 (d, *J* 25.1 Hz, aryl C-1^{maj}), 129.0 (indolyl C-$3a^{maj}$), 129.0 (indolyl C-$3a^{min}$), 128.8 (aryl C_2-2,6^{maj}), 128.84 (aryl C_2-3,5^{min}), 128.7 (phenyl C-4), 126.9 (phenyl C_2-3,5^{min}), 126.8 (phenyl C_2-3,5^{maj}), 126.73 (phenyl C_2-2,6^{min}), 126.68 (phenyl C_2-2,6^{maj}), 124.8 (indolyl C-2^{maj}), 124.5 (indolyl C-2^{min}), 123.2 (indolyl C-6^{maj}), 123.1 (indolyl C-6^{min}), 120.6 (indolyl C-5), 120.0 (indolyl C-4^{maj}), 119.9 (indolyl C-4^{min}), 114.3 (indolyl C-3^{maj}), 113.9 (indolyl C-3^{min}), 109.2 (indolyl C-7^{maj}), 109.0 (indolyl C-7^{min}), 62.9 (hydroxyethyl C-2^{maj}), 62.8 (hydroxyethyl C-2^{min}), 59.9 (C-1^{maj}), 59.7 (C-1^{min}), 47.2 (piperidinyl C_A-2,6^{maj}), 46.4 (piperidinyl C_A-2,6^{min}), 44.1 (piperidinyl C_B-2,6^{maj}), 43.6 (piperidinyl C_B-2,6^{min}), 42.5 (piperidinyl C-4^{maj}), 42.3 (piperidinyl C-4^{min}), 33.8 (piperidinyl C_A-3,5^{min}), 33.1 (piperidinyl C_A-3,5^{maj}), 33.1 (piperidinyl C_B-3,5^{maj}), 32.8 (piperidinyl C_B-3,5^{min}), 28.9 (hydroxyethyl C-1^{min}), 28.8 (hydroxyethyl C-1^{maj}); δ_F (470

MHz, $CDCl_3$): 66.1 (SO_2F); HRMS found MH^+ 521.1908. $C_{29}H_{29}FN_2O_4S$ requires *MH*, 521.1905.

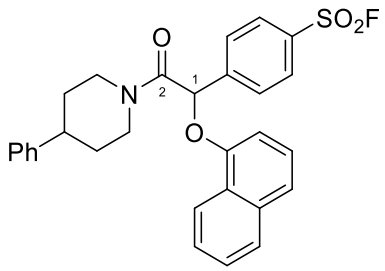
4-{1-[2-(1*H*-indol-3-yl)ethoxy]-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl}benzene-1-sulfonyl fluoride (211)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D2** (100 mM), co-substrate **Co-3** (500 mM) and $Rh_2(pfb)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *indole derivative* ***211*** (0.10 mg, 1%, *rotamers* 45:55 by ^1H NMR) as a colourless oil. R_f 0.34 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3419, 3059, 2924, 2858, 1645, 1458, 1412, 1213, 1098; δ_H (500 MHz, $CDCl_3$): 7.97 (2H, d, *J* 8.6 Hz, aryl 2,6-H^{min}), 7.96 (2H, d, *J* 8.6 Hz, aryl 2,6-H^{maj}), 7.92 (2H, br. s, NH), 7.67 (4H, app. t, *J* 8.6 Hz, aryl 3,5-H), 7.61 (2H, app. t, *J* 8.0 Hz, indolyl 4-H), 7.37-7.15 (10H, m, indolyl 6,7-H and phenyl 3,4,5-H), 7.14-7.10 (2H, m, indolyl 5-H), 7.09-7.05 (4H, indolyl 2-H and phenyl 2,6-H^{min}), 7.00 (2H, d, *J* 7.3 Hz, phenyl 2,6-H^{maj}), 5.31 (1H, s, 1-H^{maj}), 5.29 (1H, s, 1-H^{min}), 4.70-4.62 (2H, m, piperidinyl 2-H_A or piperidinyl 6-H_A), 4.09-3.85 (6H, m, piperidinyl 2-H_A or piperidinyl 6-H_A and ethoxyindolyl 2-H_2), 3.23-3.15 (4H, m, ethoxyindolyl 1-H_2), 2.70-2.48 (6H, m, piperidinyl 2,6-H_B and piperidinyl 4-H), 1.91-1.79 (2H, m, piperidinyl 3-H_A or piperidinyl 5-H_A), 1.50-1.21 (4H, m, piperidinyl 3-H_A or piperidinyl 5-H_A and piperidinyl 3-H_B or piperidinyl 5-H_B), 0.89-0.77 (2H, m, piperidinyl 3-H_B or piperidinyl 5-H_B); δ_C (125 MHz, $CDCl_3$): 167.7 (C-2^{maj}), 167.5 (C-2^{min}), 146.01 (phenyl C-1^{maj}), 145.97 (phenyl C-1^{min}),

144.4 (aryl C-4^{min}), 144.3 (aryl C-4^{maj}), 136.4 (indolyl C-7a^{maj}), 136.1 (indolyl C-7a^{min}), 128.8 (indolyl C-3a), 128.7 (aryl C_2-2,6 and phenyl C-4), 127.4 (aryl C_2-3,6), 127.0 (phenyl C_2-3,5^{min}), 126.8 (phenyl C_2-3,5^{maj}), 126.71 (phenyl C_2-2,6^{min}), 126.67 (phenyl C_2-2,6^{maj}), 122.4 (indolyl C-6), 122.2 (indolyl C-2), 119.6 (indolyl C-5), 118.9 (indolyl C-4), 112.9 (indolyl C-3), 111.4 (indolyl C-7), 83.6 (C-1^{min}), 82.7 (C-1^{maj}), 71.7 (ethoxyindolyl C-2^{maj}), 70.9 (ethoxyindolyl C-2^{min}), 45.6 (piperidinyl C_A-2,6^{maj}), 45.4 (piperidinyl C_A-2,6^{min}), 43.5 (piperidinyl C_B-2,6), 42.4 (piperidinyl C-4), 33.4 (piperidinyl C_A-3,5^{min}), 33.1 (piperidinyl C_A-3,5^{maj}), 33.0 (piperidinyl C_B-3,5^{maj}), 32.8 (piperidinyl C_B-3,5^{min}), 26.1 (ethoxyindolyl C-1^{maj}), 26.0 (ethoxyindolyl C-1^{min}); δ_F (470 MHz, $CDCl_3$): 66.2 (SO_2F^{min}), 66.1 (SO_2F^{maj}); HRMS found MNa^+ 453.1720. $C_{29}H_{29}FN_2O_4S$ requires *MNa*, 543.1724. Aryl C-1 not observed by ^{13}C NMR (125 MHz).

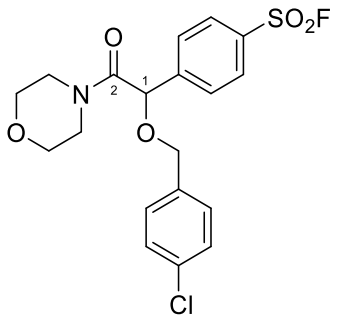
4-[1-(naphthalen-1-yloxy)-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl]benzene-1-sulfonyl fluoride (212)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D2** (100 mM), co-substrate **Co-4** (500 mM) and $Rh_2(pfb)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *napthalene derivative* ***212*** (1.10 mg, 11%, *rotamers* 44:56 by ^1H NMR) as a colourless oil. R_f 0.65 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3060, 2932, 2853, 1646, 1493, 1412, 1264, 1214, 1100; δ_H (500 MHz, $CDCl_3$): 8.43-8.32 (2H, m, napthanenyl 8-H), 8.12 (4H, d, *J* 8.5 Hz, aryl 2,6-H), 8.01-7.98 (4H, m, aryl 3,5-H), 7.90-7.95 (2H, m, napthanenyl 5-H), 7.60-7.52 (6H, m, napthanenyl 4,6,7-H), 7.41 (1H, t, *J* 8.0 Hz, napthanenyl 3-H^{maj}), 7.37 (1H, t, *J* 8.0

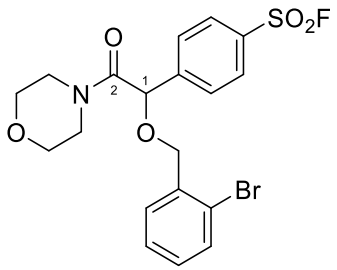
Hz, napthanenyl 3-H^{min}), 7.30-2.25 (2H, m, phenyl 3,5-H^{min}), 7.22-7.09 (4H, m, phenyl 4-H and phenyl 3,5-H^{maj}), 7.08-7.02 (3H, m, phenyl 2,6-H^{min} and napthanenyl 2-H^{maj}), 6.95 (1H, d, *J* 7.7 Hz, napthanenyl 2-H^{min}), 6.73 (2H, d, *J* 7.0 Hz, phenyl 2,6-H^{maj}), 6.29 (2H, s, 1-H), 4.73 (2H, app. t, *J* 11.7 Hz, piperidinyl 2-H_A or piperidinyl 6-H_A), 4.32 (2H, app. d, *J* 13.2 Hz, piperidinyl 2-H_A or piperidinyl 6-H_A), 3.04 (1H, td, *J* 13.2 and 2.3 Hz, piperidinyl 2-H_B^{min} or piperidinyl 6-H_B^{min}), 2.83 (1H, td, *J* 13.2 and 2.3 Hz, piperidinyl 2-H_B^{maj} or piperidinyl 6-H_B^{maj}), 2.74-2.51 (4H, m, piperidinyl 2-H_B or piperidinyl 6-H_B and piperidinyl 4-H), 1.90 (1H, app. d, *J* 13.2 Hz, piperidinyl 3-H_A^{min} or piperidinyl 5-H_A^{min}), 1.79 (1H, app. d, *J* 13.2 Hz, piperidinyl 3-H_A^{maj} or piperidinyl 5-H_A^{maj}), 1.67-1.57 (2H, m, piperidinyl 3-H_A or piperidinyl 5-H_A), 1.36-1.23 (2H, m, piperidinyl 3-H_B or piperidinyl 5-H_B), 1.13-1.00 (2H, m, piperidinyl 3-H_B or piperidinyl 5-H_B); δ_C (125 MHz, $CDCl_3$): 166.7 (C-2^{maj}), 166.6 (C-2^{min}), 152.5 (napthanenyl C-1^{maj}), 152.2 (napthanenyl C-1^{min}), 144.8 (phenyl C-1^{min}), 144.7 (phenyl C-1^{maj}), 144.6 (aryl C-4^{min}), 144.5 (aryl C-4^{maj}), 134.9 (napthanenyl C-4a), 133.1 (d, *J* 26.2 Hz, aryl C-1), 129.2 (aryl C_2-2,6^{maj}), 129.1 (aryl C_2-2,6^{min}), 128.8 (phenyl C_2-3,5^{min}), 128.6 (phenyl C_2-3,5^{maj}), 128.1 (napthanenyl C-5), 127.2 (aryl C_2-3,5^{min}), 127.1 (aryl C_2-3,5^{maj}), 126.8 (phenyl C-4), 126.7 (phenyl C_2-2,6^{min}), 126.6 (phenyl C_2-2,6^{maj}), 126.24 (napthanenyl C-6), 126.16 (napthanenyl C-7), 125.9 (napthanenyl C-3), 125.5 (napthanenyl C-$8a^{min}$), 125.4 (napthanenyl C-$8a^{maj}$), 122.3 (naphthanenyl C-4), 121.5 (napthanenyl C-8^{min}), 121.4 (napthanenyl C-8^{maj}), 106.5 (napthanenyl C-2), 80.5 (C-1^{maj}), 80.0 (C-1^{min}), 46.2 (piperidinyl C_A-2,6^{maj}), 45.8 (piperidinyl C_A-2,6^{min}), 44.2 (piperidinyl C_B-2,6^{maj}), 43.8 (piperidinyl C_B-2,6^{min}), 42.4 (piperidinyl C-4^{maj}), 42.3 (piperidinyl C-4^{min}), 33.39 (piperidinyl C_A-3,5^{maj}), 33.35 (piperidinyl C_A-3,5^{min}), 32.9 (piperidinyl C_B-3,5); δ_F (470 MHz, $CDCl_3$): 66.3 (SO_2F^{min}), 66.1 (SO_2F^{maj}); HRMS found MH^+ 504.1638. $C_{29}H_{26}FNO_4S$ requires *MH*, 504.1639.

4-{1-[(4-chlorophenyl)methoxy]-2-(morpholin-4-yl)-2-oxoethyl}benzene-1-sulfonyl fluoride (213)



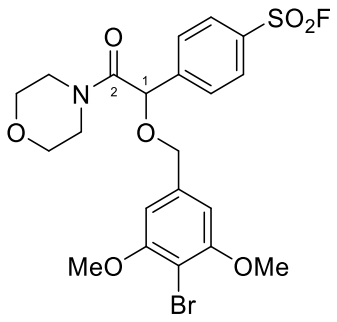
Prepared according to General procedure W – implementation of reaction array, diazo substrate **D1** (100 mM), co-substrate **Co-1** (500 mM) and $Rh_2(cap)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 35:65 → 60:40 → 95:5 MeCN–H_2O to give the *ether derivative* ***213*** (1.20 mg, 14%) as a colourless oil. R_f 0.21 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2921, 2861, 1650, 1492, 1439, 1242, 1213, 1115, 1095; δ_H (500 MHz, $CDCl_3$): 8.03 (2H, d, *J* 8.6 Hz, aryl 2,6-H), 7.72 (2H, d, *J* 8.6 Hz, aryl 3,5-H), 7.37 (2H, d, *J* 8.5 Hz, chlorophenyl 3,5-H), 7.31 (2H, d, *J* 8.5 Hz, chlorophenyl 2,6-H), 5.33 (1H, s, 1-H), 4.71 (1H, d, *J* 11.7 Hz, chlorophenylmethoxy 1-H_A), 4.65 (1H, d, *J* 11.7 Hz, chlorophenylmethoxy 1-H_B), 3.70-3.57 (4H, m, morpholinyl 2-H_2 or morpholinyl 6-H_2 and morpholinyl 3-H_2 or morpholinyl 5-H_2), 3.56-3.49 (1H, m, morpholinyl 3-H_A or morpholinyl 5-H_A), 3.47-3.40 (1H, m, morpholinyl 2-H_A or morpholinyl 6-H_A), 3.35-3.25 (2H, m, morpholinyl 3-H_B or morpholinyl 5-H_B and morpholinyl 2-H_B or morpholinyl 6-H_B); δ_C (125 MHz, $CDCl_3$): 167.5 (C-2), 145.0 (aryl C-4), 134.8 (chlorophenyl C-1), 134.6 (chlorophenyl C-4), 133.0 (d, *J* 25.0 Hz, aryl C-1), 129.6 (chlorophenyl C_2-2,6), 129.1 (chlorophenyl C_2-3,5), 129.0 (aryl C_2-2,6), 127.2 (aryl C_2-3,5), 81.7 (C-1), 72.0 (chlorophenylmethoxy C-1), 66.9 (morpholinyl C_A-2,6), 66.5 (morpholinyl C_B-2,6), 45.8 (morpholinyl C_A-3,5), 43.1 (morpholinyl C_B-3,5); δ_F (470 MHz, $CDCl_3$): 66.1 (SO_2F); HRMS found MH^+ 450.0548. $C_{19}H_{19}ClFNO_5S$ requires *MH*, 450.0549.

4-{1-[(2-bromophenyl)methoxy]-2-(morpholin-4-yl)-2-oxoethyl}benzene-1-sulfonyl fluoride (214)



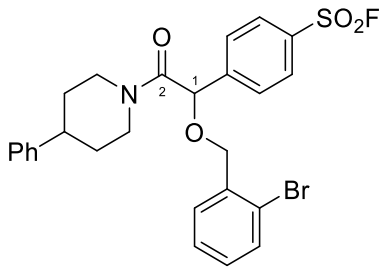
Prepared according to General procedure W – implementation of reaction array, diazo substrate **D1** (100 mM), co-substrate **Co-2** (500 mM) and $Rh_2(cap)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *ether derivative* ***214*** (1.10 mg, 12%) as a colourless oil. R_f 0.30 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2917, 2858, 1650, 1439, 1411, 1213, 1115, 1097; δ_H (500 MHz, $CDCl_3$): 8.04 (2H, d, *J* 8.6 Hz, aryl 2,6-H), 7.76 (2H, d, *J* 8.6 Hz, aryl 3,5-H), 7.61 (1H, dd, *J* 8.0 and 1.2 Hz, bromophenyl 3-H), 7.46 (1H, dd, *J* 7.6 and 1.5 Hz, bromophenyl 6-H), 7.36 (1H, td, *J* 7.6 and 1.2 Hz, bromophenyl 5-H), 7.24 (1H, td, *J* 7.8 and 1.5 Hz, bromophenyl 4-H), 5.40 (1H, s, 1-H), 4.82 (1H, d, *J* 12.1 Hz, bromophenylmethoxy 1-H_A), 4.76 (1H, d, *J* 12.1 Hz, bromophenylmethoxy 1-H_B), 3.70-3.60 (4H, m, morpholinyl 2-H_2 or morpholinyl 6-H_2 and morpholinyl 3-H_2 or morpholinyl 5-H_2), 3.56 (1H, ddd, *J* 10.4, 9.3 and 4.4 Hz, morpholinyl 3-H_A or morpholinyl 5-H_A), 3.45 (1H, ddd, *J* 10.8, 6.6 and 2.6 Hz, morpholinyl 2-H_A or morpholinyl 6-H_A), 3.37-3.27 (2H, m, morpholinyl 3-H_B or morpholinyl 5-H_B and morpholinyl 2-H_B or morpholinyl 6-H_B); δ_C (125 MHz, $CDCl_3$): 167.5 (C-2), 145.1 (aryl C-4), 135.8 (bromophenyl C-1), 130.2 (bromophenyl C-3), 132.9 (d, *J* 25.0 Hz, aryl C-1), 130.2 (bromophenyl C_2-4,6), 129.0 (aryl C_2-2,6), 127.8 (bromophenyl C-5), 127.3 (aryl C_2-3,5), 123.7 (bromophenyl C-2), 82.1 (C-1), 72.4 (bromophenylmethoxy C-1), 66.9 (morpholinyl C_A-2,6), 66.6 (morpholinyl C_B-2,6), 45.9 (morpholinyl C_A-3,5), 43.1 (morpholinyl C_B-3,5); δ_F (470 MHz, $CDCl_3$): 66.1 (SO_2F); HRMS found MNa^+ 494.0045. $C_{19}H_{19}BrFNO_5S$ requires *MNa*, 494.0044.

4-{1-[(4-bromo-3,5-dimethoxyphenyl)methoxy]-2-(morpholin-4-yl)-2-oxoethyl}benzene-1-sulfonyl fluoride (215)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D1** (100 mM), co-substrate **Co-8** (500 mM) and $Rh_2(cap)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 35:65 → 60:40 → 95:5 MeCN–H_2O to give the *ether derivative* ***215*** (1.30 mg, 12%) as a colourless oil. R_f 0.10 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2916, 2854, 1649, 1590, 1459, 1412, 1236, 1213, 1122, 1034; δ_H (500 MHz, $CDCl_3$): 8.04 (2H, d, *J* 8.6 Hz, aryl 2,6-H), 7.72 (2H, d, *J* 8.6 Hz, aryl 3,5-H), 6.58 (2H, s, dimethoxyphenyl 2,6-H), 5.34 (1H, s, 1-H), 4.71 (1H, d, *J* 12.0 Hz, dimethoxyphenylmethoxy 1-H_A), 4.65 (1H, d, *J* 12.0 Hz, dimethoxyphenylmethoxy 1-H_B), 3.91 (6H, s, OMe), 3.68-3.58 (4H, m, morpholinyl 2-H_2 or morpholinyl 6-H_2 and morpholinyl 3-H_2 or morpholinyl 5-H_2), 3.57-3.49 (1H, m, morpholinyl 3-H_A or morpholinyl 5-H_A), 3.48-3.39 (1H, m, morpholinyl 2-H_A or morpholinyl 6-H_A), 3.36-3.28 (2H, m, morpholinyl 3-H_B or morpholinyl 5-H_B and morpholinyl 2-H_B or morpholinyl 6-H_B); δ_C (125 MHz, $CDCl_3$): 167.5 (C-2), 157.5 (dimethoxyphenyl C_2-3,5), 145.0 (aryl C-4), 137.0 (dimethoxyphenyl C-1), 133.1 (d, *J* 25.1 Hz, aryl C-1), 129.1 (aryl C_2-2,6), 127.2 (aryl C_2-3,5), 104.5 (dimethoxyphenyl C_2-2,6), 101.2 (dimethoxyphenyl C-4), 81.4 (C-1), 72.7 (dimethoxyphenylmethoxy C-1), 66.9 (morpholinyl C_A-2,6), 66.5 (morpholinyl C_B-2,6), 56.7 (OMe), 45.9 (morpholinyl C_A-3,5), 43.1 (morpholinyl C_B-3,5); δ_F (470 MHz, $CDCl_3$): 66.1 (SO_2F); HRMS found MNa^+ 554.0251. $C_{21}H_{23}BrFNO_7S$ requires *MNa*, 554.0251.

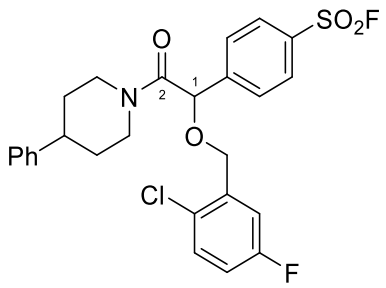
4-{1-[(2-bromophenyl)methoxy]-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl}benzene-1-sulfonyl fluoride (216)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D2** (100 mM), co-substrate **Co-2** (500 mM) and $Rh_2(cap)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *ether derivative* ***216*** (1.50 mg, 14%, *rotamers* 48:52 by ^1H NMR) as a colourless oil. R_f 0.59 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3030, 2920, 2859, 1643, 1452, 1410, 1270, 1212, 1123, 1095; δ_H (500 MHz, $CDCl_3$): 8.05 (2H, d, *J* 8.4 Hz, aryl 2,6-H^{min}), 8.04 (2H, d, *J* 8.4 Hz, aryl 2,6-H^{maj}), 7.83-7.77 (4H, m, aryl 3,5-H), 7.60 (2H, dd, *J* 8.0 and 2.0 Hz, bromophenyl 3-H), 7.54-7.50 (2H, m, bromophenyl 6-H), 7.38-7.33 (2H, m, bromophenyl 5-H), 7.32-7.26 (4H, m, phenyl 3,5-H), 7.25-7.17 (4H, m, bromophenyl 4-H and phenyl 4-H), 7.11 (2H, d, *J* 7.3 Hz, phenyl 2,6-H^{maj}), 7.04 (2H, d, *J* 7.3 Hz, phenyl 2,6-H^{min}), 5.45 (2H, s, 1-H), 4.91 (1H, d, *J* 12.3 Hz, bromophenylmethoxy 1-H$_A^{min}$), 4.84-4.71 (5H, m, bromophenylmethoxy 1-H$_A^{min}$, bromophenylmethoxy 1-H$_B$ and piperidinyl 2-H$_A$ or piperidinyl 6-H$_A$), 4.21-4.10 (2H, m, piperidinyl 2-H$_A$ or piperidinyl 6-H$_A$), 3.03 (1H, td, *J* 13.6 and 2.4 Hz, piperidinyl 2-H$_B^{min}$ or piperidinyl 6-H$_B^{min}$), 2.80-2.59 (5H, m, piperidinyl 2-H$_B^{maj}$ or piperidinyl 6-H$_B^{maj}$, piperidinyl 2-H$_B$ or piperidinyl 6-H$_B$ and piperidinyl 4-H), 1.98-1.85 (2H, m, piperidinyl 3-H$_A$ or piperidinyl 5-H$_A$), 1.74 (1H, app. d, *J* 13.1 Hz, piperidinyl 3-H$_A^{maj}$ or piperidinyl 5-H$_A^{maj}$), 1.67-1.56 (3H, m, piperidinyl 3-H$_B$ or piperidinyl 5-H$_B$ and piperidinyl 3-H$_A^{min}$ or piperidinyl 5-H$_A^{min}$), 1.45 (1H, qd, *J* 12.7 and 4.1 Hz, piperidinyl 3-H$_B^{min}$ or piperidinyl 5-H$_B^{min}$), 0.98 (1H, qd, *J* 12.7 and 4.1 Hz, piperidinyl 3-H$_B^{maj}$ or piperidinyl 5-H$_B^{maj}$); δ_C (125 MHz, $CDCl_3$): 167.3 (C-2^{maj}), 167.2 (C-2^{min}), 145.5 (aryl C-4^{min}), 145.4 (aryl C-4^{min}), 144.9 (phenyl C-1^{maj}), 144.8

(phenyl C-1^{min}), 136.1 (bromophenyl C-1), 132.8 (d, *J* 24.6 Hz, aryl C-1^{min}), 132.7 (d, *J* 24.6 Hz, aryl C-1^{maj}), 130.2 (bromophenyl C-3), 130.02 (bromophenyl C-6^{maj}), 129.99 (bromophenyl C-6^{min}), 129.0 (aryl C_2-2,6^{maj}), 128.9 (aryl C_2-2,6^{min}), 128.8 (phenyl C_2-3,5), 127.8 (bromophenyl C-5), 127.5 (aryl C_2-3,5^{min}), 127.3 (aryl C_2-3,5^{maj}), 126.7 (phenyl C_2-2,6), 126.7 (phenyl C-4), 123.7 (bromophenyl C-2^{maj}), 123.5 (bromophenyl C-2^{min}), 82.4 (C-1^{min}), 82.0 (C-1^{maj}), 72.4 (bromophenylmethoxy C-1^{maj}), 72.1 (bromophenylmethoxy C-1^{min}), 45.9 (piperidinyl C_A-2,6^{maj}), 45.8 (piperidinyl C_A-2,6^{min}), 43.73 (piperidinyl C_B-2,6^{maj}), 43.67 (piperidinyl C_B-2,6^{min}), 42.5 (piperidinyl C-4), 33.5 (piperidinyl C_A-3,5^{min}), 33.3 (piperidinyl C_A-3,5^{maj}), 33.3 (piperidinyl C_B-3,5^{maj}), 32.9 (piperidinyl C_B-3,5^{min}); δ_F (470 MHz, $CDCl_3$): 66.2 (SO_2F^{min}), 66.1 (SO_2F^{maj}); HRMS found MH^+ 546.0743. $C_{26}H_{25}BrFNO_4S$ requires *MH*, 546.0744.

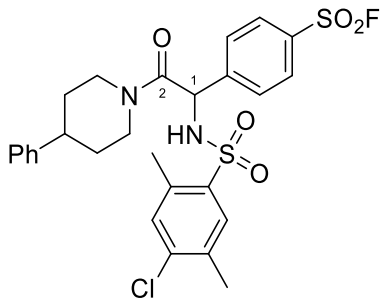
4-{1-[(2-chloro-5-fluorophenyl)methoxy]-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl}benzene-1-sulfonyl fluoride (217)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D2** (100 mM), co-substrate **Co-5** (500 mM) and $Rh_2(cap)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *ether derivative* ***217*** (1.40 mg, 14%, *rotamers* 51:49 by ^{1}H NMR) as a colourless oil. R_f 0.66 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3062, 2921, 2858, 1644, 1452, 1411, 1269, 1212, 1096; δ_H (500 MHz, $CDCl_3$): 8.06 (4H, d, *J* 7.1 Hz, aryl 2,6-H), 7.79 (4H, app. t, *J* 9.3 Hz, aryl 3,5-H), 7.39-7.34 (2H, m, chlorophenyl 3-H), 7.32-7.25 (6H, m, chlorophenyl 6-H and phenyl 3,5-H), 7.24-7.19 (2H, m phenyl 4-H), 7.10 (2H, d, *J* 7.4 Hz, phenyl 2,6-H^{maj}), 7.06 (2H,

d, *J* 7.4 Hz, phenyl 2,6-H^{min}), 7.03-6.96 (2H, m, chlorophenyl 4-H), 5.46 (2H, s, 1-H), 4.89 (1H, d, *J* 12.9 Hz, chlorophenylmethoxy 1-H_A^{min}), 4.83-4.69 (5H, m, chlorophenylmethoxy 1-H_A^{maj}, chlorophenylmethoxy 1-H_B and piperidinyl 2-H_A or piperidinyl 6-H_A), 4.14 (2H, app. t, *J* 12.7 Hz, piperidinyl 2-H_A or piperidinyl 6-H_A), 3.04 (1H, td, *J* 13.7 and 2.2 Hz, piperidinyl 2-H_B^{min} or piperidinyl 6-H_B^{min}), 2.80 (1H, td, *J* 13.7 and 2.2 Hz, piperidinyl 2-H_B^{maj} or piperidinyl 6-H_B^{maj}), 2.75-2.63 (4H, m, piperidinyl 2-H_B or piperidinyl 6-H_B and piperidinyl 4-H), 1.93 (2H, app. t, *J* 15.4 Hz, piperidinyl 3-H_A or piperidinyl 5-H_A), 1.77 (1H, app. d, *J* 13.0 Hz, piperidinyl 3-H_A^{maj} or piperidinyl 5-H_A^{maj}), 1.69-1.55 (3H, m, piperidinyl 3-H_A^{min} or piperidinyl 5-H_A^{min} and piperidinyl 3-H_B or piperidinyl 5-H_B), 1.39 (1H, qd, *J* 12.7 and 4.3 Hz, piperidinyl 3-H_B^{maj} or piperidinyl 5-H_B^{maj}), 1.02 (1H, qd, *J* 12.7 and 4.3 Hz, piperidinyl 3-H_B^{min} or piperidinyl 5-H_B^{min}); δ_C (125 MHz, $CDCl_3$): 167.0 (C-2^{maj}), 166.9 (C-2^{min}), 161.6 (d, *J* 247.1 Hz, chlorophenyl C-5), 145.1 (aryl C-4^{maj}), 145.0 (aryl C-4^{min}), 144.8 (phenyl C-1^{maj}), 144.7 (phenyl C-1^{min}), 136.7 (d, *J* 7.6 Hz, chlorophenyl C-1), 133.0 (d, *J* 24.9 Hz, aryl C-1), 131.0 (d, *J* 8.2 Hz, chlorophenyl C-3), 129.1 (aryl C_2-2,6^{min}), 129.0 (aryl C_2-2,6^{maj}), 128.8 (phenyl C_2-3,5), 127.9 (d, *J* 2.9 Hz, chlorophenyl C-2^{min}), 127.7 (d, *J* 2.9 Hz, chlorophenyl C-2^{maj}), 127.5 (aryl C_2-3,5^{maj}), 127.4 (aryl C_2-3,5^{min}), 126.8 (phenyl C_2-2,6), 126.72 (phenyl C-4^{min}), 126.68 (phenyl C-4^{maj}), 116.5 (d, *J* 22.9 Hz, chlorophenyl C-4), 116.4 (d, *J* 21.5 Hz, chlorophenyl C-6^{min}), 116.2 (d, *J* 21.5 Hz, chlorophenyl C-6^{maj}), 82.5 (C-1^{min}), 82.1 (C-1^{maj}), 69.5 (chlorophenylmethoxy C-1^{maj}), 69.2 (chlorophenylmethoxy C-1^{min}), 45.9 (piperidinyl C_A-2,6^{min}), 45.8 (piperidinyl C_A-2,6^{maj}), 43.8 (piperidinyl C_B-2,6^{maj}), 43.7 (piperidinyl C_B-2,6^{min}), 42.5 (piperidinyl C-4), 33.5 (piperidinyl C_A-3,5^{maj}), 33.3 (piperidinyl C_A-3,5^{min}), 33.2 (piperidinyl C_B-3,5^{min}), 32.9 (piperidinyl C_B-3,5^{maj}); δ_F (470 MHz, $CDCl_3$): 66.2 (SO_2F^{maj}), 66.1 (SO_2F^{min}), -114.2 (chlorophenyl CF^{min}), -114.3 (chlorophenyl CF^{maj}); HRMS found MH^+ 520.1160. $C_{26}H_{24}ClF_2NO_4S$ requires *MH*, 520.1155.

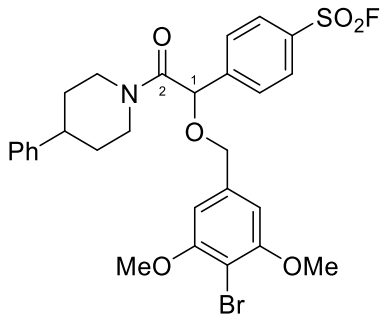
4-[1-(4-chloro-2,5-dimethylbenzenesulfonamido)-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl]benzene-1-sulfonyl fluoride (218)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D2** (100 mM), co-substrate **Co-6** (500 mM) and $Rh_2(cap)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *sulfonamide derivative* ***218*** (1.20 mg, 10%, *rotamers* 43:57 by ^{1}H NMR) as a colourless oil. R_f 0.60 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3234, 3031, 2924, 2860, 1644, 1453, 1413, 1270, 1214, 1161, 1089; δ_H (500 MHz, $CDCl_3$): 7.90 (2H, d, *J* 8.5 Hz, aryl 2,6-H^{maj}), 7.89 (2H, d, *J* 8.5 Hz, aryl 2,6-H^{min}), 7.64 (1H, s, sulfonamidophenyl 6-H^{maj}), 7.56 (1H, s, sulfonamidophenyl 6-H^{min}), 7.52-7.48 (4H, m, aryl 3,5-H), 7.34 (2H, app. t, *J* 7.6 Hz, phenyl 3,5-H^{maj}), 7.26-7.21 (4H, m, phenyl 3,5-H^{min} and phenyl 4-H), 7.17 (2H, s, sulfonamidophenyl 3-H), 7.11 (2H, d, *J* 7.6 Hz, phenyl 2,6-H^{maj}), 6.92 (2H, d, *J* 7.6 Hz, phenyl 2,6-H^{min}), 6.54 (2H, app. t, *J* 7.2 Hz, NH), 5.34 (1H, d, *J* 7.2 Hz, 1-H^{min}), 5.31 (1H, d, *J* 7.2 Hz, 1-H^{maj}), 4.67-4.61 (2H, m, piperidinyl 2-H$_A$ or piperidinyl 6-H$_A$), 3.72-3.64 (2H, m, piperidinyl 2-H$_A$ or piperidinyl 6-H$_A$), 3.05 (1H, td, *J* 13.2 and 2.6 Hz, piperidinyl 2-H$_B^{min}$ or piperidinyl 6-H$_B^{min}$), 2.78 (1H, td, *J* 13.2 and 2.6 Hz, piperidinyl 2-H$_B^{maj}$ or piperidinyl 6-H$_B^{maj}$), 2.69-2.59 (4H, m, piperidinyl 2-H$_B$ or piperidinyl 6-H$_B$ and piperidinyl 4-H), 2.58 (3H, s, sulfonamidophenyl 2-methyl^{maj}), 2.52 (3H, s, sulfonamidophenyl 2-methyl^{min}), 2.30 (3H, s, sulfonamidophenyl 5-methyl^{min}), 2.26 (3H, s, sulfonamidophenyl 5-methyl^{maj}), 1.92-1.81 (3H, m, piperidinyl 3-H$_A$ or piperidinyl 5-H$_A$ and piperidinyl 3-H$_A^{maj}$ or piperidinyl 5-H$_A^{maj}$), 1.61-1.56 (1H, m, piperidinyl 3-H$_A^{min}$ or piperidinyl 5-H$_A^{min}$) 1.48-1.20 (3H, m, piperidinyl 3-H$_B$ or piperidinyl 5-H$_B$ and piperidinyl 3-H$_B^{maj}$ or piperidinyl 5-H$_B^{maj}$), 0.56 (1H, qd, *J* 12.7 and

4.2 Hz, piperidinyl 3-H_B^{min} or piperidinyl 5-H_B^{min}); δ_C (125 MHz, $CDCl_3$): 165.6 (C-2), 144.4 (aryl C-4^{min}), 144.1 (aryl C-4^{maj}), 144.0 (phenyl C-1^{maj}), 143.9 (phenyl C-1^{min}), 139.3 (sulfonamidophenyl C-1^{maj}), 139.2 (sulfonamidophenyl C-1^{min}), 136.5 (sulfonamidophenyl C-2^{maj}), 136.4 (suldonamidophenyl C-2^{min}), 136.2 (sulfonamidophenyl C-4^{maj}), 136.1 (sulfonamidophenyl C-4^{min}), 134.0 (sulfonamidophenyl C-5^{maj}), 133.9 (sulfonamidophenyl C-5^{min}), 133.3 (d, *J* 25.4 Hz, aryl C-1), 133.0 (sulfonamidophenyl C-3^{maj}), 132.8 (sulfonamidophenyl C-3^{min}), 131.5 (sulfonamidophenyl C-6^{maj}), 131.3 (sulfonamidophenyl C-6^{min}), 129.14 (aryl C_2-2,6), 129.06 (aryl C_2-3,5), 129.0 (phenyl C_2-$3,5^{maj}$), 128.8 (phenyl C_2-$3,5^{min}$), 127.02 (phenyl C-4^{maj}), 126.99 (phenyl C-4^{min}), 126.7 (phenyl C_2-$2,6^{maj}$), 126.5 (phenyl C_2-$2,6^{min}$), 56.7 (C-1^{min}), 56.4 (C-1^{maj}), 46.4 (piperidinyl C_A-$2,6^{maj}$), 46.0 (piperidinyl C_A-$2,6^{min}$), 43.9 (piperidinyl C_B-2,6), 42.4 (piperidinyl C-4^{maj}), 42.0 (piperidinyl C-4^{min}), 33.8 (piperidinyl C_A-3,5), 32.6 (piperidinyl C_B-$3,5^{maj}$), 32.4 (piperidinyl C_B-$3,5^{min}$), 19.7 (sulfonamidophenyl 2-methyl^{maj}), 19.6 (sulfonamidophenyl 2-methyl^{min}), 19.5 (sulfonamidophenyl 5-methyl); δ_F (470 MHz, $CDCl_3$): 66.2 (SO_2F^{min}), 66.0 (SO_2F^{maj}); HRMS found MH^+ 579.1183. $C_{27}H_{28}ClFN_2O_5S_2$ requires *MH*, 579.1185.

4-{1-[(4-bromo-3,5-dimethoxyphenyl)methoxy]-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl}benzene-1-sulfonyl fluoride (219)

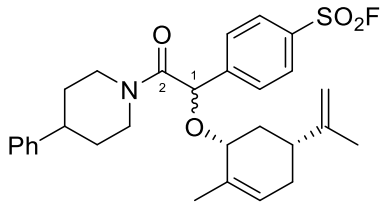


Prepared according to General procedure W – implementation of reaction array, diazo substrate **D2** (100 mM), co-substrate **Co-6** (500 mM) and $Rh_2(cap)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient

elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *ether derivative* ***219*** (1.60 mg, 13%, *rotamers* 48:52 by ^1H NMR) as a colourless oil. R_f 0.31 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2938, 2861, 1645, 1590, 1494, 1455, 1413, 1213, 1124, 1095; δ_H (500 MHz, $CDCl_3$): 8.05 (2H, d, *J* 8.1 Hz, aryl 2,6-H^{min}), 8.04 (2H, d, *J* 8.1 Hz, aryl 2,6-H^{maj}), 7.77 (2H, d, *J* 8.1 Hz, aryl 3,5-H^{maj}), 7.75 (2H, d, *J* 8.1 Hz, aryl 3,5-H^{min}), 7.32-7.26 (4H, m, phenyl 3,5-H), 7.24-7.18 (2H, m, phenyl 4-H), 7.08 (2H, d, *J* 7.3 Hz, phenyl 2,6-H^{min}), 7.04 (2H, d, *J* 7.3 Hz, phenyl 2,6-H^{maj}), 6.62 (2H, s, dimethoxyphenyl 2,6-H^{maj}), 6.59 (2H, s, dimethoxyphenyl 2,6-H^{min}), 5.39 (2H, s, 1-H), 4.81-4.61 (6H, m, dimethoxyphenylmethoxy 1-H_2 and piperidinyl 2-H_A or piperidinyl 6-H_A), 4.15-4.07 (2H, m, piperidinyl 2-H_A or piperidinyl 6-H_A), 3.89 (6H, s, OMe^{min}), 3.88 (6H, s, OMe^{maj}), 2.98 (1H, td, *J* 13.1 and 2.1 Hz, piperidinyl 2-$H_B{}^{min}$ or piperidinyl 6-$H_B{}^{min}$), 2.77-2.61 (5H, m, piperidinyl 2-$H_B{}^{maj}$ or piperidinyl 6-$H_B{}^{maj}$, piperidinyl 2-H_B or piperidinyl 6-H_B and piperidinyl 4-H), 1.92 (2H, app. t, *J* 14.8 Hz, piperidinyl 3-H_A or piperidinyl 5-H_A), 1.75 (1H, app. d, *J* 13.4 Hz, piperidinyl 3-$H_A{}^{maj}$ or piperidinyl 5-$H_A{}^{maj}$), 1.64 (1H, app. d, *J* 13.4 Hz, piperidinyl 3-$H_A{}^{min}$ or piperidinyl 5-$H_A{}^{min}$), 1.59-1.48 (2H, m, piperidinyl 3-H_B or piperidinyl 5-H_B), 1.37 (1H, qd, *J* 12.8 and 4.2 Hz, piperidinyl 3-$H_B{}^{maj}$ or piperidinyl 5-$H_B{}^{maj}$), 1.00 (1H, qd, *J* 12.8 and 4.2 Hz, piperidinyl 3-$H_B{}^{min}$ or piperidinyl 5-$H_B{}^{min}$); δ_C (125 MHz, $CDCl_3$): 167.3 (C-2^{min}), 167.1 (C-2^{maj}), 157.5 (dimethoxyphenyl C_2-$3,5^{maj}$), 157.4 (dimethoxyphenyl C_2-$3,5^{min}$), 145.4 (aryl C-4), 144.7 (phenyl C-1^{maj}), 144.6 (phenyl C-1^{min}), 137.3 (dimethoxyphenyl C-1^{maj}), 137.2 (dimethoxyphenyl C-1^{min}), 132.8 (d, *J* 25.9 Hz, aryl C-1), 129.02 (aryl C_2-$2,6^{maj}$), 128.95 (aryl C_2-$2,6^{min}$), 128.8 (phenyl C_2-3,5), 127.6 (aryl C_2-$3,5^{maj}$), 127.2 (aryl C_2-$3,5^{min}$), 126.9 (phenyl C-4), 126.6 (phenyl C_2-2,6), 104.6 (dimethoxyphenyl C_2-2,6), 101.0 (dimethoxyphenyl C-4), 82.0 (C-1^{maj}), 81.0 (C-1^{min}), 73.0 (dimethoxyphenylmethoxy C-1^{maj}), 72.5 (dimethoxyphenylmethoxy C-1^{min}), 56.7 (OMe), 45.8 (piperidinyl C_A-2,6), 43.7 (piperidinyl C_B-$2,6^{min}$), 43.6 (piperidinyl C_B-$2,6^{min}$), 42.5 (piperidinyl C-4^{min}), 42.4 (piperidinyl C-4^{maj}), 33.7 (piperidinyl C_A-$3,5^{maj}$), 33.5 (piperidinyl C_A-$3,5^{min}$), 33.0 (piperidinyl C_B-$3,5^{maj}$), 32.9 (piperidinyl C_B-$3,5^{min}$); δ_F (470 MHz, $CDCl_3$): 66.2 (SO_2F^{min}), 66.1 (SO_2F^{maj}); HRMS found MH^+ 606.0953. $C_{28}H_{29}BrFNO_6S$ requires *MH*, 606.0956.

4-[(1*R*)-1-{[(1*R*,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl]oxy}-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl]benzene-1-sulfonyl fluoride (220')

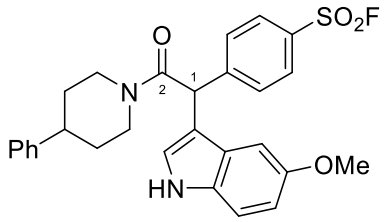
4-[(1*S*)-1-{[(1*R*,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl]oxy}-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl]benzene-1-sulfonyl fluoride (220'')



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D2** (100 mM), co-substrate **Co-14** (500 mM) and $Rh_2(cap)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *ether derivative* ***220*** (1.00 mg, 10%, *dr* 51:49 by ^{1}H NMR) as a colourless oil. R_f 0.78 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3029, 2921, 2859, 1639, 1493, 1452, 1410, 1269, 1212, 1124, 1095; δ_H (500 MHz, $CDCl_3$): 8.08-7.98 (4H, m, aryl 2,6-H), 7.86-7.74 (4H, m, aryl 3,5-H), 7.32-7.17 (6H, m, phenyl 3,5-H and phenyl 4-H), 7.14 (2H, d, *J* 7.2 Hz, phenyl 2,6-H^{maj}), 7.02-6.96 (2H, m, phenyl 2,6-H^{min}), 5.78-5.50 (2H, m, cyclohexenyl 3-H), 5.46 (1H, s, 1-H^{min}), 5.42 (1H, s, 1-H^{maj}), 4.82-4.65 (6H, m, propenyl 1-H_2 and piperidinyl 2-H_A or piperidinyl 6-H_A), 4.42-4.14 (4H, m, piperidinyl 2-H_A or piperidinyl 6-H_A and cyclohexenyl 1-H), 3.13-2.94 (1H, m, piperidinyl 2-H_B^{maj} or piperidinyl 6-H_B^{maj}), 2.74-2.54 (5H, m, piperidinyl 2-H_B^{min} or piperidinyl 6-H_B^{min}, piperidinyl 2-H_B or piperidinyl 6-H_B and piperidinyl 4-H), 2.43-2.18 (4H, m, cyclohexenyl 5-H and piperidinyl 3-H_A or piperidinyl 5-H_A), 2.15-1.50 (25H, m, piperidinyl 3-H_A or piperidinyl 5-H_A cyclohexenyl 4,6-H_2, cyclohexenyl 2-methyl, propenyl 3-H_3, piperidinyl 3-H_B or piperidinyl 5-H_B and piperidinyl 3-H_B^{maj} or piperidinyl 5-H_B^{maj}), 0.73 (1H, qd, *J* 12.8 and 4.2 Hz, piperidinyl 3-H_B^{min} or piperidinyl 5-H_B^{min}); δ_C (125 MHz, $CDCl_3$): 169.2 (C-2^{maj}), 168.8 (C-2^{min}), 148.6 (propenyl C-2^{maj}), 148.5 (propenyl C-2^{min}), 146.6 (aryl C-4), 145.1 (phenyl C-1^{maj}), 144.8 (phenyl C-1^{min}), 134.4 (cyclohexenyl C-2^{maj}), 134.3 (cyclohexenyl C-2^{min}), 132.4 (d, *J* 24.9 Hz, aryl C-1), 128.9 (aryl C_2-2,6^{min}), 128.84 (aryl C_2-2,6^{maj}), 128.76

(phenyl-3,5), 126.83 (aryl C_2-3,5^{min}), 126.76 (aryl C_2-3,5^{maj}), 126.7 (phenyl C_2-2,6^{maj}), 126.63 (phenyl C_2-2,6^{min}), 126.58 (phenyl C-4^{maj}), 126.5 (phenyl C-4^{min}), 126.0 (cyclohexenyl C-3^{maj}), 125.9 (cyclohexenyl C-3^{min}), 109.7 (propenyl C-1^{maj}), 109.6 (propenyl C-1^{min}), 83.5 (C-1^{maj}), 83.2 (C-1^{min}), 81.3 (cyclohexenyl C-1^{min}), 80.8 (cyclohexenyl C-1^{maj}), 46.1 (piperidinyl C_A-2,6^{min}), 45.6 (piperidinyl C_A-2,6^{maj}), 43.8 (piperidinyl C_B-2,6^{maj}), 43.5 (piperidinyl C_B-2,6^{min}), 42.5 (piperidinyl C-4), 40.7 (cyclohexenyl C-5^{min}), 40.6 (cyclohexenyl C-5^{maj}), 35.7 (piperidinyl C_A-3,5^{maj}), 34.8 (piperidinyl C_A-3,5^{min}), 33.8 (cyclohexenyl C-6), 33.1 (piperidinyl C_B-3,5^{min}), 32.9 (piperidinyl C_B-3,5^{maj}), 31.1 (cyclohexenyl C-4^{maj}), 31.0 (cyclohexenyl C-4^{maj}), 20.7 (propenyl C-3^{maj}), 20.6 (propenyl C-3^{min}), 19.9 (cyclohexenyl 2-methyl^{maj}), 19.8 (cyclohexenyl 2-methyl^{min}); δ_F (470 MHz, $CDCl_3$): 66.3 (SO_2F^{min}), 66.1 (SO_2F^{maj}); HRMS found MNa^+ 534.2077. $C_{29}H_{34}FNO_4S$ requires *MNa*, 534.2085.

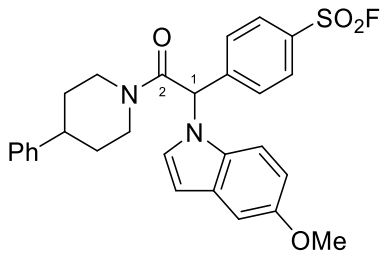
4-[1-(5-methoxy-1*H*-indol-3-yl)-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl]benzene-1-sulfonyl fluoride (221)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D2** (100 mM), co-substrate **Co-15** (500 mM) and $Rh_2(cap)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *indole derivative* ***221*** (1.10 mg, 11%, *rotamers* 51:49 by ^{1}H NMR) as a colourless oil. R_f 0.48 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3416, 2925, 1637, 1484, 1440, 1410, 1212, 1166; δ_H (500 MHz, $CDCl_3$): 9.10 (1H, br. s, NH^{maj}), 9.04 (1H, br. s, NH^{min}), 7.96 (2H, d, *J* 8.5 Hz, aryl 2,6-H^{min}), 7.94 (2H, d, *J* 8.5 Hz, aryl 2,6-H^{maj}), 7.58 (2H, d, *J* 8.5 Hz, aryl 3,5-H^{min}), 7.54 (2H, d, *J* 8.5 Hz, aryl 3,5-H^{maj}), 7.35-7.30 (2H, m, phenyl 3,5-H^{maj}), 7.29-7.17 (6H, m,

phenyl 3,5-H^{min}, phenyl 4-H and indolyl 7-H), 7.15 (2H, d, *J* 7.4 Hz, phenyl 2,6-H^{min}), 7.08 (2H, d, *J* 7.4 Hz, phenyl 2,6-H^{maj}), 7.04 (1H, d, *J* 2.5 Hz, indolyl 4-H^{maj}), 7.03 (1H, d, *J* 2.5 Hz, indolyl 4-H^{min}), 6.89-6.84 (2H, m, indolyl 6-H), 6.40 (1H, d, *J* 1.5 Hz, indolyl 2-H^{maj}), 6.37 (1H, d, *J* 1.5 Hz, indolyl 2-H^{min}), 5.66 (1H, s, 1-H^{maj}), 5.64 (1H, s, 1-H^{min}), 4.89-4.82 (2H, m piperidinyl 2-H_A or piperidinyl 6-H_A), 4.29-4.18 (2H, m, piperidinyl 2-H_A or piperidinyl 6-H_A), 3.84 (6H, s, OMe), 3.26 (2H, app. tt, *J* 13.5 and 2.5 Hz, piperidinyl 2-H_B or piperidinyl 6-H_B), 2.83-2.70 (4H, m, piperidinyl 2-H_B or piperidinyl 6-H_B and piperidinyl 4-H), 2.04-1.82 (4H, m piperidinyl 3,5-H_A), 1.73-1.56 (2H, m, piperidinyl 3-H_B or piperidinyl 5-H_B), 1.53-1.39 (2H, m, piperidinyl 3-H_B or piperidinyl 5-H_B); δ_C (125 MHz, $CDCl_3$): 168.6 (C-2), 154.6 (indolyl C-5), 147.7 (aryl C-4^{maj}), 147.6 (aryl C-4^{min}), 144.6 (phenyl C-1^{min}), 144.5 (phenyl C-1^{maj}), 134.4 (indolyl C-$3a^{min}$), 134.3 (indolyl C-$3a^{maj}$), 132.0 (d, J 24.8 Hz, aryl C-1^{maj}), 131.9 (d, J 24.8 Hz, aryl C-1^{min}), 131.80 (indolyl C-$7a^{min}$), 131.77 (indolyl C-$7a^{maj}$), 129.5 (aryl C_2-3,5^{min}), 129.4 (aryl C_2-3,5^{maj}), 129.1 (aryl C_2-2,6^{min}), 129.0 (aryl C_2-2,6^{maj}), 128.9 (phenyl C_2-3,5^{min}), 128.8 (phenyl C_2-3,5^{maj}), 128.5 (indolyl C-3^{min}), 128.4 (indolyl C-3^{maj}), 127.0 (phenyl C-4^{min}), 126.84 (phenyl C-4^{maj}), 126.80 (phenyl C_2-2,6^{maj}), 126.7 (phenyl C_2-2,6-H^{min}), 112.83 (indolyl C-6^{maj}), 112.79 (indolyl C-6^{min}), 112.2 (indolyl C-7), 102.5 (indolyl C-2^{min}), 102.4 (indolyl C-2^{maj}), 102.31 (indolyl C-4^{maj}), 102.28 (indolyl C-4^{min}), 56.0 (OMe), 47.6 (piperidinyl C_A-2,6^{maj}), 47.4 (piperidinyl C_A-2,6^{min}), 47.0 (C-1^{min}), 46.9 (C-1^{maj}), 43.7 (piperidinyl C_B-2,6^{maj}), 43.4 (piperidinyl C_B-2,6^{min}), 42.7 (piperidinyl C-4^{maj}), 42.5 (piperidinyl C-4^{min}), 34.1 (piperidinyl C_A-3,5^{maj}), 33.8 (piperidinyl C_A-3,5^{min}), 33.0 (piperidinyl C_B-3,5^{maj}), 32.9 (piperidinyl C_B-3,5^{min}); δ_F (470 MHz, $CDCl_3$): 66.22 (SO_2F^{min}), 66.16 (SO_2F^{maj}); HRMS found MH^+ 507.1755. $C_{28}H_{27}FN_2O_4S$ requires *MH*, 507.1748.

4-[1-(5-methoxy-1*H*-indol-1-yl)-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl]benzene-1-sulfonyl fluoride (222)

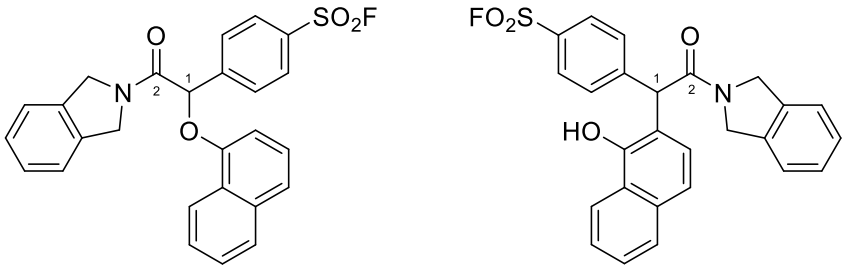


Prepared according to General procedure W – implementation of reaction array, diazo substrate **D2** (100 mM), co-substrate **Co-15** (500 mM) and $Rh_2(cap)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *indole derivative* ***222*** (0.10 mg, 1%, *rotamers* 65:35 by ^{1}H NMR) as a colourless oil. R_f 0.43 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2936, 2852, 1640, 1596, 1453, 1412, 1213, 1166, 1099; δ_H (500 MHz, $CDCl_3$): 7.98-7.92 (4H, m, aryl C_2-2,6), 7.34-7.27 (4H, m, aryl C_2-3,5), 7.25-7.22 (6H, m, phenyl 3,5-H and indolyl 2-H), 7.22 (8H, phenyl 2,6-H^{min} phenyl 4-H and indolyl 4,7-H), 6.93 (2H, d, *J* 7.1 Hz, phenyl C_2-2,6^{maj}), 6.90-6.84 (2H, m, indolyl 6-H), 6.63 (1H, dd, *J* 3.2 and 0.7 Hz, indolyl 3-H^{maj}), 6.49 (1H, dd, *J* 3.2 and 0.7 Hz, indolyl 3-H^{min}), 6.47 (2H, s, 1-H), 4.89-4.79 (2H, m, piperidinyl 2-H_A or piperidinyl 6-H_A), 3.86 (3H, s, OMe^{maj}), 3.85 (3H, s, OMe^{min}), 3.85-3.74 (2H, m piperidinyl 2-H_A or piperidinyl 6-H_A), 3.19 (1H, td, *J* 13.1 and 2.6 Hz, piperidinyl 2-H_B^{maj} or piperidinyl 6-H_B^{maj}), 2.91 (1H, td, *J* 13.1 and 2.6 Hz, piperidinyl 2-H_B^{min} or piperidinyl 6-H_B^{min}), 2.86-2.62 (4H, m, piperidinyl 2-H_B or piperidinyl 6-H_B and piperidinyl 4-H), 2.03-1.96 (1H, m, piperidinyl 3-H_A^{min} or piperidinyl 6-H_A^{min}), 1.91-1.82 (2H, m, piperidinyl 3-H_A or piperidinyl 6-H_A), 1.77-1.53 (2H, m, piperidinyl 3-H_A^{maj} or piperidinyl 6-H_A^{maj}, piperidinyl 3-H_B^{min} or piperidinyl 6-H_B^{min}), 1.50-1.43 (2H, m, piperidinyl 3-H_B or piperidinyl 6-H_B), 0.70 (1H, qd, *J* 12.8 and 4.2 Hz, piperidinyl 3-H_B^{maj} or piperidinyl 6-H_B^{maj}); δ_C (125 MHz, $CDCl_3$): 165.3 (C-2), 155.0 (indolyl C-5), 145.7 (aryl C-4^{min}), 145.5 (aryl C-4^{min}), 144.64 (phenyl C-1^{min}), 144.56 (phenyl C-1^{maj}), 130.9 (indolyl C-7a), 129.7 (indolyl C-3a^{min}), 129.6 (indolyl C-3a^{maj}), 128.89 (aryl C_2-2,6^{min}), 128.85 (aryl C_2-2,6^{maj}), 128.8 (aryl C_2-3,5^{min}),

128.72 (aryl C_2-3,5^{maj}), 128.69 (indolyl C-2), 127.2 (phenyl C_2-3,5), 126.92 (phenyl C-4^{min}), 126.9 (phenyl C-4^{maj}), 126.8 (phenyl C_2-2,6), 113.2 (indolyl C-6^{maj}), 113.1 (indolyl C-6^{min}), 110.0 (indolyl C-7), 103.8 (indolyl C-3^{maj}), 103.6 (indolyl C-3^{min}), 103.5 (indolyl C-4^{maj}), 103.4 (indolyl C-4^{min}), 60.3 (C-1^{maj}), 60.2 (C-1^{min}), 56.0 (OMe^{maj}), 55.9 (OMe^{min}), 47.3 (piperidinyl C_A-2,6), 44.1 (piperidinyl C_B-2,6^{maj}), 43.6 (piperidinyl C_B-2,6^{min}), 42.6 (piperidinyl C-4^{maj}), 42.3 (piperidinyl C-4^{min}), 33.8 (piperidinyl C_A-3,5), 33.2 (piperidinyl C_B-3,5^{min}), 32.8 (piperidinyl C_B-3,5^{maj}); δ_F (470 MHz, $CDCl_3$): 66.1 (SO_2F); HRMS found MH^+ 507.1751. $C_{28}H_{27}FN_2O_4S$ requires *MH*, 507.1748. Aryl C-1 not observed by ^{13}C NMR (125 MHz).

4-[2-(2,3-dihydro-1*H*-isoindol-2-yl)-1-(naphthalen-1-yloxy)-2-oxoethyl]benzene-1-sulfonyl fluoride (223a)

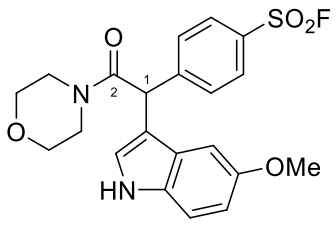
4-[2-(2,3-dihydro-1*H*-isoindol-2-yl)-1-(1-hydroxynaphthalen-2-yl)-2-oxoethyl]benzene-1-sulfonyl fluoride (223b)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D3** (100 mM), co-substrate **Co-4** (500 mM) and $Rh_2(cap)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 55:45 → 75:25 → 95:5 MeCN–H_2O to give the *naphthalene derivative* ***223*** (0.50 mg, 5%, *regioisomers* 51:49 by ^1H NMR) as a colourless oil. R_f 0.63 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3061, 2925, 2866, 1642, 1590, 1441, 1410, 1265, 1213, 1099; δ_H (500 MHz, $CDCl_3$): 10.72 (1H, br. s, OH^{min}), 8.48-8.43 (1H, m, napthanenyl 8-H^{min}), 8.35-8.32 (1H, m, napthanenyl 8-H^{maj}), 8.12 (2H, d, *J* 8.7 Hz, phenyl 2,6-H^{maj}), 8.07 (2H, d, *J* 8.7 Hz, napthanenyl 3,5-H^{maj}), 7.92 (2H, d, *J* 8.6 Hz, phenyl 2,6-H^{min}),

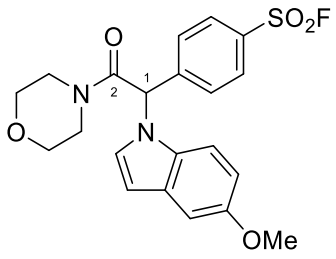
7.88-7.85 (1H, m, napthanenyl 5-H^{maj}), 7.81-7.78 (1H, m, napthanenyl 5-H^{min}), 7.65-7.27 (8H, m, phenyl 3,5-H^{min} and napthanenyl 4,6,7-H), 7.40-7.18 (9H, m, napthanenyl 3-H^{maj} and isoindolyl 4,5,6,7-H), 7.09 (1H, d, *J* 7.4 Hz, napthanenyl 3-H^{min}), 6.99 (1H, d, *J* 7.6 Hz, napthanenyl 2-H^{maj}), 6.21 (1H, s, 1-H^{maj}), 5.40 (1H, s, 1-H^{min}), 5.18 (2H, s, isoindolyl 1-H_2^{maj} or isoindolyl 3-H_2^{maj}), 4.08-4.72 (6H, m, isoindolyl 1-H_2^{min} or isoindolyl 3-H_2^{min} and isoindolyl 1,3-H_2); δ_C (125 MHz, $CDCl_3$): 172.7 (C-2^{min}), 167.3 (C-2^{maj}), 153.4 (napthanenyl C-1^{min}), 152.1 (napthanenyl C-1^{maj}), 146.1 (phenyl C-4^{min}), 143.4 (phenyl C-4^{maj}), 136.1 (napthanenyl C-4^{maj}), 135.6 (napthanenyl C-4^{min}), 135.00 (isoindolyl C_A-3a,7a^{maj}), 134.96 (isoindolyl C_A-3a,7a^{min}), 134.9 (isoindolyl C_B-3a,7a^{min}), 134.8 (isoindolyl C_B-3a,7a^{maj}), 133.3 (d, *J* 25.0 Hz, phenyl C-1^{maj}), 132.0 (d, *J* 24.8 Hz, phenyl C-1^{min}), 129.2 (aryl C-H), 129.13 (aryl C-H), 129.09 (aryl C-H), 128.9 (aryl C-H), 128.7 (aryl C-H), 128.2 (aryl C-H), 128.14 (aryl C-H), 128.05 (aryl C-H), 127.8 (aryl C-H), 127.6 (aryl C-H), 127.29 (aryl C-H), 127.27 (aryl C-H), 127.1 (aryl C-H), 126.3 (aryl C-H), 125.9 (aryl C-H), 125.8 (aryl C-H), 125.4 (aryl C_q), 123.3 (aryl C-H), 123.2 (aryl C-H), 122.9 (aryl C-H), 122.8 (aryl C-H), 122.7 (aryl C-H), 122.5 (aryl C-H), 121.4 (aryl C-H), 120.3 (aryl C-H), 114.5 (aryl C_q), 106.5 (napthanenyl C-2^{maj}), 80.1 (C-1^{maj}), 55.2 (C-1^{min}), 53.9 (isoindolyl C_A-1,3^{min}), 53.8 (isoindolyl C_A-1,3^{maj}), 53.2 (isoindolyl C_B-1,3^{maj}), 51.9 (isoindolyl C_B-1,3^{min}); δ_F (470 MHz, $CDCl_3$): 66.14 (SO_2F^{min}), 66.13 (SO_2F^{maj}); HRMS found MH^+ 462.1167. $C_{26}H_{20}FNO_4S$ requires *MH*, 462.1170. Full assignment of ^{13}C NMR not possible due to complexity of the NMR spectra.

4-[1-(5-methoxy-1*H*-indol-3-yl)-2-(morpholin-4-yl)-2-oxoethyl]benzene-1-sulfonyl fluoride (224)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D1** (100 mM), co-substrate **Co-15** (500 mM) and $Rh_2(piv)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 35:65 → 60:40 → 95:5 MeCN–H_2O to give the *indole derivative* ***224*** (0.50 mg, 6%) as a colourless oil. R_f 0.09 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3325, 2923, 2856, 1640, 1485, 1439, 1409, 1212, 1115, 1033; δ_H (500 MHz, $CDCl_3$): 8.88 (1H, br. s, NH), 7.94 (2H, d, *J* 8.5 Hz, aryl 2,6-H), 7.51 (2H, d, *J* 8.5 Hz, aryl 3,5-H), 7.24 (1H, d, *J* 8.8 Hz, indolyl 7-H), 7.03 (1H, d, *J* 2.4 Hz, indolyl 4-H), 6.86 (1H, dd, *J* 8.8 and 2.4 Hz, indolyl 6-H), 6.37 (1H, d, *J* 1.8 Hz, indolyl 2-H), 5.53 (1H, s, 1-H), 3.84 (3H, s, OMe), 3.81-5.51 (8H, m, morpholinyl 2,6-H_2 and morpholinyl 3,5-H_2); δ_C (125 MHz, $CDCl_3$): 168.9 (C-2), 154.7 (indolyl C-5), 147.1 (aryl C-4), 133.8 (indolyl C-3a), 132.2 (d, *J* 24.9 Hz, aryl C-1), 131.8 (indolyl C-7a), 129.5 (aryl C_2-3,5), 129.1 (aryl C_2-2,6), 128.4 (indolyl C-3), 113.0 (indolyl C-6), 112.2 (indolyl C-7), 102.6 (indolyl C-2), 102.3 (indolyl C-4), 66.9 (morpholinyl C_A-2,6), 66.7 (morpholinyl C_B-2,6), 56.0 (OMe), 47.1 (morpholinyl C_A-3,5), 47.0 (C-1), 42.9 (morpholinyl C_B-3,5); δ_F (470 MHz, $CDCl_3$): 66.2 (SO_2F); HRMS found MH^+ 433.1223. $C_{21}H_{21}FN_2O_5S$ requires *MH*, 433.1228.

4-[1-(5-methoxy-1*H*-indol-1-yl)-2-(morpholin-4-yl)-2-oxoethyl]benzene-1-sulfonyl fluoride (225)



Prepared according to General procedure W – implementation of reaction array, diazo substrate **D1** (100 mM), co-substrate **Co-15** (500 mM) and $Rh_2(piv)_4$ (1 mM) gave a crude material. This was then purified *via* preparative HPLC eluting with gradient elution: 5:95 → 35:65 → 60:40 → 95:5 MeCN–H_2O to give the *indole derivative* ***225*** (0.70 mg, 8%) as a colourless oil. R_f 0.14 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 2925,

2857, 1655, 1576, 1479, 1411, 1242, 1213, 1115, 1033; δ_H (500 MHz, $CDCl_3$): 7.94 (2H, d, *J* 8.5 Hz, aryl 2,6-H), 7.25 (2H, d, *J* 8.5 Hz, aryl 3,5-H), 7.17 (1H, d, *J* 3.3 Hz, indolyl 2-H), 7.14 (1H, d, *J* 2.4 Hz, indolyl 4-H), 7.07 (1H, d, *J* 8.9 Hz, indolyl 7-H), 6.89 (1H, dd, *J* 8.9 and 2.4 Hz, indolyl 6-H), 6.61 (1H, dd, *J* 3.3 and 0.7 Hz, indolyl 3-H), 6.36 (1H, s, 1-H), 3.92-3.86 (1H, m, morpholinyl 3-H_A or morpholinyl 5-H_A), 3.85 (3H, s, OMe), 3.75 (1H, ddd, *J* 10.9, 5.5 and 2.8 Hz, morpholinyl 2-H_A or morpholinyl 6-H_A), 3.65-3.54 (2H, m, morpholinyl 3-H_B or morpholinyl 5-H_B and morpholinyl 2-H_B or morpholinyl 6-H_B), 3.49 (1H, ddd, *J* 11.6, 5.5 and 3.1 Hz, morpholinyl 2-H_A or morpholinyl 6-H_A), 3.38 (1H, ddd, *J* 13.1, 7.6 and 3.1 Hz, morpholinyl 3-H_A or morpholinyl 5-H_A), 3.22 (1H, ddd, *J* 13.1, 5.5 and 3.1 Hz, morpholinyl 3-H_B or morpholinyl 5-H_B), 3.19-3.13 (1H, m, 2-H_B or morpholinyl 6-H_B); δ_C (125 MHz, $CDCl_3$): 165.7 (C-2), 155.1 (indolyl C-5), 145.2 (aryl C-4), 132.9 (d, *J* 24.9 Hz, aryl C-1), 130.7 (indolyl C-7a), 129.7 (indolyl C-3a), 128.9 (aryl C_2-2,6), 128.8 (aryl C_2-3,5), 126.7 (indolyl C-2), 113.3 (indolyl C-6), 109.7 (indolyl C-7), 104.0 (indolyl C-3), 103.5 (indolyl C-4), 66.8 (morpholinyl C_A-2,6), 66.3 (morpholinyl C_B-2,6), 60.1 (C-1), 55.9 (OMe), 46.4 (morpholinyl C_A-3,5), 43.3 (morpholinyl C_B-3,5); δ_F (470 MHz, $CDCl_3$): 66.1 (SO_2F); HRMS found MH^+ 433.1226. $C_{21}H_{21}FN_2O_5S$ requires *MH*, 433.1228.

X-Ray Structures

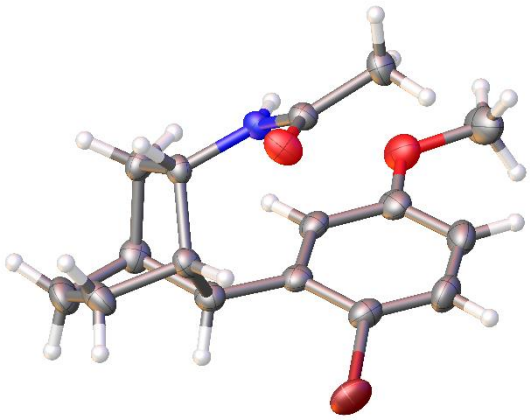


Figure 53: ORTEP diagram of compound **167b** (compound prepared through C-H arylation of *exo*-2-aminonorbornane, followed by regioselective bromination of the aryl ring).

Crystal data and structure refinement for compound 167b	
Empirical formula	$C_{16}H_{20}BrNO_2$
Formula Weight	338.24
Temperature/K	119.99(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	10.2301(7)
b/Å	9.3195(5)
c/Å	16.4452(9)
α/°	90
β/°	102.715(6)
γ/°	90
Volume/Å^3	1529.43(16)
Z	4
ρ_{calc}g/cm^3	1.469
μ/mm^{-1}	3.670
F(000)	696.0
Crystal size/mm^3	0.12 × 0.08 × 0.04
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.35 to 147.158
Index ranges	-12 ≤ h ≤ 12, -11 ≤ k ≤ 10, -20 ≤ l ≤ 18
Reflections collected	6578
Independent reflections	2889 [R_{int} = 0.0345, R_{sigma} = 0.0399]
Data/restraints/parameters	2889/0/196
Goodness-of-fit on F^2	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0393, wR_2 = 0.0935
Final R indexes [all data]	R_1 = 0.0484, wR_2 = 0.0994
Largest diff. peak/hole / e Å^{-3}	0.47/-0.45

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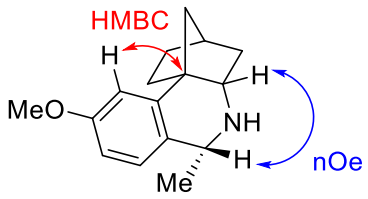
7.1 Key 2D NMR spectra



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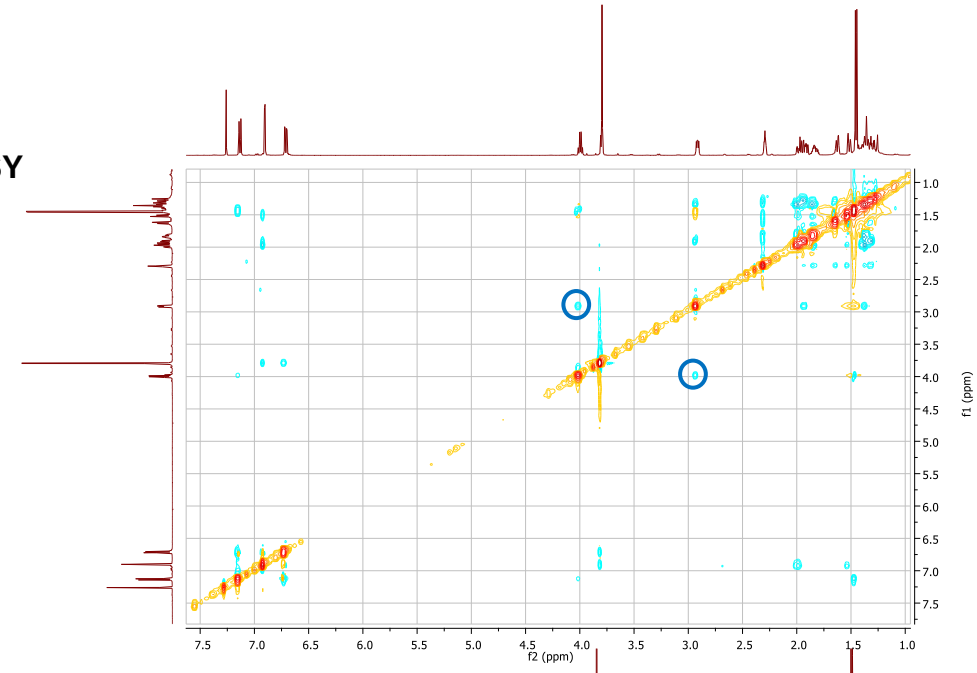

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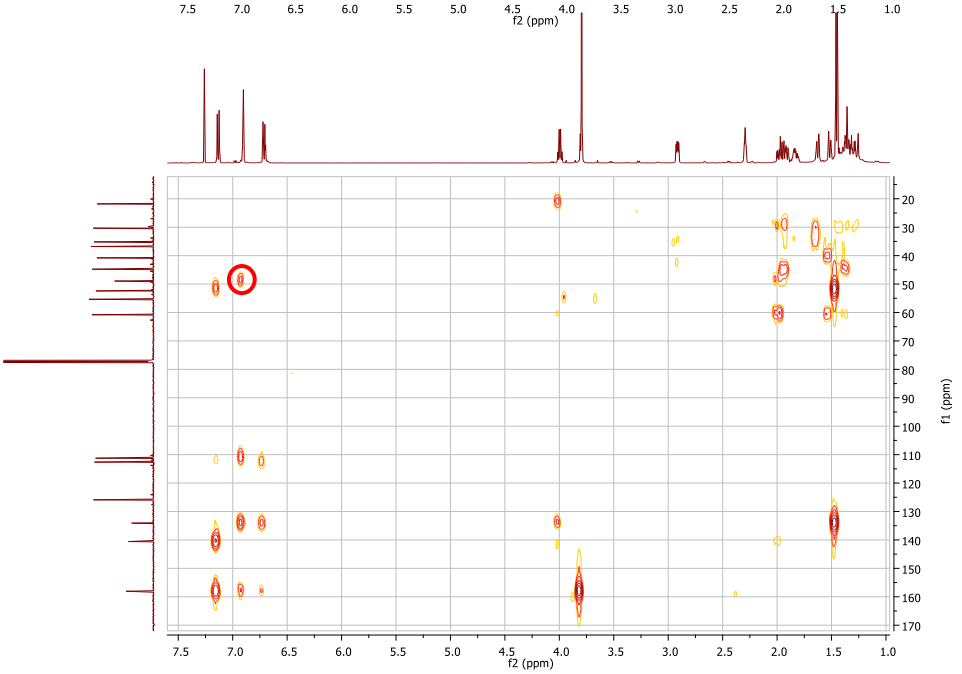

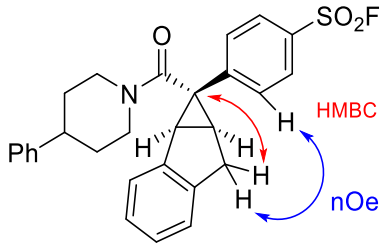

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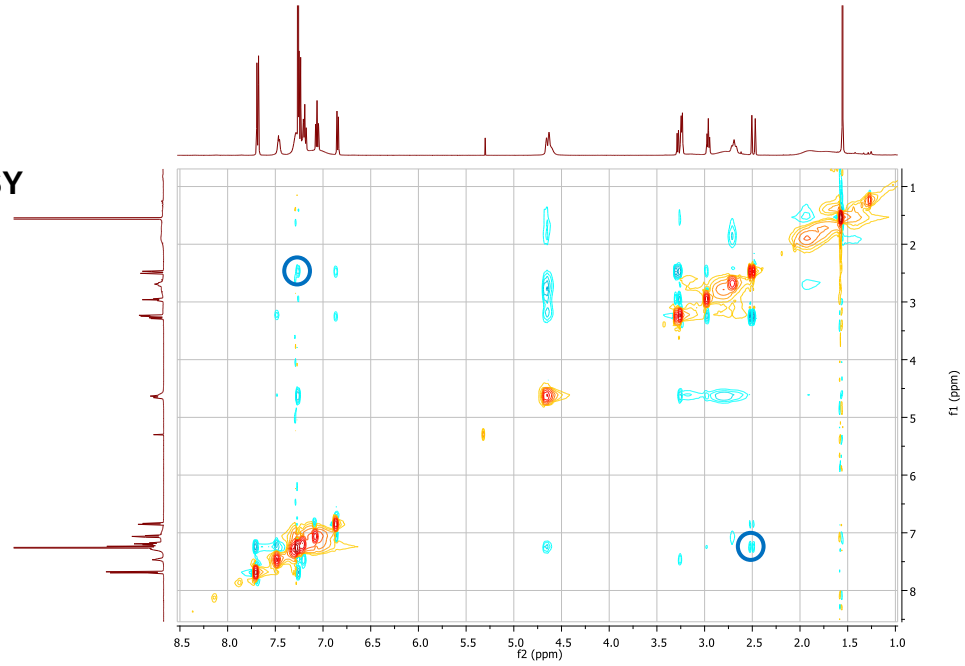

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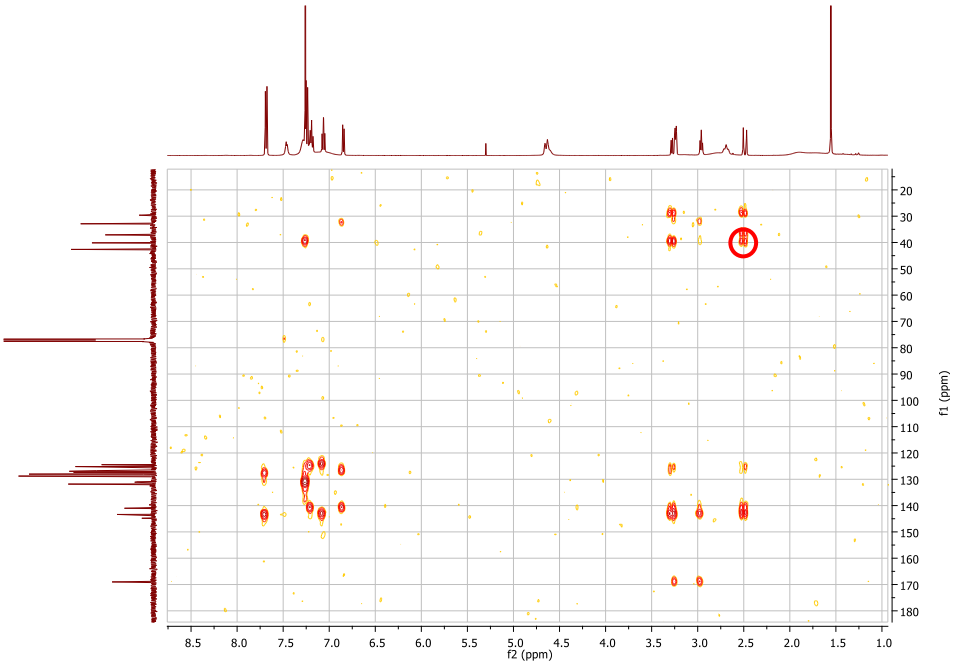

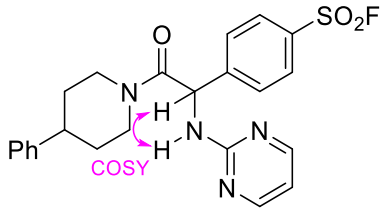

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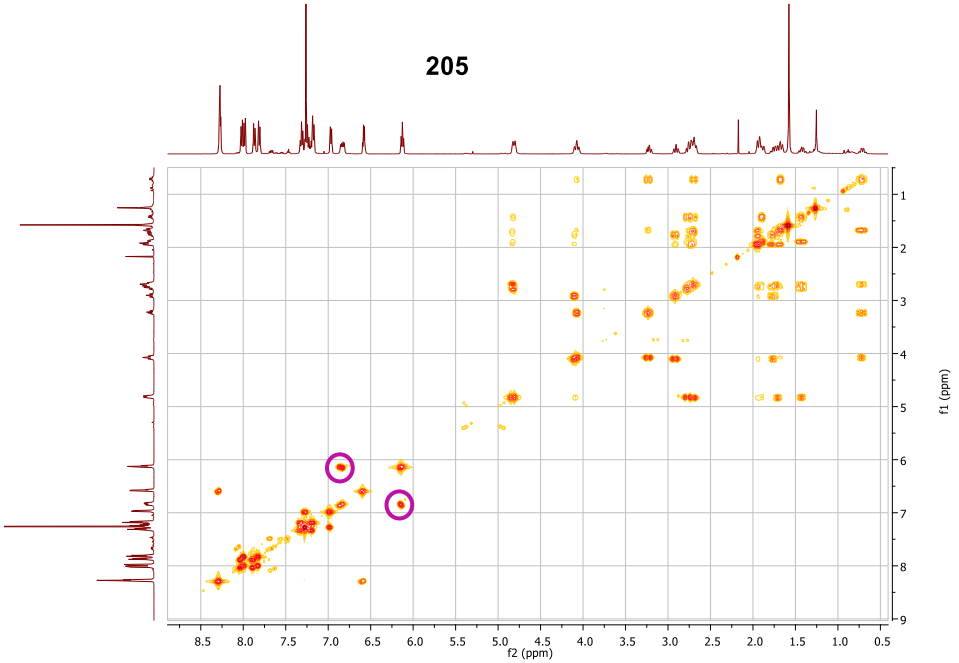

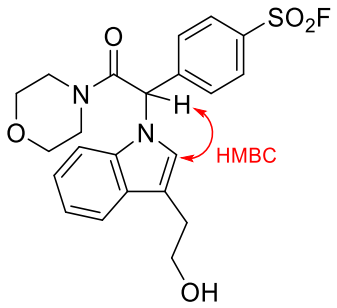

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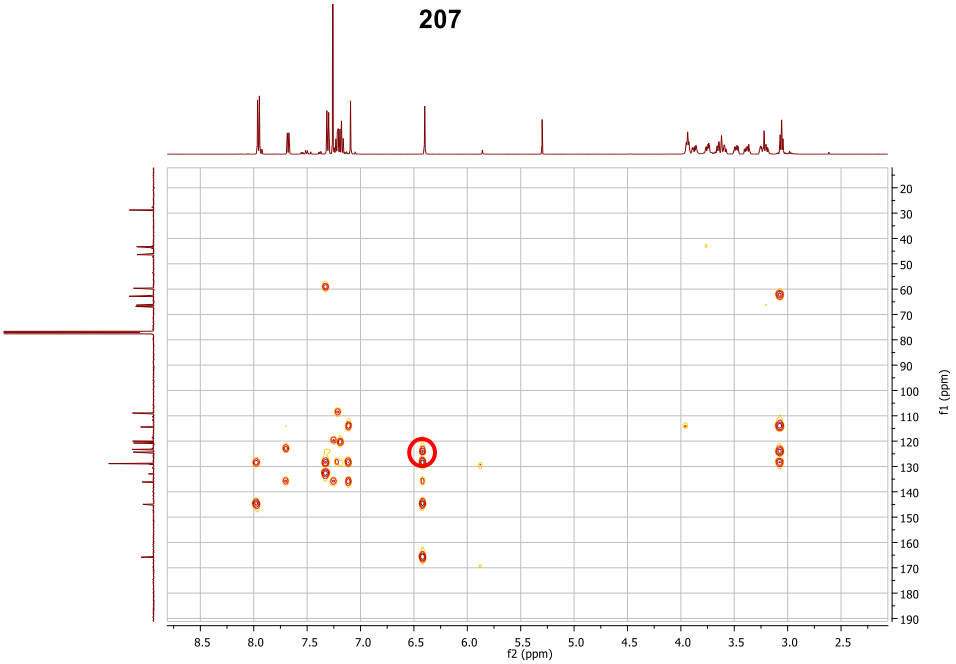

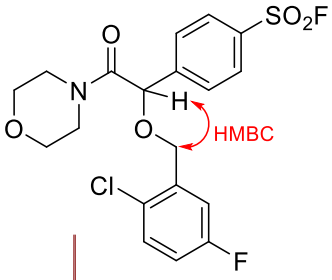

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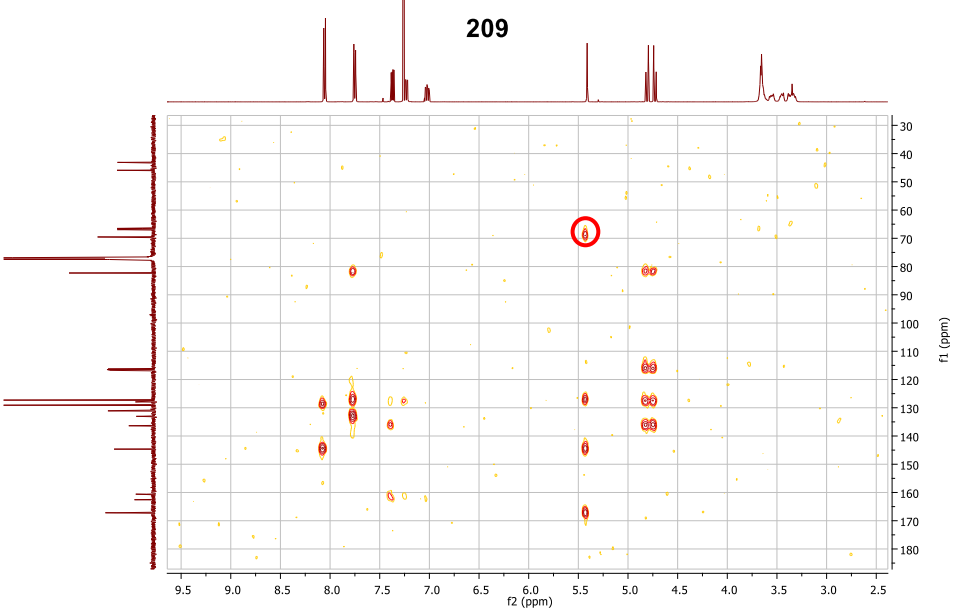

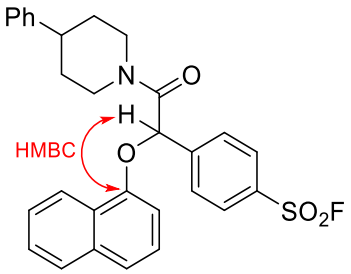

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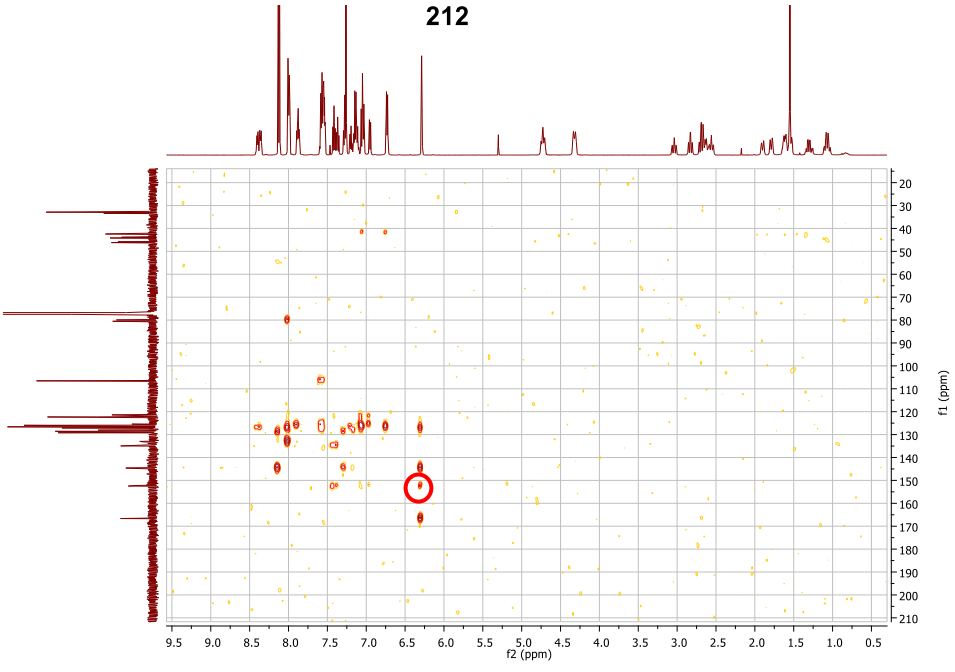

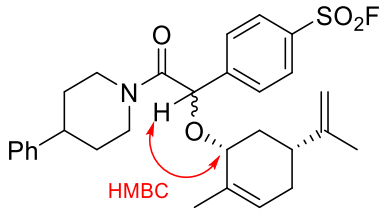

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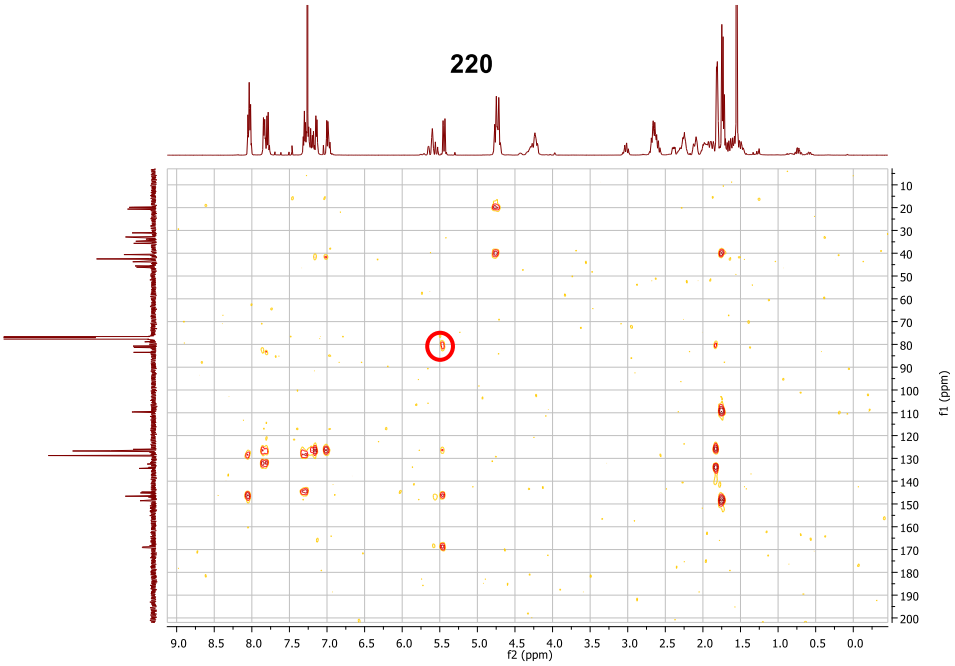

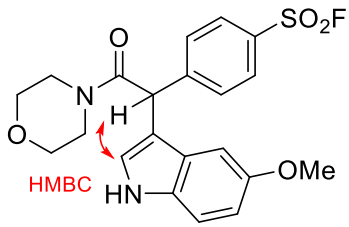

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