UNIVERSITY OF
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π-Acid Catalysed Cyclisations to Generate Sulfur Containing Compounds

by

Parmjit Heer Kaur

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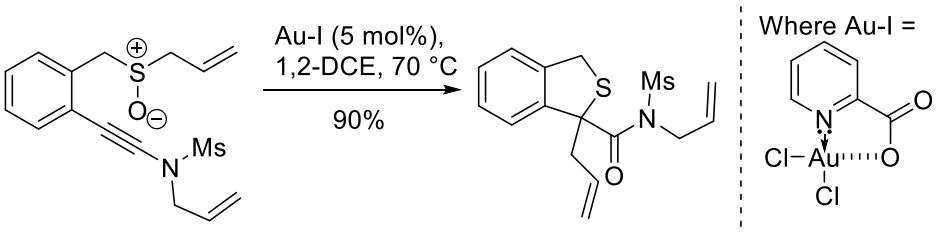
Abstract

Complex scaffolds are readily accessed *via* Gold and Platinum π-acid catalysis starting from simple precursors. These precious metal π-acids are used to generate sulfur ylides which undergo rearrangement to interesting sulfur containing compounds analogous to those formed *via* diazo-chemistry.

In this thesis the utility of these π-acids to generate sulfur ylides will be discussed by:

1) The *in situ* generation of α-carbonyl carbenoids directly from alkynes avoiding "sacrificial functionality";
2) Achieving different regiochemical outcomes using electronically biased alkyne systems;
3) Designing domino reactivity using simple functional groups.

Recent developments involve the use of ynamides as regio-directing agents for site specific oxygen-transfer from a suitable oxidant to form the α-oxo-gold-carbenoid functionality. These carbenoids mimic the reactivity observed by decomposition of diazo-compounds with non-precious transition metals. A new gold catalysed intramolecular rearrangement of ynamide tethered-sulfoxides have led to highly complex products.



Designing the starting sulfoxide substrates to allow tandem cyclisation reactions have led to formation of polycyclic sulfur heterocycles which are close to sulfur analogues of known biologically active compounds.

Acknowledgements

I would like to take this opportunity to thank my supervisor Dr Paul Davies for his support and motivation throughout this research venture. He has not only guided me through this journey, but also mentored me and has helped shape my thought process required for problem solving, presenting and processing data. I have learnt a great deal from Paul and can only wish for another sincere supervisor in the near future.

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Last but not least I would like to thank my family who have been by my side in my difficult times and have understood my ambition to go far in my studies. I couldn't have done it without them. I thank them for their patience and love.

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List of Abbreviations

Å	Amstrong
Ac	acetyl
Ar	aromatic
Bn	benzyl
°C	Celsius
δ	chemical shift
d	doublet
DIAD	diisopropylazodicarboxylate
DMDO	dimethyldioxirane
DMF	*N*, *N*-dimethylformamide
DMSO	dimethylsulfoxide
dppm	1,1-Bis(diphenylphosphino)methane
dr	diastereomeric ratio
E	electrophile
EI	electronic impact
eq	equivalent(s)
Eq.	equation(s)
ESI	electronic spray ionisation
Et	ethyl
EtOAc	ethyl acetate
EWG	electron-withdrawing group
g	gram(s)

h	hour(s)
HRMS	high resolution mass spectrometry
Hz	hertz(s)
IR	infrared
i-Pr	isopropyl
IPr	1,3-bis(2,6- diisopropylphenyl)imidazol-2-ylidene
J	coupling constant
L	litre(s)
LG	leaving group
L_n	ligand(s)
M	metal
m	multiplet
m-CPBA	*m*-chloroperbenzoic acid
Me	methyl
Mes	2,4,6-trimethylphenyl
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
n-Bu	normal-butyl
N	molar concentration
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect

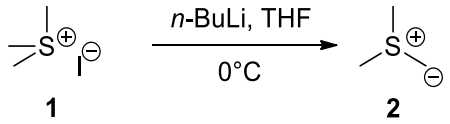
n-Pr	normal-propyl
Nu	nucleophile
m/z	mass/charge
o	ortho
p	para
Ph	phenyl
Piv	pivaloyl
ppm	part per million
Py	pyridine
q	quartet
rt	room temperature
s	singlet
T	temperature
t	triplet
Tf	trifluoromethanesulfonate
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time of flight
THP	tetrahydropyran
Ts	4-toluenesulfonyl
ν	frequency
z	atomic number

Chapter 1: Introduction

1.1 Sulfur ylides

An ylide is a 1,2-dipolar compound containing an anionic atom (normally a carbanion) directly attached to a cationic heteroatom (most commonly nitrogen, phosphorus or sulfur).[1] This thesis will concentrate on sulfur ylides; preparation of these compounds using classical approaches and the limitations of these synthetic approaches, as well as alternative advantageous routes to sulfur ylides using precious metal π-acid homogeneous catalysis. Sulfur ylides represent an important class of reactive intermediates in organic chemistry and may be utilised in versatile synthesis of highly complex molecules. They are involved in many known transformations such as epoxidation and aziridination when reacted with carbonyl groups and imines.[2] Some selected examples of classical routes to sulfur ylides are given below along with pertinent applications.

In 1962, Corey and Chaykovsky reported the generation of the simplest sulfur ylide dimethylsulfonium methylide **2** by direct deprotonation of the corresponding sulfonium iodide salt **1** (as well as chloride salts) (Scheme 1).[3] The use of analogous procedures allows highly functionalised dialkylsulfonium alkylides bearing a range of substituents, such as trialkylsilyl, alkenyl and alkynyl, to be prepared from sulfonium salts. The use of a strong base is normally required.[1,4]

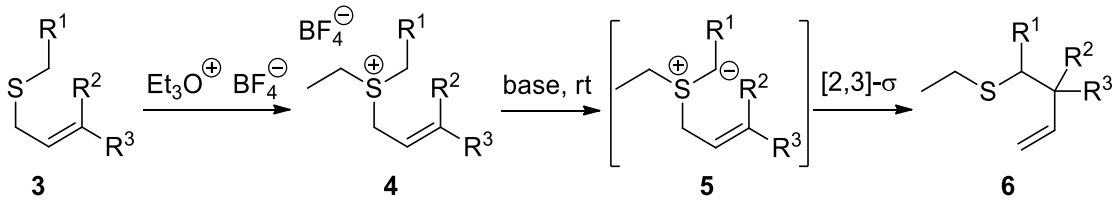


Scheme 1. Generation of dimethylsulfonium methylide **2**.

1.1.1 [2,3]-Sigmatropic rearrangements

Sulfur ylides capable of intramolecular rearrangement processes have received considerable attention and selected examples are shown below. [2,3]-Sigmatropic rearrangement reactions of allylic sulfur ylides have been explored thoroughly. The corresponding

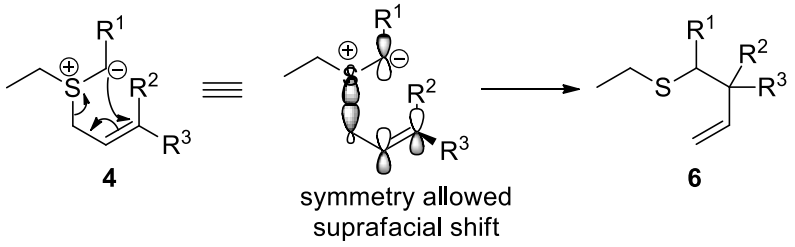
sulfonium tetrafluoroborate salts **4** are prepared by alkylation of simple sulfides **3** using Meerwein's (triethyloxonium tetrafluoroborate) salt (Scheme 2). Deprotonation of salts **4** can easily be achieved using bases such as potassium carbonate, sodium hydride or metal alkoxides when the R^1 substituent is reasonably stabilising (where R^1 = aryl or carbonyl) to give sulfur ylide **5**. A [2,3]-sigmatropic rearrangement of the sulfur ylide **5** then occurs to give products **6**.[5]



R^1 = Ph, PhCO, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$ base = K_2CO_3, NaH or NaOEt
R^2 = H, Me, Ph
R^3 = H, Me

Scheme 2. Generation and rearrangement of sulfur ylides capable of [2,3]-rearrangement.

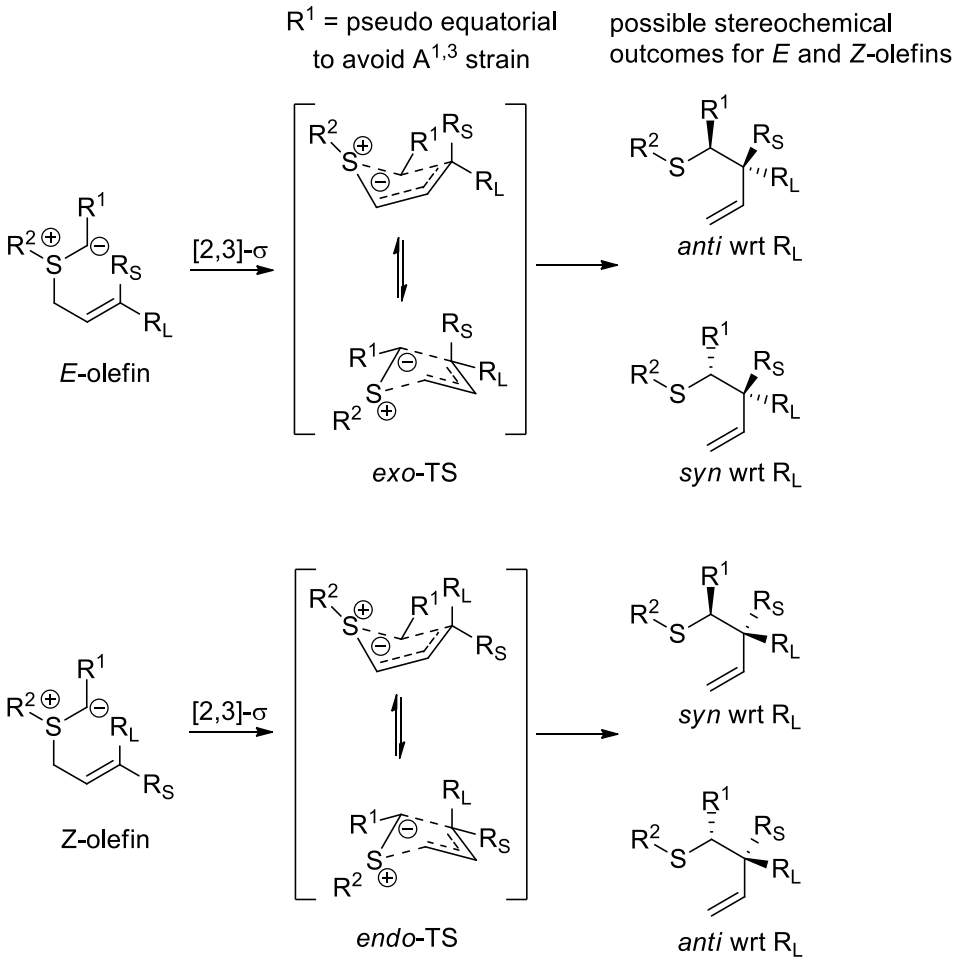
[2,3]-Sigmatropic rearrangements are concerted pericyclic reactions in which a σ-bond is migrated across a conjugated π-system such as an allylic group. A symmetry-allowed suprafacial migration (Scheme 3) leads to a C-C bond formation, resulting in an overall inversion of the allyl moiety.[5,6]



Scheme 3. Symmetry allowed suprafacial migration as a result of [2,3]-sigmatropic rearrangement.

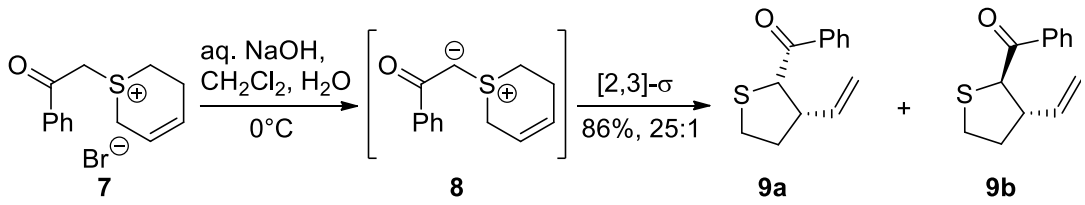
The stereochemical outcome of the chiral centre is determined by a cyclic "envelope" transition state[5,7] in which the sizes of the substituents and conformation of the allyl group influence the selectivity (Scheme 4). In the favoured 5-membered transition states the anion stabilising R^1-substituent adopts a pseudo-equatorial position to avoid unfavourable 1,3-

allylic interactions in the axial position. It is envisioned that there are two *exo* transition states leading to the formation of both the *anti*- and *syn*-product, similarly the *endo* transition states give the *syn* and *anti*-products with respect to the large substituent. The thermodynamic product should be the *anti*-product with the large substituent as far away as possible from the functional group R[1].[8]



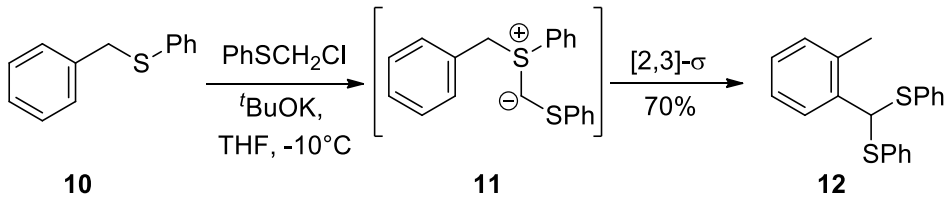
Scheme 4. *Endo*- and *exo*-cyclic envelope transition states.

Shown below is an example of an anomalous outcome where the less favourable *syn*-isomer predominates. Here ylide intermediate **8** was generated by a biphasic mixture of aqueous sodium hydroxide and dichloromethane. Subsequent ring contraction by a [2,3]-rearrangement gave tetrahydrothiophenes **9a** and **9b** (Scheme 5) in a 25:1 ratio.[9]



Scheme 5. Generation of thermodynamically less favourable *cis*-isomer.

[2,3]-Sigmatropic migrations also proceed with aromatic systems, in which case they are known as Sommelet-Hauser rearrangements.[10] Ylide **11** generated by the alkylation of benzyl phenyl sulfide **10** with chloromethyl phenyl sulfide in the presence of potassium *tert*-butoxide, undergoes a [2,3]-rearrangement and then tautomerizes to regain aromaticity and give thioacetal **12** in 70% yield in a one-pot process.



Scheme 6. Example of a Sommelet-Hauser rearrangement.

An alternative and widely used approach to sulfur ylides is *via* transition metal stabilised carbenes, which is the main focus of the next few sections. This method is employed without the reliance on harsh basic conditions previously mentioned in section **1.1**, hence allowing tolerance of a wider variety of functionality.[11]

1.2 Carbenes

Carbenes are neutral species containing a carbon atom with only six electrons in the valence shell. Carbenes are therefore highly reactive electrophilic species. Typical reactions of carbenes involve insertion into σ- and π-bonds.[12] The six electrons can be arranged to give two different electronic states, namely the singlet and triplet states. Most carbenes are bent, with bond angles between 100° to 150° suggesting a sp^2-hybridised trigonal state.[12] Four out of six electrons of the carbene centre contribute to the two sp^2 σ-bonds. For a

singlet carbene the non-bonding electron pair is located in the sp^2 hybridised orbital with the p-orbital unoccupied. For a triplet carbene the non-bonding unpaired electrons singly occupy both the sp^2 hybridised molecular orbital and the p-orbital (Figure 1). In the singlet type the unshared electron pair in the sp^2-orbital and the empty p-orbital allow the carbene to exhibit both nucleophilic and electrophilic reactivity at the sp^2 carbon centre.

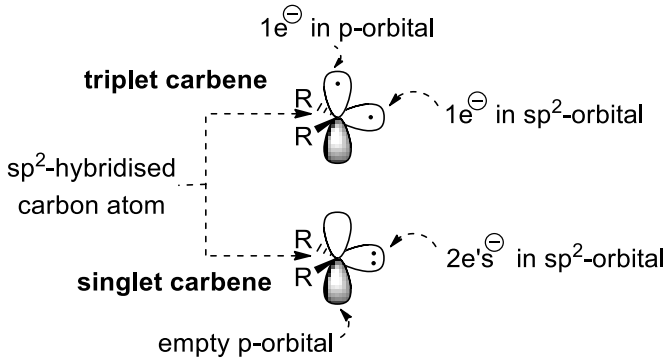


Figure 1. Arrangement of valence non-bonding electrons in triplet and singlet carbenes.

1.2.1 Metal stabilised carbenes

The formation of carbenes *via* diazo-compounds are described in section **1.3**, here the electronic features of metal stabilised carbenes are elucidated. In modern chemistry transition metal species such as copper or rhodium salts, as well as iron or palladium, are commonly used[13] to form metal stabilised carbene species, which may be classified as carbenoids.[14] These metal carbenoids consist of a singlet carbene in relation to its electronic structure and the molecular orbital picture and are commonly referred to as Fischer carbenes (See section **1.2** and Figure 1). The non-bonding lone pair of electrons from the sp^2-orbital of the Fischer-carbene forms a strong σ-bond (dative covalent) with an empty metal d_z^2 orbital and back donation from a filled d-orbital into the empty p-orbital of the carbene results in double bond character (Figure 2). As a result of this weak π-interaction the metal carbenoid is electrophilic at the sp^2 carbon centre and susceptible to nucleophilic attack.[15]

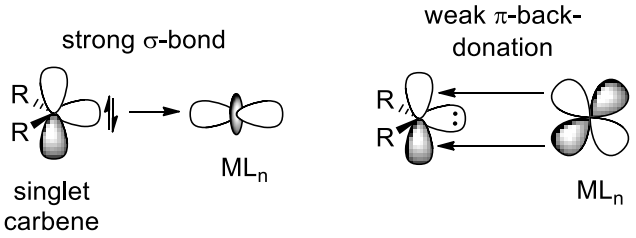


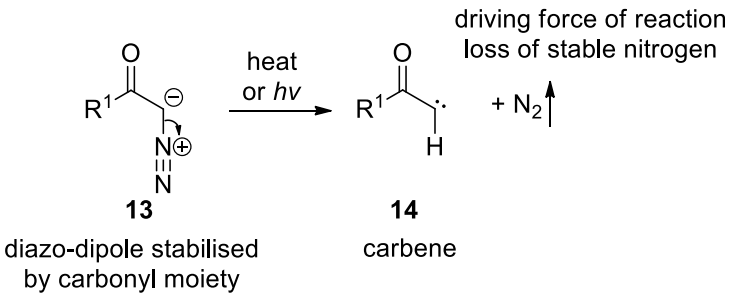
Figure 2. Molecular orbital model of metal-stabilised singlet Fischer-carbenes.

1.2.2 Gold and platinum carbenoids

Although this thesis will describe the unique reactivity of gold and platinum in detail later on, it is at a good point to mention that the carbenes of 5d transition metals have exhibited high bond energy strengths in the bonding scenario $[M{=}CH_2]^+$ peaking at platinum.[16] Experiments have been conducted in which Fischer-carbene complexes of molybdenum or tungsten undergo carbene relocation to gold salts forming thermodynamically favourable gold carbenoids. Gold and platinum can significantly back-donate electron density unlike other transition metals (see section **1.6**) from a filled d-orbital into the empty p-orbital of the carbene.

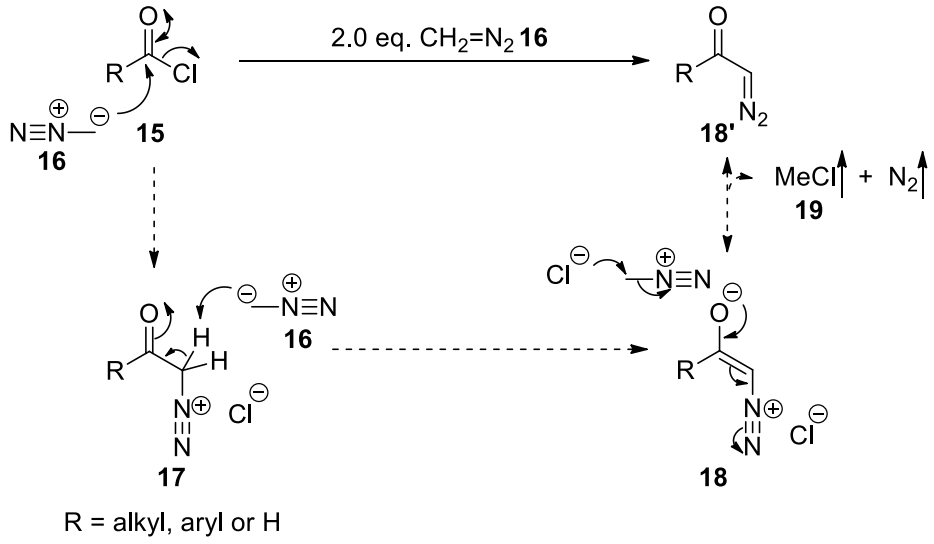
1.3 Preparation of carbonyl-diazo-compounds

Carbenes are usually formed by loss of a stable functionality, for example the loss of nitrogen from diazo-compounds under the influence of heat or irradiation with light. Diazo-carbonyl compounds **13** are commonly used because the diazo-dipole is stabilised by the electron-withdrawing carbonyl group providing a more stable, useful carbene **14** source (Scheme 7).[12]



Scheme 7. Commonly used diazo-compounds stabilised by electron-withdrawing carbonyl group.

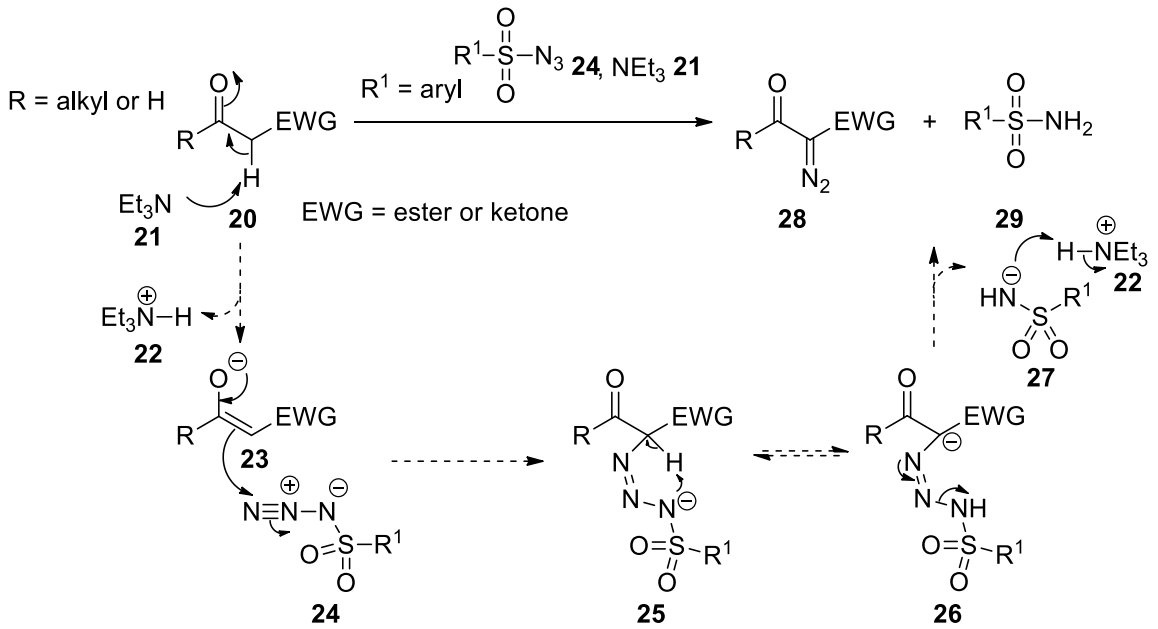
Traditional procedures for the preparation of diazo-compounds involve: 1) addition of diazo-alkanes to carboxylic acid halides or anhydrides[17] displacing the leaving group (Scheme 8); 2) diazo-transfer to active methylene sites[18] (Scheme 9). The mechanism of the former procedure involves nucleophilic substitution by diazoalkane **16** of the acid chloride **15** or anhydride, then a second diazoalkane **16** molecule deprotonates compound **17** to give enolate **18**, which is related to the desired product **18'** by a canonical form. The side products diazonium cation and the chloride anion react to give highly volatile methylchloride **19** and gaseous nitrogen.



Scheme 8. Substitution of carboxylic acid halides by diazoalkane to give diazo-compounds.

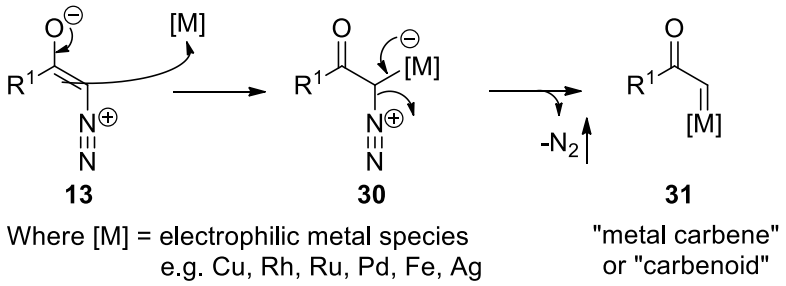
The proposed mechanism of the diazo-transfer procedure (Scheme 9) involves an initial deprotonation step of the active methylene compound **20** with NEt_3 **21** giving enolate **23**,

which attacks the electrophilic-*N* of the arylazide **24** leading to reactive intermediate **25**. The desired diazo-compound **28** and the by-product sulfonamide **29** are generated upon proton transfer within intermediate **25** followed by elimination from **26**.[18]



Scheme 9. Diazo-transfer to active methylene site.

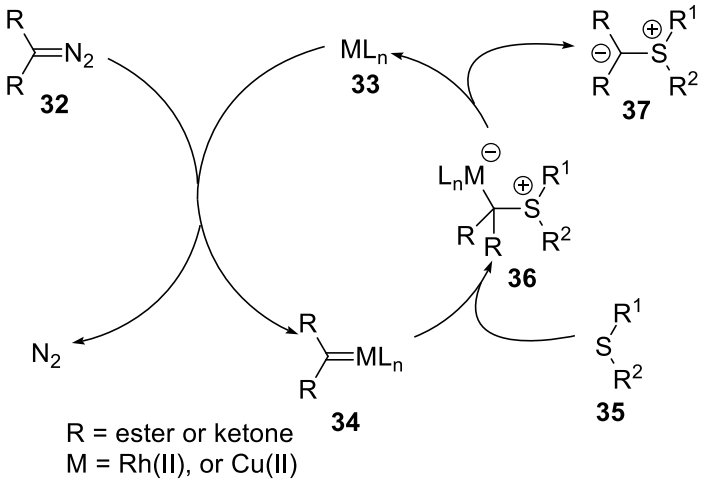
Although these reactions give diazo-product very efficiently, diazo-compounds them-selves are highly reactive and often need to be stabilised further. In the presence of transition-metal complexes, diazo-carbonyl compounds decompose to give metal stabilised carbenes by the loss of nitrogen (Scheme 10). These metal carbenes have been used in various transformations, examples include; 1) insertion of the carbene functionality into olefins[19] or carbonyl compounds[20] *via* [2+1] cycloadditions to give cyclopropanes or epoxides, or; 2) reaction with electron-rich heteroatoms such as nitrogen, phosphorus and sulfur to give ylides.[1]



Scheme 10. Decomposition of diazo-carbonyl compound to give metal carbenes.

1.3.1 Catalytic approach to sulfur ylides

The general mechanism of ylide formation through a catalytic approach (Scheme 11) involves the reaction of diazo-compound **32** with a transition metal catalyst **33** to generate the electrophilic carbene complex **34** with expulsion of nitrogen. Then nucleophilic addition of sulfide **35** affords the metal stabilised carbene **36** followed by dissociation of the catalytic metal species to form the potent sulfur ylide **37**.[2]

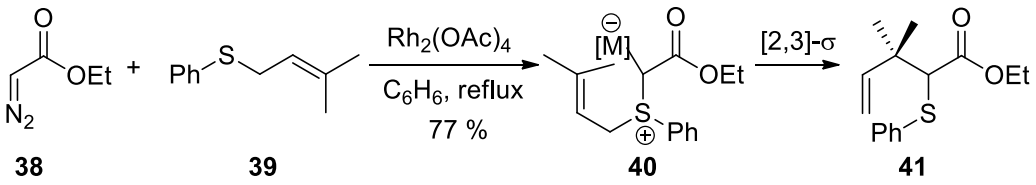


Scheme 11. Sulfur ylide generation through metal-catalysed decomposition of diazo-compounds.

1.3.1.1 Selected examples of sulfur ylide formations from metal carbenoids

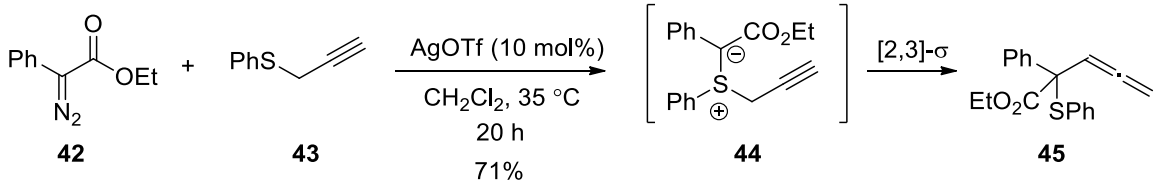
Doyle and co-workers[21] showed that intermolecular reaction of simple allyl sulfides **39** with carbenoids generated by reaction of ethyl diazoacetate **38** with rhodium(II) acetate or copper(I) complexes led to the preparation of allylic sulfur ylides **40** at low temperatures in

high yields (Scheme 12). Immediate [2,3]-sigmatropic rearrangement of ylide **40** gave sulfide **41**.



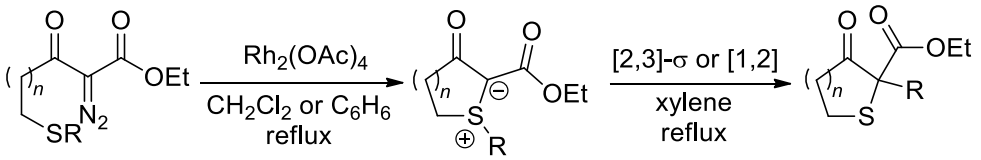
Scheme 12. Doyle-Kirmse reaction.

Recently Davies *et. al.*[22] reported a silver-catalysed Doyle-Kirmse reaction of allyl or propargyl sulfides (Scheme 13). Here decomposition of the diazo-compound **42** with AgOTf led to the presumed silver stabilised carbene[23] which was trapped with an external propargyl sulfide **43** to give ylide **44**. Subsequent [2,3]-sigmatropic rearrangement led to allene **45** formation in good yields.



Scheme 13. Silver-catalysed Doyle-Kirmse reaction of allyl or propargyl sulfides.

Davies[24] and Moody[25] have used diazo-compounds to prepare stable cyclic sulfur ylides **47** by an intramolecular reaction of rhodium carbenes generated from diazocarbonyl-tethered sulfides **46** (Scheme 14). The subsequent rearrangement of the ylide depends on the R group substituents. A [1,2]-Stevens rearrangement is observed when R = alkyl or benzyl and a [2,3]-sigmatropic rearrangement occurs when R = allyl or benzyl to give 5-8-membered cyclic sulfides **48**.



46 **47** **48**

n = 0-3

R = Et, Ph, $PhCH_2$, [1,2] 24-69%

R = $CH_2CH=CH_2$, $CH_2CH=CMe_2$, *E*-$CH_2CH=CHPh$, *Z*-$CH_2CH=CHPh$ [2,3] 59-78%

Scheme 14. Intramolecular sulfur ylide followed by either [2,3]-σ or [1,2]-Stevens depending on R.

The [1,2]-Stevens rearrangement was discovered in 1928[26] and it is an intramolecular [1,2]-migration where chirality is retained.[27] The mechanism is highly controversial[28] and the retention of configuration suggests the involvement of radical dissociation-recombination of the sigma bond of interest within a solvent cage.[29]

1.4 Limitations of the use of diazo-compounds

Although diazo-compounds are used successfully to directly access the carbenoid precursor to sulfur ylides over deprotonation methods, which require harsh basic conditions, both methods produce wasteful co-products. Poor atom economy is a result of expulsion of nitrogen for decomposition of diazo-compounds. Deprotonation requires the use of an external base which is not incorporated in the final product therefore, also results in decreased atom economy.

Furthermore, installation of the diazo-carbonyl compound leads to safety issues in their preparation. The generation of these diazo-compounds rely on the use of hazardous shock sensitive reagents[30] such as diazomethane (see section **1.3**) or the use of diazo-transfer agents such as aryl or alkylsulfonyl azides. The removal of the side-product sulfonamide from the diazo-compound is often difficult. Also, the need for electron-withdrawing

moieties for easy access to these diazo-compounds presents limitations[31] in the scope of sulfur ylide preparation.

1.5 Summary

To summarise, accessing sulfur ylides *via* the two main techniques; 1) deprotonation of sulfonium salts by strong bases; or 2) nucleophilic reaction of sulfides with transition metal α-oxo-carbenoids, requires sacrificial functionality and are potentially dangerous methods. An alternative method to α-oxo-carbenoids to access potent sulfur ylides is therefore highly attractive. In the next section gold and platinum, the precious transition metals which allow safe and atom economical access to the α-oxo-carbenoid moiety will be introduced followed by selected examples.

1.6 General overview of gold and platinum catalysis

This section will focus on frontier molecular orbitals of precious metal (gold and platinum) homogeneous catalysts, which allow the alternative approach to sulfur ylides and generation of sulfur containing compounds possible in a safe manner, as apposed to diazo-compounds.

Recent and pioneering developments in homogeneous catalysis emphasise gold and platinum transition metals, which were once under-rated due to their low tendency towards redox processes such as oxidative insertion and reductive elimination.[32] They behave as catalysts which are able to bind to the substrate *via* a π-Lewis acid complex. The Lewis acidity of transition metals allows withdrawal of electron density from electron-rich entities such as alkenes, alkynes, allenes, and heteroatoms. This has an effect of enhancing the electrophilicity at a particular site and so favouring nucleophilic addition.[33]

These catalysts provide simple, safe and atom economical[34] pathways to complex molecules from simple starting reagents without the need to use rigorously inert reaction conditions. This has led to a recent marked increase in their utilisation.[32] Incidentally Pt and Au are roughly equivalent in expense to other metals such as ruthenium (Ru), rhodium (Rh) and palladium (Pd), which are widely exploited in organic synthesis. Advances employing these catalysts in coupling, cycloisomerisation, and subsequent rearrangement, has led to; 1) the design of new transformations; 2) improvement of known reactions, and; 3) applications in natural product synthesis.[35]

1.6.1 Relativistic effects

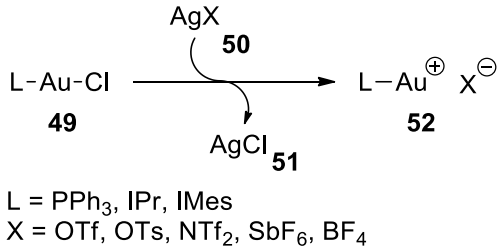
The unique reactivity of transition metals of the sixth period notably platinum, gold and mercury in comparison to other metals can be explained by strong relativistic effects they display.[36] The contraction of the s and p-orbitals are more apparent for gold(I) than other metals and therefore the 5d and 4f-orbitals are more shielded from the nucleus resulting in their expansion.

The diffuse nature of the 5d-orbitals results in reduced electron-electron repulsions and so have high ionisation energies, hence more likely to be involved in orbital interactions and so redox processes rarely occur.[37] These electronic features allow electrophilic π-Lewis acid activity with "soft" nucleophiles such as C-C unsaturated π-bonds such as allenes, alkenes and alkynes.

Another consequence of relativity effects is the increased bond strengths between a ligand and the precious metal. This effect is most pronounced for gold than any other neighbouring sixth period metal and depends on the electronegativity of the ligand; for example the effect will be more pronounced for phosphine than for a bound chloride. The

effect is reflected in the bond lengths of both ligands where the bond length of Au-P is significantly shorter than Au-Cl.[38]

$PtCl_2$ and $AuCl_3$ are isoelectronic (d^{10}) around the metal and form mostly square planar complexes with π-systems but Au(I) complexes prefer two coordinate linear complexes.[39] Commonly known Au(I) catalysts of type LAuCl **49** are treated with AgX salts **50** resulting in precipitation of AgCl **51** and formation of the highly active $LAu^+ {}^-X$ **52** bearing an empty coordination site for a reacting π-system (Scheme 15). While these are often prepared *in situ* during catalysis, air and moisture stable systems such as the $Au(PPh_3)NTf_2$ complex have been successfully prepared and isolated in this manner.[40]



Scheme 15. Formation of active cationic gold species by chloride displacement.

1.6.1.1 Carbophilic activation of π-systems

The Dewar-Chatt-Duncanson model (DCD) is used to explain the bonding state of transition metal complexes with alkenes or alkynes as ligands[41] where the π-system acts as an electron donor and the metal as a π-Lewis acid acceptor.[42]

The two main components that contribute to the bonding of C-C unsaturated bonds to metal species[32] include (Figure 3): 1) σ-bond formed by overlap of the π-system of the C-C multiple bond with an empty d_Z^2 orbital of the metal;[43] 2) back-donation of electron density from a filled metal d_{xz} orbital into an antibonding π* orbital of the alkene or the alkyne resulting in a π-interaction. In the case of alkynes the bond is more complex as a second π-

system exists (Figure 3). This qualitative system applies to (d^8) platinum and, (d^{10}) as well as (d^8) gold complexes with C-C π-bonds.

For the Au-alkyne complex the σ-interaction contributes (65%) of the bonding model between gold and alkyne. Whereas back-donation accounts for (27%), depleting electron density rendering the π-system more electrophilic. On the other hand the orthogonal contributions are much less pronounced due to insufficient overlap of the molecular orbitals and can be ignored in this explanation.[32]

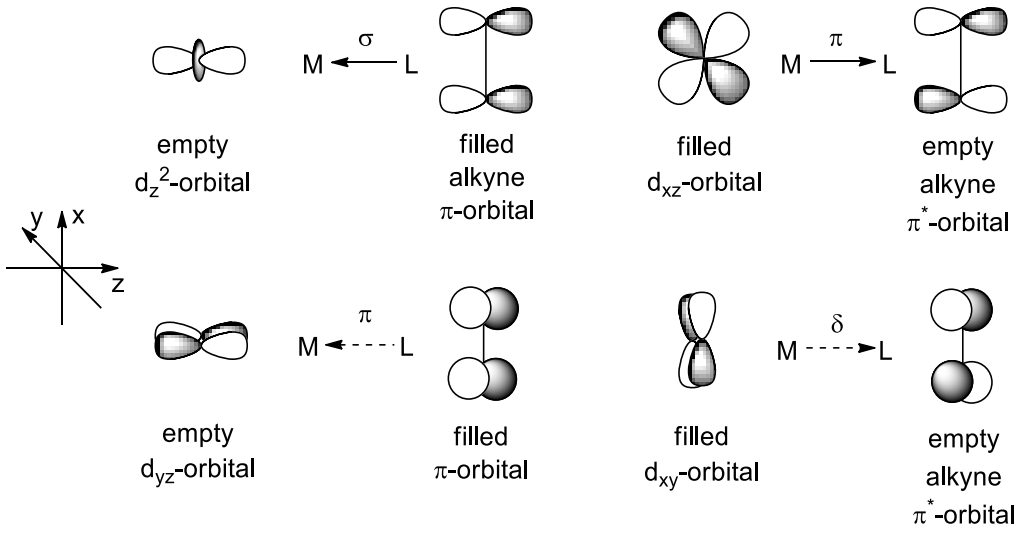


Figure 3. Bonding modes between gold or platinum to C-C triple bonds.

Authentication of the DCD model has been probed using extensive computational studies so that reaction mechanisms can be interpreted for such catalysis processes.[44]

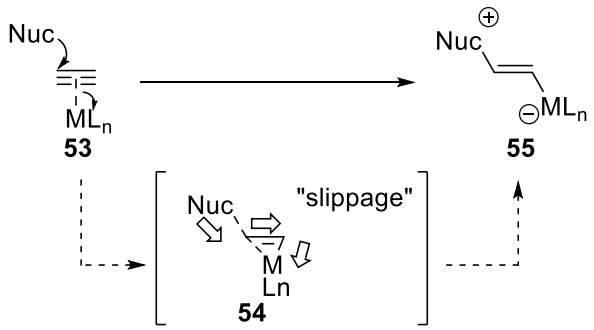
1.6.1.2 Alkyne versus alkene π-acid activation

Experimental results show that when both alkene and alkyne groups are within the same substrate these metals chemoselectively react through coordination to the alkyne followed by nucleophilic attack on the electron deprived alkyne-metal complex. This "alkynophilicity" is driven by kinetics and as a result better activation of C-C triple bonds in comparison to other π-systems is observed in the presence of the incoming nucleophile.

Computational calculations suggest gold complexes LAu^+ bind more strongly to alkenes than alkynes in the absence of an incoming nucleophile.[45] This is because the "higher occupied molecular orbital" (HOMO) is higher in energy for alkenes than alkynes and so alkenes interacts better with the "lower unoccupied molecular orbital" (LUMO) of the LAu^+ complex. It is therefore accepted that the LAu-alkyne complex forms a lower LUMO than LAu-alkene, which is preferred for the addition of nucleophiles.[46] We will only be concerned with activation of alkynes throughout this thesis. Furthermore, as predicted by the DCD model the transition state is distorted from the initial unbound alkyne. Both σ donor and π-acceptor electrostatic contributions leads to elongation of the C-C bond due to the removal of electron density from the π-bonding orbitals and to a less extent but significant increase of electron density in the antibonding π* orbital.[47]

1.6.1.3 Nucleophilic attack

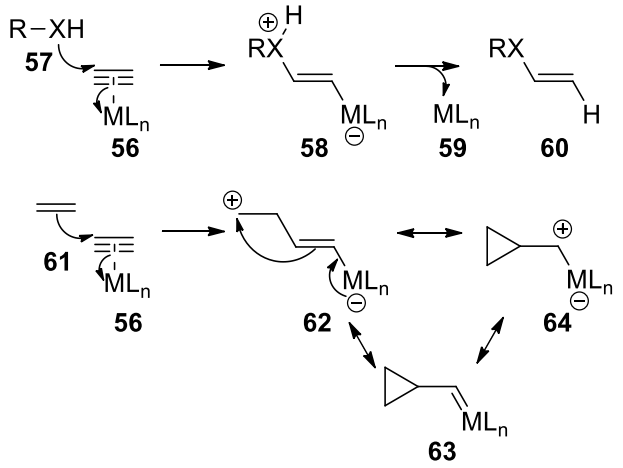
The induced electrophilicity by removal of electron density from the π-system renders the activated alkyne **53** susceptible to nucleophilic attack **55** (Scheme 16). It has been predicted and proven by computational studies that this partial slippage away from the η^2 ground state to the η^1 activated state already exists when the alkyne is activated by the metal in presence of a nucleophile **54** (Scheme 16).[48,49,50] This partial slippage ensures the nucleophile's molecular orbitals overlap efficiently with the activated alkyne complex to form a new C-X or C-C bond (when alkenes act as nucleophiles, and where X is a heteroatom; O, N, S) *via* an *anti*-addition pathway.[51]



Scheme 16. Nucleophilic attack onto metal activated alkyne and DCD distorted transition state.

1.6.1.4 Gold carbenoid or gold stabilised carbocation

When protic nucleophiles such as alcohols, X = O, **57** react with gold-activated alkynes **56** they form vinyl-gold species **58** which are prone to proto-demetallation **60** or react with suitable electrophiles such as *N*-iodosuccinimide (NIS) (Scheme 17).[52] On the other hand use of non-protic nucleophiles such as alkenes **61** open up other evolving pathways for the vinyl species **62**, it can either back-donate into the π*-antibonding orbitals to give gold carbenoid **63**; or, the non-bonding p-orbitals favour a gold-stabilised carbocation **64**. Involvement of either a gold carbenoid **63** or gold stabilised carbocation **64** in mechanisms of transformations is an on-going debate because both exist as canonical forms of each other (Scheme 17) and undergo the same catalysis processes.[53] In section **1.11** we will see how the gold stabilised carbocation representation is preferred, when describing the mechanistic pathways of catalysis processes.

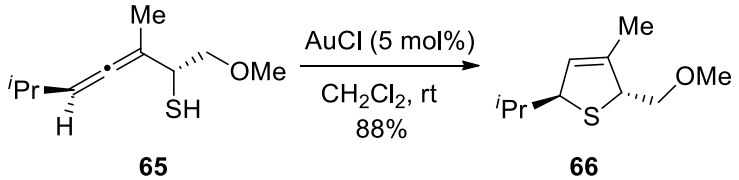


Scheme 17. Gold stabilised carbocation in resonace to gold carbenoids.

1.7 Selected examples of sulfur containing molecules

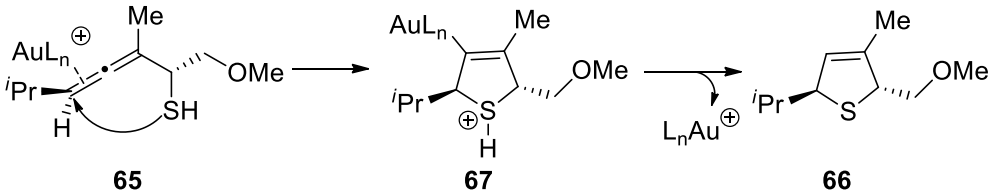
The formation of C-S bonds is rare using gold and platinum because of potential sulfur poisoning.[54] The soft nature of the sulfur atom means it can donate its electron pair to the metal, potentially preventing the catalysts from functioning as Lewis acids towards alkynes. The next section will summarise gold and platinum based catalysis reactions to generate sulfur containing intermediates, including sulfur ylides capable of rearrangement, and look at the authors mechanistic proposals based on the theory discussed above.

The first gold catalysed C-S bond formation was achieved by Krause *et. al.*[55] (Scheme 18) where a variety of precious metal precatalysts Au(I), Au(III), Ag(I) and Cu(I) were used to explore cycloisomerisation reactions of α-thioallenes **65** to 2,5-dihydrothiophenes **66**. The use of copper or silver precatalysts led to no cyclisation products but Au(I) and Au(III) allowed C-S formation showing moderate to good yields with the production of small amounts of side products.



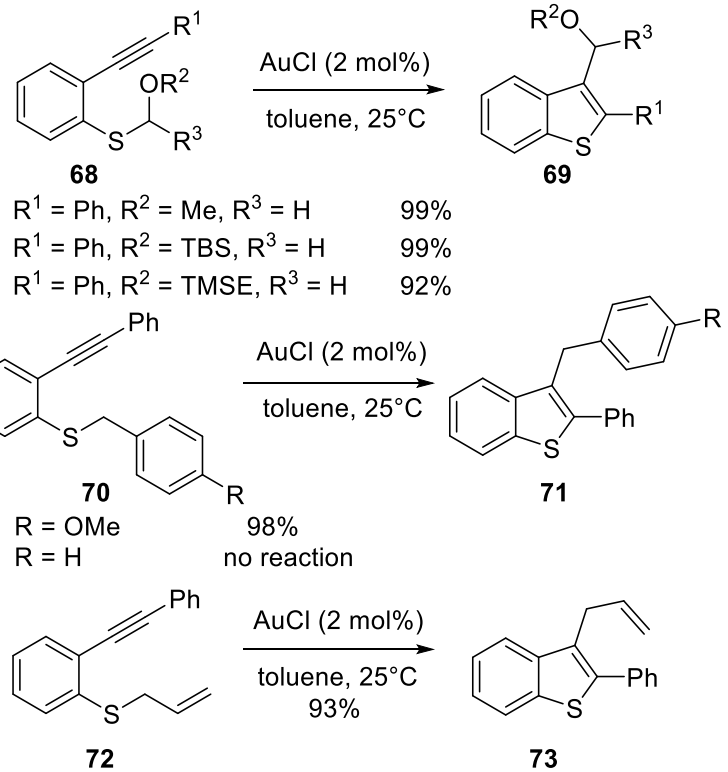
Scheme 18. Cycloisomerisation of α-thioallenes to 2,5-dihydrothiophenes using AuCl.

Krause proposed that the carbophilic gold catalyst acts as a Lewis acid and coordinates to the terminal allenic double bond **65** followed by an intramolecular addition of the thiol affording a zwitterionic species **67** (Scheme 19). Protodemetallation of the vinyl gold species then led to heterocyclic product **66** with retention of the stereochemical information initially present in the starting material.



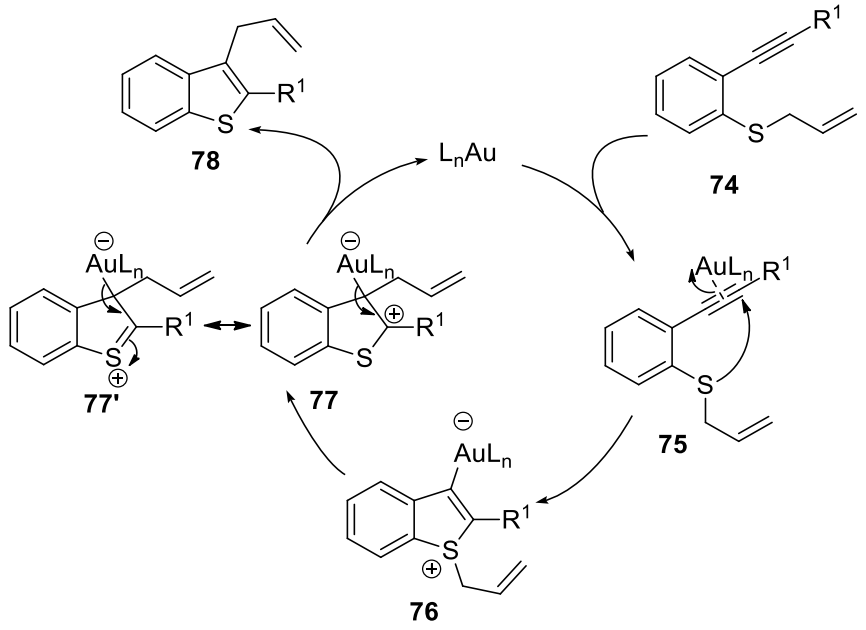
Scheme 19. Proposed mechanism of cycloisomerisation of allenes.

Nakamura's group[56] shown that *o*-alkynylthioethers can undergo cyclisations to synthesise a variety of 2,3-disubstituted benzothiophenes under AuCl or $AuCl_3$ catalysis (Scheme 20). Use of Pd was unsuccessful, probably due to catalyst poisoning by sulfur.



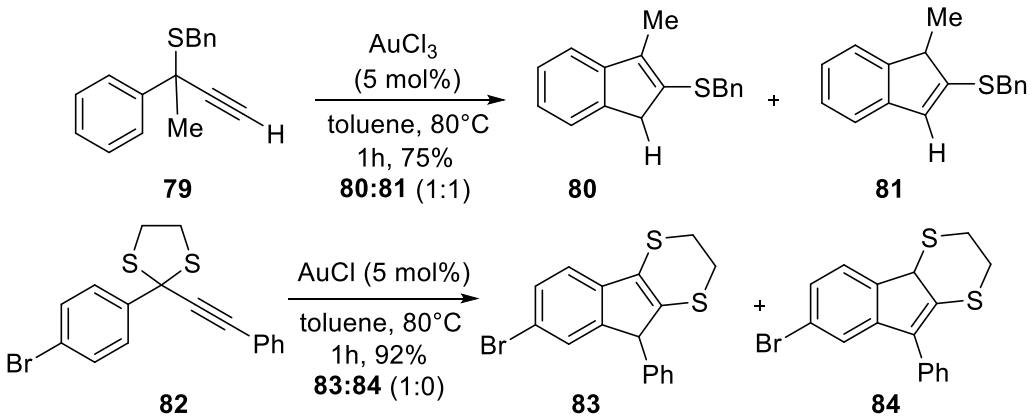
Scheme 20. Gold promoted cyclisation reactions to give a variety of 2,3-disubstituted benzothiophenes.

Nakamura proposed that the gold(I) chloride coordinates to the triple bond **74** then nucleophilic attack of the sulfide results in gold vinyl intermediate **76** (Scheme 21). Migration of the R group to the carbon atom bonded to the gold atom produces the intermediate **77**. Releasing the catalyst provides the desired benzothiophene product **78**. The nature of this migration depends on the R group. Here (R^2 = allyl) the allylic group undergoes a 1,3 allyl migration.[56]



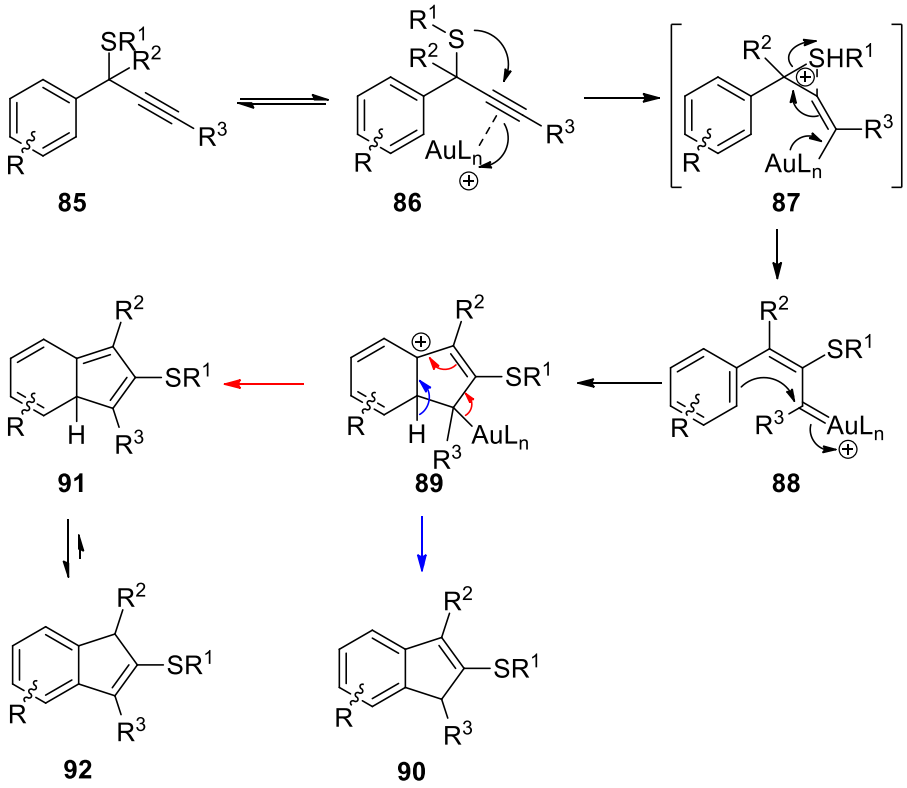
Scheme 21. Proposed mechanism of 1,3-migration *via* vinyl gold intermediate.

Wang *et. al.* reported the rearrangement of propargyl sulfides **79** and dithioacetals **82** to give indenes under the influence of Au(I) and Au(III) salts (Scheme 22).[57]



Scheme 22. Gold catalysed rearrangement of propargyl sulfides to indenes.

The authors propose a 3-*exo* nucleophilic attack of the thioether on to the activated alkyne **86**, rearrangement generates an assumed gold carbene intermediate **88** (Scheme 23). Then an intramolecular C-H functionalisation followed by rearrangement of **89** leads to the formation of regioisomeric benzothiopinone products **90** and **92** respectively.

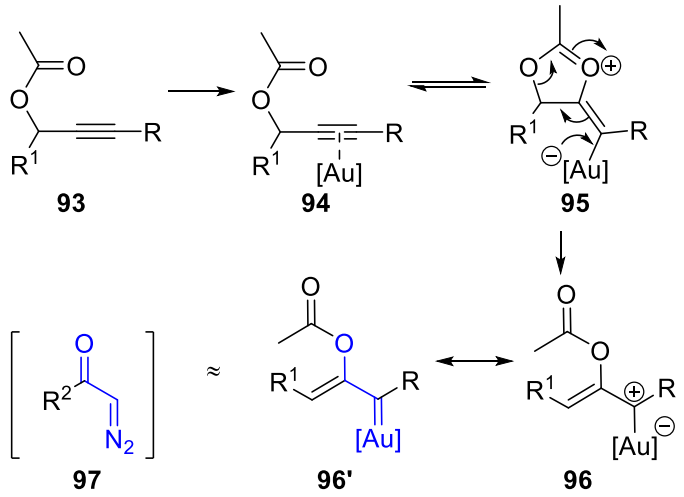


Scheme 23. Intramolecular C-H-functionalisation by gold carbenoids.

In summary, gold and platinum complexes have been used to promote nucleophilic attack onto activated C-C π-bonds and has led to the formation of new C-S bonds without hindrance of the metal catalyst by sulfur containing compounds. Sulfur ylide formation should therefore be possible.

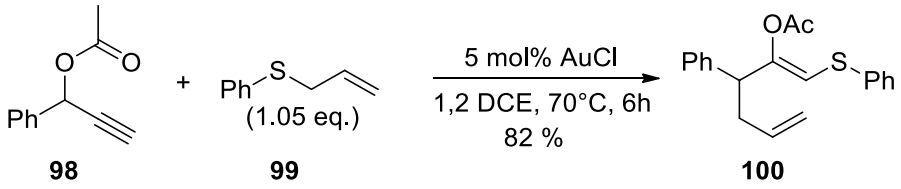
1.8 Gold-catalysed sulfur ylide formation

As seen in the previous section, metal carbenoids derived from diazo-compounds featured electron-withdrawing substituents adjacent to the metal carbenoid. To mimic sulfur ylide formation from Rh(II) or Cu(II) catalysed decomposition of diazo-compounds **97**, α-carbonyl gold carbenoids **96** from rearrangements of propargyl carboxylates **93** were investigated. Propargyl carboxylates are known to cyclise to α-enol acetate gold carbenoids **96'** and are exploited in gold catalysis reactions especially when the incoming nucleophile is carbon based (Scheme 24).[58]



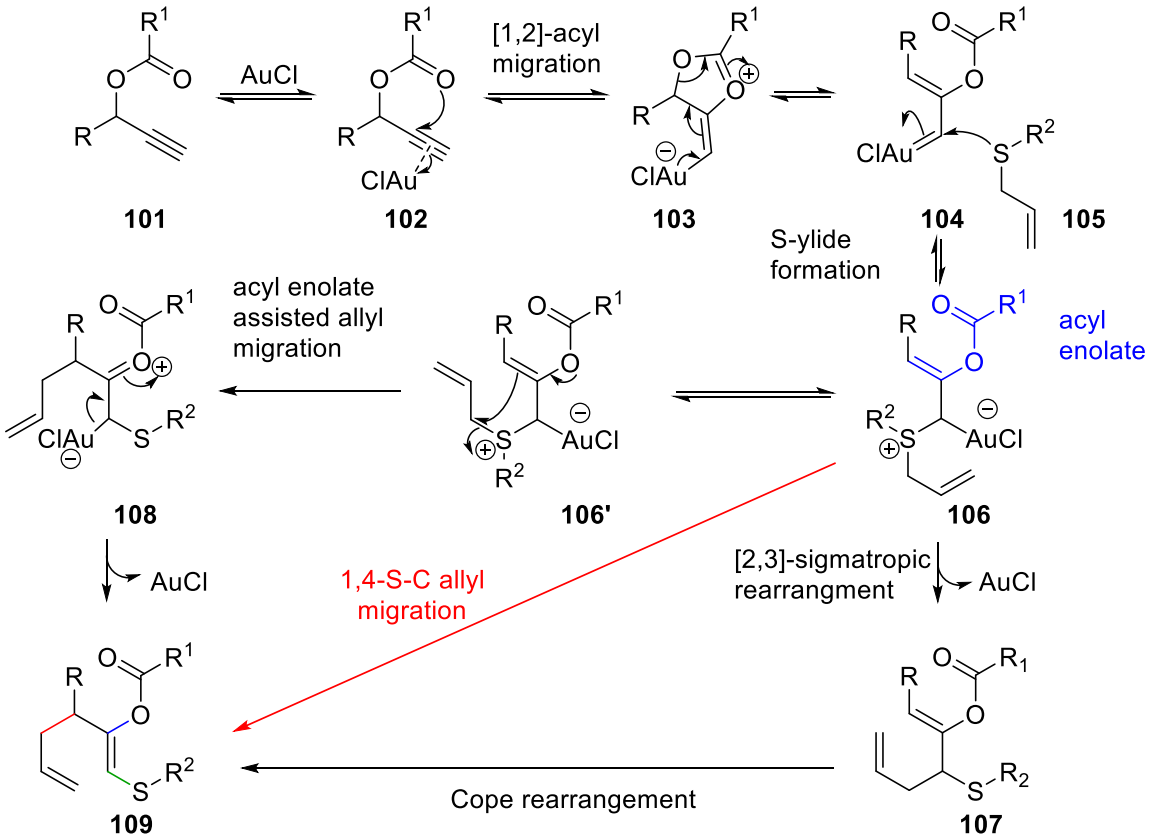
Scheme 24. Gold catalysed rearrangements of propargyl carboxylates to generate gold carbenoids

Recently, Davies and Albrecht[59] reported a new gold catalysed rearrangement coupling cascade reaction through the *in situ* generation of sulfur ylide intermediates from propargyl carboxylates (Scheme 25). The generation of sulfur ylide *via* these gold carbenoids bypass prior installation of sacrificial functionality such as the diazo group.



Scheme 25. Gold carbenoid generation followed by sulfur ylide formation and rearrangement.

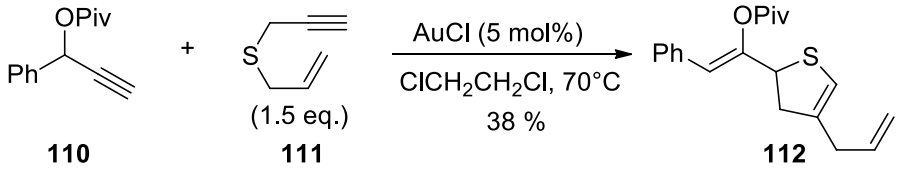
Nucleophilic attack of the carbonyl unit in **101** onto the gold activated alkyne **102** in a 5-*exo*-dig manner is followed by back donation from the metal to generate α-enol acetate gold carbenoid[58,60] **104**. Subsequent reaction with thioether **105** generates sulfur ylide **106**, which can then undergo rearrangement through two pathways; a 1,2 shift or [2,3]-sigmatropic rearrangement of the allyl fragment to give product **107**; or an oxygen assisted 1,4 allyl shift affording oxonium cation **108** with subsequent elimination of AuCl to give **109**. The presence of an acyl enolate diverts the mechanism to an acyl enolate assisted allyl migration to give **109** rather than the traditionally observed [2,3]-sigmatropic rearrangement of the allyl fragment for sulfur ylides derived from diazo-compounds. In a recent report[61] [2,3]-sigmatropic rearrangement followed by Cope rearrangement, were ruled out. Instead the mechanism has been found to proceed *via* a 1,4-S-C allyl shift from ylide **106** (Scheme 26).



Scheme 26. Mechanism of the rearrangements of sulfur ylide derived from propargyl carboxylates.

It was suggested that steric bulk between the non-migrating R^2 substituent on sulfide and the acyl enolate supresses sigmatropic rearrangement due to conformational restraints. The correct conformation of the sulfur ylide is required for sufficient orbital overlap for the [2,3]-sigmatropic rearrangement of the allyl moiety to occur. It was noted that as the R^2 S-substituent decreased in size, the quantity of [2,3]-sigmatropic product increased going from R^2 = aromatic, benzylic, allyl to methyl allowing the active ylide to adopt the correct conformation for the [2,3]-sigmatropic rearrangement.[61]

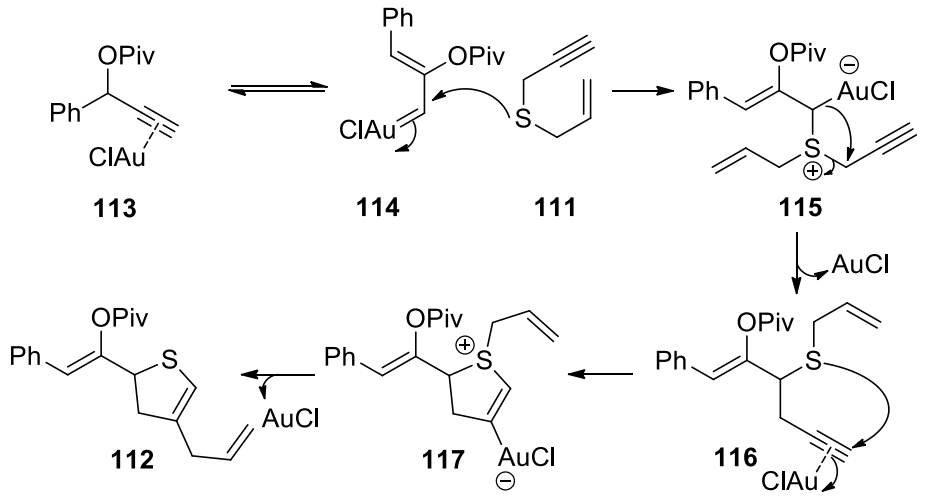
During this study Davies and Albrecht[59] have also reported the first *endo*-mode 1,2-carbothiolation of alkyne to afford semi saturated heterocycles **112** in a cascade process. The reaction involves the formation of new C-C and C-S bonds *via* three main steps (Scheme 27): 1) gold catalysed rearrangement and carbene generation; 2) ylide formation followed by rearrangement; and 3) gold catalysed cycloisomerisation.



110 **111** **112**

Scheme 27. Gold catalysed cascade reaction of propargyl carboxylates with sulfides.

Gold carbenoid **114** is generated by a similar mechanism already discussed in (Scheme 26) from the gold activated propargyl carboxylate **113**. Subsequent nucleophilic attack of the allyl propargyl thioether **111** results in the sulfur ylide **115** which is capable of undergoing an overall 1,2-propargyl shift to give **116**. Then-*endo* mode 1,2-carbothiolation involving an intramolecular nucleophilic attack of sulfide onto gold activated alkyne **116** followed by a 1,2 allyl shift **117** results in the cyclised product **112** in a modest yield (Scheme 28).



Scheme 28. Cascade cycloisomerisation reaction.

The unexpected divergence of the mechanism of that previously known for allylic sulfur ylides due to unfavourable interactions between *S*-substituents and the enol acetate moiety led to new reactions involving development of analogous sulfur ylides directly from alkynes[62] in the same group. The mechanism is discussed in detail in the results and discussion section below.

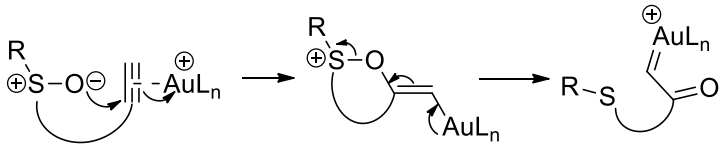
1.9 α-Oxo carbenoids from sulfoxides

The generation of the α-oxo carbenoids from intramolecular sulfur, amine and imine oxides tethered to alkyne have been shown by research groups of Toste[63], Zhang[66] and Shin[67] respectively. Furthermore, intermolecular generation of α-oxo carbenoids involving regiospecific oxygen attack of external oxidants onto gold activated internal and terminal alkynes have been developed by research groups Liu[76], Zhang[92], Davies[93] and respectively. The external oxidants here include; pyridine-*N*-oxides and diphenyl sulfoxides. Examples are shown below with mechanistic topologies probed. The work done by the Davies group[62,93] will be introduced in the results and discussion section as it is closely related to the project being undertaken in this thesis at the time of the developments of regiospecific

formation of α-oxo carbenoids using gold activated ynamides and pyridine-*N*-oxides as external oxidant.

1.9.1 Examples of α-oxo carbenoids from sulfoxides

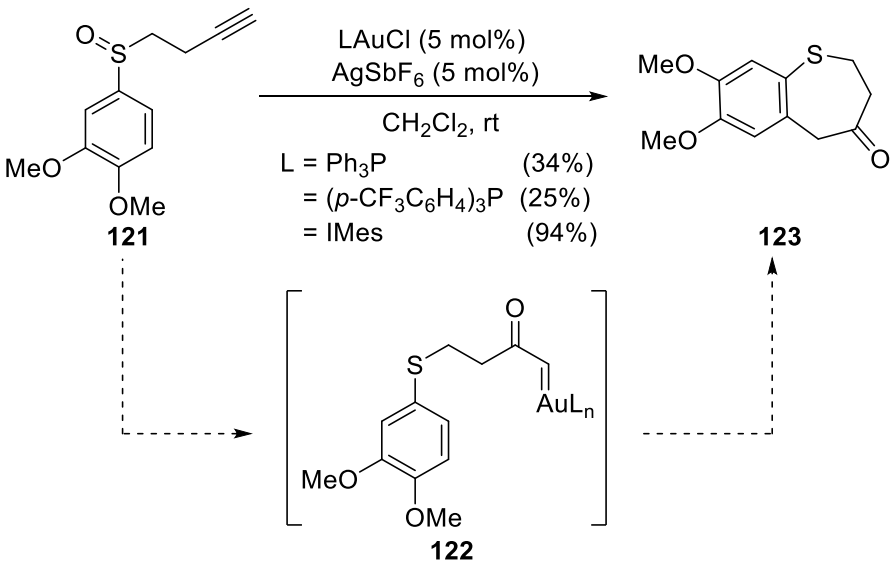
Toste *et. al.*[63] recently envisioned that α-carbonyl metal carbenoids could be generated from alkynes *via* gold(I) catalysed rearrangement in which sulfoxides serve as the oxygen donor and the sulfide as the latent leaving group (Scheme 29).



118 **119** **120**

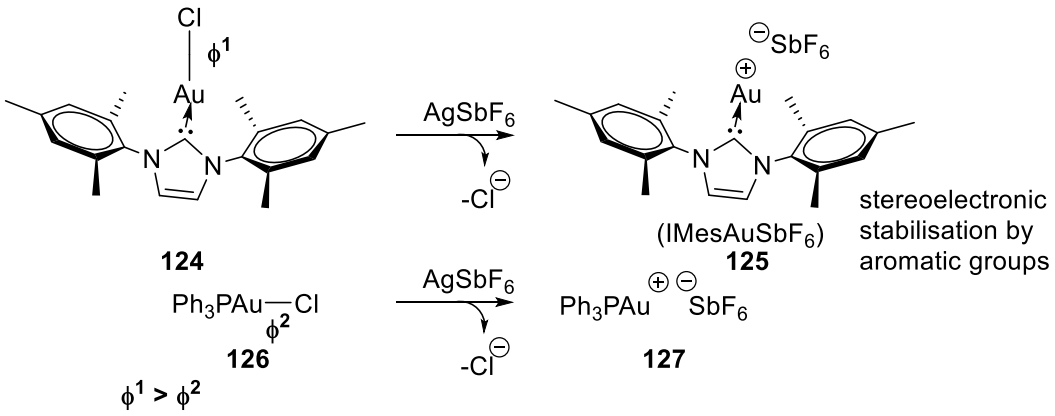
Scheme 29. Generation of α-oxo gold carbenoids analogous to those obtained from diazo-compounds.

The intramolecular reaction of this oxygen-transfer process involves an intramolecular reaction between the activated alkyne and sulfoxide tether followed by rearrangement to give benzothiepinone products in good yields. Initially homopropargyl sulfoxide **121** was treated with 5 mol% of $Ph_3PAuCl/AgSbF_6$ in dichloromethane yielding only 34% of the benzothiepinone **123** *via* gold-intermediate **122** (Scheme 31). Changing the spectator ligand on the Au centre from the electron-deficient phosphine (Ph_3P) to an electron-rich *N*-heterocyclic carbene (NHC) with L = (IMes), dramatically increased the yield of **123** to 94 % (Scheme 30).



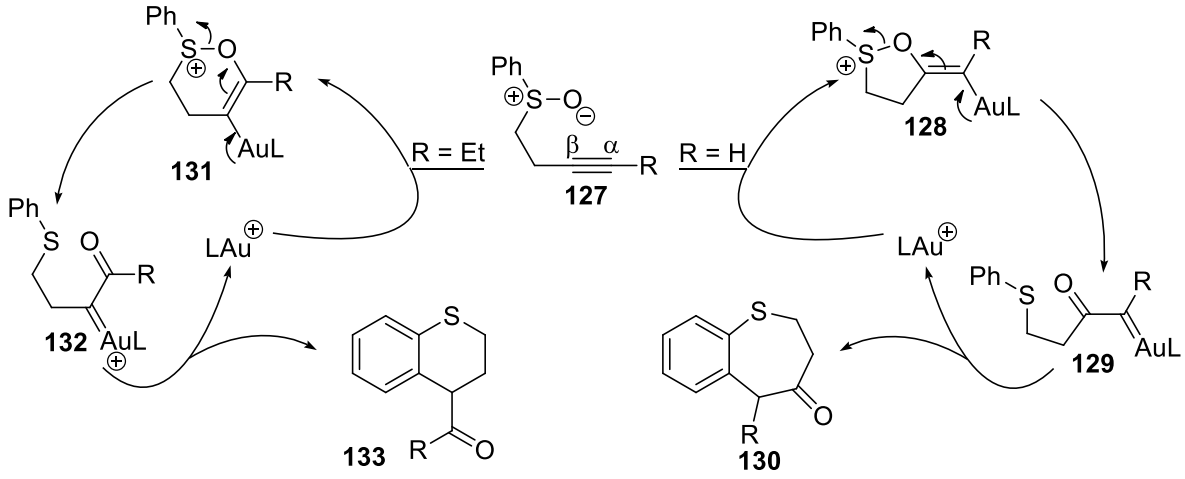
Scheme 30. Gold carbenoid formation followed by aromatic C-H functionalisation in the *ortho*-position.

The NHC is a better σ-donor than the phosphine and forms a strong dative bond with gold.[64] The lone-pair of electrons on nitrogen in the NHC are delocalised into the empty p-orbital of the carbene hence, preventing back-donation of electron density from gold. This has a profound effect on the Au-Cl bond length. Electronic repulsions between the electron-rich NHC Au and the Cl, lengthen and weaken the Au-Cl bond. Once the chloride is displaced by reaction of IMesAuCl with $AgSbF_6$, the surrounding aromatic π-interaction by the IMes arms stabilise the cationic gold species generated whereas, for $Ph_3PAuSbF_6$ no aromatic stabilisation is present and the catalyst is not as long lived as $IMesAuSbF_6$.



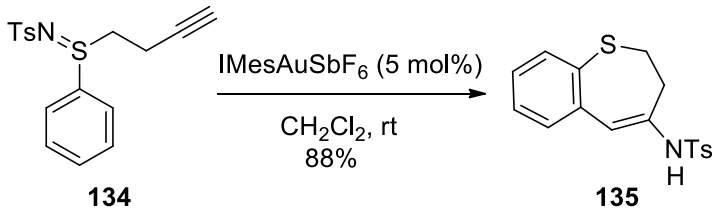
Scheme 31. Aryl stabilisation in NHC-cationic gold species compared to Ph_3PAu^+ species.

Upon activation of alkyne, an intramolecular 5-*oxo* nucleophilic attack occurs resembling the activity observed for propargyl carboxylate rearrangements[58] (Scheme 32). The proposed mechanism[64] involves coordination of the cationic gold(I) complex to the alkyne **127** that induces nucleophilic addition of the sulfoxide oxygen. Terminal alkyne or electron deficient alkynes undergo 5-*exo*-dig cyclisation to give **128**. However, if the alkyne is electron-rich (substituted with an alkyl group), the addition of sulfoxide oxygen occurs *via* a 6-*endo*-dig cyclisation to give **131**. Both modes of attack are in agreement with Baldwin's rule where the incoming nucleophile attacks the activated alkyne at 120° to allow sufficient interaction of the oxygen lone-pairs in the HOMO with the π^*-orbitals of the alkyne.[12] Here the α-carbon is rendered more electrophilic due to the electron rich alkyl group and upon π-acid activation the nucleophilic oxygen attack is biased towards the most electron deficient carbon of the alkyne. Back donation of electron density from the gold(I) complex triggers the cleavage of the S-O bond to release the sulfide forming carbenoids **129** or **132**. Subsequent intramolecular aromatic C-H functionalisation and protodemetallation of the gold(I) species leads to the formation of **130** or **133**. A theoretical study to further elucidate this mechanism was recently reported by Fang and Yang.[65] A detailed investigation of gold(I) catalysed rearrangments of homopropargyl sulfoxides to benzothiepinones or benzothiopenes was carried out using density functional theory (DFT) computational experimentation which confirmed that the mechanism proceeds *via* gold carbenoid and an electrophilic aromatic substitution at the *ortho* C-H position was proposed.



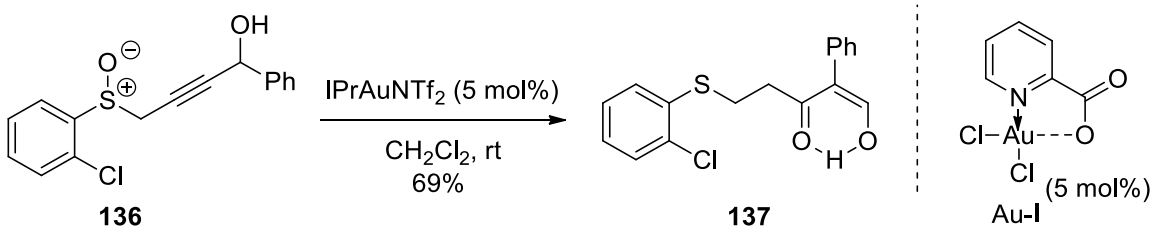
Scheme 32. Divergent reactivity of the initial sulfoxide attack depending on the electron-bias of alkyne.

They also reported sulfimines **134** that also underwent a similar transformation to form enamines **135** with good yields (Scheme 33).



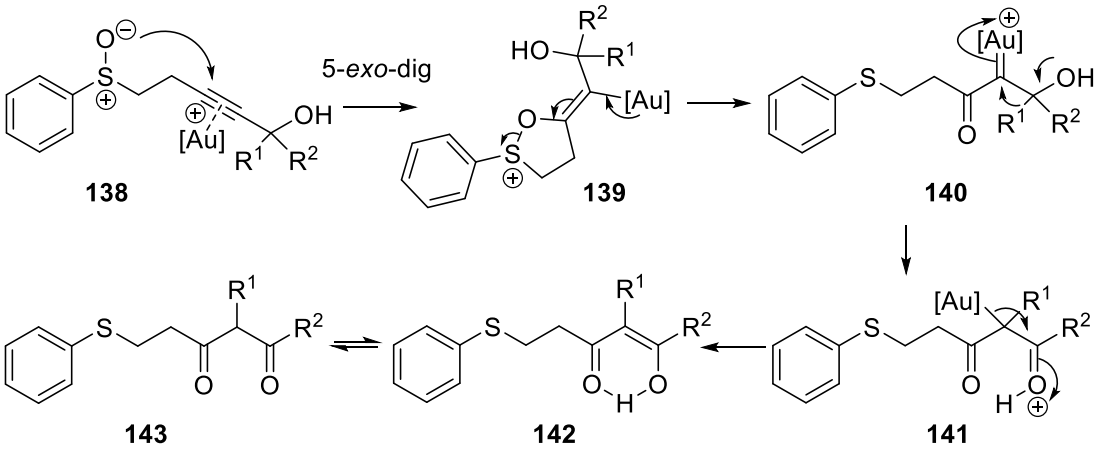
Scheme 33. Sulfimines to enamines *via* gold carbenoid intermediates.

Zhang *et. al.*[66] employed propargylic alcohols instead of simple alkynes which are further oxidised and undergo rearrangement into α,γ-diketones. Initially Au-**I** complex was utilised but was not as active as the more cationic $IPrAuNTf_2$ complex which gave better yields (Scheme 34).



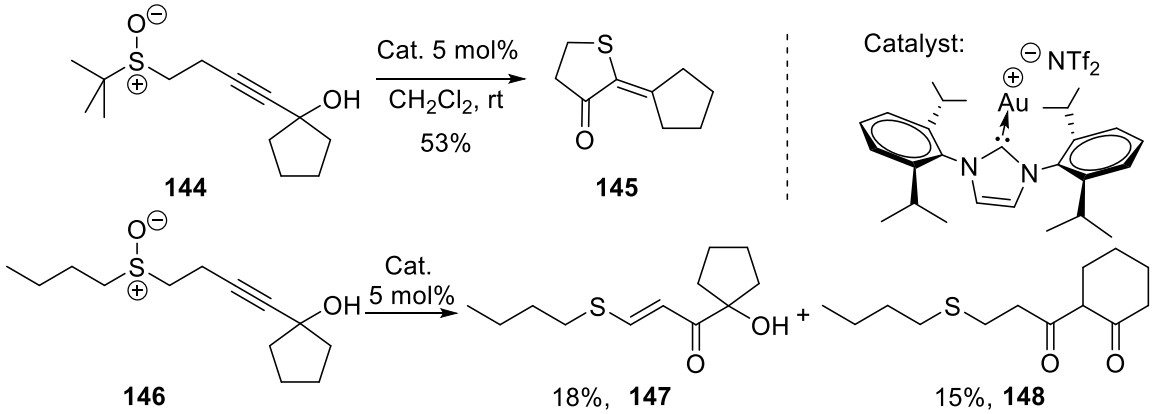
Scheme 34. Rearrangement of sulfoxides followed by 1,2-migration onto gold carbenoid.

Activation of the alkyne **138** by the Au cationic species causes an initial 5-*exo*-dig cyclisation **139** by the sulfoxide oxygen acting as the nucleophile (Scheme 35). The resulting cyclic gold species is then capable of eliminating the sulfide to form gold-carbenoid **140**. Neighbouring group participation from the hydroxyl group assists a 1,2-shift of the R^1 group to give the intermediate **141**. Finally loss of the Au species leads to the hydrogen bond stabilised latent diketone **142**, then tautomerisation leads to **143**.



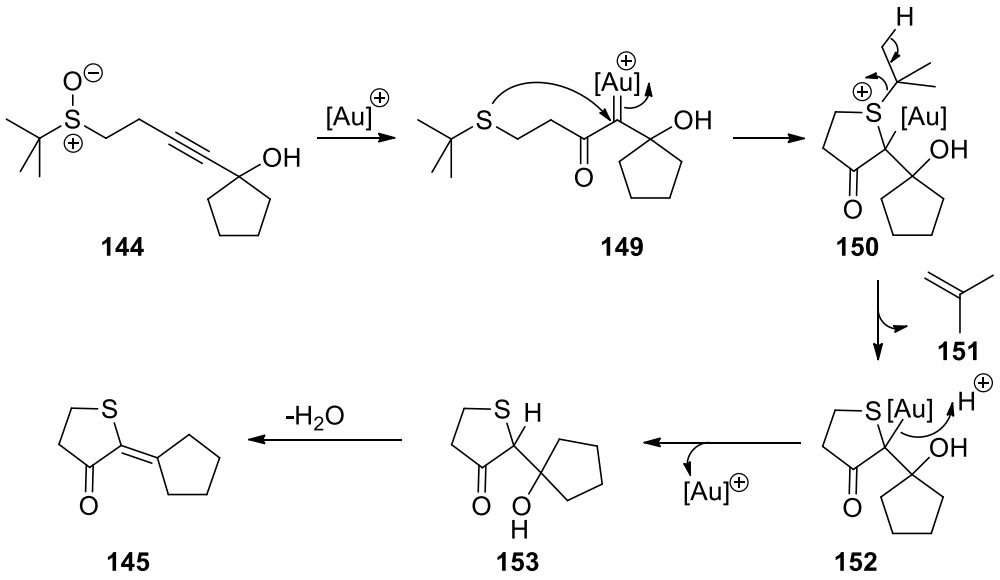
Scheme 35. Formation of gold carbenoid followed by 1,2-hydroxy aided shift onto carbenoid.

Unwanted side products were also observed besides the desired R^1 migration onto gold carbenoid (Scheme 36). *Tert*-butyl substituted sulfoxide **144** gave only **145** and no desired 1,2-migration products were isolated. On the other hand use of *n*-butyl substituted sulfoxide **146** led to 18% of **147** and 15% of the desired product **148**.



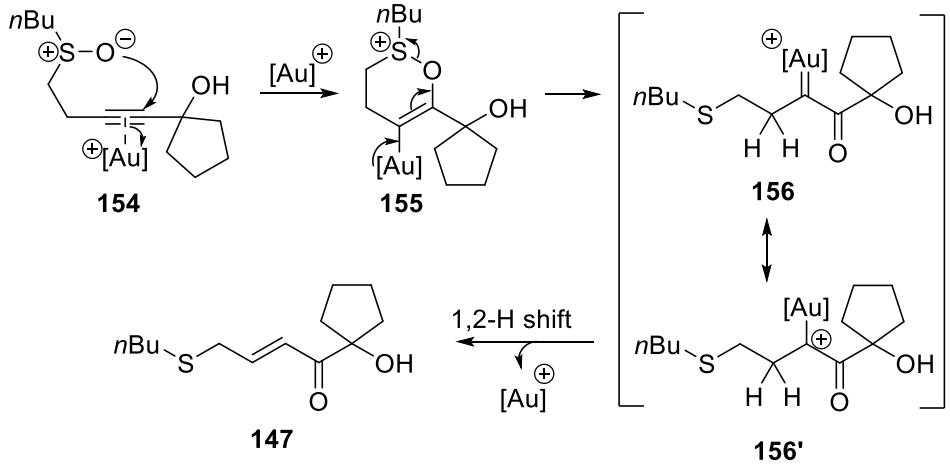
Scheme 36. Side-products when using *tert*-butyl- or *n*-butyl-substituents on sulfoxide.

When an electron-rich *tert*-butyl group is attached to sulfoxide tethered alkynes **144**, preferable sulfide attack onto gold carbenoid **149** led to **145** proposed to proceed through sulfur ylide formation **150** and fragmentation-protometallation followed by dehydration of **153**.



Scheme 37. Proposed mechanism for unexpected side product via sulfur ylide **150**.

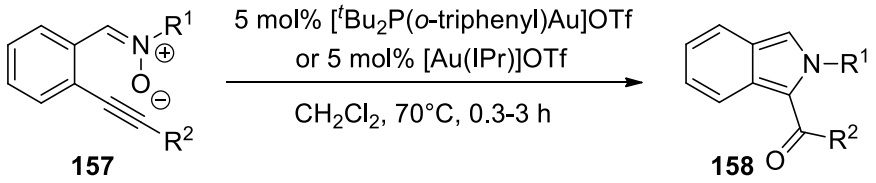
On the other hand use of *n*-butyl substituted sulfoxide tethered alkyne undergoes an initial 6-*endo*-dig attack of the oxygen from sulfoxide **154** to give gold vinyl intermediate **155**, which upon rearrangement gives **156** where gold carbenoid is in the *alpha*-position to the carbonyl. The presence of a suitable migrating group such as a hydride adjacent to the gold carbenoid **156** or gold stabilised carbocation **156'** allows a 1,2-hydride shift to give enone **147**.[66]



Scheme 38. Generation of sulfur ylides or enone products using diffent *S*-substituents.

1.9.2 α-Oxo gold carbenoids from imine oxides

Shin and coworkers[67] developed a gold catalysed oxygen transfer-rearrangement-cyclisation of nitrone tethered alkynes **157** to give isoindoles **158** using a mixture of 2.5 mol% [^{t}Bu$_2$P(*o*-biaryl)AuCl and 2.5 mol% AgOTs (Scheme 39). Internal (where R^2 = Me, *n*Bu, Ph) and terminal (R^2 = H) alkynes gave isoindoles in moderate to good yields.

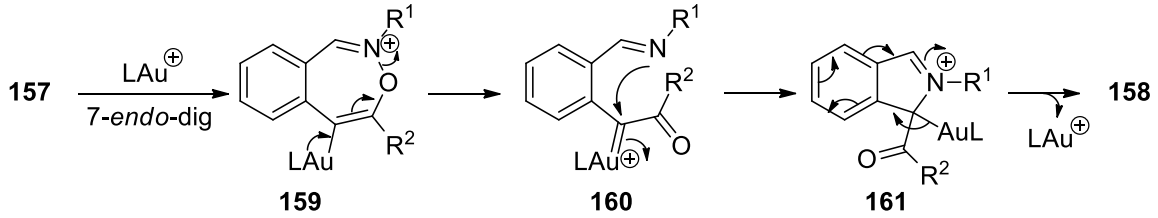


R^1 = Me, Bn
R^2 = H, Me, *n*Bu, Ph

Scheme 39. Intramolecular oxo-transfer from nitrones to generate α-oxo carbenoids.

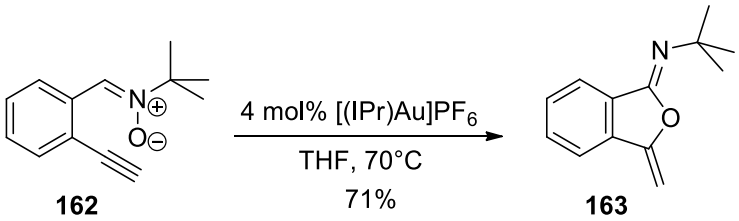
The mechanism suggests an initial 7-*endo*-cyclisation **159** followed by a redox transfer after subsequent rearrangement releasing the α-oxo gold carbenoid **160** and nucleophilic imine. Iminium intermediate **161** is then generated by attack of the imine nitrogen onto the electrophilic carbenoid in **160** which rearranges to give isoindole products **158** and release of the gold species. In this manner the same group synthesised highly complex tricyclic

heterocycles through a cascade process when alkenes have been incorporated into the starting alkyne precursor using $AuCl_3$.[68]



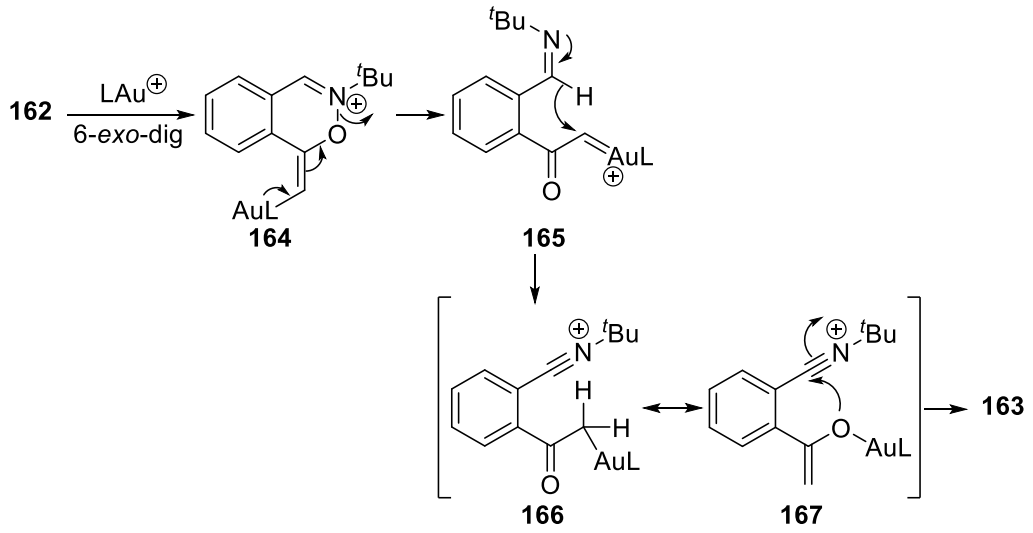
Scheme 40. Proposed mechanism of gold catalysed isoindole synthesis.

The same group later discovered that when R^1 = *tert*-butyl **162** then the regioselectivity is switched based on steric and electronic effects of the *N*-substituent, to an initial 6-*exo*-cyclisation (Scheme 42 below) to give iminoester **163** using the [(IPr)AuCl]/$AgPF_6$ system (Scheme 41).[69]



Scheme 41. Divergent reactive pathway with *tert*-butyl *N*-substituent.

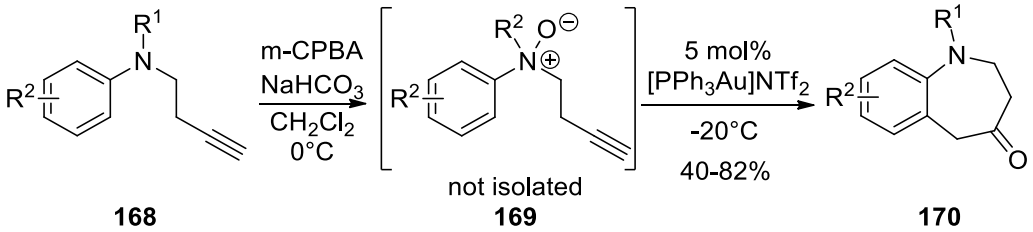
Preferential hydrogen shift from the imine **165** onto the gold carbenoid results in the intermediate **166** which tautomerises to the gold enolate species **167** (Scheme 42). The inductively electron-donating ^{t}Bu group allows the observed hydride shift over imine nitrogen attack. Subsequent gold-aided oxygen-enolate attack onto the electrophilic nitrilium **167** followed by deauration gives **163** in a good yield.



Scheme 42. Proposed mechanism of hydride-shift from imine onto gold carbenoid.

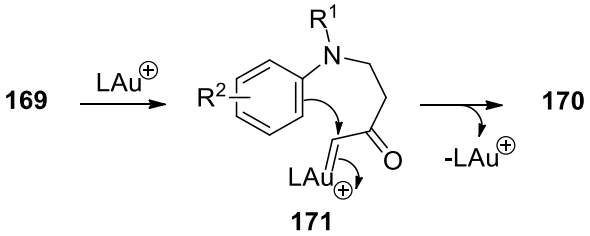
1.9.3 α-Oxo gold carbenoids from amine *N*-oxides

In 2009 Zhang *et. al.*[70] showed a new intramolecular one-pot synthesis of tetrahydrobenzazepin-4-ones **170** from tertiary *N*-(but-3-ynyl) anilines **168** following on from similar work done in the group,[71] using 5 mol% $[PPh_3Au]NTf_2$ where the amine *N*-oxide **169** is generated *in situ* using oxidant *m*-CPBA (Scheme 43).



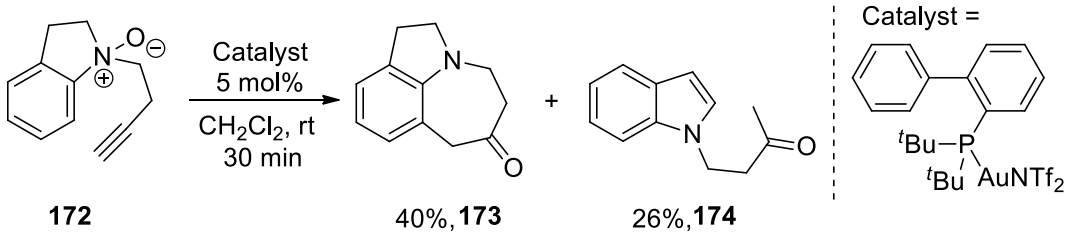
Scheme 43. *In situ* generation of amine *N*-oxide followed by oxy transfer.

The mechanism involves the formation of the gold carbenoid intermediate **171**. Subsequent electrophilic aromatic substitution in the *ortho*-position of the electron-rich aniline ring, followed by rearomatisation gives **170**.



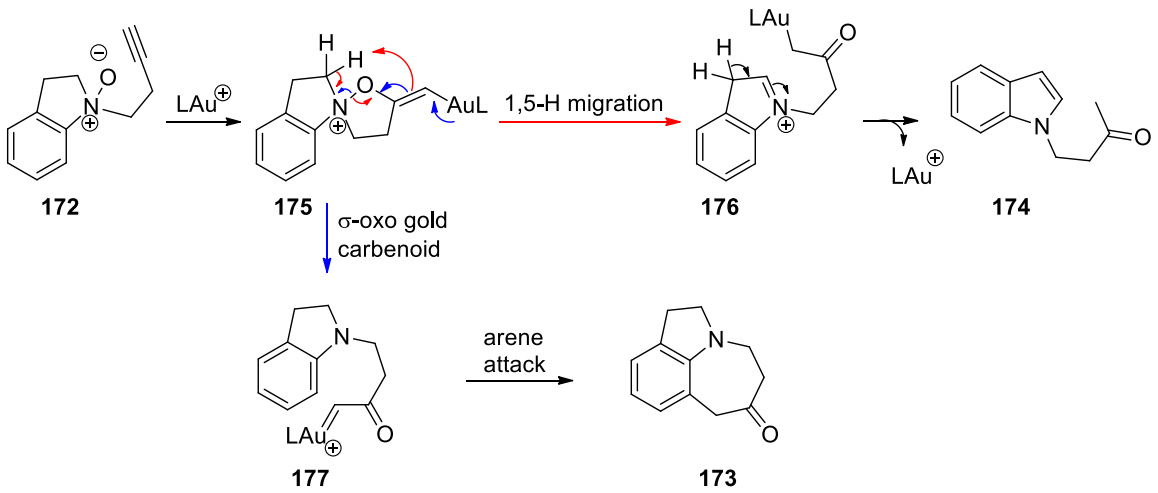
Scheme 44. Proposed gold carbenoid intermediacy.

In the presence of a small tether between the *N*-atom and the aryl ring such as **172** introduces two potentially competitive reactive pathways giving a mixture of products **173** and **174** using 5 mol% [^{t}Bu$_2$P(*o*-biaryl)AuNTf$_2$] (Scheme 45).



Scheme 45. Generation of a mixture of products from amine *N*-oxide under gold catalyst.

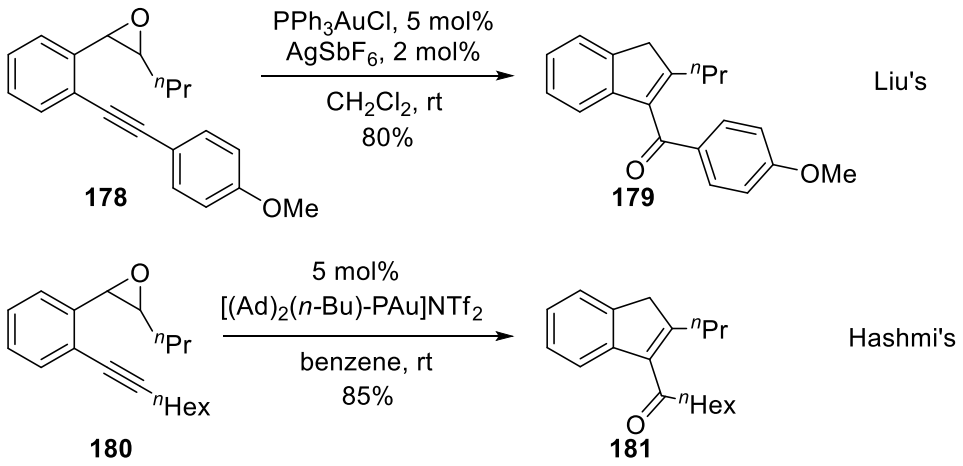
The intermediate generated by an initial 5-*exo*-dig cyclisation of oxygen onto gold activated alkyne **175** can undergo two reactive pathways to give a mixture of products. The partially restricted attack for the incoming nucleophilic aniline onto gold carbenoid leads to a formal 1,5-hydride migration **176** and protodemetallation to give **174** (Scheme 46, red pathway). Computational studies confirms the formation of **174** *via* an unusual 1,5-hydride migration. On the other hand back-donation leads to the carbenoid intermediate **177** followed by arene attack to give **173** (Scheme 46, blue pathway).



Scheme 46. Divergent reactivity: gold carbenoids prefer arene attack and vinyl gold species a 1,5-*H* shift.

1.9.4 α-Oxo gold carbenoids from epoxides

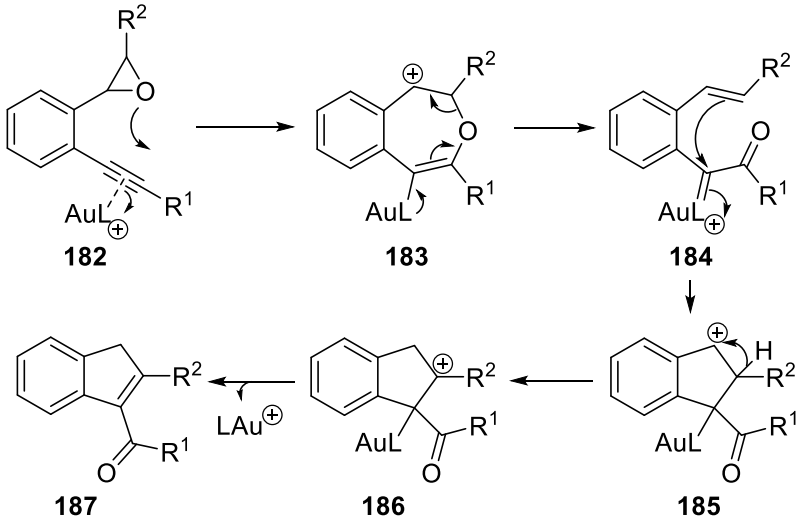
Despite the less polar character of the C-O bond in epoxides Liu *et. al.*[72] and Hashmi *et. al.*[73] independently reported the use of epoxides **178** and **180** as oxygen transfer reagents to gold activated alkynes to give ketones **179** and **181**, respectively (Scheme 47). The driving force of this reaction is the release of epoxide ring strain.



Scheme 47. Oxygen transfer from epoxides to give carbenoids.

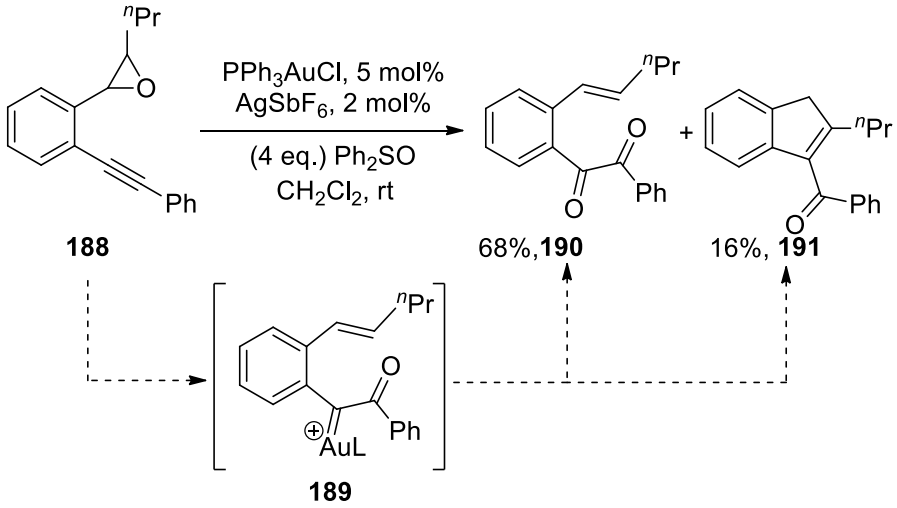
The proposed mechanism involves oxygen attack onto alkyne *via* a 7-*endo*-dig fashion to give stabilised carbocation intermediate **183** (Scheme 48). Subsequent intramolecular cation stabilisation generates α-oxo carbenoid **184** susceptible to nucleophilic attack by the

alkene to give intermediate **185**, which undergoes an apparent hydride migration (supported by deuterium labelling experiments).[73] Protodemetallation of **186** gives the ketone product **187**.



Scheme 48. Mechanism for the formation of indenes from epoxides.

The proposed generation of the carbenoid intermediate **184** was supported by a test reaction using the same reaction conditions but in the presence of excess Ph_2SO as external oxidant to trap gold carbenoid **189** giving diketone products **190** (Scheme 49).[72]

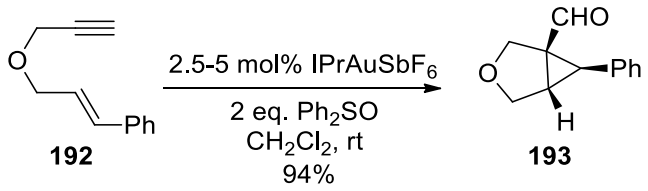


Scheme 49. Evidence of the participation of α-oxo gold carbenes as intermediates.

The above examples (Section **1.8**) have shown the key reactivity displayed by the gold carbenoid intermediate, which is readily accessible directly from alkynes tethered to an internal oxygen-transfer moiety. The highly sought gold carbenoid has been trapped intramolecularly with various nucleophiles such as sulfur or nitrogen heteroatoms, arene groups and alkenes to form complex structural motifs. Furthermore, intramolecular hydride migrations onto the gold carbenoid intermediate have also been exploited in determining the mechanistic topologhies.

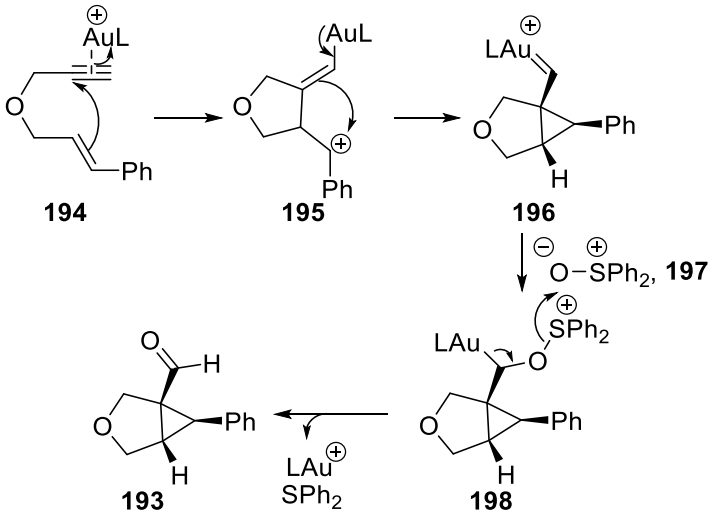
1.10 Gold catalysed sulfoxide (Ph_2SO) oxo-transfer processes

As with work done by Liu[72] in Scheme 49 above the gold carbenoid may also be trapped by a suitable external nucleophilic oxidant. Toste *et. al.*[74] initially reported the intermolecular reaction using diphenylsulfoxide as the oxygen transfer reagent (Scheme 50). A range of reactions were carried out *via* a gold(I) carbenoid generating carbonylic products **193** from 1,6-enyne **192** in good to excellent yields.



Scheme 50. Trapping of gold carbenoid with an external oxidant.

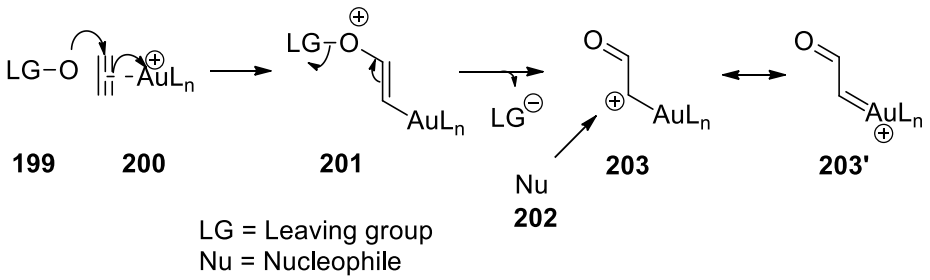
The proposed mechanism involves the activation of the alkyne **194**, followed by nucleophilic attack of the alkene moiety resulting in the formation of the cyclopropanated gold carbenoid **196** (Scheme 51). In the presence of the oxidant **197** the intermediate **198** is formed, then gold aided elimination of the sulfide gives **193**.



Scheme 51. Sulfoxide used to trap gold carbenoid to give aldehydes from 1,5-enynes.

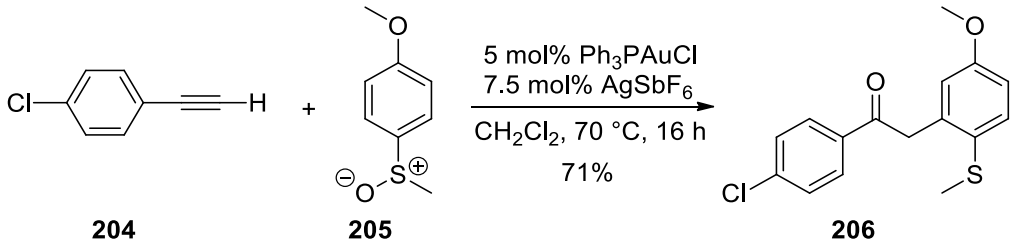
1.11 Reactivity through contrived gold carbenoids

In section **1.9** electrophilic α-oxo gold carbenoids were generated from alkynes as a result of metal back-donation and release of the latent leaving group on the oxidants. Subsequent reaction with nucleophiles led to sulfur ylides, arene addition and oxygen transfer processes. In this section the gold vinyl species **201** is involved in the release of the leaving group of the incoming oxidant after migration of a suitable nucleophile.



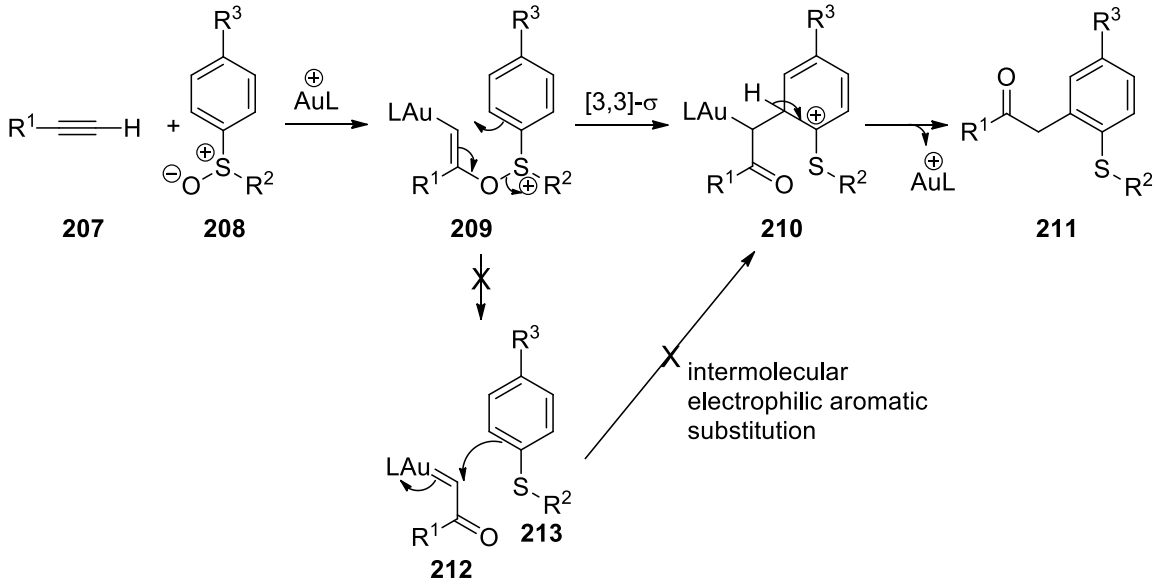
Scheme 52. Canonical forms of gold stabilised carbocations (gold carbenes **203'** is one of them).

Asensio *et. al.*[75] shown gold(I) catalysed intermolecular oxyarylation reactions of alkynes with initial regiochemical issues in the alkylation of arenes. Terminal alkyne **204** reacts with oxidant **205** to give oxyarylation product **206** using a mixture of PPh_3AuCl and $AgSbF_6$ in a good yield (Scheme 53).



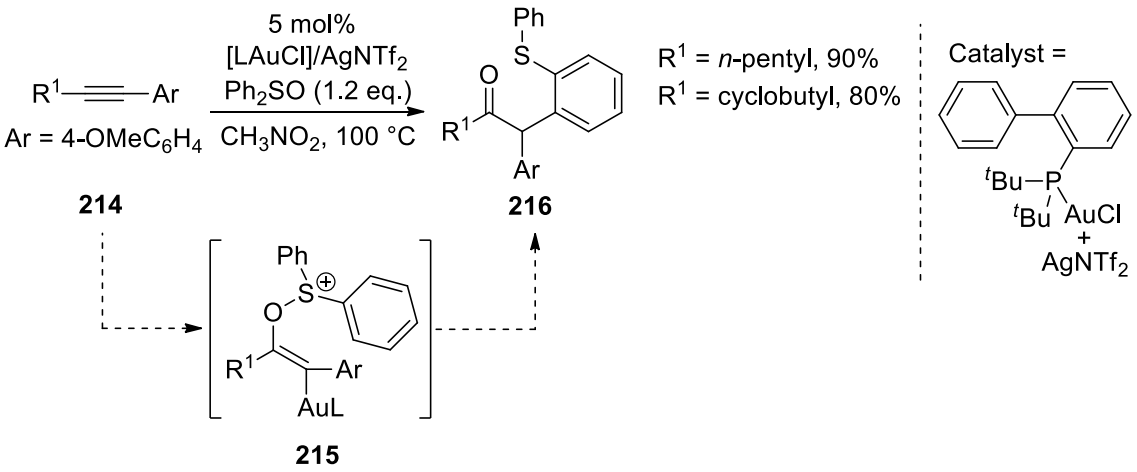
Scheme 53. Gold catalysed intermolecular oxyarylation of terminal alkynes.

The gold(I) intermediate **209** from nucleophilic addition of sulfoxide **208** with terminal alkynes **207** does not undergo the expected electrophillic aromatic substitution *via* an α-oxo gold carbenoid intermediate **212**, which would lead to the formation of a mixture of regioisomers but instead DFT calculations reveal that a [3,3]-sigmatropic rearrangement occurs to give a single regioisomer *ortho*-substituted product **211** by protodemetallation of **210** (Scheme 54).



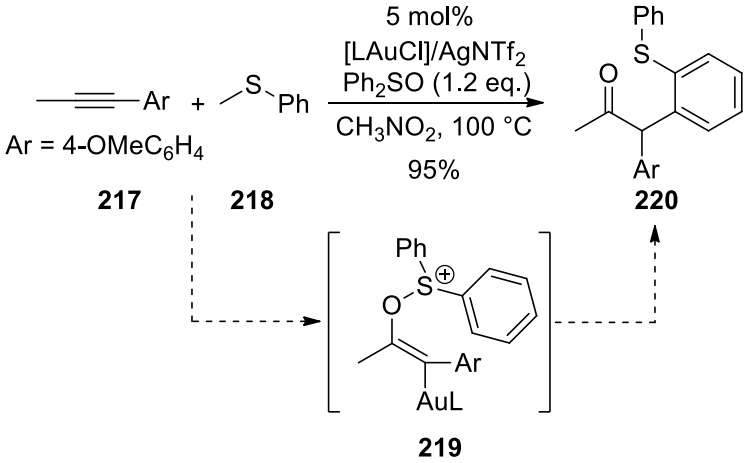
Scheme 54. Arene attack prefered on gold vinyl species, as apposed to carbene formation.

Liu and co-workers[76] recently expanded the scope of this oxyarylation by using internal alkynes. Alkyl and aryl substituted alkynes **214** reacted with diphenyl sulfoxide to give products **216** under the influence of a cationic gold species (Scheme 55).



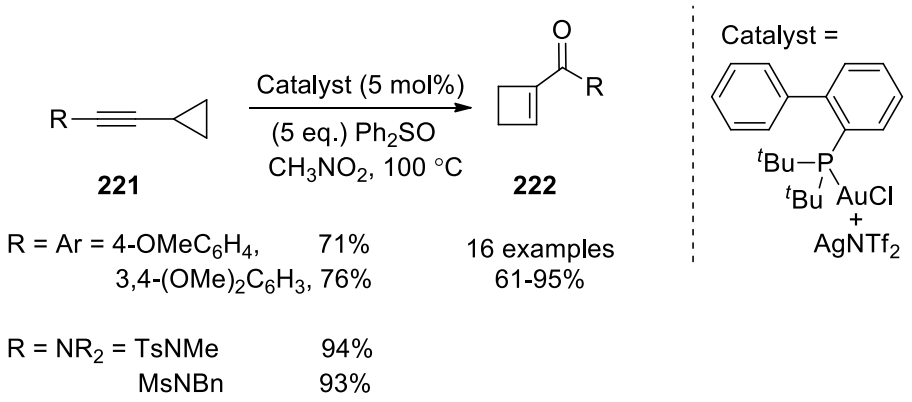
Scheme 55. Similar reactivity to sulfides of type **216**, but starting with internal alkynes.

A crossover experiment involving alkyne **217**, an external sulfide **218** and diphenyl sulfoxide provided evidence that the proposed mechanism goes *via* an [3,3]-intramolecular sigmatropic rearrangement of **219** to give product **220**, consistent with the DFT calculations carried out by Asensio and co-workers.[75] The formation of the α-oxo gold carbenoid intermediate was excluded as the external sulfide was not incorporated in the final product.



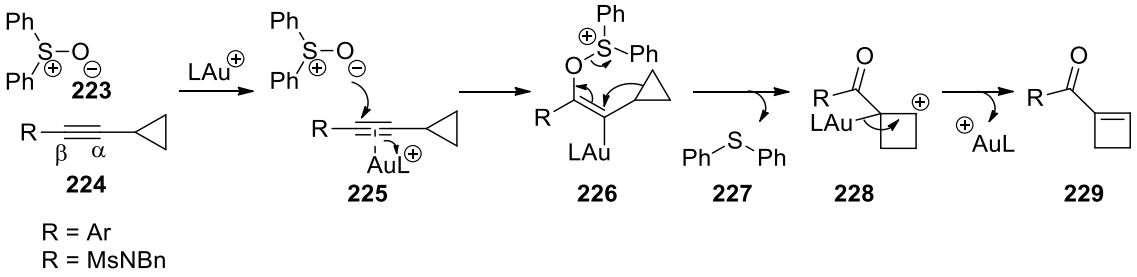
Scheme 56. Experimentation to prove [3,3]-sigmatropic rearrangements led to the desired product.

In this work Liu and co-workers[76] reported a novel gold-catalysed oxidative ring expansion of unactivated cyclopropyl substituted internal alkynes **221** to give cyclobutenes **222** using the same reaction conditions as before but using an excess of Ph_2SO as the external oxidant (Scheme 57).



Scheme 57. Gold catalysed oxidative ring expansion of cyclopropyl alkynes.

To ensure nucleophilic attack of the diphenyl sulfoxide occurred at the C_β-position, various alkynylcyclopropane derivatives bearing aryl or amino groups were tested. Regioselective oxygen transfer from **223** onto gold activated alkyne **225** generates vinyl gold intermediate **226** which undergoes a ring expansion releasing diphenyl sulfide **227** after relieving ring strain of the unactivated 3-membered ring (driving force for ring-expansion). Deauration leads to product **229**. This mechanism is supported by computational results.[76]



Scheme 58. Proposed mechanism in the ring expansion onto gold vinyl species releasing sulfide.

Through carbonyl metal carbenoids cyclobutene products similar to these were generated using silver(I) catalysed decomposition of the diazo moiety.[77]

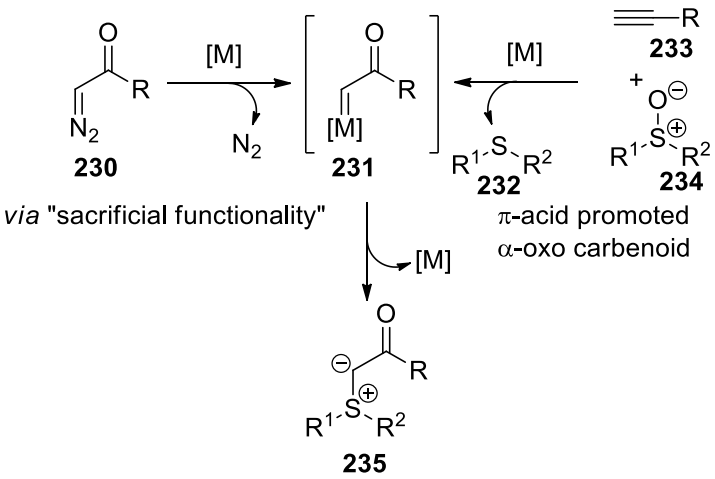
1.12 Summary

Intramolecular sulfoxides have been used to probe the reactivity of diazo derived carbenoids. These very reactive intermediates have led to α-oxo gold carbenoids directly from alkynes where regioselectivity of carbenoid formation can be controlled. The potential of alkynes as precursors to highly reactive sulfur ylide intermediates directly from alkynes has not been exploited. Although use of external oxidants allows flexibility in the scope of gold carbenoids, they are highly nucleophilic and have led to the trapping of reactive gold carbenoid with oxygen. Intramolecular oxygen transfer processes allow a site specific access to α-oxo carbenoids and do not have the problem of over oxidation.

Chapter 2: Results and discussion

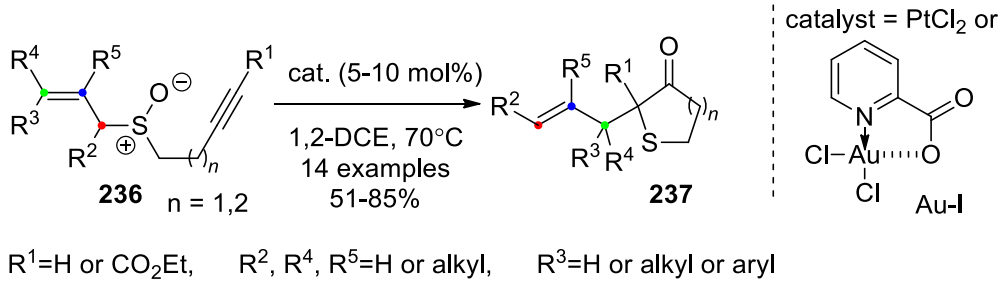
2.1 Introduction

In the light of research done by the groups of Toste[63] and Zhang[66] (Introduction, Section **1.9.1**), Davies and Albrecht[62] shown that precious metal α-oxo carbenoids generated from alkynes can be used to directly access sulfur ylides. This alternative pathway to sulfur ylides provides a safer route to these reactive intermediates that bypasses the use of sacrificial functionality such as diazo-compounds (Scheme 59).



Scheme 59. Formation of α-oxo-π-acid carbenoids **231** directly from alkynes.

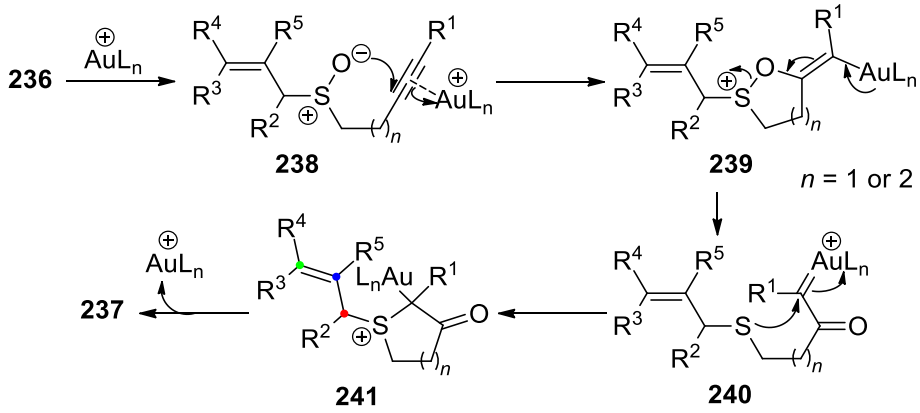
The principle of directly accessing sulfur ylides from alkynes *via* π-acid metal catalysis has proved to be successful in the synthesis of monocyclic and fused-bicyclic functionalised sulfur heterocycles (Scheme 60).



Scheme 60. Synthesis of highly functionalised monocyclic sulfur heterocycles.

Here the use of a nucleophilic sulfoxide moiety allows the simultaneous generation of the carbenoid and the allyl sulfide required for sulfur ylide formation *via* an initial

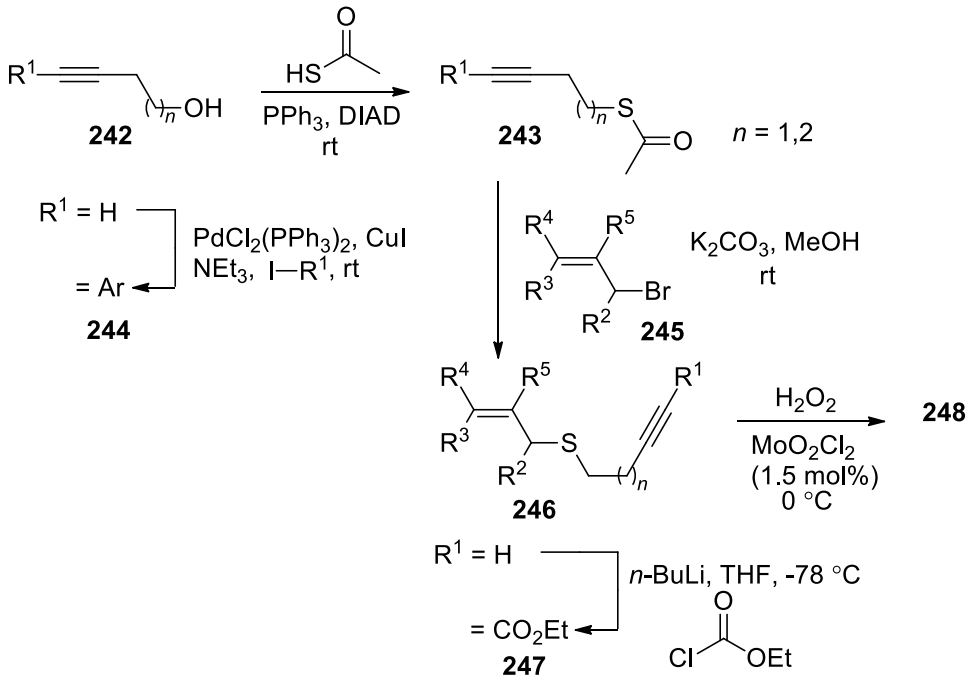
intramolecular redox process (Scheme 61). Reactive intermediate **239** is generated upon an initial 5-*exo*-dig or 6-*endo*-dig nucleophilic attack of the sulfoxide oxygen onto the π-acid activated alkyne moiety **238**, where *n*=1 or *n*=2 respectively. The α-oxo-gold carbenoid **240** is generated, releasing the substituted allyl sulfide moiety. The sulfur ylide is then generated **241** by nucleophilic sulfide attack onto the electrophilic metal carbenoid, subsequent [2,3]-sigmatropic rearrangement yields the 5- or 6-membered sulfur heterocycles **237** releasing the cationic π-acid metal catalyst.



Scheme 61. Proposed mechanism for the sulfur heterocycle synthesis.

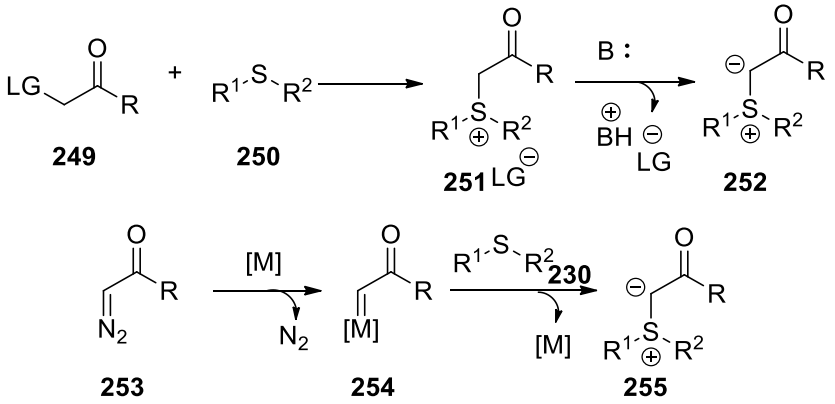
The starting sulfoxide precursors were readily prepared from commercially available propynol *n*=1, **242a** or butynol *n*=2 **242b** (Scheme 62) by an initial Mitsunobu reaction[78] to form the thioester **243**. Subsequent reaction of **243** with a variety of substituted allyl bromides **245** using potassium carbonate in methanol gave sulfide tethered enynes **246**. Chemoselective oxidation of the sulfides **246** or **247** to the corresponding type **248** sulfoxides was achieved using hydrogen peroxide and catalytic amounts of molybdenum dichloride dioxygen.[79] No purification by column chromatography was required up until the final stage making this a cost effective and efficient synthesis of sulfoxide tethered enynes. More-over the high polarity of sulfoxides provides an added benefit to the purification due

to the marked distinction between the R_f values of any by-products in comparison to the desired sulfoxide products.



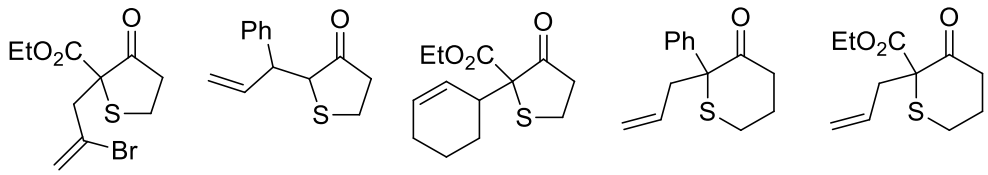
Scheme 62. General synthesis of sulfoxide tethered enynes, DIAD = diisopropylazodicarboxylate.

Incorporation of the alkyne unit required to access the ylide under π-acid catalysis was achieved earlier in comparison to the traditionally known routes to sulfur ylides which insert the ylide precursor normally immediately before the formation of the ylide providing greater retrosynthetic flexibility (Scheme 63, and see Introduction: Section **1.1**).



Scheme 63. Traditionally known routes to sulfur ylides.

The catalysis proceeded smoothly with the use of catalytic amounts of $PtCl_2$ in 1,2-dichloroethane for substrates bearing a terminal alkyne and also use of Au-**I** for internal alkynes. Use of $PtCl_2$ catalyst for internal alkynes led to poor yields and complex crude reaction mixtures in comparison to cleaner reactivity using Au-**I**. In total 14 examples of catalysis were shown to be a success with a range of substituted allyl groups tolerated to form highly congested functionalised 5- and 6-membered cyclic structures (Scheme 64).

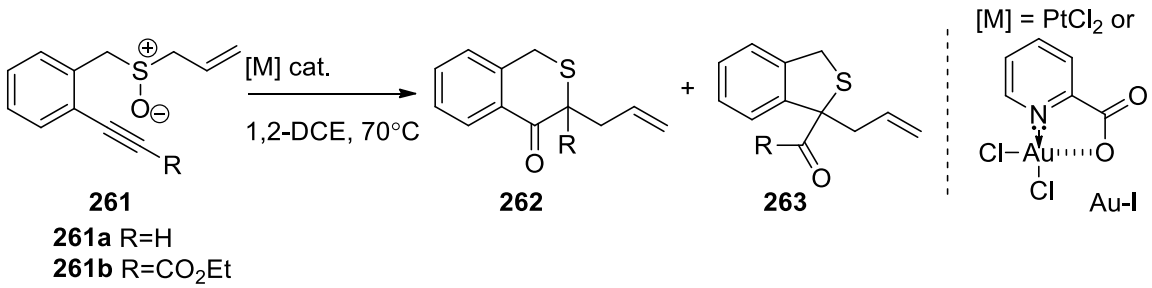


83% | 61% 2.6:1.0 *dr.* | 83% | 55% | 84%

256 | **257** | **258** | **259** | **260**

Scheme 64. Selected examples of 5- and 6-membered sulfur heterocyclic structures.

The preliminary report by the Davies group[62] showed that incorporation of a benzene group between the reactive sulfoxide and the tethered alkyne reactive entities (preparation discussed later), required to generate the ylides led to fused-bicyclic sulfur heterocycles (Scheme 65). Treating substrate **261a** featuring a terminal alkyne (Table 1, entry 1) with 10 mol% $PtCl_2$ in 1,2-DCE at 70 °C led to a mixture of two products **262a** and **263a**. The major product was the 6-membered isothiochroman-4-one **262a** with small amounts of 5-membered 1,3-dihydrobenzo[*c*]thiophene product **263a** isolated by column chromatography. Introducing an electron-withdrawing ester group on substrate **261b** led to the exclusive formation of product **262b** (Table 1, entry 2) under Au-**I** catalysis.



261
261a R=H
261b R=CO_2Et

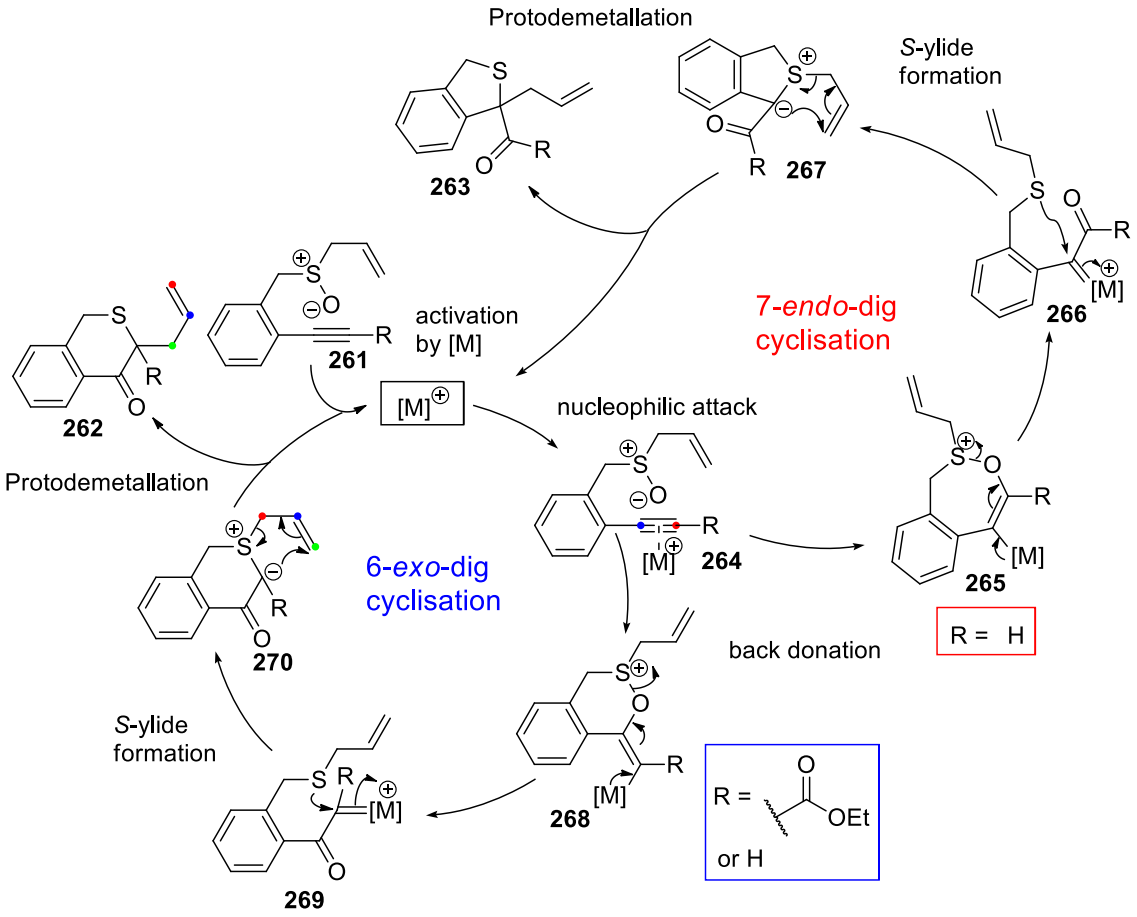
262 **263**

Scheme 65. Cyclisation to yield isothiochroman-4-ones.

Entry	**261**	[M][a]	Product	Yield[b] (%)
1	**261a**	$PtCl_2$	**262a**	55
			263a	8
2	**261b**	Au-**I**	**262b**	64

Table 1. [a] Catalyst (10 mol%) was added to a solution of **261** in 1,2-dichloroethane (0.2*N*) in a sealed Argon purged Schlenk tube and heated to 70°C for 18 h. [b] Isolated yields after flash column chromatography.

The addition of an ester group induces a partial charge across the alkyne C-C triple bond rendering the β-carbons electrophilic. This polarisation of electron density favours attack of the incoming sulfoxide oxygen nucleophile onto the β-carbon of π-acid activated alkyne **264** in a 6-*exo*-dig fashion **268** (Scheme 66). When using terminal alkynes and once activated by depletion of electron density by the π-acid the nucleophile has a possible two sites of attack, either 6-*exo*-dig **268** or 7-*endo*-dig **265**. The hydrogen atom of the alkyne is sterically undemanding and so the incoming nucleophile is not hindered for attack on either carbon of the alkyne. According to Baldwin's rules the high energy 7-*endo*-dig mode is less favoured over the more kinetically accessible 6-*exo*-dig[12] (See section **1.9.1**). Nonetheless mixtures of both 5- and 6-membered cyclic products **263** and **262** are isolated. The mechanism for the formation of the two products is shown in Scheme 66.



Scheme 66. Mechanisms for 5- and 6-membered cyclic products from electronically biased systems.

2.2 Research aims

At the start of this study, it had been shown that simple starting precursors with pre-installed alkyne functionality can be utilised to access sulfur ylides under the influence of catalytic amounts of gold or platinum catalysts. The sulfoxides were readily available by chemoselective oxidation of the sulfide and were easily purified. An intramolecular redox strategy bypassed the use of hazardous diazo-chemistry to access analogous sulfur ylides and moreso simplified the retrosynthetic approach to the starting precursors. A wide range of 5- and 6-membered cyclised products had been formed with high functional group tolerance and in good yields under mild conditions, with excellent atom economy. Also in a preliminary study, the formation of cyclised benzo-fused products proceeded *via* an exclusive 6-*exo*-dig mechanistic pathways for an electron poor biased system.

The promise of this sulfur ylide chemistry led us to explore;

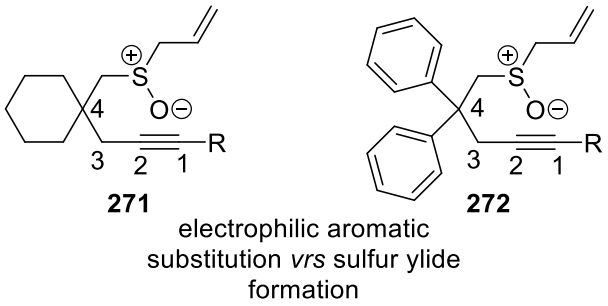
1) how well it worked for reactions where there are competing pathways for the gold carbenoid formed;

2) complex transformations involving domino reactivity from pre-designed starting sulfoxide precursors;

3) the further scope of these reactions with emphasis on the regioselective formation of the α-oxo gold carbenoid by altering the electronic bias of both aliphatic and aromatic systems.

2.3 Sulfur ylide formation *vs* electrophilic aromatic substitution

To test how facile sulfur ylide formation was over competing electrophilic aromatic insertion reactions, compounds capable of both reactivity pathways were designed. It was practical to have substituents in the 4-position for synthetic simplicity (Scheme 67). A substrate bearing the cyclohexyl group in the 4-position **271** was selected as a standard control for the sulfur ylide formation against the diphenyl substituted compound **272** and would also further expand the scope of the previous work done in the Davies group.[62]

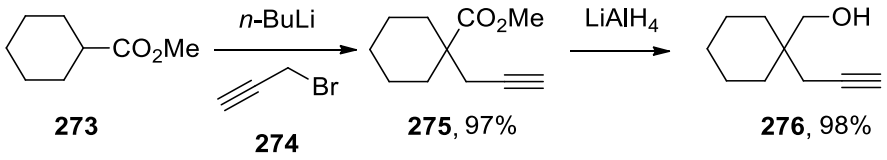


Scheme 67. Carefully designed substrates to allow competing reactivity.

2.3.1 Preparation of starting material

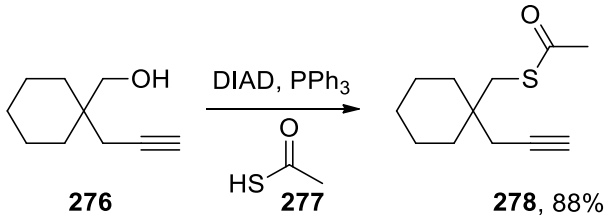
Commercially available cyclohexyl ester **273** was deprotonated by *n*-butyl lithium followed by alkylation by propargyl bromide **274** to give alkylated ester **275** in 97% yield[80] (Scheme

68). Reduction of the ester group by lithium aluminium hydride led to the alcohol **276** in 98% yield.[81]



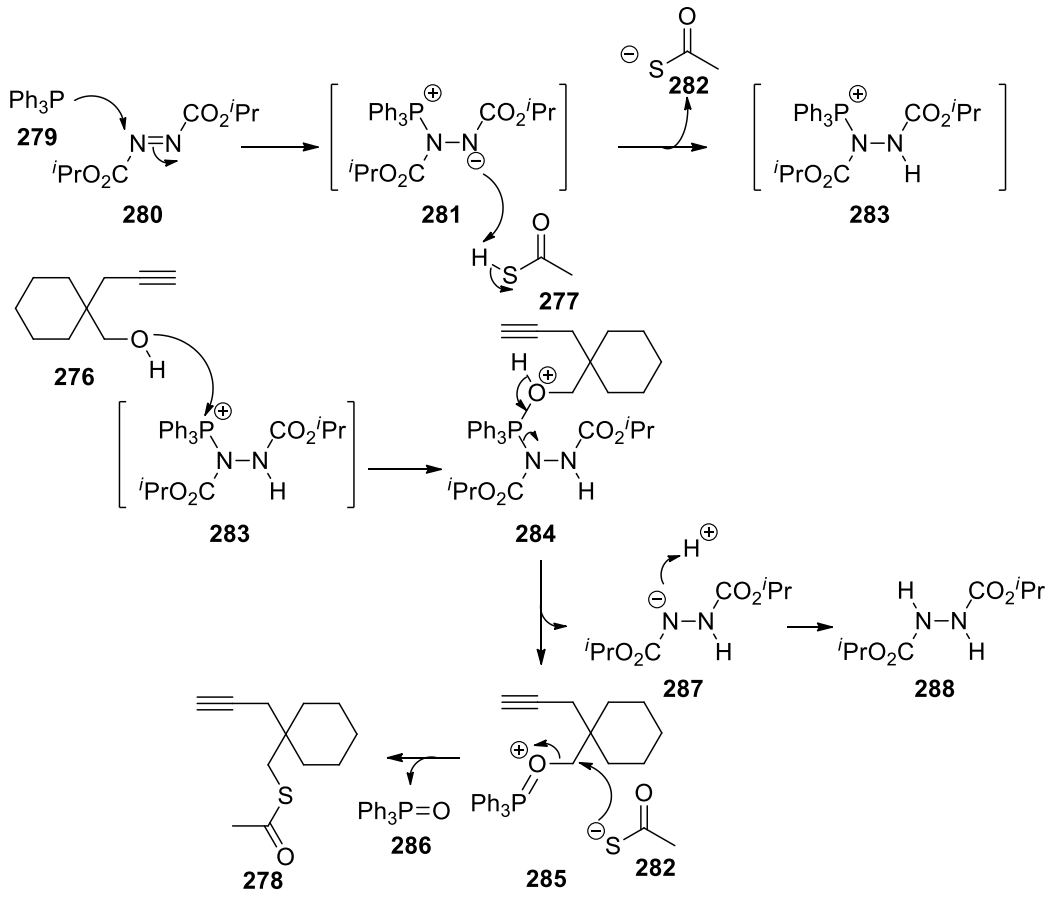
Scheme 68. Base mediated alkylation of ester then reduction to yield functionalisable -OH group.

Using previously known methods (section **2.1**, Scheme 62)[62] introduction of sulfur was achieved by the Mitsunobu reaction.[78] Triethylamine and diisopropylazodicarboxylate (DIAD) were reacted together to activate alcohol **276** allowing reactivity with thioacetic acid **277** to yield thioether **278** in 88% yield (Scheme 69).



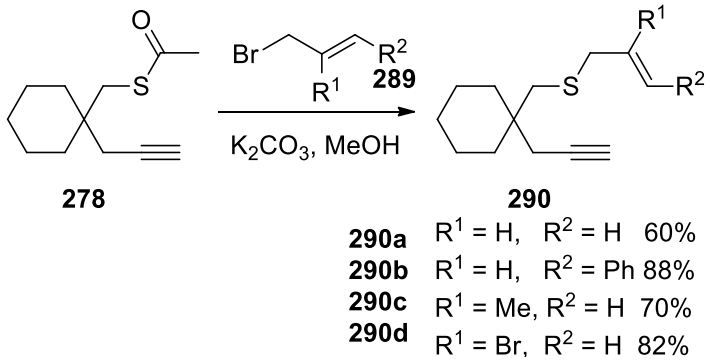
Scheme 69. Introduction of thioester by Mitsunobu reaction.

The Mitsunobu reaction[78] initially involves the reaction of triphenylphosphine **279** with DIAD **280** to give a precipitant of the zwitterion species **281** (Scheme 70). The nucleophilic thioacetate group **282** is also generated along side **281**. Nucleophilic addition of alcohol, **276** onto **283** followed by deprotonation generates the activated alcohol intermediate **285**. A subsequent S_N2 reaction with thioacetate **282** leads to thioether **278**. The driving force of this transformation is the formation of thermodynamically stable triphenylphosphine oxide **286**, which is easily removed by filtration without the need to purify by time consuming column chromatography.



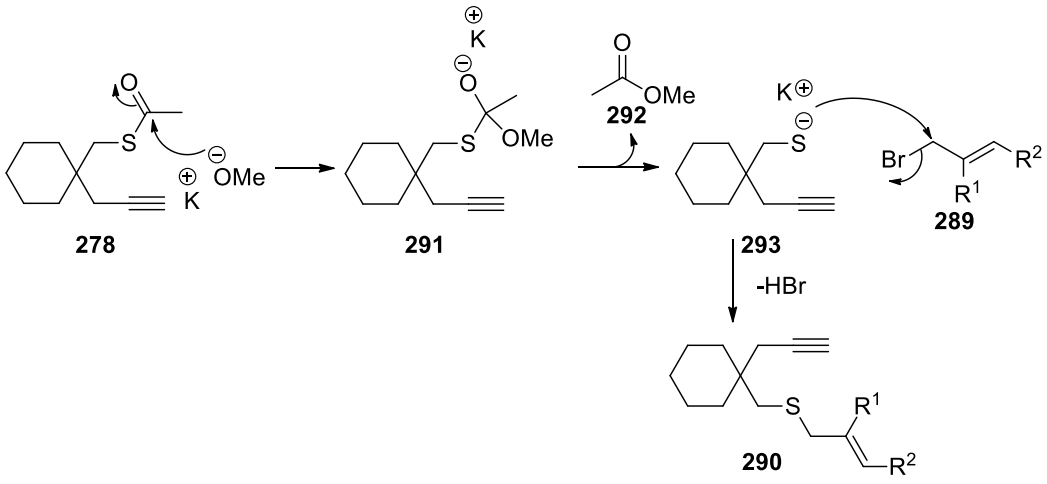
Scheme 70. Accepted mechanism of the Mitsunobu reaction.[78]

Various allyl bromides **289** were reacted with thioester under potassium carbonate in methanol to give thio-tethered 1,8-enynes containing a cyclohexyl group in the 4-position (Scheme 71). This procedure was successful for the reaction of **278** with unsubstituted allyl (R^1 and R^2 = H), α-substituted allyl (R^1 = H and R^2 = Ph) and β-substituted allyl (R^1 = Me and R^2 = H) bromides to give the corresponding desired 1,8-enyne products in good yields of 60%, 88% and 70% respectively. A β-substituted allyl group containing a functionalisable group (R = Br and R^2 = H) **290d** was also synthesised in good yield of 82% after column chromatography.



Scheme 71. Allylation by base deprotection of thioether followed by nucleophilic substitution.

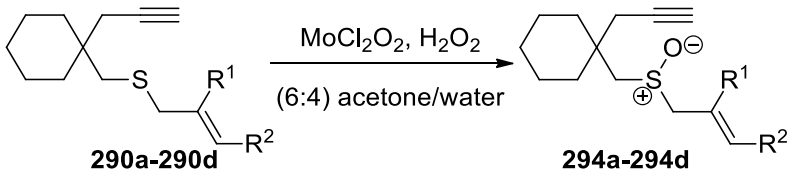
In the experimental procedure thioether is added to a partially soluble solution of potassium carbonate in methanol. It is accepted that potassium carbonate partially dissolves in methanol[82] allowing proton exchange to form potassium hydrogen carbonate and a good nucleophile potassium methoxide. Nucleophilic addition of the methoxy group leads to the formation of tetrahedral intermediate **291** which fragments into methyl acetate and thiol **293** (Scheme 72). Nucleophilic substitution of allyl bromide **289** by the thiol **293** forms a sulfide of type **290**.



Scheme 72. Formation of sulfides *via* a hemiketal intermediate.

Sulfides **290a-290d** were chemoselectively oxidised to sulfoxide using catalytic amounts of molybdenum dichloride dioxygen and hydrogen peroxide in a 6:4 ratio of a binary mixture

of solvents acetone and water.[79] Stirring the resulting reaction mixture at 0 °C led to the desired sulfoxide in good yields with the sensitive C-C unsaturated moieties untouched.



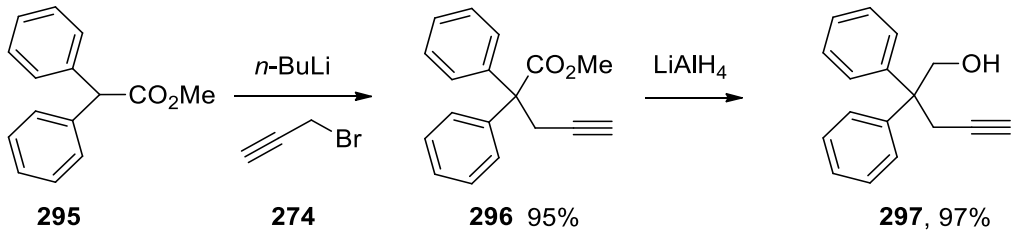
Scheme 73. Chemoselective oxidation of sulfides in the presence of sensitive olefin moieties.

Entry[a]	R^1	R^2	product	Yield[b] (%)
1	H	H	**294a**	70
2	H	Ph	**294b**	96
3	Me	H	**294c**	72
4	Br	H	**294d**	85

Table 2. [a] Reactions were carried out using catalytic amounts of MoO_2Cl_2 (1.5 mol%) and H_2O_2 (1.05 eq.) in a 6:4 ratio of binary solvent of acetone:water and stirred at 0 °C. [b] Isolated yields after flash column chromatography.

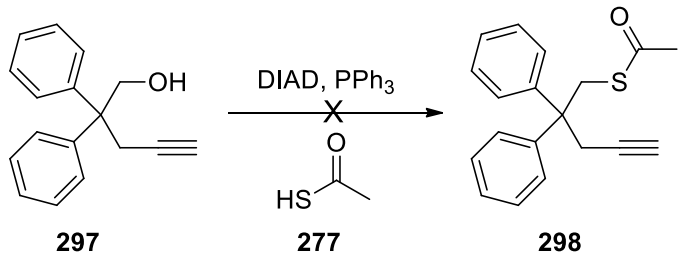
2.3.2 Preparation of diphenyl substituted sulfoxide 272

Following previously known procedures,[80] diphenyl ester **295** was deprotonated with *n*-butyllithium followed by alkylation with propargyl bromide to give **296** in excellent yield of 95%. Reduction of the ester group by lithium aluminium hydride[81] led to the corresponding alcohol **297** in 97% yield.



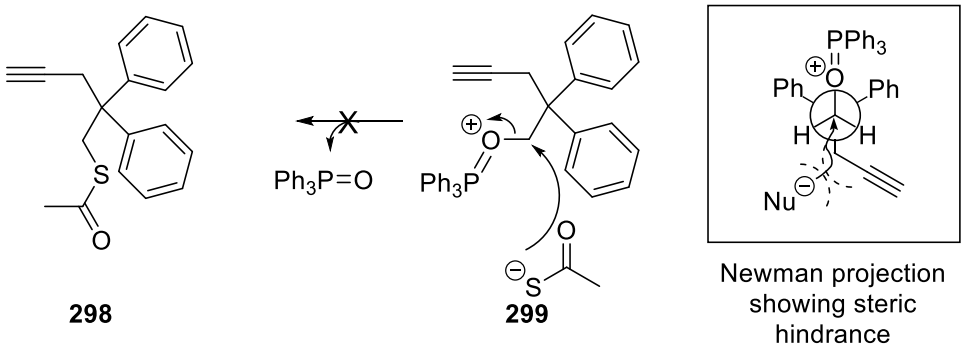
Scheme 74. Alkylation of ester **295** followed by reduction of **296** to yield alcohol.

The Mitsunobu reaction conditions however, led to no product formation and starting materials were recovered with no other side-products present by thin layer chromatography (TLC) analysis (Scheme 75).



Scheme 75. Mitsunobu reaction of alcohol to thioether.

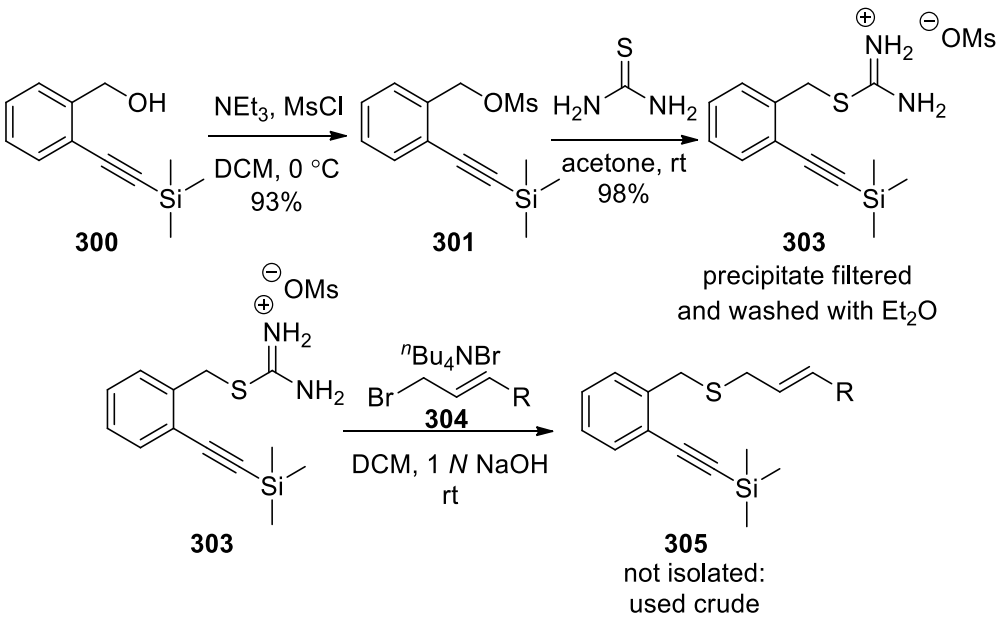
The incoming nucleophile is obstructed by sterically demanding groups on both the oxophosphonium cation and the diphenyl substituent in the 4-position. An aqueous work-up therefore led to regeneration of the starting alcohol (Scheme 76). Another scenario is that the alcohol itself does not react with the activating phosphonium intermediate due to unfavourable steric interactions (See Mitsunobu mechanism: Scheme 70).



Scheme 76. Schematic showing steric demand of the phenyl groups towards the thioacyl nucleophile.

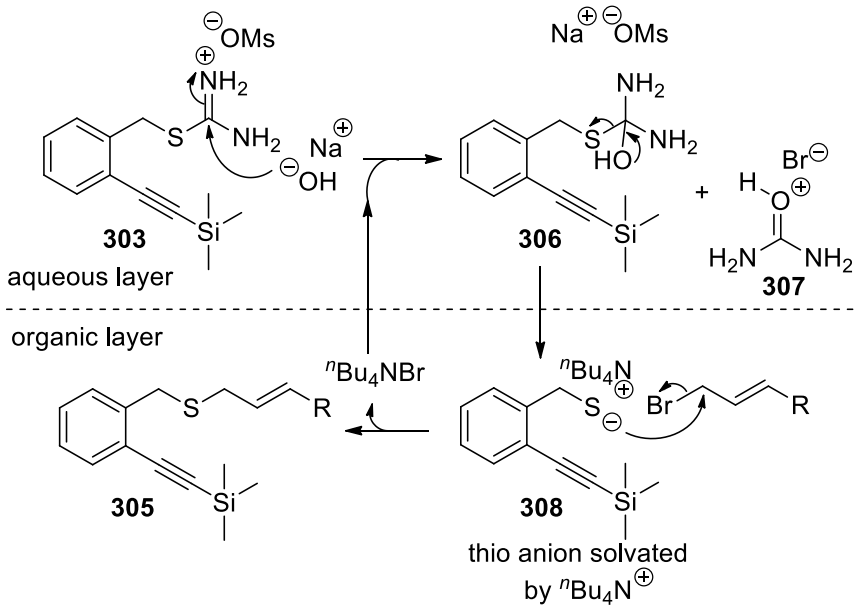
With problems installing the sulfide moiety an alternative route was required. Previously in the Davies group allyl sulfides have been synthesised *via* reaction of the activated alcohol with thiourea to give thiouronium salts[62] (Scheme 77). These salts undergo a phase transfer catalysis process to generate a variety of allyl sulfides. The desired sulfide **305** was generated in only three steps from the respective alcohol. The thiouronium salt **303**

precipitated out of the reaction mixture and was simply filtered and washed with dithylether avoiding lengthy column purification techniques.[62] The salt is insoluble in commonly used organic solvents such as DCM, ethers and toluene and easily isolated by filtration methods. Phase transfer reactions involving aqueous medium is therefore required. The salt reacts to generate clean sulfides which do not require purification by column chromatography.



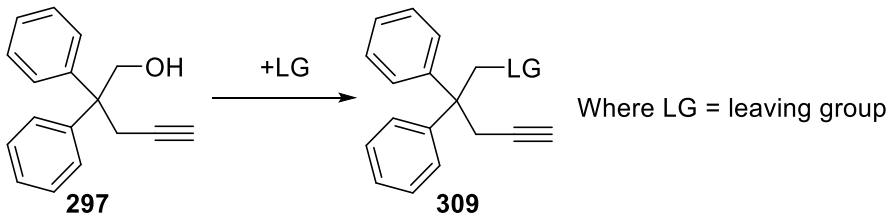
Scheme 77. Generation of allyl sulfide *via* thiouronium salt **303**.

The mechanism of the phase transfer reaction involves a base mediated deprotection of salt **303** in aqueous NaOH to give the naked thio anion which is stabilised by the tetrabutylammonium counterion and is transferred to the organic DCM layer where it reacts with a variety of allyl bromides to give sulfide. This procedure avoids the use of thiols, as most are toxic by inhalation. Furthermore, commercially available bromides can be utilised for this procedure without the need to synthesise foul smelling thiols for alternative methods to these sulfides.



Scheme 78. Proposed mechanism for the phase transfer catalysis to generate sulfides.

Generating thiouronium salts using methods discussed above could provide the required sulfides of interest. Bromination of the alcohol **297** (Table 3, entry 1) led to alkylbromide **309**, using CBr_4 and PPh_3 at 0 °C. No starting alcohol was observed on TLC. However, the bromide degraded upon attempts to purify by column chromatography. Alternativily, mesylating alcohol led to **309b** (Table 3, entry 2), with the remaining excess unreacted mesyl chloride impurity. An attempt to purify these mesylated products from the unreacted mesyl chloride led to degradation under column chromatography. To eliminate mesyl chloride from the crude product mixture, the amount of mesyl chloride used in this reaction was reduced from 1.55 to 1.10 equivalents (Table 3, entry 3) but led to an incomplete reaction with the starting alcohol still remaining on TLC, even when left overnight. Applying gentle heat from rt (18 °C) to 30 °C led to degradation of products (Table 3, entry 4), evident from streaking on the TLC plates. It was also observed that the mesylated alcohol did not survive long and was prone to degradation even when left under an inert atmosphere in the freezer. Therefore, crude mixtures of the activated alcohols were used promptly to generate the thiouronium salts.

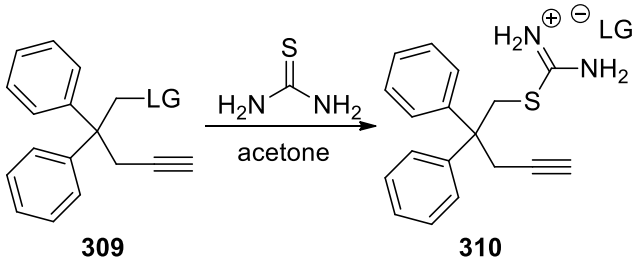


Scheme 79. Activation of alcohol by introducing a good leaving group.

Entry[a]	Reaction conditions	Leaving group	Yield[b] (%)
1	CBr_4 (1.10 eq.), PPh_3 (1.10 eq.) DCM, 0 °C, 1h	-Br, **309a**	Bromination worked[c]
2	MsCl (1.55 eq.), NEt_3 (1.66 eq.) DCM, 0 °C – rt, 1 h	-OMs, **309b**	Mesylation worked[d]
3	MsCl (1.10 eq.), NEt_3 (1.20 eq.) DCM, 0 °C – rt, 20 h	-OMs	5:4 SM:product
4	MsCl (1.10 eq.), NEt_3 (1.20 eq.) DCM, 0 °C – 30 °C, 1 h	-OMs	degradation

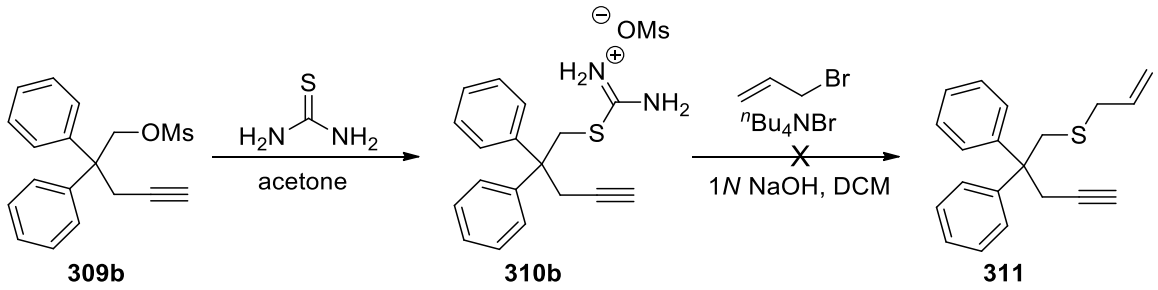
Table 3. [a] Reactions were carried out on a 0.1 mmol scale with respect to alcohol. [b] Isolated yields after flash column chromatography. [c] Brominated product degraded on column therefore was not isolated and was used crude. [d] Mesylated product was not isolated and the excess MsCl was carried through to the next reaction step.

Nucleophilic substitution of bromide **309a** by thiourea gave thiouronium salt **310** by TLC analysis but, the purification of the salt by filtration failed due to degradation (Scheme 80). Reaction of the crude mixture of mesylated alcohol **309b** and thiourea led to a very hygroscopic product which soon liquefied. Preforming the filtration under a closed argon system and using dry toluene also led to unisolable products.



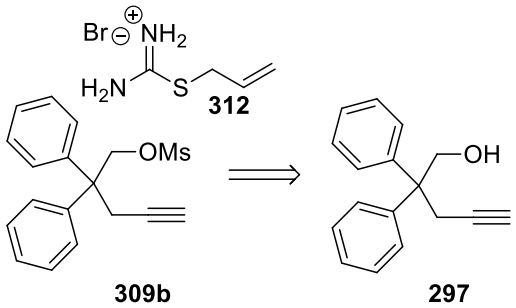
Scheme 80. Reaction of mesylated alcohol with thiourea to form crude thiouronium salt.

To successfully prepare sulfide products, a crude mixture of the hygroscopic thiouronium salt **310b** was promptly used in the next step (Scheme 81). However, these salts were very hygroscopic and therefore did not survive the phase transfer allylation conditions.



Scheme 81. Mesylation of alcohol followed by nucleophilic substitution by thiourea failed.

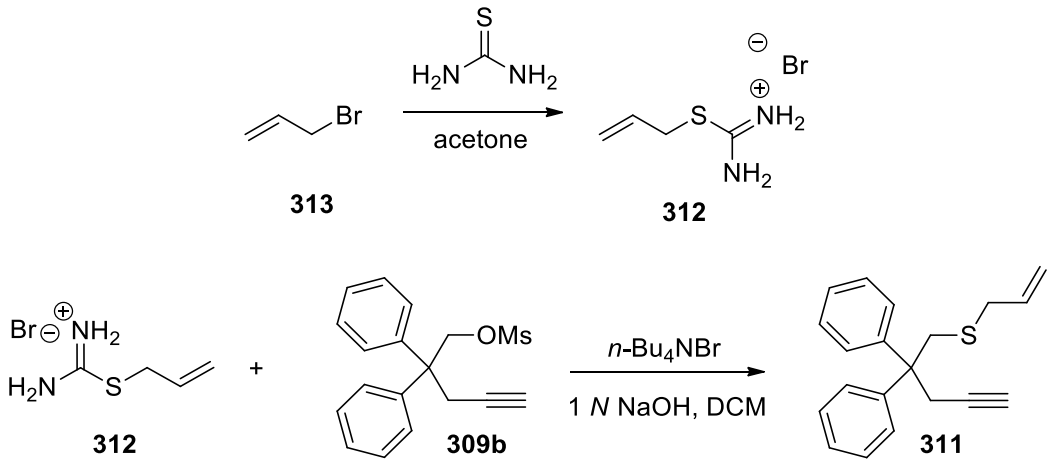
With the failed attempts to convert alcohol into sulfide an alternative approach was investigated. The reaction of mesylated alcohol **309b** with thiouronium salt **312** to give the desired sulfide was tested (Scheme 82). This strategy avoids the preparation and isolation of the very hygroscopic and problematic thiouronium salt **310** and instead makes use of the synthetically simple allylthiouronium salt **312** (Scheme 81). Moreso, this approach gets to the final product in one less step compared to the initial synthetic approach. The generation of thiouronium salt by use of a cheap and commercially available allyl bromide, allows large scale preparations and lower yields to be accommodated.



Scheme 82. Retrosynthetic analysis to reveal suitable synthons.

Allyl bromide was reacted with thiourea in acetone solvent by stirring overnight at room temperature to yield thiouronium salt **312** that readily precipitated. No problems with the

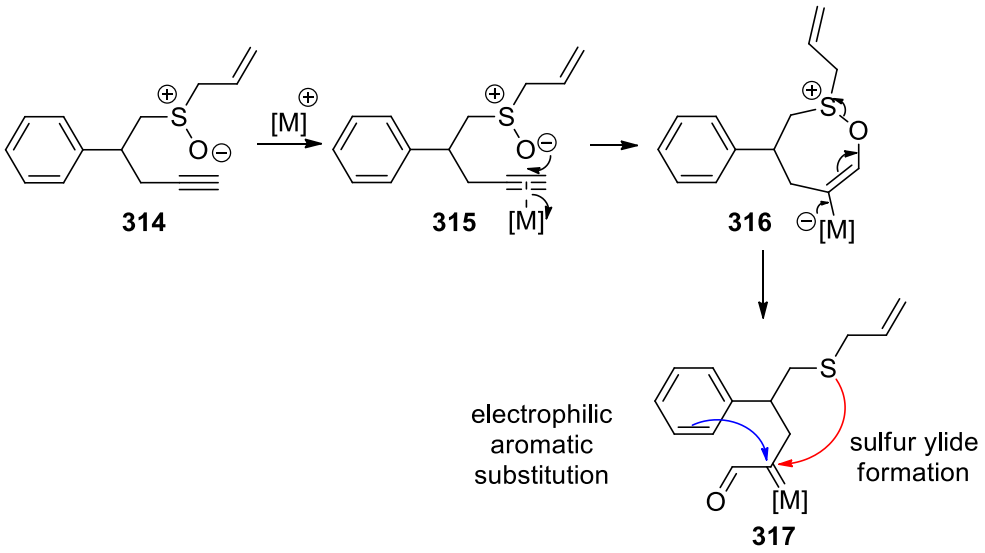
white crystalline precipitate were encountered and it was stable towards atmospheric water. Furthermore, the salt was isolated in an excellent yield and used in the next step without further purification. However, reaction of this salt with mesylated alcohol led to a complex mixture of products with several close spots on TLC making it difficult to separate the desired sulfide product from the complex mixture of products with several spots coeluting. Analysis of the crude ^{1}H NMR and attempted purification did not confirm the formation of the desired product.



Scheme 83. Generation and reaction of thiouronium salt with mesylated alcohol to yield sulfide.

To summarise, synthesis of sulfoxide starting precursors were successful for the 4-cyclohexyl substituted compounds by methods previously used by the Davies group[62], but were unsuccessful in preparing 4-diphenyl substituted sulfoxides and clean products were not obtained.

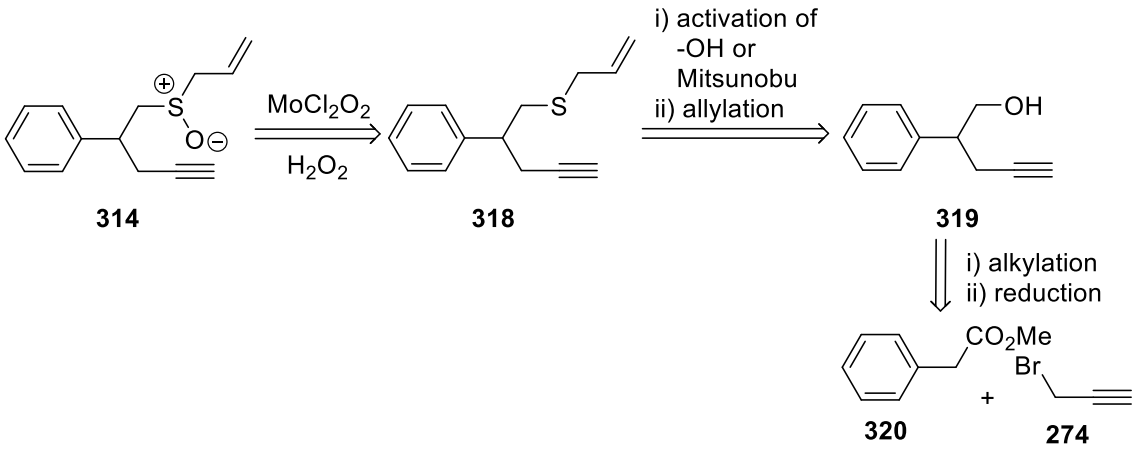
As a result of these problems, preparation of the less hindered mono-phenyl equivalent **314** was explored to test the sulfur ylide *versus* electrophilic aromatic substitution hypothesis.



Scheme 84. Sulfur ylide *vs* electrophilic aromatic substitution hypothesis for mono-substituted sulfoxide.

2.3.3 Preparation of mono-substituted sulfoxide

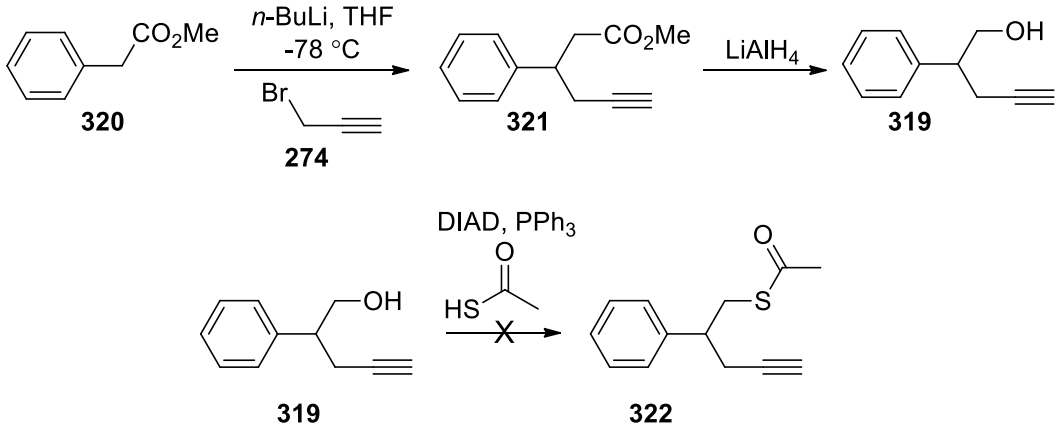
Preparation of starting material was planned using methods already described and used before.



Scheme 85. Retrosynthesis analysis for the preparation of mono-substituted sulfoxide.

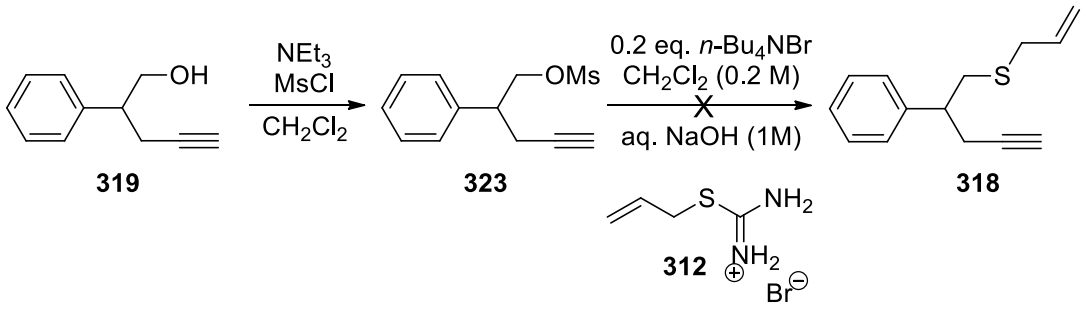
Deprotonation of methyl-2-phenylacetate **320** followed by allylation with propargyl bromide **274** led to the ester **321** in excellent yield of 95%. Reduction of **321** by lithium aluminiumhydride yielded alcohol **319** in 84% after flash column chromatography. However, attempts to introduce sulfur failed. A Mitsunobu reaction led to no desired formation of the thioester **322** and the starting material was fully consumed as analysed by

TLC. This suggested that crude mixture degraded on TLC, evident from streaking of the product spot.



Scheme 86. Sequence of reactions to synthesise the mono-substituted thioester.

Activation of the alcohol **319** by mesylation was attempted but again it proved difficult to isolate *via* column chromatography, and therefore was used crude in the next step. Reacting mesylated alcohol **323** with allylthiouronium salt **312** led to a mixture of unknown products which were not clearly resolved by TLC.

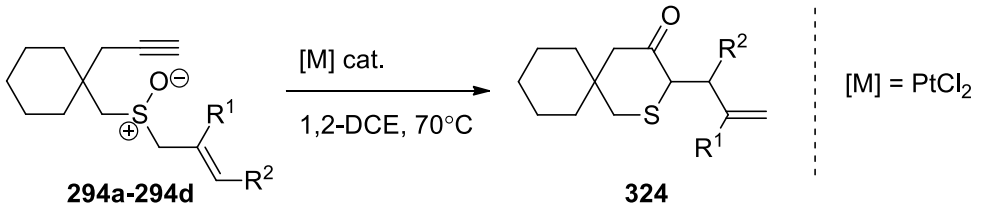


Scheme 87. Attempt to prepare sulfide **318** *via* a nucleophilic substitution reaction.

Unfortunately, the test of how facile electrophilic aromatic substitution is over sulfur ylide formation did not go as anticipated due to the issues concerning the preparation of the starting precursors. However, the previously prepared cyclohexyl substituted sulfoxides **294a**-**294d** were not discarded and were used to provide further examples of the chemistry already observed by the Davies group.[62]

2.3.4 Further examples of sulfur ylide formation *via* gold carbenes

A variety of terminal sulfoxide tethered 1,8-enynes **294a**-**294d** prepared earlier, were subjected to catalytic amounts of $PtCl_2$ (5 mol%), in 1,2-dichloroethane at 70 °C to give cyclised heterocyclic products in reasonably good yields. In this transformation simple starting sulfoxide precursors are transformed into complex structures forming new C-O, C-S and C-C bonds in only one-step under π-metal acid catalysis. As well as unsubstituted 1,8-enynes (Table 4, entry 1), α and β-substituted 1,8-enynes (Table 4, entry 2-4) led to the formation of 6-membered sulfur heterocycles. An α-phenyl substituted 1,8-enyne led to the formation of a new stereogenic centre with a 2.7:1.0 diastereomeric ratio of the cyclised products (Table 4, entry 2). Although compound **324d** was isolated in modest yield, the synthetic handle of a vinyl bromide may be subsequently used to further functionalise the compound (Table 4, entry 4) *via* palladium coupling reactions, which were not put to the test on this instance. The modest yield of 44% may be as a result of poor stability under flash column chromatography. Attempts to improve the isolated yield of **324d** by using 1% triethylamine to neutralise the silica used for column chromatography had little effect if non on the yield of the recovered cyclised product.



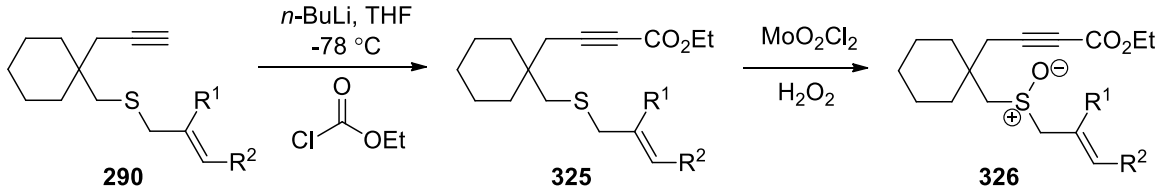
Scheme 88. Various sulfoxides subjected to $PtCl_2$ catalysis.

Entry[a]	R^1	R^2	Time/h	Yield[b] (%)
1	H	H	24	**324a** (65)
2	H	Ph	24	**324b** 1:1 *dr* (57)
3	Me	H	24	**324c** (70)
4	Br	H	24	**324d** (44)

Table 4. [a] Catalyst (10 mol%) was added to a solution of sulfoxide **294a-294d** in 1,2-dichloroethane (0.2 *N*) in a sealed Argon purged Schlenk tube and heated to 70°C for 18 h. [b] Isolated yields after flash column chromatography.

Internal sulfoxide tethered 1,8-enynes were also prepared, by deprotonation of alkyne followed by nucleophilic addition-elimination reactions with ethyl chloroformate to give an electron deficient alkyne moiety. Chemoselective oxidation of sulfide to sulfoxide using molybdenum dichloride dioxide and hydrogen peroxide was achieved in good yields for a variety of different allyl fragments containing sensitive functionalities. Introducing an ester group onto the terminal alkyne on an unsubstituted allyl moiety where R^1 and R^2 = H gave a mixture of the desired ester substituted alkyne and a unknown impurity that had identical R_f values and so the spots appeared coeluted on TLC and therefore proved difficult to isolate the desired electron deficient sulfur tethered 1,8-enyne (Scheme 89) by column chromatography. It was hoped that oxidation of sulfide to sulfoxide may produce products with resolved R_f values making it possible to separate out the desired sulfoxide from the impurities. This was not the case and the impurity remained coeluted with the desired

product and so this precursor was not pursued further. On the other hand, both, α-substituted (R^1 = H, R^2 = Ph), and β-substituted (R^1 = Br, R^2 = H) allyl fragmented sulfides reacted with ethyl chloroformate upon deprotonation with *n*-butyllithium in 59% and 71% yields to give **325b** and **325d** respectively (Scheme 89). Subsequent chemoselective oxidation of sulfide using Mo(VI) and H_2O_2[79] led to the corresponding sulfoxide in good yields even in the presence of a sensitive vinyl bromide group.

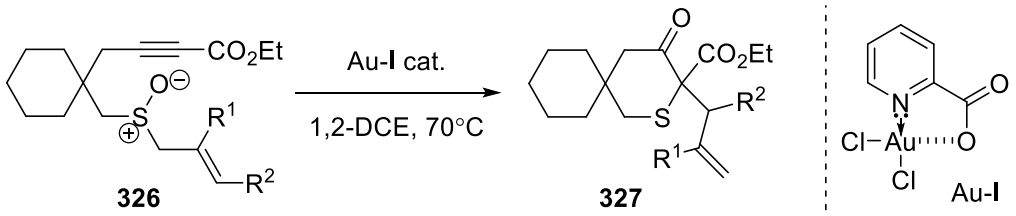


R^1 = H, R^2 = Ph, **325b**, 59%
R^1 = Br, R^2 = H, **325d**, 71%

326b, 79%
326d, 70%

Scheme 89. Generation of internal alkyne by addition of an ester group followed by oxidation of sulfide.

Subjecting these internal sulfoxide tethered 1,8-enynes containing an electron deficient alkyne moiety to catalytic amounts of Au-**I** (5 mol%) led to 6-membered cyclised sulfur heterocycles in good yields.



Scheme 90. General catalysis reaction of internal sulfoxide tethered 1,8-enynes.

Entry[a]	R^1	R^2	Time/h	Yield[b] (%)
1	H	Ph	4	**327b** 59
2	Br	H	4	**327d** 71

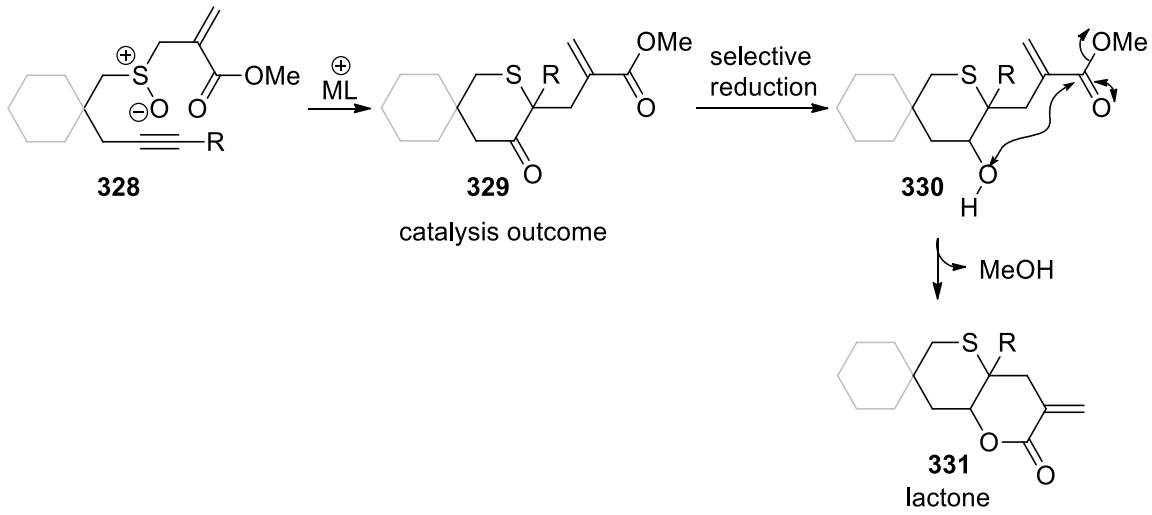
Table 5. [a] Catalyst (5 mol%) was added to a solution of **326** in 1,2-dichloroethane (0.2*N*) in a sealed Argon purged Schlenk tube and heated to 70°C for 18 h. [b] Isolated yields after flash column chromatography.

2.3.5 Conclusions

The test to see how facile sulfur ylide formation is over electrophilic aromatic substitution was not performed due to problematic synthesis of starting materials. However, further examples of sulfur heterocycles prepared from sulfoxides under $PtCl_2$ or Au-**I** catalysis was achieved successfully. As for the terminal sulfoxides, the ester substituted sulfoxides also underwent an initial oxygen attack in a 6-*exo*-dig fashion. This was expected for the later, due to the induced electron deficiency by the ester group at the β-carbon position. For the terminal systems an initial 7-*endo*-dig cyclisation is possible and would lead to a mixture of products (Section **2.1**, page 50-51), but the 6-membered heterocycles were the only products isolated. These examples will be directly compared to electron rich sulfoxide systems looked at later on in section **2.5**.

2.4 Post-catalysis-tandem cyclisations

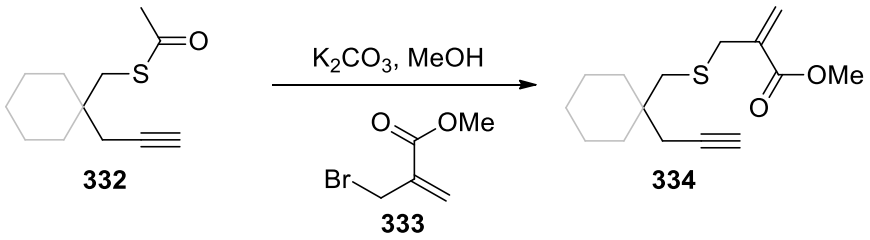
Using the sulfur ylide chemistry as the basis for domino reactions by incorporating more functionality on the allyl group was considered as a means to achieve more powerful, complexity inducing processes. The first target was to introduce a β-substituted methylester allyl moiety which under the sulfur ylide protocol may lead to the cyclic precursor **329** under standard conditions (Scheme 91). Selective reduction of the ketone in the cyclised sulfur heterocycle to the alcohol in the presence of the methyl ester, should lead to highly substituted and potentially useful exo-methylene lactone structures on elimination of methanol.



Scheme 91. Lactone formation by an intramolecular nucleophilic addition-elimination reaction.

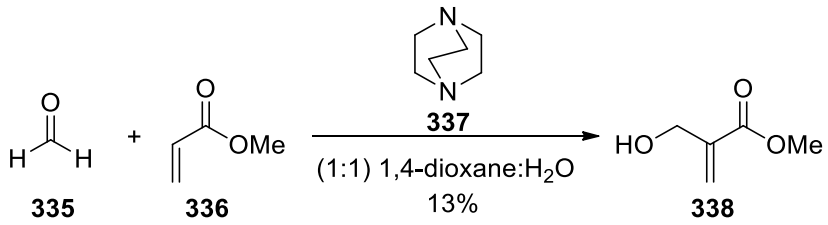
2.4.1 Preparation of starting material

The strategy was to apply the standard preparations using a more functional allyl moiety (See page 56-57 for thioether preparation) under potassium carbonate deprotection of the thioester group (Scheme 92).



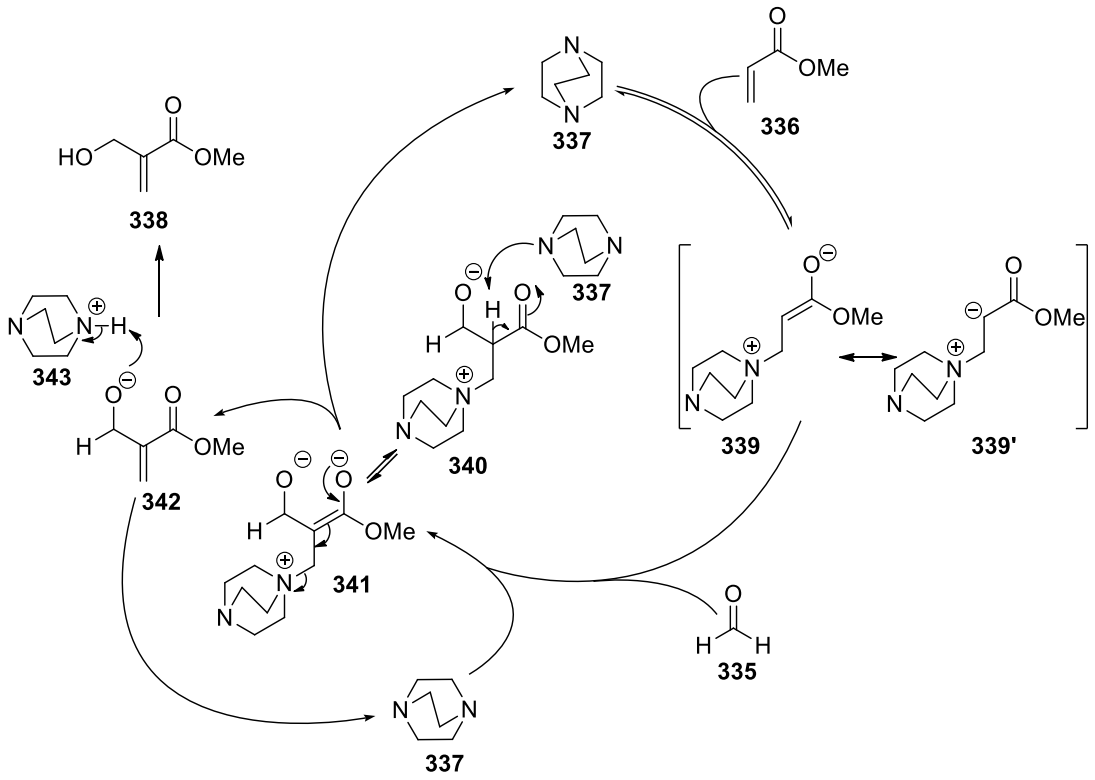
Scheme 92. Planned introduction of substituted ally moiety to thioether using K_2CO_3 in methanol.

Methyl 2-(hydroxymethyl)acrylate was prepared using Hu's method (Scheme 93).[83] Commercially available methyl acrylate was coupled to paraformaldehyde catalysed by stoichiometric amounts of DABCO (1,4-diazabicyclo-[2.2.2]-octane) base in a 1:1 binary solvent mixture of 1,4-dioxane and water and allowed to stir at room temperature to give the desired alcohol **338** in a poor yield of 13% after purification by Kugelrohr distillation (2 mbar at 60 °C).[84]



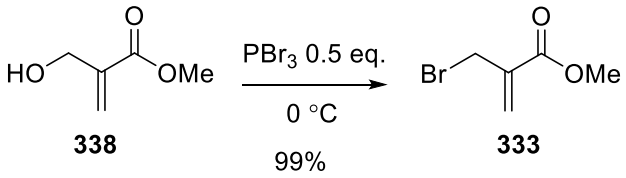
Scheme 93. Bayliss-Hillman reaction of methyl acrylate and paraformaldehyde using DABCO.

The Bayliss-Hillman reaction[85] proceeds *via* an initial addition of the amine catalyst **337** to the activated methyl acrylate alkene **336** to form a stabilised nucleophilic anion **339**. Nucleophilic addition of this *in situ* generated anion **339'** to paraformaldehyde **335** and subsequent $E_{cb}1$ elimination of the amine catalyst **341**, leads to the formation of **338**.



Scheme 94. Proposed mechanism for the Bayliss-Hillman reaction.

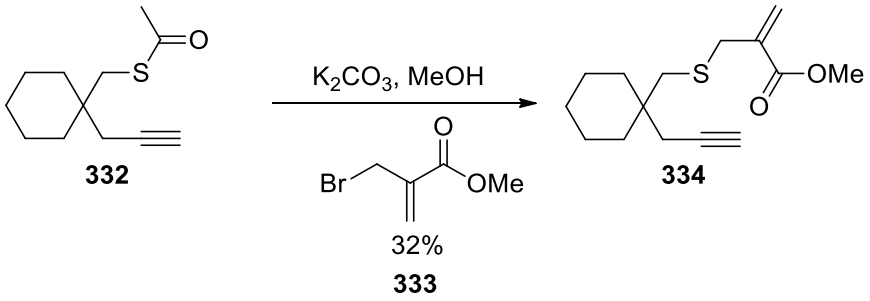
Bromination of **338** using phosphorus tribromide in diethyl ether (0.5*N*) at 0 °C led to the preparation of methyl 2-(bromomethyl)acrylate **333** in quantitative yield (Scheme 95). This product was highly unstable, even in a sealed tube under inert conditions, where rapid colour change from colourless to brown was indicative of degradation and so was used promptly in the next step.



Scheme 95. Preparation of methyl 2-(bromomethyl)acrylate.

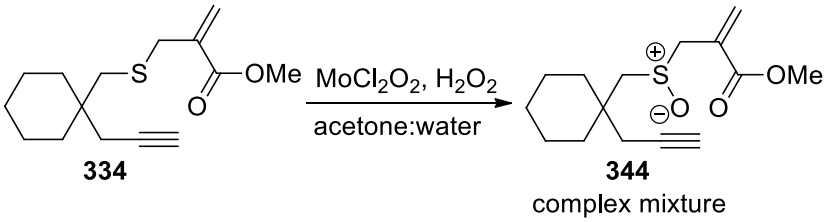
With the two synthetic entities in hand, thioester **332** was reacted with 2-(bromomethyl)acrylate **333** in the presence of potassium carbonate in methanol to generate sulfide **334**. The sulfide along with an undesired impurity was isolated in poor yield of 32%

after column chromatography. The impurity was not isolated and characterised due to its high volatility. The desired sulfide was unstable on a silica packed column and had a tendency to degrade, which may explain the low yield of this outcome.



Scheme 96. Introduction of β-substituted allyl moiety to generate sulfide **334**.

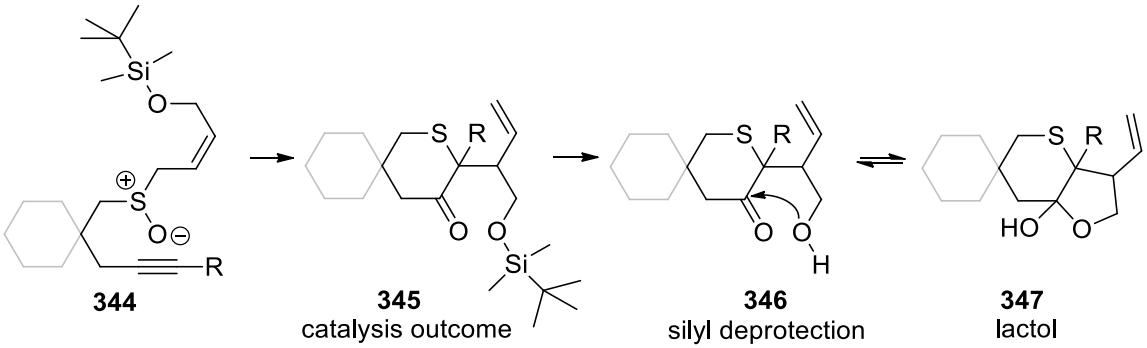
Compound **334** proved to be unstable degrading over time. Despite neutralising the silica by the addition of 1% triethylamine in the eluent **334** was only isolated in impure form and so the crude was subjected to oxidation hoping to be able to separate after this stage. However, oxidation of sulfide led to a complex mixture of the desired sulfoxide **344** and an oxidised impurity that coeluted on TLC.



Scheme 97. Chemoselective oxidation of sulfide to form sulfoxide.

With the unsuccessful preparation of sulfoxide **344**, other functionalised allyl moieties were investigated. It was envisioned that complex lactols could be generated by post catalysis intramolecular nucleophilic addition-cyclisations if silylether substituted allyl sulfoxide precursors lead to cyclised products under $PtCl_2$ or Au-**I** catalysis. Induced domino-reactivity by deprotecting the silyl group could lead to intramolecular lactolisation to give complex lactol scaffolds **347**. The ease of preparing sulfoxide precursors coupled with the

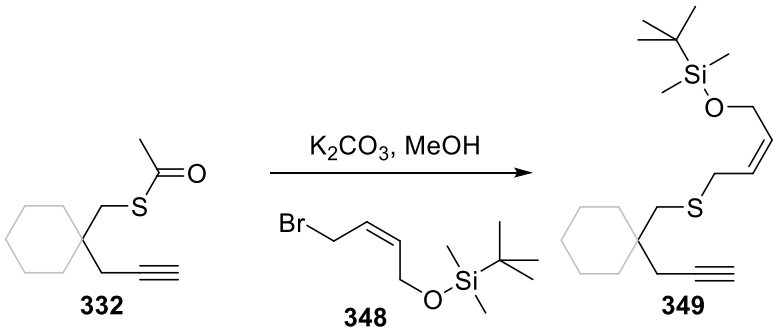
catalytic approach to cyclic sulfur heterocycles could allow the access to complex biologically active compounds in only two steps. This method may avoid lengthy laborious procedures, traditionally employed to access lactol scaffolds.



Scheme 98. Possible domino-reactivity.

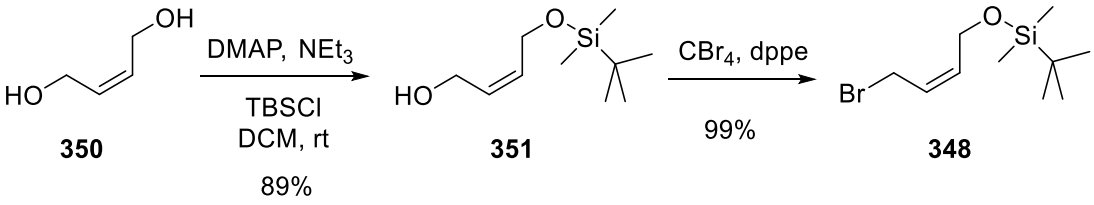
2.4.2 Preparation of starting material 349

The synthetic approach used before to prepare these sulfides was explored, but using α-substituted allyl bromide **349** instead (Scheme 99).



Scheme 99. Sulfide preparation from the reaction of thioether and substituted allyl bromide **348**.

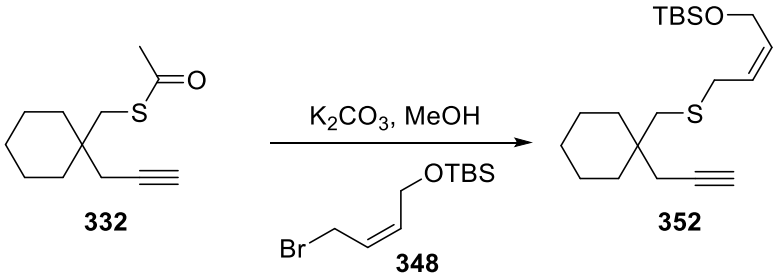
Mono-silylation of *cis*-betene-1,4-diol **350** with tetrabutyldimethylsilylchloride (TBSCl) in the presence of DMAP (4-dimethylaminopyridine) and triethylamine led to the desired silylated product **351** in excellent yield (Scheme 100). Appel type bromination of the unprotected alcohol **351** by tetrabromomethane in the presence of diphenylphosphoethane led to bromide **348** in excellent yield, which was used in the next step without further purification due to its instability detected by TLC analysis.



350 **351** **348**

Scheme 100. Preparation of (*Z*)-((4-bromobut-2-en-1-yl)oxy)(tert-butyl)dimethylsilane.

Then thioester **332** was reacted with bromide **348** in the presence of potassium carbonate in methanol to generate sulfide **352** in 20% yield but was prone to degradation on silica, hence its low yield after column chromatography (Scheme 101).

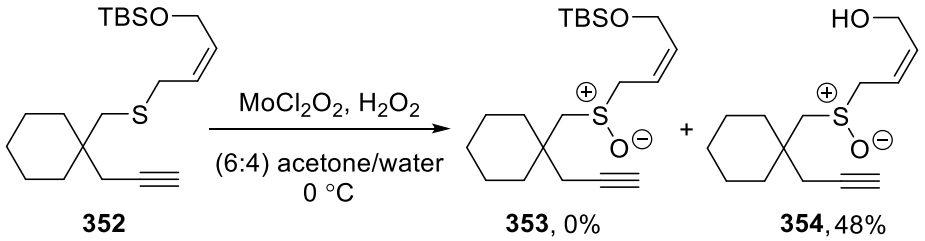


332 **348** **352**

20%

Scheme 101. Reaction of thioether with bromide **348** to yield sulfide **352** in low yield.

Although sulfide **352** was isolated in low yield, it was-nontheless subjected to chemoselective oxidation using $MoCl_2O_2$ and H_2O_2 to unexpectedly give sulfoxide **354** in 48% yield where none of the expected TBS protected alcohol sulfoxide **353** was observed.

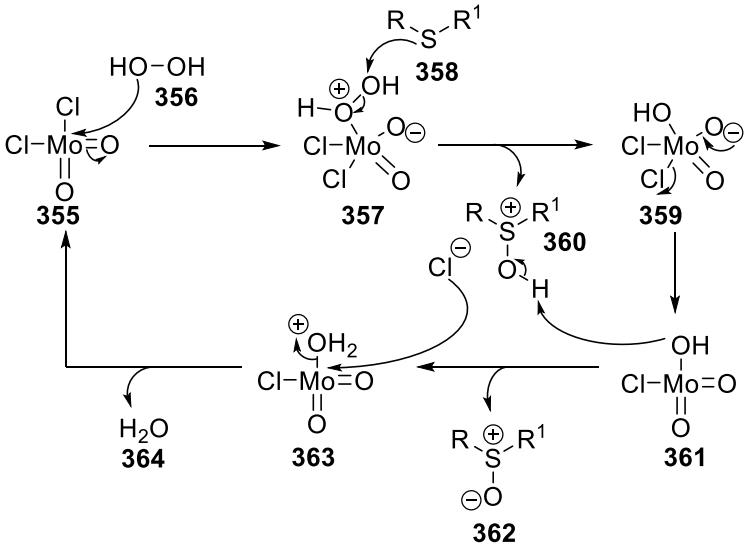


352 **353**, 0% **354**, 48%

Scheme 102. Chemoselective oxidation of sulfide **352** to sulfoxide **354**.

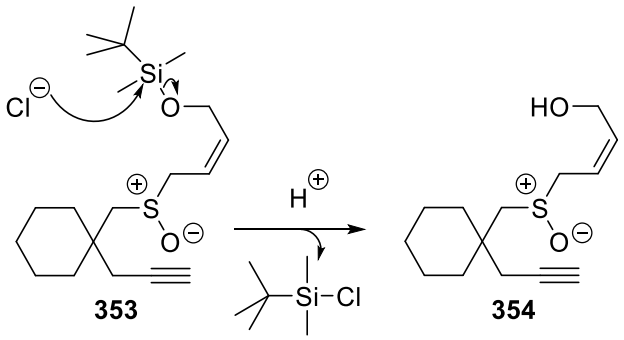
During the oxidation process hydrogen peroxide **356** reacts with the catalyst $MoCl_2O_2$ **355** to give **357** (Scheme 103). Nucleophilic attack of sulfide **358** on **357** gives sulfonium salt **360**, which is stabilised by a chloride anion dispersed from catalyst intermediate **359**.

Deprotonation of sulfonium salt **360** leads to the desired sulfoxide **362** and regeneration of the catalyst **355**.



Scheme 103. Proposed mechanism for chemoselective oxidation of sulfide to sulfoxide.

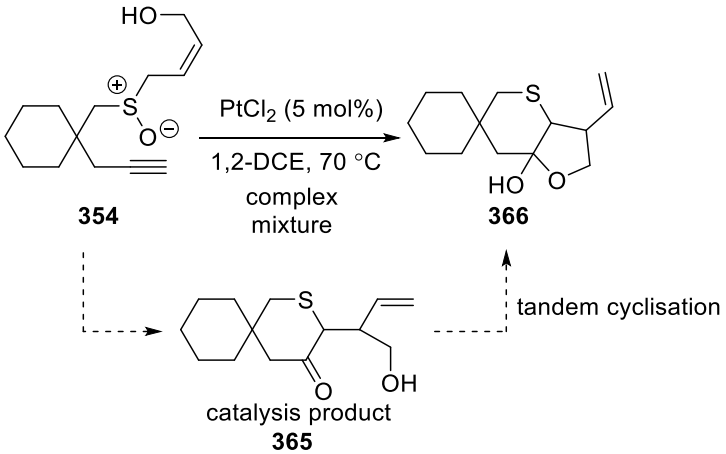
The isolation of the TBS deprotected sulfoxide is induced by a chloride anion attack onto the silyl group allowing cleavage of the Si-O bond (Scheme 104). The formation of a strong Si-Cl bond is the driving force of this reaction and aids the cleavage of the Si-O bond to give **354** after protonation. In the research proposal (Scheme 98) a free hydroxyl group is required to allow lactonisation. Coincidentally removal of the TBS could lead to complex lactones from sulfoxides in only one step, under π-acid catalysis.



Scheme 104. Chlorine anion deprotection of silyl ether to give alcohol.

It was questioned whether the free alcohol would survive catalysis conditions to yield cyclic sulfur structures. The close proximity of the sulfoxide oxygen moiety should allow its rapid addition across the triple bond under π-acid catalysis, as apposed to, the competitive intramolecular O-H addition.

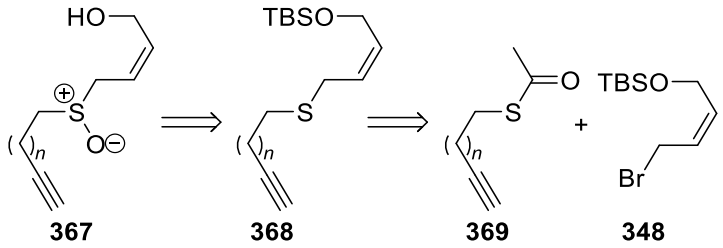
To test this hypothesis, sulfoxide **354** was subjected to catalysis using $PtCl_2$ (5 mol%), in 1,2-dichloroethane (0.2*N*) at 70 °C. Complete conversion of starting material after two hours gave a mixture of products observed by TLC analysis. By analysis of the crude ^{1}H-NMR two major products were generated by catalysis. One of the products was lactone **366** from a one-pot intramolecular tandem cyclisation reaction. For the other major product, the ^{1}H-NMR peaks did not match the peaks previously observed for these π-acid catalysed cyclised products **365** (See section **2.3.4**). Unfortunately, attempts to isolate these interesting scaffolds by column chromatography led to degradation due to instability on silica. Therefore, the study was continued using simpler starting precursors in the hope that the cascade products could be isolated and characterised.



Scheme 105. $PtCl_2$ catalysed cyclisations to give products from possible tandem reactivity.

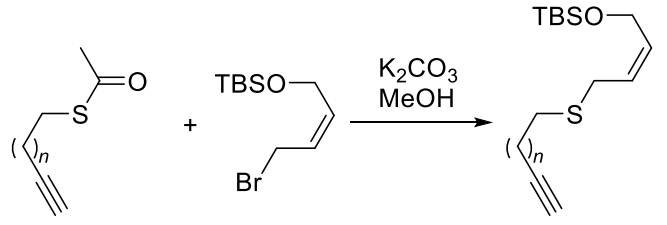
2.4.3 Preparation of simpler sulfoxide systems

A simpler starting sulfoxide precursor **367** was planned losing the cyclohexyl unit and following a similar preparation to that previously reported. Sulfoxide with TBS deprotected alcohol **367** could be prepared by $MoCl_2O_2$ and H_2O_2 oxidation conditions (Scheme 106). Sulfide **368** may be generated from base catalysed coupling of thioether **369** and α-substituted allyl bromide **348**.



Scheme 106. Reterosynthetic analysis of a simpler sulfoxide starting precursor.

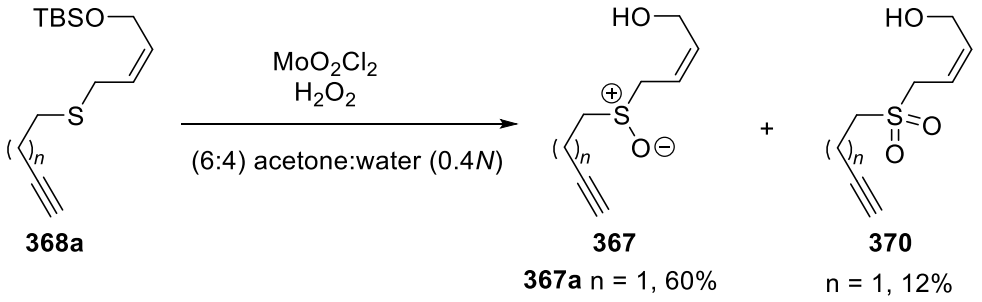
The thioethers **369a** and **369b** were prepared in one step by a Mitsunobu reaction from commercially available butynol, n=1 or pentynol, n=2 depending on the required chain length (See section **2.1**). Nucleophilic substitution of bromide **348** by thioethers **369** using potassium carbonate led to the formation of sulfides **368a**, n = 1 and **368b**, n = 2 in excellent yields.



Scheme 107. Forward synthesis of sulfide **379**.

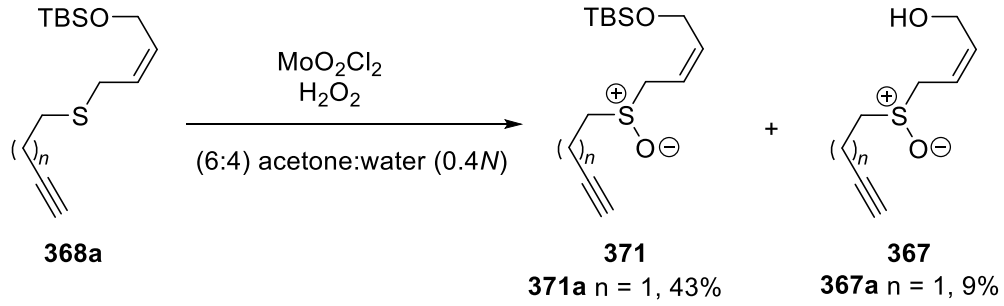
Chemoselective oxidation of the sulfide to sulfoxide led to two major products. The subsequent isolation of products by column chromatography included TBS deprotected sulfoxide in 12% and sulfone in 60%. The reaction was monitored by TLC after 1 h by

which time the sulfide over-oxidised to the unwanted sulfone. The sulfone would not lead to sulfur ylide formation, and was not considered for π-acid catalysis.



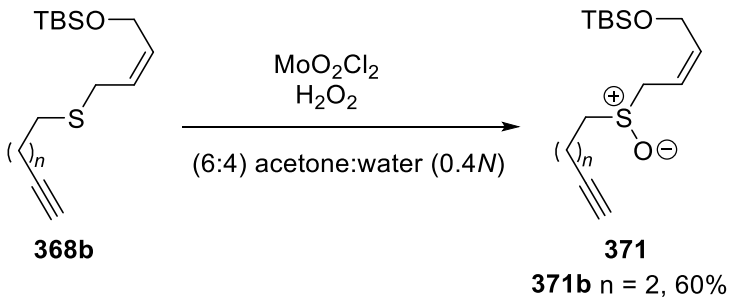
Scheme 108. Oxidation of sulfide leading to sulfoxide **367** and sulfone **370**.

This reaction was repeated, monitoring the reaction by TLC every 20 minutes to avoid over oxidation to sulfone products. This time the reaction was complete after 20 minutes (starting material fully consumed) to give TBS protected sulfoxide in 43% yield and TBS unprotected sulfoxide product in 9% yield.



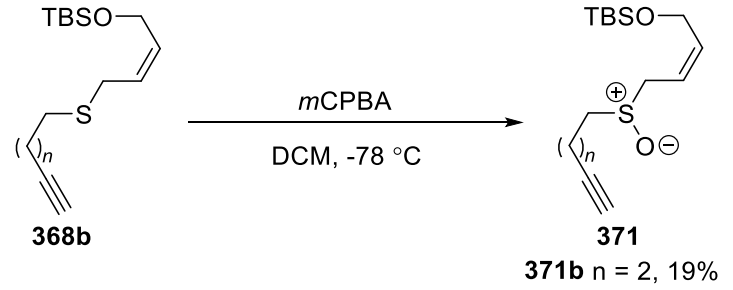
Scheme 109. Reaction monitored every 20 minutes to yield TBS protected sulfoxide product.

The reaction was repeated again and TLC was run every 5 minutes to achieve access to only one product, the TBS protected sulfoxide. In 5 minutes sulfide **368b** was transformed to the TBS protected sulfoxide **371b** isolated in 60% by column chromatography. Although the desired sulfoxide was achieved, the fast conversion of starting material to product was practically difficult to work with; therefore other oxidation conditions were looked at.



Scheme 110. Reaction monitored every 5 minutes to give only one product.

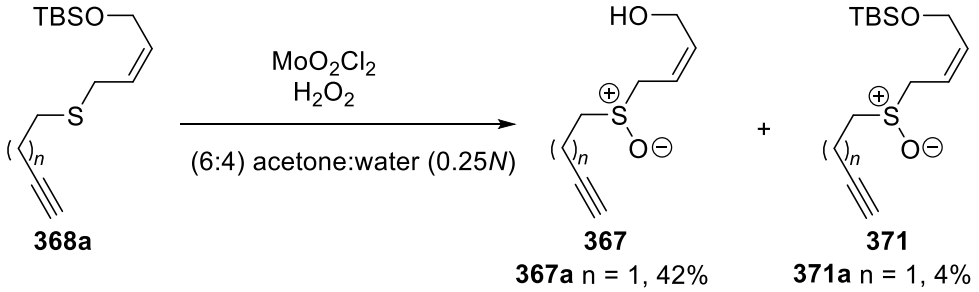
The use of *m*CPBA (*meta*-chloroperoxybenzoic acid) in dichloromethane at -78 °C in 1 h (monitored by TLC) also led to sulfoxide **371b** in 19% yield. Although the entire starting sulfide precursor **368b** was fully consumed, the resulting low yield was due to degradation of products in dichloromethane. To test the stability of sulfoxides **371a** and **371b**, they were left in two solvents, dichloromethane and acetone in separate sealed vials overnight. The resulting dichloromethane solution colour went from colourless to a brown solution, whereas the acetone solution remained colourless. The colour change of the sulfoxides left in dichloromethane overnight and streaking by TLC analysis of these solutions was indicative of degredation and reactions using DCM was avoided.



Scheme 111. Chemoselective oxidation using *m*CPBA.

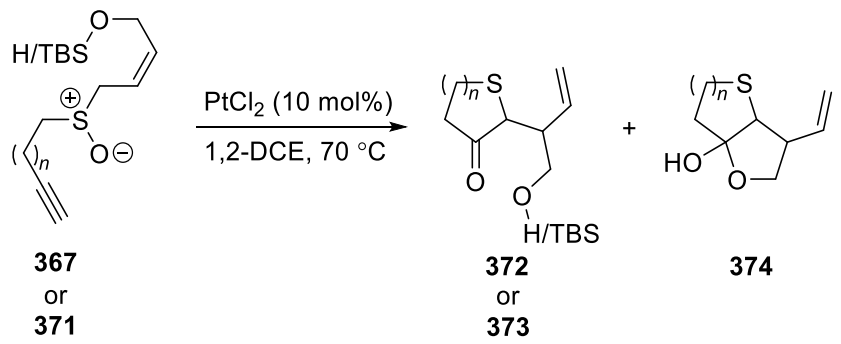
The preparation of TBS unprotected sulfoxide **367** was still required for domino lactol formation, post catalysis. It has already been observed that leaving the reaction running too long under oxidation conditions leads to the formation of the over-oxidation side product sulfone.

It was thought that dilution of the oxidation reaction from 0.4*N* to 0.25*N* with all other variables kept constant may influence the rate of regeneration of catalyst *versus* deprotection of silyl group, by the chloride anion (See Scheme 103 for mechanism). Delightfully, using the modified oxidation conditions led to the alcoholic sulfoxide **367a** as the dominant product in 42% yield with only small amounts of the undesired TBS protected sulfoxide product **371a** in 4%. With full conversion of sulfide **368a**, the rest of the material besides the products shown was not isolable due to degradation of the desired sulfoxides (Scheme 112).



Scheme 112. Modified reaction conditions to give more of the desirable TBS unprotected product **367a**.

With these useful modifications the scope of the catalytic cyclisation process to form a wide range of sulfur heterocycles or subsequent post-catalysis domino reactivity was tested. Subjecting TBS-protected sulfoxide tethered 1,8-enynes, where n = 2 (Table 6, entry 1) to $PtCl_2$ (10 mol%) in 1,2-dichloroethane at 70 °C led to the 6-membered thiopyranone products in 43% yield with a 1:1 diastereomeric ratio. Free hydroxyl sulfoxide tethered 1,7-enyne, where n = 1 (Table 6, entry 2) gave the thiophenone product in 19% yield and the post-catalytic tandem lactol product in 37% yield after separation by column chromatography.



Scheme 113. General equation for catalysis varying chain length (n) and –OH protection.

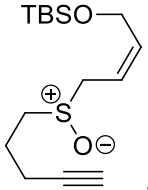
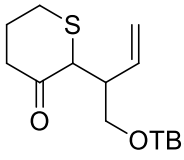
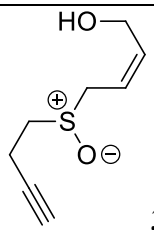
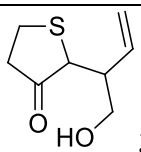
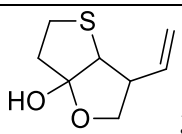
Entry[a]	Sulfoxide	Product	Domino	Yield[b] (%)
1	 **371b**	 **373b**		43(1:1 *dr*)
2	 **367a**	 **372a**	 **374a**	**372a** 19% (1:1.65 *dr*) **374a** 37% (1:1 *dr*)

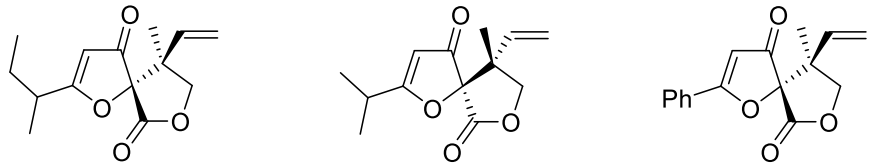
Table 6. Catalysis outcomes. [a] Catalytic amount of $PtCl_2$ (10 mol%) was added to a solution of starting sulfoxide precursor in 1,2-dichloroethane (0.2*N*). The reaction mixture was stirred and heated to 70 °C until reaction complete (monitored by TLC). [b] Isolated yields after silica column chromatography.

To summarise, hydroxy sulfoxides are required for tandem cyclisation to give lactols under π-acid catalysis therefore, TBS protected hydroxy sulfoxides were prepared. The TBS group can be easily removed using TBAF and an aqeous work-up.[86] During $MoCl_2O_2/H_2O_2$ catalysed oxidation of sulfides to sulfoxides, it was discovered that the cleavage of the Si-O bond is aided by the *in situ* generation of Cl^- to generate the hydroxyl sulfoxide. This has allowed us to access the desired hydroxyl sulfoxide precursor required for lactol formation in only two synthetic steps. Modification of the oxidation conditions allows access, to either TBS protected sulfoxides, or hydroxyl sulfoxides.

TBS protected sulfoxide **371b** led to the sulfur hetrocyclised product under catalysis as expected from previous results. More excitingly sulfoxide precursor **367a** led to the formation of sulfur heterocycle **372a** plus the hypothesised tandem cyclised lactol ptoduct **374a**. This chemistry can be applied to achieve more complex scaffolds.

2.4.4 Hyperolatone

A retrospective literature search was carried out to find oxygen derivatives of these π-acid catalysis derived dihydrothio-lactols and lactones. Hyprolactones represent a growing class of metabolites found in *Hypericum Chinese L*[87] (Scheme 114).



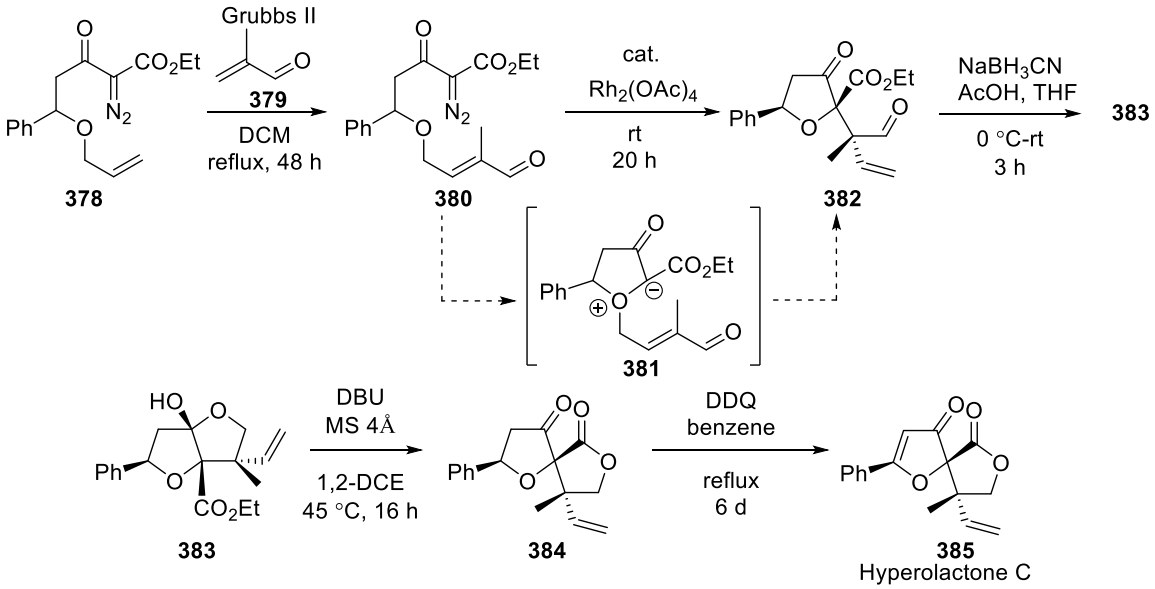
375 Hyperolactone A | **376** Hyperolactone B | **377** Hyperolactone C

Scheme 114. Hyperolactones found in *Hypericum Chinese L*.

As well as use of chiral precursors to these hyprolactones using laborious techniques,[88] direct synthetic approaches have also been looked at. Here selected synthetic methods are presented out of many.[89] Hyprolactone C is known to be a metabolite of interest as its extended conjugation through the phenyl substituent resembles other known antiviral agents.[90]

Hodgson and coworkers[91] made use of consecutive alkene cross metathesis followed by oxonium ylide formation-rearrangement reactions to prepare hyperolactone C in a one-pot operation. α-Diazo-β-ketoesters bearing allylic ether moieties underwent highly stereoselective Ru-catalysed alkene cross methathesis followed by $Rh_2(OAc)_4$-catalysed oxonium ylide formation then [2,3]-sigmatropic rearrangement with high diastereoselectively to yield hyperolactone. Stereoselective cross-metathesis of **378** with gem-disubstituted olefin **379** using Grubbs II (5 mol%) catalyst in dichloromethane at

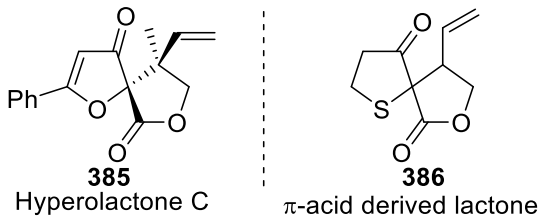
reflux for 48 h gave the *E*-enal **380** in 21% yield (Scheme 115). Dirhodiumtetraacetate catalysed oxonium ylide formation-rearrangement, led to the formation of aldehyde **382** *via* a diastereoselective [2,3]-sigmatropic rearrangement of intermediate **381**. Reduction of aldehyde **382** was achieved by sodium cyanoborohydride to yield a mixture of fused lactols in 80:13:4:3 diastereoisomer ratios. The desired isomer **383** was favoured in 69% yield, which was cleanly isolated from the mixture by column chromatography. Lactonisation of **383** under the influence of DBU gave crude lactone **384**, which was dehydrogenated with DDQ giving hyperolactone C **385**. As previously discussed, use of diazo-compounds and their synthesis may be hazardous and alternative routes to these lactols/lactones using gold chemistry may be beneficial.



Scheme 115. Access to hyperolactone C *via* diazo-compound **380**.

With these interesting methods to lactols, or subsequently lactones, use of π-acid derived lactols through sulfur ylide formation was postulated to generate sulfur derivatives of these biologically active compounds. Synthesising these possible biologically active scaffolds may lead to future work probing the stereochemical outcome of gold catalysis.

Furthermore, the biological activity of these sulfur derivatives in comparison to the oxygen equivalents may also form part of a new and exciting project.

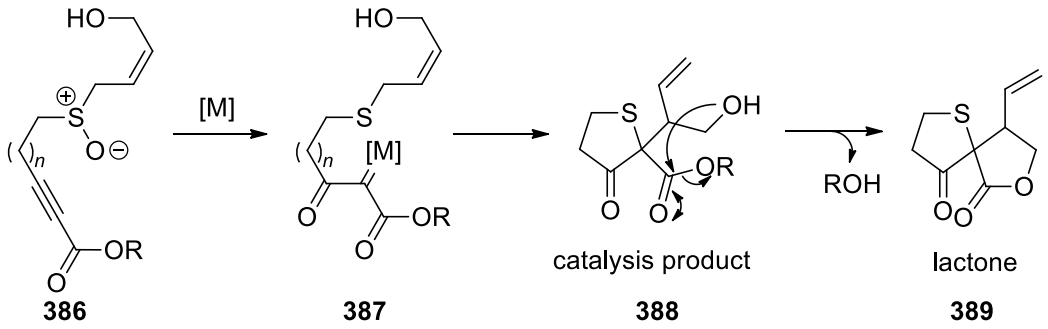


Scheme 116. Similarity of the sulfur derivative.

2.4.5 Preliminary study to access lactones

In light of the transformation in Section **2.4.3**, it was envisioned that sulfoxides containing internal alkynes substituted with an ester group may lead to the formation of spiro lactones which would offer the access to sulfur derivatives of the biologically active Hyperolactone C.[87]

It was postulated that sulfoxides of type **386** will give cyclised sulfur compounds **388** under gold catalysis via α-oxo gold carbenoids **387**. Sulfur heterocycles **388** could undergo possible intramolecular nucleophilic addition-elimination reactions, expelling alkyl alcohol to yield sulfur containing lactones **389** (Scheme 117).

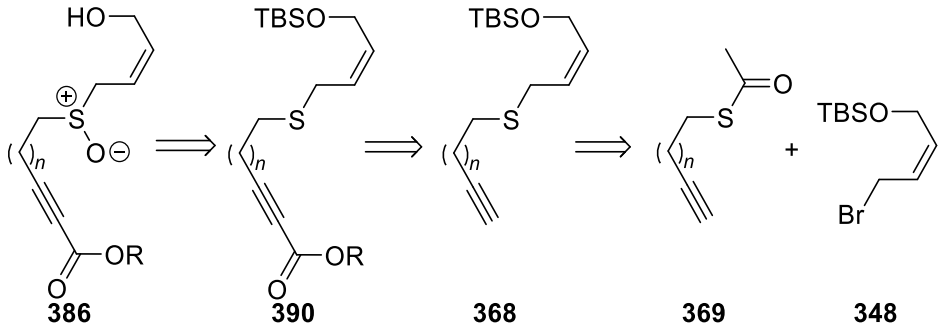


Scheme 117. Formation of lactones from ester substituted sulfoxides *via* gold catalysis.

2.4.6 Preparation of starting material 386

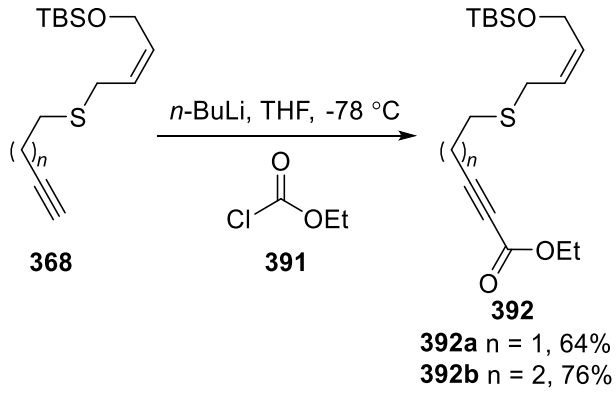
To test this hypothesis, a series of sulfoxide precursors were prepared using known procedures. The ester moiety could easily be introduced by deprotonation followed by

nucleophilic substitution of a suitable electrophile followed by chemoselective oxidation of sulfide to sulfoxide, simultaneously stripping away the TBS protection on the hydroxyl moiety as previously observed.



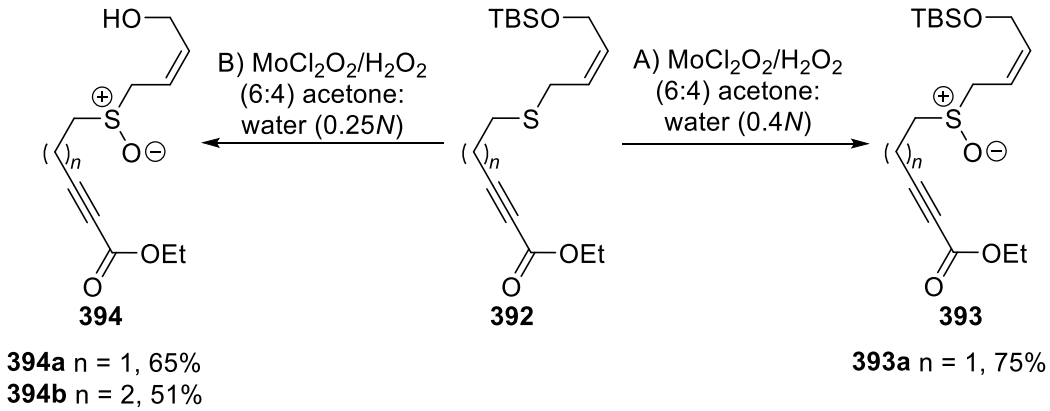
Scheme 118. Retrosynthesis of the preparation ester substituted sulfoxides.

Sulfides **368a** and **368b** (See preparation page 78, Scheme 110) were deprotonated by *n*-butyllithium in tetrahydrofuran, set-up with an acetone and dryice controlled temperature bath at -78 °C. The alkyne anion was generated *in situ* followed by nucleophilic substitution of ethylchloroformate **391** giving ester substituted sulfides **392a** and **392b**.



Scheme 119. Preparation of ester substituted sulfides **392**.

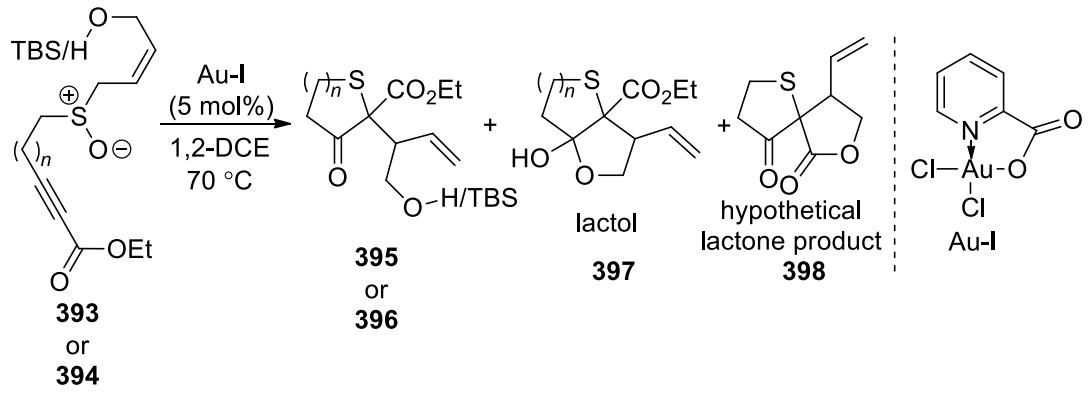
Subjecting sulfide **392** to oxidation conditions described earlier gave both, TBS protected and deprotected sulfoxides, depending on the reaction conditions. Sulfoxide products with the TBS group still intact were formed in good yields, where n = 1 yielded 75% under standard oxidation conditions A (Scheme 120). On the other hand, condition B, resulted in the formation of **394a** where n = 1 and **394b** where n = 2.



Scheme 120. Variable outcomes for oxidation with the use of different concentrations of solvent.

To test the hypothesis above, sulfoxides **393** and **394** were subjected to Au-**I** (5 mol%), in 1,2-dichloroethane at 70 °C. Sulfoxide **393a** led to the standard cyclised product in good yields (Table 7, entry 1). Interesting results were obtained when free hydroxyl sulfoxides **394a** and **394b** were subjected to these catalysis conditions. Preliminary results show that sulfoxide **394a** formed a single diastereoisomer of lactol **397a** as the major product in 38% yield (Table 7, entry 2) after, column chromatography. The other fraction was a complex mixture of two products. From ^{1}H-NMR it is notable that the two existing products are the cyclised sulfur product **396a** and the lactone product **398a** as a result of tandem reactivity. Attempts to isolate and fully characterise these compounds failed as they coeluted on TLC. Sulfoxide **394b** led to a thiopyran fused lactol **397b** in 19% (Table 7, entry 3). This lactol was isolated and characterised but was prone to degradation as evident from unknown peaks in the ^{1}H-NMR specra. Furthermore, degradation was observed when running a 2D TLC experiment that showed streaking of the isolated product. The low yield is due to degradation of **397b** on silica packed column chromatography. Although starting material was fully converted to a complex mixture of unknown products, only the lactol was isolable. This could be due to the instability of the more flexible 6-membered ring of **397b**

and the presence of more isomers in comparison to the rigid 5-membered ring structures **397a** which yielded a single diastereoisomer.



Scheme 121. General catalysis on various sulfoxides under the influence of Au-**I** catalyst.

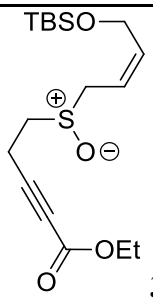
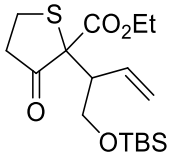
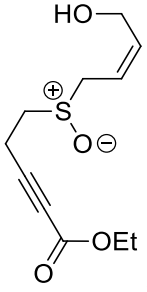
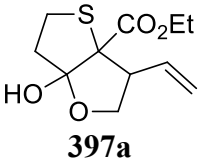
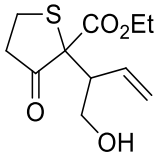
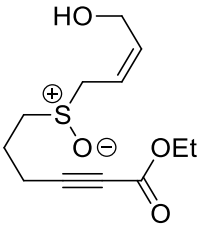
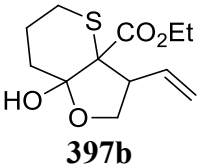
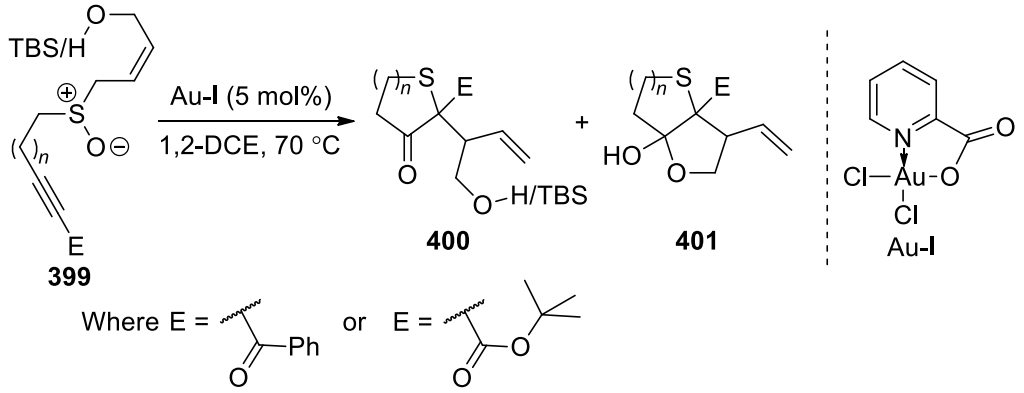
Entry[a]	Sulfoxide	Products	Yield[b] (%)
1	 **393a**	 **395a**	84% (1:1.14 *dr*)
2	 **394a**	 **397a**  **396a** + unknown **398a**	**397a** 38% **396a** +**398a** 31%
3	 **394b**	-  **397b**	19%[c]

Table 7. [a] Catalyst Au-**I** (5 mol%) was added to a solution of sulfoxide in 1,2-dichloroethane (0.2*N*) in a sealed Argon purged Schlenk tube and heated to 70 °C for 18 h. [b] Isolated yields after column chromatography. [c] Low yield due to, degradation of product **397b** at 70 °C.

To summarise, the formation and isolation of the desired lactone has proved difficult however, promising results to lactols provide synthetically useful scaffolds. It has been shown that simple sulfoxide precursors containing a free hydroxyl group undergo a one-pot π-acid process to form new C-C, C-S and C-O bonds and generate three new stereocentres. The aim of the next section is to generate scaffolds of type **397** and determine the stereochemistry by pertinent n*O*e experiments.

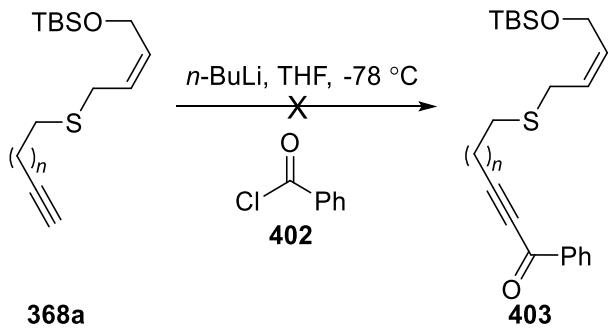
2.4.7 Synthesis of heterocycles capable of tandem cyclisation to give lactols

It was envisioned an electron-withdrawing functional group without a good leaving group (Scheme 122) may prevent the formation of the lactone product, and instead will give, a good yield of the desired lactol (domino product).



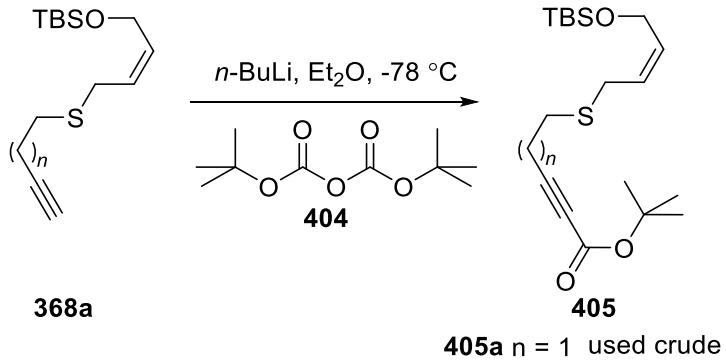
Scheme 122. Reactivity of various ester-substituted sulfoxides to prevent lactone formation with Au-**I**.

In order to assess this hypothesis, preparation of benzoyl and butylcarbonyl-substituted alkynes were looked at. Deprotonation of terminal alkyne **368a** by *n*-BuLi, followed by nucleophilic substitution of benzoyl chloride **402**, did not give benzoyl substituted alkyne **403**. Full consumption of starting sulfide was observed by TLC analysis after 24 h, but led to a complex mixture of unknown products, which degraded by column chromatography in an attempt to isolate the desired product.



Scheme 123. Reaction of sulfide with benzoyl chloride failed.

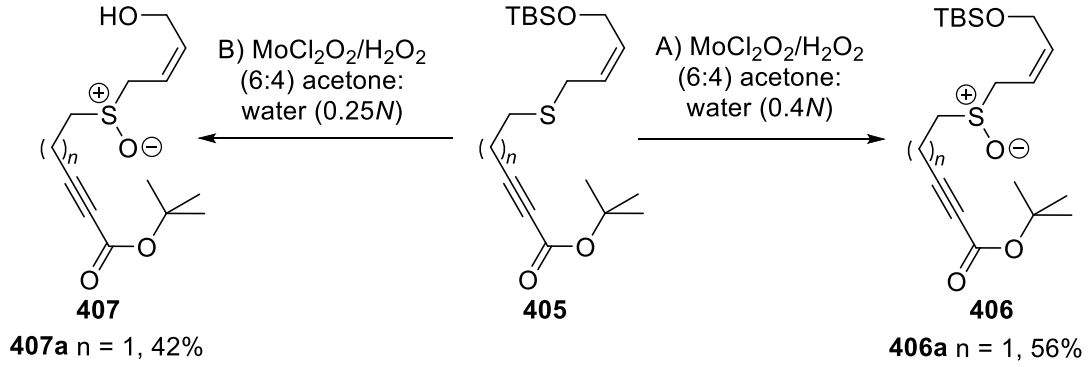
The preparation of *tert*-butyl acetate substituted alkyne was then tested. Sulfide **379a** was deprotonated by *n*-BuLi in diethyl ether at -78 °C and reaction with electrophile di-*tert*-butyldicarbonate **404** led to the clean generation of **405a**. In comparison to the reaction of **368a** with benzoyl chloride (Scheme 123), this reaction proceeded smoothly without giving a complex mixture of unkown side products. However, the ^{1}H-NMR revealed that the unreacted di-*tert*-butyldicarbonate was present after column chromatography and it was later realised that it coeluted with the desired product on TLC. Kugelrohr distillation was used in an attempt to remove the unreacted reagents (2 mbar at 56 °C) but, was unsuccessful in purifying product **405**.



Scheme 124. Preparation of *tert*-butyl acetate substituted sulfide.

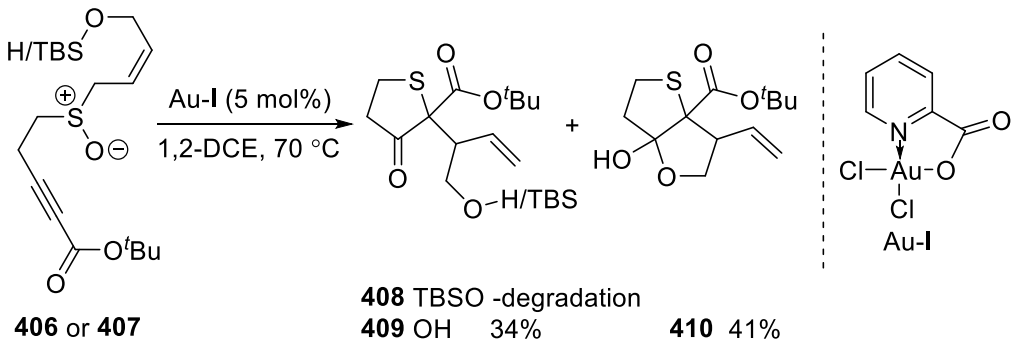
The failed attempts to fully purify sulfide, and the tendency of sulfides to degrade over time, it was suggested that oxidation of **405a** to sulfoxide may resolve the R_f values on TLC. This would allow easy removal of impurities by column chromatography. Subjecting

sulfide to both, the standard, and the modified oxidation conditions, did lead to the desired sulfoxide products, which were cleanly separated from the unwanted impurity by column chromatography. TBS protected sulfoxide **406a** was generated in 56% using conditions A (Scheme 125). On the other hand, free hydroxyl sulfoxide was generated in 42% conditions B.



Scheme 125. Different products formed using alternative concentration conditions.

Under the standard gold catalysis conditions using Au-**I** (5 mol%) in 1,2-dichloroethane at 70 °C, sulfoxides **406** did not give a clean reaction and the products were prone to degredation. However, sulfoxide **407** underwent cyclisation-sulfur ylide formation-rearrangement to give thiophenone compound **409**. The desired lactol product **410** was also obtained in 41% as a result of a tandem cyclisation process. The *tert*-butyl acetate group served its purpose and as predicted none of the lactone product was observed by TLC analysis.

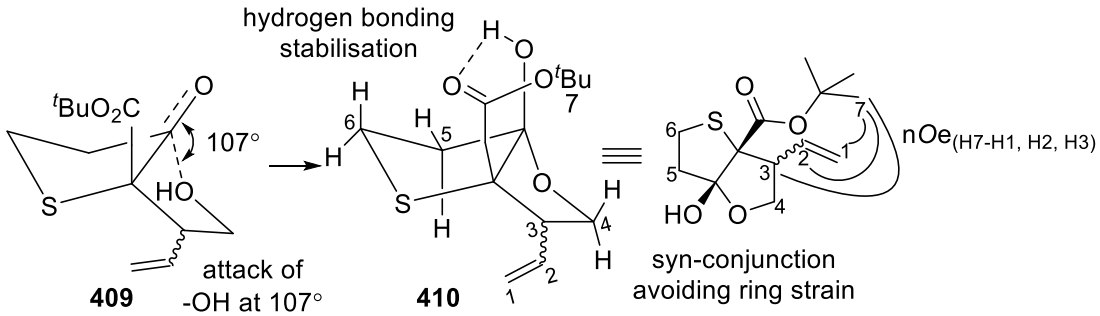


Scheme 126. Catalysis outcome overview.

It is postulated that the additive *para*-toluenesulfonicacid (*p*TSA) to gold catalysis conditions, may be used to drive the tandem reactivity towards these highly complex and potential biologically active scaffolds. The *p*TSA serves as H^+ Lewis acid which could potentially activate the carbonyl unit of the *tert*-butyl acetate group to facilitate addition of the hydroxyl group. In hope to achieve a high yield of lactol, 1.0 equivelent of *p*TSA (with respect to sulfoxide) was added to the catalysis mixture, 2 h after the catalysis reaction was started. Preliminary results showed no presence of the hydroxyester by TLC and the *p*TSA successfully drove the reaction towards formation of lactol. Unfortunately, by ^{1}H-NMR analysis, an unknown impurity was present in the lactol, which was present even after column chromatography.

2.4.7.1 ^{1}H-NMR studies towards determining the stereochemistry of 410

In order for the intramolecular lactone formation to take place the nucleophilic attack of the hydroxyl group has to occur on the least hindered face of the electrophilic carbonyl group obeying the Bürgi-Dunitz trajectory angle (107°). Attack in this manner should give a *syn*-ring conjunction with respect to the ester and hydroxyl groups. In this geometry, hydrogen bonding between the ester and the hydroxyl group is possible. In the literature Hodgson *et. al.*[91] reports the oxygen derived lactol, where the ester and hydroxyl groups are on the same face. However the vinyl group is anti to both the ester and hydroxyl groups (See Section **2.4.4** for Hyperolactone C synthesis). For lactol **410** n*O*e experiments reveal that excitation of the *tert*-butyl H7 gave signals to H1, H2 and H3, no signal was seen for H4. If **410** contained two bent cyclopentyl rings (as drawn in Scheme 127) a signal between H7 and H4 would be expected. This suggests that the geometry drawn in Scheme 127 is incorrect and needs revising. Future n*O*e experiements will fully determine the stereochemistry and geometry of these important scaffolds.



Scheme 127. Geometry of hydroxyl attack and sterically prefered *syn*-ring conjunction.

2.4.8 Summary

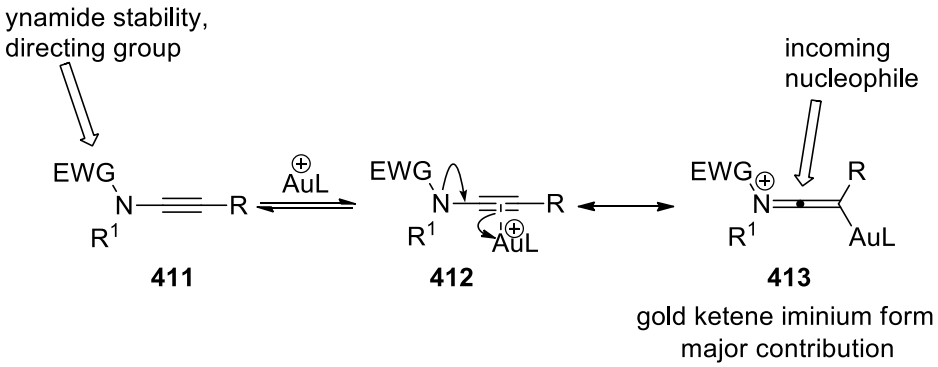
As predicted by the hypothesis, domino-reactivity of carefully designed sulfoxide precursors, led to highly complex heterocycles, from simple sulfoxides. The biologically active analogous lactone product was not successfully purified and characterised but lactols were isolated in moderate yields. The ethyl acetate tethered sulfoxide led to a mixture of products which were difficult to isolate and gave low yields of lactol. Use of a *tert*-butyl acetate tethered sulfoxide promoted lactol synthesis, but also in low to moderate yields. The lactol was isolated as a single diastereoisomer. The determination of stereochemistry of the lactol can be established by a full n*O*e analysis.

2.5 Site-specific introduction of gold carbenes (aliphatic systems)

2.5.1. Introduction

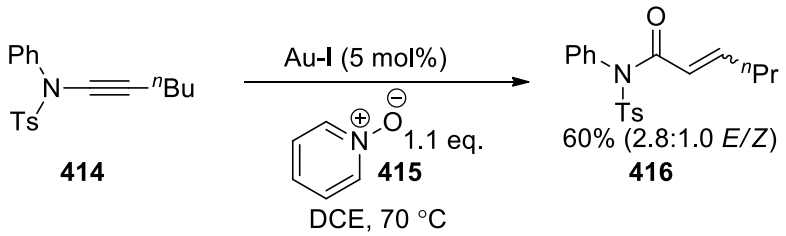
Research groups Liu[76], Zhang[92] and Davies[93] have independently shown intermolecular-site-specific oxidation across π-acid activated C-C triple bonds where Liu[76] and Davies[93] concentrated on ynamides. Ynamides are described as useful subgroups consisting of a nitrogen atom directly attached to the C-C triple bond.[94] The nitrogen atom exerts a strong electron-donating ability from its accessible lone-pair inducing a strongly polarised triple bond allowing a uniquely high level of reactivity. Upon activation of ynamide **411** by a gold species **412**, the gold ketene iminium canconical form **413** contributes to the polarised

triple bond allowing attack of an incoming nucleophile adjacent to the nitrogen atom (Scheme 128). The electron-withdrawing group on the nitrogen contributes to the ynamide's stability. Furthermore, use of amides as coupling partners to terminal alkynes has allowed their synthesis to be highly efficient and less challenging than ynamines.[94] Hence ynamides have become increasingly interesting in π-acid catalysis reactivity.



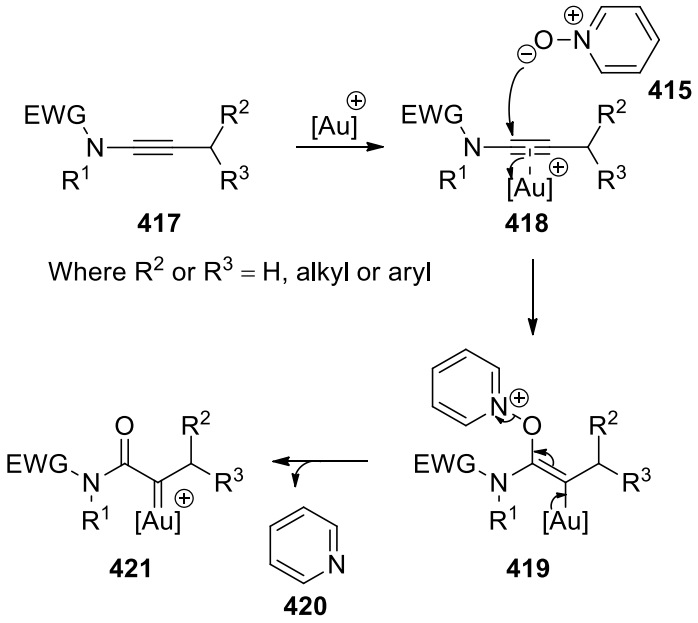
Scheme 128. Resonance picture of the major contribution to site-specificity.

It is well known that the incorporation of a functional moiety capable of migrating to the adjacent metal carbenoid or metal stabilised carbocation provides the means to terminate the reaction.[66] Suitable adjacent migrating groups onto the π-acid metal carbenoid allow many powerful transformations to occur. These involve reactivity such as hydrogen, halogen, alkyl and aryl shifts, ring expansions or pinacol-type rearrangements. Here emphasis has been placed on the possible 1,2-hydrogen shift observed by the recent work done in the Davies group.[93] It was shown that simple ynamides could be converted to α, β-unsaturated imides under the influence of Au-**I** utilising *N*-pyridine oxide in dichloroethane at 70 °C (Scheme 129).



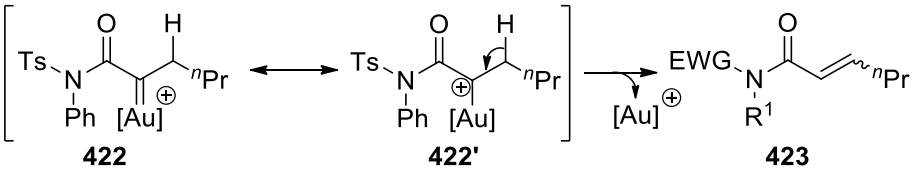
Scheme 129. Gold-catalysed oxidation reactions of ynamides.

N-pyridine oxide **415** was used as an oxygen delivery system to oxidise the carbon adjacent to nitrogen of the gold activated ynamide **418** (Scheme 130). Then back-donation of electron density from the gold species **419** allowed release of the latent leaving group pyridine **420** hence, regiospecific introduction of the reactive gold carbene to give α, α'-disubstituted imidocarbenoids **421**. [95, 96]



Scheme 130. Proposed mechanism of gold-catalysed-site-specific oxidation reactions of ynamides.

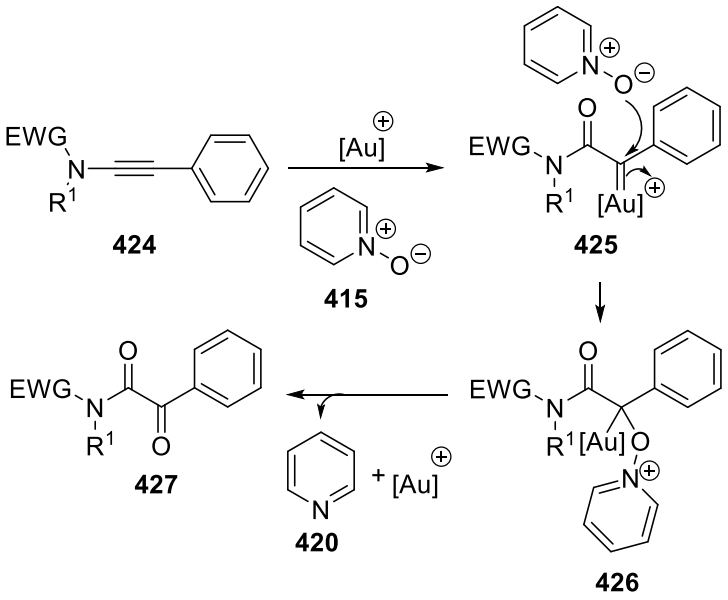
In the presence of a migrating hydrogen adjacent to the gold carbenoid the reactive α, α'-disubstituted imidocarbenoid intermediate **422** rearranges leading to α, β-unsaturated imides **423** (Scheme 131).



Scheme 131. 1,2-Hydride shift onto gold carbenoid to give α, β-unsaturated imides **423**.

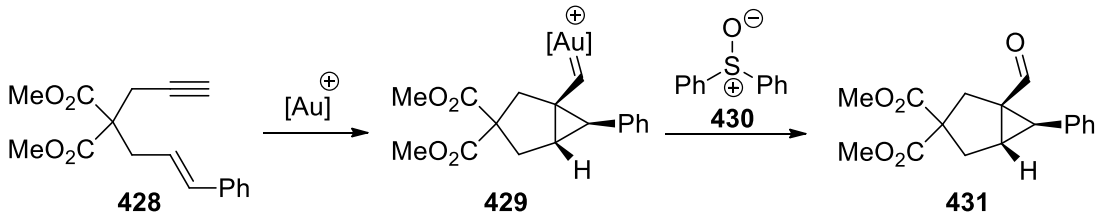
When two equivalents of oxidant was used, the reactive α, α'-disubstituted imidocarbenoid intermediate **425** reacted with a second equivalent of pyridine *N*-oxide **415**, and in the

absence of an adjacent migrating group, afforded oxoacetamides **427** releasing pyridine and the reactive gold species (Scheme 132).



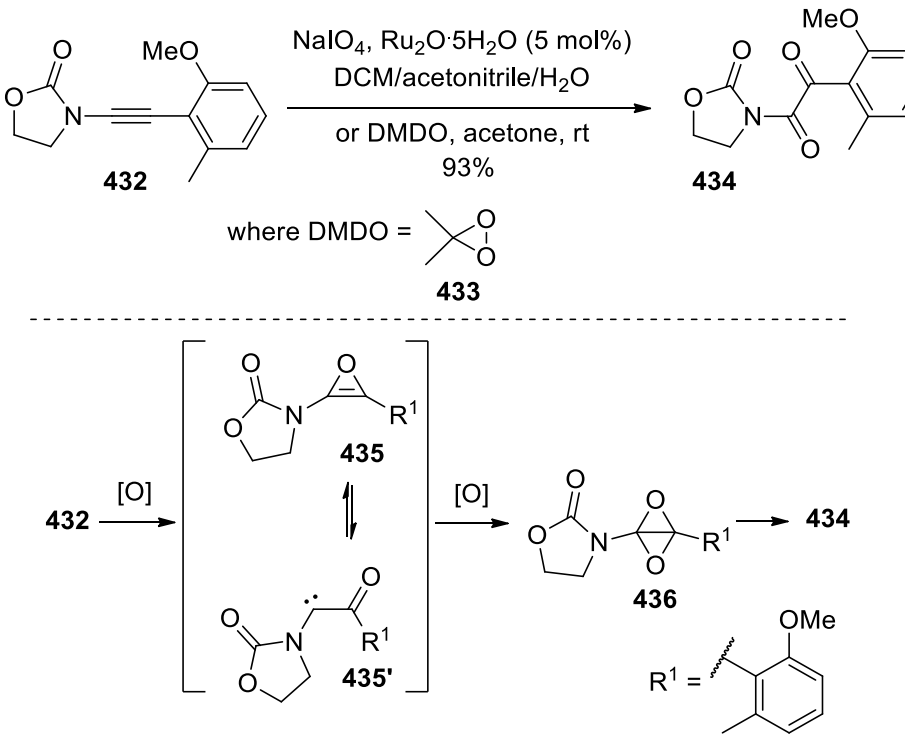
Scheme 132. Proposed mechanism of gold-catalysed double oxidation reactions of ynamides.

The Toste research group[74] have previously reported an equivalent oxygen transfer process where the carbenoid intermediate of gold catalysed 1,6-enyne cycloisomerisations was quenched with an external sulfoxide as the oxidant (See introduction: Section **1.10**).



Scheme 133. Gold-catalysed carbenoid intermediate trapped with sulfoxide external oxidant.

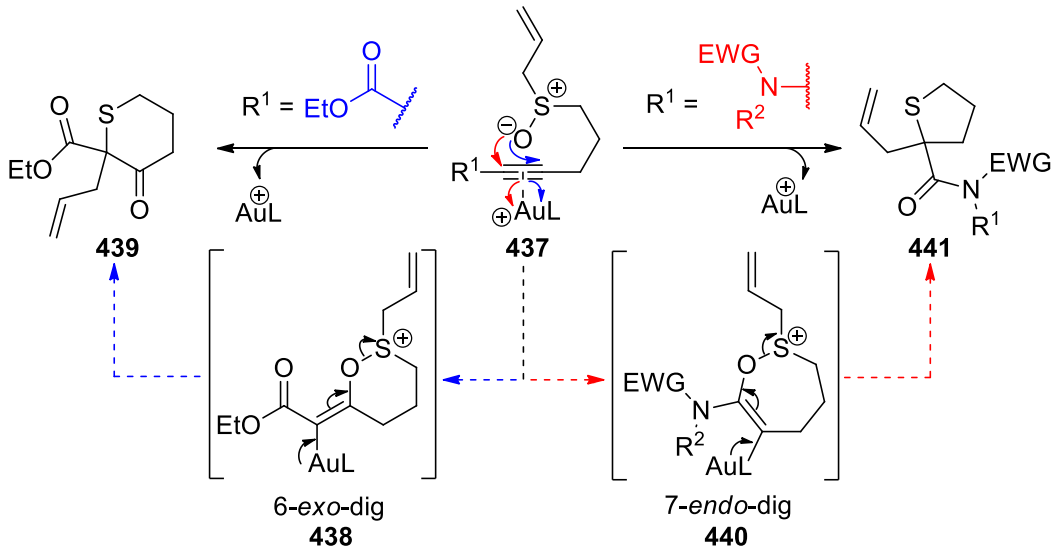
Electrophilic oxidising reagents such as RuO_2-$NaIO_4$ or DMDO **433** (dimethyldioxirane) have also been reported by Hsung's research group[97] (Scheme 133) for oxidation of ynamides **432** to oxoacetamides **434** *via* an opposite regiochemical outcome **435'** of the initial oxidation in comparison to the formation of gold carbenoids from ynamides (Scheme 134).



Scheme 134. Mechanism of Hsung's dioxidation reactions of ynamides with electrophilic oxidants.

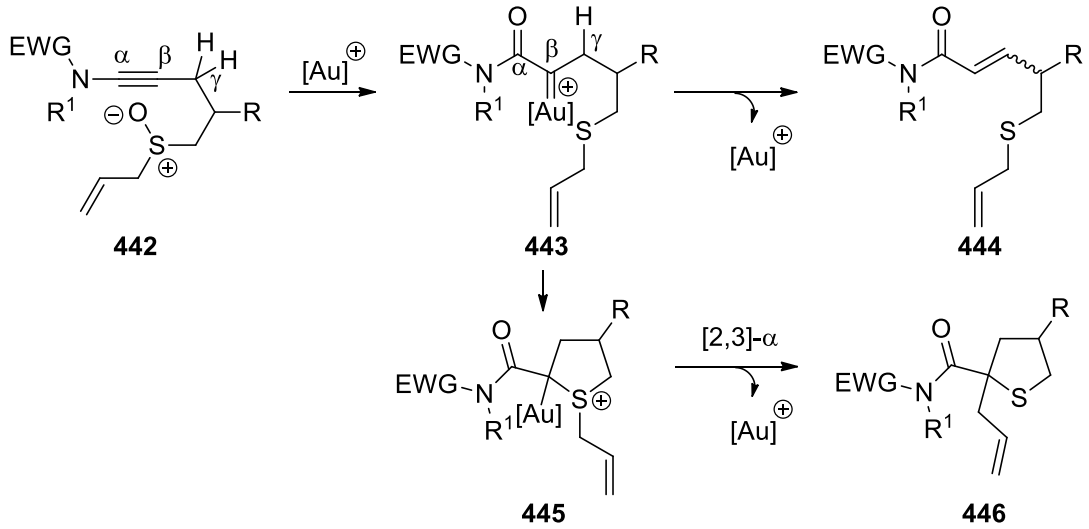
2.5.2 Research proposals

In chapter **2.3.4** we saw how the ester substituted alkyne induced a dipole across the alkyne to allow an initial regiospecific attack of the internal oxidant under gold catalysis. If by analogy, the use of an electron-withdrawing ester group on the alkyne led to exclusively 6-*exo*-dig cyclisation mode, could the use of an electron-donating group switch selectivity to induce initial sulfoxide attack through a more challenging 7-*endo*-dig process? It was envisioned that the opposite electronic bias by use of ynamides could lead to 5-membered sulfur heterocycles (Scheme 135). For the ynamide, the most electrophilic site is the carbon directly attached to nitrogen due to the contribution from the favoured gold-ketene-iminium resonance form **413** (Scheme 128 above). The intermediate formed **440** could potentially rearrange to α-oxo-β-imido-gold carbenoid which is capable of sulfur ylide formation by the intramolecular nucleophilic addition of sulfide onto the gold carbenoid.



Scheme 135. Site-specific attack of internal oxidant depending on the electronically-biased alkyne

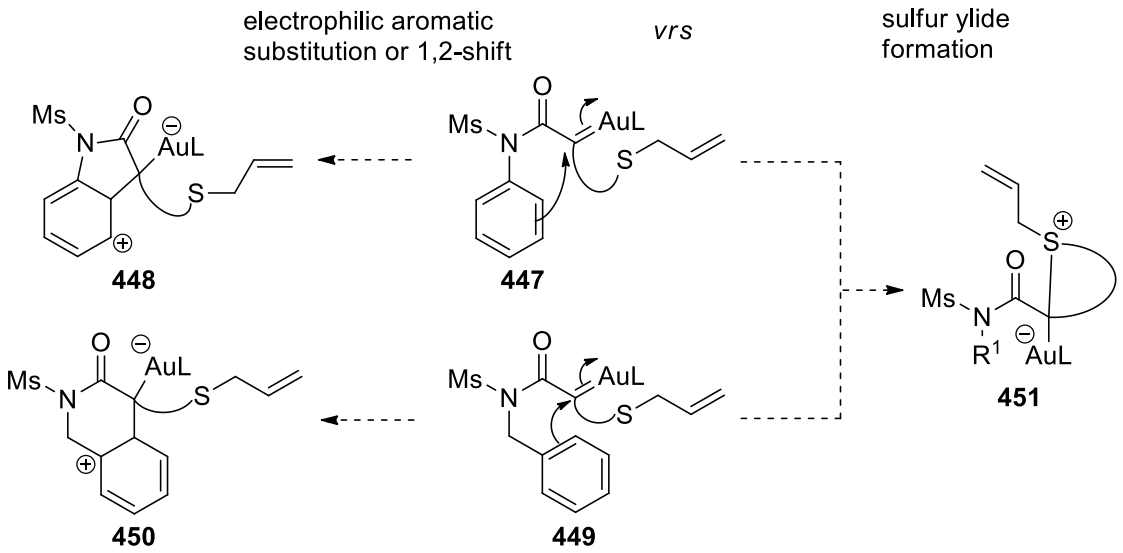
In the presence of adjacent migrating groups to the gold carbenoid, it was also envisioned that sulfoxide tethered enynamides may be prone to 1,2-hydrogen migrations to give α, β-unsaturated imides. These 1,2-hydrogen migrations will directly compete with sulfur ylide formation to give 5-membered heterocycles.



Scheme 136. Proposed mechanism of possible 1,2-hydrogen shift *verses* sulfur ylide formation

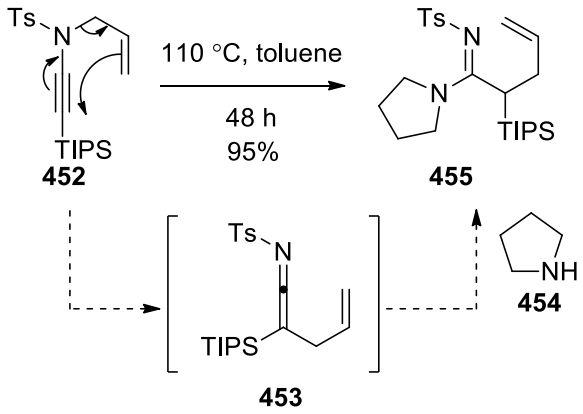
Furthermore, the careful choice of amide could lead to an array of other interesting gold catalysed outcomes deterring the pathway to sulfur ylide generation. The use of phenyl and

benzyl substituted ynamides can potentially lead to α-oxo-gold carbenoids **447** and **449** which are capable of electrophilic aromatic substitution reactions under gold catalysis.



Scheme 137. Possible competitive pathways deterring sulfur ylide formation.

The thermal or metal catalysed aza-Claisen rearrangement of silylated ynamides **452** was reported by Hsung[98] to yield isolable ketenimines **453** which were trapped by nucleophilic amines **454** to give amidine structures of the type **455** (Scheme 138). Therefore an allyl substituted ynamide was also prepared in order to test wheather these aza-Claisen rearrangements occur over sulfur ylide formation.



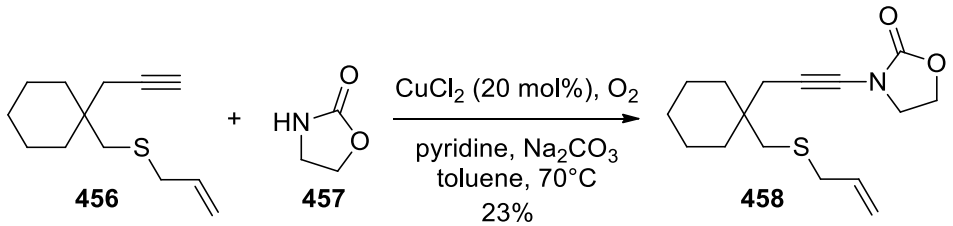
Scheme 138. Hsung group's thermal aza-Claisen rearrangement.

A variety of ynamides were prepared to test these hypotheses. Substrates containing ynamides with a cyclohexyl tether in the 4-position were looked at so that a direct

comparison may be made to results obtained from ester substituted alkynes (See chapter **2.3.4**).

2.5.3. Preparation of starting material

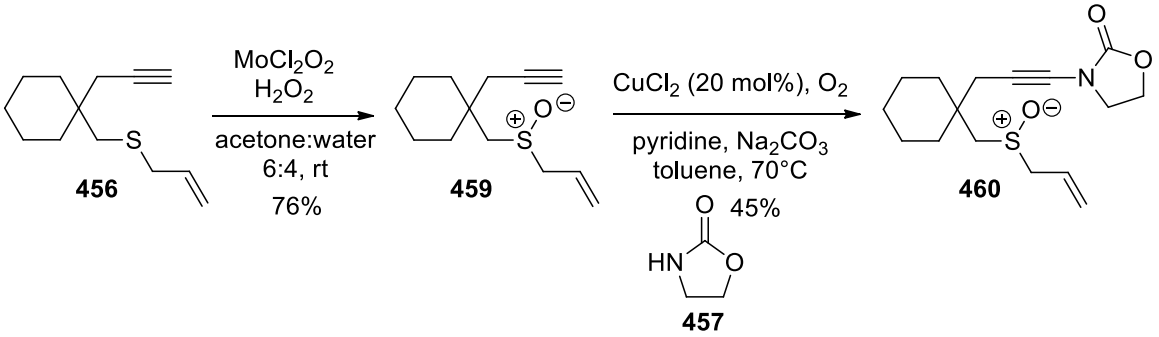
Out of all the possible synthetic strategies to ynamides Stahl's elegant oxidative alkynylation[99] (described below) of a variety of amides with terminal alkynes proved to be the most efficient and synthetically-reliable route to sulfoxide-tethered ynamides. By utilising Stahl's conditions to introduce an amide onto the terminal alkyne we bypass inefficient two-step methods such as laborious functionalisation *ie*. halogenations of the alkyne followed by a C-N cross-coupling.[100] The only drawbacks of the Stahl method is the need to use an excess amount of amide, slow addition of terminal alkyne over 4 hours *via* syringe pump and the maintenance of an external oxidant such as oxygen gas throughout the reaction at 70 °C. Initially sulfide **456** (See section **2.3.1** for preparation) was subjected to the Stahl conditions to give the coupled product **458** in a low yield of 23%. It was suggested that the low yield was due to potential sulfur poisoning of the copper(II) salt and that protecting the sulfide to sulfoxide before applying Stahl coupling conditions, may prevent sulfur poisoning and hence increase the yield of the desired ynamide product.



Scheme 139. Stahl's copper catalysed oxidative coupling of amides and sulfide.

Applying reactive conditions employed before using $MoCl_2O_2/H_2O_2$, sulfide **456** was chemoselectively oxidised to sulfoxide **459** in 76% yield after column chromatography isolation. Subjecting **459** to the Stahl conditions using commercially available oxazolidinone **457** led to a much better yield of the desired catalysis precursor **460** in 45%

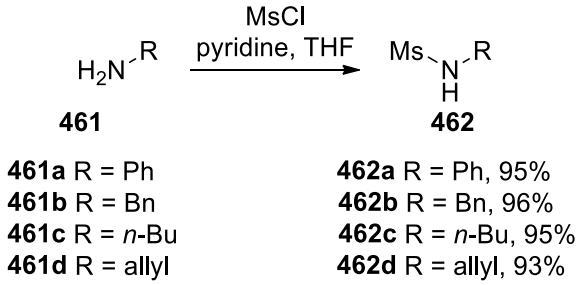
yield (Scheme 140). Delightfully as predicted the oxygen atom on the sulfoxide does behave as a shield protecting the copper(II) catalyst from poisoning under Stahl conditions and hence an improved yield of the ynamide in comparison to the naked sulfide. A variety of ynamides could potentially be prepared this way by use of different amides as coupling partners to sulfoxide **459**.



Scheme 140. Copper catalysed oxidative coupling of oxazolidinone with sulfoxide.

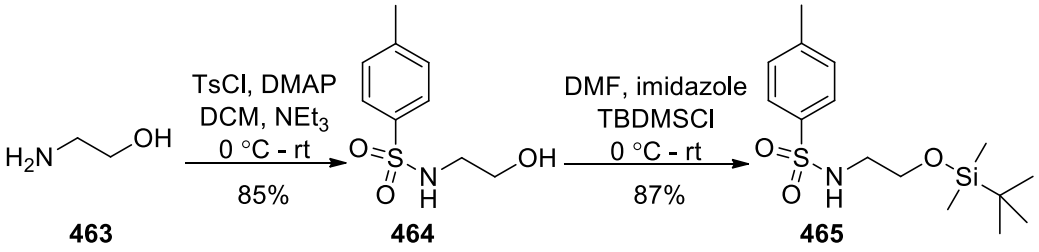
2.5.3.1 Preparation of amides

Various different amide coupling partners were readily prepared by mesylating relevant amines **461** in the presence of pyridine base in tetrahydrofuran at room temperature for 4 hours. Scheme 141 shows aniline, benzyl amine, *n*-butyl amine and allyl amine subjected to these mesylating conditions to give *N*-phenyl **462a**, *N*-benzyl **462b**, *N*-butyl **462c**, and *N*-allyl **462d** methanesulfonamide in excellent yields of 95%, 96%, 95% and 93% respectively.



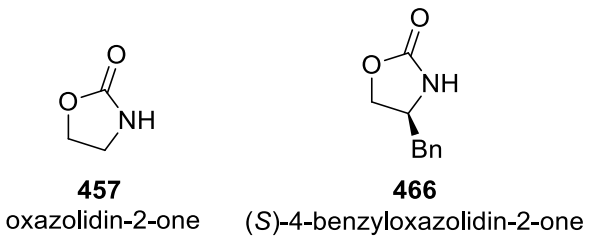
Scheme 141. Preparation of sulfonamides from a variety of amines.

Bis-protected aminoethanol **465** was prepared using Snaith's group[101] method by DMAP promoted tosyl protection of the amine **463** followed by silylation of **464** in good yields of 85% and 87% respectively (Scheme 142).



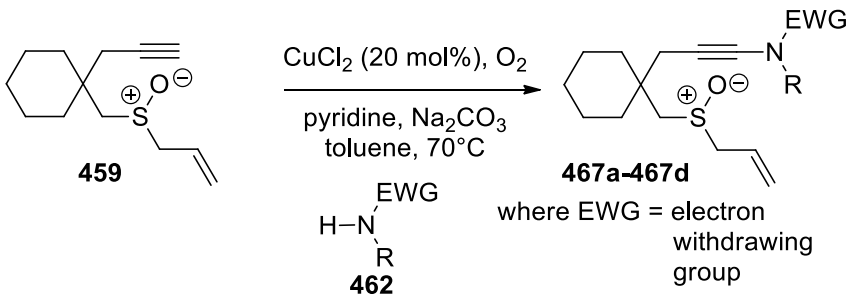
Scheme 142. Preparation of diprotected aminoethanol.

Commercially available amides were also considered as copper catalysed oxidative coupling partners to terminal alkynes (Scheme 143). The possibility of influencing the stereochemical outcome, of the heterocyclic products under gold catalysis, led us to utilise an amide containing a stereocentre **466** as a potential chiral auxiliary.



Scheme 143. Commercially available amides.

Delightfully, Table 8 entries 1-4 show various sulfonamides **462a-462d** successfully used as coupling partners to alkyne **459** giving ynamides **467a-467d** in moderate to good yields ranging from 28-66% yield. Although the desired ynamides were formed, purification by column chromatography was detrimental to the yields due to degradation on even neutralised silica by 1% Et_3N. Other purification techniques such as distillation led to degradation of the ynamide products and none was isolated.



Scheme 144. General scope of the Stahl reaction.

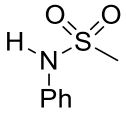
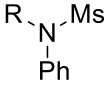
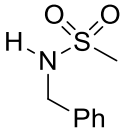
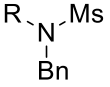
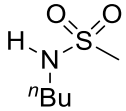
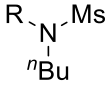
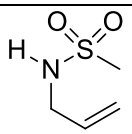
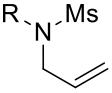
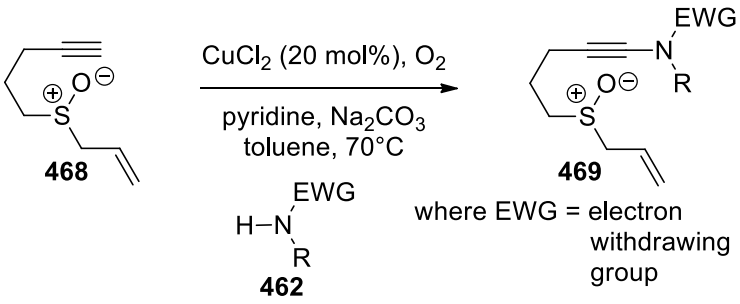
Entry[a]	H, N, EWG, R	Product	Yield[b] (%)
1	 **462a**	 **467a**	66
2	 **462b**	 **467b**	34
3	 **462c**	 **467c**	45
4	 **462d**	 **467d**	28

Table 8. [a] reactions were carried out on a 1.0 mmol scale with respect to sulfoxide under $CuCl_2$ (0.2 mmol) catalyst, Na_2CO_3 (2.0 mmol), pyridine (2.0 mmol) and the corresponding amide (5.0 mmol) in excess. [b] Isolated yields after flash column chromatography.

Similarly compound **468** with no cyclohexyl substituent in the 4-position of the pentynyl chain, also underwent copper catalysed oxidative coupling reactions to yield ynamides of type **469**. Table 9 entries 1-3 show the successful copper catalysed oxidative coupling ynamide products with modest yields ranging from 18-29%.



Scheme 145. Use of the Stahl reaction to generate ynamides.

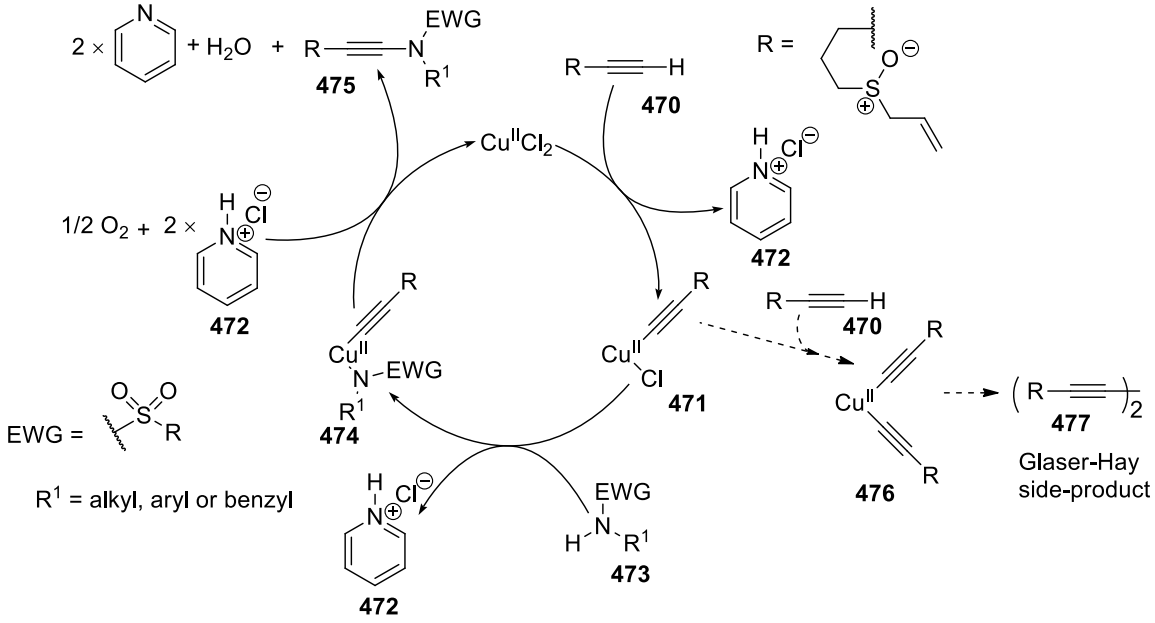
Entry[a]		Product	Yield[b] (%)
1	**462b**	**469a**	29
2	**462c**	**469b**	25
3	**465**	**469c**	18

Table 9. [a] Reactions were carried out on a 1.0 mmol scale with respect to sulfoxide under $CuCl_2$ (0.2 mmol) catalyst, Na_2CO_3 (2.0 mmol), pyridine (2.0 mmol) and the corresponding amide (5.0 mmol) in excess. [b] Isolated yields after flash column chromatography.

2.5.3.2 Mechanism of the Stahl reaction

It was postulated by Stahl and co-workers[99] that the mechanism features a sequential activation of both the alkyne and the nitrogen nucleophile with pyridine and copper chloride **474**, followed by C-N reductive elimination and aerobic reoxidation of catalyst (Scheme 146). Activation of a second equivalent of alkyne forms the unwanted bis-alkynyl-Copper(II) species **476** which upon reductive elimination yields the Glaser-Hay[102] diyne side-product **477** that is detrimental to the desired formation of the mixed alkynyl amidate-

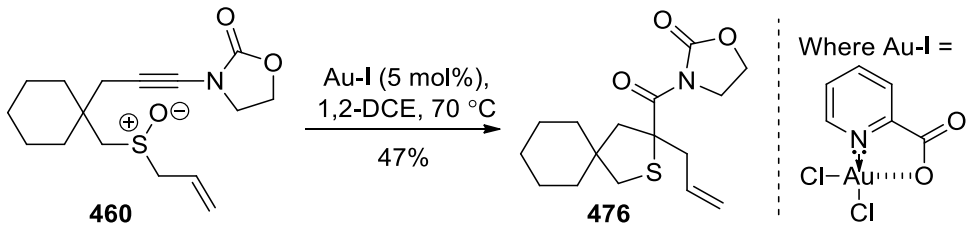
Copper(II) species **474**. This mechanism rationalised the need for an excess of nitrogen nucleophile and the slow addition of alkyne **470** to avoid the undesired diyne side-product.



Scheme 146. Proposed mechanism of the Stahl reaction.

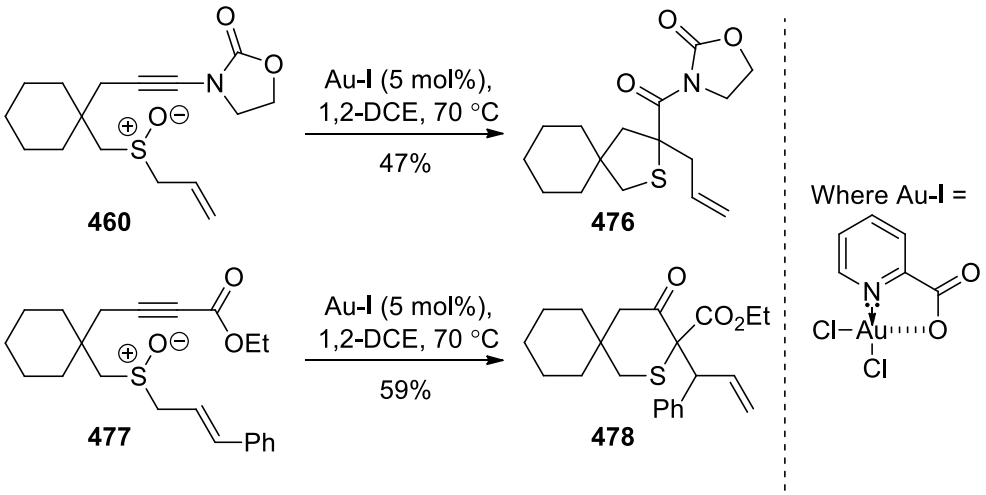
2.5.4 Catalysis results

Ynamide **460** was subjected to the standard conditions used by the Davies group[62] (Au-**I** (5 mol%), dichloroethane, at 70 °C). The reaction mixture was stirred and monitored by TLC until no starting material remained (24 h), to yield cyclised heterocycle **476** in 47% yield. Despite the moderate yield, 5-membered heterocycle has been exclusively formed over the possible 6-membered structure and 1,2-hydrogen migration pathways. The poor yield is due to degradation of **476** whilst purification on column chromatography. With all the starting material fully consumed, hypothetically the α, β-unsaturated imide is being formed and then degrading on the column during purification (See research proposal section **2.5.2**).



Scheme 147. Generation of sulfur heterocycle under standard gold conditions used before.

In comparison to the electron-poor ester system, the electron rich ynamide system allowed the initial more challenging 7-endo-dig cyclisation to take place. As predicted this reactive pathway resulted in the regiospecific formation of the α-oxo-gold carbenoid where the carbon next to the nitrogen of the ynamide was oxidised. Overall a 5-membered heterocycle has been achieved where the carbonyl bond is on the outside of the ring and accessible to further reactivity. On the other hand the ester substituted alkyne underwent an exclusive initial 6-exo-dig cyclisation to give 6-membered heterocycles with the carbonyl group within the ring and more hindered to further functionalisation.

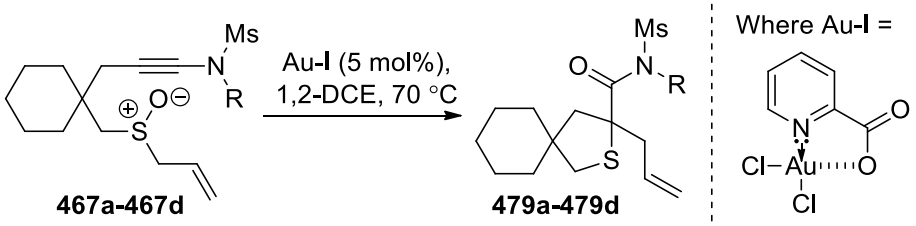


Scheme 148. Results of the two extremes of the electronically biased systems.

Pleasingly substrates **467a-467d** also gave cyclic 5-membered sulfur compounds **479a-479d** under catalytic amounts of Au-**I** (5 mol%). Phenyl and benzyl substituted ynamides (Table 10, entry 1 and 2) gave the desired cyclic structures after column chromatography in 69% and 49% yield respectively. None of the compting electrophilic aromatic substitution

products were observed. A butyl substituted ynamide was also tested which proceeded smoothly to the desired product in 69% yield (Table 10, entry 3). A high yield was expected as the butyl substituted ynamide is designed not to undergo side reactivity other than a potential 1,2-hydrogen insertion. Use of an allyl substituted ynamide also gave the desired product in 60% yield (Table 10, entry 4) favouring gold catalysed intramolecular redox reactivity over possible aza-Claisen rearrangement or cyclopropanation transformations.

On close inspection of the crude ^{1}H-NMR with a known amount of internal standard (Durol), only traces of impurities exist and the cyclic sulfur compound is present as a majority of the crude mixture and proximate consistent yields are achieved after catalysis. Purification by flash column chromatography to remove traces of gold residue and trace amounts of impurities led to isolated yields less than that determined by NMR studies. This may be due to degradation of products on a silica column. The use of 1% triethylamine in the eleuent mixture was utilised to neutralise the slightly acidic silica used for column chromatography, but led to no change in the isolated yields of the cyclic sulfur compounds.



Scheme 149. General gold catalysis.

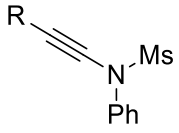
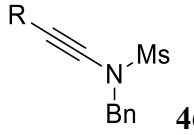
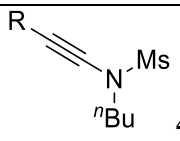
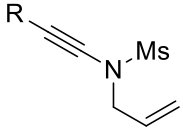
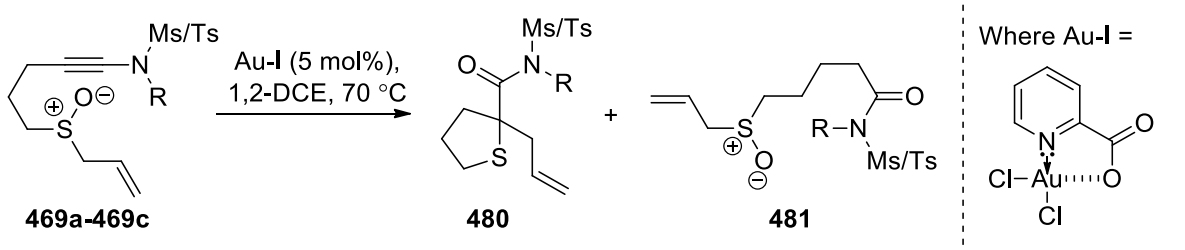
Entry[a]	Ynamide	Product	Yield[b] (%)
1	 **467a**	**479a**	69(98)[c]
2	 **467b**	**479b**	49[d]
3	 **467c**	**479c**	69
4	 **467d**	**479d**	60

Table 10. [a] reactions were carried out on a 0.1 mmol scale with respect to sulfoxide under Au-**I** catalyst (5 mol%), 1,2-dichloroethane (0.2*N*) stirred at 70 °C. [b] Isolated yields after flash column chromatography. [c] Although unknown products were isolated by column chromatography, they were prone to degradation, making the assignment and determination difficult. The yields reported are by ^{1}H-NMR analysis with internal standard (Durol). [d] Low yields isolated after column chromatography may be due to degradation of cyclic products on silica.

Subjecting cyclohexyl-free ynamide **469a** to standard catalysis conditions led to the desired cyclic sulfur compound **480a** in 31% yield along with an unexpected side product **481a** in 16% yield (Table 11, entry 1). The suspected hydration product **481a** was formed, presumably as a result of trace amounts of water being present from the solvent or substrates. Allyl substituted ynamide **469b** (Table 11, entry 2) also reacted under gold catalysis using the same batch of 1,2-dichloroethane solvent to give cyclic sulfur compound

in 29% yield and the hydration product **481b** in 11% yield. Ynamide substituted with a diprotected aminoethanol **469c** (Table 11, entry 3) led to the desired cyclic compound **480c** in 40% yield with none of the undesired hydration product. The lack of hydration product even when wet solvent was used may be explained by the steric bulk of the tosyl group hindering the incoming water molecule in comparison to a small mesyl group adjacent to the amido moiety. The mechanism of this transformation is discussed below (Scheme 151). This catalysis reaction was repeated for ynamides **469a** and **469b**, but using dry solvent to give cyclic sulfur structures **480a** and **480b** in improved, although average yields of 63% and 59% respectively. Freshly distilled 1,2-dichloroethane (CaH_2, 78 °C) was used on the day of catalysis to ensure it was dry, furthermore, it was kept under pre-dried molecular sieves and stored under an argon atmosphere in a sealed flask for its next use.



469a-469c 480 481

Scheme 150. Cyclohexyl-free ynamides give cyclic sulfur compounds and hydration product under Au-**I**

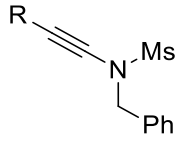
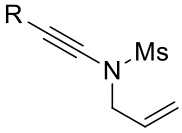
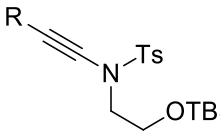
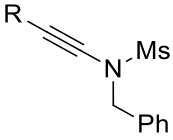
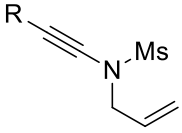
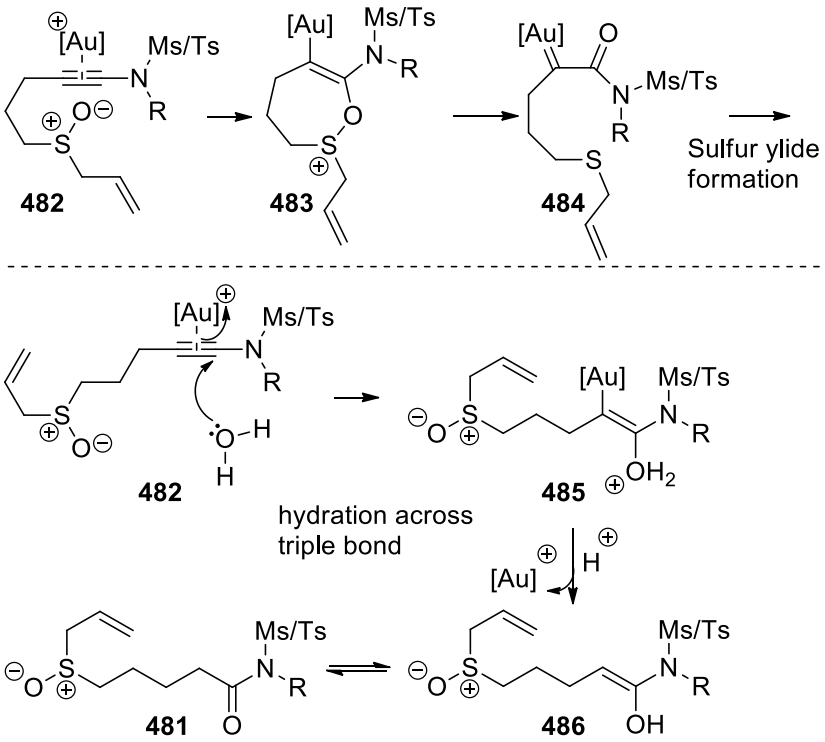
Entry[a]	Ynamide	Product	Yield[b] (%)	Yield[c] (%)
1	 **469a**	**480a**	31	**481a**, 16%
2	 **469b**	**480b**	29	**481b**, 11%
3	 **469c**	**480c**	40	-[d]
4	 **469a**	**480a**	63	-[e]
5	 **469b**	**480b**	59	-[e]

Table 11. [a] Reactions were carried out on a 0.1 mmol scale with respect to sulfoxide under Au-**I** catalyst (5 mol%), 1,2-dichloroethane (0.2*N*) stirred for 24 h at 70 °C. [b] Isolated yields after flash column chromatography. [c] Wet 1,2-dichloroethane resulted in hydrolysis products isolated by column chromatography. [d] No hydrolysis product observed. [e] Reactions carried out with freshly distilled dry 1,2-dichloroethane.

The mechanism of the hydration product results from a competitive nucleophilic attack of a water molecule **482**. This advantitious water molecule competes with sulfoxide nucleophilic oxygen attack **483** onto the π-acid activated CC triple bond of **482** to give enol

486 (Scheme 151). Favoured enol-tautomerisation then results in the generation of a substituted amide **481**.



Scheme 151. Proposed mechanism of the formation of hydration product.

2.5.5 Summary

It was noted that the yields were not good for the generation of cyclic structures **480a-480c** (Table 11, entries 1-3) in comparison to compounds **476** and **479a-479d** (Table 10, entries 1-4) using the same reaction conditions and the same batch of 1,2-dichloroethane solvent. The adventitious water molecules in the solvent did not compete with the sulfoxide attack onto the gold activated ynamide for starting precursors containing a cyclohexyl moiety in the backbone of the chain. It was presumed that the cyclohexyl ring behaved as a steric hindrance to free rotation around the CC bonds. Whereas, for the cyclohexyl-free precursors the sulfoxide-tethered-ynamide chain was free to rotate and allowed attack of the adventitious water leading to lower yields of the desired cyclic structure and generation of unwanted hydration side-products. Although hydration of alkynes using gold catalysis[103,

[104, 105] is well precedented in the literature, hydration of ynamides is rare and so these results are not entirely disregarded.

When using freshly distilled solvent the yields of **480a** and **480b** (Table 11, entry 4 and 5) were similar to those obtained in Table 10, entry 1-4. This observation suggests that the the cyclic sulfur compound is prone to degradation by column chromatography.

2.5.6 Catalysis screening

It was postulated that by the use of other catalytic systems, the generation of any side-products may be isolated and determined. Starting ynamide precursor **467a** was subjected to a variety of gold catalysis conditions (Table 12) and the extent of the reaction was calculated by crude ^{1}H-NMR analysis using a known amount of internal standard. Durol was used as internal standard as it was well distinguished from the protons highlighted in both, the sulfoxide starting precursor and the cyclised product **479a** after gold catalysis (Scheme 152). The resolution between the vinylic proton of the starting material and the mixture of products was at times difficult to assign due to overlapping peaks in complex crude ^{1}H-NMR and so rough ratio values are given (See Appendix **Chapter 4**).

The active gold species was generated *in situ* by the rapid anion exchange of the Cl of gold(I) by the silver salt anion (See introduction, section **1.9.1**), so therefore equimolar amounts of gold and silver salts were used to ultimately maintain the 5 mol% catalyst loading.

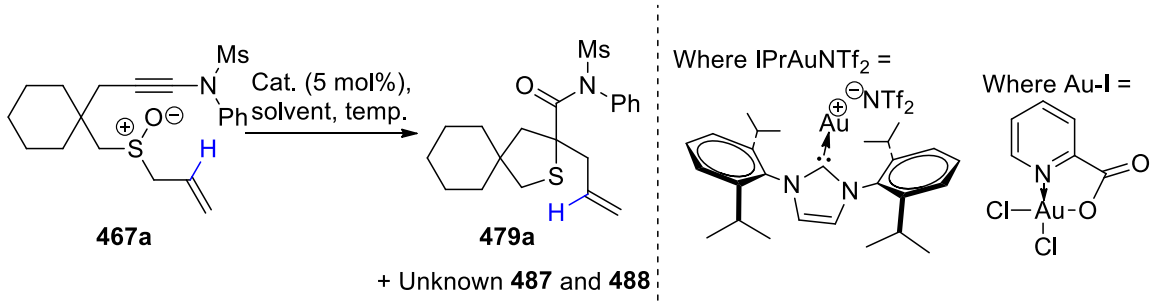
Low conversions of sulfoxide to products were observed when the catalysis was carried out at room temperature in dichloromethane with 5 mol% of IPrAuCl and various Ag salts (Table 12, entry 1, 4 and 5). $IPrAuSbF_6$ gave only 6% of the desired cyclic sulfur structure **479a** and more of the unknown product **487** (Table 12, entry 4), whereas catalytic systems IPrAuOTs and $IPrAuNTf_2$ gave 26% and 41% (Table 12, entry 1 and 5) of the desired

cyclic sulfur structure and less of the unknown product **487** with ratios **479a**:**487**, 5.4:1.0 and 3.6:1.0 respectively.

Due to low conversions of the starting material to products, it was envisioned that increasing the temperature of entries 1 and 4, could allow a better conversion and hence the isolation and characterisation of these intriguing unknown side-products. Increasing the temperature of catalytic systems IPrAuOTs and $IPrAuSbF_6$ from room temperature to 70 °C in dichloroethane could increase the yields of the desired cyclic structures but also of the unknown product **487** respectively.

The results (Table 12, entries 7 and 8) show a marked increase in the yield of the desired cyclic structures **479a** at 42% and 39%, with none of the starting precursor present, but with unknown side-products. Furthermore, electron-poor catalytic system IPrAuOTs (Table 12, entry 7) generated the desired cyclic structure and the unknown product **487** in a ratio of **479a**:**487**, 2.1:1.0 and none of the other side-product **488**, whereas the electron-rich catalytic system $IPrAuSbF_6$ (Table 12, entry 8) gave the desired product to side-product **488** in the ratio of **479a**:**488**, 6.2:1.0 and none of the side product **487**. Unfortunately, in an attempt to isolate unknown products **487** and **488**, these crude complex mixtures were passed through a silica packed column chromatography purification process and resulted in degradation of these products, whereas cyclic product survived in 25% and 32% yields for entries 7 and 8 respectively. Subjecting **467a** to electron-poor phosphite gold chloride and silvertosylate (Table 12, entry 9) or Ph_3PAuCl and silvertosylate (Table 12, entry 10) in dichloromethane at room temperature resulted in full conversion of starting material but led to a complex mixture of unknown products which appeared as streaking by TLC, indicative of degradation. Furthermore 2D-TLC confirmed that products were unstable on silica even when using 1% triethylamine in the eluent system as a result of observed streaking of diluted (DCM) product spots.

Au-**I** commonly applied as the standard catalytic species for these types of sulfoxide precursors in the Davies group[62] was tried at various temperatures in an attempt to find milder reaction conditions to do the same transformation. Using dichloromethane at room temperature resulted in low conversion of starting material to cyclic compound at 11% (Table 12, entry 6). The use of dichloromethane in comparison to 1,2-dichloroethane at room temperature (Table 12, entry 11) did result in an improved conversion, but with significant starting material present. Therefore, it was evident that heat was required to push the reaction forward. It was observed at 40 °C in solvent 1,2-dichloroethane, Au-**I** catalysed sulfoxide **467a** to sulfur heterocycle **479a** in 50% with 55% of the starting sulfoxide remaining (Table 12, entry 12) and none of the previously observed side-products **487** and/or **488**. With these findings it was concluded that the standard catalysis reactions originally used (Au-**I** (5 mol%), 1,2-dichloroethane at 70 °C) allowed the optimal generation of the desired sulfur heterocycle without the formation of side-products (Table 12, entry 13).



Scheme 152. Catalysis screening with various gold species.

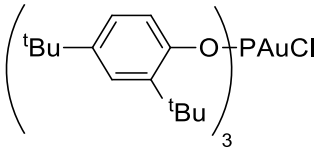
Entry[a]	Catalyst[b]	Solvent	Temp. (°C)	Yield[e]
1	IPrAuCl/AgOTs	DCM	rt[d]	**467a** 84%, **479a** 26% **479a**:**487**, 5.4:1.0, **488** -
2	PPh_3AuNTf_2	DCM	rt	**467a** -, **479a** overlaps with **487** and **488**
3	IPrAuCl/AgOTf	DCM	rt	**467a** 62%, **479a** and **487** overlap **488** -
4	IPrAuCl/$AgSbF_6$	DCM	rt	**467a** 79%, **479a** 6% **479a**:**487**, 2.1:1.0, **488** -
5	IPrAuCl/$AgNTf_2$	DCM	rt	**467a** 62%, **479a** 41% **479a**:**487** 3.6:1.0, **488** -
6	Au-**I**[c]	DCM	rt	**467a** 80%, **479a** 11% **487** and **488** -
7	IPrAuCl/AgOTs	DCE	70	**467a** -, **479a** 42% **479a**:**487** 2.1:1.0, **488** -
8	IPrAuCl/$AgSbF_6$	DCE	70	**467a** -, **479a** 39%, **487** - **479a**:**487** 6.2:1.0
9	 /AgOTs	DCM	rt	**467a** - degradation
10	PPh_3AuCl/AgOTs	DCM	rt	**467a** - degradation
11	Au-**I**	DCE	rt	**467a** 99%
12	Au-**I**	DCE	40	**467a** 55%, **479a** 50% **487** and **488** -
13	Au-**I**	DCE	70	**479a** 98%

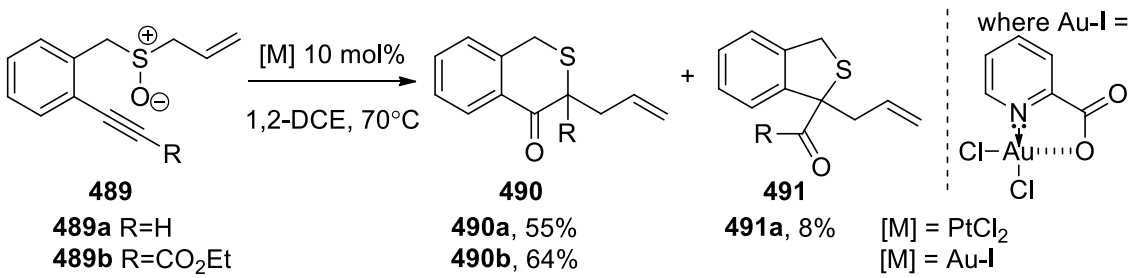
Table 12. Catalyst screenings and outcomes. [a] Yields based on highlighted hydrogen in Scheme 152. [b] 5 mol% of catalyst (2.5 mol% AuL/2.5 mol% AgL) was added to the Schlenk tube before the solution of **467a** in solvent (0.2 *M*). [c]Au-**I** was added to a Schlenk containing a solution of **467a** in solvent. [d] Room temperature measured in the range 18-22 °C. [e] Yields based on ^{1}H-NMR calculations against a known amount of internal standard (Durol).

2.5.7 Overall summary

5-Membered sulfur heterocycles have been successfully synthesised from the intramolecular reaction of sulfoxide tetherered to gold activated ynamides. These electronically biased ynamide systems allows an initial challenging 7-endo-dig cyclisation of the oxygen delivery sulfoxide group. The gold carbene is introduced regiospecifically depending on the starting catalysis precursor, to generate 6-membered sulfur ylides with electron deficient ester substituted alkynes, or 5-membered sulfur ylides with electron rich ynamides as predicted theoretically. No side-reactivity was observed in the presence of competing 1,2-hydrogen migrating groups or electrophilic aromatic substitutions with ynamides containing aromatic moieties. After catalysis screening the optimal conditions were Au-**I**, 1,2-dichloroethane heated at 70 °C to give the highest yield (before purification by column chromatography) of the desired cyclic sulfur heterocycle.

2.6 Site-specific introduction of gold carbenes (aromatic systems)

As reported in the introduction (See section **2.1**) the Davies group[62] have shown that benzofused systems of type **489** (when R=H) led to the major 6-membered isothiochroman-4-one product **490a** and only small amounts of the 5-membered 1,3-dihydrobenzothiophene product **491a**. On the other hand, when an internal alkyne was used (when alkyne substituted with an electron-poor ester group) the 6-membered cyclic product **490b** was formed exclusively.



Scheme 153. Benzofused systems led to the major 6-membered sulfur heterocycle

2.6.1 Research proposal

It was envisioned that as for the aliphatic systems, the use of electron rich systems could lead to exclusive mechanistic pathways *via* the challenging 7-*endo*-dig initial cyclisation. It has already been proven that sulfoxide tethered ynamides undergo gold catalysed intramolecular reactivity to give sulfur heterocycles. We questioned wheather the use of indirectly attached electron-rich moiety would give exclusive regiospecific outcomes (Figure 4, Structure of type A).

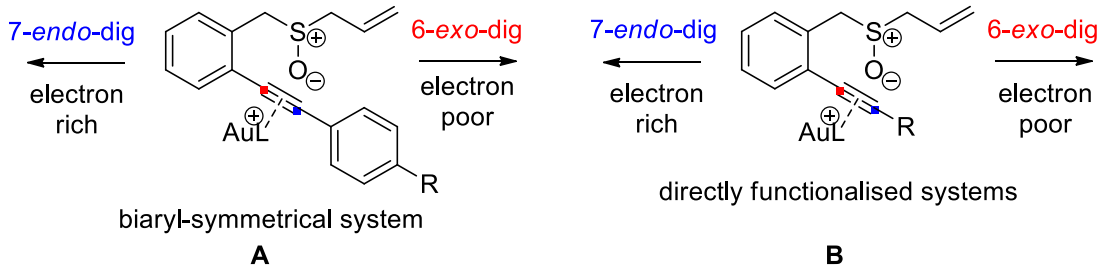
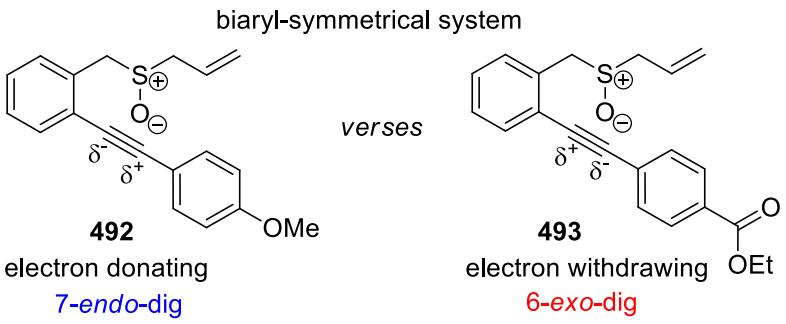


Figure 4. Indirect (A) and direct (B) electronically biased systems and predicted mechanistic pathways

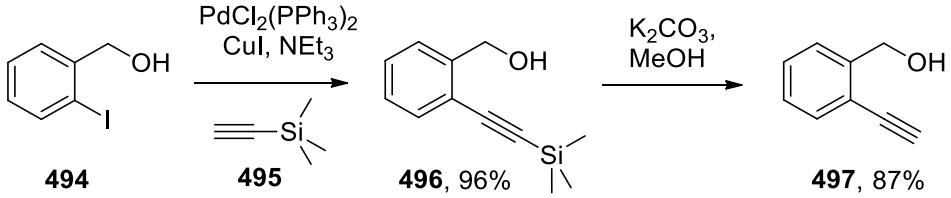
2.6.2 Preparation of starting material

First the key issue is addressed, such as retrosynthetic challenges involved in making the starting precursors. The targets selected were **492** and **493** bearing an electron-donating group (EDG) and electron-withdrawing group (EWG) respectively (Scheme 154). These particular compounds with the two extreme cases of electronical bias were designed so that the catalytic outcomes can be directly compared.



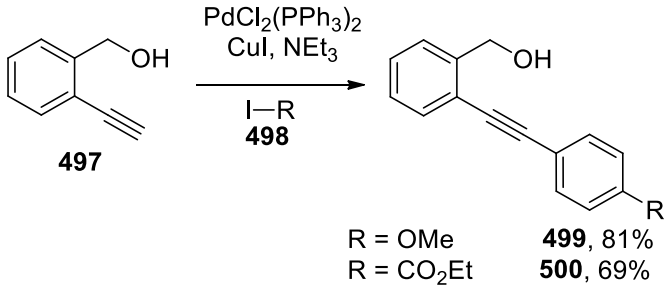
Scheme 154. Two extreme cases of electronically biased systems.

The standard preparation of these substrates was achieved by initial installation of the robust alkyne moiety by subjecting 2-iodobenzyl alcohol **494** to Pd(0) and Cu(I) catalysed Sonogashira coupling[106] with TMS-acetylene **495** in triethylamine at 40 °C to give the silylated benzyl alcohol **496** in excellent yield. Desilylation by potassium carbonate[107] in methanol stirred at room temperature led to the free alkyne product **497** in high yield (Scheme 155).



Scheme 155. Installation of terminal alkyne moiety by Sonogashira coupling.

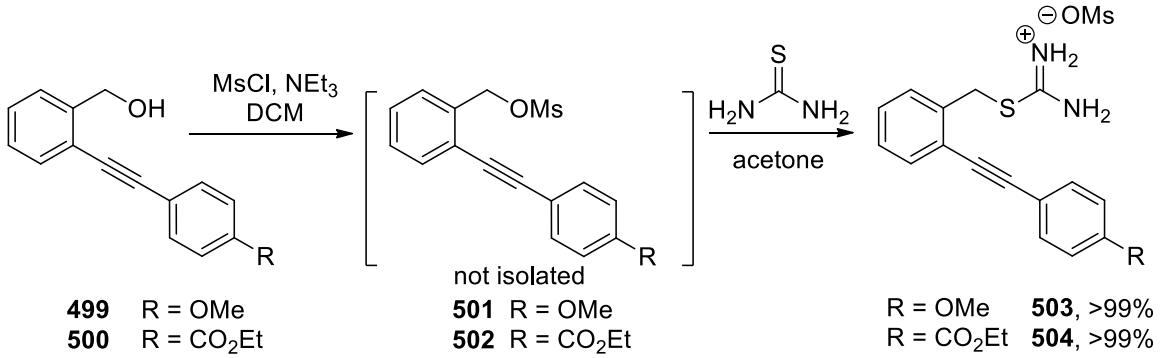
The relevant electronically-biased aromatic unit was then installed under a Sonogashira coupling reaction as before but using iodinated aromatic compounds. 4-Iodoanisole and 4-iodoethylbenzoate reacted with the coupling partner hydroxybenzyl **497** under the influence of Pd(0) and Cu(I) to give the desired biaryl fused alcohols **499**[108] in 81% and **500**[109] 69% yields respectively after flash column chromatography (Scheme 156).



Scheme 156. Sonogashira coupling using electron-rich and electron-poor iodoaryl compounds.

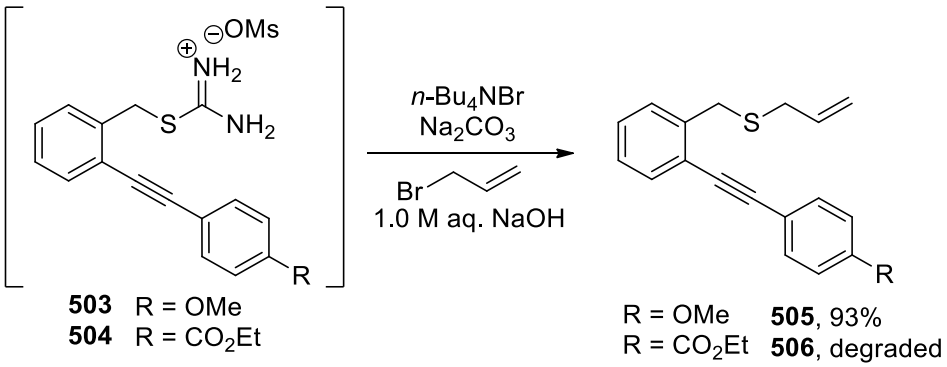
Mesylation of alcohol functional group in the presence of triethylamine as base gave activated mesylated alcohol which was used immediately without further purification due to its instability even when stored under argon and refrigerated. Sulfur was introduced by nucleophilic substitution of the mesylated alcohol by thiourea in acetone to give the

precipitated products of thiouronium salts[62] **503** and **504** in consistent yields after filtration and used without further purification (See section **2.3.2** for mechanisms). Characterisation of these salts proved difficult as they were insoluble in common deuturated NMR solvents such as chloroform, methanol and acetonitrile. They did however dissolve in deuturated water and DMSO. Removal of these solvents by evaporation in vacuu at high temperatures led to degradation of the salt. For this reason these salts were not characterised and used promptly in the next step of the synthesis towards benzofused systems.



Scheme 157. Formation of thiouronium salts.

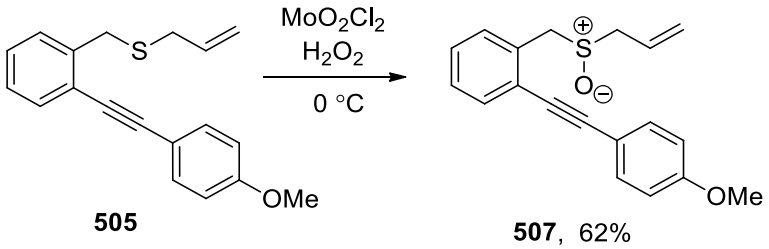
The allyl group was then installed *via* phase transfer catalysis (PTC) to give the relevant sulfides **505** and **506** (See section **2.3.2)** which required a column purification to remove any unreacted salt residues **503** or **504**. The ester substituted aryl benzofused compound **506**, degraded under PTC conditions and none of the starting precursor **504** was salvaged. The procedure to these sulfides *via* thiouronium salts **503** and **504** was implemented because it has been successfully used before in the group.[62] Also, the alternative preparation *via* an initial Mitsonobu reaction (See section **2.3.1**) with alcohols **499** and **500** to introduce the sulfur moiety led to low yields of **505**, and a complex crude mixture for **506** (unresolved spots on TLC) and non-isolable sulfide product.



Scheme 158. Installation of allyl moiety by phase transfer catalysis.

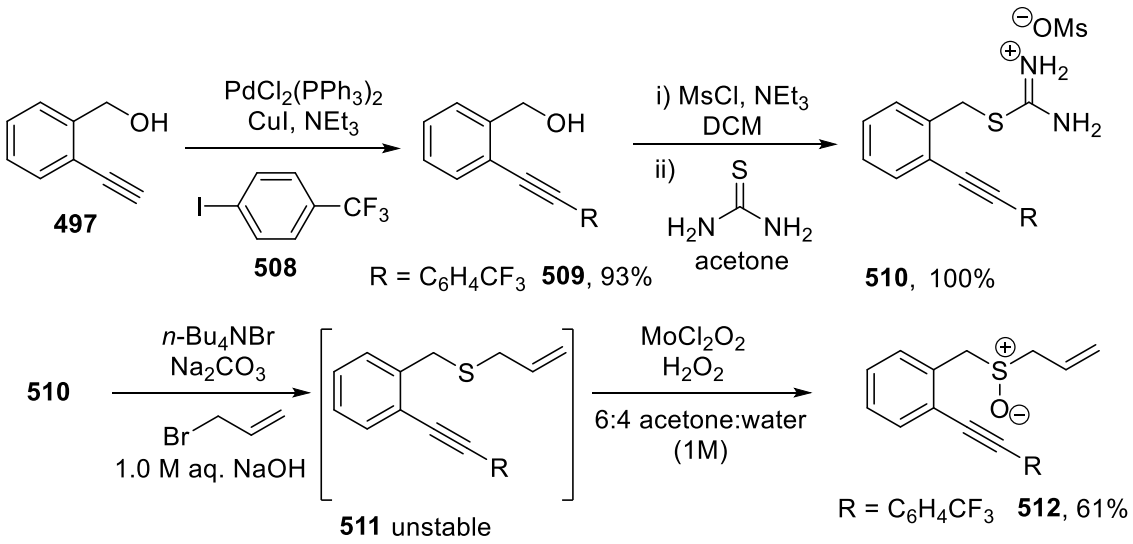
It was thought that the methylene hydrogens adjacent to the thiourea moiety in compound **504** were rendered acidic (due to the electron-withdrawing nature of the ester group) and prone to deprotonation in the presence of base giving unidentified degradation products.

The electron-rich sulfide system **505** on the other hand, was successfully prepared in the above synthesis and was chemoselectively oxidised to sulfoxide **507** in 62% yield using $MoCl_2O_2/H_2O_2$ at 0°C (Scheme 159).



Scheme 159. Oxidation of sulfide to sulfoxide using MoO_2Cl_2

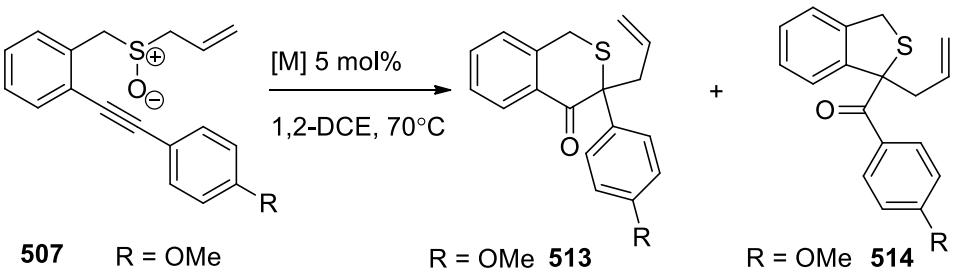
The failure to introduce a sulfur moiety in the synthesis of the electronically poor system led us to use a purely inductively electron-poor system. A system containing a trifluoromethane group was prepared instead, by the same reaction scheme (see Schemes 155-159 above) to yield 61% of the desired sulfoxide. The sulfide **511** was unstable to purification by silica packed column chromatography and was converted to sulfoxide **512** promptly.



Scheme 160. Synthesis of inductively electron-poor system.

2.6.3 Calalysis results

To our delight treating **507** with 10 mol% Au-**I** in 1,2-dichloroethane at 70 °C led to 100% conversion of starting material affording products **513** and **514** in 7% and 69% yields respectively (Table 13, entry 1) separated by column chromatography. As predicted for an electron-rich alkyne bias the predicted mechanism for initial sulfoxide attack onto the activated alkyne gave the major product **514** *via* a 7-*endo*-dig fashion (see Scheme 66 for mechanism). Much to our surprise under the same conditions **512** also gave **515** as the minor product at 8% yield and **516** as the major product at 54% (Table 13, entry 2). These products were obtained as a pure mixture and ratios are based on ^{1}H-NMR analysis as they coeluted. This is in contrast to our prediction that an electron-poor system would proceed *via* a 6-exo-dig mechanistic pathway to favour the 5-membered cyclic structure.



Scheme 161. Catalysis results of electronically biased biaryl systems.

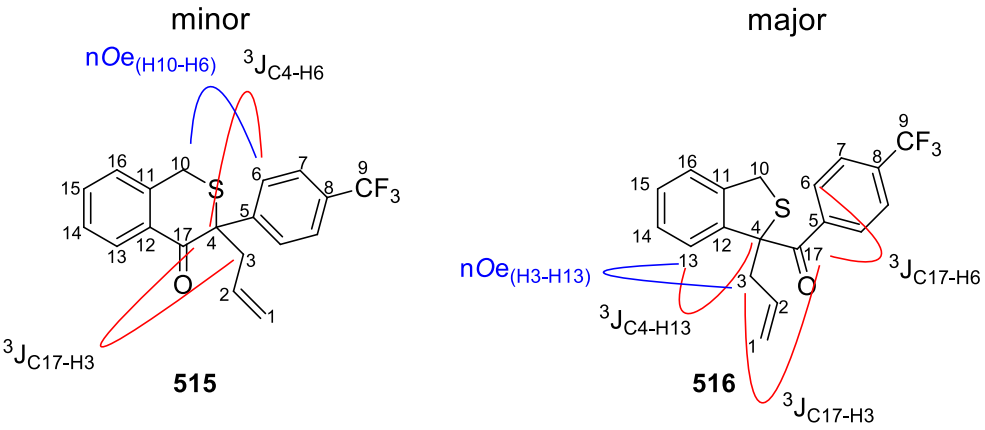
Entry	SM	[M][a]	(%) conversion	Product	Yield[b] (%)
1	**507**	Au-**I**	100	**513**	7
				514	69
2	**512**	Au-**I**	66	**515**	8[c,d]
				516	54[d]

Table 13. [a] Catalyst (10 mol%) was added to a solution of 1 in 1,2-dichloroethane (0.2*N*) in a sealed Argon purged Schlenk tube and heated to 70°C for 18 h. [b] Isolated yields after flash column chromatography. [c] Mixture of **515** and **516** was isolated (where yield of minor product **515** is based on H^1-NMR with internal standard durol). [d] Yield based on 66% conversion, 34% starting material was isolated by flash column chromatography.

2.6.4 ^{1}H-NMR studies to confirm unexpected results

Extensive NMR studies were carried out to confirm that the 5-membered cyclic structure was formed as the major product. The n*O*e diagnosis was not so straight forward for these electronically similar compounds. HMBC experiments were much more useful. It was identified that both the C17 carbonyl position and the quaternary carbon C4 may be of some use in determining major/minor products within the mixture using HMBC $^3J_{C\text{-}H}$ couplings. For the major 5-membered ring C17 shows ^{3}J to H6 of the 1,4-disubstituted aromatic ring as well as on H3 in HMBC. C4 quaternary showed HMBC to H13 and no signal to 1,4-disubstituted aromatic ring. For the minor 6-membered compound carbonyl C17 shows nothing to H6 of the 1,4-disubstituted aromatic ring but still to H3 in HMBC. C4 quaternary carbon shows HMBC to H6 but nothing to H13. Furthermore n*O*e studies

show relations between germinal H10 to H6 in the minor compound and in the minor n*O*e correlations are observed between H13 to H3. This analysis was complemented by MS analysis which showed in fragmentation of an arylketone for compound **516**.



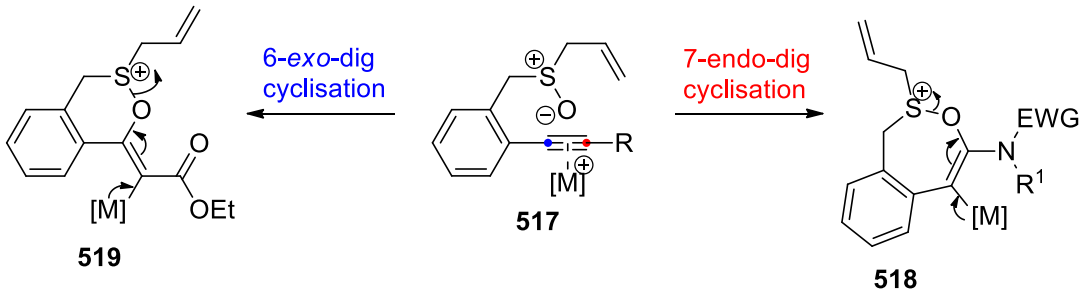
Scheme 162. HMBC ^{3}J couplings (red) and n*O*e relations (blue).

2.6.5 Summary/Conclusions

As predicted the electron-rich system gave rise to the formation of the 5-membered cyclic structure *via* the challenging 7-*endo*-dig cyclisation. The formation of **514** was not exclusive and a small amount of the 6-membered structure was also formed. This suggests that not all the regiospecific outcome is determined by the tether. It could be that the rigid benzene backbone is holding the two reactive entities to allow efficient orbital overlap to favour 7-*endo*-dig cyclisation over initial 6-*exo*-dig cyclisation. This could rationalise why incomplete selectivity is observed for the electron-poor system and why the results obtained are inconsistent with the predictions that favour formation of the 6-membered structure. Another reasoning behind this outcome may be due to the weaker inductive effects of the -CF_3 group operating through an aromatic ring tether in comparison to the directly attached ester group to the alkyne moiety (See Scheme 153 above). Though complete selectivity for 6-*exo*-dig was seen with the ester,[62] incomplete selectivity was observed in the presence of an aryl group.

2.6.6 Benzofused ynamides

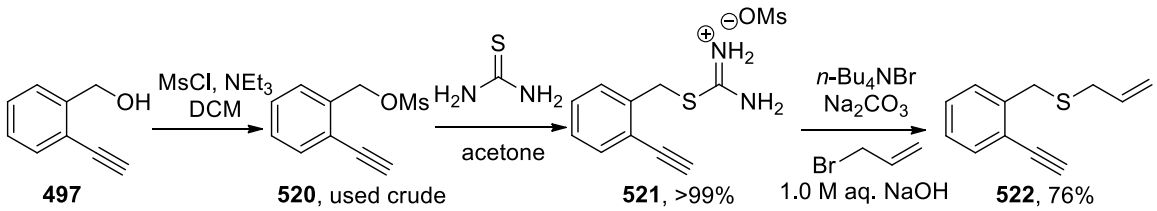
To try and improve selectivity for this pathway and access compounds of wider synthetic utility than arylketones, alkynes directly attached to electron-rich functionalities were explored. With the success of the ynamide chemistry for aliphatic systems (See section **2.5**), benzofused ynamides were investigated to allow exclusive 7-*endo*-dig cyclisation (Scheme 163).



Scheme 163. Proposed mechanistic pathways for directly attached electronic biased systems.

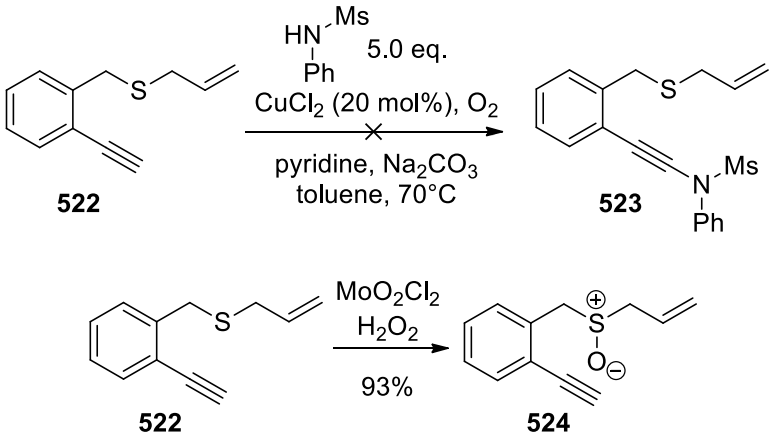
2.6.7 Preparation of sulfoxides

As previously described (See chapter **2.6.2**) benzyl alcohol was mesylated (not isolated and used crude) to create a good leaving group for the nucleophilic substitution reaction with thiourea in acetone. The resulting thioronium salt readily precipitated upon addition of hexanes to the reaction mixture and assuming a consistent yield it was used in the next step without further purification. Deprotection of sulfur with a known amount of aqueous sodium hydroxide followed by nucleophilic substitution of allyl bromide led to the desired sulfide **522** in an overall yield of 76% after column chromatography.



Scheme 164. Introduction of sulfur *via* thiouronium salt.

With the sulfur moiety in place Stahl's oxidative copper coupling conditions were applied to sulfide **522**. As a result of degradation of the starting sulfide, none of the desired amide coupled product **523** was seen on TLC. It was thought that the sulfur hinder reactivity between the copper catalyst and the terminal alkyne by so called sulfur poisoning. We therefore oxidised the sulfide to sulfoxide before attempting the Stahl amide coupling.

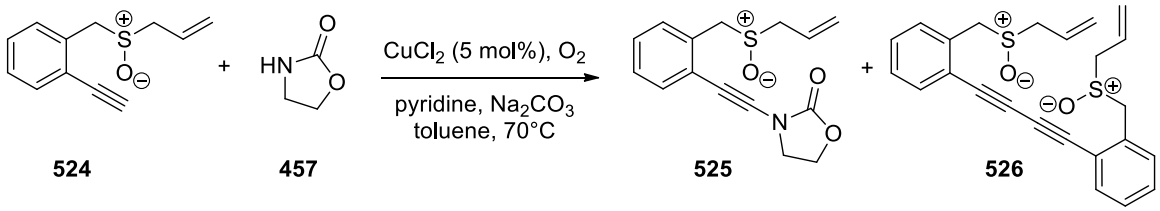


Scheme 165. Oxidative coupling failed for unprotected sulfide therefore sulfoxide **524** prepared.

With the two reactive entities, the nucleophilic sulfoxide oxygen, and the terminal alkyne held together at close proximity to each other by an aromatic group **524** we questioned if the Stahl reaction is a reliable route to ynamides. The two reactive entities present a synthetic challenge based on the possibility of copper catalysed cyclisation[110] utilising Stahl's procedure.

Commercially available oxazolidinone and its coupling partner alkyne were subjected to Stahl's conditions and much to our delight we observed a copper catalysed oxidative coupling of terminal alkynes, although only in modest yield. No copper catalysed cyclisation products were observed as initially expected, but a significant amount of the diyne byproduct was however isolated (Scheme 166, Table 14).

Modifications to the Stahl catalysis were tested to reduce or eliminate the diyne side-product. (Table 14, entry 1) shows that standard Stahl conditions with the addition of alkyne over 4 hours at 70 °C gave a considerable amount of the diyne product **526** at 40%, whereas the desired C-N coupled product **525** was isolated in only 12% yield. It was postulated that either the high temperature of 70 °C or the addition of alkyne over 4 hours was detrimental to the yield of the desired product or the mixed reactive copper(II) intermediate. To favour the mixed alkynyl amidate-copper(II) species the alkyne was added over 8 hours *via* syringe-pump (Table 14, entry 2) to keep the alkyne concentration low and minimise formation of the undesired diyne side-product. The temperature was reduced from the standard 70 °C to 50 °C to avoid degradation of the desired ynamide and to prolong its life whilst the addition of alkyne took place. Delightfully the desired C-N coupled product was formed in 20% yield and only a small amount of **526** at 5% yield was produced. With these positive results in hand the addition of alkyne was further slowed to over 10 hours and at 60 °C (Table 14, entry 3), indeed the desired product was formed in 45% yield with only trace amounts of the diyne product which was visible by TLC analysis. The diyne side-prodcut was easily removed by column chromatography as there was a large difference in the R_f values on TLC, in eluent containing 100% ethyl acetate the R_f values of **525** and **526** were 0.56 and 0.20.

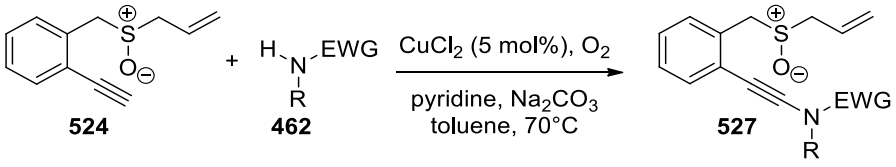


Scheme 166. Undesired side-product after subjecting sulfoxide **524** to Stahl conditions.

Entry[c]	Time/h	Temperature/°C	(%) conversion	Product	Yield[a] (%)
1	4	70	100	**525**	12
				526	40
2	8	50	60	**525**	20[b]
				526	5
3	10	60	100	**525**	45
				526	-

Table 14. Optimisation of Stahl conditions. [a] Isolated yield by column chromatography. [b] 15% of the starting sulfoxide-tethered enyne was also recovered by column. [c] Reactions were carried out on a 1.0 mmol scale with respect to sulfoxide under $CuCl_2$ (0.2 mmol) catalyst, Na_2CO_3 (2.0 mmol), pyridine (2.0 mmol) and amide **457** (5.0 mmol) in excess.

With the optimal conditions for C-N coupling by modifications to the Stahl conditions the question was posed whether these conditions could allow efficient formation of other ynamides required for catalysis using a variety of amide coupling partners? Table 15, entries 1-4 show various sulfonamides (See section **2.5.3.1** for preparation) successfully used as coupling partners to alkyne giving ynamides in moderate yields ranging from 20-49% yield. To consider diastereoselectivity, enantioenriched (*S*)-4-benzyl oxazolidinone (Table 15, entry 5) was employed to form ynamide in 48% yield.



Scheme 167. Ynamide preparation using optimised Stahl's conditions.

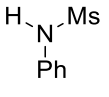
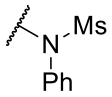
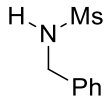
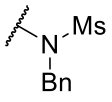
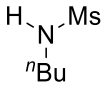
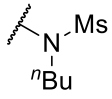
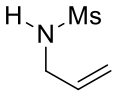
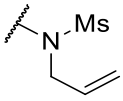
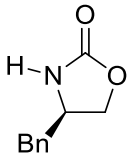
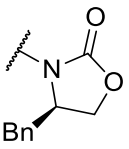
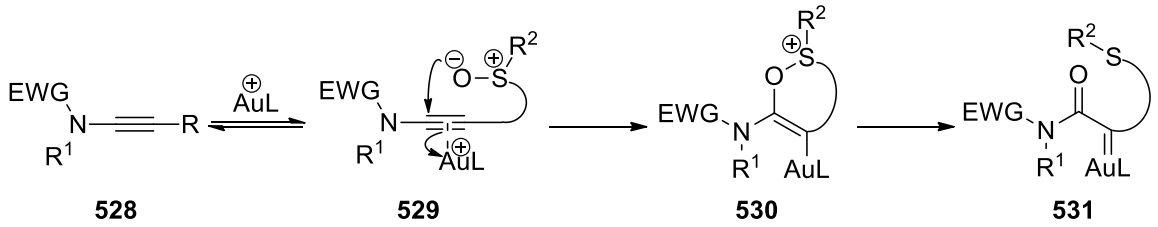
Entry[a]	H, N, EWG, R	Product	Yield[b] (%)
1	 **462a**	 **527a**	34
2	 **462b**	 **527b**	20
3	 **462c**	 **527c**	49
4	 **462d**	 **527d**	28
5	 **466**	 **527e**	48

Table 15. [a] Reactions were carried out on a 1.0 mmol scale with respect to sulfoxide under $CuCl_2$ (0.2 mmol) catalyst, Na_2CO_3 (2.0 mmol), pyridine (2.0 mmol) and the corresponding amide (5.0 mmol) in excess. [b] Isolated yields after flash column chromatography.

There were no other by-products isolated by column chromatography other than the excess amide **462** used and none of the diyne product was observed on TLC. The moderate yields could be as a result of degradation of the ynamide product **527** on silica. The column was repeated after treating the silica with 1% NEt_3, but led to no improvement of the yields. Theoretically, it could be that the steric bulk of both, the amides along with the sulfoxide starting materials do not allow the efficient formation of the desired Cu(II)-complex hindering ynamide preparation, hence the low yields. Furthermore, the sulfoxide starting material was known to be sensitive to high temperatures and prone to degradation.

2.6.8 Catalysis results

With ynamides **527a-527e** in hand, although in modest yield, they were subjected to gold catalysis to see if site-specific internal oxidation occurs to form α-oxo-gold carbenoids, followed by subsequent sulfur ylide generation as proposed.

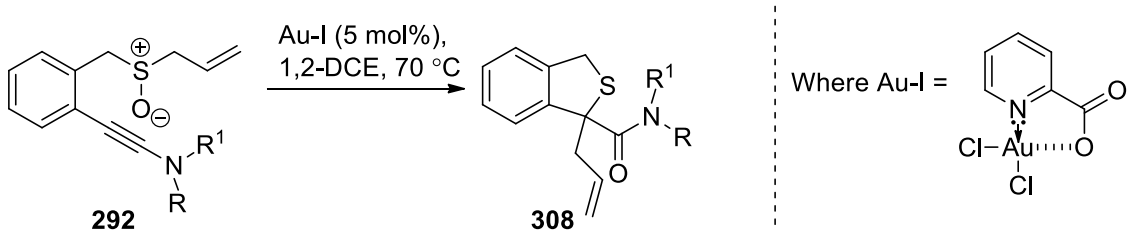


Scheme 168. Site specific introduction of gold carbenoid by regiospecific oxidation of ynamides.

As for the aliphatic systems (See section **2.5.2**), depending on the R-group substituents the mechanism could be influenced to undergo either; electrophilic aromatic substitutions, or thermal Aza-Claisen rearrangements[98] over sulfur ylide formation when R^1 is an aryl or allyl group.

Pleasingly substrates **527a-527e** gave benzofused sulfur heterocycles under catalytic amounts of Au-**I** (5 mol%) in 1,2-dichloroethane at 70 °C. Phenyl and benzyl substituted ynamides (Table 16, entry 2 and 3) gave the desired cyclic structures **533a** and **533b** in 74% and 81% yield respectively and none of the other possible side-reactivity discussed above was observed. From ^{1}H-NMR of the crude reaction mixture with internal standard durol, there were no other impurities and that consistent yields were achieved after catalysis. Purification by flash column chromatography to remove traces of gold residue led to isolated yields less than that determined by ^{1}H-NMR studies. This may be due to degradation of products on a silica column. The products were found to degrade at room temperature even when maintained under an argon atmosphere. After two days compound **533a** was left untouched under a constant flow of argon and no products could be seen by ^{1}H-NMR of the now discoloured material. Other substrates tested were a butyl substituted

ynamide **527c** which proceeded smoothly to the desired product **533c** in 88% yield (Table 16, entry 4). Use of an allyl substituted ynamide **527d** also gave the desired product **533d** in 90% yield favouring gold catalysed intramolecular redox reactivity over possible competing aza-Claisen rearrangement. Oxozolidinone substituted alkyne **525** also led to product **532** in good yield. Use of the chiral oxozolidinone ynamide **527e** led to 85% of the desired product **533e** but as a 1:1 mixture of diastereomers (Table 16, entry 6). A higher diastereomeric bias was hoped for, but with the chirality far away from the reactive site no transfer of chiral information occurred.



Scheme 169. General scheme of gold catalysis of ynamide to give cyclised sulfur compounds.

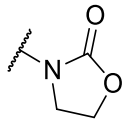
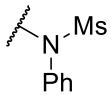
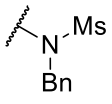
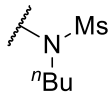
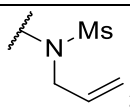
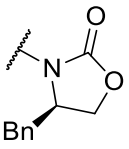
Entry[a]	Ynamide	Product	Yield[b] (%)
1	 **525**	**532**	74
2	 **527a**	**533a**	74
3	 **527b**	**533b**	81
4	 **527c**	**533c**	88
5	 **527d**	**533d**	90
6	 **527e**	**533e**	85 (1:1 *dr*)[c]

Table 16. [a] Au-**I** catalyst (5 mol%) was added to a solution of **525** or **527a**-**527e** in 1,2-dichloroethane (0.2 *N*) in a sealed Argon purged Schlenk tube and heated to 70°C for 2 h. [b] Isolated yields after flash column chromatography. [c] Where *dr* equals the diastereoisomeric ratio calculated by ^{1}H-NMR.

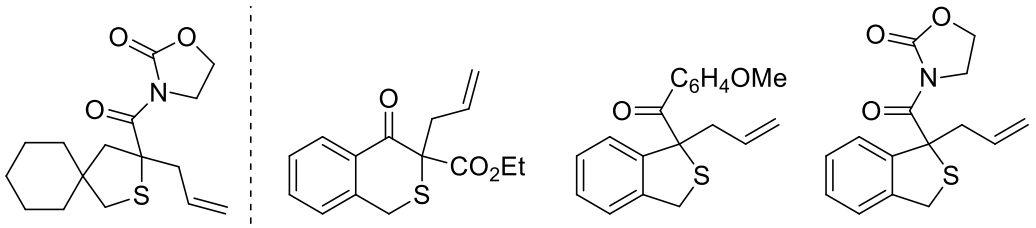
2.6.9 Summary

To summarise a variety of sulfoxide tethered ene-ynamides were synthesised by modifying conditions employed by Stahl and co-workers. Use of Au-**I** to catalyse the cyclisation-rearrangement of sulfoxide tethered alkynes has led to the formation of sulfur ylides in the presence of other competitive reactive pathways. The regio-specific control by altering the

electronical bias has allowed the access to interesting and highly complex sulfur heterocycles mimicking diazo-chemistry.

Higher yields of the benzo-fused systems of type **532** are isolated after column chromatography in comparison to the aliphatic systems (Scheme 170). It is postulated that the benzene ring in the starting material holds the alkyne moiety in a fixed position. This rotational barrier allows attack of the incoming sulfoxide nucleophile, once activated by gold to occur readily. On the other hand the flexible nature of the cyclohexyl ring allows free rotation around the CC bonds, slowing down reactivity between the sulfoxide and alkyne. Hence, the reaction times for the aliphatic systems were 18 h and for the aromatic system 2 h.

As predicted the ynamide electronic bias **532** gave the opposite outcome to the ester substituted precursor **490b**. As postulated the keto-iminium form of the gold activated ynamide allowed regiospecific reactivity, where the challenging 7-*endo*-dig cyclisation occurred exclusively. Where the electron-rich bias is directly attached to the alkyne, better selectivity and yield was observed.



476, 47%, 18 h | **490b**, 64%[a] | **514**, 69% | **532**, 74%, 2 h

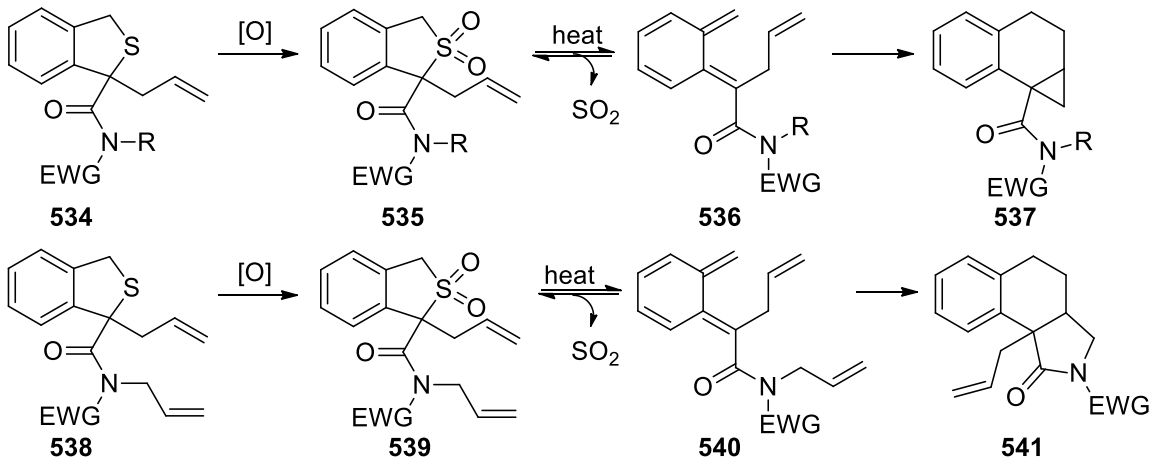
Scheme 170. Comparison of a variety of results throughout the thesis. [a] Previous result before project[62]

2.7 Reactivity post-cyclisation

Formation of even more complex structures and their possible screening for biological activity were anticipated post π-acid catalysed cyclisations. It was envisioned that oxidation of these 5-membered sulfur heterocycles could lead to sulfones. Related sulfones are known to undergo sulfur dioxide extrusion[111] under heat to form (conjugated dienes) which are ideal partners for alkenes in Diels-Alder cycloaddition reactions[112] giving complex polycyclic structures with rearomatisation.[113]

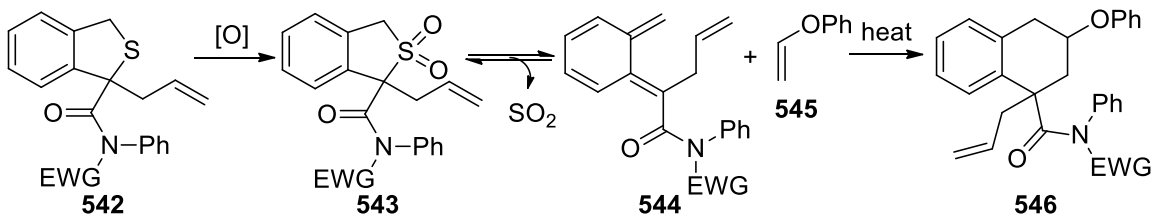
2.7.1 Research proposal

It was postulated that *in situ* generated conjugated dienes could undergo intramolecular Diels Alder reactions with the alkene tether to give either; cyclopropanated product **537**, or polycyclic amides from *N*-allyl compounds **541** (Scheme 171). For substrate **540** where two routes can be envisaged, generation of the 5-membered ring should be favoured over the 3-membered cyclopropane ring which is highly strained.



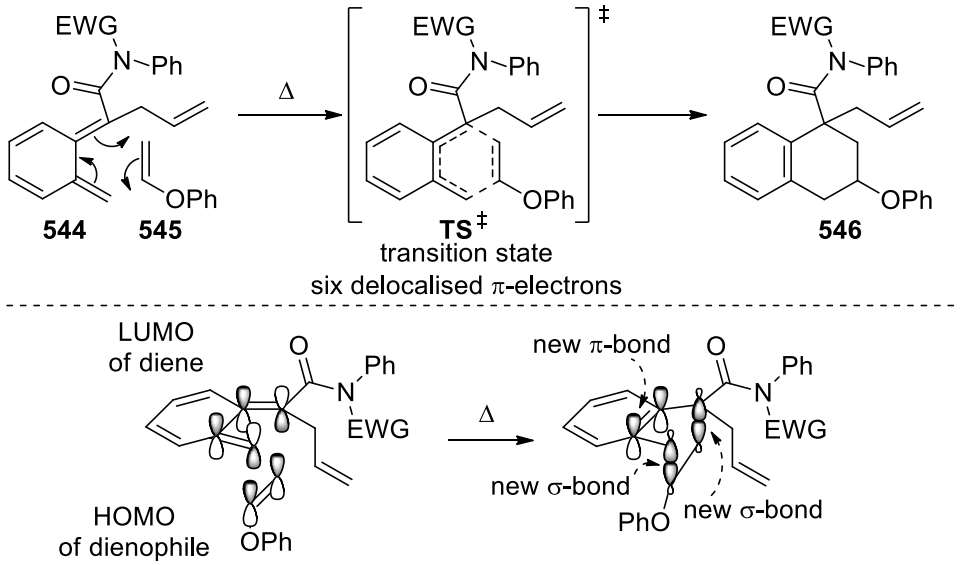
Scheme 171. Formation of complex structures with intramolecular Diels-Alder reactions.

It was also postulated that for non-allylic substituted amides **542**, intermolecular introduction of alkenes may also lead to an array of complex scaffolds of type **546**.



Scheme 172. Intermolecular cycloaddition reactions for non-allylic substituted amides

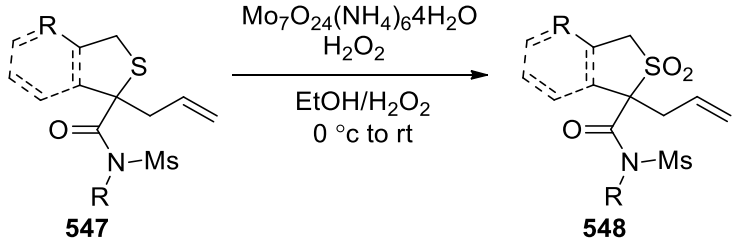
The Diels-Alder reaction occurs between a conjugated diene and an alkene (dienophile). After sulfur dioxide extrusion the diene has a fixed *cis*-conformation about the single bond which allows efficient overlap of the molecular orbitals involved with the dienophile and hence is a good Diels-Alder reagent. In order for the cycloaddition to work, two filled p-orbitals and two empty p-orbitals have to be available, with the right symmetry. In the presence of an electron-withdrawing amide moiety, the envisioned diene is electron-poor and will need an electron-rich dieneophile such as vinyl ether **545** to allow a pericyclic electron flow. The LUMO of the electron-poor diene and the HOMO of the dienophile are used because the orbitals are close in energy and give a better overlap in the transition state allowing rapid reactivity.[12]



Scheme 173. Mechanism of the Diels-Alder reaction and the frontier molecular orbital diagram involve

2.7.2 Reactivity of pre-installed functionality

Sulfide heterocycles **547** were oxidised using ammonium heptamolybdate catalyst (10 mol%) and 35% w/w aqueous solution of hydrogen peroxide (1*N*) in ethanol (1*N*) stirred at 0 °C. Allowing the reaction mixture to warm up to room temperature (18 °C) achieved sulfones **548** in excellent yields over 24-48 h (Table 17). Benzofused systems (Table 17, entry 1-3) oxidised smoothly in 24 h to sulfones **533a-533c** in excellent yields between 85-97% after purification by flash column chromatography. Aliphatic sulfur heterocycles containing allyl substituted amide **479d** (Table 17, entry 4) and tosylated amide **480c** (Table 17, entry 5) also oxidised to sulfones **548d** and **548e** under these conditions in 96% and 82% yields respectively. Sulfur heterocycles containing sensitive functional groups such as bromides **324c** and **327d** (Table 17, entry 6 and 7) also proceeded to sulfones **548f** and **548g** although in modest yield of 32% and 74% after column chromatography. The crude product **548f** was very clean and had a ^{1}H-NMR yield of 82% suggesting that passing this sulfone through an untreated silica column was detrimental to its yield. Treatment of the silica used for the column by 1% of triethylamine in the eluent still resulted in poor yields of the desired product.



Scheme 174. Chemoselective oxidation conditions for benzofused and aliphatic sulfur heterocycles.

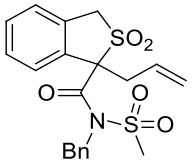
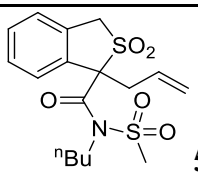
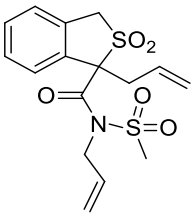
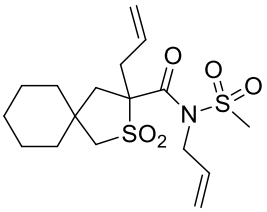
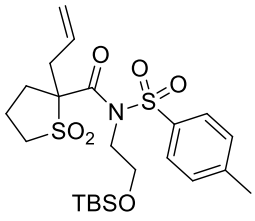
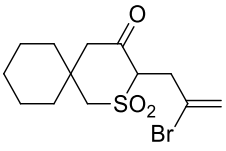
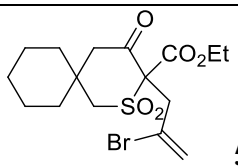
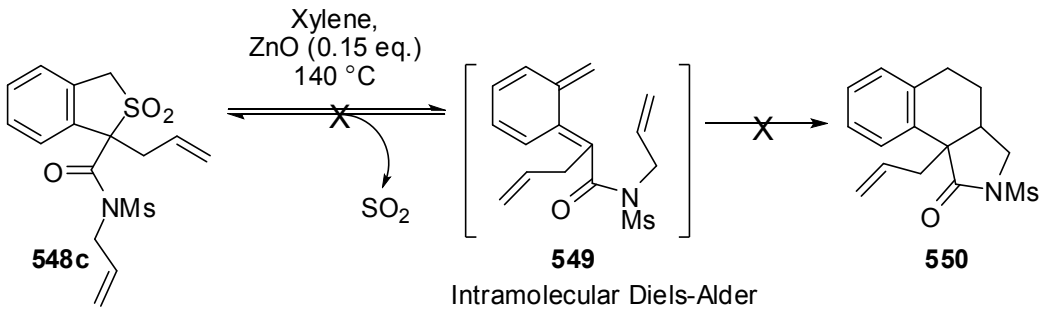
Entry[a]	Sulfide	Product	Yield[b] (%)
1	**533b**	 **548a**	92
2	**533c**	 **548b**	85
3	**533d**	 **548c**	97
4	**479d**	 **548d**	96
5	**480c**	 **548e**	82
6	**324d**	 **548f**	34(82)[c]
7	**327d**	 **548g**	79[d]

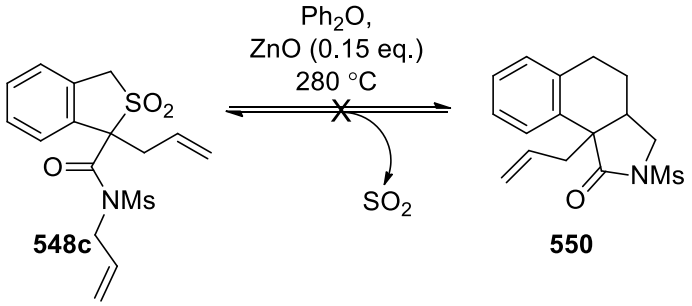
Table 17. [a] Ammonium heptamolybdate (10 mol%) was added to a solution of sulfide heterocycle in a 1:1 mixture of hydrogen peroxide and ethanol (1*N*) at 0°C. The reaction mixture was stirred and allowed to warm to room temperature until complete (monitored by TLC). [b] Isolated yields by flash column chromatography. [c] After column chromatography isolated yield dramatically dropped to 34%. The crude yield was 82% before chromatography. [d] Reaction was complete after 48 h.

With efficient oxidation conditions to yield 5-membered sulfones, sulfur extrusion was tested. Heating a solution of sulfone **548c** in xylene with a zinc oxide additive, at 140 °C led to no conversion and instead starting material was fully recovered. The xylene used was wet and the zinc oxide behaved as a drying agent.



Scheme 175. Intramolecular Diels-Alder cycloaddition after SO_2 extrusion led to 0% conversion.

This reaction was tried at elevated temperatures at 280 °C using diphenylether with 0.15 equivalents of zinc oxide additive resulting in 0% conversion of starting material to product and sulfone was recovered by flash column chromatography.

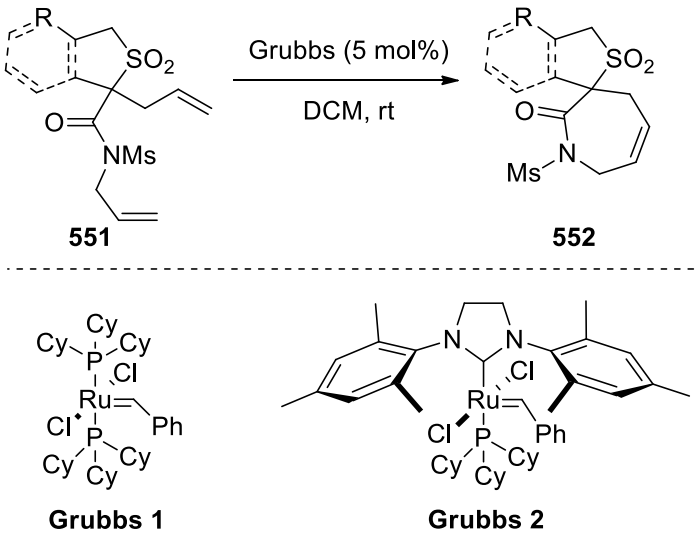


Scheme 176. Sulfur extrusion followed by intramolecular Diels-Alder cycloaddition.

Overall sulfur extrusion was unsuccessful even at elevated temperatures using known reaction conditions. Use of natural UV light also was unsuccessful, external dienophiles such as styrene also led to 0 % conversion of sulfone to products. It was concluded that vigorous reaction conditions were required to drive this reaction to give products. The starting material was highly stable and inert to high temperatures and UV light. Future experiments may involve microwaves to push the reaction forward.

2.7.3 Ring-closing metathesis

For sulfones containing two allyl units, the generation of complex 7-membered polycyclic amides was anticipated by Grubbs's catalysed ring closing metathesis.[114] These structures may lead to pharmacologically interesting scaffolds.[114] Again benzofused systems as well as aliphatic sulfur heterocycles containing allylic moieties were considered. Initially Grubbs 1 catalyst (5 mol%) was used in 1,2-dichloroethane at 70 °C to give the desired ring closed metathesis products (Table 18, entry 1 and 2 see parenthesis) in poor yields of 15-50%, where the unreacted starting material was recovered by column chromatography. However, subjecting these compounds to Grubbs's 2nd generation catalyst (5 mol%) in less toxic dichloromethane at room temperature (19 °C) led to the desired 7-membered cyclic amide products in excellent yields between 81-97% yields. Furthermore, the unoxidised sulfur heterocycle **480b** was expected to poison the Grubbs catalyst hindering reactivity, but instead led smoothly to the desired RCM product. The previously inert benzofused sulfone **548c** underwent ring closing metathesis smoothly to give amide **552c** under Grubbs catalysis.



Scheme 177. General ring-closing metathesis for benzofused as well as aliphatic sulfur heterocycles.

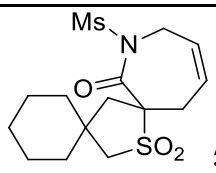
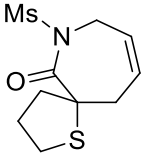
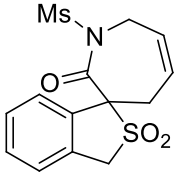
Entry[a]	SM[b]	Product	Yield[c] (%)
1	**548d**	 **552a**	87(50)[d], [e]
2	**480b**	 **552b**	81(15)[d], [e]
3	**548c**	 **552c**	97

Table 18. [a] Grubbs 2 catalyst (5 mol%) was added to a solution of sulfone or sulfide heterocycle in dichloromethane and allowed to stir at room temperature until reaction complete (monitored by TLC). [b] Where SM = starting material (5-membered post catalysis sulfide or sulfone). [c] Isolated yields by flash column chromatography. [d] Ring closing metathesis was tried with Grubbs 1 catalyst to give poor yields of the desired product and incomplete conversion of starting material. [e] Grubbs 1 catalyst (5 mol%) was added to a solution of catalysis product in 1,2-dichloeoethane and stirred. The reaction mixture was allowed to heat to 70 °C.

Chapter 3: Experimental

3.1 Instrumentation

The solvents used were purified using a Pure Solv-MD Solvent Purification System (alumina columns) from Innovative Technology and were transferred under Ar. Dichloroethane used were purified by distillation over calcium hydride as a drying agent and transferred under argon. Pyridine was distilled over calcium hydride and used directly. Asynt DrySin heating blocks on stirrer hotplates were employed with temperature control *via* an external probe. Flash chromatography: Fluorochem silica gel 60 (43-63 μm). Thin layer chromatography (TLC): Macherey Nagel silica gel $60F_{254}$ analytical plates (plastic support) which were developed using standard visualizing agents: UV fluorescence (254 and 366 nm), phosphomolybdic acid /Δ, and potassium permanganate /Δ. IR: Perkin-Elmer Spectrum 100 FTIR spectrometer, only selected absorbences (υ_{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 ^{1}H-RMS (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 compounds were purchased from Aldrich, Fluka, Acros, Strem, Alfa Aesar and used without further purification. NMR: Spectra were recorded on Bruker AVIII300 (^{1}H = 300 MHz, ^{13}C = 75.5 MHz), Bruker AVIII400 (^{1}H = 400 MHz, ^{13}C = 101 MHz) in the solvents indicated; $CDCl_3$ was purchased from Aldrich (no TMS) and Cambridge Isotope Laboratory (0.05% v/v TMS); Chemical shifts (δ) are given in ppm relative to TMS. In the absence of TMS, solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_C = 77.0 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm). Coupling constants (*J*) are reported in Hz. 1D ^{13}C-NMR spectra were recorded using the JMOD or PENDANT pulse sequences from the Bruker standard

pulse program library. Melting points were recorded using open glass capillaries on a Stuart Scientific apparatus and are uncorrected.

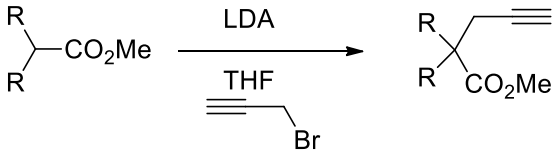
Reactions were followed by thin layer chromatography (TLC) using Macherey Nagel silica gel 60F254 analytical plates (plastic support) which were developed using standard visualising agents: UV fluorescence (254 and 366 nm), and potassium permanganate/Δ. Purification by flash chromatography was performed using Fluorochem silica gel 60 (0.043-0.063 nm).

All reactions in non-aqueous solvents were conducted in flame-dried glassware under an argon atmosphere with magnetic stirring. Volumes of less than 0.2 mL were measured and dispensed with gas-tight syringes. Evaporation and concentration under reduced pressure was performed at 10-700 mbar at 40 °C. All pure products of the reactions were dried under high vacuum (1 mbar).

Dichloroethane used was purified by distillation over calcium hydride as a drying agent and transferred under argon. Pyridine was distilled over calcium hydride and used directly.

3.2 General Methods

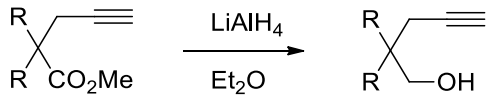
General procedure 1-Alkylation[80] (GP1)



To a stirred solution of $^{i}Pr_2NH$ (1.1 eq., 11.0 mmol, 1.5 mL) in dry THF (5 mL) at 0 °C was added *n*-BuLi (1.05 eq., 10.5 mmol, 14 mL of 2.5*N* w/w solution in hexane) dropwise over 5 min, and stirred for 30 min at 0 °C. After being cooled to -78 C methyl acetate (1.0 eq., 10.0 mmol) in dry THF (15 mL) was added slowly over 2 min to the reaction mixture and further stirred for 1.5 h at the same temperature before propargyl bromide (1.05 eq., 10.5

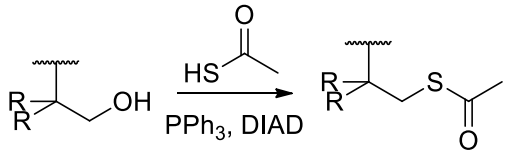
mmol, 0.8 mL) was added. The resulting reaction mixture was allowed to warm to room temperature and further stirred for 16 h. The reaction was quenched with aq. NH_4Cl and the organic phase extracted with EtOAc. The organic phase was washed with H_2O (2 × 20 mL), aq. NaCl (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography gave the desired ester.

General procedure 2-Reduction[80] (GP2)



To a stirred mixture of $LiAlH_4$ (1.04 eq.) in dry Et_2O (0.6*N*) at 0 °C was added methyl carboxylate (1.0 eq.) in dry Et_2O (5 mL). The resulting reaction mixture was allowed to warm to room temperature and further stirred for 3 h. To the reaction mixture was added 3 mL of silica gel in aq. NaOH solution (1.0*N*) slowly to avoid overspill until the precipitate turned white. H_2O (10 mL) was then added to the reaction mixture and the organic phase extracted with Et_2O (2 × 20 mL). The organic phase was filtered through a plug of silica. Et_2O was removed under reduced pressure and the crude product purified by flash column chromatography to give 2,2-disubstituted pent-4-yn-ol.

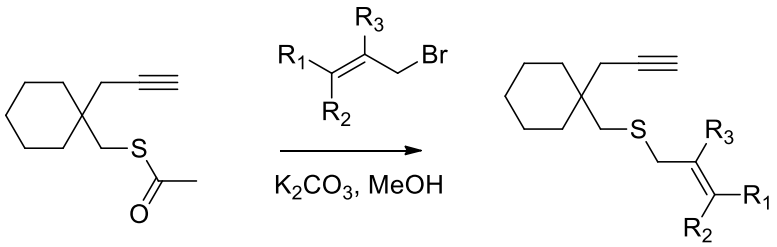
General Procedure 3-Mitsunobu reaction[78] (GP3)



To a solution of PPh_3 (1.55 eq.) in dry THF was slowly added DIAD (1.55 eq.) at 0 °C. After 30 min, a solution of relevant alcohol (1.0 eq.) and thioacetic acid (1.5 eq.) in THF was added at 0 °C. The reaction mixture was quenched with aq. NH_4Cl and extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with aq. NaCl solution, dried over Na_2SO_4 and filtered. The crude mixture was treated with hexanes, and the

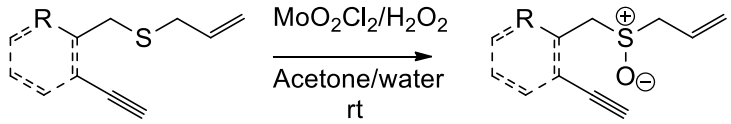
precipitate of $Ph_3P=O$ was removed by filtration. Evaporation and further purification of the filtrate by Kügelrohr distillation led to the desired thioester.

General Procedure 4-Alkylation of sulfur[82] (GP4)



To a solution of thioether (1.0 eq., 2.4 mmol, 0.5 g), in anhydrous MeOH (0.5 *N*, 5 mL) was added allyl bromide (1.1 eq.) and K_2CO_3 (1.0 eq., 2.4 mmol, 0.3 g) and stirred at room temperature for 16 h. The reaction mixture was quenched with aq. NH_4Cl solution, extracted with Et_2O (2 × 20 mL), dried over Na_2SO_4 and filtered. The crude residue was used without further purification if significantly pure, otherwise the residue was purified by column chromatography.

General Procedure 5-oxidation of sulfides to sulfoxides[79] (GP5)

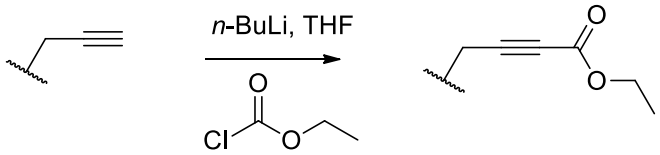


MoO_2Cl_2 (1.5 mol%, 6 mg) and H_2O_2 (1.05 eq., 2.1 mmol, 0.2 mL of a 35 % solution in water) were added successively to a solution of sulfane (1.0 eq., 2.0 mmol) in 6:4 ratio of acetone and water (0.4 *N*, 5 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred until reaction was complete (TLC analysis). The reaction mixture was quenched with aq. NaCl and the organic layers extracted with EtOAc (2 × 10 mL). The combined extracts were washed with H_2O, aq. NaCl, dried over Na_2SO_4 and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel to give the desired sulfoxide product.

General Procedure 6-Au(I) catalysis[62] (GP6)

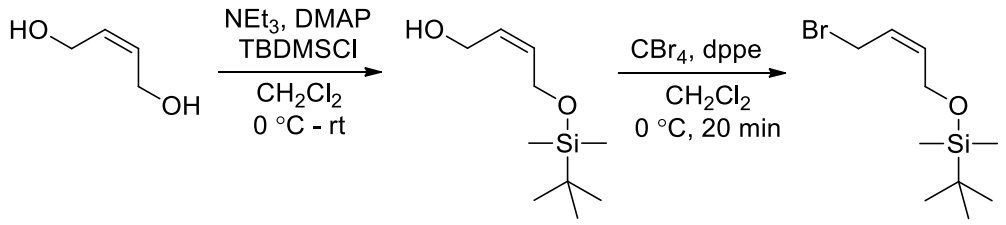
Au-**I** (5.0 mol%, 5 μmol, 2 mg) or $PtCl_2$ (10 mol%, 10 μmol, 3 mg) was added to a solution of the relevant internal or terminal sulfoxide (0.1 mmol) respectively in dry 1,2-DCE (0.2 *N*) in a flame dried Schlenk tube under an Ar atmosphere. Upon completion of the reaction (monitored by TLC) the crude mixture was passed through a small plug of silica to remove gold residues. The solvent was evaporated to give a crude mixture which was purified by column chromatography using mixtures of hexanes and ethyl acetates to give the desired cyclic products.

General procedure 7-tethering of terminal alkynes (GP7)



n-BuLi (2.5 *N* solution in hexanes, 1.1 eq., 1.7 mmol, 0.7 mL) was added to a solution of alkyne (1.0 eq., 1.5 mmol) in dry THF (0.12 *N*, 15 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 15 min before the addition of ethylchloroformate 97% pure (1.2 eq., 1.8 mmol, 0.2 mL) then was further stirred for 2 h at the same temperature. The reaction mixture was hydrolysed with aq. NH_4Cl, and extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with aq. NaCl solution, dried over Na_2SO_4 and filtered. The crude residue was purified by column chromatography on silica to remove any unreacted alkyne.

General Procedure 8-silylation[117] (GP8)



A solution of TBSCl (4.3 g, 28 mmol) and DMAP (693 mg, 10 mol%, 6.0 mmol) in DCM (12 mL) was added to a solution of *cis*-2-butene-1,4-diol (57 mmol, 5 mL) and triethylamine (34.0 mmol, 5 mL) in DCM (140 mL) dropwise over 4 h using a syringe pump. The resulting mixture was stirred at ambient temperature for a further 4 h before being quenched with aqueous ammonium chloride (100 mL). the organic layer was extracted with DCM then washed with water (2 × 100 mL) and brine (2 × 100 mL), and dried over Na_2SO_4. Concentration of the solution led to a yellow residue which was purified by flash column chromatography using hexanes and ether.

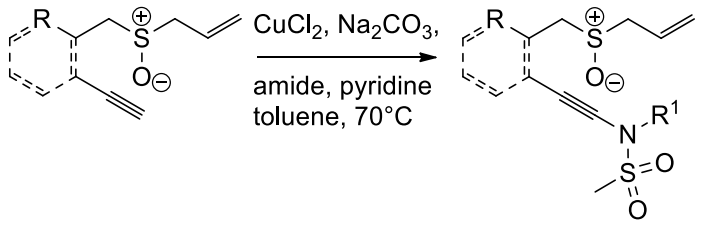
General procedure 9-bromination[118] (GP9)

Tetrabromomethane (1.8 g, 5.4 mmol) and dppe (bis(1,2-diphenylphosphino)ethane) (2.4 g, 6.0 mmol) was added to a solution of silyl ether (1.0 g, 5.0 mmol) in DCM at 0 °C. The resulting reaction mixture was stirred at room temperature (20 °C) for 20 min. the solvent was removed by rotary evaporator and the residue was extracted with hexane. The organic extracts were concentrated to yield bromide. Due to its instability it was used promptly without the need for purification by flash column chromatography.

General procedure 10-

Copper catalysed oxidative coupling of sulfoxides and amides to give ynamides[99]

(GP10)



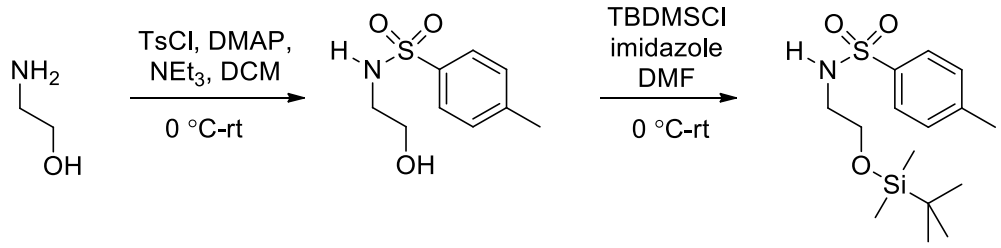
In a 250 ml three-neck round-bottom flask equipped with a stir-bar, $CuCl_2$ (0.2 eq., 0.2 mmol, 27 mg), amide (5.0 eq., 5.0 mmol) and Na_2CO_3 (2.0 eq., 2.0 mmol, 212 mg) were combined. The reaction flask was purged with oxygen gas for 15 minutes. A solution of pyridine (2.0 eq., 2.0 mmol) in 5 ml dry toluene was added to the reaction flask via a syringe. A balloon filled with oxygen gas was connected to the reaction flask via a needle. The flask was placed in an oil-bath and heated to 70 °C. A solution of the relevant acetylene (1.0 eq., 1.0 mmol) in 5 ml dry toluene was added to the flask over 4 h *via* syringe pump. After the addition of acetylene/toluene solution, the reaction mixture was allowed to stir at 70 ºC for another 10 h and then cooled to room temperature. After the crude mixture was filtered through a plug of silica using a pipette and concentrated under vacuum, the crude mixture was purified by flash chromatography on silica gel to yield the desired ynamide.

General procedure 11-Mesylation of amines[121] (GP11)

The relevant amine (1.0 eq., 20.0 mmol) was diluted in DCM (0.4 *N*, 50 mL) before NEt_3 99% pure (2.0 eq., 40.0 mmol, 6 mL) and MsCl 99+% pure (1.1 eq., 22.0 mmol, 1.7 mL) were added simultaneously at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for 4 h monitored by TLC analysis (the amide precipitated out in most cases). Then the DCM was concentrated down to 20 mL under vacuum. The

concentrated reaction mixture was then quenched with aq. NH_4Cl and the organic layer washed with H_2O, aq. NaCl and extracted with EtOAc (2 × 30 mL), dried over Na_2CO_3 and concentrated. Purification by flash column chromatography led to the desired mesylated amide.

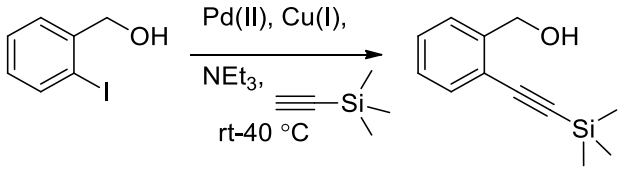
General procedure 12-tosylation[101] (GP12)



A solution of tosyl chloride (7.0 g, 37.0 mmol) in dichloromethane (40 mL) was added slowly (dropwise over 2 h) to a solution of 99.5% pure 2-aminoethanol (2.2 g, 35.0 mmol, 2 mL), DMAP (0.4 g, 3.5 mmol) and triethylamine (7.1 g, 70.0 mmol, 10 mL) in dichloromethane (80 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C overnight and allowed to warm up to room temperature before being quenched with water (2 × 120 mL). The organic layer was washed with brine (2 × 100 mL) before being extracted with dichloromethane (200 mL), dried over Na_2SO_4 and solvent removed under *vacuo*. Purification by flash column chromatography led to the desired alcohol product. Imidazole (3.2 g, 46.5 mmol) and 50% pure in toluene w/w TBSCl (4.2 g, 27.9 mmol, 10 mL) were added to a solution of alcohol (5.0 g, 23.2 mmol) in anhydrous DMF (1.17 *N*, 20 mL). The resulting reaction mixture was left to stir overnight at room temperature (19 °C) before being poured into water (100 mL) and extracted with diethyl ether (100 mL). The organic layer was washed with water (2 × 100 mL) and brine (2 × 100 mL) then dried over Na_2CO_3 and solvent removed under *vacuo.* Purification by flash column chromatography resulted in the desired silyl ether.

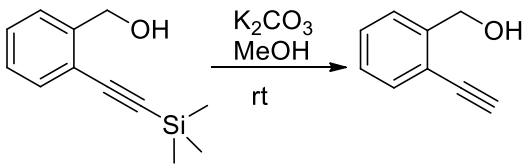
General Procedure 13-Sonogashira[106] (GP13)

Method A



TMS-acetylene (2.0 eq., 40.0 mmol, 5.5 g), $Pd(PPh_3)_2Cl_2$ (1.5 mol%, 0.3 mmol, 211 mg), CuI (3.0 mol%, 0.6 mmol, 114 mg) were purged with an N_2 atmosphere in a flame dried flask, before a solution of 2-iodo-1-benzylalcohol (1.0 eq., 20.0 mmol, 4.7 g) in NEt_3 (0.2 *N*, 100 mL) was added at 0 °C. The reaction mixture was allowed to reach room temperature under N_2 before being heated to 40 °C. The reaction mixture was filtered to remove any $HNEt_3^+I^-$ salt, residues of Pd(0) catalyst. The filtrate was diluted with EtOAc (2 × 50 mL) and the organic layer was washed with aq. NH_4Cl solution, H_2O and aq. NaCl, dried over Na_2CO_3 and concentrated. The resulting crude product was purified by flash column chromatography.

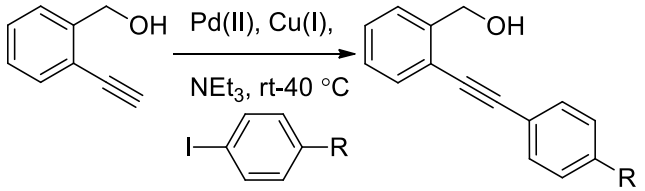
General procedure 14-base catalysed desilylation[107] (GP14)



Benzyl alcohol (1.0 eq., 20.0 mmol, 4.1 g) was dissolved in methanol (5 mL) and diluted with further methanol (0.16 *N*, 120 mL), before K_2CO_3 (2.0 eq., 40.0 mmol, 5.5 g) was added and the resulting reaction mixture was stirred at room temperature. After stirring for 4 h until reaction complete (TLC analysis) aq. NH_4Cl was added and the organic layer washed with H_2O, aq. NaCl and extracted with Et_2O (2 × 50 mL), dried over Na_2CO_3 and concentrated. The resulting crude product was purified by flash column chromatography.

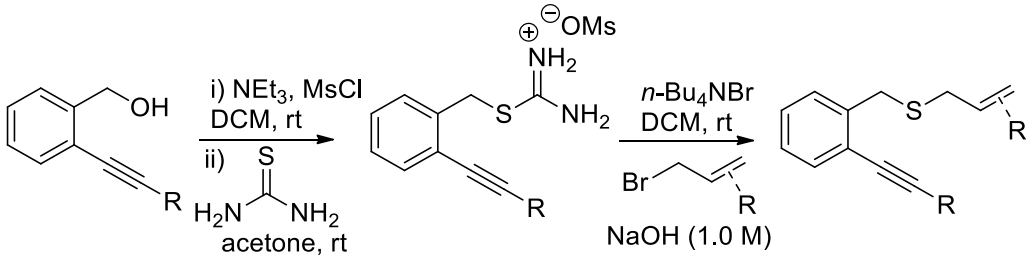
General Procedure 15-Sonogashira catalysis (GP15)

Method B



Acetylene (1.0 eq., 10.0 mmol, 1.3 g), $Pd(PPh_3)_2Cl_2$ (1.5 mol%, 0.15 mmol, 105 mg), CuI (3.0 mol%, 0.3 mmol, 57 mg) were successively added to a solution of the relevant *ortho*-iodocompound (1.1 eq., 11.0 mmol) in NEt_2 (0.2 *N*, 50 mL) at 0 °C under an N_2 atmosphere. The resulting mixture was stirred at room temperature until complete (TLC analysis), then filtered through a pad of Celite®, then diluted with Et_2O. The organic layer was washed with H_2O, and aq. NaCl before being dried over Na_2CO_3 and concentrated. The resulting crude product was purified by flash column chromatography.

General Procedure 16-Thiouronium salt formation[62] (GP16)



Benzyl alcohol (1.0 eq., 10.0 mmol, 1.3 g) was diluted in DCM (0.16*N*, 60 mL) before NEt_3 99% pure (1.6 eq., 16.0 mmol, 2.2 mL) and MsCl 99+% pure (1.5 eq., 15.0 mmol, 1.2 mL) were added simultaneously at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for 1 h (monitored by TLC analysis) before the DCM was concentrated down to 20 mL under vacuum. The concentrated reaction mixture was then quenched with aq. NH_4Cl and the organic layer washed with H_2O, aq. NaCl and extracted with EtOAc (2 × 30 mL), dried over Na_2CO_3 and concentrated to give mesylated benzyl alcohol and used crude in the next step. The mesylated benzyl alcohol (1.0 eq., 10.0 mmol,

2.1 g) was diluted with acetone (0.2 *N*, 40 mL) before thiourea (1.1 eq., 11.0 mmol, 0.8 g) was added. After stirring for 16 h the solid precipitate was collected by filtration. Hexane was added to the filtrate to allow further precipitation of the thiourea salt product before being filtered again, this process was repeated 3 times to allow sufficient extraction of product. The crude thiourea salt product (1.0 eq., 10.0 mmol, 2.9 g) was diluted with DCM (0.2*N*, 40 mL) and *n*-Bu_4NBr (0.2 eq., 2.0 mmol, 0.6 g), relevant allyl bromide (1.1 eq., 11.0 mmol) and lastly an aq., solution of 1.0*N* NaOH (0.2*N*, 40 mL). The phase transfer catalysis mixture was stirred at room temperature for 20 h before being quenched with aq. NH_4Cl and the organic layer washed with H_2O, aq. NaCl and extracted with EtOAc (2 × 50 mL), dried over Na_2CO_3 and concentrated to give benzofused allylsulfane. The resulting crude product was purified by flash column chromatography.

General procedure 17-oxidation of sulfoxide to sulfone[79] (GP17)

General procedure 5 was followed, but using cyclised heterocycle (0.1 mmol) and MoO_2Cl_2 (3.0 mol%) instead to allow complete oxidation of these heterocycles to the corresponding sulfones.

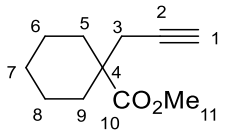
General Procedure 18-Grubbs's ring closing metathesis[114] (GP18)

To a solution of amide (0.05 mmol) in 1, 2-DCE (0.1*N*, 0.5 mL) was added Grubbs 2 catalyst (5.0 mol%, 2 mg). The reaction Schlenk was flushed with argon sealed and heated to 70 °C for 6 h. The solvent was removed under vacuum, and the crude residue purified by flash column chromatography using silica gel.

3.3. Analysis and characterisation

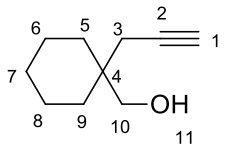
3.3.1 Sulfur ylide formation *vs* electrophilic aromatic substitutuion

Methyl 1-(prop-2-ynyl)cyclohexanecarboxylate (275)



Following GP 1, methyl 1-(prop-2-ynyl)cyclohexanecarboxylate was prepared using methyl cyclohexanecarboxylate (10.0 mmol, 1.4 g) as a yellow liquid (1.8 g, 97% yield); R_f 0.35 (6% EtOAc: 94% hexane); ν_{max}(neat) / (cm^{-1}) 3294 w (CC-H), 2935 m, (C-H), 2174 w (CC) 1729 s (C=O), 1200 s (C-O), 1133 s (C-O); δ_H (300 MHz, $CDCl_3$) 1.30-1.57 (8H, m, H-5-8, C*H*$_2$, cyclohexyl), 2.01 (1H, t, *J* 2.7, H-1, CH_2CCH), 2.06-2.09 (2H, m, H-9, C*H*$_2$, cyclohexyl), 2.40 (2H, d, *J* 2.7, H-3, C*H*$_2$CCH), 3.71 (3H, s, C-11, C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 22.9 (2C, *C*H_2, cyclohexyl), 25.5 (1C, *C*H_2CCH), 29.0 (1C, *C*H_2, cyclohexyl), 33.1 (2C, *C*H_2, cyclohexyl), 46.7 (1C, quat., *C*CO_2CH_3), 51.8 (1C, *C*H_3), 70.7 (1C, C*C*-H), 80.2 (1C, quat., *C*CH), 176.0 (1C, quat., C(O)). Data were consistent with that reported in the literature.[115]

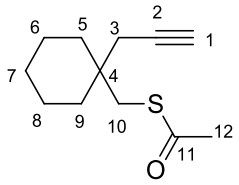
(1-(Prop-2-ynyl)cyclohexyl)methanol (276)



Following GP 2, using $LiAlH_4$ (11.5 mmol, 0.4 g) and methyl 1-(prop-2-ynyl)cyclohexane carboxylate (2.0 g, 11.1 mmol) in E_2O (20 mL) afforded alcohol as a yellow oil (1.6 g, 98% yield); R_f 0.28 (16% EtOAc: 84% hexane); ν_{max}(neat) / (cm^{-1}) 3396 brs (OH), 3307 m (CC-H), 2925 s (C-H), 2853 m (C-H), 2115 w (CC), 1453 m (C-O); δ_H (300 MHz, $CDCl_3$) 1.35-1.52 (10H, m, H-5-9, CH_2, cyclohexyl), 1.57 (1H, s, H-11, O*H*), 2.00 (1H, t, *J* 2.5, H-1,

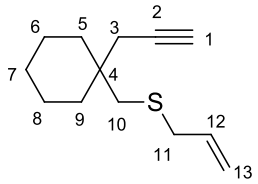
CH_2CCH), 2.27 (2H, d, *J* 2.5, H-3, CH_2CCH), 3.57 (2H, s, H-10, CH_2OH); δ_C (101 MHz, $CDCl_3$) 21.5 (2C, CH_2, cyclohexyl), 25.1 (1C, CH_2CCH), 26.1 (1C, CH_2, cyclohexyl), 31.9 (2C, CH_2, cyclohexyl), 37.6 (1C, quat., CCH_2OH), 68.6 (1C, CH_2OH), 70.4 (1C, CH_2CCH), 82.0 (1C, CH_2CCH). Data were consistent with that reported in the literature.[116]

((1-(Prop-2-yn-1-yl)cyclohexyl)methyl)ethanethioate (278)



GP 3 was followed using PPh_3 (47 mmol, 12.2 g), DIAD 94% pure (47 mmol, 10 mL), (1-(prop-2-ynyl)cyclohexyl methanol (30 mmol, 4 g) and thioacetic acid 96% pure (45 mmol, 3.4 mL) to prepare thioester as a yellow oil (5.6 g, 88% yield); R_f 0.28 (16% EtOAc:84% hexane); ν_{max}(neat) / (cm^{-1}) 3291 m (CC-H), 2923 s, 2852 m (C-H), 2116 w (CC), 1689 s (C=O); δ_H (300 MHz, $CDCl_3$) 1.20-1.53 (10H, m, H-5-9, CH_2, cyclohexyl), 1.97 (1H, t, *J* 2.7, H-1, CH_2CCH), 2.17 (2H, d, *J* 2.7, H-3, CH_2CC), 2.32 (3H, s, H-12, ($C(O)CH_3$), 3.07 (2H, s, H-10, $CH_2SC(O)$); δ_C (101 MHz, $CDCl_3$) 21.6 (2C, CH_2, cyclohexyl), 25.8 (1C, $C(O)CH_3$), 27.4 (1C, CH_2CCH), 30.7 (1C, quat., CH_2CCH_2), 34.0 (2C, CH_2, cyclohexyl), 36.5 (1C, $CH_2SC(O)CH_3$), 37.1 (1C, CH_2, cyclohexyl), 70.8 (1C, quat., CH_2CCH), 81.0 (1C, CH_2CCH), 195.3 (1C, quat., C=O); m/z (TOF MS EI^+) $[M]^+$ 210 (5%), $[M-C(O)CH_3]^+$ 168 (100%); HRMS (TOF MS EI^+) calculated for $C_{12}H_{18}SO$ 210.1078, found 210.1086.

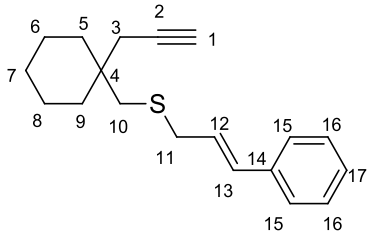
Allyl ((1-(prop-2-yn-1-yl)cyclohexyl)methyl) sulfane (290a)



Following GP 4, using allyl bromide 99+% (2.7 mmol, 0.2 mL), allyl sulfane was prepared as a colourless oil (0.3 g, 60% yield); R_f 0.29 (3% EtOAc: 97% hexane); ν_{max}(neat) / (cm^{-1})

3304 m (CC-H), 2923 s (C-H), 2850 s (C-H), 2114 m (CC), 1634 m (C=C), 1452 (C-S); δ_H (300 MHz, $CDCl_3$) 1.31-1.52 (10H, m, H-5-9, CH_2, cyclohexyl), 1.96 (1H, t, *J* 2.7, H-1, CH_2CCH), 2.29 (2H, d, *J* 2.7, H-3, CH_2CCH), 2.58 (2H, s, C-10, CH_2S), 3.13 (2H, dt, *J* 7.1, *J* 1.1, H-11, SCH_2), 5.04-5.14 (2H, m, H-13, $CHCH_2$), 5.72-5.85 (1H, m, H-12, $CHCH_2$); δ_C (101 MHz, $CDCl_3$) 21.7 (2C, CH_2, cyclohexyl), 25.9 (1C, CH_2, cyclohexyl), 26.9 (1C, CH_2), 34.5 (2C, CH_2, cyclohexyl), 36.4 (1C, CH_2), 37.2 (1C, quat., cyclohexyl), 39.8 (1C, CH_2S), 70.5 (1C, CCH), 81.9 (1C, quat., CH_2CCH), 116.8 (1C, CH_2), 134.9 (1C, CH); m/z (TOF MS EI^+) $[M]^+$ 208 (35%), $[M-C_4H_7S]^+$ 112 (100%); HRMS (TOF MS EI^+) calculated for $C_{13}H_{20}S$ 208.1286, found 208.1290.

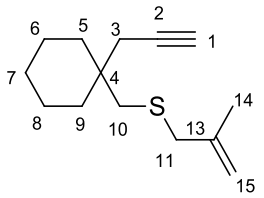
Cinnamyl((1-(prop-2-yn-1-yl)cyclohexyl)methyl)sulfane (290b)



Following GP 4, using cinnamyl bromide 97% pure (2.6 mmol, 0.5 g), cinnamyl sulfide was prepared as a viscous colourless oil (0.6 g, 88% consistent yield); R_f 0.29 (2% EtOAc: 98% hexane); ν_{max}(neat) / (cm^{-1}) 3302 m (CC-H), 2923 s (C-H), 2851 m (C-H), 2115 w (CC), 1451 m (C-S); δ_H (300 MHz, $CDCl_3$) 1.32-1.56 (10H, m, H-5-9, CH_2, cyclohexyl), 1.91 (1H, t, *J* 2.7, H-1, CCH), 2.31 (2H, d, *J* 2.7, H-3, CH_2), 2.62 (2H, s, H-10, CH_2S), 3.31 (2H, dd, *J* 7.3, *J* 1.1, H-11, CH_2), 6.17 (1H, dt, *J* 15.6, *J* 7.3, H-12, CHCHPh), 6.45 (1H, d, *J* 15.6, H-13, CHCHPh), 7.17-7.39 (5H, m, H-15-17, Ph-H); δ_C (101 MHz, $CDCl_3$) 21.7 (2C, CH_2, cyclohexyl), 25.9 (1C, CH_2, cyclohexyl), 26.9 (1C, CH_2), 34.6 (2C, CH_2, cyclohexyl), 35.9 (1C, CH_2), 37.3 (1C, quat., cyclohexyl), 39.9 (1C, CH_2S), 70.5 (1C, CCH), 81.9 (1C, quat., CCH), 126.3 (2C, PhC), 126.5 (1C, CH), 127.5 (1C, PhC), 128.5

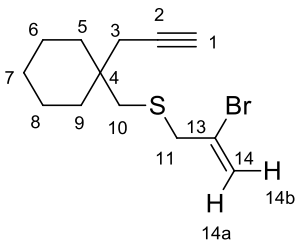
(2C, Ph*C*), 132.1 (1C, *C*H), 136.9 (1C, quat., Ph*C*); used in next step without further purification.

(2-Methylallyl)((1-(prop-2-yn-1-yl)cyclohexyl)methyl)sulfane (290c)



Following GP 4, using 3-chloro-2-methylpropene 90% pure (2.6 mmol, 0.3 mL), 2-methylallyl sulfane was prepared as a colourless liquid (0.4 g, 70%); R_f 0.30 (4% EtOAc: 96% hexane); ν_{max}(neat) / (cm^{-1}) 3307 m (CC-H), 2924 s (C-H), 2852 m (C-H), 2115 w (CC), 1648 m (C=C), 1452 s (C-S); δ_H (300 MHz, $CDCl_3$) 1.29-1.59 (10H, H-5-9, C*H*$_2$, cyclohexyl), 1.82 (3H, s, H-14, $CH_2C(CH_3)$), 1.95 (1H, t, *J* 2.6, H-1, CH_2CCH), 2.29 (2H, d, *J* 2.6, H-3, C*H*$_2$CCH), 2.53 (2H, s, H-10, C*H*$_2$S), 3.06-3.16 (2H, m, H-11, C*H*$_2$C(CH_3)), 4.77-4.90 (2H, m, C-15, C(CH_3)C*H*$_2$); δ_C (101 MHz, $CDCl_3$) 20.7 (1C, *C*H_3), 21.6 (1C, *C*H_2, cyclohexyl), 21.7 (2C, *C*H_2, cyclohexyl), 26.0 (1C, *C*H_2), 34.4 (1C, quat., cyclohexyl), 34.6 (2C, *C*H_2, cyclohexyl), 39.9 (1C, *C*H_2), 40.9 (1C, *C*H_2S), 70.4 (1C, C*C*H), 81.9 (1C, quat., *C*CH), 113.4 (1C, *C*H_2), 141.8 (1C, quat., *C*(CH_3)); m/z (TOF MS EI^+) $[M]^+$ 222 (10%), [M^+- C_5H_9S] 111 (100%); HRMS (TOF MS EI^+) mass calculated for $C_{14}H_{22}S$ 222.1442, found 222.1437.

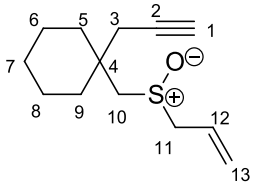
(2-Bromoallyl)((1-(prop-2-yn-1-yl)cyclohexyl)methyl)sulfane (290d)



Following GP 4, using 2,3-dibromoprop-1-ene 85% pure (2.6 mmol, 0.5 g), 2-bromoallyl sulfane was prepared as a colourless liquid (0.5 g, 82%); R_f 0.30 (5% EtOAc:95% hexane);

ν_{max}(neat) / (cm^{-1}) 3299 m (CC-H), 2924 s (C-H), 2852 m (C-H), 2115 w (CC), 1453 m (C-S), 893 s (C-Br); δ_H (300 MHz, $CDCl_3$) 1.27-1.54 (10H, H-5-9, C*H*$_2$, cyclohexyl), 1.97 (1H, t, *J* 2.6, H-1, CH_2CCH), 2.30 (2H, d, *J* 2.6, H-3, C*H*$_2$CCH), 2.62 (2H, s, H-10, C*H*$_2$S), 3.45 (2H, m, H-11, C*H*$_2$C(Br)CH_2), 5.51 (1H, d, *J* 1.7, C-14a, C(Br)C*H*$_{trans}$), 5.85 (1H, dt, *J* 1.7, *J* 1.2, C-14b, C(Br)C*H*$_{cis}$); δ_C (101 MHz, $CDCl_3$) 21.7 (2C, *C*H_2, cyclohexyl), 25.9 (1C, *C*H_2, cyclohexyl), 26.8 (1C, *C*H_2CCH), 34.6 (2C, *C*H_2, cyclohexyl), 37.2 (1C, quat., cyclohexyl), 40.5 (1C, *C*H_2S), 43.5 (1C, *C*H_2), 70.7 (1C, C*C*H), 81.8 (1C, quat., *C*CH), 118.6 (1C, *C*H_2), 130.4 (1C, quat., *C*(Br)); m/z (TOF MS EI^+) $[M(^{81}Br)]^+$ 288 (27%), $[M(^{79}Br)]^+$ 286 (25%), $[M\text{-}Br^{81}]^+$ 207 (100%); HRMS (TOF MS EI^+) mass calculated for $C_{13}H_{19}{}^{79}BrS$ 286.0391, found 286.0385.

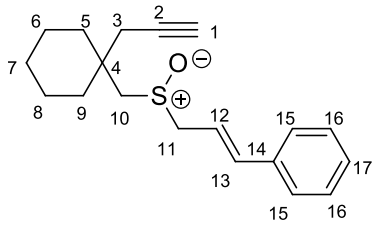
1-((Allylsulfinyl)methyl)-1-(prop-2-yn-1-yl)cyclohexane (294a)



Following GP 5 sulfoxide was obtained using allyl sulfane (2.0 mmol, 0.4 g) as a colourless needle like solid (0.3 g, 70% yield); mp 187-189; R_f 0.27 (60% EtOAc:40% hexane); ν_{max}(neat) / (cm^{-1}) 3196 s (CC-H), 2931 s (C-H), 2851 s (C-H), 2102 w (CC), 1639 m (C-S), 1454 w (S-O), 1420 m (C=C); δ_H (300 MHz, $CDCl_3$) 1.34-1.74 (10H, m, H-5-9, C*H*$_2$, cyclohexyl), 1.99 (1H, t, *J* 2.7, H-1, CH_2CCH), 2.40 (1H, dd, *J* 17.1, *J* 2.7, H-3, C*H*$_A$*H*$_B$CCH$_X$), 2.48 (1H, dd, *J* 17.1, *J* 2.7, H-3, C*H*$_A$*H*$_B$), 2.78-2.83 (2H, m, H-10, C*H*$_A$*H*$_B$), 3.44 (2H, ddt, *J* 13.1, *J* 7.5, *J* 0.9, H-11, C*H*$_A$*H*$_B$), 5.33-5.46 (2H, m, H-13, CHC*H*$_2$), 5.81-5.98 (1H, m, H-12, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 21.3 (1C, *C*H_2, cyclohexyl), 21.4 (1C, *C*H_2, cyclohexyl), 25.6 (1C, *C*H_2CC), 27.9 (1C, quat., cyclohexyl), 35.1 (1C, *C*H_2, cyclohexyl), 35.2 (1C, *C*H_2, cyclohexyl), 36.5 (1C, *C*H_2, cyclohexyl), 57.5 (1C, *C*H_2), 60.7

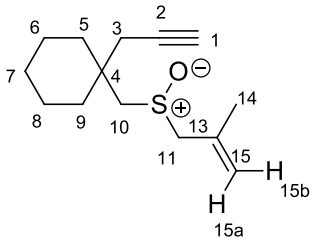
(1C, *C*H_2), 71.4 (1C, quat., C*C*H), 80.9 (1C, quat., *C*CH), 123.4 (1C, CH*C*H_2), 126.1 (1C, *C*HCH$_2$); m/z (TOF MS ES$^+$) [M+Na]$^+$ 247 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{13}H_{20}OSNa$ 247.1133, found 247.1123.

(*E*)-(3-(((1-(prop-2-yn-1-yl)cyclohexyl)methyl)sulfinyl)prop-1-en-1-yl)benzene (294b)



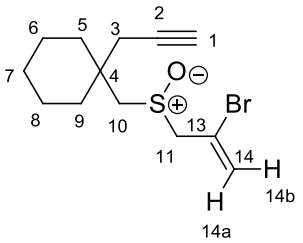
Following GP 5 sulfoxide was obtained using cinnamyl sulfane (2.0 mmol, 0.6 g) as a colourless oil (0.6 g, 96% yield); R_f 0.28 (60% EtOAc:40% hexane); ν_{max}(neat) / (cm^{-1}) 3196 s (CC-H), 2931 s (C-H), 2851 s (C-H), 2102 w (CC), 1639 m (C-S), 1454 w (S-O), 1420 m (C=C); δ_H (300 MHz, $CDCl_3$) 1.32-1.77 (10H, m, H-5-9, C*H*$_2$, cyclohexyl), 1.90 (1H, t, *J* 2.7, H-1, CC*H*), 2.37-2.52 (2H, m, H-3, CH_AH_B), 2.82 (1H, d, *J* 13.7, H-10, CH_AH_B), 2.89 (1H, d, *J* 13.7, H-10, CH_AH_B), 3.59-3.73 (2H, m, H-11, CH_AH_B), 6.26 (1H, dt, *J* 15.6, *J* 7.7, H-12, C*H*CHPh), 6.69 (1H, d, *J* 15.6, H-13, CHC*H*Ph); δ_C (101 MHz, $CDCl_3$) 21.4 (1C, *C*H_2, cyclohexyl), 21.5 (1C, *C*H_2, cyclohexyl), 25.6 (1C, *C*H_2), 27.8 (1C, quat., cyclohexyl), 35.1 (1C, *C*H_2, cyclohexyl), 35.2 (1C, *C*H_2, cyclohexyl), 36.6 (1C, *C*H_2, cyclohexyl), 57.4 (1C, *C*H_2), 60.8 (1C, *C*H_2), 71.5 (1C, C*C*H), 80.9 (1C, quat., *C*CH), 117.0 (1C, *C*HPh), 126.6 (2C, Ph*C*), 128.3 (1C, Ph*C*), 128.6 (2C, Ph*C*), 136.1 (1C, quat., Ph*C*), 137.9 (1C, *C*H); m/z (TOF MS EI$^+$) [M+Na]$^+$ 323 (100%); HRMS (TOF MS EI$^+$) mass calculated for $C_{19}H_{24}OSNa$ 323.1446, found 323.1454.

1-(((2-Methylallyl)sulfinyl)methyl)-1-(prop-2-yn-1-yl)cyclohexane (294c)



Following GP 5 sulfoxide was obtained using 2-methylallyl sulfane (2.0 mmol, 0.4 g) as a colourless oil (0.4 g, 72% yield); R_f 0.31 (70% EtOAc: 30% hexane); ν_{max}(neat) / (cm^{-1}) 3221 s (CC-H), 2926 s (C-H), 2854 s (C-H), 2114 w (CC), 1649 m (C-S), 1453 w (S-O), 1030 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.30-1.76 (10H, m, H-5-9, CH_2, cyclohexyl), 1.86 (3H, s, C-14, CH_3), 1.98 (1H, t, *J* 2.7, C-1, CC*H*), 2.38-54 (2H, m, C-3, CH_AH_B), 2.77 (1H, d, J 13.7, C-10, CH_AH_B), 2.89 (1H, d, *J* 13.7, C-10, CH_AH_B), 3.39 (1H, d, *J* 12.4, C-11, CH_AH_B), 3.53 (1H, d, *J* 12.4, C-11, CH_AH_B), 4.96-5.02 (1H, m, C-15a, C(CH_3)CH_{trans}), 5.03-5.08 (1H, m, C-15b, C(CH_3)CH_{cis}); δ_C (101 MHz, $CDCl_3$) 21.4 (1C, *C*H_2, cyclohexyl), 21.5 (1C, *C*H_2, cyclohexyl), 22.8 (1C, *C*H_3), 25.6 (1C, *C*H_2), 27.9 (1C, *C*H_2, cyclohexyl), 35.1 (1C, *C*H_2, cyclohexyl), 35.2 (1C, *C*H_2, cyclohexyl), 36.4 (1C, quat., cyclohexyl), 61.5 (1C, *C*H_2), 63.2 (1C, *C*H_2), 71.4 (1C, C*C*H), 80.8 (1C, quat., *C*CH), 118.1 (1C, *C*H_2), 135.9 (1C, quat., *C*(CH_3)); m/z (TOF MS ES^+) $[M+Na]^+$ 261 (100%); HSMS (TOF MS ES^+) mass calculated for $C_{14}H_{22}ONaS$ 261.1289, found 261.1299.

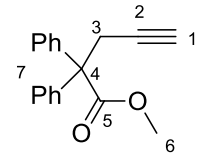
1-(((2-Bromoallyl)sulfinyl)methyl)-1-(prop-2-yn-1-yl)cyclohexane (294d)



Following GP 5 sulfoxide was obtained using 2-bromoallyl sulfane (2.0 mmol, 0.6 g) as a colourless oil (0.5 g, 85% yield); R_f 0.32 (70% EtOAc:30% hexane); ν_{max}(neat) / (cm^{-1})

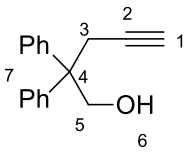
3304 s (CC-H), 2925 s (C-H), 2853 s (C-H), 2102 w (CC), 1625 m (C-S), 1454 w (S-O), 1035 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.30-1.79 (10H, m, H-5-9, CH_2, cyclohexyl), 2.02 (1H, t, *J* 2.7, H-1, CC*H*), 2.44 (1H, dd, *J* 17.1, *J* 2.7, H-3, CH_AH_B), 2.52 (1H, dd, *J* 17.1, *J* 2.7, H-3, CH_AH_B), 2.88 (1H, d, *J* 13.6, H-10, CH_2S(O)), 2.96 (1H, d, *J* 13.6, H-10, CH_2S(O)), 3.74 (1H, dd, *J* 13.2, *J* 0.6, H-11, S(O)CH_2), 3.90 (1H, d, *J* 13.2, H-11 S(O)CH_2), 5.73 (1H, d, *J* 2.1, H-14a, C(Br)CH_{trans}), 5.91-5.96 (1H, m, H-14b, C(Br)CH_{cis}); δ_C (101 MHz, $CDCl_3$) 21.4 (1C, *C*H_2, cyclohexyl), 21.5 (1C, *C*H_2, cyclohexyl), 25.6 (1C, *C*H_2), 35.1 (1C, *C*H_2, cyclohexyl), 35.2 (2C, *C*H_2, cyclohexyl), 36.6 (1C, quat., cyclohexyl), 61.5 (1C, *C*H_2S(O), 65.4 (1C, *C*H_2C(Br)), 71.7 (1C, C*C*H), 80.7 (1C, quat., CH_2*C*CH), 120.7 (1C, C(Br)*C*H_2), 123.9 (1C, quat., *C*(Br)); m/z (TOF MS ES^+) $[M+Na(^{81}Br)]^+$ 327 (100%), $[M+Na(^{79}Br)]^+$ 325 (90%); HRMS (TOF MS ES^+) mass calculated for $C_{13}H_{19}ONa^{79}BrS$ 325.0238, found 325.0237.

Methyl 2,2-diphenylpent-4-ynoate (296)



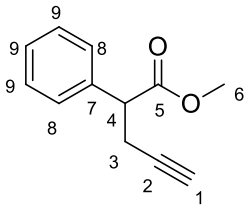
Following GP 1, methyl 2,2-diphenylpent-4-ynoate was prepared using methyl 2,2-diphenylacetate (10.0 mmol, 2.3 g) as a viscous pale yellow oil (2.5 g, 95% yield); R_f 0.35 (6% EtOAc:94% hexane); ν_{max}(neat) / (cm^{-1}) 3292 m (CC-H), 3268 m (C-H), 2948 m, (C-H), 2175 w (CC) 1725 s (C=O), 1264 s (C-O); δ_H (300 MHz, $CDCl_3$) 1.92 (1H, t, *J* 2.6, H-1, CC*H*), 3.29 (2H, d, *J* 2.6, H-3, CH_2), 3.74 (3H, s, C-6, CH_3), 7.27-7.37 (10H, m, H-7, Ph*H*); δ_C (101 MHz, $CDCl_3$) 29.3 (1C, *C*H_2), 52.7 (1C, *C*H_3), 58.1 (1C, quat., *C*Ph_2), 71.9 (1C, C*H*), 80.9 (1C, quat., *C*CH), 127.3 (2C, Ph*C*), 127.9 (4C, Ph*C*), 128.8 (4C, Ph*C*), 141.3 (2C, quat., Ph*C*), 173.8 (1C, quat., *C*(O)). Data were consistent with that reported in the literature.[115]

2,2-Diphenylpent-4-yn-1-ol (297)



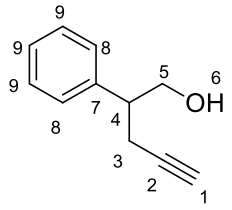
Following GP 2, using $LiAlH_4$ (0.30 g, 7.84 mmol) and methyl 2,2-diphenylpent-4-ynoate (2.0 g, 7.5 mmol) in E_2O (18 mL) afforded alcohol as a viscous colourless oil (1.8 g, 97% yield); R_f 0.21 (20% EtOAc:80% hexane); ν_{max}(neat) / (cm^{-1}) 3435 brs (OH), 3288 m (CC-H), 3057 w (C-H), 2885 w (C-H), 2116 w (CC), 1494 m (C-O); δ_H (300 MHz, $CDCl_3$) 1.42-1.57 (1H, brs, H-6, O*H*), 1.95 (1H, t, *J* 2.7, H-1, CC*H*), 3.10 (2H, d, *J* 2.7, H-3, CH_2), 4.32 (2H, s, H-5, CH_2), 7.20-7.36 (10H, H-7, Ph*H*); δ_C (101 MHz, $CDCl_3$) 27.5 (1C, *C*H_2), 49.8 (1C, quat., *C*Ph_2), 68.3 (1C, *C*H_2), 71.6 (1C, *C*H), 81.4 (1C, quat., *C*CH), 126.7 (2C, Ph*C*), 128.0 (4C, Ph*C*), 128.3 (4C, Ph*C*), 144.4 (2C, quat., Ph*C*). Data were consistent with that reported in the literature. [116]

Methyl 2-phenylpent-4-ynoate (321)



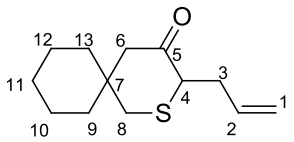
Following GP 1, methyl 2-phenylpent-4-ynoate was prepared using methyl 2-phenyl acetate (20.0 mmol, 3.0 g) as a yellow oil (3.7 g, 95% yield); R_f (6% EtOAc:94% hexane); δ_H (300 MHz, $CDCl_3$) 1.96 (1H, t, *J* 2.6, H-1, CC*H*), 2.64 (1H, ddd, *J* 16.8, *J* 7.2, *J* 2.7, H-3, CH_AH_B), 2.94 (1H, ddd, *J* 16.8, *J* 8.2, *J* 2.7, H-3, CH_AH_B), 3.70 (3H, s, H-6, CH_3), 3.82 (1H, dd, *J* 8.1, *J* 7.3, H-4, C*H*), 7.27-7.39 (5H, m, H-8-9, Ph*H*); δ_C (101 MHz, $CDCl_3$) 23.0 (1C, *C*H_2), 50.7 (1C, *C*H), 52.2 (1C, *C*H_3), 70.2 (1C, C*H*), 81.4 (1C, quat., *C*CH), 127.8 (3C, Ph*C*), 128.6 (2C, Ph*C*), 137.6 (1C, quat., Ph*C*), 172.9 (1C, quat., *C*(O)). Data were consistent with that reported in the literature.[80]

2-Phenylpent-4-yn-1-ol (319)



Following GP 2, using $LiAlH_4$ (0.8 g, 19.8 mmol) and methyl phenylpent-4-ynoate (3.7 g, 19.0 mmol) in E_2O (45 mL) afforded alcohol as a colourless oil (2.6 g, 84% yield); R_f (20% EtOAc:80% hexane); δ_H (300 MHz, $CDCl_3$) 1.76 (1H, t, *J* 5.2, H-6, O*H*), 1.98 (1H, t, *J* 2.7, H-1, CC*H*), 2.49-2.69 (2H, m, H-3, CH_AH_B), 3.04 (1H, p, *J* 6.7, C-4, C*H*), 3.79-3.95 (2H, m, H-5, CH_AH_B), 7.21-7.39 (5H, H-8-9, Ph*H*); δ_C (101 MHz, $CDCl_3$) 21.7 (1C, *C*H_2), 46.8 (1C, *C*H), 66.0 (1C, *C*H_2), 70.0 (1C, *C*H), 82.3 (1C, quat., *C*CH), 127.2 (1C, Ph*C*), 127.8 (2C, Ph*C*), 128.7 (2C, Ph*C*), 141.0 (1C, quat., Ph*C*); Data is consistent with that reported in the literature.[80]

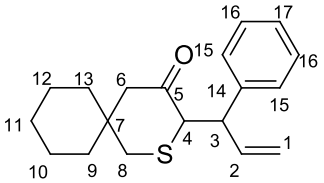
3-Allyl-2-thiaspiro[5.5]undecan-4-one (324a)



Following GP 6, heterocycle was obtained in 24 h as a colourless viscous oil (14.6 mg, 65% yield); R_f 0.28 (70%hexane:30% EtOAc); ν_{max}(neat) / (cm^{-1}) 2923 s (C-H), 2853 m (C-H), 1701 s (C=O), 1242 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.26-1.73 (10H, m, H-9-13, CH_2, cyclohexyl), 2.09 (1H, d, *J* 12.7, H-8, SCH_AH_B), 2.19 (1H, ddt, *J* 14.9, *J* 7.5, *J* 1.2, H-3, CH_AH_BCH_X), 2.34 (1H, dd, *J* 12.2, *J* 1.8, H-6, CH_AH_B), 2.55-2.70 (1H+1H, m, H-3 and H-6, CH_AH_BCH_X and CH_AH_B), 2.75 (1H, d, *J* 12.7, H-8, SCH_AH_B), 3.32-4.40 (1H, m, H-4, SC*H*), 5.00-5.14 (2H, m, H-1, CHCH_2), 5.68-5.86 (1H, m, H-2, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 21.3 (1C, C-10, *C*H_2, cyclohexyl), 21.6 (1C, C-11, *C*H_2, cyclohexyl), 26.0 (1C, C-9, *C*H_2, cyclohexyl), 32.8 (1C, C-12, *C*H_2, cyclohexyl), 33.6 (1C, C-3, *C*H_2), 38.4 (1C, C-13,

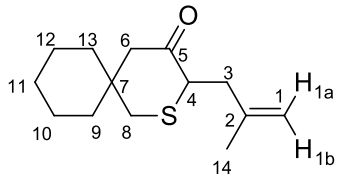
CH_2, cyclohexyl), 38.9 (1C, C-8, CH_2S), 46.4 (1C, quat., C-7, cyclohexyl), 49.8 (1C, C-4, S*C*H), 53.2 (1C, C-6, $CH_2C(O)$), 117.3 (1C, C-1, $CHCH_2$), 134.6 (1C, C-2, $CHCH_2$), 204.5 (1C, quat., C-5, *C*(O)); m/z (TOF MS EI^+) $[M]^+$ 224 (30%), $[M-C_3H_5]^+$ 183 (100%); HRMS (TOF MS EI^+) mass calculated for $C_{13}H_{20}OS$ 224.1235, found 224.1232.

3-(1-Phenylallyl)-2-thiaspiro[5.5]undecan-4-one (324b)



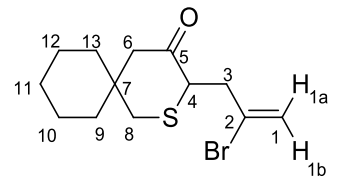
Following GP 6, heterocycle was obtained in 24 h as a colourless viscous oil in a 1:1 diastereoisomeric ratio (17.1 mg, 57% yield); R_f 0.27 (70%hexane:30% EtOAc); ν_{max}(neat) / (cm^{-1}) 2925 s (C-H), 2854 m (C-H), 1700 s (C=O), 1252 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.26-1.70 (10H, m, H-9-13, CH_2, cyclohexyl), 2.20 (1H, d, *J* 12.0, H-8, SCH_AH_B), 2.36 (1H, d, *J* 12.0, H-8, SCH_AH_B), 2.58 (1H, d, *J* 14.1, H-6, CH_AH_B), 2.68 (1H, d, *J* 14.1, H-6, CH_AH_B), 3.61 (1H, d, *J* 10.7, H-4, SC*H*), 3.82 (1H, dd, *J* 10.7, *J* 7.8, H-3, C*H*Ph), 4.94-5.10 (2H, m, H-1, CHCH_2), 5.98 (1H, ddd, *J* 17.7, *J* 17.2, *J* 7.8, H-2, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 21.3 (1C, *C*H_2, cyclohexyl), 21.5 (1C, *C*H_2, cyclohexyl), 26.0 (1C, *C*H_2, cyclohexyl), 35.5 (1C, *C*H_2, cyclohexyl), 36.9 (1C, *C*H), 37.5 (1C, *C*H_2, cyclohexyl), 47.0 (1C, *C*H_2S), 48.4 (1C, quat., cyclohexyl), 52.6 (1C, *C*H_2C(O)), 55.0 (1C, S*C*H), 116.2 (1C, $CHCH_2$), 127.0 (1C, Ph*C*), 128.4 (2C, Ph*C*), 128.5 (2C, Ph*C*), 138.4 (1C, *C*HCH_2), 140.1 (1C, quat., Ph*C*), 204.1 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 323 (100%), $[M-C_3H_4Ph]^+$ 206 (10%); HRMS (TOF MS ES^+) mass calculated for $C_{19}H_{24}OSNa$ 323.1446, found 323.1451.

3-(2-Methylallyl)-2-thiaspiro[5.5]undecan-4-one (324c)



Following GP 6, heterocycle was obtained in 24 h as a colourless viscous oil (16.7 mg, 70% yield); R_f 0.30 (70%hexane:30% EtOAc); ν_{max}(neat) / (cm^{-1}) 2926 s (C-H), 2854 m (C-H), 1706 s (C=O), 1452 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.27-1.70 (10H, m, H-9-13, CH_2, cyclohexyl), 1.72 (3H, s, C-14, CH_3), 2.12 (1H, d, *J* 12.1, H-8, SCH_AH_B), 2.16 (1H, dd, *J* 15.1, *J* 8.4, H-6, CH_AH_B), 2.38 (H, dd, *J* 12.1, *J* 1.7, H-8, SCH_AH_B), 2.63 (1H, dd, *J* 15.1, *J* 6.2, H-6, CH_AH_B), 2.66 (1H, dd, *J* 13.9, *J* 1.6, H-3, CH_2), 2.75 (1H, d, *J* 13.9, H-3, CH_2), 3.48 (1H, dd, *J* 8.3, *J* 6.2, H-4, SC*H*), 4.73 (1H, s, H-1a, C(CH_3)CH_{trans}), 4.80 (1H, s, H-1b, C(CH_3)CH_{cis}); δ_C (101 MHz, $CDCl_3$) 21.3 (1C, *C*H_2, cyclohexyl), 21.6 (1C, *C*H_2, cyclohexyl), 22.3 (1C, C(*C*H_3)), 26.0 (1C, *C*H_2, cyclohexyl), 33.8 (1C, *C*H_2, cyclohexyl), 36.5 (1C, *C*H_2), 38.3 (1C, *C*H_2, cyclohexyl), 38.6 (1C, *C*H_2S), 46.5 (1C, quat., cyclohexyl), 47.3 (1C, S*C*H), 53.0 (1C, *C*H_2C(O)), 112.9 (1C, *C*H_2), 141.8 (1C, quat., *C*(CH_3)), 204.6 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 261 (100%), HRMS (TOF MS ES^+) mass calculated for $C_{14}H_{22}ONaS$ 261.1289, found 261.1295.

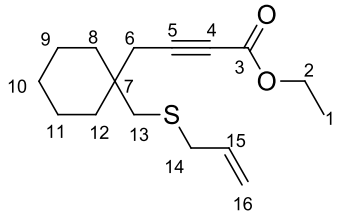
3-(2-Bromoallyl)-2-thiaspiro[5.5]undecan-4-one (324d)



Following GP 6, heterocycle was obtained in 24 h as a colourless viscous oil (13.3 mg, 44% yield); R_f 0.32 (70%hexane:30% EtOAc); ν_{max}(neat) / (cm^{-1}) 2926 s (C-H), 2857 m (C-H), 1705 s (C=O), 1076 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.28-1.72 (10H, m, H-9-13, CH_2, cyclohexyl), 2.14 (1H, d, *J* 12.1, H-8, SCH_AH_B), 2.39 (1H, dd, *J* 12.1, *J* 2.1, H-8,

SCH_AH_B), 2.46 (1H, dd, *J* 8.7, *J* 0.6, H-6, CH_AH_B), 2.51 (1H, dd, *J* 8.7, *J* 0.6, C-6, CH_AH_B), 2.65 (1H, dd, *J* 14.0, *J* 2.1, H-3, CH_AH_BC(Br)), 2.85 (1H, d, *J* 14.0, H-3, CH_AH_BC(Br)), 3.72 (1H, dd, *J* 8.7, *J* 5.3, H-4, SC*H*), 5.48 (1H, m, H-1a, C(Br)CH_{trans}), 5.65-5.71 (1H, m, H-1b, C(Br)CH_{cis}); δ_C (101 MHz, $CDCl_3$) 21.3 (1C, *C*H_2, cyclohexyl), 21.7 (1C, *C*H_2, cyclohexyl), 26.0 (1C, *C*H_2, cyclohexyl), 32.9 (1C, *C*H_2, cyclohexyl), 38.9 (1C, *C*H_2C(Br)), 39.4 (1C, *C*H_2, cyclohexyl), 40.2 (1C, *C*H_2S), 46.5 (1C, quat., cyclohexyl), 47.8 (1C, S*C*H), 53.5 (1C, *C*H_2C(O)), 119.9 (1C, *C*H_2), 129.7 (1C, quat., *C*(Br)), 203.5 (1C, quat., *C*(O)); m/z (TOF MS ES$^+$) $[M+Na(^{81}Br)]^+$ 327 (90%), $[M+Na(^{79}Br)]^+$ 325 (70%); HRMS (TOF MS ES$^+$) mass calculated for $C_{13}H_{19}ONa^{79}BrS$ 325.0238, found 325.0243.

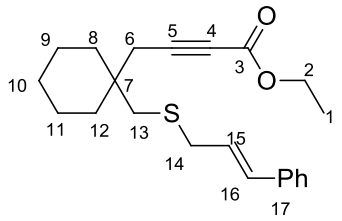
Ethyl 4-(1-((allylthio)methyl)cyclohexyl)but-2-ynoate (325a)



Following GP 7, using allyl sulfane (1.5 mmol, 0.3 g) tethered alkyne was prepared as a colourless liquid of 94% purity (0.4 g, 92%); R_f 0.30 (10% EtOAc:90% hexane); ν_{max}(neat) / (cm^{-1}) 2926 s (C-H), 2854 m (C-H), 2231 s (CC), 1707 s (C=O), 1245 s (C-O), 1070 s (C=C), 751 m (C-S); δ_H (300 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.2, H-1, OCH$_2$C*H*$_3$), 1.34-1.52 (10H, m, H-8-12, CH_2, cyclohexyl), 2.46 (2H, s, H-6, C*H*$_2$CC), 2.57 (2H, s, H-13, C*H*$_2$SCH$_2$), 3.12 (2H, dt, *J* 6.2, *J* 1.0, H-14, SC*H*$_2$), 4.20 (2H, q, *J* 7.2, H-2, OC*H*$_2$CH$_3$), 5.04-5.17 (2H, m, H-16, CH$_2$CH=C*H*$_2$), 5.70-5.86 (1H, m, H-15, CH$_2$C*H*=CH$_2$); δ_C (101 MHz, $CDCl_3$) 14.1 (1C, C-1, OCH$_2$*C*H$_3$), 21.7 (2C, C-9-10, CH_2, cyclohexyl), 25.8 (1C, C-6, *C*H$_2$CC), 27.3 (1C, quat., C-7, cyclohexyl), 34.7 (2C, C-11-12, CH_2, cyclohexyl), 36.4 (1C, C-14, S*C*H$_2$) 37.8 (1C, C-8, CH_2, cyclohxyl), 39.6 (1C, C-13, *C*H$_2$S), 61.7 (1C, C-2,

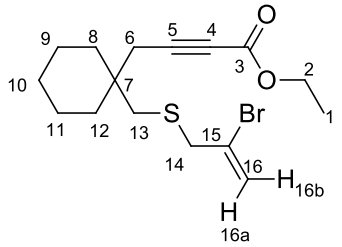
O*C*$H_2$$CH_3$), 75.4 (1C, quat., C-4, CH_2C*C*), 87.0 (1C, quat., C-5, CH_2*C*C), 117.1 (1C, CH_2, C-16, CH_2CH=*C*H_2), 134.6 (1C, C-15, CH_2*C*H=CH_2), 153.7 (1C, quat., C-3, C=O).

(*E*)-ethyl 4-(1-((cynnamylthio)methyl)cyclohexyl)but-2-ynoate (325b)



Following GP 7 using cinnamyl sulfane (1.5 mmol, 0.4 g), tethered alkyne was prepared as a colourless viscous oil (0.3 g, 59% consistent yield); R_f 0.29 (10% EtOAc:90% hexane); ν_{max}(neat) / (cm^{-1}) 2926 m (C-H), 2855 w (C-H), 2230 s (CC), 1705 s (C=O), 1246 s (C-O), 1070 s (C=C), 750 s (C-S); δ_H (300 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.2, H-1, OCH_2CH_3), 1.33-1.52 (10H, m, H-8-12, CH_2, cyclohexyl), 2.48 (2H, s, H-6, CH_2CC), 2.61 (2H, s, H-13, CH_2SCH_2), 3.30 (2H, dd, *J* 7.3, *J* 1.1, H-14, SCH_2), 4.17 (2H, q, *J* 7.2, H-2, OCH_2CH_3), 6.16 (1H, dt, *J* 15.7, *J* 7.4, H-15, C*H*CHPh), 6.48 (1H, d, *J* 15.7, H-16, CHC*H*Ph), 7.17-7.40 (5H, m, H-17, Ph*H*) used crude due to its instability.

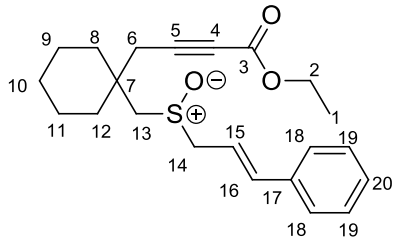
Ethyl 4-(1-(((2-bromoallyl)thio)methyl)cyclohexyl)but-2-ynoate (325d)



Following GP 7 using 2-bromoallyl sulfane (1.5 mmol, 0.4 g), tethered alkyne was prepared as a colourless viscous oil (0.4 g, 71% yield); R_f 0.35 (10% EtOAc:90% hexane); δ_H (300 MHz, $CDCl_3$) 1.29 (3H, t, *J* 2.8, H-1, OCH_2CH_3), 1.34-1.50 (10H, H-8-12, CH_2, cyclohexyl), 2.48 (2H, s, H-6, CH_2CC), 2.62 (2H, s, H-13, CH_2S), 3.45 (2H, m, H-14, CH_2C(Br)), 4.19 (2H, q, *J* 2.8, H-2, OCH_2CH_3), 5.52 (1H, d, *J* 1.8, H-16a, C(Br)CH_{trans}),

5.86 (1H, dt, *J* 1.8, *J* 1.1, H-16b, C(Br)CH_{cis}); δ_C (101 MHz, $CDCl_3$) 14.1 (1C, OCH_2CH_3), 21.6 (2C, CH_2, cyclohexyl), 25.7 (1C, CH_2, cyclohexyl), 27.1 (1C, CH_2CC), 34.8 (2C, CH_2, cyclohexyl), 37.8 (1C, quat., cyclohexyl), 40.3 (1C, CH_2S), 43.6 (1C, $CH_2C(Br)$), 61.8 (1C, OCH_2CH_3), 75.6 (1C, quat., CH_2CC), 86.8 (1C, quat., CH_2CC), 119.0 (1C, $C(Br)CH_2$), 130.2 (1C, quat., *C*(Br)), 153.7 (1C, quat., (C=O)); m/z (TOF MS EI$^+$) $[M(^{81}Br)]^+$ 383 (97%), $[M(^{79}Br)]^+$ 381 (100%); HRMS (TOF MS EI$^+$) mass calculated for $C_{16}H_{23}O_2{}^{79}BrS$ 381.0500, found 381.0503.

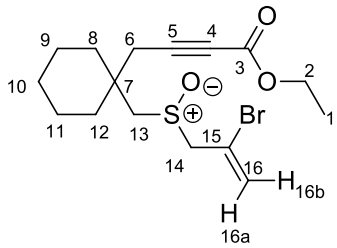
(*E*)-ethyl 4-(1-((cinnamylsulfinyl)methyl)cyclohexyl)but-2-ynoate (326b)



Following GP 5 sulfoxide was obtained using cinnamyl sulfane-ester (2.0 mmol, 0.7 g) as a colourless oil (0.6 g, 79% yield); R_f 0.30 (30% EtOAc:70% hexane); ν_{max}(neat) / (cm^{-1}) 2927 s (CC-H), 2857 s (C-H), 2230 m (CC), 1703 s (C=O), 1451 w (S-O), 1247 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.1, H-1, OCH_2CH_3), 1.34-1.77 (10H, H-8-12, CH_2, cyclohexyl), 2.58 (1H, d, J 17.5, H-6, CH_AH_B), 2.66 (1H, d, *J* 17.5, H-6, CH_AH_B), 2.82 (1H, d, *J* 13.8, H-13, CH_AH_B), 2.89 (1H, *J* 13.8, H-13, CH_AH_B), 3.55-3.78 (2H, m, H-14, CH_AH_B), 4.12 (2H, q, *J* 7.1, H-2, OCH_2CH_3), 6.25 (1H, dt, *J* 15.7, *J* 7.6, H-15, CHCHPh), 6.69 (1H, d, *J* 15.7 H-16, CHCHPh), 7.13-7.48 (5H, m, H-18-20, Ph*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (1C, OCH_2CH_3), 21.4 (1C, CH_2, cyclohexyl), 21.5 (1C, CH_2, cyclohexyl), 25.4 (1C, CH_2), 28.2 (1C, CH_2, cyclohexyl), 35.2 (1C, CH_2, cyclohexyl), 35.4 (1C, CH_2, cyclohexyl), 37.1 (1C, quat., cyclohexyl), 57.3 (1C, OCH_2), 60.4 (1C, CH_2), 61.9 (1C, CH_2), 76.2 (1C, quat., CH_2CC), 85.7 (1C, quat., C*C*), 116.7 (1C, *C*H), 126.6 (2C, Ph*C*), 128.3 (1C, Ph*C*), 128.6 (2C, Ph*C*), 136.1 (1C, quat., Ph*C*), 138.2 (1C, *C*H); m/z (TOF MS

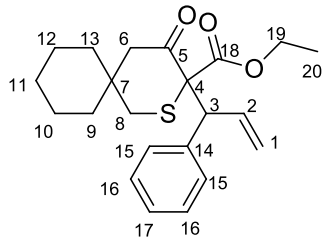
ES^+) $[M+Na]^+$ 395 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{22}H_{28}O_3NaS$ 395.1657, found 395.1635.

Ethyl 4-(1-(((2-bromoallyl)sulfinyl)methyl)cyclohexyl)but-2-ynoate (326d)



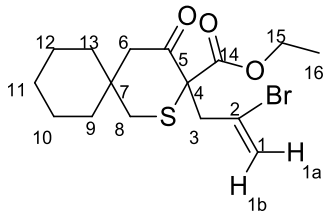
Following GP 5 sulfoxide was obtained using 2-bromoallyl sulfaneester (2.0 mmol, 0.7 g) as a colourless oil (0.5 g, 70% yield); R_f 0.28 (30% EtOAc:70% hexane); ν_{max}(neat) / (cm^{-1}) 3221 s (CC-H), 2926 s (C-H), 2854 s (C-H), 2114 w (CC), 1649 m (C-S), 1453 w (S-O), 1030 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, H-1, OCH_2CH_3), 1.33-1.77 (10H, H-8-12, CH_2, cyclohexyl), 2.59 (1H, d, J 17.5, H-6, CH_AH_B), 2.67 (H, d, *J* 17.5, H-6, CH_AH_B), 2.87 (1H, d, *J* 13.8, H-13, CH_AH_B), 2.92 (1H, d, *J* 13.8, H-13, CH_AH_B), 3.75 (1H, dd, *J* 13.2, *J* 0.7, H-14, CH_AH_B), 3.91 (1H, dd, *J* 13.2, *J* 0.7, H-14, CH_AH_B), 4.17 (2H, q, *J* 7.1, C-2, OCH_2CH_3), 5.73 (1H, d, *J* 2.2, H-16a, C(Br)CH_{trans}), 5.90-5.96 (1H, m, C-16b, C(Br)CH_{cis}); δ_C (101 MHz, $CDCl_3$) 14.1 (1C, CH_3), 21.3 (1C, CH_2, cyclohexyl), 21.4 (1C, CH_2, cyclohexyl), 25.4 (1C, CH_2), 28.3 (1C, CH_2, cyclohexyl), 35.1 (1C, CH_2, cyclohexyl), 35.4 (1C, CH_2, cyclohexyl), 37.1 (1C, quat., cyclohexyl), 60.8 (1C, OCH_2), 61.9 (1C, CH_2), 65.3 (1C, CH_2), 76.3 (1C, quat., *C*C), 85.5 (1C, quat., C*C*), 120.4 (1C, CH_2), 124.1 (1C, quat., *C*(Br)); m/z (TOF MS ES^+) $[M+Na(^{81}Br)]^+$ 399 (95%), $[M+Na(^{79}Br)]^+$ 397 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{16}H_{23}O_3Na^{79}BrS$ 399.0134, found 399.0137.

Ethyl 4-oxo-3-(1-phenylallyl)-2-thiaspiro[5.5]undecane-3-carboxylate (327b)



Following GP 6 heterocycle was obtained as inseparable diasterioisomers in 4 h as a colourless viscous oil (22.7 g, 59% yield); R_f 0.28 (70% hexane:30% EtOAc); ν_{max}(neat) / (cm^{-1}) 2927 s (C-H), 2856 m (C-H), 1705 s (C=O), 1216 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.2, H-20, OCH_2CH_3), 1.29-1.65 (10H, m, H-9-13, CH_2, cyclohexyl), 2.22 (1H, d, *J* 12.6, H-8, SCH_AH_B), 2.36 (1H, dd, *J* 12.6, *J* 2.0, H-8, SCH_AH_B), 2.46 (1H, dd, *J* 14.2, *J* 1.9, H-6, CH_AH_B), 2.70 (1H, d, *J* 14.2, H-6, CH_AH_B), 4.11-4.24 (1H, m, H-3, CHPh) overlaps with 4.19 (2H, q, *J* 7.2, H-19, OCH_2CH_3), 4.96-5.14 (2H, m, H-1, $CHCH_2$), 6.28 (1H, ddd, *J* 18.3, *J* 17.0, *J* 8.0, H-2, $CHCH_2$), 7.15-7.37 (5H, m, H-15-17, Ph*H*); δ_C (101 MHz, $CDCl_3$) 13.9 (1C, OCH_2CH_3), 21.4 (1C, CH_2, cyclohexyl), 21.5 (1C, CH_2, cyclohexyl), 26.0 (1C, CH_2, cyclohexyl), 33.0 (1C, CH_2, cyclohexyl), 37.7 (1C, CHPh), 39.2 (1C, CH_2, cyclohexyl), 46.1 (1C, CH_2S), 51.1 (1C, quat., cyclohexyl), 52.1 (1C, $CH_2C(O)$), 59.6 (1C, quat., S*C*), 62.2 (1C, OCH_2), 117.6 (1C, $CHCH_2$), 127.3 (1C, Ph*C*), 127.8 (2C, Ph*C*), 130.2 (2C, Ph*C*), 136.5 (1C, $CHCH_2$), 138.2 (1C, quat., Ph*C*), 168.9 (1C, quat., *C*(O)), 199.1 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 395 (100%), $[M-C_3H_4Ph]^+$ 278 (5%); HRMS (TOF MS ES^+) mass calculated for $C_{22}H_{28}O_3SNa$ 395.1657, found 395.1654.

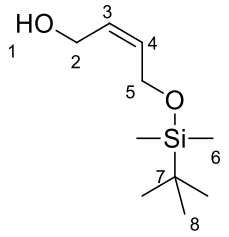
Ethyl 3-(2-bromoallyl)-4-oxo-2-thiaspiro[5.5]undecane-3-carboxylate (327d)



Following GP 6 heterocycle was obtained in 4 h as a colourless viscous oil (26.6 mg, 71% yield); R_f 0.29 (70% hexane:30% EtOAc); ν_{max}(neat) / (cm^{-1}) 2926 s (C-H), 2858 m (C-H), 1708 s (C=O), 1195 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, H-16, $OCH_2C\mathit{H_3}$), 1.32-1.73 (10H, m, H-9-13, $C\mathit{H_2}$, cyclohexyl), 2.13 (1H, d, *J* 12.3, H-8, $SC\mathit{H_AH_B}$), 2.36 (1H, dd, *J* 12.3, *J* 2.3, H-8, $SC\mathit{H_AH_B}$), 2.53 (1H, dd, *J* 14.1, *J* 2.1, H-6, $C\mathit{H_AH_B}$), 2.93 (1H, dd, *J* 15.7, *J* 0.6, H-3, $C\mathit{H_AH_B}$C(Br)), 3.03 (1H, d, *J* 14.1, H-6, $C\mathit{H_AH_B}$), 3.34 (1H, d, *J* 15.7, H-3, $C\mathit{H_AH_B}$C(Br)), 4.27 (2H, q, *J* 7.2, H-15, $OC\mathit{H_2}CH_3$), 5.55 (1H, d, *J* 1.9, H-1b, C(Br)$C\mathit{H_{trans}}$), 5.68-5.73 (1H, m, H-1a, C(Br)$C\mathit{H_{cis}}$); δ_C (101 MHz, $CDCl_3$) 14.0 (1C, $OCH_2\mathit{C}H_3$), 21.4 (1C, $\mathit{C}H_2$, cyclohexyl), 21.6 (1C, $\mathit{C}H_2$, cyclohexyl), 25.9 (1C, $\mathit{C}H_2$, cyclohexyl), 32.1 (1C, $\mathit{C}H_2$, cyclohexyl), 37.4 (1C, $\mathit{C}H_2$), 39.9 (1C, $\mathit{C}H_2$, cyclohexyl), 44.7 (1C, $\mathit{C}H_2S$), 46.8 (1C, quat., cyclohexyl), 51.0 (1C, $\mathit{C}H_2C(O)$), 61.3 (1C, quat., S*C*), 62.8 (1C, $O\mathit{C}H_2CH_3$), 122.1 (1C, C(Br)$\mathit{C}H_2$), 125.9 (1C, quat., *C*(Br)CH_2), 168.4 (1C, quat., *C*(O)), 197.9 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na(^{81}Br)]^+$ 399 (60%), $[M+Na(^{79}Br)]^+$ 397 (95%), $[M-C_3H_4Br]^+$ 278 (50%); HRMS (TOF MS ES^+) mass calculated for $C_{16}H_{23}O_3Na^{79}BrS$ 397.0449, found 397.0457.

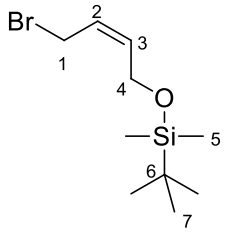
3.3.2 Post-catalysis-tandem cyclisations

(*Z*)-4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-ol (351)



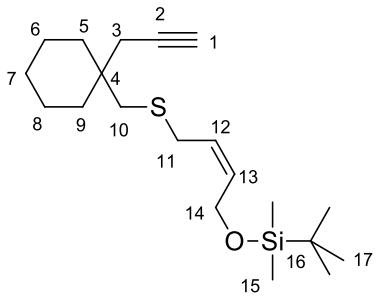
Following GP 8 ether was prepared and isolated to give a colourless oil (10.2 g, 89% yield); R_f 0.30 (25% EtOAc: 75% hexane); ν_{max}(neat) / (cm^{-1}) 3623 brs (O-H), 3016 m (C-H), 2931 s (C-H), 2858 s (C-H), 1650 s (C-O), 1251 s (C=C), 838 m (Si-O); δ_H (300 MHz, $CDCl_3$) 0.07 (6H, s, H-6, Si(C*H*$_3$)$_2$), 0.82 (9H, s, H-8, C(C*H*$_3$)$_3$), 2.44 (1H, brs, H-1, O*H*), 4.14 (2H, d, *J* 4.2, H-2, C*H*$_2$), 4.21 (2H, d, *J* 5.2, H-5, C*H*$_2$), 5.50-5.61 (2H, m, H-3 and H-4, C*H*C*H*); δ_C (101 MHz, $CDCl_3$) -5.3 (2C, Si(*C*H$_3$)$_2$), 18.3 (1C, quat., *C*(CH$_3$)$_3$), 25.9 (3C, C(C*H*$_3$)$_3$), 63.1 (1C, *C*H$_2$), 63.2 (1C, *C*H$_2$), 128.9 (1C, *C*H), 131.0 (1C, *C*H). Data were in agreement to that reported in the literature.[117]

(*Z*)-((4-bromobut-2-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (348)



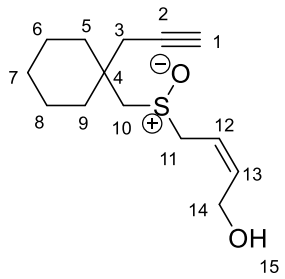
Following GP 9, bromide was isolated as a colourless oil (1.30 g, 99% yield); R_f 0.30 (2% EtOAc: 98% hexane); δ_H (300 MHz, $CDCl_3$) 0.06 (6H, s, H-5, Si(C*H*$_3$)$_2$), 0.88 (9H, s, H-7, C(C*H*$_3$)$_3$), 4.03 (2H, d, *J* 7.7, H-1, C*H*$_2$), 4.32 (2H, d, *J* 5.4, H-4, C*H*$_2$), 5.55-5.84 (2H, m, H-2 and H-3, C*H*C*H*); δ_C (101 MHz, $CDCl_3$) -5.3 (2C, Si(*C*H$_3$)$_2$), 18.3 (1C, quat., *C*(CH$_3$)$_3$), 26.0 (3C, C(C*H*$_3$)$_3$), 26.8 (1C, *C*H$_2$), 59.0 (1C, *C*H$_2$), 125.9 (1C, *C*H), 134.5 (1C, *C*H). Data were in agreement to that reported in the literature.[118]

(*Z*)-*tert*-butyldimethyl((4-(((1-(prop-2-yn-1-yl)cyclohexyl)methyl)thio)but-2-en-1-yl)oxy)silane (352)



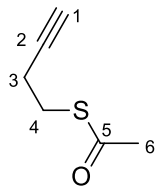
Following GP 4, using bromide (2.6 mmol, 0.7 g), thioether was prepared in this way to give a colourless oil (169 mg, 20% yield); R_f 0.30 (99% hexane:1% EtOAc:1% NEt_3); ν_{max}(neat) / (cm^{-1}) 3312 w (CC-H), 2925 s (C-H), 2854 s (C-H), 1252 s (C=C), 836 s, (Si-C); δ_H (300 MHz, $CDCl_3$) 0.08 (6H, s, H-15, Si(CH_3)$_2$), 0.90 (9H, s, H-17, C(CH_3)$_3$), 1.32-1.54 (10H, m, H-5-9, CH_2, cyclohexyl), 1.96-2.01 (1H, m, H-1, CC*H*), 2.28-2.34 (2H, m, H-3, CH_2), 2.60-2.66 (2H, m, H-10, CH_2S), 3.12-3.26 (2H, m, H-11, SCH_2), 4.15-4.28 (2H, m, H-14, CH_2O), 5.46-5.71 (2H, m, overlapping peaks H-12 and H-13, C*H*C*H*); δ_C (101 MHz, $CDCl_3$) -5.1 (2C, Si(*C*H_3)$_2$), 18.3 (1C, quat., *C*(CH_3)$_3$), 21.7 (2C, *C*H_2, cyclohexyl), 26.0 (3C, (*C*H_3)$_3$), 27.0 (1C, *C*H_2), 30.0 (1C, *C*H_2, cyclohexyl), 30.3 (1C, *C*H_2, cyclohexyl), 34.5 (1C, *C*H_2, cyclohexyl), 35.2 (1C, *C*H_2), 37.2 (1C, quat., cyclohexyl), 59.2 (1C, S*C*H_2), 63.2 (1C, *C*H_2), 70.5 (1C, C*C*H), 81.9 (1C, quat., *C*CH), 126.9 (1C, *C*HCH), 132.1 (1C, CH*C*H); used in next step without further purification.

(*Z*)-4-(((1-(prop-2-yn-1-yl)cyclohexyl)methyl)sulfinyl)but-2-en-1-ol (354)



Following GP 5 sulfide (1.0 mmol, 353 mg) was oxidised to sulfoxide in 30 minutes as a colourless oil (122 mg, 48% yield); R_f 0.28 (2% MeOH in EtOAc); ν_{max}(neat) / (cm^{-1}) 3298 brs (O-H), 2926 s (C-H), 2856 s (C-H), 1454 m (S=O), 1018 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.31-1.75 (10H, m, H-5-9, CH_2, cyclohexyl), 2.03 (1H, t, H-1, CC*H*), 2.36-2.52 (2H, m, H-3, CH_AH_B), 2.84 (2H, dd, J 21.6, J 13.7, H-10, CH_AH_BS), 3.54-3.69 (2H, m, H-11, SCH_AH_B), 3.68-3.83 (1H, brs, H-15, O*H*), 4.00-4.19 (2H, m, H-14, CH_2O), 5.60-5.73 (1H, m, H-12, C*H*), 6.20-6.32 (1H, m, H-13, C*H*); δ_C (101 MHz, $CDCl_3$) 21.3 (1C, *C*H_2, cyclohexyl), 21.4 (1C, *C*H_2, cyclogexyl), 25.6 (1C, *C*H_2, cyclohexyl), 27.8 (1C, *C*H_2), 35.1 (1C, *C*H_2, cyclohexyl), 35.2 (1C, *C*H_2, cyclohexyl), 36.6 (1C, quat., cyclohexyl), 50.5 (1C, *C*H_2), 58.2 (1C, S*C*H_2), 60.6 (1C, *C*H_2), 71.7 (1C, C*C*H), 80.7 (1C, quat., *C*CH), 117.8 (1C, *C*HCH), 139.6 (1C, CH*C*H); m/z (TOF MS ES^+) $[M+Na]^+$ 277 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{14}H_{22}O_2SNa$ 377.1238, found 377.1234.

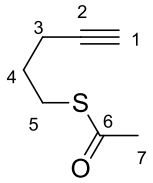
Prop-2-yn-4-methylthioate (369a)



GP 3 was followed using PPh_3 (8.1 g, 31 mmol), DIAD 94% pure (31 mmol, 6.1 mL), prop-yn-4-ol (20 mmol, 1.4 g) and thioacetic acid 96% pure (30 mmol, 2.2 mL) to prepare thioester as a colourless liquid (2.3 g, 89% yield); R_f (16% EtOAc: 84% hexane);

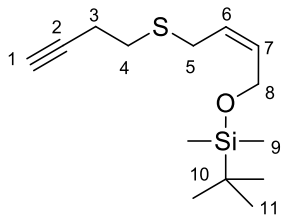
ν_{max}(neat) / (cm^{-1}) 3304 w (CC-H), 2923 s, (C-H), 2853 m (C-H), 1685 s (C=O); δ_H (300 MHz, $CDCl_3$) 2.02 (1H, t, *J* 2.5, H-1, CC*H*), 2.35 (3H, s, H-6, CH_3), 2.48 (2H, dt, *J* 7.0, *J* 2.5, H-3, CH_2), 3.04 (2H, t, *J* 7.0, H-4, CH_2). Data were consistent to that reported in the literature.[119]

But-2-yn-4-methylthioate (369b)



GP 3 was followed using PPh_3 (8.1 g, 31 mmol), DIAD 94% pure (31 mmol, 6.1 mL), but-yn-5-ol (20 mmol, 1.7 g) and thioacetic acid 96% pure (30 mmol, 2.2 mL) to prepare thioester as a colourless liquid (2.6 g, 91% yield); R_f (16% EtOAc: 84% hexane); ν_{max}(neat) / (cm^{-1}) 3260 w (CC-H), 2923 s, (C-H), 2853 m (C-H), 2115 w (CC), 1702 s (C=O); δ_H (300 MHz, $CDCl_3$) 1.78 (2H, p, *J* 7.0, H-4, CH_2), 1.96 (1H, t, *J* 2.7, H-1, CC*H*), 2.26 (2H, td, *J* 7.0, *J* 2.7, H-3, CH_2), 2.31 (3H, s, H-7, CH_3), 2.92-3.00 (2H, m, H-5, CH_2); δ_C (101 MHz, $CDCl_3$) 17.6 (1C, *C*H_2), 28.0 (1C, *C*H_2), 28.3 (1C, *C*H_2), 30.6 (1C, C(O)*C*H_3), 69.2 (1C, quat., *C*CH), 83.0 (1C, C*C*H), 195.6 (1C, quat., *C*(O)); m/z (TOF MS EI^+) $[M-H]^+$ 141 (5%), $[M-C(O)CH_3]^+$ 127 (100%). Data is consistent to that reported in the literature.[120]

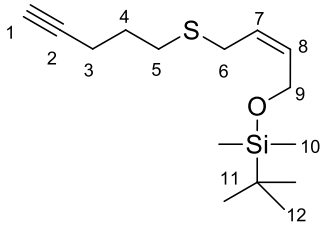
(Z)-((4-(but-3-yn-1-ylthio)but-2-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (368a)



Following GP 4 using thioether (2.4 mmol, 0.3 g) and bromide (2.6 mmol, 0.7 g), sulfane was isolated to give a colourless oil (594 mg, 97% yield); R_f 0.32 (97% hexane:3% EtOAc); ν_{max}(neat) / (cm^{-1}) 3310 m (CC-H), 2955 s (C-H), 2929 s (C-H), 2857 s (C-H),

1254 s (C=C); δ_H (300 MHz, $CDCl_3$) 0.06 (6H, s, H-9, Si(C*H*$_3$)$_2$C), 0.88 (9H, s, H-11, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$), 2.01 (1H, t, *J* 2.6, H-1, CC*H*), 2.45 (2H, td, *J* 7.1, *J* 2.6, H-3, HCC*H*$_2$), 2.64 (2H, t, *J* 7.1, H-4, CH$_2$C*H*$_2$S), 3.23 (2H, d, *J* 8.3, H-5, SC*H*$_2$CH), 4.22 (2H, d, *J* 6.2, H-8, CHC*H*$_2$O), 5.43-5.56 (1H, m, H-6, SCH$_2$C*H*CH), 5.59-5.71 (1H, m, H-7, CHC*H*CH$_2$O); δ_C (101 MHz, $CDCl_3$) -5.2 (2C, Si(*C*H$_3$)$_2$), 18.3 (1C, quat., *C*(CH$_3$)$_3$), 19.8 (1C, *C*H$_2$), 25.9 (3C, (*C*H$_3$)$_3$), 28.7 (1C, *C*H$_2$S), 29.9 (1C, S*C*H$_2$), 59.0 (1C, *C*H$_2$O), 69.4 (1C, H*C*C), 82.6 (1C, quat., HC*C*), 126.4 (1C, C*H*CH), 132.3 (1C, CHC*H*) m/z (TOF MS EI$^+$) $[M]^+$ 270 (5%), $[M-C_{10}H_{21}SiO]^+$ 85 (100%); HRMS (TOF MS EI$^+$) mass calculated for $C_{14}H_{26}OSSi$ 270.1474, found 270.1473.

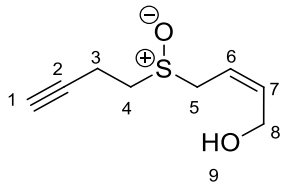
(Z)-*tert*-butyldimethyl((4-(pent-4-yn-1-ylthio)but-2-en-1-yl)oxy)silane (368b)



Following GP 4 using thioether (2.4 mmol, 0.3 g) and bromide (2.6 mmol, 0.7 g), sulfane was isolated to give a colourless oil (665 mg, 98% yield); R_f 0.35 (97% hexane:3% EtOAc); ν_{max}(neat) / (cm^{-1}) 3311 m (CC-H), 2954 s (C-H), 2930 s (C-H), 2857 s (C-H), 1253 s (C-O); δ_H (300 MHz, $CDCl_3$) 0.05 (6H, s, H-10, Si(C*H*$_3$)$_2$), 0.87 (9H, s, H-12, (C*H*$_3$)$_3$), 1.76 (2H, p, *J* 7.0, H-4, C*H*$_2$), 1.94 (1H, t, *J* 2.6, H-1, CC*H*), 2.28 (2H, td, *J* 7.0, *J* 2.6, H-3, C*H*$_2$), 2.56 (2H, t, *J* 7.0, H-5, C*H*$_2$S), 3.16 (2H, d, *J* 7.7, H-6, SC*H*$_2$), 4.21 (2H, dd, *J* 6.2, *J* 1.4, H-9, C*H*$_2$O), 5.42-5.55 (1H, m, H-7, C*H*CH), 5.56-5.69 (1H, m, H-8, CHC*H*); δ_C (101 MHz, $CDCl_3$) -5.1 (2C, CH$_3$, Si(*C*H$_3$)$_2$), 17.5 (1C, *C*H$_2$), 18.3 (1C, quat., *C*(CH$_3$)$_3$), 25.9 (3C, (*C*H$_3$)$_3$), 28.3 (1C, *C*H$_2$), 28.5 (1C, *C*H$_2$S), 30.0 (1C, S*C*H$_2$), 59.0 (1C, *C*H$_2$O), 68.9 (1C, H*C*), 83.5 (1C, quat., HC*C*), 126.6 (1C, C*H*CH), 132.0 (1C, CHC*H*) m/z (TOF

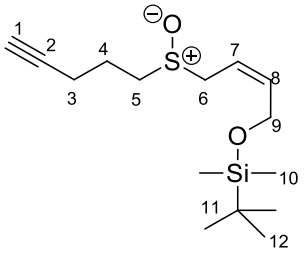
MS EI$^+$) $[M]^+$ 284 (5%), $[M\text{-}C_5H_7]^+$ 227 (100%); HRMS (TOF MS EI$^+$) mass calculated for $C_{15}H_{28}OSSi$ 284.1630, found 284.1632.

(Z)-4-(but-3-yn-1-ylsulfinyl)but-2-en-1-ol (367a)



Following GP 5 sulfide (1.0 mmol, 271 mg) was oxidised to sulfoxide in 30 minutes as a colourless oil (72 mg, 42% yield); R_f 0.30 (5% MeOH in EtOAc); ν_{max}(neat) / (cm^{-1}) 3292 brs (OH), 2924 s (C-H), 1520 w (CC), 1394 m (S=O), 1048 s (C-OH); δ_H (300 MHz, $CDCl_3$) 2.07 (1H, t, *J* 2.6, H-1, C*H*), 2.63-2.72 (2H, m, H-3, C*H*$_2$), 2.76-2.96 (2H, m, H-4, C*H*$_2$), 2.45 (1H, bs, H-9, O*H*), 2.59-2.75 (2H, m, H-5, C*H*$_2$), 4.03-4.18 (2H, m, H-8, C*H*$_2$O), 5.56-5.70 (1H, m, H-6, C*H*CH), 6.20-6.32 (1H, m, H-7, CHC*H*); δ_C (101 MHz, $CDCl_3$) 12.8 (1C, *C*H$_2$), 48.9 (1C, *C*H$_2$), 49.1 (1C, *C*H$_2$), 58.3 (1C, *C*H$_2$OH), 70.8 (1C, H*C*C), 80.5 (1C, quat., HC*C*), 117.4 (1C, C*H*CH), 139.7 (1C, CHC*H*); m/z (TOF MS ES$^+$) $[M+Na]^+$ 195 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_8H_{12}O_2SNa$ 195.0456, found 195.0461.

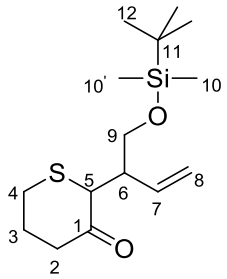
(Z)-*tert*-butyldimethyl((4-(pent-4-yn-1-ylsulfinyl)but-2-en-1-yl)oxy)silane (367b)



Following GP 5 sulfide (1.0 mmol, 285 mg) was oxidised to sulfoxide in 45 minutes as a colourless oil (180 mg, 60% yield); R_f 0.30 (6:4 EtOAc:hexane); ν_{max}(neat) / (cm^{-1}) 2956 s (C-H), 2929 s (C-H), 2858 s (C-H), 1472 m (S=O), 1252 s (C-O); δ_H (300 MHz, $CDCl_3$)

0.06 (6H, s, H-10, Si(CH_3)$_2$), 0.88 (9H, s, H-12, (CH_3)$_3$), 1.93-2.06 (3H, m, overlapping signals H-1 and H-4, C*H* and CH_2), 2.33-2.41 (2H, m, H-3, CH_2), 2.69-2.88 (2H, m, H-5, CH_2), 3.51-3.63 (2H, m, H-6, CH_2), 4.19-4.36 (2H, m, H-9, CH_2O), 5.49-5.62 (1H, m, H-7, C*H*CH), 5.89-6.01 (1H, m, H-8, CHC*H*); δ_C (101 MHz, $CDCl_3$) -5.2 (2C, Si(*C*H$_3$)$_2$), 17.7 (1C, *C*H$_2$), 18.3 (1C, quat., *C*(CH$_3$)$_3$), 21.6 (1C, *C*H$_2$), 25.9 (3C, (*C*H$_3$)$_3$), 49.8 (1C, *C*H$_2$), 50.5 (1C, *C*H$_2$), 59.7 (1C, *C*H$_2$O), 69.9 (1C, H*C*), 82.4 (1C, quat., HC*C*), 116.9 (1C, C*H*CH), 137.7 (1C, CHC*H*); m/z (TOF MS ES$^+$) $[M+Na]^+$ 323 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{15}H_{28}O_2SSiNa$ 323.1477, found 323.1465.

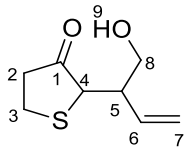
2-(1-((*tert*-butyldimethylsilyl)oxy)but-3-en-2-yl)dihydro-2*H*-thiopyran-3(4*H*)-one (373b)



Following GP 6 using sulfoxide (0.1 mmol, 30 mg) and $PtCl_2$ (10 mol%, 3 mg) in 4 h, thiopyran was isolated as a colourless oil of 1:1 diastereoisomeric ratio (13 mg, 43% yield); R_f 0.29 (92% hexane:8% EtOAc); ν_{max}(neat) / (cm^{-1}) 2952 s, (C-H), 2926 s (C-H), 2856 s (C-H), 1709 s (C=O), 1254 s (C-O), 836 s (Si-C); δ_H (300 MHz, $CDCl_3$) 0.01 (3H, s, H-10, Si(CH_3)$_2$), 0.03 (3H, s, H-10', Si(CH_3)$_2$), 0.88 (9H, s, H-12, C(CH_3)$_3$), 2.31-2.62 (4H, m, H-2 and H-3, C$H_A$$H_B$C(O) and C$H_A$$H_BCH_X$), 2.72-2.93 (3H, m, H-4 overlaps with H-6, CH_2S and C*H*), 3.59 (1H, dd, *J* 9.9, *J* 6.3, H-9, C$H_A$$H_B$CH), 3.63 (1H, d, *J* 8.3, H-5, SC*H*), 3.71 (1H, dd, *J* 9.9, *J* 4.6, H-9, C$H_A$$H_B$CH), 5.11-5.18 (2H, m, H-8, CHCH_2), 5.75 (1H, ddd, *J* 16.7, *J* 10.9, *J* 8.8, H-7, C*H*CH$_2$); δ_C (101 MHz, $CDCl_3$) -5.5 (2C, Si(*C*H$_3$)$_2$), 25.9 (3C, C(*C*H$_3$)$_3$), 28.6 (1C, *C*H$_2$S), 35.0 (1C, *C*H$_2$), 42.3 (1C, *C*H$_2$), 44.8 (1C, *C*H), 50.9 (1C,

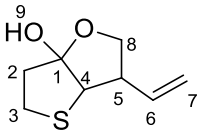
S*C*H), 64.3 (1C, *C*H_2O), 117.6 (1C, CH*C*H_2), 136.1 (1C, *C*HCH$_2$); m/z (TOF MS ES$^+$) [M+Na]$^+$ 323 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{15}H_{28}O_2SSiNa$ 323.1477, found 323.1464.

2-(1-hydroxybut-3-en-2-yl)dihydrothiophen-3(2*H*)-one (372a)



Following GP 6 using sulfoxide (0.1 mmol, 17 mg) and $PtCl_2$ (10 mol%, 3 mg) in 24 h, thiophenone was isolated as a colourless oil of 1:1.65 diastereoisomeric ratio (4 mg, 19% yield); R_f 0.30 (7:3hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 3389 brs, (O-H), 2924 s (C-H), 2853 s (C-H), 1733 s (C=O); δ_H (300 MHz, $CDCl_3$) 2.10-3.03 (4H, m, H-2 and H-3, CH_AH_BC(O) and CH_AH_BCH$_X$), 3.35-3.43 (1H, brs, H-9, O*H*), 3.45-3.49 (1H, m, H-5, C*H*), 3.72 (1H, m, H-4, C*H*), 3.93 (1H, dd, J 10.5, J 8.4, H-8, CH_AH_BOH), 4.11-4.19 (1H, m, H-8, CH_AH_BOH), 5.08-5.23 (2H, m, H-7, CHCH_2), 5.83 (1H, ddd, *J* 17.5, *J* 10.1, H-6, C*H*CH$_2$); δ_C (101 MHz, $CDCl_3$) 28.7 (1C, *C*H$_2$), 41.1 (1C, *C*H$_2$), 46.6 (1C, *C*H), 57.7 (1C, *C*H), 72.8 (1C, *C*H$_2$), 118.2 (1C, CH*C*H$_2$), 135.3 (1C, *C*HCH$_2$). Compound was very unstable.

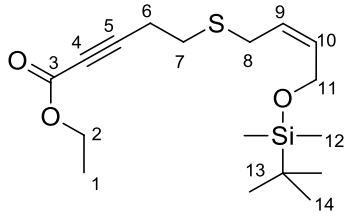
3-vinylhexahydrothieno[3,2-*b*]furanol (374a)



Following GP 6 using sulfoxide (0.1 mmol, 17 mg) and $PtCl_2$ (10 mol%, 3 mg) in 24 h, thiolactol was isolated as a colourless oil of 1:1 diastereoisomeric ratio (6 mg, 37% yield); R_f 0.29 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 3393 brs, (O-H), 2933 s (C-H), 2873 s (C-H), 1050 s (C-O); δ_H (300 MHz, $CDCl_3$) 2.17-2.29 (1H, m, H-2, CH_AH_B), 2.40 (1H, ddd, *J* 12.6, *J* 5.2, *J* 2.3, H-2, CH_AH_B), 2.78 (1H, ddd, *J* 11.0, *J* 6.6, *J* 2.3, H-3), 2.89-3.04 (2H, m,

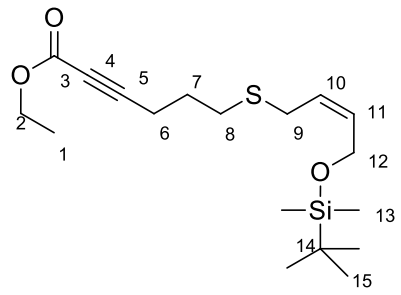
overlapping H-3 and H-5, CH_AH_B and C*H*), 3.47 (1H, d, *J* 4.5, H-4, C*H*), 3.69 (1H, brs, H-9, O*H*), 4.00 (1H, dd, *J* 8.7, *J* 6.8, H-8, CH_AH_B), 4.21 (1H, dd, *J* 8.7, *J* 7.0, H-8, CH_AH_B), 5.09-5.24 (2H, m, H-7, CHCH_2), 5.82-5.96 (1H, m, H-6, C*H*CH$_2$); δ_C (101 MHz, $CDCl_3$) 30.3 (1C, *C*H$_2$), 42.5 (1C, *C*H$_2$), 54.2 (1C, *C*H), 58.7 (1C, *C*H), 72.6 (1C, *C*H$_2$), 116.5 (1C, CH*C*H$_2$), 119.9 (1C, quat., *C*OH), 137.2 (1C, *C*HCH$_2$); m/z (TOF MS ES$^+$) $[M+Na]^+$ 195 (100%); HRMS (TOF MS EI$^+$) mass calculated for $C_8H_{12}O_2SNa$ 195.0456 found 195.0463.

(Z)-ethyl 5-((4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl)thio)pent-2-ynoate (392a)



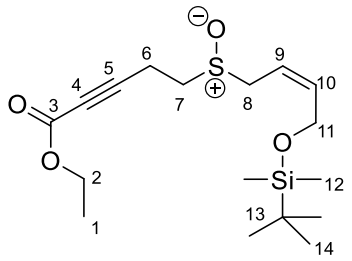
Following GP 7 using TMS-ether sulfane (1.5 mmol, 0.4 g), tethered alkyne was prepared as a colourless oil (328 mg, 64% yield); R_f 0.30 (95% hexane:5% EtOAc); ν_{max}(neat) / (cm^{-1}) 2955 s (C-H), 2923 s (C-H), 2853 s (C-H), 2246 s (CC), 1716 s (C=O), 1252 s (C-O); δ_H (300 MHz, $CDCl_3$) 0.05 (6H, s, H-12, Si(CH_3)$_2$), 0.87 (9H, s, H-14, (CH_3)$_3$), 1.28 (3H, t, *J* 7.1, H-1, OCH$_2$CH_3), 2.54-2.73 (4H, m, H-6 overlaps with H-7, CH_2CH_2), 3.22 (2H, d, *J* 11.0, H-8, SCH_2), 4.19 (2H, q, *J* 7.1, H-2, OCH_2CH$_3$), overlaps with 4.21 (2H, dd, *J* 6.2, *J* 1.5, H-11, CH_2O), 5.41-5.55 (1H, m, H-9, C*H*CH), 5.60-5.72 (1H, m, H-10, CHC*H*); δ_C (101 MHz, $CDCl_3$) -5.2 (2C, Si(*C*H$_3$)$_2$), 14.0 (1C, OCH$_2$*C*H$_3$), 18.3 (1C, quat., *C*(CH$_3$)$_3$), 20.2 (1C, *C*H$_2$), 25.9 (3C, (*C*H$_3$)$_3$), 28.7 (1C, *C*H$_2$S), 28.8 (1C, S*C*H$_2$), 59.0 (1C, *C*H$_2$O), 61.9 (1C, O*C*H$_2$CH$_3$), 73.9 (1C, quat., *C*C), 86.8 (1C, quat., C*C*), 126.3 (1C, C*H*CH), 132.4 (1C, CHC*H*), 153.5 (1C, quat., *C*(O)OEt); m/z (TOF MS ES$^+$) $[M+Na]^+$ 265 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{17}H_{30}O_3SSiNa$ 365.1583, found 365.1581.

(Z)-ethyl 6-((4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl)thio)hex-2-ynoate (392b)



Following GP 7 using TMS-ether sulfane (1.5 mmol, 0.4 g), tethered alkyne was prepared as a colourless oil (407 mg, 76% yield); R_f 0.30 (95% hexane:5% EtOAc:1% NEt_3); ν_{max}(neat) / (cm^{-1}) 2928 s (C-H), 2856 s (C-H), 2236 m (CC), 1711 s (C=O), 1250 s (C-O); δ_H (300 MHz, $CDCl_3$) 0.05 (6H, s, H-13, Si(C*H*$_3$)$_2$), 0.87 (9H, s, H-15, (C*H*$_3$)$_3$), 1.28 (3H, t, *J* 7.1, H-1, OCH$_2$C*H*$_3$), 1.81 (2H, p, *J* 7.2, H-7, C*H*$_2$), 2.44 (2H, t, *J* 7.2, H-6, C*H*$_2$), 2.55 (2H, t, *J* 7.2, H-8, C*H*$_2$), 3.15 (2H, d, *J* 7.7, H-9, SC*H*$_2$), 4.18 (2H, q, *J* 7.1, H-2, OC*H*$_2$CH$_3$), overlaps with 4.19 (2H, dd, *J* 6.2, *J* 1.4, H-12, C*H*$_2$O), 5.41-5.54 (1H, m, H-10, C*H*CH), 5.58-5.68 (1H, m, H-11, CHC*H*); δ_C (101 MHz, $CDCl_3$) -5.2 (2C, Si(*C*H$_3$)$_2$), 14.0 (1C, OCH$_2$*C*H$_3$), 17.7 (1C, *C*H$_2$), 18.3 (1C, quat., *C*(CH$_3$)$_3$), 25.9 (3C, (*C*H$_3$)$_3$), 28.5 (1C, *C*H$_2$), 30.1 (1C, *C*H$_2$S), 31.2 (1C, S*C*H$_2$), 59.0 (1C, *C*H$_2$O), 61.8 (1C, O*C*H$_2$CH$_3$), 73.7 (1C, quat., *C*C), 88.1 (1C, quat., C*C*), 126.5 (1C, C*H*CH), 132.1 (1C, CHC*H*), 153.7 (1C, quat., *C*(O)OEt); m/z (TOF MS ES$^+$) $[M+Na]^+$ 279 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{18}H_{32}O_3SSiNa$ 379.1739, found 379.1736.

(Z)-ethyl 5-((4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl)sulfinyl)pent-2-ynoate (393a)



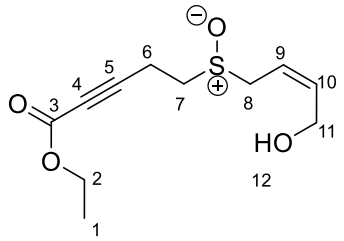
Following GP 5 sulfide (1.0 mmol, 343 mg) was oxidised to sulfoxide in 30 minutes as a colourless oil (269 mg, 75% yield); R_f 0.27 (7:3 EtOAc:hexane); ν_{max}(neat) / (cm^{-1}) 2931 s (C-H), 2857 s (C-H), 2239 s (CC), 1708 s (C=O), 1366 w (S=O), 1252 s (C-O); δ_H (300 MHz, $CDCl_3$) 0.06 (6H, s, H-12, Si(C*H*$_3$)$_2$), 0.88 (9H, s, H-14, (C*H*$_3$)$_3$), 1.28 (3H, t, *J* 7.1, H-1, OCH$_2$C*H*$_3$), 2.78-2.93 (4H, m, H-6 overlaps with H-7, C*H*$_2$C*H*$_2$), 3.62 (2H, d, *J* 8.1, H-8, C*H*$_2$), 4.20 (2H, q, *J* 7.1, H-2, OC*H*$_2$CH$_3$), overlaps with 4.13-4.38 (2H, m, H-11, C*H*$_2$O), 5.47-5.61 (1H, m, H-9, C*H*CH), 5.91-6.02 (1H, m, H-10, CHC*H*); δ_C (101 MHz, $CDCl_3$) -5.2 (2C, Si(*C*H$_3$)$_2$), 12.7 (1C, *C*H$_2$), 14.0 (1C, OCH$_2$*C*H$_3$), 18.3 (1C, quat., *C*(CH$_3$)$_3$), 25.9 (3C, (*C*H$_3$)$_3$), 48.1 (1C, *C*H$_2$S), 49.1 (1C, S*C*H$_2$), 59.7 (1C, *C*H$_2$O), 62.1 (1C, O*C*H$_2$CH$_3$), 74.6 (1C, quat., *C*C), 84.9 (1C, quat., C*C*), 116.5 (1C, *C*HCH), 138.0 (1C, CH*C*H), 153.3 (1C, quat., *C*(O)OEt); m/z (TOF MS ES$^+$) $[M+Na]^+$ 381 (100%), $[M-C_6H_{15}Si]^+$ 267 (40%); HRMS (TOF MS ES$^+$) mass calculated for $C_{17}H_{30}O_4SSiNa$ 381.1532, found 381.1514.

Procedure 5 but using 0.25*N* solvent instead of the standard 0.4*N* (GP 5B)

MoO_2Cl_2 (1.5 mol%, 3 mg) and H_2O_2 (1.05 eq., 1.1 mmol, 0.1 mL of a 35 % solution in water) were added successively to a solution of sulfane (1.0 eq., 1.0 mmol) in 6:4 ratio of acetone and water (0.25*N*, 5.0 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred until reaction was complete (TLC analysis). The reaction mixture was quenched with aq. NaCl and the organic layers extracted with EtOAc (2 × 10.0 mL). The combined extracts were washed with H_2O, aq. NaCl, dried over Na_2SO_4 and

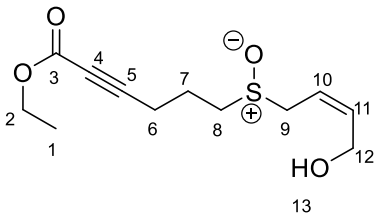
filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel to give the desired sulfoxide product.

(Z)-ethyl 5-((4-hydroxybut-2-en-1-yl)sulfinyl)pent-2-ynoate (394a)



Following GP 5B sulfide (1.0 mmol, 343 mg) was oxidised to sulfoxide in 30 minutes as a colourless oil (159 mg, 65% yield); R_f 0.30 (5% MeOH in EtOAc); ν_{max}(neat) / (cm^{-1}) 3383 brs, (OH), 2983 s (C-H), 2239 s (CC), 1706 s (C=O), 1367 w (S=O), 1252 s (C-O); δ_H (300 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.1, H-1, OCH_2CH_3), 2.75-2.93 (4H, m, H-6 overlaps with H-7, CH_2CH_2), 3.49 (1H, bs, H-12, O*H*), 3.65 (2H, ddd, *J* 21.5, *J* 13.3, *J* 8.6, H-8, CH_2), 4.02-4.12 (2H, m, H-11, CH_2OH), 4.17 (2H, q, *J* 7.1, H-2, OCH_2CH_3), 5.52-5.67 (1H, m, H-9, C*H*CH), 6.15-6.28 (1H, m, H-10, CHC*H*); δ_C (101 MHz, $CDCl_3$) 12.9 (1C, OCH_2CH_3), 14.0 (1C, CH_2), 47.9 (1C, CH_2), 49.1 (1C, CH_2), 58.3 (1C, CH_2OH), 62.1 (1C, OCH_2CH_3), 74.7 (1C, quat., *C*C), 84.6 (1C, quat., C*C*), 117.2 (1C, C*H*CH), 139.7 (1C, CHC*H*), 153.2 (1C, quat., *C*(O)OEt); m/z (TOF MS ES^+) $[M+Na]^+$ 267 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{11}H_{16}O_4SNa$ 267.0667, found 267.0676.

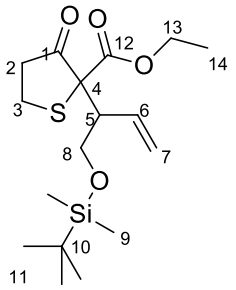
(Z)-ethyl 6-((4-hydroxybut-2-en-1-yl)sulfinyl)hex-2-ynoate (394b)



Following GP 5B sulfide (1.0 mmol, 357 mg) was oxidised to sulfoxide in 30 minutes as a colourless oil (132 mg, 51% yield); R_f 0.29 (5% MeOH in EtOAc); ν_{max}(neat) / (cm^{-1}) 3374

brs, (OH), 2937 s (C-H), 2236 s (CC), 1704 s (C=O), 1369 w (S=O), 1253 s (C-O); δ_H (300 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, H-1, OCH_2CH_3), 1.96-2.11 (2H, m, H-6, CH_2), 2.42-2.62 (2H, m, H-7, CH_2), 2.71-2.88 (2H, m, H-8, CH_2), 3.47-3.73 (3H, m, H-9 and H-13, CH_2 and OH), 4.01-4.13 (2H, m, H-12, CH_2OH), 4.18 (2H, q, *J* 7.1, H-2, OCH_2CH_3), 5.54-5.70 (1H, m, H-10, CHCH), 6.17-6.30 (1H, m, H-11, CHCH); δ_C (101 MHz, $CDCl_3$) 14.0 (1C, OCH_2CH_3), 17.9 (1C, CH_2), 21.1 (1C, CH_2), 49.1 (1C, CH_2), 49.2 (1C, CH_2), 58.3 (1C, CH_2OH), 62.0 (1C, OCH_2CH_3), 74.5 (1C, quat., CC), 86.5 (1C, quat., CC), 117.4 (1C, CHCH), 139.6 (1C, CHCH), 153.5 (1C, quat., C(O)OEt); m/z (TOF MS ES^+) $[M+Na]^+$ 281 (100%), $[M-C_4H_7O]^+$ 210 (30%); HRMS (TOF MS ES^+) mass calculated for $C_{12}H_{18}O_4SNa$ 281.0824, found 281.0829.

Ethyl 2-(1-((*tert*-butyldimethylsilyl)oxy)but-3-en-2-yl)-3-oxotetrahydrothiophene-2-carboxylate (395a)

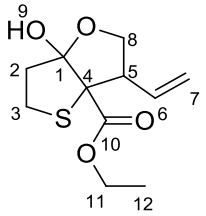


Following GP 6 using sulfoxide (0.1 mmol, 36. mg) and Au-**I** (5 mol%, 2 mg) in 2 h, tetrahydrothiophene was isolated as a colourless oil of 1:1.14 diastereoisomeric ratio (30 mg, 84% yield); R_f 0.31 (92% hexane:8% EtOAc); ν_{max}(neat) / (cm^{-1}) 3389 brs, (O-H), 2924 s (C-H), 2853 s (C-H), 1733 s (C=O), 1254 s (C-O); δ_H (300 MHz, $CDCl_3$) diasterioisomer A: 0.02 (6H, s, H-9, $Si(CH_3)_2$), 0.87 (9H, s, H-11, $C(CH_3)_3$), 1.26 (3H, t, *J* 7.1, H-14, CH_3), 2.54-2.67 (2H, m, H-3, SCH_2), 2.88-3.08 (2H, m, H-2, CH_AH_B), 3.09-3.17 (1H, m, H-5, CH), 3.62 (1H, dd, *J* 10.5, *J* 6.0, H-8, OCH_AH_B), 3.86-3.90 (1H, m, H-8, OCH_AH_B), 4.09-4.26 (2H, m, H-13, CH_2), 5.09-5.18 (2H, m, H-7, $CHCH_2$), 5.98 (1H, ddd,

J 16.9, *J* 10.6, *J* 9.4, H-6, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) -5.5 (2C, Si(*C*H_3)$_2$), 14.0 (1C, *C*H_3), 18.4 (1C, *C*(CH_3)$_3$), 23.7 (1C, *C*H_2), 25.9 (3C, C(*C*H_3)$_3$), 40.5 (1C, S*C*H_2), 50.5 (1C, *C*H), 62.1 (1C, *C*H_2), 63.6 (1C, *C*H_2), 67.0 (1C, quat., S*C*), 119.5 (1C, CH*C*H_2), 135.0 (1C, *C*HCH$_2$), 166.1 (1C, quat., *C*(O)), 208.6 (1C, quat., *C*(O)).

Diastereoismer B: 0.03 (6H, s, H-9, Si(C*H*$_3$)$_2$), 0.86 (9H, s, H-11, C(C*H*$_3$)$_3$), 1.24 (3H, t, *J* 7.1, H-14, C*H*$_3$), 2.69-2.81 (2H, m, H-3, SC*H*$_2$), 2.97-3.01 (2H, m, H-2, C*H*$_A$*H*$_B$), 3.36 (1H, td, *J* 8.8, *J* 6.0, C-5, C*H*), 3.76-3.94 (2H, m, H-8, OC*H*$_A$*H*$_B$), 4.09-4.26 (2H, m, H-13, C*H*$_2$), 5.14-5.23 (2H, m, H-7, CHC*H*$_2$), 5.56 (1H, ddd, *J* 17.2, *J* 10.3, *J* 8.7, H-6, C*H*CH$_2$); δ_C (101 MHz, $CDCl_3$) -5.7 (2C, Si(*C*H_3)$_2$), 14.0 (1C, *C*H_3), 18.5 (1C, *C*(CH_3)$_3$), 24.3 (1C, *C*H_2), 25.9 (3C, C(*C*H_3)$_3$), 40.3 (1C, S*C*H_2), 51.3 (1C, *C*H), 62.3 (1C, *C*H_2), 63.8 (1C, *C*H_2), 65.5 (1C, quat., S*C*), 119.1 (1C, CH*C*H_2), 134.4 (1C, *C*HCH$_2$), 167.0 (1C, quat., *C*(O)), 207.6 (1C, quat., *C*(O)); m/z (TOF MS ES$^+$) $[M+Na]^+$ 381 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{17}H_{30}O_4SSiNa$ 381.1532, found 381.1534.

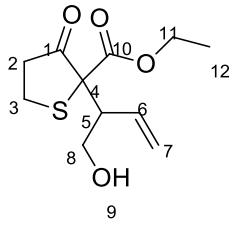
Ethyl 6a-hydroxo-3-vinylhexahydrothieno[3,2-*b*]furan-3a-carboxylate (397a)



Following GP 6 using sulfoxide (0.1 mmol, 24 mg) and Au-**I** (5 mol%, 2 mg) in 30 min, thiolactol was isolated as a colourless viscous oil (9 mg, 38% yield); R_f 0.33 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 3466 brs, (O-H), 2980 s (C-H), 2937 s (C-H), 2896 s (C-H), 1708 s (C=O), 1259 s (C-O), 1082 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1, H-12, C*H*$_3$), 2.26 (1H, td, *J* 12.5, *J* 7.3, H-2, C*H*$_A$*H*$_B$), 2.44-2.53 (1H, m, H-2, C*H*$_A$*H*$_B$), 2.60-2.69 (1H, m, H-3, C*H*$_A$*H*$_B$), 2.94 (1H, ddd, *J* 12.1, *J* 10.1, *J* 5.6, H-3, C*H*$_A$*H*$_B$), 3.19 (1H, ddd, *J* 9.5, *J* 6.3, *J* 2.7, H-5, C*H*), 4.06 (1H, dd, *J* 8.6, *J* 2.7, H-8, C*H*$_A$*H*$_B$), 4.15-4.26 (2H,

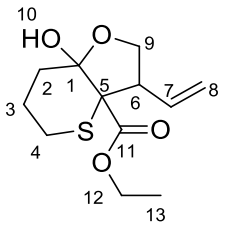
m, H-11, CH_2), 4.43 (1H, dd, *J* 8.6, *J* 6.3, H-8, CH_AH_B), 5.02 (1H, s, H-9, O*H*), 5.05-5.16 (2H, m, H-7, CHCH_2), 6.04 (1H, dt, *J* 17.0, *J* 10.0, H-6, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 13.9 (1C, *C*H_3), 27.2 (1C, *C*H_2), 40.7 (1C, *C*H_2), 53.5 (1C, *C*H), 62.0 (1C, *C*H_2), 65.2 (1C, quat., *C*S), 73.1 (1C, *C*H_2), 114.6 (1C, quat., *C*OH), 118.5 (1C, CH*C*H_2), 135.9 (1C, *C*HCH_2), 172.9 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 267 (100%), $[M-C_3H_5O_2]^+$ 194 (70%); HRMS (TOF MS ES^+) mass calculated for $C_{11}H_{16}O_4SNa$ 267.0667, found 267.0673.

Ethyl 2-(1-hydroxybut-3-en-2-yl)-3-oxotetrahydrothiophene-2-carboxylate (396a)



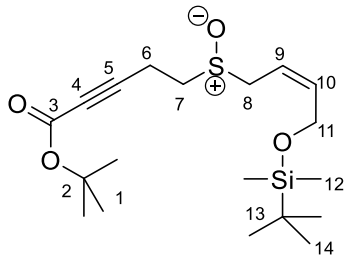
Tetrahydrothiophene was also isolated in the same catalysis reaction as a colourless viscous oil 85% pure plus unknown product (15 mg, 31% yield); R_f 0.30 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) δ_H (300 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, H-12, CH_3), 2.38-2.54 (2H, m, H-2, CH_AH_B), 2.75-2.81 (1H, m, H-3, CH_AH_B), 2.92 (1H, ddd, *J* 11.5, *J* 10.1, *J* 6.2, H-3, CH_AH_B), 3.63 (1H, m, H-5, C*H*), 3.69-3.82 (1H, brs, H-9, O*H*), 3.94 (1H, dd, *J* 10.1, *J* 8.2, H-8, CH_AH_B), 4.17-4.27 (3H, m, overlapping peaks H-8 and H-11, CH_AH_B and CH_2), 5.14-5.23 (2H, m, H-7, CHCH_2), 5.79-5.90 (1H, m, H-6, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 13.5 (1C, *C*H_3), 27.3 (1C, *C*H_2), 39.6 (1C, *C*H_2), 47.6 (1C, *C*H), 62.0 (1C, *C*H_2), 68.0 (1C, quat., *C*S), 71.7 (1C, *C*H_2), 119.0 (1C, $CHCH_2$), 134.1 (1C, $CHCH_2$), 172.4 (1C, quat., *C*(O)), 179.3 (1C, quat., *C*(O)).

Ethyl 7a-hydroxo-3-vinylhexahydro-2*H*-thiopyrano[3,2-*b*]furan-3a-carboxylate (397b)



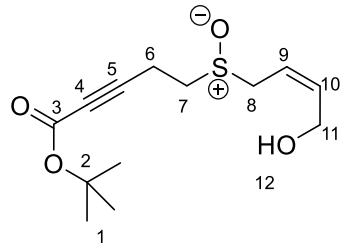
Following GP 6 using sulfoxide (0.1 mmol, 26 mg) and Au-**I** (5 mol%, 2 mg) in 24 h, thiopyranol was isolated as a mixture of diastereoisomers with 1:1.76 ratio as a colourless viscous oil (5 mg, 19% yield); R_f 0.30 (7:3 Pet.Ether:EtOAc); ν_{max}(neat) / (cm^{-1}) 3456 s, (O-H), 2958 s (C-H), 2923 s (C-H), 2853 s (C-H), 1719 s (C=O), 1263 s (C-O), 1047 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1, H-13, C*H*$_3$), 1.87-2.04 (2H, m, H-3, CH_AH_B), 2.09-2.22 (1H, m, H-2, CH_AH_B), 2.34-2.44 (1H, m, H-2, CH_AH_B), 2.60-2.73 (2H, m, H-4, CH_AH_B), 2.75-2.85 (1H, m, H-6, C*H*), 3.52 (1H, s, H-10, O*H*), 3.95 (1H, dd, *J* 8.5, *J* 2.9, H-9, CH_AH_B), 4.12-4.32 (2H, m, H-12, CH_2), 4.48 (1H, dd, *J* 8.5, *J* 7.8, H-9, CH_AH_B), 5.00-5.10 (2H, m, H-8, CHCH_2), 6.09-6.25 (1H, m, H-7, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 13.9 (1C, *C*H_3), 25.6 (1C, *C*H_2), 27.7 (1C, *C*H_2), 34.5 (1C, *C*H_2), 40.6 (1C, quat., *C*S), 52.4 (1C, *C*H), 61.6 (1C, *C*H_2), 71.4 (1C, *C*H_2), 114.5 (1C, quat., *C*OH), 117.4 (1C, CH*C*H_2), 138.7 (1C, *C*HCH$_2$), 172.8 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 281 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{12}H_{18}O_4SNa$ 281.0824, found 281.0822.

(Z)-*tert*-butyl 5-((4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl)sulfinyl)pent-2-ynoate (406a)



Following GP 5 crude sulfide 90% pure (1.0 mmol, 371 mg) was oxidised to sulfoxide in 40 minutes as a colourless oil (216 mg, 56% yield); R_f 0.35 (7:3 EtOAc:hexane); ν_{max}(neat) / (cm^{-1}) 2931 s (C-H), 2857 s (C-H), 2241 s (CC), 1703 s (C=O), 1369 s (S=O), 1278 s (C-O); δ_H (300 MHz, $CDCl_3$) 0.06 (6H, s, H-12, Si(C*H*$_3$)$_2$), 0.88 (9H, s, H-14, (C*H*$_3$)$_3$), 1.47 (9H, s, H-1, OC(C*H*$_3$)$_3$), 2.70-2.95 (4H, m, H-6 overlaps with H-7, C*H*$_2$C*H*$_2$S), 3.53-3.69 (2H, m, H-8, C*H*$_2$), 4.18-4.37 (2H, m, H-11, C*H*$_2$O), 5.47-5.62 (1H, m, H-9, C*H*CH), 5.90-6.02 (1H, m, H-10, CHC*H*); δ_C (101 MHz, $CDCl_3$) -5.2 (2C, Si(*C*H$_3$)$_2$), 12.6 (1C, *C*H$_2$), 18.3 (1C, quat., *C*(CH$_3$)$_3$), 25.9 (3C, C(*C*H$_3$)$_3$), 28.0 (3C, OC(*C*H$_3$)$_3$), 48.1 (1C, *C*H$_2$S), 50.4 (1C, *C*H$_2$), 59.7 (1C,, *C*H$_2$O), 75.8 (1C, quat., *C*C), 82.5 (1C, quat., C*C*), 83.5 (1C, quat., O*C*(CH$_3$)$_3$), 116.6 (1C, C*H*CH), 138.0 (1C, CHC*H*), 152.3 (1C, quat., *C*(O)O^{t}Bu); m/z (TOF MS ES$^+$) [M+Na]$^+$ 409 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{19}H_{34}O_4SSiNa$ 409.1845, found 409.1862.

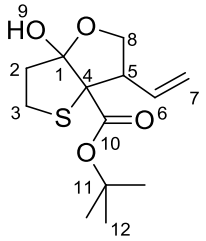
(Z)-tert-butyl 5-((4-hydroxybut-2-en-1-yl)sulfinyl)pent-2-ynoate (407a)



Following GP 5B sulfide (1.0 mmol, 371 mg) was oxidised to sulfoxide in 30 minutes as a colourless oil (114 mg, 42% yield); R_f 0.30 (5% MeOH in EtOAc); ν_{max}(neat) / (cm^{-1}) 3383

brs, (OH), 2981 s (C-H), 2936 s (C-O), 2242 s (CC), 1703 s (C=O), 1370 w (S=O), 1282 s (C-O); δ_H (300 MHz, $CDCl_3$) 1.47 (9H, s, H-1, OC(C*H*$_3$)$_3$), 1.96 (1H, bs, H-12, O*H*), 2.71-2.98 (4H, m, H-6 overlaps with H-7, C*H*$_2$C*H*$_2$), 3.59-3.77 (2H, m, H-8, C*H*$_2$), 4.05-4.17 (2H, m, H-11, C*H*$_2$OH), 5.55-5.69 (1H, m, H-9, C*H*CH), 6.20-6.32 (1H, m, H-10, CHC*H*); δ_C (101 MHz, $CDCl_3$) 13.0 (1C, *C*H$_2$), 28.0 (3C, OC(*C*H$_3$)$_3$), 48.0 (1C, *C*H$_2$), 49.1 (1C, *C*H$_2$), 50.9 (1C, quat., O*C*(CH$_3$)$_3$), 58.4 (1C, *C*H$_2$OH), 76.1 (1C, quat., *C*C), 83.7 (1C, quat., *C*C), 117.1 (1C, C*H*CH), 139.4 (1C, CHC*H*), 152.3 (1C, quat., *C*(O)O^{t}Bu); m/z (TOF MS ES$^+$) $[M+Na]^+$ 295 (100%), $[M-C_3H_5O]^+$ 239 (25%); HRMS (TOF MS ES$^+$) mass calculated for $C_{13}H_{20}O_4SNa$ 295.0980, found 295.0982.

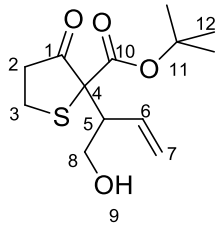
tert-butyl 6a-hydroxo-3-vinylhexahydrothieno[3,2-*b*]furan-3a-carboxylate (410)



Following GP 6 using sulfoxide (0.1 mmol, 27 mg) and Au-**I** (5 mol%, 2 mg) in 24 h, thiolactol was isolated as a colourless viscous oil (11 mg, 41% yield); R_f 0.35 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 3493 s, (O-H), 2976 s (C-H), 2935 s (C-H), 2889 s (C-H), 1709 s (C=O), 1290 s (C-O), 1082 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.46 (9H, s, H-12, C(C*H*$_3$)$_3$), 2.26 (1H, td, *J* 12.5, *J* 7.2, H-2, C*H*$_A$*H*$_B$), 2.46 (1H, dd, *J* 12.8, *J* 5.5, H-2, C*H*$_A$*H*$_B$), 2.62 (1H, dd, *J* 10.0, *J* 7.0, H-3, C*H*$_A$*H*$_B$), 2.91 (1H, ddd, *J* 12.2, *J* 10.0, *J* 5.6, H-3, C*H*$_A$*H*$_B$), 3.12 (1H, m, H-5, C*H*), 4.03 (1H, dd, *J* 8.5, *J* 2.5, H-8, C*H*$_A$*H*$_B$), 4.39 (1H, dd, *J* 8.5, *J* 6.2, H-8, C*H*$_A$*H*$_B$), 5.05-5.15 (2H, m, H-7, CHC*H*$_2$), 6.09 (1H, dt, *J* 16.9, *J* 10.0, H-6, C*H*CH$_2$); δ_C (101 MHz, $CDCl_3$) 27.1 (1C, *C*H$_2$), 27.9 (3C, C(*C*H$_3$)$_3$), 41.0 (1C, *C*H$_2$), 53.6 (1C, *C*H), 65.3 (1C, quat., *C*(CH$_3$)$_3$), 73.1 (1C, *C*H$_2$), 83.2 (1C, quat., *C*S), 114.4 (1C, quat., *C*OH), 118.2 (1C, CH*C*H$_2$), 136.3 (1C, *C*HCH$_2$), 172.8 (1C, quat., *C*(O)); m/z (TOF MS

ES$^+$) $[M+Na]^+$ 295 (100%), $[M-C_5H_9O_2]^+$ 194 (10%); HRMS (TOF MS ES$^+$) mass calculated for $C_{13}H_{20}O_4SNa$ 295.0980, found 295.0968.

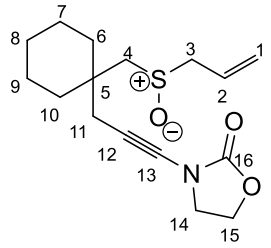
***tert*-butyl 2-(1-hydroxybut-3-en-2-yl)-3-oxotetrahydrothiophene-2-carboxylate (409)**



Tetrahydrothiophene was also isolated in the same catalysis reaction as a colourless viscous oil (9 mg, 34% yield); R_f 0.30 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 3424 s, (O-H), 2978 s (C-H), 2940 s (C-H), 2886 s (C-H), 1723 s (C=O), 1255 s (C-O), 1160 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.47 (9H, s, H-12, C(CH_3)$_3$), 2.39-2.49 (2H, m, H-3, CH_AH_B), 2.69-2.77 (1H, m, H-2, CH_AH_B), 2.89 (1H, ddd, *J* 10.1, *J* 8.4, *J* 5.3, H-2, CH_AH_B), 3.53 (1H, m, H-5, C*H*), 3.90 (1H, dd, *J* 10.1, *J* 8.2, H-8, CH_AH_B), 3.95-4.02 (1H, brs, H-9, O*H*), 4.15-4.22 (1H, m, H-8, CH_AH_B), 5.12-5.20 (2H, m, H-7, CHCH_2), 5.79-5.91 (1H, m, H-6, C*H*CH$_2$); δ_C (101 MHz, $CDCl_3$) 27.0 (1C, *C*H$_2$), 27.9 (3C, C(*C*H$_3$)$_3$), 39.7 (1C, *C*H$_2$), 47.7 (1C, *C*H), 67.8 (1C, quat., *C*(CH$_3$)$_3$), 71.5 (1C, *C*H$_2$), 83.0 (1C, quat., *C*S), 116.2 (1C, quat., *C*(O)), 118.6 (1C, CH*C*H$_2$), 134.6 (1C, *C*HCH$_2$), 204.6 (1C, quat., *C*(O)); m/z (TOF MS ES$^+$) $[M+Na]^+$ 295 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{13}H_{20}O_4SNa$ 295.0980, found 295.0992.

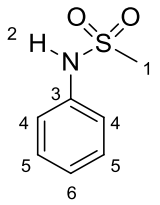
3.3.3 Site-specific introduction of gold carbenes (aliphatic systems)

3-(3-(1-((allylsulfinyl)methyl)cyclohexyl)prop-1-yn-1-yl)oxazolidin-2-one (460)



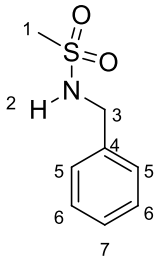
Following GP 10 using commercially available amide oxazolidinone (5.0 eq., 5.0 mmol, 435 mg) and sulfoxide (1.0 eq., 1.0 mmol, 224 mg), ynamide was obtained as a pale yellow viscous oil (139 mg, 45% yield); R_f 0.30 (80% EtOAc:20% hexane); ν_{max}(neat) / (cm^{-1}) 3196 s (CC-H), 2931 s (C-H), 2851 s (C-H), 2102 w (CC), 1639 m (C-S), 1454 w (S=O), 1420 m (C=C); δ_H (300 MHz, $CDCl_3$) 1.29-1.81 (10H, m, H-6-10, CH_2, cyclohexyl), 1.29 (2H, s, H-11, CH_2CC), 2.76 (1H, d, *J* 13.7, H-4, CH_AH_BS(O)), 2.89 (1H, d, *J* 13.7, H-4, CH_AH_BS(O)), 3.45 (1H, dd, *J* 12.9, *J* 7.5, H-3, C$H_AH_B$$CH_X$), 3.54 (1H, dd, *J* 12.9, *J* 7.3, H-3, C$H_AH_B$$CH_X$), 3.81-3.90 (2H, m, H-14, NCH_2), 4.36-4.43 (2H, m, H-15, OCH_2), 5.34-5.45 (2H, m, H-1, CH_2CH), 5.83-6.00 (1H, m, H-2, CH_2C*H*); δ_C (101 MHz, $CDCl_3$) 21.4 (1C, *C*H_2, cyclohexyl), 21.5 (1C, *C*H_2, cyclohexyl), 25.6 (1C, *C*H_2CC), 28.0 (1C, quat., cyclohexyl), 35.3 (1C, *C*H_2, cyclohexyl), 35.4 (1C, *C*H_2, cyclohexyl), 36.9 (1C, *C*H_2, cyclohexyl), 46.8 (1C, N*C*H_2), 57.4 (1C, *C*H_2), 60.8 (1C, quat., CH_2*C*CN), 62.9 (1C, O*C*H_2), 67.7 (1C, *C*H_2S(O), 73.1 (1C, quat., CH_2C*C*N), 123.3 (1C, CH*C*H_2), 126.2 (1C, *C*HCH$_2$), 156.6 (1C, quat., *C*O); m/z (TOF MS ES^+) $[M+Na]^+$ 332 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{16}H_{23}NO_3SNa$ 332.1296, found 332.1288.

_N_-phenylmethanesulfonamide (462a)



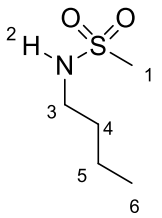
Following GP 11 using aniline 99.8% purity (20.0 mmol, 1.9 g), resulted in amide as a white solid (3.3 g, 95%%); mp 100-102 °C; R_f 0.30 (20% EtOAc:80% hexane); ν_{max}(neat) / (cm^{-1}) 3260 brs (N-H), 3022 s (C-H), 2933 s (C-H), 1599 m (C=C), 1495 m (S=O), 1324 m (C-N), 1149 s (N-S); δ_H (300 MHz, $CDCl_3$) 3.02 (3H, s, H-1, C*H*$_3$), 6.66-7.01 (1H, brs, H-2, N*H*), 7.15-7.26 (3H, m, H-5-6, Ph*H*), 7.35 (2H, t, *J* 7.8, H-4, Ph*H*); δ_C (101 MHz, $CDCl_3$) 39.3 (1C, *C*H$_3$), 120.8 (2C, Ph*C*), 125.5 (1C, Ph*C*), 129.7 (2C, Ph*C*), 136.7 (1C, quat., Ph*C*). Data consistent with those reported in the literature.[121]

_N_-benzylmethanesulfonamide (462b)



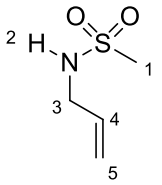
Following GP 11 using benzylamine 98+% purity (20.0 mmol, 2.2 g), resulted amide as a white solid (3.6 g, 96%); mp 64-66 °C; R_f 0.30 (40% EtOAc:60% hexane); ν_{max}(neat) / (cm^{-1}) 3230 brs (N-H), 3021 s (C-H), 1455 m (S=O), 1296 m (C-N), 1134 s (N-S); δ_H (300 MHz, $CDCl_3$) 2.86 (3H, s, H-1, C*H*$_3$), 4.32 (2H, d, *J* 6.1, H-3, C*H*$_2$), 4.75-5.02 (1H, brs, H-2, N*H*), 7.28-7.43 (5H, m, H-5-7, Ph*H*); δ_C (101 MHz, $CDCl_3$) 41.0 (1C, *C*H$_3$), 47.1 (1C, *C*H$_2$), 127.8 (2C, Ph*C*), 128.0 (1C, Ph*C*), 128.8 (2C, Ph*C*), 136.6 (1C, quat., Ph*C*). Data consistent with those reported in the literature.[121]

_N_-butylmethanesulfonamide (462c)



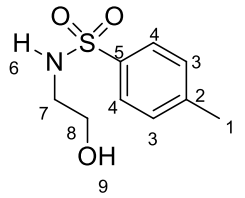
Following GP 11 using *n*-butylamine 99.8% purity (20.0 mmol, 1.46 g), resulted amide as a colourless liquid (2.9 g, 95%); R_f 0.30 (80% EtOAc:20% hexane); ν_{max}(neat) / (cm^{-1}) 3284 brs (N-H), 2964 s (C-H), 2933 s (C-H), 2874 s (C-H), 1413 m (S=O), 1308 m (C-N), 1139 s (N-S); δ_H (300 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.2, H-6, C*H*$_3$), 1.31-1.52 (4H, m, H-4-5, 2 × C*H*$_2$), 2.94 (3H, s, H-1, C*H*$_3$), 3.10 (2H, q, *J* 6.1, H-3, C*H*$_2$), 4.35-4.51 (1H, brs, H-2, N*H*); δ_C (101 MHz, $CDCl_3$) 13.6 (1C, *C*H_3), 19.7 (1C, *C*H_2), 32.0 (1C, *C*H_2), 40.0 (1C, *C*H_3), 43.0 (1C, *C*H_2). Data consistent with those reported in the literature.[122]

_N_-allylmethanesulfonamide (462d)



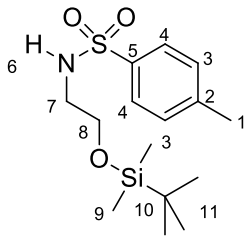
Following GP 11 using prop-2-en-1-amine 99.8% purity (20.0 mmol, 1.2 g), resulted amide as a colourless liquid (2.5 g, 93%); R_f 0.30 (80% EtOAc:20% hexane); ν_{max}(neat) / (cm^{-1}) 3284 brs (N-H), 2964 s (C-H), 2934 s (C-H), 1413 m (S=O), 1308 m (C-N), 1139 s (N-S); δ_H (300 MHz, $CDCl_3$) 2.99 (3H, s, H-1, C*H*$_3$), 3.79 (2H, H-3, C*H*$_2$), 4.50-4.55 (1H, brs, H-2, N*H*), 5.18-5.39 (2H, m, H-5, CHC*H*$_2$), 5.76-5.90 (1H, m, H-4, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 41.3 (1C, *C*H_3), 46.0 (1C, *C*H_2), 118.1 (1C, *C*H_2), 133.9 (1C, *C*H). Data consistent with those reported in the literature.[123]

_N_-(p-toluenesulfonyl)ethanolamine (464)



Following GP 12, *N*-(p-toluenesulfonyl)ethanolamine was isolated as a white solid (6.4 g, 85%); mp 56-58; R_f 0.30 (70% EtOAc:30% hexane); ν_{max}(neat) / (cm^{-1}) 3560 brs (N-H), 3262 brs (O-H), 2929 s (C-H), 2879 s (C-H), 1594 (N-S), 1491 m (S=O); δ_H (300 MHz, $CDCl_3$) 1.85 (1H, brs, H-9, O*H*), 2.43 (3H, s, H-1, CH_3), 3.06-3.13 (2H, m, H-7, CH_2), 3.65-3.71 (2H, m, H-8, CH_2), 4.82-4.92 (1H, brs, H-6, N*H*), 7.32 (2H, d, *J* 8.0, H-3, Ph*H*), 7.75 (2H, d, *J* 8.0, H-4, Ph*H*); δ_C (101 MHz, $CDCl_3$) 21.6 (1C, *C*H_3), 45.2 (1C, *C*H_2), 61.3 (1C, *C*H_2), 127.1 (1C, quat., Ph*C*), 129.8 (2C, Ph*C*), 136.5 (2C, Ph*C*), 143.6 (1C, quat., Ph*C*). Data were consistent with that reported in the literature.[101]

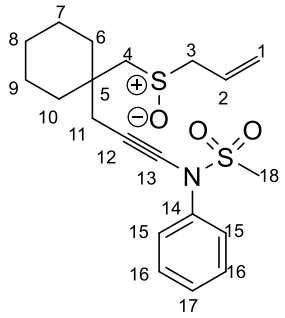
_O_-(_tert_-Butyldimethylsilyl)-_N_-(_p_-toluenesulfonyl) ethanolamine (465)



Following GP 12, the silyl ether was isolated as a colourless oil (12 g, 87%); R_f 0.28 (90% Pet.Ether:10% Et_2O); ν_{max} (neat) / (cm-1) 3287 brs (N-H), 2953 m (C-H), 2928 m (C-H), 2856 m (C-H), 1598 w (N-S), 1495 m (S=O); δ_H (300 MHz, CDCl3) -0.01 (6H, s, H-9, CH_3), 0.83 (9H, s, H-11, CH_3), 2.42 (3H, s, H-1, CH_3), 3.04 (2H, q, *J* 5.1, H-7, CH_2), 3.61 (2H, t, *J* 5.1, H-8, CH_2), 4.71-4.82 (1H, t, *J* 5.1, H-6, N*H*), 7.31 (2H, d, *J* 7.9, H-3, Ph*H*), 7.74 (2H, d, *J* 7.9, H-4, Ph*H*); δ_C (101 MHz, $CDCl_3$) -5.5 (2C, *C*H_3), 18.2 (1C, quat.,

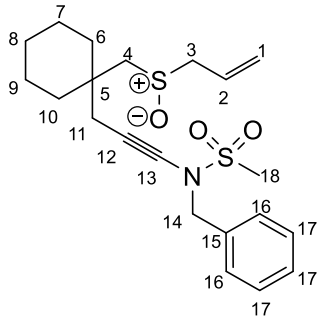
C(CH_3), 21.5 (3C, *C*H_3), 25.8 (1C, *C*H_3), 45.2 (1C, *C*H_2), 61.3 (1C, *C*H_2), 127.1 (2C, Ph*C*), 129.7 (2C, Ph*C*), 137.0 (1C, quat., Ph*C*), 143.4 (1C, quat., Ph*C*). Data were consistent with that reported in the literature.[101]

_N_-(3-(1-((allylsulfinyl)methyl)cyclohexyl)prop-1-yn-1-yl)-_N_-phenylmethanesulfonamide (467a)



Following GP 10 using *N*-phenylmethanesulfonamide (5.0 eq., 5.0 mmol, 856 mg) and sulfoxide (1.0 eq., 1.0 mmol, 224 mg), ynamide was obtained as a clear viscous oil (260 mg, 66% yield); R_f 0.29 (80%EtOAc:20%hexane); ν_{max}(neat) / (cm^{-1}) 2923 s (C-H), 2858 m (C-H), 2261 w (CC), 1491 m (S=O), 1458 m (S=O), 1363 s (C=C), 1159 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.19-1.89 (10H, m, H-6-10, C*H*$_2$, cyclohexyl), 2.60 (2H, s, H-11, C*H*$_2$CC), 2.79 (1H, d, *J* 13.9, H-4, C*H*$_A$*H*$_B$S(O)), 2.83 (1H, d, *J* 13.9, H-4, C*H*$_A$*H*$_B$S(O)), 3.05 (3H, s, H-18, SO_2C*H*$_3$), 3.49 (1H, dd, *J* 13.0, *J* 7.4, H-3, C*H*$_A$*H*$_B$CH$_X$), 3.40 (1H, dd, *J* 13.0, *J* 7.4, H-3, C*H*$_A$*H*$_B$CH$_X$), 5.28-5.40 (2H, m, H-1, CHC*H*$_2$), 5.78-5.95 (1H, m, H-2, C*H*CH$_2$), 7.26-7.56 (5H, m, C-15-17, Ph*H*); δ_C (101 MHz, $CDCl_3$) 21.4 (1C, *C*H$_2$, cyclohexyl), 21.5 (1C, *C*H$_2$, cyclohexyl), 25.7 (1C, *C*H$_2$CC), 28.1 (1C, quat., cyclohexyl), 35.5 (1C, *C*H$_2$, cyclohexyl), 35.6 (1C, *C*H$_2$, cyclohexyl), 36.4 (1C, SO_2C*H*$_3$), 37.3 (1C, *C*H$_2$, cyclohexyl), 57.4 (1C, *C*H$_2$), 60.5 (1C, quat., CH$_2$*C*C-N), 67.9 (1C, *C*H$_2$S(O), 76.0 (1C, quat., CH$_2$C*C*-N), 123.3 (1C, CH*C*H$_2$), 125.3 (2C, Ph*C*), 126.2 (1C, *C*HCH$_2$), 128.1 (1C, Ph*C*), 129.4 (2C, Ph*C*), 138.6 (1C, quat., Ph*C*).

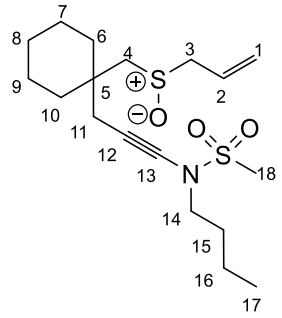
_N_-(3-(1-((allylsulfinyl)methyl)cyclohexyl)prop-1-yn-1-yl)-_N_-benzylmethanesulfonamide (467b)



Following GP 10 using *N*-benzylmethanesulfonamide (5.0 eq., 5.0 mmol, 926 mg) and sulfoxide (1.0 eq., 1.0 mmol, 224 mg), ynamide was obtained as a clear viscous oil (138 mg, 34% yield); R_f 0.29 (80%EtOAc:20%hexane); ν_{max}(neat) / (cm^{-1}) 2927 s (C-H), 2856 m (C-H), 2252 w (CC), 1454 m (S=O), 1352 s (C=C), 1160 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.27-1.86 (10H, m, H-6-10, CH_2, cyclohexyl), 2.48 (2H, s, H-11, CH_2CC), 2.63 (1H, d, *J* 13.9, H-4, CH_AH_BS(O)), 2.67, (1H, d, *J* 13.9, H-4, CH_AH_BS(O)), 2.89 (3H, s, H-18, SO_2CH_3), 3.35 (1H, dd, *J* 13.0, *J* 7.4, H-3, C$H_AH_B$$CH_X$), 3.37 (1H, dd, *J* 13.0, *J* 7.4, H-3, C$H_AH_B$$CH_X$), 4.51 (1H, d, *J* 14.3, H-14, NCH_AH_B), 4.57 (1H, d, *J* 14.3, H-14, NCH_AH_B), 5.28-5.43 (2H, m, H-1, CHCH_2), 5.75-5.93 (1H, m, H-2, C*H*CH_2), 7.30-7.46 (5H, m, C-16-17, Ph*H*); δ_C (101 MHz, $CDCl_3$) 21.3 (1C, *C*H_2, cyclohexyl), 21.4 (1C, *C*H_2, cyclohexyl), 25.5 (1C, *C*H_2CC), 27.9 (1C, quat., cyclohexyl), 35.2 (1C, *C*H_2, cyclohexyl), 35.3 (1C, *C*H_2, cyclohexyl), 37.0 (1C, *C*H_2, cyclohexyl), 38.5 (1C, SO_2CH_3), 55.2 (1C, *C*H_2Ph), 57.2 (1C, *C*H_2), 60.4 (1C, quat., CH_2*C*C-N), 68.1(1C, *C*H_2S(O), 75.6 (1C, quat., CH_2C*C*-N), 123.2 (1C, CH*C*H_2), 126.1 (1C, *C*HCH_2), 128.5 (3C, Ph*C*), 128.7 (2C, Ph*C*), 134.6 (1C, quat., Ph*C*); m/z (TOF MS ES^+) $[M+Na]^+$ 430 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{21}H_{29}NO_3S_2Na$ 430.1487, found 430.1478.

_N_-(3-(1-((allylsulfinyl)methyl)cyclohexyl)prop-1-yn-1-yl)-_N_-butylmethanesulfonamide

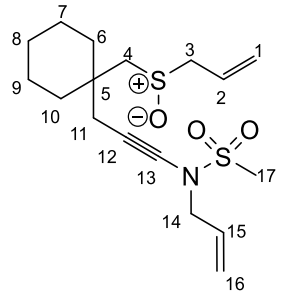
(467c)



Following GP 10 using *N*-butylmethanesulfonamide (5.0 eq., 5.0 mmol, 756 mg) and sulfoxide (1.0 eq., 1.0 mmol, 224 mg), ynamide was prepared as a colourless oil (168 mg, 45% yield); R_f 0.32 (80%EtOAc:20%hexane); ν_{max}(neat) / (cm^{-1}) 2927 s (C-H), 2857 m (C-H), 2251 w (CC), 1455 m (S=O), 1352 s (C=C), 1163 s (C-N); δ_H (300 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.3, H-17, C*H*$_3$), 1.18-1.72 (10H+4H, m, H-6-10, C*H*$_2$, cyclohexyl and H-15-16, butyl chain), 2.53 (2H, s, H-11, C*H*$_2$CC), 2.77 (2H, s, H-4, C*H*$_2$S(O)), 3.01 (3H, s, H-18, SO_2C*H*$_3$), 3.35 (2H, t, *J* 7.3, H-14, NC*H*$_2$), 3.46 (1H, dd, *J* 29.8, *J* 12.9, H-3, C$H_AH_B$$CH_X$), 3.44 (1H, dd, *J* 29.9, *J* 13.0, H-3, C$H_AH_B$$CH_X$), 5.31-5.46 (2H, m, H-1, CHC*H*$_2$), 5.80-5.98 (1H, m, H-2, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 13.5 (1C, *C*H_3), 19.3 (1C, *C*H_2CH_3), 21.3 (1C, *C*H_2, cyclohexyl), 21.4 (1C, *C*H_2, cyclohexyl), 25.6 (1C, *C*H_2CC), 28.0 (1C, quat., cyclohexyl), 30.1 (1C, *C*H_2), 35.3 (1C, *C*H_2, cyclohexyl), 35.4 (1C, *C*H_2, cyclohexyl), 37.1 (1C, *C*H_2, cyclohexyl), 37.7 (1C, SO_2*C*H_3), 50.8 (1C, N*C*H_2), 57.3 (1C, *C*H_2), 60.5 (1C, quat., CH_2*C*C-N), 67.3 (1C, *C*H_2S(O), 75.4 (1C, quat., CH_2C*C*-N), 123.2 (1C, CH*C*H_2), 126.1 (1C, *C*HCH_2); m/z (TOF MS ES^+) $[M+Na]^+$ 396 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{18}H_{31}NO_3S_2Na$ 396.1643, found 396.1655.

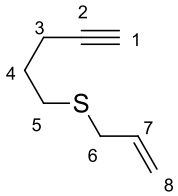
_N_-allyl-_N_-(3-(1-((allylsulfinyl)methyl)cyclohexyl)prop-1-yn-1-yl)methanesulfonamide

(467d)



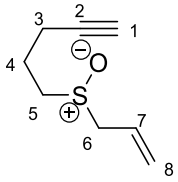
Following GP 10 using *N*-allylmethanesulfonamide (5.0 eq., 5.0 mmol, 676 mg) and sulfoxide (1.0 eq., 1.0 mmol, 224 mg), ynamide was prepared as a colourless oil (100 mg, 28% yield); R_f 0.28 (80%EtOAc:20%hexane); ν_{max}(neat) / (cm^{-1}) 2926 s (C-H), 2856 m (C-H), 2253 w (CC), 1454 m (S=O), 1351 s (C=C), 1162 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.33-1.92 (10H, m, H-6-10, C*H*$_2$, cyclohexyl), 2.52 (2H, s, H-11, C*H*$_2$CC), 2.76 (2H, s, H-4, C*H*$_2$S(O)), 3.03 (3H, s, H-17, SO_2C*H*$_3$), 3.44 (1H, dd, *J* 28.9, *J* 12.9, H-3, C*H*$_A$*H*$_B$CH$_X$), 3.46 (1H, dd, *J* 28.9, *J* 13.0, H-3, C*H*$_A$*H*$_B$CH$_X$), 3.99 (2H, dt, *J* 6.3, *J* 1.2, H-14, C*H*$_2$CHCH$_2$), 5.26-5.44 (2H+2H, m, H-1 and H-16, 2 × CHC*H*$_2$), 5.81-5.98 (1H+1H, m, H-2 and H-15, 2 × C*H*CH$_2$); δ_C (101 MHz, $CDCl_3$) 21.3 (1C, *C*H$_2$, cyclohexyl), 21.4 (1C, *C*H$_2$, cyclohexyl), 25.6 (1C, *C*H$_2$CC), 27.9 (1C, quat., cyclohexyl), 35.2 (1C, *C*H$_2$, cyclohexyl), 35.3 (1C, *C*H$_2$, cyclohexyl), 37.0 (1C, *C*H$_2$, cyclohexyl), 38.5 (1C, SO_2C*H*$_3$), 53.8 (1C, *C*H$_2$), 57.3 (1C, *C*H$_2$), 60.5 (1C, quat., CH$_2$*C*C-N), 67.5 (1C, *C*H$_2$S(O), 75.4 (1C, quat., CH$_2$C*C*-N), 120.1 (1C, CH*C*H$_2$), 123.2 (1C, CH*C*H$_2$), 126.1 (1C, *C*HCH$_2$), 131.0 (1C, *C*HCH$_2$); m/z (TOF MS ES$^+$) $[M+Na]^+$ 380 (80%); HRMS (TOF MS ES$^+$) mass calculated for $C_{17}H_{27}NO_3S_2Na$ 380.1330, found 380.1336.

allyl(pent-4-yn-1-yl)sulfane



Following GP 4, using allyl bromide 99+% (20.0 mmol, 1.8 mL), allyl sulfane was prepared as a colourless oil (2.6 g, 99% yield); R_f 0.29 (2% EtOAc: 98% hexane); ν_{max}(neat) / (cm^{-1}) 3306 m (CC-H), 2925 s (C-H), 2853 s (C-H), 2117 m (CC), 1640 m (C=C); δ_H (300 MHz, $CDCl_3$) 1.78 (2H, p, *J* 7.0, H-4, CH_2), 1.96 (1H, t, *J* 2.7, H-1, CC*H*), 2.31 (2H, td, *J* 7.0, *J* 2.7, H-3, CH_2), 2.53-2.60 (2H, m, C-5, CH_2S), 3.12 (2H, dt, *J* 7.2, *J* 1.0, H-6, SCH_2), 5.03-5.15 (2H, m, H-8, CHCH_2), 5.70-5.86 (1H, m, H-7, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 17.5 (1C, *C*H_2), 28.0 (1C, *C*H_2), 29.4 (1C, *C*H_2), 34.7 (1C, *C*H_2), 68.9 (1C, C*C*H), 83.6 (1C, quat., *C*CH), 117.0 (1C, CH*C*H_2), 134.4 (1C, *C*HCH_2); m/z (TOF MS EI$^+$) $[M]^+$ 140 (10%), $[M\text{-}C_3H_5]^+$ 97 (100%). Data were consistent with that reported in the literature.[62]

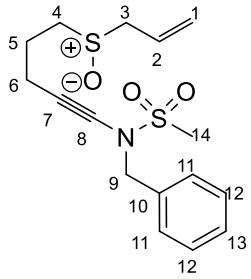
5-(allylsulfinyl)pent-1-yne (468)



Following GP 5 sulfoxide was obtained using allyl sulfane (10.0 mmol, 2.0 g) as a viscous colourless oil (1.5 g, 95% yield); R_f 0.27 (60% EtOAc:40% hexane); ν_{max}(neat) / (cm^{-1}) 3289 s (CC-H), 2920 s (C-H), 2851 s (C-H), 1637 m (C-S), 1432 w (S-O), 1036 m (C=C); δ_H (300 MHz, $CDCl_3$) 1.92-2.05 (3H, m, overlapping peaks H-1, and H-4, C*H* and CH_AH_B), 2.32-2.41 (2H, m, H-3, CH_AH_B), 2.70-2.89 (2H, m, H-5, CH_AH_B), 3.46 (2H, qd, *J* 13.0, *J* 7.5, H-6, CH_AH_B), 5.33-5.47 (2H, m, H-8, CHCH_2), 5.88 (1H, ddt, *J* 17.7, *J* 10.3, *J* 7.5, H-7, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 17.7 (1C, *C*H_2), 21.5 (1C, *C*H_2), 49.5 (1C, *C*H_2), 56.0

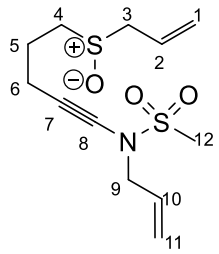
(1C, *C*H_2), 69.9 (1C, C*C*H), 82.4 (1C, quat., *C*CH), 123.6 (1C, CH*C*H_2), 125.7 (1C, *C*HCH$_2$); m/z (TOF MS ES$^+$) [M+Na]$^+$ 179 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_8H_{12}OSNa$ 179.0507, found 179.0509.

_N_-(5-(allylsulfinyl)pent-1-yn-1-yl)-_N_-benzylmethanesulfonamide (469a)



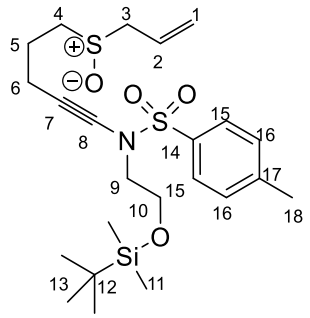
Following GP 10 using *N*-benzylmethanesulfonamide (5.0 eq., 5.0 mmol, 926 mg) and sulfoxide (1.0 eq., 1.0 mmol, 156 mg), ynamide prepared as a pale yellow oil (96 mg, 29% yield); R_f 0.28 (100%EtOAc); ν_{max}(neat) / (cm^{-1}) 2927 s (C-H), 2856 m (C-H), 2252 w (CC), 1454 m (S=O), 1352 s (C=C), 1160 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.83-2.00 (2H, m, H-5, C*H*$_2$), 2.33-2.53 (2H, m, H-4, C*H*$_A$*H*$_B$S(O)), 2.57-2.70 (2H, m, H-6, C*H*$_2$CC), 2.86 (3H, s, H-14, SO$_2$C*H*$_3$), 3.37 (1H, dd, *J* 12.9, *J* 7.3, H-3, C*H*$_A$*H*$_B$CH$_X$), 6.78 (1H, dd, *J* 12.9, *J* 7.3, H-3, C*H*$_A$*H*$_B$CH$_X$), 4.53 (2H, s, H-9, NC*H*$_2$Ph), 5.27-5.44 (2H, m, H-1, CHC*H*$_2$), 5.74-5.91 (1H, m, H-2, C*H*CH$_2$), 7.28-7.46 (5H, m, H-11-13, Ph*H*); δ_C (101 MHz, $CDCl_3$) 17.7 (1C, *C*H$_2$CC), 21.8 (1C, *C*H$_2$), 38.4 (1C, SO$_2$*C*H$_3$), 49.4 (1C, *C*H$_2$Ph), 55.3 (1C, *C*H$_2$S(O)), 55.9 (1C, S(O)*C*H$_2$), 69.4 (1C, quat., CH$_2$*C*C), 74.4 (1C, quat., CH$_2$C*C*), 123.5 (1C, CH*C*H$_2$), 125.6 (1C, *C*HCH$_2$), 128.5 (1C, Ph*C*), 128.7 (2C, Ph*C*), 128.8 (2C, Ph*C*), 134.6 (1C, quat., Ph*C*); m/z (TOF MS ES$^+$) [M+Na]$^+$ 362 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{16}H_{21}NO_3S_2Na$ 362.0861, found 362.0858.

_N_-allyl-_N_-(5-(allylsulfinyl)pent-1-yn-1-yl)methanesulfonamide (469b)



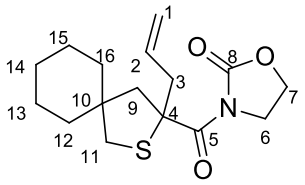
Following GP 10 using *N*-allylmethanesulfonamide (5.0 eq., 5.0 mmol, 676 mg) and sulfoxide (1.0 eq., 1.0 mmol, 156 mg), ynamide was prepared as a colourless oil (72 mg, 25% yield); R_f 0.28 (90%EtOAc:10%hexane); ν_{max}(neat) / (cm^{-1}) 2924 s (C-H), 2253 w (CC), 1422 m (S=O), 1348 s (C=C), 1160 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.86-2.01 (2H, m, H-5, C*H*$_2$), 2.35-2.55 (2H, m, H-4, C*H*$_2$S(O)), 2.63-2.84 (2H, m, H-6, C*H*$_2$CC), 2.99 (3H, s, H-12, SO_2CH_3), 3.41 (1H, dd, *J* 27.3, *J* 13.0, H-3, C*H*$_A$*H*$_B$CH$_X$), 3.44 (1H, dd, *J* 27.3, *J* 13.0, H-3, C*H*$_A$*H*$_B$CH$_X$), 3.96 (2H, dt, *J* 6.4, *J* 1.1, H-9, NC*H*$_2$), 5.22-5.35 (2H, m, H-1, CHC*H*$_2$), 5.36-5.44 (2H, m, H-11, CHC*H*$_2$), 5.75-5.93 (1H+1H, m, H-2 and H-10, 2 × C*H*CH$_2$); δ_C (101 MHz, $CDCl_3$) 17.7 (1C, *C*H$_2$CC), 21.9 (1C, *C*H$_2$), 38.4 (1C, SO_2CH_3), 49.6 (1C, *C*H$_2$), 53.9 (1C, *C*H$_2$S(O)), 55.9 (1C, S(O)*C*H$_2$), 68.8 (1C, quat., CH$_2$*C*C), 74.1 (1C, quat., CH$_2$C*C*), 120.1 (1C, CH*C*H$_2$), 123.5 (1C, CH*C*H$_2$), 125.6 (1C, *C*HCH$_2$), 130.9 (1C, *C*HCH$_2$); m/z (TOF MS ES$^+$) $[M+Na]^+$ 312 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{12}H_{19}NO_3S_2Na$ 312.0704, found 312.0702.

_N_-(5-(allylsulfinyl)pent-1-yn-1-yl)-_N_-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-methylbenzenesulfonamide (469c)



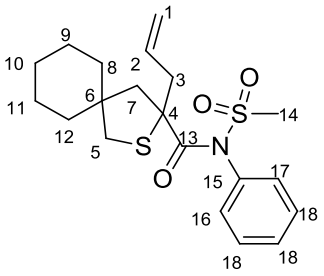
Following GP 10 using *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-methylbenzenesulfonamide (5.0 eq., 5.0 mmol, 1.7 g) and sulfoxide (1.0 eq., 1.0 mmol, 156 mg), ynamide was prepared as a colourless oil (87 mg, 18% yield); R_f 0.30 (80%EtOAc:20%hexane); ν_{max}(neat) / (cm^{-1}) 2929 s (C-H), 2857 s (C-H), 2249 w (CC), 1463 m (S=O), 1363 s (C=C), 1169 s (C-N); δ_H (300 MHz, $CDCl_3$) -0.00 (6H, s, H-11, Si(C*H*$_3$)$_2$), 081 (9H, s, H-13, (C(C*H*$_3$)$_3$), 1.84-2.02 (2H, m, H-5, C*H*$_2$), 2.40 (3H, s, H-18, C*H*$_3$), overlaps with 2.31-2.53 (2H, m, H-4, C*H*$_2$S(O)), 2.64-2.86 (2H, m, H-6, C*H*$_2$CC), 3.34 (2H, t, *J* 6.1, H-9, NC*H*$_2$), overlaps with 3.42 (1H, dd, *J* 29.7, *J* 13.0, H-3, C*H*$_A$*H*$_B$CH$_X$), 3.44 (1H, dd, *J* 29.7, *J* 13.0, H-3, C*H*$_A$*H*$_B$CH$_X$), 3.73 (2H, t, *J* 6.1, H-10, C*H*$_2$O), 5.29-5.46 (2H, m, H-1, CHC*H*$_2$), 5.76-5.95 (1H, m, H-2, C*H*CH$_2$), 7.30 (2H, d, *J* 8.2, H-16, Ph*H*), 7.72 (2H, d, *J* 8.2, H-15, Ph*H*); δ_C (101 MHz, $CDCl_3$) -5.3 (2C, Si(*C*H$_3$)$_2$), 17.7 (1C, *C*H$_2$CC), 18.3 (1C, quat., *C*(CH$_3$)$_3$), 21.5 (3C, C(*C*H$_3$)$_3$), 22.0 (1C, *C*H$_2$), 35.7 (1C, Ts*C*H$_3$), 49.6 (1C, N*C*H$_2$), 53.1 (1C, *C*H$_2$O), 56.0 (1C, *C*H$_2$S(O)), 60.4 (1C, S(O)*C*H$_2$), 67.7 (1C, quat., CH$_2$*C*C), 75.0 (1C, quat., CH$_2$C*C*), 123.5 (1C, CH*C*H$_2$), 125.6 (1C, *C*HCH$_2$), 127.4 (2C, Ph*C*), 129.6 (2C, Ph*C*), 134.8 (1C, quat., Ph*C*), 144.4 (1C, quat., Ph*C*); m/z (TOF MS ES$^+$) [M+Na]$^+$ 506 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{23}H_{37}NO_4S_2SiNa$ 506.1831, found 506.1828.

3-(3-allyl-2-thiaspiro[4.5]decane-3-carbonyl)oxazolidin-2-one (476)



Following GP 6 heterocycle was obtained in 20 h as a colourless viscous oil (15 mg, 47% yield); R_f 0.30 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 2922 s (C-H), 2850 m (C-H), 1772 s (C=O), 1680 s (C=O), 1384 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.22-1.66 (10H, m, H-12-16, CH_2, cyclohexyl), overlaps with 1.57 (1H, d, *J* 13.5, H-11, SCH_AH_B), 2.54 (1H, d, *J* 10.8, H-9, CH_AH_B), 2.60 (1H, d, *J* 10.8, H-9, CH_AH_B), 2.68 (1H, dd, *J* 14.2, *J* 6.4, H-3, CH_AH_BCH$_X$), 2.91 (1H, d, *J* 13.5, H-11, SCH_AH_B), 3.07 (1H, dd, *J* 14.2, *J* 8.1, H-3, CH_AH_BCH$_X$), 3.91-4.11 (2H, m, H-6, NCH_2), 4.32-4.49 (2H, m, H-7, OCH_2), 4.98-5.13 (2H, m, H-1, CHCH_2), 5.63-5.83 (1H, m, H-2, C*H*CH$_2$); δ_C (101 MHz, $CDCl_3$) 23.1 (1C, *C*H$_2$, cyclohexyl), 24.0 (1C, *C*H$_2$, cyclohexyl), 26.2 (1C, *C*H$_2$, cyclohexyl), 34.8 (1C, *C*H$_2$, cyclohexyl), 37.8 (1C, *C*H$_2$, cyclohexyl), 42.6 (1C, quat., cyclohexyl), 43.2 (1C, N*C*H$_2$), 44.7 (1C, *C*H$_2$), 47.3 (1C, *C*H$_2$), 49.6 (1C, *C*H$_2$S), 62.2 (1C, O*C*H$_2$), 62.7 (1C, quat., cyclohexyl), 118.4 (1C, CH*C*H$_2$), 133.9 (1C, *C*HCH$_2$), 175.4 (1C, quat., *C*(O)), 173.4 (1C, quat., N(*C*O)O); m/z (TOF MS ES$^+$) $[M+Na]^+$ 332 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{16}H_{23}NO_3SNa$ 332.1296, found 332.1287.

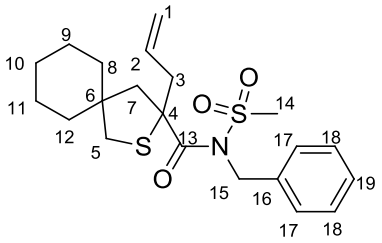
3-allyl-*N*-(methylsulfonyl)-*N*-phenyl-2-thiaspiro[4.5]decane-3-carboxamide (479a)



Following GP 6 heterocycle was obtained in 24 h as a colourless viscous oil (21 mg, 54% yield); R_f 0.30 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 2924 s (C-H), 2858 m (C-H), 1683 s

(C=O), 1353 s (C=C), 1157 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.28-1.60 (10H, m, H-8-12, CH_2, cyclohexyl), overlaps with 1.49 (1H, d, *J* 13.6, H-5, SCH_AH_B), 2.31 (1H, dd, *J* 14.8, *J* 7.2, H-3, CH_AH_BCH_X), 2.40 (1H, dd, *J* 14.8, *J* 6.6, H-3, CH_AH_BCH_X), 2.53 (1H, d, *J* 10.9, H-7, CH_AH_B), 2.59 (1H, d, *J* 10.9, H-7, CH_AH_B), 2.88 (1H, d, *J* 13.6, H-5, SCH_AH_B), 3.37 (3H, s, H-14, SO_2CH_3), 5.01-5.18 (2H, m, H-1, CHCH_2), 5.64-5.78 (1H, m, H-2, CHCH_2), 7.38-7.53 (5H, m, H-17-18, Ph*H*); δ_C (101 MHz, $CDCl_3$) 23.2 (1C, *C*H_2, cyclohexyl), 23.9 (1C, *C*H_2, cyclohexyl), 26.1 (1C, *C*H_2, cyclohexyl), 35.3 (1C, *C*H_2, cyclohexyl), 37.5 (1C, *C*H_2, cyclohexyl), 41.3 (1C, SO_2CH_3), 44.4 (1C, quat., cyclohexyl), 46.8 (1C, *C*H_2), 48.2 (1C, *C*H_2), 50.3 (1C, *C*H_2S), 63.8 (1C, quat., cyclohexyl), 118.9 (1C, CH*C*H_2), 128.7 (3C, Ph*C*), 130.4 (1C, *C*HCH_2), 132.3 (1C, Ph*C*), 133.2 (1C, Ph*C*), 134.5 (1C, quat., Ph*C*), 175.2 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 416 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{20}H_{27}NO_3S_2Na$ 416.1330, found 416.1331.

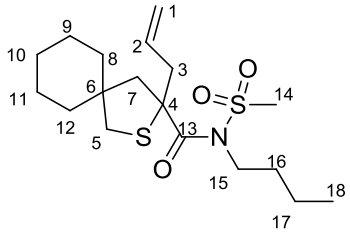
3-allyl-*N*-benzyl-*N*-(methylsulfonyl)-2-thiaspiro[4.5]decane-3-carboxamide (479b)



Following GP 6 heterocycle was obtained in 24 h as a colourless viscous oil (20 mg, 49% yield); R_f 0.30 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 2925 s (C-H), 2850 m (C-H), 1680 s (C=O), 1350 s (C=C), 1161 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.31-1.69 (10H, m, H-8-12, CH_2, cyclohexyl), overlaps with 1.59 (1H, d, *J* 13.6, H-5, SCH_AH_B), 2.56 (1H, dd, *J* 14.4, *J* 7.3, H-3, CH_AH_BCH_X), 2.72 (1H, dd, *J* 14.4, *J* 6.8, CH_AH_BCH_X), overlaps with 2.71 (1H, d, *J* 10.8, H-7, CH_AH_B), 2.79 (1H, d, *J* 10.8, H-7, CH_AH_B), 2.98 (1H, d, *J* 13.6, H-5, SCH_AH_B), 3.01 (3H, s, H-14, SO_2CH_3), 5.00 (1H, d, *J* 16.4, H-15, CH_AH_BPh), 5.03-5.18 (2H, m, H-1, CHCH_2), overlaps with 5.16 (1H, d, *J* 16.4, H-15, CH_AH_BPh), 5.68-5.86 (1H, m, H-2,

C*H*CH_2), 7.27-7.43 (5H, m, H-17-19, Ph*H*); δ_C (101 MHz, $CDCl_3$) 23.1 (1C, *C*H_2, cyclohexyl), 24.0 (1C, *C*H_2, cyclohexyl), 26.1 (1C, *C*H_2, cyclohexyl), 34.9 (1C, *C*H_2, cyclohexyl), 37.8 (1C, *C*H_2, cyclohexyl), 43.2 (1C, SO_2CH_3), 44.8 (1C, quat., cyclohexyl), 45.9 (1C, *C*H_2), 47.8 (1C, *C*H_2), 50.0 (1C, *C*H_2S), 51.4 (1C, *C*H_2Ph), 62.5 (1C, quat., *C*S), 119.6 (1C, CH*C*H_2), 127.6 (2C, Ph*C*), 127.9 (1C, *C*HCH_2), 128.6 (2C, Ph*C*), 132.4 (1C, Ph*C*), 136.1 (1C, quat., Ph*C*), 175.6 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 430 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{21}H_{29}NO_3S_2Na$ 430.1487, found 430.1498.

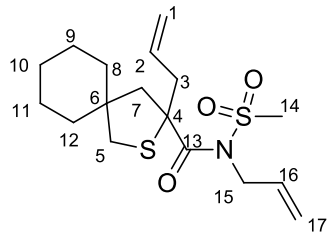
3-allyl-*N*-butyl-*N*-(methylsulfonyl)-2-thiaspiro[4.5]decane-3-carboxamide (479c)



Following GP 6 heterocycle was obtained in 8 h as a colourless oil (26 mg, 69% yield); R_f 0.30 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 2927 s (C-H), 2856 m (C-H), 1678 s (C=O), 1349 s (C=C), 1166 s (C-N); δ_H (300 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.3, H-18, CH_2CH_3), 1.18-1.62 (12H, m, H-8-12 and H-17, 5 × CH_2, cyclohexyl and CH_2), overlaps with 1.52 (1H, d, *J* 13.6, H-5, SCH_AH_B), 1.63-1.99 (2H, m, H-16, CH_2), 2.48-2.81 (4H, m, H-7 and H-3, CH_AH_BCH$_X$ and CH_AH_B), 2.96 (1H, d, *J* 13.6, H-5, SCH_AH_B), 3.30 (3H, s, H-14, SO_2CH_3), 3.55-3.85 (2H, m, H-15, CH_2), 5.03-5.20 (2H, m, H-1, CH_2CH), 5.62-5.81 (1H, m, H-2, CH_2C*H*); δ_C (101 MHz, $CDCl_3$) 13.7 (1C, *C*H_3), 19.9 (1C, *C*H_2), 23.0 (1C, *C*H_2, cyclohexyl), 24.1 (1C, *C*H_2, cyclohexyl), 26.1 (1C, *C*H_2, cyclohexyl), 32.2 (1C, *C*H_2), 34.6 (1C, *C*H_2, cyclohexyl), 37.8 (1C, *C*H_2, cyclohexyl), 43.5 (1C, SO_2CH_3), 44.4 (1C, *C*H_2), 46.2 (1C, *C*H_2), 47.6 (1C, quat., cyclohexyl), 48.1 (1C, *C*H_2), 49.9 (1C, *C*H_2S), 62.0 (1C, quat., *C*S), 119.4 (1C, CH*C*H_2), 132.5 (1C, *C*HCH_2), 174.4 (1C, quat., *C*(O)); m/z (TOF

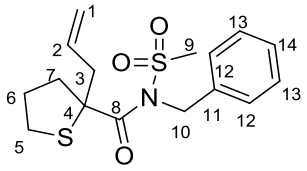
MS ES^+) $[M+Na]^+$ 396 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{18}H_{31}NO_3S_2Na$ 396.1643, found 396.1650.

_N_,3-diallyl-_N_-(methylsulfonyl)-2-thiaspiro[4.5]decane-3-carboxamide (479d)



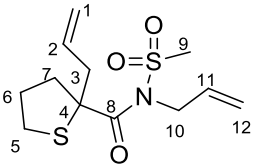
Following GP 6 heterocycle was obtained in 6 h as a colourless viscous oil (22 mg, 60% yield); R_f 0.30 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 2924 s (C-H), 2852 m (C-H), 1681 s (C=O), 1352 s (C=C), 1165 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.21-1.63 (10H, m, H-8-12, CH_2, cyclohexyl), overlaps with 1.53 (1H, d, *J* 13.6, H-5, SCH_AH_B), 2.55 (1H, dd, *J* 14.4, *J* 7.2, H-3, CH_AH_BCH_X), 2.70 (1H, dd, *J* 14.4, *J* 5.8, H-3, CH_AH_BCH_X), 2.69 (1H, d, *J* 10.7, H-7, CH_AH_B), 2.77 (1H, d, *J* 10.7, H-7, CH_AH_B), 2.96 (1H, d, *J* 13.6, H-5, SCH_AH_B), 3.28 (3H, s, H-14, SO_2CH_3), 4.39-4.56 (2H, m, H-15, CH_2), 5.05-5.20 (2H, m, H-1, CHCH_2), 5.25-5.42 (2H, m, H-17, CHCH_2), 5.63-5.81 (1H, m, H-2, C*H*CH_2), 5.86-6.03 (1H, m, H-16, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 23.0 (1C, *C*H_2, cyclohexyl), 24.0 (1C, *C*H_2, cyclohexyl), 26.1 (1C, *C*H_2, cyclohexyl), 34.6 (1C, *C*H_2, cyclohexyl), 37.8 (1C, *C*H_2, cyclohexyl), 43.3 (1C, SO_2CH_3), 44.5 (1C, *C*H_2), 45.8 (1C, *C*H_2), 46.5 (1C, quat., cyclohexyl), 47.7 (1C+1C, *C*H_2S and *C*H_2), 62.3 (1C, quat., *C*S), 119.5 (1C+1C, 2 × CH*C*H_2), 132.5 (1C, *C*HCH$_2$), 132.8 (1C, *C*HCH$_2$), 174.6 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 380 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{17}H_{27}NO_3S_2Na$ 380.1330, found 380.1338.

2-allyl-*N*-benzyl-*N*-(methylsulfonyl)tetrahydrothiophene-2-carboxamide (480a)



Following GP 6 using freshly distilled 1,2-dichloroethane, heterocycle was obtained in 24 h as a colourless oil (21 mg, 63% yield); R_f 0.31 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 2927 s (C-H), 2856 m (C-H), 1678 s (C=O), 1349 s (C=C), 1166 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.74-1.88 (1H, m, H-5, SCH_AH_BCH$_X$), 2.00-2.17 (2H, m, H-6 and H-7, 2 × CH_AH_BCH$_X$), 2.46-2.86 (3H, m, H-7 and H-3, CH_AH_BCH$_X$ and 2 × CH_AH_B), 2.92-3.10 (2H, m, H-6, and H-5, CH_AH_BCH$_X$ and SCH_AH_BCH$_X$), overlaps with 2.99 (3H, s, H-9, SO_2CH_3), 4.90-5.23 (4H, m, H-10, and H-1, CH_2Ph and CHCH_2), 5.66-5.85 (1H, m, H-2, C*H*CH$_2$), 7.24-7.46 (5H, m, Ph*H*); δ_C (101 MHz, $CDCl_3$) 29.5 (1C, CH_2, cyclopentyl), 35.1 (1C, CH_2, cyclopentyl), 40.3 (1C, CH_2), 43.2 (1C, SO_2CH_3), 44.7 (1C, CH_2Ph), 51.2 (1C, CH_2S), 62.2 (1C, quat., *C*S), 119.6 (1C, CH*C*H$_2$), 127.8 (2C, Ph-*C*), 128.0 (1C, *C*HCH$_2$), 128.6 (2C, Ph*C*), 132.4 (1C, Ph*C*), 135.9 (1C, quat., Ph*C*), 175.9 (1C, quat., *C*(O)); m/z (TOF MS ES$^+$) $[M+Na]^+$ 362 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{16}H_{21}NO_3S_2Na$ 362.0861, found 362.0879.

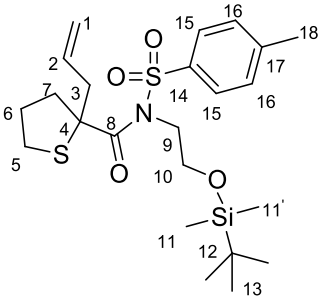
***N*-2-diallyl-*N*-(methylsulfonyl)tetrahydrothiophene-2-carboxamide (480b)**



Following GP 6 using freshly distilled 1,2-dichloroethane, heterocycle was obtained in 24 h as a colourless oil (17 mg, 59% yield); R_f 0.30 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 2938 bs (C-H), 1680 s (C=O), 1350 s (C=C), 1164 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.74 (1H, ddd, *J* 12.9, *J* 9.2, *J* 5.6, H-5, SCH_AH_BCH$_X$), 1.88-2.18 (2H, m, H-6, CH$_X$CH_AH_BCH$_X$), 2.44-

2.83 (3H, m, H-5 and H-7, SCH_AH_BCH$_X$ and 2 × CH_AH_BCH$_X$), 2.96 (2H, dd, *J* 7.4, *J* 5.6, H-3, CH_2), 3.28 (3H, s, H-9, SO_2CH_3), 4.38-4.55 (2H, m, H-10, NCH_2), 5.04-5.19 (2H, m, H-1, CH_2CH), 5.26-5.45 (2H, m, H-12, CH_2CH), 5.62-5.79 (1H, m, H-2, CH$_2$C*H*), 5.88-6.05 (1H, m, H-11, CH$_2$C*H*); δ_C (101 MHz, $CDCl_3$) 29.5 (1C, *C*H$_2$, cyclopentyl), 34.9 (1C, *C*H$_2$), 40.2 (1C, *C*H$_2$, cyclopentyl), 43.3 (1C, SO_2CH_3), 44.5 (1C, *C*H$_2$S), 49.8 (1C, *C*H$_2$), 62.0 (1C, quat., *C*S), 119.5 (1C, CH*C*H$_2$), 119.7 (1C, CH*C*H$_2$), 132.5 (1C, *C*HCH$_2$), 132.6 (1C, *C*HCH$_2$), 174.8 (1C, quat., *C*(O)); m/z (TOF MS ES$^+$) $[M+Na]^+$ 312 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{12}H_{19}NO_3S_2Na$ 312.0704, found 312.0711.

2-allyl-*N*-(2-((tert-butyldimethylsilyl)oxy)ethyl)-*N*-tosyltetrahydrothiophene-2-carboxamide (480c)

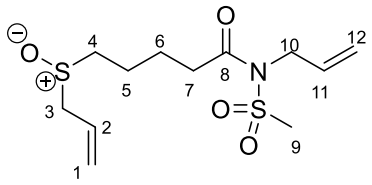


Following GP 6 using wet 1,2-dichloroethane, heterocycle was obtained in 24 h as a colourless oil (19 mg, 40% yield); R_f 0.32 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 2927 s (C-H), 2855 s (C-H), 1684 s (C=O), 1353 s (C=C), 1168 s (C-N); δ_H (300 MHz, $CDCl_3$) -0.03 (3H, s, H-11, SiCH_3), -0.02 (3H, s, H-11', SiCH_3), 0.78 (9H, s, H-13, SiC(CH_3)$_3$), 1.39-1.60 (2H, m, H-5 and H-6, SCH_AH_B and CH$_X$CH_AH_BCH$_X$), 1.72-1.90 (1H, m, H-6, CH$_X$CH_AH_BCH$_X$), 2.30 (3H, s, H-18, TsCH_3), 2.37-2.83 (5H, m, H-7, H-5 and H-3, overlapping peaks 2 × CH_AH_BCH$_X$, SCH_AH_B, and CH_AH_B), 3.78-4.02 (4H, m, H-9-10, NCH_2CH_2O), 4.81-4.95 (2H, m, H-1, CH_2CH), 5.28-5.46 (1H, m, H-2, CH$_2$C*H*), 7.16 (2H, d, *J* 8.8, H-16, Ph*C*), 7.74 (2H, d, *J* 8.8, H-15, Ph*C*); δ_C (101 MHz, $CDCl_3$) -5.3 (2C, Si(*C*H$_3$)$_2$), 21.6 (3C, C(*C*H$_3$)$_3$), 25.9 (1C, Ts*C*H$_3$), 29.1 (1C, *C*H$_2$, cyclopentyl), 34.6 (1C,

CH_2), 40.3 (1C, CH_2, cyclopentyl), 44.3 (1C, CH_2S), 49.6 (1C, NCH_2), 62.0 (1C, quat., *C*S), 62.2 (1C, OCH_2), 62.5 (1C, quat., $C(CH_3)_3$), 118.9 (1C, $CHCH_2$), 128.7 (2C, Ph*C*), 129.1 (2C, Ph*C*), 132.6 (1C, $CHCH_2$), 136.6 (1C, quat., Ph*C*), 144.3 (1C, Ph*C*), 173.4 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 506 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{23}H_{37}NO_4S_2SiNa$ 506.1831, found 506.1839.

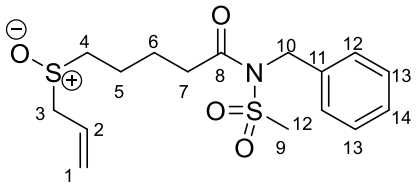
Hydrolysis products when using wet 1,2-DCE

***N*-allyl-5-(allylsulfinyl)-*N*-(methylsulfonyl)pentanamide (481a)**



Following GP 6 with wet solvent, the hydrated sulfoxide was isolated as a colourless liquid (4 mg, 11% yield); R_f 0.30 (5%MeOH:95%EtOAc); ν_{max}(neat) / (cm^{-1}) 3447 bs (O-H), 2929 w (C-H), 1695 s (C=O), 1411 w (S-O), 1342 s (C=C), 1162 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.66-1.98 (4H, m, H-5-6, 2 × CH_2), 2.52-2.77 (4H, m, H-7 and H-10, 2 × CH_2), 3.27 (3H, s, H-9, SO_2CH_3), 3.43 (1H, dd, *J* 13.0, *J* 7.6, H-3, $CH_AH_BCH_X$), 3.46 (1H, dd, *J* 13.0, *J* 6.8, H-3, $CH_AH_BCH_X$), 4.30-4.44 (2H, m, H-10, $NCH_AH_BCH_X$), 5.20-5.51 (4H, m, H-1 and H-12, 2 × CH_2CH), 5.76-5.95 (2H, m, H-2 and H-11, 2 × CH_2CH); δ_C (101 MHz, $CDCl_3$) 22.0 (1C, CH_2), 23.5 (1C, CH_2), 35.3 (1C, $S(O)CH_2$), 42.8 (1C, SO_2CH_3), 48.0 (1C, CH_2), 50.5 (1C, $CH_2C(O)$), 56.0 (1C, CH_2), 118.3 (1C, $CHCH_2$), 123.6 (1C, $CHCH_2$), 125.7 (1C, $CHCH_2$), 132.5 (1C, $CHCH_2$), 173.1 (1C, quat., *C*(O)); m/z (TOF MS EI^+) $[M]^+$ 330 (100%), HRMS (TOF MS EI^+) mass calculated for $C_{12}H_{21}NO_4S_2Na$ 330.0810, found 330.0818.

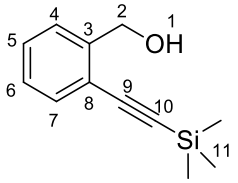
5-(allylsulfinyl)-*N*-benzyl-*N*-(methylsulfonyl)pentanamide (481b)



Following GP 6 with wet solvent, the hydrated sulfoxide was isolated as a colourless liquid (6 mg, 16% yield); R_f 0.30 (5%MeOH:95%EtOAc); ν_{max}(neat) / (cm^{-1}) 3447 bs (O-H), 2929 w (C-H), 1695 s (C=O), 1411 w (S-O), 1342 s (C=C), 1162 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.68-1.88 (4H, m, H-5 and H-6, 2 × CH_2), 2.52-2.72 (4H, m, H-4 and H-3, 2 × CH_2), 3.16 (3H, s, H-9, SO_2CH_3), 3.41 (1H, dd, *J* 13.0, *J* 7.5, H-3, $CH_AH_BCH_X$), 3.44 (1H, dd, *J* 13.0, *J* 6.9, H-3, $CH_AH_BCH_X$), 4.98 (2H, s, H-10, CH_2Ph), 5.31-5.45 (2H, m, H-1, CHCH_2), 5.74-5.93 (1H, m, H-2, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 21.9 (1C, *C*H_2), 23.6 (1C, *C*H_2), 35.7 (1C, S(O)*C*H_2), 42.9 (1C, SO_2CH_3), 48.9 (1C, *C*H_2Ph), 50.5 (1C, *C*H_2C(O)), 56.0 (1C, *C*H_2), 123.6 (1C, CH*C*H_2), 125.7 (1C, *C*HCH$_2$), 127.3 (2C, Ph*C*), 128.1 (1C, Ph*C*), 129.0 (2C, Ph*C*), 136.1 (1C, quat., Ph*C*), 173.4 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M]^+$ 380 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{16}H_{23}NO_4S_2Na$ 380.0966, found 380.0962.

3.3.4 Site-specific introduction of gold carbenes (aromatic systems)

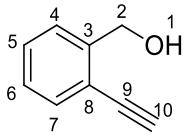
(2-((trimethylsilyl)ethynyl)phenyl)methanol (496)



Following GP 13 method A benzylalcohol was obtained as an orange/yellow oil (4.1 g, 96% yield); R_f 0.30 (30% EtOAc:70% hexane); ν_{max}(neat) / (cm^{-1}) 3310 s (O-H), 3262 s (C-H), 2106 w (CC); δ_H (300 MHz, $CDCl_3$) 0.29 (9H, s, H-11, Si(CH_3)$_3$), 2.70 (1H, t, *J* 5.5, H-1, O*H*), 4.82 (2H, d, *J* 5.5, H-2, CH_2OH), 7.23 (1H, dd, *J* 7.5, *J* 1.1, H-6, Ph*H*), 7.33 (1H,

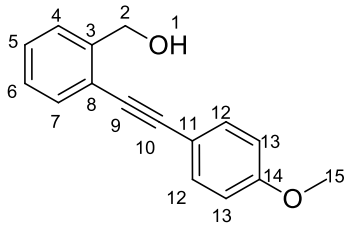
dt, *J* 6.5, *J* 1.2, H-4, Ph*H*), 7.42 (1H, d, *J* 7.5, H-7, Ph*H*), 7.47 (1H, dd, *J* 7.5, *J* 0.8, H-5, Ph*H*); δ_C (101 MHz, $CDCl_3$) 0.03 (1C, Si(*C*H_3)$_3$), 63.8 (1C, *C*H_2OH), 99.8 (1C, quat., C*C*Si(CH$_3$)$_3$), 102.2 (1C, quat., *C*CSi(CH$_3$)$_3$), 121.2 (1C, quat., PhC), 127.8 (1C, PhC), 127.9 (1C, PhC), 129.2 (1C, PhC), 132.6 (1C, PhC), 143.8 (1C, quat., PhC). Data were consistent with that reported in the literature.[106]

(2-ethynylphenyl)methanol (497)



Following GP 14 desilylated benzylalcohol product was obtained as an off-white yellow solid (2.4 g, 87% yield); mp 63-65 °C; R_f 0.30 (8:2 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 3312 s (O-H), 3262 s (C-H), 2103 w (CC), 1964 m (C-O); δ_H (300 MHz, $CDCl_3$) 1.28 (1H, br s, H-1, O*H*), 3.35 (1H, s, H-10, CC*H*), 4.83 (2H, s, H-2, C*H*$_2$OH), 7.26 (1H, dd, *J* 7.5, *J* 7.4, H-6, Ph*H*), 7.37 (1H, dd, *J* 7.6, *J* 7.4, H-5, Ph*H*), 7.45 (1H, d, *J* 7.5, H-7, Ph*H*), 7.51 (1H, d, *J* 7.6, H-4, Ph*H*); δ_C (101 MHz, $CDCl_3$) 29.9 (1C, *C*H_2OH), 63.9 (1C, C*C*H), 82.2 (1C, quat., *C*CH), 120.4 (1C, quat., PhC), 127.5 (1C, PhC), 127.6 (1C, PhC), 129.5 (1C, PhC), 133.1 (1C, PhC), 143.5 (1C, quat., PhC). Data were consistent with that reported in the literature.[107]

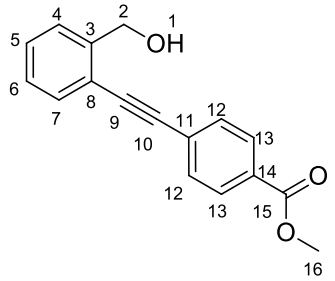
(2-((4-methoxyphenyl)ethynyl)phenyl)methanol (499)



Following GP 15 method B using 4-iodoanisole (1.1 eq., 11.0 mmol, 2.6 g) biarylacetylene was obtained as a white solid (2.0 g, 81% yield); mp 105-106 °C; R_f 0.27 (30%

EtOAc:70% hexane); ν_{max}(neat) / (cm^{-1}) 3345 brs (O-H), 3262 s (C-H), 2165 w (CC), 1510 s (C-O); δ_H (300 MHz, $CDCl_3$) 1.62 (1H, brs, H-1, O*H*), 3.82 (3H, s, H-15, OC*H*$_3$), 4.89 (2H, s, H-2, C*H*$_2$OH), 6.88 (1H, dt, *J* 8.9, *J* 2.4, H-4, Ph*H*), 7.25-7.36 (3H, m, H-5-7, Ph*H*), 7.42-7.53 (4H, m, H-12-13, Ph*H*); δ_C (101 MHz, $CDCl_3$) 55.4 (1C, O*C*H$_3$), 64.2 (1C, *C*H$_2$OH), 85.5 (1C, quat., *C*C), 94.3 (1C, quat., C*C*), 114.1 (2C, Ph*C*), 115.0 (1C, quat., Ph*C*), 121.7 (1C, quat., Ph*C*), 127.3 (1C, Ph*C*), 127.5 (1C, Ph*C*), 128.4 (1C, Ph*C*), 132.0 (1C, Ph*C*), 133.0 (2C, Ph*C*), 142.3 (1C, quat., Ph*C*), 159.9 (1C, quat., Ph*C*); m/z (TOF MS ES$^+$) $[M+Na]^+$ 261 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{16}H_{14}O_2Na$ 261.0891, found 261.0890. Data were consistent with that reported in the literature.[108]

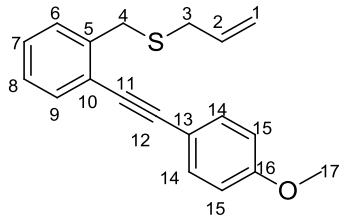
Methyl 4-((2-(hydroxymethyl)phenyl)ethynyl)benzoate (500)



Following GP 15 method B using methyl 4-iodobenzoate (1.1 eq., 11.0 mmol, 2.8 g) biarylacetylene was obtained as a white solid (1.7 g, 69% yield); mp 110-113 °C; R_f 0.28 (30% EtOAc:70% hexane); ν_{max}(neat) / (cm^{-1}) 3322 brs (O-H), 3262 s (C-H), 2214 w (CC), 1716 s (C=O); δ_H (300 MHz, $CDCl_3$) 1.55 (1H, brs, H-1, O*H*), 3.92 (3H, s, H-16, CO_2CH_3), 4.92 (2H, s, H-2, C*H*$_2$OH), 7.26-7.54 (4H, m, H-4-7, Ph*H*), 7.57 (2H, d, *J* 8.6, H-12, Ph*H*), 8.01 (2H, d, *J* 8.6, H-13, Ph*H*); δ_C (101 MHz, $CDCl_3$) 52.3 (1C, CO_2CH_3), 63.9 (1C, *C*H$_2$OH), 89.7 (1C, quat., *C*C), 93.3 (1C, quat., C*C*), 120.7 (1C, quat., PhC), 127.3 (1C, Ph*C*), 127.6 (1C, Ph*C*), 129.3 (1C, Ph*C*), 129.6 (2C, Ph*C*), 129.7 (1C, quat., Ph*C*), 131.5 (2C, Ph*C*), 132.4 (1C, Ph*C*), 142.7 (1C, quat., Ph*C*), 166.5 (1C, quat., Ph*C*), 182.3 (1C, quat., C=O); m/z (TOF MS ES$^+$) $[M+Na]^+$ 289 (100%); HRMS (TOF MS ES$^+$) mass

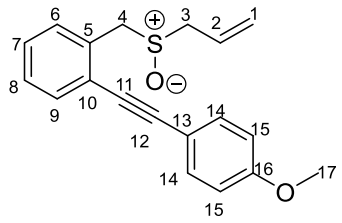
calculated for $C_{17}H_{14}O_3Na$ 289.0841, found 289.0838. Data were consistent with that reported in the literature.[109]

Allyl(2-((4-methoxyphenyl)ethynyl)benzyl)sulfane (505)



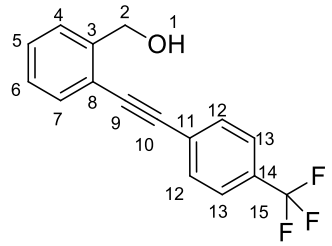
Following GP 16 using benzyl alcohol (1.0 eq., 10.0 mmol, 2.4 g), benzofused allylsulfane was obtained as a colourless viscous oil (2.2 g, 93% yield); R_f 0.30 (3% EtOAc:97% hexane); ν_{max}(neat) / cm^{-1}) 2911 m (C-H), 2214 s (CC), 1606 w (C-S), 1510 s (C-O), 1248 s (C=C); δ_H (300 MHz, $CDCl_3$) 3.65 ((2H, dt, *J* 7.1, *J* 1.1, H-3, SC*H*$_2$), 3.82 (3H, s, H-17, OC*H*$_3$), 4.58 (2H, s, H-4, C*H*$_2$S), 5.30-5.42 (2H, m, H-1, CHC*H*$_2$), 5.74-5.91 (1H, m, H-2, C*H*CH_2), 6.89 (2H, d, *J* 8.9, H-14, Ph*H*), 7.32-7.40 (2H, m, H-8-9, Ph*H*), 7.45 (2H, d, *J* 8.9, H-15, Ph*H*), 7.52-7.63 (2H, m, H-6-7, Ph*H*); δ_C (101 MHz, $CDCl_3$) 55.4 (1C, OCH_3), 56.6 (1C, SCH_2), 57.4 (1C, CH_2S), 85.7 (1C, quat., *C*C), 94.9 (1C, C*C*), 114.4 (2C, Ph*C*), 114.4 (1C, quat., Ph*C*), 123.8 (1C, C*H*CH_2), 124.7 (1C, quat., Ph*C*), 125.0 (1C, CH*C*H_2), 128.7 (1C, Ph*C*), 129.0 (1C, Ph*C*), 129.4 (1C, quat., Ph*C*), 131.3 (1C, Ph*C*), 132.5 (1C, PhC), 133.1 (2C, PhC), 160.2 (1C, quat., Ph*C*); m/z (TOF MS ES^+) $[M+Na]^+$ 317 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{19}H_{18}SONa$ 317.0976, found 317.0990.

1-((allylsulfinyl)methyl)-2-((4-methoxyphenyl)ethynyl)benzene (507)



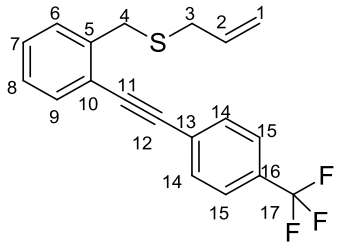
Following GP 5 oxidation of benzofused allylsulfane (2.0 mmol, 0.6 g) resulted in a sulfoxide as a white solid (0.5 g, 62% yield); mp 89-92 °C; R_f 0.28 (80% EtOAc:20% hexane); ν_{max}(neat) / cm^{-1}); 2933 s (C-H), 2838 s (C-H), 2213 w (CC), 1697 w (C-S), 1510 s (S=O), 1247 s (C=C); δ_H (300 MHz, $CDCl_3$) 3.36 (1H, dd, *J* 13.1, *J* 7.7, H-3, S(O)CH_AH_BCH$_X$), 3.50 (1H, dd, *J* 13.1, *J* 7.1, H-3, S(O)CH_AH_BCH$_X$), 3.81 (3H, s, H-17, OCH_3), 4.20 (1H, d, *J* 12.7, H-4, CH_AH_BS(O)), 4.39 (1H, d, *J* 12.7, H-4, CH_AH_BS(O)), 5.30-5.43 (2H, m, H-1, CHCH_2), 5.84-6.00 (1H, m, H-2, C*H*CH$_2$), 6.88 (2H, d, *J* 8.9, H-14, Ph*H*), 7.27-7.40 (3H, m, H-7-9, Ph*H*), 7.44 (2H, d, *J* 8.9, H-15, Ph*H*), 7.52-7.57 (1H, m, H-6, Ph*H*); δ_C (101 MHz, $CDCl_3$) 55.0 (1C, S(O)*C*H$_2$), 55.4 (1C, OCH$_3$), 56.5 (1C, *C*H$_2$S(O)), 85.9 (1C, quat., *C*CAr), 95.3 (1C, quat., C*C*Ar), 114.2 (2C, Ph*C*), 114.7 (1C, quat., Ph*C*), 123.7 (1C, *C*HCH$_2$), 124.3 (1C, quat., Ph*C*), 126.1 (1C, CH*C*H$_2$), 128.4 (1C, Ph*C*), 128.5 (1C, Ph*C*), 130.8 (1C, Ph*C*), 131.6 (1C, quat., Ph*C*), 132.4 (1C, Ph*C*), 133.0 (2C, Ph*C*), 160.0 (1C, quat., Ph*C*); m/z (TOF MS ES^+) $[M+Na]^+$ 333 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{19}H_{18}SO_2Na$ 333.0925, found 333.0921.

(2-((4-(trifluoromethyl)phenyl)ethynyl)phenyl)methanol (509)



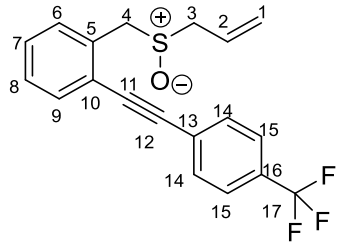
Following GP 15 method B using iodo-4-(trifluoromethyl)benzene (1.1 eq., 11.0 mmol, 3.0 g) biarylacetylene was obtained as a white solid (2.3 g, 93% yield); mp 102-104 °C; R_f 0.32 (30% EtOAc:70% hexane); ν_{max}(neat) / (cm^{-1}) 3322 brs (O-H), 3262 s (C-H), 2214 w (CC), 1716 s (C=O); δ_H (300 MHz, $CDCl_3$) 2.09 (1H, brs, H-1, O*H*), 4.93 (2H, s, H-2, CH_2OH), 7.27-7.46 (4H, m, H-4-7, Ph*H*), 7.47-7.59 (4H, m, H-12-13, Ph*H*), 7.63 (3F, s, F-1, CF_3); δ_C (101 MHz, $CDCl_3$) 63.8 (1C, *C*H_2OH), 89.1 (1C, quat., *C*C), 92.6 (1C, quat., C*C*), 120.6 (1C, quat., Ph*C*), 122.5 (1C, quat., Ph*C*), 125.4 (1C, Ph*C*), 126.8 (1C, quat., Ph*C*), 127.3 (1C, Ph*C*), 127.6 (1C, Ph*C*), 129.3 (2C, Ph*C*), 130.6 (1C, q, $J_{C\text{-}F}$ 260.0, *C*F_3), 131.8 (2C, Ph*C*), 132.4 (1C, quat., Ph*C*). Data were consistent with that reported in the literature.[124]

Allyl(2-((4-(trifluoromethyl)phenyl)ethynyl)benzyl)sulfane (511)



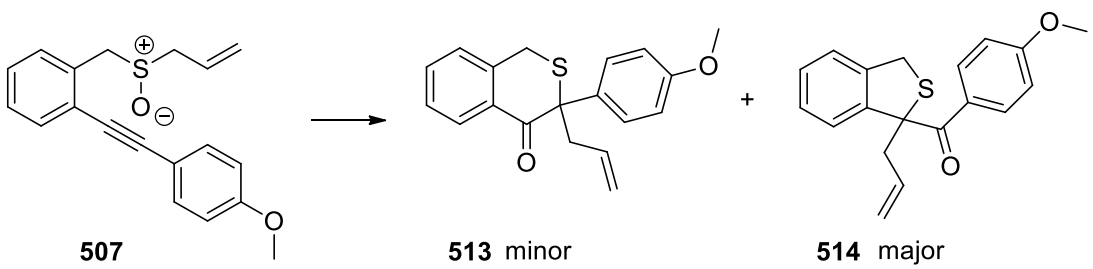
Purification by column chromatography led to degradation therefore, crude product was used promptly in the next step.

1-((allylsulfinyl)methyl)-2-((4-(trifluoromethyl)phenyl)ethynyl)benzene (512)

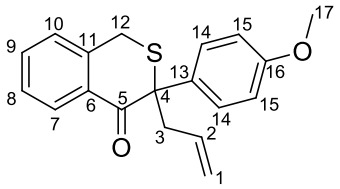


Following GP 5 oxidation of benzofused allylsulfane (2.0 mmol, 0.7 g) resulted in a sulfoxide as a white solid (0.6 g, 61% yield); mp 87-89°C; R_f 0.30 (80% EtOAc:20% hexane); ν_{max}(neat) / (cm^{-1}); 2921 s (C-H), 2851 s (C-H), 2218 w (CC), 16314 w (C-S), 1320 s (S=O), 1064 s (C=C); δ_H (300 MHz, $CDCl_3$) 3.35 (1H, dd, *J* 13.1, *J* 7.7, H-3, $SO_2CH_AH_BCH_X$), 3.50 (1H, dd, *J* 13.1, *J* 7.1, H-3, S(O)$CH_AH_BCH_X$), 4.19 (1H, d, *J* 12.7, H-4, $CH_AH_BS(O)$), 4.36 (1H, d, *J* 12.7, H-4, $CH_AH_BS(O)$), 5.32-5.47 (2H, m, H-1, $CHCH_2$), 5.83-6.01 (1H, m, H-2, $CHCH_2$), 7.30-7.45 (3H + 2H, m, H-7-9 and H-14, Ph*H*), 7.56-7.60 (1H + 2H, m, H-6 and H-15, Ph*H*), 7.61 (3F, s, CF_3); δ_C (101 MHz, $CDCl_3$) 55.2 (1C, S(O)CH_2), 56.6 (1C, $CH_2S(O)$), 89.4 (1C, quat., *C*CAr), 93.5 (1C, quat., C*C*Ar), 123.2 (1C, quat., Ph*C*), 123.7 (1C, $CHCH_2$), 125.4 (1C, q, J_{C-F} 320.6, CF_3), 125.9 (1C, $CHCH_2$), 126.4 (1C, quat., Ph*C*), 128.5 (1C, Ph*C*), 129.4 (1C, Ph*C*), 130.3 (1C, quat., Ph*C*), 130.6 (1C, quat., Ph*C*), 130.9 (1C, Ph*C*), 131.8 (2C, Ph*C*), 132.3 (1C, Ph*C*), 132.8 (2C, Ph*C*); m/z (TOF MS ES^+) $[M+Na]^+$ 371 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{19}H_{15}SOF_3Na$ 371.0693, found 371.0692.

3.3.4.1. Electron-rich system

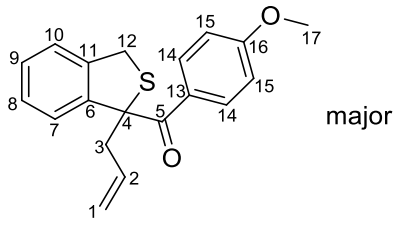


3-allyl-3-(4-methoxyphenyl)isothiochroman-4-one (513)



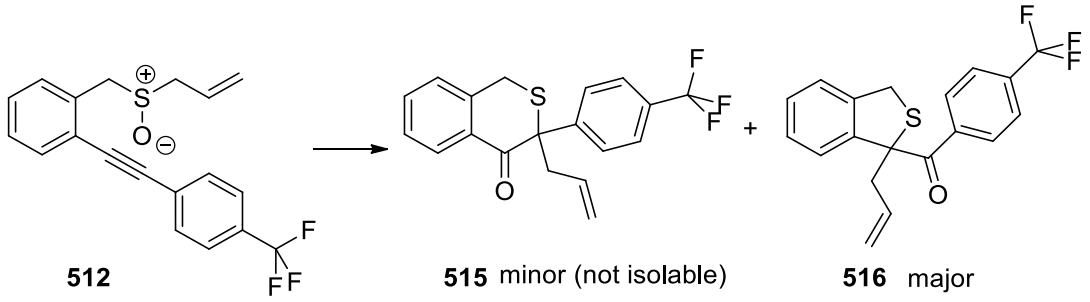
Following GP 6 heterocycle was obtained in 24 h as a colourless viscous oil (2.2 mg, 7% yield); R_f 0.30 (80% hexane:20% EtOAc); δ_H (300 MHz, $CDCl_3$) 2.72 (1H, dd, *J* 14.4, *J* 7.6, H-3, CH_AH_B), 2.92 (1H, dd, *J* 14.4, *J* 6.8, H-3, CH_AH_B), 3.44 (1H, d, *J* 16.9, H-12, SCH_AH_B), 3.75 (3H, s, H-17, CH_3), 3.83 (1H, d, *J* 16.9, H-12, SCH_AH_B), 5.04 (2H, dd, *J* 13.6, *J* 1.8, H-1, CHCH_2), 5.67-5.84 (1H, m, H-2, C*H*CH_2), 6.74-6.85 (2H, m, H-14, Ph*H*), 6.95-6.98 (1H, m, H-9, Ph*H*), 7.23-7.38 (4H, m, H-8, H-10 and H-15, Ph*H*), 8.07-8.17 (1H, m, H-7, Ph*H*); δ_C (101 MHz, $CDCl_3$) 28.1 (1C, *C*H_2), 44.0 (1C, *C*H_2), 55.2 (1C, *C*H_3), 56.9 (1C, quat., *C*S), 114.0 (2C, Ph*C*), 118.6 (1C, CH*C*H_2), 127.2 (1C, Ph*C*), 127.5 (1C, Ph*C*), 128.4 (1C, quat., Ph*C*), 128.5 (2C, Ph*C*), 129.7 (1C, Ph*C*), 132.0 (1C, Ph*C*), 133.1 (1C, *C*HCH_2), 133.3 (1C, quat., Ph*C*), 140.6 (1C, quat., Ph*C*), 158.9 (1C, quat., Ph*C*), 193.0 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 333 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{19}H_{18}SO_2Na$ 333.0925, found 333.0921.

(1-allyl-1,3-dihydrobenzo[*c*]thiophen-1-yl)(4-methoxyphenyl)methanone (514)

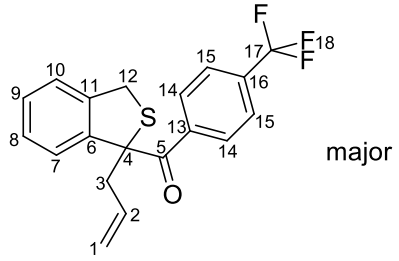


Following GP 6 heterocycle was obtained in 24 h as a colourless viscous oil (21.4 mg, 69% yield); R_f 0.32 (80%hexane:20%EtOAc); ν_{max}(neat) / (cm^{-1}) 3073 s (C-H), 2917 s (C-H), 2840 m (C-H), 1660 s (C=O), 1242 s (C=C); δ_H (300 MHz, $CDCl_3$) 2.88-2.98 (1H, m, H-3, CH_AH_B), 3.13 (1H, ddt, *J* 14.4, *J* 7.2, *J* 1.1, H-3, CH_AH_B), 3.78 (3H, s, H-17, CH_3), 4.28 (1H, d, *J* 14.0, H-12, SCH_AH_B), 4.44 (1H, d, *J* 14.0, H-12, SCH_AH_B), 4.97-5.07 (2H, m, H-1, CHCH_2), 5.66 (1H, m, H-2, C*H*CH_2), 6.68-6.75 (2H, m, H-14, Ph*H*), 7.02-7.35 (4H, m, H-7-10, Ph*H*), 7.55-7.63 (2H, m, H-15, Ph*H*); δ_C (101 MHz, $CDCl_3$) 38.1 (1C, C-12, *C*H_2), 45.2 (1C, C-3, *C*H_2), 55.3 (1C, C-17, *C*H_3), 71.6 (1C, quat., C-4, *C*S), 113.0 (2C, C-14, Ph*C*), 118.9 (1C, C-1, CH*C*H_2), 125.1 (1C, Ph*C*), 125.3 (1C, Ph*C*), 127.4 (1C, Ph*C*), 127.9 (1C, Ph*C*), 128.9 (1C, quat., C-11, Ph*C*), 131.8 (2C, C-15, Ph*C*), 133.4 (1C, C-2, *C*HCH_2), 140.9 (1C, quat., C-6, Ph*C*), 143.4 (1C, quat., C-13, Ph*C*), 162.2 (1C, quat., C-16, Ph*C*), 196.7 (1C, quat., C-5, *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 333 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{19}H_{18}SO_2Na$ 333.0925, found 333.0921.

3.3.4.2. Electron-poor system



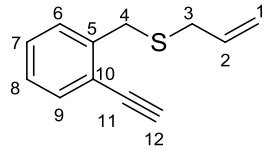
(1-allyl-1,3-dihydrobenzo[*c*]thiophen-1-yl)(4-(trifluoromethyl)phenyl)methanone (516)



Following GP 6 heterocycle was obtained in 24 h as a colourless viscous oil (18.3 mg, 54% yield with 8% impurity of minor 6-membered heterocycle **515**); major R_f 0.29 (7:3 hexane:EtOAc); minor R_f 0.31 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 3077 s (C-H), 2916 s (C-H), 1679 s (C=O), 1323 s (C=C); δ_H (300 MHz, $CDCl_3$) 2.91-3.09 (1H, m, H-3, CH_AH_B), 3.16 (1H, ddt, *J* 14.5, *J* 6.9, *J* 1.2, H-3, CH_AH_B), 4.11 (1H, d, *J* 14.1, H-12, SCH_AH_B), 4.37 (1H, d, *J* 14.1, H-12, SCH_AH_B), 5.00-5.12 (2H, m, H-1, CHCH_2), 5.61-5.76 (1H, m, H-2, CHCH_2), 7.07-7.37 (8H, m, H-7-10 and H-14-15, PhH), 7.46 (3F, s, F-18, CF_3); δ_C (101 MHz, $CDCl_3$) 38.0 (1C, C-12, CH$_2$), 43.6 (1C, C-3, CH$_2$), 72.0 (1C, quat., C-4, CS), 119.4 (1C, C-1, CHCH$_2$), 124.7 (2C, C-15, PhC), 125.1 (1C, PhC), 125.4 (1C, PhC), 127.7 (1C, PhC), 128.5 (1C, PhC), 129.0 (2C, C-14, PhC), 132.5 (1C, q, J_{C-F} 324.4, C-16, CF$_3$), 132.9 (1C, C-2, CHCH$_2$), 140.8 (1C, quat., C-13, PhC), 141.5 (1C, quat., C-6, PhC), 141.8 (1C, quat., C-11, PhC), 198.1 (1C, quat., C-5, C(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 371 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{19}H_{15}SOF_3Na$ 371.0693, found 371.0697.

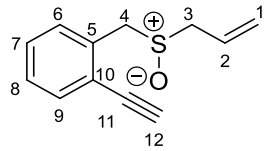
3.3.5 Benzofused ynamides

Allyl(2-ethynylbenzyl)sulfane (522)



Following GP 16 benzofused allylsulfane was obtained as a pale yellow oil over 3 steps (1.8 g, 76% yield); R_f 0.30 (1% EtOAc:99% hexane); ν_{max}(neat) / (cm^{-1}) 3289 m (C-H), 2100 w (CC), 1635 m (C-S), 1227 m (C=C); δ_H (300 MHz, $CDCl_3$) 3.08 ((2H, dt, *J* 7.1, *J* 1.1, H-3, SCH_2), 3.32 (1H, s, H-12, CC*H*), 3.84 (2H, s, H-4, CH_2S), 5.08-5.20 (2H, m, H-1, CHCH_2), 5.73-5.90 (1H, m, H-2, C*H*CH_2), 7.12-7.53 (4H, m, H-6-9, Ph*H*); δ_C (101 MHz, $CDCl_3$) 33.4 (1C, S*C*H_2), 34.6 (1C, *C*H_2S), 81.8 (1C, quat., *C*CH), 82.1 (1C, C*C*H), 117.3 (1C, C*H*CH_2), 121.9 (1C, quat., Ph*C*), 126.9 (1C, CH*C*H_2), 128.9 (1C, PhC), 129.3 (1C, PhC), 133.2 (1C, PhC), 134.3 (1C, PhC), 141.1 (1C, quat., PhC); m/z (TOF MS EI^+) $[M]^+$ 188 (10%), $[M\text{-}C_9H_7]^+$ 115 (100%); HRMS (TOF MS EI^+) mass calculated for $C_{12}H_{12}S$ 188.0660, found 188.0654.

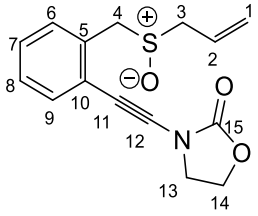
1-((allylsulfinyl)methyl)-2-ethynylbenzene (524)



Following GP 5 oxidation of benzofused allylsulfane (2.0 mmol, 0.4 g) resulted in a sulfoxide as a colourless oil (0.4 g, 93% yield) R_f 0.28 (80% EtOAc:20% hexane); ν_{max}(neat) / (cm^{-1}); 3289 s (C-H), 3202 s (C-H), 2100 w (CC), 1636 w (C-S), 1484 s (S=O), 1037 s (C=C); δ_H (300 MHz, $CDCl_3$) 3.31 (1H, dd, *J* 13.1, *J* 7.6, H-3, C$H_AH_B$$CH_X$), 3.34 (1H, s, H-12, CC*H*), 3.47 (1H, dd, *J* 13.1, *J* 7.1, H-3, S(O)C$H_AH_B$$CH_X$), 4.08 (1H, d, *J* 12.7, H-4, CH_AH_BS(O)), 4.30 (1H, d, *J* 12.7, H-4, CH_AH_BS(O)), 5.31-5.48 (2H, m, H-1, CHCH_2), 5.81-6.00 (1H, m, H-2, C*H*CH_2), 7.25-7.55 (4H, m, H-6-9, Ph*H*), δ_C (101 MHz, $CDCl_3$)

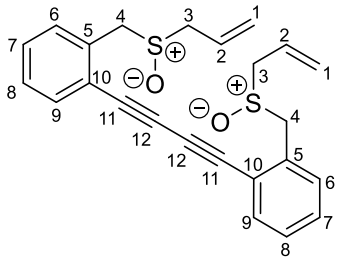
55.1 (1C, S(O)*C*H_2), 56.0 (1C, *C*H_2S(O)), 81.5 (1C, quat., *C*CH), 82.9 (1C, C*C*H), 122.7 (1C, quat., Ph*C*), 123.7 (1C, C*H*CH_2), 126.0 (1C, CH*C*H_2), 128.3 (1C, PhC), 129.4 (1C, PhC), 130.8 (1C, PhC), 132.7 (1C, quat., PhC), 133.3 (1C, PhC); m/z (TOF MS ES^+) $[M+Na]^+$ 227 (100%), $[M-H_2O]^+$ 186 (5%); HRMS (TOF MS ES^+) mass calculated for $C_{12}H_{12}SONa$ 227.0507, found 227.0503.

3-((2-((allylsulfinyl)methyl)phenyl)ethynyl)oxazolidin-2-one (525)



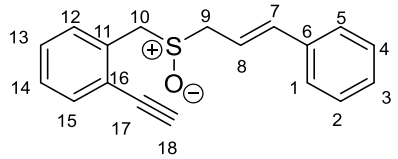
Following GP 10 using commercially available amide oxazolidinone (5.0 eq., 5.0 mmol, 435 mg) and sulfoxide (1.0 eq., 1.0 mmol, 204 mg), ynamide was prepared as a viscous colourless oil (61 mg, 21% yield); R_f 0.30 (2%MeOH in EtOAc); ν_{max}(neat) / (cm^{-1}) 2979 s (C-H), 2250 s (CC), 1759 s (C=O), 1477 m (S=O), 1407 s (C=C), 1198 s (C-N); δ_H (300 MHz, $CDCl_3$) 3.38 (1H, dd, *J* 13.1, *J* 7.9, H-3, C$H_AH_B$$CH_X$), 3.59 (1H, dd, *J* 13.1, *J* 7.0, H-3, C$H_AH_B$$CH_X$), 3.89-4.10 (2H, m, H-13, NCH_2), overlapping with 4.00 (1H, m, H-4, CH_AH_BS(O)), 4.29 (1H, d, *J* 12.7, H-4, CH_AH_BS(O)), 4.40-4.54 (2H, m, H-14, OCH_2), 5.33-5.49 (2H, m, H-1, CHCH_2), 5.86-6.05 (1H, m, H-2, C*H*CH_2), 7.21-7.47 (4H, m, H-6-9, Ph*H*); δ_C (101 MHz, $CDCl_3$) 46.6 (1C, N*C*H_2), 55.3 (1C, *C*H_2S(O)), 56.6 (1C, S(O)*C*H_2), 63.2 (1C, O*C*H_2), 69.7 (1C, quat., *C*C-N), 84.6 (1C, quat., C*C*-N), 122.9 (1C, quat., Ph*C*), 123.4 (1C, CH*C*H_2), 126.2 (1C, *C*HCH_2), 128.2 (1C, Ph*C*), 128.3 (1C, Ph*C*), 130.8 (1C, Ph*C*), 131.3 (1C, Ph*C*), 131.9 (1C, quat., Ph*C*), 156.4 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 312 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{15}H_{15}NO_3SNa$ 312.0670, found 312.0664.

1,4-bis(2-((allylsulfinyl)methyl)phenyl)buta-1,3-diyne (526)



Following GP 10 resulted in the generation of diyne side product as a white solid (1.6 g, 40% yield); R_f 0.25 (100% EtOAc); ν_{max}(neat) / (cm^{-1}); 2925 s (C-H), 2861 s (C-H), 2217 w (CC), 2143 w (CC), 1633 m (C-S), 1479 s (S=O), 1047 s (C=C); δ_H (300 MHz, $CDCl_3$) 3.39 (2H, dd, *J* 13.1, *J* 7.6, H-3, CH_AH_BCH_X), 3.53 (2H, dd, *J* 13.1, *J* 7.2, H-3, CH_AH_BCH_X), 4.12 (2H, d, *J* 12.8, H-4, CH_AH_B), 4.34 (2H, d, *J* 12.8, H-4, CH_AH_B), 5.37-5.55 (4H, m, H-1, CHCH_2), 5.96 (2H, ddt, *J* 17.5, *J* 10.2, *J* 7.4, H-2, C*H*CH_2), 7.29-7.69 (8H, m, H-6-9, Ph*H*), δ_C (101 MHz, $CDCl_3$) 55.3 (2C, *C*H_2), 56.2 (2C, *C*H_2), 78.6 (2C, quat., *C*C), 80.8 (2C, quat., C*C*), 122.1 (2C, quat., Ph*C*), 123.9 (2C, C*H*CH_2), 125.9 (2C, CH*C*H_2), 128.5 (2C, Ph*C*), 130.0 (2C, Ph*C*), 131.0 (2C, Ph*C*), 133.7 (2C, quat., Ph*C*), 133.8 (2C, Ph*C*); m/z (TOF MS ES^+) $[M+Na]^+$ 429 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{24}H_{22}S_2O_2Na$ 429.0959, found 429.0953.

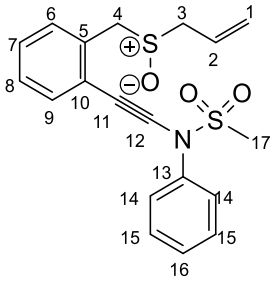
(*E*)-1-((cinnamylsulfinyl)methyl)-2-ethynylbenzene (524b)



Following GP 5 oxidation of benzofused cinnamylsulfane (2.0 mmol, 0.5 g) resulted in a sulfoxide as a colourless oil (0.3 g, 60% yield); R_f 0.28 (80% EtOAc:20% hexane); ν_{max}(neat) / (cm^{-1}); 3283 s (C-H), 3200 s (C-H), 3027 w (C-H), 1484 s (S=O), 1035 s (C=C); δ_H (300 MHz, $CDCl_3$) 3.28 (1H, s, H-18, CC*H*), 3.53 (1H, ddd, *J* 13.1, *J* 7.8, *J* 1.2, H-9, CH_AH_BCH), 3.68 (1H, ddd, *J* 13.1, *J* 7.5, *J* 1.2, H-9, CH_AH_BCH), 4.15 (1H, d, *J* 12.7,

H-10, CH_AH_B), 4.41 (1H, d, *J* 12.7, H-10, CH_AH_B), 6.23-6.36 (1H, m, H-8, C*H*CH), 6.69 (1H, d, *J* 15.9, H-7, CHC*H*), 7.19-7.63 (9H, m, H-1-5 and H-12-15, Ph*H*); δ_C (101 MHz, $CDCl_3$) 55.0 (1C, *C*H_2), 56.0 (1C, *C*H_2), 81.6 (1C, quat., *C*CH), 82.9 (1C, C*C*H), 116.9 (1C, Ph*C*), 122.7 (1C, quat., Ph*C*), 126.6 (2C, Ph*C*), 128.3 (1C, Ph*C*), 128.4 (1C, *C*H), 128.7 (2C, Ph*C*), 129.4 (1C, Ph*C*), 130.8 (1C, Ph*C*), 132.8 (1C, quat., Ph*C*), 133.3 (1C, Ph*C*), 136.1 (1C, quat., Ph*C*), 138.1 (1C, *C*H); m/z (TOF MS ES$^+$) $[M+Na]^+$ 303 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{18}H_{16}SONa$ 303.0820, found 303.0825.

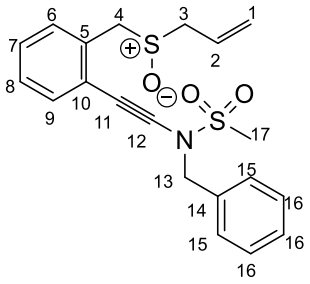
_N_-((2-((allylsulfinyl)methyl)phenyl)ethynyl)-_N_-phenylmethanesulfonamide (527a)



Following GP 10 using *N*-phenylmethanesulfonamide (5.0 eq., 5.0 mmol, 856 mg) and sulfoxide (1.0 eq., 1.0 mmol, 204 mg), ynamide was prepared as a viscous pale yellow oil (127 mg, 34% yield); R_f 0.28 (100% EtOAc); ν_{max}(neat) / (cm^{-1}) 2924 s (C-H), 2239 s (CC), 1490 m (S=O), 1364 s (C=C), 1167 s (C-N); δ_H (300 MHz, $CDCl_3$) 3.16 (3H, s, H-17, SO_2CH_3), 3.41 (1H, dd, *J* 13.0, *J* 7.1, H-3, CH_AH_BCH_X), 3.61 (1H, dd, *J* 13.0, *J* 7.1, H-3, CH_AH_BCH_X), 4.06 (1H, d, *J* 12.6, H-4, CH_AH_BS(O)), 4.25 (1H, d, *J* 12.6, H-4, CH_AH_BS(O)), 5.32-5.48 (2H, m, H-1, CHCH_2), 5.84-6.02 (1H, m, H-2, C*H*CH_2), 7.22-7.64 (4H+5H, m, H-6-9 and H-14-16, Ph*H*); δ_C (101 MHz, $CDCl_3$) 37.4 (1C, SO_2CH_3), 55.6 (1C, *C*H_2S(O)), 56.6 (1C, S(O)*C*H_2), 69.5 (1C, quat., *C*C-N), 87.3 (1C, quat., C*C*-N), 123.3 (1C, quat., Ph*C*), 123.6 (1C, CH*C*H_2), 125.6 (2C, Ph*C*), 126.3 (1C, *C*HCH_2), 128.3 (1C, Ph*C*), 128.4 (1C, Ph*C*), 128.7 (1C, Ph*C*), 129.7 (2C, Ph*C*), 131.0 (1C, Ph*C*), 131.6 (1C, Ph*C*), 132.1 (1C, quat., Ph*C*), 138.3 (1C, quat., NPh*C*); m/z (TOF MS ES$^+$) $[M+Na]^+$ 396

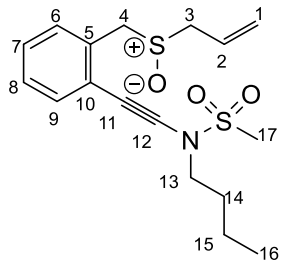
(100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{19}H_{19}NO_3S_2Na$ 396.0704, found 396.0720.

_N_-((2-((allylsulfinyl)methyl)phenyl)ethynyl)-_N_-benzylmethanesulfonamide (527b)



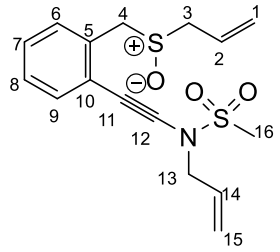
Following GP 10 using *N*-benzylmethanesulfonamide (5.0 eq., 5.0 mmol, 926 mg) and sulfoxide (1.0 eq., 1.0 mmol, 204 mg), ynamide was prepared as a viscous pale yellow oil (78 mg, 20% yield); R_f 0.30 (90% EtOAc:10% hexane); ν_{max}(neat) / (cm^{-1}) 2925 s (C-H), 2241 s (CC), 1456 m (S=O), 1356 s (C=C), 1161 s (C-N); δ_H (300 MHz, $CDCl_3$) 2.97 (3H, s, H-17, SO_2CH_3), 3.29 (1H, dd, *J* 13.1, *J* 7.8, H-3, $CH_AH_BCH_X$), 3.49 (1H, dd, *J* 13.1, *J* 7.1, H-3, $CH_AH_BCH_X$), 3.92 (1H, d, *J* 12.6, H-4, $CH_AH_BS(O)$), 4.12 (1H, d, *J* 12.6, H-4, $CH_AH_BS(O)$), 4.70 (2H, s, H-13, NCH_2), 5.29-5.46 (2H, m, H-1, $CHCH_2$), 5.81-5.99 (1H, m, H-2, $CHCH_2$), 7.18-7.51 (4H+5H, m, H-6-9 and H-15-16, Ph*H*); δ_C (101 MHz, $CDCl_3$) 39.4 (1C, SO_2CH_3), 55.3 (1C, NCH_2), 55.5 (1C, $CH_2S(O)$), 56.4 (1C, $S(O)CH_2$), 70.0 (1C, quat., *C*C-N), 87.1 (1C, quat., C*C*-N), 123.3 (1C, quat., Ph*C*), 123.4 (1C, $CHCH_2$), 126.2 (1C, $CHCH_2$), 128.1 (1C, Ph*C*), 128.2 (1C, Ph*C*), 128.8 (3C, Ph*C*), 128.9 (2C, Ph*C*), 130.8 (1C, Ph*C*), 131.4 (1C, Ph*C*), 131.9 (1C, quat., Ph*C*), 134.3 (1C, quat., NPh*C*); m/z (TOF MS ES$^+$) $[M+Na]^+$ 396 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{20}H_{21}NO_3S_2Na$ 410.0861, found 410.0868.

_N_-((2-((allylsulfinyl)methyl)phenyl)ethynyl)-_N_-butylmethanesulfonamide (527c)



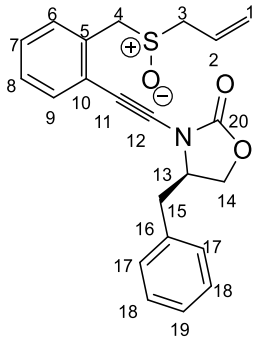
Following GP 10 using *N*-butylmethanesulfonamide (5.0 eq., 5.0 mmol, 756 mg) and sulfoxide (1.0 eq., 1.0 mmol, 204 mg), ynamide was prepared as a viscous colourless oil (173 mg, 49% yield); R_f 0.30 (80% EtOAc:20% hexane); ν_{max}(neat) / (cm^{-1}) 2924 s (C-H), 2234 s (CC), 1458 m (S=O), 1353 s (C=C), 1161 s (C-N); δ_H (300 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.3, H-16, CH_2CH_3), 1.43 (2H, hex, *J* 7.3, H-15, CH_2), 1.76 (2H, pent, *J* 7.3, H-14, CH_2) 3.13 (3H, s, H-17, SO_2CH_3), 3.40 (1H, dd, *J* 13.1, *J* 7.8, H-3, $CH_AH_BCH_X$), 3.53 (2H, t, *J* 7.3, H-13, NCH_2), 3.61 (1H, dd, *J* 13.1, *J* 7.0, H-3, $CH_AH_BCH_X$), 4.03 (1H, d, *J* 12.6, H-4, $CH_AH_BS(O)$), 4.22 (1H, d, *J* 12.6, H-4, $CH_AH_BS(O)$), 5.36-5.49 (2H, m, H-1, $CHCH_2$), 5.88-6.05 (1H, m, H-2, $CHCH_2$), 7.24-7.45 (4H+5H, m, H-6-9 and H-15-16, Ph*H*); δ_C (101 MHz, $CDCl_3$) 13.6 (1C, CH_3), 19.5 (1C, CH_2), 30.4 (1C, CH_2), 38.8 (1C, SO_2CH_3), 51.3 (1C, CH_2), 55.5 (1C, $CH_2S(O)$), 56.7 (1C, $S(O)CH_2$), 69.5 (1C, quat., *C*C-N), 87.1 (1C, quat., C*C*-N), 123.4 (1C, quat., Ph*C*), 123.5 (1C, $CHCH_2$), 126.3 (1C, $CHCH_2$), 128.2 (1C, Ph*C*), 128.3 (1C, Ph*C*), 131.0 (1C, Ph*C*), 131.5 (1C, Ph*C*), 132.0 (1C, quat., Ph*C*); m/z (TOF MS ES^+) $[M+Na]^+$ 376 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{17}H_{23}NO_3S_2Na$ 376.1017, found 376.1029.

_N_-allyl-_N_-((2-((allylsulfinyl)methyl)phenyl)ethynyl)methanesulfonamide (527d)



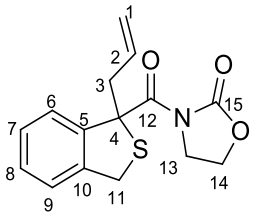
Following GP 10 using _N_-allylmethanesulfonamide (5.0 eq., 5.0 mmol, 676 mg) and sulfoxide (1.0 eq., 1.0 mmol, 204 mg), ynamide was prepared as a viscous colourless oil (95 mg, 28% yield); R_f 0.30 (80% EtOAc:20% hexane); ν_{max}(neat) / (cm^{-1}) 2923 s (C-H), 1693 s (CC), 1420 m (S=O), 1346 s (C=C), 1161 s (C-N); δ_H (300 MHz, $CDCl_3$) 3.14 (3H, s, H-16, SO_2CH_3), 3.38 (1H, dd, _J_ 13.0, _J_ 7.8, H-3, $CH_AH_BCH_X$), 3.58 (1H, dd, _J_ 13.0, _J_ 7.0, H-3, $CH_AH_BCH_X$), 4.03 (1H, d, _J_ 12.6, H-4, $CH_AH_BS(O)$), 4.16 (2H, dt, _J_ 6.4, _J_ 1.2, H-13, NCH_2), 4.20 (1H, d, _J_ 12.6, H-4, $CH_AH_BS(O)$), 5.33-5.49 (2H+2H, m, H-1 and H-15, 2 × $CHCH_2$), 5.87-6.06 (1H+1H, m, H-2 and H-14, $CHCH_2$), 7.25-7.44 (4H, m, H-6-9, Ph_H_); δ_C (101 MHz, $CDCl_3$) 39.5 (1C, SO_2CH_3), 54.2 (1C, CH_2CH), 55.5 (1C, $CH_2S(O)$), 56.6 (1C, $S(O)CH_2$), 69.6 (1C, quat., _C_C-N), 87.0 (1C, quat., C_C_-N), 120.9 (1C, $CHCH_2$), 123.4 (1C, quat., Ph-C), 123.6 (1C, $CHCH_2$), 125.2 (1C, $CHCH_2$), 125.9 (1C, $CHCH_2$), 128.2 (1C, Ph_C_), 128.3 (1C, Ph_C_), 131.1 (1C, Ph_C_), 131.6 (1C, quat., Ph_C_), 132.0 (1C, Ph_C_); m/z (TOF MS ES^+) $[M+Na]^+$ 360 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{16}H_{19}NO_3S_2Na$ 360.0704, found 360.0707.

(4*R*)-3-((2-((allylsulfinyl)methyl)phenyl)ethynyl)-4-benzyloxazolidin-2-one (527e)



Following GP 10 using commercially available amide (*R*)-4-benzyloxazolidin-2-one (5.0 eq., 5.0 mmol, 886 mg) and sulfoxide (1.0 eq., 1.0 mmol, 204 mg), ynamide was prepared as a viscous colourless oil (181 mg, 48% yield); R_f 0.27 (80% EtOAc:20% hexane); ν_{max}(neat) / (cm^{-1}) 2989 s (C-H), 2901 s (C-H), 2250 s (CC), 1770 s (C=O), 1454 m (S=O), 1408 s (C=C), 1066 s (C-N); δ_H (300 MHz, $CDCl_3$) 3.01 (1H, dd, *J* 13.8, *J* 6.7, H-3, CH_AH_BCH$_X$), 3.26-3.29 (1H, m, H-3, CH_AH_BCH$_X$), 3.41 (1H, dd, *J* 13.1, *J* 7.9, H-4, CH_AH_BS(O)), 3.63 (1H, dd, *J* 13.1, *J* 6.9, H-4, CH_AH_BS(O)), 4.03 (1H, dd, *J* 12.7, *J* 8.0, H-15, PhCH_AH_B), 4.13-4.24 (1H, m, H-15, PhCH_AH_B), 4.31-4.34 (1H, m, H-14, OCH_AH_B), 4.36-4.45 (2H, m, H-14 and H-13, NC*H* and OCH_AH_B), 5.34-5.50 (2H, m, H-1, CHCH_2), 5.87-6.07 (1H, m, H-2, C*H*CH$_2$), 7.18-7.49 (4H+5H, m, H-6-9 and H-17-19, Ph*H*); δ_C (101 MHz, $CDCl_3$) 38.2 (1C, PhCH$_2$), 55.4 (1C, *C*H$_2$S(O)), 56.7 (1C, S(O)*C*H$_2$), 58.2 (1C, N*C*H), 67.6 (1C, O*C*H$_2$), 71.7 (1C, quat., *C*C-N), 83.6 (1C, quat., C*C*-N), 122.9 (1C, quat., Ph*C*), 123.5 (1C, CH*C*H$_2$), 126.2 (1C, *C*HCH$_2$), 127.6 (1C, Ph*C*), 128.2 (1C, Ph*C*), 128.5 (1C, Ph*C*), 129.1 (2C, Ph*C*), 129.4 (1C, Ph*C*), 131.0 (1C, Ph*C*), 131.4 (2C, Ph*C*), 132.0 (1C, quat., Ph-*C*), 134.0 (1C, quat., Ph*C*), 155.4 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 402 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{22}H_{21}NO_3SNa$ 402.1140, found 402.1155.

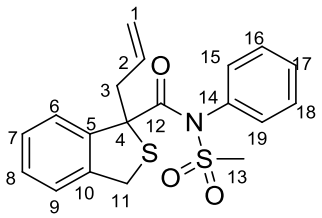
3-(1-allyl-1,3-dihydrobenzo[*c*]thiophene-1-carbonyl)oxazolidin-2-one (532)



Following GP 6, heteroaromatic was obtained as a colourless viscous oil (21 mg, 74% yield); R_f 0.30 (70% hexane:30% EtOAc); ν_{max}(neat) / (cm^{-1}) 2919 w (C-H), 1774 s (C=O), 1682 s (C=O), 1386 s (C=C), 1282 s (C-N); δ_H (300 MHz, $CDCl_3$) 3.00 (1H, ddt, *J* 14.3, *J* 6.8, *J* 1.1, H-3, CH_AH_BCH$_X$), 3.37 (1H, ddt, *J* 14.3, *J* 7.1, *J* 1.1, H-3, CH_AH_BCH$_X$), 3.85 (1H, ddd, *J* 10.9, *J* 8.6, *J* 7.1, H-13, NCH_AH_BCH$_X$), 4.04-4.16 (1H, m, H-13, NCH_AH_BCH$_X$), overlaps with 4.12-4.25 (2H, m, H-11, SCH_AH_B), 4.27-4.44 (2H, m, H-14, OCH_AH_BCH$_X$), 4.95-5.09 (2H, m, H-1, CH_2CH), 5.60 (1H, ddt, *J* 17.1, *J* 10.1, *J* 6.9, H-2, CH$_2$C*H*), 7.16-7.35 (4H, m, H-6-9, Ph*H*); δ_C (101 MHz, $CDCl_3$) 37.4 (1C, C-11, *C*H$_2$S), 42.1 (1C, C-3, *C*H$_2$), 44.5 (1C, C-13, N*C*H$_2$), 62.2 (1C, C-14, O*C*H$_2$), 69.0 (1C, quat., C-4, *C*S), 119.3 (1C, C-1, CH*C*H$_2$), 124.8 (1C, C-8, Ph*C*), 126.5 (1C, C-7, Ph*C*), 126.7 (1C, C-9, Ph*C*), 128.0 (1C, C-6, Ph*C*), 132.6 (1C, C-2, *C*HCH$_2$), 140.9 (1C, quat., C-10, Ph*C*), 141.3 (1C, quat., C-5, Ph*C*), 152.4 (1C, quat., C-15, N*C*(O)O), 172.1 (1C, quat., C-12, *C*(O)); m/z (TOF MS EI$^+$) $[M]^+$ 289 (30%); HRMS (TOF MS EI$^+$) mass calculated for $C_{15}H_{15}NO_3S_2$ 289.0773, found 289.0779.

1-allyl-*N*-(methylsulfonyl)-*N*-phenyl-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide

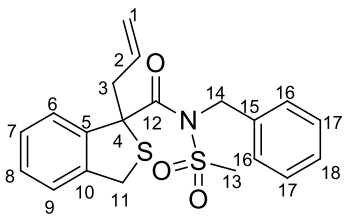
(533a)



Following GP 6 heteroaromatic was obtained as a yellow viscous oil (28 mg, 74% yield); R_f 0.30 (70% hexane:30% EtOAc); ν_{max}(neat) / (cm^{-1}) 2924 w (C-H), 1682 s (C=O), 1355 s (C=C), 1159 s (C-N); δ_H (300 MHz, $CDCl_3$) 2.90 (1H, dd, *J* 14.5, *J* 7.0, H-3, CH_AH_BCH_X), 2.97 (1H, d, *J* 13.1, H-11, SCH_AH_B), 3.09-3.18 (1H, m, H-3, CH_AH_BCH_X), 3.40 (3H, s, H-13, SO_2CH_3), 3.87 (1H, d, *J* 13.1, H-11, SCH_AH_B), 4.91-5.05 (2H, m, H-1, CH_2CH), 5.44-5.61 (1H, m, H-2, CH_2C*H*), 6.67-7.30 (9H, m, H-5-10 and H-15-19, Ph*H*); δ_C (101 MHz, $CDCl_3$) 37.6 (1C, *C*H_2), 41.1 (1C, SO_3CH_3), 46.2 (1C, *C*H_2S), 69.4 (1C, quat., *C*S), 119.5 (1C, CH*C*H_2), 124.7 (1C, Ph*C*), 124.9 (1C, Ph*C*), 127.4 (1C, *C*HCH$_2$), 128.0 (1C, Ph*C*), 128.2 (1C, Ph*C*), 128.6 (1C, Ph*C*), 129.7 (1C, Ph*C*), 131.4 (1C, Ph*C*), 132.8 (1C, Ph*C*), 133.9 (1C, quat., Ph*C*), 140.6 (1C, quat., Ph*C*), 141.9 (1C, quat., NPh*C*), 174.9 (1C, quat., *C*(O)); m/z (TOF MS ES$^+$) $[M+Na]^+$ 396 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{19}H_{19}NO_3S_2Na$ 396.0704, found 396.0698.

1-allyl-*N*-benzyl-*N*-(methylsulfonyl)-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide

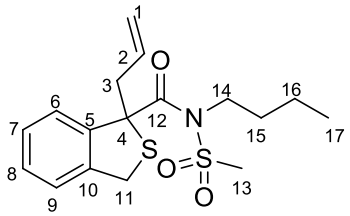
(533b)



Following GP 6, heteroaromatic was obtained as a yellow viscous oil (31 mg, 81% yield); R_f 0.30 (70% hexane:30% EtOAc); ν_{max}(neat) / (cm^{-1}) 2925 w (C-H), 1679 s (C=O), 1351 s

(C=C), 1162 s (C-N); δ_H (300 MHz, $CDCl_3$) 2.92 (3H, s, H-13, SO_2CH_3), overlaps with 3.01-2.95 (1H, m, H-3, $CH_AH_BCH_X$), 3.10 (1H, dd, *J* 14.2, *J* 7.4, H-3, $CH_AH_BCH_X$), 4.19 (1H, d, *J* 14.2, H-14, NCH_AH_B), 4.33 (1H, d, *J* 16.0, H-11, SCH_AH_B), 4.41 (1H, d, *J* 14.2, H-14, NCH_AH_B), 4.83 (1H, d, *J* 16.0, H-11, SCH_AH_B), 4.92-5.05 (2H, m, H-1, $CHCH_2$), 5.46-5.64 (1H, m, H-2, $CHCH_2$), 7.14-7.31 (9H, m, H-6-9 and H-16-18, Ph*H*); δ_C (101 MHz, $CDCl_3$) 38.0 (1C, CH_2), 43.3 (1C, SO_2CH_3), 47.2 (1C, CH_2S), 50.6 (1C, NCH_2), 69.0 (1C, quat., *C*S), 120.1 (1C, $CHCH_2$), 125.2 (1C, Ph*C*), 125.3 (1C, Ph*C*), 127.8 (2C, Ph*C*), 127.9 (1C, $CHCH_2$), 128.4 (2C, Ph*C*), 128.5 (1C, Ph-*C*), 128.6 (1C, Ph*C*), 132.2 (1C, Ph*C*), 135.6 (1C, quat., Ph*C*), 140.2 (1C, quat., Ph*C*), 141.0 (1C, quat., Ph*C*), 175.1 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 410 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{20}H_{21}NO_3S_2Na$ 410.0861, found 410.0859.

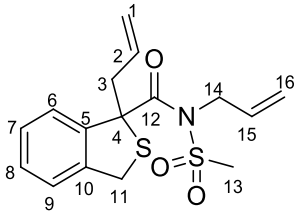
1-allyl-*N*-butyl-*N*-(methylsulfonyl)-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (533c)



Following GP 6, heteroaromatic was obtained as a colourless viscous oil (31 mg, 88% yield); R_f 0.32 (70% hexane:30% EtOAc); ν_{max}(neat) / (cm^{-1}) 2924 w (C-H), 2857 m (C-H), 1673 s (C=O), 1349 s (C=C), 1165 s (C-N); δ_H (300 MHz, $CDCl_3$) 0.54 (5H, m, H-16-17, CH_2CH_3), 1.43-1.67 (2H, m, H-15, CH_2), 2.87 (1H, dd, *J* 13.6, *J* 6.9, H-3, $CH_AH_BCH_X$), 3.03 (1H, ddd, *J* 13.6, *J* 7.1, *J* 4.0, H-3, $CH_AH_BCH_X$), 3.33 (3H, s, H-13, SO_2CH_3), 3.38-3.54 (2H, m, H-14, CH_2), 4.25 (1H, d, *J* 14.2, H-11, SCH_AH_B), 4.45 (1H, d, *J* 14.2, H-11, SCH_AH_B), 4.88-5.02 (2H, m, H-1, CH_2CH), 5.44-5.61 (1H, m, C-2, CH_2CH), 7.13-7.36 (4H, m, H-6-9, Ph*H*); δ_C (101 MHz, $CDCl_3$) 13.4 (1C, CH_2CH_3), 20.1 (1C, CH_2CH_3), 31.4

(1C, CH_2), 38.4 (1C, *C*H_2), 43.3 (1C, SO_3*C*H_3), 47.3 (1C, *C*H_2S), 47.6 (1C, N*C*H_2), 69.1 (1C, quat., *C*S), 119.9 (1C, CH*C*H_2), 124.7 (1C, Ph*C*), 125.4 (1C, Ph*C*), 127.9 (1C, Ph*C*), 128.6 (1C, Ph*C*), 132.4 (1C, *C*HCH$_2$), 140.2 (1C, quat., Ph*C*), 141.5 (1C, quat., Ph*C*), 173.8 (1C, quat., *C*(O)); m/z (TOF MS ES$^+$) $[M+Na]^+$ 376 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{17}H_{23}NO_3S_2Na$ 376.1017, found 376.1014.

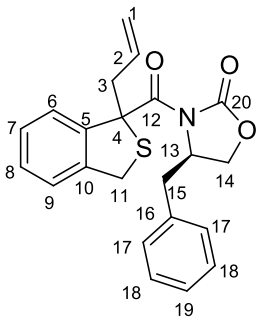
_N_,1-diallyl-_N_-(methylsulfonyl)-1,3-dihydrobenzo[_c_]thiophene-1-carboxamide (533d)



Following GP 6, heteroaromatic was obtained as a colourless viscous oil (30 mg, 90% yield); R_f 0.30 (70% hexane:30% EtOAc); ν_{max}(neat) / (cm^{-1}) 2923 w (C-H), 1674 s (C=O), 1348 s (C=C), 1163 s (C-N); δ_H (300 MHz, $CDCl_3$) 2.89 (1H, dd, *J* 14.3, *J* 6.8, H-3, C*H*$_A$*H*$_B$CH$_X$), 2.98 (1H, m, H-3, C*H*$_A$*H*$_B$CH$_X$), 3.29 (3H, s, H-13, SO_2C*H*$_3$), 4.00-4.19 (2H, m, H-14, C*H*$_A$*H*$_B$CH$_X$), 4.23 (1H, d, *J* 14.2, H-11, SC*H*$_A$*H*$_B$), 4.43 (1H, d, *J* 14.2, H-11, SC*H*$_A$*H*$_B$), 4.89-5.08 (4H, m, H-1, and H-16, 2 × C*H*$_2$CH), 5.36-5.62 (2H, m, H-2, and H-15, CH$_2$C*H*), 7.14-7.35 (4H, m, H-6-9, Ph*H*); δ_C (101 MHz, $CDCl_3$) 38.1 (1C, *C*H_2), 43.3 (1C, SO_3*C*H_3), 47.1 (1C, *C*H_2S), 49.3 (1C, *C*H_2), 69.0 (1C, quat., *C*S), 119.2 (1C, CH*C*H_2), 120.0 (1C, CH*C*H_2), 124.9 (1C, Ph*C*), 125.4 (1C, Ph*C*), 128.0 (1C, Ph*C*), 128.7 (1C, Ph*C*), 131.8 (1C, *C*HCH$_2$), 132.3 (1C, *C*HCH$_2$), 140.2 (1C, quat., Ph*C*), 141.2 (1C, quat., Ph*C*), 173.9 (1C, quat., *C*(O)); m/z (TOF MS ES$^+$) $[M+Na]^+$ 360 (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{16}H_{19}NO_3S_2Na$ 360.0704, found 360.0710.

(4*R*)-3-(1-allyl-1,3-dihydrobenzo[*c*]thiophene-1-carbonyl)-4-benzyloxazolidin-2-one

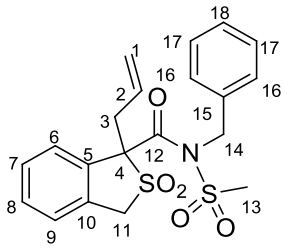
(533e)



Following GP 6, heteroaromatic was obtained as a colourless viscous oil with 1:1 diastereoisomeric ratio (32 mg, 85% yield); R_f 0.30 (70% hexane:30% EtOAc); ν_{max}(neat) / (cm^{-1}) 2988 s (C-H), 2902 s (C-H), 1394 s (C=O), 1264 s (C=O), 1066 s (C=C), 1054 s (C-N); δ_H (300 MHz, $CDCl_3$) 2.72-2.84 (1H, m, H-15, CH_AH_BCH), 3.06 (1H, td, *J* 13.9, *J* 6.8, H-3, CH_AH_BCH$_X$), 3.29-3.32 (1H, m, H-15, CH_AH_BCH), 3.51 (1H, dd, *J* 13.9, *J* 7.0, H-3, CH_AH_BCH$_X$), 4.07-4.31 (4H, m, H-11 and H-14, SCH_AH_B and OCH_AH_BCH$_X$), 4.61-4.76 (1H, m, H-13, NC*H*), 4.95-5.09 (2H, m, H-1, CH_2CH), 5.50-5.67 (1H, m, H-2, CH$_2$C*H*), 7.16-7.41 (9H, m, H-6-9 and H-17-19, Ph*H*); δ_C (101 MHz, $CDCl_3$) 37.1 (1C, *C*H$_2$), 38.1 (1C, *C*H$_2$), 41.1 (1C, SCH$_2$), 57.1 (1C, NCH), 66.2 (1C, OCH$_2$), 69.2 (1C, quat., *C*S), 119.3 (1C, CH*C*H$_2$), 124.8 (1C, Ph*C*), 126.4 (1C, Ph*C*), 127.4 (1C, Ph*C*), 127.9 (1C, Ph*C*), 128.3 (1C, Ph*C*), 128.9 (2C, Ph*C*), 129.5 (2C, PhC), 132.6 (1C, *C*HCH$_2$), 135.3 (1C, quat., Ph*C*), 141.0 (1C, quat., Ph*C*), 141.2 (1C, quat., Ph*C*), 152.2 (1C, quat., N*C*(O)), 172.2 (1C, quat., *C*(O)); m/z (TOF MS ES$^+$) [M+Na]$^+$ 402 (50%); HRMS (TOF MS ES$^+$) mass calculated for $C_{22}H_{21}NO_3SNa$ 402.1140, found 402.1133.

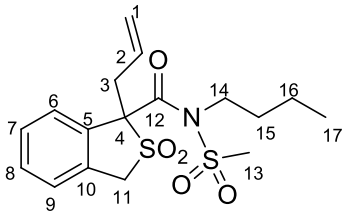
3.3.6 Reactivity post-cyclisation

1-allyl-*N*-benzyl-*N*-(methylsulfonyl)-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide 2,2-dioxide (548a)



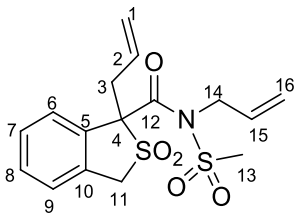
Following GP 17 using thiophene (0.1 mmol, 38 mg), sulfone was prepared in this way to give a colourless oil (39 mg, 92% yield); R_f 0.30 (8:2 EtOAc:hexane); ν_{max}(neat) / (cm^{-1}) 2925 w (C-H), 1689 s (C=O), 1353 s (C=C), 1320 s, 1161 s (C-N); δ_H (300 MHz, $CDCl_3$) 2.81 (3H, s, H-13, SO_2CH_3), overlaps with 2.90 (1H, dd, *J* 14.0, *J* 8.6, H-3, $CH_AH_BCH_X$), 3.40 (1H, ddt, *J* 14.0, *J* 5.8, *J* 1.3, H-3, $CH_AH_BCH_X$), 4.17 (H, d, *J* 15.2, H-11, $SO_2CH_AH_B$), 4.37 (1H, dd, *J* 15.9, *J* 0.8, H-14, NCH_AH_B), 4.45 (1H, d, *J* 15.2, H-11, $SO_2CH_AH_B$), 4.51 (1H, d, *J* 15.9, H-14, NCH_AH_B), 4.90-5.14 (2H, m, H-1, $CHCH_2$), 5.43-5.60 (1H, m, H-2, $CHCH_2$), 7.18-7.49 (9H, m, H-6-9 and H-16-18, Ph*H*); δ_C (101 MHz, $CDCl_3$) 42.9 (1C, CH_2), 43.6 (1C, SO_2CH_3), 52.0 (1C, CH_2SO_2), 55.9 (1C, NCH_2), 78.7 (1C, quat., CSO_2), 122.4 (1C, $CHCH_2$), 125.8 (1C, $CHCH_2$), 127.9 (1C, Ph*C*), 128.2 (1C, Ph*C*), 128.5 (2C, Ph*C*), 129.0 (3C, Ph*C*), 129.2 (1C, Ph*C*), 129.8 (1C, Ph*C*), 134.1 (1C, quat., Ph*C*), 134.5 (1C, quat., Ph*C*), 136.4 (1C, quat., Ph*C*), 169.6 (1C, quat., *C*(O)); m/z (TOF MS ES^+) 442 $[M+Na]^+$ (100%); HRMS (TOF MS ES^+) mass calculated for $C_{20}H_{21}NO_5S_2Na$ 442.0759, found 442.0757.

1-allyl-*N*-butyl-*N*-(methylsulfonyl)-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide 2,2-dioxide (548b)



Following GP 17 using thiophene (0.1 mmol, 35 mg), sulfone was prepared in this way to give a colourless oil (33 mg, 85% yield); R_f 0.33 (8:2 EtOAc:hexane); ν_{max}(neat) / (cm^{-1}) 2961 w (C-H), 2935 w (C-H), 1683 s (C=O), 1351 s (C=C), 1166 s (C-N); δ_H (300 MHz, $CDCl_3$) 0.76 (3H, t, *J* 7.2, H-17, CH_2CH_3), 0.93-1.11 (2H, m, H-16, CH_2), 1.51-1.70 (2H, m, H-15, CH_2), 2.84 (1H, dd, *J* 14.1, *J* 8.4, H-3, $CH_AH_BCH_X$), 3.16-3.36 (3H, m, C-3 and H-14, $CH_AH_BCH_X$ and CH_2), 3.37 (3H, s, C-13, SO_2CH_3), 4.32 (1H, d, *J* 15.9, H-11, $SO_2CH_AH_B$), 4.50 (1H, d, *J* 15.9, H-11, $SO_2CH_AH_B$), 4.91-5.14 (2H, m, H-1, CH_2CH), 5.40-5.58 (1H, m, H-2, CH_2CH), 7.27-7.49 (4H, m, H-6-9, Ph*H*); δ_C (101 MHz, $CDCl_3$) 13.3 (1C, CH_2CH_3), 19.9 (1C, CH_2CH_3), 31.4 (1C, CH_2), 41.9 (1C, CH_2), 44.1 (1C, SO_2CH_3), 48.6 (1C, CH_2SO_2), 56.4 (1C, NCH_2), 78.5 (1C, quat., CSO_2), 119.1 (1C, $CHCH_2$), 122.3 (1C, Ph*C*), 125.6 (1C, Ph*C*), 128.0 (1C, quat., Ph*C*), 128.2 (1C, Ph*C*), 128.9 (1C, $CHCH_2$), 129.3 (1C, Ph*C*), 134.9 (1C, quat., Ph*C*), 168.5 (1C, quat., *C*(O)); m/z (TOF MS ES^+) 408 $[M+Na]^+$ (100%), mass calculated for $C_{17}H_{23}NO_5S_2Na$ 408.0915, found 408.0938.

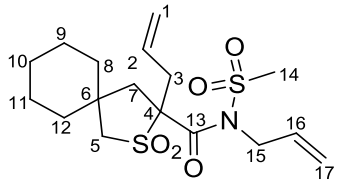
_N_-1-diallyl-_N_-(methylsulfonyl)-1,3-dihydrobenzo[_c_]thiophene-1-carboxamide 2,2-dioxide (548c)



Following GP 17 using thiophene (0.1 mmol, 34 mg), sulfone was prepared in this way to give a colourless oil (36 g, 97% yield); R_f 0.30 (8:2 EtOAc:hexane); ν_{max}(neat) / (cm^{-1}) 2935 w (C-H), 1680 s (C=O), 1344 s (C=C), 1320 s, 1164 s (C-N); δ_H (300 MHz, $CDCl_3$) 2.83 (1H, dd, *J* 13.9, *J* 8.5, H-3, C*H*$_A$*H*$_B$CH$_X$), 3.33 (3H, s, H-13, SO_2CH_3), overlaps with 3.37 (1H, m, H-3, C*H*$_A$*H*$_B$CH$_X$), 3.77-3.94 (2H, m, H-14, C*H*$_A$*H*$_B$CH$_X$), 4.36 (1H, d, *J* 16.2, H-11, $SO_2CH_AH_B$), 4.51 (1H, d, *J* 16.2, H-11, $SO_2CH_AH_B$), 4.92-5.15 (2H, m, C-16, C*H*$_2$CH), 5.16-5.30 (2H, m, C-1, C*H*$_2$CH), 5.41-5.58 (1H, m, C-15, CH$_2$C*H*), 5.70-5.88 (1H, m, C-2, CH$_2$C*H*), 7.27-7.51 (4H, m, H-6-9, Ph*H*); δ_C (101 MHz, $CDCl_3$) 42.3 (1C, *C*H$_2$), 43.9 (1C, SO_2CH_3), 50.7 (1C, *C*H$_2$SO$_2$), 56.0 (1C, *C*H$_2$), 78.4 (1C, quat., *C*SO$_2$), 121.0 (1C, CH*C*H$_2$), 122.4 (1C, CH*C*H$_2$), 125.8 (1C, Ph*C*), 127.9 (1C, Ph*C*), 128.2 (1C, quat., Ph*C*), 129.1 (1C, Ph*C*), 129.5 (1C, *C*HCH$_2$), 129.8 (1C, Ph*C*), 131.8 (1C, *C*HCH$_2$), 134.4 (1C, quat., Ph*C*), 168.8 (1C, quat., *C*(O)); m/z (TOF MS ES$^+$) 392 $[M+Na]^+$ (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{16}H_{19}NO_5S_2Na$ 392.0609, found 392.0602.

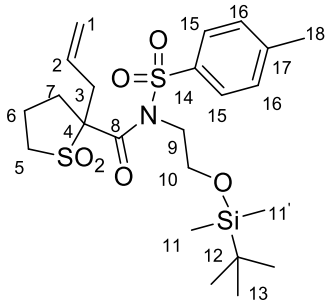
***N*-3-diallyl-*N*-(methylsulfonyl)-2-thiaspiro[4.5]decane-3-carboxamide 2,2-dioxide**

(548d)



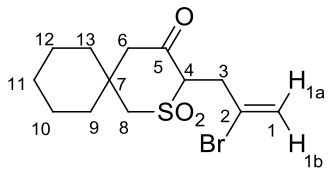
Following GP 17 using thiophene (0.1 mmol, 36 mg), sulfone was prepared in this way to give a colourless oil (37 mg, 96% yield); R_f 0.30 (7:3 EtOAc:hexane); ν_{max}(neat) / (cm^{-1}) 2930 s (C-H), 2855 m (C-H), 1684 s (C=O), 1354 s (C=C), 1306 s, 1167 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.19-1.86 (11H, m, H-8-12, C*H*$_2$, cyclohexyl and H-5, $SO_2CH_AH_B$), 2.43-2.58 (1H, m, H-3, $CH_AH_BCH_X$) 2.93-3.12 (2H, m, H-3 and H-5, $CH_AH_BCH_X$ and $SO_2CH_AH_B$), 3.19-3.47 (5H, m, H-14 and H-7, SO_2CH_3 and CH_AH_B), 4.44-4.65 (2H, m, H-15, C*H*$_2$), 5.14-5.26 (2H, m, H-1, C*H*$_2$CH), 5.27-5.46 (2H, m, H-17, C*H*$_2$CH), 5.49-5.66 (1H, m, H-2, C*H*CH_2), 5.85-6.03 (1H, m, H-16, C*H*CH_2); δ_C (101 MHz, $CDCl_3$) 22.3 (1C, *C*H_2, cyclohexyl), 22.9 (1C, *C*H_2, cyclohexyl), 25.3 (1C, *C*H_2, cyclohexyl), 35.9 (1C, *C*H_2, cyclohexyl), 36.4 (1C, quat., cyclohexyl), 39.7 (1C, *C*H_2, cyclohexyl), 40.3 (1C, *C*H_2), 42.4 (1C, SO_2CH_3), 46.1 (1C, *C*H_2), 49.7 (1C, *C*H_2SO_2), 62.5 (1C, *C*H_2), 74.2 (1C, quat., *C*SO_2), 120.0 (1C, CH*C*H_2), 121.5 (1C, CH*C*H_2), 129.9 (1C, *C*HCH_2), 132.5 (1C, *C*HCH_2), 169.0 (1C, quat., *C*(O)); m/z (TOF MS ES^+) 412 $[M+Na]^+$ (100%); HRMS (TOF MS ES^+) mass calculated for $C_{17}H_{27}NO_5S_2Na$ 412.1228, found 412.1230.

2-allyl-*N*-(2-((tert-butyldimethylsilyl)oxy)ethyl)-*N*-tosyltetrahydrothiophene-2-carboxamide dioxide (548e)



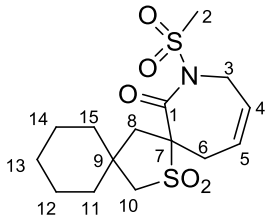
Following GP 17 using thiophene (0.1 mmol, 48 mg), sulfone was prepared in this way to give a colourless oil (42 mg, 82% yield); R_f 0.30 (8:2 EtOAc:hexane); ν_{max}(neat) / (cm^{-1}) 2951 s (C-H), 2856 s (C-H), 1683 s (C=O), 1354 s (C=C), 1169 s (C-N); δ_H (300 MHz, $CDCl_3$) 0.06 (3H, s, H-11, SiC*H*$_3$), 0.07 (3H, s, H-11', SiC*H*$_3$), 0.89 (9H, s, H-13, SiC(C*H*$_3$)$_3$), 1.84-1.98 (2H, m, H-6, C*H*$_A$*H*$_B$CH$_X$), 2.04 (1H, dd, *J* 7.2, *J* 4.8, H-7, CH$_X$C*H*$_A$*H*$_B$CH$_X$), 2.40 (3H, s, H-18, TsC*H*$_3$), 2.49 (1H, dd, *J* 15.0, *J* 9.1, H-3, C*H*$_A$*H*$_B$CH$_X$), 2.71-2.84 (1H, m, H-7, C*H*$_A$*H*$_B$CH$_X$), 3.05-3.14 (2H, m, overlapping dd, H-5, 2 × SO$_2$C*H*$_A$*H*$_B$), 3.27 (1H, dd, *J* 15.0, *J* 4.8, H-3, C*H*$_A$*H*$_B$CH$_X$), 3.93-4.21 (4H, m, H-9 and H-10, NC*H*$_2$C*H*$_2$O), 5.11-5.22 (2H, m, H-1, C*H*$_2$CH), 5.44-5.61 (1H, m, H-2, CH$_2$C*H*), 7.27 (2H, d, *J* 8.2, H-16, Ph*C*), 7.83 (2H, d, *J* 8.2, H-15, Ph*C*); δ_C (101 MHz, $CDCl_3$) -5.3 (2C, Si(*C*H$_3$)$_2$), 18.4 (1C, *C*H$_2$, cyclopentyl), 21.7 (3C, C(*C*H$_3$)$_3$), 25.9 (1C, Ts*C*H$_3$), 34.5 (1C, *C*H$_2$), 37.7 (1C, C*C*H$_2$, cyclopentyl), 49.9 (1C, *C*H$_2$S), 54.2 (1C, N*C*H$_2$), 62.2 (1C, quat., *C*(CH$_3$)$_3$), 62.3 (1C, O*C*H$_2$), 72.3 (1C, quat., *C*SO$_2$), 120.9 (1C, CH*C*H$_2$), 128.7 (2C, Ph*C*), 129.2 (2C, Ph*C*), 130.6 (1C, *C*HCH$_2$), 136.2 (1C, quat., Ph*C*), 144.6 (1C, quat., Ph*C*), 167.1 (1C, quat., *C*(O)); m/z (TOF MS ES$^+$) 538 [M+Na]$^+$ (100%); HRMS (TOF MS ES$^+$) mass calculated for $C_{23}H_{37}NO_6S_2SiNa$ 538.1729, found 538.1739.

3-(2-bromoallyl)-2-thiaspiro[5.5]undecan-4-one 2,2-dioxide (548f)



Following GP 17, using thiopyran (0.1 mmol, 30 mg), heterocycle was isolated as a colourless viscous oil (11 mg, 34% yield); R_f 0.30 (7:3 EtOAc:hexane); ν_{max}(neat) / (cm^{-1}) 2924 s (C-H), 2854 m (C-H), 1723 w (C=O), 1456 w (S=O), 1066 s (C=C); δ_H (300 MHz, $CDCl_3$) 1.31-1.85 (10H, m, H-9-13, CH_2, cyclohexyl), 2.50 (1H, d, *J* 12.6, H-8, CH_AH_B), 2.76 (1H, dd, *J* 12.6, *J* 1.8, H-8, CH_AH_B), 3.05 (1H, dd, *J* 15.1, *J* 4.6, H-3, CH_AH_B), 3.16-3.34 (2H, m, H-3 and H-6, 2 × CH_AH_B), 3.52 (1H, dt, *J* 8.4, *J* 4.2, H-6, SO_2C*H*), 4.34 (1H, dd, *J* 7.7, *J* 4.6, H-4, SO_2C*H*), 5.55 (1H, d, *J* 2.0, H-1a, C(Br)CH_{trans}), 5.85-5.91 (1H, m, H-1b, C(Br)CH_{cis}); δ_C (101 MHz, $CDCl_3$) 21.2 (1C, *C*H_2, cyclohexyl), 21.4 (1C, *C*H_2, cyclohexyl), 25.3 (1C, *C*H_2, cyclohexyl), 32.1 (1C, *C*H_2C(Br)), 32.2 (1C, *C*H_2, cyclohexyl), 34.0 (1C, quat., cyclohexyl), 40.1 (1C, *C*H_2, cyclohexyl), 52.6 (1C, *C*H_2), 59.9 (1C, *C*H_2), 71.9 (1C, *C*H), 121.4 (1C, C(Br)*C*H_2), 128.0 (1C, quat., *C*(Br)CH_2), 195.0 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na(^{81}Br)]^+$ 359 (95%), $[M+Na(^{79}Br)]^+$ 357 (100%), HRMS (TOF MS ES^+) mass calculated for $C_{13}H_{19}O_3Na^{79}BrS$ 357.0136, found 357.0129.

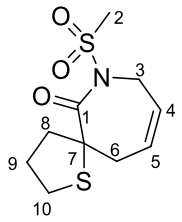
7-(methylsulfonyl)-1-thia-7-azaspiro[4.6]undec-9-en-6-one 1,1-dioxide (552a)



Following GP 18 ring closed metathesis product was obtained as a colourless oil (16 mg, 87% yield); R_f 0.29 (1:1 EtOAc:hexane); ν_{max}(neat) / (cm^{-1}) 2929 m (C-H), 2856 m (C-H), 1689 s (C=O), 1454 w (S-O), 1348 s (C=C), 1309 s, 1165 s (C-N); δ_H (300 MHz, $CDCl_3$)

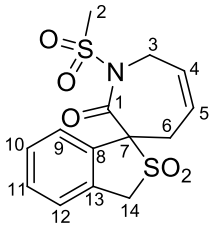
1.15-1.79 (11H, m, H-8 and H-11-15, CH_AH_B and 5 × CH_2, cyclohexyl), 2.66-2.96 (2H, m, H-6, CH_AH_BCH), 3.02-3.29 (3H, m, H-8 and H-10, CH_AH_B and 2 × C$H_AH_B$$SO_2$), 3.32 (3H, s, H-2, SO_2CH_3), 4.49-4.70 (2H, m, H-3, NCH_AH_BCH), 5.83-6.01 (2H, m, H-5 and H-4, 2 × CH_2C*H*); δ_C (101 MHz, $CDCl_3$) 22.5 (1C, *C*H_2, cyclohexyl), 22.9 (1C, *C*H_2, cyclohexyl), 25.3 (1C, *C*H_2, cyclohexyl), 35.2 (1C, *C*H_2, cyclohexyl), 36.8 (1C, *C*H_2, cyclohexyl), 39.0 (1C, *C*H_2SO_2), 41.1 (2C, 2 × *C*H_2), 41.9 (1C, SO_2*C*H_3), 49.7 (1C, quat., cyclohexyl), 61.9 (1C, N*C*H_2), 74.1 (1C, quat., *C*C(O)), 125.1 (1C, CH_2C*H*CH), 129.2 (1C, CH*C*H), 170.5 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M]^+$ 384 (100%), mass calculated for $C_{15}H_{23}NO_5S_2Na$ 384.0915, found 384.0921.

7-(methylsulfonyl)-1-thia-7-azaspiro[4.6]undec-9-en-6-one (552b)



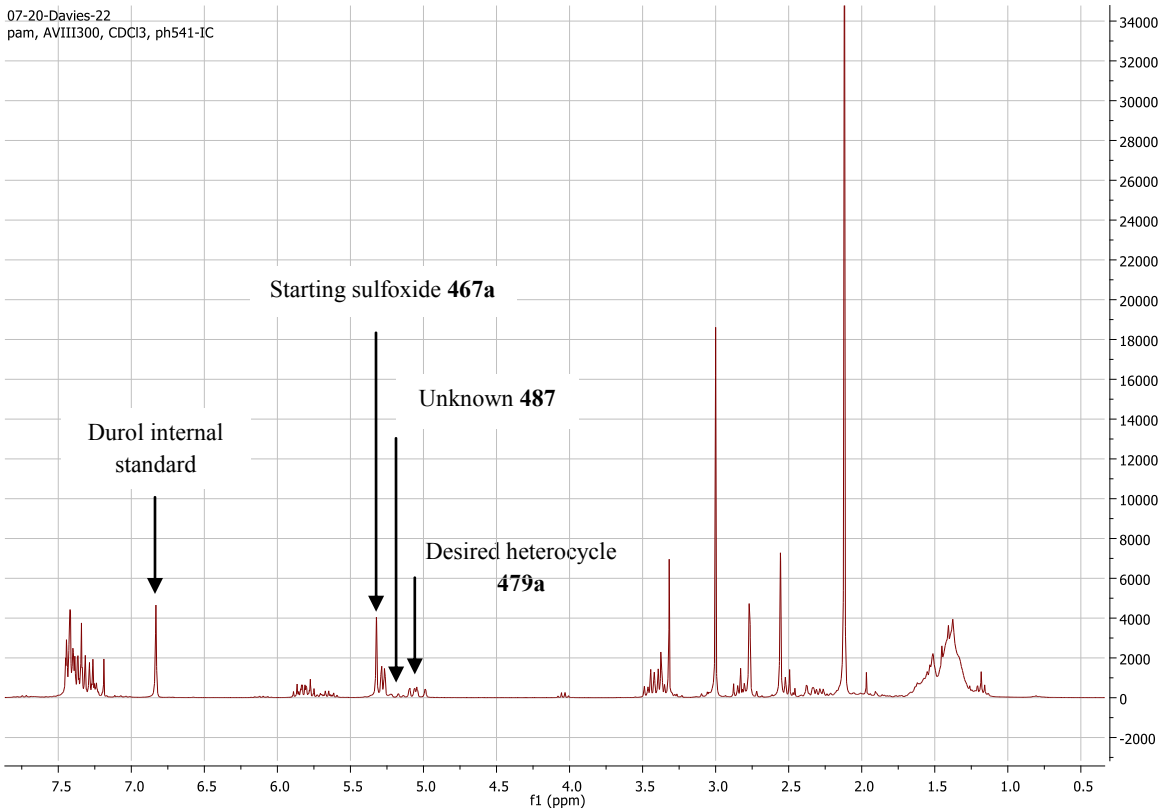
Following GP 18 ring closed metathesis product was obtained as a colourless oil (11 mg, 81% yield); R_f 0.29 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 2932 m (C-H), 1683 s (C=O), 1344 s (C=C), 1163 s (C-N); δ_H (300 MHz, $CDCl_3$) 1.57-1.69 (1H, m, H-9, C$H_AH_B$$CH_X$), 2.00-2.22 (2H, m, H-8, C$H_AH_B$$CH_X$), 2.39-2.53 (1H, m, H-9, C$H_AH_B$$CH_X$), 2.87-3.10 (4H, m, H-10 and H-6, 2 × C$H_AH_B$$CH_X$), 3.31 (3H, s, H-2, SO_2CH_3), 4.61-4.83 (2H, m, H-3, NCH_AH_BCH), 5.65-5.85 (2H, m, H-4 and H-5, 2 × CH_2C*H*); δ_C (101 MHz, $CDCl_3$) 29.8 (1C, *C*H_2, cyclopentyl), 34.5 (1C, *C*H_2, cyclopentyl), 39.7 (1C, *C*H_2), 41.9 (1C, *C*H_2), 42.4 (1C, SO_2*C*H_3), 43.1 (1C, N*C*H_2), 60.4 (1C, quat., *C*C(O)), 123.4 (1C, CH_2C*H*CH), 129.8 (1C, CH*C*H), 174.5 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 284 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{10}H_{15}NO_3S_2Na$ 284.0391, found 284.0386.

1-(methylsulfonyl)-1,7-dihydro-3'H-spiro[azepine-3,1'-benzo[c]thiophen]-2(4H)-one 2',2'-dioxide (552c)

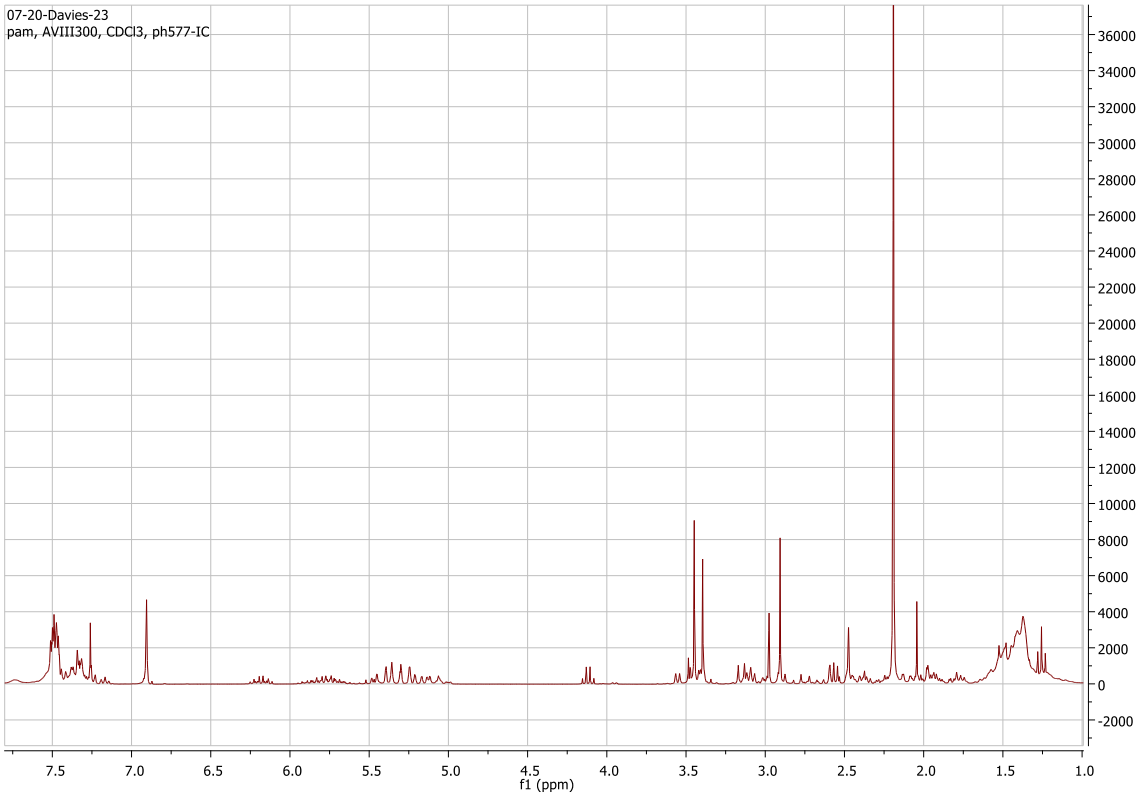


Following GP 18 ring closed metathesis product was obtained as a colourless oil (16 mg, 81% yield); R_f 0.29 (7:3 hexane:EtOAc); ν_{max}(neat) / (cm^{-1}) 2934 m (C-H), 1667 s (C=O), 1347 s (C=C), 1317 s (C=C), 1164 s (C-N); δ_H (300 MHz, $CDCl_3$) 2.96-3.04 (1H, m, H-6,), 3.31 (3H, s, H-2, SO_2CH_3), 3.32-3.40 (1H, m, H-6, $CH_AH_BCH_X$), 4.29-4.75 (4H, m, H-3 and H-14, $CH_AH_BCH_X$ and NCH_AH_BCH), 6.08-6.33 (2H, m, H-4 and H-5, 2 × CH_2CH), 7.25-7.46 (4H, H-9-12, Ph*H*); δ_C (101 MHz, $CDCl_3$) 29.9 (1C, CH_2), 39.7 (1C, CH_2), 41.8 (1C, CH_2), 42.0 (1C, SO_2CH_3), 56.4 (1C, NCH_2), 79.2 (1C, quat., *C*C(O)), 125.4 (1C, CH_2CHCH), 125.6 (1C, Ph*C*), 127.9 (1C, Ph*C*), 129.3 (1C, Ph*C*), 129.8 (1C, Ph*C*), 130.0 (1C, CH*C*H), 130.3 (1C, quat., Ph*C*), 138.4 (1C, quat., Ph*C*), 170.1 (1C, quat., *C*(O)); m/z (TOF MS ES^+) $[M+Na]^+$ 342 (100%); HRMS (TOF MS ES^+) mass calculated for $C_{14}H_{15}NO_5S_2Na$ 342.0470, found 342.0466.

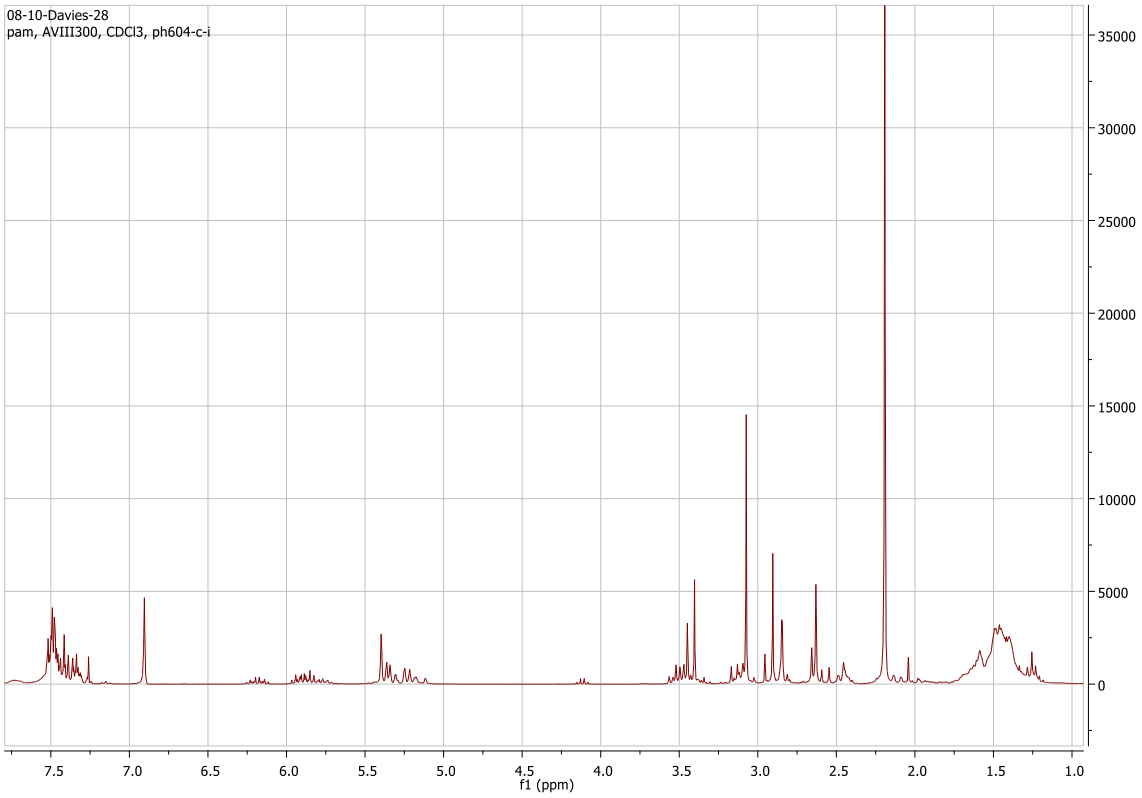
Chapter 4. Appendices



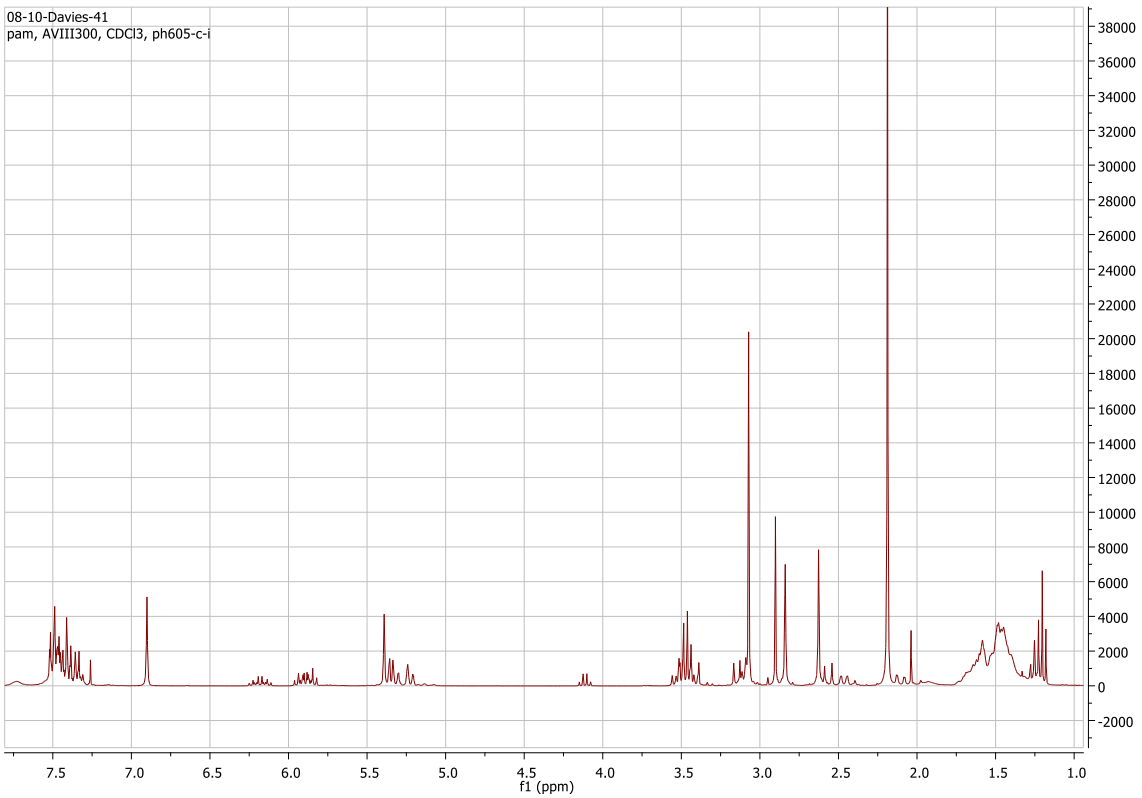
Spectra 1. IPrAuCl/AgOTs, dichloromethane, rt.



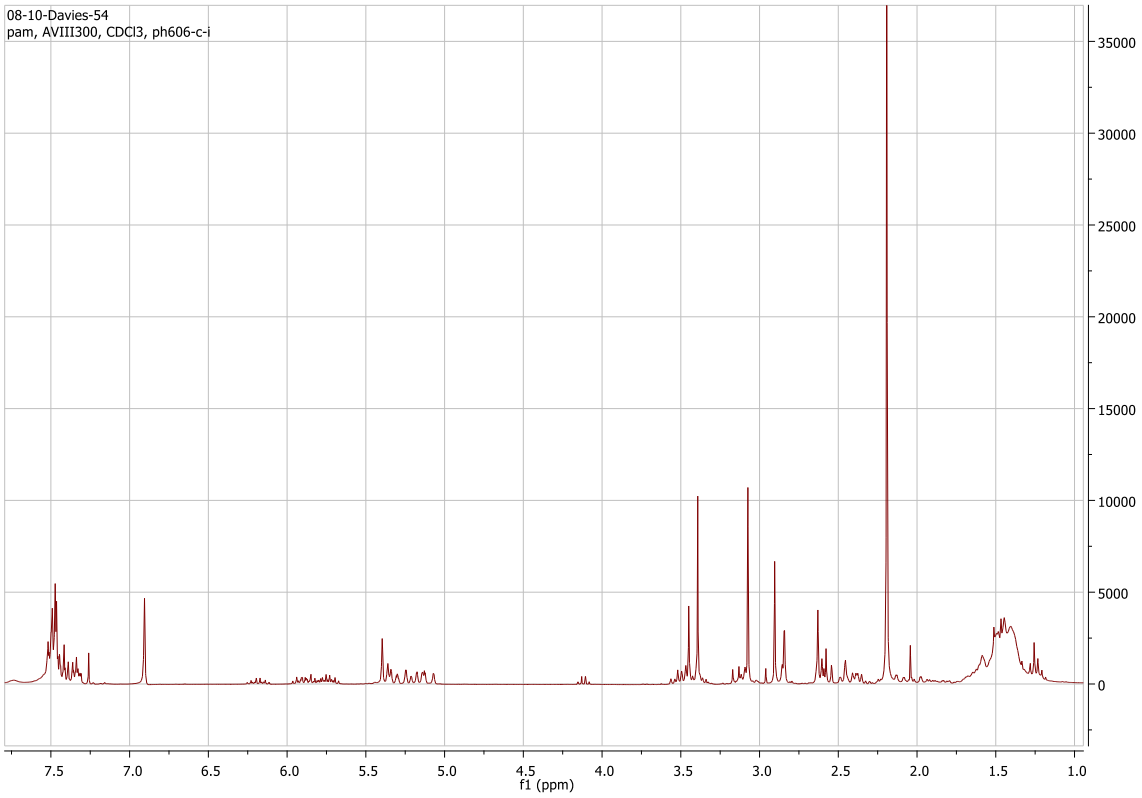
Spectra 2. PPh_3AuNTf_2, dichloromethane, rt.



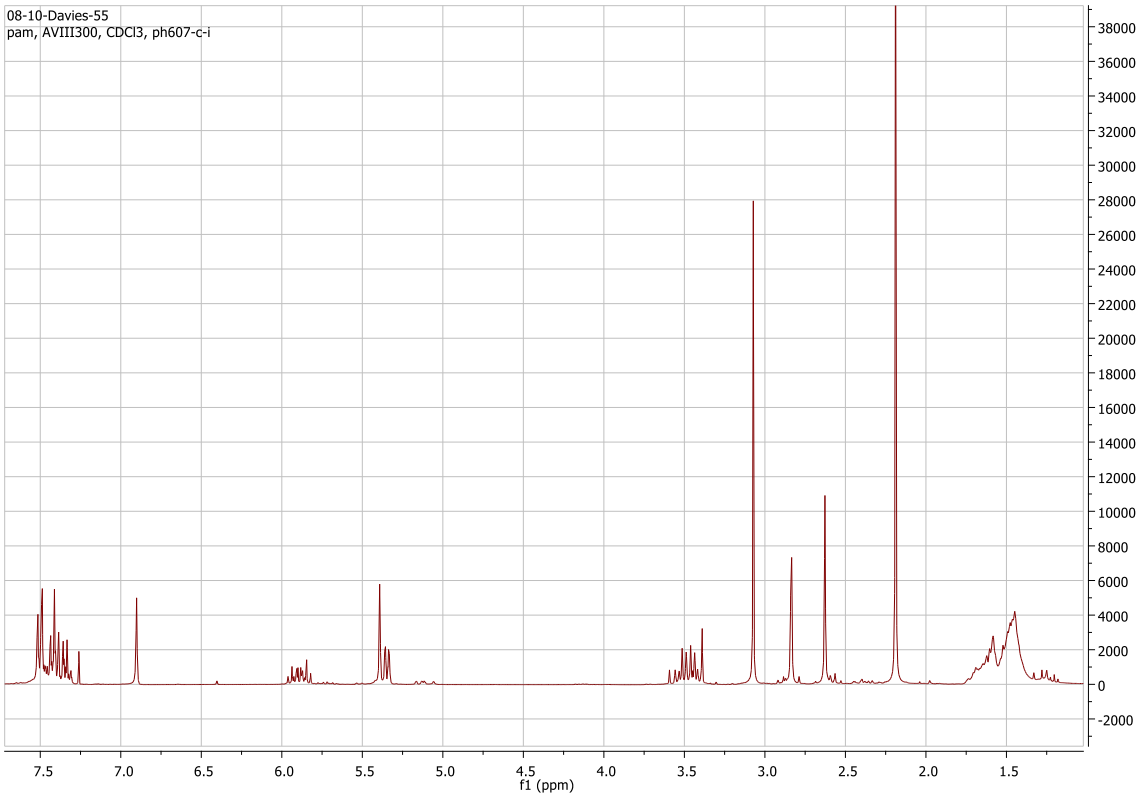
Spectra 3. IPrAuCl/AgOTf, dichloromethane, rt.



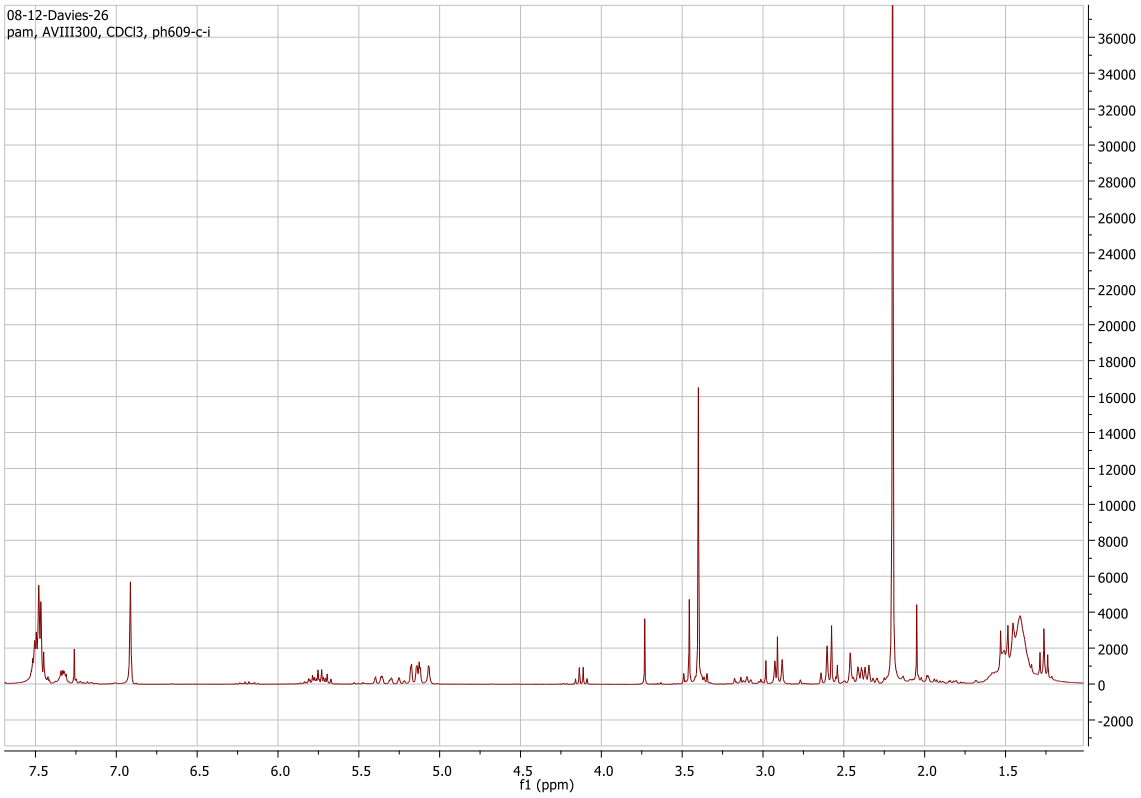
Spectra 4. IPrAuCl/$AgSbF_6$, dichloromethane, rt.



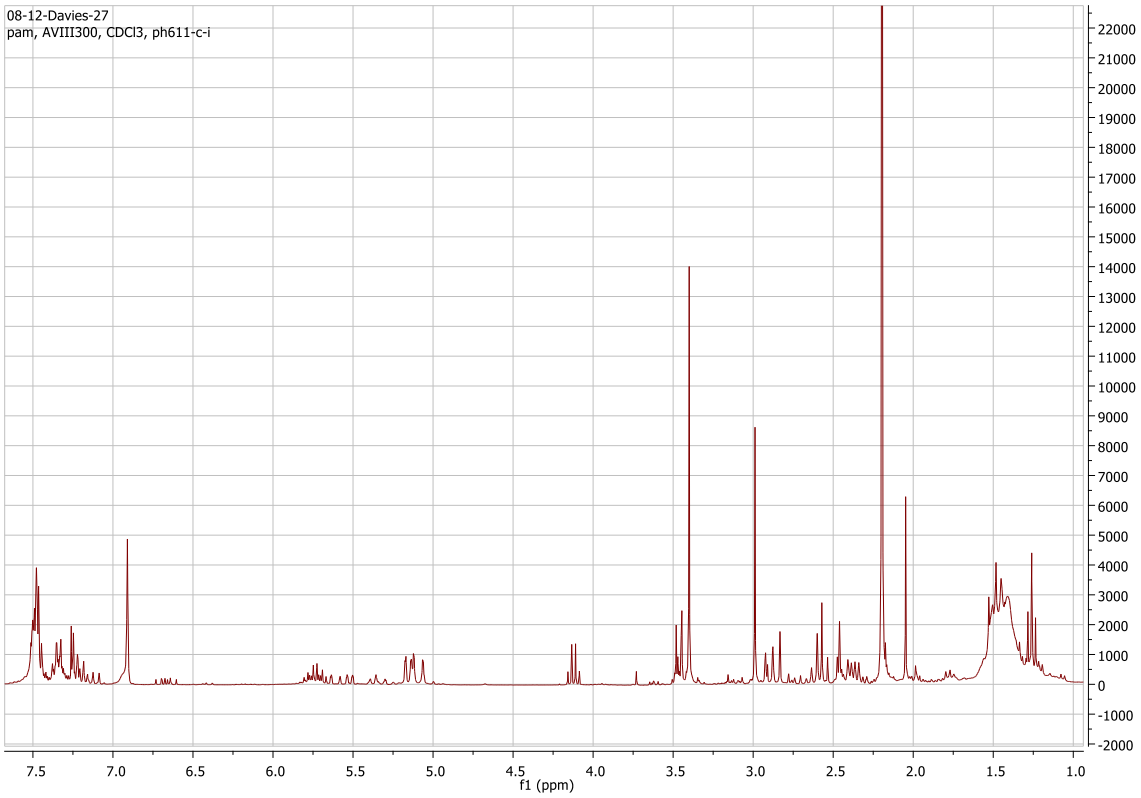
Spectra 5. IPrAuCl/$AgNTf_2$, dichloromethane, rt.



Spectra 6. Au-**I**, dichloromethane, rt.



Spectra 7. PrAuCl/AgOTs, 1,2-dichloroethane, 70°C.



Spectra 8. IPrAuCl/$AgSbF_6$/ 1,2-dichloroethane, 70°C.

Chapter 5. References

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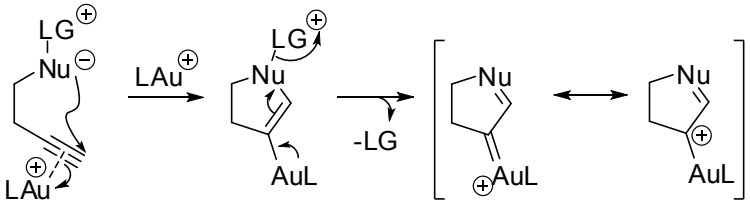

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