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Gold-Catalysed Reactions of Alkynyl Sulfoxides

by

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A Thesis submitted to

The University of Birmingham

For the Degree of

Master of Science by Research

School of Chemistry

University of Birmingham

September 2015

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Acknowledgements

Firstly I would like to thank both of my wonderful supervisors, Dr. Paul Davies and Dr.

Richard Grainger for being the best supervisors I could have asked for, for giving me the opportunity to work on this fantastic project and for all of their valuable insight and support during my Masters.

I'd like to thank the entire analytical facility in the School of Chemistry, Chi Tsang, Peter Ashton, Neil Spencer and Lianne Hill. Thanks to Pele for all the IT support and Stuart Arkless for always doing a great job.

To Matthew Barrett for all his time and greatly appreciated advice during this project – thank you.

I'm eternally grateful to the Grainger group which made my time here so enjoyable; our lab was definitely the most fun, comfortable and happy place to work. Thank yous go to: Snainger group member Dr. Glenn Lees for all the tips, tricks and random chemistry I learnt from him and of course the dishwasher which I cherished. Richard Myerson for all his wise counsel be it chemistry or cars. Matthew Ball, for all the gossip and chit chat – mainly gossip, thank you. Dr. Michael Kyle for his terrible taste in music (which I pretended not to share) and for making the lab and office such a lively and fun place to work. Dr. Carlotta Figliola for her friendship, the 'coffee+stories' and listening to my complaints. Thanks to all the project students who brought life into the lab during my time here.

And Sanaz Ahmadipour, thank you for being so kind, caring and welcoming and thank you for all those wonderful times, the trips, the laughs which made working until very late seem less

painful, for feeding me Turkish delight and all those wonderful Iranian treats and for being a genuine friend.

Last but not least, I'd also like to thank all of my friends and family, including my brilliant chemistry teacher Mr. Randhawa for not only being a great chemistry teacher but for also encouraging me and always being on my side.

But most importantly my grandmother, thank you – none of this would have been possible without all of your hard effort and love.

Abstract

Gold π -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 α -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.

List of Figures

Figure 1: Change in number of publications relating to gold-catalysis in recent years	7
Figure 2: Relativistic contraction of the 6s shell for element Cs to Fm.....	8
Figure 3: Structure of AuCl(PPh ₃)	9
Figure 4: Qualitative orbital diagram showing the interaction between gold and acetylene .	11
Figure 5: Representation of partial slippage and the redistribution of electron density	12
Figure 6: Singlet and triplet carbene spin states	14
Figure 7: Dominant orbital interactions in a Fischer carbene	14
Figure 8: Orbital interactions in Schrock carbene	15
Figure 9: Structure of IMes, a NHC ligand	16
Figure 10: Structure of TsN ₃	17
Figure 11: Structure of an α -Diazocarbonyl species.....	23
Figure 12: Structure of a sulfoxide	25
Figure 13: Structure of an α -diazo- β -keto sulfoxide	26
Figure 14: Diastereomeric bicyclic sulfoxides	31
Figure 15: Maguire's mechanistic interpretation of instability of diazosulfoxides	32
Figure 16: Structure of the Davis Reagent, <i>trans</i> -2-(phenylsulfonyl)-3-phenyloxaziridine ...	46
Figure 17: Structure of ligand and <i>N</i> -oxides used in the preliminary study	50
Figure 18: Unfavourable interactions influencing regioselective oxidation	52
Figure 19: Structures of ligands and <i>N</i> -oxides used as part of the optimisation	55
Figure 20: Orientation of sulfinyl oxygen in bicyclic sulfides and the corresponding chemical shifts of neighbouring protons	76
Figure 21: X-ray crystal structure (obtained from M. Barrett) for compound 82	77
Figure 22: Comparison of chemical shifts for thiabicyclo catalysis product 82.....	77
Figure 23: Structures of possible diastereoisomeric configurations.....	78
Figure 24: Resonance structures representing methoxy electron donating activation of the phenyl ring.....	90
Figure 25: Two dimensional HSQC spectrum analysis of compound 84	136

List of Schemes

Scheme 1: Ito's gold-catalysed asymmetric aldol reaction	5
Scheme 2: Addition of an alcohol to an alkyne	6
Scheme 3: Metathesis reaction between gold chloride and a counterion	10
Scheme 4: Gold species alkyne activation towards nucleophilic attack.'	12
Scheme 5: Diazo dipole stabilisation by the carbonyl group	16
Scheme 6: Reaction of an acyl chloride with diazomethane	17
Scheme 7: Reaction mechanism of an acyl chloride with diazomethane	17
Scheme 8: Reaction of carbonyl with TsN ₃	17
Scheme 9: Removal of diazo group to form a carbene	18
Scheme 10: Safe synthesis of an α -oxo gold carbene	19
Scheme 11: Carbene installation α to a sulfide.....	20
Scheme 12: Installation of a carbene in the α -position relative to a sulfide	20
Scheme 13: Sulfur ylide generation <i>via</i> gold-catalysed rearrangement	21
Scheme 14: Range of cycloisomerisation reactions observed during catalysis with 1,6-enynes	22
Scheme 15: Gold-catalysed skeletal rearrangement of a 1,6-enyne	23
Scheme 16: Regitz method	24
Scheme 17: Diazo transfer attempted by Hodson and Holt	27
Scheme 18: Proposed decomposition of α -diazo- β -keto sulfoxides.....	27
Scheme 19: First reported isolated α -diazosulfoxide.....	28
Scheme 20: Attempted diazo transfer to acyclic α -sulfinyl esters	29
Scheme 21: Synthesis of bicyclic α -diazosulfoxides	30
Scheme 22: General scheme depicting the Wolff rearrangement	33
Scheme 23: Wolff rearrangement of cyclic α -diazosulfoxide	34
Scheme 24: Formation and trapping of the α -oxo-sulfine	35
Scheme 25: Zhang's cyclopropanation	39
Scheme 26: Formation of bicyclic heterocyclic structure	40

Scheme 27: Proposed catalytic cycle for the expected transformation of 1,6-enynes to thiabicyclo[3.1.0]hexane like structures	41
Scheme 28: Williamson ether synthesis mechanism with thiol.....	42
Scheme 29: Zheng's one pot alkynyl sulfide synthesis.....	44
Scheme 30: Oxidation of sulfide to sulfoxide.....	45
Scheme 31: Oxidation of alkynyl sulfide to corresponding alkynyl sulfoxide	47
Scheme 32: Synthesis of the aryl alkynyl sulfide and consequent oxidation.....	48
Scheme 33: Gold-catalysed reaction of the aryl alkynyl sulfoxide.....	49
Scheme 34: Synthesis of substrate 77	53
Scheme 35: Gold-catalysed reaction of the alkyl alkynyl sulfoxide	53
Scheme 36: Synthesis and reaction of 4-phenyl-1-butyne alkynyl sulfoxide 88.....	60
Scheme 37: Synthesis and reaction of cyclopropyl alkynyl sulfoxide 92	61
Scheme 38: Synthesis and reaction of TBDPS ether 94	62
Scheme 39: Synthesis and reaction of <i>tert</i> -butyl alkynyl sulfoxide 100	63
Scheme 40: Protection of propargyl alcohol with tetrahydropyran	63
Scheme 41: <i>n</i> -BuLi one-pot synthesis using THP ether 103	64
Scheme 42: LiHMDS synthesis and reactions of THP ether 103	65
Scheme 43: Attempted synthesis of <i>N</i> -propargylphthalimide substituted alkynyl sulfide	66
Scheme 44: Corey-Fuchs homologation.....	67
Scheme 45: General mechanism for the Corey-Fuchs homologation reaction	67
Scheme 46: Poor yielding sulfide synthesis.....	68
Scheme 47: Terminal alkyne synthesis from the dibromo olefin.....	68
Scheme 48: <i>n</i> -BuLi synthesis of alkynyl sulfoxide	69
Scheme 49: LiHMDS method synthesis of alkynyl sulfoxide	69
Scheme 50: Dibromo olefin 131 synthesis	70
Scheme 51: Synthesis and reaction of 1,7-enyne substrate	71
Scheme 52: Synthesis of 1,5-enyne variants.....	72
Scheme 53: General mechanism of C-H insertion.....	85
Scheme 54: Orbital interactions during a singlet carbene C-H insertion reaction	85
Scheme 55: Toste's postulated C-H insertion	86

Scheme 56: Gold-catalysed cycloisomerisation/C-H insertion	87
Scheme 57: Fürstner's intramolecular arylation	87
Scheme 58: Proposed C-H insertion	88
Scheme 59: Synthesis and reaction of diphenyl substrate	89
Scheme 60: Synthesis and reaction of <i>para</i> -methoxy benzyl sulfoxide.....	91
Scheme 61: Synthesis and reaction of <i>meta</i> -methoxy benzyl sulfoxide.....	92
Scheme 62: Stereochemistry and proton shifts of compound 93	122

List of Tables

Table 1: Preliminary optimisation of the gold-catalysed reaction of alkynyl sulfoxides	49
Table 2: Optimisation of the gold-catalysed oxidative cyclopropanation	54
Table 3: Summary of final results	73
Table 4: ^1H -NMR comparison table for the resonance (ppm) observed for the indicated proton in the major and minor diastereoisomers.....	79
Table 5: ^{13}C -NMR comparison table for characteristic peaks (ppm).....	80
Table 6: Gold catalysed reactions results for aryl systems and continuation of alkyl systems	82

List of Abbreviations

°C	degrees Celsius
Å	angstrom (10^{-10} m)
Ac	acetyl
app.	apparent
aq.	aqueous
br	broad
Bu	butyl
cat.	catalyst
cm ⁻¹	wavenumbers
d	doublet
1,2-DCE	1,2-dichloroethene
DHP	3,4-dihydropyran
DPAA	diphenylacetic acid
d.r.	diastereomeric ratio
δ	chemical shift
EDG	electron donating group
EI	electron impact ionisation
ES	electronspray ionisation
Et	ethyl
EWG	electron withdrawing group
eq	equivalent

FT-IR	Fourier transform infrared
G	gram(s)
h	hour(s)
hex	hexyl
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
Im	imidazole
IMes	1,3-bis(2,4,6-trimethylphenyl)-imidazolium
IPr	1,3-bis(2,4,6-diisopropylphenyl)-imidazolium
ⁱ Pr	isopropyl
IR	infrared
<i>J</i>	coupling constant (hertz)
K	Kelvin
L	litres
L	ligand
LG	leaving group
LMCT	ligand-to-metal charge transfer
LiHMDS	lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	molar (mol l ⁻¹)
[M]	metal
Me	methyl

<i>m</i> CPBA	<i>meta</i> -chloroperbenzoic acid
mg	milligram(s)
min	minute(s)
MLCT	metal-to-ligand charge transfer
mm	millimetre(s)
mol	moles
m.p.	melting point
<i>m/z</i>	mass/charge
<i>n</i> -BuLi	<i>n</i> -Butyllithium
NHC	<i>N</i> -heterocyclic carbene
nm	nanometre(s)
NMR	nuclear magnetic resonance
Nu	nucleophile
[O]	oxidation
Ph	phenyl
PKF	perfluorokerosene
ppm	part(s) per million
Pr	propyl
Py	pyridine
q	quartet
quin	quintet
R _f	retention factor
RT	room temperature
s	singlet
t	triplet

TBDPS	<i>tert</i> -butyldiphenylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMB	1,2,4,5-tetramethylbenzene
TMS	tetramethylsilane
ν	frequency

Table of Contents

Chapter 1: Introduction	1
1.1 Gold.....	2
1.2 Gold as a catalyst.....	3
1.2.1 Reactivity	4
1.2.2 Relativistic effects.....	7
1.2.3 Alkyne π -acid activation	10
1.2.4 Nucleophilic addition.....	11
1.3 Carbenes	13
1.3.1 Types of carbene	14
1.3.2 Carbene formation	16
1.3.3 α -Oxo gold carbene formation	18
1.4 Selected examples of gold-catalysis	19
1.4.1 Sulfur ylide formation.....	19
1.4.2 Gold-catalysed enyne cycloisomerisation	21
1.5 α -Diazo chemistry.....	23
1.5.1 α -Diazocarbonyl species.....	23
1.5.2 α -Diazosulfoxides	24

1.5.2.1 Cyclic α -diazosulfoxides.....	26
1.5.2.2 Degradation of α -diazosulfoxides.....	31
1.6 Wolff rearrangement.....	33
1.6.1 Wolff rearrangement of α -diazosulfoxides	34
1.7 Summary.....	35
Chapter 2: Gold-catalysed oxidative cyclopropanation of alkynyl sulfoxides	37
2.1 Gold-catalysed cyclopropanation.....	38
2.2 Aims and objectives.....	39
2.3 Starting material synthesis	41
2.3.1 Sulfide synthesis	41
2.3.2 Oxidation of sulfides to corresponding sulfoxides	45
2.4 Aromatic substrate	48
2.4.1 Preliminary optimisation of reaction conditions.....	49
2.5 Regioselective oxidation of internal alkynes	51
2.6 Aliphatic substrate.....	53
2.7 Optimisation of reaction conditions.....	53
2.7.1 Application of optimised conditions	59
2.8 Synthesis and reaction of substrates.....	59
2.9 Gold-catalysis results.....	73
2.9.1 X-ray data.....	74

2.9.2 NMR data comparison	78
2.9.2.1 ^1H NMR data comparison	78
2.9.2.2 ^{13}C NMR data comparison	80
2.10 Collaborative work.....	81
2.11 Summary.....	82
Chapter 3: Gold-catalysed intramolecular C-H insertion	84
3.1 C-H insertion	85
3.2 Selected examples	86
3.2.1 Intramolecular gold-catalysed C-H insertion.....	86
3.3 Aims and objectives.....	88
3.4 Synthesis of substrates	88
3.5 Activation of substrates.....	89
3.5.1 <i>Para</i> -methoxy activation	90
3.5.2 <i>Meta</i> -methoxy activation	91
3.6 Summary.....	92
Chapter 4: Experimental.....	93
4.1 General Experimental	94
4.2 Analysis	95
4.3 General procedures for the preparation of starting materials	96

4.4 Analysis and characterisation of starting materials	99
4.5 Analysis and characterisation of products of gold-catalysis	122
Appendices	128
Appendix A – NMR Spectra	129
Appendix B – NMR Yield Calculations	160
References	163

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 immortals¹ 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 dissolved 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}

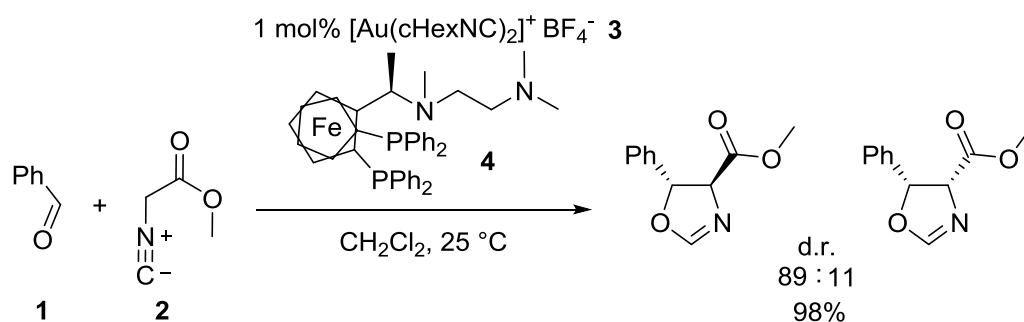
1.2.1 Reactivity

Gold in particular can adopt a number of coordination numbers and has been studied from an organometallic view point,¹² but unlike platinum or iridium, gold was wrongfully regarded to be '*catalytically dead*', whereby the catalyst was totally or partially deactivated.^{13,14} 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.¹⁵ 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.¹⁶ But there was still little progression in the field until the 1980s,^{17,18} until Hutchings and Haruta both published on heterogeneous catalysis, describing the oxidation of CO¹⁹ and later the formation of vinyl chloride from ethyne *via* hydrochlorination,²⁰ 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.²¹

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.²²

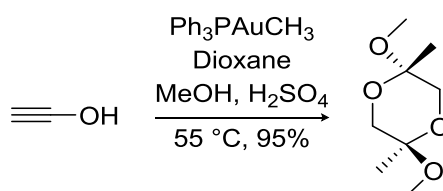
Utilising gold-catalysis in organic synthesis for varied types of reactions offers many advantages over conventional methods, such as: mild reactions at lower temperatures, good chemoselectivity, less complex work-ups, tolerance of water and more efficient access to highly complex compounds. There is 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



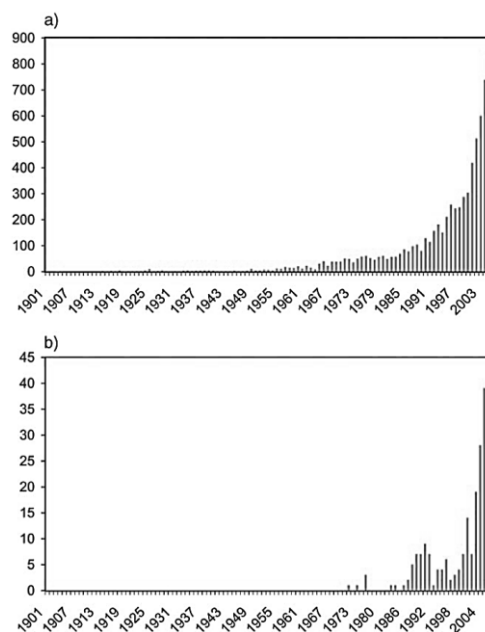
Scheme 1: Ito's gold-catalysed asymmetric aldol reaction

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).²⁴



Scheme 2: Addition of an alcohol to an alkyne

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 syntheses²⁵ There has been an increase in reports of methodology²¹ and proposed processes⁵ of these catalysis reactions.^{26,27} 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.⁸

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 Pyykkö²⁸ 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.^{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 2²⁸ 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.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.

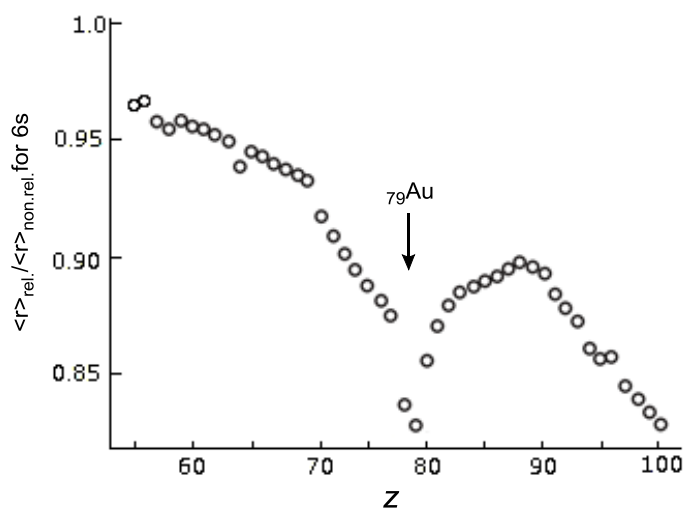


Figure 2: Relativistic contraction of the 6s shell for element Cs to Fm

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 $\text{AuCl(PPh}_3\text{)}$ **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.³²

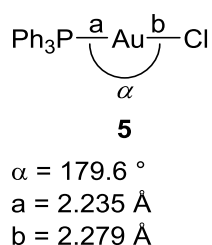
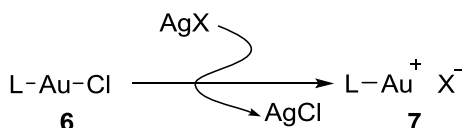


Figure 3: Structure of AuCl(PPh₃)

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 $\text{LAu}^+ \text{X}^-$ 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.³³ 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.



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.^{34, 35} 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 2007.³⁶

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.²⁷

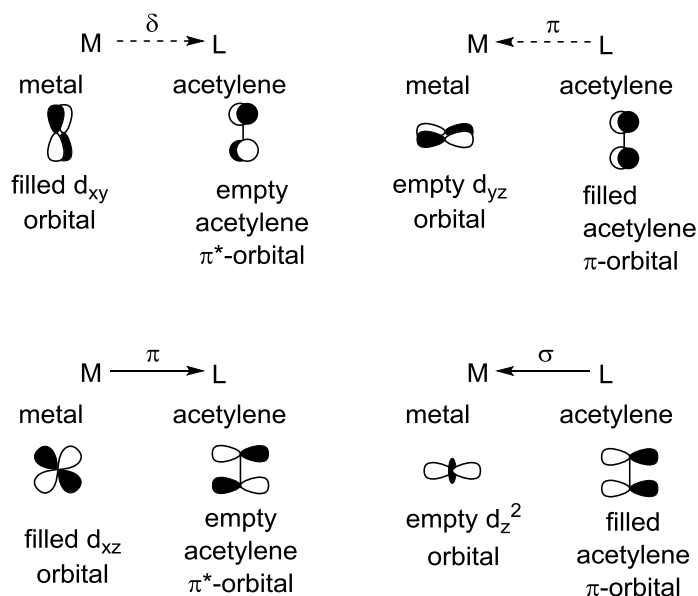


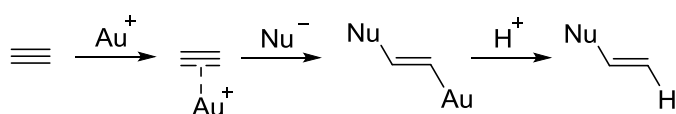
Figure 4: Qualitative orbital diagram showing the interaction between gold and acetylene

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 σ donation received from the alkene unit.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.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.^{38,39,40}

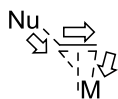
Fukuda and Utimoto examined hydrochlorination with respect to alcohols, water and amines⁴¹ which detailed the addition of nucleophiles to alkynes and was similar in theory to the heterogeneous hydrochlorination carried out by Hutchings.⁹

π -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.



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

As the nucleophile approaches the activated π -system slippage occurs away from the η_2 ground state to the η_1 activated state, which leads to an increase in the electrophilicity as a result of mixing of orbitals which were previously orthogonal.⁴⁴ It also aids the charge transfer to the π -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.^{45,46} Figure 5 shows the reallocation of electron density once nucleophilic attack has occurred to the π -acid bound alkene.



Arrows represent the redistribution of electrons upon nucleophilic attack on an alkene which is attached to a π -acid

Figure 5: Representation of partial slippage and the redistribution of electron density⁴⁷

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 valence 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 (sp²) trigonal hybridisation. This is because a linear (sp) carbene would have to distribute six electrons amongst two σ -orbitals and two degenerate p-orbitals; the electrons in the p-orbital would be unpaired, due to the electron repulsion. However; sp² hybridisation allows for the carbene to spread its electrons amongst three sp² 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 sp² and p-orbitals or paired (both in sp²). 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

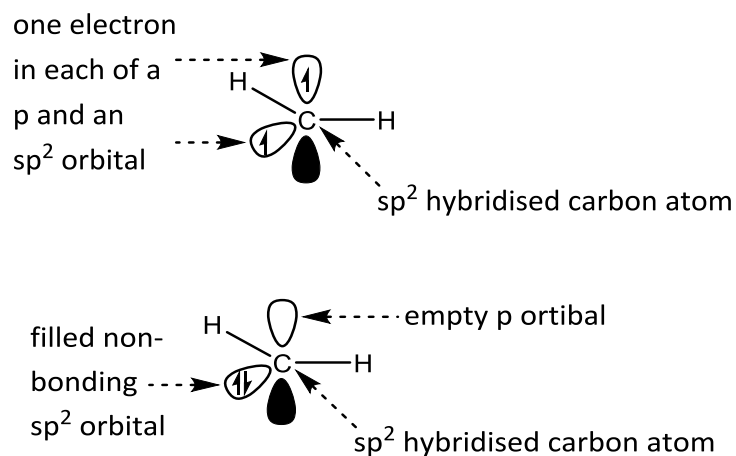


Figure 6: Singlet and triplet carbene spin states

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

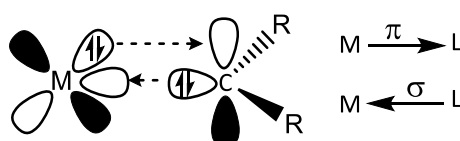


Figure 7: Dominant orbital interactions in a Fischer carbene

Fischer carbenes are metal carbenes in which the metal (such as a low oxidation, π -electron acceptor metal i.e. Fe (0)) is bound to a carbon. The bonding within a Fischer carbene is a σ -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 π -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 π -acceptor ligands, instead consist of π -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.

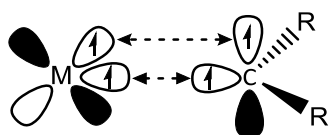


Figure 8: Orbital interactions in Schrock carbene

Persistent carbenes

Persistent carbenes are a class of stable carbenes, which can be isolated, the largest subgroup of persistent carbenes is *N*-heterocyclic carbenes (NHCs) and π -donating substituents on the NHCs play an important role in stabilising the carbene. Although NHCs can act as good σ -donors their π -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.⁴⁹

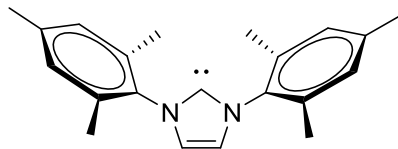
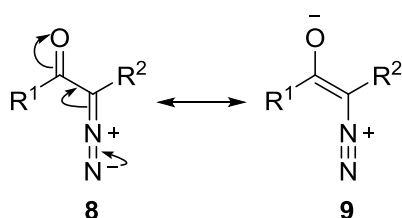


Figure 9: Structure of IMes, a NHC ligand

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.⁴⁰

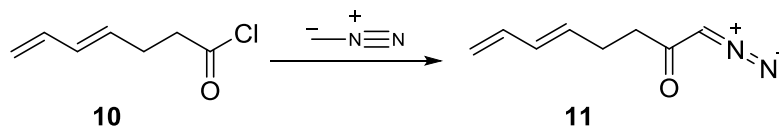


Scheme 5: Diazo dipole stabilisation by the carbonyl group

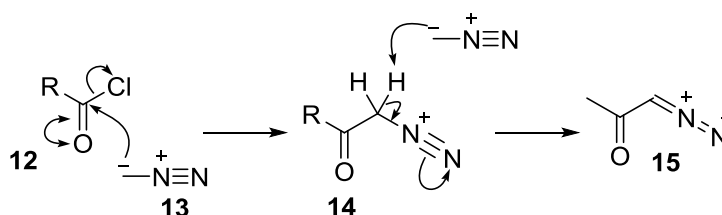
There are two methods regularly employed by which diazocarbonyl compounds are synthesised, see Scheme 6 and Scheme 7.

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.

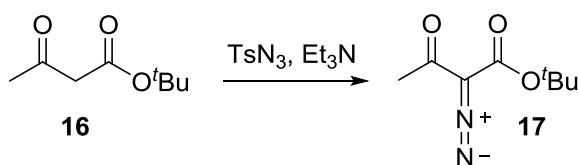


Scheme 6: Reaction of an acyl chloride with diazomethane



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.⁴⁰



Scheme 8: Reaction of carbonyl with TsN₃

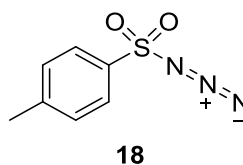
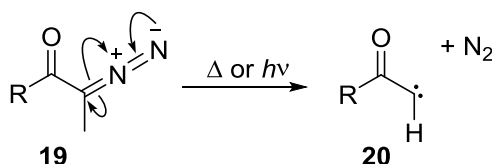


Figure 10: Structure of TsN₃

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 N₂, which compensates for the formation of the carbene.



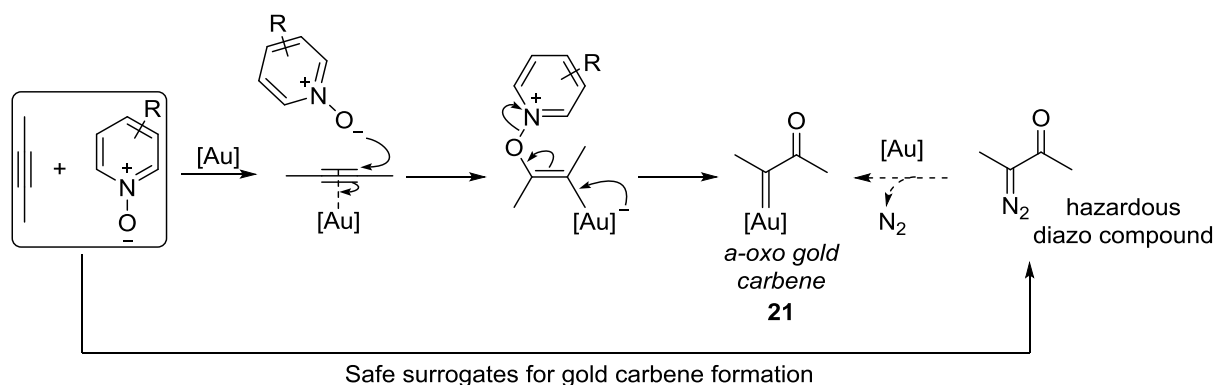
Scheme 9: Removal of diazo group to form a carbene

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 Zhang¹¹⁸

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.



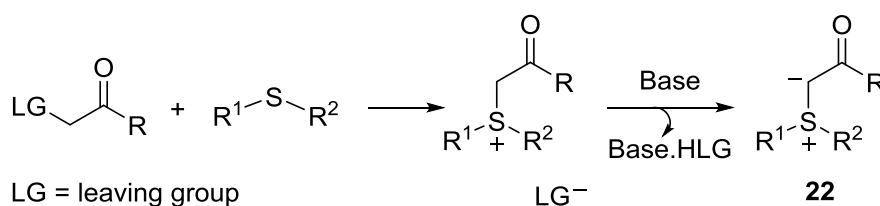
Scheme 10: Safe synthesis of an α -oxo gold carbene⁵³

1.4 Selected examples of gold-catalysis

1.4.1 Sulfur ylide formation

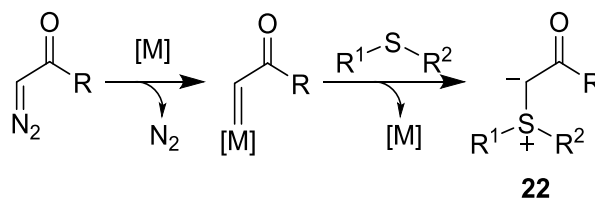
A number of reactions with gold-catalysis have been reported; some of the most interesting have accessed compounds and precursors which have been either impossible or difficult to access using conventional methods. An example of this is the gold-catalysed formation of sulfur ylides.

Sulfur ylides are useful in the synthesis of C-C and C-X, (X=heteroatom) bonds.⁵⁴ 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.⁵⁵ 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.⁵⁶

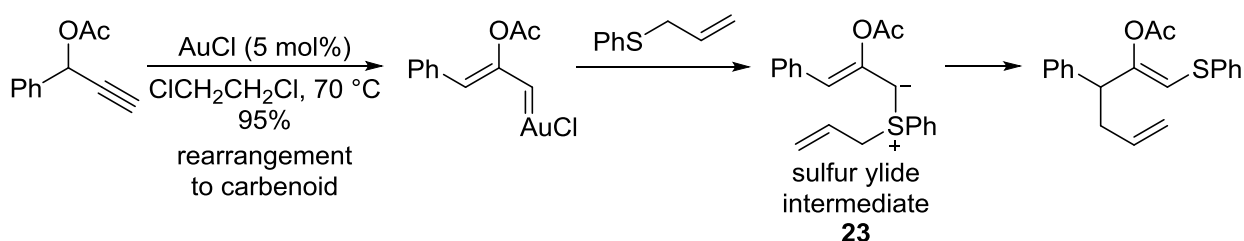


Scheme 12: Installation of a carbene in the α -position relative to a sulfide

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.⁵⁷



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

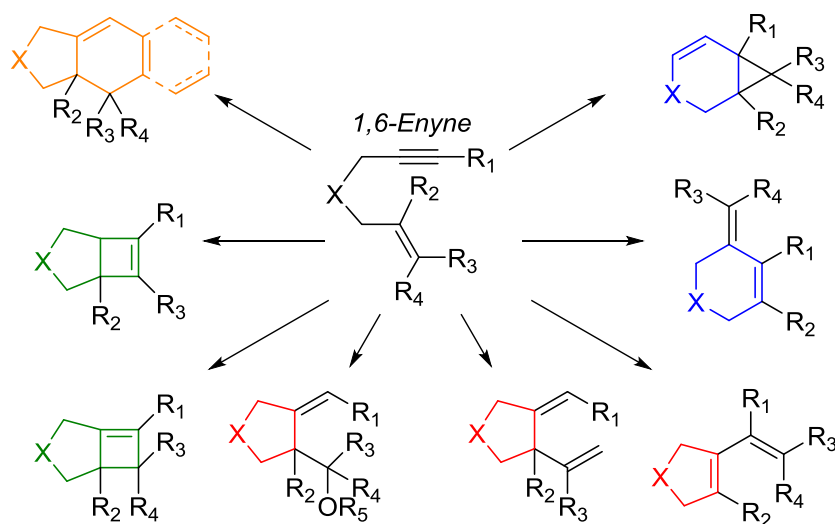
This method of accessing the ylide also portrays a rare example of a gold-catalysis reaction that incorporates sulfur.¹¹

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.

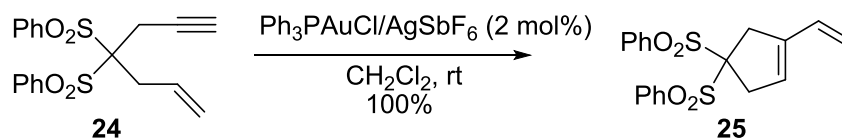
A review published by Zhang detailed a range of metal-catalysed reactions achieved using soft alkynophilic metals such as gold.⁵⁸ The reactions include cycloisomerisations of 1,6-enynes and 1,5-enynes to bicyclo[4.3.0]heptanes and bicyclo[3.1.0]hexanes respectively these were accomplished by Trost *et al.* over a decade ago⁵⁹ – 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-enynes

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 η^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.⁶⁰



Scheme 15: Gold-catalysed skeletal rearrangement of a 1,6-enyne⁶¹

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.

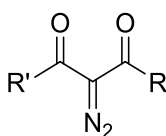
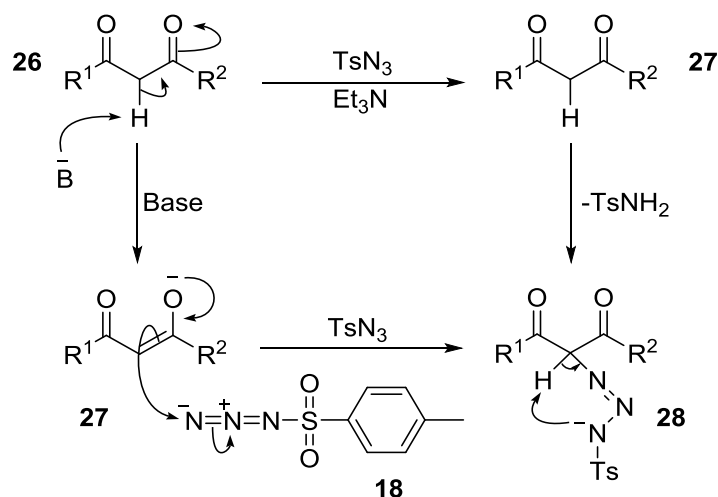


Figure 11: Structure of an α -Diazocarbonyl species

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.^{62,63}

Sulfoxides are often depicted structurally as tetrahedral, taking into account the lone pair.⁶⁴ Griffiths *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.⁶⁵

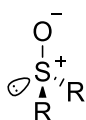


Figure 12: Structure of a sulfoxide

The synthesis of α -diazo- β -keto sulfoxides is a scarcely reported and remains somewhat elusive. Maguire mentions that her initial interest in α -diazosulfoxides was first ignited when work by Taber *et al* was published in 1986⁶⁶ detailing an intramolecular cyclisation of α -diazoesters *via* C-H insertion⁶⁷ with good diastereoselectivity.⁶⁸

Due to a gap in the literature concerning the synthesis of α -diazosulfoxides, Maguire *et al.*⁶⁹ investigated introducing a diazo group α to a range β -keto sulfoxides in order to successfully create the α -diazosulfoxide to achieve carbene functionality *via* diazo removal and thus open up the position α to the sulfoxide to lend itself to a variety of different chemical transformations. Although they showed some success with affixing this group α to β -keto sulfones and β -keto phosphonates, they experienced little luck with corresponding sulfoxides due to the species' characteristic instability.⁷⁰ The aim of their research was to explain this inherent instability of α -diazosulfoxides.

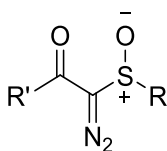
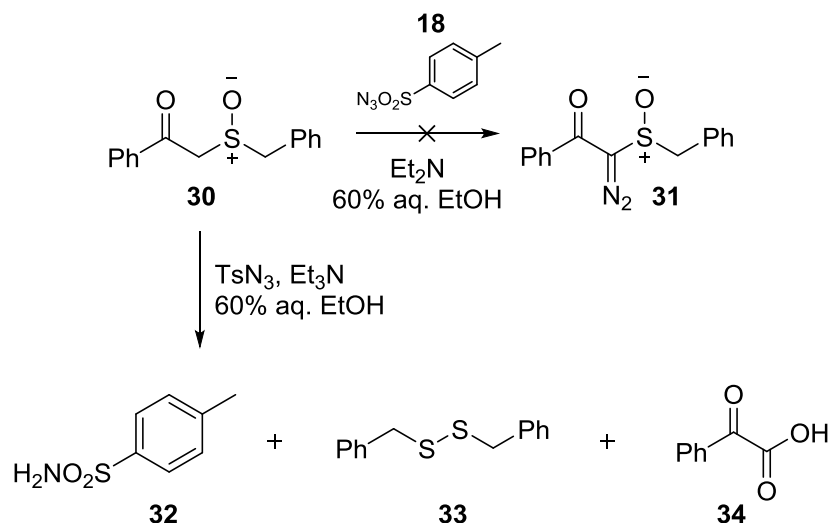


Figure 13: Structure of an α -diazo- β -keto sulfoxide

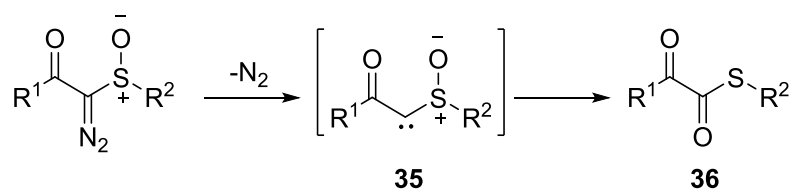
1.5.2.1 Cyclic α -diazosulfoxides

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 1962.⁷¹ Hodson and Holt had attempted to conduct diazo transfer to β -keto sulfones 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.



Scheme 17: Diazo transfer attempted by Hodson and Holt

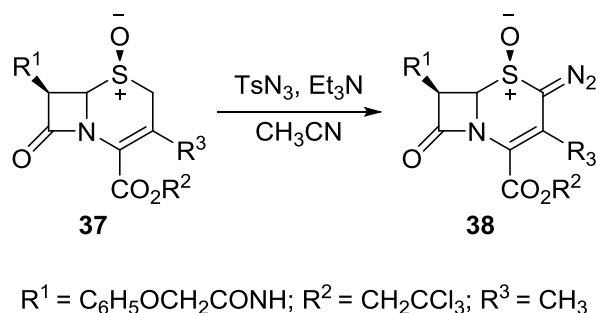
Isolation of **32**, *p*-toluenesulfonamide, suggested diazo transfer to the keto sulfoxide did in fact take place but **31** was intrinsically unstable and this led to the dibenzylsulfide **33** and benzoyl formic acid **34** forming *via* the carbene intermediate **35**.



Scheme 18: Proposed decomposition of α -diazo- β -keto sulfoxides

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 N_2 group.

The first reports of isolated and stable α -diazosulfoxides came from Campbell^{72,73} and Rosati⁷⁴ 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

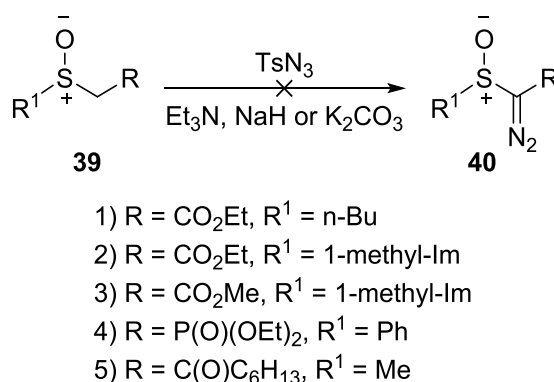
Though this was the first time that these species had been synthesised and isolated, neither the Rosati nor the Campbell groups remarked on this significance.

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.^{75,76,77} However, all attempts were unsuccessful.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.



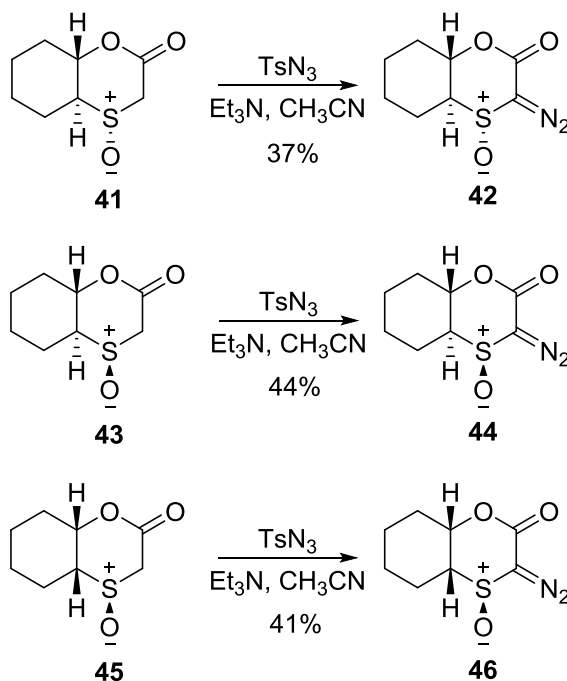
Scheme 20: Attempted diazo transfer to acyclic α -sulfinyl esters

There was evidence that the α -diazosulfoxide **40** was forming: *m*CPBA 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 1998⁷⁷ with more detailed results following in 2013.⁷⁹ 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

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 conformational 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.

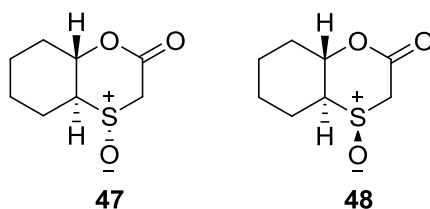


Figure 14: Diastereomeric bicyclic sulfoxides

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 15.⁷⁹ 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.⁴⁰

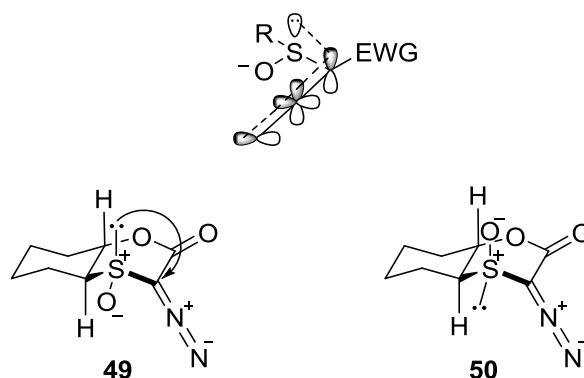


Figure 15: Maguire's mechanistic interpretation of instability of diazosulfoxides

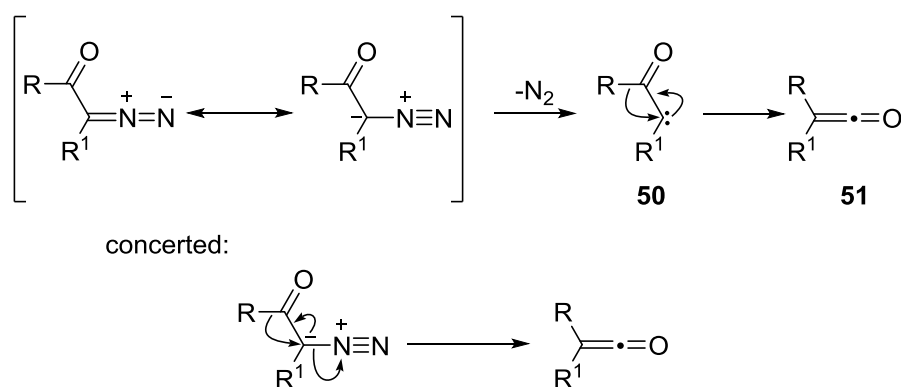
It was proposed that the instability of the α -diazosulfoxides in acyclic structures was most likely born from the overlap of the sulfanyl lone pair and the unsaturated diazo group – leading to the collapse of the diazo group.

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 sulfanyl 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

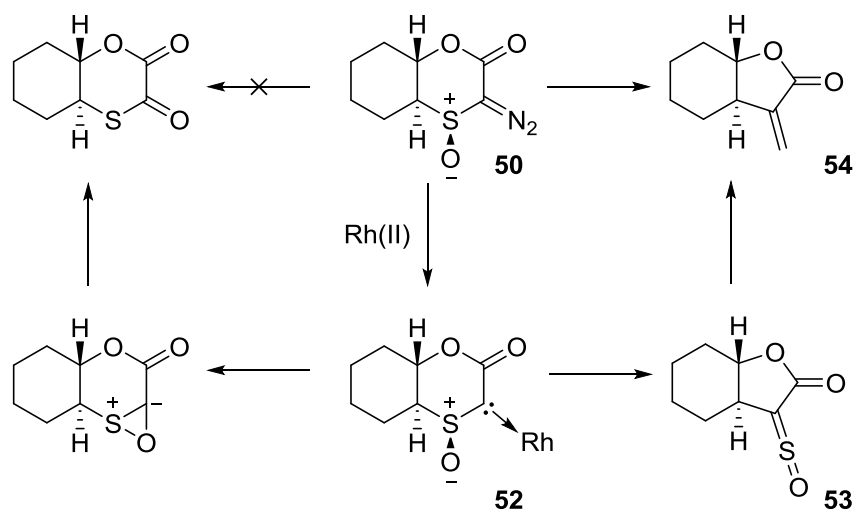
The Wolff rearrangement was first reported by Ludwig Wolff in 1902⁸⁰ and is a reaction by which α -diazocarbonyl species can be converted to ketenes *via* the loss of a diazo group and a 1,2-rearrangement. This can occur in a step-wise fashion *via* a carbene intermediate or in a concerted fashion. Wolff 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

1.6.1 Wolff rearrangement of α -diazosulfoxides

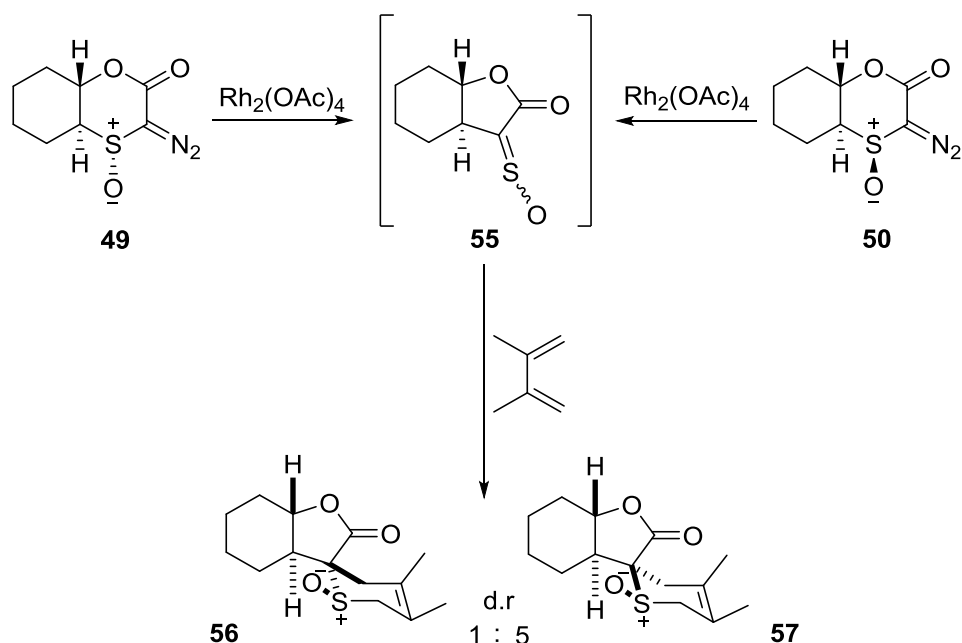
Following the synthesis of the locked cyclic α -diazosulfoxides, Maguire *et al.* wished to explore their reactivity upon treatment with rhodium catalysts. Prior work in the area indicated that oxygen transfer from the sulfoxide to the carbenoid carbon would occur.⁸¹ However, there was little indication that this was occurring; instead they obtained alkene **54** (when the reaction was conducted with CH_2Cl_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.⁸² 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

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 α -oxo sulfine.



Scheme 24: Formation and trapping of the α -oxo-sulfine

Detailed studies of the reactions of α -diazo- β -oxo sulfoxides using a range of conditions utilising transition metal catalysis, microwave and photolysis have demonstrated that these α -diazo- β -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 π -systems to cycloadditions, there is great diversity in reactions involving gold-catalysts, providing an economical means to attaining molecular complexity and reaction diversity.

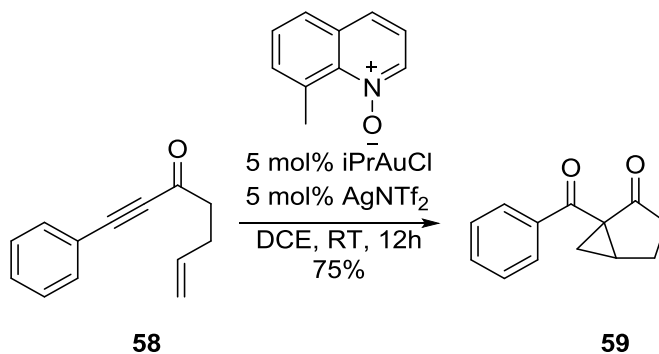
Previously difficult and challenging synthesis such as such as the installation of a diazo group adjacent to a sulfoxide group can be addressed using gold-catalysis to combat '*sacrificial functionality*' and access formerly elusive species.

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.⁸⁴ 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 method⁸⁵ 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.⁸⁶

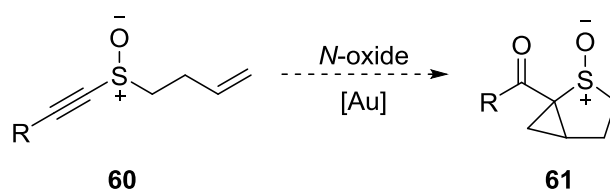
Following on from the work of Toste *et al.* in 2007 where they utilised sulfoxides as oxidants to generate the α -oxo gold carbenoid synthons⁸⁷ – Yeom and Shim, reported the use of nitrones and hydroxylamines as N-O oxidisers of alkynes to generate the α -oxo gold species in 2008. Zhang *et al.* built upon this work, publishing on the use of pyridine *N*-oxides as intermolecular oxidants.⁸⁸ Zhang's method is a safe and effective route to the α -oxo gold carbenoid species from which a number of pathways have been observed, such as cyclopropanation⁸⁹, 1,2-alkyl shift⁹⁰ 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 α -gold carbenoids which react with the pendant alkene functionality of the molecule to cyclopropanate.⁹¹ Scheme 25 depicts the reaction.



Scheme 25: Zhang's cyclopropanation

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.⁹² 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.

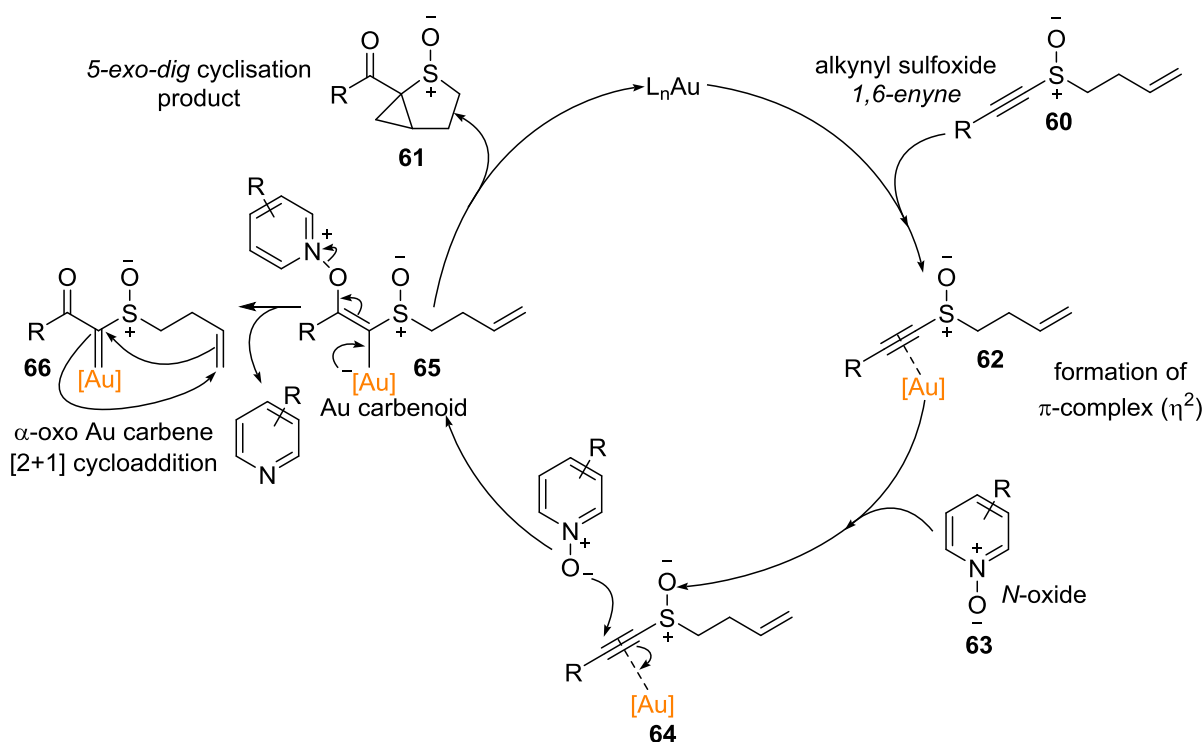


Scheme 26: Formation of bicyclic heterocyclic structure

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.^{93,94}

The design of the substrate molecule **60** is similar to that in work by researchers such as Toste *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.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 *via* the gold(I) singlet carbenoid through a one-step concerted [2+1] intramolecular cycloaddition or through the carbene to form a thiabicyclo[3.1.0]hexane heterocyclic structure by a 5-*exo-dig* reaction from the 1,6-enyne.



Scheme 27: Proposed catalytic cycle for the expected transformation of 1,6-enynes to thiabicyclo[3.1.0]hexane like structures

Results and Discussion

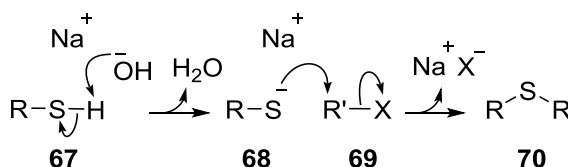
2.3 Starting material synthesis

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 χ and 2.96 χ 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 α 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.⁹⁶

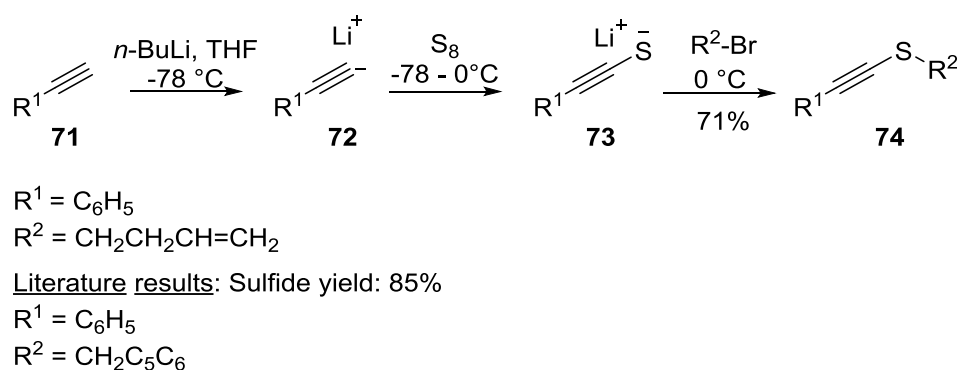
Another method involves the cleavage of sulfur-sulfur bond of a disulfide by a metallic alkynyl species which are made *in situ* from terminal alkynes.⁹⁷

Zheng *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 *via* the lithium alkynyl thiolate; this method had not been previously reported.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.



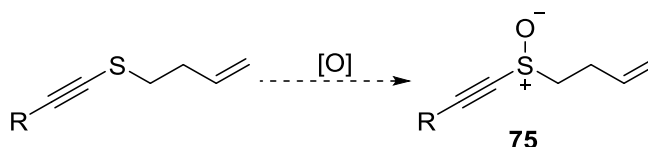
Scheme 29: Zheng's one pot alkynyl sulfide synthesis

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** *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

No problems were envisaged concerning the oxidation of the alkynyl sulfide to the corresponding sulfoxide as there is ample literature detailing the transformation.⁹⁹ 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: *m*CPBA, Oxone®,¹⁰⁰ sodium periodate NaIO₄¹⁰¹ and the Davis reagent.

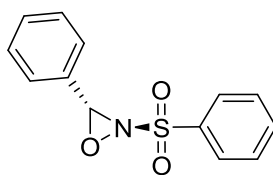


Figure 16: Structure of the Davis Reagent, *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine

Their results showed that neither the Davis reagent nor NaIO_4 , under normal conditions (KHSO_3 , $\text{MeOH}/\text{H}_2\text{O}$, $0\text{ }^\circ\text{C}$, 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.¹⁰² Research in 1983 by Davis *et al.*, demonstrated that the Davis reagent could be used to instantly oxidise diphenyl sulfide at $0\text{ }^\circ\text{C}$.

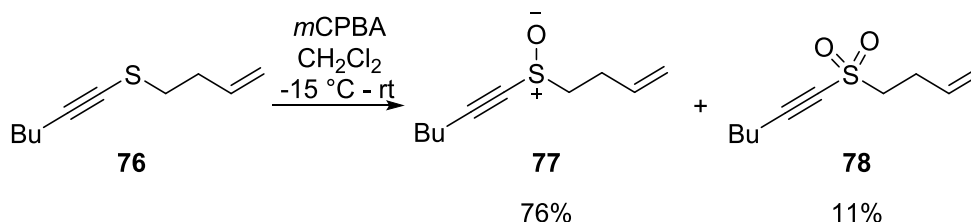
To account for this unexpected resistance to oxidation from the alkynyl sulfide MaGee suggested that the decreased nucleophilicity of the sulfur and consequently its ability to be oxidised may be a result of the proximate alkyne group. He suggested that the sulfur lone pair may delocalise into the π -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 $60\text{ }^\circ\text{C}$ (CHCl_3 , reflux), in all substrates tested by Magee *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 *m*CPBA 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 *m*CPBA 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 *m*CPBA (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.

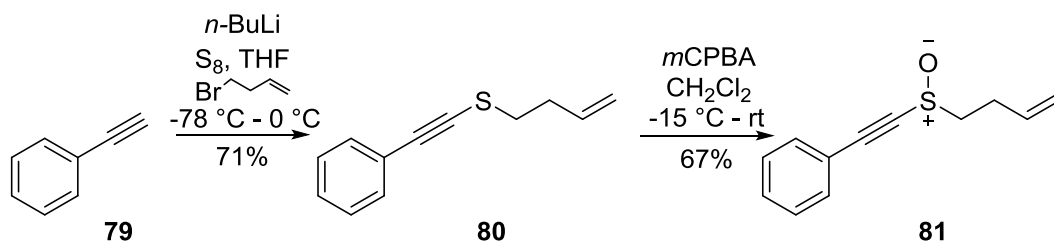


Scheme 31: Oxidation of alkynyl sulfide to corresponding alkynyl sulfoxide

*m*CPBA 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 *m*CPBA 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.



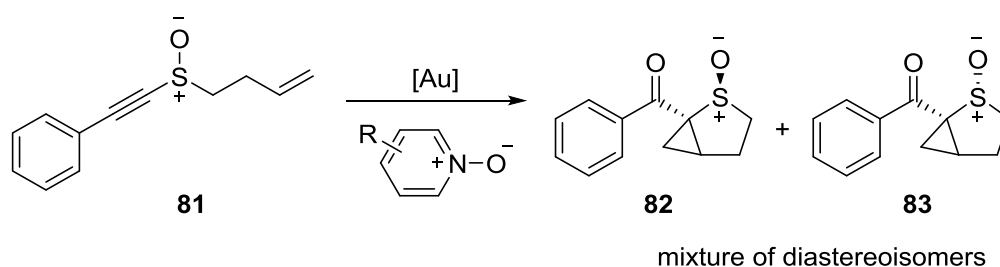
Scheme 32: Synthesis of the aryl alkynyl sulfide and consequent oxidation

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

Entry ^a	Catalyst ^b	Solvent ^c	T (°C)	N-Oxide ^d	NMR yield (%) ^e
1	XPhosAuCl/AgSbF ₆	Nitromethane	RT	N4	18
2	XPhosAuCl/AgSbF ₆	Nitromethane	50	N4	33
3	XPhosAuCl/AgSbF ₆	Nitromethane	80	N4	33
4	XPhosAuCl/AgSbF ₆	Nitromethane	50	N4	33
5	XPhosAuCl/AgSbF ₆	Nitromethane	50	N5	23
6	XPhosAuCl/AgSbF ₆	Nitromethane	50	N6	43
7	XPhosAuCl/AgSbF ₆	Nitromethane	50	N7	15
8	XPhosAuCl/AgSbF ₆	Nitromethane	50	N1	57

Table 1: Gold-catalysed synthesis of cyclopropanated product 82. ^aAll reactions were carried out on a 0.1 mmol scale and stirred for 16 h. ^b5 mol% catalyst loading was used for all reactions. ^cAll reactions were conducted at a concentration of 0.05 M. ^dN-oxides were added to the reaction in 1.2 eq. ^eAll yields correspond to the major diastereoisomer of the cyclopropanated product and were determined by ¹H NMR analysis with an internal standard (TMB).

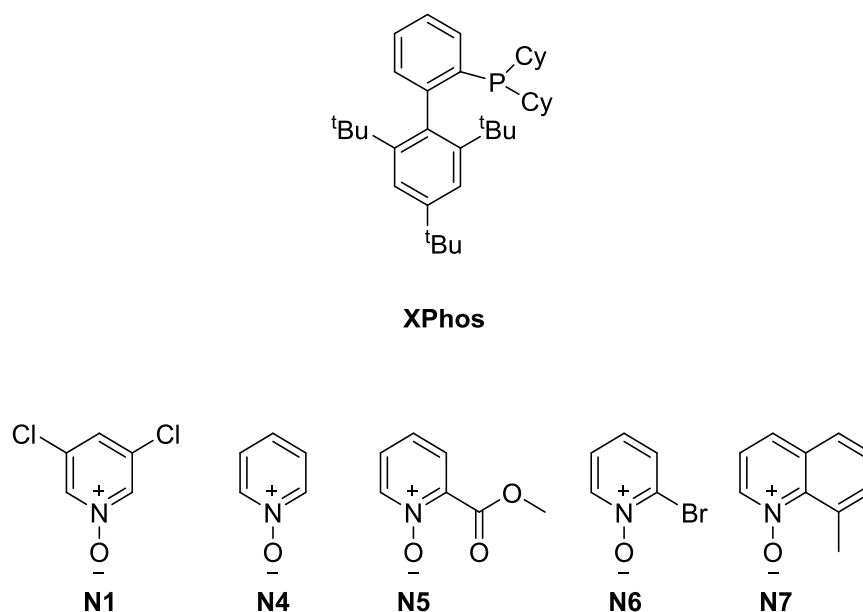


Figure 17: Structure of ligand and *N*-oxides used in the preliminary study

The ^1H 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 *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**.

2.5 Regioselective oxidation of internal alkynes

Zhang *et al.* reported the utilisation of pyridine *N*-oxides as external oxidants when synthesising α -oxo gold carbenoid intermediates. In the specific case of the 1,6-enyne 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 2010¹⁰⁴ and 2013,¹⁰⁵ 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 α 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.¹⁰⁶ The figure below shows the factors hindering one end of the internal alkyne.

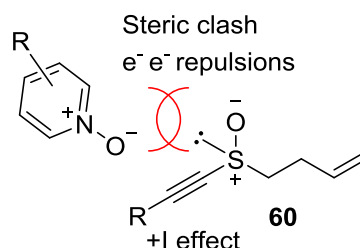
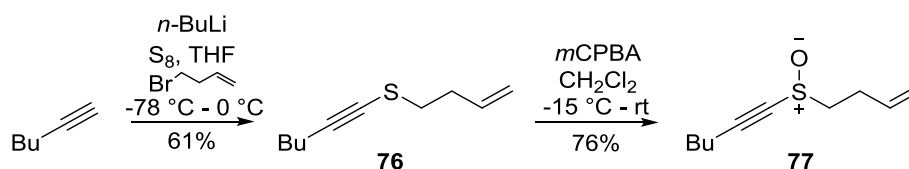


Figure 18: Unfavourable interactions influencing regioselective oxidation

2.6 Aliphatic substrate

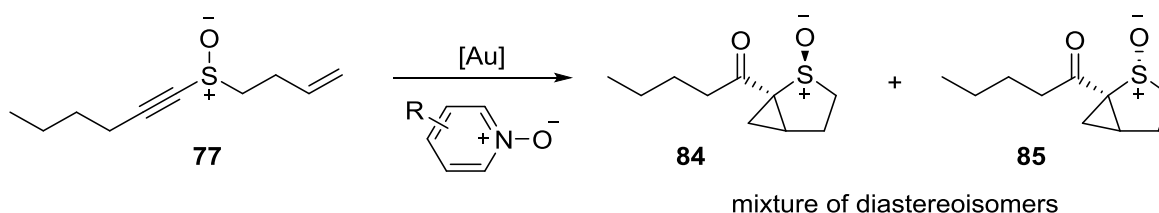
Upon evaluation it was decided that synthesis of the aryl substituted compounds should be halted and the optimisation of the gold-catalysis step should occur with a more stable compound which could be made in a large quantity, stored and used without issues concerning purity.

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

Entry ^a	Ligand ^b	Cat. Mol %	Solvent ^c	T (°C)	N-oxide	N-oxide (eq.)	Conc. (M)	NMR yield (%) ^d
1	L1	5	Dioxane	80	N1	1.2	0.05	66
2	L1	5	Dioxane	80	N2	1.2	0.05	63
3	L1	5	Dioxane	80	N3	1.2	0.05	59
4	L1	5	Dioxane	80	N4	1.2	0.05	70
5	L1	5	Dioxane	60	N1	1.2	0.05	69
6	L1	5	1,2-DCE	60	N1	1.2	0.05	45
7	L1	5	THF	60	N1	1.2	0.05	37
8	L1	5	CH ₂ Cl ₂	RT	N1	1.2	0.05	26
9	L1	5	Toluene	60	N1	1.2	0.05	39
10	L1	5	Dioxane	65	N1	1.2	0.05	66
11	L2	5	Dioxane	65	N1	1.2	0.05	45
12	L3	5	Dioxane	65	N1	1.2	0.05	59
13	L4	5	Dioxane	65	N1	1.2	0.05	42
14	L5	5	Dioxane	65	N1	1.2	0.05	47
15	L1	5	Dioxane	80	N1	1.2	0.2	42
16	L1	5	Dioxane	80	N1	1.2	0.1	52
17	L1	5	Dioxane	80	N1	1.2	0.025	65
18	L1	5	Dioxane	80	N1	2.0	0.05	54
19	L1	2.5	Dioxane	80	N1	1.2	0.05	62
20	L1	1	Dioxane	80	N1	1.2	0.05	27
21	L1	5	Dioxane	80	N1	1.2	0.05	69
22	L1	5	Dioxane	65	N1	1.2	0.05	66
23	L1	5	Dioxane	50	N1	1.2	0.05	64
24	L1	5	Dioxane	RT	N1	1.2	0.05	56

Table 2: Gold-catalysed synthesis of cyclopropanated product 84. ^aAll reactions were carried out on a 0.1 mmol scale and stirred for 17h. ^bAll ligands were complexed with AuNTf₂. ^cDioxane used was 1,4-Dioxane in all cases. ^dAll yields correspond to the major diastereoisomer of the cyclopropanated product and were determined by ¹H NMR analysis with an internal standard (TMB).

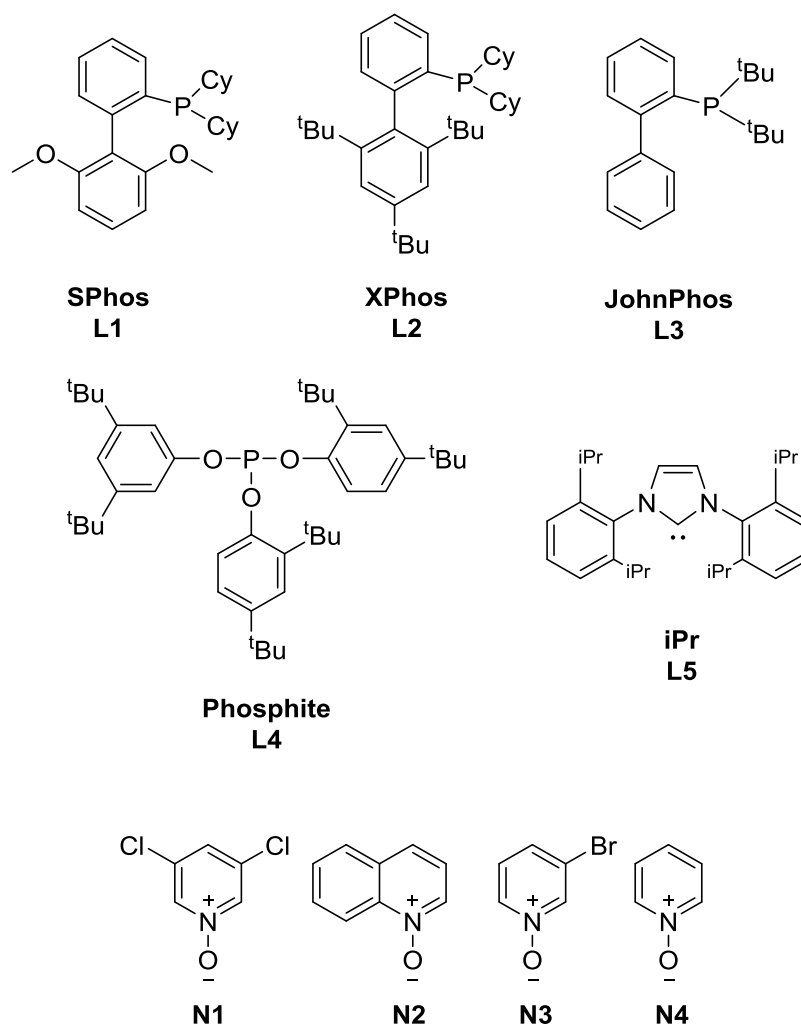


Figure 19: Structures of ligands and *N*-oxides used as part of the optimisation

***N*-oxide**

Zhang *et al.* demonstrated in 2010 that *N*-oxides were used in preference over sulfoxides as external oxidants.¹⁰⁷ 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

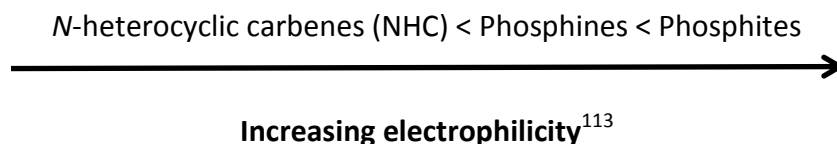
(entry 4). Quinoline *N*-oxide (entry 2) gave the product in a moderate 63% yield. Commenting on the results it may seem that the oxygen of the pyridine *N*-oxide may have been more accessible for reaction as it is less sterically hindered in comparison with the other *N*-oxides employed. 3,5-dichloropyridine *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.¹⁰⁸ 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:



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 SPhosAuNTf₂ 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 **84** 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 CH₂Cl₂ (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 closely 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

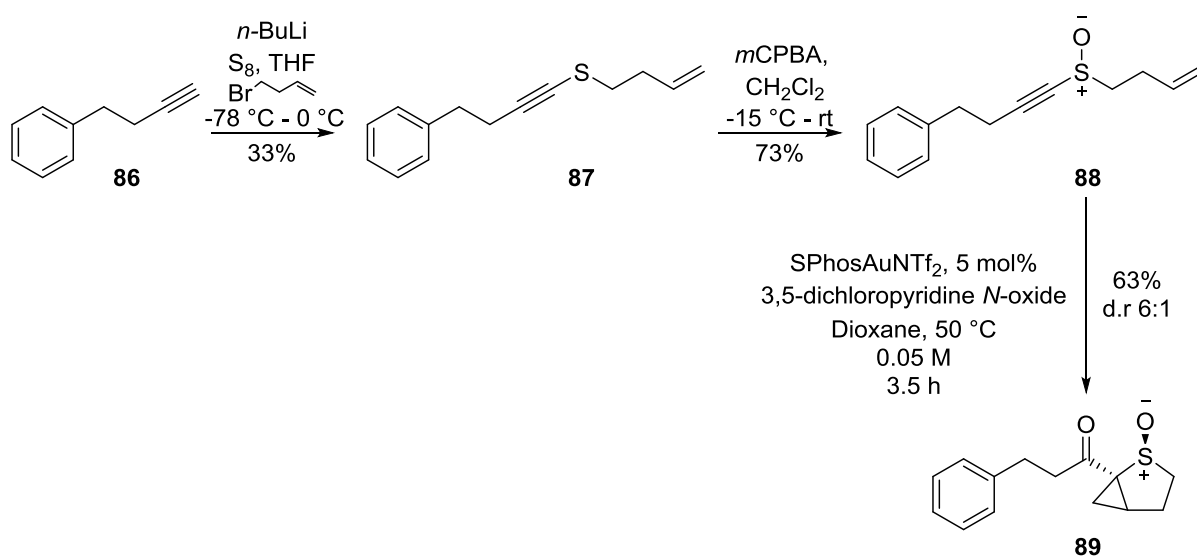
Sulfoxide **77** underwent [2+1] intramolecular cycloaddition to form **84** in a 73% isolated yield as a mixture of diastereoisomers using the the following optimised conditions:

SPhosAuNTf₂ 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.

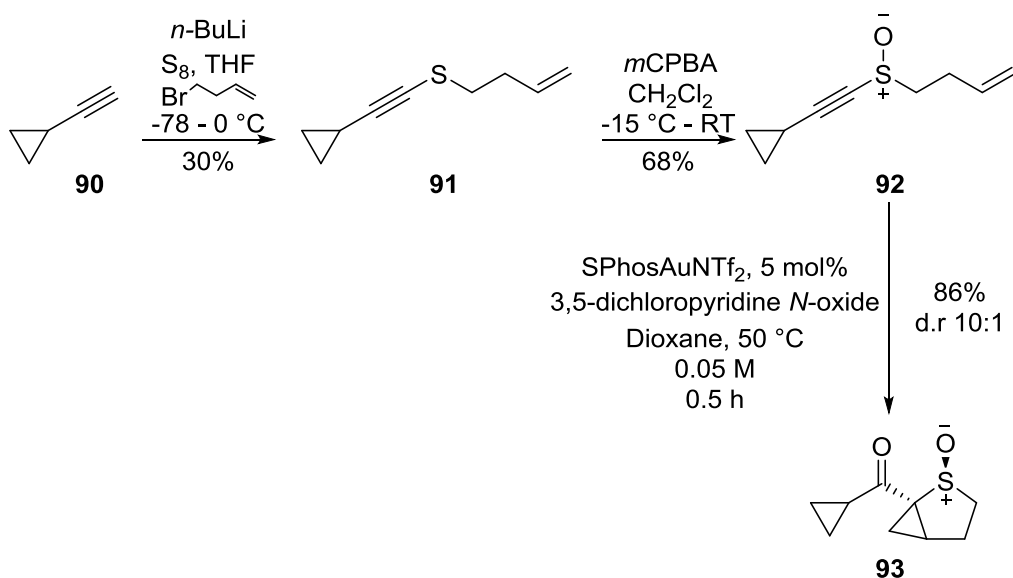
The 4-phenyl-1-butyne sulfoxide **88** was chosen as a good starting material as it assessed how placing an aryl group further from the electron rich alkyne bond would alter interactions within the molecule and ultimately the stability. The first most notable effect was that **88** was inherently more 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**

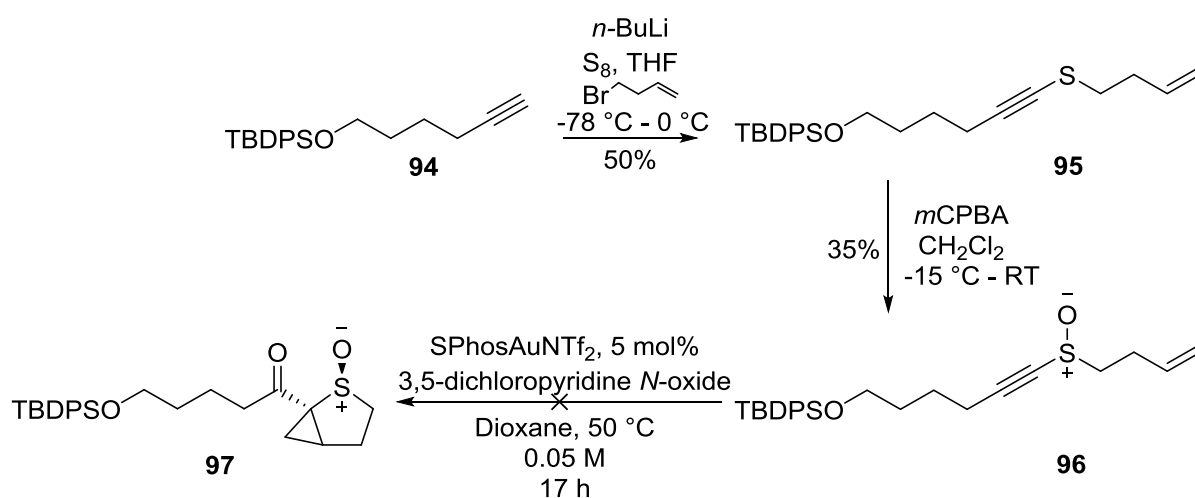
Using a cyclopropyl group would allow assessment of a small group with a 3° carbon centre in the gold-catalysis reaction. It would also yield a ketone group flanked by two cyclopropane rings. Synthesis of sulfide **91** was straightforward, however the volatility of the cyclopropyl compound meant that **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.



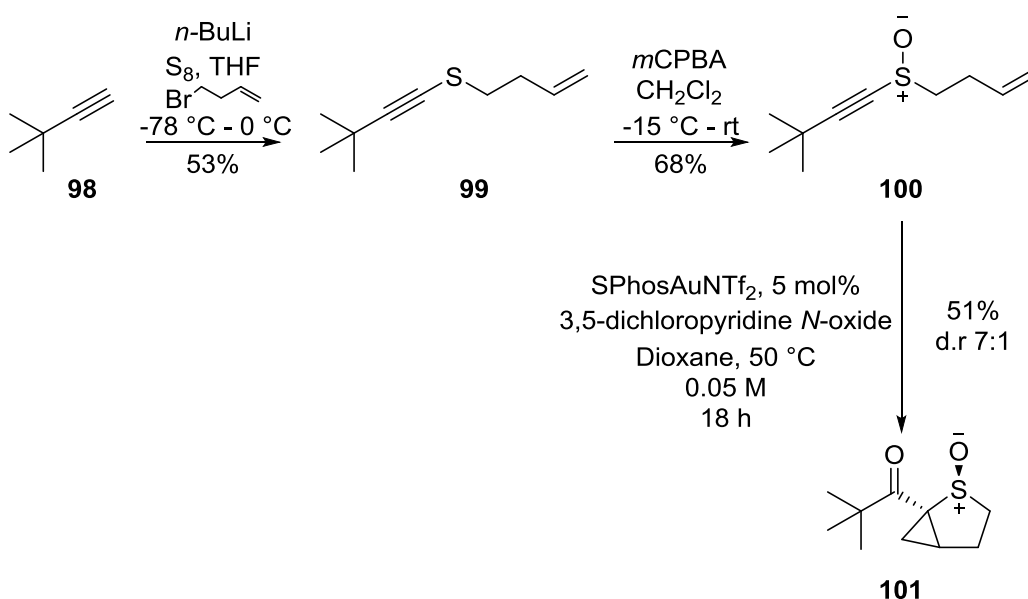
Scheme 37: Synthesis and reaction of cyclopropyl alkynyl sulfoxide **92**

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 SPhosAuNTf_2 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 been flexible enough to cause an unfavorable steric clash to occur.



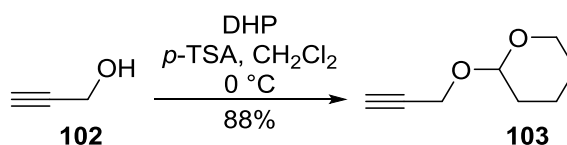
Scheme 38: Synthesis and reaction of TBDPS ether **94**

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

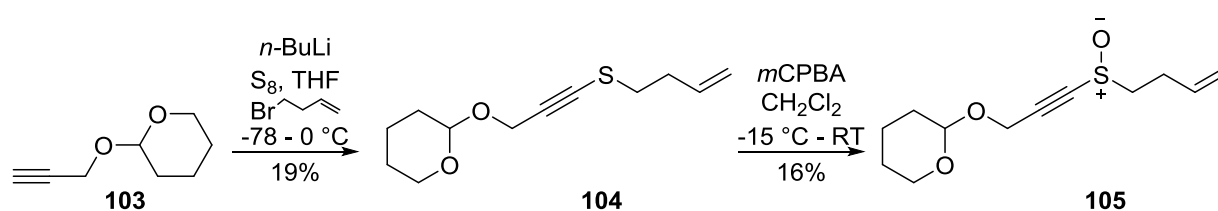
After the failure of the TBDPS ether sulfoxide **96** to react in the catalysis step, another ether was attempted, to prove that protected alcohols could successfully be taken through the conditions. A smaller alcohol was chosen, propargyl alcohol **102**, with a smaller protection group, this time a 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).

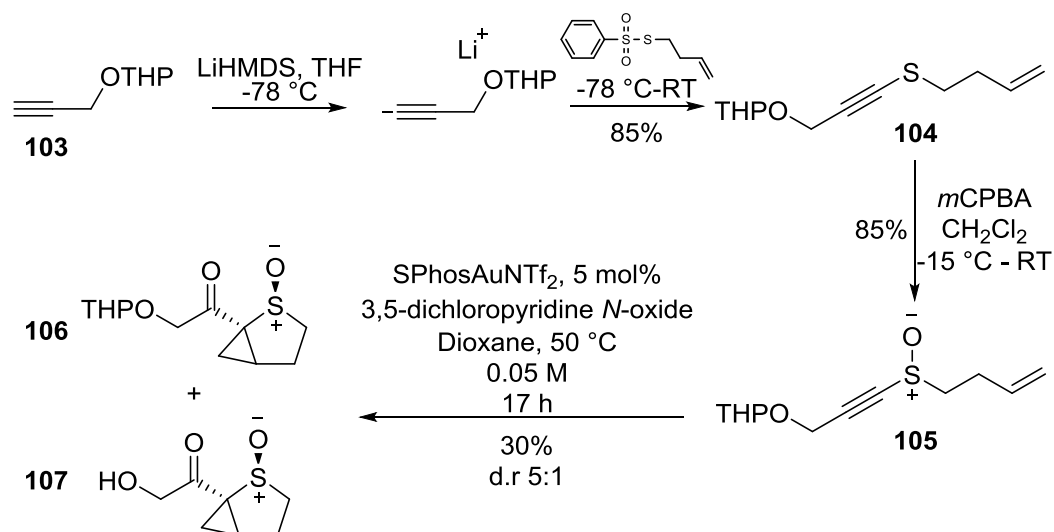
With the protected alcohol **102** in hand it was used in the one-pot *n*-BuLi method of sulfide synthesis (Scheme 41). However this gave very poor yields (~19%), and an equally poor yield (~16%) was obtained for the oxidation step, consequently there was hardly any sulfoxide to use for the gold reaction. 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**

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.

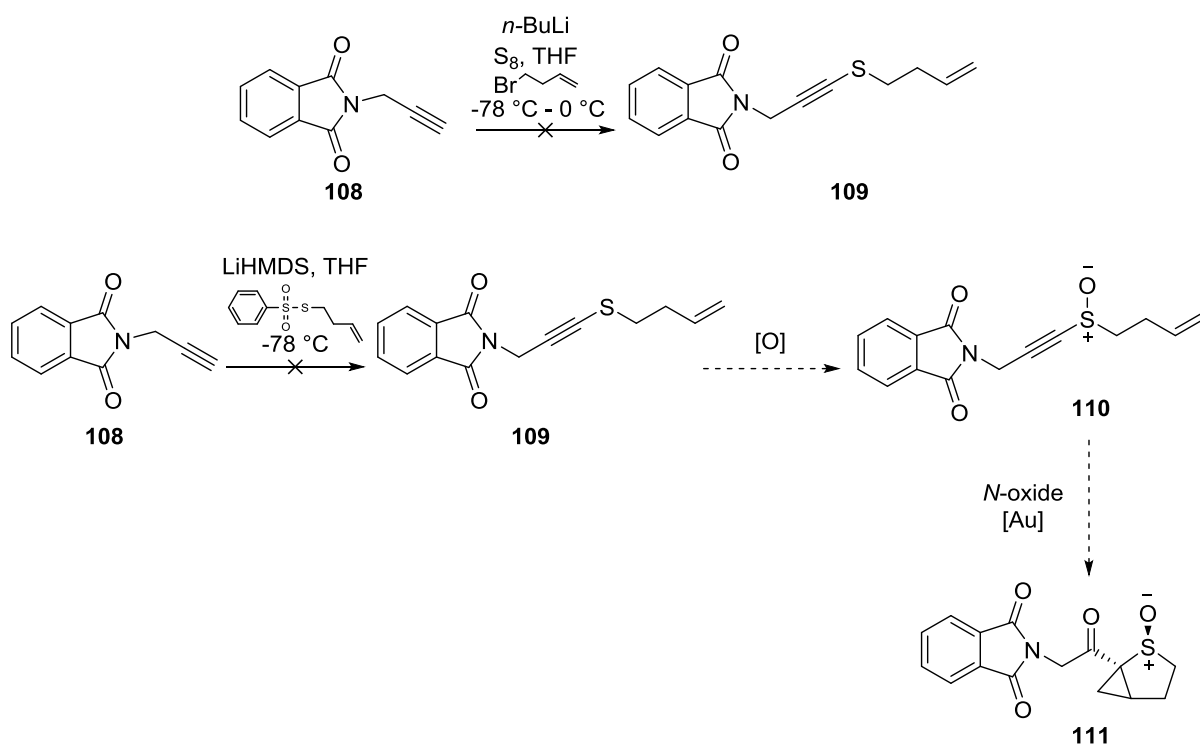


Scheme 42: LiHMDS synthesis and reactions of THP ether 103

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 $\text{C}_{12}\text{H}_{18}\text{O}_4\text{NaS}$ ($\text{M}+\text{Na}$)⁺ 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). ^1H 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 uncertainty of at the time of purification it is not possible to report a yield without further investigation. However from the ^1H NMR which shows resonances only

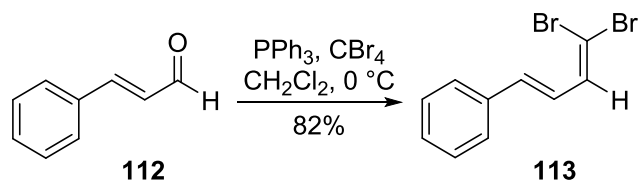
belonging to the alcohol **107** it is possible to obtain a d.r. value of 5:1 for the inseparable diastereoisomers formed.

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 ^1H NMR gave no indication of any reaction however significant degradation of the starting materials was observed.



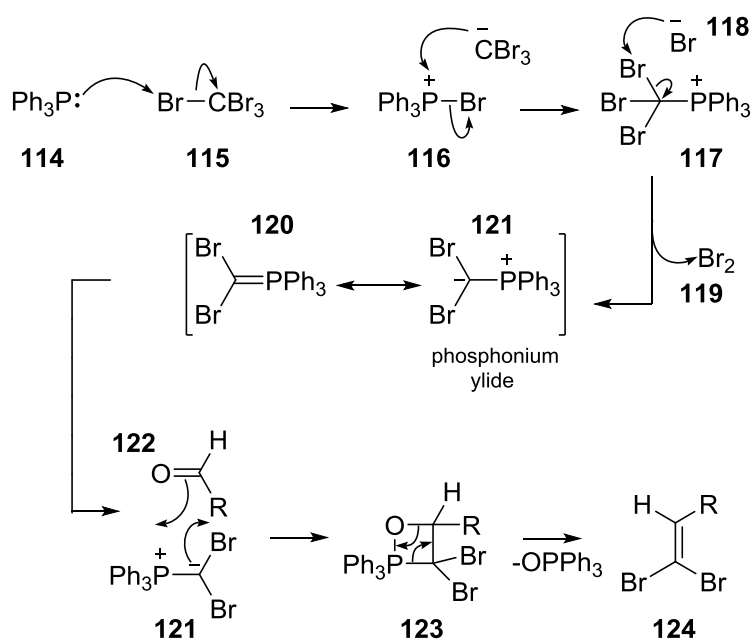
Scheme 43: Attempted synthesis of *N*-propargylphthalimide substituted alkynyl sulfide

Substrate **128** was designed as it would provide an interesting example of a dienyne substrate in the catalysis.



Scheme 44: Corey-Fuchs homologation

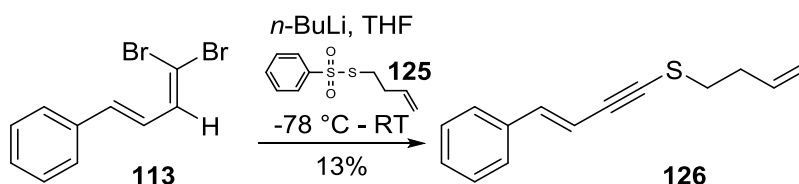
For this the Corey-Fuchs synthesis was employed to convert the *trans*-cinnamaldehyde **112** to the corresponding dibromo olefin **113**. This was achieved in an excellent yield of 82%. The mechanism for the reaction is detailed below in Scheme 45.



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

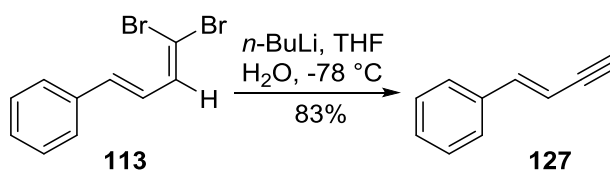
The reaction is similar to the Wittig reaction where the phosphonium ylide is generated *in situ* from the reaction between triphenylphosphine and carbon tetrabromide. This betaine

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.¹¹⁴



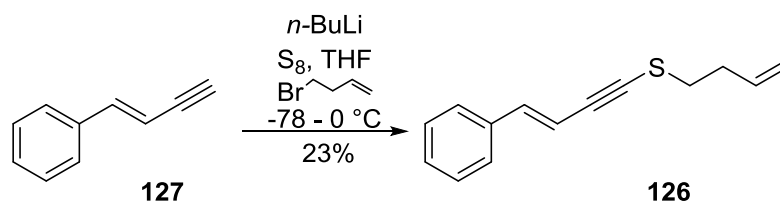
Scheme 46: Poor yielding sulfide synthesis

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 β -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%.



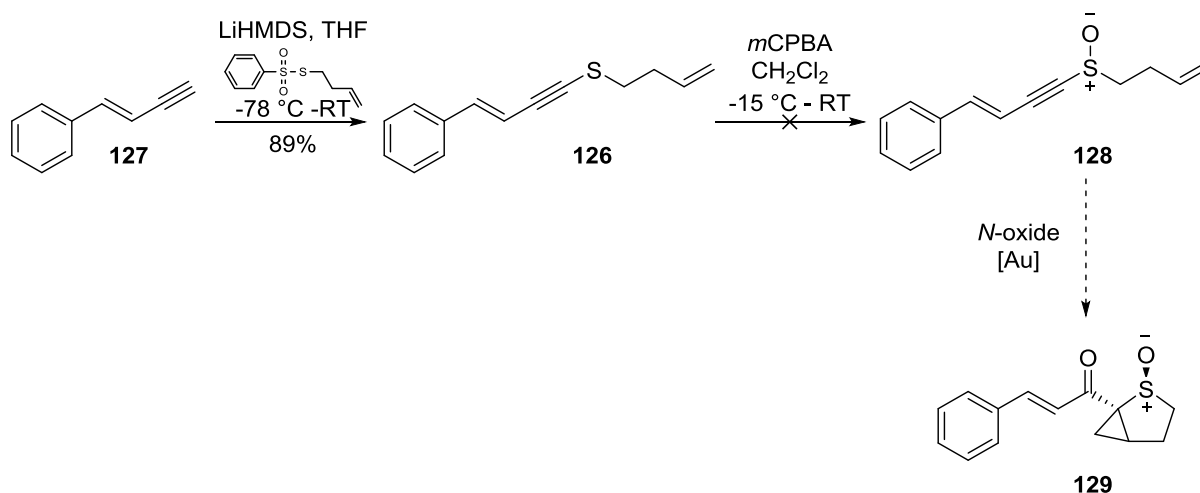
Scheme 47: Terminal alkyne synthesis from the dibromo olefin

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.



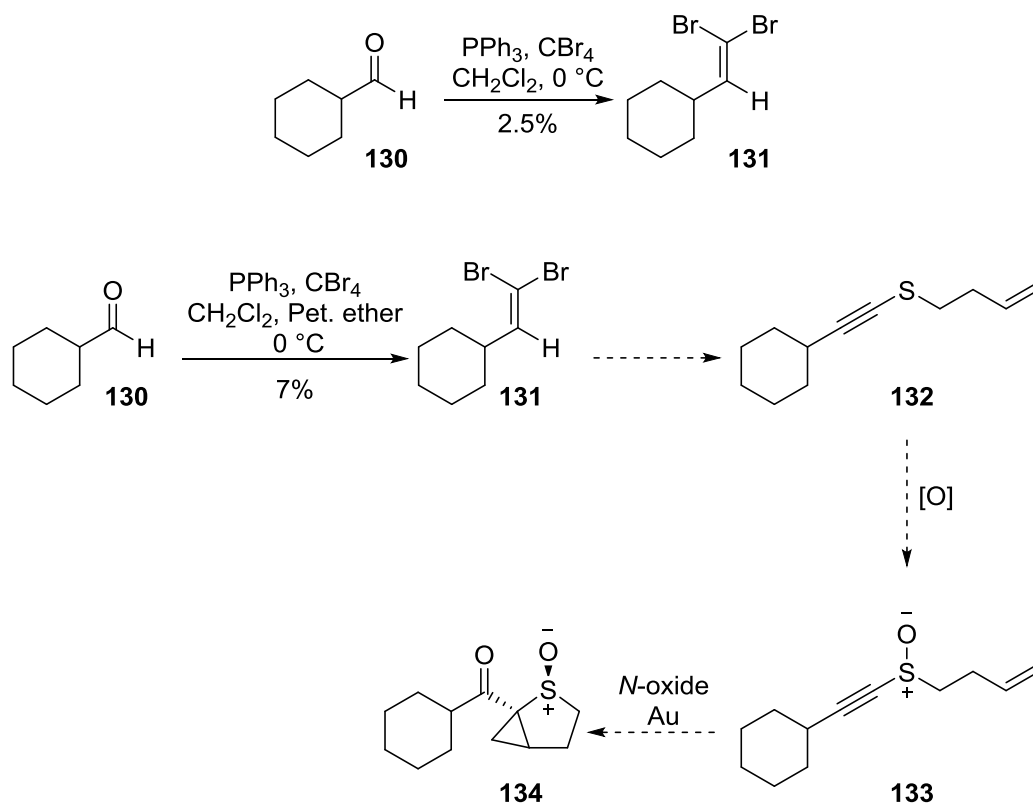
Scheme 48: *n*-BuLi synthesis of alkynyl sulfide

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.



Scheme 49: LiHMDS method synthesis of alkynyl sulfide

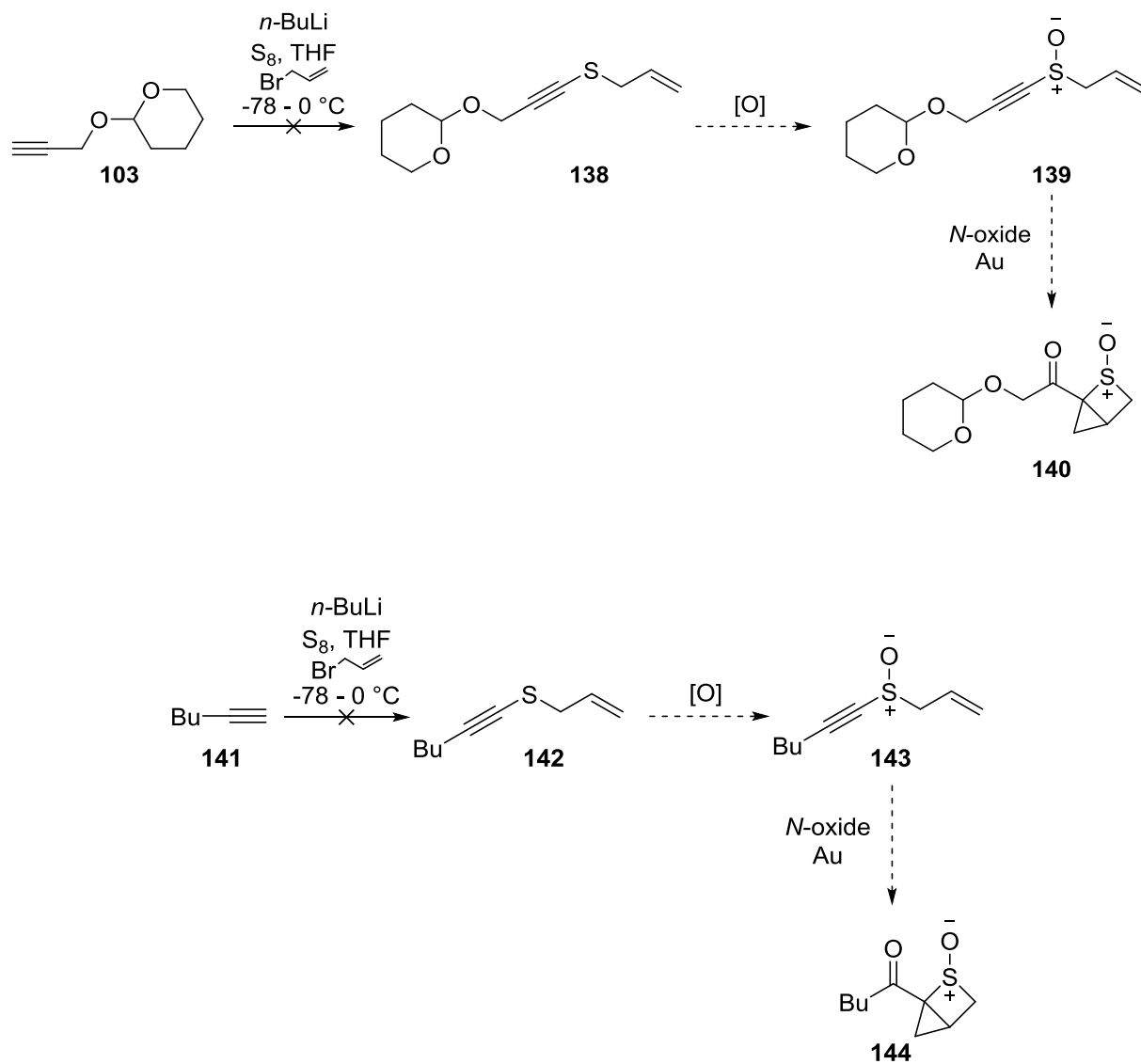
The Corey-Fuchs homologation was attempted again, this time with the cyclohexanecarboxaldehyde **130**. However the dibromo olefin **131** was obtained in very poor yields using the traditional Corey-Fuchs synthesis and a modified method (see Experimental (2,2-Dibromovinyl)cyclohexane).



Scheme 50: Dibromo olefin 131 synthesis

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.

strained 3 membered ring fused to a 4 membered ring in a bicyclo[2.1.0]pentane (compounds **140** and **144**) like structure.

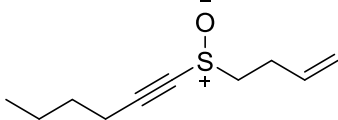
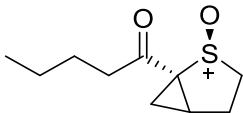
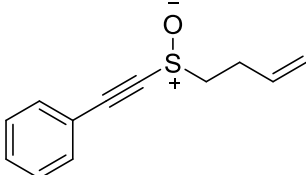
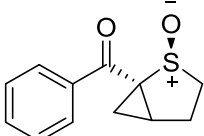
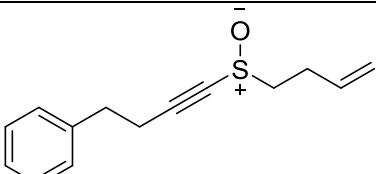
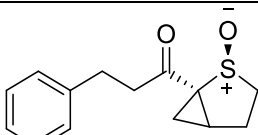
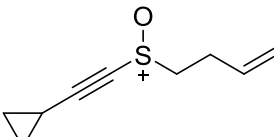
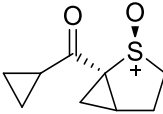
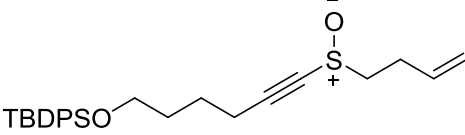
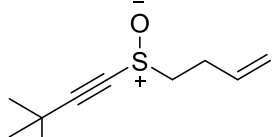
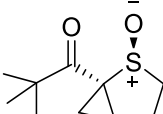
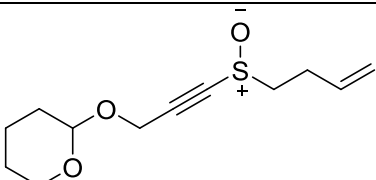
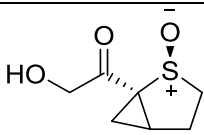


Scheme 52: Synthesis of 1,5-enyne variants

However as seen from Scheme 52 neither sulfide was formed.

2.9 Gold-catalysis results

Table 3: Summary of final results

Entry ^a	Starting Material	Time (h)	Major product	Isolated yield (%) ^b
1	 77	17	 84	73 d.r 5:1
2	 81	17	 82	57 d.r 33:1
3	 88	3.5	 89	63 d.r 6:1
4	 92	0.5	 93	86 d.r 10:1
5	 96	-	-	-
6	 100	18	 101	51 d.r 7:1
7	 105	17	 107	Yield cannot be confidently reported d.r 5:1

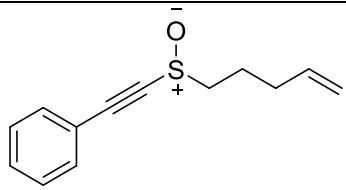
8	 <p>136</p>	-	-	-
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Table 3 ^aAll reactions were conducted using the optimised conditions: SPhosAuNTf₂ at 5 Mol% in dioxane (0.05 M) with 3,5-dichloropyridine *N*-oxide (1.2 eq.). ^bD.r values were determined by ¹H NMR analysis.

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 Evans¹¹⁷ 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.

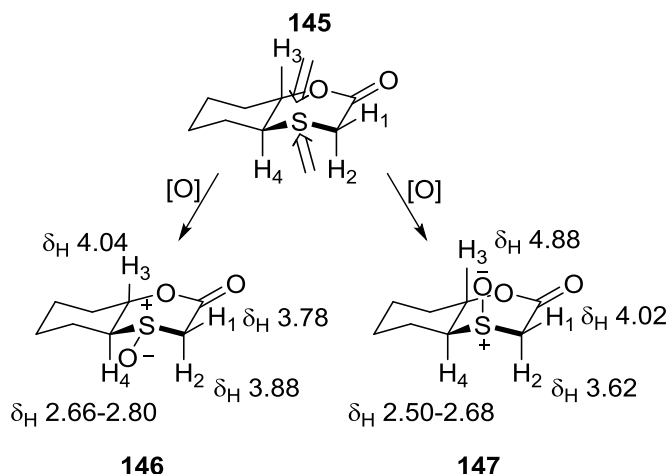


Figure 20: Orientation of sulfinyl oxygen in bicyclic sulfides and the corresponding chemical shifts of neighbouring protons

The β -proton H₃ in the axial sulfoxide compound **147** at δ_{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**, H₃ is then *syn*-axial with the sulfinyl lone pair and is relatively shielded in comparison and the proton is observed at δ_{H} 4.04.

Notably protons oriented in the same direction as the sulfoxide oxygen are shifted more downfield than their counterparts. H₁ and H₂ 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, H₁: δ_{H} 4.02 in comparison to H₂: δ_{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.

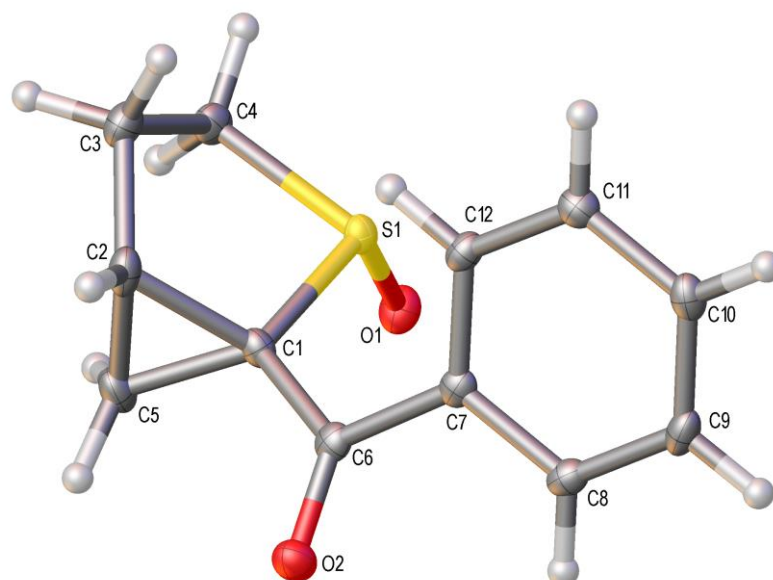


Figure 21: X-ray crystal structure (obtained from M. Barrett) for compound 82

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

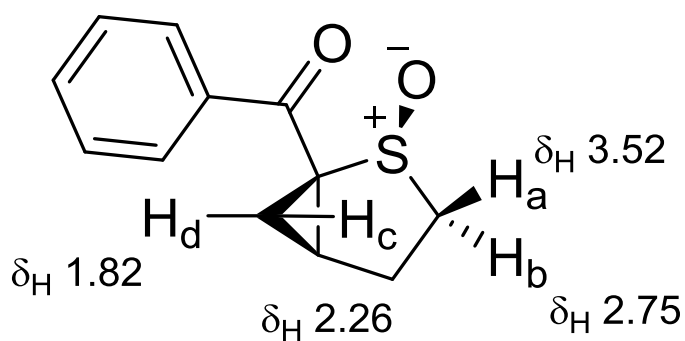


Figure 22: Comparison of chemical shifts for thiabicyclo catalysis product 82

As expected the α -proton H_a – orientated on the same side as the sulfoxide oxygen – displays appreciable de-shielding at δ_H 3.52. The same effect is observed in the minor diastereoisomer, but de-shielding occurs to a lesser extent at δ_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: δ_{H} 2.26 in comparison to H_d: δ_{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: δ_{H} 1.41 in comparison to H_d: δ_{H} 1.21.

2.9.2 NMR data comparison

Using the X-ray data for comparison and the δ_{H} /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.

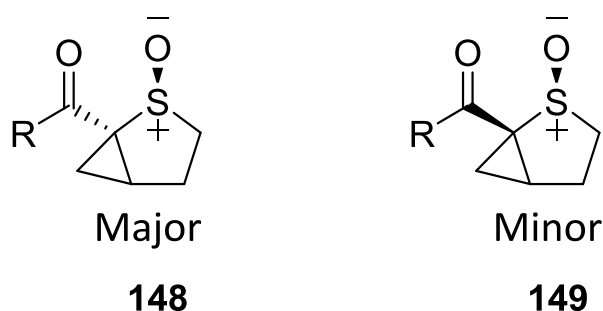
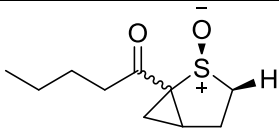
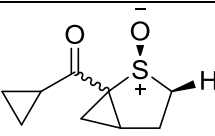
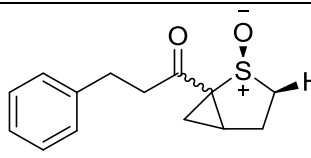
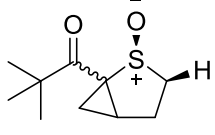
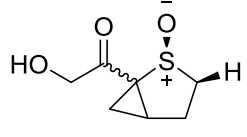
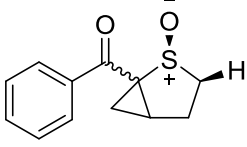


Figure 23: Structures of possible diastereoisomeric configurations

2.9.2.1 ¹H NMR data comparison

Similar proton shifts are observed for the indicated proton in the major diastereoisomer δ_{H} 3.54 ppm, and δ_{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 ¹H NMR are shifted more downfield for the major isomer than the minor, as see in **Table 4**.

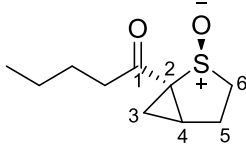
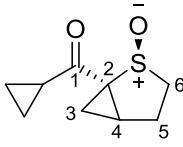
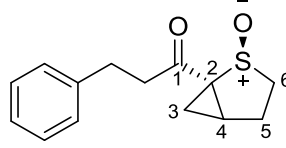
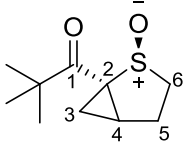
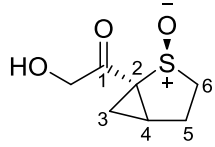
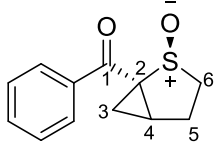
Table 4: ^1H -NMR comparison table for the resonance (ppm) observed for the indicated proton in the major and minor diastereoisomers

Compound	Major	Minor
 150	3.52	3.07
 151	3.55	3.08
 152	3.50	3.08
 153	3.51	3.08
 154	3.55	3.07
 155	3.52	3.03

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)

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

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

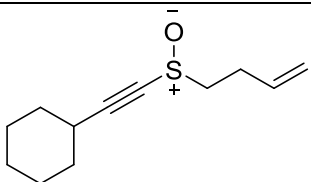
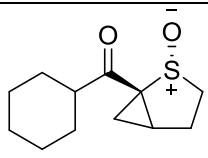
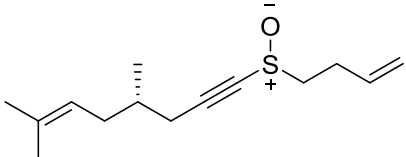
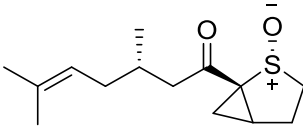
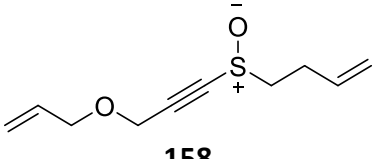
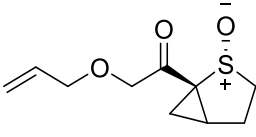
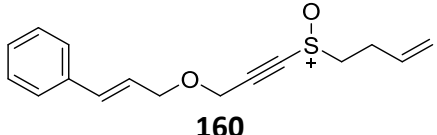
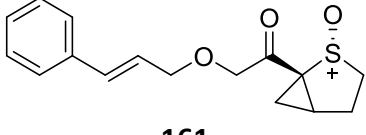
Entry	Starting Material	Major product ^a	Yield (%) Cond. A ^b	Yield (%) Cond. B ^c
1	 133	 134	45	-
2	 156	 157	70	-
3	 158	 159	65	54
4	 160	 161	68	30

Table 6 ^aAll 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. ^bConditions A are identical to the conditions established in this work: SPhosAuNTf₂ 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. ^cModified conditions B were conducted at RT with SPhosAuNTf₂ 2.5 Mol% – unless otherwise indicated the reactions were stirred for 17h.

2.11 Summary

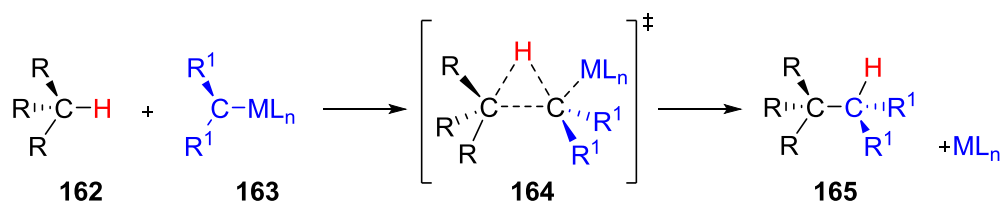
In summary, an effective and efficient synthesis of thiabicyclo[3.1.0]hexanes was achieved *via* gold(I) catalysed alkyne oxidation followed by cyclopropanation. The reaction proceeded through the gold(I) carbenoid in a one-step [2+1] intramolecular cycloaddition to form the

thiabicyclo[3.1.0]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 thiabicyclo 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

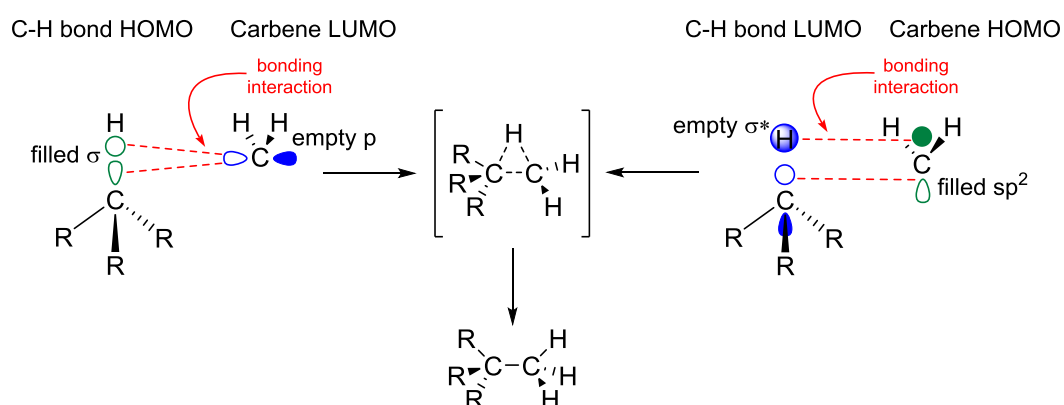
3.1 C-H insertion

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

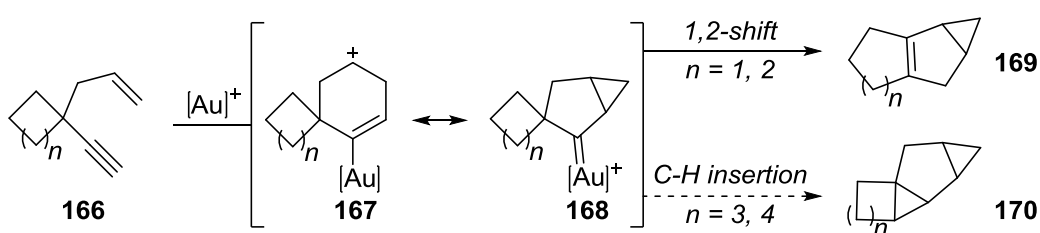
The above mechanism suggests that insertion into a stereogenic C-H centre would result in the retention of stereochemistry.

3.2 Selected examples

3.2.1 Intramolecular gold-catalysed C-H insertion

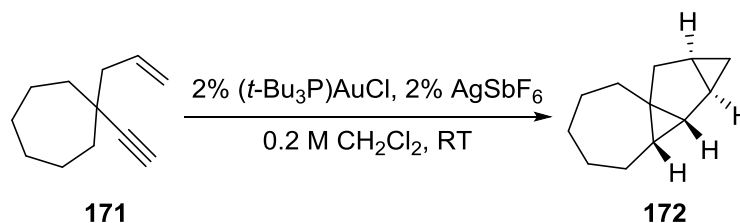
Although α -oxo gold carbenes are able to undergo a variety of transformation including cyclopropanation with a pendant alkene (as described in Chapter 2) – the use of these gold species in C-H insertion reactions is rare, unlike rhodium catalysed C-H insertion is well documented.¹¹⁸

Toste *et al.* reported in 2008¹¹⁹ 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 sp^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 *via* a 1,2-shift,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.



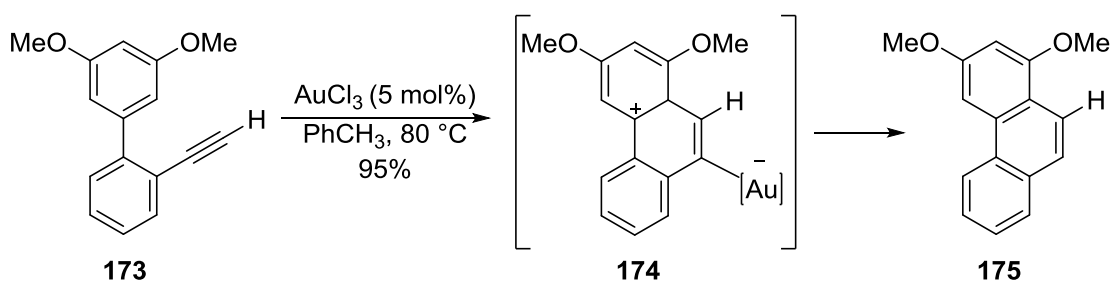
Scheme 55: Toste's postulated C-H insertion

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.



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

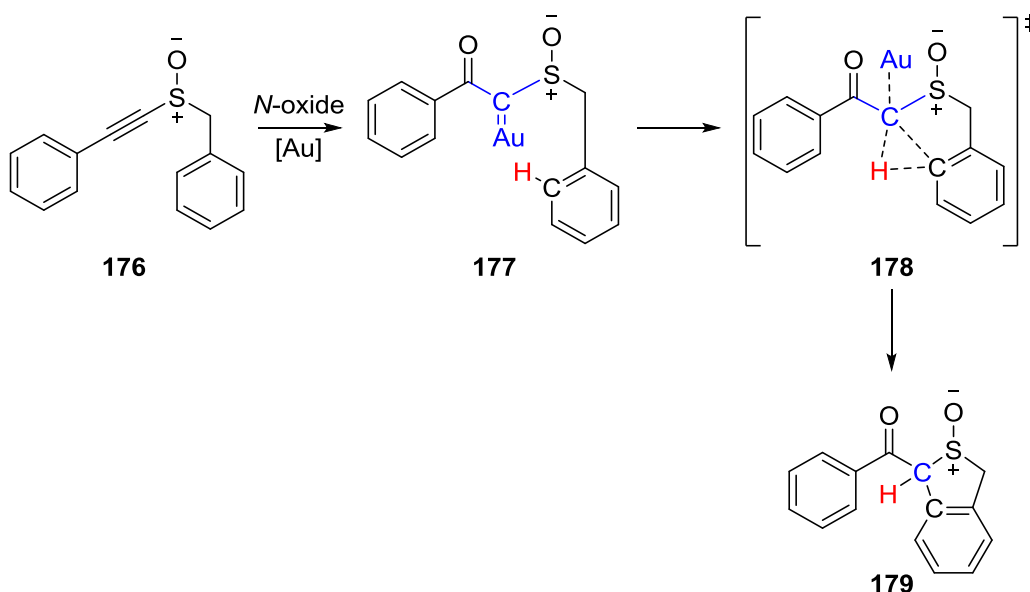
Another example of overall C-H insertion was published in 2004 by Fürstner *et al.* they reported on the synthesis of substituted phenanthrenes *via* gold-catalysis. A biphenyl substrate **173** which contained a terminal alkyne unit was treated with AuCl_3 . The product, a substituted phenanthrene **175** 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 η^2 -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 57: Fürstner's intramolecular arylation¹²¹

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.



Scheme 58: Proposed C-H insertion

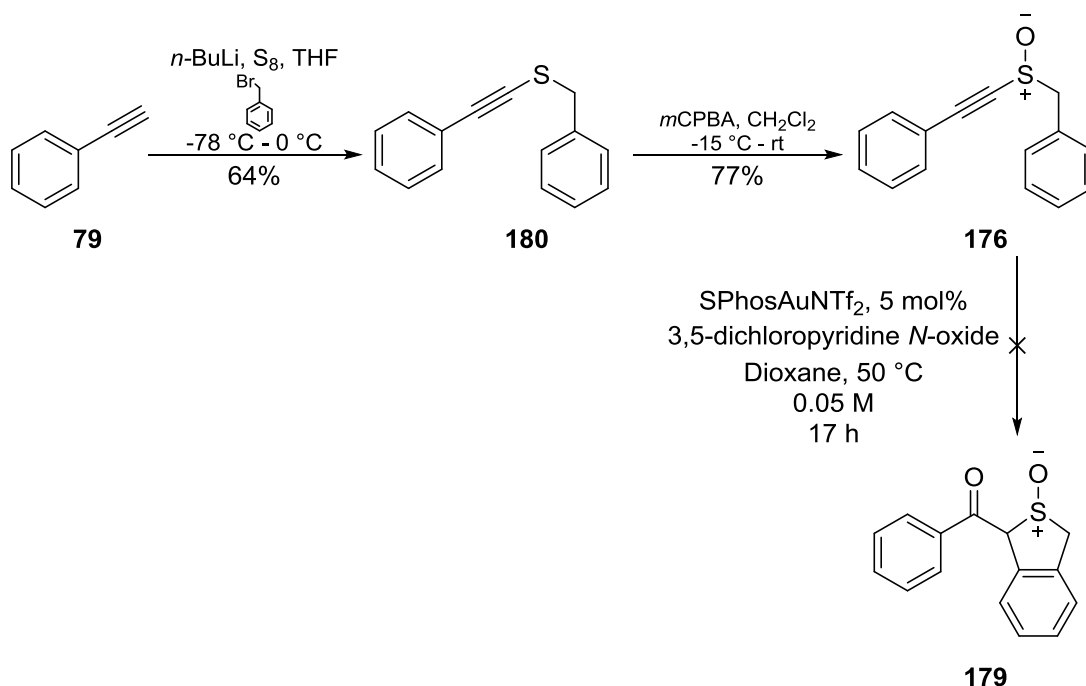
Scheme 58 shows how the reaction is proposed to proceed.

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 *ortho/para* directing, and in the scheme below the canonical forms depict how this electron donating activation occurs.

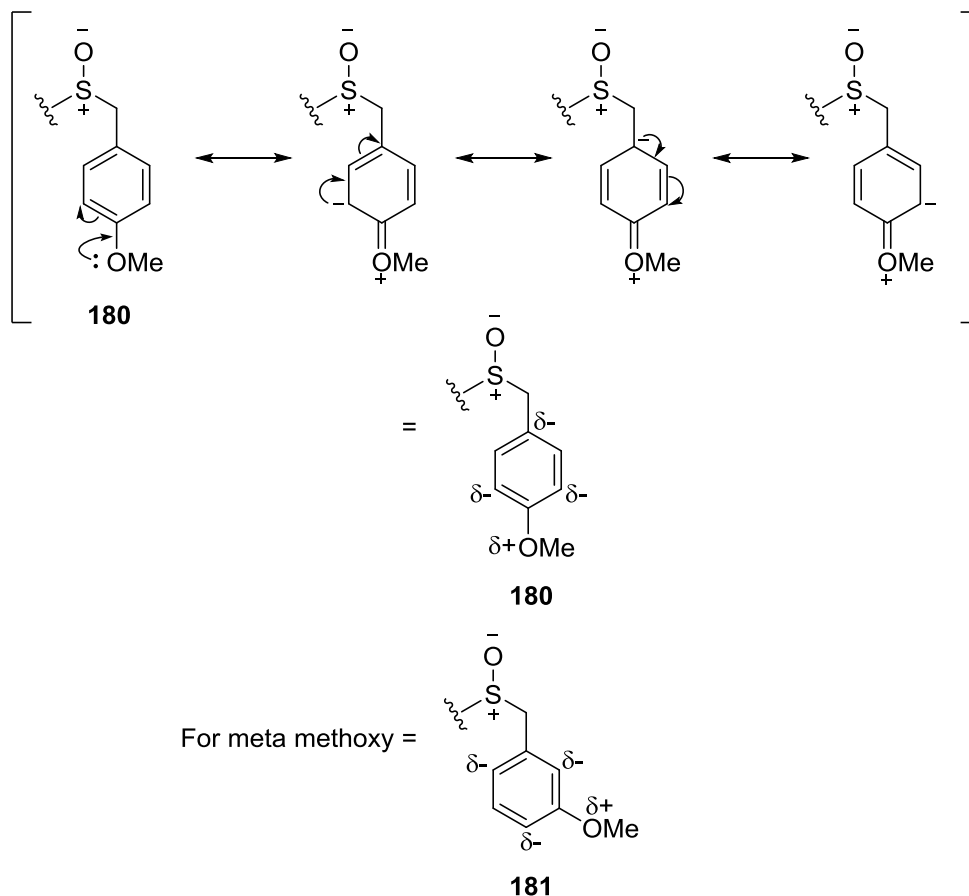
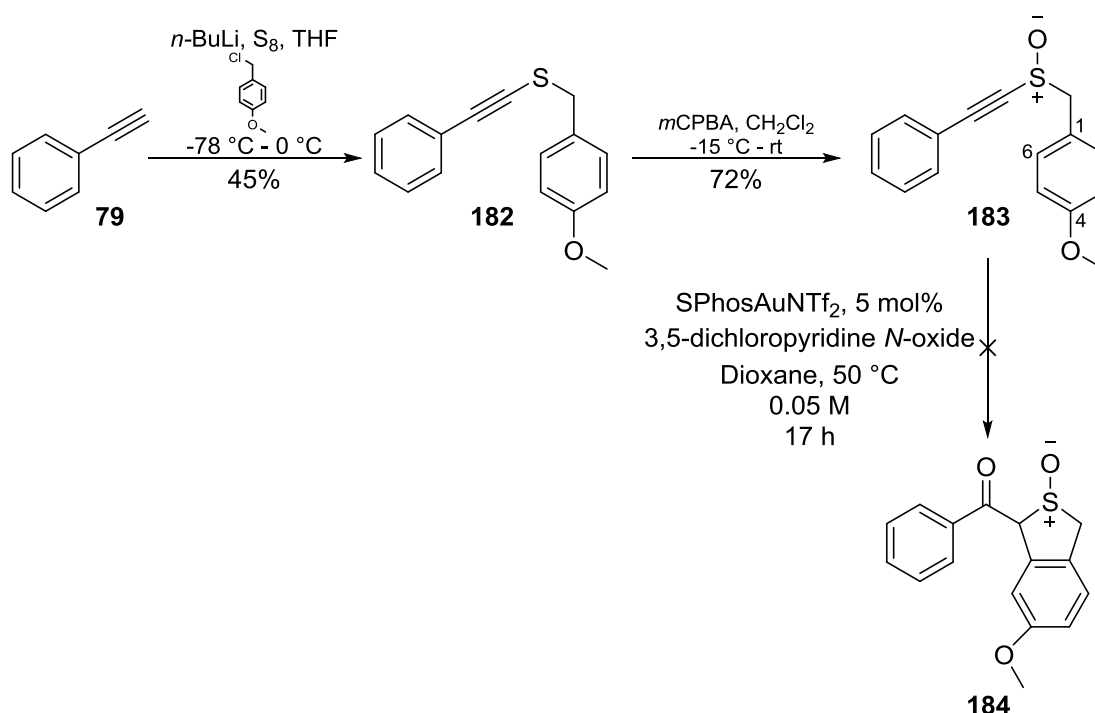


Figure 24: Resonance structures representing methoxy electron donating activation of the phenyl ring

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 be seen in the resonance structures above, although this imparts electron density into the π -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

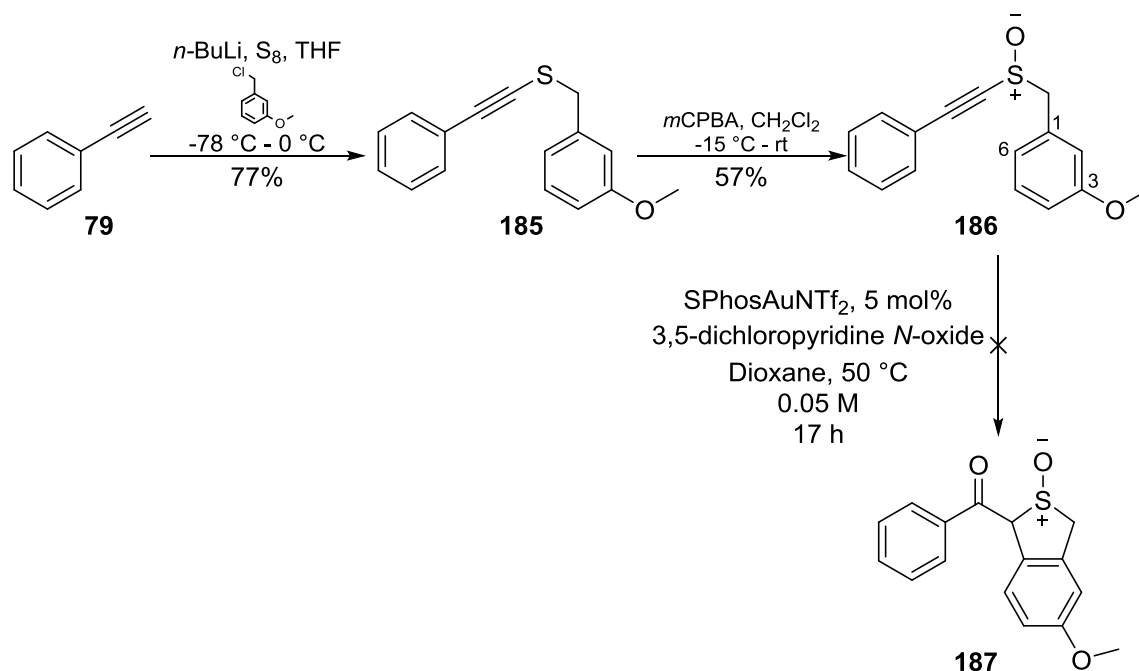
sulfide **182** and later the sulfoxide **183** was achieved in with good yields; however upon gold-catalysis the C-H insertion product **184** was not synthesised, instead a variety of products were formed which were not isolated.



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 (SPhosAuNTf_2), 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

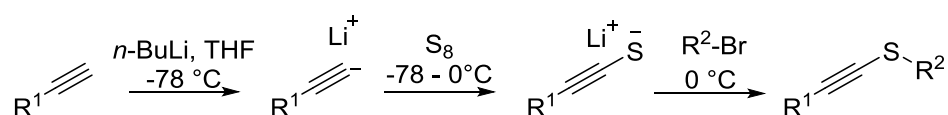
All reagents which were available commercially were purchased from Acros, Alfa Aesar, Fisher Scientific or Sigma Aldrich and used without further purification. *n*-BuLi was purchased as either a 1.6 M or 2.5 M solution in hexanes and was titrated before each use using diphenylacetic acid (DPAA). Sulfur 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 KH₂PO₄ (94 mL), distilled water was added up to 376 mL. A solution of *m*CPBA (77% w/w, 10 g) in Et₂O (100 mL) was washed with the buffer solution ($\times 3$); the combined organic layers were then dried over MgSO₄, 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 60F₂₅₄ 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 (ν_{max}) are reported in cm^{-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). ^1H and ^{13}C NMR spectra were recorded on a Bruker AVIII300 (^1H , 300 MHz; $T = 298\text{K}$) and Bruker AVIII400 (^1H , 400MHz; ^{13}C , 101 MHz; $T = 298\text{K}$) in the solvents indicated. Chemical shifts (δ) 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_3 (^1H , 7.26 ppm; ^{13}C , 77.16 ppm). Coupling constants (J) are reported in Hz. The following abbreviations are used to describe multiplicity in ^1H -NMR: m (multiplet), s (singlet), d (doublet), t (triplet) and q (quartet) and in ^{13}C -NMR: C (quaternary), CH (tertiary), CH_2 (secondary) and CH_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

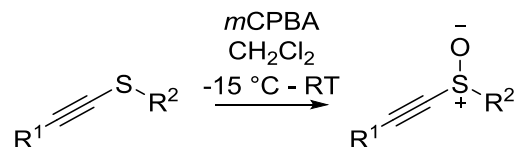
Preparation of alkynyl sulfides from terminal alkynes and substituted halide: general procedure 1 (GP1)



n-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 alkyl halide (1.0 eq.) was added to the thiolate and the reaction stirred until starting materials had been consumed. 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 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 *m*CPBA:

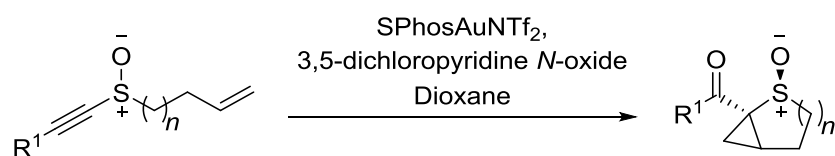
general procedure 2 (GP2)



Purified *m*CPBA (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

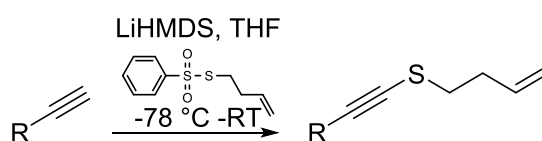
(GP3)



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

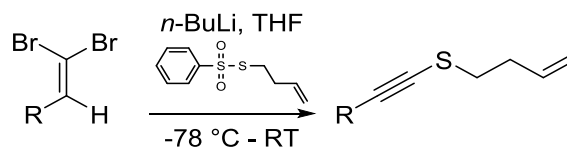
reaction was stirred at 50 °C for the indicated time until the reaction was complete as determined by TLC. Upon completion the crude mixture was passed through a pad of silica using portions of CH₂Cl₂, EtOAc and [MeOH/EtOAc (1:9)] to remove residual gold. The solvent was removed under reduced pressure 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. R_f values were obtained using [hexane/EtOAc (99:1)].

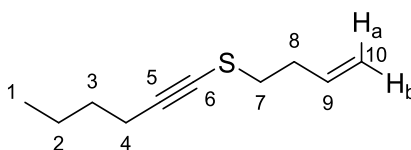
Preparation of alkynyl sulfides from corresponding dibromo-olefins using *S*-butyl benzenesulfonylthioate: general procedure 5 (GP5)



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 °C at which point the solution became bright orange/red, stirring was maintained for 2 h at -78 °C before the addition of *S*-butyl benzenesulfonylthioate (1.0 eq.), the mixture was allowed to warm to RT over 17 h whilst stirring was maintained. Upon completion NH_4Cl (0.1 M) was added into the solution to quench the reaction. The aqueous layer was extracted with Et_2O (\times 3). The combined organic extracts were washed with brine (0.1 M) and dried over 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

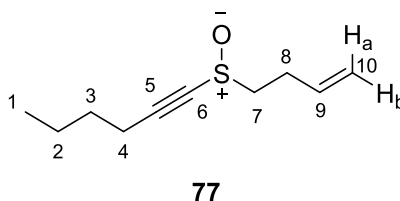
But-3-en-1-yl(hex-1-yn-1-yl)sulfane



76

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%). $R_f = 0.81$. ^1H NMR (300 MHz CDCl_3): δ 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, H-2-3), 0.91 (t, $J = 7.1$, 3H, H-1); ^{13}C NMR (101 MHz CDCl_3): δ 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: ν_{max} (cm^{-1}) 3079, 2960, 2929, 2167, 1641, 1571, 1442, 1417, 752, 689; HRMS (ES) m/z calculated for $\text{C}_{10}\text{H}_{16}\text{S}$ ($\text{M}+\text{H}$) $^+$ 168.0973, found 168.0979.

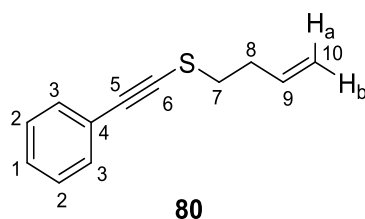
1-(But-3-en-1-ylsulfanyl)hex-1-yne



Following **GP2** using sulfide **76** (371 mg, 3.0 mmol), *m*CPBA (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%). $R_f = 0.26$. ^1H NMR (300 MHz CDCl_3): δ 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, H-2-3), 0.93 (t, $J = 7.3$, 3H, H-1); ^{13}C NMR (101 MHz CDCl_3): δ 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: ν_{max}

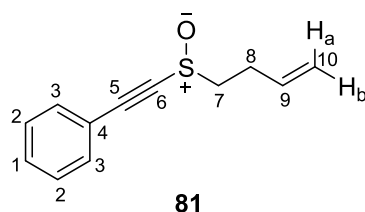
(cm^{-1}) 2959, 2933, 2873, 2181, 1641, 1466, 1056, 916; HRMS (ES) m/z calculated for $\text{C}_{10}\text{H}_{16}\text{OSNa}$ ($\text{M}+\text{Na}$) $^{+}$ 207.0820, found 207.0825.

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



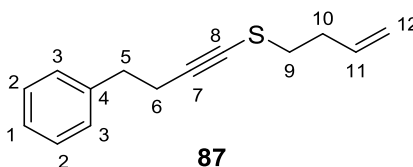
Following **GP1** using phenylacetylene (409 mg, 440 μL , 4.0 mmol), $n\text{-BuLi}$ (2.2 mL, 2.0 M, 4.4 mmol), sulfur powder (128 mg, 4.0 mmol), 4-bromo-1-butene (540 mg, 406 μL , 4.0 mmol) stirred for 17 h gave sulfide **80** as a pale yellow oil (534 mg, 71%). $R_f = 0.83$. ^1H NMR (300 MHz CDCl_3): δ 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): δ 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: ν_{max} (cm^{-1}) 3077, 2932, 2166, 1641, 1595, 1486, 990, 912, 752, 689; HRMS (ES) m/z calculated for $\text{C}_{12}\text{H}_{12}\text{S}$ ($\text{M}+\text{H}$) $^{+}$ 188.0660, found 188.0663.

((But-3-en-1-ylsulfinyl)ethynyl)benzene



Following **GP2** using sulfide **80**, (226 mg, 1.2 mmol), *m*CPBA (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); ^{13}C NMR (101 MHz CDCl_3): δ 134.6 (CH, C-9), 132.2 (2 \times CH, C-3), 130.6 (CH, C-1), 128.6 (2 \times 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 $\text{C}_{12}\text{H}_{12}\text{OSNa}$ ($\text{M}+\text{Na}$) $^+$ 227.0507, found 227.0504.

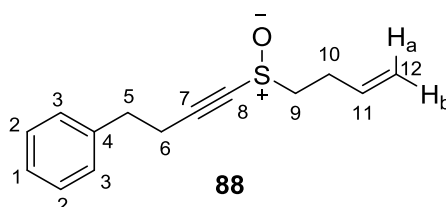
But-3-en-1-yl(4-phenylbut-1-yn-1-yl)sulfane



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); ^{13}C NMR (101 MHz CDCl_3): δ 140.6 (C, C-4), 135.9 (CH, C-11), 128.5 (2 \times CH, C-2), 128.4 (2 \times 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,

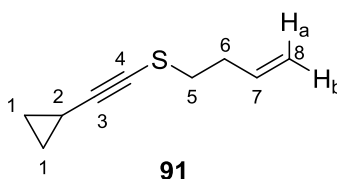
1640, 1537, 1453, 1337, 1276, 1030, 993, 915, 747, 697; HRMS (ES) m/z calculated for $C_{14}H_{16}S$ ($M+H$)⁺ 217.1048, found 217.1051.

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



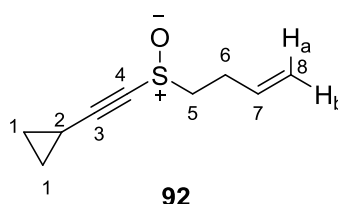
Following **GP2** using sulfide **87** (86 mg, 0.40 mmol), *m*CPBA (76 mg, 0.44 mmol) stirred for 4 h gave sulfoxide **88**, purified using [hexane/EtOAc(75:25)] as a pale yellow oil (67 mg, 73%). R_f = 0.35. 1H NMR (300 MHz $CDCl_3$): δ 7.38 – 7.22 (m, 5H, H1-3), 5.85 (ddt, J = 17.1, 10.2, 6.6, 1H, 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); ^{13}C NMR (101 MHz $CDCl_3$): δ 140.8 (C, C-4), 136.1 (CH, C-11), 128.7 (2 \times CH_2 , C-2), 128.6 (2 \times 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



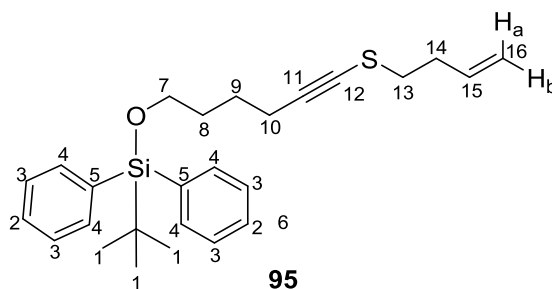
Following **GP1** using cyclopropylacetylene (198 mg, 254 μ L, 3.0 mmol), *n*-BuLi (2.1 mL, 1.6 M, 3.3 mmol), sulfur powder (96 mg, 3.0 mmol), 4-bromo-1-butene (405 mg, 0.3 mL, 3.0 mmol) stirred for 17 h gave sulfide **90** as a pale yellow oil (139 mg, 30%). R_f = 0.77. ^1H NMR (300 MHz CDCl_3): δ 5.86 (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); ^{13}C NMR (101 MHz CDCl_3): δ 135.9 (CH, C-7), 116.6 (CH_2 , C-8), 98.6 (C, C-3), 63.8 (C, C-4), 34.7 (CH_2 , C-6), 33.4 (CH_2 , C-5), 9.0 ($2 \times \text{CH}_2$, C-1), 0.8 (CH, C-2); IR: ν_{max} (cm^{-1}) 3080, 3011, 2979, 1640, 1429, 989, 916, 839, 810, 725; HRMS (ES) m/z calculated for $\text{C}_9\text{H}_{13}\text{S}$ ($\text{M}+\text{H}$) $^+$ 153.0738, found 153.0735.

((But-3-en-1-ylsulfinyl)ethynyl)cyclopropane



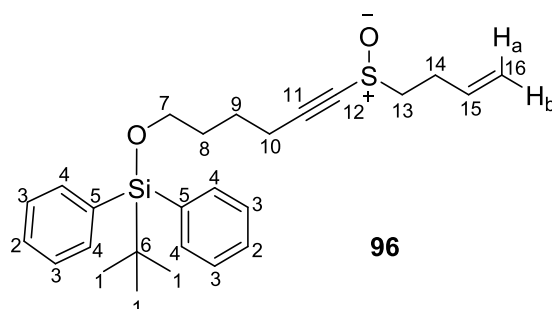
Following **GP2** using sulfide **91** (91.4 mg, 0.60 mmol), *m*CPBA (114 mg, 0.66 mmol) stirred for 4 h gave sulfoxide **92**, purified using [hexane/EtOAc(8:2)] as a yellow oil (69 mg, 68%). R_f = 0.27. ^1H NMR (300 MHz CDCl_3): δ 5.82 (ddt, J = 17.2, 10.3, 6.6, 1H, H-7), 5.14 (dd, J = 17.2, 1.5, 1H, 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); ^{13}C NMR (101 MHz CDCl_3): δ 134.7 (CH, C-7), 117.4 (CH_2 , C-8), 109.6 (C, C-3), 72.1 (C, C-4), 55.5 (CH_2 , C-5), 26.7 (CH_2 , C-6), 9.6 ($2 \times \text{CH}_2$, C-1), 0.33 (CH, C-2); IR: ν_{max} (cm^{-1}) 3080, 3012, 2920, 2178, 1641, 1441, 1348, 1277, 1052, 995, 916, 828, 781; HRMS (ES) m/z calculated for $\text{C}_9\text{H}_{13}\text{S}$ ($\text{M}+\text{H}$) $^+$ 169.0687, found 169.0692.

((6-(But-3-en-1-ylthio)hex-5-yn-1-yl)oxy)(tert-butyl)diphenylsilane



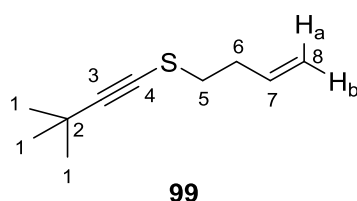
Following **GP1** using *tert*-butyl(hex-5-yn-1-yloxy)diphenylsilane (TBDPS protected 5-hexyn-1-ol) obtained from Matthew Barrett, (633 mg, 1.9 mmol), *n*-BuLi (1.1 mL, 1.9 M, 2.1 mmol), sulfur powder (60.3 mg, 1.9 mmol), 4-bromo-1-butene (254 mg, 190 μ L, 1.9 mmol) stirred for 17 h gave sulfide **95** as a pale yellow oil (386 mg, 50%). R_f = 0.76. ^1H NMR (300 MHz CDCl_3): δ 7.66 – 7.36 (m, 10H, H2-4), 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, H8-9), 1.04 (s, 9H, H-1); ^{13}C NMR (101 MHz CDCl_3): δ 135.8 (CH, C-15), 134.2 (2 \times C, C-5), 129.7 (2 \times CH, C-2), 129.7 (4 \times CH, C-4), 127.8 (4 \times CH, C-3), 116.8 (CH_2 , C-16), 94.8 (C, C-11), 65.6 (C, C-12), 34.8 (CH_2 , C-7), 33.6 (CH_2 , C-14), 31.9 (CH_2 , C-8), 27.1 (3 \times CH_3 , C-1), 25.5 (C, C-6), 20.1 (CH_2 , C-13), 19.4 (CH_2 , C-9), 18.4 (CH_2 , C-10); IR: ν_{max} (cm^{-1}) 3071, 2931, 2858, 1689, 1589, 1428, 1106, 997, 917, 822, 739, 700, 613; HRMS (ES) m/z calculated for $\text{C}_{26}\text{H}_{34}\text{SiS}$ ($\text{M}+\text{Na}$) $^+$ 445.1997, found 445.1996.

((6-(But-3-en-1-ylsulfinyl)hex-5-yn-1-yl)oxy)(tert-butyl)diphenylsilane



Following **GP2** using sulfide **95**, (390 mg, 0.9 mmol), *m*CPBA (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%). $R_f = 0.36$. ^1H 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).

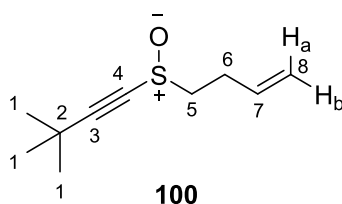
But-3-en-1-yl(3,3-dimethylbut-1-yn-1-yl)sulfane



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. ^1H 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

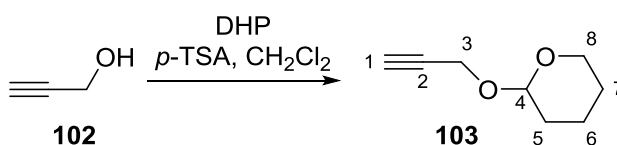
(s, 9H, H-1). ^{13}C NMR (101 MHz CDCl_3): δ 136.2 (CH, C-7), 116.7 (CH_2 , C-8), 103.0 (C, C-3), 66.7 (C, C-4), 34.8 (CH_2 , C-6), 33.5 (CH_2 , C-5), 31.2 ($3 \times \text{CH}_3$, C-1), 29.0 (C, C-2). IR: ν_{max} (cm^{-1}) 2963, 2865, 1706, 1640, 1467, 1393, 1362, 1218, 991, 914, 744. HRMS (ES) m/z calculated for $\text{C}_{10}\text{H}_{16}\text{S}$ 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), *m*CPBA (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%). $R_f = 0.31$. ^1H 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 ($3 \times \text{CH}_3$, C-1), 29.9 (C, C-2), 26.7 (CH_2 , C-6); IR: ν_{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 $\text{C}_{10}\text{H}_{17}\text{OS}$ ($\text{M}+\text{H}$) $^+$ 185.1000 found 185.1001.

Tetrahydro-2-(2-propynyloxy)-2H-pyran

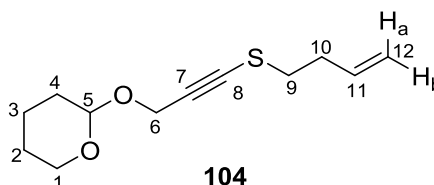


A known compound was prepared using literature precedent.¹²³

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 CH₂Cl₂ (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 CH₂Cl₂ (5 mL) the reaction mixture was stirred for a further 3 h. Upon completion the crude mixture was dried over MgSO₄, 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*_f = 0.72. ¹H NMR (300 MHz CDCl₃): 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); ¹³C NMR (101 MHz CDCl₃): δ 96.9 (CH, C-4), 74.0 (CH, C-1), 79.8 (C, C-2), 62.0 (CH₂, C-8), 54.0 (CH₂, C-3), 30.2 (CH₂, C-4), 25.4 (CH₂, C-7), 19.0 (CH₂, C-6); IR: ν_{max} (cm⁻¹) 3286, 2943, 2870, 1442, 1390, 1202, 1120, 1058, 1026, 948, 902, 871, 815. Analytical data in agreement with literature values.¹²⁴

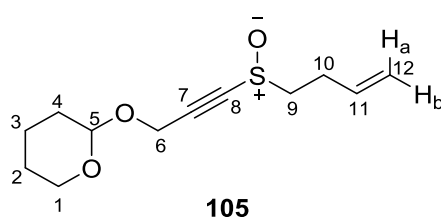
2-((3-(But-3-en-1-ylthio)prop-2-yn-1-yl)oxy)tetrahydro-2H-pyran



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 CDCl_3): 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); ^{13}C NMR (101 MHz CDCl_3): δ 135.8 (CH, C-11), 117.0 (CH_2 , C-12), 96.9 (CH, C-5), 90.8 (C, C-7), 76.5 (C, C-8), 62.3 (CH_2 , C-1), 55.3 (CH_2 , C-6), 34.7 (CH_2 , C-10), 33.6 (CH_2 , C-9), 30.5 (CH_2 , C-4), 25.6 (CH_2 , C-2), 19.3 (CH_2 , 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 $\text{C}_{12}\text{H}_{19}\text{O}_2\text{S}$ ($\text{M}+\text{H}$) $^+$ 227.1106, found 227.1110.

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

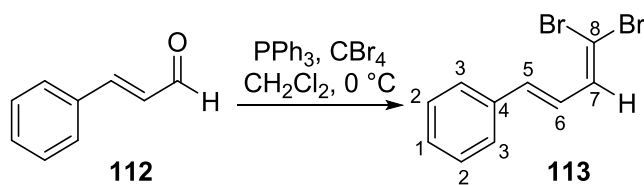


Following **GP2** using sulfide **104** (777 mg, 3.4 mmol), *m*CPBA (652 mg, 3.7 mmol) stirred for 5 h gave sulfoxide **105** purified using [hexane/EtOAc (75:25)] as a pale yellow oil (700 mg, 85%) as a mixture of diastereoisomers, the data for the major is assigned. $R_f = 0.26$. ^1H NMR (300 MHz CDCl_3): 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); ^{13}C NMR (101 MHz CDCl_3): δ 134.3 (CH, C-11), 117.6 (CH_2 , C-12), 100.0 (C, C-7), 97.4 (CH, C-5), 82.2 (C, C-8), 62.1 (CH_2 , C-1), 55.1 (CH_2 , C-6), 54.2 (CH_2 , C-9), 30.1 (CH_2 , C-4), 26.5 (CH_2 , C-10), 25.2 (CH_2 , C-2), 18.8 (CH_2 , 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 $C_{12}H_{19}O_3S$ ($M+H$)⁺ 243.1055 found 243.1052.

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

A known compound was prepared using literature precedent.¹¹⁴

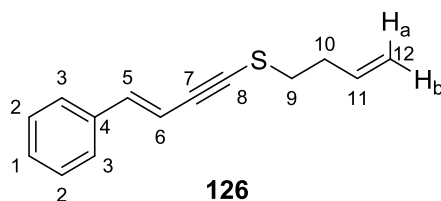


Corey-Fuchs conversion of aldehydes to corresponding dibromo-olefins:

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_2Cl_2 (0.1 M) at $0\text{ }^{\circ}C$, the resultant mixture was stirred for 30 mins at $0\text{ }^{\circ}C$ before the addition of *trans*-cinnamaldehyde (0.66 g, 0.63 mL, 5 mmol), the reaction was stirred at $0\text{ }^{\circ}C$ for 3 h. Upon completion the mixture was diluted with further CH_2Cl_2 (0.1 M) and washed with H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_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 **113** as a white solid (1.2 g, 82%); m.p: $54 - 56\text{ }^{\circ}C$., lit. m.p: $55 - 56\text{ }^{\circ}C$. $R_f = 0.89$. 1H NMR (300 MHz $CDCl_3$): δ 7.48 – 7.42 (m, 2H, H-3), 7.38 – 7.33 (m, 2H, H-2), 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); ^{13}C NMR (101 MHz $CDCl_3$): δ 143.2 (CH, C-5), 135.9 (C, C-4), 129.0 (2 \times CH, C-2), 128.8 (2 \times CH, C-3), 126.4 (CH, C-1), 107.0 (CH, C-7), 82.9 (C, C-

8), 79.3 (CH, C-6); IR: ν_{\max} (cm⁻¹) 3015, 2850, 2924, 1948, 1558, 1484, 1446, 1232, 1212, 1138, 1029, 959, 802, 744, 687, 629. Analytical data in agreement with literature values.^{125,126}

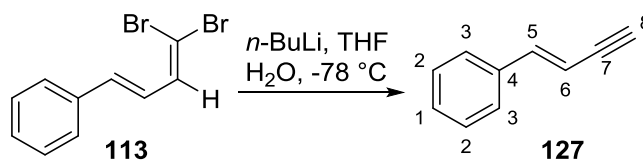
(E)-But-3-en-1-yl(4-phenylbut-3-en-1-yn-1-yl)sulfane



Following **GP5** using *n*-BuLi (2.2 mL, 2.0 M, 4.4 mmol), dibromo-olefin **113** (282 mg, 2.2 mmol), *S*-butyl benzenesulfonylthioate (457 mg, 397 μ L, 2.0 mmol) stirred for 17 h gave sulfide **126** as a pale yellow oil (56mg, 13%). R_f 0.73. ¹H NMR (300 MHz CDCl₃): δ 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); ¹³C NMR (101 MHz CDCl₃): δ 140.4 (CH, C-5), 137.0 (C, C-4), 135.6 (CH, C-11), 128.7 (2 \times CH, C-2), 128.5 (2 \times CH, C-3), 126.2 (CH, C-1), 116.9 (CH₂, C-12), 108.2 (CH, C-6), 93.1 (C, C-7), 81.5 (C, C-8), 35.1 (CH₂, C-10), 33.5 (CH₂, C-9); IR: ν_{\max} (cm⁻¹) 3078, 3023, 2924, 2134, 1639, 1546, 1489, 1446, 1221, 966, 915, 818, 745, 688; HRMS (ES) m/z calculated for C₁₄H₁₄S 214.0816, found 214.0813.

(E)-But-1-en-3-yn-1-ylbenzene

A known compound was prepared using literature precedent.¹¹⁴

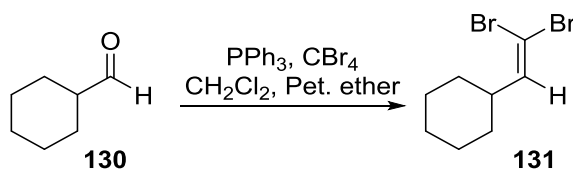


Preparation of a terminal alkyne *via* dihydrohalogenation and metal-halogen exchange of the dibromo-olefin using *n*-BuLi:

$n\text{-BuLi}$ (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 $-78\text{ }^\circ\text{C}$ 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 H_2O (25 mL), and the aqueous layer extracted with pentane ($\times 3$), the combined organic extracted were dried over 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 **127** as a colourless oil (163mg, 82%). $R_f = 0.76$. ^1H NMR (300 MHz CDCl_3): δ 7.42 – 7.30 (m, 5H, H1-3), 7.05 (d, $J = 16.4$, 1H, H-5), 6.13 (dd, $J = 16.4$, 2.4, 1H, H-6), 3.05 (d, $J = 2.4$, 1H, H-8); ^{13}C NMR (101 MHz CDCl_3): δ 143.2 (CH, C-5), 135.9 (C, C-4), 128.9 (2 \times CH, C-2), 128.8 (2 \times CH, C-3), 126.4 (CH, C-1), 107.0 (CH, C-6), 82.9 (C, C-7), 79.3 (CH, C-8); IR: ν_{max} (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.¹²⁷

(2,2-Dibromovinyl)cyclohexane

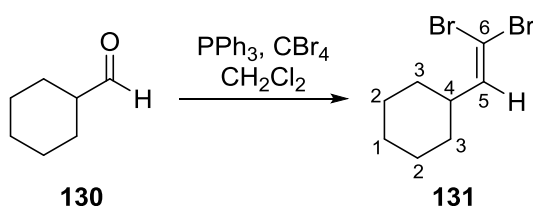
A known compound was prepared using literature precedent.¹²⁸



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

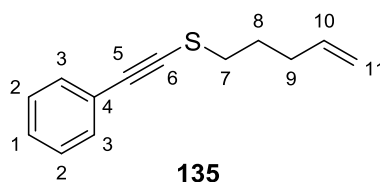
Triphenylphosphine (4.33 g, 16.5 mmol) was added in portions over 5 mins to a solution of cyclohexanecarboxyaldehyde (0.56 g, 0.6 mL, 5.0 mmol) in anhydrous CH_2Cl_2 (0.1 M) at 0 °C and stirred for 5 mins before the addition of a prepared solution of CBr_4 (3.56 g, 11.0 mmol) in anhydrous CH_2Cl_2 (0.1 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_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 **131** as a colourless oil (93.8 mg, 7%) $R_f = 0.86$.

Corey-Fuchs conversion of aldehydes to corresponding dibromo-olefins:¹¹⁴



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 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 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 **131** as a colourless oil (33.5 mg, 2.5%). *R*_f = 0.88. ¹H NMR (300 MHz CDCl₃): 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); ¹³C NMR (101 MHz CDCl₃): δ 143.8 (CH, C-5), 87.0 (C, C-6), 42.5 (CH, C-1), 31.3 (2 × CH₂, C-3), 25.8 (C, C-4), 25.5 (2 × CH₂, C-2); IR: *v*_{max} (cm⁻¹) 2924, 2850, 1610, 1448, 1350, 1257, 1140, 965, 893, 833, 764, 813, 669. Analytical data in agreement with literature values.¹²⁸

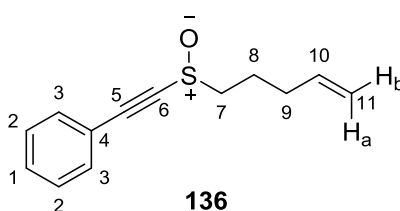
Pent-4-en-1-yl(phenylethynyl)sulfane



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. ¹H NMR (300 MHz

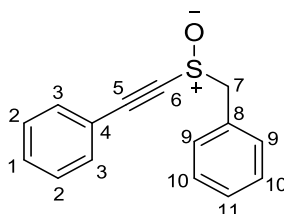
CDCl₃): δ 7.44 – 7.26 (m, 5H, H-1-3), 5.81 (ddt, J = 17.1, 10.2, 6.6, 1H, H-10), 5.08 (dd, J = 17.1, 1.8, 1H, H-11), 5.02 (dd, J = 10.2, 1.8, 1H, H-11), 2.81 (t, J = 7.1, 2H, H-7), 2.24 (td, J = 7.3, 6.6, 2H, H-9), 1.91 (tt, J = 7.3, 7.1, 2H, H-8); ¹³C NMR (101 MHz CDCl₃): δ 137.4 (CH, C-10), 131.5 (2 × 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.

((Pent-4-en-1-ylsulfinyl)ethynyl)benzene



Following **GP2** using sulfide **135** (457 mg, 2.3 mmol), *m*CPBA (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%). R_f = 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.

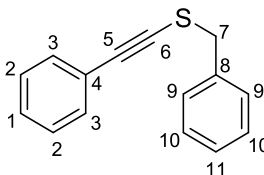
((Benzylsulfinyl)ethynyl)benzene



176

Following **GP2** using sulfide **180**, (146 mg, 0.65 mmol), *m*CPBA (123 mg, 0.72 mmol) gave sulfoxide **176**, purified using [hexane/EtOAc(75:25)] as a pale yellow oil (121 mg, 77%). $R_f = 0.27$. ^1H NMR (300 MHz CDCl_3): δ 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): δ 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: ν_{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 $\text{C}_{15}\text{H}_{12}\text{OSNa}$ ($\text{M}+\text{Na}$) $^+$ 263.0507, found 263.0512.

Benzyl(phenylethynyl)sulfane

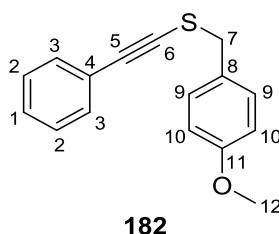


180

Following **GP1** using phenylacetylene (204 mg, 220 μL , 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 μL , 2.0 mmol) stirred for 18 h gave sulfide **180** as a pale yellow oil (287 mg, 64%). $R_f = 0.77$. ^1H NMR (300 MHz

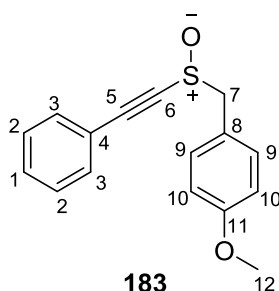
CDCl₃): δ 7.43 – 7.28 (m, 10H, H1-3, H9-11), 4.06 (s, 2H, H-7); ¹³C NMR (101 MHz CDCl₃): δ 136.8 (C, C-8), 131.5 (2 × CH, C-3), 129.3 (2 × CH, C-10), 128.8 (CH, C-1), 128.5 (2 × CH, C-2), 128.3 (2 × CH, C-9), 128.0 (CH, C-11), 123.5 (C, C-4), 94.7 (C, C-5), 79.4 (C, C-6), 40.6 (CH₂, C-7); IR: ν_{max} (cm⁻¹) 3060, 3029, 2924, 2165, 1879, 1595, 1486, 1419, 1237, 840, 751, 659; HRMS (ES) m/z calculated for C₁₅H₁₃S (M+H)⁺ 225.0738, found 225.0736.

(4-Methoxybenzyl)(phenylethynyl)sulfane



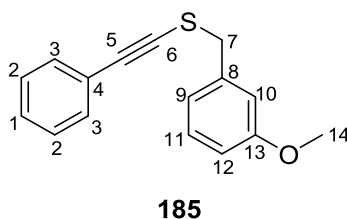
Following **GP1** using phenylacetylene (409 mg, 439 μ L, 4.0 mmol), *n*-BuLi (2.1 mL, 2.1 M, 4.4 mmol), sulfur powder (128 mg, 4.0 mmol), 4-methoxybenzyl bromide (804 mg, 577 μ L, 4.0 mmol) stirred for 18 h gave sulfide **182** as a pale yellow oil (458 mg, 45%). R_f 0.80. ¹H NMR (300 MHz CDCl₃): δ 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); ¹³C NMR (101 MHz CDCl₃): δ 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 (CH₃, C-12), 40.3 (CH₂, C-7); IR: ν_{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 C₁₆H₁₄OS 254.0765, found 254.0770.

1-Methoxy-4-(((phenylethynyl)sulfinyl)methyl)benzene



Following **GP2** using sulfide **182**, (458, 1.8 mmol), *m*CPBA (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%). R_f = 0.40. ^1H NMR (300 MHz CDCl_3): 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); ^{13}C NMR (101 MHz CDCl_3): δ 158.7 (C, C-11), 132.2 (2 \times CH, C-3), 131.9 (2 \times CH, C-9), 130.6 (CH, C-1), 129.5 (2 \times CH, C-2), 128.6 (2 \times 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 (CH_2 , C-7), 55.3 (CH_3 , C-12); IR: ν_{max} (cm^{-1}) 3000, 2933, 2835, 2164, 1667, 1609, 1510, 1442, 1302, 1245, 1175, 1059, 1029, 826, 755, 688; HRMS (ES) m/z calculated for $\text{C}_{16}\text{H}_{15}\text{O}_2\text{S}$ ($\text{M}+\text{H}$) $^+$ 271.0793, found 271.0800.

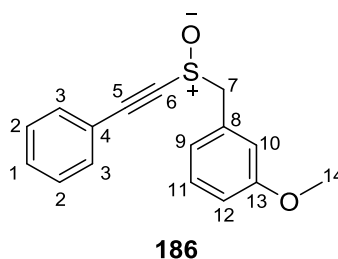
(3-Methoxybenzyl)(phenylethynyl)sulfane



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%). R_f 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 \times CH, C-3), 129.7 (CH, C-11), 128.4 (CH, C-1), 128.2 (2 \times 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: ν_{max} (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.

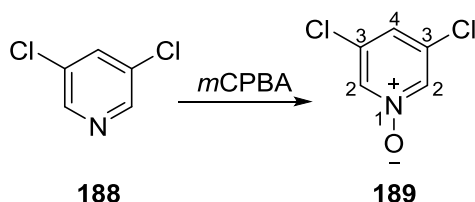
1-Methoxy-3-(((phenylethynyl)sulfinyl)methyl)benzene



Following **GP2** using sulfide **185**, (778 mg, 3.1 mmol), *m*CPBA (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%). R_f = 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 \times CH, C-3), 130.7 (CH, C-11), 130.4 (C, C-8), 129.8 (CH, C-1), 128.6 (2 \times 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: ν_{max} (cm⁻¹) 2941, 2835, 2163, 1666, 1597, 1488, 1450, 1297, 1264, 1153, 1042, 831, 784, 739, 757, 687; HRMS (ES) m/z calculated for C₁₆H₁₄O₂SN_a (M+Na)⁺ 293.0612, found 293.0610.

3,5-dichloropyridine *N*-oxide

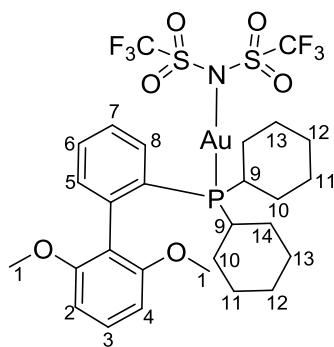
A known compound was prepared using a modified literature precedent.¹²⁹



Oxidation of 3,5-dichloropyridine to the corresponding *N*-oxide by *m*CPBA:

Purified *m*CPBA (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 CH₂Cl₂ (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 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 to yield a pale yellow crystalline solid (549 mg, 67%). *R*_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. ¹H NMR (300 MHz CDCl₃): δ 8.15 (d, *J* = 1.6, 2H, H-2), 7.31 (t, *J* = 1.4, 1H, H-4). ¹³C NMR (101 MHz CDCl₃): δ 137.4 (CH, C-4), 133.4 (2 × C, C-3), 126.2 (2 × CH, C-2). IR: *v*_{max} (cm⁻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.¹³⁰

SPhosAuNTf₂



190

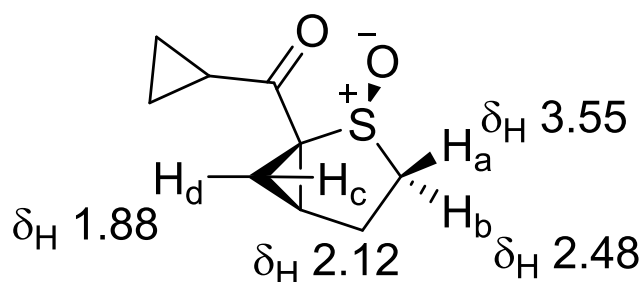
Dimethylsulfide, Me₂S (98 mg, 115 μ L, 1.6 mmol) as a solution in MeOH (0.8 mL) was added drop-wise to a foil-wrapped flask containing potassium gold(III) chloride, K(AuCl₄) (205 mg, 0.50 mmol) as a solution in MeOH (3.2 mL) and stirred for 1 h at RT. Upon completion the reaction mixture was filtered 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: ν_{max} (cm⁻¹) 2930, 2853, 1589, 1472, 1433, 1396, 1353, 1251, 1191, 1130, 1110, 1002, 956, 824, 777, 728, 661.

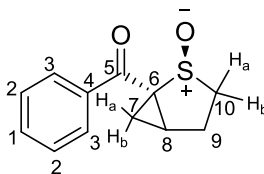
4.5 Analysis and characterisation of products of gold-catalysis



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.

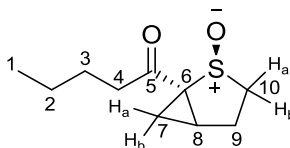
(2-Oxido-2-thiabicyclo[3.1.0]hexan-1-yl)(phenyl)methanone



82

Following **GP3** using sulfoxide **81** (20.4 mg, 0.10 mmol), 3,5-dichloropyridine *N*-oxide (19.7 mg, 0.12 mmol), SPhosAuNTf₂ (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. ¹H NMR (300 MHz CDCl₃): 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); ¹³C NMR (101 MHz CDCl₃): 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 (CH₂, C-10), 33.9 (CH, C-8), 26.4 (CH₂, C-9), 19.4 (CH₂, C-7); IR: ν_{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 C₁₂H₁₂O₂SNa (M+Na)⁺ 243.0456, found 243.0453.

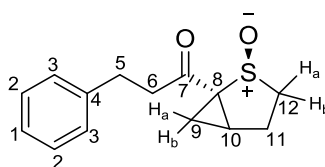
1-(2-Oxido-2-thiabicyclo[3.1.0]hexan-1-yl)pentan-1-one



84

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

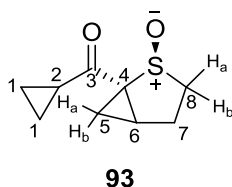


89

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),

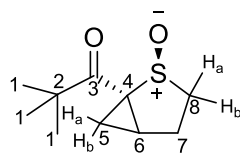
2.07 (app t, $J = 5.9$, 1H, H-9a), 1.86 (dd, $J = 8.4$, 5.9, 1H, H-9b); ^{13}C NMR (101 MHz CDCl_3): δ 202.9 (C, C-7), 140.4 (C, C-4), 128.6 (2 \times CH, C-2), 128.5 (2 \times CH, C-3), 126.3 (CH, C-1), 58.9 (C, C-8), 50.9 (CH_2 , C-12), 42.9 (CH_2 , C-6), 35.6 (CH, C-10), 29.7 (CH_2 , C-5), 25.4 (CH_2 , C-11), 18.1 (CH_2 , C-9); IR: ν_{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 $\text{C}_{14}\text{H}_{17}\text{O}_2\text{S}$ ($\text{M}+\text{H}$) $^+$ 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), SPhosAuNTf₂ (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. ^1H 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 \times CH_2 , C-1); IR: ν_{max} (cm^{-1}) 3412, 2934, 1167, 1445, 1394, 1250, 1057, 1022, 988, 872, 885, 677; HRMS (ES) m/z calculated for $\text{C}_9\text{H}_{12}\text{O}_2\text{SNa}$ ($\text{M}+\text{Na}$) $^+$ 207.0456, found 207.0461.

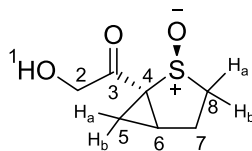
2,2-Dimethyl-1-(2-oxido-2-thiabicyclo[3.1.0]hexan-1-yl)propan-1-one



101

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%). *R*_f 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: ν_{max} (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.

1-(2-Oxido-2-thiabicyclo[3.1.0]hexan-1-yl)-2-((tetrahydro-2H-pyran-2-yl)oxy)ethan-1-one



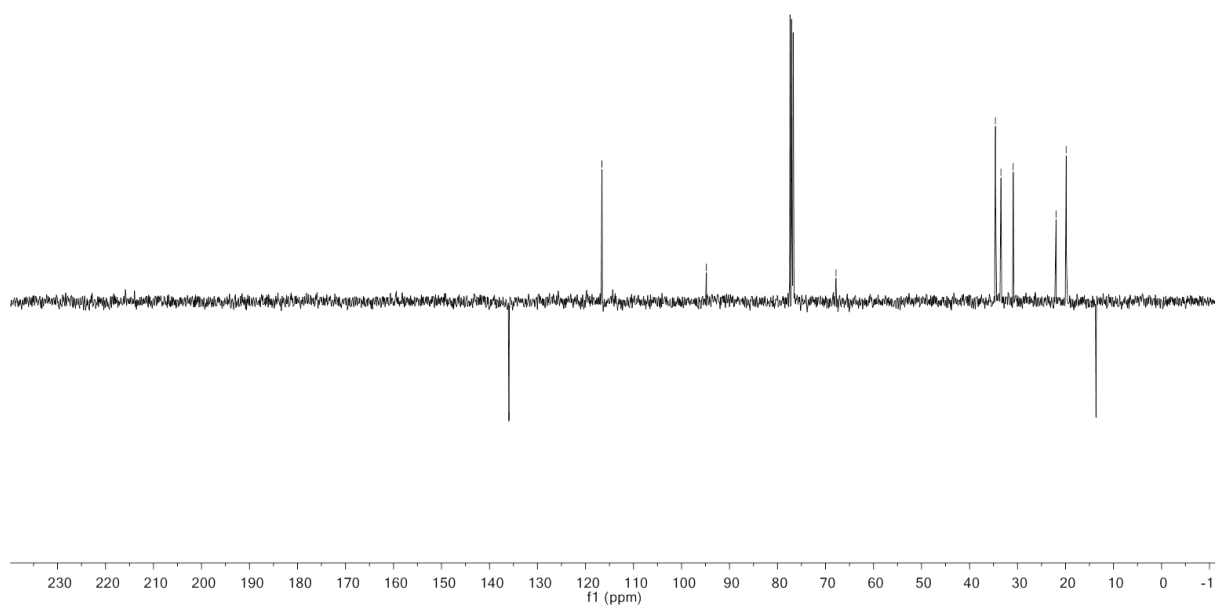
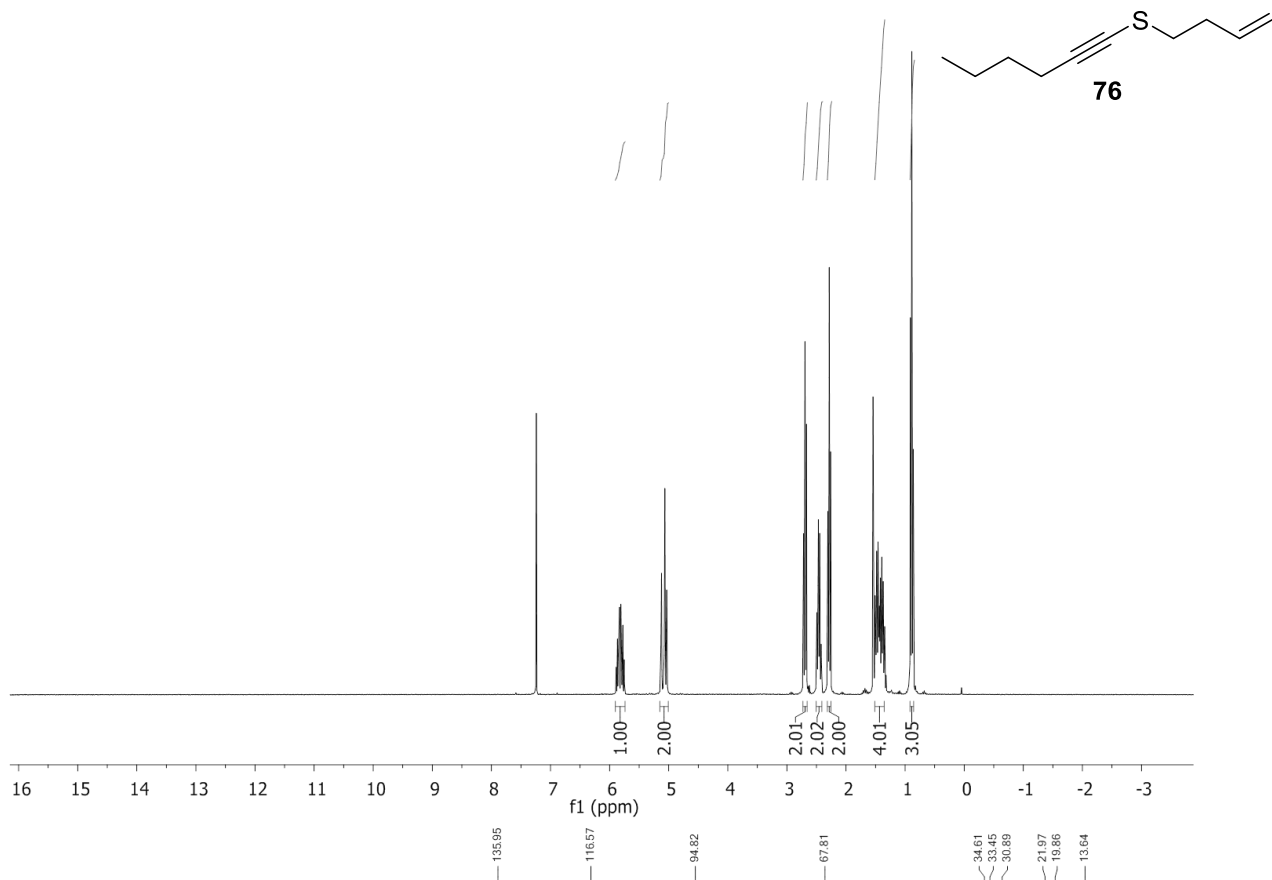
107

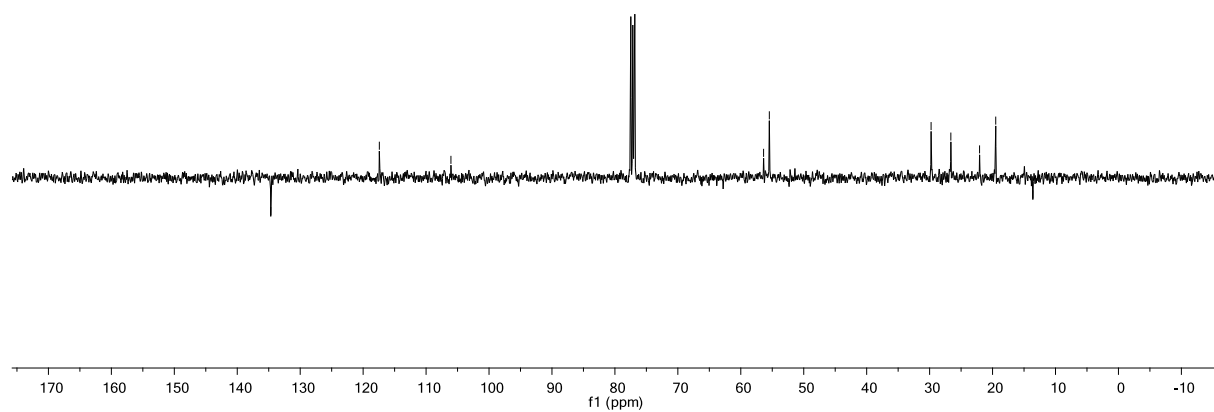
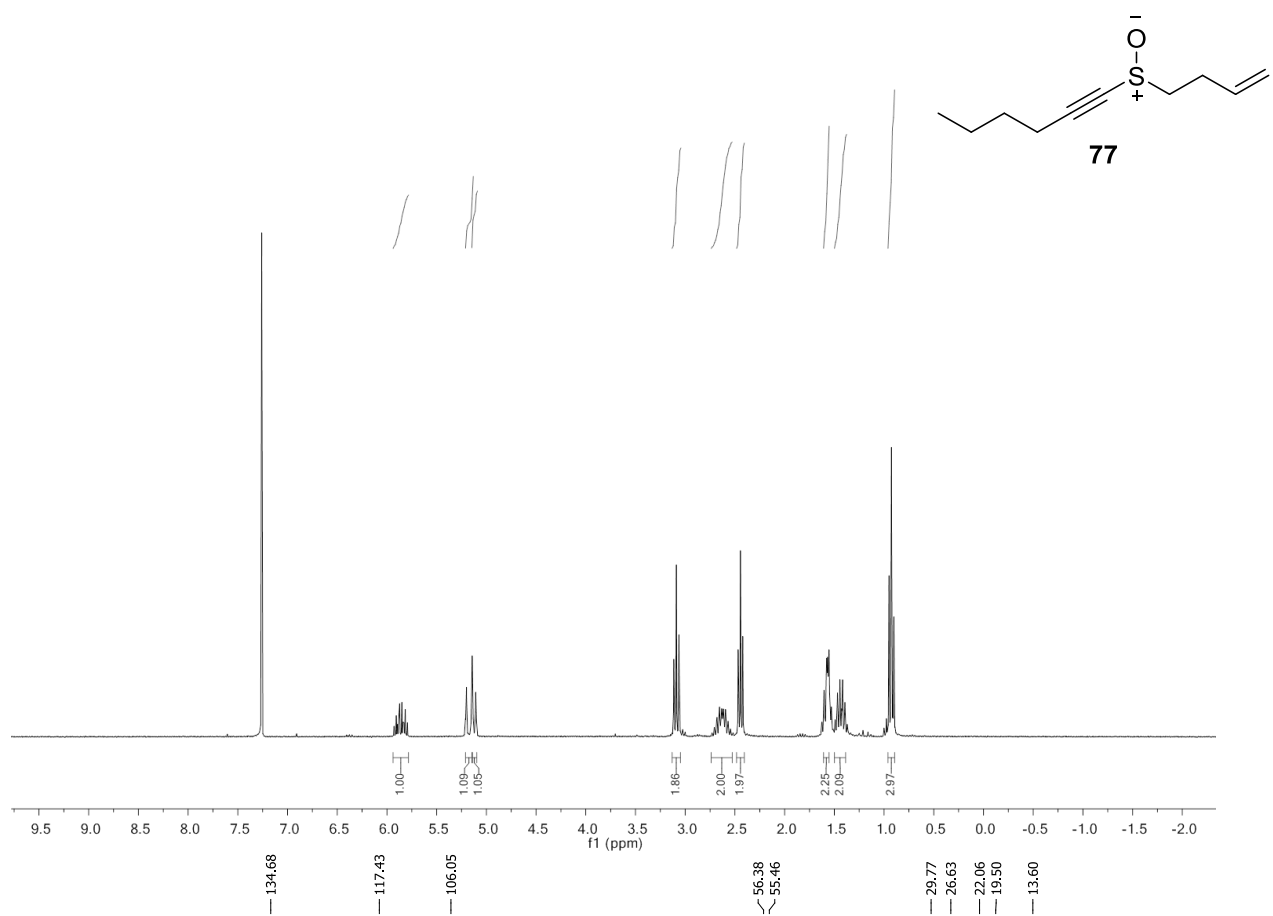
Following **GP3** using sulfoxide **105** (96.9 mg, 0.40 mmol), 3,5-dichloropyridine *N*-oxide (78.7 mg, 0.48 mmol), SPhosAuNTf₂ (17.7 mg, 5 mol%), stirred for 17 h gave **107** (a mixture of inseparable diastereoisomers) purified using [EtOAc/MeOH (9:1)] as a pale yellow oil (*R*_f

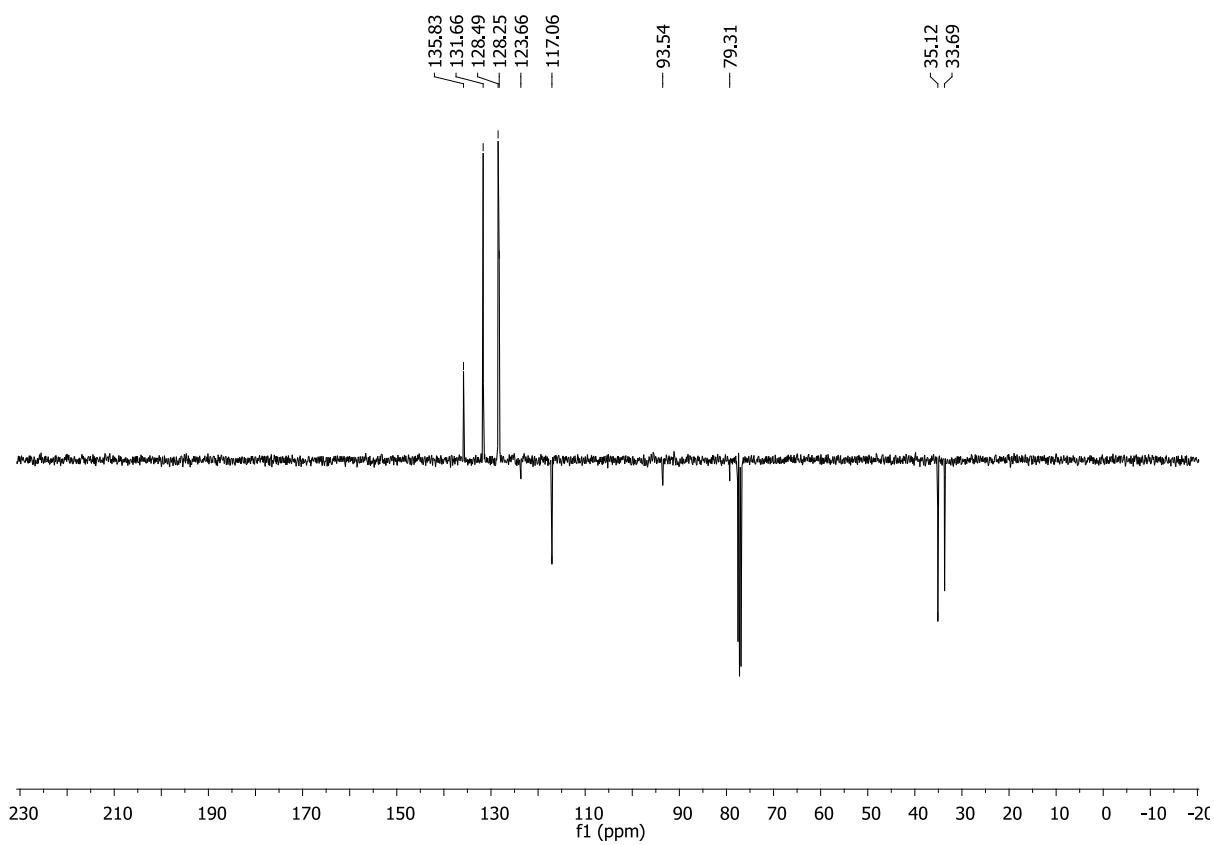
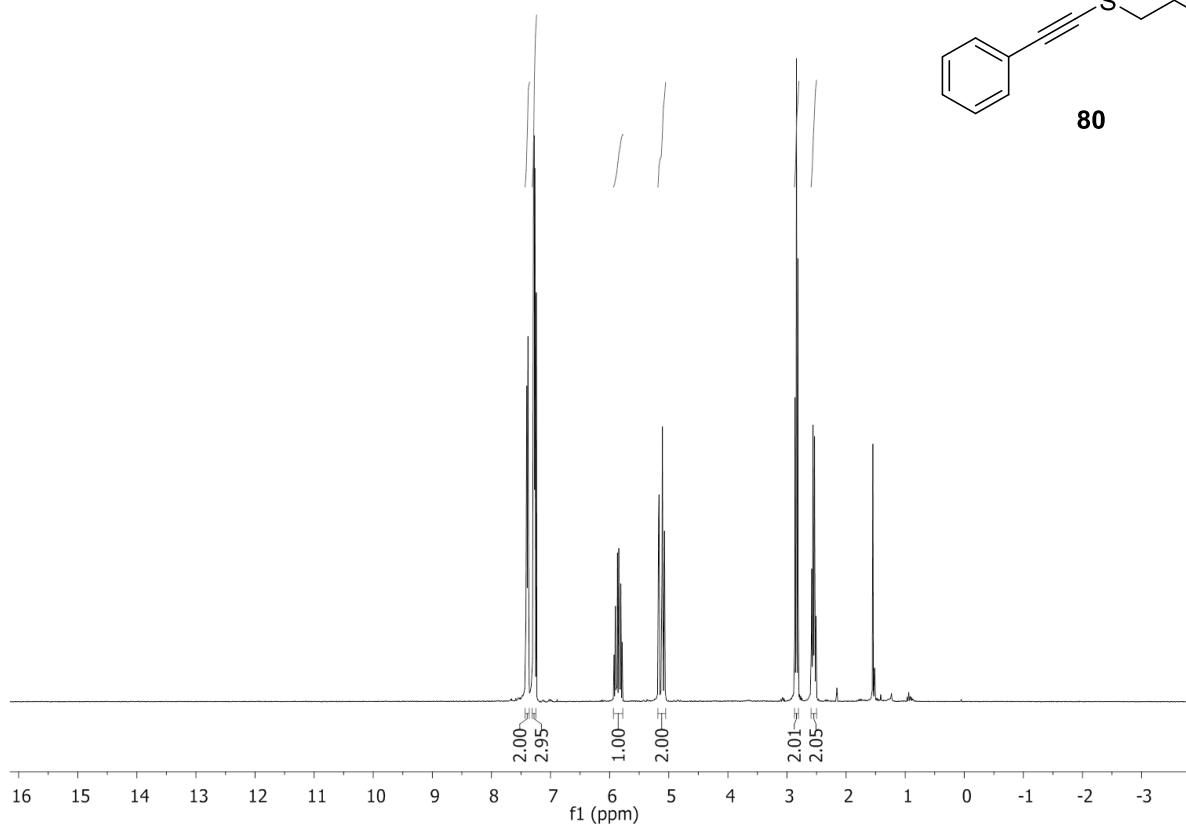
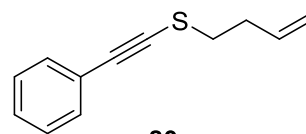
0.10. A yield cannot be confidently reported (see Section 2.8). The data for the major diastereoisomer is assigned where possible; some doubling is seen in the ^{13}C NMR, in which case the ppm for the major diastereoisomer is quoted before the ppm of the minor. ^1H NMR (300 MHz CDCl_3): 4.78 (app d, $J = 3.0$, 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): δ 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: ν_{max} (cm^{-1}) 3342, 2940, 2289, 2216, 2113, 2010, 1698, 1251, 1082, 994, 872, 728, 694; LRMS (ES) m/z found $\text{C}_7\text{H}_{10}\text{O}_3\text{SNa}$ ($\text{M}+\text{Na}$) $^+$ 197.1.

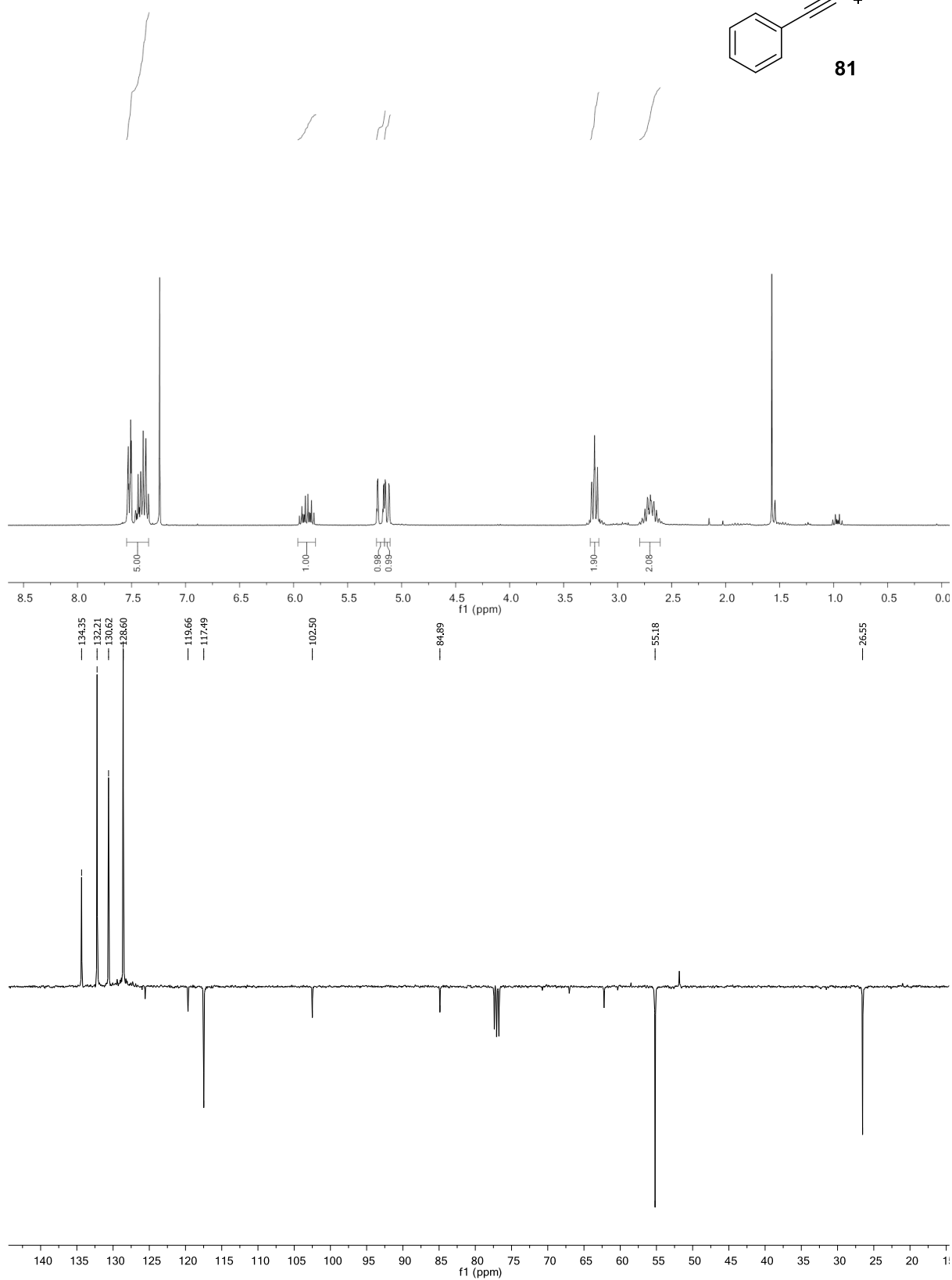
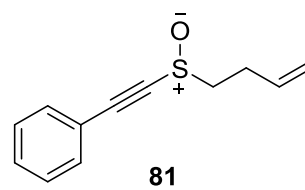
Appendices

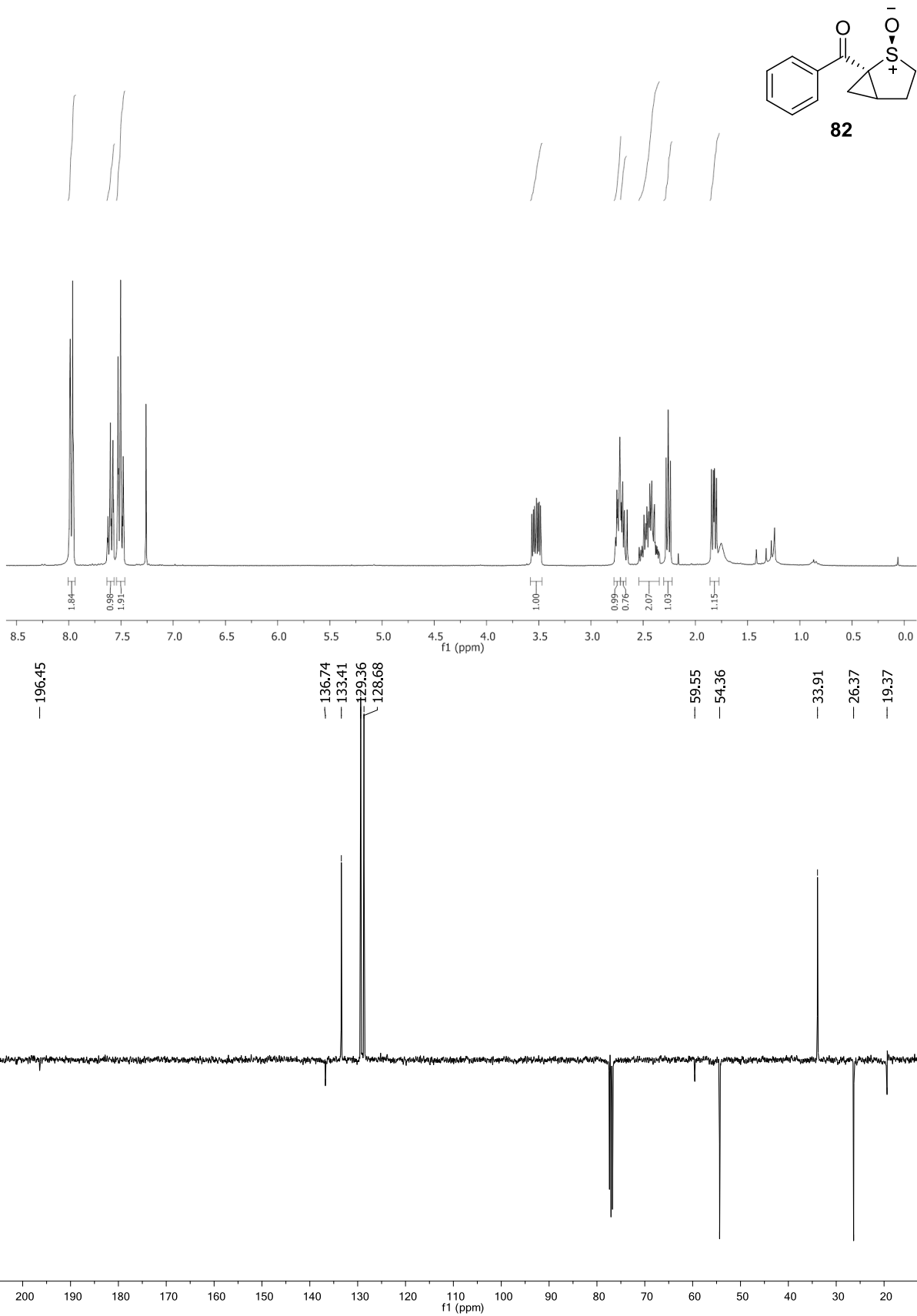
Appendix A – NMR Spectra

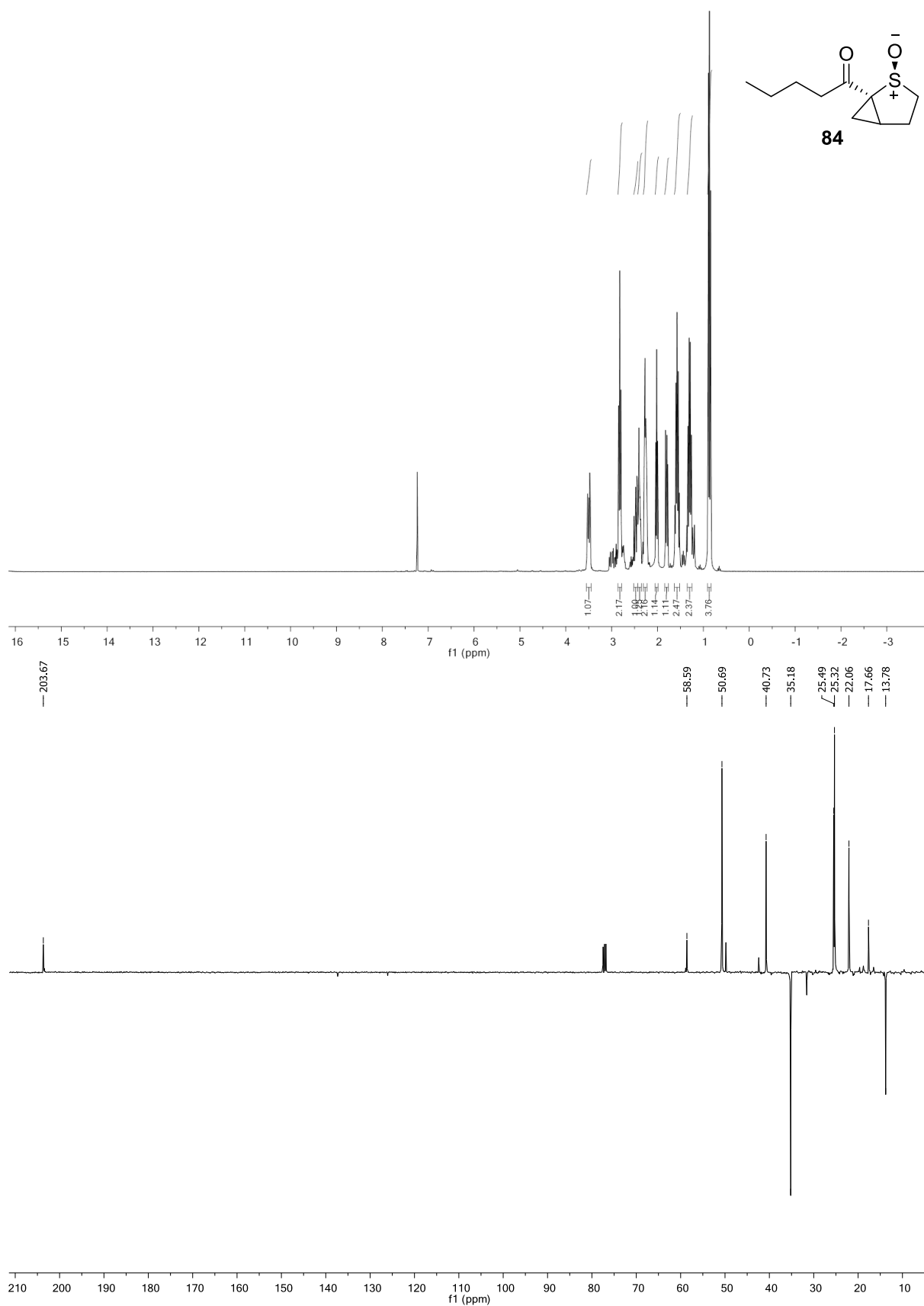












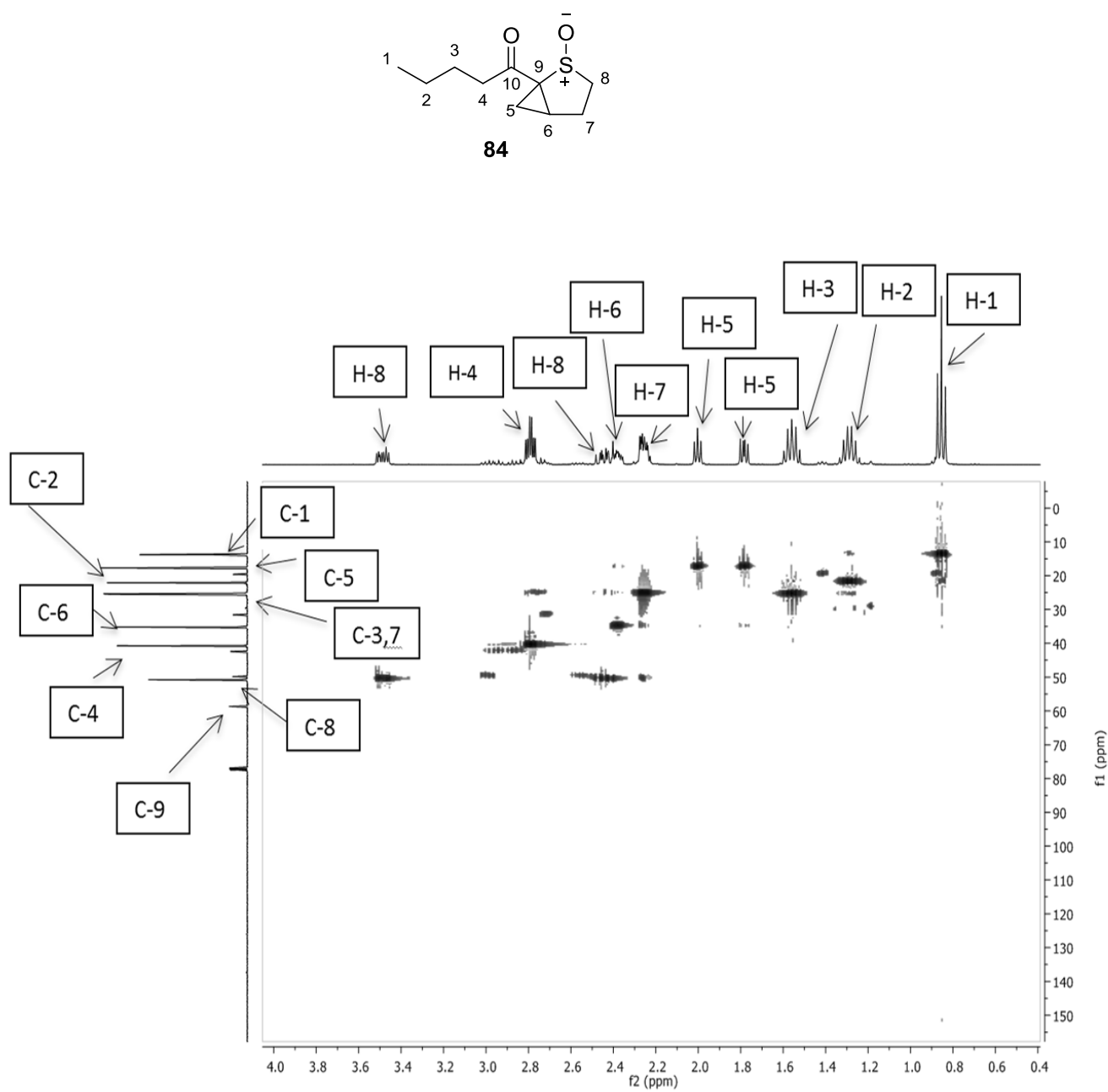
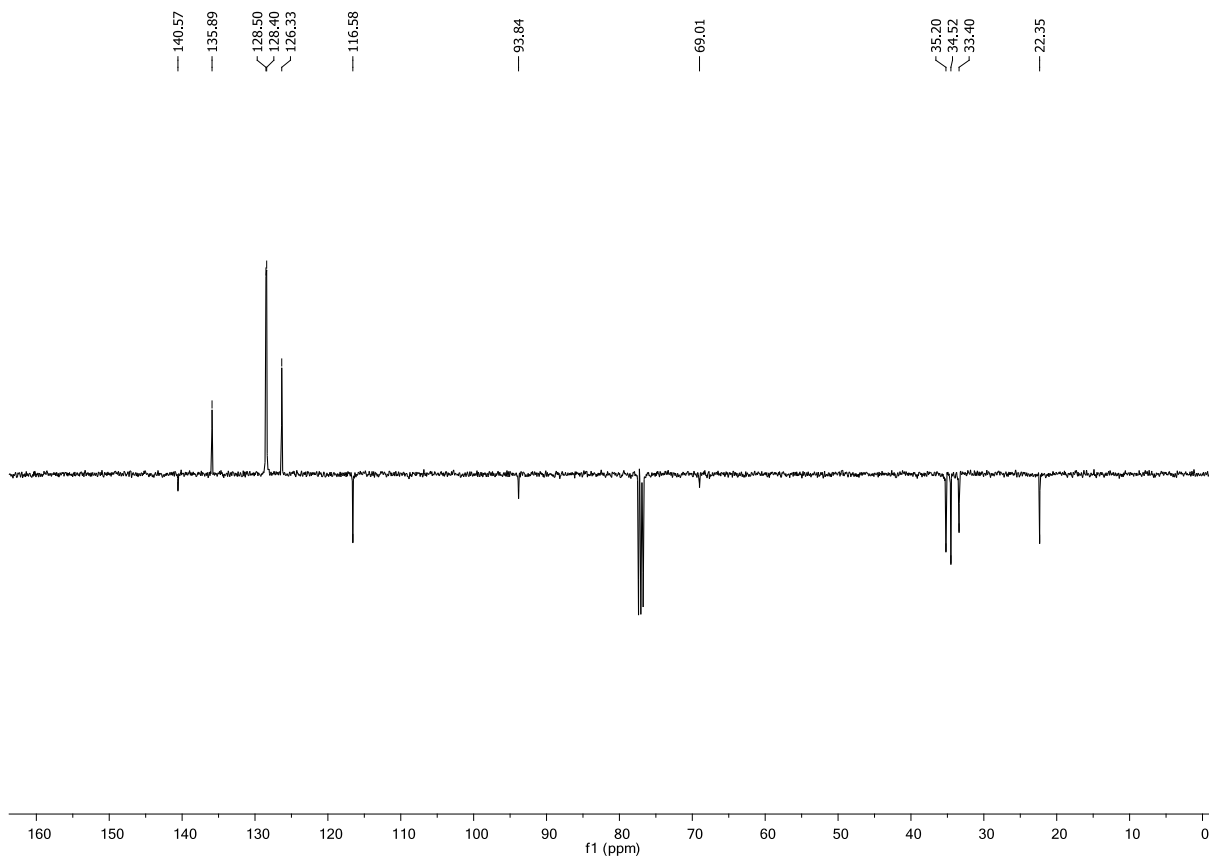
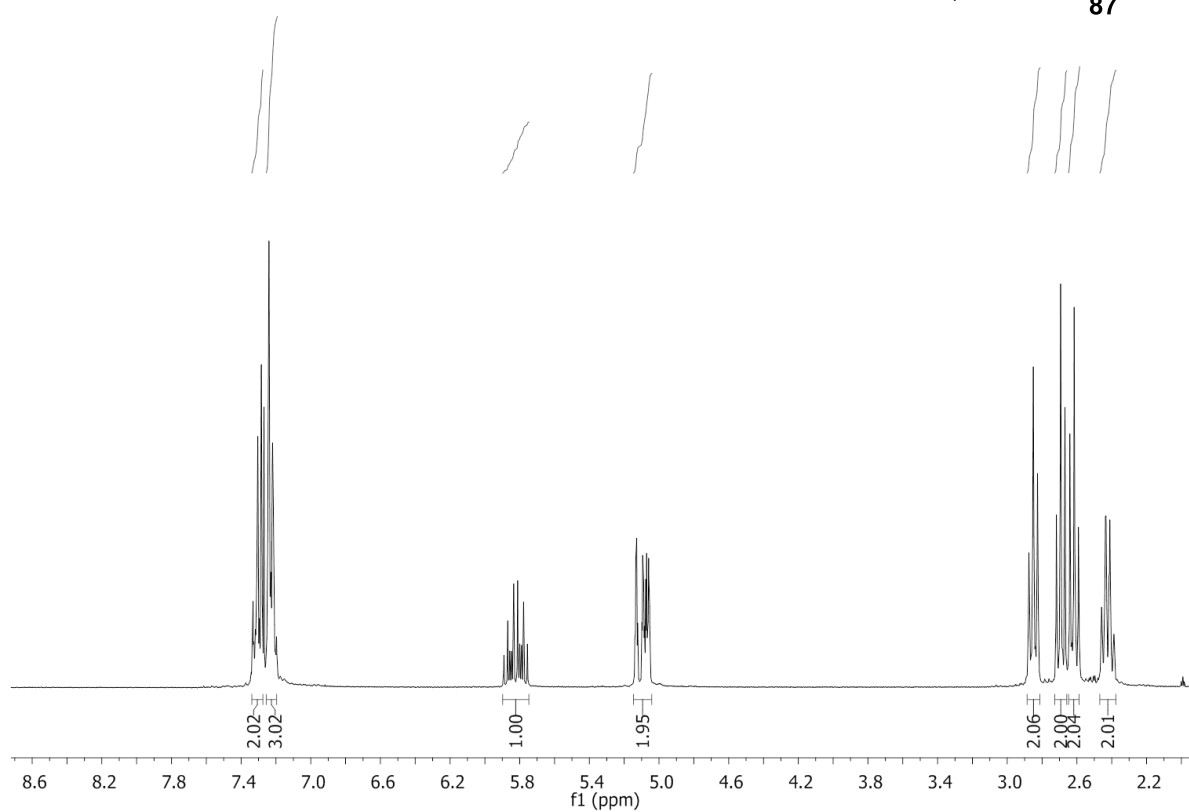
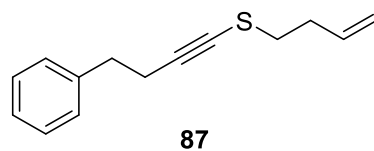
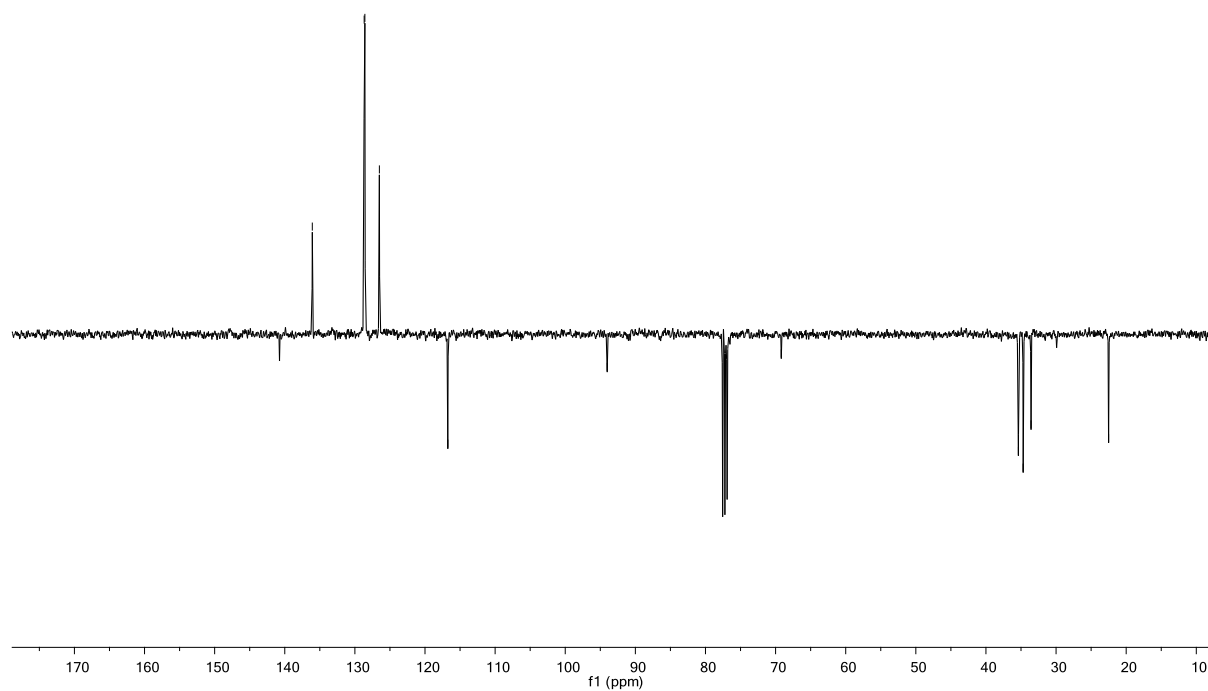
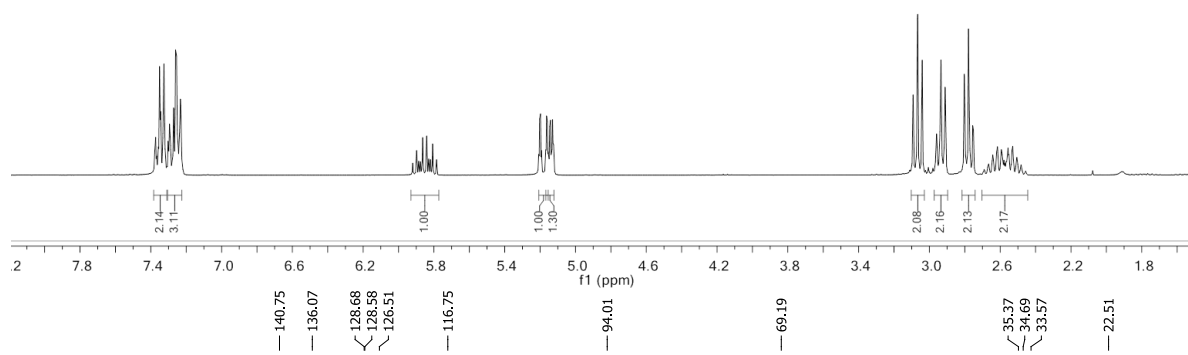
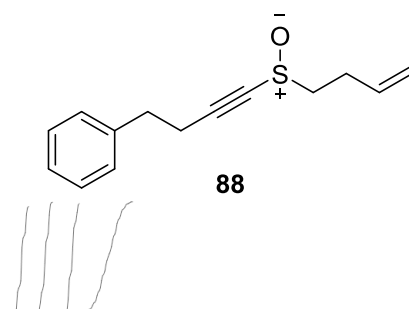
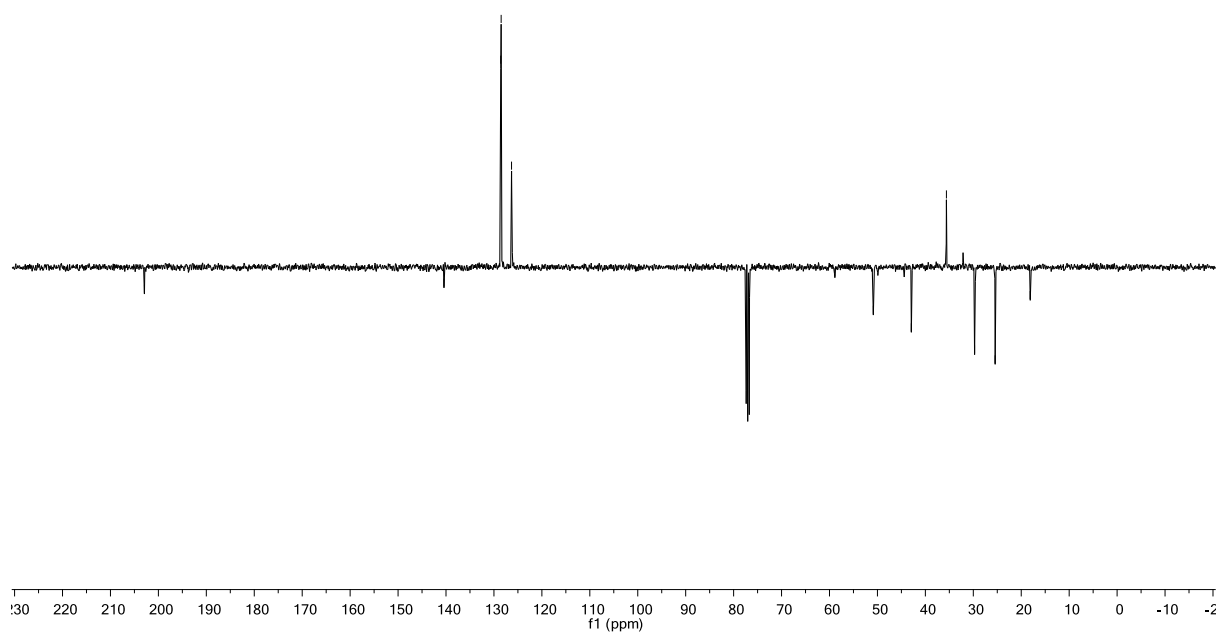
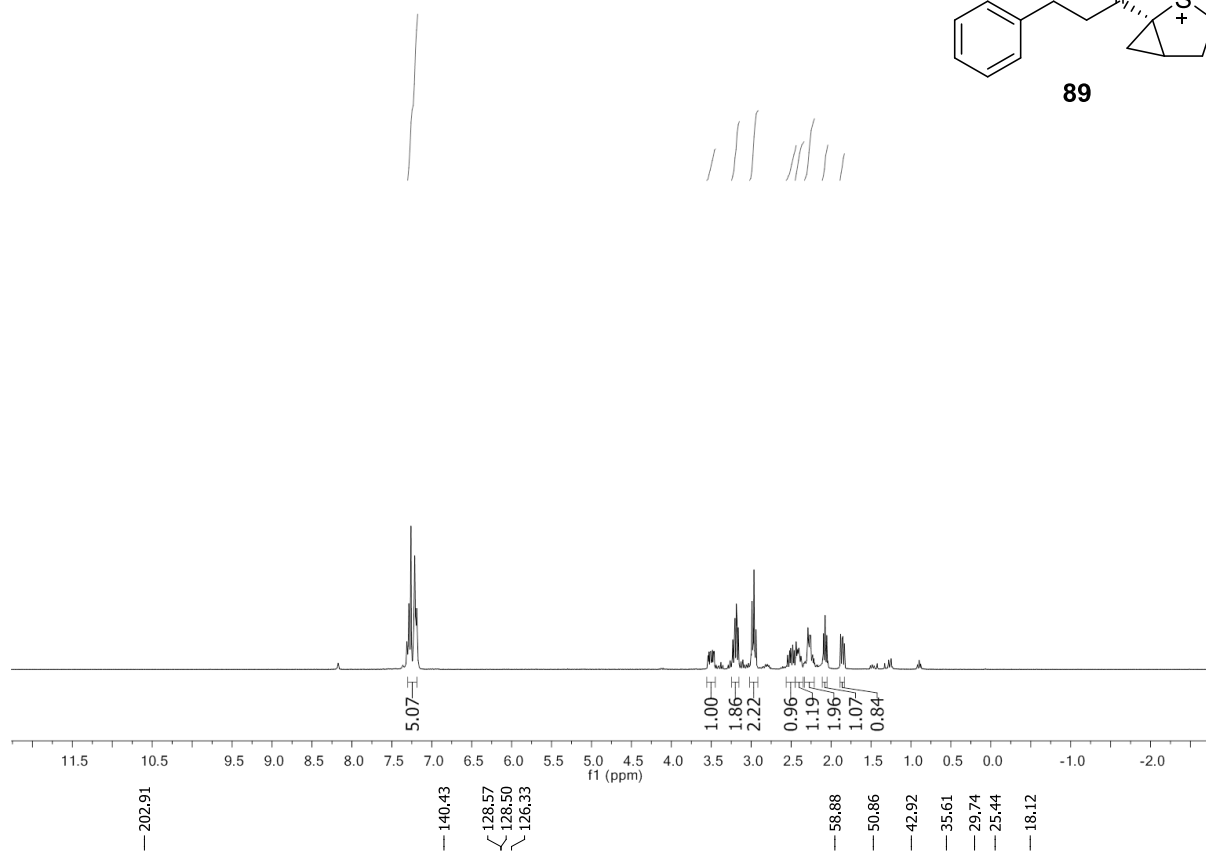
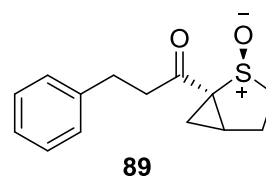
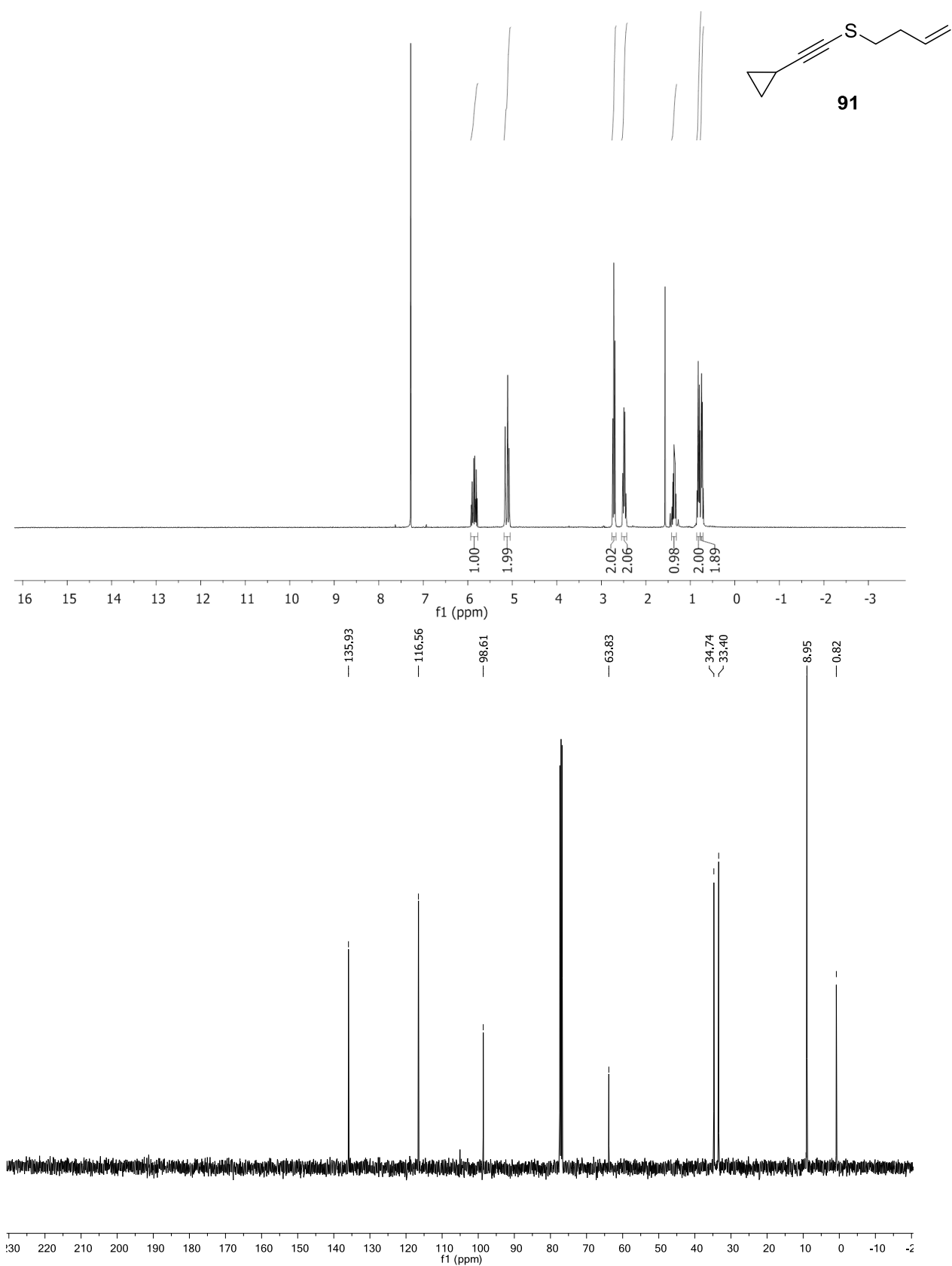


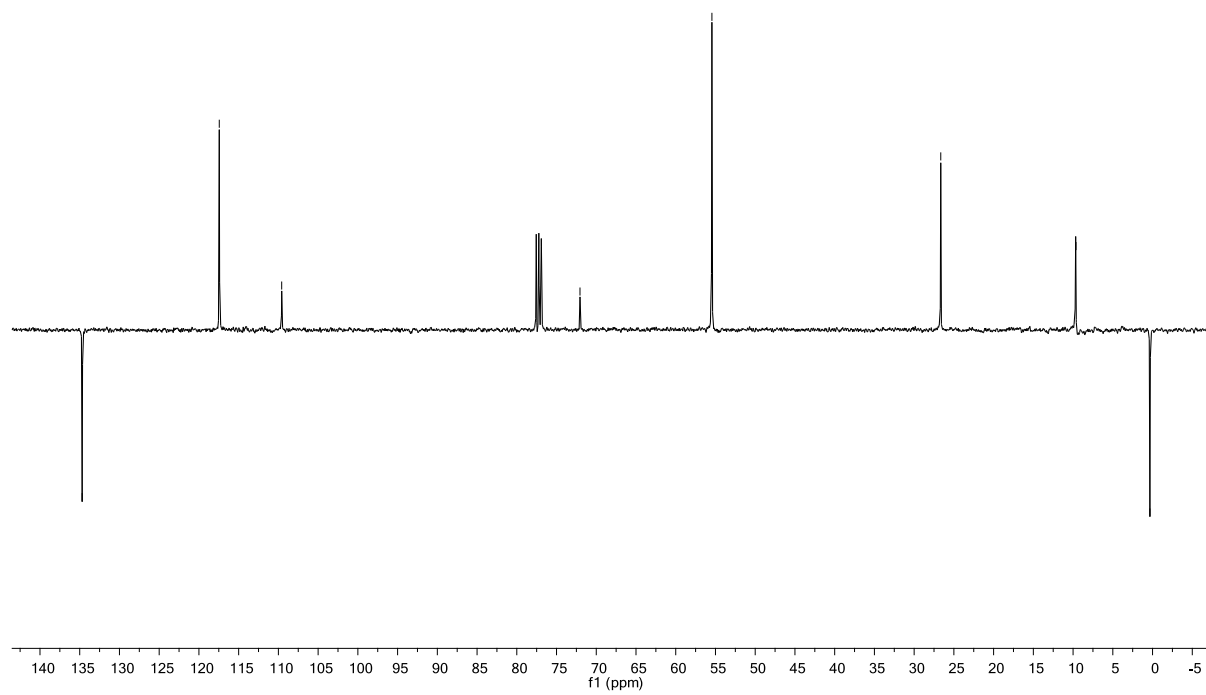
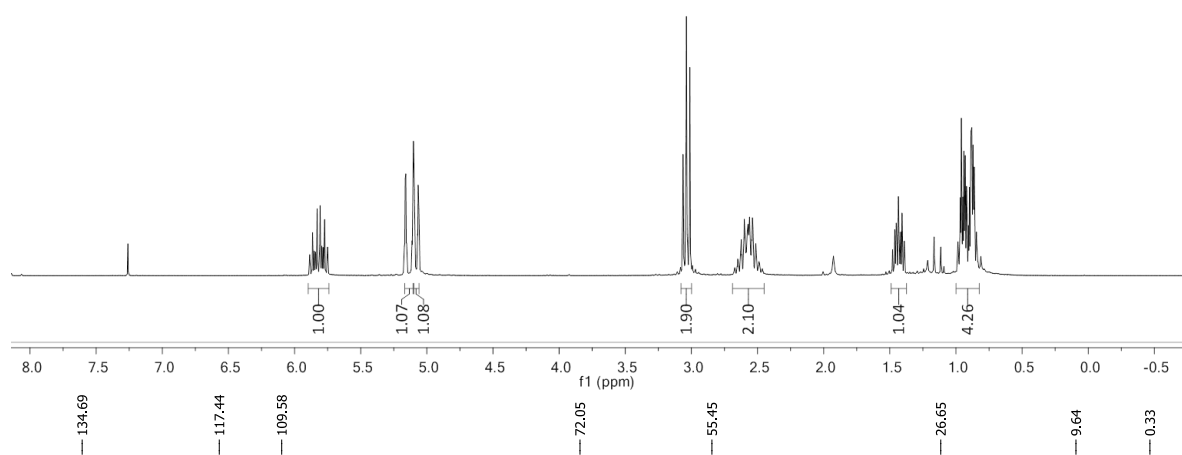
Figure 25: Two dimensional HSQC spectrum analysis of compound 84

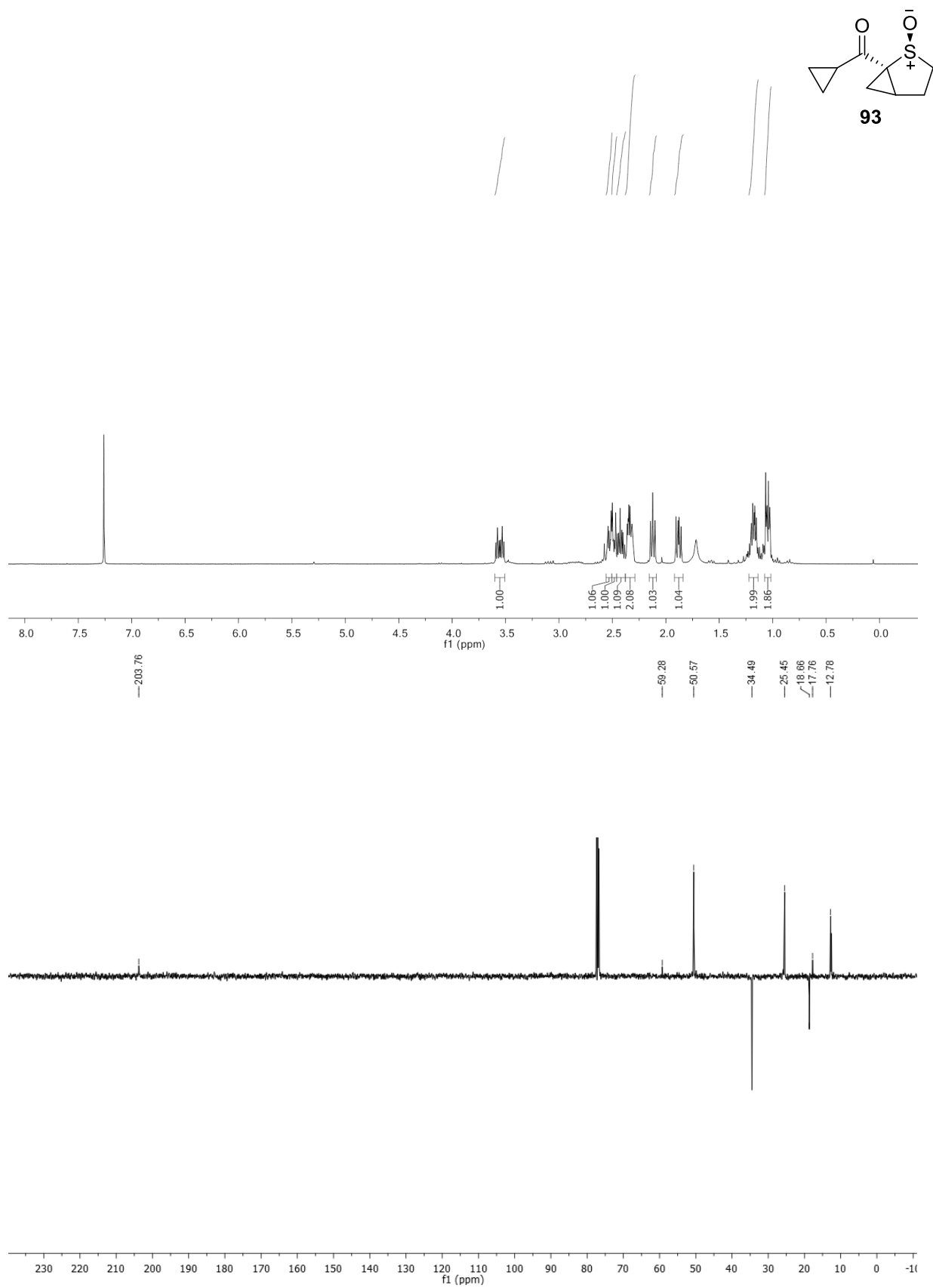


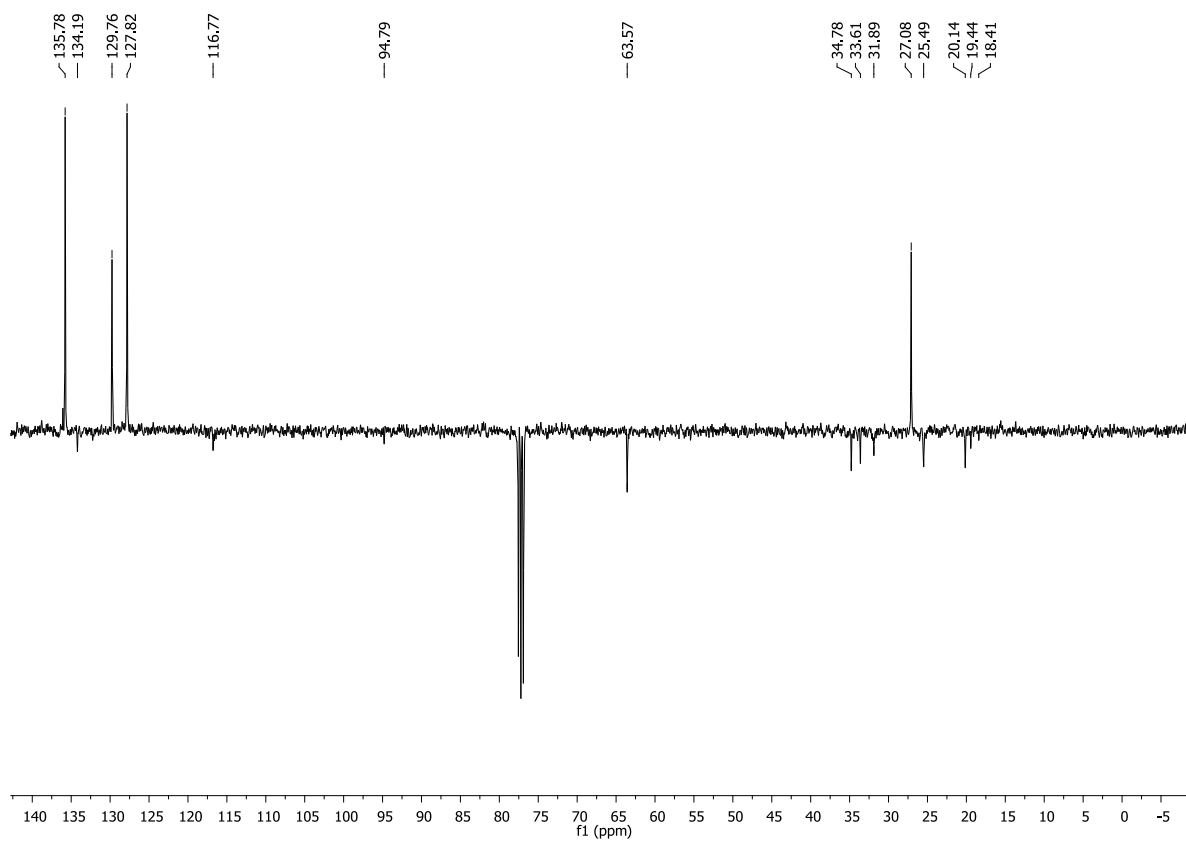
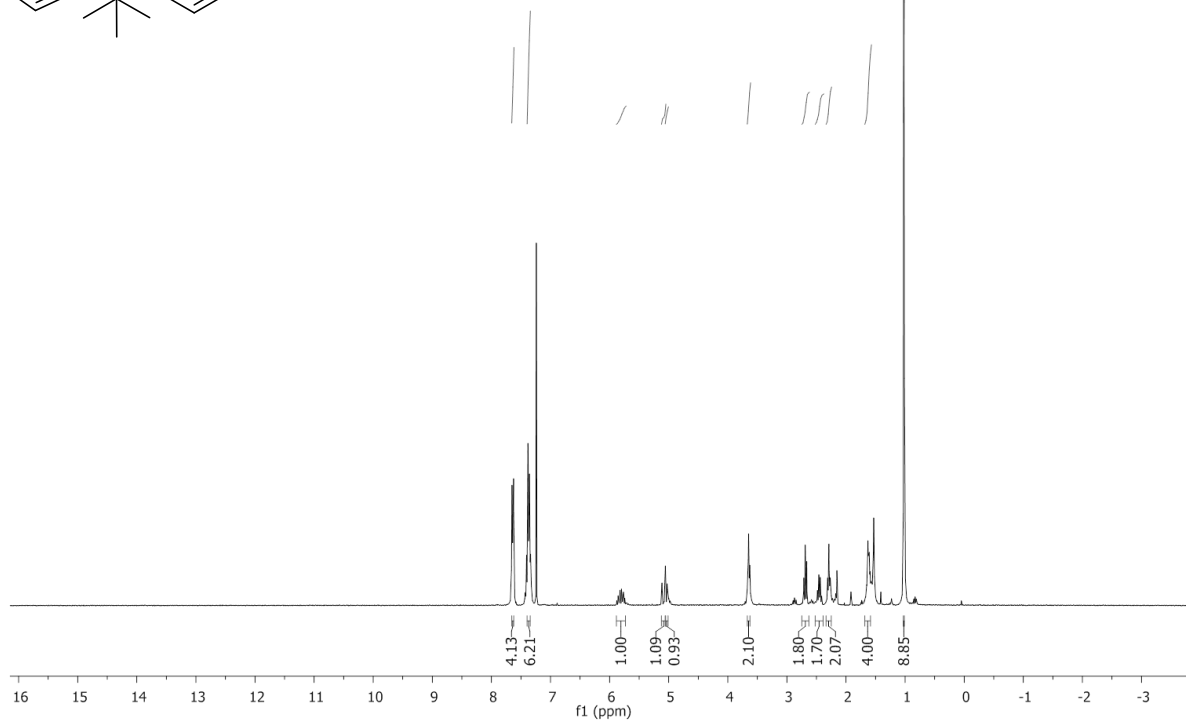
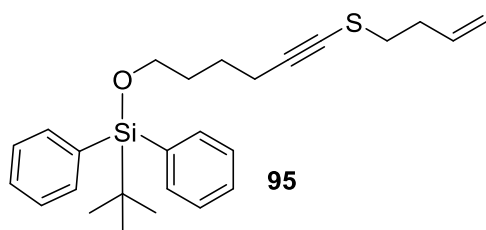


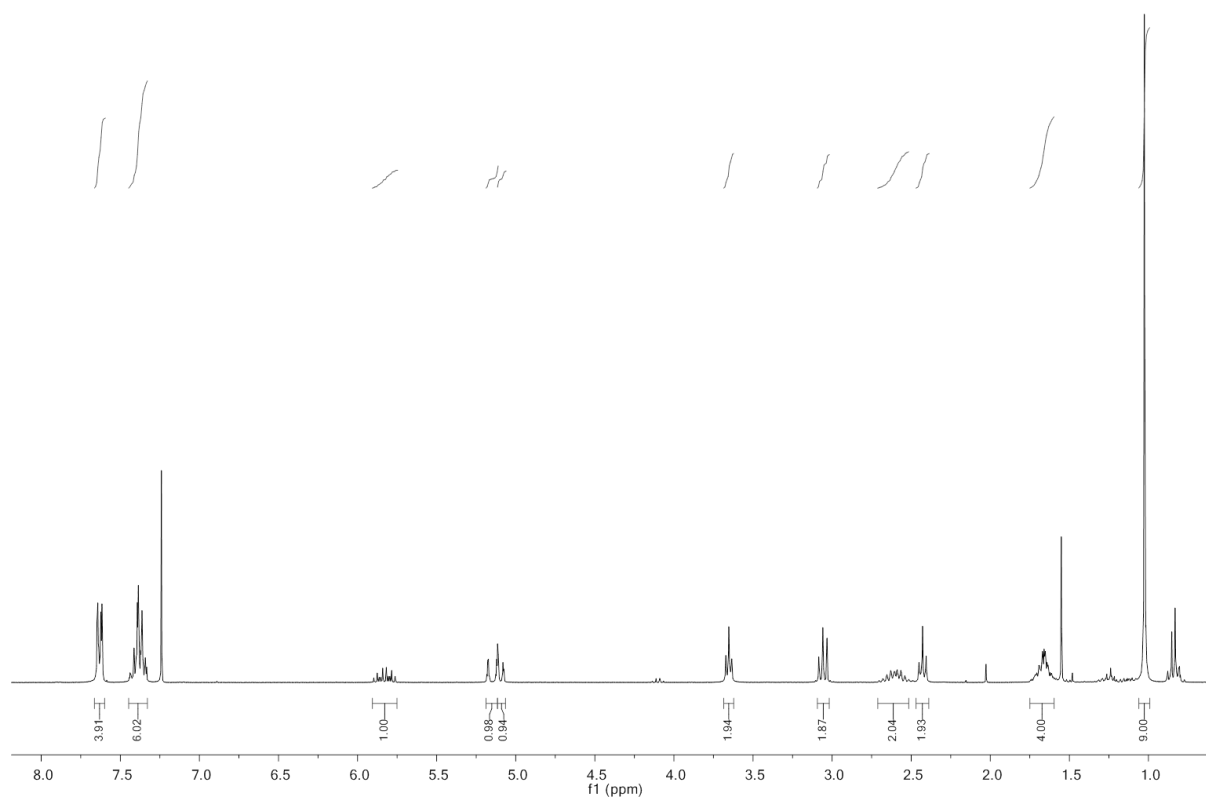
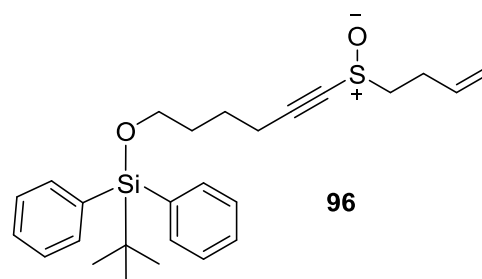


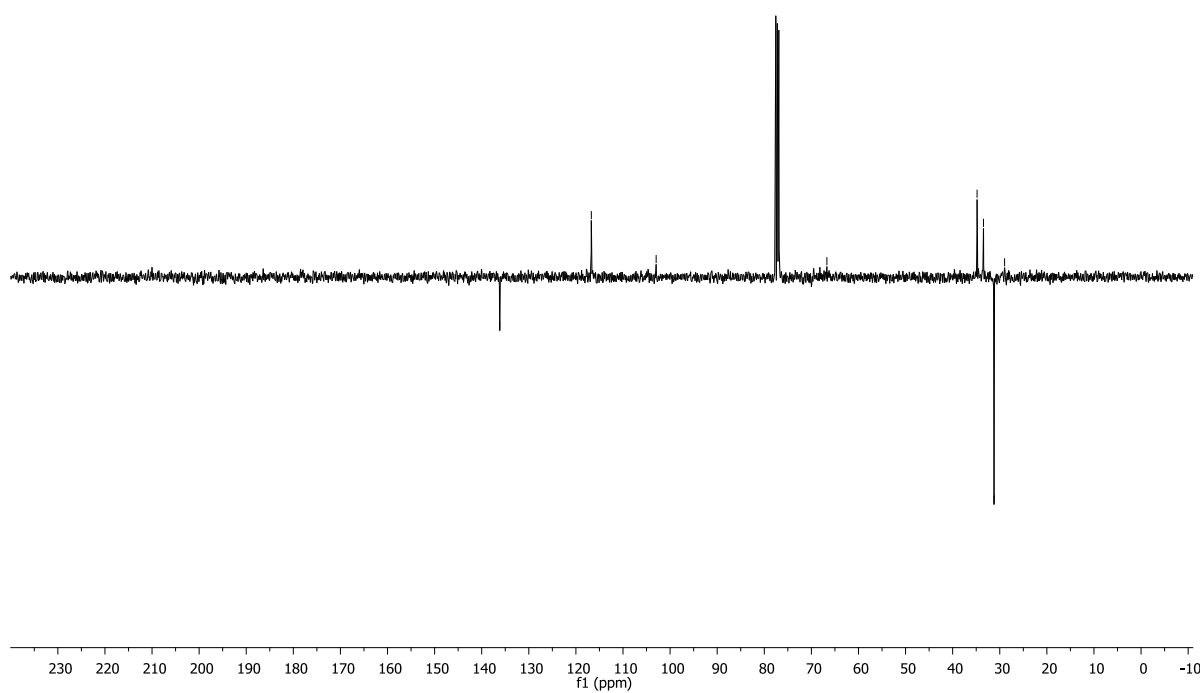
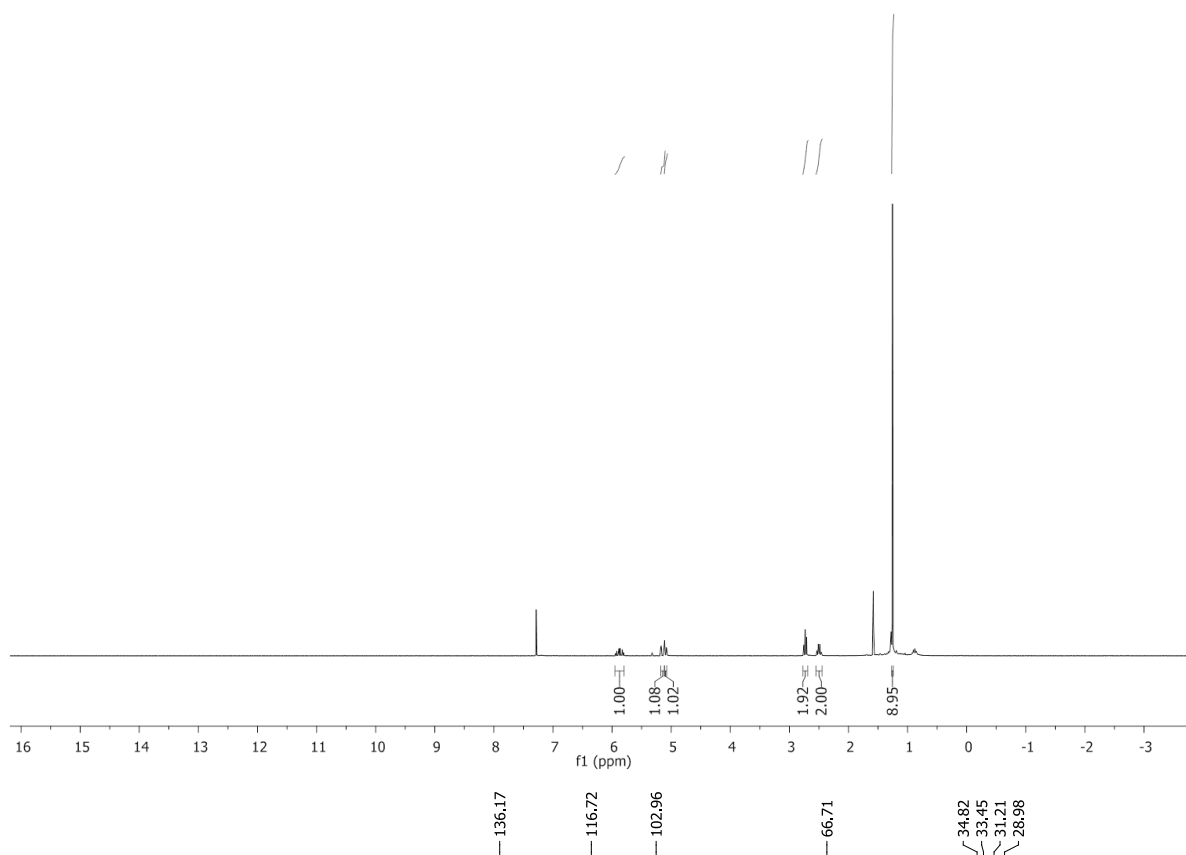
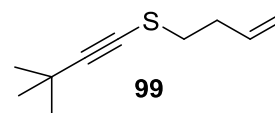


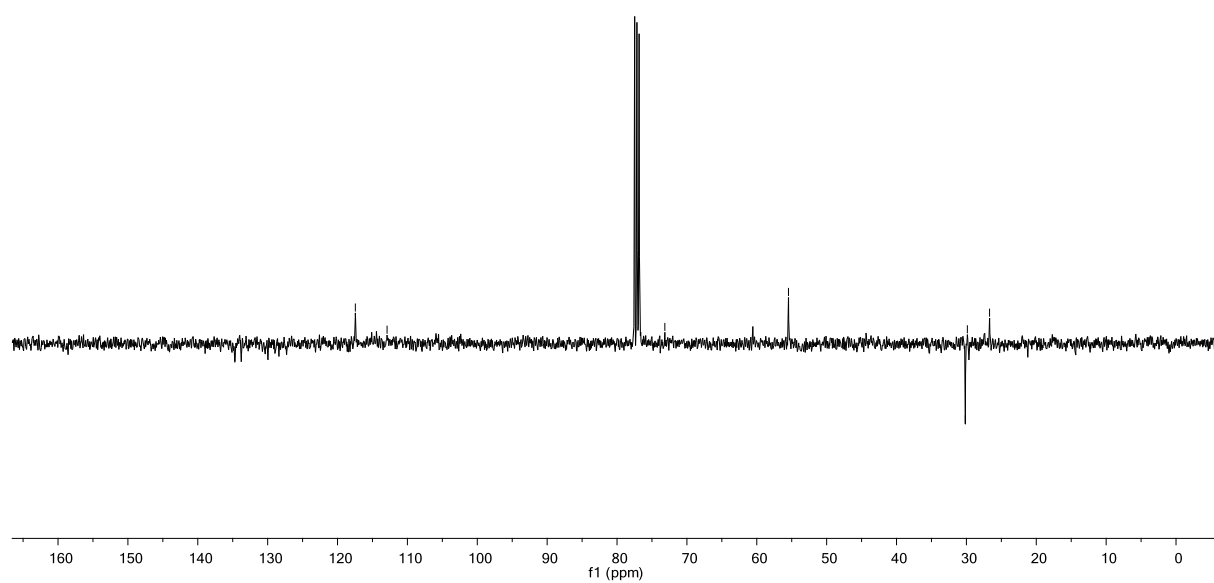
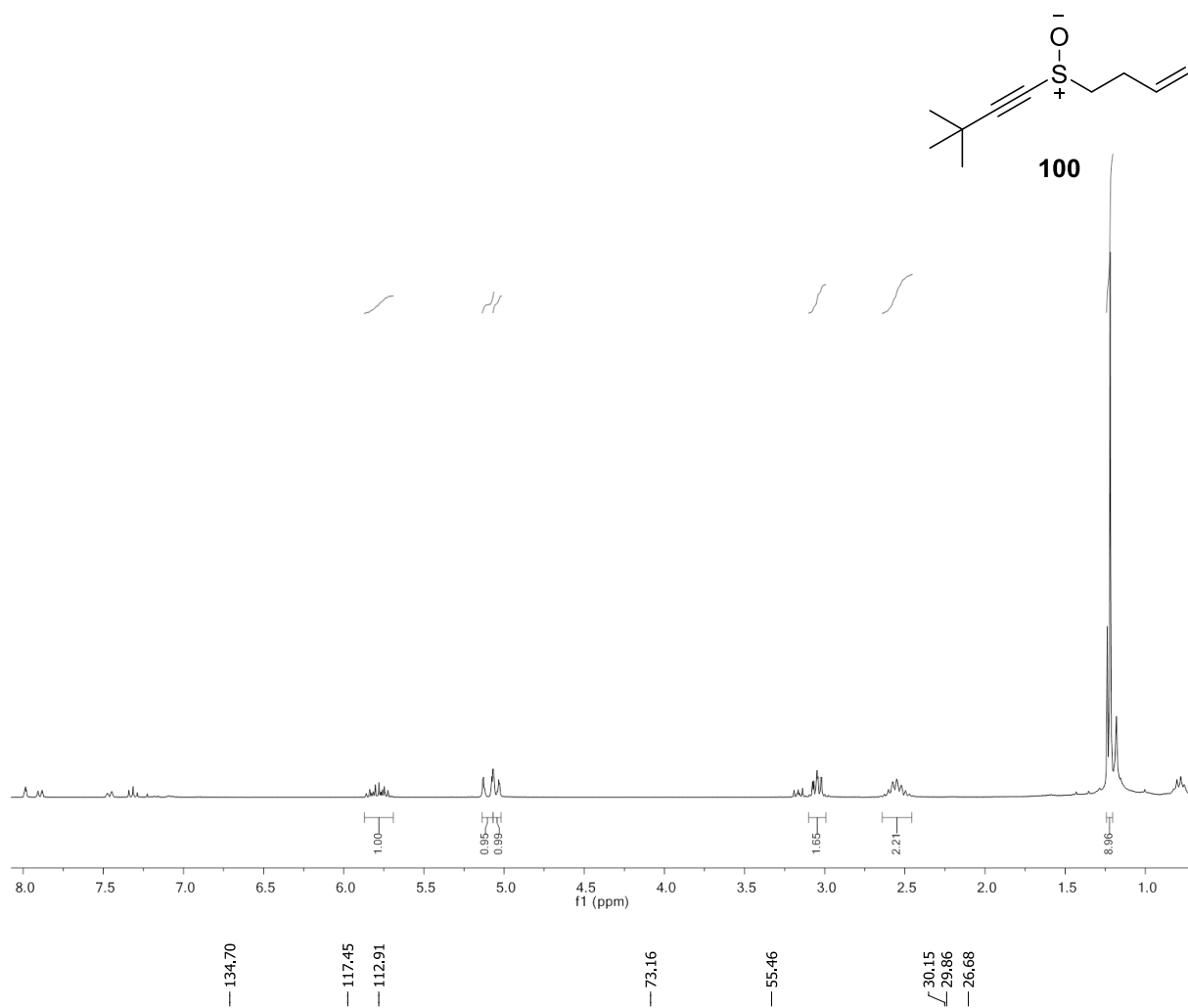


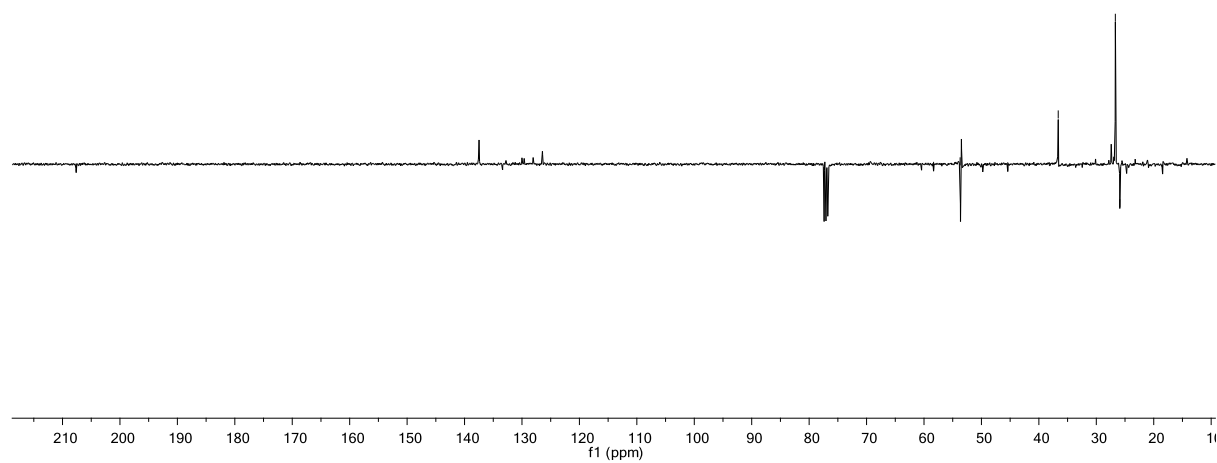
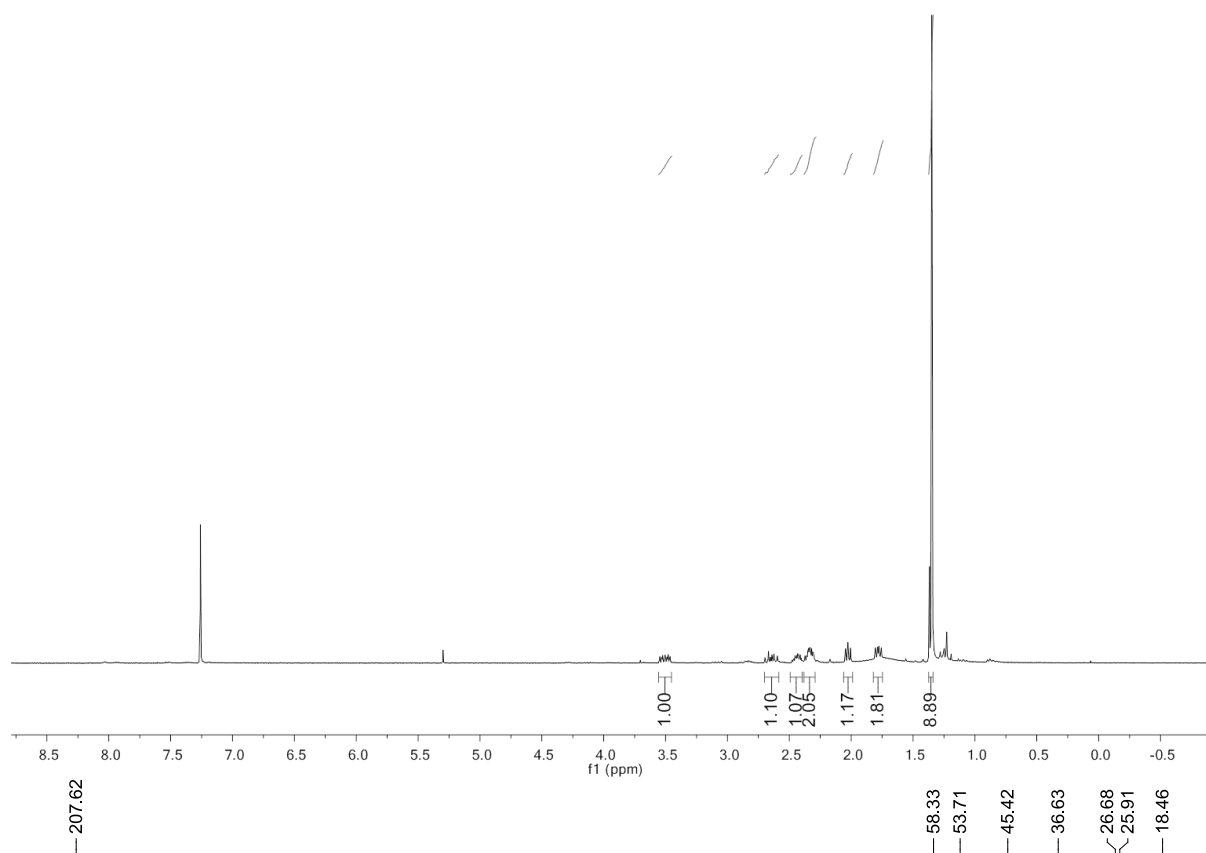
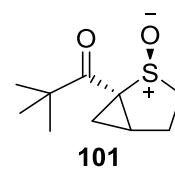


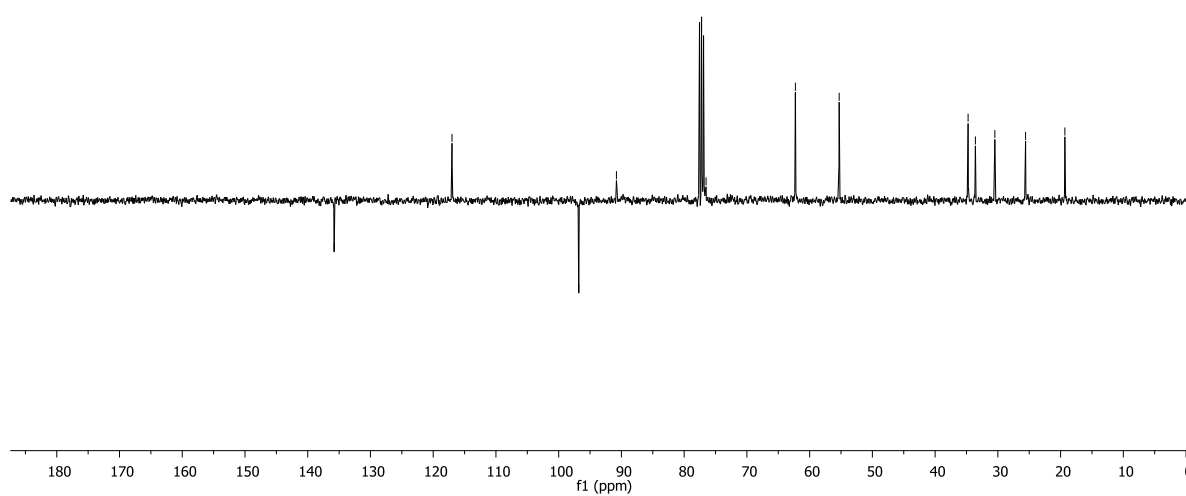
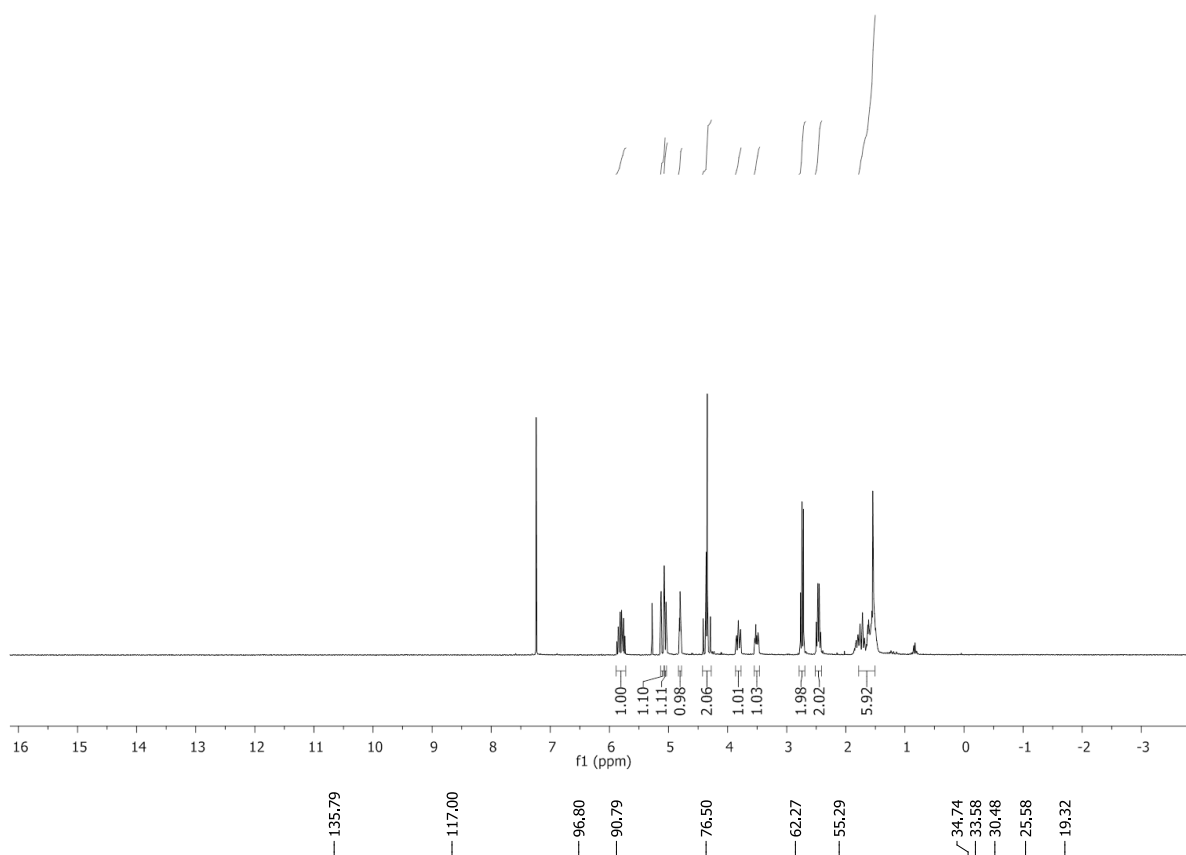
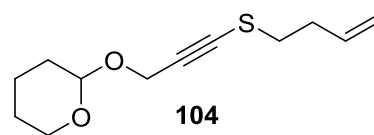


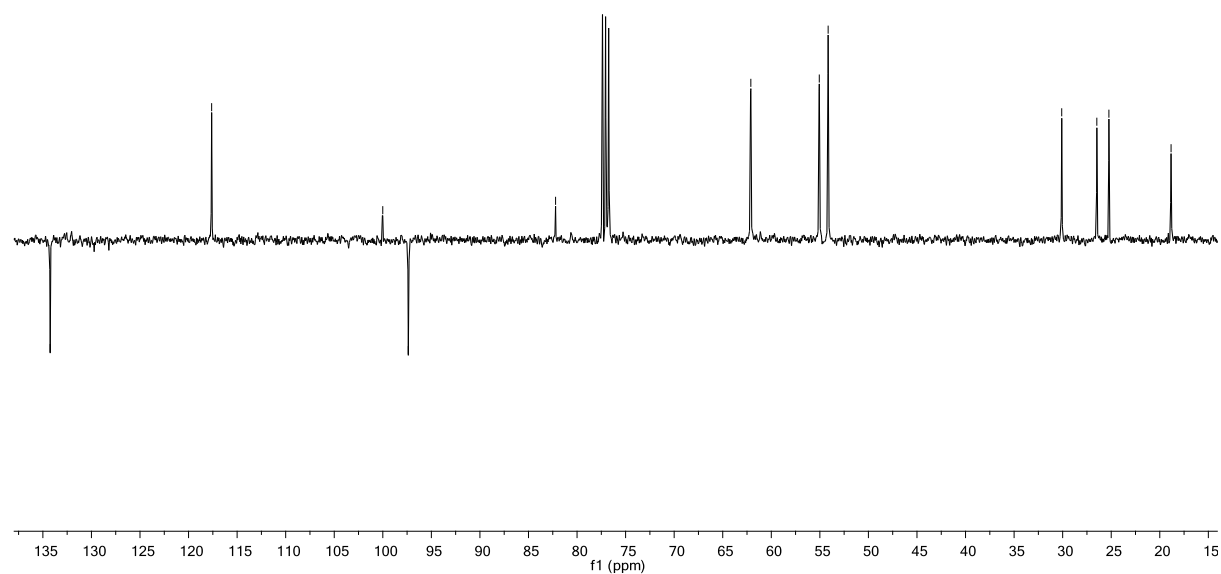
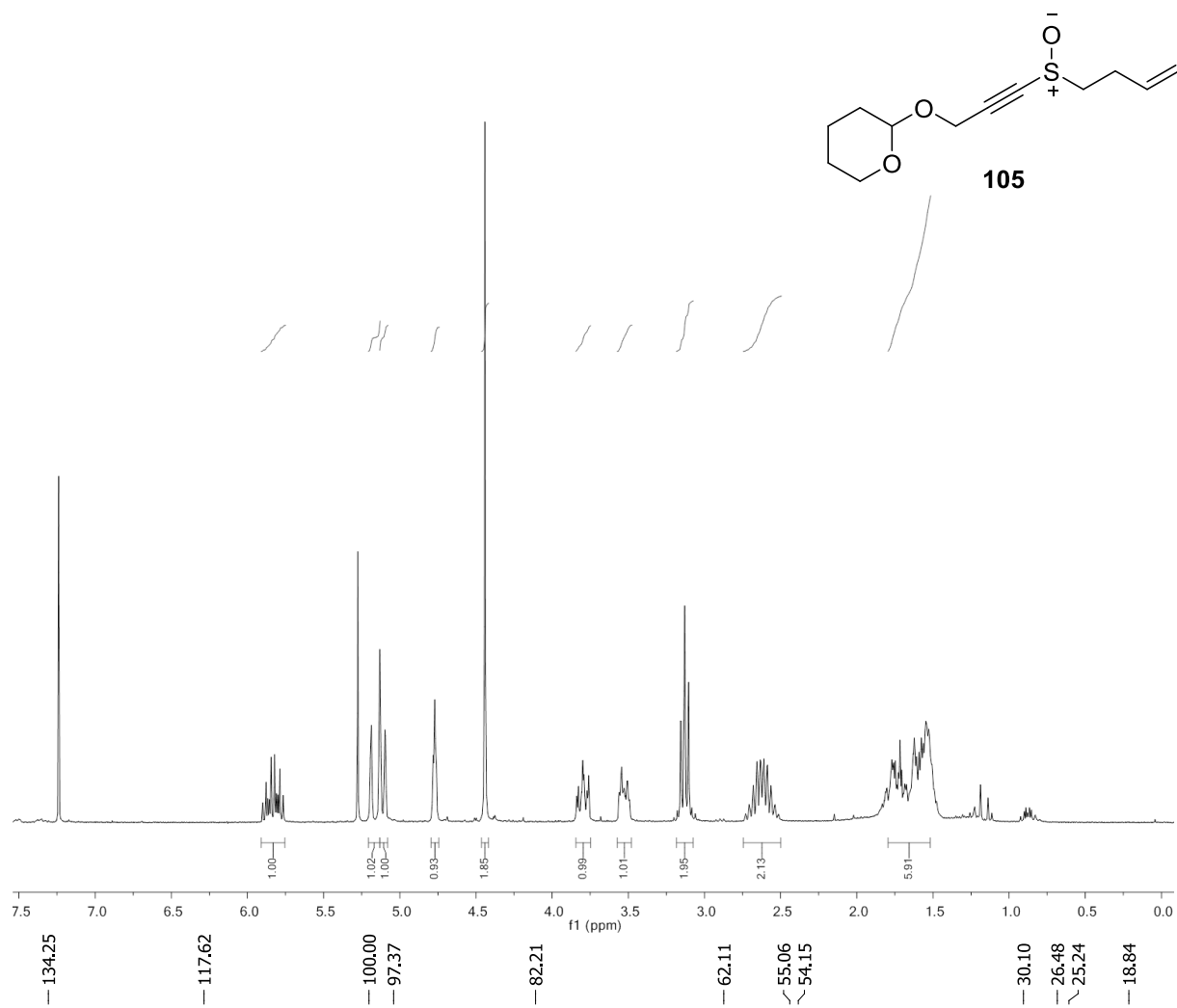


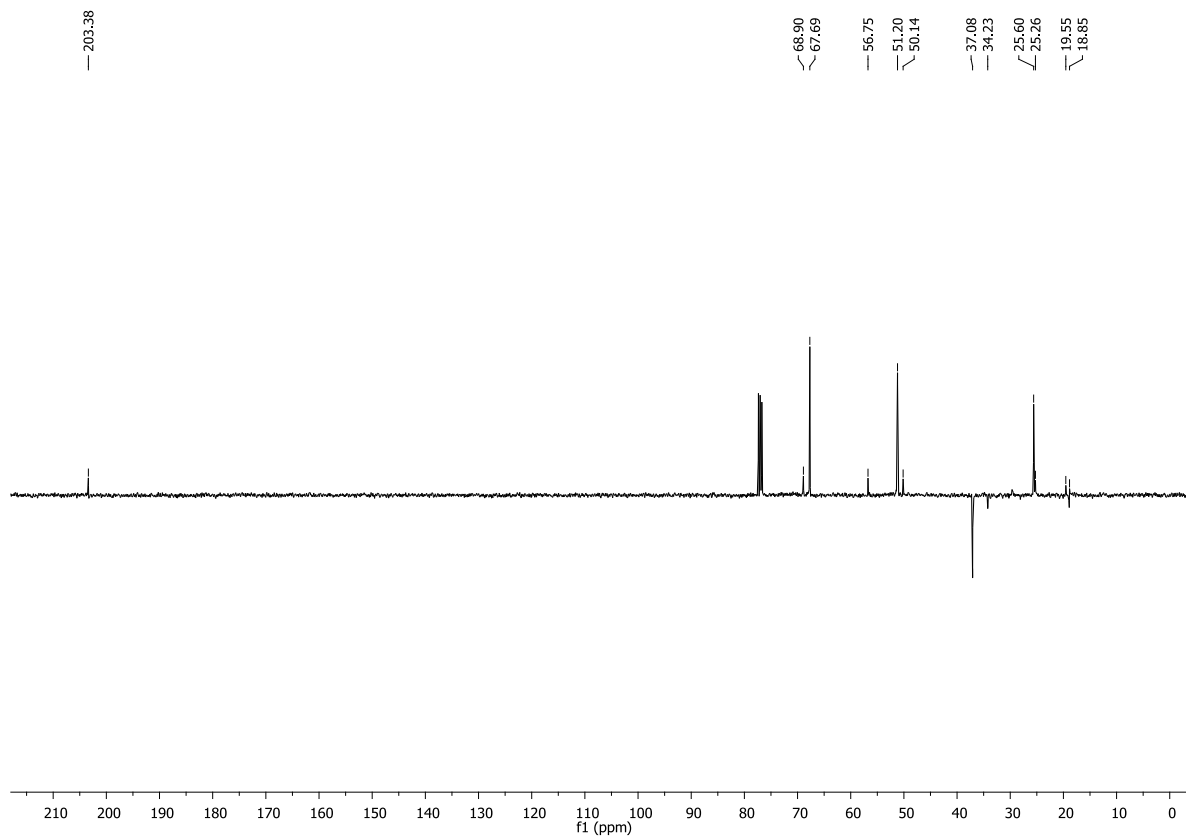
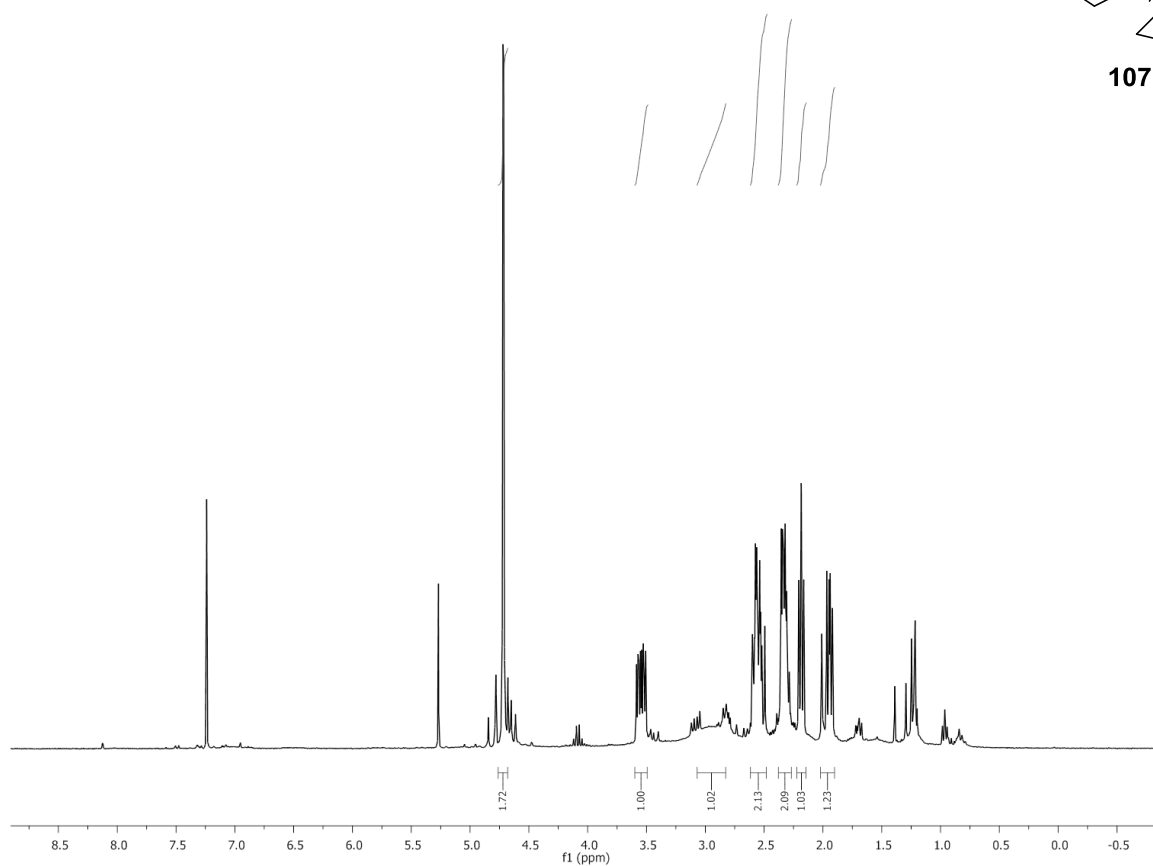
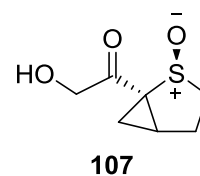


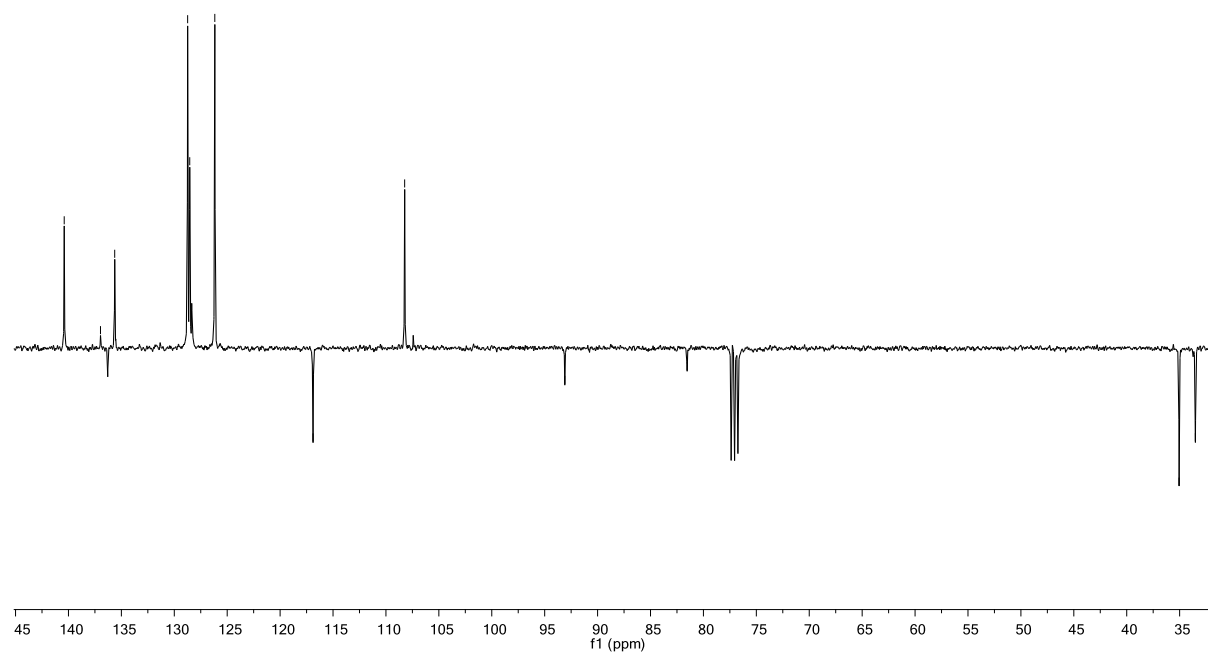
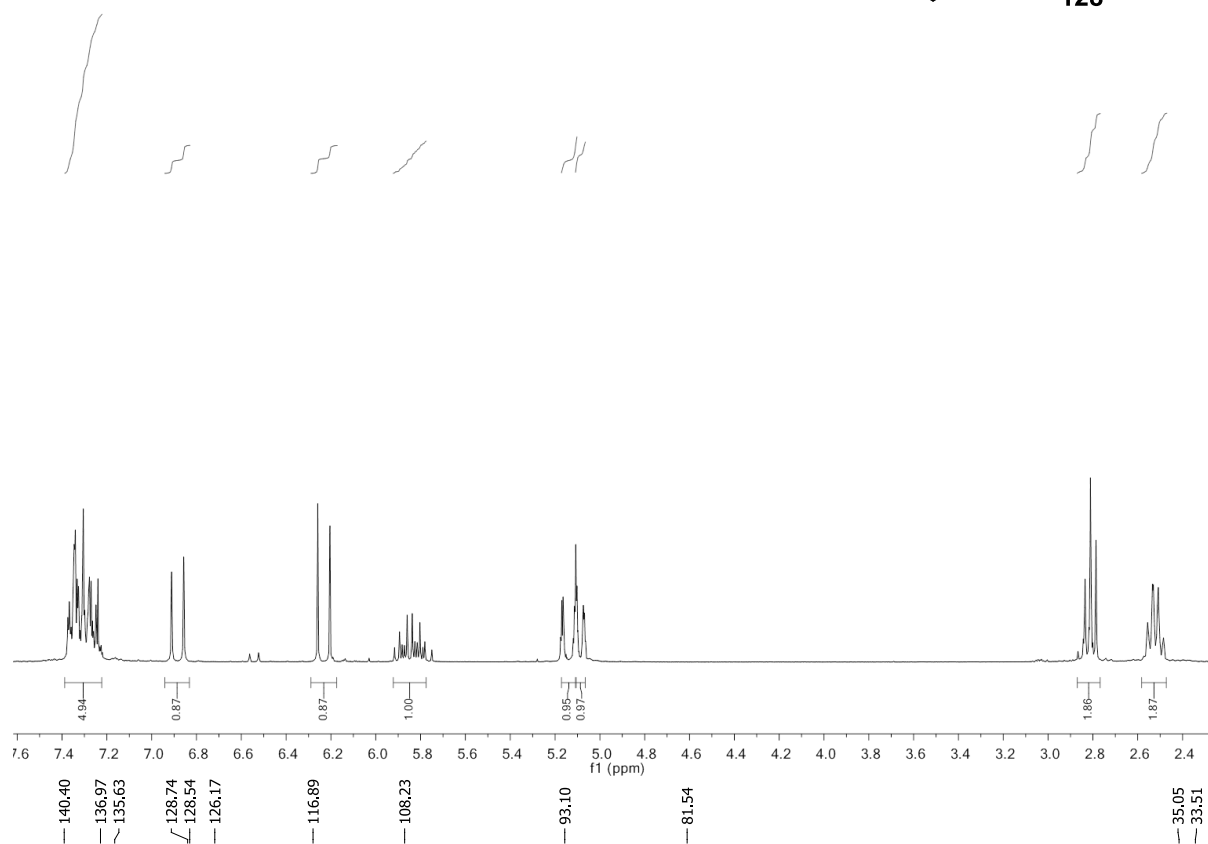
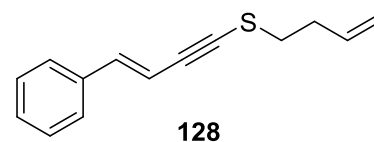


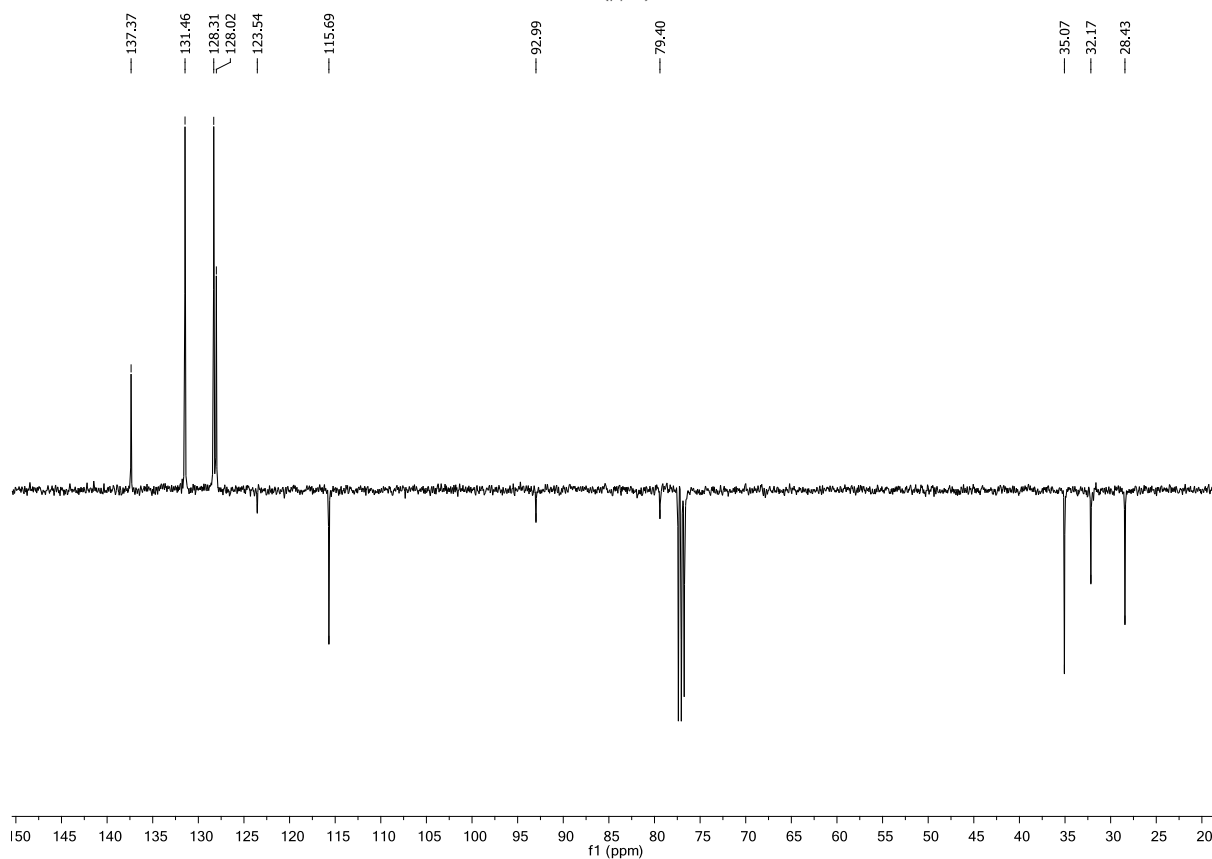
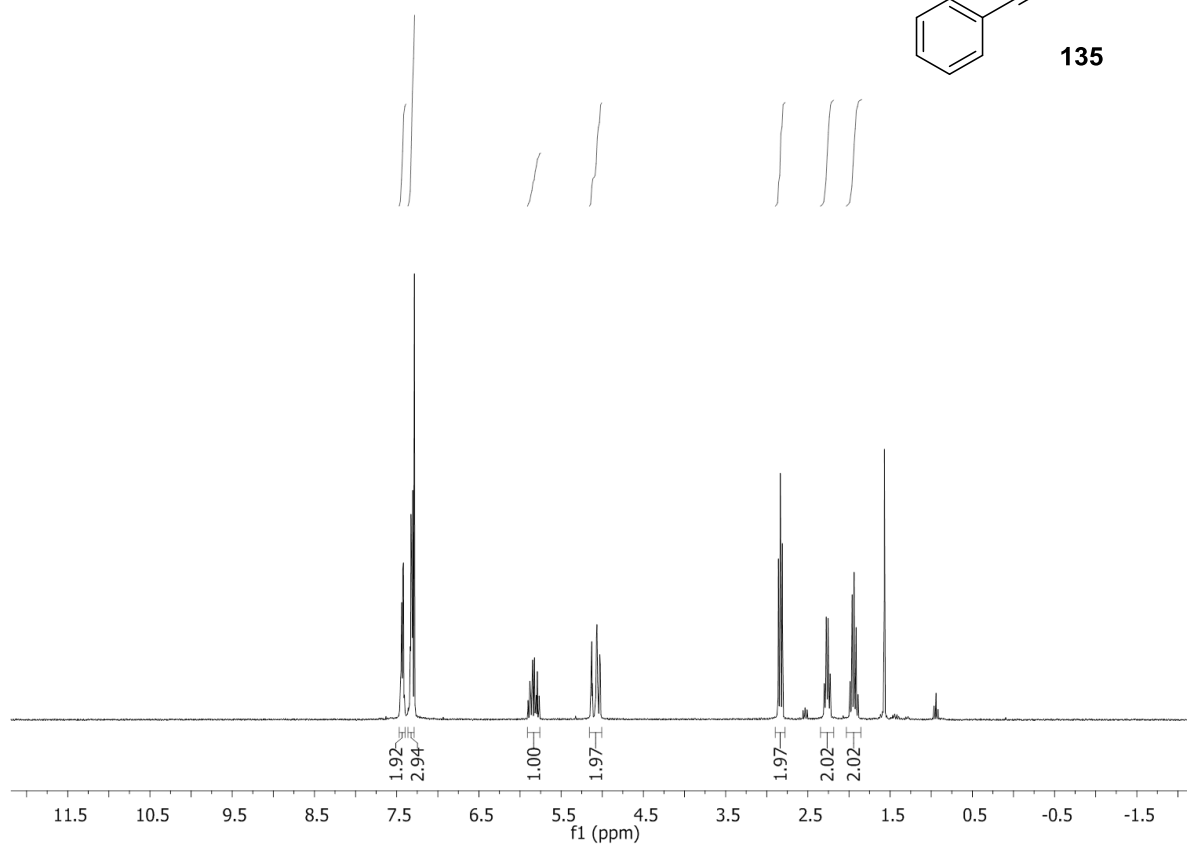
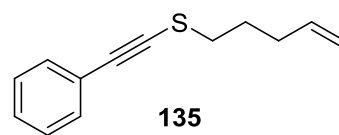


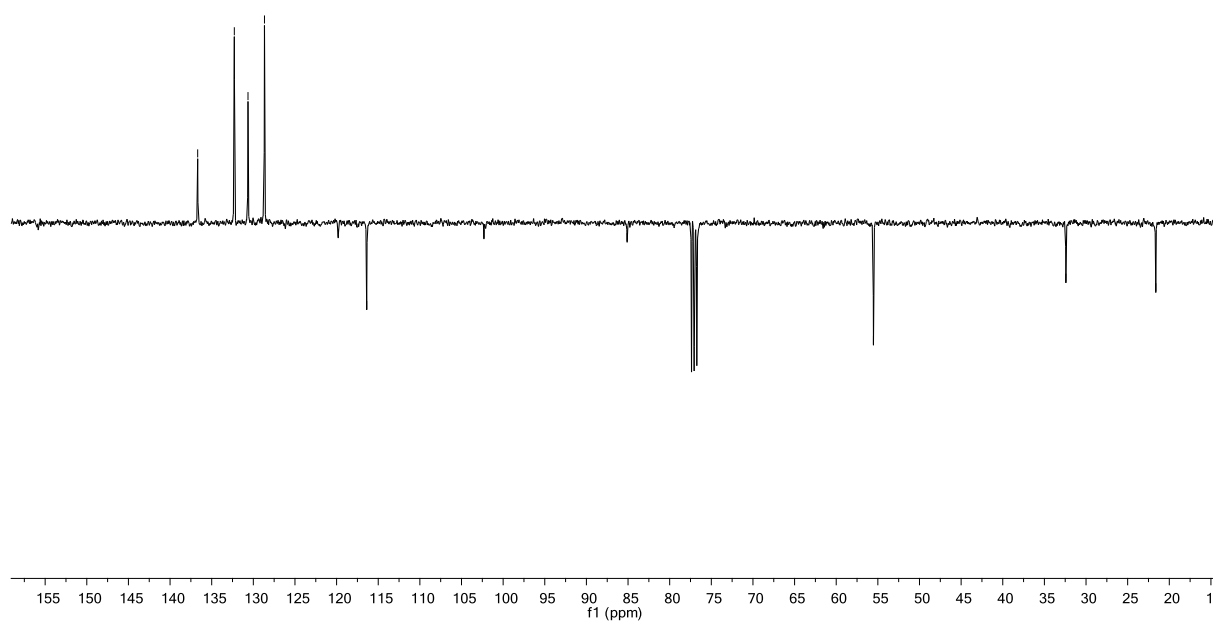
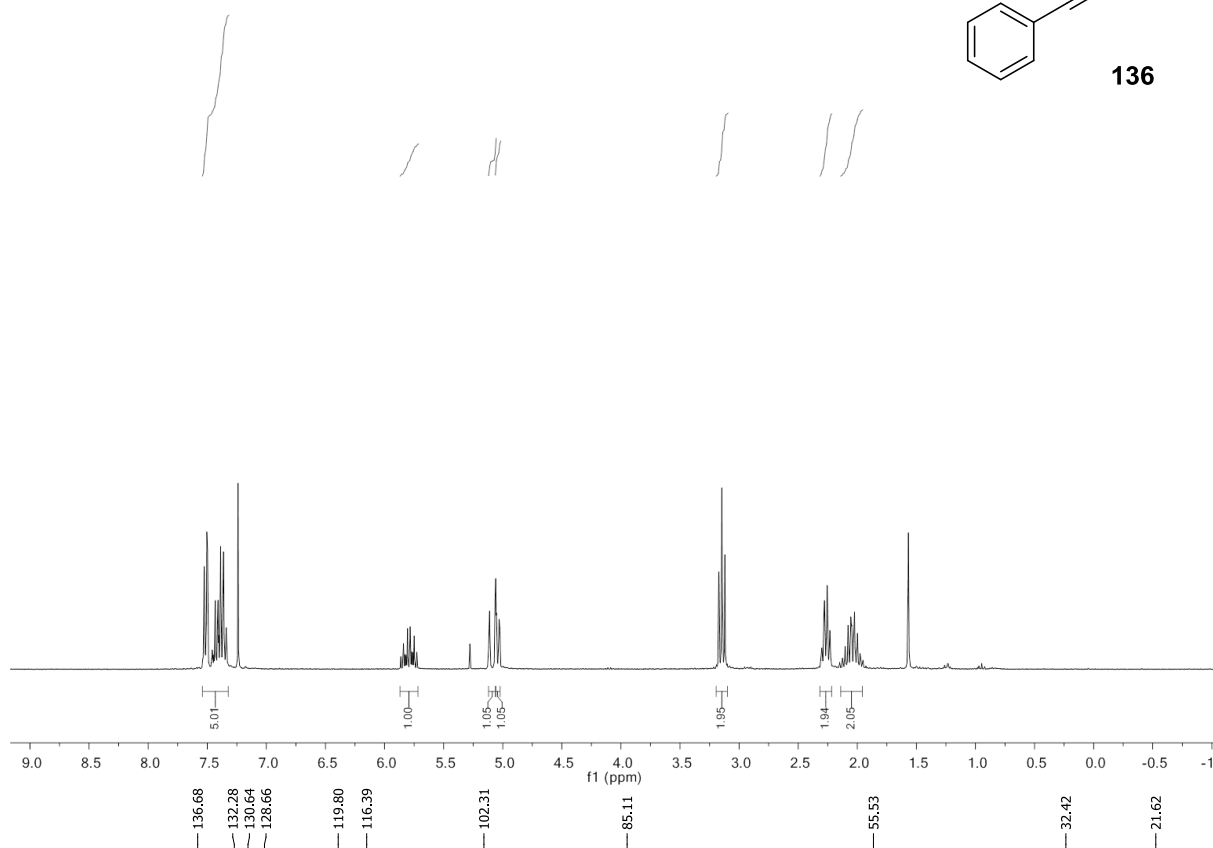
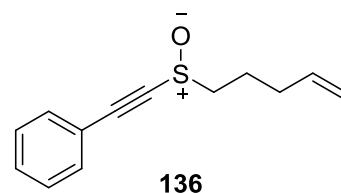


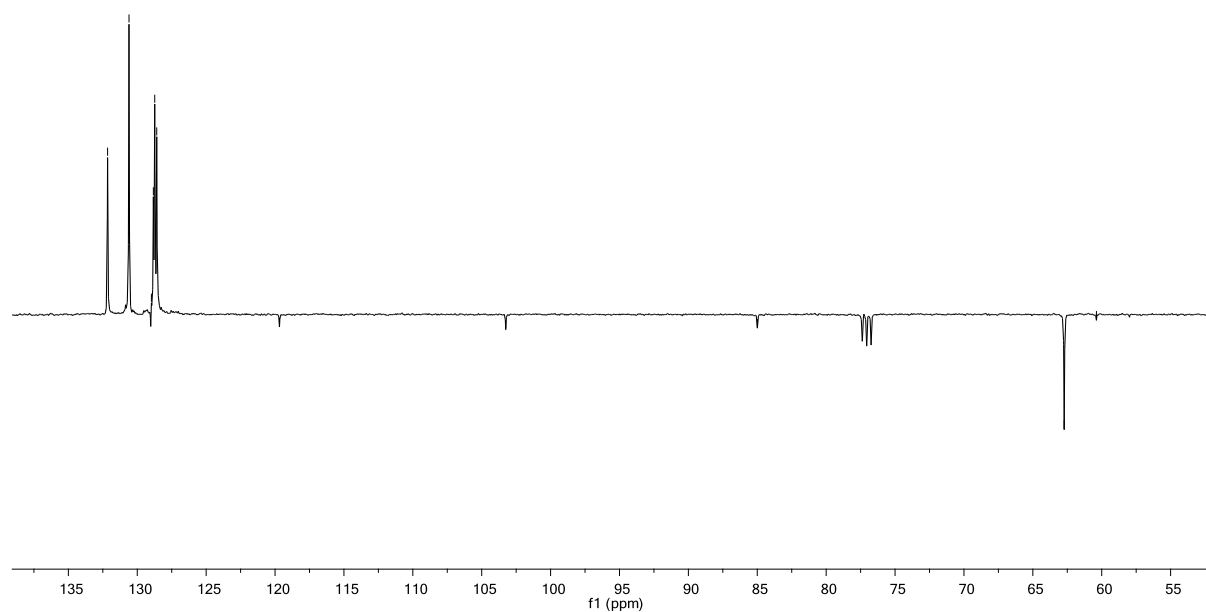
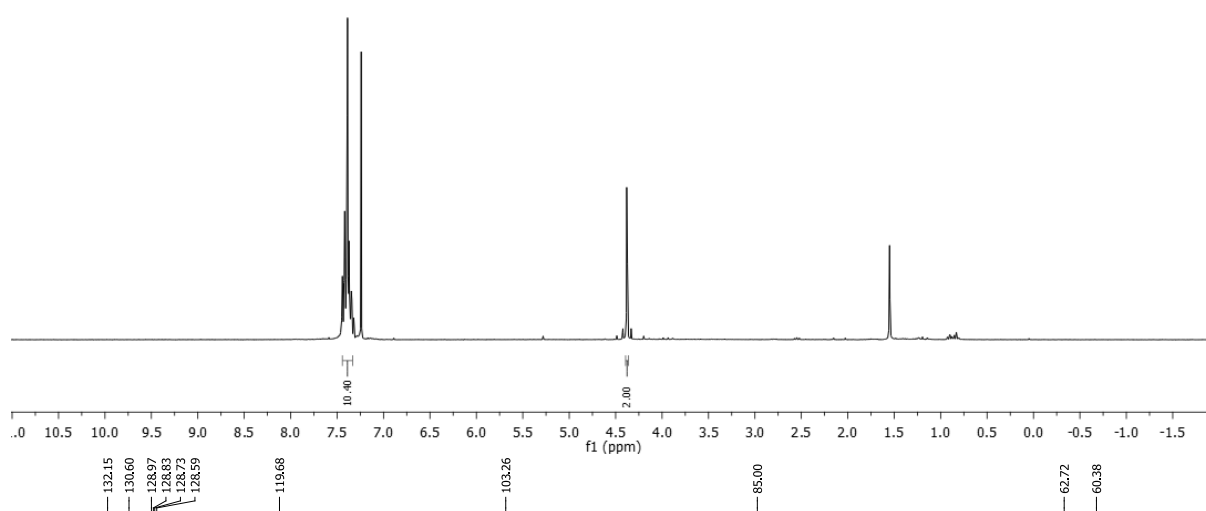
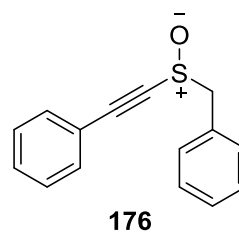


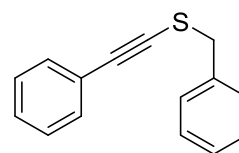




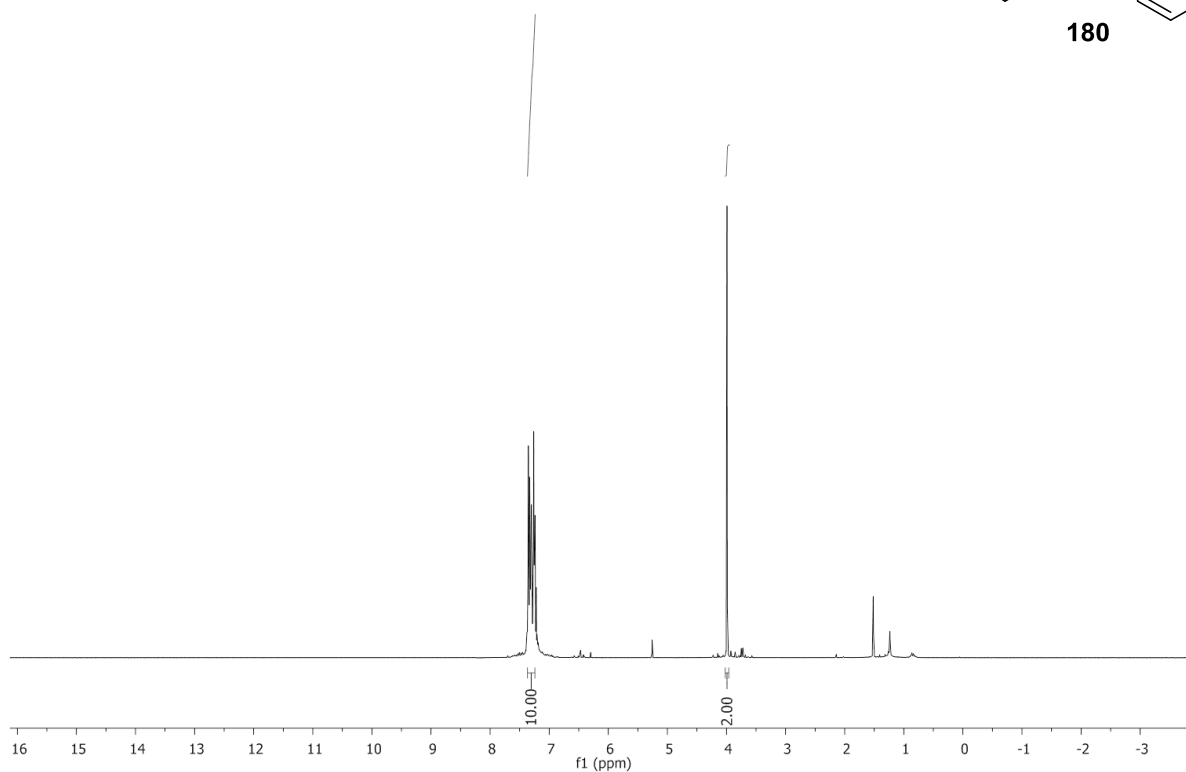




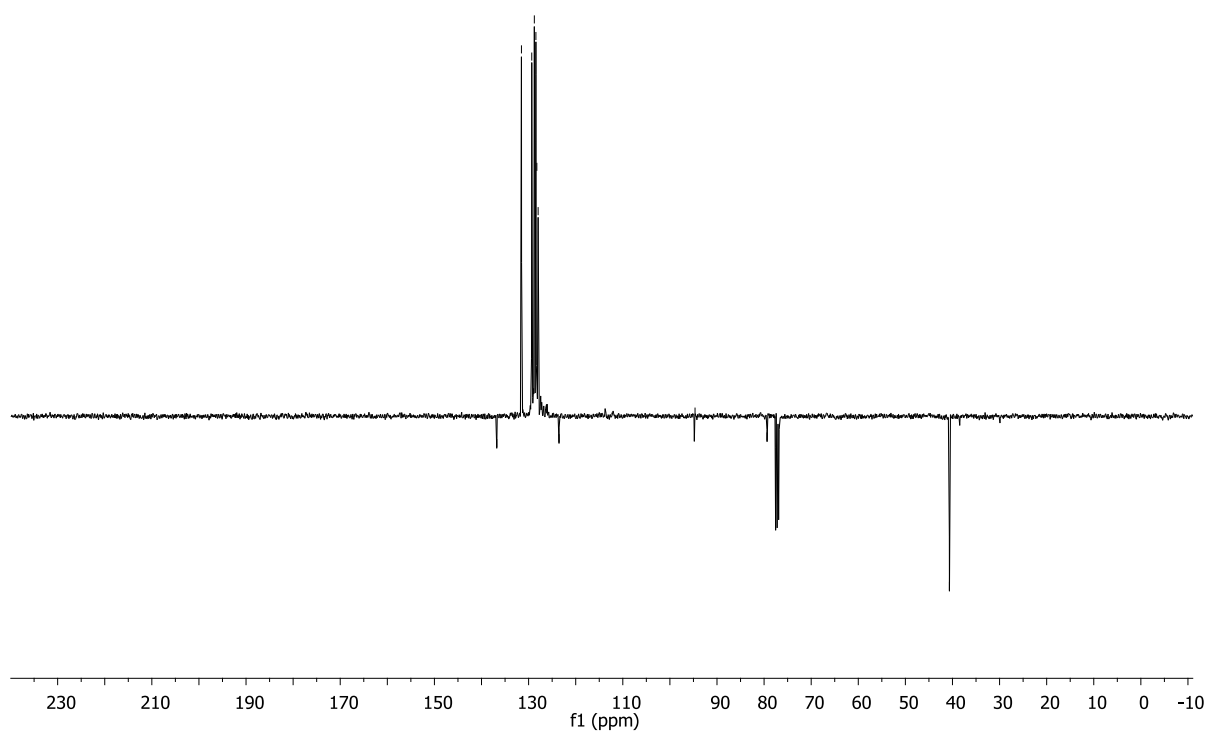


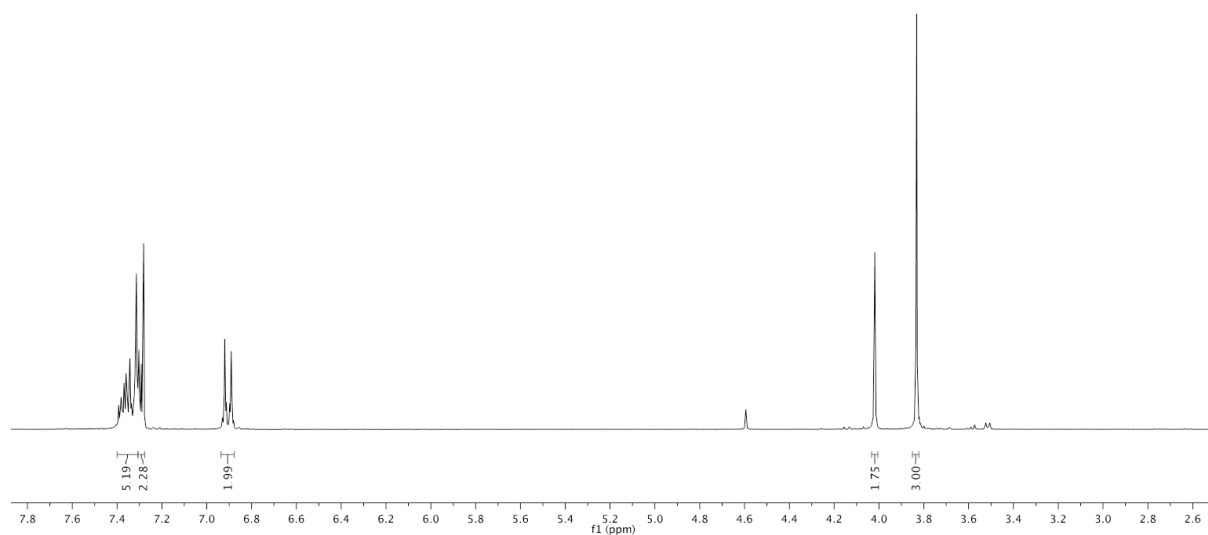
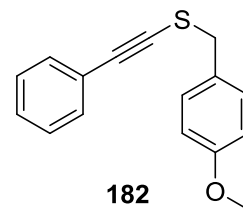


180

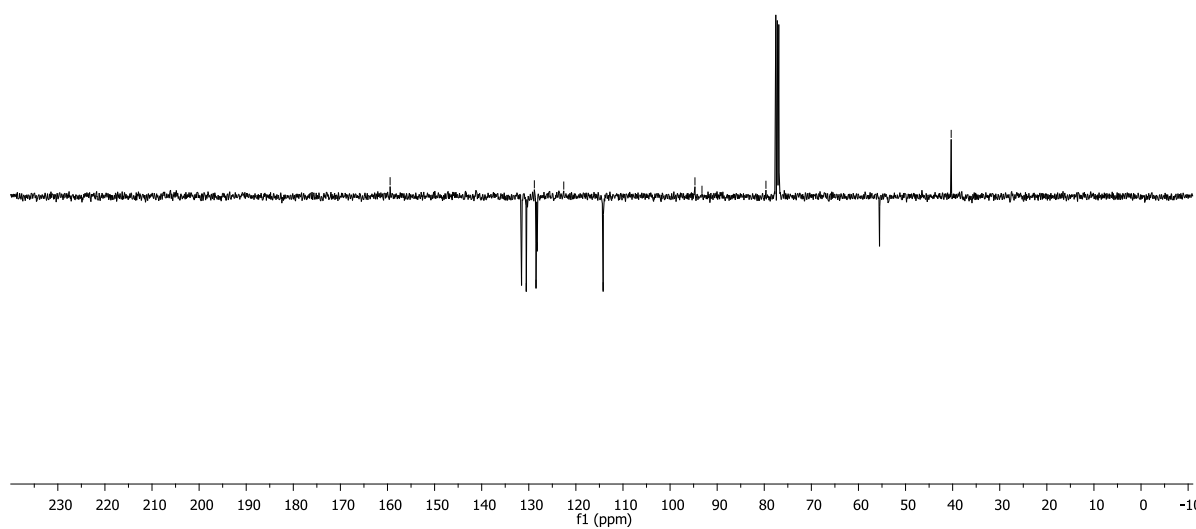


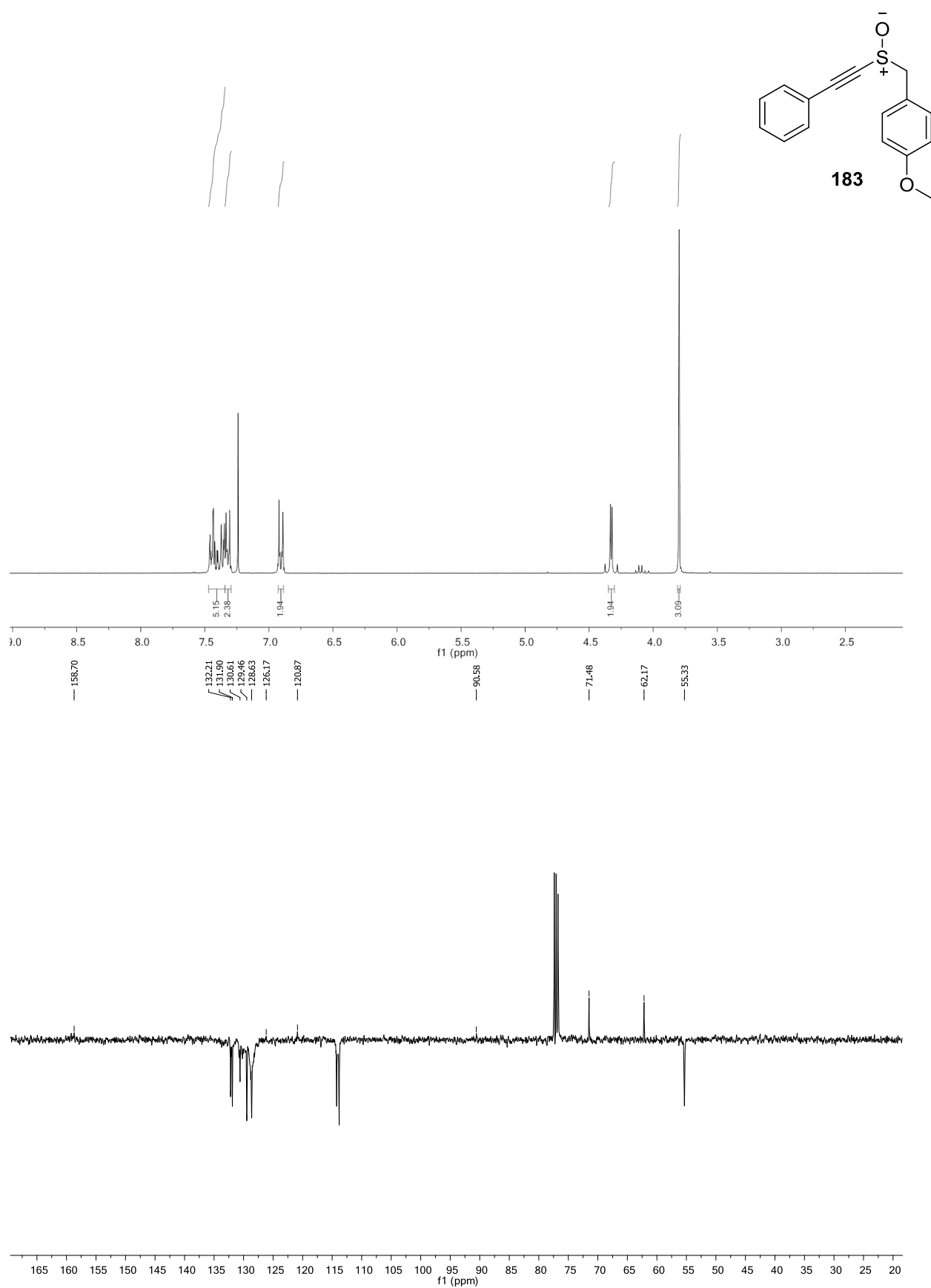
136.76
128.78
128.45
128.25
127.98
123.54
94.66
79.37
40.64

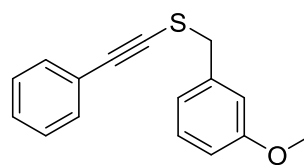




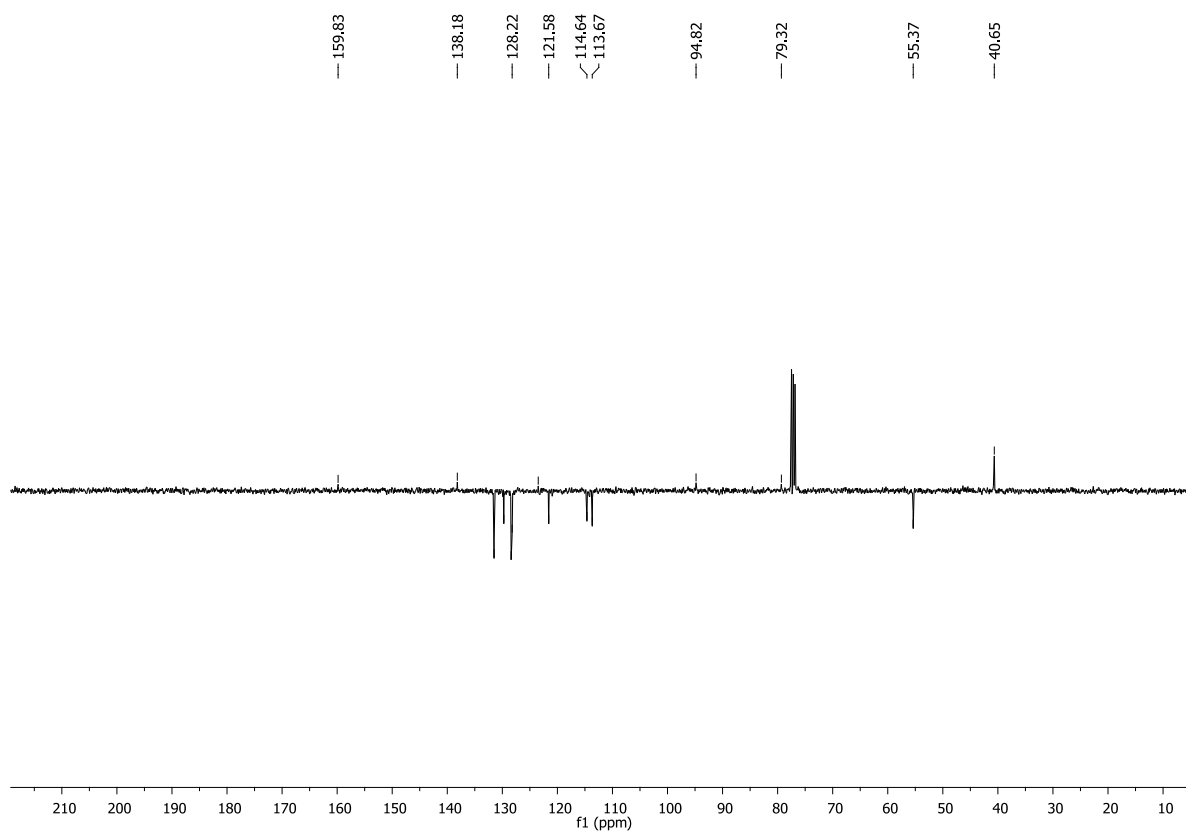
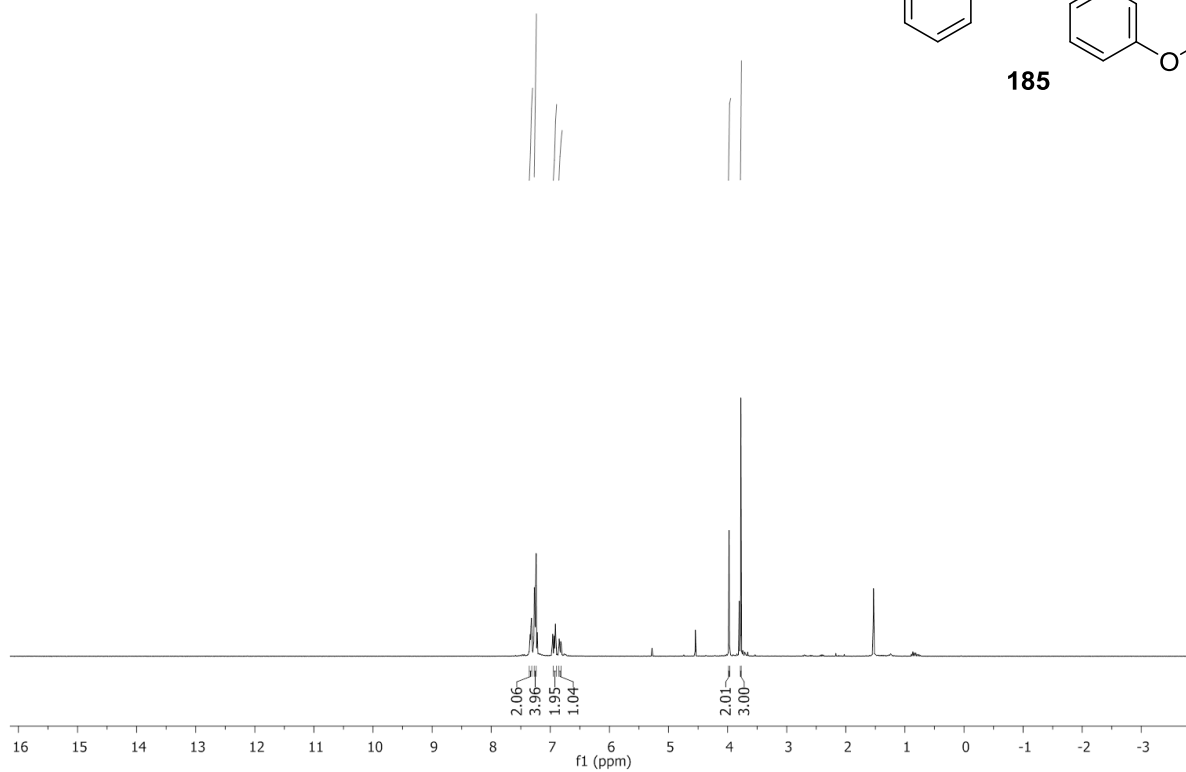
— 159.44
131.54
130.53
128.82
128.46
128.23
— 122.57
— 114.20
94.72
93.22
— 79.64
— 55.53
— 40.31

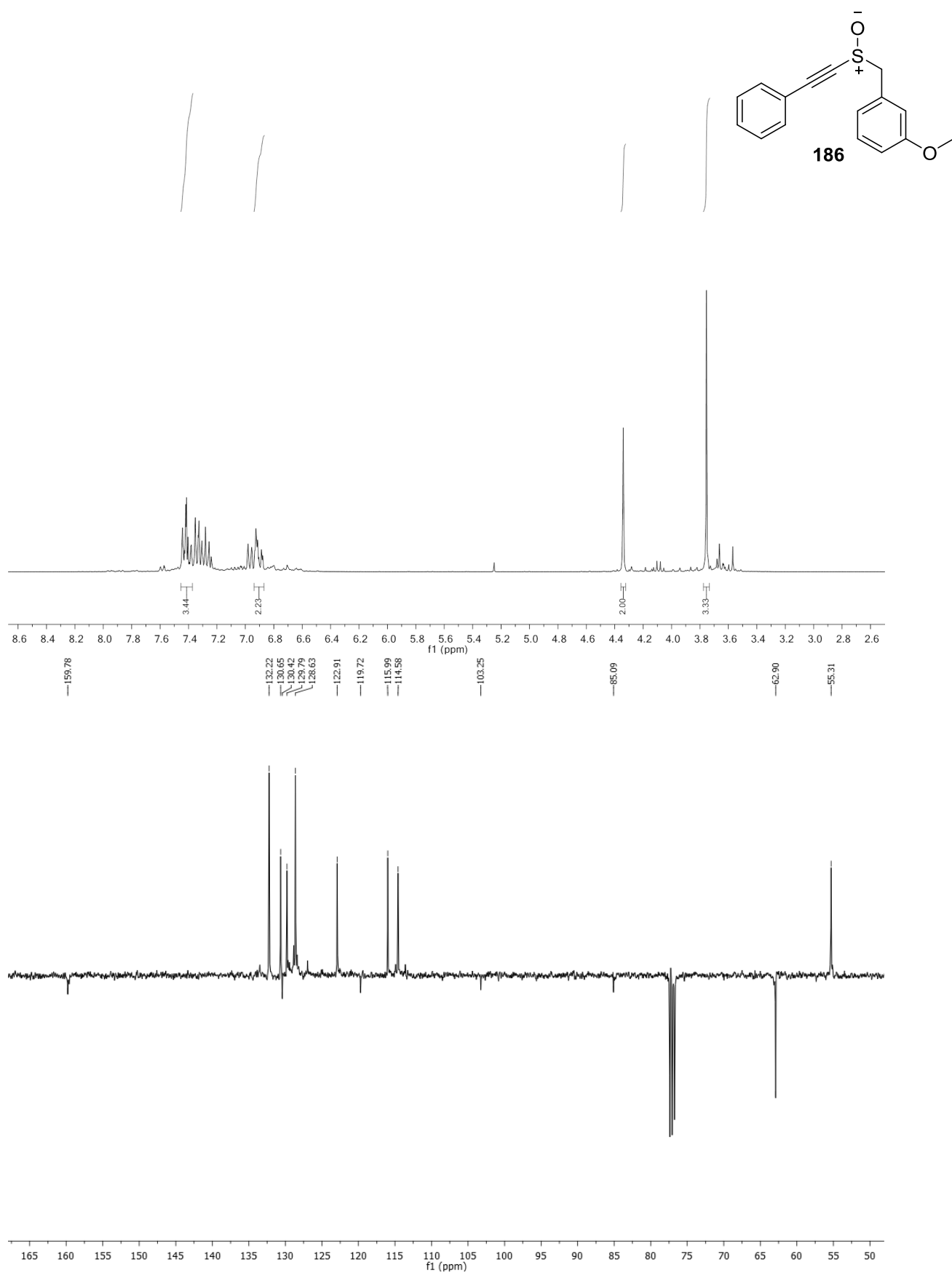






185





Appendix B – NMR Yield Calculations

Molar quantity of internal standard (TMB): $\frac{2.4}{134.22} = 0.018$ mmols

Using integrals of characteristic peaks from ^1H NMR:

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

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

$$\frac{IS}{2} : SM : P$$

$$\frac{\frac{IS}{2}}{\frac{IS}{2}} : \frac{SM}{\frac{IS}{2}} : \frac{P}{\frac{IS}{2}}$$

Enter integral values:

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

Molar ratio:

$$1 : 0.66 : 2.74$$

Multiply by molar quantity of IS to give the molar quantities present in the crude mixture:

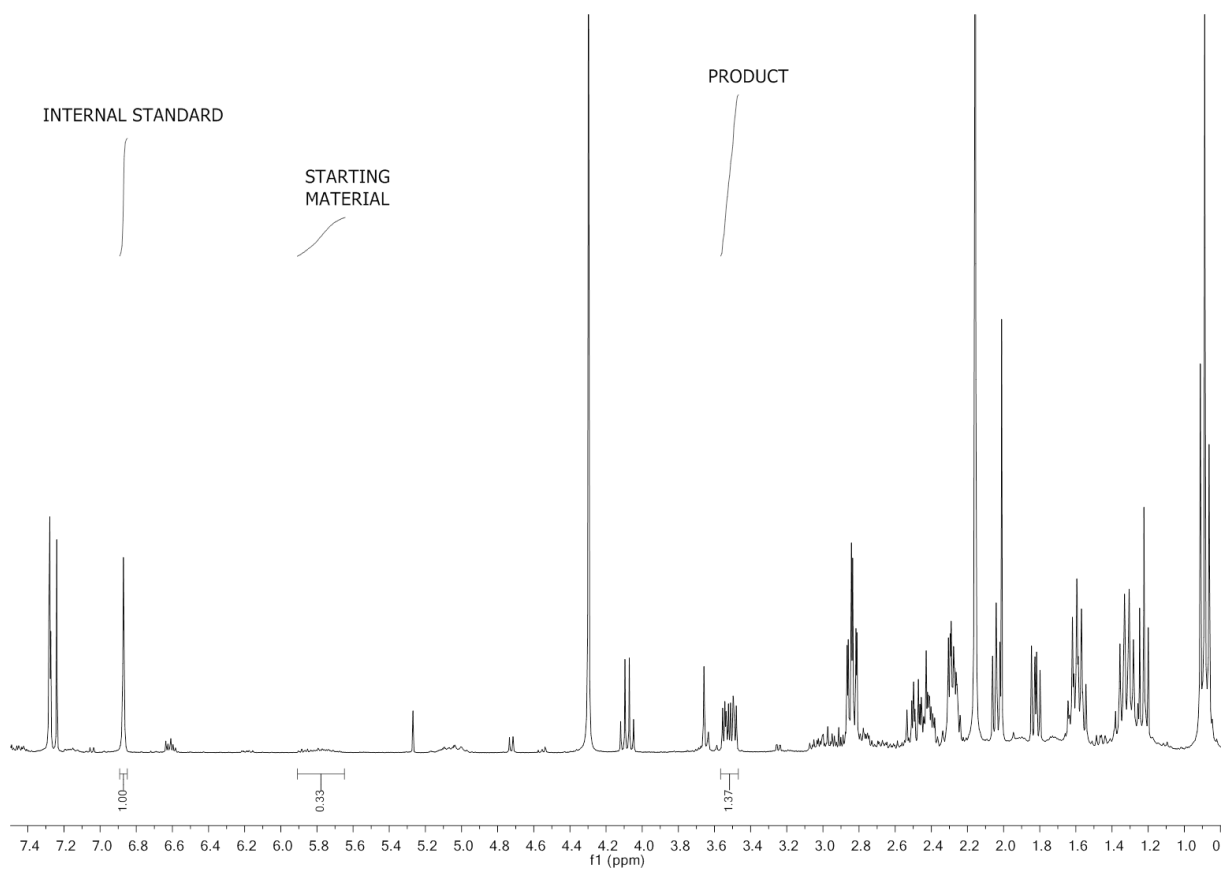
(IS) 0.018 mmols: (SM) 0.012 mmols: (P) 0.049 mmols

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

SM: 12%

P: 49%

Example:



References

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- ¹ Homer, *The Iliad*, Trans. R. Fagles, 1990, Penguin Books, New York.
- ² A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180 – 3211.
- ³ W. P. Griffith, *The Chemistry of the Rarer Platinum Metals*, 1967, Interscience, London.
- ⁴ M. Dub *Organometallic Compounds*, 2nd Edition., 1966, Springer, New York.
- ⁵ B. Armerr and H. Schmidbaur, *Angew. Chem., Int. Ed.*, 1970, **2**, 101 – 113.
- ⁶ C. A. Busacca, D. R. Fandrick, J. J. Song and C. H. Senanayake, *Adv. Synth. Catal.*, **2011**, 353, 1825 – 1864.
- ⁷ A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2010, **49**, 5232 – 5241.
- ⁸ M. Rudolph and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2012, **41**, 2448 – 2462.
- ⁹ A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem., Int. Ed.*, 2006, **45**, 7896 – 7936.
- ¹⁰ P. H.-Y. Cheong, P. Morganelli, M. R. Luzung, K. Houk and N. Toste, *F. D. J. Am. Chem. Soc.*, 2008, **130**, 4517 – 4526.
- ¹¹ M. C. B. Jaimes, C. R. N. Bçhling, J. M. Serrano-Becerra and A. S. K. Hashmi, *Angew. Chem. Int. Ed.*, 2013, **52**, 7963 – 7966.
- ¹² B. Armera and H. Schmidbaur, *Angew. Chem.*, 1970, **82**, 120 – 133.

-
- ¹³ H. Schmidbaur, *Naturwiss. Rundsch.*, 1995, **48**, 443 – 451.
- ¹⁴ A. S. K. Hashmi, *GoldBull.*, 2004, **37**, 51 – 65.
- ¹⁵ G. C. Bond, *GoldBull.*, 1972, **5**, 11 – 13.
- ¹⁶ G. C. Bond, P. A. Sermon, G. Webb, D. A. Buchanan and P. B. Wells, *J. Chem. Soc. Chem. Commun.*, 1973, **13**, 444 – 445.
- ¹⁷ M. Haruta, *Nature*, 2005, **437**, 1098 – 1099.
- ¹⁸ G. J. Hutchings, *Catal. Today*, 2005, **100**, 55 – 61.
- ¹⁹ M. Haruta, T. Kobayashi, H. Sano and N. Yamada, *Chem. Lett.*, 1987, **16**, 405 – 408.
- ²⁰ G. J. Hutchings, *J. Catal.*, 1985, **96**, 292 – 295.
- ²¹ A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem. Int. Ed*, 2006, **45**, 7896 – 7936.
- ²² G. C. Bond, C. Louis and D. T. Thompson, *Angew. Chem., Int. Ed.*, 2007, **41**, 7734 – 7735.
- ²³ Y. Ito, M. Sawamura and T. Hayashi, *J. Am. Chem. Soc.*, 1986, **108**, 6405 – 6406.
- ²⁴ J. H. Teles, S. Brode and M. Chabanas, *Angew. Chem.*, 1998, **110**, 1475 – 1478.
- ²⁵ M. Rudolph and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2012, **41**, 2448 – 2462.
- ²⁶ P. H. Y. Cheong, P. Morganelli, M. R. Luzung, K. Houk and N. Toste, *F. D. J. Am. Chem. Soc.*,

2008, **130**, 4517 – 4526.

²⁷ M. C. B. Jaimes, C. R. N. Bçhling, J. M. Serrano-Becerra and A. Stephen K. Hashmi, *Angew. Chem. Int. Ed.*, 2013, **52**, 7963 – 7966.

²⁸ P. Pyykkö, *Chem. Rev.*, 1988, **88**, 563 – 594.

²⁹ P. Pyykkö, *Angew. Chem., Int. Ed.*, 2004, **43**, 4412 – 4456.

³⁰ P. Pyykkö, *Inorg. Chim. Acta*, 2005, **358**, 4113 – 4130.

³¹ N. D. Shapiro and F. D. Toste, *Proc. Natl. Acad. Sci. U.S.A*, 2008, **46**, 3410 – 3449.

³² N. C. Baenziger, W. E. Bennett and D. M. Soboroff, *Acta Crystallogr., Sect. B*, 1976, **32**, 962 – 963.

³³ N. Mezailles, L. Ricard and F. Gagosz, *Org. Lett.*, 2005, **7**, 4133 – 4136.

³⁴ M. J. S. Dewar, *Bull. Soc. Chim. Fr.*, 1951, **18**, 71 – 79.

³⁵ L. A. Chatt and J. Duncanson, *Chem. Soc.*, 1953, **2**, 2939 – 2947.

³⁶ A. Fürstner and P. W. Davies, *Angew. Chem. Int. Ed.*, 2007, **46**, 3410 – 3449.

³⁷ M. S. Nechaev, V. M. Rayón and G. Frenking, *J. Phys. Chem. A*, 2004, **108**, 3134 – 3142.

³⁸ I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, 1976, Wiley, Chichester.

-
- ³⁹ R. H. Hertwig, W. Koch, D. Schröder, H. Schwarz, S. Hrusak and P. Schwedtfeger, *J. Phys. Chem.*, 1996, **100**, 12253 – 12260.
- ⁴⁰ J. Clayden, N. Greeves, S. Warren, *Organic Chemistry* 2nd Edition, 2012, Oxford University Press Inc., New York.
- ⁴¹ Y. Fukuda and K. Utimoto, *J. Org. Chem.*, 1991, **56**, 3729 – 3731.
- ⁴² H. G. Raubenheimer, H. Schmidbaur . *S. Afr. J. Sci.*, **107**, 1 – 13.
- ⁴³ a) O. Eisenstein, R. Hoffmann, *J. Am. Chem. Soc.*, 1981, **103**, 4308 – 4320; b) H. M. Senn, P. E. Blöchl, A. Togni, *J. Am. Chem. Soc.*, 2000, **122**, 4098 – 4107.
- ⁴⁴ M. J. S. Dewar, K. M. Merz Jr, *Organometallics*, 1985, **4**, 1967 – 1972.
- ⁴⁵ L. Maresca and G. Natile, *J. Chem. Soc. Chem. Commun.*, 1983, **1**, 40 – 41.
- ⁴⁶ L. L. Wright, R. M. Wing, M. F. Rettig, *J. Am. Chem. Soc.*, 1982, **104**, 610 – 612.
- ⁴⁷ A. Fürstner *Chem. Soc. Rev.*, 2009, **38**, 3208 – 3221.
- ⁴⁸ <<http://www.britannica.com/EBchecked/topic/94658/carbene>> (accessed 6th December 2014)
- ⁴⁹ L. Hintermann, *Beilstein J. Org. Chem.*, 2007, **3**, 1 – 5.
- ⁵⁰ M. P. Doyle and D. C. Forbes, *Chem. Rev.*, 1998, **98**, 911 – 936.

-
- ⁵¹ (a) M. P. Doyle, *Acc. Chem. Res.*, 1986, **19**, 348 – 356. (b) D. T. Nowlan, T. M. Gregg, H. M. L. Davies and D. A. Singleton, *J. Am. Chem. Soc.*, 2004, **125**, 15902 – 15911.
- ⁵² a) M.R. Fructos, T.R. Belderrain, P. de Fremont, N. M. Scott, S. P. Nolan, M. M. Diaz-Requejo, P. J. Perez, *Angew. Chem., Int. Ed.*, 2005, **44**, 5284 – 5288. b) A. Prieto, M. R. Fructos, M. Mar Díaz-Requejo, P. J. Perez, P. Perez-Galan, N. Delpont, A. M. Echavarren, *Tetrahedron*, 2009, **65**, 1790 – 1793.
- ⁵³ F. D. Toste, *Beilstein J. Org. Chem.* 2013, **9**, 1925 – 1930
- ⁵⁴ J. S. Clark, Nitrogen, Oxygen and Sulfur Ylide Chemistry: A Practical Approach in Chemistry, 2002, Oxford University Press, Oxford.
- ⁵⁵ E. Schaumann, "Sulfur Mediated Rearrangements": Topics in Current Chemistry, 2007, Springer, Heidelberg.
- ⁵⁶ Y. Kato, K. Miki, F. Nishino, K. Ohe and S. Uemura, *Org. Lett.*, 2003, **5**, 2619 – 2621.
- ⁵⁷ P. W. Davies and S. J.-C. Albrecht, *Angew. Chem., Int. Ed.*, 2009, **48**, 8372 – 8375.
- ⁵⁸ L. Zhang, J. Sun, and S. A. Kozmin, *Adv. Synth. Catal.*, 2006, **348**, 2271 – 2296.
- ⁵⁹ For selected examples, see: a) B. M. Trost and M. Lautens, *J. Am. Chem. Soc.*, 1985, **107**, 1781 – 1783; b) B. M. Trost and M. Lautens, *Tetrahedron Lett.*, 1985, **26**, 4887 – 4890; c) B. M. Trost, *Acc. Chem. Res.*, 1990, **23**, 34 – 42; d) B. M. Trost and G. J. Tanoury, *J. Am. Chem. Soc.*, 1988, **110**, 1636 – 1638; e) B.M. Trost, M. Lautens, C. Chan, D. J. Jebaratnam and T.

Mueller, *J. Am. Chem. Soc.*, 1991, **113**, 636–644; f) B. M. Trost and C. Pedregal, *J. Am. Chem. Soc.*, 1992, **114**, 7292 – 7294; g) B. M. Trost, G. J. Tanoury, M. Lautens, C. Chan and D. T. MacPherson, *J. Am. Chem. Soc.*, 1994, **116**, 4255 – 4267; h) B. M. Trost, D. L. Romero and F. Rise, *J. Am. Chem. Soc.*, 1994, **116**, 4268 – 4278.

⁶⁰ C. Nevado, D. J. Cárdenas and A. M. Echavarren, *Chem. Eur. J.*, 2003, **9**, 2627 – 2635.

⁶¹ C. Nieto-Oberhuber, M. P. Munoz, E. Bunuel, C. Nevado, D. J. Cardenas, and A. M. Echavarren, *Angew. Chem. Int. Ed.*, 2004, **43**, 2402 – 2406.

⁶² S. Patai and Z. Rappoport, *The Syntheses of Sulphones, Sulphoxides and Cyclic Sulphides*, 1995, John Wiley & Sons, New York.

⁶³ R. Thomas, C. B. Shoemaker and K. Eriks, *Acta Cryst.*, 1966, **21**, 12 – 20.

⁶⁴ T. P. Cunningham, D. L. Cooper, J. Gerratt, P. B. Karadakov and M. Raimondi, *J. Chem. Soc., Faraday Trans.*, 1997, **93**, 2247 – 2254.

⁶⁵ R. J. Abraham, J. J. Byrne and L. Griffiths, *Magn. Reson. Chem.*, 2008, **46**, 667 – 675.

⁶⁶ D. F. Taber and R. E. Ruckle, *J. Am. Chem. Soc.*, 1986, **108**, 7686 – 7693.

⁶⁷ D. F. Taber, K. K. You and A. L. Rheingold, *J. Am. Chem. Soc.*, 1996, **118**, 547 – 556.

⁶⁸ D. F. Taber and K. Raman, *J. Am. Chem. Soc.*, 1983, **105**, 5935 – 5937.

-
- ⁶⁹ S. G. Collins, O. C. M. O'Sullivan, P. G. Kellehera and A. R. Maguire, *Org. Biomol. Chem.*, 2013, **11**, 1706 – 1725.
- ⁷⁰ S. Servi, *Synthesis*, 1990, **1**, 1 – 25.
- ⁷¹ D. Hodson and G. Holt, *J. Chem. Soc. C.*, 1968, 1602 – 1603.
- ⁷² D. H. Bremner and M. M. Campbell, *J. Chem. Soc., Chem. Commun.*, 1976, **14**, 538 – 539.
- ⁷³ D. H. Bremner and M. M. Campbell, *J. Chem. Soc., Perkin Trans. 1*, 1977, **20**, 2298 – 2308.
- ⁷⁴ C. F. Ebbinghaus, P. Morrissey and R. L. Rosati, *J. Org.Chem.*, 1979, **44**, 4697 – 4699.
- ⁷⁵ G. Glahsl and R. Herrmann, *J. Chem. Soc., Perkin Trans. 1*, 1988, **7**, 1753 – 1757.
- ⁷⁶ I. Shahak and J. Almog, *Synthesis*, 1970, **3**, 145 – 146.
- ⁷⁷ A. R. Maguire, P. G. Kelleher, G. Ferguson and J. F. Gallagher, *Tetrahedron Lett.*, 1998, **39**, 2819 – 2822.
- ⁷⁸ A. Rosowsky and K. K. N. Chen, *J. Org. Chem.*, 1973, **38**, 2073 – 2077.
- ⁷⁹ S. G. Collins, O. C. M. O'Sullivan, P. G. Kellehera and A. R. Maguire, *Org. Biomol. Chem.*, 2013, **11**, 1706 – 1725.
- ⁸⁰ L. Wolff, *Justus Liebigs Ann. Chem.*, 1902, **325**, 129 – 195.

⁸¹ a) C. L. Moody, A. M. Z. Slawin, R. J. Taylor and D. J. Williams, *Tetrahedron Lett.*, 1988, **29**, 6009 – 6012. b) M. Takebayashi, T. Kashiwadw, M. Hamaguchi, and T. Ibata, *Chem. Lett.*, 1973, **8**, 809 – 812.

⁸² D. Collomb and A. Doutheau, *Tetrahedron Lett.*, 1997, **38**, 1397 – 1398.

⁸³ S. G. Collins, O. C. M. O'Sullivan, P. G. Kellehera and A. R. Maguire, *Org. Biomol. Chem.*, 2013, **11**, 1706 – 1725.

⁸⁴ a) W. A. Donaldson, *Tetrahedron*, 2001, **57**, 8589 – 8627. b) D. Y.-K. Chen, R. H. Pouwer and J.-A. Richard, *Chem. Soc. Rev.*, 2012, **41**, 4631 – 4642. c) H. M. L. Davies and W. R. Cantrell Jr, *Tetrahedron Lett.*, 1991, **32**, 6509 – 6512.

⁸⁵ a) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353 – 1353. b) T. D. Avery, G. Fallon, B. W. Greatrex, S. M. Pyke, D. K. Taylor and E. R. T. Tiekink, *J. Org. Chem.*, 2001, **66**, 7955 – 7966.

⁸⁶ a) R. P. Wurz and A. Charette, *Org. Lett.*, 2003, **5**, 2327 – 2329; b) R. P. Wurz and A. B. Charette, *Org. Lett.*, 2002, **4**, 4531 – 4533; c) V. K. Aggarwal, J. Vicente and R. V. Bonnert, *Org. Lett.*, 2001, **3**, 2785 – 2788; d) V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd and M. Porcelloni, *Angew. Chem., Int. Ed.*, 2001, **40**, 1433 – 1436.

⁸⁷ a) N. D. Shapiro and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 4160 – 4161; b) G. Li and L. Zhang, *Angew. Chem., Int. Ed.*, 2007, **46**, 5156 – 5159; c) A. B. Cuenca, S. Montserrat, K. M.

Hossain, G. Mancha, A. Lledós, M. Medio-Simón, G. Ujaque and G. Asensio, *Org. Lett.*, 2009, **11**, 4906 – 4909.

⁸⁸ L. Ye, L. Cui, G. Zhang and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 3258 – 3259.

⁸⁹ W. He, C. Li and L. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 8482 – 8485.

⁹⁰ A. S. K. Hashmi, T. Wang, S. Shi and M. Rudolph, *J. Org. Chem.*, 2012, **77**, 7761 – 7767.

⁹¹ D. Qian and J. Zhang, *Chem. Commun.*, 2011, **47**, 11152–11154.

⁹² a) N. Bongers, N. Krause, *Angew. Chem.*, 2008, **120**, 2208 – 2211. b) Z. Li, C. Brouwer, C. He, *Chem. Rev.*, 2008, **108**, 3239 – 3265. c) A. Arcadi, *Chem. Rev.* 2008, **108**, 3266 – 3325. d) R. A. Widenhoefer, *Chem. Eur. J.*, 2008, **14**, 5382 – 5391.

⁹³ a) B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.*, 2001, **101**, 2067 – 2096. b) B. M. Trost, M. J. Krische, *Synlett*, 1998, **1**, 1 – 16. c) G. C. Lloyd-Jones, *Org. Biomol. Chem.*, 2003, **1**, 215 – 236. d) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.*, 2002, **102**, 813 – 834. e) B. M. Trost, *Chem. Eur. J.*, 1998, **4**, 2405 – 2412. f) I. Ojima, M. Tzamarioudaki, Z. Y. Li, R. J. Donovan, *Chem. Rev.*, 1996, **96**, 635 – 662. g) B. Jiang, T. Rajale, W. Wever, S. Tu, G. Li, *Chem. Asian J.*, 2010, **5**, 2318 – 2335. h) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.*, 2009, **38**, 3051 – 3060. i) M. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 2243 – 2270. j) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285 – 2310.

-
- ⁹⁴ X. Li and J. Xiao, *Angew. Chem. Int. Ed.*, 2011, **50**, 7226 – 7236.
- ⁹⁵ D. J. Gorin, B. D. Sherry and F. Dean Toste, *Chem. Rev.*, 2008, **108**, 3351 – 3378.
- ⁹⁶ B. Godoi, A. Sperança, D. F. Back, R. Brandão, C. W. Nogueira and G. Zeni, *J. Org. Chem.*, 2009, **74**, 3469 – 3477.
- ⁹⁷ N. Riddell and W. Tam, *J. Org. Chem.*, 2006, **71**, 1934 – 1937.
- ⁹⁸ W. Zheng, F. Zheng, Y. Hong, and L. Hu, *Heteroat. Chem.*, 2012, **23**, 105 – 110.
- ⁹⁹ a) M. Madesclaire, *Tetrahedron*, 1986, **42**, 5459 – 5495. b) S. Patai, E. Block. In *The chemistry of ethers, crown ethers, hydroxyl groups and their sulphur analogues*, 1980, Interscience, Chichester. c) G. A. Russel and L. A. Ochrynowycz, *J. Org. Chem.*, 1970, **35**, 2106 – 2108. d) V. I. Laba, A. V. Sviridovaa and E. N. Prilezhaeva, *Russ. Chem. Bull.*, 1972, **21**, 212 – 213. e) M. A. Brimble, M. T Brimble and J. J. Gibson, *Chem. Soc. Perkin Trans. 1*, 1989, **1**, 179 – 184.
- ¹⁰⁰ B. M. Trost and D. P. Curran, *Tetrahedron Lett.*, 1981, **22**, 1287 – 1290.
- ¹⁰¹ R. G. Hisley and M. A. Harpold, *J. Org. Chem.*, 1967, **32**, 3191 – 3198.

-
- ¹⁰² a) F. A. Davis, S. B. Awad, R. H. Jenkins Jr., R. L. Billmers, and L. A. Jenkins, *J. Org. Chem.*, 1983, **48**, 3071 – 3074. b) F. A. Davis, R. Jenkins Jr. and S. G. Yocklovich, *Tetrahedron Lett.*, 1978, **19**, 5171 – 5174.
- ¹⁰³ M. Jia and M. Bandini, *ACS Catal.*, 2015, **5**, 1638 – 1652.
- ¹⁰⁴ B. Lu, C. Li, L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 14070 – 14072.
- ¹⁰⁵ K. Ji, J. Nelson and L. Zhang, *Beilstein J. Org. Chem.*, 2013, **9**, 1925 – 1930.
- ¹⁰⁶ Y-C. Lin and C-H. Lin, *Org. Lett.*, **9**, 2007, 2075 – 2078.
- ¹⁰⁷ L. Ye, L. Cui, G. Zhang and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 3258 – 3259.
- ¹⁰⁸ N. Mézailles, L. Ricard and F. Gagosz, *Org. Lett.*, 2005, **7**, 4133 – 4136.
- ¹⁰⁹ L. Ricard and F. Gagosz, *Organometallics*, 2007, **26**, 4704 – 4707.
- ¹¹⁰ S. Antoniotti, V. Dalla and E. Duñach, *Angew. Chem., Int. Ed.*, 2010, **49**, 7860 – 7888.
- ¹¹¹ E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326 – 3350.
- ¹¹² D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351 – 3378.
- ¹¹³ P. Perez-Galan, E. Herrero-Gomez, D. T. Hog, N. J. A. Martin, F. Maseras and A. M. Echavarren, *Chem. Sci.*, 2011, **2**, 141 – 149.
- ¹¹⁴ E. J. Corey, and P. L. Fuchs, *P. L. Tetrahedron Lett.* **1972**, 13, 3769–3772.

-
- ¹¹⁵ J. Kovacs, G. Toth, A. Simon, A. Levai, A. Koch and E. Kleinpeter, *Magn. Reson. Chem.*, 2003, **41**, 193 – 201.
- ¹¹⁶ R. J. Abraham, J. J. Byrne and L. Griffiths, *Magn. Reson. Chem.*, 2008, **46**, 667 – 675.
- ¹¹⁷ a) D. M. Frieze, P. F. Hughes, R. L. Merrill and S. A. Evans, *J. Org. Chem.*, 1977, **42**, 2206 – 2211. b) R. P. Rooney and S. A. Evans, *J. Org. Chem.*, 1980, **45**, 180 – 183.
- ¹¹⁸ L. Zhang, *Acc. Chem. Res.*, 2014, **47**, 877 – 888.
- ¹¹⁹ Y. Horino, T. Yamamoto, K. Ueda, S. Kuroda and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 2809–2811.
- ¹²⁰ M. R. Luzung, J. P. Markham and F. D. Toste, *J. Am. Chem. Soc.*, 2004, **126**, 10858 – 10859.
- ¹²¹ V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.*, 2004, **10**, 4556 – 4575.
- ¹²² Patel, B. *Peri-substituted dithianaphthalenes as sources of reactive intermediates in organic chemistry*, PhD Dissertation, 2009, University of Birmingham.
- ¹²³ H. Suzuki, M. Mori, and M. Shibakami, *Synlett*, 2003, **14**, 2163 – 2166.
- ¹²⁴ Patent for the synthesis of THP protected propargyl alcohol: P. Mátyus, P. Huleatt, C. Christina, B. Sperlágh, M. L. khoo, K. Magyar, Á. Papp-behr, R. Deme, G. Túrós and K. Gyires: *New arylalkenylpropargylamine derivatives exhibiting neuroprotective action for the treatment of neurodegenerative diseases*: Filed: Dec 10, 2013, WO2015/87094 A1.
- ¹²⁵ I. N. Michaelides, B. Darses, and D. J. Dixon, *Org. Lett.*, 2011, **13**, 664 – 667.

-
- ¹²⁶ A. Torrado, S. Lopez, R. Alvarez and A. R. de Lera, *Synthesis*, **3**, 285 – 293.
- ¹²⁷ T. Satoh, Y. Hayashi and K. Yamakawa, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 1866 – 1869.
- ¹²⁸ J. P.A. Harrity, W. J. Kerr, D. Middlemiss and J. S. Scott, *J. Organomet. Chem.*, 1997, **532**, 219 – 227.
- ¹²⁹ R. D. Chambers, C. W. Hall, J. Hutchinson and R. W. Millar, *J. Chem. Soc., Perkin Trans. 1.*, 1998, **10**, 1705 – 1713.
- ¹³⁰ C. D. Johnson, A. R. Katritzky and N. Shakir, *J. Chem. Soc. B.*, 1967, 1235 – 1237.