UNIVERSITY OF BIRMINGHAM

Transition Metal Catalysed Cycloisomerisation of Ene-Ynamides

by

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A thesis submitted to the University of Birmingham

for the degree of DOCTOR OF PHILOSOPHY

School of Chemistry

College of Engineering and Physical Sciences

University of Birmingham

January 2018

Abstract

This thesis highlights the use of transition metal catalysts in the synthesis of highly functionalised nitrogen heterocycles using ene-ynamides as starting materials.

Relying on the initial discovery of copper-catalysed cascade reaction, a one pot carbon nitrogen bond formation and rearrangement cascade sequence has been developed to synthesise functionalised oxyisoquinolines with the use of an environmentally benign, inexpensive copper catalyst. The reaction proceeds through ynamide formation, followed by an initial aza-Claisen rearrangement, subsequent [1,5]-hydride transfer and 6π electrocyclisation. Exploration of the substrate scope and its limitations have allowed increased access to novel functionalised fused pyridine derivatives.

Finally, generation of five membered nitrogen based heterocycles with dienamide moieties through gold catalysed cycloisomerisation of 1,6-ene-ynamides is described. Polycyclisation of ynamides was also achieved through gold catalysis to afford tetracyclic products.

Acknowledgements

Special thanks goes to my supervisor Dr. Paul Davies for giving me this great opportunity to study in his research group. It has been the joy of my life. I thank you for all the support you have given me all these years and to make me understand chemistry better.

I am very grateful to Tertiary Education Trust Fund (TETFund), Nigeria for the sponsorship into the programme.

Worthy of mention is the staff of the analytical facilities for their support in this research

I would equally like to thank my family, and friends including past and present members of Davies group.

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List of Abbreviations

Ac	acetyl
Alk	alkyl
Ar	aromatic
Bu	butyl
C	Celsius
Cy	cyclohexyl
DMEDA	*N*,*N*-dimethylethylenediamine
DMF	*N,N*-dimethylformamide
d.r.	diastereomeric ratio
1,2-DCE	1,2-dichloroethane
EI	electron impact
ES	electrospray
Et	ethyl
EWG	electron withdrawing group
EDG	electron donationg group
ERC	electrocyclic ring closure
equiv.	equivalent
FT-IR	Fourier transform infrared

g	gram(s)
h	hour(s)
H	hydride transfer
H	Hertz
HRMS	high resolution mass spectrometry
IR	infrared
J	coupling constant
L	litre
m	metre(s)
[M]	metal complex
M	molar
M	methyl
Mol	moles
M	melting point
Ms	methanesulfonyl
MS	mass spectrometry
m/z	mass/charge
NBS	*N*-bromosuccinimde
Nu	nucleophile

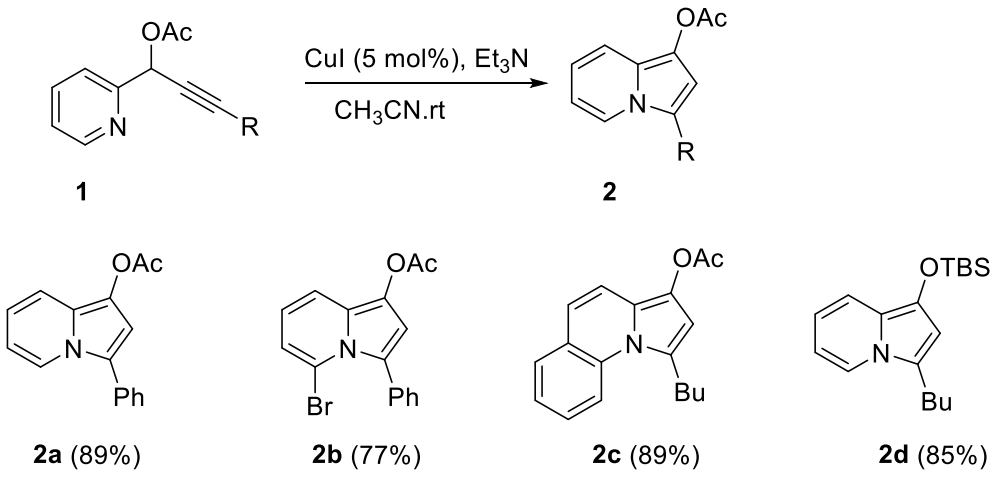
NMR	nuclear magnetic resonance
P	para
Ph	phenyl
Rt	room temperature
s	singlet
TBS	tertiary-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	trifluoromethanesulfonyl
t	triplet
quant.	quantitative

Chapter 1 Copper catalysis in organic synthesis

1. Introduction

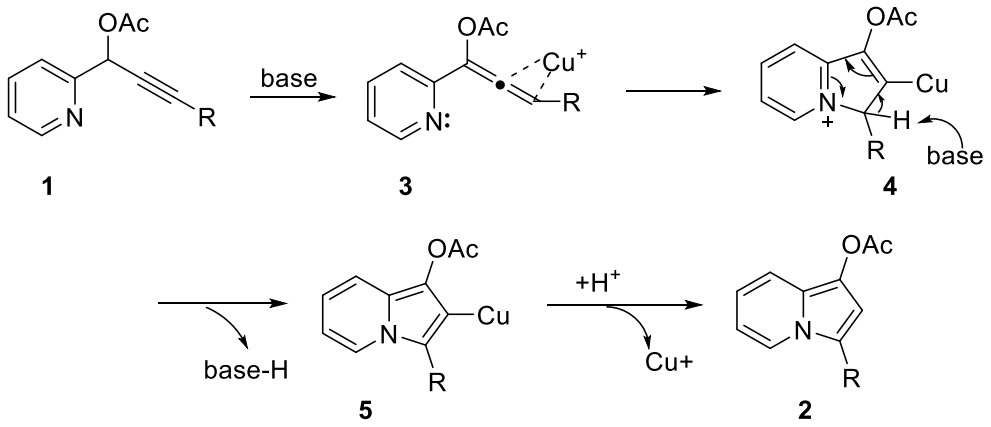
Transition metal catalysis has been a driving force among the organic synthetic community leading to highly functionalised and novel transformations that could not be achieved by other synthetic routes.[1-3] Among the transition metal series, the use of copper as a catalyst in achieving these transformations has been attracting wide attention over the last decade. Research activities in this area have led to the emergence of molecules ranging from the very simple ones to functionalised, complex and biologically relevant products.[4, 5] The potential on the use of copper as catalysts in achieving transformations lies on the factors of cost, availability and toxicity.[6]

Copper-catalysed cyclisation reactions have led to a wide range of molecules with different biological activities and alkynes have emerged as important building blocks in such synthesis.[7] The carbon-carbon triple bond of alkynes makes them versatile and act as a synthons for different array of synthetic routes. In 2007, Yan and its co-workers reported the copper-catalysed cyclisation of propargylic acetate (Scheme 1).[8]



Scheme 1: Cu-catalysed cycloisomerisation of propargylic acetate

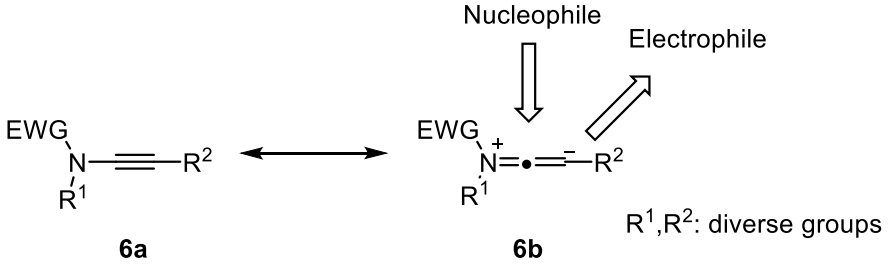
In the presence of copper(I)iodide, propargylic acetates bearing pyridine ring undergo cyclisation to yield functionalised indolizines. According to the proposed mechanism (Scheme 2), activation and coordination of the triple bond by the copper catalyst produces an allene **3** followed by nucleophilic attack of the lone pair of pyridyl nitrogen to yield **4**. Subsequent deprotonation and demetalation affords the desired product **2** in high yields.



Scheme 2: Proposed mechanism for the formation of indolizine

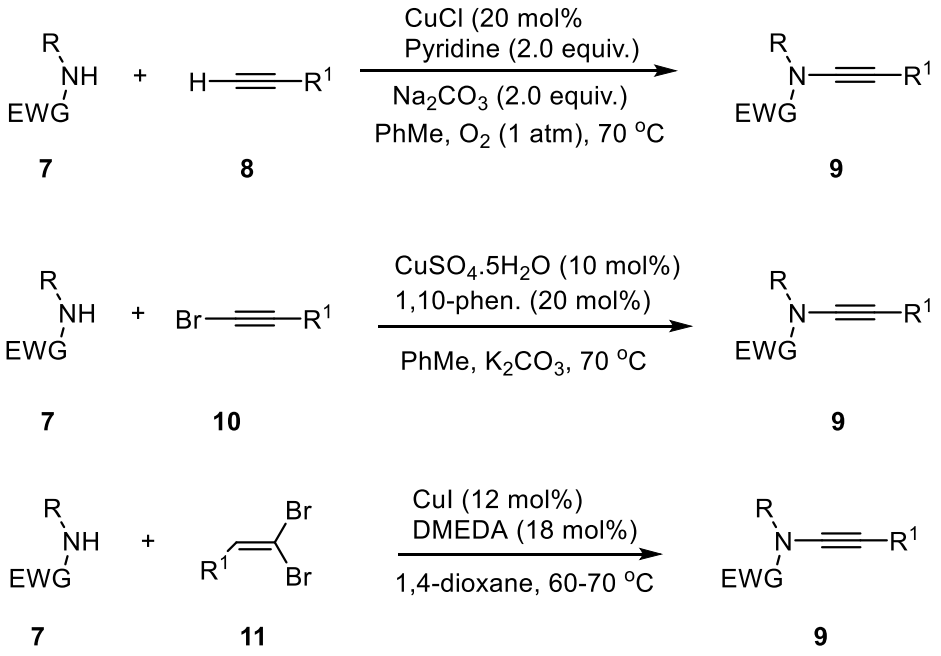
2. Synthesis of ynamides

Ynamides are electron-rich π systems possessing an electron-withdrawing group on a nitrogen atom. The electronic bias created by the nitrogen atom is responsible for the highly regioselective transformations within the molecule (Scheme 3). They are used as versatile motifs in increasing number of novel transformations.[9-11]



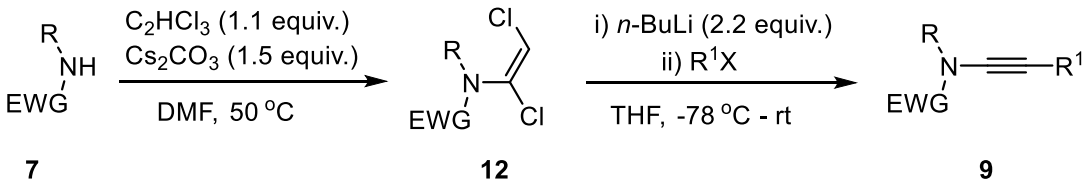
Scheme 3: Reactivity of ynamides

Ynamides are synthesised mainly through copper-mediated cross-coupling reactions though they vary in scope and reaction conditions. Each of the methods has its own limitations but this section tends to highlight the methods used in this work and those that are mainly used in the group. Through copper catalysed amidation reactions, ynamides with diverse functionalities can be assembled (Scheme 4).[12-15]



Scheme 4: Copper catalysed ynamide formation

One of the major limitations of the above methods is the failure to access ynamides with C-terminus functionalities such as hydrogen and esters. Recently, the research group of Anderson provided a solution by the use of trichloroethylene to access 1,2-dichloroenamides **12**. Subsequent treatment of dichloroenamides with butylithium and trapping with an electrophile forms ynamides with functionalities like esters at the C-terminus (Scheme 5)

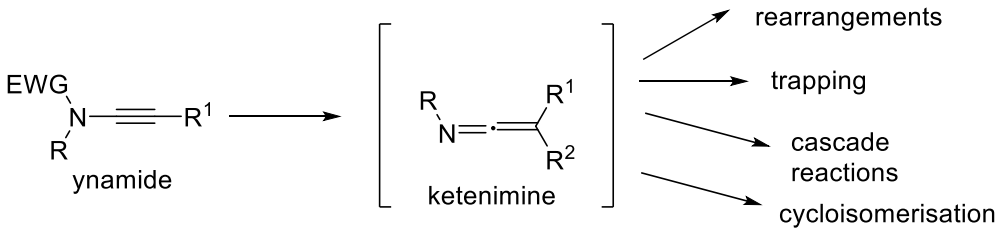


Scheme 5: Ynamide formation via 1,2-dichloroenamides

3. Synthesis and reactions of ketenimines from ynamides.

3.1 Thermal methods

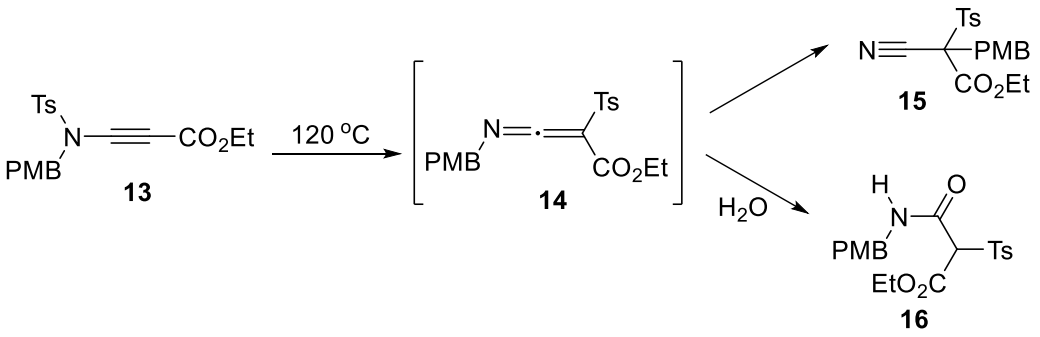
Ynamides can serve as starting materials for the synthesis of highly reactive ketenimines which can subsequently undergo numerous transformations (Scheme 6).[16]



Scheme 6: ketenimine synthesis from ynamides

Ketenimines belong to the sub-class of unsaturated nitrogen-containing compounds which can be employed as building blocks to introduce an N, C, C triatomic moiety.[16] They are characterized by the presence of an sp-hybridized carbon or a carbon backbone with a strong polarization.

The research group of Wudl reported the first synthesis of ketenimine from ynamide via a thermal process (Scheme 7).[17]

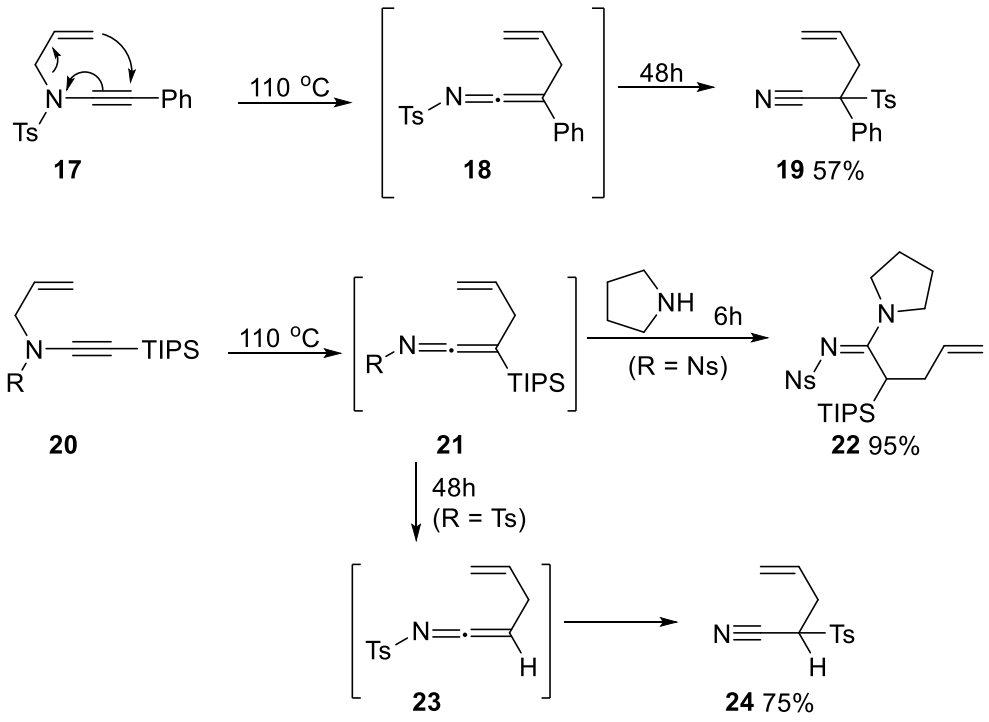


Scheme 7: Use of sulfonylynamides to generate ketenimines via thermal methods

At 120 °C, ester ynamide **13** was converted to ketenimine **14** which subsequently led to the formation of a tertiary nitrile **15** as a result of nitrogen to carbon migration. Further hydrolysis of **13** afforded amide **16**.

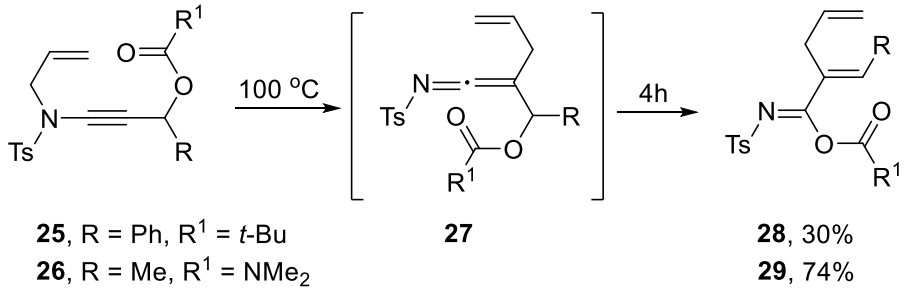
Similarly, Hsung and his research group explored the use of *N*-allylsulfonylynamide as starting materials for the generation of ketenimines (Scheme 8).[18] Ketenimine **18** was generated from ynamide **17** through an aza-Claisen rearrangement. Upon further heating of **18**, 1,3-sulfonyl shift gave the tertiary nitrile **19** in relatively good yield.

When the *N*-allylsulfonylynamide was substituted by a triisopropylsily (TIPS) group **20**, the corresponding ketenimine **21** was isolated which can further be trapped with pyrrolidine through nucleophilic addition to give amidine **22** in excellent yield. Extended heating caused desilylation to produce **23** which rearranged further to generate the secondary nitrile **24**.



Scheme 8: Ketenimine generation through aza-Claisen rearrangement

In a similar fashion, Hsung and his group further explored the synthesis of amidine by simple modification of ynamides (scheme 9).[19]

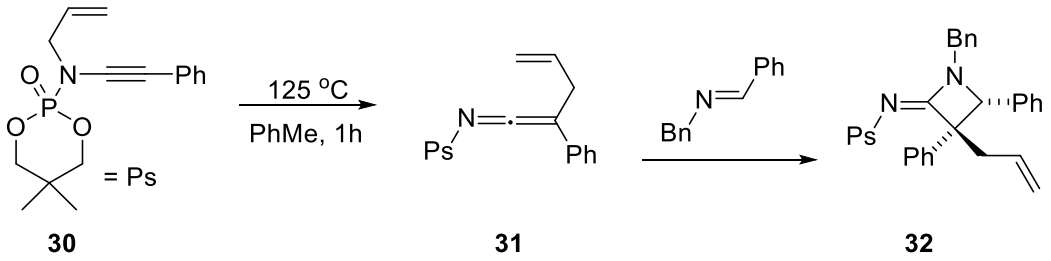


Schemem 9: Imidates synthesis via aza-Claisen/[3,3] sigmatropic rearrangement

With the use of carboxy-substituted ynamides **25** and **26**, imidates **28** and **29** were obtained through a tandem aza-Claisen and [3,3]-sigmatropic rearrangements.

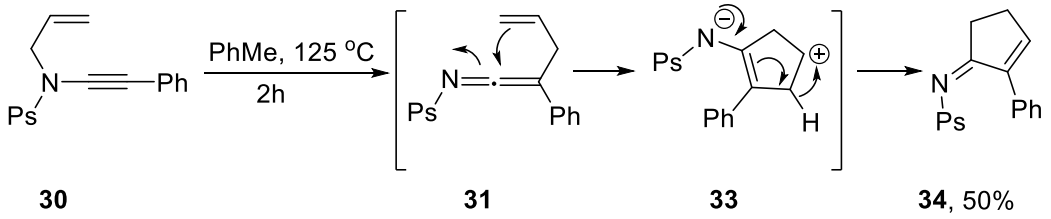
In order to prevent the 1,3-sulfonyl shift, Hsung and his members employed the use of *N*-phosphorylynamide in the generation of ketenimines (scheme 10).[20] Ketenimine **31** was

generated from ynamide **30** bearing a cyclic phosphoramidate moiety which further reacted with an imine in a [2+2] cycloaddition manner to yield azetidimine **32**.



Scheme 10: Azetidinimine synthesis using *N*-phosphorylynamide

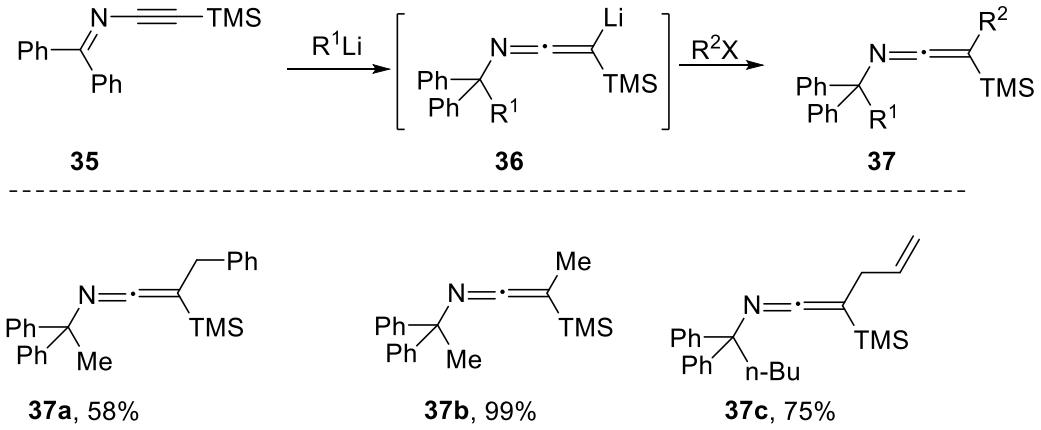
In the absence of an imine, *N*-phosphorylynamide **30** underwent a carbocyclization process to yield a zwitterions **33** which afforded a cyclopentenimine **34** in moderate yield through a Wagner-Meerwein 1,2-H shift (scheme 11).[21]



Scheme 11: Cyclopentenimine generation via carbocyclization/1,2-H shift

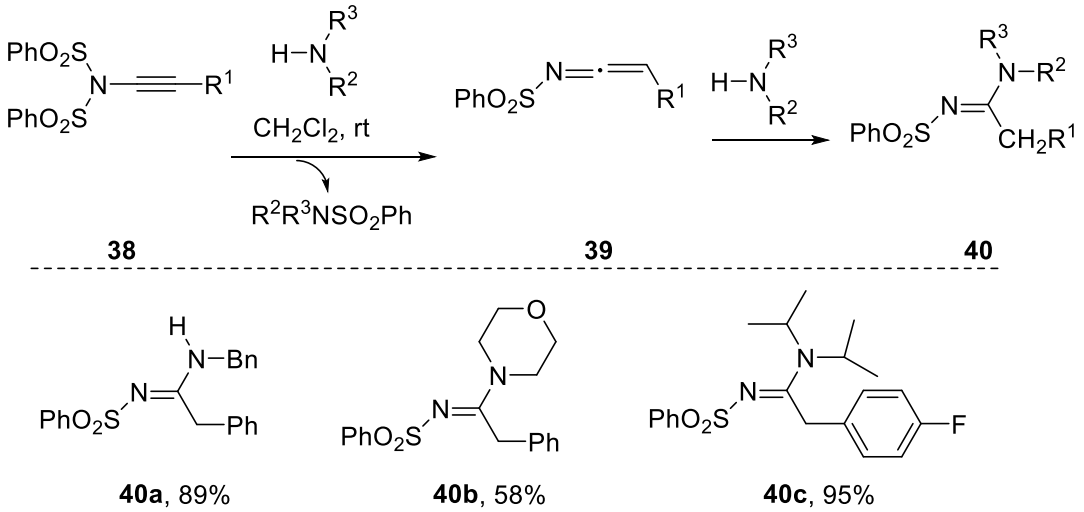
3.2 Base-mediated methodologies.

Evano and his group explored the syntheses of ketenimines using ynimines as starting materials (scheme 12).[22] Ynimines represent class of ynamides in which imino substituents are responsible for their stabilization. Treatment of silyl-substitued ynimine **35** with an organolithium reagent generated ketenimine lithium anion **26**. Trapping of **36** with an alkyl halide afforded ketenimines **37** from good to excellent yields. It was noticed that the silyl groups provided enough stabilization that led to the isolation of the ketenimines.



Scheme 12: Isolation of sily-ketenimines

The research group of Cao generated ketenimines by simple removal of the electron-withdrawing group on the ynamide using anionic conditions (scheme 13).[23]

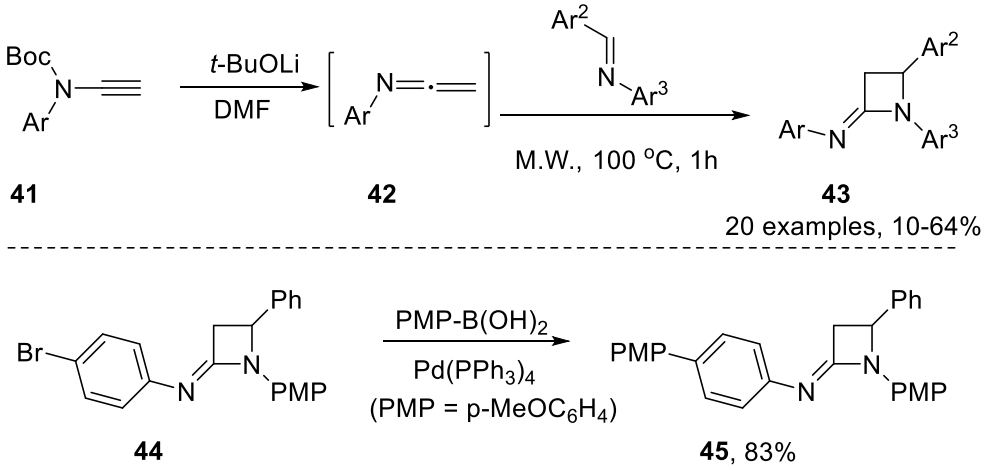


Scheme 13: Desulfonylation followed by nucleophilic reaction

Deprotection of bis-phenylsulfonyl ynamide **38** using amine gave **39**. Nucleophilic reaction of **39** with a second equivalent of amine yielded amidines **40**. Steric hindrance on the amine component posed some challenges on the overall reaction progress.

Dodd and Cariou got access to azetidinimines through ketenimines using [2+2] cycloaddition reaction (scheme 14).[24] Treatment of *N*-tert-butylcarbamate ynamide **41** with lithium tert-butoxide gave ketenimine **42**. Reaction of **42** with an imine under microwave heating

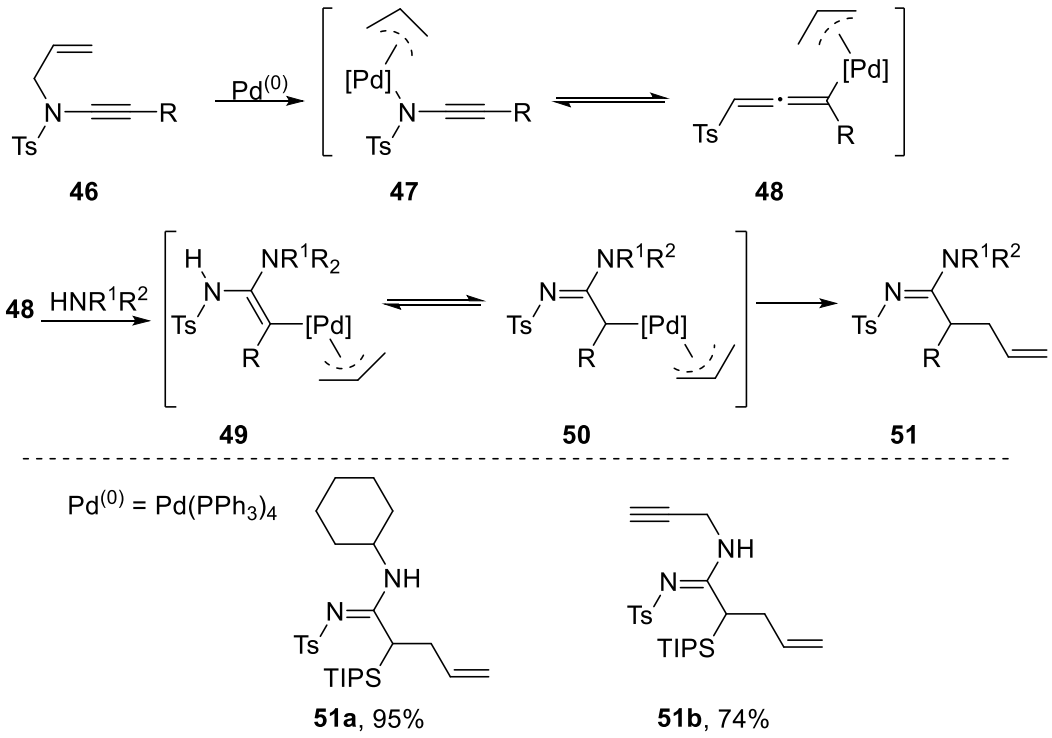
produced azetidinimines **43**. Biaryl azetidinimines **45** were obtained by further functionalization of **44** using known cross-coupling reactions.



Scheme 14: Azetidinimines synthesis

3.3 Transition metal-catalysed method

Apart from the investigation of thermal aza-Claisen rearrangement of *N*-ally ynamides, the research group of Hsung extended their studies with the use of transition metals (scheme 15).[25] Activation of *N*-allyl ynamide **46** with $Pd(PPh_3)_4$ gave ynamide-π-allyl complex **47** through oxidative addition. Complex **47** is in equilibrium with ketenimine complex **48**. Trapping of ketenimine complex **48** with a primary/secondary amine gave complex **49**. Tautomerization of **49** gave a π-allyl complex **50** and reductive elimination of **50** afforded amidines **51** in good to excellent yields.



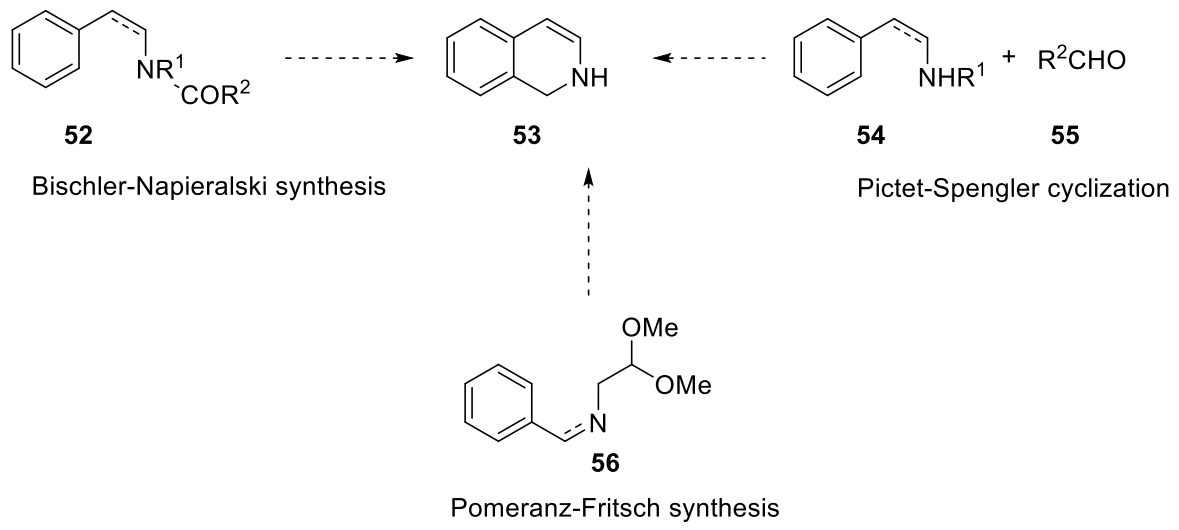
Scheme 15: Ketenimine and amidine synthesis using Pd catalysis

Chapter 2 Transition metal catalysed synthesis of isoquinoline derivatives

1 Introduction

The synthesis of nitrogen heterocycles is vital for both organic synthesis and medicinal chemistry. Isoquinolines and their reduced derivatives are present in numerous naturally occurring alkaloids,[26-30] commonly found in natural products. Such alkaloids have showed antitumor,[31] antimicrobial[32] and other biological activities.[33-35] Heterocyles containing isoquinoline motifs can also be utilised in pharmaceutical[27, 36] and material sciences.[37] In addition, they are widely employed as chiral ligands for transition metal catalysts[38-41] and some of their iridium complexes find application in organic light emitting diodes.[42-45]

The traditional or classic methods for the construction of these heterocyclic scaffolds include Pictet-Spengler cyclization,[46-48] Bischler-Napieralski synthesis[49, 50]and Pomeranz-Fritsch synthesis [51, 52] (Scheme 16).



Scheme 16: Access to isoquinoline skeleton

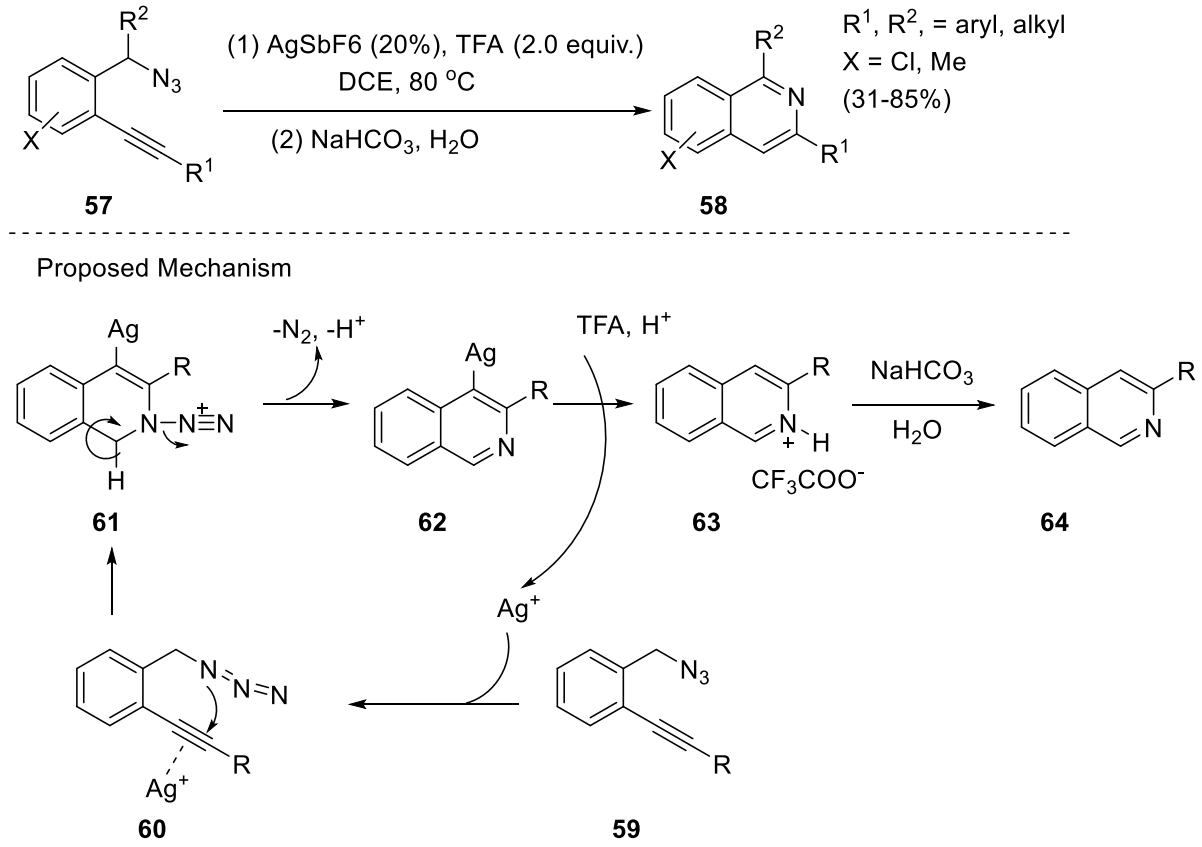
These classic methods used to access these heterocycles have some fundamental problems that make them less attractive. They usually require strong acids[53-55] or tedious reaction procedures, making it difficult to access substrates with different functional and protecting groups. To overcome these limitations, a general, flexible and convergent approach to these

isoquinoline derivatives is highly needed. Over the last two decades, protocols involving metals which serve as an alternative to the traditional methods, have been developed. New activation modes have been proposed leading to enhanced efficiency, atom economy and mild reaction conditions. The metal catalysed methodologies will be discussed in the subsequent sections.

2. Metal-catalysed formation of isoquinoline and its derivatives

2.1 Silver-catalysed synthesis of isoquinolines

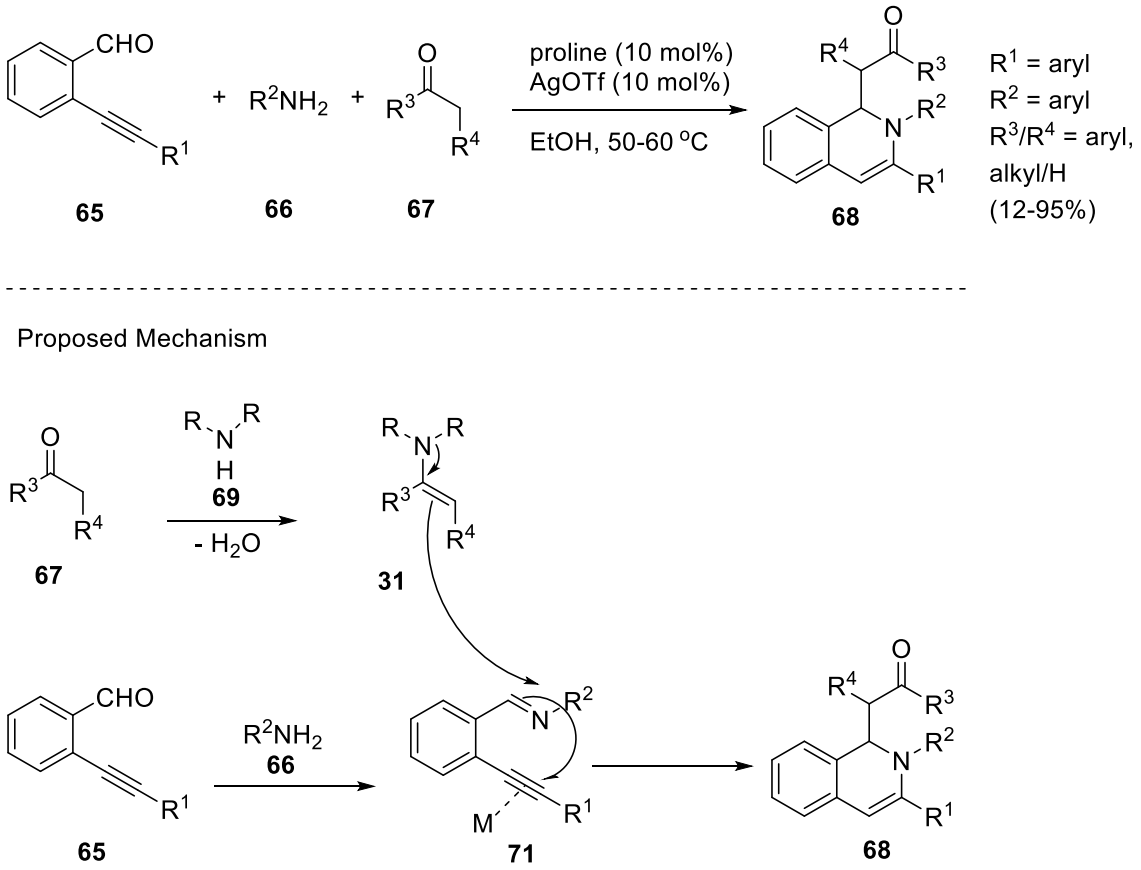
In 2009, Liang and co-workers reported the cyclization of 2-alkynyl benzyl azides **57** to access isoquinoline derivatives via silver catalysis (Scheme 17).[56]



Scheme 17: Silver catalysed cyclisation of azides

They proposed that the coordination of Ag catalyst to the alkyne **60** generates **61**. Regioselective nucleophilic attack of the nitrogen atom onto the electron deficient triple bonds gave **61** via 6-*endo*-*dig* cyclization, followed by the loss of nitrogen and proton to form **62**. Treatment of **62** with TFA gave the isoquinoline salt **64**. The reaction of the isoquinoline salt with sodium bicarbonate gave the corresponding functionalised isoquinoline **64**. They equally observed that an increase in temperature to about 90 °C produces the Huisgen 1,3-dipolar cycloaddition product and lower yields of isoquinoline.

The research group of Wu developed a methodology for the synthesis of dihydroisoquinolines using a dual activation mode of catalysts (Scheme 18).[57] They combined silver triflate and proline in the multicomponent reaction of 2-alkynylbenzaldehydes **65**, amines **66** and ketones **67** to yield dihydroisoquinolines, all in one pot.

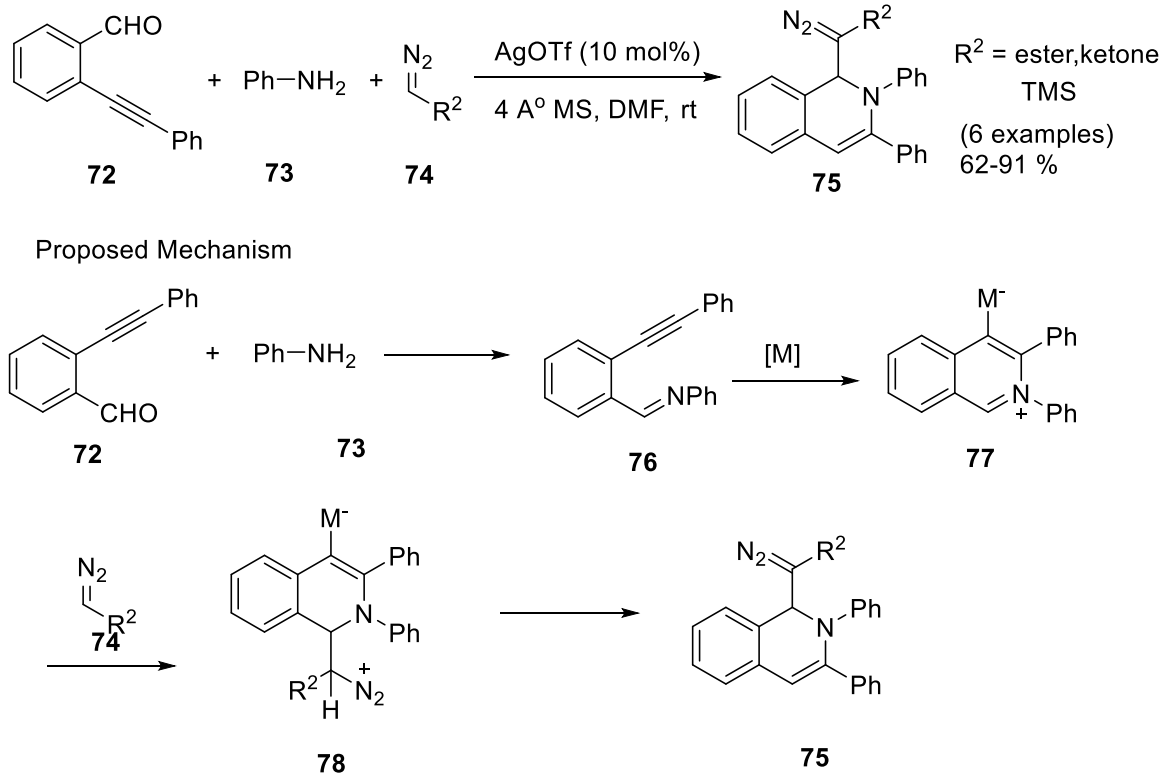


Scheme 18 Lewis acid and organocatalyst-cocatalysed reaction

The condensation of ketone **67** with proline **69** produces enamine **70** which attacks the π activated system of **71** through its imine in a cascade fashion. Anilines **66** with both electron-donating and electron withdrawing groups were well tolerated. Their findings highlighted an important and efficient strategy of lewis acid and organocatalyst combination in synthetic organic chemistry.

Similarly, Zhou and co-workers developed a three component, silver catalysed synthesis of diazo-containing dihydroisoquinolines through a cascade imine-yne cyclization of 2-alkynylbenzaldehydes **72**, amines **73** and diazo compounds **74** (Scheme 19)[58] The proposed mechanism invokes the formation of imine **76** by the condensation of the aldehyde **72** and amine **73**, followed by an intramolecular imine-yne cyclisation to produce intermediate **77**.

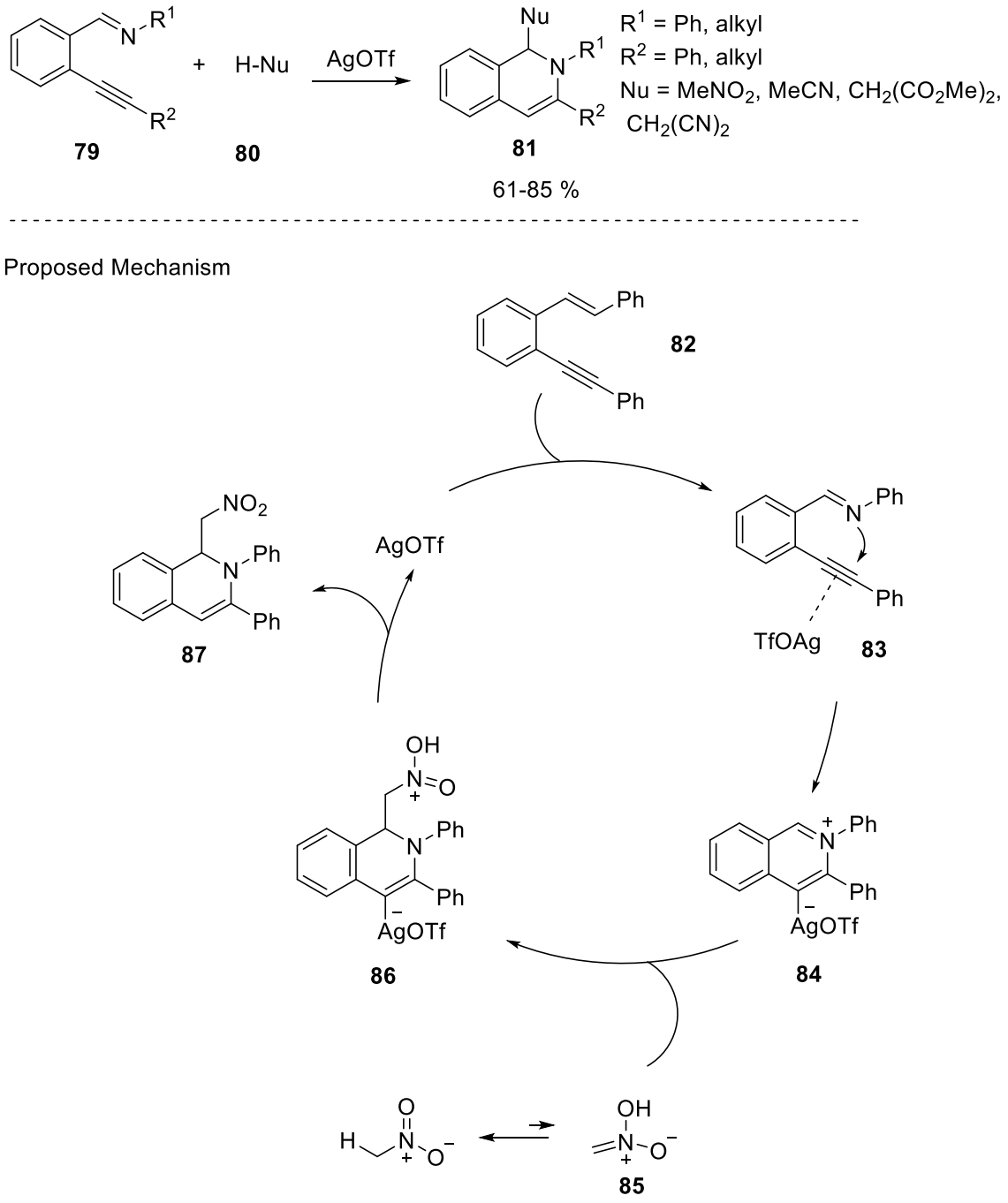
Subsequent nucleophilic attack of the diazo compound via an intermolecular version forms **78**. Loss of proton and protonation produces the desired compound **75**.



Scheme 19: Silver catalysed multicomponent reaction

The substrate scope was not broad. Substitution at the aromatic region was very limited and the amine used was limited to aniline.

Yamamoto and co-workers reported the synthesis of 1,2-dihydroisoquinolines by direct addition of pronucleophiles **80** to imines **79** using silver triflate as a catalyst (Scheme 20).[59] The reaction is proposed to proceed via the coordination of silver to the triple bond which triggers the attack of the nitrogen onto the triple bond to give the isoquinolinium species **84**. Subsequent addition of the carbon pronucleophile **85** gives the desired product **87** via **86**.

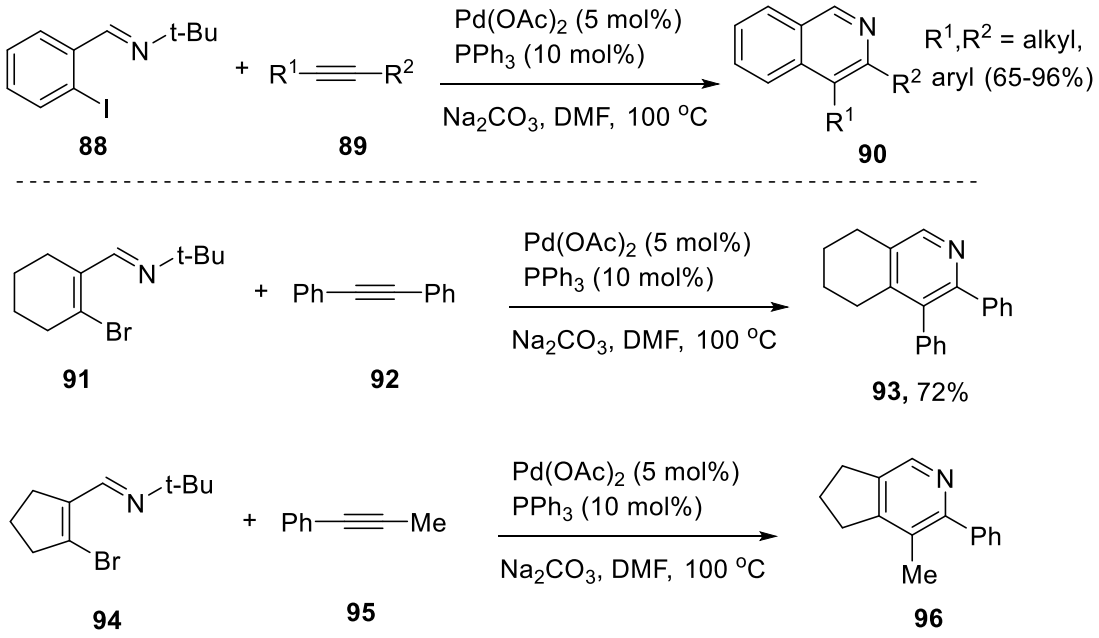


Scheme 20: Silver-catalysed addition of pronucleophiles to generate 1,2-dihydroisoquinolines

The formation of the reactive isoquinolinium species was assumed to be the key step since the amines were not activated by any electron-withdrawing group. The substrate scope was limited and terminal alkynes were also used as carbon pronucleophiles.

2.2 Palladium-catalysed synthesis of isoquinoline

The use of palladium catalysis towards the synthesis of isoquinoline derivatives has been greatly explored by Larock and his co-workers.[60-62] In 1988, they carried out the palladium catalysed synthesis of isoquinolines via annulation process (Scheme 21)[63] In this protocol, *tert*-butylimine of *o*-iodobenzaldehyde **88** was combined with internal alkynes **89**, in the presence of palladium(II)acetate to give 3,4-disubstitued isoquinolines **90** in good to excellent yields.

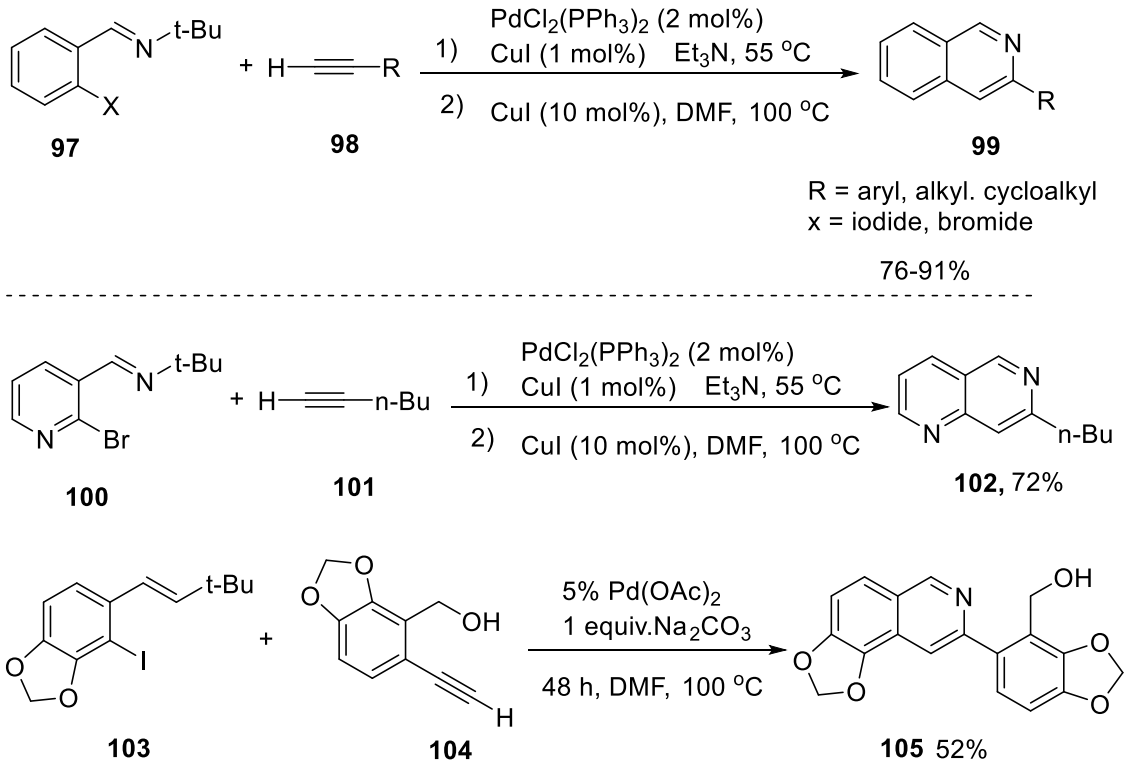


Scheme 21: Palladium catalysed iminoannulation of alkynes

The methodology was extended to vinylic imines **91** and **94** which gave the desired products as tetrahydroisoquinoline and pyridine derivatives **93** and **96** respectively. The annulation chemistry failed when alkyl-substituted alkynes for example 4-octyne and 3-hexyne were incorporated. This was attributed to numerous alkyne insertion products which were not isolated. The proposed mechanism[60] was in tandem to the various work they have done on

annulation chemistry. Reduction of palladium (II) to palladium (0) leads to oxidative insertion to give an organopalladium intermediate. Coordination to the alkyne moiety followed by insertion leads to vinylic palladium species. Such species reacts with the imine to generate a seven membered ring palladacyclic salt. Reductive elimination leads to demetalation and generation of tert-butylisoquinolinium salt. Subsequent fragmentation delivers the annulated product.

Furthermore, Larock and co-workers reported the synthesis of isoquinolines via cyclisation of terminal alkynes **98** using palladium and copper catalysis (Scheme 22)[64]



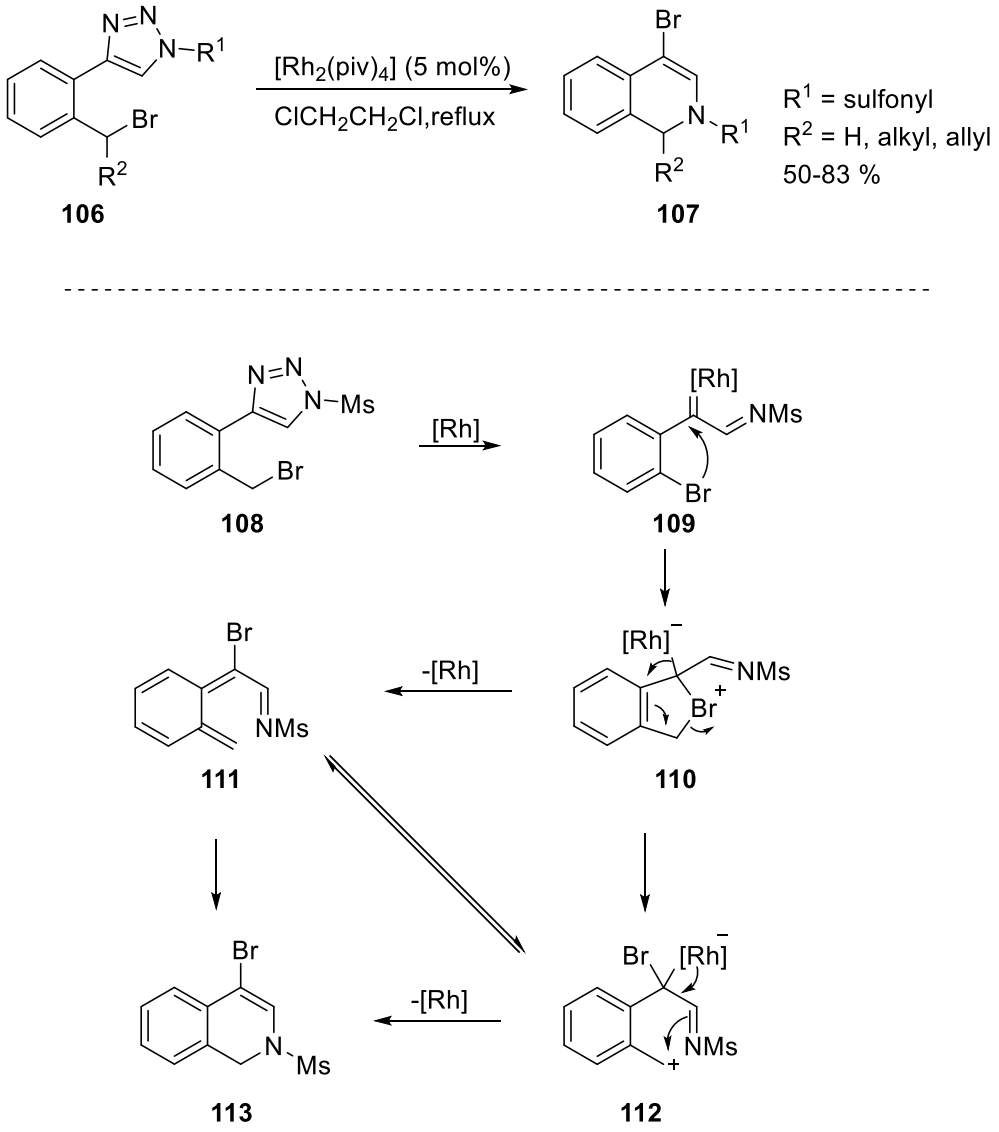
Scheme 22: Synthesis of isoquinolines via Pd and Cu catalysis

3-Substitued isoquinolines **99** were accesed via the coupling/cyclisation of *tert*-butylimine of *o*-iodobenzaldehyde **97** with terminal alkyne **98** .The coupling was effected by the palladium catalyst while the subsequent cyclisation of the iminoalkyne was brought about by copper.

Good to excellent yields of the desired products were obtained. The substrate scope was extended to pyridine derivative **100** which generated a product with two heterocyclic rings fused together **102**. The synthetic utility of the coupling/cyclisation cascade was demonstrated in the synthesis of the naturally occurring alkaloids, decumbens B **105** in relatively good yield.

2.3 Rhodium-catalysed synthesis of isoquinolines

Limited work has been done on the synthesis of isoquinolines using rhodium as a catalyst. Recently, Li and his group reported the synthesis of functionalised 4-Bromo-1,2-dihydroisoquinolines **107** under rhodium catalysis (Scheme 23).[65]



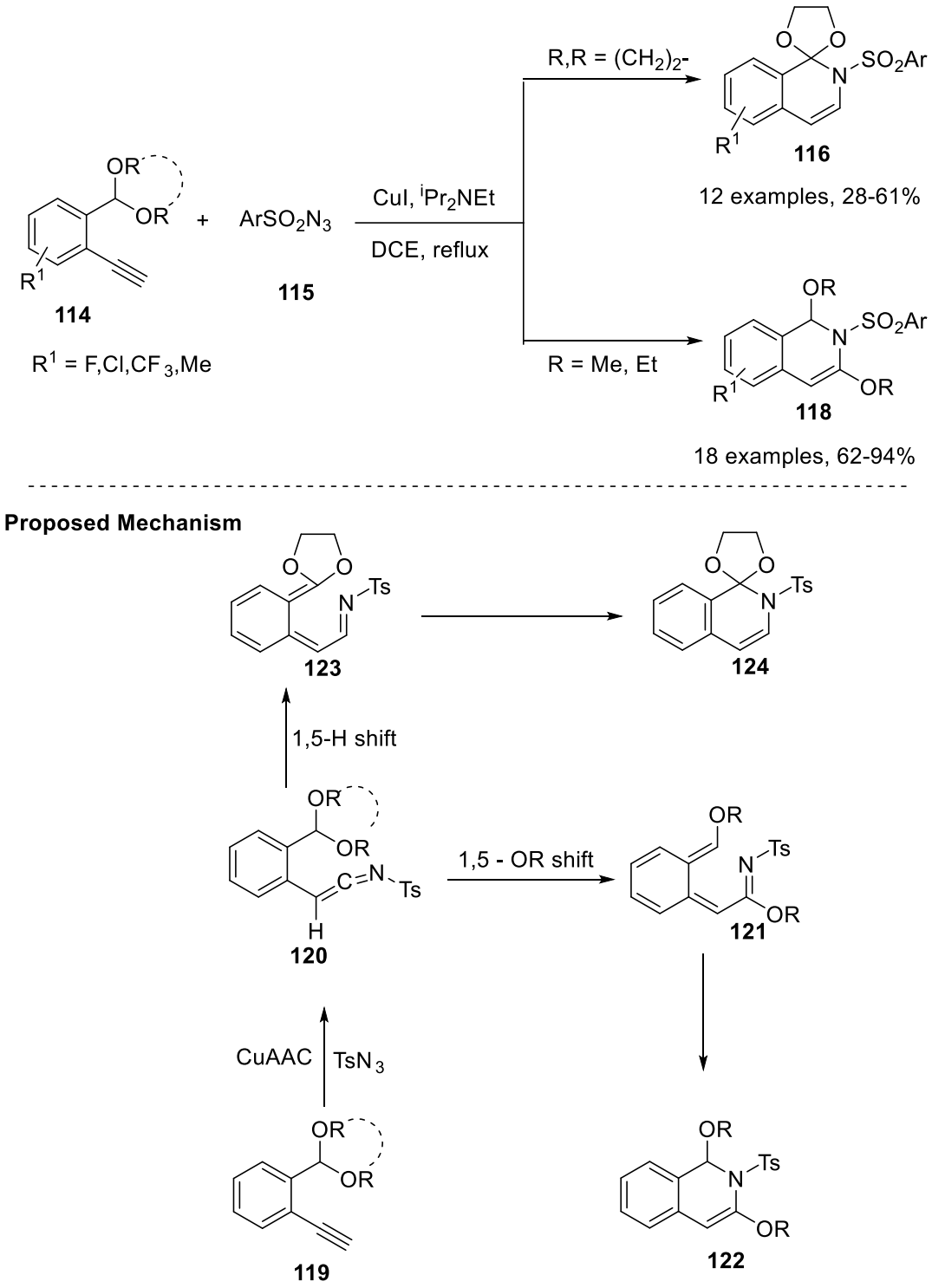
Scheme 23: Rhodium-catalysed formation of dihydroisoquinolines

The formation of α-imino rhodium carbene **109** from the sulfonyl triazole **108** triggers the nucleophilic attack intramolecularly to give the bromonium ylide **110**. Formation of the ylide is the key step. Demetalation gives **111** which is in equilibrium with **112**. Subsequent 6π electrocyclisation furnishes the desired product **113**. The substrate scope was quite broad as isoquinolines with different electronic demands involving electron donating and electron withdrawing groups were accommodated. Further functionalisation were achieved through the vinyl bromide moiety present in the products. Classical transition metals catalysed

coupling reactions like Heck, Sonogashira and Suzuki reactions were performed and their corresponding products were obtained in good to excellent yields.

2.4 Copper-catalysed formation of isoquinolines

Wang and co-workers reported that 1,2-dihydroisoquinolines can be synthesised from *o*-ethysnyl benzacetals **114** and sulfonyl azides **115** using copper iodide as a catalyst (Scheme 24).[66]

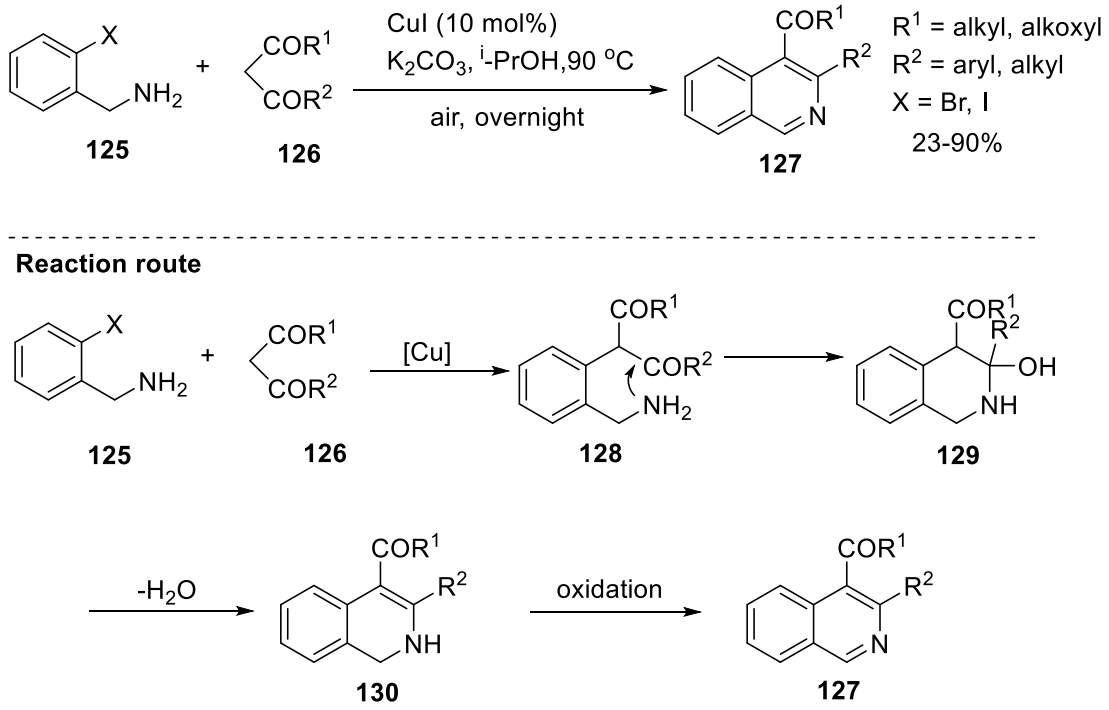


Scheme 24: 1,2-dihydroisoquinolines synthesis via Cu catalysis

Reaction of **119** with sulfonyl azide through copper-catalysed alkyne-azide cycloaddition and Dimroth rearrangement gives ketenimine **120**. Depending on the groups present in the ketenimine, **120** can undergo 1,5-OR or 1,5-H shift to generate **121** or **123** respectively. 6π

electrocyclic ring closure of **121** and **123** generates **122** and **124** respectively. Both electron donating and electron withdrawing groups were tolerated in their products. The methodology was also extended in the synthesis of different isoquinolium salts.

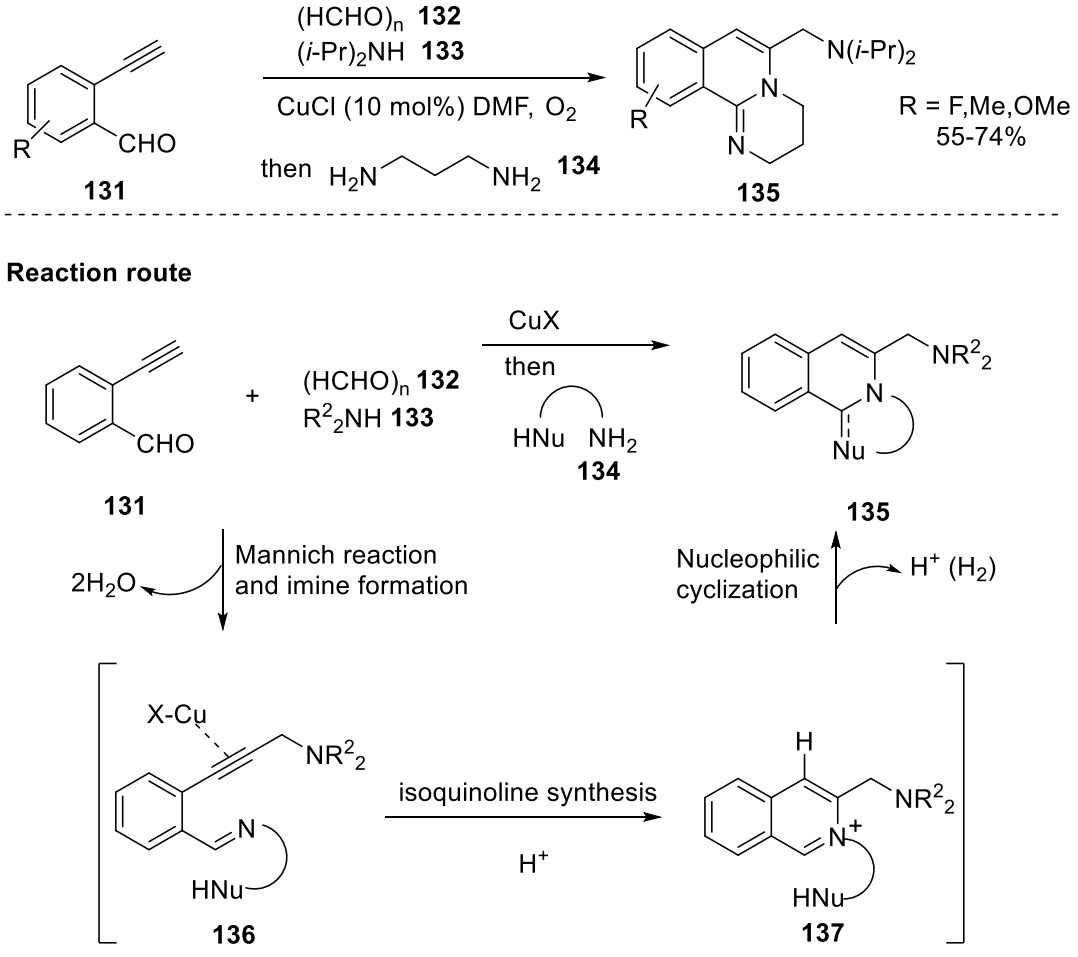
Ma and co-workers discovered access to substituted isoquinolines **127** via copper catalysed cascade of *o*-halobenzylamines **125** and β-keto esters **126** (Scheme 25).[67] Coupling of the halobenzylamines **125** with β-keto esters **126** generates **128**. Subsequent condensation and cyclization yields **130**, which after dehydrogenation under the presence of air affords the desired product **127**. β-keto esters with bulky groups gave low yields of the substituted isoquinolines due to steric hindrance.



Scheme 25: Cu-mediated formation of isoquinolines from keto esters and halobenzylamines

Ohno and co-workers highlighted the synthesis of isoquinoline-fused polycycles in an atom economical manner via copper catalysis (Scheme 26).[68] Their strategy employed the

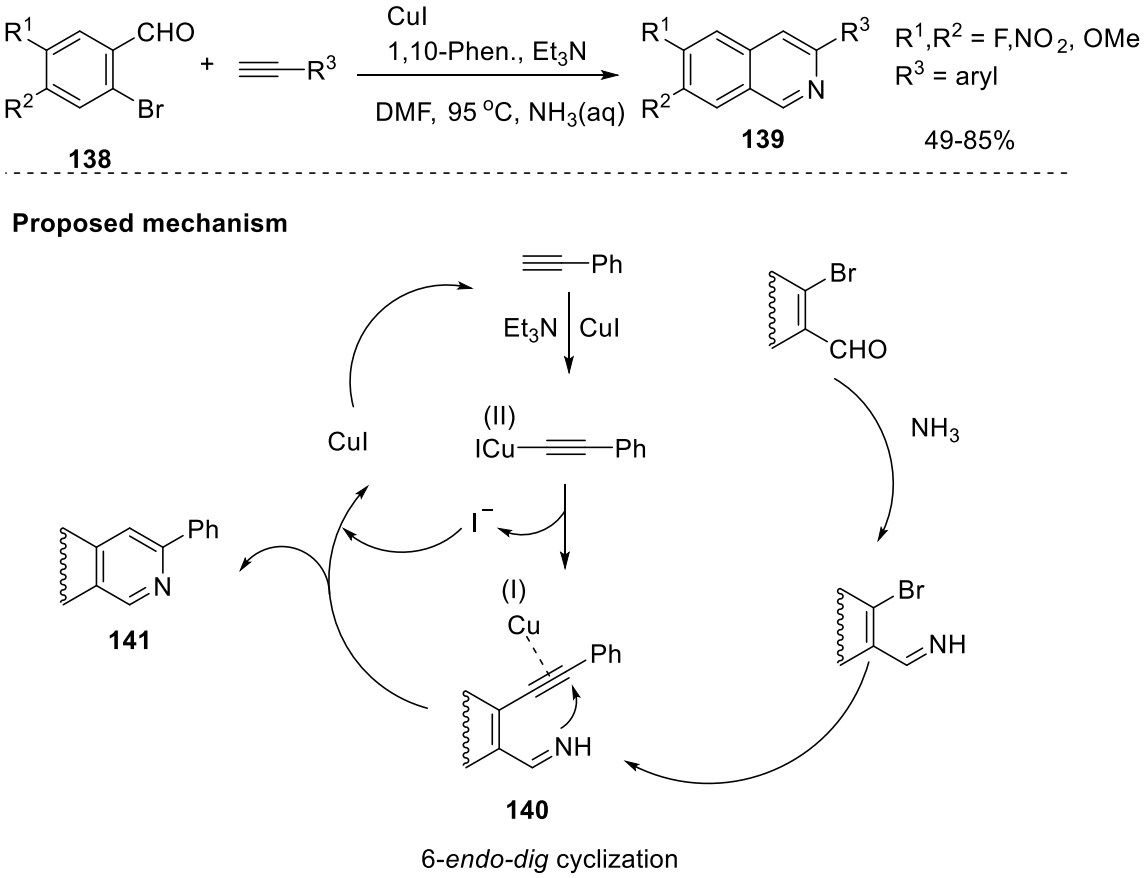
assembly of four components **131**, **132**, **133** and **134** through the coupling reaction of Mannich and imine formation to generate **136**. Subsequent cascade cyclisation and oxidation generate the desired fused polycycle **135**. Various substitution on 2-ethynylbenzaldehyde **131**, amine **133** and nucleophile **134** were accommodated in the synthesis. The formation of one carbon-carbon and four carbon-nitrogen bonds contributed to the importance of atom economy concept in organic chemistry.



Scheme 26: Access to isoquinoline fused polycycles via Cu catalysis

Furthermore, the research group of Ray reported the copper mediated synthsesis of 3-substituted isoquinolines **139** via cascade cross coupling and cyclisation (Scheme 27).[69] From

the proposed mechanism, three basic steps namely imine formation, Sonogashira cross coupling and 6-*endo-dig*-cyclisation were responsible for the formation of the product **141**. Electron rich and electron deficient groups were tolerated in the aromatic region of the bromobenzaldehyde. However, the terminal alkyne was limited to phenylacetylene mainly.

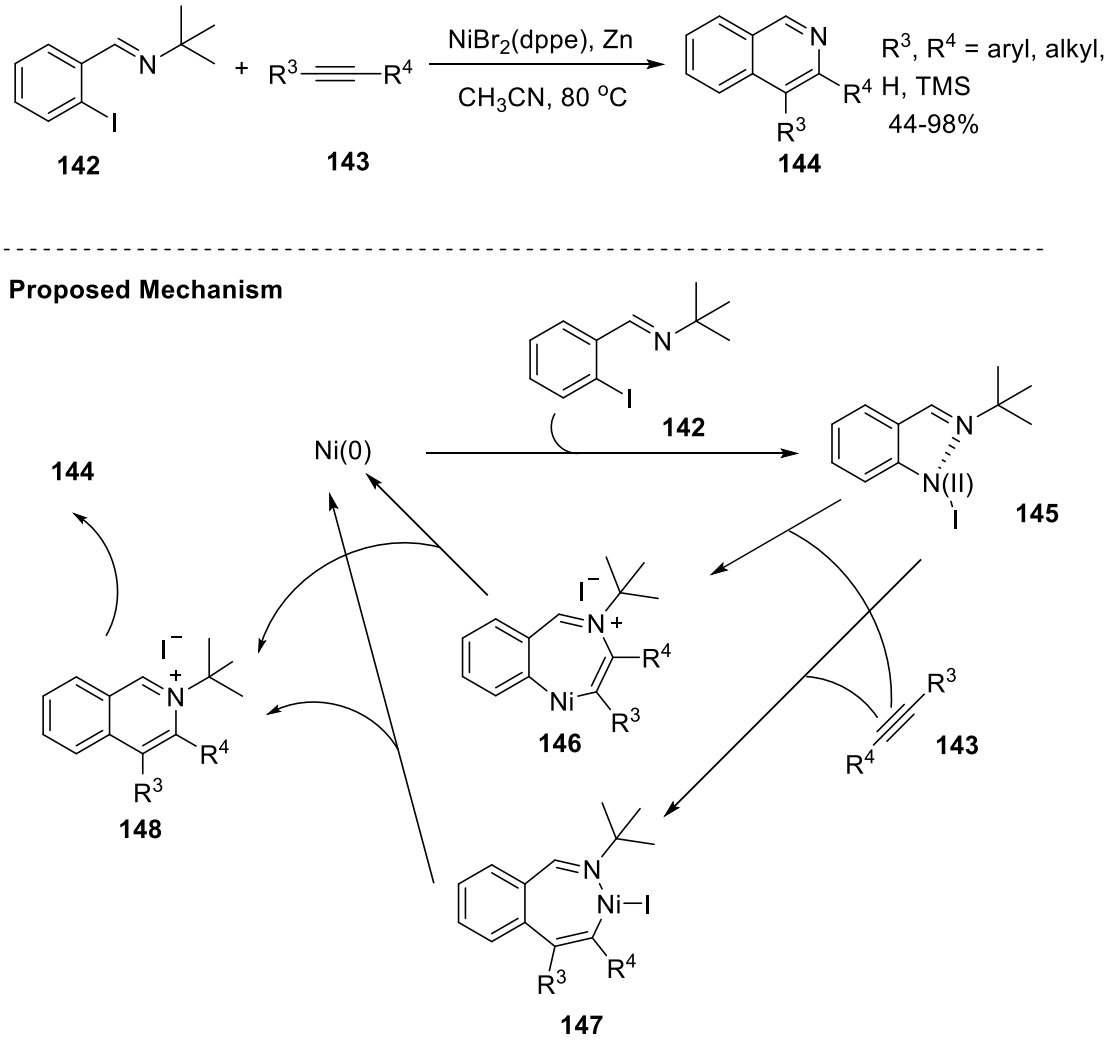


Scheme 27: Cu-catalysed isoquinoline formation

2.5 Nickel-mediated synthesis of isoquinolines

Cheng and co-workers provided a novel route to isoquinolines via annulation of 2-iodobenzaldimines **142** with alkynes **143** using nickel as catalyst (Scheme 28).[70]. A plausible mechanism was proposed commencing with the reduction of Ni(II) to Ni(0). Generation of the nickelacycle **145** was as a result of the oxidative insertion of **142** to Ni(0). Subsequent coordinative insertion of **145** onto **143** generates either **146** or **147**, which undergoes demetalation to give cation **148**. The nucleophilic attack of iodide ion generated leads to the

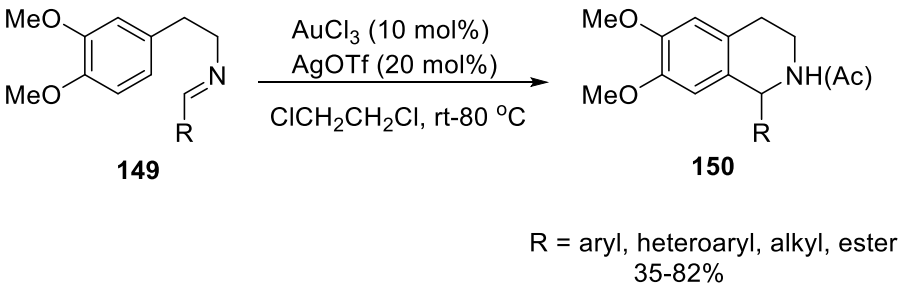
cleavage of the tert-butyl group on **148** to give the final product **144**. The two regioisomers observed in some of the isoquinolines made accounts for the dual insertion pathways proposed in the mechanism. The substrate scope was quite broad and alkynes ranging from terminal, internal and dialkyl substituted ones were all tolerated compared with their counterpart reactions that use palladium as a catalyst. In addition, they achieved a faster reaction rate.



Scheme 28: Ni-mediated isoquinoline synthesis

2.6 Gold-catalysed formation of isoquinolines.

In 2005, Youn reported the metal catalysed version of Pictect-Spengler reaction using $AuCl_3$/AgOTf (Scheme 29).[48] The conditions were mild as some of the acylated derivatives of the tetrahydroisoquinoline **150** were achieved at room temperature. The imines investigated ranged from electron rich, electron deficient, aliphatic as well as heteroaromatics. According to the proposed mechanism, coordination of the gold complex to the imine leads to its activation in an electrophilic pathway.

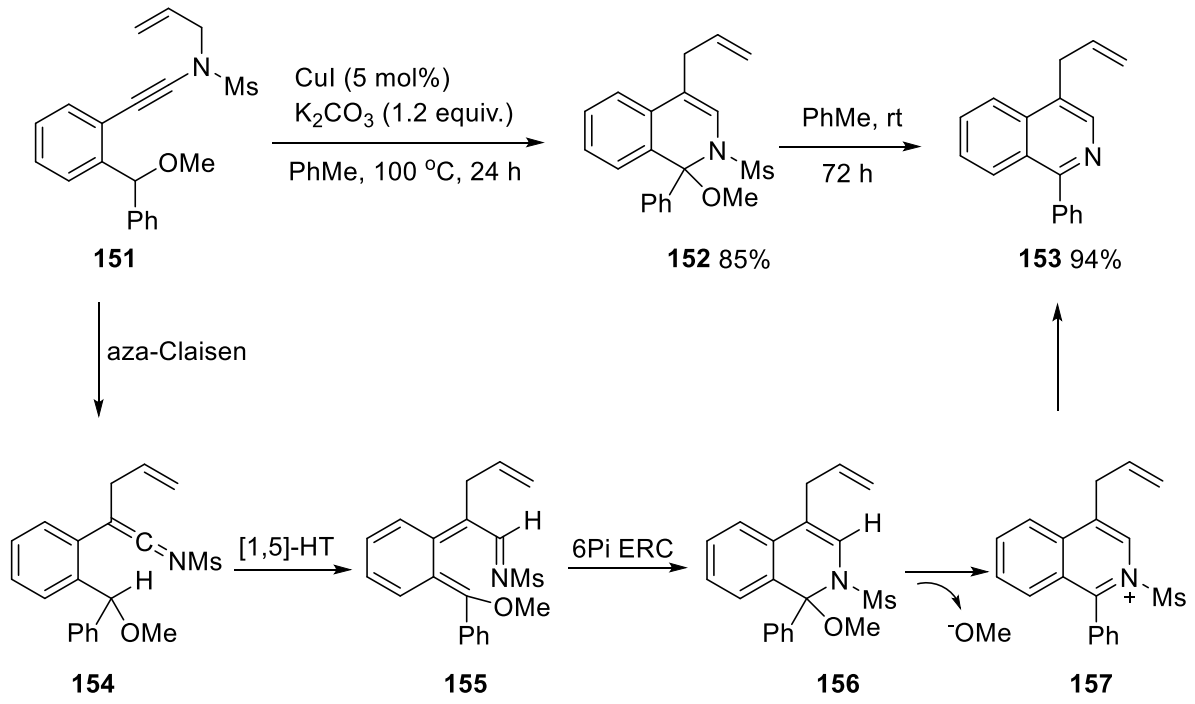


Scheme 29: Au-catalysed version of Pictet-Spengler reaction

3 Results and Discussion

3.1 Reaction design

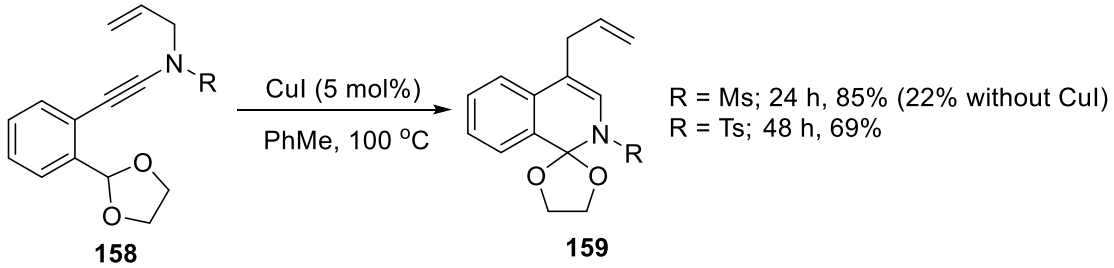
Investigation into a 1,5-hydride/cascade cyclisation of *N*-allyl ynamides was underway in our group which led to the assembly of highly functionalised and complex nitrogen heterocycles. In the course of these investigations, a new reaction was discovered for the synthesis of isoquinolines and oxyisoquinolines (Scheme 30)[71]



Scheme 30: Cu-catalysed isoquinoline formation

Depending on the conditions of the reaction, oxyisoquinoline **152** or isoquinoline **153** are formed in high yields. According to the proposed mechanism, benzyhdric ether containing ynamide **151** undergoes aza-Claisen rearrangement to generate ketenimine **154**. [1,5]-Hydride transfer and subsequent 6π electrocyclisation produce oxyisoquinoline **156**. Further elimination and desulfonylation affords the isoquinoline **153** in excellent yields.

This was subsequently extended to *N*-allyl ynamides bearing an acetal group. It was discovered that when **158** was treated with copper(I)iodide and without a base, dialkoxy 1,2-dihydroisoquinoline **159** was formed in very good yield (Scheme 31).



Scheme 31: Synthesis of dihydroisoquinoline via copper catalysis

Further revelation indicated that mesyl ynamides gave a cleaner reaction and increased yield than tosyl equivalents. The reaction can also proceed without the catalyst in low yield (22%), suggesting the thermal nature of the reaction. In the absence of copper catalyst, pronounced degradation was observed.

The utility of this reaction in accessing a functionalised oxyisoquinoline core led to further investigaton of the substrate scope (Figure 1). Various groups on the *N*-substituent of the ynamide, variations on the hydride donor-acceptor linker, substitution on the acetal region and possibly variations on the protecting groups can generate interesting scaffolds with wide application.

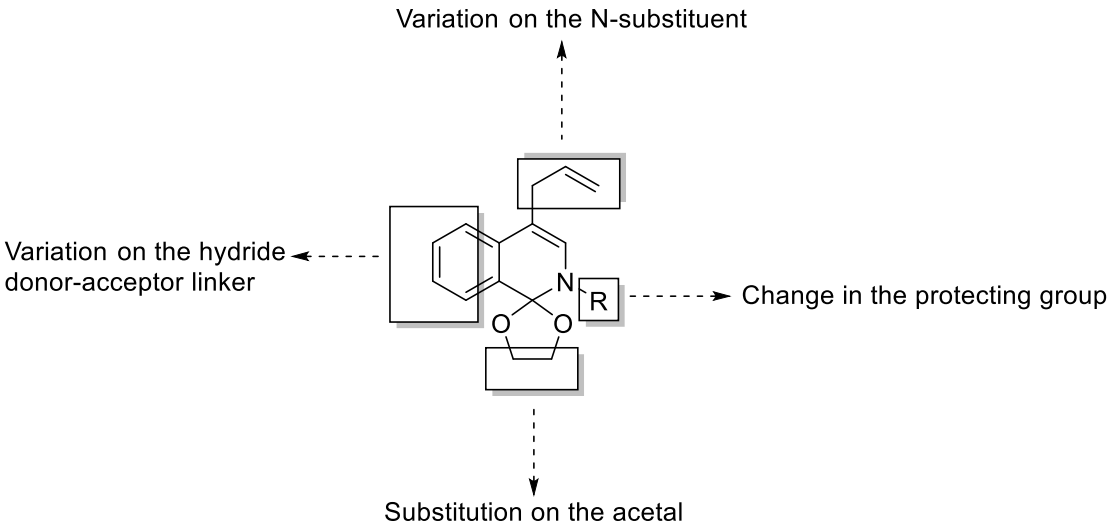


Figure 1: Substrate scope of dihydroisoquinoline synthesis

These parameters were chosen for us to have a better understanding of the nature of this newly discovered reaction and hopefully more insights will be achieved on the reaction mechanism. Addition of various groups on the *N*-substituent of ynamdes may give us some information on the aza-Claisen rearrangement assuming we get regio-isomers. In addition, introducing various groups on the ally region can provide useful handle for further

functionalisation. In the course of the investigation, we planned to modify the donor-acceptor linker by the incorporation of both electron donating and electron withdrawing groups. Such groups may potentially play a role on the rate of the reaction leading to increased or low yields of dihydroisoquinolines.

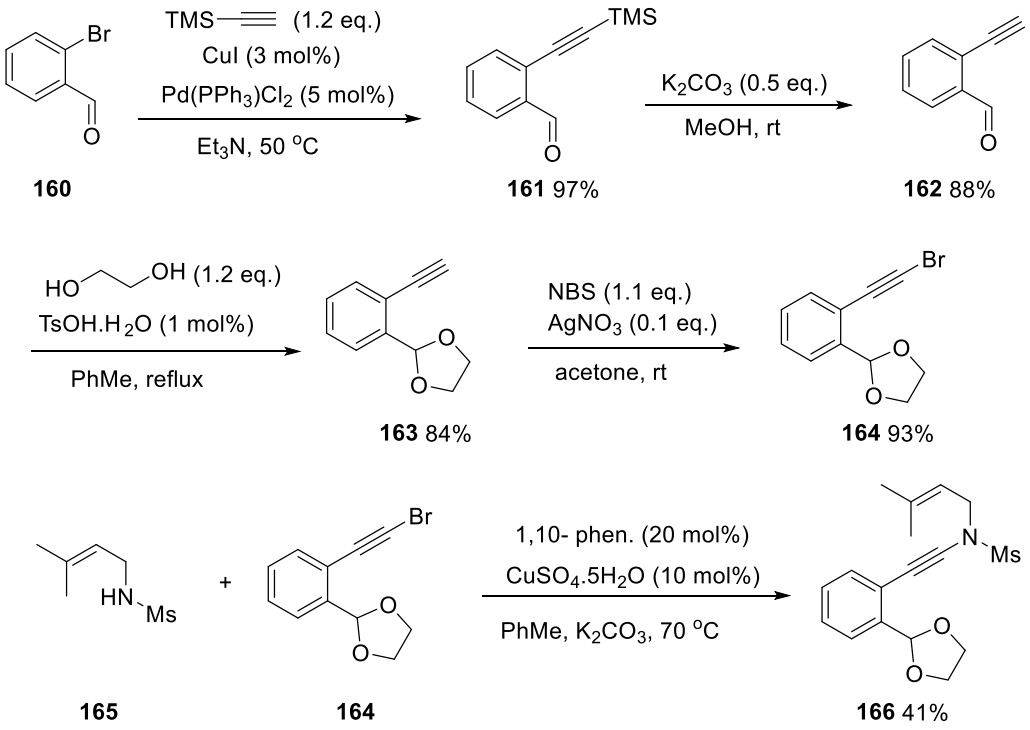
As the reaction was proposed to proceed through [1,5]-hydride transfer, various substituents on the acetal region may affect the rate of such shift. Apart from the common mesyl and tosyl groups on the nitrogen, other stabilising or protecting groups will be investigated. Whilst the formation of the desired 1,2-dihydroisoquinolines and ynamide formation are catalysed by copper catalysts, though from different sources, we planned to investigate and possibly develop the synthesis of these dihydroisoquinolines using a one-pot strategy. The advantages of one-pot methodology can be seen from the perspective of cost, minimal handling and time. With these hypothesis and questions in mind, we began the investigation exploring the reactivity of ynamides with various groups on the allyl region.

3.2 Variation on the *N*-substituent of ynamide

In order to investigate the effects of substituted allyl groups, an ynamide bearing the prenyl group was prepared by five step route (Scheme 32)

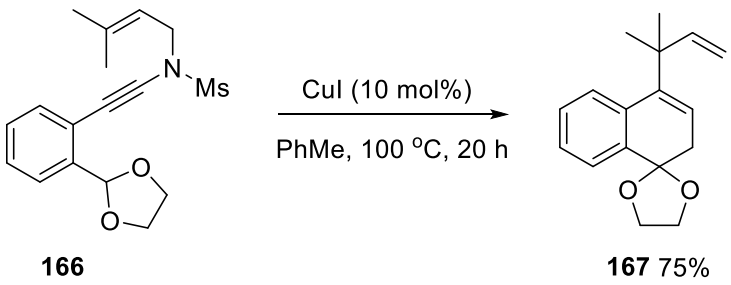
From the commercially available 2-bromobenzaldehde **160**, Sonogashira coupling with trimethylsilylacetylene gave the silylated alkyne **161** in an excellent yield. Cleavage of the trimethylsilyl group using potassium carbonate and methanol gave the terminal alkyne **162**. Acid catalysed acetalisation with ethylene glycol gave the acetal derivative **163** in high yields. Bromination of **163** to furnish the alkynyl bromide **164** was achieved using *N*-bromosuccinamide. Flash column chromatography purification of **164** was done with triethylamine deactivated silica as it was observed that non-deactivated column may lead to

opening of the acetal ring. The copper catalysed coupling of the bromoalkyne **164** wth prenyl sulfonamide **165** produced the ynamide **166** in low yield. Substantial amounts of formation of the ynamide was developed by Hsung and co-workers.[15]



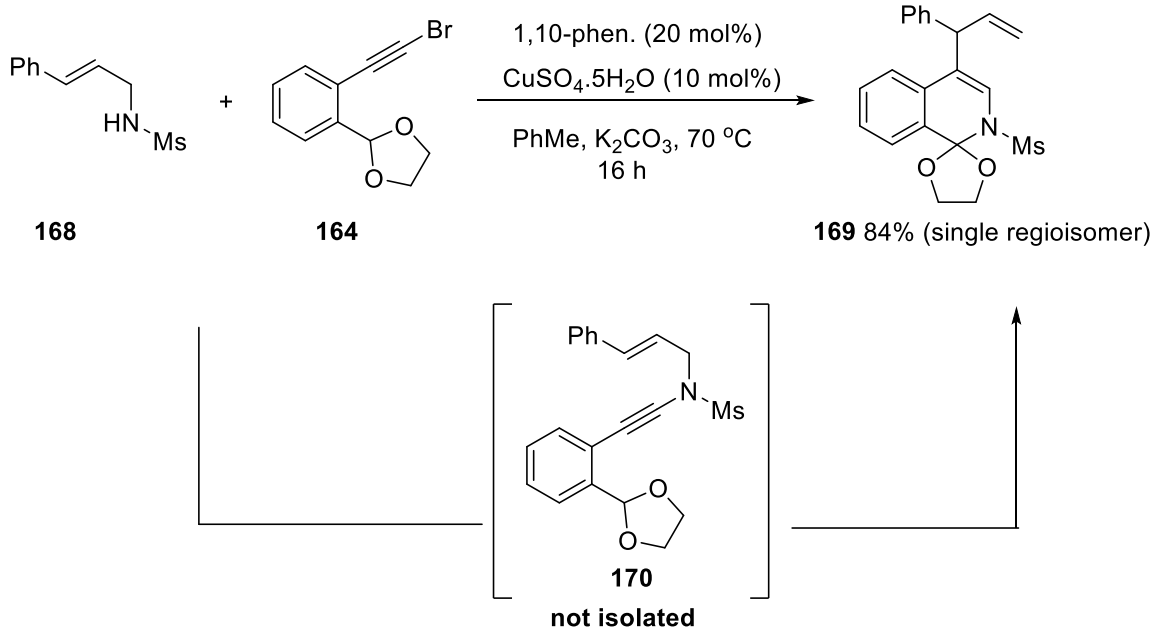
Scheme 32: Initial ynamide preparation in a five step route

When the prenyl substituted ynamide **166** was subjected to the optimised condition for the formation of heterocycle, it reacted cleanly, affording the quaternary carbon dihydroisoquinoline containing product **167** in high yield (Scheme 33)



Scheme 33: Copper-catalysed synthesis of oxyisoquinoline

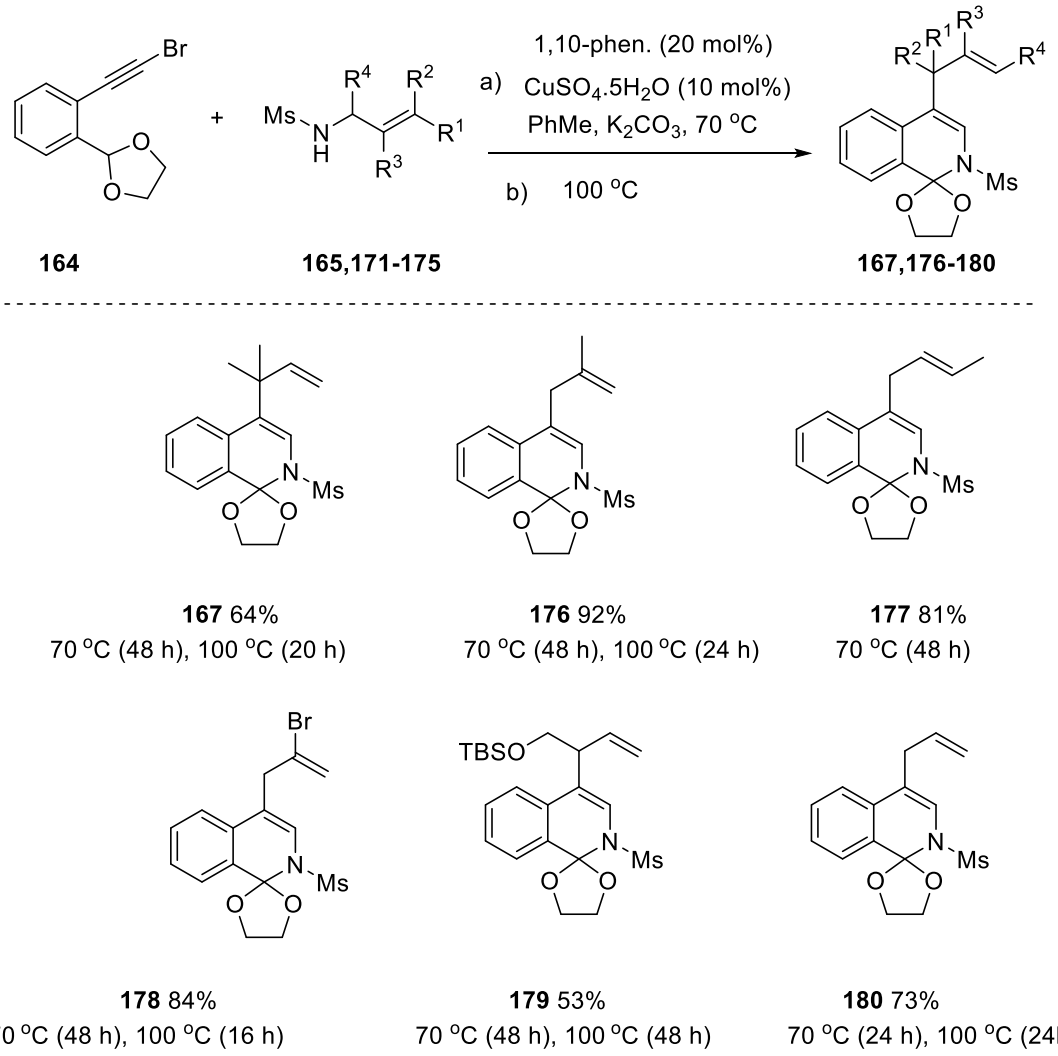
We turned our attention to the synthesis of ynamide bearing the cinnamyl group **170**. Surprisingly, applying the copper catalysed coupling conditions developed by Hsung led to the direct formation of the oxyisoquinoline **169** isolated in very high yield (84%) from cinnamyl sulfonamide **168** and alkynyl bromide **164** without the ynamide **170** being isolated (Scheme 34). The cyclic heterocycle-dihydroisoquinoline **169** was isolated as a single regioisomer. In this new discovery, we were glad that oxyisoquinoline synthesised was not affected by the additives inherent in the reaction as no degradation or any other spot were seen on the TLC.



Scheme 34: One pot ynamide formation rearrangement cascade

The formation of a single isomer of **169** with complete allylic inversion validates the concerted aza-Claisen rearrangement as proposed in the mechanism. Without the formation of branched or linear isomers, the cationic step-wise process is ruled out.

With clean conversion in this case, we investigated the viability of applying the one pot reaction conditions more widely, with the advantages of minimal handling, cost and saving time. Through treating bromoalkyne **164**, with various allylsulfonamide derivatives **165**, **171-175** under Hsung's conditions, we explored the simple modification of increasing the reaction temperature on complete consumption of the limiting reagent or apparently no further reaction (Scheme 35). All the different allylsulfonamide derivatives **165**, **171-175** explored gave their corresponding oxyisoquinolines **167**, **176-180** from good to excellent yields, with their corresponding ynamides not isolated. Generally, monitoring of the ynamide formation with thin layer chromatography (TLC) analysis showed the reaction to be quite slow, and longer times were required for completion. Whilst the prenyl ynamide **166** was earlier isolated through a two-step process, its one pot reaction proceeded cleanly to afford the quaternary containing cyclic product **167** in good yield. The excellent yield of **176** proved the viability of the one-pot two step strategy. Oxyisoquinoline **177** was formed in high yield and isolated as mixture of E/Z isomers in the ratio 0.4:1 without raising the temperature to 100 ^{o}C



164 **165,171-175** **167,176-180**

167 64%
70 °C (48 h), 100 °C (20 h)

176 92%
70 °C (48 h), 100 °C (24 h)

177 81%
70 °C (48 h)

178 84%
70 °C (48 h), 100 °C (16 h)

179 53%
70 °C (48 h), 100 °C (48 h)

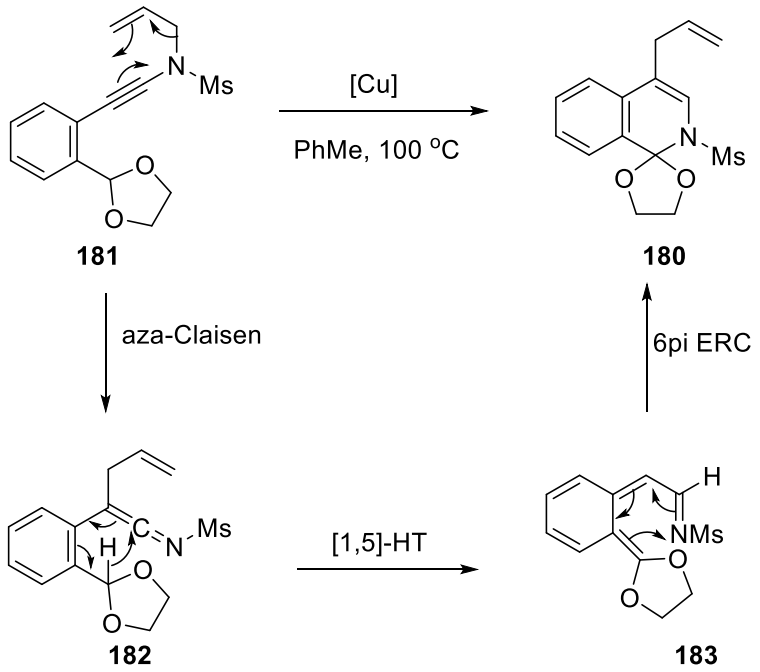
180 73%
70 °C (24 h), 100 °C (24h)

Scheme 35: One pot formation of dihydroisoquinoline with substituted allyl groups

The complexity of the ^{1}H-NMR spectroscopy arising from many overlapping resonances made it difficult to identify the isomers. Equally, their separations during flash column chromatography were unsuccessful. Although the yield of **179** was lower, the additional functionality of the protected alcohol makes it attractive. The low yield can be explained by an indication of some deprotected silyl product in the reaction mixture. However, such product was never isolated. The vinyl bromide moiety present in **178** can serve as a useful tool for the incorporation of many functional groups via the transition metal catalysed coupling reactions.

3.3 Reaction mechanism

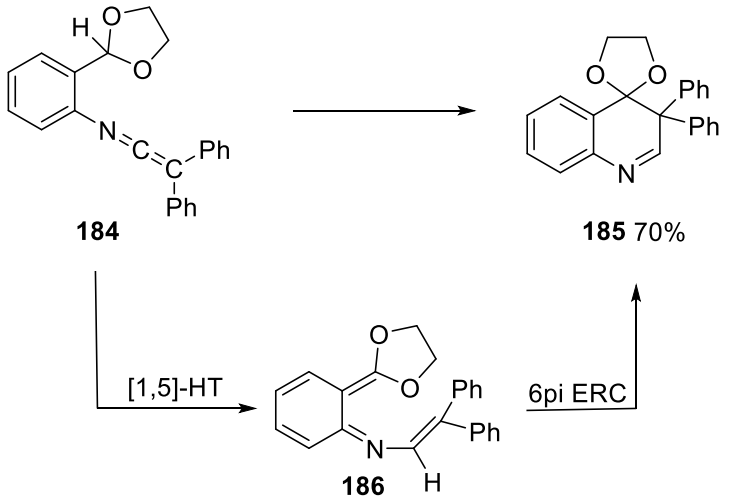
The reaction mechanism for the formation of the dihydroisoquinoline (Scheme 36) is proposed to proceed via the aza-Claisen rearrangement of ynamide **181** to yield the ketenimine **182**. Subsequent [1,5] hydride transfer will give the imine intermediate **183**, with corresponding destruction of the benzene aromaticity. A 6π electrocyclisation gives the cyclic product **180** with restoration of the aromaticity. At this stage, we don't know the exact role of copper, however we believe that the copper catalyst could potentially play a role during each stage of this thermally viable cascade.



Scheme 36: Proposed mechanism for the formation of dihydroisoquinoline

The mechanism is supported by the works of the research groups of Alajarin[72, 73]and Wang[66] in the synthesis of quinolone and dihydroisoquinolines respectively. Alajarin and co-workers discovered the synthesis of 4-quinolone **185** via tandem [1,5]-hydride transfer/6π electrocyclisation of acetalic ketenimines (Scheme 27)[73]. [1,5]-Hydride transfer of

ketenimine **184** generates **186** which undergoes 6π electrocyclic ring closure to give **185**. The formation of **186** via [1,5]-hydride migration was attributed to the "hydricity" of the acetalic hydrogen and high electrophilicity of the central carbon of the ketenimine making it susceptible to hydride shift/attack. "Hydricity" literally means hydride transfer ability. They opined that the "hydricity" of 1,3-dioxolanes is as a result of the interaction of the lone pair electrons present on the oxygen atoms. Such interaction weakens and polarises the carbon-hydrogen bond of 1,3-dioxolanes, conferring negative charge on the hydrogen atom.



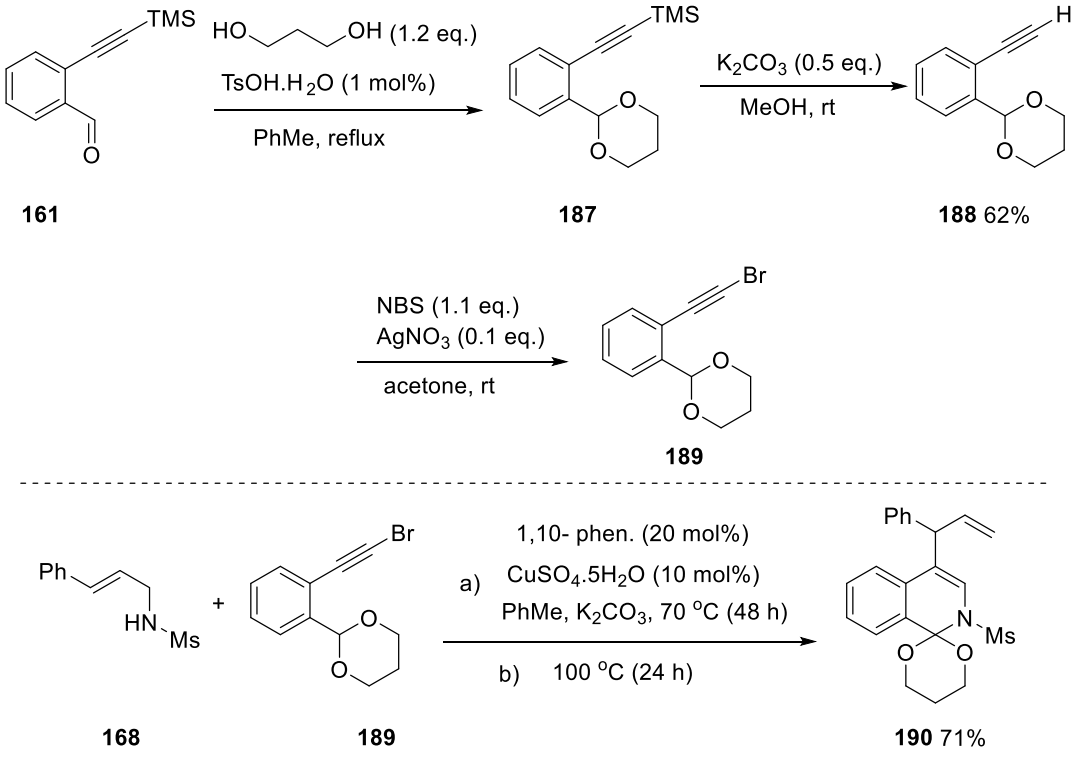
Scheme 37: 4-Quinoline synthesis

3.4 Variations on the ynamide acetal

3.4.1 Dioxane derivatives

Our next objective was to vary the ring size of the acetal function and monitor change in behaviour in the one-pot rearrangement cascade. Treatment of the Sonogashira protected alkyne **161** with 1,3-propanediol under acidic condition gave the six membered acetal **187** which was used without purification (Scheme 38). Deprotection **188** and subsequent bromination formed the bromoalkyne **189** in an excellent yield, which was used

immediately in the next step. When the bromoalkyne **189** was subjected to the one pot two step cyclisation conditions with *N*-mesylcinnamyl amine **168**, the oxyisoquinoline **190** was obtained in high yield. From this result, it can be seen that the yield of **190** is lower when compared with its corresponding cyclic product **169** bearing the five membered acetal group (1,3-dioxolane). The reaction time for the formation of **190** is also longer. This is in complete agreement with the findings of Alajarin and co-workers. [72] Through computational studies, they found out that the activating order for "hydricity" of acetalic hydrogens is observed to occur in this range: 1.3-dioxolane > 1,3-dithiolane > 1,3-dioxane > 1,3-dithiane.

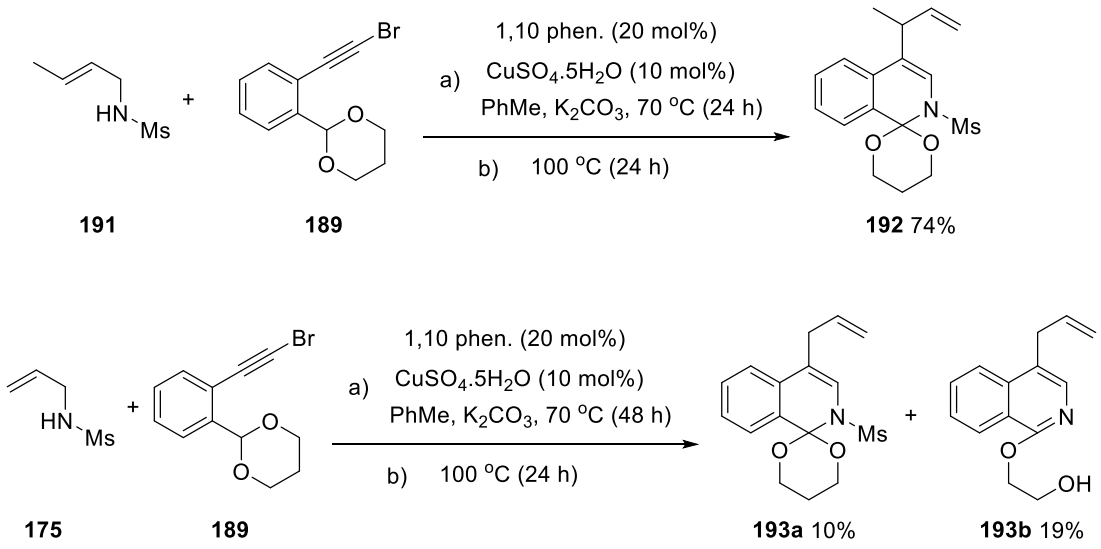


161 **187** **188** 62% **189**

168 **189** **190** 71%

Scheme 38: The synthesis of dihydroisoquinoline with 1,3-dioxane group

Further reactivity was explored with crotyl sulfonamide **191** (Scheme 39). Bromoalkyne **189** reacted cleanly to afford **192** in good yield.

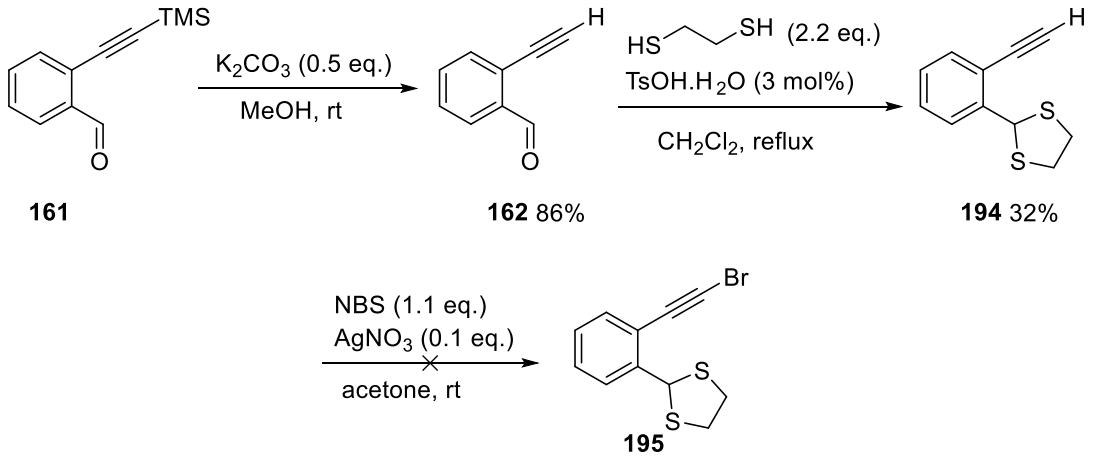


Scheme 39: Substrate scope of heterocycle with 1,3-dioxane function

The reaction of **189** with *N*-mesylallyl amine **175** under copper catalysis was problematic as substantial degradation was seen inside the reaction mixture. At the end of the reaction, TLC analysis indicated the presence of ynamide and other spots. Efforts to isolate the remaining ynamide proved unsuccessful. The desired cyclic product **193a** came off in a very low yield alongside another product **193b**. The product **193b** was as a result of neighbouring-group assisted breaking on the ring and subsequent demesylation. It was difficult to determine whether **193b** was formed during the course of the reaction or during purification by flash column chromatography. We opined that lower hydricity of acetalic hydrogen in 1,3-dioxanes may contribute to the opening of the ring.

3.4.2 Dithiolane fragment

Apart from using 1,3-dioxane as a source of hydride donor, we investigated the use of 1,3-dithiolane in the cyclisation reaction (Scheme 40)

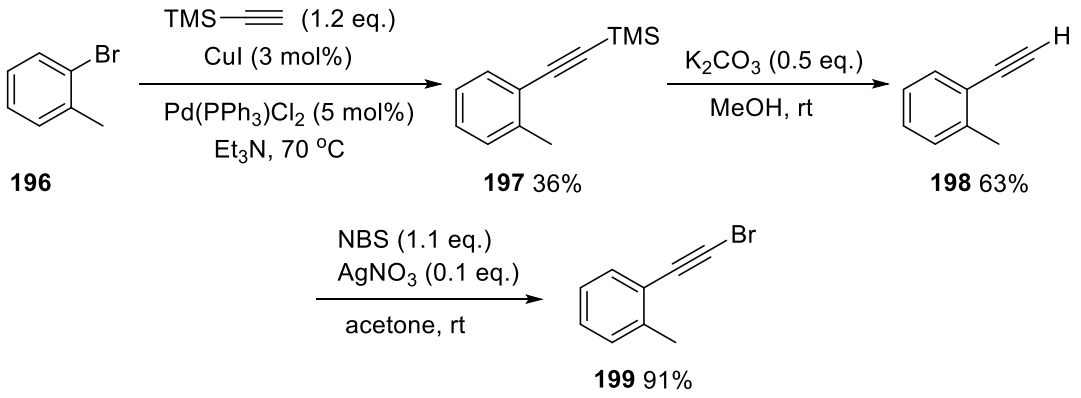


Scheme 40: Synthesis of dithiolane derived alkynyl bromide

Deprotection of **161** and subsequent treatment of **162** with 1,2-ethanedithiol gave the dithiolane **194** in low yield. Bromination of terminal alkyne **194** failed. It was observed that the reaction mixture turned into a black solution after twenty minutes. ^{1}H-NMR spectrum of the reaction mixture was very complex and such that no useful interpretation could be made. The investigation was discontinued after several failed attempt to generate bromoalkyne **195**.

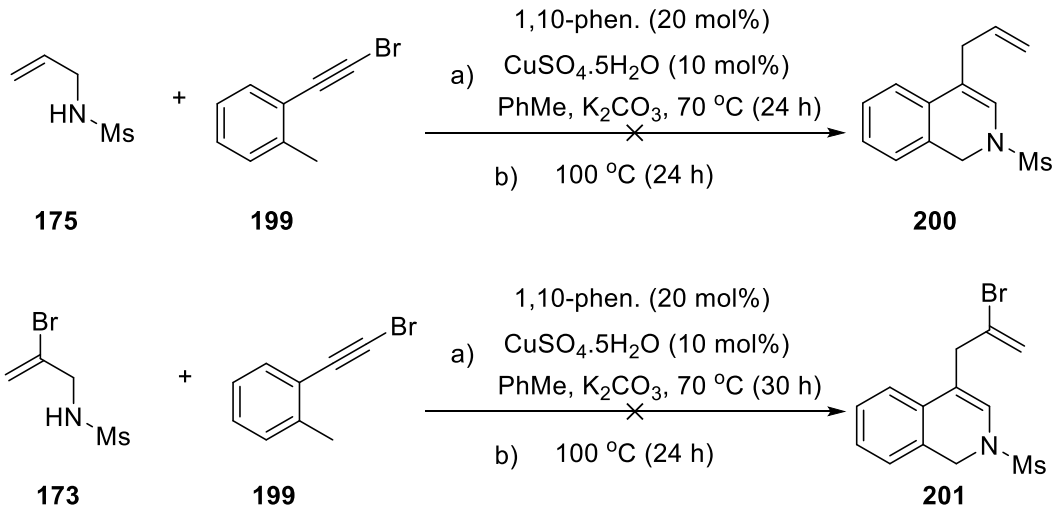
3.4.3 Alkyl substituent

Moving from dithiolane synthesis, we decided to explore the possibility of using an alkyl group as a hydride source in the one-pot two step strategy. This was investigated to determine the extent in which alkyl group can be used to facilitate hydride shifts. To achieve this, the synthesis of a methyl derived alkynyl bromide **199** was made in three steps (Scheme 41). Sonogashira coupling of commercially available 2-bromotoluene **196**, deprotection of **197** and bromination of **198** afforded the alkynyl bromide **199** in an excellent yield.



Scheme 41: Formation of methyl derived bromoalkynes

When the methyl derived bromoalkyne **199** was reacted with *N*-mesylallyl amine **175** under copper catalysis, the expected dihydroisoquinoline **200** was not formed (Scheme 42)

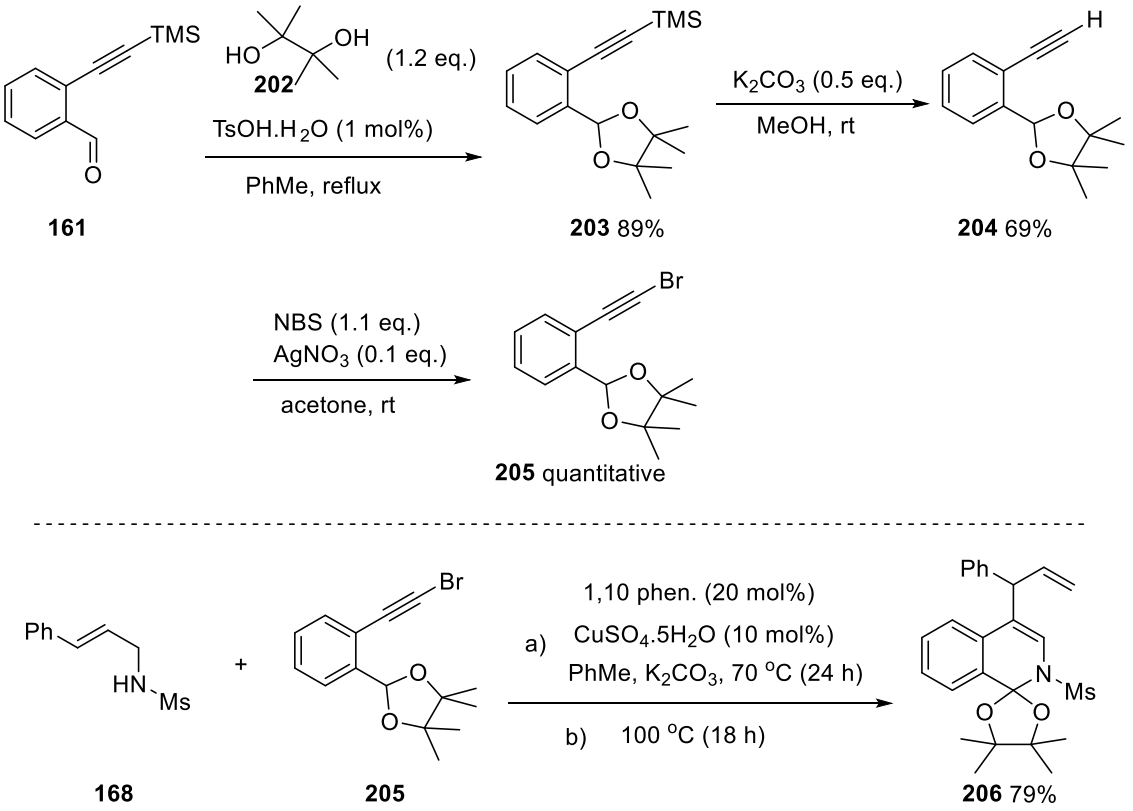


Scheme 42: Methyl derived bromoalkynes under copper catalysis

From TLC analysis, complete consumption of sulfonamide was seen at 24 hours. Subsequent increase in temperature led to degradation. Purification and isolation of the cyclic product using flash column chromatography was unsuccessful. Complex mixtures were seen as observed by ^{1}H-NMR spectroscopy. This observation can be explained by the lack of "hydricity" of methyl groups when compared to dioxolanes or dithiolanes. This is supported by the work of Alajarin and co-workers[73]. Complex mixtures and degradation were also seen when **199** was reacted with bromo substituted allyl sufonamide **173**.

3.4.4 Pinacol derivative.

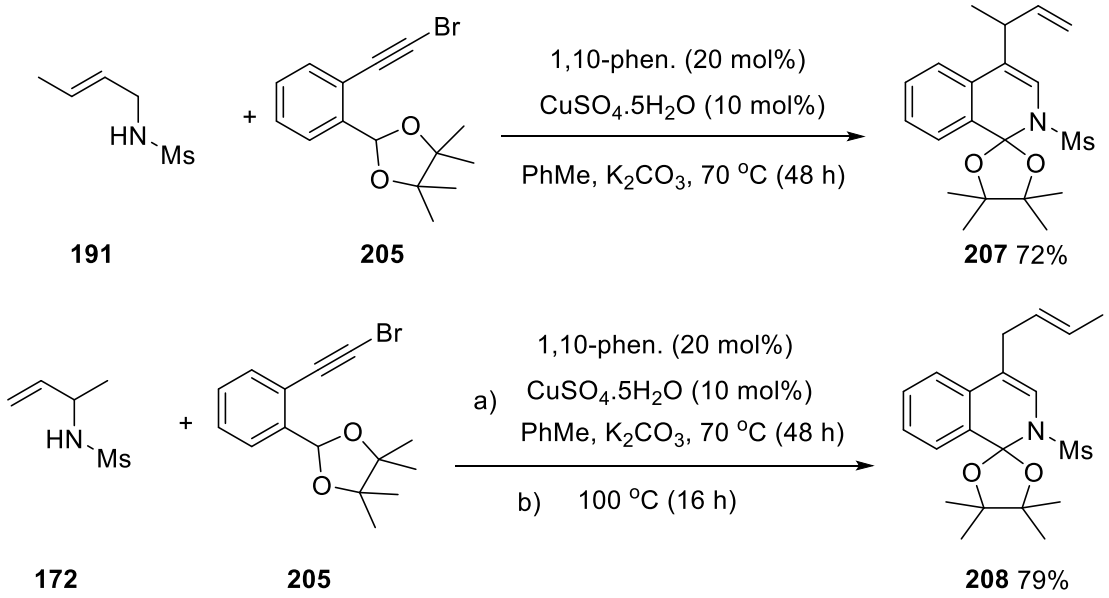
To test the influence of substituted dioxolane unit on the ynamide aza-Claisen-initiated cascade, we synthesised the cyclic product **206** using pinacol as the acetalating agent (Scheme 43)



Scheme 43: Preparation and cyclisation of isoquinoline with pinacol unit

Using the developed reaction sequence, treatment of the silylated alkyne **161** with pinacol **202** led to the formation of substituted product **203**. Cleavage of the trimethylsilyl group and bromination gave **205** in quantitative yield. The reaction of the pinacol containing bromoalkyne **205** proceeded cleanly with *N*-mesylcinnamyl amine **168** in the one-pot strategy to give the dihydroisoquinoline **206** in high yield. This promising result motivated us to expand the scope of the reaction with different sulfonamides so as to access cyclic products with different molecular architectures/scaffolds (Scheme 44). Clean and rapid

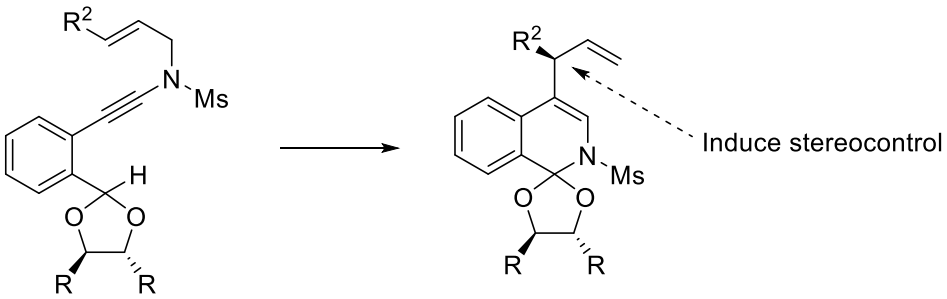
reactivity was observed with *N*-mesylcrotyl amine **191**, affording the cyclic product **207** in high yield. In addition, **208** was formed under the same reaction conditions of ynamide formation without further increase in temperature. Interestingly, **208** was isolated as mixture of E/Z isomers in 0.4:1 ratio. Efforts to isolate the isomers were unsuccessful.



Scheme 44: Reaction scope of pinacol derived isoquinoline

3.4.5 Use of chiral dioxolane

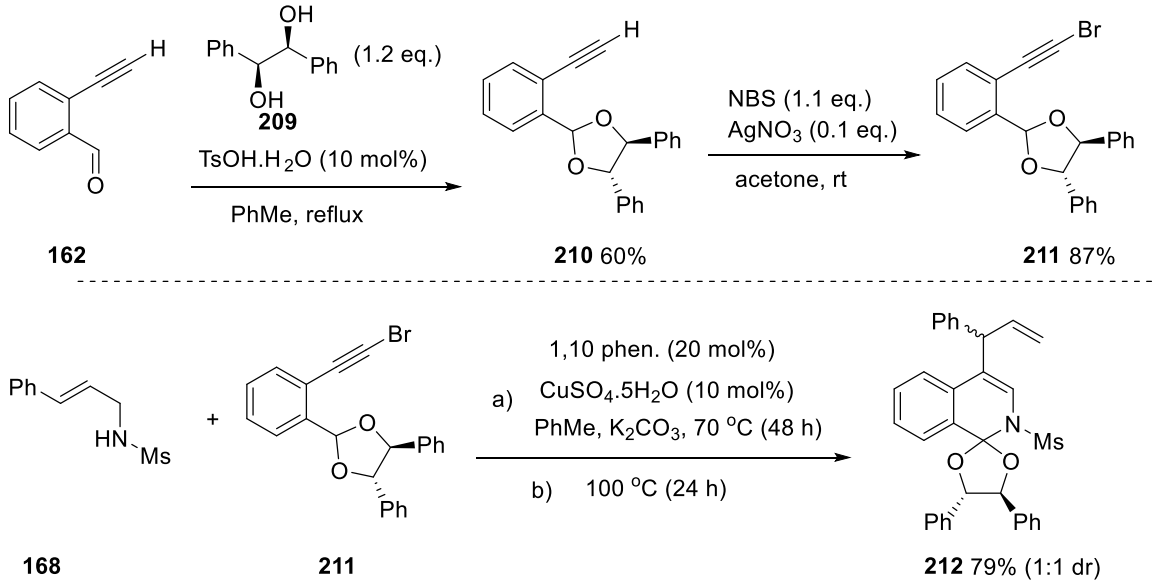
Following the results obtained with the use of dioxolanes in the copper catalysis, we then investigated the use of chiral dioxolanes with the intention of incorporating stereocontrol into the cascade cyclisation as they are being used as chiral inducers (Scheme 45).



Scheme 45: Chiral diols as "chiral inducers"

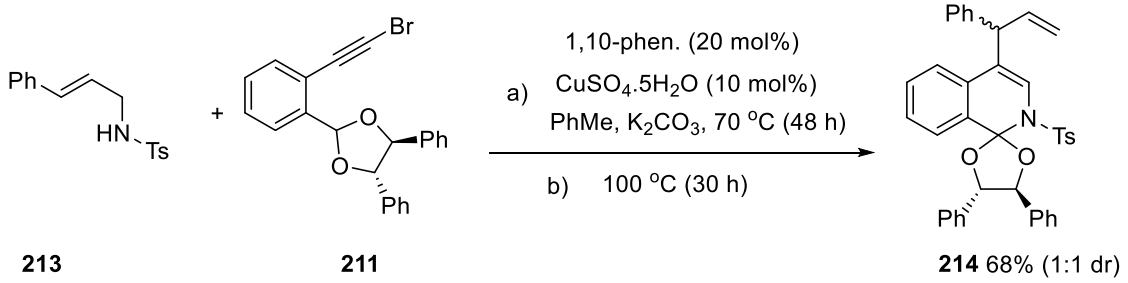
This approach can bring some advantages. Firstly, the enesulfonamide moiety in the resulting oxyisoquinoline provides a useful group for the elaboration of the heterocyclic core in a manner generating stereogenic centres, the asymmetry of which may be controlled by a chiral dioxolane. We also hypothesized that the considerable congestion around the ynamide, coupled to a well-defined transition state for the Claisen rearrangement, might result in transfer of remote stereochemical information from the stereogenic centres on the dioxalane to the newly forming stereogenic centres when 1,2-disubstituted alkenes are used in the cascade. Furthermore, the use of C_2-symmetric, optically active 1,2-diols will increase the extent of diastereoselection in the formation of the new stereogenic centre, thereby reducing the complexity of diastereodifferentiating events. Induction of high degrees of diastereoselection have been achieved with the use of C_2-symmetric, optically active 1,2-diols.[74]

With the terminal alkyne **162** obtained from the corresponding Sonogashira coupling and deprotection (Scheme 46), acetalisation with (S,S)-(-)-hydrobenzoin **209** gave the chiral acetal **210**. Bromination of **210** furnished the bromoalkyne **211** in good yield. The purification of the bromoalkyne was a bit difficult as small impurities could not be removed even after subjecting it to flash column chromatography



Scheme 46: Formation of chiral oxyisoquinoline

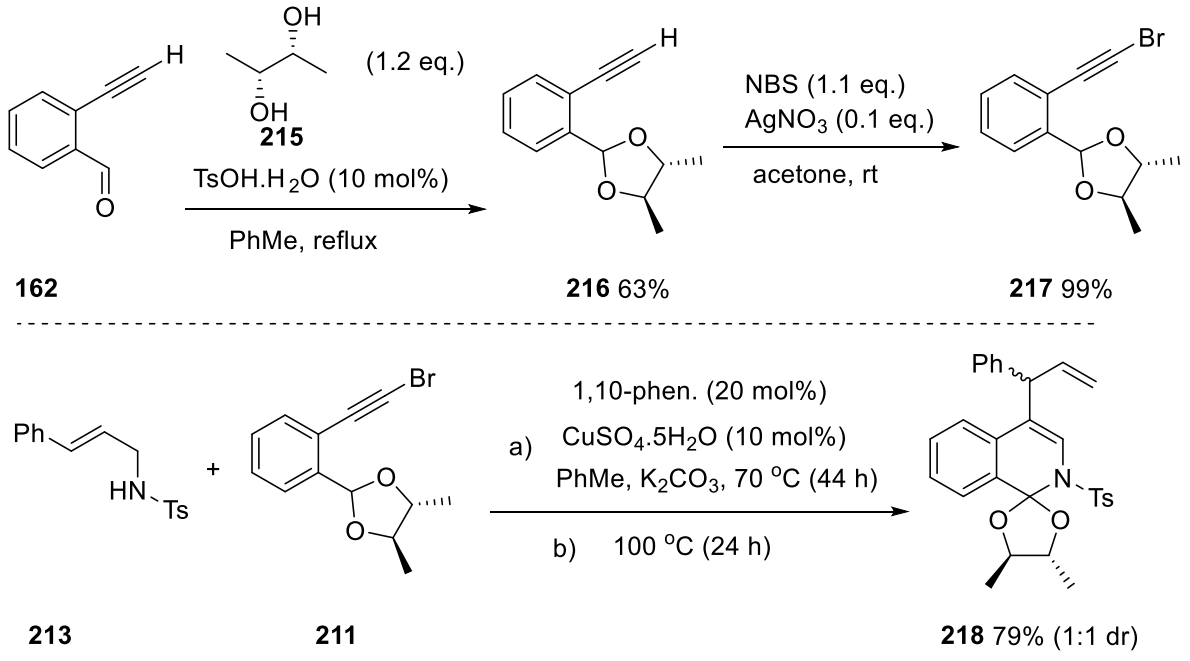
The one pot cascade of bromoalkyne **211** with *N*-mesylcinnamyl amine **168** led to the optically active oxyisoquinoline **212** in high yield and as a 1:1 mixture of diastereoisomers, which could not be separated by flash column chromatography or recrystallization. No level of stereocontrol found in the synthesis of oxyisoquinoline **212** led us to investigate the effect of having a tosyl group on the nitrogen atom of the ynamide that is generated in the reaction mixture (Scheme 47). We opined that introducing a bulky group like tosyl group could potentially induce some levels of stereocontrol.



Scheme 47: Synthesis of chiral tosylated oxyquinoline

The level of diastereoselection did not improve when *N*-tosylcinnamyl amine **213** was used, as it still gave 1:1 mixture of **214**. The isomers were non-isolable/separable with flash column chromatography or recrystallization.

The use of (*R*,*R*)-butane-2,3-diol as a chiral inducer was also investigated (Scheme 48). Following the usual sequence of reaction, treatment of **162** with (2R,3R)-butane-2,3-diol **215** using Dean-Stark trap gave the chiral acetal **216**. Bromination of **216** occured in excellent yield. The one-pot ynamide formation rearrangement cascade of **217** with *N*-tosylcinnamyl amine **213** generated the desired chiral spiroisoquinoline **218** in 1:1 mixture of diastereoisomers and in high yield. The isomers could not be separated using flash column chromatography or recrystallisation

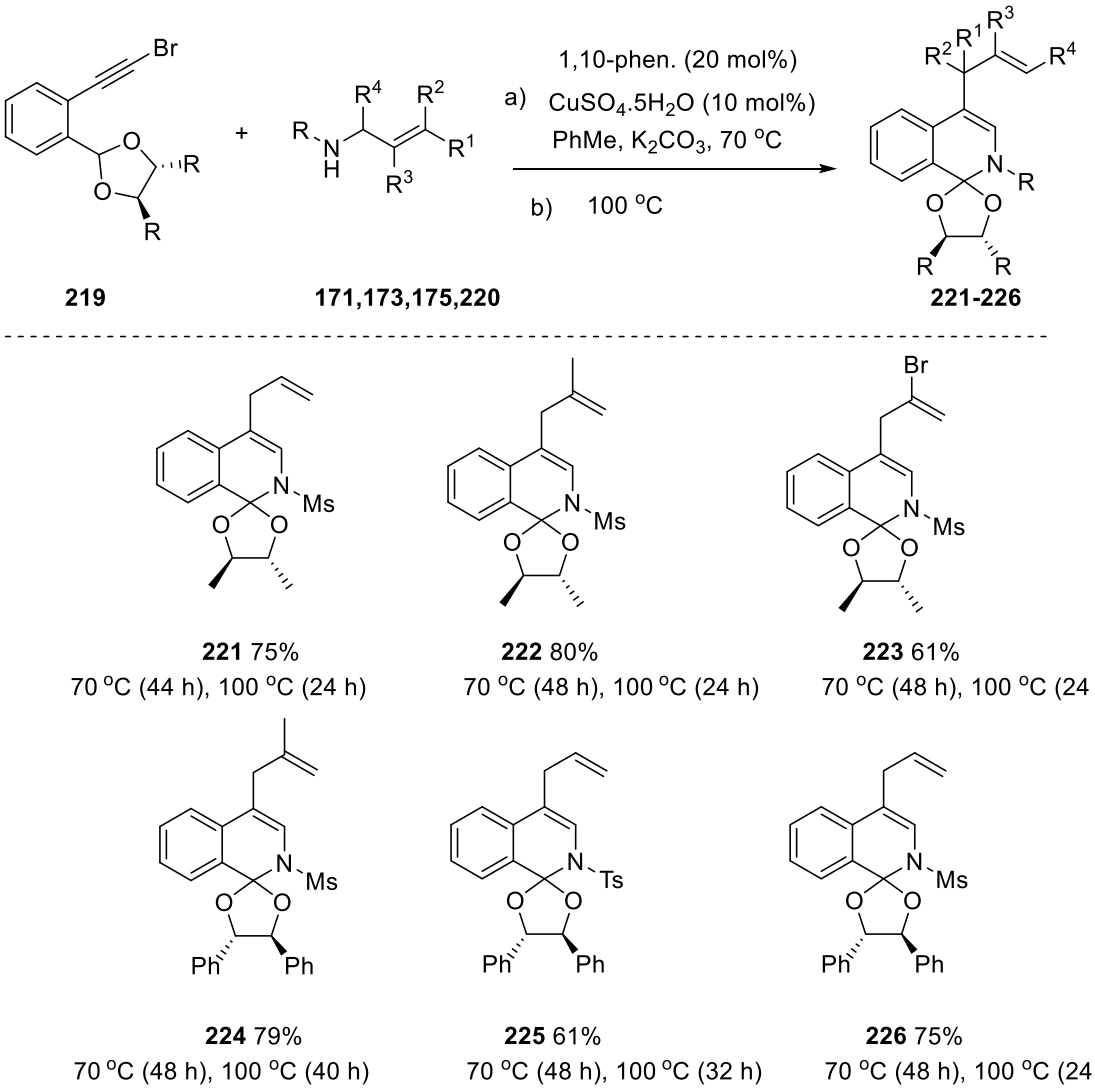


Scheme 48: Preparation and stereoinduction of 218

Although there is no degree of stereoinduction in these cases, the ability to generate these chiral compounds opens a different avenue for further investigation. Changes in the reaction conditions might lead to high degree of selectivity.

To access a library of chiral oxyisoquinolines derived from chiral diols, we applied the one pot cyclisation cascade by varying the sulfonamides (Scheme 49). The versatility and convergence of our methodology was shown in these syntheses as they were formed in good yields with no trace of degradation.

The vinyl bromide moiety present in **223** is interesting as it opens a new route for further functionalisation. Substitution of the methyl group on the allyl region of **222** did not affect the reactivity as the reaction proceeded in high yield.



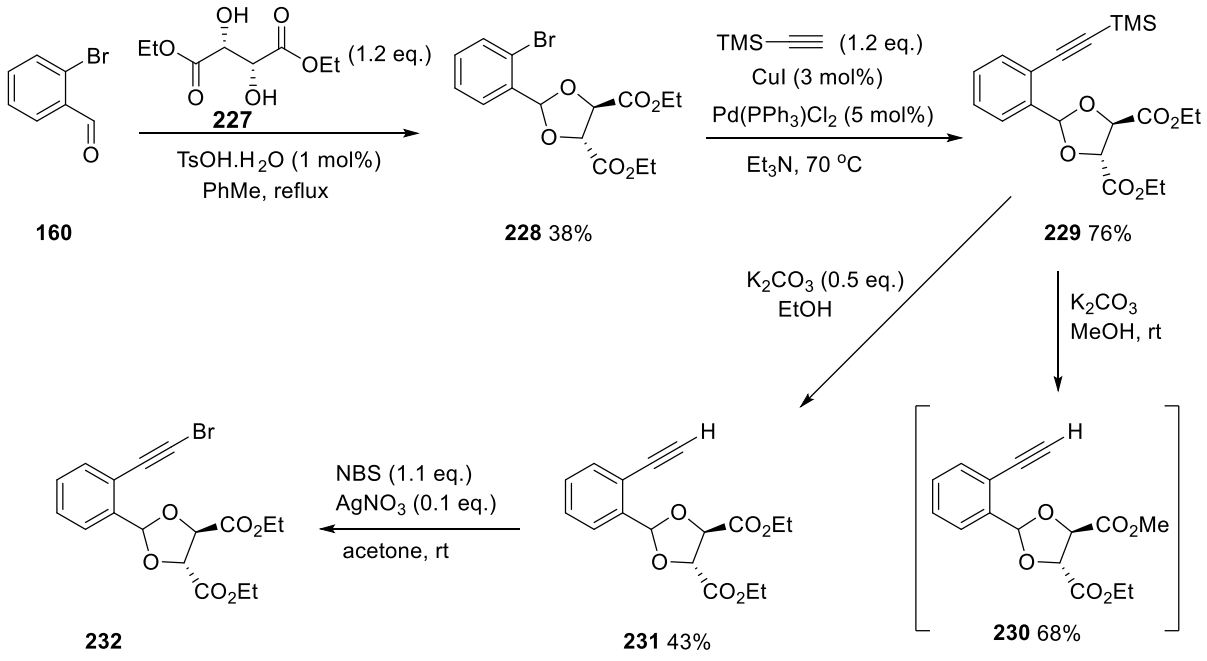
Scheme 49: Examples of spiroisoquinoline derived from chiral 1,2-diols

Chiral oxyisoquinoline **224** was afforded in high yield with methaallyl sulfonamide. Reactivity was observed with both tosyl and mesyl protecting groups on the nitrogen, **225** and **226** respectively. Generally, mesyl groups reacted faster with higher yields when compared to the tosyl protected equivalents.

Furthermore, we investigated how the use of (+)-diethyl L-tartrate **227** as a chiral auxiliary, would affect the reaction. Initially we started with the synthesis of the chiral diol derived alkynyl bromide **232** (Scheme 50). Starting from 2-bromobenzaldehyde **160**, treatment with (+)-diethyl L-tartrate **227** under acidic conditions gave the chiral acetal **229** in low yield.

Efforts to improve the yield by increasing the catalytic loading and longer reaction time were not successful. Sonogashira coupling with trimethyl acetylene gave **229** in high yield. This yield required increase in temperature (50 to 70 °C) and longer reaction time (72 h). Deprotection of **229** with potassium carbonate and methanol caused the cleavage of the trimethylsilyl group as well as transesterification of the ester group to generate **230**.

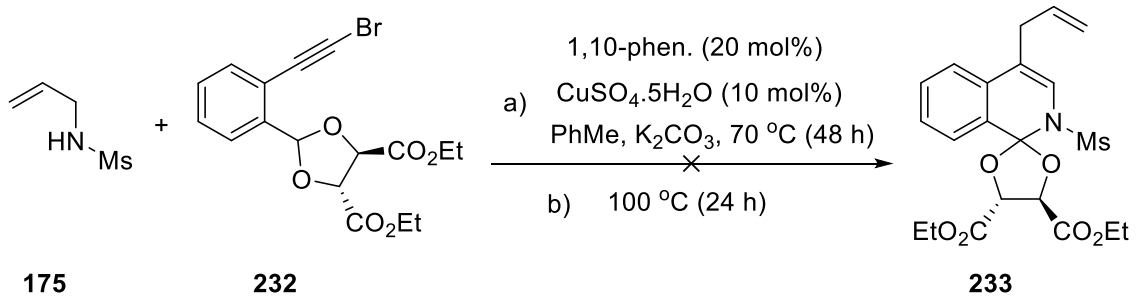
The transesterification problem was solved by the replacement of methanol with ethanol, although **231** was formed in low yield after extending the reaction time to 24 h. Subsequent bromination led to the formation of alkynyl bromide **232** which was used immediately in the next step.



Scheme 50: Synthesis of chiral derived alkynyl bromide 232

The reaction of chiral diol derived alkynyl bromide **232** with allyl sulfonamide **175** failed to deliver the desired product (Scheme 51). The formation of its ynamide was however seen on

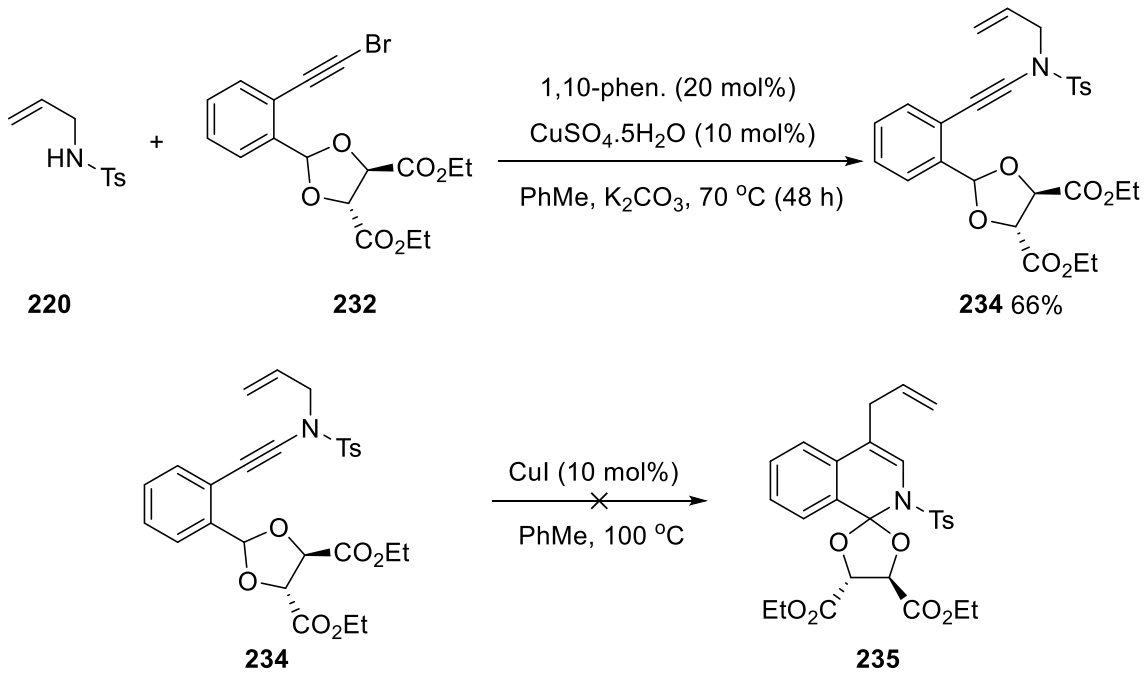
TLC analysis. Complex mixtures were seen as observed by the ^{1}H-NMR spectrum of the reaction mixture. Flash column chromatography of the reaction mixture did not work.



175 **232** **233**

Scheme 51: Formation of spiroisoquinoline 233

The inability to make the spiroisoquinoline **233** inspired us to synthesize its corresponding ynamide and subject it to the optimised conditions (Scheme 52) developed by a member of our group-Holly Adcock to achieve a clearer picture of the reactivity of the substrate. Copper-catalysed coupling of **220** and **232** generated the ynamide **234** in moderate yield. When the ynamide **234** was subjected to the optimised conditions, the desired oxyisoquinoline **235** was not formed. The ynamide **234** was completely unreacted as it was recovered back from flash column chromatography. Extending the reaction time to more than 24 h did not improve the reaction. One possible explanation to this effect is that the electron withdrawing ability of the ester group attached to the acetal can cause deactivation, thereby reducing the relative capabilities of the acetal to act as a hydride donor. This can cause the complete shutdown of the reaction/reactivity.

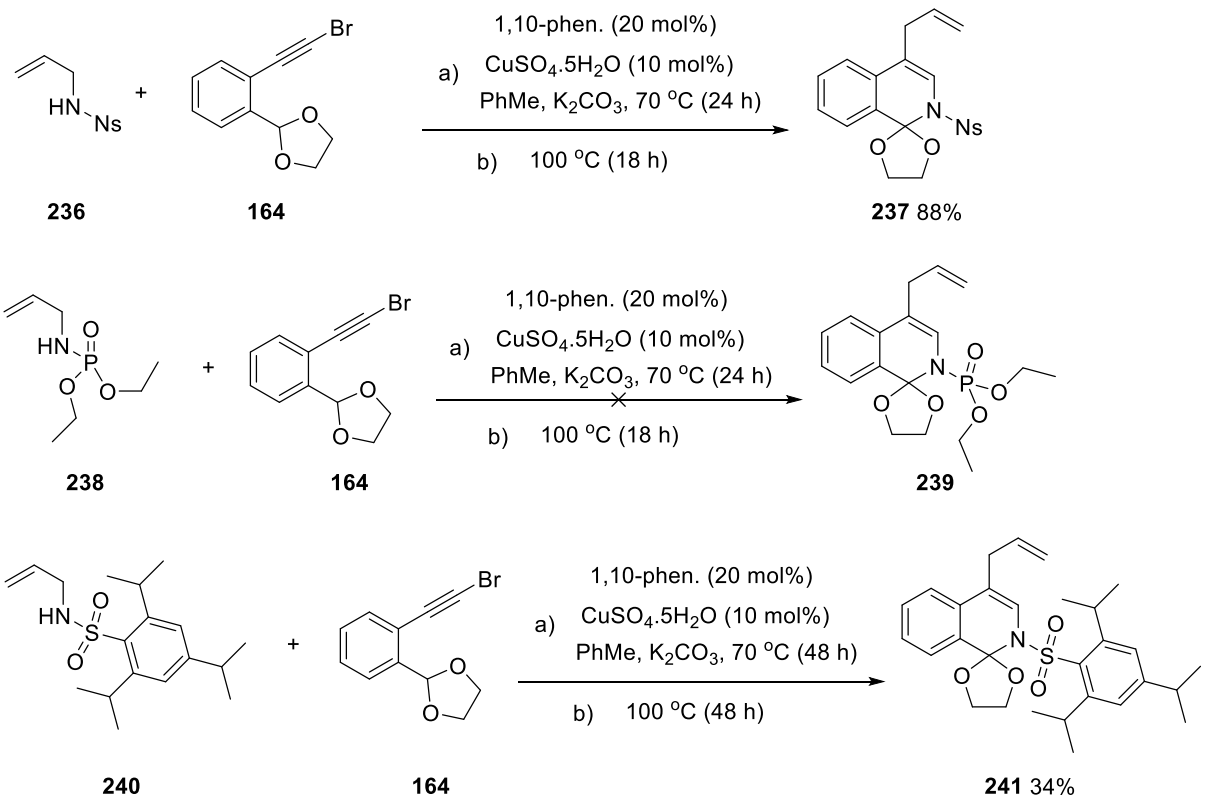


Scheme 52: Formation of ynamide 234 and its copper catalysis

The lack of reactivity in terms of diastereoinduction discouraged us from investigating other substrates containing chiral dioxolanes with ester groups.

3.4.6 Alteration of the protecting group

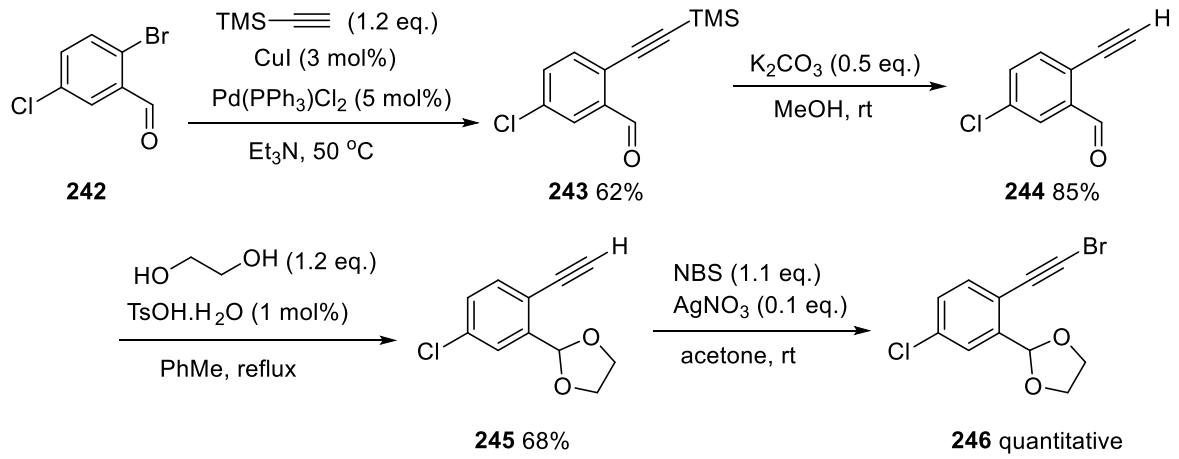
Mesyl and tosyl nitrogen protecting groups were all tolerated in our synthesis. For further elaboration, we attempted the synthesis of dihydroisoquinoline with different protecting groups (Scheme 53). Pleasingly, oxyisoquinoline **237** containing a nosyl group was formed in very high yield. Deprotection of the nosyl group may potentially open a new route for further functionalisation. No reactivity was observed with the reaction of bromoalkyne **164** and diethyl allylphosphoramide **238**. The starting materials were simply recovered. The formation of **241** containing triisopropylphenyl group is encouraging as it serves as an alternative to the tosyl group. Its low yield may be due to steric hindrance as some of *N*-allyltriisopropylbenzene sulfonamide **240** were recovered during flash column chromatography



Scheme 53 Oxyisoquinolines with different protecting groups

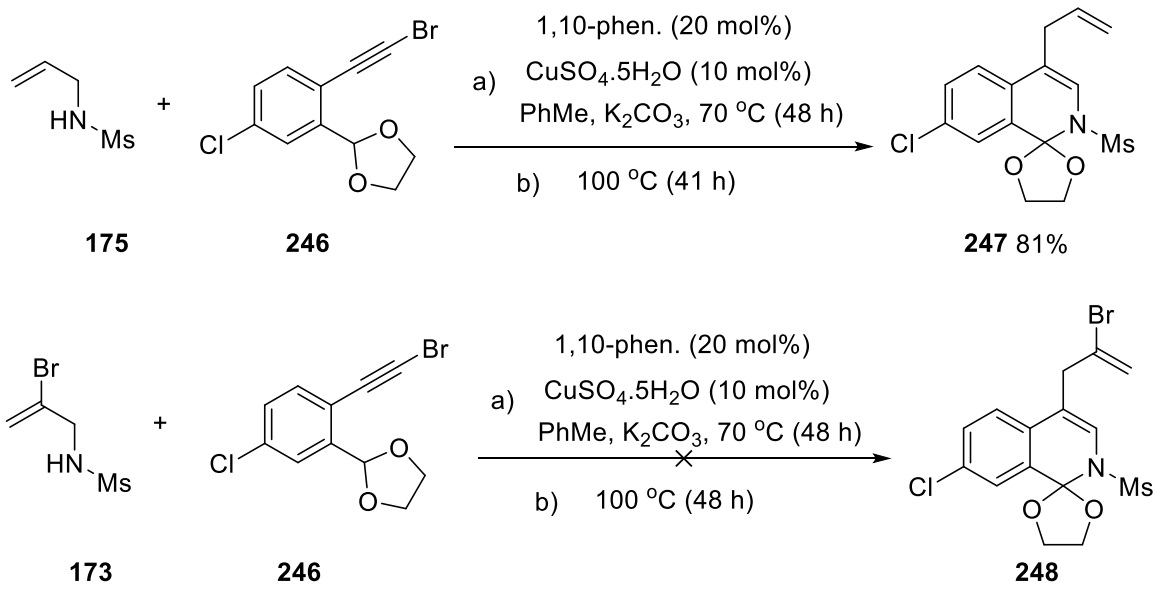
3.4.7 Modification of the connector tether.

The modification of the benzene ring acting as the hydride donor-acceptor linker or connector tether was then explored in our synthsesis to achieve alternative functionalised cyclic products. A chloro group was incorporated into the *meta*-position relative to the hydride donor and *para* relative to the hydride acceptor (Scheme 54). Sonogashira coupling of commercially available 2-bromo-5-chlorobenzaldehyde **242** with trimethylsilyl acetylene gave the protected alkyne **243**. Deprotection and subsequent acetal formation with ethylene glycol under acidic conditions, using a Dean-Stark trap furnished **245**. Bromination of acetal **245** using *N*-bromosuccinamide gave the bromoalkyne **246**, containing chloro group in a *meta* position relative to the acetal group in an excellent yield.



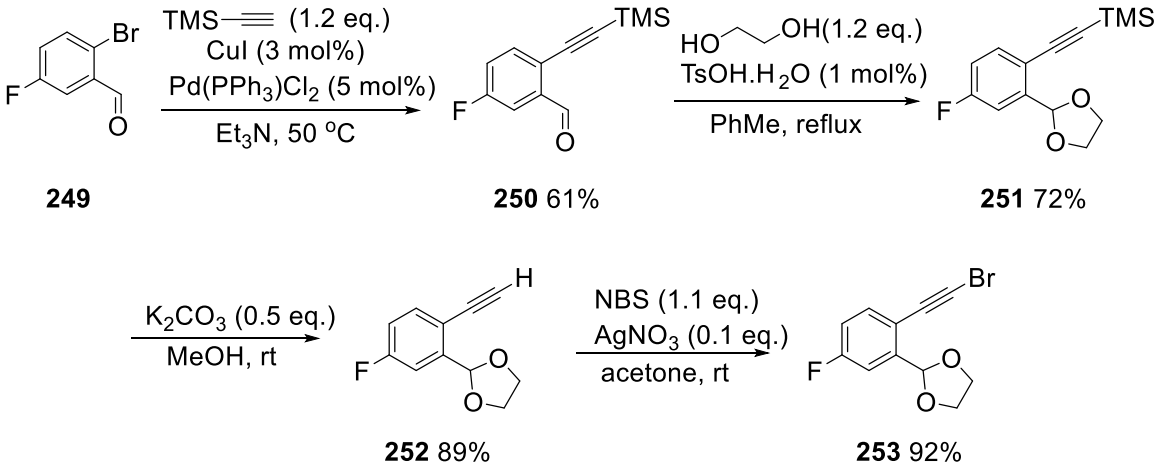
Scheme 54: Towards the synthesis of *para* chloro substituted bromoalkyne

The synthesised bromoalkyne was tried in the one-pot ynamide formation rearrangement with two different sulfonamides (Scheme 55). Clean reactivity was observed with the use of allylmesyl sulfnamide **175**, giving the desired product **247** in a very high yield. The reaction with the bromo-substitued sulfonamide **173** was not straight forward. Multiple spots were seen from the TLC analysis. After flash column chromatography, the desired product **248** was observed from ^{1}H-NMR spectroscopy but contaminated with solvents. However, efforts to get the complete data proved abortive as the product underwent degradation during the process of solvent removal and drying.



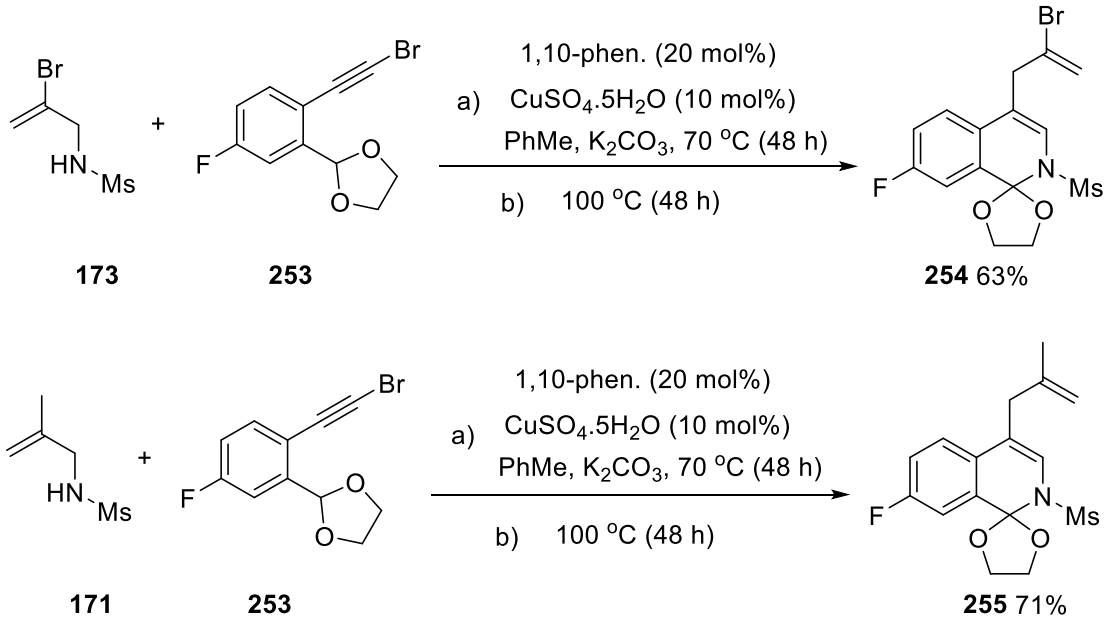
Scheme 55: Chloro-substituted oxyisoquinolines

The incorporation of a fluoro substituent in a *meta* position relative to the acetal was also explored. The same reaction sequence was followed commencing from the commercially available 2-bromo-5-fluorobenzaldehyde (Scheme 56)



Scheme 56: Installing a fluoro substituent in the *meta* relative to the hydride donor

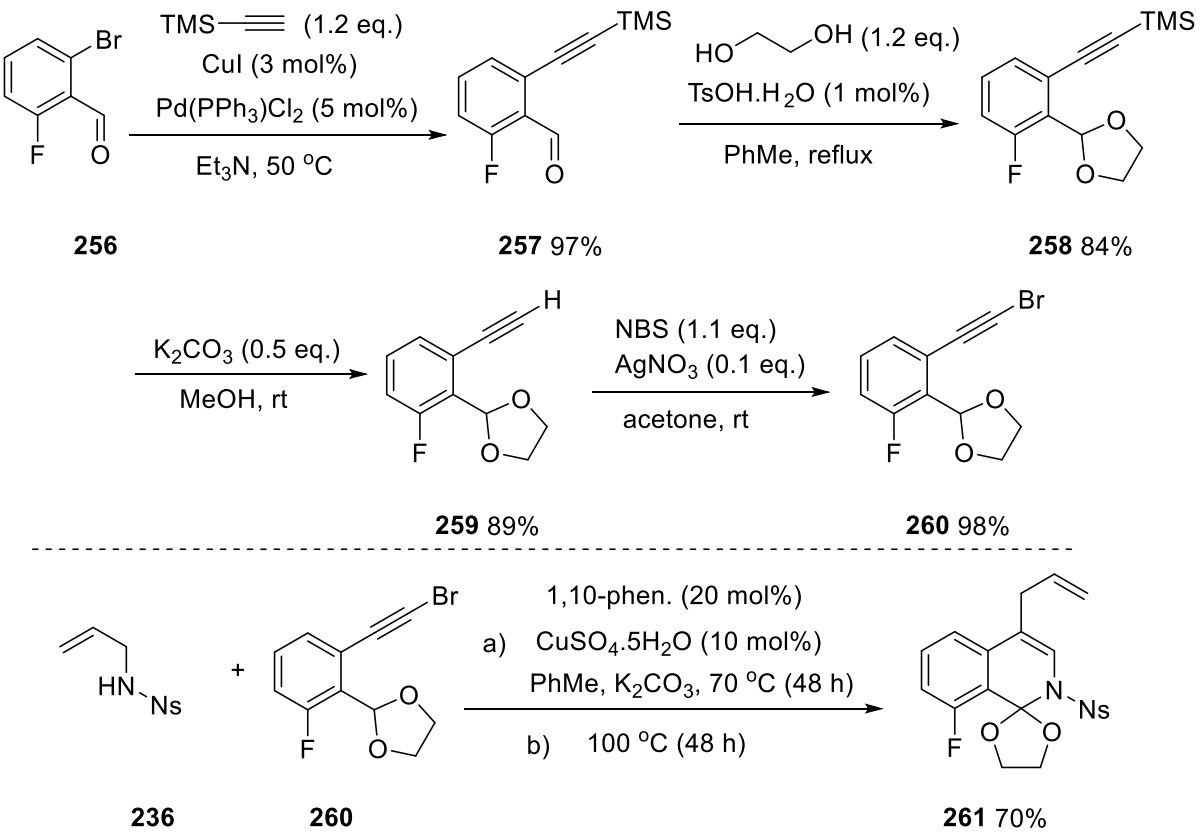
The one-pot cyclisation cascade was successful with the use of sulfonamides **171** and **173** (Scheme 57). The methodology enabled the formation of oxyisoquinolines with various heteroatoms.



Scheme 57: Fluoro-substituted oxyisoquinolines

This highlights the compatibility of our methodology in a convergent manner. Spiroisoquinoline **255** was formed in a high yield with no trace of degradation.

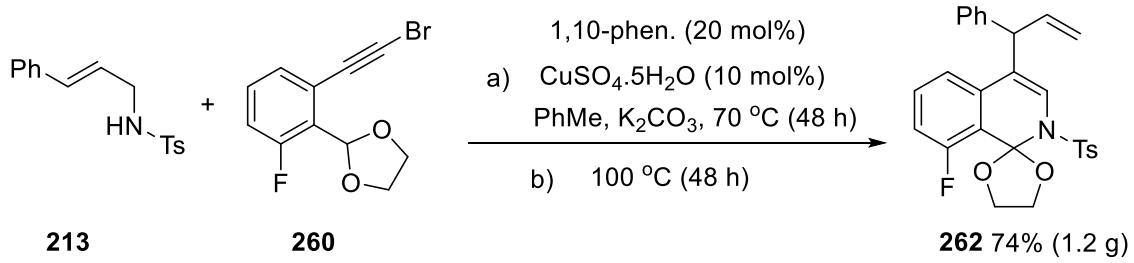
We also turned our attention to investigate the presence of a fluoro substituent on the connector tether in an *ortho* position relative to the hydride donor (acetal). We followed this strategy to see if there will be change in reactivity. Similarly, the same reaction sequence was followed starting from 2-bromo-6-fluorobenzaldehyde (Scheme 58)



Scheme 58: Oxyisoquinoline 261 with fluoro group in *ortho* relative to the acetal

The syntheses of the starting materials were more robust when compared with 2-bromo-5-bromobenzaldehyde. The one pot process gave the desired cyclic product **261** in high yield. The nosyl nitrogen protecting group was well tolerated in the synthesis.

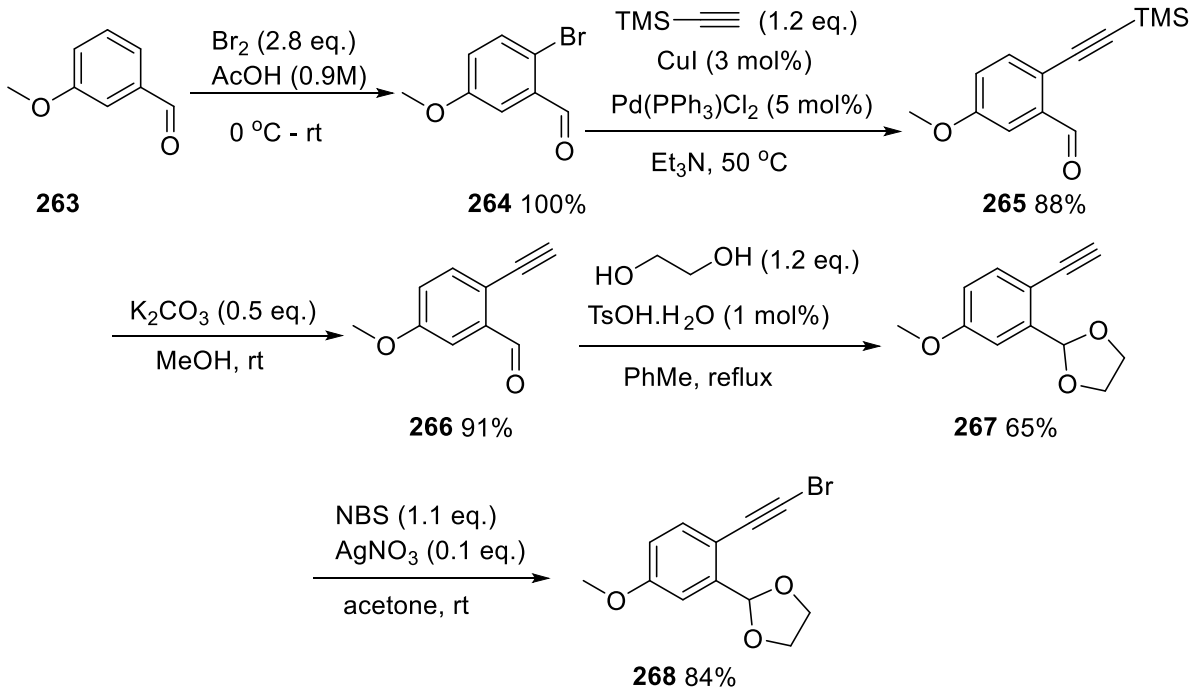
The scalability of the one-pot ynamide cyclisation cascade was demonstrated by the reaction of the alkynyl bromide **260** with *N*-tosylcinnamyl amine **213** (Scheme 59). Dihydroisoquinoline **262** was synthesised on a gram-scale in good yield.



213 **260** **262** 74% (1.2 g)

Scheme 59: Gram scale synthesis of 262

For further comparison, we explored the effect of an electron donating group (EDG) on the aromatic hydride donor-acceptor linker. The preparation of the alkynyl bromide with a methoxy group was achieved following the usual protocol (Scheme 60). Bromination of 3-methoxybenzaldehyde **263** generated 2-bromo-5-methoxybenzaldehyde **264** in quantitative yield. Subsequent Sonogashira coupling **265**, deprotection **266**, acetal formation **267** and bromination gave **268** in very high yield.



263 **264** 100% **265** 88%

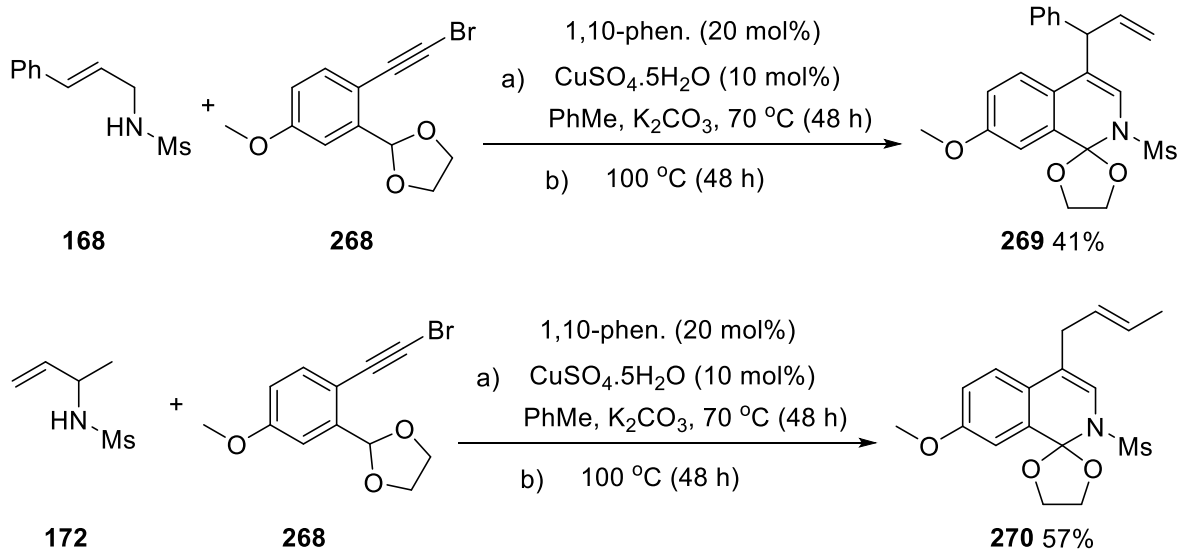
266 91% **267** 65%

268 84%

Scheme 60: Preparation of alkynyl bromide with an EWG

The one-pot cyclisation cascade involving substrate with an electron donating group furnished the oxyisoquinolines in moderate yields (Scheme 61). The electron rich, methoxy

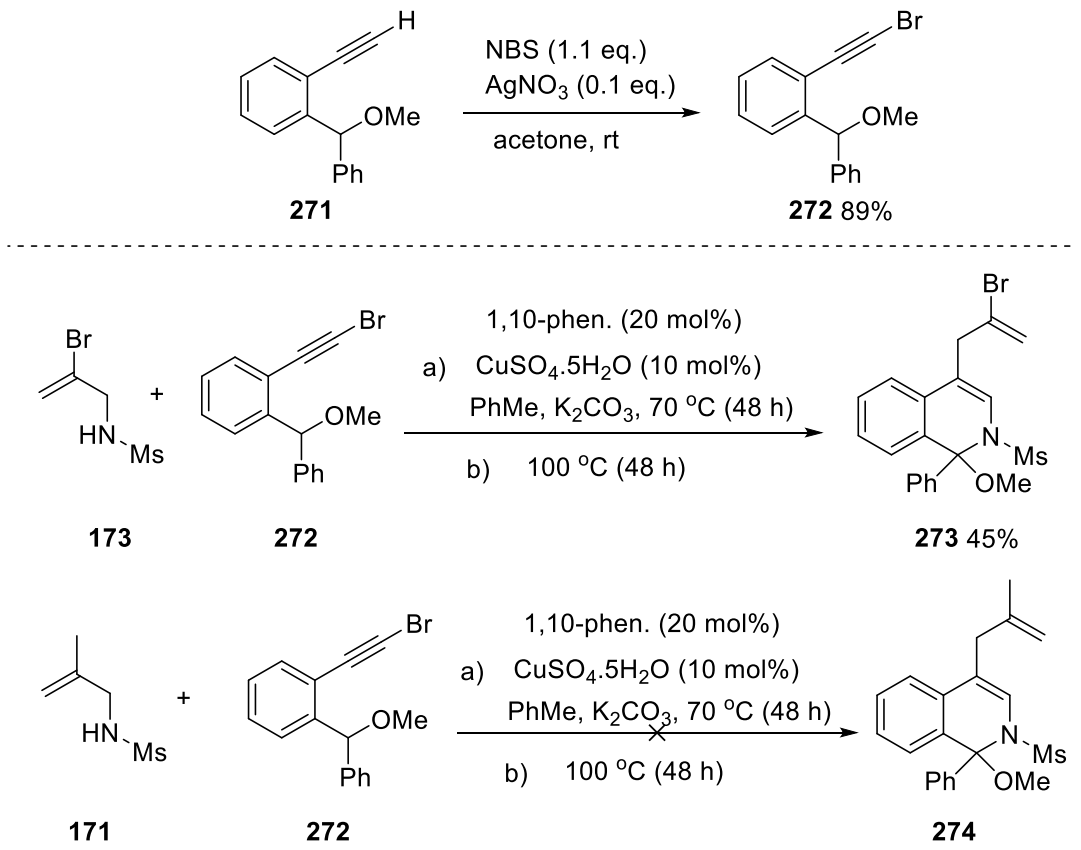
group which is in *para* position relative to the hydride acceptor can reduce the electrophilicity of the ketenimine generated through mesomerism. In addition, its *meta* position relative to the hydride donor can equally decrease the "hydricity" of the acetal via inductive effect.[75] It is likely that these two synergistic effects can contribute to the moderate yields of isoquinolines **269** and **270**. Similarly, the desired product **270** was isolated as a mixture of E/Z isomers in the ratio 0.5:1. The complexity of the ^{1}H-NMR spectroscopy prevented us from identifying the isomers.



Scheme 61: Effect of EDG on the aromatic connector tether

3.4.8 Modification at the benzylic position

The use of benzylic ethers as a hydride donor was explored (Scheme 62). We were particularly interested to observe if the benzhydric ether containing ynamide will react under the developed one-pot cascade cyclisation as previous investigation in the group showed their reactivity in the presence of CuI, K_2CO_3 and toluene to form oxyisoquinolines.



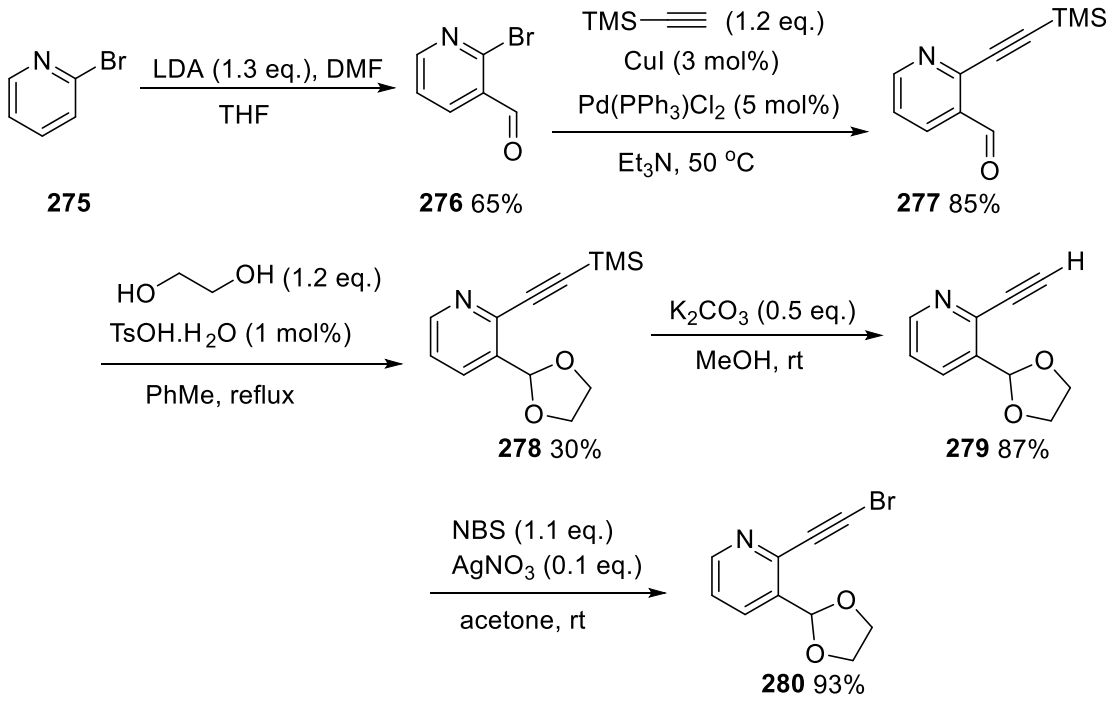
Scheme 62: Systems with benzylic ethers under cyclisation

Terminal alkyne **271** was available in the group made by Holly Adcock. Bromination of **271** was achieved in a very high yield. One pot process of **272** with bromoallyl sulfonamide **171** gave dihydroisoquinoline **273** in moderate yield. In addition, we did not observe the formation of isoquinoline as a result of neighbouring-group elimination and desulfonylation as indicated by Holly Adcock when she tried such systems under copper catalysis.[71] Full conversion was not achieved as the starting materials were not all consumed. Complex reaction mixtures were obtained from the formation of **274**. TLC analysis indicated three spots but their purification and isolation was not fruitful

3.4.9 Heteroaromatic linkages

In the proposed mechanism, the [1,5] hydride transfer is accompanied with a corresponding disruption of aromaticity in the benzene ring. We became interested in looking at the

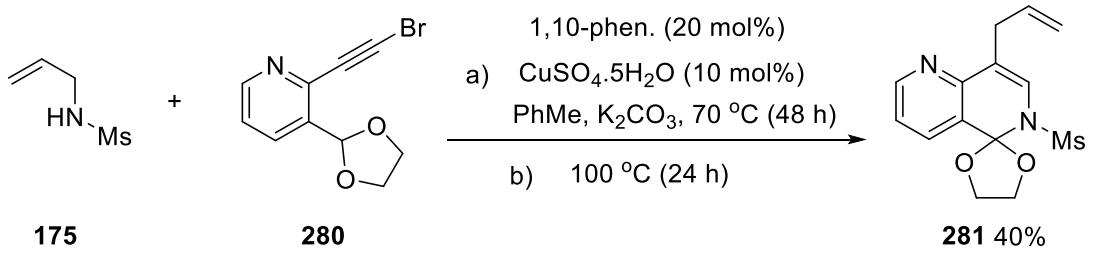
possibility of incorporating other aromatic systems apart from benzene in the cascade reaction. We reasoned that the degree of aromaticity of such systems may affect the outcome of the reaction and potentially provide access to desirable substrates containing hetero-aromatic motifs. To achieve this, alkynyl bromide with pyridine ring was was synthesised (Scheme 63) in order to subject it to copper catalysis.



Scheme 63: Towards the synthesis of pyridine derived alkynyl bromide

Formylation of the 3-position of freshly distilled 2-bromopyridine with lithium diisopropylamide gave **276** in moderate yield. The purity of 2-bromopyridine is vital as slight impurities from the commercially available reagent can shut down the reaction completely. Sonogashira coupling of **276** gave the silyated alkyne **277** in high yield. Acetalisation with ethylene glycol gave the acetal **278** in poor yield. Increased reaction yield of **278** was not achieved as degradation occurred upon longer reaction time. Deprotection **279** and subsequent bromination furnished the pyridine derived alkynyl bromide **280**. However,

upon removal of solvent using rotary evaporator, the clear solution turned into a black and sticky solution. The ^{1}H-NMR spectrum of the black solution was clean and clearly showed the correct signals of the alkynyl bromide product with no seen impurities. It was used immediately in the one pot cyclisation cascade (Scheme 64).

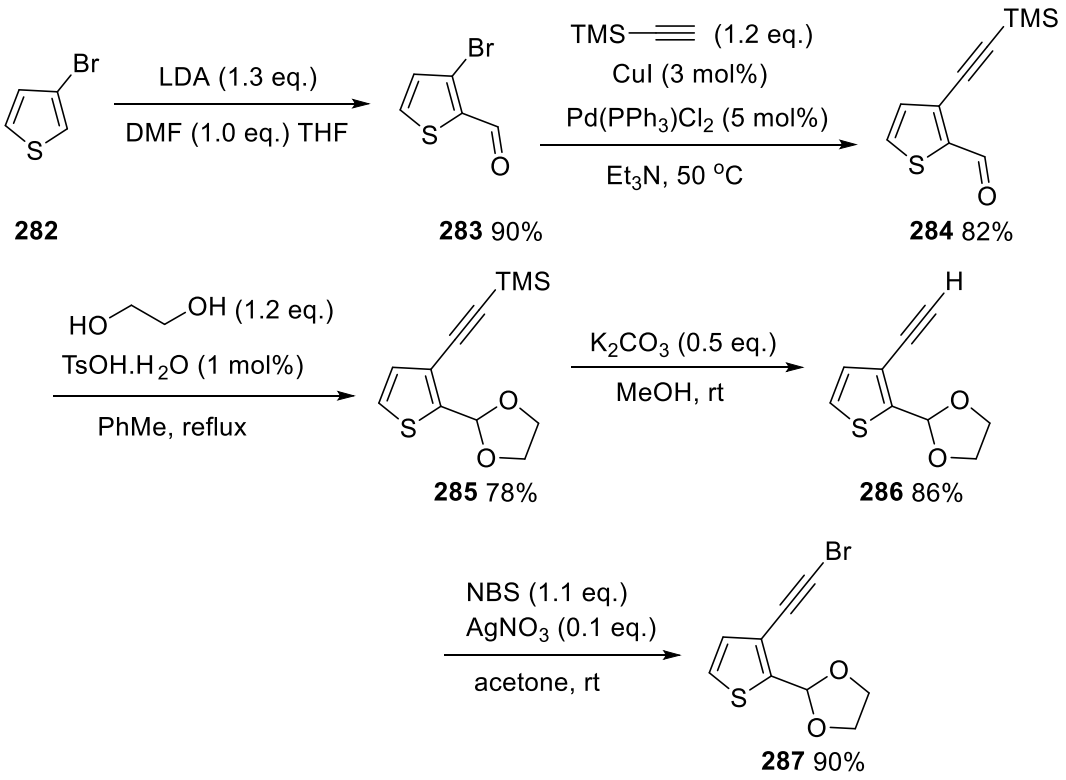


175 **280** **281** 40%

Scheme 64: Pyridine ring system under copper catalysis

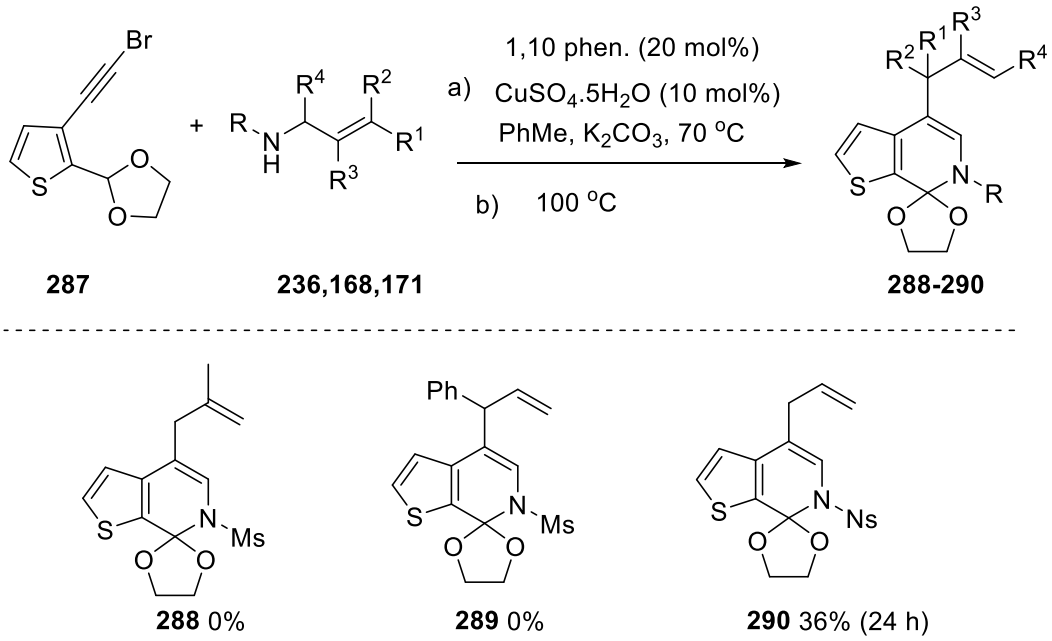
The pyridine derived alkynyl bromide **280** underwent the desired reaction with allylmesyl amine **175** to form the spiroisoquinoline **281** in moderate yield. This methodology has proved the ability to access diverse heteroaromatic compounds fused together. Not all the sulfonamide was consumed in the reaction and the alkynyl bromide **280** was not very soluble in toluene. This may account for the moderate yield of the cyclic product **281**.

Following up on the studies on pyridine based cyclic product, the synthesis of thiophene-derived alkynyl bromide was attempted using the usual reaction sequence. (Scheme 65)



Scheme 65: Formation of thiophene derived alkynyl bromide

The catalysis profile of the copper catalysis of **287** with different sulfonamides is shown in (Scheme 66). Complex mixtures and degradation were seen in the formation of **288** and **289**. Moderate yield was obtained for the formation of **290** with nosyl protecting group.



287 **236,168,171** **288-290**

288 0% **289** 0% **290** 36% (24 h)

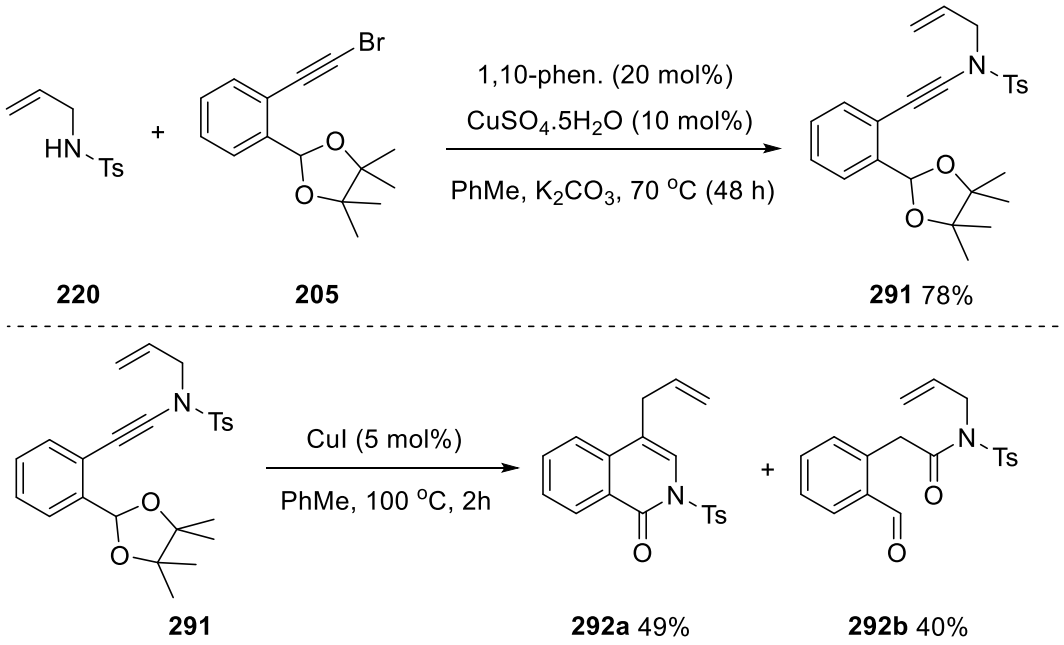
Scheme 66: Thiophene based system under copper catalysis

However, the cyclic product is not very pure as some impurities which cannot be removed by flash column chromatography exist.

3.4.10 Reactivity of other ynamides.

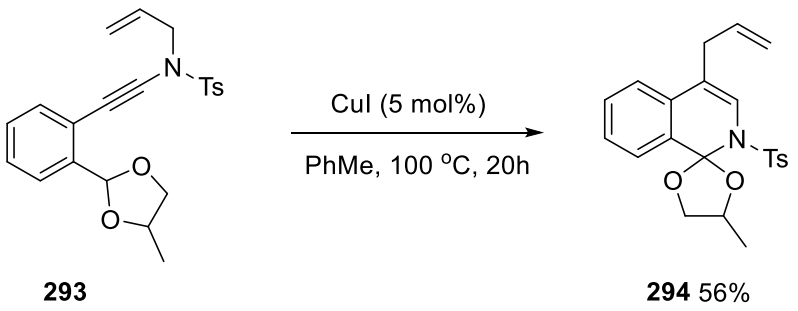
Some interesting ynamides were made for their reactivity in gold-catalysed reactions. We decided to subject some of them under the optimised conditions developed by Holly Adcock and observe their reactivity towards copper catalysis. Pinacol acetal derived ynamide **291** was synthesised and subjected to the optimised condition of copper catalysed cyclisation reaction (Scheme 67). Interestingly two spots were seen on TLC and the purification and isolation of the reaction mixture revealed the formation of **292a** and **292b** in moderate yields. Cyclic product **292a** was the desired product of copper catalysed cyclisation cascade, but in its deprotected form as the pinacol acetal was cleaved under the reaction conditions. The substituted benzaldehyde product **292b** arose from the direct addition of water across the triple bond and cleavage of pinacol acetal. The source of water that is responsible for

this side product is likely to come from the solvent or an air ingress into the reaction mixture. The reaction was quite fast as it took only two hours to go to completion.



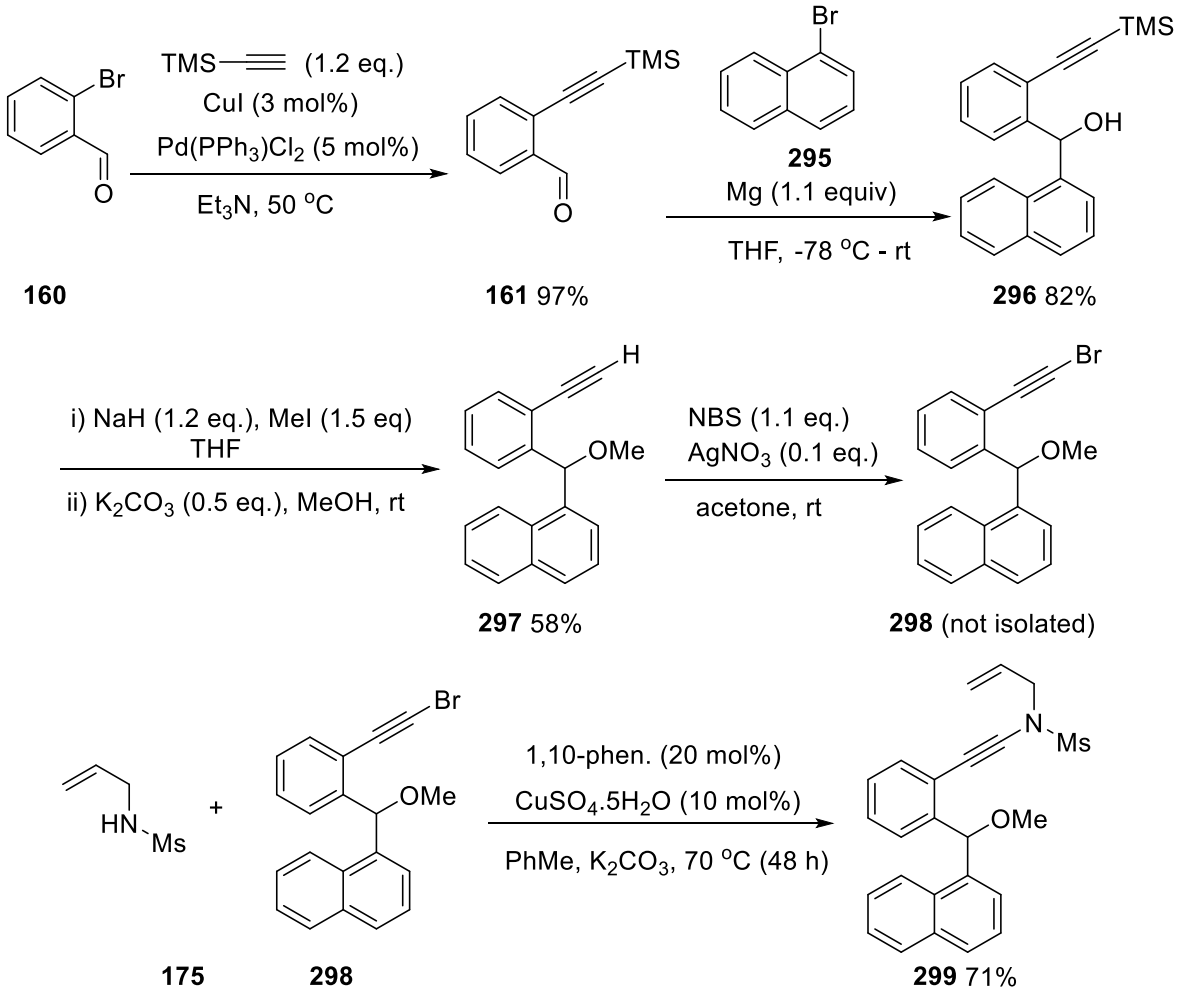
Scheme 67: Synthesis and copper catalysis of pinacol acetal derived ynamide 291

Ynamide **293** containing an acetal made from propylene glycol was donated by Holly Adcock and was investigated. (Scheme 68). Clean reactivity was seen with the formation of spiroisoquinoline in moderate yield. The moderate yield could not be accounted for as no side products were seen in the reaction mixture.



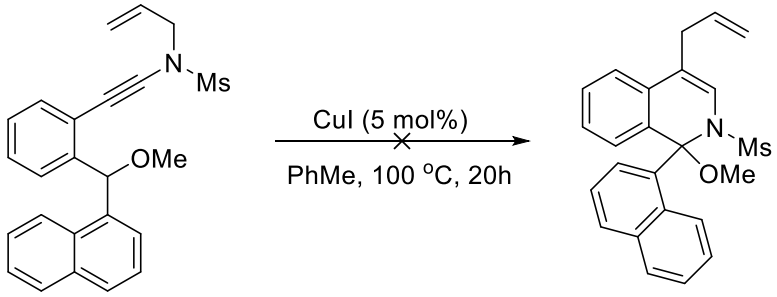
Scheme 68: Cyclisation cascade of ynamide 293

Exploration into the use of benzydric ether-containing ynamides followed next. Naphthalene-containing ynamide **299** was prepared in six steps (Scheme 69). Sonogashira coupling of 2-bromobenzaldehyde **160** with trimethylsilylacetylene gave the protected alkyne **161**. Treatment of protected alkyne **161** with freshly prepared Grignard reagent **295** generated the secondary alcohol **296** in high yield. Methylation and deprotection of secondary alcohol **296**, all in one pot led to the formation of terminal alkyne **297**. Bromination of **297** gave the alkynyl bromide **298** which was used immediately in the next step. Copper catalysed coupling of bromoalkyne **298** with allyl sulfonamide **175** furnished the ynamide **299** in good yield.



Scheme 69: Preparation of naphthalene containing ynamide

Under copper catalysis, ynamide **299** was not compatible with the one pot cascade reaction (Scheme 70). Whilst ynamide **299** was consumed in the reaction, a complex mixture was generated prior to purification.

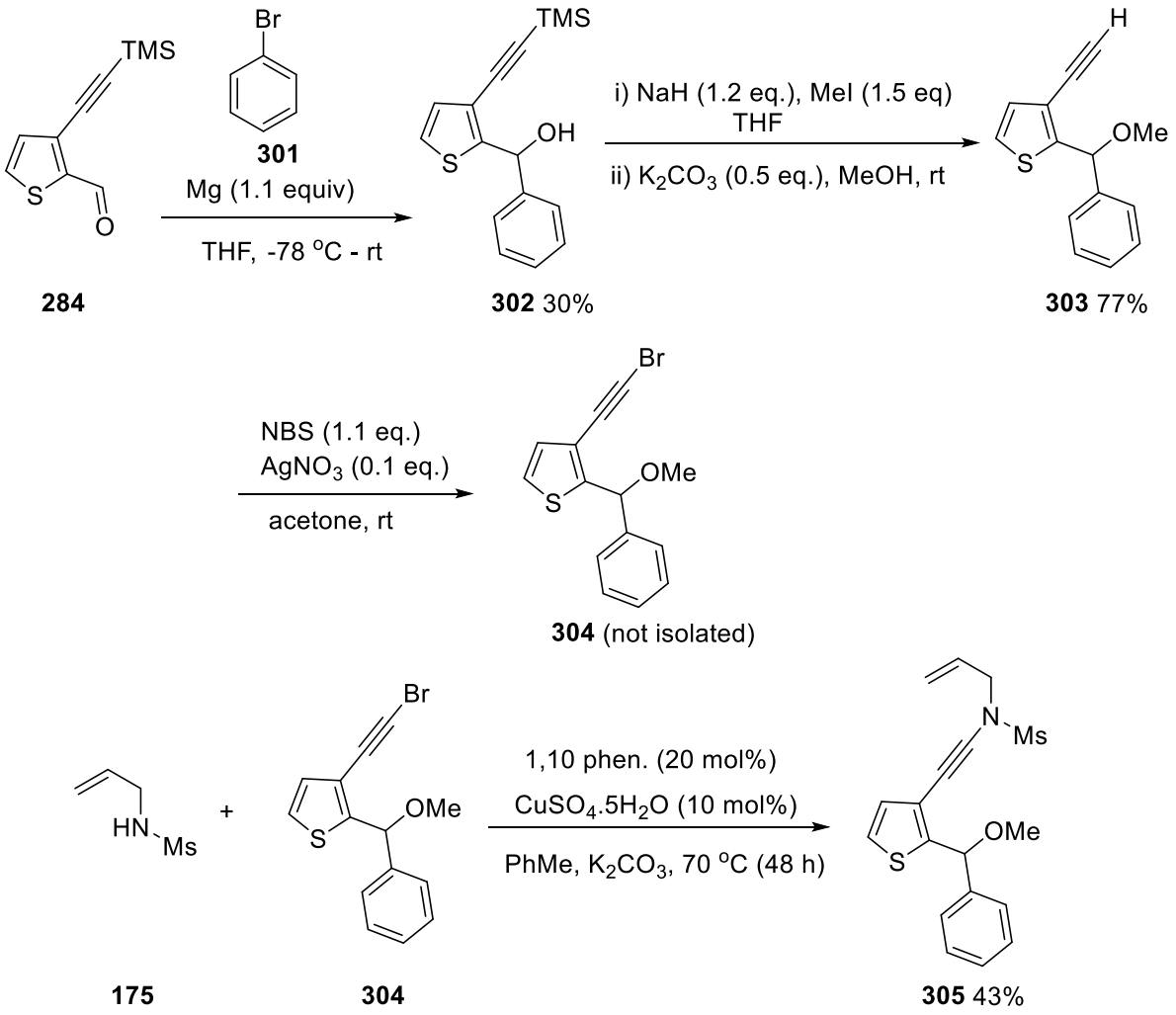


299 **300**

Scheme 70: Naphthalene containing ynamide under copper catalysis

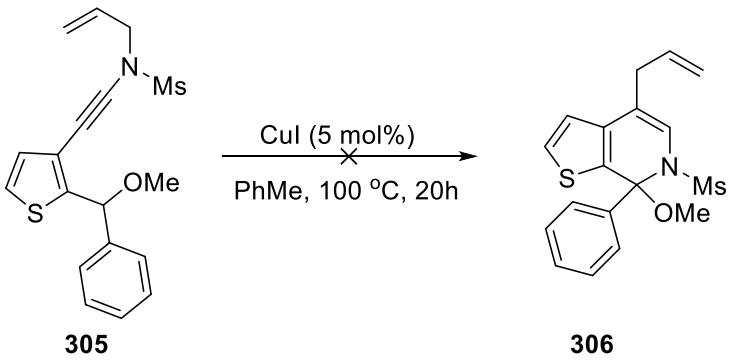
Isolation by flash column chromatography failed due to the complexity of the mixture. Change in solvent to *m*-xylene and increased reaction temperature did not improve the reaction.

A different benzydric ether ynamide **305** was made via the same reaction sequence as the naphthalene containing one **299** (Scheme 71).



Scheme 71: Formation of benzydric ether ynamide 305

Disappointedly, the copper catalysed rearrangement cascade of ynamide **305** failed (Scheme 72). Complex mixtures and degradation were observed. The unsuccessful results led us not to probe other substrates.



305 **306**

Scheme 72: Ynamide 305 under copper catalysis

4. Conclusion

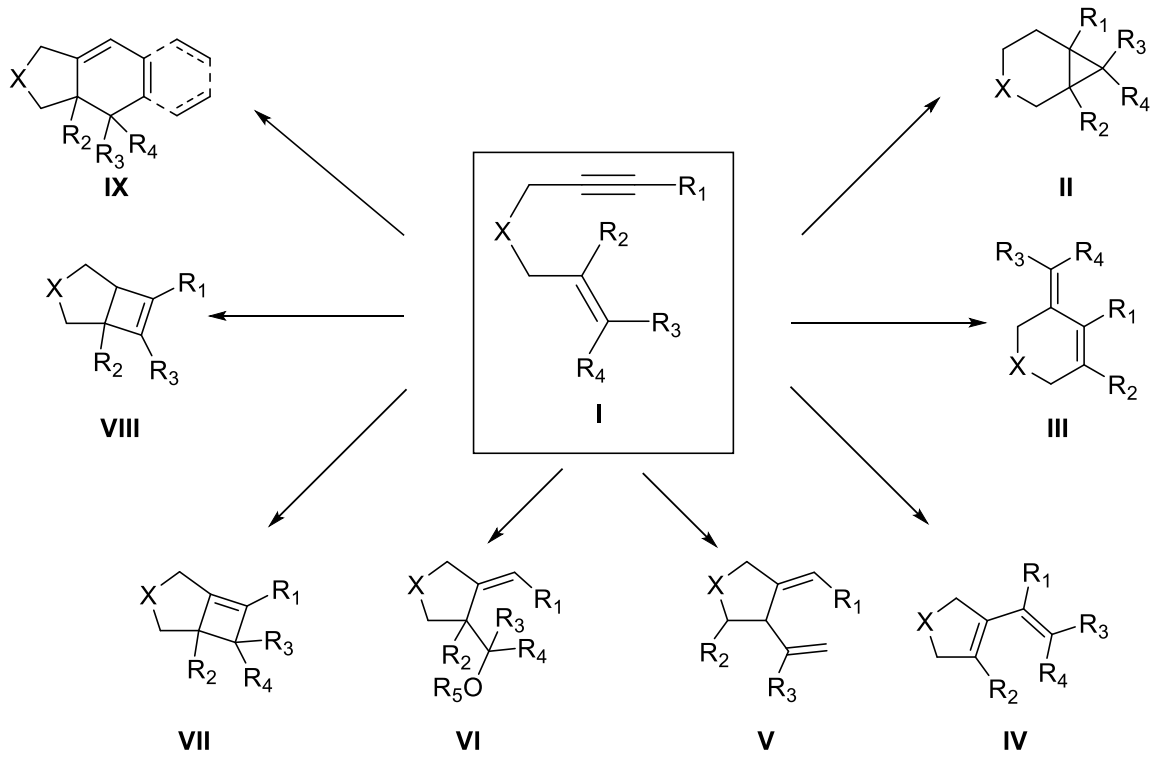
A one pot carbon-nitrogen bond formation and rearrangement cascade sequence has been developed in which ynamide formation is followed by [1,5]-hydride transfer/cascade cyclisation to synthesize oxyisoquinolines with the use of an environmentally benign, inexpensive copper catalyst. Exploration of the substrate scope and limitations have allowed access to highly functionalised fused heterocycles. The introduction of various groups in the novel isoquinolines can serve as synthetic handles for further cross-coupling reactions. In the developed one pot process, an initial aza-Claisen rearrangement, subsequent [1,5]-hydride transfer and 6π electrocyclisation has generated diverse fused pyridine derivatives from moderate to excellent overall yield.

Chapter 3
Cycloisomerisation of ene-ynamides

1. Introduction.

As seen in the previous chapter, the use of ynamides as starting materials to access functionalised heterocycles under transition metal catalysis is of much interest in our group. Apart from copper, the use of gold catalysts to achieve novel transformations has also been at the centre of our research and modification of ynamides can provide alternative pathways for new reactions. In line with this perspective, numerous studies on the transition metal-catalysed reactions have been explored[76-78]. In the midst of these reactions, transition metal catalysed cycloisomerisation of enynes has been widely explored because of the accessibility of substrates with different functionalities and diversities, derived from simple starting materials[3, 79-83]. Among the enynes,1,6-enynes have proved to be versatile substrates for cycloisomerisations due to their ease of preparation and change in functionality (Scheme 73)[3, 84, 85]

Generally, electrophilic activation of the alkyne component by a π Lewis acid brings about the nucleophilic attack of the alkene fragment, which triggers the entire skeletal transformation. Studies have indicated that the various pathways are also dependent on the nature of substrates and catalyst used[3, 86]. The numerous pathways of cycloisomerisation of 1,6-enynes can generate six membered alkenes, five membered heterocycles with a diene moiety,cyclobutenes and other tricyclic products, all with different functionalities. Following the importance of cycloisomerisation to generate different interesting products, the transition metal-catalysed versions will be discussed in the subsequent sections.



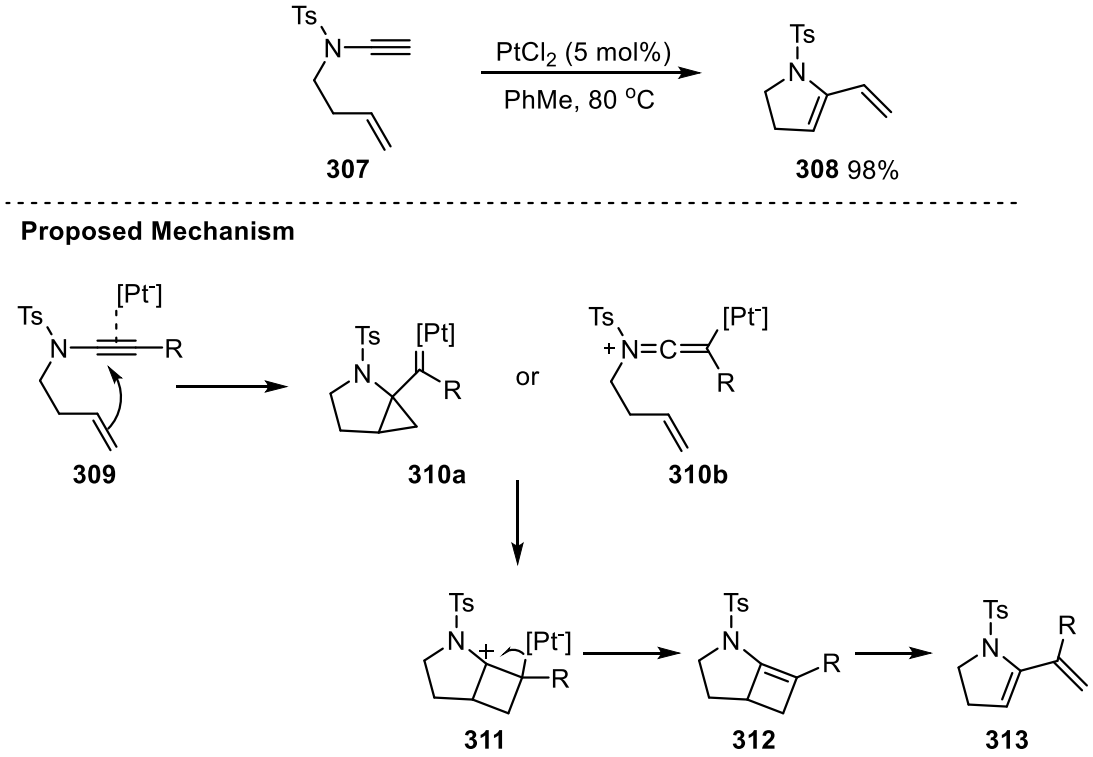
Scheme 73: Reaction pathways of 1,6-enyne cycloisomerisation

2. Transition metal catalysed cycloisomerisation of 1,6-enynes

2.1 Platinum catalysed cycloisomerisations.

Malacria and co-workers reported the Pt(II)-catalysed cycloisomerisation of 1,6-ene-tosylynamides affording a five-membered nitrogen heterocycle containing 1,3-diene moiety **308** (Scheme 74)[87]. According to the proposed mechanism, the electrophilic activation of the triple bond in **309** by the platinum catalyst followed by the nucleophilic attack of double bond of alkene generates the platinum cyclopropyl carbene intermediate **310a** or keteniminium species **310b**. Ring opening of cyclopropylplatina carbene **310a** generates the zwitterion **311** and subsequent demetalation forms cyclobutenamide **312**. The nitrogen heteroatom provides some sort of stabilisation to zwitterion **311**. Finally, electrocyclic ring opening of **312** furnishes the desired product **313**. This mechanism is supported by the theoretical DFT calculations carried out by the research groups of Soriano[88] and

Echavarren[89]. It is equally important to note that this mechanism holds true for other transition metal complexes or salts including gold,palladium and ruthenium[88]. From a different pathway, the generation of keteniminium species as supported by Hsung and co-workers[90] can form the cyclobutyl cation **311** via [2 + 2] cycloaddition. Subsequent steps can equally lead to the formation of the cyclic product **313**

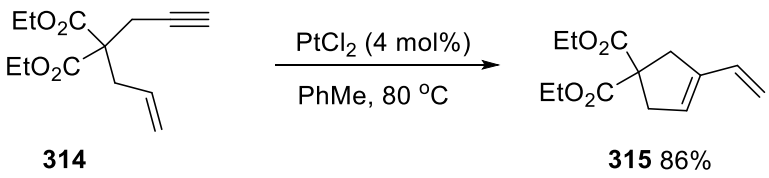


Scheme 74: Platinum-catalysed cycloisomerisation of ene-ynamide 307

Extending the reaction sequence to 1,7-ene-ynamides gave cyclobutanones due to hydrolysis of enamines[91]. The substrate scope was limited to ene-ynamides with a terminal alkyne moiety.

In a similar version, Murai and co-workers investigated the cycloisomerisation of 1,6-enynes under platinum catalysis (Scheme 75)[92]. Substrate scope ranged from mono-substituted alkenes to di and tri-derivatives. They found out that the use of platinum complexes with

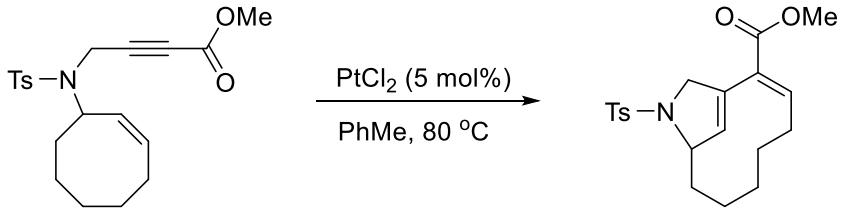
different coordinating ligands inhibited the reaction, proving that the presence of halide ions was necessary for the reaction to proceed.



314 **315** 86%

Scheme 75: Cycloisomerisation of 314 under platinum catalysis

Furstner and co-workers explored the use of cycloisomerisation to macrocyclic synthesis[93, 94]. Treatment of enyne **316** with platinum(II)chloride gave the diene **317** containing a ten-membered ring (Scheme 76). Dienes containing twelve-and fourteen-membered rings were also synthesised. The build-up of high complexity from simple starting materials was remarkable. The methodology was extended to the synthesis of streptorubin B and metacycloprodigiosin, that belong to the prodiginine family of antibiotics[95]



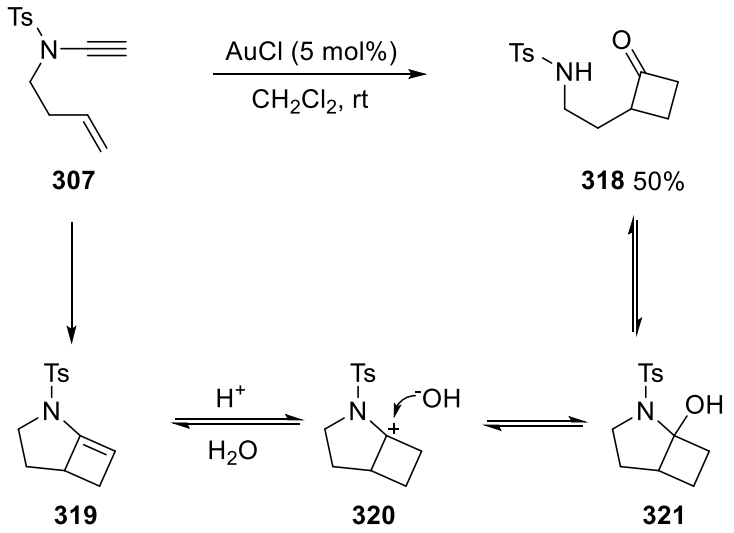
316 **317** 85%

Scheme 76: Cycloisomerisation of 316

2.2 Gold catalysed cycloisomerisation

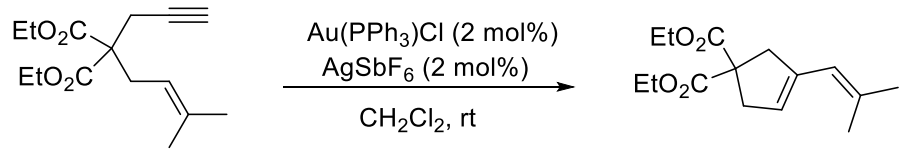
The reactivity of 1,6-ene-ynamides under gold catalysis was investigated by the research group of Couty (Scheme 77)[96]. Ene-ynamide **307** gave rise to cyclobutanone **318** when reacted with gold(I)chloride at room temperature. The product of the cycloisomerisation

was different when the same substrate was employed under platinum catalysis (see scheme 74). The mild reaction condition promoted the hydrolysis of cyclobutenamide intermediate **319** that is generated according to the proposed mechanism (Scheme 77) to yield the final product **318**. The exposure to air during work-up of the crude reaction mixture was assumed to be the source of water that resulted in hydrolysis. Cyclobutanones were equally obtained when the substrates were extended to 1,7-ene-ynamides. No product with dienamide moiety was isolated. The substrate scope was limited to ene-ynamides with terminal alkynes,trimethylsilyl and propargylic alcohol moieties



Scheme 77: Gold-catalysed cycloisomerisation of 307

In 2004, Echavarren and co-workers reported the synthesis of 1,3-dienes **323** from the cycloisomerisation of 1,6-enynes **322** in the presence of a gold(I)complex (Scheme 78)[97]. The reaction followed the same pathway as those reported under platinum catalysis[92]



322 **323** 91%

Scheme 78: Cycloisomerisation of enyne using gold(I)complex

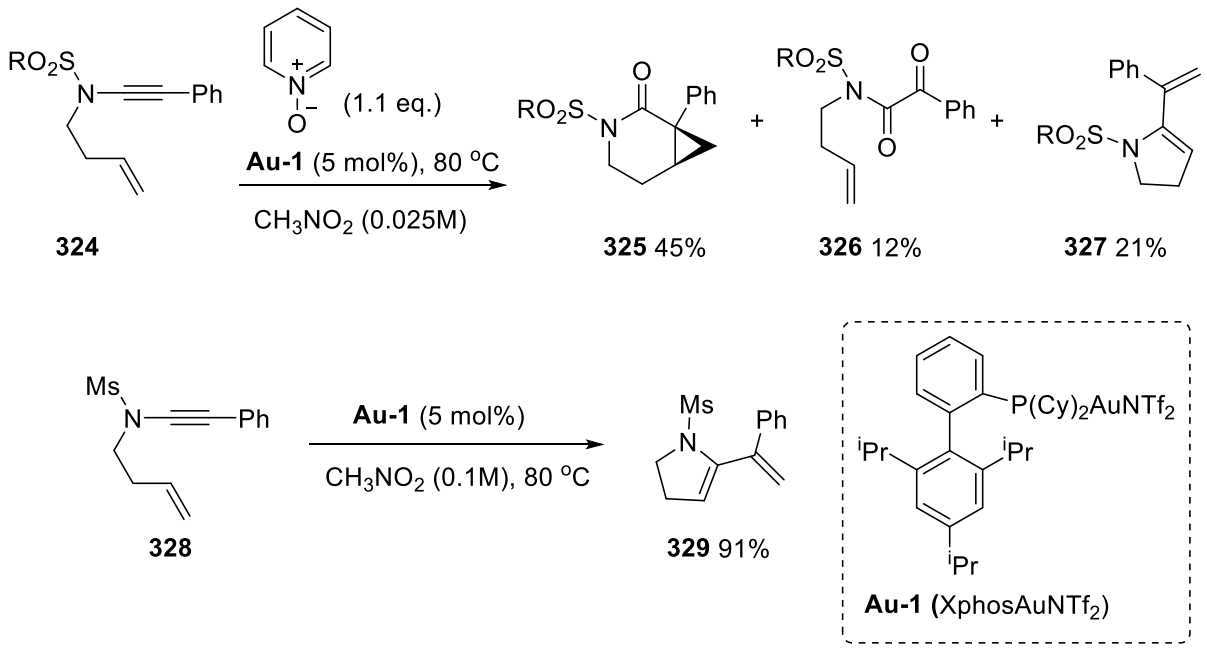
Similarly Gagosz and co-workers discovered that the use bis(trifluoromethanesulfonyl)imidate (Tf_2N^-) as a counteranion in the gold complex can promote the same reaction[98], hence the use of $Au(PPh_3)NTf_2$ gave comparable results.

Despite the huge advances recorded in the field of cycloisomerisation, limitations still exist for the synthesis of heterocycles containing dienamide moiety via gold catalysis. In the same vein, most of the previous investigations of substrate scope were mainly limited to terminal alkynes[99, 100]. The extensive work on the reactivity of ynamides under gold catalysis[9, 101, 102], being carried out in our group encouraged us to investigate the gold-catalysed cycloisomerisation of substituted ene-ynamides.

3 Results and discussion

3.1 Reaction design

The reactivity of ynamides under oxidative gold catalysis was ongoing in our group when it was discovered that the treatment of 1,6-ene-ynamide **324** in the presence of an *N*-oxide can generate the desired cyclopropane **325** alongside the over-oxidised product **326** and the cycloisomerised product **327** (Scheme 79)



Scheme 79: Cyclopropane formation under oxidative gold catalysis

Keen to increase the yield of cycloisomerised product **327**, Fernando Sanchez-Cantalejo (a member of Davies group) did some optimisation studies and discovered that **329** can be generated in an excellent yield when ene-ynamide **328,** was subjected to gold(I)complex,**Au-1 .** Higher concentration of nitromethane was required to achieve this result. Following the optimisation of the reaction, we decided to investigate the functionalisation of these five membered nitrogen heterocycles with dienamide moiety by exploring the substrate scope (Figure 2).

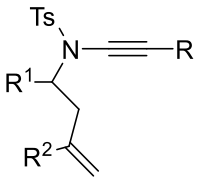


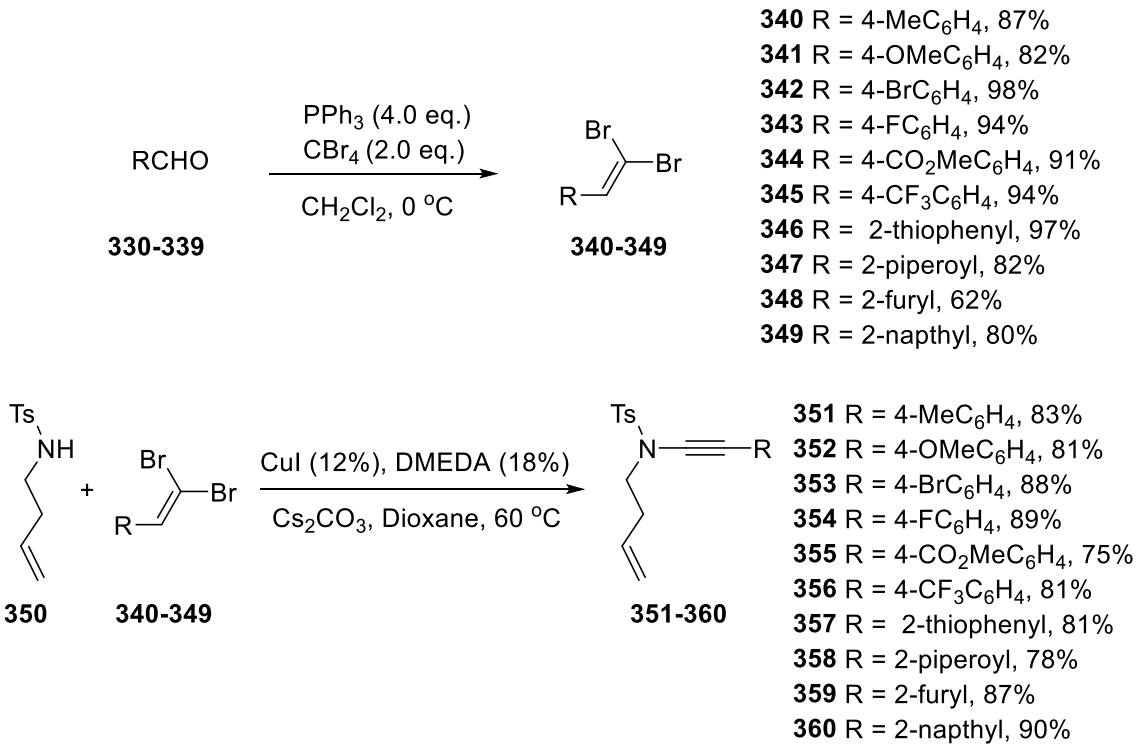
Figure 2: Variations of 1,6-ene-ynamide towards gold catalysis

Variations at the C-terminus of alkyne, substituents on the α-position of nitrogen and groups on the alkene region can generate heterocycles that can be remarkable.

3.2 Variations at the C-terminus of alkyne

To explore the reactivity of substituted ene-ynamides towards gold catalysis, 1,6-ene-ynamides bearing various groups at the C-terminus of alkyne were prepared in a two-step sequence (Scheme 80)

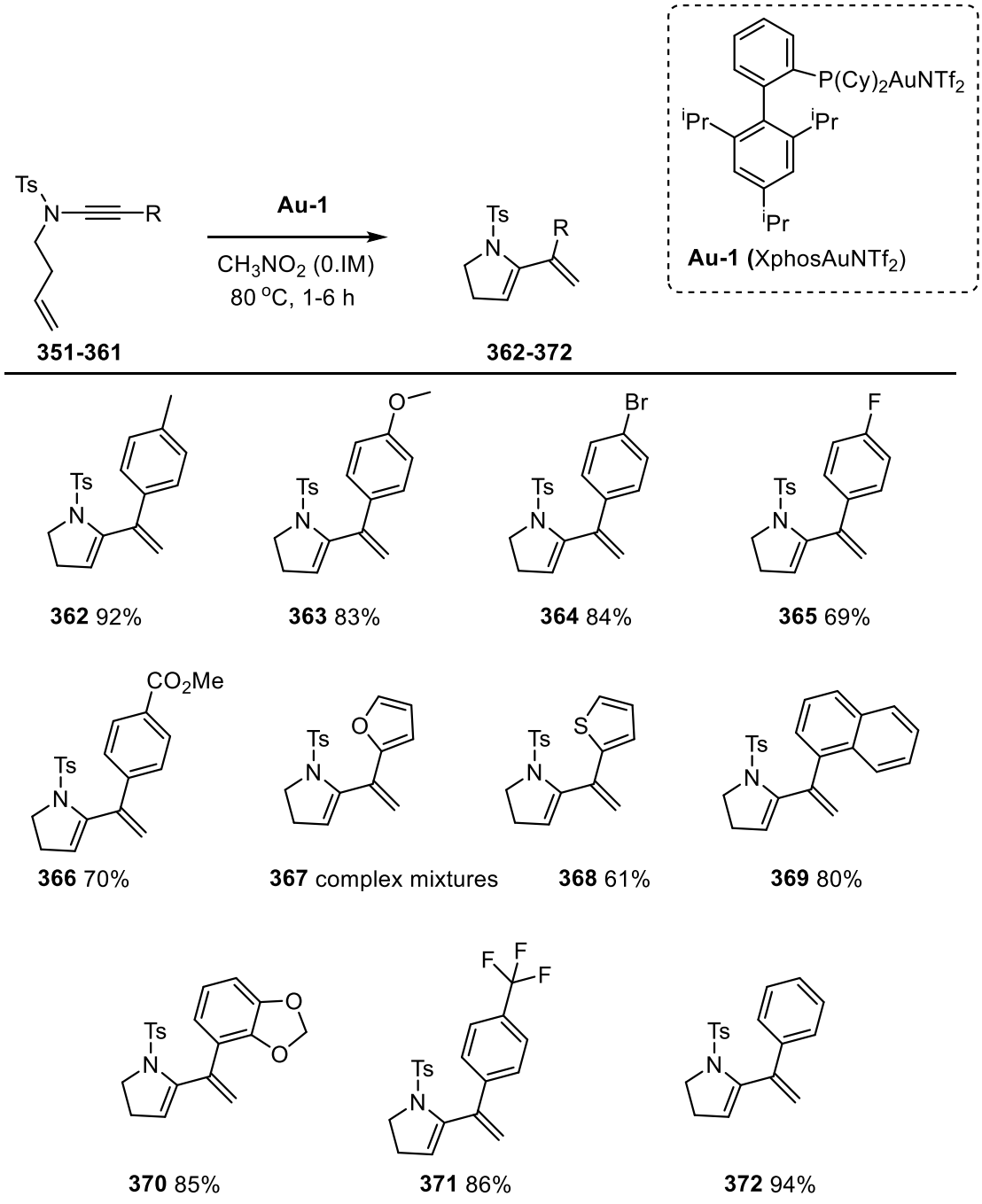
Starting from the commercially available aromatic aldehydes **330-339**, treatment with tetrabromomethane gave the corresponding dibromo olefins **340-349** from good to excellent yields. In most cases, the crude reaction mixtures were pure enough that no flash column chromatography was required. Access to functionalised ene-ynamides **351-360** was achieved by the copper-catalysed cross coupling of homoallyl sulfonamide **350** with dibromo olefins **340-349** by the method used by Evano and his research group[14]. Yields ranged from good to excellent ones and groups with different electronics were accommodated



Scheme 80: Synthesis of substituted ene-ynamides

With the optimised conditions at hand, the substituted 1,6-ene-ynamides **351-360** where subjected to gold catalysis (Scheme 81). Intriguingly they were reactive under the optimised conditions thereby generating highly functionalised five membered nitrogen heterocycles containing 1,3-diene moieties. Fast and clean reactivity (1 h) were observed in all substrates except **364** and **366** that were generated in four and six hours respectively. The cycloisomerisation chemistry generated motifs with electron rich substituents **362-363** in excellent yields. Similarly the catalysis was compatible with electron deficient groups **366** and **371**. Halo substituted products **364-365** were equally tolerated.

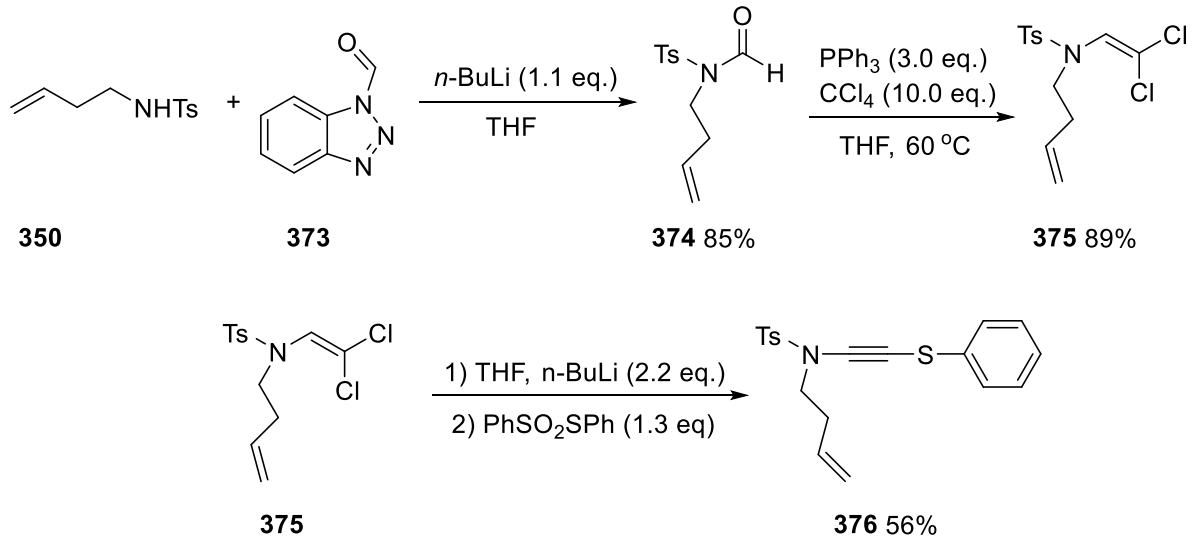
Introduction of heteroaromatic group was possible with the generation of the cyclised product **368** in moderate yield. Furan derivative **367** gave a complex mixture under the reaction conditions and purification by flash column chromatography led to massive degradation as observed by ^{1}H-NMR spectroscopy. Reduction of the reaction temperature did not improve the outcome of the reaction as degradation was also seen. Other bicyclic aromatic systems **369** and **370** showed high reactivity in the cycloisomerisation conditions. Generally, it should be noted that the catalysis does not necessarily require a dry solvent as the synthesis of the carbocyclic products **362**, **363**, **365**, and **368** were also achieved with nitromethane obtained directly from the reagent bottle.



Scheme 81: Substrate scope for the formation of 5-membered heterocycle with dienamide moiety

Following the successful synthesis of cyclic dienamide bearing a thiophene group **368**, we decided to explore the reactivity of thio-ynamides towards gold catalysis as the generation of dienamides with a thio group will provide an alternative functionalised heterocycle that can be interesting and potentially useful motifs. Thio-ynamide **376** was made in a four step

reaction sequence (Scheme 82). Reaction of sulfonamide **350** with formylbenzotriazole **373** gave the tolylated formamide **374** in good yield. Formamide **374** was converted to vinyldichloride **375** with tetrachloromethane and triphenylphosphine.

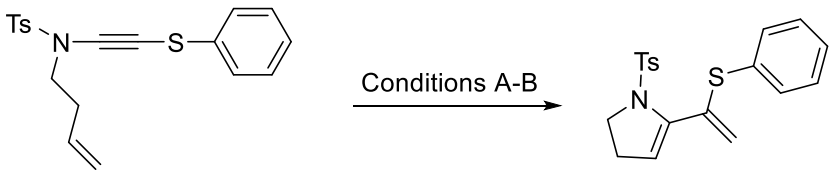


Scheme 82: Synthesis of thio-ynamide

Subsequent treatment of tolylated vinyldichloride **375** with *n*-butyllithium and trapping it with the electrophile-phenyl benzenethiosulfonate furnished the thio-ynamide **376** in moderate yield.

The cycloisomerisation of thio-ynamide **376** under the optimised reaction conditions failed to generate the desired product in reasonable yield (Scheme 83). Although the starting material was consumed at a longer reaction time (24 h), complex mixtures along with degradation were seen as there are many spots located on TLC. The ^{1}NMR spectrum of the crude reaction mixture showed some signals relating to the desired compound and subsequent purification by flash column chromatography afforded the dienamide in less than 10% yield. In addition, ^{1}NMR spectra of other fractions collected appeared to be very

messy. The change in condition to the use of a different gold(I)catalyst-**Au-2** and different solvent-dichloromethane did not improve the yield as complex mixtures were seen.



376 **377** <10%

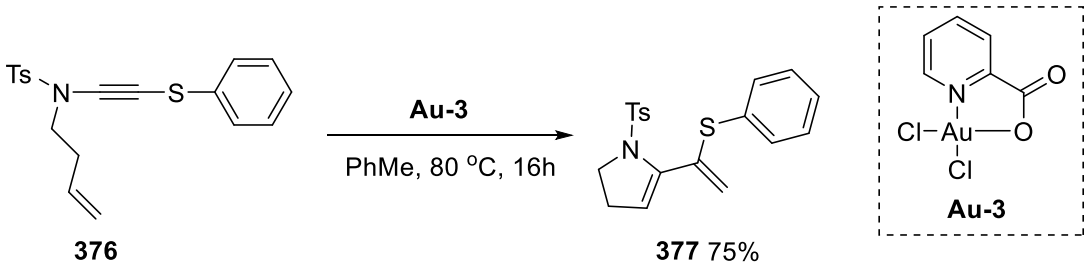
Conditions:

A. **Au-1** $XphosAuNTf_2$ (5 mol%), CH_3NO_2, 80 ^oC, 24 h

B. **Au-2** PPh_3AuOTf (5 mol%), CH_2Cl_2, rt, 24 h

Scheme 83: Thio-ynamide 376 under gold catalysis

The use of commercially available catalyst dichloro(picolinate)gold(III) (**Au-3**) changed the course of the reaction (Scheme 84). Treatment of thio-ynamide **376** with the gold(III) precatalyst in the presence of toluene, promoted the cycloisomerisation reaction affording the cyclic dienamide **377** in very good yield. Longer reaction time was recorded in converting the starting material into the desired product as the reaction was completed in 16 h.

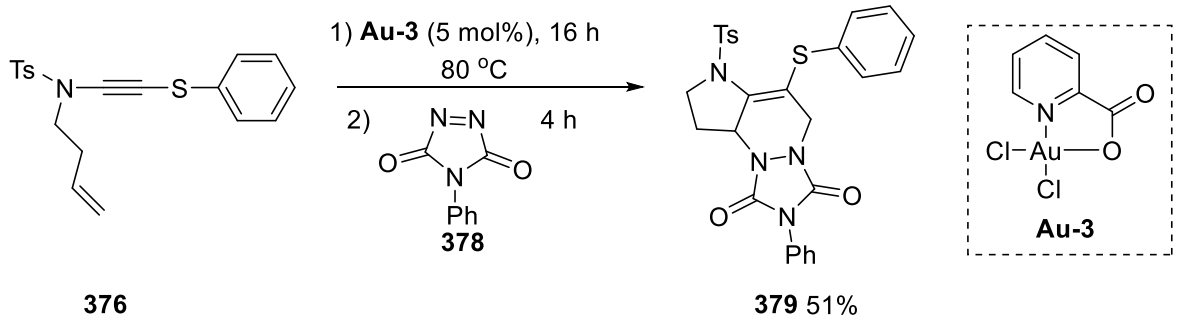


376 **377** 75%

Scheme 84 : Formation of cyclic dienamide from thio-ynamide 376

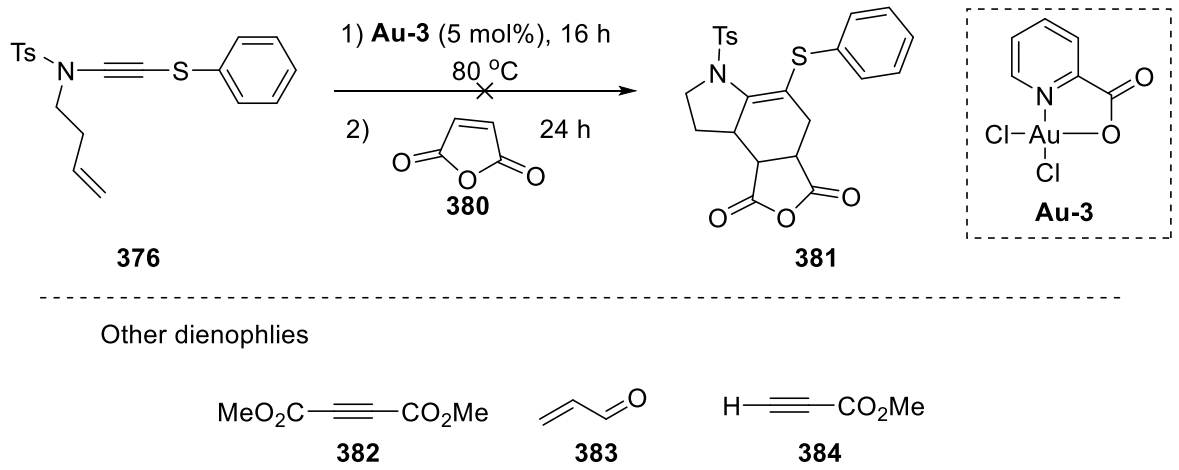
Further reactivity of cyclic dienamide with a thio group **377** was shown by one-pot reaction of thio-ynamide **376** with 4-phenyl-1,2,3-triazoline-3,5-dione **378** (Scheme 85). Injection of triazoline-3,5-dione into the reaction mixture, immediately after the formation of the

desired cycloisomerised product (as seen by TLC) generated the tricyclic product **379** in good yield. The overall reaction time was 20 h.



Scheme 85: Further reactivity of thio-ynamide under gold catalysis

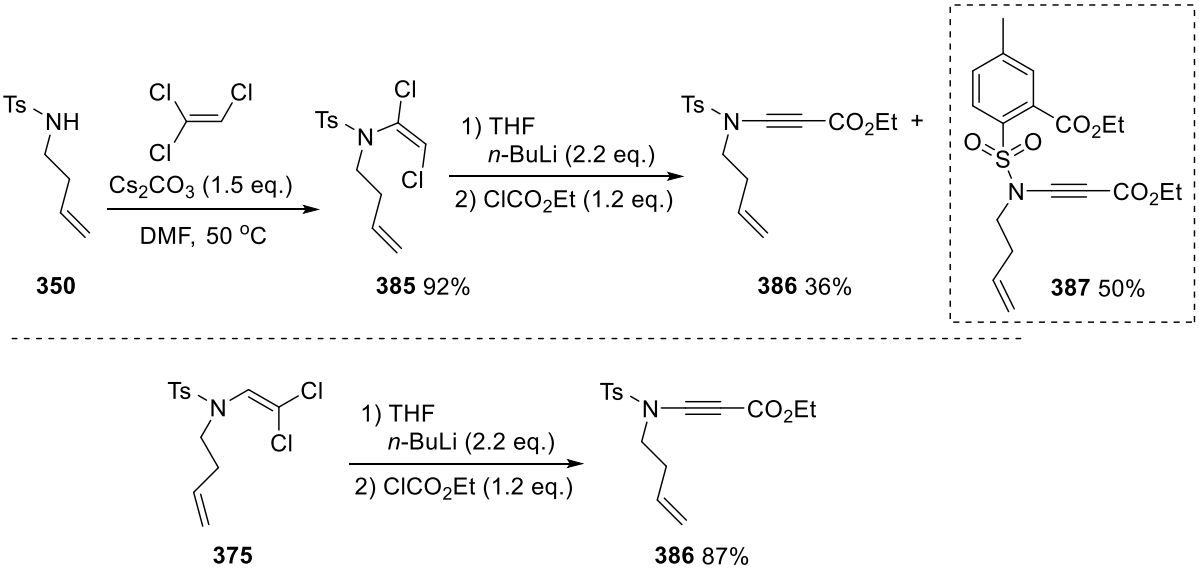
Intrigued with the successful synthesis of tricycle **379**, attention was focused on the use of dienophiles in the one-pot sequence since the gold-catalysed cycloisomerisation protocol produces a heterocycle with a dienamide moiety which can be considered as a good precursor for a Diels-Alder reaction. Furthermore, toluene has been successfully used to drive Diels-Alder reactions[103]. Exploration of Diels-Alder reaction started with the use of maleic anhydride **380** as a dienophile (Scheme 86). Unfortunately, no reactivity was observed as the cycloisomerised diene product **377** was isolated at the end of the reaction.



Scheme 86: Diels-Alder reaction with dienamide generated in situ

Further increase of the reaction temperature to 100 °C and longer reaction time (48 h) did not improve the outcome of the reaction. Employment of other dienophiles like dimethyl ethylenedicarboxylate **382**, acrolein **383** and methyl propiolate **384** showed absolute no reactivity in the reaction sequence. In each case, the cyclic dienamides generated in situ were all recovered. The observed non-reactivity seen in these reactions can be explained by the presence of the thio-group or other substituted groups located on the exo-cyclic double bond of cyclic dienamide **377**. It is reasoned that groups on the exo-cyclic double bond of cyclic dienamide cause some sort of distortion thereby preventing the diene from adopting the *s-cis* conformation which is a requirement for dienes to undergo Diels-Alder reaction. Such distortion can push the dienamide into the non-reactive conformer hence no reaction.

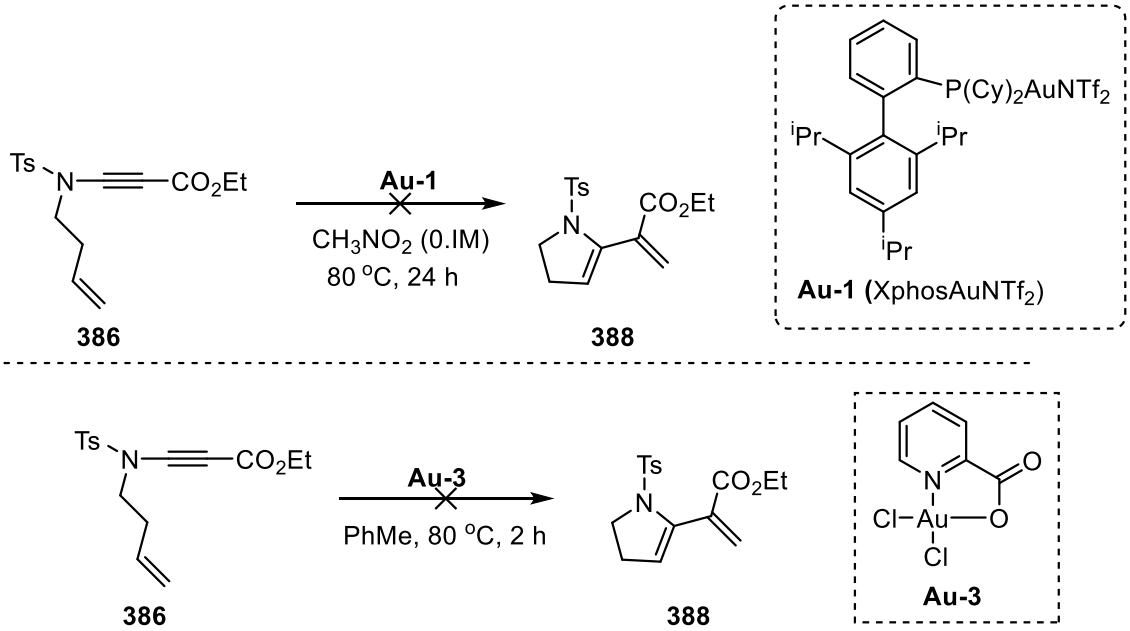
Additional substituent effect on the alkyne region of ene-ynamide was equally investigated by the incorporation of an ester group (Scheme 87)



Scheme 87: Formation of ene-ynamide with ethoxycarbonyl group

The reaction protocol of ynamide synthesis developed by Anderson and co-workers was used in the formation of **386**[104]. Reaction of homoallyl sulfonamide **350** with trichloroethene gave the 1,2-dichloroenamide **385** in excellent yield. Further treatment with *n*-butyllithium and trapping with an electrophile-ethyl chloroformate generated ene-ynamide **386** in low yield, together with a side product **387** in moderate yield. The side product orginated as a result of deprotonation of phenyl hydrogen of the tosyl group and was isolated as the major product. The result was rather strange as the authors[104] did not report the occurrence of such side products in their synthesis especially when tosyl groups are used. The reaction was carefully examined and performed by very slow addition of the base and electrophile while maintaining the low temperature that is required of the reaction. Dry conditions of reaction in terms of solvent and reaction vessel were strictly adhered to. These actions did not improve the reaction as the side product **387** was continuously isolated as the main product. The exact reason for this outcome is unknown to us. Alternatively the method used by Mori and co-workers[103] was followed which employs the use of tolylated vinyldichloride **375** and the desired ene-ynamide **386** was isolated in very good yield without any side product.

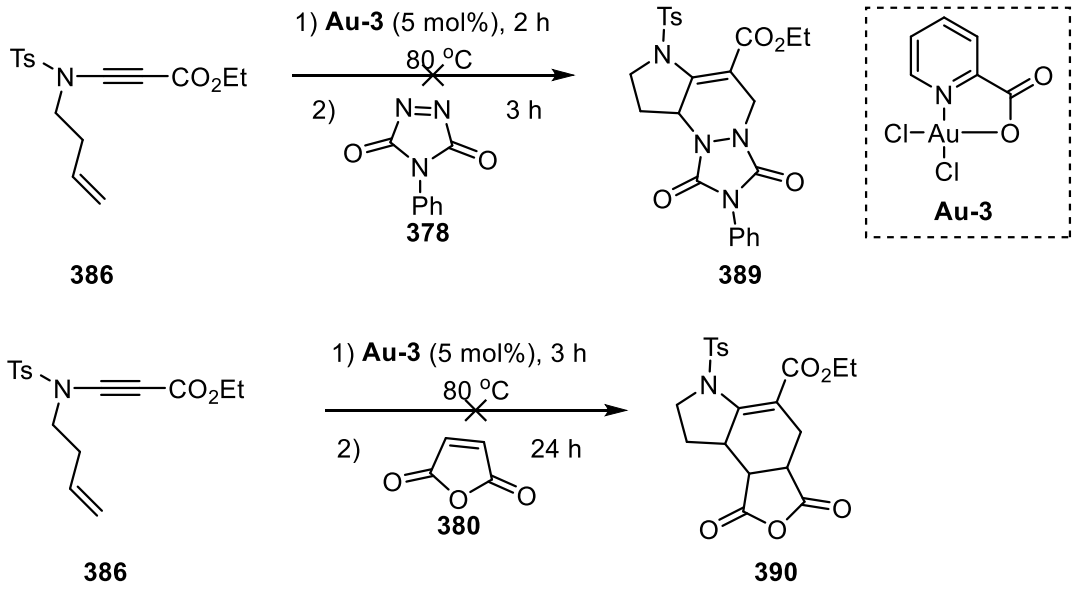
Ene-ynamide with ester group **386** was not compatible with the optimised conditions of the cycloisomerisation protocol (Scheme 88). Complex mixtures accompanied with massive degradation were observed and purification of the crude mixture was abortive.



Scheme 88: Cycloisomerisation of 386

Whilst purification was not achieved, clean and rapid reactivity was seen when ynamide **386** was treated with gold(III) precatalyst ,as monitored by TLC. The ^{1}H-NMR of the crude reaction mixture indicated the formation of the desired diene **388**. However, purification by flash column chromatography was unsuccessful as degradation was observed.

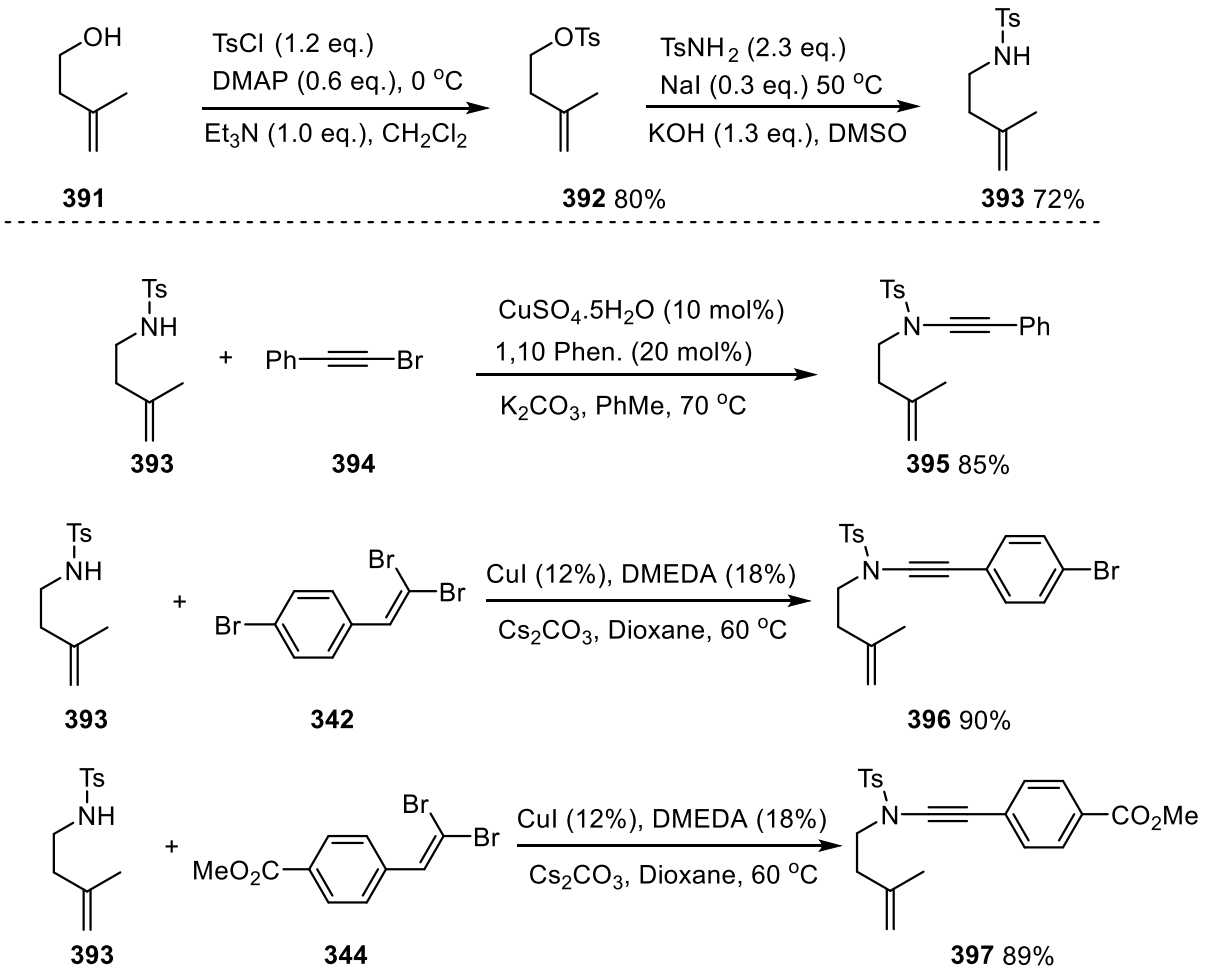
In the same context, alternative functionalisation of **386** was carried out (Scheme 89). No reactivity was observed when **386** reacted with 4-Phenyl-1,2,4-triazoline-3,5-dione. Diels-Alder reaction with maleic anhydride completely failed as complex mixtures were observed and numerous spots on TLC. Different dienophiles mentioned above did not react as well.



Scheme 89: Functionalisation of 386

3.3 Alteration at the alkene region

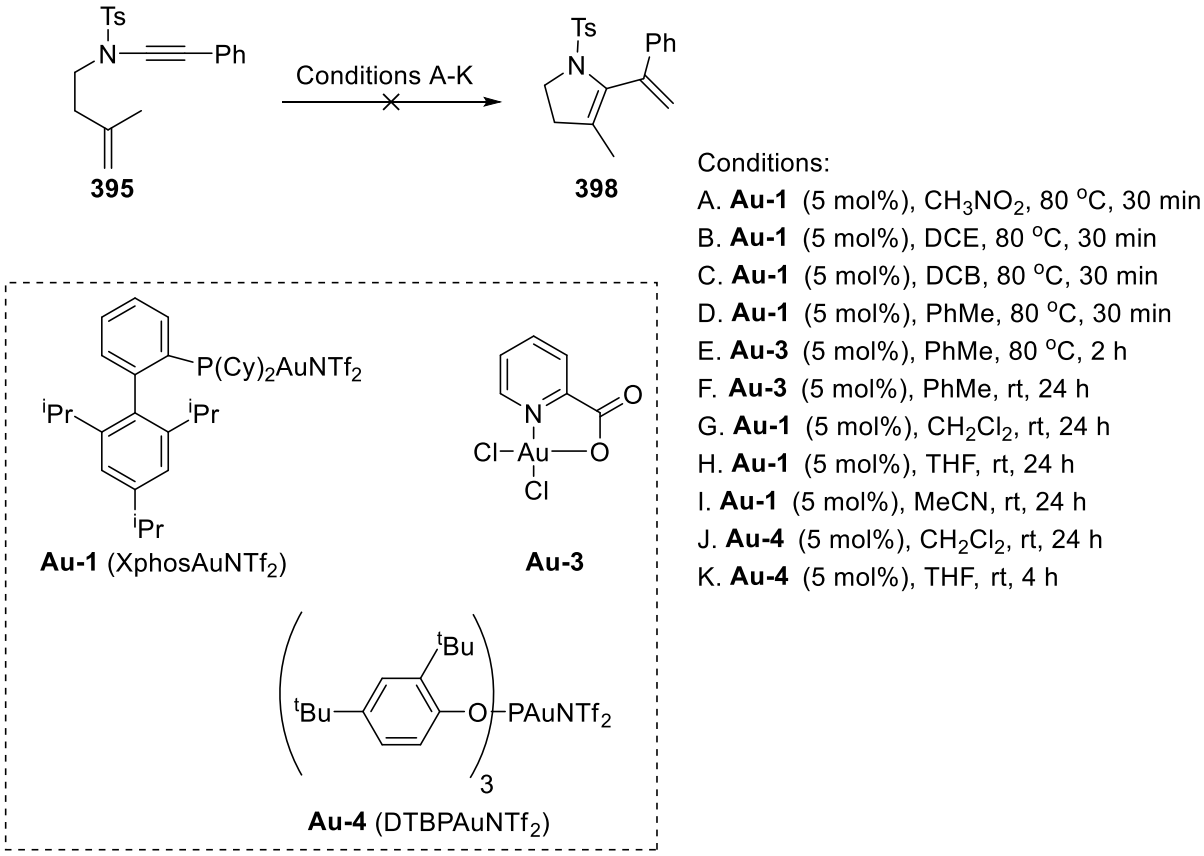
Following the outcome of the use of substituted ene-ynamide at the alkyne region towards the cycloisomerisation process, we examined the outcome with the use of ene-ynamides bearing an electron rich methyl group at the alkene region. Substituted homoallylic sulfonamide **393** were made via two steps (Scheme 90). Tosylation of commercially available primary alcohol **391** gave **392** and further displacement with an amine gave the substituted homoallylic sulfonamide **393** in good yield. Copper-catalysed cross coupling reaction of **393** with various bromide derivatives **394**,**342** and **344** formed the substituted ene-ynamides **395**,**396** and **397** in good yields.



Scheme 90: Formation of ene-ynamide with substituents at the alkene region

Ene-ynamide **395** was not compatible with the optimised gold-catalysed cycloisomerisation conditions (Scheme 91). The most striking observation is the rapidity of the reaction yet very complex mixtures were obtained. In the presence of catalyst Au-1 and solvent-nitromethane, total consumption of the starting material was seen by TLC in less than 30 minutes of reaction. Further optimisation of reaction in terms of change of solvents (toluene, acetonitrile, dichloromethane, 1,2-dichlorobenzene,1,2-dichloroethane and tetrahydrofuran),different sources of gold catalysts and varying reaction temperatures did not improve the outcome of the reaction in any form. Extensive efforts to isolate the product or characterise the side products were practically impossible due to the complexity

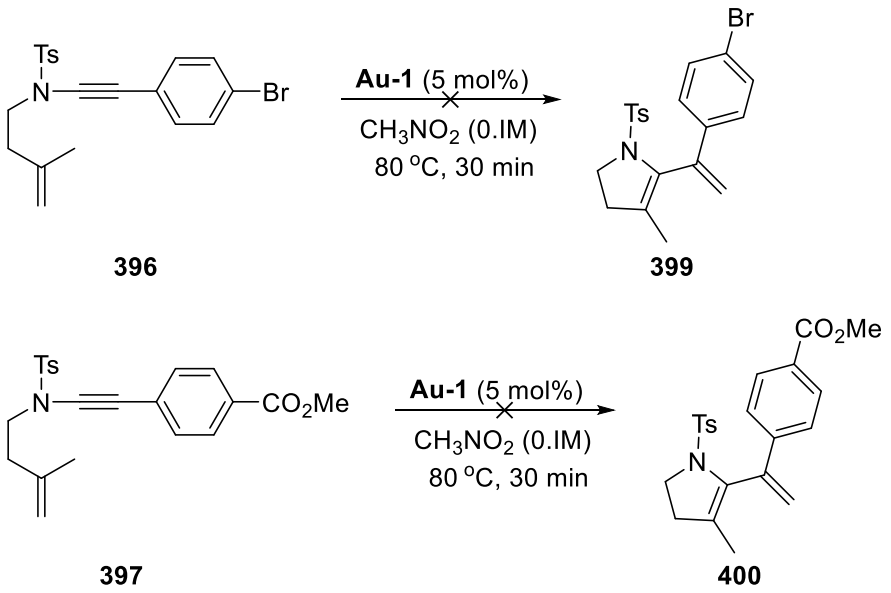
of the reaction mixture. The inability of ene-ynamide **395** to cyclise into the desired product cannot be clearly defined at this point; however we speculate that different reaction pathways may be possible generating side products that cannot be identified.



Conditions:
A. **Au-1** (5 mol%), CH_3NO_2, 80 °C, 30 min
B. **Au-1** (5 mol%), DCE, 80 °C, 30 min
C. **Au-1** (5 mol%), DCB, 80 °C, 30 min
D. **Au-1** (5 mol%), PhMe, 80 °C, 30 min
E. **Au-3** (5 mol%), PhMe, 80 °C, 2 h
F. **Au-3** (5 mol%), PhMe, rt, 24 h
G. **Au-1** (5 mol%), CH_2Cl_2, rt, 24 h
H. **Au-1** (5 mol%), THF, rt, 24 h
I. **Au-1** (5 mol%), MeCN, rt, 24 h
J. **Au-4** (5 mol%), CH_2Cl_2, rt, 24 h
K. **Au-4** (5 mol%), THF, rt, 4 h

Scheme 91: Reactivity of ynamide 395 under gold catalysis

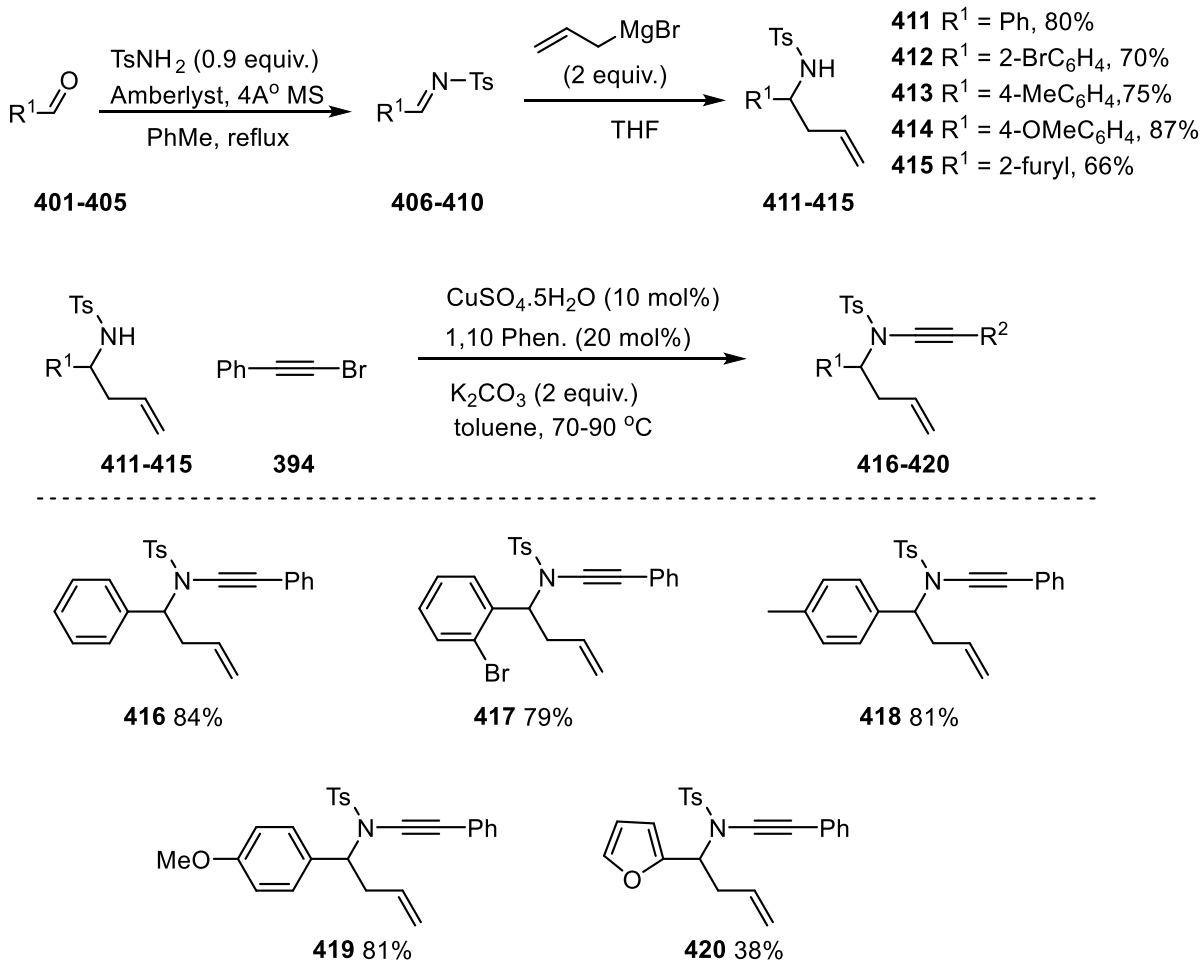
Reactivity of analogues ene-ynamide **396** and **397** were tested and both failed to deliver the cyclised products (Scheme 92). Complex mixtures that were inseparable by flash column chromatography were obtained in each case. Frustrated with these unsuccessful results, no further attempts were made to synthesise analogous ene-ynamides with different substituents at the alkene region.



Scheme 92: Reactivity of ynamide 396 and 397 under optimised gold conditions

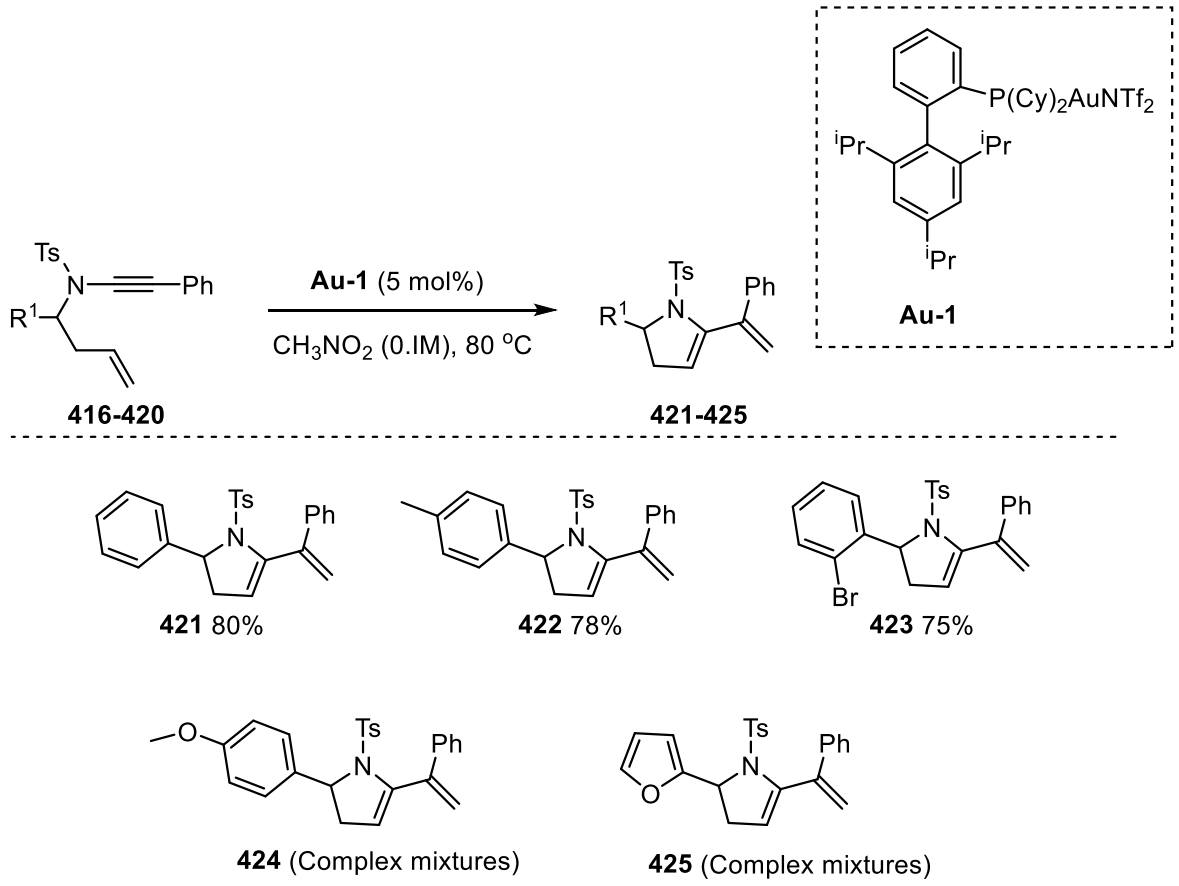
3.4 Substituents on the α-position of nitrogen.

For further substrate scope of the cycloisomerisation reaction, attempts were made to synthesise various ene-ynamides with groups at the α-position relative to the nitrogen atom (Scheme 93). Condensation of aromatic aldehydes **401-405** with amine led to the formation of imines **406-410** with the use of Dean stark apparatus. Treatment of the imines with freshly prepared allyl magnesium bromide generated the sulfonamide **411-415** with groups on the α-position relative to the nitrogen atom. The imines were used immediately they were formed as they are prone to degradation and further purification by flash column chromatography wasn't performed. Following the successful formation of various sulfonamide **411-415**, they were reacted with freshly prepared bromoalkyne **394** under the standard copper catalysed reaction. Higher temperature and longer reaction time were required to get the reactions into completion. The substituted ynamides **416-420** were made in low to high yields. Low reactivity was seen for the formation of ene-ynamde **420**, with furan ring. Improvement of its reactivity using different method gave almost the same result with the traditional method.[105]



Scheme 93: Functionalised ene-ynamide synthesis

Catalysis of the ene-ynamides with substituted aromatic groups on the α-position of nitrogen atom proved suitable with the optimised conditions (Scheme 94). Carbocylic compounds with dienamide moiety **421** and **422** were generated in very good yield. Incorporation of bulky group like bromine in *ortho* position was possible in the formation of **423**. Complex mixtures that are inseparable by flash column chromatography resulted in the formation of **424** and **425**, bearing a para methoxy phenyl group and furan ring respectively. Employment of other sources of gold catalyst and solvent change followed the same trend of complexity

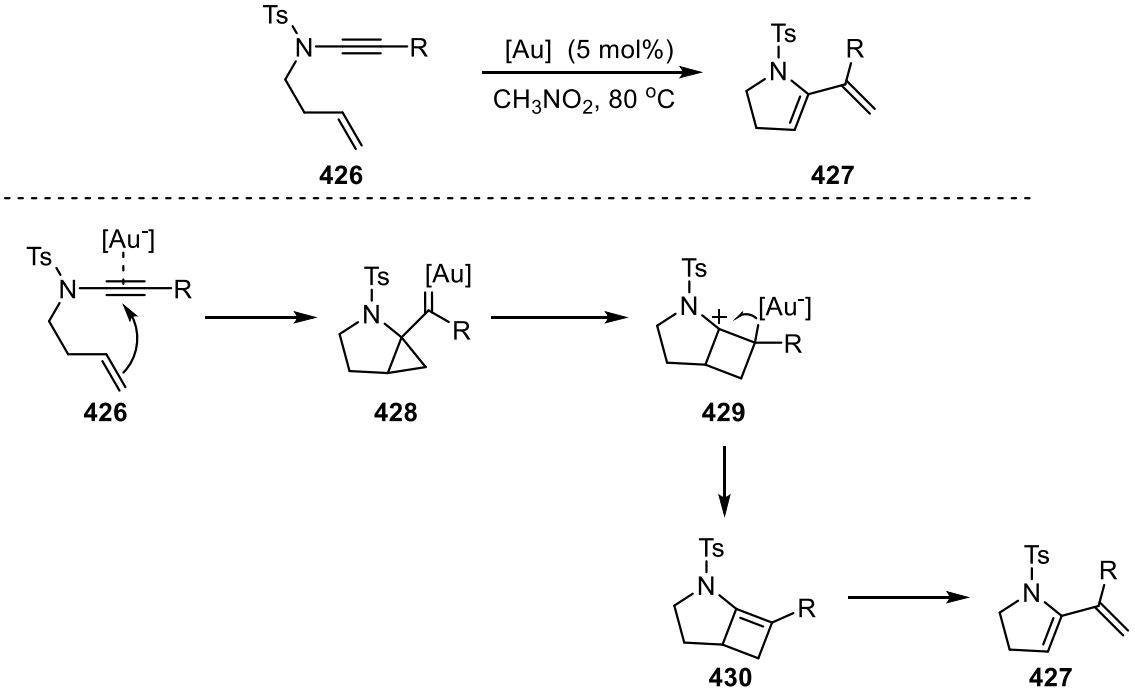


Scheme 94: Catalysis and substrate scope

3.5 Proposed mechanism

According to the proposed mechanism (Scheme 95), selective coordination and activation of the triple bond by the electrophilic gold catalyst, followed by concomitant nucleophilic attack of alkene generates the gold cyclopropylcarbene **428**. Ring expansion of carbene intermediate **428** produces cyclobutyl cation **426** that is stabilised by the adjacent nitrogen atom. Subsequent elimination of gold catalyst furnishes cyclobutenamide **430** and electrocyclic ring opening of **430** gives the desired cycloisomerised product **427** with 1,3-diene moiety. As earlier discussed in (Scheme 74), this proposed mechanism is in total agreement with the ones proposed by the research groups of Malacria[87, 91] and Cossy[96].

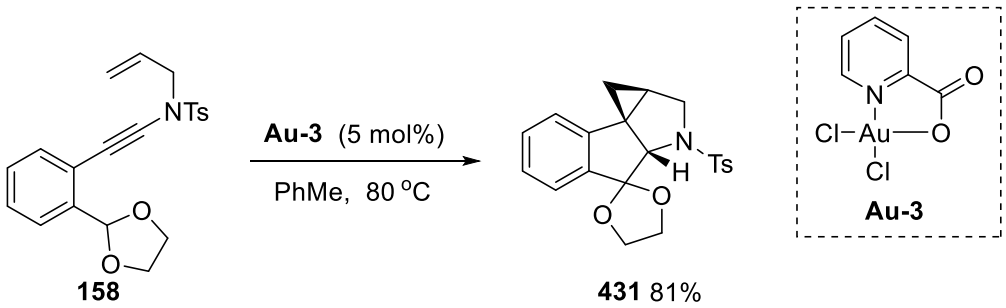
Experimental data provided through DFT calculations done by Soriano[106] and Echavarren[89] supported the mechanism.



Scheme 95: Proposed mechanism for cycloisomerisation of ene-ynamide 426

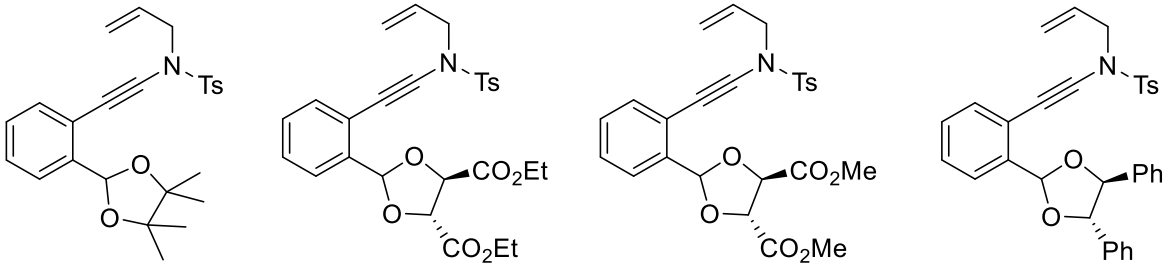
3.6. Other reactivity

Holly Adcock and Elli Chatzopoulou (members of Davies group) reported the synthesis of polycycles via gold-catalysed [1,5]-hydride transfer-cyclisation cascades of *N*-allyl ynamides[71] (Scheme 96)



Scheme 96: Au-catalysed polycycle formation from ynamide 158

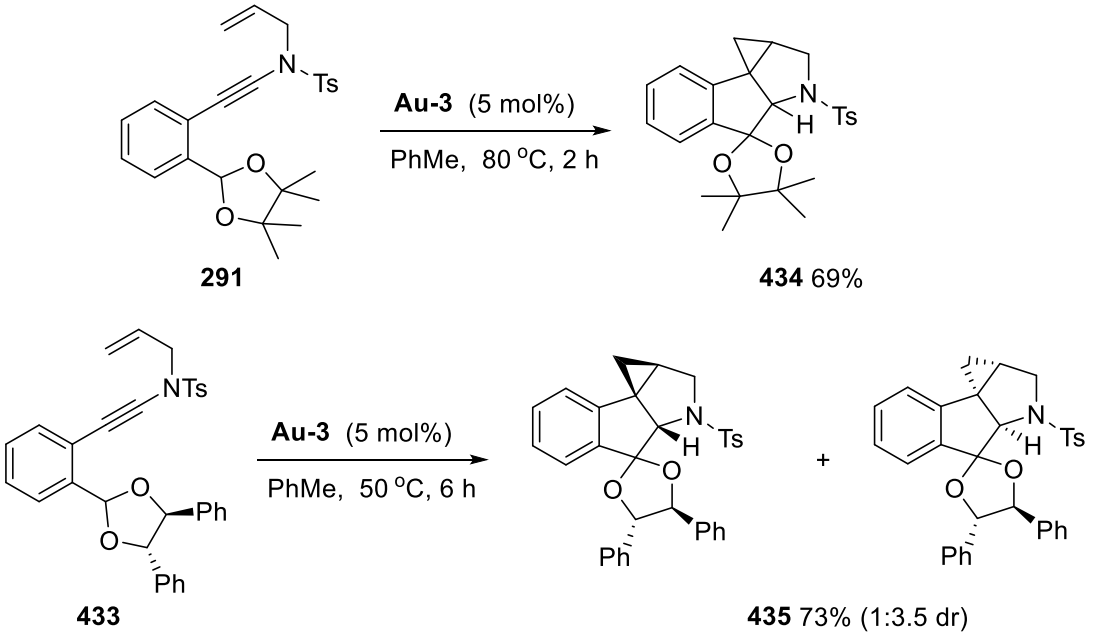
Treatment of **158** with gold(III)catalyst Au-3,generated the 3D fused nitrogen heterocycle **431** as a single diastereoisomer in which the migrated hydrogen and the cyclopropane ring were in the same face as confirmed by nOe experiments. Substrate scope was quite broad as variations on the aromatic and allyl regions were all tolerated. The synthetic versatility of this methodology which provides access to highly functionalised molecules motivated us to investigate the reactivity of ynamides with substituted dioxolane groups. Ynamides **234**,**291**,**432** and **433** were made from freshly prepared alkynyl bromides in moderate to good yields (Figure 97).



291 78% **234** 66% **432** 36% **433** 58%

Scheme 97: Ynamides with substituted dioxolane groups

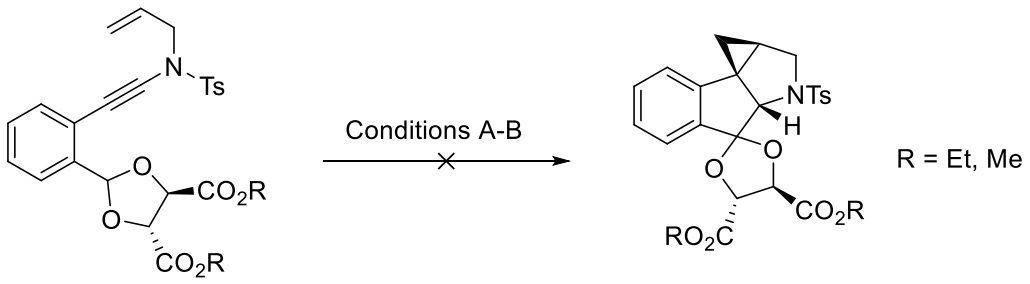
Ynamide **291** reacted cleanly in two hours with full consumption of starting material to give the tetracycle **434** containing a pinacol group in good yield (Scheme 98). The chiral hydrobenzoin derived ynamide **433** did not react at room temperature when treated with catalyst **Au-3**.



Scheme 98: Formation of tetracycles from ynamides

When the temperature was increased to 50 °C, ynamide **433** underwent smooth gold-catalysed [1,5]-hydride transfer/cyclisation process to generate polycycle **435** in high yield as a 1:3.5 mixture of diastereoisomers. Unfortunately the two diastereoisomers were inseparable by flash column chromatography or recrystallization.

Chiral ynamides **234** and **432** with an ester group were not reactive under the gold catalysed polycyclisation conditions (Scheme 99). Change in reaction conditions employing the use of higher temperature and 1,4-dioxane did not improve the outcome. Starting materials and degradation products were seen as observed by ^{1}H-NMR spectroscopy.



234, 432 **436, 437**

Conditions
A. **Au-3** (5 mol%), PhMe, 80 °C, 24 h
B. **Au-3** (5 mol%), 1,4-dioxane, 120 °C, 24 h

Scheme 99: Chiral ynamides under gold catalysis

It is likely that gold catalyst is also coordinating to the carbonyl oxygen atom of the ester group which creates some sort of competition over gold, binding between the triple bond and oxygen atom. Such competition will lead to inefficient activation of triple bond and possibly shut down the reaction.

4 Conclusion

New five-membered nitrogen heterocycles bearing dienamide moieties have been achieved through gold-catalysed cycloisomerisation of 1,6-ene-ynamides. Ene-ynamides with internal alkynes or substituents at the α-position relative to the nitrogen atom have been successfully used as substrates to achieve these important transformations. Introduction of thio-ynamide in the catalytic process opens a new route for further functionalisation. Finally, additional functionalisation of tetracycles bearing different groups at the dioxolane region have been generated through gold-catalysed [1,5] hydride transfer/cascade cyclisation of *N*-allyl ynamides.

Chapter 4 Experimental section

General Experimental

All reagents were purchased from Aldrich, Fluka, Fisher, Acros, Johnson Matthey, Alfa Aesar or VWR and used without further purification unless otherwise stated. For all reactions carried out under an atmosphere other than air, solvents were purified using a Pure Solv-MD solvent purification system, except for nitromethane, which was dried over 4 Å molecular sieves. The solvents were transfer under nitrogen or argon. Paraffin oil baths and stirrer hot plates were used with an external temperature probe. Reaction progress was monitored by thin layer chromatography (TLC) performed using Merck Silica gel 60 F_{254}. Visualisation was achieved by a combination of ultraviolet light (254 nm) and potassium permanganate solution. Flash column chromatography was performed using 60 Å pore size (40-63µm) silica gel as the stationary phase. The following cooling bath mixture were used for low temperature reactions: 0 °C (ice/water), -40 °C (dry ice/water) and -78 °C (dry ice/acetone) All ^{1}H NMR and ^{13}C NMR experiments were recorded using Bruker AVIII400(^{1}H = 400 MHz, ^{13}C = 101 MHz) and AVIII300(^{1}H = 300 MHz, ^{13}C = 75 MHz), with the spectrometers at 300 K. ^{13}C NMR were recorded using the PENDANT pulse sequence from the Bruker standard pulse program library. Chemical shifts (δ) are given in ppm relative to TMS and coupling constants (*J*) are quoted in Hz to one decimal place. For spectra recorded in chloroform-*d* the 7.26 ppm resonance of residual $CHCl_3$ for proton spectra and 77.16 ppm resonance of $CDCl_3$ for carbon spectra were used as internal references. Spectral data for ^{1}H NMR is reported as follows: chemical shift (multiplicity, coupling constant, number of protons); and for ^{13}C NMR: chemical shift (assignment). The following abbreviations were used for multiplicity in ^{1}H NMR: s (singlet), d (doublet), t (triplet), q (quadruplet), br (broad), m (multiplet) app.(apparent). Collected NMR spectra were processed using MestReNova software. Infra-red spectra were recorded neat on a Perkin-Elmer Spectrum 100 FTIR

spectrometer. Wavelengths (ν) are reported in cm^{-1}. Waters Synapt (ES), Waters GCT (EI) or Waters LCT (ES) spectrometers were used to obtain the mass spectra. Melting points were determined using open glass capillaries on a Gallenkamp melting point.

Preparation of sulfonamides

General procedure 1 (GP1)

The required sulfonyl chloride (1.0 equiv.) was added in a dropwise fashion to a solution of the relevant amine (1.2 equiv.), pyridine (3.0 equiv.) in dichloromethane (0.3 M) at 0 °C. The resulting solution was warmed up to room temperature and stirred for 16 hours. 1.0 M HCl was added and the aqueous layer extracted with CH_2Cl_2 (× 3). The combined organic layers were washed with water (× 2), brine, dried over Na_2SO_4 and concentrated to give the sulfonamide which was used without further purification.

General procedure 2 (GP2)

Based on existing literature procedure [107]

The relevant bromide (1.1 equiv.) and K_2C0_3 (2.0 equiv.) were added to a solution of the requisite amine (1.0 equiv.) in acetone (1.0 M) and the resulting mixture was at 60 °C for 24 hours. The reaction mixture was cooled, filtered through celite with EtOAc as eluent. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography

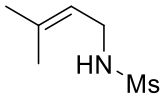
General procedure 3 (GP3)

Based on existing literature procedure.[108]

A solution of relevant aldehyde (1.0 equiv), 4-methylbenzenesulfonamide (0.9 equiv.),amberlyst 15 ion-exchange resin (1 0 g) and activated 4 Å molecular sieves (1.0 g) in toluene (0.33 M) was heated at reflux using a Dean Stark trap for 16 hours. The reaction

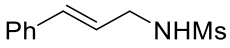
mixture was cooled and filtered, concentrated and the residue was washed with hexane to give the imine. Freshly prepared allylmagnesium bromide (2.0 equiv.) was added to the solution of the imine (1.0 equiv.) in THF and the resulting mixture was stirred at room temperature. The reaction was monitored by TLC. The reaction mixture was quenched by saturated NH_4Cl solution and extracted with EtOAc (× 3). The combined organic extracts were successively washed with water, brine, dried over Na_2SO_4 and solvent removed under reduced pressure. The crude residue was purified by flash column chromatography

_N_-(3-Methylbut-2-en-1-yl)methanesulfonamide (165)



The sulfonamide was prepared by a group member (Fernando Sanchez-Cantalejo).

_N_-Cinnamylmethanesulfonamide (168)

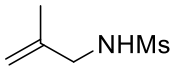


Prepared according to **GP2** using methanesulfonamide (1.90 g, 20.0 mmol, 1.0 equiv.) and cinnamyl bromide (4.33 g, 22.0 mmol, 1.1 equiv.). Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the sulfonamide as a white soild (1.94 g, 46%); mp: 71-73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H), 6.62 (d *J* = 15.8 Hz, 1H), 6.20 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.57 (br. s, 1H), 3.94 (td, *J* = 6.3, 1.5 Hz, 2H), 3.00 (s, 3H); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 136.1 (C), 133.5 (CH), 128.8 (2 × CH), 128.3 (CH), 126.6 (2 × CH), 124.6 (CH), 45.5 (CH_2), 41.3 (CH_3).

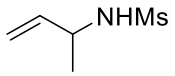
Data matches that reported in the literature.[109]

***N*-(2-Methylallyl)methanesulfonamide (171)**



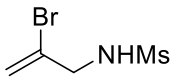
Prepared according to modified **GP2** using methanesulfonamide (3.14 g, 33.0 mmol, 2.2 equiv.) and 3-chloro-2-methylprop-1-ene (1.50 mL, 15.0 mmol, 1.0 equiv.). Purification by flash column chromatography [7:3 (hexane:EtOAc)] gave the sulfonamide as a colourless oil (1.07 g, 48%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (d, *J* = 1.4 Hz, 1H), 4.93 (d, *J* = 1.4 Hz, 1H), 4.60 (br. s, 1H), 3.68 (d, *J* = 6.4 Hz, 2H), 2.96 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0 (C), 112.9 (CH_2), 49.1 (CH_2), 41.0 (CH_3), 20.1 (CH_3); IR ν_{max}/cm^{-1} 3287, 2972, 2939, 1658, 1412, 1308, 1142, 1064, 975, 899, 754.

***N*-(But-3-en-2-yl)methanesulfonamide (172)**



The sulfonamide was prepared by a group member (Fernando Sanchez-Cantalejo).

N-**(2-Bromoallyl)methanesulfonamide (173)**

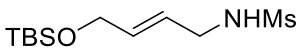


Prepared following literature procedure.[110]

2,3-Dibromo-1-propene (2.17 mL, 22.2 mmol, 2.0 equiv.) was added to a mixture of tert-butyl (methylsulfonyl)carbamate (MsNHBoc), (2.17 g, 11.1 mmol) and K_2CO_3 (2.45 g, 1.6 equiv.) dissolved in DMF. The mixture was stirred at 35 °C for 4 h. The reaction was quenched with water, extracted with Et_2O (× 3) and the solvent removed under reduced pressure to give a crude residue that was dissolved in CH_2Cl_2 (6 mL). Dropwise addition of trifluoroacetic acid (8.3 mL) followed and the mixture stirred at room temperature for

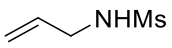
additional 12 hours. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the sulfonamide as a brown solid (1.87 g, 67% over two steps) mp: 57-59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (d, *J* = 2.3 Hz, 1H), 5.65 (d, *J* = 2.3 Hz, 1H), 4.98 (br. s, 1H), 4.00 (d, *J* = 6.4 Hz, 2H), 3.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.2 (C), 119.8 (CH_2), 51.2 (CH_2), 42.1 (CH_3); IR ν_{max}/cm^{-1} 3271, 2936, 1636, 1449, 1410, 1307, 1140, 1073, 898, 747.

(E)-*N*-(4-((Tert-butyldimethylsilyl)oxy)but-2-en-1-yl)methanesulfonamide (174)



The sulfonamide was prepared by a group member (Fernando Sanchez-Cantalejo).

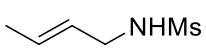
***N*-Allylmethanesulfonamide (175)**



Prepared according to **GP1** using methanesulfonyl chloride (0.78 mL, 10.0 mmol, 1.0 equiv.) and allylamine (0.9 mL, 12.0 mmol, 1.2 equiv.) to give the sulfonamide as a yellow oil(0.95 g, 70%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddt, *J* = 17.1, 10.2, 5.8 Hz, 1H), 5.35 – 5.26 (m, 1H), 5.26 – 5.19 (m, 1H), 4.57 (br. s, 1H, NH), 3.78 (td, *J* = 5.1, 2.8 Hz, 2H), 2.97 (s, 3H); IR ν_{max}/cm^{-1} 3280, 2937, 1440, 1413, 1308, 1141, 1064, 926, 752.

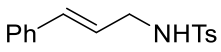
Data matches that reported in the literature.[111]

(E)-*N*-(But-2-en-1-yl)methanesulfonamide (191)



The sulfonamide was prepared by a group member (Holly Adcock).

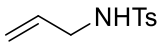
***N*-Cinnamyl-4-methylbenzenesulfonamide (213)**



Prepared according to **GP2** using 4-methylbenzenesulfonamide (3.42 g, 20.0 mmol, 1.0 equiv.) and cinnamyl bromide (4.33 g, 22.0 mmol, 1.1 equiv.). Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the sulfonamide as a yellow soild (2.59 g, 45%); mp: 108-110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.22 (m, 7H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.02 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.56 (t, *J* = 6.2 Hz, 1H), 3.76 (td, *J* = 6.4, 1.5 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (C), 137.3 (C), 136.2 (C), 133.2 (CH), 129.9 (2 × CH), 128.7 (2 × CH), 128.1 (CH), 127.4 (2 × CH), 126.5 (2 × CH), 124.2 (CH), 45.6 (CH_2), 21.6 (CH_3).

Data matches that reported in the literature.[112]

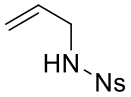
_N_-(But-3-en-1-yl)-4-methylbenzenesulfonamide (220)



Prepared according to **GP1** using 4-methylbenzenesulfonyl chloride (1.91 g, 10.0 mmol, 1.0 equiv.) and allylamine (0.9 mL, 12.0 mmol, 1.2 equiv.) to give the sulfonamide as a white solid (1.94 g, 86%); mp: 63-65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.29 (m, 2H), 5.72 (ddt, *J* = 17.1, 10.2, 5.8 Hz, 1H), 5.24 – 5.06 (m, 2H), 4.49 (t, *J* = 6.3 Hz, 1H, NH), 3.58 (app. tt, *J* = 6.0, 1.5 Hz, 2H), 2.43 (s, 3H); IR ν_{max}/cm^{-1} 3240, 3088, 3029, 2849, 1650, 1330, 1163, 935, 671.

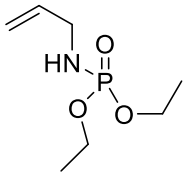
Data matches that reported in the literature.[113]

_N_-Allyl-4-nitrobenzenesulfonamide (236)



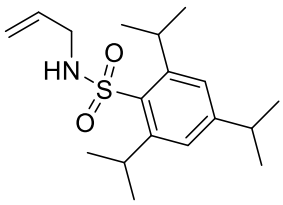
The sulfonamide was prepared by a group member (Holly Adcock).

Diethyl allylphosphoramidate (238)



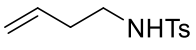
The sulfonamide was prepared by a group member (Holly Adcock).

***N*-Allyl-2,4,6-triisopropylbenzenesulfonamide (240)**



The sulfonamide was prepared by a group member (Holly Adcock).

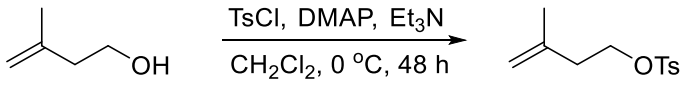
***N*-(But-3-en-1-yl)-4-methylbenzenesulfonamide (350)**



Prepared according to **GP2** using 4-methylbenzenesulfonamide (1.71 g, 10.0 mmol, 1.0 equiv.) and 4-bromobut-1-ene (1.1 mL, 11.0 mmol, 1.1 equiv.). Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the sulfonamide as a clear oil (1.30 g, 58%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.62 (ddt, *J* = 17.1, 10.4, 6.9 Hz, 1H), 5.12 – 4.97 (m, 2H), 4.44 (t, *J* = 6.2 Hz, 1H, NH), 3.02 (app. q, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 2.25 – 2.15 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6 (C), 137.1 (C), 134.3 (CH), 129.8 (2 × CH), 127.2 (2 × CH), 118.3 (CH_2), 42.2 (CH_2), 33.7 (CH_2), 21.7 (CH_3); IR ν_{max}/cm^{-1} 3280, 2926, 1596, 1423, 1322, 1156, 1074, 811, 662.

Data matches that reported in the literature.[107]

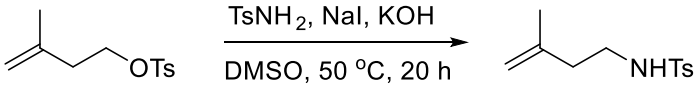
3-Methylbut-3-en-1-yl 4-methylbenzenesulfonate (392)



A flame dried flask, under nitrogen, was charged with 3-methylbut-3-en-1-ol (1.72 g, 20.0 mmol, 1.0 equiv.) and dichloromethane (40 mL) at 0 °C. Successively, 4-dimethylaminopyridine (1.47 g, 12.0 mmol, 0.6 equiv.), tosylchloride (4.58 g, 24.0 mmol, 1.2 equiv.) and triethylamine (2.8 mL, 20.0 mmol, 1.0 equiv.) were added dropwise and the resulting solution was stirred magnetically at same temperature for 48 hours. The reaction was quenched by slow addition of water (30 mL) and the organic phase was washed with sat.NH_4Cl solution and brine. The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under pressure to yield a colourless oil (3.84 g, 80%) which was used without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 4.79 (d, *J* = 0.9 Hz, 1H), 4.68 (d, *J* = 1.0 Hz, 1H), 4.12 (t, *J* = 6.9 Hz, 2H), 2.45 (s, 3H), 2.35 (t, *J* = 6.3 Hz, 2H), 1.66 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 140.3 (C), 133.4 (C), 130.0 (2 × CH), 128.1 (2 × CH), 113.2 (CH_2), 68.7 (CH_2), 36.9 (CH_2), 22.5 (CH_3), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2970, 1598, 1356, 1173, 1096, 960, 897, 661.

Data matches that reported in the literature.[114]

4-Methyl-N-(3-methylbut-3-en-1-yl)benzenesulfonamide (393)

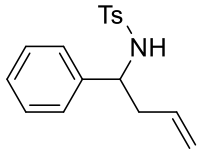


A round-bottomed flask fitted with a condenser was charged with tosylamine (4.10 g, 24.2 mmol, 2.3 equiv.), finely powdered potassium hydroxide (0.77 g, 13.7 mmol, 1.3 equiv.), dimethylsulfoxide (13 mL) and heated at reflux for 2 hours. The reaction mixture was cooled

at room temperature followed by dropwise addition of tosylated alcohol (2.52 g, 10.5 mmol, 1.0 equiv.) in DMSO (1.5 mL) and sodium iodide (0.47 g, 3.15 mmol, 0.3 equiv.). The resulting solution was heated at reflux for 20 hours. Upon cooling, cold water (25 mL) was added and e×tracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the sulfonamide (1.81 g, 72%) as a white solid; mp: 38-39 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 4.80 (d, *J* = 1.7 Hz, 1H), 4.65 (d, *J* = 1.9 Hz, 1H), 4.34 (t, *J* = 6.1 Hz, 1H), 3.06 (q, *J* = 6.6 Hz, 2H), 2.43 (s, 3H), 2.14 (t, *J* = 6.7 Hz, 2H), 1.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6 (C), 141.6 (C), 137.0 (C), 129.9 (2 × CH), 127.3 (2 × CH), 113.5 (CH_2), 40.6 (CH_2), 37.3 (CH_2), 21.8 (CH_3), 21.7 (CH_3); IR ν_{max}/cm^{-1} 2854, 1596, 1487, 1349, 1160, 1086, 1008, 813, 658.

Data matches that reported in the literature.[115]

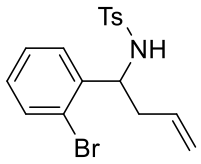
4-Methyl-N-(1-phenylbut-3-en-1-yl)benzenesulfonamide (411)



Prepared according to **GP3** (80% yield over 2 steps, white solid); mp: 68-70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.20 – 7.12 (m, 5H), 7.10 – 7.05 (m, 2H), 5.50 (ddt, *J* = 18.9, 9.3, 7.1 Hz, 1H), 5.12 – 5.01 (m, 2H), 4.83 (d, *J* = 6.4 Hz, 1H, NH), 4.38 (app. q, *J* = 6.6 Hz, 1H), 2.51 – 2.41 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0 (C), 140.4 (C), 137.5 (C), 133.1 (CH), 129.2 (2 × CH), 128.2 (2 × CH), 127.3 (CH), 127.1 (2 × CH), 126.6 (2 × CH), 119.1 (CH_2), 57.3 (CH), 41.8 (CH_2), 21.3 (CH_3).

Data matches that reported in the literature.[116]

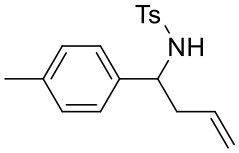
_N_-(1-(2-Bromophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide (412)



Prepared according to **GP3** (70% yield over 2 steps, white solid); mp: 112-114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.42 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.22 – 7.10 (m, 4H), 7.09 – 6.96 (m, 1H), 5.54 – 5.38 (m, 1H), 5.13 – 5.03 (m, 2H), 4.98 (d, *J* = 6.3 Hz, 1H, NH), 4.76 (dt, *J* = 7.9, 5.7 Hz, 1H), 2.53 – 2.40 (m, 1H), 2.36 (s, 3H), 2.34 – 2.27 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (C), 139.6 (C), 136.8 (C), 133.0 (CH), 132.8 (CH), 129.5 (2 × CH), 128.8 (CH), 128.7 (CH), 127.5 (CH), 127.4 (2 × CH), 122.4 (C), 119.9 (CH_2), 56.1 (CH), 40.5 (CH_2), 21.6 (CH_3).

Data matches that reported in the literature.[117]

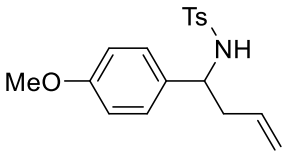
4-Methyl-N-(1-(p-tolyl)but-3-en-1-yl)benzenesulfonamide (413)



Prepared according to **GP3** (75% yield over 2 steps, colourless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.02 – 6.93 (m, 4H), 5.50 (ddt, *J* = 19.7, 9.5, 7.1 Hz, 1H), 5.07 (d, *J* = 1.2 Hz, 1H), 5.05 – 5.00 (m, 1H), 4.77 (d, *J* = 6.3 Hz, 1H, NH), 4.32 (app. q, *J* = 6.6 Hz, 1H), 2.48 – 2.41 (m, 2H), 2.38 (s, 3H), 2.28 (s, 3H); IR ν_{max}/cm^{-1} 3254, 1643, 1428, 1324, 1156, 1093, 941, 748, 681,666.

Data matches that reported in the literature.[116]

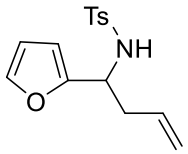
***N*-(1-(4-Methoxyphenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide (414)**



Prepared according to **GP3** (87% yield over 2 steps, colourless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.20 – 7.13 (m, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 8.7 Hz, 2H), 5.50 (ddt, *J* = 19.5, 9.5, 7.1 Hz, 1H), 5.07 (d, *J* = 1.1 Hz, 1H), 5.06 – 5.01 (m, 1H), 4.78 (d, *J* = 6.2 Hz, 1H, NH), 4.31 (app.q, *J* = 6.6 Hz, 1H), 3.75 (s, 3H), 2.44 (dd, *J* = 11.8, 6.9 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C), 143.2 (C), 137.7 (C), 133.4 (CH), 132.5 (C), 129.4 (2 × CH), 127.9 (2 × CH), 127.3 (2 × CH), 119.3 (CH_2), 113.9 (2 × CH), 56.8 (CH_3), 55.4 (CH), 42.0 (CH_2), 21.6 (CH_3).

Data matches that reported in the literature.[116]

***N*-(1-(Furan-2-yl)but-3-en-1-yl)-4-methylbenzenesulfonamide (415)**

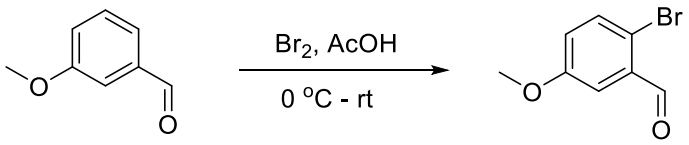


Prepared according to **GP3** (66% yield over 2 steps, yellow oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.24 – 7.18 (m, 2H), 7.17 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.14 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.96 (dd, *J* = 3.3, 0.8 Hz, 1H), 5.56 (ddt, *J* = 15.9, 11.3, 7.1 Hz, 1H), 5.11 – 5.00 (m, 2H), 4.81 (d, *J* = 8.3 Hz, 1H), 4.50 (dt, *J* = 8.4, 6.6 Hz, 1H), 2.64 – 2.43 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7 (C), 143.3 (C), 142.0 (CH), 137.8 (C), 132.8 (CH), 129.9 (2 × CH), 127.2 (2 × CH), 119.5 (CH_2), 110.2 (CH), 107.3 (CH), 51.1 (CH), 39.2 (CH_2), 21.6 (CH_3).

Data matches that reported in the literature.[118]

Preparation of 2-bromo aldehydes

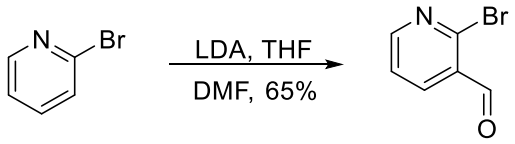
2-Bromo-5-methoxybenzaldehyde (264)



Bromine (2.9 mL, 56.0 mmol, 2.8 equiv.) was added dropwise to a solution of *m*-anisaldehyde (2.4 mL, 20.0 mmol, 1.0 equiv.) and acetic acid (22 mL, 0.9 M) in an ice bath and stirred for 15 minutes. After this time, the ice bath was removed and the reaction mixture was warmed up to room temperature for 16 hours. Ice water (100 mL) was added, the solid filtered off and the filtrate washed with DCM (3 × 30 mL). This was followed by dissolution of the solid in the organics and subsequent washing with saturated $NaHCO_3$ (2 × 50 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 and the solvent removed under reduced pressure to afford the product as a pale yellow solid (4.30 g, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 3.2 Hz, 2H), 7.03 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9 (CHO), 159.4 (C), 134.7 (CH), 134.1 (C), 123.3 (CH), 118.1 (C), 112.8 (CH), 55.9 (CH_3); IR ν_{max}/cm^{-1} 2941, 2875, 1674, 1569, 1469, 1382, 1277, 1013, 818, 753.

Data matches that reported in the literature.[119]

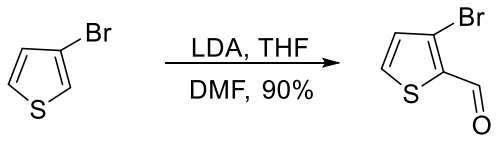
2-Bromonicotinaldehyde (276)



Lithium diisopropylamide solution was prepared by dropwise addition of *n*-butyllithium (13.8 mL, 1.6 M solution in hexane, 22.0 mmol, 1.1 equiv.) to a solution of diisopropylamine (3.6 mL, 26.0 mmol, 1.3 equiv.) in THF (67 mL, 0.3M) at -78 °C which was warmed to 0 °C. After 1 hour, the solution was cooled to -78 °C and freshly distilled 2-bromopyridine (1.9 mL, 20.0 mmol, 1.0 equiv) was added in a dropwise manner. After further stirring at -78 °C, for 4 hours, DMF (13 mL) was added dropwise and the reaction mixture was warmed up to room temperature over 1 hour. Saturated aqueous NH_4Cl was added and the organic layer was extracted with Et_3O for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure Purification by flash column chromatography [85:15 (hexane:EtOAc)] gave the aldehyde **236** as a red oil (2.42 g, 65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.34 (d, *J* = 0.8 Hz, 1H), 8.57 (dd, *J* = 4.7, 2.1 Hz, 1H), 8.18 (dd, *J* = 7.7, 2.1 Hz, 1H), 7.44 (ddd, *J* = 7.6, 4.7, 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2 (CHO), 154.5 (CH), 145.4 (C), 138.0 (CH), 130.6 (C), 123.5 (CH); IR ν_{max}/cm^{-1} 3024, 2872, 1692, 1571, 1369, 1255, 1049, 802, 704

Data matches that reported in the literature [120]

3-Bromothiophene-2-carbaldehyde (283)



Lithium diisopropylamide solution was prepared by dropwise addition of *n*-butyllithium (6.30 mL, 1.6 M solution in hexane, 10.0 mmol, 1.0 equiv.) to a solution of diisopropylamine (1.4 mL, 10.0 mmol, 1.0 equiv.) in THF (17 mL, 0.6M) at 0 °C, followed by slow addition of 3-bromothiophene (0.95 mL, 10.0 mmol, 1.0 equiv.) at the same temperature. After stirring for 1 hour, DMF (0.8 mL, 10.0 mmol, 1.0 equiv.) was added dropwise and the reaction mixture was warmed up to room temperature for 4 hours. Water was added, followed by extraction with Et_3O for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure which gave the aldehyde **283** as a brown liquid (1.72 g, 90%), and used immediately without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.99 (d, *J* = 1.4 Hz, 1H), 7.72 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.15 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.2 (CHO), 137.1 (C), 134.9 (CH), 132.2 (CH), 120.5 (C); IR ν_{max}/cm^{-1} 3104, 2843, 1657, 1496, 1414, 1208, 886, 661, 606.

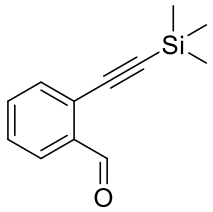
Data matches that reported in the literature [121]

Preparation of 2-ethynyl aldehydes/internal alkynes

General procedure 4 (GP4)

The required bromide (1.0 equiv.), $Pd(PPh_3)Cl_2$ (5 mol%), CuI (3 mol%), and degassed Et_3N (0.2 M) were combined in a flame dried round bottom flask and stirred at room temperature for 10 minutes. Trimethylsilylacetylene (1.2 equiv.) was added gently and the resulting mixture was stirred at 50 °C. The reaction was monitored by TLC. After cooling at room temperature, the reaction mixture was filtered through a pad of celite and washed with EtOAc. Solvent was removed under reduced pressure and the crude residue was purified by flash column chomatoghrapy.

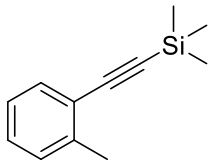
2-((Trimethylsilyl)ethynyl)benzaldehyde (161)



Prepared according to **GP4** using 2-bromobenzaldehdye (3.70 g, 20.0 mmol). Purification by flash column chromatography [98:2 (hexane:EtOAc)] gave the silylated alkyne **161** as a brown solid (3.92 g, 97%); mp: 49-51 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.56 (d, *J* = 0.8 Hz, 1H), 7.93 – 7.88 (m, 1H), 7.60 – 7.50 (m, 2H), 7.47 – 7.40 (m, 1H), 0.28 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0 (CHO), 136.3 (C), 133.8 (CH), 133.6 (CH), 129.0 (CH), 127.0 (CH), 126.9 (C), 102.6 (C), 100.2 (C), -0.08 (3 × CH_3).

Data matches that reported in the literature.[122]

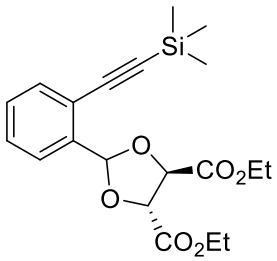
Trimethyl(o-tolylethynyl)silane (197)



Prepared according to **GP4** using 1-bromo-2-methylbenzene (1.71 g, 10.0 mmol). Purification by flash column chromatography [100% (hexane)] gave the protected alkyne **197** as a yellow oil (0.68 g, 36%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.22 – 7.18 (m, 2H), 7.14 – 7.08 (m, 1H), 2.44 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (C), 132.2 (CH), 129.5 (CH), 128.6 (CH), 125.6 (CH), 123.0 (C), 104.2 (C), 98.3 (C), 20.8 (CH_3), 0.22 (3 × CH_3); IR ν_{max}/cm^{-1} 2959, 2155, 1482, 1249, 866, 835, 754, 455.

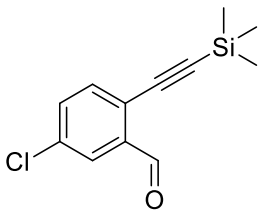
Data matches that reported in the literature.[123]

Diethyl (4R,5R)-2-(2-((trimethylsilyl)ethynyl)phenyl)-1,3-dioxolane-4,5-dicarboxylate (229)



Prepared according to **GP4** using bromide **228** (1.20 g, 3.2 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the protected alkyne **229** as a brown oil (0.95 g, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 1H), 7.50 – 7.45 (m, 1H), 7.41 – 7.29 (m, 2H), 6.61 (s, 1H), 4.93 (d, *J* = 4.2 Hz, 1H), 4.85 (d, *J* = 4.2 Hz, 1H), 4.37 – 4.25 (m, 4H), 1.36 (t, *J* = 5.3 Hz, 3H), 1.31 (t, *J* = 5.3 Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6 (CO), 169.3 (CO), 137.1 (C), 132.6 (CH), 129.7 (CH), 128,9 (CH), 127.1 (CH), 123.1 (C), 104.6 (CH), 101.7 (C), 99.9 (C), 77.9 (2 × CH), 62.2 (CH_2), 62.1 (CH_2), 14.3 (CH_3), 14.3 (CH_3), 0.0 (3 × CH_3); IR ν_{max}/cm^{-1} 2964, 2160, 1747, 1376, 1227, 839, 755, 685; HRMS(EI-TOF): *m/z*: calcd for $C_{20}H_{26}SiO_6$: 390.1499, found: 390.1501 $[M]^+$.

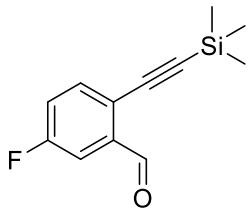
5-Chloro-2-((trimethylsilyl)ethynyl)benzaldehyde (243)



Prepared according to **GP4** using 2-bromo-5-chlorobenzaldehdye (2.19 g, 10.0 mmol). Purification by flash column chromatography [98:2 (hexane:EtOAc)] gave the protected alkyne **243** as a yellow liquid (1.46 g, 62%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.47 (s, 1H), 7.86

(dd, *J* = 1.6, 1.1 Hz, 1H), 7.56 – 7.46 (m, 2H), 0.28 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6 (CHO), 137.4 (C), 135.5 (C), 134.9 (CH), 133.8 (CH), 127.1 (CH), 125.1 (C), 103.8 (C), 99.1 (C), -0.15 (3 × CH_3); IR ν_{max}/cm^{-1} 2961, 2843, 2158, 1696, 1587, 1470, 1250, 1178, 1109, 839, 759, 677, 643.

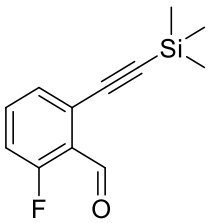
5-Fluoro-2-((trimethylsilyl)ethynyl)benzaldehyde (250)



Prepared according to **GP4** using 2-bromo-5-fluorobenzaldehdye (2.03 g, 10.0 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the protected alkyne **250** as a brown oil (1.34 g, 61%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (d, *J* = 3.2 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.00 – 6.92 (m, 1H), 0.01 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7 (CHO), 162.6 (d, J_{C-F} = 252.8 Hz, C), 138.4 (d, J_{C-F} = 6.7 Hz, C), 135.7 (d, J_{C-F} = 7.7 Hz, CH), 123.0 (d, J_{C-F} = 3.6 Hz, C), 121.3 (d, J_{C-F} = 22.8 Hz, CH), 113.6 (d, J_{C-F} = 23.1 Hz,CH), 102.3 (C), 99.1 (C), -0.11 (3 × CH_3); IR ν_{max}/cm^{-1} 2962, 2158, 1693, 1601, 1483, 1420, 1251, 1146, 839, 734, 645.

Data matches that reported in the literature.[124]

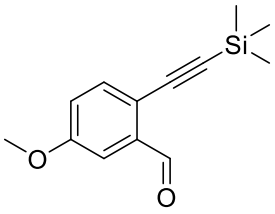
2-Fluoro-6-((trimethylsilyl)ethynyl)benzaldehyde (257)



Prepared according to **GP4** using 2-bromo-6-fluorobenzaldehdye (2.03 g, 10.0 mmol). Purification by flash column chromatography [98:2 (hexane:EtOAc)] gave the protected alkyne **257** as a brown oil (2.13 g, 97%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.53 (d, *J* = 0.6 Hz, 1H), 7.49 (ddd, *J* = 8.3, 7.8, 5.3 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.16 – 7.07 (m, 1H), 0.27 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.9 (CHO), 162.1 (d, J_{C-F} = 263.7 Hz, C), 134.9 (d, J_{C-F} = 10.5 Hz, CH), 130.0 (d, J_{C-F} = 3.8 Hz, CH), 127.7 (d, J_{C-F} = 3.8 Hz, C), 124.7 (d, J_{C-F} = 8.3 Hz, C), 117.4 (d, J_{C-F} = 21.5 Hz, CH), 103.7 (C), 99.8 (d, J_{C-F} = 4.0 Hz, C), -0.18 (3 × CH_3); IR ν_{max}/cm^{-1} 2960, 1703, 1599, 1567,1463, 1250, 1187, 1005, 840, 759, 657.

Data matches that reported in the literature.[125]

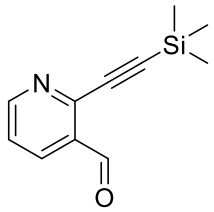
5-Methoxy-2-((trimethylsilyl)ethynyl)benzaldehyde (265)



Prepared according to **GP4** using 2-bromo-5-methoxybenzaldehdye (2.58 g, 12.0 mmol). Purification by flash column chromatography [95:5 (hexane:EtOAc)] gave the protected alkyne **265** as a white solid (2.45 g, 88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.51 (s, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.38 (d, *J* = 2.8 Hz, 1H), 7.08 (dd, *J* = 8.6, 2.8 Hz, 1H), 3.86 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9 (CHO), 160.0 (C), 137.8 (C), 135.0 (CH), 121.7 (CH), 119.6 (C), 109.7 (CH), 100.7 (C), 100.3 (C), 55.8 (CH_3), 0.0 (3 × CH_3); IR ν_{max}/cm^{-1} 2968, 2845, 2150, 1693, 1598, 1386, 1313, 846, 719, 646.

Data matches that reported in the literature.[124]

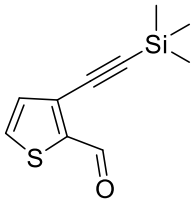
2-((Trimethylsilyl)ethynyl)nicotinaldehyde (277)



Prepared according to **GP4** using 2-bromonicotinaldehyde (1.15 g, 6.20 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the protected alkyne **277** as a brown solid; mp: 49-51 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (d, *J* = 0.9 Hz, 1H), 8.77 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.39 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 0.30 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.1 (CHO), 154.5 (CH), 145.9 (C), 134.7 (CH), 132.2 (C), 123.6 (CH), 103.1 (C), 99.4 (C), -0.32 (3 × CH_3).

Data matches that reported in the literature.[126]

3-((Trimethylsilyl)ethynyl)thiophene-2-carbaldehyde (284)



Prepared according to **GP4** using 3-bromothiophene-2-carbaldehyde (1.68 g, 8.8 mmol). Purification by flash column chromatography [95:5 (hexane:EtOAc)] gave the protected alkyne **284** as an orange oil (1.50 g, 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.12 (d, *J* = 1.3 Hz, 1H), 7.64 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.17 (d, *J* = 5.0 Hz, 1H), 0.27 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.2 (CHO), 144.7 (C), 133.8 (CH), 131.9 (CH), 131.0 (C), 102.6 (C), 96.5 (C), -0.15 (3 × CH_3); IR ν_{max}/cm^{-1} 3663, 2966, 2154, 1666, 1414, 1249, 997, 835, 707, 654.

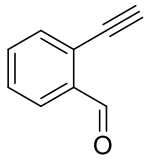
Data matched that reported in the literature.[127]

Preparation of terminal alkynes

General procedure 5 (GP5)

The required trimethylsilyl derivative (1.0 equiv.) was dissolved in methanol (0.2 M). Potassium carbonate (0.5 equiv.) was added and the resulting mixture was stirred at room temperature for 1 hour. The reaction was quenched with saturated $NaHCO_3$ solution and the aqueous layer was extracted with EtOAc (× 2). The combined organic layers were washed with brine, dried over Na_2SO_4 and solvent removed under reduced pressure to give terminal alkyne which is pure enough or may require purification by flash column chromatography.

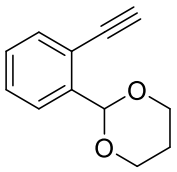
2-Ethynylbenzaldehyde (162)



Prepared according to **GP5** using protected alkyne **161** (2.63 g, 13.0 mmol). Purification by flash column chromatography [96:4 (hexane:EtOAc)] gave the terminal alkyne **162** as a white solid (1.49 g, 88%); mp: 65-67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.54 (d, *J* = 0.8 Hz, 1H), 7.93 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.62 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.57 (td, *J* = 7.4, 1.5 Hz, 1H), 7.52 – 7.44 (m, 1H), 3.46 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5 (CHO), 136.7 (C), 134.1 (CH), 133.8 (CH), 129.4 (CH), 127.4 (CH), 125.6 (C), 84.4 (CH), 79.4 (C).

Data matches that reported in the literature.[68]

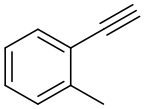
2-(2-Ethynylphenyl)-1,3-dioxane (188)



Prepared according to **GP5** using protected alkyne **187** (1.52 g, 5.84 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave the terminal alkyne **188** as a yellow oil (0.68 g, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.5, Hz, 1H), 7.39 (td, *J* = 7.7, 1.4 Hz, 1H), 7.30 (td, *J* = 7.7, 1.4 Hz, 1H), 5.92 (s, 1H), 4.27 (ddd, *J* = 11.9, 5.1, 1.4 Hz, 2H), 4.09 – 3.98 (m, 2H), 3.29 (s, 1H), 2.35 – 2.18 (m, 1H), 1.51 – 1.38 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6 (C), 132.9 (CH), 129.3 (CH), 128.8 (CH), 126.1 (CH), 120.6 (C), 100.0 (CH), 81.5 (CH), 81.1 (C), 67.8 (2 × CH_2), 25.9 (CH_2).

Data matches that reported in the literature.[128]

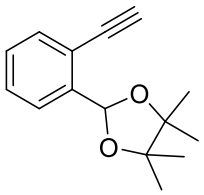
1-Ethynyl-2-methylbenzene (198)



Prepared according to **GP5** using protected alkyne **197** (0.62 g, 3.29 mmol) to give the terminal alkyne **198** as a pale yellow oil (240 mg, 63%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.25 – 7.11 (m, 3H), 3.28 (s, 1H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9 (C), 132.7 (CH), 129.6 (CH), 128.9 (CH), 125.7 (CH), 122.1 (C), 82.7 (C), 81.1 (CH), 20.7 (CH_3); IR ν_{max}/cm^{-1} 3291, 1484, 1455, 1248, 841, 755, 610, 452.

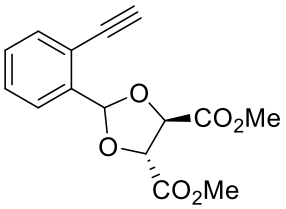
Data matches that reported in the literature.[123]

2-(2-Ethynylphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (204)



Prepared according to **GP5** using protected alkyne **203** (1.60 g, 5.29 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave the terminal alkyne **204** as a yellowish white solid (0.84 g, 69%); mp: 78-80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.38 (td, *J* = 7.6, 1.4 Hz, 1H), 7.30 (dd, *J* = 7.5, 1.4 Hz, 1H), 6.38 (s, 1H), 3.31 (s, 1H), 1.35 (s, 6H), 1.31 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3 (C), 133.2 (CH), 129.1 (CH), 128.6 (CH), 126.0 (CH), 121.6 (C), 97.9 (CH), 82.9 (CH), 82.1 (2 × C), 81.1 (C), 24.6 (2 × CH_3), 22.4 (2 × CH_3); IR ν_{max}/cm^{-1} 3242, 2986, 1394, 1214, 1144, 1112, 1063, 979, 758, 714.

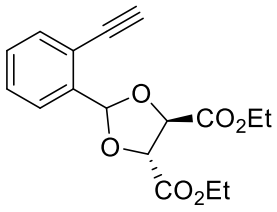
Dimethyl (4R,5R)-2-(2-ethynylphenyl)-1,3-dioxolane-4,5-dicarboxylate (230)



Prepared according to **GP5** using protected alkyne **229** (1.10 g, 3.03 mmol). Purification by flash column chromatography [85:15 (hexane:EtOAc)] gave the terminal alkyne **230** as a pink solid (0.60 g, 68%); mp: 62-64 °C; ^{1}H NMR (300 MHz $CDCl_3$) δ 7.78 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.52 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.42 (td, *J* = 7.6, 1.6 Hz, 1H), 7.36 (td, *J* = 7.4, 1.6 Hz, 1H), 6.59 (s, 1H), 5.01 (d, *J* = 4.0 Hz, 1H), 4.89 (d, *J* = 4.0 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H) 3.33 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9 (CO), 169.4 (CO), 137.0 (C), 132.9 (CH), 129.6 (CH),

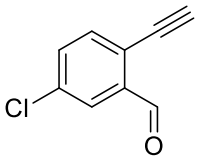
129.1 (CH), 126.8 (CH), 121.8 (C), 104.4 (CH), 82.2 (CH), 80.3 (C), 77.5 (CH), 76.6 (CH), 52.8 (2 × CH_3); HRMS (ES-TOF): *m/z*: calcd for $C_{15}H_{14}O_6Na$: 313.0688, found: 313.0687 $[M + Na]^+$.

Diethyl (4R,5R)-2-(2-ethynylphenyl)-1,3-dioxolane-4,5-dicarboxylate (231)



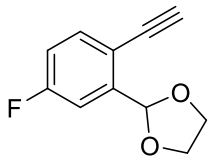
Prepared according to **GP5** using protected alkyne **229** (1.10 g, 2.82 mmol) and ethanol to give crude **231** as a colourless oil which was used immediately in the next step

5-Chloro-2-ethynylbenzaldehyde (244)



Prepared according to **GP5** using protected alkyne **243** (1.38 g, 5.83 mmol). Purification by flash column chromatography [96:4 (hexane:EtOAc)] gave the terminal alkyne **244** as a yellow oil (0.82 g, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.47 (s, 1H), 7.89 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.59 – 7.50 (m, 2H), 3.50 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2 (CHO), 137.8 (C), 136.0 (C), 135.2 (CH), 133.9 (CH), 127.4 (CH), 123.8 (C), 85.3 (CH), 78.4 (C); IR ν_{max}/cm^{-1} 3671, 3247, 2971, 2104, 1692, 1587, 1472, 1396, 1258, 1065, 832, 723, 676; HRMS (EI-TOF): *m/z*: calcd for C_9H_5OCl: 164.0029, found: 164.0033 $[M]^+$.

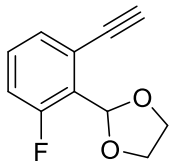
2-(2-Ethynyl-5-fluorophenyl)-1,3-dioxolane (252)



Prepared according to **GP5** using protected alkyne **251** (0.55 g, 2.32 mmol) to give the terminal alkyne **252** as an orange oil (340 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.5, 5.5 Hz, 1H), 7.29 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.02 (td, *J* = 8.3, 2.8 Hz, 1H), 6.18 (d, *J* = 1.5 Hz, 1H), 4.21 – 4.12 (m, 2H), 4.10 – 4.02 (m, 2H), 3.29 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (d, J_{C-F} = 250.5 Hz, C), 142.8 (d, J_{C-F} = 7.5 Hz, C), 135.3 (d, J_{C-F} = 8.3 Hz, CH), 117.4 (d, J_{C-F} = 3.5 Hz, C), 116.4 (d, J_{C-F} = 22.2 Hz, CH), 113.6 (d, J_{C-F} = 23.7 Hz, CH), 101.2 (CH), 81.8 (CH), 80.0 (C), 65.8 (2 × CH_2); IR ν_{max}/cm^{-1} 3297, 2891, 1608, 1488, 1270, 1160, 1112, 1063, 881, 825.

Data matches that reported in the literature [129]

2-(2-Ethynyl-6-fluorophenyl)-1,3-dioxolane (259)

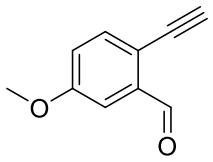


Prepared according to **GP5** using protected alkyne **258** (2.00 g, 7.57 mmol). to give the terminal alkyne **259** as reddish brown oil (1.29 g, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.07 (ddd, *J* = 10.6, 7.9, 1.7 Hz, 1H), 6.37 (d, *J* = 0.9 Hz, 1H), 4.30 – 4.19 (m, 2H), 4.11 – 4.00 (m, 2H), 3.34 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6 (d, J_{C-F} = 251.9 Hz, C), 130.6 (d, J_{C-F} = 9.8 Hz, CH), 129.8 (d, J_{C-F} = 3.7 Hz, CH), 127.1 (d, J_{C-F} = 11.8 Hz, C), 123.8 (d, J_{C-F} = 5.3 Hz, C), 117.3 (d, J_{C-F} = 22.4 Hz, CH), 100.2 (d, J_{C-F} = 3.6 Hz, CH), 82.6 (CH), 80.4 (d, J_{C-}

$_F$ = 4.3 Hz, C), 66.3 (2 × CH_2); IR ν_{max}/cm^{-1} 3290, 2896, 1609, 1574, 1467, 1402, 1212, 1092, 956, 795, 634.

Data matches that reported in the literature.[71]

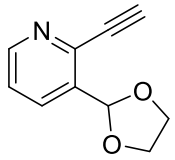
2-Ethynyl-5-methoxybenzaldehyde (266)



Prepared according to **GP5** using protected alkyne **265** (2.15 g, 9.25 mmol). Purification by flash column chromatography [96:4 (hexane:EtOAc)] gave the terminal alkyne **266** as a yellow solid (1.34 g, 91%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.49 (s, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.40 (d, *J* = 2.8 Hz, 1H), 7.10 (dd, *J* = 8.6, 2.8 Hz, 1H), 3.86 (s, 3H), 3.37 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4 (CHO), 160.3 (C), 138.2 (C), 135.3 (CH), 121.6 (CH), 118.2 (C), 110.1 (CH), 82.9 (C), 79.3 (C), 55.8 (CH_3); IR ν_{max}/cm^{-1} 3253, 2958, 1163, 1600, 1490, 1318, 1088, 785, 660.

Data matches that reported in the literature.[68]

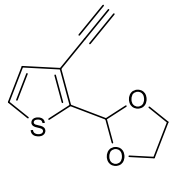
3-(1,3-Dioxolan-2-yl)-2-ethynylpyridine (279)



Prepared according to **GP5** using protected alkyne **278** (1.43 g, 5.78 mmol) to give the terminal alkyne **279** as a brown oil (0.88 g, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.89 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.31 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.19 (s, 1H), 4.20 – 4.13 (m, 2H), 4.10 – 4.03 (m, 2H), 3.39 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6 (CH),

141.4 (C), 136.0 (C), 134.3 (CH), 123.6 (CH), 100.9 (CH), 81.6 (CH), 80.3 (C), 65.8 (2 × CH_2); IR ν_{max}/cm^{-1} 3257, 2889, 2109, 1567, 1436, 1380, 1116, 1068, 940, 786, 631; HRMS (EI-TOF): *m/z*: calcd for $C_{10}H_9NO_2$: 175.0633, found: 175.0628 $[M]^+$.

2-(3-Ethynylthiophen-2-yl)-1,3-dioxolane (286)



Prepared according to **GP5** using protected alkyne **285** (1.11 g, 4.40 mmol) to give the terminal alkyne **286** as an orange oil (0.68 g, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 5.1 Hz, 1H), 7.11 (d, *J* = 5.1 Hz, 1H), 6.34 (s, 1H), 4.27 – 4.15 (m, 2H), 4.14 – 4.03 (m, 2H), 3.30 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7 (C), 130.5 (CH), 125.6 (CH), 120.6 (C), 99.2 (CH), 81.0 (CH), 77.1 (C), 65.6 (2 × CH_2); IR ν_{max}/cm^{-1} 3282, 2971, 2889, 1668, 1535, 1443, 1364, 1187, 1069, 934, 612, 546.

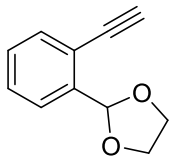
Data matches that reported in the literature.[71]

Preparation of acetals

General procedure 6 (GP6)

The required aldehyde (1.0 equiv.) was dissolved in toluene (0.1 M) followed by addition of the requisite diol (1.2 equiv.) and *p*-TsOH.H_2O (5 mol%). The resulting mixture was heated at reflux using Dean Stark apparatus. The reaction was monitored by TLC. After cooling, the reaction mixture was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc (× 2), washed with brine, dried over Na_2SO_4 and solvent removed under reduced pressure. The crude residue was purified by flash column chromatography.

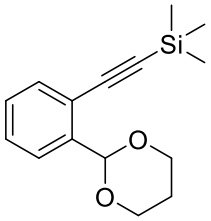
2-(2-Ethynylphenyl)-1,3-dioxolane (163)



Prepared according to **GP6** using aldehyde **162** (1.30 g, 10.0 mmol) and ethylene glycol. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave the acetal **163** as an orange oil (1.46 g, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.39 (app. td, *J* = 7.6, 1.6 Hz, 1H), 7.33 (app. td, *J* = 7.4, 1.6 Hz, 1H), 6.22 (s, 1H), 4.23 – 4.12 (m, 2H), 4.10 – 4.02 (m, 2H), 3.32 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8 (C), 133.4 (CH), 129.1 (2 × CH), 126.2 (CH), 121.5 (C), 101.9 (CH), 82.0 (CH), 81.0 (C), 65.7 (2 × CH_2).

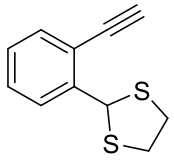
Data matches that reported in the literature.[66]

((2-(1,3-Dioxan-2-yl)phenyl)ethynyl)trimethylsilane (187)



Prepared according to **GP6** using aldehyde **161** (1.21 g, 5.98 mmol) and propane-1,3-diol to give the crude acetal **187** as a brown solid which was used immediately in the next step without further purification.

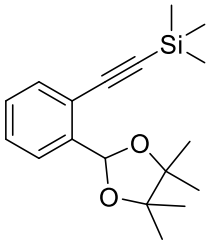
2-(2-Ethynylphenyl)-1,3-dithiolane (194)



2-Ethynylbenzaldehyde **162** (1.00 g, 7.68 mmol) was dissolved in CH_2Cl_2 (77 mL, 0.1 M) and 1,2-ethanedithiol (1.4 mL, 16.9 mmol, 1.12 equiv.), p-TsOH.H_20 (3 mol%) and silica gel (4.0 g) were added. The reaction mixture was heated at reflux and monitored by TLC. After cooling, the mixture was filtered through a plug of cotton wool and solvent removed under reduced pressure. Purification by flash column chromatography [97:3 (hexane:EtOAc), 1% Et_3N] gave the dithiol **194** as an orange oil (0.51 g, 32%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.36 (td, *J* = 7.7, 1.4 Hz, 1H), 7.21 (td, *J* = 7.6, 1.3 Hz, 1H), 6.22 (s, 1H), 3.53 – 3.43 (m, 2H), 3.41 (s, 1H), 3.40 – 3.32 (m, 2H); IR ν_{max}/cm^{-1} 3662, 3283, 2970, 2921, 1471, 1443, 1274, 1041, 753, 618, 546

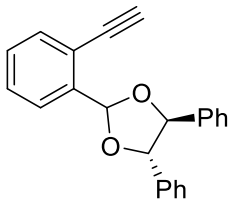
Data matches that reported in the literature.[71]

Trimethyl((2-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenyl)ethynyl)silane (203)



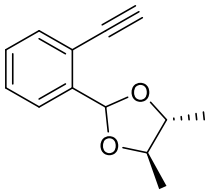
Prepared according to **GP6** using aldehyde **161** (1.21 g, 5.98 mmol) and pinacol to give the acetal **203** as a brown oil (1.61 g, 89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.37 – 7.30 (m, 1H), 7.29 – 7.22 (m, 1H), 6.39 (s, 1H), 1.35 (s, 6H), 1.31 (s, 6H), 0.25 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (C), 132.5 (CH), 128.8 9 (CH), 128.5 (CH), 125.8 (CH), 122.6 (C), 102.4 (C), 99.5 (C), 98.0 (CH), 82.8 (2 × C), 24.7 (2 × CH_3), 22.3 (2 × CH_3), 0.05 (3 × CH_3).

(4S,5S)-2-(2-Ethynylphenyl)-4,5-diphenyl-1,3-dioxolane (210)



Prepared according to **GP6** using aldehyde **162** (0.71 g, 5.45 mmol) and (S,S)-(-)-hydrobenzoin to give the acetal **210** as a yellow oil which was used immediately in the next step.

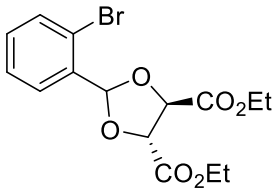
(4R,5R)-2-(2-Ethynylphenyl)-4,5-dimethyl-1,3-dioxolane (216)



Prepared according to **GP6** using aldehyde **162** (0.60 g, 4.61 mmol) and (2R, 3R)-butane-2,3-diol. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave the acetal **216** as a colourless oil (0.59 g, 63%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.51 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.39 (td, *J* = 7.6, 1.5 Hz, 1H), 7.31 (td, *J* = 7.6, 1.5 Hz, 1H), 6.35 (s, 1H), 3.90 – 3.78 (m, 2H), 3.31 (s, 1H), 1.40 (d, *J* = 5.9 Hz, 3H), 1.34 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5 (C), 133.3 (CH), 129.2 (CH), 129.0 (CH), 126.5 (CH), 121.4 (C), 100.8 (CH), 82.0 (CH), 81.1 (C), 80.7 (CH), 78.9 (CH), 17.3 (CH_3), 16.9 (CH_3); IR ν_{max}/cm^{-1} 3282, 2974, 1449, 1379, 1080, 978, 759, 648.

Data matches that reported in the literature.[71]

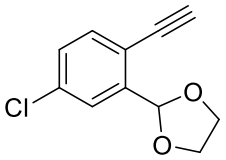
Diethyl (4R,5R)-2-(2-bromophenyl)-1,3-dioxolane-4,5-dicarboxylate (228)



Prepared according to **GP6** using 2-bromobenzaldehyde (3.70 g, 20.0 mmol) and (+)-diethyl-L-tartrate. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the acetal **228** as a colourless oil (2.83 g, 38%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.56 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 7.30 – 7.22 (m, 1H), 6.48 (s, 1H), 4.98 (d, *J* = 3.8 Hz, 1H), 4.87 (d, *J* = 3.8 Hz, 1H), 4.41 – 4.30 (m, 2H), 4.30 – 4.24 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6 (CO), 169.2 (CO), 134.6 (C), 132.9 (CH), 131.4 (CH), 129.0 (CH), 127.7 (CH), 123.4 (C), 105.4 (CH), 78.0 (CH), 77.4 (CH), 62.3 (CH_2), 62.2 (CH_2), 14.3 (CH_3), 14.2 (CH_3).

Data matches that reported in the literature.[130]

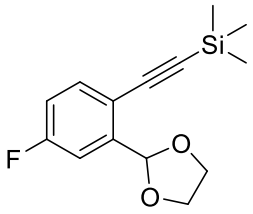
2-(5-Chloro-2-ethynylphenyl)-1,3-dioxolane (245)



Prepared according to **GP6** using aldehyde **244** (1.65 g, 10.0 mmol) and ethylene glycol. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] gave the acetal **245** as a red solid (1.42 g, 68%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.2 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.30 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.17 (s, 1H), 4.22 – 4.12 (m, 2H), 4.12 – 4.02 (m, 2H), 3.36 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7 (C), 135.3 (C), 134.5 (CH), 129.4 (CH), 126.6 (CH), 119.9 (C), 101.2 (CH), 82.9 (CH), 80.0 (C), 65.8 (2 × CH_2); IR ν_{max}/cm^{-1} 3675, 3242,

2971, 2900, 1595, 1476, 1390, 1259, 1214, 1095, 1065, 964, 878, 556; HRMS (EI-TOF): *m/z*: calcd for $C_{11}H_9O_2Cl$: 208.0291, found: 208.0284 $[M]^+$.

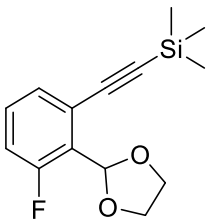
((2-(1,3-Dioxolan-2-yl)-4-fluorophenyl)ethynyl)trimethylsilane (251)



Prepared according to **GP6** using aldehyde **250** (1.29 g, 5.86 mmol) and ethylene glycol Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] gave the acetal **250** as a colourless oil (1.11 g, 72%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.5, 5.5 Hz, 1H), 7.28 – 7.23 (m, 1H), 6.99 (td, *J* = 8.3, 2.8 Hz, 1H), 6.14 (d, *J* = 1.5 Hz, 1H), 4.22 – 4.14 (m, 2H), 4.09 – 4.01 (m, 2H), 0.25 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (d, $J_{C\text{-}F}$ = 250.4 Hz, C), 142.4 (d, $J_{C\text{-}F}$ = 7.3 Hz, C), 134.9 (d, $J_{C\text{-}F}$ = 8.1 Hz, CH), 118.6 (d, $J_{C\text{-}F}$ = 3.7 Hz, C), 116.3 (d, $J_{C\text{-}F}$ = 22.2 Hz, CH), 113.6 (d, $J_{C\text{-}F}$ = 23.3 Hz, CH), 101.4 (CH), 101.2 (C), 99.2 (C), 65.7 (2 × CH_2), 0.04 (3 × CH_3); IR ν_{max}/cm^{-1} 2960, 2892, 2158, 1607, 1491, 1251, 1160, 1064, 839,758.

Data matches that reported in the literature.[71]

((2-(1,3-Dioxolan-2-yl)-3-fluorophenyl)ethynyl)trimethylsilane (258)

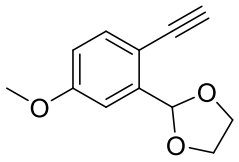


Prepared according to **GP6** using aldehyde **257** (1.52 g, 6.90 mmol) and ethylene glycol. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] gave the acetal

258 as a brown oil (1.52 g, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 1H), 7.25 – 7.21 (m, 1H), 7.02 (ddd, *J* = 10.6, 7.6, 1.9 Hz, 1H), 6.35 (d, *J* = 0.9 Hz, 1H), 4.30 – 4.21 (m, 2H), 4.11 – 4.01 (m, 2H), 0.25 (s, 9H); ^{13}C NMR (101 MHz, CDC_{l3}) δ 161.6 (d, $J_{C\text{-}F}$ = 251.9 Hz, C), 130.5 (d, $J_{C\text{-}F}$ = 10.0 Hz, CH), 129.8 (d, $J_{C\text{-}F}$ = 3.3 Hz, CH), 126.6 (d, $J_{C\text{-}F}$ = 11.5 Hz, C), 124.8 (d, $J_{C\text{-}F}$ = 5.3 Hz, C), 116.8 (d, $J_{C\text{-}F}$ = 22.5 Hz, CH), 101.5 (d, $J_{C\text{-}F}$ = 4.0 Hz, C), 100.2 (d, $J_{C\text{-}F}$ = 3.8 Hz, CH), 100.1 (C), 66.3 (2 × CH_2), 0.04 (3 × CH_3); IR ν_{max}/cm^{-1} 2959, 2897, 2153, 1573, 1467, 1401, 1249, 1095, 1004, 838, 648.

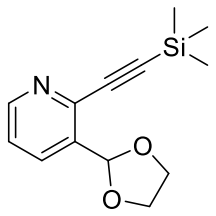
Data matches that reported in the literature.[71]

2-(2-Ethynyl-5-methoxyphenyl)-1,3-dioxolane (267)



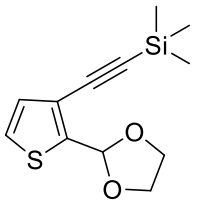
Prepared according to **GP6** using aldehyde **266** (1.10 g, 6.87 mmol) and ethylene glycol. Purification by flash column chromatography [85:15 (hexane:EtOAc), 1% Et_3N] gave the acetal **267** as an orange solid (0.93 g, 65%); mp: 45-47 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 1H), 7.12 (d, *J* = 2.7 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.18 (s, 1H), 4.21 – 4.14 (m, 2H), 4.10 – 4.03 (m, 2H), 3.83 (s, 3H), 3.24 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2 (C), 141.5 (C), 134.8 (CH), 115.2 (CH), 113.6 (C), 111.3 (CH), 101.7 (CH), 81.0 (C), 80.5 (C), 65.7 (2 × CH_2), 55.5 (CH_3); IR ν_{max}/cm^{-1} 3251, 2976, 2899, 1610, 1487, 1397, 1297, 1063, 894, 650, 512; HRMS (EI-TOF): *m/z*: calcd for $C_{12}H_{12}O_3$: 204.0786, found: 204.0781 $[M]^+$.

3-(1,3-Dioxolan-2-yl)-2-((trimethylsilyl)ethynyl)pyridine (278)



Prepared according to **GP6** using aldehyde **277** (1.00 g, 4.92 mmol) and ethylene glycol Purification by flash column chromatography [8:2 (hexane:EtOAc), 1% Et_3N] gave the acetal **278** as a colourless oil (360 mg, 30%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.76 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.21 – 7.13 (m, 1H), 6.06 (s, 1H), 4.12 – 4.04 (m, 2H), 4.00 – 3.92 (m, 2H), 0.17 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6 (CH), 142.2 (C), 135.6 (C), 134.3 (CH), 123.2 (CH), 101.1 (CH), 101.0 (C), 99.9 (C), 65.8 (2 × CH_2), -0.17 (3 × CH_3); IR ν_{max}/cm^{-1} 3675, 2971, 1116, 1057, 661, 573; HRMS (ES-TOF): *m/z*: calcd for $C_{13}H_{18}NO_2Si$: 248.1107, found: 248.1106 $[M + H]^+$.

((2-(1,3-Dioxolan-2-yl)thiophen-3-yl)ethynyl)trimethylsilane (285)



Prepared according to **GP6** using aldehyde **284** (1.21 g, 5.81 mmol) and ethylene glycol. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] gave the acetal **285** as a yellow oil (1.15 g, 78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 5.1, 0.6 Hz, 1H), 7.02 (d, *J* = 5.1 Hz, 1H), 6.26 (s, 1H), 4.20 – 4.14 (m, 2H), 4.06 – 4.00 (m, 2H), 0.24 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (C), 130.3 (CH), 125.5 (CH), 122.1 (C), 99.3 (CH), 98.3 (C), 98.0

(C), 65.6 (2 × CH_2), 0.09 (3 × CH_3).; IR ν_{max}/cm^{-1} 2959, 2892, 2153, 1531, 1248, 1189, 1073, 834, 758, 646.

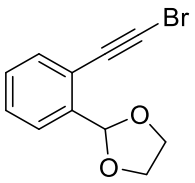
Data matches that reported in the literature.[71]

Preparation of bromoalkynes

General procedure 7 (GP7)

The required terminal alkyne (1.0 equiv.) was combined with NBS (1.1 equiv.), $AgNO_3$ (0.1 equiv.) in acetone (0.2 M) and the resulting solution was stirred at room temperature for 1 hour. 2-3 Spatula of silica gel was added to the flask and the solvent removed under reduced pressure. The resulting solid was loaded onto a pad of silica gel and elution was done using (hexane:EtOAc, 9:1). Solvent was concentrated to give the pure bromoalkyne which is used directly in the next step. Further purification by flash column chromatography was done for impure substrates

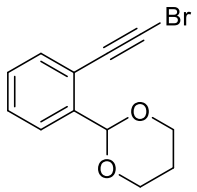
2-(2-(Bromoethynyl)phenyl)-1,3-dioxolane (164)



Prepared according to **GP7** using terminal alkyne **163** (0.68 g, 3.90 mmol) and *N*-bromosuccinimde. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave the alkynyl bromide **164** as a yellow oil (0.92 g, 93%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.38 (app. td, *J* = 7.6, 1.6 Hz, 1H), 7.32 (app. td, *J* = 7.5, 1.6 Hz, 1H), 6.14 (s, 1H), 4.24 – 4.13 (m, 2H), 4.11 – 4.02 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9 (C), 133.3 (CH), 130.2 (C), 129.2 (CH), 129.0 (CH), 126.5 (CH), 121.0 (C),

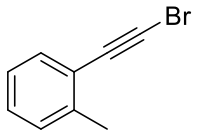
103.5 (C), 102.1 (CH), 65.8 (2 × CH_2); IR ν_{max}/cm^{-1} 2971, 2885, 2195, 1698, 1449, 1392, 1114, 1069, 941, 757; HRMS (EI-TOF): *m/z*: calcd for $C_{11}H_9O_2Br$: 251.9786, found: 251.9789 $[M]^+$.

2-(2-(Bromoethynyl)phenyl)-1,3-dioxane (189)



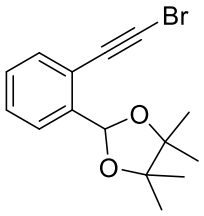
Prepared according to **GP7** using terminal alkyne **188** (0.67 g, 3.56 mmol) and N-bromosuccinimde to give the alkynyl bromide **189** as a yellow oil which was used immediately without further purification.

1-(Bromoethynyl)-2-methylbenzene (199)



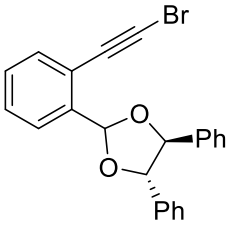
Prepared according to **GP7** using terminal alkyne **198** (0.21 g, 1.81 mmol) and *N*-bromosuccinimde. Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the alkynyl bromide **199** as a brown oil (320 mg, 91%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.25 – 7.09 (m, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0 (C), 132.5 (CH), 129.6 (CH), 128.8 (CH), 125.7 (CH), 122.7 (C), 79.2 (C), 52.9 (C), 20.7 (CH_3); IR ν_{max}/cm^{-1} 3675, 2971,2901, 1669, 1411, 1250, 1066, 842, 759, 709; HRMS(EI-TOF): *m/z*: calcd for C_9H_7Br: 193.9731, found: 193.9736 $[M]^+$.

2-(2-(Bromoethynyl)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (205)



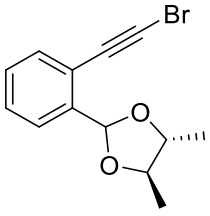
Prepared according to **GP7** using terminal alkyne **204** (311 mg, 1.35 mmol) and *N*-bromosuccinimde to give the alkynyl bromide **205** as a colourless oil which was used immediately without further purification.

(4S,5S)-2-(2-(Bromoethynyl)phenyl)-4,5-diphenyl-1,3-dioxolane (211)



Prepared according to **GP7** using terminal alkyne **210** (0.72 g, 2.21 mmol) and *N*-bromosuccinimde to give the alkynyl bromide **211** as a yellow oil which was used immediately without further purification.

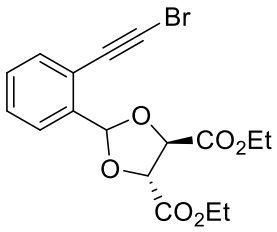
(4R,5R)-2-(2-(Bromoethynyl)phenyl)-4,5-dimethyl-1,3-dioxolane (217)



Prepared according to **GP7** using terminal alkyne **216** (0.70 g, 3.46 mmol) and *N*-bromosuccinimde to give the alkynyl bromide **217** as a colourless oil (0.96 g, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.37 (td, *J* = 7.6, 1.6 Hz,

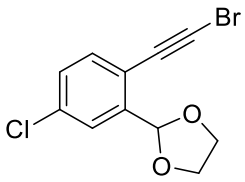
1H), 7.30 (td, *J* = 7.6, 1.6 Hz, 1H), 6.25 (s, 1H), 3.93 – 3.78 (m, 2H), 1.41 (d, *J* = 5.8 Hz, 3H), 1.34 (d, *J* = 5.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5 (C), 133.4 (CH), 129.1 (CH), 129.0 (CH), 126.9 (CH), 121.9 (C), 101.0 (CH), 80.7 (CH), 79.1 (CH), 77.8 (C), 54.1 (C), 17.4 (CH_3), 16.9 (CH_3); IR ν_{max}/cm^{-1} 2973, 2878, 1449, 1379, 1080, 978, 751, 625; HRMS(EI-TOF): *m/z*: calcd for $C_{13}H_{12}O_2Br$: 279.0021, found: 279.0029 $[M]^+$.

Diethyl (4R,5R)-2-(2-(bromoethynyl)phenyl)-1,3-dioxolane-4,5-dicarboxylate (232)



Prepared according to **GP7** using terminal alkyne **231** (0.53 g, 1.66 mmol) and *N*-bromosuccinimde to give the alkynyl bromide **232** as an off white solid which was used immediately without further purification.

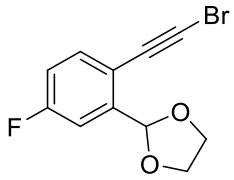
2-(2-(Bromoethynyl)-5-chlorophenyl)-1,3-dioxolane (246)



Prepared according to **GP7** using terminal alkyne **245** (430 mg, 2.06 mmol) and *N*-bromosuccinimde. Purification by flash column chromatography [8:2 (hexane:EtOAc),1% Et_3N] gave the alkynyl bromide **246** as a light brown solid (0.59 g, 100%); mp: 100-112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 2.2 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.29 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.09 (s, 1H), 4.22 – 4.12 (m, 2H), 4.11 – 4.02 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$)

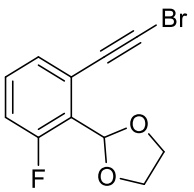
δ 141.8 (C), 135.1 (C), 134.4 (CH), 129.4 (CH), 126.8 (CH), 120.5 (C), 101.3 (CH), 76.7 (C), 65.8 (2 × CH_2), 55.5 (C); IR ν_{max}/cm^{-1} 2986, 2883, 2193, 1592, 1466, 1123, 1095, 1069, 958, 944, 817, 677, 566; HRMS (EI-TOF): *m/z*: calcd for $C_{11}H_8O_2ClBr$: 285.9396, found: 285.9398 $[M]^+$.

2-(2-(Bromoethynyl)-5-fluorophenyl)-1,3-dioxolane (253)



Prepared according to **GP7** using terminal alkyne **252** (300 mg, 1.56 mmol) and *N*-bromosuccinimde. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave the alkynyl bromide **253** as a pale yellow solid (390 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.5, 5.4 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.01 (td, *J* = 8.3, 2.8 Hz, 1H), 6.11 (d, *J* = 1.5 Hz, 1H), 4.21 – 4.14 (m, 2H), 4.10 – 4.03 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (d, $J_{C\text{-}F}$ = 250.7 Hz, C), 142.8 (d, $J_{C\text{-}F}$ = 7.4 Hz, C), 135.2 (d, $J_{C\text{-}F}$ = 8.3 Hz, CH), 118.0 (d, $J_{C\text{-}F}$ = 3.7 Hz, C), 116.5 (d, $J_{C\text{-}F}$ = 22.3 Hz, CH), 113.8 (d, $J_{C\text{-}F}$ = 23.7 Hz, CH), 101.3 (CH), 76.6 (C), 65.8 (2 × CH_2), 54.1 (C); IR ν_{max}/cm^{-1} 3675, 2971, 2903, 1606, 1476, 1401, 1054, 881, 540; HRMS (EI-TOF): *m/z*: calcd for $C_{11}H_8O_2FBr$: 269.9692, found: 269.9699 $[M]^+$.

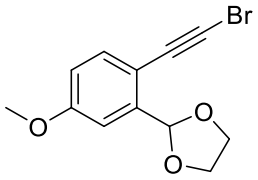
2-(2-(Bromoethynyl)-6-fluorophenyl)-1,3-dioxolane (260)



Prepared according to **GP7** using terminal alkyne **259** (400 mg, 2.08 mmol) and *N*-bromosuccinimde. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1%

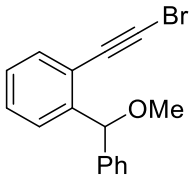
Et_3N] gave the alkynyl bromide **260** as a yellow soild (0.55 g, 98%); mp: 35-38 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.05 (ddd, *J* = 10.5, 6.0, 3.6 Hz, 1H), 6.30 (d, *J* = 0.7 Hz, 1H), 4.32 – 4.18 (m, 2H), 4.14 – 4.01 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (d, $J_{C\text{-}F}$ = 252.2 Hz, C), 130.7 (d, $J_{C\text{-}F}$ = 9.8 Hz, CH), 129.8 (d, $J_{C\text{-}F}$ = 3.6 Hz, CH), 127.2 (d, $J_{C\text{-}F}$ = 11.7 Hz, C), 124.2 (d, $J_{C\text{-}F}$ = 5.4 Hz, C), 117.1 (d, $J_{C\text{-}F}$ = 22.4 Hz, CH), 99.9 (d, $J_{C\text{-}F}$ = 4.4 Hz, CH), 66.3 (2 × CH_2), 55.1 (C), (one quaternary carbon unaccounted for); IR ν_{max}/cm^{-1} 3674, 2973, 2901, 2190, 1577, 1461, 1212, 1088, 1057, 959, 793,521; HRMS(EI-TOF): *m/z*: calcd for $C_{11}H_7O_2BrF$: 268.9613, found: 268.9617 $[M]^+$.

2-(2-(Bromoethynyl)-5-methoxyphenyl)-1,3-dioxolane (268)



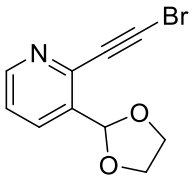
Prepared according to **GP7** using terminal alkyne **267** (0.58 g, 2.84 mmol) and *N*-bromosuccinimde. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave the alkynyl bromide **268** as a white soild (0.67 g, 84%); mp: 83-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.84 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.10 (s, 1H), 4.21 – 4.15 (m, 2H), 4.10 – 4.04 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1 (C), 141.6 (C), 134.7 (CH), 115.3 (CH), 114.4 (C), 114.2 (C), 111.5 (CH), 101.9 (CH), 65.7 (2 × CH_2), 55.6 (CH_3), 52.2 (C); IR ν_{max}/cm^{-1} 3674, 2973, 2899, 1607, 1395, 1294, 1067, 891, 818, 548; HRMS(ES-TOF): *m/z*: calcd for $C_{12}H_{12}O_3Br$: 282.9970, found: 282.9971 $[M + H]^+$.

1-(Bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (272)



Prepared according to **GP7** using terminal alkyne **271** (320 mg, 1.44 mmol) and *N*-bromosuccinimde. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave the alkynyl bromide **272** as a colourless oil (386 mg, 89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 1H), 7.45 – 7.29 (m, 6H), 7.25 – 7.17 (m, 2H), 5.71 (s, 1H), 3.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 141.3 (C), 132.8 (CH), 129.3 (CH), 128.4 (2 × CH), 127.7 (CH), 127.4 (CH), 127.2 (2 × CH), 126.3 (CH), 121.6 (C), 82.7 (CH), 78.7 (C), 57.3 (CH_3), 54.5 (C); IR ν_{max}/cm^{-1} 3028, 2926, 2822, 2194, 1450, 1189, 1100, 1083, 756, 696, 524; HRMS(EI-TOF): *m/z*: calcd for $C_{16}H_{12}BrO$: 299.0072, found: 299.0066 $[M]^+$.

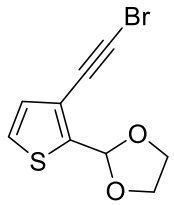
2-(Bromoethynyl)-3-(1,3-dioxolan-2-yl)pyridine (280)



Prepared according to **GP7** using terminal alkyne **279** (200 mg, 1.14 mmol) and *N*-bromosuccinimde. Purification by flash column chromatography [6:4 (hexane:EtOAc), 1% Et_3N] gave the alkynyl bromide **280** as a black liquid (270 mg, 93%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.88 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.31 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.13 (s, 1H), 4.22 – 4.14 (m, 2H), 4.12 – 4.05 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7 (CH), 141.8 (C), 136.1 (C), 134.5 (CH), 123.5 (CH), 100.9 (CH), 65.9 (2 × CH_2), 56.0 (C), (one

quaternary carbon is unaccounted for); IR ν_{max}/cm^{-1} 3662, 2971, 2901, 1393, 1075, 904, 727, 649; HRMS (EI-TOF): *m/z*: calcd for $C_{10}H_8NO_2Br$: 252.9738, found252.9737 $[M]^+$.

2-(3-(Bromoethynyl)thiophen-2-yl)-1,3-dioxolane (287)



Prepared according to **GP7** using terminal alkyne **286** (0.64 g, 3.55 mmol) and *N*-bromosuccinimde. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave the alkynyl bromide **287** as a brown soild (0.83 g, 90%); mp: 38-40 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 5.1, 0.6 Hz, 1H), 7.02 (d, *J* = 5.1 Hz, 1H), 6.25 (d, *J* = 0.6 Hz, 1H), 4.22 – 4.10 (m, 2H), 4.10 – 3.99 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6 (C), 130.3 (CH), 125.6 (CH), 121.2 (C), 99.1 (CH), 73.8 (C), 65.6 (2 × CH_2), 53.4 (C); IR ν_{max}/cm^{-1} 3088, 2898, 1658, 1537, 1199, 1012, 939, 728, 648, 520; HRMS(EI-TOF): *m/z*: calcd for $C_9H_7O_2BrS$: 257.9350, found: 257.9341 $[M]^+$.

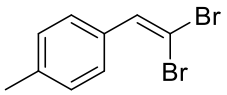
Preparation of dibromoalkenes

General procedure 8 (GP8)

A solution of PPh_3 (4.0 equiv.) and CBr_4 (2.0 equiv.) in CH_2Cl_2 (0.15 M) was stirred at 0 °C for 10 minutes. The relevant aldehyde was added over a period of 5 minutes while maintaining the temperature at 0 °C. After the addition, the reaction mixture was warmed up to room temperature and monitored by TLC. The reaction was quenched by addition of water and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (× 3) and the

combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography

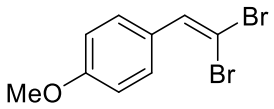
1-(2,2-Dibromovinyl)-4-methylbenzene (340)



Prepared according to **GP8** (87% yield, colourless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 3H), 7.18 (d, *J* = 8.1 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8 (C), 136.9 (CH), 132.6 (C), 129.3 (2 × CH), 128.5 (2 × CH), 88.7 (C), 21.5 (CH_3).

Data matches that reported in the literature.[131]

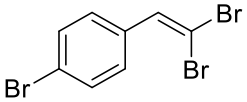
1-(2,2-Dibromovinyl)-4-methoxybenzene (341)



Prepared according to **GP8** (82% yield, yellow solid); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 2H), 7.41 (s, 1H), 6.93 – 6.86 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (C), 136.5 (CH), 130.0 (2 × CH), 128.0 (C), 114.0 (2 × CH), 87.4 (C), 55.4 (CH_3); IR ν_{max}/cm^{-1} 2964, 2840, 1602, 1506, 1455, 1253, 1176, 1025, 802, 731.

Data matches that reported in the literature.[132]

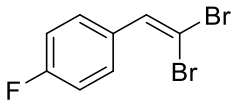
1-Bromo-4-(2,2-dibromovinyl)benzene (342)



Prepared according to **GP8** (98% yield, yellow oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H), 7.42 (br. s, 2H), 7.39 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9 (C), 134.3 (C), 131.8 (2 × CH), 130.1 (2 × CH), 122.8 (C), 90.7 (CH).

Data matches that reported in the literature.[133]

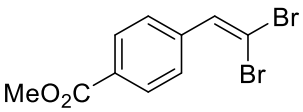
1-(2,2-Dibromovinyl)-4-fluorobenzene (343)



Prepared according to **GP8** (94% yield, yellow oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 2H), 7.44 (s, 1H), 7.12 – 7.02 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (d, $J_{C\text{-}F}$ = 249.5 Hz, C), 135.9 (CH), 131.6 (d, $J_{C\text{-}F}$ = 3.3 Hz, C), 130.4 (d, $J_{C\text{-}F}$ = 8.3 Hz, 2 × CH), 115.6 (d, $J_{C\text{-}F}$ = 21.7 Hz, 2 × CH), 89.8 (C).

Data matches that reported in the literature.[134]

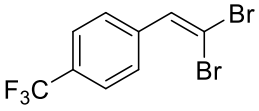
Methyl 4-(2,2-dibromovinyl)benzoate (344)



Prepared according to **GP8** (91% yield, yellow solid); mp: 57-59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.64 – 7.56 (m, 2H), 7.52 (s, 1H), 3.92 (s, 3H).

Data matches that reported in the literature.[135]

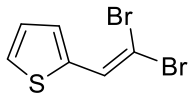
1-(2,2-Dibromovinyl)-4-(trifluoromethyl)benzene (345)



Prepared according to **GP8** (94% yield, colourless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 4H), 7.52 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9 (C), 135.7 (CH), 130.5 (q, J_{C-F} = 32.3 Hz, C)), 128.8 (2 × CH), 125.6 (q, J_{C-F} = 3.3 Hz, 2 × CH)), 124.1 (q, J_{C-F} = 272.4 Hz, C)), 92.5 (C).

Data matches that reported in the literature.[136]

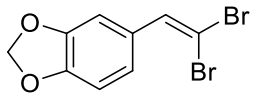
2-(2,2-Dibromovinyl)thiophene (346)



Prepared according to **GP8** (97% yield, brown solid); mp: 55-56 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.39 (ddd, *J* = 5.1, 1.3, 0.6 Hz, 1H), 7.25 (dd, *J* = 1.3, 0.6 Hz, 1H), 7.04 (dd, *J* = 5.1, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (C), 131.0 (CH), 130.2 (CH), 127.3 (CH), 126.7 (CH), 87.1 (C).

Data matches that reported in the literature [137]

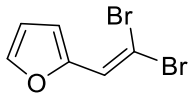
5-(2,2-Dibromovinyl)benzo[d][1,3]dioxole (347)



Prepared according to **GP8** (82% yield, colourless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.19 (d, *J* = 1.8 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); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9 (C), 147.8 (C), 136.4 (CH), 129.3 (C), 123.5 (CH), 108.4 (CH), 108.3 (CH), 101.5 (CH_2), 88.0 (C)

Data matches that reported in the literature.[131]

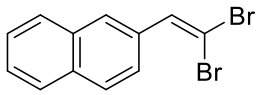
2-(2,2-Dibromovinyl)furan (348)



Prepared according to **GP8** (62% yield, brown oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.41 (s, 1H), 6.95 (d, *J* = 3.6 Hz, 1H), 6.46 (dd, *J* = 3.6, 1.8 Hz, 1H); changed colour and appeared to degrade which was used immediately in the ne×t step

Data matches that reported in the literature.[138]

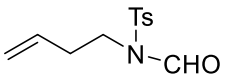
2-(2,2-Dibromovinyl)naphthalene (349)



Prepared according to **GP8** (80% yield, colourless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.88 – 7.80 (m, 3H), 7.67 – 7.62 (m, 2H), 7.54 – 7.48 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.1 (CH), 133.1 (C), 133.1 (C), 132.9 (C), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 126.9 (CH), 126.7 (CH), 125.8 (CH), 90.0 (C).

Data matches that reported in the literature.[139]

***N*-(But-3-en-1-yl)-N-tosylformamide (374)**

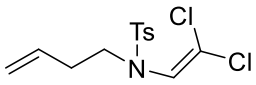


Prepared following literature procedure.[140]

N-BuLi (4.1 mL, 1.6 M in hexane, 6.60 mmol) was gently added to a solution of *N*-(But-3-en-1-yl)-4-methylbenzenesulfonamide **350** (1.35 g, 6.00 mmol) in THF (30 mL) at -10 °C. After stirring for 30 minutes, a solution of formylbenzotriazole (0.97 g, 1.10 mmol) in THF (6 mL) was added and the resulting mixture was warmed at room temperature. The reaction was

monitored by TLC. It was then quenched with saturated NH_4Cl solution and extracted with Et_2O (× 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and solvent removed under reduced pressure. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the formamide **374** as a colourless oil (1.29 g, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 5.65 (ddt, *J* = 18.1, 9.2, 6.9 Hz, 1H), 5.02 (app. t, *J* = 1.3 Hz, 1H), 5.00 – 4.95 (m, 1H), 3.57 – 3.42 (m, 2H), 2.46 (s, 3H), 5.65 (dt, *J* = 11.1, 5.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4 (CHO), 145.7 (C), 135.3 (C), 134.0 (CH), 130.4 (2 × CH), 127.6 (2 × CH), 117.7 (CH_2), 42.2 (CH_2), 32.7 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} 3067, 2979, 1692, 1596, 1415, 1354, 1222, 1157, 670; HRMS (EI-TOF): *m/z*: calcd for $C_{12}H_{15}NO_3NaS$: 276.0670, found: 276.0674 $[M + Na]^+$.

_N_-(But-3-en-1-yl)-N-(2,2-dichlorovinyl)-4-methylbenzenesulfonamide (375)



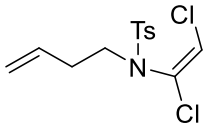
Prepared following literature protocol.[140]

To a flask containing formamide (0.91 g, 3.60 mmol, 1.0 equiv.) and PPh_3 (2.80 g, 10.8 mmol, 3.0 equiv.) dissolved in THF (24 mL) was added a solution of CCl_4 (3.5 mL, 36.0 mmol, 10.0 equiv.) in THF (12 mL) for over a period of 6 hours with the help of a syringe. The reaction mixture was heated at 60 °C and monitored by TLC. Quenching was done using saturated $NaHCO_3$ solution and extracted with Et_2O (× 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and solvent removed under reduced pressure. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the vinylchloride **375** as a white soild (1.03 g, 89%); mp: 53-55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 6.26 (s, 1H), 5.64 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.05 – 4.99 (m, 1H), 4.99 – 4.96 (m, 1H), 3.40 – 3.31 (m, 2H), 2.37 (s, 3H), 2.29 – 2.17 (m, 2H); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 144.3 (C), 135.8 (C), 134.2 (CH), 130.0 (2 × CH), 127.4 (2 × CH), 125.0 (CH), 124.2 (C), 117.7 (CH_2), 48.7 (CH_2), 33.1 (CH_2), 21.7 (CH_3).

Data matches that reported in the literature [100]

(E)-*N*-(But-3-en-1-yl)-*N*-(1,2-dichlorovinyl)-4-methylbenzenesulfonamide (385)



Sulfonamide **310** (450 mg, 2.00 mmol, 1.0 equiv.), Cs_2CO_3 (0.98 g, 3.00 mmol, 1.5 equiv.) and DMF (1.5 mL) were heated at 50 °C with dropwise addition of $CHCl_3$ (0.2 mL, 2.20 mmol, 1.1 equiv.) for 10 minutes. After 3 hours, the reaction was cooled and extracted with EtOAc:H_2O (2:1). The combined organic layers were washed with brine, dried over Na_2SO_4 and solvent removed under reduced pressure. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the dichloroenamide **385** as a clear oil (0.59 g, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 6.51 (s, 1H), 5.74 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.08 (ddd, *J* = 11.0, 6.3, 1.5 Hz, 2H), 3.29 (br. s, 2H), 2.44 (s, 3H), 2.30 (dd, *J* = 14.4, 7.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 135.3 (C), 134.0 (CH), 129.8 (2 × CH), 129.8 (CH), 128.5 (2 × CH), 121.7 (CH), 117.6 (CH_2), 47.6 (CH_2), 32.2 (CH_2), 21.8 (CH_3); HRMS (EI-TOF): *m/z*: calcd for $C_{13}H_{15}NO_2NaSCl2$: 342.0098, found: 342.0100 $[M + Na]^+$.

Preparation of ynamides

General procedure 9 (GP9)

Prepared following literature procedure.[15]

Sulfonamide (1.0 equiv.), K_2CO_3 (2.0 equiv.), $CuSO_4{\cdot}5H_2O$ (10 mol%) and 1,10-phenanthroline (20 mol%) were added to a solution of 1-bromoalkyne (1.1 equiv.) in dry

toluene (1.0 M). The reaction mixture was stirred under argon atmosphere at 70 °C and monitored by TLC. 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 residue was purified by flash column chromatography.

General procedure 10 (GP10)

Prepared following literature procedure.[12]

A reaction vessel was charged with sulfonamide (1.0 equiv.), 1,1-dibromo-1-alkene (1.5 equiv.), Cs_2CO_3 (4.0 equiv.) and CuI (12 mol%). The vessel was fitted with a rubber septum, evacuated under high vacuum and backfilled with argon (this operation was repeated three times). Dry 1,4-dioxane (0.5 M with respect to the sulfonamide) and *N*,*N*'-dimethylethylenediamine (DMEDA) (18 mol%) were then added and the mixture was stirred at 60 °C until complete consumption of the limiting reagent by TLC. 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 residue was purified by flash column chromatography.

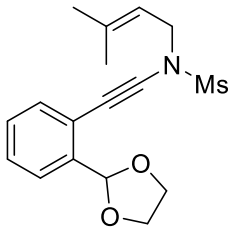
General procedure 11 (GP11)

Prepared following literature protocol.[104]

Under an argon atmosphere, *n*-BuLi (1.2 equiv.) was added carefully added to a solution of dichloroenamide (1.0 equiv) in THF (0.006 M with respect to dichloroenamide) at -78 °C. After stirring at this temperature for 5 minutes, the solution was warmed up to -41 °C for 30 minutes. The mixture was cooled back to -78 °C and another portion of *n*-BuLi (1.0 equiv.) was added for over 10 minutes and also stirred for another additional 10 minutes. Following

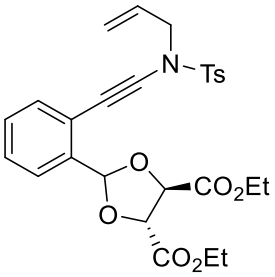
this, the required electrophile (1.2 equiv.) was added (at -78 °C) and the resulting solution was warmed up to room temperature for 1 hour. Quenching was done with water followed by extraction with Et_2O (× 2). The combined organic layers were washed with brine, dried over Na_2SO_4 and solvent removed under reduced pressure. Crude residue was purified by flash column chromatography.

_N_-((2-(1,3-Dioxolan-2-yl)phenyl)ethynyl)-_N_-(3-methylbut-2-en-1-yl)methanesulfonamide (166)



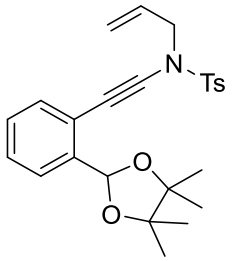
Prepared according to **GP9** using freshly prepared 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane **164** (310 mg, 1.22 mmol) and sulfonamide **165** (180 mg, 1.10 mmol). Purification by flash column chromatography [8:2 (hexane:EtOAc) + 1% Et_3N] gave the ynamide **166** as a colourless oil (150 mg, 41%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 1H), 7.39 – 7.34 (m, 1H), 7.33 – 7.28 (m, 2H), 6.12 (s, 1H), 5.48 – 5.40 (m, 1H), 4.21 – 4.13 (m, 4H), 4.07 – 4.01 (m, 2H), 3.14 (s, 3H), 1.81 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1 (C), 138.4 (C), 131.3 (CH), 129.0 (CH), 127.8 (CH), 126.0 (CH), 122.3 (C), 117.2 (CH), 102.1 (CH), 87.1 (C), 69.0 (C), 65.5 (2 × CH_2), 49.8 (CH_2), 39.1 (CH_3), 26.0 (CH_3), 18.3 (CH_3); IR ν_{max}/cm^{-1} 2973, 1621, 1440, 1321, 1160, 1073, 578, 501; HRMS (EI-TOF): *m/z*: calcd for $C_{17}H_{22}NO_4S$: 336.1270, found: 336.1274 $[M + H]^+$.

Diethyl (4R,5R)-2-(2-(((*N*-allyl-4-methylphenyl)sulfonamido)ethynyl)phenyl)-1,3-dioxolane-4,5-dicarboxylate (234)



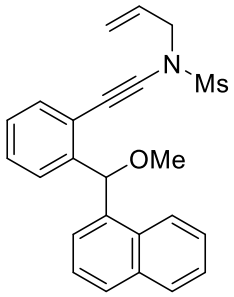
Prepared according to **GP9** using freshly prepared diethyl (4R,5R)-2-(2-(bromoethynyl)phenyl)-1,3-dioxolane-4,5-dicarboxylate **232** (0.52 g, 1.31 mmol) and sulfonamide **220** (250 mg, 1.18 mmol). Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the ynamide **234** as a colourless oil (410 mg, 66%); $[\alpha]_{\mathrm{D}}^{25}$ = -117.73; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.77 – 7.72 (m, 1H), 7.37 – 7.29 (m, 5H), 6.49 (s, 1H), 5.78 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 1H), 5.29 (dd, *J* = 17.0, 1.3 Hz, 1H), 5.22 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.93 (d, *J* = 4.4 Hz, 1H), 4.85 (d, *J* = 4.4 Hz, 1H), 4.35 – 4.20 (m, 4H), 4.06 (dd, *J* = 6.4, 1.2 Hz, 2H), 2.43 (s, 3H), 1.35 – 1.31 (m, 3H), 1.31 – 1.27 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (CO), 169.3 (CO), 144.9 (C), 135.9 (C), 135.0 (C), 131.4 (CH), 131.1 (CH), 130.1 (2 × CH), 129.7 (CH), 128.1 (2 × CH), 128.0 (CH), 127.0 (CH), 123.1 (C), 120.4 (CH_2), 104.6 (CH), 87.5 (C), 77.8 (CH), 77.5 (CH), 68.6 (C), 62.3 (CH_2), 62.2 (CH_2), 54.5 (CH_2), 21.8 (CH_3), 14.4 (CH_3), 14.3 (CH_3); IR ν_{max}/cm^{-1} 2984, 2233, 1739, 1365, 1202, 1169, 1087, 1023, 760, 661; HRMS(ES-TOF): *m/z*: calcd for $C_{27}H_{30}NO_8S$: 528.1692, found: 528.1686 $[M + H]^+$.

***N*-Allyl-4-methyl-*N*-((2-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenyl)ethynyl)benzenesulfonamide (291)**



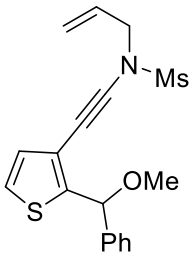
Prepared according to **GP9** using freshly prepared 2-(2-(bromoethynyl)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane **205** (370 mg, 1.20 mmol) and sulfonamide **220** (210 mg, 0.994 mmol). Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the ynamide **291** as a white solid (340 mg, 78%); mp: 43-45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.65 (dd, *J* = 6.8, 2.7 Hz, 1H), 7.36 – 7.27 (m, 4H), 7.25 – 7.20 (m, 1H), 6.31 (s, 1H), 5.80 (ddt, *J* = 16.6, 10.1, 6.3 Hz, 1H), 5.29 (app. ddd, *J* = 17.0, 2.6, 1.2 Hz, 1H), 5.22 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.05 (app. dt, *J* = 6.3, 1.2 Hz, 2H), 2.43 (s, 3H), 1.32 (s, 6H), 1.30 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 139.8 (C), 135.0 (C), 131.4 (CH), 131.1 (CH), 129.9 (2 × CH), 128.5 (CH), 128.1 (2 × CH), 127.7 (CH), 125.8 (CH), 122.5 (C), 120.1 (CH_2), 98.1 (CH), 87.0 (C), 82.8 (2 × C), 69.0 (C), 54.5 (CH_2), 24.7 (2 × CH_3), 22.4 (2 × CH_3), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2977, 2238, 1597, 1363, 1168, 1057, 984, 769, 662; HRMS (ES-TOF): *m/z*: calcd for $C_{25}H_{29}NO_4SNa$: 462.1715, found: 462.1716 $[M + Na]^+$.

***N*-Allyl-*N*-((2-(methoxy(naphthalen-1-yl)methyl)phenyl)ethynyl)methanesulfonamide (299)**



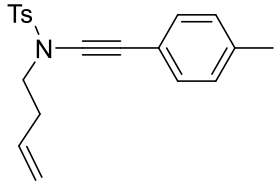
Prepared according to **GP9** using freshly prepared 1-((2-(bromoethynyl)phenyl)(methoxy)methyl)naphthalene **298** (0.7 g, 1.99 mmol) and sulfonamide **175** (240 mg, 1.78 mmol). Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the ynamide **299** as a pale yellow oil (510 mg, 71%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 1H), 7.87 – 7.82 (m, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.55 – 7.41 (m, 5H), 7.33 (dd, *J* = 7.4, 1.3 Hz, 2H), 7.29 (t, *J* = 1.8 Hz, 1H), 6.43 (s, 1H), 5.71 (ddt, *J* = 16.5, 10.1, 6.3 Hz, 1H), 5.24 (app. ddd, *J* = 16.8, 2.4, 1.2 Hz, 1H), 5.18 (dd, *J* = 10.1, 1.2 Hz, 1H), 3.99 (ddt, *J* = 15.0, 6.3, 1.2 Hz, 1H), 3.89 (ddt, *J* = 14.9, 6.3, 1.2 Hz, 1H), 3.55 (s, 3H), 2.71 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0 (C), 136.8 (C), 134.1 (C), 132.5 (CH), 131.8 (C),130.9 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 127.6 (CH), 126.4 (CH), 125.8 (CH), 125.5 (CH), 124.9 (CH), 124.0 (CH), 122.4 (C), 120.5 (CH_2), 86.5 (C), 79.9 (CH), 69.3 (C), 58.0 (CH_3), 54.3 (CH_2), 38.7 (CH_3); IR ν_{max}/cm^{-1} 2931, 2231, 1418, 1356, 1162, 960, 781, 653; HRMS (ES-TOF): *m/z*: calcd for $C_{24}H_{23}NO_3SNa$: 428.1296, found: 428.1294 $[M + Na]^+$.

***N*-Allyl-*N*-((2-(methoxy(phenyl)methyl)thiophen-3-yl)ethynyl)methanesulfonamide (305)**



Prepared according to **GP9** using freshly prepared 3-(bromoethynyl)-2-(methoxy(phenyl)methyl)thiophene **304** (0.89 g, 2.90 mmol) and sulfonamide **175** (320 mg, 2.37 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **305** as a pale yellow oil (370 mg, 43%);. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.38 – 7.27 (m, 3H), 7.18 (d, *J* = 5.2 Hz, 1H), 6.94 (d, *J* = 5.2 Hz, 1H), 5.96 (ddt, *J* = 16.5, 10.1, 6.4 Hz, 1H), 5.72 (s, 1H), 5.47 – 5.32 (m, 2H), 4.15 (dd, *J* = 6.4, 1.2 Hz, 2H), 3.41 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8 (C), 141.2 (C), 131.1 (CH), 129.8 (CH), 128.6 (2 × CH), 128.0 (CH), 126.8 (2 × CH), 124.7 (CH), 120.7 (CH_2), 119.0 (C), 84.7 (C), 80.3 (CH), 65.5 (C), 57.3 (CH_3), 54.5 (CH_2), 39.1 (CH_3); IR ν_{max}/cm^{-1} 2824, 2237, 1419, 1355, 1161, 1083, 1879, 776, 699, 669; HRMS (ES-TOF): *m/z*: calcd for $C_{18}H_{19}NO_3S_2Na$: 384.0704, found: 384.0710 $[M + Na]^+$.

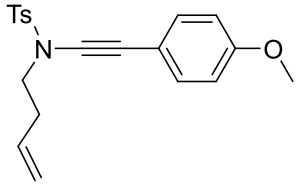
***N*-(But-3-en-1-yl)-4-methyl-*N*-(p-tolylethynyl)benzenesulfonamide (351)**



Prepared according to **GP10** using sulfonamide **350** (360 mg, 1.60 mmol) and dibromoalkene **340** (0.66 g, 2.39 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **351** as a colourless liquid (450 mg, 83%); ^{1}H NMR (300

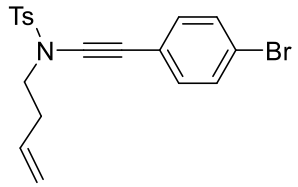
MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 5.75 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.17 – 5.01 (m, 2H), 3.45 (t, *J* = 7.4 Hz, 2H), 2.51 – 2.40 (m, 5H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 138.2 (C), 134.8 (C), 133.9 (CH), 131.6 (2 × CH), 129.9 (2 × CH), 129.2 (2 × CH), 127.9 (2 × CH), 119.8 (C), 117.8 (CH_2), 81.6 (C), 71.1 (C), 51.1 (CH_2), 32.4 (CH_2), 21.8 (CH_3), 21.6 (CH_3); IR ν_{max}/cm^{-1} 2923, 2234, 1597, 1362, 1167, 1089, 955, 812, 735, 661; HRMS (ES-TOF): *m/z*: calcd for $C_{20}H_{21}NO_2S23Na$: 362.1191, found: 362.1193 $[M + Na]^+$.

_N_-(But-3-en-1-yl)-_N_-((4-methoxyphenyl)ethynyl)-4-methylbenzenesulfonamide (352)



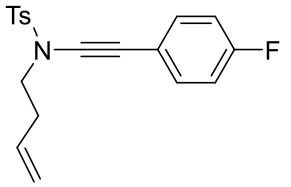
Prepared according to **GP10** using sulfonamide **350** (360 mg, 1.60 mmol) and dibromoalkene **341** (0.70 g, 2.40 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **352** as a colourless oil (460 mg, 81%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.29 (m, 4H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.75 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.18 – 5.00 (m, 2H), 3.81 (s, 3H), 3.44 (t, *J* = 7.4 Hz, 2H), 2.51 – 2.38 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (C), 144.6 (C), 134.8 (C), 133.9 (CH), 133.5 (2 × CH), 129.8 (2 × CH), 127.8 (2 × CH), 117.8 (CH_2), 114.9 (C), 114.0 (2 × CH), 80.8 (C), 70.7 (C), 55.4 (CH_3), 51.1 (CH_2), 32.4 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2842, 2235, 1605, 1511, 1360, 1246, 1167, 1089, 1028, 830, 734, 662; HRMS (ES-TOF): *m/z*: calcd for $C_{20}H_{21}NO_3SNa$: 378.1140, found: 378.1142 $[M + Na]^+$.

***N*-((4-Bromophenyl)ethynyl)-*N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (353)**



Prepared according to **GP10** using sulfonamide **350** (360 mg, 1.60 mmol) and dibromoalkene **342** (0.82 g, 2.41 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **353** as a yellow oil (570 mg, 88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 5.74 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.18 – 5.02 (m, 2H), 3.46 (t, *J* = 7.4 Hz, 2H), 2.49 – 2.39 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 134.7 (C), 133.7 (CH), 132.8 (2 × CH), 131.7 (2 × CH), 130.0 (2 × CH), 127.8 (2 × CH), 122.0 (C), 118.0 (2 × CH)|, 83.4 (C), 70.3 (C), 51.0 (CH_2), 32.5 (CH_2), 21.8 (CH_3). One quaternary carbon unaccounted for; IR ν_{max}/cm^{-1} 2903, 2231, 1488, 1360, 1167, 1089, 956, 917, 810, 688, 656; HRMS (ES-TOF): *m/z*: calcd for $C_{19}H_{18}NO_2SNa^{79}Br$: 426.0139, found: 426.0140 $[M + Na]^+$.

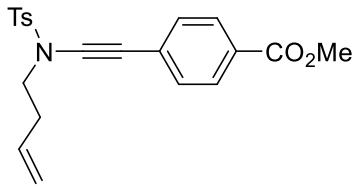
***N*-(But-3-en-1-yl)-*N*-((4-fluorophenyl)ethynyl)-4-methylbenzenesulfonamide (354)**



Prepared according to **GP10** using sulfonamide **350** (360 mg, 1.60 mmol) and dibromoalkene **343** (0.67 g, 2.39 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **354** as a colourless oil (490 mg, 89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.31 (m, 4H), 7.03 – 6.95 (m, 2H), 5.74 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.18 – 5.02 (m, 2H), 3.46 (t, *J* = 7.4 Hz, 2H), 2.51 – 2.38 (m, 5H); ^{13}C NMR

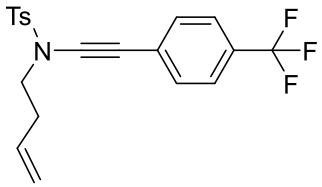
(101 MHz, $CDCl_3$) δ 162.4 (d, $J_{C\text{-}F}$ = 249.0 Hz, C), 144.8 (C), 134.8 (C), 133.8 (CH), 133.6 (d, $J_{C\text{-}F}$ = 8.4 Hz, 2 × CH), 129.9 (2 × CH), 127.8 (2 × CH), 119.0 (d, $J_{C\text{-}F}$ = 3.5 Hz C), 117.9 (CH_2), 115.7 (d, $J_{C\text{-}F}$ = 22.2 Hz, 2 × CH), 81.9 (C), 70.0 (C), 51.1 (CH_2), 32.4 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2936, 2237, 1598, 1508, 1363, 1229, 1169, 1090, 956, 834, 813, 737, 662; HRMS (ES-TOF): *m/z*: calcd for $C_{19}H_{18}NO_2SFNa$: 366.0940, found: 366.0941 $[M + Na]^+$.

Methyl 4-(((*N*-(but-3-en-1-yl)-4-methylphenyl)sulfonamido)ethynyl)benzoate (355)



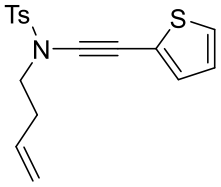
Prepared according to **GP10** using sulfonamide **350** (360 mg, 1.60 mmol) and dibromoalkene **344** (0.77 g, 2.41 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **355** as a white solid (460 mg, 75%); mp: 72-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.43 – 7.33 (m, 4H), 5.75 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.16 – 5.04 (m, 2H), 3.92 (s, 3H), 3.49 (t, *J* = 7.4 Hz, 2H), 2.52 – 2.40 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (CO), 145.0 (C), 134.7 (C), 133.6 (CH), 130.7 (2 × CH), 130.0 (2 × CH), 129.6 (2 × CH), 128.9 (C), 128.0 (C), 127.8 (2 × CH), 118.1 (CH_2), 85.6 (C), 71.2 (C), 52.3 (CH_3), 51.0 (CH_2), 32.5 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2949, 2229, 1716, 1603, 1440, 1361,1272, 1166,763, 655; HRMS (ES-TOF): *m/z*: calcd for $C_{21}H_{21}NO_4SNa$: 406.1089, found: 406.1093 $[M + Na]^+$.

***N*-(But-3-en-1-yl)-4-methyl-*N*-((4-(trifluoromethyl)phenyl)ethynyl)benzenesulfonamide (356)**



Prepared according to **GP10** using sulfonamide **350** (360 mg, 1.60 mmol) and dibromoalkene **345** (0.79 g, 2.39 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **356** as a yellow oil (510 mg, 81%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 5.75 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.21 – 5.01 (m, 2H), 3.49 (t, *J* = 7.4 Hz, 2H), 2.51 – 2.41 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1 (C), 134.7 (C), 133.6 (CH), 131.1 (2 × CH), 130.0 (2 × CH), 129.4 (q, $J_{C\text{-}F}$ = 31.8 Hz, C)), 127.8 (2 × CH), 127.1 (C), 125.4 (q, $J_{C\text{-}F}$ = 3.9 Hz, 2 × CH)), 124.1 (q, $J_{C\text{-}F}$ = 273.0 Hz, C)), 118.1 (CH_2), 85.0 (C), 70.5 (C), 51.0 (CH_2), 32.5 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2934, 2233, 1614, 1367, 1319, 1166, 1103, 1064, 840, 812, 705, 680, 657; HRMS (EI-TOF): *m/z*: calcd for $C_{20}H_{18}NO_2SF_3$: 393.1010, found: 393.1006 $[M]^+$.

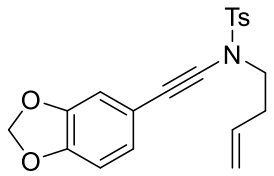
***N*-(But-3-en-1-yl)-4-methyl-*N*-(thiophen-2-ylethynyl)benzenesulfonamide (357)**



Prepared according to **GP10** using sulfonamide **350** (360 mg, 1.60 mmol) and dibromoalkene **346** (0.64 g, 2.39 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **357** as a brown solid (430 mg, 81%); mp: 38-40 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.26 (m, 1H),

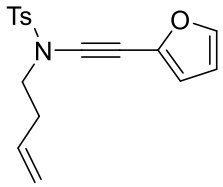
7.18 (dd, *J* = 3.6, 1.1 Hz, 1H), 6.97 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.73 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.17 – 5.00 (m, 2H), 3.46 (t, *J* = 7.4 Hz, 2H), 2.47 (s, 3H), 2.45 – 2.38 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 134.7 (C), 133.7 (CH), 133.1 (CH), 129.9 (2 × CH), 127.9 (CH), 127.8 (2 × CH), 127.1 (CH), 123.0 (C), 118.0 (CH_2), 85.9 (C), 64.4 (C), 51.2 (CH_2), 32.4 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2929, 2225, 1493, 1431, 1364, 1167, 1089, 920, 813, 702, 662; HRMS (ES-TOF): *m/z*: calcd for $C_{17}H_{17}NO_2S_2Na$: 354.0598, found: 354.0601 $[M + Na]^+$.

_N_-(Benzo[d][1,3]dioxol-5-ylethynyl)-_N_-(but-3-en-1-yl)-4-methylbenzenesulfonamide (358)



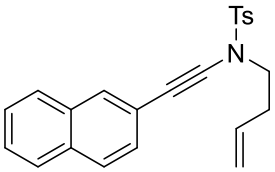
Prepared according to **GP10** using sulfonamide **350** (360 mg, 1.60 mmol) and dibromoalkene **347** (0.73 g, 2.39 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **358** as a colourless oil (460 mg, 78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 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), 5.96 (s, 2H), 5.74 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.15 – 5.02 (m, 2H), 3.44 (t, *J* = 7.4 Hz, 2H), 2.46 (s, 3H), 2.45 – 2.38 (m, 2H); ^{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 (2 × CH), 127.8 (2 × CH), 126.6 (CH), 117.8 (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); IR ν_{max}/cm^{-1} 2896, 2234, 1598, 1491, 1444, 1361; 1221; 1168; 1089, 1036; 811; 745, 677; HRMS (ES-TOF): *m/z*: calcd for $C_{20}H_{19}NO_4SNa$: 392.0932, found: 392.0930 $[M + Na]^+$.

***N*-(But-3-en-1-yl)-*N*-(furan-2-ylethynyl)-4-methylbenzenesulfonamide (359)**



Prepared according to **GP10** using sulfonamide **350** (360 mg, 1.60 mmol) and dibromoalkene **348** (0.60 g, 2.38 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **359** as a reddish brown solid (440 mg, 87%); mp: 63-65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.39 (dd, *J* = 1.9, 0.7 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.62 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.39 (dd, *J* = 3.4, 1.9 Hz, 1H), 5.71 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.18 – 5.01 (m, 2H), 3.46 (t, *J* = 7.5 Hz, 2H), 2.46 (s, 3H), 2.45 – 2.38 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (C), 144.1 (CH), 136.9 (C), 134.8 (C), 133.6 (CH), 130.0 (2 × CH), 127.8 (2 × CH), 118.0 (CH), 117.3 (CH), 111.2 (CH_2), 86.3 (C), 61.9 (C), 51.2 (CH_2), 32.4 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2971, 1707, 1353, 1157, 1086, 813, 663; HRMS (ES-TOF): *m/z*: calcd for $C_{17}H_{17}NO_3SNa$: 338.0827, found: 338.0832 $[M + Na]^+$.

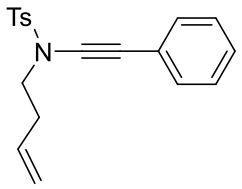
***N*-(But-3-en-1-yl)-4-methyl-*N*-(naphthalen-2-ylethynyl)benzenesulfonamide (360)**



Prepared according to **GP10** using sulfonamide **350** (360 mg, 1.60 mmol) and dibromoalkene **349** (0.75 g, 2.40 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **360** as a colourless oil (540 mg, 90%); 1H NMR (300 MHz, CDCl3) δ 7.90 – 7.85 (m, 3H), 7.82 – 7.74 (m, 3H), 7.52 – 7.45 (m, 2H), 7.42 (dd, J = 8.5, 1.6 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 5.78 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 5.19 – 5.05 (m, 2H),

3.51 (t, J = 7.4 Hz, 2H), 2.54 – 2.48 (m, 2H), 2.46 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 144.8 (C), 134.8 (C), 133.8 (CH), 133.1 (C), 132.7 (C), 130.9 (CH), 129.9 (2 × CH), 128.5 (CH), 128.0 (CH), 127.9 (2 × CH), 127.8 (CH), 127.7 (CH), 126.7 (CH), 126.6 (CH), 120.3 (C), 118.0 (CH_2), 82.6 (C), 71.6 (C), 51.1 (CH_2), 32.5 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} HRMS (ES-TOF): *m/z*: calcd for $C_{23}H_{21}NO_2SNa$: 398.1191, found: 398.1192 $[M + Na]^+$.

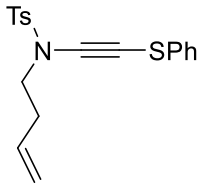
_N_-(But-3-en-1-yl)-4-methyl-_N_-(phenylethynyl)benzenesulfonamide (361)



Prepared according to **GP9** using sulfonamide **310** (230 mg, 1.02 mmol) and freshly prepared bromoalkyne (bromoethynyl)benzene (314 mg, 1.20 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **361** as a colourless oil (290 mg, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.33 (m, 4H), 7.32 – 7.27 (m, 3H), 5.75 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.18 – 5.02 (m, 2H), 3.47 (t, *J* = 7.4 Hz, 2H), 2.51 – 2.40 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (C), 134.7 (C), 133.8 (CH), 131.5 (2 × CH), 129.9 (2 × CH), 128.4 (2 × CH), 127.9 (CH), 127.9 (2 × CH), 123.0 (C), 117.9 (CH_2), 82.3 (C), 71.1 (C), 51.1 (CH_2), 32.4 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2938, 2234, 1597, 1442, 1362, 1168, 1089, 912, 752, 676.

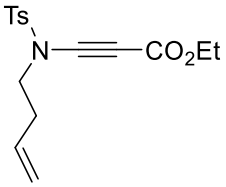
Data matches that reported in the literature.[141]

***N*-(But-3-en-1-yl)-4-methyl-*N*-((phenylthio)ethynyl)benzenesulfonamide (376)**



Prepared according to **GP11** using dichlorovinylamide **375** (380 mg, 1.19 mmol) and electrophile- Phenyl benzenethiosulfonate (390 mg, 1.56 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **376** as a colourless liquid (240 mg, 56%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.27 (m, 4H), 7.25 – 7.17 (m, 1H), 5.71 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.14 – 5.02 (m, 2H), 3.52 (t, *J* = 7.3 Hz, 2H), 2.46 (s, 3H), 2.45 – 2.38 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (C), 134.8 (C), 134.5 (C), 133.6 (CH), 129.9 (2 × CH), 129.2 (2 × CH), 128.0 (2 × CH), 126.5 (CH), 125.7 (2 × CH), 118.1 (CH_2), 92.7 (C), 61.9 (C), 51.2 (CH_2), 32.6 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2921, 2155, 1582, 1478, 1441, 1364, 1169, 1089, 740, 689, 665; HRMS (ES-TOF): *m/z*: calcd for $C_{19}H_{19}NO_2S_2Na$: 380.0755, found: 380.0752 $[M + Na]^+$.

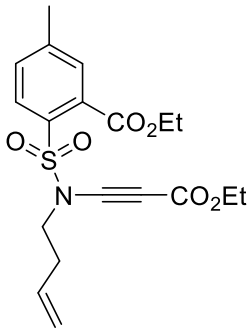
Ethyl 3-((*N*-(but-3-en-1-yl)-4-methylphenyl)sulfonamido)propiolate (386)



Prepared according to **GP11** using dichlorovinylamide **375** (0.61 g, 1.90 mmol) and electrophile- chloroethylformate (250 mg, 2.28 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **386** as a colourless oil (530 mg, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 5.66 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.16 – 5.02 (m, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.48 (t, *J* = 7.4 Hz, 2H),

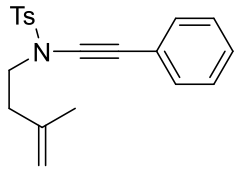
2.46 (s, 3H), 2.44 – 2.36 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3 (CO), 145.7 (C), 134.4 (C), 133.0 (CH), 130.2 (2 × CH), 128.0 (2 × CH), 118.6 (CH_2), 82.4 (C), 68.2 (C), 61.7 (CH_2), 50.8 (CH_2), 32.5 (CH_2), 21.9 (CH_3), 14.3 (CH_3); IR ν_{max}/cm^{-1} 2982, 2214, 1699, 1597, 172, 1231, 1168, 1088, 1026, 877, 708, 657; HRMS (ES-TOF): *m/z*: calcd for $C_{16}H_{19}NO_4SNa$: 344.0932, found: 344.0930 $[M + Na]^+$.

Ethyl 2-(*N*-(but-3-en-1-yl)-*N*-(3-ethoxy-3-oxoprop-1-yn-1-yl)sulfamoyl)-5-methylbenzoate (387)



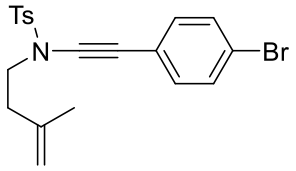
Prepared according to **GP11** using 1,2-dichlorovinylamide **385** (0.83 g, 2.59 mmol) and electrophile- chloroethylformate (340 mg, 3.12 mmol). Purification by flash column chromatography [90:10 (hexane:EtOAc)] gave the ynamide **387** as a colourless oil (510 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.38 (s, 1H), 5.73 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.19 – 5.03 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.62 (t, *J* = 7.4 Hz, 2H), 2.53 – 2.39 (m, 5H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1 (CO), 154.3 (CO), 145.5 (C), 133.5 (C), 133.2 (CH), 131.9 (C), 131.3 (CH), 130.8 (CH), 129.6 (CH), 118.4 (CH_2), 82.3 (C), 68.7 (C), 62.7 (CH_2), 61.7 (CH_2), 50.9 (CH_2), 32.7 (CH_2), 21.6 (CH_3), 14.3 (CH_3), 14.2 (CH_3); IR ν_{max}/cm^{-1}; HRMS (ES-TOF): *m/z*: calcd for $C_{19}H_{23}NO_6SNa$: 416.1144, found: 416.1141 $[M + Na]^+$.

4-Methyl-*N*-(3-methylbut-3-en-1-yl)-*N*-(phenylethynyl)benzenesulfonamide (395)



Prepared according to **GP9** using sulfonamide **393** (290 mg, 1.21 mmol) and freshly prepared bromoalkyne (bromoethynyl)benzene **394** (260 mg, 1.44 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **395** as a colourless liquid (350 mg, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.33 (m, 4H), 7.32 – 7.27 (m, 3H), 4.80 (br. s, 1H), 4.74 (br. s, 1H), 3.52 (t, *J* = 7.5 Hz 2H), 2.46 (s, 3H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (C), 141.4 (C), 134.8 (C), 131.5 (2 × CH), 129.9 (2 × CH), 128.4 (2 × CH), 127.9 (CH), 127.9 (2 × CH), 123.0 (C), 113.0 (CH_2), 82.3 (C), 71.1 (C), 50.2 (CH_2), 36.1 (CH_2), 22.5 (CH_3), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2935, 2234, 1443, 1363, 1166, 1091, 956, 813, 753, 690; HRMS (ES-TOF): *m/z*: calcd for $C_{20}H_{22}NO_2S$: 340.1371, found: 340.1373 $[M + H]^+$.

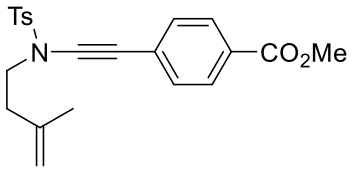
***N*-((4-Bromophenyl)ethynyl)-4-methyl-*N*-(3-methylbut-3-en-1-yl)benzenesulfonamide (396)**



Prepared according to **GP10** using sulfonamide **393** (380 mg, 1.59 mmol) and dibromoalkene **342** (0.82 g, 2.41 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **396** as a white solid (0.60 g, 90%); mp: 58-60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H),

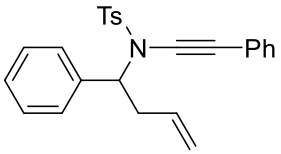
7.22 (d, *J* = 8.5 Hz, 2H), 4.80 (br. s, 1H), 4.73 (br. s, 1H), 3.52 (t, *J* = 7.5 Hz, 2H), 2.46 (s, 3H), 2.38 (t, *J* = 7.5 Hz, 2H), 1.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 141.3 (C), 134.8 (C), 132.8 (2 × CH), 131.7 (2 × CH), 130.0 (2 × CH), 127.8 (2 × CH), 122.0 (C), 122.0 (C), 113.1 (CH_2), 83.5 (C), 70.3 (C), 50.1 (CH_2), 36.2 (CH_2), 22.5 (CH_3), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2935, 2229, 1487, 1364, 1186, 1168, 1092, 953, 894, 823, 707, 687; HRMS (ES-TOF): *m/z*: calcd for $C_{20}H_{20}NO_2SNa^{79}Br$: 440.0296, found: 440.0295 $[M + Na]^+$.

Methyl 4-(((4-methyl-*N*-(3-methylbut-3-en-1-yl)phenyl)sulfonamido)ethynyl)benzoate (397)



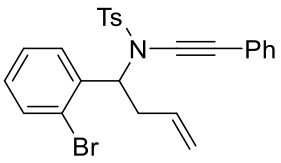
Prepared according to **GP10** using sulfonamide **393** (380 mg, 1.59 mmol) and dibromoalkene **344** (0.77 g, 2.41 mmol). Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the ynamide **397** as a white solid (560 mg, 89%); mp: 89-91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.43 – 7.34 (m, 4H), 4.81 (br. s, 1H), 4.74 (br. s, 1H), 3.92 (s, 3H), 3.54 (t, *J* = 7.5 Hz, 2H), 2.46 (s, 3H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (CO), 145.0 (C), 141.2 (C), 134.8 (C), 130.7 (2 × CH), 130.0 (2 × CH), 129.6 (2 × CH), 128.9 (C), 128.0 (C), 127.8 (2 × CH), 113.2 (CH_2), 85.8 (C), 71.2 (C), 52.3 (CH_3), 50.1 (CH_2), 36.2 (CH_2), 22.5 (CH_3), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2944, 2227, 1715, 1601, 1430, 1363, 1271, 1163, 1091, 898, 770, 687; HRMS (ES-TOF): *m/z*: calcd for $C_{22}H_{23}NO_4SNa$: 420.1245, found: 420.1248 $[M + Na]^+$.

4-Methyl-*N*-(1-phenylbut-3-en-1-yl)-*N*-(phenylethynyl)benzenesulfonamide (416)



Prepared according to **GP9** using freshly prepared (bromoethynyl)benzene **394** (430 mg, 2.38 mmol) and sulfonamide **411** (0.60 g, 1.99 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **416** as a yellow solid (0.67 g, 84%); mp: 43-45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.28 (m, 7H), 7.25 – 7.20 (m, 3H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.66 (ddt, *J* = 17.1, 10.1, 6.9 Hz, 1H), 5.13 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.06 (dd, *J* = 9.1, 6.5 Hz, 1H), 5.00 (dd, *J* = 10.1, 1.6 Hz, 1H), 2.92 – 2.79 (m, 1H), 2.72 – 2.59 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (C), 138.9 (C), 135.4 (C), 133.6 (CH), 131.3 (2 × CH), 129.4 (2 × CH) , 128.5 (2 × CH), 128.4 (2 × CH), 128.2 (CH), 127.9 (2 × CH), 127.8 (CH), 127.3 (2 × CH), 123.3 (C), 118.5 (CH_2), 80.7 (C), 73.7 (C), 63.5 (CH), 38.5 (CH_2), 21.7 (CH_3); IR ν_{max}/cm^{-1} 3033, 2234, 1598, 1493, 1359, 1167, 1088, 959, 657, HRMS(ES-TOF): *m/z*: calcd for $C_{25}H_{24}NO_2S$: 402.1528, found: 402.1530 $[M + H]^+$.

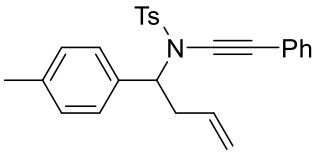
***N*-(1-(2-bromophenyl)but-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide (417)**



Prepared according to **GP9** using freshly prepared (bromoethynyl)benzene **394** (220 mg, 1.22 mmol) and sulfonamide **412** (380 mg, 1.00 mmol). Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the ynamide **417** as a yellow oil (380 mg, 79%);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.54 – 7.48 (m, 2H), 7.45 – 7.39 (m, 2H), 7.36 – 7.30 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.10 – 7.04 (m, 2H), 5.69 (ddt, *J* = 17.0, 10.1, 6.9 Hz, 1H), 5.51 (dd, *J* = 9.8, 5.3 Hz, 1H), 5.16 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.01 (dd, *J* = 10.1, 1.5 Hz, 1H), 2.83 – 2.69 (m, 1H), 2.66 – 2.55 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5 (C), 139.3 (C), 135.1 (C), 133.2 (CH), 132.9 (CH), 131.3 (2 × CH), 129.4 (2 × CH), 129.2 (CH), 128.5 (2 × CH), 127.9 (CH), 127.9 (2 × CH), 127.7 (CH), 127.5 (CH), 123.2 (C), 122.9 (C), 118.8 (CH_2), 81.2 (C), 73.7 (C), 62.0 (CH), 38.8 (CH_2), 21.7 (CH_3); IR ν_{max}/cm^{-1} 3057, 2234, 1596, 1440, 1360, 1165, 1185, 746, 654; HRMS(ES-TOF): *m/z*: calcd for $C_{25}H_{22}NO_2SNaBr$: 502.0452, found: 502.0447 $[M + Na]^+$.

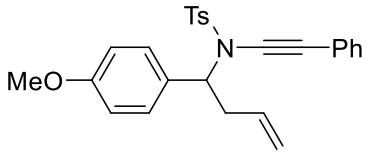
4-Methyl-N-(phenylethynyl)-*N*-(1-(p-tolyl)but-3-en-1-yl)benzenesulfonamide (418)



Prepared according to **GP9** using freshly prepared (bromoethynyl)benzene **394** (220 mg, 1.22 mmol) and sulfonamide **413** (320 mg, 1.01 mmol). Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the ynamide **418** as a colourless oil (340 mg, 81%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.33 – 7.28 (m, 3H), 7.22 – 7.14 (m, 4H), 7.03 (d, *J* = 7.9 Hz, 2H), 5.64 (ddt, *J* = 17.1, 10.1, 6.9 Hz, 1H), 5.12 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.07 – 4.95 (m, 2H), 2.89 – 2.77 (m, 1H), 2.71 – 2.58 (m, 1H), 2.39 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2 (C), 138.0 (C), 135.8 (C), 135.5 (C), 133.8 (CH), 131.3 (2 × CH), 129.3 (2 × CH), 129.1 (2 × CH), 128.4 (2 × CH), 127.9 (2 × CH), 127.8 (CH), 127.3 (2 × CH), 123.3 (C), 118.4 (CH_2), 80.7 (C), 73.6 (C), 63.3 (CH), 38.4 (CH_2),

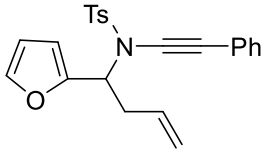
21.7 (CH_3), 21.3 (CH_3); IR ν_{max}/cm^{-1} 2922, 2232, 1597, 1362, 1166, 1089, 967, 754, 659; HRMS(ES-TOF): *m/z*: calcd for $C_{26}H_{26}NO_2S$: 416.1684, found: 416.1685 $[M + H]^+$.

_N_-(1-(4-methoxyphenyl)but-3-en-1-yl)-4-methyl-_N_-(phenylethynyl)benzenesulfonamide (419)



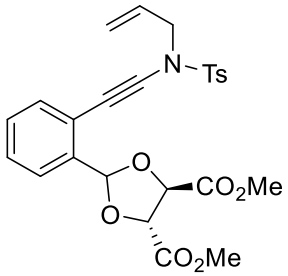
Prepared according to **GP9** using freshly prepared (bromoethynyl)benzene **394** (220 mg, 1.22 mmol) and sulfonamide **414** (330 mg, 0.996 mmol). Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the ynamide **419** as a yellow oil (350 mg, 81%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.33 – 7.27 (m, 3H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 5.64 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.11 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.06 – 4.95 (m, 2H), 3.77 (s, 3H), 2.89 – 2.75 (m, 1H), 2.70 – 2.57 (m, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (C), 144.2 (C), 135.6 (C), 133.8 (CH), 131.3 (2 × CH), 130.9 (C), 129.4 (2 × CH), 128.6 (2 × CH), 128.4 (2 × CH), 127.9 (2 × CH), 127.8 (CH), 123.3 (C), 118.4 (CH_2), 113.8 (2 × CH), 80.7 (C), 73.7 (C), 63.1 (CH_3), 55.4 (CH), 38.4 (CH_2), 21.7 (CH_3); IR ν_{max}/cm^{-1} 2933, 2231, 1610, 1513, 1360, 1167, 1088, 754, 659; HRMS(ES-TOF): *m/z*: calcd for $C_{26}H_{25}NO_3SNa$: 454.1453, found: 454.1450 $[M + Na]^+$.

_N_-(1-(furan-2-yl)but-3-en-1-yl)-4-methyl-_N_-(phenylethynyl)benzenesulfonamide (420)



Prepared according to **GP9** using freshly prepared (bromoethynyl)benzene **394** (220 mg, 1.22 mmol) and sulfonamide **415** (290 mg, 0.995 mmol). Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the ynamide **420** as a brown oil (150 mg, 38%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.25 (m, 7H), 7.23 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.23 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.20 (d, *J* = 3.3 Hz, 1H), 5.71 (ddt, *J* = 17.1, 10.1, 6.9 Hz, 1H), 5.22 – 5.12 (m, 2H), 5.06 (dd, *J* = 10.2, 1.6 Hz, 1H), 2.81 – 2.73 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (C), 144.5 (C), 142.3 (CH), 135.5 (C), 133.0 (CH), 131.4 (2 × CH), 129.5 (2 × CH), 128.4 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 123.2 (C), 118.9 (CH_2), 110.3 (CH), 108.5 (CH), 79.8 (C), 73.5 (C), 57.5 (CH), 36.3 (CH_2), 21.8 (CH_3; IR ν_{max}/cm^{-1} 3079, 2984, 2234, 1597, 1360, 1167, 1089, 753, 663; HRMS(ES-TOF): *m/z*: calcd for $C_{23}H_{21}NO_3SNa$: 414.1140, found: 414.1137 $[M + Na]^+$.

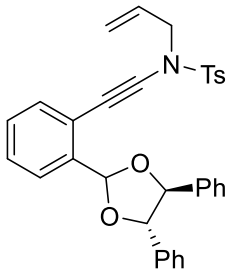
Dimethyl(4R,5R)-2-(2-(((*N*-allyl-4-methylphenyl)sulfonamido)ethynyl)phenyl)-1,3-dioxolane-4,5-dicarboxylate (432)



Prepared according to **GP9** using freshly prepared dimethyl (4R,5R)-2-(2-(bromoethynyl)phenyl)-1,3-dioxolane-4,5-dicarboxylate (530 mg, 1.44 mmol) and sulfonamide **220** (250 mg, 1.18 mmol). Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the ynamide **432** as a colourless oil (210 mg, 36%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.78 – 7.71 (m, 1H), 7.39 – 7.29 (m, 5H), 6.49 (s, 1H), 5.77 (ddt, *J* = 16.6, 10.1, 6.3 Hz, 1H), 5.29 (dd, *J* = 17.0, 1.3 Hz, 1H), 5.22 (dd, *J* = 10.1, 1.2 Hz, 1H),

4.98 (d, *J* = 4.3 Hz, 1H), 4.90 (d, *J* = 4.3 Hz, 1H), 4.06 (d, *J* = 6.3 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (CO), 169.6 (CO), 144.9 (C), 135.6 (C), 134.9 (C), 131.2 (CH), 131.0 (CH), 130.0 (2 × CH), 129.7 (CH), 128.0 (2 × CH), 127.9 (CH), 126.9 (CH), 123.0 (C), 120.3 (CH_2), 104.6 (CH), 87.4 (C), 77.6 (CH), 77.3 (CH), 68.5 (C), 54.4 (CH_2), 53.0. (CH_3), 53.0 (CH_3), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2956, 2233, 1743, 1205, 1168, 1107, 760, 661; HRMS (ES-TOF): *m/z*: calcd for $C_{25}H_{25}NO_8SNa$: 522.1199, found: 522.1206 [M + Na]$^+$.

_N_-Allyl-_N_-((2-((4S,5S)-4,5-diphenyl-1,3-dioxolan-2-yl)phenyl)ethynyl)-4-methylbenzenesulfonamide (433)



Prepared according to **GP9** using freshly prepared diethyl (4S,5S)-2-(2-(bromoethynyl)phenyl)-4,5-diphenyl-1,3-dioxolane **211** (280 mg, 0.690 mmol) and sulfonamide **220** (130 mg, 0.615 mmol). Purification by flash column chromatography [8:2 (hexane:EtOAc) + 1% Et_3N] gave the ynamide **433** as a colourless oil (190 mg, 58%); $[\alpha]_D^{25}$ = -93.21; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 3H), 7.43 – 7.29 (m, 13H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.77 (s, 1H), 5.78 (ddt, *J* = 16.6, 10.1, 6.3 Hz, 1H), 5.27 (dd, *J* = 17.0, 1.3 Hz, 1H), 5.18 (dd, *J* = 10.1, 1.3 Hz, 1H), 5.02 – 4.93 (m, 2H), 4.06 (dd, *J* = 6.3, 1.3 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 138.5 (C), 138.4 (C), 136.7 (C), 134.9 (C), 131.6 (CH), 131.0 (CH), 129.9 (2 × CH), 129.2 (CH), 128.7 (2 × CH), 128.7 (2 × CH), 128.6 (CH), 128.3 (CH), 128.0 (2 × CH), 127.1 (2 × CH), 126.7 (2 × CH), 126.2 (CH), 122.7 (C), 120.3 (CH_2), 102.9 (CH),

87.4 (CH), 87.3 (C), 85.6 (CH), 68.9 (C), 54.4 (CH_2), 21.7 (CH_3), (one CH unaccounted for); IR ν_{max}/cm^{-1} 3670, 2987, 2901, 2231, 1494, 1454, 1364, 1168, 1060, 757, 697, 599, 544; HRMS(ES-TOF): *m/z*: calcd for $C_{33}H_{29}NO_4SNa$: 558.1715, found: 558.1718 $[M + Na]^+$.

Catalysis products

General procedure 12 (GP12)

Sulfonamide (1.0 equiv.), bromoalkyne (1.2 equiv.), K_2CO_3 (2.0 equiv.), 1, 10-phenanthroline (20 mol%),CuSO4 (10 mol%) and toluene (1.0 M) were 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 residue was purified by flash column chromatography.

General procedure 13 (GP13)

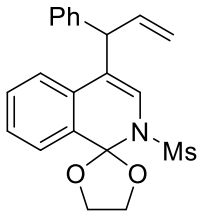
The required ynamide (1.0 equiv.) was dissolved in CH_3NO_2 (0.1 M), XphosAuNTf$_2$ (5 mol%) was added and the resulting mixture was heated 80 °C until complete by TLC. The mixture was cooled to room temperature, diluted with EtOAc and filtered through a plug of silica gel. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography.

General procedure 14 (GP14)

The required ynamide (1.0 equiv.) was dissolved in toluene (0.1 M), dichloro-2-pyridinecarboxylato gold (III) (5 mol%) was added and the resulting mixture was heated 80 °C until complete by TLC. The mixture was cooled to room temperature, diluted with

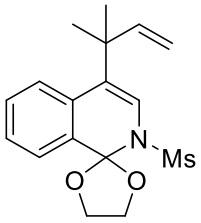
EtOAc and filtered through a plug of silica gel. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography.

2-(Methylsulfonyl)-4-(1-phenylallyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (169)



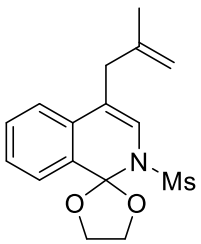
Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (**GP7**, 330 mg, 1.30 mmol) and sulfonamide **168** (250 mg, 1.18 mmol) at 70 °C for 16 h. Purification by flash column chromatography [8:2 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **169** as a white foam (380 mg, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 1H), 7.34 – 7.26 (m, 5H), 7.25 – 7.16 (m, 3H), 6.92 (s, 1H), 6.20 (ddd, J = 16.9, 10.2, 6.5 Hz, 1H), 5.24 (app. dt, J = 10.2, 1.4 Hz, 1H), 4.94 (app. dt, J = 17.1, 1.3 Hz, 1H), 4.81 (d, J = 6.2 Hz, 1H), 4.63 – 4.49 (m, 2H), 4.28 – 4.15 (m, 2H), 3.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2 (C), 139.2 (CH), 131.3 (C), 131.2 (C), 129.4 (CH), 128.7 (2 × CH), 128.6 (2 × CH), 127.2 (CH), 126.8 (CH), 124.6 (CH), 123.5 (CH), 123.1 (CH), 119.2 (C), 117.6 (CH_2), 112.8 (C), 67.0 (CH_2), 66.3 (CH_2), 49.0 (CH), 43.5 (CH_3); IR ν_{max}/cm^{-1} 2987, 2901, 1450, 1343, 1264, 1165, 1073,959, 702, 618; HRMS (ES-TOF): *m/z*: calcd for $C_{21}H_{22}NO_4S$: 384.1270, found: 384.1274 $[M + H]^+$.

4-(2-Methylbut-3-en-2-yl)-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (167)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (**GP7**, 280 mg, 1.11 mmol) and sulfonamide **165** (160 mg, 0.980 mmol) for 20 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **167** as a colourless liquid (210 mg, 64%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 1H), 7.54 – 7.48 (m, 1H), 7.38 – 7.27 (m, 2H), 7.02 (s, 1H), 6.10 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.11 (d, *J* = 7.2 Hz, 1H), 5.06 (s, 1H), 4.58 – 4.46 (m, 2H), 4.26 – 4.16 (m, 2H), 3.08 (s, 3H), 1.43 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2 (CH), 132.0 (C), 131.0 (C), 128.5 (CH), 126.7 (CH), 126.1 (CH), 124.2 (C), 123.4 (CH), 122.3 (CH), 112.4 (C), 112.3 (C), 66.6 (2 × CH_2), 43.5 (CH_3), 40.1 (C), 28.8 (2 × CH_3); IR ν_{max}/cm^{-1} 2970, 1623, 1485, 1340, 1267, 1160, 1073, 948, 756, 516; HRMS (ES-TOF): *m/z*: calcd for $C_{17}H_{21}NO_4NaS$: 358.1089, found: 358.1090 $[M + Na]^+$.

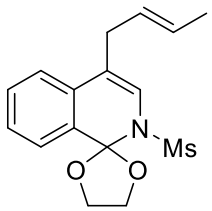
4-(2-Methylallyl)-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (176)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (**GP7**, 280 mg, 1.11 mmol) and sulfonamide **171** (150

mg, 1.01 mmol) for 24 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **176** as a colourless liquid (300 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 1H), 7.45 – 7.30 (m, 3H), 6.88 (s, 1H), 4.84 (br. s, 1H), 4.78 (br. s, 1H), 4.59 – 4.47 (m, 2H), 4.27 – 4.17 (m, 2H), 3.22 (s, 2H), 3.06 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (C), 131.7 (C), 131.0 (C), 129.5 (CH), 127.3 (CH), 123.7 (CH), 123.5 (CH), 122.8 (CH), 116.1 (C), 112.8 (C), 112.5 (CH_2), 66.6 (2 × CH_2), 43.3 (CH_3), 38.5 (CH_2), 22.5 (CH_3); IR ν_{max}/cm^{-1} 3675, 2988, 2901, 1650, 1451, 1342,1260, 1163, 1066, 1026, 768, 514; HRMS (ES-TOF): *m/z*: calcd for $C_{16}H_{19}NO_4NaS$: 344.0932, found: 344.0934 [M + Na]$^+$.

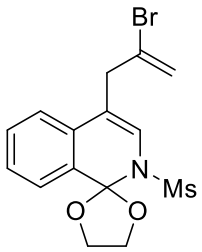
(E)-4-(But-2-en-1-yl)-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (177)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (**GP7**, 310 mg, 1.22 mmol) and sulfonamide **172** (160 mg, 1.07 mmol) at 70 °C for 48 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **177** as a yellow oil (280 mg, 81%, mixture of E/Z isomers in 0.4:1 ratio); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 1H), 7.47 – 7.41 (m, 1H), 7.39 – 7.32 (m, 2H), 6.85 (s, 1H), 5.68 – 5.47 (m, 2H), 4.59 – 4.47 (m, 2H), 4.25 – 4.16 (m, 2H), 3.28 – 3.17 (m, 2H), 3.06 (s, 3H), 1.75 – 1.65 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.8 (C, minor), 131.7 (C, major), 131.1 (C, minor), 131.0 (C, major), 129.6 (CH, minor), 129.6 (CH, major), 128.0 (CH, major), 127.8 (CH, major), 127.4 (CH, minor), 127.3 (CH, minor), 127.3 (CH, major), 126.3 (CH, minor), 123.7 (CH, minor), 123.6 (CH, major),

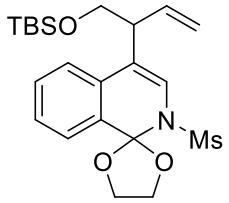
122.7 (CH, major), 122.6 (CH, major), 122.5 (CH, minor), 122.3 (CH, minor), 117.1 (C, major), 116.9 (C, minor), 112.8 (C, major and minor), 66.6 (2 × CH_2, major and minor), 43.3 (CH_3, major and minor), 32.9 (CH_2, major), 27.5 (CH_2, minor), 18.1 (CH_3, major), 13.1 (CH_3, minor); IR ν_{max}/cm^{-1} 2988, 1647, 1587, 1527, 1174, 1038, 767,523; HRMS (ES-TOF): *m/z*: calcd for $C_{16}H_{20}NO_4S$: 322.1113, found: 322.1119 $[M + H]^+$.

4-(2-Bromoallyl)-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (178)



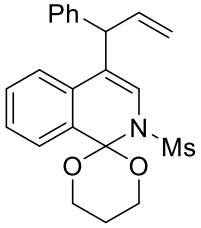
Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (**GP7**, 280 mg, 1.11 mmol) and sulfonamide **173** (210 mg, 0.981 mmol) for 16 h. Purification by flash column chromatography [8:2 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **178** as a brown solid (320 mg, 84%); mp: 123 – 125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.48 – 7.33 (m, 2H), 7.29 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.00 (s, 1H), 5.60 (d, *J* = 1.9 Hz, 1H), 5.50 (d, *J* = 1.9 Hz, 1H), 4.61 – 4.47 (m, 2H), 4.28 – 4.16 (m, 2H), 3.63 (s, 2H), 3.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.1 (C), 131.0 (C), 130.8 (C), 129.7 (CH), 127.6 (CH), 125.3 (CH), 123.7 (CH), 122.4 (CH), 118.4 (CH_2), 114.2 (C),112.8 (C), 66.7 (2 × CH_2), 43.6 (CH_3), 42.1 (CH_2); IR ν_{max}/cm^{-1}2894, 1650, 1348, 1257, 1168, 1013, 769, 522; HRMS (ES-TOF): *m/z*: calcd for $C_{15}H_{16}NO_4NaSBr$: 407.9881, found: 407.9881 $[M + Na]^+$.

4-(1-((Tert-butyldimethylsilyl)oxy)but-3-en-2-yl)-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (179)



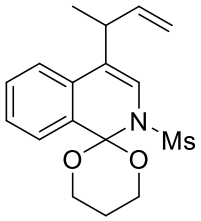
Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (**GP7**, 330 mg, 1.30 mmol) and sulfonamide **174** (330 mg, 1.18 mmol) for 48 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **179** as a light yellow liquid (280 mg, 53%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.40 – 7.30 (m, 1H), 6.91 (s, 1H), 6.06 – 5.92 (m, 1H), 5.19 (app. dt, *J* = 6.3, 1.5 Hz, 1H), 5.15 (d, *J* = 1.3 Hz, 1H), 4.60 – 4.45 (m, 2H), 4.26 – 4.15 (m, 2H), 3.90 – 3.75 (m, 2H), 3.65 (app. q, *J* = 5.7 Hz, 1H), 3.06 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0 (CH), 131.6 (C), 131.2 (C), 129.4 (CH), 127.1 (CH), 123.6 (CH), 123.3 (CH), 122.4 (CH), 117.5 (C), 117.0 (CH_2), 112.6 (C), 66.7 (CH_2), 66.5 (CH_2), 65.5 (CH_2), 45.1 (CH), 43.4 (CH_3), 26.0 (3 × CH_3), 18.4 (C), -5.21 (2 × CH_3); IR ν_{max}/cm^{-1} 2929, 2856, 1472, 1349, 1258, 1167, 1093, 948, 834, 770, 520; HRMS (ES-TOF): *m/z*: calcd for $C_{22}H_{34}NO_5SSi$: 452.1927, found: 452.1937 $[M + H]^+$.

2-(Methylsulfonyl)-4-(1-phenylallyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxane] (190)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-1,3-dioxane (**GP7**, 290 mg, 1.09 mmol) and sulfonamide **168** (210 mg, 0.994 mmol) for 24 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **190** as a white foam (280 mg, 71%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.65 (m, 1H), 7.33 – 7.26 (m, 2H), 7.25 – 7.14 (m, 6H), 6.57 (s, 1H), 6.17 (ddd, *J* = 16.9, 10.2, 6.4 Hz, 1H), 5.22 (app. dt, *J* = 10.2, 1.3 Hz, 1H), 4.93 (app. dt, *J* = 17.1, 1.4 Hz, 1H), 4.81 (dd, *J* = 6.4, 1.0 Hz, 1H), 4.58 (ddd, *J* = 11.2, 10.2, 4.6 Hz, 1H), 4.45 (ddd, *J* = 11.2, 10.2, 4.8 Hz, 1H), 4.11 – 4.01 (m, 1H), 4.00 – 3.90 (m, 1H), 2.57 (s, 3H), 2.24 – 2.06 (m, 1H), 2.00 – 1.86 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0 (C), 139.0 (CH), 133.7 (C), 131.0 (C), 129.3 (CH), 128.8 (2 × CH), 128.7 (2 × CH), 127.8 (CH), 127.5 (C), 126.8 (CH), 125.8 (CH), 123.7 (CH), 123.5 (CH), 117.6 (CH_2), 103.6 (C), 61.7 (CH_2), 60.6 (CH_2), 49.1 (CH), 40.2 (CH_3), 23.7 (CH_2); IR ν_{max}/cm^{-1} 2971, 1651, 1450, 1340, 1164, 1039, 927, 754, 522; HRMS (ES-TOF): *m/z*: calcd for $C_{22}H_{24}NO_4S$: 398.1426, found: 398.1423 $[M + H]^+$.

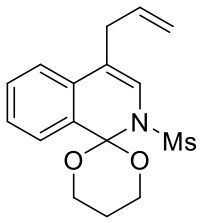
4-(But-3-en-2-yl)-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxane] (192)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-1,3-dioxane (**GP7**, 290 mg, 1.09 mmol) and sulfonamide **191** (150 mg, 1.01 mmol) for 24 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **192** as a colourless viscous oil (250 mg, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.69 (m, 1H), 7.47 – 7.33 (m, 3H), 6.50 (s, 1H), 5.97 (ddd, *J* = 17.3, 10.3, 6.1 Hz, 1H), 5.17 – 5.03 (m, 2H), 4.58 – 4.41 (m, 2H), 4.04 – 3.89 (m, 2H), 3.70 – 3.58

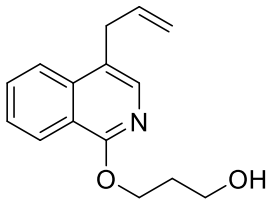
(m, 1H), 2.52 (s, 3H), 2.23 – 2.04 (m, 1H), 1.96 – 1.81 (m, 1H), 1.34 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4 (CH), 133.9 (C), 131.0 (C), 129.5 (C), 129.3 (CH), 127.9 (CH), 123.7 (CH), 123.2 (CH), 123.1 (CH), 115.1 (C), 115.0 (CH_2), 61.4 (CH_2), 61.0 (CH_2), 39.7 (CH_3), 36.5 (CH), 23.7 (CH_2), 18.9 (CH_3); IR ν_{max}/cm^{-1} 2968, 1650, 1607, 1449, 1328, 1223, 1157, 1037, 769, 522; HRMS (ES-TOF): *m/z*: calcd for $C_{17}H_{22}NO_4S$: 336.1270, found: 336.1270 [M + H]$^+$.

4-Allyl-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxane] (193a)



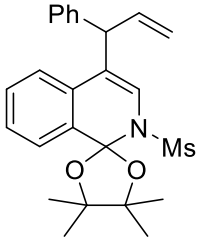
Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-1,3-dioxane (**GP7**, 290 mg, 1.09 mmol) and sulfonamide **175** (140 mg, 1.04 mmol) for 24 h. Purification by flash column chromatography [8:2 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **193a** as a colourless liquid (35.0 mg, 10%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.69 (m, 1H), 7.45 – 7.33 (m, 3H), 6.54 (s, 1H), 5.94 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.17 – 5.06 (m, 2H), 4.51 (ddd, *J* = 11.4, 10.4, 4.7 Hz, 2H), 4.03 – 3.93 (m, 2H), 3.29 (ddd, *J* = 6.0, 2.8, 1.5 Hz, 2H), 2.56 (s, 3H), 2.22 – 2.07 (m, 1H), 1.95 – 1.84 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3 (CH), 133.6 (C), 131.0 (C), 129.5 (CH), 128.1 (CH), 124.6 (C), 124.4 (CH), 123.7 (CH), 123.3 (CH), 117.3 (CH_2), 103.7 (C), 61.2 (2 × CH_2), 39.8 (CH_3), 34.0 (CH_2), 23.7 (CH_2); IR ν_{max}/cm^{-1} 3661, 2971, 2923, 1651, 1450, 1325, 1161, 1039, 768, 552; HRMS (ES-TOF): *m/z*: calcd for $C_{16}H_{20}NO_4S$: 322.1113, found: 322.1111 [M + H]$^+$.

3-((4-Allylisoquinolin-1-yl)oxy)propan-1-ol (193b)



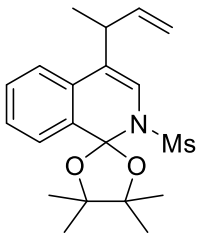
Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-1,3-dioxane (**GP7**, 290 mg, 1.09 mmol) and sulfonamide **175** (140 mg, 1.04 mmol) for 24 h. Purification by flash column chromatography [8:2 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **193b** as a colourless liquid (49.0 mg, 19%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 – 8.20 (m, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.79 (s, 1H), 7.73 – 7.66 (m, 1H), 7.58 – 7.51 (m, 1H), 6.05 (ddt, *J* = 16.7, 10.4, 6.2 Hz, 1H), 5.11 (dd, *J* = 3.8, 1.7 Hz, 1H), 5.07 (app. dq, *J* = 10.7, 1.6 Hz, 1H), 4.73 (t, *J* = 5.8Hz 2H), 3.72 (t, *J* = 5.8 Hz, 2H), 3.64 (dd, *J* = 6.2, 0.7 Hz, 2H), 2.12 – 2.03 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5 (C), 138.5 (CH), 137.1 (C), 136.6 (C), 130.7 (CH), 126.5 (CH), 124.9 (CH), 123.4 (CH), 123.4 (CH), 119.6 (C), 116.5 (CH_2), 63.0 (CH_2), 58.8 (CH_2), 34.1 (CH_2), 32.9 (CH_2); IR ν_{max}/cm^{-1} 3662, 2970, 2901, 1621, 1570, 1506, 1407, 1325, 1086, 913, 765, 673; HRMS (ES-TOF): *m/z*: calcd for $C_{15}H_{18}NO_2$: 244.1338, found: 244.1341 $[M + H]^+$.

4',4',5',5'-Tetramethyl-2-(methylsulfonyl)-4-(1-phenylallyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (206)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (**GP7**, 400 mg, 1.29 mmol) and sulfonamide **168** (250 mg, 1.18 mmol) for 18 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **206** as a light yellow foam (410 mg, 79%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.39 – 7.26 (m, 5H), 7.25 – 7.22 (m, 2H), 6.57 (s, 1H), 6.19 (ddd, *J* = 16.9, 10.2, 6.4 Hz, 1H), 5.22 (app. dt, *J* = 10.2, 1.4 Hz, 1H), 4.94 (app. dt, *J* = 17.0, 1.4 Hz, 1H), 4.85 (dd, *J* = 6.4, 0.9 Hz, 1H), 2.59 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.32 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (C), 139.2 (CH), 133.0 (C), 132.1 (C), 129.1 (CH), 128.9 (2 × CH), 128.6 (2 × CH), 127.7 (CH), 127.2 (C), 126.8 (CH), 123.3 (CH), 122.5 (CH), 117.6 (CH_2), 109.7 (C),87.2 (C), 87.0 (C) 48.9 (CH), 41.1 (CH_3), 25.8 (CH_3), 25.1 (CH_3), 23.6 (CH_3), 23.1 (CH_3).(One CH unaccounted for); IR ν_{max}/cm^{-1} 3675, 2974, 1450, 1343, 1264, 1158, 1074, 960, 749, 544; HRMS (ES-TOF): *m/z*: calcd for $C_{25}H_{30}NO_4S$: 440.1896, found: 440.1898 $[M + H]^+$.

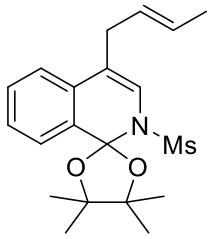
4-(But-3-en-2-yl)-4',4',5',5'-tetramethyl-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (207)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (**GP7**, 370 mg, 1.20 mmol) and sulfonamide **191** (160 mg, 1.07 mmol) for 48 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **207** as a colourless

gummy liquid (290 mg, 72%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.57 (m, 1H), 7.43 – 7.30 (m, 3H), 6.51 (s, 1H), 6.00 (ddd, *J* = 17.3, 10.3, 6.1 Hz, 1H), 5.14 (app. dt, *J* = 17.3, 1.4 Hz, 1H), 5.07 (d, *J* = 10.3 Hz, 1H), 3.70 – 3.59 (m, 1H), 2.55 (s, 3H), 1.60 (s, 6H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6 (C), 133.0 (C), 132.1 (C), 129.1 (CH), 127.8 (CH), 127.6 (CH), 124.3 (CH), 123.0 (CH), 122.8 (CH), 114.8 (CH_2), 109.6 (C), 86.8 (C), 86.3 (C), 40.8 (CH_3), 36.4 (CH), 25.6 (CH_3), 25.3 (CH_3), 23.4 (CH_3), 23.2 (CH_3), 19.0 (CH_3); IR ν_{max}/cm^{-1} 2974, 1450, 1343,1264, 1159, 1067, 1030, 955, 749, 513; HRMS (ES-TOF): *m/z*: calcd for $C_{20}H_{28}NO_4S$: 378.1739, found: 378.1746 $[M + H]^+$.

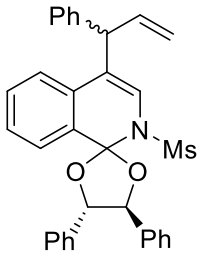
(E)-4-(But-2-en-1-yl)-4',4',5',5'-tetramethyl-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (208)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (**GP7**, 340 mg, 1.10 mmol) and sulfonamide **172** (150 mg, 1.01 mmol) for 16 h. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **208** as a white solid (300 mg, 79%, mixture of E/Z isomers in 0.4:1 ratio); mp: 128 -130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.54 (m, 1H), 7.46 – 7.30 (m, 3H), 6.51 (s, 1H), 5.70 – 5.48 (m, 2H), 3.34 – 3.18 (m, 2H), 2.56 (s, 3H), 1.77 – 1.66 (m, 3H), 1.60 (s, 6H), 1.29 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.7 (C, minor), 132.7 (C, major), 132.4 (C, minor), 132.3 (C, major), 129.3 (CH, minor), 129.2 (CH, major), 127.9 (CH, major and minor), 127.8 (CH, major), 127.8 (CH,

minor), 127.2 (CH, major and minor), 126.5 (CH, major and minor), 125.1 (CH, major), 124.9 (CH, minor), 124.8 (C, major and minor), 123.0 (CH, minor), 122.9 (CH, major), 109.7 (2 × C, major and minor), 86.6 (C, major and minor), 42.2 (CH_3, minor), 40.7 (CH_3, major), 32.8 (CH_2, major), 27.6 (CH_2, minor), 25.5 (2 × CH_3, major and minor), 23.3 (2 × CH_3, major and minor), 18.1 (CH_3, major), 13.1 (CH_3, minor); IR ν_{max}/cm^{-1} 2982, 1484, 1338, 1150, 1032, 963, 749, 513; HRMS (ES-TOF): *m/z*: calcd for $C_{20}H_{28}NO_4S$: 378.1739, found: 378.1746 $[M + H]^+$.

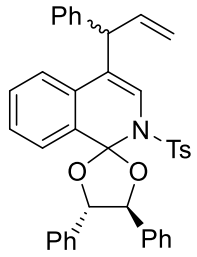
(4'S,5'S)-2-(Methylsulfonyl)-4',5'-diphenyl-4-(1-phenylallyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (212)



Prepared according to **GP12** using freshly prepared bromoalkyne (4'S,5'S)-2-(methylsulfonyl)-4',5'-diphenyl-4-(1-phenylallyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (**GP7**, 440 mg, 1.09 mmol) and sulfonamide **168** (210 mg, 0.994 mmol) for 24 h. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **212** as a white foam (420 mg, 79% dr. 1:1); $[\alpha]_D^{25}$ = -114.12; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.76 (m, 2H), 7.63 – 7.53 (m, 4H), 7.42 – 7.29 (m, 27H), 7.25 – 7.21 (m, 5H), 7.15 (s, 1H), 7.09 (s, 1H), 6.30 – 6.16 (m, 2H), 5.89 (d, *J* = 9.3 Hz, 2H), 5.29 – 5.20 (m, 2H), 5.08 (d, *J* = 3.5 Hz, 1H), 5.05 (d, *J* = 3.5 Hz, 1H), 5.03 – 4.89 (m, 2H), 4.87 – 4.80 (m, 2H), 3.27 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 141.1, 139.3, 139.2, 136.0, 134.8, 134.4, 132.3, 132.2, 131.5, 131.3, 129.4, 129.3, 129.2, 128.9, 128.8, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 126.9, 126.7, 126.6, 126.4, 124.9, 124.5, 123.5, 123.4, 118.4, 118.2, 117.6, 112.3,

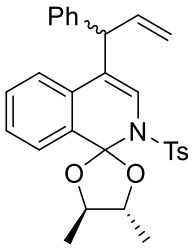
112.2, 85.5, 85.1, 84.8, 84.7, 49.1, 49.0, 44.4, 44.3 IR ν_{max}/cm^{-1} 3031, 1488, 1346, 1255, 1064, 1024, 959, 698, 520; HRMS (ES-TOF): *m/z*: calcd for $C_{33}H_{29}NO_4SNa$: 558.1715, found: 558.1716 $[M + Na]^+$.

(4'S,5'S)-4',5'-Diphenyl-4-(1-phenylallyl)-2-tosyl-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (214)



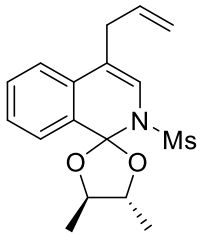
Prepared according to **GP12** using freshly prepared bromoalkyne (4'S,5'S)-2-(methylsulfonyl)-4',5'-diphenyl-4-(1-phenylallyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (**GP7**, 440 mg, 1.09 mmol) and sulfonamide **213** (290 mg, 1.01 mmol) for 30 h. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **214** as a off-white foam (420 mg, 68% dr. 1:1); $[\alpha]_D^{25}$ = -190.03; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.48 (m, 11H), 7.45 – 7.27 (m, 21H), 7.25 – 7.04 (m, 16H), 6.35 – 6.21 (m, 2H), 5.98 (dd, *J* = 9.1, 6.7 Hz, 2H), 5.31 (d, *J* = 10.2 Hz, 1H), 5.25 (d, *J* = 10.2 Hz, 1H), 5.08 – 4.89 (m, 4H), 4.88 – 4.79 (m, 2H), 2.32 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 143.6, 141.4, 141.2, 139.4, 139.3, 138.8, 138.7, 136.4, 135.5, 135.1, 132.1, 131.2, 131.0, 129.3, 129.2, 129.2, 129.1, 129.0, 129.0, 128.8, 128.8, 128.7, 128.7, 128.5, 128.4, 128.4, 127.2, 127.0, 126.8, 126.7, 126.6, 126.3, 125.8, 125.3, 123.5, 123.5, 123.1, 120.4, 119.9, 117.6, 117.6, 112.2, 112.1, 85.2, 84.9, 84.8, 84.5, 49.1, 48.9, 21.6; IR ν_{max}/cm^{-1} 2988, 2901, 1449, 1349, 1256, 1170, 1065, 750, 697, 547; HRMS (ES-TOF): *m/z*: calcd for $C_{39}H_{33}NO_4SNa$: 634.2028, found: 634.2026 $[M + Na]^+$.

(4'R,5'R)-4',5'-Dimethyl-4-(1-phenylallyl)-2-tosyl-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (218)



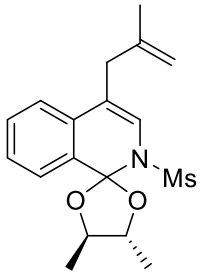
Prepared according to **GP12** using freshly prepared bromoalkyne (4R,5R)-2-(2-(bromoethynyl)phenyl)-4,5-dimethyl-1,3-dioxolane (**GP7**, 250 mg, 0.889 mmol) and sulfonamide **213** (230 mg, 0.800 mmol) for 24 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **218** as a white foam (310 mg, 79% dr. 1:1); $[\alpha]_D^{25}$ = -18.84; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.55 (2 × m, 2H), 7.32 – 7.27 (2 × m, 5H), 7.25 – 7.09 (2 × m, 7H), 6.33 – 6.20 (2 × m, 1H), 5.26 (2 × ddd, *J* = 10.2, 2.9, 1.5 Hz, 1H), 4.94 (2 × ddd, *J* = 17.1, 3.2, 1.6 Hz, 1H), 4.86 – 4.77 (2 × m, 1H), 4.60 – 4.48 (2 × m, 1H), 3.96 – 3.81 (2 × m, 1H), 2.33 (2 × s, 3H), 1.47 (2 × dd, *J* = 6.1, 5.3 Hz, 3H), 1.33 (2 × dd, *J* = 6.1, 4.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (C), 141.4 (C), 139.5 (CH), 132.5 (C), 131.0 and 130.9 (C), 129.3 (2 × CH), 128.8 (CH), 128.8 (2 × CH), 128.7 (2 × CH), 126.9 (2 × CH), 126.8 (CH), 126.7 (CH), 125.6 (CH), 123.4 and 123.3 (CH), 122.8 (CH), 119.1 and 119.0 (C), 117.5 and 117.4 (CH_2), 111.6 (C), 81.5 and 81.0 (CH), 78.9 and 78.6 (CH), 49.0 (CH), 21.6 (CH_3), 16.4 and 16.3 (CH_3), 15.4 and 15.3 (CH_3), (one quartenary carbon unaccounted for); IR ν_{max}/cm^{-1} 2974, 1450, 1345, 1260, 1170, 1077, 702, 545; HRMS (ES-TOF): *m/z*: calcd for $C_{29}H_{29}NO_4SNa$: 510.1715, found: 510.1720 $[M + Na]^+$.

(4'R,5'R)-4-Allyl-4',5'-dimethyl-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (221)



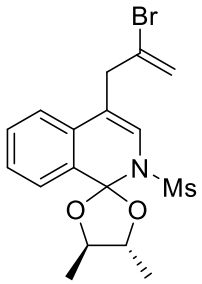
Prepared according to **GP12** using freshly prepared bromoalkyne (4R,5R)-2-(2-(bromoethynyl)phenyl)-4,5-dimethyl-1,3-dioxolane (**GP7**, 190 mg, 0.676 mmol) and sulfonamide **175** (81.0 mg, 0.599 mmol) for 24 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **221** as a colourless liquid (150 mg, 75%); $[\alpha]_D^{25}$ = -8.12; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 1H), 7.45 – 7.39 (m, 1H), 7.37 – 7.31 (m, 2H), 6.98 (s, 1H), 5.96 (ddt, *J* = 16.3, 10.1, 6.2 Hz, 1H), 5.21 – 5.08 (m, 2H), 4.51 (dq, *J* = 9.0, 6.1 Hz, 1H), 3.98 (dq, *J* = 8.9, 6.1 Hz, 1H), 3.27 (ddd, *J* = 6.1, 2.6, 1.3 Hz, 2H), 3.15 (s, 3H), 1.44 (d, *J* = 6.1 Hz, 3H), 1.37 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (CH), 132.3 (C), 131.4 (C), 129.2 (CH), 127.0 (CH), 123.4 (CH), 123.1 (CH), 122.5 (CH), 117.1 (CH_2), 114.8 (C), 111.8 (C), 81.4 (CH), 79.0 (CH), 44.2 (CH_3), 34.1 (CH_2), 16.5 (CH_3), 15.3 (CH_3); IR ν_{max}/cm^{-1} 2975, 1643, 1342, 1256, 1166, 1076, 960, 753, 519; HRMS (ES-TOF): *m/z*: calcd for $C_{17}H_{21}NO_4SNa$: 358.1089, found: 358.1090 $[M + Na]^+$.

(4'R,5'R)-4',5'-Dimethyl-4-(2-methylallyl)-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (222)



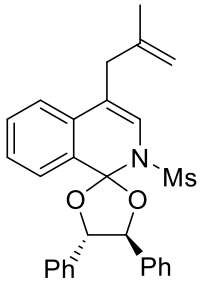
Prepared according to **GP12** using freshly prepared bromoalkyne (4R,5R)-2-(2-(bromoethynyl)phenyl)-4,5-dimethyl-1,3-dioxolane (**GP7**, 150 mg, 0.534 mmol) and sulfonamide **171** (74.6 mg, 0.500 mmol) for 24 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **222** as a colourless liquid (140 mg, 80%); $[\alpha]_D^{25}$ = 3.32; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 1H), 7.42 – 7.29 (m, 3H), 6.97 (s, 1H), 4.84 (br. s, 1H), 4.79 (br. s, 1H), 4.51 (dq, *J* = 8.9, 6.1 Hz, 1H), 3.98 (dq, *J* = 8.9, 6.1 Hz, 1H), 3. 20 (s, 2H), 3.14 (s, 3H), 1.76 (s, 3H), 1.44 (d, *J* = 6.1 Hz, 3H), 1.36 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (C), 132.4 (C), 131.6 (C), 129.2 (CH), 126.9 (CH), 123.8 (CH), 123.3 (CH), 122.8 (CH), 114.6 (C), 112.5 (CH_2), 111.8 (C), 81.4 (CH), 79.0 (CH), 44.1 (CH_3), 38.5 (CH_2), 22.6 (CH_3), 16.5 (CH_3), 15.3 (CH_3); IR ν_{max}/cm^{-1} 3675, 2972,2901, 1342, 1256, 1166, 1077, 962, 753, 515; HRMS (ES-TOF): *m/z*: calcd for $C_{18}H_{23}NO_4SNa$: 372.1245, found: 372.1242 $[M + Na]^+$.

(4'R,5'R)-4-(2-Bromoallyl)-4',5'-dimethyl-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (223)



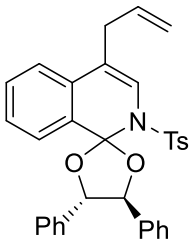
Prepared according to **GP12** using freshly prepared bromoalkyne (4R,5R)-2-(2-(bromoethynyl)phenyl)-4,5-dimethyl-1,3-dioxolane (**GP12**, 150 mg, 0.534 mmol) and sulfonamide **173** (110 mg, 0.514 mmol) for 24 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **223** as a brown liquid (130 mg, 61%); $[\alpha]_D^{25}$ = -4.49; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.46 – 7.27 (m, 3H), 7.09 (s, 1H), 5.59 (d, *J* = 1.5 Hz, 1H), 5.50 (d, *J* = 1.5 Hz, 1H), 4.52 (dq, *J* = 8.9, 6.1 Hz, 1H), 3.98 (dq, *J* = 8.9, 6.1 Hz, 1H), 3.62 (s, 2H), 3.17 (s, 3H), 1.45 (d, *J* = 6.1 Hz, 3H), 1.37 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.3 (C), 131.2 (C), 130.7 (C), 129.4 (CH), 127.3 (CH), 125.4 (CH), 123.5 (CH), 122.4 (CH), 118.4 (CH_2), 112.9 (C), 111.8 (C), 81.5 (CH), 79.1 (CH), 44.3 (CH_3), 42.2 (CH_2), 16.5 (CH_3), 15.2 (CH_3); IR ν_{max}/cm^{-1} 3675, 2987, 2901, 1342, 1256, 1075, 961, 754, 519; HRMS (ES-TOF): *m/z*: calcd for $C_{17}H_{20}NO_4SBrNa$: 436.0194, found: 436.0191 $[M + Na]^+$.

(4'S,5'S)-4-(2-Methylallyl)-2-(methylsulfonyl)-4',5'-diphenyl-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (224)



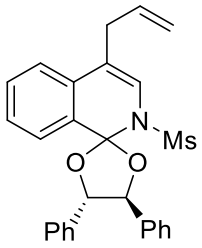
Prepared according to **GP12** using freshly prepared bromoalkyne (4'S,5'S)-2-(methylsulfonyl)-4',5'-diphenyl-4-(1-phenylallyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (**GP7**, 440 mg, 1.09 mmol) and sulfonamide **171** (150 mg, 1.01 mmol) for 40 h. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **224** as a white foam (380 mg, 79%); $[\alpha]_D^{25}$ = -134.04; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.80 (m, 1H), 7.57 – 7.51 (m, 2H), 7.44 – 7.32 (m, 11H), 7.09 (s, 1H), 5.87 (d, *J* = 9.2 Hz, 1H), 5.05 (d, *J* = 9.2 Hz, 1H), 4.84 (br. s, 1H), 4.80 (br. s, 1H), 3.36 – 3.12 (m, 5H), 1.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (C), 135.9 (C) , 134.7 (C), 132.0 (C), 131.8 (C), 129.4 (CH), 129.2 (CH), 128.9 (2 × CH), 128.8 (2 × CH), 128.6 (CH), 128.6 (2 × CH), 127.1 (CH), 126.5 (2 × CH), 123.8 (CH), 123.5 (CH), 123.2 (CH), 115.3 (C), 112.6 (CH_2), 112.3 (C), 85.1 (CH), 85.1 (CH), 44.1 (CH_3), 38.5 (CH_2), 22.6 (CH_3); IR ν_{max}/cm^{-1} 2972, 2901, 1650, 1450, 1347, 1254, 1168, 1168, 958, 751, 698, 520; HRMS (ES-TOF): *m/z*: calcd for $C_{28}H_{27}NO_4SNa$: 496.1558, found: 496.1560 $[M + Na]^+$.

(4'S,5'S)-4-Allyl-4',5'-diphenyl-2-tosyl-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (225)



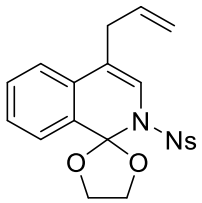
Prepared according to **GP12** using freshly prepared bromoalkyne (4'S,5'S)-2-(methylsulfonyl)-4',5'-diphenyl-4-(1-phenylallyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (**GP7**, 310 mg, 0.764 mmol) and sulfonamide **220** (150 mg, 0.710 mmol) for 32 h. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **225** as a white foam (230 mg, 61%); $[\alpha]_D^{25}$ = -174.16; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.50 (m, 5H), 7.44 – 7.27 (m, 10H), 7.23 (s, 1H), 7.23 – 7.18 (m, 1H), 7.08 (d, *J* = 7.8 Hz, 2H), 6.08 – 5.92 (m, 2H), 5.23 – 5.10 (m, 2H), 4.96 (d, *J* = 9.2 Hz, 1H), 3.32 (ddd, *J* = 7.3, 5.1, 1.4 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6 (C), 138.9 (C), 136.3 (C), 135.8 (CH), 135.2 (C), 131.9 (C), 131.3 (C), 129.2 (2 × CH), 129.1 (CH), 128.8 (2 × CH), 128.8 (2 × CH), 128.8 (2 × CH), 128.7 (CH), 128.4 (CH), 127.1 (2 × CH), 127.0 (CH), 126.3 (2 × CH), 123.9 (CH), 123.6 (CH), 122.7 (CH), 117.1 (CH_2), 116.9 (C), 112.2 (C), 85.0 (CH), 84.5 (CH), 34.1 (CH_2), 21.6 (CH_3); IR ν_{max}/cm^{-1} 2973, 1643, 1450, 1349, 1254, 1170, 1024, 674, 547; HRMS (ES-TOF): *m/z*: calcd for $C_{33}H_{29}NO_4SNa$: 558.1715, found: 558.1714 $[M + Na]^+$.

(4'S,5'S)-4-Allyl-2-(methylsulfonyl)-4',5'-diphenyl-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (226)



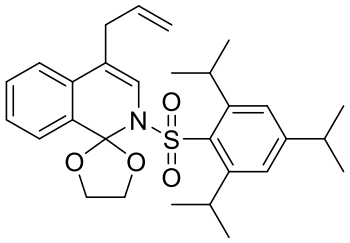
Prepared according to **GP12** using freshly prepared bromoalkyne (4'S,5'S)-2-(methylsulfonyl)-4',5'-diphenyl-4-(1-phenylallyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (**GP7**, 405 mg, 1.00 mmol) and sulfonamide **175** (122 mg, 0.903 mmol) for 24 h. Purification by flash column chromatography [95:5 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **226** as a white solid (310 mg, 75%); $[\alpha]_D^{25}$ = -113.57; mp: 96-98 °C; Dihydoisoquinoline **226** (90% purity): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 1H), 7.59 – 7.53 (m, 2H), 7.49 – 7.33 (m, 11H), 7.09 (s, 1H), 6.05 – 5.93 (m, 1H), 5.89 (d, *J* = 9.3 Hz, 1H), 5.23 – 5.09 (m, 2H), 5.05 (d, *J* = 9.3 Hz, 1H), 3.32 – 3.27 (m, 2H), 3.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9 (C), 135.7 (CH), 134.5 (C), 132.0 (C), 131.6 (C), 129.5 (CH), 129.3 (CH), 129.1 (CH), 128.9 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.6 (CH), 126.4 (2 × CH), 123.7 (CH), 123.1 (CH), 122.8 (CH), 117.2 (CH_2), 115.2 (C), 112.3 (C), 85.0 (2 × CH), 44.3 (CH_3), 34.1 (CH_2); IR ν_{max}/cm^{-1} 2988, 2901, 1670, 1347, 1167, 1064, 963, 698, 516; HRMS (ES-TOF): *m/z*: calcd for $C_{27}H_{25}NO_4SNa$: 482.1402, found: 482.1408 $[M + Na]^+$.

4-Allyl-2-((4-nitrophenyl)sulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (237)



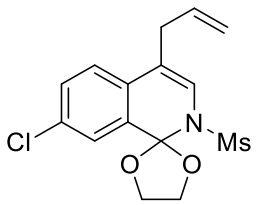
Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (**GP7**, 280 mg, 1.11 mmol) and sulfonamide **236** (240 mg, 0.929 mmol) for 18 h. Purification by flash column chromatography [8:2 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **237** as a yellow solid (340 mg, 88%); mp: 93 – 95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.9 Hz, 2H), 7.84 (d, *J* = 8.9 Hz, 2H), 7.38 – 7.27 (m, 2H), 7.25 – 7.17 (m, 2H), 6.99 (s, 1H), 5.98 (ddt, *J* = 16.5, 10.3, 6.1 Hz, 1H), 5.18 (app. dq, *J* = 7.6, 1.5 Hz, 1H), 5.13 (app. t, *J* = 1.5 Hz, 1H), 4.64 – 4.51 (m, 2H), 4.26 – 4.13 (m, 2H), 3.32 (dd, *J* = 6.1, 1.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9 (C), 147.2 (C), 135.3 (CH), 131.0 (C), 130.4 (C), 129.7 (CH), 128.0 (2 × CH), 127.8 (CH), 123.9 (2 × CH), 123.5 (CH), 123.0 (CH), 122.7 (CH), 119.7 (C), 117.4 (CH_2), 112.7 (C), 66.4 (2 × CH_2), 34.0 (CH_2); IR ν_{max}/cm^{-1} 2900, 1526, 1348, 1306, 1172, 1079, 737, 606, 572; HRMS (ES-TOF): *m/z*: calcd for $C_{20}H_{19}N_2O_6S$: 415.0964, found: 415.0967 $[M + H]^+$.

4-Allyl-2-((2,4,6-triisopropylphenyl)sulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (241)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (**GP7**, 170 mg, 0.672 mmol) and sulfonamide **240** (190 mg, 0.587 mmol) for 48 h. Purification by flash column chromatography [90:10 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **241** as a colourless liquid (100 mg, 34%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.26 – 7.18 (m, 2H), 7.09 (s, 1H), 7.04 (s, 2H), 5.99 (ddt, *J* = 17.1, 10.1, 6.2 Hz, 1H), 5.21 (app. dq, *J* = 17.1, 1.6 Hz, 1H), 5.13 (ddd, *J* = 10.1, 2.9, 1.4 Hz, 1H), 4.50 – 4.36 (m, 2H), 4.16 – 4.07 (m, 2H), 4.01 (sep, *J* = 6.7 Hz, 2H), 3.35 (dd, *J* = 6.2, 1.1 Hz, 2H), 2.84 (sep, *J* = 6.9 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 6H), 1.04 (d, *J* = 6.8 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6 (C), 150.3 (2 × C), 136.1 (CH), 135.8 (C), 131.8 (C), 131.8 (C), 129.1 (CH), 127.1 (CH), 123.8 (2 × CH), 123.6 (CH), 122.4 (CH), 117.2 (C), 117.0 (CH_2), 113.3 (C), 66.5 (2 × CH_2), 34.2 (CH_2), 34.1 (CH), 29.1 (2 × CH), 24.7 (4 × CH_3), 23.6 (2 × CH_3), (one CH unaccounted for); IR ν_{max}/cm^{-1} 2928, 1600, 1364, 1333, 1166, 1066, 1020,673, 578, 553; HRMS (ES-TOF): *m/z*: calcd for $C_{29}H_{38}NO_4S$: 496.2522, found: 496.2517 $[M + H]^+$.

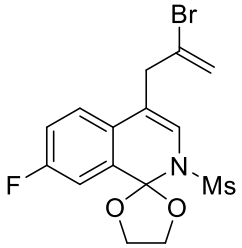
4-Allyl-7-chloro-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (247)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)-5-chlorophenyl)-1,3-dioxolane (**GP7**, 160 mg, 0.556 mmol) and sulfonamide **175** (68.0 mg, 0.503 mmol) for 41 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **247** as an orange liquid (140 mg, 81%);.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 2.2 Hz, 1H), 7.36 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.23 (s, 1H), 6.86 (s, 1H), 5.90

(ddt, *J* = 16.5, 10.3, 6.1 Hz, 1H), 5.15 – 5.06 (m, 2H), 4.56 – 4.44 (m, 2H), 4.25 – 4.16 (m, 2H), 3.22 (dd, *J* = 6.2, 1.1 Hz, 2H), 3.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3 (CH), 132.9 (C), 132.4 (C), 130.2 (C), 129.7 (CH), 124.0 (CH), 123.9 (CH), 123.4 (CH), 117.3 (CH_2), 115.4 (C), 112.2 (C), 66.8 (2 × CH_2), 43.5 (CH_3), 34.0 (CH_2); IR ν_{max}/cm^{-1} 3675, 2988, 2901, 1640, 1488, 1344, 1250, 1166, 1067, 960, 761, 509; HRMS (ES-TOF): *m/z*: calcd for $C_{15}H_{17}NO_4S35Cl$: 342.0567, found: 342.0566 $[M + H]^+$.

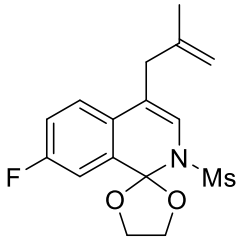
4-(2-Bromoallyl)-7-fluoro-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (254)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)-5-fluorophenyl)-1,3-dioxolane (**GP7**, 150 mg, 0.553 mmol) and sulfonamide **173** (110 mg, 0.514 mmol) for 48 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **254** as a white solid (130 mg, 63%);.mp: 94-96 °C; ^{1}H NMR (300 MHz, CDCl3) δ 7.27 (dd, *J* = 9.2, 4.7 Hz, 1H), 7.21 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.13 (td, *J* = 8.4, 2.7 Hz, 1H), 6.96 (s, 1H), 5.59 (d, *J* = 1.7 Hz, 1H), 5.51 (d, *J* = 1.7 Hz, 1H), 4.61 – 4.47 (m, 2H), 4.28 – 4.18 (m, 2H), 3.61 (s, 2H), 3.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1 (d, J_{C-F} = 247.2 Hz, C), 132.9 (d, J_{C-F} = 6.8 Hz, C), 130.9 (C), 127.2 (d, J_{C-F} = 3.1 Hz, C), 124.7 (CH), 124.4 (d, J_{C-F} = 7.8 Hz, CH), 118.5 (CH_2), 116.9 (d, J_{C-F} = 22.1 Hz, CH), 113.6 (C), 112.3 (C), 110.9 (d, J_{C-F} = 23.8 Hz, CH), 66.8 (2 × CH_2), 43.6 (CH_3), 42.2 (CH_2); IR ν_{max}/cm^{-1} 3110, 2907,

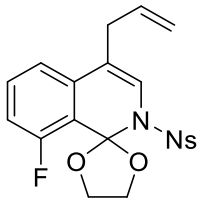
1634, 1499, 1339, 1155, 1028, 966, 819, 518; HRMS (ES-TOF): *m/z*: calcd for $C_{15}H_{16}NO_4SBrF$: 403.9967, found: 403.9966 $[M + H]^+$.

7-Fluoro-4-(2-methylallyl)-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (255)



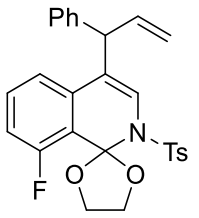
Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)-5-fluorophenyl)-1,3-dioxolane (**GP7**, 150 mg, 0.553 mmol) and sulfonamide **171** (74.6 mg, 0.500 mmol) for 48 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **255** as a colourless liquid (120 mg, 71%);.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.7, 5.4 Hz, 1H), 7.20 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.10 (td, *J* = 8.5, 2.7 Hz, 1H), 6.84 (s, 1H), 4.84 (br. s, 1H), 4.76 (br. s, 1H), 4.59 – 4.46 (m, 2H), 4.26 – 4.17 (m, 2H), 3.19 (s, 2H), 3.06 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0 (d, $J_{C\text{-}F}$ = 247.0 Hz, C), 143.1 (C), 132.9 (d, $J_{C\text{-}F}$ = 6.9 Hz, C), 128.1 (d, $J_{C\text{-}F}$ = 3.2 Hz, C), 124.8 (d, $J_{C\text{-}F}$ = 7.8 Hz, CH), 123.1 (CH), 116.8 (d, $J_{C\text{-}F}$ = 21.7 Hz, CH), 115.5 (C), 112.7 (CH_2), 112.2 (C), 110.7 (d, $J_{C\text{-}F}$ = 23.9 Hz, CH), 66.7 (2 × CH_2), 43.3 (CH_3), 38.6 (CH_2), 22.4 (CH_3); IR ν_{max}/cm^{-1} 3675, 2988, 2901, 1650, 1500, 1343, 1261, 1159, 1057, 950, 826, 763, 649, 517; HRMS (ES-TOF): *m/z*: calcd for $C_{16}H_{18}NO_4FS23Na$: 362.0838, found: 362.0841 $[M + Na]^+$.

4-Allyl-8-fluoro-2-((4-nitrophenyl)sulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (261)



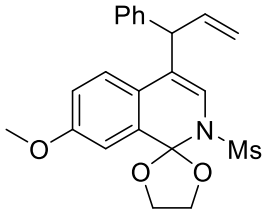
Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)-6-fluorophenyl)-1,3-dioxolane (**GP7**, 210 mg, 0.775 mmol) and sulfonamide **236** (170 mg, 0.658 mmol) for 48 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **261** as a yellow solid (200 mg, 70%);.mp: 105-108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.9 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 2H), 7.32 (td, *J* = 8.1, 5.2 Hz, 1H), 7.13 (s, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.92 (ddd, *J* = 11.8, 8.2, 0.7 Hz, 1H), 6.05 – 5.85 (m, 1H), 5.17 (app. t, *J* = 1.5 Hz, 1H), 5.13 (dd, *J* = 7.0, 1.5 Hz, 1H), 4.63 – 4.48 (m, 2H), 4.37 – 4.23 (m, 2H), 3.27 (dd, *J* = 6.1, 1.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (d, $J_{C\text{-}F}$ = 252.8 Hz, C), 150.1 (C), 147.7 (C), 135.2 (CH), 133.4 (C), 130.9 (d, $J_{C\text{-}F}$ = 9.9 Hz, CH), 127.8 (2 × CH), 124.3 (2 × CH), 123.4 (CH), 119.2 (d, $J_{C\text{-}F}$ = 9.1 Hz, C), 118.6 (d, $J_{C\text{-}F}$ = 3.5 Hz, CH), 117.5 (CH_2), 116.1 (d, $J_{C\text{-}F}$ = 3.4 Hz, C)), 115.4 (d, $J_{C\text{-}F}$ = 23.5 Hz, CH), 113.2 (C), 67.1 (CH_2), 67.1 (CH_2), 34.5 (CH_2); IR ν_{max}/cm^{-1} 3114, 2915, 1650, 1531, 1359, 1263, 1171, 1023, 845, 743, 629, 564; HRMS (ES-TOF): *m/z*: calcd for $C_{20}H_{18}N_2O_6SF$: 433.0870, found: 433.0867 $[M + H]^+$.

8-Fluoro-4-(1-phenylallyl)-2-tosyl-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (262)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)-6-fluorophenyl)-1,3-dioxolane (**GP7**, 1.00 g, 3.69 mmol) and sulfonamide **213** (0.98 g, 3.41 mmol) for 48 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **262** as a white foam (1.21 g, 74%);. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.27 (m, 2H), 7.25 – 7.19 (m, 5H), 7.16 (s, 1H), 7.14 – 7.10 (m, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.83 (dd, *J* = 12.0, 8.1 Hz, 1H), 6.22 (ddd, *J* = 16.8, 10.2, 6.3 Hz, 1H), 5.28 (app. dt, *J* = 10.2, 1.4 Hz, 1H), 4.92 (app. dt, *J* = 17.1, 1.3 Hz, 1H), 4.74 (d, *J* = 6.3 Hz, 1H), 4.66 – 4.56 (m, 2H), 4.40 – 4.27 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (d, $J_{C\text{-}F}$ = 252.1 Hz, C), 143.8 (C), 141.1 (C), 139.1 (d, $J_{C\text{-}F}$ = 4.1 Hz, CH)), 133.4 (C), 130.3 (d, $J_{C\text{-}F}$ = 9.9 Hz, CH), 129.6 (2 × CH), 128.7 (2 × CH), 128.7 (2 × CH), 126.9 (CH), 126.7 (2 × CH), 126.1 (CH), 119.7 (d, $J_{C\text{-}F}$ = 9.1 Hz, C), 118.6 (d, $J_{C\text{-}F}$ = 3.4 Hz, CH)), 117.7 (CH_2), 116.3 (C) 116.2 (C), 114.6 (d, $J_{C\text{-}F}$ = 23.8 Hz, CH), 113.4 (C), 67.4 (CH_2), 67.4 (CH_2), 49.2 (CH), 21.7 (CH_3); IR ν_{max}/cm^{-1} 2971, 1639, 1476, 1340, 1243, 1168, 1101, 1042, 1027, 853, 699, 674, 576; HRMS (ES-TOF): *m/z*: calcd for $C_{27}H_{24}NO_4SFNa$: 500.1308, found: 500.1315 $[M + Na]^+$.

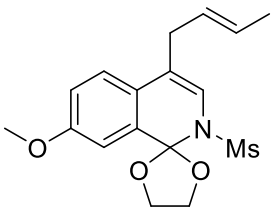
7-Methoxy-2-(methylsulfonyl)-4-(1-phenylallyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (269)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)-5-methoxyphenyl)-1,3-dioxolane (**GP7**, 220 mg, 0.778 mmol) and sulfonamide **168** (150 mg, 0.710 mmol) for 48 h. Purification by flash column chromatography [85:15 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **269** as a fluffy solid (120 mg, 41%);.mp: 113-115 °C; ^{1}H

NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.10 (d, *J* = 2.7 Hz, 1H), 6.90 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.86 (s, 1H), 6.27 (ddd, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.30 (app. dt, *J* = 10.2, 1.4 Hz, 1H), 5.00 (app. dt, *J* = 17.1, 1.4 Hz, 1H), 4.83 (d, *J* = 6.4 Hz, 1H), 4.69 – 4.54 (m, 2H), 4.34 – 4.24 (m, 2H), 3.87 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C), 141.3 (C), 139.2 (CH), 132.7 (C), 128.7 (2 × CH), 128.7 (2 × CH), 126.8 (CH), 124.7 (CH), 124.6 (C), 122.6 (CH), 119.7 (C), 117.5 (CH_2), 115.1 (CH), 112.5 (C), 108.9 (CH), 67.0 (CH_2), 66.2 (CH_2), 55.6 (CH_3), 49.2 (CH), 43.3 (CH_3); IR ν_{max}/cm^{-1} 3675, 2988, 2901,1407, 1394, 1337, 1154, 1066, 953, 523; HRMS (ES-TOF): *m/z*: calcd for $C_{22}H_{24}NO_5S$: 414.1375, found: 414.1373 $[M + H]^+$.

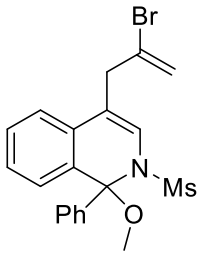
(E)-4-(But-2-en-1-yl)-7-methoxy-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (270)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(2-(bromoethynyl)-5-methoxyphenyl)-1,3-dioxolane (**GP7**, 190 mg, 0.671 mmol) and sulfonamide **172** (89.5 mg, 0.600 mmol) for 48 h. Purification by flash column chromatography [85:15 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **270** as a viscous colourless liquid (120 mg, 57%, a mixture of E/Z isomers in 0.5:1 ratio); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 1H), 7.07 – 7.03 (m, 1H), 7.01 – 6.95 (m, 1H), 6.74 – 6.69 (m, 1H), 5.66 – 5.47 (m, 2H), 4.58 – 4.46 (m, 2H), 4.26 – 4.12 (m, 2H), 3.85 (s, 3H), 3.27 – 3.14 (m, 2H), 3.02 (s, 3H), 1.76 – 1.63 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (C, minor), 159.2 (C, major), 132.5 (C, minor), 132.4 (C, major), 128.1 (CH, major), 127.6 (CH, major), 127.5 (CH, minor), 126.2 (CH, minor), 125.1 (C,

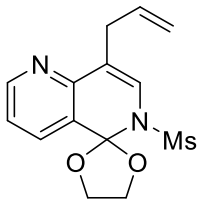
minor), 125.0 (C, major), 124.2 (CH, major), 123.9 (CH, minor), 120.7 (CH, major), 120.5 (CH, minor), 117.7 (C, major), 117.5 (C, minor), 115.3 (CH, major and minor), 112.5 (C, major and minor), 109.2 (CH, minor), 109.1 (CH, major), 66.5 (2 × CH_2, major and minor), 55.6 (CH_3, major and minor), 43.0 (CH_3, major and minor), 33.1 (CH_2, major), 27.6 (CH_2, minor), 18.1 (CH_3, major), 13.1 (CH_3, minor); IR ν_{max}/cm^{-1} 3675, 2988, 2901, 1614, 1499, 1332, 1294, 1216, 1144, 1029, 966, 948, 818, 648, 521; HRMS (ES-TOF): *m/z*: calcd for $C_{17}H_{22}NO_5S$: 352.1219, found: 352.1217 $[M + H]^+$.

4-(2-Bromoallyl)-1-methoxy-2-(methylsulfonyl)-1-phenyl-1,2-dihydroisoquinoline (273)



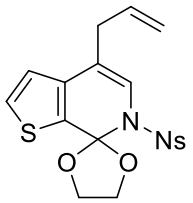
Prepared according to **GP12** using freshly prepared bromoalkyne 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (**GP7**, 160 mg, 0.531 mmol) and sulfonamide **173** (110 mg, 0.513 mmol) for 48 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **273** as a yellow liquid (100 mg, 45%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 2H), 7.37 – 7.28 (m, 3H), 7.25 – 7.17 (m, 2H), 7.12 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.08 (s, 1H), 6.96 (dd, *J* = 7.9, 1.0 Hz, 1H), 5.74 (d, *J* = 1.7 Hz, 1H), 5.59 (d, *J* = 1.7 Hz, 1H), 3.60 (s, 2H), 3.20 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (C), 134.0 (C), 132.2 (C), 130.3 (C), 129.3 (CH), 128.7 (CH), 128.2 (CH), 127.8 (2 × CH), 127.6 (2 × CH), 127.4 (CH), 126.4 (CH), 121.2 (CH), 118.5 (CH_2), 108.5 (C), 93.7 (C), 51.1 (CH_3), 42.6 (CH_2), 42.3 (CH_3); IR ν_{max}/cm^{-1} 3059, 1630, 1386, 1167, 1038, 765, 700, 523; HRMS (ES-TOF): *m/z*: calcd for $C_{20}H_{20}NO_3SBrNa$: 456.0245, found: 456.0248 $[M + Na]^+$.

8'-Allyl-6'-(methylsulfonyl)-6'H-spiro[[1,3]dioxolane-2,5'-[1,6]naphthyridine] (281)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(bromoethynyl)-3-(1,3-dioxolan-2-yl)pyridine (**GP7**, 220 mg, 0.866 mmol) and sulfonamide **175** (110 mg, 0.814 mmol) for 24 h. Purification by flash column chromatography [8:2 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **281** as a brown solid (100 mg, 40%);. mp: 88-90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.75 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.10 (s, 1H), 6.05 (ddt, *J* = 16.5, 10.1, 6.4 Hz, 1H), 5.20 – 5.06 (m, 2H), 4.64 – 4.49 (m, 2H), 4.29 – 4.14 (m, 2H), 3.44 (ddd, *J* = 6.4, 2.6, 1.3 Hz, 2H), 3.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5 (CH), 149.5 (C), 135.9 (CH), 131.6 (CH), 126.5 (C), 126.3 (CH), 121.8 (CH), 118.0 (C), 116.7 (CH_2), 113.2 (C), 66.9 (2 × CH_2), 43.6 (CH_3), 32.4 (CH_2); IR ν_{max}/cm^{-1} 3675, 2989, 2901, 1640, 1587, 1459, 1337, 1259, 1157, 1057, 963, 948, 760, 521; HRMS (ES-TOF): *m/z*: calcd for $C_{14}H_{17}N_2O_4S$: 309.0909, found: 309.0907 $[M + H]^+$.

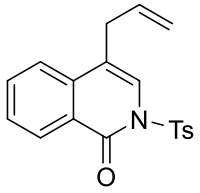
4-Allyl-6-((4-nitrophenyl)sulfonyl)-6H-spiro[thieno[2,3-c]pyridine-7,2'-[1,3]dioxolane] (290)



Prepared according to **GP12** using freshly prepared bromoalkyne 2-(3-(bromoethynyl)thiophen-2-yl)-1,3-dioxolane (**GP7**, 200 mg, 0.772 mmol) and sulfonamide

236 (170 mg, 0.658 mmol) for 24 h. Purification by flash column chromatography [90:10 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **290** as a yellow solid (100 mg, 36%);. mp: 138-140 °C; ^{1}H NMR (300 MHz, CDCl3) δ 8.22 (d, *J* = 8.9 Hz, 2H), 8.16 (d, *J* = 5.3 Hz, 1H), 8.07 (d, *J* = 8.9 Hz, 2H), 7.87 (s, 1H), 7.59 (d, *J* = 5.3 Hz, 1H), 5.94 (ddt, *J* = 16.5, 10.1, 6.3 Hz, 1H), 5.28 – 5.09 (m, 2H), 5.07 – 4.96 (m, 2H), 4.20 – 4.07 (m, 2H), 3.66 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9 (C), 151.3 (C), 150.9 (C), 148.7 (C), 139.7 (CH), 133.5 (CH), 129.3 (CH), 127.5 (2 × CH), 124.5 (C), 123.7 (2 × CH), 123.4 (CH), 119.2 (C), 119.0 (CH_2), 75.1 (CH_2), 61.0 (CH_2), 34.6 (CH_2); IR ν_{max}/cm^{-1} 3392, 2973, 2901, 1667, 1603, 1320, 1348, 1232, 1178, 1121, 1031, 853, 740, 637, 551; HRMS (ES-TOF): *m/z*: calcd for $C_{18}H_{17}N_2O_6S_2$: 421.0528, found: 421.0530 $[M + H]^+$.

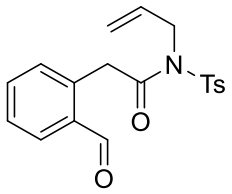
4-Allyl-2-tosylisoquinolin-1(2H)-one (292a)



Prepared according to **GP12** using ynamide **291** (66.0 mg, 0.150 mmol), stirring at 100 ^{o}C for 24 h. Purification by flash column chromatography [8:2 (hexane:EtOAc), 1% Et_3N] gave isoquinoline (alongside diketone **292b**) **292a** as a brown solid (25.0 mg, 49%); mp: 163-165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.9 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.77 (s, 1H), 7.72 – 7.58 (m, 2H), 7.50 – 7.41 (m, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 6.02 (ddt, *J* = 16.6, 10.5, 6.1 Hz, 1H), 5.26 – 5.11 (m, 2H), 3.47 (d, *J* = 5.9 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5 (CO), 145.9 (C), 136.7 (C), 135.1 (CH), 134.6 (C), 133.9 (CH), 129.7 (2 × CH), 129.6 (2 × CH), 129.0 (CH), 127.7 (CH), 126.7 (C), 123.8 (CH), 123.2 (CH), 117.8 (CH_2), 115.8 (C) 34.1

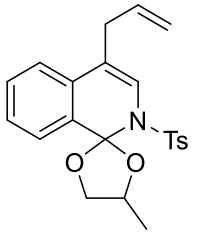
(CH_2), 21.9 (CH_3); IR ν_{max}/cm^{-1} 2921, 1677,1594, 1353, 1241, 1162,771 676, 543; HRMS (ES-TOF): *m/z*: calcd for $C_{19}H_{18}NO_3S$: 340.1007, found: 340.1008 $[M + H]^+$.

N-Allyl-2-(2-formylphenyl)-N-tosylacetamide (292b)



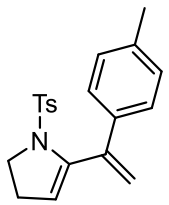
Prepared according to **GP12** using ynamide **291** (66.0 mg, 0.150 mmol), stirring at 100 ^oC for 24 h. Purification by flash column chromatography [8:2 (hexane:EtOAc), 1% Et_3N] gave diketone **292b** as a white soild solid (21.4 mg, 40%); mp: 100 – 112 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.76 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.22 – 7.18 (m, 1H), 5.93 (ddt, *J* = 17.1, 10.3, 5.7 Hz, 1H), 5.32 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.24 (dd, *J* = 10.3, 1.2 Hz, 1H), 4.52 (app. dt, *J* = 5.7, 1.4 Hz, 2H), 4.34 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3 (CHO), 170.7 (CO), 144.9 (C), 136.7 (C), 135.6 (CH), 135.2 (C), 134.3 (C), 133.9 (CH), 133.0 (CH), 132.8 (CH), 129.8 (2 × CH), 128.2 (2 × CH), 128.1 (CH), 118.5 (CH_2), 49.1 (CH_2), 42.0 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} 1698, 1347, 1169, 1086, 758, 665, 537; HRMS (ES-TOF): *m/z*: calcd for $C_{19}H_{19}NO_4SNa$: 380.0932, found: 380.0936 $[M + Na]^+$.

4-Allyl-4'-methyl-2-tosyl-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane] (294)



Prepared according to **GP12** using ynamide **293**(119 mg, 0.3 mmol), stirring at 100 ^{o}C for 20 h. Purification by flash column chromatography [9:1 (hexane:EtOAc), 1% Et_3N] gave dihydroisoquinoline **294** as a brown liquid (67.0 mg, 56%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.36 – 7.27 (m, 3H), 7.26 – 7.16 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.02 (s, 1H), 5.99 (ddt, *J* = 17.0, 10.1, 6.1 Hz, 1H), 5.20 – 5.08 (m, 2H), 5.03 – 4.89 (m, 1H), 4.60 (dd, *J* = 7.2, 6.3 Hz, 1H), 3.66 (app. t, *J* = 7.2 Hz, 1H), 3.30 (ddd, *J* = 6.0, 2.6, 1.4 Hz, 2H), 2.29 (s, 3H), 1.35 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (C), 139.2 (C), 135.9 (CH), 131.5 (C), 131.1 (C), 129.3 (2 × CH), 129.3 (2 × CH) 127.4 (CH), 126.8 (CH), 124.2 (CH), 123.8 (CH), 122.4 (CH), 118.1 (C), 117.1 (CH_2), 112.7 (C), 73.6 (CH_3), 72.9 (CH_2), 34.2 (CH_2), 21.7 (CH), 18.4 (CH_3); IR ν_{max}/cm^{-1} 2978, 1640, 1450, 1347, 1266, 1168, 982, 671, 581, 544; ; HRMS (ES-TOF): *m/z*: calcd for $C_{22}H_{24}NO_4S$: 398.1426, found: 398.1432 $[M + H]^+$.

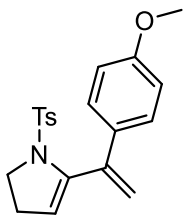
5-(1-(*p*-Tolyl)vinyl)-1-tosyl-2,3-dihydro-1H-pyrrole (362)



Prepared according to **GP13** using ynamide **351** (51.0 mg, 0.150 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the dienamide **362** as a white solid (46.9 mg, 92%); mp: 114-116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.25 (m, 4H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.49 – 5.44 (m, 3H), 3.95 (t, *J* = 8.3 Hz, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 2.12 (td, *J* = 8.3, 2.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 143.7 (C), 142.2 (C), 137.7 (C), 136.3 (C), 134.9 (C), 129.5 (2 × CH), 129.0 (2 × CH), 128.0 (2 × CH), 127.2 (2 × CH), 119.7 (CH), 115.9 (CH_2), 51.4 (CH_2), 28.2 (CH_2), 21.7

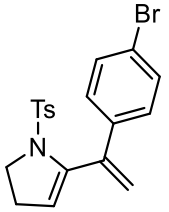
(CH_3), 21.4 (CH_3); IR ν_{max}/cm^{-1} 2959, 1513, 1351, 1162, 1085,984, 820, 666, 582, 546; HRMS (EI-TOF): *m/z*: calcd for $C_{20}H_{21}NO_2S$: 339.1293, found: 339.1294 $[M]^+$.

5-(1-(4-Methoxyphenyl)vinyl)-1-tosyl-2,3-dihydro-1H-pyrrole (363)



Prepared according to **GP13** using ynamide **352** (71.1 mg, 0.200 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the dienamide **363** as a white solid (59.0 mg, 83%); mp:94-96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.25 (m, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.48 (t, *J* = 2.8 Hz, 1H), 5.43 (d, *J* = 1.4 Hz, 1H), 5.40 (d, *J* = 1.4 Hz, 1H), 3.95 (t, *J* = 8.3 Hz, 2H), 3.82 (s, 3H), 2.43 (s, 3H), 2.12 (td, *J* = 8.3, 2.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (C), 144.8 (C), 143.6 (C), 141.7 (C), 134.8 (C), 131.6 (C),129.4 (2 × CH) 128.3 (2 × CH), 127.9 (2 × CH), 119.5 (CH), 115.0 (CH_2), 113.5 (2 × CH), 55.3 (CH_3), 51.2 (CH_2), 28.0 (CH_2), 21.6 (CH_3); IR ν_{max}/cm^{-1} 3392, 2930, 1720, 1609, 1509, 1354, 1277, 1245, 1166, 1020, 711, 667, 580, 548; HRMS (ES-TOF): *m/z*: calcd for $C_{20}H_{22}NO_3S$: 356.1320, found: 356.1319 $[M + H]^+$.

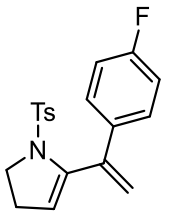
5-(1-(4-Bromophenyl)vinyl)-1-tosyl-2,3-dihydro-1H-pyrrole (364)



Prepared according to **GP13** using ynamide **353** (80.9 mg, 0.200 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the

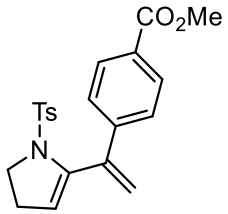
dienamide **364** as a brown foam (68.0 mg, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.24 – 7.17 (m, 4H), 5.48 – 5.38 (m, 3H), 3.87 (t, *J* = 8.3 Hz, 2H), 2.36 (s, 3H), 2.08 (td, *J* = 8.3, 2.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2 (C), 143.9 (C), 141.6 (C), 138.0 (C), 134.7 (C), 131.4 (2 × CH), 129.6 (2 × CH), 128.9 (2 × CH), 127.9 (2 × CH), 122.0 (C), 120.1 (CH), 116.8 (CH_2), 51.3 (CH_2), 28.2 (CH_2), 21.7 (CH_3); IR ν_{max}/cm^{-1} 2959, 2833, 1687, 1487, 1347, 1250, 1163, 1085, 898, 844, 655; HRMS (ES-TOF): *m/z*: calcd for $C_{19}H_{18}NO_2SNa^{79}Br$: 426.0139, found: 426.0141 $[M + Na]^+$.

5-(1-(4-Fluorophenyl)vinyl)-1-tosyl-2,3-dihydro-1H-pyrrole (365)



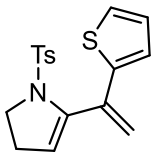
Prepared according to **GP13** using ynamide **354** (103 mg, 0.300 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the dienamide **365** as a white solid (71.1 mg, 69%); mp:107-109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.37 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.01 (t, *J* = 8.7 Hz, 2H), 5.50 (t, *J* = 2.8 Hz, 1H), 5.47 (d, *J* = 1.1 Hz, 1H), 5.44 (d, *J* = 1.1 Hz, 1H), 3.94 (t, *J* = 8.3 Hz, 2H), 2.43 (s, 3H), 2.13 (td, *J* = 8.3, 2.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (d, J_{C-F} = 246.6 Hz, C), 144.5 (C), 143.9 (C), 141.6 (C), 135.2 (d, J_{C-F} = 3.7 Hz, C), 134.8 (C), 129.6 (2 × CH), 128.9 (d, J_{C-F} = 7.9 Hz, 2 × CH)), 128.0 9 (2 × CH), 129.0 (CH), 116.3 (CH_2), 115.1 (d, J_{C-F} = 21.5 Hz, 2 × CH)), 51.3 (CH_2), 28.2 (CH_2), 21.7 (CH_3); IR ν_{max}/cm^{-1} 2972, 1599, 1507, 1350, 1218, 1162, 1085, 844, 688, 666, 576, 545; HRMS (ES-TOF): *m/z*: calcd for $C_{19}H_{19}NO_2SF$: 344.1121, found: 344.1119 $[M + H]^+$.

Methyl 4-(1-(1-tosyl-4,5-dihydro-1H-pyrrol-2-yl)vinyl)benzoate (366)



Prepared according to **GP13** using ynamide **355** (76.7 mg, 0.200 mmol), heating at 80 °C for 4 hours. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the dienamide **366** as a white solid (53.7 mg, 70%); mp: 91-93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.23 (m, 2H), 5.58 (s, 2H), 5.52 (t, *J* = 2.8 Hz, 1H), 4.00 – 3.90 (m, 5H), 2.43 (s, 3H), 2.17 (td, *J* = 8.4, 2.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1 (CO), 144.0 (C), 143.9 (C), 143.6 (C), 141.8 (C), 134.7 (C), 129.6 (2 × CH), 129.6 (2 × CH), 129.5 (C), 127.9 (2 × CH), 127.2 (2 × CH), 120.2 (CH), 118.0 (CH_2), 52.2 (CH_3), 51.2 (CH_2), 28.2 (CH_2), 21.7 (CH_3); IR ν_{max}/cm^{-1} 2955, 1719, 1608, 1428, 1339, 1278, 1160, 1016, 710, 656; HRMS (ES-TOF): *m/z*: calcd for $C_{21}H_{21}NO_4SNa$: 406.1089, found: 406.1091 $[M + Na]^+$.

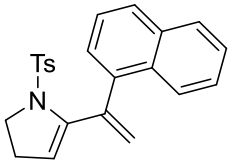
5-(1-(Thiophen-2-yl)vinyl)-1-tosyl-2,3-dihydro-1H-pyrrole (368)



Prepared according to **GP13** using ynamide **357** (66.3 mg, 0.200 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [90:10 (hexane:EtOAc)] gave the dienamide **368** as a dark liquid (40.4 mg, 61%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 4.9 Hz, 1H), 7.14 (d, *J* = 3.6 Hz, 1H), 6.98 (dd, *J* = 4.9, 3.6 Hz, 1H), 5.60 (s, 1H), 5.55 (t, *J* = 2.8 Hz, 1H), 5.42 (s, 1H), 3.98 (t, *J* = 8.3 Hz, 2H), 2.44

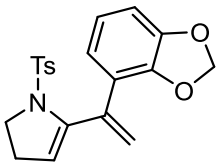
(s, 3H), 2.08 (td, *J* = 8.3, 2.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (C), 143.9 (C), 142.5 (C), 135.5 (C), 134.6 (C), 129.6 (2 × CH), 128.1 (2 × CH), 127.3 (CH), 125.7 (CH), 124.9 (CH), 119.8 (CH), 115.7 (CH_2), 51.5 (CH_2), 28.1 (CH_2), 21.7 (CH_3); IR ν_{max}/cm^{-1} 2958, 1597, 1384, 1160, 1088, 908, 813, 663, 588, 544; HRMS (EI-TOF): *m/z*: calcd for $C_{17}H_{17}NO_2S_2$: 331.0701, found: 331.0702 $[M]^+$.

5-(1-(Naphthalen-1-yl)vinyl)-1-tosyl-2,3-dihydro-1H-pyrrole (369)



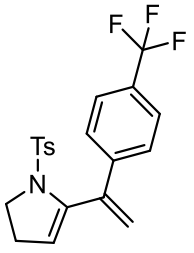
Prepared according to **GP13** using ynamide **360** (75.1 mg, 0.200 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the dienamide **369** (90% purity) as a brown foam (60.1 mg, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 4H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.55 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.64 (d, *J* = 1.2 Hz, 1H), 5.61 (d, *J* = 1.2 Hz, 1H), 5.54 (t, *J* = 2.8 Hz, 1H), 4.02 (t, *J* = 8.3 Hz, 2H), 2.40 (s, 3H), 2.21 (td, *J* = 8.3, 2.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 143.7 (C), 142.3 (C), 136.5 (C), 135.0 (C), 133.4 (C), 133.2 (C), 129.5 (2 × CH), 128.4 (CH), 128.0 (2 × CH), 127.8 (CH), 127.7 (CH), 126.3 (CH), 126.1 (CH), 126.0 (CH), 125.5 (CH), 119.8 (CH), 117.2 (CH_2), 51.4 (CH_2), 28.3 (CH_2), 21.7 (CH_3); IR ν_{max}/cm^{-1} 3055, 2851, 1596, 1347, 1160, 1087, 1021, 815, 669; HRMS (ES-TOF): *m/z*: calcd for $C_{23}H_{22}NO_2S$: 376.1371, found: 376.1374 $[M + H]^+$.

5-(1-(Benzo[d][1,3]dioxol-4-yl)vinyl)-1-tosyl-2,3-dihydro-1H-pyrrole (370)



Prepared according to **GP13** using ynamide **358** (111 mg, 0.300 mmol), heating at 80 °C for 2 hours. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the dienamide **370** as a white solid (94.4 mg, 85%); mp: 138-140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.26 (m, 2H), 6.95 – 6.86 (m, 2H), 6.77 (d, *J* = 7.9 Hz, 1H), 5.96 (s, 2H), 5.48 (t, *J* = 2.8 Hz, 1H), 5.41 (d, *J* = 1.3 Hz, 1H), 5.40 (d, *J* = 1.3 Hz, 1H), 3.95 (t, *J* = 8.3 Hz, 2H), 2.43 (s, 3H), 2.13 (td, *J* = 8.3, 2.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6 (C), 147.5 (C), 144.7 (C), 143.8 (C), 142.0 (C), 134.8 (C), 133.3 (C), 129.5 (2 × CH), 128.0 (2 × CH), 121.0 (CH), 119.8 (CH), 115.5 (CH_2), 108.1 (CH), 107.8 (CH), 101.2 (CH_2), 51.3 (CH_2), 28.1 (CH_2), 21.7 (CH_3);); IR ν_{max}/cm^{-1} 2960, 1596, 1489, 1441, 1347, 1228, 1157, 1034, 900, 816, 671; HRMS (ES-TOF): *m/z*: calcd for $C_{20}H_{19}NO_4SNa$: 392.0932, found: 392.0934 $[M + Na]^+$.

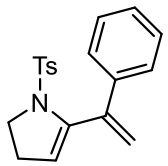
1-Tosyl-5-(1-(4-(trifluoromethyl)phenyl)vinyl)-2,3-dihydro-1H-pyrrole (371)



Prepared according to **GP13** using ynamide **356** (78.7 mg, 0.200 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the dienamide **371** as a colourless liquid (67.7 mg, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.30 – 7.25 (m, 2H), 5.61 – 5.51

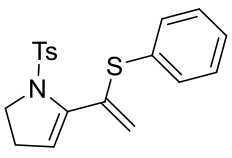
(m, 3H), 3.95 (t, *J* = 8.4 Hz, 2H), 2.43 (s, 3H), 2.18 (td, *J* = 8.4, 2.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (C), 144.0 (C), 142.6 (C), 141.7 (C), 134.7 (C), 129.8 (q, J_{C-F} = 31.8 Hz, C)), 129.6 (2 × CH), 127.9 (2 × CH), 127.5 (2 × CH), 125.3 (q, J_{C-F} = 3.7 Hz, 2 × CH)), 123.0 (q, J_{C-F} = 264.1 Hz, C)), 120.3 (CH), 118.0 (CH_2), 51.2 (CH_2), 28.2 (CH_2), 21.7 (CH_3). IR ν_{max}/cm^{-1}.2960, 1720, 1597, 1322, 1162, 1112, 1064, 657, 547, 532; HRMS (EI-TOF): *m/z*: calcd for $C_{20}H_{18}NO_2SF_3$: 393.1010, found: 393.1008 $[M]^+$.

5-(1-Phenylvinyl)-1-tosyl-2,3-dihydro-1H-pyrrole (372)



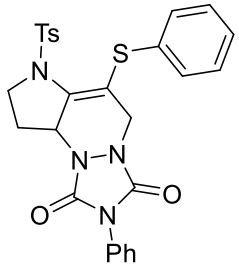
Prepared according to **GP13** using ynamide **361** (65.1 mg, 0.200 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the dienamide **372** as a brown solid (61.8 mg, 94%); mp: 113-115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.32 – 7.26 (m, 2H), 7.25 – 7.20 (m, 3H), 5.46 (br. s, 2H), 5.44 (t, *J* = 2.8 Hz, 1H), 3.91 (t, *J* = 8.3 Hz, 2H), 2.38 (s, 3H), 2.08 (td, *J* = 8.3, 2.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 143.8 (C), 142.4 (C), 139.1 (C), 134.8 (C), 129.5 (2 × CH), 128.2 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 127.3 (2 × CH), 119.9 (CH), 116.6 (CH_2), 51.4 (CH_2), 28.2 (CH_2), 21.7 (CH_3); IR ν_{max}/cm^{-1} 3089, 2850, 1597, 1348, 1163, 1088, 977, 895, 776, 690; HRMS (ES-TOF): *m/z*: calcd for $C_{19}H_{19}NO_2SNa$: 348.1034, found: 348.1037 $[M + Na]^+$.

5-(1-(Phenylthio)vinyl)-1-tosyl-2,3-dihydro-1H-pyrrole (377)



Prepared according to **GP14** using ynamide **376** (71.5 mg, 0.200 mmol), heating at 80 °C for 22 hours. chromatography [8:2 (hexane:EtOAc)] gave the dienamide **377** as a red viscous liquid (53.6 mg, 75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.53 (m, 4H), 7.39 – 7.30 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.94 (s, 1H), 5.75 (t, *J* = 3.0 Hz, 1H), 5.49 (s, 1H), 3.77 (t, *J* = 7.9 Hz, 2H), 2.40 (s, 3H), 1.73 (td, *J* = 7.9, 3.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 143.5 (C), 136.2 (C), 134.0 (C), 133.7 (C), 133.0 (2 × CH), 129.5 (2 × CH), 129.2 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 122.3 (CH), 121.0 (CH_2), 52.2 (CH_2), 28.3 (CH_2), 21.7 (CH_3); IR ν_{max}/cm^{-1} 3056, 2984, 1597, 1439, 1343, 1158, 1086, 910, 666; HRMS (ES-TOF): *m/z*: calcd for $C_{19}H_{20}NO_2S_2$: 358.0935, found: 358.0938 $[M + H]^+$.

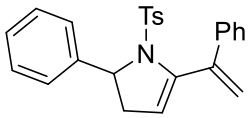
2-Phenyl-6-(phenylthio)-7-tosyl-7,8,9,9a-tetrahydro-1H,5H-pyrrolo[3,2-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (379)



Prepared according to modified **GP14** using ynamide **376** (71.5 mg, 0.200 mmol), and 4-phenyl-1,2,3-triazole-3,5-dione **378** (38.5 mg, 0.220 mmol), heating at 80 °C for 24 hours. Purification by flash column chromatography [80:20 (hexane:EtOAc)] gave the dione **379** as a white solid (54.6 mg, 51%) over two steps; mp: 108-110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.56 – 7.30 (m, 12H), 4.39 (dd, *J* = 15.9, 2.6 Hz, 1H), 3.88 – 3.77 (m, 2H), 3.67 (td, *J* = 10.6, 7.6 Hz, 2H), 2.78 – 2.64 (m, 1H), 2.46 (s, 3H), 2.12 – 1.95 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9 (CO), 151.6 (CO), 145.0 (C), 135.2 (C), 134.2 (C), 133.0 (2 × CH), 131.7 (C), 130.9 (C), 130.2 (2 × CH), 129.6 (2 × CH), 129.4 (2 × CH), 128.7 (CH), 128.6

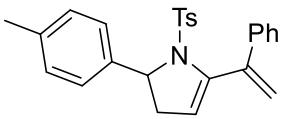
(CH), 128.1 (2 × CH), 125.5 (2 × CH), 117.8 (C), 57.0 (CH), 48.6 (CH_2), 46.5 (CH_2), 27.9 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} 2920, 1780, 1718, 1502, 1413, 1355, 1166, 750, 674; HRMS (ES-TOF): *m/z*: calcd for $C_{27}H_{24}N_4O_4S_2Na$: 555.1137, found: 555.1151 $[M + Na]^+$.

2-Phenyl-5-(1-phenylvinyl)-1-tosyl-2,3-dihydro-1H-pyrrole (421)



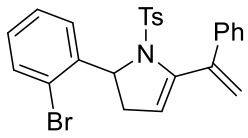
Prepared according to **GP13** using ynamide **416** (40.1 mg, 0.0999 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [9:1 (hexane:EtOAc)] gave the dienamide **421** as a brown solid (32.1 mg, 80%); mp:83-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.33 – 7.27 (m, 8H), 5.60 (br. s, 1H), 5.49 (d, *J* = 1.3 Hz, 1H), 5.42 (dd, *J* = 3.6, 2.1 Hz, 1H), 5.34 (dd, *J* = 9.4, 2.3 Hz, 1H), 2.69 – 2.58 (m, 1H), 2.49 – 2.41 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (C), 143.9 (C), 142.5 (C), 142.4 (C), 139.3 (C), 135.1 (C), 129.6 (2 × CH), 128.6 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 127.7 (2 × CH), 127.6 (CH), 126.3 (2 × CH), 118.5 (CH), 117.3 (CH_2), 64.8 (CH), 36.3 (CH_2), 21.8 (CH_3); IR ν_{max}/cm^{-1} 3029, 1645, 1597, 1494, 1351, 1163, 1089, 988, 777, 695; HRMS (ES-TOF): *m/z*: calcd for $C_{25}H_{23}NO_2SNa$: 424.1347, found: 424.1352 $[M + Na]^+$.

5-(1-Phenylvinyl)-2-(p-tolyl)-1-tosyl-2,3-dihydro-1H-pyrrole (422)



Prepared according to **GP13** using ynamide **418** (83.1 mg, 0.200 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the dienamide **422** as a brown solid (64.8 mg, 78%); mp:97-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.26 (m, 9H), 7.17 (d, *J* = 7.9 Hz, 2H), 5.60 (br. s, 1H), 5.49 (d, *J* = 1.3 Hz, 1H), 5.42 (dd, *J* = 3.5, 2.2 Hz, 1H), 5.30 (dd, *J* = 9.3, 2.1 Hz, 1H), 2.67 – 2.56 (m, 1H), 2.45 (s, 3H), 2.42 – 2.39 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (C), 143.8 (C), 142.5 (C), 139.5 (C), 139.3 (C), 137.3 (C), 135.2 (C), 129.6 (2 × CH), 129.3 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 127.7 (2 × CH), 126.3 (2 × CH), 118.5 (CH), 117.2 (CH_2), 64.7 (CH), 36.4 (CH_2), 21.8 (CH_3), 21.2 (CH_3); IR ν_{max}/cm^{-1} 3026, 1644, 1514, 1445, 1352, 1291, 1163, 1088, 988, 775, 679,; HRMS (ES-TOF): *m/z*: calcd for $C_{26}H_{25}NO_2SNaBr$: 438.1504, found: 438.1507 $[M + Na]^+$.

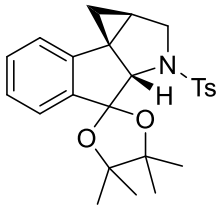
2-(2-Bromophenyl)-5-(1-phenylvinyl)-1-tosyl-2,3-dihydro-1H-pyrrole (423)



Prepared according to **GP13** using ynamide **417** (96.1 mg, 0.200 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the dienamide **423** as a white solid (72.1 mg, 75%); mp:119-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.61 – 7.53 (m, 2H), 7.49 – 7.44 (m, 2H), 7.41 – 7.28 (m, 6H), 7.17 – 7.11 (m, 1H), 5.71 (br. s, 1H), 5.56 – 5.50 (m, 2H), 5.25 (dd, *J* = 3.4, 2.2 Hz, 1H), 2.90 – 2.79 (m, 1H), 2.47 (s, 3H), 2.24 – 2.09 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4 (C), 144.2 (C), 142.5 (C), 142.5 (C), 139.8 (C), 134.4 (C), 132.9 (CH), 129.8 (CH), 128.9 (CH), 128.3 (3 × CH), 128.1 (CH), 128.0 (2 × CH), 127.7 (CH), 121.6 (C), 118.2 (CH_2), 117.5 (CH), 64.8 (CH), 37.7

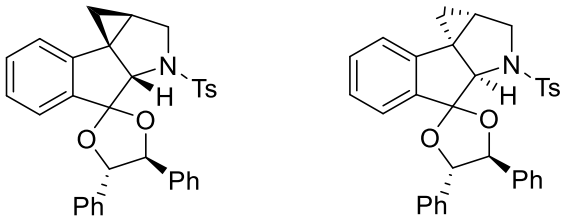
(CH_2), 21.81 (CH_3); IR ν_{max}/cm^{-1}2975, 2231, 1595, 1463, 1359, 1267, 1169, 984, 744, 653; HRMS (ES-TOF): *m/z*: calcd for $C_{25}H_{22}NO_2SNaBr$: 502.0452, found: 502.0453 $[M + Na]^+$.

4',4',5',5'-Tetramethyl-3-tosyl-1a,2,3,3a-tetrahydro-1H-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane] (434)



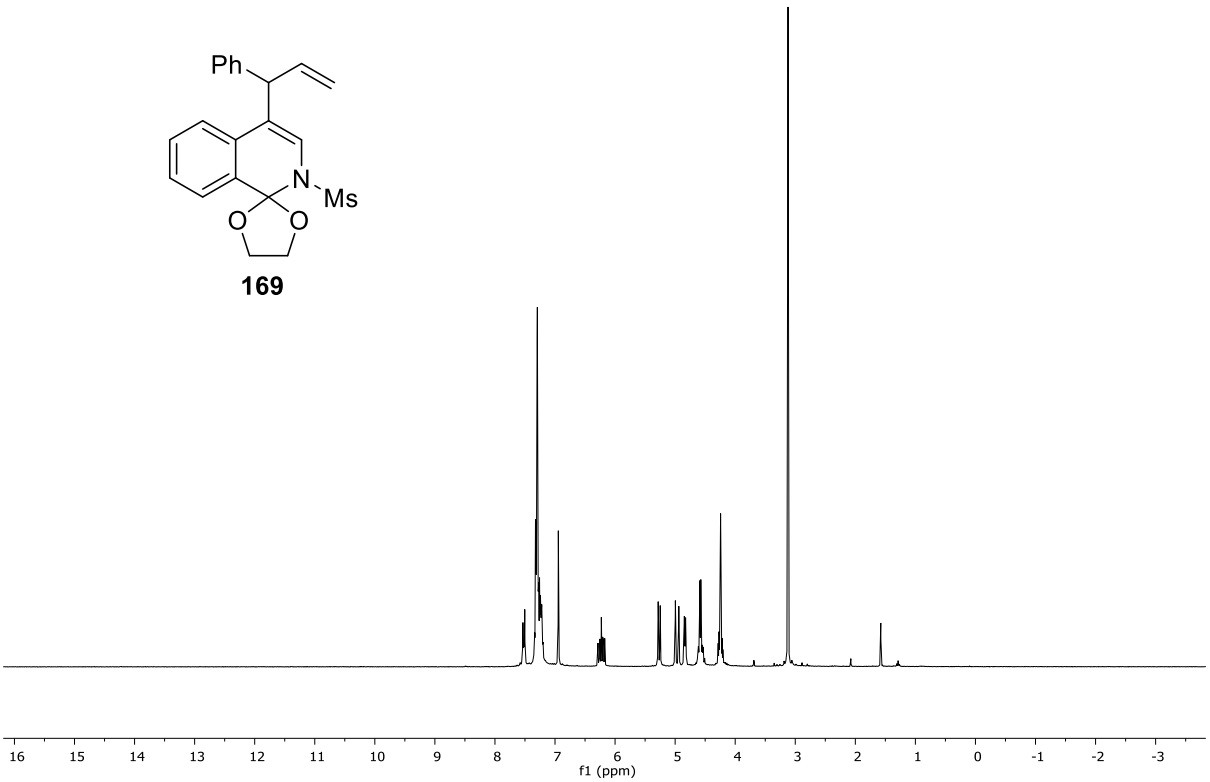
Following the general procedure **GP14** using ynamide **291** (44.0 mg, 0.100 mmol) for 2 hours. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the polycycle **434** as a white solid (30.3 mg, 69%); mp: 192-194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.48 (dd, *J* = 5.7,2.9 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.24 – 7.19 (m, 2H), 6.72 (dd, *J* = 5.7,2.9 Hz, 1H), 4.39 (s, 1H), 4.09 (dd, *J* = 11.7, 4.1 Hz, 1H), 3.68 (d, *J* = 11.7 Hz, 1H), 2.44 (s, 3H), 1.58 (d, *J* = 4.3 Hz, 4H), 1.54 (s, 3H), 1.48 (s, 3H), 1.31 (s, 3H), 0.99 – 0.92 (m, 1H) , -0.57 (dd, *J* = 6.3, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 143.8 (C), 139.5 (C), 137.0 (C), 130.1 (2 × CH), 129.5 (CH), 127.5 (2 × CH), 127.1 (CH), 124.0 (CH), 119.9 (CH), 113.1 (C), 84.8 (C), 84.4 (C), 75.1 (CH), 54.4 (CH_2), 37.1 (C), 26.6 (CH), 26.1 (CH_3), 26.0 (CH_3), 25.9 (CH_3), 25.3 (CH_3), 21.7 (CH_3), 10.2 (CH_2); IR ν_{max}/cm^{-1} 2984, 2948, 1370, 1239, 1157, 1134, 1102, 756, 666; HRMS (ES-TOF): *m/z*: calcd for $C_{25}H_{29}NO_4SNa$: 462.1715, found: 462.1716 $[M + Na]^+$.

(4'S,5'S)-4',5'-diphenyl-3-tosyl-1a,2,3,3a-tetrahydro-1H-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane] (435)

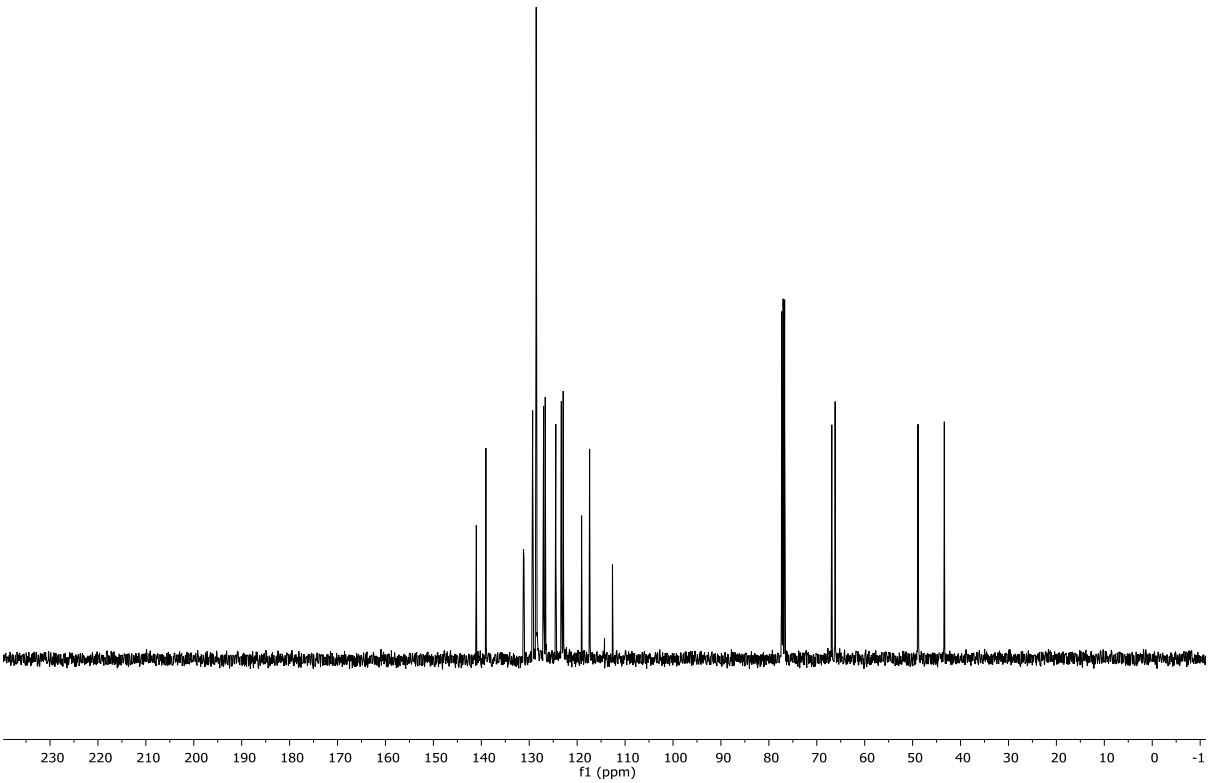


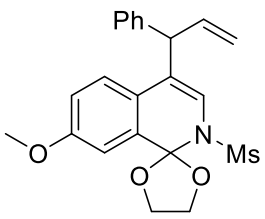
Following the general procedure **GP14** using ynamide **433** (53.6 mg, 0.100 mmol) for 4 hours. Purification by flash column chromatography [8:2 (hexane:EtOAc)] gave the polycycle **435** as a white solid (39.1 mg, 73%, dr, 1:3.5); mp: 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.82 (m, 1H, minor), 7.80 (d, *J* = 8.3 Hz, 2H, major), 7.73 – 7.70 (m, 1H, minor), 7.64 – 7.60 (m, 2H, major), 7.54 – 7.51 (m, 2H, minor), 7.40 – 7.28 (m, 11H, major and 11H, minor), 7.25 – 7.21 (m, 2H, major and 2H, minor), 6.81 (ddd, *J* = 7.3, 4.1, 1.6 Hz, 1H, major and 1H, minor), 5.48 (d, *J* = 8.9 Hz, 1H, minor), 5.20 (d, *J* = 8.7 Hz, 1H, major), 5.14 (d, *J* = 8.7 Hz, 1H, major), 4.92 (d, *J* = 8.9 Hz, 1H, minor), 4.72 (s, 1H, major), 4.67 (s, 1H, minor), 4.15 (dd, *J* = 11.4, 4.3 Hz, 1H, minor), 4.06 (dd, *J* = 11.5, 4.3 Hz, 1H, major), 3.82 (d, *J* = 11.4 Hz, 1H, minor), 3.69 (d, *J* = 11.5 Hz, 1H, major), 2.46 (s, 3H, major), 2.44 (s, 3H, minor), 1.50 – 1.46 (m, 1H, minor), 1.46 – 1.41 (m, 1H, major), 1.28 (d, *J* = 5.0 Hz, 1H, minor), 1.24 (dd, *J* = 8.2, 6.4 Hz, 1H, major), -0.13 (app. t, *J* = 5.6 Hz, 1H, minor), -0.17 (app. t, *J* = 5.6 Hz, 1H, major); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8 (C, major and minor), 142.8 (C, major), 142.6 (C, minor), 140.1 (C, major), 139.9 (C, minor), 136.6 (C, major), 136.4 (C, minor), 136.1 (C, major), 135.5 (C, minor), 135.1 (C major and minor), 130.4 (CH, minor), 130.3 (CH major), 130.1 (2 × CH, major and minor), 130.0 (2 × CH, major and minor), 128.8 (CH minor), 128.6 (CH major), 128.5 (2 × CH, major), 128.3 (2 × CH, minor), 128.1 (2 × CH, minor), 127.9 (2 × CH major), 127.5 (2 × CH, major and minor), 127.3 (2 × CH, major and minor), 126.5 (CH, major and minor), 123.9 (CH, minor), 123.8 (CH major), 119.7 (CH, minor), 119.5 (CH, major), 113.6 (CH

major and minor), 113.0 (C, major and minor), 88.2 (CH, major), 85.9 (CH, minor), 85.7 (CH major), 85.4 (CH, minor), 74.4 (CH, minor), 74.3 (CH, major), 54.5 (CH_2, minor), 54.2 (CH_2, major), 37.7 (C, major and minor), 26.7 (CH_3, major), 26.4 (CH_3, minor), 21.7 (CH, major and minor), 11.8 (CH_2, minor), 11.5 (CH_2, major); IR ν_{max}/cm^{-1} 2899, 1598, 1454, 1343, 1217, 1161, 1023, 998, 758, 599, 546; HRMS (ES-TOF): *m/z*: calcd for $C_{33}H_{29}NO_4SNa$: 558.1715, found: 558.1714 $[M + Na]^+$.


Ph
N
Ms
O
O
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)

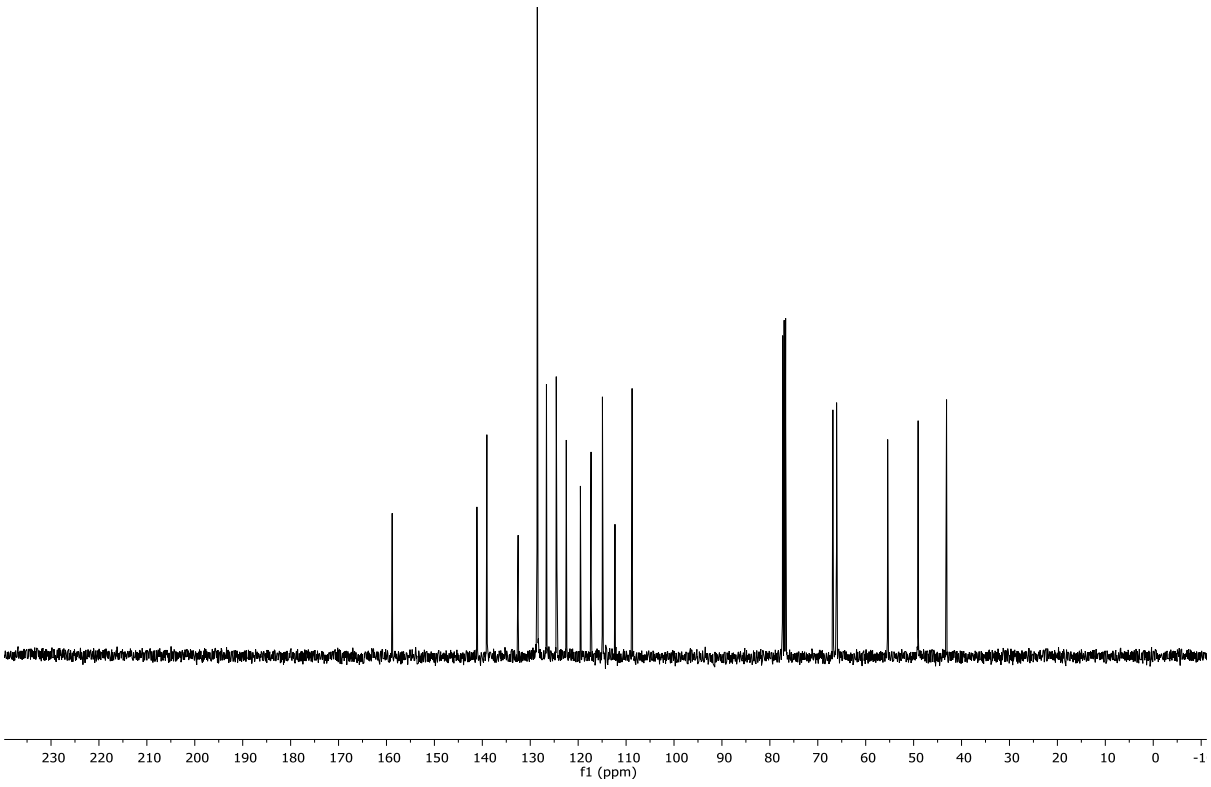
169

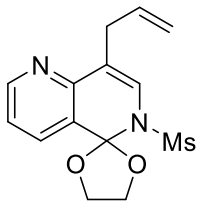

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


Ph
N
Ms
O
O
O

269

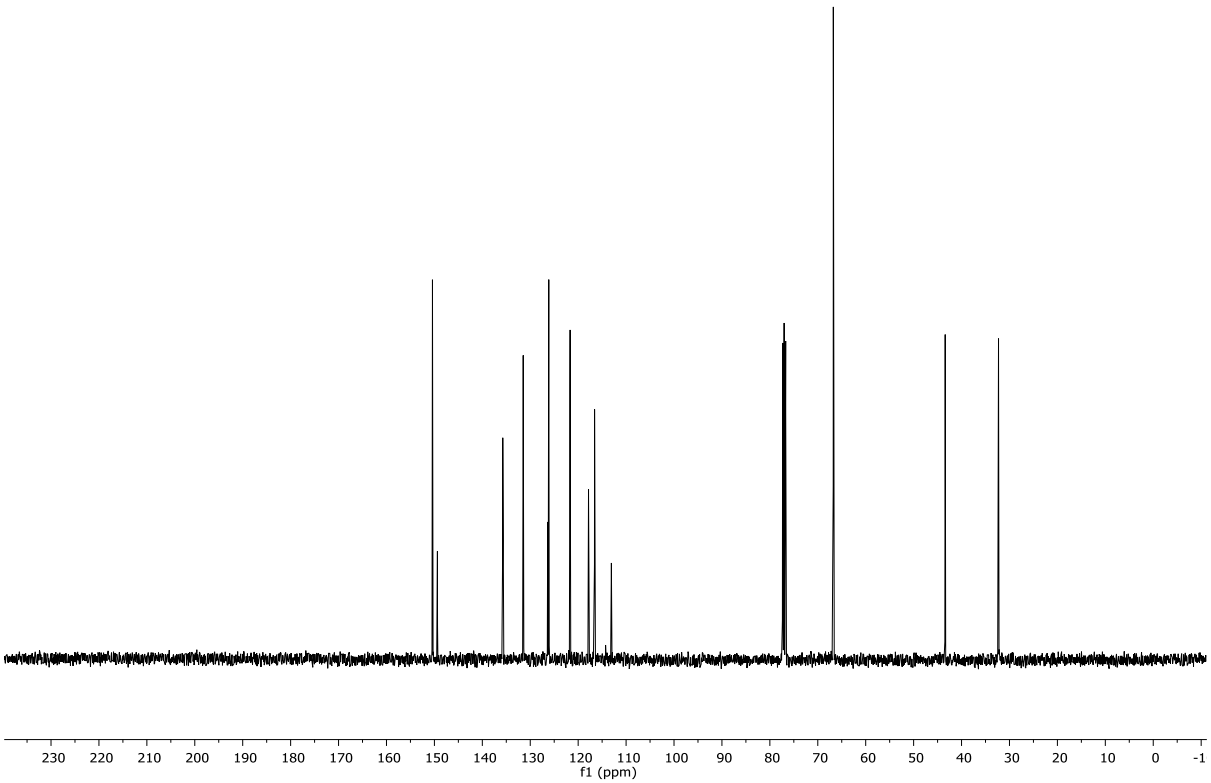
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)

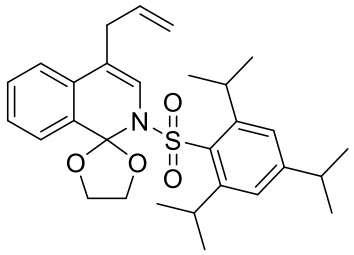

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


N
N
Ms
O
O

281

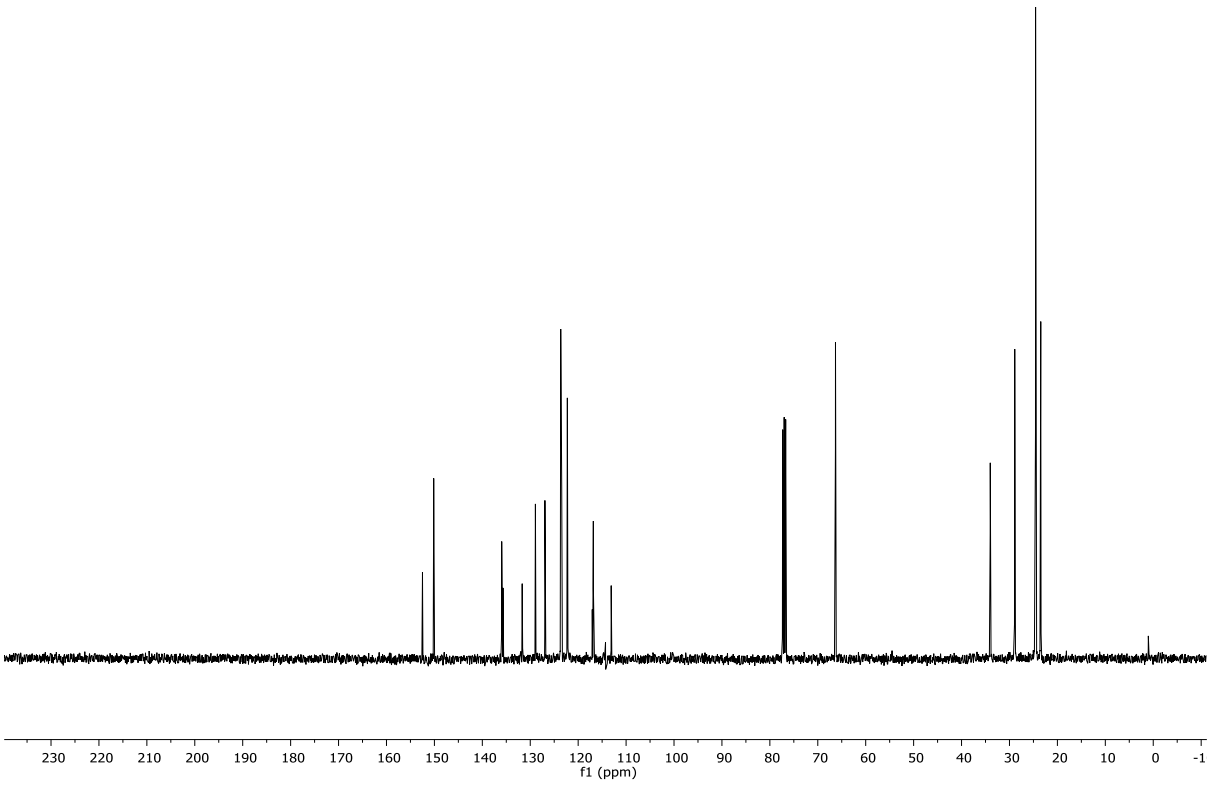
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)

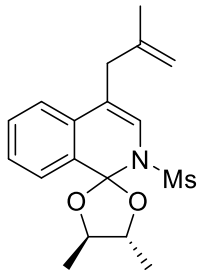

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)



241

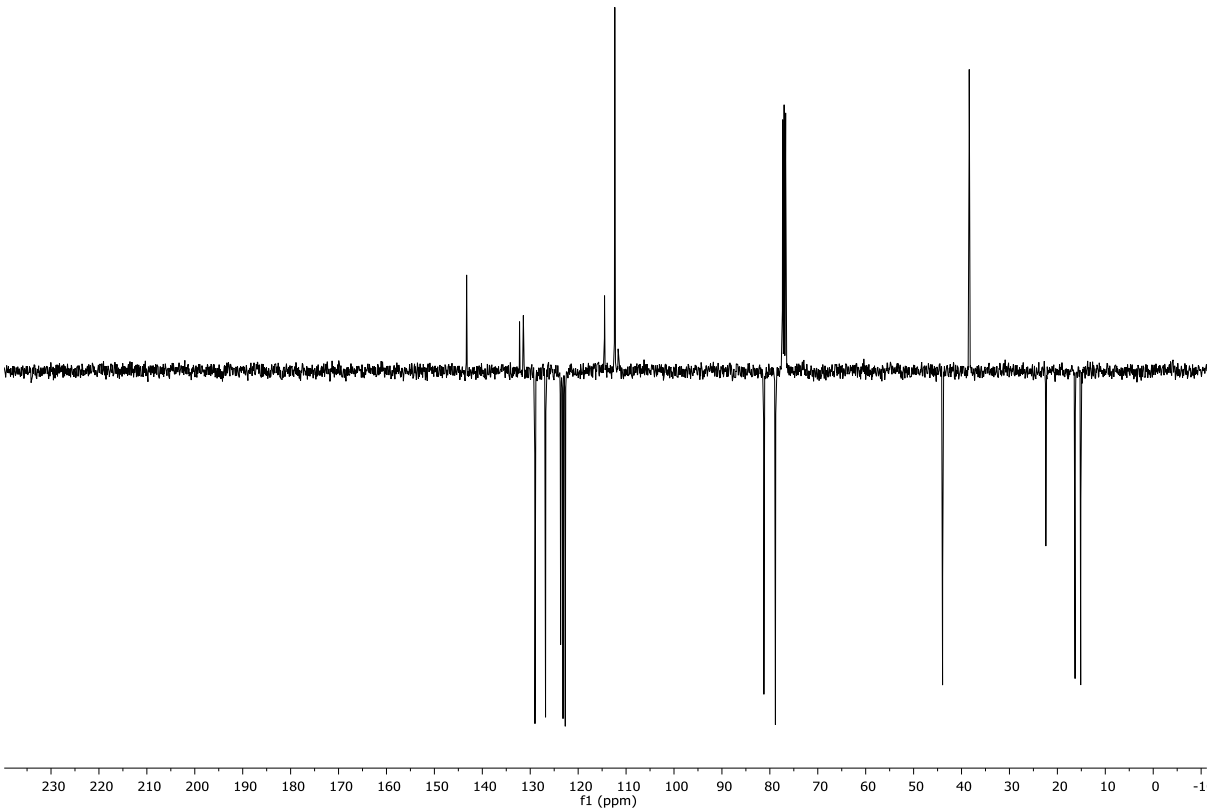
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


N
Ms
O
O

222

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

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