UNIVERSITY OF BIRMINGHAM

Developing Ynamide-based Transformations for Potential Use in Scaffold Synthesis

by

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Abstract

The nitrogen-heterocyclic motif is an ever-growing source of interest for medicinal and pharmaceutical fields owing to its presence in numerous biologically active structures and medicinally relevant compounds. This thesis describes the development and elaboration of new methodologies suitable as preparative tools to access structurally diverse building blocks containing nitrogen heterocyclic motifs as potential bioactive motifs. The synthesis of complex ynamides and their combination with transition metal catalysts (cobalt, copper, gold) are explored as starting points in the synthesis of highly functionalised azacyclic systems.

This research work discusses the exploration of a cobalt-catalysed polycyclisation sequence that offers rapid access to a range of novel bicyclic aza-cycles from easily prepared ynamides and *N*-(pivaloyloxy)amides. The substrate scope and limitations of this new method are described as well as its efficiency and robustness. This polycyclisation process shows functional group compatibility across a range of ynamides and *N*-(pivaloyloxy)amides catalysis precursors through a range of diverse sulfonyl groups and heteroaryl substituents. Post-catalytic transformations deliver new opportunities for diversification on this framework.

A complementary synthetic route was discovered allowing the construction of two structurally unique scaffolds comprising of nitrogen containing heterocycles from related starting materials through selection of a suitable transition metal catalyst (copper or gold). Post-catalytic transformations are explored on these scaffolds, detailing the difficulties encountered due to the complex/reactive nature of these inherent functionality contained within the polycycles.

Acknowledgements

I would like to thank my supervisor Dr. Paul Davies for giving me the opportunity to join his research group and for his strong support throughout my PhD. I am very pleased and proud to have worked within the Davies group for my last years of study.

I would like to acknowledge and thank all of the staff in the analytical services team for their excellent work over the years.

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Most importantly, I would like to thank my family for their endless help, support and encouragement. I could not have done this work without their precious support.

Contents

List of Abbreviations

Å	Ångström(s)
Ac	acetyl
Ar	aryl
ASAP	atmospheric solids analysis probe
aq.	aqueous
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
C	Celsius
Calcd	calculated
Cbz	carboxybenzyl
COSY	correlation spectroscopy
Cp*	pentamethylcyclopentadienyl
d.r.	diastereomeric ratio
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DMAP	dimethylaminopyridine
DME	dimethoxyethane
DMED	*N,N*-dimethylethylamine
DMSO	dimethylsulfoxide
eq.	equivalent(s)
EI	electron impact
ES	electrospray

Et	ethyl
EWG	electron-withdrawing group
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
i	*iso*
IR	infrared
J	coupling constant
K	Kelvin
L	Litre
LA	Lewis acid
M	molar
mp	melting point
m/z	mass/charge
Me	methyl
min	minutes
mol	moles
Ms	methanesulfonyl
MS	molecular sieves
MW	molecular weight
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide

NMR	nuclear magnetic resonance
Ns	4-nitrobenzenesulfonyl
Nu	nucleophile
PG	protecting group
Ph	phenyl
Pic	Pyridinecarboxylato
PMP	*para*-methoxyphenyl
PNBSA	*para*-nitrobenzenesulfonic acid
ppm	parts per million
Pr	propyl
r.t.	room temperature
RO5	rules-of-five
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
TLC	thin layer chromatography
TM	transition metal
TMS	trimethylsilyl
TOF	time of flight
Ts	4-methylbenzenesulfonyl
UV	ultraviolet
ν	wavenumber
XRD	X-Ray diffraction

Chapter 1: Synthesis and diversification of novel *N*-heterocyclic frameworks from transition metal catalysed reactions of ynamides

1.1 Introduction to *N*-heterocycles

Nitrogen containing heterocycles represent the largest and the most varied family of organic compounds.[1-4] They are found in various natural products, biologically active structures and medicinally relevant compounds.[1, 3-5] *N*-Heterocycles are commonly involved in physiological processes in the human body and are biosynthesised by plants and animals; consequently, many pharmaceutical compounds which mimic the biological activity of natural products contain an *N*-heterocyclic moiety.[6] As such, the development of increasingly efficient synthetic methodologies toward *N*-heterocyclic core structures constitutes a major focus in modern synthetic chemistry research.[7-11]

Many bioactive *N*-heterocycles are extracted from natural sources, with the number of isolated compounds continually increasing owing to their medicinal use.[10] For example, natural products containing a quinoline, isoquinoline, indole or benzothiazole moiety have displayed desirable pharmacological behaviour, including: antioxidant, antifungal, antibacterial and anticancer activity.[12-18] Piperidines and pyridines are the most widely found azacycles in FDA approved drugs.[19-20] Shown below are some examples of drug and natural product molecules with *N*-heterocyclic motifs relevant to this work (Figure 1).[21-25]

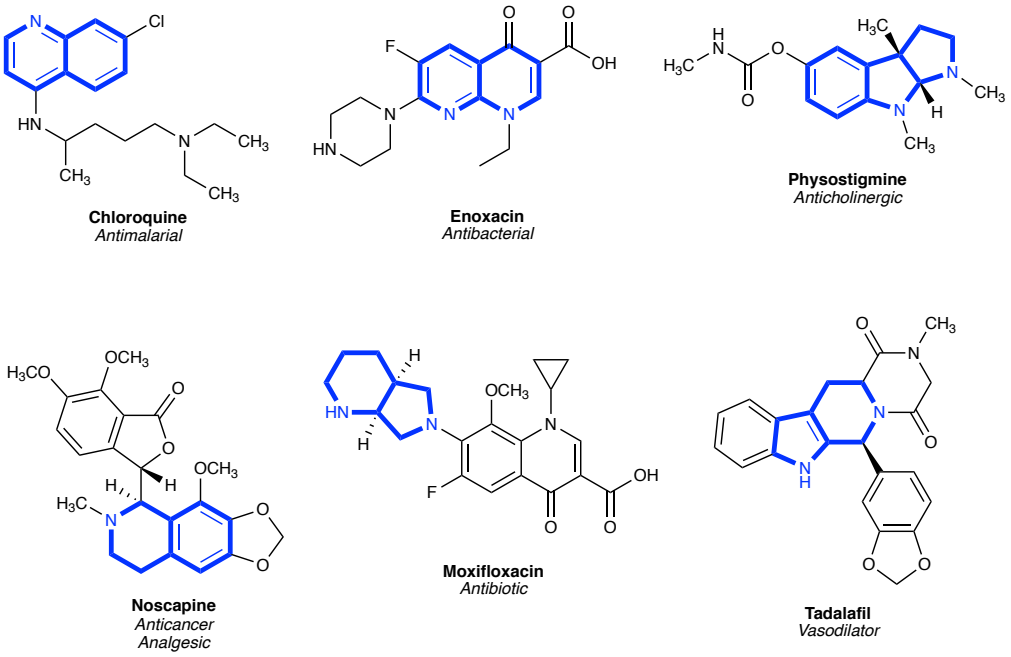


Figure 1: Examples of drugs and natural product alkaloids containing *N*-heterocyclic core.

1.2 Molecular design in drug discovery and LLAMA library

1.2.1 Molecular properties of lead-like scaffolds

Straightforward access to potential new drug candidates is still a challenge for synthetic chemistry.[26-28] Lead-oriented synthesis is a new concept allowing the effective preparation of small molecules as a starting point for drug discovery process.[29] This approach has shown considerable advances with the preparation and exploration of diverse molecular architectures and novel chemical space,[26-27] using nature as a source of inspiration.[30] When analysing marketed drugs and bioactive natural products, there were clear trends for the type of functionality, 3D structure and properties identified from the pool of these small molecules. Thus, researchers have worked on trying to describe the parameters that can lead to successful drug candidates.[31-32]

In drug design, molecular properties are crucial in predicting the success of the progression of a lead molecule into clinical trials. Lipinski's rule-of-five outlines what have been generally considered as desirable parameters for oral bioavailability of drugs.[27, 33] This includes

hydrogen-bonding parameters (no more than 5-H bond donors and not more than 10-H bond acceptors), molecular weight (under 500 g/mol), lipophilicity (an octanol-water partition coefficient logP not greater than 5).[26-27] These rules are often followed consciously by researchers during drug design processes to maximise chance of success.[31, 34-36] For instance if two or more properties are not respected by molecules in the Lipinski rules, highlights possible bioavailability issues that these molecules can encounter during trials. Likewise, bioavailability is a really important parameter to consider showing how easily a substance can be absorbed by the body *ie.* the time for the drug to have an action on the desired area in the body. Even if a drug molecule has high activity, if it has low bioavailability it may never reach its target.[26, 33]

Medicinal chemists also use the term "molecular obesity" to describe molecules which are too heavy and lipophilic to be good candidates in drug design.[37] They have created measures such as ligand efficiency measures LE (Ligand Efficiency) and LLE (lipophilic Ligand Efficiency) to identify and quantify the molecular properties of fragments required to gain binding affinity to a drug target.[38] Thus, lead compounds do respect certain stringent criteria such as a smaller number of rings and molecular weight, less rotatable bonds and higher hydrophilicity to observe their successfully progression in the drug development stages.[26, 29]

1.2.2. Drug development process

Drug development is a long process which can take up to 15 years from discovery to new pharmaceutical entities to the market.[39] Nowadays, the successful development of new drugs is more challenging for scientists despite the enhancement in medicinal knowledges and new technologies.[40-41] The growing need from patients for effective medicines to many different diseases, the requirements for innovative drugs rather than derivatives and the higher safety standards for drugs allowed on the market, make this process more challenging.[40-41]

Drug discovery is composed of several stages (Figure 2).[39] The first steps are crucial for future research with the choice on the disease to investigate, and the identification and validation of the druggable targets.[39] Thereafter the exploratory research starts with a screening to identify HIT molecules *ie.* molecules with a promising affinity to the target, and to select a molecule which react specifically to the target. The lead compound selected is optimised into a library of potential drug candidates.[39]

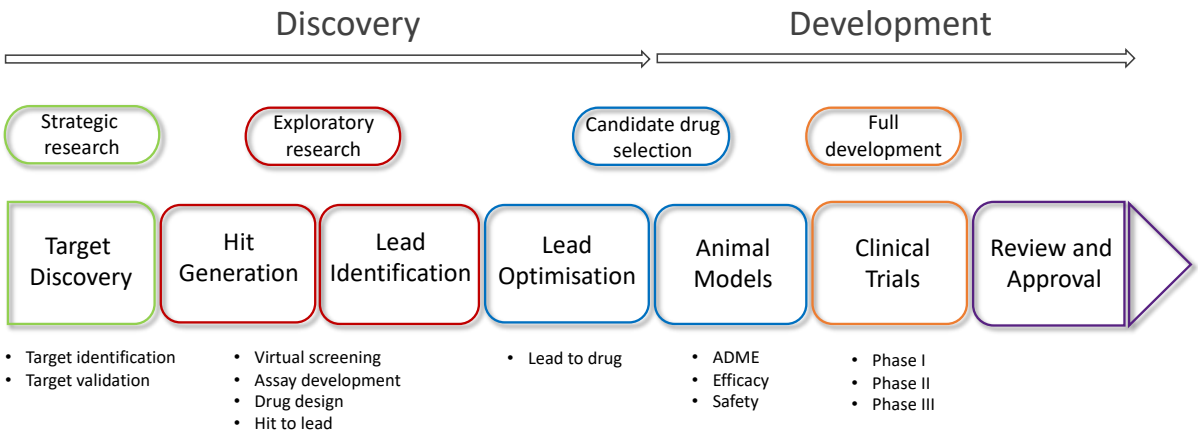


Figure 2: Drug discovery and development stages from the target discovery to the approval on the launch drug market.

When a drug candidate shows promising results during the screening, it directly advances into pre-clinical testing.[39] At this stage, the efficiency and safety are tested as well as biological parameters named ADME (absorption, distribution, metabolism and excretion) on microorganisms and animals.[39] The drug candidate fulfilling all regulatory compliances can continue through to the clinical trials on humans. This stage is the first trial on human body and the last step before the approval by authorities and the launch of the product.[39] The clinical trials are organised in three phases and in each phase the scale of the study increases. Drug candidates can fail at any of these phases and not reach the market. Phase I is a test on the safety of the compounds, the effects of the drug in the human body (ADME) and the correct dosage.[39] Phase II gives clear information about the effectiveness of the future drug. Only one-third of entities passed the phase I and II studies with success and are considered as drugs. Phase III provides a more exhaustive understanding on the effectiveness of the treatment it was

developed for, therapeutic benefits and possible side-effects.[39] After a final approval from the relevant regulatory authority, the successful drug is ready to be launched into the market. Despite the drug being accessible to the population, trials and monitoring are still required. This process is named post-marketing safety surveillance.[39]

1.2.3. Design of new fragments using LLAMA

Nowadays high-quality tools are available to identify and calculate the predicted molecular properties of the desired scaffolds with medicinally-relevant chemical reactions associated. LLAMA (Lead-Likeness And Molecular Analysis)[42] is useful for visualising the predicted chemical properties of the virtual libraries generated by assessing their compliance with Lipinski's rules and other important drug design metrics (such as AlogP, heavy atom count, aromatic ring count and undesirable functional groups) and representing them as lead-likeness penalties.[42] These penalties are plotted between molecular weight and ALogP and indicate how close the lead compound is with respect to lead-like space. The smallest number of penalty points have greater flexibility and influence on the probability of successful progression to the drug-target.

1.3 Ynamides and transition metals to build molecular complexity

Alkynes are important and versatile compounds in organic chemistry and when connected to a nitrogen atom form a new subgroup of alkynes called ynamines and ynamides (Figure 3).[43-44] The incorporation of a nitrogen atom modulates the electronic properties and reactivity of alkynes and making them attractive species for the construction of versatile building blocks.[43-44] Over the last twenty years, ynamines and ynamides generated increasing interest within the synthetic community because of their potential to create new reactive functionalities.[43-44]

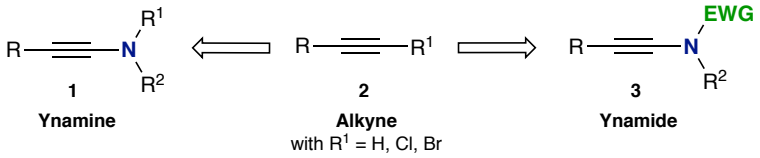
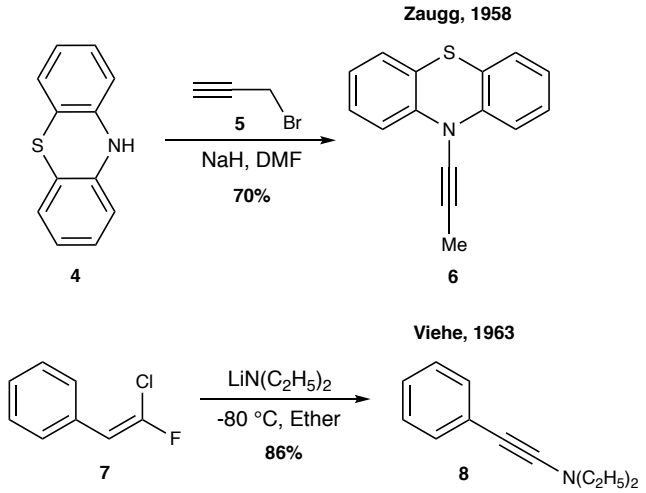


Figure 3: General model of ynamine and ynamide.

1.3.1 Ynamines and their reactivity

Ynamines were first prepared by Bode in 1892[43] and the structure was confirmed by characterisation by Zaugg[45] in 1958 (Scheme 1). However, it was in the 1960's when significant advances were made when Viehe[43, 46-47] and Ficini[43, 48] pioneered the first feasible synthesis of ynamines (Scheme 1). In the late 1960's, Viehe continued his studies developing diverse routes for the preparation of ynamines and investigating their practical applications,[47] whereas Ficini based her research on the study of their reactivity.[48]



Scheme 1: First preparations of ynamines by Zaugg and Viehe.

Organic chemists recognised the great potential of ynamines for their ability to polarise carbon-carbon triple bonds. Delocalisation of the lone pair of electrons from the nitrogen atom means that one carbon of the alkyne is nucleophilic and the other becomes electrophilic.[43, 47-50] Compared to other heteroatoms nitrogen strongly polarises the triple bond, giving a more pronounced nucleophilic character than their oxygen analogues.[43, 47-50] The reactivity of ynamines is essentially determined by the substituents on the nitrogen atom. Whilst the

polarisation of the triple bond is responsible for the strong reactivity of ynamines, it also renders them unstable in some cases which dramatically hampered the development of ynamine chemistry.[43, 51] Ynamines are particularly sensitive to water, thus the general handling and purification can often be difficult.[43, 48] The hydration of ynamines is thought to occur through a keteniminium intermediate and affords amides. Nevertheless, this stability issue can be solved by straightforward modification of the ynamine backbone.[43]

1.3.2 Emergence of ynamides

The stability of ynamines was improved by functionalisation of the nitrogen atom with an electron-withdrawing group such as CF_3, imidazole or benzotriazole.[44, 52-55] The electron-deficient alternative to ynamines were classified as ynamides. The simple modification revived interest in this chemistry in recent years.[43-44] The incorporation of the electron-withdrawing group on the nitrogen tempered the reactivity of the ynamides, allowing thermal stability and straightforward handling.[43, 56] Ynamides provide a balance between reactivity and stability which permit them to be employed in a range of regioselective and intra-intermolecular reactions (Figure 4).[43, 56]

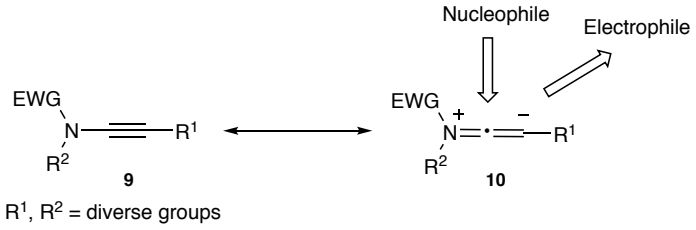


Figure 4: Reactivity of ynamides.

Nowadays ynamides are firmly established in the efficient construction of versatile nitrogen-containing building blocks in organic chemistry.[10, 44, 56-57] In the case of a carbonyl group attached onto the nitrogen atom, the donating ability of the nitrogen lone pair to the triple bond is strongly decreased as the electrons can be delocalised into the π-system of the carbonyl.[44, 57]

Ynamides also give regiocontrol during gold-catalysed reactions with coordination of the gold species to the triple bond giving rise to an electrophilic alkyne terminal and a nucleophilic alkyne terminal (Figure 5).[58-59] This mode of reactivity of ynamides has been extensively utilised by a number of research groups for reaction discovery.[44, 59-62]

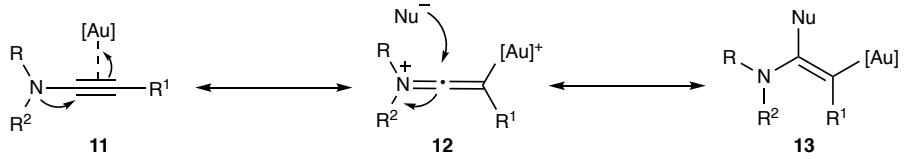
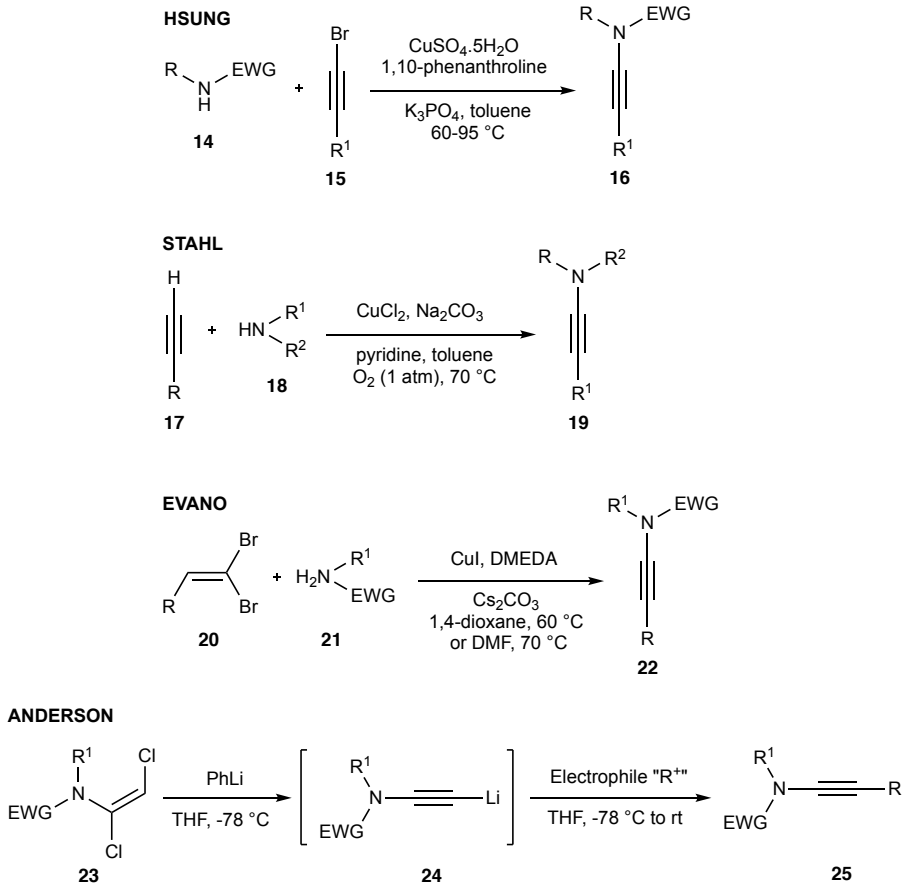


Figure 5: Regiocontrol of ynamides during gold catalysis.

1.3.3 Preparations of ynamides

Ynamides have attracted the attention of the organic synthetic community since several straightforward and efficient new methods for their preparation have been developed. Their preparation has evolved considerably over the last few decades. Ynamides are synthesised mainly through copper-mediated cross-coupling reactions, with diverse functional group tolerance and under various conditions. The following efficient methods have been developed recently for ynamide preparation include Hsung in 2004,[63] Stahl in 2008,[64] Evano in 2009[56] and Anderson in 2015[65] (Scheme 2).

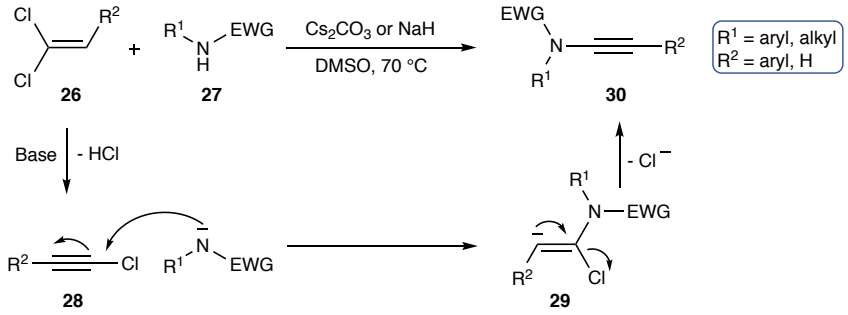


Scheme 2: Main routes developed recently to access straightforwardly to ynamides.

The research of Hsung involves the synthesis of ynamides **16** from a copper (I) catalyzed cross coupling reaction between amides **14** and alkynyl bromides **15**.[63] In Stahl's method, terminal alkynes **17** and nitrogen nucleophiles **18** are used in presence of a copper (II) catalyst under 1 atm of O_2 to obtain the desired functionalised ynamide **19**.[64] Evano's method uses the same type of catalyst and nitrogen nucleophiles with 1,1-dibromo-1-alkenes **20**, with Cs_2CO_3 as base in 1,4-dioxane provides moderate to excellent yields for the desired ynamide **22**.[56] Anderson's method is the most recent with a different approach using 1,2-dichloroenamide **23** and phenyllithium (or *n*BuLi) to generate intermediate lithium acetylide **24**.[65] Following trapping of lithium species with an electrophile such as methyl, phenyl and ester afford the substituted ynamides **25**.[65] To prevent side-reactions, additions of electrophiles are controlled at -78°C.

Another way to synthesise ynamides **30** was described by Zhao and co-workers in 2018,[66] with a one-step procedure involving vinyl dichlorides **26** and electron deficient amides **27** as starting

materials. The reaction proceeds under mild conditions and in the absence of a transition metal catalyst, with yields up to 98% (Scheme 3).

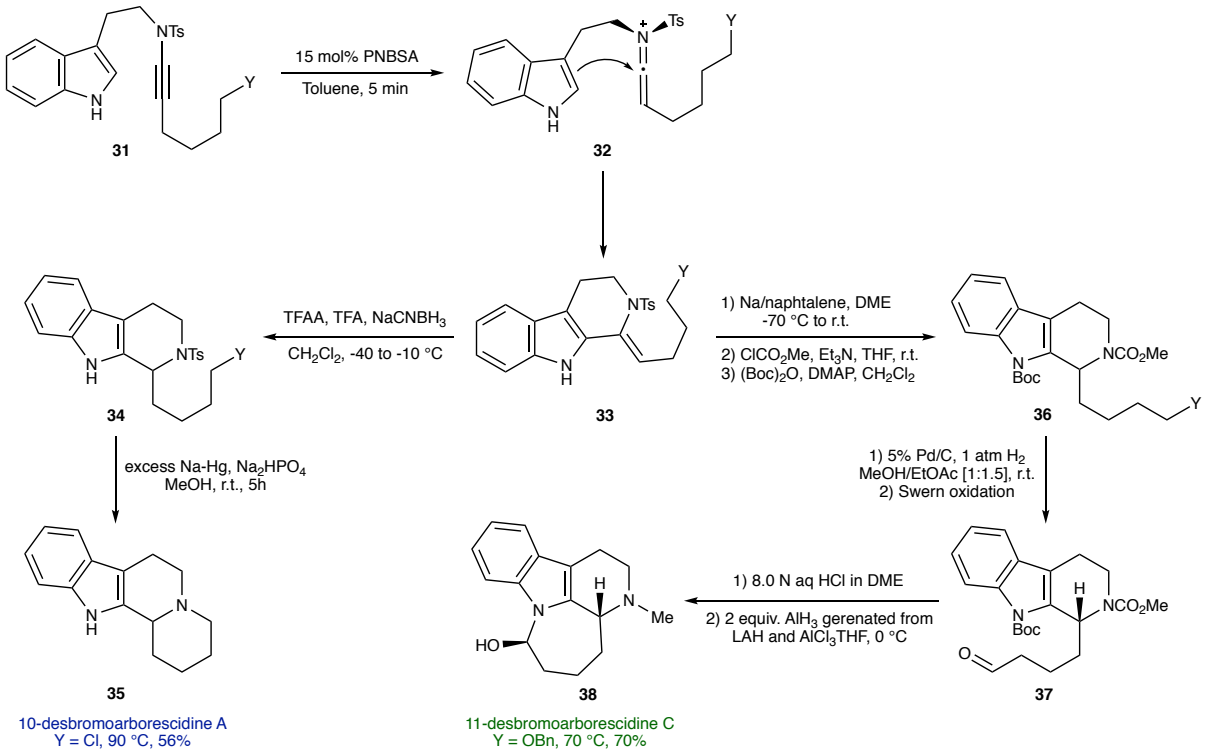


Scheme 3: Recent advance to synthesis ynamides without transition metal catalyst.

These newly developed methods highlight the rapid progress made for the efficient synthesis of diverse ynamides. This important step by the scientific community for their preparation has had a considerable impact on the use of ynamides in organic chemistry and more widely in the construction of versatile and powerful *N*-heterocycles, with potential biological activities.

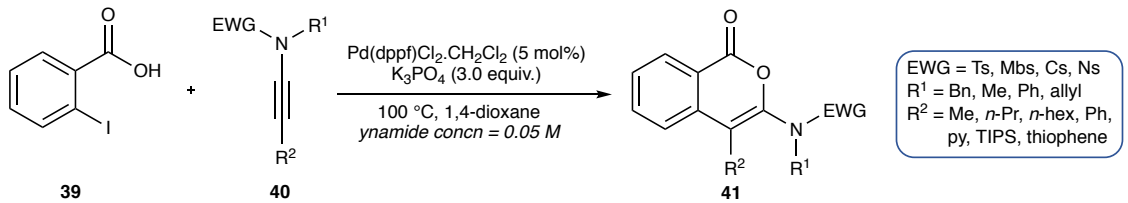
1.3.4 Recent developments using ynamides

Ynamides are very attractive nitrogen-substituted alkynes and have proven to be efficient and versatile building blocks in organic synthesis, offering access to a range of novel complex structural entities and that these can be expanded into pharmaceutical field. Hsung was the first to employ ynamides in the total synthesis of 10-desbromoarborescidine A **35** and 11-desbromoarborescidine C **38** (Scheme 4).[43] The indole tethered ynamide **31** was activated by Bronsted acid catalyst and underwent a Pictet-Spengler cyclisation through the keteniminium species **32**. The tricyclic enamide **33** was then reduced and underwent an intramolecular *N*-alkylation to provide the compound **34**. The compound **38** was obtained after 7 additional steps from **33**.



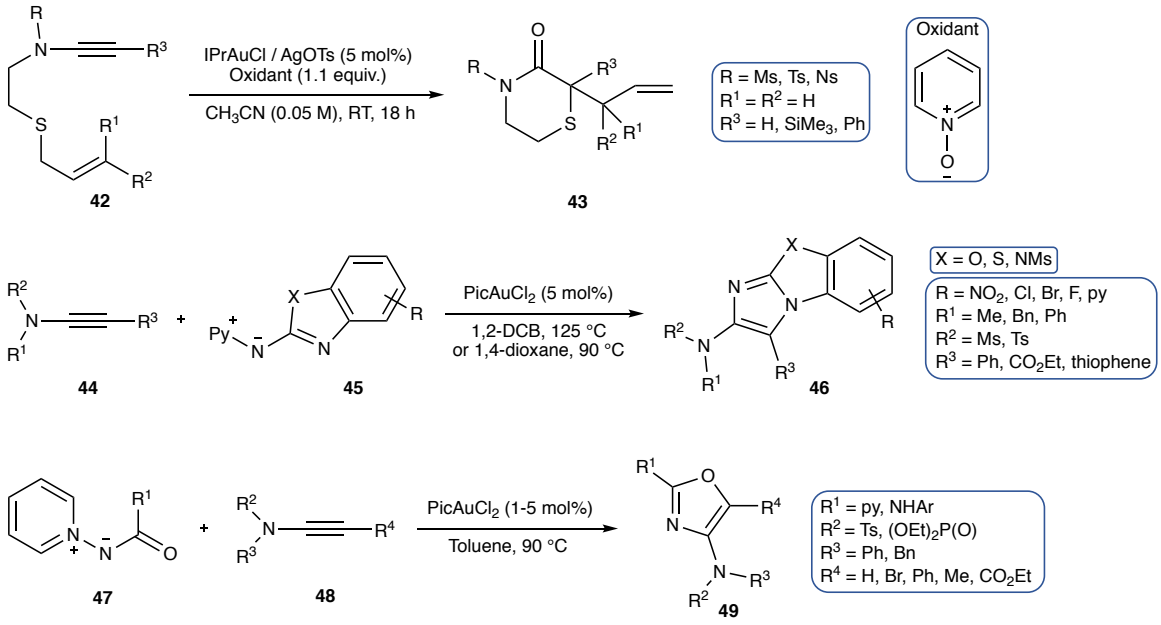
Scheme 4: First examples of synthesis of natural products from ynamides.

Isocoumarins are a structural core in numerous natural products and biologically active molecules.[67-69] The 3,4-disubstituted isocoumarin derivatives present a range of biological activities such as antifungal, antitumor, anti-microbial, anti-inflammatory and anticancer activities.[70-73] Chang[71] and co-workers described an efficient synthesis of 3,4-disubtituted isocoumarins **41** in 2016. This novel procedure allows the building of O-C and C-C bonds between 2-iodoaromatic acids **39** and ynamides **40** by a palladium catalysed annulation reaction (Scheme 5). A wide functional group tolerance was demonstrated and excellent regioselectivities obtained.



Scheme 5: Synthesis of 3,4-disubstituted isocoumarin derivatives across functionalised ynamides.

Transition metal catalysis has attracted significantly the interest of the organic and pharmaceutical fields becoming a reliable and modular tool in the syntheses of drug candidates or marketed drugs.[3, 74] Moreover, transition metal catalysis improved the development of advanced synthetic methodologies and provided new entries toward structural complex building blocks using a variety of transition metals such as Pd, Ni, Cu, Zn and Co.[7-9] The study of ynamides has been explored with a range of new functionalities and a number of transformations have been performed using transition metals.



Scheme 6: Examples of novel gold-catalysed reactions from functionalised ynamides developed the last decade in the Davies group.

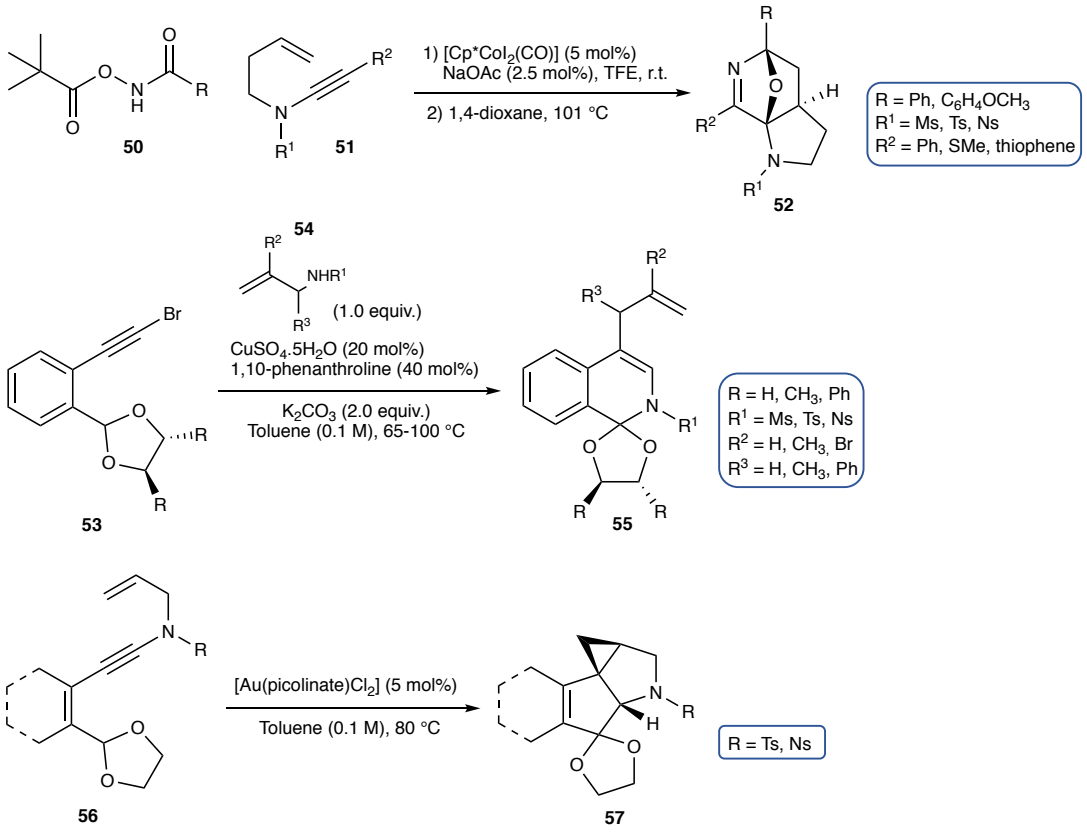
The Davies group worked on the development of several novel gold-catalyzed reactions from functionalised ynamides, which are illustrated below (Scheme 6). α-Aryl thiomorpholin-3-ones **43** were prepared from readily assembled ynamides **42** bearing tethered thioethers by a gold catalysed oxidative *N*-cyclisation cascade process under mild conditions.[75] Four new bonds and a sulfur substituted quaternary centre are generated from a triple bond during this rearrangement. The reaction was undertaken with IPrAuCl/AgOTs as an efficient catalysed and pyridine *N*-oxide as an oxidant.[75] New types of heteroatom-substituted carbimidoyl nitrenoids

46 are efficiently synthesised from robust and bench-stable *N*-(heteroaryl)-pyridinium-*N*-aminides **45** by a formal gold-catalysed [3+2]-dipolar cycloadditions across ynamides **44**.[76] A variety of functional groups are tolerated providing rapid access into functionalised scaffolds with new heteroaromatic cores **46**.[76] Another gold-catalysed intermolecular [3+2]-dipolar cycloaddition was used for the efficient and flexible synthesis of functionalised 4-aminooxazoles **49** from ynamides **48**.[77]

All these methods discovered and developed within the Davies group give potentially valuable routes to make new highly functionalised *N*-heterocycles and to generate potential future drug candidates.

1.4 Aim and objectives

The goal was to see whether the new transition metal catalysed ynamide-based methodologies would be suitable as preparative tools to access novel scaffolds containing a potential bioactive motif with reactive sites for subsequent compound library enumeration. The aim was to explore quick access to structural diversity of building blocks containing potential bioactivity and open up opportunities for further development in drug design. Three transformations based on ynamides and selected transition metal catalysts (cobalt, copper, gold) were investigated to establish the scalability and practicality of the methods in order to validate them as the possible basis for library development for drug discovery (Scheme 7). The study of the substrate scope and post-catalytic transformations would help to answer these questions.



Scheme 7: Novel catalysis reactions elaborated within the Davies group and discussed in the thesis.

In the cobalt chemistry, the ynamides **51** were combined with *N*-(pivaloyloxy) amides **50** providing complex *N*-heterocyclic scaffolds **52** in a cobalt-catalysed and Diels-Alder polycyclisation sequence. The study of substrate scope and method limitations would be examined for the key transformation elaborated with cobalt transition metal with respect to structural and functional group changes across precursors (chapter 2). In the copper catalysed, the bromoalkynes **53** combined with sulfonamides **54** formed the dihydroisoquinolines **55**, following Hsung's methodology and in elevating temperature to 100 °C. Finally, the ynamides **56** were involved in an intramolecular gold-catalysed polycyclisation cascade and provided fucntionalised tetracycles **57**. Post-catalytic transformations would be explored onto these three complex building blocks toward target molecules (chapters 2, 3 and 4).

The computational tool LLAMA was used to inform the molecular design of the novel scaffolds (Figure 6) to increase the probability of successful progression for any resulting compounds in

drug development. The potential reactive sites of the desired scaffolds (highlighted in blue) were decorated using LLAMA. In the gold and copper projects, the nitrogen was used as a starting point of the scaffold diversification and easily deprotectable groups which work in the catalysis were selected. In the cobalt projects, in addition to find nitrogen deprotectable groups, the development and the feasibility of this new method were explored by modifying the group connected to the molecule.

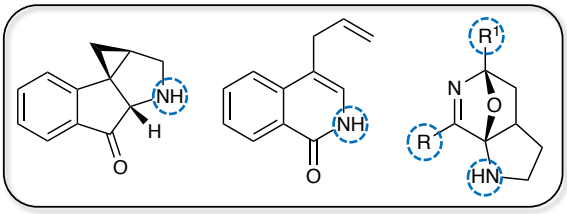


Figure 6: Novel scaffolds studied in this research project using LLAMA software.

The graphs below showed the lead-likeness and principal moment of inertia plots from studied scaffolds calculated from LLAMA software (Figure 8). Principal moments of inertia plots described the molecular shape varying from linear to flat to spherical and indicated the potential bioactivity of the decorated scaffolds from LLAMA. The penalty system tables showed the distance of decorated molecules from the ideal space (Figure 7). LLAMA analyses on selected scaffolds (Figure 8) showed encouraging outcomes with the set of singular decorations due to high molecular weight of structures. Despite this, many of decorated structures fell within the lead-like space which is highly desirable to proceed further investigations.

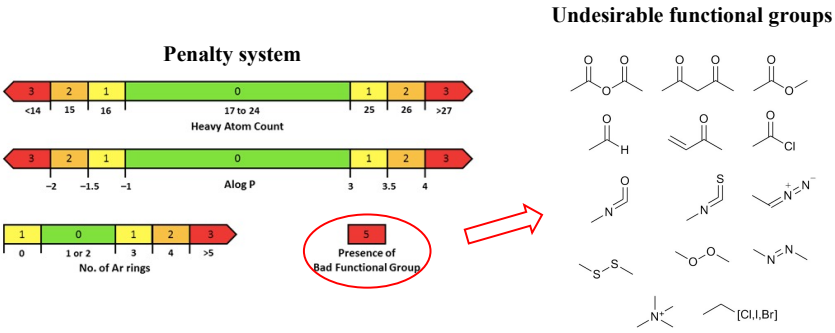


Figure 7: Penalty system tables depending on the distance of the molecules from the ideal space.

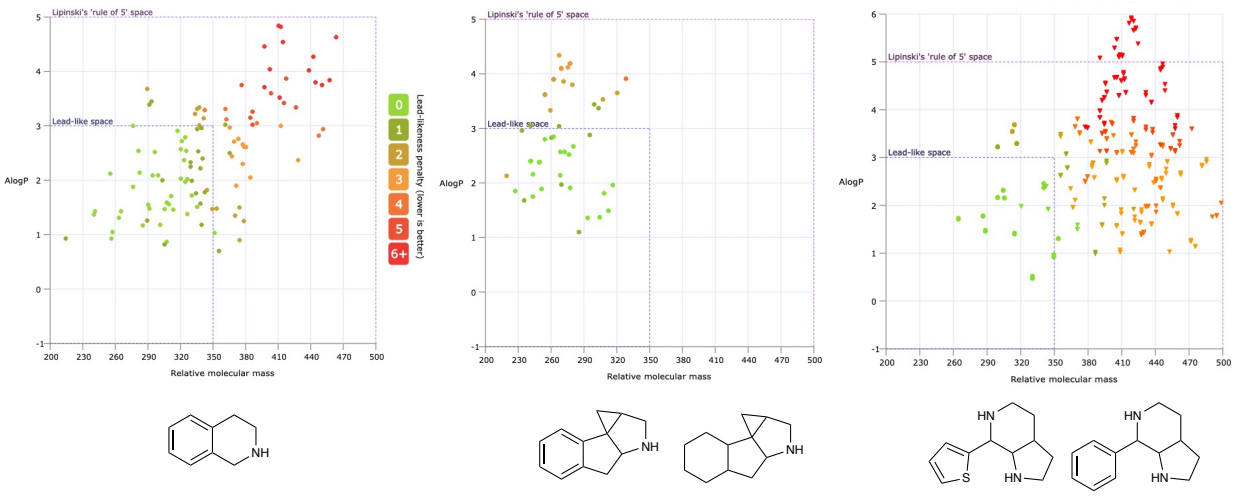


Figure 8: Lead-likeness and principal moment of inertia plots of studied scaffolds derived from LLAMA calculation.

Chapter 2: Cobalt-mediated sequence to build sp^3-rich azabicycles

2.1 Piperidine cores in drug discovery

Nature is a source of nitrogen heterocyclic structures with a very broad range of molecular diversity and architectures.[2, 78-79] One of the most frequently encountered nitrogen heterocycles are piperidines, according to the FDA drugs approval.[19, 31] Of 640 nitrogen heterocycles listed by Njardarson in 2014,[19] piperidines are the prevalent non-aromatic nitrogen ring systems appearing in 72 small-molecule drugs. Pyridine and piperazine cores are the next most commonly encountered in 62 and 59 small-molecules drugs respectively. Piperidine cores are extensively employed in the preparation of different classes of drugs including analgesics, antipsychotics, antihistamines, anticholinergics and antihypertensives for instance.[80-82] A few examples of drugs containing piperidine motif are listed in *Figure 9*.

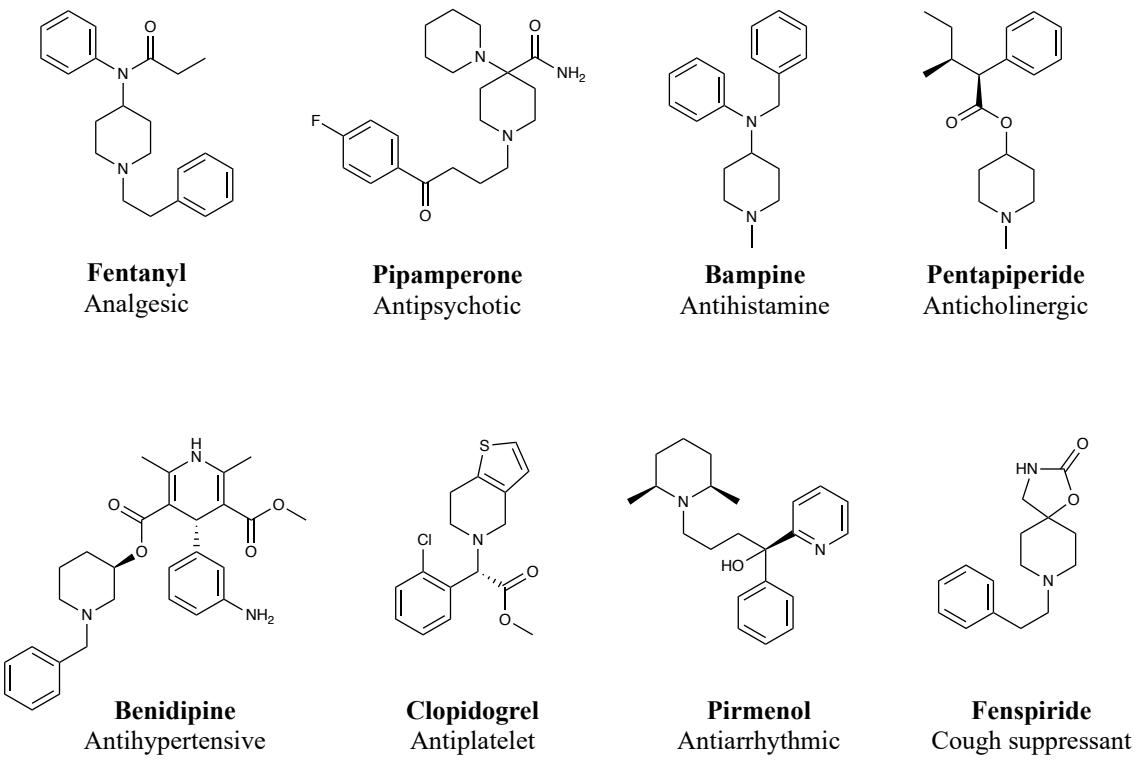
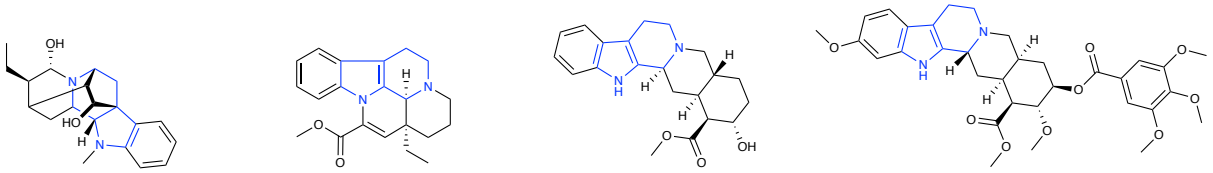


Figure 9: Drugs containing piperidine core and their pharmacological activity.

Njardarson's study highlights the considerable interest of the scientific community on the nitrogen heterocyclic structures, in particular the important role of piperidine played in the development process in drug discovery.[19, 81, 83-85] Fused piperidines, are common building blocks found in alkaloid-based natural products[81-82, 86-87] displaying diverse bioactivities.[88-89] In *Figure 10* are listed some representative examples of fused piperidine alkaloid structures extracted from natural products. The fused piperidine motif (highlighted in blue) was the target scaffold in this project.



Ajmaline
Rauwolfia serpentina
Antiarrhythmic agent

Apovincamine
Apocynaceae
Anti-melanogenesis agent
and vasodilator

Corynanthine
Rauvolfia and *Corynanthe*
Antihypertensive agent
and serotonin receptor

Reserpine
Rauwolfia serpentina
Antihypertensive agent
and vasodilator

Figure 10: Alkaloids containing fused piperidine motif from natural extracts and their bioactivity.

Natural products are structurally complex and used in the treatment of various diseases such as cancers.[40, 90] They are a key starting point for medicinal research and a precious source of inspiration for drug design.[91-92] However, the quantities extracted from natural sources are not sufficient to allow library design and diversification.[28, 40] To overcome this disadvantage**,** new synthetic approaches have been introduced to generate natural product-like scaffolds directly inspired from biologically active compounds.[28, 88]

Functionalised six-membered nitrogen heterocycles have stayed attractive targets for the synthetic chemists, with the development of efficient and stereoselective methods for the construction of enantioenriched *N*-heterocyclic frameworks.[93-96] This project sought to explore the potential of a new methodology discovered within the Davies group which combines cobalt catalysis and an intramolecular Diels-Alder cycloaddition sequence. This synthesis has the

potential to provide ready access into sp^3-rich piperidine motifs such as those found in various natural alkaloids (Figure 10) *via* oxazole intermediates.

2.2 Metal-catalysed cyclisation to access functionalised oxazoles

1,3-Oxazole is a five-membered heterocyclic ring containing oxygen and nitrogen atoms in the 1,3-positions, respectively.[97-98] The 1,3-azole class of heterocyclic compounds, consisting of oxazole, imidazole and thiazole, are widely found in natural products in terrestrial and marine organisms.[99-101] The 1,3-oxazole moiety in particular drew the consideration of researchers due to its presence in a large spectrum of molecules with interesting biological activities including antimicrobial, anti-inflammatory, antitubercular and anticancer properties.[100, 102-106] Below are key examples of 1,3-oxazoles containing molecules and their associate pharmacological properties (Figure 11).

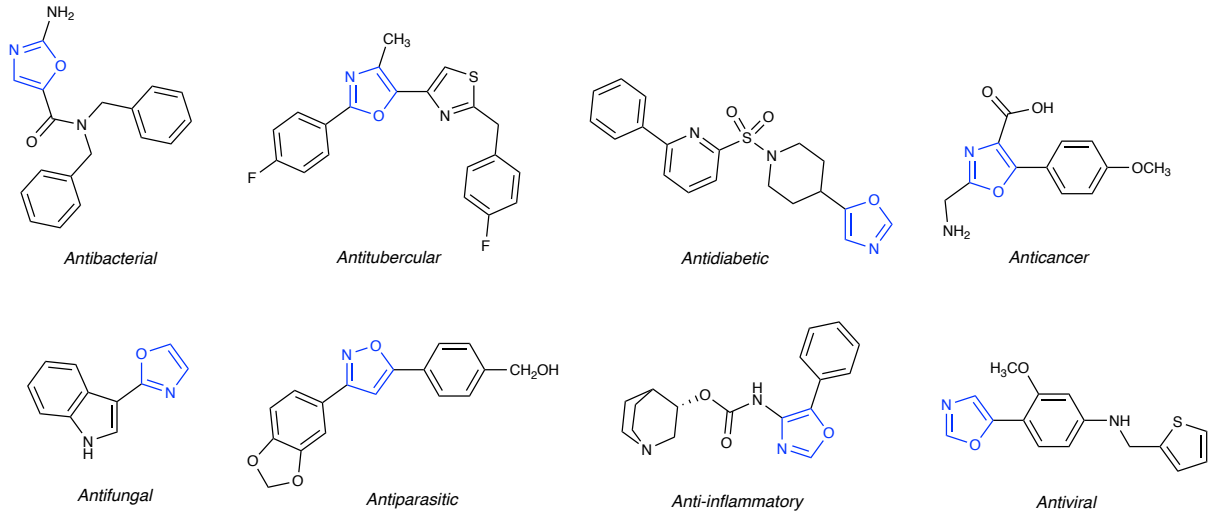
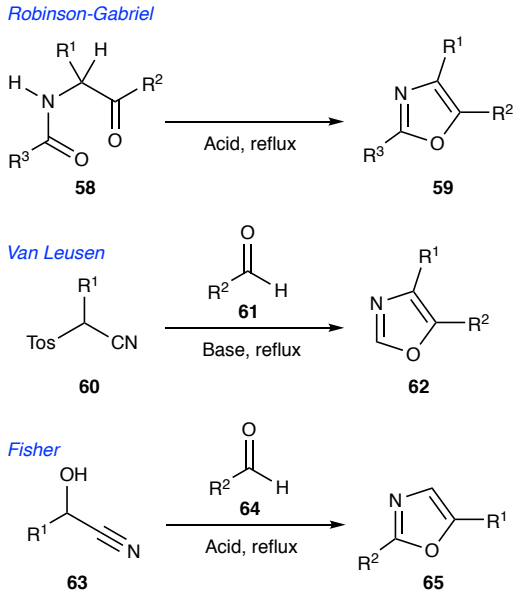


Figure 11: Examples of 1,3-oxazole-containing molecules and their associated pharmacological properties.

The preparation of 1,3-oxazoles was reported for the first time by Zinin in 1840,[107] from a reaction of benzil and alcoholic ammonia, and since its discovery many ingenious methodologies have been explored for their preparation. Robinson-Gabriel, Van Leusen and Fisher oxazole syntheses are the most common methods to synthesis oxazoles (Scheme 8).[100, 102] The Robinson-Gabriel procedure involves an intramolecular reaction with 2-acylamino

ketone **58** that requires harsh dehydration conditions towards the functionalised oxazole.[100, 102] These harsh conditions reduce the functional group tolerance for this reaction.[100, 102] The Fisher procedure also required harsh acidic dehydration, in presence of cyanohydrins **60** and aldehydes **61**. On the other hand, the Van Leusen synthesis is a rapid and practical procedure for the preparation of molecules containing an oxazole core and is the most developed in the past decades with a notably broad substrate scope and a simple operation.[100] The Van Leusen oxazole synthesis is known to prepare 5-substituted oxazoles from aldehydes **64** and TosMIC precursor **63** in a one pot [3+2] cycloaddition under mild conditions.[100]

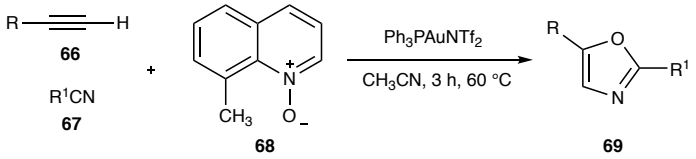


Scheme 8: Synthetic strategies for the synthesis of oxazole motif.

2,5- and 2,4,5-substituted oxazoles are particularly attractive intermediates in medicinal chemistry due to their structural diversity through substitution around the oxazole core.[102] The most relevant modern approaches developed by various research groups outlined below display simple and practical routes using transition metals to access functionalised oxazoles.

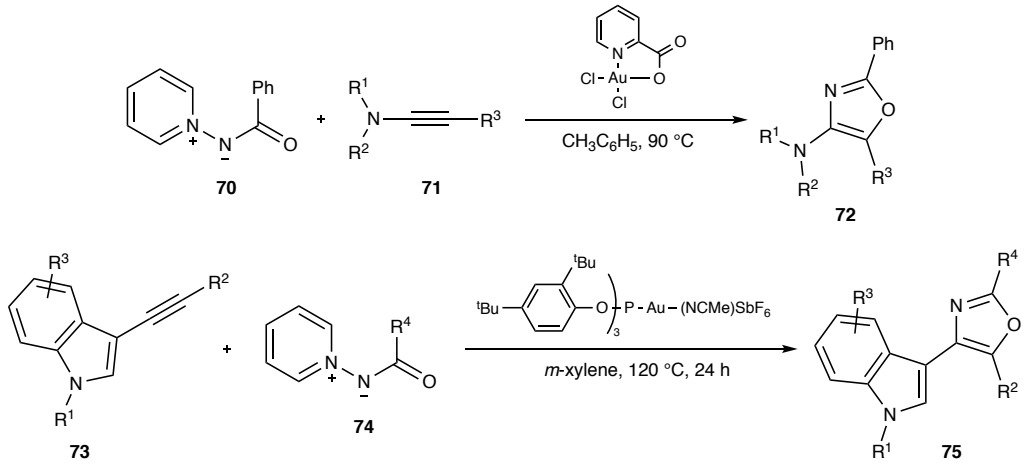
In 2011, Zhang[108] and co-workers developed the first synthesis of 2,5-disubstituted oxazoles **69** *via* gold carbene intermediates through gold-catalysed alkyne oxidation (Scheme 9). This [2+2+1] annulation, performed under mild conditions, involves a reaction between a terminal

alkyne **66**, a nitrile **67** from the solvent and an oxidant **68**. Furthermore, the reaction scope is broad where a range of terminal alkynes and nitriles are tolerated, as well as sensitive functional groups such as THP or Boc.[108]



Scheme 9: Zhang procedure for the synthesis of 2,5-disubstituted oxazoles through a gold-catalysed alkyne oxidation.

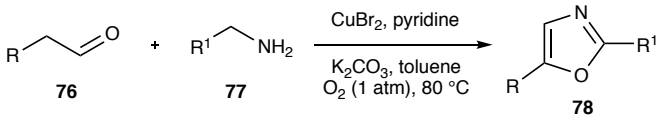
The same year, relevant works have been demonstrated within the Davies research group through the efficient and convergent syntheses of 2,4,5-trisubstituted oxazoles. A regioselective gold-catalysed intermolecular [3+2] cycloaddition strategy has been exploited across *N*-ylides **70** and ynamide **71** as chemoselective *N*-nucleophilic *N*-acyl nitrene/1,3-N,O-dipole equivalents in 2011,[109] subsequently across electron-rich internal alkynes **73** and *N*-aminides **74** as acyl nitrene equivalents in 2013[110] (Scheme 10).



Scheme 10: Two direct routes in the synthesis of oxazole using *N*-acyl nitrene developed in Davies group.

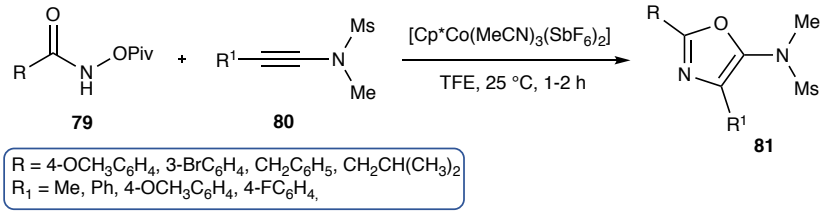
In 2012, Jiao[111] and co-workers reported a copper-mediated oxidative dehydrogenative annulation to access 2,5-disubstituted oxazoles through from simple and convenient starting materials such as aldehydes **76**, amines **77** and molecular oxygen by C-H functionalisation and dioxygen activation (Scheme 11). This transformation demonstrated a high efficiency with a

range of substituted amines to afford desired oxazoles in good yields, despite the fact that the aldehyde scope was limited to aromatic units.[111]



Scheme 11: Jiao procedure for the synthesis of oxazole through a copper-mediated oxidative dehydrogenative annulation.

Li[112] and co-workers developed in 2017 a rapid and practical method for the regioselective synthesis of 5-aminooxazoles **81** by using a cobalt-catalysed formal [3+2] cycloaddition from *N*-(pivaloyloxy)amides **79** and readily accessible ynamides **80** (Scheme 12). This is a regiocomplementory method to the gold approach discussed in the chapter 1.

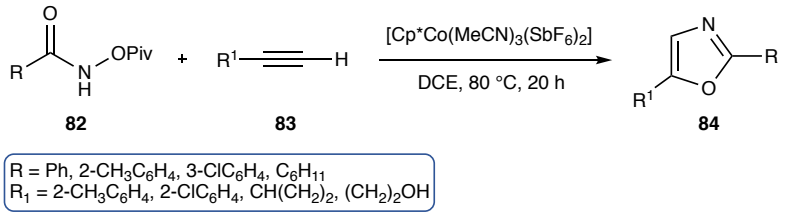


Scheme 12: Synthesis of oxazole through a cobalt-catalysed [3+2] cycloaddition using Li protocol.

The gold (*c.f.* **Chapter 4**) and cobalt-catalysed cascade strategies provide a direct access to different three-dimensional sp^3-rich polycycles containing a nitrogen atom in different position on the ring (or where the nitrogen position on the ring changed).

Shortly afterwards, Zhu[113] and co-workers reported a very similar process to synthesise 2,5-disubstituted oxazoles *via* a cobalt-catalysed cross-coupling of *N*-(pivaloyloxy)amides **82** and terminal alkynes **83** (Scheme 13). A different Co-catalyst was employed; the catalyst [Cp*CoI_2(CO)] used in the other research work was tested and showed no conversion with the terminal alkyne species **83**. This reaction featured a broad substrate scope for both starting

materials as well as a synthetic utility in the efficient construction of natural product scaffolds. However and despite the success of the procedure, a toxic solvent was used.



Scheme 13: Zhu procedure for the synthesis of oxazole via a cobalt-catalysed cross-coupling.

2.3. Diels-Alder reactions of oxazoles to build sp^3-rich polycycles

The Diels-Alder reaction is the most famous pericyclic reactions by far and is widely used in synthetic procedures.[114] Otto Diels and his research student Kurt Alder made this major discovery in 1928 and were rewarded by a Nobel prize in 1950.[115] Diels-Alder reactions are an efficient method to build highly functionalised six-membered rings under thermal conditions (Figure 12).[116-117] The concerted reaction that occurs between a conjugated diene and a dienophile (usually an alkene).[114, 116]

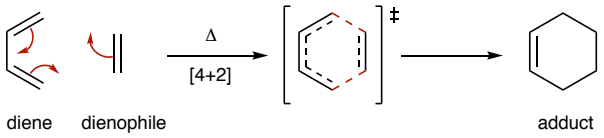
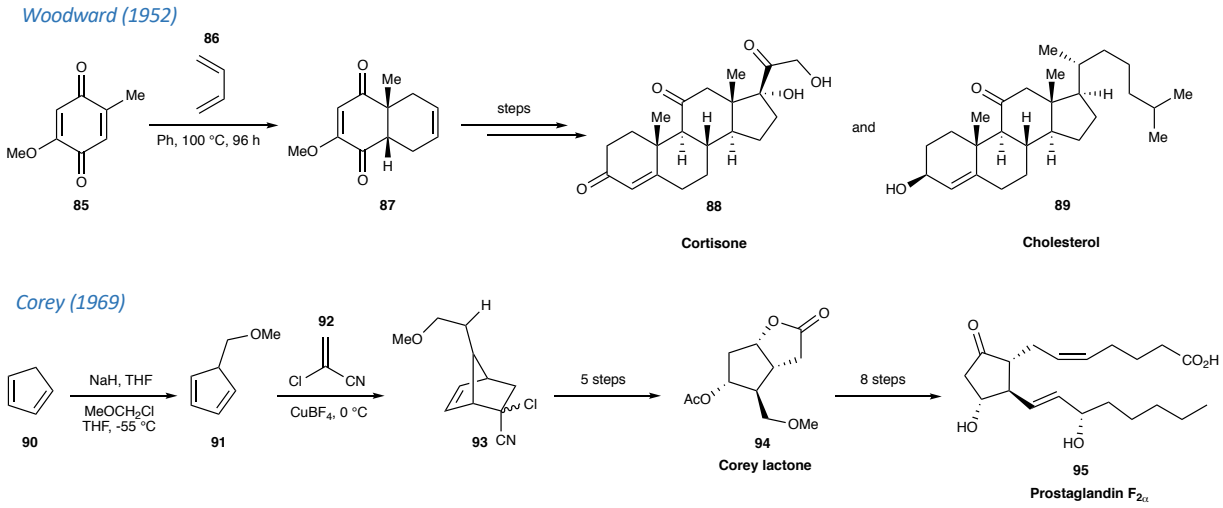


Figure 12: A Diels-Alder mechanism between a conjugated diene and a dienophile.

This [4+2] cycloaddition is regioselective and stereospecific, where two new bonds are created and up to four stereogenic centres can be introduced. This reaction is highly versatile as a large variety of substrates are tolerated.[117-118] The Diels-Alder reaction has been extensively used in the construction of complex molecular architectures and in the total synthesis of various natural products and pharmaceuticals compounds.[117, 119] Woodward and co-workers demonstrated the important role of Diels-Alder reactions in the total synthesis of biologically active molecules such as the steroid cortisone and cholesterol in 1952,[115, 120-121] and Corey in the total synthesis of prostaglandin F_{2a} in 1969 (Scheme 14).[120, 122-123]



Scheme 14: Diels-Alder cycloaddition involved in the total synthesis of bioactive molecules of cortisone and cholesterol (1952) and prostaglandin F_{2a} (1969).

Diels-Alder reactions can proceed through a normal or an inverse-electron demand reaction depending on the electron density of the diene and dienophile (Figure 13).[116] In the case of normal-electron demand Diels-Alder reaction, the oxazole is an electron-rich diene and the homo-allyl substituent is an electron-deficient dienophile.[116, 124] Contrary to a reverse-electron demand, the normal-electron demand reaction is controlled by the energy gap between the lowest occupied molecular orbital (HOMO) and the highest unoccupied molecular orbital (LUMO). The cycloaddition can occur when the energy gap is sufficiently low, and the reaction can be accelerated by attaching an EDG to the diene or an EWG to the dienophile (EWG lowers LUMO and EDG raises HOMO).[116, 124-125]

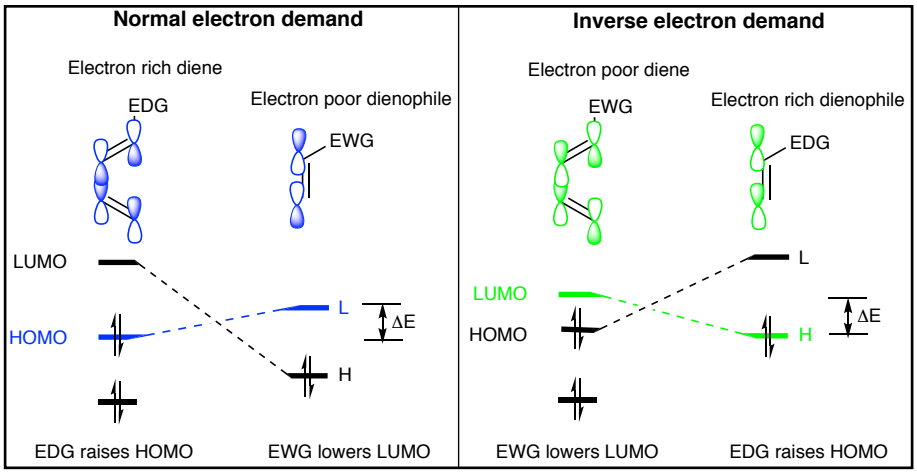
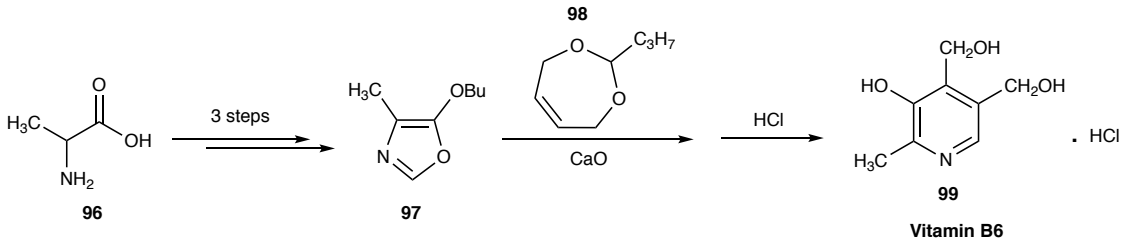


Figure 13: Normal and inverse-electron demand Diels-Alder reactions.

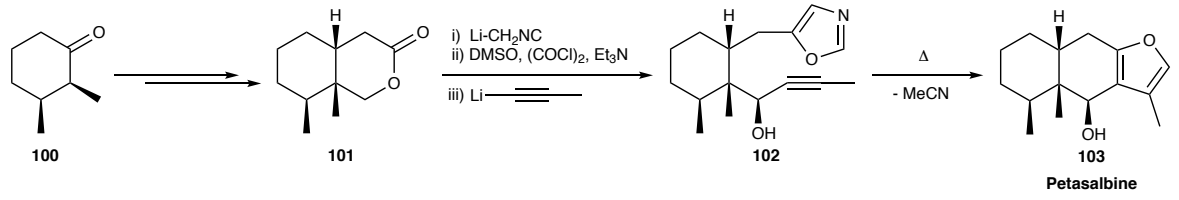
Intramolecular Diels-Alder cycloadditions of azole heterocycles have demonstrated efficient outcomes in the preparation of heterocyclic intermediates and natural products. Among five-membered heterocycles, oxazoles are broadly employed in the total synthesis of natural products.[117, 126] The following examples highlight key bond forming steps of diversified polyheterocycles present in natural product synthesis, where intramolecular Diels-Alder cyloadditions have been used between oxazoles as dienes and alkenes or disubstituted alkynes as dienophiles.[117]

An efficient and commercially viable process for vitamin B6 **99** was developed recently,[127] where a Diels-Alder cycloaddition was performed between the oxazole **97** prepared in three steps and diene **98**, under 150 °C (Scheme 15). Calcium oxide was found to increase the yield of this reaction to 80%.



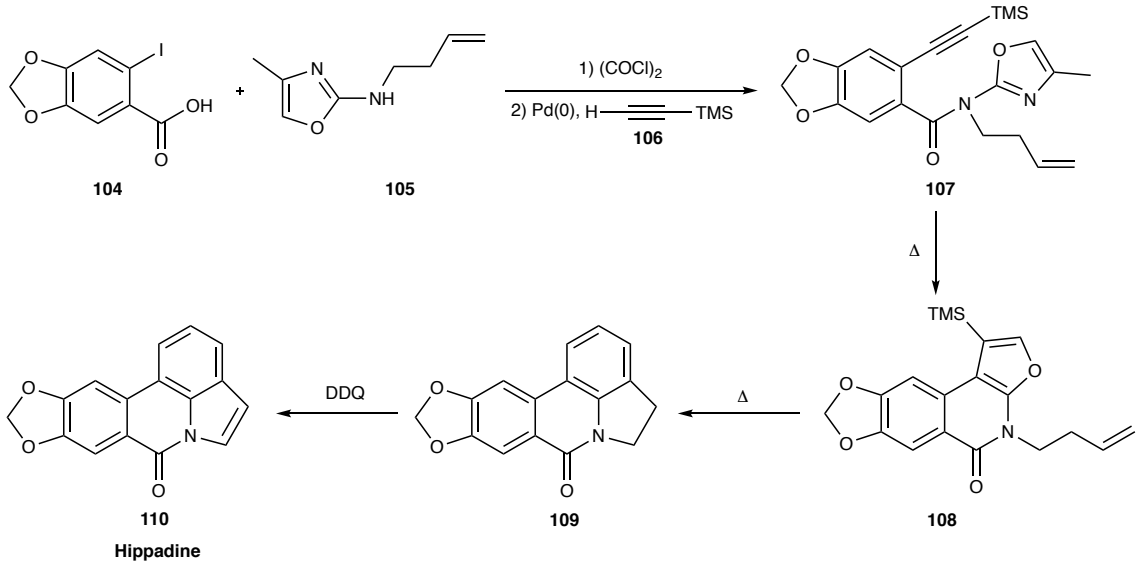
Scheme 15: Total synthesis of vitamin B6 involving a Diels-Alder reaction.

Jacobi and co-workers have developed a synthetic route in 1981, to the natural product petasalbine *via* an intramolecular Diels-Alder strategy (Scheme 16).[126, 128] The synthesis started with commercially available cyclohexanone **100** to generate in three steps the oxazole **102** in 51% yield. The final step was a direct conversion to petasalbine **103** *via* Diels-Alder cycloaddition at reflux, which afforded the product in 84% yield.



Scheme 16: Total synthesis of petasalbine using Diels-Alder reaction in the final step.

The synthesis of hippadine proceeded with 2-amidooxazole **107**, obtained from a cross-coupling of 6-iodopiperonyclic acid **104** and 2-(but-3-enylamino)oxazole **105** in the presence of oxalyl chloride.[126] After Sonagoshira reaction with TMS acetylene, a first intramolecular Diels-Alder reaction carried out at reflux for 20 h to afford the intermediate in good yield (87%). The resulting 2-amidofuran **108** underwent successively a second Diels-Alder cyclisation on the furan and an oxidation with DDQ to give hippadine natural product **110** (Scheme 17).

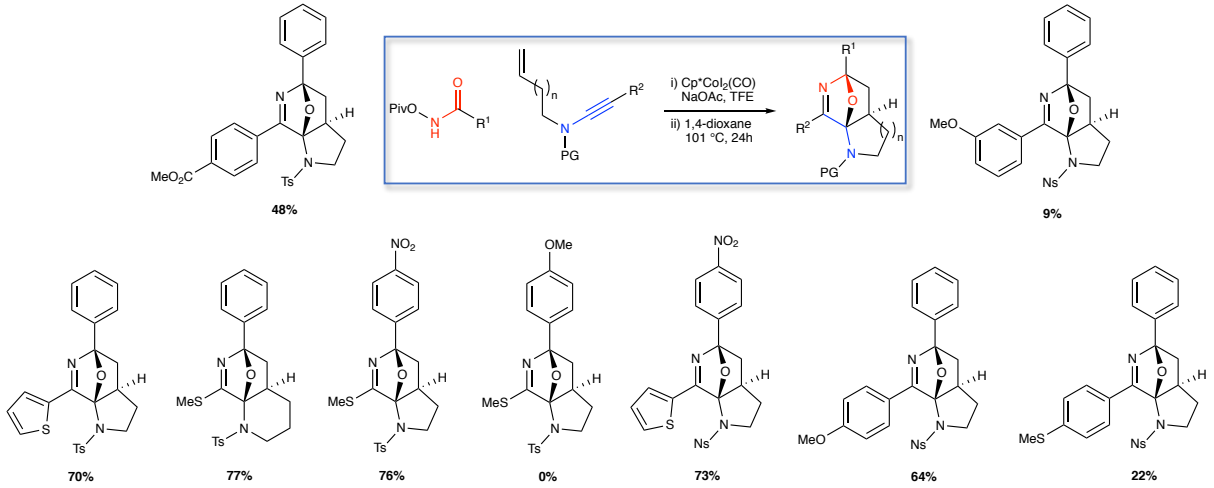


Scheme 17: Total synthesis of hippadine involving twice a Diels-Alder reaction.

2.4 Aim and objectives

A novel cobalt-catalysed polycyclisation was designed to provide a scalable, modular and straightforward route into bicyclic azacycles. A reduction of the bicyclic azacycles formed might lead to another desirable motif; piperidine representing a current challenge for synthetic and medicinal chemists owing to its presence in numerous biologically active molecules and pharmaceuticals. The aim of this research project was to investigate and demonstrate the potential of this novel methodology as an efficient preparative tool to access natural product-like molecules suitable for future drug discovery screening.

A cobalt-catalysed cycloaddition and an intramolecular Diels-Alder cycloaddition were combined in a cascade sequence and preliminary studies have showed the viability of this process in the preparation of 3-amino-azacycles (Scheme 18).[129-130] A sulfur group attached to ynamide improved the reaction yield owing to the increase of the reactivity of the Diels-Alder reaction. A degradation of the oxazole was observed with an electron-donating group (methoxy) attached in the C2 position. The incorporation of a nosyl functional group could have provided opportunities for further derivatisation, unfortunately starting materials showed solubility issues.



Scheme 18: Preliminary results on the cobalt-catalysed and intramolecular Diels-Alder cycloadditions strategy.

The goal was to explore whether the reaction could tolerate structural changes on starting materials (position, type of groups, functionality). Furthermore, the use of a substituted tether on the dienophile might lead to a diastereoselective Diels-Alder cyclisation (Figure 14).

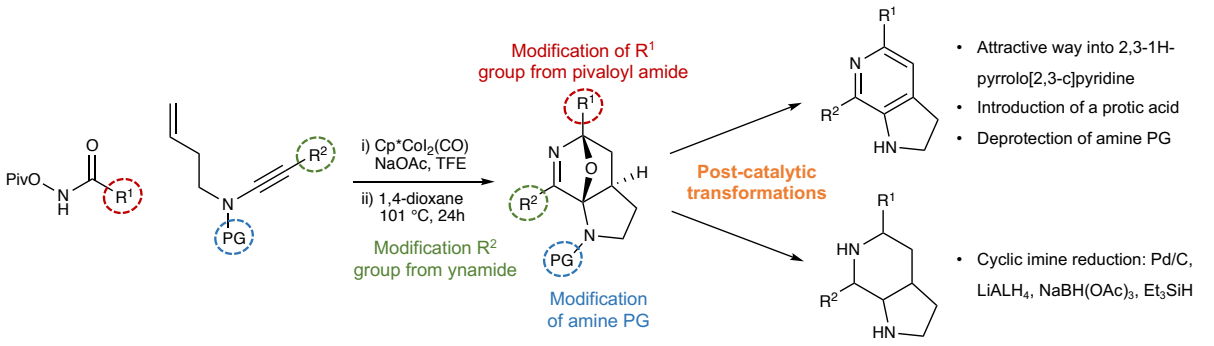


Figure 14: Chapter plan including the study of substrate scope of the new strategy elaborated and post-catalytic transformations.

The selected functional groups would show a variety of compatibility and allow post-catalytic transformations to be carried out in a regioselective manner. The variety of new sp^3-rich polycycles might offer significant potential for further post-catalytic reactions such as deprotection of reactive sites, dehydration, oxygen bridge opening and imine reduction, and the goal was to explore their potential in this way. Finally, the novel diversified polycycles produced from the methodology elaborated might contain significant biologically active motifs and target for further research in drug discovery.

2.5.1 Exploration of substrate scope: modification of amine protecting group

The exploratory work described in the following section investigates the substrate scope with respect to the novel cascade sequence developed within the Davies group.[129-130] The catalysis substrates accessed in a short sequence have several advantages including non-toxicity, uses of abundant transition metals, to save time and cost and above all to build complex molecular scaffolds in a minimum of steps. *Figure 15* displays the initial steps required for the preparation of precursors before the exploration of the novel cycloaddition sequence.

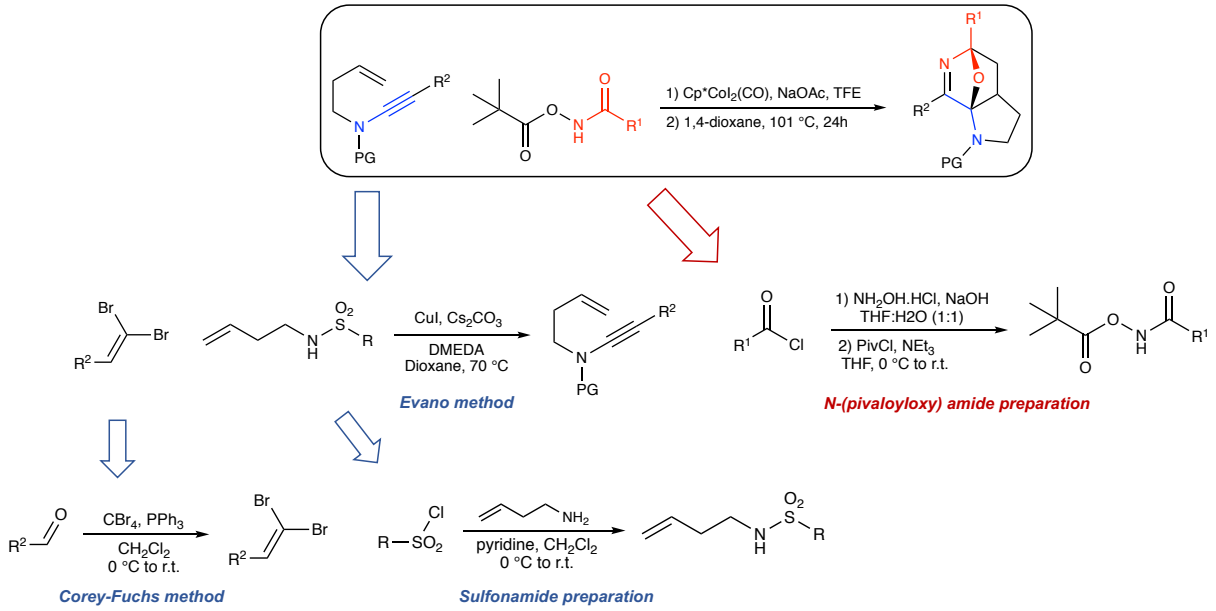


Figure 15: Initial steps required to prepare precursors for the exploration of novel cascade cycloaddition.

The modification of the protecting group on the ynamide nitrogen was the primary focus. Sulfonamides were selected as protecting groups, being essential structural motifs found in a series of drugs[131] and continue to be attractive functional groups in the development of potential drug-candidates.[132-133] Also, to investigate their compatibility with the cascade process and in the case where the *N*-substituent would stay in the final product, their attractiveness for medicinal chemistry in post-catalytic reactions.

The choice of the nitrogen protecting group was selected from the analysis of the defined piperidine scaffolds **111** and **112** with the computational tool LLAMA,[42] and predicting potential molecular properties by the decoration of the reactive sites. Promising trends were found to exist within the computed library with many molecules falling within Lipinski's rule-of-five and showing a good spread of permeabilities. Most encouraging was the set of singly decorated structures, many of which fell within the lead-like space that is highly desirable for further investigation. While some of the structures exhibited undesirable properties such as heavy atoms for the scaffolds **111** and **112**, this can help us to better plan our library to synthesis more lead-like structures (Figure 16).

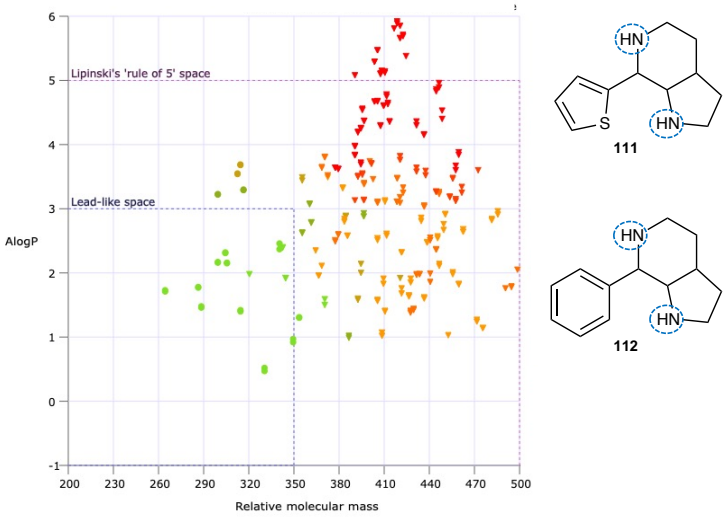
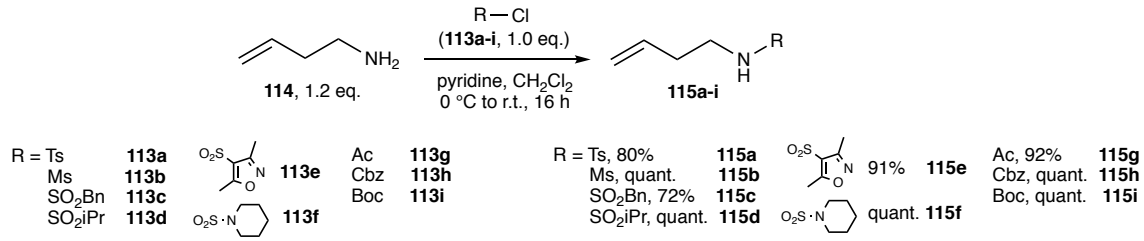


Figure 16: Lead-likeness plots of products derived from the piperidine scaffold using LLAMA computational tool. Circle and triangle shapes correspond to scaffold decorated one and twice respectively. The penalty colour system shows the accrued penalties for the decorated scaffolds.

During the drug discovery process, the complexity of the scaffold increases so it is essential to start at this stage with the minimum of penalty. The following sulfonamides: dimethyloxazole, piperidyl, isopropyl, acetyl and benzyl have been identified as good candidates for new potentially biologically active molecules.

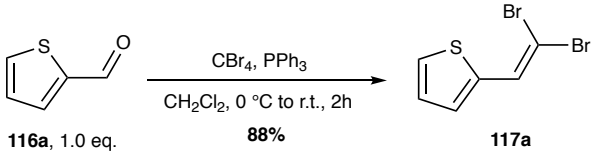
Common groups such as mesyl, tosyl and nosyl sulfonamides were also selected for this study, due to their prevalence in organic chemistry.[134-135] Carbamates such as Cbz, Boc and Alloc were explored as alternative groups to the protected amines. These protecting groups display significant role in medicinal chemistry and in drug discovery.[136-137]

The sulfonamides **115a-j** were prepared from but-3-en-1-amine **114**, sulfonyl chlorides **113a-j** and pyridine in dichloromethane (Scheme 19). A range of sulfonamides were made in good yields, with only sulfonamides **115g-h** requiring further purification by flash column chromatography after aqueous work up.



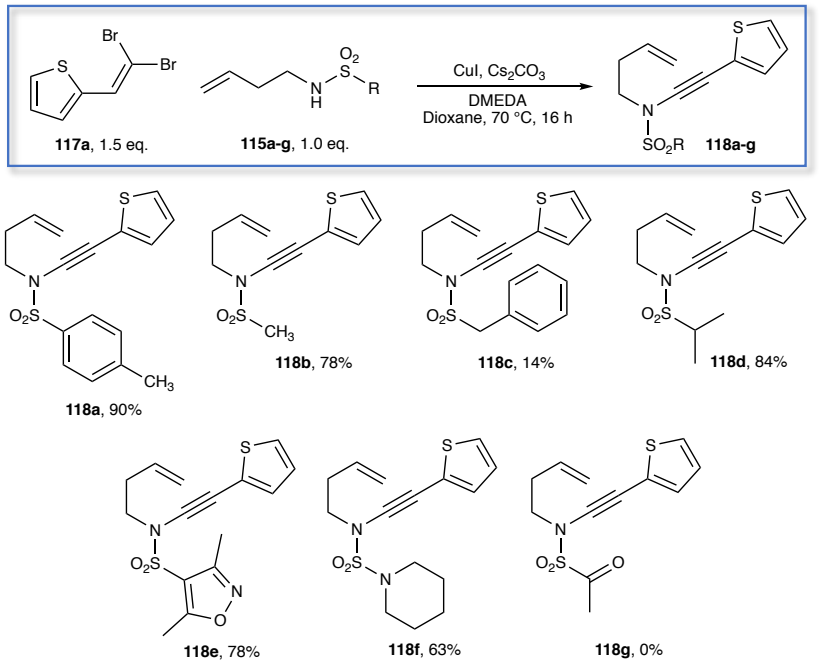
Scheme 19: Synthesis of sulfonamides from but-3-en-1-amine and relevant sulfonyl chlorides.

The 2-thiophene carbaldehyde **116a** was selected as the coupling partner for ynamide formation owing to preliminary studies showed that it was a good substituent in the Co-catalysed chemistry. It was prepared in a two-gram scale following the Corey-Fuchs[138] procedure and synthesised in 88% yield (Scheme 20).



Scheme 20: Corey-Fuchs for the preparation of the dibromoolefin 117a.

The Evano[56] ynamide synthesis procedure was employed to prepare a series of new ynamides by combining the sulfonamides (**115a-i**) with vinyl dibromide **117a**. This copper-mediated process is straightforward, reliable and tolerates diverse functional groups. A range of ynamides **118a-g** containing different functionalities on the sulfonamide were synthesized successfully (Scheme 21).

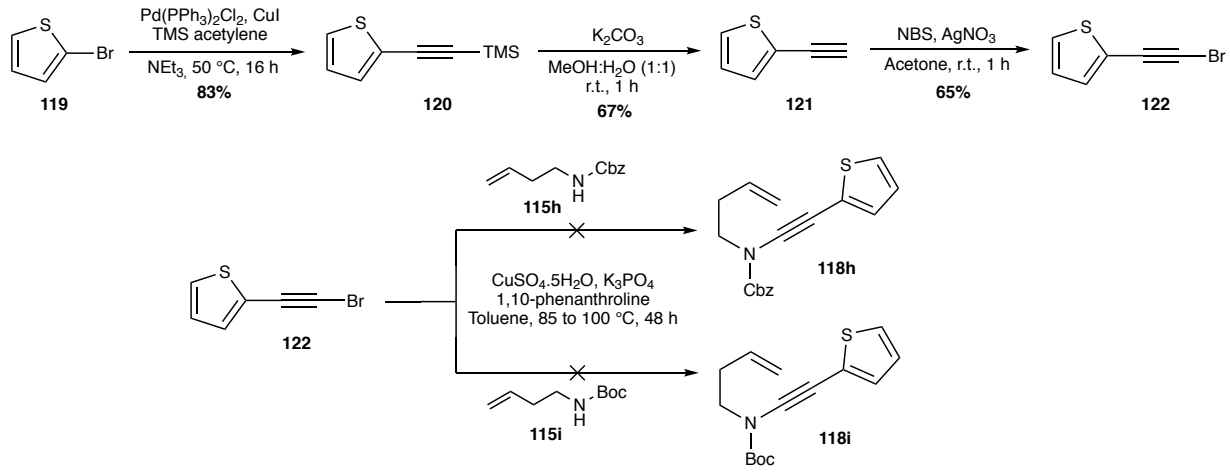


Scheme 21: Evano's method to synthesis ynamides from vinyl dibromide 117a.

Ynamides **118a-b** and **118d-f** were synthesized in good yields. A lower yield (14%) was obtained for the ynamide **118c** due to difficulties in purification. Fortunately, the material recovered was enough to use in the cobalt catalysis. The acetyl sulfonamide **115g** did not react at 70 °C in 1,4-dioxane. Further investigations using different solvents (toluene, DMF) and temperature (80-100 °C) were undertaken but were not successful. The same poor reactivity was observed when carbamates **115h** and **115i** were tested under the Evano procedure, with only starting materials being recovered. The reaction does not tolerate carbonyl protecting groups.

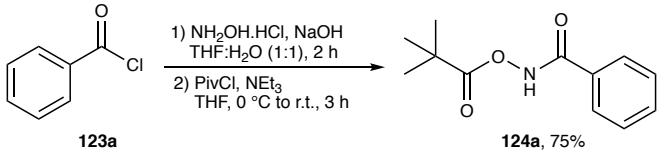
Carbamates were highly desired functional groups owing to their impact in the drug development. Their ease of deprotection could bring flexibility to our novel polycyclisation sequence developed. An alternative route to access functionalised ynamides was attempted with carbamate sulfonamides **115h** and **115i** by using Hsung's methodology developed in 2004.[63] Hsung and co-workers made examples of carbamates on the ynamides nitrogen.

Bromoalkyne **122**, the coupling partner to the carbamates in this reaction, was prepared successfully in three steps (Scheme 22). Being air sensitive, prepared **122** was used immediately in the next step. It was combined with carbamates **115h** and **115i** and a $CuSO_4.5H_2O$ catalyst in increasing the reaction temperature gradually to 100 °C. Despite repeated attempts and variations, the combination of groups could not be assembled using this route.



Scheme 22: Hsung's method to synthesis ynamides 118h-i from sulfonyl carbamates 115h-i.

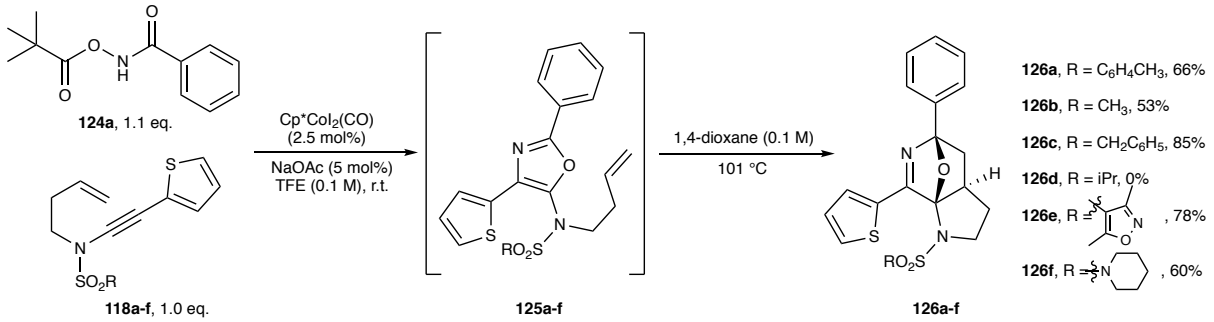
N-(Pivaloyloxy)amide **124a** was prepared in two simple steps through a dual acylation process (Scheme 23),[139] in which the hydroxamic acid intermediate was used directly in the next step without requiring purification. The *N*-(pivaloyloxy)benzamide **124a** was obtained with a good yield (74%) after recrystallisation from heptane/toluene.



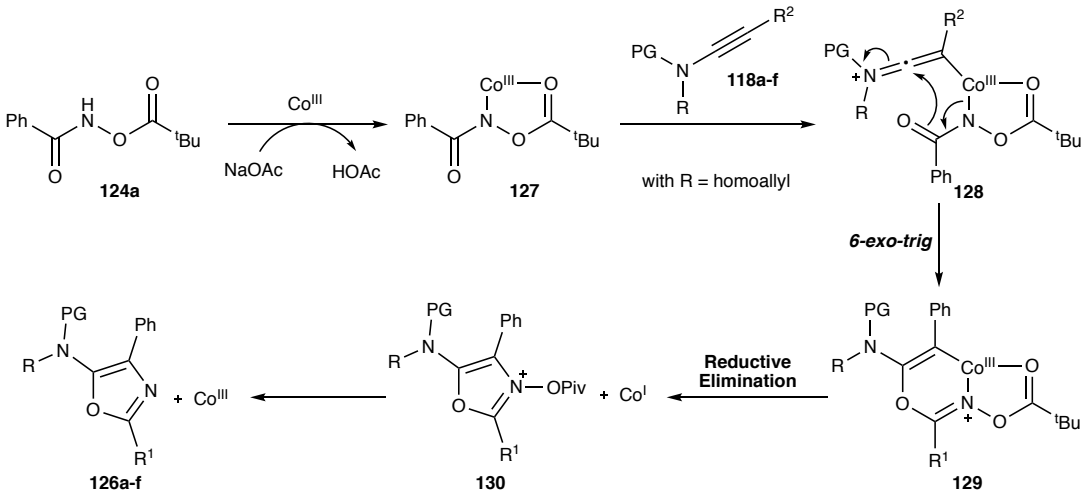
Scheme 23: Synthesis of *N*-(pivaloyloxy)benzamide 124a *via* benzoyl chloride 123a.

The prepared ynamides **118a-f** were then tested across the cobalt-catalysed polycyclisation with *N*-(pivaloyloxy)benzamide **124a** to probe the effect of using different functional groups (Schemes 24). Li[112] and co-workers proposed a mechanism where the amide **124a** coordinated initially to the cobalt(III) catalyst to form an amido complex **127**. Nucleophilic attack of the ynamide **118** then led to the formation of the keteniminium ion **128**, followed by an intramolecular *6-exo-trig* cyclisation to generate the cyclocobalt species **129**. Reductive elimination allowed the formation of the *N*-(pivaloyloxy)oxazole cation and cobalt(I) species. Finally, the cobalt(I) was oxidised to cobalt(III) by the N-O bond and the expected oxazole **126** was formed (Scheme 25).

The work up at this stage of the cascade sequence is crucial for the success of the Diels -Alder reaction as the presence of TFE and/or cobalt catalyst in the reaction mixture had previously been shown to adversely affect the Diels-Alder reaction.[129] An improved procedure, involving the removal of TFE by evaporation at maximum vacuum (10 mbar) for 10 min, followed by filtration through a pad of silica with EtOAc to remove the catalyst was found to be sufficient prior to refluxing the oxazole intermediate in 1,4-dioxane for 24 h.



Scheme 24: Cobalt catalysis and intramolecular Diels-Alder cycloaddition sequence from a range of new ynamides and *N*-(pivaloyloxy)benzamide 124a.



Scheme 25: Proposed mechanism for the cobalt (III)-catalysed oxazole formation reaction.

For all cases, complete consumption of ynamides **118a-f** was observed under Co-catalysis and one major spot corresponding to the oxazoles **125a-f**, was visible under UV *via* TLC analysis. In the case of **118d** the product was not oxazole **125d**, the ^{1}H NMR analysis identified traces of material **124a** and consumption of ynamide **118d** with the major product corresponding to ynamide hydration product, although this was not isolated cleanly enough for full characterisation.

After monitoring the reaction Diels-Alder by TLC when refluxing in dioxane, incomplete conversion of all intermediate oxazoles was observed. However upon purification, a series of new functionalised Diels-Alder cycloadducts were obtained in good to excellent yields (Scheme 24). The Diels-Alder products **126b** and **126e** were purified by recrystallisation from hot ethanol whereas **126a**, **126c** and **126f** required purification by flash column chromatography. Attempts to improve the amount of Diels-Alder cycloaddition by maintaining the reaction at reflux for longer or by elevating the temperature further (through the use of different solvents) leads to the formation of a new product which was determined to be the pyridine by dehydration. The Diels-Alder cycloadduct **126a** was synthesised in 66% at gram scale. This

demonstrates the robustness of this method and provided the material required for further post-catalytic reactions discussed in the post-catalytic part (*c.f.* **Section 2.6**).

The choice of sulfonyl group had an effect on the result of the sequential cascade cycloaddition. According to the results and the yields of new Diels-Alder adducts synthesised, bulky protecting groups such as tosyl, piperidine and benzyl sulfonyls are beneficial leading to higher amounts of intramolecular cycloaddition relative to the methanesulfonyl group. This interesting observation might be interpreted in terms of reactive rotamer[140] and Thorpe-Ingold[141] effects. According to the Thorpe-Ingold principle, steric hindrance of groups attached to the carbon atoms leads to internal compression affecting bond angles to favour ring closure. The reactive rotamer analysis would state that the size of the protecting group on the dienophile increases of the population of the reactive rotamers properly oriented for the Diels-Alder cyclisation.

2.5.2 Exploration of substrate scope: modification of *N*-(pivaloyloxy)amide

Attention was then turned to the influence of the *N*-(pivaloyloxy)amide substituents on the Diels-Alder cyclisation from the C2 position of the oxazole and their potential reactivity in further post-catalytic transformations. Preliminary studies using a phenyl and nitro substituents on the aromatic ring to access the cycloadducts **126h-i** were encouraging (Figure 17).
However, the polycycle **126j** using a *p*ara methoxy substituent on the aromatic ring was not isolable after refluxing in 1,4-dioxane, with extensive degradation observed by TLC and NMR. An electron-donating group in the *para* position could encourage a number of subsequential reaction pathways, including the ring opening of the ether bridge once **126j** is prepared.

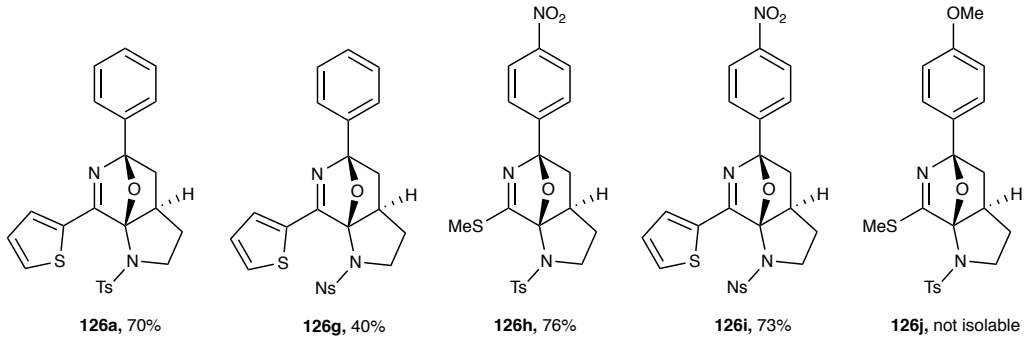
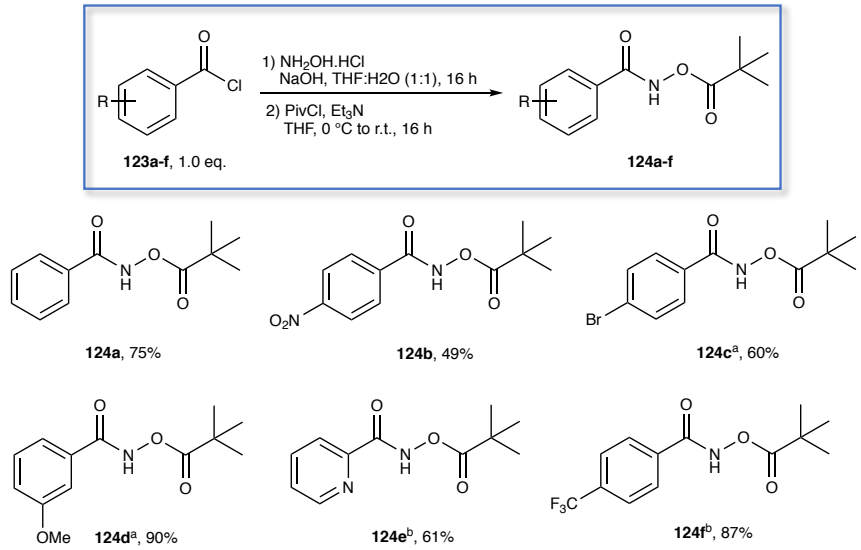


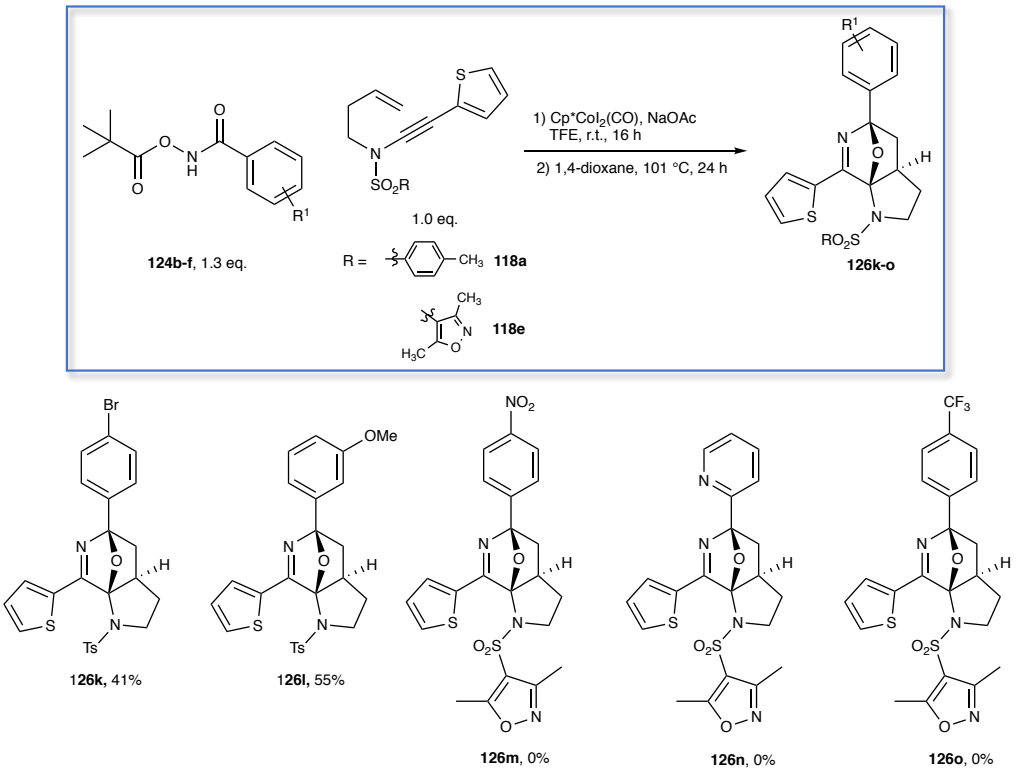
Figure 17: Catalysis results from previous studies using enynamides and pivaloyloxy amides.[142-143]

A variety of known and novel *N*-(pivaloyloxy)amides **124a-f** were prepared in two simple steps following literature procedures and the final products were purified by flash column chromatography (Scheme 26).[144]



Scheme 26: Main route to prepare a range of new *N*-(pivaloyloxy)amide 124a-f from acid chlorides. [a] prepared in the first step with K_2CO_3 and EtOAc:H_2O (2:1); [b] prepared by MGW.

To investigate the flexibility of the cobalt polycyclisation process to make Diels-Alder cycloadducts, this reaction was tested with ynamide **118a** and selected pivaloyloxy amides **124c** and **124d** to afford novel Diels-Alder adducts **126n** and **126o** in 41% and 55% yields respectively (Scheme 27). The moderate yields could be explained by the incomplete conversion of the oxazoles towards Diels-Alder cycloaddition.



Scheme 27: Cobalt-catalysis polycyclisation from ynamide 118a,e and various pivaloyloxy amides 124b-f.

Encouraged by the good yield obtained for the cycloadduct **126e** (78%) and to investigate the influence of various pivaloyl materials to make Diels-Alder cycloadducts, the cascade reaction was attempted on the ynamide **118e** and selected pivaloyl materials to probe the new functional group combination on this scaffold. Whilst the initial reactivity appeared promising with the formation of the Diels-Alder adduct **126e**, the pivaloyloxy amides **124b**, **124f** and **124g** showed no conversion through to the desired oxazoles **125k-o** (Scheme 27). The conditions were modified by the elevation of the temperature up to 78 °C, with no consumption of starting materials. These results showed the limit of synthetic compatibility of ynamide **118e**.

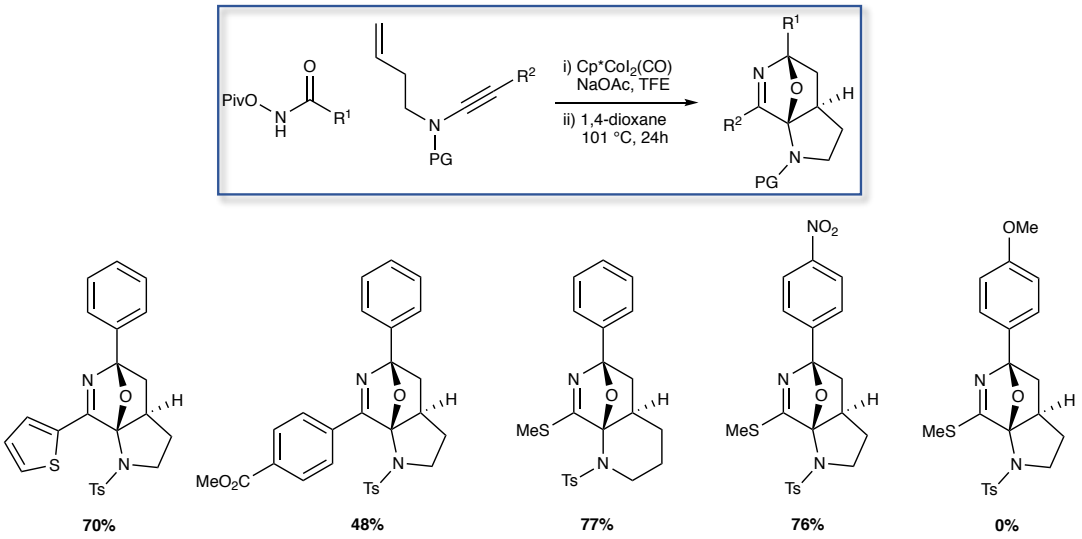
However, due to positive preliminary results obtained from ynamide **118a**, the study of the substrate scope was carried on using this ynamide.

2.5.3 Modification of the ynamide substrate

The objectives of this aspect of the project were to study the substrate scope of the ynamide and to investigate their influence on the catalytic sequence as well as to study the potential for a

diastereoselective Diels-Alder cycloaddition from the oxazoles generated *in situ* by incorporating functional groups alpha to the nitrogen.

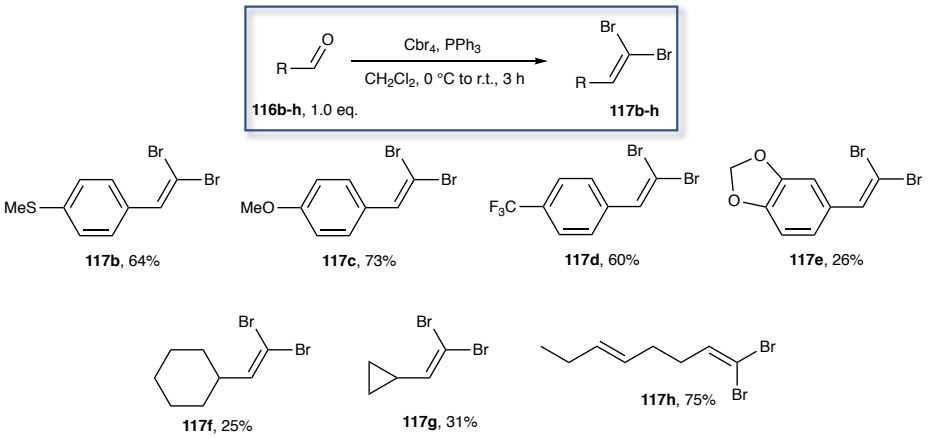
Preliminary results showed the synthesis of new Diels-Alder adducts in good yields (Figure 17). An improvement of the reaction yield was observed when a sulfur group was attached to ynamide, with the increase of the Diels-Alder reaction reactivity.



Scheme 28: Preliminary results of the synthesis of Diels-Alder cycloadducts.

A range of novel ynamides were prepared and probed in the cobalt-catalysed cycloaddition sequence with *N*-(pivaloyloxy)benzamide **124a** to generate new polycyclic compounds. This involved a Corey Fuchs olefination and followed by Evano's ynamide procedure (*c.f.* **Schemes 20 and 21**). Tosyl sulfonamide **118a** was selected for this investigation owing to successful preliminary results obtained within the Davies group[129] and simple preparation.

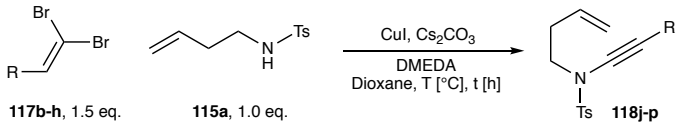
To expand the scope of the transformation, a range of dibromoolefin intermediates **117b-h** were prepared by a Corey-Fuchs reaction.[138] The dibromoolefins of electron-donating and -withdrawing groups were prepared on a 1 or 2 g scale in reasonable yields, from 25 to 75% (Scheme 29). The reactions were performed at room temperature until complete consumption of starting material by TLC. Lower yields were obtained for the aliphatic dibromoolefins **117f** and **117g** due to volatility.

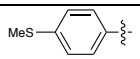
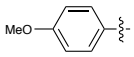
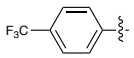
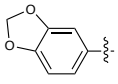
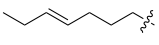


Scheme 29: Synthesis of novel dibromoolefins 117b-h using Corey-Fuchs method.

Whilst the aryl dibromolefins reacted under Evano´s standard conditions,[56] the temperature was elevated to 100 °C for the alkyl derivatives (Table 1, entries 5-7) to accelerate the reaction. The desired electron-donating and-withdrawing aryl ynamides **118j-k** were synthesised in good to excellent yields (Table 1, entries 1-4), whilst aliphatic ynamides **118n-p** were synthesised in lower yields.

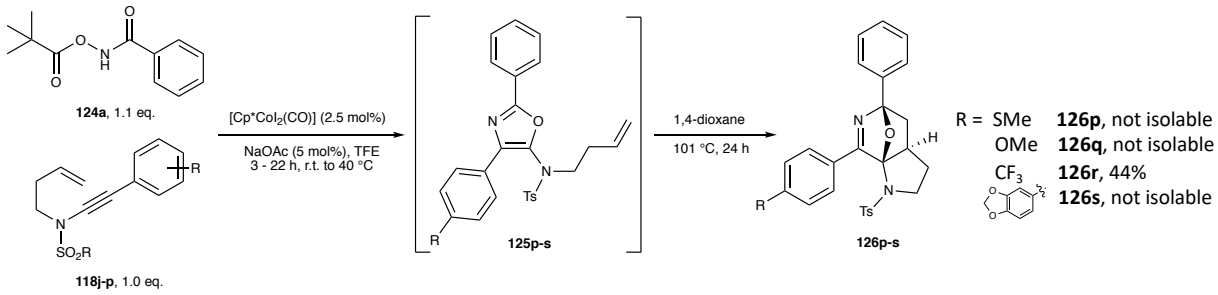
Table 1: Synthesis of ynamides 118j-p using dibromoolefins 117b-h and sulfonamide 115a.



Entry	117b-h	R	T [°C]	t [h]	118j-p	Yield [%]
1	117b		70	20	118j	57
2	117c		70	20	118k	81
3	117d		70	20	118l	91
4	117e		70	22	118m	90
5	117f		100	96	118n	22
6	117g		100	96	118o	20
7	117h		100	96	118p	28

Reaction conditions: CuI (12 mol%), Cs_2CO_3 (4.0 eq.), DMEDA (18 mol%), solvent (0.32 M).

With a range of homoallyl ynamides in hand, their reactivity under the cobalt-catalysed cycloaddition protocol was examined with *N*-(pivaloyloxy)benzamide **124a** to assess their compatibility with the specific conditions optimised within the Davies group (Scheme 30).



Scheme 30: Substrate scope of cascade polycyclisations with materials 124a and 118j-p.

Ynamides **118j-k** were first selected to explore the effect of electron-donating and -withdrawing substituents on the aryl group in the formation of the oxazole intermediates, under similar conditions developed by Li[112] and co-workers in 2017. The oxazole intermediates **125p**, **125q**, **125r** and **125s** were synthesised at room temperature. Analysis of the ^{1}H NMR spectra of the crude reaction mixture indicated formation of the oxazole intermediates **125p-s**. *Figure 18* shows the stacked spectra for the cobalt-catalysed cycloaddition of the ynamide **118l** and *N*-(pivaloyloxy)benzamide **124a** and the characteristic a chemical shift for the homoallyl group (highlighted in blue) that indicated a successful reaction.

For aliphatic ynamides **118n**, **118o** and **118p**, analysis of the ^{1}H NMR spectra confirmed consumption of the starting materials but the formation of the oxazoles was difficult to confirm and the allyl resonances were lost. The reactions were not successful with aliphatic substituents and were not furthered.

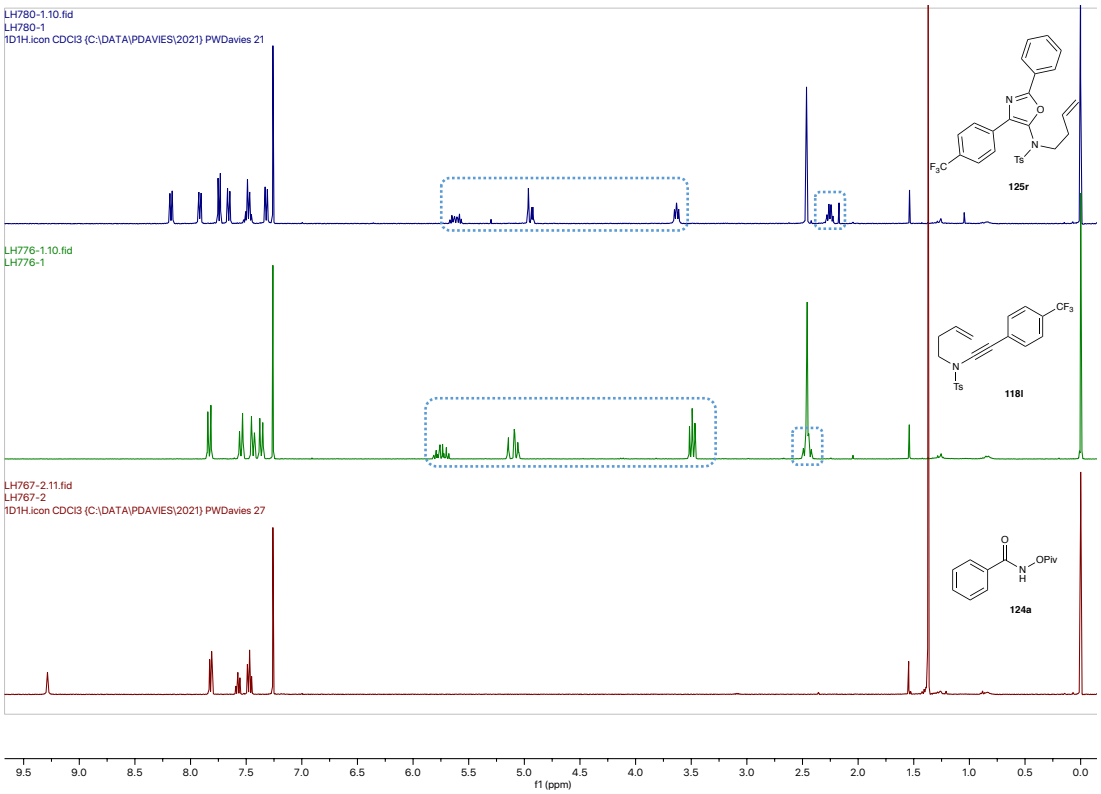


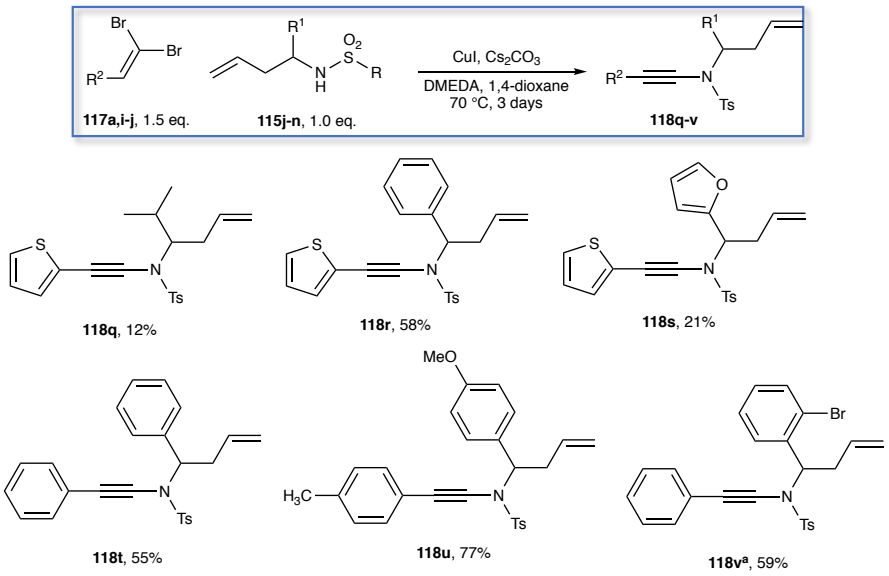
Figure 18: Stacked spectra showing the chemical shifts of the homoallyl peaks in the formation of oxazole 125r. ^{1}H NMRs of oxazole 125r after purification (top), ynamide 118l (middle) and *N*-(pivaloyloxy)benzamide 124a (bottom).

All reaction mixtures were then subjected to the Diels-Alder conditions in 1,4-dioxane at reflux. The oxazoles **125p** and **125q** showed degradation on TLC after a few hours. Repeating this reaction for the oxazoles **125p** and **125q** in the same solvent at 80 °C saw completion consumption of the oxazoles by TLC. However, the ^{1}H NMR spectra were complex with mixtures even following attempted purification using flash column chromatography. While the vinylic protons were lost, indicating that a Diels-Alder process might have occurred. The complexity of the mixtures might indicate that the resulting cycloadducts were unstable at elevated temperatures.

The cycloadduct **126r** was isolated in modest yield 44%, confirming the low conversion of the oxazole **125r**. A higher reaction temperature of 140 °C with the 1,2-dichlorobenzene was trialled over a shorter time (4 hours) using the recovered **125r** material, but again incomplete oxazole conversion was observed. The cycloadduct **126s** was generated after 24 h reaction at

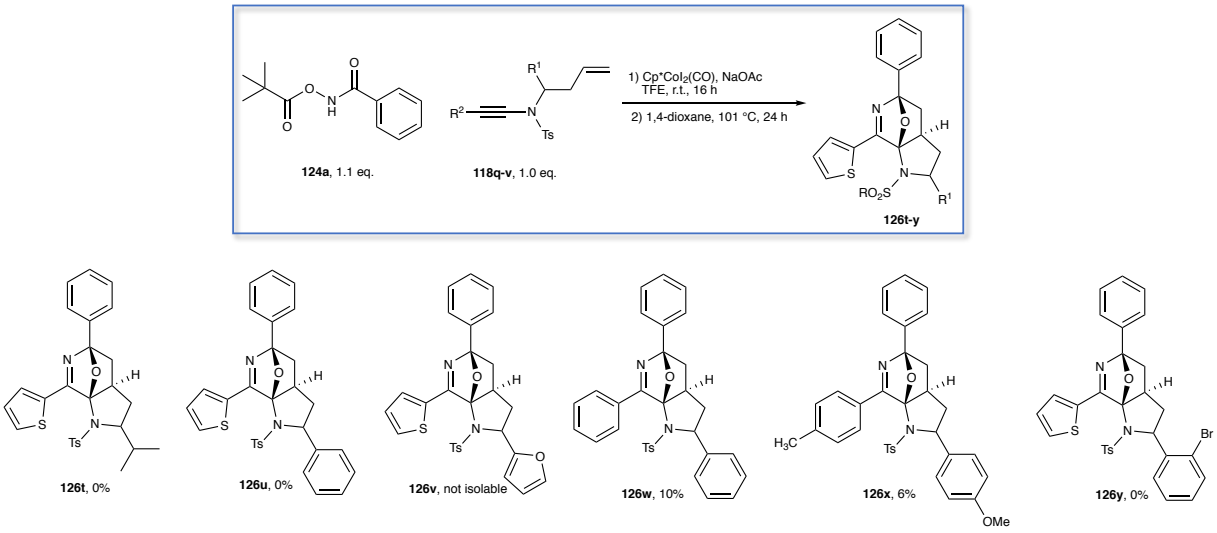
101 °C confirmed by ^{1}H NMR analysis. However, and despite purification by flash column chromatography, additional peaks were observed on the spectrum preventing the isolation of the cycloadduct **126s**.

Then, the modification of the dienophile tether was studied. To do this, novel ynamides **113q-v** were prepared according to Evano´s synthesis[56] from dibromoolefins in low to good yields (Scheme 31). Various bulky substituents on the alpha position of the nitrogen were introduced to study the steric and electronic impact as well as to test the flexibility of the Diels-Alder reactions. The bulky substituents might hamper the Diels-Alder cycloaddition or on the contrary lead to new functionalised structures interesting for further diversification.



Scheme 31: Evano synthetic route to prepare new ynamides 118q-v containing a stereogenic centre. [a] prepared by OFO.

Due to the increased steric bulk near the nitrogen, the reactivity of the sulfonamides was found to be considerably slower than previous examples, requiring extended reaction times of 3 days. These ynamides were then tested in a cobalt-catalysed polycyclisation sequence to study diastereoselectivity of the process and functional groups compatibility (Scheme 32).



Scheme 32: Cobalt catalysis and intramolecular Diels-Alder reaction one pot from ynamides 118q-v and *N*-(pivaloyloxy)benzamide 124a.

Ynamides **118r**, **118t** and **118v** required an elevation to 50-60 °C to observe consumption on TLC, while ynamides **118s** and **118u** were completely consumed after 48 to 72 hours reactions at room temperature. A degradation of the ynamide **118q** was observed on TLC after elevating temperature to 60 °C.

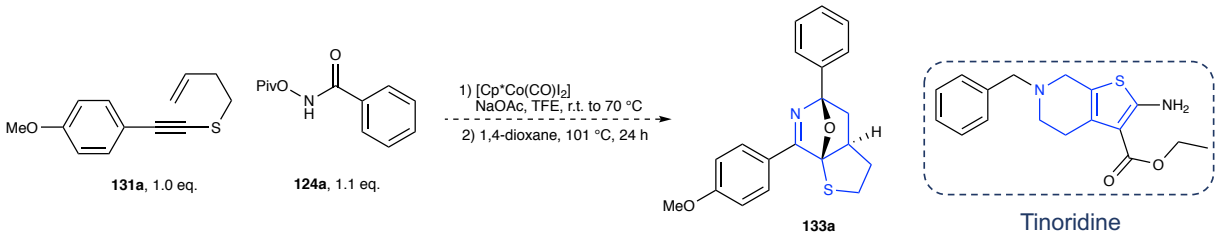
Diels-Alder reaction was performed with the crude intermediates **125w-x** in 1,4-dioxane at reflux. The cycloadducts **126w** and **126x** were isolated in poor yields (10% and 6% yields respectively) after 6 hours reaction. The low yields could be explained by the steric hindrances with the introduction of bulky groups on the homoallylic ynamides. Only one spot was observed on TLC, after completion of the cycloaddition. The ^{1}H NMR spectra showed additional peaks confirmed the mixture of diastereoisomers in a 4:1 ratio for the compound **121w** and 3:1 for the compound **121x**.

However, the Diels-Alder reaction for the oxazole **125y** did not afford the desired cycloadduct **126y** despite the elevation of the temperature gradually from 80 to 101 °C. TLC showed the degradation of the oxazole **125y** after few hours at 101 °C.

The construction of the cycloadduct **126v** with a furyl substituent on the C2 position of pyrrolidine system looked promising in the initial attempt, the oxazole **125v** appeared to be formed. The alkene resonances were then lost in the Diels-Alder step. However, the analysis of the crude ^{1}H NMR showed complicated spectrum and desired product **126v** could not be fully characterised.

2.5.4. Cascade cycloaddition of sulfur-substituted alkyne

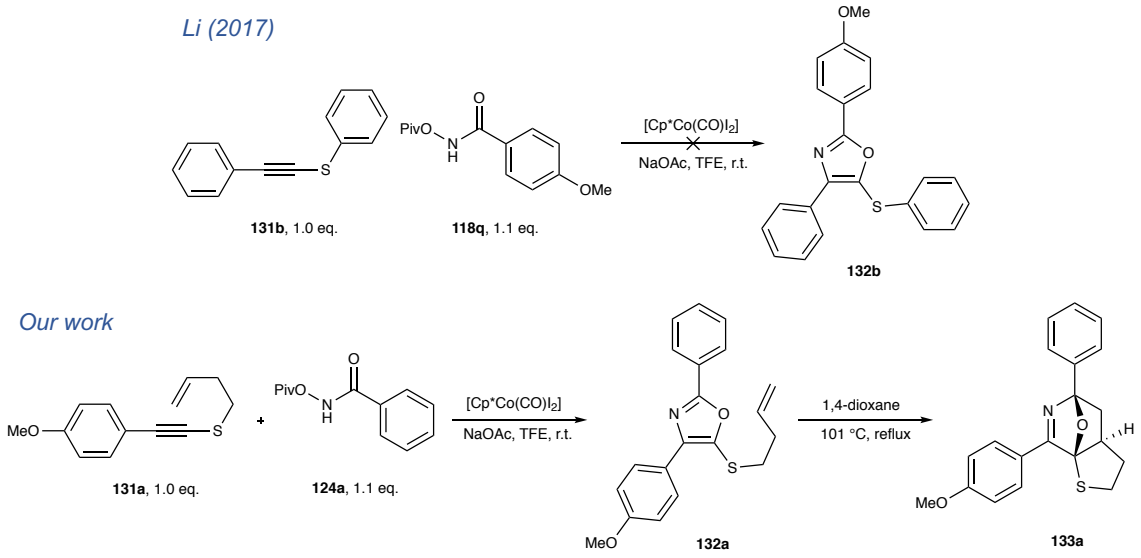
Sulfur heteroatom attracts a significant attention from scientific community due to its abundance in natural products;[134] up to 2018 a thousand of sulfur-containing natural products were isolated from terrestrial and marine sources.[134] Many sulfur-containing compounds display potent biological activities and pharmaceutical properties.[145-146] Over the past years, several synthetic approaches have been developed on the construction of sulfur-containing frameworks in the total synthesis of natural products.[134, 147] Tinoridine is a recent example of such a framework containing a thieno[2,4]pyridine motif.[148] This medicine showed efficient anti-inflammatory and analgesic actions and is currently in phase IV clinical trials.



Scheme 33: Synthetic route attempted to access sulfur-containing oxazoles from known starting materials 131a/124a.

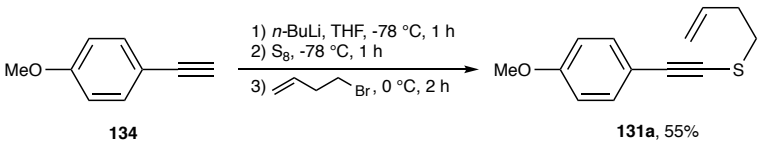
Our idea was to develop novel analogues containing sulfur such as **133a** using the same straightforward methodology described in this chapter with a nitrogen atom (Scheme 33). Thus, thioalkynes could be employed as suitable coupling partners for the polycyclisation sequence and access novel molecular frameworks for further developments. Li[112] and co-workers had tested the sulfur-substituted alkyne **131b** in the cobalt-catalysed formal [3+2] cycloaddition to

form the oxazole **132b** without success (Scheme 34). Based on other results within the group in gold catalysis, we reasoned that using a more electron rich alkyne might enhance its reactivity by polarisation of the triple bond and so a methoxy substituent was incorporated in the *para* position of the aromatic ring to activate the internal alkyne.



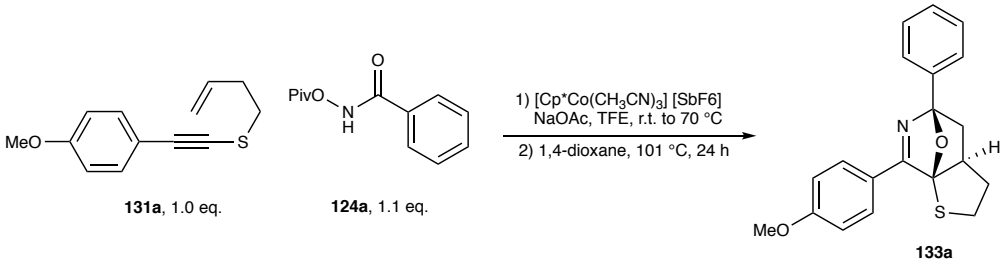
Scheme 34: Cobalt-catalysis tested on the sulfur substituted-alkynes 131a-b to access novel oxazoles.

The starting material **131a** was prepared successfully in 55% yield by a one pot process[149] from the 1-ethynyl-4-methoxybenzene **134** in THF (Scheme 35). Unfortunately, the cobalt-catalysed cycloaddition did not afford the desired oxazole **132a**, the starting material was not consumed (Scheme 34).



Scheme 35: Preparation of the starting material 131a developed within Davies group.

An alternative Co(III)-type catalyst: $[Cp^*Co(CH_3CN)_3][SbF_6]_2$ was then tested in an attempt to synthesis the sulfur-containing oxazole **132a** (Scheme 36). This catalyst was chosen to test the cobalt-catalysed cycloaddition owing to previous study showed success in the preparation of oxazoles with this catalyst.[113] This catalyst was readily prepared in 35% yield from the initial cobalt catalyst $[Cp^*Co(CO)I_2]$, following Glorius modified procedure.[139]



Scheme 36: Cobalt-catalysis tested on the material 131a using an alternative cobalt(III) catalyst.

The polycyclisation was attempted on the sulfur-substituted alkyne **131a** and *N*-(pivaloyloxy)benzamide **124a** in TFE using the freshly prepared catalyst $[Cp^*Co(CH_3CN)_3][SbF_6]_2$. No reaction was seen by TLC at room temperature and so the temperature was increased to 70 °C at which point complete consumption of the starting material **131a** was observed.

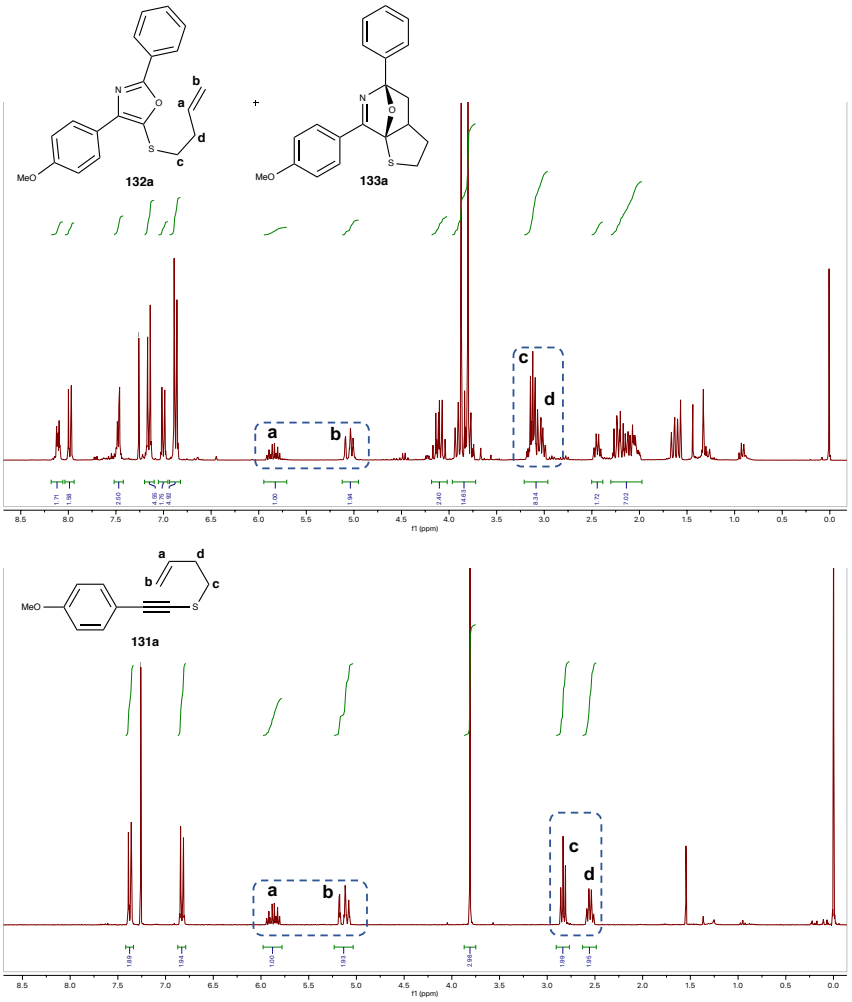


Figure 19: ^{1}H NMR of the starting material 131a (bottom) and the material suspected a mixture of oxazole and Diels-Alder adduct (top).

From analysis of the NMR spectra, several components were identified. Only one of the components incorporated the allyl unit, and this could be correlated to resonances at 5.85 ppm, 5.04 ppm, 3.12 ppm and 3.04 ppm (Figure 19, highlighted peaks a-d), which could indicate some of the oxazole product. The characteristic resonances matched those seen in the ^{1}H NMR spectrum of the starting material.

From these observations, I inferred that the ^{1}H NMR spectrum showed a mixture of the oxazole **132a** and the desired cycloadduct **133a**, and so this indicated a promising direction for further diversification studies.

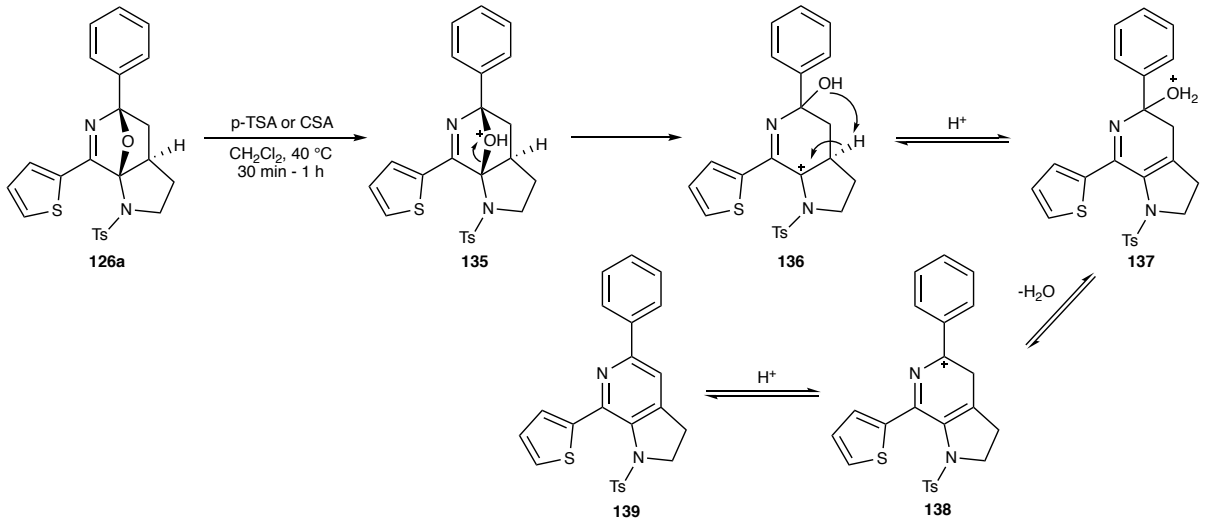
The mixture was further heated at 101 °C and 140 °C respectively in 1,4-dioxane and 1,2-dichlorobenzene, to force the formation of the cyloadduct **133a**. Despite the variation of parameters such as temperature and solvent, the ^{1}H NMR spectrum still showed the mixture of compounds and degradation due to the high temperature used.

2.6 Post-catalytic transformations on resulting cycloadducts

Having explored the substrate scope of the newly developed cobalt catalysed cascade process with a variety of ynamides and *N*-(pivaloyloxy)amides, post-catalysis modifications were explored. The unique reactivity contained within the polycyclic compounds provided multiple points of reactivity to explore and to demonstrate the significant potential of these sp^{3}-rich motifs, such as reduction of the imine and opening the oxygen bridge, dehydration, and deprotection at the nitrogen.

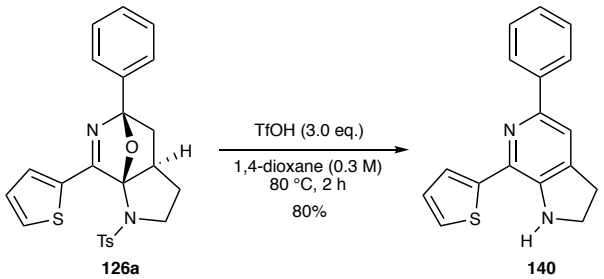
Preliminary work began with the introduction of a Bronsted acid in an attempt to synthesise new azaindoline polycycles. CSA and *p*-TSA were selected for this study in dichloromethane. For both attempts at 40 °C, TLC showed complex mixtures not isolable despite the complete consumption of the Diels-Alder material. The protic acid would induce the cleavage of the

cyclic ether bridge followed by a dehydration to generate the desired pyridine motif (Scheme 37). A complex mixture was isolated showing the formation of several compounds.



Scheme 37: Proposed mechanism for the formation of a pyridine motif using strong acid and temperature.

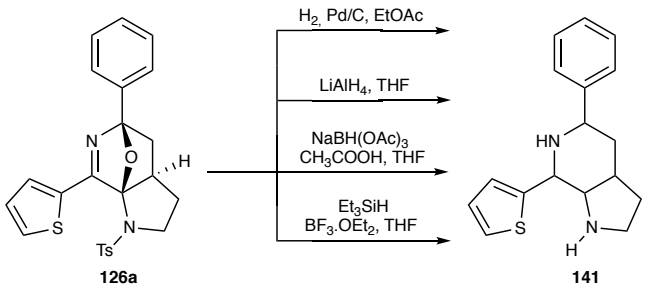
The tosyl protecting group was then cleaved from the compound **126a** using trifluoromethanesulfonic acid in 1,4-dioxane at 80 °C.[150] After 2 hours reaction under these conditions, 80% of the *N*-deprotected pyridine **140** was obtained (Scheme 38).



Scheme 38: Deprotection of the tosyl protecting group using TfOH to access the aminopyridine 140 in one pot.

The reduction of the imine motif was the final post-catalytic transformation attempted in this chapter. Diastereocontrol is an important question in the reduction of this scaffold with three new stereogenic centres set in the reduction leading to 8 possible diastereoisomers. Initial studies focused on seeing whether reactivity could be achieved under different conditions (Scheme 39). The possibility of tuning conditions and reagents to enhance any observed diastereoselectivity was then planned should reactivity be obtained. Under Pd/C catalysed

hydrogenation conditions starting materials were recovered even at elevated temperature at 70 °C.

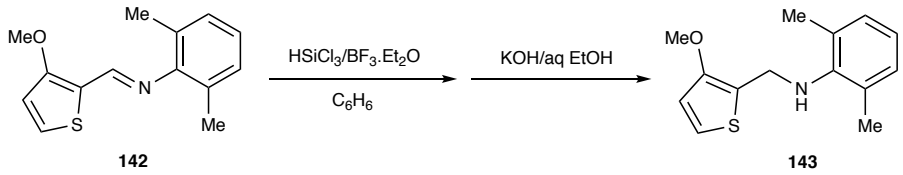


Scheme 39: Different imine reduction conditions attempted on the cycloadduct 126a.

It was interesting for a first study focused on the reduction of cyclic imine to probe a selection of various hydride source strength. The nucleophilic reducing agents $LiAlH_4$, $NaBH(OAc)_3$, and Et_3SiH as potent sources of hydrides for the reduction of the cyclic imine **126a**.

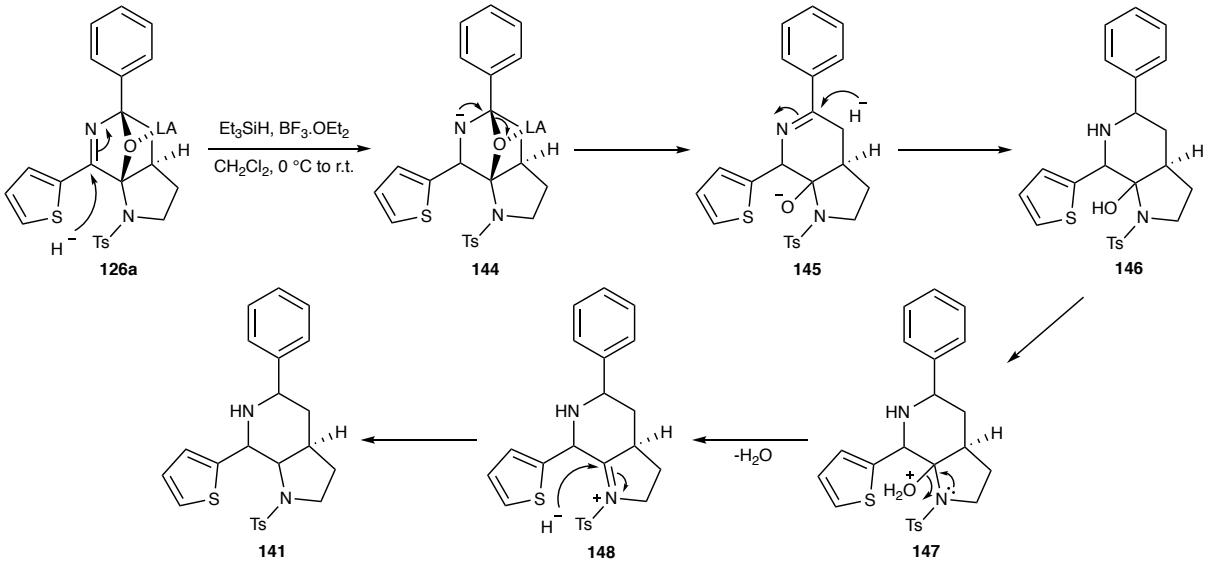
$LiAlH_4$ was employed as a stronger and non-chemoselective reducing agent. $NaBH(OAc)_3$ in acetic acid is a highly selective reducing agent especially for reductive aminations, as well a mild silicon-based reducing agent Et_3SiH selected. Despite the variation of reductant and temperature from 0 °C to 60 °C probed for the imine reduction, the desired cyclic **141** amine was unfortunately not observed, only starting materials were observed on the ^1H NMR analyses.

The reductive process was also studied to access to cyclic amine **141** by a treatment of the Lewis acid and $BF_3.OEt_2$ from 0 °C to room temperature. A reductive process developed in 1991 by Okamoto[151] and co-workers using a silane Cl_2SiH_2 and a Lewis acid $BF_3.OEt_2$ showed an efficient imine reduction in 90 % yield (Scheme 40).



Scheme 40: Reductive imine procedure *via* a silane and a Lewis acid developed by Okamoto.

The Lewis acid would coordinate to the oxygen bridge to help the attack of a lone pair electron from one of the nitrogens connected from each side of the oxygen bridge. The nitrogen lone pair electrons being too far in the plan to readily participate in the opening oxygen bridge, a source of hydrides was necessary (Scheme 41).



Scheme 41: Proposed mechanism of cyclic imine reduction through a Lewis acid and dehydration.

Thus, this strategy was adapted to our study and the cycloadduct **126a** was treated with Et_3SiH combined to the Lewis acid $BF_3.OEt_2$. After 20 h at room temperature, TLC showed the consumption of the starting material. After purification by flash column chromatography, the ^1H NMR spectrum showed the formation of a new compound. The shift of aromatic peaks and additional aliphatic peaks between 4.84 ppm and 1.48 ppm might highlight a ring opening single reduction and might conduct to the piperidine system **131** (Figure 20). This reaction will be repeated to confirm the outcome by full characterisation.

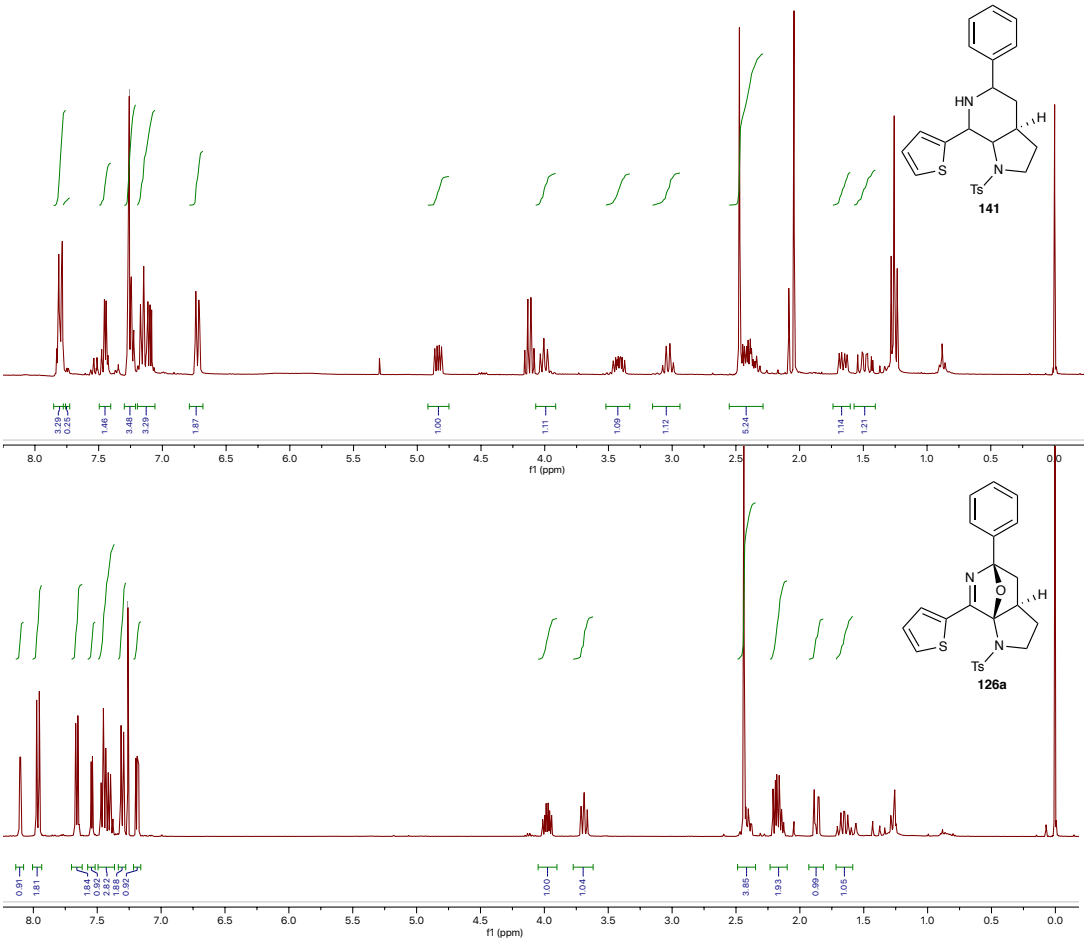


Figure 20: Stacked spectra showing the imine reduction through Et_3SiH and $BF_3.Et_2O$ (top) and the starting material 126a (bottom).

2.7 Outlook and future work

The cobalt-catalysed polycyclisation process elaborated within the lab has been provided a direct access to a range of bicyclic azacycles. The efficiency and robustness of this methodology has been demonstrated with successful preparation of the Diels-Alder adduct in a gram scale, allowing to undertake further post-catalytic diversification.

The outcomes of the polycyclisation process have showed functional group compatibility with varied sulfonyl groups and heteroaryl substituents across ynamides and *N*-(pivaloyloxy)amides starting materials (Figure 21), but no compatibility with aliphatic substituents. The incorporation of stereocentres on the dienophile tether and the application of a thioalkyne as a

coupling partner for the polycyclisation sequence were both challenging works but offered promising indications for further developments.

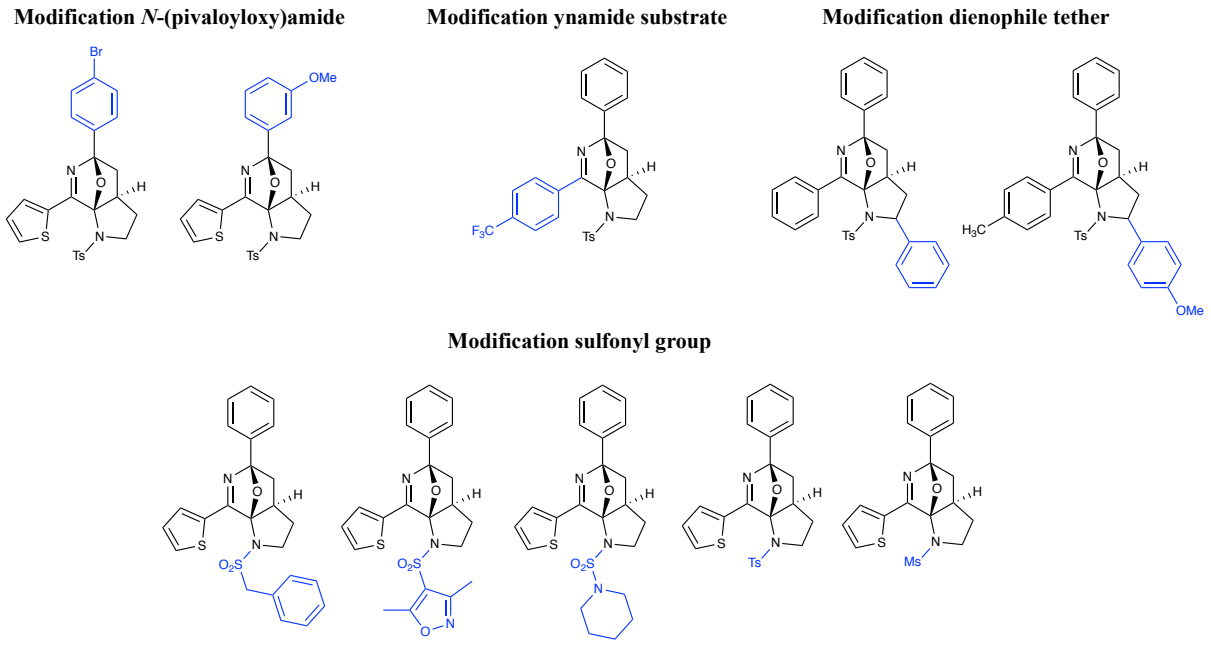


Figure 21: 3-amino-azacyclic scaffolds accessed through cobalt-catalysed polycyclisation process.

Finally, post-catalytic transformations provided pyridine products with tosyl cleavage, which provides a straightforward route into 6-azaindolines. Furthermore, initial studies have indicated possible piperidine-fused system after reduction of the cyclic imine and oxy-bridged motif. These studies demonstrate the potential of the ynamide-based polycyclisation approach as a tool to access structural diversification from the same core.

Chapter 3: Copper-catalysed coupling-cascade sequence and diversification of isoquinoline derivatives

3.1 The isoquinoline motif in natural products and drug development

Isoquinoline is a common heterocyclic motif that appears in numerous natural alkaloids displaying a wide spectrum of structural diversity and biological activity.[152-153] These alkaloids exhibit pharmacologically relevant properties such as antimicrobial, antibacterial, antifungal and anti-inflammatory.[154-166] Some examples of natural alkaloids and pharmaceuticals containing isoquinoline motif are listed below (Figure 22).

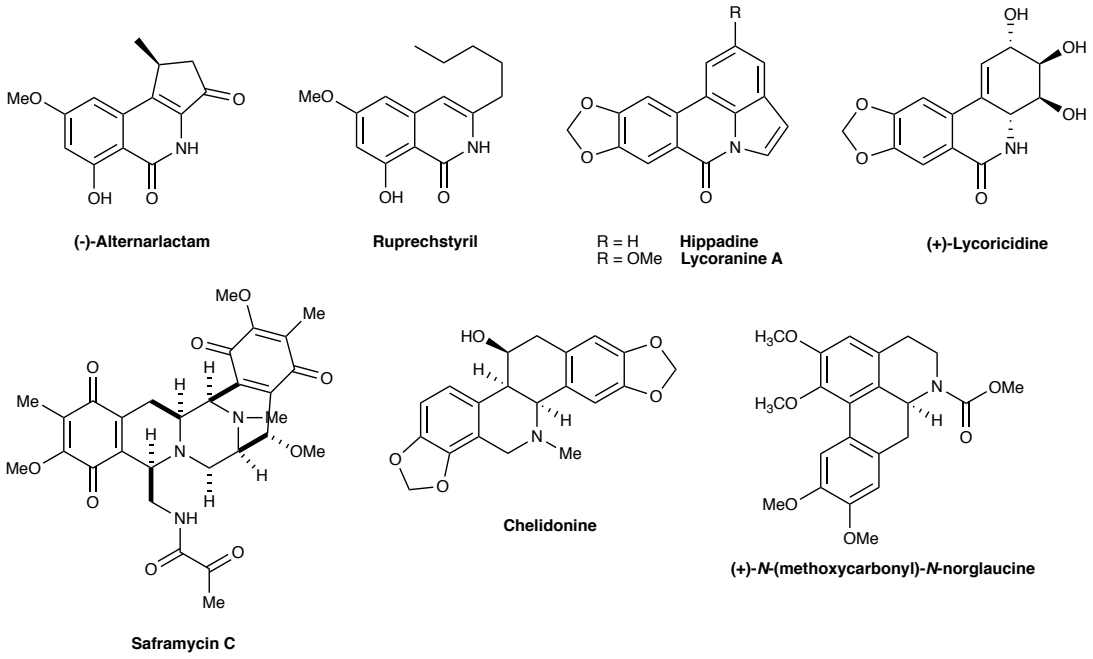
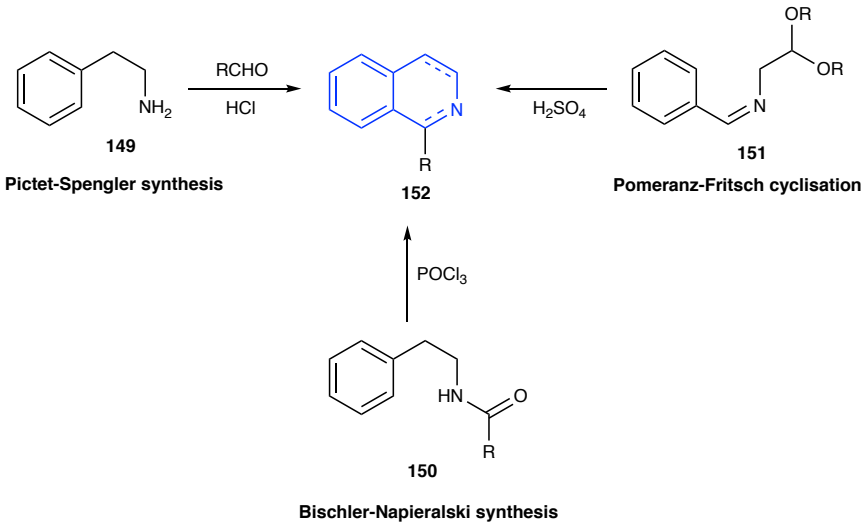


Figure 22: Examples of naturally occurring alkaloids containing the isoquinoline motif.

This heterocyclic ring system is considered to be a "privileged backbone" in drug development, with a range of drug candidates containing this core having reached pre-clinical or clinical trials.[167-168] Over the last decade, the development of novel and efficient strategies have been developed for the construction of highly substituted isoquinoline derivatives, and such derivatives are still a desirable target in modern synthetic chemistry.[153, 169]

3.2 Synthesis of isoquinolines

The well-established methods such as Pictet-Spengler,[170] Bischler-Napieralski[171-172] and Pomeranz-Fritsch[171, 173] reactions have frequently been employed in the construction of isoquinoline alkaloids at different situation levels (Scheme 42). However, these methods developed in the late 1800's and early 1900's require high temperatures and strongly acidic conditions to generate imines before cyclisation into aromatic systems.[152, 169] The harsh reaction conditions are required to compensate for the weak electrophilicity of the imine generated, however this also has an effect on the structural and functional group tolerance of the reaction. Thus it is desirable to have methods which lead to this skeleton under mild conditions.[152]

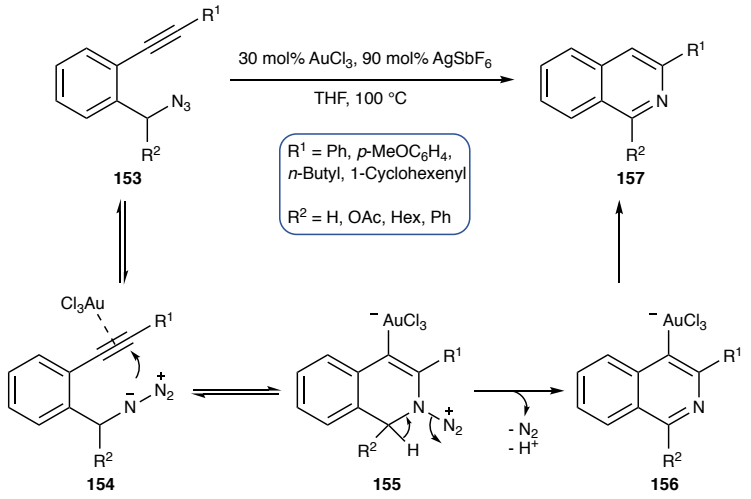


Scheme 42: Classical methods to access (hydro)isoquinoline skeletons at different oxidation levels.

Due to a growing interest in the preparation of structurally and stereochemically complex alkaloids, efficient alternative methods have been developed involving different transition metals.[169, 174] The mild conditions of these new approaches allow access into more varied isoquinoline structures, as described below.

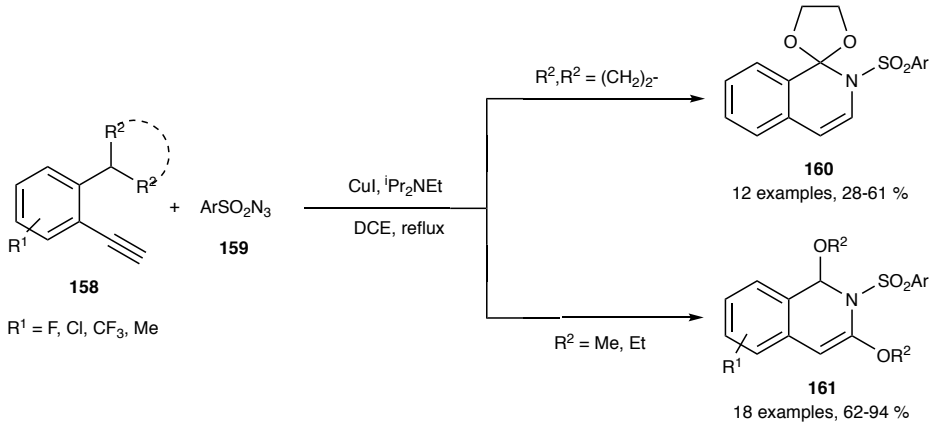
In 2009, Yamamoto[175] and co-workers reported an efficient synthesis for the preparation of isoquinolines **157** from 2-alkynylbenzyl azides **153** *via* a gold-catalysed cycloaddition in good yields (Scheme 43). However, this method is still limited as it involves the use of potentially

explosive starting materials, high loading of expensive catalyst, an elevated temperature for the reaction to occur and a limited functional groups tolerance.



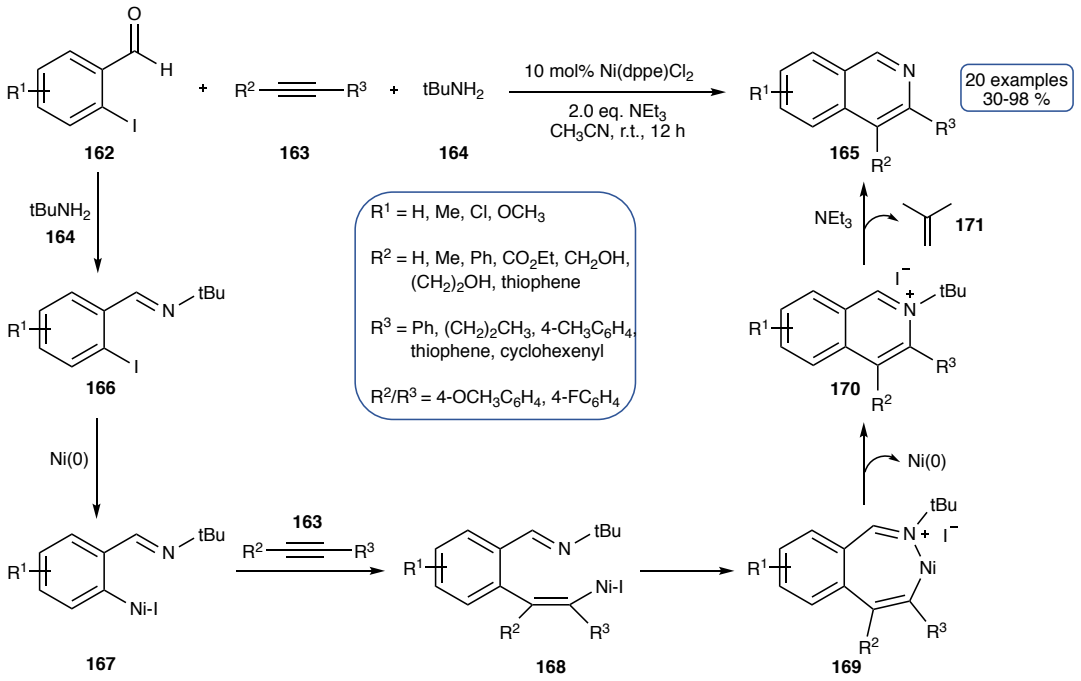
Scheme 43: Gold-catalysed cycloaddition of 2-alkynylbenzyl azides 153.

In 2013, Wang[176] and co-workers developed a method for the preparation of dihydroisoquinoline derivatives from *o*-ethynylbenzacetals **158** and sulfonyl azides **159** using a copper catalyst, under mild reaction conditions. A cascade process involved a copper-catalysed alkyne-azide cycloaddition (CuAAC), Dimroth rearrangement, 1,5-OR or 1,5-H shift and 6π-electrocyclic ring closure to generate 1,3 and 1,1-dialkoxy 1,2-dihydroisquinolines **160** and **161** in moderate to excellent yields (Scheme 44). Despite varied functional group tolerance, the use of azides and a hazardous solvent is still undesirable.



Scheme 44: Copper-catalysed cycloaddition from *o*-ethynylbenzacetals 158 and sulfonyl azides 159.

In 2018, Zhang[177] and co-workers reported an efficient and scalable route for the synthesis of 3,4-disubstituted and 3-substituted isoquinolines **165** at room temperature (Scheme 45). Through this nickel-catalysed one pot three component reaction, a broad substrate scope was achieved from simple starting materials: 2-halobenzaldehydes **162**, alkynes **163** and *tert*-butylamine **164**. Moreover, an inexpensive air-stable nickel precatalyst was employed, combined with triethylamine which was found to be crucial to obtain high yields.

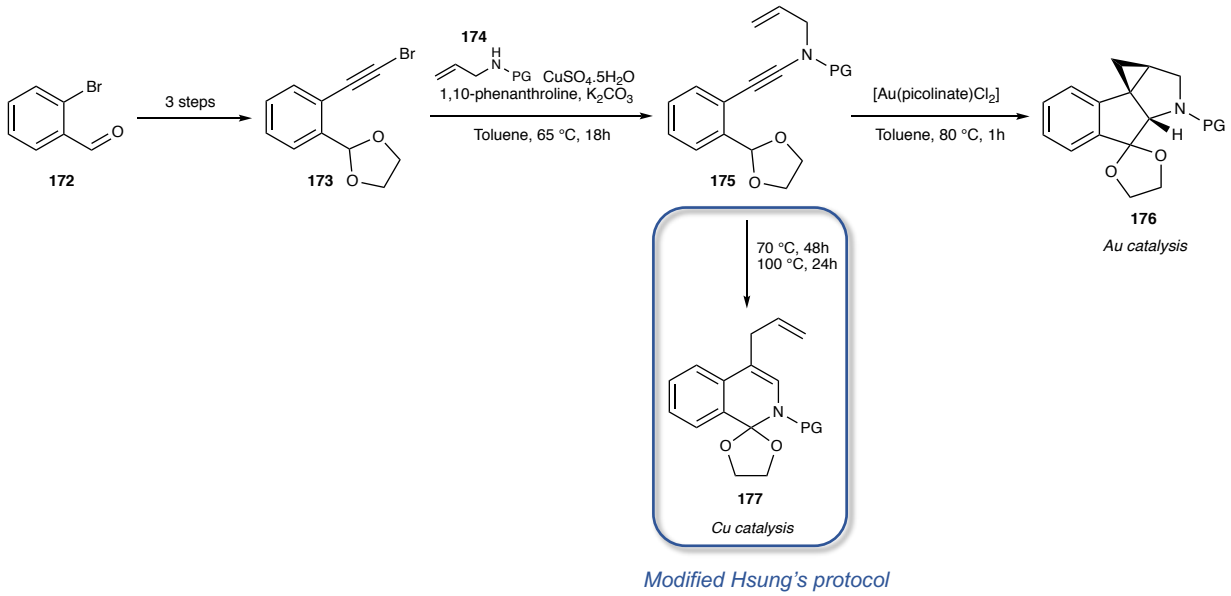


Scheme 45: Nickel-catalysed one pot three-component reaction with 2-halobenzaldehydes 162, alkynes 163 and tert-butylamine 164.

These processes represent some examples of intermolecular transition metal catalysed syntheses to effectively access a wide variety of isoquinolines. Despite the advances in the synthesis of functionalised isoquinolines, such methods still require hazardous materials, high catalyst loading and high temperatures. Although requiring an elevated temperature of 100 °C, our method is appealing owing to the advantages of safe and easily accessible precursors, the use of an inexpensive copper catalyst and the formation of several bonds in a one step.

3.3 Copper-catalysed coupling-cascade reactions to access isoquinoline derivatives

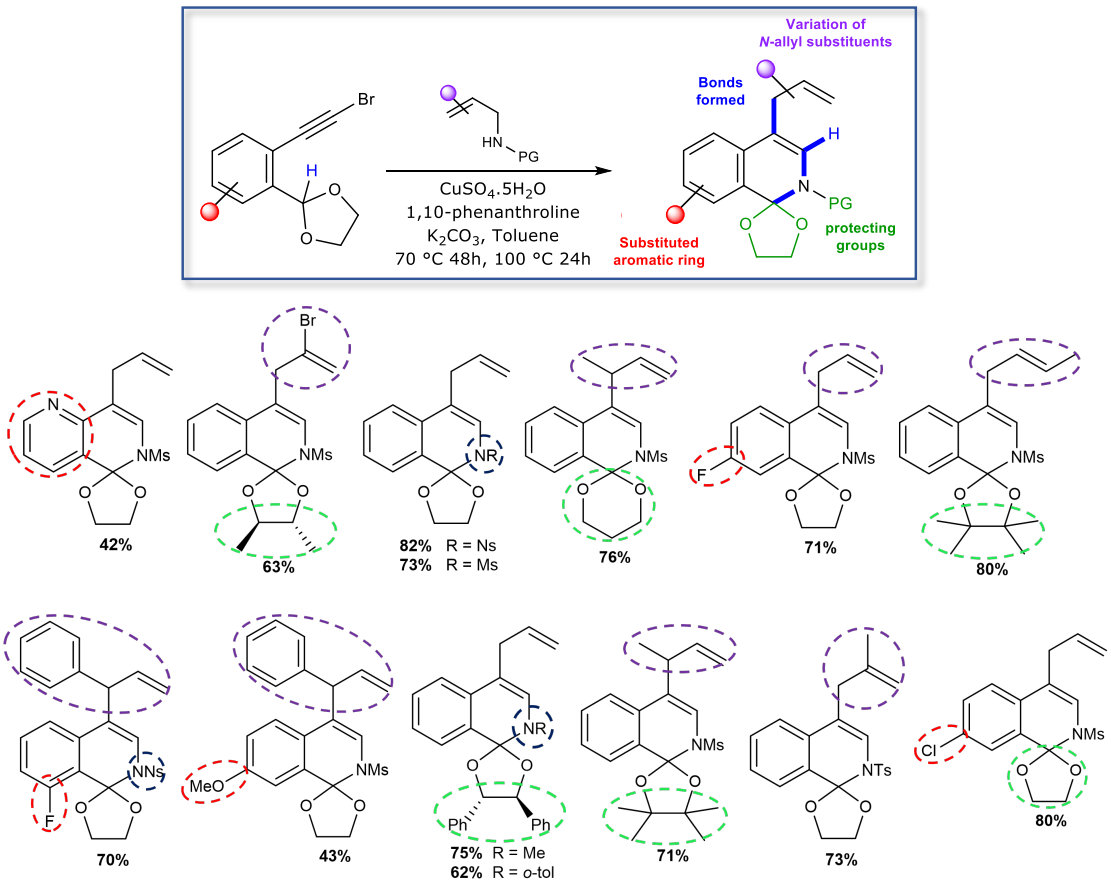
Davies group members discovered a rapid and straightforward route to access the isoquinoline core from ynamides.[43] This interesting finding was made during the exploration of gold-catalysed intramolecular cycloisomerisation reactions from *N*-allyl ynamides to access functionalised tetracycles.[59] Ynamide precursors were prepared in five simple steps and are discussed later in this chapter. Several cascade pathways were accessible from ynamide species, one of them was the cobalt-catalysed method to make functionalised azabicycles which is previously described in chapter 2. Modification of the temperature and catalyst allows the selective formation of polycycles **176** or **177** (Scheme 46). The polycycle **176** is accessible in simple two steps: first by formation of ynamide **175** according to Hsung[63] methodology then by an intramolecular gold-catalysed cycloisomerisation. Subsequently it was found that modifying the ynamide formation step by elevating the temperature up to 100 °C, the ynamide **175** underwent an internal cyclisation in presence of the copper catalyst to form the polycycle **177**.



Scheme 46: Synthetic routes for the formation of two different polycycles *via* gold or copper catalysis.

Following on from the discovery of the new route to yield isoquinoline **177** from ynamides **175**, the two steps can be combined in a one pot copper-catalysed cascade coupling and cyclisation.[178]

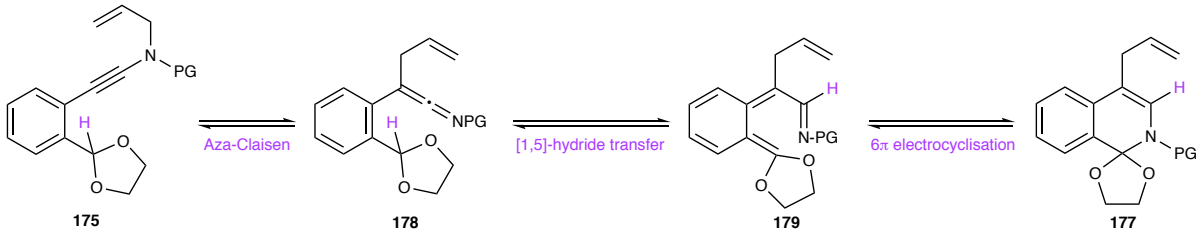
The copper catalyst used is environmentally safe and inexpensive thus reducing the number of steps and purifications as well as chemical waste.[179-181] The transformation into azacycle was optimised by applying an elevation of temperature to 70 °C for 48 hours and then to 100 °C for 24 h, and permitted to generate a series of highly functionalised isoquinoline systems in moderate to excellent yields (Scheme 47).[178] The Hsung conditions[43] were adapted for these particular substrates.



Scheme 47: A series of dihydroisoquinolinone derivatives prepared through the copper-mediated cascade cyclisation.[178]

The proposed mechanism for this cascade cyclisation occurs initially by aza-Claisen rearrangement of the ynamide intermediate **175** to generate a ketenimine species **178** *in situ*. A

subsequent [1,5]-migration of the acetalic proton of **178** yield the imine intermediate **179**. The [1,5]-hydride migration is facilitated by the hydricity (hydride transfer ability) of the acetalic function. Finally, a 6π-electrocyclic ring closure of **179** was proposed to restore aromaticity and afford the dihydroisoquinolines **177** (Scheme 48).[178]



Scheme 48: Proposed mechanism of the formation of isoquinoline motif *via* copper catalysis.

The exact role of the copper is not completely established at this stage. However, the copper catalyst might potentially play a role during each stage of the cascade cycloaddition. Alajardin[182-183] and Wang[176] studied the hydricity of acetalic proton atoms in [1,5]-hydride shifts for the syntheses of 4-quinolinones and 1,2-dihydroisoquinolines. Thus, the [1,5]-hydride transfer and 6π-ERC steps are analogous to our mechanistic approach.

3.4 Aim and objectives

The aim of the following work was to determine whether this new method is a practical and scalable tool to access the isoquinoline core and to determine the attractiveness of such scaffolds for accessing drug-like chemical space. Preliminary studies showed the potential of this method for the synthesis of a series of functionalised isoquinoline systems. To complete this study and test the practical aspect of this method, the copper-catalysed cascade reaction was scaled up. It would be advantageous to easily prepare material on a large scale for the creation of a compound library and for further developments.

The functional group reactivity on this novel scaffold was then tested by performing post-catalytic reactions such as hydrogenation, hydroboration and deprotection of reactive sites.

Specifically, the reactivity of the internal alkene was investigated to know whether this alkene can be functionalised selectively (Figure 23). The deprotection would also offer an easy way to oxyisoquinoline, a desirable system due to its presence in natural products.

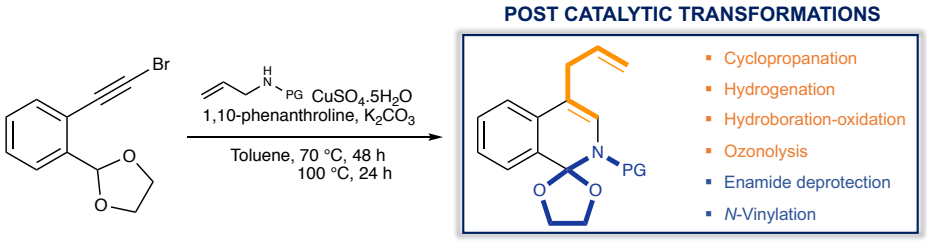


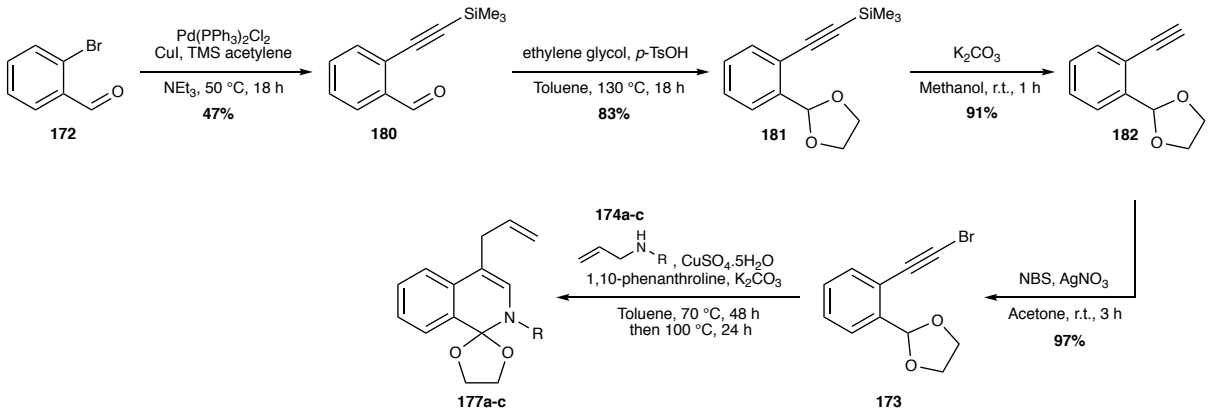
Figure 23: Plan of post-catalytic transformations on the new dihydroisoquinoline scaffold.

Thus, we wanted to demonstrate whether the one pot copper-catalysed polycyclisation strategy allowed rapid access to diversified dihydroisoquinolines and whether those frameworks could be used to access oxyisoquinoline systems or could be used as building blocks.

3.5 Post-catalytic reactions: deprotection of reactive sites

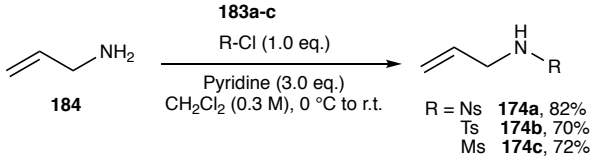
3.5.1 Preparation of starting materials

The ynamide precursors employed in the study of the copper-catalysed cascade reaction were prepared by a simple five step route and were scaled up (Scheme 49).[59] The first reaction was the silylation of the commercially available 2-bromobenzaldehyde **172** through a Sonogashira coupling to afford silylated alkyne **180** in a 47% yield. The ketone functionality was then protected through the acid catalysed acetalisation using ethylene glycol to give the acetal derivative **181** in a good yield (83%). The trimethylsilyl group on **181** was cleaved in presence of potassium carbonate in methanol to afford the terminal alkyne **182** in a good yield (91%). These three steps required a purification by flash column chromatography to give pure materials for the next step reactions. The last step before the copper-catalysed polycyclisation was the bromination of the alkyne **182** using *N*-bromosuccinimide and silver nitrate in acetone. A quick filtration in a pad of silica afforded the bromoalkyne **173** in 97% yield.



Scheme 49: A five step route to successfully access a protected dihydroisoquinolinone scaffold.

Following the procedure used in chapter 2, the sulfonamides **174a**, **174b** and **174c** were prepared in 82%, 70% and 72% respectively, and in sufficient amount for the copper-catalysed coupling to be undertaken on a 1 g scale (Scheme 50).



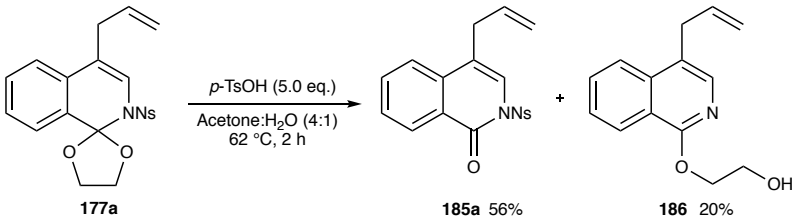
Scheme 50: Preparation of sulfonamides using allylamine 184 and various sulfonyl chlorides 183a-c.

The dihydroisoquinoline systems were prepared in a cascade reaction initiated using the adaptation Hsung's methodology (Scheme 49).[63, 178] The ynamide intermediates were prepared after a 48 h reaction in toluene at 70 °C, confirmed with TLC on consumption of the sulfonamide used as the limiting reagent. The temperature was then elevated to 100 °C for 24 h until consumption of the ynamide intermediate was observed by TLC. After purification by flash column chromatography in a hexane/ethyl acetate, the dihydroisoquinoline products were synthesised in good yields (56% for **177a**, 80% for **177b** and 66% for **177c**).

This demonstrated the ease of the synthesis and handling on a large scale and enabled study of these scaffolds in post-catalytic transformations aimed at exploring whether the new heterocyclic motifs could be used to novel scaffolds with potential bioactivity.

3.5.2 Deprotection of the enamide

The first post-catalytic reaction attempted was the acetal deprotection on the dihydroisoquinoline in acidic conditions (Scheme 51).[184] The nosyl protected isoquinoline **177a** was reacted with excess *p*-TsOH under reflux in acetone:water (4:1); after 2 h complete consumption of starting material and the appearance of two distinct products was observed by TLC under UV. Flash column chromatography on silica gel allowed isolation of both products and following full characterisation they were identified as the desired deprotected enamide **185a** and the ether **186,** formed simultaneously during the reaction in 56% and 20% yield respectively.

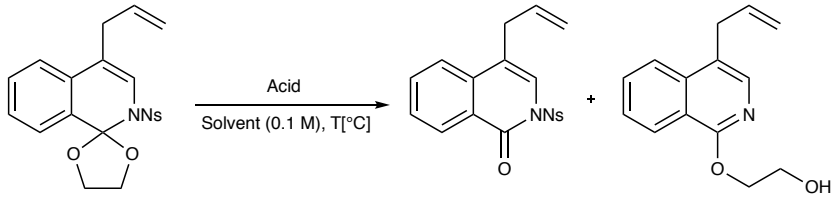


177a **185a** 56% **186** 20%

Scheme 51: First enamide deprotection attempted in acidic conditions.

Using isoquinoline **177a** as a model substrate, the reaction was optimised by varying the acid, reaction stoichiometry and the solvent system, as summarised in Table 2. The use of 1 and 5 equivalents of *p*-TsOH in acetone:water (4:1) provided similar results, with **185a** the predominant product in both case (Table 2, entries 1 and 2); whereas reaction with 5 equivalents of *p*-TsOH in methanol or acetone afforded product **186** only (Table 2, entries 3 and 4), with a higher yield of 75% when methanol was used. Using 1 eq of HCl in THF gave **186** predominantly (Table 2, entry 5), whilst 5 eq afforded the formation of both **185a** and **186** in a roughly equal ratio (Table 2, entry 6).

Table 2: Optimisation study for the deprotection of enamide 177a.

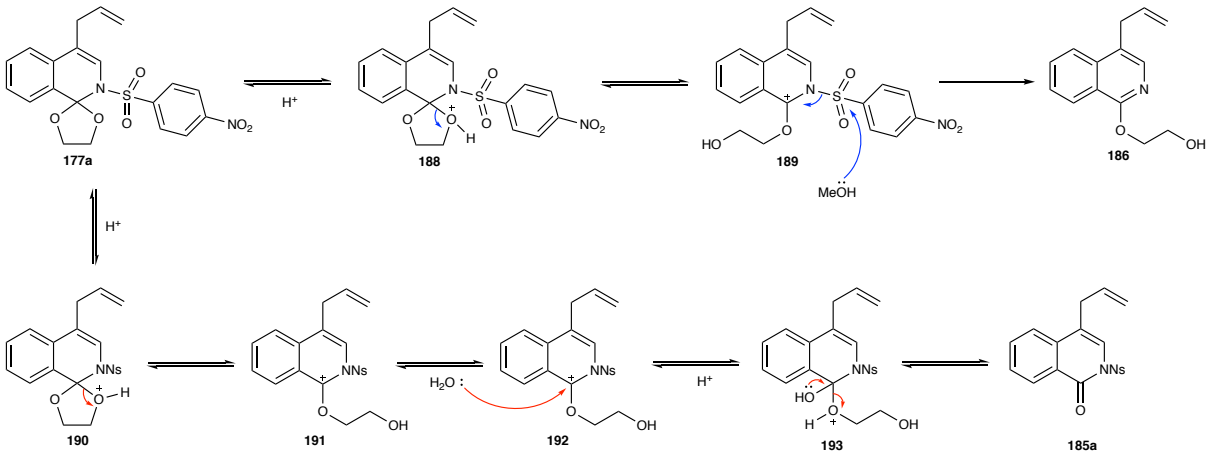


177a **185a** **186**

Entry	Equiv. Acid	Acid	Solvents	Ratio solvents	T[°C]	Yield [%][c] 185a : 186
1	1.0	*p*-TsOH	Acetone:H_2O	4 : 1	62	51 : 37
2	5.0	*p*-TsOH	Acetone:H_2O	4 : 1	62	50 : 39
3	5.0	*p*-TsOH	Methanol	-	62	- : 75
4	5.0	*p*-TsOH	Acetone	-	62	- : 46
5	1.0	$HCl_{(aq)}$	THF	-	50	15 : 57
6	5.0	$HCl_{(aq)}$	THF	-	50	31 : 35
7	5.0	$HCl_{(aq)}$	THF:H_2O	4 : 1	50	22 : 38
8	5.0	$HCl_{(aq)}$	THF:H_2O	1 : 1	50	37 : 43

Reaction conditions: **177a** (0.035 mmol, 1.0 equiv), HCl [2.0 M], yield calculated by ^{1}H NMR spectroscopy against a known quantity of internal standard (1,2,4,5-tetramethylbenzene).

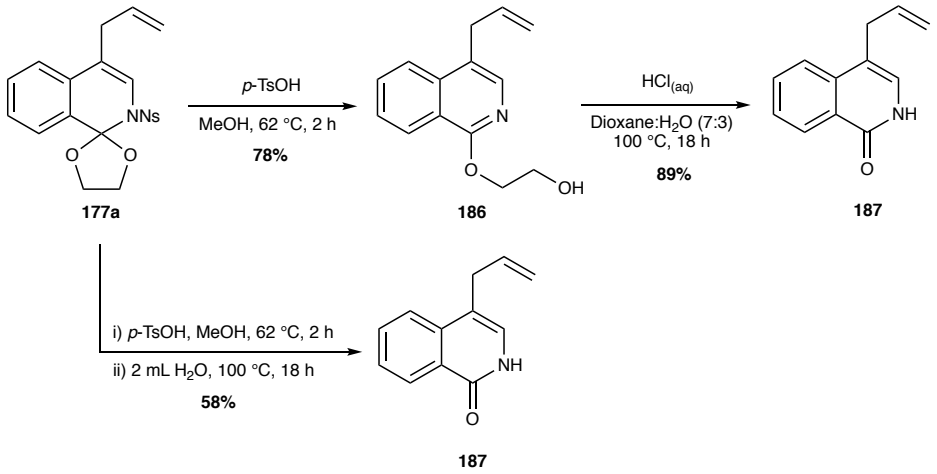
Two findings in particular were of note: reaction with *p*-TsOH in acetone:water predominantly formed *N*-sulfonylisoquinolinone **185a**, whereas *p*-TsOH in methanol formed only the ether **186** (*c.f.* entry 1 vs 3 and 4).The reason why products **185a** or **186** were favoured under certain conditions might be explained by the absence of water; nosyl deprotection occurs before acetal hydrolysis so there is a strong driving force for the formation of aromatic ether **186** (Scheme 52, top mechanism).



Scheme 52: Proposed mechanismes of acetal hydrolysis of scaffold 177a.

Moreover under acidic conditions (HCl in dioxane:water) at 100 °C, **186** could be cleaved to **170** in good yield (89%).[185] Based on these results above I found a way to combine the two

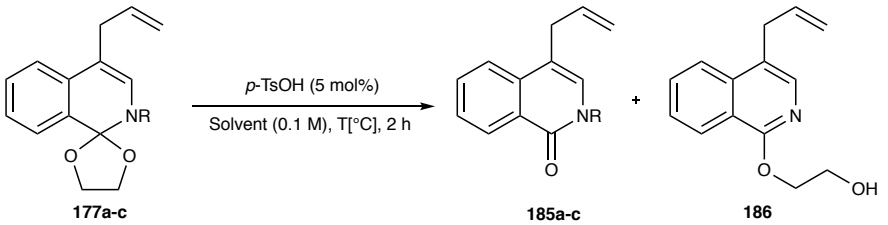
conditions in a one pot process which allows **185a** and **187** to be accessed directly as shown in *Scheme 53*. The substrate **177a** was reacted under reflux with *p*-TsOH in methanol until its consumption was observed by TLC; water was then added to the reaction mixture followed by heating the reaction at 100 °C for 18 hours. Subsequent flash column chromatography allowed the isolation of the enamide **170** in 58% yield.



Scheme 53: One pot reaction developed to access full-deprotected enamide 187.

The conditions described in Table 3 were repeated using different amine protecting groups. Tosyl and mesyl sulfonamides have been shown to be well tolerated in copper catalysis and were selected for the post-catalytic study. All conditions probed are summarised in Table 3, below. As with the nosyl protected isoquinoline **177a,** the reaction using *p*-TsOH in MeOH provided only the ether **186** in 92% and 79% yield from the tosyl and mesyl protected isoquinolines respectively. However, contrary to nosyl protected **177a**, the reaction with *p*-TsOH in acetone:water saw predominant formation of product **186** from both **177b** and **177c** rather than products **185b** and **185c** (Table 3, entries 5 and 6, Scheme 53).

Table 3: Influence of the sulfonyl groups in the enamide deprotection.



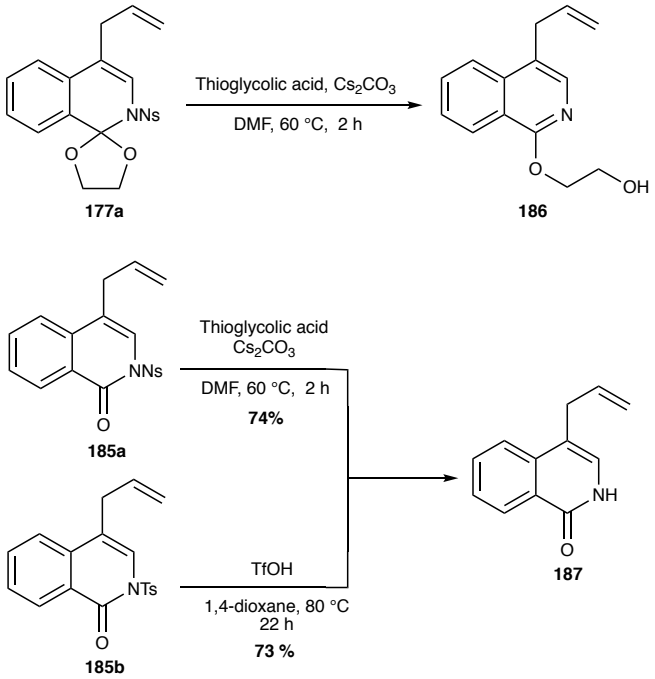
177a-c 185a-c 186

Entry	177a-c	R	Acid	Solvents	Ratio solvents	T[°C]	Yield [%] 185a-c : 186
1	**177a**	Ns	*p*-TsOH	Methanol	-	62	- : 78
2	**177b**	Ts	*p*-TsOH	Methanol	-	62	- : 92
3	**177c**	Ms	*p*-TsOH	Methanol	-	62	- : 79
4	**177a**	Ns	*p*-TsOH	Acetone:H_2O	4 : 1	62	50 : 41
5	**177b**	Ts	*p*-TsOH	Acetone:H_2O	4 : 1	62	22 : 66
6	**177c**	Ms	*p*-TsOH	Acetone:H_2O	4 : 1	62	9 : 56
7	**177a**	Ns	$HCl_{(aq)}$	Dioxane:H_2O	7 : 3	80	34 : 57
8	**177b**	Ts	$HCl_{(aq)}$	Dioxane:H_2O	7 : 3	80	13 : 80
9	**177c**	Ms	$HCl_{(aq)}$	Dioxane:H_2O	7 : 3	80	17 : 56

Reaction conditions: **177a-c** (0.12 mmol, 1.0 equiv), HCl (2.0 M).

3.5.3 Deprotection of the amine protecting groups

Thioglycolic acid was used successfully to remove the nosyl protecting group from piperidine-fused systems (discussed in the chapter 2).[186-187] Nosyl deprotection of substrate **177a** was first attempted with thioglycolic acid and cesium carbonate in DMF at 60 °C providing the isoquinoline ether **186** and confirmed by the crude ^{1}H NMR spectrum (Scheme 54). Enamide **185a**, which had already been subject to ketone deprotection, afforded the desired unprotected isoquinolinone **187** in 74% yield (Scheme 54).



Scheme 54: Nosyl and tosyl amine deprotection from substrates 177a and 185a-b.

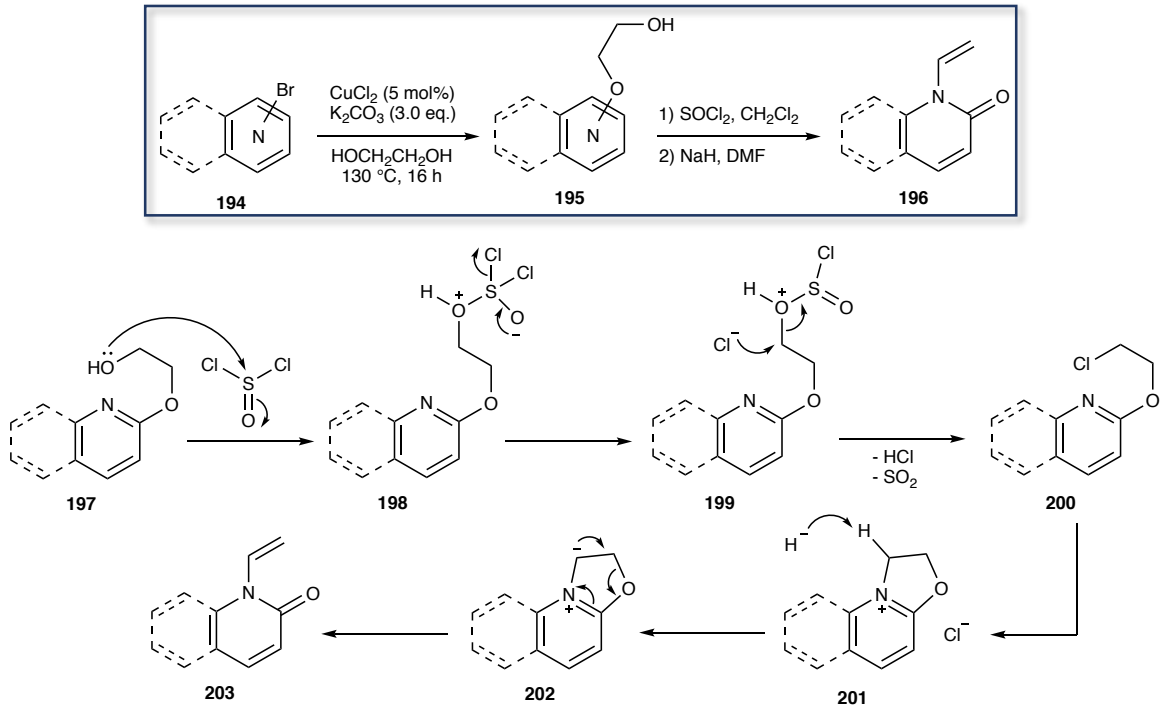
The *N*-tosyl oxyisoquinoline **185b** can also be successfully deprotected to the 4-allylisoquinolinone **187** under acidic conditions, using trifluromethanesulfonic acid in dioxane at 80 °C,[150] providing **187** in a good yield of 73% (Scheme 54).[150]

As discovered in this section, we can make the isoquinoline ether **186** or deprotected enamide **187** selectively under acidic conditions and also showed that a one pot process to make is also possible. Time and resources are saved by removing work up and purification steps, while chemical waste is minimized. The simple cleavage process is useful in our project goal opening up diversity on the scaffold.

3.5.4 *N*-Vinylation of ether 186

In 2016, Dujardin[188] and co-workers developed a convenient method for the synthesis of *N*-heteroaromatic vinyl ethers from corresponding *N*-heteroaromatic bromides through a three-step sequence, consisting of copper-catalysed C-O coupling with ethylene glycol, dehydrochlorination and then dehydrohalogenation of the resultant β-chloroether (Scheme 55).

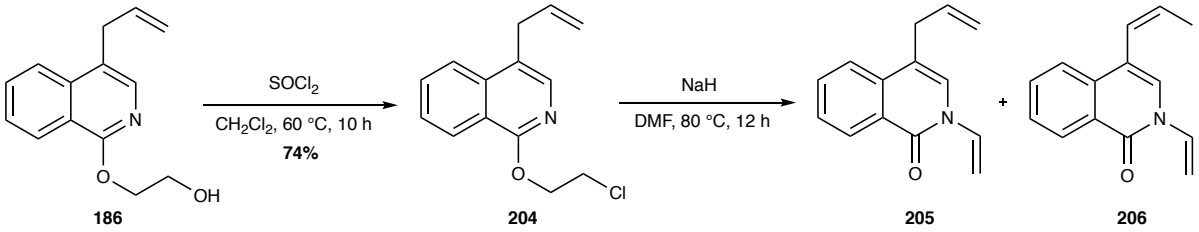
They also demonstrated facile access to *N*-heteroaryl vinyl ethers derived from α-hydroxy pyridines and α-hydroxy quinolines. As we have shown ether substituted isoquinoline **186** to be easily accessible, we sought to explore *N*- vinylation of **186** as a method of further functionalisation.



Scheme 55: *N*-Vinylation of α-bromo-*N*-heteroaromatics *via* 3-step method and proposed mechanism.

The incorporation of a vinyl group on the nitrogen of the isoquinoline would allow introduction of diversity and increase complexity on this part of the scaffold. The *N*-vinylation of **186** was performed in two steps, the first of which was dehydrochlorination using thionyl chloride in refluxing CH_2Cl_2. The chlorinated intermediate **204** was isolated in 74% yield after flash column chromatography. Intermediate **204** then underwent a base mediated *O*- to *N*-vinyl migration employing NaH in DMF at 80 °C for 18 hours to afford a mixture of *N*-vinylisoquinolinones **205** and **206** (Scheme 56). The consumption of the starting material was observed on TLC with the appearance of a new spot corresponding to the mixture of **205** and **206**, confirmed by ^{1}H NMR analysis. This outcome could be explained by the acidic conditions and temperature used in this reaction. Under these conditions, the alkene was protonated to

form a carbocation intermediate and the alkene was re-formed by losing a proton from the other position. This reprotonation allowed the more stable product to form preferentially under thermodynamic control.



Scheme 56: Two step reaction in the methylation of the ether substrate 186.

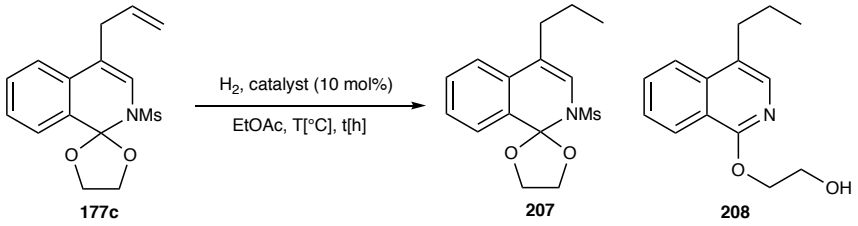
3.6 Post-catalytic reactions: reactions of the exocyclic alkene

3.6.1 Hydrogenation

Further scaffold diversification was explored through by the exocyclic alkene as a handle for introducing diversity. Previously the substrate scope has shown that different allyl groups were readily introduced. Hydrogenation was performed on the scaffold **177c**, utilising Pd/C and PtO_2 as catalysts under H_2 at both room temperature and 70 °C (Table 4).[189-190] In both cases the more reactive exocyclic alkene was selectively hydrogenated to yield **207**, in 40% and 95% yield when using Pd/C and PtO_2, respectively.

Hydrogenation was re-attempted with Pd/C at 70 °C. TLC analysis showed initial hydrogenation of **177c** to **207**, which could be seen to undergo further transformation at elevated temperatures, yielding acetal deprotected isoquinoline **208** as the sole product in 43% yield.

Table 4: Hydrogenation of the alkene on the scaffold 177c.



177c 207 208

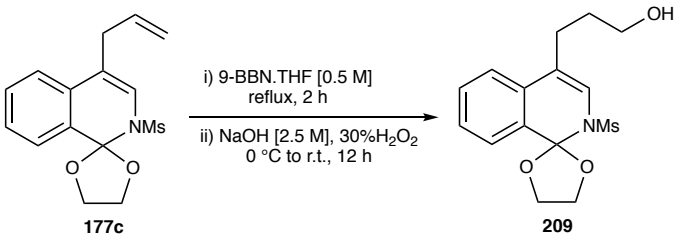
Entry	Catalyst	T [°C]	t [h]	Yield [%] 207 : 208
1	Pd/C	25	1	50 : -
2	PtO_2	25	1	95 : -
3	Pd/C	70	4	- : 43

The hydrogenation showed that the internal alkene was unreactive under the tested conditions (*c.f.* **Table 4**), owing to stabilisation of the internal nitrogen by conjugation. Furthermore, at higher temperatures the reaction conditions induced the enamide deprotection readily after hydrogenation of the exocyclic alkene.

3.6.2 Hydroboration-oxidation one pot strategy

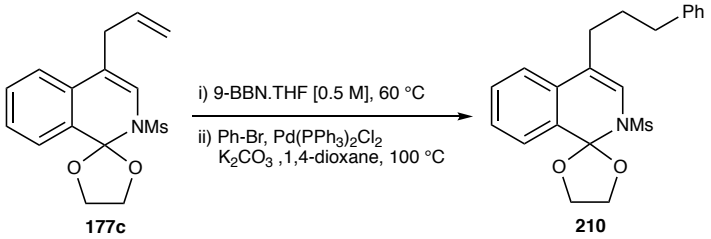
Catechol borane and $Me_2S.BH_3$ were first probed in the alkene hydroboration of substrate **177c**. For both reagents, only starting material was recovered. 9-Borabicyclo[3.3.1]nonane (9-BBN) was then selected for its thermal stability, commercial availability and considerable use in synthetic applications.[191] Moreover, in 2000 Bertozzi[192] and co-workers demonstrated a one pot hydroboration-oxidation strategy on disaccharide substrates employing 9-BBN.

Hydroboration of the exocyclic alkene of **177c** was performed as per Scheme 15; upon reaction with 9-BBN at 60 °C in THF, consumption of the starting material was confirmed via TLC and the excess of 9-BBN was quenched with ethanol at 0 °C. The oxidation was attempted on the crude organoborane with successive addition of NaOH [2.0 M] and 30% H_2O_2 (Scheme 57). The analysis of ^1H NMR spectrum indicated the formation of the desired alcohol **209**. However, this spectrum showed impurities difficult to remove after purification by flash column chromatography.



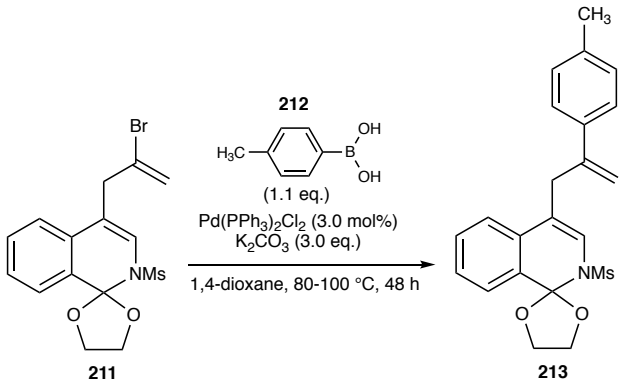
Scheme 57: Hydroboration-oxidation one pot reaction of the alkene 177c.

I also explored a one pot hydroboration and Suzuki cross-coupling, as this could potentially provide a rapid and easy way to introduce diversity on the exocyclic alkene (Scheme 58).[193-194]



Scheme 58: Hydroboration-Suzuki cross-coupling one pot strategy attempted.

Before to attempt this new strategy, the Suzuki coupling was first tried on the material **211** available in the Davies group inventory. The vinyl bromide **211** was reacted $PdCl_2(PPh_3)_2$ catalyst, phenyl boronic acid and K_2CO_3 in 1,4-dioxane (Scheme 59). The temperature was increased gradually from 80 to 100 °C. An intractably complex mixture was observed by TLC and was confirmed by analysis of the ^1H NMR spectrum.



Scheme 59: Attempted Suzuki cross-coupling reaction using the substrate 211 and phenylboronic acid 212.

Unfortunately, this cross-coupling was unproductive and the lack of success was possibly indicated an incompatibility of catalyst and functional groups. This approach was not pursued any further.

3.6.3 Ozonolysis

Ozonolysis can be a clean and effective oxidative reaction, and is used extensively in organic synthesis to provide aldehyde or ketone species by the cleavage of alkenes.[195] Despite the reaction requiring careful risk assessment due to the formation of explosive peroxides, ozonolysis is extensively employed in pharmaceutical synthesis as well as in the preparation of biologically active molecules.[196-199] Recent studies reported the use of the ozonolysis in the final step in the total synthesis of (+)-artemisinin, a potent antimalarial stable peroxide[196] and in the synthesis of D,L-camptothecin analogues showing antitumor properties.[196]

Our project goal was to generate a library of structural diversity of molecules which potentially could be used as building blocks. As hydroboration-oxidation, ozonolysis appeared an attractive route to access structural diversity on our scaffold **177c** *via* an aldehyde. With these reactions, we are able to have different numbers of carbon atoms on the external alkene by oxidation on different carbon atoms (ozonolysis with one carbon less). Thus, we can obtain different homologues from the same starting material **177c**.

Ozonolysis was performed by dissolving the substrate **177c** in methanol at -78 °C. The ozone was generated from oxygen and directly passed through the cold reaction mixture. The blue color solution indicated the presence of unreacted ozone and the complete cleavage of the alkene. Dimethyl sulfide was then introduced to safely reduce ozonides, whilst the excess of sulfide could be removed easily by evaporation.

The ^{1}H NMR spectrum showed a peak at 9.4 ppm which could correspond to an aldehyde functionality and the disappearance of allyl peaks at 5.9 ppm and 5.1 ppm corresponding to the starting material (Figure 24). Despite these results, the spectrum showed a mixture of compounds and the aldehyde could not be isolated completely pure.

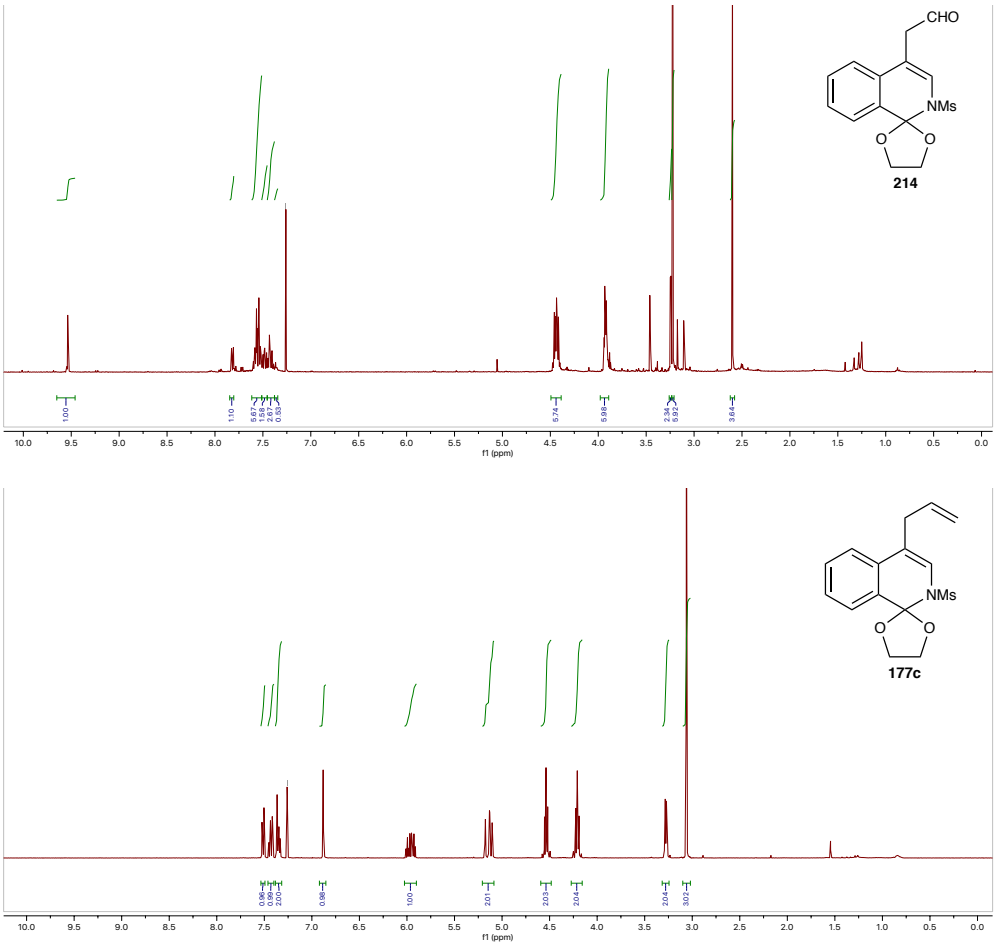


Figure 24: ^{1}H NMR spectra of ozonolysis product 214 (top spectrum) and starting material 177c (bottom spectrum).

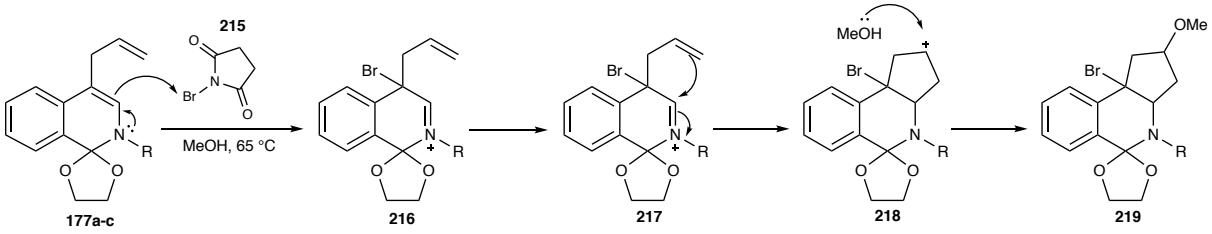
For the future work, the ozonolysis could be re-attempted to access aldehyde **214**, then directly used in the next step reaction such as a reductive amination and to be able to isolate a more stable compound.

3.6.4 Cyclopentane formation from the exocyclic alkene

Another diversification was attempted focusing on the exocyclic alkene as a reactive point for diversification, with formation of tricyclic structure **219** envisioned (Scheme 60). This cyclisation would bring about an increase in molecular complexity, increasing the probability of successful progression in the synthesis of natural product-like frameworks,[33, 200] with molecular complexity being an important parameter involved in drug design.[201-202]

With this cyclisation, we wanted to study the reactivity of both alkenes in this framework. The

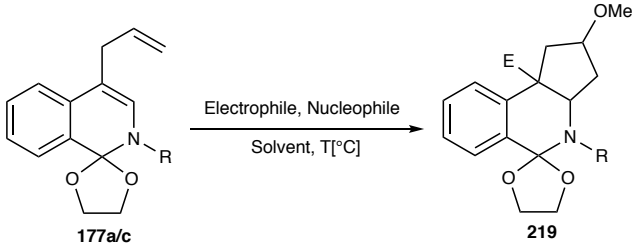
mechanism proposed in the *Scheme 60* showed that the internal alkene was more reactive. Although the hydrogenation studies showed that the exocyclic alkene reacted preferentially due to easy accessibility without any steric hindrance. Our goal in this section was according to the conditions selected to get the internal alkene more reactive and make the tricyclic structure **219**.



Scheme 60: Proposed mechanism for the cyclopentane formation using NBS as electrophile and MeOH as nucleophile.

A halocyclization strategy (Scheme 60) was pursued for the elaboration of **177a-c** to tricyclic **219**. The reaction of **177a-c** with a suitable electrophile, such as NBS or NCS, may generate an iminium cation which can then be quenched by the alkene to yield tricyclic carbocation **218**; attack of a suitable nucleophile, such as MeOH or iPrOH, onto this carbocation may yield desired tricyclic target **219**. The cyclisation was first attempted with the substrates **177a** and **177c**; for some conditions, methanol was used as both a nucleophile and solvent (Table 5).

Table 5: Various conditions attempted for the cyclopentane formation on the exocyclic alkenes 177a and 177c.



Entry	R	Electrophile	Nucleophile	Solvent	T[°C]
1	Ns	NBS	MeOH	-	65
2	Ms	NBS	MeOH	-	65
3	Ns	NBS	MeOH	Toluene	65
4	Ns	NBS	MeOH	1,4-dioxane	80
5	Ns	NCS	MeOH	-	65
6	Ms	NCS	MeOH	-	65
7	Ns	NCS	MeOH	1,4-dioxane	80

Reaction conditions: **177a/c** (0.048 mmol, 1.0 equiv), electrophile (1.1-5.0 equiv.), nucleophile (5.0 equiv.) and solvent (0.2 M).

Despite the variation of the electrophile (NBS and NCS), solvent (toluene and dioxane) and temperature, complex mixtures were observed *via* TLC. The outcome could be explained by potentially formation of diastereoisomers with the presence of three stereocenters and by the deprotection of the acetal. The previous post-catalytic reactions showed the potential of the protected enamide undergo *N*-deprotection at low temperatures under suitably acidic conditions.

In order to facilitate the cyclisation, the *N*-substituted alkene must be suitably electron rich to readily form the necessary cationic iminium intermediate **216**, with the efficiency of this process most likely crucial in avoiding side reactions. As such, for further attempts enamine **187** was used. The cyclisation was attempted using NCS as the electrophile and MeOH as the nucleophile, with solvent and temperature varied. NCS was selected as the electrophile owing to its greater stability than NBS. For all conditions showed in Figure 25, the ^{1}H NMR spectra showed the disappearance of the vinylic proton of the enamine at 7.1 ppm, however resonances assigned to the allyl protons were still observed.

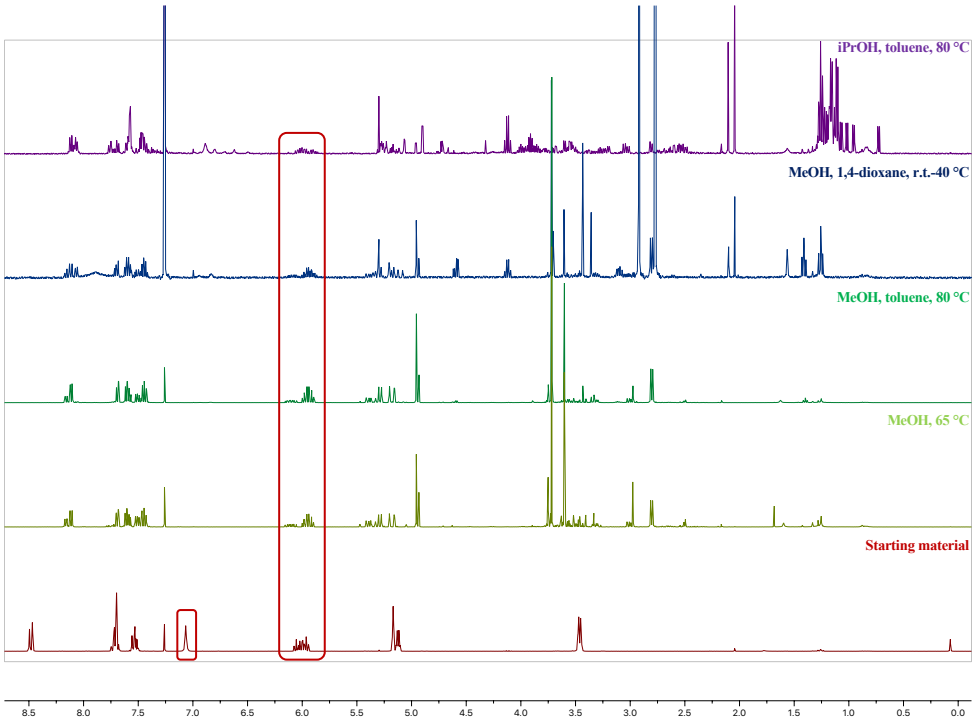
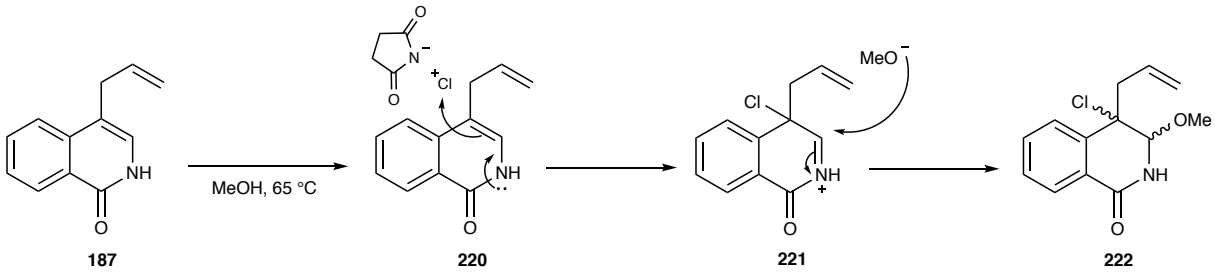


Figure 25: ^{1}H NMR spectra of isolated compounds attempted in various conditions from starting material 187 (bottom spectrum).

Moreover, resonances attributable to incorporation of the MeOH were observed in each instance. This is indicative of alkoxychlorination of the enamine to yield; following initial nucleophilic attack of the enamine unto NCS to yield iminium **196**, nucleophilic addition is by the alcohol additive rather than the pendant alkene (Scheme 61). The complexity of the spectra at 6.00 ppm indicates mixtures of diastereoisomers.



Scheme 61: Proposed mechanism according to the diastereoisomers observed on ^{1}H NMR spectra.

With alkoxychlorination identified as the main competing pathway to the desired cyclisation, the reaction was trialed using a bulkier alcohol, isopropanol, in the hope of avoiding competing alcoholic quenching of the iminium intermediate. The ^{1}H NMR spectrum resulting from this amended protocol is shown in Figure 25 (top), with complex peaks, attributable to the formation of multiple diastereomeric products, observed.

Although varied conditions were tested and the deprotected substrate **187** more electron-rich necessary for the cyclisation strategy was selected, the lack of success might indicate an issue with the choice of the nucleophile. This approach was not pursued any further.

3.7 Conclusion

The copper-catalysed reaction was successfully scaled up to one gram and showed the efficiency of the one pot method to access highly functionalised nitrogen heterocycles from easily accessible precursors. Moreover, the dihydroisoquinoline systems were prepared in sufficient amounts to allow diversification of the scaffold for further post-catalytic transformations.

The dihydroisoquinoline was successfully deprotected to the attractive the oxyisoquinoline system and itself deprotected to the NH system under acidic conditions, opening up to a range of possibility for further diversification. A one pot strategy was also elaborated to access the full deprotected enamide **187** and the ether **186** formed unexpectedly during the deprotection was used successfully in the *N*-vinylation.

The various post-catalytic reactions tested (hydrogenation, hydroboration-oxidation and ozonolysis) on this scaffold showed the exocyclic alkene was the more reactive alkene.

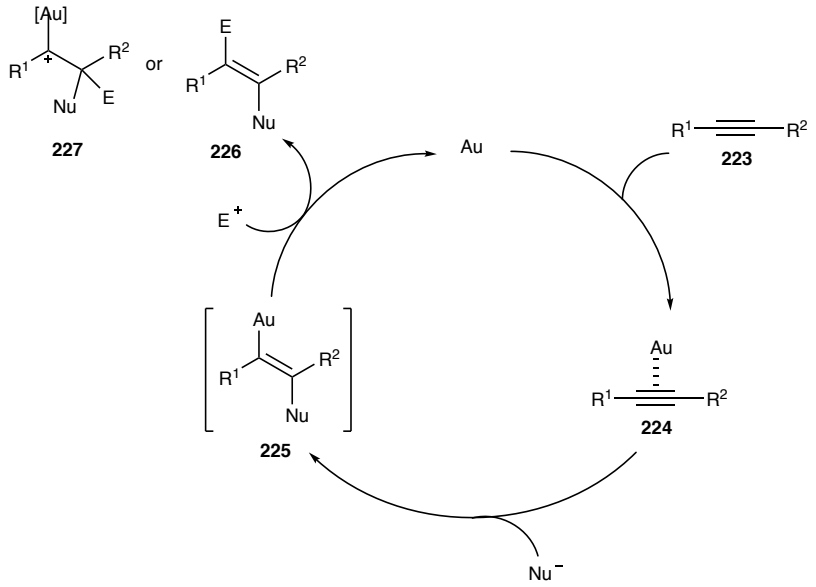
Chapter 4: Gold-catalysed cascade polycyclisation of *N*-allyl ynamides and diversification of sp^3-rich systems

4.1 Introduction to gold catalysis

Gold catalysis has shown impressive advances[203-204] over the last decades and become a fundamental tool with various applications, especially in synthetic chemistry.[203, 205-206] New methodologies have been developed using gold catalysis to activate all π-systems in particular alkenes, alkynes, allenes and involved a number of reactions such as cascades, intra- and intermolecular reactions and cycloadditions.[205, 207-210] A new approach discovered and developed within the Davies group utilised *N*-allyl ynamides in a gold-catalysed cascade reaction, leading to a novel fused nitrogen heterocyclic scaffold.[58-59]

4.2 Reactivity of gold complexes

Gold species has a stronger Lewis acid character than other transition metals and the potential stabilisation of its cationic intermediate lead to a shorter and stronger metal-ligand bond and to a larger and more diffuse d orbitals.[205, 210] Thus, gold complexes are more sensitives to orbital interactions compared to other catalysts such as palladium and activate soft nucleophilic π-system such as alkenes and alkynes to inter- or intramolecular nucleophilic additions.[209, 211] Hence the name of π-acid for the gold complexes.[211] This selectivity operates in the development of new synthesis methods.[209, 211]



Scheme 62: General mechanism of gold catalysis.

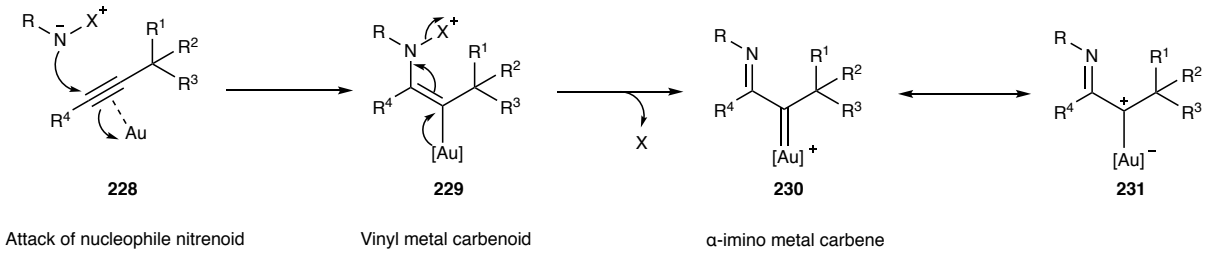
Scheme 62 shows the mechanism of gold catalysis by the attack of nucleophile.[211] Gold catalyst coordinates first to the nucleophilic π-system **223** to give electrophilic intermediates **225**. Two cases are then possible: the addition of an electrophile to α-position to the metal to afford the 1,2-anti addition compound **226** or the addition to the β-position in the nucleophilic π-system to generate a gold carbene **227**.[211]

Gold catalysts are now considered as the catalysts of choice in many reactions, owing to their mild reaction conditions, their nontoxicity and their aptitude returning to their original reactive forms in the catalytic cycle.[204, 209] Moreover, they offer key features such as a rapid access to molecular complexity from simple starting materials and an excellent functional group tolerance.[207, 212] All these characteristics mentioned are highly sought after by chemists and in particular those working in the field of the synthesis of natural products.[206, 212]

4.3 Synthetic applications of gold catalysis

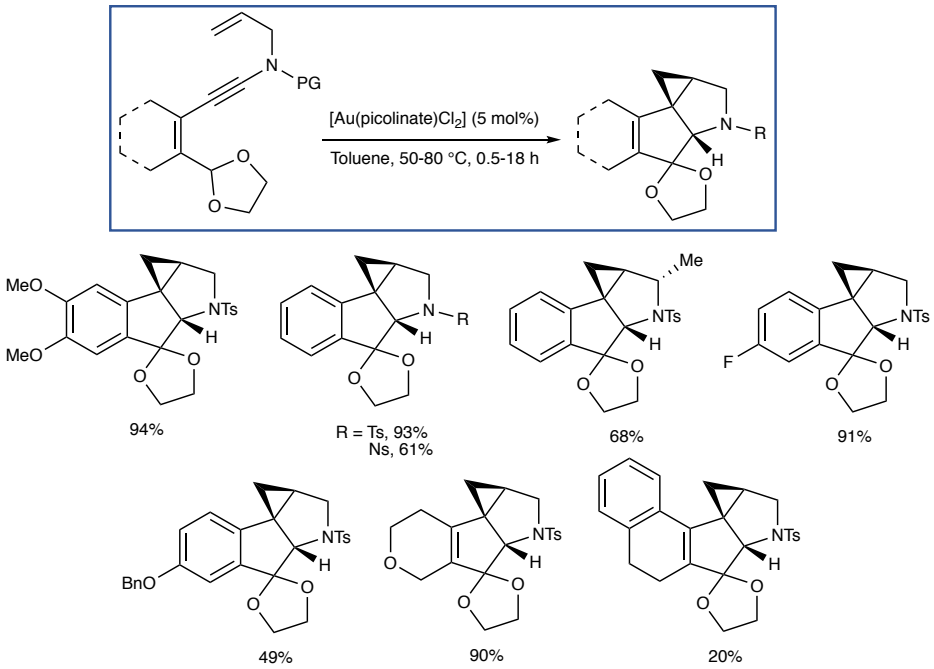
Gold catalysts are good activators of all carbon-carbon π-systems towards intra and intermolecular nucleophilic addition of various heteronucleophiles.[205, 213] Among them,

nitrogen heterocycles are one of the most substantial motifs in synthetic chemistry owing to numerous natural products containing nitrogen heterocycles.[1, 20, 207] *Scheme 63* illustrated the reactivity of gold-activated alkynes using nucleophilic nitrenoids.[207]

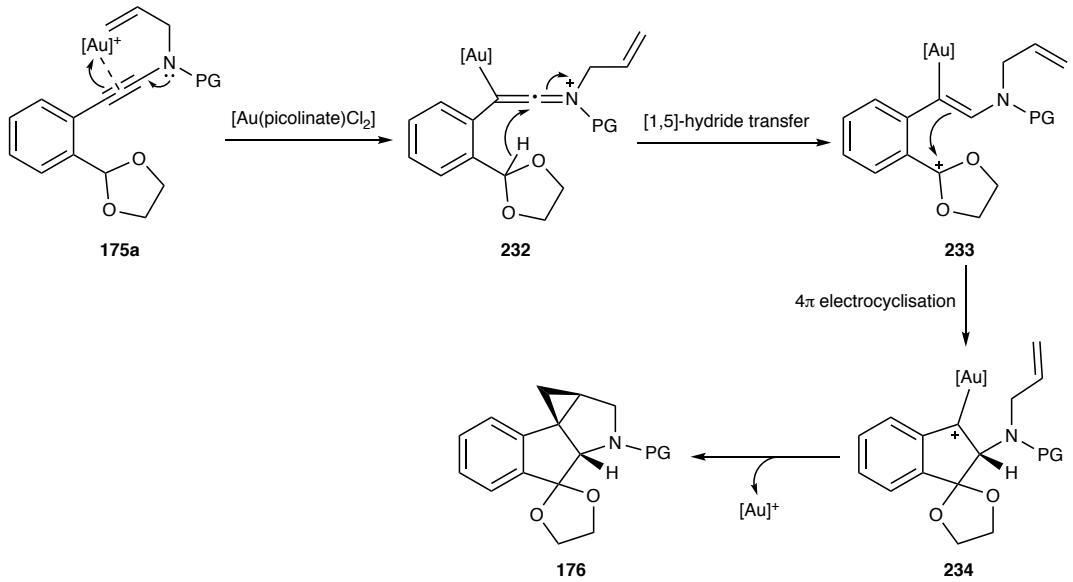


Scheme 63: Reactivity of nucleophilic nitrenoids in the formation of a-imino gold carbene.

Dr. Holly V. Adcock and Dr. Elli Chatzopoulou developed within the Davies lab a novel gold-catalysed polycyclisation cascade from easily prepared *N*-allyl ynamides (Scheme 64 and Scheme 65).[214] This transformation provided a practically straightforward access into fused nitrogen heterocyclic scaffolds with an important molecular complexity in a single step. These starting materials underwent a C-H insertion-cyclopropanation cascade where three new $C(sp^3)$-$C(sp^3)$ bonds, three contiguous stereocenters, two of which are quaternary carbons are notably formed. A range of highly functionalised tetracycles were prepared from moderate to good yields (Scheme 64). In this chapter, further diversifications were undertaken to study whether this novel scaffold could use as a potential drug candidate.



Scheme 64: Gold-catalysed polycyclisation cascade to access a range of novel functionalised tetracycles.



Scheme 65: Proposed mechanism for the formation of tetracycle 176 from *N*-allyl ynamide 175.

4.4 Aim and objectives

The goal of this chapter was to explore the potential of functionalised tetracycles as building blocks for further developments in drug discovery. Previous studies showed the potential of this method to access sp^3-rich tetracycles from readily accessible precursors *via* a gold-catalysed polycyclisation. Thus, the functionality behaviour of this structurally complex

framework was investigated through post-catalytic transformations including denosylation to release the amine as a site for library building, acetal cleavage to access the unsaturated ketone with a number of elaborations and library building processes potentially arising the structural complexity of this polycycle and the density of functionality in this system raised some potential challenges.

The structural effect on the gold-catalysed cascade was also studied by modifying its backbone. A non-aromatic system was incorporated and might generate a new library of more sp^3-rich polycycles.

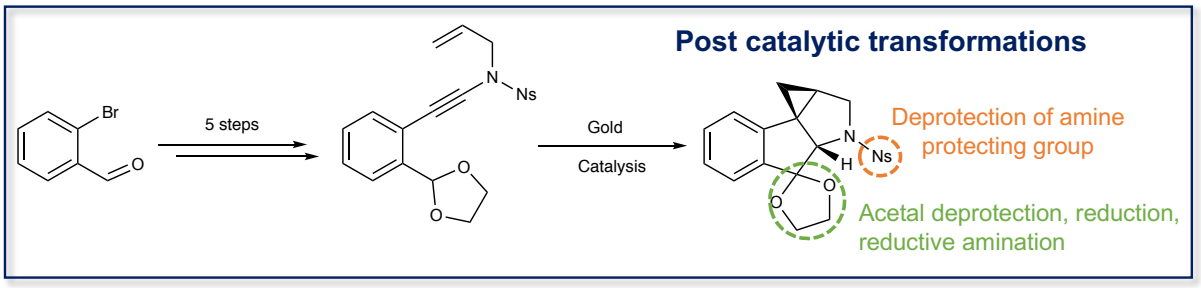
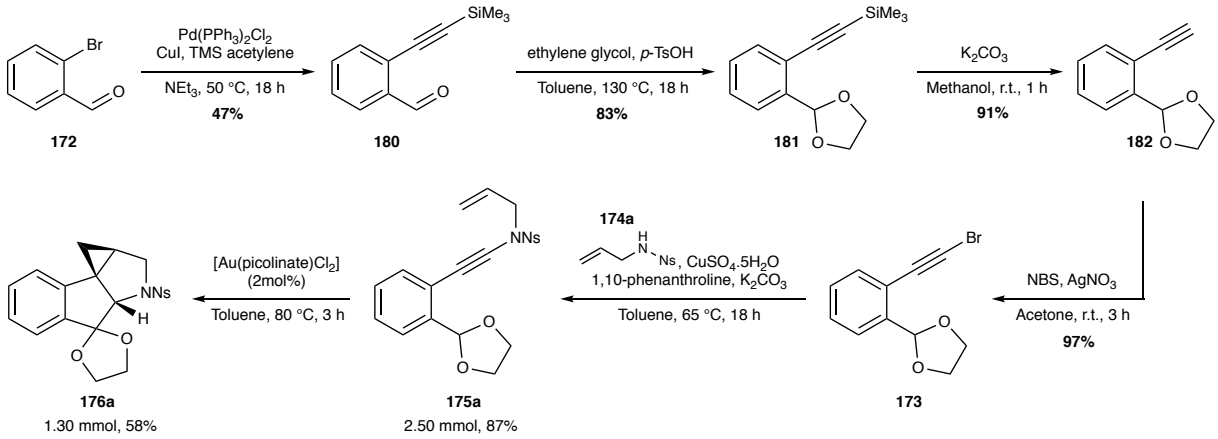


Figure 26: Chapter plan of post-catalytic transformations on the novel functionalised tetracycles.

4.5 Synthetic route to access functionalised tetracycles

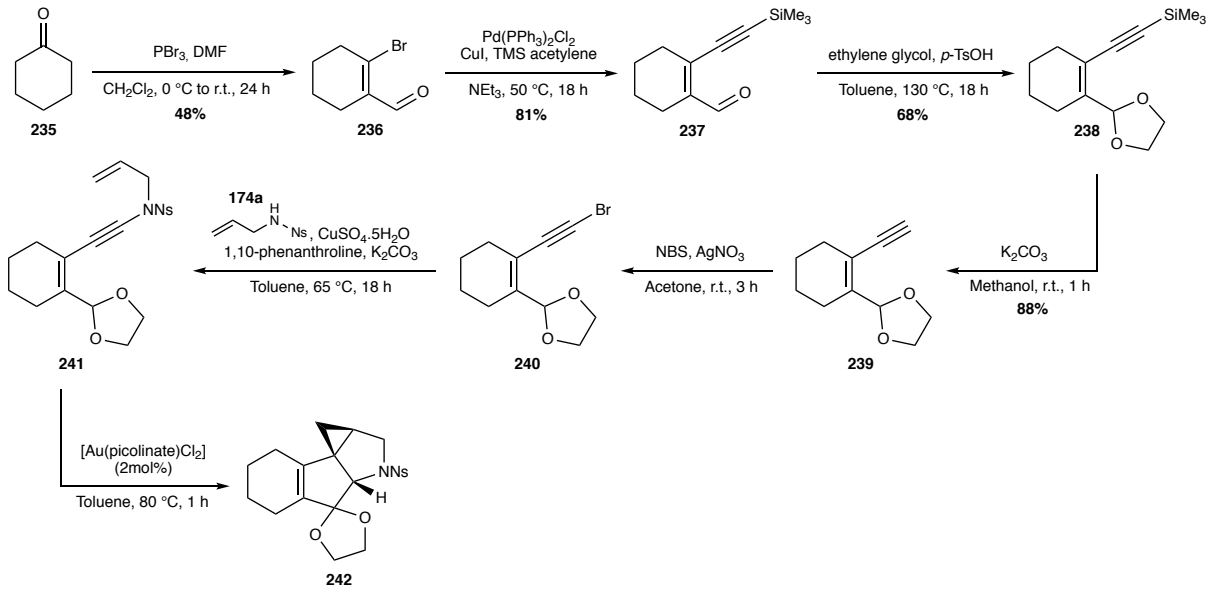
A few years ago, Dr Holly Adcock developed within the Davies group a route into the complex sp^3-rich polycycle.[211] In order to study the elaboration of polycycle **176a**, the scaling up of the process was performed to provide enough material to explore the reactivity of scaffold **176a**.

En-ynamide **173** was prepared in five steps, detailed in chapter 3 (*c.f.* **Section 3.5.1**). Subsequently, an ynamide polycyclisation cascade *via* gold catalysis was pursued using the ynamide **175a** (Scheme 66). The gold-catalysed cascade reaction was successfully scaled up for the material **175a** to afford the functionalised polycycle **176a** in a good yield (58%) providing enough material to be tested in post-catalytic transformations.



Scheme 66: Synthetic route to access functionalised tetracycle 176a in a six-step reaction.

The reactivity of the polycycle was also studied by modifying its backbone. The aromatic system was readily replaced with cyclohexene, providing a more sp^3-rich system and reducing the planarity of the scaffold. This modification proved more challenging to handle as the intermediates were less stable, however allowed the creation of a library of novel diversified frameworks. The same synthetic route described above was applied on the cyclohexene backone to try delivering the tetracycle **242** (Scheme 67) with minor modifications to the purification and handling.



Scheme 67: Synthetic route to access cyclohexene tetracycle 242.

An initial step was required to form the precursor 2-bromocyclohex-1-ene-1-carbaldehyde **236** by Vilsmeier-Haack haloformylation[215] of cyclohexanone **235** in a 48% yield (Scheme 67) allowing for the installation of the alkyne. Despite numerous attempts to optimise the process, the yield remained below 50%. However, enough material **236** was prepared to carry on the ynamide synthesis.

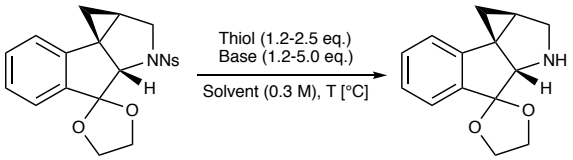
The bromide material **236** underwent a Sonogashira coupling to afford the silylated alkyne **237** in a good yield (81%), followed by an acid-catalysed acetalisation to give acetal **238** in 68% yield. The TMS protected group was cleaved after 20 hours stirring under basic conditions to give terminal alkyne **239** in good yield (88%). For both scaffolds bromination is a sensitive and crucial step before the synthesis of ynamides **241**. Bromoalkyne **240** was found to rapidly decompose into a dark brown oil after work up, indicated by the formation of several new spots observed on TLC analysis. To prevent the degradation of **240**, the filtration through a pad of silica was performed using volatile solvents such as pentane and diethyl ether, thus enabling a rapid evaporation of solvents with a decreased water bath temperature of 30 °C. Despite these precautions, the degradation of the alkynyl bromide **240** was observed and this approach was stopped at this stage of the project to be continued in a more in depth study by a PhD student solely focused on the use of this chemistry in library synthesis.

4.6 Deprotection of reactive sites on the polycycle 176a

4.6.1 Denosylation on the polycycle 176a

The cleavage of the amine protecting group was the first post-catalytic diversification attempted on this novel tetracyclic scaffold. A range of denosylation conditions were tested with a variety of thiols (1-dodecanethiol, thioglycolic acid and thiophenol) and bases (LiOH and Cs_2CO_3) in different solvents.[186, 216-218] The various conditions attempted on functionalised polycycle **176a** are summarised in Table 6.

Table 6: Various denosylation conditions tested on the tetracycle 176a.



176a 243

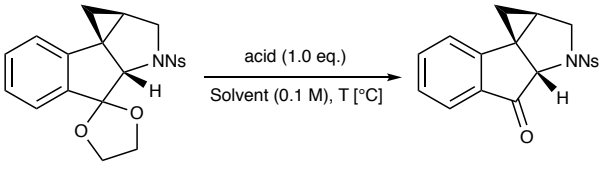
Entry	Thiol	Base	Solvent	T[°C]
1	1-Dodecanethiol	Cs_2CO_3	DMF	0
2	Thioglycolic acid	LiOH	DMF	25
3	Thiophenol	K_2CO_3[a]	CH_3CN	25
4	Thiophenol	DBU	CH_3CN	50

Despite the variation of the thiols, bases and an increased reaction temperature of 50 °C, only starting material was observed *via* TLC and confirmed by ^{1}H NMR analysis. These outcomes could be explained by the steric hindrance with the proximity of the acetal group and the nosyl group prevented deprotection of the amine.

4.6.2 Deprotection of the ketone before denosylation

As nosyl deprotection of the acetal compound had failed, the order of deprotection was changed so that acetal removal was tested before denosylation. Several conditions were tested on the tetracycle **176a** to cleave the acetal group and summarised in the Table 7 varying acids, solvent system, temperature and reaction time.[219]

Table 7: Study of the acetal deprotection conditions attempted on the compound 176a.



176a 244

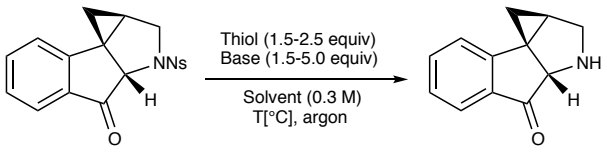
Entry	Acid	Solvents	Ratio	T[°C]	t[h]	Yield [%]
1[a]	$HCl_{(aq)}$	THF	-	50	1	-
2[b]	$HCl_{(aq)}$	THF	-	50	18	-
3[a]	*p*-TsOH	Acetone:H_2O	7:1	25	1	-
4[b]	*p*-TsOH	Acetone:H_2O	7:1	25	24	-
5[c]	*p*-TsOH	Acetone:H_2O	4:1	50	48	66

Reaction conditions: [a] **176a** (0.05 mmol, 1.0 equiv), [b] **176a** (0.08 mmol, 1.0 equiv), [c] **176a** (0.50 mmol, 1.0 equiv), HCl [2.0 M].

On elevating the temperature to 50 °C, complex mixtures via TLC analysis were observed without full consumption of the starting material (Table 7, entries 1 and 2). In the presence of a milder acid, no conversion was observed at room temperature (Table 7, entries 3 and 4). However, an efficient acetal cleavage procedure was found with *p*-TsOH in acetone:water (4:1) at reflux for 48 hours to provide pure ketone **244** (Table 7, entry 5) in good yield (66%) after purification by flash column chromatography. The cleavage of the acetal took 48 hours as monitored by TLC analysis. This deprotection time might be explained by the structural complexity of the polycycle.

Denosylation was re-attempted under similar reaction conditions employed previously on tetracycle **176a**. The denosylation conditions described in Table 8 were attempted differing thiols, bases and solvents.

Table 8: Study of the denosylation conditions tested on the compound 244.



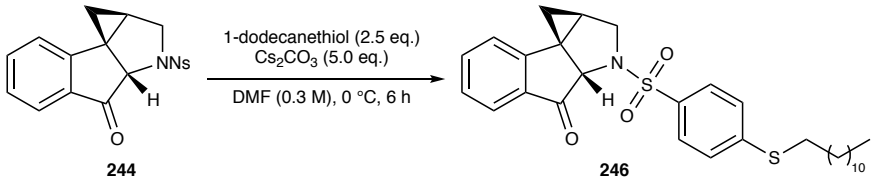
244 **245**

Entry	Thiol	Base	Solvent	T[°C]	12
1	thiophenol	DBU	CH_3CN	50	-
2	thiophenol	K_2CO_3	CH_3CN	50	-
3	thioglycolic acid	LiOH	DMF	50	-
4	1-dodecanethiol	Cs_2CO_3	DMF	0	-
5[a]	thioglycolic acid	Cs_2CO_3	DMF	0	-
6[b]	thioglycolic acid	Cs_2CO_3	DMF	50	-

Reaction conditions: [a] See Scheme 67; [b] MeOH (3.0 eq.) to scavenge the nosyl leaving group on the material **244**.

None of the employed reaction conditions delivered the desired product, with only starting material observed *via* TLC analysis, despite the variation of thiols, bases and solvents (Table 8, entries 1, 2 and 3). Nevertheless, deprotection of **244** was attempted with 1-dodecanethiol and Cs_2CO_3 in DMF (Table 8, entry 4 and Scheme 68) at a lower temperature of 0 °C. The consumption of the starting material was observed on TLC and although not isolated completely

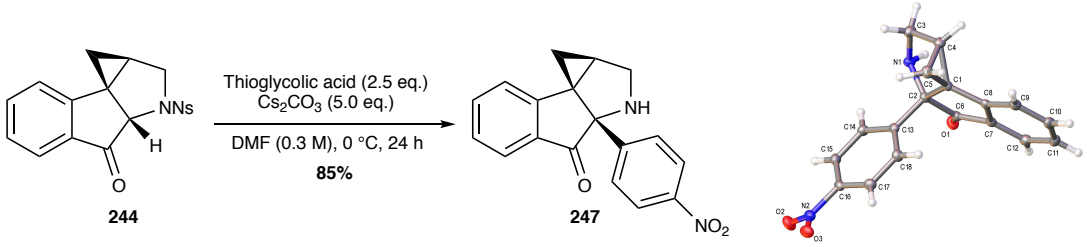
pure, analysis of the ^{1}H NMR spectrum showed that the aromatic CH peaks associated with the nosyl group were shifted up field consistent with replacing an electron-withdrawing group, whilst the integration of aliphatic CH peaks indicated the presence of the thiol. This outcome is consistent with substitution of the nitro group with thiol, suggesting the formation of the compound **246**.



244 246

Scheme 68: Denosylation of material 244 attempted using 1-dodecanethiol at 0 °C.

An unexpected molecule was formed after 24 hours stirring at 0 °C in thioglycolic acid and DMF (Table 8, entry 5). Denosylation of the amine was achieved but the unexpected product **247** with the incorporation of the nosyl leaving group was formed in 85% yield (Scheme 69). The structure, regioselectivity and stereochemistry of the structure was confirmed through ^{1}H NMR and single crystal X-ray analysis. Although intriguing, as no similar transformations could be found in the literature, this was not productive to the overall project goal as the resulting structure is too large to be a useful starting point for library development.

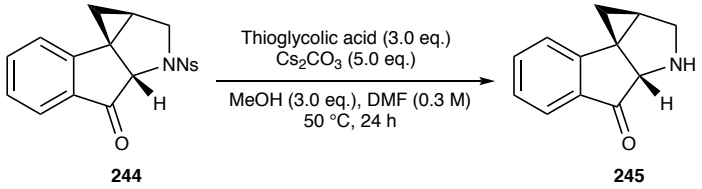


244 247

Scheme 69: Denosylation attempted on the material 244 and accessed unexpected nitro-benzene substituted compound.

Another option was the use of a scavenger such as methanol to prevent the attack of nosyl leaving group on the scaffold **244** (Table 8, entry 6 and Scheme 70). This additive was added to the reaction mixture to trap any possible electrophiles involved in aryl migration, by transformation of the leaving group to a methoxy substituted form which should be unreactive

(Scheme 69). However, no reaction was observed, the additional reagent hindered the initial reaction of deprotection and the denosylated compound **245** was not obtained.



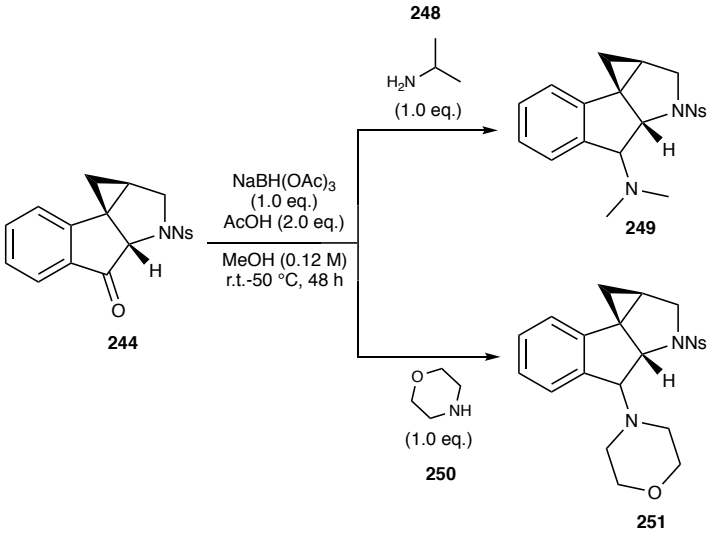
244 **245**

Scheme 70: Denosylation conditions attempted on the material 244 using a scavenger.

4.6.3 Reductive amination of the carbonyl

Reductive amination is an important method in the C-N bond formation within pharmaceutical and medicinal chemistry, owing to the extensive presence of amines among biologically active compounds.[220-221] This reaction is particularly appealing for library generation on these scaffolds in the later stage diversification.

This C-N bond forming reaction was attempted on the carbonyl of compound **244** obtained previously after acetal deprotection. Morpholine and isopropylamine, which have been employed in a broad range of applications including pharmaceuticals, were selected for this test.[220] The reduction was probed under argon with an excess of a mild and reducing agent sodium acetoxyborohydride in acetonitrile (Scheme 71). Acetic acid was added during the reaction to speed up condensation of the amines with the carbonyl unit.



Scheme 71: Reductive amination attempted on the tetracycle 244 after deprotection of the ketone.

Despite several hours reaction and an elevation of the temperature up to 50 °C, only starting material was observed on TLC and was confirmed by ^{1}H NMR analysis. The difficult reductive amination of compound **244** might be explained by the limited accessibility of the ketone with the presence of a bulky amine protecting group. This issue might be solved using primary amines.

4.7 Conclusion

For the aromatic framework, the ynamide synthesis and the gold-catalysed polycyclisation stages were successfully scaled up to one gram and thus showed the effectiveness of the gold catalysed approach to access novel sp^3-rich frameworks from easily prepared precursors. Enough material was prepared to undertake post-catalytic transformations on this scaffold.

The structural complexity of this framework was a challenge. Acetal cleavage was successfully achieved. However, denosylation from either the acetal **176a** or the ketone **244** proved ultimately unsuccessful. With the acetal, steric hindrance between protected reactive sites was identified as a possible reason for no reactivity. Denosylation on the ketone deprotected material **244** afforded the formation of an unexpected compound **247** in which the nitrobenzene

moiety has been incorporated into the polycycle at the bridgehead position. This interesting transformation worked very well, but was undesirable with respect to the further diversifications from this scaffold. Reduction aminations were also probed on the scaffold **244** with unfortunately no success, could be explained by the structural complexity of the molecule.

Finally, the synthesis of the cyclohexene framework was challenging due to the sensitive nature of the bromoalkyne and remained so despite handling precautions. This part of the project was not pursued further as the alkene position on the polycycle allowed the opening of the acetal group during reactions. The outcome was used to inform the further development of the polycyclic scaffolds performed by a new PhD student in the group.

Chapter 5: Supporting information

General Experimental

Commercial chemicals were purchased from major suppliers (Sigma-Aldrich, Acros organics, Fisher Scientific or VWR international) and used without prior purification unless otherwise specified. Glassware used for reactions carried out under an argon atmosphere were flame-dried with a hot air gun under vacuum at 0.1 mbar and backfilled with argon. The vacuum/argon purge was carried out three times. Reaction set ups were performed with standard air sensitive Schlenk techniques. Solvents were dried under the following conditions: CH_2Cl_2, THF and toluene were drawn through a PureSolv EN solvent purification system through alumina packed columns and transferred under argon onto activated 3 Å molecular sieves. DMF, DCE and 1,4-dioxane were stored over activated 4 Å molecular sieves for 24 h prior to use. All reactions were stirred using Teflon coated magnetic stirrer bars. Reactions which required heating were submerged in preheated paraffin oil baths or aluminium heating mantles and the temperature controlled by an external probe. Reactions which required cooling were submerged in the following baths: 0 °C (ice/water), -10 °C (NaCl/ice/water), -40 °C (dry ice/MeCN), -78 °C (dry ice/acetone). All reactions were monitored using thin layer chromatography on Merck silica gel 60 F_{254} (aluminium support) plates which were developed using the standard visualising agents: UV fluorescence (254 nm), potassium permanganate/Δ, vanillin/Δ or anisaldehyde/Δ. Flash chromatography was carried out on Sigma Aldrich silica gel (60 Å, 230-400 mesh, 40–63 μm) or Interchim prepacked 40 g and 25 g spherical silica columns (60 Å, 30 μm) and were run manually or with a CombiFlash® NextGen 300+ using UV detection. Reagents measured in mL are recorded to appropriate significant figures to represent the accuracy of measurement. Melting points were measured in open ended capillaries using a Stuart Scientific melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR experiments were recorded using Bruker

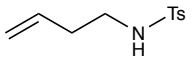
AVIII400 (^{1}H = 400 MHz, ^{13}C = 101 MHz), Bruker AVNEO400 (^{1}H = 400 MHz, ^{13}C = 101 MHz) or AVIII300 (^{1}H = 300 MHz, ^{13}C = 75 MHz) spectrometers at 295-300 K. ^{13}C NMR spectra were recorded using the UDEFT, JMOD or the PENDANT pulse sequence from the Bruker standard pulse program library. 2D NMR spectra were recorded using the Bruker standard pulse program library. Spectra were processed using MestReNova 12.0.3. Chemical shifts (δ) are given in ppm relative to TMS and are calibrated using residual solvent peaks ($CDCl_3$: $\delta_C \equiv 77.16$ ppm, DMSO–*d*$_6$: $\delta_C \equiv 39.52$ ppm, Acetone-*d*$_6$: $\delta_C \equiv 29.84$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.26$ ppm, residual DMSO in DMSO-*d*$_6$: $\delta_H \equiv 2.50$ ppm, residual acetone in Acetone-*d*$_6$: $\delta_H \equiv 2.05$ ppm). Spectral data for ^{1}H NMR spectroscopy are reported as follows: chemical shift (multiplicity, coupling constant, number of protons); and for ^{13}C NMR spectroscopy: chemical shift. The following abbreviations were used for multiplicity: s (singlet), d (doublet), t (triplet), q (quadruplet), quin (quintuplet), hept (heptet), br. (broad), m (multiplet), app. (apparent). Coupling constants (*J*) are quoted in Hz to one decimal place. Infrared spectra were recorded neat on a Perkin-Elmer Spectrum 100 FTIR spectrometer. Wavenumbers (ν) are reported in cm^{-1}. Mass spectra were obtained using Waters LCT (ES) or Waters Synapt (ES) spectrometers. High resolution spectra used a lock-mass to adjust the calibrated mass scale.

Formation of sulfonamides

General procedure 1: sulfonamides (GP1)

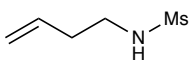
The required amine (1.2 eq.) and a base (3.0 eq.) were dissolved in CH_2Cl_2 (0.3 M) and cooled to -10 °C. The required sulfonyl chloride (1.0 eq.) was added in small portions and the resulting mixture was allowed to warm to room temperature and stirred for 20 h. 2.0 M HCl was added and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The resulting sulfonamides did not usually required further purification.

N-(But-3-en-1-yl)-4-methylbenzenesulfonamide 115a



Prepared according to **GP1** using 3-buten-1-amine **114** (0.57 mL, 6.29 mmol), 4-methylbenzenesulfonyl chloride **113a** (1.0 g, 5.24 mmol) and NEt_3 (2.20 mL, 15.7 mmol) in CH_2Cl_2 (17 mL) to afford sulfonamide **115a** as a pale yellow oil (1.13 g, 80%); IR (neat): ν = 3284, 1424, 1321, 1155, 1092, 916, 813, 735, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 ($d_{AA'XX'}$, *J* = 8.3 Hz, 2H), 7.31 ($d_{AA'XX'}$, *J* = 7.9 Hz, 2H), 5.62 (ddt, *J* = 17.1, 10.3, 6.9 Hz, 1H), 5.11 – 4.99 (m, 2H), 4.42 (br. s, 1H), 3.02 (app. q, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 2.20 (app. q, *J* = 6.7, 1.3 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.6 (C), 137.1 (C), 134.3 (CH), 129.8 (2CH), 127.2 (2CH), 118.3 (CH_2), 42.1 (CH_2), 33.7 (CH_2), 21.6 (CH_3) ppm; MS (EI-TOF): m/z: [M] Calcd for $C_{11}H_{15}NO_2S$ 225.0824; found 225.0832.[129]

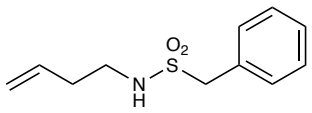
N-(But-3-en-1-yl)methanesulfonamide 115b



Prepared according to **GP1** using 3-buten-1-amine **114** (0.49 mL, 5.24 mmol), methanesulfonyl chloride **113b** (0.35 mL, 4.36 mmol) and NEt_3 (1.90 mL, 13.1 mmol) in CH_2Cl_2 (14.5 mL) to afford **115b** as a colourless oil (0.77 g, 100%); IR (neat): ν = 3287, 1642, 1308, 1139, 1074, 970, 916, 754, 630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.75 (ddt, *J* = 16.5, 10.8, 6.9 Hz, 1H), 5.20 – 5.12 (m, 2H), 3.22 (app. q, *J* = 6.6, 6.0 Hz, 2H), 2.96 (br. s, 3H),

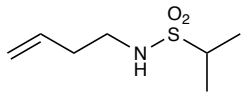
2.34 (app. q, J = 6.7, 1.3 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.2 (CH), 118.6 (CH_2), 42.3 (CH_2), 40.6 (CH_3), 34.4 (CH_2) ppm. Data matches that reported in the literature.[222]

N-Benzylbut-3-en-1-amine 115c



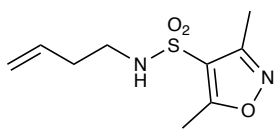
Prepared according to **GP1** using 3-buten-1-amine **114** (0.29 mL, 3.14 mmol), phenylmethanesulfonyl chloride **113c** (0.50 g, 2.62 mmol) and pyridine (0.63 mL, 70.2 mmol) in CH_2Cl_2 (8 mL). Purification by flash column chromatography (8:2 hexane/EtOAc) afforded **115c** as an off-white solid (0.42 g, 72%); IR (neat): ν = 3258, 3065, 1640, 1435, 1303, 1134, 1071, 915, 778, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 – 7.35 (m, 5H), 5.66 (ddt, J = 18.1, 9.5, 6.9 Hz, 1H), 5.12 – 5.03 (m, 2H), 4.26 (s, 2H), 4.05 (br. s, 1H), 3.03 (app. q, J = 6.6, 6.0 Hz, 2H), 2.23 (app. q, J = 6.7, 1.3 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.2 (CH), 130.7 (2CH), 129.5 (C), 129.0 (3CH), 118.4 (CH_2), 59.0 (CH_2), 42.7 (CH_2), 34.5 (CH_2) ppm; MS (EI-TOF): m/z: [M] Calcd for $C_{11}H_{15}NO_2S$ 225.0824; found 225.0830.

N-(But-3-en-1-yl)propane-2-sulfonamide 115d



Prepared according to **GP1** using 3-buten-1-amine **114** (0.15 mL, 1.68 mmol), isopropylsulfonyl chloride **113d** (0.16 mL, 1.40 mmol) and NEt_3 (0.60 mL, 4.20 mmol) in CH_2Cl_2 (5 mL) to afford **115d** as a yellow oil (0.33 g, 100%); IR (neat): ν = 3289, 1428, 1310, 1130, 1079, 914, 686 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.75 (ddt, J = 17.2, 10.3, 6.9 Hz, 1H), 5.23 – 5.08 (m, 2H), 4.03 (br. s, 1H), 3.26 – 3.17 (m, 2H), 3.21 – 3.08 (m, 1H), 2.33 (app. q, J = 6.7, 1.3 Hz, 2H), 1.37 (d, J = 6.8 Hz, 6H) ppm. Data matches that reported in the literature.[129]

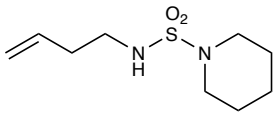
N-(But-3-en-1-yl)-3,5-dimethylisoxazole-4-sulfonamide 115e



Prepared according to **GP1** using 3-buten-1-amine **114** (0.11 mL, 1.23 mmol), 3,5-dimethyloxazole-4-sulfonyl chloride **113e** (0.20 g, 1.0

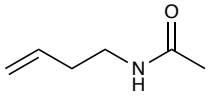
mmol) and NEt_3 (0.43 mL, 3.10 mmol) in CH_2Cl_2 (3.5 mL) to afford **115e** as a pale yellow oil (0.21 g, 91%); IR (neat): ν = 3294, 2938, 1443, 1320, 1140, 1051, 924, 712, 593, 496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.66 (ddt, *J* = 17.1, 10.3, 6.9 Hz, 1H), 5.19 – 5.04 (m, 2H), 4.53 (br. s, 1H), 3.06 (q, *J* = 6.4 Hz, 2H), 2.64 (s, 3H), 2.40 (s, 3H), 2.27 (qt, *J* = 6.7, 1.3 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.3 (C), 157.6 (C), 133.9 (CH), 118.9 (CH_2), 116.1 (C), 41.7 (CH_2), 33.7 (CH_2), 12.8 (CH_3), 10.9 (CH_3) ppm; MS (ES-TOF): m/z: [M+H] Calcd for $C_9H_{14}N_2O_3S$ 229.0647; found 229.0643.

N-(But-3-en-1-yl)piperidine-1-sulfonamide 115f



Prepared according to **GP1** using 3-buten-1-amine **114** (0.12 mL, 1.31 mmol), 1-piperidinesulfonyl chloride **113f** (0.15 mL, 1.10 mmol) and NEt_3 (0.45 mL, 3.27 mmol) in CH_2Cl_2 (4 mL) to afford **115f** as a yellow oil (0.36 g, 100%); IR (neat): ν = 3295, 2939, 2854, 1443, 1320, 1140, 1051, 922, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.74 (ddt, *J* = 17.1, 10.3, 6.9 Hz, 1H), 5.21 – 5.09 (m, 2H), 4.04 (br. s, 1H), 3.23 – 3.14 (m, 4H), 3.12 (app. q, *J* = 6.5 Hz, 2H), 2.31 (app. q, *J* = 6.7, 1.3 Hz, 2H), 1.70 – 1.59 (m, 4H), 1.59 – 1.50 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.6 (CH), 118.2 (CH_2), 47.1 ($2CH_2$), 42.6 (CH_2), 34.1 (CH_2), 25.5 ($2CH_2$), 23.9 (CH_2) ppm; MS (ES-TOF): m/z: [M+H] Calcd for $C_9H_{18}N_2O_2S$ 219.1167; found 219.1164.

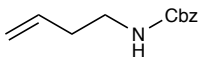
N-(But-3-en-1-yl)acetamide 115g



Prepared according to **GP1** using 3-buten-1-amine **114** (0.28 mL, 3.10 mmol), acetyl chloride **113g** (0.18 mL, 2.55 mmol) and NEt_3 (1.10 mL, 7.70 mmol) in CH_2Cl_2 (8.5 mL). Purification by flash column chromatography (2:8 hexane/EtOAc) afforded **115g** as a yellow oil (0.27 g, 92%); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.76 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.46 (br. s, 1H), 5.14 – 5.05 (m, 2H), 3.32 (app. q, *J* = 6.7, 5.7 Hz, 2H), 2.26 (app. q, *J* = 6.8, 1.4 Hz, 2H), 1.97 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1

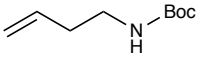
(C), 135.4 (CH), 117.4 (CH_2), 38.6 (CH_2), 33.8 (CH_2), 23.5 (CH_3) ppm. Data matches that reported in the literature.[223]

Benzyl but-3-en-1-ylcarbamate 115h



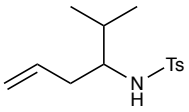
Prepared according to **GP1** using 3-buten-1-amine **114** (0.11 mL, 1.17 mmol), benzyl chloroformate **113h** (0.17 mL, 1.17 mmol) and NEt_3 (0.41 mL, 2.93 mmol) in CH_2Cl_2 (4 mL). Purification by flash column chromatography (8:2 hexane/EtOAc) afforded **115h** as a colourless oil (0.33 g, 100%); IR (neat): ν = 3333, 1694, 1519, 1244, 1132, 1025, 735, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 4.7 Hz, 4H), 7.34 – 7.29 (m, 1H), 5.75 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.22 – 4.99 (m, 4H), 4.76 (br. s, 1H), 3.28 (app. q, *J* = 6.5 Hz, 2H), 2.27 (app. q, *J* = 6.8 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.2 (C), 136.7 (CH), 135.0 (C), 128.6 (4CH), 128.2 (CH), 117.5 (CH_2), 66.8 (CH_2), 40.2 (CH_2), 34.2 (CH_2) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{12}H_{15}NO_2$ 206.1181; found 206.1189.

Preparation of *tert*-butyl but-3-en-1-ylcarbamate 115i



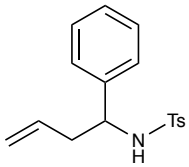
3-Buten-1-amine **114** (0.10 mL, 1.14 mmol, 1.0 eq.) and NEt_3 (0.63 mL, 4.56 mmol, 4.0 eq.) were dissolved in CH_2Cl_2 (4 mL) and cooled to -10 °C with an ice/acetone bath. Di-*tert*-butyl dicarbonate solution 1.0 M in THF (2.30 mL, 2.29 mmol, 2.0 equiv.) was added slowly and the resulting mixture was allowed to warm to room temperature and stirred for 21 h. 2.0 M HCl (13 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford *tert*-butyl but-3-en-1-ylcarbamate **110i** as a colourless oil (0.31 g, 100%); IR (neat): ν = 3355, 2979, 1692, 1513, 1365, 1249, 1168, 1117, 1069, 914, 844, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.76 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.16 – 5.02 (m, 2H), 4.53 (br. s, 1H), 3.19 (app. q, *J* = 6.5 Hz, 2H), 2.24 (app. q, *J* = 6.8, 1.4 Hz, 2H), 1.44 (s, 9H) ppm. Data matches that reported in the literature.[224]

4-Methyl-N-(2-methylhex-5-en-3-yl)benzenesulfonamide 115j



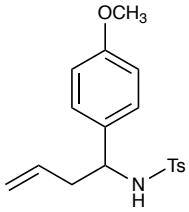
This sulfonamide was prepared by a previous Davies group member Matthew G. Wakeling (MGW-063).

4-Methyl-N-(1-phenylbut-3-en-1-yl)benzenesulfonamide 115k



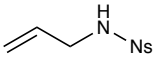
This sulfonamide was prepared by a previous Davies group member Holly V. Adcock (HVA-1293).

N-(1-(4-Methoxyphenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide 115l



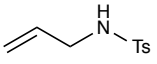
This sulfonamide was prepared by a previous Davies group member Onyeka F. Obumselu (OFO-285).

N-Allyl-4-nitrobenzenesulfonamide 174a



Prepared according to **GP1** using allylamine **183** (0.41mL, 5.41 mmol), 4-nitrobenzenesulfonyl chloride **184a** (1.0 g, 4.51 mmol) and pyridine (1.10 mL, 13.5 mmol) in CH_2Cl_2 (15 mL) to afford **158a** as an orange solid (0.89 g, 82%); IR (neat): ν = 3255, 1520, 1323, 1309, 1157, 1046, 853, 739, 680, 635, 552, 463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.37 ($d_{AA'XX'}$, *J* = 8.9 Hz, 2H), 8.06 ($d_{AA'XX'}$, *J* = 8.9 Hz, 2H), 5.71 (ddt, *J* = 17.1, 10.2, 5.8 Hz, 1H), 5.26 – 5.08 (m, 2H), 4.73 (s, 1H), 3.69 (tt, *J* = 6.0, 1.5 Hz, 2H) ppm. Data matches that reported in the literature.[211]

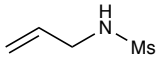
N-Allyl-4-methylbenzenesulfonamide 174b



Prepared according to **GP1** using allylamine **184** (1.50 mL, 18.8 mmol), *p*-toluenesulfonyl chloride **183b** (3.0 g, 15.7 mmol) and pyridine (3.8 mL, 47.1 mmol) in CH_2Cl_2 (53 mL). Purification by flash column chromatography (8:2 hexane/EtOAc) afforded **174b** as a white solid (2.80 g, 70%); mp: 63-65 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 ($d_{AA'XX'}$, *J* =

8.4 Hz, 2H), 7.31 ($d_{AA'XX'}$, J = 7.8 Hz, 2H), 5.72 (ddt, J = 17.1, 10.2, 5.8 Hz, 1H), 5.25 – 5.03 (m, 2H), 4.46 (s, 1H), 3.59 (tt, J = 6.0, 1.5 Hz, 2H), 2.43 (s, 3H) ppm. Data matches that reported in the literature.[211]

N-Allylmethanesulfonamide 174c



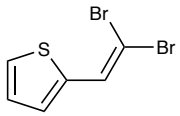
Prepared according to **GP1** using allylamine **184** (1.60 mL, 21.0 mmol), methanesulfonyl chloride **183c** (1.40 mL, 17.5 mmol) and pyridine (4.2 mL, 52.5 mmol) in CH_2Cl_2 (60 mL) to afford **174c** as a colourless oil (1.70 g, 72%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.88 (ddt, J = 17.1, 10.2, 5.8 Hz, 1H), 5.37 – 5.18 (m, 2H), 4.42 (s, 1H), 3.78 (tt, J = 6.0, 1.5 Hz, 2H), 2.97 (s, 3H) ppm; MS (ES-TOF): m/z 135 [M+H]. Data matches that reported in the literature.[211]

Formation of dibromoolefins

General procedure 2: dibromoolefins (GP2)

Following the method of Corey-Fuch,[138] PPh_3 (4.0 eq.) was added to a solution of CBr_4 (2.0 eq.) in CH_2Cl_2 (0.4 M) at 0 °C. After 10 min stirring, the relevant carboxaldehyde (1.0 eq.) was slowly added over 10 min and the reaction mixture was allowed to warm to room temperature and stirred for 1 h. H_2O was added and the organic phase was collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified through flash column chromatography (hexane) to give the corresponding dibromooelefins.

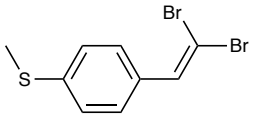
2-(2,2-Dibromovinyl)thiophene 117a



Following **GP2** with PPh_3 (18.7 g, 71.3 mmol), CBr_4 (11.8 g, 35.6 mmol) and thiophenecarboxaldehyde **116a** (1.64 mL, 17.8 mmol) in CH_2Cl_2 (45 mL). Purification by flash column chromatography (hexane) gave dibromoolefin **117a** as a pale grey solid (4.20 g, 88%); mp: 54-56 °C; IR (neat): ν = 1420, 1346, 1209, 1050, 855, 817, 702 cm^{-1};

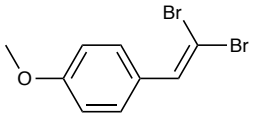
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (s, 1H), 7.39 (d, *J* = 5.1 Hz, 1H), 7.25 (d, *J* = 3.1 Hz, 1H), 7.04 (dd, *J* = 5.1, 3.7 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.2 (C), 131.0 (CH), 130.2 (CH), 127.3 (CH), 126.6 (CH), 87.0 (C) ppm. Data matches that reported in the literature.[129]

(4-(2,2-Dibromovinyl)phenyl)(methyl)sulfane 117b



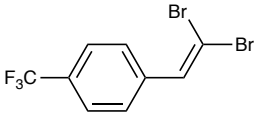
Following **GP2** with PPh_3 (13.8 g, 52.5 mmol), CBr_4 (8.69 g, 26.2 mmol) and 4-(methylthio)benzaldehyde **116b** (1.75 mL, 13.1 mmol) in CH_2Cl_2 (35 mL). Purification by flash column chromatography (hexane) gave **117b** as a pale yellow solid (2.57 g, 64%); mp: 69-73 °C; IR (neat): ν = 1894, 1588, 1489, 1402, 1097, 863, 805, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.3 Hz, 2H), 7.42 (s, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 2.49 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.7 (C), 136.4 (CH), 131.9 (C), 128.9 (2CH), 125.9 (2CH), 89.0 (C), 15.4 (CH_3) ppm; MS (EI-TOF): m/z: [M] Calcd for $C_9H_8{}^{79}Br_2S$ 305.8713; found 305.8726.

1-(2,2-Dibromovinyl)-4-methoxybenzene 117c



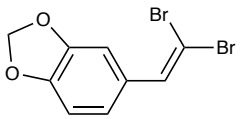
Following **GP2** with PPh_3 (15.4 g, 58.8 mmol), CBr_4 (9.75 g, 29.4 mmol) and 4-methoxybenzaldehyde **116c** (1.78 mL, 14.7 mmol) in CH_2Cl_2 (37 mL). Purification by flash column chromatography (hexane) gave **117c** as an off-white solid (3.12 g, 73%); mp: 37-39 °C; IR (neat): ν = 1603, 1506, 1455, 1252, 1176, 1025, 863, 802 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.4 Hz, 2H), 7.41 (s, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.8 (C), 136.4 (CH), 130.0 (C), 127.9 (2CH), 113.9 (2CH), 87.4 (C), 55.4 (CH_3) ppm; HRMS (ASAP): m/z: [M] Calcd for $C_9H_8{}^{79}Br_2O$ 289.8942; found 289.8949.

1-(2,2-Dibromovinyl)-4-(trifluoromethyl)benzene 117d



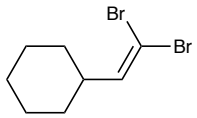
Following **GP2** with PPh_3 (6.0 g, 22.9 mmol), CBr_4 (3.83 g, 11.5 mmol) and 4-(trifluoromethyl)benzaldehyde **116d** (0.78 mL, 5.74 mmol) in CH_2Cl_2 (14 mL). Purification by flash column chromatography (hexane) gave **117d** as a pale yellow oil (1.14 g, 60%); IR (neat): ν = 1617, 1408, 1319, 1109, 1066, 1016, 876, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.59 (m, 4H), 7.52 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.9 (q, *J* = 1.4 Hz) (C), 135.8 (CH), 130.6 (q, *J* = 32.7 Hz) (C), 128.8 (CH), 125.5 (q, *J* = 3.8 Hz) (CH), 123.7 (q, *J* = 273.0 Hz) (C), 92.4 (C) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = 62.82 ppm; HRMS (ASAP): m/z: [M] Calcd for $C_9H_5{}^{79}Br_2{}^{19}F_3$ 327.8710; found 327.8717.

5-(2,2-Dibromovinyl)-1,3-benzodioxole 117e



Following **GP2** with PPh_3 (14.0 g, 53.2 mmol), CBr_4 (8.82 g, 26.6 mmol) and 1,3-benzodioxole-5-carboxaldehyde **116e** (2.0 g, 13.3 mmol) in CH_2Cl_2 (35 mL). Purification by flash column chromatography (hexane) gave **117e** as a pale yellow oil (1.07 g, 26%); mp: 39-42 °C; IR (neat): ν = 2907, 1599, 1443, 1255, 1033, 925, 864, 799 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (s, 1H), 7.19 (d, *J* = 1.6 Hz, 1H), 6.95 (ddd, *J* = 8.1, 1.8, 0.7 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 5.99 (s, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.9 (C), 147.7 (C), 136.4 (CH), 129.3 (C), 123.5 (CH), 108.4 (CH), 108.2 (CH), 101.5 (CH_2), 88.0 (C) ppm; MS (EI-TOF): m/z: [M] Calcd for $C_9H_6Br_2O_2$ 303.8734; found 303.8745.

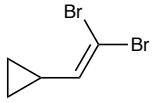
(2,2-Dibromovinyl)cyclohexane 117f



Following **GP2** with PPh_3 (18.7 g, 71.3 mmol), CBr_4 (11.8 g, 35.6 mmol) and cyclohexanecarbaldehyde **116f** (2.2 mL, 17.8 mmol) in CH_2Cl_2 (45 mL). Purification by flash column chromatography (hexane) gave **117f** as a colourless oil (1.19 g, 25%); IR (neat): ν = 2923, 2850, 1447, 965, 893, 812, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):

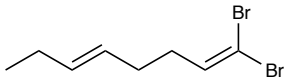
δ = 6.23 (d, *J* = 9.0 Hz, 1H), 2.28 (tdt, *J* = 11.1, 9.0, 3.6 Hz, 1H), 1.80 – 1.59 (m, 5H), 1.40 – 1.04 (m, 5H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.5 (CH), 86.8 (C), 42.3 (CH), 31.1 (CH_2), 25.5 (CH_2), 25.3 (CH_2) ppm. Data matches that reported in the literature.[225]

(2,2-Dibromovinyl)cyclopropane 117g



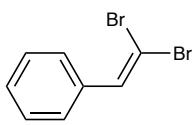
Following **GP2** with PPh_3 (29.9 g, 0.114 mol), CBr_4 (18.9 g, 57.0 mmol) and cyclopropanecarbaldehyde **116g** (2.1 mL, 28.5 mmol) in CH_2Cl_2 (71 mL). Purification by flash column chromatography (hexane) gave **117g** as a colourless oil (2.0 g, 31%); IR (neat): ν = 3086, 3009, 1790, 1259, 1172, 954, 881, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78 (d, *J* = 9.3 Hz, 1H), 1.64 (dtt, *J* = 9.5, 8.2, 4.8 Hz, 1H), 0.95 – 0.84 (m, 2H), 0.61 – 0.50 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.3 (CH), 15.41 (CH), 6.83 (CH_2), 6.61 (CH_2) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_5H_6{}^{79}Br_2$ 224.8738; found 224.8749.

Cis-1,1-dibromoocta-1,5-diene 117h



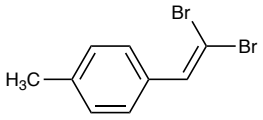
Following **GP2** with PPh_3 (18.7 g, 71.2 mmol), CBr_4 (11.8 g, 35.6 mmol) and cis-4-heptenal **116h** (2.35 mL, 17.8 mmol) in CH_2Cl_2 (44 mL). Purification by flash column chromatography (hexane) gave **117h** as a colourless oil (3.59 g, 75%); IR (neat): ν = 2962, 2931, 1622, 1438, 965, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 – 6.33 (m, 1H), 5.58 – 5.22 (m, 2H), 2.22 – 1.94 (m, 6H), 0.97 (td, *J* = 7.5, 1.3 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.3 (CH), 133.7 (CH), 127.3 (CH), 88.8 (C), 33.2 (CH_2), 30.8 (CH_2), 25.7 (CH), 20.7 (CH), 14.0 (CH_3) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_8H_{12}{}^{79}Br_2$ 266.9207; found 266.9210.

(2,2-Dibromovinyl)benzene 117i



This dibromoolefin was prepared by a previous Davies group member Matthew G. Wakeling (MGW-063).

1-(2,2-Dibromovinyl)-4-methylbenzene 117j



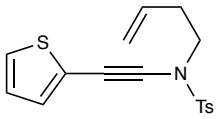
This dibromoolefin was prepared by a previous MSci student in the Davies group Melodie J. Zehnder (MJZ-066).

Formation of ynamides

General procedure 3: ynamides (GP3a)

Following the general procedure of Evano,[56] dibromoolefin (1.5 eq.), sulfonamide (1.0 eq.), CuI (12 mol%) and Cs_2CO_3 (4.0 eq.) were combined in a flame-dried Schlenk tube which was evacuated and backfilled with the argon three times. Degassed dioxane (0.32 M) was then added followed by DMEDA (18 mol%) and the reaction mixture was heated at 70 °C for 16 h. After allowing to cool at room temperature, the reaction mixture was diluted with EtOAc and flushed through a pad of silica (EtOAc) and concentrated under reduced pressure. The crude residues were purified by flash column chromatography (hexane/EtOAc) to afford the expected ynamides.

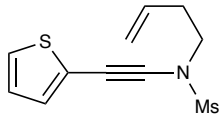
N-(But-3-en-1-yl)-4-methyl-N-(thiophen-2-ylethynyl)benzenesulfonamide 118a



Prepared according to **GP3** using 2-(2,2-dibromovinyl)thiophene **117a** (417 mg, 1.55 mmol), *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **115a** (233 mg, 1.0 mmol), CuI (24.6 mg, 0.124 mmol), Cs_2CO_3 (1.36 g, 4.14 mmol) in 1,4-dioxane (3 mL) and DMEDA (50 μL, 0.186 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118a** as a yellow oil (0.31 g, 90%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 ($d_{AA'XX'}$, *J* = 8.3 Hz, 2H), 7.36 ($d_{AA'XX'}$, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 1.2 Hz, 1H), 7.18 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.97 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.73 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.15 – 5.02 (m, 2H), 3.46 (dd, *J* = 7.9, 7.0 Hz, 2H), 2.47 (s, 3H), 2.42 (ddt, *J* = 8.2, 6.9, 1.3 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.8 (C), 134.7 (C), 133.7 (CH), 133.1 (CH), 129.9 (2CH), 127.9 (CH), 127.8 (2CH), 127.1 (CH), 123.0 (C), 118.0 (CH_2),

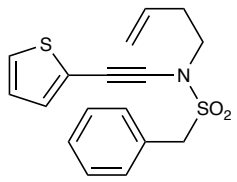
85.8 (C), 64.4 (C), 51.2 (CH_2), 32.4 (CH_2), 21.8 (CH_3) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{17}H_{17}NO_2S_2$ 332.0779; found 332.0786. Data matches that reported in the literature.[129]

N-(But-3-en-1-yl)-N-(thiophen-2-ylethynyl)methanesulfonamide 118b



Prepared according to **GP3** using 2-(2,2-dibromovinyl)thiophene **117a** (540 mg, 2.01 mmol), *N*-(but-3-en-1-yl)methanesulfonamide **115b** (200 mg, 1.34 mmol), CuI (30.6 mg, 0.161 mmol), Cs_2CO_3 (1.75 g, 5.36 mmol) in 1,4-dioxane (4 mL) and DMEDA (30 μL, 0.241 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118b** as a pale yellow oil (0.27 g, 78%); IR (neat): ν = 2227, 1430, 1347, 1158, 966, 927, 784, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.24 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.99 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.82 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.27 – 5.08 (m, 2H), 3.63 (t, *J* = 7.2 Hz, 2H), 3.14 (s, 3H), 2.54 (qt, *J* = 7.0, 1.3 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 133.8 (CH), 133.6 (CH), 128.2 (CH), 127.2 (CH), 122.6 (C), 118.4 (CH_2), 85.0 (C), 64.8 (C), 51.1 (CH_2), 38.9 (CH_3), 32.8 (CH_2) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{11}H_{13}NO_2S_2$ 256.0466; found 256.0471.

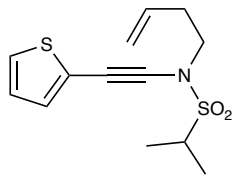
N-(But-3-en-1-yl)-1-phenyl-N-(thiophen-2-ylethynyl)methanesulfonamide 118c



Prepared according to **GP3** using 2-(2,2-dibromovinyl)thiophene **117a** (478 mg, 1.78 mmol), *N*-benzylbut-3-en-1-amine **115c** (268 mg, 1.19 mmol), CuI (27.4 mg, 0.143 mmol), Cs_2CO_3 (1.55 g, 4.76 mmol) in 1,4-dioxane (4 mL) and DMEDA (50 μL, 0.214 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118c** as a yellow solid (53.7 mg, 14%); mp: 87-91 °C; IR (neat): ν = 2934, 2227, 1429, 1351, 1152, 915, 851, 788, 717, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 – 7.40 (m, 5H), 7.31 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.24 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.00 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.66 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.12 – 5.02 (m,

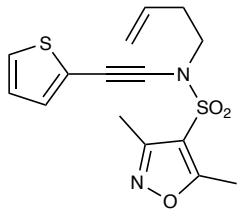
2H), 4.53 (s, 2H), 3.27 – 3.06 (m, 2H), 2.34 – 2.25 (m, 2H) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{17}H_{17}NO_2S_2$ 332.0779; found 332.0785.

N-(But-3-en-1-yl)-N-(thiophen-2-ylethynyl)propane-2-sulfonamide 118d



Prepared according to **GP3** using 2-(2,2-dibromovinyl)thiophene **117a** (500 mg, 1.86 mmol), *N*-(but-3-en-1-yl)propane-2-sulfonamide **115d** (200 mg, 1.24 mmol), CuI (28.4 mg, 0.149 mmol), Cs_2CO_3 (1.61 g, 4.95 mmol) in 1,4-dioxane (4 mL) and DMEDA (25 μL, 0.223 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118d** as a yellow oil (0.30 g, 84%); IR (neat): ν = 2982, 2226, 1346, 1145, 1056, 922, 849, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.21 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.97 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.82 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.26 – 5.10 (m, 2H), 3.68 – 3.51 (m, 3H), 2.60 – 2.49 (m, 2H), 1.47 (d, *J* = 6.9 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 133.7 (CH), 133.3 (CH), 128.0 (CH), 127.1 (CH), 123.0 (C), 118.2 (CH_2), 85.9 (C), 63.2 (C), 54.6 (CH_2), 51.9 (CH), 33.2 (CH_2), 16.7 ($2CH_3$) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{13}H_{17}NO_2S_2$ 284.0779; found 284.0782.

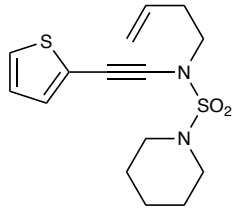
N-(But-3-en-1-yl)-3,5-dimethyl-N-(thiophen-2-ylethynyl)isoxazole-4-sulfonamide 118e



Prepared according to **GP3** using 2-(2,2-dibromovinyl)thiophene **117a** (350 mg, 1.32 mmol), *N*-(but-3-en-1-yl)-3,5-dimethylisoxazole-4-sulfonamide **115e** (200 mg, 0.884 mmol), CuI (20.7 mg, 0.11 mmol), Cs_2CO_3 (1.15 g, 3.54 mmol) in 1,4-dioxane (3 mL) and DMEDA (20 μL, 0.159 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118e** as a yellow oil (0.23 g, 78%); IR (neat): ν = 2229, 1586, 1358, 1187, 1121, 922, 849, 706, 616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.19 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.99 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.76 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.25 – 5.06 (m, 2H), 3.58 (t, *J* = 7.2

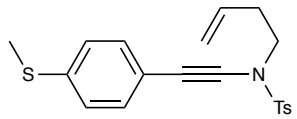
Hz, 2H), 2.68 (s, 3H), 2.56 – 2.47 (m, 2H), 2.47 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.1 (C), 158.0 (C), 133.5 (CH), 133.3 (CH), 128.5 (CH), 127.3 (CH), 122.2 (C), 118.5 (CH_2), 115.1 (C), 84.5 (C), 65.8 (C), 50.9 (CH_2), 32.5 (CH_2), 13.2 (CH_3), 11.4 (CH_3) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{15}H_{16}N_2O_3S_2$ 337.0681; found 337.0683.

N-(But-3-en-1-yl)-N-(thiophen-2-ylethynyl)piperidine-1-sulfonamide 118f



Prepared according to **GP3** using 2-(2,2-dibromovinyl)thiophene **117a** (375 mg, 1.39 mmol), *N*-(but-3-en-1-yl)piperidine-1-sulfonamide **115f** (203 mg, 0.931 mmol), CuI (22.4 mg, 0.112 mmol), Cs_2CO_3 (1.21 g, 3.72 mmol) in 1,4-dioxane (3 mL) and DMEDA (20 μL, 0.167 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118f** as a colourless oil (0.19 g, 63%); IR (neat): ν = 2940, 2225, 1433, 1366, 1171, 1053, 926, 848, 724, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 1.2 Hz, 1H), 7.18 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.98 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.82 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.26 – 5.07 (m, 2H), 3.61 – 3.52 (m, 2H), 3.46 – 3.36 (m, 4H), 2.52 (dtt, *J* = 8.2, 6.9, 1.4 Hz, 2H), 1.73 – 1.62 (m, 4H), 1.62 – 1.53 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.1 (CH), 132.7 (CH), 127.7 (CH), 127.2 (CH), 123.4 (C), 117.9 (CH_2), 87.0 (C), 63.9 (C), 52.3 (CH_2), 48.1 ($2CH_2$), 32.8 (CH_2), 25.5 ($2CH_2$), 23.8 (CH_2) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{15}H_{20}N_2O_2S_2$ 325.1044; found 325.1051.

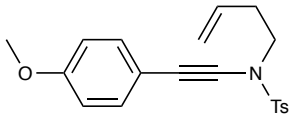
N-(But-3-en-1-yl)-4-methyl-N-((4-(methylthio)phenyl)ethynyl)benzenesulfonamide 118h



Prepared according to **GP3** using (4-(2,2-Dibromovinyl)phenyl)(methyl)sulfane **117b** (645 mg, 2.093 mmol), *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **115a** (314 mg, 1.39 mmol), CuI (32.4 mg, 0.167 mmol), Cs_2CO_3 (1.82 g, 5.56 mmol) in 1,4-dioxane (5 mL) and DMEDA (50 μL, 0.25 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118h** as a pale yellow oil (0.44 g, 84%); mp: 67-71 °C; IR (neat): ν = 2916, 2231, 1595, 1492, 1360, 1164,

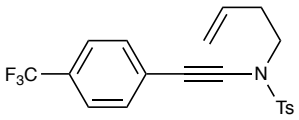
1087, 904, 828, 812, 704, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 ($d_{AA'XX'}$, *J* = 8.4 Hz, 2H), 7.35 ($d_{AA'XX'}$, *J* = 7.8 Hz, 2H), 7.28 ($d_{AA'XX'}$, *J* = 8.6 Hz, 2H), 7.16 ($d_{AA'XX'}$, *J* = 8.5 Hz, 2H), 5.74 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.16 – 5.02 (m, 2H), 3.45 (app. t, *J* = 7.4 Hz, 2H), 2.48 (s, 3H), 2.45 (s, 3H), 2.47 – 2.44 (app. q, *J* = 9.2 Hz, 2H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 144.7 (C), 139.0 (C), 134.7 (C), 133.8 (CH), 132.0 (2CH), 129.9 (2CH), 127.8 (2CH), 126.1 (2CH), 119.2 (C), 117.9 (CH_2), 82.3 (C), 70.7 (C), 51.0 (CH_2), 32.4 (CH_2), 21.8 (CH_3), 15.6 (CH_3) ppm. Data matches that reported in the literature.[226]

N-(But-3-en-1-yl)-N-((4-methoxyphenyl)ethynyl)-4-methylbenzenesulfonamide 118i



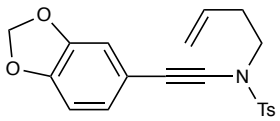
Prepared according to **GP3** using 1-(2,2-dibromovinyl)-4-methoxybenzene **117c** (600 mg, 2.055 mmol), *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **115a** (310 mg, 1.37 mmol), CuI (31.6 mg, 0.164 mmol), Cs_2CO_3 (1.79 g, 5.48 mmol) in 1,4-dioxane (5 mL) and DMEDA (50 μL, 0.25 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118i** as a white solid (0.38 g, 78%); mp: 34-36 °C; IR (neat): ν = 2964, 2234, 1604, 1510, 1462, 1359, 1245, 1164, 1019, 962, 904, 836, 810, 738, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 ($d_{AA'XX'}$, *J* = 8.3 Hz, 2H), 7.35 ($d_{AA'XX'}$, *J* = 7.8 Hz, 2H), 7.32 ($d_{AA'XX'}$, *J* = 9.0 Hz, 2H), 6.83 ($d_{AA'XX'}$, *J* = 8.9 Hz, 2H), 5.75 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.15 – 5.02 (m, 2H), 3.81 (s, 3H), 3.44 (app. q, *J* = 7.9, 7.0 Hz, 2H), 2.49 – 2.39 (m, 5H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.6 (C), 144.6 (C), 134.7 (C), 133.9 (CH), 133.5 (2CH), 129.8 (2CH), 127.8 (2CH), 117.8 (CH_2), 114.9 (C), 114.0 (2CH), 80.8 (C), 70.6 (C), 55.4 (CH_3), 51.1 (CH_2), 32.4 (CH_2), 21.8 (CH_3) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{20}H_{21}NO_3S$ 356.1320; found 356.1326. Data matches that reported in the literature.[226]

N-(But-3-en-1-yl)-4-methyl-N-((4-(trifluoromethyl)phenyl)ethynyl)benzenesulfonamide 118j



Prepared according to **GP3** using 1-(2,2-dibromovinyl)-4-(trifluoromethyl)benzene **117d** (481 mg, 1.45 mmol), *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **115a** (219 mg, 0.972 mmol), CuI (22.3 mg, 0.117 mmol), Cs_2CO_3 (1.27 g, 3.89 mmol) in 1,4-dioxane (5 mL) and DMEDA (50 µL, 0.175 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118j** as a white solid (0.35 g, 91%); IR (neat): ν = 2929, 2232, 1367, 1318, 1166, 1103, 1064, 1017, 956, 839, 812, 679, 576, 541 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 ($d_{AA'XX'}$, *J* = 8.3 Hz, 2H), 7.54 ($d_{AA'XX'}$, *J* = 7.9 Hz, 2H), 7.44 ($d_{AA'XX'}$, *J* = 7.9 Hz, 2H), 7.37 ($d_{AA'XX'}$, *J* = 7.7 Hz, 2H), 5.75 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.16 – 5.04 (m, 2H), 3.53 – 3.45 (m, 2H), 2.51 – 2.41 (m, 5H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.1 (C), 134.6 (C), 133.5 (CH), 131.1 (2CH), 130.0 (2CH), 129.5 (C), 127.8 (2CH), 127.0 (C), 125.3 (2CH), 122.7 (C), 118.1 (CH_2), 84.9 (C), 70.5 (C), 51.0 (CH_2), 32.5 (CH_2), 21.8 (CH_3) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.7 ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{20}H_{18}{}^{19}F_3NO_2S$ 394.1089; found 394.1094.

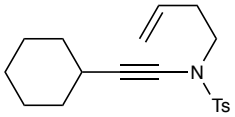
N-(1,3-Benzodioxole-5-ylethynyl)-N-(but-3-en-1-yl)-4-methylbenzenesulfonamide 118k



Prepared according to **GP3** using 5-(2,2-dibromovinyl)-1,3-benzodioxole **117e** (900 mg, 2.97 mmol), *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **115a** (447 mg, 1.98 mmol), CuI (46.1 mg, 0.238 mmol), Cs_2CO_3 (2.58 g, 7.92 mmol) in 1,4-dioxane (7 mL) and DMEDA (50 µL, 0.356 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118k** as an orange oil (0.66 g, 90%); IR (neat): ν = 2900, 2236, 1491, 1443, 1360, 1167, 1035, 899, 809, 740, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 ($d_{AA'XX'}$, *J* = 8.3 Hz, 2H), 7.35 ($d_{AA'XX'}$, *J* = 7.9 Hz, 2H), 6.90 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.82 (d, *J* = 1.6 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 2H), 5.74 (ddt, *J* = 17.0, 10.3, 6.8 Hz, 1H), 5.15 – 5.02 (m, 2H), 3.49 – 3.40 (m, 2H), 2.46 (s, 3H), 2.45 – 2.39

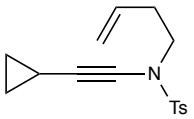
(m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.9 (C), 147.5 (C), 144.7 (C), 134.7 (C), 133.8 (CH), 129.9 (2CH), 127.8 (2CH), 126.6 (CH), 117.9 (CH_2), 116.0 (C), 112.0 (CH), 108.5 (CH), 101.4 (CH_2), 80.6 (C), 70.8 (C), 51.1 (CH_2), 32.4 (CH_2), 21.8 (CH_3) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{20}H_{19}NO_4S$ 370.1113; found 370.1117.

N-(But-3-en-1-yl)-N-(cyclohexylethynyl)-4-methylbenzenesulfonamide 118l



Prepared according to **GP3** using (2,2-dibromovinyl)cyclohexane **117f** (300 mg, 1.12 mmol), *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **115a** (170 mg, 0.75 mmol), CuI (17.3 mg, 0.10 mmol), Cs_2CO_3 (0.738 g, 2.25 mmol) in 1,4-dioxane (3 mL) and DMEDA (50 μL, 0.135 mmol). Purification by flash column chromatography (9:1 pentane/Et_2O) gave **118l** as a colourless oil (55.5 mg, 22%); IR (neat): ν = 2928, 2246, 1365, 1167, 1090, 812, 687, 656 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 ($d_{AA'XX'}$, *J* = 8.3 Hz, 2H), 7.33 ($d_{AA'XX'}$, *J* = 8.0 Hz, 2H), 5.72 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.12 – 5.00 (m, 2H), 3.39 – 3.27 (m, 2H), 2.48 (tt, *J* = 8.2, 3.9 Hz, 1H), 2.45 (s, 3H), 2.36 (app. q, *J* = 8.2, 6.1, 1.4 Hz, 2H), 1.83 – 1.59 (m, 4H), 1.52 – 1.21 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.1 (CH), 129.6 (2CH), 127.8 (2CH), 117.6 (CH_2), 50.9 (CH_2), 32.9 ($2CH_2$), 32.2 (CH_2), 28.8 (CH), 26.9 (CH_2), 26.0 (CH_2), 24.8 (CH_2), 21.8 (CH_3) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{19}H_{25}NO_2S$ 332.1684; found 332.1677.

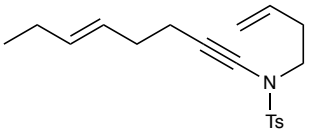
N-(But-3-en-1-yl)-N-(cyclopropylethynyl)-4-methylbenzenesulfonamide 118l



Prepared according to **GP3** using (2,2-dibromovinyl)cyclopropane **117g** (610 mg, 2.69 mmol), *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **115a** (400 mg, 1.79 mmol), CuI (41.3 mg, 0.215 mmol), Cs_2CO_3 (2.34 g, 7.16 mmol) in 1,4-dioxane (3 mL) and DMEDA (50 μL, 0.322 mmol). Purification by flash column chromatography (9:1 pentane/Et_2O) gave **118l** as a colourless oil (98.3 mg, 20%); IR (neat): ν = 2927, 1597, 1365, 1166, 1090, 995, 899, 811, 751, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 ($d_{AA'XX'}$, *J* =

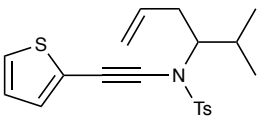
8.3 Hz, 2H), 7.33 ($d_{AA'XX'}$, *J* = 8.6 Hz, 2H), 5.70 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.11 – 4.99 (m, 2H), 3.31 (app. q, *J* = 7.9, 6.9 Hz, 2H), 2.45 (s, 3H), 2.40 – 2.30 (m, 2H), 1.30 (tt, *J* = 8.1, 4.8 Hz, 1H), 0.81 – 0.75 (m, 2H), 0.66 – 0.60 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.0 (CH), 129.7 (2CH), 127.8 (2CH), 117.6 (CH_2), 50.9 (CH_2), 32.3 (CH_2), 21.8 (CH_3), 8.9 ($2CH_2$), -0.6 (CH) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{16}H_{19}NO_2S$ 290.1215; found 290.1222.

(E)-N-(But-3-en-1-yl)-4-methyl-N-(oct-5-en-1-yn-1-yl)benzenesulfonamide 118m



Prepared according to **GP3** using cis-1,1-dibromoocta-1,5-diene **117g** (300 mg, 1.14 mmol), *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **115a** (172 mg, 0.76 mmol), CuI (17.8 mg, 0.10 mmol), Cs_2CO_3 (1.0 g, 3.0 mmol) in 1,4-dioxane (3 mL) and DMEDA (50 µL, 0.137 mmol). Purification by flash column chromatography (9:1 pentane/Et_2O) gave **118m** as a colourless oil (71.0 mg, 28%); IR (neat): ν = 2930, 2254, 1597, 1362, 1167, 1090, 987, 967, 812, 673, 657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 ($d_{AA'XX'}$, *J* = 8.3 Hz, 2H), 7.33 ($d_{AA'XX'}$, *J* = 7.8 Hz, 2H), 5.71 (ddt, *J* = 17.0, 10.3, 6.8 Hz, 1H), 5.55 – 5.29 (m, 2H), 5.12 – 5.00 (m, 2H), 3.36 – 3.28 (m, 2H), 2.45 (s, 3H), 2.41 – 2.28 (m, 4H), 2.26 – 2.12 (m, 2H), 2.08 – 1.93 (m, 2H), 0.95 (td, *J* = 7.5, 4.2 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 133.9 (CH), 129.7 (2CH), 127.8 (2CH), 127.3 (CH_2), 117.7 (2CH), 50.9 (CH_2), 32.2 ($2CH_2$), 25.7 (CH_2), 21.7 (CH_3), 19.2 (CH_2), 13.6 (CH_3) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{19}H_{25}NO_2S$ 332.1684; found 332.1691.

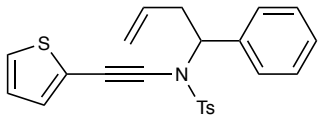
4-Methyl-N-(2-methylhex-5-en-3-yl)-N-(thiophen-2-ylethynyl)benzenesulfonamide 118o



Prepared according to **GP3** using 2-(2,2-dibromovinyl)thiophene **117a** (379 mg, 1.40 mmol), 4-methyl-*N*-(2-methylhex-5-en-3-yl)benzenesulfonamide **115j** (251 mg, 0.937 mmol), CuI (21.4 mg, 0.112 mmol), Cs_2CO_3 (1.22 g, 3.75 mmol) in 1,4-dioxane (3 mL) and DMEDA (50 µL, 0.169 mmol). Purification by flash

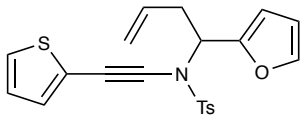
column chromatography (9:1 hexane/EtOAc) gave **118o** as a pale yellow oil (40.7 mg, 12%); IR (neat): ν = 2965, 2219, 1358, 1166, 1087, 967, 919, 851, 812, 721, 656, 583, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 ($d_{AA'XX'}$, *J* = 8.4 Hz, 2H), 7.31 ($d_{AA'XX'}$, *J* = 7.9 Hz, 2H), 7.26 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.16 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.97 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.55 – 5.40 (m, 1H), 4.98 (dd, *J* = 17.0, 1.8 Hz, 1H), 4.77 (ddt, *J* = 10.1, 2.0, 1.0 Hz, 1H), 3.73 (ddd, *J* = 9.5, 7.8, 4.3 Hz, 1H), 2.45 (s, 3H), 2.40 – 2.21 (m, 2H), 2.01 – 1.84 (m, 1H), 0.97 (dd, *J* = 27.9, 6.8 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.1 (CH), 132.6 (CH), 129.4 (2CH), 128.0 (2CH), 127.7 (CH), 127.0 (CH), 117.9 (2CH), 99.9 (CH_2), 67.0 (CH), 32.0 (CH), 21.5 (CH_3); 19.8 (CH_3), 19.4 (CH_3) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{20}H_{23}NO_2S_2$ 374.1248; found 374.1254.

4-Methyl-N-(1-phenylbut-3-en-1-yl)-N-(thiophen-2-ylethynyl)benzenesulfonamide 118p



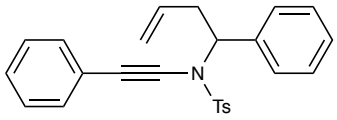
Prepared according to **GP3** using 2-(2,2-dibromovinyl)thiophene **117a** (95.5 mg, 0.354 mmol), 4-methyl-*N*-(1-phenylbut-3-en-1-yl)benzenesulfonamide **115k** (71.1 mg, 0.236 mmol), CuI (5.8 mg, 0.03 mmol), Cs_2CO_3 (308 mg, 0.944 mmol) in 1,4-dioxane (0.80 mL) and DMEDA (50 µL, 0.042 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118p** as a pale orange oil (56 mg, 58%); IR (neat): ν = 2919, 2223, 1363, 1166, 1088, 919, 811, 696, 661, 572, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 ($d_{AA'XX}$, *J* = 8.4 Hz, 2H), 7.32 – 7.26 (m, 2H), 7.25 – 7.21 (m, 4H), 7.19 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.16 ($d_{AA'XX}$, *J* = 7.9 Hz, 2H), 6.99 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.69 – 5.56 (m, 1H), 5.12 (dq, *J* = 17.0, 1.5 Hz, 1H), 5.08 – 4.96 (m, 2H), 2.88 – 2.75 (m, 1H), 2.62 (dtt, *J* = 14.4, 6.5, 1.3 Hz, 1H), 2.39 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 133.2 (CH), 132.9 (CH), 129.2 (2CH), 128.4 (3CH), 128.2 (CH), 127.7 (4CH), 118.3 (CH_2), 118.0 (CH), 63.7 (CH), 38.0 (CH_2), 21.3 (CH_3) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{23}H_{21}NO_2S_2$ 408.1092; found 408.1102.

N-(1-(Furan-2-yl)but-3-en-1-yl)-4-methyl-N-(thiophen-2-ylethynyl)benzenesulfonamide 118q



Prepared according to **GP3** using 2-(2,2-dibromovinyl)thiophene **117a** (159 mg, 0.592 mmol), *N*-(1-(furan-2-yl)but-3-en-1-yl)-4-methylbenzenesulfonamide **115k** (115 mg, 0.395 mmol), CuI (10.1 mg, 0.047 mmol), Cs_2CO_3 (516 mg, 1.58 mmol) in 1,4-dioxane (2 mL) and DMEDA (50 μL, 0.071 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118q** as a pale yellow oil (32.9 mg, 21%); IR (neat): ν = 2921, 2216, 1432, 1361, 1171, 1087, 1008, 928, 815, 710, 661, 573, 543 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 ($d_{AA'XX'}$, *J* = 8.4 Hz, 2H), 7.27 ($d_{AA'XX'}$, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 1.2 Hz, 1H), 7.23 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.14 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.96 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.23 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.18 (dt, *J* = 3.3, 0.8 Hz, 1H), 5.68 (ddt, *J* = 17.1, 10.1, 6.9 Hz, 1H), 5.23 – 5.12 (m, 2H), 5.05 (ddt, *J* = 10.1, 2.0, 1.1 Hz, 1H), 2.73 (ddt, *J* = 8.7, 7.5, 1.4 Hz, 2H), 2.43 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.4 (C), 144.5 (C), 142.3 (CH), 135.3 (C), 133.1 (CH), 132.9 (CH), 129.5 (2CH), 128.0 (CH), 127.9 (2CH), 127.1 (CH), 123.1 (C), 118.9 (CH_2), 110.3 (CH), 108.4 (CH), 83.3 (C), 66.7 (C), 57.6 (CH), 36.2 (CH_2), 21.8 (CH_3) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{21}H_{19}NO_3S_2$ 398.0885; found 398.0894.

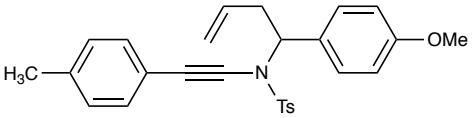
4-Methyl-N-(1-phenylbut-3-en-1-yl)-N-(phenylethynyl)benzenesulfonamide 118r



Prepared according to **GP3** using 2-(2,2-dibromovinyl)thiophene **117i** (309 mg, 1.18 mmol), 4-methyl-*N*-(1-phenylbut-3-en-1-yl)benzenesulfonamide **115k** (237 mg, 0.786 mmol), CuI (18.0 mg, 0.094 mmol), Cs_2CO_3 (1.026 g, 3.14 mmol) in 1,4-dioxane (3 mL) and DMEDA (50 μL, 0.141 mmol). Purification by flash column chromatography (95:5 hexane/EtOAc) gave **118r** as a pale yellow oil (174 mg, 55%); IR (neat): ν = 3032, 2230, 1362, 1166, 1088, 966, 752, 690, 658, 572, 544 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.59 ($d_{AA'XX'}$, *J* = 8.4 Hz, 2H), 7.41 – 7.35 (m, 2H), 7.36 – 7.26

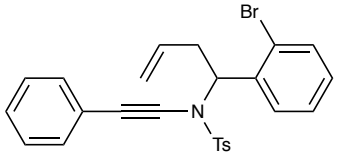
(m, 4H), 7.27 – 7.17 (m, 2H), 7.15 ($d_{AA'XX'}$, *J* = 7.8 Hz, 2H), 5.66 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.18 – 5.03 (m, 2H), 5.00 (ddt, *J* = 10.2, 1.9, 1.0 Hz, 1H), 2.92 – 2.78 (m, 2H), 2.66 (dtt, *J* = 14.4, 6.5, 1.4 Hz, 2H), 2.38 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.3 (C), 138.9 ;(C), 135.4 (C), 133.6 (CH), 131.3 (2CH), 129.3 (2CH), 128.5 (2CH), 128.4 (2CH), 128.2 (CH), 127.9 (2CH), 127.8 (CH), 127.3 (2CH), 123.3 (C), 118.5 (CH_2), 80.6 (C), 73.7 (C), 63.5 (CH), 38.5 (CH_2), 21.7 (CH_3) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{25}H_{23}NO_2S$ 402.1528; found 402.1531. Data matches that reported in the literature.[226]

N-(1-(4-Methoxyphenyl)but-3-en-1-yl)-4-methyl-N-(p-tolylethynyl)benzenesulfonamide 118s



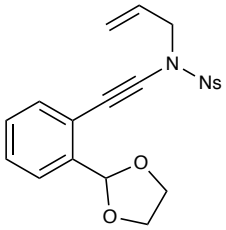
Prepared according to **GP3** using 2-(2,2-dibromovinyl)thiophene **117j** (187 mg, 0.677 mmol), *N*-(1-(4-methoxyphenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide **115l** (151 mg, 0.451 mmol), CuI (11.1 mg, 0.80 mmol), Cs_2CO_3 (588 mg, 1.80 mmol) in 1,4-dioxane (3 mL) and DMEDA (50 μL, 0.071 mmol). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **118s** as a pale yellow oil (155 mg, 77%); IR (neat): ν = 2916, 2231, 1610, 1512, 1360, 1249, 1165, 1088, 1033, 960, 812, 662, 588, 545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 ($d_{AA'XX'}$, *J* = 8.3 Hz, 2H), 7.26 ($d_{AA'XX'}$, *J* = 8.1 Hz, 2H), 7.23 ($d_{AA'XX'}$, *J* = 8.8 Hz, 2H), 7.16 ($d_{AA'XX'}$, *J* = 8.1 Hz, 2H), 7.11 ($d_{AA'XX'}$, *J* = 7.9 Hz, 2H), 6.75 ($d_{AA'XX'}$, *J* = 8.7 Hz, 2H), 5.64 (ddt, *J* = 20.1, 10.2, 7.1 Hz, 1H), 5.17 – 4.94 (m, 2H), 3.77 (s, 3H), 2.88 – 2.75 (m, 1H), 2.71 – 2.57 (m, 2H), 2.38 (s, 3H), 2.35 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.5 (C), 144.1 (C), 138.0 (C), 135.6 (C), 133.8 (CH), 131.5 (2CH), 131.0 (2CH), 129.3 (2CH), 129.2 (C), 128.6 (2CH), 127.9 (2CH), 120.1 (C), 118.4 (CH_2), 113.8 (2CH), 79.8 (C), 73.6 (C), 63.1 (CH_3), 55.4 (CH_3), 38.4 (CH_2), 21.7 (CH_3) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{27}H_{27}NO_3S$ 446.1790; found 446.1800.

N-(1-(2-Bromophenyl)but-3-en-1-yl)-4-methyl-N-(phenylethynyl)benzenesulfonamide 118t



This ynamide was prepared by a previous Davies group member Onyeka F. Obumselu.

Formation of ynamide 175a (Chapter 4)



Following the general procedure of Hsung,[43] the *N*-allyl-4-nitrobenzenesulfonamide **174a** (627 mg, 2.58 mmol, 1.0 eq.), 1,10-phenanthroline (185 mg, 1.03 mmol, 0.4 eq.), $CuSO_4.5H_2O$ (128 mg, 0.52 mmol, 0.2 eq.), K_2CO_3 (718 mg, 5.16 mmol, 2.0 eq.) and the 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane **173** (782 mg, 3.10 mmol, 1.2 eq.) were combined in a Schlenk flask. Toluene (3 mL, 2.58 mmol, 1.0 M) was added and the resulting solution was stirred at 65 °C until completion monitored by TLC. After, the mixture was diluted with CH_2Cl_2 and filtered through a pad of silica eluted with CH_2Cl_2. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography [7:3:1 hexane/EtOAc/NEt_3] to afford **175a** as a yellow oil (0.77 g, 72%); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.39 (d, *J* = 8.9 Hz, 2H), 8.22 (d, *J* = 8.9 Hz, 2H), 7.64 – 7.56 (m, 1H), 7.39 – 7.27 (m, 3H), 6.10 (s, 1H), 5.77 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 1H), 5.40 – 5.21 (m, 2H), 4.22 – 4.09 (m, 4H), 4.09 – 4.01 (m, 2H) ppm; MS (ES-TOF): m/z 437 [M+Na] (100%). Data matches that reported in the literature.[211]

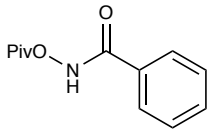
Formation of *N*-(pivaloyloxy)amides

General procedure 4: *N*-(pivaloyloxy)amides (GP4a)

The relevant acid derivative (1.0 eq.) was added dropwise to a solution of $NH_2OH.HCl$ (4.0 eq.) and NaOH (5.0 eq.) in THF/H_2O (0.25 M). After stirring for 2 h, 2.0 M HCl was added and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over

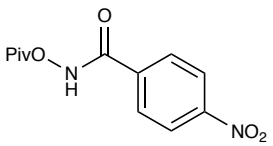
Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford the desired hydroxamic acid, which was used directly in the next step without further purification. The hydroxamic acid (1.2 eq.) was dissolved in THF (0.25 M) and cooled to 0 °C, to which pivaloyl chloride (1.0 eq.) and NEt_3 (1.2 eq.) were added in sequence. The resulting mixture was allowed to warm to room temperature and stirred for 3 h. H_2O was added and the aqueous layer was extracted with EtOAc (3x) and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude materials were purified by recrystallisation to give the corresponding *N*-(pivaloyloxy)amides.

N-(Pivaloyloxy)benzamide 124a



Following **GP4a** for the first step with benzoyl chloride **123a** (0.82 mL, 7.11 mmol), $NH_2OH.HCl$ (1.97 g, 28.4 mmol), NaOH (1.47 g, 35.5 mmol) in THF/H_2O (30 mL) and for the second step with hydroxamic acid (1.037 g, 7.56 mmol), pivaloyl chloride (0.77 mL, 6.30 mmol), NEt_3 (1.1 mL, 7.56 mmol) in THF (25 mL). Purification by recrystallisation (toluene/heptane) gave **124a** as an off-white solid (1.18 g, 75%); mp: 108-110 °C; IR (neat): ν = 3234, 2975, 1779, 1650, 1482, 1289, 1063, 1022, 901, 708, 540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.37 (br. s, 1H), 7.87 – 7.76 (m, 2H), 7.50-7.41 (m, 2H), 1.36 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.2 (C), 167.0 (C), 132.9 (CH), 131.0 (C), 129.0 (2CH), 127.6 (2CH), 38.6 (C), 27.1 ($3CH_3$) ppm. Data matches that reported in the literature.[129]

4-Nitro-N-(pivaloyloxy)benzamide 124b



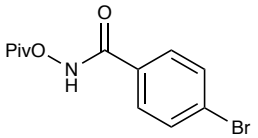
Following **GP4a** for the first step with 4-nitrobenzoyl chloride **123b** (0.50 g, 2.69 mmol), $NH_2OH.HCl$ (752 mg, 10.8 mmol), NaOH (577 mg, 13.4 mmol) in THF/H_2O (11 mL) and for the second step with hydroxamic acid (468 mg, 2.57 mmol), pivaloyl chloride (0.26 mL, 2.14 mmol), NEt_3 (0.34 mL, 2.57 mmol) in THF (9 mL). Purification by recrystallisation (toluene/heptane) gave **124b** as an off-white solid (0.28

g, 49%); IR (neat): ν = 3144, 2974, 1782, 1663, 1522, 1479, 1348, 1298, 1069, 1029, 849, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.45 (s, 1H), 8.32 ($d_{AA'XX'}$, *J* = 8.8 Hz, 2H), 7.99 ($d_{AA'XX'}$, *J* = 8.8 Hz, 2H), 1.36 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 128.7 (2CH), 124.0 (2CH), 27.0 ($3CH_3$) ppm. Data matches that reported in the literature.[129]

General procedure 4: *N*-(pivaloyloxy)amides (GP4b)

Adapted from procedure of Rees,[227] the relevant acid derivative (1.0 eq.) was added dropwise to a solution of $NH_2OH.HCl$ (1.2 eq.) and K_2CO_3 (2.0 eq.) in EtOAc/H_2O (0.08 M). After stirring for 2 h, HCl (2.0 M) was added and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford the desired hydroxamic acid, which was used directly in the next step without further purification. The hydroxamic acid (1.0 eq.) was dissolved in THF (0.1 M) and cooled to 0 °C, to which pivaloyl chloride (1.2 eq.) and NEt_3 (1.2 eq.) were added in sequence. The resulting mixture was allowed to warm to room temperature and stirred for 6 h. H_2O was added and the aqueous layer was extracted with EtOAc (3x) and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude materials were purified by flash column chromatography to give the corresponding *N*-(pivaloyloxy)amides.

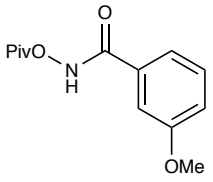
4-Bromo-N-(pivaloyloxy)benzamide 124c



Following **GP4b** for the first step with 4-bromobenzoyl chloride **123c** (2.20 g, 10.0 mmol), $NH_2OH.HCl$ (835 mg, 12.0 mmol), K_2CO_3 (2.76 g, 20.0 mmol) in EtOAc/H_2O (120 mL) and for the second step with hydroxamic acid (1.31 g, 6.0 mmol), pivaloyl chloride (0.88 mL, 7.2 mmol), NEt_3 (1.1 mL, 7.2 mmol) in THF (60 mL). Purification by flash column chromatography (9:1 petroleum ether/EtOAc) gave **124c** as a white solid (1.069 g, 60%); mp: 138-141 °C; IR (neat): ν = 3156, 2970, 1781, 1652, 1588, 1513, 1476, 1304, 1067, 1008, 869, 836, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.29 (s, 1H),

7.68 ($d_{AA'XX'}$, J = 8.6 Hz, 2H), 7.61 ($d_{AA'XX'}$, J = 8.6 Hz, 2H), 1.36 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.2 (C), 166.1 (C), 132.3 (2CH), 129.8 (C), 129.1 (2CH), 127.8 (C), 38.6 (C), 27.1 ($3CH_3$) ppm; MS (ESI-TOF): m/z: [M+Na] Calcd for $C_{12}H_{14}{}^{79}BrNO_3$ 322.0055; found 322.0056.

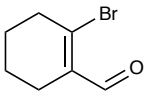
3-Methoxy-N-(pivaloyloxy)benzamide 124d



Following **GP4b** for the first step with 3-methoxybenzoyl chloride **123d** (0.70 mL, 5.0 mmol), $NH_2OH.HCl$ (420 mg, 6.0 mmol), K_2CO_3 (1.39 g, 10.0 mmol) in EtOAc/H_2O (63 mL) and for the second step with hydroxamic acid (1.069 g, 6.40 mmol), pivaloyl chloride (0.65 mL, 5.33 mmol), NEt_3 (0.89 mL, 6.40 mmol) in THF (21 mL). Purification by flash column chromatography (95:5 hexane/EtOAc) gave **124d** as a pale orange oil (1.13 g, 90%); mp: 56-61 °C; IR (neat): ν = 3201, 2975, 1781, 1648, 1580, 1478, 1291, 1071, 1029, 887, 742, 682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.27 (s, 1H), 7.39 – 7.33 (m, 3H), 7.15 – 7.06 (m, 1H), 3.85 (s, 3H), 1.37 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.2 (C), 166.8 (C), 160.0 (C), 132.3 (C), 130.0 (CH), 119.4 (CH), 119.3 (CH), 112.5 (CH), 55.6 (CH_3), 38.6 (C), 27.2 ($3CH_3$) ppm; MS (ESI-TOF): m/z: [M+Na] Calcd for $C_{13}H_{17}NO_4$ 274.1055; found 274.1056.

Formation of catalysis precursors (Chapters 2, 3 and 4)

Preparation of 2-bromocyclohex-1-ene-1-carbaldehyde 236



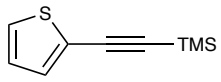
DMF (2.3 mL, 30.0 mmol, 3.0 eq.) was dissolved in CH_2Cl_2 (33 mL, 0.3 M) and cooled to 0 °C. PBr_3 (2.5 mL, 27.0 mmol, 2.7 equiv.) was added dropwise and the resulting solution was stirred for 1 h at this temperature. Cyclohexanone **235** dried in sieves (1.0 mL, 10.0 mmol, 1.0 equiv.) was added dropwise and the stir was continued for 24 h at room temperature. The reaction mixture was poured slowly into an ice-cooled, saturated solution of $NaHCO_3$ (600 mL) until neutral solution checked with pH paper. The organic phase

was extracted with CH_2Cl_2 (3x 100 mL), washed with water (100 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford without further purification the 2- bromocyclohex-1-ene-1-carbaldehyde **236** (0.91 g, 48%) as an orange oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.02 (s, 1H), 2.79 – 2.69 (m, 2H), 2.34 – 2.22 (m, 2H), 1.84 – 1.60 (m, 4H) ppm; MS (EI-TOF): m/z 188 [M+H] (95%). Data matches that reported in the literature.[211]

General procedure 5: preparation of 2-ethynyl aldehydes (GP5)

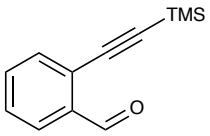
The required bromides (1.0 eq.) was dissolved in NEt_3 (0.25 M) at room temperature. The resulting solution was degazed for 10 min. $Pd(PPh_3)Cl_2$ (2-5 mol%), CuI (1-3 mol%) and trimethylsilyl acetylene (1.2-1.4 eq.) were added and the resulting mixture was stirred at 50 °C until completion monitored by TLC. After cooling to room temperature, the solids were removed by filtration through a pad of celite and the solvent removed under reduced pressure. The crude residues were purified by flash column chromatography to give the corresponding 2-ethynyl aldehydes.

Trimethyl(thiophen-2-ylethynyl)silane 120



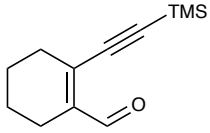
Prepared according to **GP5** from 2-bromothiophene **119** (0.60 mL, 6.13 mmol), $Pd(PPh_3)Cl_2$ (219 mg, 0.31 mmol), CuI (35.5 mg, 0.184 mmol) and trimethylsilyl acetylene (1.20 mL, 8.58 mmol) in NEt_3 (30 mL). Purification by flash column chromatography (hexane) gave **120** as a brown oil (0.92 g, 83%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23 (d, *J* = 4.4 Hz, 2H), 6.97 – 6.93 (m, 1H), 0.25 (s, 9H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 132.7 (CH), 127.4 (CH), 127.0 (CH), 0.01 ($3CH_3$) ppm; MS (EI-TOF): m/z: [M] Calcd for $C_9H_{12}SSi$ 180.0429; found 180.0430. Data matches that reported in the literature.[228]

2-((Trimethylsilyl)ethynyl)benzaldehyde 180



Prepared according to **GP5** from 2-bromobenzaldehyde **172** (3.60 mL, 30.0 mmol), $Pd(PPh_3)Cl_2$ (1.0 g, 1.5 mmol), CuI (172 mg, 0.9 mmol) and trimethylsilyl acetylene (6.0 mL, 42.0 mmol) in NEt_3 (150 mL). Purification by flash column chromatography (95:5 hexane/EtOAc) gave **180** as a pale brown solid (2.87 g, 47%); mp: 51-53 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.56 (s, 1H), 7.95 – 7.86 (m, 1H), 7.62 – 7.48 (m, 2H), 7.49 – 7.37 (m, 1H), 0.28 (s, 9H) ppm. Data matches that reported in the literature.[211]

2-((Trimethylsilyl)ethynyl)cyclohex-1-ene-1-carbaldehyde 237

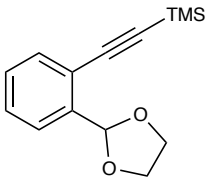


Prepared according to **GP5** from 2-bromocyclohex-1-ene-1-carbaldehyde **236** (1.51 g, 8.0 mmol), $Pd(PPh_3)Cl_2$ (113 mg, 0.16 mmol), CuI (15.2 mg, 0.08 mmol) and trimethylsilyl acetylene (1.35 mL, 9.6 mmol) in NEt_3 (32 mL). Purification by flash column chromatography (9:1 hexane/EtOAc) gave **237** as a brown oil (1.33 g, 81%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.20 (s, 1H), 2.43 – 2.37 (m, 2H), 2.29 – 2.20 (m, 2H), 1.72 – 1.58 (m, 4H), 0.21 (s, 9H) ppm; MS (EI-TOF): m/z 206 [M] (15%). Data matches that reported in the literature.[211]

General procedure 6: preparation of acetals from 2-ethynyl aldehydes (GP6)

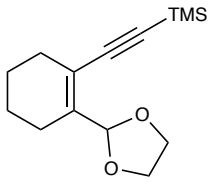
The required aldehyde (1.0 eq.), ethylene glycol (1.2 eq.) and *p*-TsOH.H_2O (5 mol%) were dissolved in toluene (0.2 M) and heated at reflux with azeotropic removal of water using Dean Stark apparatus until completion monitored by TLC. The reaction mixture was cooled to room temperature and saturated $NaHCO_3$ solution was added. The aqueous layer was extracted with EtOAc (x3), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude residues were purified by flash column chromatography to give the corresponding acetals.

((2-(1,3-Dioxolan-2-yl)phenyl)ethynyl)trimethylsilane 181



Prepared according to **GP6** from aldehyde **180** (2.86 g, 14.1 mmol), ethylene glycol (0.95 mL, 16.9 mmol), *p*-TsOH.H_2O (149 mg, 0.70 mmol) in toluene (70 mL). Purification by flash column chromatography (95:5:1 hexane/EtOAc/NEt_3) gave **181** as a yellow oil (2.87 g, 83%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 – 7.44 (m, 2H), 7.39 – 7.26 (m, 2H), 6.18 (s, 1H), 4.27 – 4.10 (m, 2H), 4.14 – 3.99 (m, 2H), 0.26 (s, 9H) ppm; MS (ES): m/z 246 [M] (31%). Data matches that reported in the literature.[211]

((2-(1,3-Dioxolan-2-yl)cyclohex-1-en-1-yl)ethynyl)trimethylsilane 238

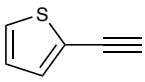


Prepared according to **GP6** from aldehyde **237** (1.10 g, 5.31 mmol), ethylene glycol (0.40 mL, 6.40 mmol), *p*-TsOH.H_2O (54.9 mg, 0.266 mmol) in toluene (25 mL). Purification by flash column chromatography (97:3 hexane/EtOAc) gave **238** as an orange solid (0.90 g, 68%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.88 (s, 1H), 4.06 – 3.97 (m, 2H), 3.97 – 3.87 (m, 2H), 2.25 – 2.15 (m, 2H), 2.17 – 2.03 (m, 2H), 1.72 – 1.57 (m, 4H), 0.17 (s, 9H) ppm; MS (EI-TOF): m/z 250 [M] (20%). Data matches that reported in the literature.[211]

General procedure 7: preparation of terminal alkynes (GP7)

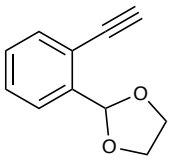
The required 2-((trimethylsilyl)ethynyl)benzaldehyde derivative (1.0 eq.) was dissolved in MeOH (0.2 M). K_2CO_3 (0.5 eq.) was added and the mixture was stirred at room temperature until completion monitored by TLC. Saturated $NaHCO_3$ solution was added and the aqueous phase was extracted with EtOAc (x2) and dried over Na_2SO_4. The solid was filtered off and the solvent removed under reduced pressure. The crude residues were purified by flash column chromatography to give the corresponding terminal alkynes.

2-Ethynylthiophene 121



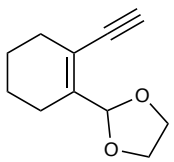
Prepared according to **GP7** from trimethyl(thiophen-2-ylethynyl)silane **120** (915 mg, 5.10 mmol), K_2CO_3 (351 mg, 2.53 mmol) in methanol/CH_2Cl_2 (25 mL) to afford **121** as a pale brown oil (0.37 g, 67%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.27 (m, 2H), 6.98 (dd, *J* = 5.2, 3.6 Hz, 1H), 3.33 (s, 1H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 133.2 (CH), 127.6 (CH), 127.0 (CH) ppm; MS (EI-TOF): m/z: [M] Calcd for C_6H_4S 108.0034; found 108.0032. Data matches that reported in the literature.[229]

2-(2-Ethynylphenyl)-1,3-dioxolane 182



Prepared according to **GP7** from ((2-(1,3-dioxolan-2-yl)phenyl)ethynyl)trimethylsilane **181** (2.85 g, 11.6 mmol), K_2CO_3 (800 mg, 5.77 mmol) in methanol (62 mL). Purification by flash column chromatography (9:1:1 hexane/EtOAc/NEt_3) gave **182** as a yellow oil (1.85 g, 91%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = δ 7.59 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.53 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.46 – 7.27 (m, 2H), 6.22 (s, 1H), 4.24 – 4.14 (m, 2H), 4.12 – 4.02 (m, 2H), 3.32 (s, 1H) ppm; MS (EI): m/z 174 [M] (39%). Data matches that reported in the literature.[211]

2-(2-Ethynylcyclohex-1-en-1-yl)-1,3-dioxolane 239



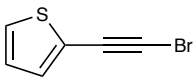
Prepared according to **GP7** from ((2-(1,3-dioxolan-2-yl)cyclohex-1-en-1-yl)ethynyl)trimethylsilane **238** (890 mg, 3.57 mmol), K_2CO_3 (462 mg, 1.78 mmol) in methanol (22 mL). Purification by flash column chromatography (9:1:1 hexane/EtOAc/NEt_3) gave **239** as a yellow oil (0.54 g, 86%); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.88 (s, 1H), 4.06 – 3.97 (m, 2H), 3.97 – 3.86 (m, 2H), 3.12 (s, 1H), 2.28 – 2.16 (m, 2H), 2.17 – 2.05 (m, 2H), 1.68 – 1.57 (m, 4H) ppm; MS (EI-TOF): m/z 178 [M] (80 %). Data matches that reported in the literature.[211]

General procedure 8: preparation of bromoalkynes (GP8)

N-Bromosuccinimide (1.1 eq.) and $AgNO_3$ (0.1 equiv) were added to a solution of the required terminal alkyne (1.0 eq.) in acetone (0.2 M) at room temperature and the solution was stirred for 1 h. 2-3 spatulas of silica were added to the flask and the solvent removed under reduced pressure. The resulting solid was loaded onto a pad of silica and the product was eluted into a receiving flask. The solvent was removed under reduced pressure to give the corresponding bromoalkyne.

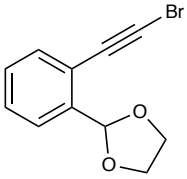
N.B.: After filtration through a pad of silica, bromoalkyne was evaporated in vacuo at 25-30 °C to avoid degradation.

2-(Bromoethynyl)thiophene 122



Prepared according to **GP8** from NBS (200 mg, 1.11 mmol), $AgNO_3$ (25.5 mg, 0.10 mmol), 2-ethynylthiophene **121** (110 mg, 1.0 mmol), in acetone (3 mL). Purification by flash column chromatography [95:5 hexane/EtOAc] gave **122** as an orange oil (0.12 g, 65%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.21 (m, 2H), 6.96 (dd, *J* = 5.1, 3.7 Hz, 1H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 133.0 (CH), 127.5 (CH), 126.9 (CH) ppm; MS (EI-TOF): m/z: [M] Calcd for $C_6H_3{}^{79}BrS$ 185.9139; found 185.9126. Data matches that reported in the literature.[230]

2-(2-(bromoethynyl)phenyl)-1,3-dioxolane 173



Prepared according to **GP8** from NBS (2.10 g, 11.7 mmol), $AgNO_3$ (181 mg, 1.06 mmol), 2-(2-ethynylphenyl)-1,3-dioxolane **182** (1.84 g, 10.6 mmol), in acetone (35 mL). Purification by flash column chromatography [8:2:1 hexane/EtOAc/NEt_3] gave **173** as a yellow oil (2.59 g, 97%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.49 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.43 – 7.26 (m, 2H), 6.14 (s, 1H),

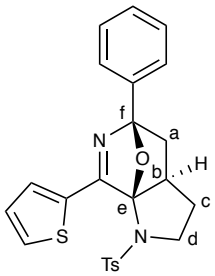
4.24 – 4.15 (m, 2H), 4.14 – 4.02 (m, 2H) ppm; MS (EI): *m/z* 253 [M] (99%). Data matches that reported in the literature.[211]

Polycyclisation catalysis products

General procedure 9: Diels-Alder cycloadduct (GP9)

The relevant ynamide (1.0 eq.), *N*-(pivaloyloxy)amide (1.5 eq.), [Cp*CoI_2(CO)] (2.5 mol%) and NaOAc (5 mol%) were dissolved in TFE (0.1 M) and stirred at the given temperature for 3-18 h. After allowing to cool to r.t., the solvent was removed under reduced pressure (10 min at 10 mbar). The residue was dissolved in EtOAc and filtered through a 3 cm pad of silica (EtOAc) and concentrated under reduced pressure (10 min at 10 mbar). The residue was then heated in dioxane (0.1 M) at reflux for the indicated time and concentrated under reduced pressure. The crude residue was purified by recrystallisation or flash column chromatography to afford the corresponding Diels-Alder cycloadduct.

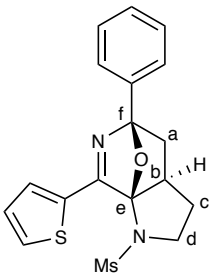
(3aR,5R,7aR)-5-Phenyl-7-(thiophen-2-yl)-1-tosyl-1,2,3,3a,4,5-hexahydro-5,7a-epoxypyrrolo[2,3-c]pyridine 126a



Prepared according to **GP9** from ynamide **118a** (1.0 g, 3.0 mmol), *N*-(pivaloyloxy)amide **124a** (741 mg, 3.30 mmol), [Cp*CoI_2(CO)] (36.4 mg, 0.08 mmol), NaOAc (12.3 mg, 0.152 mmol) in TFE (30 mL) for 15 h at r.t. followed by 24 h at 101 °C in 1,4-dioxane (36 mL). Purification by flash column chromatography [3:1 hexane/EtOAc] to afford **126a** as a pale brown solid (0.82 g, 66%); mp: 198-200 °C; IR (neat): ν = 2921, 1579, 1339, 1250, 1160, 1121, 1038, 769, 702, 670, 540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.96 ($d_{AA'XX'}$, *J* = 8.3 Hz, 2H), 7.70 – 7.62 (m, 2H), 7.54 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.49 – 7.35 (m, 3H), 7.30 ($d_{AA'XX'}$, *J* = 7.7 Hz, 2H), 7.19 (dd, *J* = 5.0, 3.8 Hz, 1H), 3.98 (app. td, *J* = 10.9, 6.3 Hz, $1H_d$), 3.69 (app. t, *J* = 10.4, 9.0 Hz, $1H_d$), 2.44 (s, 3H), 2.43 – 2.37 (m, $1H_b$), 2.19 (dd, *J* = 11.7, 7.6 Hz, $1H_a$), 2.20 – 2.10 (m, $1H_c$), 1.87 (dd, *J* = 11.8, 3.3 Hz, $1H_a$), 1.73 – 1.57 (m, $1H_c$) ppm; ^{13}C

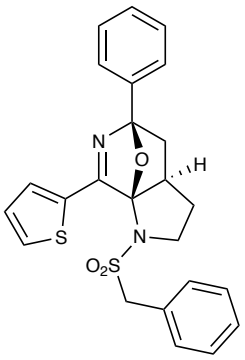
NMR (101 MHz, Chloroform-*d*) δ 131.5 (CH), 130.5 (CH), 129.2 (2CH), 129.1 (2CH), 128.5 (CH), 128.3 (2CH), 128.1 (CH), 126.1 (2CH), 52.7 (C_dH_2), 45.5 (C_bH), 40.5 (C_aH_2), 29.3 (C_cH_2), 21.5 (CH_3) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{24}H_{22}N_2O_3S_2$ 451.1150; found 451.1157. Data matches that reported in the literature.[129]

(3aR,5R,7aR)-1-(Methylsulfonyl)-5-phenyl-7-(thiophen-2-yl)-1,2,3,3a,4,5-hexahydro-5,7a-epoxypyrrolo[2,3-c]pyridine 126b



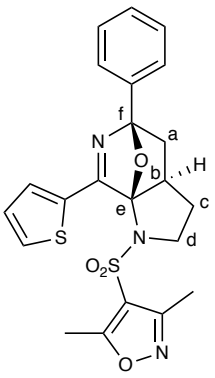
Prepared according to **GP9** from ynamide **118b** (76.5 mg, 0.30 mmol), *N*-(pivaloyloxy)amide **124a** (72.9 mg, 0.33 mmol), [Cp*CoI_2(CO)] (3.6 mg, 0.008 mmol), NaOAc (1.20 mg, 0.015 mmol) in TFE (3 mL) for 3 h at r.t. followed by 24 h at 101 °C in 1,4-dioxane (4 mL). Purification by hot recrystallisation in EtOH to afford **126b** as a white solid (60.2 g, 53%); mp: 234-237 °C; IR (neat): ν = 2981, 1577, 1339, 1252, 1154, 1027, 966, 917, 766, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.73 – 7.67 (m, 2H), 7.52 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.48 – 7.36 (m, 3H), 7.14 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.06 (app. td, *J* = 11.3, 6.1 Hz, $1H_d$), 3.97 (app. t, *J* = 9.6 Hz, $1H_d$), 3.09 (s, 3H), 2.53-2.41 (m, $1H_b$), 2.39 – 2.28 (m, $1H_c$), 2.24 (dd, *J* = 11.8, 7.5 Hz, $1H_a$), 2.07 (dd, *J* = 11.8, 3.3 Hz, $1H_a$), 2.04 – 1.94 (m, $1H_c$) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.0 (C), 137.3 (C), 133.2 (C), 132.0 (CH), 131.0 (CH), 128.9 (CH), 128.5 (2CH), 128.2 (CH), 126.5 (2CH), 104.7 (C_f), 102.4 (C_e), 54.0 (C_dH_2), 45.7 (C_bH), 40.7 (C_aH_2), 39.1 (CH_3), 29.8 (C_cH_2) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{18}H_{18}N_2O_3S_2$ 375.0837; found 375.0836.

(3aR,5R,7aR)-1-(Benzylsulfonyl)-5-phenyl-7-(thiophen-2-yl)-1,2,3,3a,4,5-hexahydro-5,7a-epoxypyrrolo[2,3-c]pyridine 126c



Prepared according to **GP9** from ynamide **118c** (26.1 mg, 0.08 mmol), *N*-(pivaloyloxy)amide **124a** (19.5 mg, 0.09 mmol), [Cp*CoI_2(CO)] (1.12 mg, 0.002 mmol), NaOAc (0.33 mg, 0.004 mmol) in TFE (1 mL) for 4 h at r.t. followed by 24 h at 101 °C in 1,4-dioxane (1.5 mL). Purification by flash column chromatography [8:2 hexane/EtOAc] to afford **126c** as a white solid (40.7 g, 85%); mp: 182-185 °C; IR (neat): ν = 1574, 1355, 1249, 1155, 1041, 787, 731, 693, 631, 537, 523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.79 (d, *J* = 6.9 Hz, 1H), 7.63 – 7.33 (m, 10H), 7.13 (dd, *J* = 5.1, 3.8 Hz, 1H), 4.68 – 4.39 (m, 2H), 3.80 (app. td, *J* = 11.4, 5.8 Hz, $1H_d$), 3.29 (dd, *J* = 10.9, 8.4 Hz, $1H_d$), 2.46 – 2.34 (m, $1H_b$), 2.26 (dd, *J* = 11.8, 7.6 Hz, $1H_a$), 2.13 – 2.01 (m, H_c+H_a), 1.86 – 1.72 (m, $1H_c$) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 137.5 (C), 133.2 (C), 131.9 (C), 131.1 (C), 130.9 (3CH), 129.0 (CH), 128.9 (CH), 128.8 (5CH), 128.7 (CH), 128.1 (CH), 126.4 (CH), 104.7 (C_f), 102.3 (C_e), 60.0 (CH_2), 55.3 (C_dH_2), 46.1(C_bH), 40.9 (C_aH_2), 29.6 (C_cH_2) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{24}H_{22}N_2O_3S_2$ 451.1150; found 451.1162.

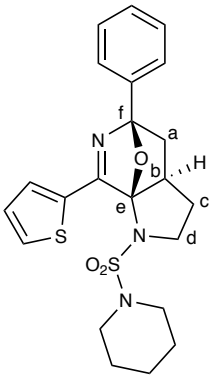
(3aR,5R,7aR)-1-((3,5-Dimethylisoxazol-4-yl)sulfonyl)-5-phenyl-7-(thiophen-2-yl)-1,2,3,3a,4,5-hexahydro-5,7a-epoxypyrrolo[2,3-c]pyridine 126e



Prepared according to **GP9** from ynamide **118e** (101mg, 0.30 mmol), *N*-(pivaloyloxy)amide **124a** (73.0 mg, 0.33 mmol), [Cp*CoI_2(CO)] (3.6 mg, 0.008 mmol), NaOAc (1.60 mg, 0.015 mmol) in TFE (3 mL) for 20 h at r.t. followed by 24 h at 101 °C in 1,4-dioxane (4 mL). Purification by hot recrystallisation in EtOH to afford **126e** as an off-white solid (0.11 g, 78%); mp: 185-189 °C; IR (neat): ν = 3094, 1576, 1348, 1251, 1179, 1118, 1042, 829, 760, 734, 653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.56 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.48 – 7.35 (m, 3H), 7.18 (dd, *J* = 5.0, 3.8 Hz,

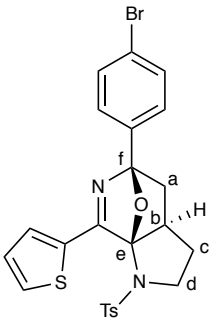
1H), 4.08 (app. td, J = 10.6, 6.6 Hz, 1H$_d$), 3.81 (app. t, J = 10.4, 9.8, 1.4 Hz, 1H$_d$), 2.57 (s, 3H), 2.51 – 2.38 (m, 1H$_b$), 2.42 (s, 3H), 2.35 – 2.25 (m, 1H$_a$), 2.19 – 2.10 (m, 1H$_c$), 1.94 (dd, J = 11.9, 3.3 Hz, 1H$_a$), 1.92 – 1.77 (m, 1H$_c$) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 174.9 (C), 165.9 (C), 158.6 (C), 137.1 (C), 133.4 (C), 131.8 (CH), 131.0 (CH), 128.9 (CH), 128.6 (2CH), 128.2 (CH), 126.2 (2CH), 115.3 (C), 104.8 (C$_f$), 102.3 (C$_e$), 52.7 (C$_d$H$_2$), 45.7 (C$_b$H), 41.7 (C$_a$H$_2$), 29.3 (C$_c$H$_2$), 13.6 (CH$_3$), 11.6 (CH$_3$) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{22}H_{21}N_3O_4S_2$ 456.1052; found 456.1051.

(3aR,5R,7aR)-5-Phenyl-1-(piperidin-1-ylsulfonyl)-7-(thiophen-2-yl)-1,2,3,3a,4,5-hexahydro-5,7a-epoxypyrrolo[2,3-c]pyridine 126f



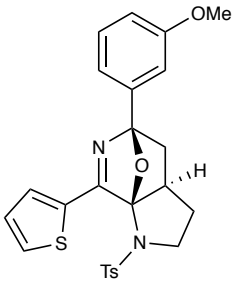
Prepared according to **GP9** from ynamide **118f** (97.5 mg, 0.30 mmol), *N*-(pivaloyloxy)amide **124a** (73.0 mg, 0.33 mmol), [Cp*CoI$_2$(CO)] (3.8 mg, 0.008 mmol), NaOAc (2.0 mg, 0.015 mmol) in TFE (3 mL) for 20 h at r.t. followed by 24 h at 101 °C in 1,4-dioxane (1.4 mL). Purification by flash column chromatography [8:2 hexane:EtOAc] to afford **126f** as an off-white solid (35.9 g, 60%); mp: 181-184 °C; IR (neat): ν = 2942, 1575, 1341, 1252, 1145, 1028, 943, 829, 731, 695, 616, 568, 547, 496 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, J = 3.8, 1.1 Hz, 1H), 7.72 – 7.65 (m, 2H), 7.50 (dd, J = 5.1, 1.1 Hz, 1H), 7.47 – 7.36 (m, 3H), 7.14 (dd, J = 5.1, 3.7 Hz, 1H), 3.92 (app. q, J = 10.1, 3.6 Hz, 2H$_d$), 3.50 – 3.29 (m, 4H), 2.45 – 2.35 (m, 1H$_b$), 2.33 – 2.25 (m, 1H$_c$), 2.26 – 2.15 (m, 1H$_a$), 2.01 (dd, J = 11.8, 3.4 Hz, 1H$_a$), 1.98 – 1.89 (m, 1H$_c$), 1.67 – 1.49 (m, 6H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.4 (C), 138.0 (C), 133.5 (C), 131.3 (CH), 130.5 (CH), 128.7 (CH), 128.5 (2CH), 128.2 (CH), 126.4 (2CH), 105.0 (C$_f$), 101.6 (C$_e$), 52.8 (C$_d$H$_2$), 47.5 (2CH$_2$), 45.6 (C$_b$H), 41.1 (C$_a$H$_2$), 29.8 (C$_c$H$_2$), 26.0 (2CH$_2$), 24.0 (CH$_2$) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{22}H_{25}N_3O_3S_2$ 444.1416; found 444.1418.

(3aR,5R,7aR)-5-(4-Bromophenyl)-7-(thiophen-2-yl)-1-tosyl-1,2,3,3a,4,5-hexahydro-5,7a-epoxypyrrolo[2,3-c]pyridine 126k



Prepared according to **GP9** from ynamide **118a** (99.4 mg, 0.30 mmol), *N*-(pivaloyloxy)amide **124c** (99.0 mg, 0.33 mmol), [Cp*CoI_2(CO)] (3.7 mg, 0.008 mmol), NaOAc (1.3 mg, 0.015 mmol) in TFE (3 mL) for 24 h at r.t. followed by 24 h at 101 °C in 1,4-dioxane (4 mL). Purification by flash column chromatography [2:8 hexane:EtOAc] to afford **126k** as an off-white solid (64.7 mg, 41%); mp: 193-196 °C; IR (neat): ν = 1583, 1341, 1256, 1158, 1039, 1003, 839, 808, 728, 673, 591, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.93 ($d_{AA'XX'}$, *J* = 8.3 Hz, 2H), 7.60 – 7.56 (m, 3H), 7.55 – 7.51 (m, 2H), 7.30 ($d_{AA'XX'}$, *J* = 7.8 Hz, 2H), 7.19 (dd, *J* = 5.0, 3.8 Hz, 1H), 3.98 (app. td, *J* = 10.9, 6.3 Hz, $1H_d$), 3.74 – 3.64 (m, $1H_d$), 2.44 (s, 3H), 2.22 – 2.10 (m, $1H_c$+H_a), 1.82 (dd, *J* = 11.8, 3.4 Hz, $1H_a$), 1.72 – 1.60 (m, $1H_c$) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.6 (C), 144.3 (C), 136.9 (C), 134.9 (C), 133.3 (C), 131.9 (CH), 131.6 (CH), 131.0 (2CH), 129.4 (2CH), 129.2 (2CH), 128.3 (CH), 128.1 (2CH), 122.8 (C), 105.0 (C_f), 101.5 (C_e), 52.9 (C_dH_2), 45.7 (C_bH), 40.8 (C_aH_2), 29.5(C_cH_2), 21.8 (CH_3) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{24}H_{21}{}^{79}BrN_2O_3S_2$ 529.0255; found 529.0265.

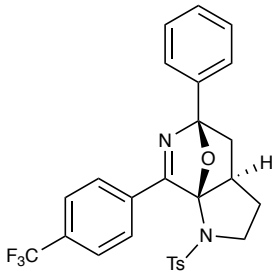
(3aR,5R,7aR)-5-(3-Methoxyphenyl)-7-(thiophen-2-yl)-1-tosyl-1,2,3,3a,4,5-hexahydro-5,7a-epoxypyrrolo[2,3-c]pyridine 126l



Prepared according to **GP9** from ynamide **118a** (99.5 mg, 0.03 mmol), *N*-(pivaloyloxy)amide **124d** (83.0 mg, 0.33 mmol), [Cp*CoI_2(CO)] (3.6 mg, 0.0075 mmol), NaOAc (1.40 mg, 0.015 mmol) in TFE (3 mL) for 18 h at r.t. followed by 24 h at 101 °C in 1,4-dioxane (4 mL). Purification by flash column chromatography [5:5 hexane/EtOAc] to afford **126l** as a brown solid (79.1 mg, 55%); mp: 193-196 °C; IR (neat): ν = 2924, 1572, 1345, 1159, 1031, 847, 786, 699, 669, 590, 521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.96 ($d_{AA'XX'}$, *J* = 8.4

Hz, 2H), 7.55 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.30 ($d_{AA'XX'}$, *J* = 7.9 Hz, 2H), 7.23 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.21 – 7.17 (m, 2H), 6.94 (dd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 3.98 (td, *J* = 10.9, 6.3 Hz, $1H_d$), 3.87 (s, 3H), 3.69 (app. t, *J* = 9.7 Hz, $1H_d$), 2.43 (s, 3H), 2.42 – 2.35 (m, $1H_b$), 2.21 – 2.11 (m, H_a+H_c), 1.85 (dd, *J* = 11.8, 3.4 Hz, $1H_a$), 1.71 – 1.58 (m, $1H_c$) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.4 (C), 159.7 (C), 144.2 (C), 139.4 (C), 135.1 (C), 131.8 (C), 130.8 (CH), 129.6 (CH), 129.4 (2CH), 129.3 (2CH), 128.3 (3CH), 118.5 (CH), 111.8 (CH), 104.9 (C_f), 101.9 (C_e), 55.5 (CH_3), 52.9 (C_dH_2), 45.7 (C_bH), 40.8 (C_aH_2), 29.5 (C_cH_2), 21.7 (CH_3) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{25}H_{24}N_2O_4S_2$ 481.1256; found 481.1253.

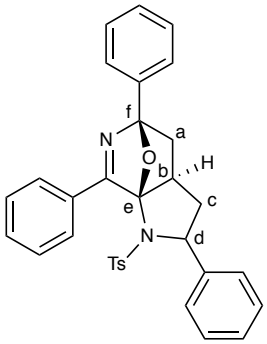
(3aR,5R,7aR)-5-Phenyl-1-tosyl-7-(4-(trifluoromethyl)phenyl)-1,2,3,3a,4,5-hexahydro-5,7a-epoxypyrrolo[2,3-c]pyridine 126r



Prepared according to **GP9** from ynamide **118l** (26.1 mg, 0.08 mmol), *N*-(pivaloyloxy)amide **124a** (19.5 mg, 0.09 mmol), [Cp*CoI_2(CO)] (1.12 mg, 0.002 mmol), NaOAc (0.33 mg, 0.004 mmol) in TFE (1 mL) for 4 h at r.t. followed by 24 h at 101 °C in 1,4-dioxane (1.5 mL). Purification by flash column chromatography [8:2 hexane/EtOAc] to afford **126r** as a white solid (53.5 mg, 44%); mp: 184-187 °C; IR (neat): ν = 2953, 1325, 1257, 1160, 1110, 1015, 930, 837, 760, 698, 670, 592, 542 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 ($d_{AA'XX'}$, *J* = 8.1 Hz, 2H), 7.90 ($d_{AA'XX'}$, *J* = 8.4 Hz, 2H), 7.73 ($d_{AA'XX'}$, *J* = 7.9 Hz, 2H), 7.69 – 7.64 (m, 2H), 7.52 – 7.40 (m, 3H), 7.30 ($d_{AA'XX'}$, *J* = 7.8 Hz, 2H), 4.04 (app. td, *J* = 10.6, 6.6 Hz, $1H_d$), 3.71 (app. t, *J* = 10.3, 9.0, 1.2 Hz, $1H_d$), 2.53 – 2.43 (m, $1H_b$), 2.44 (s, 3H), 2.33 – 2.21 (m, $1H_c$), 2.16 (dd, *J* = 11.9, 7.5 Hz, $1H_a$), 1.88 (dd, *J* = 12.0, 3.2 Hz, $1H_a$), 1.85 – 1.70 (m, $1H_c$) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.5 (C), 144.3 (C), 137.6 (C), 134.9 (C), 134.4 (C), 132.5 (C), 129.4 (2CH), 129.1 (2CH), 128.8 (C), 128.6 (3CH), 127.9 (2CH), 126.1 (C), 125.7 (2CH), 125.6 (2CH), 104.9 (C_f), 101.8 (C_e), 52.3 (C_dH_2), 45.3 (C_bH), 40.5 (C_aH_2), 29.5 (C_cH_2), 21.7

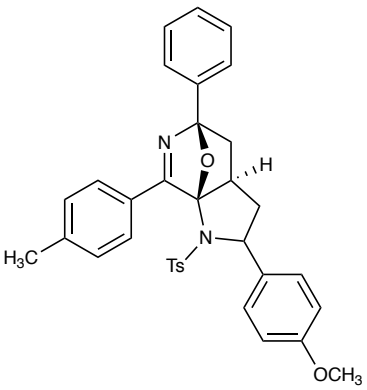
(CH_3) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{27}H_{23}{}^{19}F_3N_2O_3S$ 513.1460; found 513.1472.

(3a*R*,5*R*,7a*R*)-2,5,7-Triphenyl-1-tosyl-1,2,3,3a,4,5-hexahydro-5,7a-epoxypyrrolo[2,3-*c*]pyridine 126w



Prepared according to **GP9** from ynamide **118t** (118 mg, 0.29 mmol), *N*-(pivaloyloxy)amide **124a** (71.0 mg, 0.32 mmol), [Cp*CoI_2(CO)] (3.5 mg, 0.0074 mmol), NaOAc (1.60 mg, 0.014 mmol) in TFE (3 mL) for 72 h at r.t. to 50 °C followed by 6 h at 101 °C in 1,4-dioxane (1 mL). Purification by flash column chromatography [95:5 hexane/EtOAc] to afford **126w** as an off-white solid (15.4 mg, 10%); mp: 185-188 °C; IR (neat): ν = 2980, 1559, 1353, 1166, 1111, 1043, 919, 763, 671, 564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 6.4 Hz, 2H), 7.92 ($d_{AA'XX'}$, *J* = 8.3 Hz, 2H), 7.74 – 7.66 (m, 2H), 7.55 – 7.39 (m, 8H), 7.39 – 7.31 (m, 3H), 7.29 ($d_{AA'XX'}$, *J* = 8.1 Hz, 2H), 4.97 (dd, *J* = 8.1, 2.7 Hz, $1H_d$), 2.74 – 2.63 (m, $1H_b$), 2.45 (s, 3H), 2.24 (dd, *J* = 8.3, 2.6 Hz, $1H_a$), 2.22 – 2.13 (m, $2H_c$), 1.85 (dd, *J* = 11.9, 3.0 Hz, $1H_a$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.3 (C), 142.2 (C), 138.2 (C), 135.0 (C), 131.3 (CH), 131.0 (CH), 129.9 (2CH), 129.2 (2CH), 128.8 (2CH), 128.7 (2CH), 128.6 (2CH), 128.5 (2CH), 127.9 (2CH), 126.7 (CH), 126.2 (2CH), 106.8 (C_f), 101.4 (C_e), 68.7 (C_dH), 43.2 (C_bH), 40.8 (C_cH_2), 40.6 (C_aH), 39.2 (C_aH), 21.8 (CH_3) ppm; HRMS (ASAP): m/z: [M] Calcd for $C_{32}H_{28}N_2O_3S$ 521.1899; found 521.1893.

(3a*R*,5*R*,7a*R*)-2-(4-Methoxyphenyl)-5-phenyl-7-(*p*-tolyl)-1-tosyl-1,2,3,3a,4,5-hexahydro-5,7a-epoxypyrrolo[2,3-*c*]pyridine 126x



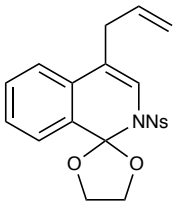
Prepared according to **GP9** from ynamide **118u** (127 mg, 0.28 mmol), *N*-(pivaloyloxy)amide **124a** (68.5 mg, 0.31 mmol), [Cp*CoI_2(CO)] (3.5 mg, 0.0074 mmol), NaOAc (1.50 mg, 0.014 mmol) in TFE (3 mL) for 72 h at r.t. followed by 6 h at 101 °C in 1,4-dioxane (1 mL). Purification by flash column chromatography [9:1 hexane/EtOAc] to afford **126x** as a yellow solid (9.3 mg, 6%); mp: 90-93 °C; IR (neat): ν = 2919, 1610, 1512, 1351, 1247, 1162, 1031, 910, 822, 727, 669 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.22 ($d_{AA'XX'}$, *J* = 8.3 Hz, 2H), 7.93 ($d_{AA'XX'}$, *J* = 8.4 Hz, 2H), 7.69 ($d_{AA'XX'}$, *J* = 6.9 Hz, 2H), 7.46 ($d_{AA'XX'}$, *J* = 5.5 Hz, 2H), 7.46 – 7.39 (m, 1H), 7.38 ($d_{AA'XX'}$, *J* = 8.7 Hz, 2H), 7.31 – 7.26 (m, 4H), 6.91 ($d_{AA'XX'}$, *J* = 8.7 Hz, 2H), 4.91 (dd, *J* = 8.6, 2.1 Hz, $1H_d$), 3.84 (s, 3H), 2.75 – 2.64 (m, H_b+H_c), 2.45 (s, 3H), 2.42 (s, 3H), 2.25 – 2.12 (m, H_a+H_c), 1.84 (dd, *J* = 11.9, 3.0 Hz, $1H_a$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 129.7 (2CH), 129.2 (4CH), 128.5 (3CH), 128.3 (4CH), 128.4 (2CH), 126.0 (2CH), 68.2 (C_dH), 55.4 (CH_3), 43.1 (C_bH), 40.6 (C_aH_2), 39.2 (C_cH_2), 21.6 (CH_3), 21.4 (CH_3) ppm; HRMS (ASAP): m/z: [M] Calcd for $C_{34}H_{32}N_2O_4S$ 565.2161; found 565.2173.

General procedure 10: preparation of dihydroisoquinolines from bromoalkynes (GP10)

Following the procedure described by Hsung,[43] the required sulfonamide (1.0 eq.), 1,10-phenanthroline (0.4 eq.), $CuSO_4.5H_2O$ (0.2 eq.), K_2CO_3 (2.0 eq.) and the 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane **173** (1.2 eq.) were combined in a Schlenk flask. Toluene (1.0 M) was added and the resulting solution was stirred at 70 °C until TLC indicated complete consumption of ynamide formed. The reaction temperature was then raised to 100 °C and stirred at the indicated time. The mixture was cooled to room temperature, diluted with EtOAc and filtered through a plug of silica gel. The filtrate was concentrated under reduced pressure and

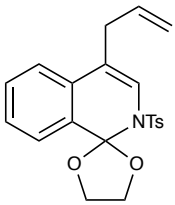
the crude residues were purified by flash column chromatography to give the corresponding dihydroisoquinolines.

4-Allyl-2-((4-nitrophenyl)sulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] 177a



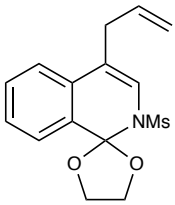
Prepared according to **GP10** from *N*-(but-3-en-1-yl)-4-nitrobenzenesulfonamide **174a** (600 mg, 2.48 mmol), 1,10-phenanthroline (181 mg, 1.0 mmol), $CuSO_4.5H_2O$ (124 mg, 0.50 mmol), K_2CO_3 (687 mg, 4.96 mmol) and 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane **173** (745 mg, 2.98 mmol) in toluene (4 mL). Purification by flash column chromatography [7:3 hexane/EtOAc] gave **177a** as a orange solid (0.58 g, 56%); mp: 88-92 °C; IR (neat): ν = 2899, 1525, 1347, 1306, 1172, 1088, 1037, 975, 911, 855, 737, 683, 606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 ($d_{AA'XX'}$, *J* = 9.1 Hz, 2H), 7.85 ($d_{AA'XX'}$, *J* = 9.1 Hz, 2H), 7.38 – 7.27 (m, 2H), 7.25 – 7.18 (m, 2H), 6.98 (s, 1H), 5.98 (ddt, *J* = 17.1, 10.2, 6.1 Hz, 1H), 5.23 – 5.10 (m, 2H), 4.66 – 4.52 (m, 2H), 4.27 – 4.12 (m, 2H), 3.32 (app. dd, *J* = 6.2, 1.5 Hz, 2H) ppm. Data matches that reported in the literature.[211]

4-Allyl-2-tosyl-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] 177b



Prepared according to **GP10** from *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **174b** (367 mg, 1.73 mmol), 1,10-phenanthroline (125 mg, 0.692 mmol), $CuSO_4.5H_2O$ (86.4 mg, 0.346 mmol), K_2CO_3 (479 mg, 3.46 mmol) and 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane **173** (510 mg, 2.0 mmol) in toluene (2 mL). Purification by flash column chromatography [8:2:1 hexane/EtOAc/NEt_3] gave **177b** as a colourless oil (0.54 g, 80%); mp: 82-84 °C; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.57 ($d_{AA'XX'}$, *J* = 8.4 Hz, 2H), 7.36 – 7.26 (m, 2H), 7.24 – 7.15 (m, 1H), 7.11 ($d_{AA'XX'}$, *J* = 7.9 Hz, 2H), 7.06 (s, 1H), 5.99 (ddt, *J* = 17.1, 10.1, 6.0 Hz, 1H), 5.20 – 5.08 (m, 2H), 4.63 – 4.51 (m, 2H), 4.23 – 4.10 (m, 2H), 3.30 (app. dd, *J* = 6.1, 1.5 Hz, 2H), 2.31 (s, 3H) ppm. Data matches that reported in the literature.[211]

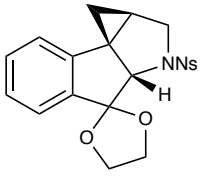
4-Allyl-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] 177c



Prepared according to **GP10** from *N*-(but-3-en-1-yl)methanesulfonamide **174c** (1.15 g, 8.50 mmol), 1,10-phenanthroline (613 mg, 3.4 mmol), $CuSO_4.5H_2O$ (424 mg, 1.70 mmol), K_2CO_3 (2.35 g, 17.0 mmol) and 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane **173** (2.59 g, 10.2 mmol) in toluene (15 mL). Purification by flash column chromatography [95:5:1 hexane/EtOAc/NEt_3] gave **177c** as a colourless oil (1.72 g, 66%); IR (neat): ν = 3305, 3080, 1650, 1588, 1446, 1324, 1205, 1156, 1037, 907, 718, 550, 522 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.55 – 7.48 (m, 1H), 7.47 – 7.40 (m, 1H), 7.39 – 7.32 (m, 2H), 6.88 (s, 1H), 5.96 (ddt, *J* = 17.1, 10.1, 6.1 Hz, 1H), 5.22 – 5.06 (m, 2H), 4.60 – 4.47 (m, 2H), 4.27 – 4.14 (m, 2H), 3.28 (app. dd, *J* = 6.2, 1.4 Hz, 2H), 3.06 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.6 (CH), 131.5 (C), 131.0 (C), 129.6 (CH), 127.3 (CH), 123.6 (CH), 123.1 (CH), 122.5 (CH), 117.1 (CH_2), 116.2 (C), 112.8 (C), 66.6 ($2CH_2$), 43.3 (CH_3), 34.0 (CH_2) ppm. Data matches that reported in the literature.[211]

Preparation of functionalised tetracycle 176a from ynamide 175a

(1aR,3aS,8bS)-3-((4-nitrophenyl)sulfonyl)-1a,2,3,3a-tetrahydro-1H-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane] 176a



The ynamide **175a** (0.937 g, 2.26 mmol, 1.0 eq.) was dissolved in toluene (23 mL, 2.26 mmol, 0.1 M) at room temperature. Dichloro(2-pyridinecarboxylato)gold (28.8 mg, 0.07 mmol, 3.3 mol%) was added and the mixture was stirred at 80 °C for 3 h. The reaction mixture was filtered through a pad of silica (1 cm) and eluting with EtOAc. The solvents were removed under reduced pressure. The crude residue was purified by flash column chromatography [8:2:1 hexane/EtOAc/NEt_3] to afford **176a** as pale yellow solid (0.54 g, 58%); ^1H NMR (300 MHz, Chloroform-*d*) δ 8.46 – 8.34 (m, 2H), 8.10 – 8.00 (m, 2H), 7.39 – 7.23 (m, 3H), 6.82 – 6.72 (m, 1H), 4.47 – 4.40 (m, 1H), 4.40 (s, 1H), 4.36 – 4.18 (m, 3H), 4.13 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.69 (d, *J* = 11.2 Hz,

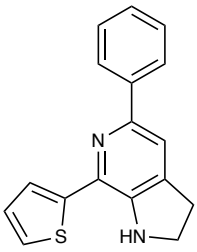
1H), 1.55 – 1.45 (m, 1H), 1.38 – 1.27 (m, 1H), -0.18 (dd, *J* = 6.3, 4.9 Hz, 1H) ppm; MS (ES-TOF): m/z 414.09 [M+Na] (100%). Data matches that reported in the literature.[211]

Post-catalytic transformations

General procedure 11: deprotection of tosyl sulfonyl group (GP11)

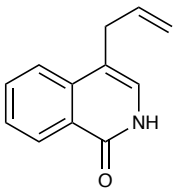
In a flame-dried Schlenk tube, the required tosyl amine (1.0 eq.) was dissolved in 1,4-dioxane (0.3 M). Trifluoromethanesulfonic acid (3.0 eq.) was added and the reaction mixture was heated at 80 °C for 2 h. After cooled down to room temperature, the mixture was quenched with $NaHCO_3$ saturated solution, then extracted with EtOAc (3x), brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography to afford the desired compound.

5-Phenyl-7-(thiophen-2-yl)-2,3-dihydro-1H-pyrrolo[2,3-c]pyridine 140



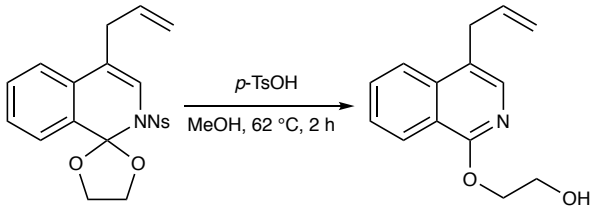
Prepared according to **GP11** using **126a** (30.2 mg, 0.07 mmol), trifluoromethanesulfonic acid (18 μL, 0.20 mmol) in 1,4-dioxane (0.25 mL). Purification by flash column chromatography [9:1 hexane/EtOAc] to afford *N*-protected pyridine **140** as a yellow solid (14.9 mg, 80%); mp: 168-171 °C; IR (neat): ν = 3369, 2887, 1561, 1456, 1271, 1253, 1075, 862, 775, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 – 8.02 (m, 2H), 7.54 – 7.48 (m, 2H), 7.49 – 7.40 (m, 2H), 7.39 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.15 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.25 (s, 1H), 3.74 (t, *J* = 8.5 Hz, 2H), 3.19 (td, *J* = 8.5, 1.1 Hz, 2H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 128.7 (3CH), 127.9 (CH), 127.8 (CH), 126.4 (2CH), 124.0 (2CH), 47.4 (CH_2), 29.9 (CH_2) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{17}H_{14}N_2S$ 279.0956; found 279.0964.

4-Allylisoquinolin-1(2H)-one 187



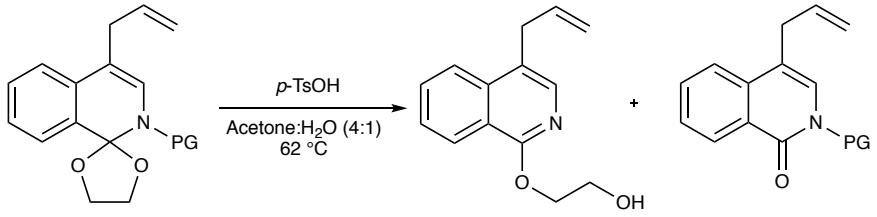
Prepared according to **GP11** using **185b** (38.6 mg, 0.114 mmol), trifluoromethanesulfonic acid (30 μL, 0.341 mmol) in 1,4-dioxane (0.40 mL). Purification by flash column chromatography [5:5 hexane/EtOAc] to afford **187** as a pale yellow solid (15.5 mg, 73%). Data matches that reported below (*c.f.* **Preparation of 4-allylisoqinolin-1(2H)-one 187**).

Deprotection of dihydroisoquinoline 177a



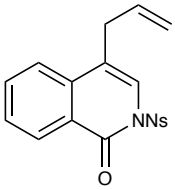
The dihydroisoquinoline **177a** (50.7 mg, 0.122 mmol, 1.0 eq.) was dissolved in methanol (1.4 mL mL, 0.1 M), *p*-TsOH (116 mg, 0.61 mmol, 5.0 eq.) was added and the mixture was heated on a pre-heated block at 62 °C for 2 h. The reaction mixture was cooled to room temperature and quenched with $NaHCO_3$ saturated solution, then extracted with CH_2Cl_2, (3x), brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography [8:2 hexane:EtOAc] to afford **186** as a colourless oil (21.9 mg, 78%); IR (neat): ν = 3352, 3076, 2941, 1622, 1570, 1507, 1403, 1324, 1094, 1075, 995, 908, 766, 722, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (ddd, *J* = 8.3, 1.4, 0.7 Hz, 1H), 7.88 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.79 (s, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.56 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 6.05 (ddt, *J* = 17.1, 10.2, 6.1 Hz, 1H), 5.21 – 5.00 (m, 2H), 4.81 – 4.63 (m, 2H), 4.42 (s, 1H), 4.04 (td, *J* = 5.1, 1.8 Hz, 2H), 3.66 (dtd, *J* = 6.1, 1.6, 0.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3 (CH), 136.6 (CH), 130.9 (CH), 126.7 (CH), 124.9 (CH), 123.5 (CH), 116.6 (CH_2), 69.9 (CH_2), 63.1 (CH_2), 34.1 (CH_2) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{14}H_{15}NO_2$ 230.1181; found 230.1187.

General procedure 12: deprotection of *o*-acetal 4-allyl-isoquinoline-1(2H) (GP12)



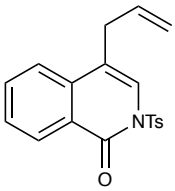
The required *o*-acetal 4-allyl-isoquinoline-1(2H) (1.0 eq.) was dissolved in solvents system acetone:H_2O (4:1, 0.1 M), *p*-TsOH (5 mol%) was added and the mixture was heated on a pre-heated block at 62 °C until consumption of starting material was observed by TLC. The reaction mixture was cooled to room temperature and quenched with $NaHCO_3$ saturated solution, then extracted with EtOAc (3x), brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography to isolate compounds.

4-Allyl-2-((4-nitrophenyl)sulfonyl)isoquinolin-1(2H)-one 185a



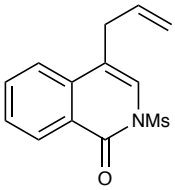
Prepared according to **GP12** using **177a** (51 mg, 0.122 mmol) and *p*-TsOH (116 mg, 0.61 mmol) in acetone:H_2O (3 mL). Purification by flash column chromatography [6:4 hexane/EtOAc] to afford **186** as a colourless oil (12 mg, 41%) and **185a** as a yellow solid (55.6 mg, 66%); mp: 152-155 °C; IR (neat): ν = 3102, 1675, 1604, 1522, 1361, 1343, 1241, 1174, 1065, 1013, 934, 848, 738, 728, 680, 609, 557, 454 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.39 ($d_{AA'XX'}$, *J* = 9.1 Hz, 2H), 8.34 ($d_{AA'XX'}$, *J* = 9.2 Hz, 2H), 8.28 (ddd, *J* = 8.1, 1.4, 0.6 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.68 – 7.61 (m, 1H), 7.49 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 6.03 (ddt, *J* = 17.1, 10.2, 6.2 Hz, 1H), 5.28 – 5.16 (m, 2H), 3.49 (app. dq, *J* = 6.2, 1.5 Hz, 2H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.5 (C), 151.1 (C), 143.1 (C), 136.7 (C), 134.7 (CH), 134.4 (C), 131.0 (2CH), 128.9 (CH), 128.2 (CH), 126.2 (C), 124.2 (2CH), 124.0 (CH), 122.3 (CH), 118.2 (CH_2), 116.9 (C), 34.0 (CH_2) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{18}H_{14}N_2O_5S$ 371.0702; found 371.0706.

4-Allyl-2-((4-methylphenyl)sulfonyl)isoquinolin-1(2H)-one 185b



Prepared according to **GP12** using *o*-acetal 4-allyl-2-tosylisoquinoline-1(2H) **177b** (47 mg, 0.122 mmol) and *p*-TsOH (116 mg, 0.61 mmol) in acetone:H_2O (3 mL). Purification by flash column chromatography [6:4 to 2:8 hexane/EtOAc] to afford **186** as a colourless oil (18 mg, 66%) and **185b** as an off-white solid (9 mg, 22%); mp: 176-181 °C; IR (neat): ν = 3106, 2919, 1677, 1627, 1487, 1353, 1242, 1162, 1087, 1021, 995, 909, 878, 770, 676, 644 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.32 (ddd, *J* = 8.1, 1.4, 0.6 Hz, 1H), 8.03 ($d_{AA'XX'}$, *J* = 8.5 Hz, 2H), 7.77 (s, 1H), 7.69 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H), 7.61 (br. app d, *J* = 7.9, 1.1 Hz, 1H), 7.45 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.35 ($d_{AA'XX'}$, *J* = 7.9 Hz, 1H), 6.02 (ddt, *J* = 16.6, 10.4, 6.2 Hz, 1H), 5.26 – 5.13 (m, 2H), 3.47 (app. dq, *J* = 6.2, 1.5 Hz, 2H), 2.43 (s, 3H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.5 (C), 145.8 (C), 136.8 (C), 135.1 (CH), 134.5 (C), 133.8 (CH), 129.6 (2CH), 128.9 (CH), 127.7 (CH), 126.6 (C), 123.7 (CH), 123.2 (CH), 117.8 (CH_2), 115.7 (CH_2), 34.1(CH_2), 21.9 (CH_3) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{19}H_{17}NO_3S$ 340.1007; found 340.1015.

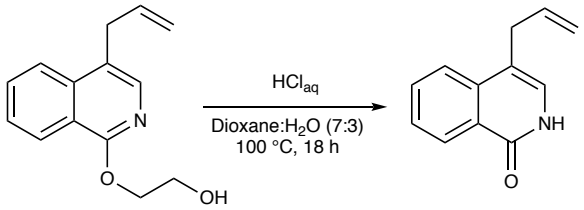
4-Allyl-2-(methylsulfonyl)isoquinolin-1(2H)-one 185c



Prepared according to **GP12** using *o*-acetal 4-allyl-2-mesylisoquinoline-1(2H) **177c** (38 mg, 0.122 mmol) and *p*-TsOH (116 mg, 0.61 mmol) in acetone:H_2O 2 mL). Purification by flash column chromatography [6:4 to 2:8 hexane/EtOAc] to afford **186** as a colourless oil (18 mg, 56%) and **185c** as an off-white solid (2.4 mg, 9%); mp: 71-75 °C; IR (neat): ν = 3013, 2919, 1662, 1488, 1345, 1245, 1163, 1068, 1025, 975, 916, 843, 756, 718, 695, 657, 568, 517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (ddd, *J* = 8.0, 1.5, 0.6 Hz, 1H), 7.76 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H), 7.66 (br. app. d, *J* = 8.1 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.54 (s, 1H), 5.99 (ddt, *J* = 16.7, 10.4, 6.2 Hz, 1H), 5.24 – 5.13 (m, 2H), 3.64 (s, 3H), 3.46 (app. dq, *J* = 6.3, 1.4 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8 (CH), 134.1 (CH), 128.9 (CH), 127.9 (CH), 123.8 (CH), 122.2 (CH), 117.9 (CH_2), 42.2 (CH_3),

34.0 (CH_2) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{13}H_{13}NO_3S$: 264.0694; found 264.0701.

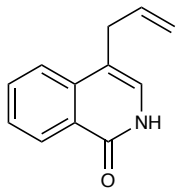
Acidic cleavage of the ether 186



2-((4-allylisoquinolin-1-yl)oxy)ethan-1-ol **186** (18.3 mg, 0.08 mmol, 1.0 eq.) was dissolved in dioxane:H_2O (0.50 mL, 7:3, 0.1 M). The HCl (0.10 mL, 2.0 M, 4.4 eq.) was added and the mixture was heated on a pre-heated block at 100 °C for 18 h. The reaction mixture was cooled to room temperature and quenched with $NaHCO_3$ saturated solution, then extracted with CH_2Cl_2 (3x), brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography [2:8 hexane/EtOAc] to afford **187** as a white solid (13.1 mg, 89%); mp: 147-150 °C; IR (neat): ν = 3159, 3002, 2851, 1637, 1606, 1498, 1477, 1356, 914, 850, 771, 684, 654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.48 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H), 7.76 – 7.66 (m, 2H), 7.53 (ddd, *J* = 8.2, 6.3, 2.0 Hz, 1H), 7.03 (s, 1H), 6.07 – 5.94 (m, 1H), 5.19 – 5.10 (m, 2H), 3.46 (app. dq, *J* = 6.2, 1.4 Hz, 2H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.0 (C), 137.8 (C), 135.8 (CH), 132.6 (CH), 127.9 (CH), 126.7 (CH), 126.2 (C), 126.0 (CH), 123.5 (CH), 117.3 (CH_2), 114.9 (C), 33.6 (CH_2) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{12}H_{11}NO$ 186.0919; found 186.0924.

Denosylation of dihydroisoquinoline 185a

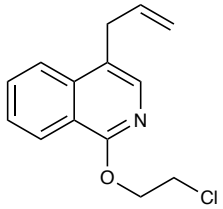
4-Allylisoquinolin-1(2H)-one 187



In a flame-dried Schlenk tube, the 4-allyl-2-nosylisoquinoline **185a** (27.7 mg, 0.075 mmol, 1.0 eq.), thioglycolic acid (25 μL, 0.224 mmol, 3.0 eq.) and Cs_2CO_3 (122 mg, 0.37 mmol, 5.0 eq.) in DMF (0.30 mL, 0.3 M) were heated at 60 °C for 3 h. The reaction mixture was cooled to room temperature and quenched with H_2O, then extracted with EtOAc (2x), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography [2:8 hexane/EtOAc] to afford **187** as colourless oil (10.2 mg, 74%). Data matches that reported above.

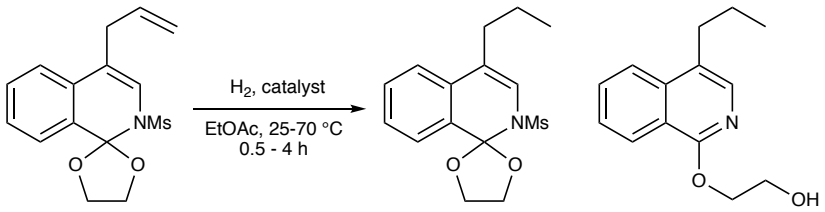
***N*-Vinylation of ether 186**

4-Allyl-1-(2-chloroethoxy)isoquinoline 204



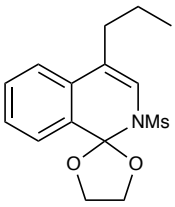
In a flame-dried Schlenk tube, the 2-((4-allylisoquinolin-1-yl)oxy)ethan-1-ol **186** (47.7 mg, 0.21 mmol, 1.0 eq.) and thionyl chloride (62 μL, 0.85 mmol, 4.1 eq.) in CH_2Cl_2 (1.1 mL, 0.2 M) were heated at 60 °C for 18 h. The reaction mixture was concentrated in reduced pressure and the crude chloride was purified by flash column chromatography [5:5 hexane/EtOAc] to afford **204** as a white solid (38.2 mg, 74%); mp: 61-63 °C; IR (neat): ν = 3064, 2884, 1651, 1625, 1485, 1440, 1375, 1286, 1192, 930, 873, 764, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (ddd, *J* = 8.1, 1.4, 0.7 Hz, 1H), 7.74 – 7.62 (m, 2H), 7.51 (ddd, *J* = 8.2, 6.7, 1.6 Hz, 1H), 6.96 (s, 1H), 6.08 – 5.94 (m, 1H), 5.20 – 5.11 (m, 2H), 4.29 (t, *J* = 5.9 Hz, 2H), 3.91 (t, *J* = 5.8 Hz, 2H), 3.45 (app. dq, *J* = 6.1, 1.4 Hz, 2H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.0 (C), 136.9 (C), 135.7 (CH), 132.4 (CH), 131.0 (CH), 128.3 (CH), 126.9 (CH), 126.1 (C), 123.3 (CH), 117.3 (CH_2), 114.1 (C), 51.7 (CH_2), 42.2 (CH_2), 33.6 (CH_2) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{14}H_{14}{}^{35}ClNO$ 248.0842; found 248.0844.

General procedure 13: hydrogenation of dihydroisoquinoline 177c (GP13)



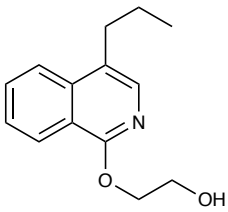
In a Schlenk tube, the *o*-acetal 4-allyl-2-mesylisoquinoline-1(2H) **177c** (1.0 eq.) was dissolved in EtOAc (0.05 M). The solution was degassed under argon for 5 min. The catalyst (10-30 mol%) was transferred in the flask and the solution was degassed a second under argon for 5 min. A balloon of H_2 was connected to the flask and the solution was degassed for 5 min. The reaction was stirred under H_2 atmosphere until consumption of starting material was observed by TLC. The reaction mixture was degassed under argon for 5 min, then filtered through a pad of celite (EtOAc) and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography to isolate the compound.

2-(Methylsulfonyl)-4-propyl-2H-spiro[isoquinoline-1,2-[1,3]dioxolane] 207



Prepared according to **GP13** using *o*-acetal 4-allyl-2-mesylisoquinoline-1(2H) **177c** (31.3 mg, 0.10 mmol) and PtO_2 (2.5 mg, 0.010 mmol) in EtOAc (2 mL) for 0.5 h to afford **207** as a colourless oil (31.0 mg, 95%); IR (neat): ν = 3017, 2965, 2936, 2861, 1640, 1452, 1338, 1260, 1137, 1032, 947, 776, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (ddd, *J* = 7.6, 1.5, 0.8 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.39 – 7.33 (m, 2H), 6.83 (s, 1H), 4.60 – 4.46 (m, 2H), 4.25 – 4.13 (m, 2H), 3.03 (s, 3H), 2.49 (ddd, *J* = 8.6, 6.5, 1.0 Hz, 2H), 1.69 – 1.53 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 131.6, 131.1, 129.6 (CH), 127.2 (CH), 123.7 (CH), 122.3 (CH), 122.0 (CH), 118.4, 66.5 ($2CH_2$), 43.1 (CH_3), 31.9 (CH_2), 21.8 (CH_2), 14.0 (CH_3) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{15}H_{19}NO_4S$ 310.1113; found 310.1115.

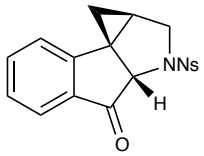
2-((4-Propylisoquinolin-1-yl)oxy)ethan-1-ol 208



Prepared according to **GP11** using *o*-acetal 4-allyl-2-mesylisoquinoline-1(2H) **177c** (30 mg, 0.099 mmol) and Pd/C (9.2 mg, 0.030 mmol) in EtOAc (2 mL) at 70 °C for 4 h. Purification by flash column chromatography [7:3 hexane/EtOAc] to afford **208** as a colourless oil (10.1 mg, 43%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (ddd, *J* = 8.4, 1.4, 0.7 Hz, 1H), 7.89 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.76 (s, 1H), 7.76 – 7.65 (m, 1H), 7.55 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.70 – 4.66 (m, 2H), 4.58 (s, 1H), 4.06 – 4.02 (m, 2H), 2.90 – 2.83 (m, 2H), 1.87 – 1.61 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.0 (C), 137.6 (C), 137.2 (CH), 130.7 (CH), 126.4 (CH), 126.1 (C), 124.9 (CH), 123.2 (CH), 119.7 (C), 69.9 (CH_2), 63.1 (CH_2), 31.9 (CH_2), 23.7 (CH_2), 14.2 (CH_3) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{14}H_{17}NO_2$ 232.1338; found 232.1336.

Deprotection of ketone on tetracycle 176a

(1aR,3aS,8bS)-3-((4-nitrophenyl)sulfonyl)-1a,2,3,3a-tetrahydrocyclopropa[c]indeno[2,1-b]pyrrol-4(1H)-one 244

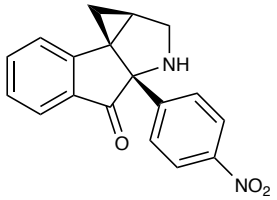


The acetal **176a** (295 mg, 0.72 mmol, 1.0 eq.) was dissolved in a mixture of acetone/H_2O (6 mL, 4:1). The *p*-TsOH (142 mg, 0.72 mmol, 1.0 eq.) was added and the reaction was refluxed at 60 °C for 48 h. The reaction mixture was concentrated *in vacuo* to remove solvents, then diluted in H_2O and neutralised by the addition of K_2CO_3. The crude residue was extracted EtOAc (5x 30 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography [7:3 hexane/EtOAc] to afford **244** as a pale yellow solid (162 mg, 61%); IR (neat): ν = 3105, 2943, 1727, 1608, 1526, 1475, 1336, 1311, 1237, 1160, 1089, 987, 909, 856, 762, 735, 682, 623, 592, 556, 461 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 ($d_{AA'XX'}$, *J* = 8.9 Hz, 2H), 8.28 ($d_{AA'XX'}$, *J* = 9.1 Hz, 2H), 7.66 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.61 (td, *J* = 7.6, 1.2 Hz, 1H), 7.37 (td, *J* = 7.5, 1.0 Hz, 1H), 7.09 (dt, *J* = 7.8, 0.9 Hz, 1H), 4.83 (s, 1H), 3.96 (d,

J = 10.0 Hz, 1H), 3.66 (dd, *J* = 10.4, 4.7 Hz, 1H), 1.91 (ddd, *J* = 8.4, 6.5, 0.7 Hz, 1H), 1.63 – 1.54 (m, 1H), 1.35 – 1.27 (m, 1H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 201.2 (C), 150.4 (C), 146.4 (C), 136.3 (CH), 135.0 (C), 129.2 (2CH), 128.3 (CH), 124.6 (2CH), 124.2 (CH), 120.7 (CH), 70.8 (CH), 52.8 (CH_2), 35.9 (C), 29.8 (C), 27.1 (CH), 14.2 (CH_2) ppm; HRMS (ASAP): m/z: [M+H] Calcd for $C_{18}H_{14}N_2O_5S$ 371.0702; found 371.0706.

Denosylation of tetracycle 244

(1aR,3aS,8bS)-3a-(4-nitrophenyl)-1a,2,3,3a-tetrahydrocyclopropa[c]indeno[2,1-b]pyrrol-4(1H)-one 247



The tetracycle **244** (34.3 mg, 0.09 mmol, 1.0 eq.) was dissolved in DMF (0.35 mL, 0.3 M). The thioglycolic acid (16 μL, 0.23 mmol, 2.5 eq.) and Cs_2CO_3 (152 mg, 0.46 mmol, 5.0 eq.) was added and the reaction was cooled to 0 °C and stirred for 26 h. The crude residue was extracted with EtOAc (3x) and H_2O to remove excess of base, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography [5:5:1 hexane:EtOAc:NEt_3] to afford **247** as a brown solid (14.2 mg, 85%); IR (neat): ν = 3314, 2920, 2851, 1696, 1602, 1513, 1467, 1348, 1251, 1016, 994, 911, 874, 852, 752, 696, 536, 461 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 ($d_{AA'XX'}$, *J* = 8.8 Hz, 2H), 7.69 – 7.64 (m, 2H), 7.62 ($d_{AA'XX'}$, *J* = 8.9 Hz, 2H), 7.37 (td, *J* = 7.5, 1.0 Hz, 1H), 7.28 – 7.21 (m, 1H), 3.58 (dd, *J* = 11.1, 4.9 Hz, 1H), 3.26 (d, *J* = 11.2 Hz, 1H), 2.01 (dd, *J* = 8.5, 6.1 Hz, 1H), 1.73 – 1.62 (m, 1H), 1.25 (s, 1H), 1.19 (t, *J* = 5.9 Hz, 1H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 205.7 (C), 152.5 (C), 147.4 (C), 146.5 (C), 136.4 (CH), 134.9 (C), 128.2 (2CH), 127.8 (CH), 125.2 (CH), 123.8 (2CH), 120.3 (CH), 81.50 (C), 50.8 (CH_2), 41.5 (C), 31.9 (CH), 29.8 (CH), 15.0 (CH_2) ppm; MS (ESI-TOF): m/z: [M+H] Calcd for $C_{18}H_{14}N_2O_3$ 307.1083;found 307.1090.

X-Ray data of tetracycle 247

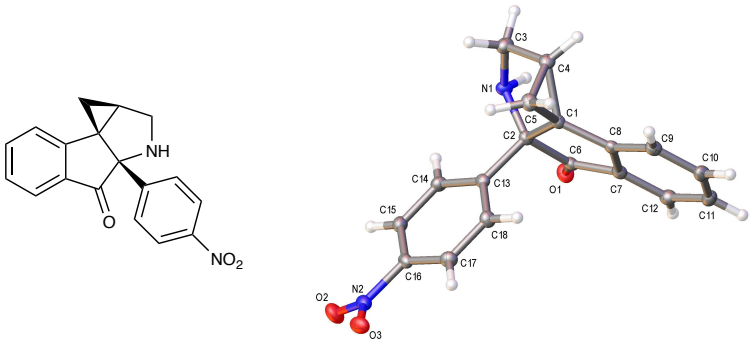


Table 1 Crystal data and structure refinement for LH91-1.

Identification code	LH91-1
Empirical formula	$C_{18}H_{14}N_2O_3$
Formula weight	306.31
Temperature/K	100.01(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	13.6775(4)
b/Å	7.2332(2)
c/Å	14.7297(4)
α/°	90
β/°	105.323(3)
γ/°	90
Volume/Å^3	1405.44(7)
Z	4
ρ_{calc}g/cm^3	1.448
μ/mm^{-1}	0.821
F(000)	640.0
Crystal size/mm^3	0.139 × 0.112 × 0.076
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	12.462 to 148.848
Index ranges	-17 ≤ h ≤ 12, -8 ≤ k ≤ 5, -18 ≤ l ≤ 17
Reflections collected	5293
Independent reflections	2761 [R_{int} = 0.0183, R_{sigma} = 0.0247]
Data/restraints/parameters	2761/0/212
Goodness-of-fit on F^2	1.082
Final R indexes [I>=2σ (I)]	R_1 = 0.0349, wR_2 = 0.0889
Final R indexes [all data]	R_1 = 0.0395, wR_2 = 0.0926
Largest diff. peak/hole / e Å^{-3}	0.32/-0.22

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for LH91-1. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)	
C1		2306.8(9)	6411.5(17)	1715.5(8)	14.1(2)
C2		1994.9(9)	5970.5(17)	2617.5(8)	13.8(2)
C3		2060.0(10)	9244.9(18)	2519.0(9)	19.3(3)
C4		2283.4(9)	8504.8(18)	1621.0(9)	16.6(3)

C5	3264.0(9)	7460.5(18)	1741.1(9)	17.9(3)
C6	1099.9(9)	4611.1(17)	2263.6(8)	14.4(2)
C7	1088.4(9)	4031.3(17)	1302.2(8)	15.2(2)
C8	1788.3(9)	5083.9(17)	984.3(8)	14.5(2)
C9	1886.5(9)	4829.2(18)	73.7(9)	17.6(3)
C10	1268.6(10)	3522.4(18)	-490.9(9)	19.9(3)
C11	565.7(10)	2475.4(18)	-172.0(9)	20.1(3)
C12	464.2(9)	2728.2(18)	731.7(9)	18.2(3)
C13	2799.4(8)	4966.0(17)	3373.3(8)	13.8(2)
C14	2780.5(9)	5119.9(17)	4312.0(8)	16.2(3)
C15	3465.0(9)	4148.8(18)	5012.1(9)	17.5(3)
C16	4174.6(9)	3045.2(17)	4757.7(9)	15.9(3)
C17	4213.3(9)	2843.5(18)	3831.1(9)	17.8(3)
C18	3512.8(9)	3808.3(18)	3138.2(8)	17.1(3)
N1	1653.7(8)	7698.8(15)	2967.2(7)	15.8(2)
N2	4917.8(8)	2052.6(15)	5500.5(8)	19.0(2)
O1	507.9(6)	4181.7(14)	2716.3(6)	19.4(2)
O2	4720.6(8)	1822.8(15)	6261.9(7)	27.9(2)
O3	5701.6(7)	1508.4(14)	5330.3(7)	23.0(2)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for LH91-1. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	13.5(5)	15.7(6)	13.7(5)	2.3(4)	4.7(4)	0.7(4)
C2	13.1(5)	15.3(6)	13.4(5)	0.9(4)	4.3(4)	0.8(4)
C3	23.2(6)	16.3(6)	19.6(6)	-0.1(5)	7.8(5)	-1.6(5)
C4	18.5(6)	15.0(6)	16.8(6)	2.2(4)	5.7(5)	-2.1(5)
C5	15.1(6)	21.5(6)	18.1(6)	1.9(5)	6.1(5)	-2.8(5)
C6	12.5(5)	14.7(6)	15.4(5)	3.4(4)	2.6(4)	1.8(4)
C7	14.3(5)	15.5(6)	15.7(6)	1.8(5)	3.7(4)	3.1(4)
C8	13.1(5)	14.6(6)	15.5(5)	2.0(5)	3.2(4)	3.5(4)
C9	19.0(6)	18.1(6)	16.9(6)	1.9(5)	6.8(5)	3.2(5)
C10	25.2(6)	19.5(6)	15.1(6)	-1.0(5)	5.5(5)	5.3(5)
C11	21.1(6)	17.1(6)	19.8(6)	-3.5(5)	1.3(5)	0.9(5)
C12	16.4(6)	16.3(6)	21.4(6)	1.5(5)	4.3(5)	-0.4(5)
C13	11.8(5)	13.5(6)	15.8(5)	0.8(4)	3.2(4)	-2.1(4)
C14	17.0(5)	15.4(6)	17.2(6)	-0.9(5)	6.4(5)	0.7(5)
C15	20.6(6)	16.9(6)	14.5(5)	-0.4(5)	3.9(5)	-1.6(5)
C16	13.3(6)	15.3(6)	17.2(6)	2.4(5)	0.7(5)	-1.9(4)
C17	14.5(6)	18.1(6)	21.7(6)	0.5(5)	6.2(5)	1.4(5)
C18	16.7(6)	20.2(6)	15.2(6)	0.6(5)	5.8(5)	0.2(5)
N1	16.2(5)	14.9(5)	17.4(5)	1.0(4)	6.5(4)	2.5(4)
N2	17.9(5)	16.4(5)	19.9(5)	1.5(4)	0.2(4)	-1.1(4)
O1	16.2(4)	25.7(5)	17.6(4)	2.7(4)	6.5(3)	-3.1(4)
O2	31.5(5)	32.2(6)	18.1(5)	6.0(4)	3.1(4)	5.8(4)
O3	14.0(4)	21.5(5)	30.8(5)	3.2(4)	1.2(4)	1.1(3)

Table 4 Bond Lengths for LH91-1.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.5325(15)	C8	C9	1.3951(16)
C1	C4	1.5201(17)	C9	C10	1.3885(19)
C1	C5	1.5049(16)	C10	C11	1.3989(19)
C1	C8	1.4769(17)	C11	C12	1.3865(18)
C2	C6	1.5491(16)	C13	C14	1.3942(16)
C2	C13	1.5267(16)	C13	C18	1.3970(17)
C2	N1	1.4740(16)	C14	C15	1.3867(18)
C3	C4	1.5307(17)	C15	C16	1.3826(18)
C3	N1	1.4796(16)	C16	C17	1.3875(18)
C4	C5	1.5084(17)	C16	N2	1.4690(16)
C6	C7	1.4730(16)	C17	C18	1.3891(18)
C6	O1	1.2176(15)	N2	O2	1.2321(15)
C7	C8	1.3972(17)	N2	O3	1.2285(15)
C7	C12	1.3944(18)			

Table 5 Bond Angles for LH91-1.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C4	C1	C2	106.42(10)	C12	C7	C8	122.08(11)
C5	C1	C2	121.52(10)	C7	C8	C1	110.46(10)
C5	C1	C4	59.82(8)	C9	C8	C1	129.59(11)
C8	C1	C2	107.87(10)	C9	C8	C7	119.92(11)
C8	C1	C4	125.91(10)	C10	C9	C8	117.89(12)
C8	C1	C5	126.37(10)	C9	C10	C11	122.08(12)
C1	C2	C6	102.51(9)	C12	C11	C10	120.20(12)
C13	C2	C1	114.78(9)	C11	C12	C7	117.84(12)
C13	C2	C6	107.25(9)	C14	C13	C2	119.11(10)
N1	C2	C1	108.23(10)	C14	C13	C18	119.40(11)
N1	C2	C6	111.15(9)	C18	C13	C2	121.37(10)
N1	C2	C13	112.49(10)	C15	C14	C13	120.75(11)
N1	C3	C4	107.79(10)	C16	C15	C14	118.37(11)
C1	C4	C3	105.87(10)	C15	C16	C17	122.63(11)
C5	C4	C1	59.59(8)	C15	C16	N2	118.52(11)
C5	C4	C3	116.62(11)	C17	C16	N2	118.85(11)
C1	C5	C4	60.59(8)	C16	C17	C18	118.14(12)
C7	C6	C2	108.12(10)	C17	C18	C13	120.68(11)
O1	C6	C2	123.95(11)	C2	N1	C3	107.11(9)
O1	C6	C7	127.90(12)	O2	N2	C16	117.97(11)
C8	C7	C6	109.44(11)	O3	N2	C16	118.29(11)
C12	C7	C6	128.40(11)	O3	N2	O2	123.73(11)

Table 6 Hydrogen Bonds for LH91-1.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1	O1[1]	0.911(18)	2.208(19)	3.0548(14)	154.3(16)

[1]-X,1/2+Y,1/2-Z

Table 7 Torsion Angles for LH91-1.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C2	C6	C7	12.20(12)	C8	C1	C2	C6	-11.95(12)
C1	C2	C6	O1	-165.71(12)	C8	C1	C2	C13	103.95(11)
C1	C2	C13	C14	155.47(11)	C8	C1	C2	N1	-129.49(10)
C1	C2	C13	C18	-28.54(16)	C8	C1	C4	C3	132.87(12)
C1	C2	N1	C3	-18.76(12)	C8	C1	C4	C5	-115.20(13)
C1	C8	C9	C10	-177.13(12)	C8	C1	C5	C4	114.47(14)
C2	C1	C4	C3	5.41(12)	C8	C7	C12	C11	0.94(18)
C2	C1	C4	C5	117.33(10)	C8	C9	C10	C11	-0.12(19)
C2	C1	C5	C4	-91.54(12)	C9	C10	C11	C12	0.3(2)
C2	C1	C8	C7	7.80(13)	C10	C11	C12	C7	-0.68(18)
C2	C1	C8	C9	-174.51(12)	C12	C7	C8	C1	177.15(11)
C2	C6	C7	C8	-8.21(13)	C12	C7	C8	C9	-0.79(18)
C2	C6	C7	C12	175.20(12)	C13	C2	C6	C7	-109.03(10)
C2	C13	C14	C15	176.52(11)	C13	C2	C6	O1	73.06(15)
C2	C13	C18	C17	-177.29(11)	C13	C2	N1	C3	109.12(11)
C3	C4	C5	C1	93.47(12)	C13	C14	C15	C16	0.87(19)
C4	C1	C2	C6	125.56(10)	C14	C13	C18	C17	-1.32(19)
C4	C1	C2	C13	-118.54(11)	C14	C15	C16	C17	-1.41(19)
C4	C1	C2	N1	8.02(12)	C14	C15	C16	N2	178.42(11)
C4	C1	C8	C7	-119.07(12)	C15	C16	C17	C18	0.57(19)
C4	C1	C8	C9	58.61(18)	C15	C16	N2	O2	19.63(17)
C4	C3	N1	C2	22.25(13)	C15	C16	N2	O3	-159.97(12)
C5	C1	C2	C6	-170.17(11)	C16	C17	C18	C13	0.81(19)
C5	C1	C2	C13	-54.27(16)	C17	C16	N2	O2	-160.54(12)
C5	C1	C2	N1	72.29(14)	C17	C16	N2	O3	19.87(17)
C5	C1	C4	C3	-111.92(11)	C18	C13	C14	C15	0.46(18)
C5	C1	C8	C7	164.67(11)	N1	C2	C6	C7	127.63(10)
C5	C1	C8	C9	-17.6(2)	N1	C2	C6	O1	-50.28(15)
C6	C2	C13	C14	-91.38(13)	N1	C2	C13	C14	31.14(15)
C6	C2	C13	C18	84.61(13)	N1	C2	C13	C18	-152.88(11)
C6	C2	N1	C3	-130.60(10)	N1	C3	C4	C1	-16.99(13)
C6	C7	C8	C1	0.30(14)	N1	C3	C4	C5	-80.49(13)
C6	C7	C8	C9	-177.64(10)	N2	C16	C17	C18	-179.26(11)
C6	C7	C12	C11	177.15(12)	O1	C6	C7	C8	169.60(12)
C7	C8	C9	C10	0.36(17)	O1	C6	C7	C12	-7.0(2)

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for LH91-1.

Atom	*x*	*y*	*z*	U(eq)
H3A	2675.67	9720.67	2944.1	23
H3B	1568.2	10239.75	2366.89	23
H4	1955.52	9073.65	1012.88	20
H5A	3537.85	7362.23	1199.03	21
H5B	3768.16	7561.69	2341.55	21
H9	2351.11	5512.91	-148.15	21
H10	1323.68	3337.37	-1100.19	24
H11	165.31	1607.15	-567.41	24
H12	-4.95	2050.58	950.33	22
H14	2303.51	5882.46	4470.48	19
H15	3447.21	4237.57	5637.39	21

H17	4694.7	2083.64	3678.12	21
H18	3518.78	3682.3	2511.4	20
H1	964(14)	7760(20)	2794(12)	25(4)

Experimental

Single crystals of $C_{18}H_{14}N_2O_3$ [LH91-1] were []. A suitable crystal was selected and [] on a SuperNova, Dual, Cu at home/near, Atlas diffractometer. The crystal was kept at 100.01(10) K during data collection. Using Olex2 [1], the structure was solved with the ShelXT [2] structure solution program using Intrinsic Phasing and refined with the ShelXL [3] refinement package using Least Squares minimisation.

Crystal structure determination of [LH91-1]

Crystal Data for $C_{18}H_{14}N_2O_3$ (M =306.31 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 13.6775(4) Å, b = 7.2332(2) Å, c = 14.7297(4) Å, β = 105.323(3)°, V = 1405.44(7) Å^3, Z = 4, T = 100.01(10) K, μ(CuKα) = 0.821 mm^{-1}, $Dcalc$ = 1.448 g/cm^3, 5293 reflections measured (12.462° ≤ 2Θ ≤ 148.848°), 2761 unique (R_{int} = 0.0183, R_{sigma} = 0.0247) which were used in all calculations. The final R_1 was 0.0349 (I > 2σ(I)) and wR_2 was 0.0926 (all data).

Refinement model description

Number of restraints – 0, number of contraints – Unknown.

Details:

1. Fixed Uiso
   At 1.2 times of:
   All C(H) groups, All C(H,H) groups
2.a Ternary CH refined with riding coordinates:
   C4(H4)
2.b Secondary CH2 refined with riding coordinates:
   C3(H3A,H3B), C5(H5A,H5B)
2.c Aromatic/amide H refined with riding coordinates:
   C9(H9), C10(H10), C11(H11), C12(H12), C14(H14), C15(H15), C17(H17), C18(H18)

Chapter 6: References

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