UNIVERSITY OF BIRMINGHAM

Novel Transformations for the Synthesis of Nitrogen Containing Carbo- and Heterocycles

by

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Abstract

This thesis details the discovery and development of several novel gold-catalysed reactions for the synthesis of nitrogen containing carbo- and heterocyclic frameworks from carbon-carbon triple bonds. The realisation of a 1,1-carboalkoxylation strategy to generate gold carbenes from ynamides is described. This novel skeletal rearrangement proceeds with a previously unreported nitrogen migration onto a gold carbene for the synthesis of highly functionalised indenes. The mechanism has been investigated using isotopic labelling which confirms the predicted mode of cyclisation, enforced by the electronic properties of ynamides.

This work led to the discovery of a gold-catalysed polycyclisation reaction to generate complex three-dimensional tetracyclic products. The scope and limitations of this method are described, and the mechanism has been probed using isotopic labelling. A novel copper-catalysed cascade reaction has also been demonstrated towards the synthesis of valuable nitrogen heterocycles.

Finally a gold-catalysed rearrangement of electron deficient alkynes under oxidative conditions is detailed along with the reaction optimisation and difficulties encountered.

Acknowledgments

I would like to thank my supervisor Dr. Paul Davies for giving me to opportunity to join his research group and for his wisdom and patience over the years. It has been a fantastic experience.

I am grateful to AstraZeneca and the EPSRC for funding my PhD studies. I would like to acknowledge and thank the staff of the analytical facility for their sterling work over the years.

I would like to thank the Davies group members past and present for their enormous support, friendship and banter. I have been very lucky to have the pleasure of such a fine research group and I leave Birmingham with some life-long friends.

Most importantly, I would like to thank my friends and family, especially my partner Pete for their endless help and support.

Contents

List of Abbreviations

Å	Ångström
Ac	acetyl
Ar	aryl
BOM	benzyloxymethyl
Bn	benzyl
Bu	butyl
C	celsius
Cy	cyclohexyl
DMF	*N*-*N*-Dimethylformamide
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
EI	electron impact
ERC	electrocyclic ring closure
ES	electro spray
Et	ethyl
equiv.	equivalent(s)
g	gram(s)
h	hour(s)
hv	light

Hz	Hertz
hex	hexyl
i	iso
IR	infrared
L	litre
LA	Lewis acid
LDA	lithium diisopropylamide
m-CPBA	*meta*-chloroperbenzoic acid
[M]	metal
Me	methyl
M	molar
mol	moles
mmol	millimoles
mp	melting point
Ms	methanesulfonyl
min	minutes
MS	molecular sieves
m/*z*	mass/charge
NBS	*N*-bromosuccinimide
Ns	4-nitrobenzenesulfonyl
nOe	nuclear Overhauser effect
Nu	nucleophile
o	*ortho*

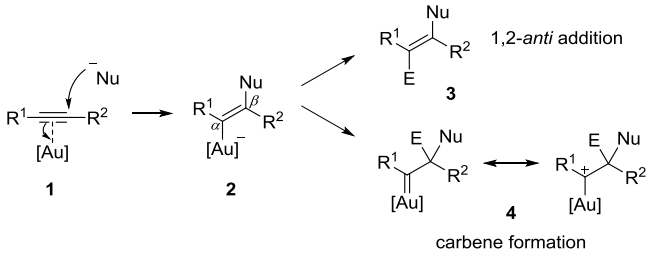
p	*para*
Piv	pivaloyl
Ph	phenyl
Pr	propyl
py	pyridine
RT	room temperature
t	*tertiary*
THF	tetrahydrofuran
TBS	*tert*-butyldimethylsilyl
TMS	trimethylsilyl
TIPS	triisopropylsilyl
Tf	trifluoromethanesulfonyl
Ts	4-methylbenzenesulfonyl
quant.	quantitative
v	wavenumber

Chapter 1: Generation of Gold Carbenes from C-C Triple Bonds

1.1 Gold Catalysis in Organic Synthesis

The use of gold catalysis in organic synthesis has seen a dramatic increase over the past decade and has led to the discovery of a wide range of new transformations through the functionalisation of carbon-carbon multiple bonds. Gold (as well as platinum) is termed a π-acid and its chemistry has been extensively reviewed in recent years.[1,2] The Lewis acidic character of gold complexes derives from relativistic effects, which are more pronounced for gold than for any other metal, leading to a shorter and stronger metal-to-ligand bond as well as large and diffuse d-orbitals.[3] This makes gold complexes more susceptible to orbital interactions over charge interactions and therefore they activate 'soft' nucleophilic π-systems such as alkenes, alkynes and allenes towards inter- and intramolecular nucleophilic attack.

Gold catalysts exhibit remarkable functional group tolerance and allow for the rapid generation of complex molecules from simple starting materials. One of the most appealing aspects of gold catalysts, and the main theme behind my PhD research is the formation of gold carbene intermediates and their subsequent utility (Scheme 1).

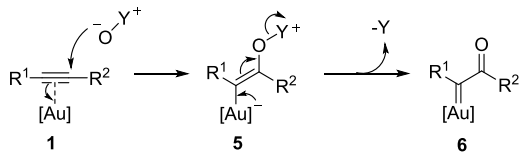


Scheme 1: Formation of gold carbenes from gold-activated C-C triple bonds

Coordination of a gold species to a triple bond (**1**) promotes nucleophilic attack to form vinyl gold species **2**.[4] This now nucleophilic π-system can undergo addition of an electrophile to positions α- or β-to the metal. In the first case, addition to the α-position gives 1,2-addition products **3**. This reactivity is exemplified in 1,2-carbofunctionalisation processes as described in detail in Chapter 2 (Section 2.2). Alternatively, addition to the β-position generates a gold carbene **4**. Computational models show that on formation of a gold carbene from a vinyl gold species, there is an increase in π-bonding and a decrease in σ-bonding, however the overall bond order is close to or less than one.[5] The exact structure of these intermediates is still a matter of debate amongst the scientific community with the exact structure probably lying closer to a metal-stabilised carbocation than a metal-carbon double bond.[6] The nature of these intermediates is also expected to be influenced by the gold ligands as well as the substitution around the carbene centre.[7] These intermediates are known to possess a highly electrophilic carbon atom which is stabilised by back-donation of electron density from the metal to the vacant p-orbital. Throughout the following chapters, gold carbenes are depicted as a classical metal carbene for simplicity. A small number of relevant aspects of gold carbene chemistry are detailed below.

α-Oxo gold carbenes have been identified as potent reactive intermediates in the last several years allowing access to highly valuable transformations, such as CH-functionalisation, cyclopropanation and ylide formation.[8,9] In these cases, the nucleophile shown in Scheme 1 is oxygen, and the α-oxo gold carbene is formed on expulsion of a leaving group from the vinyl gold intermediate **5**. A simplified mechanism is shown in Scheme 2. Subsequent attack of a

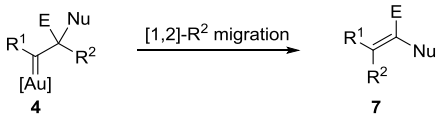
nucleophile onto the gold-bound metal centre may occur from carbene **6** or prior to the expulsion of the leaving group (**5**) and so the term carbenoid is often used to describe the reactive intermediate. The tolerance of gold catalysts to aqueous media is demonstrated by the ability to carry out these reactions in water.[10]



Scheme 2: Formation of an α-oxo gold carbene through oxidation of a C-C triple bond

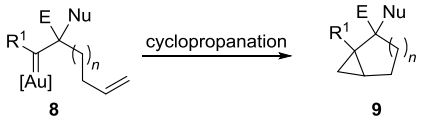
The formation of gold carbenes through these pathways is highly attractive as it avoids the use of diazo compounds, which have traditionally been employed to access these intermediates through transition metal-catalysed decomposition processes.[11] The use of diazo compounds requires extra synthetic steps and therefore reduces efficiency. Furthermore, the explosive and toxic nature of these compounds limits large scale use.[12]

Development of gold-catalysed processes has led to the realisation of cascade reactions which combine several distinct transformations in a single step. 1,2-Migrations of adjacent groups onto gold carbenes are often involved in these reactions and represent a fundamental process for these intermediates. When available, 1,2-hydrogen migration usually prevails, however when the adjacent centre is fully substituted, 1,2-alkyl and aryl migrations are commonly observed to generate a diverse range of products (Scheme 3, see Chapter 2 for 1,2-*N* and 1,2-*O* migrations).[13,14]



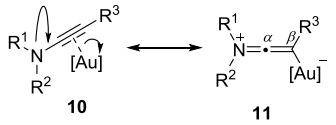
Scheme 3: 1,2-R migration onto a gold carbene

Gold carbenes can also undergo reaction with olefins to generate products of cyclopropanation (Scheme 4). This can occur in an inter- or intramolecular fashion.[15] The latter case is illustrated in the cycloisomerisations of enynes and represents a key strategy for the rapid build-up of molecular complexity.[16] The formation of a distorted gold carbene is proposed for these transformations[2d] where the formation of the 3-membered ring is thought to occur in a concerted fashion (see Chapter 3 for examples of cyclopropanation onto gold carbenes).[17]



Scheme 4: Formation of cyclopropanes from gold carbenes

Whilst well reported for alkyne activation, the use of gold catalysis for the activation of electron-rich ynamides is much less explored, however the number of available transformations is beginning to grow rapidly.[18] Ynamides readily coordinate to gold species and the relative electron deficiency of the α-carbon, as depicted in the keteniminium resonance form below (Scheme 5), leads to highly predictable nucleophilic attack. As well as alkynes, ynamides have been shown to allow access to gold carbene intermediates.[19]



Scheme 5: Keteniminium resonance form of a gold-bound ynamide

The following chapters will detail the use of ynamides and alkynes in gold-catalysed reactions, with introductions addressing the relevant literature context. The overall goal of this research programme has been to develop efficient means to access and employ gold carbene intermediates in a novel manner and / or in a unique environment.

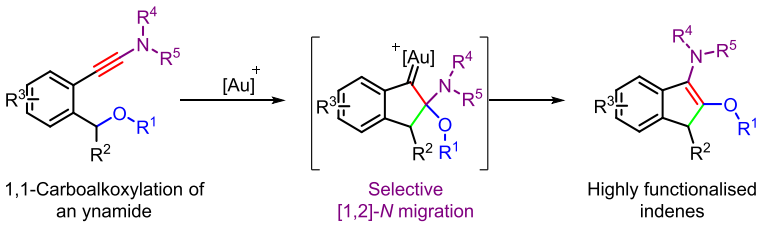
Chapter 2 details an ynamide carboalkoxylation approach for the formation of functionalised indenes. This work later led to the discovery and development of a gold-catalysed cascade reaction of *N*-allyl ynamides, initiated by [1,5]-hydride transfer, which is discussed in Chapter 3. Chapter 4 details a copper-catalysed cascade reaction for isoquinoline synthesis, again involving a [1,5]-hydride shift. Finally, formation and rearrangement of ammonium ylides *via* α-oxo gold carbene intermediates is discussed in Chapter 5.

These investigations have resulted in the discovery of four novel, complexity increasing catalysis-based transformations which generate valuable nitrogen containing carbo- and heterocycles. Furthermore, several examples are described where Derivatisation of products has been achieved, expanding the scope of materials that can be accessed through these methodologies.

Chapter 2: 1,2-*N*-Migration in a Gold-Catalysed Synthesis of Functionalised Indenes by the 1,1-Carboalkoxylation of Ynamides

2.1 Introduction

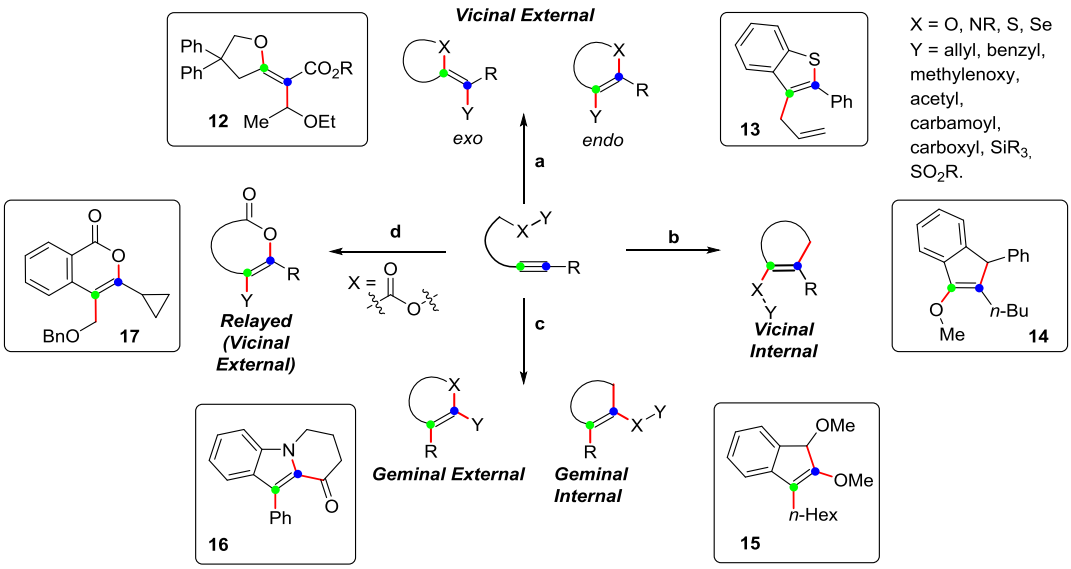
Interest within the Davies group in the generation of gold carbenes directly from triple bonds[19a,20] led to the exploration of ynamides in order to access reactivity pathways divergent to those available for alkyne equivalents, in a regioselective manner. This chapter details how an ynamide 1,1-carboalkoxylation strategy has been developed to synthesise highly functionalised indenes through the intermediacy of a unique gold carbene environment (Scheme 6).[21]



Scheme 6: Formation of a gold carbene through the 1,1-carboalkoxylation of an ynamide

Carboalkoxylation refers to the formal insertion of a C-C multiple bond into a C-O σ-bond. These processes are typified by attack of an oxygen nucleophile onto a C-C multiple bond to generate a charged oxonium species, which can evolve through migration of a suitable group with overall C-O addition.[22] These types of carbofunctionalisations are not limited to C-O bonds (*vide infra*) and a diverse range of transformations can be accessed through the application of these reactivity principles to different heteroatoms. Variation in the connectivity between the heteroatom, the C-C multiple bond and the migrating group will dictate the mode of cyclisation and the evolution of the reactive intermediate.

During my PhD studies I was able to co-author a detailed review in which we categorised the area of π-acid mediated C-X insertion into C-C triple bonds as outlined in Scheme 7.[22b]



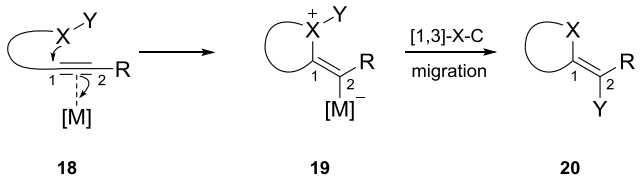
Scheme 7: Outline of π-acid mediated C-X insertion into C-C triple bonds

Path a shows 1,2-carbofunctionalisation where external migration occurs, i.e. with loss of connectivity between the migrating group (Y) and the triple bond. When allyl groups are involved, sigmatropic or cationic migrations are possible. Path b shows 1,2-carbofunctionalisation with alternative internal migration, i.e. no loss of connectivity between the migrating group and the alkyne. Path c demonstrates 1,1-carbofunctionalisation of the triple bond, shown here for both internal and external migrations. Finally, path d shows the 1,5-external migration mode available for benzoic acid derived substrates. The examples shown next to each pathway are taken from the following introductory sections.

From the overall reactivity picture we developed, it was proposed that the use of an ynamide instead of an alkyne could provide sufficient control over regioselectivity to provide access to a relatively unexplored but valuable mode of carboalkoxylation. Despite the number of examples of this chemistry in the literature, there were no studies employing ynamides at the outset of my investigation. The following sections outline literature examples and key aspects of reactivity and applicability within this area, before detailing the discovery of an ynamide 1,1-carboalkoxylation.[21]

2.2 [1,2]-Addition of Carbon-Heteroatom Bonds Across Alkynes

The most common transformations in this field involve an overall 1,2-addition of a carbon-heteroatom σ-bond across an alkyne (see above, Scheme 7, path a). Nucleophilic attack of the heteroatom (X) into the π-acid activated alkyne (**18**) generates charged intermediate **19**, which evolves through a 1,3-migration of tethered group Y to the metallated centre to give products of type **20** with overall 1,2-X-Y addition (Scheme 8).

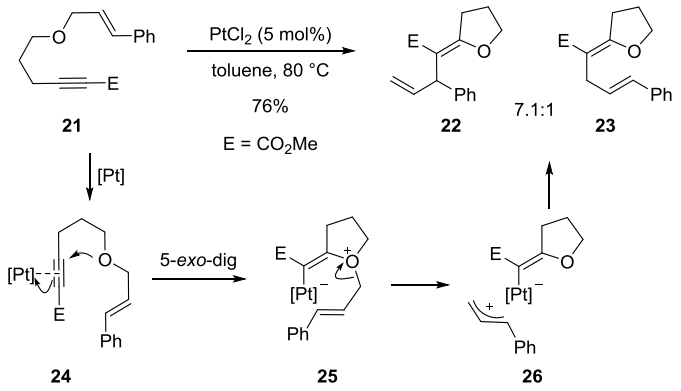


Scheme 8: π-Acid catalysed 1,2-addition of an X-Y σ-bond across an alkyne, shown here for *exo*-mode cyclisation

2.2.1 Heteroatom to Carbon Allyl Migration (Cationic Pathway)

π-Acid mediated carboalkoxylations involving alkynes were first realised by Fürstner and co-workers in the synthesis of tetrahydrofuran derivatives (Scheme 9).[23,24,25,26] Conjugated

electron-deficient alkynes with a tethered allyl ether moiety, such as **21**, underwent $PtCl_2$-catalysed *exo*-cyclisation to generate oxonium intermediate **25** which evolves to form the most stable cation with cleavage of the O-C bond. Migration of the unsymmetrical allylic cation to the metallated position generates a mixture of branched and linear isomers **22** and **23** with an O→C allyl migration. The formation of these isomers eliminates the possibility of a fully concerted migration.

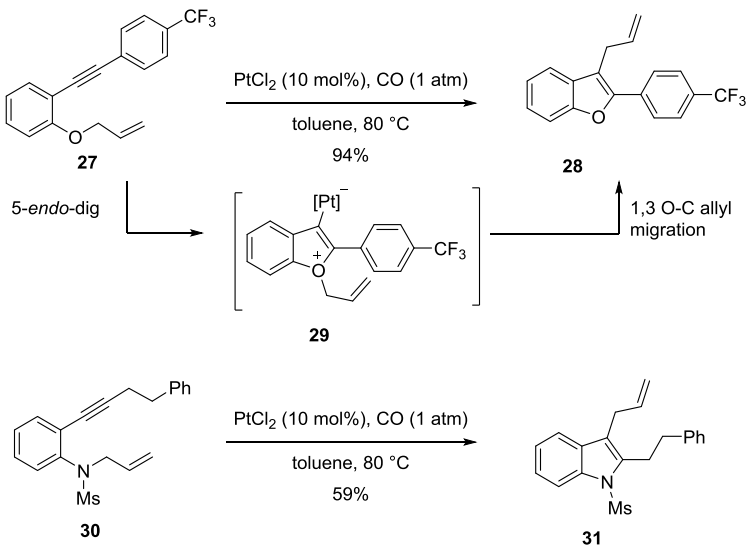


Scheme 9: Synthesis of tetrahydrofuran derivatives by $PtCl_2$-catalysed carboalkoxylation of an alkyne with a tethered allyl ether moiety

Endo-mode cyclisation of *ortho*-alkynyl phenol allyl ethers such as **27** was also achieved by Fürstner and Davies in the synthesis of substituted benzofurans **28** (Scheme 10).[27] Again, it was proposed that an allylic cation is formed which migrates to the metallated position.

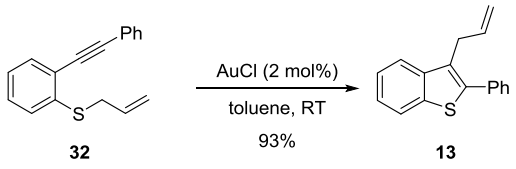
As well as insertion into C-O σ-bonds, analogous carboamination processes are also well known, whereby the alkyne inserts into a C-N σ-bond. Aniline derivatives **30** were shown to undergo similar *endo*-cyclisation and 1,3-N→C allyl migration in the preparation of 2,3-disubstituted indoles **31** (Scheme 10). For both transformations, a carbon monoxide atmosphere was

employed alongside a platinum catalyst which led to a significant increase in reaction rate. This was attributed to the potential of π-acidic CO ligands to increase the electrophilicity of the metal.[28]



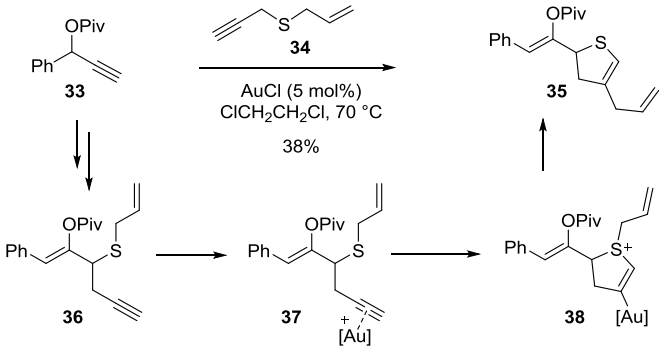
Scheme 10: Synthesis of benzofurans and indoles by platinum-catalysed carboalkoxylation and carboamination, with *endo*-mode cyclisation

The first example of 1,2-carbothiolation (C-S addition) across an alkyne was demonstrated by Nakamura and co-workers. *Endo*-mode cyclisation of *ortho*-alkynyl thiophenol derivatives **32** was achieved using simple AuCl as the catalyst to give benzothiophenes **13** in excellent yields (Scheme 11).[29]



Scheme 11: Synthesis of benzothiophenes by 1,2-carbothiolation

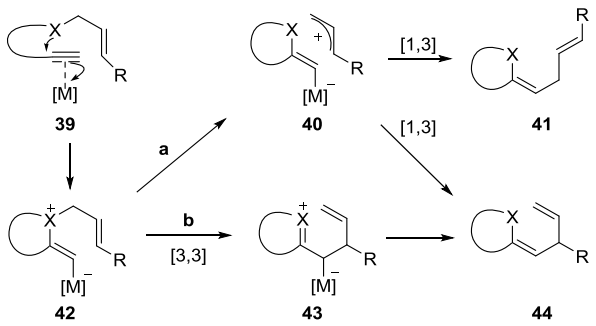
Davies and Albrecht demonstrated the 1,2-carbothiolation of a non-aromatic system in a cascade reaction (Scheme 12).[30] Cycloisomerisation precursor **36** was formed *in situ* in this case, through the intermolecular gold-mediated coupling of propargylic carboxylate **33** and allyl propargyl sulfide **34**. Gold-catalysed carbothiolation then afforded dihydrothiophene **35** by 1,3-S→C allyl migration.



Scheme 12: Gold-catalysed cascade reaction with 1,2-carbothiolation

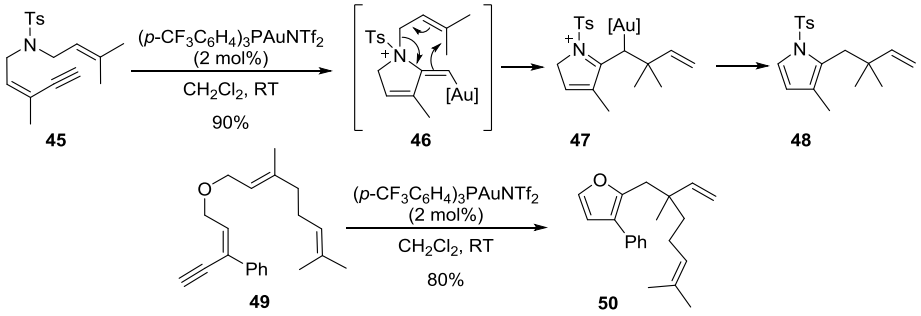
2.2.2 Heteroatom to Carbon Allyl Migration by Sigmatropic Rearrangement

The examples discussed so far have involved the 1,2-carbofunctionalisation of triple bonds by 1,3-heteroatom-to-carbon migration through formation of an allylic cation which adds to the metallated position. In the case of unsymmetrical allylic cations, mixtures of branched and linear isomers can be formed (Scheme 13, path a). Intermediates such as **42** may also evolve in a concerted fashion by [3,3]-sigmatropic rearrangement (Scheme 13, path b). In these cases, a single product **44** is formed with allylic inversion.



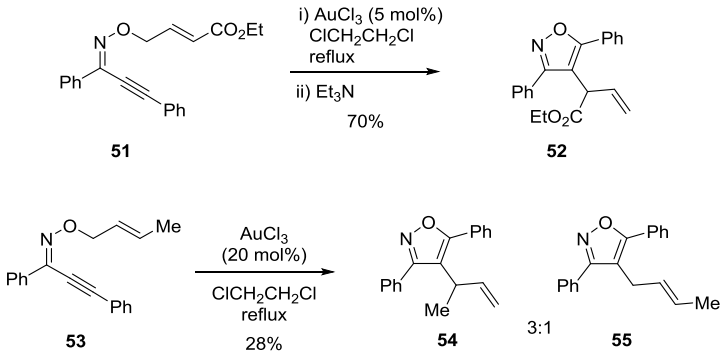
Scheme 13: Possible allyl migration modes from onium intermediate 43

This reaction type was first identified by Gagosz and co-workers in the formation of *N*-tosyl pyrroles **48** (Scheme 14).[31] Activation of the alkyne moiety of **45** by a cationic gold complex triggers an *exo*-mode cyclisation to generate intermediate **46** which undergoes an aza-Claisen-type rearrangement to give **47**. Demetallation and double bond isomerisation afford the aromatic product **48**. The concerted nature of the allyl migration was confirmed by complete inversion of the prenyl substituent. Acyclic alkynyl allyl ethers **49** afforded analogous furan products **50** through the related reaction.[32]



Scheme 14: Formation of pyrroles and furans *via* a cyclisation-triggered concerted aza-Claisen-type rearrangement

The synthesis of trisubstituted isoxazoles by cyclisation of alkynyl oxime ethers has been reported by Miyata and co-workers (Scheme 15).[33] The same Claisen-type rearrangement is invoked here and crossover reactions confirmed that the process is intramolecular. In this case however, incomplete allylic inversion of the migrating crotyl group was observed in the reaction of **53**, suggested that a potential cationic mechanism cannot be ignored.

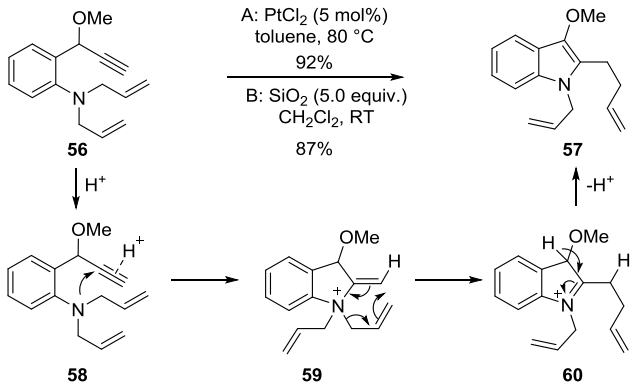


Scheme 15: Formation of trisubstituted isoxazoles through Claisen-type rearrangement and with incomplete allylic inversion

Computational studies into related cycloisomerisations showed that a gold species was integral for the formation of the charged intermediate required for sigmatropic rearrangement. However, the presence of a gold phosphine substituent had only a small effect on the energy barrier for the subsequent Claisen-type rearrangement.[34]

In these reactions, the role of the metal catalyst can be considered to be acting predominantly as an electron sink to trigger [3,3]-sigmatropic rearrangements. This was supported in work by Fensterbank, Malacria and co-workers in the generation of substituted indoles such as **57** (Scheme 16).[35] The charge-accelerated aza-Claisen rearrangement was observed to proceed

under both platinum catalysis (conditions A) and metal-free conditions (conditions B) by protic activation of the triple bond using silica.

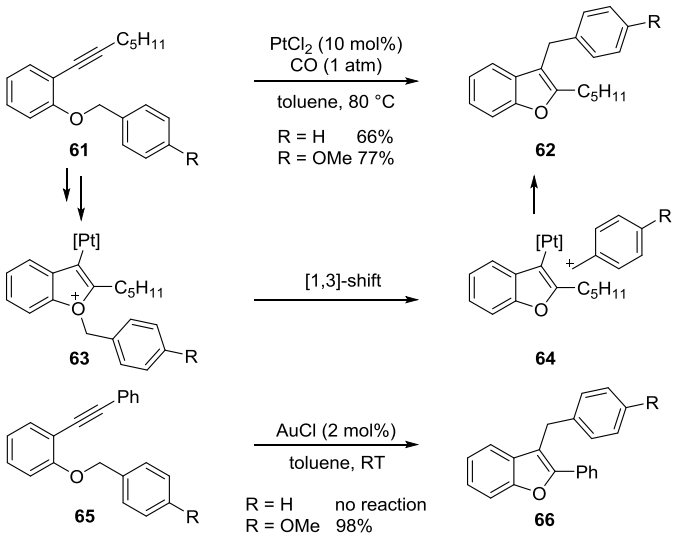


Scheme 16: Indole formation using platinum catalysis and metal-free conditions with mechanism shown for protic activation

2.2.3 Migration of Benzyl Groups

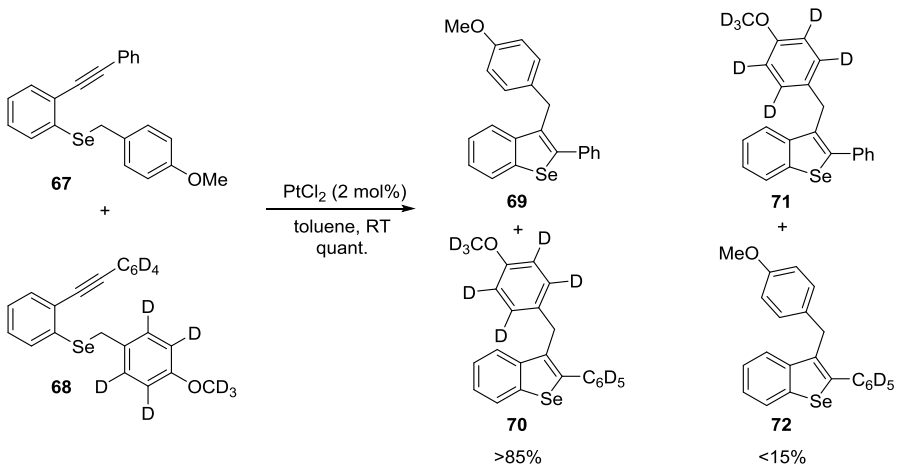
1,2-Carbofunctionalisations are not limited to allylic systems, so long as the migrating group is able to stabilise the developing positive charge in the X→C migration step. Benzyl groups have been successfully employed independently by Fürstner and Davies, and Nakamura and co-workers in the platinum or gold-catalysed syntheses of benzofurans (**62** and **66**, Scheme 17).[27,29]

In both reports, a *p*-methoxybenzyl derivative was observed to be more amenable to migration than a simple benzyl group. This observation is consistent with the methoxy group being able to add extra stabilisation to the migrating cation (**64**).



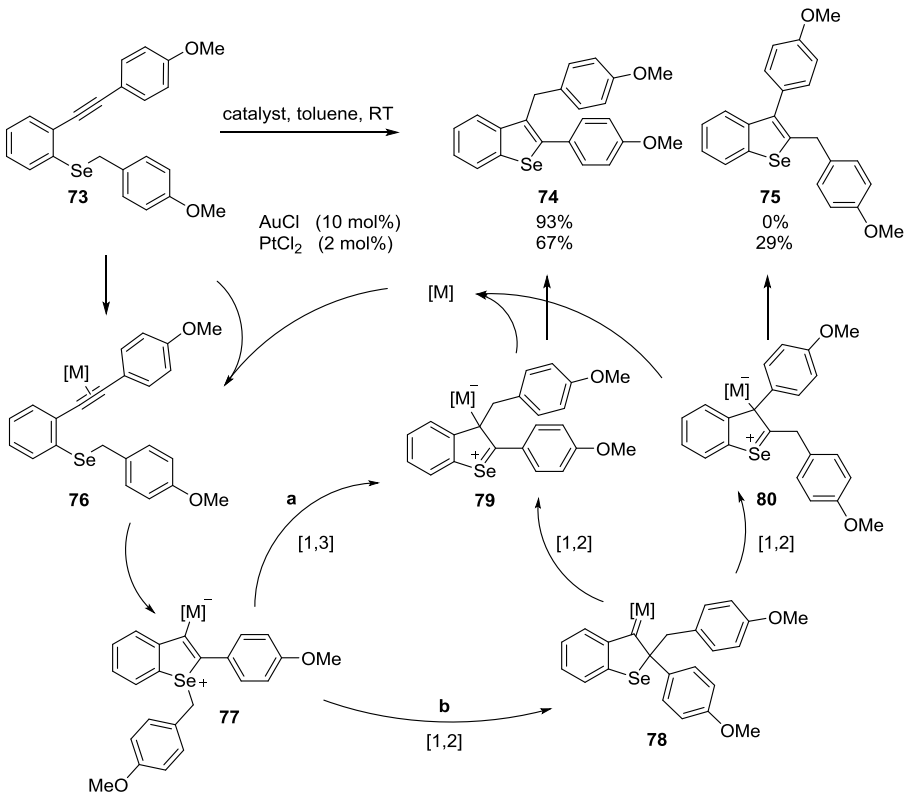
Scheme 17: Migration of benzyl groups to generate benzofurans and benzothiophenes

Transfer of the benzylic group as a cationic fragment in such X→C migrations was supported in crossover studies for the platinum-catalysed cycloisomerisation of *ortho*-alkynyl phenyl selenides in the formation of benzoselenophenes by Nakamura and co-workers (Scheme 18).[36] Reaction of a 1:1 mixture of **67** and **68**, with **68** containing deuterium labels on both the migrating group and alkyne substituent, resulted in the predominant formation of products **69** and **70** from intramolecular reaction, alongside small amounts of products **71** and **72** from intermolecular reaction.



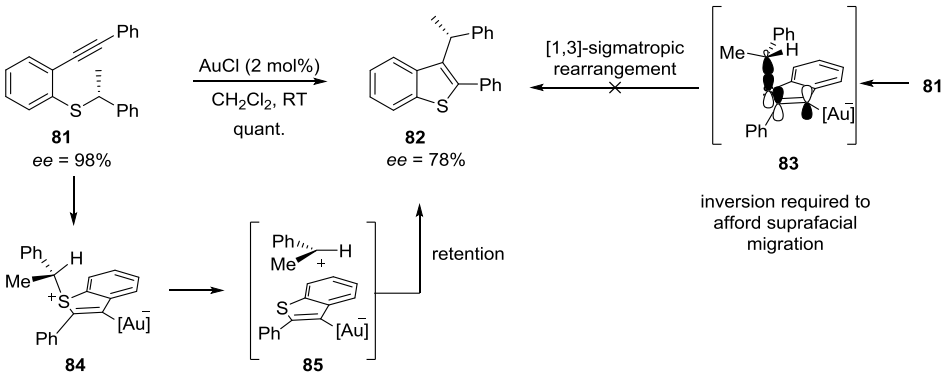
Scheme 18: Formation of crossover products through intra- and intermolecular cationic benzyl migration

When *ortho*-alkynyl phenyl selenide **73** was subjected to gold catalysis, the sole formation of benzoselenophene **74** was observed from the expected Se→C 1,3-migration of the *p*-methoxybenzyl group (Scheme 19, path a). When a platinum catalyst was employed, regioisomer **75** was also observed from a competing migration pathway (Scheme 19, path b). This isomer was proposed to arise from an alternative 1,2-migration of the *p*-methoxybenzyl group β- to the metal to form a metal carbene **78**. Evolution of this intermediate can occur through a second 1,2-shift either of the same group, leading to the expected product **74**, or of the *p*-methoxybenzene group, quenching the carbene and generating regioisomer **75**. Vinyl metal species are known to display nucleophilic character at both the α- and β-positions,[3,37] which helps to rationalise this competing 1,2-shift pathway. The formation of a single product under gold catalysis can be attributed to the reduced susceptibility of gold chloride to form a metal carbene in this system, thus favouring path a.[5,6c]



Scheme 19: Divergent pathways available in the gold- and platinum-catalysed formation of benzoselenophenes

Nakamura and co-workers observed an interesting transfer of chirality in a direct 1,3-X→C migration process in the synthesis of benzothiophenes such as **82** (Scheme 20).[38] Single enantiomers of sulfides such as **81**, incorporating a stereogenic centre at the migrating benzylic position, were employed in a gold-catalysed carbothiolation. The transfer of stereochemical information was then monitored across the migration step. Depending on the substitution at the alkyne, retention of stereochemical information was observed to varying degrees. This indicates the migration proceeds through a close contact ion pair **85** and rules out a [1,3]-sigmatropic rearrangement (**83**) as the required suprafacial migration would result in inversion of the stereogenic centre.

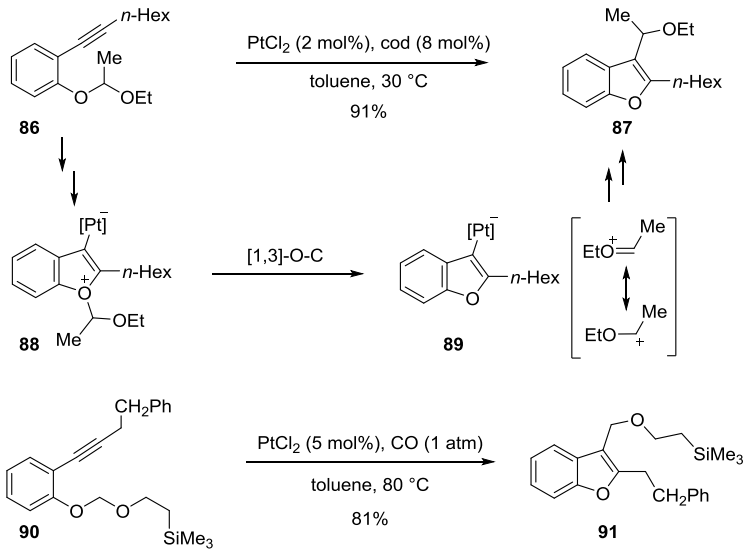


Scheme 20: Intermediates arising from close contact ion pair and [1,3]-sigmatropic pathways

The formation of a close contact ion pair was further supported by the observation that chirality was less effectively preserved when conditions were employed that would be expected to increase separation of the ion pair, such as the use of higher temperatures and more polar solvents. Finally, deuterium labelling was used to confirm a direct 1,3-migration over two sequential 1,2-migrations.

2.2.4 Migration of Acetal groups

Besides allyl and benzyl groups, heteroatom-stabilised groups such as acetals can also undergo efficient 1,3-X→C migration. This was first demonstrated independently by the groups of Fürstner and Nakamura in platinum-catalysed preparations of highly functionalised benzofuran derivatives (Scheme 21).[27,39] In-keeping with the mechanisms discussed so far, activation of *ortho*-alkynyl phenol derived acetals **86** and **90** led to *endo*-mode cyclisation and transfer of an oxonium species to the metallated, nucleophilic C-3 position of the newly-formed benzofuran ring.

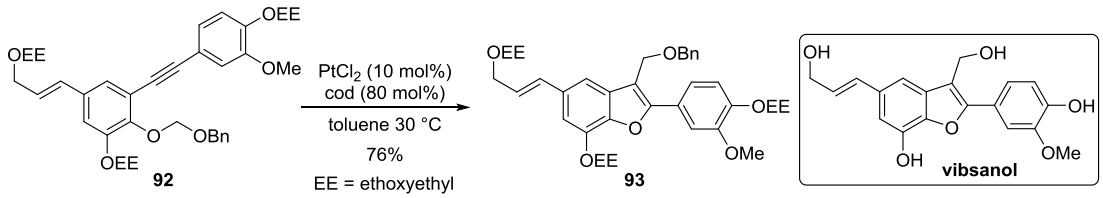


Scheme 21: Carboalkoxylation with migration of oxygenated carbon units under platinum catalysis. (cod = cyclooctadiene)

The transformation of substrates of type **86** was significantly accelerated on addition of substoichiometric quantities of cyclooctadiene (cod) to the reaction.[39] Interestingly, $PtCl_2$(cod) did not promote the reaction at all. This effect was tentatively assigned to the generation of a more reactive platinum species by aiding the disaggregation of polymeric $PtCl_2$. In contrast to the use of olefin additives, a CO atmosphere in the reaction of substrate **90** proved beneficial once again (*vide supra*) allowing for the formation of functionalised benzofuran **91** in high yield.[27]

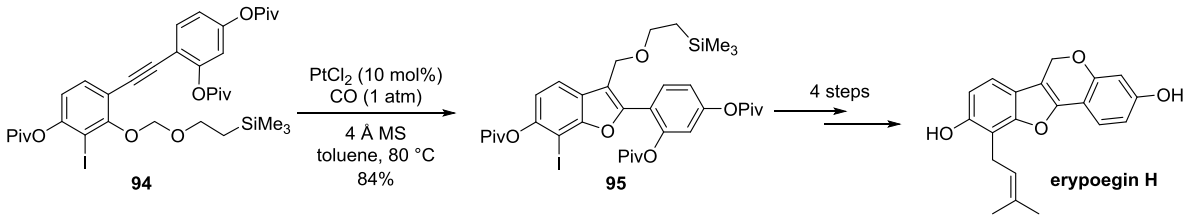
Acetal migrations in benzofuran synthesis are particularly useful transformations as they install a protected alkoxy group at the C-3 position. A protected form of vibsanol, an inhibitor of lipid peroxidation, was prepared in a platinum-catalysed 1,2-carboalkoxylation by Nakamura and co-

workers (Scheme 22).[40] In the presence of the $PtCl_2$ / cod catalyst system, functionalised mixed acetal **92** underwent smooth transformation to the desired benzofuran **93**.



Scheme 22: 1,2-Carboalkoxylation strategy towards the synthesis of vibsanol

The first total synthesis of erypoegin H, which shows activity against various MRSA strains and vancomycin-resistant enterococci,[41] was synthesised using a similar strategy by Fürstner and co-workers. A range of natural products based around the pterocarpene skeleton were synthesised through platinum-catalysed 1,2-carboalkoxylation of acetal **94** on a multigram scale (Scheme 23).[42] Smooth cycloisomerisation occurred to generate the desired benzofuran **95** in high yield, importantly leaving the reactive C-I bond intact for further manipulation. The benzofuran core was then elaborated in four steps to the natural product.

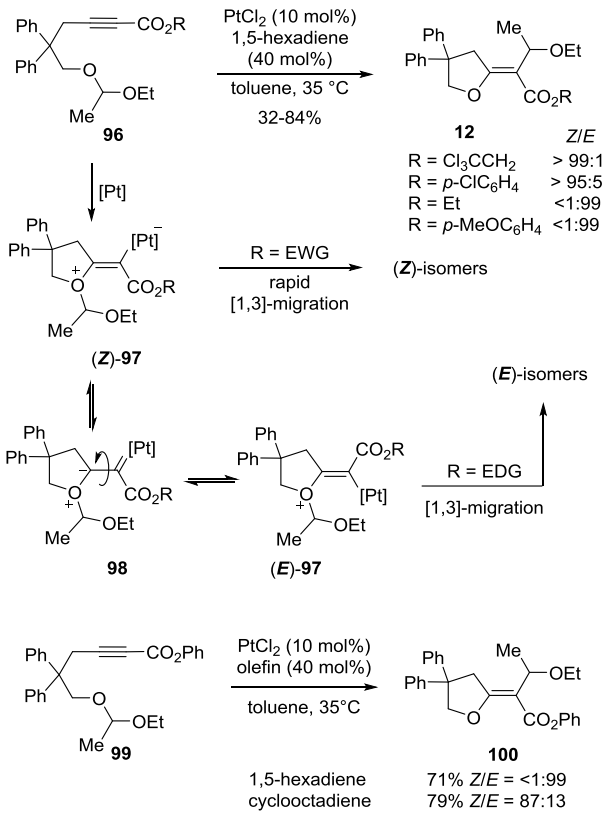


Scheme 23: 1,2-Carboalkoxylation towards the total synthesis of erypoegin H

Acetal migrations have also been reported by Nakamura and co-workers where the oxonium intermediate is formed through *exo*-mode cyclisation using an electronically biased alkyne

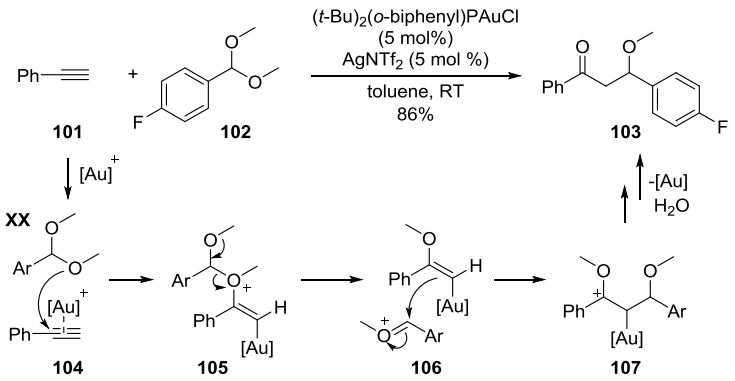
(Scheme 24).[43] Platinum catalysis was employed to promote carboalkoxylation with oxonium migration to form multisubstituted dihydrofuran derivatives **12**. Substitution of the ester at the alkyne terminus was observed to influence the stereoselectivity of these reactions. Electron-deficient substituents promoted a rapid [1,3]-migration from oxonium (***Z***)-**97** to give the (*Z*)-alkene products. When an electron-rich substituent was employed however, the (*E*)-alkenes were formed. This was attributed to a slower rate of reaction, presumably due to increased electron density at the metallated C-3 position, allowing interconversion of (***Z***)-**97** into (***E***)-**97**.

Interestingly, the stereochemical outcome of the reaction with these substrates was also influenced by the choice of olefin additive. The use of 1,5-hexadiene gave rise to near complete (*E*)-selectivity from **99**, whilst the use of cyclooctadiene favoured the formation of the (*Z*)-isomer.[44]



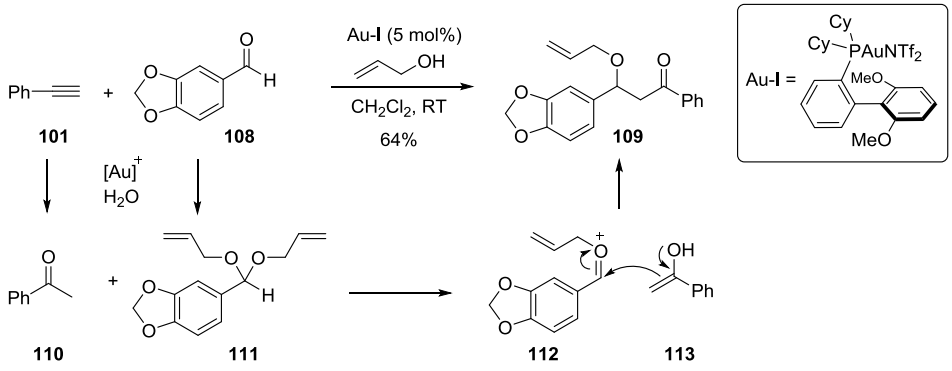
Scheme 24: Influence of the ester group on *E* / *Z* selectivity for acetal migration

The first examples of intermolecular carboalkoxylation of terminal alkynes have recently been reported. Hu and co-workers developed a novel gold-catalysed reaction between a terminal alkyne **101** and a dimethyl acetal **102** with a formal addition of C-O across the alkyne and subsequent hydrolysis of the enol ether to afford the ketone **103** (Scheme 25).[45]



Scheme 25: Gold-catalysed formal intermolecular carboalkoxylation of an alkyne

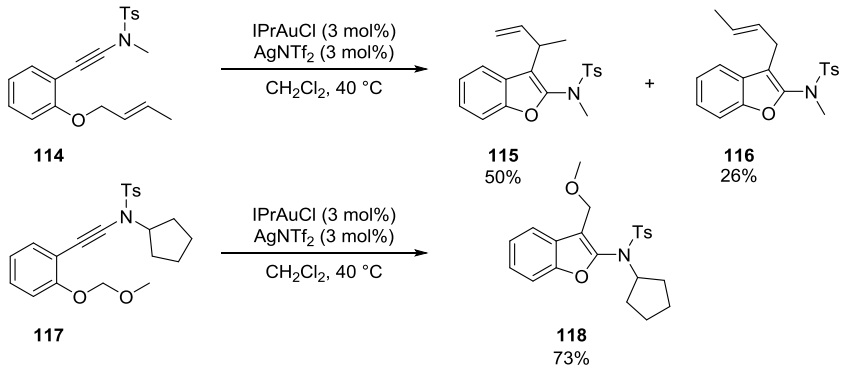
Shortly after, Schultz and co-workers reported the related transformation with aldehydes, in the presence of a range of alcohol coupling partners, removing the requirement for a pre-formed acetal (Scheme 26).[46] In the proposed mechanism, ketone **110** is formed through gold-catalysed hydration of the alkyne **101**. Acetal **111** is also formed under the reaction conditions from the aldehyde **108**, which on fragmentation to the oxonium **112**, gives rise to the aldol addition product through coupling with tautomer **113**.



Scheme 26: Gold-catalysed 3-component coupling of an aldehyde, alkyne and alcohol

2.2.5 [1,2]-Carboalkoxylation of Ynamides

During the preparation of our own manuscript,[21] Hashmi and co-workers reported the first example of carboalkoxylation using ynamides in the synthesis of benzofurans (Scheme 27).[47] Following the generally accepted mechanism discussed so far for 1,2-carbofunctionalisations, and previous reports on carboalkoxylation of *o*-alkynylphenol derivatives, cationic migration of unsymmetrical allyl groups to the metallated position was observed in the formation of branched and linear isomers **115** and **116**. Due to the connectivity of the substrates employed, the same regioselectivity was observed as with alkyne substrates. The goal of my own work was to override this cyclisation bias to access an alternative 1,1-carboalkoxylation pathway (see Scheme 7, path c) in a regioselective manner (*vide infra*).

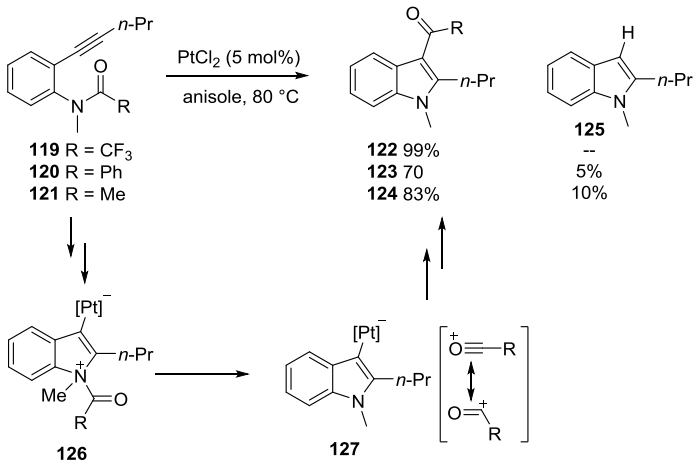


Scheme 27: 1,2-Carboalkoxylation of ynamides (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)

2.2.6 Migrating Centres at Higher Oxidation Levels

An early example of π-acid mediated 1,2-carboamination was demonstrated by Nakamura and co-workers in the formation of 2,3-disubstituted indoles **122**-**124** by the platinum-catalysed intramolecular amino-acylation of alkynes (Scheme 28).[48] Migration of the acyl moiety through

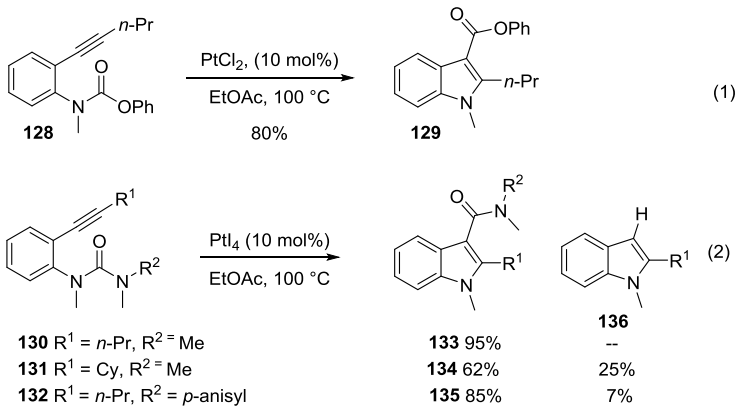
an acylium cation demonstrates the migration of a carbon centre at the ketone oxidation level. When the acyl group was substituted with an electron withdrawing CF_3 group, complete transfer was observed to give 3-substituted indole **122**. In certain cases, for example, when a simple acyl group was employed, small amounts of 3-H indole **125** were observed from incomplete acyl transfer, allowing protodemetallation of the organo-platinum intermediate.



Scheme 28: Intramolecular amino acylation of alkynes under platinum catalysis

Nakamura and co-workers went on to demonstrate the migration of alkoxycarbonyl and carbamoyl groups where the carbon is at the carboxylic acid oxidation level, in the platinum-catalysed formation of functionalised indoles (Scheme 29).[49] No 3-H products were observed for alkoxycarbonyl migration (**128**-**129**, Scheme 29, Eq. [1]), however carbamoyl migration appears less efficient allowing some protodemetallation to occur to give **136** (Scheme 29, Eq. [2]). The use of molecular sieves in the reaction did not affect the levels of **136** generated. Furthermore, when the reactions were carried out in deuterated solvent, 3-deuterated indoles were not

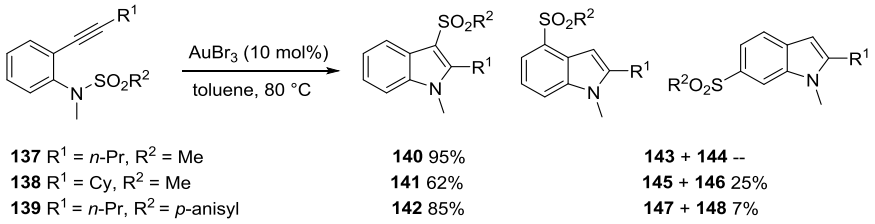
observed, indicating the proton involved in protodemetallation originates from the migrating group.



Scheme 29: Migration of alkoxycarbonyl and carbamoyl groups

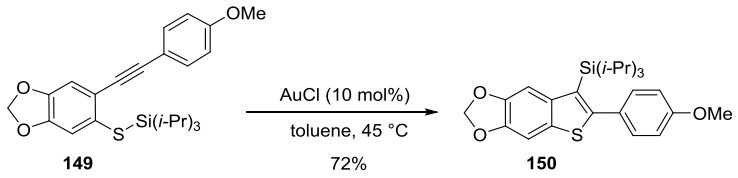
2.2.7 Migration of Heteroatoms

As well as carbon-based units, Nakamura and co-workers have shown that sulfonyl groups are able to participate in related [1,3]-migration processes.[50] The gold-catalysed cycloisomerisations of *ortho*-alkynyl-*N*-sulfonyl anilines **137**-**139** afforded sulfonylated indole products **140**-**142** (Scheme 30). Whilst the sulfonyl group predominantly migrated to the C-3 position, some substitution onto C-5 and C-7 was also observed with the formation of isomeric indoles **145**-**148**.



Scheme 30: Competitive migrations of sulfonyl groups

1,3-S→C Silyl migration has also been reported in the preparation of 3-silyl benzothiophenes **150** by Nakamura and co-workers (Scheme 31).[51] No substitution onto the benzene ring was observed in this case, however the formation of crossover products, arising from intermolecular transfer of the silyl group, was observed.

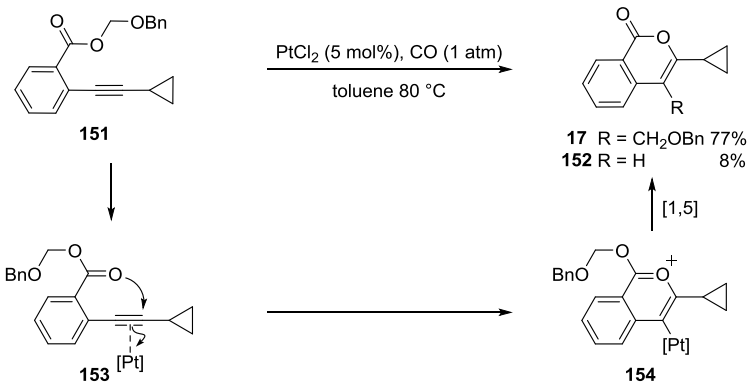


Scheme 31: 1,3-S→C silyl migration to give 3-silyl benzothiophenes

2.2.8 [1,5]-Heteroatom→Carbon Migrations

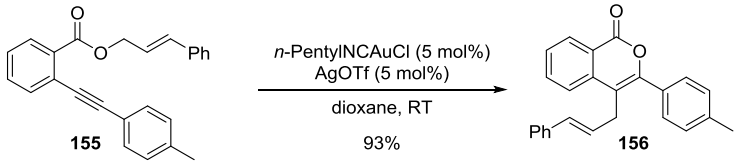
In the examples discussed so far, the migrating group has been directly bound to the nucleophilic heteroatom. This does not need to be the case, however, as demonstrated by Fürstner and co-workers in the synthesis of isochromenone **17** from *ortho*-alkynyl benzoate **151** (Scheme 32).[27] The carbonyl oxygen attacks the π-acid activated triple bond to generate charged intermediate **153**. The connectivity of the benzoic acid derived substrates allows for an alternative 1,5-O→C migration of the oxymethylene unit to yield isochromenone **17**. Small

quantities of the protonated isochromenone **152** were also isolated as a result of incomplete migration of the benzyl ether.



Scheme 32: Carboalkoxylation of alkynyl benzoates through [1,5]-benzyl ether migration

Related allyl and benzyl migrations have also been reported under cationic gold(I) catalysis by Hashmi and co-workers in the generation of isochromenones such as **156** (Scheme 33).[52] Crossover experiments in this case demonstrated an intramolecular delivery of the migrating group.

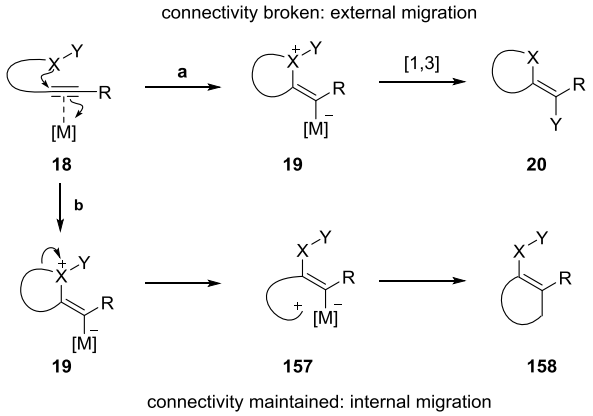


Scheme 33 Gold-catalysed formation of isochromenones by [1,5]-allyl migration.

2.2.9 Internal vs. External Migrations

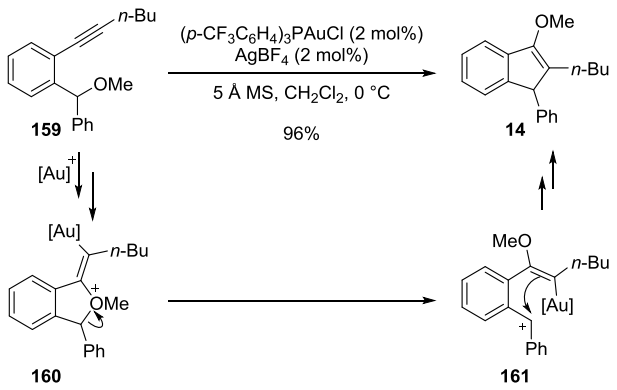
All of the carbofunctionalisations discussed so far can be classified as *external migration* processes. The migrating group is tethered to the alkyne through the nucleophilic heteroatom,

and so the connectivity between the migrating group and the alkyne is broken over the course of the transformation (Scheme 34, path a).[22] *Internal migration* processes can therefore also be classified where the connectivity between the migrating group and the alkyne is maintained from starting material to product (Scheme 34, path b).



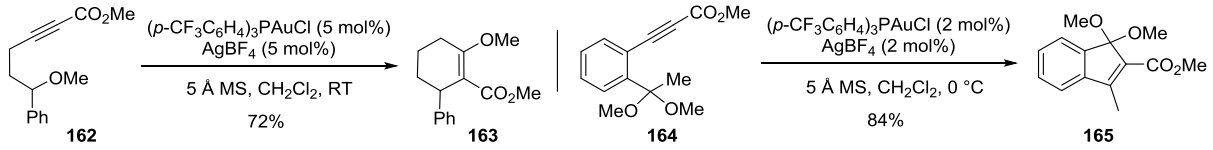
Scheme 34: External (path a) and internal (path b) migration pathways

The first example of this type of reaction pathway was demonstrated in the synthesis of indenyl ethers **14** under cationic gold(I) catalysis by Toste and co-workers (Scheme 35).[53] Oxonium species **160** is generated through 5-*exo*-dig cyclisation, initiated by nucleophilic attack of the methoxy oxygen onto the gold-activated triple bond. Evolution of this intermediate by external migration is not feasible as this would require formation of a methyl cation. Instead, C-O bond cleavage occurs to generate the most stable cation at the dibenzylic position (**161**), maintaining connectivity between the migrating methoxy unit and the alkyne. Following bond rotation, the benzylic cation is trapped by the newly-formed nucleophilic vinyl gold species to complete an overall 1,2-carboalkoxylation reaction.



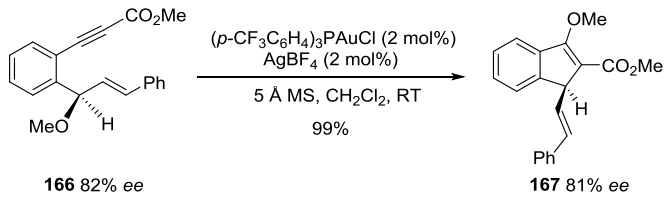
Scheme 35: Access to indenyl ethers through internal migration under gold catalysis

This reactivity was also applied to the synthesis of substituted cyclohexenes **163** and protected 1-indenones **165** (Scheme 36). In the same manner, C-O bond cleavage occurs to form the most stable carbocation. The use of activated molecular sieves was required to minimize hydrolysis of the resulting enol ether or acetal products.



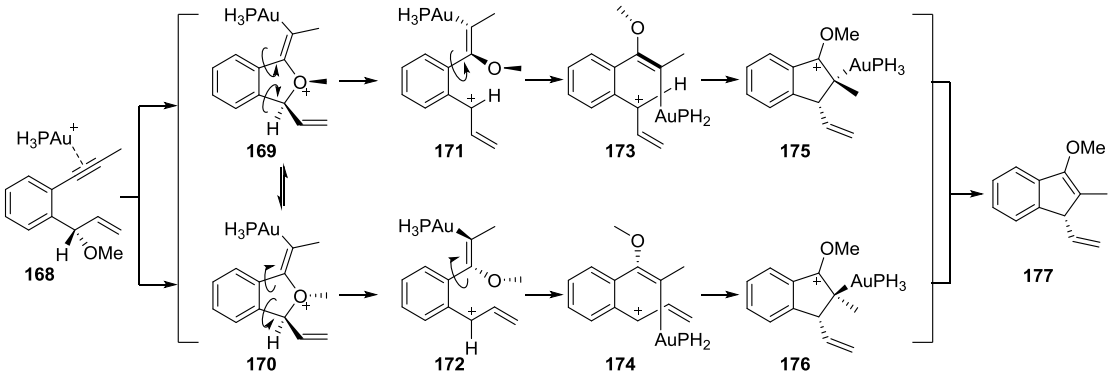
Scheme 36: Access to cyclohexenes and indenones through internal migration under gold catalysis

Interestingly, when enantioenriched substrates were employed, no racemisation of the starting material was observed over the course of the reaction. When substrate **166** was subjected to the reaction conditions, indene **167** was isolated with near complete transfer of chirality (Scheme 37).



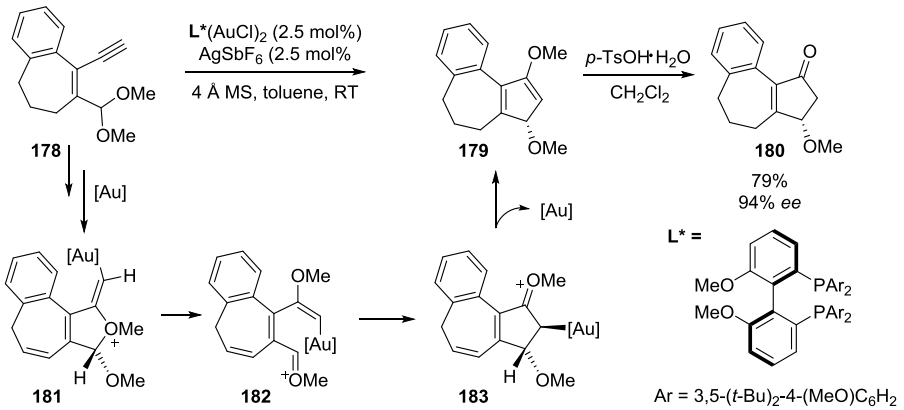
Scheme 37: Transfer of chirality across a 1,2-carboalkoxylation reaction.

Despite the mechanism invoking planarisation at the benzylic position, it was proposed that a helical transition state for the ionisation of the C-O bond was responsible for the observed 'memory of chirality' effect (**171**, **172**, Scheme 38). Maximising overlap between the cation and the aromatic π-system, the resulting intermediate (**173**, **174**) is primed for facially selective C-C bond formation on minimal bond rotation about the sp^2-sp^2 centre. This hypothesis was supported by a subsequent computational study[54] which highlights how small energy differences associated with conformational changes in gold-catalysed transformations can be product determining (Scheme 38).



Scheme 38: Computed pathways for the intramolecular carboalkoxylation with 'memory of chirality'

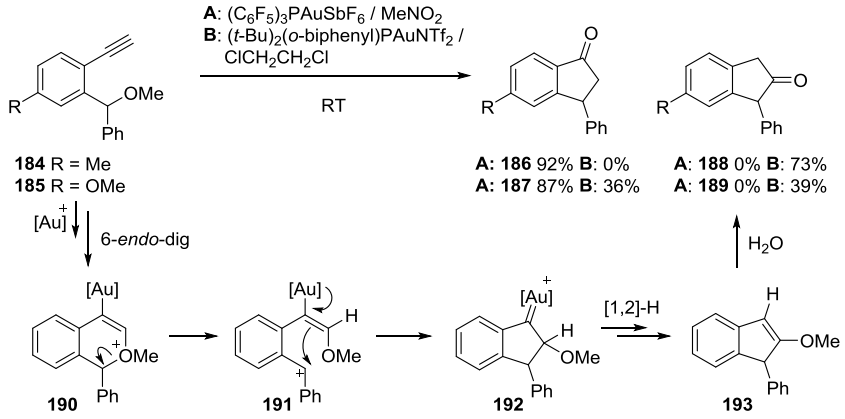
As well as the transfer of chiral information,[55] recently Toste and co-workers reported their development of an enantioselective method where chirality was imparted on alkynyl acetal substrates by the use of a single enantiomer of a chiral gold catalyst (Scheme 39).[56] 3-Methoxycyclopentenones such as **180** were synthesised with high enantioselectivity following hydrolysis of the corresponding enol ethers (**179**). The enantiodetermining step was thought to be cyclisation of planar vinyl gold species **182** where the gold ligands are positioned close to the stereogenic centre being formed.



Scheme 39: Enantioselective carboalkoxylation of alkynyl acetals

During the course of our study, Liu and co-workers observed interesting catalyst-dependent chemoselective carboalkoxylations in the synthesis of indanones **186** and **188** (Scheme 40).[57] When an electron deficient acidic gold species in 'wet' nitromethane was employed (conditions **A**), selective formation of 1-indanone **186** was observed in most cases following *in situ* hydrolysis of the enol ether. When an electron-rich gold species was employed in a less polar solvent (conditions **B**), selective formation of 2-indanone **188** was instead observed. In certain

cases, erosion of the selectivity occurred. For example when methoxy substituted alkyne **185** was employed under conditions **B**, a 1:1 mixture of the two isomers **187** and **189** was obtained.



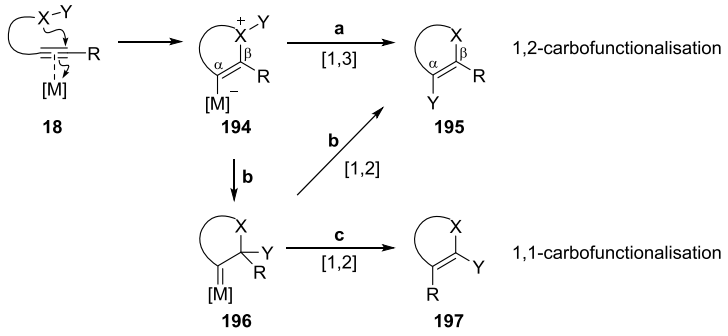
Scheme 40: Chemoselective carboalkoxylations to generate isomeric indanones

The observed selectivity was tentatively assigned to the potential of an electron deficient catalyst to generate a positive charge at the internal carbon of the alkyne, promoting the 5-*exo*-dig cyclisation which has been previously observed for these substrates (*vide supra*). An electron-rich catalyst may cause development of a positive charge at the terminal carbon of the alkyne, promoting a 6-*endo*-dig cyclisation of the methoxy onto the alkyne (**190**). This may provide an alternative pathway with the formation of a gold carbene **192** (*vide infra*). [1,2]-H-shift followed by hydrolysis of the enol ether **193** would generate 2-indanones **188** and **189** with an alternative 1,1-carboalkoxylation of the alkyne (*vide infra*).

Finally the same group very recently reported further interesting product divergence in the reactions of the same substrates when gold or Brønsted acid catalysts were employed to generate 1- and 3-substituted 2-methoxy-1-H-indenes.[58]

2.2.10 1,1-Carbofunctionalisations

Alongside the direct formation of the C-C and C-heteroatom bonds in a 1,2 fashion across the starting alkyne, it is also possible to form these bonds in a 1,1 fashion, as seen in the final example above by Lui and co-workers. Aside the competing 1,1- and 1,2-carbofunctionalisations that were observed in the synthesises of benzoselenophenes (*vide supra*, Scheme 19), all other transformations described have involved an overall 1,2-alkyne carbofunctionalisation. This has, in most cases, been realised by [1,3]-external migration from the heteroatom to the metallated carbon (**194**-**195**, Scheme 41, path a).

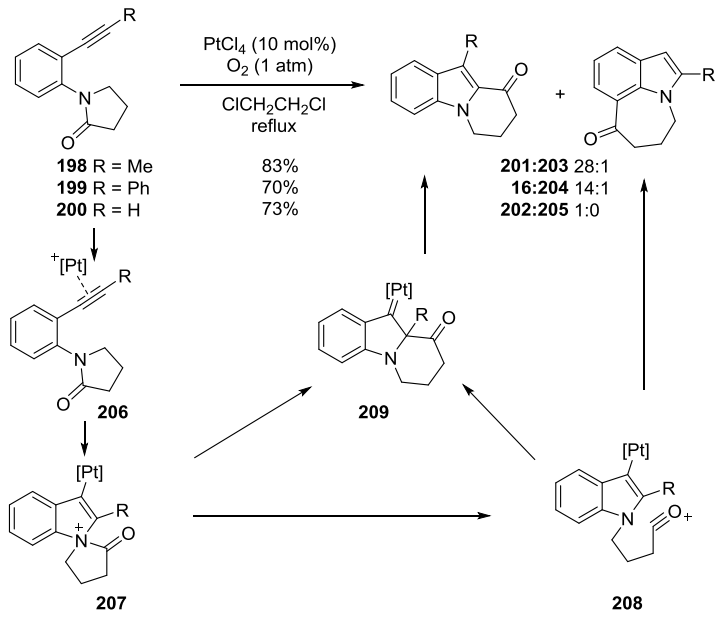


Scheme 41: Pathways arising from nucleophilic attack onto an activated alkyne for *endo*-cyclisation with external migration

As mentioned previously, vinyl-gold or platinum intermediates **194** are capable of displaying nucleophilic character at the β-carbon as well as the α-carbon. The migrating group can in certain cases undergo initial 1,2-shift onto the β-carbon to generate a gold carbene **196**. This valuable intermediate, which will be discussed further in section 2.4, can then be quenched by 1,2-insertion of a neighbouring group (**196**-**197**, Scheme 41, path c).[13,59] The outcome of this second step will be dictated by the relative migratory aptitude of the groups adjacent to the

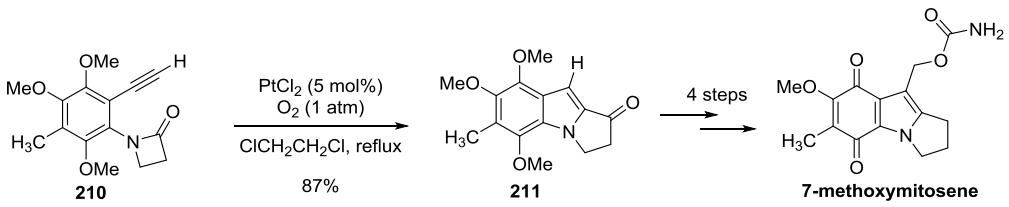
metal carbene (**196**). It seems reasonable to assume that [1,3]-migrations may in some cases arise through an initial 1,2-shift followed by 1,2-insertion of the same group to quench the newly formed carbenoid (**196**-**195**, *cf*. Scheme 19).

Though the 1,2-carboamination of alkynes with amides has been clearly demonstrated (Scheme 41, path a, *vide supra*), this pathway can be blocked when the amide bond is constrained within a lactam, allowing access to 1,1-carboamination products (Scheme 41, path c) as demonstrated by Zhang and co-workers.[60] Useful polycyclic amines **201**, **16** and **202** were generated from readily prepared precursors **198**-**200** using $PtCl_4$ as a catalyst under an O_2 atmosphere (Scheme 42). Hydrogen, alkyl and aryl substituents at the alkyne terminus underwent [1,2]-migration onto the metal carbene **209** formed in the initial 1,1-carboamination process (**206**-**209**). Isomeric side products **203** and **204** were identified in certain cases in small quantities as a result of the migrating acylium cation being trapped by the adjacent benzene ring, in a similar way to that observed with sulfonyl migration (*c.f.* Scheme 30).



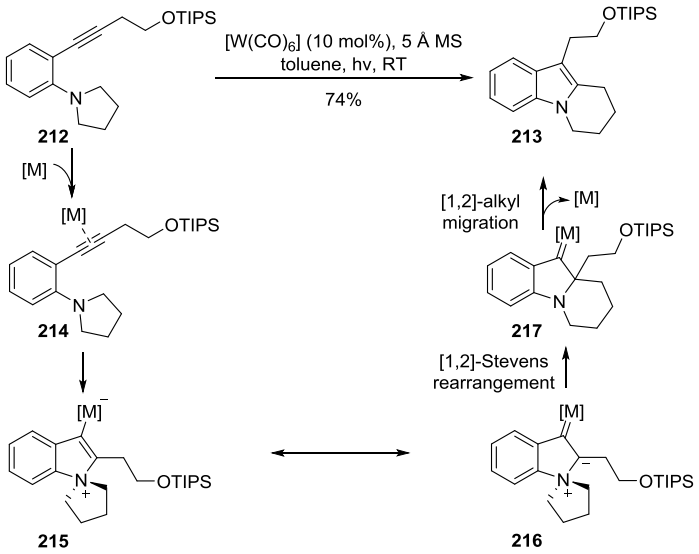
Scheme 42: Formation of fused indoles through 1,1-carboamination

This platinum-catalysed 1,1-carboamination strategy was the recently applied to the formation of the tricyclic core of the natural product 7-methoxymitosene,[61] effective against Gram positive bacteria.[62] Despite the hindered nature of substrate **210**, cycloisomerisation occurred efficiently to form the fused indole **211** which was readily converted into the target molecule in four steps (Scheme 43).



Scheme 43: Platinum-catalysed 1,1-carbofunctionalisation in the synthesis of 7-methoxymitosene.

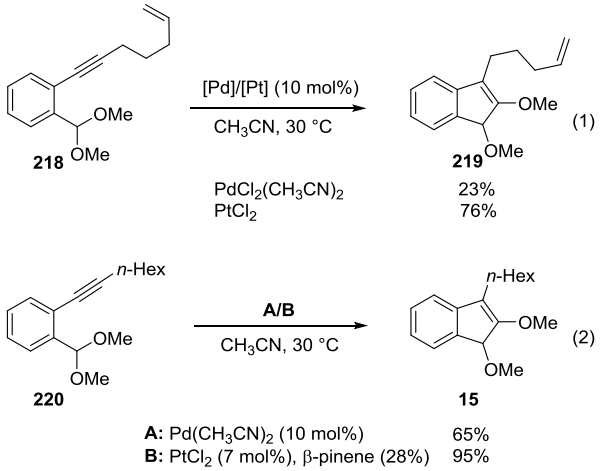
In a related process, Iwasawa and co-workers reported the generation of *N*-fused tricyclic indoles with overall 1,1-carboamination of an alkyne (Scheme 44).[63] Though the presence of the amine proved incompatible with gold and platinum in this case, the use of a tungsten or rhenium catalyst allowed for effective reaction of pyrolidine derivatives such as **213**. Alkyne activation and cyclisation results in the formation of metal containing ammonium ylide **215**/**216** which undergoes sequential [1,2]-Stevens-type rearrangement, then [1,2]-alkyl shift to quench the metal carbene **217**.



Scheme 44: Indole formation through sequential [1,2]-Stevens rearrangement and [1,2]-alkyl shift

The 1,1-carbofunctionalisation reactivity pattern was observed in one of the earliest studies on transition metal-catalysed reactions of aryl alkynes bearing *ortho*-acetals by Nakamura and co-workers.[25] Palladium-catalysed carboalkoxylation of alkyne **218** gave indenol ether **219** with cleavage of the sp-sp^3 C-C bond at the alkyne terminus, following an internal migration of a methoxy group (Scheme 45, Eq. [1]). Employment of $PtCl_2$ as the catalyst led to a significant

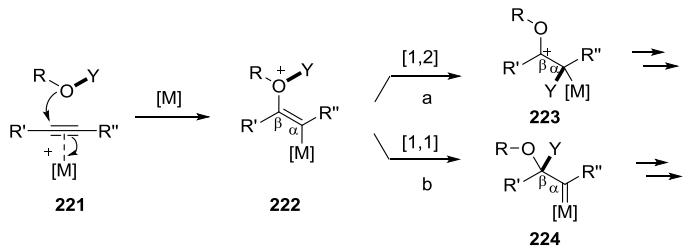
increase in yield when the substrate contained a tethered alkene.[26] A number of olefin additives were therefore explored alongside $PtCl_2$, with β-pinene producing the best results to give **15** in excellent yield (Scheme 45, Eq. [2]). The positive influence of an alkene additive was later exploited in related 1,2-carboalkoxylations (*vide supra*). The formation of a metal carbene is invoked, which is quenched by a [1,2]-alkyl shift of the alkyne substituent.



Scheme 45: 1,1-Carboalkoxylation of *ortho*-acetal aryl alkynes under palladium and platinum catalysis

2.3 Summary

Whilst many of the examples discussed above have featured a 1,2-carbofunctionalisation of a triple bond, the 1,1-pathway is much less explored. Specifically, the only example of the 1,1-carboalkoxylation of an alkyne at the outset of my work was that reported by Nakamura and co-workers (Scheme 45).The use of a 1,1-carboalkoxylation strategy to generate metal carbenes directly from alkynes is an attractive proposal which avoids the use of hazardous diazo compounds (Scheme 46, path b). The next sections detail the realisation of the use of ynamides to enforce a 1,1-carboalkoxylation pathway in order to generate gold carbenes **224**.[21]

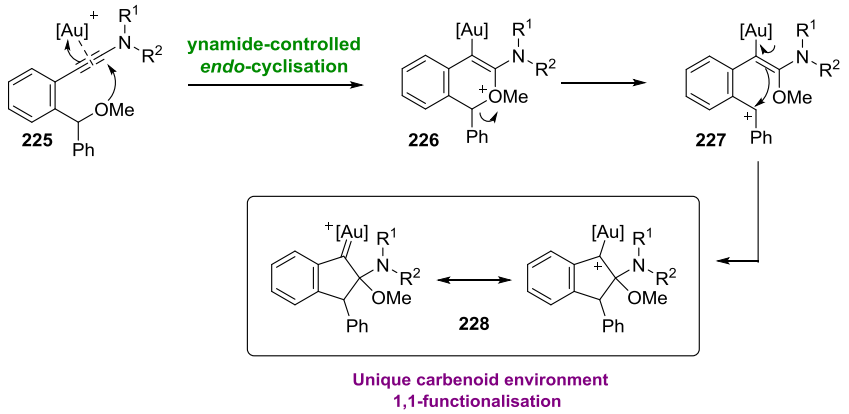


Scheme 46: 1,1- and 1,2-carboalkoxylation pathways

2.4 Results and Discussion

Ynamides of type **225** were chosen for study to allow direct comparison with the alkyne 1,2-carboalkoxylations reported by Toste and co-workers (*vide supra*, Scheme 35).[53] It was proposed that the electronic influence of an ynamide would lead to an alternative 6-*endo*-cyclisation pathway (**225**-**226**, Scheme 47) over the 5-*exo*-pathway previously described. On formation of intermediate **226**, ring-opening to form the more stable dibenzylic cation would generate a vinyl gold intermediate **227**, with migration of the methoxy group to the alkyne in an internal fashion. On ring closure, a gold carbene **228** would be formed in a unique environment bearing an adjacent hemiaminal ether, with a 1,1-carboalkoxylation of the ynamide.

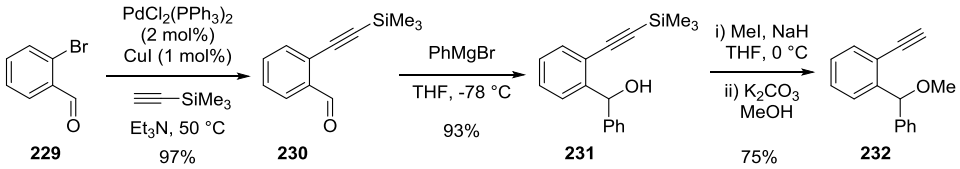
On formation of such a carbene, there are several possible outcomes that could be envisaged such as insertion or migration of adjacent groups to form functionalised indenes. These carbocyclic cores are synthetically important and serve as core structures in many natural products[64] and pharmaceuticals,[65] as well as being useful ligands for transition metals.[66]



Scheme 47: Proposed ynamide-dictated gold-catalysed carboalkoxylation

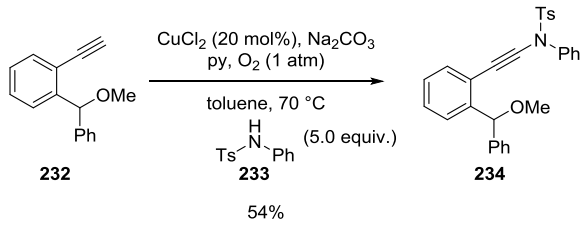
2.4.1 Initial Results

Many of the ynamides employed in this study were accessed through copper-catalysed coupling of a sulfonamide with terminal alkyne **232**, which was synthesised in four steps from 2-bromobenzaldehyde **229** (Scheme 48). Trimethylsilyl-protected alkyne **230** was prepared in high yield by Sonagashira coupling under standard conditions.[67] Grignard addition to the aldehyde gave the alcohol **231** in excellent yield following the procedure reported by Toste and co-workers.[53] All Grignard reagents used in this work were freshly prepared from the relevant aryl bromide. Alkylation of the alcohol with methyl iodide was carried out, again according to Toste's procedures, with purification conducted only after the deprotection of the terminal alkyne.



Scheme 48: Synthesis of terminal alkyne 232

Ynamide **234**, was synthesised directly from alkyne **232** using the copper-catalysed amidation procedure reported by Stahl and co-workers (Scheme 49).[68] This coupling reaction represents a very general route to a variety of differently functionalised ynamides from terminal alkynes and is therefore an attractive option. Five equivalents of the sulfonamide are required to achieve good yields, however, the unreacted sulfonamide can be recouped on purification (85% recovery of **233** based on four remaining equivalents in this example). Slow addition of a solution of the alkyne to the reaction vessel is required to minimize formation of the alkyne dimer and was carried out using a syringe pump. When using sterically bulky *ortho*-substituted arylalkynes, as in this work, the yields tend to be modest as a result of dimer formation even when the concentration of alkyne relative to sulfonamide is kept low by slow addition.



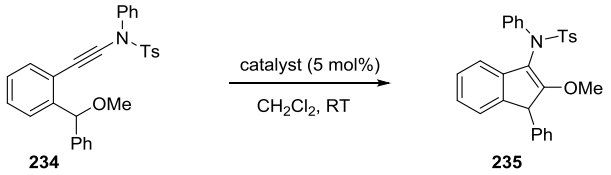
Scheme 49: Copper-catalysed amidation of terminal alkyne 232 to form ynamide 234

An alternative method *via* formation of a bromoalkyne was used to prepare several of the ynamides (*vide infra*) however, this approach was found to be ineffective when aniline-derived sulfonamides were used.

With ynamide **234** in hand, its reactivity in the presence of a range of gold catalysts was investigated (Table 1). On reaction with AuCl at room temperature, a novel skeletal rearrangement of ynamide **234** was observed with the sole formation of *N*-indenyl sulfonamide

235 in 27% yield alongside a substantial amount of unreacted starting material (Table 1, Entry 1). $PtCl_2$ did not promote the reaction at all, with only starting material observed by ^{1}H-NMR spectroscopy (Entry 2).

Table 1: Survey of reaction conditions[a]



Entry	Catalyst	Time / h	**234** / %[b]	**235** / %[b]
1	AuCl	24	53	27
2	$PtCl_2$	24	>95	33
3	Au**L**Cl_2[c]	24	17	63
4	PPh_3AuCl / $AgNTf_2$	6	--	79
5	(*t*-Bu)$_2$(*o*-biphenyl)PAuCl / $AgNTf_2$	20	--	73
6	(*p*-$CF_3C_6H_4)_3$PAuCl / $AgNTf_2$	2	--	89
7	(*p*-$CF_3C_6H_4)_3$PAuCl / $AgBF_4$	2	--	88
8	(*p*-$CF_3C_6H_4)_3$PAuCl / AgOTs	6	--	78
9	(*p*-$CF_3C_6H_4)_3$PAuCl	24	>95%	--
10	(*p*-$CF_3C_6H_4)_3$PAuNTf$_2$	2	--	88
11	$AgNTf_2$	24	>95%	--
12	$HNTf_2$	24	66	--
13	$BF_3{\cdot}OEt_2$	24	31	--
14	SiO_2	24	80	--

[a] Reaction conditions: 234 (0.1 mmol, 1.0 equiv.), CH_2Cl_2 (0.1 M), time as indicated [b] Yields calculated by ^{1}H-NMR spectroscopy against a known quantity of internal standard (1,2,4,5-tetramethylbenzene). [c] L=Picolinate.

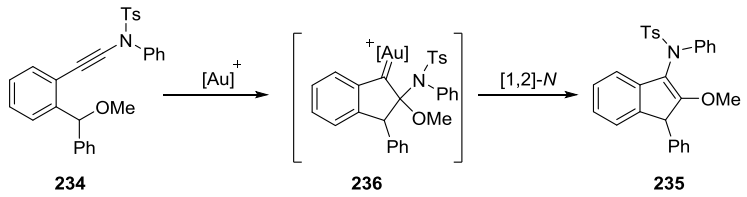
Dichloro(picolinate)gold(III) gave a much higher conversion than AuCl after 24 hours, although unreacted starting material still remained (Entry 3). Greater conversion to the desired product was achieved using cationic gold(I) phosphine complexes (Entries 4-8). The PPh_3AuCl / $AgNTf_2$ catalyst system led to complete consumption of starting material after 6 hours to give **235** in high yield (Entry 4).

A more electron-rich biphenyl phosphine ligand gave a similar result in terms of yield, although the reaction rate was greatly reduced (Entry 5). The use of a phosphine ligand with an electron withdrawing substituent led to improvement in both the yield and rate of the cycloisomerisation (Entry 6). Changing the silver salt was found not to be beneficial (Entries 7 and 8).

The use of $AgBF_4$ gave an identical result to $AgNTf_2$ (Entry 7) however, its sensitivity to heat and moisture rendered it less appealing as compared to bench-stable $AgNTf_2$. The requirement for activation of the gold complex with a poorly-coordinating counterion was demonstrated by the absence of reaction when the silver salt was omitted (Entry 9).

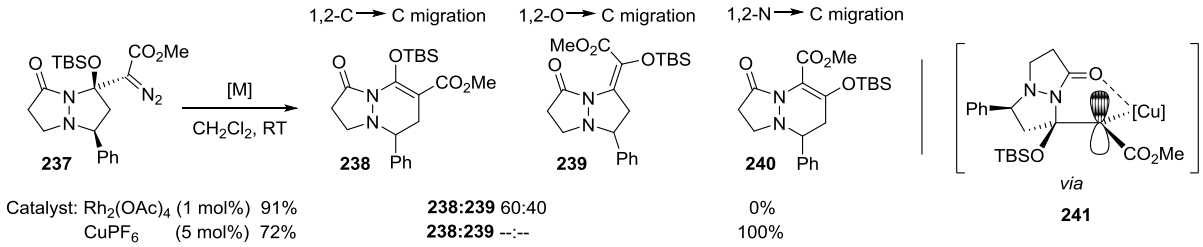
When preformed $(p\text{-}CF_3C_6H_4)_3PAuNTf_2$ was used as the catalyst for formation of **235**, an identical result was obtained as with the *in situ* formed catalyst (Entry 10 vs. 6), and so this was used for the remainder of the work. Clearly silver species are not required to promote the reaction, nevertheless $AgNTf_2$ was tested for activity and, as anticipated, failed to catalyse the reaction (Entry 11). Brønsted or σ-Lewis-acid activation was also ineffective with only degradation of the starting material observed (Entries 12-14).

The formation of indene **235** is thought to arise from the proposed α-hemiaminal ether gold carbene **228** (Scheme 47). Selective 1,2-*N* migration from the adjacent quaternary centre onto gold carbene **236** would generate the observed product (Scheme 50).



Scheme 50: Selective 1,2-*N* migration from α-hemi aminal ether gold carbene 236

Nitrogen migrations onto carbenes are not well known,[69] and to the best of our knowledge, this transformation represents the first example of nitrogen migration onto a gold carbene. A rare example of nitrogen migration onto copper carbenes generated from the metal-catalysed decomposition of β-methylene-β-silyloxy-β-amido-α-diazoacetates **237** was recently reported by Doyle and co-workers detailing competing O-,C-, and N-migrations (Scheme 51).[70]



Scheme 51: Catalyst dependant migrations onto rhodium and copper carbenes

When using a rhodium catalyst, mixtures of **238** and **239** were obtained from competitive [1,2]-*C*- or [1,2]-*O*-migrations onto the carbene centre. When a copper catalyst was used however, exclusive formation of **240** was observed arising from an selective [1,2]-*N* migration. This

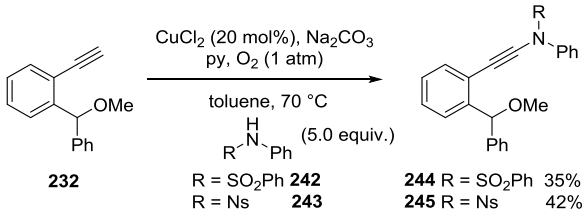
catalyst dependant pathway was attributed to the vacant coordination sites available for copper which allow coordination to the pyrazolidinone carbonyl (**241**), providing a directing effect for *N*-migration. In contrast, the coordinatively saturated dirhodium complex is unlikely to form such an interaction.

In contrast to this system, where the adjacent substitution pattern is installed prior to carbene formation, the ynamide carboalkoxylation approach sees this system formed concurrently with the gold carbene, without need for sacrificial functionality such as a diazo group. Overall, the process is highly efficient with new C-C, C-O and C-N bonds formed in a single step. In addition, this reaction proceeds through a rare example of C-N bond cleavage of an ynamide.

2.4.2 Reaction Scope

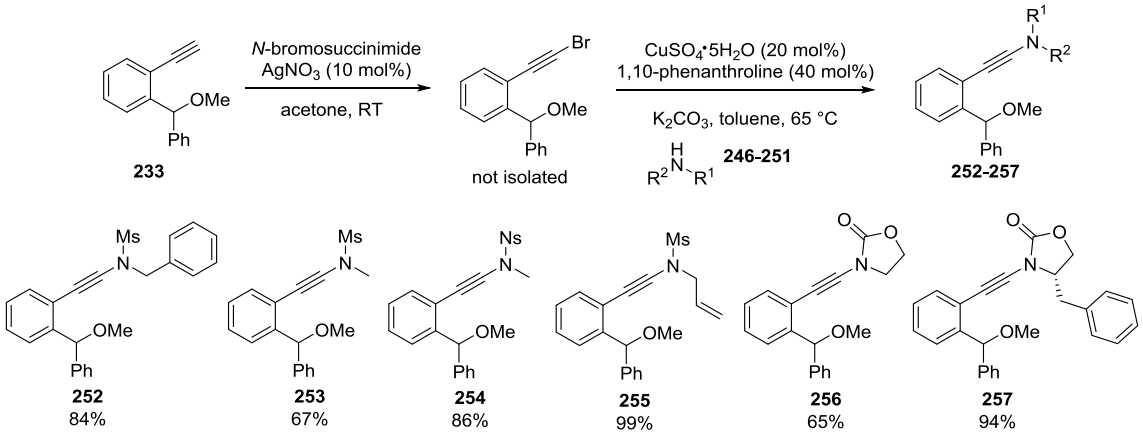
2.4.2.1 Modification of the Nitrogen Migrating Group

In order to further develop and understand this novel reaction, a series of ynamides were synthesised from terminal alkyne **232** to assess the migratory aptitude of different amides. In the cases of aniline derived sulfonamides, conditions reported by Stahl and co-workers were employed (Scheme 52).[68]



Scheme 52: Synthesis of ynamides 244 and 245

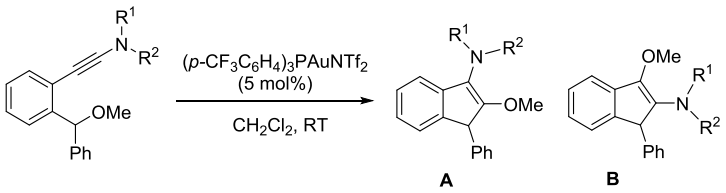
As mentioned previously, this method presents certain limitations in terms of product yield, due the formation of the undesired alkyne dimer. For the remaining substrates, which did not contain an aniline-derived sulfonamide, the method reported by Hsung and co-workers was instead employed.[71] Whilst adding an extra synthetic step to form the bromoalkyne coupling partner, purification was not required at this stage and the crude bromoalkyne could be used directly in the copper-catalysed amidation reactions (Scheme 53). This method employs the sulfonamide as the limiting reagent, with a slight excess of the bromoalkyne (1.2 equiv.). The resulting ynamides **252**-**257** were isolated in good to excellent yields following flash column chromatography.



Scheme 53: Synthesis of ynamides incorporating different migrating groups

The ynamides were then subjected to the optimised reaction conditions, with isolated yields given following flash column chromatography or recrystallisation (Table 2).

Table 2: Study of the *N*-migrating group[a]

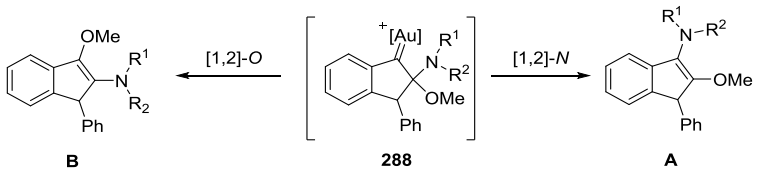


Entry	NR^1R^2	Time / h	**A** / %[b]	**B** / %[b]
1	**234** NPhTs	1	**235** / 78	--
2	**244** $NPhSO_2Ph$	1	**258** / 68[c],[d]	--
3	**245** NPhNs	0.75	**259** / 76	--
4	**252** NBnMs	3	**260** / 72[c]	--
5	**253** NMeMs	48	**261** / 23	**262** / 20[e]
6	**254** NMeNs	24	**263** / 29	**264** / 23
7	**255** N-AllylMs	1	**265** / 74	**266** / 9
8[f]	**255** N-AllylMs	24	**265** / 58	**266** / 10
9[g]	**255** N-AllylMs	24	**265** / 64	**266** / 5
10	**256** N(Ox)[h]	2	**267** / 78	--
11	**257** N(5-(*S*)Bn-Ox)	24	--[i]	--

[a] Reaction conditions: ynamide (0.2 mmol, 1.0 equiv.), [b] Isolated yields after flash column chromatography unless otherwise stated. [c] Isolated yield after recrystallisation without chromatography. [d] 3.0 mmol, 1.4 g scale.[e] Yield calculated by ^{1}H-NMR spectroscopy: present as an inseparable mixture with 253. [f] Catalyst: $(C_5F_5)_3PAuCl$ / $AgNTf_2$. [g] Catalyst: $[AuLCl_2]$ L = picolinate.[h] Ox = 2-oxazolidinone. [i] 37% of 257 remaining.

Aniline-derived sulfonamide groups underwent the reaction smoothly to give the expected regioisomer from 1,2-*N*-migration (Table 2, Entries 1-3). The scalability of the reaction was demonstrated by the formation of indene **258** in good yield from 1.4 grams (3.0 mmol) of

ynamide **244** (Entry 2). Column chromatography was not required in this case, and pure **258** was obtained after filtration to remove metal residues, evaporation and subsequent recrystallisation. Reaction of the corresponding nosyl-substituted ynamide **254** was also slow. Whilst starting material was consumed after 24 hours, the isolated yields of the two regioisomers were modest (Entry 6). The erosion of regioselectivity observed with these substrates is proposed to arise from competitive 1,2-*O*-migration onto the gold carbene **288** (Scheme 54, *vide infra*).



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Scheme 54: Competitive [1,2]-*N* and [1,2]-*O*-migrations onto the gold carbene

Regioisomer **266** was also isolated in small quantities when *N*-allyl substituted ynamide **255** was employed (Entries 7-9), although a high yield of the major regioisomer **265** was obtained (Entry 7). The use of a more electron deficient catalyst system $(C_6F_5)_3PAuCl$ / $AgNTf_2$, and a gold(III) complex had no dramatic effect on the ratio of the regioisomers. It is important to note that no cyclopropanation between the proposed gold carbene and the tethered alkene was observed, indicating the 1,2-migration is rapid in this system.

Oxazolidinone substituted ynamide **256** underwent smooth reaction to give the expected regioisomer in 78% yield (Entry 10). The use of a more hindered chiral benzyl substituted

oxazolidinone derivative, however, led to a complex mixture including unreacted ynamide (Entry 11).

It was possible to grow single crystals of **235** and **265** that were suitable for X-ray analysis using a pentane / dichloromethane solvent system. Confirmation of these structures, which had previously been assigned based on ^{1}H- and ^{13}C-NMR data, was therefore obtained (Figure 1).

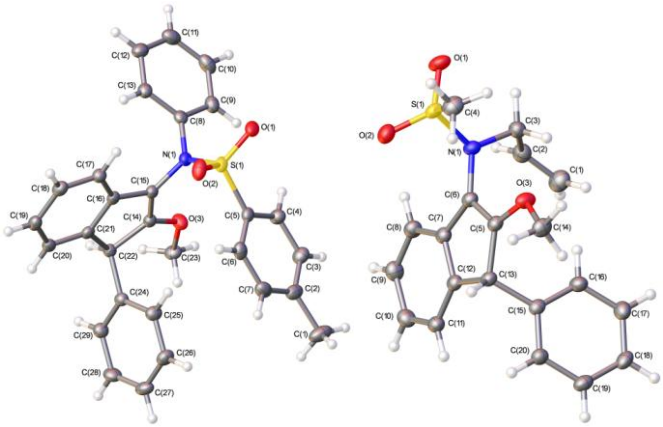
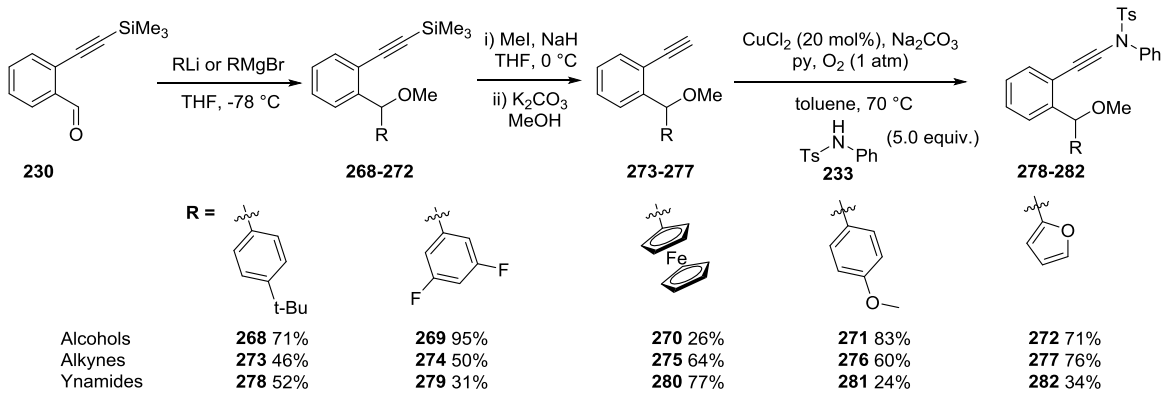


Figure 1: Crystal structures of 235 (left) and 265 (right) with ellipsoids drawn at the 50% probability level. X-Ray crystallography was carried out and data solved by Dr Louise Male (University of Birmingham).

2.4.2.2 Modification at the Benzylic Position

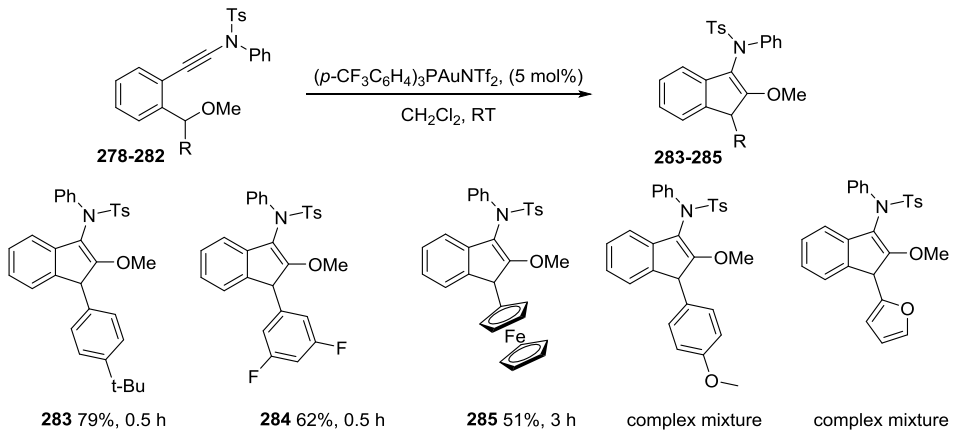
The impact of modifications elsewhere on the substrates was then investigated, initially by varying the groups at the benzylic position. According to the proposed mechanism, the benzylic position requires a substituent capable of stabilising positive charge. Therefore substituted aryl groups, ferrocene and furan groups were chosen for investigation. Ynamides **278**-**282** were synthesised through addition of the relevant freshly prepared organolithium or Grignard reagent to aldehyde **230** (Scheme 55). Alcohols **268**-**272** were methylated and the silyl group

cleaved using the conditions previously described to give terminal alkynes **273**-**277**. Copper-catalysed coupling with *N*-tosyl benzenesulfonamide **233** gave the desired ynamides in modest to good yields.



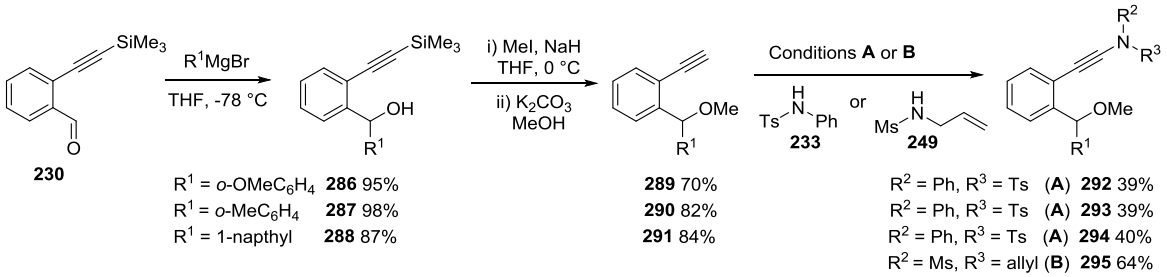
Scheme 55: Synthesis of ynamides 272-282 from aldehyde 230

Substrates substituted with electron-donating and electron-withdrawing aryl groups (**278** and **279**) underwent the desired reaction smoothly to give indenes **283** and **284** in good yields (Scheme 56). An electron-rich ferrocene-substituent was also tolerated to give indene **285** as a single regioisomer in moderate yield.



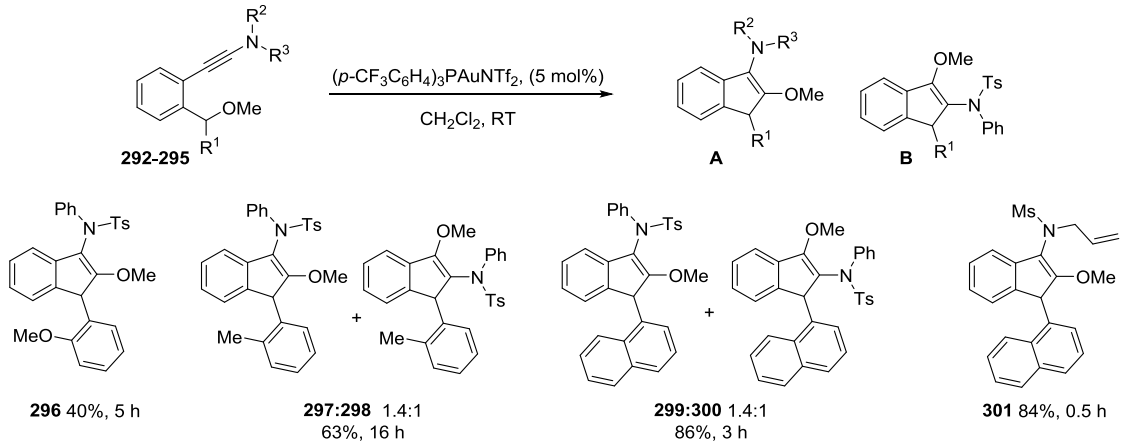
Scheme 56: Exploration of various benzylic substituents in the gold-catalysed indene formation

A *p*-methoxybenzyl substituent was not compatible for the cycloisomerisation. Whilst ynamide **281** was consumed, a complex mixture was obtained following column chromatography. In the proposed mechanism, methoxy migration precedes formation of the more stable benzyl cation (*vide supra*, Scheme 47). As the oxygen lone pair of *p*-methoxybenzene can be delocalised onto the benzylic position, it is possible that the benzylic cation is sufficiently long-lived to undergo side reactions. It was not possible however to isolate and characterise any products from this reaction due to the complexity of the mixture. A furan substituent gave a similar result. A surprising loss of regioselectivity was observed when certain ynamides bearing larger substituents at the benzylic position were employed. 1-Naphthyl, *o*-tolyl and *o*-anisole derived substrates **292**-**294** were synthesised as previously described using the relevant Grignard reagent (Scheme 57).



Scheme 57: Synthesis of ynamides with larger substituents at the benzylic position. Conditions A: $CuCl_2$, py., Na_2CO_3, O_2 (1 atm), 233 (5.0 equiv.), toluene, 70 °C, Conditions B = (i) NBS, $AgNO_3$, acetone, RT, (ii) $CuSO_4 \cdot 5H_2O$, 1,10-phenanthroline, K_2CO_3, 249 (1.0 equiv), toluene, 65 °C

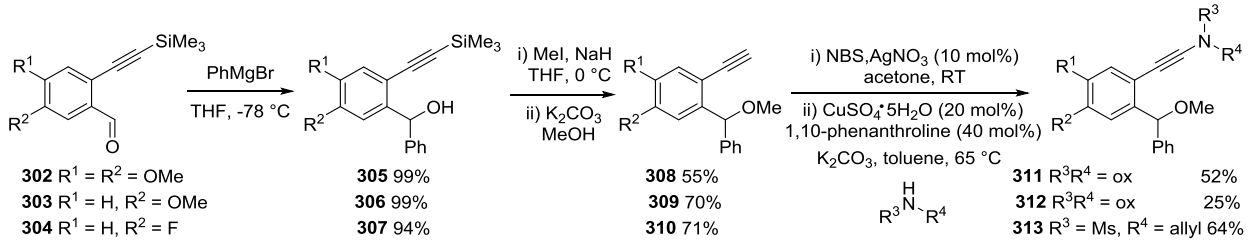
When ynamide **292** was subjected to the reaction conditions, only 40% of the expected indene **296** was isolated (Scheme 58). It was not possible to isolate what appeared to be the indene (**B**) resulting from 1,2-*O*-migration, based on ^{1}H-NMR analysis of the crude reaction mixture. An *o*-tolyl substituted system **293** reacted in a similar fashion, although it was possible to isolate and characterise the two regioisomers **297** and **298** in this case in good yield. A naphthyl substituted system **294** gave the same loss of selectivity to give indenes **299** and **300** as a separable mixture in high yield. It was supposed that the reduced selectivity might be a result of π-stacking and through-space interactions[72] between the benzylic and aromatic nitrogen substituents, therefore stabilising the intermediate for *O*-migration (*vide infra*). To test this, ynamide **295** bearing *N*MsAllyl substituents was prepared, where these stabilising interactions are unavailable. The sole formation of indene **301** in high yield from selective *N*-migration is consistent with this hypothesis.



Scheme 58: Erosion of regioselectivity with larger benzylic substituents

2.4.2.3 Modification of the Benzene Backbone

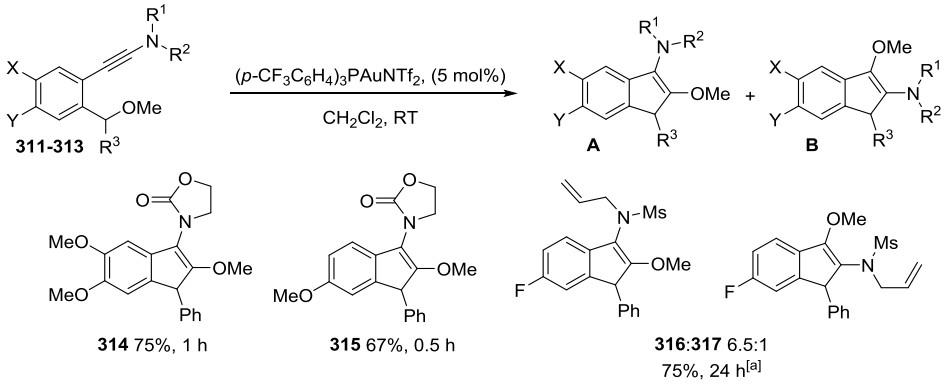
Some electronic effects on the reaction were then tested by modifying the benzene backbone (Scheme 59). Methoxy- and fluorine-substituted 2-bromobenzaldehydes **302**-**304** were converted in three steps to the terminal alkynes **308**-**310** using previously discussed procedures. Coupling of the alkynes with *N*-mesyl-*N*-allyl sulfonamide **249** or oxazolidinone **250** were carried from the relevant bromoalkynes, to yield ynamides **311**-**313**.



Scheme 59: Synthesis of ynamides 311-313 incorporating substituents on the benzene backbone

These functionalities were well-tolerated in the gold-catalysed transformation and indenes **314** and **315**, with electron-rich benzene rings were formed in good yields (Scheme 60). 4-Fluoro-

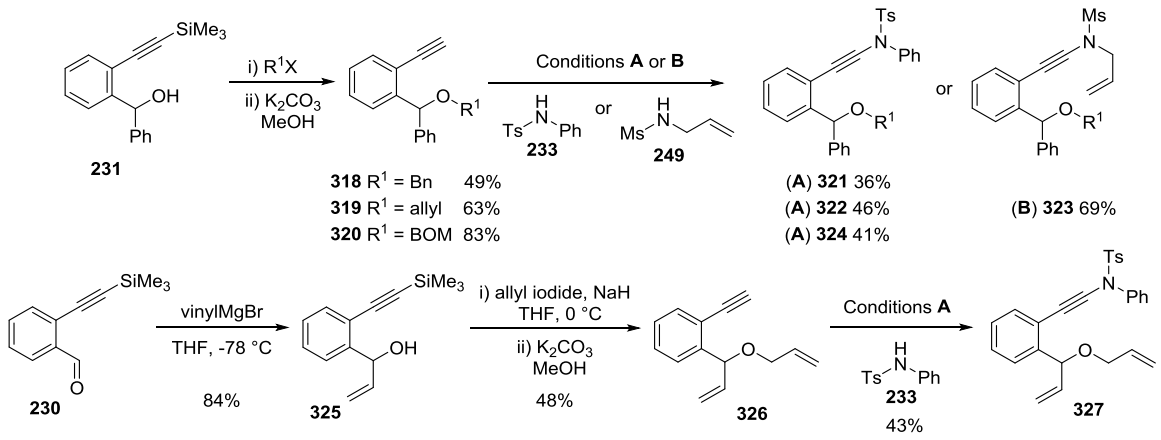
substituted ynamide **313** required a longer reaction time and an increased catalyst loading however, a good yield of **316** was achieved alongside expected regioisomeric indene **317**. This lower reactivity could be attributed to the destabilisation of the benzyl cation following methoxy migration.



Scheme 60: Synthesis of functionalised indenes with modification of the benzene backbone. [a] 10 mol% catalyst required

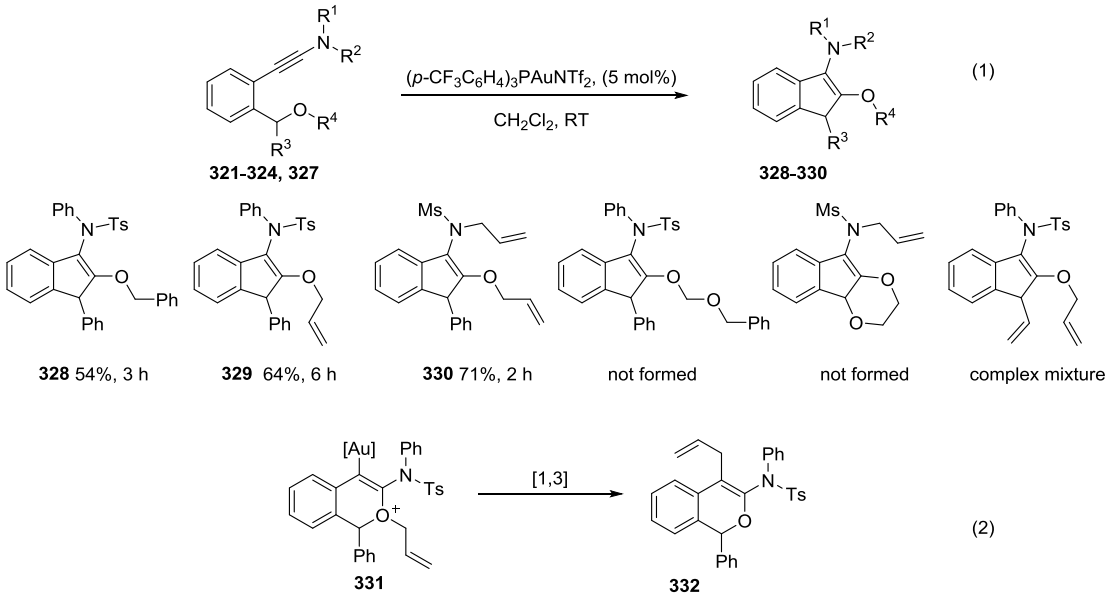
2.4.2.4 Modification of the Oxygen Migrating Group

Variation of the oxygen migrating group was also explored with the synthesis of benzyl, allyl and BOM ethers. Following literature procedures,[53,73] *O*-alkylation was carried out prior to alkyne deprotection to give terminal alkynes **318**-**320** in moderate to high yields over two steps. Depending on the sulfonamide required, different conditions were employed in the final stages to yield ynamides **321**-**324** in moderate to good yields (Scheme 61). An *O*-allyl protected ynamide **327** with a vinyl group at the benzylic position was also synthesised in the same way, with alternative employment of vinylmagnesium bromide to give alcohol **325** in high yield.



Scheme 61: Synthesis of ynamides 321-324 and 327 with variation of the *O*-protecting group: Conditions A: $CuCl_2$, py., Na_2CO_3, O_2 (1 atm), 233 (5.0 equiv.), toluene, 70 °C. Conditions B: (i) NBS, $AgNO_3$, acetone, RT, (ii) $CuSO_4 \cdot 5H_2O$, 1,10-phenanthroline, K_2CO_3, 249 (1.0 equiv), toluene, 65 °C

O-Benzyl and *O*-allyl protected ynamides **321** and **322** underwent the desired skeletal rearrangement to give the indenes **328** and **329** in moderate to good yields (Scheme 62, Eq. [1]). Allyl and benzyl groups, among others, are well known to be capable of [1,3]-migration to the metallated centre in 1,2-carbofunctionalisations, following initial nucleophilic attack of the heteroatom (*vide supra*). Pleasingly, no traces of this competing pathway were observed. (**331**-**331**, Scheme 61, Eq. [2]). Bis-allylated indene **330** was also generated in good yield as a single regioisomer on reaction of ynamide **323**, which allowed for further derivatisation by ring closing metathesis (*vide infra*).



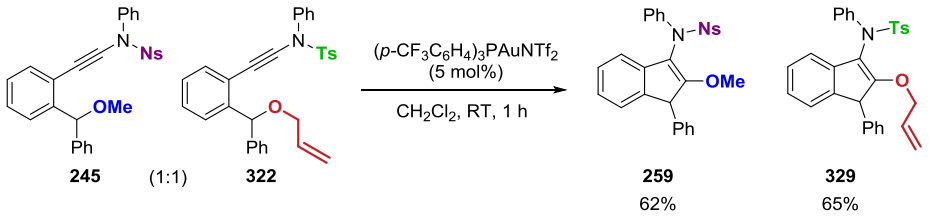
Scheme 62: Incorporation of different *O*-substituents (Eq. [1]) and potential competing 1,3-migration pathway (Eq.[2])

BOM-ether substituted ynamide **324** did not undergo the desired reaction, with only starting material observed by ^{1}H-NMR spectroscopy. A 5-membered cyclic acetal was also not compatible under the reaction conditions, with only cleavage of the acetal in low levels observed after 6 hours by ^{1}H-NMR spectroscopy. The synthesis of this type of ynamide is described in Chapter 3. Whilst an *O*-allyl substituted ynamide **327** bearing a vinyl group at the benzylic position was consumed under the reaction conditions, complex mixtures were obtained following column chromatography.

2.4.3 Mechanistic Studies

A crossover-study was conducted in order to confirm that the proposed 1,2-*N*-migration is an intramolecular process. A 1:1 mixture of ynamides **245** and **322**, bearing different nitrogen and

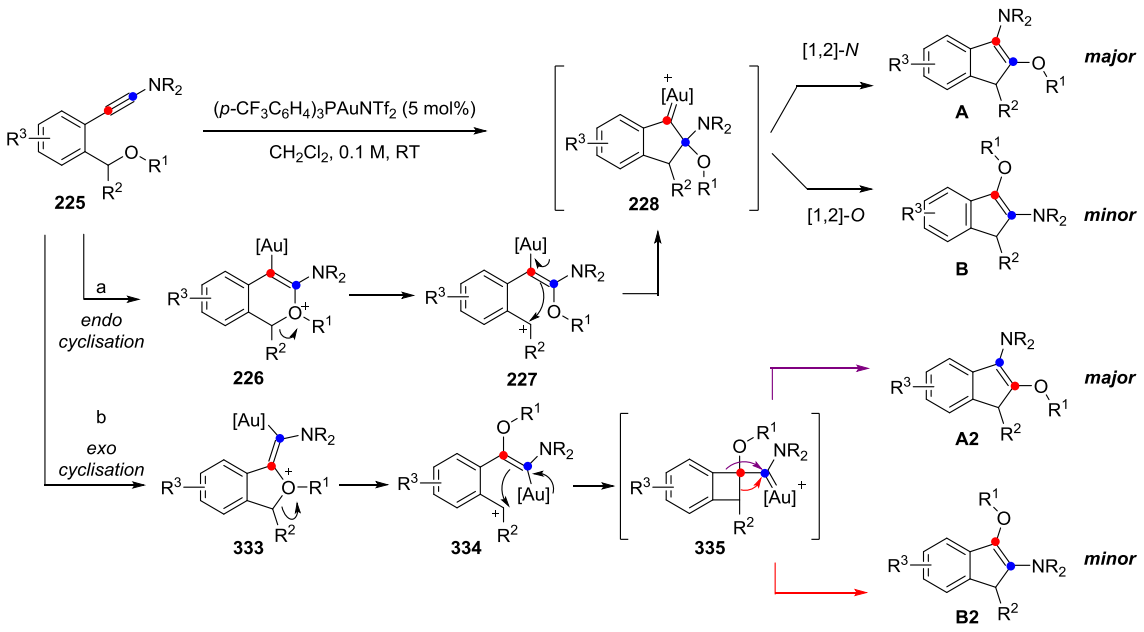
oxygen substituents, reacted to give the expected indenes **259** and **329** as the only observed products by ^{1}H-NMR spectroscopy. No crossover products resulting from intermolecular pathways were detected (Scheme 63).



Scheme 63: Crossover study

In the proposed mechanism (Scheme 64, path a), ynamide-controlled *endo*-mode cyclisation occurs onto the gold-activated triple bond to give 6-membered oxonium intermediate **226**. Fragmentation to form the most stable carbocation would then generate a benzylic cation tethered to form vinyl gold species **227**. Gold carbene **228** would then result on ring closure.

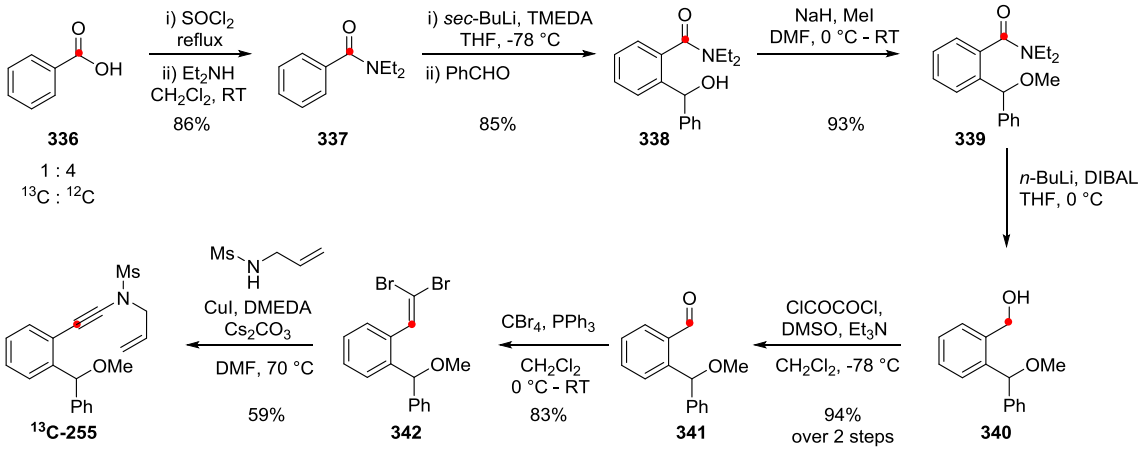
The major indene product **A** in most cases would result from selective 1,2-*N*-migration whereas regioisomeric indene **B** would arise from competitive 1,2-*O*-migration onto the same carbene intermediate. An alternative pathway could also be envisaged, initiated by an *exo*-mode cyclisation onto the triple bond as proposed by Toste and co-workers for alkyne substrates (Scheme 64, path b).[53] Fragmentation of the 5-membered oxonium intermediate **333** would generate an alternative vinyl gold species **334** which could then, on ring closure, potentially form *exo*-gold carbene **335**. Migration of one of the carbon-carbon bonds of the cyclobutene ring would then generate the same observed products.



Scheme 64: Possible *endo*- and *exo*-mode cyclisations for the formation of regioisomeric indenes

A ^{13}C-labelling study was therefore designed to confirm an *endo*-mode cyclisation. In the proposed 1,2-*N*-migration pathway, connectivity between the alkyne and the aryl group is maintained over the transformation (Scheme 64, path a). In contrast, if the alternative mechanism was in operation, this connectivity would be broken and, for the major isomer **A2**, these two carbons would become switched (Scheme 64, path b). ^{13}C-Labelling of one of the carbons of the triple bond would therefore allow analysis of the connectivity in the indene products. *N*-Allyl ynamide **255** was chosen for this study as both regioisomers are formed on cycloisomerisation. The structures of both isomers have been thoroughly analysed by ^{1}H- and ^{13}C-2D NMR spectroscopy (see Appendix) and the structure of the major indene confirmed by X-ray crystal diffraction (*vide supra*, Figure 1). Following analysis of several possible routes and options in terms of the source of the ^{13}C-label, a synthesis from ^{13}C-labelled benzoic acid was

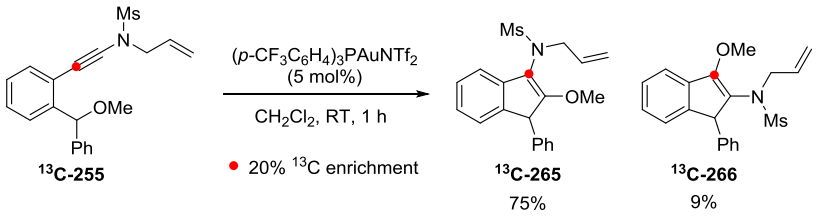
designed and implemented (Scheme 65). A 1:4 mixture of ^{13}C- and ^{12}C-benzoic acid **336** was converted to the diethyl benzamide **337** *via* the acid chloride in excellent yield over two steps. This functionality was then employed as a directing group for *ortho*-lithiation, following a modified literature procedure.[74,75] The metallated intermediate was trapped *in-situ* using freshly distilled benzaldehyde. Initially, a diisopropylamide was employed to direct the lithiation, however inefficient trapping was observed, presumably due to the larger alkyl groups blocking the *ortho*-position. With alcohol **338** in hand, alkylation was conducted using MeI to give **339** in excellent yield.



Scheme 65: Synthesis of ^{13}C-labelled ynamide ^{13}C-255 from benzoic acid. (TMEDA: tetramethylenediamine, DIBAL: diisobutylaluminium hydride, DMEDA: dimethylethylenediamine)

Attempts were then made to reduce the amide directly to the aldehyde **341**. Unfortunately suitable conditions could not be found, with mixtures of aldehyde **341** and alcohol **340** always generated. It was decided to force the reduction through to the alcohol and re-oxidise it back to the aldehyde, despite the addition of an extra synthetic step. An excess of DIBAL was activated with *n*-BuLi to form an 'ate' complex which afforded effective reduction. Crude alcohol **340** was

subjected to Swern oxidation conditions to give aldehyde **341** in excellent yield over two steps. The aldehyde was readily converted using a Corey-Fuchs olefination to dibromoolefin **342** under standard conditions.[76] Finally, the copper-catalysed amidation conditions reported by Evano and co-workers[77] were employed alongside *N*-mesyl-*N*-allyl sulfonamide **249** to form the desired ynamide **^{13}C-255** in moderate yield.



Scheme 66: Reaction of ^{13}C-labelled ynamide ^{13}C-255 with no scrambling of the carbons of the triple bond

On subjecting ynamide **^{13}C-255** to the standard reaction conditions, isomeric indenes **^{13}C-265** and **^{13}C-266** were isolated in an identical ratio and yield to that observed for the non-labelled substrate (Scheme 66). The maintenance of connectivity of the starting triple bond was confirmed as well as the cleavage of the C-N (**^{13}C-265**, Figure 2) or C-O (**^{13}C-266**, Figure 3) bonds with the migrated group connected to the labelled carbon.

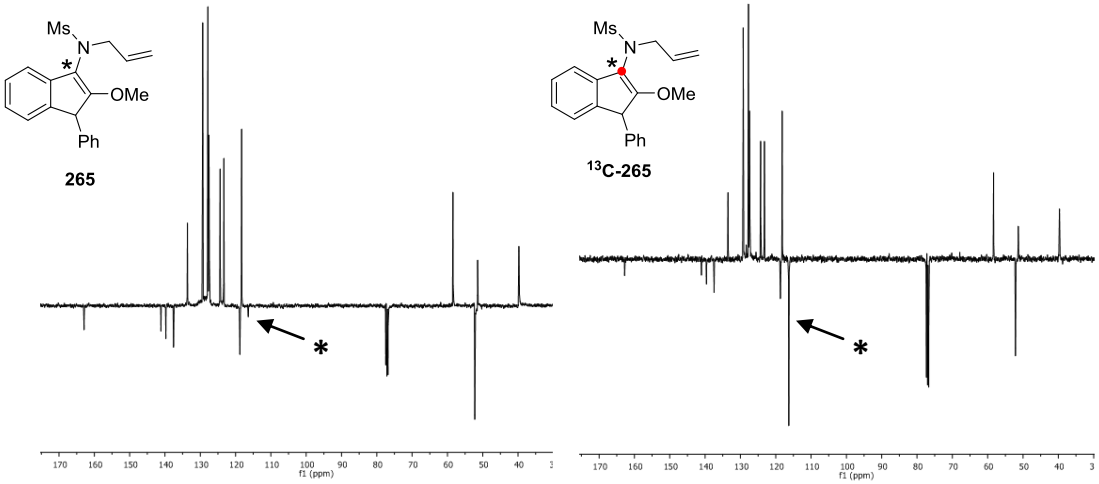


Figure 2: ^{13}C-NMR spectra of 265 and ^{13}C-265

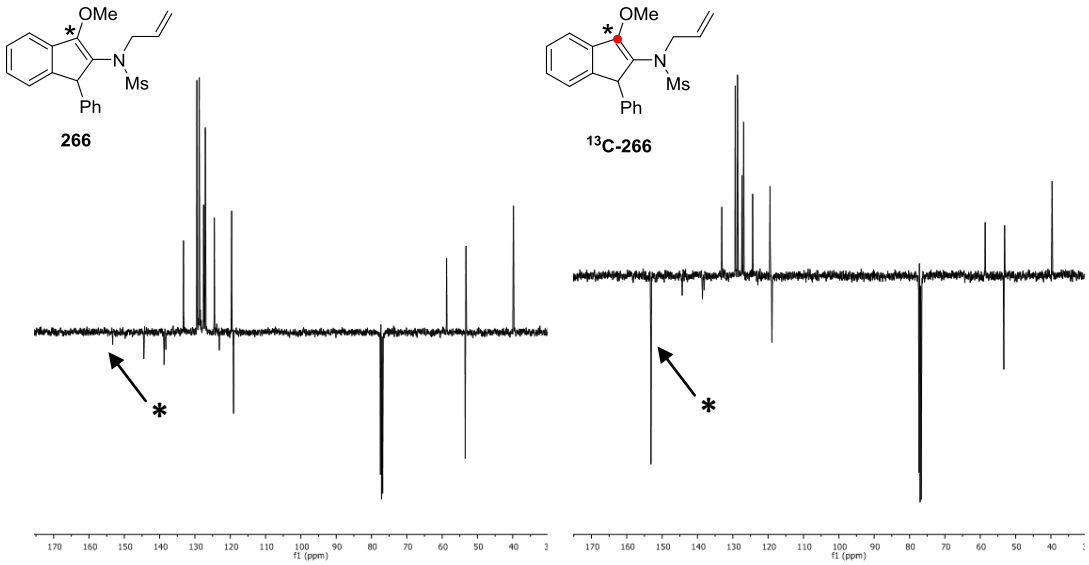
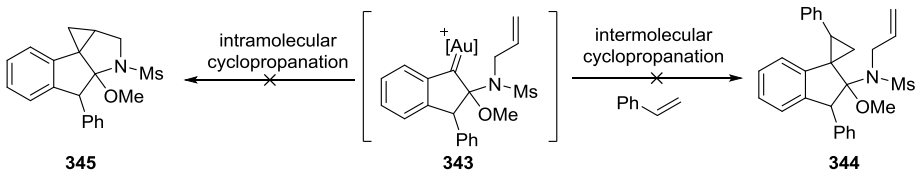


Figure 3: ^{13}C-NMR spectra of 266 and ^{13}C-266

While no intramolecular cyclopropanation had been seen, attempts to trap the gold carbene in an intramolecular fashion with an external olefin were similarly unsuccessful (Scheme 67). The rapid [1,2]-migrations can be attributed to the sterically congested nature of the gold carbene

intermediate, and perhaps more importantly the neighbouring group aided migration step (see below).



Scheme 67: Intra- and intermolecular cyclopropanation pathways from gold carbene 343

2.4.4 Origin of Selectivity for [1,2]-*N*-Migration

Whilst a clearer understanding of the mechanism had been obtained, the regioselectivity of nitrogen migration had not been addressed. As mentioned previously, the alternative regioisomer was proposed to arise from competitive 1,2-*O*-migration from the same gold carbene. When ynamides were employed with smaller nitrogen substituents, mixtures of isomers were observed (Figure 4). In the case of methyl substituted systems, there was almost no selectivity.

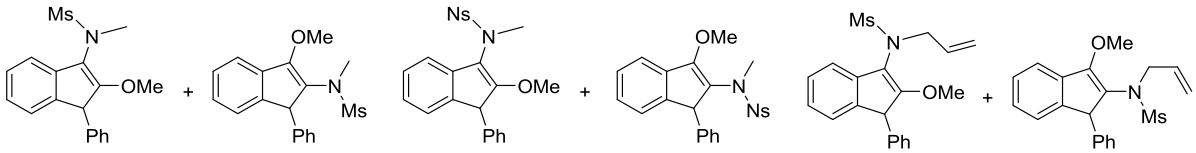
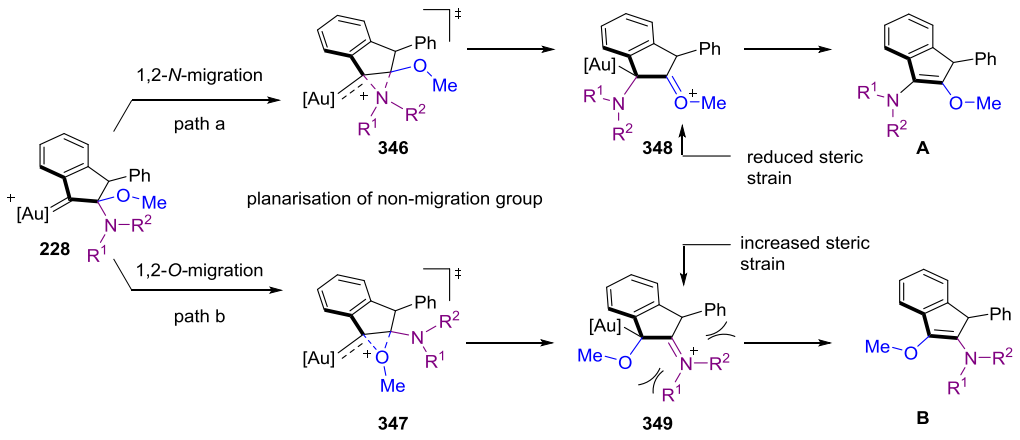


Figure 4: Loss of selectivity with smaller nitrogen substituents

These observations can begin to be rationalised by considering the gold carbene prior to migration (Scheme 68). [1,2]-Migration must proceed with planarisation of the non-migrating

group as sp^2-character at the α-carbon develops. If [1,2]-*N*-migration occurs, steric strain is minimised by formation of oxonium **348** (Scheme 68, path a). In contrast, if [1,2]-*O*-migration occurs, substantial steric strain would arise as the larger nitrogen substituents are forced into the plane (**349**, Scheme 68, path b). This pathway is therefore largely disfavoured due to the high energy intermediates involved.

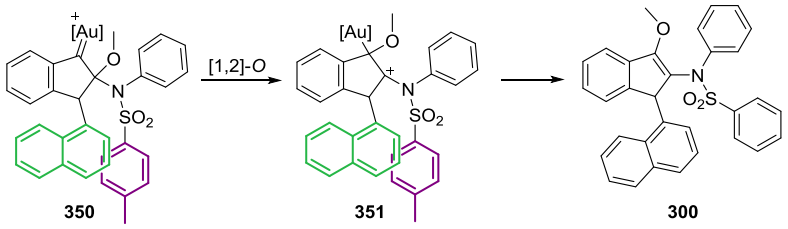
This model can therefore be used to explain why erosion of selectivity is observed for substrates containing smaller *N*-substituents. A planar configuration **349** can be more easily adopted in these cases meaning pathway b is less disfavoured. Regioisomers **B** could potentially result from an initial *exo*-mode cyclisation, however, this pathway seems an unlikely scenario for smaller substituents when it is not observed with larger groups.



Scheme 68: Rationalisation of regioselectivity

Larger aromatic substituents at the benzylic position were also observed to reduce the selectivity when aromatic nitrogen substituents were also employed (*vide supra*, Scheme 58). π-

Stacking and through-space interactions with the *N*-phenyl-tolyl sulfonamide may help to stabilise the intermediate **349**/**351**, therefore lowering the energy barrier for *O*-migration (Scheme 69).

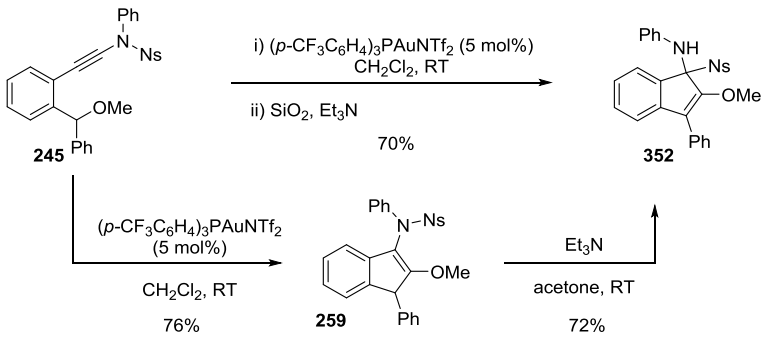


Scheme 69: Possible π- and through-space interactions behind the formation of regioisomer 300

As well as a model based purely on the development steric strain, the greater ability of nitrogen to stabilise the build up of positive charge during migration, as compared to oxygen, would also expect to contribute to the observed selectivity (**346** versus **347**).

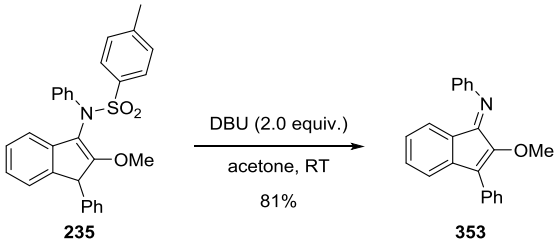
2.4.5 Derivatisation of Products

The functionalised indene products were found to be sensitive to basic conditions. On purification of the product arising from cycloisomerisation of ynamide **245**, triethylamine was added to the eluent in order to improve chromatographic separation. Instead of the expected indene **259**, novel C-sulfonylated indene **352** was instead isolated in good yield (Scheme 70). **352** Could be deliberately prepared in comparable yield on isolation of **259** and treatment with triethylamine.



Scheme 70 Synthesis of C-sulfonylated indene 352

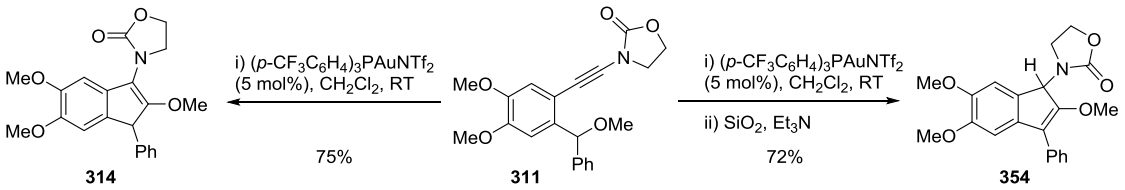
Interestingly, the tosylated variant **235** did not undergo rearrangement in the presence of triethylamine. When a stronger base, (DBU) was used however, α-alkoxy conjugated imine **353** was isolated in high yield from expulsion of the sulfonyl group, (Scheme 71). For the nosyl protected indene **259**, the same elimination mechanism is thought to occur, likely assisted by the adjacent methoxy group, although the electron poor sulfonyl should act as a better leaving group and so a milder base is sufficient. Formation of C-sulfonylated indene **352** likely occurs though attack of the sulfonyl anion onto the electrophilic centre of the imine.



Scheme 71: Formation of α-alkoxy conjugated imine 353. (DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene)

The reason behind the difference in reactivity between the two substrates is not completely clear, as we might expect the more electron-rich tosyl group to behave as a better nucleophile

for the imine. Coordination of the tosyl anion to the conjugate acid of DBU may hinder this second step. The X-ray crystal structure of **235** (Figure 1) shows the N-S bond of the sulfonyl aligned with the enol π-system, which may help to explain the ready elimination of this group. Similar base lability was observed when oxazolidinone-substituted indene **314**, generated from ynamide **311** was exposed to triethylamine on purification by column chromatography (Scheme 72). Indene **354** arising from double bond migration was isolated in good yield.

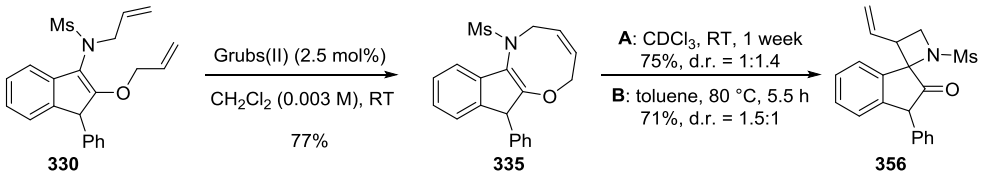


Scheme 72: Formation of indene 354 arising from base-mediated double bond migration

Bis-allylated indene **330** was subjected to ring closing metathesis to generate the unusual, not previously reported tricylic oxazocine core **355** (Scheme 73). Only one isomer was formed in the ring closing reaction, and while the (*E*)/(*Z*) stereochemistry could not be unequivocally confirmed due to broadened and overlapping signals in the ^{1}H-NMR spectrum, it seems reasonable to assume that this would be the (*Z*)-isomer, based on previous reports of formation of 8-membered rings by ring closing metathesis reactions.[78]

On standing in chloroform at room temperature, clean rearrangement of the 8-membered ring was observed over the course of one week to give synthetically valuable vinyl azetidine **356** as a 1:1.4 mixture of diastereoisomers in 75% yield. When **355** was heated in toluene for 5.5 hours, the vinyl azetidine **356** was isolated in 71% yield, however in this case the ratio of

diastereoisomers was 1.5:1. The actual reaction time required for conversion at this temperature is uncertain as it was not possible to follow the reaction by TLC.

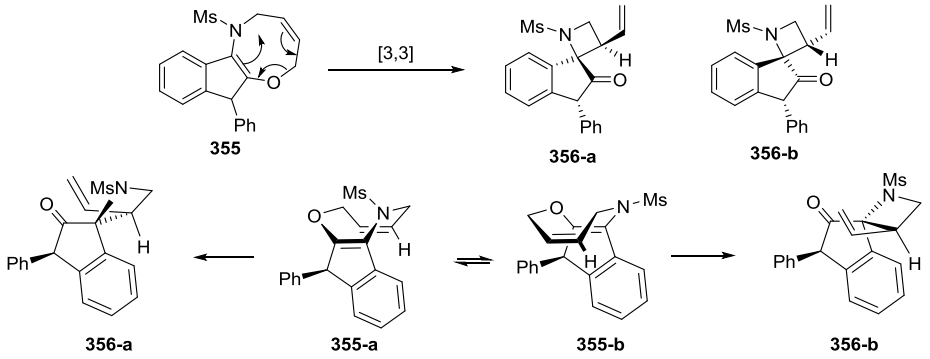


Scheme 73: Ring closing metathesis reaction to form oxazocine 335 and subsequent rearrangement. Grubbs(II) = (1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium

This unusual transformation is thought to proceed through a [3,3]-Claisen rearrangement which sets the relative stereochemistry of the two stereogenic centres of the azetidine ring (Scheme 74). Providing the assumption of a (*Z*)-double bond is correct, the oxazocine ring of **335** is expected to adopt a boat-type conformation with alignment of the two double bonds (**355-a** or **355-b**) (Shown in an untwisted form for simplicity, following Hedberg's analysis of cyclooctadiene).[79] This conformation would bring the reactive molecular orbitals into alignment, allowing carbon-carbon bond formation to occur. As the benzylic carbon is also stereogenic, two diastereoisomers are formed with a *cis*-relationship between the vinyl group and the C-O σ-bond. Formation of **356-a** or **356-b** would arise from reaction through one of the two boat conformations **355-a** or **355-b** shown in Scheme 74. Unfortunately, it was not possible to assign the two isomers by nOe experiment due to overlapping resonances.

This analysis assumes that the formation of a boat-like conformation can be adopted with a formally sp^2-nitrogen centre in the ring. Based on the X-ray crystal structures of related indene

precursors (Figure 1), this centre does not appear to be planar, with the nitrogen resonance-decoupled from the C-C π-system. The ready elimination of the sulfonyl group of **259** under mildly basic conditions was also attributed to this observation (Scheme 70).



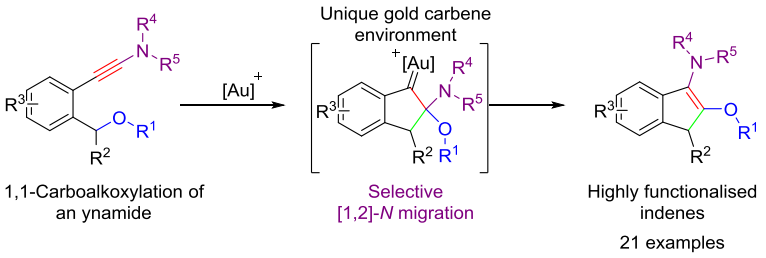
Scheme 74: Formation of vinyl azetidine 356 from oxazocine 355

This transformation would be expected to be irreversible due to the formation of a strong carbonyl-oxygen double bond and so discussion into the formation of kinetic and thermodynamic products is inappropriate. The difference in selectivity observed when a polar solvent is employed at room temperature as compared to the use of a non-polar solvent at high temperature might suggest different mechanisms are in operation. Optimisation of reaction conditions could potentially lead to selective access to either diastereoisomer.

Azetidines are valuable *N*-heterocyclic cores due to their valuable biological properties and use as synthetic intermediates.[80,81] Routes towards these motifs are somewhat limited however, as ring strain makes synthesis more challenging. The ability to access these rare motifs through rearrangement of 8-membered oxazocines could potentially lead to new and exciting methodologies.

2.5 Summary and Conclusions

The generation of gold carbene intermediates directly from ynamides through a 1,1-carboalkylation process has been realised. Adding a valuable contribution to a field dominated by alkyne carbofunctionalisations, a novel series of ynamides have been successfully implemented to control the regioselectivity of initial cyclisation, thereby forcing an alternative reaction pathway (Scheme 75).



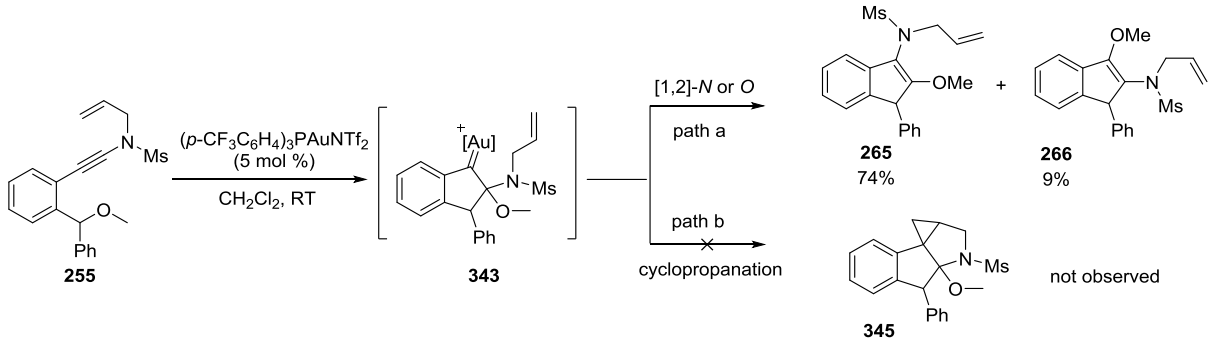
Scheme 75: Formation of functionalised indenes *via* a gold carbene generated from an ynamide

This work represents a novel skeletal rearrangement, invoking a unique α-hemiaminal ether gold carbene and previously unknown, regioselective [1,2]-nitrogen migration onto a gold carbene. The [1,2]-shift pathway has been confirmed by isotopic labelling. Generally high selectivity has been observed for nitrogen migration and a model has been proposed to rationalise this based on developing steric congestion of the carbene intermediate. Several of the indene products have been further elaborated to generate interesting carbo- and heterocyclic cores.

Chapter 3: Gold-Catalysed Polycyclisation of *N*-Allyl Ynamides Initiated by [1,5]-Hydride Transfer

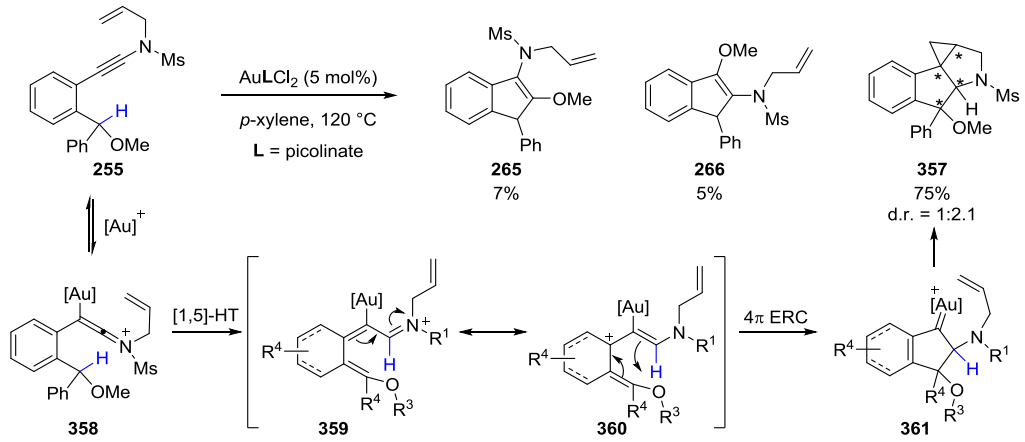
3.1 Introduction

As mentioned in Chapter 2, attempts to trap gold carbene **343**, generated from the 1,1-carboalkoxylation of ynamide **255** in an intermolecular fashion were unsuccessful. Similarly, intramolecular trapping of the carbene with a tethered *N*-allyl moiety to generate cyclopropane **345** was not observed (Scheme 76, path b), indicating that the 1,2-*N*-migration is a favourable and rapid process under these conditions (Scheme 76, path a).



Scheme 76: Potential pathways for gold carbene 343

Reaction conditions were therefore explored to promote intramolecular cyclopropanation using *N*-allyl ynamide **255**. After some study (*vide infra*) it was discovered that when the Au(III) precatalyst Au**L**Cl_2 (**L** = picolinate) was employed at high temperature, a new tetracyclic product **357** was generated in good yield as a mixture of diastereisomers, alongside small quantities of the carboalkoxylation products **265** and **266** (Scheme 77). On analysis of ^{1}H- and ^{13}C-2D-NMR spectroscopic data and later, of X-ray crystallographic data, it became clear that the new tetracycle observed was not the product predicted from a carboalkoxylation-based process (**345**).



Scheme 77: Formation of novel tetracycle 357 through a [1,5]-hydride transfer / cyclisation cascade

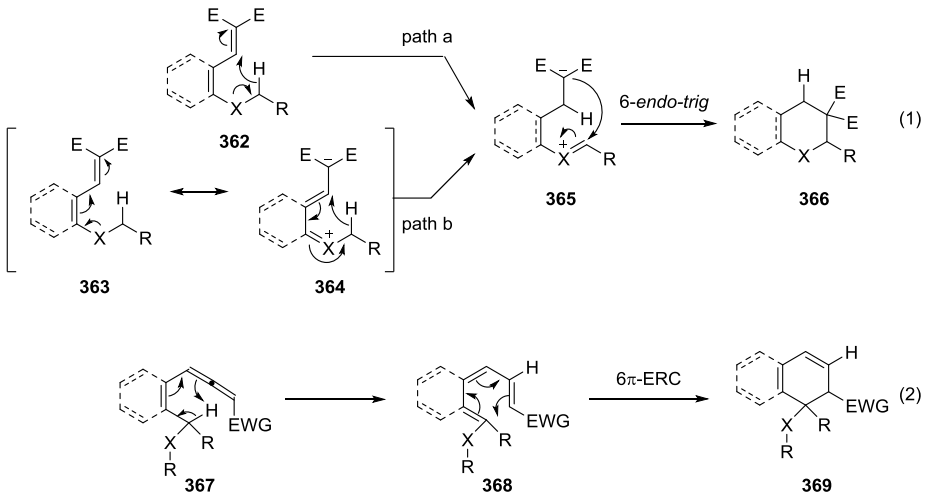
It was proposed that the tetracyclic product **357** was generated through an alternative gold carbene **361**, formed through a [1,5]-sigmatropic hydride transfer onto the gold-keteneiminium ion **358** and 4π-electrocyclisation (**360**→**361**). Subsequent cyclopropanation of the tethered alkene would provide the observed tetracyclic product.

This transformation is distinct from previous examples of [1,5]-hydride transfer / cyclisation methodologies and generates a complex 3D structure from a relatively simple ynamide. Three new carbon-carbon bonds and four contiguous stereocentres (shown by *), two of which are quaternary carbon centres, are formed in a single step. The scope and mechanism of this novel transformation will be discussed alongside relevant examples from the literature.

3.2 [1,5]-Hydride Transfer / Cyclisation Reactions

Hydride transfer reactions provide powerful and flexible methods for the activation of sp^3-CH bonds.[82] These types of reactions provide a valuable contribution to the rapidly emerging field of CH-activation and are complementary to methods whereby a transition metal inserts directly into a C-H σ-bond. The ability to activate CH bonds allows new retrosynthetic disconnections to be realised and while progress in the field is beginning to gather pace, selective functionalisation of 'inert' sp^3-CH bonds remains one of the greatest challenges in modern synthetic organic chemistry.[83]

Generally accepted proposals for [1,5]-migration / cyclisation mechanisms are depicted below (Scheme 78). Zwitterionic intermediate **365** may be generated by [1,5]-through-space migration of a hydride anion (path a). Alternatively, charge separated resonance form **364** may be invoked which can undergo [1,5]-sigmatropic hydrogen shift (path b). Cyclisation of **365** in a 6-*endo*-trig fashion generates the 6-membered heterocycles **366** (Scheme 78, Eq. [1]).



Scheme 78: Modes of [1,5]-hydride shift and subsequent cyclisation pathways

[1,5]-Sigmatropic hydride migration can also be envisaged (Scheme 78, Eq. [2]) as shown for allenic system **367**. In this case, there is no formation of charges and cyclisation of the conjugated intermediate **368** occurs though a 6π-electrocyclic ring closure (ERC) to give **369**. The reactions discussed below generally follow one of these proposed reaction pathways.

Intramolecular hydride transfer reactions generally involve Lewis acid, π-acid or thermal activation and evolve along different pathways depending on the connectivity of the hydride donor and acceptor components of the substrate. An extensive review in the area of [1,*n*]-hydrogen transfer / cyclisation processes was very recently published by Wang and Xiao.[84] Various hydride acceptors such as activated alkenes, alkynes and allenes have been explored in recent years, as well as variations of the hydride donor. The examples described in this section are ordered based upon the type of acceptor employed and only focus on selected, relevant examples. Whilst [1,4]-[85],[1,6]-[86] and other modes of hydride shift have been reported, the

examples here will focus on reactions involving the most commonly encountered [1,5]-hydride shift, and subsequent cyclisation for the generation of hetero- and carbocycles.

3.2.1 Hydride Donors

In order to increase hydride donating ability, the carbon donor will usually contain an α-heteroatom which can stabilise developing cationic character at the migrating centre through p-orbital overlap. Historically, this has been realised in ring closing reactions using aniline substrates, taking advantage of the so called '*tert*-amino effect.'[87] The second purpose of the heteroatom is to increase hydridic character by polarising and weakening the C-H bond, a factor important in both cationic and sigmatropic mechanisms.[84,88,89] A number of examples have also been described in which an α-aryl group was sufficient to promote the migration. In fact, the use of a sterically restricted aliphatic system has been recently reported to undergo hydride transfer under gold catalysis (*vide infra*). Figure 5 shows the relative efficiencies of heteroatoms, aryl and *tert*-alkyl groups to stabilise adjacent carbocations.[84]

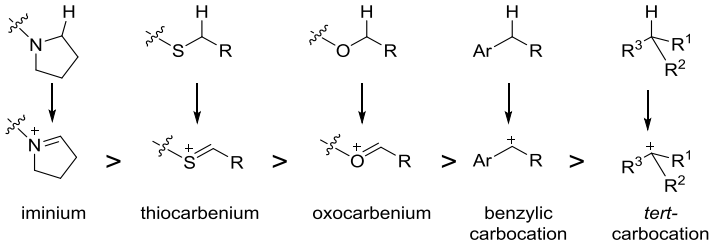


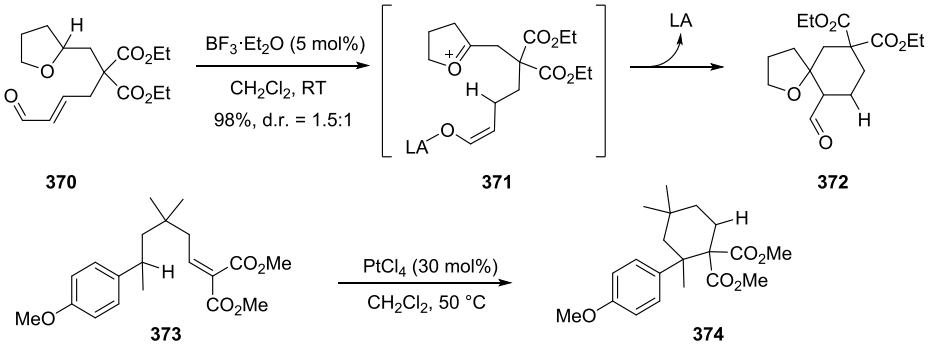
Figure 5: Stabilisation of α-carbocations on hydride migration

Whether the migration step is sigmatropic or through-space depends on the type of the substrate. A suitable distance between the donor and acceptor moieties is crucial for efficient hydride transfer. Popular substrates are therefore *ortho*-substituted aromatics.

3.2.2 Hydride Acceptors

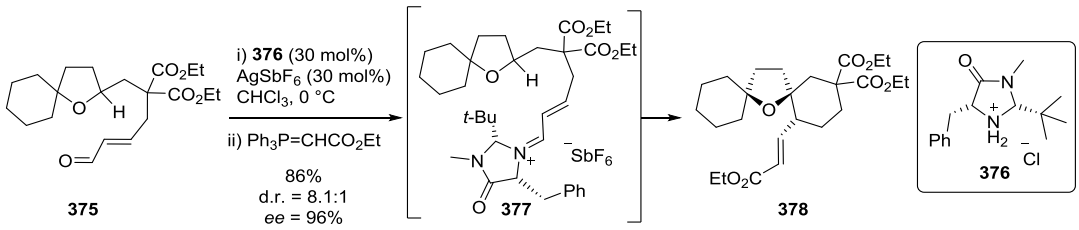
3.2.2.1 Electron Deficient Alkenes

Sames reported the first example of through-space [1,5]-hydride transfer of non-conjugated systems with activated alkenes through a Lewis acid-catalysed hydroalkylation (Scheme 79).[90] α,β-Unsaturated aldehyde acceptors were tethered to tetrahydropyran, -furan and -pyrrole donors by an alkyl chain. Spirocyclic ethers **372** and amides were accessed in high yields through [1,5]-hydride transfer and 6-*endo*-trig cyclisation of intermediates such as **371**. A range of Lewis acid catalysts were found to be active for this transformation and the reactions were conducted at room temperature. Sames also demonstrated the use of alkylidene malonate **373** with a benzylic C-H donor to generate cyclohexene derivative **374**, although in this case, a Pt catalyst and an elevated temperature were essential.



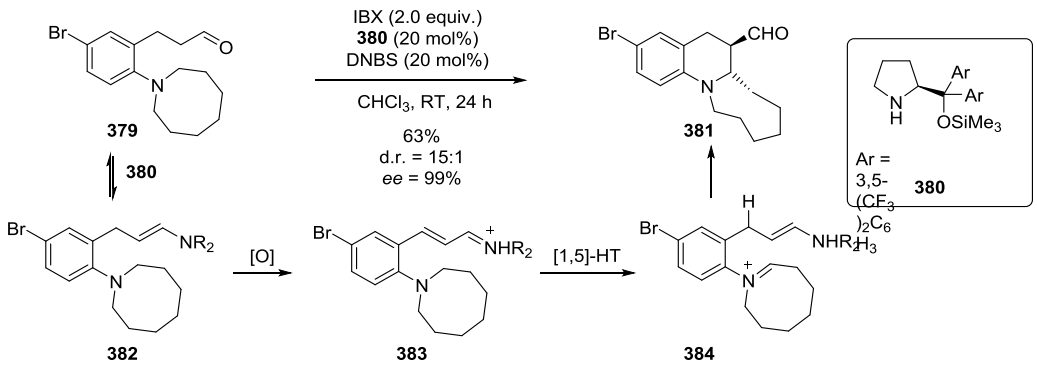
Scheme 79: Synthesis of spirocyclic ethers and cyclohexanes by through-space [1,5]-hydride shift

Several years later Tu and co-workers developed an enantioselective variant of Sames' seminal work in the synthesis of spiroethers with high enantiopurity (Scheme 80).[91] α,β-Unsaturated aldehydes such as **375** were converted *in situ* into iminium ion-activated hydride acceptors (**377**) using a chiral organocatalyst **376**. In order to measure the *ee* values, the aldehyde products were converted directly to the corresponding unsaturated ethyl esters **378** using a Wittig reaction.



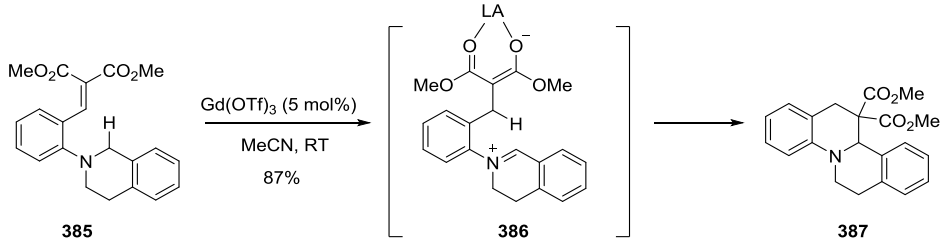
Scheme 80: Use of a chiral organocatalyst to generate enantiopure spiroethers

In related work, Kim and co-workers recently reported enantioselective oxidative enamine catalysis for the synthesis of tetrahydroquinolines **381** (Scheme 81).[92] α,β-Unsaturated iminium species **383** were generated from aldehydes such as **379** through *in situ* reaction with the amine organocatalyst **380** and subsequent oxidation using IBX. Following [1,5]-hydride transfer, the enantioselectivity was determined upon ring closure, controlled by the bulky amine catalyst.



Scheme 81: Enantioselective organocatalytic synthesis of tetrahydroquinolines from aldehydes (IBX: 2-Iodoxybenzoic acid, DNBS: 2,4-dinitrobenzene sulfonic acid)

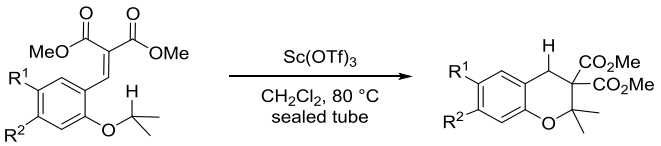
Alkylidene and benzylidine malonates are highly activated systems towards [1,5]-hydride transfer due to the polarisation of the olefin. Seidel and co-workers reported the synthesis of a range of polycyclic tetrahydroquinolines such as **387** using $Gd(OTf)_3$ as a chelating Lewis acid catalyst, without the need for harsh conditions (Scheme 82).[87,93] The tertiary amine stabilises the carbocation **386** formed on [1,5]-hydride transfer and the dipolar intermediate undergoes ready cyclisation. Luo and co-workers recently developed an enantioselective version of this reaction in which magnesium salts were employed alongside a chiral phosphoric acid.[94]



Scheme 82: [1,5]-Hydride shift using a chelating Lewis acid catalyst

A later report by Sames and co-workers detailed the synthesis of benzopyrans in a similar fashion from benzylidene malonates using catalytic $Sc(OTf)_3$ (Scheme 83).[95] The substitution

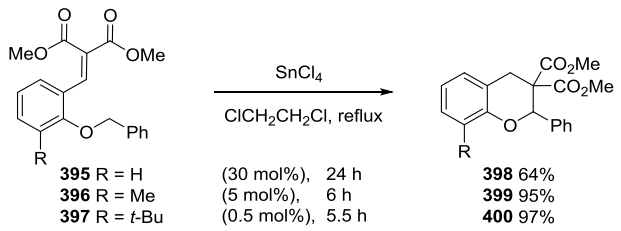
pattern around the benzene ring was found to greatly influence the reactivity. When a methoxy group was installed *para*- to the donor group (**388**), resonance stabilisation of the developing oxocarbenium ion accelerated the reaction. In contrast, a methoxy substituent *para*- to the acceptor group (**389**) reduced the rate and yield of the reaction and required a higher catalyst loading. This is in agreement with the decreased ability of a more electron rich alkene to accept a hydride. Bromide substitution *meta*- to the hydride acceptor had no effect on the yield of **394**, however no reaction took place when bromide was incorporated *meta*- to the donor (**391**).



388 R^1 = OMe, R^2 = H	(10 mol%), 12 h	**392** 95%
389 R^1 = H, R^2 = OMe	(50 mol%), 60 h	**393** 56%
390 R^1 = Br, R^2 = H	(10 mol%), 36 h	**394** 95%
391 R^1 = H, R^2 = Br	(10 mol%), 96 h	--

Scheme 83: Effect of electron donating and electron withdrawing substituents on the [1,5]-hydride shift

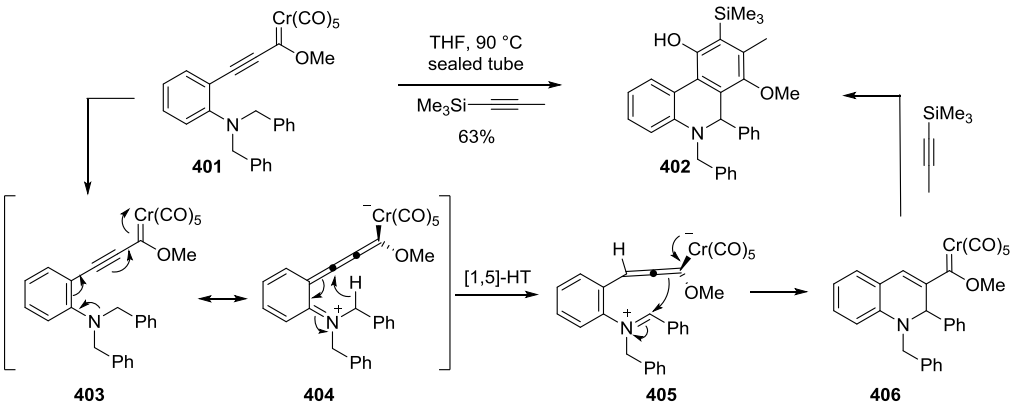
Akiyama and co-workers observed an interesting steric effect in their synthesis of benzopyrans from benzylic ethers catalysed by $SnCl_4$ (Scheme 84).[96] On installation of substituents *ortho*- to the benzyl ether donor (**395**-**397**), reactivity was greatly enhanced compared to unsubstituted systems. This can be rationalised by the donor and acceptor reactive partners being forced into closer spatial proximity, reducing the energy barrier for migration. The effect was most pronounced for *tert*-butyl substituents (**398**-**400**).



Scheme 84: Effect of *ortho*-substituents on [1,5]-hydride transfer

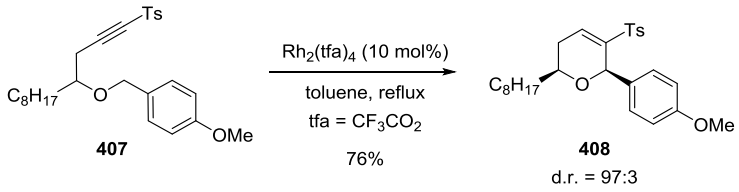
3.2.2.2 Alkynes as Hydride Acceptors

Barluenga and co-workers published the first example of a [1,5]-hydride transfer / cyclisation reaction using carbon-carbon triple bonds in their work on alkynyl Fischer carbenes.[97] A range of stable 1,2-dihydroquinolinyl carbene complexes such as **406** were synthesised in high yields (Scheme 85). The addition of alkynes to the reaction mixture gave rise to the Dötz benzannulation products **402**, adding a further dimension of complexity to the one-pot cascade. The strongly electron-withdrawing properties of the chromium carbene **401**, (**403**→**404**) overcame the high energy barrier associated with 1,5-hydride transfer.[82] Furthermore, DFT calculations confirmed the cleavage of the C-H bond as the rate determining step (**404**→**405**), with the subsequent cyclisation being of low energy.



Scheme 85: Use of 1,2-dihydroquinolinyl chromium carbenes to promote a [1,5]-hydride shift

Sulfonylated alkynyl ethers **407** have been employed in the synthesis of dihydropyrans **408** using rhodium catalysis by Urabe and co-workers (Scheme 86).[98] The sulfonyl substitution was found to be crucial as terminal, internal and even α,β-unsaturated carboxylic ester substituted alkynes did not undergo the desired transformation. The intramolecular migration of a benzylic proton was confirmed by deuterium labelling.

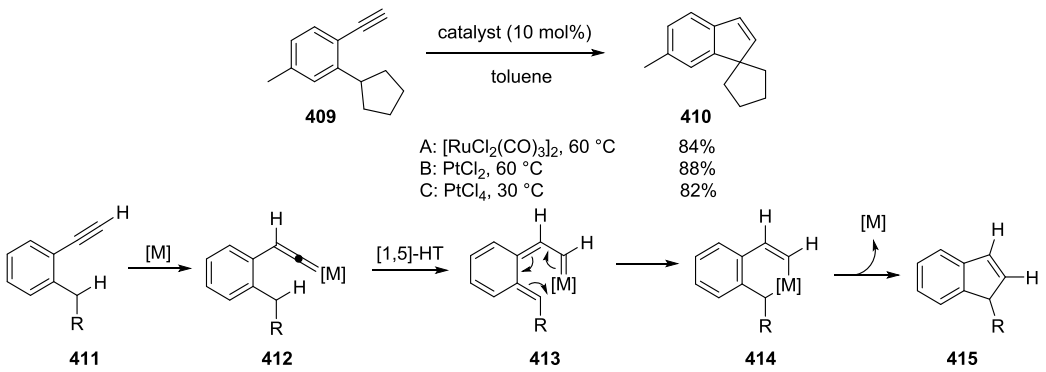


Scheme 86: Use of sulfonylated alkynes to promote a [1,5]-hydride shift

The use of electronically unbiased alkynes as hydride acceptors was found to require a transition metal catalyst for sufficient activation of the system. The first examples of the use of unactivated alkynes as hydride acceptors focussed on aromatic substrates, generating substituted indenes through the [1,5]-hydride transfer / cyclisation of ethynyl substituted benzenes.

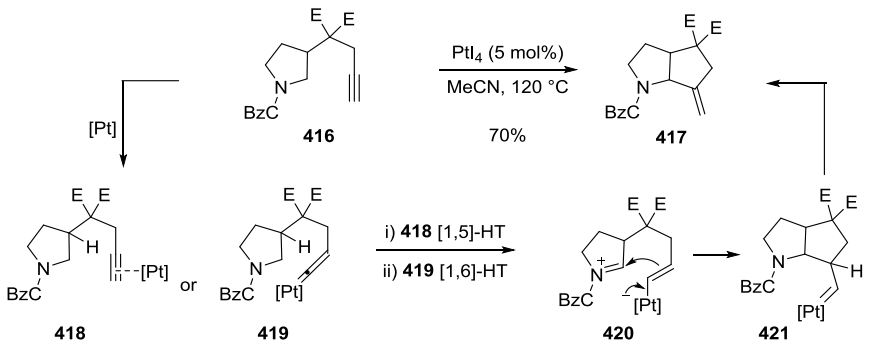
Examples of Pt- and Ru-catalysed reactions have been reported which generally invoke the formation of a metal vinylidene species. These species could potentially evolve through insertion of the vinylidene into the benzylic CH-bond[99] or through a [1,5]-hydride transfer / cyclisation pathway.[100,101] In the latter case (Scheme 87), a likely mechanism would involve the formation of a metallocycle **414**, formed by electrocyclisation of the metal carbene **413**, which then demetallates to give the indene product **415**. The metal carbene **413** could also be

envisaged as a metal stabilised carbocation which might undergo 4π-electrocyclic ring closure to give the 5-membered indene directly.



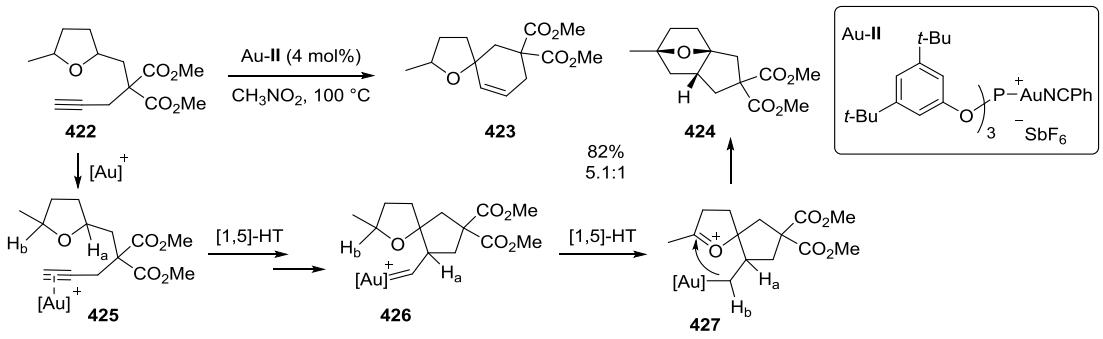
Scheme 87: [1,5]-Hydride shift invoking a metal vinylidene intermediate by Chatini and co-workers

Having been previously limited to aromatic alkynyl substrates, Sames and co-workers reported α-alkenylation of cyclic ethers and amides linked to terminal alkynes at the C-3 position (**416**, Scheme 88).[102] This work was the first to demonstrate through-space [1,5]-hydride transfer using terminal alkynes and gave exclusively 5-*exo*-alkenylation products such as **417**. PtI_4 was found to be superior to other platinum halide catalysts due to its higher Lewis acidity, whilst gold salts did not promote the reaction effectively. A [1,6]-hydride transfer mechanism, following formation of a Pt vinylidene species **419**, was also suggested. Deuterium labelling studies with a related substrate provided evidence for an intramolecular hydride shift but could not distinguish between the formation of the two possible intermediates **418** and **419**. Amides linked at the C-2 position of the ring also underwent reaction, however the tetrahydrofuran equivalents required the less active K_2PtCl_4 as a catalyst to prevent decomposition of starting material.



Scheme 88: Formation of 5-*exo*-alkenylation products by α-alkylation of a cyclic amide

Soon after this Gagosz and co-workers reported their work on these substrates with the use of electron rich gold(I) catalysts (Scheme 89).[103] They found that cyclisation of tetrahydrofurans and dioxolanes linked at the 2-position was selective for 6-membered ring formation (**423**), with only traces of the isomeric 5-membered ring that was reported by Sames.

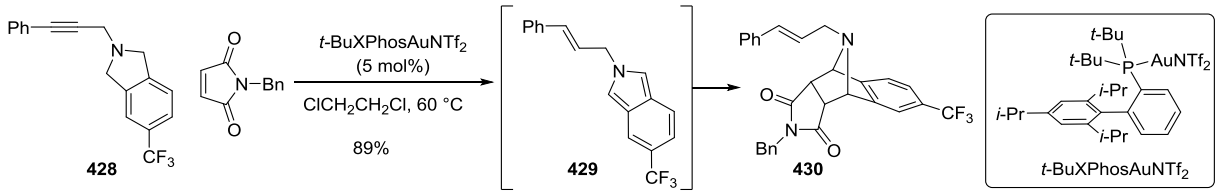


Scheme 89: Formation of alternative 6-membered rings in spiroether synthesis

Deuterium labelling studies supported the mechanism where [1,5]-hydride transfer occurs directly onto the activated alkyne instead of *via* formation of a gold vinylidene intermediate. Tricyclic compound **424** was also formed as the minor product by formal [3+2]-cycloaddition of the alkyne onto the tetrahydrofuran ring. The proposed mechanism is shown above whereby [1,5]-hydride transfer onto the gold-activated alkyne **425** generates a 5-membered ring **426**

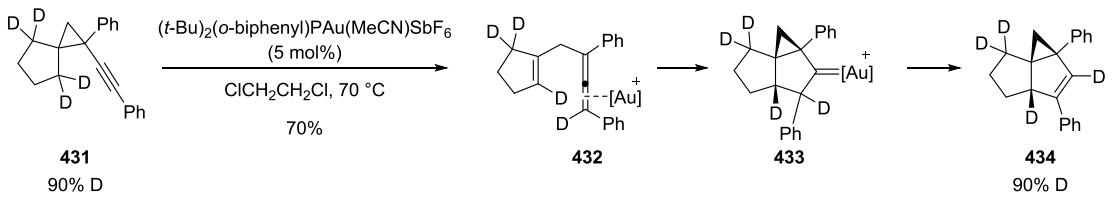
with an exocyclic gold carbene which might then undergo [1,5]-hydride transfer to generate oxonium **427**, cyclisation then forms the second ring of the tricycle **424**.

A very recent contribution employing internal unactivated alkynes as hydride acceptors was reported by Gong and co-workers (Scheme 90).[104] *N*-Cinnamylisoindole **429**, which was generated by a [1,5]-hydride transfer onto the gold-activated alkyne of **428** could be trapped in an intermolecular fashion with a variety of dienophiles to access complex polycyclic scaffolds such as **430** under mild reaction conditions.



Scheme 90: [1,5]-Hydride shift / Diels-Alder cascade

The examples discussed so far have involved transfer of a hydride which is assisted electronically by a neighbouring heteroatom or aryl substituent. Barluenga, Ballesteros and co-workers recently showed that this migration could also be promoted from a non-benzylic, aliphatic position by employing sterically restricted alkynylspirocyclopropanes such as **431** (Scheme 91), which brings together the reacting centres and helps to stabilise the carbocation formed on hydride migration.[105]

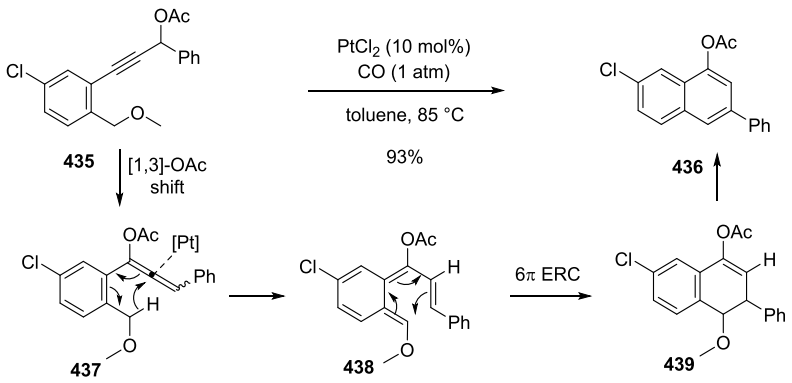


Scheme 91: [1,5]-Deuteride transfer in an aliphatic system

In the proposed mechanism, [1,5]-hydride / deuteride migration onto the gold-activated alkyne occurs with cleavage of the cyclopropane ring to give intermediate allene **432**. Cyclisation and 1,2-hydride insertion onto the gold carbene **433** gave tricycles **434**. As shown, complete deuterium incorporation was observed, demonstrating an intramolecular process. Under harsher conditions, tricycles such as **434** could be transformed into divergent products through gold-assisted ring opening of the newly formed cyclopropane.

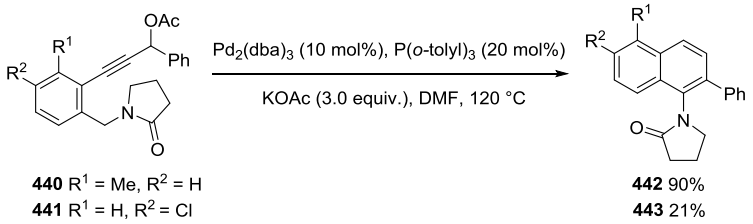
3.2.3.3 Allenes as Hydride Acceptors

Propargylic esters provide useful substrates for [1,5]-hydride shift / cyclisation. On exposure to a π-acid catalyst, such as gold and platinum, they undergo facile rearrangement,[106] generating allenyl-metal complexes which can act as hydride acceptors. Liang and co-workers were the first to describe a [1,5]-sigmatropic hydride shift using propagylic esters **435** under platinum catalysis (Scheme 92).[107] The resulting intermediate **438** underwent 6π-electrocyclic ring closure to generate **439**. Elimination of methanol was observed in most cases, generating aromatic naphthalenes (**436**).



Scheme 92: Rearrangement of propagylic esters to generate *in situ* allene acceptors

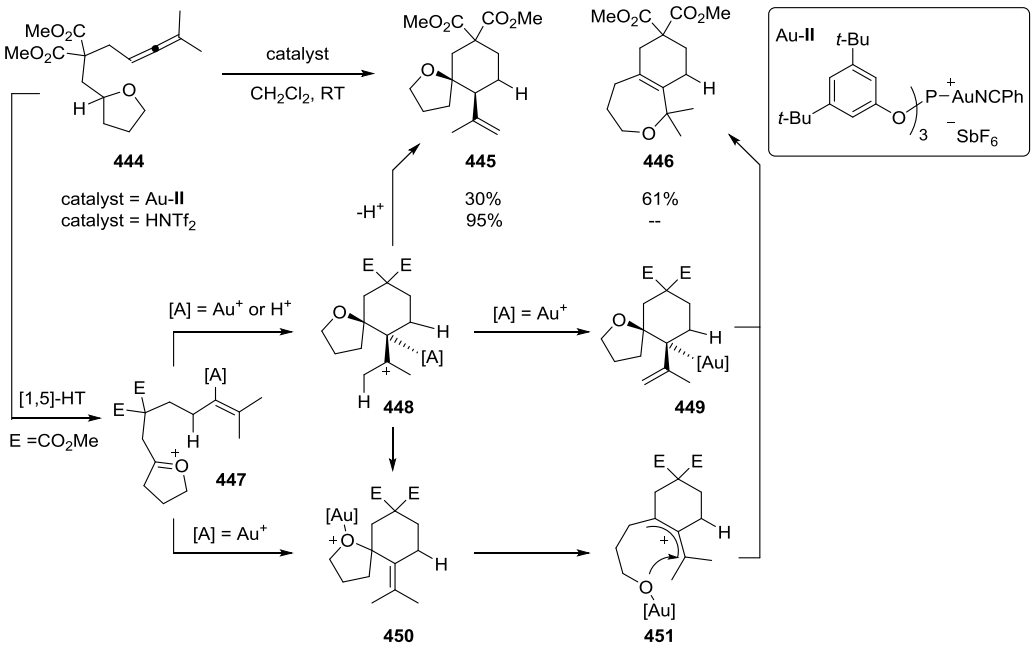
Due to the ready elimination of the heteroatom substituents used to aid hydride shift, this methodology is limited to the formation of naphthalene acetates. In a complementary study, the same group went on to develop a synthesis of naphthylamine derivatives under Pd catalysis (Scheme 93).[108] An *N*-acyl or *N*-sulfonyl group was essential for activation of the adjacent sp^3-CH bond, with a simple dimethylamine substituted system leading to complete decomposition of starting material. The addition of a methyl group to the benzene ring of **449** gave an excellent yield of naphthylamine **442**, however when a mildly electron withdrawing substituent was introduced (**441**), the yield dropped dramatically.



Scheme 93: Synthesis of naphthylamines using palladium catalysis (dba: dibenzylideneacetone)

The use of a tetrahydrofuran moiety as a hydride donor has previously been discussed with activated alkene and alkyne acceptors (*vide supra*). Gagosz and co-workers have also explored

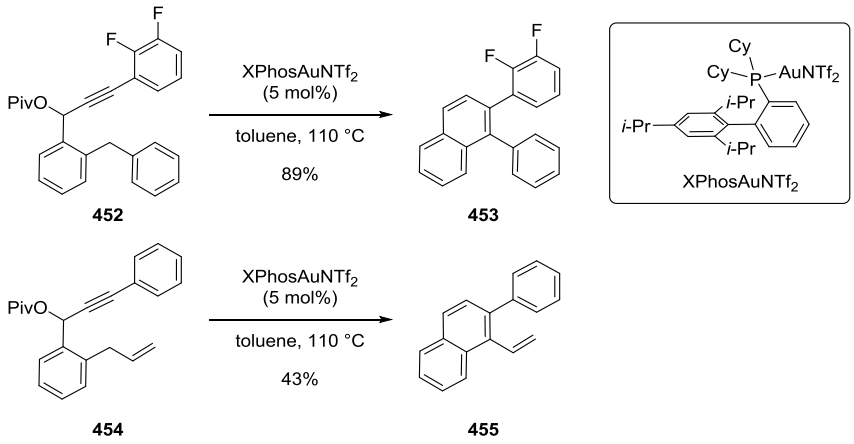
the application of these systems alongside allene acceptors to generate fused- and spiro-tetrahydrofurans and –pyrans (Scheme 94).[109] When optimising the reaction conditions for allenes of type **444**, interesting product divergence was observed depending on whether a Brønsted acid or gold catalyst was used. Whilst both products **445** and **446** arose following [1,5]-hydride transfer onto the proton- or gold-activated allene, the gold bound intermediate **448** could evolve through a number of stepwise processes giving rise to both **445** and **446**. Under Brønsted acid catalysis however, the regioselective loss of a proton from **448** gave rise selectively to the isopropenyl compound **445**.



Scheme 94: Product divergence under gold- or Brønsted acid-catalysis

Recently, Bandini and co-workers reported the gold-catalysed synthesis of substituted naphthalenes through the activation of benzhydryl sp^3-CH bonds (Scheme 95).[110] A [1,5]-hydride shift was proposed following gold-mediated rearrangement of the propagylic ester which then

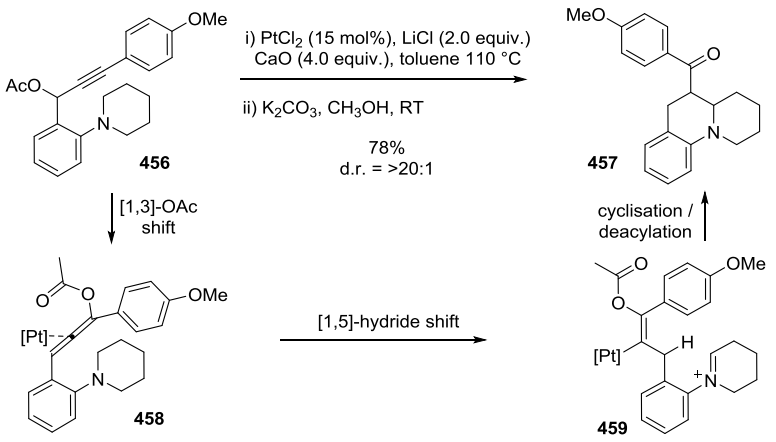
underwent cyclisation and aromatisation. As well as biaryl systems **452**, allylbenzene substrates **454** underwent the same reaction in moderate yield. Following deuterium labelling studies, the primary kinetic isotope effect was measured as k_H/k_D = 1.94 by ^{1}H-NMR spectroscopy, indicating that cleavage of the benzylic sp^3-CH bond is the turnover limiting step.



Scheme 95: [1,5]-Hydride transfer from benzhydryl sp^3-CH bonds

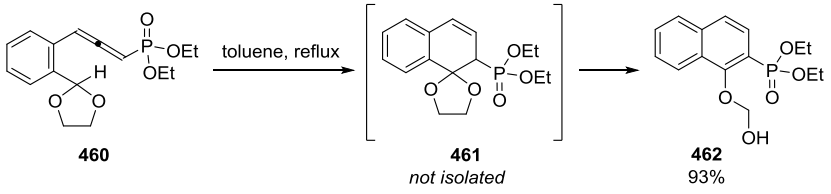
While the examples above feature [1,5]-hydride transfer onto the C-2 carbon of the allene, Liang and co-workers reported [1,5]-hydride transfer onto the C-1 carbon in the platinum-catalysed synthesis of ring-fused tetrahydroquinolines (Scheme 96).[111]

Hydride transfer onto the *in situ* formed allenyl acetate **458**, and subsequent cyclisation of iminium **459** is followed by deacylation to give stable products. LiCl as an additive was found to increase the yield and molecular sieves or CaO were also beneficial, presumably in order to reduce side products from hydrolysis of the acetate.



Scheme 96: Hydride transfer to the C-1 position of allene 456

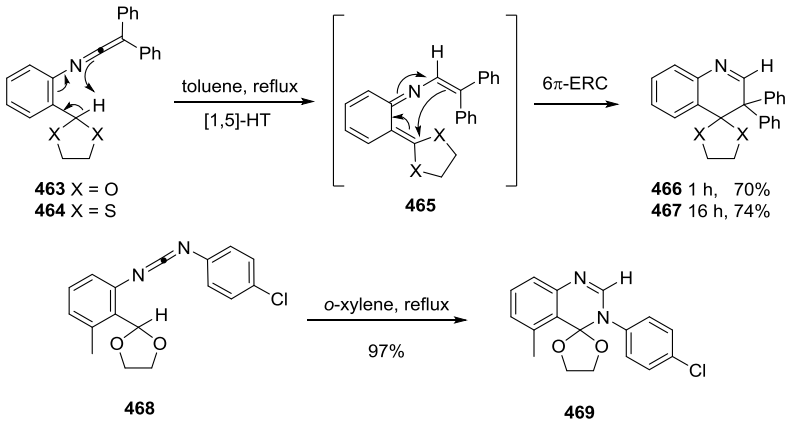
Alajarin, Vidal and Sánchez-Andrada recently showed that allenes could be sufficiently activated by electron withdrawing groups to participate in [1,5]-hydride shift reactions under thermal conditions (Scheme 97).[112] The proposed mechanism is in line with the group's previous work which will be discussed in the next section. In most cases the spirocycle **461** was not isolated due to favourable aromatisation and opening of the acetal to give naphthalenes such as **462**. Sulfonyl- and alkoxycarbonyl substituted allenes also could be generated *in situ* on exposure of the relevant alkynes to catalytic triethylamine in refluxing toluene, which then participated smoothly in the cascade reaction.



Scheme 97: Electron withdrawing group activation of allenes for [1,5]-hydride transfer

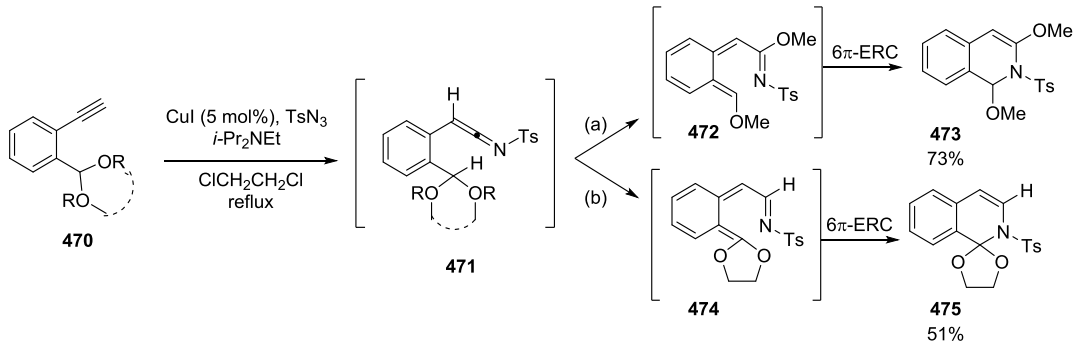
3.2.3.4 Ketenimines as Hydride Acceptors

Alajarin and Vidal have made significant contributions to the field using ketenimine (**463**, **464**) and carbodiimide (**468**) acceptors, both possessing an electrophilic central carbon.[89,113] They found that acetals and thioacetals promoted [1,5]-hydride shifts by behaving as hydride releasing fragments, allowing ready access to isoquinolines (**466**, **467**) using only thermal activation (Scheme 98). They proposed a [1,5]-sigmatropic hydride shift / 6π-electrocyclic ring closure mechanism throughout their work, where the hydride migration was the rate determining step. This was supported by detailed computational studies. Although carbodiimide substrates such as **468** required more forcing thermal conditions, the acetal system cleanly cyclised to give quinazoline **469** (Scheme 98). The corresponding dithioacetal did not react under these conditions. Triaryl methane units were also found to be suitable hydride donors, undergoing the cascade reaction in refluxing *ortho*-xylene.[114] In this work, the beneficial effect of a substituent *ortho*- to the donor group was also observed.



Scheme 98: Ketenimine and carbodiimide hydride acceptors

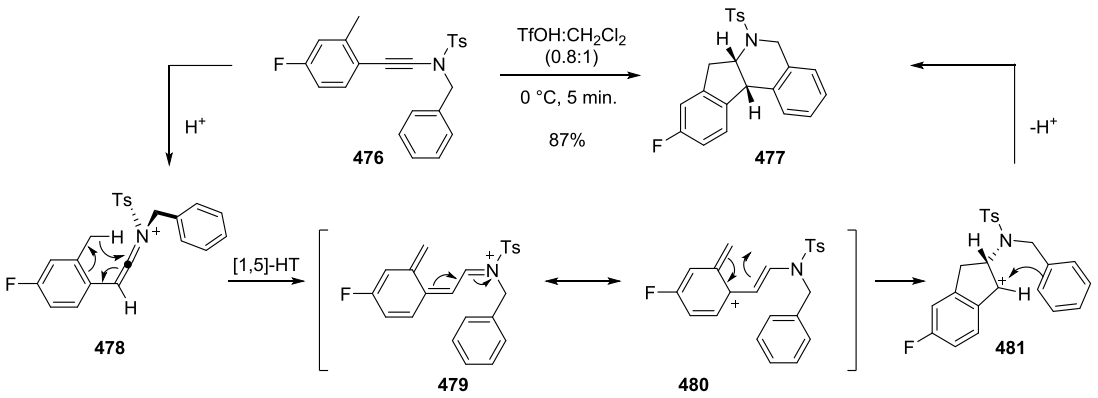
The synthesis of oxyisoquinolines **473** and **475** from *ortho*-ethynyl benzacetals **470** by the copper-catalysed *in situ* formation of C-aryl ketenimines **471** was recently published by Lu and Wang (Scheme 99).[115] When acyclic acetals were employed, a [1,5]-*O* shift of a methoxy group onto the C-aryl keteniminium was observed to give intermediate **472** (path a). With cyclic acetals however, a [1,5]-hydride shift prevailed to give imine intermediate **474** (path b). In both cases, 6π-electrocyclic ring closure was proposed to generate the oxyisoquinolines **473** and **475** in moderate to good yields.



Scheme 99: *In situ* formation of C-aryl ketenimine hydride acceptors

3.2.3.5 Keteniminium Ion Acceptors

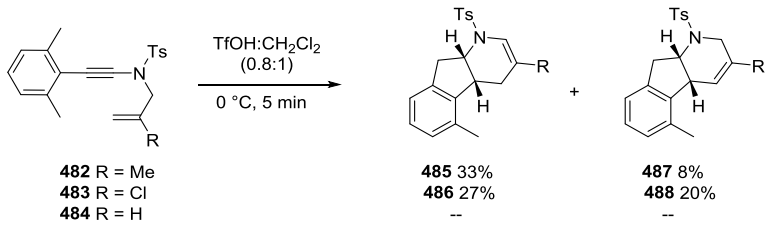
During the final stages of our own study, Evano and co-workers published the first example of keteniminium ion acceptors which were generated from treatment of simple ynamides using strong acids and resulted in a rapid polycyclisation (Scheme 100).[116] The mechanistic rationale behind this work draws several parallels to our own in which keteniminium formation is promoted by a gold catalyst (*vide infra*).



Scheme 100: Acid promoted polycyclisation of ynamides *via* a keteniminium ion

In this study, triflic acid or bistriflimide were employed to initiate the formation of the keteniminium intermediate **478** which is proposed to undergo a [1,5]-sigmatropic hydride shift to generate intermediate **479**. A Nazarov-type 4π-electrocyclisation from **480** would then give the first carbocycle. The resulting carbocation **481** could then react with the tethered benzyl group selectively on the lower face, giving the tetracyclic product **477** upon loss of a proton. In a deuterium labelling study, the preferential migration of hydride over deuteride suggested the presence of a kinetic isotope effect for this step.

Whilst high yields and complete diastereoselectivity were achieved, the strongly acidic reaction conditions limited the scope to simple aromatics. Some success was however achieved with allyl substituted ynamides. As expected, no reaction was observed with simple allyl groups (**484**), but polycyclisation took place when a substituted allyl group was employed (**482**, **483**, Scheme 101).



Scheme 101: Polycyclisation using *N*-allyl ynamides

3.2.4 Summary

[1,5]-Hydride transfer / cyclisation reactions have been demonstrated to be powerful processes, allowing functionalisation of 'inert' sp^3-CH bonds for the formation of pharmaceutically valuable carbo- and heterocycles. The formation of multiple new bonds is often achieved in a single step which allows for the rapid development of complexity from simple starting materials in an atom-economical fashion. The following section details the discovery and optimisation of a novel gold-catalysed [1,5]-hydride shift initiated polycyclisation to generate complex three-dimensional structures from simple ynamides.

3.3 Results and Discussion

3.3.1 Reaction Discovery and Optimisation

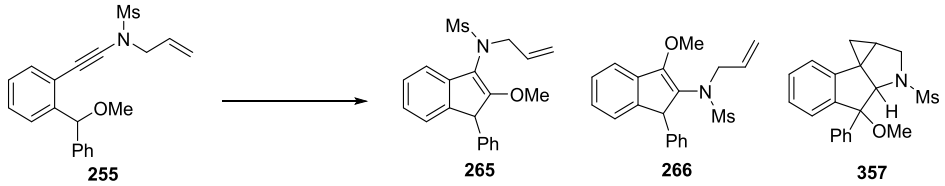
Following the initial discovery of the gold-catalysed [1,5]-hydride shift cascade reaction, a survey of reaction conditions was conducted to promote this pathway for ynamide **255** (Table 3). When phosphines bearing neutral or electron-deficient aryl groups were employed, only products of carboalkoxylation were observed (Table 3, Entries 1 and 2). The electron-rich biaryl phosphine ligand XPhos provided poor conversion of starting material, however resonances

typical of a cyclopropane ring system were visible in the ^{1}H-NMR spectrum (Table 3, Entry 3). Commercially available catalyst dichloro(picolinate)gold(III) (Au**L**Cl_2) gave full consumption of starting material, although only trace amounts of tetracycle **357** were observed, alongside indenes **265** and **266** from competing carboalkoxylation pathways (Table 3, Entry 4). The yield of **357** was not particularly influenced by the solvent used with this catalyst (Table 3, Entries 5-7). *N*-Heterocyclic carbene ligated IPrAuCl also failed to promote the desired reaction (Table 3, Entry 8). When ynamide **255** was heated with Au**L**Cl_2 in toluene however, the competing pathways were suppressed (Table 3, Entry 9). The choice of a less polar solvent appeared important at this temperature as the ratio of **357** to indenes **256** and **266** was eroded on using $MeNO_2$ under otherwise identical conditions (Table 3, Entry 10).

The formation of the undesired indenes could be reduced to low levels on heating in *m*-xylene at 120 °C to give tetracycle **357** in 75% as a 1:2.3 mixture of diastereoisomers (Table 3, Entry 13). Whilst the major diastereomer was isolated by column chromatography, the minor isomer could not be separated from indene **266**.

An alternative gold(III) source promoted the desired reaction at high temperature but less cleanly (Table 3, Entry 14). To ensure the gold catalyst was responsible for promoting the cascade, a test reaction was conducted in the absence of catalyst, at high temperature (Table 3, Entry 15). Starting material remained after 6 hours with the only product observed being a new isoquinoline product in 16% yield. The formation of this compound will be discussed in Chapter 4. Finally, the use of an alternative σ-Lewis acid led to complete degradation of the starting material (Table 3, Entry 16).

Table 3: Optimisation of reaction conditions[a]



Entry	Catalyst	Temp/°C	Solvent	**255**/%[b]	**265**/%[b]	**266**/%[b]	**357**/%[b]
1	(*p*-$CF_3C_6H_4$)AuCl/$AgNTf_2$	RT	CH_2Cl_2	--	74	9	--
2	PPh_3AuCl/$AgBF_4$	RT	CH_2Cl_2	13	16	--	--
3	XPhosAuCl/$AgNTf_2$	RT	CH_2Cl_2	54	--	13	7
4	Au**L**Cl_2[c]	RT	CH_2Cl_2	--	67	25	4
5	Au**L**Cl_2	RT	MeCN	--	52	21	6
6	Au**L**Cl_2	RT	THF	--	50	12	8
7	Au**L**Cl_2	RT	toluene	--	54	32	9
8	IPrAuCl/$AgNTf_2$	RT	toluene	--	60	30	trace
9	Au**L**Cl_2	80	toluene	--	21	7	61
10	Au**L**Cl_2	80	$MeNO_2$	--	45	19	9
11	Au**L**Cl_2	100	*p*-xylene	--	8	4	56
12	Au**L**Cl_2	100	toluene	--	11	6	66
13	Au**L**Cl_2	120	*p*-xylene	--	7	5	75
14	$AuBr_3$	120	*p*-xylene	--	8	4	48
15	None	120	*p*-xylene	23[d]	--	--	--
16	$BF_3{\cdot}OEt_2$	80	toluene	--	--	--	--

[a] Reaction conditions: 255 (0.1 mmol, 1.0 equiv.), catalyst (5 mol%), solvent (0.1 M), all reactions were stirred for 6 hours at the temperature indicated. [b] Yields calculated by ^{1}H-NMR spectroscopy against a known quantity of internal standard (1,2,4,5-tetramethylbenzene). [c] L=Picolinate. [d] 16% isoquinoline product observed. XPhos = 2-Dicyclohexylphosphino-2,4,6-triisopropylbiphenyl. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

A single crystal of the major diastereoisomer of tetracycle **357**, suitable for X-ray analysis was grown using a pentane / dichloromethane solvent system. The resulting structure shows that the migrated hydrogen is *syn* to the methylene group of the cyclopropane ring at the [5,5]-ring junction (Figure 6), with both groups also on the same face as the phenyl substituent at the benzylic position.

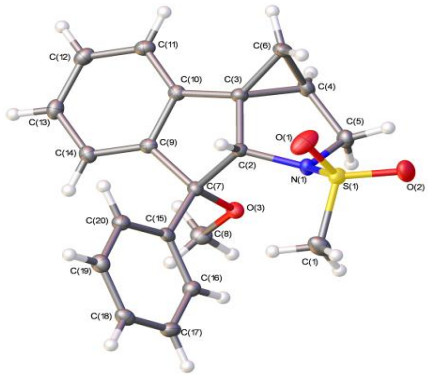
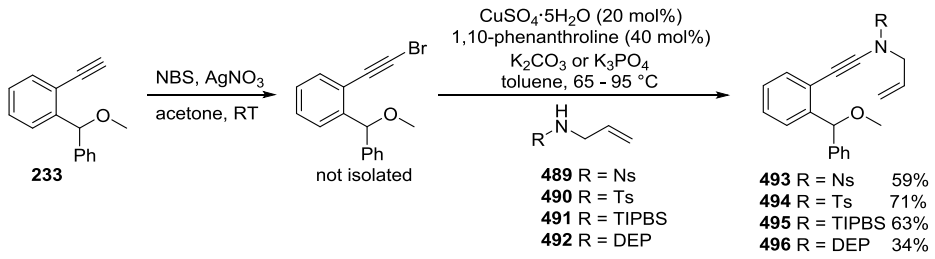


Figure 6: Crystal structure of 357 with ellipsoids drawn at the 50% probability level. X-Ray crystallography was carried out and data solved by Dr Louise Male (University of Birmingham)

3.3.2 Reaction Scope

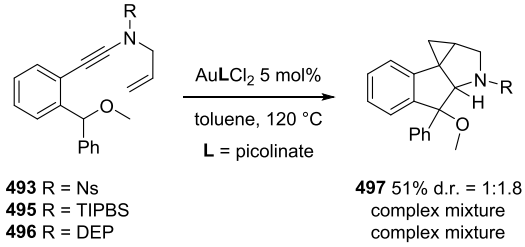
3.3.2.1 Modification of the Nitrogen Protecting Group

With conditions optimised for the [1,5]-hydride shift / cyclisation cascade for ynamide **255**, the effect of varying the nitrogen protecting group was then investigated. Many of the substrates discussed in this section were synthesised using methods presented in Chapter 2 from the appropriate, freshly prepared bromoalkyne (Scheme 102).[71]



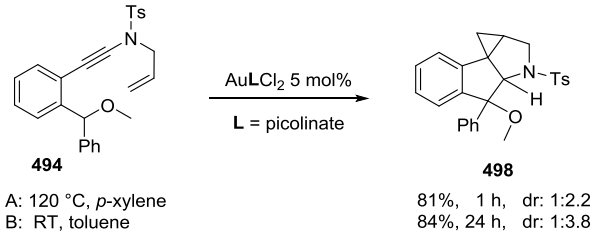
Scheme 102: Formation of ynamides with variation of the protecting group (TIPBS = triisopropylbenzenesulfonyl, DEP = diethylphosphonate)

Under the standard conditions, nosyl substituted ynamide **493** produced the desired tetracycle **497**, however, the yield was reduced and unidentified contaminants could not be removed. The use of a more sterically bulky sulfonyl group in **495** led to a complex mixture, including starting material, with no desired product generated. A similar result was obtained with a phosphoramidate substituted system **496**.



Scheme 103: Modification of the *N*-protecting group

N-Tosyl allyl substituted ynamide **494** had previously proved to be a poor substrate for carboalkoxylation and therefore had not been investigated for the initial optimisation studies for the present reaction, which had been based upon the idea that carboalkoxylation was required. However, when **494** was subjected to the optimised reaction conditions, tetracycle **498** was formed exclusively in high yield (Scheme 104). The major diastereoisomer was confirmed to be the same as the *N*-mesyl tetracycle (Figure 6) by nOe experiment.



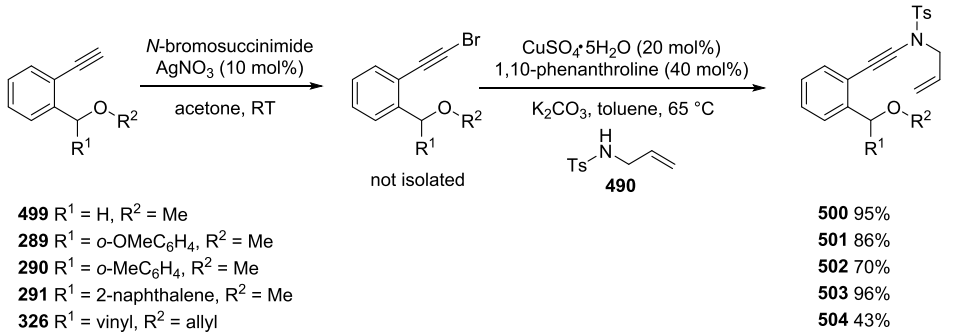
Scheme 104: Use of the tosyl nitrogen protecting group

Pleasingly, while the reaction rate was greatly decreased at room temperature, only traces of indene side products were observed in the ^{1}H-NMR spectrum of the crude reaction mixture, which were easily removed by column chromatography. The ratio of diastereoisomers was also improved at this temperature. Note that only two of the possible four diastereoisomers were generated in this transformation, due to a favoured *syn*-configuration at the [5,5]-ring junction. This was confirmed by nOe experiment (*vide infra*).

3.3.2.2 Modification at the Benzylic position

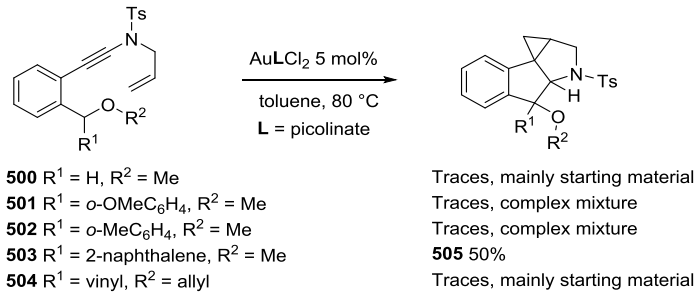
Further elaboration of the benzylic position was then explored. As a heteroatom is generally required to stabilise the developing carbocationic character on hydride transfer, the methoxy substituent was maintained. Terminal alkyne **499**, was synthesised in three steps from 2-iodobenzyl alcohol.

Terminal alkynes **289-291** and **326** were prepared as described in Chapter 2 using the appropriate freshly prepared Grignard reagent (*vide supra*). Ynamides **500**-**504** were then synthesised in good to excellent yields *via* the bromoalkyne (Scheme 105).



Scheme 105: Synthesis of ynamides with variation at the benzylic position

Without the additional substitution of an aryl group, a simple methyl ether **500** group did not provide the desired product (Scheme 106). This is potentially due to the phenyl group assisting with adoption of the required conformation for [1,5]-hydride transfer. Alternatively in a direct hydride transfer mechanism, the phenyl substituent would assist in cation stabilisation. Larger aryl groups with *ortho*-substitution (**501** and **502**) were not suitable, leading to complex mixtures.



Scheme 106: Attempts to modify benzylic position

While naphthyl substituted ynamide **503** gave the desired tetracyclic product **505** in 50% yield (determined by ^{1}H-NMR spectroscopy), attempts to isolate the product by column chromatography were unsuccessful due to co-elution of unidentified side products. A vinyl

substituted system was also unsuitable, generating a highly complex mixture, although weak resonances characteristic of cyclopropane rings could be observed in the ^{1}H-NMR spectrum.

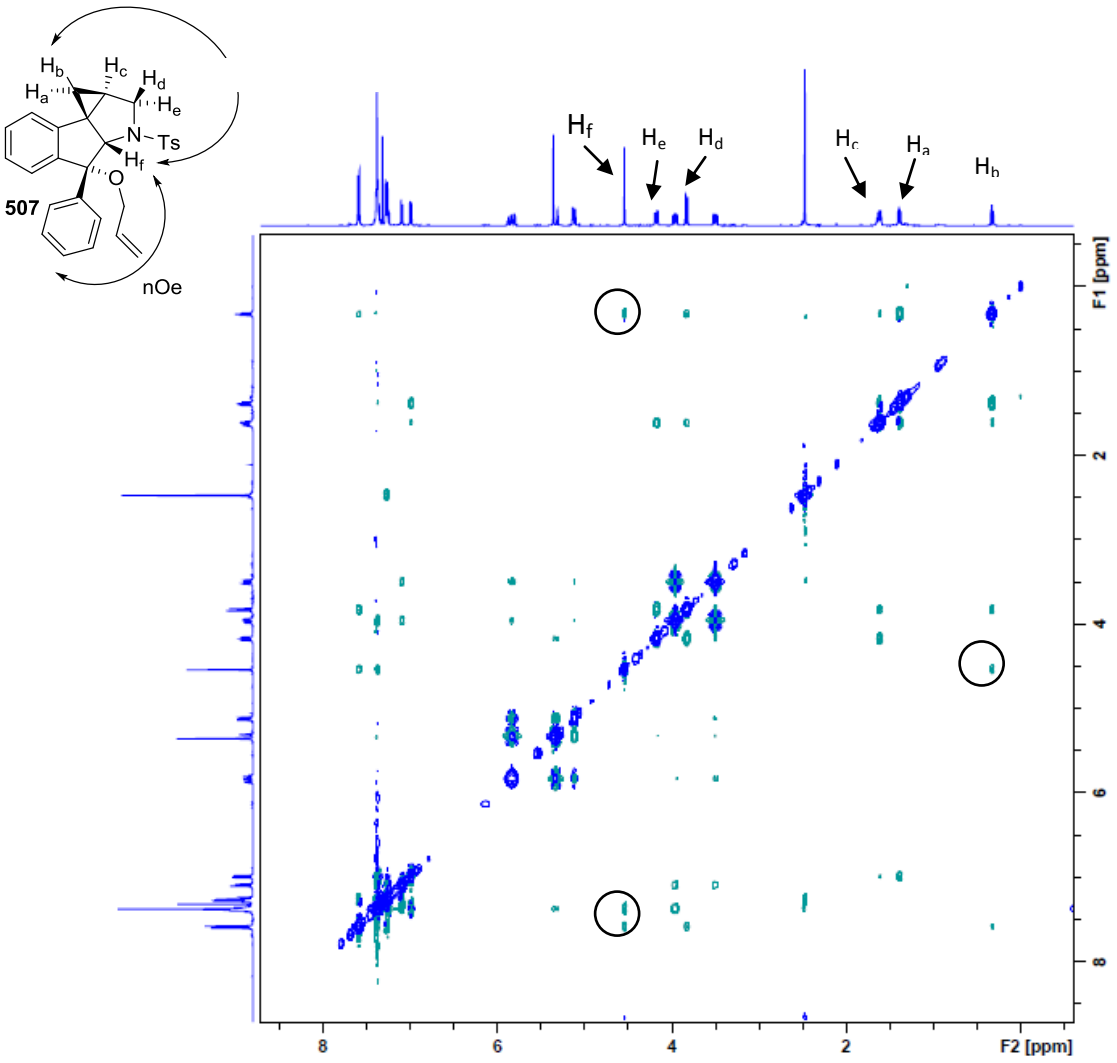
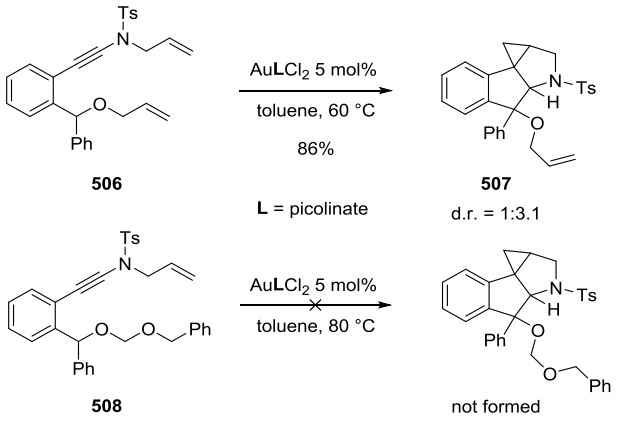


Figure 7: ^{1}H-^{1}H NOSEY experiment showing the through-space relationship of the migrated hydrogen, cyclopropane ring and phenyl substituent

Modifications to the *O*-protecting group were conducted using the same methods described in Chapter 2 (*vide supra*, Scheme 61) employing instead the tosyl sulfonamide **490** for the ynamide formation. Bis-allylated system **506** reacted cleanly when heated to 60 °C to give the tetracyclic

product **507** in high yield as a mixture of diastereoisomers (Scheme 107). The major diastereoisomer was isolated by recrystallisation and the relative stereochemistry confirmed by nOe experiment (Figure 7).

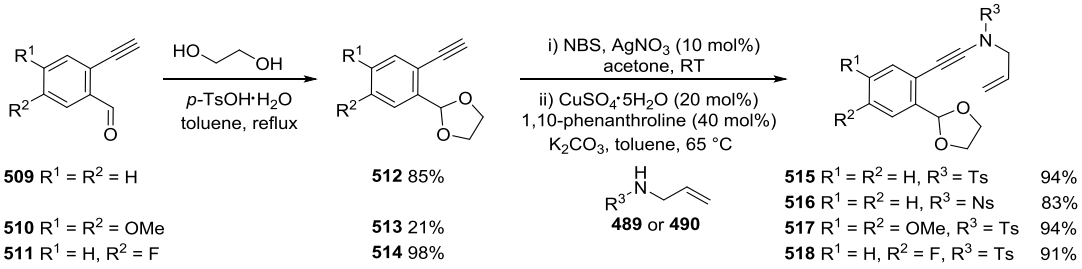
The temperature required for the cascade reaction to proceed appears to be highly substrate dependant since no reaction was observed at room temperature in this case. BOM-ether substituted ynamide **508** was not reactive under the reaction conditions even at 80 °C with only starting material and degradation observed by ^{1}H-NMR spectroscopy (Scheme 107).



Scheme 107: Modification of the *O*-protecting group

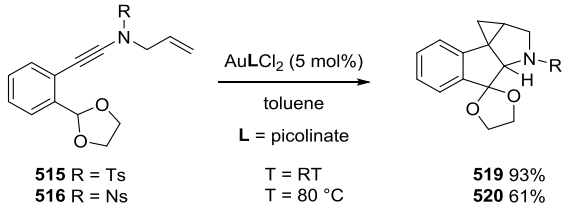
As discussed in the introduction, the acetal functionality is reported to increase the 'hydricity' of the migrating hydrogen, weakening the C-H bond and stabilising the resulting intermediate (*vide supra*).[89,112,113,114] The incorporation of an acetal also provides a synthetic handle for further functionalisation of products. A number of *ortho*-acetal substrates were therefore synthesised with **517** and **518** incorporating electron donating and electron withdrawing substituents respectively (Scheme 108). *Ortho*-ethynyl benzaldehydes **509**-**511** were converted to the corresponding cyclic acetals under acid-catalysed condensation conditions. Unsubstituted and

electron deficient aldehydes underwent acetal formation smoothly, however the electron rich system **510** proved prone to degradation under the reaction conditions. A poor yield was obtained in this case as a result, whether the alkyne was protected with $SiMe_3$ or not. Regardless, 2-(2-ethynylphenyl)-1,3-dioxolanes **512–514** were converted into the corresponding ynamides **515**-**518** under standard conditions in high yields.



Scheme 108: Synthesis of *ortho*-acetal substituted ynamides

Pleasingly, *ortho*-acetal functionalised ynamide **515** reacted cleanly at room temperature to give tetracycle **519** in excellent yield and as a single diastereoisomer (Scheme 109). Again, the *syn*-relationship between the migrated hydrogen and the cyclopropane ring was confirmed by nOe experiment (Figure 8).



Scheme 109: Generation of tetracycles with *ortho*-acetal functionality

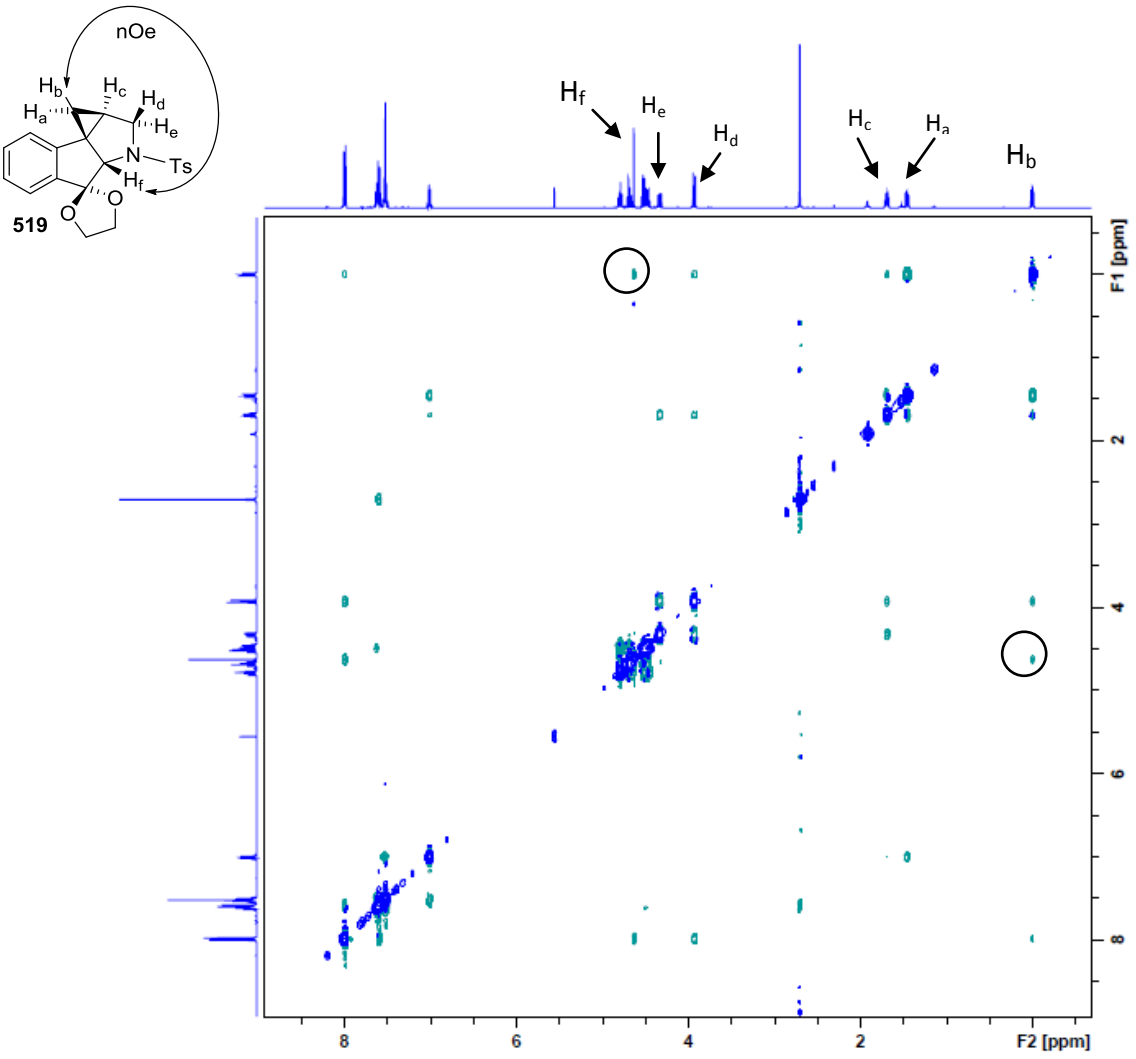


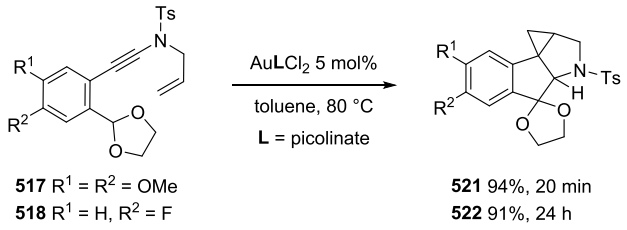
Figure 8: ^{1}H-^{1}H NOSEY experiment showing the through-space relationship of the migrated hydrogen and the cyclopropane ring

Furthermore, it was possible to obtain nosyl protected tetracycle **520** in good yield. No reaction took place at room temperature and was sluggish at 50 °C, however when heated to 80 °C, ynamide **516** was consumed within one hour. A phosphoramidate substituted system was also prepared, however unacceptable levels of impurities meant that it could not be used in the catalysis.

The ability to bring acid-labile acetal groups through this transformation untouched, serves to demonstrate the high functional group tolerance of gold catalysts and the mild conditions required. Conditions employed by Evano and co-workers for the polycyclisation of ynamides using strong acids were tested with ynamide **515** (TfOH, 5.0 equiv., CH_2Cl_2, 0 °C, 5 minutes).[116] Unsurprisingly, while **515** was consumed, no traces of a cyclisation product could be identified from the crude mixture by ^{1}H-NMR spectroscopy.

3.3.2.3 Modification of the Alkyne-Acetal Linker

When the substrates **517** and **518** bearing electron-donating and withdrawing-substituents on the benzene backbone, were subjected to gold catalysis at 80 °C, a significant effect on the rate of conversion was observed (Scheme 110).

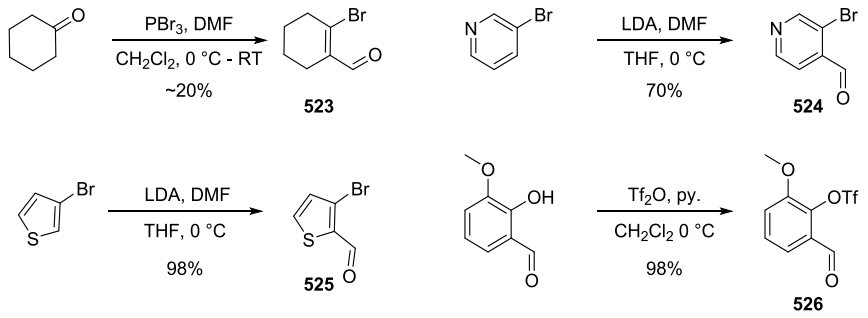


Scheme 110: Effect of electron withdrawing and donating substituents on the rate of reaction

The fluoro-substituted ynamide **518** went to completion at 80 °C in 24 hours to give the tetracycle **522** in excellent yield. Poor reactivity was observed at lower temperatures. In contrast, dimethoxy-substituted ynamide **517** was consumed in just 20 minutes to give **521**, again in excellent yield. The reduced rate of reaction for ynamide **518** can be rationalised by the inductively withdrawing effect of the fluorine atom, removing electron density from the benzylic

position and thereby reducing hydridic character of the migrating group. The methoxy in the 4-position can stabilise cationic character, helping to activate the hydride donor and increasing the rate of the reaction. The significant electronic effect is consistent with the turnover-limiting step involving development of carbocationic character at the benzylic position as the CH bond is cleaved. The methoxy in the 5-position could be expected to reduce the reaction rate by pushing electron density into the keteneiminium ion, decreasing its hydride accepting ability. However, it seems the effect on the hydride donor group is the more important factor in this case. These results are in line with those observed by Sames and co-workers in their benzopyran synthesis.[95]

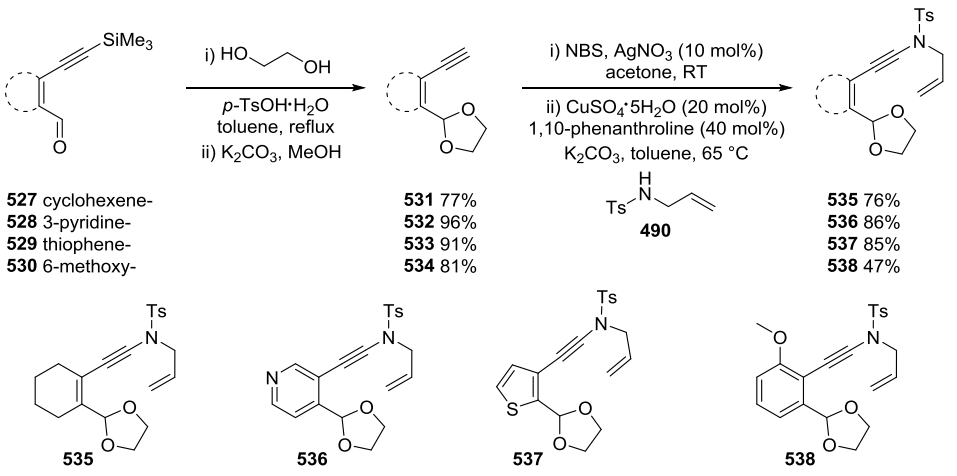
To further study this new transformation, a non-aromatic cyclohexene and heteroaromatic pyridine and thiophene substrates were chosen as important target substrates, not only to evaluate the limits of the reaction but also to provide synthetically valuable fused systems. An *ortho*-vanillin derived system was also synthesised. In order to access the common bromo-aldehyde motif, aldehydes **523**–**526** were synthesised from commercially available materials using known procedures (Scheme 111).[122,117,118,119] Whilst generally straightforward transformations, the Vilsmeier-Haack haloformylation of cyclohexene to form **523** was problematic.



Scheme 111: Synthesis of 2-bromoaldehydes

Despite numerous procedures in the literature reporting yields of 80-85%,[120] the yield obtained in our case was always close to 20%, despite consumption of starting material by TLC. Every component of the reaction was investigated, with fresh bottles of anhydrous DMF and PBr_3. The water content of the dichloromethane from the solvent purification system was checked by Karl Fischer titration, and undried solvent was also used as supplied. The cyclohexanone was checked for purity by TLC and ^{1}H- and ^{13}C-NMR spectroscopy. Variation of the reaction duration was tested and the work up method was modified several times in terms of quenching and number of extractions. The result, however, was frustratingly, always the same. Further investigation by a colleague (Elli Chatzopoulou) indicated that the use of diethyl ether instead of dichloromethane in the extraction process, increased the yield with certain substrates, however this was not the general case.

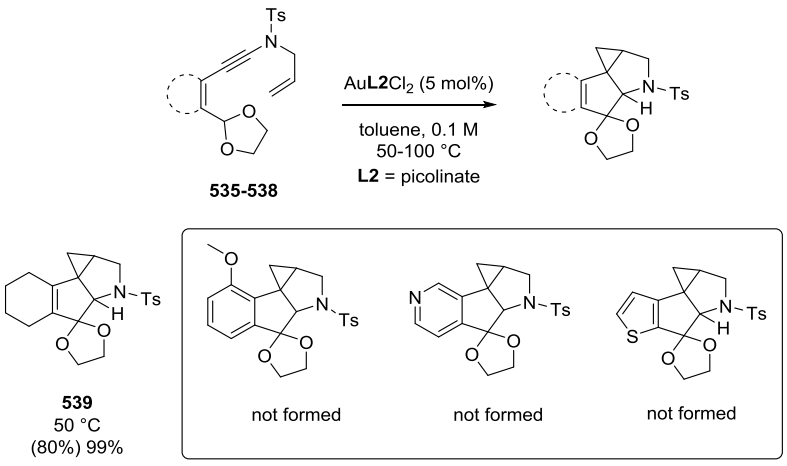
Nevertheless, enough material was obtained to continue with the ynamide synthesis. Sonagashira couplings of the bromides gave the *ortho*-ethynyl aldehydes **527**–**530** which were then converted to acetals **531**-**534** following deprotection to the alkynes in high yields (Scheme 112).



Scheme 112: Synthesis of ynamides 535-538 from *ortho*-ethynyl aldehydes 527-530

In the case of cyclohexene **531**, some loss of product through degradation was observed on the walls of the reaction flask during acetal formation. *N*-Allyl ynamides **535**-**538** were synthesised *via* formation of the bromoalkyne under standard conditions. The formation of ynamide **538** with a methoxy substituent *ortho*- to the triple bond was slow and gave a reduced yield due to congestion around the reacting centre.

Ynamides **535**-**538** were then subjected to the catalysis conditions (Scheme 113). Cyclohexene derivative **535** did not undergo reaction at all at room temperature after 5 hours. When the reaction was repeated at 50 °C however, consumption of starting material was complete in 20 minutes and tetracycle **539** was isolated in 80% yield. When the reaction was scaled up to 0.6 mmol (usually 0.2 mmol scale), a quantitative yield of **539** was obtained.



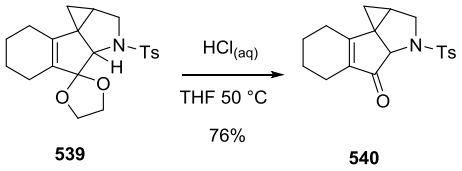
Scheme 113: Results from catalysis using ynamides 535-538

Ynamides **536**-**538** however, did not participate in the reaction. In the case of the pyridine substituted ynamide **536**, the lack of reactivity can be rationalised in two possible ways. Firstly, deactivation of the aromatic ring by the electronegative nitrogen atom would increase the pKa at the benzylic position and so make CH bond cleavage more difficult. The other factor to consider is that the pyridine nitrogen can bind to gold (as evident in the precatalyst employed throughout this work), and so competition for binding of gold between the triple bond and pyridine nitrogen may shut down the reaction.

The thiophene based ynamide **537** was also unreactive and only degradation was observed by ^{1}H-NMR spectroscopy. A potential rationale for this could be the greater bond angle associated with a 5-membered thiophene ring, which may create too great a distance between the hydride donor and acceptor for migration to occur. Methoxy substituted ynamide **538** did not undergo reaction after 8 hours at 80 °C and raising the temperature to 100 °C had no effect. This lack of reactivity is unlikely to be a result of the methoxy blocking the triple bond towards activation as

ortho-methoxy substituted aryl ynamides and alkynes have been reported to undergo gold-catalysed transformations.[121] A smaller gold(I) species Me_2SAuCl, was also tested against this substrate under otherwise identical conditions by a colleague (Elli Chatzopoulou) but again, no consumption of starting material was observed. A possible explanation is that the position of the methoxy group prevents the keteniminium from adopting the required conformation for [1,5]-hydride transfer. Deactivation of the keteniminium ion through donation of electron density could also be invisaged. Me_2SAuCl, which has seen success in related systems, was also tested against **537** and **538** (Elli Chatzopoulou), however the same results were observed.

Pleasingly, it was possible to cleave the acetal of cyclohexene **539** to give the enone **540** in good yield (Scheme 114). A very preliminary study of reactivity saw no conversion when **540** was exposed to organo-copper reagents.

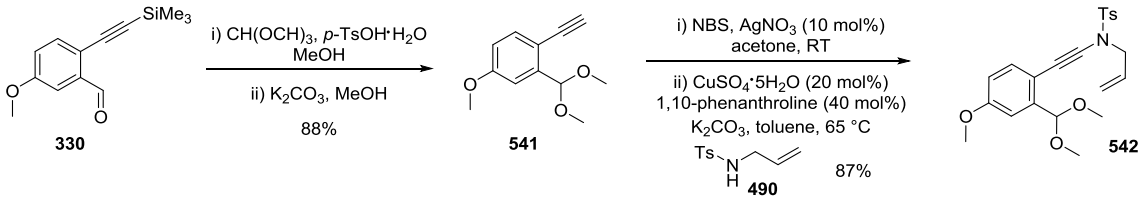


Scheme 114: Hydrolysis of acetal 539

3.3.2.4 Variation of the Acetal

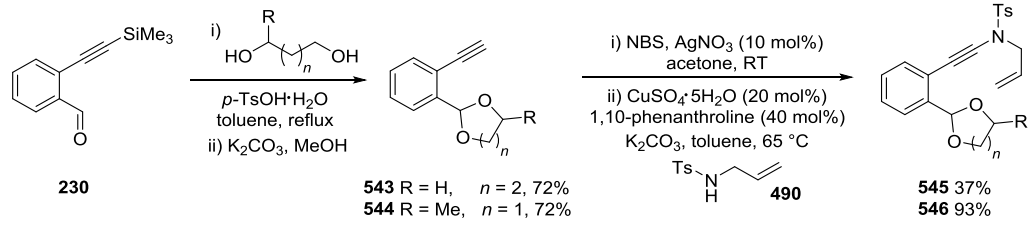
Attention was next turned to modification of the acetal. Dimethyl acetal substituted ynamide **542** was prepared readily under standard conditions in high yield (Scheme 115).[122] When subjected to gold catalysis, no consumption of starting maternal was observed at room temperature. At 50 °C the ynamide was consumed in 5 hours, however, a complex mixture was

obtained. A number of aldehyde peaks were visible in the crude ^{1}H-NMR spectrum arising from acetal hydrolysis in the presence of a Lewis acid.



Scheme 115: Synthesis of *ortho*-dimethylacetal ynamide 542

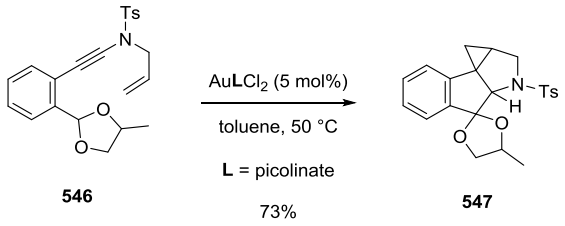
The preparation of different cyclic acetal derivatives was readily achieved using propane 1,3-diol or propane 1,2-diol to generate the precursor for ynamides **545** and **546** (Scheme 116). When ynamide **545**, substituted with a 6-membered ring acetal was heated at 80 °C under gold catalysis, no consumption of starting material was observed.



Scheme 116: Synthesis of methyl substituted and 6-membered ring acetal containing ynamides

Alajarin and co-workers have reported successful [1,5]-hydride transfer / cyclisation with these donors under thermal conditions,[113] although higher temperatures were required, as compared to the 5-membered ring acetal series (refluxing *o*-xylene, 22-24 hours). For this reason, the reaction was repeated at 120 °C in *p*-xylene. Complete consumption of starting material was observed after 3 hours, however, the ^{1}H-NMR spectrum of the crude reaction mixture showed

complete acetal degradation, with a number of aldehyde peaks visible, and no desired tetracycle. When ynamide **546**, with a methyl-substituted 5-membered ring acetal was subjected to gold catalysis at 50 °C for 45 minutes, tetracycle **547** was isolated in good yield as a mixture of four diastereoisomers (Scheme 117).



Scheme 117: Formation of tetracycle 547 under gold catalysis

Due to the number of overlapping resonances in the ^{1}H-NMR spectrum, it was not possible to accurately assign a ratio to the full mixture of diastereoisomers. Four resonances corresponding to the methyl group of the acetal, split onto distinctive doublets were observed, however, overlap with cyclopropane ring resonances limited interpretation. There does appear to be two major diastereoisomers in a 1:1 proportion, alongside two minor diastereoisomers. The reaction of ynamide **546** leads to products with five stereocentres, which could potentially generate 32 diastereoisomers. As the relative stereochemistry of three of these centres is set, this number is limited to just four.

The diastereoisomers which would arise from reaction of ynamide **546**, are shown below (Figure 9). The complexity of the ^{1}H-NMR spectra however, meant it was not possible to assign structures of the major products. The stereoselectivity observed in systems with unsymmetrical groups at the benzylic position is discussed in section 3.3.3 (*c.f.* Scheme 136).

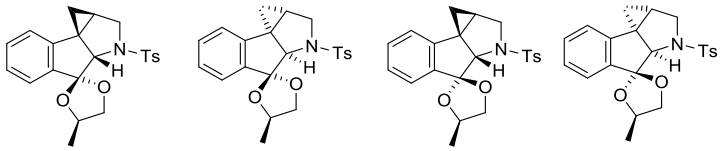
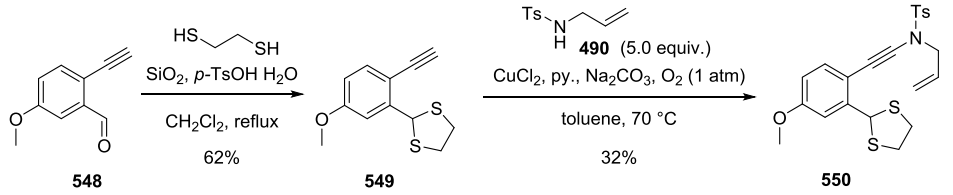


Figure 9: Diastereoisomers arising from reaction of ynamide 546

The use of a dithioacetal hydride donor was next explored. The dithiolane ring of **549** was constructed using 1,2-ethane dithiol with an acid catalyst in good yield (Scheme 118).[123] Bromination of the alkyne, prior to ynamide formation failed due to incompatibility, therefore copper-catalysed amidation conditions using terminal alkynes reported by Stahl and co-workers[68] were employed. As mentioned in Chapter 2, the yields for this method, with *ortho*-substituted alkynes tend to be modest, with dimer formation leading to significant consumption of the starting alkyne. This strategy has however been necessary to synthesise certain substrates.



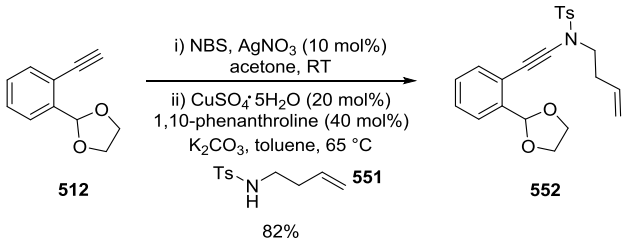
Scheme 118: Synthesis of ynamide 550 with an *ortho*-thioacetal functionality

When dithioacetal substituted ynamide **550** was subjected to gold catalysis, only traces of the desired product were seen in the ^{1}H-NMR spectrum. The crude mixture contained starting material alongside significant degradation products after heating to 80 °C for 9 hours. The position of the methoxy group on the benzene ring may also play a role as mesomeric effects

might be expected to decrease the ability of the triple bond to accept a hydride.[95] This was however, later investigated by a colleague (Elli Chatzopoulou), who found the equivalent substrate without methoxy substitution was similarly unreactive when heated to 90 °C for 6 hours, with only degradation observed by ^{1}H-NMR spectroscopy. Repeating the reaction of this *S,S*-acetal at even higher temperature might be a useful follow-up, as Alajarin and co-workers reported successful [1,5]-hydride transfer / cyclisation with these donors in related systems, although harsher conditions were required.[89,113]

3.3.2.5 Modification of *N*-Substituents

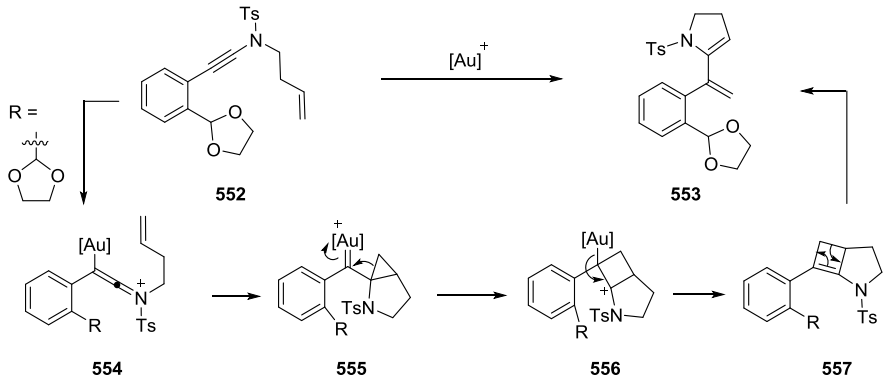
Modifications of the *N*-allyl group was then investigated, initially with homoallyl substituted ynamide **552**. The required *N*-homoallyl sulfonamide **551**, readily prepared from reaction of commercially available 4-bromobut-1-ene with tosylamine,[124] was coupled with alkyne **512** under standard conditions (Scheme 119).[71]



Scheme 119: Synthesis of *N*-homoallyl substituted ynamide 552

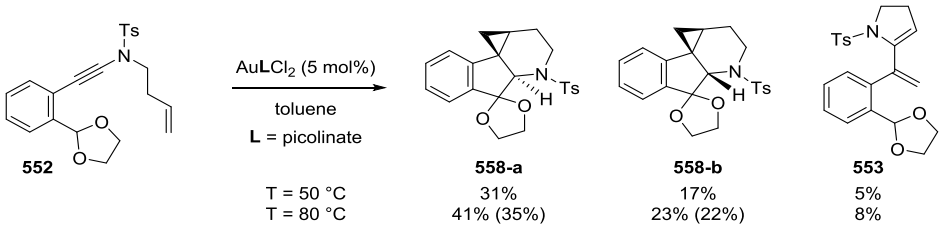
In the desired reaction, substrate such **552** would give rise to formation of a 6,3-ring system. However, 1,6-eneynamides have previously been shown to undergo cycloisomerisation reactions such as the formation of 1,3-dienes in the presence of π-acids.[125] A possible

mechanism for occurrence of this pathway in the present work is shown below (Scheme 120) which is based upon the cationic manifold originally proposed by Fürstner and co-workers for platinum catalysed enyne cycloisomerisations.[24] Due to the longer tether, the alkene is now able to cyclise onto the triple bond and so activation of ynamide **552** by gold may alternatively precede formation of α-amido carbene **555**. The carbene can undergo ring expansion to form the cyclobutyl cation **556**, stabilised by the adjacent heteroatom. Demetallation and cyclobutene ring opening would lead to 1,3-diene **553**.



Scheme 120: Proposed mechanism for the formation of 1,3-diene 553

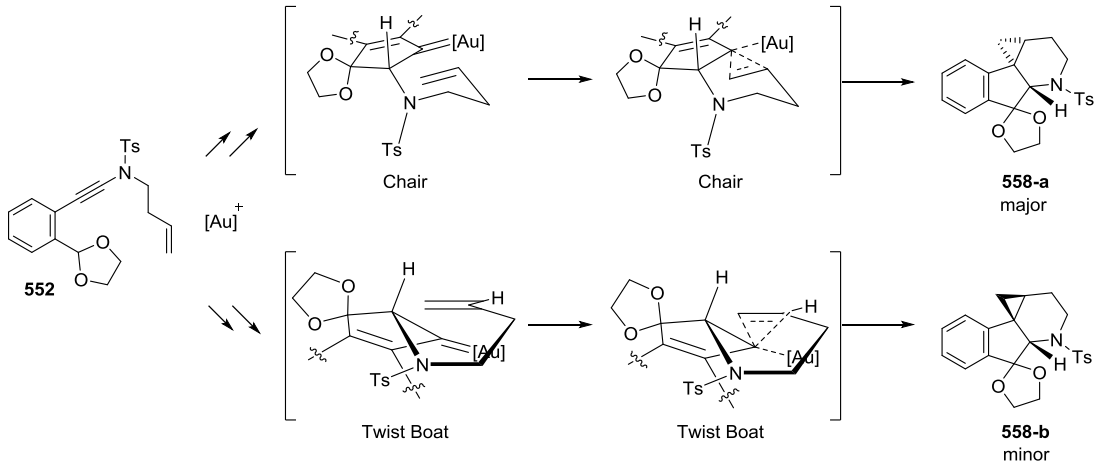
In order to test this, **552** was subjected to gold catalysis initially at 50 °C (Scheme 121). Diastereomeric tetracycles **558-a** and **558-b** were isolated in a 2:1 ratio. The formation of the diastereoisomer **558-a**, with an *anti*-relationship between the hydrogen and the cyclopropane ring not observed with allylic systems, was attributed to the greater flexibility associated with a larger ring size. The relative stereochemistry was confirmed by nOe experiments, with the major diastereoisomer having the cyclopropane ring and the migrated hydrogen on opposite faces.



Scheme 121: Reactivity of homoallyl ynamide 552 (^{1}H-NMR yields with isolated yields shown in brackets)

In all other examples, when allyl groups are employed, the cyclopropane and the migrated hydrogen are on the same face due to the steric requirements of ring formation. It was surprising to observe that with a 6-membered ring, derived from a homoallyl group, the major isomer had the opposite configuration around this ring junction.

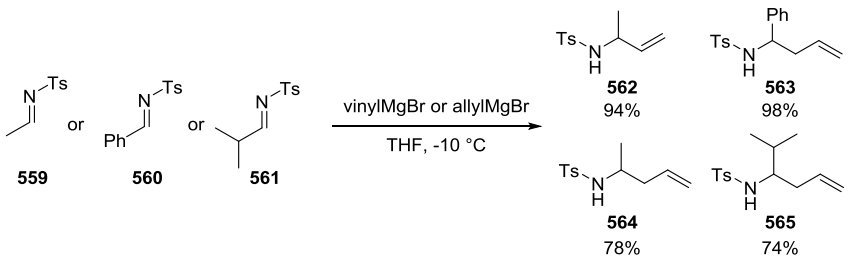
This modest selectivity should arise from difference in the relative energies of the transition states on formation on the 6,3-ring system through reaction of the alkene onto the gold carbene (Scheme 122). Based on the use of molecular models, a possible explanation can be suggested. In order to generate the major diastereoisomer **558-a**, a chair conformation for the approach of the alkene appears feasible. To achieve the opposite selectivity, where the cyclopropane ring is formed on the same face as the migrated hydrogen **558-b**, a higher energy twist-boat conformation is required to achieve the correct alignment between the gold carbene and the alkene.



Scheme 122: Possible rationale for the migrated hydrogen and the cyclopropane ring to occupy opposite faces when a homoallyl substituted system is employed

Alongside the formation of the two diastereomeric tetracycles, the 1,3-diene **553** was observed by ^{1}H-NMR spectroscopy of the crude reaction mixture in low levels. Although isolation was not possible in this case, the likely structure is drawn above. The reaction of ynamide **552** was then repeated at higher temperature, resulting in an improved yield of **558** and a cleaner reaction, although this had no effect on the ratio of diastereoisomers. At both temperatures, formation of the enyne cycloisomerisation side product **553** was observed.

In order to investigate the effects of substituents adjacent to the ynamide nitrogen, α-substituted allyl- and homoallyl sulfonamides were prepared by reaction of freshly prepared vinyl or allyl magnesium bromide with the relevant imine.



Scheme 123: Formation of α-substituted allyl- and homoallyl sulfonamides

Ynamides **566**-**569** were then synthesised from freshly prepared bromoalkynes under standard conditions in moderate to good yields (Figure 10).[71] When the bulky isopropyl substituted sulfonamide **565** was employed however, no coupling was observed.

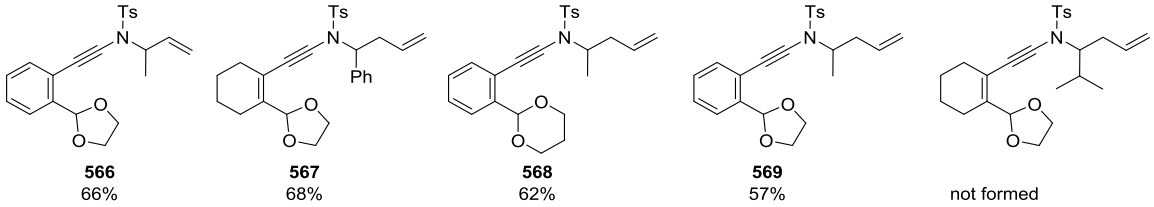
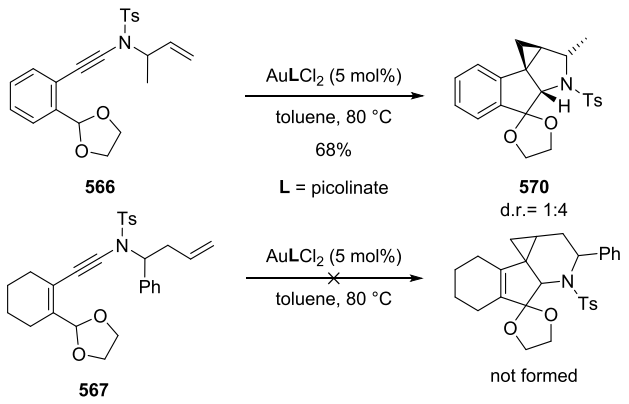


Figure 10: Substituted *N*-allyl-and *N*-homoallyl ynamides

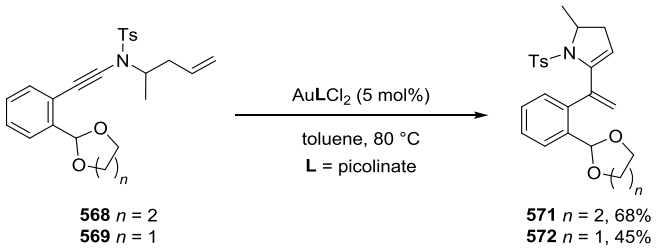
α-Methyl substituted *N*-allyl ynamide **566** underwent smooth gold-catalysed polycyclisation at 80 °C in one hour to give tetracycle **570** in a good yield as a 1:4 mixture of diastereoisomers (Scheme 124). The major diastereoisomer was isolated by recrystallisation and its structure confirmed by nOe experiment. Rationalisation for this selectivity is discussed later (see Scheme 136). α-Phenyl substituted *N*-homoallyl ynamide **567** was unreactive towards the reaction conditions and only degradation of starting material was observed.



Scheme 124: α-Methyl and α-phenyl substituted ynamides

Allyl and homoallyl ynamides **545** and **568** containing a 6-membered ring acetal were prepared simultaneously as it was not known that this functionality was unsuitable for the transformation. When α-methyl substituted *N*-homoallyl ynamide **568** was subjected to the reaction conditions, complete consumption of starting material was observed after 45 minutes at 80 °C, however, the single product was not the desired tetracycle. Instead, the enyne cycloisomerisation pathway, previously detected with homoallyl ynamide **552**, was favoured giving 1,3-diene **571** in good yield (Scheme 125). The structure of **571** was assigned using ^{1}H- and ^{13}C-NMR spectroscopy.

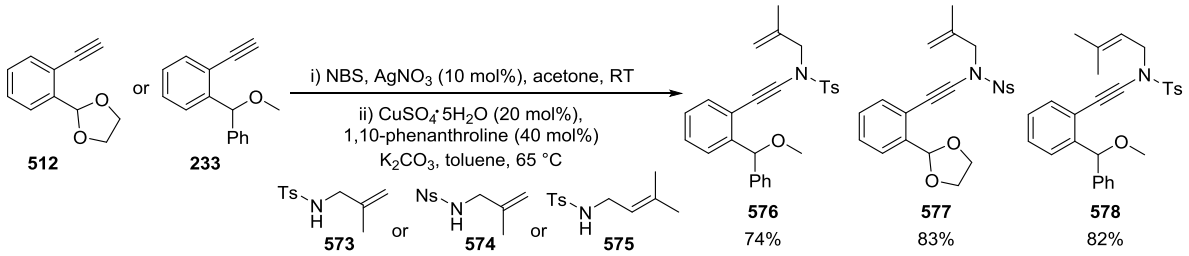
In parallel, α-methyl *N*-homoallyl ynamide **569**, substituted with a 5-membered ring acetal in the benzylic position was subjected to identical reaction conditions. The corresponding 1,3-diene **572** was again formed as the sole product, as observed by ^{1}H-NMR spectroscopy, although isolation of an acceptably pure compound was not possible in this case.



Scheme 125: Formation of 1,3-dienes with α-methyl substituted *N*-homoallyl ynamides

As mentioned previously (Scheme 121), small amounts of the 1,3-diene were observed for the non-substituted homoallyl ynamide **552**, though the major product was the desired tetracycle **558**. The α-methyl group appears to play a critical role in orientating the ene component, increasing the rate of the undesired enyne cycloisomerisation pathway, which is consistent with a reactive rotomer effect.

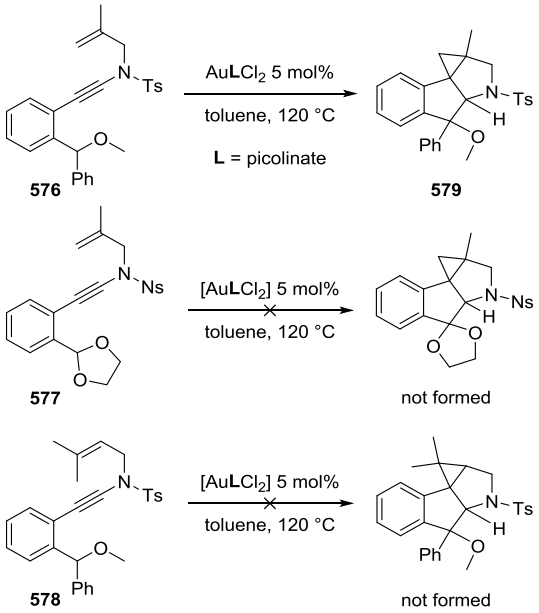
Substitution around the double bond of the allyl group was also investigated. Methyl-substituted sulfonamides were kindly donated by colleagues and coupled with alkynes **223** or **512** *via* the bromoalkyne under standard conditions (Scheme 126).



Scheme 126: Synthesis of ynamides 576-578 with methyl substituted *N*-allyl groups

Ynamide **576** was heated at 120 °C for 24 hours in an attempt to generate the tetracyclic product **579** with methyl substitution at the [5,3]-ring junction (Scheme 127). A complex

mixture was generated which included unreacted starting material, an isoquinoline side product (this pathway is discussed in Chapter 4) and what appeared to be the desired product based on ^{1}H-NMR spectroscopy of the crude reaction mixture. The complexity of the mixture however meant it was not possible to isolate and characterise the tetracycle **579**.



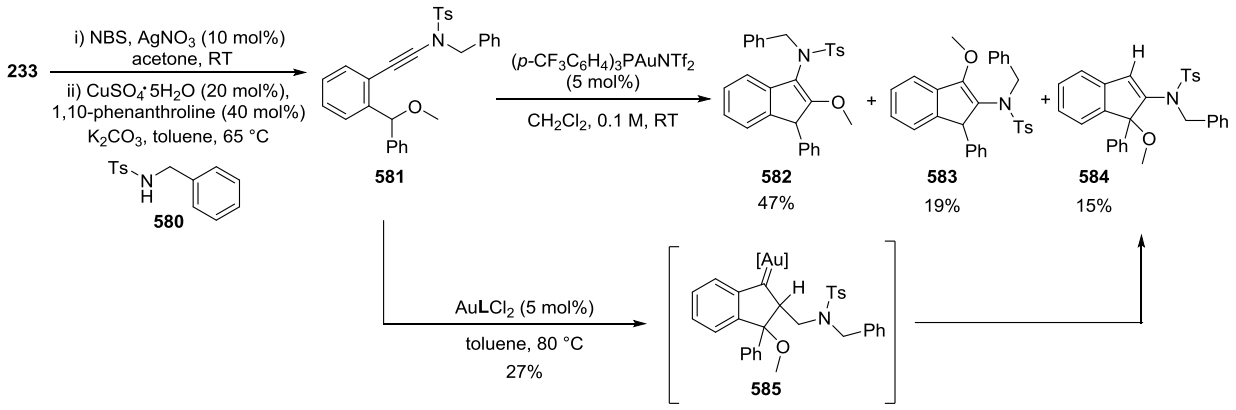
Scheme 127: Substitution of the alkene

This reaction was followed up with the acetal substituted ynamide **577** with a Ns protecting group, also known to undergo smooth polycyclisation when the allyl is unsubstituted. After subjecting **577** to gold catalysis, however, only degradation alongside unreacted starting material was observed by ^{1}H-NMR spectroscopy. A gem-dimethyl substitution pattern was similarly unsuccessful with only unreacted starting material **578** and degradation visible by ^{1}H-NMR spectroscopy. This type of substitution might be expected to affect the cyclopropanation step in the proposed mechanism, however, the lack of conversion of starting ynamides is less

readily explained. Due to the presence of inductively donating methyl groups, the electron rich alkene may become a better ligand for the gold catalyst rendering ynamide activation for [1,5]-hydride shift unproductive.

3.3.2.7 Alternative Carbene Traps

While an *N*-mesyl *N*-benzyl substituted system gave high yields of *N*-migration product in the previously described carboalkoxylation chemistry (*vide supra*), an *N*-tosyl *N*-benzyl system, generated from sulfonamide **580** gave a mixture of isomeric products which could be separated by column chromatography and characterised (Scheme 128). Alongside the expected indene **582** arising from a 1,2-*N* migration (47%) and the minor regioisomer from 1,2-*O* migration **583** (19%), a third indene product **584** was also isolated in a 15% yield. The structure of **584** was assigned based on ^{1}H- and ^{13}C-NMR spectroscopy.

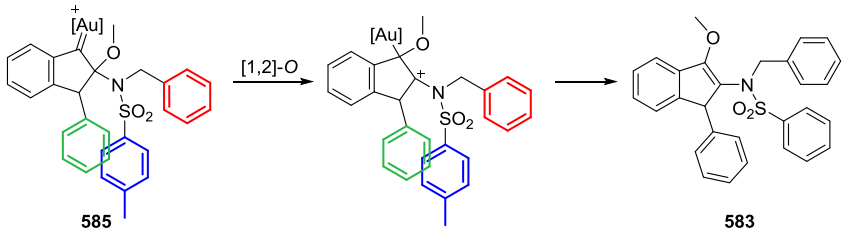


Scheme 128: Formation of isomeric indenes through competing carboalkoxylation and [1,5]-hydride shift / cyclisation pathways

Indene **584** was proposed to arise from a 1,2-hydride shift into gold carbene **585**, generated through the [1,5]-hydride migration / cyclisation pathway. Electrophilic aromatic substitution of the benzyl substituent onto the gold carbene was not observed (cf. Evano's polycyclisations).[116]

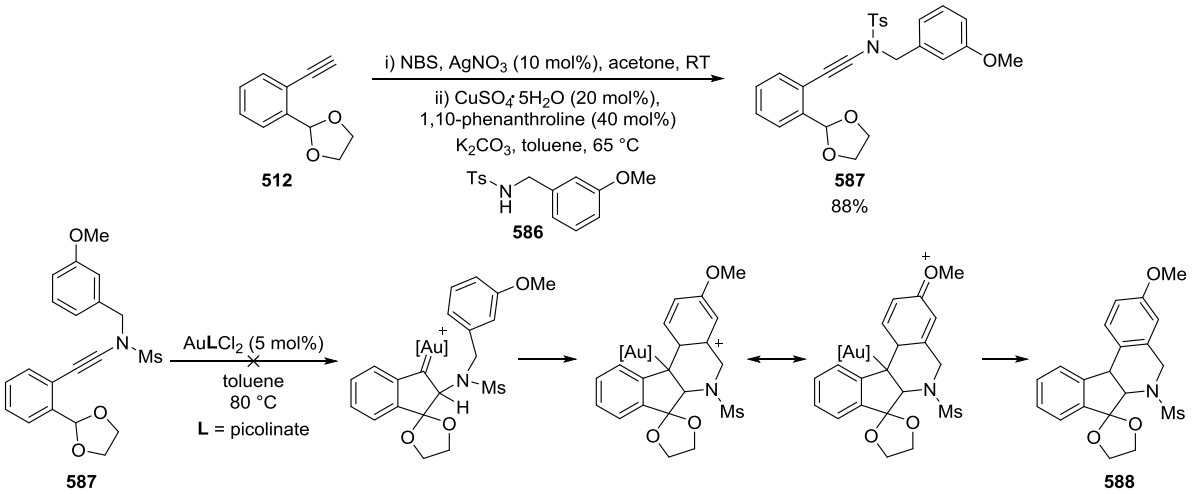
The difference in reactivity as compared to the mesyl substituted system could be due to the larger size of the nitrogen substituents of **581**, slightly hindering nucleophilic attack by oxygen onto the gold-activated triple bond, providing opportunity for [1,5]-hydride migration to occur, due to the smaller size of the hydride. Ynamide **581** was also subjected to conditions established for the [1,5]-hydride transfer cascade (Scheme 128). While reaction at room temperature and at 50 °C gave little consumption of starting material after 24 hours, when heated to 80 °C, formation of **584** was observed, albeit in a 27% yield. No other isomeric products were observed in the ^{1}H-NMR spectrum of the crude reaction mixture although degradation was apparent. A through-space interaction between the tolyl and phenyl groups could be envisaged, preventing adoption of the required reactive conformation for [1,5]-hydride transfer.

The formation of two regioisomeric carboalkoxylation products seems counter-intuitive based on the model proposed to explain the usually observed regioselectivity (Scheme 68, Chapter 2). This result could be rationalised by invoking π- and through-space interactions between the benzyl and tosyl substituents, stabilising the intermediate required for methoxy migration (Scheme 129).



Scheme 129: Possible rationalisation for observance of methoxy migration product 583 by π- and through-space interactions

In order to favour electrophilic aromatic substitution onto the gold carbene in benzylic systems, substrate **587** was synthesised from sulfonamide **586** (Scheme 130). It was proposed that incorporation of an election donating methoxy substituent in the 3-position of the benzene ring would promote an electrophilic aromatic substitution pathway by providing additional stabilisation of the carbocation generated on cyclisation onto the gold carbene to generate fused system **588** (Scheme 130). It was known that the *ortho*-acetal substrates did not undergo carboalkoxylation so competition from this pathway would not be an issue.

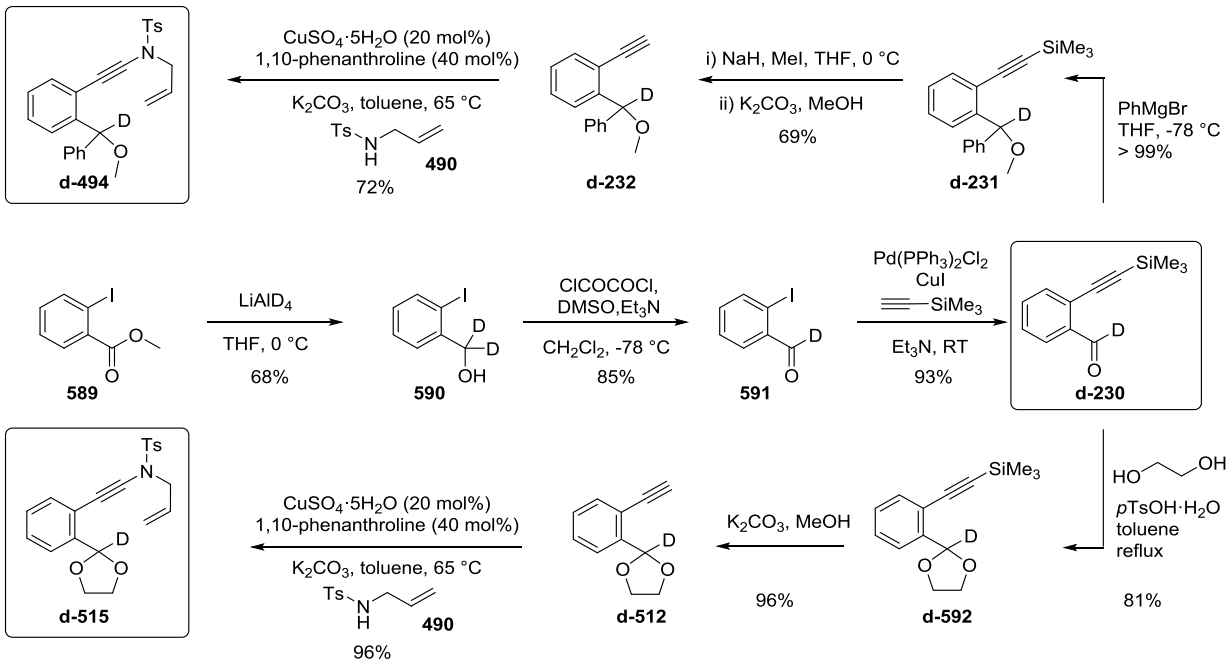


Scheme 130: Electrophilic aromatic substitution pathway for the gold carbene

When subjected to gold catalysis under standard conditions, ynamide **587** showed little reactivity and when the reaction was conducted at even higher temperatures, complex mixtures were obtained. A variety of different gold catalysts and solvents were therefore tested, however in many cases, very little reactivity was observed. Whilst for a number of phosphine gold(I) catalyst systems, complete consumption of ynamide was observed however, the complexity of the reaction mixture prevented the isolation of any single product.

3.3.3 Mechanistic Considerations: Deuterium Labelling Studies

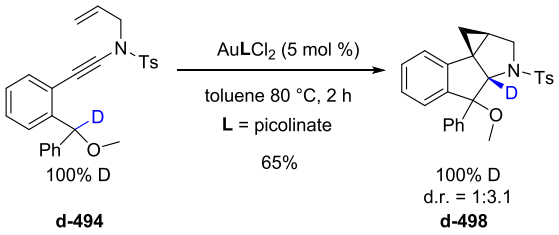
In order to gain insight into the mechanism of this reaction, deuterated ynamides **d-494** and **d-515** were prepared (Scheme 131).



Scheme 131: Synthesis of deuterated ynamides d-494 and d-515

The common deuterated aldehyde precursor **d-230** was prepared by reduction of methyl 2-iodobenzoate **589** with $LiAlD_4$ to give the alcohol **590** which was converted to the deuterated aldehyde **591** by a Swern oxidation.[126] Sonagashira coupling with trimethylsilyl acetylene gave **d-230**. The dibenzylether and cyclic acetal substituted ynamides were then synthesised using previously described procedures.

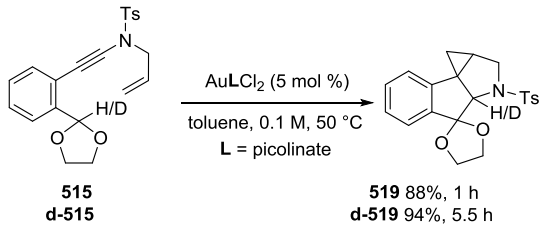
The first experiment employed ynamide **d-494** which, in contrast to its protonated counterpart, did not react at room temperature after 24 hours. The reaction was repeated at 80 °C and the tetracycle **d-498** was isolated as a mixture of diastereoisomers in good yield (Scheme 132). Full deuterium incorporation was observed in the product, confirming that the hydride migration is an intramolecular process. The reluctance of **d-494** to undergo reaction at room temperature also indicated a kinetic isotope effect with the CH/CD bond cleavage involved in the turnover-limiting step. This is in line with observations in previous studies.[110,116]



Scheme 132: Complete transfer of deuterium through intramolecular [1,5]-hydride migration

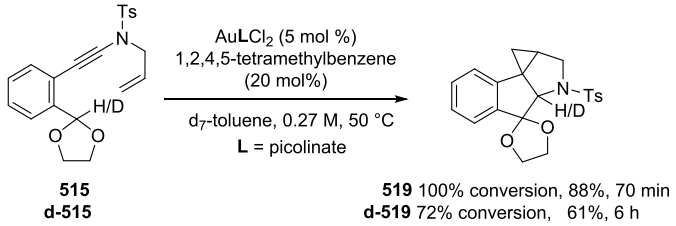
It was decided to investigate the kinetic isotope effect further by comparing the rates of reaction of labelled and unlabeled substrates by ^{1}H-NMR spectroscopy. As the *ortho*-acetal substituted systems displayed superior reactivity to give single diastereoisomers in high yields,

the study was performed using ynamide **d-515** (Scheme 131). Reactions of ynamides **515** and **d-515** under gold catalysis were run side-by-side at 50 °C to ensure both had suitable reaction times at a moderate temperature. It was important to ensure the reaction temperature was relatively mild, so as not to hold the NMR machine at high temperature for extended periods, avoiding potential damage. As expected, the deuterated ynamide reacted more slowly. Unlabelled ynamide **515** was consumed in one hour whereas ynamide **d-515** was consumed over 5.5 hours (Scheme 133) with complete deuterium incorporation (See Appendix).



Scheme 133: Comparison of reaction times for labelled and non labelled ynamides (^{1}H-NMR yields)

The reactions were then repeated separately in NMR tubes at 50 °C, with 20 mol% of 1,2,4,5-tetramethylbenzene as an internal standard (Scheme 134). In the case of ynamide **515** ^{1}H-NMR spectra were recorded every five minutes for a total of 70 minutes, over which time the reaction was complete (Graph 1).



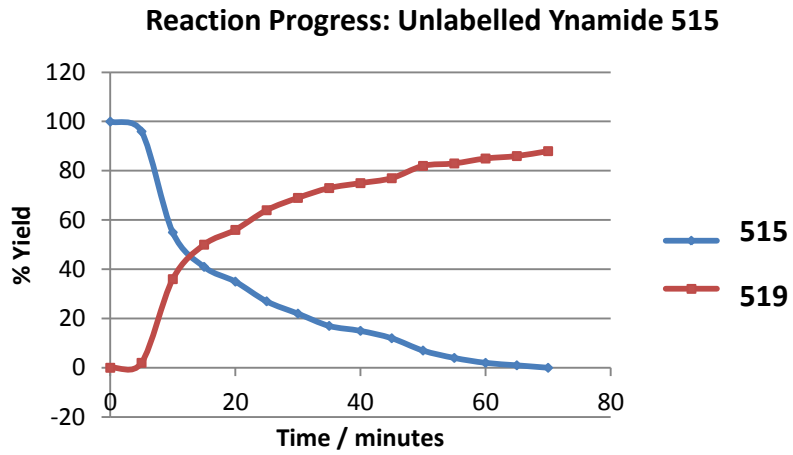
Scheme 134: ^{1}H-NMR experiment with ynamides 519 and d-519 at 50 °C

Due to the slower rate of reaction for ynamide **d-515**, spectra were recorded every ten minutes over a six hour period. Surprisingly, the reaction only reached 72% conversion in this time (Graph 2), however, it was not possible to run the reaction for a longer time period. Fluctuations above the set temperature of the oil bath and stirrer hotplate, used in the first case (Scheme 132) may be the cause of the increased reaction rate as compared to the ^{1}H-NMR experiment. Also, the reactions conducted in NMR tubes were almost three times as concentrated as the standard conditions, which may also play a factor. As both ^{1}H-NMR studies were conducted under identical conditions this discrepancy was not a concern.

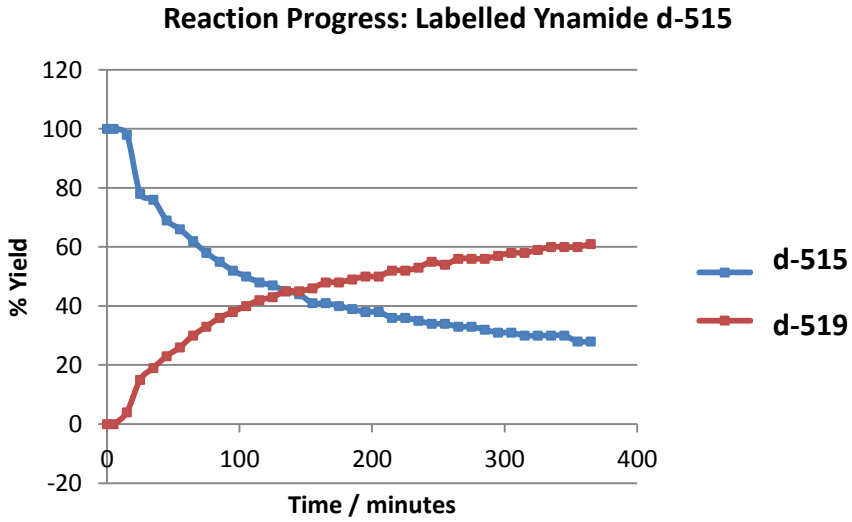
The rate of reaction in both cases is essentially zero for the first 5-10 minutes which corresponds to the induction period whereby the active gold catalyst is formed from the picolinate-ligated gold precatalyst, first developed by Hashmi and co-workers.[127] The rate of reaction then increases sharply before decreasing steadily over time (Graph 1 and Graph 2). It was not possible to deduce the rate constants, which are required to calculate the primary kinetic isotope effect for this type of experiment,[128] from the ^{1}H-NMR data of these catalytic reactions. Rate laws could not be determined as they did not remain constant over time. Furthermore, calculating rate constants from the initial rates is prevented due the induction period of the catalyst.

In order to gain this information, the use of a catalyst which does not require an induction period is required. Alternatively, the catalyst could be pre-activated by first adding a small, known quantity of ynamide (or an alternative substrate). Upon consumption of this initial

material, the required quantity of ynamide could be added to the same reaction tube containing the now activated catalyst.

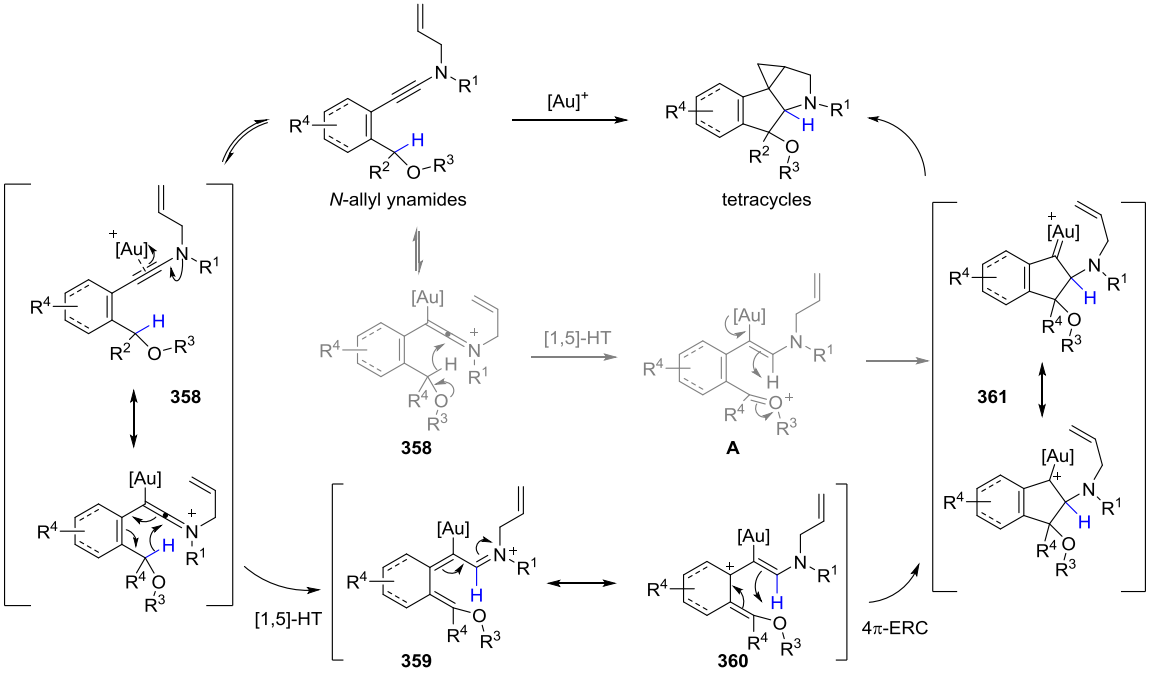


Graph 1: Complete consumption of ynamide 515 in 70 minutes at 50 °C



Graph 2: 72% Consumption of ynamide d-515 in 6 hours at 50 °C

Whilst it is difficult to quantify accurately, there is clearly a kinetic isotope effect in operation, whereby the rate of reaction is greatly reduced on substitution with a deuterium atom, due to the cleavage of the CH/CD bond being involved in the turnover-limiting step. Based on this information, observations made throughout the project, and relevant examples in the literature, a mechanism for the [1,5]-hydride transfer cascade is proposed below (Scheme 135).



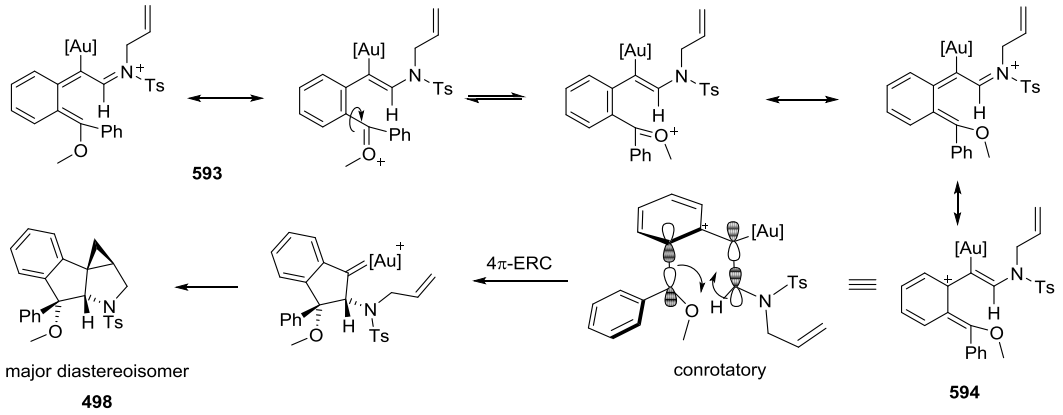
Scheme 135: Proposed mechanism for the formation of tetracycles from *N*-allyl ynamides

Upon activation of the triple bond by the gold catalyst, a [1,5]-sigmatropic hydride shift occurs, as proposed in systems such as those reported by Evano,[116] Liang[107] and Alajarin.[89,113] This step is high energy and turnover-limiting, as proven by isotopic labelling. The resulting highly conjugated iminium ion **359** is in resonance with carbocation **360** which undergoes 4π-electrocyclisation in a conrotatory fashion to give gold carbene **361**. Whilst a sigmatropic

hydride shift is proposed above, a through-space [1,5] hydride transfer mechanism, as initially proposed by Sames for aliphatic systems, should not be ignored.[90] In this case, hydride transfer would occur with formation of oxonium **A** with subsequent ring closure leading to the same gold carbene **361**.

As previously discussed, this mechanism draws parallels to work by Evano and co-workers whereby keteniminium formation from an ynamide is promoted by a strong acid (*vide supra*).[116] In Evano's studies however, only a small number of substituted allyl groups could be trapped to generate cyclohexenes as mixtures of isomers in moderate yields. In the present work, unsubstituted allyl groups react with the gold carbene smoothly to generate the observed tetracycles. Pleasingly, when an *N*-allyl ynamide is employed, only the *syn*-relationship between the cyclopropane ring and the migrated hydrogen is observed, as confirmed by ^{1}H-NMR spectroscopy. When an *N*-homoallyl ynamide is employed, a mixture of diastereoisomers arise from formation of the opposite configuration around the [5,6]-ring junction (Scheme 121).

Mixtures of diastereoisomers were generated when the substrate contained a stereogenic centre at the benzylic position. According to the mechanism, this position becomes planarised with developing sp^2 character. Selectivity must therefore arise prior to the 4π-conrotatory ring closure which forms the first ring (**360**–**361**, Scheme 135).



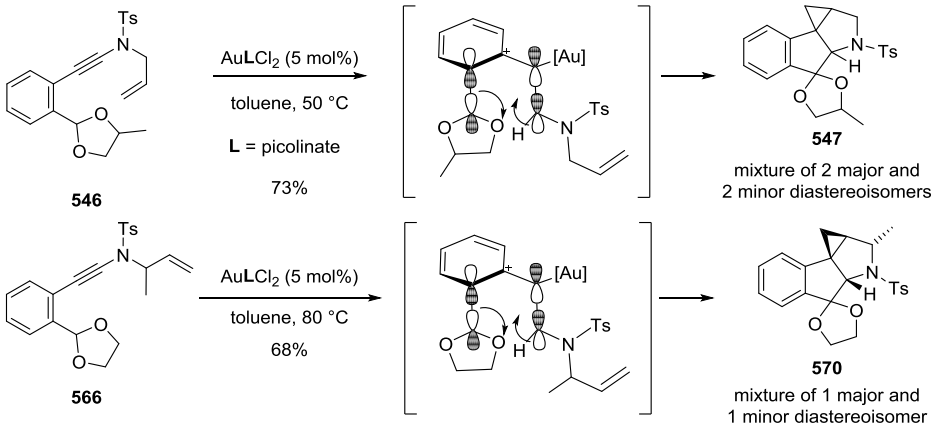
Scheme 136: Rationalisation of regioselectivity for polycyclisation of *N*-allyl ynamides

[1,5]-Sigmatropic hydride transfer generates a planar, conjugated intermediate. Bond rotation around the C-O bond can occur as some resonance forms have more single bond character (Scheme 136, **593**) which would allow the larger substituents, i.e. the phenyl and *N*-allyl groups in this example to move away from each other, reducing steric strain. The enamine component has always been drawn in one geometry, however rotation around the gold-bound C-C bond would also be possible. Nazarov-type conrotatory cyclisation of carbocation **594** sets the relative stereochemistry at the benzylic and adjacent positions. Note that only one of the possible stereochemical outcomes is shown (Scheme 136).

Formation of the final two stereocentres through cyclopropanation onto the carbene is stereospecific when an allyl group is employed, adopting the favoured *syn*-configuration around the [5,5]-ring junction. Based on this analysis, we might expect the major diastereoisomer to be that which has the phenyl ring and the nitrogen heterocycle on opposite faces. This is indeed the case based upon the X-ray crystal structure of the major isomer of **357** and is also apparent

from nOe experiments of *O*-allyl substituted tetracycle **507** which shows the phenyl ring and the migrated hydrogen to be on the same face (*vide supra*). The ratio of isomers is affected by temperature with selectivity improved at lower temperatures.

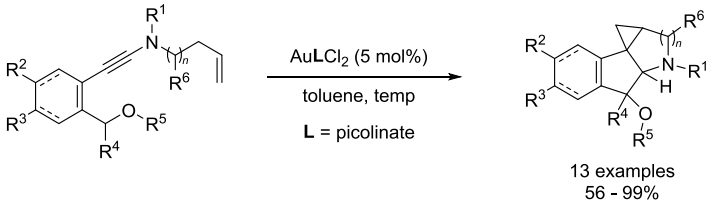
When an acetal was employed at the benzylic position, a single diastereoisomer was obtained in most cases. With ynamides **546** and **566** with methyl substitution on the acetal and allyl groups respectively, mixtures of diastereoisomers were generated. The same model described above is tentatively invoked to rationalise the formation of major and minor diastereoisomers in these cases based on steric repulsion between the amide and the acetal groups (Scheme 137). In the case of **566**, this effect is thought to be more pronounced with the conformation adopted prior to conrotatory cyclisation presumed to be similar to that shown below, with the amide group positioned away from the acetal. The formation of diastereoisomers in this case is attributed to the clockwise or anticlockwise formation of the new σ-bond.



Scheme 137: Rationalisation for the formation of diastereoisomers for reaction of ynamides 546 and 566

3.4 Conclusions

A novel gold-catalysed cascade has been discovered and developed, initiated by a [1,5]-hydride shift onto an ynamide. This transformation generates two new carbocycles and a nitrogen heterocycle in a single step by formation of three new carbon-carbon bonds and three contiguous stereocentres, two of which are quaternary carbons.



Scheme 138: Summary of the [1,5]-hydride transfer cascade

The mechanism of this reaction has been explored through by deuterium labelling studies which indicate that cleavage of the CH bond is turnover limiting. Finally, the diastereoselectivity observed for ynamides containing a stereogenic carbon at the benzylic position has been rationalised based on reduction of steric strain prior to a conrotatory 4π-electrocyclisation.

Chapter 4: Isoquinoline Synthesis through a Novel Copper-Catalysed Cascade of *N*-Allyl Ynamides

4.1 Introduction

During studies into the cycloisomerisation of *N*-allyl ynamides (Chapter 3), a novel copper-catalysed [1,5]-hydride transfer cascade was discovered leading to the generation of valuable isoquinoline cores. In addition to the discussion of literature concerning the mechanistic details of this type of transformation, a selection of recent contributions towards the transition metal catalysed synthesis of isoquinolines are detailed below.

4.1.1 Traditional Syntheses

Isoquinolines are privileged motifs, abundant in biologically active natural products[129] such as imerubrine[130] and annocherine,[131] as well as pharmaceuticals[132] such as the opium alkaloid papaverine (Figure 11).[133] The development of novel and efficient routes for their synthesis therefore continues to be an important goal in modern synthetic chemistry.

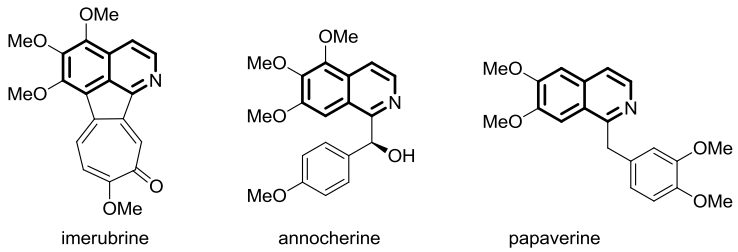


Figure 11: Natural products and pharmaceuticals containing the isoquinoline motif

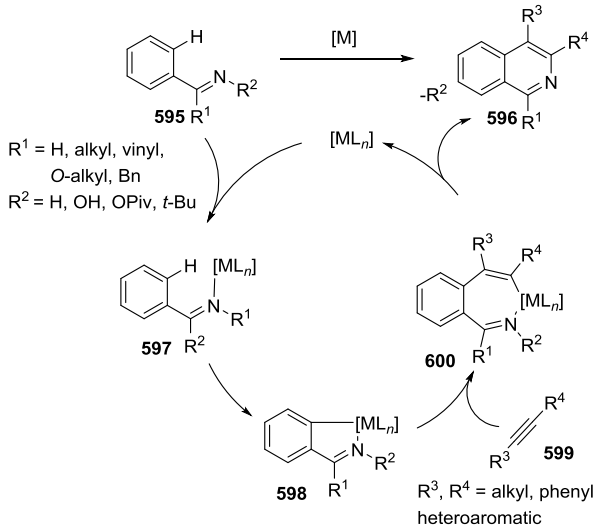
Traditionally, methods based on Friedel Crafts-type acylation such as the Bischler-Napieralski,[134] Pomeranz-Fritsch[135] and Pictet-Spengler[136] syntheses have been used to generate these heteroaromatic cores. These methods, initially developed in the late 1800s and early 1900s,

require strongly acidic conditions to generate an imine or a nitrile which then cyclises onto an aromatic ring. These procedures tend to be limited by the need for electron rich carbocycles and the functional group incompatibility inherent to the use of acidic conditions.

More recent methods have therefore been developed to widen the scope of isoquinoline syntheses by developing milder conditions and multi-component strategies. Some selected approaches towards this goal are shown below.

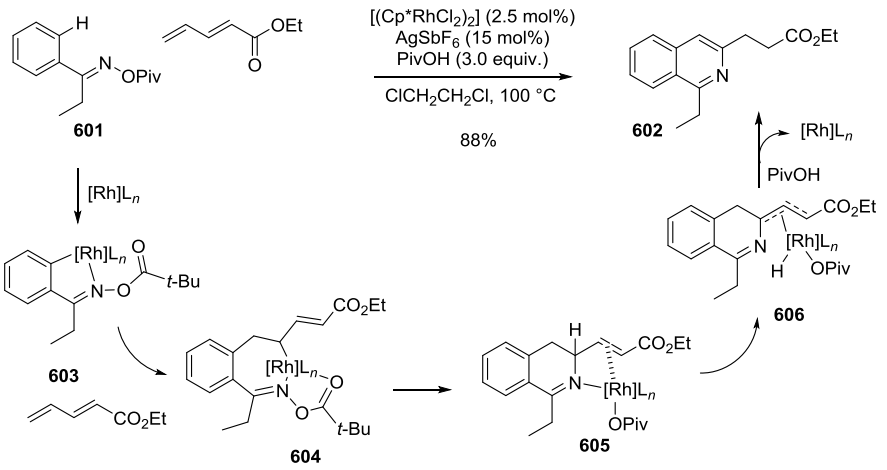
4.1.2 sp^2-CH Activation Approaches

A significant number of modern methods have focused on the use of transition metal-catalysed multi-component annulations to assemble the isoquinoline ring system. Such approaches allow minimal prefunctionalisation of substrates and offer high atom- and step-economy. Rh, Ru and Mn catalysts, among others, have been employed to mediate sp^2-CH activation / annulations employing internal alkynes.[137,138] A simplified general mechanism is shown below (Scheme 139). Nitrogen sources such as *N*-substituted and N-H imines, oximes, oxime ethers and amines (**595**) have been employed to direct insertion of a metal into the *ortho*-sp^2-CH bond, generating a 5-membered metallocycle **598**. Alkyne insertion then occurs into the carbon-metal bond, forming a 7-membered metallocycle **600**. Reductive elimination regenerates the catalyst and gives substituted isoquinolines of type **596**. Whilst an impressive range of isoquinolines have been generated through these methods, drawbacks include restrictions in the substituents possible when using internal alkynes and limited regioselectivity for unsymmetrical alkynes in certain cases.



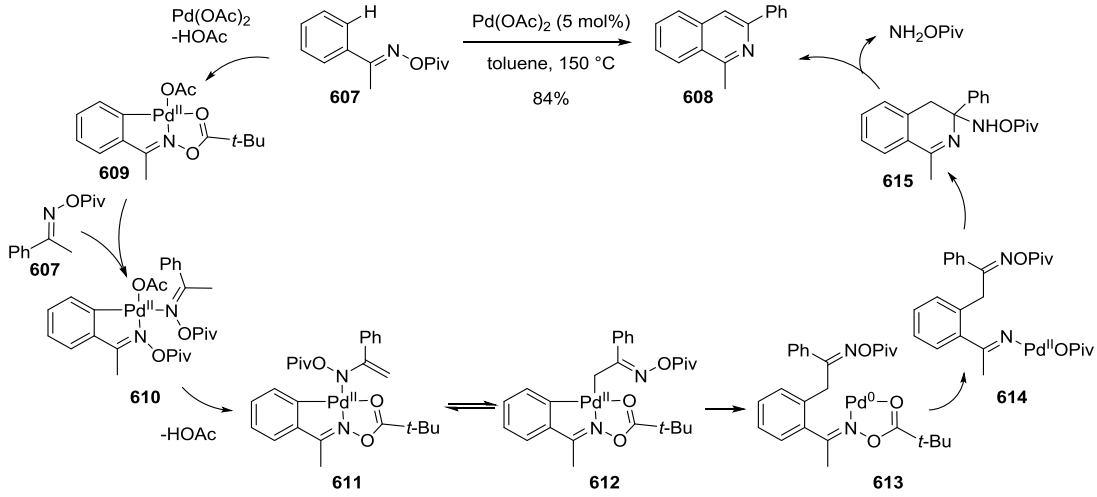
Scheme 139: sp^2-CH Activation / annulation using internal alkynes

Different substitution patterns can be accessed using coupling partners other than alkynes. Glorius and co-workers recently reported the first example of the use of 1,3-dienes in a sp^2-Rh(III) catalysed CH-activation / annulation strategy (Scheme 140).[139] Nitrogen directed insertion of Rh generates a 5-membered rhodacycle **603** as proposed in the general mechanism above. Insertion of a 1,3-diene generates 7-membered rhodacycle **604** which undergoes C-N bond formation and N-O bond cleavage to give intermediate **606** where Rh is co-ordinated to the alkene. β-Hydride abstraction and acid mediated isomerisation gives the observed isoquinoline. A range of 1,3-dienes were employed with complete regioselectivity to generate 3-alkyl substituted isoquinolines such as **602**. A silver additive was required to abstract chloride from the Rh pre-catalyst and form the active catalyst alongside AgCl.



Scheme 140: Use of 1,3-dienes and aryl oximes as coupling partners (Cp = cyclopentadienyl)

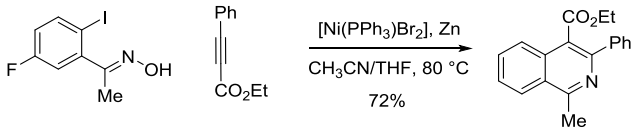
Under Pd-catalysis, Yang and co-workers successfully employed aryloxime pivolates **607** without the need for an external oxidant, generating 3-aryl substituted isoquinolines **608** (Scheme 141).[140]



Scheme 141: Isoquinoline synthesis by Pd-catalysed self coupling of acetophenone oxime acetate

In the proposed mechanism, palladacycle **609** undergoes ligand exchange with a second molecule of aryloxime pivolate. Loss of acetic acid and equilibration of enamine **611** generates **612** which undergoes reductive elimination, forming the required C-C bond in the *ortho* position. Regeneration of the catalyst and condensation generates isoquinoline **608**. It was also possible to access products of cross coupling, when a non-acetophenone partner was used and **607** was employed in excess.

As well as functionalisation of 'inert' sp^2-CH bonds, Cheng and co-workers developed a Ni-catalysed annulation method for the synthesis of isoquinolines and isoquinolinium salts using prefunctionalised *ortho*-halo ketoximines (**616**) (Scheme 142).[141] 1,3,4-Trisubstituted isoquinolines **618** were accessed in a highly regioselective manner using unsymmetrical aryl alkynes such as **617** with the aryl group of the alkyne preferentially adding to the position adjacent to nitrogen. The proposed mechanism follows the general scheme shown above (Scheme 139) with oxidative addition of Ni(II) into the C-I bond preceding formation of a 7-membered metallocycle on insertion of the alkyne.

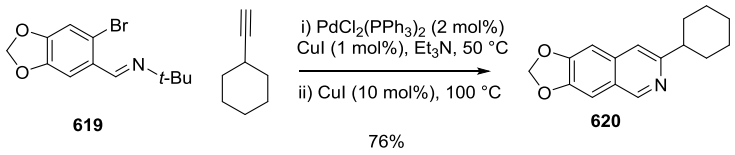


616 **617** **618**

Scheme 142: Ni-catalysed annulation of *ortho*-halo ketoximines with unsymmetrical alkynes

4.1.3 Imine Cyclisation onto *ortho*-Alkynes

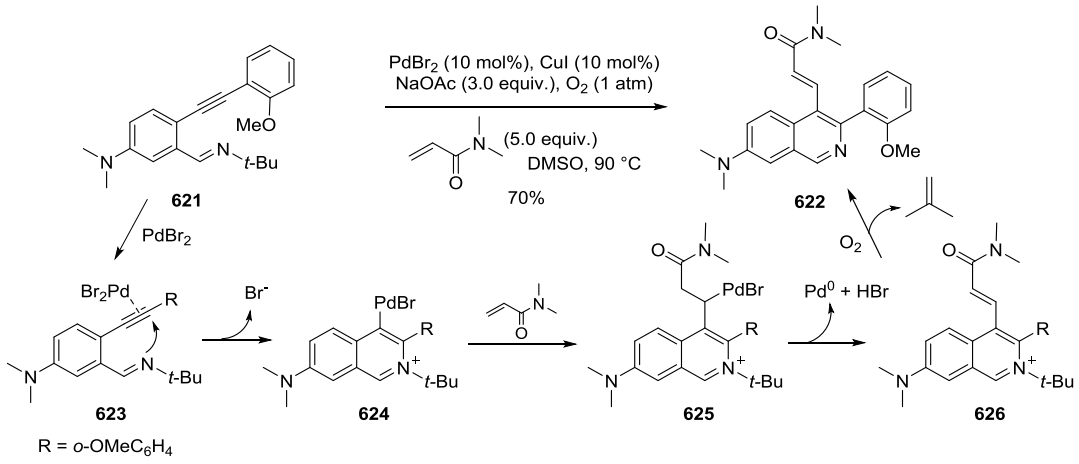
Larock and co-workers have developed several methodologies towards the synthesis of isoquinolines, including the copper-catalysed cyclisation of *ortho*-alkynyl imines **619** (Scheme 143).[142] Following palladium / copper co-catalysed Sonagashira coupling, the crude *ortho*-alkynyl imines were used directly to generate 1,4-unsubstituted isoquinolines **620** through cyclisation, elimination of *iso*-butene and protodemetallation.



619 **620**

Scheme 143: Cu-Catalysed cyclisation of *ortho*-alkynyl imines

3,4-Substitution patterns were also achieved by a Pd-catalysed cyclisation / Heck coupling cascade for the synthesis of highly functionalised isoquinolines **622** (Scheme 144).[143] Following cyclisation of the imine onto the palladium activated alkyne (**623**), the external olefin is added to the metallated position to give **625**. β-Hydride elimination reinstates the double bond and isoquinolium **626** fragments to give the product. Optimum conditions were found to require a copper-co-catalyst, an excess of base and O_2 as an oxidant. The group also demonstrated cyclisation of related substrates using electophiles such as sulfides and halogens under mild conditions.[144] An earlier contribution from the same group described the generation of dihydroisoquinolines from *ortho*-halo acylated benzylamines and alkynes using Pd catalysis.[145]



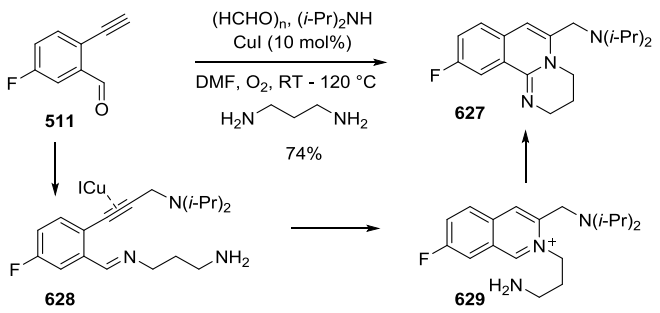
Scheme 144: Pd-catalysed cyclisation / Heck coupling methodology

Valuable 4-carboxylated isoquinolines could also be accessed through cyclisation of 2-alkynyl benzaldoximes by a Ag / Cu co-catalysed annulation reported by Yu and co-workers.[146] In a contrasting approach, $AuCl_3$ catalysed room-temperature benzannulation of oxo-alkyne substituted pyridines and electron deficient alkynes was reported by Sarkar and co-workers in the synthesis of quinolines and isoquinolines.[147]

4.1.4 Copper-Catalysed Cascade Reactions

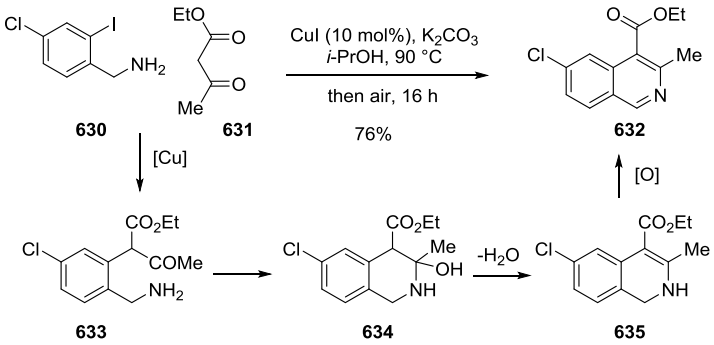
Fujii and Ohno reported a 4-component, one-pot synthesis of isoquinolines[148] and fused isoquinolines[149] (Scheme 145). Simple 2-ethynyl benzaldehydes such as **511** underwent a Mannich-type reaction alongside imine formation from the condensation of the aldehyde and primary amine to give **628** which subsequently cyclised to give isoquinolinium ion **629**. The tethered nucleophile can then attack the charged species, and following oxidation, polycyclic isoquinolines such as **627** can be accessed with high atom economy. Whilst an air atmosphere

was sufficient in many cases, the use of pure O_2 atmosphere was found to accelerate product formation.



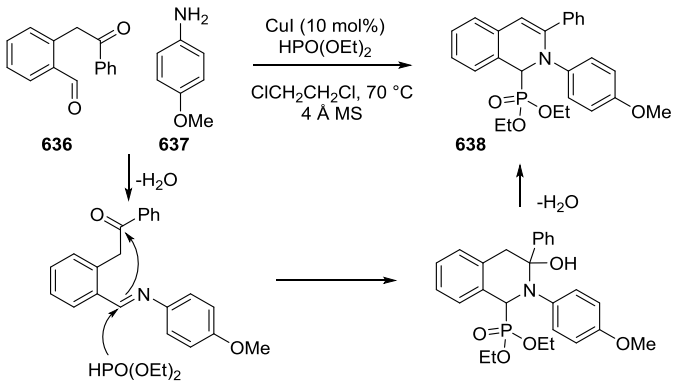
Scheme 145: Cu-catalysed 4 component synthesis of fused isoquinolines

In an alternative approach, Ma and co-workers found that 1,3-diketones and β-keto esters (**631**) underwent copper-catalysed coupling with *ortho*-halo benzylamines **630** (Scheme 146).[150] Subsequent cyclisation by condensation occurred smoothly in the presence of a mild base and the resulting dihydroisoquinolines **625** were oxidised in the presence of air to give 3,4-difunctionalised isoquinolines such as **632**.



Scheme 146: Cu-catalysed coupling of β-keto esters and *ortho*-halo benzylamines

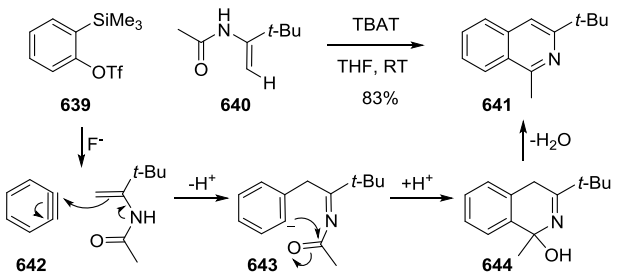
Wu and co-workers also recently described the synthesis of 1,2-dihydroisoquinolin-1-ylphosphonates **638** by a copper-catalysed 3-component cascade reaction between aromatic aldehydes **636**, anilines **637** and diethyl phosphate (Scheme 147).[151]



Scheme 147: Synthesis of 1,2-dihydroisoquinolin-1-ylphosphonates 638

4.1.5 Non-Metal Approaches

As well as the use of transition metals to promote isoquinoline formation, metal free examples have also been reported.[152,144] An elegant example of this was demonstrated by Stoltz and co-workers for the synthesis of isoquinolines and indolines through the annulation of benzynes with enamines (Scheme 148).[153] Silyl aryl triflates **639** were treated with a fluoride source to generate benzyne **642** which undergoes formal [4+2]-cycloaddition with enamine **640**. Aromatisation with loss of water gave isoquinolines such as **641** with a range of substitution patterns. It was also possible to apply this approach to the synthesis of the pharmaceutical papaverine (see Figure 11).



Scheme 148: Isoquinoline formation through benzyne annulation (TBAT = Tetrabutylammonium difluorotriphenylsilicate)

4.1.6 [1,5]-Hydride Transfer / Cyclisation

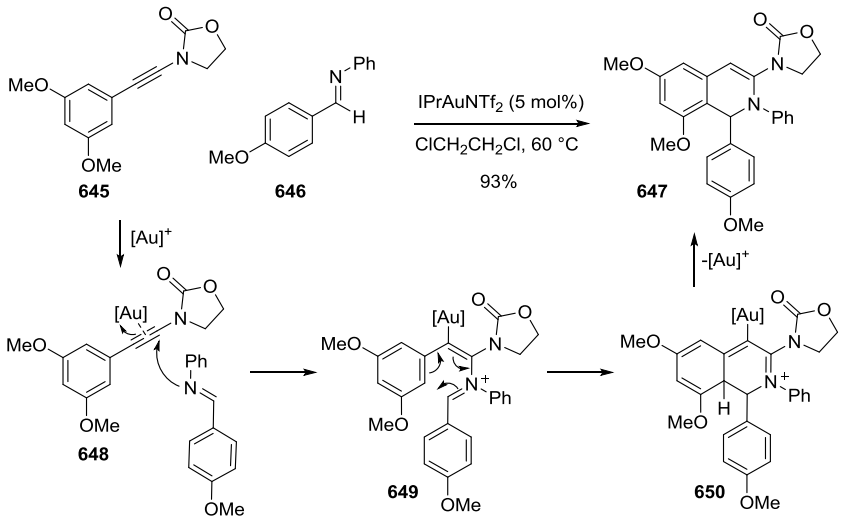
It is proposed that the isoquinoline synthesis described in section 4.2.2 occurs through a [1,5]-hydride shift / electrocyclisation mechanism (*vide supra/infra*). As discussed in Chapter 3, Lu and Wang recently described a copper-catalysed cascade for the synthesis of dihydroisoquinolines (see Scheme 99).[115] In this work, a ketenimine hydride acceptor was generated *in situ* which underwent cyclisation initiated by a [1,5]-hydride migration.

[1,5]-Hydride transfer / cyclisation of *ortho*-ketenimine benzacetals, reported by Alajarin, Vidal and co-workers for the synthesis of quinolines was also described. (Scheme 97 and Scheme 98).[89,112,113] The work of these two groups most closely resembles our own cascade reaction and the mechanistic similarities will be discussed in Section 4.2.

4.1.7 Ynamides in Isoquinoline Synthesis

During the course of our work, Skrydstrup and co-workers reported the gold-catalysed formal [4+2]-cycloaddition between ynamides and imines in the synthesis of highly functionalised dihydroisoquinolines (Scheme 149).[154] As exploited throughout our own work, regiocontrol is

ensured by the electronic properties of the ynamide (*vide infra*). Nucleophilic attack by imine **646** occurs at the α-carbon of the ynamide **645**. The imine intermediate **649** could then be trapped directly by the electron rich aryl group to give **650** which provides the observed product **647** on protodemetallation. An alternative mechanism through formation of an α-aziridine gold carbene was also suggested. The mechanism does not allow for 4-substitution of the isoquinoline and electron rich aromatics were required on the ynamide terminus. The isoquinolines obtained were highly functionalised however, and this work represents the first use of ynamides in the synthesis of isoquinolines.



Scheme 149: The use of ynamides in a gold-catalysed synthesis of isoquinolines.

4.2 Results and Discussion

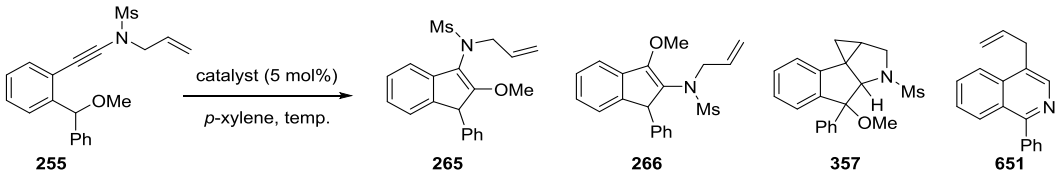
4.2.1 Reaction Discovery and Optimisation

Whilst the optimisation of reaction conditions for the gold-catalysed [1,5]-hydride transfer cascade were being investigated for *N*-allyl ynamide **255**, a new pathway was observed. At high temperature with $PPh_3AuCl/AgNTf_2$ as the catalyst system a new, structurally distinct product was observed by ^{1}H-NMR spectroscopy. Isolation of the new structure was possible by column chromatography and it was assigned as isoquinoline **651** (Table 4).

^{1}H-NMR spectra of a side product which was isolated following column chromatography of the crude reaction mixture of a copper-catalysed ynamide formation[68] to generate the *N*-allyl ynamide **255** was subsequently reanalysed. It appeared that the new isoquinoline **651** product had been previously observed in trace quantities. This observation led to a later short optimisation study focusing on the use of inexpensive copper salts (Table 4).

Several other Au(I) complexes were also tested at high temperature, and low yields of the isoquinoline product **651** were observed, alongside mixtures of other cycloisomerisation products reported in previous chapters (Table 4, Entries 1-4). Au(III) complex Au**L**Cl_2 (**L** = picolinate), used for the polycyclisation described in the previous chapter did not lead to any observable traces of isoquinoline **651** in the ^{1}H-NMR spectrum of the crude reaction mixture (Table 4, Entry 5). $AuCl_3$ however gave 22% yield of **651** (Table 4, Entry 6) at high temperature.

Table 4: Optimisation of reaction conditions[a]

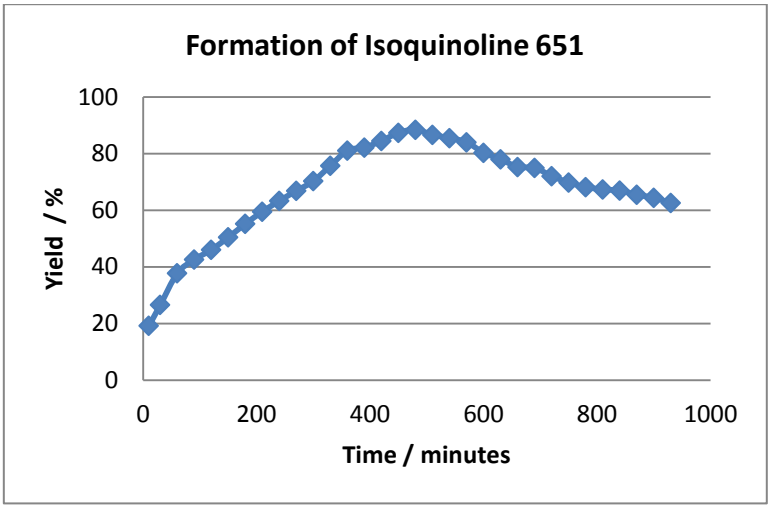


Entry	Catalyst	T/°C	Time/h	**255** /%[b]	**265** /%[b]	**266** /%[b]	**357** /%[b]	**651** /%[b]
1	$IPrAuCl/AgNTf_2$	120	6	--	14	9	traces	8
2	$XPhosAuCl/AgNTf_2$	120	3	--	traces	traces	traces	25
3	$PPh_3AuCl/AgNTf_2$	120	3	--	--	--	--	41 (37)
4	$JohnPhosAuCNMeSbF_6$	120	5	--	--	--	traces	27
5	$AuLCl_2$[c]	120	6	--	7	5	75	--
6	$AuCl_3$	120	4	--	7	3	32	22
7	$CuCl_2$	120	4	--	--	--	--	40
8	$CuOTf_2$	120	4	--	--	--	--	34
9	$Cu(MeCN)_4BF_4$	120	4	traces	--	--	--	18
10	CuI	120	4	--	--	--	--	58 (50)
11	CuI[d]	100	8	--	--	--	--	68 (65)
12	CuI[d]	80	24	40	--	--	--	32
13	None	120	24	23	--	--	--	16

[a] Reaction conditions: 255 (0.1 mmol, 1.0 equiv.), catalyst (5 mol%), solvent (0.1 M). [b] Yields calculated by ^{1}H-NMR spectroscopy against a known quantity of internal standard (1,2,4,5-tetramethylbenzene). Isolated yields shown in brackets. [c] L = picolinate. [d] solvent = toluene.

Simple copper salts CuI, $CuOTf_2$, $Cu(MeCN)_4BF_4$ and $CuCl_2$ were all found to promote the reaction generating isoquinoline **651** as the sole product in moderate yields (Table 4, Entries 7-10). Whilst in all cases the starting ynamide **255** was consumed, CuI gave the best yield of 58% (Table 4, Entry 10). High temperatures are necessary to promote this transformation, however

they also lead to product degradation. It was found that on reduction of the reaction temperature to 100 °C over a reaction time of 8 hours, a good yield of isoquinoline **651** could be isolated by column chromatography (Table 4, Entry 11). Even at the reduced temperature, care must be taken with the reaction time as degradation of the products begins to become significant after 8 hours. This could be clearly observed when the reaction was sampled every 30 minutes, and the samples analysed by HPLC (Graph 3).

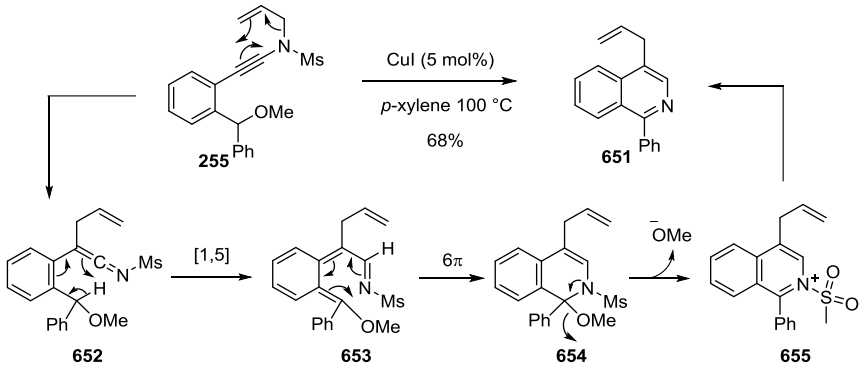


Graph 3: Formation and degradation of isoquinoline 651 at 100 °C using CuI (5 mol%) in toluene (0.1 M)

When the temperature was reduced to 80 °C, only 32% of **651** was formed, with significant starting material remaining after 24 hours (Table 4, Entry 12). Finally, as a control reaction, ynamide **255** was subjected purely to thermal conditions (Table 4, Entry 13). Whilst the isoquinoline was observed in 16% yield, unreacted starting material remained after 24 hours at 120 °C.

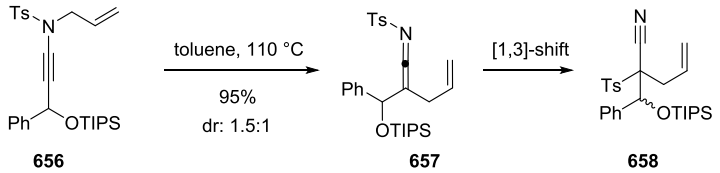
4.2.2 Reaction Mechanism

A mechanism is proposed below to account for the formation of the observed isoquinoline **651** (Scheme 150). The first step is an aza-Claisen rearrangement of the *N*-allyl ynamide **255**, to generate the sulfonyl ketene imine species **652**.



Scheme 150: Proposed mechanism for isoquinoline formation from ynamide 255

Hsung and co-workers have contributed a substantial amount of research to the formation of allyl ketenimines from rearrangement of *N*-allyl ynamides, promoted thermally or by palladium salts.[155] Ketenimine intermediate **657** is generated on heating ynamide **656** in toluene which evolves in this case through a 1,3-sulfonyl shift to generate nitriles such as **658** in excellent yields (Scheme 151).

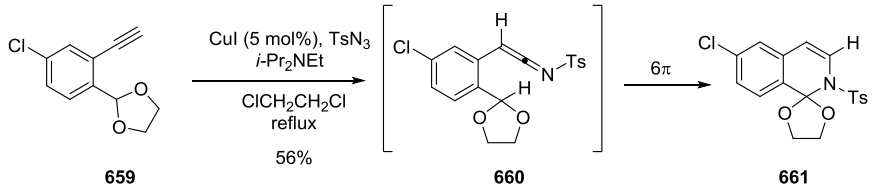


Scheme 151: Nitrile formation through aza-Claisen rearrangement / 1,3-sulfonyl shift

Following the formation on the sulfonyl ketene imine **652**, subsequent [1,5]-sigmatropic hydride migration occurs with dearomatisation of the benzene ring, generating imine **653**. The sulfonylated imine intermediate likely evolves through a 6π-electrocyclic ring closure with rearomatisation of the benzene ring, forming dihydroisoquinoline **654**, a mechanism supported by the work of Alajarin, Lu and Wang, and Liang in the synthesis of quinoline, isoquinoline and napthalene derivatives (*vide infra*).

Formation of isoquinolinium **655** should then proceed through the nitrogen-assisted expulsion of the methoxy group, gaining aromaticity in the second ring. In the final step, the formation of isoquinoline **651** could be envisaged in two ways. Substitution of the sulfonamide by the released methoxide may occur followed by release of the isoquinoline, a mechanism potentially valid for both mesyl and tosyl substituted systems (*vide supra*). Alternatively, deprotonation of the mesyl group by the released methoxide, generating methanol may precede release of the isoquinoline **651** by formation of a sulfonylmethane fragment.

Whilst ketenimine acceptors have been reported for [1,5]-hydride migration,[89,113,114] the only example of C-aryl ketenimines functioning as hydride acceptors was that recently published by Lu and Wang in the generation of isoquinolines (Scheme 152).[115]



Scheme 152: *In situ* formed C-aryl ketenimine hydride acceptors

It was possible to probe the proposed mechanism through intermediate trapping, substrate design and deuterium labelling (*vide supra*). It should be noted that the exact role of the copper catalyst is not included in the reaction mechanism. As observed (Table 4, Entry 13) the reaction proceeds at a reduced rate in the absence of catalyst. As the ynamide substrate **255** is formed under copper catalysis, traces of copper species in the reaction mixture cannot be ruled out entirely, however, each step is readily envisaged and supported by thermal activation. The catalyst may accelerate the reaction through binding to (a) the ketenimine, thereby promoting [1,5]-hydride shift, (b) the resulting imine, promoting 6π-electrocyclic ring closure (although these processes are generally expected to be thermally activated), or (c) the methoxy group, assisting aromatisation.

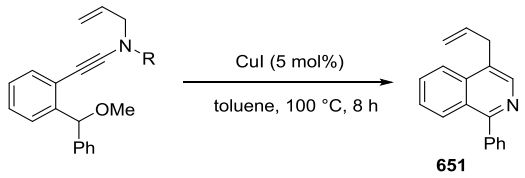
4.2.3 Reaction Scope

4.2.3.1 Modification of the Nitrogen Protecting Group

The use of the mesyl nitrogen protecting group on the ynamide was found to be crucial for the formation of isoquinoline **651** in high yield, reflecting the relative ease of removal in the final stage of the mechanism (Table 5). Ynamides **493**, **494** and **496** incorporating different *N*-protecting groups were prepared as described in chapter 3. Reaction of nosyl protected ynamide **493** failed to generate any isoquinoline **651** and the reaction appeared to stop at the dihydroisoquinoline stage (*c.f.* **654**, Scheme 150). Isolation was impossible in this case due to the complexity of the mixture (Entry 1). Tosyl and diethylphosphoramidate substituted

ynamides **494** and **496** underwent the reaction but afforded the isoquinoline in low yields alongside unreacted starting material and degradation (Entries 2 and 3).

Table 5: Effect of different nitrogen protecting groups[a]



651

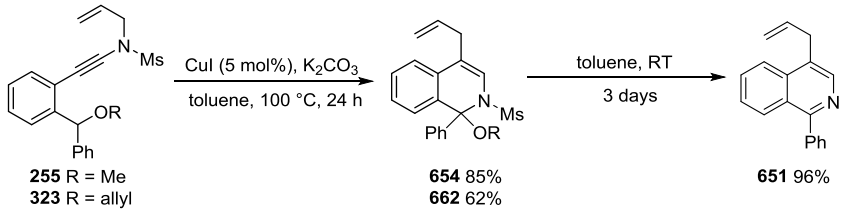
Entry	R	**Ynamide** / %[b]	**651** / %[b]
1	**493** R = Ns	9	--[c]
2	**494** R = Ts	25	20
3	**496** R = $P(O)(OEt)_2$	19	9

[a] Reaction conditions: ynamide (0.1 mmol, 1.0 equiv.), solvent (0.1 M). [b] Yields calculated by 1H-NMR spectroscopy against a known quantity of internal standard (1,2,4,5-tetramethylbenzene). [c] Dihydroisoquinoline product observed by ^{1}H-NMR spectroscopy but isolation not possible.

4.2.3.2 Trapping of Dihydroisoquinoline Intermediates

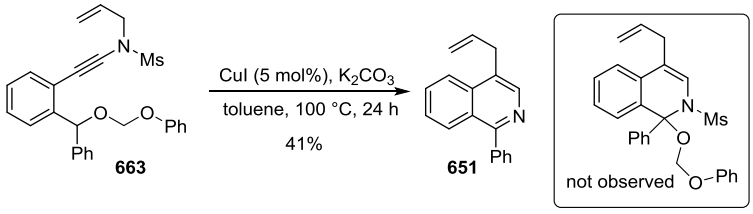
It was postulated that the breakdown of dihydroisoquinoline **654** (Scheme 150) may be promoted by a proton from adventitious water or from traces of acid present in the reaction mixture. To eliminate this pathway and potentially observe this intermediate, the reaction was conducted in the presence of a slight excess of K_2CO_3. It was indeed possible to isolate **654** in high yield following column chromatography with triethylamine-treated silica (Scheme 153). To further support the intermediacy of **654**, on standing in toluene at room temperature, slow conversion was observed over 3 days to yield the isoquinoline **651** in 96% yield (based on **654**). It was also possible to access dihydroisoquinoline **662** in good yield by reaction of bis-allylated

ynamide **323**. In both cases, the products are stable under the basic reaction conditions, even after 24 hours, making their synthesis more attractive as degradation is not observed.



Scheme 153: Isolation of dihydroisoquinolines by addition of K_2CO_3 to the reaction

A BOM-ether protected ynamide **663** was also prepared and subjected to the same conditions (Scheme 154). The labile functionality however was eliminated and **633** was converted directly to isoquinoline **651**, which was isolated as the sole product in moderate yield.

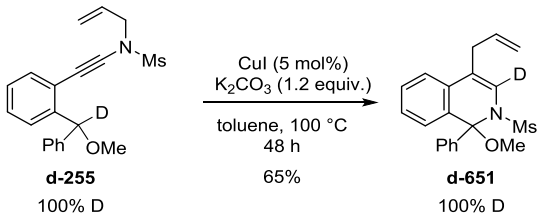


Scheme 154: Attempt to incorporate a BOM-ether functionality

4.2.3.3 Deuterium Labelling Studies

In order to confirm the intramolecular nature of this reaction, deuterium labelled ynamide **d-255** was synthesised in the same manner as that as described in Chapter 3 for the tosylated variant (Compound **d-494**, Scheme 131) and subjected to the reaction conditions (Scheme 155). Complete Deuterium incorporation at the C-3 position was observed in the dihydroisoquinoline product **d-651** (see Apendix) which is in line with the proposed mechanism whereby

protonation of the sulfonyl ketene imine occurs *via* intramolecular [1,5]-hydride migration from the benzylic position. A kinetic isotope effect was indicated with the reaction rate of **d-255** being approximately half that observed for the non-deuterated example (Scheme 153). As mentioned previously, computational,[97,113] and isotopic labelling studies in our own work (Chapter 3, Section 3.5) and the work of others,[110,116] have indicated that for [1,5]-hydride migration processes, cleavage of the C-H bond is the rate determining step (or the turnover-limiting step for catalytic reactions).

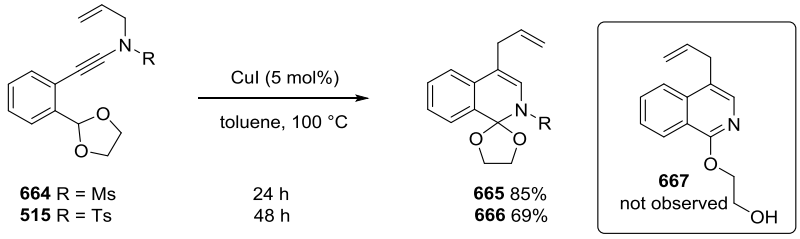


Scheme 155: Complete deuterium incorporation for the Cu-catalysed cascade

4.2.3.4 *ortho*-Benzacetals as Hydride Donors

Based on the previous work of Alajarin and co-workers[89,112,113,114] and previous success in my own work, employing acetals to increase the 'hydricity' of the donor, a series of ynamides were synthesised incorporating a cyclic acetal at the benzylic position. Copper catalysed amidation reactions were again employed as described in Chapters 2 and 3.[71] The addition of K_2CO_3 was initially maintained due to the stability of the dihydroisoquinolines **654** and **662** under the reaction conditions (Scheme 153). It was anticipated that in the absence of a base the isoquinoline **667** would be formed through aromatisation and ring opening of the acetal (Scheme 156). When ynamide **664** was subjected to the reaction conditions however, no

consumption of starting material was observed after 24 hours. When this was repeated, omitting the K_2CO_3 additive, the protected oxyisoquinoline derivative **665** was isolated in high yield. No degradation or traces of **667** in the reaction mixture were observed by ^{1}H-NMR, indicating these products are stable even over long reaction times at high temperature.

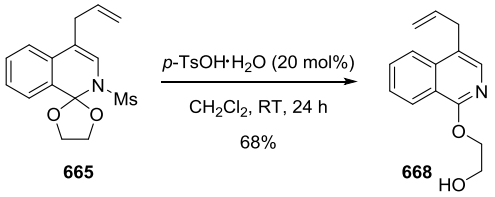


Scheme 156: Formation of dioxyoisoquinolines 665 and 666

The reason behind the lack of reactivity of ynamide **664** in the presence of K_2CO_3 is unclear at this stage. In the case of benzyl ether substituted ynamide **255**, under basic conditions, the reaction rate was reduced, although consumption of starting material was complete in 24 hours. In contrast, when base was omitted, the formation of isoquinoline **651** was observed after just 8 hours (Table 4, Entry 11 vs. Scheme 153). K_2CO_3 could be preventing the copper catalyst from binding, which might be a more important factor in the present case as benzyl ether substrate **255** was shown to undergo slow reaction in the absence of copper. Another possibility is that the base eliminates any traces of acid, which may act as the catalyst in this system.

It was possible to incorporate a larger tosyl protecting group in this type of substrate, to generate **666** in good yield (Scheme 156). Unfortunately, the reaction rate was doubled as

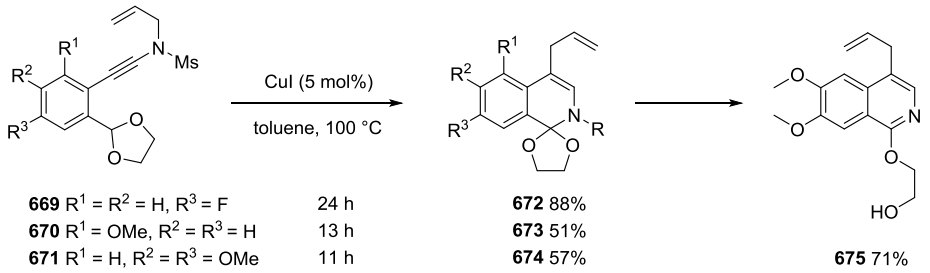
compared to the mesyl substituted system **665** and so for this reason, it was not practical to subject the *N*-allyl-*N*-tosyl ynamides synthesised in Chapter 3 to the present chemistry. Acetal-derived mesyl protected ynamides were synthesised for the remainder of the study, and K_2CO_3 was omitted from the reaction conditions. In a preliminary study, deprotection of the dioxyisoquinoline **665** was demonstrated in the presence of a mild acid. Aromatisation with cleavage of the acetal ring to give **668** was observed by ^{1}H-NMR (Scheme 157).



Scheme 157: Deprotection of dioxyisoquinoline 665

4.2.3.5 Modification of the Benzene Backbone

In light of these promising results incorporating the acetal functionality, the scope of this intriguing transformation was explored. A fluorine substituent on the benzene backbone was well tolerated (Scheme 158) with no observable effect on the reaction rate, compared to the non-substituted system **664**. Dihydroisoquinoline **672** was isolated in high yield after 24 hours and no degradation was observed by TLC or ^{1}H-NMR spectroscopy.



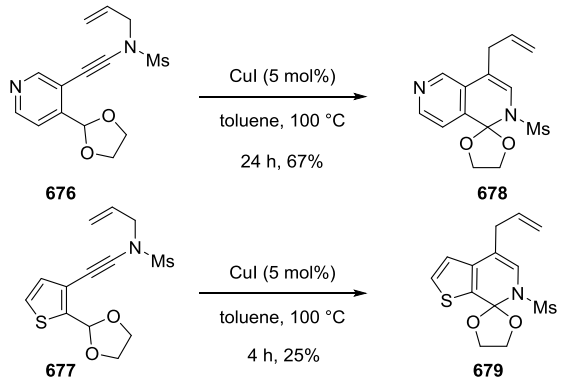
Scheme 158 Substitution of the benzene ring with F and OMe substituents

In the gold-catalysed cascade described in Chapter 3, a methoxy group *ortho* to the triple bond completely suppressed the reaction. This was assigned to the gold-bound keteniminium acceptor not being able to adopt the required conformation for 1,5-hydride transfer. In the present case, the first step in the proposed mechanism is an aza-Claisen rearrangement of the *N*-allyl ynamide, which generates an alternative ketenimine hydride acceptor which appears not to be restricted by the neighbouring group in terms of adopting the required conformation. A moderate yield of oxyisoquinoline **673** was isolated. Whilst the ynamide **670** was consumed, the reduced yield is attributed to product degradation.

When the more electron-rich dimethoxy substituted ynamide **671** was left to react for 16 hours, all of the product **674** (the formation of which was observed by TLC) was lost through degradation pathways and a complex mixture was observed by ^{1}H-NMR spectroscopy. The reaction was repeated with careful monitoring, and consumption of starting ynamide **670** was complete after 11 hours. The desired dihydroisoquinoline **674** was then isolated following column chromatography, however, the sample was contaminated by traces of grease (only a ^{1}H-NMR spectrum was obtained). Several attempts to recrystallise the product were subsequently

made and on repeating the ^{1}H-NMR experiment, a new product **675** had been isolated. For this electron rich system, aromatisation and opening of the acetal ring occurred spontaneously on standing in solvent to give alcohol **675** in good yield (based on conversion from **674**).

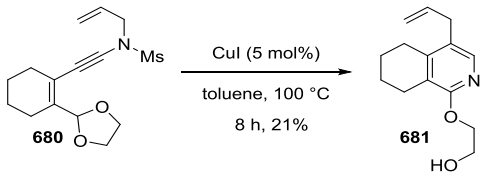
Whilst the pyridine and thiophene based ynamides were not reactive under gold-catalysed conditions, the mesylated equivalents **676** and **677** did react in the current transformation (Scheme 159). This demonstrates differences in the nature of the hydride acceptors in the two transformations. Deactivation of the gold catalyst by competing coordination to sulfur or nitrogen may also be a factor. The 2,6-naphthyridine ring system **678** was generated smoothly in good yield although some degradation was visible on the walls of the reaction tube. The thiophene equivalent **677** also underwent the desired reaction, however, degradation was more substantial in this case and only 25% of the thieno-pyridine fused system **679** was isolated after two independent reactions.



Scheme 159: Reactions of pyridine and thiophene systems

Finally, cyclohexane derived ynamide **680** was prepared and subjected to the reaction conditions, however, none of the expected tetrahydroxyisoquinoline product was observed

(Scheme 160). As seen with the dimethoxy substituted system **671** (Scheme 158), aromatisation alongside opening of the acetal ring appears facile after cyclisation. The alcohol **681** could only be isolated in approximately 21% yield and the purity was not of an acceptable level to report. As discussed in Chapter 3, a similar elimination pathway was observed by Alajarin and co-workers where a series of spironapthalenes were converted into the corresponding 1-(2-hydroxy)ethoxy-2-substituted napthalenes *in situ* through a β-elimination pathway (*vide supra*, Scheme 97).[112] In the dimethoxybenzene and cyclohexene derived substrates **675** and **681**, the driving force for aromatisation appears stronger than for unsubstituted or fluorine substituted benzenes. Presumably in the dimethoxy example, the more electron rich nature of the π-system drives aromatisation. In the case of the cyclohexene, transformation from a fully non-aromatic system to an aromatic one, should be a stronger driving force than for the benzenoid systems.

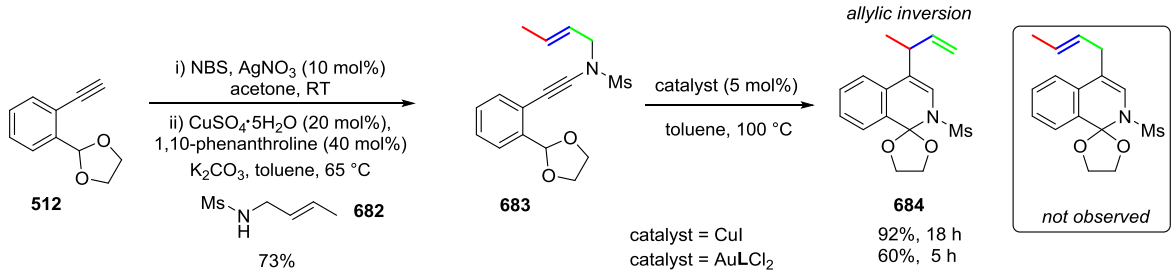


Scheme 160: Reaction of cyclohexane derived ynamide 680

4.2.3.6 Support for an Aza-Claisen Mechanism

In order to test our proposed mechanism, whereby the ketenimine hydride acceptor is generated through a concerted aza-Claisen rearrangement, ynamide **683** was prepared incorporating a methyl substituted *N*-allyl substituent (Scheme 161). The proposed rearrangement of this group was confirmed by isolation of a single isomer **684** in excellent yield,

with inversion of the allyl group. If a cationic, step-wise mechanism was in operation, we would expect a mixture of branched and linear isomers.



Scheme 161: Confirmation of a concerted rearrangement of the *N*-allyl group (L = picolinate)

Interestingly, when ynamide **683** was subjected to the gold-catalysed conditions reported in Chapter 3, no tetracycle was formed at 80 °C. However, oxyisoquinoline **684** was isolated in 60% yield when the temperature was increased to 100 °C. As described in the previous chapter, methyl substitution of the *N*-allyl group for the gold-catalysed transformation was met with failure in all cases. This was assigned to the possibility of the more electron-rich alkene providing a better ligand for gold than the triple bond, therefore ynamide activation was unavailable. Whilst the yield of **684** is reduced, gold is clearly capable of promoting the reaction. With the gold-bound keteniminium not accessible, the competing isoquinoline formation can occur. This is in agreement with the initial optimisation studies where certain gold catalysts were found to promote isoquinoline formation (Table 4).

4.3 Conclusions

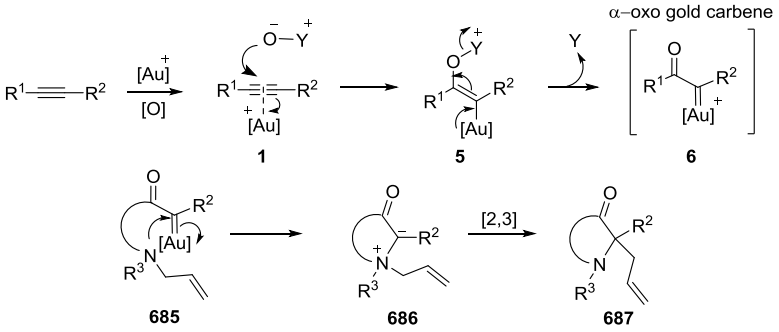
The first synthesis of valuable isoquinolines and oxyisoquinolines directly from *N*-allyl ynamides has been demonstrated using an inexpensive copper catalyst through a [1,5]-hydride transfer / cyclisation cascade. The intriguing mechanism of this transformation has been probed and the intermediacy of a dihydroisoquinoline has been proven. A range of 1,4-disubstituted isoquinolines have been generated in moderate to excellent yields. Acetal substituted products are readily accessed, including pyridine and thiophene fused systems.

Deuterium labelling has confirmed the intramolecular nature of the hydride transfer, as well as suggesting a kinetic isotope effect, with cleavage of the CH / CD bond being involved in the turnover limiting step. The concerted nature of the initial aza-Claisen rearrangement of the *N*-allyl ynamide has also been demonstrated through substitution of the allyl group.

Chapter 5: Generation of Ammonium Ylides Directly from Alkynes and Ynamides

5.1 Introduction

As discussed in Chapter 1, α-oxo gold carbenes are highly valuable intermediates and the ability to generate these species directly from alkynes has been a highly active area of research in recent years. Generated through a π-acid catalysed redox reaction between an alkyne and a nucleophilic oxidant (**1**→**6**), it was proposed an α-oxo gold carbene could be trapped by attack of a suitable nitrogen nucleophile, to generate an ammonium ylide such as **686**. There is still debate about the order of steps for this type of process.[8,9] The vinyl gold intermediate **5** is also electrophilic and so attack of the nitrogen nucleophile may occur prior to elimination of the leaving group, to give the same outcome. Throughout this chapter, formation of a distinct α-oxo gold carbenoid is drawn for simplicity. Shown here for an allyl containing system, [2,3]-sigmatropic rearrangement of **686** could be exploited to access a range of functionalised nitrogen heterocycles (Scheme 162).



Scheme 162: Formation of an α-oxo gold carbene and intramolecular trapping with a nitrogen nucleophile to generate an ammonium ylide

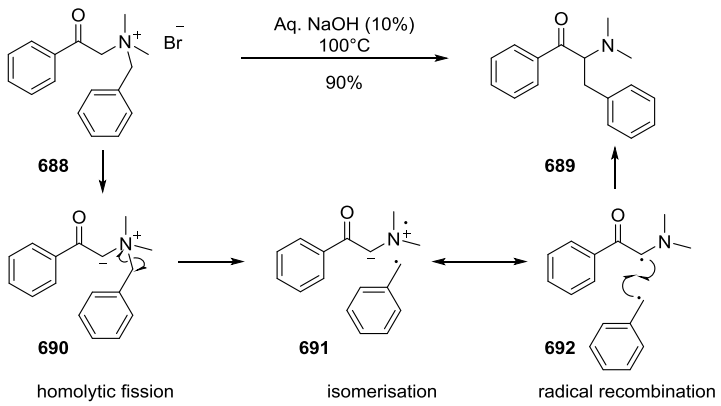
Nitrogen heterocycles are widespread throughout nature and pharmaceuticals and so their efficient generation from simple starting materials is highly attractive and is an ongoing target in

organic chemistry. Traditional methods for the generation of ylides involve sacrificial functionality[9c] which reduces synthetic efficiency by increasing the number of manipulations required. In contrast, mechanisms such as that shown above (Scheme 162), lead to more step- and process- efficient transformations and are therefore an interesting target area for research.[156] This methodology would mean alkynes could be employed as 'masked' ammonium ylides and therefore a direct precursor to this highly reactive intermediate could be introduced earlier in a target synthesis, allowing greater flexibility when designing retrosyntheses. This chapter will detail work towards the realisation of this goal using gold catalysis.

5.1.1 Rearrangements of Ammonium Ylides

5.1.1.1 [1,2]-Rearrangements

In 1928, Stevens and co-workers were the first to observe the rearrangement of a benzyl group as a result of the formation of an ammonium ylide.[157,158] The rearrangement of 2-(benzyldimethyl)ammonium acetophenone **688** into 2-benzyl-2-dimethylamino acetophenone **689** was observed in the presence of aqueous sodium hydroxide at high temperature (Scheme 163). Stevens deduced that the reaction was intramolecular based on crossover studies.[159] A concerted electrocyclic mechanism is stereoelectronically unfeasible due to orbital symmetry requirements, and would lead to a highly strained transition state. The reaction likely involves diradical intermediates (**690**-**692**).[160,161]

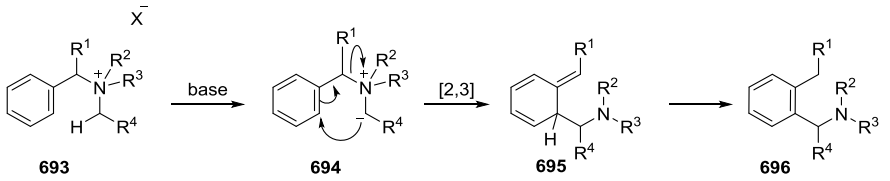


Scheme 163: Discovery of the Stevens rearrangement

Radical recombination reactions are usually inefficient processes, which contrasts with the high yields observed here. It was proposed that the two reactive components are held together by a solvent cage, the diffusion from which is slower than the reaction steps, giving the radical recombination step intramolecular efficiency.

5.1.1.2 [2,3]-Rearrangements

[2,3]-Sigmatropic rearrangements can also occur for benzylic ammonium ylides (**694**). They produce stable, neutral tertiary amines and are therefore favourable processes. This is reflected in the observation that even aromatic ring systems can participate in such processes, despite the reduced thermodynamic favourability associated with dearomatisation. Such benzylic rearrangements are known as Sommelet-Hauser rearrangements (Scheme 164)[162] and are initiated by deprotonation of ammonium salt **693** with a suitable base.



Scheme 164: The Sommelet-Hauser Rearrangement

There is often competition between the [1,2]- and [2,3]-rearrangement mechanisms for benzylic ammonium ylides with the distribution of products depending on the reaction conditions and substrate structure. When favourable allylic [2,3]-rearrangement is possible however, [1,2]- and [2,3]-benzyl rearrangement mechanisms are not usually observed.[160]

[2,3]-Rearrangements of acyclic allyl sulfonium ylides were first reported by Baldwin and co-workers in 1968.[163] Ollis and co-workers subsequently published their work in this area, which they extended to include ammonium ylide rearrangements.[164]

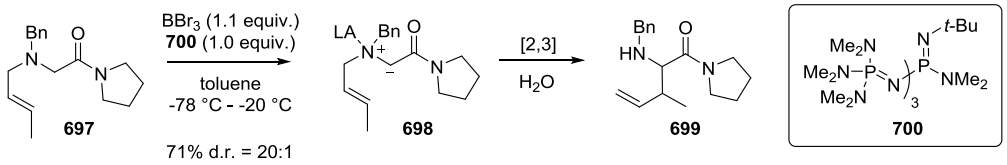
5.1.2 Formation of Ammonium Ylides

5.1.2.1 Non-Metal Approaches to Ammonium Ylides

Ammonium ylides are traditionally prepared *via* alkylation of an amine and subsequent deprotonation of the ammonium salt using a suitable base, a method first reported by Stevens and co-workers.[157] Desilylation of α-silylammonium salts using a fluoride source represents another method.[165]

[2,3]-Sigmatropic rearrangements of acyclic ammonium ylides can proceed with low stereoselectivity and the formation of a tertiary amine also requires that a protecting group is

installed to allow for further Derivatisation. To improve on these limitations, Lewis acids can be employed. For example, Blid and Somfai demonstrated that complexation of a Lewis acid to an acyclic amine, such as **697** prior to ylide formation by deprotonation (**698**), can lead to an allylic [2,3]-sigmatropic rearrangement. Following work-up, a secondary amine **699** is formed, with good control of diastereoselectivity (Scheme 165).[166]



Scheme 165: Lewis acid mediated [2,3]-sigmatropic rearrangement

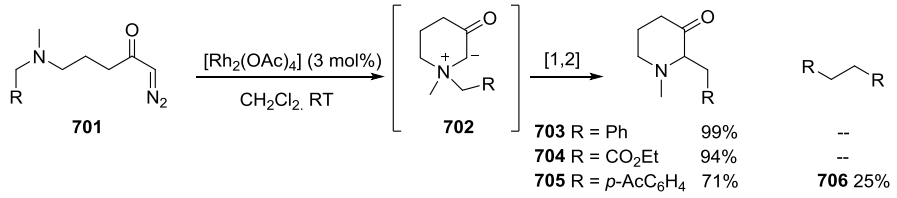
Nitrile substituted ammonium ylides have also been reported, where the nitrile group provides additional stabilisation for the ylide and also acts as a traceless protecting group. The nitrile is readily removed following rearrangement of the ylide, which is generally formed in the presence of base. [167]

5.1.2.2 Decomposition of Diazo Compounds

Ammonium ylides can be formed by the direct reaction of carbenes with a suitable nitrogen nucleophile, however, the high reactivity of carbenes renders this method of limited use.[160] Carbene precursors, such as diazo compounds, can be employed which allow the *in situ* generation of metal carbenes in the presence of substoichiometric quantities of transition metals such as copper or rhodium, generally under mild reaction conditions.[168] Attack of a neutral nitrogen nucleophile onto the carbene centre displaces the metal to generate an ylide.

This methodology was first reported by Doyle[169] and co-workers although its development has been somewhat hindered by competing carbene reaction pathways such as C-H insertion, dimerisation and cyclopropanation, or by the deactivation of the metal catalyst by heteroatoms.[170]

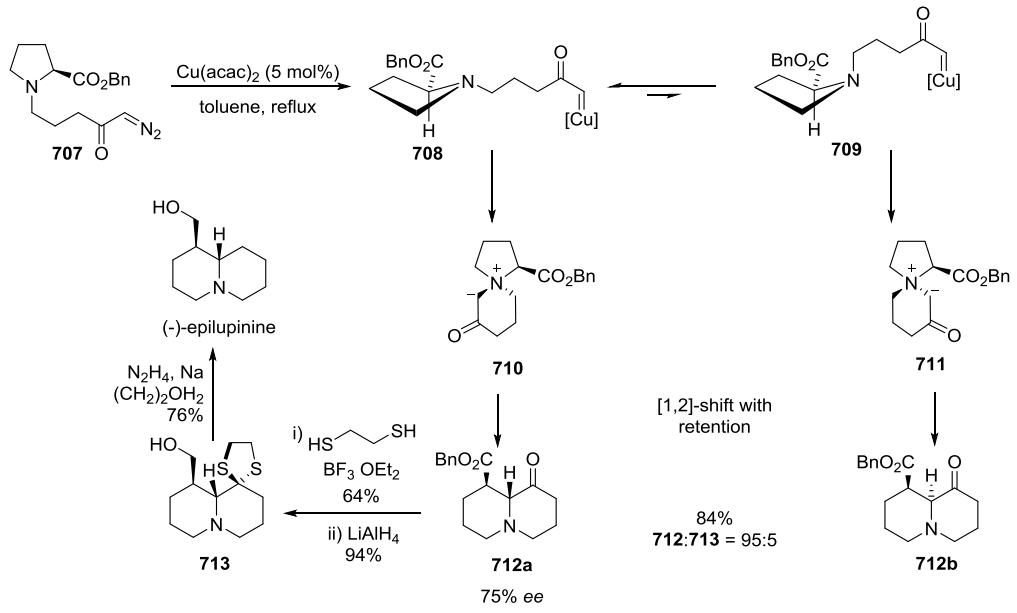
West and co-workers have reported the formation of cyclic ammonium ylides from the metal-catalysed decomposition of α-oxo diazo compounds (Scheme 166). The tertiary amine **701** cyclises onto an *in situ* formed metal carbene to generate cyclic ylide **702** which can evolve through an *exo*-[1,2]-Stevens rearrangement.[171,172] Using rhodium catalysis at room temperature, substituted piperizines **703** and **704** were formed as the sole products in excellent yields, with catalyst deactivation through amine coordination not apparent. High-dilution and slow addition techniques, usually employed to minimize side products, were not required. When substituted benzyl migrating groups were used, some formation of the homocoupled dimer **706** was observed which was rationalised by a greater tendency for the aryl radical to be displaced from the proposed solvent cage.



Scheme 166: [1,2]-Stevens rearrangement of cyclic ammonium ylides

Ammonium ylide chemistry lends itself well to the formation of synthetically important fused nitrogen heterocycles. West and co-workers also reported the generation of spirocyclic

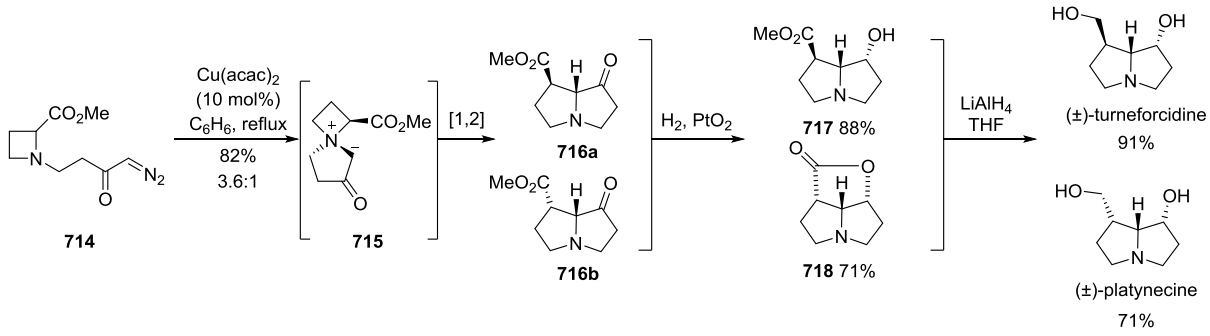
ammonium ylides through the copper-catalysed decomposition of (*S*)-proline derived α-oxo diazo compound **707** (Scheme 167).[173] Quinolizidine core **712** was generated in high diastereoselectivity from the preferential formation of ylide **710**. Ring expansion through a 1,2-Stevens shift occurred with stereochemical retention and the major diastereoisomer **712a** was formed in 75% *ee*. The transfer of chiral information was thought to occur due to rapid recombination of radicals, occurring faster than bond rotation. The major diastereoisomer **712a** was then converted to the alkaloid (-)-epilupinine in three steps.



Scheme 167: Diastereo- and enantioselective formation of the quinolizidine core from a proline derivative

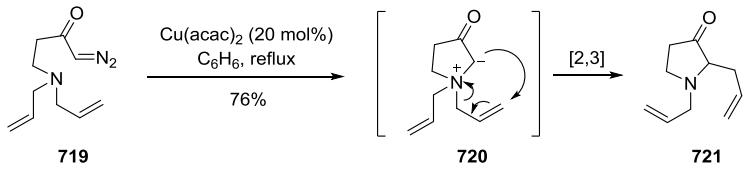
A ring expansion strategy was also employed for the synthesis of bicyclic alkaloids from spirocyclic azetidinium ylides such as **715** by West and co-workers (Scheme 168).[174] Using copper catalysis, α-oxo diazo **714** was converted into an inseparable mixture of bicyclic diastereoisomers **716a** and **716b** in high yield. The ketones were then reduced to give a

separable mixture of **717** and **718** which were then treated with $LiAlH_4$ to give the racemic alkaloids (±)-turneforcidine and (±)-platynecine in 5 steps from commercially available materials. Yu, Che and co-workers have also reported the total synthesis of (±)-platynecine in 8 steps, including a [2,3]-sigmatropic rearrangement of an cyclic ammonium ylide.[175]



Scheme 168: [1,2]-Rearrangement of a spirocyclic ammonium ylide in the synthesis of bicyclic alkaloids

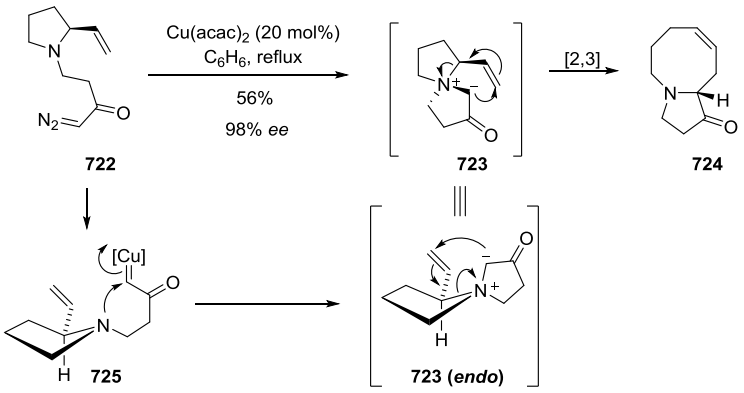
Clark and co-workers reported the intramolecular [2,3]-sigmatropic rearrangement of cyclic allylic ammonium ylides **720**, generated by the $Cu(acac)_2$-catalysed decomposition of α-oxo diazo compounds such as **719** (Scheme 169).[176] The formation of five- to eight-membered *N*-heterocycles was achieved in modest to good yields.



Scheme 169: Preparation of cyclic amines by the [2,3]-sigmatropic rearrangement of ammonium ylides

Substrates were then explored where the allyl group was incorporated as part of the cyclic amine and so [2,3]-sigmatropic rearrangements lead to fused bicycles such as **724** (Scheme

170).[177] Enantiopure α-oxo diazo compound **722**, derived from (*S*)-prolinol was subjected to copper catalysis to generate spirocyclic ammonium ylide **723**. Using a similar model to that proposed by West, one of the diastereomers available from nitrogen inversion is favoured, generating a spirocyclic ylide where the vinyl group is positioned *endo*- to the newly formed ring. Cyclisation of the ylide generates the observed product with high enantioselectivity. Similar transformations have been reported by McMills, using (*S*)-proline derived α-diazo esters to generate azacene rings.[178]



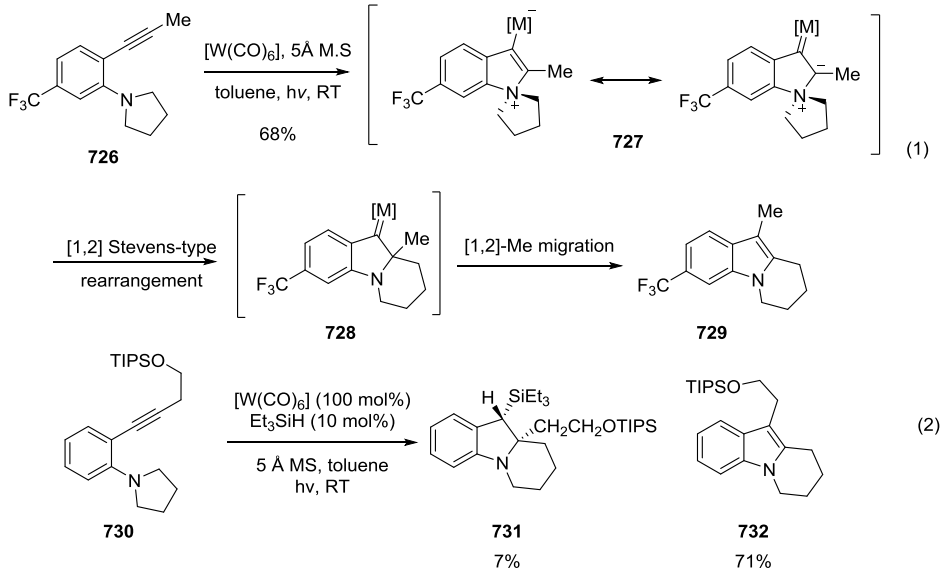
Scheme 170: Enantioselective synthesis of the core of manzamine-type alkaloids

5.1.2.3 Ylides Directly From Alkynes

As discussed in Chapter 1, there is a demand to replace the use of diazo compounds as carbene precursors due to the potentially explosive nature of these compounds, alongside the need to incorporate extra synthetic steps.[12] Therefore the prospect of the generation of carbenes directly from alkynes is an attractive one.

As described in Chapter 2 for a 1,1-carboamination strategy, metal-containing ammonium ylides **727** were invoked as important intermediates in the formation of polycyclic indoles **729** by

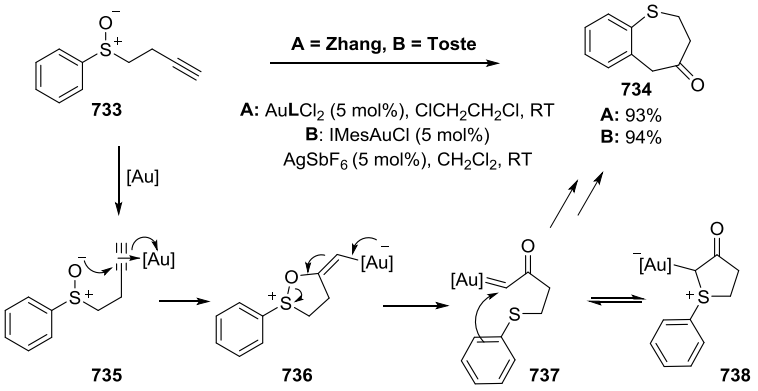
Iwasawa and co-workers (Scheme 171, Eq. [1]).[63] Activation of *ortho*-alkynylphenyl pyrrolidine or piperidine derivatives with an electrophilic transition metal catalyst leads to nucleophilic attack of the alkyne by nitrogen. The ammonium ylide **727** then undergoes ring expansion through a [1,2]-Stevens-type rearrangement to give metal carbene **728**. 1,2-alkyl migration to quench the carbene affords the observed *N*-fused tricyclic indole derivatives with an overall 1,1-carboamination of the alkyne (*vide supra*, Chapter 2). Whilst gold and platinum catalysts failed to give the desired product, tungsten and rhenium catalysts promoted the reaction efficiently. The intermediacy of the metal carbene was proven by trapping with triethylsilane to afford observable quantities of **731** (Scheme 171, Eq. [2]).



Scheme 171: [1,2]-Stevens-type rearrangement of metal-containing ammonium ylides

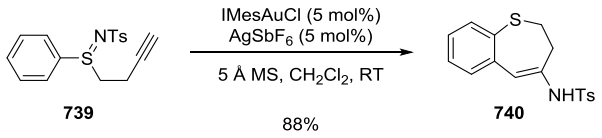
5.1.2 Rearrangements of Sulfonium Ylides

α-Oxo gold carbenoids can be generated by the reaction of a gold-activated alkyne with an oxygen-delivering oxidant in an inter- or intramolecular fashion (*vide supra*, Chapter 1). Attack of a suitable nucleophile onto the carbene centre has the potential to generate ylides. This reactivity was initially proposed independently by the research groups of Toste[9a] and Zhang[179] in some of the earliest reports of α-oxo gold carbenoid formation directly from alkynes. Both groups aimed to determine whether these intermediates could be generated *via* a gold-catalysed rearrangement whereby a sulfoxide acts as the nucleophile and also as the leaving group (Scheme 172). In both cases, formation of tetrahydrobenzothiepinones such as **734** was observed in excellent yields. The initially proposed mechanism is detailed below, whereby α-oxo gold carbene formation (**737**) precedes Freidel-Crafts-type cyclisation to form products **734** in excellent yields. The potential reversible formation of gold-containing sulfur ylide **738** was also proposed by Zhang as a means of assisting stabilisation of the gold carbene.



Scheme 172: Proposed mechanism for the formation of tetrahydrobenzothiepinone. IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazolium

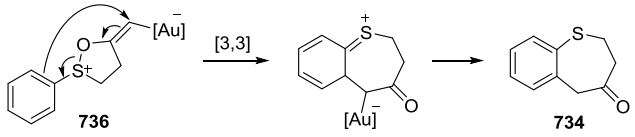
In order to confirm the transfer of oxygen from the sulfoxide gave the ketone in the final product, a sulfimine **739** was subjected to the same cyclisation conditions by Toste and co-workers to give the *N*-tosyl enamine **740** (Scheme 173).



739 **740**

Scheme 173: Formation of an *N*-tosyl enamine

This mechanism was recently further investigated by Zhang and co-workers who expanded the reaction scope and carried out computational studies.[180] As a result, a high energy barrier for the proposed Friedel-Crafts type cyclisation was calculated for this system (**737**–**734**, Scheme 172). Instead, an alternative [3,3]-sigmatropic rearrangement of **736** was proposed following initial cyclisation, without the formation of a gold carbene or sulfur ylide (Scheme 174).

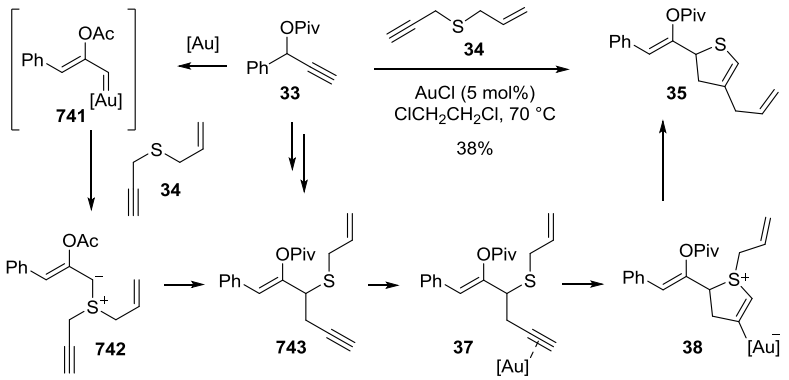


736 **734**

Scheme 174: Alternative [3,3]-sigmatropic rearrangement of intermediate 736

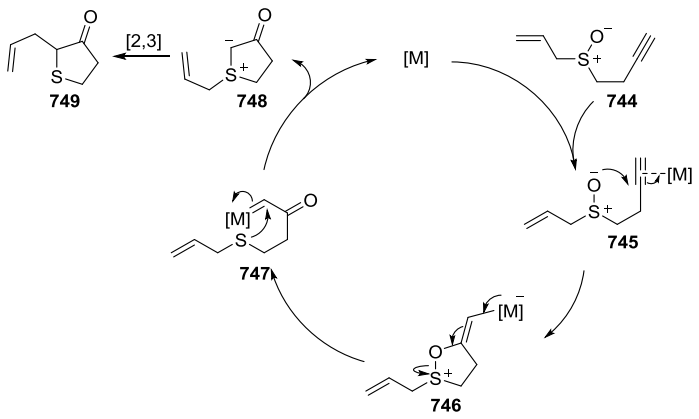
This pathway had previously been reported by Asensio, Ujaque and co-workers in a related intermolecular sulfoxide addition to an alkyne. Experimental and computational studies ruled out a Friedel-Crafts type reaction.[181]

In an alternative system, Davies and Albrecht reported the generation of sulfur ylides directly from alkynes, *via* the gold catalysed rearrangement of a propargylic carboxylate (Scheme 175).[30]



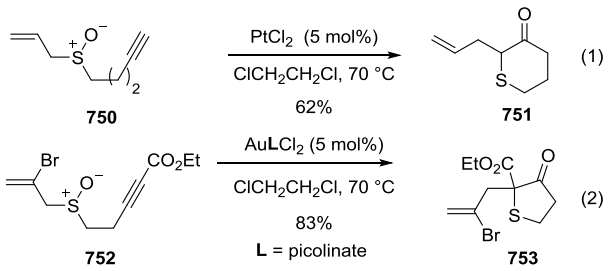
Scheme 175: Gold-catalysed rearrangement of a propargylic carboxylate and subsequent cascade reaction

Gold carbene **741**, generated from such a rearrangement, can undergo attack by a low valent sulfur nucleophile to generate a sulfur ylide **742** without poisoning of the catalyst. Following rearrangement of the ylide to give **743**, gold-catalysed 1,2-carbothiolation occurs to give **35** (*vide supra*, Chapter 2, Scheme 12). In these initial studies, the concept for the formation of sulfur ylides from gold carbenes was proved. Building on this work, Davies and Albrecht explored the generation of functionalised sulfur heterocycles directly from sulfoxide tethered alkynes under π-acid catalysis (Scheme 176).[20] In the proposed mechanism, an *α*-oxo gold carbenoid is generated alongside a sulfide (**747**) *via* an internal redox process, providing the moieties needed for ylide formation. Attack of the carbenoid by the sulfide generates the ylide intermediate **748** and subsequent [2,3]-sigmatropic rearrangement of the allyl group gives sulfur heterocycles such as **749** with formation of new carbon-carbon, carbon-oxygen, and carbon-sulfur bonds in a single step. This methodology was successfully applied to the generation of a wide range of monocyclic and fused bicyclic sulfur heterocycles.



Scheme 176: Ylide formation *via* gold-catalysed rearrangement of alkynyl sulfoxides

The desired ylide formation and rearrangement was observed when functionalised sulfoxide substrates were treated with platinum or gold π-acids (Scheme 177). The use of $PtCl_2$ in dichloroethane with mild heating was found to be the most effective conditions for terminal alkynes such as **750** (Scheme 177, Eq. [1]). Lower yields were observed for those substrates containing an internal alkyne when subjected to platinum catalysis however, this was greatly improved by the use of dichloro(picolinate)gold(III) (Scheme 177, Eq. [2])

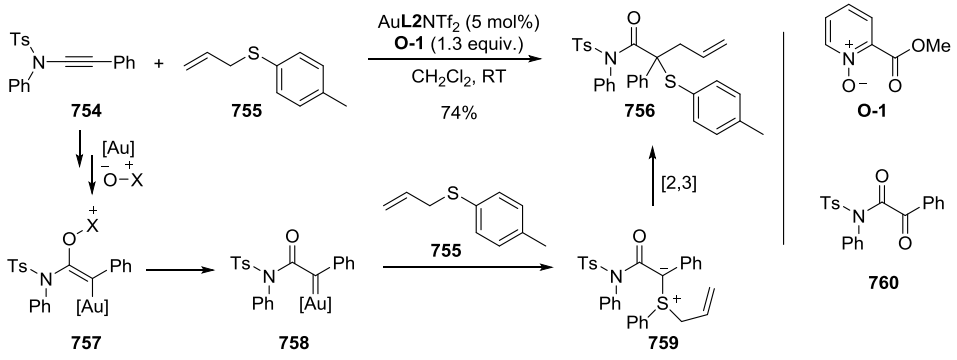


Scheme 177: Gold and platinum catalysed synthesis of sulfur heterocycles

The cyclisation reactions proceed with complete allylic inversion owing to a concerted [2,3]-sigmatropic rearrangement of the sulfur ylide. Synthetic flexibility was achieved by the

incorporation of a range of functionality in the sulfoxide precursors, including a vinyl bromide substituent which remained intact under the mild reaction conditions.

Recently, Davies and Dos Santos reported their work on the formation of sulfur ylides using ynamides (Scheme 178).[20] Under gold catalysis, ynamides such as **754** underwent regioselective addition of a nucleophilic oxidant to generate electrophilic vinyl gold species **757**. As mentioned previously for ammonium ylide generation (*vide supra*, Scheme 162), addition of the allyl sulfide nucleophile may occur directly onto this species, prior to elimination of the pyridine leaving group or onto α-oxo gold carbenoid **758** following an internal redox process (the latter case is again drawn for simplicity). On formation of sulfur ylide **759**, [2,3]-sigmatropic rearrangement of the allyl group occurs to generate structurally complex thioethers such as **756**. This is a challenging intermolecular transformation with all reagents added at the beginning of the reaction. Diketone **760** was observed in all cases from competing attack of a second molecule of oxidant onto the carbenoid, however, good selectivity was achieved for the desired pathway.

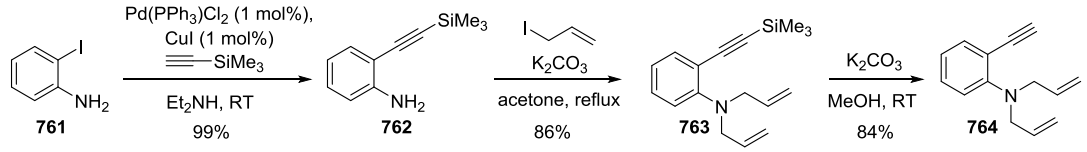


Scheme 178**: Formation of sulfur ylides through formation of an α-oxo gold carbenoid from an ynamide. L2 = tris(2,4-di-tert-butylphenyl) phosphite**

5.2 Results and Discussion

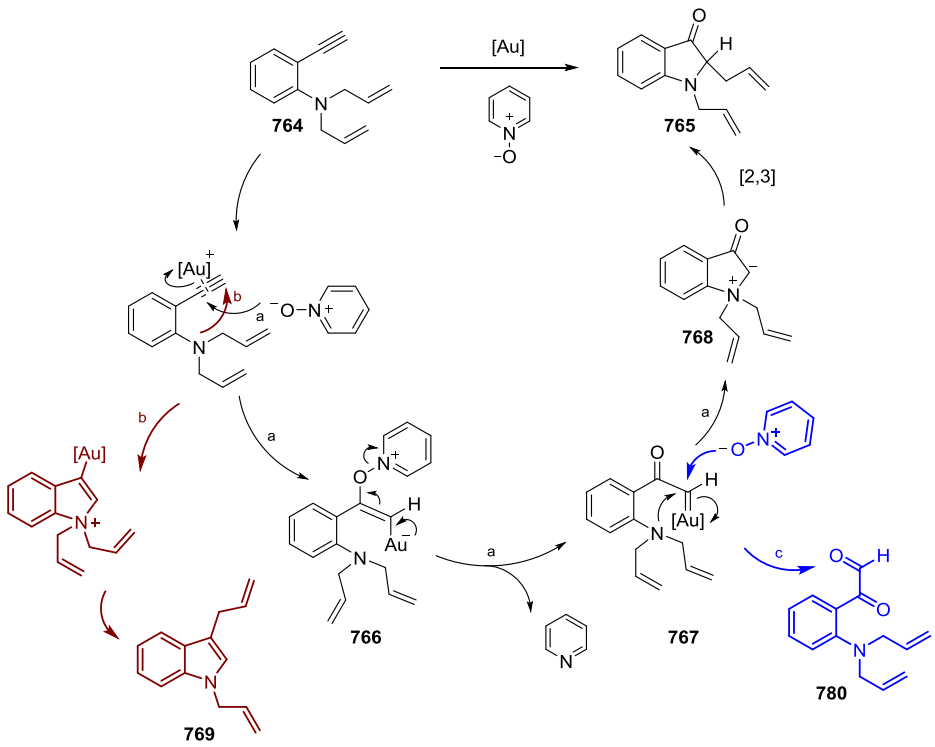
5.2.1 Aniline-Based Substrates

With the concept of sulfur ylide generation directly from alkynes, and later ynamides, already established within the Davies group, the next goal was to expand this methodology to include ammonium ylide formation. Due to the ease of synthesis and handling, aniline-derived substrates were chosen for investigation. *N,N*-Diallyl-2-ethynylaniline **764** was synthesised according to literature procedures over three steps (Scheme 179) in a 90% overall yield.[182]



Scheme 179: Synthesis of terminal alkyne 764 from 2-iodoaniline

In keeping with work ongoing within the Davies research group, and the work of others,[8,19a,20] employing pyridine *N*-oxides as intermolecular nucleophilic oxidants, it was decided to pursue a similar approach using substrate **764**. It was anticipated that pyridine *N*-oxide would attack the gold-activated triple bond to generate vinyl gold species **766** (Scheme 180). An internal redox process would then generate the required α-oxo gold carbenoid **767** with expulsion of the pyridine leaving group. Nucleophilic attack of the tertiary amine onto the electrophilic metal centre would yield ammonium ylide **768**, which could evolve through a [2,3]-sigmatropic rearrangement of one of the allyl substituents to generate isooxindole **765**.

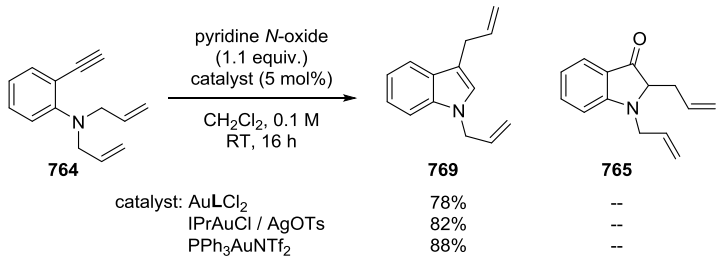


Scheme 180: Gold-catalysed isooxindole formation using an external oxidant

This is an inherently challenging transformation, with competing intra- and intermolecular pathways available. In the first case, direct attack of the aniline nitrogen onto the gold activated triple bond would generate substituted indole **769** (Scheme 180, path b) through the intramolecular 1,2-carboamination pathway discussed in Chapter 2.

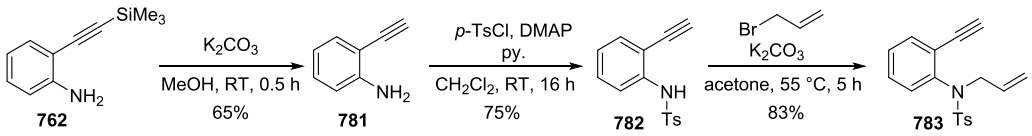
The second issue is the double oxidation of the triple bond to yield diketone **780**. In this case, a second molecule of oxidant attacks the α-oxo gold carbenoid (Scheme 180, path c). In line with these potential issues, the nucleophilicity of both the aniline nitrogen and the pyridine based oxidant would be crucial. *N*,*N*-Diallyl-2-ethynylaniline **764** was subjected to three different gold catalysts using standard pyridine *N*-oxide as the external oxidant (Scheme 181). In all cases, no

formation of the desired isooxindole **765** was detected and clean conversion to the 1,3-diallyl indole **769** was observed by ^{1}H-NMR spectroscopy.



Scheme 181: Rearrangement of 764 under gold catalysis. L = picolinate

The intramolecular formation of **769** from **764** has previously been reported by Lin and co-workers who reported a concerted aza-Claisen rearrangement of the allyl group under both gold and ruthenium catalysis.[182] Whilst no desired product **765** was observed, neither was the diketone product **780** arising from double oxidation of the triple bond (Scheme 180, path c). It was supposed that the competing intramolecular reaction was too rapid to allow other pathways to occur due to the high reactivity of the aniline nitrogen of **764**. It was decided to reduce the nucleophilicity at this centre by substitution with an electron withdrawing group. Consequently, tosyl-substituted aniline derivative **783** was synthesised in three steps from 2-((trimethylsilyl)ethynyl)aniline **762** (Scheme 182) according to literature procedures.[183]

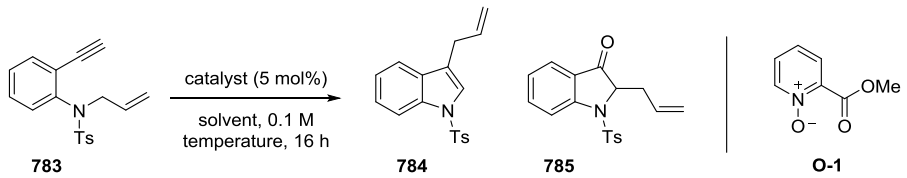


Scheme 182: Synthesis of tosylated substrate 783 (DMAP = dimethylamino pyridine)

With the *N*-deactivated substrate in hand, a variety of gold catalysts, solvents and oxidants were explored. The use of standard pyridine N-oxide at room temperature with gold(I) and gold(III) catalysts was unproductive with no consumption of starting material observed (Entries 1-3). It was thought that traces of basic pyridine may be competitively binding to the gold catalyst and prevent the reaction proceeding. Acid additives have been employed successfully by several groups in gold-catalysed reactions to counteract basic pyridine by-products. For example, Zhang and co-workers observed significant improvement in yield and reaction rate in their synthesis of dihydrofuran-3-ones and oxetan-3-ones in the presence of strong acids. Based on this observation, methanesulfonic acid was added to the reaction, however, a complex mixture was observed by ^{1}H-NMR spectroscopy with no clear indication of product formation (Entry 4). Methyl picolinate *N*-oxide O-1, the use of which has seen previous success in our laboratory,[20] had no effect on the reactivity of the system, although it was only tested at room temperature (Entry 5). Heating the reaction in dichloroethane with PPh_3AuNTf_2 as the catalyst also gave no consumption of starting material (Entry 6). Diphenyl sulfoxide was also tested as an oxidant. When heated to 80 °C in either dichloroethane or nitromethane low levels of conversion of starting material were observed (Entries 7 and 8).

While isolation of a new product was not possible, analysis by ^{1}H- and ^{13}C-NMR spectroscopy and mass spectrometry indicated that the undesired 1,2-carboamination product **784** had been formed with no oxidation of the alkyne. The *in situ* formation of an *N*-oxide by *m*-CPBA oxidation prior to addition of the gold catalyst had already been reported by Zhang and co-workers in the gold-catalysed synthesis of bicyclic piperidin-4-ones and related systems.[184]

Table 6: Exploration of rearrangement conditions for 783[a]



Entry	Catalyst	Oxidant	Temp/°C	Solvent	**783**/%[b]	**784**/%[b]
1	IPrAuCl[c]/AgOTs	py. *N*-oxide	RT	CH_2Cl_2	--	--
2	Au**L**Cl_2[d]	py. *N*-oxide	RT	CH_2Cl_2	--	--
3	PPh_3AuNTf_2	py. *N*-oxide	RT	CH_2Cl_2	--	--
4	PPh_3AuNTf_2[e]	py. *N*-oxide	RT	CH_2Cl_2	--[f]	--[f]
5	PPh_3AuNTf_2	**O-1**	RT	CH_2Cl_2	--	--
6	PPh_3AuNTf_2	py. *N*-oxide	70	$ClCH_2CH_2Cl$	--	--
7	IPrAuCl / AgOTs	Ph_2SO	80	$MeNO_2$	--	10
8	IPrAuCl / $AgSbF_6$	Ph_2SO	80	$ClCH_2CH_2Cl$	--	10
9	PPh_3AuNTf_2	*m*-CPBA[g]	RT	CH_2Cl_2	--	32
10	IPrAuCl / AgOTs	none	80	$MeNO_2$	--	50

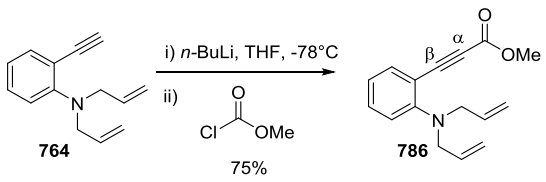
[a] Reaction conditions: 783 (0.1 mmol, 1.0 equiv.), oxidant (1.1 equiv.), solvent (0.1 M). [b] Yields calculated by ^{1}H-NMR spectroscopy against a known quantity of internal standard (1,2,4,5-tetramethylbenzene). [c] IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [d] L=Picolinate. [e] 1.1 equiv. MsOH added at beginning of reaction. [f] Complex mixture observed by ^{1}H-NMR. [g] *m*-CPBA (1.1 equiv) added at 0 °C and stirred for 16 hours before addition of catalyst at room temperature.

It was hoped that an intramolecular oxidation pathway could be accessed analogous to that reported by Davies and Albrecht for the formation of sulfur ylides (*vide supra*, Scheme 176). However, using conditions reported by Zhang, no oxidation of the aniline nitrogen was observed by TLC and addition of a gold catalyst led to undesired carboamination product **784** alongside remaining starting material (*c.f.* Entries 3 and 9). The increased yield of **784** may be due to the traces of acid from the oxidant which assist in promoting the rearrangement. As a control

reaction, **783** was heated in nitromethane in the absence of an oxidant Table 6, Entry 10), leading to a 50% yield of rearranged product **784**. More forceful conditions are certainly required to effect the 1,2-carboamination pathway than observed previously with the diallyl system. In all cases, however, no oxidation of the triple bond was observed, indicating the alkyne moiety is not sufficiently activated to undergo nucleophilic oxidation.

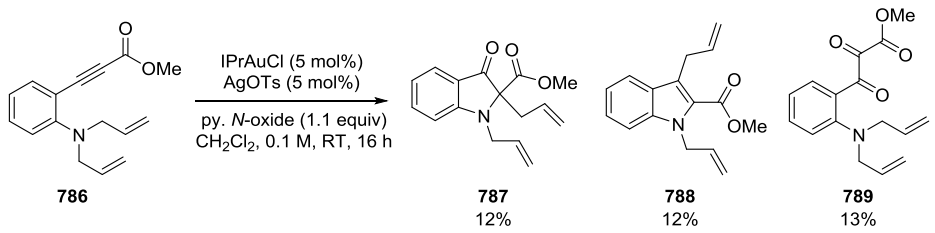
5.2.2 Use of Electron Deficient Alkynes

Consequently, it was decided to try and favour the desired process using an alkyne substituted with an electron withdrawing ester group. **786** was synthesised in one step from **764** by deprotonation of the alkyne with *n*-BuLi and trapping with methyl chloroformate (Scheme 183). Electronically-biasing the alkyne in this manner was intended to increase the reactivity at the β-position toward the external oxidant while decreasing competing cyclisation of the nitrogen directly onto the alkyne at the α-position.



Scheme 183: Synthesis of methyl ester substituted alkyne 786

When alkyne **764** was subjected to gold catalysis using an IPrAuCl / AgOTs catalyst system in the presence of pyridine *N*-oxide, over 40% conversion of starting material was observed (Scheme 184). Chromatographic separation was possible in this case and three new products were isolated and characterised.



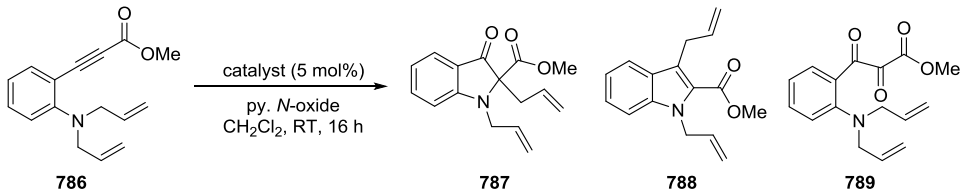
Scheme 184: Initial results from catalysis with 786 indicating ylide formation

As well as the expected undesired indole product **788** from 1,2-carboamination of the alkyne, diketone **789** (*vide supra*, Scheme 180, path c) was also isolated, demonstrating the increased reactivity of the triple bond. Pleasingly, desired isooxindole **787** was also isolated, arising from the proposed oxidation of the triple bond, ammonium ylide formation and [2,3]-sigmatropic rearrangement of an allyl group. Encouraged by these promising initial results, a thorough optimisation study was conducted and selected entries are detailed below.

Variation of the counterion had a negative effect on the desired pathway with this gold catalyst (Table 7, Entries 1 and 2). When an excess of oxidant was employed, diketone **789** was observed at the major product, with no formation of isooxindole **787** (Entry 3).

Unsurprisingly, in the absence oxidant, **788** was formed in excellent yield (Entry 4). A phosphite-ligated gold complex also led to sole formation of **788** in the presence of oxidant (Entry 5). Simple gold(I) and gold(III) catalysts promoted the reaction, although starting material remained in both cases (Entries 6 and 7).

Table 7: Investigation of catalysts for ammonium ylide formation[a]



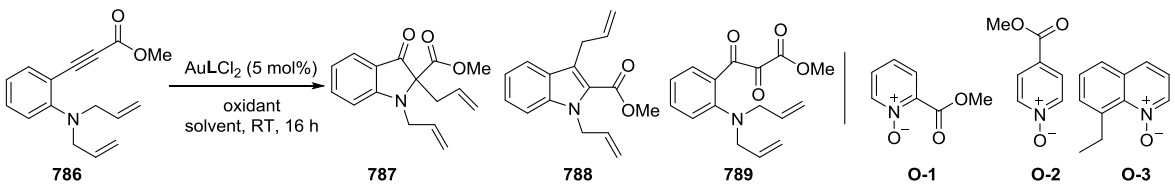
786 787 788 789

Entry	Catalyst	**786** / %[b]	Yield **787** / %[b]	Yield **788** / %[b]	**789** / %[b]
1	IPrAuCl / $AgSbF_6$	--	trace	51	23
2	IPrAuCl / $AgNTf_2$	--	--	68	34
3	IPrAuCl / $AgNTf_2$	--	--[e]	29	71
4	IPrAuCl[c] / AgOTs	--	--[d]	95	--
5	**L2**AuCl / $AgNTf_2$	23	--	76	--
6	AuCl	31	8	56	15
7	$AuCl_3$	6	7	41	7
8	Au**L**Cl_2[f]	trace	20	66	12

[a] Reaction conditions: 786 (0.1 mmol, 1.0 equiv.), py. N-oxide (1.1 equiv.), all reactions were run for 16 hours. [b] Yields calculated by ^{1}H-NMR spectroscopy against a known quantity of internal standard (1,2,4,5-tetramethylbenzene). [c] IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]. [d] No oxidant used. [e] 4 equivalents of oxidant used. [e] L=Picolinate. [f] L2 = tris(2,4-di-tert-butylphenyl) phosphite.

The gold(III) precatalyst dichloro(picolinate)gold gave more promising results with near complete consumption of starting material and 20% of the desired product observed (Entry 8). This commercially available, air-stable catalyst was therefore used for the remainder of the study. A wide variety of oxidants and solvents were then tested for this transformation, with selected examples detailed below (Table 8).

Table 8: Investigation of oxidants and solvents for ammonium ylide formation[a]



Entry	Solvent	Oxidant	**786** / %[b]	**787** / %[b]	**788** / %[b]	**789** / %[b]
1	CH_2Cl_2	**O-2**	--	23	39	4
2	CH_2Cl_2	**O-1**	7	11	54	14
3	$MeNO_2$	**O-1**	trace	21	50	27
4	toluene	**O-1**	trace	6	68	17
5	H_2O	**O-1**	--	--	85	5
6	THF[c]	**O-1**	trace	42 (41)	41 (39)	7 (7)
7	THF[d]	**O-1**		41	42	6
8	THF	**O-3**	--	45	31	16
9	THF	**O-3**[e]	--	32	67	3
10	THF	**O-3**[f]	15	29	23	19
11	DMF	**O-1**	--	46	21	6
12	DMF	**O-3**	--	46	36	5
13	DMF	**O-3**[g]	--	50	50	--

[a] Reaction conditions: 786 (0.1 mmol, 1.0 equiv.), oxidant (1.1 equiv.), all reactions run for 16 hours. [b] Yields calculated by ^{1}H-NMR spectroscopy against a known quantity of internal standard (1,2,4,5-tetramethylbenzene). [c] 50 ppm water already present in solvent. [d] 4 Å MS used. [e] Reaction conducted at 50 °C. [f] Reaction conducted at 0 °C. [g] Reaction conducted at 80 °C, using 4.0 equiv. of oxidant.

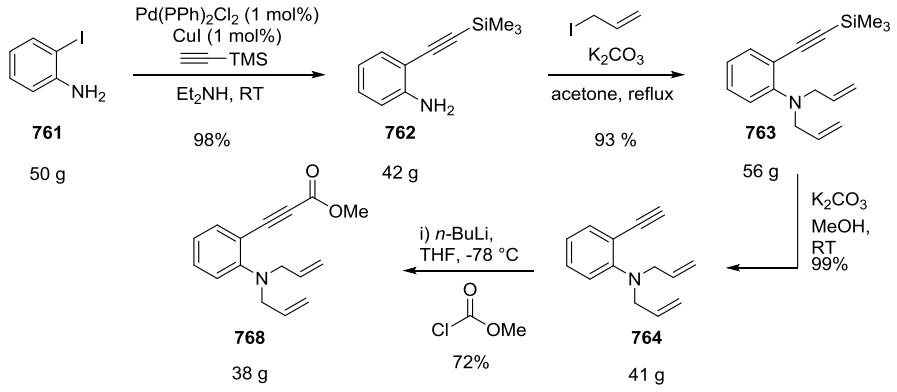
4- and 2-(Methoxycarbonyl)pyridine *N*-oxides (**O-2** and **O-1**) did not improve the yield of desired product in dichloromethane. The ratio of **787** to **788** was improved, although overall recovery was decreased (Entries 1 and 2). The use of a more polar solvent, nitromethane, had a positive effect on oxidation, although the yield of diketone **789** was also higher (27%, Entry 3). A less polar solvent such as toluene was not beneficial (Entry 4). Impressively, the 1,2-carboamination

pathway was promoted when water was used as the solvent (Entry 5), demonstrating the practical advantages of gold catalysts. The use of THF as the solvent gave a large improvement in terms of yield of desired product **787** and reduced over oxidation (Entries 6 and 7). Traces of water in the reaction solvent were found not to affect the outcome. In the first case (Entry 6), the THF used was found by Karl Fisher titrations to have a water content of 50 ppm. In the second case (Entry 7), activated molecular sieves were used in the reaction tube. 8-Ethyl quinoline *N*-oxide also performed well, to yield 45% of the desired product, although diketone **789** was observed in higher yield (16%, Entry 8). Heating the reaction to 50 °C reduced the level of diketone but led to a large increase of the rearranged product **788** (Entry 9). Conducting the reaction at 0 °C led to much lower selectivity, with 19% diketone observed and starting material remaining after 16 hours (Entry 10).

The use of DMF as the solvent gave very promising initial results (Entries 11-13). When the reaction was heated to 80 °C in the presence of four equivalents of **O-1**, no diketone was formed. Only a 1:1 mixture of the desired product **787** and rearranged product **788** were observed by ^{1}H-NMR (Entry 13). Unfortunately, these results were not readily repeated, with the yields of products varying when a new bottle of solvent was used. Whilst similar results between runs could be obtained when reactions were repeated using a single batch of solvent, the initial results shown above could not be matched. This could be attributed to fluctuations in organic and inorganic impurities introduced during manufacture between batches of the solvent purchased, and also variations between different suppliers. Distillation of the solvent prior to

use did not improve matters. As a result of these investigations, the most effective system was deemed to be 2-(methoxycarbonyl)pyridine *N*-oxide (**O-1**) in THF at room temperature (Entry 6).

During time spent at AstraZeneca (Macclesfield, UK), further attempts were made to optimise the desired pathway, taking advantage of the automated equipment available in a process chemistry laboratory. The first step was to perform a scaled-up synthesis of alkyne **768** starting from 50 g of 2-iodoaniline **761** (Scheme 185) which was successfully carried out in 91% yield over four steps to afford 38 g of **768**.



Scheme 185: Large scale synthesis of alkyne 768

A Design of Experiment (DoE) was conducted using a factorial experimental design approach in order to optimise the desired pathway. It was decided to look at four experimental factors: temperature, concentration, catalyst loading and the equivalents of oxidant. Each factor was expected to have an effect on the product yield and rate of reaction. The advantage of investigating multiple factors at the same time is that information can be gained about which experimental factors, if any, are influenced by each other. The use of a high concentration may only be beneficial at low temperature, for example, a relationship that may be missed when

employing the more traditional 'one factor at a time' approach. This also limits the number of required experiments, saving time and resources.[185] Using Modde software, an experimental design was generated (see Appendix), which suggested a series of 19 experiments based upon ranges input into the program, over which each factor would be tested. Ranges were chosen as follows: Oxidant: 1-5 equivalents, concentration: 0.05-0.2 M, temperature: 10-40 °C, catalyst loading: 2.5-7.5 mol%. The run order or experiments was randomised to reduce operator errors.

The 19 reactions were carried out over two days, using an Integrity 10 Stem reaction block which allowed each reaction (up to 10) to be held at a different temperature whilst stirring, under a nitrogen atmosphere. An Amigo workstation auto-sampler was used to take 10 samples from each reaction over a 24 hour period. Once taken, each 40 µL sample was automatically diluted with 1200 µL of a MeCN / H_2O mixture. The high dilution was sufficient to halt further reaction, which was later proven by HPLC analysis of samples taken several days previously. The samples (190 in total) were analysed by HPLC and the % area was used to generate a graph for each reaction. Three of the resulting graphs are shown below with the reaction number referring to the run order (see Appendix for all graphs). Reaction 10 (Figure 12) was conducted at the highest temperature employed in this study, also with the highest catalyst loading. The rate of reaction is therefore unsurprisingly rapid with the starting alkyne **786** consumed after 3 hours. Because of this, and the restrictions on the frequency of sampling, little information can be obtained about the early stages of the reaction. As previously observed, the use of higher temperatures tends to promote the formation of undesired 1,3-diallyl indole **788**.

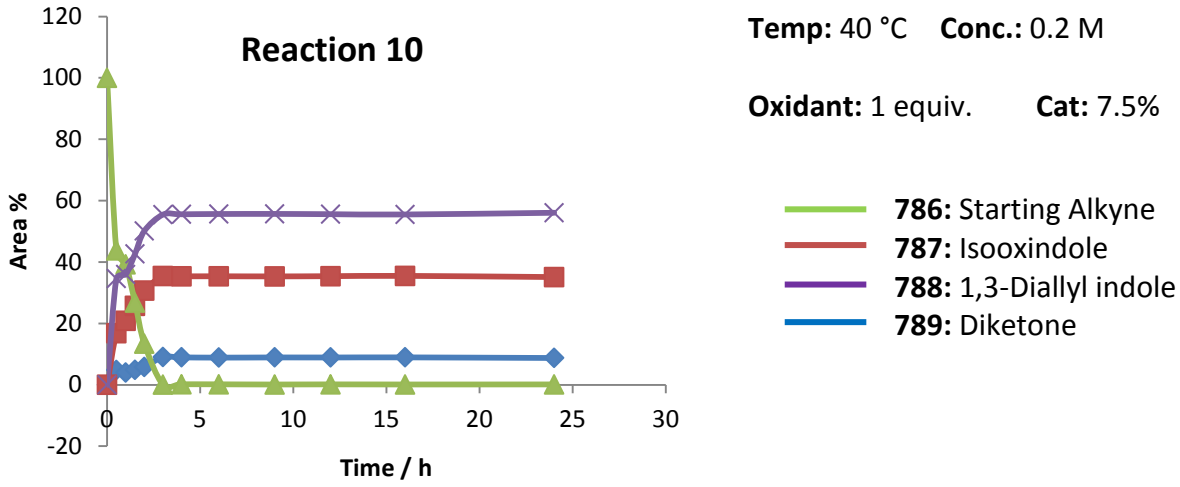


Figure 12: Relative formations of products 787-789 as determined by HPLC analysis. Reaction conducted at high temperature, high concentration, with low oxidant loading and high catalyst loading

When the same conditions were employed at low temperature (10 °C), the formation of undesired indole **788** was slightly suppressed, and diketone **789** was only detected in low levels (Figure 13).

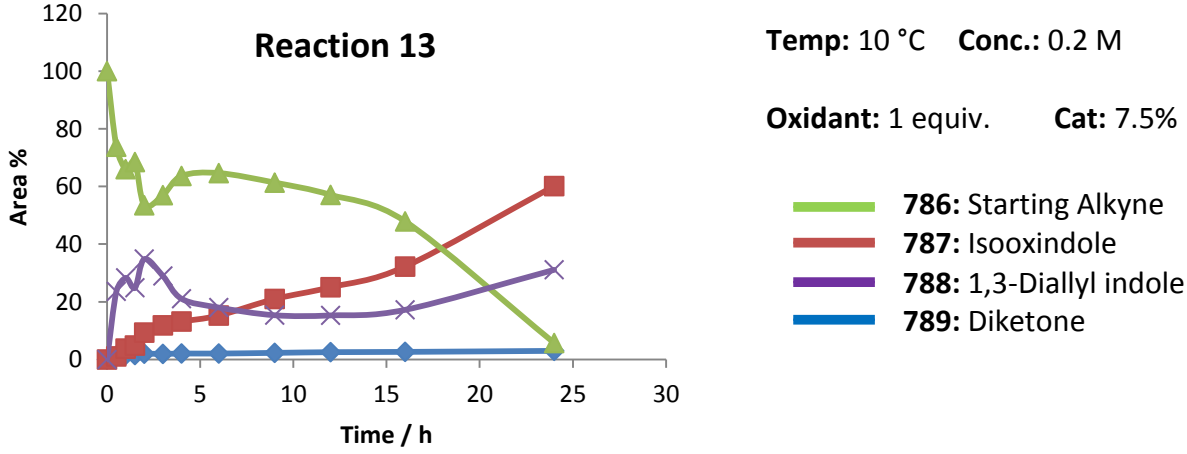


Figure 13: Reaction conducted at low temperature, high concentration with low oxidant loading and high catalyst loading

When these conditions were repeated employing a high oxidant loading, the formation of the desired product **787** was further increased. Interestingly, the level of formation of the diketone **789** remained low at this temperature despite the large excess of oxidant. The reaction rate was much slower in this case and the starting material was consumed only after 40 hours at 10 °C. A trend observed throughout this study is clearly visible in this example. The formation of **788**, arising from 1,2-carboamination of the alkyne is rapid at the beginning of the reaction, after which, the concentration remains reasonably constant. In contrast, the rate of formation of desired product **786** is slow in the initial stages of the reaction and then the rate steadily increases. This suggests that the catalytic species which promotes 1,2-carboamination, is distinct from that which catalyses ammonium ylide formation.

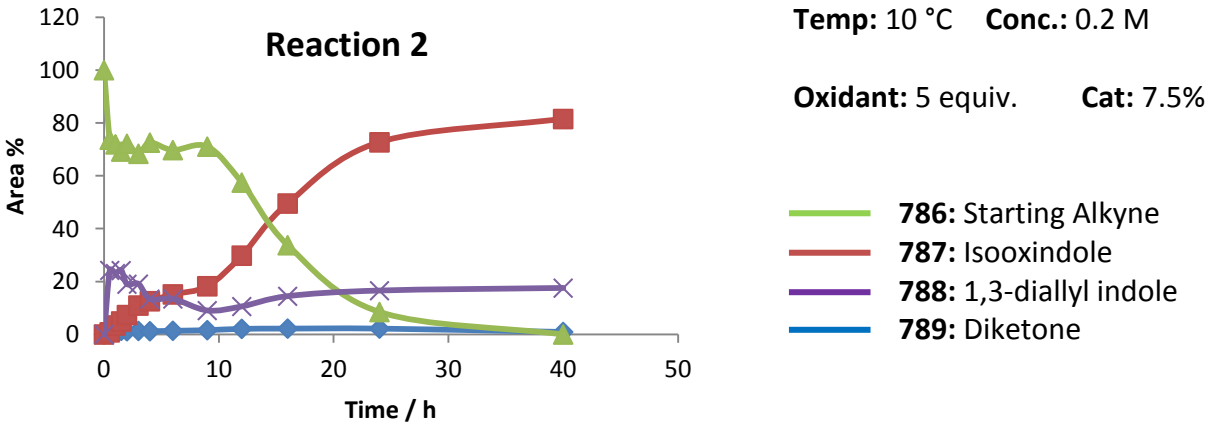
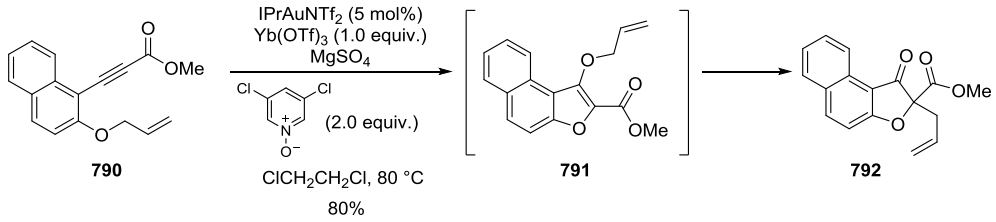


Figure 14: Reaction conducted at low temperature, high concentration with high oxidant loading and high catalyst loading

This catalyst, first reported by Hashmi,[127] is known to require an induction period where the active catalytic species is formed, although it is not known what that actual active catalyst is.

This induction period was clearly observed in ^{1}H-NMR studies conducted in Chapter 2. The reason behind the changing rates of reaction for the formation of **787** and **788** is unclear at present. Unfortunately, due to time constraints and preferential focus on other projects, it was not possible to further investigate this interesting reaction.

Following my own work in this area, Yang, Tang and co-workers published their studies on the synthesis and rearrangement of oxonium ylides through formation of an α-oxo gold carbenoid from an alkyne under oxidative gold catalysis (Scheme 186).[186] Interestingly, formation of 1,2-carboalkoxylation or double oxidation products were not observed in this system, highlighting the inherent difficulties of ammonium ylide formation in related systems. In initial optimisation studies for reaction of phenol derived alkyne **790**, the only side product observed was that arising from deallylation.



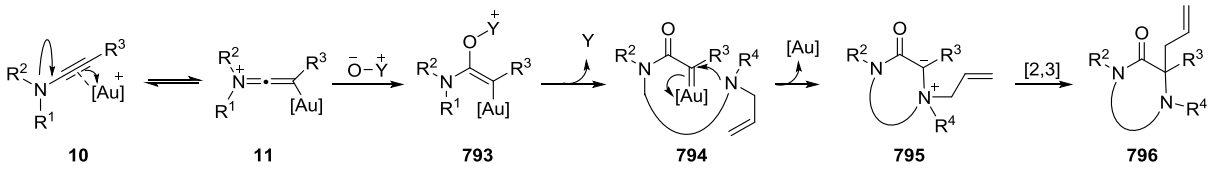
Scheme 186: Synthesis of dihydrofuran-3-ones through gold catalysed oxoinium ylide formation

The use of a stoichiometric rare-earth Lewis acid was required for high conversion alongside molecular sieves or anhydrous $MgSO_4$. For aromatic substrates of type **790**, the oxonium ylide (analogous to the proposed ammonium ylide in the above work) evolves through 1,4-migration of the allyl group to form *O*-allyl ether **791** which would then undergo a Claisen rearrangement to give the observed dihydrofuran-3-one **792**. The intermediacy of **791** was confirmed by its

isolation in a related system. Depending on the substrate employed, different migration mechanisms, including direct allylic [2,3]-sigmatropic rearrangement, were invoked.

5.2.2 Ynamide Substrates

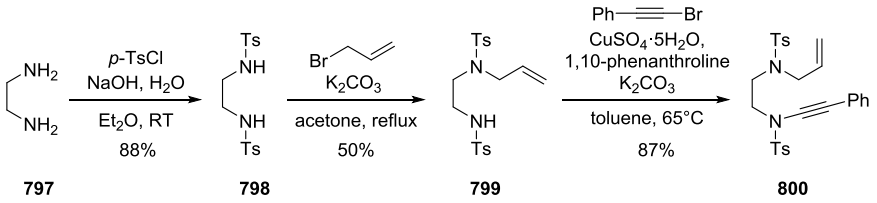
Building on work ongoing at the time in the Davies group into the generation of sulfur ylides from ynamides, *via* an α-oxo-gold carbenoid (*vide supra*, Scheme 178), the use of ynamides to access ammonium ylides was also briefly explored (prior to the research carried out at AstraZeneca discussed in the previous section). It was proposed that if an ynamide with a tethered *N*-allyl nitrogen nucleophile was employed, under oxidative gold-catalysis, ammonium ylides could be accessed which could then evolve through a [2,3]-sigmatropic rearrangement to generate valuable nitrogen heterocycles (Scheme 187). In principle, the allylamine moiety could be tethered to either the N or C terminus of the ynamide.



Scheme 187: Proposed formation of ammonium ylides from ynamides

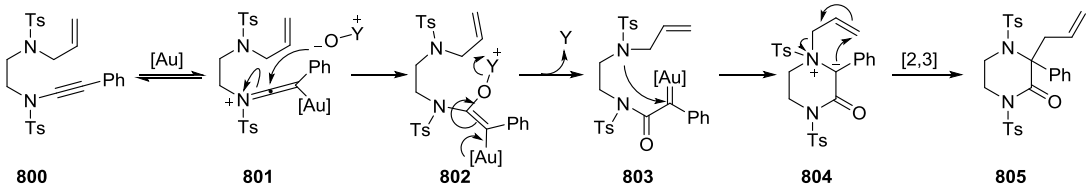
To test this hypothesis, ynamide **800** was designed and synthesised to potentially access substituted piperizines (Scheme 188). Readily available ethylene diamine **797** was sulfonylated and mono-allylated according to literature procedures.[187,188] The allylation step gave only a moderate yield of **799** due to some formation of the bis-allylated product, which was easily removed by column chromatography. The sulfonamide was then coupled with

bromophenylacetylene under standard conditions[71] to give functionalised ynamide **800** in high yield.



Scheme 188: Synthesis of acyclic ynamide 800

Based on the general mechanism above, it was proposed that, on exposure to a gold catalyst and pyridine *N*-oxide, the triple bond of ynamide **800** would undergo regioselective oxidation and internal redox, with expulsion of pyridine to form **803**. Formation of ammonium ylide **804** would precede allylic [2,3]-sigmatropic rearrangement to generate the oxygenated piperizines **805** (Scheme 189). Competing against this would, as before, be direct carboamination as well as over oxidation.

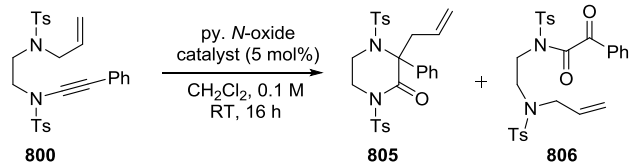


Scheme 189: Proposed formation of piperizine 805

In order to test this hypothesis, initial screening reactions of ynamide **800** were carried out using standard pyridine *N*-oxide and a variety of gold(I) and gold(III) catalysts, in dichloromethane (

Table 9). Encouragingly, all catalysts tested led to some activation of the triple bond. IPrAuCl showed poor reactivity and the starting ynamide was largely untouched (Entries 1 and 2). Over-oxidation to diketone **806**, which was an expected side product, was observed in all cases by ^{1}H-NMR spectroscopy.

Table 9: Initial screening of ynamide 800[a]



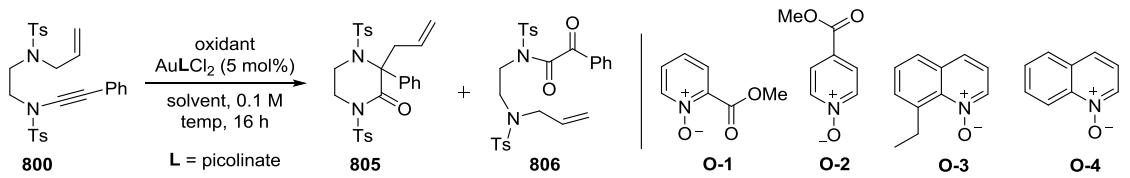
Entry	Catalyst	**800** / %[b]	**805** / %[b]	**806** / %[b]
1	IPrAuCl / AgOTs	91	--	5
2	IPrAuCl / $AgSbF_6$	87	traces	5
3	PPh_3AuNTf_2	44	12	41
4	$AuCl_3$	44	8	36
5	AuCl	34	--	58
6	Au**L**Cl_2[c]	41	14	44
7	Au**L**Cl_2[d]	--	5	88
8	none	98%		

[a] Reaction conditions: 800 (0.1 mmol, 1.0 equiv.), py. N-oxide (1.1 equiv.). [b] Yields calculated by ^{1}H-NMR spectroscopy against a known quantity of internal standard (1,2,4,5-tetramethylbenzene). [c] L=Picolinate. [d] 5.0 equivalents of oxidant used. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

Several catalysts promoted the generation of a new product in low yields, the mass of which was in agreement with the desired mono-oxidised rearrangement product **805**. The most promising results were those using PPh_3AuNTf_2 (Entry 3) and Au**L**Cl_2 (Entry 6). An experiment was carried out using five equivalents of pyridine *N*-oxide (Entry 7) in order to obtain solely the over oxidised product **806**. While **806** was formed in 88% yield, full characterisation was not

possible due to co-elution with **805** and other unidentified impurities on purification by column chromatography. The R_f values of the three species are nearly identical and so clean isolation was not possible, although analysis of crude ^{1}H- and ^{13}-C-NMR spectra, as well as mass spectrometry, supported the formation of the desired product **805** and the diketone **806**. In this system, the 1,2-carboamination pathway was not observed to compete with either the oxidation pathways.

Table 10: Survey of solvents and oxidants[a]



Entry	Solvent	Oxidant	Temp / °C	**800** / %[b]	**805** / %[b]	**806** / %[b]
1	$MeNO_2$	py. *N*-oxide	RT	40	traces	38
2	THF	py. *N*-oxide	RT	61	5	33
3	toluene	py. *N*-oxide	RT	38	15	47
4	toluene	py. *N*-oxide	80	37	--	37
5	MeCN	py. *N*-oxide	RT	54	4	31
6	MeCN	py. *N*-oxide	70	54	16	34
7	CH_2Cl_2	Ph_2SO	RT	43	4	30
8	CH_2Cl_2	**O-1**	RT	46	--	42
9	CH_2Cl_2	**O-2**	RT	31	3	41
10	CH_2Cl_2	**O-3**	RT	44	--	52
11	CH_2Cl_2	**O-4**	RT	42	3	41
12	CH_2Cl_2	py. *N*-oxide	RT	41	14	44

[a] Reaction conditions: 800 (0.1 mmol, 1.0 equiv.), oxidant (1.1 equiv.). [b] Yields calculated by ^{1}H-NMR spectroscopy against a known quantity of internal standard (1,2,4,5-tetramethylbenzene).

The function of the gold catalyst in promoting consumption of ynamide **800** was confirmed when no reaction was observed in the absence of catalyst (Entry 8).A variety of different solvents were next screened using the gold(III) pre-catalyst Au**L**Cl_2 (**L** = picolinate,

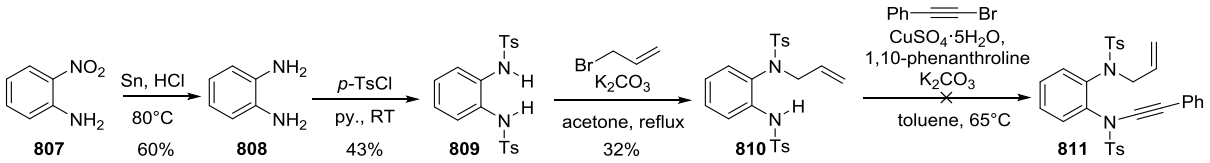
Table 10).

Variation of the polarity of the solvent and the use of an increased temperature did not offer any improvement as compared to the use of dichloromethane at room temperature (Entries 1-6). A number of different *N*-oxides were also tested (Entries 8-11) however, none gave any real improvement on the consumption of starting material or formation of the desired product. Despite the success of methyl picolinate *N*-oxide **O-1** in the previous oxidation chemistry, no desired product was detected by ^{1}H-NMR spectroscopy (Entry 8).

It has been shown that the triple bond of ynamide **800** is sufficiently activated by a gold catalyst to undergo oxidation by an external nucleophilic oxidant. Oxygenated piperizine **805** and diketone **806** had been observed by ^{1}H- and ^{13}C-NMR as well as by mass spectrometry, although isolation was not possible. Due to the high levels of diketone formation, alongside poor conversion of starting material, it was decided not to continue the optimisation of this system.

Finally, the synthesis of the benzene-derived ynamide was attempted (Scheme 190). It was thought that a more rigid system would help to bring the desired reactive components together in space and reduce the levels of over-oxidation by favouring the desired ylide formation. 2-Nitroaniline **807** was reduced under acidic conditions to give the diamine **808** which was

sulfonylated in moderate yield to give **809** (Scheme 190). Using the same conditions as for the acyclic substrate (Scheme 188), monoallylated sulfonamide **810** was prepared.



Scheme 190: Attempted synthesis of benzene derivative 811

Unfortunately, the final step in the synthesis, copper-catalysed coupling with bromophenylacetylene,[71] failed to generate the desired ynamide, with only starting material visible in the ^{1}H-NMR spectrum of the crude reaction mixture. This might be explained by chelate complexation of the diamine derivative with the copper catalyst, as well as intramolecular hydrogen bonding between the secondary and tertiary amides, made possible by the reduced flexibility of this system. Evidence for the latter can be seen in the ^{1}H-NMR spectrum where two distinct resonances are observed for the allylic protons which suggests restricted rotation.

5.3 Summary

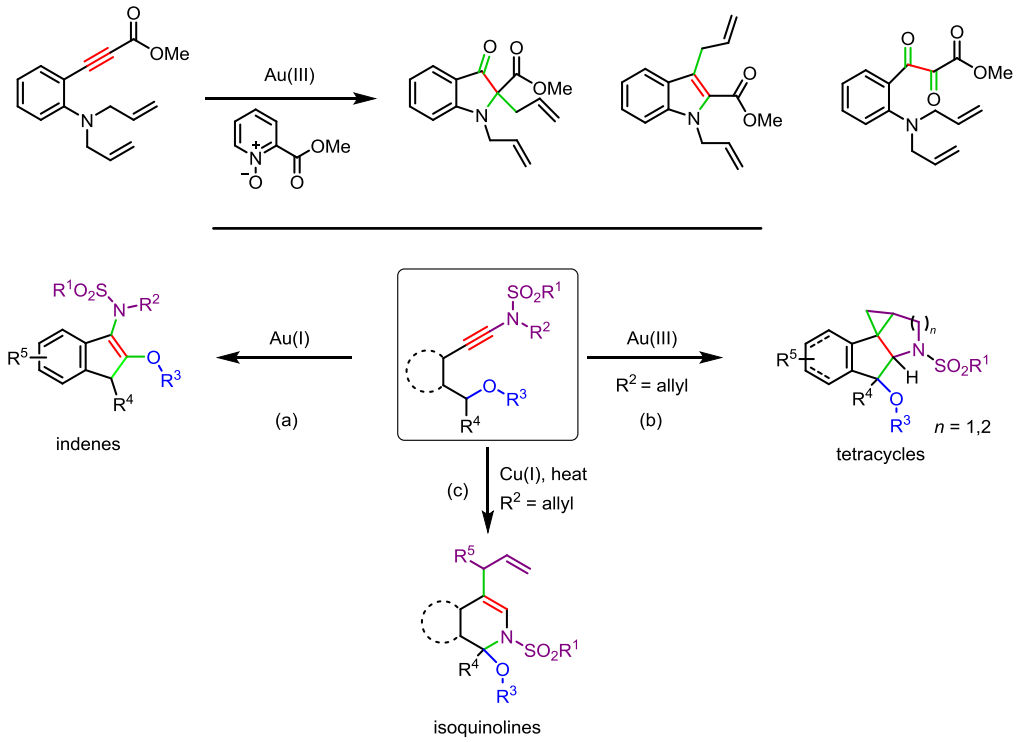
Several systems have been prepared and investigated towards the realisation of gold-catalysed ammonium ylide generation directly from triple bonds. Despite terminal alkynes being used successfully in other oxidative gold-catalysed transformations,[9a,179] *ortho*-ethynyl aniline-derived substrates were not suitable in this case due to lack of reactivity towards oxidation, and competing intramolecular 1,2-carboamination processes. Substitution of the alkyne terminus

with an electron withdrawing ester group, however, led to the formation of the desired isooxindole product which is expected to arise from formation of the proposed ammonium ylide intermediate. The formation of the diketone side product supports the intermediacy of an α-oxo-gold carbenoid.

Extensive optimisation studies have been carried out for aniline-derived systems, with the formation of the desired product maximised at low temperature with high catalyst loading. Intriguingly, formation of the desired product and the indole arising from competitive 1,2-carboamination, appear to be promoted by distinct catalytic species. Preliminary work has also been conducted into the formation of ammonium ylides from ynamides. Future work would seek to modify the reactivity of the nitrogen nucleophile to promote ylide formation.

6 Outlook and Future Work

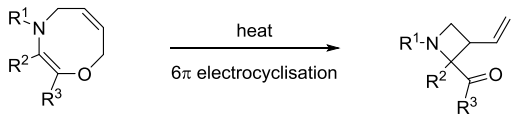
Throughout the course of this research, I have discovered and developed four novel transformations for the synthesis of valuable nitrogen heterocycles and carbocycles from C-C triple bonds using gold and copper catalysis.



Scheme 191: Summary of motifs accessed from gold- and copper-catalysed transformations of triple bonds

The concept of ammonium ylide generation directly from alkynes has been demonstrated in the synthesis of an isoxindole using gold catalysis under oxidative conditions (Scheme 191). This proved to be a very challenging transformation due to competing inter- and intramolecular pathways. Whilst this chemistry has been established for sulfonium and oxonium ylides, examples of the ammonium equivalent remain unreported. Future work should aim to develop

an understanding of the catalytic species involved in the promotion of the observed pathways. This would assist in the further optimisation and exploitation of the potential of this highly valuable reaction. The power of π-acid catalysed insertion of C-C triple bonds into C-X σ-bonds has been demonstrated in the first reported example of the 1,1-carboalkoxylation of ynamides (Scheme 191, path a). A novel range of functionalised indenes have been generated, with formation of new C-C, C-O and C-N bonds in a single step. By controlling the initial cyclisation, a novel gold carbene intermediate has been accessed which evolves through a selective [1,2]-*N*-migration, previously unreported in gold catalysis. The observed selectivity has been rationalised based on developing steric strain adjacent to the gold carbene. ^{13}C-Labelling studies have confirmed the proposed *endo*-mode cyclisation, with cleavage of the C-N bond of the ynamide. Furthermore, by derivatising the functionalised indene products a novel 8-membered oxazocine core was prepared and observed to undergo ready conversion into a valuable vinyl azetidine motif. This 6-π electrocyclisation of the 8-membered ring potentially offers a powerful new route into functionalised azetidines. Future work should aim to explore whether this chemistry can be more widely used on systems other than the indene support and realise a more general route to these cores (Scheme 192).



Scheme 192: A general rearrangement of an oxazocine ring to give functionalised vinyl azetidines

The generation of an alternative gold carbene has also been realised through a [1,5]-hydride shift onto a gold-bound keteneiminium acceptor. *N*-allyl substituted ynamides were employed

to access a novel polycylisation cascade to form functionalised tetracyclic products through cyclopropanation onto the carbene (Scheme 191, path b). The scope and limitations of this reaction have been investigated to include the incorporation of acid sensitive acetal groups, which makes this transformation highly appealing. Further Derivatisation of the products, through carbonyl addition in a 1,2-, 1,4- or a 1,7-sense, would add considerable value to this chemistry. Deuterium labelling studies have confirmed the intramolecular nature of the hydride shift and a primary kinetic isotope effect has been observed, indicating the cleavage of the C-H / C-D bond is involved in the turnover-limiting step. Work on the further development of this fascinating transformation is ongoing in our laboratory (Elli Chatzopoulou) and the substrate scope has already been expanded considerably as a result.

Finally, using related *N*-allyl ynamide substrates, a novel copper-catalysed cascade has been realised for the synthesis of range of functionalised isoquinoline derivatives, through an rare [1,5]-shift pathway onto a sulfonyl ketene imine (Scheme 191, path c). Deuterium labelling has again confirmed the intramolecular nature of the hydride transfer and indicated cleavage of the C-H / C-D is involved in the turnover limiting step.

This work has demonstrated the wide utility of ynamides, and the use of these motifs to control regioselectivity and therefore, reaction outcomes. The use of ynamides in gold catalysis is still a relatively undiscovered area and I have demonstrated how it can be used to effect a rapid development of complexity in processes. As these processes inherently involve nitrogen incorporation into hetero- and carbocyclic products, they, and related reactions should lend themselves well to the synthesis of natural products and biologically active target molecules.

7 Experimental Section

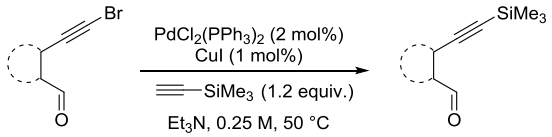
General Experimental

Flash column chromatography: Fluorochem silica gel 60 (0.043-0.063 mm). Thin layer chromatography (TLC): Merck silica gel 60F254 analytical plates which were developed using standard visualizing agents: UV fluorescence (254 and 366 nm), potassium permanganate /Δ and vanillin /Δ. IR: Perkin–Elmer Spectrum 100 FTIR spectrometer. Only selected absorbencies (ν_{max}) are reported in cm^{-1}. MS and HRMS (EI): VG ProSpec or VG-ZabSpec at 70 eV. High resolution EI spectra were measured using perfluorokerosene (PFK) as an internal calibrant. MS and HRMS (ES): Micromass LCT using a methanol mobile phase. HRMS was obtained using a lock-mass to adjust the calibrated mass scale. MS data are reported as m/z (relative intensity). Commercially available chemicals/reagents were purchased from Sigma Aldrich, Acros, Alfa Aesar and used without further purification unless reported. All Grignard reagents were freshly prepared according to **GP2**. All catalysis reactions were carried out under argon in heat gun-dried glassware. The solvents used were purified using a Pure Solv-MD solvent purification system and were transferred under argon. The following cooling baths were used: 0 °C (ice/water), -10 °C (NaCl/ice/water) and -78 °C (dry ice/acetone). Paraffin oil baths on stirrer hotplates were employed for reactions with temperature controlled via an external probe. NMR: Spectra were recorded on Bruker AVIII300 (^{1}H = 300 MHz) and Bruker AVIII400 (^{1}H = 400 MHz, ^{13}C = 101 MHz) and Bruker AVIII500 (^{1}H = 500 MHz, ^{13}C = 126 MHz) in the solvents indicated; $CDCl_3$, d_6-DMSO and d_7-toluene were purchased from Sigma Aldrich. High temperature NMR were recorded on Brucker AV400 (^{1}H = 400 MHz, ^{13}C = 101 MHz). Chemical shifts (δ) are given in ppm relative to TMS. The solvent signals were used as references and the

chemical shifts converted to the TMS scale ($CDCl_3$: $\delta_C \equiv$ 77.16 ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv$ 7.26 ppm). Coupling constants (*J*) are reported in Hz. Multiplicity is denoted in ^{1}H-NMR by: m (multiplet), d (doublet), t (triplet) and q (quartet) and ^{13}C-NMR by: C (quaternary) CH (tertiary), CH_2 (secondary) and CH_3 (primary). 1D ^{13}C-NMR spectra were recorded using the UDEFT or PENDANT pulse sequences from the Bruker standard pulse program library. 2D ^{13}C-NMR HSQC and HMBC spectra were recorded using the Bruker standard pulse program library. 2D ^{1}H-NMR spectra were recorded using the Bruker standard pulse program library. Spectra were processed using MestReNova version 6.0.2 or Topspin version 2.1.

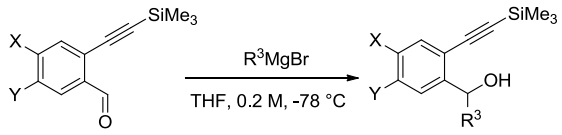
General Procedures

General Procedure 1 (GP1): Preparation of 2-Ethynyl Aldehydes



The required bromide (1.0 equiv.) was dissolved in Et_3N (0.25 M) at room temperature. $Pd(PPh_3)Cl_2$ (2 mol%), CuI (1 mol%) and trimethylsilyl acetylene were added and the resulting mixture was stirred at 50 °C until complete by TLC. After cooling to room temperature, the solids were removed by filtration through a pad of celite (ca. 3 cm) and the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography to give the desired 2-ethynyl aldehydes.

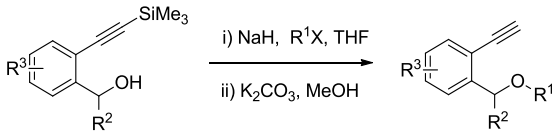
General Procedure 2 (GP2): Preparation of Benzhydric Alcohols



Procedure is based on that reported by Dubé and Toste,[53] using freshly prepared Grignard reagents: Magnesium turnings (3.0 equiv.) were added to a 2-neck flask fitted with a reflux condenser. THF or Et_2O (1 M) was then added followed by a catalytic quantity of iodine (5-50 mg). The aryl bromide (3.0 equiv.) was added slowly and the reaction stirred for 0.5-1 hour until the magnesium turnings had been consumed. Once the flask had cooled to room temperature, stirring was stopped and the solution was used directly. The alcohol (1.0 equiv.), was dissolved

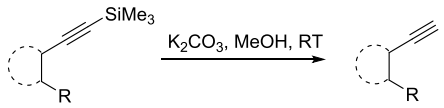
in THF (0.2 M) and cooled to -78 °C. The relevant Grignard solution (1 M in THF or Et_2O, 2.0 equiv.) was added dropwise and the resulting solution stirred at this temperature for 10 minutes. The solution was then warmed to room temperature and stirred for 1 hour before the addition of saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O (× 2) and washed with brine before drying over Na_2SO_4, filtering and concentrating under reduced pressure. Purification using flash column chromatography afforded the desired alcohols.

General Procedure 3 (GP3): Preparation of Terminal Alkynes



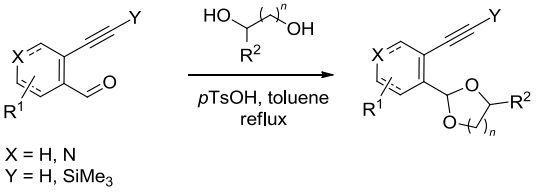
Following the procedure described by Dubé and Toste,**Error! Bookmark not defined.** the required benzhydric alcohol (1 equiv.) was dissolved in THF (0.2 M) and cooled using an ice bath. NaH (60% dispersion in mineral oil, 1.2 equiv.) was added in one portion and the resulting mixture stirred for 30 minutes at this temperature. The relevant alkyl halide (1.5 equiv.) was added and the mixture stirred at room temperature for 2 hours. Saturated NH_4Cl solution was added, and the aqueous phase extracted with Et_2O (× 2), washed with brine and dried over Na_2SO_4. The solid was filtered off and the solvent removed under reduced pressure. The crude residue was dissolved in MeOH (0.2 M) and stirred at room temperature with K_2CO_3 (0.5 equiv.) for 1 hour. The inorganic salt was removed by filtration through a pad of silica (1 cm), eluting with CH_2Cl_2, and the solvent was removed under reduced pressure. Purification by flash column chromatography gave the desired terminal alkynes.

General Procedure 4 (GP4): Preparation of Terminal Alkynes



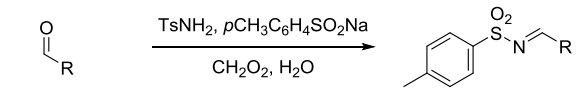
The required 2-((trimethylsilyl)ethynyl)benzaldehyde derivative (1.0 equiv.) was dissolved in MeOH (0.2 M), K_2CO_3 (0.5 equiv.) was added and the mixture was stirred at room temperature for up to 1 hour, until complete by TLC. Saturated $NaHCO_3$ solution was added and the aqueous phase was extracted with EtOAc (× 2) and dried over Na_2SO_4. The solid was filtered off and the solvent removed under reduced pressure to give the terminal alkynes which were used without further purification.

General Procedure 5 (GP5): Preparation of Acetals from Ethynyl Aldehydes



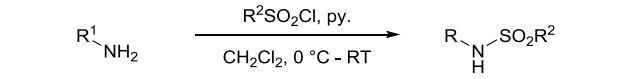
The required aldehyde (1.0 equiv.), diol (1.2 equiv.) and *p*-TsOH·H_2O (5 mol%) were dissolved in toluene (0.2 M) and heated at reflux with azeotropic removal of water using Dean Stark apparatus. Once complete by TLC (generally between 30 minutes and 4 hours), the reaction mixture was cooled to room temperature and saturated $NaHCO_3$ solution was added. The aqueous layer was extracted with EtOAc (× 3), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude acetals were purified by flash column chromatography.

General Procedure 6 (GP6): Preparation of N-Tosyl Alkyl Imines



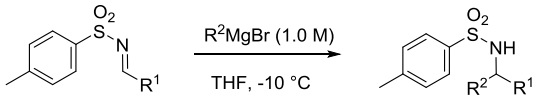
The required alkyl aldehyde (1.0 equiv.), *p*-methylbenzene sulfonamide (1.0 equiv.) and sodium *p*-methylbenzene sulfinate (1.0 equiv.) were dissolved in a 1:1 mixture of formic acid and H_2O (0.3 M) and the resulting solution was stirred at room temperature for 16 hours. The precipitate was filtered under vacuum and the filter bed was washed with H_2O (× 3), and pentane. The solid was dissolved in CH_2Cl_2 and washed rapidly with saturated $NaHCO_3$ solution (ca. 45 seconds). The aqueous layer was extracted with CH_2Cl_2 (× 3), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give the pure imines.

General Procedure 7 (GP7): Preparation of Sulfonamides



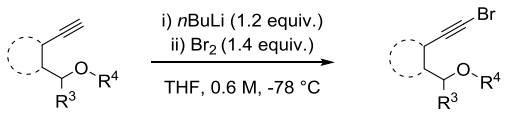
The required amine (1.2 equiv.) and pyridine (3.0 equiv.) were dissolved in CH_2Cl_2 (0.3 M) and cooled to 0 °C. The required sulfonyl chloride (1.0 equiv.) was added in small portions and the resulting mixture was stirred at room temperature for 16 hours. 1.0 M HCl solution was added and the aqueous layer was extracted with CH_2Cl_2 (× 3). The combined organic extracts were washed with H_2O (× 2), brine, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The resulting sulfonamides did not usually require further purification.

General Procedure 8 (GP8): Preparation of Substituted N-Allyl and N-Homoallyl Sulfonamides



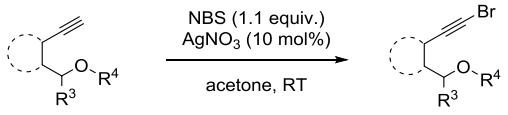
Vinyl and allyl Grignard reagents were freshly prepared as described in **GP2**. The sulfonyl imine (1.0 equiv.) was dissolved in THF (0.2 M) and cooled to -10 °C. The Grignard solution (1.0 M, 2.0 equiv.) was added dropwise. The solution was allowed to warm to room temperature and stirred for 1 hour. Saturated NH_4Cl solution was added and the aqueous layer was extracted with Et_2O (× 2) and washed with brine before drying over Na_2SO_4, filtering and concentrating under reduced pressure. Purification by flash column chromatography afforded the substituted *N*-allyl- or *N*-homoallyl sulfonamides.

General Procedure 9 (GP9): Preparation of Bromoalkynes using n-BuLi / Br_2



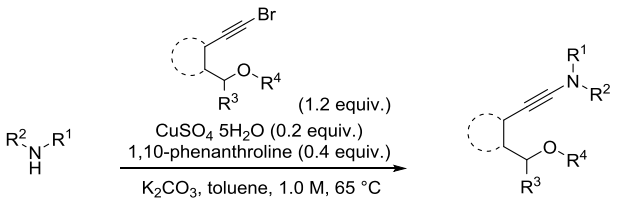
The terminal alkyne (1.0 equiv.) was dissolved in THF (0.6 M) and cooled to -78 °C. *n*-BuLi (2.5 M in hexane, 1.2 equiv.) was added dropwise and the resulting solution stirred for 10 minutes. Br_2 (1.4 equiv.) was added dropwise and the solution was warmed to room temperature. Saturated NH_4Cl solution was added and the product extracted with Et_2O (× 2). The combined organic fractions were washed with brine, dried over $NaSO_4$ and filtered. The solvent was removed under reduced pressure to give the bromoalkynes which were used immediately in the next step without further purification.

General Procedure 10 (GP10): Preparation of Bromoalkynes using NBS/$AgNO_3$



N-Bromosuccinimide (1.1 equiv.) and $AgNO_3$ (0.1 equiv) were added to a solution of the terminal alkyne (1.0 equiv.) in acetone (0.2 M) at room temperature and the solution was stirred for 1 hour. 2-3 spatulas of silica were added to the flask and the solvent removed under reduced pressure. The resulting solid was loaded onto a pad (ca. 2 cm) of silica and the product was eluted [hexane:EtOAc (95:5)] into a receiving flask. The solvent was removed under reduced pressure to give the bromoalkynes which were used immediately in the next step without further purification.

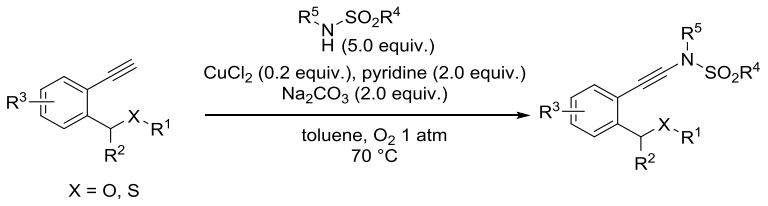
General Procedure 11 (GP11): Preparation of Ynamides from Bromoalkynes



Following the procedure described by Hsung,[71] sulfonamide (1.0 equiv.), 1,10-phenanthroline (0.4 equiv.), $CuSO_4 \cdot 5H_2O$ (0.2 equiv.), K_2CO_3 (2.0 equiv.) and the bromoalkyne (1.2 equiv.) were combined in a flask which was purged with argon for 5 minutes. Toluene (1.0 M) was added and the resulting solution was heated to 65 °C and stirred for 16 hours unless specified. The resulting mixture was diluted with CH_2Cl_2 and filtered through a short pad (ca. 1 cm) of silica,

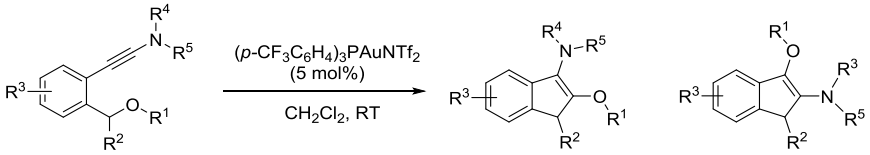
eluting with CH_2Cl_2. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography to give the desired ynamides.

General Procedure 12 (GP12): Preparation of Ynamides from Terminal Alkynes



Following the procedure reported by Stahl,[68] sulfonamide (5.0 equiv.), Na_2CO_3 (2.0 equiv.) and $CuCl_2$ (0.2 equiv.) were added to a 500 mL 3-necked flask which was purged with O_2 for 15 minutes. Toluene (1.0 M with respect to sulfonamide) and then pyridine (2.0 equiv.) were added and the mixture heated to 70 °C. 2 large balloons were filled with O_2 and attached to the flask using needles. A solution of alkyne (1.0 equiv.) in toluene (0.2 M with respect to alkyne) was added over 8 hours using a syringe pump and stirring was continued for 16 hours. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography to give the desired ynamides. The unreacted amide is recoverable by column chromatography.

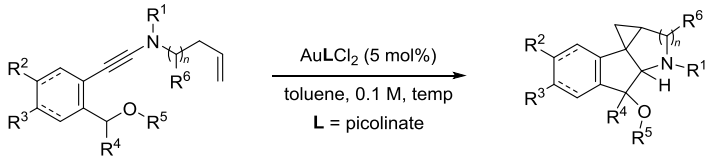
General procedure 13 (GP13): Preparation of Functionalised Indenes



The relevant ynamide (1.0 equiv.) was dissolved in CH_2Cl_2 (0.1 M), (p-$CF_3C_6H_4)_3PAuNTf_2$ (5 mol%) was added and the reaction was stirred at room temperature until complete by TLC. The

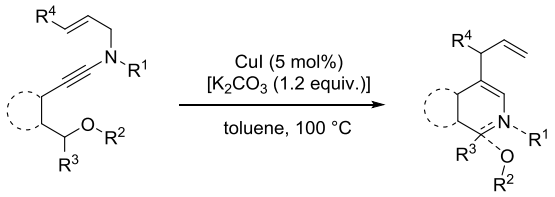
reaction mixture was filtered through a pipette containing a short silica pad (ca. 1 cm), eluting with EtOAc (15 mL) and the solvent removed under reduced pressure. Purification by flash column chromatography or recrystallisation gave the desired indene derivatives.

General Procedure 14 (GP14): Preparation of Functionalised Tetracycles



The relevant ynamide (1.0 equiv.) was dissolved in toluene (0.1 M) and if required, the reaction tube was placed in a preheated oil bath at the specified temperature. Dichloro(2-pyridinecarboxylato)gold (5 mol%) was added and the reaction stirred until complete by TLC. The reaction mixture was cooled to room temperature as necessary and filtered through a pipette containing a short (ca. 1 cm) pad of silica, eluting with EtOAc (15 mL). In the case of acetal protected substrates, Et_3N (0.1 mL, 1%) was added to the eluent. The solvent was removed under reduced pressure and purification by flash column chromatography gave the desired functionalised tetracycles.

General procedure 15 (GP15): Preparation of Functionalised Isoquinolines (I)



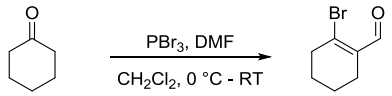
The required *N*-allyl ynamide (1.0 equiv.) was dissolved in toluene (0.1 M) before the addition of CuI (5 mol%) and K_2CO_3 (1.2 equiv.). The reaction tube was placed in an oil bath, preheated to 100 °C and stirred until complete by TLC. The reaction mixture was cooled to room temperature and filtered through a pipette containing a short (ca. 1 cm) pad of silica, eluting with a mixture of EtOAc (15 mL) and Et_3N (0.2 mL, 1%). The solvent was removed under reduced pressure and purification by flash column chromatography gave the desired functionalised isoquinolines.

General procedure 16 (GP16): Preparation of Functionalised Isoquinolines (II)

GP14 was followed without the addition on K_2CO_3.

Preparation of 2-Bromo Aldehydes

2-Bromocyclohex-1-ene-1-carbaldehyde 523



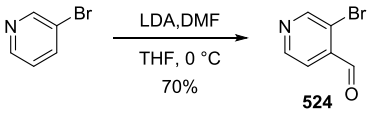
523

DMF (3.5 mL, 45.0 mmol, 3.0 equivs.) was dissolved in CH_2Cl_2 (50 mL, 0.3 M) and cooled to 0 °C. PBr_3 (3.8 mL, 40.5 mmol, 2.7 equiv.) was added dropwise and the resulting solution was stirred for 1 hour at this temperature. Cyclohexanone (1.6 mL, 15.0 mmol, 1.0 equiv.) was added dropwise and stirring was continued for 16 hours at room temperature. The reaction mixture was poured **slowly** into an ice-cooled, saturated solution of $NaHCO_3$ (150 mL). The organic phase was extracted with CH_2Cl_2 (3 × 100 mL), washed with water (100 mL), dried over Na_2SO_4, filtered and the solvent removed was under reduced pressure. Purification by flash column

chromatography [hexane:EtOAc (95:5)] gave the 2-bromo aldehyde **523** (624 mg, 22%) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.01 (s, 1H), 2.79 – 2.69 (m, 2H), 2.30 – 2.23 (m, 2H), 1.81 – 1.64 (m, 4H); IR: ν_{max} (cm^{-1}) 2968, 2955, 2945, 2855, 2821, 1680, 1210, 947. Data matches that reported in the literature.[120a]

Note: Employment of reduced reaction time and increased number of extractions made little difference to the yield of isolated product.

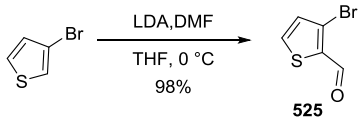
3-Bromoisonicotinaldehyde 524



524

n-BuLi (4.2 mL, 2.4 M solution in hexane, 10.0 mmol, 1.0 equiv.) was added dropwise to a solution of diisopropylamine (1.4 mL, 10.0 mmol, 1.0 equiv) in THF (17 mL, 0.6 M) at room temperature. After 10 minutes, the solution was cooled to -78 °C and 3-bromopyridine (1.0 mL, 10.0 mmol, 1.0 equiv) was added dropwise. After a further 10 minutes, DMF (0.8 mL, 10.0 mmol, 1.0 equiv.) was added slowly and the resulting solution was stirred for 30 minutes. The reaction mixture was warmed to room temperature and water (20 mL) was added. The organic layer was extraced with EtOAc (3 × 20 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give the aldehyde **524** (1.3 g, 73%) as a white solid which was used without further purification; mp: 79-81 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.35 (s, 1H), 8.90 (s, 1H), 8.70 (d, *J* = 4.9 Hz, 1H), 7.69 (d, *J* = 4.9 Hz, 1H); IR: ν_{max} (cm^{-1}) 3080, 3045, 3008, 2899, 1692, 1276, 1012, 764, 750. Data matches that reported in the literature.[189]

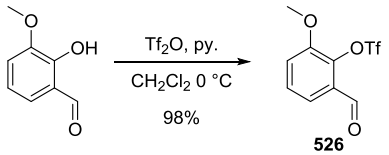
3-Bromothiophene-2-carbaldehyde 525



525

n-BuLi (6.2 mL, 2.4 M solution in hexane, 15.0 mmol, 1.0 equiv.) was added dropwise to a solution of diisopropylamine (2.1 mL, 15.0 mmol, 1.0 equiv) in THF (26 mL, 0.6 M) at room temperature. After 10 minutes, the solution was cooled to 0 °C and 3-bromothiophene (1.4 mL, 15.0 mmol, 1.0 equiv.) was added dropwise. After strirring for 1 hour, DMF (1.2 mL, 10.0 mmol, 1.0 equiv.) was added slowly and the resulting solution was stirred for a further 4 hours. Water (30 mL) was added and the mixture was warmed to room temperature. The organic layer was extraced with Et_2O (3 × 30 mL), washed with brine (30 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give aldehyde **525** (2.8 g, 97%) as a brown oil which was used without further purification; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.97 (d, *J* = 1.4 Hz, 1H), 7.71 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.14 (d, *J* = 5.1 Hz, 1H); IR: ν_{max} (cm^{-1}) 3105, 2844, 2816, 2776, 1658, 1496, 1415, 1371, 1342, 886, 730, 661. Data matches that reported in the literature.[118]

2-Formyl-6-methoxyphenyl trifluoromethanesulfonate 526



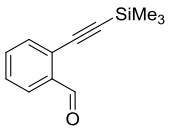
526

A solution of *o*-vanillin (1.0 g, 6.6 mmol, 1.0 equiv.) and pyridine (1.1 mL, 13.1 mmol, 2.0 equiv.) in CH_2Cl_2 (25 mL, 0.3 M) was cooled to 0 °C and Tf_2O (1.4 mL, 8.5 mmol, 1.3 equiv.) was added over 1 hour. The resulting solution was warmed to room temperature and filtered through a

short pad (ca. 2 cm) of silica, eluting with CH_2Cl_2 (50 mL). The solvent was removed under reduced pressure to give the triflate **XX** (1.8 g,98%) as a yellow oil which was used without further purification; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.23 (s, 1H), 7.52 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.46 (app. t, *J* = 7.8 Hz, 1H), 7.31 (dd, *J* = 7.8, 1.9 Hz, 1H), 3.96 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 186.9 (CH), 151.8 (C), 139.4 (C), 129.7 (C), 129.2 (CH), 123.8 (q, $J_{C\text{-}F}$ = 320.7 Hz, C), 121.3 (CH), 118.8 (CH), 56.7 (CH_3); IR: ν_{max} (cm^{-1}) 3083, 2966, 2875, 2767, 1701, 1480, 1418, 1408, 1129, 882. Data matches that reported in the literature.[119a]

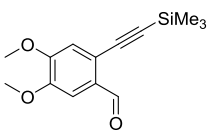
Preparation of 2-Ethynyl Aldehydes

2-((Trimethylsilyl)ethynyl)benzaldehyde 230



Prepared according to **GP1** from 2-bromobenzaldehyde (2.0 g, 10.8 mmol). Purification by flash column chromatography [hexane:EtOAc (92:8)] gave the protected alkyne **230** (2.1 g, 97%) as a pale brown solid; mp: 49-51 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.56 (d, *J* = 0.8 Hz, 1H), 7.94 – 7.88 (m, 1H), 7.61 – 7.51 (m, 2H), 7.48 – 7.39 (m, 1H), 0.28 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 192.0 (CH), 136.3 (C), 133.8 (CH), 133.6 (CH), 129.0 (CH), 127.0 (CH), 126.9 (C), 102.6 (C), 100.2 (C), -0.1 (3 × CH_3); MS (EI): *m/z* 202 $[M]^+$ (10 %), 187 (100). Data matches that reported in the literature.[190]

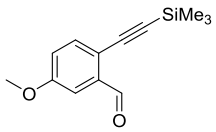
4,5-Dimethoxy-2-((trimethylsilyl)ethynyl)benzaldehyde 302



Prepared according to **GP1** from 6-bromoveratraldehyde (2.45 g, 10.0 mmol) using 5 mol% Pd and Cu catalysts. Purification by flash column

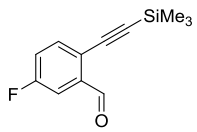
chromatography [hexane:EtOAc (92.5:7.5)] gave the protected alkyne **302** (2.5 g, 96%) as a yellow solid; mp: 113-115 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.38 (d, *J* = 0.6 Hz, 1H), 7.36 (s, 1H), 6.97 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 0.27 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 190.7 (CH), 153.6 (C), 150.0 (C), 130.8 (C), 121.5 (C), 114.7 (CH), 108.2 (CH), 100.9 (C), 100.2 (C), 56.4 (CH_3), 56.2 (CH_3), -0.05 (3 × CH_3). Data matches that reported in the literature.[191]

5-Methoxy-2-((trimethylsilyl)ethynyl)benzaldehyde 303



Prepared according to **GP1** from 2-bromo-5-methoxybenzaldehyde (2.0 g, 9.2 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the protected alkyne **303** (2.0 g, 94%) as a white solid; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.50 (s, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 7.36 (d, *J* = 2.8 Hz, 1H), 7.07 (dd, *J* = 8.6, 2.8 Hz, 1H), 3.85 (s, 3H), 0.26 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 191.8 (CH), 160.0 (C), 137.7 (C), 135.0 (CH), 121.6 (CH), 120.0 (C), 109.7 (CH), 100.6 (C), 100.3 (C), 55.72 (CH_3), -0.02 (3 × CH_3); IR: ν_{max} (cm^{-1}) 2998, 2971, 2965, 2846, 2151, 1695, 1599, 1489, 1387, 1314, 1076, 1028. Data matches that reported in the literature.[192]

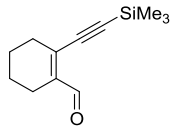
5-Fluoro-2-((trimethylsilyl)ethynyl) benzaldehyde 304



Prepared according to **GP1** from 2-bromo-5-fluorobenzaldehyde (1.5 g, 7.5 mmol) using 5 mol% Pd and Cu catalysts. Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the protected alkyne **304** (1.6 g, 96%) as a yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.49 (d, *J* = 3.2 Hz, 1H), 7.57 (dd, *J* = 8.6, 1.5 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.24 (ddd, *J* = 8.6, 7.9, 2.7 Hz, 1H), 0.27 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7 (CH), 162.6 (d, $J_{C\text{-}F}$ = 252.9 Hz, C), 138.4 (d, $J_{C\text{-}F}$ = 6.7 Hz, C), 135.7 (d, $J_{C\text{-}F}$ =

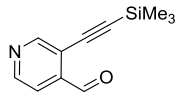
7.7 Hz, CH), 123.0 (d, J_{C-F} = 3.4 Hz, C), 121.3 (d, J_{C-F} = 22.8 Hz, CH), 113.6 (d, J_{C-F} = 23.0 Hz, CH),102.3 (C), 99.15 (C), -0.13 (3 × CH_3); IR: ν_{max} (cm^{-1}) 2961, 2158, 1707, 1695, 1601, 1485, 1421, 1188, 1149, 887, 737. Data matches that reported in the literature.[191]

2-((Trimethylsilyl)ethynyl)cyclohex-1-ene-1-carbaldehyde 527



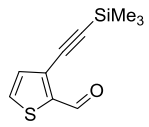
Prepared according to **GP1** from 2-bromocyclohex-1-ene-1-carbaldehyde **523** (1.2 g, 6.1 mmol), using 5 mol% Pd and Cu catalysts. Purification by flash column chromatography [hexane:EtOAc (98:2)] gave the protected alkyne **527** (691 mg, 55%) as a brown oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.20 (s, 1H), 2.44 – 2.35 (m, 2H), 2.28 – 2.19 (m, 2H), 1.71 – 1.58 (m, 4H), 0.21 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 193.2 (CH), 143.7 (C), 139.9 (C), 104.8 (C), 101.6 (C), 32.3 (CH_2), 22.1 (CH_2), 21.9 (CH_2), 21.1 (CH_2), -0.1 (3 × CH_3); IR: ν_{max} (cm^{-1}) 3052, 2987, 2947, 2849, 2843, 1670, 1598, 1485, 1265. Data matches that reported in the literature.[193]

3-((Trimethylsilyl)ethynyl)isonicotinaldehyde 528



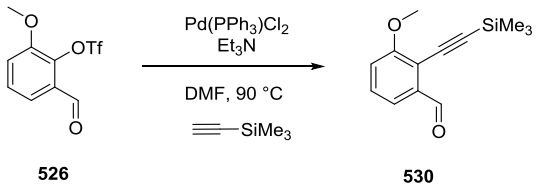
Prepared according to **GP1** from 3-(bromoethynyl)isonicotinaldehyde **524** (600 mg, 3.3 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the protected alkyne **528** (467 mg, 74%) as an orange solid; mp: 162-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.52 (d, *J* = 0.7 Hz, 1H), 8.88 (d, *J* = 0.7 Hz, 1H), 8.72 – 8.68 (m, 1H), 7.67 (dd, *J* = 5.1, 0.8 Hz, 1H), 0.29 (s, 9H); IR: ν_{max} (cm^{-1}) 2955, 2934, 2880, 2836, 1705, 1345, 1159, 809, 663. Data matches that reported in the literature.[194]

3-((Trimethylsilyl)ethynyl)thiophene-2-carbaldehyde 529



Prepared according to **GP1** from 3-(bromoethynyl)thiophene-2-carbaldehyde **525** (1.0 g, 5.0 mmol). Purification by flash column chromatography [hexane:EtOAc (97:3)] gave the protected alkyne **529** (512 mg, 49%) as an orange oil; ^{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 183.3 (CH), 144.7 (C), 133.8 (CH), 131.9 (CH), 131.1 (C), 102.7 (C), 96.5 (C), -0.2 (3 × CH_3); IR: ν_{max} (cm^{-1}) 2960, 2900, 2842, 2812, 2154, 1666, 1415, 1250, 997, 835.Data matches that reported in the literature.[195]

3-Methoxy-2-((trimethylsilyl)ethynyl)benzaldehyde **530** was prepared according to the following procedure:



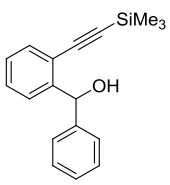
526 **530**

Triflate **526** (1.7 g, 6.0 mmol, 1.0 equiv.), was dissolved in DMF (18 mL, 0.3 M). $Pd(PPh_3)Cl_2$ (126 mg, 0.2 mmol, 3 mol%), Et_3N (3.7 mL, 26.5 mmol, 4.4 equiv.) and trimethylsilylacetylene (1.2 mL, 8.9 mmol, 1.5 equiv.) were added and the mixture heated at 90 °C for 4 hours. Once cooled to room temperature, the resulting mixture was diluted with water (50 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with water (30 mL), brine (30 mL) and then dried over Na_2SO_4. The solids were filtered off and the solvent removed under reduced pressure. Purification by flash column chromatography [hexane:Et_2O (95:5)] gave the desired alkyne (969 mg, 70%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.55 (d, *J* = 0.8 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.41 – 7.33 (m, 1H), 7.09 (dd, *J* = 8.2, 0.8 Hz, 1H), 3.92 (s, 3H), 0.28

(s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 192.3 (CH), 161.1 (C), 137.8 (C), 129.7 (CH), 119.0 (CH), 116.4 (C), 115.9 (CH), 107.4 (C), 96.2 (C), 56.5 (CH_3), 0.1 (3 × CH_3); IR: ν_{max} (cm^{-1}) 2960, 2905, 2843, 2744, 2154, 1699, 1269, 1244, 859, 839; HRMS (ES) *m/z* calculated for $C_{13}H_{16}O_2NaSi$ $(M+Na)^+$ 255.0817, found 255.0823.

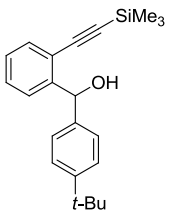
Preparation of Benzhydric Alcohols

Phenyl(2-((trimethylsilyl)ethynyl)phenyl)methanol 231



Prepared according to **GP2** from aldehyde **230** (1.0 mg, 5.0 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the alcohol **231** (1.1 g, 79%) as an off-white solid; mp: 47-49 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.54 – 7.40 (m, 4H), 7.40 – 7.17 (m, 5H), 6.28 (s, 1H), 0.23 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 146.1 (C), 143.1 (C), 132.9 (CH), 129.1 (CH), 128.4 (2 × CH), 127.6 (CH), 127.4 (CH), 126.8 (2 × CH), 126.5 (CH), 121.2 (C), 103.3 (C), 100.3 (C), 74.2 (CH), -0.0 (3 × CH_3); MS (ES): *m/z* 303 $[M+Na]^+$ (100 %).Data matches that reported in the literature.[53]

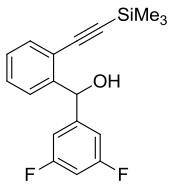
(4-(t-Butyl)phenyl)(2-((trimethylsilyl)ethynyl)phenyl)methanol 268



Prepared according to **GP2** using aldehyde **230** (1.20 g, 5.9 mmol) and (4-*t*-butylphenyl)magnesium bromide (1 M in THF, 11.9 mL, 11.9 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the alcohol **268** (1.41 g, 71%) as a white solid; mp: 74-78 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.39 – 7.32 (m, 4H), 7.22 (app. td, *J* = 7.5, 1.3 Hz, 1H), 6.25 (s, 1H), 2.60 (s, 1H), 1.30 (s, 9H), 0.22 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 150.6 (C), 146.5 (C), 140.5

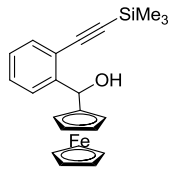
(C), 133.1 (CH), 129.3 (CH), 127.5 (CH), 126.8 (2 × CH), 126.6 (CH), 125.6 (2 × CH), 121.3 (C), 103.5 (C), 100.4 (C), 74.3 (CH), 34.8 (C), 31.7 (3 × CH_3), 0.20 (3 × CH_3); IR: ν_{max} (cm^{-1}) 3379, 3068, 2960, 2903, 2867, 2153, 1246, 1010, 828, 839; HRMS (ES) *m/z* calculated for $C_{22}H_{28}ONaSi$ $(M+Na)^+$ 359.1807 found 359.1801.

(3,5-Difluorophenyl)(2-((trimethylsilyl)ethynyl)phenyl)methanol 269



Prepared according to **GP2** using aldehyde **230** (1.20 g, 5.9 mmol) and (3,5-difluorophenyl)magnesium bromide (1 M in THF, 11.9 mL, 11.9 mmol). Purification by flash column chromatography [hexane:EtOAc (93:7)] gave the alcohol **269** (1.79 g, 95%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.42 (m, 2H), 7.35 (app. td, *J* = 7.6, 1.4 Hz, 1H), 7.25 (app. td, *J* = 7.5, 1.4 Hz, 1H), 6.99 (dd, *J* = 8.3, 1.7 Hz, 2H), 6.68 (tt, *J* = 8.9, 2.4 Hz, 1H), 6.22 (d, *J* = 4.4 Hz, 1H), 2.80 (br s, 1H), 0.25 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 163.3 (dd, $J_{C\text{-}F}$ = 248.2, 12.5 Hz, 2 × C), 147.5 (C), 145.2 (C), 133.3 (CH), 129.6 (CH), 128.2 (CH), 126.7 (CH), 121.3 (C), 109.7 (d, $J_{C\text{-}F}$ = 25.7 Hz, 2 × CH), 103.0 (t, $J_{C\text{-}F}$ = 25.4 Hz, CH), 103.1 (C), 101.1 (C), 73.5 (CH), 0.12 (3 × CH_3); IR: ν_{max} (cm^{-1}) 3331, 3068, 2961, 2900, 2156, 1623, 1597, 1454, 1250, 1117; HRMS (ES) *m/z* calculated for $C_{18}H_{17}F_2Si$ $(M\text{-}OCH_3)^+$ 299.1068 found 299.1078.

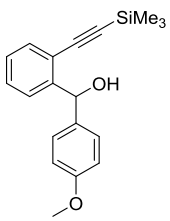
***(Ferrocene)(2-((trimethylsilyl)ethynyl)phenyl)methanol* 270**



Ferrocene (1.08 g, 5.8 mmol, 1.0 equiv.) was dissolved in THF (7.3 mL, 0.8 M) and cooled to -20 °C. *t*-BuLi (1.9 M in pentane, 2.5 mL, 4.7 mmol, 0.8 equiv.) was added dropwise and the mixture was stirred for 30 minutes at this temperature. Aldehyde **230** (1.20 g, 5.9 mmol) was then added in one portion and the mixture stirred overnight at room temperature. Saturated NH_4Cl solution (20 mL) was added and the aqueous

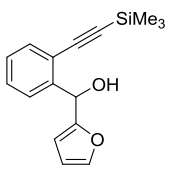
layer was extracted with Et_2O (2 × 20 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography gave the alcohol **270** (0.58 g, 26%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.41 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.32 (app. td, *J* = 7.7, 1.3 Hz, 1H), 7.18 (app. td, *J* = 7.6, 1.3 Hz, 1H), 5.97 (d, *J* = 3.6 Hz, 1H), 4.35 (app. dt, *J* = 2.4, 1.2 Hz, 1H), 4.27 – 4.23 (m, 1H), 4.22 (s, 5H), 4.17 – 4.12 (m, 2H), 2.63 (d, *J* = 3.6 Hz, 1H), 0.28 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 146.2 (C), 132.6 (CH), 129.1 (CH), 127.3 (CH), 125.8 (CH), 121.0 (C), 103.7 (C), 99.8 (C), 94.2 (C), 70.0 (CH), 68.7 (5 × CH), 68.3 (CH), 68.0 (CH), 67.6 (CH), 66.1 (CH), 0.39 (3 × CH_3); IR: ν_{max} (cm^{-1}) 3530, 3094, 2957, 2897, 2154, 1478, 1446, 1248, 864, 837, 756; HRMS (ES) *m/z* calculated for $C_{22}H_{24}OSiFe$ $(M+H)^+$ 388.0946 found 388.0950.

***(4-Methoxyphenyl)(2-((trimethylsilyl)ethynyl)phenyl)methanol* 271**



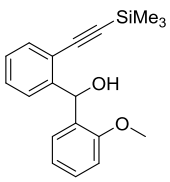
Prepared according to **GP2** from aldehyde **230** (1.0 g, 4.9 mmol). Purification by flash column chromatography [hexane:EtOAc (85:15)] gave the alcohol **271** (1.3 g, 83%) as a clear oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.45 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.38 – 7.32 (m, 3H), 7.21 (td, *J* = 7.5, 1.2 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.23 (d, *J* = 4.1 Hz, 1H), 3.78 (s, 3H), 2.58 (d, *J* = 4.1 Hz, 1H), 0.24 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 159.1 (C), 146.4 (C), 135.4 (C), 132.9 (CH), 129.1 (CH), 128.2 (2 × CH), 127.2 (CH), 126.1 (CH), 121.0 (C), 113.8 (2 × CH), 103.3 (C), 100.2 (C), 73.8 (CH), 55.4 (CH_3), 0.0 (3 × CH_3); IR: ν_{max} (cm^{-1}) 3320, 2958, 2154, 1612, 1511, 1250, 1172, 1035, 842, 760; HRMS (ES) *m/z* calculated for $C_{19}H_{22}O_2NaSi$ $(M+Na)^+$ 333.1287, found 333.1279.

Furan-2-yl(2-((trimethylsilyl)ethynyl)phenyl)methanol 272



Furan (0.33 mL, 4.5 mmol, 1.0 equiv) was dissolved in THF (22 mL, 0.2 M) and cooled to -10 °C. *n*-BuLi (2.5 M solution in hexane, 1.8 mL, 4.5 mmol, 1.0 equiv.) was added dropwise and the resulting solution stirred for 2 hours at this temperature. Aldehyde **230** (1.0 g, 4.9 mmol, 1.1 equiv.) was added in small portions and the reaction was stirred at room temperature for 16 hours. Water (15 mL) was added and the organic layer was extracted with EtOAc (3 × 15 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography [hexane:Et_2O (90:10), then hexane:EtOAc (90:10)] gave the alcohol **272** (947 mg, 71%) as a yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.26 (td, *J* = 7.5, 1.2 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.23 (s, 1H), 6.06 (d, *J* = 3.2 Hz, 1H), 2.78 (br. s, 1H), 0.20 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 155.3 (C), 143.1 (C), 142.5 (CH), 132.6 (CH), 129.0 (CH), 127.8 (CH), 126.5 (CH), 121.3 (C), 110.4 (CH), 107.8 (CH), 102.5 (C), 100.6 (C), 68.5 (CH), 0.0 (3 × CH_3); IR: ν_{max} (cm^{-1}) 3340, 2960, 2989, 2157, 1500, 1479, 1448, 1249, 1009, 864, 837; HRMS (ES) *m/z* calculated for $C_{16}H_{18}O_2NaSi$ $(M+Na)^+$ 293.0974, found 293.0960.

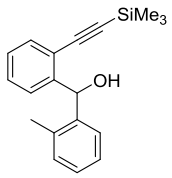
***(2-Methoxyphenyl)(2-((trimethylsilyl)ethynyl)phenyl)methanol* 286**



Prepared according to **GP2** using aldehyde **230** (1.2 g, 5.9 mmol) and *o*-anisole magnesium bromide (1 M in THF, 11.9 mL, 11.9 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the alcohol **286** (1.76 g, 95%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.47 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.35 (app. td, *J* = 7.6, 1.4 Hz, 1H), 7.30 – 7.19 (m, 2H), 7.09 – 7.03 (m, 1H), 6.93 –

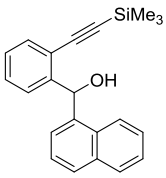
6.85 (m, 2H), 6.51 (s, 1H), 3.86 (s, 3H), 0.14 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 157.4 (C), 145.2 (C), 132.6 (CH), 131.4 (C), 129.0 (CH), 129.0 (CH), 128.2 (CH), 127.3 (CH), 127.0 (CH), 121.9 (C), 120.9 (CH), 110.6 (CH), 103.4 (C), 100.0 (C), 70.2 (CH), 55.7 (CH_3), 0.1 (3 × CH_3); IR: ν_{max} (cm^{-1}) 3447, 3066, 2959, 2900, 2837, 2156, 1589, 1600, 1490, 1462, 1244, 1024, 839; HRMS (ES) *m/z* calculated for $C_{19}H_{22}O_2NaSi$ $(M+Na)^+$ 333.1287 found 333.1300.

***o*-Tolyl(2-((trimethylsilyl)ethynyl)phenyl)methanol 287**



Prepared according to **GP2** using aldehyde **230** (1.20 g, 5.9 mmol) and *o*-toluene magnesium bromide (1 M in THF, 11.9 mL, 11.9 mmol). Purification by flash column chromatography [hexane:EtOAc (92.5:7.5)] gave the alcohol **287** (1.72 g, 98%) as a white solid; mp: 111-113 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.1 Hz, 1H), 7.46-7.42 (m, 1H), 7.36 – 7.15 (m, 6H), 6.46 (d, *J* = 4.0 Hz, 1H), 2.55 (d, *J* = 4.0 Hz, 1H), 2.31 (s, 3H), 0.24 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 145.1 (C), 140.4 (C), 135.9 (C), 132.7 (CH), 130.3 (CH), 129.0 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 126.3 (CH), 126.0 (CH), 122.0 (C), 102.8 (C), 99.8 (C), 71.0 (CH), 19.4 (CH_3), -0.11 (3 × CH_3); IR: ν_{max} (cm^{-1}) 3179, 3063, 3031, 2959, 2154, 1492, 1477, 1462, 1249, 1036, 1020, 851; HRMS (ES) *m/z* calculated for $C_{19}H_{23}OSi$ $(M+H)^+$ 295.1518 found 295.1514.

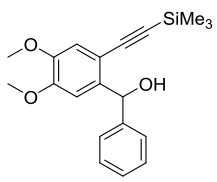
***Naphthalen-1-yl*(2-((trimethylsilyl)ethynyl)phenyl)methanol 288**



Prepared according to **GP2** using aldehyde **230** (1.40 g, 6.9 mmol) and 1-bromonaphthalene magnesium bromide (1 M in THF, 13.8 mL, 13.8 mmol). Purification by flash column chromatography [hexane:EtOAc (92.5:7.5)] gave the alcohol **288** (1.98 g, 87%) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15 – 8.10 (m, 1H), 7.91 –

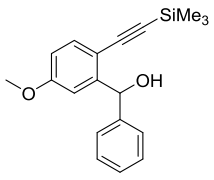
7.86 (m, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.44 (m, 5H), 7.36 – 7.21 (m, 3H), 7.03 (s, 1H), 2.65 (s, 1H), 0.08 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 145.4 (C), 138.1 (C), 133.8 (C), 132.6 (CH), 131.1 (C), 128.9 (CH), 128.7 (CH), 128.3 (CH), 127.5 (CH), 127.0 (CH), 126.2 (CH), 125.5 (CH), 125.3 (CH), 124.2 (CH), 123.8 (CH), 121.8 (C), 102.7 (C), 100.4 (C), 70.8 (CH), -0.4 (3 × CH_3); IR: ν_{max} (cm^{-1}) 3298, 3056, 2957, 2897, 2155, 1248, 857, 839; HRMS (ES) *m/z* calculated for $C_{22}H_{22}O_2SiNa$ $(M+Na)^+$ 353.1338 found 353.1341.

***(4,5-Dimethoxy-2-((trimethylsilyl)ethynyl)phenyl)(phenyl)methanol* 305**



Prepared according to **GP2** using aldehyde **302** (1.15 g, 4.4 mmol) and phenyl magnesium bromide (1 M in THF, 8.8 mL, 8.8 mmol). Purification by flash column chromatography [hexane:EtOAc (80:20)] gave the alcohol **305** (1.46 g, 99%) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.32 (app. t, *J* = 7.3 Hz, 2H), 7.25 (tt, *J* = 7.3, 1.9 Hz, 1H), 7.01 (s, 1H), 6.92 (s, 1H), 6.26 (s, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 2.55 (s, 1H), 0.23 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 149.9 (C), 147.8 (C), 143.3 (C), 139.8 (C), 128.3 (2 × CH), 127.4 (CH), 126.4 (2 × CH), 114.7 (CH), 112.9 (C), 109.1 (CH), 103.3 (C), 98.2 (C), 73.5 (CH), 56.0 (CH_3), 55.9 (CH_3), -0.1 (3 × CH_3); IR: ν_{max} (cm^{-1}) 3498, 3314, 3062, 3033, 3006, 2958, 2900, 2851, 2147, 1605, 1505, 1245, 1195, 1104; HRMS (ES) *m/z* calculated for $C_{20}H_{25}O_3Si$ $(M+H)^+$ 341.1567 found 341.1570.

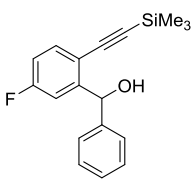
***(5-Methoxy-2-((trimethylsilyl)ethynyl)phenyl)(phenyl)methanol* 306**



Prepared according to **GP2** using aldehyde **303** (1.0 g, 4.3 mmol) and phenyl magnesium bromide (1 M in Et_2O, 8.6 mL, 8.6 mmol). Purification by flash

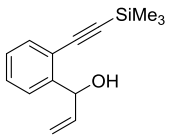
column chromatography [hexane (100%) then CH_2Cl_2 (100%)] gave the alcohol **306** (1.33 g, 99%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.10 (m, 6H), 6.96 (d, *J* = 2.7 Hz, 1H), 6.63 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.12 (d, *J* = 3.9 Hz, 1H), 3.69 (s, 3H), 2.54 (d, *J* = 3.9 Hz, 1H), 0.10 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 160.1 (C), 147.9 (C), 142.8 (C), 134.2 (CH), 128.3 (2 × CH), 127.5 (CH), 126.7 (2 × CH), 113.2 (C), 112.9 (CH), 111.8 (CH), 103.3 (C), 98.3 (C), 74.0 (CH), 55.3 (CH_3), -0.1 (3 × CH_3); IR: ν_{max} (cm^{-1}) 3404, 2959, 2900, 2842, 2150, 1603, 1488, 1247, 1028, 836; HRMS (ES) *m/z* calculated for $C_{19}H_{22}O_2SiNa$ $(M+Na)^+$ 333.1287 found 333.1295.

***(5-Fluoro-2-((trimethylsilyl)ethynyl)phenyl)(phenyl)methanol* 307**



Prepared according to **GP2** using aldehyde **304** (1.50 g, 6.8 mmol) and phenyl magnesium bromide (1 M in THF, 13.6 mL, 13.6 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the alcohol **307** (1.91 g, 94%) as a pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 3H), 7.33 – 7.22 (m, 4H), 6.88 (ddd, *J* = 8.7, 8.3, 2.7 Hz, 1H), 6.21 (d, *J* = 3.6 Hz, 1H), 2.55 (d, *J* = 3.6 Hz, 1H), 0.21 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) 162.9 (d, $J_{C\text{-}F}$ = 250.5 Hz, C), 148.8 (d, $J_{C\text{-}F}$ = 7.3 Hz, C), 142.3 (C) 134.6 (d, $J_{C\text{-}F}$ = 8.4 Hz, CH), 128.4 (2 × CH), 127.8 (CH), 126.8 (2 × CH), 117.0 (C), 114.5 (d, $J_{C\text{-}F}$ = 22.2 Hz, CH), 113.5 (d, $J_{C\text{-}F}$ = 23.4 Hz, CH), 102.1 (C), 99.7 (C), 73.6 (CH), -0.2 (3 × CH_3); IR: ν_{max} (cm^{-1}) 3326, 3066, 3033, 2960, 2899, 2156, 1604, 1482, 1250; HRMS (ES) *m/z* calculated for $C_{18}H_{20}FOSi$ $(M+H)^+$ 299.1262 found 299.1274.

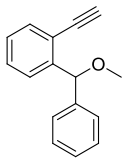
1-(2-((Trimethylsilyl)ethynyl)phenyl)prop-2-en-1-ol 325



Prepared according to **GP2** from aldehyde **230** (2.5 g, 12.4 mmol). Purification by flash column chromatography [hexane:EtOAc (94:6)] gave the alcohol **325** (2.4 g, 84%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.49 – 7.43 (m, 2H), 7.38 – 7.31 (m, 1H), 7.22 (td, *J* = 7.4, 1.4 Hz, 1H), 6.05 (ddd, *J* = 17.1, 10.4, 5.7 Hz, 1H), 5.69 – 5.60 (m, 1H), 5.39 (app. dt, *J* = 17.1, 1.5 Hz, 1H), 5.19 (dt, *J* = 10.4, 1.5 Hz, 1H), 2.39 (d, *J* = 4.6 Hz, 1H), 0.26 (s, 9H); IR: ν_{max} (cm^{-1}) 3352, 2954, 2865, 2832, 2141, 1562, 1433, 1412; MS (ES): *m/z* 230 $[M]^+$ (60%), 185 (85), 153 (100). Data matches that reported in the literature.[196]

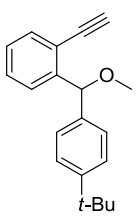
Preparation of Terminal Alkynes

1-Ethynyl-2-(methoxy(phenyl)methyl)benzene 232



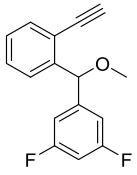
Prepared according to **GP3** from alcohol **231** (1.1 g, 3.7 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the terminal alkyne **232** (821 mg, 72%) as a white solid; mp: 34-36 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.54 – 7.47 (m, 2H), 7.47 – 7.41 (m, 2H), 7.40 – 7.17 (m, 5H), 5.83 (s, 1H), 3.40 (s, 3H), 3.35 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.7 (C), 141.6 (C), 133.0 (CH), 129.5 (CH), 128.4 (2 × CH), 127.6 (CH), 127.3 (CH), 127.0 (3 × CH), 126.4 (CH), 121.1 (C), 82.3 (CH), 82.1 (C), 57.2 (CH_3);MS (EI): *m/z* 222 $[M]^+$ (20 %), 207 (100%). Data matches that reported in the literature.[122]

***1-((4-(t-Butyl)phenyl)(methoxy)methyl)-2-ethynylbenzene* 273**



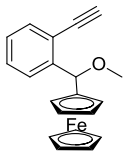
Prepared according to **GP3** using alcohol **268** (1.0 g, 3.0 mmol) and methyl iodide (0.28 mL, 4.5 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:Et_2O (98:2)] gave the terminal alkyne **273** (384 mg, 46% over 2 steps) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.49 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.36 (m, 5H), 7.22 (app. td, *J* = 7.5, 1.3 Hz, 1H), 5.82 (s, 1H), 3.40 (s, 3H), 3.36 (s, 1H), 1.29 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 150.6 (C), 145.1 (C), 138.8 (C), 133.2 (CH), 129.7 (CH), 127.5 (CH), 126.9 (2 × CH), 126.6 (CH), 125.5 (2 × CH), 121.3 (C), 82.4 (2 × CH), 82.3 (C), 57.5 (3 × CH_3), 34.8 (C), 31.7 (CH_3); IR: ν_{max} (cm^{-1}) 3290, 2962, 2904, 2869, 2823, 1463, 1099, 1081, 759; HRMS (ES) *m/z* calculated for $C_{19}H_{19}$ $(M(-OCH_3)+H)^+$ 247.1487 found 247.1501.

***1-((2-Ethynylphenyl)(methoxy)methyl)-3,5-difluorobenzene* 274**



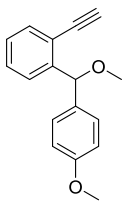
Prepared according to **GP3** using alcohol **269** (1.0 g, 3.2 mmol) and methyl iodide (0.30 mL, 4.8 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:CH_2Cl_2 (95:5)] gave the terminal alkyne **274** (408 mg, 50% over 2 steps) as a pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.44 (dd, *J* = 7.9, 1.5 Hz, 1H) 7.38 (ddd, *J* = 7.9, 7.8, 1.5 Hz, 1H), 7.26 (app. td, *J* = 7.7, 7.6, 1.5 Hz, 1H), 7.03 – 6.94 (m, 2H), 6.67 (tt, *J* = 8.9, 2.4 Hz, 1H), 5.80 (s, 1H), 3.40 (s, 1H), 3.39 (s, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 163.3 (dd, $J_{C\text{-}F}$ = 248.2, 12.5 Hz, *ipso*-2 × C), 146.2 (t, $J_{C\text{-}F}$ = 8.3 Hz, *meta*-C), 143.6 (C), 133.3 (CH), 129.9 (CH), 128.1 (CH), 126.6 (CH), 121.2 (C), 109.8 (d, $J_{C\text{-}F}$ = 25.7 Hz, *ortho*-2 × CH), 103.1 (t, $J_{C\text{-}F}$ = 25.4 Hz, *ortho*-CH), 82.8 (CH), 82.0 (C), 81.3 (CH), 57.5 (CH_3); IR: ν_{max} (cm^{-1}) 3298, 3068, 2994, 2994, 2934, 2827, 1624, 1596, 1454, 1437, 1116, 1102, 1083, 757; HRMS (ES) *m/z* calculated for $C_{15}H_9F_2$ $(M(-OCH_3)+H)^+$ 227.0672 found 227.0680.

***1-Ethynyl-2-(methoxy(ferrocene)methyl)benzene* 275**



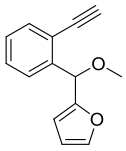
Prepared according to **GP3** using alcohol **270** (0.60 g, 1.4 mmol) and methyl iodide (0.13 mL, 2.1 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:Et_2O (97:3)] gave the terminal alkyne **275** (297 mg, 64% over 2 steps) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.53 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.39 (app. td, *J* = 7.8, 1.3 Hz, 1H), 7.29-7.21 (m, 1H), 5.62 (s, 1H), 4.28 (app. dt, *J* = 2.5, 1.3 Hz, 1H), 4.16 (app. dt, *J* = 2.5, 1.3 Hz, 1H), 4.14 – 4.07 (m, 2H), 4.10 (s, 5H), 3.40 (s, 1H), 3.31 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 132.0 (CH), 128.5 (CH), 126.6 (CH), 125.9 (CH), 120.5 (C), 89.6 (C), 81.4 (C), 81.2 (CH), 78.4 (CH), 68.1 (5 × CH), 67.2 (CH), 66.8 (2 × CH), 65.8 (CH), 56.3 (CH_3); IR: ν_{max} (cm^{-1}) 3291, 3102, 2982, 2931, 2819, 1478, 1446, 1105, 1079, 728; HRMS (ES) *m/z* calculated for $C_{20}H_{18}OFe$ $(M)^+$ 330.0707 found 330.0695.

***1-Ethynyl-2-(methoxy(4-methoxyphenyl)methyl)benzene* 276**



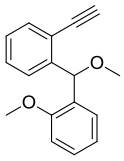
Prepared according to **GP3** using alcohol **271** (1.2 g, 3.9 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the alcohol **276** (590 mg, 60%) as a clear oil; ^{1}H NMR-(400 MHz, $CDCl_3$): δ 7.57 – 7.51 (m, 1H), 7.49 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.41 – 7.31 (m, 3H), 7.21 (td, *J* = 7.7, 1.3 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.77 (s, 1H), 3.78 (s, 3H), 3.39 (s, 3H), 3.34 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 159.1 (2 × C), 144.9 (C), 133.7 (C), 133.1 (CH), 129.4 (CH), 128.4 (2 × CH), 127.2 (CH), 126.2 (CH), 121.0 (C), 113.8 (2 × CH), 82.3 (CH), 82.1 (CH), 57.1 (CH_3), 55.3 (CH_3); HRMS (ES) *m/z* calculated for $C_{17}H_{16}O_2Na$ $(M+Na)^+$ 275.1040, found 275.1043. Data matches that reported in the literature.

***2-((2-Ethynylphenyl)(methoxy)methyl)furan* 277**



Prepared according to **GP3** using alcohol **272** (909 mg, 3.4 mmol) and methyl iodide (0.31 mL, 5.0 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the terminal alkyne **277** (541 mg, 76% over 2 steps) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.70 – 7.64 (m, 1H), 7.50 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.39 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.32 – 7.25 (m, 1H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.11 (d, *J* = 3.2 Hz, 1H), 5.82 (s, 1H), 3.41 (s, 3H), 3.30 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 153.7 (C), 142.9 (CH), 141.4 (C), 132.9 (CH), 129.4 (CH), 127.9 (CH), 126.8 (CH), 121.3 (C), 110.2 (CH), 108.8 (CH), 82.4 (CH), 81.2 (C), 76.3 (CH), 57.3 (CH_3); IR: ν_{max} (cm^{-1}) 3290, 2989, 2935, 2823, 1480, 1447, 1188, 1143, 1078, 1012, 761, 740; HRMS (ES) *m/z* calculated for $C_{14}H_{12}O_2$ $(M+H)^+$ 212.0837, found 212.0841.

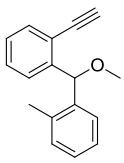
***1-Ethynyl-2-(methoxy(2-methoxyphenyl)methyl)benzene* 289**



Prepared according to **GP3** using alcohol **286** (1.0 g, 3.2 mmol) and methyl iodide (0.30 mL, 4.8 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:Et_2O (95:5)] gave the terminal alkyne **289** (534 mg, 66% over 2 steps) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.53 – 7.48 (m, 1H), 7.41 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.34 – 7.18 (m, 4H), 6.98 (app. td, *J* = 7.6, 0.9 Hz, 1H), 6.85 (dd, *J* = 8.2, 0.8 Hz, 1H), 6.13 (s, 1H), 3.76 (s, 3H), 3.43 (s, 3H), 3.29 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 157.5 (C), 144.2 (C), 133.1 (CH), 129.8 (C), 129.2 (CH), 128.9 (CH), 127.7 (CH), 127.4 (CH), 127.4 (CH), 122.3 (C), 120.8 (CH), 110.9 (CH), 82.3 (C), 81.5 (CH), 77.2 (CH), 57.8 (CH_3), 55.7 (CH_3); IR: ν_{max} (cm^{-1}) 3267, 3013, 2963,

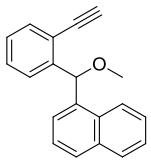
2934, 2837, 2824, 1600, 1588, 1487, 1458, 1239, 1080, 1025; HRMS (ES) *m/z* calculated for $C_{16}H_{13}O$ $(M(-OCH_4)+H)^+$ 221.0966 found 221.0974.

***1-Ethynyl-2-(methoxy(o-tolyl)methyl)benzene* 290**



Prepared according to **GP3** using alcohol **287** (1.40 g, 4.8 mmol) and methyl iodide (0.44 mL, 7.1 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:Et_2O (95:5)] gave the terminal alkyne **290** (922 mg, 82% over 2 steps) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.57 – 7.52 (m, 1H), 7.42 – 7.11 (m, 7H), 5.94 (s, 1H), 3.45 (s, 3H), 3.32 (s, 1H), 2.27 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.1 (C), 139.1 (C), 136.6 (C), 133.1 (CH), 130.6 (CH), 129.3 (CH), 127.8 (CH), 127.7 (2 × CH), 126.7 (CH), 126.1 (CH), 122.5 (C), 82.1 (C), 82.0 (CH), 79.8 (CH), 57.8 (CH_3), 19.6 (CH_3); IR: ν_{max} (cm^{-1}) 3289, 3066, 3026, 2932, 2822, 1479, 1461, 1447, 1077, 750; HRMS (ES) *m/z* calculated for $C_{16}H_{13}$ $(M(-OCH_3)+H)^+$ 205.1017 found 205.1025.

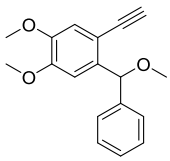
***1-((2-Ethynylphenyl)(methoxy)methyl)naphthalene* 291**



Prepared according to **GP3** using alcohol **288** (2.0 g, 5.9 mmol) and methyl iodide (0.59 mL, 8.9 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:Et_2O (96.5:3.5)] gave the terminal alkyne **291** (1.34 g, 84% over 2 steps) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.07 – 8.00 (m, 1H), 7.89 – 7.79 (m, 2H), 7.67 – 7.57 (m, 2H), 7.54 – 7.42 (m, 3H), 7.28 – 7.23 (m, 3H), 6.53 (s, 1H), 3.55 (s, 3H), 3.37 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.3 (C), 136.4 (C), 133.9 (C), 133.1 (CH), 131.4 (C), 129.3 (CH), 128.8 (CH), 128.3 (CH), 127.7 (CH), 127.7 (CH), 126.2 (CH), 125.5 (CH), 125.4 (CH), 124.4 (CH), 123.8 (CH), 122.1 (C), 82.2 (CH), 82.0 (C), 79.5 (CH), 57.9 (CH_3); IR: ν_{max} (cm^{-1}) 3284, 3058,

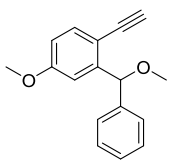
2929, 2821, 1597, 1509, 1478, 1446, 1086, 1071,757; HRMS (ES) *m/z* calculated for $C_{20}H_{16}ONa$ $(M+Na)^+$ 295.1099 found 295.1088.

***1-Ethynyl-4,5-dimethoxy-2-(methoxy(phenyl)methyl)benzene* 308**



Prepared according to **GP3** using alcohol **305** (1.40 g, 4.1 mmol) and methyl iodide (0.38 mL, 6.2 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the terminal alkyne **308** (640 mg, 55% over 2 steps) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.33 (m, 2H), 7.28 – 7.23 (m, 2H), 7.19 – 7.15 (m, 1H), 6.91 (s, 1H), 6.90 (s, 1H), 5.74 (s, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 3.34 (s, 3H), 3.22 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 150.3 (C), 147.9 (C), 141.8 (C), 138.1 (C), 128.2 (2 × CH), 127.3 (CH), 126.5 (2 × CH), 114.6 (CH), 112.9 (C), 108.7 (CH), 82.0 (C), 81.8 (CH), 80.5 (CH), 57.0 (CH_3), 55.9 (CH_3), 55.9 (CH_3); IR: ν_{max} (cm^{-1}) 3279, 2982, 2934, 2907, 2824, 1602, 1507, 1462, 1451, 1395, 1356, 1258, 1212, 1185, 1096, 1082; HRMS (ES) *m/z* calculated for $C_{18}H_{18}O_3Na$ $(M+Na)^+$ 305.1154 found 305.1149.

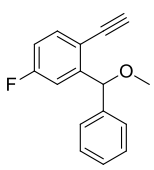
***1-Ethynyl-4-methoxy-2-(methoxy(phenyl)methyl)benzene* 309**



Prepared according to **GP3** using alcohol **306** (1.39 g, 4.5 mmol) and methyl iodide (0.42 mL, 6.7 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:diethyl ether (95:5)] gave the terminal alkyne **309** (797 mg, 70% over 2 steps) as a yellow solid; mp: 70-72 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.47 – 7.39 (m, 3H), 7.36 – 7.20 (m, 3H), 7.06 (d, *J* = 2.7 Hz, 1H), 6.76 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.80 (s, 1H), 3.80 (s, 3H), 3.41 (s, 3H), 3.27 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 160.4 (C), 146.4 (C), 141.3 (C), 134.2 (CH), 128.2 (2 × CH), 127.4 (CH), 126.8 (2 × CH), 113.3 (CH), 113.1 (C), 111.3 (CH), 82.1

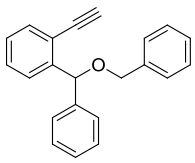
(CH_3), 82.0 (C), 80.7 (CH), 57.1 (CH), 55.3 (CH_3); IR: ν_{max} (cm^{-1}) 3294, 3067, 2982, 2928, 2889, 2819, 2103, 1600, 1484, 1444, 1301, 1092, 1070, 1026; HRMS (ES) *m/z* calculated for $C_{17}H_{17}O_2$ $(M+H)^+$ 253.1229 found 253.1231.

1-Ethynyl-4-fluoro-2-(methoxy(phenyl)methyl)benzene **310**



Prepared according to **GP3** using alcohol **307** (1.47 g, 4.9 mmol) and methyl iodide (0.46 mL, 7.4 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:CH_2Cl_2 (95:5)] gave the terminal alkyne **310** (847 mg, 71% over 2 steps) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.44 – 7.31 (m, 3H), 7.29 – 7.16 (m, 4H), 6.85 (app. td, *J* = 8.3, 2.7 Hz, 1H), 5.70 (s, 1H), 3.33 (s, 3H), 3.26 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 163.2 (d, $J_{C\text{-}F}$ = 250.6 Hz, C), 147.7 (d, $J_{C\text{-}F}$ = 7.4 Hz, C), 140.8 (C), 134.8 (d, $J_{C\text{-}F}$ = 8.4 Hz, CH), 128.4 (2 × CH), 127.8 (CH), 126.9 (2 × CH), 116.8 (d, $J_{C\text{-}F}$ = 3.3 Hz, C), 114.7 (d, $J_{C\text{-}F}$ = 22.4 Hz, CH), 113.5 (d, $J_{C\text{-}F}$ = 23.2 Hz, CH), 81.9 (2 CH), 81.1 (C), 57.2 (CH_3); IR: ν_{max} (cm^{-1}) 3064, 3032, 2988, 2933, 2824, 1605, 1487, 1453, 2100, 1077; HRMS (ES) *m/z* calculated for $C_{16}H_{13}OFNa$ $(M+Na)^+$ 263.0848 found 263.0839.

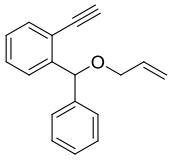
1-((Benzyloxy)(phenyl)methyl)-2-ethynylbenzene 318



Prepared according to **GP3** using alcohol **231** (0.49 g, 1.7 mmol) and benzyl bromide (0.31 mL, 2.6 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:toluene (90:10) then hexane:EtOAc (98:2)] gave the terminal alkyne **318** (252 mg, 49% over 2 steps) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.53 – 7.44 (m, 3H), 7.41 – 7.20 (m, 10H), 6.06 (s, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 3.29 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.7 (C), 141.6 (C),

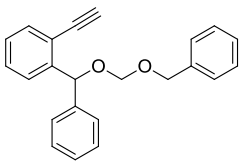
138.3 (C), 132.9 (CH), 129.4 (CH), 128.3 (4 × CH), 127.8 (2 × CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 126.8 (2 × CH), 121.0 (C), 82.2 (CH), 81.9 (C), 79.8 (CH), 70.89 (CH_2); IR: ν_{max} (cm^{-1}) 3249, 3088, 3063, 3024, 2996, 2897, 1495, 1475, 1453, 1394, 1337, 1076, 1052, 1010, 761, 742; HRMS (ES) *m/z* calculated for $C_{22}H_{18}ONa$ $(M+Na)^+$ 321.1255 found 321.1258.

***1-((Allyloxy)(phenyl)methyl)-2-ethynylbenzene* 319**



Prepared according to **GP3** using alcohol **231** (1.0 g, 3.5 mmol) and allyl iodide (0.49 mL, 5.3 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:CH_2Cl_2 (95:5) then hexane:Et_2O (95:5)] gave the terminal alkyne **319** (554 mg, 63% over 2 steps) as a pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.51 – 7.42 (m, 3H), 7.40 – 7.18 (m, 5H), 6.00 (s, 1H), 5.98 (ddt, *J* = 17.2, 10.4, 5.3 Hz, 1H), 5.31 (ddt, *J* = 17.2, 3.0, 1.5 Hz, 1H), 5.19 (ddt, *J* = 10.4, 3.0, 1.5 Hz, 1H), 4.03 (app. dt, *J* = 5.3, 1.5 Hz, 2H), 3.34 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.7 (C), 141.6 (C), 134.6 (CH), 132.8 (CH), 129.3 (CH), 128.2 (2 × CH), 127.4 (CH), 127.2 (CH), 126.9 (2 × CH), 126.5 (CH), 120.9 (C), 116.9 (CH_2), 82.1 (CH), 81.9 (C), 79.6 (CH), 69.9 (CH_2); IR: ν_{max} (cm^{-1}) 3290, 3065, 3029, 2859, 1494, 1478, 1449, 1060, 920; HRMS (ES) *m/z* calculated for $C_{18}H_{16}ONa$ $(M+Na)^+$ 271.1099, found 271.1082.

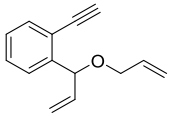
1-(((Benzyloxy)methoxy)(phenyl)methyl)-2-ethynylbenzene 320



Alcohol **231** (1.0 g, 3.6 mmol,1.0 equiv.) was dissolved in CH_2Cl_2 (18 mL, 0.2M) and cooled to 0 °C. Benzyl chloromethyl ether (1.0 mL, 7.1 mmol, 2.0 equiv.) and diisopropylethylamine (0.9 mL, 5.3 mmol, 1.5 equiv.) were added and the mixture stirred at 0 °C for 1 hour, before stirring at room temperature for 16

hours. The resulting solution was diluted with Et_2O (20 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude residue was dissolved in MeOH (18 mL, 0.2 M), K_2CO_3 (246 mg, 0.5 equiv.) was added and the mixture stirred at room temperature for one hour. Saturated $NaHCO_3$ solution was added and the aqueous phase was extracted with EtOAc (× 2) and dried over Na_2SO_4. The solid was filtered off and the solvent removed under reduced pressure. Purification by flash column chromatography [hexane:toluene (50:50) gave the terminal alkyne **320** (977 mg, 83%) as a yellow oil; 1H-NMR (300 MHz, CDCl3): δ 7.62 (d, J = 7.3 Hz, 1H), 7.53 – 7.42 (m, 3H), 7.42 – 7.18 (m, 10H), 6.38 (s, 1H), 4.89 – 4.82 (m, 2H), 4.62 (s, 2H), 3.30 (s, 1H); 13C-NMR (101 MHz, CDCl3): δ 144.5 (C), 141.4 (C), 137.9 (C), 133.0 (CH), 129.4 (CH), 128.4 (4 × CH), 128.1 (2 × CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 127.3 (2 × CH), 126.8 (CH), 121.0 (C), 92.8 (CH2), 82.5 (CH), 81.9 (C), 76.7 (CH), 69.9 (CH2); IR: ν_{max} (cm^{-1}) 3287, 3064, 3030, 2945, 2886, 1453, 1035, 1023; HRMS (ES) m/z calculated for $C_{23}H_{19}O_2$ $(M+H)^+$ 327.1385, found 327.1382.

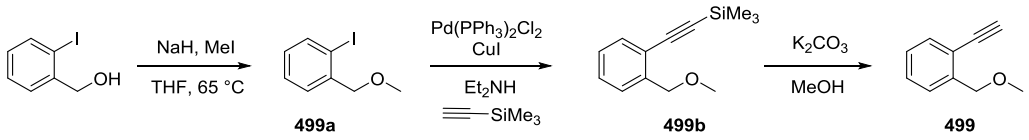
1-(1-(Allyloxy)allyl)-2-ethynylbenzene 326



Prepared according to **GP3** using alcohol **325** (1.0 g, 4.3 mmol) and allyl iodide (0.6 mL, 6.5 mmol) as the alkyl halide. Purification by flash column chromatography [hexane:Et_2O (90:10)] gave the terminal alkyne **326** (414 mg, 48% over 2 steps) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.54 – 7.46 (m, 2H), 7.38 (app. td, *J* = 7.6, 1.2 Hz, 1H), 7.24 (app. dt, *J* = 7.6, 1.4 Hz, 1H), 5.39-5.31 (m, 2H), 5.36 (app. t, *J* = 1.4 Hz, 1H), 5.29 (ddd, *J* = 17.2, 3.4, 1.7 Hz, 2H), 5.22-5.14 (m, 2H), 3.98 (ddt, *J* = 5.6, 2.9, 1.4 Hz, 2H), 3.30 (s, 1H); ^{13}C-

NMR (101 MHz, $CDCl_3$): δ 143.6 (C), 137.9 (CH), 134.8 (CH), 133.0 (CH), 129.5 (CH), 127.4 (CH), 126.5 (CH), 120.9 (C), 117.0 (CH_2), 116.2 (CH_2), 82.1 (CH), 81.6 (C), 79.3 (CH), 69.6 (CH_2); IR: ν_{max} (cm^{-1}) 3070, 3023, 2993, 2860, 1479, 1446, 1414, 1064, 989, 925, 760; HRMS (ES) *m/z* calculated for $C_{18}H_{16}ONa$ $(M+Na)^+$ 271.1099, found 271.1082.

1-Ethynyl-2-(methoxymethyl)benzene 499

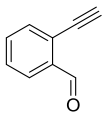


NaH (60% dispersion in mineral oil, 615 mg, 15.3 mmol, 1.2 equiv.) was weighed into a flask and washed with hexane (2 × 10 mL). THF (25 mL, 0.5 M) was added and 2-iodobenzyl alcohol (3.0 g, 12.9 mmol, 1.0 equiv.) was added in portions at room temperature. The mixture was heated to 65 °C for 3 hours and cooled to 0 °C before the dropwise addition of MeI (1.2 mL, 19.2 mmol, 1.5 equiv.). The resulting solution was stirred at room temperature for 3 hours and quenched by addition of saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL) and dried over Na_2SO_4. The solid was filtered off and the solvent removed under reduced pressure. Purification by flash column chromatography [hexane:CH_2Cl_2 (80:20) gave the methyl ether **499a** (2.0 g, 61%) as a clear oil.; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.42 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.35 (td, *J* = 7.6, 1.1 Hz, 1H), 6.99 (td, *J* = 7.6, 1.8 Hz, 1H), 4.45 (s, 2H), 3.47 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 140.6 (C), 139.3 (CH), 129.3 (CH), 128.8 (CH), 128.4 (CH), 97.9 (C), 78.5 (CH_3), 58.7 (CH_2); MS (EI): *m/z* 248 $[M]^+$ (10%), 217 (10), 121 (100). Data matches that reported in the literature.[197]

Aryl iodide **499a** (1.6 g, 6.5 mmol, 1.0 equiv.) was dissolved in Et_3N (16 mL, 0.4 M). $Pd(PPh_3)Cl_2$ (45.9 mg, 0.1 mmol, 1 mol%) and CuI (12.4 mg, 0.1 mmol, 1 mol%) were added and the solution stirred for 5 minutes. Trimethylsilylacetylene (1.1 mL, 7.8 mmol, 1.2 equiv.) was added slowly and the resulting solution stirred at room temperature for 14 hours. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography [hexane:CH_2Cl_2 (80:20)] to give the protected alkyne **499b** (1.3 g, 94%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.49 – 7.41 (m, 2H), 7.33 (td, *J* = 7.5, 1.4 Hz, 1H), 7.22 (td, *J* = 7.5, 1.1 Hz, 1H), 4.62 (s, 2H), 3.45 (s, 3H), 0.26 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 140.6 (C), 132.4 (CH), 128.9 (CH), 127.5 (CH), 127.3 (CH), 121.9 (C), 102.8 (C), 99.1 (C), 72.7 (CH_3), 58.7 (CH_2), 0.1 (3 × CH_3); MS (EI): *m/z* 218 $[M]^+$ (100%). Data matches that reported in the literature.[198]

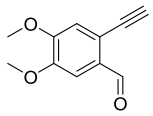
Alkyne **499b** (1.3 g, 6.1 mmol, 1.0 equiv.) was dissolved in MeOH (30 mL, 0.2 M), K_2CO_3 (419 mg, 0.5 equiv.) was added and the mixture stirred at room temperature for one hour. Saturated $NaHCO_3$ solution (20 mL) was added and the aqueous phase was extracted with EtOAc (3 × 20 mL) and dried over Na_2SO_4. The solid was filtered off and the solvent removed under reduced pressure to give the terminal alkyne **499** which did not require further purification; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 7.25 (td, *J* = 7.5, 1.3 Hz, 2H), 4.64 (s, 2H), 3.45 (s, 3H), 3.30 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 140.8 (C), 132.9 (CH), 129.1 (CH), 127.6 (CH), 127.4 (CH), 120.8 (C), 81.8 (CH), 81.1 (C), 72.7 (CH_2), 58.7 (CH_3); HRMS (ES) m/z calculated for $C_{10}H_{10}O$ $(M+H)^+$ 146.0732, found 146.0727. Data matches that reported in the literature.[199]

2-Ethynylbenzaldehyde 509



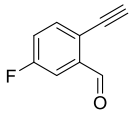
Prepared according to **GP4** using alkyne **230** (1.2 g, 3.9 mmol) to give the terminal alkyne **509** (1.4 g, 88%) as an off-white solid; mp: 65-67 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.54 (d, *J* = 0.8 Hz, 1H), 7.93 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.62 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.57 (td, *J* = 7.4, 1.4Hz, 1H), 7.52 – 7.43 (m, 1H), 3.46 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 191.6 (CH) 136.7 (C), 134.0 (CH), 133.9 (CH), 129.4 (CH), 127.4 (CH), 125.6 (C), 84.4 (CH), 79.3 (C); IR: ν_{max} (cm^{-1}) 3032, 3001, 2887, 2098, 1685, 1080, 768; Data matches that reported in the literature.[149]

2-Ethynyl-4,5-dimethoxybenzaldehyde 510



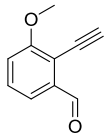
Prepared according to **GP4** using alkyne **302** (2.6 g, 9.7 mmol) to give the terminal alkyne **510** (1.8 g, 98%) as a yellow solid; mp: 154-156 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.38 (s, 1H), 7.40 (s, 1H), 7.02 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.38 (s, 1H); MS (ES): *m/z* 191 $[M+H]^+$ (20%), 190 (100). Data matches that reported in the literature.[200]

2-Ethynyl-5-fluorobenzaldehyde 511



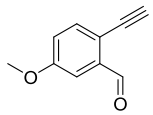
Prepared according to **GP4** using alkyne **304** (634 mg, 2.9 mmol) to give the terminal alkyne **511** (381 g, 89%) as an off-white solid; mp: 107-109 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.48 (d, *J* = 3.2 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.28 (ddd, *J* = 8.5, 7.8, 2.8 Hz, 1H), 3.44 (d, *J* = 0.5 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 190.3 (CH), 162.9 (d, J_{C-F} = 253.4 Hz, C), 138.8 (d, J_{C-F} = 6.7 Hz, C), 136.1 (d, J_{C-F} = 7.7 Hz, CH), 121.7 (C), 121.4 (d, J_{C-F} = 22.8 Hz, CH), 113.9 (d, J_{C-F} 23.1 Hz, CH), 84.2 (CH), 78.35 (C); IR: ν_{max} (cm^{-1}) 3020, 2976, 2887, 2832, 2103, 1690, 976, 750. Data matches that reported in the literature.[149]

2-Ethynyl-3-methoxybenzaldehyde 534a



Prepared according to **GP4** using aldehyde **530** (928 mg, 4.0 mmol). Recrystallisation [CH_2Cl_2:hexane] gave the terminal alkyne **534a** (415 mg, 65%) as a purple solid; mp: 103-105 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.54 (d, *J* = 0.8 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.47 – 7.39 (m, 1H), 7.14 (dd, *J* = 8.2, 0.8 Hz, 1H), 3.92 (s, 3H), 3.70 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 191.8 (CH), 161.5 (C), 138.1 (C), 130.2 (CH), 119.3 (CH), 115.9 (CH), 114.9 (C), 88.8 (CH), 75.5 (C), 56.6 (CH_3); IR: ν_{max} (cm^{-1}) 3275, 3070, 3008, 2867, 1687, 1588, 1279, 1247, 795; HRMS (ES) m/z calculated for $C_{10}H_8O_2Na$ $(M+Na)^+$ 183.0422 found 183.0426.

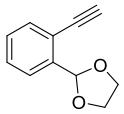
2-Ethynyl-5-methoxybenzaldehyde 548



Prepared according to **GP4** using alkyne **303** (907 mg, 3.9 mmol) to give the terminal alkyne **548** (631 g, >99%) as a pale yellow solid; mp: 95-97; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.49 (s, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 2.8 Hz, 1H), 7.10 (dd, *J* = 8.5, 2.8 Hz, 1H), 3.86 (s, 3H), 3.37 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5 (CH), 160.3 (C), 138.1 (C), 135.3 (CH), 121.6 (CH), 118.2 (C), 110.1 (CH), 82.9 (CH), 79.3 (C), 55.8 (CH_3); HRMS (ES) m/z calculated for $C_{10}H_9O_2$ $(M+H)^+$ 161.0603, found 161.0605. Data matches that reported in the literature.[149]

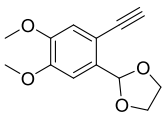
Preparation of Acetals From 2-Ethynyl Aldehydes

2-(2-Ethynylphenyl)-1,3-dioxolane 512



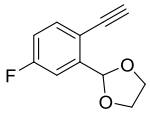
Prepared according to **GP5** using aldehyde **509** (1.2 g, 9.2 mmol) and ethylene glycol. Purification by flash column chromatography [hexane:EtOAc (95:5), 1% Et_3N] gave the acetal **512** (1.4 g, 85%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.56 – 7.51 (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), 4.22 – 4.12 (m, 2H), 4.13 – 4.01 (m, 2H), 3.33 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 139.8, (C) 133.3 (CH), 129.1 (2 × CH), 126.1 (CH), 121.4 (C), 101.9 (CH), 82.0 (CH), 81.0 (C), 65.7 (2 × CH_2); MS (ES): *m/z* 175 $[M+H]^+$ (100%), 167 (40). Data matches that reported in the literature.[201]

2-(2-Ethynyl-4,5-dimethoxyphenyl)-1,3-dioxolane 513



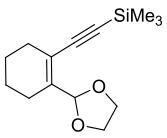
Prepared according to **GP5** using aldehyde **510** (1.9 g, 9.9 mmol) and ethylene glycol. Purification by flash column chromatography [hexane:EtOAc (90:10), 1% Et_3N, then hexane:EtOAc (80:20)] gave the acetal **513** (480 g, 21%) as an orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.97 (s, 1H), 6.13 (s, 1H), 4.26 – 4.11 (m, 2H), 4.12 – 3.98 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.24 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 150.0 (C), 149.4 (C), 132.9 (C), 114.9 (CH), 113.8 (C), 108.7 (CH), 101.7 (CH), 81.0 (C), 80.5 (CH), 65.6 (2 × CH_2), 56.1 (CH_3), 56.0 (CH_3); HRMS (ES) *m/z* calculated for $C_{13}H_{14}O_4Na$ $(M+Na)^+$ 257.0789, found 257.0796. Data matches that reported in the literature.[201]

2-(2-Ethynyl-5-fluorophenyl)-1,3-dioxolane 514



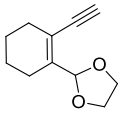
Prepared according to **GP5** using aldehyde **511** (370 mg, 2.5 mmol) and ethylene glycol. Purification by flash column chromatography [hexane:Et_2O (90:10), 1% Et_3N] gave the acetal **514** (470 g, 98%) as an orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.5, 5.5 Hz, 1H), 7.29 (dd, *J* = 9.4, 2.7 Hz, 1H), 7.02 (app. td, *J* = 8.5, 2.9 Hz, 1H), 6.18 (d, *J* = 1.5 Hz, 1H), 4.25 – 4.11 (m, 2H), 4.11 – 4.00 (m, 2H), 3.30 (s, 1H); IR: ν_{max} (cm^{-1}) 3293, 2956, 2921, 2890, 2108, 1610, 1581, 1563, 1495, 1390, 1257, 1101, 1072, 856. Data matches that reported in the literature.[201]

((2-(1,3-Dioxolan-2-yl)cyclohex-1-en-1-yl)ethynyl)trimethylsilane 531a



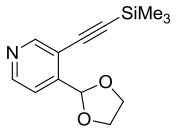
Prepared according to **GP5** using aldehyde **527** (1.0 g, 4.9 mmol) and ethylene glycol to give the crude acetal **531a** which was used directly in the next step without purification.

2-(2-Ethynylcyclohex-1-en-1-yl)-1,3-dioxolane 531



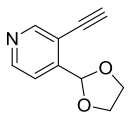
Prepared according to **GP4** from alkyne **531a** to give the terminal alkyne **531** (523 mg, 77% over 2 steps) as a brown oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.90 (s, 1H), 4.05 – 3.97 (m, 2H), 3.97 – 3.89 (m, 2H), 3.12 (s, 1H), 2.26 – 2.06 (m, 4H), 1.65 – 1.58 (m, 4H); IR: ν_{max} (cm^{-1}) 3260, 2933, 2884, 2085, 1386, 1274, 1224, 1143, 1102, 1054, 943. Data matches that reported in the literature.[202]

***4-(1,3-Dioxolan-2-yl)-3-((trimethylsilyl)ethynyl)pyridine* 532a**



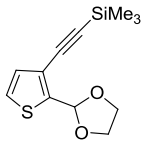
Prepared according to **GP5** using aldehyde **528** (450 mg, 2.2 mmol) and ethylene glycol. Purification by flash column chromatography [hexane:EtOAc (80:20), 1% Et_3N] gave the acetal **532a** (503 mg, 92%) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.69 (d, *J* = 0.6 Hz, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 7.42 (d, *J* = 5.1 Hz, 1H), 6.09 (s, 1H), 4.21 – 4.11 (m, 2H), 4.12 – 4.01 (m, 2H), 0.27 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 153.5 (CH), 149.2 (CH), 147.6 (C), 120.1 (CH), 119.2 (C), 103.2 (C), 100.9 (CH), 98.9 (C), 65.9 (2 × CH_2), -0.07 (3 × CH_3); IR: ν_{max} (cm^{-1}) 2959, 2891, 2159, 1587, 1481, 1399, 1249, 1089, 836, 758; HRMS (ES) *m/z* calculated for $C_{13}H_{18}NO_2Si$ $(M+H)^+$ 248.1107, found 248.1112.

***4-(1,3-Dioxolan-2-yl)-3-ethynylpyridine* 532**



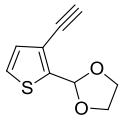
Prepared according to **GP4** from alkyne **532a** (463 mg, 1.9 mmol) to give terminal alkyne **532** (310 mg, 99%) as an orange oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.59 (d, *J* = 5.1 Hz, 1H), 7.47 (d, *J* = 5.1 Hz, 1H), 6.13 (s, 1H), 4.17 – 4.11 (m, 2H), 4.11 – 4.06 (m, 2H), 3.45 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 153.8 (CH), 149.6 (CH), 148.1 (C), 120.0 (CH), 118.1 (C), 100.6 (CH), 85.0 (CH), 78.0 (C), 65.9 (2 × CH_2); IR: ν_{max} (cm^{-1}) 1259, 2891, 2107, 1590, 1482, 1401, 1234, 1161, 1091, 943, 836; HRMS (ES) *m/z* calculated for $C_{10}H_{10}NO_2$ $(M+H)^+$ 176.0712, found 176.0713.

***((2-(1,3-Dioxolan-2-yl)thiophen-3-yl)ethynyl)trimethylsilane* 533a**



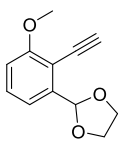
Prepared according to **GP5** using aldehyde **529** (491 mg, 2.4 mmol) and ethylene glycol. Purification by flash column chromatography [hexane:Et_2O (95:5), 1% Et_3N] gave the acetal **533a** (171 mg, 72%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 5.1, 0.5 Hz, 1H), 7.02 (d, *J* = 5.1 Hz, 1H), 6.26 (s, 1H), 4.25 – 4.10 (m, 2H), 4.10 – 3.97 (m, 2H), 0.24 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 145.0 (C), 130.3 (CH), 125.5 (CH), 122.0 (C), 99.2 (CH), 98.3 (C), 98.0 (C), 65.55 (2 × CH_2) 0.08 (3 × CH_3); IR: ν_{max} (cm^{-1}) 2959, 2894, 2154, 1671, 1249, 1073, 834; HRMS (ES) *m/z* calculated for $C_{12}H_{16}O_2NaSSi$ $(M+Na)^+$ 275.0538, found 275.0543.

***2-(3-Ethynylthiophen-2-yl)-1,3-dioxolane* 533**



Prepared according to **GP4** from alkyne **533a** (472 mg, 1.9 mmol) to give terminal alkyne **533** (324 mg, 96%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J* = 5.1 Hz, 1H), 7.05 (d, *J* = 5.1 Hz, 1H), 6.29 (s, 1H), 4.21 – 4.09 (m, 2H), 4.10 – 3.97 (m, 2H), 3.25 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 145.7 (C), 130.4 (CH), 125.6 (CH), 120.6 (C), 99.1 (2 × CH_2), 81.0 (CH), 77.1 (C), 65.6 (CH_3); IR: ν_{max} (cm^{-1}) 3282, 3108, 2957, 2889, 2109, 1667, 1190, 1070, 948, 935; HRMS (ES) *m/z* calculated for $C_9H_9O_2S$ $(M+H)^+$ 181.0323, found 181.0321.

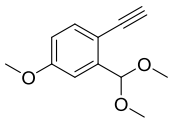
***2-(2-Ethynyl-3-methoxyphenyl)-1,3-dioxolane* 534**



Prepared according to **GP5** using aldehyde **534a** (400 mg, 2.5 mmol) and ethylene glycol (0.2 mL, 3.0 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10), 1% Et_3N] gave the acetal **534** (386 mg, 97%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.34 (app. t, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.90 (dd, *J* = 8.0, 0.8 Hz,

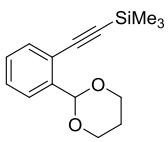
1H), 6.23 (s, 1H), 4.18 – 4.10 (m, 2H), 4.10 – 4.02 (m, 2H), 3.90 (s, 3H), 3.58 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 161.1 (C), 141.8 (C), 129.9 (CH), 118.1 (CH), 111.3 (CH), 110.7 (C), 101.8 (CH), 86.4 (CH), 77.0 (C), 65.7 (2 × CH_2), 56.2 (CH_3); IR: ν_{max} (cm^{-1}) 3006, 2947, 2900, 2868, 2842, 1686, 1587, 1573, 1471, 1272, 1245, 1050, 738; HRMS (ES) *m/z* calculated for $C_{12}H_{13}O_3$ $(M+H)^+$ 205.0865, found 205.0863.

2-(Dimethoxymethyl)-1-ethynyl-4-methoxybenzene 542



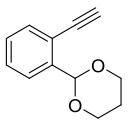
5-Methoxy-2-((trimethylsilyl)ethynyl)benzaldehyde (181 mg, 0.8 mmol, 1.0 equiv.), *p*-TsOH·H_2O (14.9 mg, 0.08 mmol, 0.1 equiv.) and trimethylorthoformate (0.4 mL, 3.9 mmol, 5.0 equiv.) were stirred in MeOH (4 mL, 0.2M) at room temperature for 1 hour. $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL), washed with brine (10 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude residue was dissolved redissolved in MeOH (4 mL) and stirred with K_2CO_3 (10.8 mg, 0.08 mmol, 0.1 equiv.) for 1 hour. $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL), washed with brine (10 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography [hexane:EtOAc (9:1), 1% Et_3N] gave the acetal **XX** (141 mg, 88% over two steps) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 2.7 Hz, 1H), 6.83 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.68 (s, 1H), 3.83 (s, 3H), 3.40 (s, 6H), 3.24 (s, 1H); IR: ν_{max} (cm^{-1}) 3292, 3066, 3002, 2137, 1557, 1456, 1120, 758. Data matches that reported in the literature.[122]

((2-(1,3-Dioxan-2-yl)phenyl)ethynyl)trimethylsilane 543a



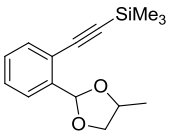
Prepared according to **GP5** using aldehyde **230** (607 mg, 3.0 mmol) and propane-1,3-diol to give the crude acetal **543a** which was used directly in the next step without purification.

2-(2-Ethynylphenyl)-1,3-dioxane 543



Prepared according to **GP4** from alkyne **543a**. Purification by flash column chromatography [hexane:Et_2O (95:5), 1% Et_3N] gave the acetal **543** (406 mg, 72%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.71 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.42 (td, *J* = 7.5, 1.4 Hz, 1H), 7.32 (td, *J* = 7.5, 1.4 Hz, 1H), 5.94 (s, 1H), 4.34 – 4.25 (m, 2H), 4.05 (ddd, *J* = 12.3, 3.8, 2.5 Hz, 2H), 3.32 (s, 1H), 2.37 – 2.18 (m, 1H), 1.52 – 1.42 (m, 1H); IR: ν_{max} (cm^{-1}) 3246, 2981, 2960, 2863, 2105, 1394, 1381, 1277, 1109, 1087, 1006, 753. Data matches that reported in the literature.[112]

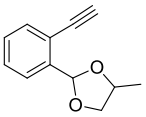
***Trimethyl((2-(4-methyl-1,3-dioxolan-2-yl)phenyl)ethynyl)silane* 544a**



Prepared according to **GP5** using aldehyde **230** (405 mg, 2.0 mmol). Purification by flash column chromatography [hexane:Et_2O (98:2), 1% Et_3N] gave the acetal **543a** (464 mg, 89%) as a yellow oil as a 1:1 mixture of diastereoisomers; ^{1}H-NMR (300 MHz, $CDCl_3$): δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.51 (m, 1H), 7.50 – 7.45 (m, 1H), 7.39 – 7.26 (m, 2H), 6.30 and 6.21 (2 × s, 1H), 4.51 – 4.26 (m) and 4.14 (dd, *J* = 7.3, 6.5 Hz, 2H), 3.67 – 3.55 (m, 1H), 1.43 (d, *J* = 6.1 Hz) and 1.37 (d, *J* = 6.1 Hz, 3H), 0.26 (2 × s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 139.8 and 139.3 (C), 132.9 (CH), 129.0 and 128.9 (CH), 128.8 and 128.8 (CH), 126.5 and 126.2

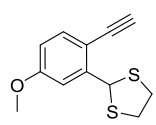
(CH), 122.6 and 122.4 (C), 102.3 (C), 102.2 and 101.6 (CH), 99.4 and 99.3 (C), 73.8 and 72.8 (CH), 72.5 and 71.6 (CH_2), 18.6 and 18.5 (CH_3), 0.1 (3 × CH_3); IR: ν_{max} (cm^{-1}) 2961, 2898, 2869, 2158, 1699, 1249, 1064, 864, 839, 757; HRMS (ES) *m/z* calculated for $C_{15}H_{20}O_2SiNa$ $(M+Na)^+$ 283.1130, found 283.1136.

***2-(2-Ethynylphenyl)-4-methyl-1,3-dioxolane* 544**



Prepared according to **GP4** alkyne **544a** (450 mg, 1.7 mmol) to give terminal alkyne **544** (319 mg, 98%) as a yellow oil as a 1:1 mixture of diastereoisomers; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.68 – 7.48 (m, 2H), 7.44 – 7.28 (m, 2H), 6.36 and 6.25 (2 × s, 1H), 4.45 – 4.26 (m) and 4.15 (dd, *J* = 7.4, 6.4 Hz, 2H), 3.66 – 3.56 (m, 1H), 3.33 and 3.31 (2 × s, 1H), 1.42 and 1.37 (2 × d, *J* = 6.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 140.4 and 139.7 (C), 133.4 and 133.2 (CH), 129.2 and 129.1 (CH), 129.1 and 129.0 (CH), 126.4 and 126.1 (CH), 121.5 and 121.3 (C), 102.0 and 101.3 (CH), 82.1 and 82.0 (CH), 81.0 (C), 73.8 and 72.8 (CH), 72.4 and 71.6 (CH_2), 18.5 (CH_3); IR: ν_{max} (cm^{-1}) 2976, 2930, 2877, 1697, 1379, 1061, 759; HRMS (ES) m/z calculated for $C_{12}H_{12}O_2$ $(M+H)^+$ 188.0837, found 188.0843.

***2-(2-Ethynyl-5-methoxyphenyl)-1,3-dithiolane* 549**

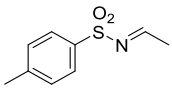


Aldehyde **548** (300 mg, 1.9 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (15 mL, 0.1 M) and silica gel (1.0 g), 1,2-ethanedithiol (0.4 mL, 4.1 mmol, 2.2 equiv.) and *p*-TsOH·H_2O (12.0 mg, 0.1 mmol, 3 mol%) were added. The mixture was heated at reflux for 1 hour before cooling to room temperature. The solution was filtered through a plug of cotton wool and the solvent was removed under reduced pressure. Purification by flash column

chromatography [hexane:EtOAc (96:4), 1% Et_3N] gave the thioacetal **549** (281 mg, 63%) as a pale yellow solid; mp: 60-62 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 2.7 Hz, 1H), 6.75 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.17 (s, 1H), 3.83 (s, 3H), 3.52 – 3.42 (m, 2H), 3.41 – 3.30 (m, 3H), 3.34 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 160.3 (C), 145.5 (2 × C), 134.3 (CH), 113.5 (CH), 113.3 (CH), 82.0 (CH), 81.4 (C), 55.5 (CH_3), 53.4 (CH), 40.0 (2 × CH_2); IR: ν_{max} (cm^{-1}) 3355, 3259, 1598, 1527, 1500, 1386, 1299, 1153, 1097, 901, 813; HRMS (ES) *m/z* calculated for $C_{12}H_{13}OS_2$ $(M+H)^+$ 237.0408, found 237.0405.

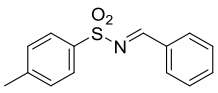
Preparation of Imines

N-Ethylidene-4-methylbenzenesulfonamide 559



Prepared according to **GP6** using acetaldehyde (0.6 mL, 10.0 mmol) to give imine **559** (1.3 g, 67%) as a white solid. mp: 114-116 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.31 (q, *J* = 4.9 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 2H), 1.90 (s, 3H), 1.33 (d, *J* = 4.9 Hz, 3H); IR: ν_{max} (cm^{-1}) 3277, 3060, 2988, 2922, 1630, 1595, 1427, 1314, 1290, 1155, 1089, 146, 670. Data matches that reported in the literature.[203]

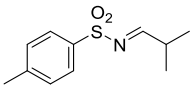
N-Benzylidene-4-methylbenzenesulfonamide 560



Benzaldehyde (1.0 mL, 10.0 mmol, 1.1 equiv.) and $TsNH_2$ (1.5 g, 9.0 mmol, 1.0 equiv.) were dissolved in toluene in a flask containing activated molecular sieves (1.0 g, 3 Å). Amberlyst 15 (1.0 g) was added and the mixture was heated to reflux for 4 hours with azetropic removal of water using Dean Stark aparatus. Once cooled to room

temperature, the mixture was filtered through a cotton wool plug and the solvent was removed under reduced pressure. The resulting solid was triturated with hexane and the crystals were filtered and washed with pentane (30 mL) to give pure imine **560** (1.9 g, 72%) as a white solid; mp: 104-106 °C, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.03 (s, 1H), 7.60 – 7.87 (m, 5H), 7.46 – 7.50 (m, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 2.43 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.5 (C), 136.6 (C),134.9(C), 132.3 (CH), 131.2 (2 × CH), 129.8 (2 × CH), 129.1 (2 × CH), 128.0 (2 × CH), 21.6 (CH_3); IR: ν_{max} (cm^{-1}) 2932, 2864, 1650, 1570, 1414, 1380, 1322, 1280, 1064, 861, 753. Data matches that reported in the literature.[204]

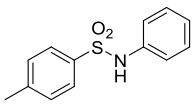
4-Methyl-*N*-(2-methylpropylidene)benzenesulfonamide 561



Prepared according to **GP6** using butyraldehyde (0.9 mL, 10.0 mmol) to give imine **561** (1.4 g, 64%) as a white solid; mp: 78-80 °C, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.51 (d, *J* = 4.3 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 2.72 (m, 1H), 2.41 (s, 3H), 1.20 (d, *J* = 7.2 Hz, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 181.8 (CH), 144.6 (C), 134.6 (C), 129.7 (2 × CH), 128.0 (2 × CH), 34.6 (CH), 21.5 (CH_3), 17.9 (2 × CH_3); IR: ν_{max} (cm^{-1}) 3305, 3067, 2973, 1633, 1601, 1458, 1160, 1140, 1089, 750. Data matches that reported in the literature.[203]

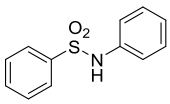
Preparation of Sulfonamides

4-Methyl-*N*-phenylbenzenesulfonamide 233



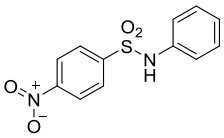
Prepared according to **GP7** using aniline (1.2 mL, 12.9 mmol) and *p*-methylbenzenesufonyl chloride (1.7 g, 10.7 mmol). Purification by flash column chromatography [hexane:Et_2O (90:10)] gave the sulfonamide **XX** (2.5 g, 94%) as a white solid; mp: 101-103 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.20 (m, 4H), 7.12 – 7.06 (m, 3H), 6.85 (br. s, 1H), 2.37 (s, 3H); IR: ν_{max} (cm^{-1}) 3236, 3061, 2980, 2899, 1596, 1479, 1414, 1319, 1290, 1223, 1186, 1153, 1089, 1031, 909, 754. Data matches that reported in the literature.[205]

***N*-Phenylbenzenesulfonamide 242**



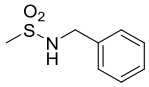
Prepared according to **GP7** using aniline (6.0 mL, 65.8 mmol) and benzenesulfonyl chloride (3.0 mL, 54.9 mmol). Purification by flash column chromatography [hexane:Et_2O (80:20)] gave the sulfonamide **242** (11.9 g, 93%) as a white solid; mp: 110-112 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.78 (m, 2H), 7.54 – 7.49 (m, 1H), 7.45 – 7.39 (m, 2H), 7.26 – 7.17 (m, 2H), 7.14 – 7.07 (m, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 139.0 (C), 136.6 (C), 133.1 (CH), 129.4 (2 × CH), 129.2 (2 × CH), 127.4 (2 × CH), 125.5 (CH), 121.7 (2 × CH); MS (EI): *m/z* 256 $[M+Na]^+$ (100 %). Data matches that reported in the literature.[206]

4-Nitro-*N*-phenylbenzenesulfonamide 243



Prepared according to **GP7** using aniline (2.0 mL, 21.9 mmol) and *p*-nitrobenzenesulfonyl chloride (4.0 g, 18.3 mmol) to give sulfonamide **243** (4.6 g, 90%) as an off-white solid; mp: 167-169 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.9 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 2H), 7.33 – 7.24 (m, 2H), 7.23 – 7.15 (m, 1H), 7.14 – 7.02 (m, 2H), 6.72 (br. s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 150.4 (C), 144.7 (C), 135.4 (C), 129.8 (2 × CH), 128.7 (2 × CH), 126.7 (CH), 124.4 (2 × CH), 122.6 (2 × CH); IR: ν_{max} (cm^{-1}) 3284, 3236, 1596, 1517, 1340, 1296, 1186, 1164, 909, 754. Data matches that reported in the literature.[207]

***N*-Benzylmethanesulfonamide 246**

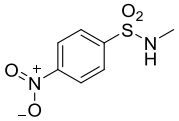


This sulfonamide was donated by a group member (Fernando Sanchez-Cantalejo).

***N*-Methylmethanesulfonamide 247**

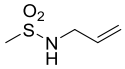
This sulfonamide was donated by a group member (Andrew Gillie).

***N*-Methyl-4-nitrobenzenesulfonamide 248**



This sulfonamide was donated by a group member (Michel-Frank Boissennet).

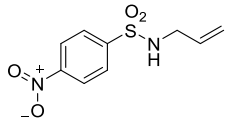
***N*-Allylmethanesulfonamide 249**



Prepared according to **GP7** using allylamine (1.8 mL, 24.0 mmol) and methanesulfonyl chloride (1.5 mL, 20.0 mmol) to give sulfonamide **249** (2.1 g, 78%) as yellow oil;^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.87 (ddt, *J* = 17.0, 10.2, 5.8 Hz, 1H), 5.31 (ddd, *J* =

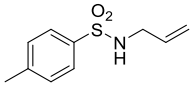
17.0, 2.8, 1.6 Hz, 1H), 5.23 (ddd, *J* = 10.2, 2.8, 1.2 Hz, 1H), 4.48 (br. s, 1H), 3.78 (app. tt, *J* = 5.8, 1.6 Hz, 2H), 2.97 (s, 3H); IR: ν_{max} (cm^{-1}) 3286, 3019, 2933, 1434, 1412, 1308, 1141, 1062, 1141, 967, 754; MS (EI): *m/z* 136 $[M+H]^+$ (10 %), 135 (50), 134 (100). Data matches that reported in the literature.[208]

_N_-Allyl-4-nitrobenzenesulfonamide 489



Prepared according to **GP7** using allylamine (1.8 mL, 24.0 mmol) and *p*-nitrobenzenesulfonyl chloride (4.4 g, 20.0 mmol) to give sulfonamide **489** (4.6 g, 95%) as white solid; mp: 110-112 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.37 (d, *J* = 9.0 Hz, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 5.71 (ddt, *J* = 17.0, 10.2, 5.8 Hz, 1H), 5.19 (app. ddd, *J* = 17.0, 2.6, 1.5 Hz, 1H), 5.13 (d, *J* = 10.2, 2.6, 1.2 Hz, 1H), 4.73 (br. t, *J* = 5.8 Hz, 1H), 3.69 (app. tt, *J* = 5.8, 1.5 Hz, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 150.3 (C), 146.3 (C), 132.5 (CH), 128.4 (2 × CH), 124.6 (2 × CH), 118.6 (CH_2), 46.0 (CH_2); MS (EI): *m/z* 242 $[M]^+$ (15 %), 186 (50), 122 (100). Data matches that reported in the literature.[209]

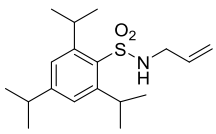
_N_-Allyl-4-methylbenzenesulfonamide 490



Prepared according to **GP7** using allylamine (0.9 mL, 12.0 mmol) and *p*-methylbenzenesulfonyl chloride (1.9 g, 10.0 mmol) to give sulfonamide **490** (2.0 g, 83%) as white solid; mp: 63-65 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 5.71 (ddt, *J* = 17.0, 10.2, 5.8 Hz, 1H), 5.15 (app. ddd, *J* = 17.0, 2.8, 1.5 Hz, 1H), 5.08 (app. ddd, *J* = 10.2, 2.8, 1.3 Hz, 1H), 4.75 (br. t, *J* = 6.1 Hz, 1H), 3.57 (app. tt, *J* = 6.1, 1.4 Hz,

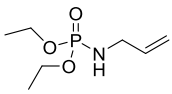
2H), 2.42 (s, 3H); IR: ν_{max} (cm^{-1}) 3241, 3099, 3041, 2851, 1650, 1423, 1330, 1165, 937, 671. Data matches that reported in the literature.[208]

_N_-Allyl-2,4,6-triisopropylbenzenesulfonamide 491



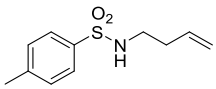
This sulfonamide was donated by a group member (Alex Cremonesi).

Diethyl allylphosphoramidate 492



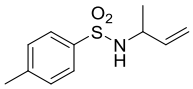
Allylamine (1.3 mL, 17.5 mmol, 1.0 equiv.) and Et_3N (2.7 mL, 26.3 mmol, 1.5 equiv.) were dissolved in CH_2Cl_2 (30 mL, 0.6 M) and cooled to 0 °C. Diethylchlorophosphate (3.0 mL, 21.0 mmol, 1.2 equiv.) was added dropwise and the resulting solution stirred at room temperature for 16 hours. H_2O (50 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography [hexane:Et_2O (75:25)] gave the phosphoramidate **492** (3.0 g, 89%) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.94 – 5.80 (m, 1H), 5.28 – 5.16 (m, 1H), 5.16 – 5.07 (m, 1H), 4.24 – 3.88 (m, 4H), 3.71 – 3.44 (m, 2H), 1.56 – 1.14 (m, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 136.2 (CH), 115.4 (CH_2), 62.4 (d, $J_{C\text{-}P}$ = 5.0 Hz, 2 × CH_2), 43.8 (CH_2), 16.3 (d, $J_{C\text{-}P}$ = 6.9 Hz, 2 × CH_3); IR: ν_{max} (cm^{-1}) 3223, 2982, 2906, 1444, 1228, 1024, 956, 794. Data matches that reported in the literature.[210]

_N_-(But-3-en-1-yl)-4-methylbenzenesulfonamide 551



p-Methylbenzenesulfonamide (1.0 g, 5.8 mmol, 1.0 equiv.) and 4-bromo-1-butene (0.65 mL, 6.4 mmol, 1.1 equiv.) were dissolved in acetone (5.8 mL, 1.0 M). K_2CO_3 (1.6 g, 11.7 mmol, 2.0 equiv.) was added and the mixture was heated to 60 °C for 16 hours. Saturated NH_4Cl solution (15 mL) was added and the aqueous phase was extracted with Et_2O (3 × 20mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography [hexane:EtOAc (9:1), then hexane:EtOAc (8:2)] gave the sulfonamide **551** (795 mg, 60%) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.62 (ddt, *J* = 17.1, 10.4, 6.8 Hz, 1H), 5.09 – 4.97 (m, 2H), 4.56 (br. s, 1H), 3.00 (q, *J* = 6.6 Hz, 2H), 2.43 (s, 3H), 2.24 – 2.15 (m, 2H); IR: ν_{max} (cm^{-1}) 3280, 2928, 1598, 1423, 1322, 1305, 1156, 1093, 1074, 813, 661. Data matches that reported in the literature.[211]

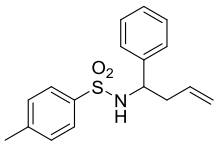
_N_-(But-3-en-2-yl)-4-methylbenzenesulfonamide 562



Prepared according to **GP8** using imine **559** (395 mg, 2.0 mmol) and vinylmagnesium bromide (4.0 mL, 1.0 M solution in THF, 4.0 mmol). Purification by filtration through a short (ca. 3 cm) pad of silica, eluting with CH_2Cl_2 (40 mL) gave the sulfonamide **562** (423 mg, 94%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.63 (ddd, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.05 (d, *J* = 17.2 Hz, 1H), 4.96 (d, *J* = 10.4 Hz, 1H), 4.67 (br. s, 1H), 3.95 – 3.81 (m, 1H), 2.42 (s, 3H), 1.16 (d, *J* = 6.8 Hz, 3H); IR: ν_{max} (cm^{-1}) 3274, 2979, 2931, 2880, 1599, 1427, 1323, 1305, 1152, 1092, 814; HRMS (ES) *m/z*

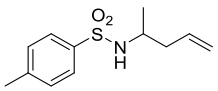
calculated for $C_{11}H_{15}NO_2S$ $(M+H)^+$ 226.0919, found 226.1918. Data matches that reported in the literature.[212]

4-Methyl-*N*-(1-phenylbut-3-en-1-yl)benzenesulfonamide 563



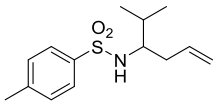
Prepared according to **GP8** using imine **560** (518 mg, 2.0 mmol) and allylmagnesium bromide (4.0 mL, 1.0 M solution in THF, 4.0 mmol) to give the sulfonamide **563** (588 mg, 98%) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.20 – 7.11 (m, 5H), 7.11 – 7.03 (m, 2H), 5.58 – 5.43 (m, 1H), 5.08 (d, *J* = 1.0 Hz, 1H), 5.05 – 5.01 (m, 1H), 4.96 (br. d, *J* = 6.6 Hz, 1H), 4.37 (app. q, *J* = 6.6 Hz, 1H), 2.49 – 2.41 (m, 2H), 2.37 (s, 3H); IR: ν_{max} (cm^{-1}) 3255, 3064, 3031, 2984, 2923, 1643, 1600, 1497, 1457, 1447, 1318, 1307, 1278, 1157, 918. Data matches that reported in the literature.[213]

4-Methyl-*N*-(pent-4-en-2-yl)benzenesulfonamide 564



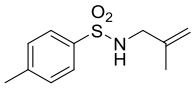
Prepared according to **GP8** using imine **559** (395 mg, 2.0 mmol) and allylmagnesium bromide (4.0 mL, 1.0 M solution in THF, 4.0 mmol). Purification by flash column chromatography [hexane:EtOAc (80:20)] gave the sulfonamide **564** (373 mg, 78%) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.56 (ddt, *J* = 17.4, 10.3, 6.8 Hz, 1H), 5.07 – 4.94 (m, 2H), 4.53 (br. s, 1H), 3.36 (app. dt, *J* = 12.8, 6.5 Hz, 1H), 2.42 (s, 3H), 2.11 (app. t, *J* = 6.8 Hz, 2H), 1.06 (d, *J* = 6.5 Hz, 3H); IR: ν_{max} (cm^{-1}) 3278, 3062, 2982, 2938, 1640, 1596, 1423, 1321, 1301, 1144, 1086, 1035, 815, 659. Data matches that reported in the literature.[214]

***4-Methyl-N-(2-methylhex-5-en-3-yl)benzenesulfonamide* 565**



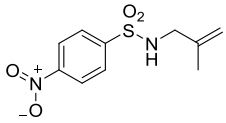
Prepared according to **GP8** using imine **561** (1.3 g, 5.8 mmol) and allylmagnesium bromide (11.5 mL, 1.0 M solution in THF, 11.5 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the sulfonamide **565** (1.1 g, 74%) as a white solid; mp: 66-68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.47 (ddt, *J* = 17.6, 10.4, 7.2 Hz, 1H), 5.00 – 4.87 (m, 2H), 4.54 (br. d, *J* = 8.4 Hz, 1H), 3.08 (app. dq, *J* = 8.4, 6.2 Hz, 1H), 2.42 (s, 3H), 2.05 (dd, *J* = 7.2, 6.2 Hz, 2H), 1.83 – 1.69 (m, 1H), 0.83 (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.2 (C), 138.3 (C), 133.9 (CH), 129.6 (2 × CH), 127.2 (2 × CH), 118.3 (CH_2), 58.8 (CH), 36.2 (CH_2), 30.9 (CH), 21.6 (CH_3), 18.7 (CH_3), 17.9 (CH_3); IR: ν_{max} (cm^{-1}) 3262, 3070, 2958, 2876, 1642, 1600, 1427, 1317, 1158, 907, 812, 665; HRMS (ES) *m/z* calculated for $C_{14}H_{21}NO_2NaS$ $(M+Na)^+$ 290.1191, found 290.1196.

4-Methyl-*N*-(2-methylallyl)benzenesulfonamide 573



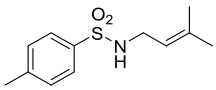
This sulfonamide was donated by a group member (Fernando Sanchez-Cantalejo).

***N*-(2-Methylallyl)-4-nitrobenzenesulfonamide 574**



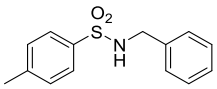
This sulfonamide was donated by a group member (Fernando Sanchez-Cantalejo).

4-Methyl-N-(3-methylbut-2-en-1-yl)benzenesulfonamide 575



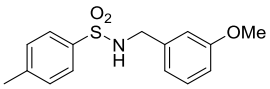
This sulfonamide was donated by a group member (Alex Cremonesi).

***N*-Benzyl-4-methylbenzenesulfonamide 580**



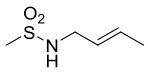
Prepared according to **GP7** using benzylamine (1.3 mL, 12.0 mmol) and *p*-methylbenzenesulfonyl chloride (1.9 g, 10.0 mmol) to give sulfonamide **580** (2.3 g, 89%) as white solid; mp: 109-110 °C;^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.23 (m, 5H), 7.23 – 7.17 (m, 2H), 4.88 (br. t, *J* = 6.2 Hz, 1H), 4.11 (d, *J* = 6.2 Hz, 2H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.6 (C), 137.0 (C), 136.4 (C), 129.8 (2 × CH), 128.8 (2 × CH), 128.0 (3 × CH), 127.3 (2 × CH), 47.4 (CH_2), 21.7 (CH_3); MS (EI): *m/z* 261 $[M]^+$ (20 %), 196 (100). Data matches that reported in the literature.[215]

***N*-(3-Methoxybenzyl)-4-methylbenzenesulfonamide 586**



This sulfonamide was donated by a group member (Joshua Priest).

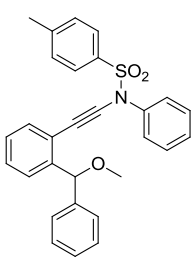
(*E*)-*N*-(But-2-en-1-yl)methanesulfonamide 682



This sulfonamide was donated by a group member (Fernando Sanchez-Cantalejo).

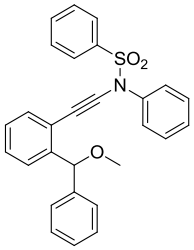
Preparation of Ynamides

***N-((2-(Methoxy(phenyl)methyl)phenyl)ethynyl)-4-methyl-N-phenylbenzenesulfonamide* 234**



Prepared according to **GP12** using alkyne **232** (750 mg, 3.4 mmol) and sulfonamide **233** (4.91 g, 16.9 mmol). Purification by flash column chromatography [hexane:EtOAc (92:8) then hexane:EtOAc (90:10)] gave the ynamide **234** (632 mg, 54%) as an orange oil alongside the recovered sulfonamide (2.98 g, 85%, based on the consumption of 1.0 equiv. over the reaction); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.50 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.39 – 7.16 (m, 15H), 5.71 (s, 1H), 3.35 (s, 3H), 2.41 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 145.0 (C), 143.3 (C), 141.5 (C), 138.9 (C), 133.2 (C), 132.4 (CH), 129.6 (2 × CH), 129.2 (2 × CH), 128.8 (CH), 128.5 (CH), 128.3 (4 × CH), 127.3 (3 × CH), 127.2 (CH), 127.0 (CH), 126.3 (2 × CH), 121.6 (C), 87.4 (C), 82.4 (CH), 68.7 (C), 57.1 (CH_3), 21.7 (CH_3); IR: ν_{max} (cm^{-1}) 3063, 2235, 3030, 2984, 2926, 2822, 2235, 1594, 1491, 1169, 1089; HRMS (ES) *m/z* calculated for $C_{29}H_{25}NO_3NaS$ $(M+Na)^+$ 490.1453 found 490.1455.

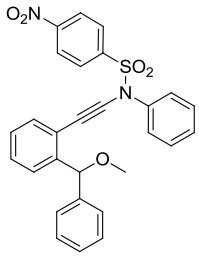
***N-((2-(Methoxy(phenyl)methyl)phenyl)ethynyl)-N-phenylbenzenesulfonamide* 244**



Prepared according to **GP12** using alkyne **233** (2.0 g, 9.0 mmol) and sulfonamide **242** (10.5 g, 45.0 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10) then hexane:EtOAc (80:20)] gave the ynamide **244** (1.41 g, 35%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.66 – 7.60 (m, 1H), 7.52 – 7.49 (m, 1H), 7.46 – 7.41 (m, 2H), 7.38 – 7.17

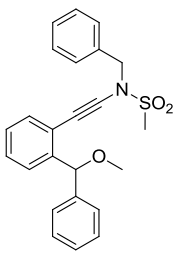
(m, 13H), 5.71 (s, 1H), 3.35 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 143.7 (C), 141.8 (C), 139.1 (C), 136.4 (C), 134.2 (CH), 132.4 (CH), 129.6 (2 × CH), 129.3 (2 × CH), 128.9 (CH), 128.8 (CH), 128.6 (2 × CH), 128.5 (2 × CH), 127.7 (C), 127.6 (C), 127.4 (2 × CH), 126.7 (CH), 126.7 (2 × CH), 121.8 (C), 87.5 (C), 82.8 (CH), 69.1 (C), 57.5 (CH3); IR: ν_{max} (cm^{-1}) 2988, 2973, 2902, 1615, 1596, 1581, 1155, 1075; HRMS (ES) m/z calculated for $C_{28}H_{24}NO_3S$ $(M+H)^+$ 454.1471 found 454.1475.

***N-((2-(Methoxy(phenyl)methyl)phenyl)ethynyl)-4-nitro-N-phenylbenzenesulfonamide* 245**



Prepared according to **GP12** using alkyne **233** (0.39 g, 1.7 mmol) and sulfonamide **243** (2.42 g, 8.7 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the ynamide **245** (366 mg, 42%) as a yellow solid; mp: 112-114 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.9 Hz, 2H), 7.76 (d, *J* = 8.9 Hz, 2H), 7.54 – 7.50 (m, 1H), 7.41 – 7.20 (m, 13H), 5.69 (s, 1H), 3.37 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 151.0 (C), 143.6 (C), 141.6 (C), 141.4 (C), 138.4 (C), 132.4 (CH), 129.9 (2 × CH), 129.7 (2 × CH), 129.4 (CH), 129.3 (CH), 128.6 (2 × CH), 127.9 (CH), 127.7 (CH), 127.5 (2 × CH), 127.0 (CH), 126.5 (2 × CH), 124.5 (2 × CH), 121.3 (C), 86.5 (C), 82.9 (CH), 69.7 (C), 57.6 (CH_3); IR: ν_{max} (cm^{-1}) 2970, 2901, 2156, 1603, 1482, 1453, 1407, 1394, 1250, 858, 836; HRMS (ES) *m/z* calculated for $C_{28}H_{22}N_2O_5SNa$ $(M+Na)^+$ 521.1147 found 521.1135.

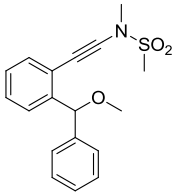
***N-Benzyl-N-((2-(methoxy(phenyl)methyl)phenyl)ethynyl)methanesulfonamide* 252**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (324 mg, 1.1 mmol, **GP9**) and sulfonamide **246** (166 mg, 0.9 mmol). Purification by flash column chromatography [hexane:EtOAc

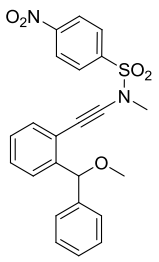
(90:10) then hexane:EtOAc (85:15)] gave the ynamide **252** (305 mg, 84%) as pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.53 – 7.16 (m, 14H), 5.58 (s, 1H), 4.75 (d, *J* = 14.4 Hz, 1H), 4.66 (d, *J* = 14.4 Hz, 1H), 3.33 (s, 3H), 2.86 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.1 (C), 141.3 (C), 134.4 (C), 132.0 (CH), 128.9 (2 × CH), 128.8 (CH), 128.5 (CH), 128.2 (2 × CH), 127.4 (CH), 127.2 (CH), 127.0 (4 × CH), 126.4 (CH), 121.4 (C), 86.3 (C), 82.4 (CH), 70.0 (C), 57.1 (CH_3), 55.7 (CH_2), 39.0 (CH_3); IR: ν_{max} (cm^{-1}) 2988, 2930, 2234, 1359, 1276, 1261, 1162, 1076, 764, 751; HRMS (ES) *m/z* calculated for $C_{24}H_{23}NO_3SNa$ $(M+Na)^+$ 428.1296 found 428.1276.

N-((2-(Methoxy(phenyl)methyl)phenyl)ethynyl)-N-methylmethanesulfonamide **253**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (390 mg, 1.3 mmol, **GP9**) and sulfonamide **247** (168 mg, 1.1 mmol). Purification by flash column chromatography [hexane:EtOAc (80:20)] gave the ynamide **253** (240 mg, 67%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.53 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.42 – 7.18 (m, 8H), 5.70 (s, 1H), 3.40 (s, 3H), 3.28 (s, 3H), 3.01 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.1 (C), 141.3 (C), 131.9 (CH), 128.4 (CH), 128.3 (2 × CH), 127.5 (3 × CH), 127.2 (CH), 126.3 (CH), 121.2 (C), 87.6 (C), 82.7 (CH), 68.0 (C), 57.2 (CH_3), 39.1 (CH_3), 36.8 (CH_3); IR: ν_{max} (cm^{-1}) 3028, 2932, 2823, 2234, 1159, 1077; HRMS (ES) *m/z* calculated for $C_{18}H_{19}NO_3NaS$ $(M+Na)^+$ 352.0983 found 352.0964.

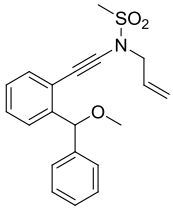
N-((2-(Methoxy(phenyl)methyl)phenyl)ethynyl)-N-methyl-4-nitrobenzenesulfonamide **254**



Prepared according to **GP11** using the freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (325 mg, 1.1 mmol, **GP9**) and sulfonamide **248**

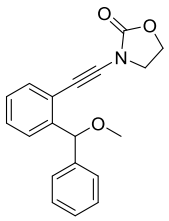
(194 mg, 0.9 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the ynamide **254** (338 mg, 86%) as a yellow solid; mp: 109-111 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J* = 9.0 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H), 7.52 (dd, *J* = 7.2, 0.5 Hz, 1H), 7.39 – 7.18 (m, 8H), 5.68 (s, 1H), 3.39 (s, 3H), 3.21 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 151.0 (C), 143.6 (C), 141.9 (C), 141.6 (C), 132.3 (CH), 129.2 (2 × CH), 128.6 (2 × CH), 127.9 (2 × CH), 127.7 (CH), 127.5 (2 × CH), 126.9 (CH), 124.8 (2 × CH), 121.2 (C), 87.2 (C), 82.8 (CH), 68.5 (C), 57.5 (CH_3), 39.9 (CH_3); IR: ν_{max} (cm^{-1}) 3121, 3061, 3031, 2989, 2930, 2873, 2826, 2238, 1530, 1369, 1347, 1170, 1085, 967; HRMS (ES) *m/z* calculated for $C_{23}H_{20}N_2O_5NaS$ $(M+Na)^+$ 459.0991 found 459.1001.

***N-Allyl-N-((2-(methoxy(phenyl)methyl)phenyl)ethynyl)methanesulfonamide* 255**



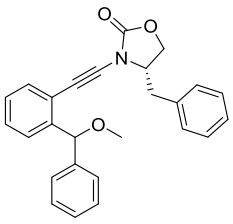
Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (174 mg, 0.58 mmol, **GP9**) and sulfonamide **249** (65 mg, 0.48 mmol). Purification by flash column chromatography [hexane:EtOAc (85:15)] gave the ynamide **255** (170 mg, 99%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 7.8 Hz, 1H), 7.43 – 7.17 (m, 8H), 5.95 (ddt, *J* = 17.0, 10.1, 6.4 Hz, 1H), 5.72 (s, 1H), 5.41 (dd, *J* = 17.0, 1.1 Hz, 1H) 5.35 (dd, *J* = 10.1, 1.1 Hz, 1H), 4.15 (ddd, *J* = 6.4, 2.5, 1.1 Hz, 2H), 3.40 (s, 3H) 3.04 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.1 (C), 141.4 (C), 132.0 (CH), 130.9 (CH), 128.5 (CH), 128.2 (2 × CH), 127.4 (CH), 127.2 (CH), 127.1 (2 × CH), 126.4 (CH), 121.4 (C), 120.6 (CH_2), 86.1 (C), 82.6 (CH), 69.6 (C), 57.2 (CH_3), 54.3 (CH_2), 39.0 (CH_3); IR: ν_{max} (cm^{-1}) 3028, 2984, 2931, 2823, 2232, 1164; HRMS (ES) *m/z* calculated for $C_{20}H_{21}NO_3NaS$ $(M+Na)^+$ 378.1140, found 378.1142.

***3-((2-(Methoxy(phenyl)methyl)phenyl)ethynyl)oxazolidin-2-one* 256**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (348 mg, 1.2 mmol, **GP9**) and commercially available 2-oxazolidinone **250** (84 mg, 1.0 mmol). Purification by flash column chromatography [hexane:EtOAc (70:30)] gave the ynamide **256** (193 mg, 65%) as a pale orange solid; mp: 128-130 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.7 Hz, 1H), 7.48 – 7.17 (m, 8H), 5.75 (s, 1H), 4.49 (dd, *J* = 8.8, 7.2 Hz, 2H), 3.96 (dd, *J* = 8.8, 7.2 Hz, 2H), 3.40 (s, 3 H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 155.7 (C), 143.4 (C), 141.3 (C), 131.8 (CH), 128.5 (CH), 128.2 (2 × CH), 127.4 (CH), 127.2 (2 × CH), 127.2 (CH), 126.1 (CH), 121.0 (C), 83.7 (C), 82.5 (CH), 69.6 (C), 63.0 (CH_2) , 57.1 (CH_3), 46.8 (CH_2); IR: ν_{max} (cm^{-1}) 3068, 2949, 2928, 2876, 2824, 2253, 1770, 1205, 1075; HRMS (ES) *m/z* calculated for $C_{19}H_{17}NO_3Na$ $(M+Na)^+$ 330.1106 found 330.1108.

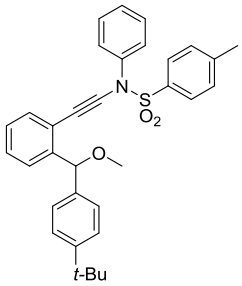
***(4S)-4-Benzyl-3-((2-(methoxy(phenyl)methyl)phenyl)ethynyl)oxazolidin-2-one* 257**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (324 mg, 1.1 mmol, **GP9**) and commercially available (*S*)-4-benzyl-2-oxazolididnone **251** (159 mg, 0.9 mmol). Purification by flash column chromatography [hexane:EtOAc (8:2)] gave the ynamide **257** (335 mg, 94%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 – 7.48 (m, 1H), 7.46 – 7.08 (m, 13H), 5.78, 5.77 (2 × s, 1H), 4.37 – 4.18 (m, 2H), 4.12 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.38, 3.38 (2 × s, 3H), 3.13 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.88 (dd, *J* = 13.8, 8.0 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 155.6 (C), 143.7 (C), 141.7, 141.6 (C), 134.4 (C), 132.5, 132.5 (CH), 129.7 (2 ×

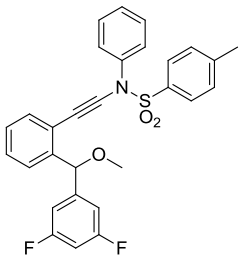
CH), 129.4 (2 × CH), 129.0 (C), 128.6 (2 × CH), 127.9 (CH), 127.8 (CH), 127.6 (3 × CH), 126.7 (CH) 121.5, 121.4 (1 × C), 83.0 (C), 83.0, 83.0 (1 × CH), 72.0 (C), 67.8, 67.8 (1 × CH_2), 58.8, 58.7 (1 × CH), 57.6 (CH_3), 38.3 (CH_2); IR: ν_{max} (cm^{-1}) 3062, 3030, 2983, 2930, 2823, 2950, 1768, 1406, 1208, 1188,1088, 1074; HRMS (ES) *m/z* calculated for $C_{26}H_{23}NO_3Na$ $(M+Na)^+$ 420.1576 found 420.1578.

***N-((2-((4-(t-Butyl)phenyl)(methoxy)methyl)phenyl)ethynyl)-4-methyl-N-phenylbenzenesulfonamide* 278**



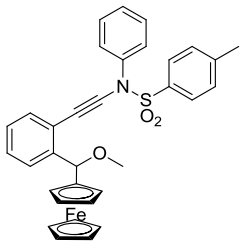
Prepared according to **GP12** using alkyne **273** (269 mg, 1.0 mmol) and sulfonamide **233** (1.20 g, 4.8 mmol). Purification by flash column chromatography [hexane:Et_2O (90:10)] gave the ynamide **278** (261 mg, 52%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.59 - 7.51 (m, 3H), 7.39 – 7.16 (m, 14H), 5.69 (s, 1H), 3.35 (s, 3H), 2.41 (s, 3H), 1.27 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 150.4 (C), 145.3 (C), 143.8 (C), 139.2 (C), 138.7 (C), 133.5 (C), 132.3 (CH), 129.9 (2 × CH), 129.5 (2 × CH), 128.8 (CH), 128.7 (CH), 128.5 (2 × CH), 127.4 (CH), 127.0 (2 × CH), 126.7 (2 × CH), 126.6 (CH), 125.5 (2 × CH), 121.9 (C), 87.7 (C), 82.6 (CH), 69.1 (C), 57.4 (CH_3), 34.8 (C), 31.7 (3 × CH_3), 22.0 (CH_3); IR: ν_{max}/cm^{-1} 3062, 2961, 2903, 2869, 2822, 2236, 1594, 1491, 1373, 1171, 1088; HRMS (ES) *m/z* calculated for $C_{33}H_{34}NO_3S$ $(M+H)^+$ 524.2259 found 524.2257.

***N-((2-((3,5-Difluorophenyl)(methoxy)methyl)phenyl)ethynyl)-4-methyl-N-phenylbenzenesulfonamide* 279**



Prepared according to **GP12** using alkyne **274** (250 mg, 1.0 mmol) and sulfonamide **233** (1.20 g, 4.8 mmol). Purification by flash column chromatography [hexane:Et_2O (90:10)] gave the ynamide **279** (150 mg, 31%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.16 (m, 11H), 6.88 (dd, *J* = 8.3, 1.7 Hz, 2H), 6.65 (tt, *J* = 8.9, 2.3 Hz, 1H), 5.70 (s, 1H), 3.36 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (dd, $J_{C\text{-}F}$ = 248.2, 12.5 Hz, 2 × C), 146.3 (t, $J_{C\text{-}F}$ = 8.4 Hz, C), 145.6 (C), 142.4 (C), 139.0 (C), 133.5 (C), 132.3 (CH), 130.0 (2 × CH), 129.6 (2 × CH), 129.0 (CH), 128.8 (CH), 128.4 (2 × CH), 128.1 (CH), 126.6 (2 × CH), 122.1 (C), 109.9 (d, $J_{C\text{-}F}$ = 25.6 Hz, 2 × CH), 102.9 (t, $J_{C\text{-}F}$ = 25.6 Hz, CH), 88.1 (C), 81.5 (CH), 68.8 (C), 66.2 (C), 57.5 (CH_3), 22.0 (CH_3); IR: ν_{max}/cm^{-1} 3066, 2989, 2932, 2826, 2235, 1623, 1595, 1491, 1454, 1373, 1171, 1116, 1089; HRMS (ES) *m/z* calculated for $C_{20}H_{21}NO_3SF$ $(M+H)^+$ 504.1445 found 504.1458.

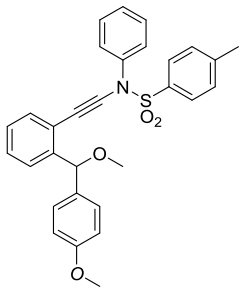
***N-((2-(Methoxy(ferrocene)methyl)phenyl)ethynyl)-4-methyl-N-phenylbenzenesulfonamide* 280**



Prepared according to **GP12** using alkyne **275** (194 mg, 0.6 mmol) and sulfonamide **233** (0.87 g, 3.5 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the ynamide **280** (261 mg, 77%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 2H), 7.44 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.37 – 7.17 (m, 9H), 7.14 (app. td, *J* = 7.5, 1.4 Hz, 1H), 5.41 (s, 1H), 4.08 (app. d, *J* = 1.7 Hz, 2H), 4.01 – 3.98 (m, 2H), 3.94 (s, 5H), 3.21 (s, 3H), 2.36 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 145.4 (C), 143.9 (C), 139.2 (C), 133.5 (C), 131.9 (CH), 130.0 (2 × CH_2), 129.6 (2

× CH_2), 128.7 (CH), 128.5 (3 × CH), 127.5 (CH), 126.8 (CH), 126.7 (2 × CH), 122.0 (C), 90.6 (C), 87.6 (C), 79.4 (CH), 69.3 (C), 69.1 (5 × CH), 68.3 (CH), 67.8 (CH), 67.6 (CH), 66.7 (CH), 57.3 (CH_3), 22.1 (CH_3); IR: ν_{max}/cm^{-1} 3102, 3069, 2937, 2236, 1678, 1594, 1490, 1372, 1171, 1088; HRMS (ES) *m/z* calculated for $C_{33}H_{29}NO_3SFe$ $(M+H)^+$ 575.1218 found 575.1223.

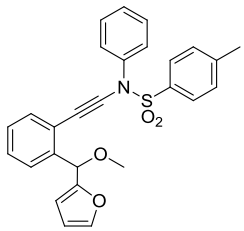
***N-((2-(methoxy(4-methoxyphenyl)methyl)phenyl)ethynyl)-4-methyl-N-phenylbenzenesulfonamide* 281**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(4-methoxyphenyl)methyl)benzene (841 mg, 2.24 mmol, **GP9**) and sulfonamide **233** (493 mg, 2.1 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the ynamide **281** (300 mg, 24%) as an orange oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.7 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.36 (app. t, *J* = 7.9 Hz, 2H), 7.30 – 7.20 (m, 3H), 7.18 – 7.14 (m, 3H), 7.15 – 7.07 (m, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 5.56 (s, 1H), 3.67 (s, 3H), 3.25 (s, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 159.0 (C), 143.7 (C), 138.9 (C), 136.1 (C), 134.1 (CH), 133.7 (C), 132.2 (CH), 129.3 (2 × CH), 129.1 (2 × CH), 129.1 (C), 128.6 (CH), 128.6 (2 × CH), 128.3 (2 × CH), 127.2 (CH), 126.5 (2 × CH), 126.2 (CH), 121.4 (C), 113.7 (2 × CH), 87.4 (C), 82.3 (CH), 68.8 (C), 57.2 (CH_3), 55.3 (CH_3); IR: ν_{max} (cm^{-1}) 3065, 2933, 2908, 2236, 1610, 1590, 1510, 1448, 1373, 1246, 1171, 1087, 1031, 723, 686; HRMS (ES) *m/z* calculated for $C_{29}H_{26}NO_4S$ $(M+H)^+$ 484.1589, found 484.1577.

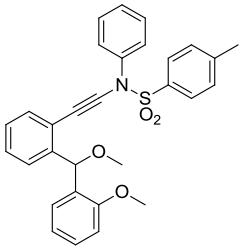
N-((2-(Furan-2-yl(methoxy)methyl)phenyl)ethynyl)-4-methyl-N-phenylbenzenesulfonamide

282



Prepared according to **GP11** using alkyne **277** (250 mg, 1.2 mmol) and sulfonamide **233** (1.5 g, 5.9 mmol). Purification by flash column chromatography [hexane:EtOAc (94:4)] gave the ynamide **282** (184 mg, 34%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.4 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.20 (m, 9H), 6.26 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.04 (d, *J* = 3.2 Hz, 1H), 5.73 (s, 1H), 3.37 (s, 3H), 2.42 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 153.7 (C), 145.1 (C), 142.8 (CH), 140.3 (C), 138.9 (C), 133.2 (C), 131.8 (CH), 129.7 (2 × CH), 129.3 (2 × CH), 128.4 (2 × CH), 128.3 (CH), 127.8 (CH), 126.8 (CH), 126.3 (2 × CH), 121.8 (C), 110.2 (CH), 109.0 (CH), 87.8 (C), 76.4 (CH), 68.3 (C), 57.2 (CH_3), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3070, 2928, 2825, 2238, 1595, 1491, 1373, 1170, 1088, 692; HRMS (ES) m/z calculated for $C_{27}H_{23}NO_4NaS$ $(M+Na)^+$ 480.1245 found 480.1244.

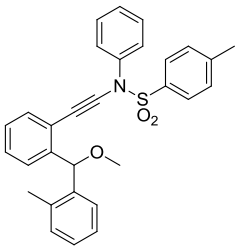
***N-((2-(Methoxy(2-methoxyphenyl)methyl)phenyl)ethynyl)-4-methyl-N-phenylbenzenesulfonamide* 294**



Prepared according to **GP12** using alkyne **289** (252 mg, 1.0 mmol) and sulfonamide **233** (1.24 g, 5.0 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5) then hexane:EtOAc (90:10)] gave the ynamide **294** (192 mg, 39%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.37 (m, 1H), 7.35 – 7.16 (m, 12H), 6.92 (app. td, *J* = 7.5, 0.9 Hz, 1H), 6.76 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.00 (s, 1H), 3.57 (s, 3H), 3.30 (s, 3H), 2.40 (s, 3H); ^{13}C-NMR

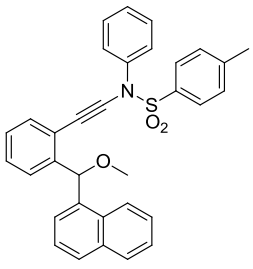
(101 MHz, $CDCl_3$): δ 157.5 (C), 145.2 (C), 142.9 (C), 139.4 (C), 133.4 (C), 132.5 (CH), 129.9 (C), 129.8 (2 × CH), 129.4 (2 × CH), 128.8 (CH), 128.6 (2 × CH), 128.4 (2 × CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 126.4 (2 × CH), 122.9 (C), 120.5 (CH), 110.8 (CH), 86.9 (C), 77.5 (CH), 69.3 (C), 57.6 (CH_3), 55.5 (CH_3), 22.0 (CH_3); IR: ν_{max}/cm^{-1} 2968, 2901, 2238, 1711, 1595, 1372, 1244, 1172, 1084; HRMS (ES) *m/z* calculated for $C_{30}H_{28}NO_4S$ $(M+H)^+$ 498.1739 found 498.1741.

***N-((2-(Methoxy(o-tolyl)methyl)phenyl)ethynyl)-4-methyl-N-phenylbenzenesulfonamide* 293**



Prepared according to **GP11** using alkyne **290** (236 mg, 1.0 mmol) and sulfonamide **233** (1.24 g, 5.0 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the ynamide **293** (190 mg, 39%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.39 (m, 1H), 7.35 – 7.06 (m, 14H), 5.81 (s, 1H), 3.36 (s, 3H), 2.41 (s, 3H), 2.14 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 145.3 (C), 141.7 (C), 139.5 (C), 139.2 (C), 137.3 (C), 133.4 (C), 132.3 (CH), 130.8 (CH), 129.9 (2 × CH), 129.5 (2 × CH), 128.6 (CH), 128.5 (CH), 128.5 (2 × CH), 128.0 (CH), 127.8 (2 × CH), 126.8 (CH), 126.5 (2 × CH), 126.0 (CH), 123.2 (C), 87.7 (C), 80.3 (CH), 69.0 (C), 57.8 (CH_3), 22.0 (CH_3), 19.5 (CH_3); IR: ν_{max} (cm^{-1}) 2981, 2923, 2901, 2235, 1595, 1488, 1372, 1170; HRMS (ES) *m/z* calculated for $C_{30}H_{28}NO_3S$ $(M+H)^+$ 482.1790 found 482.1803.

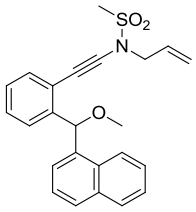
***N-((2-(Methoxy(naphthalen-1-yl)methyl)phenyl)ethynyl)-4-methyl-N-phenylbenzenesulfonamide* 294**



Prepared according to **GP11** using alkyne **291** (0.80 g, 2.9 mmol) and sulfonamide **233** (3.63 g, 14.7 mmol). Purification by flash column

chromatography [(hexane:EtOAc (92:8) then hexane:EtOAc (90:10)] followed by recrystallization (hexane:CH_2Cl_2) gave the ynamide **294** (605 mg, 40%) as a white solid; mp: 136-138 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.4 Hz, 1H), 7.84 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.78 (dd, *J* = 7.3, 2.0 Hz, 1H), 7.55 – 7.10 (m, 17H), 6.38 (s, 1H), 3.44 (s, 3H), 2.37 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.9 (C), 141.9 (C), 138.7 (C), 136.6 (C), 133.9 (C), 133.1 (C), 132.3 (CH), 131.3 (C), 129.5 (2 × CH), 129.1 (2 × CH), 128.6 (2 × CH), 128.4 (CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 127.7 (CH), 126.2 (2 × CH), 125.5 (CH), 125.2 (CH), 124.3 (CH), 123.9 (CH), 122.6 (C), 87.5 (C), 79.7 (CH), 68.6 (C), 57.5 (CH_3), 21.6 (CH_3); IR: ν_{max} (cm^{-1}) 3062, 2930, 2820, 2235, 1596, 1482, 1456, 1368, 1173, 1088, 1076; HRMS (ES) *m/z* calculated for $C_{33}H_{27}NO_3NaS$ $(M+Na)^+$ 540.1609 found 540.1611.

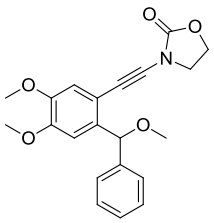
***N-Allyl-N-((2-(methoxy(naphthalen-1-yl)methyl)phenyl)ethynyl)methanesulfonamide* 295**



Prepared according to **GP11** using freshly prepared 1-((2-(bromoethynyl)phenyl)(methoxy)methyl)naphthalene (380 mg, 1.08 mmol, **GP10**) and sulfonamide **249** (122 mg, 0.9 mmol). Purification by flash column chromatography [(hexane:EtOAc (90:10)] gave the ynamide **295** (280 mg, 64%) as pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.2 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.58 – 7.39 (m, 5H), 7.37 – 7.23 (m, 3H), 6.44 (s, 1H), 5.71 (ddt, *J* = 17.1, 10.1, 6.3 Hz, 1H), 5.24 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.19 (dd, *J* = 10.1, 1.0 Hz, 1H), 4.05-4.83, (m, 2H), 3.56 (s, 3H), 2.71 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 142.2 (C), 137.0 (C), 134.2 (C), 132.7 (CH), 132.0 (C), 131.0 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 127.9 (CH), 127.8 (CH), 126.6 (CH), 126.0 (CH), 125.6 (CH), 125.1 (CH), 124.2 (CH), 122.6 (C), 120.7 (CH_2), 86.7 (C), 80.1 (CH), 69.5

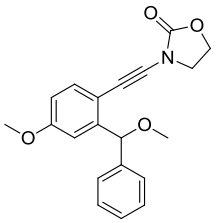
(C), 58.1 (CH_3), 54.5 (CH_2), 38.9 (CH_3); IR: ν_{max} (cm^{-1}) 3073, 2929, 2822, 2232, 1356, 1162; HRMS (ES) *m/z* calculated for $C_{24}H_{24}NO_3S$ $(M+H)^+$ 406.1477 found 406.1476.

3-((4,5-Dimethoxy-2-(methoxy(phenyl)methyl)phenyl)ethynyl)oxazolidin-2-one **311**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-4,5-dimethoxy-2-(methoxy(phenyl)methyl)benzene (815 mg, 2.26 mmol, **GP9**) and commercially available 2-oxazolidinone **250** (162 mg, 1.9 mmol), stirring for 42 hours. Purification by flash column chromatography [hexane:EtOAc (55:45)] gave the ynamide **311** (358 mg, 52%) a yellow solid; mp: 137-139 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.45 – 7.38 (m, 2H), 7.35 – 7.17 (m, 3H), 6.99 (s, 1H), 6.90 (s, 1H), 5.72 (s, 1H), 4.49 (dd, *J* = 8.8, 7.2 Hz, 2H), 3.95 (dd, *J* = 8.8, 7.2 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.39 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 156.2 (C), 150.2 (C), 148.1 (C), 142.1 (C), 137.6 (2 × C), 128.6 (2 × CH), 127.7 (CH), 127.2 (2 × CH), 114.7 (CH), 113.2 (C), 109.2 (CH), 82.5 (CH), 69.8 (C), 63.3 (CH_2), 57.4 (CH_3), 56.3 (CH_3), 56.3 (CH_3), 47.3 (CH_2); IR: ν_{max} (cm^{-1}) 2991, 2836, 2827, 2257, 1748, 1605, 1514, 1424, 1392, 1259, 1209, 1066; HRMS (ES) *m/z* calculated for $C_{21}H_{21}NO_5$ $(M)^+$ 367.1420 found 367.1411.

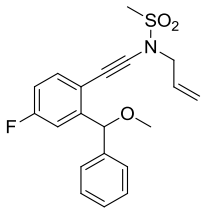
3-((4-Methoxy-2-(methoxy(phenyl)methyl)phenyl)ethynyl)oxazolidin-2-one **312**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-4-methoxy-2-(methoxy(phenyl)methyl)benzene (225 mg, 0.89 mmol, **GP9**) and commercially available 2-oxazolidinone **250** (65 mg, 0.7 mmol). Purification by flash column chromatography [hexane:EtOAc (65:35)] gave the ynamide **312** (64 mg, 25%) as an white solid; mp: 184-185 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.47 – 7.40 (m, 2H), 7.38-7.20 (m, 4H),

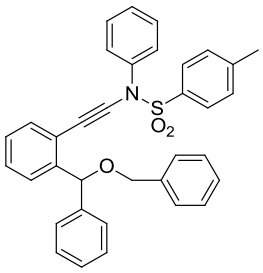
7.09 (d, *J* = 2.7 Hz, 1H), 6.75 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.72 (s, 1H), 4.49 (dd, *J* = 8.8, 7.2 Hz, 2H), 3.94 (dd, *J* = 8.8, 7.1 Hz, 2H), 3.81 (s, 3H), 3.40 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 160.4 (C), 156.2 (C), 146.1 (C), 141.6 (C), 134.2 (CH), 128.6 (2 × CH), 127.8 (CH), 127.6 (2 × CH), 113.6 (CH), 113.3 (C), 111.7 (CH), 82.8 (CH), 82.6 (C), 69.70 (C), 63.3 (CH_2), 57.5 (CH_3), 55.7 (CH_3), 47.3 (CH_2); IR ν_{max} (cm^{-1}) 2927, 2918, 2840, 2823, 2259, 1761, 1608, 1457, 1076, 709; HRMS (ES) *m/z* calculated for $C_{20}H_{19}NO_4Na$ $(M+Na)^+$ 360.1212 found 360.1209.

***N-Allyl-N-((4-fluoro-2-(methoxy(phenyl)methyl)phenyl)ethynyl)methanesulfonamide* 313**



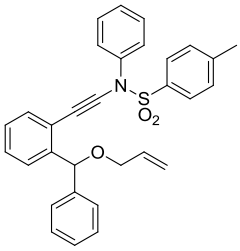
Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-4-fluoro-2-(methoxy(phenyl)methyl)benzene (377 mg, 1.18 mmol, **GP10**) and sulfonamide **249** (133 mg, 1.0 mmol). Purification by flash column chromatography [hexane:EtOAc (80:20)] gave the ynamide **313** (293 mg, 64%) as pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42 – 7.21 (m, 7H), 6.91 (td, *J* = 8.3, 2.8 Hz, 1H), 5.93 (ddt, *J* = 16.5, 10.1, 6.4 Hz, 1H), 5.67 (s, 1H), 5.40 (ddd, *J* = 16.5, 2.5, 1.2 Hz, 1H), 5.34 (ddd, *J* = 10.1, 2.0, 1.0 Hz, 1H), 4.14 (ddt, *J* = 6.4, 2.5, 1.2 Hz, 2H), 3.39 (s, 3H), 3.04 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 163.1 (d, $J_{C\text{-}F}$ = 249.8 Hz, C), 146.7 (d, $J_{C\text{-}F}$ = 7.2 Hz, C), 141.0 (C), 134.5 (d, *J* = 8.2 Hz, CH), 131.2 (CH), 128.7 (2 × CH), 128.1 (CH), 127.5 (2 × CH), 121.0 (CH_2), 117.5 (C), 115.0 (d, *J* = 22.3 Hz, CH), 113.9 (d, *J* = 23.3 Hz, CH), 86.1 (C), 82.6 (CH), 68.8 (C), 57.6 (CH_3), 54.6 (CH_2), 39.4 (CH_3); IR: ν_{max} (cm^{-1}) 2990, 2902, 2932, 2826, 2236, 1604, 1493, 1358, 1164, 1096, 1074; HRMS (ES) *m/z* calculated for $C_{20}H_{21}NO_3SF$ $(M+H)^+$ 374.1226 found 374.1230.

***N*-((2-((Benzyloxy)(phenyl)methyl)phenyl)ethynyl)-4-methyl-*N*-phenylbenzenesulfonamide 321**



Prepared according to **GP12** using alkyne **318** (200 mg, 0.7 mmol) and sulfonamide **233** (0.83 g, 3.4 mmol). Purified by flash column chromatography [hexane:EtOAc (94:6)] to give the ynamide **321** (133 mg, 36%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.33 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.30 – 7.09 (m, 19H), 5.88 (s, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 2.33 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 145.3 (C), 143.7 (C), 142.0 (C), 139.1 (C), 138.7 (C), 133.4 (C), 132.4 (CH), 130.0 (2 × CH), 129.5 (2 × CH), 128.9 (CH), 128.6 (2 × CH), 128.5 (2 × CH), 128.5 (3 × CH), 128.0 (2 × CH), 127.8 (CH), 127.6 (2 × CH), 127.4 (2 × CH), 127.1 (CH), 126.7 (2 × CH), 122.0 (C), 87.8 (C), 80.5 (CH), 71.2 (CH_2), 69.0 (C), 22.0 (CH_3); IR: ν_{max} (cm^{-1}) 3064, 3031, 2925, 2864, 2235, 1595, 1492, 1453, 1373, 1171; HRMS (ES) *m/z* calculated for $C_{35}H_{29}NO_3NaS$ $(M+Na)^+$ 566.1766 found 566.1751.

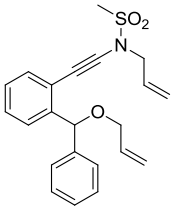
***N*-((2-((Allyloxy)(phenyl)methyl)phenyl)ethynyl)-4-methyl-*N*-phenylbenzenesulfonamide 322**



Prepared according to **GP12** using alkyne **319** (250 mg, 1.0 mmol) and sulfonamide **233** (1.24 g, 5.0 mmol). Purification by flash column chromatography [hexane:EtOAc (94:6)] gave the ynamide **XX** (228 mg, 46%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.57 – 7.51 (m, 3H), 7.39 – 7.16 (m, 13H), 5.94 (ddt, *J* = 17.2, 10.4, 5.4 Hz, 1H), 5.87 (s, 1H), 5.24 (ddt, *J* = 17.2, 3.0, 1.6 Hz, 1H), 5.13 (app. ddt, *J* = 10.4, 3.0, 1.6 Hz, 1H), 3.97 (app. ddd, *J* = 5.4, 3.1, 1.6 Hz, 2H), 2.41 (s, 3H); [c] 145.3 (C), 143.8 (C), 142.0 (C), 139.2 (C), 135.0 (CH), 133.5 (C), 132.3 (CH), 129.9 (2 × CH), 129.5 (2 × CH), 128.8 (CH), 128.7 (CH), 128.5 (3 × CH), 127.6 (CH), 127.5 (CH), 127.4 (2 × CH), 126.9

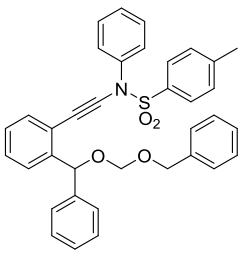
(CH), 126.7 (2 × CH), 121.9 (C), 117.2 (CH_2), 87.7 (C), 80.3 (CH), 70.2 (CH_2), 69.0 (C), 22.0 (CH_3); IR: ν_{max}/cm^{-1} 3064, 3030, 2860, 2235, 1594, 1491, 1451, 1372, 1170, 1056; HRMS (ES) *m/z* calculated for $C_{31}H_{27}NO_3NaS$ $(M+Na)^+$ 516.1609 found 516.1611.

***N-Allyl-N-((2-((allyloxy)(phenyl)methyl)phenyl)ethynyl)methanesulfonamide* 323**



Prepared according to **GP11** using freshly prepared 1-((allyloxy)(phenyl)methyl)-2-(bromoethynyl)benzene (738 mg, 1.93 mmol, **GP10**) and sulfonamide **249** (254 mg, 1.9 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the ynamide **323** (0.50 g, 69%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, J = 7.8, 1.1 Hz, 1H), 7.45 – 7.17 (m, 8H), 6.06 – 5.86 (m, 2H), 5.89 (s, 1H), 5.40 (app. ddd, *J* = 17.1, 2.4, 1.1 Hz, 1H), 5.34 (dd, *J* = 10.1, 1.1 Hz, 1H), 5.32 (app. ddd, *J* = 17.2, 3.4, 1.7 Hz, 1 H), 5.20 (app. ddd, *J* = 10.4, 3.0, 1.3 Hz, 1H), 4.15 (dd, *J* = 6.4, 1.2 Hz, 2H), 4.06 – 4.00 (m, 2H), 3.03 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.6 (C), 141.9 (C), 135.1 (CH), 132.4 (CH), 131.2 (CH), 128.9 (CH), 128.6 (2 × CH), 127.7 (CH), 127.6 (2 × CH), 127.5 (CH), 127.0 (CH), 121.6 (C), 120.9 (CH_2), 117.3 (CH_2), 86.4 (C), 80.3 (CH), 70.3 (CH_2), 69.8 (C), 54.7 (CH_2), 39.4 (CH_3); IR: ν_{max} (cm^{-1}) 3064, 3028, 2930, 2860, 2233, 1356, 1324, 1163, 922; HRMS (ES) *m/z* calculated for $C_{22}H_{24}NO_3S$ $(M+H)^+$ 382.1477 found 382.1478.

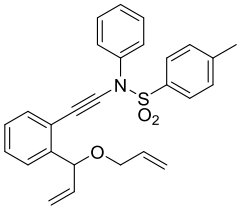
***N-((2-(((Benzyloxy)methoxy)(phenyl)methyl)phenyl)ethynyl)-4-methyl-N-phenylbenzenesulfonamide* 324**



Prepared according to **GP12** using alkyne **320** (400 mg, 1.2 mmol) and sulfonamide **233** (1.5 g, 6.1 mmol). Purification by flash column

chromatography [hexane:EtOAc (95:5) then (92:8)] gave the ynamide **324** (284 mg, 41%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.9 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.18 (m, 17H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.24 (s, 1H), 4.84 – 4.79 (m, 2H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 11.8 Hz, 1H), 2.34 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 145.0 (C), 143.4 (C), 141.6 (C), 138.9 (C), 138.0 (C), 133.2 (C), 132.2 (CH), 129.7 (2 × CH), 129.2 (2 × CH), 128.5 (3 × CH), 128.4 (2 × CH), 128.3 (3 × CH), 128.1 (2 × CH), 127.7 (CH), 127.5 (CH), 127.4 (2 × CH), 127.4 (CH), 126.8 (CH), 126.5 (2 × CH), 121.6 (C), 93.0 (CH_2), 87.7 (C), 77.2 (CH), 69.9 (CH_2), 68.7 (C), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3064, 3031, 2945, 2887, 1595, 1492, 1373, 1169, 1035, 1024, 749, 691, 653; HRMS (ES) *m/z* calculated for $C_{36}H_{32}NO_4S$ $(M+H)^+$ 575.7145, found 575.7137.

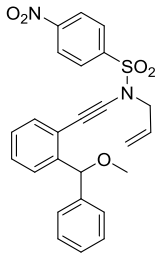
***N-((2-(1-(Allyloxy)allyl)phenyl)ethynyl)-4-methyl-N-phenylbenzenesulfonamide* 327**



Prepared according to **GP12** using alkyne **326** (200 mg, 1.0 mmol) and sulfonamide **233** (1.2 g, 5.1 mmol). Purification by flash column chromatography [hexane:EtOAc (94:6)] gave the ynamide **XX** (192 mg, 43%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.48 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.40 – 7.27 (m, 9H), 7.21 (td, *J* = 7.5, 1.4 Hz, 1H), 5.99 – 5.78 (m, 2H), 5.28 – 5.24 (m, 2H), 5.21 (app. dt, *J* = 4.8, 1.5 Hz, 1H), 5.11 (app. ddd, *J* = 10.4, 2.9, 1.5 Hz, 2H), 3.93 (ddd, *J* = 5.4, 2.7, 1.3 Hz, 2H), 2.43 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 145.3 (C), 142.6 (C), 139.1 (C), 138.2 (CH), 135.0 (CH), 133.4 (C), 132.1 (CH), 129.8 (2 × CH), 129.4 (2 × CH), 128.7 (CH), 128.6 (CH), 128.5 (2 × CH), 127.5 (CH), 126.6 (CH), 126.5 (2 × CH), 121.6 (C), 117.0 (CH_2), 116.3 (CH_2), 87.6 (C), 79.6 (CH), 69.7 (CH_2), 68.6 (C), 22.0 (CH_3); IR: ν_{max} (cm^{-1}) 3067, 2989, 2925,

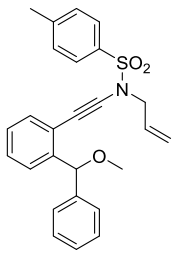
2858, 2236, 1595, 1491, 1374, 1187, 1174, 763, 751; HRMS (ES) *m/z* calculated for $C_{27}H_{25}NO_3NaS$ $(M+Na)^+$ 466.1453, found 466.1454.

***N-Allyl-N-((2-(methoxy(phenyl)methyl)phenyl)ethynyl)-4-nitrobenzenesulfonamide* 493**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (325 mg, 1.1 mmol, **GP10**) and sulfonamide **489** (205 mg, 0.9 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the ynamide **493** (246 mg, 59%) as a yellow solid; mp: 68-70 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.9 Hz, 2H), 8.00 (d, *J* = 8.9 Hz, 2H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.40 – 7.17 (m, 8H), 5.79 (ddt, *J* = 16.5, 10.2, 6.7 Hz, 1H), 5.68 (s, 1H), 5.33 – 5.27 (m, 1H), 5.26 (dd, *J* = 10.3, 0.9 Hz, 1H), 4.21 – 4.05 (m, 2H), 3.37 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 150.7 (C), 143.3 (C), 143.2 (C), 141.5 (C), 132.3 (CH), 130.3 (CH), 129.0 (3 × CH), 128.4 (2 × CH), 127.7 (CH), 127.5 (CH), 127.2 (2 × CH), 126.8 (CH), 124.5 (2 × CH), 121.2 (C), 121.0 (CH_2), 85.4 (C), 82.5 (CH), 70.0 (C), 57.3 (CH_3), 55.0 (CH_2); IR: ν_{max} (cm^{-1}) 3108, 3067, 2992, 2926, 2879, 2822, 2243, 1537, 1369, 1351, 1172, 1086, 1076, 853; HRMS (ES) *m/z* calculated for $C_{25}H_{22}N_2O_5NaS$ $(M+Na)^+$ 485.1147, found 485.1133.

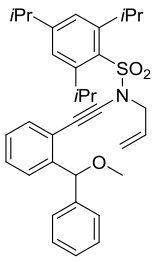
***N-Allyl-N-((2-(methoxy(phenyl)methyl)phenyl)ethynyl)-4-methylbenzenesulfonamide* 494**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (555 mg, 1.8 mmol, **GP10**) and sulfonamide **490** (324 mg, 1.5 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the ynamide **494** (488 mg, 74%) as an orange solid; mp: 81-82 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.40 –

7.14 (m, 10H), 5.77 (ddt, *J* = 16.9, 10.2, 6.8 Hz, 1H), 5.70 (s, 1H), 5.26 (dd, *J* = 16.9, 1.2 Hz, 1H), 5.21 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.15 – 3.98 (m, 2H), 3.36 (s, 3H), 2.43 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.9 (C), 143.3 (C), 141.8 (C), 134.9 (C), 132.1 (CH), 131.1 (CH), 130.0 (2 × CH), 128.5 (CH), 128.4 (2 × CH), 127.8 (2 × CH), 127.4 (CH), 127.3 (CH), 127.0 (2 × CH), 126.5 (CH), 121.9 (C), 120.3 (CH_2), 86.7 (C), 82.4 (CH), 69.4 (C), 57.2 (CH_3), 54.6 (CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 2989, 2934, 2874, 2827, 2232, 1596, 1448, 1360, 1170, 1075, 764, 658; HRMS (ES) *m/z* calculated for $C_{26}H_{25}NO_3NaS$ $(M+Na)^+$ 454.1453, found 454.1468.

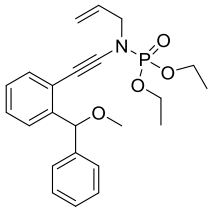
N-Allyl-2,4,6-triisopropyl-N-((2-(methoxy(phenyl)methyl)phenyl)ethynyl)-benzenesulfonamide 495



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (348 mg, 1.2 mmol, **GP10**) and sulfonamide **491** (173 mg, 0.9 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the ynamide **495** (125 mg, 34%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.9 Hz, 1H), 7.34 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.29 – 7.16 (m, 6H), 7.16 – 7.06 (m, 2H), 5.93 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 1H), 5.64 (s, 1H), 5.34 (dd, *J* = 17.0, 1.2 Hz, 1H), 5.28 (dd, *J* = 10.1, 1.0 Hz, 1H), 4.22 – 4.09 (m, 4H), 3.28 (s, 3H), 2.91 (app. dt, *J* = 13.8, 6.9 Hz, 1H), 1.27 – 1.20 (m, 18H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 154.4 (C), 152.2 (2 × C), 143.6 (C), 142.0 (C), 132.6 (CH), 131.8 (CH), 130.5 (C), 128.5 (CH), 128.4 (2 × CH), 127.4 (CH), 127.2 (CH), 126.9 (2 × CH), 126.5 (CH), 124.3 (2 × CH), 122.1 (C), 120.6 (CH_2), 86.6 (C), 83.0 (CH), 70.9 (C), 57.2 (CH_3), 52.7 (CH_2), 34.5 (CH), 30.1 (2 × CH), 25.1 (2 × CH_3), 25.0 (2 × CH_3), 23.8 (2 × CH_3);

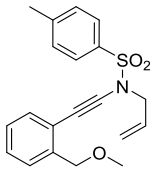
IR: ν_{max} (cm^{-1}) 2960, 2929, 2871, 2823, 2229, 1599, 1370, 1335, 1168, 1097, 1076, 757, 698, 663; HRMS (ES) *m/z* calculated for $C_{34}H_{42}NO_3S$ $(M+H)^+$ 544.2885, found 544.2878.

***Diethyl allyl((2-(methoxy(phenyl)methyl)phenyl)ethynyl)phosphoramidate* 496**



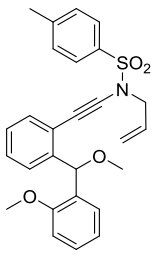
Prepared using a modified version of **GP11**: Freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (349 mg, 1.2 mmol, 1.3 equiv., **GP9**), diethyl allylphosphoramidate **492** (173 mg, 0.9 mmol, 1.0 equiv.), K_3PO_4 (379 mg, 1.8 mmol, 2.0 equiv.), $CuSO_4{\cdot}5H_2O$ (33.4 mg, 0.1 mmol, 0.15 equiv.) and 1,10-phenanthroline (48.3 mg, 0.3 mmol, 0.3 equiv.) were combined in a flask which was purged with argon for 5 minutes. Toluene (1.0 M) was added and the resulting solution was heated to 95 °C and stirred 24 hours. Once cooled to room temperature, the resulting mixture was diluted with CH_2Cl_2 and filtered through a short pad (ca. 1 cm) of silica, eluting with CH_2Cl_2 (20 mL). The solvent was removed under reduced pressure and purification by flash column chromatography [hexane:EtOAc (90:10)] gave the ynamide XX (125 mg, 34%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.46 – 7.41 (m, 3H), 7.35 – 7.13 (m, 6H), 5.96 (ddt, *J* = 16.7, 10.1, 6.2 Hz, 1H), 5.77 (s, 1H), 5.36 (app. dq, *J* = 16.7, 1.2 Hz, 1H), 5.28 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.25 – 4.10 (m, 4H), 4.05 – 3.97 (m, 2H), 3.38 (s, 3H), 1.36 (app. tdd, *J* = 7.1, 4.2, 1.0 Hz, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 142.7 (C), 142.0 (C), 133.0 (CH), 131.6 (CH), 128.3 (2 × CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 126.8 (2 × CH), 126.3 (CH), 122.9 (C), 119.1 (CH_2), 90.1 (C), 90.1 (C), 82.4 (CH), 63.9 (CH_2), 57.1 (CH_3), 53.9 (CH_2), 53.9 (CH_2), 16.2 (CH_3), 16.2 (CH_3); IR: ν_{max} (cm^{-1}) 3063, 2983, 2933, 2822, 2235, 1268, 1019, 758; HRMS (ES) *m/z* calculated for $C_{23}H_{28}NO_4PNa$ $(M+Na)^+$ 436.1654, found 436.1651.

***N-Allyl-N-((2-(methoxymethyl)phenyl)ethynyl)-4-methylbenzenesulfonamide* 500**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxymethyl)benzene (377 mg, 1.7 mmol, **GP10**) and sulfonamide **490** (188 mg, 1.4 mmol). Purification by flash column chromatography [hexane:Et_2O (80:20)] gave the ynamide **500** (472 mg, 95%) as a white solid; mp: 33-35 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.14 (m, 6H), 5.80 (ddt, *J* = 16.5, 10.1, 6.3 Hz, 1H), 5.31 (app. dq, *J* = 17.1, 1.2 Hz, 1H), 5.26 (app. dq, *J* = 10.1, 1.2 Hz, 1H), 4.53 (s, 2H), 4.07 (app. dt, *J* = 6.3, 1.2 Hz, 2H), 3.42 (s, 3H), 2.45 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.9 (C), 139.5 (C), 134.9 (C), 131.6 (CH), 131.1 (CH), 130.0 (2 × CH), 128.0 (CH), 127.9 (2 × CH), 127.6 (CH), 127.3 (CH), 121.6 (C), 120.3 (CH_2), 86.7 (C), 72.8 (CH_2), 69.0 (C), 58.6 (CH_3), 54.5 (CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3066, 2997, 2925, 2857, 2814, 2228, 1363, 1166, 1109, 758, 662; HRMS (ES) *m/z* calculated for $C_{20}H_{21}NO_3SNa$ $(M+Na)^+$ 378.1140, found 378.1147.

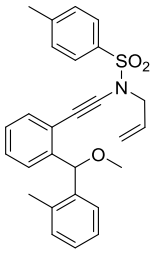
***N-Allyl-N-((2-(methoxy(2-methoxyphenyl)methyl)phenyl)ethynyl)-4-methylbenzenesulfonamide* 501**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(2-methoxyphenyl)methyl)benzene (276 mg, 0.8 mmol, **GP10**) and sulfonamide **490** (147 mg, 0.7 mmol). Purification by flash column chromatography [hexane:EtOAc (92:8) then hexane:EtOAc (90:10)] gave the ynamide **501** (276 mg, 86%) as a pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.14 (m, 8H), 6.95 (app. td, *J* = 7.5, 0.9 Hz, 1H), 6.83 (dd, *J* = 8.2, 0.7 Hz, 1H), 5.99 (s,

1H), 5.75 (ddt, *J* = 16.8, 10.1, 6.3 Hz, 1H), 5.25 (ddd, *J* = 16.8, 2.6, 1.3 Hz, 1H), 5.18 (dd, *J* = 10.1, 1.1 Hz, 1H), 4.04 (ddt, *J* = 6.3, 4.1, 1.1 Hz, 2H), 3.71 (s, 3H), 3.34 (s, 3H), 2.42 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 157.3 (C), 144.7 (2 × C), 142.4 (C), 134.9 (C), 132.1 (CH), 131.1 (CH), 129.8 (2 × CH), 128.6 (CH), 128.0 (CH), 127.9 (2 × CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 122.9 (C), 120.3 (CH), 120.1 (CH_2), 110.6 (CH), 86.1 (C), 77.3 (CH), 69.3 (C), 57.5 (CH_3), 55.5 (CH_3), 54.7 (CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3073, 3027, 2933, 2838, 2232, 1599, 1490, 1463, 1364, 1243, 1169, 1087, 661, 753; HRMS (ES) *m/z* calculated for $C_{27}H_{27}NO_4SNa$ $(M+Na)^+$ 484.1559, found 484.1568.

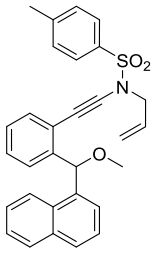
***N-Allyl-N-((2-(methoxy(o-tolyl)methyl)phenyl)ethynyl)-4-methylbenzenesulfonamide* 502**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(o-tolyl)methyl)benzene (243 mg, 0.8 mmol, **GP10**) and sulfonamide **490** (113 mg, 0.5 mmol). Purification by flash column chromatography [hexane:EtOAc (92.5:7.5)] gave the ynamide **502** (238 mg, 99%) as an orange solid; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.32 (m, 1H), 7.29 – 7.10 (m, 9H), 5.82 (s, 1H), 5.70 (ddt, *J* = 16.8, 10.1, 6.3 Hz, 1H), 5.20 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.17 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.06 (app. ddt, *J* = 14.6, 6.3, 1.2 Hz, 1H), 3.96 (app. ddt, *J* = 14.6, 6.3, 1.2 Hz, 1H), 3.40 (s, 3H), 2.42 (s, 3H), 2.20 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.8 (C), 141.5 (C), 139.4 (C), 136.9 (C), 134.9 (C), 132.2 (CH), 131.0 (CH), 130.6 (CH), 129.9 (2 × CH), 128.3 (CH), 127.9 (CH), 127.8 (2 × CH), 127.5 (2 × CH), 126.5 (CH), 125.8 (CH), 123.2 (C), 120.2 (CH_2), 86.7 (C), 80.0 (CH), 69.2 (C), 57.6 (CH_3), 54.6 (CH_2), 21.8 (CH_3), 19.4 (CH_3); IR: ν_{max} (cm^{-1}) 3065,2993, 2931, 2876, 2818, 2232, 1595, 1448, 1365, 1170, 1086, 1066, 757, 662; HRMS (ES) *m/z* calculated for $C_{27}H_{28}NO_3S$ $(M+H)^+$ 446.1790, found 446.1787.

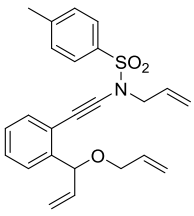
N-Allyl-N-((2-(methoxy(naphthalen-1-yl)methyl)phenyl)ethynyl)-4-methylbenzenesulfonamide

503



Prepared according to **GP11** using freshly prepared ((2-(bromoethynyl)phenyl)-(methoxy)methyl)naphthalene (275 mg, 0.8 mmol, **GP10**) and sulfonamide **490** (138 mg, 0.7 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the ynamide **503** (302 mg, 96%) as a pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.96 – 7.89 (m, 1H), 7.87 – 7.76 (m, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.52 – 7.35 (m, 5H), 7.33 – 7.17 (m, 5H), 6.37 (s, 1H), 5.60 (ddt, *J* = 16.8, 10.2, 6.2 Hz, 1H), 5.11 (ddd, *J* = 16.8, 2.5, 1.3 Hz, 1H), 5.04 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.00 (ddt, *J* = 14.6, 6.2, 1.3 Hz, 1H), 3.84 (ddt, *J* = 14.6, 6.2, 1.2 Hz, 1H), 3.48 (s, 3H), 2.38 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.9 (C), 142.1 (C), 137.0 (C), 135.0 (C), 134.1 (C), 132.4 (CH), 131.6 (C), 131.0 (CH), 130.0 (2 × CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.9 (3 × CH), 127.8 (CH), 126.3 (CH), 125.7 (CH), 125.5 (CH), 124.5 (CH), 124.2 (CH), 123.0 (C), 120.3 (CH_2), 87.1 (C), 79.7 (CH), 69.3 (C), 57.8 (CH_3), 54.5 (CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3055, 2987, 2923, 2821, 2230, 1597, 1365, 1168, 1088, 757, 660; HRMS (ES) *m/z* calculated for $C_{30}H_{28}NO_3S$ $(M+H)^+$ 482.1790, found 482.1786.

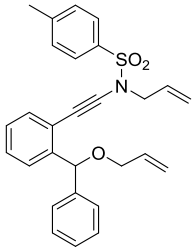
***N-Allyl-N-((2-(1-(allyloxy)allyl)phenyl)ethynyl)-4-methylbenzenesulfonamide* 504**



Prepared according to **GP11** using freshly prepared 1-(1-(allyloxy)allyl)-2-(bromoethynyl)benzene (338 mg, 1.2 mmol, **GP9**) and sulfonamide **490** (215 mg, 1.0 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the ynamide **504** (235 mg, 43%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.48 – 7.43 (m, 1H), 7.38 – 7.27 (m, 4H), 7.23 – 7.16 (m, 1H), 6.00 – 5.71 (m,

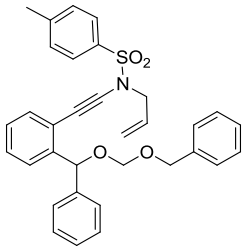
3H), 5.34 – 5.21 (m, 5H), 5.17 – 5.09 (m, 2H), 4.07 (app. dt, *J* = 6.3, 1.2 Hz, 2H), 3.93 (app. dt, *J* = 5.5, 1.4 Hz, 2H), 2.45 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.9 (C), 142.3 (C), 138.1 (CH), 134.9 (CH), 131.9 (CH), 131.1 (CH), 130.0 (2 × CH), 128.4 (CH), 127.9 (2 × CH), 127.3 (CH), 126.4 (CH), 121.6 (C), 120.3 (CH_2), 116.8 (CH_2), 116.3 (C), 115.9 (CH_2), 86.8 (C), 79.4 (CH), 69.6 (CH_2), 69.0 (C), 54.5 (CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3069, 2926, 2858, 2232, 1645, 1597, 1447, 1419, 1366, 1170, 762; HRMS (ES) *m/z* calculated for $C_{24}H_{25}NO_3SNa$ $(M+Na)^+$ 430.1453, found 430.1444.

N-Allyl-N-((2-((allyloxy)(phenyl)methyl)phenyl)ethynyl)-4-methylbenzenesulfonamide **506**



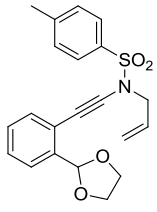
Prepared according to **GP11** using freshly prepared *N*-allyl-*N*-((2-((allyloxy)(phenyl)methyl)phenyl)ethynyl)methanesulfonamide (340 mg, 1.0 mmol, **GP10**) and sulfonamide **490** (183 mg, 0.9 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the ynamide **506** (361 mg, 91%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.53 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.42 – 7.13 (m, 10H), 5.96 (ddt, *J* = 17.2, 11.4, 5.5 Hz, 1H), 5.96 (s, 1H) 5.76 (ddt, *J* = 16.5, 10.1, 6.3 Hz, 1H), 5.30 (app. dq, *J* = 17.2, 1.7 Hz, 1H), 5.30 – 5.13 (m, 2H), 5.21 (dt, *J* = 11.4, 1.2 Hz, 1H), 4.14 – 4.03 (m, 2H), 4.03 – 3.91 (m, 2H), 2.43 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.9 (C), 143.5 (2 × C), 142.0 (C), 134.9 (CH), 132.1 (CH), 131.1 (CH), 130.0 (2 × CH), 128.5 (CH), 128.3 (2 × CH), 127.8 (2 × CH), 127.4 (CH), 127.3 (CH), 127.0 (2 × CH), 126.7 (CH), 121.8 (C), 120.3 (CH_2), 116.9 (CH_2), 86.7 (C), 80.0 (CH), 70.0 (CH_2), 69.4 (C), 54.5 (CH_2), 21.8 (CH_3);); IR: ν_{max} (cm^{-1}) 3075, 3035, 2987, 2927, 2861, 2231, 1597, 1364, 1168, 758, 699, 661; HRMS (ES) *m/z* calculated for $C_{28}H_{28}NO_3S$ $(M+H)^+$ 458.1790, found 458.1779.

***N-Allyl-N-((2-(((benzyloxy)methoxy)(phenyl)methyl)phenyl)ethynyl)-4-methylbenzenesulfonamide* 508**



Prepared according to **GP11** using freshly prepared 1-(((benzyloxy)methoxy)(phenyl)methyl)-2-(bromoethynyl)benzene (331 mg, 0.8 mmol, **GP10**) and sulfonamide **490** (143 mg, 0.7 mmol). Purification by flash column chromatography [hexane:EtOAc (93:7), 1% NEt_3] gave the ynamide **508** (329 mg, 90%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.66 – 7.53 (m, 1H), 7.40 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.38 – 7.16 (m, 15H), 6.26 (s, 1H), 5.71 (ddt, *J* = 16.8, 10.1, 6.3 Hz, 1H), 5.20 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.13 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.85 (d, *J* = 6.8 Hz, 1H), 4.82 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 11.8 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.02 – 3.97 (m, 1H), 2.37 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 143.1 (C), 141.7 (C), 138.0 (C), 134.8 (C), 132.0 (CH), 131.0 (CH), 129.9 (2 × CH), 128.4 (2 × CH), 128.4 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 127.5 (CH), 127.3 (3 × CH), 126.82 (CH), 121.8 (C), 120.3 (CH_2), 92.9 (CH_2), 86.9 (C), 77.0 (CH), 69.9 (CH_2), 69.2 (C), 54.5 (CH_2), 21.7 (CH_3); IR: ν_{max} (cm^{-1}) 3060, 3030, 2931, 2886, 2231, 1394, 1598, 1494, 1453, 1366, 1169, 1024, 732, 696, 661; HRMS (ES) *m/z* calculated for $C_{33}H_{31}NO_4SNa$ $(M+Na)^+$ 560.1871, found 560.1879.

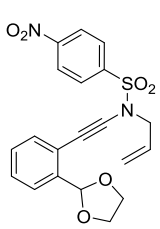
***N-((2-(1,3-Dioxolan-2-yl)phenyl)ethynyl)-N-allyl-4-methylbenzenesulfonamide* 515**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (462 mg, 1.8 mmol, **GP10**) and sulfonamide **490** (323 mg, 1.5 mmol). Purification by flash column chromatography [hexane:EtOAc (80:20), 1%

Et_3N] gave the ynamide **515** (536 mg, 91%) as a white solid; mp: 38-40 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.59 – 7.55 (m, 1H), 7.38 – 7.25 (m, 5H), 6.10 (s, 1H), 5.79 (ddt, *J* = 16.8, 10.1, 6.3 Hz, 2H), 5.29 (app. dq, *J* = 16.8, 1.3 Hz, 1H), 5.22 (ddd, *J* = 10.1, 2.2, 1.0 Hz, 1H), 4.24 – 4.11 (m, 2H), 4.11 – 3.97 (m, 4H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.8 (C), 138.0 (C), 134.8 (C), 131.4 (CH), 130.9 (CH), 129.9 (2 × CH), 129.0 (CH), 127.9 (2 × CH), 127.7 (CH), 125.9 (CH), 122.4 (C), 120.2 (CH_2), 101.9 (CH), 86.9 (C), 68.7 (C), 65.5 (2 × CH_2), 54.4 (CH_2), 21.7 (CH_3); IR: ν_{max} (cm^{-1}) 3077, 2951, 2889, 2226, 1358, 1167, 1066, 763, 661; HRMS (ES) *m/z* calculated for $C_{21}H_{21}NO_4NaS$ $(M+Na)^+$ 406.1089, found 406.1076.

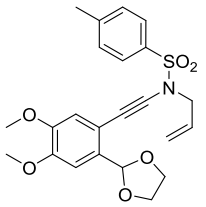
N-((2-(1,3-Dioxolan-2-yl)phenyl)ethynyl)-N-allyl-4-nitrobenzenesulfonamide **516**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (293 mg, 1.2 mmol, **GP10**) and sulfonamide **490** (235 mg, 1.0 mmol). Purification by flash column chromatography [toluene:hexane (80:20), 1% Et_3N] gave the ynamide **516** (288 mg, 72%) as a bright yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.39 (d, *J* = 9.0 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 2H), 7.63 – 7.55 (m, 1H), 7.38 – 7.11 (m, 5H), 6.10 (s, 1H), 5.78 (ddt, *J* = 16.5, 10.1, 6.4 Hz, 1H), 5.35 (app. ddd, *J* = 17.1, 2.4, 1.2 Hz, 1H), 5.27 (dd, *J* = 10.1, 1.0 Hz, 1H), 4.23 – 4.10 (m, 4H), 4.08 – 4.01 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 150.7 (C), 143.2 (C), 138.5 (C), 131.7 (CH), 130.2 (CH), 129.3 (2 × CH), 129.1 (CH), 128.4 (CH), 126.1 (CH), 124.6 (2 × CH), 121.6 (C), 121.0 (CH_2), 101.9 (CH), 85.6 (C), 69.4 (C), 65.6 (2 × CH_2), 54.9 (CH_2); IR: ν_{max} (cm^{-1}) 3105, 3021, 2979, 2887, 2237, 1532, 1375, 1349,1174, 1068, 909, 754, 730; HRMS (ES) *m/z* calculated for $C_{20}H_{19}N_2O_6S$ $(M+H)^+$ 415.0964, found 415.0970.

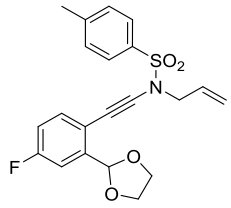
N-((2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl)ethynyl)-N-allyl-4-methylbenzenesulfonamide

517



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)-4,5-dimethoxyphenyl)-1,3-dioxolane (259 mg, 0.8 mmol, **GP10**) and sulfonamide **490** (146 mg, 0.7 mmol). Purification by flash column chromatography [hexane:EtOAc (80:20), 1% Et_3N then hexane:EtOAc (60:40), 1% Et_3N] gave the ynamide **517** (288 mg, 94%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.07 (s, 1H), 6.80 (s, 1H), 5.99 (s, 1H), 5.78 (ddt, *J* = 16.8, 10.1, 6.3 Hz, 1H), 5.28 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.22 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.21 – 4.14 (m, 2H), 4.05 (app. dt, *J* = 6.3, 1.2 Hz, 1H), 4.03 – 3.97 (m, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 149.4 (C), 149.3 (C), 144.7 (C), 134.9 (C), 131.6 (C), 131.1 (CH), 129.9 (2 × CH) , 128.0 (2 × CH), 120.1 (CH_2), 114.7 (C), 114.2 (CH), 108.7 (CH), 101.8 (CH), 85.3 (C), 68.2 (C), 65.4 (2 × CH_2), 56.2 (CH_3), 56.0 (CH_3), 54.5 (CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 2948, 2888, 2839, 2237, 1603, 1515, 1361, 1167, 1089, 732, 661; HRMS (ES) *m/z* calculated for $C_{23}H_{25}NO_6NaS$ $(M+Na)^+$ 466.1300, found 466.1307.

***N-((2-(1,3-Dioxolan-2-yl)-4-fluorophenyl)ethynyl)-N-allyl-4-methylbenzenesulfonamide* 518**

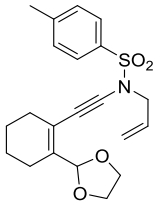


Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)-5-fluorophenyl)-1,3-dioxolane (204 mg, 0.8 mmol, **GP10**) and sulfonamide **490** (132 mg, 0.63 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10), 1% Et_3N] gave the ynamide **518** (229 mg, 91%) as a yellow oil; ^{1}H-NMR

(300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.36 – 7.31 (m, 2H), 7.31 – 7.25 (m, 2H), 6.97 (td, *J* = 8.3, 2.8 Hz, 1H), 6.05 (d, *J* = 1.5 Hz, 1H), 5.77 (ddt, *J* = 16. 8 10.1, 6.3 Hz, 1H), 5.29 (app. dq, *J* = 16.8, 1.2 Hz, 1H), 5.23 (ddd, *J* = 10.1, 2.2, 1.2 Hz, 1H), 4.19 – 4.11 (m, 2H), 4.09 – 3.99 (m, 4H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 162.2 (d, $J_{C\text{-}F}$ = 249.0 Hz, C), 144.9 (C), 141.1 (d, *J* = 7.1 Hz, C), 134.9 (C), 133.5 (d, $J_{C\text{-}F}$ = 7.9 Hz, CH), 130.9 (CH), 129.9 (2 × CH), 127.9 (2 × CH), 120.3 (CH_2), 118.4 (C), 116.3 (d, $J_{C\text{-}F}$ = 22.3 Hz, CH), 113.4 (d, $J_{C\text{-}F}$ = 23.6 Hz, CH), 101.2 (CH), 86.5 (C), 67.7 (C), 65.6 (2 × CH_2), 54.4 (CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3076, 2957, 2890, 2237, 1486, 1363, 1168, 661; HRMS (ES) *m/z* calculated for $C_{21}H_{21}NO_4SF$ $(M+H)^+$ 402.1175, found 402.1179.

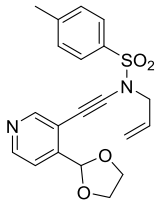
N-((2-(1,3-Dioxolan-2-yl)cyclohex-1-en-1-yl)ethynyl)-N-allyl-4-methylbenzenesulfonamide **535**

Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)cyclohex-1-en-1-yl)-1,3-



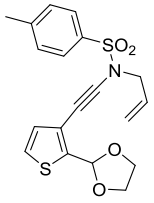
dioxolane (403 mg, 1.6 mmol, **GP10**) and sulfonamide **490** (276 mg, 1.3 mmol). Purification by flash column chromatography [hexane:EtOAc (85:15), 1% Et_3N] gave the ynamide **535** (384 mg, 76%) as a pale yellow solid; mp: 51-53 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 5.72 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.71 (s, 1H), 5.23 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.19 (dd, 10.1, 1.1 Hz, 1H), (dd, *J* = 6.6, 1.1 Hz, 1H), 4.03 – 3.93 (m, 4H), 3.92 – 3.85 (m, 2H), 2.44 (s, 3H), 2.17 – 2.08 (m, 4H), 1.58 - 1.72 (m, *J* = 7.7, 4.7 Hz, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.7 (C), 138.7 (C), 134. 8 (C), 131.1 (CH), 129.9 (2 × CH), 127.9 (2 × CH), 121.6 (C), 120.2 (CH_2), 103.4 (CH), 86.3 (C), 70.0 (C), 65.5 (2 × CH_2), 54.4 (CH_2), 30.7 (CH_2), 22.3 (CH_2), 21.9 (CH_2), 21.8 (CH_2), 21.6 (CH_3); IR: ν_{max} (cm^{-1}) 2932, 2872, 2227, 1671, 1343, 1163, 662; HRMS (ES) *m/z* calculated for $C_{21}H_{25}NO_4SNa$ $(M+Na)^+$ 410.1402, found 410.1407.

***N-((4-(1,3-Dioxolan-2-yl)pyridin-3-yl)ethynyl)-N-allyl-4-methylbenzenesulfonamide* 536**



Prepared according to **GP11** using freshly prepared 3-(bromoethynyl)-4-(1,3-dioxolan-2-yl)pyridine (215 mg, 0.8 mmol, **GP10**) and sulfonamide **490** (149 mg, 0.7 mmol). Purification by flash column chromatography [hexane:EtOAc (65:35), 1% Et_3N] gave the ynamide **536** (233 mg, 86%) as a pale orange solid; mp: 44-46 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.49 (d, *J* = 5.1 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 5.1 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.02 (s, 1H), 5.78 (ddt, *J* = 16.9, 10.2, 6.4 Hz, 1H), 5.30 (dd, *J* = 16.9, 1.1 Hz, 1H), 5.26 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.19 – 4.11 (m, 2H), 4.11 – 4.03 (m, 4H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 152.0 (CH), 148.2 (CH), 146.2 (C), 145.1 (C), 134.8 (C), 130.8 (CH), 130.0 (2 × CH), 128.0 (2 × CH), 120.6 (CH_2), 119.9 (CH), 119.3 (C), 100.8 (CH), 89.9 (C), 66.3 (C), 65.8 (2 × CH_2), 54.4 (CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1})2293, 2957, 2889, 2232, 1596, 1363, 1166, 1086, 940, 661; HRMS (ES) *m/z* calculated for $C_{20}H_{21}N_2O_4S$ $(M+H)^+$ 385.1222, found 285.1225.

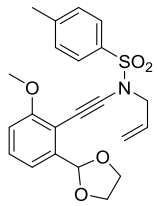
***N-((2-(1,3-Dioxolan-2-yl)thiophen-3-yl)ethynyl)-N-allyl-4-methylbenzenesulfonamide* 537**



Prepared according to **GP11** using freshly prepared 2-(3-(bromoethynyl)thiophen-2-yl)-1,3-dioxolane (181 mg, 0.7 mmol, **GP10**) and sulfonamide **490** (124 mg, 0.6 mmol). Purification by flash column chromatography [hexane:EtOAc (85:15), 1% Et_3N] gave the ynamide **537** (195 mg, 85%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 5.1 Hz, 1H), 6.92 (d, *J* = 5.1 Hz, 1H), 6.14 (s, 1H), 5.76 (ddt, 16.8, 10.2, 6.3 Hz, 1H), 5.27 (app. ddd, *J* = 17.2, 2.6, 1.3 Hz, 1H),

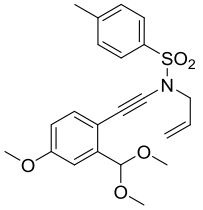
5.22 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.19 – 4.09 (m, 2H), 4.08 – 3.94 (m, 4H), 2.45 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.8 (C), 143.3 (C), 134.8 (C), 130.9 (CH), 130.1 (CH), 129.9 (2 × CH), 128.0 (2 × CH), 125.5 (CH), 121.3 (C), 120.3 (CH_2), 99.3 (CH), 85.6 (C), 65.5 (2 × CH_2), 64.6 (C), 54.5 (CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3109, 3091, 2996, 2952, 2895, 2242, 1648, 1596, 1544, 1447, 1360, 1346, 1166, 936, 745; HRMS (ES) *m/z* calculated for $C_{19}H_{20}NO_4S_2$ $(M+H)^+$ 390.0834, found 390.0840.

***N-((2-(1,3-Dioxolan-2-yl)-6-methoxyphenyl)ethynyl)-N-allyl-4-methylbenzenesulfonamide* 538**



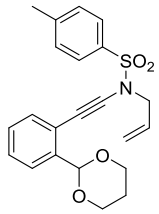
Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)-3-methoxyphenyl)-1,3-dioxolane (264 mg, 1.1 mmol, **GP10**) and sulfonamide **490** (195 mg, 0.9 mmol). Purification by flash column chromatography [toluene:EtOAc (98:2), 1% Et_3N] gave the ynamide **XX** (180 mg, 47%) as a white solid; mp: 84-86 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.15 (m, 3H), 6.85 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.11 (s, 1H), 5.83 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.32 (app. dq, *J* = 16.8, 1.3 Hz, 1H), 5.23 (dd, *J* = 10.1, 1.1 Hz, 1H), 4.19 – 4.13 (m, 2H), 4.09 – 3.99 (m, 4H), 3.84 (s, 3H), 2.43 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 159.6 (C), 144.6 (C), 139.7 (C), 135.0 (C), 131.0 (CH), 129.8 (2 × CH), 128.4 (CH), 128.1 (2 × CH), 120.3 (CH_2), 118.0 (CH), 112.2 (C), 111.3 (CH), 101.9 (CH), 91.2 (C), 65.5 (2 × CH_2), 65.0 (C), 56.1 (CH_3), 54.5 (CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3237, 2967, 2887, 2840, 2241, 1674, 1596, 1355, 1278, 1167, 1051, 1028, 663; HRMS (ES) *m/z* calculated for $C_{22}H_{24}NO_5S$ $(M+H)^+$ 414.1375, found 414.1375.

***N-Allyl-N-((2-(dimethoxymethyl)-4-methoxyphenyl)ethynyl)-4-methylbenzenesulfonamide* 542**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(dimethoxymethyl)-4-methoxybenzene (175 mg, 0.6 mmol, **GP10**) and sulfonamide **490** (108 mg, 0.5 mmol). Purification by flash column chromatography [hexane:EtOAc (85:15), 1% Et_3N] gave the ynamide **542** (184 mg, 91%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.10 (d, *J* = 2.7 Hz, 1H), 6.79 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.80 (ddt, *J* = 16.8, 10.1, 6.3 Hz, 1H), 5.55 (s, 1H), 5.29 (dd, *J* = 16.8, 1.3 Hz, 1H), 5.23 (dd, *J* = 10.1, 1.1 Hz, 1H), 4.05 (d, *J* = 6.3 Hz, 2H), 3.81 (s, 3H), 3.38 (s, 6H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 159.6 (C), 144.7 (C), 141.4 (C), 134.9 (C), 133.6 (CH), 131.2 (CH), 129.9 (2 × CH), 127.9 (2 × CH), 120.2 (CH_2), 115.1 (CH), 113.9 (C), 110.9 (CH), 102.7 (CH), 85.0 (C), 68.3 (C), 55.5 (2 × CH_3), 54.6 (CH_3), 54.5 (CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 2996, 2936, 2833, 2236, 1607, 1496, 1358, 1293, 1165, 1072, 661; HRMS (ES) *m/z* calculated for $C_{22}H_{26}NO_5S$ $(M+H)^+$ 416.1532, found 416.1519.

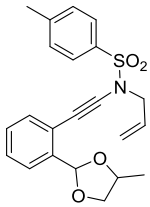
***N-((2-(1,3-Dioxan-2-yl)phenyl)ethynyl)-N-allyl-4-methylbenzenesulfonamide* 545**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)phenyl)-1,3-dioxane (261 mg, 1.0 mmol, **GP10**) and sulfonamide **490** (172 mg, 0.8 mmol). Purification by flash column chromatography [toluene:EtOAc (95:5), 1% Et_3N] gave the ynamide **543** (121 mg, 37%) as a white solid; mp: 110-112 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.34 – 7.08 (m, 5H), 5.83 (s, 1H), 5.70 (ddt, *J* = 17.0, 10.1, 6.3 Hz, 1H), 5.22 (ddd, *J* = 17.0, 2.8, 1.5 Hz, 1H), 5.16 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.19 – 4.11 (m, 2H), 4.04 – 3.92 (m, 4H), 2.34 (s, 3H), 2.25 – 2.04 (m, 1H), 1.39 – 1.30 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.9 (C), 139.3 (C), 134.9 (C), 131.1 (CH), 131.0 (CH), 130.0 (2

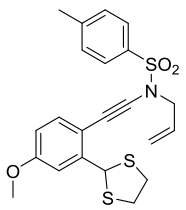
× CH), 128.7 (CH), 128.0 (CH), 127.8 (2 × CH), 126.0 (CH), 121.4 (C), 120.3 (CH_2), 100.1 (CH), 86.5 (C), 69.0 (C), 67.7 (2 × CH_2), 54.4 (CH_2), 26.0 (CH_2), 22.0 (CH_3); IR: ν_{max} (cm^{-1}) 2979, 2957, 2933, 2865, 2233, 1356, 1159, 1002, 757, 658; HRMS (ES) *m/z* calculated for $C_{22}H_{23}NO_4SNa$ $(M+Na)^+$ 420.1245, found 420.12468.

***N-Allyl-4-methyl-N-((2-(4-methyl-1,3-dioxolan-2-yl)phenyl)ethynyl)benzenesulfonamide* 546**



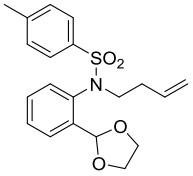
Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)phenyl)-4-methyl-1,3-dioxolane (381 mg, 1.4 mmol, **GP10**) and sulfonamide **490** (251 mg, 1.2 mmol). Purification by flash column chromatography [hexane:toluene:Et_2O (50:48:2), 1% Et_3N then hexane:EtOAc (90:10), 1% Et_3N] gave the ynamide **544** (440 mg, 93%) as a yellow oil as a 1:1 mixture of diastereoisomers; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.89 and 7.88 (2 × d, *J* = 8.4 Hz, 2H), 7.65 – 7.60 and 7.59 – 7.53 (2 × m, 1H), 7.37 – 7.23 (m, 5H), 6.26 and 6.15 (2 × s, 1H), 5.88 – 5.71 (m, 1H), 5.34 – 5.20 (m, 2H), 4.47 – 4.28 (m) and 4.13 (dd, *J* = 7.4, 6.6 Hz, 2H), 4.08 – 4.03 (m, 2H), 3.62 (t, *J* = 8.0 Hz) and 3.57 (dd, *J* = 8.5, 8.0 Hz, 1H), 2.44 (s, 3H), 1.41 and 1.35 (2 × d, *J* = 6.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.8 (C), 138.6 and 138.1 (C), 134.9 (C), 131.5 (CH), 131.3 and 131.0 (CH), 129.9 (2 × CH), 129.0 and 128.9 (CH), 128.0 (2 × CH), 127.9 and 127.7 (CH), 126.1 and 126.0 (CH), 122.5 and 122.3 (C), 120.3 (CH_2), 101.9 and 101.2 (CH), 87.0 and 86.9 (C), 73.6 and 72.6 (CH), 72.4 and 71.5 (CH_2), 68.9 and 68.8 (C), 54.4 (CH_2), 21.8 (CH_3), 18.7 and 18.6 (CH_3); IR: ν_{max} (cm^{-1}) 2977, 2934, 2875, 2233, 1597, 1362, 1169, 1088, 759, 661; HRMS (ES) *m/z* calculated for $C_{22}H_{23}NO_4SNa$ $(M+Na)^+$ 420.1245, found 420.1238.

***N-((2-(1,3-dithiolan-2-yl)-4-methoxyphenyl)ethynyl)-N-allyl-4-methylbenzenesulfonamide* 550**



Prepared according to **GP12** using alkyne **549** (160 g, 0.8 mmol) and sulfonamide **490** (715 mg, 3.9 mmol). Purification by flash column chromatography [hexane:toluene (50:50), 1% Et_3N] gave the ynamide **550** (98 mg, 32%) as a bright red oil with some low level impurities which could not be removed; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.31 (m, 2H), 7.31 – 7.22 (m, 1H), 7.20 – 7.14 (m, 1H), 6.72 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.96 (s, 1H), 5.81 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.31 (ddd, *J* = 16.8, 2.5, 1.1 Hz, 1H), 5.25 (dd, *J* = 10.1, 1.1 Hz, 1H), 4.08 (app. dt, *J* = 6.4, 1.1 Hz, 2H), 3.81 (s, 3H), 3.51 – 3.36 (m, 2H), 3.36 – 3.25 (m, 2H), 2.45 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 159.7 (C), 144.8 (2 × C), 134.8 (C), 133.7 (CH), 131.1 (CH), 123.0 (2 × CH), 128.0 (2 × CH), 120.4 (CH_2), 114.1 (C), 113.4 (CH), 113.1 (CH) , 86.6 (C), 68.4 (C), 55.5 (CH), 54.6 (CH_2), 53.6 (CH_3), 39.8 (2 × CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3066, 2925, 2838, 2234, 1603, 1362, 1277, 1168, 814, 663; HRMS (ES) *m/z* calculated for $C_{22}H_{24}NO_3S_3$ $(M+H)^+$ 446.0981, found 446.0905.

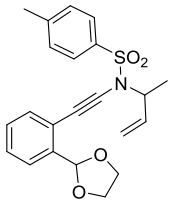
N-(2-(1,3-Dioxolan-2-yl)phenyl)-N-(but-3-en-1-yl)-4-methylbenzenesulfonamide **552**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (580 mg, 2.3 mmol, **GP10**) and sulfonamide **551** (429 mg, 1.9 mmol). Purification by flash column chromatography [hexane:EtOAc (85:15), 1% Et_3N] gave the ynamide **552** (758 mg, 99%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.62 – 7.55 (m, 1H), 7.38 – 7.28 (m, 5H), 6.12 (s, 1H), 5.75 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.12 (ddd, *J* = 17.1, 3.1, 1.3 Hz, 1H), 5.05 (d, *J* = 10.2, 2.6, 1.3 Hz, 1H), 4.21 – 4.11 (m, 2H), 4.11 – 4.01 (m, 2H), 2.51 – 2.42 (m, 2H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.7 (C), 138.2 (C), 134.8 (C), 133.7 (CH), 131.5 (CH), 129.9 (2 × CH), 129.0 (CH), 127.8 (2 × CH), 127.8

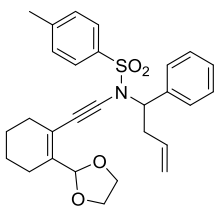
(CH), 125.9 (CH), 122.4 (C), 117.9 (CH_2), 101.9 (CH), 86.9 (C), 68.9 (C), 65.5 (2 × CH_2), 51.0 (CH_2), 32.3 (CH_2), 21.7 (CH_3); IR: ν_{max} (cm^{-1}) 3082, 2984, 2885, 2233, 1642, 1597, 1363, 1168, 1067, 757; HRMS (ES) m/z calculated for $C_{20}H_{24}NO_4S$ $(M+H)^+$ 374.4659, found 374.4687.

N-((2-(1,3-Dioxolan-2-yl)phenyl)ethynyl)-N-(but-3-en-2-yl)-4-methylbenzenesulfonamide **566**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (134 mg, 0.5 mmol, **GP10**) and sulfonamide **562** (100 mg, 0.4 mmol). Purification by flash column chromatography [hexane:toluene:Et_2O (50:47:3), 1% Et_3N] gave the ynamide **566** (117 mg, 66%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.58 (app. dt, *J* = 5.7, 3.1 Hz, 1H), 7.38 – 7.24 (m, 5H), 6.10 (s, 1H), 5.73 (ddd, *J* = 17.0, 10.6, 6.5 Hz, 1H), 5.16 (app. dt, *J* = 17.0, 1.1 Hz, 1H), 5.08 (app. dt, *J* = 10.6, 1.0 Hz, 1H), 4.68 – 4.61 (m, 1H), 4.20 – 4.10 (m, 2H), 4.09 – 3.98 (m, 2H), 2.43 (s, 3H), 1.33 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.6 (C), 138.0 (C), 136.3 (CH), 135.8 (C), 131.4 (CH), 129.8 (2 × CH), 129.0 (CH), 127.9 (2 × CH), 127.7 (CH), 125.9 (CH), 122.7 (C), 117.1 (CH_2), 101.9 (CH), 84.7 (C), 70.5 (C), 65.5 (2 × CH_2), 58.2 (CH), 21.8 (CH_3), 18.7 (CH_3); IR: ν_{max} (cm^{-1}) 3067, 2982, 2887, 2232, 1598, 1360, 1168, 1088, 1066, 942, 729, 666; HRMS (ES) *m/z* calculated for $C_{22}H_{24}NO_4S$ $(M+H)^+$ 389.1426, found 398.1420.

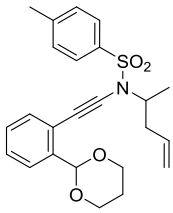
N-((2-(1,3-Dioxolan-2-yl)cyclohex-1-en-1-yl)ethynyl)-N-(1-phenylbut-3-en-1-yl)benzenesulfonamide **567**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)cyclohex-1-en-1-yl)-1,3-dioxolane (191 mg, 0.7 mmol, **GP10**)

and sulfonamide **563** (203 mg, 0.7 mmol). Purification by flash column chromatography [hexane:toluene:Et_2O (50:47:3), 1% Et_3N] gave the ynamide **567** (219 mg, 68%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.3 Hz, 2H), 7.29 – 7.17 (m, 5H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.70 (s, 1H), 5.61 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.08 (ddd, *J* = 17.1, 2.9, 1.3 Hz, 1H), 5.04 – 4.94 (m, 3H), 4.04 – 3.93 (m, 2H), 3.93 – 3.84 (m, 2H), 2.81 – 2.68 (m, 1H), 2.64 – 2.52 (m, 1H), 2.36 (s, 3H), 2.24 – 2.09 (m, 4H), 1.68 – 1.61 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.1 (C), 138.9 (C), 138.0 (C), 135.3 (C), 133.6 (CH), 129.3 (2 × CH), 128.5 (2 × CH), 128.1 (CH), 127.8 (2 × CH), 127.3 (2 × CH), 121.8 (C), 118.4 (CH_2), 103.4 (CH), 84.5 (C), 72.6 (C), 65.5 (2 × CH_2), 63.4 (CH), 38.4 (CH_2), 30.6 (CH_2), 22.3 (CH_2), 22.0 (CH_2), 21.8 (CH_2), 21.7 (CH_3); IR: ν_{max} (cm^{-1}) 3073, 3034, 2934, 2860, 1669, 1322, 1155, 1087, 918, 667; HRMS (ES) *m/z* calculated for $C_{19}H_{20}NO_4S_2$ $(M+H)^+$ 478.2052, found 478.2060.

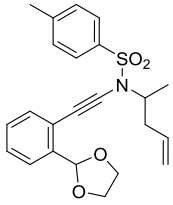
N-((2-(1,3-Dioxan-2-yl)phenyl)ethynyl)-4-methyl-N-(pent-4-en-2-yl)benzenesulfonamide **568**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)phenyl)-1,3-dioxane (261 mg, 1.0 mmol, **GP10**) and sulfonamide **564** (172 mg, 0.8 mmol). Purification by flash column chromatography [hexane:toluene:Et_2O (50:47:3), 1% Et_3N] gave the ynamide **568** (216 mg, 62%) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.73 – 7.64 (m, 1H), 7.36 – 7.13 (m, 5H), 5.96 (s, 1H), 5.65 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.06 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.01 – 4.96 (m, 1H), 4.30 – 4.19 (m, 2H), 4.18 – 4.00 (m, 3H), 2.43 (s, 3H), 2.35 – 2.16 (m, 2H), 1.47 – 1.39 (m, 2H), 1.16 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.6 (C), 139.2 (C), 136.2 (C), 133.8 (CH), 131.2 (CH), 129.9 (2 × CH), 128.7 (CH), 127.9 (CH), 127.6 (2 × CH), 126.1 (CH), 121.8 (C), 118.2 (CH_2), 100.1 (CH), 83.7 (C), 71.0 (C), 67.7 (2 ×

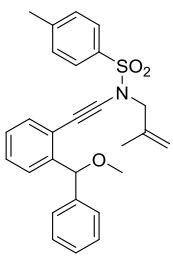
CH_2), 56.6 (CH), 39.7 (CH_2), 26.0 (CH_2), 21.8 (CH_3), 18.8 (CH_3); IR: ν_{max} (cm^{-1}) 3073, 2976, 2930, 2855, 2232, 1598, 1361, 1169, 1100, 1088, 977, 759, 735, 676; HRMS (ES) *m/z* calculated for $C_{24}H_{27}NO_4SNa$ $(M+Na)^+$ 448.1559, found 448.1541.

***N-((2-(1,3-Dioxolan-2-yl)phenyl)ethynyl)-4-methyl-N-(pent-4-en-2-yl)benzenesulfonamide* 569**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (162 mg, 0.6 mmol, **GP10**) and sulfonamide **564** (128 mg, 0.5 mmol). Purification by flash column chromatography [hexane:toluene:Et_2O (50:47:3), 1% Et_3N] gave the ynamide **569** (126 mg, 57%) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.65 – 7.59 (m, 1H), 7.45 – 7.23 (m, 5H), 6.16 (s, 1H), 5.67 (ddt, *J* = 17.0, 10.1, 7.1 Hz, 1H), 5.08 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.03 – 4.96 (m, 1H), 4.24 – 4.02 (m, 5H), 2.46 (s, 3H), 2.45 – 2.20 (m, 2H), 1.17 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.6 (C), 138.0 (C), 136.1 (C), 133.9 (CH), 131.5 (CH), 129.9 (2 × CH), 129.0 (CH), 127.7 (2 × CH), 127.7 (CH), 125.9 (CH), 122.8 (C), 118.2 (CH_2), 102.0 (CH), 84.4 (C), 70.7 (C), 65.5 (2 × CH_2), 56.8 (CH), 39.6 (CH_2), 21.8 (CH_3), 18.8 (CH_3); IR: ν_{max} (cm^{-1}) 3070, 2979, 2936, 2889, 2231, 1598, 1361, 1168, 1089, 1066, 971, 942, 757, 674; HRMS (ES) *m/z* calculated for $C_{23}H_{25}NO_4SNa$ $(M+Na)^+$ 434.1402, found 434.1399.

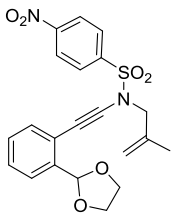
***N-((2-(Methoxy(phenyl)methyl)phenyl)ethynyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide* 576**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (301 mg, 1.0 mmol, **GP10**) and sulfonamide

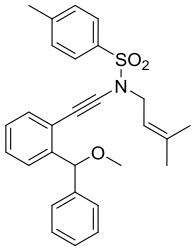
573 (139 mg, 0.6 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the ynamide **576** (203 mg, 74%) as an orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.41 – 7.12 (m, 10H), 5.70 (s, 1H), 4.95 (s, 2H), 3.97 (d, *J* = 2.8 Hz, 2H), 3.35 (s, 3H), 2.43 (s, 3H), 1.75 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.9 (C), 143.2 (C), 141.9 (C), 138.9 (C), 134.8 (C), 132.0 (CH), 129.9 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 127.8 (2 × CH), 127.4 (CH), 127.3 (CH), 126.9 (2 × CH), 126.5 (CH), 122.0 (C), 116.2 (CH_2), 86.7 (C), 82.3 (CH), 69.3 (C), 58.1 (CH_2), 57.2 (CH_3), 21.8 (CH_3), 19.8 (CH_3); IR: ν_{max} (cm^{-1}) 3065, 3032, 2978, 2927, 2825, 2232, 1598, 1494, 1451, 1169, 1092, 760; HRMS (ES) *m/z* calculated for $C_{27}H_{27}NO_3SNa$ $(M+Na)^+$ 468.1609, found 468.1607.

***N-((2-(1,3-Dioxolan-2-yl)phenyl)ethynyl)-N-(2-methylallyl)-4-nitrobenzenesulfonamide* 577**



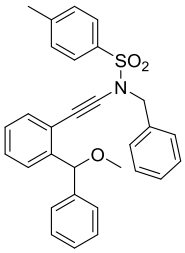
Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (274 mg, 1.1 mmol, **GP10**) and sulfonamide **574** (233 mg, 0.9 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10), 1% Et_3N then hexane:EtOAc (85:15), 1% Et_3N] gave the ynamide **577** (324 mg, 83%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.39 (d, *J* = 9.0 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.37 – 7.27 (m, 3H), 6.10 (s, 1H), 5.03 – 4.98 (m, 2H), 4.21 – 4.12 (m, 2H), 4.11 – 3.99 (m, 4H), 1.74 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 150.7 (C), 143.1 (C), 138.5 (C), 138.2 (C), 131.7 (CH), 129.2 (2 × CH), 129.1 (CH), 128.3 (CH), 126.0 (CH), 124.5 (2 × CH), 121.7 (C), 116.8 (CH_2), 101.9 (CH), 85.7 (C), 69.3 (C), 65.6 (2 × CH_2), 58.5 (CH_2), 19.8 (CH_3); IR: ν_{max} (cm^{-1}) 3105, 2986, 2950, 2887, 2237, 1530, 1372, 1348, 1173, 1066, 733; HRMS (ES) *m/z* calculated for $C_{21}H_{20}N_2O_6SNa$ $(M+Na)^+$ 451.0940, found 451.0938.

***N-((2-(Methoxy(phenyl)methyl)phenyl)ethynyl)-4-methyl-N-(3-methylbut-2-en-1-yl)benzenesulfonamide* 578**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (266 mg, 0.9 mmol, **GP10**) and sulfonamide **575** (176 mg, 0.7 mmol). Purification by flash column chromatography [hexane:EtOAc (93:7)] gave the ynamide **578** (277 mg, 82%) as a pale orange solid; mp: 49-51 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.33 – 7.13 (m, 9H), 5.71 (s, 1H), 5.22 – 5.15 (m, 1H), 4.08 (dd, *J* = 6.4, 5.4 Hz, 2H), 3.36 (s, 3H), 2.42 (s, 3H), 1.66 (s, 3H), 1.66 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.7 (C), 143.2 (C), 141.9 (C), 139.4 (C), 135.1 (C), 131.8, (CH) 129.8 (2 × CH), 128.4 (2 × CH), 128.3 (CH), 127.8 (2 × CH), 127.4 (CH), 127.3 (CH), 126.9 (2 × CH), 126.5 (CH), 122.2 (C), 117.3 (CH), 87.3 (C), 82.3 (CH), 69.1 (C), 57.1 (CH_3), 49.8 (CH_2), 25.9 (CH_3), 21.8 (CH_3), 18.2 (CH_3); IR: ν_{max} (cm^{-1}) 2980, 2931, 2823, 2231, 1598, 1493, 1449, 1363, 1166, 1090, 1075, 756, 699; HRMS (ES) *m/z* calculated for $C_{28}H_{29}NO_3SNa$ $(M+Na)^+$ 482.1766, found 482.1760.

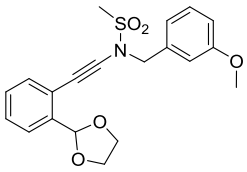
***N-Benzyl-N-((2-(methoxy(phenyl)methyl)phenyl)ethynyl)-4-methylbenzenesulfonamide* 581**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (366 mg, 1.2 mmol, **GP9**) and sulfonamide **580** (264 mg, 1.0 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the ynamide **581** (367 mg, 73%) as pale yellow solid; mp: 80-82 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H) 7.43 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.34 – 7.19 (m,

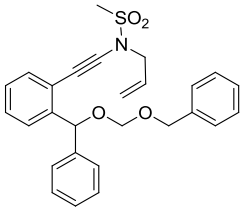
14H), 7.18 – 7.12 (m, 1H), 5.50 (s, 1H), 4.66 (d, *J* = 13.9 Hz, 1H), 4.58 (d, *J* = 13.9 Hz, 1H), 3.27 (s, 3H), 2.43 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.7 (C), 143.1 (C), 141.6 (C), 134.6 (C), 134.3 (C) 131.7 (CH), 129.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.2 (CH), 127.1 (CH), 126.7 (CH), 126.3 (CH), 121.7 (C), 86.7 (C), 82.0 (CH), 69.7 (C), 56.9 (CH_3), 55.7 (CH_2), 21.7 (CH_3); IR: ν_{max} (cm^{-1}) 3063, 3030, 2983, 2929, 2231, 1168, 1076; HRMS (ES) *m/z* calculated for $C_{30}H_{27}NO_3NaS$ $(M+Na)^+$ 504.1609 found 504.1598.

***N-((2-(1,3-Dioxolan-2-yl)phenyl)ethynyl)-N-(3-methoxybenzyl)methanesulfonamide* 587**



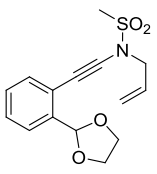
Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (779 mg, 3.1 mmol, **GP10**) and sulfonamide **586** (552 mg, 2.6 mmol). Purification by flash column chromatography [toluene:EtOAc (94:4), 1% Et_3N] gave the ynamide **587** (870 mg, 88%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60 – 7.54 (m, 1H), 7.39 – 7.25 (m, 4H), 7.12 – 7.01 (m, 2H), 6.91 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.00 (s, 1H), 4.69 (s, 2H), 4.18 – 4.06 (m, 2H), 4.06 – 3.93 (m, 2H), 3.81 (s, 3H), 2.99 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 160.0 (C), 138.4 (C), 136.1 (C), 131.5 (CH), 130.0 (CH), 129.0 (CH), 128.0 (CH), 125.9 (CH), 121.9 (C), 121.3 (CH), 114.5 (CH), 114.4 (CH), 101.9 (CH), 86.8 (C), 69.7 (C), 65.4 (2 × CH_2), 55.7 (CH_2), 55.4 (CH_3), 39.1 (CH_3); IR: ν_{max} (cm^{-1}) 3017, 2945, 2890, 2842, 2236, 1601, 1587, 1355, 1160, 753; HRMS (ES) *m/z* calculated for $C_{20}H_{22}NO_5S$ $(M+H)^+$ 388.1219, found 388.1208.

***N-Allyl-N-((2-(((benzyloxy)methoxy)(phenyl)methyl)phenyl)ethynyl)methanesulfonamide* 663**



Prepared according to **GP11** using freshly prepared 1-(((benzyloxy)methoxy)(phenyl)methyl)-2-(bromoethynyl)benzene (269 mg, 0.7 mmol, **GP10**) and sulfonamide **249** (74 mg, 0.6 mmol). Purification by flash column chromatography [hexane:EtOAc (85:15), 1% Et_3N] gave the ynamide **633** (127 mg, 50%) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.48 – 7.19 (m, 13H), 6.31 (s, 1H), 5.88 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.35 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.27 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.86 (d, *J* = 6.9 Hz, 1H), 4.82 (d, *J* = 6.9 Hz, 1H), 4.68 (d, *J* = 11.6 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.06 (dd, *J* = 6.4, 0.9 Hz, 2H), 2.88 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.1 (C), 141.6 (C), 137.9 (C), 132.1 (CH), 131.0 (CH), 128.6 (2 × CH), 128.5 (3 × CH), 128.2 (2 × CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.3 (2 × CH), 127.1 (CH), 121.6 (C), 120.7 (CH_2), 92.7 (CH_2), 86.3 (C), 76.6 (CH), 70.0 (CH_2), 69.5 (C), 54.4 (CH_2), 38.9 (CH_3); IR: ν_{max} (cm^{-1}) 3062, 3031, 2931, 2885, 2234, 1359, 1165, 1035, 1024, 732, 697; HRMS (ES) *m/z* calculated for $C_{27}H_{27}NO_4NaS$ $(M+Na)^+$ 484.1558, found 484.1554.

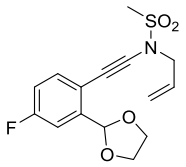
***N-((2-(1,3-Dioxolan-2-yl)phenyl)ethynyl)-N-allylmethanesulfonamide* 664**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)phenyl)-1,3-dioxolane (462 mg, 1.8 mmol, **GP10**) and sulfonamide **249** (206 mg, 1.5 mmol). Purification by flash column chromatography [toluene:EtOAc (95:5), 1% Et_3N] gave the ynamide **664** (392 mg, 84%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.61 – 7.55 (m, 1H), 7.41 – 7.36 (m, 1H), 7.35 – 7.28 (m, 2H), 6.12 (s, 1H), 6.01 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.45 (app. dq, *J* = 16.8, 1.3 Hz, 1H), 5.38 (dd, *J* = 10.1, 1.1 Hz, 1H), 4.21 – 4.13 (m, 4H), 4.11 – 4.00 (m,

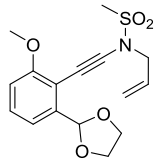
2H), 3.17 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 138.4 (C), 131.5 (CH), 131.0 (CH), 129.0 (CH), 128.0 (CH), 125.9 (CH), 121.9 (C), 120.8 (CH_2), 102.0 (CH), 86.5 (C), 69.3 (C) 65.5 (2 × CH_2), 54.4 (CH_2), 39.2 (CH_3); IR: ν_{max} (cm^{-1}) 3017, 2981, 2938, 2889, 2234, 1354, 1326, 1162, 1066, 940, 759; HRMS (ES) *m/z* calculated for $C_{15}H_{18}NO_4S$ $(M+H)^+$ 308.0957, found 308.0948.

***N-((2-(1,3-Dioxolan-2-yl)-4-fluorophenyl)ethynyl)-N-allylmethanesulfonamide* 669**



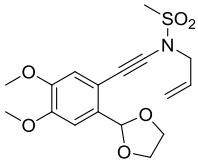
Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)-5-fluorophenyl)-1,3-dioxolane (204 mg, 0.8 mmol, **GP10**) and sulfonamide **249** (85 mg, 0.6 mmol). Purification by flash column chromatography [hexane:EtOAc (80:20), 1% Et_3N] gave the ynamide **669** (159 mg, 78%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 8.4, 5.4 Hz, 1H), 7.29 (dd, *J* = 9.4, 2.8 Hz, 1H), 6.99 (app. td, *J* = 8.4, 2.8 Hz, 1H), 6.08 (d, *J* = 1.3 Hz, 1H), 6.00 (ddt, *J* = 17.0, 10.1, 6.4 Hz, 1H), 5.44 (ddd, *J* = 17.0, 2.5, 1.2 Hz, 1H), 5.38 (dd, *J* = 10.1, 1.0 Hz, 1H), 4.19 – 4.10 (m, 4H), 4.10 – 3.99 (m, 2H), 3.16 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 162.3 (d, $J_{C\text{-}F}$ = 249.4 Hz, C), 141.5 (d, $J_{C\text{-}F}$ = 7.2 Hz, C), 133.6 (d, $J_{C\text{-}F}$ = 8.0 Hz, CH), 131.0 (CH), 120.8 (CH_2), 117.9 (C), 116.3 (d, $J_{C\text{-}F}$ = 22.3 Hz, CH), 113.4 (d, $J_{C\text{-}F}$ = 23.7 Hz, CH), 101.3 (CH), 86.0 (C), 68.1 (C), 65.6 (2 × CH_2), 54.3 (CH_2), 39.2 (CH_3); IR: ν_{max} (cm^{-1}) 3020, 2991, 2935, 2892, 2239, 1607, 1496, 1355, 1326, 1268, 1158, 733; HRMS (ES) *m/z* calculated for $C_{15}H_{17}NO_4SF$ $(M+H)^+$ 326.0862, found 326.0872.

***N*-((2-(1,3-Dioxolan-2-yl)-6-methoxyphenyl)ethynyl)-*N*-allylmethanesulfonamide 670**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)-3-methoxyphenyl)-1,3-dioxolane (264 mg, 1.1 mmol, **GP10**) and sulfonamide **249** (125 mg, 0.9 mmol). Purification by flash column chromatography [toluene:EtOAc (93:7), 1% Et_3N] gave the ynamide **670** (140 mg, 73%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.27 (app. t, *J* = 7.8 Hz, 1H), 7.18 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.86 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.10 (s, 1H), 6.04 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.46 (app. dq, *J* = 16.8, 1.3 Hz, 1H), 5.37 (ddd, *J* = 10.1, 2.1, 1.0 Hz, 1H), 4.18 (app. dt, *J* = 6.5, 1.1 Hz, 2H), 4.16 – 4.08 (m, 2H), 4.08 – 3.99 (m, 2H), 3.85 (s, 3H), 3.20 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 159.7 (C), 140.0 (C), 131.1 (CH), 128.7 (CH), 120.7 (CH_2), 118.0 (CH), 111.6 (C), 111.3 (CH), 101.9 (CH), 90.7 (C), 65.5 (2 × CH_2, C), 56.1 (CH_3), 54.3 (CH_2), 38.9 (CH_3); IR: ν_{max} (cm^{-1}) 3003, 2989, 2900, 2924, 2246, 1578, 1478, 1458, 1441, 1396, 1344, 1276, 1158, 1053, 774; HRMS (ES) *m/z* calculated for $C_{16}H_{19}NO_5SNa$ $(M+Na)^+$ 360.0882, found 360.0876.

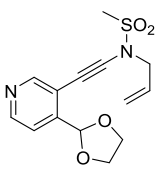
***N*-((2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl)ethynyl)-*N*-allylmethanesulfonamide 671**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)-4,5-dimethoxyphenyl)-1,3-dioxolane (259 mg, 0.8 mmol, **GP10**) and sulfonamide **249** (93 mg, 0.7 mmol). Purification by flash column chromatography [toluene:EtOAc (60:40), 1% Et_3N] gave the ynamide **671** (186 mg, 73%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.08 (s, 1H), 6.86 (s, 1H), 6.05 (s, 1H), 6.01 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 1H), 5.44 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.37 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.22 – 4.12 (m, 4H), 4.09 – 3.98 (m,

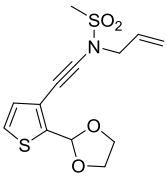
2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.16 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 149.4 (C), 149.3 (C), 132.0 (2 × C), 131.1 (CH), 120.6 (CH_2), 114.3 (CH), 108.7 (CH), 101.8 (CH), 84.8 (C), 68.7 (C), 65.4 (2 × CH_2), 56.2 (CH_3), 56.1 (CH_3), 54.4 (CH_2), 39.1 (CH_3); IR: ν_{max} (cm^{-1}) 2988, 2978, 2901, 2234, 1603, 1513, 1350, 1160, 1089; HRMS (ES) *m/z* calculated for $C_{15}H_{19}NO_6SNa$ $(M(-C_2H_2)+Na)^+$ 364.0831, found 364.0837.

***N-((4-(1,3-Dioxolan-2-yl)pyridin-3-yl)ethynyl)-N-allylmethanesulfonamide* 676**



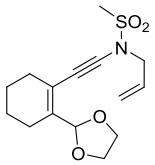
Prepared according to **GP11** using freshly prepared 3-(bromoethynyl)-4-(1,3-dioxolan-2-yl)pyridine (215 mg, 0.8 mmol, **GP10**) and sulfonamide **249** (95 mg, 0.7 mmol). Purification by flash column chromatography [hexane:EtOAc (40:60), 1% Et_3N] gave the ynamide **676** (123 mg, 86%) as a clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.60 (d, *J* = 0.6 Hz, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 7.45 (d, *J* = 5.1 Hz, 1H), 6.04 (s, 1H), 6.00 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 1H), 5.46 (ddd, *J* = 16.8, 2.4, 1.2 Hz, 1H), 5.40 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.21 – 4.18 (m, 2H), 4.17 – 4.09 (m, 2H), 4.09 – 4.02 (m, 2H), 3.19 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 151.9 (CH), 148.5 (CH), 146.6 (C), 130.8 (CH), 121.0 (CH_2), 119.9 (CH), 118.8 (C), 100.8 (CH), 89.3 (C), 66.7 (C), 65.7 (2 × CH_2), 54.4 (CH_2), 39.5 (CH_3); IR: ν_{max} (cm^{-1}) 3011, 2993, 2929, 2891, 2234, 1713, 1354, 1161, 1086, 963, 939; HRMS (ES) *m/z* calculated for $C_{14}H_{17}N_2O_4S$ $(M+H)^+$ 309.0909, found 309.0899.

***N-((2-(1,3-Dioxolan-2-yl)thiophen-3-yl)ethynyl)-N-allylmethanesulfonamide* 677**



Prepared according to **GP11** using freshly prepared 2-(3-(bromoethynyl)thiophen-2-yl)-1,3-dioxolane (171 mg, 0.7 mmol, **GP10**) and sulfonamide **249** (79 mg, 0.6 mmol). Purification by flash column chromatography [hexane:EtOAc (80:20), 1% Et_3N] gave the ynamide **677** (110 mg, 50%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J* = 5.1 Hz, 1H), 6.98 (d, *J* = 5.1 Hz, 1H), 6.22 (s, 1H), 5.98 (ddt, *J* = 16.9, 10.1, 6.4 Hz, 1H), 5.43 (ddd, *J* = 16.9, 2.5, 1.2 Hz, 1H), 5.37 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.21 – 4.08 (m, 4H), 4.07 – 3.97 (m, 2H), 3.14 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.0 (C), 130.9 (CH), 130.1 (CH), 125.5 (CH_2), 120.8 (CH), 120.7 (C), 99.4 (CH), 85.0 (C), 65.5 (2 × CH_2), 64.9 (C), 54.4 (CH_2), 39.1 (CH_3); IR: ν_{max} (cm^{-1}) 3115, 3085, 2936, 2892, 2240, 1356, 1164, 1072, 960; HRMS (ES) *m/z* calculated for $C_{13}H_{15}NO_4S_2Na$ $(M+Na)^+$ 336.0340, found 336.0343.

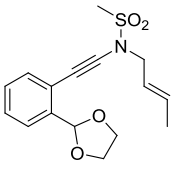
***N-((2-(1,3-Dioxolan-2-yl)cyclohex-1-en-1-yl)ethynyl)-N-allylmethanesulfonamide* 680**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)cyclohex-1-en-1-yl)-1,3-dioxolane (263 mg, 1.0 mmol, **GP10**) and sulfonamide **249** (180 mg, 0.9 mmol). Purification by flash column chromatography [hexane:EtOAc (70:30), 1% Et_3N] gave the ynamide **680** (190 mg, 72%) as a clear oil with some low level impurities which could not be identified; ^{1}H-NMR (300 MHz, $CDCl_3$): δ ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.91 (ddt, *J* = 16.9, 10.1, 6.4 Hz, 1H), 5.74 (s, 1H), 5.40 (app. ddd, *J* = 16.9, 2.5, 1.2 Hz, 1H), 5.32 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.07 (app. dt, *J* = 6.4, 1.1 Hz, 2H), 4.03 – 3.94 (m, 2H), 3.94 – 3.86 (m, 2H), 3.06 (s, 3H), 2.24 – 2.06 (m, 4H), 1.65 – 1.56 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 139.0 (C),

131.0 (CH), 121.2 (C), 120.6 (CH_2), 103.3 (CH), 85.7 (C), 70.3 (C), 65.6 (2 × CH_2), 54.3 (CH_2), 38.9 (CH_3), 30.7 (CH_2), 22.2 (CH_2), 22.0 (CH_2), 21.8 (CH_2); IR: ν_{max} (cm^{-1}) 3025, 2933, 2885, 2844, 2227, 1357, 1324, 1163, 1056, 943, 750; HRMS (ES) *m/z* calculated for $C_{15}H_{22}NO_4S$ $(M+H)^+$ 312.1270, found 312.1258.

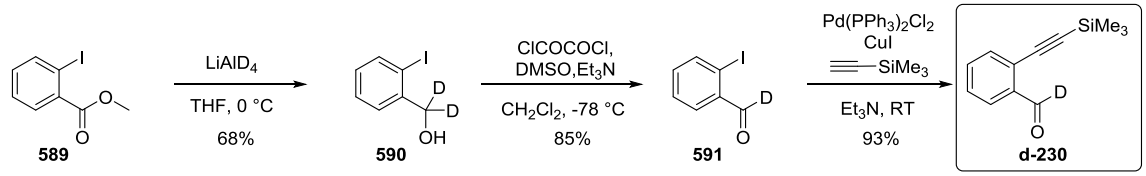
***(E)-N-((2-(1,3-Dioxolan-2-yl)phenyl)ethynyl)-N-(but-2-en-1-yl)methanesulfonamide* 683**



Prepared according to **GP10** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl)benzene (289 mg, 1.1 mmol, **GP9**) and sulfonamide **682** (142 mg, 1.0 mmol). Purification by flash column chromatography [toluene:EtOAc (80:20), 1% Et_3N] gave the ynamide **683** (224 mg, 73%) as a white solid; mp: 126-127 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.61 – 7.55 (m, 1H), 7.41 – 7.35 (m, 1H), 7.33 – 7.28 (m, 2H), 6.12 (s, 1H), 5.96 – 5.83 (m, 1H), 5.74 – 5.60 (m, 1H), 4.19 – 4.08 (m, 4H), 4.08 – 4.01 (m, 2H), 3.15 (s, 3H), 1.78 (dd, *J* = 6.4, 1.2 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 138.4 (C), 133.0 (CH), 131.5 (CH), 129.0 (CH), 127.9 (CH), 125.9 (CH), 123.8 (CH), 122.2 (C), 102.1 (CH), 86.8 (C), 69.3 (C), 65.5 (2 × CH_2), 54.0 (CH_2), 39.2 (CH_3), 18.0 (CH_3); IR: ν_{max} (cm^{-1}) 3067, 2997,2888, 2857, 2814, 2280, 1597, 1362, 1165, 1108, 771, 758; HRMS (ES) *m/z* calculated for $C_{16}H_{20}NO_4S$ $(M+H)^+$ 322.1113, found 322.1106.

Synthesis of Deuterated Ynamides

***2-((Trimethylsilyl)ethynyl-d)benzaldehyde* d-230**



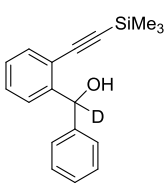
A solution of methyl-2-iodobenzoate (2.0 g, 7.6 mmol, 1.0 equiv.) in THF (5 mL) was added dropwise to a suspension of $LiAlD_4$ (450 mg, 10.7 mmol, 1.4 equiv.) in THF (15 mL, 0.2 M) at 0 °C. The mixture was stirred at room temperature for 1 hour and then cooled again to 0 °C. Water (10 mL) was added slowly (take care!) to quench the reaction. Saturated potassium sodium tartrate solution (20 mL) was added to help solubilise the suspension and the aqueous phase was extracted with Et_2O (4 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give the pure alcohol **590** (1.2 g, 68%) as colourless solid; mp: 82-84 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.46 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.37 (td, *J* = 7.5, 1.1 Hz, 1H), 7.04 – 6.98 (m, 1H), 2.01 (br. s, OH); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 142.7 (C), 139.4 (CH), 129.5 (CH), 128.7 (CH), 128.7 (CH), 97.7 (C); IR: ν_{max} (cm^{-1}) 3276, 3175, 3059, 1463, 1432, 1010, 736; HRMS (ES) *m/z* calculated for $C_7H_4D_2I$ $(M+H(-H_2O))^+$ 218.9640 found 218.9643.

Oxalyl chloride (0.4 mL, 4.8 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (3 mL, 0.6 M) and cooled to -78 °C. DMSO (1.0 mL, 14.4 mmol, 3 equiv.) was added slowly and the solution stirred for 45 minutes. Deuterated alcohol **590** (1.1 g, 4.8 mmol, 1.0 equiv.) in CH_2Cl_2 (5mL) was added slowly

and the solution stirred for a further 45 minutes. Et_3N (4.0 mL, 28.8 mmol, 6.0 equiv.) was added and the solution stirred for 45 minutes before warming to room temperature. Water (15 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 ml). The organic fractions were washed with brine (15 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give the desired aldehyde **d-230** (956 mg, 4.1 mmol, 85%) which was used directly.

Deuterated aldehyde **591** (934 mg, 4.0 mmol, 1.0 equiv.) was dissolved in Et_3N (20 mL, 0.2 M). $Pd(PPh_3)Cl_2$ (85 mg, 0.1 mmol, 3 mol%) and CuI (46 mg, 0.2 mmol, 6 mol%) were added and the solution stirred for 5 minutes. Trimethylsilylacetylene (0.7 mL, 4.8 mmol, 1.2 equiv.) was added slowly and the resulting solution stirred at room temperature for 14 hours. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography [hexane:Et_2O (98:2)] to give aldehyde **d-230** (761 mg, 93%) as a pale yellow solid; mp: 44-46 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.91 (ddd, *J* = 7.7, 1.2, 0.7 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.43 (ddd, *J* = 7.7, 6.6, 2.1 Hz, 1H), 0.28 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 136.2 (C), 133.8 (CH), 133.6 (CH), 129.0 (CH), 127.0 (CH), 126.9 (C), 102.5 (C), 100.2 (C), -0.1 (3 × CH_3); IR: ν_{max} (cm^{-1}) 2958, 2900, 2123, 1675, 1593, 1246, 841, 756; HRMS (ES) *m/z* calculated for $C_{12}H_{14}DOSi$ $(M+H)^+$ 204.0955 found 201.0952.

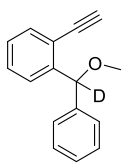
Phenyl(2-((trimethylsilyl)ethynyl)phenyl)methan-d-ol d-231



Prepared according to **GP2** from aldehyde **d-230** (545 mg, 2.7 mmol). Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the alcohol **d-231**

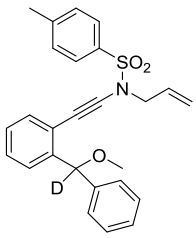
(747 mg, 99%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.53 – 7.39 (m, 4H), 7.40 – 7.17 (m, 5H), 0.24 (s, 9H); MS (ES): *m/z* 304 $[M+Na]^+$ (100 %). Data matches that reported in the literature.[57]

1-Ethynyl-2-(methoxy(phenyl)methyl-d)benzene d-232



Prepared according to **GP3** using alcohol **d-231** (784 mg, 2.8 mmol). Purification by flash column chromatography [hexane:Et_2O (95:5)] gave the terminal alkyne **d-232** (427 mg, 69%) as a yellow oil;^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 – 7.41 (m, 5H), 7.41 – 7.19 (m, 4H), 3.41 (s, 3H), 3.36 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.6 (C), 141.5 (C), 133.0 (CH), 129.5 (CH), 128.4 (2 × CH), 127.6 (CH), 127.4 (CH), 127.0 (3 × CH), 126.4 (CH), 121.1 (C), 82.2 (CH), 82.1 (C), 57.2 (CH_3); IR: ν_{max} (cm^{-1}) 3292, 3077, 2864, 1550, 1435, 1118, 756. Data matches that reported in the literature.**Error! Bookmark not defined.**

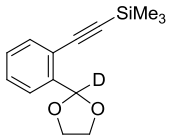
***N-Allyl-N-((2-(methoxy(phenyl)methyl-d)phenyl)ethynyl)-4-methylbenzenesulfonamide* d-494**



Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl-d)benzene (243 mg, 0.8 mmol, **GP10**) and sulfonamide **490** (142 mg, 0.7 mmol). Purification by flash column chromatography [hexane:Et_2O (90:10)] gave the ynamide **d-494** (274 mg, 95%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.48 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.40 – 7.15 (m, 10H), 5.77 (ddt, *J* = 16.8, 10.2, 6.3 Hz, 1H), 5.26 (dd, *J* = 16.8, 1.2 Hz, 2H), 5.22 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.15 – 3.99 (m, 2H), 3.36 (s, 3H), 2.43 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.9 (C), 143.3 (C), 141.7 (C), 134.9 (C), 132.1 (CH), 131.1 (CH), 123.0 (2 × CH), 128.5

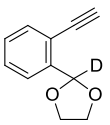
(CH), 128.4 (2 × CH), 127.9 (2 × CH), 127.4 (CH), 127.3 (CH), 127.0 (2 × CH), 126.5 (CH), 121.9 (C), 120.4 (CH_2), 86.7 (C), 69.4 (C), 57.2 (CH_3), 54.6 (CH_2), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3023, 2990, 2931, 2233, 1596, 1493, 1447, 1361, 1171, 1085, 736; HRMS (ES) *m/z* calculated for $C_{26}H_{25}DNO_3S$ $(M+H)^+$ 433.1696, found 433.1692.

***((2-(1,3-Dioxolan-2-yl-d)phenyl)ethynyl)trimethylsilane* d-592**



Prepared according to **GP5** using aldehyde **d-230** (670 mg, 3.3 mmol) and ethylene glycol. Purification by flash column chromatography [hexane:EtOAc (95:5), 1% Et_3N] gave the acetal **d-592** (663 mg, 81%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.57 – 7.51 (m, 1H), 7.52 – 7.46 (m, 1H), 7.38 – 7.26 (m, 2H), 4.26 – 4.12 (m, 2H), 4.12 – 4.00 (m, 2H), 0.26 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 139.3 (C), 133.0 (CH), 129.1 (CH), 128.8 (CH), 126.3 (CH), 122.5 (C), 102.2 (C), 99.3 (C), 65.7 (2 × CH_2), 0.1 (3 × CH_3); IR: ν_{max} (cm^{-1}) 2959, 2889, 2157, 1680, 1249, 1075, 861, 839, 757; HRMS (ES) *m/z* calculated for $C_{14}H_{18}DO_2Si$ $(M+H)^+$ 248.1217, found 248.1222.

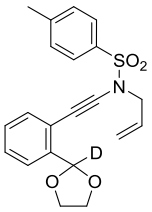
***2-(2-Ethynylphenyl)-1,3-dioxolane-d* d-512**



Prepared according to **GP4** from alkyne **d-592** (609 mg, 2.5 mmol) to give terminal alkyne **d-512** (414 mg, 96%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.53 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.39 (app. td, *J* = 7.5, 1.6 Hz, 1H), 7.32 (app. td, *J* = 7.5, 1.6 Hz, 1H), 4.23 – 4.12 (m, 2H), 4.12 – 4.02 (m, 2H), 3.33 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 139.7 (C), 133.3 (CH), 129.1 (2 × CH), 126.1 (CH), 121.4 (C), 82.0 (CH), 80.9 (C), 65.7 (2 × CH_2),

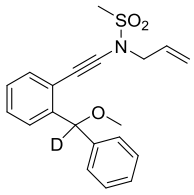
the C-D carbon was not visible; IR: ν_{max} (cm^{-1}) 3288, 2935, 2884, 2124, 1666, 1592, 755, HRMS (ES) *m/z* calculated for $C_{11}H_9DO_2$ $(M+H)^+$ 175.0744, found 175.0741.

N-((2-(1,3-Dioxolan-2-yl-2-d)phenyl)ethynyl)-N-allyl-4-methylbenzenesulfonamide **d-515**



Prepared according to **GP11** using freshly prepared 2-(2-(bromoethynyl)phenyl-d)-1,3-dioxolane (230 mg, 0.9 mmol, **GP10**) and sulfonamide **490** (160 mg, 0.8 mmol). Purification by flash column chromatography [hexane:EtOAc (90:10), 1% Et_3N, then hexane:EtOAc (80:20), 1% Et_3N] gave the ynamide **d-515** (279 mg, 96%) as a white solid; mp: 67-69 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.59 – 7.55 (m, 1H), 7.37 – 7.23 (m, 5H), 5.79 (ddt, *J* = 16.8, 10.1, 6.3 Hz, 1H), 5.30 (app. dq, *J* = 16.8, 1.3 Hz, 1H), 5.24 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.20 – 4.12 (m, 2H), 4.11 – 4.00 (m, 4H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.8 (C), 138.0 (C), 134.9 (C), 131.5 (CH), 131.0 (CH), 123.0 (2 × CH), 129.0 (CH), 1278.0 (2 × CH), 127.8 (CH), 126.0 (CH), 122.4 (C), 120.3 (CH_2), 87.0 (C), 68.8 (C), 65.5 (2 × CH_2), 54.4 (CH_2), 45.9 (C), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3102, 3066, 2994, 2952, 2893, 2230, 1597, 1351, 1167, 766, 660; HRMS (ES) *m/z* calculated for $C_{21}H_{20}DNO_4SNa$ $(M+Na)^+$ 407.1152, found 407.1160.

N-Allyl-N-((2-(methoxy(phenyl)methyl-d)phenyl)ethynyl)methanesulfonamide **d-255**

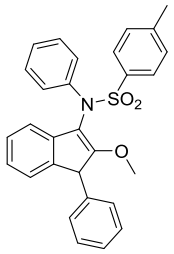


Prepared according to **GP11** using freshly prepared 1-(bromoethynyl)-2-(methoxy(phenyl)methyl-d)benzene (243 mg, 0.8 mmol, **GP10**) and sulfonamide **249** (91 mg, 0.7 mmol). Purification by flash column chromatography [hexane:Et_2O (85:15)] gave the ynamide **d-255** (171 mg, 72%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.37 (m, 3H), 7.37 – 7.17 (m, 5H), 5.95 (ddt, *J* = 16.9,

10.1, 6.4 Hz, 1H), 5.41 (d, *J* = 16.9 Hz, 1H), 5.35 (d, *J* = 10.1 Hz, 1H), 4.16 (dd, *J* = 6.4, 1.1 Hz, 2H), 3.40 (s, 3H), 3.04 (s, 3H);^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.2 (C), 141.5 (C), 132.2 (CH), 131.1 (CH), 128.6 (CH), 128.4 (2 × CH), 127.6 (CH), 127.4 (CH), 127.2 (2 × CH), 126.6 (CH), 121.5 (C), 120.8 (CH_2), 86.2 (C), 82.3 (t, $J_{C\text{-}D}$ = 21.8 Hz, CD), 69.7 (C), 57.3 (CH_3), 54.5 (CH_2), 39.2 (CH_3); IR: ν_{max} (cm^{-1}) 3025, 2931, 2820, 2232, 1448, 1356, 1324, 1164, 1084, 1076, 755, 699; HRMS (ES) *m/z* calculated for $C_{20}H_{20}DNO_3NaS$ $(M+Na)^+$ 379.1203, found 379.1217.

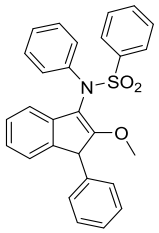
Preparation of Functionalised Indenes

***N-(2-Methoxy-1-phenyl-1H-inden-3-yl)-4-methyl-N-phenylbenzenesulfonamide* 235**



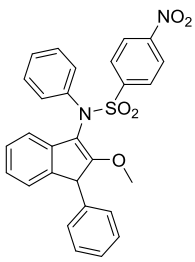
Prepared according to **GP13** from ynamide **234** (93.5 mg, 0.2 mmol), stirring for 2 hours. Purification by flash column chromatography [hexane:EtOAc (93:7) then hexane:EtOAc (80:20)] gave the indene **235** (68.6 mg, 73%) as a white solid; mp: 172-174 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.39 – 7.16 (m, 10H), 7.16 – 6.91 (m, 4H), 4.65 (s, 1H), 3.63 (s, 3H), 2.41 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 163.8 (C), 143.4 (C), 141.0 (2 × C), 139.4 (C), 138.0 (C), 137.7 (C) 129.1 (6 × CH), 128.1 (2 × CH), 127.8 (2 × CH), 127.3 (CH), 127.1 (CH), 126.5 (CH), 125.8 (2 × CH), 124.1 (CH), 123.0 (CH), 118.1 (CH), 117.6 (C), 58.2 (CH), 51.6 (CH_3), 21.5 (CH_3); IR: ν_{max} (cm^{-1}) 2988, 2973, 2902, 1615, 1596, 1581, 1155, 1075; HRMS (ES) *m/z* calculated for $C_{29}H_{25}NO_3NaS$ $(M+Na)^+$ 490.1453 found 490.1440.

***N-(2-Methoxy-1-phenyl-1H-inden-3-yl)-N-phenylbenzenesulfonamide* 258**



Prepared according to **GP13** from ynamide **244** (90.7 mg, 0.2 mmol or 1.37 g, 3.0 mmol) stirring for 1 hour (0.2 mmol scale) or 2 hours (3.0 mmol scale). Recrystallisation [hexane:CH_2Cl_2] gave the indene **258** as a white solid (61.9 mg, 68%, 0.2 mmol scale or 856.2 mg, 62%, 3.0 mmol scale); mp: 199-201 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.91 – 7.86 (m, 2H), 7.59 – 7.51 (m, 3H), 7.48 – 7.40 (m, 2H), 7.36 – 7.18 (m, 8H), 7.17 – 6.94 (m, 4H), 4.64 (s, 1H), 3.58 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 163.8 (C), 140.9 (2 × C), 140.9 (C), 139.4 (C), 137.6 (C), 132.6 (CH), 129.2 (2 × CH), 129.1 (2 × CH), 128.5 (2 × CH), 128.0 (2 × CH), 127.7 (2 × CH), 127.4 (CH), 127.2 (CH), 126.8 (CH), 126.2 (2 × CH), 124.1 (CH), 123.3 (CH), 118.1 (CH), 118.0 (C) 58.1 (CH), 51.5 (CH_3); IR: ν_{max} (cm^{-1}) 3076, 2948, 2856, 1614, 1489, 1342, 1167, 1159, 757, 691; HRMS (ES) *m/z* calculated for $C_{28}H_{24}NO_3S$ $(M+H)^+$ 454.1477 found 454.1476.

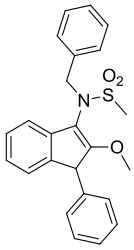
***N-(2-Methoxy-1-phenyl-1H-inden-3-yl)-4-nitro-N-phenylbenzenesulfonamide* 259**



Prepared according to **GP13** from ynamide **245** (149.6 mg, 0.3 mmol) stirring for 45 minutes. Purification by flash column chromatography [hexane:Et_2O (90:10) then hexane:EtOAc (90:10)] gave the indene **259** (113.9 mg, 76%) as a yellow solid; mp: 187-189 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.27 (d, *J* = 9.0 Hz, 2H), 8.00 (d, *J* = 9.0 Hz, 2H), 7.56 – 7.49 (m, 2H), 7.39 – 7.27 (m, 6H), 7.20 – 7.15 (m, 4H), 7.02 – 6.97 (m, 2H), 4.66 (s, 1H), 3.52 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 163.9 (C), 150.3 (C), 146.9 (C), 140.7 (C), 140.5 (C), 139.8 (C), 137.5 (C), 129.8 (2 × CH), 129.7 (2 × CH), 129.6 (2 × CH), 128.2 (CH), 128.0 (CH), 127.8 (3 × CH), 127.6 (2 × CH), 124.9 (CH), 124.0 (CH), 123.8 (2 × CH), 118.3 (C),

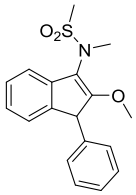
118.1 (CH), 58.4 (CH), 51.6 (CH_3); IR: ν_{max} (cm^{-1}) 3100, 3071, 3029, 2945, 2859, 1607, 1533, 1345, 1321, 1154, 696; HRMS (ES) *m/z* calculated for $C_{28}H_{23}N_2O_5S$ $(M+H)^+$ 499.1328 found 499.1315.

***N-Benzyl-N-(2-methoxy-1-phenyl-1H-inden-3-yl)methanesulfonamide* 260**



Prepared according to **GP13** from ynamide **252** (81.1 mg, 0.2 mmol), stirring for 3 hours. Recrystallisation [hexane:CH_2Cl_2] gave the indene **260** (62.5 mg, 77%) as a white solid; mp: 198-199 °C; ^{1}H-NMR (400 MHz, DMSO, 110 °C): δ: 7.38 (d, *J* = 7.3 Hz, 2H), 7.32 – 7.07 (m, 8H), 7.00 (d, *J* = 5.0 Hz, 2H), 6.95 – 6.85 (m, 2H), 4.85 (s, 1H), 4.83 (d, *J* = 14.3 Hz, 1H), 4.77 (d, *J* = 14.3 Hz, 1H), 3.60 (s, 3H), 3.14 (s, 3H); ^{13}C-NMR (101 MHz, DMSO, 110 °C) δ: 162.6 (C), 140.5 (C), 139.3 (C), 137.4 (C), 136.1 (C), 128.2 (2 × CH), 128.0 (2 × CH), 127.5 (3 × CH), 126.9 (3 × CH), 126.4 (CH), 126.0 (CH), 123.0 (CH), 122.2 (CH), 117.5 (CH_2), 115.6 (C), 57.5 (CH), 51.8 (CH_3), 49.8 (CH_3); IR: ν_{max} (cm^{-1}) 3032, 2947, 2932, 1620, 1458, 1338, 1320, 1159, 1148, 759; HRMS (ES) *m/z* calculated for $C_{24}H_{23}NO_3S$ $(M+H)^+$ 405.1399 found 405.1382.

***N-(2-Methoxy-1-phenyl-1H-inden-3-yl)-N-methylmethanesulfonamide* 261**

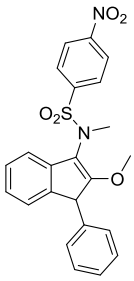


Prepared according to **GP13** from ynamide **253** (65.8 mg, 0.2 mmol), stirring for 24 hours. Purification by flash column chromatography [hexane:EtOAc (85:15)] gave the indene **261** (15.1 mg, 23%) as a white solid; mp: 180-182 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.35 – 7.17 (m, 7H), 7.03 – 6.99 (m, 2H), 4.64 (s, 1H), 3.78 (s, 3H), 3.33 (s, 3H), 3.04 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 162.2 (C), 140.5 (C), 139.6 (C), 137.5 (C), 129.2 (2 × CH), 127.6 (2 × CH), 127.4 (CH), 127.3 (CH), 124.3 (CH), 123.4 (CH), 118.0 (CH), 117.9 (C), 58.4 (CH), 51.5 (CH_3), 38.1 (CH_3), 36.9 (CH_3); IR: ν_{max} (cm^{-1}) 3024, 2952, 2857, 1619, 1452, 1330, 1318, 1255,

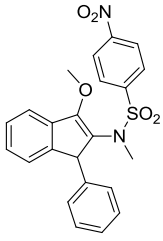
1230, 1153, 1133, 956, 854; HRMS (ES) *m/z* calculated for $C_{18}H_{19}NO_3SNa$ $(M+Na)^+$ 352.0993 found 352.1002.

***N-(2-methoxy-1-phenyl-1H-inden-3-yl)-N-methyl-4-nitrobenzenesulfonamide* 263 and *N-(3-methoxy-1-phenyl-1H-inden-2-yl)-N-methyl-4-nitrobenzenesulfonamide* 264**

Prepared according to **GP13** from ynamide **254** (76.8 mg, 0.18 mmol), stirring for 24 hours. Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the indenes **263** and **264**.



263: Further purification was necessary by recrystallisation [hexane:CH_2Cl_2] to give **263** (22.2 mg, 29%) as a yellow solid; mp: 68-70 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 7.1 Hz, 2H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.19 – 7.08 (m, 3H), 7.00 (d, *J* = 4.2 Hz, 2H), 6.90 (br. s, 1H), 4.57 (s, 1H), 3.51 (broad s, 3H), 3.32 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 163.4 (C), 150.4 (C), 145.4 (C), 140.2 (C), 139.7 (C), 137.5 (C), 129.6 (2 × CH), 129.4 (2 × CH), 128.0 (3 × CH), 127.5 (CH), 124.7 (CH), 124.2 (2 × CH), 123.8 (CH), 118.3 (CH), 117.0 (C), 58.5 (CH), 51.9 (CH_3), 37.6 (CH_3); IR: ν_{max} (cm^{-1}) 3105, 3072, 3026, 2945, 1622, 1606, 1527, 1348, 1318, 1161, 849; HRMS (ES) *m/z* calculated for $C_{23}H_{20}N_2O_5SNa$ $(M+Na)^+$ 459.0991 found 459.1000.

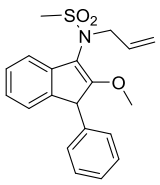


264: (17.6 mg, 23%); Yellow solid; mp: 121-123 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 8.9 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 2H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.27 – 7.16 (m, 4H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.86 (dd, *J* = 7.5, 1.9 Hz, 2H), 4.66 (s, 1H), 3.88 (s, 3H), 2.90 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 153.6 (C), 150.3 (C), 145.4 (C), 144.9 (C), 138.9 (C), 137.8 (C), 129.0 (4 × CH), 128.7 (2 × CH), 127.7 (2 × CH),

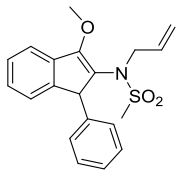
127.4 (CH), 124.8 (CH), 124.4 (2 × CH), 124.3 (C), 120.0 (CH), 58.9 (CH), 53.6 (CH_3), 39.3 (CH_3); IR: ν_{max} (cm^{-1}) 3111, 1988, 1954, 2902, 1628, 1607, 1537, 1346, 1067, 736; HRMS (ES) *m/z* calculated for $C_{23}H_{21}N_2O_5S$ $(M+H)^+$ 437.1171 found 437.1158.

N-Allyl-N-(2-methoxy-1-phenyl-1H-inden-3-yl)methanesulfonamide **265** **and** ***N-allyl-N-(3-methoxy-1-phenyl-1H-inden-2-yl)methanesulfonamide*** **266**

Prepared according to **GP13** from ynamide **255** (71.1 mg, 0.2 mmol) stirring for 1 hour. Purification by flash column chromatography [hexane:EtOAc (85:15) then hexane:EtOAc (70:30)] gave the indenes **265** and **266**.



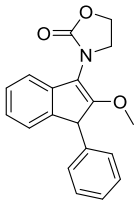
265: (52.7 mg, 74%); White solid; mp: 156-158 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.34-7.18 (m, 7H), 7.03-6.97 (m, 2H), 5.95 (ddt, *J* = 16.5, 10.0, 6.5 Hz 1H), 5.28 (d, *J* = 16.5 Hz, 1H), 5.17 (d, *J* = 10.0 Hz, 1H), 4.68 (s, 1H), 4.29 (d, *J* = 6.5 Hz, 2H), 3.73 (s, 3H), 3.06 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 162.9 (C), 141.2 (C), 139.8 (C), 137.6 (C), 133.6 (CH), 129.3 (2 × CH), 127.8 (2 × CH), 127.6 (CH), 127.5 (CH), 124.4 (CH), 123.3 (CH), 118.8 (CH_2), 118.3 (CH), 116.4 (C), 58.5 (CH_3), 52.3 (CH_2), 51.5 (CH), 39.8 (CH_3); IR: ν_{max} (cm^{-1}) 2986, 2951, 2926, 2858, 1602, 1495, 1451, 1145; HRMS (ES) *m/z* calculated for $C_{20}H_{21}NO_3NaS$ $(M+Na)^+$ $C_{20}H_{21}NO_3NaS$ 378.1140 found 378.1145.



266: (6.4 mg, 9%); Clear oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.6 Hz, 1H), 7.32 (td, *J* = 7.8, 0.9 Hz, 1H), 7.29 – 7.19 (m, 4H), 7.14 – 7.09 (m, 3H), 5.45 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 5.10 (dd, *J* = 17.0, 1.2 Hz, 1H), 5.02 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.67 (s, 1H), 4.16 (s, 3H), 3.96 (dd, *J* = 6.5, 1.2 Hz, 2H), 2.54 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 153.2 (C), 144.3 (C), 138.6 (C), 138.1 (C), 133.1 (CH), 129.3 (2 × CH), 128.7 (2 × CH),

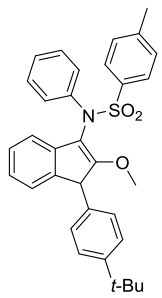
127.4 (CH), 126.9 (2 × CH), 124.4 (CH), 123.0 (C), 119.5 (CH), 118.9 (CH_2), 58.6 (CH_3), 53.3 (CH_2), 53.1 (CH), 39.7 (CH_3); IR: ν_{max} (cm^{-1}) 3070, 3025, 2992, 2945, 2876, 2848, 1624, 1604, 1585, 1147, 1079; HRMS (ES) *m/z* calculated for $C_{20}H_{21}NO_3NaS$ $(M+Na)^+$ 378.1140 found 378.1137.

***3-(2-Methoxy-1-phenyl-1H-inden-3-yl)oxazolidin-2-one* 267**



Prepared according to **GP13** from ynamide **256** (92.2 mg, 0.3 mmol), stirring for 2 hours. Purification by flash column chromatography [toluene:EtOAc (95:5)] gave the indene **276** (71.8 mg, 78%) as white needles; mp: 175-177 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.12 (m, 7H), 7.05 – 7.00 (m, 2H), 4.65 (s, 1H), 4.60 – 4.52 (m, 2H), 4.09 – 4.00 (m, 2H), 3.76 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 160.5 (C), 156.7 (C), 139.7 (C), 139.3 (C), 137.4 (C), 129.1 (2 × CH), 127.8 (2 × CH), 127.4 (CH), 127.2 (CH), 124.3 (CH), 123.5 (CH), 117.5 (CH), 113.8 (C), 62.7 (CH_2), 58.3 (CH_3), 51.9 (CH), 46.2 (CH_2); IR: ν_{max} (cm^{-1}) 3057, 3005, 2948, 2923, 2855, 1740, 1641, 1465, 1412, 1325, 1106, 1033, 754; HRMS (ES) *m/z* calculated for $C_{19}H_{17}NO_3Na$ $(M+Na)^+$ 330.1106 found 330.1111.

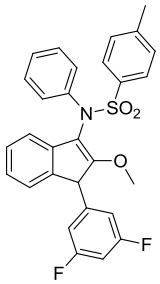
***N-(1-(4-(t-Butyl)phenyl)-2-methoxy-1H-inden-3-yl)-4-methyl-N-phenylbenzenesulfonamide* 283**



Prepared according to **GP13** from ynamide **278** (104.7 mg, 0.2 mmol), stirring for 30 minutes. Purification by flash column chromatography [hexane:Et_2O (95:5) then hexane:Et_2O (90:10)] gave the indene **283** (83.2 mg, 79%) as a white solid; mp: 174-176 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.34 – 7.27 (m, 4H), 7.25 – 7.17 (m, 3H), 7.17 – 7.05 (m, 3H), 7.04 – 6.93 (m, 3H), 4.63 (s, 1H), 3.65 (s, 3H), 2.41 (s, 3H), 1.28 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 164.4 (C), 150.5 (C), 143.7 (C), 141.4 (C), 141.3 (C), 139.9 (C), 138.4 (C), 134.7 (C), 129.5 (2 × CH), 129.4 (2 ×

CH), 128.5 (2 × CH), 127.6 (2 × CH), 127.3 (CH), 126.8 (CH), 126.4 (CH), 126.1 (2 × CH), 124.3 (2 × CH), 123.7 (CH), 118.4 (CH), 117.7 (C), 58.5 (CH_3), 51.5 (CH), 34.8 (C), 31.7 (3 × CH_3), 21.9 (CH_3); IR: ν_{max} (cm^{-1}) 3049, 3025, 2948, 2912, 2852, 1621, 1489, 1460, 1348, 1332, 1161, 1131, 1094, 1053, 760; HRMS (ES) *m/z* calculated for $C_{33}H_{33}NO_3SNa$ $(M+Na)^+$ 546.2079 found 546.2100.

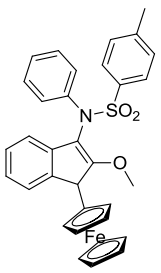
***N-(1-(3,5-Difluorophenyl)-2-methoxy-1H-inden-3-yl)-4-methyl-N-phenylbenzenesulfonamide* 284**



Prepared according to **GP13** from ynamide **279** (100.7 mg, 0.2 mmol), stirring for 30 minutes. Recrystallisation [hexane:CH_2Cl_2] gave the indene **284** (62.1 mg, 62%) as a white solid; mp: 185-187 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.08 (m, 6H), 7.04 – 6.94 (m, 3H), 6.80 – 6.65 (m, 3H), 4.60 (s, 1H), 3.70 (s, 3H), 2.41 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 163.2 (dd, $J_{C\text{-}F}$ = 249.4, 12.8 Hz, 2 × C), 163.0 (C), 144.0 (C), 142.1 (t, $J_{C\text{-}F}$ = 9.0 Hz, C), 141.3 (C), 141.2 (C), 138.4 (C), 138.1 (C), 129.6 (4 × CH), 128.4 (2 × CH), 127.9 (CH), 126.9 (CH), 125.8 (2 × CH), 124.8 (CH), 123.6 (CH), 119.0 (CH), 118.3 (C), 111.2 (d, $J_{C\text{-}F}$ = 25.5 Hz, 2 × CH), 103.4 (t, $J_{C\text{-}F}$ = 25.3 Hz, CH), 58.7 (CH), 51.5 (CH_3), 21.90 (CH_3); IR: ν_{max} (cm^{-1}) 3082, 3055, 3019, 2945, 2855, 1622, 1595, 1491, 1464, 1449, 1330, 1156, 1123, 1046, 764; HRMS (ES) *m/z* calculated for $C_{29}H_{23}NO_3F_2NaS$ $(M+Na)^+$ 526.1264 found 526.1270.

***N-(2-Methoxy-1-ferrocene-1H-inden-3-yl)-4-methyl-N-phenylbenzenesulfonamide* 285**

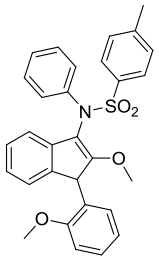
Prepared according to **GP13** from ynamide **280** (115.1 mg, 0.2 mmol), stirring for 3 hours. Purification by flash column chromatography [hexane:EtOAc (90:10) then hexane:Et_2O (90:10)] gave the indene **285** (58.4 mg, 51%) as a viscous orange oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.51 (d,



J = 8.3 Hz, 2H), 7.45 – 7.38 (m, 2H), 7.32 – 7.09 (m, 9H), 4.86 (s, 1H), 4.11 (d, *J* = 1.3 Hz, 1H), 4.02 (app. t, *J* = 2.0 Hz, 2H), 3.95-3.93 (m, 1H), 3.87 (s, 3H), 3.47 (s, 5H), 2.33 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 147.8 (C), 144.0 (C), 142.3 (2 × C), 140.1 (C), 137.0 (C), 129.5 (2 × CH), 129.4 (2 × CH), 128.6 (CH), 128.5 (2 × CH), 128.1 (CH), 127.6 (CH), 126.7 (2 × CH), 122.8 (C), 121.7 (CH), 120.2 (CH), 89.9 (C), 68.7 (5 × CH), 67.8 (CH), 67.7 (CH), 67.1 (2 × CH), 60.0 (CH), 48.6 (CH_3), 21.9 (CH_3); IR: ν_{max} (cm^{-1}) 3059, 3014, 2943, 2923, 2842, 1695, 1590, 1489, 1353, 1158, 1091; HRMS (ES) *m/z* calculated for $C_{33}H_{29}NO_3SFe$ $(M+H)^+$ 575.1218 found 575.1199.

N-(2-Methoxy-1-(2-methoxyphenyl)-1H-inden-3-yl)-4-methyl-N-phenylbenzenesulfonamide

296

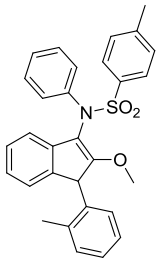


Prepared according to **GP13** from ynamide **292** (99.5 mg, 0.2 mmol), stirring for 5 hours. Purification by flash column chromatography [hexane:toluene:Et_2O (50:46:4)] then recrystallization [hexane:CH_2Cl_2] gave the indene **296** (39.8 mg, 40%) as a white solid; mp: 170-171 °C; ^{1}H-NMR (400 MHz, DMSO, 110 °C): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.51 – 7.46 (m, 2H), 7.39 - 7.32 (m, 4H), 7.28 – 7.19 (m, 2H), 7.14 - 7.04 (m, 3H), 7.01 – 6.92 (m, 2H), 6.86 – 6.80 (m, 2H), 5.27 (s, 1H), 3.85 (s, 3H), 3.52 (s, 3H), 2.98 (s, 3H); ^{13}C-NMR (101 MHz, DMSO, 110 °C): δ 163.7 (C), 156.8 (C), 143.0 (2 × C), 140.5 (C), 140.4 (C), 139.2 (C), 137.2 (C), 128.7 (2 × CH), 128.4 (2 × CH), 128.0 (CH), 127.1 (2 × CH), 126.0 (CH), 125.7 (CH), 125.3 (CH), 124.8 (2 × CH), 123.1 (CH), 122.1 (CH), 120.4 (CH), 116.9 (CH), 111.7 (CH), 57.1 (CH_3), 55.5 (CH_3), 43.8 (CH), 20.3 (CH_3); In this case, it was not possible to observe the N-bound quaternary carbon of the indene core; IR: ν_{max} (cm^{-1}) 3031, 2952, 2836, 1630, 1595, 1492, 1462,

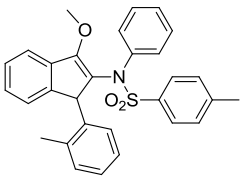
1344, 1244, 1162, 1048; HRMS (ES) *m/z* calculated for $C_{30}H_{28}NO_4S$ $(M+H)^+$ 498.1739 found 498.1757.

***N-(2-Methoxy-1-(o-tolyl)-1H-inden-3-yl)-4-methyl-N-phenylbenzenesulfonamide* 297 and *N-(3-methoxy-1-(o-tolyl)-1H-inden-2-yl)-4-methyl-N-phenylbenzenesulfonamide* 298**

Prepared according to **GP13** from ynamide **293** (96.3 mg, 0.2 mmol), stirring for 16 hours. Purification by flash column chromatography [hexane:EtOAc (95:5) then hexane:EtOAc (85:15)] gave the indenes **297** and **298**.



297: (35.7 mg, 37%); White solid; mp: 208-210 °C; Broadening and splitting of some signals due to restricted rotation, some nuclei therefore have 2 resonances assigned to them; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.78 - 7.72 (m, 2H) 7.59 – 7.41 (m, 2H), 7.37 – 6.86 (m, 13H), 4.97 and 4.68 (s, 1H), 3.62 and 3.57 (s, 3H), 2.66 (s, 3H), 2.41 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ: 164.4 and 163.3 (C), 143.4 (C), 141.3 (C). 141.1 (C), 139.7 (C), 138.1 (C), 136.0, (C) 135.5 (C), 132.5 and 130.8 (CH), 131.6 and 129.1 (4 × CH), 128.13 (2 × CH), 128.1 and 127.7 (CH), 127.2 (CH), 127.1 and 126.9 and 126.7 (2 × CH), 126.5 and 126.3 (CH), 126.1 and 125.8 (CH), 124.0 (CH), 122.9 (CH), 118.3 and 118.1 (CH), 117.4 (C), 58.66 and 57.77 (CH_3), 53.8 and 47.3 (CH), 21.6 (CH_3), 20.1 (CH_3); IR: ν_{max} (cm^{-1}) 3062, 3019, 2947, 2855, 1623, 1592, 1487, 1461, 1334, 1165, 1053, 963; HRMS (ES) *m/z* calculated for $C_{30}H_{28}NO_3S$ $(M+H)^+$ 482.1790 found 482.1795.

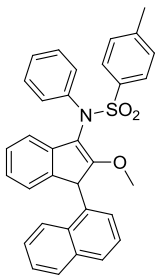


298: (26.7 mg, 28%); White solid; mp: 183-185 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.3 Hz, 2H) 7.50 – 7.45 (m, 2H), 7.42 (d, *J* = 7.5 Hz, 1H),

7.33 – 7.15 (m, 8H), 7.13 – 7.02 (m, 3H), 6.98 (dd, *J* = 7.3, 0.7 Hz, 1H), 5.55 (s, 1H), 3.64 (s, 3H), 2.47 (s, 3H), 2.38 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 148.3 (C), 143.9 (C), 142.7 (C), 141.6 (C), 139.9 (C), 139.5 (C), 137.1 (C), 135.4 (C), 130.6 (CH), 129.5 (2 × CH), 129.3 (2 × CH), 128.6 (2 × CH), 128.5 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 127.1 (CH), 126.8 (CH), 126.6 (2 × CH), 121.3 (CH), 120.5 (C), 120.3 (CH), 58.44 (CH), 52.3 (CH_3), 21.9 (CH_3), 20.1 (CH_3); IR: ν_{max} (cm^{-1}) 3068, 2988, 2973, 2902, 1693, 1587, 1349, 1224, 1166, 1066, 1054; HRMS (ES) *m/z* calculated for $C_{30}H_{27}NO_3NaS$ $(M+Na)^+$ 504.1609 found 504.1610.

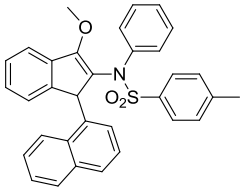
N-(2-Methoxy-1-(naphthalen-1-yl)-1H-inden-3-yl)-4-methyl-N-phenylbenzenesulfonamide **299 and** ***N-(3-methoxy-1-(naphthalen-1-yl)-1H-inden-2-yl)-4-methyl-N-phenylbenzenesulfonamide*** **300**

Prepared according to **GP13** from ynamide **294** (103.5 mg, 0.2 mmol), stirring for 3 hours. Purification by flash column chromatography [toluene:hexane:Et_2O (49:49:2) then hexane:EtOAc (80:20)] gave the indenes **299** and **300**.



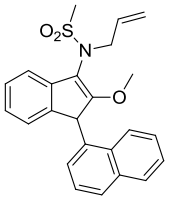
299: (52.0 mg, 50%); White solid; mp: 202-204 °C; Broadening and splitting of some signals due to restricted rotation, some nuclei therefore have 2 resonances assigned to them; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.33 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.73 – 7.60 (m, 3H), 7.60 – 7.50 (m, 1H), 7.50 – 7.30 (m, 3H), 7.29 - 6.66 (m, 11H), 5.45 and 4.86 (s, 1H), 3.40 and 3.37 (s, 3H), 2.28 and 2.26 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 164.2 (C), 143.8 and 143.6 (C), 141.4 and 141.2 (C), 140.0 (C), 138.9 (C), 138.6 and 138.4 (C), 134.8 and 134.5 (C), 133.9 and 133.7 (C), 132.3 and 131.8 (C), 129.7 (CH), 129.5, 129.1 (4 × CH), 128.7 and 128.5 (2 × CH), 128.4 (CH), 128.1 (CH), 127.7 and 127.5 (CH), 127.3

and 127.1 (1 × CH), 127.0 (CH), 126.9 (CH), 126.6 and 126.4 (2 × CH), 126.1 and 125.7 (CH), 124.5 and 124.3 (CH), 123.4 (2 × CH), 123.3 and 123.1 (CH), 117.4 and 117.3 (C), 58.9 and 58.4 (CH), 46.3 (CH_3), 21.9 (CH_3); IR: ν_{max} (cm^{-1}) 3058, 3022, 2948, 2855, 1632, 1594, 1491, 1462, 1344, 1328, 1161, 1092, 1050; HRMS (ES) *m/z* calculated for $C_{33}H_{28}NO_3S$ $(M+H)^+$ 518.1790 found 518.1808.



300: (37.6 mg, 36%); White solid; mp: 172-173 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.62 – 7.57 (m, 1H), 7.57 – 7.50 (m, 4H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.39 – 7.30 (m, 3H), 7.27 – 7.17 (m, 4H), 7.08-6.96 (m, 2H), 6.11 (s, 1H), 3.72 (s, 3H), 2.39 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 148.2 (C), 143.8 (C), 142.1 (2 × C), 139.8 (C), 136.8 (2 × C), 134.1 (C), 131.5 (C), 129.3 (2 × CH), 129.2 (2 × CH), 129.0 (CH), 128.5 (CH), 128.4 (2 × CH), 127.9 (CH), 127.5 (2 × CH), 126.5 (2 × CH), 126.3 (CH), 126.1 (CH), 125.8 (CH), 124.3 (CH), 123.7 (CH), 121.2 (CH), 120.2 (CH), 119.3 (C), 58.5 (CH), 52.1 (CH_3), 21.7 (CH_3); IR: ν_{max} (cm^{-1}) 3062, 2953, 2849, 1701, 1353, 1225, 1160, 1092, 937, 750; HRMS (ES) *m/z* calculated for $C_{33}H_{28}NO_3S$ $(M+H)^+$ 518.1790 found 518.1788.

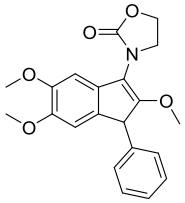
***N-Allyl-N-(2-methoxy-1-(naphthalen-1-yl)-1H-inden-3-yl)methanesulfonamide* 301**



Prepared according to **GP13** from ynamide **295** (81.1 mg, 0.2 mmol), stirring for 1 hour. Purification by flash column chromatography [hexane:EtOAc (90:10) then hexane:EtOAc (80:20)] gave the indene **301** (66.8 mg, 82%) as a white solid; mp: 166-168 °C; Broadening and splitting of some signals due to restricted rotation, some nuclei therefore have 2 resonances assigned to them; ^{1}H-NMR (400 MHz, DMSO, 70 °C): δ

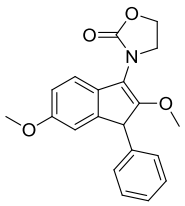
8.72 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.97 – 7.78 (m, 2H), 7.73 (app. t, *J* = 7.4 Hz, 1H), 7.67 – 7.51 (m, 1H), 7.44 – 7.03 (m, 3H), 7.01 – 6.79 (m, 2H), 5.98 (ddt, *J* = 16.6, 10.2, 6.3 Hz, 1H), 5.93 (s, 1H), 5.40-5.30 (m, 1H), 5.20 (d, *J* = 10.2 Hz, 1H), 4.29 (d, *J* = 6.3 Hz, 2H), 3.67, 3.62 (2 × s, 3H), 3.17, 3.11 (2 × s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 162.9 (C), 140.9 (C), 139.8 and 138.6 (C), 134.5 and 134.2 (C), 133.7 (CH), 133.3 and 133.1 (C), 131.5 and 130.1 (C), 129.4 and 128.9 (CH), 128.5 and 127.9 (CH), 127.6 and 127.4 (CH), 126.7 (CH), 126.1 (CH), 125.9 and 125.4 (CH), 124.4 and 124.1 (CH), 123.4 (CH), 123.0 (CH), 122.8 and 122.7 (CH), 118.7 and 118.5 (CH_2), 118.3 (CH), 116.7 (C), 58.8 and 58.3 (CH), 52.3 and 52.2 (CH_2), 45.8 (CH_3), 39.8 (CH_3); IR: ν_{max} (cm^{-1}) 3014, 2939, 2852, 1622, 1463, 1334, 1319, 1148, 760; HRMS (ES) *m/z* calculated for $C_{24}H_{23}NO_3NaS$ $(M+Na)^+$ 428.1296 found 428. 1294.

3-(2,5,6-Trimethoxy-1-phenyl-1H-inden-3-yl)oxazolidin-2-one **314**



Prepared according to **GP13** from ynamide **311** (73.5 mg, 0.2 mmol), stirring for 1 hour. Purification by flash column chromatography [hexane:EtOAc (50:50) then hexane:EtOAc (40:60)] then recrystallisation [EtOH] gave the indene **314** (55.1 mg, 75%) as a white solid; mp: 164-166 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.23 (m, 3H), 7.23 – 7.17 (m, 2H), 6.76 (s, 1H), 6.62 (s, 1H), 4.57 (t, *J* = 8.1 Hz, 2H), 4.57 (s, 1H), 4.10 – 4.01 (m, 2H), 3.89 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 159.2 (C), 159.1 (C), 156.8 (C), 149.0 (C), 146.9 (C), 137.9 (C), 132.0 (C), 129.2 (2 × CH), 128.0 (2 × CH), 127.5 (CH), 114.3 (C), 108.7 (CH), 102.6 (CH), 62.9 (CH_2), 58.6 (CH), 56.6 (CH_3), 56.4 (CH_3), 51.6 (CH_3), 46.3 (CH_2); IR: ν_{max} (cm^{-1}) 2954, 2923, 2854, 1747, 1716, 1640, 1493, 1454, 1406, 1302, 1210, 1086, 1031; HRMS (ES) *m/z* calculated for $C_{21}H_{21}NO_5Na$ $(M+Na)^+$ 390.1317 found 390.1320.

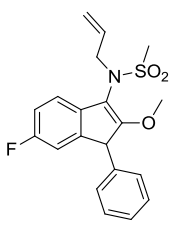
3-(2,6-Dimethoxy-1-phenyl-1H-inden-3-yl)oxazolidin-2-one **315**



Prepared according to **GP13** from ynamide **312** (27.9 mg, 0.08 mmol), stirring for 30 minutes. Purification by flash column chromatography [hexane:EtOAc (65:35)] gave the indene **315** (18.8 mg, 67%) as a white solid; mp: 150-152 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.18 (m, 5H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.76 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), 4.61 (s, 1H), 4.59 – 4.51 (m, 2H), 4.09 – 4.01 (m, 2H), 3.72 (s, 3H), 3.70 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.6 (C), 157.9 (C), 157.0 (C), 141.9 (C), 138.0 (C), 132.2 (C), 129.4 (2 × CH), 128.2 (2 × CH), 127.7 (CH), 118.6 (CH), 114.3 (C), 112.3 (CH), 111.5 (CH), 63.1 (CH_2), 58.7 (CH), 55.9 (CH_3), 52.1 (CH_3), 46.5 (CH_2); IR: ν_{max} (cm^{-1}) 2944, 2834, 1743, 1649, 1479, 1453, 1416, 1107, 1025; HRMS (ES) *m/z* calculated for $C_{20}H_{19}NO_4Na$ $(M+Na)^+$ 360.1212 found 360.1210.

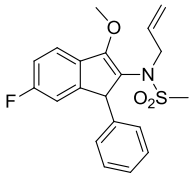
N-Allyl-N-(6-fluoro-2-methoxy-1-phenyl-1H-inden-3-yl)methanesulfonamide **316** **and** ***N-allyl-N-(6-fluoro-3-methoxy-1-phenyl-1H-inden-2-yl)methanesulfonamide*** **317**

Prepared according to **GP13** from ynamide **315** (108.7 mg, 0.3 mmol), using 10 mol% (p-$CF_3C_6H_4)_3PAuNTf_2$ and stirring for 24 hours. Purification by flash column chromatography [hexane:EtOAc (87.5:12.5) then hexane:EtOAc (85:15)] gave the indenes **316** and **317**.



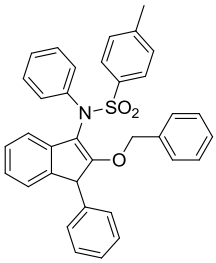
316: (70.7 mg, 65%); White solid; mp: 147-149 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.16 (m, 6H), 6.92 (ddd, *J* = 9.8, 8.6, 2.4 Hz, 1H), 6.70 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.92 (ddt, *J* = 17.3, 10.0, 6.3 Hz, 1H), 5.27 (d, *J* = 17.3 Hz, 1H), 5.17 (d, *J* = 10.0 Hz, 1H), 4.65 (s, 1H), 4.26 (d, *J* = 6.3 Hz, 2H), 3.71 (s, 3H), 3.05 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 161.8 (C), 161.2 (d, $J_{C\text{-}F}$ = 242.9 Hz, C), 141.3 (d, $J_{C\text{-}F}$ = 7.7 Hz, C), 136.8 (2 × C),

133.4 (CH), 129.3 (2 × CH), 127.7 (2 × CH), 127.6 (CH), 119.1 (d, $J_{C\text{-}F}$ = 8.0 Hz, CH), 118.8 (CH_2), 116.0 (C) 114.1 (d, $J_{C\text{-}F}$ = 22.6 Hz, CH), 111.2 (d, $J_{C\text{-}F}$ = 24.2 Hz, CH), 58.3 (CH), 52.1 (CH_2), 51.14 (CH_3), 39.42 (CH_3); IR: ν_{max} (cm^{-1}) 3064, 3034, 2957, 2927, 2861, 1623, 1601, 1478, 1478, 1329, 1318, 1037; HRMS (ES) *m/z* calculated for $C_{20}H_{20}NO_3FNaS$ $(M+Na)^+$ 396.1046 found 396.1052.



317: (13.9 mg, 13%); White solid; mp: 76-78 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 8.4, 5.0 Hz, 1H), 7.34 – 7.22 (m, 3H), 7.15 – 7.08 (m, 2H), 7.06 – 6.96 (m, 1H), 6.81 (dd, *J* = 8.4, 2.3 Hz, 1H), 5.47 (ddt, *J* = 17.0, 10.0, 6.7 Hz, 1H), 5.12 (dd, *J* = 17.0, 1.3 Hz, 1H), 5.05 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.62 (s, 1H), 4.15 (s, 3H), 3.95 (d, *J* = 6.7 Hz, 2H), 2.47 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) :δ 162.9 (d, $J_{C\text{-}F}$ = 245.9 Hz, C), 153.0 (C), 146.8 (d, $J_{C\text{-}F}$ = 8.3 Hz, C), 138.4 (C), 134.3 (C), 133.3 (CH), 129.6 (2 × CH), 129.2 (2 × CH), 128.0 (CH), 122.2 (C), 120.9 (d, $J_{C\text{-}F}$ = 8.5 Hz, CH), 119.5 (CH_2), 114.4 (d, $J_{C\text{-}F}$ = 22.9 Hz, CH), 112.4 (d, $J_{C\text{-}F}$ = 23.4 Hz, CH), 58.9 (CH), 53.7 (CH_2), 53.4 (CH_3), 40.1 (CH_3); IR: ν_{max} (cm^{-1}) 3034, 2951, 2926, 3034, 1630, 1609, 1484, 1361, 1333, 1149, 1127, 964; HRMS (ES) *m/z* calculated for $C_{20}H_{21}NO_3FS$ $(M+H)^+$ 374.1226 found 374.1227.

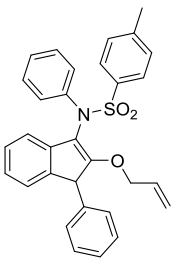
***N-(2-(Benzyloxy)-1-phenyl-1H-inden-3-yl)-4-methyl-N-phenylbenzenesulfonamide* 328**



Prepared according to **GP13** from ynamide **321** (108.7 mg, 0.2 mmol), stirring for 3 hours. Purification by flash column chromatography [hexane:Et_2O (9:1)] then recrystallisation [hexane:CH_2Cl_2] gave the indene **328** (58.7 mg, 54%) as a white solid; mp: 176-178 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 7.5 Hz, 2H), 7.38 – 7.11 (m, 13H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.01 – 6.95 (m, 4H), 4.90 (d, *J* = 11.8 Hz, 1H), 4.84 (d, *J* = 11.8 Hz, 1H), 4.66 (s, 1H), 2.33 (s, 3H); ^{13}C-NMR (101 MHz,

$CDCl_3$) δ 163.0 (C), 143.6 (C), 141.3 (C), 141.2 (C), 139.9 (C), 138.2 (C), 138.0 (C), 136.5 (C), 129.6 (2 × CH), 129.5 (2 × CH), 129.4 (2 × CH), 128.7 (2 × CH), 128.5 (2 × CH), 128.4 (CH), 128.2 (2 × CH), 127.8 (3 × CH), 127.6 (CH), 126.9 (CH), 126.5 (2 × CH), 124.6 (CH), 123.6 (CH), 119.1 (C), 118.7 (CH), 72.6 (CH_2), 52.1 (CH), 21.9 (CH_3); IR: ν_{max} (cm^{-1}) 2981, 2970, 2901, 1624, 1596, 1329, 1224, 1161, 1092, 1033; HRMS (ES) *m/z* calculated for $C_{35}H_{30}NO_3S$ $(M+H)^+$ 544.1946 found 544.1941.

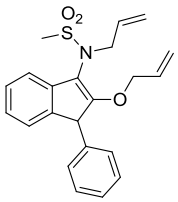
***N-(2-(Allyloxy)-1-phenyl-1H-inden-3-yl)-4-methyl-N-phenylbenzenesulfonamide* 329**



Prepared according to **GP13** from ynamide **322** (98.7 mg, 0.2 mmol), stirring for 6 hours. Recrystallisation [hexane:CH_2Cl_2] gave the indene **XX** (63.4 mg, 64%) as a white solid; mp: 176-178 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.59 – 7.48 (m, 12H), 7.34 – 7.13 (m, 2H), 6.98 (dd, *J* = 3.5, 2.5 Hz, 2H), 5.63 (ddt, *J* = 17.5, 10.5, 5.4 Hz, 1H), 5.12-5.09 (m, 1H), 5.07-5.05 (m, 1H), 4.65 (s, 1H), 4.35 (d, *J* = 5.4 Hz, 2H), 2.40 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 162.8 (C), 143.4 (C), 141.0 (2 × C), 139.6 (C), 138.1 (C), 137.7 (C), 132.8 (CH), 129.2 (4 × CH), 129.1 (2 × CH), 128.2 (2 × CH), 127.8 (2 × CH), 127.4 (CH), 127.2 (CH), 126.7 (CH), 126.4 (2 × CH), 124.2 (CH), 123.3 (CH), 118.5 (C), 118.3 (CH), 117.7 (CH_2), 71.2 (CH_2), 51.7 (CH), 21.6 (CH_3); IR: ν_{max} (cm^{-1}) 3061, 3043, 3025, 2917, 1621, 1596, 1489, 1455, 1325, 1160, 1126, 1090, 757, 694; HRMS (ES) *m/z* calculated for $C_{31}H_{27}NO_3SNa$ $(M+Na)^+$ 516.1609 found 516.1592.

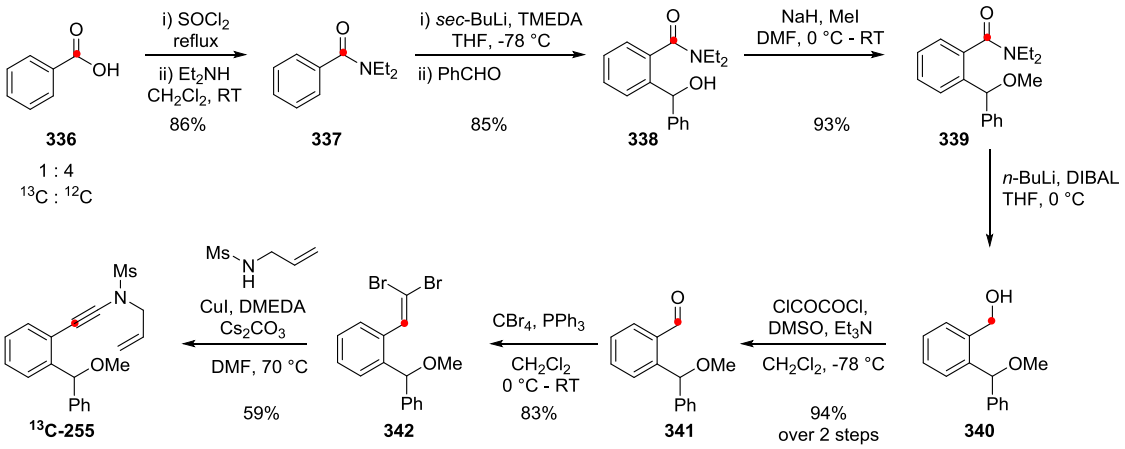
***N-Allyl-N-(2-(allyloxy)-1-phenyl-1H-inden-3-yl)methanesulfonamide* 330**

Prepared according to **GP13** from ynamide **324** (114.4 mg, 0.3 mmol), stirring for 2 hours. Purification by flash column chromatography [hexane:EtOAc (90:10) then hexane:EtOAc (85:15)]

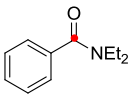


gave the indene **330** (80.8 mg, 71%) as a white solid; mp 112-114 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.11 (m, 7H), 6.97 – 6.87 (m, 2H), 5.87 (ddt, *J* = 17.2, 10.0, 6.4 Hz, 1H), 5.74 (ddt, *J* = 16.2, 10.6, 5.5 Hz, 1H), 5.28 (d, *J* = 17.2 Hz, 1H) 5.19 (app. ddd, *J* = 17.2, 3.0, 1.5 Hz, 1H), 5.13 (app. ddd, *J* = 10.6, 2.4, 1.2 Hz, 1H), 5.08 (d, *J* = 10.0 Hz, 1H), 4.62 (s, 1H), 4.35 (m, 2H), 4.23 (d, *J* = 6.4 Hz, 2H), 3.00 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 161.7 (C), 141.0 (C), 139.7 (C), 137.4 (C), 133.6 (CH), 132.8 (CH), 129.3 (2 × CH), 127.7 (2 × CH), 127.5 (CH), 127.4 (CH), 124.4 (CH), 123.1 (CH), 118.6 (C), 118.4 (2 × CH_2), 118.3 (CH), 71.4 (CH_2), 52.1 (CH_2), 51.5 (CH), 39.8 (CH_3); IR: ν_{max} (cm^{-1}) 3084, 2986, 2921, 1620, 1335, 1343, 1318, 1148; HRMS (ES) *m/z* calculated for $C_{22}H_{23}NO_3NaS$ $(M+Na)^+$ 404.1296 found 404.1283.

^{13}C-Labelling Study: Substrates Preparation



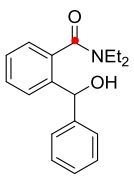
^{13}C-*N*,*N*-Diethylbenzamide 337



^{13}C-Enriched benzoic acid (1.25 g, 10.2 mmol, ^{13}C:^{12}C 1:4) was dissolved in thionyl chloride (5.0 mL, 2.0 M) and heated at reflux for 3 hours. The excess thionyl chloride

was removed under reduced pressure and the crude residue dissolved in CH_2Cl_2 (5.0 mL, 2.0 M). Diethylamine (2.0 mL, 19.4 mmol, 1.9 equiv.) in CH_2Cl_2 (7.5 mL) was added dropwise and the resulting solution was stirred for 16 hours at room temperature. The solution was diluted with CH_2Cl_2 (20 mL) and washed with a saturated $NaHCO_3$ solution (20 mL), 1 M HCl solution (20 mL) and water (20 mL). After drying over Na_2SO_4 and filtering, the solvent removed under reduced pressure to give the ^{13}C enriched amide **337** (1.55 g, 86% over two steps) as a brown liquid which immediately without further purification.

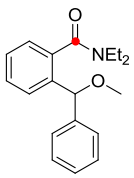
***^{13}C-N,N-Diethyl-2-(hydroxy(phenyl)methyl)benzamide* 338**



A solution of TMEDA (2.8 mL, 19.0 mmol, 2.4 equiv.) in THF (70 mL, 0.3 M) was cooled to -78 °C before the dropwise addition of *sec*-BuLi (1.4 M in cyclohexane, 13.5 mL, 19.0 mmol, 2.4 equiv.). After stirring at this temperature for 10 minutes, a solution of the ^{13}C-enriched amide **338** (1.40 g, 7.9 mmol, ^{13}C:^{12}C 1:4, 1.0 equiv.) in THF (70 mL) was added dropwise and the resulting solution stirred for a further 20 minutes. A solution of benzaldehyde (1.9 mL, 19.0 mmol, 2.4 equiv.) in THF (2 mL) was added dropwise and stirring continued for 3 hours at -78 °C. The reaction warmed to room temperature and a saturated solution of NH_4Cl (100 mL) was added slowly. The aqueous layer was extracted with Et_2O (2 × 75 mL), and washed with brine (75 mL) before drying over Na_2SO_4, filtering and removal of the solvent under reduced pressure. Purification by flash column chromatography [hexane:EtOAc (70:30)] gave the ^{13}C-enriched benzhydric alcohol **S35** (1.90 g, 85%) as pale yellow oil; ^1H-NMR (300 MHz, $CDCl_3$) δ: 7.63 – 7.12 (m, 9H), 5.92 and 5.72 (bs, 1H), 4.15 (bs, 1 H), 3.51 and 3.17 (bs, 2H), 2.91 and 2.41 (bs, 2H), 0.93 and 0.84 (bs, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: Resonances not

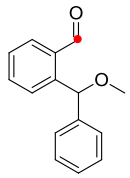
listed due to the complex spectra arising from restricted rotation of the amide; IR: ν_{max} (cm^{-1}) 3357, 3029, 2975, 2936, 2874, 2936, 1608, 1595, 1431; HRMS (ES) *m/z* calculated for $C_{17}{}^{13}CH_{21}NO_2Na$ $(M+Na)^+$ 306.1470 found 306.1478.

^{13}C-N,N-Diethyl-2-(methoxy(phenyl)methyl)benzamide **339**



^{13}C-enriched benzhydric alcohol **338** (1.80 g, 6.4 mmol, 1 equiv.) was dissolved in THF (32 mL, 0.2 M) and cooled to 0 °C with an ice bath. NaH (60% dispersion in mineral oil, 0.56 g, 14.0 mmol, 2.2 equiv.) was added in one portion and the resulting mixture stirred at 0 °C for 30 minutes. MeI (0.7 mL, 11.4 mmol, 1.8 equiv.) was added dropwise, the ice bath removed and the mixture was stirred at room temperature for 45 minutes. Saturated NH_4Cl solution (50 mL) was added and the aqueous layer was extracted with Et_2O (2 × 50 mL), and washed with brine (50 mL) before drying over Na_2SO_4, filtering and removal of the solvent under reduced pressure. Purification by flash column chromatography [hexane:EtOAc (80:20)] gave the ^{13}C-enriched methyl ether **339** (1.76 g, 93%) as a pale yellow solid; mp: 54-56 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.95 – 6.91 (m, 9H), 5.58 and 5.46 (bs, 1H), 3.93 – 3.09 (m, 3H), 3.35 (s, 3H), 2.51 and 2.21 (bs, 1H), 1.32 - 0.78 (m, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: Resonances not listed due to the complex spectra arising from restricted rotation of the amide; IR: ν_{max} (cm^{-1}) 2994, 2974, 2942, 2924, 2821, 1618, 1579, 1453, 1432, 1096; HRMS (ES) *m/z* calculated for $C_{18}{}^{13}CH_{21}NO_2Na$ $(M+Na)^+$ 320.1626 found 306.1617.

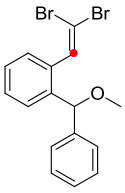
***^{13}C-2-(Methoxy(phenyl)methyl)benzaldehyde* 341**



n-BuLi (2.5 M in hexane, 10.6 mL, 26.9 mmol, 5.0 equiv.) was added dropwise to a solution of DIBAL (1.0 M in cyclohexane, 26.9 mL, 26.9 mmol, 5.0 equiv.) in THF (18 mL, 1.5 M) at 0 °C and the resulting solution stirred for 30 minutes. A solution of benzamide **339** (1.60 g, 5.4 mmol, 1.0 equiv.) in THF (18 mL, 1.5 M) was added dropwise and the mixture was allowed to warm to room temperature over 1.5 hours. 0.5 M solution (20 mL) was added carefully and the product extracted using Et_2O (2 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give the crude ^{13}C-benzyl alcohol **340**. A small sample (ca. 40 mg) was removed for analysis and the remaining material was used directly. DMSO (1.1 mL, 15.7 mmol, 3.0 equiv.) was added to a solution of oxalyl chloride (0.4 mL, 5.3 mmol, 1.0 equiv.) in CH_2Cl_2 (3.0 mL, 1.8 M) cooled to -78 °C. After stirring for 45 minutes at this temperature, the crude alcohol (1.20 g, 5.3 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL) was added and the resulting mixture stirred for a further 45 minutes. Et_3N (4.4 mL, 31.5 mmol, 6.0 equiv.) was added and stirring continued for 45 minutes. The mixture was allowed to warm to room temperature and water (ca. 20 mL) was added before extraction with Et_2O (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give the aldehyde **341** (1.14 g, 94% over two steps) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.23 (s, 1H, ^{13}C satellite peaks at 10.52 and 9.93, $J_{C\text{-}H}$ = 176.6 Hz), 7.84 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.73 – 7.57 (m, 2H), 7.47 (td, *J* = 7.5, 1.4 Hz, 1H), 7.41 – 7.23 (m, 5H), 6.17 (s, 1H), 3.40 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 192.7 (CH, ^{13}C-enriched signal), 143.9 (C), 141.1 (C), 133.9 (CH), 133.6 (C),

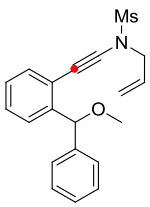
132.6 (CH), 128.5 (2 × CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 127.5 (2 × CH), 81.1 (CH), 57.2 (CH_3); IR: ν_{max} (cm^{-1}) 3064, 3030, 2986, 2932, 2901, 2822, 1694, 1597, 1451, 1085, 1075; HRMS (ES) *m/z* calculated for $C_{14}{}^{13}CH_{14}O_2Na$ $(M+Na)^+$ 249.2605 found 249.2611.

***^{13}C-1-(2,2-Dibromovinyl)-2-(methoxy(phenyl)methyl)benzene* 342**



CBr_4 (1.47 g, 4.4 mmol, 2.0 equiv.) and PPh_3 (2.32 g, 8.8 mmol, 4.0 equiv.) were combined in a flask which was evacuated and refilled (× 3). CH_2Cl_2 (15 mL, 0.2 M) was added and the resulting solution stirred for 10 minutes at room temperature. Aldehyde **S37** (0.50 g, 2.2 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) was added at 0 °C and stirred for 45 minutes, slowly warming to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in the minimum quantity of CH_2Cl_2. Hexane was added to the flask and quickly filtered through a pad of silica. This was repeated until all the contents had been transferred to the filter bed. The filter cake was washed with a hexane:Et_2O mixture (95:5, 200 mL) and the solvent removed to give the dibromoolefin **342** (0.70 g, 83%) as a yellow oil which was used immediately in the ynamide formation.

***^{13}C-N-Allyl-N-((2-(methoxy(phenyl)methyl)phenyl)ethynyl)methanesulfonamide* ^{13}C-255**

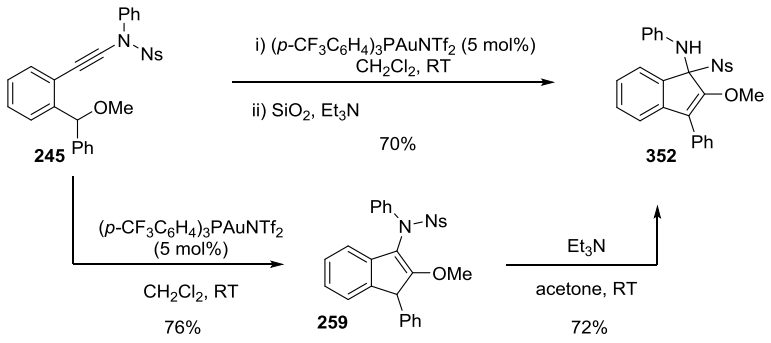


Cs_2CO_3 (1.1 g, 4.8 mmol, 4.0 equiv.) and CuI (27 mg, 0.1 mmol, 12 mol%) were combined in a flask which was evacuated and refilled with argon (× 3). A solution of dibromoolefin **342** (0.68 g, 1.8 mmol, 1.5 equiv.) and sulfonamide **249** (0.16 g, 1.2 mmol, 1.0 equiv.) in DMF (2.4 mL, 0.5 M) was added, followed by DMEDA (24 µL, 0.2 mmol, 19 mol%). The resulting solution was stirred at 70 °C for 14 hours. The reaction mixture was filtered through a short (ca. 1 cm) pad of silica, eluting with Et_2O (50 mL). The filtrate was

washed with water (2 × 30 mL), then brine (30 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography [hexane:EtOAc (8.5:1.5)] gave the ^{13}C-labelled ynamide (0.250 mg, 59%) as a yellow oil. Data matches that reported above for **255**.

Derivatisation on Indenes

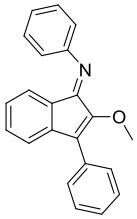
***2-Methoxy-1-((4-nitrophenyl)sulfonyl)-N,3-diphenyl-1H-inden-1-amine* 352**



Indene **259** (34.9 mg, 0.07 mmol, 1.0 equiv.) was dissolved in acetone (0.8 mL, 0.06 M) containing Et_3N (20 µL, 0.1 mmol, 2.0 equiv.) and the resulting solution was stirred for 1 hour at room temperature. The solvent was removed under reduced pressure and the crude solid was recrystallised [hexane:CH_2Cl_2] to give the C-sulfonylated amine **352** (25.3 mg, 72%) as a yellow solid; mp: 198-199 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.9 Hz, 2H), 7.88 (d, *J* = 8.9 Hz, 2H), 7.46 – 7.34 (m, 5H), 7.27 (d, *J* = 5.8 Hz, 1H), 7.19 (td, *J* = 7.5, 0.8 Hz, 1H), 7.10 – 7.02 (m, 3H), 6.94 (d, *J* = 7.4 Hz, 1H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 7.8 Hz, 2H), 4.43 (s, 1H, NH), 3.41 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 161.4 (C), 150.2 (C), 147.9 (C), 146.0 (C), 144.3 (C), 141.8 (C), 133.7 (C), 130.2 (2 × CH), 129.1 (3 × CH), 128.8 (2 × CH), 128.1 (CH), 127.2 (2 × CH), 125.4 (CH),

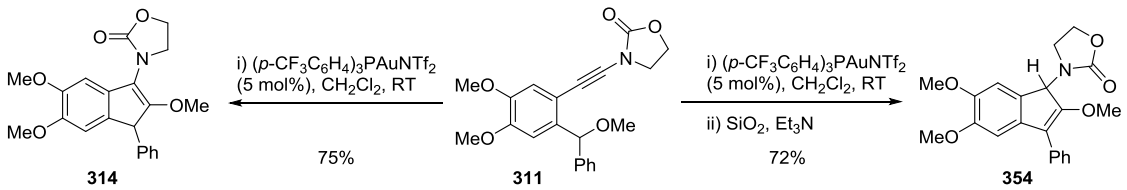
124.5 (2 × CH), 123.7 (CH), 120.4 (CH), 120.0 (CH), 119.1 (C), 117.6 (2 × CH), 72.8 (C), 60.6 (CH_3); IR: ν_{max} (cm^{-1}) 3341, 3082, 3051, 3014, 2988, 2939, 2844, 1635, 1594, 1514, 1451, 1345, 1329, 1047; HRMS (ES) *m/z* calculated for $C_{28}H_{22}N_2O_5NaS$ $(M+Na)^+$ 521.1147 found 521.1121.

***(E)-N-(2-Methoxy-3-phenyl-1H-inden-1-ylidene)aniline* 353**



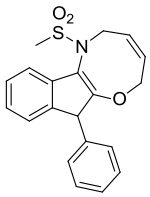
Indene **235** (35.0 mg, 0.075 mmol, 1 equiv.) was dissolved in acetone (1.3 mL, 0.06 M) at room temperature. Diazabicyclo[5.4.0]undec-7-ene (22 µL, 0.2 mmol, 2 equiv.) was added and the solution stirred for 1.5 h. The solvent was removed under reduced pressure and purification of the crude residue by flash column chromatography [hexane:EtOAc (95:5)] gave the imine **353** (18.8 mg, 81%) as a red solid; mp: 118-119 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.51 – 7.45 (m, 2H), 7.43 – 7.37 (m, 3H), 7.23 - 7.17 (m, 1H), 7.09 (td, *J* = 7.6, 1.0 Hz, 1H), 7.02 – 6.98 (m, 2H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.74 (td, *J* = 7.6, 1.0 Hz, 1H), 6.32 (d, *J* = 7.4 Hz, 1H), 3.85 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 162.2 (C), 151.9 (C), 151.5 (C), 145.6 (C), 132.7 (C), 131.6 (CH), 129.5 (2 × CH), 129.5 (2 × CH), 128.8 (CH), 128.6 (2 × CH), 127.9 (C), 125.9 (CH), 125.7 (CH), 124.7 (C), 124.5 (CH), 119.8 (CH), 118.5 (2 × CH), 61.1 (CH_3); IR: ν_{max} (cm^{-1}) 3079, 3058, 2931, 2852, 1643, 1618, 1592, 1483, 1457, 1347, 1059, 1020; HRMS (ES) *m/z* calculated for $C_{22}H_{18}NO$ $(M+H)^+$ 312.1388 found 312.1386.

***3-(2,5,6-trimethoxy-3-phenyl-1H-inden-1-yl)oxazolidin-2-one* 354**



Prepared according to **GP13** from ynamide **311** (110.2 mg, 0.3 mmol), stirring for 1.5 hours. Purification by flash column chromatography [hexane:EtOAc (65:35), 1% Et_3N] gave the isomeric indene **354** (79.6 mg, 72%) as a white solid; mp: 181-183 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 – 7.43 (m, 4H), 7.40 – 7.32 (m, 1H), 6.95 (s, 1H), 6.76 (s, 1H), 5.66 (s, 1H), 4.45 – 4.30 (m, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.35 (td, *J* = 8.8, 6.8 Hz, 1H), 3.15 (app. dd, *J* = 16.1, 8.8 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 159.0 (C), 155.6 (C), 149.7 (C), 147.0 (C), 136.4 (C), 132.7 (C), 128.9 (2 × CH), 128.5 (2 × CH), 127.6 (CH), 126.5 (C), 120.5 (C), 108.2 (CH), 103.9 (CH), 62.4 (CH_2), 59.6 (CH), 56.8 (CH_3), 56.6 (CH_3), 56.2 (CH_3), 40.2 (CH_2); IR: ν_{max} (cm^{-1}) 2995, 2928, 2827, 1735, 1621, 1496, 1418, 1305, 1172, 1073; HRMS (ES) *m/z* calculated for $C_{21}H_{22}NO_5Na$ $(M+H)^+$ 368.1498 found 368.1496.

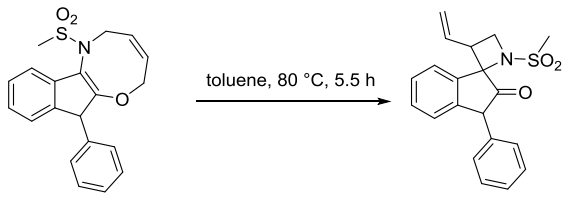
***(Z)-6-(Methylsulfonyl)-11-phenyl-2,5,6,11-tetrahydroindeno[2,1-b][1,4]oxazocine* 355**



Indene **330** (50.0 mg, 0.13 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (44 mL, 0.003 M) and Grubbs(II) catalyst (2.8 mg, 2.5 mol%) was added. The resulting solution was stirred at room temperature for 4.5 hours before filtering through a short pad (ca. 1 cm) of silica, eluting with CH_2Cl_2 (50 mL). The solvent was removed under reduced pressure and the crude solid was recrystallised [hexane:CH_2Cl_2] to give the oxazocine **335** (38.3 mg, 77%) as a white solid; mp: 144-146 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.19 (m, 4H), 7.19 – 7.13 (m, 3H), 7.10 – 6.97 (m, 2H), 5.91 – 5.75 (m, 2H), 5.27 – 5.00 (m, 2H), 4.64-4.33 (m, 2H), 4.46 (s, 1H), 3.20 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 164.2 (C), 141.4 (C), 140.3 (C), 138.2 (C), 134.4 (CH), 129.2 (2 × CH), 128.5 (2 × CH), 127.6 (CH), 127.5 (CH), 124.5 (CH), 124.4 (CH), 123.2 (CH), 116.2 (CH), 111.5 (C), 62.5 (CH_2), 53.74 (CH), 50.8 (CH_2), 42.4 (CH_3); IR: ν_{max} (cm^{-1})

3028, 3010, 2977, 2937, 1617, 1465, 1455, 1439, 1329, 1146, 962; HRMS (ES) *m/z* calculated for $C_{20}H_{19}NO_3NaS$ $(M+Na)^+$ 376.0983 found 376.0988.

***1-(Methylsulfonyl)-3'-phenyl-3-vinylspiro[azetidine-2,1'-inden]-2'(3'H)-one* 356**

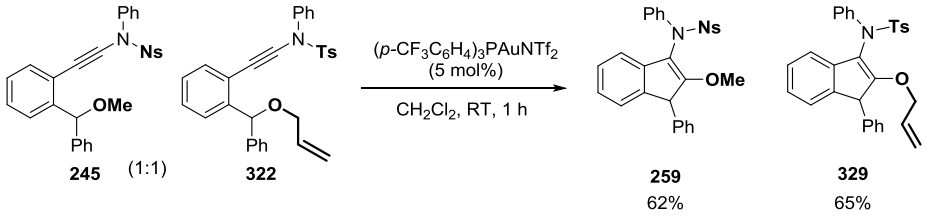


355 356

Oxazocine **355** (20 mg, 0.06 mmol) was heated in toluene (1.0 mL, 0.06 M) for 5.5 hours (it was not possible to monitor the reaction by TLC). One cooled to room temperature, the solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography [hexane:EtOAc (80:20)] to give the vinyl azetidine **356** (14.2 mg, 71%) as a clear oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.75 (app. d, *J* = 7.6 Hz, 1H, major and 1H, minor), 7.57 – 7.40 (m, 1H, major, 2H, minor), 7.39 – 7.23 (m, 4H, major, 4H, minor), 7.21 (d, *J* = 7.6 Hz, 1H, minor), 7.15 – 7.10 (m, 1H, major, 1H, minor), 7.03 (d, *J* = 7.7 Hz, 2H, major), 5.91 (ddd, *J* = 17.0, 10.2, 9.1 Hz, 1H, major), 5.52 (ddd, *J* = 17.0, 10.1, 9.0 Hz, 1H, minor), 5.21 (d, *J* = 9.1 Hz, 1H, major), 5.18 (d, *J* = 17.0 Hz, 1H, major), 4.96 (d, *J* = 17.0 Hz, 1H, minor), 4.81 (d, *J* = 10.1 Hz, 1H, minor), 4.80 (s, 1H, minor), 4.43 (s, 1H, major), 4.27 – 4.16 (m, 2H, major and 1H, minor) and 4.09 (dd, *J* = 8.3, 6.3 Hz, 1H, minor), 3.54 – 3.41 (m, 1H, major and 1H minor), 2.96 (s, 3H, major), 2.94 (s, 3H, minor); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 212.2 (C, major), 210.7 (C, minor), 140.6 (C, minor), 140.4 (C, major), 140.3 (C, major), 140.1 (C, minor), 137.3 (C, major), 137.3 (C, minor), 132.3 (CH, major), 132.2 (CH, minor), 130.6 (CH, minor), 130.1 (CH, major), 129.6 (2 × CH, major),

129.1 (CH, minor), 129.0 (CH, major), 128.8 (2 × CH, major), 128.7 (2 × CH, minor), 128.5 (2 × CH, minor), 127.6 (CH, major), 127.4 (CH, minor), 126.1 (CH, minor), 125.5 (CH, major), 124.3 (CH, minor), 123.8 (CH, major), 121.1 (CH_2, minor), 120.2 (CH_2, major), 82.0 (C, major), 81.5 (C, minor), 57.4 (CH, major), 56.9 (CH, minor), 52.9 (CH_2, minor), 52.6 (CH_2, major), 48.7 (CH, major), 47.3 (CH, minor), 40.7 (CH_3, major), 40.0 (CH_3, minor); IR: ν_{max} (cm^{-1}) 2893, 1754, 1496, 1328, 1145, 1053, 1036, 967, 738, 700; HRMS (ES) *m/z* calculated for $C_{20}H_{19}NO_3NaS$ $(M+Na)^+$ 376.0983, found 376.0983.

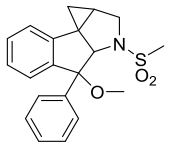
Carboalkoxylation Crossover Study



Ynamides **245** (24.9 mg, 0.05 mmol, 1.0 equiv.) and **322** (24.7 mg, 0.05 mmol, 1.0 equiv.) were dissolved in CH_2Cl_2 (1.0 mL, 0.1 M). (p-$CF_3C_6H_4)_3PAuNTf_2$ (4.7 mg, 0.0026 mmol) was added and the solution stirred at room temperature for 2 hours. The reaction mixture was filtered through a pipette containing a short silica pad (ca. 1 cm), eluting with EtOAc (10 mL) and the solvent removed under reduced pressure. 1,2,4,5-Tetramethyl benzene (2.5 mg, 0.019 mmol) was added to the flask as an internal standard and the mixture was taken up in $CDCl_3$ for analysis. ^{1}H-NMR yields were calculated from ^{1}H-NMR spectroscopy: **259** = 62% and **329** = 65% based on the internal standard. Formation of crossover products was not observed.

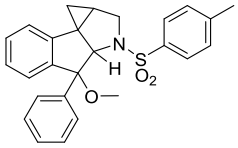
Preparation of Functionalised Tetracycles

***3a-Methoxy-3-(methylsulfonyl)-4-phenyl-1,1a,2,3,3a,4-hexahydrocyclopropa[c]indeno[2,1-b]pyrrole* 357**



Prepared according to **GP14** from ynamide **255** (71.1 mg, 0.2 mmol), heating at 120 °C for 6 hours. Purification by flash column chromatography [hexane:EtOAc (90:10), then hexane:EtOAc (80:20)] gave the tetracycle **357** (34.8 mg, 49%) as a single diastereoisomer as a white solid. (It was not possible to isolate the minor diastereoisomer (25% by ^{1}H-NMR)); mp: 138 -140 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.39-7.31 (m, 6H), 7.21 (app. td, *J* = 7.5, 1.1 Hz, 1H) 7.01 (dd, *J* = 9.9, 7.5 Hz, 2H), 4.55 (s, 1H), 3.98 (dd, *J* = 9.8, 3.6 Hz, 1H), 3.90 (d, *J* = 9.8 Hz, 1H), 3.10 (s, 3H), 2.70 (s, 3H), 1.69-1.55 (m, 2H), 1.07 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 142.8 (C), 142.4 (C), 141.2 (C), 129.6 (CH), 128.3 (2 × CH), 127.8 (CH), 127.6 (2 × CH), 127.3 (CH), 126.2 (CH), 120.1 (CH), 88.9 (C), 80.0 (CH), 54.0 (CH_2), 52.5 (CH_3), 41.4 (CH_3), 38.5 (C), 26.6 (CH), 11.3 (CH_2); IR: ν_{max} (cm^{-1}) 3026, 2939, 2829, 2827, 1152; HRMS (ES) *m/z* calculated for $C_{20}H_{21}NO_3NaS$ $(M+Na)^+$ 378.1140, found 378.1137.

***4-Methoxy-4-phenyl-3-tosyl-1,1a,2,3,3a,4-hexahydrocyclopropa[c]indeno[2,1-b]pyrrole* 498**



Prepared according to **GP14** from ynamide **494** (86.3 mg, 0.2 mmol), heating at 120 °C for 1 hour. Purification by flash column chromatography [hexane:EtOAc (90:10)] gave tetracycle **498** (69.5 mg, 81%) as a 1:2.2 mixture of diastereoisomers as a white solid; mp: 146-148 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.3 Hz, 2H, minor), 7.34 (d, *J* = 8.3 Hz, 2H, major), 7.21 – 7.11 (m, 6H, major and 6H, minor), 7.10 –

7.00 (m, 3H, major and 3H minor), 6.92 – 6.86 (m, 1H, major, 1H, minor) 6.76 (d, *J* = 7.4 Hz, 1H, major) 6.72 – 6.69 (m, 1H, minor), 4.86 (s, 1H, minor), 4.24 (s, 1H, major), 3.94 (dd, *J* = 10.6, 4.1 Hz, 1H, major), 3.57 (d, *J* = 10.6 Hz, 1H, major), 3.35 (s, 3H, minor), 3.04 (d, *J* = 11.3 Hz, 1H, minor), 2.88 (s, 3H, major), 2.27 (s, 3H, minor), 2.24 (s, 3H, major), 2.22 – 2.15 (m, 1H, minor), 1.40 – 1.34 (m, 1H, major), 1.15 – 1.03 (m, 1H, major, 2H, minor), -0.03 (app. t, *J* = 5.4 Hz, 1H, major), -0.20 – -0.28 (m, 1H, minor); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.4 (C, minor), 143.1 (C, major), 143.0 (C, minor), 142.7 (C, major), 142.2 (C, major), 141.7 (C, minor), 141.1 (C, minor), 140.2 (C, major), 137.3 (C, major), 137.1 (C, minor), 129.8 (2 × CH, minor), 129.6 (2 × CH, major), 129.4 (CH, major), 129.2 (CH, minor), 128.1 (2 × CH, minor), 127.9 (2 × CH, major), 127.8 (2 × CH, minor), 127.7 (2 × CH, major and CH, minor), 127.6 (2 × CH, minor), 127.2 (CH, major), 127.20 (2 × CH, major and CH, minor), 127.15 (CH, major), 126.1 (CH, major), 125.7 (CH, minor), 119.9 (CH, major), 119.4 (CH, minor), 91.8 (C, major), 88.9 (C, minor), 80.0 (CH, major), 72.9 (CH, minor), 54.7 (CH_2, major), 52.7 (CH_2, minor), 52.0 (CH, minor), 51.9 (CH, major), 38.5 (C, major), 37.7 (C, minor), 27.1 (CH_3, minor), 26.7 (CH_3, major), 21.6 (CH_3, major and CH_3 minor), 11.5 (CH_2, minor), 11.0 (CH_2, major); IR: ν_{max} (cm^{-1}) 3052, 2950, 2930, 2892, 2862, 1598, 1492, 1462, 1447, 1349, 1161, 1100, 1079, 664; HRMS (ES) *m/z* calculated for $C_{26}H_{26}NO_3S$ $(M+H)^+$ 432.1633, found 432.1611.

Note: The reaction can also be conducted at room temperature over a 24 hour period to give the tetracycle **498** (72.4 mg, 84%) as a 1:3.8 mixture of diastereoisomers as a white solid.

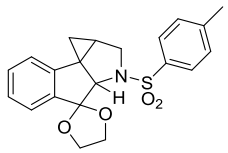
***4-(Allyloxy)-4-phenyl-3-tosyl-1,1a,2,3,3a,4-hexahydrocyclopropa[c]indeno[2,1-b]pyrrole* 507**

Prepared according to **GP14** from ynamide **506** (91.5 mg, 0.2 mmol) heating at 60 °C for 2 hours. Purification by flash column chromatography [hexane:EtOAc (92:8)] gave tetracycle **507** (78.7 mg, 86%) as a 1:3 mixture of diastereoisomers as a white solid. Recrystallisation [hexane:CH_2Cl_2] allowed isolation of the major diastereoisomer (54.2 mg, 59%); mp: 146-147 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2H minor), 7.53 (d, *J* = 8.3 Hz, 2H, major), 7.35 – 7.27 (m, 6H major and 6H minor), 7.24 – 7.16 (m, 3H major and 3H minor), 7.07 (dd, *J* = 6.1, 3.1 Hz, 1H, minor), 7.03 (d, *J* = 7.5 Hz, 1H, major), 6.93 (d, *J* = 7.5 Hz, 1H, major), 6.88 – 6.85 (m, 1H, minor), 6.08 (ddt, *J* = 17.2, 10.4, 5.1 Hz, 1H, minor), 5.77 (ddt, *J* = 17.2, 10.5, 4.4 Hz, 1H, major), 5.47 (app. dq, *J* = 17.2, 1.7 Hz, 1H, minor), 5.27 (app. ddd, *J* = 17.2, 3.8, 1.9 Hz, 1H, major), 5.21 (app. ddd, *J* = 10.4, 3.2, 1.7 Hz, 1H, minor), 5.06 (app. dq, *J* = 10.5, 1.9 Hz, 1H, major), 5.00 (s, 1H, minor), 4.48 (s, 1H, major), 4.35 (ddt, *J* = 12.4, 5.1, 1.7 Hz, 1H, minor), 4.11 (dd, *J* = 10.5, 4.4 Hz, 1H, major), 4.02 (app. ddt, *J* = 12.4, 5.1, 1.7 Hz, 1H, minor), 3.90 (app. ddt, *J* = 13.2, 4.5, 1.8 Hz, 1H, major), 3.77 (d, *J* = 10.5 Hz, 1H, major), 3.44 (app. ddt, *J* = 13.2, 4.4, 1.9 Hz, 1H, major), 3.23 (d, *J* = 11.3 Hz, 1H, minor), 2.44 (s, 3H, minor), 2.41 (s, 3H, major), 2.40 – 2.34 (m, 1H, minor), 1.58 – 1.52 (m, 1H, major), 1.33 (dd, *J* = 8.0, 6.2 Hz, 1H, major), 1.29 – 1.20 (m, 2H, minor), 0.28 (app. t, *J* = 5.4 Hz, 1H, major), -0.05 (app. t, *J* = 3.3 Hz, 1H, minor); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.5 (C, minor), 143.6 (C, minor), 143.1 (C, major), 142.8 (C, major), 142.7 (C, major), 141.6 (C, minor), 141.1 (C, minor), 140.6 (C, major), 137.6 (C, major), 137.2 (C, minor), 135.3 (CH, minor), 135.2 (2 × CH, major), 129.8 (CH, major), 129.6 (3 × CH, major), 129.4 (2 × CH, minor), 129.3 (2 × CH, minor), 128.1 (2 ×

CH, minor), 128.0 (2 × CH, major), 127.9 (2 × CH, minor), 127.6 (2 × CH, minor), 127.5 (2 × CH, major and 2 × CH, minor), 127.4 (CH, major), 127.3 (2 × CH, major), 126.3 (CH, major), 125.7 (CH, minor), 120.0 (CH, major), 119.4 (CH, minor), 116.1 (CH_2, minor), 115.0 (CH_2, major), 88.6 (C, major, corresponding minor C is not visible), 80.2 (CH, major), 74.5 (CH, minor), 65.5 (CH_2, minor), 64.9 (CH_2, major), 54.7 (CH_2, major), 52.8 (CH_2, minor), 38.5 (C, major), 37.8 (C, minor), 27.2 (CH, minor), 26.9 (CH, major), 21.7 (CH_3, major and CH_3, minor), 11.5 (CH_2, minor), 11.0 (CH_2, major); IR: ν_{max} (cm^{-1}) 2951, 2938, 2888, 2845, 1645, 1599, 1483, 1461, 1447, 1343, 1161, 1099, 757, 665; HRMS (ES) *m/z* calculated for $C_{28}H_{27}NO_3SNa$ $(M+Na)^+$ 480.1609, found 480.1601.

3-Tosyl-1a,2,3,3a-tetrahydro-1H-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane]

519

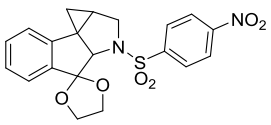


Prepared according to **GP14** from ynamide **515** (76.7 mg, 0.2 mmol) stirring at 80 °C for 1 hour. Purification by flash column chromatography [hexane:EtOAc (80:20), 1% Et_3N] then recrystallisation [CH_2Cl_2:hexane] gave tetracycle **519** (62.1 mg, 81%) as a white solid; mp: 168-170 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.35 (m, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.30 – 7.22 (m, 2H), 6.76 – 6.73 (m, 1H), 4.57 – 4.50 (m, 1H), 4.45 – 4.38 (m, 1H), 4.37 (s, 1H), 4.25 (dd, *J* = 12.9, 6.3 Hz, 1H), 4.24 – 4.17 (m, 1H), 4.07 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.67 (d, *J* = 11.3 Hz, 1H), 2.44 (s, 3H), 1.46 – 1.39 (m, 1H), 1.22 – 1.17 (m, 1H), -0.25 – -0.28 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.8 (C), 141.2 (C), 140.1 (C), 136.3 (C), 130.4 (CH), 130.0 (2 × CH), 127.8 (CH), 127.2 (2 × CH), 123.9 (CH), 119.3 (CH), 113.4 (C), 74.5 (CH), 66.7 (CH_2), 66.1 (CH_2), 54.1 (CH_2), 37.6 (C), 26.4 (CH_3), 21.7 (CH),

11.6 (CH_2); IR: ν_{max} (cm^{-1}) 2982, 2951, 2918, 2896, 1615, 1598, 1463, 1345, 1279, 1156, 754; HRMS (ES) *m/z* calculated for $C_{21}H_{22}NO_4S$ $(M+H)^+$ 384.1265, found 384.1276.

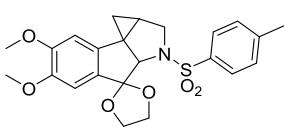
Note: The reaction can also be conducted at room temperature over a 16 hour period to give the tetracycle **519** (71.3 mg, 93%) as a white solid.

***3-((4-Nitrophenyl)sulfonyl)-1a,2,3,3a-tetrahydro-1H-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane]* 520**



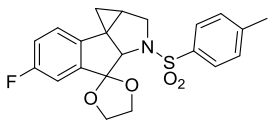
Prepared according to **GP14** from ynamide **516** (82.9 mg, 0.2 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [hexane:EtOAc (9:1)] gave tetracycle **520** (50.2 mg, 61%) as a white solid; mp: 216-217 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.40 (d, *J* = 8.9 Hz, 2H), 8.05 (d, *J* = 8.9 Hz, 2H), 7.39 – 7.23 (m, 3H), 6.81 – 6.73 (m, 1H), 4.46 – 4.40 (m, 1H), 4.39 (s, 1H), 4.36 – 4.17 (m, 3H), 4.13 (dd, *J* = 11.2, 4.3 Hz, 1H), 3.69 (d, *J* = 11.2 Hz, 1H), 1.54 – 1.45 (m, 1H), 1.32 (dd, *J* = 7.8, 6.4 Hz, 1H), -0.19 (dd, *J* = 6.4, 5.1 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 150.3 (C), 145.0 (C), 141.2 (C), 139.3 (C), 130.6 (CH), 128.4 (2 × CH), 128.0 (CH), 124.7 (2 × CH) 123.9 (CH), 119.5 (CH), 113.4 (C), 74.4 (CH), 66.8 (CH_2), 65.9 (CH_2), 54.3 (CH_2), 37.5 (C), 26.0 (CH), 11.9 (CH_2); IR: ν_{max} (cm^{-1}) 3065, 3029, 3007, 2972, 2912, 2941, 2840, 1636, 1355, 1165, 908, 859; HRMS (ES) *m/z* calculated for $C_{20}H_{19}N_2O_6S$ $(M+H)^+$ 415.4395, found 415.4389.

6,7-Dimethoxy-3-tosyl-1a,2,3,3a-tetrahydro-1H-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane] **521**



Prepared according to **GP14** from ynamide **517** (88.7 mg, 0.2 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [hexane:EtOAc (70:30), 1% Et_3N] gave tetracycle **521** (86.8 mg, 98%) as a pale yellow solid; mp: 168-170 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 6.86 (s, 1H), 6.21 (s, 1H), 4.61 – 4.51 (m, 1H), 4.51 – 4.40 (m, 1H), 4.33 (s, 1H), 4.29 – 4.16 (m, 2H), 4.06 (dd, *J* = 11.4, 4.3 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.65 (d, *J* = 11.4 Hz, 1H), 2.44 (s, 3H), 1.40 – 1.31 (m, 1H), 1.11 (dd, *J* = 8.0, 6.3 Hz, 1H), -0.35 (dd, *J* = 6.3, 5.1 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 151.6 (C), 149.5 (C), 143.8 (C), 136.2 (C), 132.4 (C), 132.2 (C), 130.0 (2 × CH), 127.2 (2 × CH), 113.8 (C), 106.6 (CH), 102.3 (CH), 76.9 (CH), 66.5 (CH_2), 66.0 (CH_2), 56.3 (CH_3), 56.2 (CH_3), 54.2 (CH_2), 37.6 (C), 25.3 (CH), 21.7 (CH_3), 11.3 (CH_2); IR: ν_{max} (cm^{-1}) 3004, 2961, 2923, 2890, 2869, 1614, 1596, 1507, 1467, 1454, 1340, 1159, 1009, 663; HRMS (ES) *m/z* calculated for $C_{23}H_{26}NO_6S$ $(M+H)^+$ 444.1481, found 444.1501.

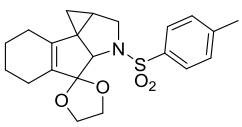
6-Fluoro-3-tosyl-1a,2,3,3a-tetrahydro-1H-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane] **522**



Prepared according to **GP14** from ynamide **518** (80.3 mg, 0.2 mmol), heating at 80 °C for 24 hours. Purification by flash column chromatography [hexane:EtOAc (85:15), 1% Et_3N] gave tetracycle **522** (59.5 mg, 74%) as a white solid; mp: 176-178 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz,

2H), 7.05 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.02 – 6.92 (m, 1H), 6.70 (dd, *J* = 8.2, 4.7 Hz, 1H), 4.55 – 4.48 (m, 1H), 4.47 – 4.38 (m, 1H), 4.37 (s, 1H), 4.28 – 4.16 (m, 2H), 4.06 (dd, *J* = 11.4, 4.3 Hz, 1H), 3.66 (d, *J* = 11.4 Hz, 1H), 2.45 (s, 3H), 1.44 – 1.38 (m, 1H), 1.17 (dd, *J* = 7.9, 6.6 Hz, 1H), -0.24 – -0.29 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 162.4 (d, $J_{C\text{-}F}$ = 246.0 Hz, C), 143.9 (C), 143.3 (d, $J_{C\text{-}F}$ = 7.2 Hz, C), 136.2 (C), 135.6 (C), 130.1 (2 × CH), 127.2 (2 × CH), 120.8 (d, $J_{C\text{-}F}$ = 8.2 Hz, CH), 117.6 (d, $J_{C\text{-}F}$ = 23.0 Hz, CH), 112.9 (C), 111.2 (d, $J_{C\text{-}F}$ = 22.7 Hz, CH), 74.6 (CH), 66.8 (CH_2), 66.2 (CH_2), 54.1 (CH_2), 37.2 (C), 26.2 (CH), 21.7 (CH_3), 11.6 (CH_2); IR: ν_{max} (cm^{-1}) 2996, 2972, 2948, 2893, 1494, 1345, 1157, 732, 658; HRMS (ES) *m/z* calculated for $C_{21}H_{21}NO_4SF$ $(M+H)^+$ 402.1175, found 404.1159.

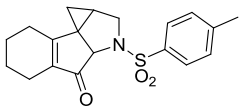
3-Tosyl-1a,2,3,3a,5,6,7,8-octahydro-1H-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane] **539**



Prepared according to **GP14**, from ynamide **535** (77.5 mg, 0.2 mmol), heating at 50 °C for 15 minutes. Purification by flash column chromatography [toluene:EtOAc (95:5), 1% Et_3N] gave tetracycle **539** (62.3 mg, 80%) as a white solid. When the reaction was carried out on a 0.6 mmol scale, 99% of pure product was isolated following flash column chromatography; mp: 189-191 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 4.14 – 3.89 (m, 2H), 4.11 – 3.91 (m, 3H), 4.02 (s, 1H), 3.62 (d, *J* = 11.5 Hz, 1H), 2.43 (s, 3H), 2.14 – 1.99 (m, 1H), 1.98 – 1.82 (m, 1H), 1.78 – 1.41 (m, 6H), 1.22 – 1.16 (m, 1H), 0.74 (dd, *J* = 8.0, 6.2 Hz, 1H), -0.56 – -0.61 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.6 (C), 138.4 (C), 136.0 (C), 135.0 (C), 129.9 (2 × CH), 127.3 (2 × CH), 115.5 (C), 73.8 (CH), 66.2 (CH_2), 66.2 (CH_2), 54.4 (CH_2), 40.5 (C), 22.3 (CH_2), 22.1 (CH_2), 21.9 (CH_2), 21.7 (CH_3),

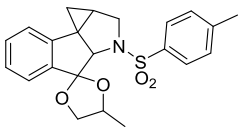
20.2 (CH_2), 19.5 (CH), 10.8 (CH_2); IR: ν_{max} (cm^{-1}) 2934, 2880, 2855, 2836, 1344, 1158, 1001, 808, 663; HRMS (ES) *m/z* calculated for $C_{21}H_{26}NO_4S$ $(M+H)^+$ 388.1583, found 388.1591.

***3-Tosyl-1a,2,3,3a,5,6,7,8-octahydrocyclopropa[c]indeno[2,1-b]pyrrol-4(1H)-one* 540**



Tetracyclic acetal **539** (194 mg, 0.5 mmol, 1.0 equiv.) was dissolved in THF (2.5 m, 0.2 M). Aqueous HCl solution (2.0 M solution, 0.9 mL) was added and the mixture was heated to 50 °C for 1 hour. One cooled to room temperature, the mixture was neutralised by the dropwise addition NaOH solution (2.0 M). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), dried over $NaSO_4$, filtered and the solvent removed under reduced pressure. No further purification was required and the enone **540** was isolated as a white solid (129 mg, 75%); mp: 158-160 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 4.32 (s, 1H), 3.79 (d, *J* = 11.0 Hz, 1H), 3.69 (dd, *J* = 11.0, 4.3 Hz, 1H), 2.41 (s, 3H), 2.16 – 2.01 (m, 3H), 1.91 – 1.59 (m, 5H), 1.47 – 1.32 (m, 2H), 0.66 (app. t, *J* = 5.0 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 203.2 (C), 167.4 (C), 143.7 (C), 136.9 (C), 136.8 (C), 129.8 (2 × CH), 128.0 (2 × CH), 69.5 (CH), 53.6 (CH_2), 39.8 (C), 29.9 (CH_2), 23.7 (CH_2), 21.8 (CH) 21.7 (CH_2), 21.5 (CH_3), 20.3 (CH_2), 14.5 (CH_2); IR: ν_{max} (cm^{-1}) 2928, 2891, 2864, 1701, 1619, 1345, 1161, 1091, 1044, 663; HRMS (ES) *m/z* calculated for $C_{19}H_{22}NO_3S$ $(M+H)^+$ 344.1320, found 344.1325.

4'-Methyl-3-tosyl-1a,2,3,3a-tetrahydro-1H-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane] **547**

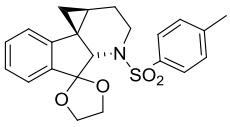


Prepared according to **GP14** from ynamide **546** (79.5 mg, 0.2 mmol) heating at 50 °C for 45 minutes. Purification by flash column chromatography [hexane:EtOAc (90:10), 1% Et_3N] gave tetracycle **547** (58.2 mg, 73%) as a mixture of four diastereoisomers as a white solid; mp: 72-74 °C; **Note:** Due to the complexity of the ^{1}H-NMR spectrum, it was not possible to assign structures or a ratio of diastereoisomers due to overlapping resonances. Two major diastereoisomers were formed in a 1:1 ratio and two minor diastereoisomers were also formed in low levels. For simplicity, only the two major diastereoisomers are assigned as a mixture in the ^{1}H- and ^{13}C- spectra. It was not possible to fully assign the minor diastereoisomers. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.74 and 7.73 (2 × d, *J* = 8.3 Hz, 2H), 7.42 – 7.31 (m, 3H), 7.29 – 7.22 (m, 2H), 6.78 – 6.69 (m, 1H), 4.93 and 4.85 (app. dd, *J* = 12.4, 6.2 Hz and app. dt, *J* = 7.7, 6.1 Hz, 1H), 4.63 – 4.58 and 4.55 – 4.50 (2 × m, 1H), 4.36 and 4.32 (2 × s, 1H), 4.16 – 4.01 (m, 1H), 3.76 – 3.61 (m, 2H), 2.44 (s, 3H), 1.47 and 1.38 (2 × d, *J* = 6.1 Hz, 3H), 1.45 – 1.36 (m, 1H), 1.17 (dd, *J* = 8.2, 6.5 Hz, 1H), -0.29 – -0.38 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.9 and 143.8 (C), 141.4 and 141.2 (C), 140.0 (C), 136.3 and 136.1 (C), 130.4 (CH), 130.0 (2 × CH), 127.9 and 127.8 (CH), 127.3 and 127.2 (2 × CH), 124.1 and 124.0 (CH), 119.3 (CH), 113.8 (C), 74.8 (CH), 73.8 and 73.5 (CH), 73.1 and 72.1 (CH_2), 54.2 and 54.1 (CH_2), 37.7 and 37.5 (C), 26.4 (CH), 21.7 (CH_3), 19.9 and 19.0 (CH_3), 11.6 and 11.5 (CH_2);.IR: ν_{max} (cm^{-1}) 2974, 2936, 2888, 1613, 1597, 1347, 1161, 1099, 1073, 1010, 729, 666, 661; HRMS (ES) *m/z* calculated for $C_{22}H_{23}NO_4SNa$ $(M+Na)^+$ 420.1245, found 420.1245.

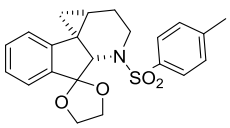
4-Tosyl-1,1a,2,3,4,4a-hexahydrospiro[cyclopropa[c]indeno[2,1-b]pyridine-5,2'-[1,3]dioxolane]

558-a and 558-b

Prepared according to **GP14** from ynamide **552** (79.5 mg, 0.2 mmol), heating at 80 °C for 2 hours. Purification by flash column chromatography [hexane:EtOAc (90:10), 1% Et_3N] allowed isolation of diastereoisomeric tetracycles **558-a** and **558-b** as white solids.



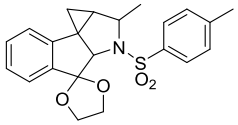
558-a: (17.2 mg, 22%); mp: 193-195 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.26 (m, 4H), 7.22 (app. td, *J* = 7.5, 1.1 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 4.72 (s, 1H), 4.29 – 4.06 (m, 4H), 3.81 (app. dd, *J* = 14.2, 4.7 Hz, 1H), 3.46 (app. td, *J* = 14.2, 3.8 Hz, 1H), 2.44 (s, 3H), 1.90 – 1.74 (m, 1H), 1.31 – 1.09 (m, 3H), 0.12 (app. t, *J* = 5.1 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 145.1 (C), 143.4 (C), 140.1 (C), 139.0 (C), 130.6 (CH), 129.8 (2 × CH), 127.3 (2 × CH), 127.0 (CH), 123.4 (CH), 118.9 (CH), 115.1 (C), 66.5 (CH_2), 66.0 (CH_2), 62.0 (CH), 40.8 (CH_2), 22.6 (C), 22.3 (CH_2), 21.7 (CH_3), 21.5 (CH), 18.6 (CH_2); IR: ν_{max} (cm^{-1}) 3060, 3026, 2979, 2900, 1601,1578, 1485, 1466, 1245, 1179, 1166, 1088, 752; HRMS (ES) *m/z* calculated for $C_{22}H_{24}NO_4S$ $(M+H)^+$ 398.1426, found 398.1409.



558-b: (27.5 mg, 35%) mp: 185-187 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.27 (m, 3H), 7.22 (app. td, *J* = 6.8, 1.5 Hz, 2H), 6.72 (dd, *J* = 6.3, 1.5 Hz, 1H), 4.56 – 4.51 (m, 1H), 4.47 – 4.36 (m, 2H), 4.22 - 4.14 (m, 1H), 3.80 (s, 1H), 3.59 (ddd, *J* = 13.9, 5.9, 3.1 Hz, 1H), 3.49 – 3.38 (m, 1H), 2.40 (s, 3H), 1.94 – 1.81 (m, 2H), 1.75 – 1.62 (m, 2H), 0.59 (dd, *J* = 8.0, 5.6 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.5 (C), 142.8 (C), 142.5 (C), 134.2 (C), 129.7 (2 × CH), 129.6 (CH), 128.4 (2 × CH), 126.9 (CH), 122.8 (CH), 118.1

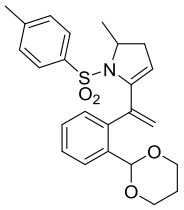
(CH), 114.3 (C), 66.7 (CH_2), 64.9 (CH_2), 61.7 (CH), 44.9 (CH_2), 23.0 (C), 22.3 (CH_2), 21.7 (CH_3), 16.7 (CH_2), 14.1 (CH); IR: ν_{max} (cm^{-1}) 3067, 2984, 2901, 1598, 1486, 1461, 1347, 1240, 1168, 1091, 732, 664; HRMS (ES) *m/z* calculated for $C_{22}H_{24}NO_4S$ $(M+H)^+$ 398.1426, found 398.1415.

2-Methyl-3-tosyl-1a,2,3,3a-tetrahydro-1H-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane] **570**



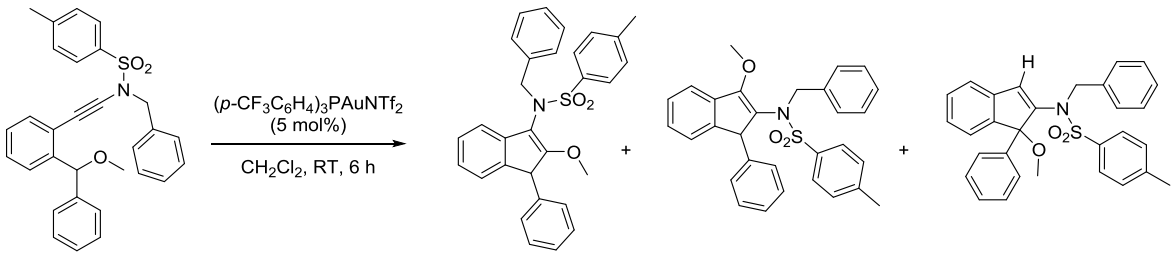
Prepared according to **GP14** from ynamide **566** (79.5 mg, 0.2 mmol), heating at 80 °C for 1 hour. Purification by flash column chromatography [hexane:toluene:EtOAc (50:47:3), 1% Et_3N] gave tetracycle **570** (54.3 mg, 68%) as a 1:4 mixture of diastereoisomers as a white solid; Recrystallisation [hexane:CH_2Cl_2] allowed isolation of one diastereoisomer (38.6 mg, 49% from ynamide **566**); mp: 202-204 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.36 (m, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.24 (m, 2H), 6.72 – 6.67 (m, 1H), 4.60 – 4.47 (m, 2H), 4.32 (s, 1H), 4.28 – 4.20 (m, 2H), 3.98 (q, *J* = 6.6 Hz, 1H), 2.44 (s, 3H), 1.58 (d, *J* = 6.6 Hz, 3H), 1.24 (dd, *J* = 8.3, 4.8 Hz, 1H), 1.10 (dd, *J* = 8.3, 6.0 Hz, 1H), -0.39 – -0.44 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.9 (C), 141.5 (C), 140.4 (C), 135.5 (C), 130.4 (CH), 130.0 (2 × CH), 127.9 (CH), 127.4 (2 × CH), 124.3 (CH), 119.2 (CH), 112.6 (C), 75.5 (CH), 66.6 (CH_2), 66.0 (CH_2), 64.6 (CH), 38.6 (C), 32.6 (CH), 23.1 (CH_3), 21.7 (CH_3), 12.8 (CH_2); IR: ν_{max} (cm^{-1}) 3065, 2982, 2903, 1597, 1491, 1461, 1337, 1276, 1261, 1162, 763, 751; HRMS (ES) *m/z* calculated for $C_{22}H_{24}NO_4S$ $(M+H)^+$ 389.1426, found 398.1430.

***5-(1-(2-(1,3-Dioxan-2-yl)phenyl)vinyl)-2-methyl-1-tosyl-2,3-dihydro-1H-pyrrole* 571**



Prepared according to **GP14**, from ynamide **568** (85.1 mg, 0.2 mmol), heating at 80 °C for 45 minutes. Purification by flash column chromatography [toluene:Et_2O (97:3), 1% Et_3N] gave 1,3-diene **571** (54.0 mg, 63%) as a white solid; mp: 54-56 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.78 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.37 (app. td, *J* = 7.6, 1.2 Hz, 1H), 7.33 – 7.24 (m, 3H), 7.19 (dd, *J* = 7.6, 1.1 Hz, 1H), 5.98 (s, 1H), 5.85 (s, 1H), 5.34 (s, 1H), 5.19 (dd, *J* = 3.5, 2.1 Hz, 1H), 4.28 – 4.15 (m, 3H), 4.04 – 3.89 (m, 2H), 2.41 (s, 3H), 2.32 – 2.16 (m, 1H), 1.90 (dd, *J* = 17.2, 7.7 Hz, 1H), 1.62 (dd, *J* = 17.2, 3.5 Hz, 1H), 1.39 (d, *J* = 13.4 Hz, 1H), 1.22 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.0 (C), 143.9 (C), 139.2 (C), 138.4 (C), 137.1 (C), 135.1 (C), 129.6 (2 × CH), 129.1 (CH), 128.4 (CH), 128.2 (CH), 128.1 (2 × CH), 127.0 (CH), 121.0 (CH), 120.2 (CH_2), 99.8 (CH), 67.7 (CH_2), 67.4 (CH_2), 59.8 (CH), 35.7 (CH_2), 26.1 (CH_2), 22.0 (CH_3), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3061, 2963, 2926, 2851, 1598, 1347, 1163, 1096, 982, 755, 733, 684, 657; HRMS (ES) *m/z* calculated for $C_{24}H_{27}NO_4SNa$ $(M+Na)^+$ 448.1559, found 448.1553.

Formation of Isomeric Indenes from Ynamide 581



581 | **582** 49% | **583** 15% | **584** 25%

Prepared according to **GP13** from ynamide **581** (96.3 mg, 0.2 mmol), stirring for 6 hours. Purification by flash column chromatography [hexane:EtOAc (95:5) then hexane:EtOAc (85:15)] gave the isomeric indenes **582**-**584**.

***N-Benzyl-N-(2-methoxy-1-phenyl-1H-inden-3-yl)-4-methylbenzenesulfonamide* 582:**

(46.9 mg, 49%); White solid; mp: 204-206 °C; ^{1}H-NMR (400 MHz, DMSO, 110 °C): δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.32 (dd, *J* = 7.4, 2.0 Hz, 2H), 7.29 – 7.15 (m, 6H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.96 – 6.81 (m, 5H), 4.81 (d, *J* = 14.0 Hz, 1H), 4.77 (s, 1H), 4.69 (d, *J* = 14.0 Hz, 1H), 3.29 (s, 3H), 2.42 (s, 3H); Broadening and splitting of some signals due to restricted rotation, some nuclei therefore have 2 resonances assigned to them; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 164.1 and 163.4 (C), 143.4 (C), 141.0 (C), 139.6 (C), 138.0 and 137.6 (C), 136.8 (C), 136.4 and 136.1 (C), 129.4 (2 × CH), 129.1 and 128.9 (4 × CH), 128.4 (2 × CH), 128.1 (2 × CH), 127.9 (2 × CH), 127.7 (CH), 127.4 and 127.1 (CH), 127.0 (CH), 123.9 (CH), 123.0 (CH), 118.9 and 118.4 (CH), 115.5 (C), 57.9 (CH), 52.8 and 52.5 (CH_2), 51.8 and 51.5 (CH_3), 21.7 (CH_3); IR: ν_{max} (cm^{-1}) 3065, 3033, 2953, 2857, 1623, 1598, 1457, 1344, 1158, 1093, 1016, 750; HRMS (ES) *m/z* calculated for $C_{30}H_{27}NO_3S$ $(M)^+$ 481.1712 found 481.1729.

***N-Benzyl-N-(3-methoxy-1-phenyl-1H-inden-2-yl)-4-methylbenzenesulfonamide* 583:**

(14.0 mg, 15%); White solid; mp: 139-141 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.19 – 7.14 (m, 1H), 7.10 – 6.98 (m, 3H), 6.98 – 6.88 (m, 5H), 6.84 – 6.79 (m, 2H), 6.54 (d, *J* = 7.1 Hz, 2H), 4.63 (s, 1H), 4.45 (d, *J* = 14.1 Hz, 1H), 4.15 (d, *J* = 14.1 Hz, 1H), 3.42 (s, 3H), 2.36 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 153.2 (C), 145.3

(C), 143.5 (C), 138.7 (C), 138.1 (C), 137.3 (C), 135.9 (C), 129.7 (2 × CH), 129.2 (2 × CH), 129.0 (2 × CH), 128.5 (2 × CH), 128.2 (2 × CH), 128.0 (2 × CH), 127.5 (CH), 126.9 (CH), 126.8 (CH), 126.7 (CH), 124.5 (CH), 124.0 (C), 119.3 (CH), 58.8 (CH), 53.4 (CH_3), 52.9 (CH_2), 21.7 (CH_3); IR: ν_{max} (cm^{-1}) 3030, 2937, 2850, 1620, 1600, 1494, 1453, 1346, 1159, 908, 724, 697; HRMS (ES) *m/z* calculated for $C_{30}H_{28}NO_3S$ $(M+H)^+$ 482.1790 found 482.1804.

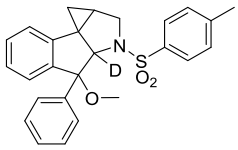
***N-Benzyl-N-(1-methoxy-1-phenyl-1H-inden-2-yl)-4-methylbenzenesulfonamide* 584:**

(23.7 mg, 25%); White solid; mp: 60-62 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.30 (s, 1H), 7.31 – 7.28 (m, 2H), 7.22 – 7.06 (m, 8H), 7.00 – 6.85 (m, 5H), 6.73 – 6.69 (m, 1H), 5.00 (d, *J* = 17.3 Hz, 1H), 4.84 (d, *J* = 17.3 Hz, 1H), 2.48 (s, 3H), 2.42 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.1 (C), 144.0 (C), 143.7 (C), 141.3 (C), 139.5 (C), 139.2 (C), 135.9 (C), 129.5 (2 × CH), 128.8 (CH), 128.3 (6 × CH), 127.2 (CH), 126.8 (CH), 126.5 (2 × CH), 125.6 (CH), 125.2 (2 × CH), 123.2 (CH), 121.2 (CH), 120.9 (CH), 90.9 (C), 51.8 (CH_3), 51.1 (CH_2), 21.7 (CH_3); IR: ν_{max} (cm^{-1}) 3064, 3030, 2932, 2856, 2830, 1599, 1572, 1494, 1469, 1450, 1160, 1085, 1073, 749; HRMS (ES) *m/z* calculated for $C_{30}H_{28}NO_3S$ $(M+H)^+$ 482.1790 found 482.1771.

Note: Indene **584** could also be prepared using **GP14** from ynamide **581** (96.3 mg, 0.2 mmol), stirring for 5 hours at 80 °C. Purification by flash column chromatography [hexane:Et_2O (95:5)] gave the indene **584** (25.9 mg, 27%).

4-Methoxy-4-phenyl-3-tosyl-1,1a,2,3,3a,4-hexahydrocyclopropa[c]indeno[2,1-b]pyrrole-3a-d

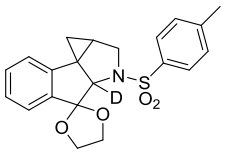
d-498



Prepared according to **GP14** from ynamide **d-494** (86.5 mg, 0.2 mmol) heating at 80 °C for 2 hours. Purification by flash column chromatography [hexane:EtOAc (9:1)] gave tetracycle **d-498** (56.2 mg, 65%) as a 1:3.1 mixture of diastereoisomers as a white solid; mp: 128-130 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.3 Hz, 2H, minor), 7.33 (d, *J* = 8.3 Hz, 2H, major), 7.20 – 7.10 (m, 6H, major and 6H, minor), 7.10 – 7.00 (m, 3H, major and 3H, minor), 6.91 – 6.85 (m, 1H, major, 1H, minor) 6.76 (d, *J* = 7.4 Hz, 1H, major) 6.72 – 6.69 (m, 1H, minor), 3.92 (dd, *J* = 10.6, 4.1 Hz, 1H, major), 3.56 (d, *J* = 10.6 Hz, 1H, major), 3.34 (s, 3H, minor), 3.03 (d, *J* = 11.3 Hz, 1H, minor), 2.87 (s, 3H, major), 2.26 (s, 3H, minor), 2.23 (s, 3H, major), 2.21 – 2.14 (m, 1H, minor), 1.40 – 1.33 (m, 1H, major), 1.15 – 1.02 (m, 1H, major, 2H, minor), -0.03 (app. t, *J* = 5.4 Hz, 1H, major), -0.20 – -0.27 (m, 1H, minor); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.4 (C, minor), 143.1 (C, major), 143.0 (C, minor), 142.7 (C, major), 142.2 (C, major), 141.7 (C, minor), 141.1 (C, minor), 140.2 (C, major), 137.3 (C, major), 137.1 (C, minor), 129.8 (2 × CH, minor), 129.6 (2 × CH, major), 129.4 (CH, major), 129.2 (CH, minor), 128.1 (2 × CH, minor), 127.9 (2 × CH, major), 127.8 (2 × CH, minor), 127.7 (2 × CH, major and CH, minor), 127.6 (2 × CH, minor), 127.2 (CH, major), 127.20 (2 × CH, major and CH, minor), 127.15 (CH, major), 126.1 (CH, major), 125.7 (CH, minor), 119.9 (CH, major), 119.4 (CH, minor), 91.8 (C, major), 88.9 (C, minor), 54.7 (CH_2, major), 52.7 (CH_2, minor), 52.0 (CH, minor), 51.9 (CH, major), 38.5 (C, major), 37.7 (C, minor), 27.1 (CH_3, minor), 26.7 (CH_3, major), 21.6 (CH_3, major and CH_3 minor), 11.5 (CH_2, minor), 11.0 (CH_2, major), C-D carbon was not apparent in this

case; IR: ν_{max} (cm^{-1}) 3050, 2996, 2947, 2929, 1598, 1492, 1462, 1447, 1349, 1161, 1079, 662; HRMS (ES) *m/z* calculated for $C_{26}H_{25}NO_3SD$ $(M+H)^+$ 433.1696, found 433.1687.

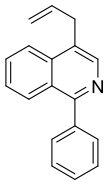
3-Tosyl-1a,2,3,3a-tetrahydro-1H-spiro[cyclopropa[c]indeno[2,1-b]pyrrole-4,2'-[1,3]dioxolane]-3a-d **d-519**



Prepared according to **GP14** from ynamide **d-515** (38.4 mg, 0.1 mmol), stirring at 80 °C for 5.5 hours. Purification by flash column chromatography [toluene:Et_2O (97:3), 1% Et_3N] gave tetracycle **d-519** (34.5 mg, 90%) as a white solid; mp: 132-134 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.30 (m, 3H), 7.30 – 7.22 (m, 2H), 6.78 – 6.71 (m, 1H), 4.56 – 4.48 (m, 1H), 4.42 (dd, *J* = 13.0, 6.4 Hz, 1H), 4.32 – 4.16 (m, 2H), 4.07 (dd, *J* = 11.4, 4.3 Hz, 1H), 3.67 (d, *J* = 11.4 Hz, 1H), 2.44 (s, 3H), 1.46 – 1.40 (m, 1H), 1.19 (dd, *J* = 7.8, 6.4 Hz, 1H), -0.23 – -0.28 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.8 (C), 141.2 (C), 140.1 (C), 136.3 (C), 130.4 (CH), 130.0 (2 × CH), 127.8 (CH), 127.2 (2 × CH), 123.9 (CH), 119.3 (CH), 113.4 (C), 77.1 (t, $J_{C\text{-}D}$ = 22.7 Hz, CD), 66.7 (CH_2), 66.1 (CH_2), 54.1 (CH_2), 37.6 (C), 26.4 (CH_3), 21.7 (CH), 11.6 (CH_2); IR: ν_{max} (cm^{-1}) 2985, 2952, 2918, 2896, 1615, 1598, 1463, 1345, 1337, 1277, 1255, 1017, 759, 666; HRMS (ES) *m/z* calculated for $C_{21}H_{20}DNO_4SNa$ $(M+Na)^+$ 407.1152, found 407.1143.

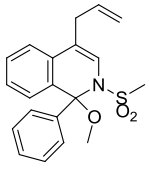
Preparation of Functionalised Isoquinolines

***4-Allyl-1-phenylisoquinoline* 651**



Prepared according to **GP16** from ynamide **255** (71.1 mg, 0.2 mmol), stirring for 8 hours. Purification by flash column chromatography [hexane:EtOAc (95:5)] gave the isoquinoline (46.2 mg, 65%) as a pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.82 – 7.65 (m, 3H), 7.61 – 7.44 (m, 4H), 6.13 (ddt, *J* = 16.5, 10.9, 6.2 Hz, 1H), 5.16 (app, dt, *J* = 16.5, 1.5 Hz, 1H), 5.17 (app. dt, *J* = 10.9, 1.5 Hz, 1H), 3.84 (d, *J* = 6.2 Hz, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 159.9 (C), 142.2 (CH), 139.7 (C), 136.2 (CH), 135.8 (C), 130.1 (CH), 130.0 (2 × CH), 128.6 (CH), 128.4 (2 × CH), 128.4 (CH), 126.9 (CH), 126.6 (C), 123.7 (CH), 117.0 (CH_2 and C), 34.6 (CH_2); IR: ν_{max} (cm^{-1}) 3058, 2923, 2953, 1638, 1615, 1580, 1550, 1383, 913, 776, 760, 697, 675; HRMS (ES) *m/z* calculated for $C_{18}H_{16}N$ $(M+H)^+$ 246.1283, found 246.1290.

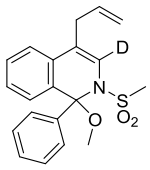
***4-Allyl-1-methoxy-2-(methylsulfonyl)-1-phenyl-1,2-dihydroisoquinoline* 654**



Prepared according to **GP15** from ynamide **255** (71.1 mg, 0.2 mmol), stirring for 24 hours. Purification by flash column chromatography [hexane:EtOAc (90:10), 1% Et_3N] followed by recrystallisation [hexane:CH_2Cl_2] gave the isoquinoline **654** (60.4 mg, 85%) as a white solid; mp: 64-66 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.54 – 7.45 (m, 2H), 7.37 – 7.22 (m, 5H), 7.09 (ddd, *J* = 8.4, 5.4, 3.2 Hz, 1H), 6.97 (s, 1H), 6.96 – 6.92 (m, 1H), 6.00 (ddt, *J* = 17.0, 10.1, 6.0 Hz, 1H), 5.19 (app. dq, *J* = 17.0, 1.5 Hz, 1H), 5.16 (app. ddd, *J* = 10.1, 3.0, 1.5 Hz, 1H), 3.25 (ddd, *J* = 6.0, 3.0, 1.5 Hz, 2H), 3.18 (s, 3H), 2.49 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ

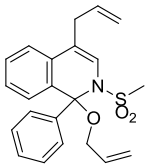
145.0 (C), 136.0 (CH), 134.0 (C), 130.9 (C), 129.2 (CH), 128.5 (CH), 128.1 (CH), 127.8 (2 × CH), 127.5 (2 × CH), 127.2 (CH), 124.0 (CH), 121.4 (CH), 117.0 (CH_2), 110.6 (C), 93.5 (C), 51.0 (CH_3), 42.0 (CH_3), 34.4 (CH_2); IR: ν_{max} (cm^{-1}) 3060, 2936, 2851, 1638, 1494, 1447, 1388, 1347, 1224, 1166, 1041, 775; HRMS (ES) *m/z* calculated for $C_{20}H_{21}NO_3SNa$ $(M+Na)^+$ 378.1140, found 378.1146.

4-Allyl-1-methoxy-2-(methylsulfonyl)-1-phenyl-1,2-dihydroisoquinoline-3-d **d-654**



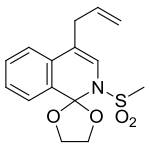
Prepared according to **GP15** from ynamide **d-255** (71.3 mg, 0.2 mmol) stirring for 48 hours. Purification by flash column chromatography [hexane:Et_2O (90:10), 1 % Et_3N] gave the isoquinoline **d-654** (46.0 mg, 65%) as a white solid; mp: 66-68 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.54 – 7.46 (m, 2H), 7.37 – 7.21 (m, 5H), 7.09 (ddd, *J* = 8.5, 5.2, 3.3 Hz, 1H), 6.98 – 6.91 (m, 1H), 6.00 (ddt, *J* = 17.0, 10.1, 6.0 Hz, 1H), 5.19 (app. dq, *J* = 17.1, 1.5 Hz, 1H), 5.16 (app. ddd, *J* = 10.1, 3.0, 1.5 Hz, 1H), 3.25 (ddd, *J* = 6.0, 3.0, 1.5 Hz, 2H), 3.18 (s, 3H), 2.49 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.9 (C), 135.9 (CH), 134.0 (C), 130.9 (C), 129.2 (CH), 128.5 (CH), 128.1 (CH), 127.8 (2 × CH), 127.5 (2 × CH), 127.2 (CH), 123.7 (t, $J_{C\text{-}D}$ = 27.5 Hz, CD), 121.4 (CH), 117.0 (CH_2), 110.4 (C), 93.4 (C), 51.0 (CH_3), 42.0 (CH_3), 34.3 (CH_2); IR: ν_{max} (cm^{-1}) 3063, 3029, 3008, 2975, 2932, 2841, 1637, 1492, 1354, 1164, 908, 859, 749; HRMS (ES) *m/z* calculated for $C_{20}H_{20}DNO_3SNa$ $(M+Na)^+$ 379.1203, found 379.1195.

***4-Allyl-1-(allyloxy)-2-(methylsulfonyl)-1-phenyl-1,2-dihydroisoquinoline* 662**



Prepared according to **GP15** from ynamide **323** (76.3 mg, 0.2 mmol) stirring for 48 hours. Purification by flash column chromatography [hexane:Et_2O (90:10), 1 % Et_3N] gave the isoquinoline **XX** (47.5 mg, 62%) as a white solid; mp: 50-52 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.58 – 7.48 (m, 2H), 7.38 – 7.22 (m, 5H), 7.09 (ddd, *J* = 8.4, 5.1, 3.5 Hz, 1H), 7.01 – 6.93 (m, 2H), 6.08 – 5.84 (m, 2H), 5.33 (app. dq, *J* = 17.2, 1.7 Hz, 1H), 5.24 – 5.14 (m, 2H), 5.15 (ddd, *J* = 17.3, 3.1, 1.5 Hz, 1H), 4.04 (ddt, *J* = 12.5, 5.2, 1.6 Hz, 1H), 3.60 (ddt, *J* = 12.5, 5.2, 1.6 Hz, 1H), 3.25 (d, *J* = 5.9 Hz, 2H), 2.49 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 145.0 (C), 135.9 (CH), 134.3 (C), 134.1 (CH), 130.7 (C), 129.2 (CH), 128.6 (CH), 128.1 (CH), 127.8 (2 × CH), 127.6 (2 × CH), 127.2 (CH), 123.9 (CH), 121.4 (CH), 117.0 (CH_2), 116.5 (CH_2), 110.7 (C), 92.8 (C), 64.5 (CH_2), 42.0 (CH_3), 34.4 (CH_2); IR: ν_{max} (cm^{-1}) 3004, 2987, 2890, 1608, 1584, 1489, 1427, 1393, 1272, 1160, 1113, 1063, 750; HRMS (ES) *m/z* calculated for $C_{22}H_{23}NO_3SNa$ $(M+Na)^+$ 404.1296, found 404.1299.

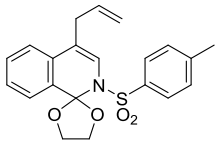
***4'-Allyl-2'-(methylsulfonyl)-2'H-spiro[[1,3]dioxolane-2,1'-isoquinoline]* 665**



Prepared according to **GP16** from ynamide **255** (61.5 mg, 0.2 mmol), stirring for 24 hours. Purification by flash column chromatography [hexane:Et_2O (85:15), 1 % Et_3N] gave the isoquinoline **665** (52.4 mg, 85%) as a white solid; mp: 72-74 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.54 – 7.48 (m, 1H), 7.48 – 7.39 (m, 1H), 7.39 – 7.31 (m, 2H), 6.88 (s, 1H), 5.96 (ddt, *J* = 16.9, 10.1, 6.2 Hz, 1H), 5.15 (app. dq, *J* = 17.1, 1.4 Hz, 1H), 5.12 (app. ddd, *J* = 10.1, 3.0, 1.4 Hz, 1H), 4.54 (m, 2H), 4.21 (m, 2H), 3.28 (ddd, *J* = 6.1, 3.0, 1.4 Hz, 2H), 3.06 (s, 3H);

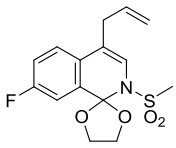
^{13}C-NMR (101 MHz, $CDCl_3$): δ 135.6 (CH), 131.5 (C), 131.0 (C), 129.6 (CH), 127.3 (CH), 123.6 (CH), 123.1 (CH), 122.5 (CH), 117.2 (CH_2), 116.3 (C), 112.8 (C), 66.6 (2 × CH_2), 43.3 (CH_3), 34.0 (CH_2); IR: ν_{max} (cm^{-1}) 3080, 3007, 2974, 2898, 2848, 1641, 1343, 1268, 1167; HRMS (ES) *m/z* calculated for $C_{15}H_{18}NO_4S$ $(M+H)^+$ 308.0957, found 308.0951.

***4-Allyl-2-tosyl-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane]* 666**



Prepared according to **GP16** from ynamide **515** (76.7 mg, 0.2 mmol) stirring for 48 hours. Purification by flash column chromatography [hexane:Et_2O (93:7), 1 % Et_3N] gave the isoquinoline **666** (53.2 mg, 69%) as a white solid; mp: 82-84 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.3 Hz, 2H), 7.29 – 7.17 (m, 3H), 7.16 – 7.08 (m, 1H), 7.06 – 6.95 (m, 3H), 5.91 (ddt, *J* = 16.2, 10.1, 6.1 Hz, 1H), 5.10 (app. ddd, *J* = 17.1, 3.3, 1.6 Hz, 1H), 5.04 (dd, *J* = 10.1, 1.6 Hz, 1H), 4.54 - 4.44 (m, 2H), 4.15 – 4.05 (m, 2H), 3.22 (app. dd, *J* = 6.1, 1.1 Hz, 2H), 2.22 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.4 (C), 139.1 (C), 135.8 (CH), 131.3 (C), 130.9 (C), 129.3 (3 × CH), 127.2 (CH), 126.7 (2 × CH), 123.8 (CH), 123.6 (CH), 122.3 (CH), 117.1 (C), 117.0 (CH_2), 112.8 (C), 66.4 (2 × CH_2), 34.1 (CH_2), 21.6 (CH_3); IR: ν_{max} (cm^{-1}) 3076, 2978, 2903, 1640, 1599, 1348, 1264, 1168, 1016, 981, 949, 670; HRMS (ES) *m/z* calculated for $C_{21}H_{22}NO_4S$ $(M+H)^+$ 387.1270, found 384.1265.

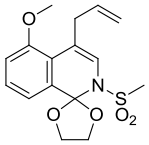
***4-Allyl-7-fluoro-2-(methylsulfonyl)-2H-spiro[isoquinoline-1,2'-[1,3]dioxolane]* 672**



Prepared according to **GP16** from ynamide **669** (65.1 mg, 0.2 mmol), stirring for 24 hours. Purification by flash column chromatography [hexane:EtOAc (90:10), 1% Et_2N] gave the isoquinoline **672** (57.2 mg, 88%) as a white solid; mp: 86-88 °C; ^{1}H-NMR (300

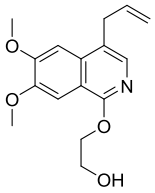
MHz, $CDCl_3$): δ 7.32 (dd, *J* = 8.5, 5.3 Hz, 1H), 7.20 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.13 (td, *J* = 8.5, 2.7 Hz, 1H), 6.84 (s, 1H), 5.93 (ddt, *J* = 17.2, 10.1, 6.1 Hz, 1H), 5.14 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.12 (dd, *J* = 10.1, 1.5 Hz, 1H), 4.60 – 4.46 (m, 2H), 4.27 – 4.14 (m, 2H), 3.25 (dd, *J* = 6.1, 1.2 Hz, 2H), 3.06 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 162.0 (d, $J_{C\text{-}F}$ = 246.9 Hz, C), 135.4 (CH), 132.9 (d, $J_{C\text{-}F}$ = 6.8 Hz, C), 127.95 (d, $J_{C\text{-}F}$ = 2.1 Hz, C), 124.5 (d, $J_{C\text{-}F}$ = 7.7 Hz, CH), 122.4 (CH), 117.3 (CH_2), 116.7 (d, $J_{C\text{-}F}$ = 21.8 Hz, CH), 115.6 (C), 110.8 (d, $J_{C\text{-}F}$ = 23.8 Hz, CH), 66.7 (2 × CH_2), 46.3 (C), 43.4 (CH_3), 34.1 (CH_2); IR: ν_{max} (cm^{-1}) 3090, 3024, 2981, 2907, 1643, 1612, 1582, 1501, 1345, 1262, 1160, 963, 750; HRMS (ES) *m/z* calculated for $C_{15}H_{17}NO_4FS$ $(M+Na)^+$ 326.0862, found 326.0854.

***4'-Allyl-5'-methoxy-2'-(methylsulfonyl)-2'H-spiro[[1,3]dioxolane-2,1'-isoquinoline]* 673**



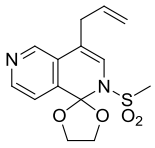
Prepared according to **GP16** from ynamide **670** (67.5 mg, 0.2 mmol), stirring for 13 hours. Purification by flash column chromatography [hexane:EtOAc (85:15), 1% Et_2N] gave the isoquinoline **673** (34.6 mg, 51%) as a white solid; mp: 91-93 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.25 (dd, *J* = 8.2, 7.7 Hz, 1H), 7.11 (dd, *J* = 7.7, 1.0 Hz, 1H), 6.91 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.66 (s, 1H), 5.92 (ddt, *J* = 16.8, 10.2, 6.1 Hz, 1H), 5.00 (app. dq, *J* = 16.8, 1.4 Hz, 1H), 4.93 (ddd, *J* = 10.2, 3.2, 1.4 Hz, 1H), 4.57 – 4.46 (m, 2H), 4.25 – 4.13 (m, 2H), 3.80 (s, 3H), 3.45 (dd, *J* = 6.1, 1.2 Hz, 2H), 2.96 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 155.7 (C), 137.6 (CH), 133.6 (C), 128.3 (CH), 122.9 (CH), 120.9 (C), 118.5 (C), 115.9 (CH), 115.3 (CH_2), 112.5 (CH), 66.4 (2 × CH_2), 55.7 (CH_3), 46.3 (C), 43.1 (CH_3), 37.5 (CH_2); IR: ν_{max} (cm^{-1}) 3017, 2918, 2905, 2839, 1638, 1597, 1570, 1470, 1342, 1263, 1167, 1141, 1052, 1022, 963, 951, 733; HRMS (ES) *m/z* calculated for $C_{16}H_{19}NO_5SNa$ $(M+Na)^+$ 360.0882, found 360.0885.

***2-((4-Allyl-6,7-dimethoxyisoquinolin-1-yl)oxy)ethan-1-ol* 675**



Prepared according to **GP15** from ynamide **671** (73.5 mg, 0.2 mmol), stirring for 11 hours. Purification by flash column chromatography [hexane:EtOAc (70:30), 1% Et_2N] gave the isoquinoline **674** (42.0 mg, 57%) as a white solid. Several unsuccessful attempts at recrystallisation were then made [hexane:CH_2Cl_2]. The solvents were removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (ca. 0.5 mL) and filtered in a pipette through a short pad (ca. 1 cm) of silica, eluting with CH_2Cl_2 (10 mL, 1 % Et_3N. The solvents were removed under reduced pressure to give the alcohol **675** (29.4 mg, 70% from the acetal) as a white solid; mp: 102-104 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.47 (s, 1H), 7.06 (s, 1H), 5.96 (ddt, *J* = 17.1, 10.3, 6.2 Hz, 1H), 5.04 (app. ddd, *J* = 17.1, 3.3, 1.6 Hz, 1H), 5.02 (app. ddd, *J* = 10.3, 3.3, 1.6 Hz, 1H), 4.64 – 4.58 (m, 2H), 3.96 (s, 3H), 3.97 – 3.94 (m, 2H), 3.94 (s, 3H), 3.54 (d, *J* = 6.2 Hz, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 159.2 (C), 152.9 (C), 149.4 (C), 136.9 (CH), 136.5 (CH), 133.6 (C), 122.7 (C), 116.4 (CH_2), 114.3 (C), 103.4 (CH), 102.6 (CH), 70.1 (CH_2), 63.3 (CH_2), 56.1 (CH_3), 55.9 (CH_3), 34.5 (CH_2); IR: ν_{max} (cm^{-1}) 3349, 3071, 2930, 2854, 1646, 1611, 1504, 1424, 1212, 1169, 1040; HRMS (ES) *m/z* calculated for $C_{16}H_{20}NO_4$ $(M+H)^+$ 290.1392, found 290.1389.

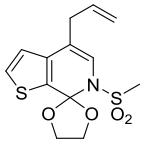
***4'-Allyl-2'-(methylsulfonyl)-2'H-spiro[[1,3]dioxolane-2,1'-[2,6]naphthyridine]* 678**



Prepared according to **GP16** from ynamide **676** (59.9 mg, 0.2 mmol) stirring for 24 hours. Purification by flash column chromatography [toluene:Et_2O (90:10), 1 % Et_3N] gave the isoquinoline **678** (39.3 mg, 67%) as a pale orange solid; mp: 112-114 °C; ^{1}H-NMR

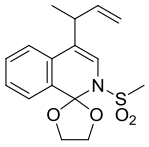
(300 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.59 (d, *J* = 5.1 Hz, 1H), 7.34 (d, *J* = 5.1 Hz, 1H), 6.97 (s, 1H), 5.94 (ddt, *J* = 16.7, 10.2, 6.1 Hz, 1H), 5.17 (app. dq, *J* = 16.7, 1.5 Hz, 1H), 5.14 (app. dq, *J* = 10.2, 1.5 Hz, 1H), 4.62 – 4.49 (m, 2H), 4.30 – 4.16 (m, 2H), 3.32 (ddd, *J* = 6.1, 2.6, 1.5 Hz, 2H), 3.09 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 148.4 (CH), 144.5 (CH), 138.0 (C), 134.9 (CH), 126.6 (C), 124.5 (CH), 117.7 (CH_2), 117.6 (CH), 113.3 (C), 111.7 (C), 67.0 (2 × CH_2), 43.7 (CH_3), 33.4 (CH_2); IR: ν_{max} (cm^{-1}) 3119, 3037, 3007, 2985, 2956, 2987, 1364, 1414, 1333, 1277, 1149, 1088, 1024, 967, 950, 751; HRMS (ES) *m/z* calculated for $C_{14}H_{17}N_2O_4S$ $(M+H)^+$ 309.0909, found 309.0899.

***4-Allyl-6-(methylsulfonyl)-6H-spiro[thieno[2,3-c]pyridine-7,2'-[1,3]dioxolane]* 679**



Prepared according to **GP16** from ynamide **677** (62.7 mg, 0.2 mmol), stirring for 4 hours. Purification by flash column chromatography [hexane:EtOAc (80:10), 1% Et_2N] followed by recrystallisation [hexane:CH_2Cl_2] gave the isoquinoline **679** (15.7 mg, 25%) as a white solid; mp: 104-105 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38 (d, *J* = 5.4 Hz, 1H), 7.24 (d, *J* = 5.4 Hz, 1H), 6.65 (s, 1H), 5.67 (ddt, *J* = 16.9, 10.2, 6.4 Hz, 1H), 5.36 (dd, *J* = 16.9, 1.2 Hz, 1H), 5.27 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.22 – 4.13 (m, 1H), 4.13 – 4.01 (m, 3H), 3.30 (dd, *J* = 13.9, 6.4 Hz, 1H), 3.22 (dd, *J* = 13.9, 6.4 Hz, 1H), 2.95 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.1 (C), 129.2 (CH), 128.8 (CH), 126.3 (CH), 125.6 (C), 122.9 (CH_2), 116.4 (2 × C), 97.9 (CH), 66.0 (CH_2), 65.6 (CH_2), 37.9 (CH_3), 37.2 (CH_2); IR: ν_{max} (cm^{-1}) 3112, 3012, 2985, 2931, 2894, 1445, 1321, 1146, 1074, 937, 731; HRMS (ES) *m/z* calculated for $C_{13}H_{15}NO_4S_2Na$ $(M+Na)^+$ 336.0340, found 336.0345.

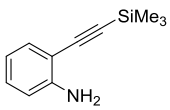
***4'-(But-3-en-2-yl)-2'-(methylsulfonyl)-2'H-spiro[[1,3]dioxolane-2,1'-isoquinoline]* 684**



Prepared according to **GP16** from ynamide **683** (64.3 mg, 0.2 mmol), stirring for 18 hours. Purification by flash column chromatography [hexane:EtOAc (90:10), 1 % Et_3N] gave the isoquinoline **684** (59.2 mg, 92%) as a white solid; mp: 68-70 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.52 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.39 – 7.31 (m, 1H), 6.86 (d, *J* = 0.9 Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.3, 6.1 Hz, 1H), 5.12 (app. dt, *J* = 17.3, 1.5 Hz, 1H), 5.09 (app. dt, *J* = 10.3, 1.4 Hz, 1H), 4.58 – 4.48 (m, 2H), 4.26 – 4.16 (m, 2H), 3.67 – 3.55 (m, 1H), 3.06 (s, 3H), 1.36 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 141.7 (CH), 131.4 (C), 131.2 (C), 129.5 (CH), 127.2 (CH), 123.6 (CH), 122.5 (CH), 122.0 (CH), 121.2 (C), 114.7 (CH_2), 112.6 (C), 66.7 (CH_2), 66.5 (CH_2), 43.4 (CH), 36.3 (CH_3), 19.1 (CH_3); IR: ν_{max} (cm^{-1}) 3104, 3013, 2973, 2937, 2917, 2867, 1640, 1342, 1327, 1263, 1169, 944, 750; HRMS (ES) *m/z* calculated for $C_{16}H_{20}NO_4S$ $(M+H)^+$ 322.1113, found 322.1121.

Compounds from Chapter 5

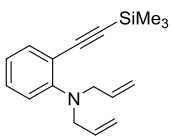
2-((Trimethylsilyl)ethynyl) aniline 762



Trimethylsilylacetylene (35.5 mL, 0.25 mol, 1.1 equiv.), was added to a solution of 2-iodoaniline (50 g, 0.22 mol) in diethylamine (500 mL, 0.45 M). $Pd(PPh_3)_2Cl_2$ (1.6 g, 1 mol%), and CuI (430 mg, 1 mol%) were added and mixture stirred for 18 hours at room temperature. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography [hexane:EtOAc (96:4)] to give the protected alkyne **762** (42.4 g, 98%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 7.7, 1.4, Hz, 1H), 7.07 - 7.15 (m, 1H), 6.62 - 6.71 (m, 2H), 4.22 (br. s, 2H), 0.26 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ

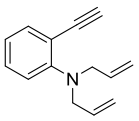
148.3 (C), 132.8 (CH), 130.2 (CH), 118.1 (CH), 114.5 (CH), 107.9 (C), 102.4 (C), 99.9 (C), 0.2 (3 × CH_3); MS (EI): *m/z* 189 (M^+, 58%), 174 (100), 146 (5). Data matches that reported in the literature.[216]

_N_,_N_-Diallyl-2-((trimethylsilyl)ethynyl)aniline 763



Allyl iodide (102 mL, 1.1 mol, 5.0 equiv.) was added to a solution of 2-((trimethylsilyl)ethynyl) aniline **762** (42.3 g, 0.22 mol) and potassium carbonate (123.4 g, 0.89 mol, 4.0 equiv.) in acetone (1.1 L, 0.2 M). The mixture was heated at reflux for 16 hours and then cooled and filtered through a plug of celite. Purification by flash column chromatography [hexane:CH_2Cl_2 (95:5)] gave the diallyl aniline deriviative **763** (55.7 g, 93%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.17 (ddd, *J* = 8.3, 7.8, 1.7 Hz, 1H), 6.77 - 6.88 (m, 2H), 5.88 (ddt, *J* = 16.9, 10.2, 5.5 Hz, 2H), 5.20 (dd, *J* = 16.9, 1.6, Hz, 2H), 5.16 (dd, *J* = 10.2, 1.6 Hz, 2H), 3.93 (d, *J* = 5.5 Hz, 4H), 0.24 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 152.8 (C), 135.4 (CH), 135.0 (CH), 129.1 (2 × CH_2), 120.1 (CH), 119.0 (CH), 117.0 (2 × CH_2), 115.0 (C), 104.6 (C), 99.1 (C), 54.0 (2 × CH_2), 0.2 (3 × CH_3); MS (EI): *m/z* 269 (M^+, 36%), 242 (100), 196 (55), 73 (32). Data matches that reported in the literature.[182]

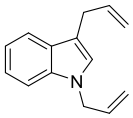
_N_,_N_-Diallyl-2-ethynylaniline 764



Potassium carbonate (14.2 g, 0.10 mol, 0.5 equiv.) was added to a solution of *N,N*-diallyl-2-((trimethylsilyl)ethynyl)aniline **763** (55.5 g, 0.21 mol, 1.0 equiv.) in methanol (1.0 L, 0.2 M) and the mixture was stirred for 2 hours at room temperature. Saturated $NaHCO_3$ solution (500 mL) was added and the aqueous layer was extracted with EtOAc (2 × 200

mL). The combined organic layers were dried over Na_2SO_4, the solid filtered off and the solvent removed under reduced pressure to give the terminal alkyne **764** (40.5 g, >99%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 7.6, 1.7, 1H), 7.22 - 7.21 (m, 1H), 6.82 - 6.93 (m, 1H), 6.82 - 6.93 (m, 1H), 5.86 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 2H), 5.19 (dd, *J* = 17.1, 1.5 Hz, 2H), 5.15 (dd, *J* = 10.2, 1.5 Hz, 2H), 3.90 (d, *J* = 6.0 Hz, 4H), 3.38 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 153.3 (C), 134.9 (CH), 134.5 (CH), 129.6 (2 × CH), 121.1 (CH), 119.9 (CH), 117.6 (2 × CH_2), 115.1 (C), 83.4 (C), 82.5 (CH), 54.8 (2 × CH_2); MS (EI): *m/z* 197 (M^+, 100%), 170 (95), 154 (10), 128 (8); HRMS (ES) *m/z* calculated for $C_{15}H_{14}N$ $(M)^+$ 197.1204, found 197.1208. Data matches that reported in the literature.[182]

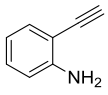
1,3-Diallyl-1H-indole 769



$Ph_3PAuNTf_2$ (2:1 $Ph_3PAuNTf_2$:toluene, 3.9 mg, 5 mol%) was added to a solution of *N,N*-diallyl-2-ethynylaniline **764** (19.7 mg, 0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (1.0 mL, 0.1 M). The reaction was stirred for 16 hours at room temperature and filtered through a short (ca. 1 cm) plug of silica, eluting with CH_2Cl_2 (15 mL) and the solvent was removed under reduced pressure. Tetramethylbenzene (2.7 mg, 20 mol%) was added to the flask before being taken up in $CDCl_3$ to carry out NMR and mass spectrometry analysis; 88% ^{1}H NMR yield; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.22 (app. t, *J* = 6.9 Hz, 1H), 7.12 (app. t, *J* = 6.9 Hz, 1H), 6.93 (s, 1H), 6.17 - 5.93 (m, 2H), 5.06 - 5.23 (m, 4H), 4.71 (dd, *J* = 5.4, 1.6, 2H), 3.54 (dd, *J* = 6.5, 1.3 Hz, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 137.5 (CH), 136.6 (C), 133.7 (CH), 128.1 (C), 125.5 (CH), 121.6 (CH), 119.3 (CH), 118.8 (CH), 117.2 (CH_2), 115.1 (CH_2), 113.4 (C),

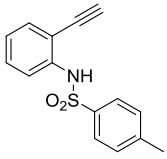
109.5 (CH), 48.7 (CH_2), 29.8 (CH_2); MS (EI): *m/z* 197 (M^+, 100%), 170 (52), 156 (44), 128 (21). Data matches that reported in the literature.[182]

2-Ethynylaniline 781



Potassium carbonate (1.4 g, 10.4 mmol, 2.0 equiv.) was added to a solution of 2-(trimethylsilyl)ethynyl) aniline **762** (0.8 g, 5.2 mmol, 1.0 equiv.) in methanol (8 mL, 0.7 M) and the mixture was stirred for 30 minutes. Saturated $NaHCO_3$ solution (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, the solid filtered off and the solvent removed under reduced pressure to give the terminal alkyne **781** (390 mg, 65%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 8.2, 2.4, Hz, 1H), 7.15 (dd, *J* = 8.2, 7.1 Hz, 1H), 6.71 - 6.66 (m, 2H), 4.25 (s, 2H), 3.39 (s, 1H); MS (EI): *m/z* 117 (M^+, 100%), 102 (34), 66 (21).Data matches that reported in the literature.[217]

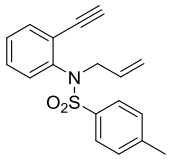
***N*-(2-Ethynylphenyl)-4-methylbenzenesulfonamide 782**



Pyridine (0.4 mL, 5.1 mmol, 5.0 equiv.), and DMAP (20 mg), were added to a solution of 2-ethynylaniline **781** (118 mg, 1.0 mmol, 1.0 equiv.) in CH_2Cl_2 (6 mL, 0.2 M) at 0 °C and the mixture was stirred for 5 minutes at this temperature. *p*-TsCl (1.9 g, 1.2 mmol, 1.2 equiv.) was added portionwise and mixture stirred at 0 °C for 30 minutes before being allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched with 1 M HCl solution (10 mL) and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. Purification by flash column

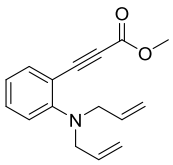
chromatography [hexane:EtOAc (90:10)] gave the sulfonylamide **782** (201 mg, 75%) as a white solid; mp: 86-88 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.70 - 7.58 (m, 2H), 7.61 - 7.58 (m, 1H), 7.35 - 7.20 (m, 5H), 7.04 - 6.99 (m, 1H), 3.37 (s, 1H), 2.37 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.5 (C), 138.9 (CH), 136.3 (C), 132.9 (C), 130.9 (CH), 130.0 (CH), 127.2 (C), 124.6 (2 × CH), 119.8 (CH), 112.7 (2 × CH), 84.9 (C), 78.8 (CH), 21.8 (CH_3); IR: ν_{max} (cm^{-1}) 3278, 2924, 2845, 1736, 1599, 1490, 1344, 1169, 1091, 760; MS (EI): *m/z* 294 ($[M+Na]^+$, 100%).Data matches that reported in literature.[183]

_N_-Allyl-N-(2-ethynylphenyl)-4-methylbenzenesulfonamide 783



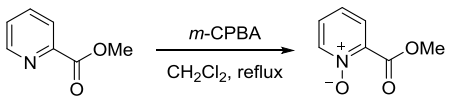
Allyl bromide (0.13 mL, 1.4 mmol, 1.6 equiv.), and potassium carbonate (0.19 g, 1.4 mmol, 1.5 equiv.) were added to a solution amide **782** (0.24 g, 0.9 mmol, 1.0 equiv.) in acetone (0.2 M) and the resulting mixture was stirred at reflux for 5 hours. The solvent was removed under reduced pressure and the residue dissolved in EtOAc (20 mL). The organic layer was washed with water (3 × 15 mL), brine (3 × 15 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography [hexane:EtOAc (90:10)] gave the N-allyl amine **783** (0.27 g, 83 %) as a clear oil; 1H-NMR (300 MHz, $CDCl_3$): δ 7.62 (d, J = 8.3 Hz, 2H), 7.49 (dd, J = 7.3, 2.0 Hz, 1H), 7.22 - 7.35 (m, 4H), 7.13 (dd, J = 7.8, 2.0 Hz, 1H), 5.82 (ddt, J = 17.2, 10.1, 6.5 Hz, 1H), 5.05 (dd, J = 17.2, 1.2 Hz, 1H), 5.02 (dd, J = 10.1, 1.2 Hz, 1H), 4.27 (d, J = 6.5 Hz, 2H), 2.96 (s, 1H), 2.43 (s, 3H); MS (EI): m/z 334 ($[M+Na]^+$, 100%), 284 (75), 101 (30). Data matches that reported in literature.[218]

Methyl 3-(2-(diallylamino)phenyl)propiolate 786



Terminal alkyne **764** (40.5 g, 0.21 mol, 1.0 equiv.) was dissolved in THF (0.82 L, 0.25 M) and cooled to -78 °C . *n*-BuLi (98.6 mL, 2.5 M in hexane, 0.25 mol, 1.2 equiv.) was added dropwise and the resulting solution stirred for 1 hour. Methyl chloroformate (23.8 mL, 0.31 mol, 1.5 equiv.) was added slowly and the solution warmed to room temperature. After stirring for a further hour, aqueous NH_4Cl solution (300 mL) was added and the aqueous layer was extracted with Et_2O (3 × 300 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography [hexane:EtOAc (97:3)] gave the substituted alkyne **786** (37.8 g, 72%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.32 – 7.24 (m, 1H), 6.92 – 6.88 (m, 1H), 6.83 (td, *J* = 7.6, 1.0 Hz, 1H), 5.90 (ddt, *J* = 16.4, 10.5, 5.8 Hz, 2H), 5.20 (app. dt, *J* = 16.4, 1.5 Hz, 2H), 5.19 (app. dt, *J* = 10.5, 1.5 Hz, 2H), 3.94 (d, *J* = 5.8 Hz, 4H), 3.82 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 155.0 (C), 154.4 (C), 136.3 (CH), 134.7 (2 × CH), 131.5 (CH), 120.1 (CH), 119.0 (CH), 117.6 (2 × CH_2), 110.4 (C), 87.2 (C), 85.6 (C), 54.7 (2 × CH_2), 52.7 (CH_3); IR: ν_{max} (cm^{-1}) 3078, 2952, 2841, 2212, 1705, 1487, 1417, 1299, 1273, 1169, 746; HRMS (EI) *m/z* calculated for $C_{16}H_{17}NO_2$ $(M+H)^+$ 255.1259, found 255.1256.

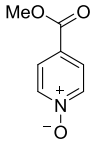
2-(Methoxycarbonyl)pyridine 1-oxide O-1



O-1

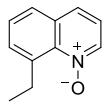
Methyl picolinate (50.0 g, 0.4 mol, 1.0 equiv.) was dissolved in CH_2Cl_2 (1.5 L, 0.25 M) and *m*-CPBA (77% pure, 84.6 g, 0.5 mol, 1.4 equiv.) was added in portions at room temperature. The resulting solution was heated to relux for 16 hours. Once cooled to room temperature, saturated $NaHCO_3$ solution (500 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (6 × 300 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography [EtOAc:MeOH (88:12)] gave the *N*-oxide **O-1** (40.5 g, 73%) as a white solid; mp: 70-72 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.76 – 8.73 (m, 1H), 8.14 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.85 (td, *J* = 7.8, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.8, 4.7, 1.7 Hz, 1H), 4.01 (s, 3H). Data matches that reported in literature.[219]

4-(Methoxycarbonyl)pyridine 1-oxide O-2



This *N*-oxide was donated by a collegue (Mickaël Dos Santos).

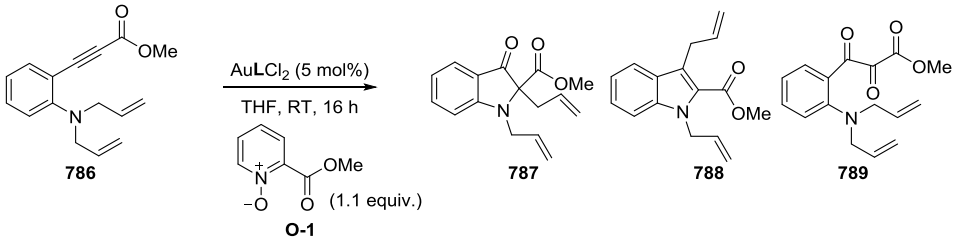
8-Ethylquinoline 1-oxide O-3



O-3

This *N*-oxide was donated by a collegue (Mickaël Dos Santos).

Products from oxidative gold catalysis of alkyne 786



Methyl picolinate *N*-oxide **O-1** (50.5 mg, 0.3 mmol, 1.1 equiv.) and alkyne **786** (76.6 mg, 0.3 mmol, 1.0 equiv.) were dissolved in THF (3.0 mL, 0.1 M) at room temperature. Dichloro(2-pyridinecarboxylato)gold(III) (5.8 mg, 5 mol%) was added and the solution stirred for 16 hours at room temperature. The reaction mixture was filtered through a pipette containing a short (ca. 0.5 cm) pad of silica, eluting with CH_2Cl_2 (20 mL). The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography [hexane:EtOAc (92:8), then hexane:EtOAc (90:10)] to give the products **787**-**789**.

***Methyl 1,2-diallyl-3-oxoindoline-2-carboxylate* 787**

(29.9 mg, 39%), yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.46 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H), 6.85 – 6.74 (m, 2H), 5.88 (ddt, *J* = 17.0, 10.5, 5.6 Hz, 1H), 5.45 (ddt, *J* = 17.0, 10.0, 7.2, 1H), 5.34 – 4.95 (m, 4H), 4.03 (dd, *J* = 16.8, 5.5 Hz, 1H), 3.93 (dd, *J* = 16.8, 5.5 Hz, 1H), 3.68 (s, 3H), 3.02 (dd, *J* = 14.7, 6.8 Hz, 1H), 2.93 (dd, *J* = 14.7, 7.2 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 195.7 (C), 168.2 (C), 161.5 (C), 137.9 (CH), 133.5 (CH), 130.7 (CH), 125.2 (CH), 120.1 (CH_2), 119.7 (C), 118.2 (CH), 117.6 (CH_2), 109.7 (CH), 53.1 (CH_3), 47.3 (CH_2), 37.0 (CH_2), 29.9 (C); IR: ν_{max} (cm^{-1}) 2958, 2924, 2854, 1744, 1705; HRMS (EI) *m/z* calculated for $C_{16}H_{17}NO_3Na$ $(M+Na)^+$ 294.1106, found 294.1101.

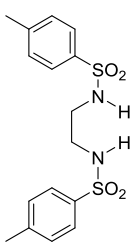
***Methyl 1,3-diallyl-1H-indole-2-carboxylate* 788**

(31.4 mg, 41%), yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.70 (app. dt, *J* = 8.1, 0.9 Hz, 1H), 7.34 (d, *J* = 4.3, 1H), 7.35 (d, *J* = 4.3 Hz, 1H), 7.18 – 7.12 (m, 1H), 6.08 – 5.93 (m, 2H), 5.16 (dt, *J* = 4.9, 1.7 Hz, 2H), 5.12 – 4.85 (m, 4H), 3.93 (s, 3H), 3.87 (dt, *J* = 6.2, 1.6 Hz, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 163.2 (C), 138.6 (C), 137.3 (CH), 134.4 (CH), 126.9 (C), 125.6 (CH), 124.4 (C), 122.9 (C), 121.1 (CH), 120.3 (CH), 116.0 (CH_2), 114.8 (CH_2), 110.7 (CH), 51.6 (CH_3), 47.3 (CH_2), 30.1 (CH_2); IR: ν_{max} (cm^{-1}) 3085, 2951, 1706; HRMS (EI) *m/z* calculated for $C_{16}H_{17}NO_2Na$ $(M+Na)^+$ 278.1157, found 278.1151.

***Methyl 3-(2-(diallylamino)phenyl)-2,3-dioxopropanoate* 789**

(5.4 mg, 7%), yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.96 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.63 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H), 7.36 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 5.73 (ddt, *J* = 17.0, 10.2, 6.9 Hz, 2H), 5.19 (dd, *J* = 10.2, 1.5 Hz, 2H), 5.13 (dd, *J* = 17.0, 1.5 Hz, 2H), 3.84 (s, 3H), 3.42 (d, *J* = 6.9 Hz, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 193.7 (C), 177.3 (C), 160.4 (C), 152.5 (C), 135.3 (CH), 132.7 (C), 131.2 (2 × CH), 129.7 (CH), 126.9 (CH), 124.8 (CH), 120.8 (2 × CH_2), 57.1 (2 × CH_2), 53.0 (CH_3); IR: ν_{max} (cm^{-1}) 2954, 2924, 2851, 1756, 1731, 1707, 1671; HRMS (EI) *m/z* calculated for $C_{16}H_{17}NO_4Na$ $(M+Na)^+$ 310.3048, found 310.3051.

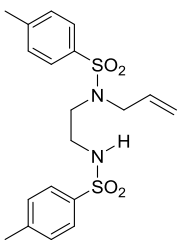
***N*,*N*'-(Ethane-1,2-diyl)bis(4-methylbenzenesulfonamide) 798**



p-TsCl (9.6 g, 59.8 mmol, 2.0 equiv.) was suspended in diethyl ether (24 mL) and cooled to 0 °C. A mixture of sodium hydroxide (2.4 g, 59.8 mmol, 2.0 equiv.) and ethylene diamine (2.0 mL, 29.9 mmol, 1.0 equiv.) dissolved in water (24 mL) was

added dropwise. The white suspension was then stirred for 16 hours at room temperature. The solvent was removed under reduced pressure and the aqueous layer extracted with dichloromethane (3 × 15 mL). Recrystallisation [methanol] gave the sulfonamide **798** (9.6 g, 88 %) as a white solid; mp: 160-161 °C; ^{1}H-NMR (300 MHz, d_6-DMSO): δ 7.61 (d, *J* = 8.2, 4H), 7.37 (d, *J* = 8.2 Hz, 4H), 2.70 (s, 4H), 2.38 (s, 6H); ^{13}C-NMR (101 MHz, d_6-DMSO): δ 142.7 (2 × C), 137.3 (2 × C), 129.6 (4 × CH), 126.4 (4 × CH), 42.1 (2 × CH_2), 20.9 (2 × CH_3); MS (EI): *m/z* 391 ($[M+Na]^+$,100%). Data matches that reported in literature.[187]

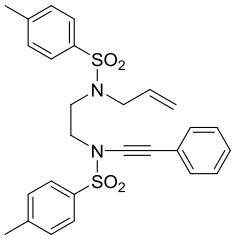
***N-Allyl-N,N'-(ethane-1,2-diyl)bis(4-methylbenzenesulfonamide)* 799**



N,N-Ditosyl-1,2-ethanediamine **789** (750 mg, 2.0 mmol, 1.2 equiv.) was dissolved in acetone (12.5 mL, 0.1 M) and the mixture was cooled to 0 °C. Potassium carbonate (203 mg, 1.5 mmol, 0.9 equiv.) and allyl bromide (0.4 mL, 1.6 mmol, 1.0 equiv.) were then added and the mixture was heated at reflux for 16 hours. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate and washed with water (3 × 20 mL) and brine (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography [hexane:CH_2Cl_2:EtOAc (50:50:10)] *N*-allulsulfonamide **799** (421 mg, 50%) as a white solid; mp 53-55°C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.30 Hz, 2H), 7.64 (d, *J* = 8.31 Hz, 2H), 7.31 - 7.37 (m, 4H), 5.43 - 5.57 (m, 1H), 5.09 - 5.15 (m, 2H), 5.03 (br. s, 1H), 3.71 (d, *J* = 6.6 Hz, 2H), 3.13 - 3.15 (m, 4H), 2.47 (s, 3H), 2.45 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.3 (C), 144.1 (C), 132.6 (2 × CH), 129.9 (2 × CH), 129.7 (2 × CH), 127.2 (2 × CH), 119.8 (2 × C), 52.2 (CH_2),

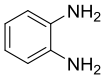
47.1 (CH_2), 42.2 (CH_2), 21.5 (2 × CH_3); IR: ν_{max} (cm^{-1}) 3311, 3072, 2962, 2898, 1415, 1334, 1150; HRMS (EI) *m/z* calculated for $C_{19}H_{24}N_2O_4NaS_2$ $(M+Na)^+$ 431.1075, found 431.1069.

***N-Allyl-N-phenylacetylene-N,N'-(ethane-1,2-diyl)bis(4-methylbenzenesulfonamide)* 800**



Prepared according to **GP11** using freshly prepared (bromoethynyl)benzene (452 mg, 2.5 mmol, **GP9**) and *N*-allyl-*N*,*N*-ditosyl-1,2-ethanediamine (850 mg, 2.1 mmol). Purification by flash column chromatography [hexane:EtOAc (80:20)] gave the ynamide **800** (920 mg, 88%) as a white solid; mp: 94-96 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.28 - 7.48 (m, 9H), 5.67 (ddt, *J* = 16.6, 10.0, 6.6 Hz, 1H), 5.19 - 5.25 (m, 2H), 3.83 (d, *J* = 6.6 Hz, 2H), 3.62 (app. t, *J* = 7.2 Hz, 2H), 3.41 (t, *J* = 7.2 Hz, 2H), 2.49 (s, 3H), 2.43 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.9 (C), 143.6 (C), 136.1 (C), 134.3 (C), 132.6 (2 × CH), 131.3 (CH), 129.9 (2 × CH), 129.8 (CH), 129.4 (2 x CH), 128.6 (CH), 128.3 (2 × CH), 127.9 (CH), 127.7 (CH), 127.4 (CH), 122.6 (C), 120.0 (CH_2), 82.1 (C), 70.7 (C), 52.0 (CH_2), 50.9 (CH_2), 45.2 (CH_2), 21.7 (CH_3), 21.5 (CH_3); IR: ν_{max} (cm^{-1}) 3075, 2950, 2929, 2862, 2240, 1597, 1367, 1341, 1160; HRMS (EI) *m/z* calculated for $C_{27}H_{28}N_2O_4NaS_2$ $(M+H)^+$ 531.1382, found 531.1388.

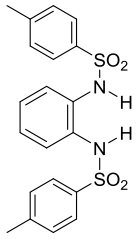
Benzene-1,2-diamine 808



2-Nitroaniline (6.0 g, 36.4 mmol) and tin granules (12.0 g, 101.4 mmol, 2.8 equiv.) and hydrochloric acid (130 mL, 6 M) were heated at 80°C until the tin had completely dissolved. The flask was cooled using an ice bath and sodium hydroxide solution (10 M) was added dropwise with stirring until a pH of 10 was achieved. The precipitate was removed by hot

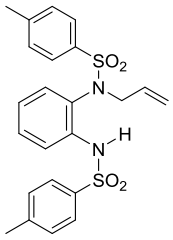
filtration and the solids washed with boiling water (100 mL). Once cooled, the precipitate formed from the filtrate was collected by suction filtration to give the diamine **808** (3.3 g, 60 %) as a yellow solid; mp: 100-101°C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.72 (s, 4H), 3.38 (br. s, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 134.7 (2 × C), 120.3 (2 × CH), 116.3 (2 × CH); IR: ν_{max} (cm^{-1}) 3384, 3362, 3181, 1590, 1499, 1458; MS (EI): *m/z* 108 (100 %), 80 (34). Data matches that reported in literature.[220]

***N*,*N*'-(1,2-Phenylene)bis(4-methylbenzenesulfonamide) 809**



p-TsCl (4.9 g, 30.6 mmol, 2.2 equiv.) was added portion-wise to a solution of benzene-1,2-diamine **808** (1.5 g, 13.9 mmol) in pyridine (28 mL, 0.5 M) at room temperature and stirred for 6 hours. The mixture was diluted with CH_2Cl_2 (100 ml) and washed with 1 M HCl solution (3 × 30 mL). The organic layer was dried ober Na_2SO_4, filtered, and concentrated under reduced pressure. Recrystallisation [methanol] gave sulfonamide **809** (2.5 g, 43 %) as an off-white solid; mp: 204-206 °C; ^{1}H-NMR (300 MHz, d_6-DMSO): δ 9.29 (br. s, 2H) 7.60 (d, *J* = 8.2 Hz, 4H), 7.34 (d, *J* = 8.2 Hz, 4H), 6.99 (m, 4H), 2.35 (s, 6H); ^{13}C-NMR (101 MHz, d_6-DMSO): δ 143.6 (2 × C), 136.0 (2 × C), 130.4 (2 × C), 129.7 (4 × CH), 126.9 (4 × CH), 125.8 (2 × CH), 123.3 (2 × CH), 21.0 (2 × CH_3); MS (EI): *m/z* 439 ([M+Na^+], 100 %). Data matches that reported in literature.[221]

***N*-Allyl-4-methyl-*N*-(2-(4-methylphenylsulfonamido)phenyl)benzenesulfonamide 810**

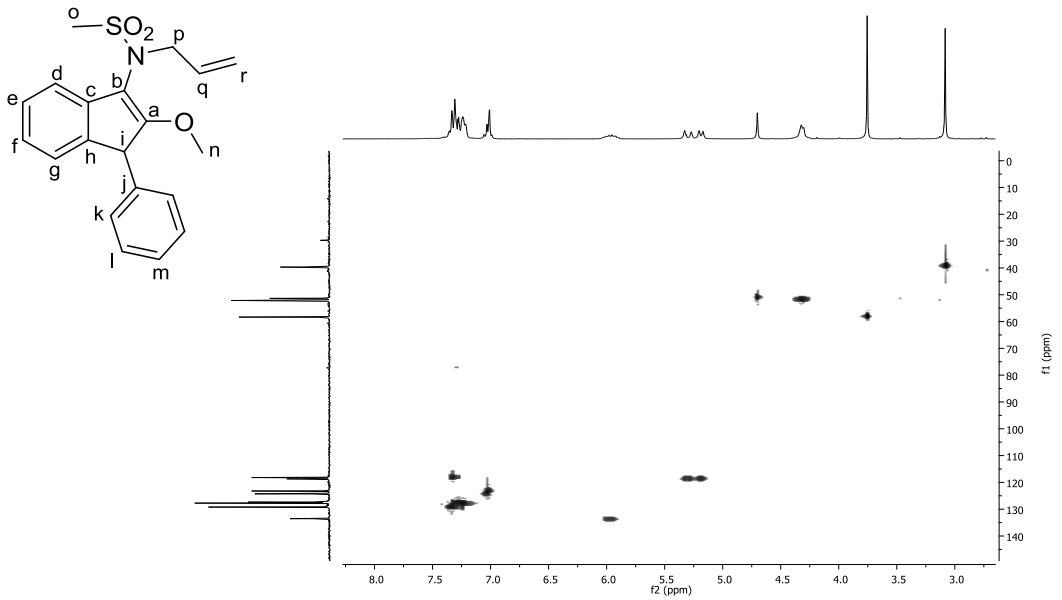


Sulfonamide **809** (1.0 g, 2.4 mmol, 1.2 equiv.) was dissolved in acetone (15 mL, 0.2 M) and cooled to 0 °C. Potassium carbonate (240 mg, 1.7 mmol, 0.9 equiv.), and allyl bromide (0.2 mL, 1.9 mmol, 1.0 equiv.) were added at 0°C and the mixture was heated at reflux for 16 hours. The solvent was removed under reduced pressure and the residue dissolved in EtOAc (20 mL), and washed with water (3 × 20 mL) and brine (3 × 20 mL) before drying over Na_2SO_4 and concentrating under reduced pressure. Purification by flash column chromatography [hexane:EtOAc (70:30)] gave the *N*-allyl sulfonamide **810** (284 mg, 32%) as a white solid; mp: 181-183 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.64 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.26-7.31 (m, 4H), 7.21 (ddd, *J* = 8.3, 7.5, 1.4, 1H), 6.83 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.29 (dd, *J* = 8.0, 1.4 Hz, 1H), 5.22-5.39 (m, 1H), 4.81-4.90 (m, 2H), 4.21 (dd, *J* = 13.7, 5.4 Hz, 1H), 3.64 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.45 (s, 3H), 2.40 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.4 (C), 143.9 (C), 137.1 (C), 136.9 (C), 133.6 (C), 131.2 (CH), 129.6 (2 × CH), 129.4 (2 × CH), 128.5 (C), 128.3 (2 × CH), 128.2 (CH), 127.6 (2 × CH), 123.6 (2 × CH), 120.2 (CH_2), 119.9 (CH), 54.9 (CH_2), 21.6 (CH_3), 21.5 (CH_3); IR: ν_{max} (cm^{-1}) 3274, 3073, 2860, 1643, 1596, 1494, 1404, 1338, 1165; HRMS (EI) *m/z* calculated for $C_{23}H_{24}N_2O_4NaS_2$ $(M+Na)^+$ 479.1075, found 479.1084.

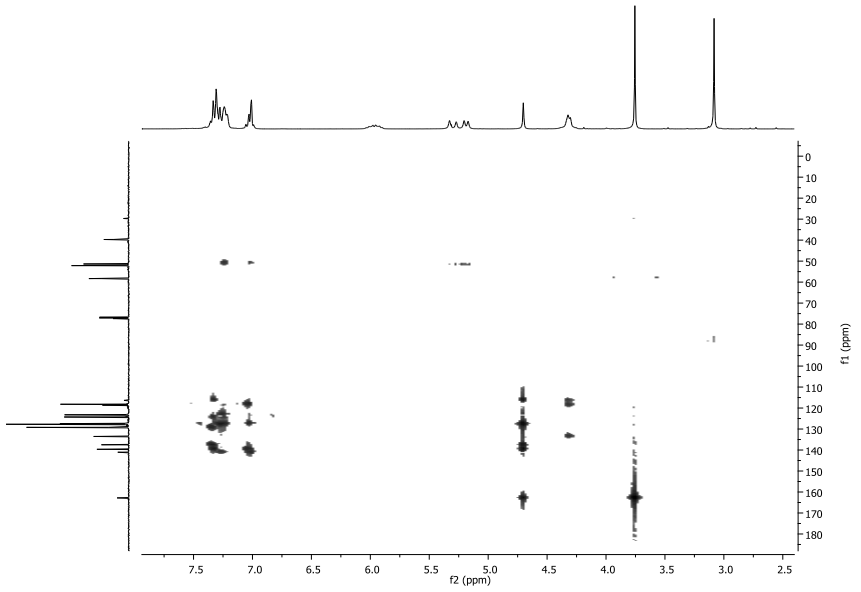
8 Appendix

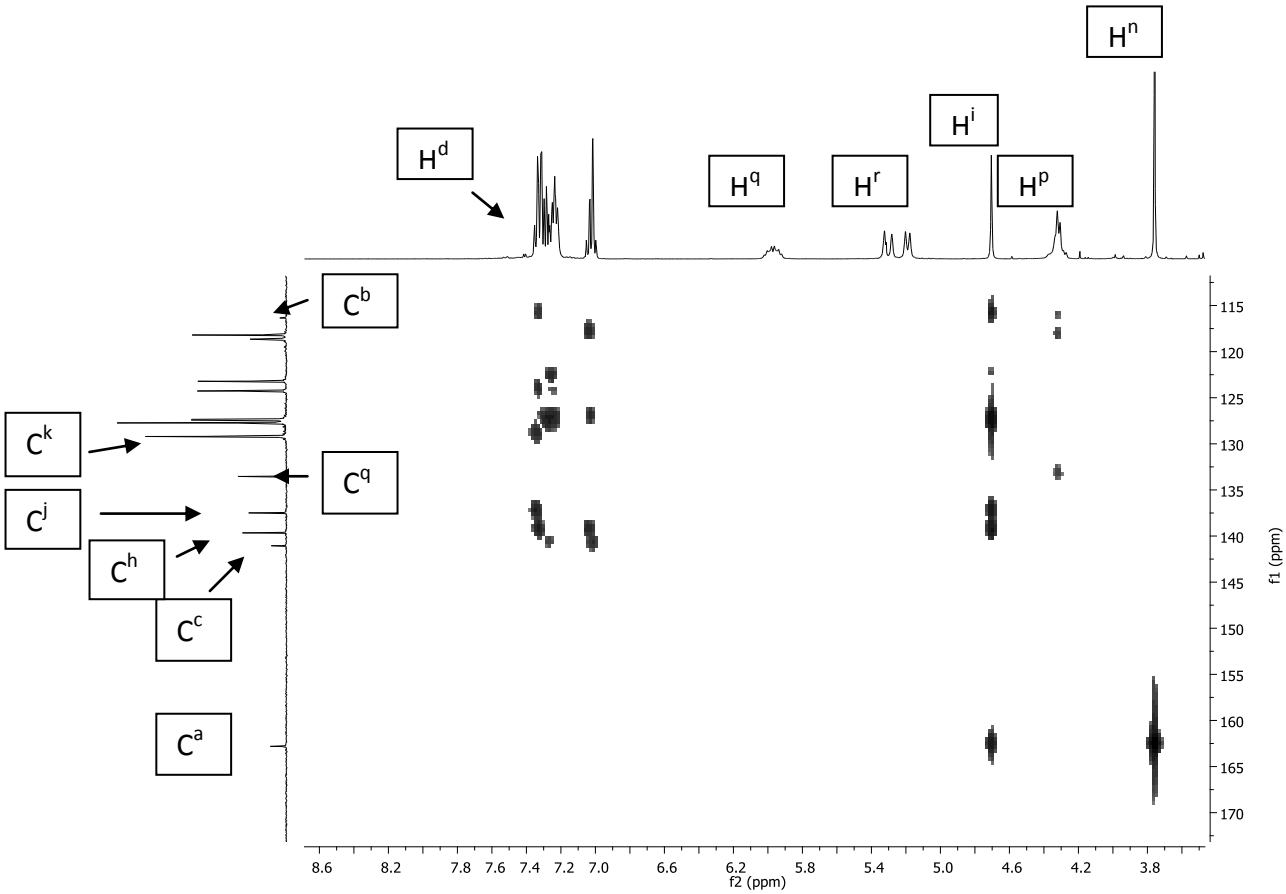
Spectral Analysis of Compounds 265 and 266

HSQC of Compound 265

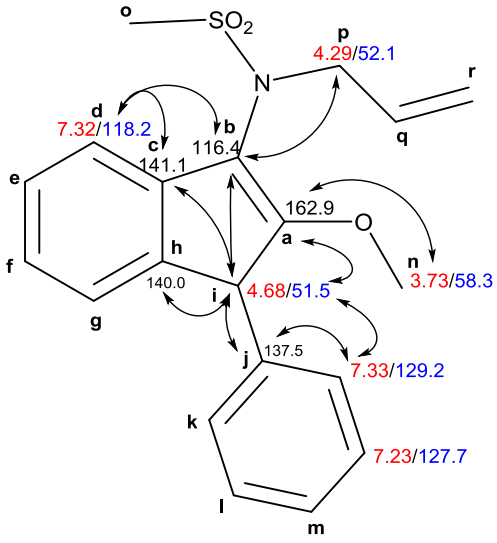


HMBC of Compound 265





Spectral Analysis of Compound 265

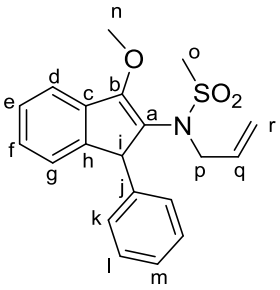


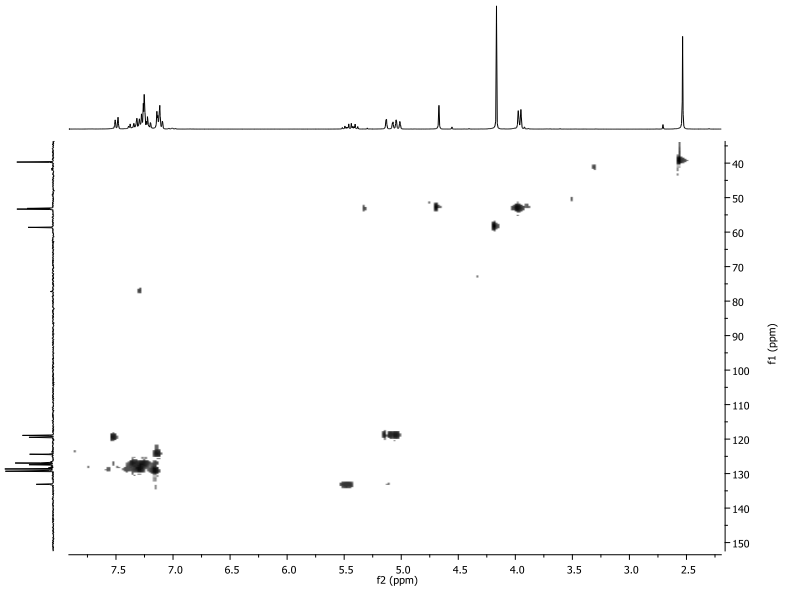
Key correlations observed in HSQC and HMBC NMR spectroscopy are detailed below for structure **2g**. Chemical shifts in ppm are shown in black (quaternary C), blue (C) and red (H).

- **H**^{i} is coupled to quaternary carbons: **C**^{a}, **C**^{h}, **C**^{j} (^{2}J-couplings) as well as **C**^{b}, **C**^{c} (^{3}J-couplings).

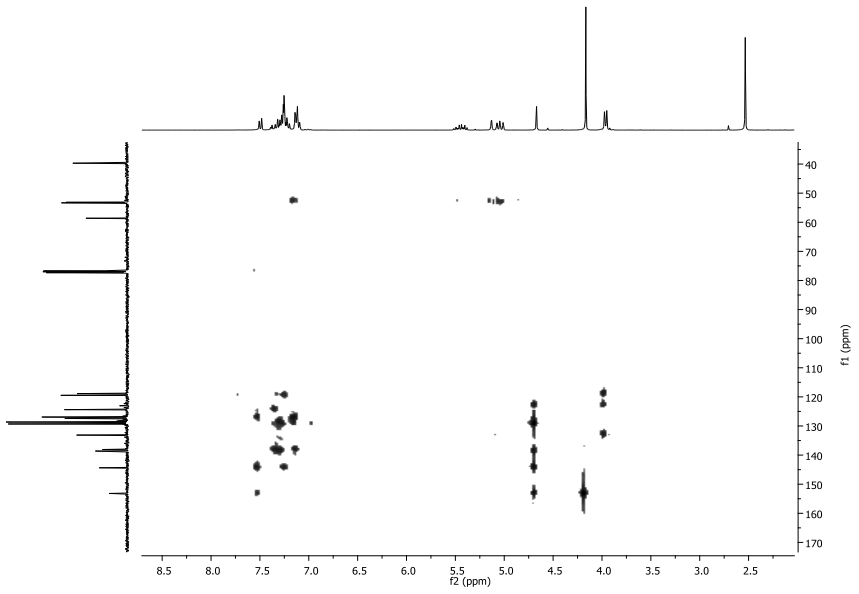
- **H**^{i} coupled to **C**^{a} (^{2}J-coupling) which is in turn coupled to methoxy protons **H**^{n} (^{3}J-coupling).
- Quaternary carbon **C**^{b} is coupled to the allylic protons **H**^{p} as well as the aryl proton **H**^{d} (^{3}J-couplings).

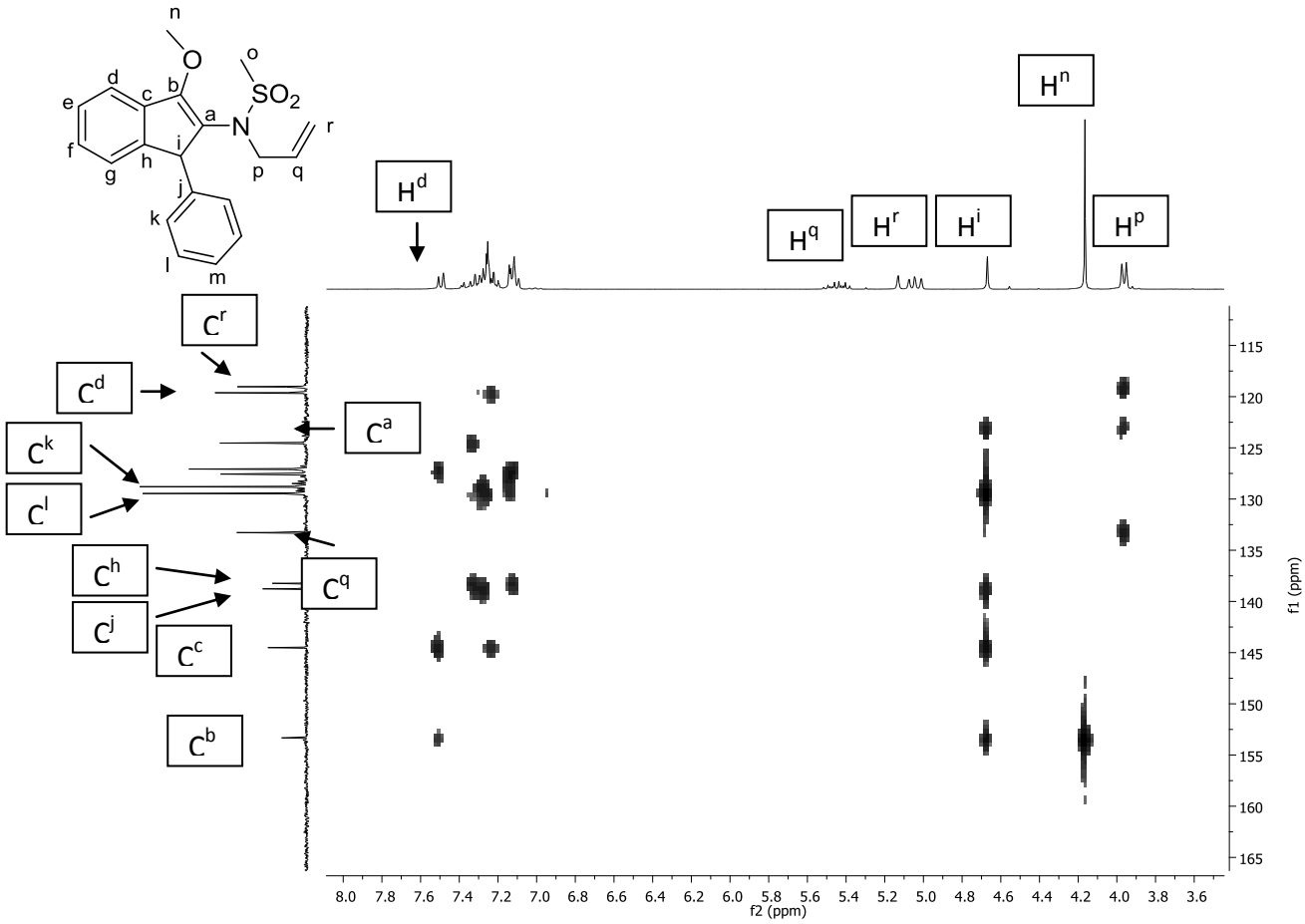
HSQC of Compound 266



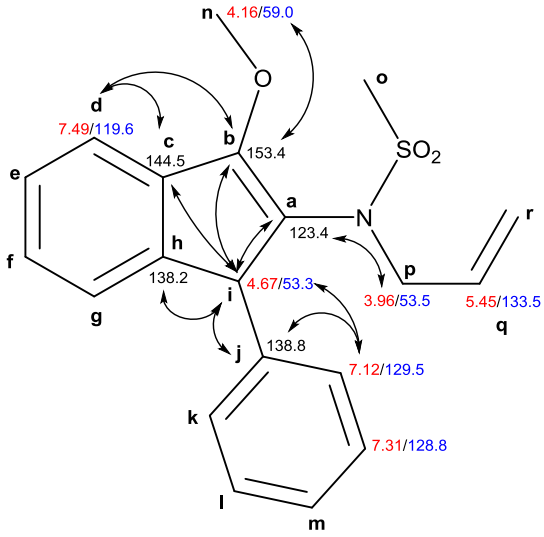


HMBC of Compound 266





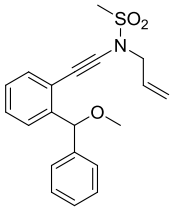
Spectral Analysis of Compound 266

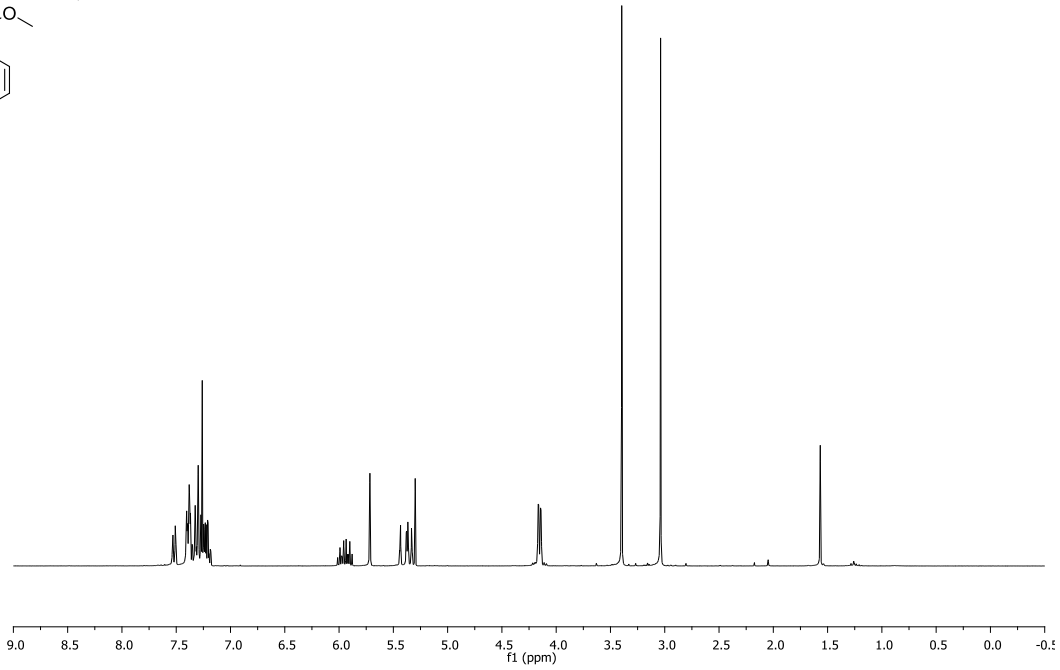


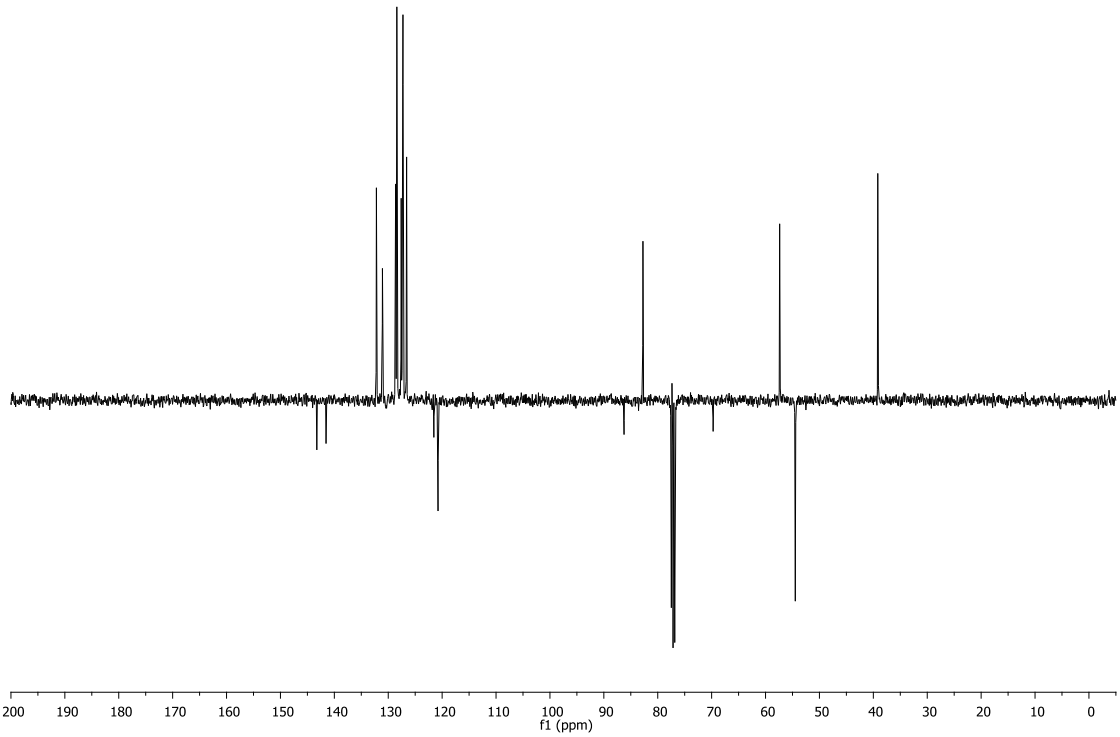
Key correlations observed in HSQC and HMBC NMR spectroscopy are detailed below for structure **3g**. Chemical shifts in ppm are shown in black (quaternary C), blue (C) and red (H).

- **H^{i}** is coupled to quaternary carbons: **C^{a}**, **C^{h}**, **C^{j}** (^{2}J-couplings) as well as **C^{b}**, **C^{c}** (^{3}J-couplings).
- **H^{i}** coupled to **C^{a}** (^{2}J-coupling) which is in turn coupled to allylic protons **H^{p}** (^{3}J-coupling).
- Quaternary carbon **C^{b}** is coupled to the methoxy protons **H^{n}** as well as the aryl proton **H^{d}** (^{3}J-couplings). **C^{c}** is also coupled to **H^{d}** (^{2}J-coupling).

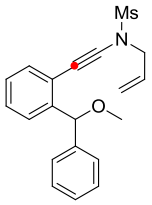
^{1}H- and ^{13}C- NMR spectra of ynamide 255

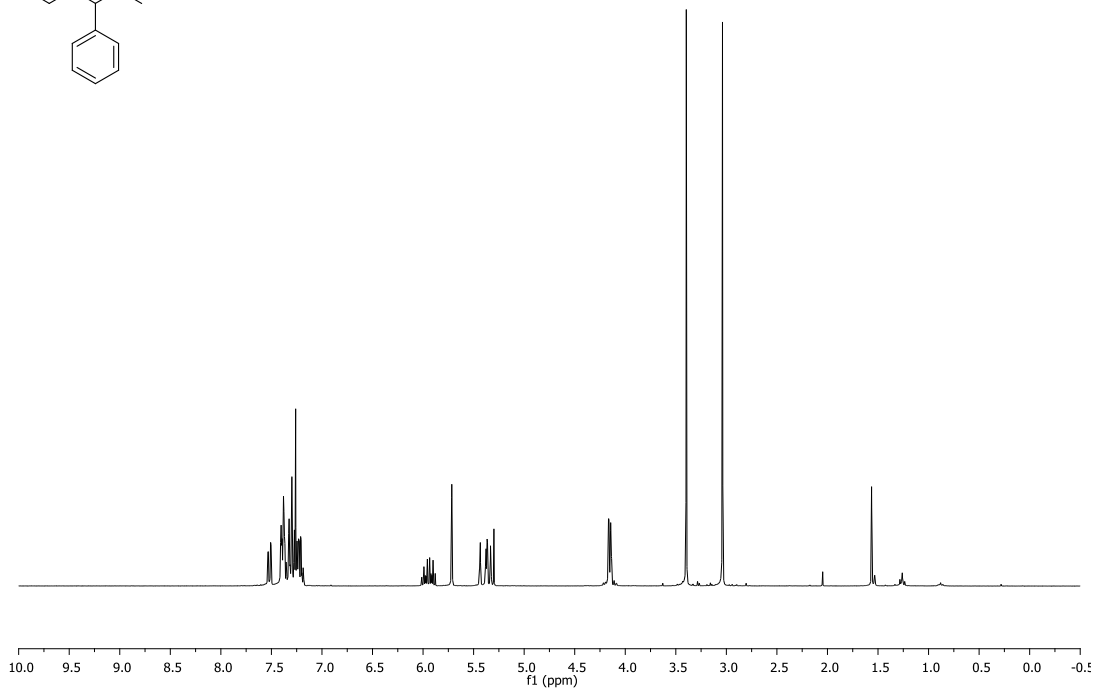


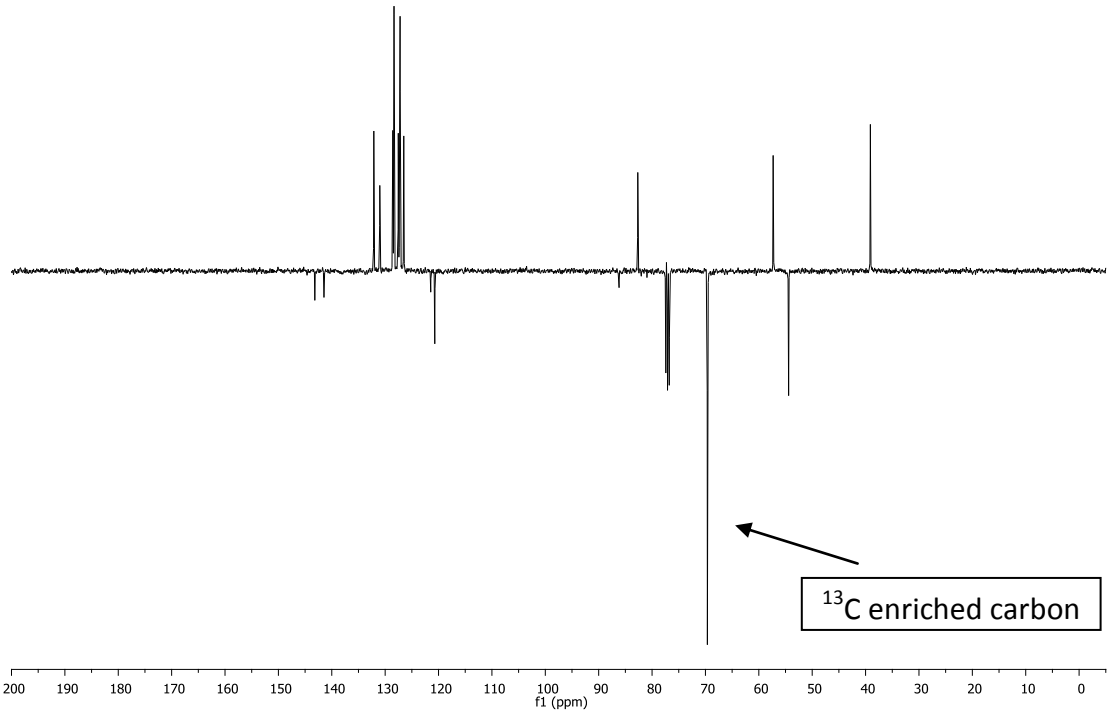




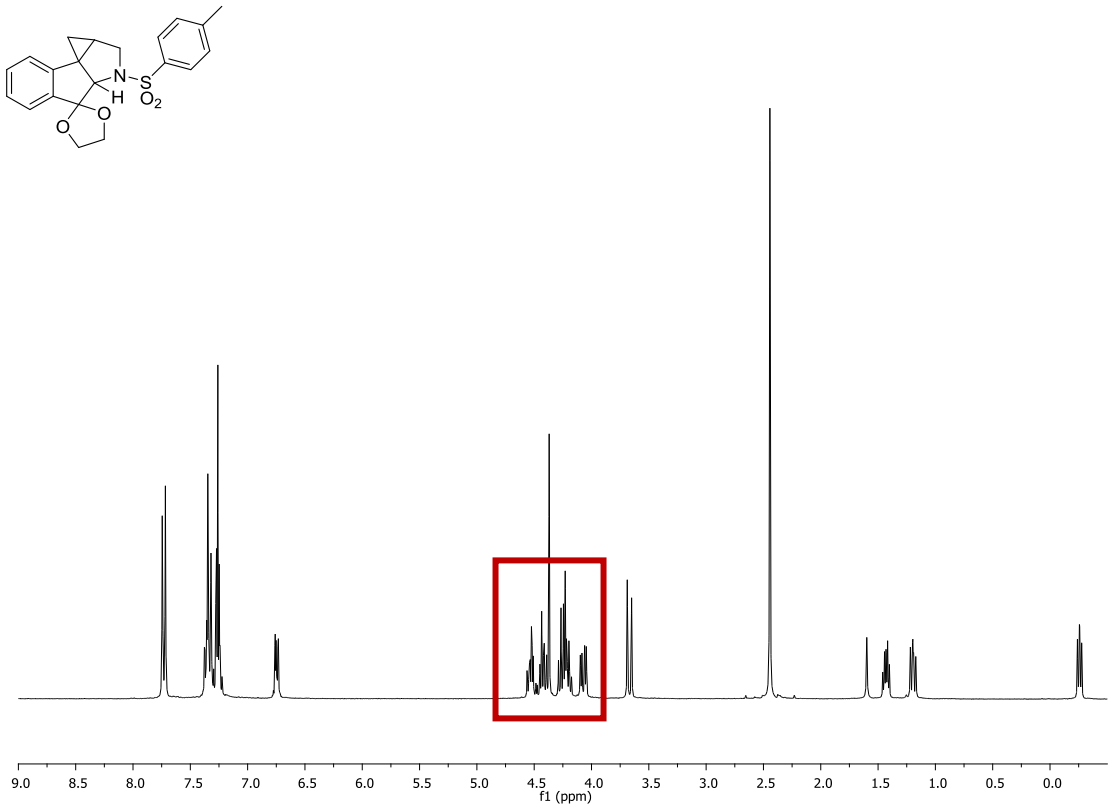
^{1}H- and ^{13}C- NMR spectra of ynamide d-255

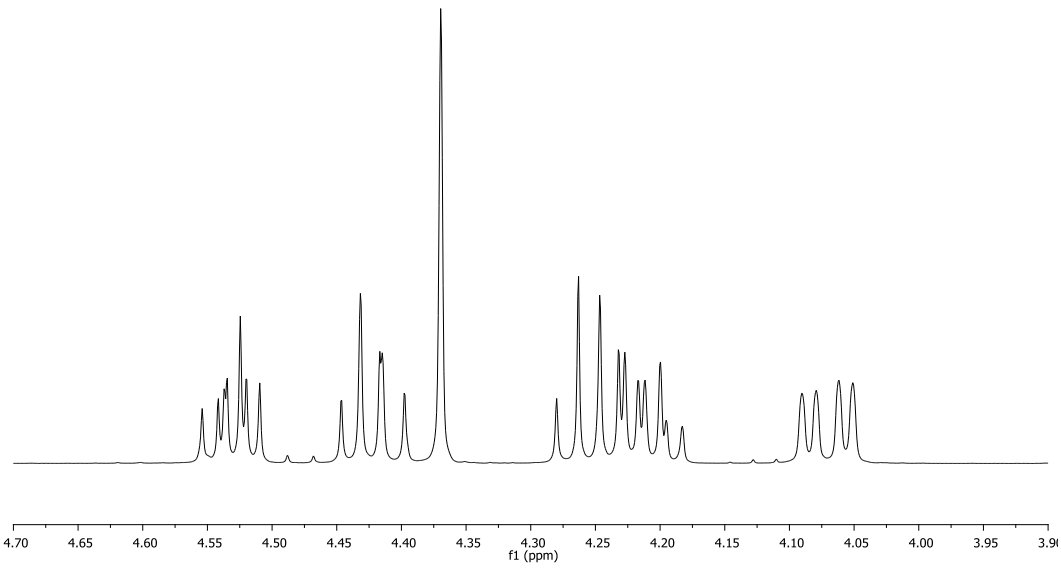




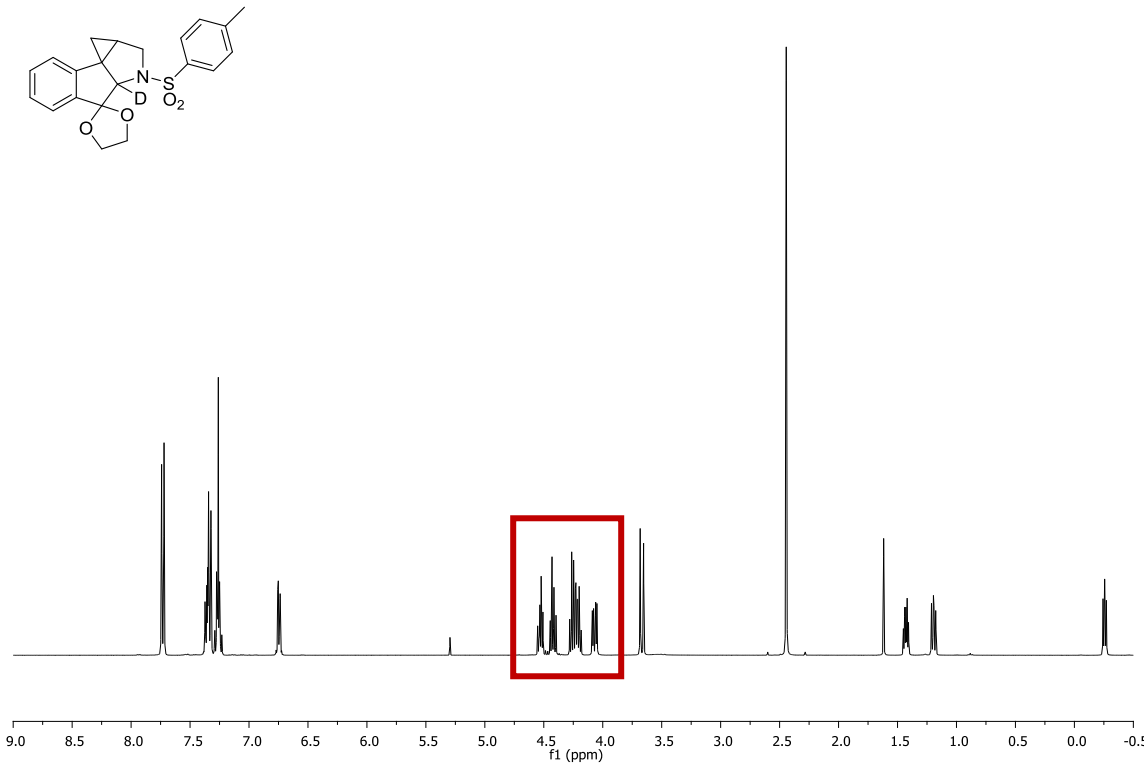


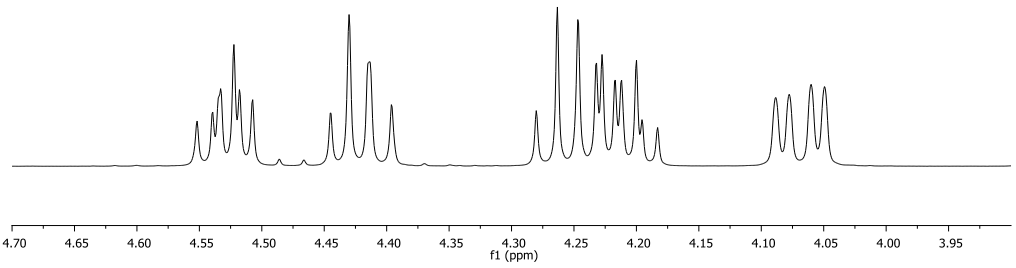
^{1}H-NMR Spectrum of Tetracycle 519



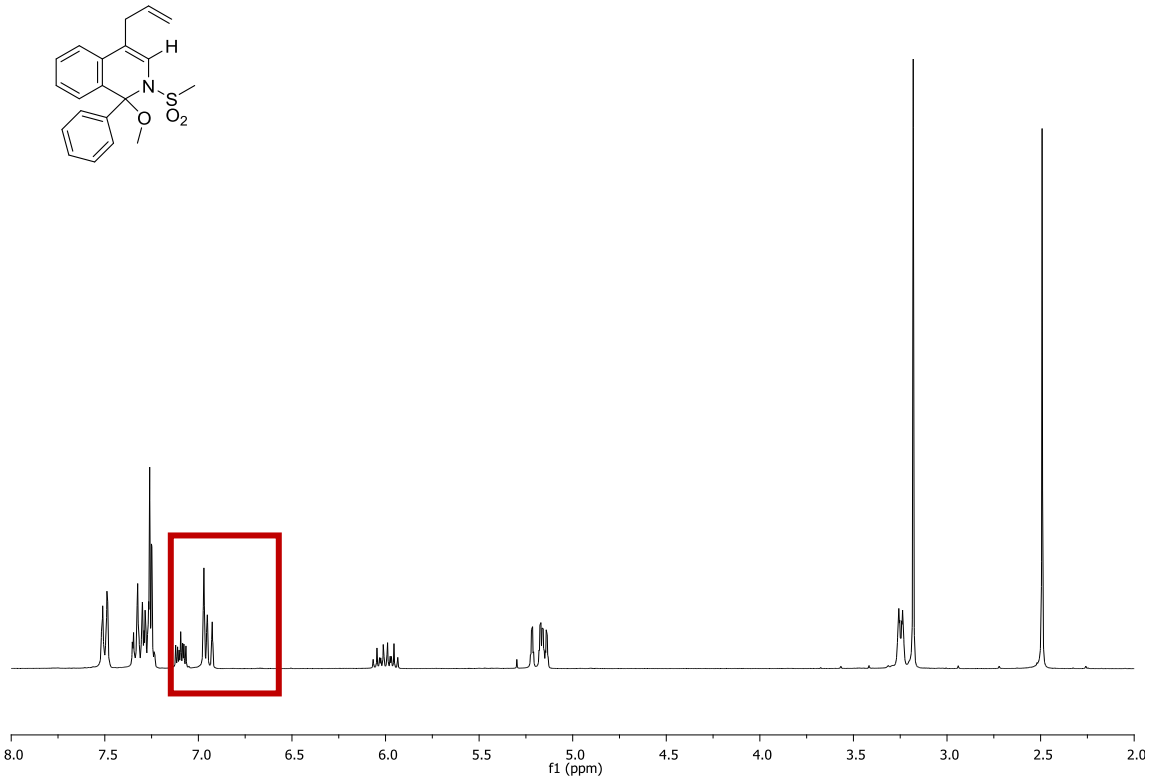


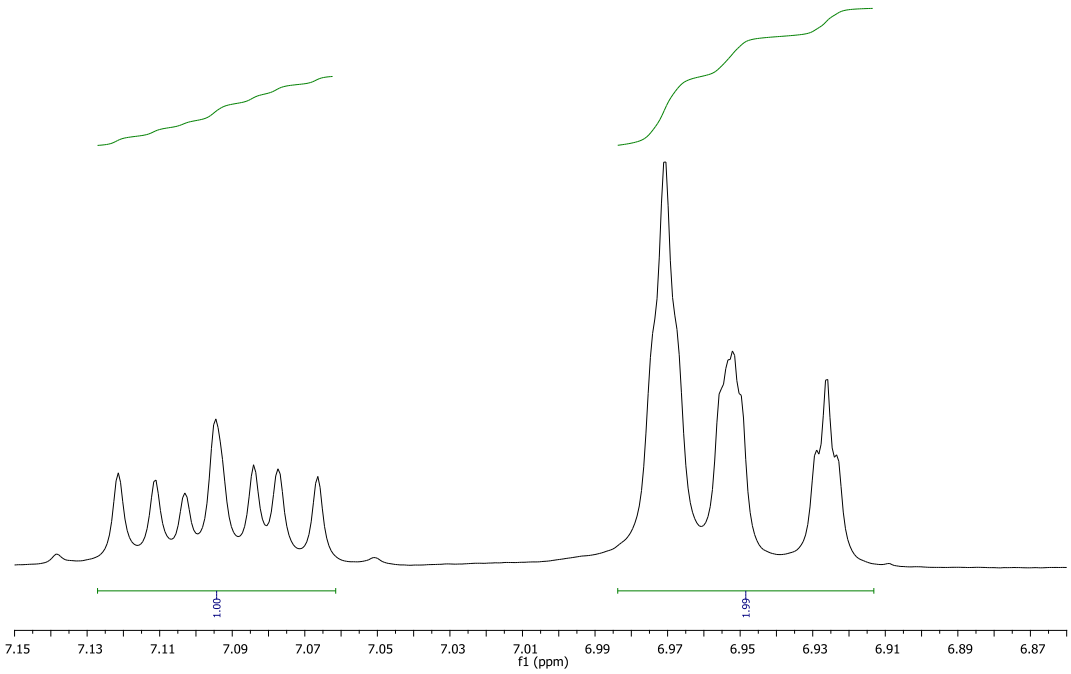
^{1}H-NMR Spectrum of Tetracycle d-519



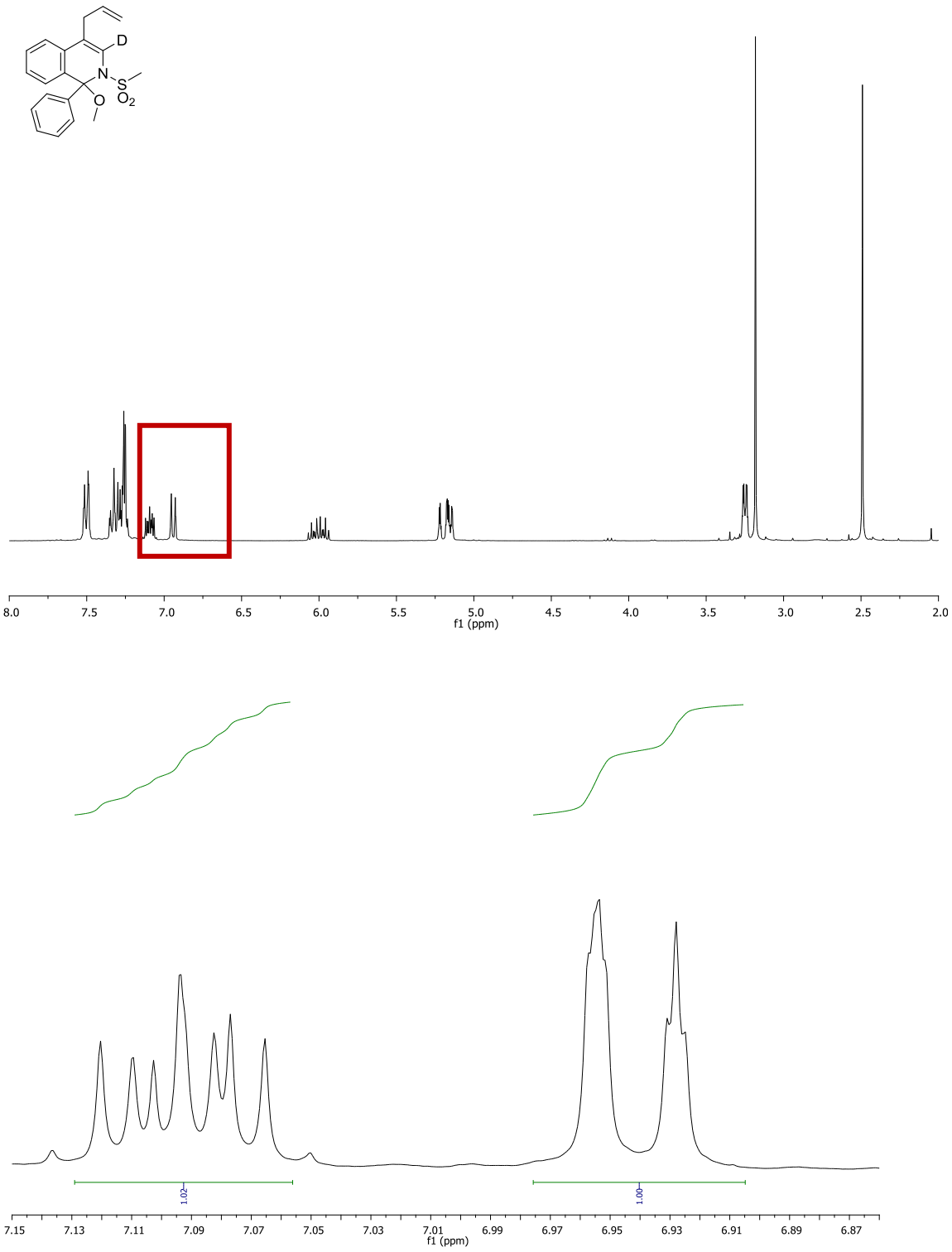


^{1}H-NMR Spectrum of Isoquinoline 651





^{1}H-NMR Spectrum of Isoquinoline d-651



Crystal data and structure refinement for 235

Empirical formula	$C_{29}H_{25}NO_3S$	
Formula weight	467.56	
Temperature	120(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 10.19700(10) Å	□= 81.7780(10)°.
	b = 10.29440(10) Å	□= 79.5540(10)°.
	c = 11.15720(10) Å	□ = 88.0600(10)°.
Volume	1139.906(19) $Å^3$	
Z	2	
Density (calculated)	1.362 Mg/m^3	
Absorption coefficient	1.523 mm^{-1}	
F(000)	492	
Crystal size	0.20 x 0.18 x 0.17 mm^3	
Theta range for data collection	6.36 to 66.60°.	
Index ranges	-11<=h<=12, -12<=k<=12, -13<=l<=13	
Reflections collected	11629	
Independent reflections	3947 [R(int) = 0.0253]	
Completeness to theta = 66.60°	97.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7818 and 0.7505	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3947 / 0 / 309	
Goodness-of-fit on F^2	1.093	
Final R indices [I>2sigma(I)]	R1 = 0.0387, wR2 = 0.1067	
R indices (all data)	R1 = 0.0399, wR2 = 0.1088	
Largest diff. peak and hole	0.328 and -0.331 $e.Å^{-3}$	

Notes:

The hydrogen atoms have been fixed as riding models. Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for **235**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3661(2)	5240(2)	4160(2)	42(1)
C(2)	3015(2)	5881(2)	5258(2)	28(1)
C(3)	2619(2)	5132(2)	6400(2)	28(1)
C(4)	1998(2)	5711(2)	7407(1)	24(1)
C(5)	1752(1)	7053(1)	7257(1)	20(1)
C(6)	2148(2)	7821(2)	6134(1)	26(1)
C(7)	2792(2)	7229(2)	5141(2)	30(1)
C(8)	1490(1)	7327(1)	10748(1)	20(1)
C(9)	1338(2)	5999(2)	11185(2)	26(1)
C(10)	922(2)	5606(2)	12434(2)	32(1)
C(11)	673(2)	6532(2)	13244(2)	32(1)
C(12)	843(2)	7854(2)	12800(2)	29(1)
C(13)	1244(1)	8257(2)	11549(1)	23(1)
C(14)	4341(1)	7898(1)	8808(1)	18(1)
C(15)	3126(1)	8466(1)	9027(1)	18(1)
C(16)	3275(1)	9900(1)	8841(1)	19(1)
C(17)	2346(2)	10910(1)	8992(1)	21(1)
C(18)	2798(2)	12197(2)	8767(1)	24(1)
C(19)	4152(2)	12476(1)	8398(1)	24(1)
C(20)	5086(2)	11458(2)	8253(1)	22(1)
C(21)	4639(1)	10179(1)	8477(1)	19(1)
C(22)	5440(1)	8910(1)	8405(1)	18(1)
C(23)	5876(2)	6088(2)	8757(1)	25(1)
C(24)	6251(1)	8812(1)	7129(1)	19(1)
C(25)	5600(2)	8718(2)	6148(1)	25(1)
C(26)	6323(2)	8606(2)	4987(1)	28(1)
C(27)	7705(2)	8592(2)	4788(1)	29(1)
C(28)	8355(2)	8691(2)	5756(2)	29(1)

C(29)	7635(2)	8801(2)	6923(1)	24(1)
N(1)	1918(1)	7748(1)	9450(1)	21(1)
O(1)	-222(1)	6926(1)	9131(1)	28(1)
O(2)	540(1)	9091(1)	8026(1)	30(1)
O(3)	4531(1)	6586(1)	8952(1)	25(1)
S(1)	851(1)	7767(1)	8501(1)	21(1)

Table 3. Bond lengths [Å] and angles [°] for **235**

C(1)-C(2)	1.510(2)	C(13)-H(13)	0.9500
C(1)-H(1A)	0.9800	C(14)-O(3)	1.3483(18)
C(1)-H(1B)	0.9800	C(14)-C(15)	1.349(2)
C(1)-H(1C)	0.9800	C(14)-C(22)	1.5185(19)
C(2)-C(3)	1.390(2)	C(15)-N(1)	1.4277(18)
C(2)-C(7)	1.390(2)	C(15)-C(16)	1.4700(19)
C(3)-C(4)	1.388(2)	C(16)-C(17)	1.390(2)
C(3)-H(3)	0.9500	C(16)-C(21)	1.404(2)
C(4)-C(5)	1.387(2)	C(17)-C(18)	1.391(2)
C(4)-H(4)	0.9500	C(17)-H(17)	0.9500
C(5)-C(6)	1.384(2)	C(18)-C(19)	1.395(2)
C(5)-S(1)	1.7588(15)	C(18)-H(18)	0.9500
C(6)-C(7)	1.390(2)	C(19)-C(20)	1.398(2)
C(6)-H(6)	0.9500	C(19)-H(19)	0.9500
C(7)-H(7)	0.9500	C(20)-C(21)	1.382(2)
C(8)-C(13)	1.388(2)	C(20)-H(20)	0.9500
C(8)-C(9)	1.389(2)	C(21)-C(22)	1.5218(19)
C(8)-N(1)	1.4414(19)	C(22)-C(24)	1.5257(19)
C(9)-C(10)	1.386(2)	C(22)-H(22)	1.0000
C(9)-H(9)	0.9500	C(23)-O(3)	1.4379(18)
C(10)-C(11)	1.392(3)	C(23)-H(23A)	0.9800
C(10)-H(10)	0.9500	C(23)-H(23B)	0.9800
C(11)-C(12)	1.385(2)	C(23)-H(23C)	0.9800
C(11)-H(11)	0.9500	C(24)-C(29)	1.388(2)
C(12)-C(13)	1.387(2)	C(24)-C(25)	1.395(2)
C(12)-H(12)	0.9500	C(25)-C(26)	1.388(2)

C(25)-H(25)	0.9500	C(28)-H(28)	0.9500
C(26)-C(27)	1.386(2)	C(29)-H(29)	0.9500
C(26)-H(26)	0.9500	N(1)-S(1)	1.6481(12)
C(27)-C(28)	1.383(2)	O(1)-S(1)	1.4327(11)
C(27)-H(27)	0.9500	O(2)-S(1)	1.4363(11)
C(28)-C(29)	1.392(2)		
C(2)-C(1)-H(1A)	109.5	C(9)-C(10)-C(11)	120.36(15)
C(2)-C(1)-H(1B)	109.5	C(9)-C(10)-H(10)	119.8
H(1A)-C(1)-H(1B)	109.5	C(11)-C(10)-H(10)	119.8
C(2)-C(1)-H(1C)	109.5	C(12)-C(11)-C(10)	119.79(15)
H(1A)-C(1)-H(1C)	109.5	C(12)-C(11)-H(11)	120.1
H(1B)-C(1)-H(1C)	109.5	C(10)-C(11)-H(11)	120.1
C(3)-C(2)-C(7)	118.84(15)	C(11)-C(12)-C(13)	120.23(15)
C(3)-C(2)-C(1)	120.67(16)	C(11)-C(12)-H(12)	119.9
C(7)-C(2)-C(1)	120.49(16)	C(13)-C(12)-H(12)	119.9
C(4)-C(3)-C(2)	120.95(15)	C(12)-C(13)-C(8)	119.61(14)
C(4)-C(3)-H(3)	119.5	C(12)-C(13)-H(13)	120.2
C(2)-C(3)-H(3)	119.5	C(8)-C(13)-H(13)	120.2
C(5)-C(4)-C(3)	119.07(14)	O(3)-C(14)-C(15)	123.04(13)
C(5)-C(4)-H(4)	120.5	O(3)-C(14)-C(22)	125.17(12)
C(3)-C(4)-H(4)	120.5	C(15)-C(14)-C(22)	111.78(12)
C(6)-C(5)-C(4)	121.07(14)	C(14)-C(15)-N(1)	123.71(13)
C(6)-C(5)-S(1)	119.73(12)	C(14)-C(15)-C(16)	109.25(12)
C(4)-C(5)-S(1)	119.12(12)	N(1)-C(15)-C(16)	126.92(12)
C(5)-C(6)-C(7)	119.06(15)	C(17)-C(16)-C(21)	120.42(13)
C(5)-C(6)-H(6)	120.5	C(17)-C(16)-C(15)	131.70(13)
C(7)-C(6)-H(6)	120.5	C(21)-C(16)-C(15)	107.86(12)
C(6)-C(7)-C(2)	120.96(15)	C(16)-C(17)-C(18)	118.60(14)
C(6)-C(7)-H(7)	119.5	C(16)-C(17)-H(17)	120.7
C(2)-C(7)-H(7)	119.5	C(18)-C(17)-H(17)	120.7
C(13)-C(8)-C(9)	120.62(14)	C(17)-C(18)-C(19)	121.00(14)
C(13)-C(8)-N(1)	119.50(13)	C(17)-C(18)-H(18)	119.5
C(9)-C(8)-N(1)	119.88(13)	C(19)-C(18)-H(18)	119.5
C(10)-C(9)-C(8)	119.38(15)	C(18)-C(19)-C(20)	120.35(14)
C(10)-C(9)-H(9)	120.3	C(18)-C(19)-H(19)	119.8
C(8)-C(9)-H(9)	120.3	C(20)-C(19)-H(19)	119.8

C(21)-C(20)-C(19)	118.70(14)
C(21)-C(20)-H(20)	120.7
C(19)-C(20)-H(20)	120.7
C(20)-C(21)-C(16)	120.93(14)
C(20)-C(21)-C(22)	129.02(14)
C(16)-C(21)-C(22)	110.05(12)
C(14)-C(22)-C(21)	101.02(11)
C(14)-C(22)-C(24)	113.49(11)
C(21)-C(22)-C(24)	113.48(11)
C(14)-C(22)-H(22)	109.5
C(21)-C(22)-H(22)	109.5
C(24)-C(22)-H(22)	109.5
O(3)-C(23)-H(23A)	109.5
O(3)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
O(3)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(29)-C(24)-C(25)	118.86(13)
C(29)-C(24)-C(22)	121.21(13)
C(25)-C(24)-C(22)	119.92(13)
C(26)-C(25)-C(24)	120.61(14)
C(26)-C(25)-H(25)	119.7
C(24)-C(25)-H(25)	119.7
C(27)-C(26)-C(25)	120.22(15)
C(27)-C(26)-H(26)	119.9
C(25)-C(26)-H(26)	119.9
C(28)-C(27)-C(26)	119.40(14)
C(28)-C(27)-H(27)	120.3
C(26)-C(27)-H(27)	120.3
C(27)-C(28)-C(29)	120.59(15)
C(27)-C(28)-H(28)	119.7
C(29)-C(28)-H(28)	119.7
C(24)-C(29)-C(28)	120.31(14)
C(24)-C(29)-H(29)	119.8
C(28)-C(29)-H(29)	119.8
C(15)-N(1)-C(8)	119.91(11)
C(15)-N(1)-S(1)	118.11(10)
C(8)-N(1)-S(1)	119.92(10)
C(14)-O(3)-C(23)	118.31(11)
O(1)-S(1)-O(2)	118.46(7)
O(1)-S(1)-N(1)	106.29(7)
O(2)-S(1)-N(1)	110.77(6)
O(1)-S(1)-C(5)	109.79(7)
O(2)-S(1)-C(5)	106.84(7)
N(1)-S(1)-C(5)	103.74(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **235**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	36(1)	63(1)	27(1)	-17(1)	-5(1)	12(1)
C(2)	19(1)	43(1)	24(1)	-11(1)	-6(1)	2(1)
C(3)	27(1)	27(1)	30(1)	-9(1)	-6(1)	6(1)
C(4)	25(1)	24(1)	24(1)	-4(1)	-3(1)	2(1)
C(5)	17(1)	23(1)	24(1)	-8(1)	-6(1)	0(1)
C(6)	28(1)	25(1)	27(1)	-3(1)	-12(1)	-4(1)
C(7)	29(1)	40(1)	22(1)	-1(1)	-7(1)	-7(1)
C(8)	13(1)	23(1)	24(1)	-5(1)	-3(1)	0(1)
C(9)	22(1)	23(1)	34(1)	-6(1)	-6(1)	-1(1)
C(10)	28(1)	29(1)	39(1)	5(1)	-9(1)	-7(1)
C(11)	24(1)	46(1)	26(1)	1(1)	-4(1)	-7(1)
C(12)	23(1)	39(1)	26(1)	-10(1)	-1(1)	-1(1)
C(13)	19(1)	23(1)	27(1)	-7(1)	-3(1)	1(1)
C(14)	19(1)	20(1)	16(1)	-4(1)	-4(1)	0(1)
C(15)	18(1)	20(1)	17(1)	-5(1)	-4(1)	-2(1)
C(16)	21(1)	21(1)	16(1)	-5(1)	-5(1)	-1(1)
C(17)	19(1)	23(1)	21(1)	-5(1)	-4(1)	0(1)
C(18)	28(1)	22(1)	22(1)	-5(1)	-4(1)	4(1)
C(19)	32(1)	20(1)	19(1)	-3(1)	-3(1)	-4(1)
C(20)	23(1)	26(1)	16(1)	-4(1)	-2(1)	-5(1)
C(21)	21(1)	22(1)	13(1)	-5(1)	-4(1)	0(1)
C(22)	17(1)	21(1)	17(1)	-3(1)	-4(1)	0(1)
C(23)	23(1)	24(1)	26(1)	-5(1)	-1(1)	6(1)
C(24)	20(1)	18(1)	19(1)	-2(1)	-2(1)	1(1)
C(25)	20(1)	32(1)	22(1)	-5(1)	-5(1)	2(1)
C(26)	32(1)	33(1)	20(1)	-6(1)	-6(1)	3(1)
C(27)	32(1)	27(1)	23(1)	-5(1)	5(1)	3(1)
C(28)	20(1)	34(1)	32(1)	-6(1)	3(1)	2(1)
C(29)	20(1)	28(1)	25(1)	-5(1)	-5(1)	0(1)

N(1)	16(1)	24(1)	22(1)	-7(1)	-3(1)	-3(1)
O(1)	16(1)	35(1)	34(1)	-16(1)	-3(1)	-3(1)
O(2)	30(1)	23(1)	43(1)	-12(1)	-18(1)	7(1)
O(3)	19(1)	20(1)	34(1)	-3(1)	-3(1)	2(1)
S(1)	17(1)	21(1)	28(1)	-10(1)	-6(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **235**.

	x	y	z	U(eq)
H(1A)	3235	5567	3454	62
H(1B)	3554	4286	4354	62
H(1C)	4612	5452	3959	62
H(3)	2776	4212	6492	33
H(4)	1744	5195	8187	29
H(6)	1982	8740	6042	31
H(7)	3083	7753	4372	36
H(9)	1518	5366	10634	31
H(10)	806	4700	12738	39
H(11)	389	6259	14100	39
H(12)	683	8486	13353	35
H(13)	1350	9164	11244	27
H(17)	1423	10726	9245	25
H(18)	2174	12898	8865	29
H(19)	4442	13361	8246	29
H(20)	6010	11643	8006	26
H(22)	6049	8821	9022	22
H(23A)	6263	6263	7879	37
H(23B)	5874	5139	9028	37
H(23C)	6409	6522	9229	37
H(25)	4653	8731	6276	29
H(26)	5869	8538	4326	34

H(27)	8201	8516	3993	34
H(28)	9302	8683	5624	35
H(29)	8092	8870	7581	29

Table 6. Torsion angles [°] for **235**

C(7)-C(2)-C(3)-C(4)	0.7(2)
C(1)-C(2)-C(3)-C(4)	-178.52(15)
C(2)-C(3)-C(4)-C(5)	1.1(2)
C(3)-C(4)-C(5)-C(6)	-1.7(2)
C(3)-C(4)-C(5)-S(1)	175.15(12)
C(4)-C(5)-C(6)-C(7)	0.5(2)
S(1)-C(5)-C(6)-C(7)	-176.34(11)
C(5)-C(6)-C(7)-C(2)	1.4(2)
C(3)-C(2)-C(7)-C(6)	-2.0(2)
C(1)-C(2)-C(7)-C(6)	177.28(15)
C(13)-C(8)-C(9)-C(10)	0.7(2)
N(1)-C(8)-C(9)-C(10)	-179.75(14)
C(8)-C(9)-C(10)-C(11)	-0.8(2)
C(9)-C(10)-C(11)-C(12)	0.0(3)
C(10)-C(11)-C(12)-C(13)	0.7(2)
C(11)-C(12)-C(13)-C(8)	-0.8(2)
C(9)-C(8)-C(13)-C(12)	0.0(2)
N(1)-C(8)-C(13)-C(12)	-179.50(13)
O(3)-C(14)-C(15)-N(1)	0.9(2)
C(22)-C(14)-C(15)-N(1)	-178.22(12)
O(3)-C(14)-C(15)-C(16)	177.24(12)
C(22)-C(14)-C(15)-C(16)	-1.89(16)
C(14)-C(15)-C(16)-C(17)	-177.26(15)
N(1)-C(15)-C(16)-C(17)	-1.1(2)
C(14)-C(15)-C(16)-C(21)	0.98(16)
N(1)-C(15)-C(16)-C(21)	177.16(13)
C(21)-C(16)-C(17)-C(18)	0.5(2)
C(15)-C(16)-C(17)-C(18)	178.52(14)
C(16)-C(17)-C(18)-C(19)	-0.1(2)
C(17)-C(18)-C(19)-C(20)	-0.2(2)
C(18)-C(19)-C(20)-C(21)	0.3(2)
C(19)-C(20)-C(21)-C(16)	0.1(2)
C(19)-C(20)-C(21)-C(22)	-178.99(13)
C(17)-C(16)-C(21)-C(20)	-0.4(2)

C(15)-C(16)-C(21)-C(20)	-178.92(12)
C(17)-C(16)-C(21)-C(22)	178.78(12)
C(15)-C(16)-C(21)-C(22)	0.31(15)
O(3)-C(14)-C(22)-C(21)	-177.16(13)
C(15)-C(14)-C(22)-C(21)	1.95(15)
O(3)-C(14)-C(22)-C(24)	61.02(17)
C(15)-C(14)-C(22)-C(24)	-119.87(13)
C(20)-C(21)-C(22)-C(14)	177.85(14)
C(16)-C(21)-C(22)-C(14)	-1.30(14)
C(20)-C(21)-C(22)-C(24)	-60.33(19)
C(16)-C(21)-C(22)-C(24)	120.53(13)
C(14)-C(22)-C(24)-C(29)	-131.34(14)
C(21)-C(22)-C(24)-C(29)	114.07(15)
C(14)-C(22)-C(24)-C(25)	48.02(18)
C(21)-C(22)-C(24)-C(25)	-66.57(17)
C(29)-C(24)-C(25)-C(26)	0.5(2)
C(22)-C(24)-C(25)-C(26)	-178.88(14)
C(24)-C(25)-C(26)-C(27)	-0.3(2)
C(25)-C(26)-C(27)-C(28)	0.0(2)
C(26)-C(27)-C(28)-C(29)	0.1(2)
C(25)-C(24)-C(29)-C(28)	-0.4(2)
C(22)-C(24)-C(29)-C(28)	178.98(14)
C(27)-C(28)-C(29)-C(24)	0.1(2)
C(14)-C(15)-N(1)-C(8)	84.83(17)
C(16)-C(15)-N(1)-C(8)	-90.84(17)
C(14)-C(15)-N(1)-S(1)	-111.47(14)
C(16)-C(15)-N(1)-S(1)	72.87(16)
C(13)-C(8)-N(1)-C(15)	60.00(18)
C(9)-C(8)-N(1)-C(15)	-119.53(15)
C(13)-C(8)-N(1)-S(1)	-103.41(14)
C(9)-C(8)-N(1)-S(1)	77.06(16)
C(15)-C(14)-O(3)-C(23)	-176.62(13)
C(22)-C(14)-O(3)-C(23)	2.4(2)
C(15)-N(1)-S(1)-O(1)	177.14(10)
C(8)-N(1)-S(1)-O(1)	-19.16(12)
C(15)-N(1)-S(1)-O(2)	-52.93(12)

C(8)-N(1)-S(1)-O(2)	110.77(12)
C(15)-N(1)-S(1)-C(5)	61.38(12)
C(8)-N(1)-S(1)-C(5)	-134.92(11)
C(6)-C(5)-S(1)-O(1)	136.87(12)
C(4)-C(5)-S(1)-O(1)	-40.05(14)
C(6)-C(5)-S(1)-O(2)	7.23(14)
C(4)-C(5)-S(1)-O(2)	-169.70(12)
C(6)-C(5)-S(1)-N(1)	-109.87(13)
C(4)-C(5)-S(1)-N(1)	73.21(13)

Symmetry transformations used to generate equivalent atoms:

Crystal data and structure refinement for 265

Empirical formula	$C_{20}H_{21}NO_3S$	
Formula weight	355.44	
Temperature	120(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 2_1/n	
Unit cell dimensions	a = 10.65260(10) Å	□= 90°.
	b = 14.6878(2) Å	□= 97.7890(10)°.
	c = 10.79310(10) Å	□ = 90°.
Volume	1673.14(3) $Å^3$	
Z	4	
Density (calculated)	1.411 Mg/m^3	
Absorption coefficient	1.881 mm^{-1}	
F(000)	752	
Crystal size	0.24 x 0.18 x 0.16 mm^3	
Theta range for data collection	6.97 to 70.85°.	
Index ranges	-12<=h<=12, -17<=k<=17, -12<=l<=13	
Reflections collected	16957	
Independent reflections	3152 [R(int) = 0.0415]	
Completeness to theta = 70.85°	98.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7529 and 0.6610	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3152 / 0 / 228
Goodness-of-fit on F^2	1.085
Final R indices [I>2sigma(I)]	R1 = 0.0439, wR2 = 0.1179
R indices (all data)	R1 = 0.0446, wR2 = 0.1196
Largest diff. peak and hole	0.371 and -0.480 e.$Å^{-3}$

Notes:

The hydrogen atoms have been fixed as riding models.
The structure is in a centrosymmetric space group and, as such in 50 % of molecules C(2) and C(13) are *R* and C(5) and C(6) are *S* and in the other 50 % C(2) and C(13) are *S* and C(5) and C(6) are *R*.
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for **265** U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1572(2)	3863(1)	5321(1)	19(1)
C(2)	1715(1)	2888(1)	4917(1)	18(1)
C(3)	841(1)	2542(1)	3786(1)	18(1)
C(4)	-246(2)	3730(1)	549(1)	24(1)
C(5)	2121(1)	3745(1)	3078(1)	13(1)
C(6)	2533(1)	3636(1)	4471(1)	14(1)
C(7)	3930(1)	3718(1)	4647(1)	14(1)
C(8)	4778(2)	3873(1)	5725(1)	17(1)
C(9)	6060(1)	3958(1)	5618(1)	19(1)
C(10)	6493(1)	3898(1)	4454(2)	18(1)
C(11)	5643(1)	3728(1)	3376(1)	16(1)
C(12)	4365(1)	3637(1)	3480(1)	14(1)
C(13)	3276(1)	3379(1)	2470(1)	13(1)
C(14)	4231(1)	1911(1)	2190(1)	20(1)
C(15)	3292(1)	3789(1)	1180(1)	13(1)

C(16)	2893(1)	3285(1)	108(1)	17(1)
C(17)	2784(1)	3687(1)	-1070(1)	19(1)
C(18)	3065(1)	4602(1)	-1187(1)	18(1)
C(19)	3465(1)	5112(1)	-124(1)	19(1)
C(20)	3587(1)	4709(1)	1054(1)	17(1)
N(1)	934(1)	3236(1)	2793(1)	15(1)
O(1)	-248(1)	4732(1)	2511(1)	32(1)
O(2)	-1422(1)	3281(1)	2413(1)	25(1)
O(3)	3130(1)	2408(1)	2418(1)	16(1)
S(1)	-332(1)	3790(1)	2160(1)	17(1)

Table 3. Bond lengths [Å] and angles [°] for **265**

C(1)-C(6)	1.502(2)
C(1)-C(2)	1.511(2)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.519(2)
C(2)-C(6)	1.5201(19)
C(2)-H(2)	1.0000
C(3)-N(1)	1.4914(17)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-S(1)	1.7557(16)
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(4)-H(4C)	0.9800
C(5)-N(1)	1.4649(17)
C(5)-C(6)	1.5162(19)
C(5)-C(13)	1.5654(18)
C(5)-H(5)	1.0000
C(6)-C(7)	1.479(2)
C(7)-C(8)	1.391(2)
C(7)-C(12)	1.405(2)
C(8)-C(9)	1.392(2)
C(8)-H(8)	0.9500

C(9)-C(10)	1.398(2)
C(9)-H(9)	0.9500
C(10)-C(11)	1.397(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.387(2)
C(11)-H(11)	0.9500
C(12)-C(13)	1.5282(18)
C(13)-O(3)	1.4344(16)
C(13)-C(15)	1.5199(18)
C(14)-O(3)	1.4317(17)
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-C(16)	1.391(2)
C(15)-C(20)	1.3979(19)
C(16)-C(17)	1.391(2)
C(16)-H(16)	0.9500
C(17)-C(18)	1.386(2)
C(17)-H(17)	0.9500
C(18)-C(19)	1.389(2)
C(18)-H(18)	0.9500
C(19)-C(20)	1.392(2)
C(19)-H(19)	0.9500
C(20)-H(20)	0.9500
N(1)-S(1)	1.6420(12)
O(1)-S(1)	1.4351(12)
O(2)-S(1)	1.4379(11)
C(6)-C(1)-C(2)	60.60(9)
C(6)-C(1)-H(1A)	117.7
C(2)-C(1)-H(1A)	117.7
C(6)-C(1)-H(1B)	117.7
C(2)-C(1)-H(1B)	117.7
H(1A)-C(1)-H(1B)	114.8
C(1)-C(2)-C(3)	118.29(13)
C(1)-C(2)-C(6)	59.42(9)
C(3)-C(2)-C(6)	107.57(11)

C(1)-C(2)-H(2)	118.8
C(3)-C(2)-H(2)	118.8
C(6)-C(2)-H(2)	118.8
N(1)-C(3)-C(2)	104.81(11)
N(1)-C(3)-H(3A)	110.8
C(2)-C(3)-H(3A)	110.8
N(1)-C(3)-H(3B)	110.8
C(2)-C(3)-H(3B)	110.8
H(3A)-C(3)-H(3B)	108.9
S(1)-C(4)-H(4A)	109.5
S(1)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	109.5
S(1)-C(4)-H(4C)	109.5
H(4A)-C(4)-H(4C)	109.5
H(4B)-C(4)-H(4C)	109.5
N(1)-C(5)-C(6)	106.26(11)
N(1)-C(5)-C(13)	116.24(11)
C(6)-C(5)-C(13)	103.92(11)
N(1)-C(5)-H(5)	110.0
C(6)-C(5)-H(5)	110.0
C(13)-C(5)-H(5)	110.0
C(7)-C(6)-C(1)	131.34(13)
C(7)-C(6)-C(5)	105.66(12)
C(1)-C(6)-C(5)	116.87(12)
C(7)-C(6)-C(2)	128.92(12)
C(1)-C(6)-C(2)	59.97(10)
C(5)-C(6)-C(2)	106.80(11)
C(8)-C(7)-C(12)	120.54(14)
C(8)-C(7)-C(6)	130.40(13)
C(12)-C(7)-C(6)	109.04(12)
C(7)-C(8)-C(9)	118.56(14)
C(7)-C(8)-H(8)	120.7
C(9)-C(8)-H(8)	120.7
C(8)-C(9)-C(10)	121.03(14)
C(8)-C(9)-H(9)	119.5
C(10)-C(9)-H(9)	119.5

C(9)-C(10)-C(11)	120.30(14)
C(9)-C(10)-H(10)	119.8
C(11)-C(10)-H(10)	119.8
C(12)-C(11)-C(10)	118.82(14)
C(12)-C(11)-H(11)	120.6
C(10)-C(11)-H(11)	120.6
C(11)-C(12)-C(7)	120.72(13)
C(11)-C(12)-C(13)	128.68(13)
C(7)-C(12)-C(13)	110.44(12)
O(3)-C(13)-C(15)	111.86(11)
O(3)-C(13)-C(12)	110.07(11)
C(15)-C(13)-C(12)	116.93(12)
O(3)-C(13)-C(5)	105.68(10)
C(15)-C(13)-C(5)	110.81(11)
C(12)-C(13)-C(5)	100.37(10)
O(3)-C(14)-H(14A)	109.5
O(3)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
O(3)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(16)-C(15)-C(20)	118.72(13)
C(16)-C(15)-C(13)	120.76(12)
C(20)-C(15)-C(13)	120.21(12)
C(15)-C(16)-C(17)	120.83(13)
C(15)-C(16)-H(16)	119.6
C(17)-C(16)-H(16)	119.6
C(18)-C(17)-C(16)	120.16(13)
C(18)-C(17)-H(17)	119.9
C(16)-C(17)-H(17)	119.9
C(17)-C(18)-C(19)	119.55(13)
C(17)-C(18)-H(18)	120.2
C(19)-C(18)-H(18)	120.2
C(18)-C(19)-C(20)	120.37(13)
C(18)-C(19)-H(19)	119.8
C(20)-C(19)-H(19)	119.8

C(19)-C(20)-C(15)	120.38(13)
C(19)-C(20)-H(20)	119.8
C(15)-C(20)-H(20)	119.8
C(5)-N(1)-C(3)	109.69(11)
C(5)-N(1)-S(1)	118.14(9)
C(3)-N(1)-S(1)	120.45(9)
C(14)-O(3)-C(13)	115.27(10)
O(1)-S(1)-O(2)	118.32(7)
O(1)-S(1)-N(1)	110.47(7)
O(2)-S(1)-N(1)	107.59(6)
O(1)-S(1)-C(4)	107.41(8)
O(2)-S(1)-C(4)	108.30(7)
N(1)-S(1)-C(4)	103.76(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for HVA/**357** The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	19(1)	24(1)	14(1)	-2(1)	6(1)	0(1)
C(2)	17(1)	21(1)	17(1)	4(1)	4(1)	-1(1)
C(3)	18(1)	18(1)	19(1)	4(1)	3(1)	-2(1)
C(4)	22(1)	30(1)	19(1)	6(1)	3(1)	4(1)
C(5)	12(1)	14(1)	12(1)	-1(1)	2(1)	0(1)
C(6)	15(1)	16(1)	12(1)	0(1)	2(1)	1(1)
C(7)	15(1)	12(1)	16(1)	1(1)	2(1)	1(1)
C(8)	21(1)	17(1)	14(1)	0(1)	1(1)	2(1)
C(9)	19(1)	15(1)	20(1)	-1(1)	-3(1)	1(1)
C(10)	13(1)	16(1)	26(1)	2(1)	0(1)	1(1)
C(11)	16(1)	14(1)	18(1)	2(1)	4(1)	1(1)
C(12)	16(1)	11(1)	14(1)	1(1)	2(1)	1(1)
C(13)	13(1)	13(1)	15(1)	0(1)	3(1)	0(1)
C(14)	21(1)	17(1)	24(1)	-1(1)	4(1)	5(1)
C(15)	11(1)	17(1)	14(1)	1(1)	4(1)	2(1)
C(16)	17(1)	16(1)	17(1)	-1(1)	2(1)	0(1)

C(17)	18(1)	23(1)	14(1)	-3(1)	1(1)	1(1)
C(18)	17(1)	22(1)	15(1)	4(1)	3(1)	4(1)
C(19)	20(1)	15(1)	21(1)	3(1)	5(1)	1(1)
C(20)	17(1)	17(1)	17(1)	-2(1)	3(1)	0(1)
N(1)	12(1)	17(1)	17(1)	2(1)	2(1)	-1(1)
O(1)	23(1)	22(1)	47(1)	-12(1)	-7(1)	8(1)
O(2)	14(1)	36(1)	27(1)	3(1)	3(1)	-2(1)
O(3)	17(1)	12(1)	19(1)	0(1)	5(1)	1(1)
S(1)	12(1)	18(1)	20(1)	-2(1)	1(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **265**

	x	y	z	U(eq)
H(1A)	801	4196	4957	23
H(1B)	1889	4022	6199	23
H(2)	2116	2438	5545	22
H(3A)	1121	1938	3522	22
H(3B)	-40	2492	3973	22
H(4A)	-973	4049	90	35
H(4B)	-258	3091	286	35
H(4C)	540	4018	371	35
H(5)	1976	4403	2868	15
H(8)	4487	3920	6517	21
H(9)	6651	4058	6347	22
H(10)	7369	3974	4397	22
H(11)	5935	3675	2586	19
H(14A)	4560	2166	1459	30
H(14B)	4007	1270	2033	30
H(14C)	4881	1956	2922	30
H(16)	2691	2659	180	20
H(17)	2518	3333	-1795	22

H(18)	2983	4878	-1990	22
H(19)	3657	5739	-200	22
H(20)	3872	5061	1775	20

Table 6. Torsion angles [°] for **265**

C(6)-C(1)-C(2)-C(3)	-94.59(14)
C(1)-C(2)-C(3)-N(1)	50.35(16)
C(6)-C(2)-C(3)-N(1)	-13.83(15)
C(2)-C(1)-C(6)-C(7)	-117.26(17)
C(2)-C(1)-C(6)-C(5)	94.67(13)
N(1)-C(5)-C(6)-C(7)	152.21(11)
C(13)-C(5)-C(6)-C(7)	29.06(13)
N(1)-C(5)-C(6)-C(1)	-52.15(16)
C(13)-C(5)-C(6)-C(1)	-175.30(12)
N(1)-C(5)-C(6)-C(2)	12.19(15)
C(13)-C(5)-C(6)-C(2)	-110.96(12)
C(1)-C(2)-C(6)-C(7)	120.92(17)
C(3)-C(2)-C(6)-C(7)	-126.10(15)
C(3)-C(2)-C(6)-C(1)	112.98(13)
C(1)-C(2)-C(6)-C(5)	-111.76(13)
C(3)-C(2)-C(6)-C(5)	1.22(15)
C(1)-C(6)-C(7)-C(8)	13.3(2)
C(5)-C(6)-C(7)-C(8)	163.94(14)
C(2)-C(6)-C(7)-C(8)	-68.3(2)
C(1)-C(6)-C(7)-C(12)	-165.06(14)
C(5)-C(6)-C(7)-C(12)	-14.40(15)
C(2)-C(6)-C(7)-C(12)	113.35(16)
C(12)-C(7)-C(8)-C(9)	0.8(2)
C(6)-C(7)-C(8)-C(9)	-177.39(14)
C(7)-C(8)-C(9)-C(10)	0.6(2)
C(8)-C(9)-C(10)-C(11)	-1.6(2)
C(9)-C(10)-C(11)-C(12)	1.2(2)
C(10)-C(11)-C(12)-C(7)	0.2(2)
C(10)-C(11)-C(12)-C(13)	-174.72(13)
C(8)-C(7)-C(12)-C(11)	-1.2(2)

C(6)-C(7)-C(12)-C(11)	177.35(12)
C(8)-C(7)-C(12)-C(13)	174.55(12)
C(6)-C(7)-C(12)-C(13)	-6.91(15)
C(11)-C(12)-C(13)-O(3)	88.43(16)
C(7)-C(12)-C(13)-O(3)	-86.88(13)
C(11)-C(12)-C(13)-C(15)	-40.63(19)
C(7)-C(12)-C(13)-C(15)	144.06(12)
C(11)-C(12)-C(13)-C(5)	-160.51(13)
C(7)-C(12)-C(13)-C(5)	24.18(14)
N(1)-C(5)-C(13)-O(3)	-33.45(15)
C(6)-C(5)-C(13)-O(3)	82.90(12)
N(1)-C(5)-C(13)-C(15)	87.91(14)
C(6)-C(5)-C(13)-C(15)	-155.74(11)
N(1)-C(5)-C(13)-C(12)	-147.88(12)
C(6)-C(5)-C(13)-C(12)	-31.53(13)
O(3)-C(13)-C(15)-C(16)	14.69(18)
C(12)-C(13)-C(15)-C(16)	142.89(13)
C(5)-C(13)-C(15)-C(16)	-102.96(14)
O(3)-C(13)-C(15)-C(20)	-171.87(12)
C(12)-C(13)-C(15)-C(20)	-43.67(18)
C(5)-C(13)-C(15)-C(20)	70.48(16)
C(20)-C(15)-C(16)-C(17)	-0.1(2)
C(13)-C(15)-C(16)-C(17)	173.41(13)
C(15)-C(16)-C(17)-C(18)	-0.6(2)
C(16)-C(17)-C(18)-C(19)	0.6(2)
C(17)-C(18)-C(19)-C(20)	0.1(2)
C(18)-C(19)-C(20)-C(15)	-0.8(2)
C(16)-C(15)-C(20)-C(19)	0.8(2)
C(13)-C(15)-C(20)-C(19)	-172.76(13)
C(6)-C(5)-N(1)-C(3)	-21.67(14)
C(13)-C(5)-N(1)-C(3)	93.37(14)
C(6)-C(5)-N(1)-S(1)	121.65(10)
C(13)-C(5)-N(1)-S(1)	-123.31(11)
C(2)-C(3)-N(1)-C(5)	22.19(15)
C(2)-C(3)-N(1)-S(1)	-120.14(11)
C(15)-C(13)-O(3)-C(14)	74.41(14)

C(12)-C(13)-O(3)-C(14)	-57.35(14)
C(5)-C(13)-O(3)-C(14)	-164.91(11)
C(5)-N(1)-S(1)-O(1)	-27.42(13)
C(3)-N(1)-S(1)-O(1)	111.86(12)
C(5)-N(1)-S(1)-O(2)	-157.93(10)
C(3)-N(1)-S(1)-O(2)	-18.65(12)
C(5)-N(1)-S(1)-C(4)	87.44(11)
C(3)-N(1)-S(1)-C(4)	-133.29(11)

Symmetry transformations used to generate equivalent atoms:

Crystal data and structure refinement for 357

Empirical formula	$C_{20}H_{21}NO_3S$	
Formula weight	355.44	
Temperature	120(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.53990(10) Å	□= 83.5660(10)°.
	b = 8.68330(10) Å	□= 85.8150(10)°.
	c = 12.1209(2) Å	□ = 84.8840(10)°.
Volume	887.80(2) $Å^3$	
Z	2	
Density (calculated)	1.330 Mg/m^3	
Absorption coefficient	1.772 mm^{-1}	
F(000)	376	
Crystal size	0.24 x 0.16 x 0.13 mm^3	
Theta range for data collection	6.57 to 66.59°.	
Index ranges	-9<=h<=10, -10<=k<=10, -14<=l<=14	
Reflections collected	8609	
Independent reflections	3049 [R(int) = 0.0223]	
Completeness to theta = 66.59°	97.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8023 and 0.6757	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	3049 / 0 / 228
Goodness-of-fit on F^2	1.068
Final R indices [I>2sigma(I)]	R1 = 0.0394, wR2 = 0.1075
R indices (all data)	R1 = 0.0414, wR2 = 0.1101
Largest diff. peak and hole	0.455 and -0.393 e.$Å^{-3}$

Notes:

The hydrogen atoms have been fixed as riding models.

The space group is centrosymmetric which means that there will be an equal number of molecules where C(13) is *R* and where C(13) is *S* in the structure.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **357**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7455(2)	7646(2)	5670(2)	36(1)
C(2)	6195(2)	7021(2)	6151(1)	28(1)
C(3)	4558(2)	7796(2)	6123(1)	26(1)
C(4)	861(2)	9253(2)	7426(2)	31(1)
C(5)	4692(2)	10523(2)	7714(1)	21(1)
C(6)	4729(2)	8959(2)	7878(1)	21(1)
C(7)	5875(2)	8369(2)	8696(1)	21(1)
C(8)	6342(2)	6867(2)	9138(1)	25(1)
C(9)	7537(2)	6655(2)	9879(1)	28(1)
C(10)	8234(2)	7924(2)	10179(1)	27(1)
C(11)	7742(2)	9436(2)	9759(1)	24(1)
C(12)	6563(2)	9645(2)	9020(1)	20(1)
C(13)	5847(2)	11143(2)	8410(1)	20(1)
C(14)	3574(2)	13048(2)	7023(2)	28(1)
C(15)	7083(2)	12075(2)	7729(1)	20(1)
C(16)	7491(2)	11861(2)	6624(1)	25(1)
C(17)	8630(2)	12717(2)	6017(1)	28(1)
C(18)	9377(2)	13786(2)	6521(1)	27(1)
C(19)	8987(2)	13997(2)	7626(2)	27(1)
C(20)	7837(2)	13151(2)	8230(1)	23(1)
N(1)	3924(2)	7988(2)	7271(1)	22(1)

O(1)	1730(1)	6421(1)	7039(1)	32(1)
O(2)	2129(1)	7218(1)	8886(1)	31(1)
O(3)	3807(1)	11393(1)	6959(1)	26(1)
S(1)	2142(1)	7566(1)	7706(1)	23(1)

Table 3. Bond lengths [Å] and angles [°] for **357**.

C(1)-C(2)	1.317(3)	C(10)-H(10)	0.9500
C(1)-H(1A)	0.9500	C(11)-C(12)	1.382(2)
C(1)-H(1B)	0.9500	C(11)-H(11)	0.9500
C(2)-C(3)	1.497(2)	C(12)-C(13)	1.523(2)
C(2)-H(2)	0.9500	C(13)-C(15)	1.525(2)
C(3)-N(1)	1.477(2)	C(13)-H(13)	1.0000
C(3)-H(3A)	0.9900	C(14)-O(3)	1.4439(19)
C(3)-H(3B)	0.9900	C(14)-H(14A)	0.9800
C(4)-S(1)	1.7657(18)	C(14)-H(14B)	0.9800
C(4)-H(4A)	0.9800	C(14)-H(14C)	0.9800
C(4)-H(4B)	0.9800	C(15)-C(16)	1.389(2)
C(4)-H(4C)	0.9800	C(15)-C(20)	1.395(2)
C(5)-C(6)	1.348(2)	C(16)-C(17)	1.393(2)
C(5)-O(3)	1.350(2)	C(16)-H(16)	0.9500
C(5)-C(13)	1.515(2)	C(17)-C(18)	1.390(2)
C(6)-N(1)	1.4290(19)	C(17)-H(17)	0.9500
C(6)-C(7)	1.464(2)	C(18)-C(19)	1.385(2)
C(7)-C(8)	1.388(2)	C(18)-H(18)	0.9500
C(7)-C(12)	1.405(2)	C(19)-C(20)	1.394(2)
C(8)-C(9)	1.396(2)	C(19)-H(19)	0.9500
C(8)-H(8)	0.9500	C(20)-H(20)	0.9500
C(9)-C(10)	1.393(2)	N(1)-S(1)	1.6328(13)
C(9)-H(9)	0.9500	O(1)-S(1)	1.4321(12)
C(10)-C(11)	1.394(2)	O(2)-S(1)	1.4274(13)
C(2)-C(1)-H(1A)	120.0	N(1)-C(3)-C(2)	109.34(13)
C(2)-C(1)-H(1B)	120.0	N(1)-C(3)-H(3A)	109.8
H(1A)-C(1)-H(1B)	120.0	C(2)-C(3)-H(3A)	109.8
C(1)-C(2)-C(3)	124.32(17)	N(1)-C(3)-H(3B)	109.8
C(1)-C(2)-H(2)	117.8	C(2)-C(3)-H(3B)	109.8
C(3)-C(2)-H(2)	117.8	H(3A)-C(3)-H(3B)	108.3

S(1)-C(4)-H(4A)	109.5	O(3)-C(14)-H(14A)	109.5
S(1)-C(4)-H(4B)	109.5	O(3)-C(14)-H(14B)	109.5
H(4A)-C(4)-H(4B)	109.5	H(14A)-C(14)-H(14B)	109.5
S(1)-C(4)-H(4C)	109.5	O(3)-C(14)-H(14C)	109.5
H(4A)-C(4)-H(4C)	109.5	H(14A)-C(14)-H(14C)	109.5
H(4B)-C(4)-H(4C)	109.5	H(14B)-C(14)-H(14C)	109.5
C(6)-C(5)-O(3)	123.15(14)	C(16)-C(15)-C(20)	119.18(14)
C(6)-C(5)-C(13)	111.54(14)	C(16)-C(15)-C(13)	121.36(14)
O(3)-C(5)-C(13)	125.15(13)	C(20)-C(15)-C(13)	119.45(14)
C(5)-C(6)-N(1)	126.25(14)	C(15)-C(16)-C(17)	120.51(15)
C(5)-C(6)-C(7)	109.50(14)	C(15)-C(16)-H(16)	119.7
N(1)-C(6)-C(7)	123.91(13)	C(17)-C(16)-H(16)	119.7
C(8)-C(7)-C(12)	120.38(15)	C(18)-C(17)-C(16)	120.01(15)
C(8)-C(7)-C(6)	131.57(15)	C(18)-C(17)-H(17)	120.0
C(12)-C(7)-C(6)	108.05(13)	C(16)-C(17)-H(17)	120.0
C(7)-C(8)-C(9)	118.60(15)	C(19)-C(18)-C(17)	119.81(15)
C(7)-C(8)-H(8)	120.7	C(19)-C(18)-H(18)	120.1
C(9)-C(8)-H(8)	120.7	C(17)-C(18)-H(18)	120.1
C(10)-C(9)-C(8)	120.65(15)	C(18)-C(19)-C(20)	120.18(15)
C(10)-C(9)-H(9)	119.7	C(18)-C(19)-H(19)	119.9
C(8)-C(9)-H(9)	119.7	C(20)-C(19)-H(19)	119.9
C(9)-C(10)-C(11)	120.90(16)	C(19)-C(20)-C(15)	120.29(15)
C(9)-C(10)-H(10)	119.6	C(19)-C(20)-H(20)	119.9
C(11)-C(10)-H(10)	119.6	C(15)-C(20)-H(20)	119.9
C(12)-C(11)-C(10)	118.40(15)	C(6)-N(1)-C(3)	116.69(12)
C(12)-C(11)-H(11)	120.8	C(6)-N(1)-S(1)	119.22(10)
C(10)-C(11)-H(11)	120.8	C(3)-N(1)-S(1)	121.74(11)
C(11)-C(12)-C(7)	121.05(15)	C(5)-O(3)-C(14)	118.26(12)
C(11)-C(12)-C(13)	129.33(14)	O(2)-S(1)-O(1)	119.59(7)
C(7)-C(12)-C(13)	109.59(13)	O(2)-S(1)-N(1)	107.18(7)
C(5)-C(13)-C(12)	101.32(12)	O(1)-S(1)-N(1)	106.67(7)
C(5)-C(13)-C(15)	113.87(13)	O(2)-S(1)-C(4)	107.45(8)
C(12)-C(13)-C(15)	112.48(12)	O(1)-S(1)-C(4)	107.65(8)
C(5)-C(13)-H(13)	109.6	N(1)-S(1)-C(4)	107.81(8)
C(12)-C(13)-H(13)	109.6		
C(15)-C(13)-H(13)	109.6		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **357**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	29(1)	38(1)	40(1)	-8(1)	6(1)	-2(1)
C(2)	29(1)	27(1)	28(1)	-6(1)	1(1)	-1(1)
C(3)	26(1)	28(1)	23(1)	-4(1)	-2(1)	-5(1)
C(4)	22(1)	31(1)	40(1)	-3(1)	-2(1)	0(1)
C(5)	17(1)	22(1)	23(1)	-2(1)	0(1)	-3(1)
C(6)	18(1)	22(1)	22(1)	-4(1)	0(1)	-4(1)
C(7)	19(1)	23(1)	21(1)	-3(1)	2(1)	-2(1)
C(8)	27(1)	21(1)	27(1)	-4(1)	0(1)	-3(1)
C(9)	30(1)	24(1)	28(1)	-1(1)	-2(1)	3(1)
C(10)	23(1)	33(1)	26(1)	-2(1)	-5(1)	1(1)
C(11)	22(1)	27(1)	23(1)	-3(1)	-1(1)	-5(1)
C(12)	18(1)	22(1)	21(1)	-2(1)	2(1)	-3(1)
C(13)	18(1)	20(1)	23(1)	-3(1)	-1(1)	-4(1)
C(14)	27(1)	21(1)	35(1)	0(1)	-4(1)	0(1)
C(15)	16(1)	19(1)	25(1)	0(1)	-2(1)	-1(1)
C(16)	22(1)	28(1)	27(1)	-6(1)	-2(1)	-6(1)
C(17)	21(1)	37(1)	25(1)	-1(1)	1(1)	-3(1)
C(18)	18(1)	28(1)	33(1)	5(1)	-1(1)	-5(1)
C(19)	22(1)	24(1)	36(1)	-1(1)	-6(1)	-5(1)
C(20)	23(1)	21(1)	25(1)	-2(1)	-2(1)	-3(1)
N(1)	19(1)	24(1)	25(1)	-5(1)	-1(1)	-5(1)
O(1)	28(1)	30(1)	42(1)	-10(1)	-1(1)	-12(1)
O(2)	29(1)	32(1)	31(1)	1(1)	2(1)	-9(1)
O(3)	25(1)	20(1)	35(1)	1(1)	-10(1)	-3(1)
S(1)	20(1)	21(1)	29(1)	-3(1)	-1(1)	-6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **357**

	x	y	z	U(eq)
H(1A)	7358	8653	5273	43
H(1B)	8461	7089	5720	43
H(2)	6333	6012	6542	34
H(3A)	4572	8825	5680	31
H(3B)	3877	7155	5768	31
H(4A)	-221	9029	7675	47
H(4B)	917	9579	6624	47
H(4C)	1175	10089	7822	47
H(8)	5858	6003	8939	30
H(9)	7879	5634	10183	33
H(10)	9056	7757	10677	33
H(11)	8205	10302	9974	29
H(13)	5260	11797	8959	24
H(14A)	3113	13245	7764	42
H(14B)	2860	13520	6459	42
H(14C)	4589	13504	6890	42
H(16)	6990	11124	6278	30
H(17)	8896	12569	5259	34
H(18)	10153	14371	6108	32
H(19)	9504	14720	7973	32
H(20)	7566	13308	8985	28

Table 6. Torsion angles [°] for **357**

C(1)-C(2)-C(3)-N(1)	-119.40(18)
O(3)-C(5)-C(6)-N(1)	2.9(2)
C(13)-C(5)-C(6)-N(1)	-172.72(13)
O(3)-C(5)-C(6)-C(7)	176.26(13)
C(13)-C(5)-C(6)-C(7)	0.64(18)
C(5)-C(6)-C(7)-C(8)	-179.79(16)
N(1)-C(6)-C(7)-C(8)	-6.2(3)
C(5)-C(6)-C(7)-C(12)	-0.75(18)
N(1)-C(6)-C(7)-C(12)	172.80(13)
C(12)-C(7)-C(8)-C(9)	-1.9(2)
C(6)-C(7)-C(8)-C(9)	177.00(16)
C(7)-C(8)-C(9)-C(10)	0.7(2)
C(8)-C(9)-C(10)-C(11)	0.9(3)
C(9)-C(10)-C(11)-C(12)	-1.2(2)
C(10)-C(11)-C(12)-C(7)	-0.1(2)
C(10)-C(11)-C(12)-C(13)	-177.73(14)
C(8)-C(7)-C(12)-C(11)	1.7(2)
C(6)-C(7)-C(12)-C(11)	-177.49(14)
C(8)-C(7)-C(12)-C(13)	179.72(13)
C(6)-C(7)-C(12)-C(13)	0.56(17)
C(6)-C(5)-C(13)-C(12)	-0.29(16)
O(3)-C(5)-C(13)-C(12)	-175.80(14)
C(6)-C(5)-C(13)-C(15)	120.72(15)
O(3)-C(5)-C(13)-C(15)	-54.8(2)
C(11)-C(12)-C(13)-C(5)	177.65(16)
C(7)-C(12)-C(13)-C(5)	-0.19(16)
C(11)-C(12)-C(13)-C(15)	55.7(2)
C(7)-C(12)-C(13)-C(15)	-122.16(14)
C(5)-C(13)-C(15)-C(16)	-23.7(2)
C(12)-C(13)-C(15)-C(16)	90.87(18)
C(5)-C(13)-C(15)-C(20)	157.20(14)
C(12)-C(13)-C(15)-C(20)	-88.25(17)
C(20)-C(15)-C(16)-C(17)	-0.5(2)
C(13)-C(15)-C(16)-C(17)	-179.63(15)

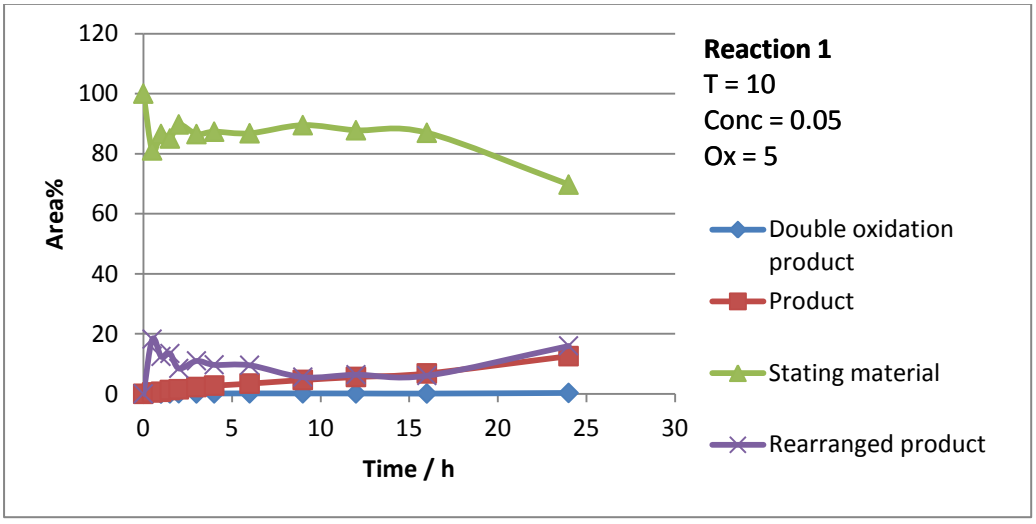
C(15)-C(16)-C(17)-C(18)	0.5(3)
C(16)-C(17)-C(18)-C(19)	0.0(3)
C(17)-C(18)-C(19)-C(20)	-0.6(3)
C(18)-C(19)-C(20)-C(15)	0.7(2)
C(16)-C(15)-C(20)-C(19)	-0.1(2)
C(13)-C(15)-C(20)-C(19)	179.05(15)
C(5)-C(6)-N(1)-C(3)	73.1(2)
C(7)-C(6)-N(1)-C(3)	-99.32(17)
C(5)-C(6)-N(1)-S(1)	-89.77(18)
C(7)-C(6)-N(1)-S(1)	97.77(16)
C(2)-C(3)-N(1)-C(6)	62.79(18)
C(2)-C(3)-N(1)-S(1)	-134.77(13)
C(6)-C(5)-O(3)-C(14)	166.09(14)
C(13)-C(5)-O(3)-C(14)	-18.9(2)
C(6)-N(1)-S(1)-O(2)	-42.90(13)
C(3)-N(1)-S(1)-O(2)	155.09(12)
C(6)-N(1)-S(1)-O(1)	-172.11(12)
C(3)-N(1)-S(1)-O(1)	25.88(14)
C(6)-N(1)-S(1)-C(4)	72.50(14)
C(3)-N(1)-S(1)-C(4)	-89.51(14)

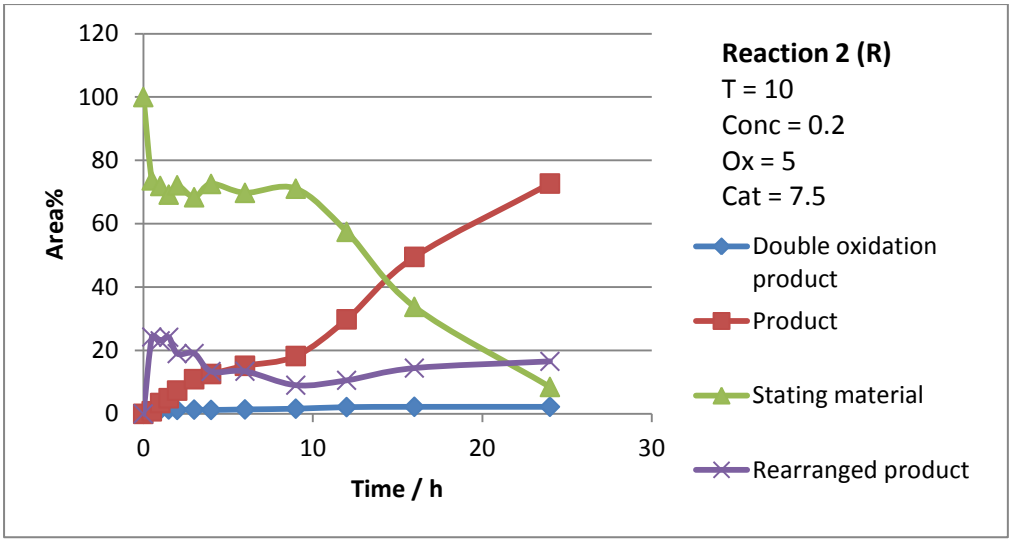
Symmetry transformations used to generate equivalent atoms:

Factorial Experimental Design (Chapter 5)

Exp No	Exp Name	Run Order	Temperature	Concentration	Oxidant	Catalyst
5	N5	1	10	0.05	5	2.5
15	N15	2	10	0.2	5	7.5
16	N16	3	40	0.2	5	7.5
6	N6	4	40	0.05	5	2.5
7	N7	5	10	0.2	5	2.5
14	N14	6	40	0.05	5	7.5
2	N2	7	40	0.05	1	2.5
8	N8	8	40	0.2	5	2.5
19	N19	9	25	0.125	3	5
12	N12	10	40	0.2	1	7.5
4	N4	11	40	0.2	1	2.5
10	N10	12	40	0.05	1	7.5
11	N11	13	10	0.2	1	7.5
17	N17	14	25	0.125	3	5
9	N9	15	10	0.05	1	7.5
3	N3	16	10	0.2	1	2.5
13	N13	17	10	0.05	5	7.5
1	N1	18	10	0.05	1	2.5
18	N18	19	25	0.125	3	5

Note: reaction number refers to run order:

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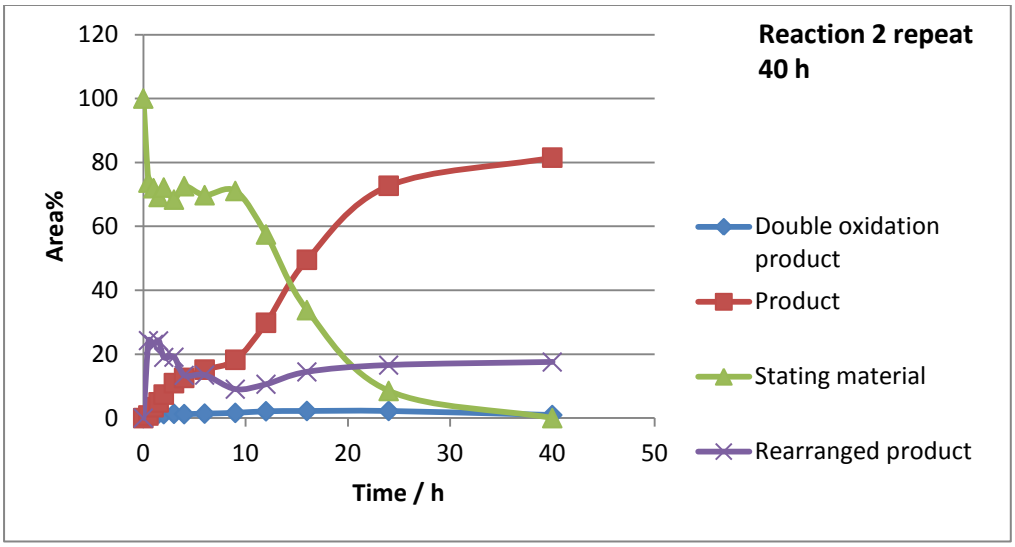
Product
Stating material
Rearranged product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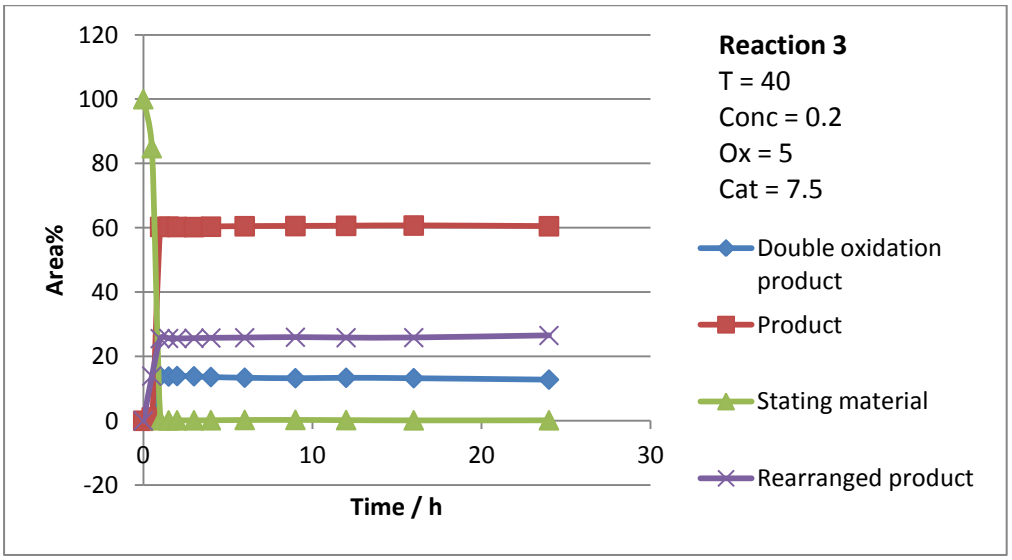
Area%
Time / h
Double oxidation product
Product
Stating material
Rearranged product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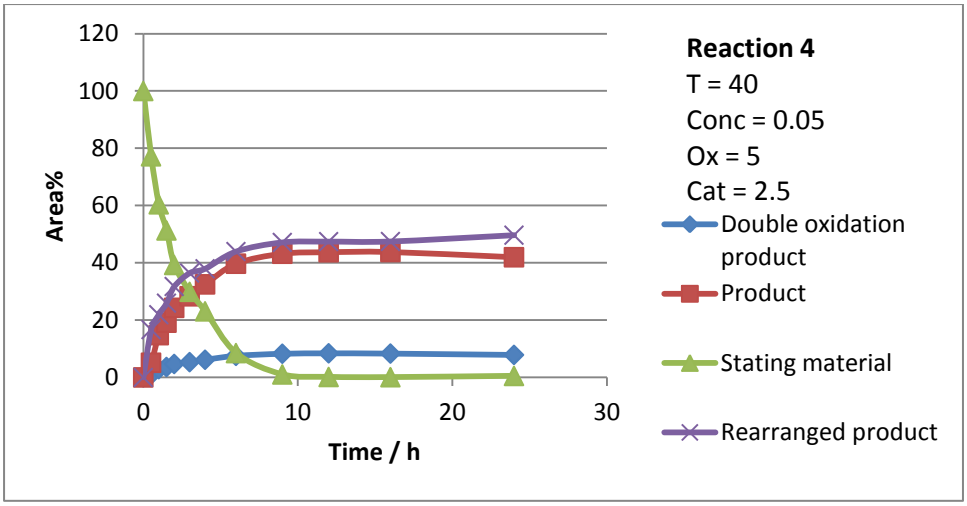
Product
Stating material
Rearranged product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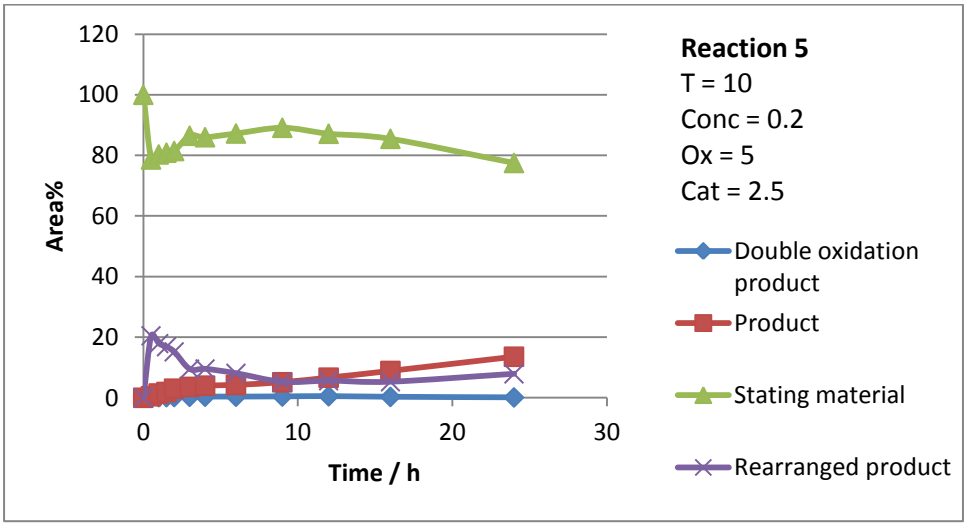
Product
Stating material
Rearranged product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Time / h
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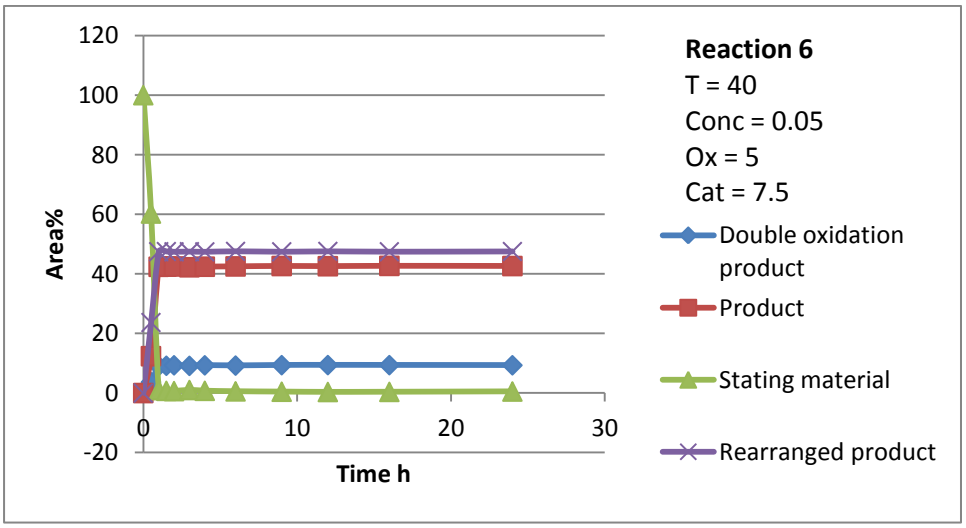
Ox = 5
Cat = 2.5
Double oxidation product
Product
Stating material
Rearranged product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Area%
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30
Time h
Reaction 6
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Ox = 5
Cat = 7.5
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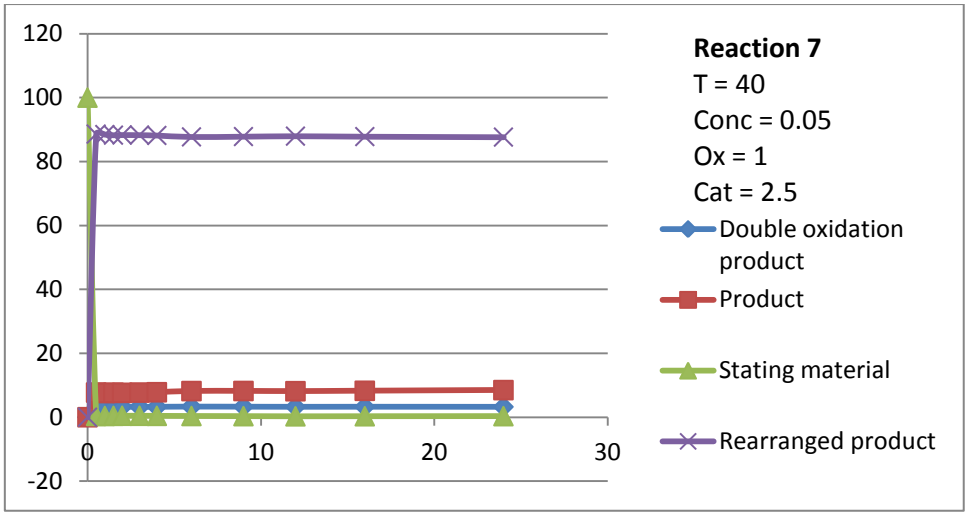
Product
Stating material
Rearranged product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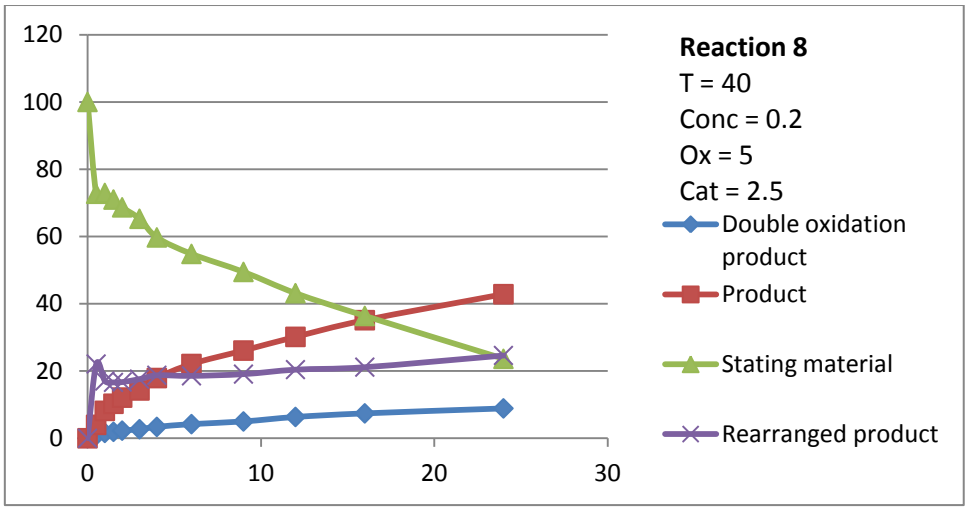
Product
Stating material
Rearranged product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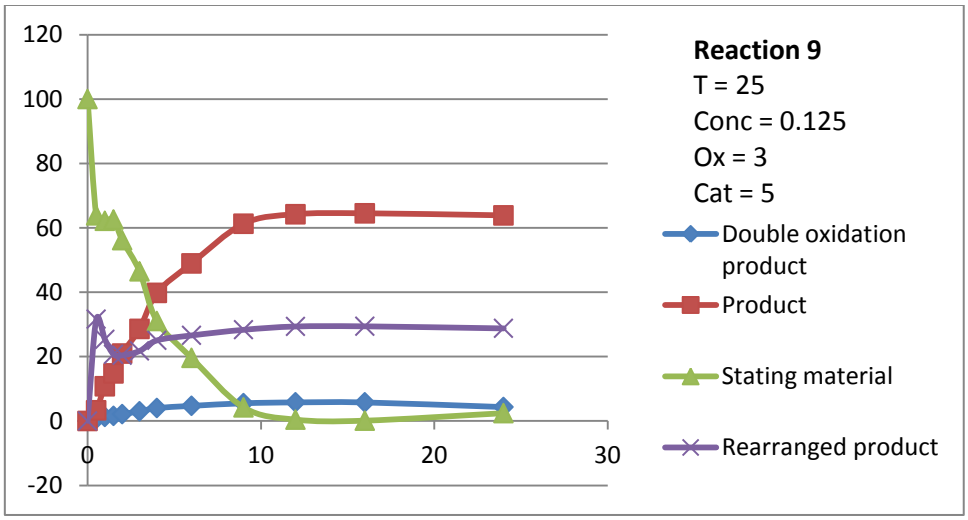
Rearranged product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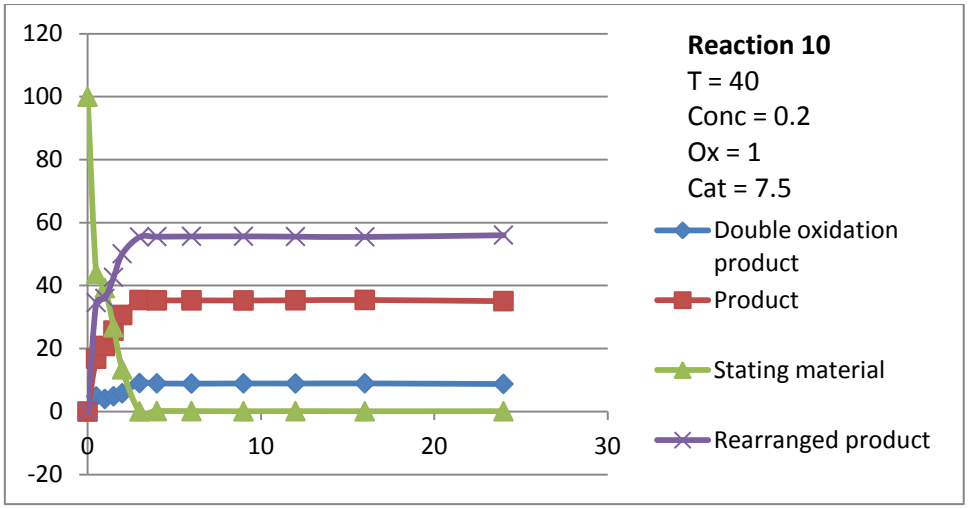
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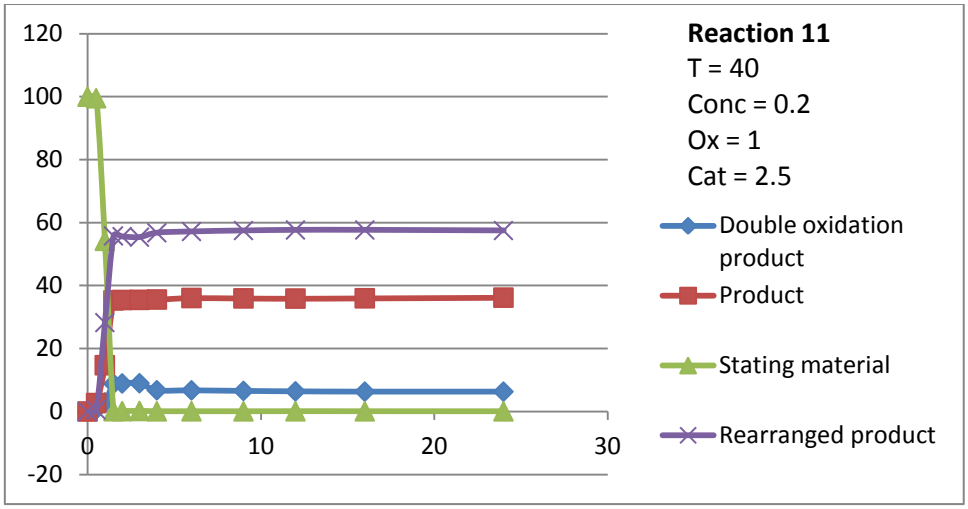
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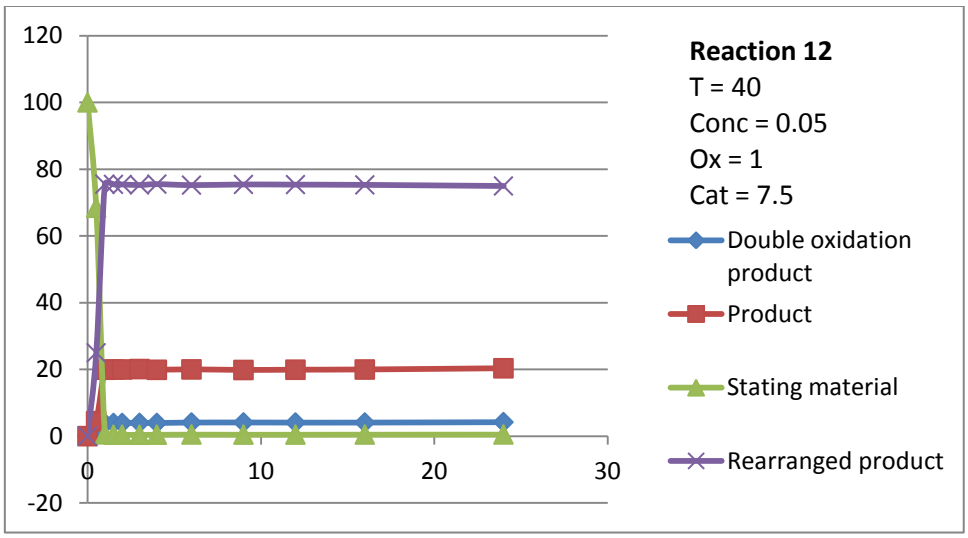
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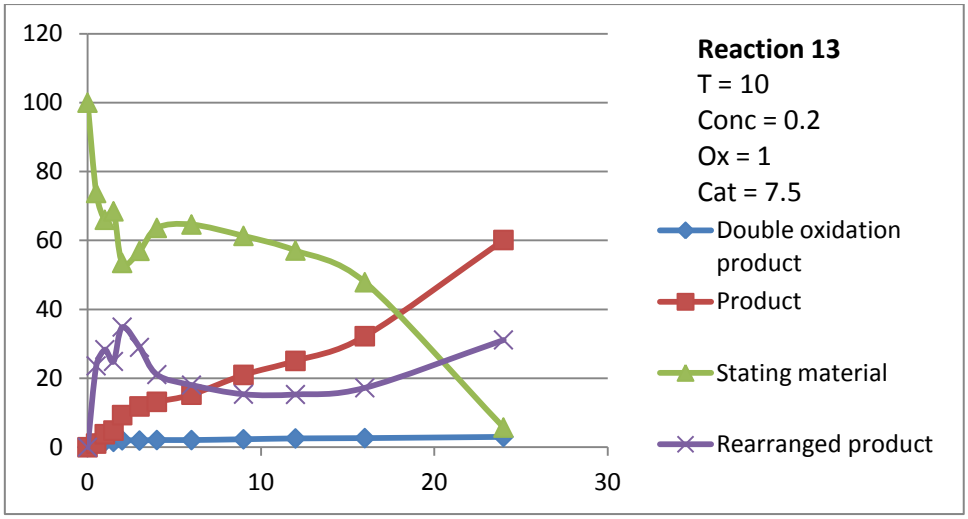
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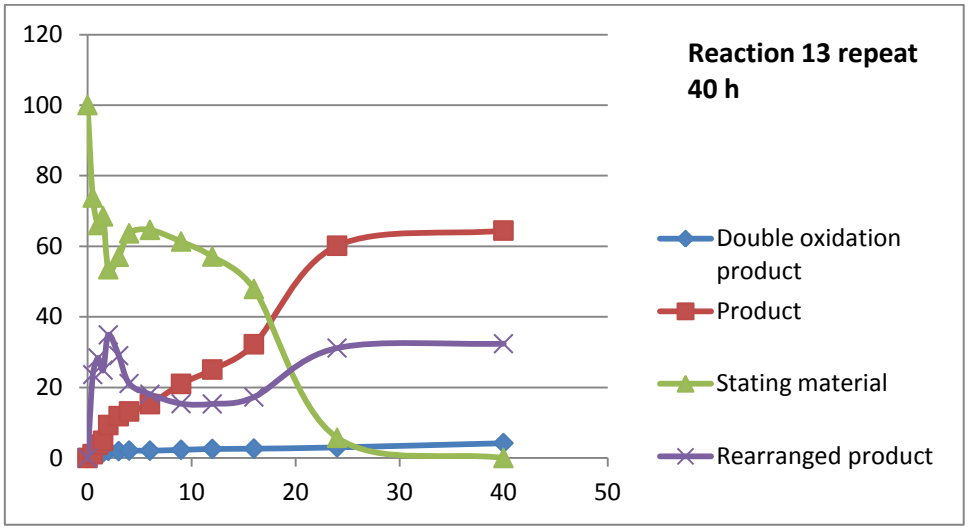
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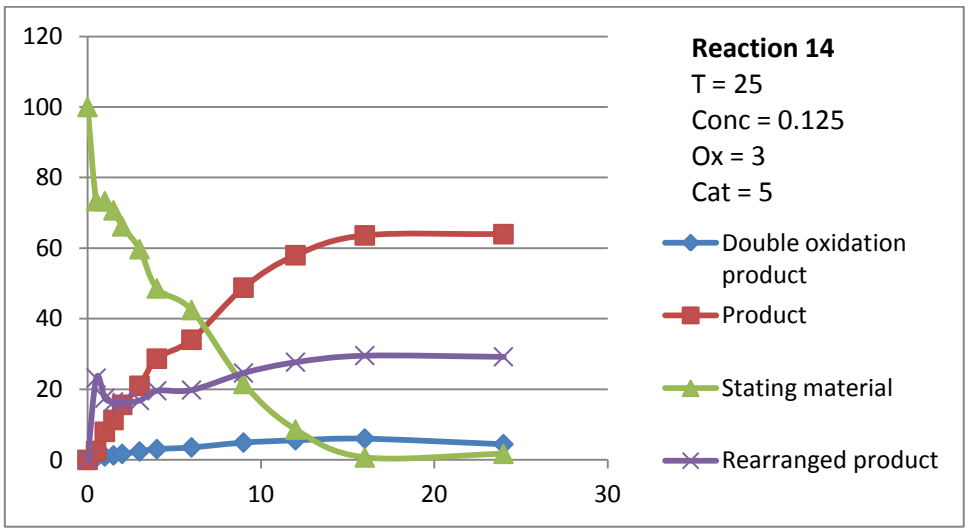
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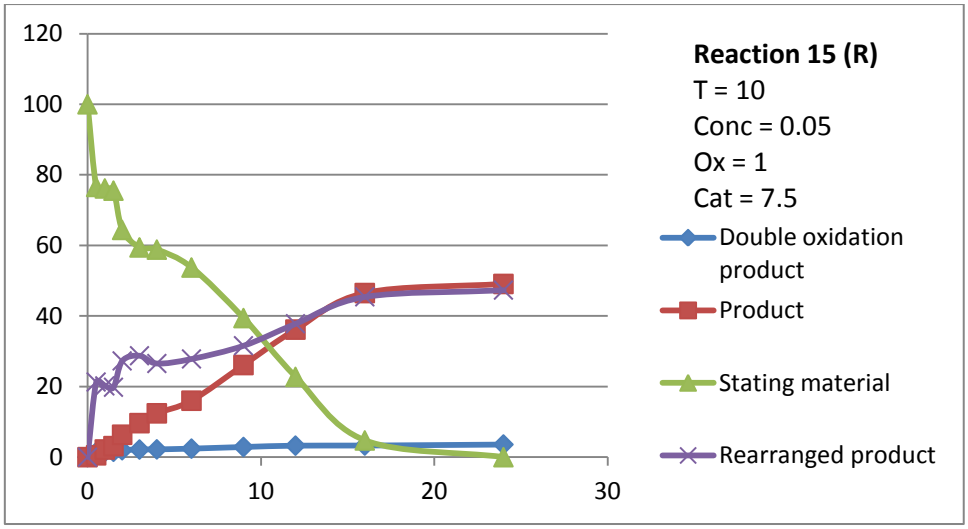
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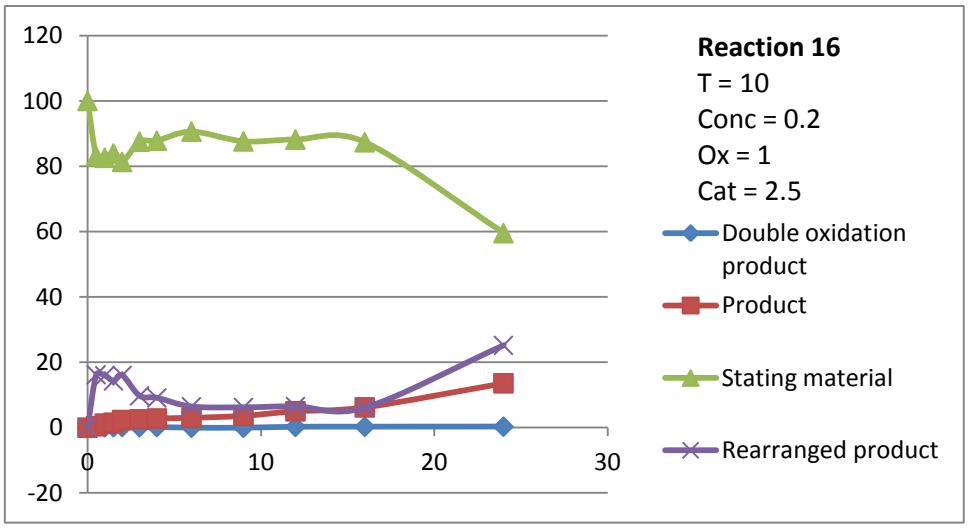
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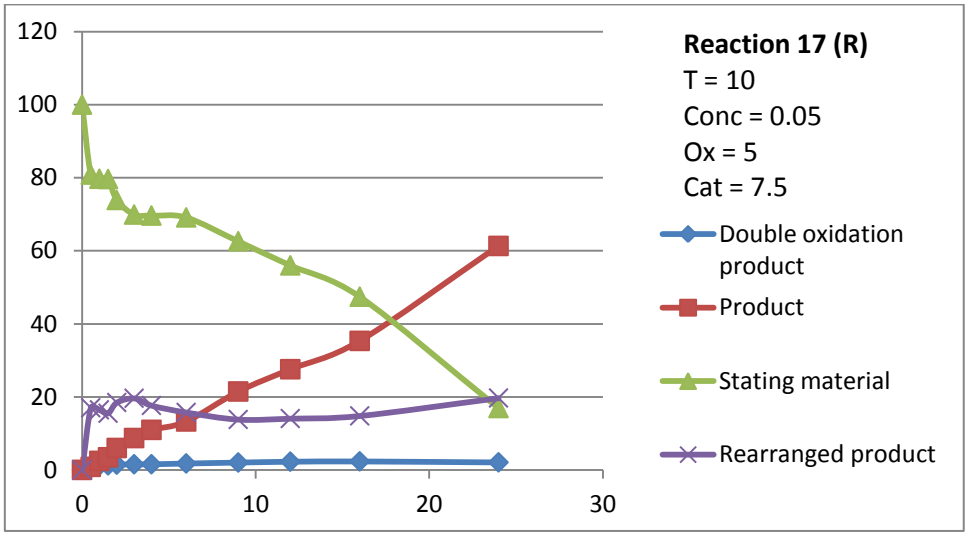
Rearranged product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Double oxidation product
Product
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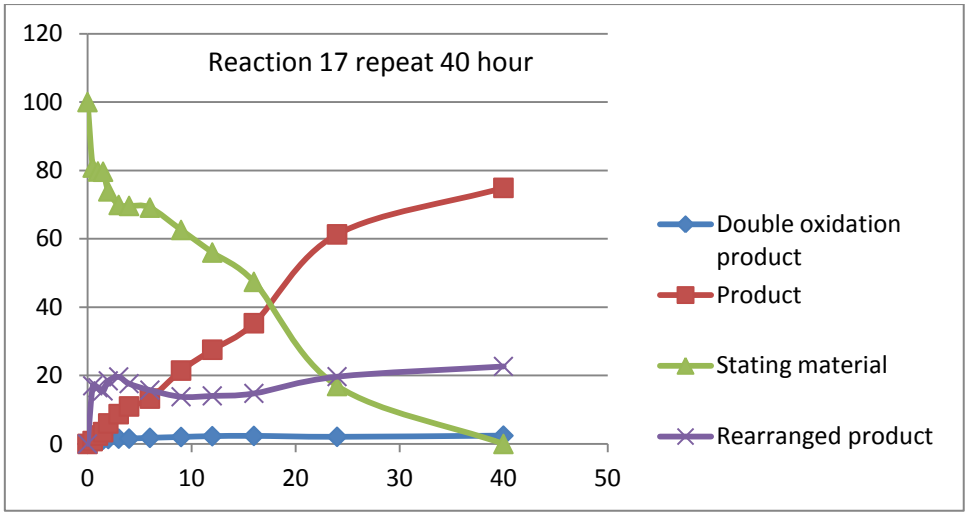
Rearranged product


Reaction 17 repeat 40 hour
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Product
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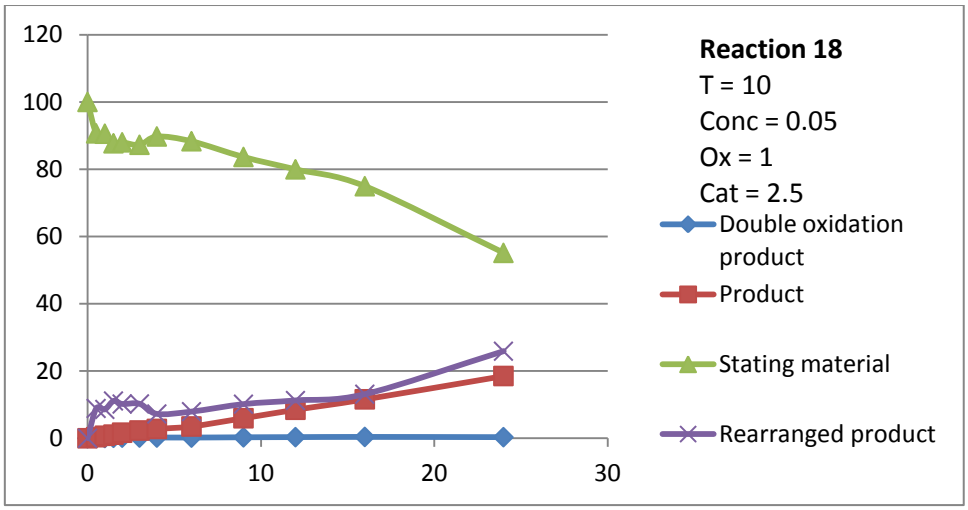
Rearranged product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Product
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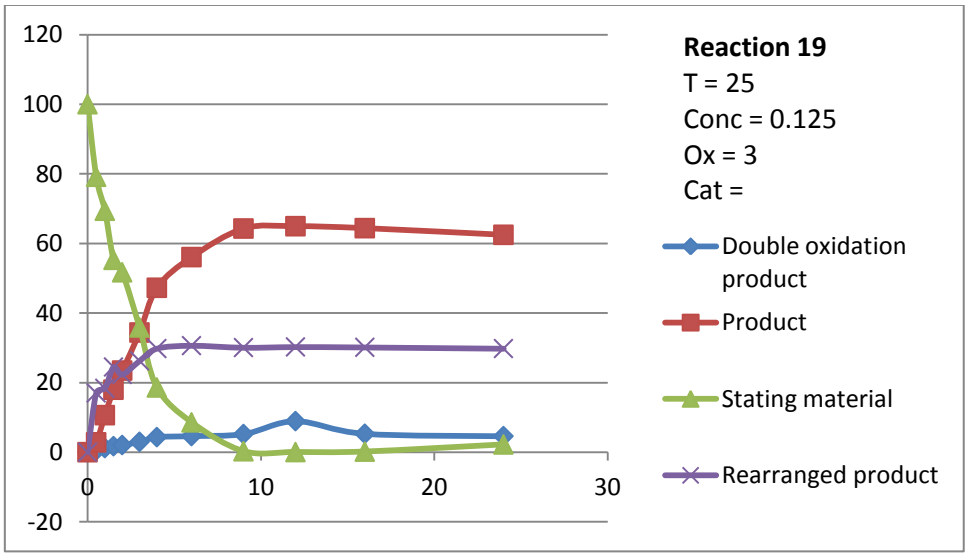
Rearranged product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Cat =
Double oxidation product
Product
Stating material
Rearranged product

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