Gold-Catalysed Reactions of Alkynyl Sulfoxides

by

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Abstract

Gold $\pi$-catalysis has been used to overcome many challenges in synthesis, either by achieving complexity over few steps or providing a means to access formerly elusive functionality.

This thesis details the development of a gold-catalysed reaction of alkynyl sulfoxides. The reaction of these 1,6-enynes proceeds via an intramolecular oxidative [2+1] cycloaddition. These transformations gave a range of novel, isolable thiabicyclo[3.1.0]hexanes. This previously unreported methodology gives rise to a new way of synthesising heterocycles but also proceeds via a carbenoid centre adjacent to a sulfoxide moiety – this combination of functionality is the first of its kind in acyclic systems – opening up a new class of $\alpha$-carbenoid sulfoxides. The same functionality has not been achieved using classical approaches. Optimisation of the reaction was performed. The conditions were then applied to a range of alkynyl sulfoxides to explore their reaction profiles.
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<tr>
<td>°C</td>
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<tr>
<td>Å</td>
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</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>app.</td>
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<tr>
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</tr>
<tr>
<td>br</td>
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</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>cat.</td>
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</tr>
<tr>
<td>cm(^{-1})</td>
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<td>doublet</td>
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<tr>
<td>1,2-DCE</td>
<td>1,2-dichloroethene</td>
</tr>
<tr>
<td>DHP</td>
<td>3,4-dihydropyran</td>
</tr>
<tr>
<td>DPAA</td>
<td>diphenylacetic acid</td>
</tr>
<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>EDG</td>
<td>electron donating group</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact ionisation</td>
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<td>electronspray ionisation</td>
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<tr>
<td>Et</td>
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</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>eq</td>
<td>equivalent</td>
</tr>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>mCPBA</td>
<td><em>meta</em>-chloroperbenzoic acid</td>
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<tr>
<td>mg</td>
<td>milligram(s)</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
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<tr>
<td>MLCT</td>
<td>metal-to-ligand charge transfer</td>
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<tr>
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<td>nanometre(s)</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>[O]</td>
<td>oxidation</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PKF</td>
<td>perfluorokerosene</td>
</tr>
<tr>
<td>ppm</td>
<td>part(s) per million</td>
</tr>
<tr>
<td>Pr</td>
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<td>Py</td>
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</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>quin</td>
<td>quintet</td>
</tr>
<tr>
<td>Rf</td>
<td>retention factor</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
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<td>Definition</td>
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<td>----------------------</td>
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</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyl diphenylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMB</td>
<td>1,2,4,5-tetramethylbenzene</td>
</tr>
<tr>
<td>TMS</td>
<td>tetramethylsilane</td>
</tr>
<tr>
<td>$\nu$</td>
<td>frequency</td>
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Chapter 1: Introduction
1.1 Gold

The beauty of gold has seen many men admire it, fight for it and die for it. Its glimmering lustrous splendour meant that gold was long regarded as precious before it was ever used as currency by the Hittites as early as 1600 BC. From Homer in the “Iliad” mentioning gold as the glory of immortals and Jason and the Argonauts’ quest to search for the Golden Fleece – gold has always been associated with power, wealth and influence. It gave birth to the beginnings of chemistry in the form of alchemy, in which the most sought after goal in the west was the philosopher’s stone which could fashion gold from metals such as lead and was also the elixir of life. It is the scarcity of the metal and its resistance to tarnish, malleability and durability, even once dissolves in aqua regia it can be recovered: which has meant gold has survived as a source of fortune whilst around it civilisations have risen and fallen.

More recently, within the last century it has been employed not only as a gold standard or admired as decorative pieces but utilised in technology – in semi-conductors, wires, relay contacts, its inert nature means it is ideal inside peoples’ mouths as gold crowns on decayed teeth or as a treatment for diseases such as arthritis. Although branches of science embraced gold – organic chemistry was slow to do so at first, until interest in this rare, beautiful and versatile element sparked the second and some would argue more important gold rush.
1.2 Gold as a catalyst

Organo-gold chemistry, the chemistry of compounds containing one or more Au-C σ or π-bonds still remains a fairly new but rapidly growing field of research.² By the 1970s there was already significant research into the chemistry of ‘noble metals’³ and also their potential organic compounds, particularly the chemistry of iridium and platinum.⁴ This led to a natural progression of research into gold compounds and the potential to explore similar reactivity to previously studied organometallic species and their possible uses as heterogeneous or homogenous catalysts in organic synthesis.⁵

In recent years there has been significant proliferation in the use of catalysis in industry⁶ and it has fast become one of the most important features of large-scale production. The attraction is based on lower activation energies, higher selectivity and reduced costs. There are social implications of developing better catalysts too, as over 80% of all man-made resources are synthesised using some form of catalyst.⁷

The last decade has seen an increase in the number of articles published focusing on homogenous gold-catalysis and its various applications to solve complex compound syntheses⁸ as a means of accessing structures in fewer steps with much higher yields. As a result, much research has been undertaken to understand and report methodology⁹ and mechanisms⁵ of these catalysis reactions.¹⁰,¹¹
1.2.1 Reactivity

Gold in particular can adopt a number of coordination numbers and has been studied from an organometallic viewpoint, but unlike platinum or iridium, gold was wrongfully regarded to be ‘catalytically dead’, whereby the catalyst was totally or partially deactivated. Although there were some articles prior to the 1970s showing some applications of gold as a catalyst, no one had yet demonstrated or postulated any novel research which could reveal any reactivity which would set gold apart as better than previously studied metals.

However in 1973 a communication from Bond and co-workers was published which proved gold’s ability to act as a good catalyst with the hydrogenation of olefins. But there was still little progression in the field until the 1980s, until Hutchings and Haruta both published on heterogeneous catalysis, describing the oxidation of CO and later the formation of vinyl chloride from ethyne via hydrochlorination, they provided for the first time more convincing results of gold’s ability to catalyse reactions, this research was the first of its kind to indicate gold as a preferred catalyst over other transition metals.

Gold-catalysis is divided into two domains, heterogeneous catalysis and homogenous catalysis. The use of thiol-monolayer gold surfaces or nanoparticles is classed as heterogeneous catalysis, this is commonly known as a ‘supported metal catalyst’ and because of its solid nature, it is usually in a different phase from the reaction mixture, which is most likely to be in the liquid phase. Homogenous catalysis usually occurs when the gold(I) or (III) species is present in a salt form or part of a larger organometallic complex, which is dissolved in liquid, and therefore in the same phase as the reactants, this type of catalysis can be applied to organic synthesis in an easier manner.
Utilising gold-catalysis in organic synthesis for varied types of reactions offers many advantages over conventional methods, such as: mild reactions at lower temperatures, good chemoselectivity, less complex work-ups, tolerance of water and more efficient access to highly complex compounds. There is also a stability arising from that fact that there is a high oxidation potential between gold(I) and gold(III) – this makes gold very stable under non-inert conditions.\(^5\)

It was not until the late 1980s that there were reports of successful homogenous gold-catalysis in an interesting and transferable context. Ito et al. were the first to use gold-catalysis to carry out an asymmetric aldol reaction. There had been interest in enantioselective aldol reactions of enolates with aldehydes with the aim of synthesising β-hydroxycarbonyl species, however with little luck using conventional methods which had been focussing on the development of chiral enolates, Ito’s research used a chiral ferrocenylphosphine ligand 4 complexed with a gold(I) species 3, to catalyse the reaction between methyl isocyanoacetate 2 with aldehydes 1 – a reaction which added a carbon nucleophile to a carbonyl.\(^23\)

![Scheme 1: Ito’s gold-catalysed asymmetric aldol reaction](image)
Utimoto and co-workers used a gold(III) species in a reaction between water and alkynes, however it was not until nearly a decade later that Telas demonstrated that this method was not ideal as it rendered the gold(III) species ‘catalytically dead’ as a result of the gold-catalyst being reduced to a metallic gold species and instead proposed his own process for the addition of alcohols to alkynes, using a ligand complexed gold(I) species (Scheme 2) this amendment yielded very good turnover numbers (TONs) and turnover frequencies (TOFs).

![Scheme 2: Addition of an alcohol to an alkyne](image)

The last decade has seen a sharp increase in the number of articles published focusing on homogenous gold-catalysis as its utilisation in complex compound syntheses. There has been an increase in reports of methodology and proposed processes of these catalysis reactions. Figure 1 shows how the number of publications relating to gold-catalysis has changed within the past century.
a) number of articles published on ‘gold-catalysis’, b) number of articles published on ‘homogenous catalysis’. There is a large increase of interest in homogenous catalysis starting in 2005 and continuing up until today.

Figure 1: Change in number of publications relating to gold-catalysis in recent years

1.2.2 Relativistic effects

Gold as a group 11 transition metal, along with copper and silver; has the ground atomic state of $^2S$ with an atomic mass of 196.97 amu, the s electrons in atoms with a large nuclear charge (Z) are more likely to be influenced by relativistic effects. Reviews by Pyykkö\textsuperscript{28} have discussed these relativistic effects in detail. These relativistic effects can be used to explain the many properties of gold, from its colour to its differing chemistry from neighbouring elements.\textsuperscript{29,30}

Because of the relativistic effects the s and p electrons in the core states become more tightly held and the orbitals appear as if contracted in comparison to the lack of this effect, due to experiencing the unshielded potential of the nucleus and therefore display a much
larger ionisation energy. Figure 2\textsuperscript{28} shows the relativistic contraction of the 6s shell for element Cs to Fm, the contraction seen for gold is largest from any of the other elements. The d and f electrons however become increasingly shielded and do not feel the same attraction to the nucleus and therefore the orbitals become larger, expanding further away from the core. The 6s levels and 5d levels move closer to becoming degenerate, with the 6s stabilising and moving down in energy and vice versa with the 5d levels, to a point where sd hybridised bonding is improved. This would not be observed if gold did not display relativistic effects.

As the d-orbital becomes more spacious there is a decrease in the electron-electron repulsions and as a direct result of this there is a drop in the ionisation energy and the likeliness of the atom being involved in orbital interactions increases as the possibility of charge interactions decreases.\textsuperscript{31} These electronic characteristics of gold gear it towards its ability to act in an electrophilic nature with π-systems; as a π-Lewis acid.

![Figure 2: Relativistic contraction of the 6s shell for element Cs to Fm](image-url)
A result of this relativistic effect can be seen in the shortening of the bond lengths between the metal centre and the ligand. This was noted by Soboroff in 1975. Analysis of the complex AuCl(PPh₃)₅ showed a pronounced difference between the bond length of Au-PPh₃ and Au-Cl (the bond lengths being 2.235 Å and 2.279 Å respectively), hence the metal-ligand bond is shortened and strengthened. This difference was reported to be a consequence of electronegativity but also the presence of relativistic effects as this variance was observed to occur more drastically with gold in comparison to the other transition metals.  

\[
\text{Ph₃P} \overset{a}{\text{Au}} \overset{b}{\text{Cl}}
\]

\[
\begin{align*}
\alpha &= 179.6^\circ \\
n &= 2.235 \text{ Å} \\
b &= 2.279 \text{ Å}
\end{align*}
\]

**Figure 3: Structure of AuCl(PPh₃)**

Whilst gold(III) complexes prefer to adopt a square planar conformation, gold(I) complexes more readily assume a linear conformation in LAuCl compounds. Usually in homogenous catalysis the active species LAu⁺X⁻ is formed by combining AuCl and AgX *in situ*. This provides a suitable coordination site for the π-system. However LAuX compounds can be formed prior to the catalysis and stored, this pre-formed catalyst is usually more stable in air than the corresponding AgX salt.  

Pre-formed catalysts allow for a more thorough investigation of the function of the ancillary ligand by eliminating the prospect of co-catalysis by the silver salt that remains in the reaction vessel when using gold halide species and counterions separately.
10

Scheme 3: Metathesis reaction between gold chloride and a counterion

1.2.3 Alkyne π-acid activation

Gold is able to coordinate to C-C multiple bonds as a π-ligand; this interaction can then be described using the inorganic Dewar-Chatt-Duncanson (DCD) model. From an organometallic perspective the model is able to describe the interactions which occur between the π-Lewis acid metal centre and the C-C multiple bond in the π-complex. A σ-bond is formed when there is good overlap between the π-system of the ligand, the C-C multiple bond in this case and an empty d-orbital belonging to the gold species, this \( M \leftarrow L \) donation is followed by the metal donating electrons back to the ligand, from a filled d-orbital to an empty π*-orbital, a \( M \rightarrow L \) donation. The term π-acid was first used in connection with these species by Fürstner and Davies in 2007.

Figure 4 shows the four interactions, which are possible, the σ symmetric \( M \leftarrow L \) donation and the π symmetric \( M \rightarrow L \) back-donation, which occurs via the in-plane π-orbitals. Other orbitals, such as the out-of-plane π-orbital, which are orthogonal to the system can contribute \( M \leftarrow L \) electron donation. This orthogonal relationship is particularly significant for alkyne compounds where the C-C multiple bonds are able to contribute up to four electrons. Mixing can also occur between the empty π*-orbital on the alkyne and the filled d-orbital on the gold, this also contributes to \( M \rightarrow L \) back donation; however this effect is much weaker than the aforementioned interactions. These effects of donating and back donating lead to a
decrease in the bond order of the C-C bond, which results in longer C-C distances and therefore lower vibrational frequencies.\textsuperscript{27}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{orbid.png}
\caption{Qualitative orbital diagram showing the interaction between gold and acetylene}
\end{figure}

\subsection*{1.2.4 Nucleophilic addition}

Computational models have predicted that Au-alkene complexes are more stable and indeed preferred to the corresponding Au-alkyne complexes due to the better $\sigma$ donation received from the alkene unit.\textsuperscript{37} From this, one can expect gold to show chemoselectivity towards a double bond however the Au-triple bond complex is a more reactive species and nucleophilic attack is induced more rapidly from the Au-alkyne.\textsuperscript{37} The origin of this ‘alkynophilicity’ is kinetic, alkynes have a lower HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) it is envisaged that the LAu-alkyne complexes, as a consequence also have a lower LUMO than LAu-alkene complexes.\textsuperscript{38,39,40}
Fukuda and Utimoto examined hydrochlorination with respect to alcohols, water and amines\textsuperscript{41} which detailed the addition of nucleophiles to alkynes and was similar in theory to the heterogeneous hydrochlorination carried out by Hutchings.\textsuperscript{9}

\(\pi\)-Activation of the alkyne allowed electron density to be transferred to the gold, leaving the triple bond susceptible to nucleophilic attack from electron rich species.

\[
\begin{align*}
\equiv & \xrightarrow{\text{Au}^+} \equiv \\
\equiv & \xrightarrow{\text{Au}^+} \equiv \text{Nu}^-
\end{align*}
\]

Scheme 4: Gold species alkyne activation towards nucleophilic attack.\textsuperscript{42,43}

As the nucleophile approaches the activated \(\pi\)-system slippage occurs away from the \(\eta_2\) ground state to the \(\eta_1\) activated state, which leads to an increase in the electrophilicity as a result of mixing of orbitals which were previously orthogonal.\textsuperscript{44} It also aids the charge transfer to the \(\pi\)-ligand from the nucleophile and also to the metal centre. This slippage is crucial in improving overlap of molecular orbitals and assisting with relevant charge transfer to achieve new bond formation.\textsuperscript{45,46} Figure 5 shows the reallocation of electron density once nucleophilic attack has occurred to the \(\pi\)-acid bound alkene.

Arrows represent the redistribution of electrons upon nucleophilic attack on an alkene which is attached to a \(\pi\)-acid

Figure 5: Representation of partial slippage and the redistribution of electron density\textsuperscript{47}
1.3 Carbenes

Carbenes are a class of highly reactive species containing a neutral divalent carbon atom. They are of extensive importance in organic synthesis and occur most frequently as transient intermediates during reactions.\(^{48}\)

**Classes of carbenes**

Carbenes are reactive species, which contain only six electrons in their valance shells and can be formed by the loss of small, stable molecules from a species.\(^{40}\) The expected configuration of a carbene would be linear as they consist of a 2-coordinate carbon centre, which like an alkyne is expected to adopt a linear (sp) digonal hybridisation, instead they adopt a bent structure with bond angles within the range of 100 – 150° which suggests a (sp\(^2\)) trigonal hybridisation. This is because a linear (sp) carbene would have to distribute six electrons amongst two \(\sigma\)-orbitals and two degenerate p-orbitals; the electrons in the p-orbital would be unpaired, due to the electron repulsion. However; sp\(^2\) hybridisation allows for the carbene to spread its electrons amongst three sp\(^2\) orbitals with one higher energy p-orbital, there are two differing ways in which the carbene can do this – either the final two electrons can be unpaired in sp\(^2\) and p-orbitals or paired (both in sp\(^2\)). These two possibilities in electron distribution give rise to the two classes of carbenes. Carbenes can be sorted into two types: singlet and triplet in regards to their electronic configuration.\(^{40}\)
Triplet and singlet carbenes

There are two potential spin states which the carbene can adopt, shown above. There are two unpaired electrons observed in the triplet carbene and therefore less repulsion between the $sp^2$ electrons and groups on the carbon atom – hence the bond angles are larger, between $130 - 150^\circ$. In the singlet carbene there is more repulsion from the paired electrons residing in the $sp^2$ hybridised orbital, leading to a smaller bond angle of approximately $100 - 110^\circ$. Due to having an unshared pair of electrons and an empty $p$-orbital, the singlet carbene is able to function as both a nucleophile and an electrophile.

1.3.1 Types of carbene

Fischer carbenes

Figure 6: Singlet and triplet carbene spin states

Figure 7: Dominant orbital interactions in a Fischer carbene
Fischer carbenes are metal carbenes in which the metal (such as a low oxidation, $\pi$-electron acceptor metal i.e. Fe (0)) is bound to a carbon. The bonding within a Fischer carbene is a $\sigma$-electron donation from the carbene’s lone pair in the sp$^2$ to the metal’s empty dz$^2$ orbital to form a dative covalent bond and an additional interaction of $\pi$-electron back bonding from the filled metal d-orbital to the empty p-orbital on the carbene resulting in some double bond character which renders the sp$^2$ carbon centre vulnerable to attack from nucleophiles.

**Schrock carbenes**

Unlike Fischer carbenes Schrock carbenes do not possess $\pi$-acceptor ligands, instead consist of $\pi$-donor ligands. The metal is usually a high oxidation metal such as Ti(IV), hence the bond is heavily polarised towards the carbenoid carbon and the carbon atom is nucleophilic overall.

![Figure 8: Orbital interactions in Schrock carbene](image)

**Persistent carbenes**

Persistent carbenes are a class of stable carbenes, which can be isolated, the largest sub-group of persistent carbenes is $N$-heterocyclic carbenes (NHCs) and $\pi$-donating substituents on the NHCs play an important role in stabilising the carbene. Although NHCs can act as good $\sigma$-donors their $\pi$-bonding with the metal is weak hence they do not bind with metals as strongly as Fischer or Schrock carbenes. They are most commonly employed as spectator
ligands in catalysis reactions, in which their influence arises from steric or electronic effects rather than directing binding to the substrate.  

![Figure 9: Structure of IMes, a NHC ligand](image)

1.3.2 Carbene formation

Carbenes are often formed from the loss of a diazo group. They can be synthesised from simple diazo compounds such as diazomethane, but this is a potentially dangerous route as it involves the risk of explosion on heating or impact. An alternative is to use a diazocarbonyl compound. The diazo dipole can be stabilised via resonance by the electron withdrawing carbonyl group.  

![Scheme 5: Diazo dipole stabilisation by the carbonyl group](image)

There are two methods regularly employed by which diazocarbonyl compounds are synthesised, see Scheme 6 and Scheme 7.

Scheme 6 shows the diazomethane reacting with the acyl chloride; the first step entails an acylation to yield the diazonium compound which is converted to the diazocarbonyl
compound in the presence of an excess of diazomethane which can function as a base and deprotonate.

\[
\text{Scheme 6: Reaction of an acyl chloride with diazomethane}
\]

\[
\text{Scheme 7: Reaction mechanism of an acyl chloride with diazomethane}
\]

This second way of accessing the diazo species is a much more straightforward reaction, as depicted in Scheme 8, with the incoming diazo group attached to a diazo transfer reagent.

\[
\text{Scheme 8: Reaction of carbonyl with TsN}_3\]

Figure 10: Structure of TsN₃
These diazo groups, once installed, can be removed from the molecule with either heat, light or under Lewis-acid catalysis by Cu or Rh. The driving force is the formation of N$_2$, which compensates for the formation of the carbene.

\[
\begin{align*}
\text{R} & \quad \text{N} \quad \text{O} \\
19 & \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{O} & \quad \text{R} \\
\text{20} & \quad \text{H} \\
\end{align*}
\]

\[\Delta \text{ or } \text{hv} \]

Scheme 9: Removal of diazo group to form a carbene

It is much more common to remove the diazo group using a transition metal complex such as rhodium (RhL$_n$), however the metal does not fully detach from the carbene and a carbenoid is formed. More stable carbenoids are formed if the diazo group is removed with chromium or tungsten,$^50$ these form isolable metallocarbenes otherwise known as Fischer carbenes.$^51$

1.3.3 α-Oxo gold carbene formation

Metal-catalysed dediazotizations of diazo carbonyl species as mentioned in Section 1.3.2 are the most frequently utilised methods of forming α-oxo metal carbene species. However, these methods proceed via the diazo group, a high energy group with the potential to explode – these factors limit the scale of such reactions thus impacting productivity. As a result, the design and utilisation of safer surrogates to these diazo carbonyl species was required, whilst also preserving the ease of preparation and use. Nolan, Perez and Echavarren reported the use of α-oxo gold carbenes in place of α-oxo diazo carbenes, however they still proceeded via the diazo carbonyl species,$^52$ an alternative by Zhang.$^{118}$
proceeded by oxidising an alkyne in the presence of gold, this method was capable of generating the same intermediate but without the use of the hazardous diazo group. It was perceived that α-diazo carbonyl species could be replaced entirely with the substitution of safer and easier to handle alkynes. Scheme 10 shows the strategy.

Scheme 10: Safe synthesis of an α-oxo gold carbene

1.4 Selected examples of gold-catalysis

1.4.1 Sulfur ylide formation

A number of reactions with gold-catalysis have been reported; some of the most interesting have accessed compounds and precursors which have been either impossible or difficult to access using conventional methods. An example of this is the gold-catalysed formation of sulfur ylides.

Sulfur ylides are useful in the synthesis of C-C and C-X, (X=heteroatom) bonds. Ylides were classically made using ‘sacrificial functionality’ (whereby a functional group is affixed then subsequently removed to attain a reactive species) as seen in Scheme 11.
Scheme 11: Carbene installation α to a sulfide

The above example shows how a functional group is eliminated from the molecule by the sulfide – this is closely followed by a deprotonation, yielding the sulfonium salt. Scheme 12 shows another method by which a sulfur ylide is formed; the carbene is initially generated by first installing the diazo group followed by metal mediated decomposition, from which the sulfur ylide is synthesised.

Scheme 12: Installation of a carbene in the α-position relative to a sulfide

However, both of these methods are wasteful, the number of steps involved in the starting material preparation can lead to an overall decrease in efficiency and result in low yields, other problems include the high toxicity of the diazo group. As a result of their problematic synthesis, ylides have remained unappealing for many years. In 2008 Davies et al. reported the synthesis of sulfur ylides without dependency on ‘sacrificial functionality’ by conducting a gold-catalysed 1,2-rearrangement of propargylic carboxylates in the presence of an allyl sulfide resulted in a sulfonium ylide. Proof that the ylide had formed came from C-C bond formation and not from a consequential 2,3-rearrangement.
They studied the synthesis of the ylide from an alkyne using gold-catalysis. The propargylic carboxylate can act as an α-diazocarbonyl upon rearrangement to a metal carbenoid. This gold carbenoid was converted to the sulfur ylide intermediate 23 by reaction with a sulfide. Following a rearrangement 23 was successfully transformed into the sulfur ylide.

Scheme 13 depicts this strategy.\(^5^7\)

\[
\begin{align*}
\text{Ph} & \quad \text{OAc} \quad \frac{\text{AuCl (5 mol\%)} \quad \text{ClCH}_2\text{CH}_2\text{Cl}, 70^\circ\text{C}}{95\% \quad \text{rearrangement} \quad \text{to} \quad \text{carbenoid}} \quad \text{Ph} & \quad \text{OAc} \\
& \quad \text{AuCl} & \quad \text{PhS} \quad \text{OAc} \quad \text{AuCl} & \quad \text{PhS} \quad \text{OAc} \quad \text{AuCl} \\
& & \quad \text{sulfur ylide intermediate} \quad 23 \\
\end{align*}
\]

**Scheme 13: Sulfur ylide generation via gold-catalysed rearrangement**

This method of accessing the ylide also portrays a rare example of a gold-catalysis reaction that incorporates sulfur.\(^1^1\)

1.4.2 Gold-catalysed enyne cycloisomerisation

Another example of the scope of gold is its use in the catalysis of the cycloisomerisations of enyne species.

A review published by Zhang detailed a range of metal-catalysed reactions achieved using soft alkynophilic metals such as gold.\(^5^8\) The reactions include cycloisomerisations of 1,6-enynes and 1,5-enynes to bicyclo[4.3.0]heptanes and bicyclo[3.1.0]hexanes respectively these were accomplished by Trost et al. over a decade ago\(^5^9\) – these types of transformations are of great interest as they can achieve molecular complexity within a few
steps, efficiently and economically. A great variety of possibilities in structure are possible, as can be seen in Scheme 14 – here a range of skeletal rearrangements are observed from a single acyclic 1,6-enyne substrate.

**Scheme 14: Range of cycloisomerisation reactions observed during catalysis with 1,6-ynes**

The enyne can be converted to six-membered ring systems, but also to five-membered dienes. Highly strained bicyclo[3.2.0] compounds are also obtainable, substitution at the terminal alkyne can allow for the synthesis of bicyclic and tricyclic compounds as a result of [4+2]-cycloaddition. The outcomes of these reactions rely heavily on the structure of the starting substrate but also the gold-catalyst itself. In 2004 Echavarren and co-workers also reported similar work to this, on the cyclisation of an acyclic 1,6-enyne via a 5-exo-dig and 6-endo-dig pathway (Scheme 15). The gold-catalyst binds to the alkyne moiety (due to the inherent alkynophilicity of gold) to form the $\eta^2$-alkyne complex. They reported gold as a highly reactive metal catalyst in skeletal rearrangements; they conducted the first gold-catalysed endocyclic rearrangement of an enyne. Scheme 15 shows their work.\(^\text{60}\)
1.5 α-Diazo chemistry

1.5.1 α-Diazocarbonyl species

In the context of the work detailed in this thesis, it is important to consider and describe some of the literature pertaining to α-diazo species and in particular to α-diazosulfoxides. α-Diazocarbonyl species are important and valued precursors in organic synthesis due to both the simplicity in their formation and the wide array of conversions to other chemical species that they can undertake. One of the attractive features of this diazo chemistry is their degradation to carbenes and carbene-like species such as carbenoids and carbonyl ylides which act as reactive intermediates. α-Diazocarbonyl compounds have been widely explored and as a result, many of the reaction pathways open to these species are already documented from cyclopropanation, α,α-substitution, the Wolff rearrangement, C-H insertion and ylide generation.

Figure 11: Structure of an α-Diazocarbonyl species
Diazo transfer can easily be achieved using the Regitz diazo transfer (RDT) method on compounds such as β-keto esters and β-keto sulfones. There are certain limits associated with the Regitz diazo transfer method (Scheme 16) such as base selection, as a base of suitable strength must be chosen to generate the enolate which is a vital intermediate for the reaction to occur. There are also issues with the application of the RDT method to simple ketones as the proton α to the ketone is less acidic, due to the drop in resonance stabilisation in comparison with β-diketones, the RDT method is best suited with species containing an active methylene site.

Scheme 16: Regitz method

1.5.2 α-Diazosulfoxides

Sulfoxides contain the sulfinyl (S-O) functional group flanked by two carbon atoms. The sulfoxide group is very polar as it consists of a highly polarised bond between oxygen and sulfur. The sulfoxide moiety displays substantial dipolar character with electron density.
residing on the oxygen and therefore a partial negative charge is assigned to the oxygen atom.\textsuperscript{62,63}

Sulfoxides are often depicted structurally as tetrahedral, taking into account the lone pair.\textsuperscript{64} Griffiths \textit{et al.} in 2008 also suggested that the sulfoxide S-O bond exists dominantly as a single S-O bond; this was ascertained by considering the small value of anisotropy.\textsuperscript{65}

![Diagram](image)

**Figure 12: Structure of a sulfoxide**

The synthesis of \(\alpha\)-diao\(-\beta\)-keto sulfoxides is a scarcely reported and remains somewhat elusive. Maguire mentions that her initial interest in \(\alpha\)-diasosulfoxides was first ignited when work by Taber \textit{et al} was published in 1986\textsuperscript{66} detailing an intramolecular cyclisation of \(\alpha\)-diaoesters \textit{via} C-H insertion\textsuperscript{67} with good diastereoselectivity.\textsuperscript{68}

Due to a gap in the literature concerning the synthesis of \(\alpha\)-diasosulfoxides, Maguire \textit{et al}.\textsuperscript{69} investigated introducing a diazo group \(\alpha\) to a range \(\beta\)-keto sulfoxides in order to successfully create the \(\alpha\)-diasosulfoxide to achieve carbene functionality \textit{via} diazo removal and thus open up the position \(\alpha\) to the sulfoxide to lend itself to a variety of different chemical transformations. Although they showed some success with affixing this group \(\alpha\) to \(\beta\)-keto sulfones and \(\beta\)-keto phosphonates, they experienced little luck with corresponding sulfoxides due to the species’ characteristic instability.\textsuperscript{70} The aim of their research was to explain this inherent instability of \(\alpha\)-diasosulfoxides.
Figure 13: Structure of an α-diazo-β-keto sulfoxide

1.5.2.1 Cyclic α-diazosulfoxides

Maguire *et al.* found that investigating the α-diazosulfoxides was difficult in their acyclic conformations; in fact the conformational mobility had to be locked using a bicyclic lactone before diazo transfer could successfully occur to form an isolable species, without this conformational constraint it was impossible to isolate the α-diazosulfoxides. Maguire was unable to isolate the acyclic α-diazosulfoxide, this correlated with the findings of Hodson and Holt in 1962. Hodson and Holt had attempted to conduct diazo transfer to β-keto sulfoxides however they reported that under diazo transfer conditions, where β-keto sulfones give the corresponding α-diazo-β-keto sulfones, the same was not true for the sulfoxides and α-diazo-β-keto sulfoxides were not isolated. Scheme 17 illustrates the outcome of their attempts, a series of side products was isolated but not the acyclic α-diazo-β-keto sulfoxide.
Isolation of 32, p-toluenesulfonamide, suggested diazo transfer to the keto sulfoxide did in fact take place but 31 was intrinsically unstable and this led to the dibenzylsulfide 33 and benzoyl formic acid 34 forming via the carbene intermediate 35.

Hodson and Holt suggested that a factor destabilising the α-diazosulfoxide and providing a driving force leading to the formation of the keto acid and the disulfide upon hydrolysis was the oxygen transfer from the sulfoxide to the carbene centre. This was thought to have occurred before or concerted with the loss of the N₂ group.
The first reports of isolated and stable α-diazosulfoxides came from Campbell\textsuperscript{72,73} and Rosati\textsuperscript{74} who were working on the synthesis of cephalosporins. The α-diazosulfoxides which were cephalosporin derivatives are shown in Scheme 19.

![Scheme 19: First reported isolated α-diazosulfoxide](image)

Though this was the first time that these species had been synthesised and isolated, neither the Rosati nor the Campbell groups remarked on this significance.

By the early 90s, after the research of Hodson and Holt and sparse examples, which had included that from Rosati and Campbell there had been little interest expressed in terms of published literature concerning α-diazosulfoxides. At this point it was known that previous attempts to convert acyclic β-ketosulfoxides to the corresponding α-diazosulfoxides had been unsuccessful – perhaps because of the facile oxygen transfer from sulfur to the carbene alongside the displacement of nitrogen, as suggested by Hodson and Holt. There was precedent that, α-diazosulfoxides could be isolated as a cyclic species.

Maguire wished to justify the unexpected stability of the cephalosporin analogues which had been published by Campbell and Rosati. They suggested two possible explanations:
1) Firstly, vinylic conjugation to the ester group may impart stability. This could explain why Hodson and Holt had failed to effect diazo transfer as they had been using β-sulfinyl ketones.

2) Secondly, the rigid locked conformation of the bicyclic system may have been offering additional kinetic stability to the species – and thus lessening the likelihood of rapid oxygen transfer facilitated diazo decomposition.

Although Maguire proposed that the ester conjugation could only play a minor role in terms of stabilisation of the diazo moiety a study was conducted to investigate diazo transfer to α-sulfinyl esters.\textsuperscript{75,76,77} However, all attempts were unsuccessful.\textsuperscript{78} The addition of a strongly electron withdrawing group on the sulfoxide such as methyl imidazole was not adequate to stabilise the labile α-diazosulfoxides in the acyclic systems, thus establishing the stabilising effect did not lie with simple electronic effects.

![Scheme 20: Attempted diazo transfer to acyclic α-sulfinyl esters](image)

There was evidence that the α-diazosulfoxide \( 40 \) was forming: mCPBA was added to the reaction mixture soon after the diazo transfer reagent yielding the corresponding α-
diazosulfones in low amounts, confirming the α-diazosulfoxide was synthesised from the sulfinyl esters but rapidly decomposing upon isolation.

To test their second proposed hypothesis Maguire et al. synthesised a variety of bicyclic sulfoxide lactones and upon diazo transfer isolated a range of cyclic α-diazosulfoxides. The initial results were published in 1998 with more detailed results following in 2013. A variety of sulfoxides were used containing monocyclic and bicyclic lactones and lactams, which were specifically designed to test the influence of the relative stereochemistry of the sulfoxide and diazo groups and the importance of conformational rigidity, ranging from rigid bicyclic compounds to relatively flexible monocyclic structures.

Maguire et al. published the formation of α-diazosulfoxides, which were successfully synthesised from the corresponding sulfoxides (Scheme 21).

![Scheme 21: Synthesis of bicyclic α-diazosulfoxides](image-url)
They also accomplished diazo transfer to the more flexible monocyclic sulfoxides. Their work confirmed that stability of the compounds was related fundamentally to conformational rigidity. There was also an indication that diazo transfer could be conducted with higher yields to axial diazo sulfoxides in comparison to their equatorial equivalents – demonstrating the importance of orientation of the sulfoxide.

1.5.2.2 Degradation of α-diazosulfoxides

Maguire demonstrated that the only stable and isolable α-diazosulfoxides were ones in which the conformations mobility had been restricted by locking the sulfoxide as cyclic structures prior to diazo transfer. The mechanistic explanation provided by Hodson and Holt in 1962 proposed that the instability of the α-sulfoxide was directly linked to the orientation of the sulfoxide oxygen and the interaction of this oxygen with the diazo group, with the oxygen transfer directly facilitating the loss of the diazo group. The diastereoisomers 47 and 48 below were synthesised specifically to examine Hodson and Holt’s theory that oxygen transfer from the axial sulfoxide 48 would occur faster than in the corresponding equatorial sulfoxide 47. It was hoped that these investigations would shed some light on the mechanism of decomposition.

![Diastereomeric bicyclic sulfoxides](image-url)

Figure 14: Diastereomeric bicyclic sulfoxides
This theory was contradicted by the findings of Maguire. Hodson and Holt’s theory was that the equatorial sulfoxide 37 would be the more stable than its axial counterpart 38 as oxygen transfer from the axial would be more likely to occur. However, Maguire’s work demonstrated the opposite was true; the sulfoxide lying in the axial conformation was the more stable, as seen in Figure 15. This is reminiscent of the anomeric effect – where heteroatomic substituents which lie adjacent to a heteroatom in a cyclohexane ring will prefer to adopt an axial orientation rather than the expected and less hindered equatorial orientation.

![Figure 15: Maguire’s mechanistic interpretation of instability of diazosulfoxides](image)

It was proposed that the instability of the α-diazosulfoxides in acyclic structures was most likely born from the overlap of the sulfinyl lone pair and the unsaturated diazo group – leading to the collapse of the diazo group.

The same proposal can be used to rationalise the stability of cyclic α-diazosulfoxides. Within the conformational confines of the cyclic structures electron donation from the sulfinyl lone pair becomes more difficult, and as can be expected from this alteration, the stability of the
α-diazosulfoxide also increases consequently. This description of stability is also consistent with the findings that that ‘axial’ α-diazosulfoxide 50 was more stable than the ‘equatorial’ α-diazosulfoxide 49. The electron pair is more easily donated when the compound is in the equatorial conformation, enabling the ready loss of the diazo group.

1.6 Wolff rearrangement

The Wolff rearrangement was first reported by Ludwig Wolff in 1902 and is a reaction by which α-diazocarbonyl species can be converted to ketenes via the loss of a diazo group and a 1,2-rearrangement. This can occur in a step-wise fashion via a carbene intermediate or in a concerted fashion. Wolff rearrangements are most often photochemically promoted. The formed ketene moiety is highly reactive and is often rapidly converted to another species shortly after formation following a nucleophilic attack with weakly acidic compounds to yield the corresponding carboxylic acids.

![Scheme 22: General scheme depicting the Wolff rearrangement](image)

33
1.6.1 Wolff rearrangement of α-diazosulfoxides

Following the synthesis of the locked cyclic α-diazosulfoxides, Maguire et al. wished to explore their reactivity upon treatment with rhodium catalysts. Prior work in the area indicated that oxygen transfer from the sulfoxide to the carbenoid carbon would occur. However, there was little indication that this was occurring; instead they obtained alkene 54 (when the reaction was conducted with CH$_2$Cl$_2$ as the solvent) via a Wolff type rearrangement (Scheme 23). Although Wolff rearrangements are often photochemically promoted there was also sparse literature precedent that these rearrangements could occur whilst using a rhodium acetate catalyst. Once the α-oxo sulfine 53 forms via the Wolff rearrangement, the intermediate can then produce alkene 54.

![Scheme 23: Wolff rearrangement of cyclic α-diazosulfoxide](image)

The carbene functionality which is produced once the diazo group is removed is rapidly lost as the compound transforms to the sulfine via the Wolff rearrangement. This sulfine intermediate, although not isolated, was confirmed to be the precursor to the alkene once it
was trapped via a Diels-Alder cycloaddition to form an isolable species (Scheme 24). This was the first report of this type of route to the $\alpha$-oxo sulfine.

Scheme 24: Formation and trapping of the $\alpha$-oxo-sulfine

Detailed studies of the reactions of $\alpha$-diazo-$\beta$-oxo sulfoxides using a range of conditions utilising transition metal catalysis, microwave and photolysis have demonstrated that these $\alpha$-diazo-$\beta$-oxo sulfoxides undergo hetero Wolff rearrangement of the carbene centre to form species analogous to 55.$^{83}$

1.7 Summary

Homogenous gold-catalysis has exploded in interest in recent years, made attractive by its highly selective alkyne activation whereby gold is able to coordinate to the C-C triple bond in accordance with the Dewar-Chatt-Duncanson model; also attractive are the mild reaction conditions employed and scope for a variety of functional groups. It has been especially
utilised for its ability in achieving new C-C and C-X bonds, which may not have been possible using pre-existing synthetic strategies.

From enyne cycloisomerisations, C-H additions across \(\pi\)-systems to cycloadditions, there is great diversity in reactions involving gold-catalysts, providing an economical means to attaining molecular complexity and reaction diversity.

Previously difficult and challenging synthesis such as such as the installation of a diazo group adjacent to a sulfoxide group can be addressed using gold-catalysis to combat ‘sacrificial functionality’ and access formerly elusive species.
Chapter 2: Gold-catalysed oxidative cyclopropanation of alkynyl sulfoxides
2.1 Gold-catalysed cyclopropanation

Cyclopropane rings are found to occur in a variety of natural compounds – from terpenes to amino acids, they are increasingly present in drugs.\(^4\) As a result there has been much focus applied to synthesising cyclopropane rings efficiently. Although syntheses exist, such as the Simmons-Smith reaction or the use of ylides in the Corey-Chaykovsky method\(^5\) to more modern metal-catalysed decomposition of diazo acetates to form metal carbenoids (which can react with olefins to yield cyclopropane rings) – these methods are either not efficient or are dangerous, as a result research has favoured diazo free alternatives.\(^6\)

Following on from the work of Toste et al. in 2007 where they utilised sulfoxides as oxidants to generate the \(\alpha\)-oxo gold carbenoid synthons\(^7\) – Yeom and Shim, reported the use of nitrones and hydroxylamines as N-O oxidisers of alkynes to generate the \(\alpha\)-oxo gold species in 2008. Zhang et al. built upon this work, publishing on the use of pyridine N-oxides as intermolecular oxidants.\(^8\) Zhang’s method is a safe and effective route to the \(\alpha\)-oxo gold carbenoid species from which a number of pathways have been observed, such as cyclopropanation\(^9\), 1,2-alkyl shift\(^10\) and C-H insertion. In 2011 Junliang Zhang published on the gold-catalysed synthesis of cyclopropane containing compounds from 1,6-enynes using \(N\)-oxides to form the \(\alpha\)-gold carbenoids which react with the pendant alkene functionality of the molecule to cyclopropanate.\(^11\) Scheme 25 depicts the reaction.
2.2 Aims and objectives

Considering the work of Maguire et al., the advances in gold chemistry and the pre-existing literature precedent of using gold-catalysis to eliminate the need for ‘sacrificial functionality’, the aim of this work is to highlight the advantages of using gold-catalysis over previous preferred routes to form the α-oxo gold carbenoid and to achieve carbene functionality α to the sulfoxide. Advantages of abandoning the diazo route, apart from avoiding the Wolff rearrangement include safer reaction conditions and the ability to work outside the rigidity of the cyclic systems employed by Maguire. To test the hypothesis of achieving carbene like functionality α to a sulfoxide via gold-catalysis, a series of substrates will be prepared and reaction conditions optimised and the molecule will be designed to consist of an in-built trap in the form of pendant alkene functionality so that it will display a characteristic intramolecular cyclisation – to prove the formation of the fleeting carbenoid species, as gold compounds act as soft Lewis acids which are capable of activating alkynes towards nucleophiles and initiating cyclization, see Scheme 26.
Upon successful formation of the gold carbenoid species the molecule will form the
cyclopropanated product which will act as confirmation of the success in achieving carbene
functionality α to a sulfoxide moiety – potentially opening up a whole new class of
sulfoxides. As well as forming a gold carbenoid adjacent to a sulfoxide it is possible to form
heterocycles – heterocycles are often found in natural products and pharmaceuticals and
their development and resourceful synthesis is still an attractive subject of research for
chemists.\textsuperscript{93,94}

The design of the substrate molecule 60 is similar to that in work by researchers such as
Toste \textit{et al.} who in 2008 detailed that 1,6-enyne systems can be used as ideal substrates for
gold-catalysed reactions with in-built pendant functionality for trapping proposed
intermediates.\textsuperscript{95} Based on various reports of 1,6-enyne reactions the molecule (60)
represented in Scheme 26, shows the typical structure of molecule designed to test the
hypothesis.

The proposed reaction will follow the oxidative cyclopropanation reaction mode, however
the mechanism by which it does this is more complicated, formation of the product may
occur \textit{via} the gold(I) singlet carbenoid through a one-step concerted [2+1] intramolecular
cycloaddition or through the carbene to form a thiabicyclic[3.1.0]hexane heterocyclic
structure by a \textit{5-exo-dig} reaction from the 1,6-enyne.
Results and Discussion

2.3 Starting material synthesis

2.3.1 Sulfide synthesis

Alkynyl sulfides are considered to be valuable starting material in organic synthesis. They participate in reactions such as hydrostannation, [2+1] and [4+2] cycloadditions.

There are many methods for making sulfides and also alkenyl sulfides, represented by the thiol-yne reaction (alkyne hydrothiolation), which works via a radical mechanism and the sulfanyl radical species; however there are few examples for the synthesis of alkynyl sulfides.
A synthetic route to the sulfide could be envisaged by considering the Williamson ether synthesis, to which there are obvious sulfur analogues to the reactants involved, and this can in fact be applied quite easily to thiols as it can to alcohols, see Scheme 28.

**Scheme 28: Williamson ether synthesis mechanism with thiol**

The first step, involves the removal of the acidic proton; there is a much less pronounced difference in electronegativity with the thiol than there is with the alcohol (in the traditional Williamson ether synthesis) owing to the lesser degree of electronegativity separation between the heteroatom and carbon. However the thiol is much more acidic than the corresponding alcohol as the sulfur atom is larger than the oxygen and the negative charge can be better spread out over the larger surface area and as a result thiols are more acidic than alcohols.

Once the thiol has been deprotonated there are 3 electron lone pairs on sulfur and a formal negative charge. The thiolate anion is a stable entity. The halide then adds to the thiolate anion, the alkyl halide has a strongly polarised bond because of the difference in electronegativities of carbon and bromine being around: 2.55 $\chi$ and 2.96 $\chi$ respectively. Thiolate anions are good nucleophiles, better than their corresponding thiols and participate in $S_N2$ type reactions where they play the part of the strong nucleophile whilst the carbon $\alpha$ to the halogen has some of its electron density shifted towards the bromine therefore
possesses a partial positive charge, and functions as the electrophile. The reaction occurs and the electrons are transferred to the halogen leaving group.

This is one of many examples of sulfide synthesis, there are few which show the formation of an alkynyl sulfide. Using the Williamson ether method would be troublesome as it would require synthesis of a range of thiols containing internal alkynes, as there are none available for purchase, this would add another step to the process, elongate the procedure and could lead to complication. The inclusion of the internal alkyne is the most problematic element of synthesising the sulfide when considering using traditional routes to sulfides.

There has been some research into the synthesis of alkynyl sulfides; one method involves the nucleophilic substitution of a RSX compound by a lithium acetylide in which the X is an electron withdrawing substituent which acts as the leaving group. Although this preparation could yield the alkynyl sulfide, this method generally requires the sulfur moiety to be installed via an odorous thiol.\textsuperscript{96}

Another method involves the cleavage of sulfur-sulfur bond of a disulfide by a metallic alkynyl species which are made \textit{in situ} from terminal alkynes.\textsuperscript{97}

Zheng \textit{et al.} reported in 2012, a modified procedure which combined some elements from previous syntheses of alkynyl sulfides. They envisaged that the use of elemental sulfur could eradicate the need for toxic precursors such as thiols. Zheng reported a one-pot synthesis \textit{via} the lithium alkynyl thiolate; this method had not been previously reported.\textsuperscript{98}

The Zheng method was deemed the most efficient synthesis to use, there are many diverse terminal alkynes available for purchase and they are also straightforward to prepare using
either the Corey-Fuchs method or the Ohira-Bestmann synthesis. The Zheng synthesis bears some similarities to the Williamson ether synthesis.

Scheme 29 below depicts the results achieved using the Zheng method with a precursor of interest, the reaction worked well giving a yield of 71%. The scheme also shows the literature yield, although for a slightly different precursor.

\[
\begin{align*}
R^1 &= \text{C}_6\text{H}_5 \\
R^2 &= \text{CH}_2\text{CH}_2\text{CH}=&\text{CH}_2
\end{align*}
\]

**Literature results:** Sulfide yield: 85%

\[
\begin{align*}
R^1 &= \text{C}_6\text{H}_5 \\
R^2 &= \text{CH}_2\text{C}_6\text{C}_6
\end{align*}
\]

**Scheme 29: Zheng’s one pot alkynyl sulfide synthesis**

The commercially available terminal alkyne, phenylacetylene 71, was deprotonated using a base, in this case n-butyl lithium (n-BuLi) was used as it was readily available and suitably basic to remove the acidic proton from the terminal alkyne to generate the lithium acetylide 72 \textit{in situ} at -78 °C. This was followed by the addition of sulfur to give the thiolate 73 as a deep red solution, to which was added 4-bromo-1-butene at 0 °C, resulting in the attack of the alkyl halide by the thiolate anion with displacement of the halide to form the alkynyl sulfide 74 in a 71% yield.

Another benefit of this method is that the alkyl halides are available to purchase at a lower cost and in more variation than alkyl thiols or disulfides, allowing for a wider scope in the synthesis of the alkynyl sulfides.
Terminal alkynes (pKa 25) are valuable and useful species, as they; unlike other simple hydrocarbons can be deprotonated to form a carbanion which can act as a C centred nucleophile. The conjugate base of a terminal alkyne boasts increased s character in comparison to a deprotonated alkane or alkene – this closer proximity to the nucleus of the carbanion results in greater stabilisation.

2.3.2 Oxidation of sulfides to corresponding sulfoxides

![Scheme 30: Oxidation of sulfide to sulfoxide](image)

No problems were envisaged concerning the oxidation of the alkynyl sulfide to the corresponding sulfoxide as there is ample literature detailing the transformation.\(^9\) However, upon delving deeper into the literature a more thorough survey of the oxidation of alkynyl sulfides to alkynyl sulfoxides was discovered, undertaken by MaGee in 1992. Magee et al. had initially begun investigations to optimise the oxidation of the alkynyl sulfides to corresponding sulfoxides to avoid the formation of alkynyl sulfones and the decreasing of yields.

Their study comprised of the use of a small range of commercially available and cheap oxidising agents: mCPBA, Oxone\(^{\textregistered}\),\(^{1\text{0}}\) sodium periodate NaIO\(_4\),\(^{1\text{0}}\) and the Davis reagent.
Figure 16: Structure of the Davis Reagent, \textit{trans}-2-(phenylsulfonyl)-3-phenyloxaziridine

Their results showed that neither the Davis reagent nor NaIO$_4$, under normal conditions (KHSO$_3$, MeOH/H$_2$O, 0 °C, RT) oxidised the alkynyl sulfide to the alkynyl sulfoxide, even after a 24 h period no reactivity was observed. This discovery was at the time surprising as both the Davis reagent and sodium periodate have been known to quickly and efficiently form sulfoxides from sulfides, especially the Davis reagent.\textsuperscript{102} Research in 1983 by Davis \textit{et al.}, demonstrated that the Davis reagent could be used to instantly oxidise diphenyl sulfide at 0 °C.

To account for this unexpected resistance to oxidation from the alkynyl sulfide MaGee suggested that the decreased nucleophilicity of the sulfur and consequently its ability to be oxidised may be a result of the proximate alkyne group. He suggested that the sulfur lone pair may delocalise into the $\pi$-orbitals of the alkyne. He concluded that the prohibiting factor of the oxidation was that the acetylene adjacent to the sulfur which was most likely responsible for deactivating the sulfide towards oxidation.

Further study by MaGee found that alkynyl sulfides could be converted to their corresponding sulfoxides in high yields using the Davis reagent once the temperature had been increased to 60 °C (CHCl$_3$, reflux), in all substrates tested by Magee \textit{et al.} there was no over oxidation to the sulfone observed. The utilisation of the oxaziridine eliminated
problems they had encountered with the use of mCPBA such as lower yields and the loss of selectivity with some sulfone forming.

In the context of the work detailed in the thesis: the Davis reagent was not available for purchase and the synthesis of the reagent is time consuming, it was decided to opt for mCPBA for the oxidation of the sulfides to their corresponding sulfoxides, any formation of the sulfone was expected to be removed quite easily using flash column chromatography because of the difference in polarities between the sulfoxide and the sulfone.

Oxidation was achieved by mCPBA (100%) which was added to the synthesised alkynyl sulfide 76 and allowed to stir until no starting material was visible by TLC, the major product formed was the alkynyl sulfoxide 77 with small amounts of the over reacted product (sulfone) 78 present.

\[ \text{Bu}_3C\text{SS}_3 \xrightarrow{m\text{CPBA}, \text{CH}_2\text{Cl}_2, -15^\circ\text{C} - rt} \text{Bu}_3C\text{SO}_3 \]

\[ \text{Bu} \]

\[ \text{Bu} \]

\[ \text{Bu} \]

\[ \text{Bu} \]

\[ 76 \quad 77 \quad 78 \]

\[ 76\% \quad 77 \quad 78 \quad 11\% \]

Scheme 31: Oxidation of alkynyl sulfide to corresponding alkynyl sulfoxide

mCPBA is commercially available in only 72% purity as shock can cause it to detonate, it usually contains ~30% impurities: ~20% water and ~10% 3-chlorobenzoic acid. For the oxidation of the alkynyl sulfides pure mCPBA was required to avoid over-oxidation such as epoxidation.
2.4 Aromatic substrate

Synthesis and purification of the alkynyl sulfide 80 was straightforward and proceeded well to give a good yield, but once the sulfide was converted into the sulfoxide the compound was prone to rapid degradation.

\[
\text{Scheme 32: Synthesis of the aryl alkynyl sulfide and consequent oxidation}
\]

At first it was assumed that aryl alkynyl sulfoxide 81 was degrading on the silica column, so a triethylamine deactivated silica was used for the purification, this still led to the isolation of an impure material, an alumina column was also employed to no avail. Leaving the crude mixture in the fridge under argon still led to significant increases in degradation of the compound over 3 days. This indicated that the compound had to be used immediately after purification before it underwent degradation and was rendered unusable for the gold-catalysis step.

Replacing the pendant alkene functionality of these aryl alkynyl sulfoxides with an aryl group results in significant increases in the stability of the sulfoxide. 81 and its aryl analogues are unreported in the literature, this observation of instability is novel and there is no discussion to date to explain the increased susceptibility of the aromatic substituted compounds towards degradation.
2.4.1 Preliminary optimisation of reaction conditions

However, before the realisation of the short lifespan of the molecule, the phenyl system was submitted to catalysis. The conditions (solvent/catalyst/counterion) initially employed were based on preliminary results obtained by Matthew Barrett for compounds similar to precursor 81. The following reaction (Scheme 33) was briefly optimised.

Scheme 33: Gold-catalysed reaction of the aryl alkynyl sulfoxide

Table 1: Preliminary optimisation of the gold-catalysed reaction of alkynyl sulfoxides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>N-Oxide</th>
<th>NMR yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>XPhosAuCl/AgSbF$_6$</td>
<td>Nitromethane</td>
<td>RT</td>
<td>N4</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>XPhosAuCl/AgSbF$_6$</td>
<td>Nitromethane</td>
<td>50</td>
<td>N4</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>XPhosAuCl/AgSbF$_6$</td>
<td>Nitromethane</td>
<td>80</td>
<td>N4</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>XPhosAuCl/AgSbF$_6$</td>
<td>Nitromethane</td>
<td>50</td>
<td>N4</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>XPhosAuCl/AgSbF$_6$</td>
<td>Nitromethane</td>
<td>50</td>
<td>N5</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>XPhosAuCl/AgSbF$_6$</td>
<td>Nitromethane</td>
<td>50</td>
<td>N6</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>XPhosAuCl/AgSbF$_6$</td>
<td>Nitromethane</td>
<td>50</td>
<td>N7</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>XPhosAuCl/AgSbF$_6$</td>
<td>Nitromethane</td>
<td>50</td>
<td>N1</td>
<td>57</td>
</tr>
</tbody>
</table>

Table 1: Gold-catalysed synthesis of cyclopropanated product 82. a All reactions were carried out on a 0.1 mmol scale and stirred for 16 h. b 5 mol% catalyst loading was used for all reactions. c All reactions were conducted at a concentration of 0.05 M. d N-oxides were added to the reaction in 1.2 eq. e All yields correspond to the major diastereoisomer of the cyclopropanated product and were determined by $^1$H NMR analysis with an internal standard (TMB).
The $^1$H NMR spectra of the catalysis product was complex due to significant degradation of the starting material 81, this meant that the d.r was not established – however these initial results confirmed the plausibility of the catalytic cycle presented (Scheme 27).

Two parameters were initially investigated, temperature and $N$-oxides. The results obtained from the temperature screen showed only a small increase in yields from RT up to 50 °C (entry 2) and no change in yield when increasing the temperature from 50 °C to 80 °C (entry 3) so this parameter was set at 50 °C.

A fairly wide $N$-oxide screen was conducted; 8-methylquinoline $N$-oxide (entry 7) being the worst gave only a 15% yield of compound 82, this may have been a consequence of the oxygen being less available to attack due to the unfavourable steric interaction encountered with a methyl unit in close proximity to the oxygen. There was some improvement in the
yield with the use of halogen substituted pyridine \(N\)-oxides, 2-bromopyridine \(N\)-oxide (entry 6) improved the yield to 43% and 3,5-dichloropyridine \(N\)-oxide (entry 8) improved it further to 57%.

AgSbF\(_6^-\) was the only counterion investigated; commonly when counterions are screened a gold halide species is condensed with a halide scavenger \textit{in situ} this counterion is usually derived from a silver compound. Echavarren has discussed the role of the resulting silver in the catalysis reaction. Different catalytic properties can be observed by altering the counterion used. OTf\(^-\), SbF\(_6^-\) and BF\(_4^-\) are amongst the most weakly coordinating counterions, of which SbF\(_6^-\) is the most widely employed in gold chemistry.\(^{103}\)

Unfortunately because of the sensitivity of the phenyl system and its inherent instability the optimisation was abandoned in favour of using a more stable aliphatic system. Data gathered on preference of temperature and \(N\)-oxide provided a basis for further investigation into the optimisation – but this data was used cautiously and re-analysed with respect to sulfoxide \(^{77}\).

\textbf{2.5 Regioselective oxidation of internal alkynes}

Zhang \textit{et al.} reported the utilisation of pyridine \(N\)-oxides as external oxidants when synthesising \(\alpha\)-oxo gold carbenoid intermediates. In the specific case of the 1,6-enzyme systems already prepared it is imperative to be able to predict which end of the internal triple bond will be susceptible to attack from the \(N\)-oxide.
Reports of regioselective oxidation of internal alkynes were published by Zhang et al. in 2010\textsuperscript{104} and 2013,\textsuperscript{105} their results in 2010 displayed that regioselectivity could be achieved if the two ends of the internal alkyne were biased in some way, either one end by steric hindrance or conjugation, these factors would prevent attack from the oxygen adjacent to that particular end. In 2013 they published in the same field, this time detailing the advantages of placing an electron withdrawing group on one end of the alkyne leading to an inductive polarisation of the C-C triple bond which encourages adjacent oxidation to occur.

In the context of the 1,6-enyne systems (See Figure 18) there is an R group on one end of the alkyne and although it may impart some electron density towards the C-C triple bond rendering the carbon $\delta^\delta$, this is outweighed by the large steric clash from the sulfoxide oxygen and the lone pair and also the electronic clash from the same factors that the oxygen on the N-oxide would face if it attempted oxidation at the carbon $\alpha$ to the sulfoxide. Also of consideration is the electron withdrawing properties of the sulfoxide group. Thus by deactivating one end of the alkyne the other end is favoured and a regioselective oxidation predicted to occur.\textsuperscript{106} The figure below shows the factors hindering one end of the internal alkyne.

![Figure 18: Unfavourable interactions influencing regioselective oxidation](image-url)
2.6 Aliphatic substrate

Upon evaluation it was decided that synthesis of the aryl substituted compounds should be halted and the optimisation of the gold-catalysis step should occur with a more stable compound which could be made in a large quantity, stored and used without issues concerning purity.

77 Was chosen to be used to optimise conditions on, as it was easy to prepare using the aforementioned one-pot procedure, it could be stored for months showing no signs of degradation and was economical to produce large quantities of.

Scheme 34: Synthesis of substrate 77

2.7 Optimisation of reaction conditions

Scheme 35: Gold-catalysed reaction of the alkyl alkynyl sulfoxide

A comprehensive study was carried out to determine the optimum reaction conditions for the intramolecular cyclopropanation of the alkene.

Table 2 below details selected results, which highlight the findings of the optimisation study.
Table 2: Optimisation of the gold-catalysed oxidative cyclopropanation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Cat. Mol %</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>N-oxide</th>
<th>N-oxide (eq.)</th>
<th>Conc. (M)</th>
<th>NMR yield (%)$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>5</td>
<td>Dioxane</td>
<td>80</td>
<td>N1</td>
<td>1.2</td>
<td>0.05</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
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<td>5</td>
<td>Dioxane</td>
<td>80</td>
<td>N2</td>
<td>1.2</td>
<td>0.05</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
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<td>5</td>
<td>Dioxane</td>
<td>80</td>
<td>N3</td>
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<td>1,2-DCE</td>
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<td>THF</td>
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<td>50</td>
<td>N1</td>
<td>1.2</td>
<td>0.05</td>
<td>64</td>
</tr>
<tr>
<td>24</td>
<td>L1</td>
<td>5</td>
<td>Dioxane</td>
<td>RT</td>
<td>N1</td>
<td>1.2</td>
<td>0.05</td>
<td>56</td>
</tr>
</tbody>
</table>

Table 2: Gold-catalysed synthesis of cyclopropanated product 84. $^a$All reactions were carried out on a 0.1 mmol scale and stirred for 17h. $^b$All ligands were complexed with AuNTf$_2$. $^c$Dioxane used was 1,4-Dioxane in all cases. $^d$All yields correspond to the major diastereoisomer of the cyclopropanated product and were determined by $^1$H NMR analysis with an internal standard (TMB).
Zhang et al. demonstrated in 2010 that N-oxides were used in preference over sulfoxides as external oxidants. In this study N-oxides were used to oxidise the internal triple bond of the alkynyl sulfoxide, a series of N-oxides with differences in electronics were analysed. There was only a 10% yield variation between the oxidants, the worst being the 3-bromopyridine N-oxide (entry 3), and the best result obtained by using pyridine N-oxide...
Quinoline N-oxide (entry 2) gave the product in a moderate 63% yield. Commenting on the results it may seem that the oxygen of the pyridine N-oxide may have been more accessible for reaction as it is less sterically hindered in comparison with the other N-oxides employed. 3,5-dichloropyridine N-oxide (entry 1) was chosen as the results obtained from using it were only slightly lower than those of pyridine N-oxide, however it is easier to handle and store thus eliminating the use of the glove box. Once the N-oxide had been established the equivalents of it were analysed, however switching the amount to 2.0 eq. (entry 18) from 1.2 eq. (entry 5) saw the yield fall from 69% to 54%. However; with additional factors such as the small variation in yield, the expense of nearly doubling the amount of N-oxide required (considering it is unrecoverable), the easier purification, the equivalents were fixed at 1.2.

**Catalyst**

In general the pre-formed catalysts were used as they were convenient to store and use, there was also literature precedent detailing their use in the cycloisomerisation of enyne systems. The only counterion used in the preparation of these pre-formed catalysts was NTf₂⁻, Gagosz published the superiority of NTf₂⁻ in terms of moisture tolerance, increased nucleophilicity and coordination strength in comparison to SbF₆⁻.¹⁰⁹,¹¹⁰ A range of ligands were used to form the gold(I) complex, in order to examine their abilities to increase the electrophilicity of the gold(I) and hence increase the yield of product.¹¹¹,¹¹² As the ability of the ligand to donate electrons into the complex decreases so does the
electrophilicity of the gold species, in general cationic gold(I) complexes attached to various ligands follow the order below:

\[
N\text{-heterocyclic carbenes (NHC)} < \text{Phosphines} < \text{Phosphites}
\]

Increasing electrophilicity

The results obtained from the optimisation reactions showed that the NHC (entry 15), XPhos (entry 11) and phosphite (entry 13) both gave moderate yields which were nearly indistinguishable. The best results were obtained with JohnPhos (entry 12) and SPhos (entry 10).

**Catalyst loading**

The loading of SPhosAuNTf$_2$ was probed with the temperature set at 80 °C and a concentration of 0.05 M. Reactions with 1.0, 2.5 and 5.0 mol% of the gold-catalyst were studied, 1.0 mol% (entry 20) gave a yield of 27% of the cyclopropanated product compared to the much improved 62% yield achieved by using 2.5 mol% (entry 19), lower catalyst loading was not sufficient to form reasonable quantities of product. Loading at 5.0 mol% (entry 5) was satisfactorily providing yields of just under 70%; this parameter was consequently fixed at 5 mol%.

**Solvent**

As gold-catalysis encompasses the association/dissociation phenomenon of the gold species in solution with the reactants and the counterion it is envisaged that screening a variety of solvents can make a marked difference to the reaction outcome. A range of solvents were
employed, the results varied from 26%, obtained from using CH$_2$Cl$_2$ (entry 8) for which the reaction was run at RT to accommodate the low boiling point of dichloromethane, to the best results which were obtained using 1,4-dioxane (entry 5) – which yielded a 69% conversion of the sulfoxide 77 to the cyclopropanated product 84. 1,2-DCE (entry 6) gave moderate results of 45%, this coupled with the additional safety measures which had to be put in place to use it, 1,2-DCE was abandoned, THF (entry 7) and toluene (entry 9) were equally matched in their efficacy as solvents: yielding 37% and 39% respectively.

**Temperature**

Altering the temperature was examined; reactions were performed at RT, 50 °C, 65 °C and 80 °C. The reaction proceeded moderately at RT (entry 24); a yield of 56% was achieved, which was not significantly lower than the yields achieved from raising the temperature to 65 °C (entry 22) which gave 66% and further raising of the temperature to 80 °C (entry 21) yielded 69% of cyclopropanated product 84 the parameter was fixed at 50 °C (entry 23) which gave a yield of 64% as there was no significant changes in the yield in correlation with the temperature, this parameter was set at 50 °C.

**Concentration**

The effect of concentration was studied; results from reactions at 0.2 M (entry 15), 0.1 M (entry 16) and 0.025 M (entry 17) were compared to data obtained from reactions at 0.05 M, the results showed that the yields of the cyclopropanated product 84 decreased as concentration was increased. Total conversion was not observed with any of the
concentrations tested. The concentration was fixed at 0.05 M to avoid large quantities of solvent needed to achieve the dilute reaction mixture at 0.025 M.

**Reaction time**

Finally, reaction time was considered, the reaction was followed closed by TLC, the first 30 mins showed little to no consumption of starting materials, however after 4 h there was indication of reaction, disappearance of starting material along with the appearance of a new spot for the catalysis product was observed. After 17 h yields of nearly 70% were achieved, however no progress was observed after 17 h. Upon leaving the reaction to stir for 24 h there was no increase in yield.

**2.7.1 Application of optimised conditions**

Sulfoxide 77 underwent [2+1] intramolecular cycloaddition to form 84 in a 73% isolated yield as a mixture of diastereoisomers using the following optimised conditions:

SPhosAuNTf$_2$ at 5 Mol% in dioxane (0.05 M) with 3,5-dichloropyridine N-oxide (1.2 eq.) for 17 h at 50 °C.

**2.8 Synthesis and reaction of substrates**

With the optimised conditions in hand the next aim was to assess the scope of the reaction by exposing a range of interesting substrates to these conditions, for this a variety of substrates had to be prepared.
The 4-phenyl-1-butyne sulfoxide 88 was chosen as a good starting material as it assessed how placing an aryl group further from the electron rich alkyne bond would alter interactions within the molecule and ultimately the stability. The first most notable effect was that 88 was inherently more stable than the phenyl sulfoxide 81, which indicated it was the proximity of the π-electrons in the phenyl ring to the alkyne group which were destabilising 81, this also meant that the 4-phenyl-1-butyne sulfoxide could be stored and submitted to the gold-catalysis conditions in a purer form, it gave a good yield of 63% with a d.r. of 6:1 in less than 4 hours.

Scheme 36: Synthesis and reaction of 4-phenyl-1-butyne alkynyl sulfoxide 88

Using a cyclopropyl group would allow assessment of a small group with a 3° carbon centre in the gold-catalysis reaction. It would also yield a ketone group flanked by two cyclopropane rings. Synthesis of sulfide 91 was straightforward, however the volatility of the cyclopropyl compound meant that 91 was difficult to dry under reduced pressure – it was obtained in a modest 30% yield. However the oxidation step was good, yielding 68% of the
sulfoxide 92. The catalysis step worked excellently, with a 10:1 d.r. and a yield of 86% in 30 mins, reducing the temperature to RT saw no significant decrease in yield, but a change in the d.r. to 7:1.

Scheme 37: Synthesis and reaction of cyclopropyl alkynyl sulfoxide 92

TBDPS protected alcohol was chosen to demonstrate the ability to take large groups as well as alcohols through the optimised gold conditions. The synthesis of the TBDPS protected hexan-yn-1-ol sulfoxide 96 was straightforward; the oxidation step gave a very modest yield of 35%. Once submitted to gold-catalysis, disappointingly there was no indication of any reaction occurring between sulfoxide 96 and the SPhosAuNTf2 gold-catalyst by either TLC or crude NMR. The reaction of the TBDPS ether derivative in the gold-catalysis step may not have been successful due to the bulk of the TBDPS group. This bulk may have interfered with the reacting centre, though the TBDPS group is positioned quite some way away from the alkyne, the carbon chain may have be flexible enough to cause an unfavorable steric clash to occur.
The tert-butyl group was seen a good substrate as it would demonstrate both a volatile substance and a 4° carbon centre in the catalysis. 3,3-Dimethyl-1-butyne was purchased and used without further purification, and although it is only slightly larger in molecular weight than the cyclopropylacetylene there were less complications associated with volatility in the synthesis of sulfide 99 which was procured in a good 53% yield. Once subjected to catalysis it gave product 101 in a good 51% yield with a good d.r. of 7:1.
Scheme 39: Synthesis and reaction of tert-butyl alkynyl sulfoxide 100

After the failure of the TBDPS ether sulfoxide 96 to react in the catalysis step, another ether was attempted, to prove that protected alcohols could successfully be taken through the conditions. A smaller alcohol was chosen, propargyl alcohol 102, with a smaller protection group, this time a tetrahydropyran (THP). Not only would a successful gold-catalysis reaction extend the scope to alcohols but also the accommodation of acid sensitive groups such as THP.

Scheme 40: Protection of propargyl alcohol with tetrahydropyran

The first step was to synthesise the protected alcohol, which was achieved in an excellent 88% yield using dihydropyran (DHP).
With the protected alcohol 102 in hand it was used in the one-pot \( n \)-BuLi method of sulfide synthesis (Scheme 41). However this gave very poor yields (~19%), and an equally poor yield (~16%) was obtained for the oxidation step, consequently there was hardly any sulfoxide to use for the gold reaction. This method was employed several times, with all attempts unable to yield the quality or quantity of product needed for catalysis.

![Scheme 41: \( n \)-BuLi one-pot synthesis using THP ether 103](image)

This method was abandoned in favour of the LiHMDS method, see Scheme 42. This preparation saw the yield of sulfide 104 increase to 85% which was obtained in high purity; this purity also influenced the oxidation step, increasing the yield over this step from a dismal 16% to an excellent 85%.

Advantages of this preparation are firstly that the LiHMDS has a much lower pKa (~ 28) than \( n \)-BuLi (~ 50) which may prevent unwanted side reactions from occurring and secondly it eliminates one step from the \( n \)-BuLi synthesis. Here the electrophilic addition of sulfur occurs with the homoallyl group via the phenylsulfonylsulfide over one step rather than in two as seen in Scheme 41.
Once exposed to the optimised gold-catalysis conditions, the THP sulfoxide 105 showed signs of reaction by TLC. However, owing to the sensitivity of the THP group and the ease of its removal the true nature of the product was important to thoroughly investigate. The reaction was worked up and purified via flash column chromatography after which HRMS (ES) m/z calculated for $\text{C}_{12}\text{H}_{18}\text{O}_4\text{Na}_5$ (M+Na)$^+$ 281.0824, found 281.0815 corresponded to product 106. Low resolution mass spectrometry showed a peak for 197.1 which corresponds to product 107 and the sodium ion. It was evident that the product of the reaction was a mixture of the two compounds 106 and 107 which had been inseparable by flash column chromatography (as both were present in the mass spectrum). $^1$H NMR indicated only the presence of the alcohol as did the $^{13}$C NMR. It is unclear when the THP group was removed from the compound, either during the work-up, purification or NMR sample make-up. As a result a result of this uncertainly of at the time of purification it is not possible to report a yield without further investigation. However from the $^1$H NMR which shows resonances only
belonging to the alcohol 107 it is possible to obtain a d.r. value of 5:1 for the inseparable diastereoisomers formed.

The phthalimide group is used for the protection of amines; using N-propargylphthalimide would demonstrate if the reaction conditions for the gold-catalysis would be suitable with the use of protected amines, and extend to cyclise amine containing compounds via gold-catalysis. Unfortunately, there was no reaction via the n-BuLi method and no evidence of it forming in the LiHMDS reaction either (Scheme 43); the $^1$H NMR gave no indication of any reaction however significant degradation of the starting materials was observed.

![Scheme 43: Attempted synthesis of N-propargylphthalimide substituted alkynyl sulfide](image-url)
Substrate 128 was designed as it would provide an interesting example of a dienyne substrate in the catalysis.

Scheme 44: Corey-Fuchs homologation

For this the Corey-Fuchs synthesis was employed to convert the *trans*-cinnamaldehyde 112 to the corresponding dibromo olefin 113. This was achieved in an excellent yield of 82%. The mechanism for the reaction is detailed below in Scheme 45.

Scheme 45: General mechanism for the Corey-Fuchs homologation reaction

The reaction is similar to the Wittig reaction where the phosphonium ylide is generated *in situ* from the reaction between triphenylphosphine and carbon tetrabromide. This betaine
can undergo a Wittig type reaction with the incoming aldehyde to form the oxaphosphetane 123 which decomposes to yield the dibromo olefin. Formation of molecular bromine is not a feature of traditional Corey-Fuchs mechanisms, however in this case it may provide an explanation for the change of colour in the reaction vessel to dark brown.\textsuperscript{114}

\[
\begin{align*}
\text{Scheme 46: Poor yielding sulfide synthesis} \\
\text{The next step, shown here in Scheme 46 consists of a deprotonation of the weakly acidic olefinic proton with } n\text{-BuLi which yield the lithio-olefinic species in situ which undergoes a } \beta\text{-elimination to produce the bromoalkyne, exposing this bromoalkyne to further } n\text{-BuLi allows for lithium-halogen exchange and quenching the intermediate with the sulfur electrophile 125 to yield sulfide 126. Although 126 was achieved, it was achieved in a very poor yield of 13%. Instead, quenching with water was tried after the lithium-halogen exchange to form the terminal alkyne, see Scheme 47 below. This gave much improved yield of 83%.
}\end{align*}
\]

\[
\begin{align*}
\text{Scheme 47: Terminal alkyne synthesis from the dibromo olefin}
\end{align*}
\]
The alkyne 127 was subjected to the regular *n*-BuLi sulfide preparation; however it produced the sulfide 126 in an unacceptable 23% yield, which would only diminish further after the oxidation step, so this route was re-thought.

\[
\begin{align*}
\text{Scheme 48: } & n\text{-BuLi synthesis of alkynyl sulfoxide} \\
\text{127} & \xrightarrow{n\text{-BuLi}} \text{S}_2, \text{THF} \xrightarrow{Br-} \text{S}_{\text{Bu}} \xrightarrow{-78 \text{ - 0 } ^\circ \text{C}} 23\%
\end{align*}
\]

The alkyne was then used in the LiHMDS method, which gave the sulfide in an excellent 89% yield; however, unfortunately oxidation of the sulfide to sulfoxide 128 was not possible.

\[
\begin{align*}
\text{Scheme 49: } & \text{LiHMDS method synthesis of alkynyl sulfoxide} \\
\text{127} & \xrightarrow{\text{LiHMDS, THF}} \text{S}_{\text{Bu}} \xrightarrow{-78 \text{ C - RT}} 89\% \\
\text{126} & \xrightarrow{\text{mCPBA}} \text{CH}_2\text{Cl}_2 \xrightarrow{-15 \text{ C - RT}} 128 \\
\text{129} & \xrightarrow{N\text{-oxide}} [\text{Au}]
\end{align*}
\]

The Corey-Fuchs homologation was attempted again, this time with the cyclohexanecarboxaldehyde 130. However the dibromo olefin 131 was obtained in very poor yields using the traditional Corey-Fuchs synthesis and a modified method (see Experimental (2,2-Dibromovinyl)cyclohexane).
Moving away from the 1,6-enyne system and substitution on the alkyne side of the molecule, a 1,7-enyne system was designed in hope of providing some variance in the cyclisation products formed from the catalysis steps. The 1,7-enyne system could potentially cyclise to form a thiabicyclo[4.1.0]heptane system.

Scheme 50: Dibromo olefin 131 synthesis
Scheme 51: Synthesis and reaction of 1,7-enzyme substrate

Although sulfide 135 and sulfoxide 136 were procured in good yields, there was no reaction observed in the gold-catalysis step by TLC or $^1$H NMR of the crude mixture. The failure of the 1,7-enzyme system was disappointing, the alkynyl sulfoxide was predicted to react via a 6-exo-dig cyclisation to form the cyclisation product 137. Increasing the size of the carbon chain from 4 to 5 carbons results in greater flexibility, which may have been the issue here. The alkene pendant functionality may manoeuver away from the tethered gold carbenoid and thus fail to react.

Again moving away from the 1,6-enzyme structure, 1,5-enynes were attempted, as 1,7-enynes were possibly too long and flexible. These 1,5 systems with an allyl group attached to the sulfoxide moiety are shorter and thus were expected to undergo cyclisation without fear of flexibility. Successful reaction of the 1,5-enzyme in the gold-catalysis step would produce a
strained 3 membered ring fused to a 4 membered ring in a bicyclo[2.1.0]pentane (compounds 140 and 144) like structure.

Scheme 52: Synthesis of 1,5-ene variants

However as seen from Scheme 52 neither sulfide was formed.
2.9 Gold-catalysis results

Table 3: Summary of final results

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Starting Material</th>
<th>Time (h)</th>
<th>Major product</th>
<th>Isolated yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="" /> 77</td>
<td>17</td>
<td><img src="image2.png" alt="" /> 84</td>
<td>73 d.r 5:1</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="" /> 81</td>
<td>17</td>
<td><img src="image4.png" alt="" /> 82</td>
<td>57 d.r 33:1</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="" /> 88</td>
<td>3.5</td>
<td><img src="image6.png" alt="" /> 89</td>
<td>63 d.r 6:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="" /> 92</td>
<td>0.5</td>
<td><img src="image8.png" alt="" /> 93</td>
<td>86 d.r 10:1</td>
</tr>
<tr>
<td>5</td>
<td>TBDPSO</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td><img src="image9.png" alt="" /> 100</td>
<td>18</td>
<td><img src="image10.png" alt="" /> 101</td>
<td>51 d.r 7:1</td>
</tr>
<tr>
<td>7</td>
<td><img src="image11.png" alt="" /> 105</td>
<td>17</td>
<td><img src="image12.png" alt="" /> 107</td>
<td>Yield cannot be confidently reported d.r 5:1</td>
</tr>
</tbody>
</table>
All reactions were conducted using the optimised conditions: SPhosAuNTf₂ at 5 Mol% in dioxane (0.05 M) with 3,5-dichloropyridine N-oxide (1.2 eq.). D.r values were determined by ¹H NMR analysis.

The optimised conditions were used to explore the reactivity of a range of substrates with alkyl groups after preliminary results demonstrated that aryl groups destabilise the substrate and purity is an issue because of their rapid degradation. However these aryl substituted sulfoxides were explored in detail by Matthew Barrett and will be discussed in the further work Section 2.10.

As discussed in some detail in the substrate scope Section 2.8 a variety of alkyl sulfoxide were synthesised and subjected to the optimised conditions of gold-catalysis. All of the products from the catalysis step were isolated as inseparable mixtures of diastereoisomers. The best results were obtained with sulfoxide 92 which gave the catalysis product 93 in an 86% yield with little reduction in yield at lower temperature and a good diastereomeric ratio. The 3° carbon example, using the tert-butyl group gave a moderately good yield and a good diastereomeric ratio of 7:1.

2.9.1 X-ray data

Sulfoxides are important and frequently occurring features in pharmaceutical chemistry, of particular importance is the significance of the effect the sulfoxide group has on the chemical shifts of nearby protons.¹¹⁵
In 2008 Griffiths et al. found that the long and short range effects (α- and β-effects) of the sulfoxide moieties de-shield neighbouring protons, and that when investigating any γ-effects the placement of the sulfoxide oxygen is important to consider, the protons on the same face (on cyclic sulfoxides) are likely to be significantly more de-shielded as the γ-effect is orientation dependent. Their results also confirmed that the sulfoxide S-O bond exists dominantly as a single +S-O- bond; this was ascertained by considering the small value of anisotropy obtained. 116

Maguire et al. in 2013 synthesised a range of bicyclic sulfoxides, the difference between equatorial and axial conformers was easily established from the 1H NMR spectra, where the chemical shifts for the protons display characteristic differences. Cyclic sulfoxides had been previously synthesised and their 1H NMR assignment studied by Evans 117 in the 1970s and early 1980s.

A notable effect to be aware of when characterising cyclic sulfoxides is the ‘syn-axial’ effect which results in extensive de-shielding (up to 1 ppm) of the neighbouring protons which happen to be syn-diaxial in relation to the S-O sulfoxide bond. Figure 20 shows the chemical shifts of various protons in cyclic sulfoxides obtained by Maguire.
The β-proton $H_3$ in the axial sulfoxide compound 147 at $\delta_H$ 4.88 is significantly de-shielded due to this ‘syn-axial’ effect, however when the S-O is in the equatorial position, as it is in compound 146, $H_3$ is then syn-axial with the sulfinyl lone pair and is relatively shielded in comparison and the proton is observed at $\delta_H$ 4.04.

Notably protons oriented in the same direction as the sulfoxide oxygen are shifted more downfield than their counterparts. $H_1$ and $H_2$ in both the conformers have very different chemical shifts, but the effect is more pronounced for compound 147 in which the sulfoxide oxygen is axial, $H_1$: $\delta_H$ 4.02 in comparison to $H_2$: $\delta_H$ 3.62. Van der Waals forces also play an important role, the VDW interaction between the sulfoxide oxygen and the syn protons is thought to be a determining interaction in the ‘syn-axial’ effect.

This effect can be expected to occur with the cyclic sulfoxides synthesised via the gold-catalysis step. The absolute stereochemistry of compound 82 was obtained from a single crystal of the major diastereoisomer.
Figure 21: X-ray crystal structure (obtained from M. Barrett) for compound 82

From the crystal structure obtained the following configuration is reported for the major diastereoisomer.

![Chemical Structure](image)

Figure 22: Comparison of chemical shifts for thiabicylo catalysis product 82

As expected the α-proton $H_a$ – orientated on the same side as the sulfoxide oxygen – displays appreciable de-shielding at $\delta_H$ 3.52. The same effect is observed in the minor diastereoisomer, but de-shielding occurs to a lesser extent at $\delta_H$ 3.03. The β-protons $H_c$ and $H_d$ are also shifted in accordance to the predication, $H_c$ is on the same side as the sulfoxide.
oxygen and is therefore de-shielded to a further extent, \( H_c: \delta_H 2.26 \) in comparison to \( H_d: \delta_H 1.82 \) in the major product. Again, the same observation is made where de-shielding occurs to a lesser extent in the minor product \( H_c: \delta_H 1.41 \) in comparison to \( H_d: \delta_H 1.21 \).

2.9.2 NMR data comparison

Using the X-ray data for comparison and the \( \delta_H/\text{ppm} \) values from the major diastereoisomer it is possible to assign the configuration of analogous compounds.

Below are the two possible diastereomeric configurations possible for the gold-catalysis products.

![Figure 23: Structures of possible diastereoisomeric configurations](image)

2.9.2.1 \(^1\text{H} \) NMR data comparison

Similar proton shifts are observed for the indicated proton in the major diastereoisomer \( \delta_H 3.54 \) ppm, and \( \delta_H 3.08 \) ppm for the minor diastereoisomer. It is consistently seen that the indicated proton is shifted more downfield than its neighbouring protons, however, all protons signals in the \(^1\text{H} \) NMR are shifted more downfield for the major isomer than the minor, as see in Table 4.
Table 4: ^1^H-NMR comparison table for the resonance (ppm) observed for the indicated proton in the major and minor diastereoisomers

<table>
<thead>
<tr>
<th>Compound</th>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>3.52</td>
<td>3.07</td>
</tr>
<tr>
<td>151</td>
<td>3.55</td>
<td>3.08</td>
</tr>
<tr>
<td>152</td>
<td>3.50</td>
<td>3.08</td>
</tr>
<tr>
<td>153</td>
<td>3.51</td>
<td>3.08</td>
</tr>
<tr>
<td>154</td>
<td>3.55</td>
<td>3.07</td>
</tr>
<tr>
<td>155</td>
<td>3.52</td>
<td>3.03</td>
</tr>
</tbody>
</table>
2.9.2.2 $^{13}$C NMR data comparison

The $^{13}$C NMR experiments revealed similar shifts in ppm for the indicated carbon atoms, re-confirming the synthesis of the same skeletal structure in all the compounds.

Table 5: $^{13}$C-NMR comparison table for characteristic peaks (ppm)

<table>
<thead>
<tr>
<th>Compound</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
</tr>
</thead>
<tbody>
<tr>
<td>84</td>
<td>203.7</td>
<td>58.6</td>
<td>17.7</td>
<td>35.2</td>
<td>25.3</td>
<td>50.7</td>
</tr>
<tr>
<td>93</td>
<td>203.8</td>
<td>59.3</td>
<td>17.8</td>
<td>34.5</td>
<td>25.5</td>
<td>50.6</td>
</tr>
<tr>
<td>89</td>
<td>202.9</td>
<td>58.9</td>
<td>18.1</td>
<td>35.6</td>
<td>25.4</td>
<td>50.9</td>
</tr>
<tr>
<td>101</td>
<td>207.6</td>
<td>58.3</td>
<td>18.5</td>
<td>36.6</td>
<td>25.9</td>
<td>53.7</td>
</tr>
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<td>107</td>
<td>203.4</td>
<td>56.8</td>
<td>19.6</td>
<td>37.1</td>
<td>25.6</td>
<td>51.2</td>
</tr>
<tr>
<td>82</td>
<td>196.5</td>
<td>59.6</td>
<td>19.4</td>
<td>33.9</td>
<td>26.4</td>
<td>54.4</td>
</tr>
</tbody>
</table>
2.10 Collaborative work

The project detailed in this thesis was conducted in collaboration with Matthew Barrett; the optimised conditions which were developed as part of this work for the alkyl substrates were applied by M. Barrett to aryl substrates. Preliminary studies outlined in Section 2.4 indicated that the aromatic substituted alkynyl sulfoxides are notably more prone to rapid degradation than their alkyl counterparts. Initial testing of the aryl derivatives and results obtained suggested that the aryl substituted alkynyl sulfoxides reacted with reduced reaction times and on average gave higher yields than the alkyl sulfoxides. A second set of conditions were applied to these substrates with reduced catalyst loading and at RT – although the reactions still gave modest to good yields with these less forcing conditions, the original optimised conditions (detailed in Section 2.7) gave greater percentage of conversion in all cases with reduced reaction times. The diastereomeric ratio however was generally unaffected when employing less forcing conditions and for all reactions an 8:1 d.r. value was observed which implied that temperature was not a factor in determining diastereoselectivity of the reaction.

The work was extended to some alkyl alkynyl sulfoxides, such as entry 1 which shows the reaction of the cyclohexyl substrate in the catalysis – this only gave a modest yield of 45%, other protected propargyl alcohol derivatives (entries 2-4) were also attempted, and the yields obtained were modest to good at best.
Table 6: Gold catalysed reactions results for aryl systems and continuation of alkyl systems

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Major product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%) Cond. A&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield (%) Cond. B&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
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<td><img src="image" alt="157" /></td>
<td>70</td>
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<tr>
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<td>54</td>
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<tr>
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<td><img src="image" alt="161" /></td>
<td>68</td>
<td>30</td>
</tr>
</tbody>
</table>

<sup>a</sup>All aromatic products of gold catalysis were able to be separated by column chromatography and the major diastereoisomer isolated in each case. Entries 15-18 were obtained as an inseparable mixture of diastereoisomers. <sup>b</sup>Conditions A are identical to the conditions established in this work: SPhosAuNTf<sub>2</sub> 5 Mol%, 0.05 M dioxane, 3,5-dichloropyridine N-oxide (1.2 eq.) at 50 °C – unless otherwise indicated the reactions were stirred for 17 h. <sup>c</sup>Modified conditions B were conducted at RT with SPhosAuNTf<sub>2</sub> 2.5 Mol% – unless otherwise indicated the reactions were stirred for 17 h.

2.11 Summary

In summary, an effective and efficient synthesis of thiabicyclo[3.1.0]hexanes was achieved via gold(I) catalysed alkyne oxidation followed by cyclopropanation. The reaction proceeded through the gold(I) carbenoid in a one-step [2+1] intramolecular cycloaddition to form the
thiabicyclo[3.10]hexane product via a 5-exo-dig reaction from the 1,6-enyne. The scope of the reaction was explored through the application of optimised conditions on a range of substrates, from this were prepared a variety of thiabicylo derivatives containing two stereocentres and multiple functionalities, yields were generally good to modest with d.r. values up to 10:1 under mild reaction conditions. Moreover the efficiency of the gold carbenoids as safe surrogates of diazo reagents was recognised especially in regards to past failures in establishing carbene functionality, which could be later exploited, adjacent to a sulfoxide moiety in acyclic structures.
Chapter 3: Gold-catalysed intramolecular C-H insertion
3.1 C-H insertion

C-H insertion reactions are valuable transformations within the organic chemist’s repertoire as they allow new bonds to be made at sites which were previously un-functionalised.

Scheme 53: General mechanism of C-H insertion

Singlet carbenes insert into a carbon-hydrogen bond in a concerted manner once the orbitals involved are overlapping effectively. Scheme 53 shows the mechanism by which C-H insertion proceeds. Below the orbital interactions involved are depicted.⁴⁰

Scheme 54: Orbital interactions during a singlet carbene C-H insertion reaction

The above mechanism suggests that insertion into a stereogenic C-H centre would result in the retention of stereochemistry.
3.2 Selected examples

3.2.1 Intramolecular gold-catalysed C-H insertion

Although α-oxo gold carbenes are able to undergo a variety of transformation including cyclopropanation with a pendant alkene (as described in Chapter 2) – the use of these gold species in C-H insertion reactions is rare, unlike rhodium catalysed C-H insertion is well documented.\textsuperscript{118}

Toste \textit{et al.} reported in 2008\textsuperscript{119} a rare example of gold-catalysed C-H insertion which occurred via a sequential pathway, following the cycloisomerisation of 1,5-enynes. C-H insertion by the gold stabilised cationic intermediate into \textit{sp}\textsuperscript{3} C-H bonds was observed. Previous work in the Toste group had shown the gold-catalysed cycloisomerisation of 1,5-enynes which went on to form tricyclic products \textit{via} a 1,2-shift,\textsuperscript{120} however they postulated (Scheme 55) that increasing the ring size and consequently the flexibility in the starting material would facilitate intramolecular C-H insertion.

\begin{center}
\textbf{Scheme 55: Toste’s postulated C-H insertion}
\end{center}

In these larger more flexible systems the only product obtained was the result of C-H insertion; they formed product 170 in an 86% yield.
Another example of overall C-H insertion was published in 2004 by Fürstner et al. They reported on the synthesis of substituted phenanthrenes via gold-catalysis. A biphenyl substrate 173 which contained a terminal alkyne unit was treated with AuCl₃. The product, a substituted phenanthrene 175 was achieved in a 95% yield. The gold intermediate 174 was formed from the alkynophilic coordination of the gold species to the triple bond. The resulting η²-complex was proposed to proceed via interception by the neighbouring π-system to undergo a 6-endo-dig reaction to produce the tricyclic compound 175.

Scheme 56: Gold-catalysed cycloisomerisation/C-H insertion

Scheme 57: Fürstner’s intramolecular arylation
3.3 Aims and objectives

Using a diphenyl alkynyl sulfoxide, and based on literature precedent which predicts the interception of the gold carbenoid species by a neighbouring π-system a similar C-H insertion reaction was envisaged to occur when using compound 176 as the starting substrate.

![Chemical structure]

Scheme 58: Proposed C-H insertion

Scheme 58 shows how the reaction is proposed to proceed.

3.4 Synthesis of substrates

In order to test this proposed reactivity an initial substrate was prepared. It was prepared similarly to the substrates used for the cyclopropanation reactions, using commercially available alkynes, sulfur and the corresponding substituted halides.

The initial substrate prepared was a diphenyl compound, to assess whether C-H insertion could occur using the pre-established conditions used for the cyclopropanation of similar
substrates. The synthesis of the sulfide 180 was achieved in a good 64% yield and oxidation to the sulfoxide 176 posed no real challenges. However submission to the gold-catalysis conditions was unfruitful and yielded no evidence of the formation of the C-H insertion product 179.

Scheme 59: Synthesis and reaction of diphenyl substrate

3.5 Activation of substrates

In order to address the poor reactivity observed with sulfoxide 176 a possible solution was to activate the phenyl system by placing an electron donating group on to it as it would donate some of its electron density into the π-system of the aromatic ring, rendering the phenyl more nucleophilic and therefore more likely to participate in electrophilic substitution type reactions. In this case the ring was activated with the use of a methoxy functional group. This
type of inductive activation is \textit{ortho/para} directing, and in the scheme below the canonical forms depict how this electron donating activation occurs.

![Resonance structures](image)

\textbf{Figure 24: Resonance structures representing methoxy electron donating activation of the phenyl ring}

\subsection{3.5.1 Para-methoxy activation}

The first substrate to be activated was sulfoxide 183; see Scheme 60 with the methoxy group in the 4’ position. As can been seen in the resonance structures above, although this imparts electron density into the $\pi$-system, it does not activate strongly at the 6’ position which is predicted to undergo the C-H insertion. It was used to test whether increasing the overall electron density was enough to instigate the reaction with the gold species. Synthesis of the
sulfide 182 and later the sulfoxide 183 was achieved in with good yields; however upon gold-catalysis the C-H insertion product 184 was not synthesised, instead a variety of products were formed which were not isolated.

Scheme 60: Synthesis and reaction of para-methoxy benzyl sulfoxide

3.5.2 Meta-methoxy activation

The next logical step was to activate both the ring and the 6’ position towards reaction by placing the methoxy group at the 3’ position with the gold carbenoid species, see Scheme 61. Disappointingly the meta-methoxy benzyl sulfoxide 186 did not cyclise to produce the expected product 187 when subjected to the gold-catalysis conditions; however significant degradation of the starting material 186 was observed.
Scheme 61: Synthesis and reaction of meta-methoxy benzyl sulfoxide

3.6 Summary

C-H insertion was attempted using a gold(I) catalyst (SPhosAuNTf₂), however none of the substrates tested indicated that the interception of the gold carbenoid species had occurred to yield the desired fused ring system. Electron donating groups on the phenyl group activated the ring towards electrophilic attack however neither were enough to effect C-H insertion.

The conditions used in this study were identical to those used for the oxidative cyclopropanation, in order to full explore the potential of the reaction further work is needed, with a more thorough optimisation for this C-H insertion in order to access these novel sulfoxide systems.
Chapter 4: Experimental
4.1 General Experimental

All reagents which were available commercially were purchased from Acros, Alfa Aesar, Fisher Scientific or Sigma Aldrich and used without further purification. \(n\)-BuLi was purchased as either a 1.6 M or 2.5 M solution in hexanes and was titrated before each use using diphenylacetic acid (DPAA). Sulfur was recrystallized from toluene. \(m\)CPBA was purified by washing with a pH 7 phosphate buffer which was prepared from 0.1 M NaOH (154 mL) and 0.2 M \(\text{KH}_2\text{PO}_4\) (94 mL), distilled water was added up to 376 mL. A solution of \(m\)CPBA (77% w/w, 10 g) in \(\text{Et}_2\text{O}\) (100 mL) was washed with the buffer solution (\(\times\) 3); the combined organic layers were then dried over \(\text{MgSO}_4\), filtered using a vacuum pump and evaporated under reduced pressure to yield pure \(m\)CPBA (8.5 g, 85%).\(^{122}\) All reactions in non-aqueous solvents were conducted in flame dried glassware and under an argon atmosphere with a magnetic stirring device. Catalysis reactions were conducted in sealed Radleys tubes to avoid air sensitivity. Volumes of less than 0.2 mL were measured and dispensed with a gastight syringe. The solvents were purified and used directly from a Pure Solv-MD solvent purification system and were transferred under argon. All reactions which required heating were conducted in paraffin oil baths on stirrer hotplates and the temperature controlled by an external probe. Reactions requiring lower temperatures used the following cooling baths: -78 °C (dry ice/acetone), -15 °C (NaCl/ice/water) and 0 °C (ice/water).
4.2 Analysis

Reactions were followed by thin layer chromatography (TLC) using Merck silica gel 60F\textsubscript{254} analytical plates (aluminium support) and were developed using standard visualising agents: UV fluorescence (254 and 366 nm), potassium permanganate/Δ and vanillin/Δ. Purification via flash column chromatography was conducted using Fluorochem silica gel 60 (0.043-0.063 mm). Infra-red spectra were recorded neat on a Perkin Elmer Spectrum 100 FT-IR spectrometer, only selected absorbencies ($v_{\text{max}}$) are reported in cm\textsuperscript{-1}. MS and HRMS (EI) were recorded on a VG ProSpec or a VG-ZabSpec at 70 eV. High resolution EI spectra were measured using perfluorokerosene (PKF) as an internal calibrant. MS and HRMS (ES) were obtained using 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). $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AVIII300 ($^1$H, 300 MHz; $T = 298K$) and Bruker AVIII400 ($^1$H, 400MHz; $^{13}$C, 101 MHz; $T = 298K$) in the solvents indicated. Chemical shifts ($\delta$) are given in ppm relative to tetramethylsilane (TMS). The solvent signals were used as references and the chemical shifts converted to the TMS scale, residual CHCl\textsubscript{3} ($^1$H, 7.26 ppm; $^{13}$C, 77.16 ppm). Coupling constants ($J$) are reported in Hz. The following abbreviations are used to describe multiplicity in $^1$H-NMR: m (multiplet), s (singlet), d (doublet), t (triplet) and q (quartet) and in $^{13}$C-NMR: C (quaternary), CH (tertiary), CH\textsubscript{2} (secondary) and CH\textsubscript{3} (primary). 1D $^{13}$C-NMR spectra was recorded using UDEFT or PENDANT pulse sequences from the Bruker standard pulse program library. 2D $^{13}$C-NMR HSQC and HMBC spectra were recorded using the Bruker standard pulse program library. Spectra were processed using MestReNova version 6.0.
4.3 General procedures for the preparation of starting materials

Preparation of alkynyl sulfides from terminal alkynes and substituted halide: general procedure 1 (GP1)

\[
\begin{align*}
\text{R}^1 & \quad \xrightarrow{n\text{-BuLi, THF, -78 °C}} \quad \text{Li}^+ & \quad \xrightarrow{\text{Li}^+ \cdot \text{S}_8, \ -78 \ - 0 \ ^\circ \text{C}} \quad \text{Li}^+ \cdot \text{S}^- & \quad \xrightarrow{\text{R}^2 \cdot \text{Br}, \ 0 \ ^\circ \text{C}} \quad \text{R}^1 & \quad \xrightarrow{\text{S}^- \cdot \text{R}^2}
\end{align*}
\]

\(n\text{-BuLi}\) (1.1 eq.) was added drop-wise over 5 mins to a solution of the relevant alkyne (1.0 eq.) in anhydrous THF (0.1 M) at -78 °C. The solution was stirred for 1 h at -78 °C, sulfur powder (1.0 eq.) was added to the solution and it was stirred at -78 °C for 1 h. The mixture was then allowed to warm over 45 mins to 0 °C at which point the sulfur was completely consumed to produce a red lithium alkynyl thiolate. Relevant allyl halide (1.0 eq.) was added to the thiolate and the reaction stirred until starting materials had been consumed. \(\text{NH}_4\text{Cl}\) (0.1 M) was added into the solution to quench the reaction. The aqueous layer was extracted with \(\text{Et}_2\text{O} \times 3\). The combined organic extracts were washed with brine (0.1 M) and dried over \(\text{MgSO}_4\), filtered and concentrated under reduced pressure which yielded an oil. The crude product was purified by flash column chromatography on silica gel [hexane/EtOAc (99:1)] to afford the alkynyl sulfide as an oil. \(R_f\) values were obtained using [hexane/EtOAc (99:1)].
Preparation of alkynyl sulfoxides from the corresponding alkynyl sulfides using mCPBA: general procedure 2 (GP2)

Purified mCPBA (1.1 eq.) was added in portions over 15 mins to a solution of the relevant alkynyl sulfide (1.0 eq.) in anhydrous CH₂Cl₂ (0.1 M) at -15 °C, the resultant mixture was stirred for 30 mins at -15 °C before being allowed to warm gradually over 1 h to RT and stirred for the time indicated. Upon completion the mixture was diluted with further CH₂Cl₂ (0.1 M) before the addition of NaHCO₃ (0.1 M). The organic phase was extracted using CH₂Cl₂ (× 3). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel [hexane/EtOAc] to afford the alkynyl sulfoxide.

Gold-catalysed cyclisation of alkynyl sulfoxides using SPhosAuNTf₂: general procedure 3 (GP3)

The relevant sulfoxide (1 eq.) as a solution in dry 1,4-dioxane (0.05 M) was added into a flame dried Radleys tube to which was added of 3,5–dichloropyridine N-oxide (1.2 eq.) and the mixture stirred for 10 mins at 50 °C before the addition of SPhosAuNTf₂ (5 mol%). The
reaction was stirred at 50 °C for the indicated time until the reaction was complete as determined by TLC. Upon completion the crude mixture was passed through a pad of silica using portions of CH₂Cl₂, EtOAc and [MeOH/EtOAc (1:9)] to remove residual gold. The solvent was removed under reduced pressure and the crude mixture was purified via flash column chromatography on silica gel using the indicated solvents to give the desired cyclic products.

**Preparation of alkynyl sulfides from terminal alkynes and S-butyl benzenesulfonothioate:**

**general procedure 4 (GP4)**

LiHMDS (1.1 eq.) was added drop-wise over 5 mins to a solution of the relevant alkyne (1.1 eq.) in anhydrous THF (0.1 M) at -78 °C. The solution was stirred for 1 h at -78 °C, S-butyl benzenesulfonothioate (1.0 eq.) (obtained from Matthew Barrett) was added drop-wise to the solution and the reaction mixture warmed to RT over 17 h whilst stirring was maintained. Upon completion NH₄Cl (0.1 M) was added into the solution to quench the reaction. The aqueous layer was extracted with Et₂O (× 3). The combined organic extracts were washed with brine (0.1 M) and dried over MgSO₄, filtered and concentrated under reduced pressure which yielded a pale yellow oil. The crude product was purified by flash column chromatography on silica gel [hexane/EtOAc (99:1)] to afford the alkynyl sulfide as an oil. Rₚ values were obtained using [hexane/EtOAc (99:1)].
Preparation of alkynyl sulfides from corresponding dibromo-olefins using S-butyl benzenesulfonothioate: general procedure 5 (GP5)

\[
\begin{align*}
&\text{Br} \quad \text{Br} \\
&\text{R} \quad \text{H}
\end{align*}
\]

\[
\begin{align*}
n-\text{BuLi, THF} & \quad -78 \, ^\circ \text{C} - \text{RT}
\end{align*}
\]
\[
\begin{align*}
&\text{S} \\
&\text{R} \quad \text{H}
\end{align*}
\]

\(n\)-BuLi (2.2 eq.) was added drop-wise to a solution of the relevant dibromo-olefin (1.1 eq.) in anhydrous THF (0.1 M) at \(-78^\circ \text{C}\) at which point the solution became bright orange/red, stirring was maintained for 2 h at \(-78^\circ \text{C}\) before the addition of S-butyl benzenesulfonothioate (1.0 eq.), the mixture was allowed to warm to RT over 17 h whilst stirring was maintained. Upon completion \(\text{NH}_4\text{Cl}\) (0.1 M) was added into the solution to quench the reaction. The aqueous layer was extracted with \(\text{Et}_2\text{O}\) (× 3). The combined organic extracts were washed with brine (0.1 M) and dried over \(\text{MgSO}_4\), filtered and concentrated under reduced pressure, which yielded a pale yellow oil. The crude product was purified by flash column chromatography on silica gel [hexane/EtOAc (95:5)] to afford the alkynyl sulfide as an oil.

4.4 Analysis and characterisation of starting materials

\textit{But-3-en-1-yl(hex-1-yn-1-yl)sulfane}
Following **GP1** using 1-hexyne (822 mg, 1.15 mL, 10.0 mmol), n-BuLi (6.9 mL, 1.6 M, 11.0 mmol), sulfur powder (321 mg, 10.0 mmol), 4-bromo-1-butene (1.35 g, 1.0 mL, 10.0 mmol) stirred for 15 h gave sulfide 76 as a pale yellow oil (1.03 g, 61%). $R_I = 0.81$. $^1H$ NMR (300 MHz CDCl$_3$): $\delta$ 5.84 (ddt, $J = 17.3, 10.4, 6.6, 1H, H-9$), 5.12 (dd, $J = 17.3, 1.3, 1H, H-10a$), 5.07 (dd, $J = 10.4, 1.3, 1H, H-10b$), 2.71 (t, $J = 7.4, 2H, H-7$), 2.48 (td, $J = 7.4, 6.6, 2H, H-8$) 2.30 (t, $J = 6.8, 2H, H-4$), 1.55 – 1.34 (m, 4H, H2-3), 0.91 (t, $J = 7.1, 3H, H-1$); $^{13}C$ NMR (101 MHz CDCl$_3$): $\delta$ 136.0 (CH, C-9), 116.6 (CH$_2$, C-10), 94.8 (C, C-5), 67.8 (C, C-6), 34.6 (CH$_2$, C-8), 33.4 (CH$_2$, C-7), 30.9 (CH$_2$, C-3), 22.0 (CH$_2$, C-2), 19.9 (CH$_2$, C-4), 13.6 (CH$_3$, C-1); IR: $\nu_{\text{max}}$ (cm$^{-1}$) 3079, 2960, 2929, 2167, 1641, 1571, 1442, 1417, 752, 689; HRMS (ES) m/z calculated for C$_{10}$H$_{16}$S (M+H)$^+$ 168.0973, found 168.0979.

**1-(But-3-en-1-ylsulfinyl)hex-1-yne**

Following **GP2** using sulfide 76 (371 mg, 3.0 mmol), mCPBA (569 mg, 3.3 mmol), stirred for 4 h gave sulfoxide 77, purified using [hexane/EtOAc(8:2)], as a colourless oil (308 mg, 76%). $R_I = 0.26$. $^1H$ NMR (300 MHz CDCl$_3$): $\delta$ 5.66 (ddt, $J = 17.2, 10.3, 6.6, 1H, H-9$), 5.17 (dd, $J = 17.2, 1.4, 1H, H-10a$), 5.12 (dd, $J = 10.3, 1.4, 1H, H-10b$), 3.09 (app t, $J = 7.7, 2H, H-7$), 2.63 (m, 2H, H-8), 2.44 (t, $J = 7.0, 2H, H-4$), 1.60 – 1.37 (m, 4H, H2-3), 0.93 (t, $J = 7.3, 3H, H-1$); $^{13}C$ NMR (101 MHz CDCl$_3$): $\delta$ 134.7 (CH$_3$, C-9), 117.4 (CH$_2$, C-10), 106.1 (C, C-5), 56.4 (C, C-6), 55.5 (CH$_2$, C-7), 29.8 (CH$_2$, C-3), 26.6 (CH$_2$, C-8), 22.1 (CH$_2$, C-2), 19.5 (CH$_2$, C-4), 13.6 (CH$_3$, C-1); IR: $\nu_{\text{max}}$
(cm$^{-1}$) 2959, 2933, 2873, 2181, 1641, 1466, 1056, 916; HRMS (ES) m/z calculated for C$_{10}$H$_{16}$OSNa (M+Na)$^+$ 207.0820, found 207.0825.

**But-3-en-1-yl(phenylethynyl)sulfane**

Following GP1 using phenylacetylene (409 mg, 440 μL, 4.0 mmol), n-BuLi (2.2 mL, 2.0 M, 4.4 mmol), sulfur powder (128 mg, 4.0 mmol), 4-bromo-1-butene (540 mg, 406 μL, 4.0 mmol) stirred for 17 h gave sulfide 80 as a pale yellow oil (534 mg, 71%). $R_f = 0.83$. $^1$H NMR (300 MHz CDCl$_3$): $\delta$ 7.44-7.26 (m, 5H, H1-3), 5.88 (ddt, $J = 17.1$, 10.5, 6.6, 1H, H-9), 5.18 (dd, $J = 17.1$, 1.5, 1H, H-10a), 5.12 (dd, $J = 10.5$, 1.5, 1H, H-10b), 2.86 (t, $J = 7.3$, 2H, H-7), 2.57 (td, $J = 7.3$, 6.6, 2H, H-8); $^{13}$C NMR (101 MHz CDCl$_3$): $\delta$ 135.8 (CH, C-9), 131.7 (2 $\times$ CH, C-3), 128.5 (2 $\times$ CH, C-2), 128.3 (CH, C-1), 123.7 (C, C-4), 117.1 (CH$_2$, C-10), 93.5 (C, C-5), 79.3 (C, C-6), 35.1 (CH$_2$, C-8), 33.7 (CH$_2$, C-7); IR: $\nu_{\text{max}}$ (cm$^{-1}$) 3077, 2932, 2166, 1641, 1595, 1486, 990, 912, 752, 689; HRMS (ES) m/z calculated for C$_{12}$H$_{12}$S (M+H)$^+$ 188.0660, found 188.0663.

**((But-3-en-1-ylsulfinyl)ethynyl)benzene**
Following GP2 using sulfide 80, (226 mg, 1.2 mmol), mCPBA (228 mg, 1.3 mmol) stirred for 18 h gave sulfoxide 81, purified using [hexane/EtOAc(7:3)] as a pale yellow oil (164 mg, 67%). R_f = 0.35. ^1H NMR (300 MHz CDCl_3): δ 7.57 – 7.36 (m, 5H, H1-3), 5.90 (ddt, J = 17.1, 10.3, 6.6, 1H, H-9), 5.21 (dd, J = 17.1, 1.4, 1H, H-10a), 5.15 (dd, J = 10.3, 1.4, 1H, H-10b), 3.23 (td, J = 7.2, 1.5, 2H, H-7), 2.83 – 2.59 (m, 2H, H-8); ^13C NMR (101 MHz CDCl_3): δ 134.6 (CH, C-9), 132.2 (2 × CH, C-3), 130.6 (CH, C-1), 128.6 (2 × CH, C-2), 119.7 (C, C-4), 117.5 (CH_2, C-10), 103.5 (C, C-5), 84.9 (C, C-6), 55.2 (CH_2, C-7), 26.6 (CH_2, C-8); IR: ν_max (cm⁻¹) 3068, 2920, 2164, 1719, 1574, 1282, 1244, 1057, 1023, 917, 832, 753, 688; HRMS (ES) m/z calculated for C_{12}H_{12}OSNa (M+Na)^+ 227.0507, found 227.0504.

But-3-en-1-yl(4-phenylbut-1-yn-1-yl)sulfane

Following GP1 using 4-phenyl-1-butyne (391 mg, 422 μL, 3.0 mmol), n-BuLi (2.1 mL, 1.6 M, 3.3 mmol), sulfur powder (96 mg, 3.0 mmol), 4-bromo-1-butene (405 mg, 0.3 mL, 3.0 mmol) stirred for 16 h gave sulfide 87 as a pale yellow oil (214 mg, 33%). R_f 0.80. ^1H NMR (300 MHz CDCl_3): δ 7.36 – 7.21 (m, 5H, H1-3), 5.84 (ddt, J = 17.1, 10.2, 6.6, 1H, H-11), 5.17-5.05 (m, 2H, H-12), 2.87 (t, J = 7.5, 2H, H-9), 2.71 (t, J = 7.4, 2H, H-6), 2.64 (t, J = 7.4, H-5), 2.44 (td, J = 7.5, 6.6, 2H, H-10); ^13C NMR (101 MHz CDCl_3): δ 140.6 (C, C-4), 135.9 (CH, C-11), 128.5 (2 × CH, C-2), 128.4 (2 × CH, C-3), 126.3 (CH, C-1), 116.6 (CH_2, C-12), 93.8 (C, C-7), 69.0 (C, C-8), 35.2 (CH_2, C-5), 34.5 (CH_2, C-10), 33.4 (CH_2, C-9), 22.3 (CH_2, C-6); IR: ν_max (cm⁻¹) 3063, 3027, 2923,
1640, 1537, 1453, 1372, 1276, 1030, 993, 915, 747, 697; HRMS (ES) m/z calculated for C_{14}H_{16}S (M+H)^+ 217.1048, found 217.1051.

(4-(But-3-en-1-ylsulfinyl)but-3-yn-1-yl)benzene

Following GP2 using sulfide 87 (86 mg, 0.40 mmol), mCPBA (76 mg, 0.44 mmol) stirred for 4 h gave sulfoxide 88, purified using [hexane/EtOAc(75:25)] as a pale yellow oil (67 mg, 73%). R_f = 0.35. ¹H NMR (300 MHz CDCl_3): δ 7.38 – 7.22 (m, 5H, H-1-3), 5.85 (ddt, J = 17.1, 10.2, 6.6, 1H, H-11), 5.17 (dd, J = 17.1, 1.4, 1H, H-12a), 5.15 (dd, J = 10.2, 1.4, 1H, H-12b), 3.07 (app t, J = 7.7, 2H, H-9), 2.94 (t, J = 7.2, 2H, H-6), 2.78 (t, J = 7.2, 2H, H-5), 2.70 – 2.44 (m, 2H, H-10); 

¹³C NMR (101 MHz CDCl_3): δ 140.8 (C, C-4), 136.1 (CH, C-11), 128.7 (2 × CH_2, C-2), 128.6 (2 × CH_2, C-3), 126.5 (CH, C-1), 116.8 (CH_2, C-12), 94.0 (C, C-7), 69.2 (C, C-8), 35.4 (CH_2, C-9), 34.7 (CH_2, C-5), 33.6 (CH_2, C-10), 22.5 (CH_2, C-6); IR: ν_max (cm⁻¹) 3028, 2925, 2182, 1780, 1641, 1454, 1338, 1055, 994, 920, 748, 700, 626; HRMS (ES) m/z calculated for C_{14}H_{17}OS (M+H)^+ 233.100, found 233.1004.

But-3-en-1-yl(cyclopropylethynyl)sulfane

103
Following GP1 using cyclopropylacetylene (198 mg, 254 μL, 3.0 mmol), n-BuLi (2.1 mL, 1.6 M, 3.3 mmol), sulfur powder (96 mg, 3.0 mmol), 4-bromo-1-butene (405 mg, 0.3 mL, 3.0 mmol) stirred for 17 h gave sulfide 90 as a pale yellow oil (139 mg, 30%). Rf = 0.77. 1H NMR (300 MHz CDCl3): δ 5.86 (ddt, J = 17.2, 10.3, 6.6, 1H, H-7), 5.12 (dd, J = 17.2, 1.7, 1H, H-8a), 5.06 (dd, J = 10.3, 1.7, 1H, H-8b), 2.72 (t, J = 7.4, 2H, H-5), 2.48 (td, J = 7.4, 6.6, 2H, H-6) 1.34 (tt, J = 7.5, 6.0, 1H, H-2), 0.84-0.78 (m, 2H, H-1), 0.77-0.72 (m, 2H, H-1); 13C NMR (101 MHz CDCl3): δ 135.9 (CH, C-7), 116.6 (CH2, C-8), 98.6 (C, C-3), 63.8 (C, C-4), 34.7 (CH2, C-6), 33.4 (CH2, C-5), 9.0 (2 × CH2, C-1), 0.8 (CH, C-2); IR: νmax (cm⁻¹) 3080, 3011, 2979, 1640, 1429, 989, 916, 839, 810, 725; HRMS (ES) m/z calculated for C9H13S (M+H)+ 153.0738, found 153.0735.

$$\text{((But-3-en-1-ylsulfinyl)ethynyl)cyclopropane}$$

Following GP2 using sulfide 91 (91.4 mg, 0.60 mmol), mCPBA (114 mg, 0.66 mmol) stirred for 4 h gave sulfoxide 92, purified using [hexane/EtOAc(8:2)] as a yellow oil (69 mg, 68%). Rf = 0.27. 1H NMR (300 MHz CDCl3): δ 5.82 (ddt, J = 17.2, 10.3, 6.6, 1H, H-7), 5.14 (dd, J = 17.2, 1.5, 1H, H-8a), 5.10 (dd, J = 10.3, 1.5, 1H, H-8b), 3.04 (app t, J = 7.7, 2H, H-5), 2.74 – 2.51 (m, 2H, H-6), 1.43 (tt, J = 8.2, 5.1, 1H, H-2), 1.03 – 0.91 (m, 4H, H-1); 13C NMR (101 MHz CDCl3): δ 134.7 (CH, C-7), 117.4 (CH2, C-8), 109.6 (C, C-3), 72.1 (C, C-4), 55.5 (CH2, C-5), 26.7 (CH2, C-6), 9.6 (2 × CH2, C-1), 0.33 (CH, C-2); IR: νmax (cm⁻¹) 3080, 3012, 2920, 2178, 1641, 1441, 1348, 1277, 1052, 995, 916, 828, 781; HRMS (ES) m/z calculated for C9H13S (M+H)+ 169.0687, found 169.0692.
Following **GP1** using **tert-butyl**(**hex-5-yn-1-yloxy**)diphenylsilane (TBDPS protected 5-hexyn-1-ol) obtained from Matthew Barrett, (633 mg, 1.9 mmol), n-BuLi (1.1 mL, 1.9 M, 2.1 mmol), sulfur powder (60.3 mg, 1.9 mmol), 4-bromo-1-butene (254 mg, 190 μL, 1.9 mmol) stirred for **17 h** gave sulfide **95** as a pale yellow oil (386 mg, 50%). R<sub>f</sub> = 0.76. ¹H NMR (300 MHz CDCl<sub>3</sub>): δ 7.66 – 7.36 (m, 10H, H<sub>2</sub>-4), 5.83 (ddt, J = 17.0, 9.9, 6.5, 1H, H-15), 5.10 (dd, J = 17.0, 1.4, 1H, H-16a), 5.06 (dd, J = 9.9, 1.4, 1H, H-16b), 3.67 (t, J = 5.9, 2H, H-7), 2.71 (t, J = 7.4, 2H, H-13), 2.47 (td, J = 7.4, 6.5, 2H, H-14), 2.31 (t, J = 6.6, 2H, H-10), 1.69 – 1.60 (m, 4H, H<sub>8</sub>-9), 1.04 (s, 9H, H-1); ¹³C NMR (101 MHz CDCl<sub>3</sub>): δ 135.8 (CH, C-15), 134.2 (2 × C, C-5), 129.7 (2 × CH, C-2), 129.7 (4 × CH, C-4), 127.8 (4 × CH, C-3), 116.8 (CH<sub>2</sub>, C-16), 94.8 (C, C-11), 65.6 (C, C-12), 34.8 (CH<sub>2</sub>, C-7), 33.6 (CH<sub>2</sub>, C-14), 31.9 (CH<sub>2</sub>, C-8), 27.1 (3 × CH<sub>3</sub>, C-1), 25.5 (C, C-6), 20.1 (CH<sub>2</sub>, C-13), 19.4 (CH<sub>2</sub>, C-9), 18.4 (CH<sub>2</sub>, C-10); IR: ν<sub>max</sub> (cm<sup>-1</sup>) 3071, 2931, 2858, 1689, 1589, 1428, 1106, 997, 917, 822, 739, 700, 613; HRMS (ES) m/z calculated for C<sub>26</sub>H<sub>34</sub>SiS (M+Na)<sup>+</sup> 445.1997, found 445.1996.
Following GP2 using sulfide 95, (390 mg, 0.9 mmol), mCPBA (175 mg, 1.0 mmol) stirred for 17 h gave sulfoxide 96, purified using [hexane/EtOAc(8:2)] as a pale yellow oil (142 mg, 35%). R_f = 0.36. ^1^H NMR (300 MHz CDCl_3): δ 7.68 – 7.62 (m, 4H, H-3), 7.44 – 7.35 (m, 6H, H-2, H-4), 5.85 (ddt, J = 17.1, 10.2, 6.6, 1H, H-15), 5.17 (dd, J = 17.1, 1.4, 1H, H-16a), 5.11 (dd, J = 10.2, 1.4, 1H, H-16b), 3.67 (t, J = 5.6, 2H, H-7), 3.08 (t, J = 7.8, 2H, H-13), 2.74 – 2.51 (m, 2H, H-14), 2.45 (t, J = 6.8, 2H, H-10), 1.77 – 1.60 (m, 4H, H8-9), 1.05 (s, 9H, H-1).

**But-3-en-1-yl(3,3-dimethylbut-1-yn-1-yl)sulfane**

Following GP1 using 3,3-dimethyl-1-butyne (247 mg, 369 μL, 3.0 mmol), n-BuLi (2.1 mL, 1.6 M, 3.3 mmol), sulfur powder (96 mg, 3.0 mmol), 4-bromo-1-butene (405 mg, 0.3 mL, 3.0 mmol) stirred for 17 h gave sulfide 99 as a pale yellow oil (268 mg, 53%). R_f 0.71. ^1^H NMR (300 MHz CDCl_3): δ 5.85 (ddt, J = 17.2, 10.2, 6.6, 1H, H-7), 5.12 (dd, J = 17.2, 1.7, 1H, H-8a), 5.07 (dd, J = 10.2, 1.7, 1H, H-8b), 2.71 (t, J = 7.2, 2H, H-5), 2.48 (td, J = 7.2, 6.6, 2H, H-6), 1.23
(s, 9H, H-1). $^{13}$C NMR (101 MHz CDCl$_3$): δ 136.2 (CH, C-7), 116.7 (CH$_2$, C-8), 103.0 (C, C-3), 66.7 (C, C-4), 34.8 (CH$_2$, C-6), 33.5 (CH$_2$, C-5), 31.2 (3 × CH$_3$, C-1), 29.0 (C, C-2). IR: $\nu_{\text{max}}$ (cm$^{-1}$) 2963, 2865, 1706, 1640, 1467, 1393, 1362, 1218, 991, 914, 744. HRMS (ES) $m/z$ calculated for C$_{10}$H$_{16}$S 168.0973, found 168.0976.

4-((3,3-Dimethylbut-1-yn-1-yl)sulfinyl)but-1-ene

Following GP2 using sulfide 99 (289 mg, 1.70 mmol), mCPBA (323 mg, 1.87 mmol) stirred for 4 h gave sulfoxide 100 purified using [hexane/EtOAc(7:3)] as a pale yellow oil (180mg, 68%). $R_f = 0.31$. $^1$H NMR (300 MHz CDCl$_3$): δ 5.81 (ddt, $J = 17.1$, 10.2, 6.6, 1H, H-7), 5.14 (dd, $J = 17.1$, 1.4, 1H, H-8a), 5.08 (dd, $J = 10.2$, 1.4, 1H, H-8b), 3.08 (td, $J = 7.7$, 2.1, 2H, H-5), 2.67 – 2.51 (m, 2H, H-6), 1.25 (s, 9H, H-1); $^{13}$C NMR (101 MHz CDCl$_3$): δ 134.7 (CH, C-7), 117.5 (CH$_2$, C-8), 112.9 (C, C-3), 73.2 (C, C-4), 55.5 (CH$_2$, C-5), 30.2 (3 × CH$_3$, C-1), 29.9 (C, C-2), 26.7 (CH$_2$, C-6); IR: $\nu_{\text{max}}$ (cm$^{-1}$) 2973, 2928, 2870, 2162, 1720, 1642, 1575, 1456, 1365, 1252, 1141, 1060, 918, 838, 768, 752, 701; HRMS (ES) $m/z$ calculated for C$_{10}$H$_{17}$OS (M+H)$^+$ 185.1000 found 185.1001.

Tetrahydro-2-(2-propynylxy)-2H-pyran
A known compound was prepared using literature precedent.\textsuperscript{123}

**Preparation of THP protected propargyl alcohol:**

Propargyl alcohol (1.1 g, 1.2 mL, 20 mmol) was added drop wise over 5 mins to a solution of dihydropyran (2.1 g, 2.3 mL, 25 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (0.1 M) at 0 °C and stirred for 5 mins before the addition of p-TSA (38 mg, 0.22 mmol) as a solution in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (5 mL) the reaction mixture was stirred for a further 3 h. Upon completion the crude mixture was dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel [hexane/EtOAc (97:3)] to yield a colourless oil (2.5 g, 88%). R\textsubscript{f} = 0.72. \textsuperscript{1}H NMR (300 MHz CDCl\textsubscript{3}): δ 4.82 (app t, J = 3.2, 1H, H-4), 4.26 (dd, J = 7.3, 2.4, 2H, H-3), 3.89 – 3.49 (m, 2H, H-8), 2.41 (t, J = 2.4, 1H, H-1), 1.85 – 1.52 (m, 6H, H5-7); \textsuperscript{13}C NMR (101 MHz CDCl\textsubscript{3}): δ 96.9 (CH, C-4), 74.0 (CH, C-1), 79.8 (C, C-2), 62.0 (CH\textsubscript{2}, C-8), 54.0 (CH\textsubscript{2}, C-3), 30.2 (CH\textsubscript{2}, C-4), 25.4 (CH\textsubscript{2}, C-7), 19.0 (CH\textsubscript{2}, C-6); IR: ν\textsubscript{max} (cm\textsuperscript{-1}) 3286, 2943, 2870, 1442, 1390, 1202, 1120, 1058, 1026, 948, 902, 871, 815. Analytical data in agreement with literature values.\textsuperscript{124}

\[ 2\text{-}((3\text{-}(\text{But}-3\text{-en}-1\text{-ylthio})\text{prop}-2\text{-yn}-1\text{-yl})\text{oxy})\text{tetrahydro-2H-pyran} \]

Following GP4 using LiHMDS (4.6 mL, 1.0 M, 4.6 mmol), tetrahydro-2-(2-propynyloxy)-2H-pyran (638 mg, 640 μL, 4.6 mmol) and S-butylbenzenesulfonothioate (944 mg, 821 μL, 4.1
mmol) gave sulfide 104 as a yellow oil (795 mg, 85%). R_f = 0.81. ¹H NMR (300 MHz CDCl₃): δ 5.83 (ddt, J = 16.7, 9.9, 6.4, 1H, H-11), 5.12 (dd, J = 16.7, 1.8, 1H, H-12a), 5.08 (dd, J = 9.9, 1.8, 1H, H-12b), 4.82 (app t, J = 3.2, 1H, H-5), 4.44 – 4.30 (s, 2H, H-6), 3.89 – 3.48 (m, 2H, H-1), 2.76 (t, J = 7.5, 2H, H-9), 2.48 (td, J = 7.5, 6.4, 2H, H-10), 1.80 – 1.51 (m, 6H, H2-4); ¹³C NMR (101 MHz CDCl₃): δ 135.8 (CH, C-11), 117.0 (CH₂, C-12), 96.9 (CH, C-5), 90.8 (C, C-7), 76.5 (C, C-8), 62.3 (CH₂, C-1), 55.3 (CH₂, C-6), 34.7 (CH₂, C-10), 33.6 (CH₂, C-9), 30.5 (CH₂, C-4), 25.6 (CH₂, C-2), 19.3 (CH₂, C-3); IR: ν_max (cm⁻¹) 2940, 2851, 2181, 1641, 1440, 1388, 1264, 1201, 1118, 1037, 1014, 901, 870, 815; HRMS (ES) m/z calculated for C₁₂H₁₉O₂S (M+H)⁺ 227.1106, found 227.1110.

2-((3-(But-3-en-1-ylsulfinyl)prop-2-yn-1-yl)oxy)tetrahydro-2H-pyran

Following GP2 using sulfide 104 (777 mg, 3.4 mmol), mCPBA (652 mg, 3.7 mmol) stirred for 5 h gave sulfoxide 105 purified using [hexane/EtOAc (75:25)] as a pale yellow oil (700 mg, 85%) as a mixture of diastereoisomers, the data for the major is assigned. R_f = 0.26. ¹H NMR (300 MHz CDCl₃): δ 5.85 (ddt, J = 16.7, 10.2, 6.6, 1H, H-11), 5.19 (dd, J = 16.7, 1.1, 1H, H-12a), 5.13 (dd, J = 10.2, 1.1, 1H, H-12b), 4.80 (app t, J = 3.0, 1H, H-5), 4.46 (s, 2H, H-6), 3.87 – 3.77 (m, 1H, H-1), 3.59 – 3.50 (m, 1H, H-1), 3.16 (td, J = 7.8, 1.6, 2H, H-9), 2.76 – 2.52 (m, 2H, H-10), 1.83 – 1.51 (m, 6H, H₂-4); ¹³C NMR (101 MHz CDCl₃): δ 134.3 (CH, C-11), 117.6 (CH₂, C-12), 100.0 (C, C-7), 97.4 (CH, C-5), 82.2 (C, C-8), 62.1 (CH₂, C-1), 55.1 (CH₂, C-6), 54.2 (CH₂, C-9), 30.1 (CH₂, C-4), 26.5 (CH₂, C-10), 25.2 (CH₂, C-2), 18.8 (CH₂, C-3); IR: ν_max (cm⁻¹) 2942, 2872,
2185, 1719, 1641, 1440, 1390, 1344, 1263, 1120, 1058, 1023, 940, 901, 870, 815; HRMS (ES) m/z calculated for C₁₂H₁₉O₃S (M+H)⁺ 243.1055 found 243.1052.

**(E)**-(4,4-Dibromobuta-1,3-dien-1-yl)benzene

A known compound was prepared using literature precedent.¹¹⁴

![Corey-Fuchs conversion of aldehydes to corresponding dibromo-olefins:](image)

Corey-Fuchs conversion of aldehydes to corresponding dibromo-olefins:

Triphenylphosphine (5.25 g, 20 mmol) was added in portions over 5 mins to a solution of carbon tetrabromide (3.32 g, 10 mmol) in anhydrous CH₂Cl₂ (0.1 M) at 0 °C, the resultant mixture was stirred for 30 mins at 0 °C before the addition of trans-cinnamaldehyde (0.66 g, 0.63 mL, 5 mmol), the reaction was stirred at 0 °C for 3 h. Upon completion the mixture was diluted with further CH₂Cl₂ (0.1 M) and washed with H₂O (30 mL). The aqueous layer was extracted with CH₂Cl₂ (× 3), the combined organic extracts were washed with brine (0.1 M) and dried over MgSO₄, filtered and concentrated under reduced pressure to yield a dark brown oil. The crude product was purified by flash column chromatography on silica gel [hexane/EtOAc (95:5)] to afford the dibromo-olefin **113** as a white solid (1.2 g, 82%); m.p: 54 – 56 °C., lit. m.p: 55 – 56 °C. Rᵣ = 0.89. ¹H NMR (300 MHz CDCl₃): δ 7.48 – 7.42 (m, 2H, H₃), 7.38 – 7.33 (m, 2H, H₂), 7.33 (d, J = 6.8, 1H, H-7), 7.31 – 7.28 (m, 1H, H-1), 7.10 (d, J = 9.3, 1H, H-5), 6.76 (dd, J = 9.3, 6.8, 1H, H-6); ¹³C NMR (101 MHz CDCl₃): δ 143.2 (CH, C-5), 135.9 (C, C-4), 129.0 (2 × CH, C-2), 128.8 (2 × CH, C-3), 126.4 (CH, C-1), 107.0 (CH, C-7), 82.9 (C, C-
8), 79.3 (CH, C-6); IR: \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3015, 2850, 2924, 1948, 1558, 1446, 1232, 1212, 1138, 1029, 959, 802, 744, 687, 629. Analytical data in agreement with literature values.\(^{125,126}\)

**\((E)-\text{But-3-en-1-yl(4-phenylbut-3-en-1-yn-1-yl)sulfane}\)**

Following GP5 using \( n \)-BuLi (2.2 mL, 2.0 M, 4.4 mmol), dibromo-olefin 113 (282 mg, 2.2 mmol), S-butyl benzenesulfonothioate (457 mg, 397 \( \mu \)L, 2.0 mmol) stirred for 17 h gave sulfide 126 as a pale yellow oil (56mg, 13%). \( R_f \) 0.73. \(^1\)H NMR (300 MHz CDCl\(_3\)): \( \delta \) 7.39 – 7.25 (m, 5H, H-3), 6.90 (d, \( J = 16.2 \), 1H, H-5), 6.25 (d, \( J = 16.2 \), 1H, H-6), 5.86 (ddt, \( J = 17.2, 10.2, 6.6 \), 1H, H-11), 5.15 (dd, \( J = 17.2, 1.6, 1H, H-12a \)), 5.10 (dd, \( J = 10.2, 1.6, 1H, H-12b \)), 2.82 (t, \( J = 7.2, 2H, H-9 \)), 2.54 (td, \( J = 7.2, 6.6, 2H, H-10 \)); \(^{13}\)C NMR (101 MHz CDCl\(_3\)): \( \delta \) 140.4 (CH, C-5), 137.0 (C, C-4), 135.6 (CH, C-11), 128.7 (2 × CH, C-2), 128.5 (2 × CH, C-3), 126.2 (CH, C-1), 116.9 (CH\(_2\), C-12), 108.2 (CH, C-6), 93.1 (C, C-7), 81.5 (C, C-8), 35.1 (CH\(_2\), C-10), 33.5 (CH\(_2\), C-9); IR: \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3078, 3023, 2924, 2134, 1639, 1546, 1489, 1446, 1221, 966, 915, 818, 745, 688; HRMS (ES) \( m/z \) calculated for \( C_{14}H_{14}S \) 214.0816, found 214.0813.
(E)-But-1-en-3-yn-1-ylbenzene

A known compound was prepared using literature precedent.\textsuperscript{114}

\[\begin{align*}
\text{Br} & \quad \text{Br} & & n-\text{BuLi, THF} & & \text{H}_2\text{O, }-78 \degree \text{C} \\
\text{H} & & & & & \text{113} \quad \text{2} \quad \text{3} \quad \text{4} \quad \text{5} \quad \text{6} \quad \text{7} \quad \text{8} \quad \text{127}
\end{align*}\]

Preparation of a terminal alkyne \textit{via} dihydrohalogenation and metal-halogen exchange of the dibromo-olefin using \textit{n-}BuLi:

\textit{n-}BuLi (1.7 mL, 1.9 M, 3.2 mmol) was added dropwise over 5 mins to a solution of the relevant dibromo-olefin (441 mg, 1.5 mmol) in anhydrous THF (0.1 M) at -78 \degree \text{C} and stirred for 1 h. The reaction was allowed to warm to RT over 1 h and stirring maintained for an additional 1 h. Upon completion the reaction mixture was quenched with \textit{H}_2\text{O} (25 mL), and the aqueous layer extracted with pentane (\times 3), the combined organic extracted were dried over \textit{MgSO}_4, filtered and concentrated under reduced pressure to yield a colourless oil. The crude product was purified by flash column chromatography on silica gel [hexane/EtOAc (75:25)] to afford the terminal alkyne \textbf{127} as a colourless oil (163mg, 82\%). \textit{R}_f = 0.76. \textsuperscript{1}H NMR (300 MHz CDCl\textsubscript{3}): δ 7.42 – 7.30 (m, 5H, H-1-3), 7.05 (d, \textit{J} = 16.4, 1H, H-5), 6.13 (dd, \textit{J} = 16.4, 2.4, 1H, H-6), 3.05 (d, \textit{J} = 2.4, 1H, H-8); \textsuperscript{13}C NMR (101 MHz CDCl\textsubscript{3}): δ 143.2 (CH, C-5), 135.9 (C, C-4), 128.9 (2 × CH, C-2), 128.8 (2 × CH, C-3), 126.4 (CH, C-1), 107.0 (CH, C-6), 82.9 (C, C-7), 79.3 (CH, C-8); IR: \textit{v}_\text{max} (\text{cm}^{-1}) 3292, 3030, 2926, 2855, 2098, 1598, 1575, 1491, 1448, 1297, 1269, 1205, 1074, 953, 746, 689. Analytical data in agreement with literature values.\textsuperscript{127}
(2,2-Dibromovinyl)cyclohexane

A known compound was prepared using literature precedent.\textsuperscript{128}

\[
\begin{align*}
\text{cyclohexanecarboxyaldehyde} & \rightarrow \text{dibromo-olefin}
\end{align*}
\]

\textbf{Modified Corey-Fuchs conversion of aldehydes to corresponding dibromo-olefins:}

Triphenylphosphine (4.33 g, 16.5 mmol) was added in portions over 5 mins to a solution of cyclohexanecarboxyaldehyde (0.56 g, 0.6 mL, 5.0 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (0.1 M) at 0 °C and stirred for 5 mins before the addition of a prepared solution of CBr\textsubscript{4} (3.56 g, 11.0 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (0.1 M) in a dropwise fashion over 5 mins, upon addition the reaction mixture became a dark orange/brown colour, the reaction was stirred for a further 1.5 h at 0 °C before the addition of petrol (200 mL) in one portion resulting in the precipitation of triphenylphosphine oxide which was removed by filtration through a pad of silica, dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel [hexane/EtOAc (95:5)] to afford the dibromo-olefin \textbf{131} as a colourless oil (93.8 mg, 7%) \(R_f = 0.86\).

\textbf{Corey-Fuchs conversion of aldehydes to corresponding dibromo-olefins:}\textsuperscript{114}

\[
\begin{align*}
\text{cyclohexanecarboxyaldehyde} & \rightarrow \text{dibromo-olefin}
\end{align*}
\]
Triphenylphosphine (5.25 g, 20 mmol) was added in portions over 5 mins to a solution of carbon tetrabromide (3.32 g, 10 mmol) in anhydrous CH$_2$Cl$_2$ (0.1 M) at 0 °C, the resultant mixture was stirred for 30 mins at 0 °C before the addition of cyclohexanecarboxyaldehyde (0.56 g, 0.6 mL, 5 mmol) the reaction was stirred at 0 °C for 3 h. Upon completion the mixture was diluted with further CH$_2$Cl$_2$ (0.1 M) and washed with H$_2$O (30 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ ($\times$ 3), the combined organic extracts were washed with brine (0.1 M) and dried over MgSO$_4$, filtered and concentrated under reduced pressure to yield a dark brown oil. The crude product was purified by flash column chromatography on silica gel [hexane/EtOAc (95:5)] to afford the dibromo-olefin 131 as a colourless oil (33.5 mg, 2.5%). $R_f$ = 0.88. $^1$H NMR (300 MHz CDCl$_3$): δ 6.33 (d, $J$ = 9.0, 1H, H-5), 2.27 (ttd, $J$ = 9.0, 7.8, 3.6, 1H, H-4), 1.72 (td, $J$ = 7.8, 3.6, 4H, H-3), 1.37 – 1.05 (m, 6H, H1-2); $^{13}$C NMR (101 MHz CDCl$_3$): δ 143.8 (CH, C-5), 87.0 (C, C-6), 42.5 (CH, C-1), 31.3 (2 × CH$_2$, C-3), 25.8 (C, C-4), 25.5 (2 × CH$_2$, C-2); IR: $\nu_{\text{max}}$ (cm$^{-1}$) 2924, 2850, 1610, 1448, 1350, 1257, 1140, 965, 893, 833, 764, 813, 669. Analytical data in agreement with literature values.$^{128}$

**Pent-4-en-1-yl(phenylethynyl)sulfane**

Following GP1 using phenylacetylene (562 mg, 604 μL, 5.5 mmol), n-BuLi (3.2 mL, 1.9 M, 6.1 mmol), sulfur powder (176 mg, 5.5 mmol), 5-bromo-1-pentene (820 mg, 652 μL, 5.5 mmol) stirred for 17 h gave sulfide 135 as a pale yellow oil (485mg, 48%). $R_f$ 0.82. $^1$H NMR (300 MHz...
CDCl₃: δ 7.44 – 7.26 (m, 5H, H-1-3), 5.81 (ddt, J = 17.1, 10.2, 6.6, 1H, H-10), 5.08 (dd, J = 17.1, 1.8, 1H, H-11), 5.02 (dd, J = 10.2, 1.8, 1H, H-11), 2.81 (t, J = 7.1, 2H, H-7), 2.24 (td, J = 7.3, 6.6, 2H, H-9), 1.91 (tt, J = 7.3, 7.1, 2H, H-8); ¹³C NMR (101 MHz CDCl₃): δ 137.4 (CH, C-10), 131.5 (2 × CH, C-3), 128.3 (CH, C-1), 128.0 (2 × CH, C-2), 123.5 (C, C-4), 115.7 (CH₂, C-11), 93.0 (C, C-5), 79.4 (C, C-6), 35.1 (CH₂, C-7), 32.2 (CH₂, C-9), 28.4 (CH₂, C-8); IR: ν_max (cm⁻¹) 3077, 2932, 2166, 1641, 1571, 1441, 1254, 1027, 990, 912, 752, 688; HRMS (ES) m/z calculated for C₁₃H₁₄S: 202.0816, found 202.819.

Following GP2 using sulfide 135 (457 mg, 2.3 mmol), mCPBA (429 mg, 2.5 mmol) stirred for 17 h gave sulfoxide 136 purified using [hexane/EtOAc(75:25)] as a pale yellow oil (336 mg, 67%). Rᵣ = 0.29. ¹H NMR (300 MHz CDCl₃): 7.56 – 7.35 (m, 5H, H1-3), 5.81 (ddt, J = 17.0, 10.2, 6.6, 1H, H-10), 5.11 (dd, J = 17.0, 1.6, 1H, H-11a), 5.07 (dd, J = 10.2, 1.6, 1H, H-11b), 3.17 (app t, J = 7.8, 2H, H-7), 2.29 (td, J = 7.2, 6.6, H-9), 2.18 – 1.96 (m, 2H, H-8); ¹³C NMR (101 MHz CDCl₃): δ 136.7 (CH, C-10), 132.3 (2 × CH, C-3), 130.6 (CH, C-1), 128.7 (2 × CH, C-2), 119.9 (C, C-4), 116.4 (CH₂, C-11), 102.3 (C, C-5), 85.1 (C, C-6), 55.5 (CH₂, C-7), 32.4 (CH₂, C-9), 21.6 (CH₂, C-8); IR: ν_max (cm⁻¹) 3063, 2930, 2163, 1715, 1667, 1487, 1443, 1265, 1058, 914, 831, 756, 689; HRMS (ES) m/z calculated for C₁₃H₁₅OS (M+H)⁺ 219.0844, found 219.0846.
Following GP2 using sulfide 180, (146 mg, 0.65 mmol), mCPBA (123 mg, 0.72 mmol) gave sulfoxide 176, purified using [hexane/EtOAc(75:25)] as a pale yellow oil (121 mg, 77%). \( R_f = 0.27 \). \(^1\)H NMR (300 MHz CDCl\(_3\)): \( \delta \) 7.47 – 7.34 (m, 10H, H1-3, H9-11), 4.40 (d, \( J = 1.8 \), 2H, H-7); \(^{13}\)C NMR (101 MHz CDCl\(_3\)): \( \delta \) 132.2 (2 \( \times \) CH, C-3), 130.6 (2 \( \times \) CH, C-9), 129.0 (2 \( \times \) CH, C-10), 128.8 (CH, C-1), 128.7 (2 \( \times \) CH, C-2), 128.6 (CH, C-11), 119.7 (C, C-8), 103.3 (C, C-4), 85.0 (C, C-5), 62.7 (C, C-6), 60.4 (CH\(_2\), C-7); IR: \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3059, 2971, 2916, 2159, 1973, 1668, 1573, 1496, 1487, 1441, 1407, 1225, 1158, 1045, 834, 768, 751, 700, 632; HRMS (ES) \( m/z \) calculated for C\(_{15}\)H\(_{12}\)OSNa (M+Na)\(^+\) 263.0507, found 263.0512.

Benzyl(phenylethynyl)sulfane

Following GP1 using phenylacetylene (204 mg, 220 \( \mu \)L, 2.0 mmol), \( n \)-BuLi (1.05 mL, 2.1 M, 2.2 mmol), sulfur powder (64 mg, 2.0 mmol), benzyl bromide (171 mg, 238 \( \mu \)L, 2.0 mmol) stirred for 18 h gave sulfide 180 as a pale yellow oil (287 mg, 64%). \( R_f = 0.77 \). \(^1\)H NMR (300 MHz
CDCl$_3$: $\delta$ 7.43 – 7.28 (m, 10H, H1-3, H9-11), 4.06 (s, 2H, H-7); $^{13}$C NMR (101 MHz CDCl$_3$): $\delta$
136.8 (C, C-8), 131.5 (2 × CH, C-3), 129.3 (2 × CH, C-10), 128.8 (CH, C-1), 128.5 (2 × CH, C-2),
128.3 (2 × CH, C-9), 128.0 (CH, C-11), 123.5 (C, C-4), 94.7 (C, C-5), 79.4 (C, C-6), 40.6 (CH$_2$, C-
7); IR: $\nu_{\text{max}}$ (cm$^{-1}$) 3060, 3029, 2924, 2165, 1879, 1595, 1486, 1419, 1237, 840, 751, 659;
HRMS (ES) m/z calculated for C$_{15}$H$_{13}$S (M+H)$^+$ 225.0738, found 225.0736.

**{(4-Methoxybenzyl)(phenylethynyl)sulfane}**

Following **GP1** using phenylacetylene (409 mg, 439 µL, 4.0 mmol), n-BuLi (2.1 mL, 2.1 M, 4.4
mmol), sulfur powder (128 mg, 4.0 mmol), 4-methoxybenzyl bromide (804 mg, 577 µL, 4.0
mmol) stirred for 18 h gave sulfide **182** as a pale yellow oil (458 mg, 45%). R$_f$ 0.80. $^1$H NMR
(300 MHz CDCl$_3$): $\delta$ 7.35 – 7.27 (m, 5H, H1-3), 7.29 (d, $J$ = 7.6, 2H, H-9), 6.91 (d, $J$ = 7.6, 2H, H-
10), 4.00 (s, 2H, H-7), 3.81 (s, 3H, H-13); $^{13}$C NMR (101 MHz CDCl$_3$): $\delta$ 159.4 (C, C-11), 131.5 (2
× CH, C-3), 130.5 (2 × CH, C-2), 128.8 (C, C-8), 128.5 (2 × CH, C-9), 128.2 (CH, C-1), 122.6 (C,
C-4), 114.2 (2 × CH, C-10), 94.7 (C, C-5), 79.6 (C, C-6), 55.5 (CH$_3$, C-12), 40.3 (CH$_2$, C-7); IR:
$\nu_{\text{max}}$ (cm$^{-1}$) 2999, 2932, 2834, 2165, 1609, 1584, 1511, 1486, 1302, 1247, 1175, 1033, 831,
755, 730, 663.; HRMS (ES) m/z calculated for C$_{16}$H$_{14}$OS 254.0765, found 254.0770.
Following GP2 using sulfide 182, (458, 1.8 mmol), mCPBA (342 mg, 1.9 mmol) stirred for 16 h gave sulfoxide 183, purified using [hexane/EtOAc(8:2)] as a pale yellow oil (350 mg, 72%). Rf = 0.40. 1H NMR (300 MHz CDCl3): 7.49 – 7.32 (m, 5H, H1-3), 7.32 (d, J = 8.7, 2H, H-9), 6.91 (d, J = 8.7, 2H, H-10), 4.35 (d, J = 3.6, 2H, H-7), 3.82 (s, 3H, H-12); 13C NMR (101 MHz CDCl3): δ 158.7 (C, C-11), 132.2 (2 × CH, C-3), 131.9 (2 × CH, C-9), 130.6 (CH, C-1), 129.5 (2 × CH, C-2), 128.6 (2 × CH, C-10), 126.2 (C, C-8), 120.9 (C, C-4), 90.6 (C, C-5), 71.5 (C, C-6), 62.2 (CH2, C-7), 55.3 (CH3, C-12); IR: νmax (cm⁻¹) 3000, 2933, 2835, 2164, 1667, 1609, 1510, 1442, 1302, 1245, 1175, 1059, 1029, 826, 755, 688; HRMS (ES) m/z calculated for C16H15O2S (M+H)+ 271.0793, found 271.0800.

(3-Methoxybenzyl)(phenylethynyl)sulfane

Following GP1 using phenyl acetylene (613 mg, 659 μL, 6.0 mmol), n-BuLi (3.5 mL, 1.9 M, 6.6 mmol), sulfur powder (192 mg, 6.0 mmol), 3-methoxybenzyl bromide (1.2 g, 8.4 mL, 6.0 mmol) stirred for 17 h gave sulfoxide 185 as a pale yellow oil (1.2 g, 77%). Rf 0.78. 1H NMR
(300 MHz CDCl₃): δ 7.37 – 7.26 (m, 6H, H1-3, H-11) 6.98 – 6.93 (m, 2H, H9-10), 6.88 – 6.83 (m, 1H, H-12), 4.00 (s, 2H, H-7), 3.80 (s, 3H, H-14); ¹³C NMR (101 MHz CDCl₃): δ 159.8 (C, C-13), 138.2 (C, C-8), 131.5 (2 × CH, C-3), 129.7 (CH, C-11), 128.4 (CH, C-1), 128.2 (2 × CH, C-2), 123.5 (C, C-4), 121.6 (CH, C-9), 114.6 (CH, C-10), 113.7 (CH, C-12), 94.8 (C, C-5), 79.3 (C, C-6), 55.4 (CH₃, C-14), 40.7 (CH₂, C-7); IR: νmax (cm⁻¹) 3000, 2932, 2165, 1884, 1609, 1510, 1462, 1302, 1243, 1174, 1031, 828, 752, 689; HRMS (ES) m/z calculated for C₁₆H₁₄OS (M+H)⁺ 255.0844, found 255.0842.

1-Methoxy-3-((((phenylethynyl)sulfinyl)methyl)benzene

Following GP2 using sulfide 185, (778 mg, 3.1 mmol), mCPBA (580 mg, 3.4 mmol) stirred for 16 h gave sulfoxide 186, purified using [hexane/EtOAc(8:2)] as a pale yellow oil (471 mg, 57%). Rf = 0.37. ¹H NMR (300 MHz CDCl₃): 7.47 – 7.25 (m, 7H, H1-3, H-9, H-11), 6.96 – 6.89 (m, 2H, H-10, H-12), 4.36 (app s, 2H, H-7), 3.77 (s, 3H, H-14); ¹³C NMR (101 MHz CDCl₃): 156.8 (C, C-13), 132.2 (2 × CH, C-3), 130.7 (CH, C-11), 130.4 (C, C-8), 129.8 (CH, C-1), 128.6 (2 × CH, C-2), 122.9 (CH, C-9), 119.7 (C, C-4), 116.0 (CH, C-10), 114.6 (CH, C-12), 103.3 (C, C-5), 85.1 (C, C-6), 62.9 (CH₂, C-7), 55.3 (CH₃, C-14); IR: νmax (cm⁻¹) 2941, 2835, 2163, 1667, 1597, 1488, 1450, 1297, 1264, 1153, 1042, 831, 784, 739, 757, 687; HRMS (ES) m/z calculated for C₁₆H₁₄O₂SNa (M+Na)⁺ 293.0612, found 293.0610.
A known compound was prepared using a modified literature precedent.\textsuperscript{129}

**3,5-dichloropyridine N-oxide**

Oxidation of 3,5-dichloropyridine to the corresponding N-oxide by mCPBA:

Purified mCPBA (985 mg, 5.5 mmol) was added in portions over 15 mins to a solution of 3,5-dichloropyridine (740 mg, 5.0 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (0.1 M) at -15 °C. The resultant mixture was stirred for 30 mins at -15 °C before being warmed gradually over 1 h to 0 °C and stirred for an additional 3 h. Upon completion the mixture was diluted with further CH\textsubscript{2}Cl\textsubscript{2} (0.1 M) before the addition of NaHCO\textsubscript{3} (0.1 M). The organic phase was extracted using CH\textsubscript{2}Cl\textsubscript{2} (× 3). The combined organic extracts were dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure to yield a pale yellow crystalline solid (549 mg, 67%). R\textsubscript{f} = 0.22. The crude product was purified by flash column chromatography on silica gel [hexane/EtOAc (70:30)]. m.p: 111 – 113 °C, lit. m.p: 109 – 110 °C. \textsuperscript{1}H NMR (300 MHz CDCl\textsubscript{3}): \(\delta\) 8.15 (d, \(J = 1.6, 2H, H-2\)), 7.31 (t, \(J = 1.4, 1H, H-4\)). \textsuperscript{13}C NMR (101 MHz CDCl\textsubscript{3}): \(\delta\) 137.4 (CH, C-4), 133.4 (2 × C, C-3), 126.2 (2 × CH, C-2). IR: \(\nu_{\text{max}}\) (cm\textsuperscript{-1}) 3049, 3010, 1588, 1538, 1448, 1406, 1272, 1131, 1110, 1090, 1045, 963, 892, 836, 822, 751, 664. Analytical data in agreement with literature values.\textsuperscript{130}
Dimethylsulfide, Me₂S (98 mg, 115 μL, 1.6 mmol) as a solution in MeOH (0.8 mL) was added drop-wise to a foil-wrapped flask containing potassium gold(III) chloride, K(AuCl₄) (205 mg, 0.50 mmol) as a solution in MeOH (3.2 mL) and stirred for 1 h at RT. Upon completion the reaction mixture was filtered through paper using a vacuum pump and the filtrate washed with 10 mL portions of MeOH, Et₂O and pentane and left to dry under suction for 10 mins to yield chloro(dimethylsulfide)gold(I), (Me₂S)AuCl as a white powder which was used in the next step without further purification.

2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl, SPhos (98 mg, 0.24 mmol) was added to a foil-wrapped flask containing (Me₂S)AuCl (70 mg, 0.24 mmol) as a solution in anhydrous CH₂Cl₂ (7 mL) and stirred for 2 h at RT. Upon completion the reaction mixture was concentrated under reduced pressure. SPhosAuCl was obtained as a white solid and used in the next step without further purification.

AgNTf₂ (66 mg, 0.20 mmol) was added to a solution of SPhosAuCl (110 mg, 0.20 mmol) in anhydrous CH₂Cl₂ (3 mL) and stirred for 30 mins at RT. Upon completion the reaction mixture was filtered through a pad of celite using portions of anhydrous CH₂Cl₂, the solvent was
removed under reduced pressure and SPhosAuNTf₂ was obtained as a white solid (150 mg, 85%) and used without further purification. m.p: 60 – 62 °C. ¹H NMR (300 MHz CDCl₃): δ 7.64 – 7.54 (m, 2H, H-5, H-7), 7.53 – 7.46 (m, 1H, H-6), 7.43 (t, J = 8.4, 1H, H-3), 7.21 (ddd, J = 8.3, 4.6, 1.5, 1H, H-8), 6.71 (d, J = 8.4, 2H, H-2, H-4), 3.69 (s, 6H, H-1), 2.25 – 1.93 (m, 4H, H-12), 1.92 – 1.60 (m, 8H, H-11, H-13), 1.46 – 1.00 (m, 10H, H-9, H-10, H-14); ³¹P NMR (122 MHz, CDCl₃): δ = 37.9; IR: νₘₐₓ (cm⁻¹) 2930, 2853, 1589, 1472, 1433, 1396, 1353, 1251, 1191, 1130, 1110, 1002, 956, 824, 777, 728, 661.

4.5 Analysis and characterisation of products of gold-catalysis

Scheme 62: Stereochemistry and proton shifts of compound 93

Relative stereochemistry of the major diastereoisomer and proton shifts are shown above for compound 93, the gold-catalysis products are assigned in correlation with this.
Following GP3 using sulfoxide 81 (20.4 mg, 0.10 mmol), 3,5-dichloropyridine N-oxide (19.7 mg, 0.12 mmol), SPhosAuNTf$_2$ (4.4 mg, 5 mol%), stirred for 17 h gave 82 (a 33:1 mixture of diastereoisomers), purified using [EtOAc/MeOH (9:1)] as a pale yellow oil (12.6 mg, 57%). $R_f$ 0.11. The data for the major diastereoisomer is assigned. $^1$H NMR (300 MHz CDCl$_3$): 7.98 (dt, $J = 7.2, 1.5, 2H, H-3$), 7.60 (tt, $J = 7.2, 1.5, 1H, H-1$), 7.50 (td, $J = 7.2, 1.5, 2H, H-2$), 3.52 (ddd, $J = 13.2, 7.7, 4.3, 1H, H-10a$), 2.78 – 2.72 (m, 1H, H-10b), 2.72 – 2.67 (m, 1H, H-8), 2.55 – 2.33 (m, 2H, H-9), 2.26 (t, $J = 5.9, 1H, H-7a$), 1.82 (dd, $J = 8.7, 5.9, 1H, H-7b$); $^{13}$C NMR (101 MHz CDCl$_3$): δ 196.5 (C, C-5), 136.7 (C, C-4), 133.4 (CH, C-1), 129.4 (2 × CH, C-3), 128.7 (2 × CH, C-2), 59.6 (C, C-6), 54.4 (CH$_2$, C-10), 33.9 (CH, C-8), 26.4 (CH$_2$, C-9), 19.4 (CH$_2$, C-7); IR: $\nu$$_{max}$ (cm$^{-1}$) 3400, 3079, 3003, 2929, 2257, 2219, 2198, 1973, 1907, 1659, 1597, 1449, 1319, 1278, 1059, 1041, 1006, 914, 751, 691, 664; HRMS (ES) $m/z$ calculated for C$_{12}$H$_{12}$O$_2$SNa (M+Na)$^+$ 243.0456, found 243.0453.

$1$-(2-Oxido-2-thiabicyclo[3.1.0]hexan-1-yl)pentan-1-one
Following GP3 using sulfoxide 77 (36.8 mg, 0.20 mmol), 3,5–dichloropyridine N-oxide (39.4 mg, 0.24 mmol), SPhosAuNTf₂ (8.8 mg, 5 mol%), stirred for 17 h gave 84 (a 5:1 mixture of inseparable diastereoisomers) purified using [EtOAc/MeOH (9:1)] as a pale yellow oil (29.4 mg, 73%). R_f 0.12. The data for the major diastereoisomer is assigned. ¹H NMR (300 MHz CDCl₃): δ 3.57 – 3.47 (m, 1H, H-10a), 2.85 (t, J = 7.4, 2H, H-4), 2.54 – 2.45 (m, 1H, H-10b), 2.44 – 2.36 (m, 1H, H-8), 2.33 – 2.25 (m, 2H, H-9), 2.04 (app t, J = 5.7, 1H, H-7a), 1.83 (dd, J = 8.4, 5.7, 1H, H-7b), 1.59 (tt, J = 7.5, 7.4, 2H, H-3), 1.31 (app quin., J = 7.5, 2H, H-2), 0.89 (t, J = 7.3, 3H, H-1); ¹³C NMR (101 MHz CDCl₃): δ 203.7 (C, C-5), 58.6 (C, C-6), 50.7 (CH₂, C-10), 40.7 (CH₂, C-4), 35.2 (CH, C-8), 25.5 (CH₂, C-3), 25.3 (CH₂, C-9), 22.1 (CH₂, C-2), 17.7 (CH₂, C-7), 13.8 (CH₃, C-1); IR: ν_max (cm⁻¹) 2957, 2933, 2871, 1687, 1450, 1375, 1260, 1055, 1031, 992, 875; HRMS (ES) m/z calculated for C₁₀H₁₇O₂S (M+H)⁺ 201.0949, found 201.0950.

1-(2-Oxido-2-thiabicyclo[3.1.0]hexan-1-yl)-3-phenylpropan-1-one

Following GP3 using sulfoxide 88 (23.2 mg, 0.10 mmol), 3,5–dichloropyridine N-oxide (19.7 mg, 0.12 mmol), SPhosAuNTf₂ (4.4 mg, 5 mol%) stirred for 3.5 h gave 89 (a 6:1 mixture of inseparable diastereoisomers) as a pale yellow oil purified using [EtOAc/MeOH (9.5:0.5)] (15.7 mg, 63%). R_f 0.20. The data for the major diastereoisomer is assigned. ¹H NMR (300 MHz CDCl₃): δ 3.50 (ddd, J = 13.2, 6.9, 2.9, 1H, H-12a), 3.20 – 3.17 (m, 2H, H-5), 2.97 (t, J = 7.4, 2H, H-6), 2.55 – 2.45 (m, 1H, H-12b), 2.45 – 2.35 (m, 1H, H-10), 2.31 – 2.24 (m, 2H, H-11),
2.07 (app t, J = 5.9, 1H, H-9a), 1.86 (dd, J = 8.4, 5.9, 1H, H-9b); $^{13}$C NMR (101 MHz CDCl$_3$): δ 202.9 (C, C-7), 140.4 (C, C-4), 128.6 (2 × CH, C-2), 128.5 (2 × CH, C-3), 126.3 (CH, C-1), 58.9 (C, C-8), 50.9 (CH$_2$, C-12), 42.9 (CH$_2$, C-6), 35.6 (CH, C-10), 29.7 (CH$_2$, C-5), 25.4 (CH$_2$, C-11), 18.1 (CH$_2$, C-9); IR: $\nu_{\text{max}}$ (cm$^{-1}$) 3410, 3028, 2931, 1689, 1584, 1536, 1400, 1372, 1251, 1107, 1058, 967, 842, 730, 699, 615; HRMS (ES) m/z calculated for C$_{14}$H$_{17}$O$_2$S (M+H)$^+$ 249.0949, found 249.0952.

*Cyclopropyl(2-oxido-2-thiabicyclo[3.1.0]hexan-1-yl)methanone*

Following GP3 using sulfoxide 92 (17.0 mg, 0.10 mmol), 3,5-dichloropyridine N-oxide (19.7 mg, 0.12 mmol), SPhosAuNTf$_2$ (4.4 mg, 5 mol%) stirred for 0.5 h gave 93 (a 10:1 mixture of inseparable diastereoisomers) as a pale yellow oil purified using [EtOAc/MeOH (9:1)] (15.8 mg, 86%). R$_f$ 0.15. The data for the major diastereoisomer is assigned. $^1$H NMR (300 MHz CDCl$_3$): δ 3.55 (app dt, J = 13.5, 4.8, 1H, H-8a), 2.56 – 2.50 (m, 1H, H-2), 2.50 – 2.46 (m, 1H, H-8b), 2.43 – 2.38 (m, 1H, H-6), 2.38 – 2.29 (m, 2H, H-7), 2.12 (app t, J = 6.1, 1H, H-5a), 1.88 (dd, J = 8.6, 6.1, 1H, H-5b), 1.22 – 1.13 (m, 2H, H-1), 1.09 – 0.99 (m, 2H, H-1); $^{13}$C NMR (101 MHz CDCl$_3$): δ 203.8 (C, C-3), 59.3 (C, C-4), 50.6 (CH$_2$, C-8), 34.5 (CH, C-6), 25.5 (CH$_2$, C-7), 18.7 (CH, C-2), 17.8 (CH$_2$, C-5), 12.8 (2 × CH$_2$, C-1); IR: $\nu_{\text{max}}$ (cm$^{-1}$) 3412, 2934, 1167, 1445, 1394, 1250, 1057, 1022, 988, 872, 885, 677; HRMS (ES) m/z calculated for C$_9$H$_{12}$O$_2$SNa (M+Na)$^+$ 207.0456, found 207.0461.
Following GP3 using sulfoxide 100 (36.8 mg, 0.20 mmol), 3,5-dichloropyridine N-oxide (39.4 mg, 0.24 mmol), SPhosAuNTf₂ (8.8 mg, 5 mol%) stirred for 18 h gave 101 (a 7:1 mixture of inseparable diastereoisomers) as a pale yellow oil purified using [EtOAc/MeOH (9.5:0.5)] (20.4 mg, 51%). R₆ 0.17. The data for the major diastereoisomer is assigned. ¹H NMR (300 MHz CDCl₃): δ 3.51 (ddd, J = 13.2, 6.8, 4.9, 1H, H-8a), 2.65 (ddd, J = 13.2, 6.8, 4.9, 1H, H-8b), 2.48 – 2.39 (m, 1H, H-6), 2.38 – 2.29 (m, 2H, H-7), 2.03 (app t, J = 5.7, 1H, H-5a), 1.78 (dd, J = 8.6, 5.7, 1H, H-5b), 1.36 (s, 9H, H-1); ¹³C NMR (101 MHz CDCl₃): δ 207.6 (C, C-3), 58.3 (C, C-4), 53.7 (CH₂, C-8), 45.4 (C, C-2), 36.6 (CH, C-6), 26.7 (3 × CH₃, C-1), 25.9 (CH₂, C-7), 18.5 (CH₂, C-5); IR: νmax (cm⁻¹) 3470, 2971, 2871, 1678, 1478, 1367, 1225, 1169, 1091, 1057, 994; HRMS (ES) m/z calculated for C₁₀H₁₆O₂S (M+H)⁺ 200.0871, found 200.0879.

Following GP3 using sulfoxide 105 (96.9 mg, 0.40 mmol), 3,5-dichloropyridine N-oxide (78.7 mg, 0.48 mmol), SPhosAuNTf₂ (17.7 mg, 5 mol%), stirred for 17 h gave 107 (a mixture of inseparable diastereoisomers) purified using [EtOAc/MeOH (9:1)] as a pale yellow oil (R₆
0.10. A yield cannot be confidently reported (see Section 2.8). The data for the major diastereoisomer is assigned where possible; some doubling is seen in the $^{13}$C NMR, in which case the ppm for the major diastereoisomer is quoted before the ppm of the minor. $^1$H NMR (300 MHz CDCl$_3$): 4.78 (app d, $J = 3.0$, 2H, H-2), 3.65 – 3.57 (m, 1H, H-8a), 3.08 – 2.80 (m, 1H, H-1), 2.66 – 2.62 (m, 1H, H-8b), 2.60 – 2.57 (m, 1H, H-6), 2.41 – 2.36 (m, 2H, H-7), 2.25 (app t, $J = 6.3$, 1H, H-5a), 1.99 (dd, $J = 8.7$, 6.3, 1H, H-5b); $^{13}$C NMR (101 MHz CDCl$_3$): $\delta$ 203.4 (C, C-3), 67.7/68.9 (CH$_2$, C-2), 56.8 (C, C-4), 51.2/50.4 (CH$_2$, C-8), 37.1/34.2 (CH, C-6), 25.6/25.3 (CH$_2$, C-7), 19.6/18.9 (CH$_2$, C-5); IR: $\nu_{\max}$ (cm$^{-1}$) 3342, 2940, 2289, 2216, 2113, 2010, 1698, 1251, 1082, 994, 872, 728, 694; LRMS (ES) $m/z$ found C$_7$H$_{10}$O$_3$SNa (M+Na)$^+$ 197.1.
Appendices
Appendix A – NMR Spectra
Figure 25: Two dimensional HSQC spectrum analysis of compound 84
Appendix B – NMR Yield Calculations
Molar quantity of internal standard (TMB): \( \frac{2.4}{134.22} = 0.018 \text{ mmols} \)

Using integrals of characteristic peaks from \( ^1H \) NMR:

Internal standard (2H): starting material (1H): product (1H)

Factor ratio to give 1H: 1H: 1H:

\[
\frac{IS}{2} : SM : P
\]

\[
\frac{IS}{2} : \frac{SM}{2} : \frac{P}{2}
\]

Enter integral values:

\[
\left( \frac{1.00}{2} \right) : 0.33 : 1.37
\]

Molar ratio:

1: 0.66: 2.74

Multiply by molar quantity of IS to give the molar quantities present in the crude mixture:
(IS) 0.018 mmols: (SM) 0.012 mmols: (P) 0.049 mmols

For a 0.1 mmol scale reaction, yields are calculated as:

SM: 12%
P: 49%

Example:
References


2008, **130**, 4517 – 4526.


