A Novel Enediyne Synthesis from Alkynyl Sulfonamides via Non-Classical Carbenoids

A dissertation presented by

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Declaration

I, Theodore Hayes, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

In the last forty years *Z*-enediynes have been found to facilitate a unique and powerful class of antitumour agent, which has already shown some clinical application, and possesses great potential for further use. Meanwhile, an area of continued research interest within the Wilden group has been exploration of the chemistry of alkynyl sulfonamides, which remains relatively unreported to date. Furthermore, within the literature there has been a growing concern to find alternative synthetic routes that obviate the necessity of transition metal catalysts, given their often high toxicity, expense and difficulty of removal from final products.

In this thesis, an original synthesis of *Z*-enediynes upon treatment of alkynyl sulfonamides with lithiated acetylene derivatives is described, without the use of transition metals. Alongside this, alkenyl sulfonamide and 1,3-diyne side-products were usually observed, the latter of which has various useful applications itself.

Extensive investigations involving classical experimentation and computational modelling revealed a fascinating collection of mechanistic routes, significantly differing from other alkynyl sulfonamide reactions performed within the group. It was subsequently discovered, that an unusual non-classical carbenoid intermediate is responsible for the formation of the *Z*-enediyne and alkenyl sulfonamide products. Meanwhile, a conventional addition-elimination pathway produces the 1,3-diyne.

The proportions of the three products can be regulated to a degree by altering the synthetic parameters, however these effects are limited. Determination of the optimum conditions for each product was attempted using DoE experiments, although these were relatively unsuccessful. Work was also done to incorporate the novel *Z*-enediyne synthesis into the existing preparations of enediyne antitumour agents, but was hindered by polymerisation side-reactions.

Finally, the scope of suitable starting material substrates was explored, which yielded curious changes to the reaction's progression. Possible explanations are provided for these observations, contributing further to the continued research of alkynyl sulfonamide chemistry.

Impact Statement

The impact of the research detailed in this thesis sits primarily within academia. The formation of enediynes involving a non-classical carbene/carbenoid intermediary species presents an unusual mechanism, previously unreported in the literature. Likewise, the knowledge base of the relatively overlooked field of sulfonamide chemistry, and particularly that of alkynyl sulfonamides, has been expanded.

Furthermore, a previously unknown functional series dubbed "alkenyl sulfonamides" has been discovered, as well as several novel examples of the alkynyl sulfonamide, diyne and enediyne compound types.[i]

The impact outside of academia is principally rooted within possible incorporation of the novel enediyne synthesis, into manufacture of enediyne antitumour agents. At present, this route does not present a superior preparation of the functional group to those currently employed in the corresponding total syntheses, though future research may refine this work to the point where it offers a cheaper and more sustainable option.

Finally, if suitably tailored, the diyne forming side-reaction may be applied to an additional selective preparation of a variety of useful unsymmetrical diynes, without the use of transition metal catalysis. At present however, the cumbersome production of starting materials makes diyne synthesis from alkynyl sulfonamides comparatively undesirable.

[i] Hayes, T. O. P.; Slater, B.; Horan, R. A. J.; Radigois, M.; Wilden, J. D., *Org. Biomol. Chem.*, **2017**, *15*, 9895-9902.

Contents

Abbreviations

^{1}H-NMR	Proton nuclear magnetic resonance
^{13}C-NMR	Carbon-13 nuclear magnetic resonance
Ac	Acetate
add.	Addition
BHT	Butylated hydroxytoluene
CI	Chemical ionisation
conc.	Concentration
DFT	Density functional theory
dist.	Distilled
DMEDA	*N*,*N*'-Dimethylethylenediamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DoE	Design of experiments
E	Entgegen
EDG	Electron donating group
EI	Electron ionisation
EPR	Electron paramagnetic resonance
eq.	Equivalents
ESI	Electrospray ionisation

Et	Ethyl
EWG	Electron withdrawing group
FBW	Fritsch–Buttenberg–Wiechell
FTIR	Fourier-transform infrared
HRMS	High resolution mass spectrometry
HSAB	Hard and soft acids and bases
IC_{50}	Half-inhibiting concentration
ID_{50}	Half-inhibiting dosage
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
LRMS	Low resolution mass spectrometry
m	Meta
Me	Methyl
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced)
NaHMDS	Sodium bis(trimethylsilyl)amide
^{n}Bu	*n*-Butyl
NIS	*N*-Iodosuccinimide
NOESY	Nuclear Overhauser effect spectroscopy
o	Ortho
p	Para

PCC	Pyridinium chlorochromate
PE	Petroleum ether
RT	Room temperature
SET	Single electron transfer
SM	Starting material
^{t}Bu	*tert*-Butyl
temp.	Temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
UV	Ultraviolet
Z	Zusammen

Acknowledgements

To Jesus Christ my Lord and saviour, thank you most of all for rescuing me and carrying me through the highs and lows of the last four years. May I never fall away and be only for your glory, only by your grace can anything be accomplished.

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Thank you to Glaxosmithkline for their generous joint sponsorship, and extending me the opportunity to work in their Stevenage labs over the winter of 2016-17. A special thank you to Richard Horan and David Stevens for their supervision during my time there. Thank you also to University College London for their joint sponsorship, and providing unique experiences in both my Undergraduate and Doctoral studies.

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Finally, thank you so very much to my parents Audrey and Justin Hayes for their multifaceted love and support, wise counsel, constant affirmation, financial aid, fantastic company, comfort

in darker seasons, patient endurance of my assorted ramblings, invaluable assistance with bicycle maintenance and so much more. Thank you for providing me with two priceless examples of how to live for others, as well as living out faith with integrity.

O my Lord of Heavenly Hosts, Father, Son and Holy Ghost, years I searched with half a heart, but on the second from my start, you crashed right in, my heart full of sin, and carried me through, the joy and the blue, what is to come I do not know, but may you always be with me so.

"And he said to man, 'Behold, the fear of the Lord, that is wisdom, and to turn away from evil is understanding.'"

Job 28:28 (English Standard Version)

"Rejoice in the Lord always; again I will say, rejoice. Let your reasonableness be known to everyone. The Lord is at hand; do not be anxious about anything, but in everything by prayer and supplication with thanksgiving let your requests be made known to God. And the peace of God, which surpasses all understanding, will guard your hearts and your minds in Christ Jesus.

Finally, brothers, whatever is true, whatever is honorable, whatever is just, whatever is pure, whatever is lovely, whatever is commendable, if there is any excellence, if there is anything worthy of praise, think about these things. What you have learned and received and heard and seen in me—practice these things, and the God of peace will be with you."

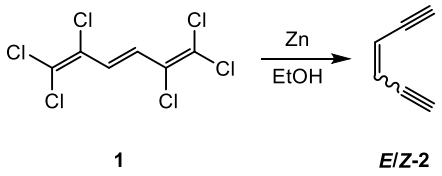
Philippians 4:4-9 (English Standard Version)

1. Introduction

1.1. Application of Enediynes

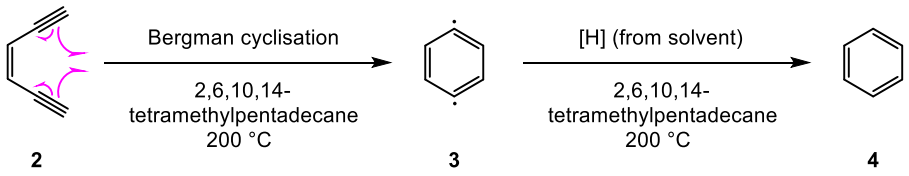
1.1.1. Early Developments in Enediyne Chemistry

Enediynes are a fascinating and relatively unusual compound type comprised of two alkyne units interconnected by an alkene group. The first recorded synthesis was carried out in 1955 by Roedig,[1] where the simplest possible enediyne **2** was prepared by treating the hexa-chlorinated triene **1** with zinc, thought to be a mixture of stereoisomers (**Scheme 1**).



Scheme 1: The first recorded synthesis of an enediyne

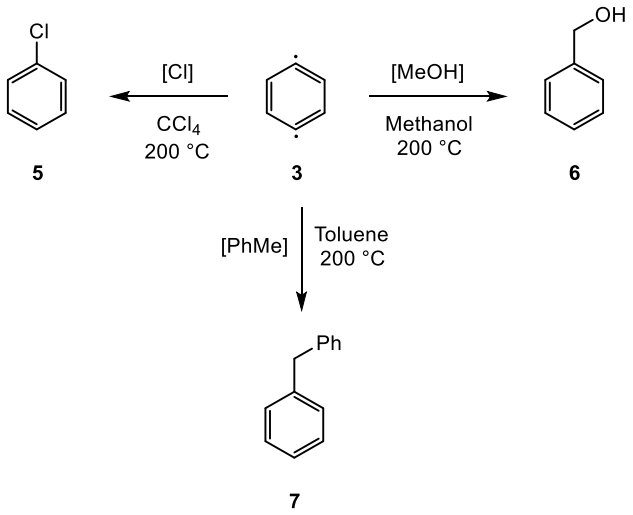
A pivotal event in the distinction of *Z*-enediynes (from here on referred to simply as enediynes) as an independent functional group occurred in 1972, when Jones & Bergman reported on unique rearrangement capabilities (the Bergman cyclisation).[2] Upon heating enediyne **2** to 200 °C in a solution of high-boiling point hydrocarbon (2,6,10,14-tetramethylpentadecane), benzene **4** was obtained as the product (**Scheme 2**). It was proposed that ring closure produces an aromatic biradical species **3**, whose formation is aided by the higher stability provided by aromaticity, but is rapidly quenched by hydrogen atoms from the solvent.



Scheme 2: The formation of an aromatic ring from the Bergman cyclisation, and subsequent quenching of the radical species

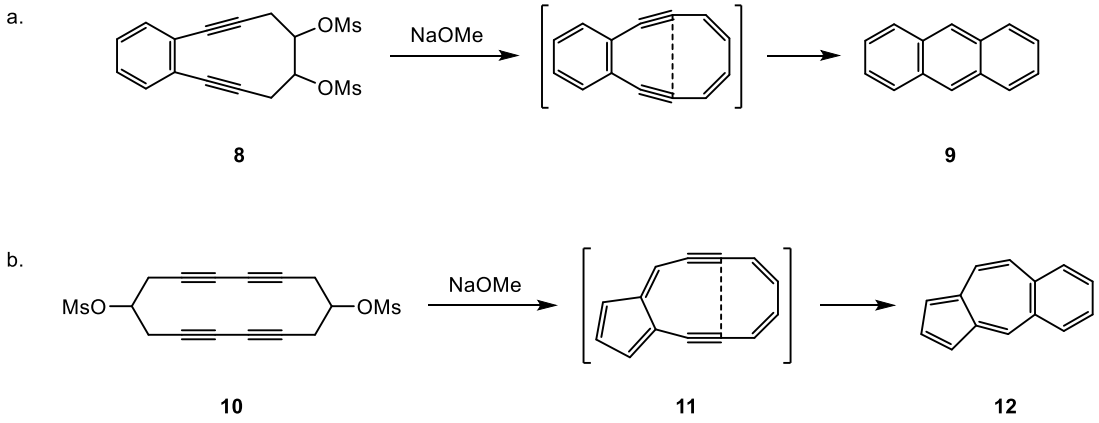
A simple zwitterionic intermediate was also considered as an alternative to the theoretical radical **3**, and to investigate this possibility the hydrocarbon solvent was substituted with carbon tetrachloride, methanol and toluene in turn. Upon yielding chlorobenzene **5**, benzyl alcohol **6** and diphenylmethane **7** respectively, it was however concluded that only radical **3**

could be present (**Scheme 3**), since the extractions associated with these products were unfeasible with an ionic species.



Scheme 3: Different products formed from quenching of the radical species by alternative solvents

Report of an analogous cyclisation was in fact made before Jones & Bergman's work, by Darby *et al.* in 1971.[3] This detailed the rearrangement of a bicyclic enediyne system **8** to form a tricyclic arene **9**, induced by sodium methoxide (**Scheme 4a**). Going back even further to 1966, Mayer & Sondheimer[4] described the transformation of a polyyne system **10** to a tricyclic arene **12** when treated with potassium hydroxide. It is possible that this rearrangement may also have occurred *via* an intermediary enediyne species **11** (**Scheme 4b**).



Scheme 4: Examples of historical Bergman-type cyclisation reactions

Whilst the work of Jones & Bergman[2] came after these examples, their major innovation lay in the suggestion of a biradical species. This factor was later found to be crucial for the enediyne group's main application in a special class of antitumour agents.

1.1.2. Enediyne Antitumour Antibiotics

Despite the Bergman cyclisation's potential for preparing substituted arenes, the availability of alternative routes such as the Negishi,[5] Stille[6] or Suzuki[7] couplings, which proceed without employing such high temperatures, limited research interest until relatively recently.[8] This began to change however in 1985, when the Tokyo based laboratories of the Bristol-Myers company published their discovery of a novel family of natural products. These were isolated from the bacterial strain *Actinomadura verrucosospora*, and named esperamicins after the location of sample collection in Puerto Esperanza, Argentina.[9]

Esperamicins were found to be highly potent against Gram positive bacteria, as well as tumourous tissue (with an IC_{50} *in vitro* of 0.3-8.3 nM and an ID_{50} of 0.1-0.2 µg/kg when tested *in vivo* on murine tumours).[9-10] The complex structure of esperamicin A_1 (**Figure 1**) was fully determined in 1987 by Golik *et al.*,[11-12] at which point it was also first suggested that the anticancer action, was due to biradical formation *via* Bergman cyclisation.

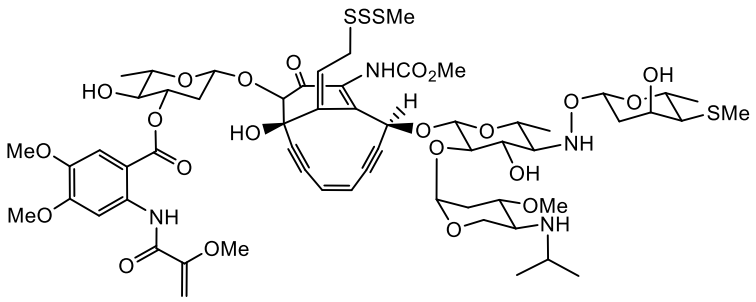


Figure 1: The enediyne based antitumour antibiotic esperamicin A_1

Contemporary with the work on esperamicins in Japan, investigations into a strikingly similar family of antitumour molecules were being carried out in the USA. In that same year of 1987, Lederle laboratories published their findings regarding the antitumour activity of calicheamicins.[13-14]

The full structure of the prominent compound calicheamicin γ_1 (**Figure 2**) was determined in the very same journal issue as the report on esperamicins,[11-12] and here biradical intermediates

were also deemed responsible for the associated antitumour properties. This natural product family was produced by *Micromonospora echinospora*, and named with reference to the chalky (caliche) soils in Texas where the samples were collected. Calicheamicins were found to exhibit antibacterial and antitumour properties comparable to esperamicins (*in vitro* IC_{50} of 6-9 nM and *in vivo* ID_{50} of 0.5-1.5 µg/kg on murine tumours),[15-16] and 4000 times more potent than the common chemotherapy drug doxorubicin.[12-13, 16]

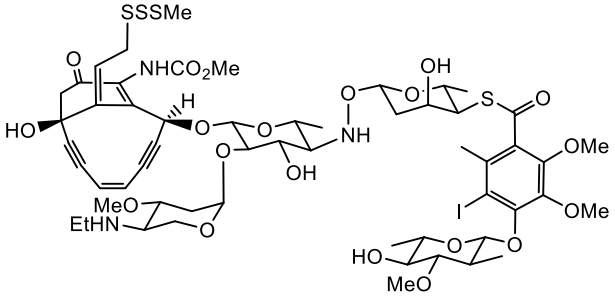
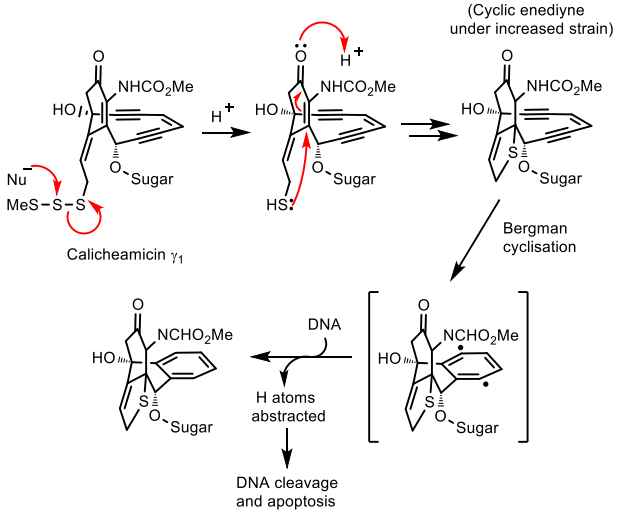


Figure 2: Th enediyne based antitumour antibiotic calicheamicin γ_1

The action of esperamicins and calicheamicins is based on their ability to undergo Bergman cyclisation, yet the high temperatures required for this rearrangement in open chain enediynes (see **Scheme 2**, **page 14**) obviously makes their use *in vivo* unsuitable. Fortunately, in cases where the enediyne is incorporated into a ring structure, cyclisation may occur at temperatures lower than 37 °C. This was significantly demonstrated by Nicolaou *et al.*,[17] with the observation of a simple 10-membered cyclic enediyne rearrangement, with a half-life of 18 hours at 25 °C. This relatively low temperature reactivity is thought to be promoted by the associated ring strain, and is significant in theoretically permitting the enediyne's antitumour action to function at human body temperature.[8, 18-23]

Whilst the complex structures of enediynes such as esperamicin A_1 and calicheamicin γ_1 stabilise the compounds against spontaneous Bergman cyclisation, an appropriate trigger can provide the required strain to initiate a cascade reaction leading to rearrangement. In the case of calicheamicin γ_1, attack by a nucleophile such as cellular glutathione on the allylic trisulfide bond, produces the biradical species.[19, 23] The compound is then capable of abstracting hydrogen atoms from the deoxyribose backbone of DNA strands within a cell, causing devastating cleavage (**Scheme 5**).[17-20, 23-24] This severely reduces the ability of DNA to replicate, subsequently arresting the cell reproduction cycle and inducing apoptosis

(programmed cell death), which if targeted to tumourous cells yields highly effective results.[25-26]



Scheme 5: The mechanism of calicheamicin γ_1 undergoing DNA cleaving action

The enediyne antitumour antibiotic neocarzinostatin, was in fact discovered in 1965 by Ishida *et al.*,[27] much earlier than esperamicins or calicheamicins, when it was isolated from *Streptomyces carzinostaticus*. It was later found in 1980 that neocarzinostatin consists of two components, when extraction with methanol yielded a non-protein chromophore and a residual apoprotein fraction.[28-30]

At this time it was also deduced that the antibacterial and antitumour activities were exclusive to the chromophore component, yet the apoprotein played an important role in stabilising the active enediyne to the point of DNA delivery.[31-32] This is facilitated by the chromophore possessing a much higher affinity for the apoprotein than for DNA strands (K_d = 20 nM for chromophore-apoprotein complex whereas K_d = 33 µM for chromophore-DNA),[33] enabling initiation of destructive cleavage only when suitably triggered by a thiol compound such as 2-mercaptoethanol.[28, 30-31, 33]

In 1985 the structure of the neocarzinostatin chromophore was fully resolved by Edo *et al.*,[34] elucidating the presence of an enediyne group (**Figure 3**). Whilst lower than that of esperamicin A_1 or calicheamicin γ_1, the cytotoxicity exhibited is still substantial (*in vitro* IC_{50} of 225-900 nM and *in vivo* ID_{50} of 380 µg/kg on murine tumours).[35-36]

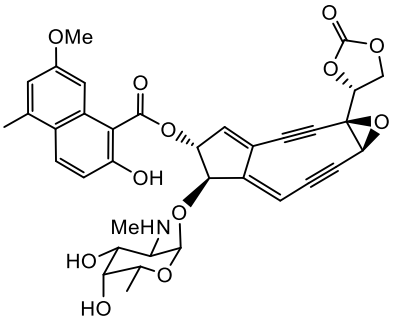
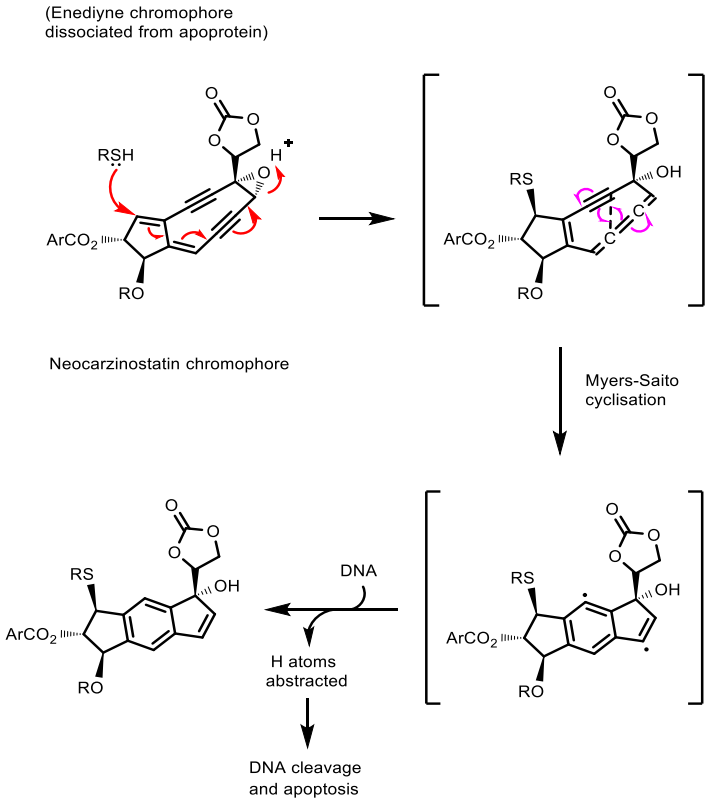


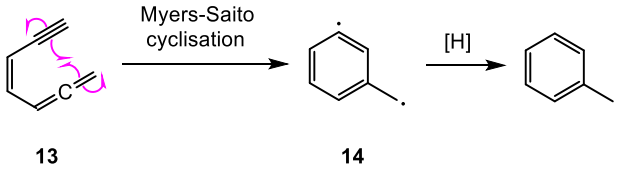
Figure 3: The active enediyne based chromophore section of the antitumour antibiotic neocarzinostatin

This fascinating novel structure was however met with little interest until 1987, when the associated mechanism of DNA cleavage *via* formation of a biradical (**Scheme 6**) was proposed by Myers.[37] This pathway bore a striking similarity to the contemporary reports of scission by esperamicins and calicheamicins, though exhibited a rearrangement subtly different from the classic Bergman cyclisation.



Scheme 6: The mechanism of the neocarzinostatin chromophore undergoing DNA cleaving action

In 1989, independent experiments were carried out concurrently by both Myers *et al.*[38-39] and Nagata *et al.*,[40] successfully mimicking the neocarzinostatin chromophore enediyne cyclisation within non-complex enyne-allenes **13**. This rearrangement yields the aromatic biradical species **14**. The generic reaction was eventually named the Myers-Saito cyclisation (**Scheme 7**), and unlike the Bergman cyclisation, this rearrangement often occurs easily at or below room temperature.[41]



Scheme 7: The formation of an aromatic ring from Myers-Saito cyclisation and subsequent quenching of the radical species formed

1.1.3. Subclasses of Enediyne Antitumour Agents

Broadly speaking, enediyne antitumour agents can be placed in one of three categories: neocarzinostatin, calicheamicin or dynemicin-type structures.[19, 26] These three subclasses function in notably different ways and possess unique characteristics.

Neocarzinostatin-types incorporate a 9-membered cyclic enediyne, and naturally occur as a chromophore non-covalently bound to an apoprotein co-factor. The non-protein component holds the enediyne group and associated antitumour properties,[19, 26, 42] whereas the apoprotein plays an invaluable role in stabilising and protecting the chromophore. Outside of the protein complex the chromophore is found to be unstable.[43] One exception to this generalisation is N1999A2 (**Figure 4**), which was isolated from *Streptomyces sp.* AJ9493 in 1998 by Ando *et al.*,[44] and found to be moderately stable at 37 °C in the absence of any co-factor.[45]

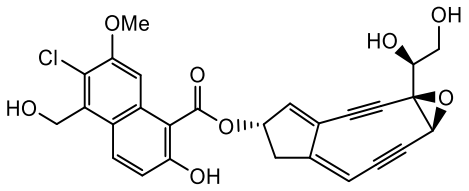


Figure 4: The antitumour antibiotic N1999A2 is unusual among neocarzinostatin-types as it does not require an apoprotein co-factor to remain stable

It was previously concluded by Zein *et al.*[46-47] that the apoproteins could selectively cleave histone H1 (a protein responsible for providing a stable scaffold for DNA),[48] enhancing the

DNA targeting capability of the drug complex. Further investigations however, demonstrated that the proteolytic activities that had been observed were false-positives, and due to minor protease contaminants rather than the apoproteins themselves.[49-50]

Neocarzinostatin-type antitumour agents share a common 12-membered bicyclic system, in which attack on the smaller ring starts a chemical cascade leading to Myers-Saito cyclisation, providing the DNA cleaving biradical species (see example mechanism of neocarzinostatin chromophore in **Scheme 6**, **page 19**).[19, 26] The relatively low temperatures at which this rearrangement occurs compared to Bergman cyclisation, aids explanation of why the chromophore components generally require stabilisation from the apoproteins. In addition to neocarzinostatin and N1999A2, significant examples of this subclass and their producing strains include: kedarcidin (**Figure 5a**) from *Actinomycete* L585-6,[51-54] lidamycin (**Figure 5b**) from *Streptomyces globisporus* C-1027[55-58] and maduropeptin (**Figure 5c**) from *Actinomadura madurea*.[42, 59]

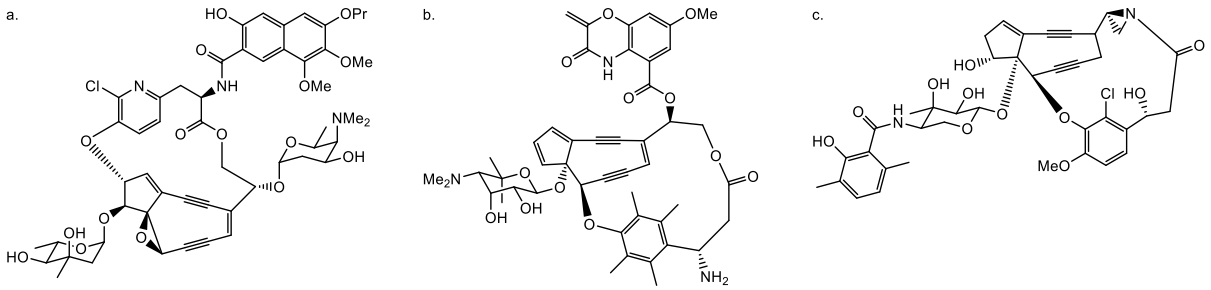


Figure 5: The neocarzinostatin-type antitumour antibiotics a. kedarcidin, b. lidamycin and c. maduropeptin

Calicheamicin and dynemicin-types differ from the neocarzinostatin kind by possession of a 10-membered cyclic enediyne, which provides a substantially higher stability and negates the requirement of co-factors.[19, 26] Within calicheamicin-type structures, the iconic cyclic enediyne is generally attached to an oligosaccharide chain and a trisulfide group. The appended trisulfide functions as the trigger to initiate a cascade reaction. This contorts the molecule, providing sufficient ring strain for formation of the DNA cleaving biradical species at relatively low temperatures.[17, 23] Apart from calicheamicin γ_1 and esperamicin A_1, prominent examples of this subclass include: namenamicin from *Polysyncraton lithostrotum*[60] and much more recently Shishijimicin A-C from *Didemnum proliferum*.[61]

Dynemicin-types differ from the calicheamicin variety by their lack of oligosaccharide and trisulfide components, with the cyclic enediynes instead attached to a relatively simple anthraquinone chromophore (characteristic of anthracycline drugs such as doxorubicin).[18, 23] The first member of this subclass to be discovered was dynemicin A (**Figure 6**), isolated in 1989 from samples of *Micromonospora chersina* collected in the Gujarat state, India, by Bristol-Myers laboratories.[62-63] The chromophore core gives this compound a violet colour,[62-63] and the drug demonstrates high antibacterial and antitumour efficiency (*in vitro* IC_{50} of 0.9-10 nM and *in vivo* ID_{50} of 30-60 µg/kg on murine tumours).[62, 64]

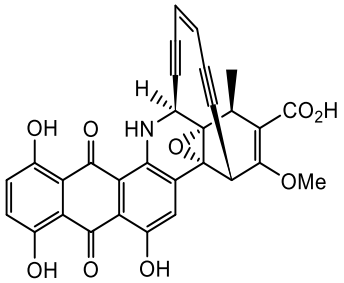
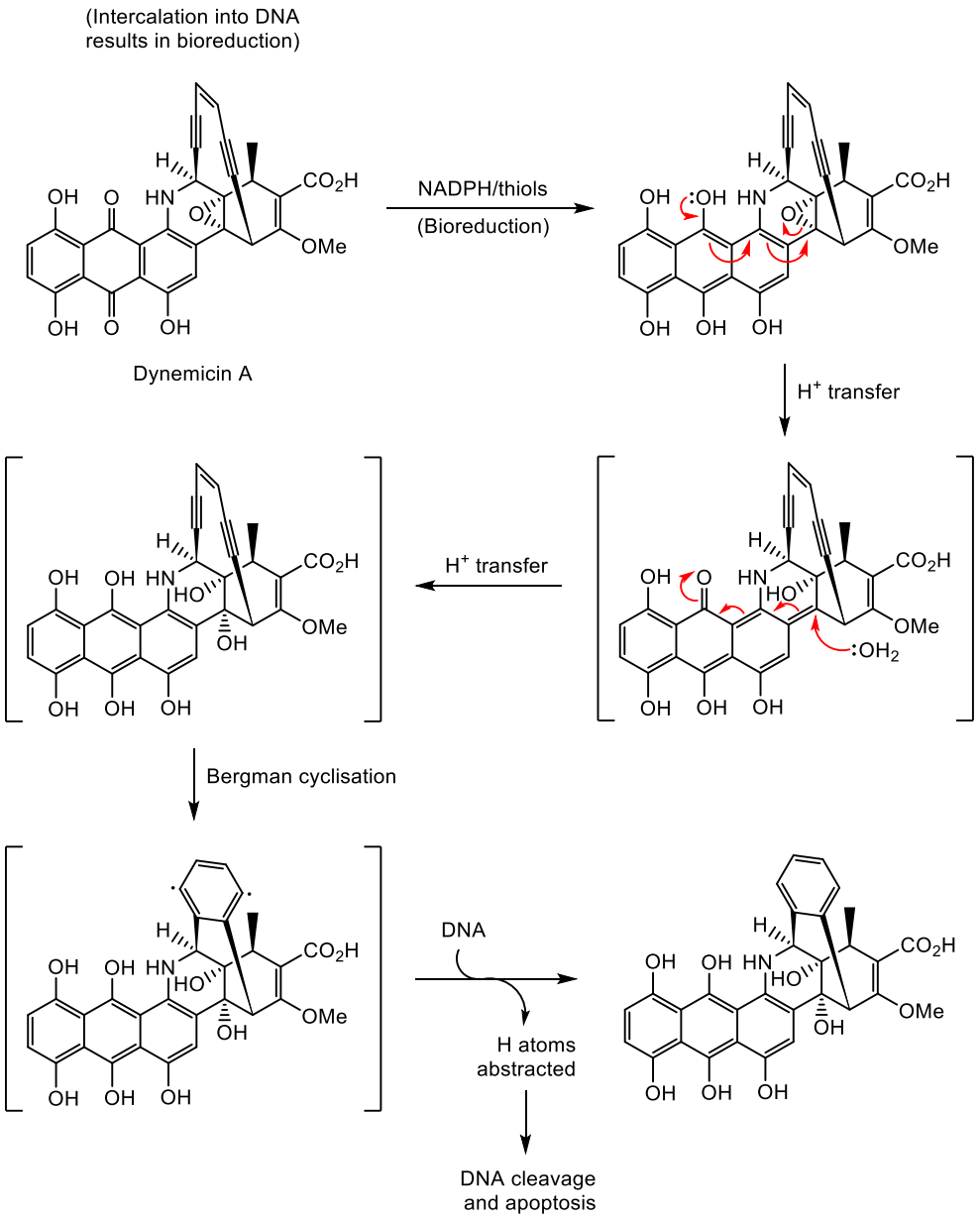


Figure 6: The enediyne based antitumour antibiotic dynemicin A

When incorporated into a 10-membered ring, enediynes will rearrange *via* the Bergman, rather than Myers-Saito cyclisation. The high activation energy in the absence of additional priming, likely contributes to the greater stability of these compounds. The mechanism by which biradicals form is similar among different compounds of dynemicin-type, but significantly different to those of the calicheamicin subclass (see example mechanism of calicheamicin γ_1 in **Scheme 5**, **page 18**).

Notably, it is proposed that the chemical cascade for these compounds is initiated by bioreduction of the quinone with NADPH or thiols, rather than nucleophilic attack (**Scheme 8**).[17, 65-67] Apart from the prominent dynemicin A, other members of the subclass include: deoxydynemicin A from the related strain *Micromonospora globose*,[68-69] and more recently uncialamycin from *Cladonia uncialis*.[70]



Scheme 8: The mechanism of dynemicin A chromophore undergoing DNA cleaving action

1.1.4. Common Features of Enediyne Antitumour Agents

Despite the variations detailed in **section 1.1.3**, enediyne antitumour agents throughout all subclasses feature three key structural and functional components. Somewhat reminiscent of a conventional missile, these consist of: 1. a "delivery system" which ensures the drug reaches its target; 2. a "triggering device" to activate biradical formation at the appropriate time; 3. An enediyne "warhead" responsible for the actual DNA cleavage.[19, 22-23, 25-26]

Specific sections of each drug's extended molecular structure give rise to the delivery systems, as they selectively bind into minor grooves within the DNA double helix. For calicheamicin-types, the oligosaccharide chains (**Figure 7a**) provide this function,[71-74] substantially reorganising their conformation to do so.[75] For the neocarzinostatin counterparts, the appended naphthoate derivatives (**Figure 7b**) act as the recognition elements,[20, 45] whereas in the dynemicin subclass, the anthraquinone core (**Figure 7c**) does this.[76-77] For all three subclasses there is a degree to which the DNA itself rearranges during intercalation, demonstrating an "induced fit" process.[78-82]

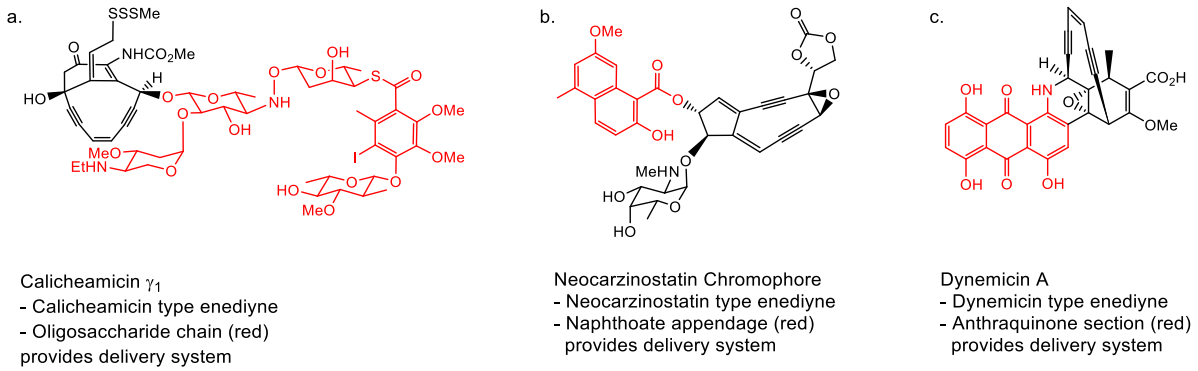


Figure 7: The structural features of enediyne antitumour agents contributing to DNA targeting (highlighted in red)

A drawback common to many chemotherapy agents is a lack of cell selectivity, whereby the drug's cytotoxicity negatively effects healthy cells in addition to tumours.[83-84] In this regard, enediyne based treatments are no exception.[26, 85] Fortunately, better targeted therapies making use of conjugated antibodies or other ligands, which recognise markers and receptors specific to cancerous cells, are under development and have already shown some clinical potential.[86-91] This ingenious biotechnology may be applied to enediyne antitumour agents in the future, which would significantly improve the efficacy of their drug delivery systems as a whole.

Once an enediyne antitumour agent has reached the vicinity of DNA, the molecular trigger within the drug is activated by a localised reagent within the cell nucleus. As briefly detailed in **sections 1.1.2** and **1.1.3**, the nature of the triggering device is unique to each of the three subclasses.

With the calicheamicin subclass, this trigger consists of a trisulfide moiety which undergoes nucleophilic attack, usually by a thiol such as dithiothreitol, glutathione or cysteine, leading to Bergman cyclisation (see **Scheme 5**, **page 18**).[25, 92-94] The neocarzinostatin variety functions in

a similar way, but instead initiates Myers-Saito cyclisation. In this pathway, the drug undergoes addition of a sulfurous nucleophile to the conjugated alkene component, *via* epoxide ring opening (see **Scheme 6**, **page 19**).[24, 95-96] Triggering of dynemicin-types contains elements from both of the previous two mechanisms. In this distinct route, bioreduction of the anthraquinone ketone by NADPH or even a thiol, results in Bergman cyclisation occurring, though it is mediated *via* epoxide ring opening (see **Scheme 8**, **page 23**).[65-67]

An additional layer of complexity is associated with the triggering of neocarzinostatin-type enediynes. As outlined in **section 1.1.3**, the active drug chromophores (with the exception of N1999A2) generally possess an apoprotein co-factor to aid stability *in vivo*, during travel to their DNA targets.[26] In the case of neocarzinostatin for example, binding with this co-factor forces the epoxide of the chromophore into a hydrophobic "pocket", which inhibits ring opening (see **Scheme 6**, **page 19**) and therefore prevents biradical formation.[97] Upon reaching the DNA target therefore, the chromophore must first undergo controlled release from its associated apoprotein, before opening the way for cyclisation to be triggered.[98]

Whilst it is not completely understood whether the enediynes must be intercalated to DNA before biradical formation is triggered, it is clear that the drug must first be in close proximity. Since triggering agents such as thiols or NADPH are present throughout the cell, it is apparent that conditions specific to the environment immediately surrounding DNA are required for activation of the enediyne warhead.[17, 82] It is possible that the reorganisation of drug molecules which occurs in close contact with the DNA primes them for attack by a co-factor.

The ease with which an enediyne undergoes cyclisation is primarily determined by: 1. the intramolecular distance between the carbons undergoing bonding (*cd* distance); 2. the effect of acetylenic substituents; 3. the relative strain between the starting material's ground and transition states.[99-100]

The effect of *cd* distance (**Figure 8**) was first proposed in 1988 by Nicolaou *et al.*,[101] with relation to enediyne warheads. They proposed that distances below 3.20 Å would result in spontaneous cyclisation, whereas those above 3.31 Å would provide stability at room temperature. Once triggered, rearrangement of enediyne drug molecules contorts the warhead to the extent that distances between *c* and *d* carbons is short enough to permit facile covalent interaction.

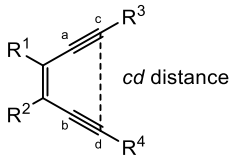
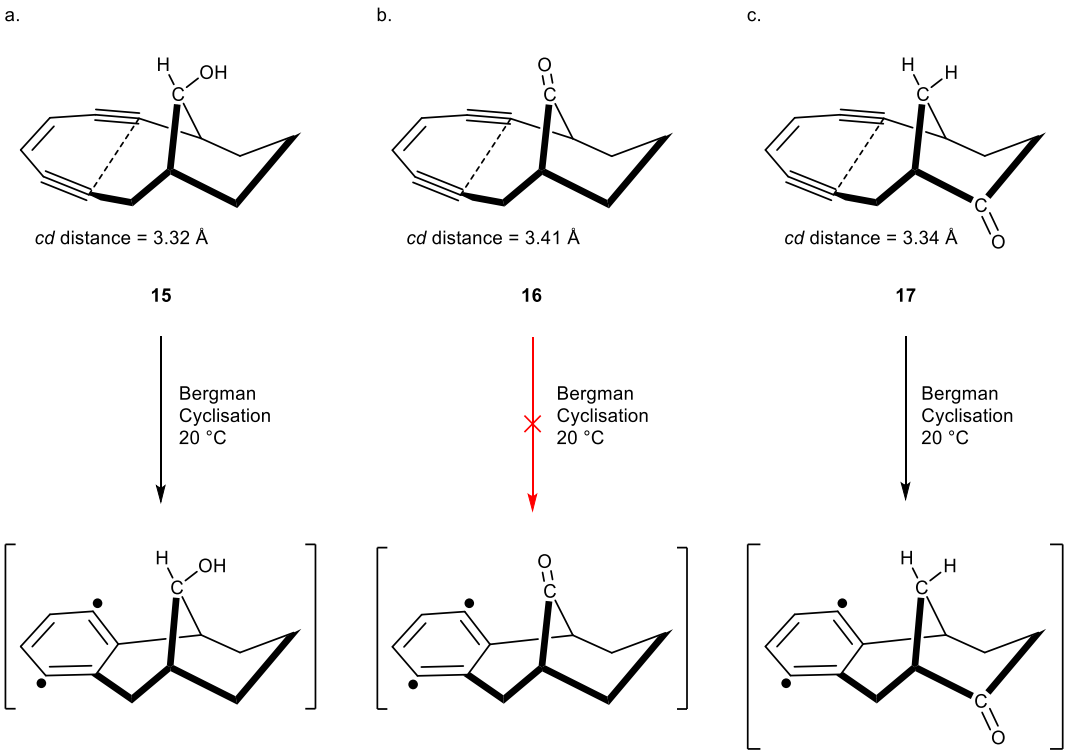


Figure 8: The intramolecular distance between the *c* and *d* carbons of an enediyne group (the *cd* distance)

This helps to explain why 10-membered cyclic enediynes (comprising both calicheamicin and dynemicin-types) remain moderately stable at 37 °C for several hours, as they possess *cd* distances in the order of 3.25 Å. Conversely, their 9-membered counterparts (neocarzinostatin-types) with distances closer to 2.84 Å, require a cofactor to survive *in vivo*.[17, 101]

Normally, the nature of the enediyne's acetylenic substituents are themselves noted to have a substantial effect on the ease at which cyclisation occurs. In the case of antitumour agents however, these substrates are effectively incorporated into the warhead ring structure. Their influence is therefore not generally considered separately, but is instead factored into that of the *cd* distance.

Whist theories of the effect of *cd* distances enables a good preliminary assessment of enediyne cyclisation propensity, the influence of relative strain between ground and transition states has been found to be of greater significance. Work by both Snyder *et al.*,[102] Magnus *et al.*[103-104] and Carter *et al.*,[105] investigated many cases of cyclic enediyne systems with similar internuclear distances, which nevertheless greatly differed in their relative strains. A striking example is the comparison of cyclic enediynes **15** and **16**, with *cd* distances of 3.32 Å and 3.41 Å respectively (**Scheme 9**).[102] Despite this meagre variation, and both compounds being above the threshold for cyclisation proposed by Nicolaou *et al.*,[101] alcohol bridged enediyne **15** rearranges easily at 20 °C, whilst carbonyl bridged enediyne **16** remains stable.



Scheme 9: The effect of transition state ring strain on the feasibility of Bergman cyclisation

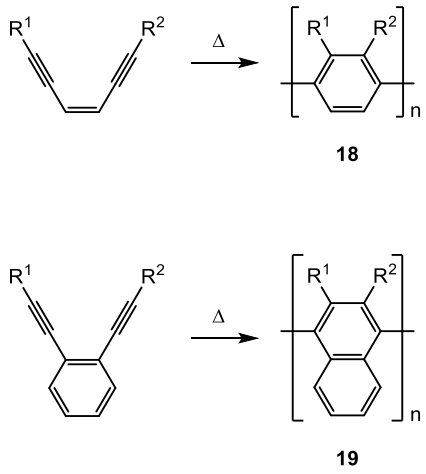
It appears that the presence of a carbonyl puts a strain on the transitionary biradical formed from enediyne **16**, which is so large that Bergman cyclisation is prohibited at 20 °C (**Scheme 9b**). Meanwhile, the stability offered by an aromatic and triple 6-membered ring system, appears to be sufficient to overcome the strain of the 10-membered ring ground state from the alcohol bridged enediyne **15** (**Scheme 9a**). Furthermore, relocation of the carbonyl away from the bridging carbon of enediyne **16**, permits cyclisation of the structural isomer **17** (**Scheme 9c**). This becomes feasible since the transition state does not suffer from the same strain as that of carbonyl bridged enediyne **16**, imposed by the rigidity of an aromatic ring incorporated into the bridged bicyclic species.

In summary, for enediyne warhead systems in which the ground states are significantly more strained than their respective transitionary biradicals, cyclisation quickly occurs to relieve the tension once the trigger is activated.[23, 25, 106] Within each enediyne subclass the basic mode of DNA cleavage is the same, with the main differences being potency, the precise sequence within the helix where scission occurs, and whether attack is single or double stranded.

1.1.5. Further Applications of Enediynes

Much of the literature surrounding enediynes has focused on their antitumour and antibacterial capabilities. Whilst this general application is arguably the most important and interesting one, examples of other uses such as in polymer manufacture, functionalisation of fullerenes and porphyrinoid chemistry, have all been reported.

During investigations into the Bergman cyclisation, a curiously low yield of arene product, compared to the amounts expected based on starting material quantities, has often been noted.[100] It was found that significant amounts of radical homopolymerisation were responsible, and in 1994 John & Tour[107] endeavoured to harness this reactivity for polymer synthesis. A series of polyphenylenes **18** and polynaphthalenes **19** were prepared, encapsulating various functional groups (**Scheme 10**). These possessed excellent thermal and chemical resistance, as well as potential semi-conductor properties when appropriately doped.

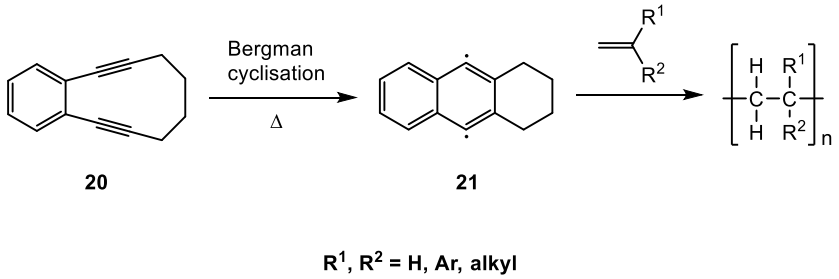


Scheme 10: Chain growth polymerisation to form polyphenylenes and polynaphthalenes by employing the Bergman cyclisation

This approach to homopolymers presented several advantages, such as obviating the need for a catalyst or another initiator reagent, moderately simple starting material preparation, and good scope for functionalisation *via* substitution of the enediyne.[100] These factors improve the overall processability and tuning capabilities of the polymer products. Photoinitiation as an alternative to thermally triggered polymerisation was also explored using vanadium based catalysts,[108] thereby expanding the diversity of suitable starting materials.

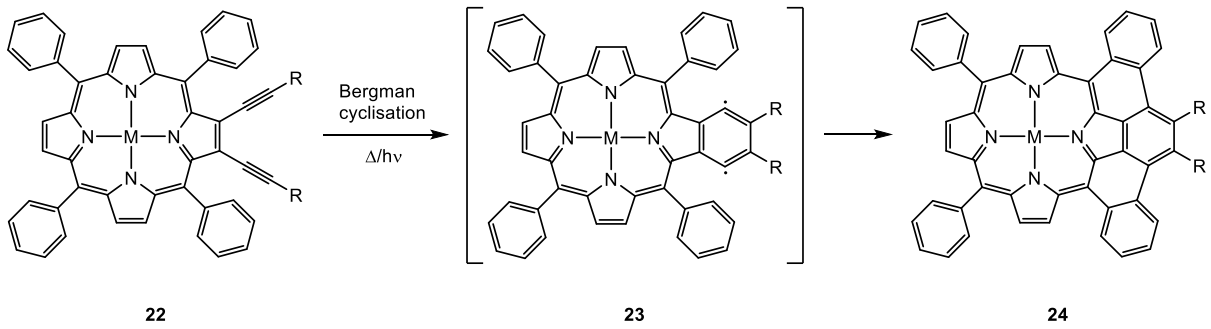
In the field of polymer chemistry, enediynes have also found applicability as initiators, making use of their controlled formation of biradicals. Polymerisation induced by radical initiators can often suffer from the occurrence of two radical centres of a growing chain meeting and undergoing intramolecular termination. This results in a considerable proportion of oligomers and reduces the material's quality.[100]

To combat this, Rule *et al.*[109-110] experimented with 1,4-biradical initiators **21** produced by 10-membered cyclic enediynes **20** (**Scheme 11**). The possession of two radical centres improved the potential for sustaining extensive chain growth. Higher polymer yields were indeed generally obtained compared to control experiments, especially when hydrogen of the starting material was substituted, presumably resulting in intramolecular termination being sterically hindered.



Scheme 11: Employment of the Bergman cyclisation as a radical initiator

The highly reactive biradicals produced by Bergman cyclisation have also been employed in the functionalisation of fullerenes, such as multi-layer fullerenes (carbon nano-onions)[111] and buckminsterfullerenes (buckyballs).[112] This develops their prospects for application in photoelectrochemical cells. Furthermore, enediyne reactivity may be harnessed in the expansion of conjugated π-networks within porphyrinoids **22**, by incorporating the moiety into the porphyrin core.[113] In the absence of highly concentrated quenching agents, the porphyrinoid biradical **23** formed upon thermal or photochemical triggering will enact intramolecular bonding, producing an extended porphyrinoid network **24**, and increasing overall conjugation (**Scheme 12**).



Scheme 12: Employment of the Bergman cyclisation in expansion of porphyrinoid conjugated π-networks

Porphyrinoid building blocks have found use in various technologies such as antitumour photodynamic therapy,[114] optoelectronic devices[115] and photovoltaic materials.[116] Since application in these areas is heavily dependent on highly conjugated constructions, the ability to expand the π-system in this way is of great importance.

1.1.6. Syntheses of Enediynes

An early success story of antitumour enediyne total synthesis, was that of calicheamicin γ_1, where the oligosaccharide substrate was prepared in 1990 by Nicolaou *et al.*,[117] and the warhead containing fragment in 1992 by Smith *et al.*.[118] The two sections were finally combined to produce the complete drug in 1993 by Nicolaou *et al.*.[119]

In keeping with its later discovery date, dynemicin A was artificially prepared by Shair *et al.*[120] in 1995. The total synthesis of 9-membered cyclic enediyne chromophores proved much more cumbersome, largely due to their facile degradation in the absence of stabilising apoproteins.[121] Extremely careful use of protecting groups and environmental controls finally yielded results for Myers *et al.*,[122] who successfully prepared the neocarzinostatin chromophore in 1998.

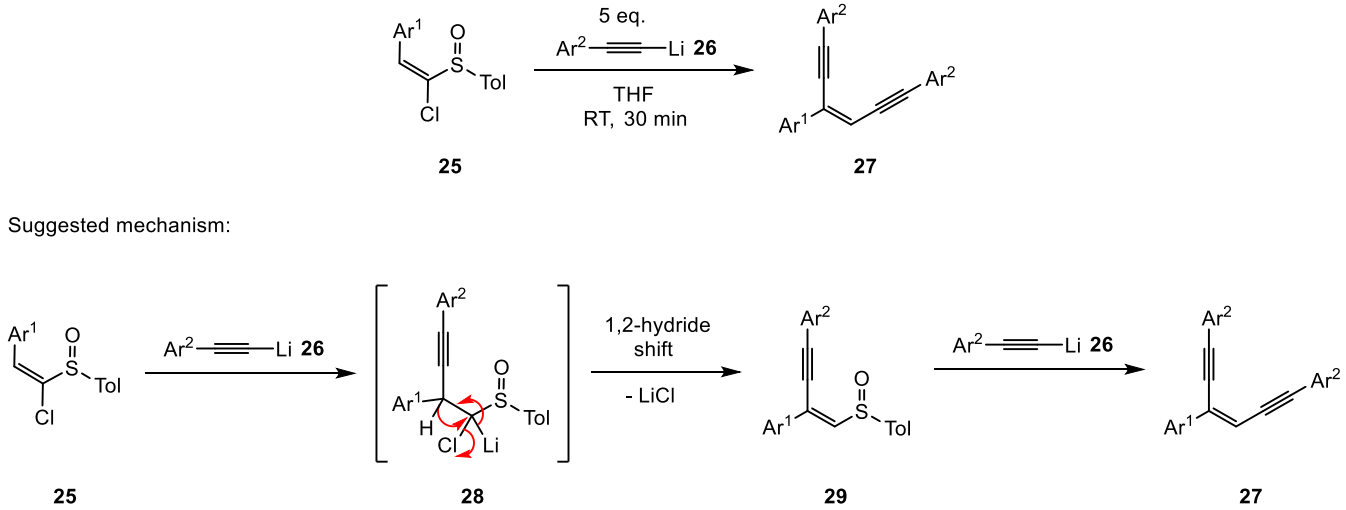
Neocarzinostatin was the first enediyne antitumour agent to find clinical use. When trialled as a sole treatment, it effected full and partial remission in some cases of leukaemia, as well as gastric, pancreatic, lung, liver and other blood cancers.[123-127] Its efficacy was substantially enhanced by administration in conjunction with surgery[128] and other chemotherapy drugs.[129]

Allergic reactions and toxicity to bone marrow were found to be serious side effects,[19] and to combat this neocarzinostatin was coupled with a styrene maleic acid polymer.[130] The resultant styrene maleic acid neocarzinostatin (SMANCS) complex counteracted these negative

responses, and had the additional benefit of improving tumour permeability and retention. SMANCS was officially approved as a drug for commercial use by the Japanese government in 1993,[131] making it the first of its kind.

Various preparations of the enediyne functional group itself using metal catalysis have been developed, generally possessing good stereoselectivity, and affording moderate to high yields at ambient temperatures, without the need for strong acid or base. Aided by palladium and copper catalysts, crosslinking of alkenyl stannanes with bromoalkynes was carried out by Wang & Wang[132] in 1994, and that of 1,2-diiodoalkenes and alkynyl stannanes by Ryan & Stang[133] in 1996. In 2000, palladium catalysts were also employed by Dabdoub *et al.*,[134] sequentially coupling alkenyl tellurium species with alkynyl zinc compounds.

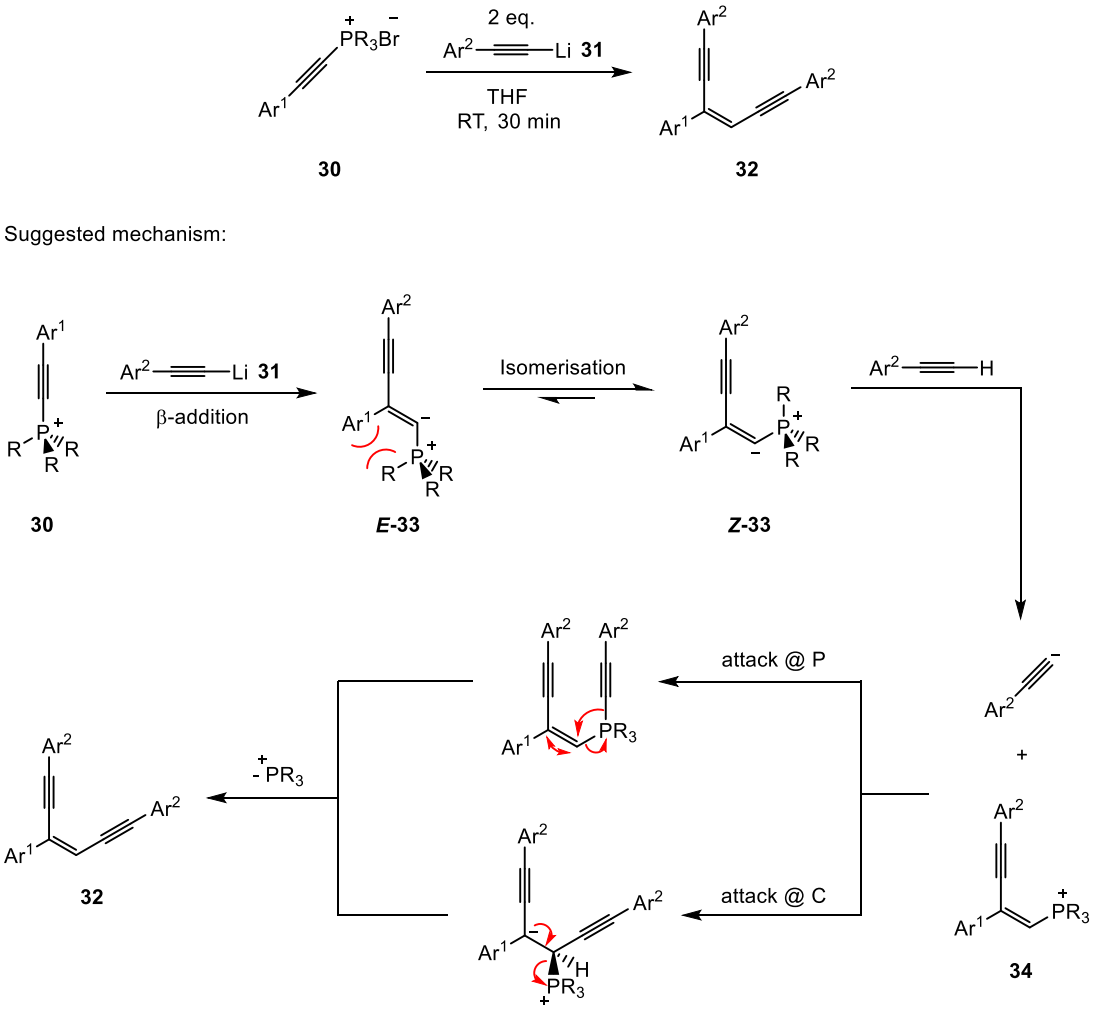
A highly stereoselective route to triaryl *Z*-enediynes **27** in low to moderate yield (19-75%), free from metal catalysis, was reported by Kimura *et al.*[135] in 2013. In this work, arylchlorovinyl sulfoxides **25** underwent sequential alkynylation by a lithiated arylacetylene derivative **26** (**Scheme 13**). An interesting mechanism was proposed, where conjugate addition of the first acetylide **26** occurs producing intermediary species **28**, immediately followed by a 1,2-hydride shift to yield sulfinyl alkene **29**. The exact mechanistic nature of the successive acetylide **26** addition that gave enediyne **27** was however, not fully understood.



Scheme 13: Synthesis of the enediyne functional group by sequential alkynylation of arylchlorovinyl sulfoxides

In 2014, another metal free stereoselective synthesis of enediynes **32** in moderate to good yield (37-75%) was described by Reichl & Radosevich,[136] obtained by treatment of alkynyl

phosphonium salts **30** with acetylide **31** (**Scheme 14**). A mechanism rather different from Satoh's work (see **Scheme 13**, **page 31**) was suggested however, initiated by a Michael-type addition on the alkynyl β-carbon to produce destabilised intermediate ***E*-33**. This itself isomerises to the *Z*-isomer (***Z*-33**) in order to reduce steric clashing. The alkynylated intermediate ***Z*-33** then undergoes proton transfer and successive alkynylation to produce an enediyne **32**, *via* attack on either the carbon ("attack @ C") or phosphorus ("attack @ P") atoms.



Scheme 14: Synthesis of the enediyne functional group by sequential alkynylation of alkynyl phosphonium salts

Curiously, no quenched form of the alkynylated intermediate **33** (**34**) was reported to have been isolated, but a small amount of 1,4-diphenylbutadiyne was obtained from this reaction, presumed to have resulted from a degree of initial α-addition.

1.2. Synthesis of Diynes

1.2.1. Applications of Diynes

The 1,3-diyne (from here on referred to simply as diyne) moiety is found in various natural products of which a total synthesis has been achieved,[137] such as the dietary supplement panaxytriol,[138] and the plant toxin cicutoxin, found in water hemlock.[139] It is also found in many significant pharmaceutical compounds and intermediates, isolated from plants, animals and fungi. Examples include *anti*-MRSA drug falcarindiol (**Figure 9a**) from wildflower *Angelica dahurica,*[140] antitumour agent repandiol (**Figure 9b**) from mushroom *Hydnum repandum,*[141] and HIV inhibitor diplyne E (**Figure 9c**) from sponge *Diplastrella* sp..[142]

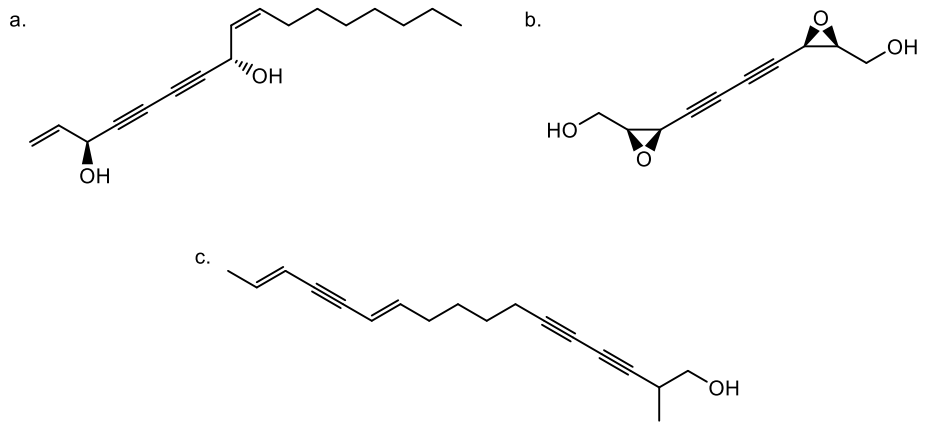
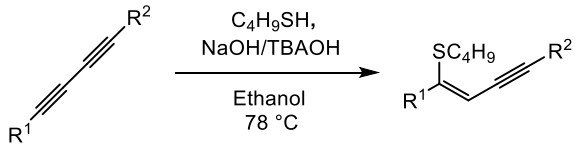


Figure 9: Pharmaceutically important diyne containing compounds a. falcarindiol b. repandiol and c. diplyne E

Due to their extensive conjugation, aromatic diynes tend to exhibit good thermal and moisture stability, and may be stored at ambient conditions for extended periods without degradation.[143] Despite their high stability, they exhibit useful reactivity when slightly harsher conditions are employed. For instance, with elevated temperatures and the use of a strong base, conjugate-addition to the alkyne subunit is possible. A notable example is the work of Santana *et al.*,[144] which employed butanethiol for nucleophilic attack on a range of diynes **35** (**Scheme 15**). This provided a stereo and regio selective route to alkenyl sulfides **36** in moderate to excellent yields (52-95%).



35 **36**

R^1, R^2 = H, Ar, alkyl

Scheme 15: Employing high temperature and a strong base to affect nucleophilic addition of butanethiol to diynes

Conversely, analogous syntheses with monoalkyne starting materials tend to suffer from selectivity issues.[145-148] The alkenyl sulfide motif is found in various molecules with important biological activity, such as the streptogramin antibiotic griseoviridin (**Figure 10a**),[149-150] and the yellow pigment benzylthiocrellidone (**Figure 10b**).[151]

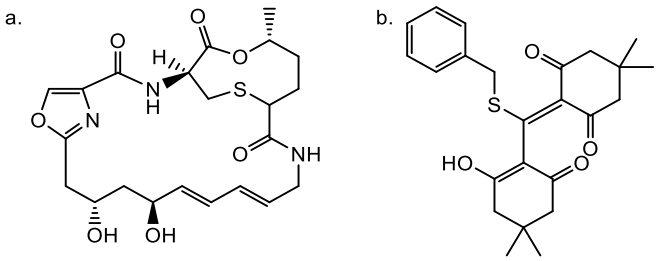
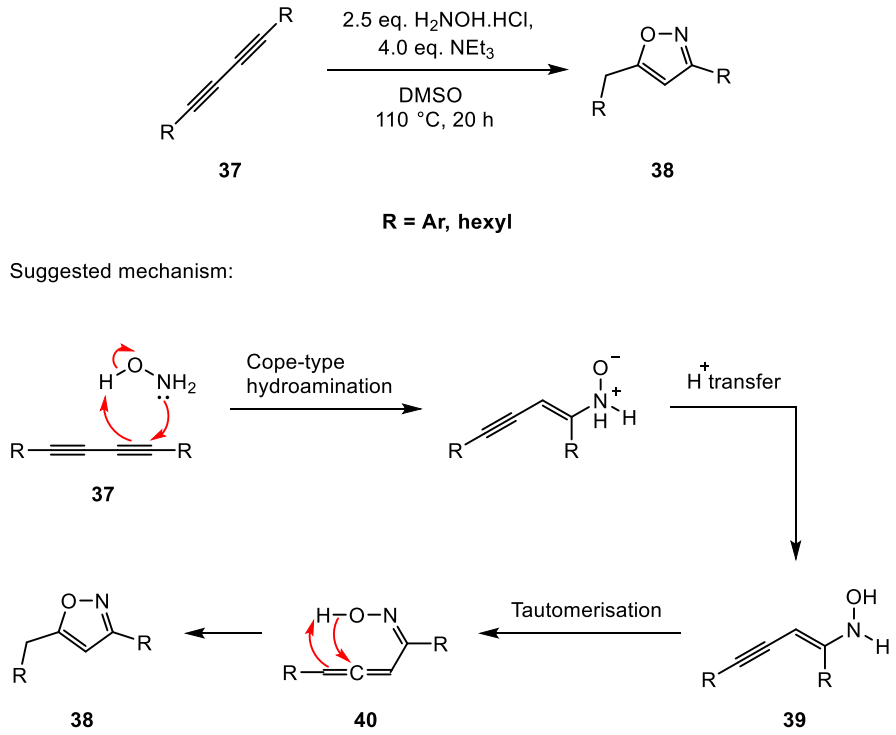


Figure 10: Biologically active alkenyl sulfide containing compounds a. griseoviridin and b. benzylthiocredllidone

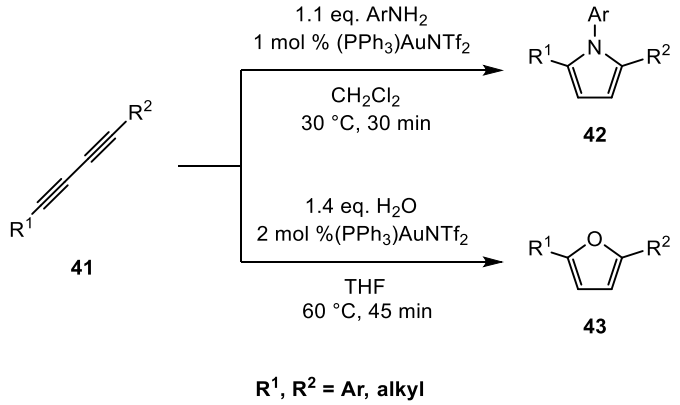
Further examples of diyne based reactions were reported by Wang *et al.*,[152] where a high yielding (66-98%) novel preparation of 3,5-disubstituted isoxazoles **38** was carried out, using diynes **37** and hydroxylamine hydrochloride (**Scheme 16**). This synthesis was thought to proceed *via* a Cope-type hydroamination producing a hydroaminated intermediate **39**, followed by tautomerisation to the imine **40**, and finally cyclisation.



Scheme 16: Cope-type hydroamination of diynes to form 3,5-disubstituted isoxazoles

Isoxazoles **38** are important intermediates in the total syntheses of isoquinoline and indole alkaloids (such as derivatives of the anti-protozoal agent emetine, and the veterinary reverse sedation drug Yohimbine respectfully),[153-155] as well as cobyric acid (a component of vitamin B_{12}).[156]

Diyne reactivity has also been harnessed using transition metal catalysts, such as copper,[157] palladium,[158] iron,[159] and silver[160] based ones. A particularly interesting example by Kramer *et al.*,[161] employed a gold catalyst to enact a double hydroamination/hydration of diynes **41** (**Scheme 17**). These transformations yielded substituted pyrroles **42** (90-96%) and furans **43** (51-82%) respectively.



Scheme 17: Synthesis of substituted pyrroles/furans from gold catalysed double hydroamination/hydration of diynes

The highly conjugated nature of diynes also lends excellent potential for their use as components in the assembly of linear π-conjugated oligomers, for application in molecular scale electronic devices.[162-163] Potential application of such oligomers as molecular wires, switches or other multi-nanometre dimensioned circuitry, could aid ongoing efforts to miniaturise traditional silicon-based electronics.[164] Some success has already been observed by groups such as that of Wen *et al.*,[165] who employed 1,4-butadiyne in bridging ruthenium(II) centres.

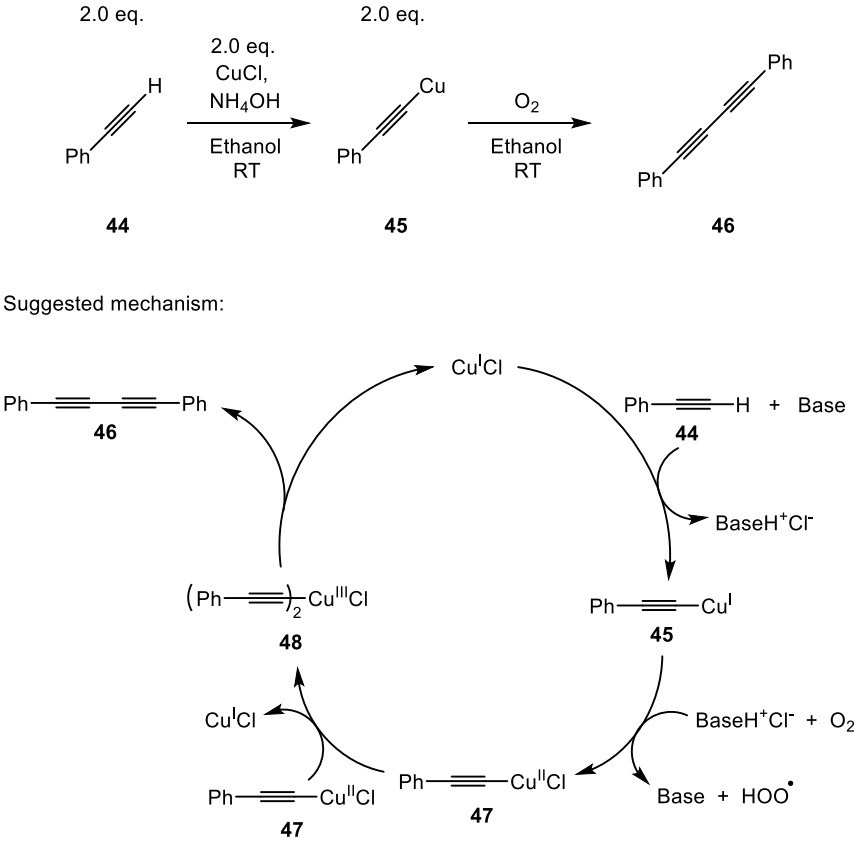
Additionally, diyne functionalised fullerenes have the remarkable ability to self-assemble into thin films *via* solid-state polymerisation, when subjected to sufficient heat, pressure or irradiation. This chemistry can be used to create nanoscale fullerene scaffolds by groups such as those of Wang *et al.*[166] and Tisserant *et al.*,[167] who exploited to serve as organic semi-conductors in solar cells.

1.2.2. Traditional Transition Metal Based Routes to Diynes

The diyne functional group has been studied for almost a hundred years longer than that of the enediyne, and has historically had broader application. It is unsurprising therefore, that a much wider variety of synthetic approaches have been developed. Normally, diynes are classified according to whether their substituents are symmetrical or unsymmetrical, the latter tending to be more challenging to prepare.[168] Syntheses of both types were originally facilitated by transition metal catalysts.

The first recorded preparation of a diyne was that of 1,4-diphenylbuta-1,3-diyne (**46**), by Glaser[169-170] in 1869. The synthesis ensued by first preparing (phenylethynyl)copper (**45**) from

phenylacetylene **44**, using stoichiometric amounts of copper(I) chloride (**Scheme 18**). Soon after in 1882, the reaction was exploited by Baeyer[171] for the synthesis of the industrially important dye indigo.

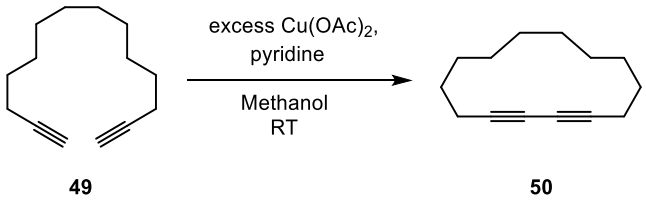


Scheme 18: The original Glaser-type coupling of alkynes to form diynes

It is proposed that the coupling is initiated by deprotonation of phenylacetylene **44** and reaction with copper(I) chloride to give alkynyl copper **45**, with ammonium hydroxide acting as the base. Exposure to atmospheric oxygen causes conversion to the oxidised copper species **47**, which experiences further oxidative addition by another molecule of itself **47**. Finally, dialkynylated copper **48** undergoes reductive elimination to yield the diyne product **46**, and regenerate the copper(I) catalyst. It has also been thought possible that the homocoupling of alkynyl copper **47** occurs *via* alkynyl radicals.[172]

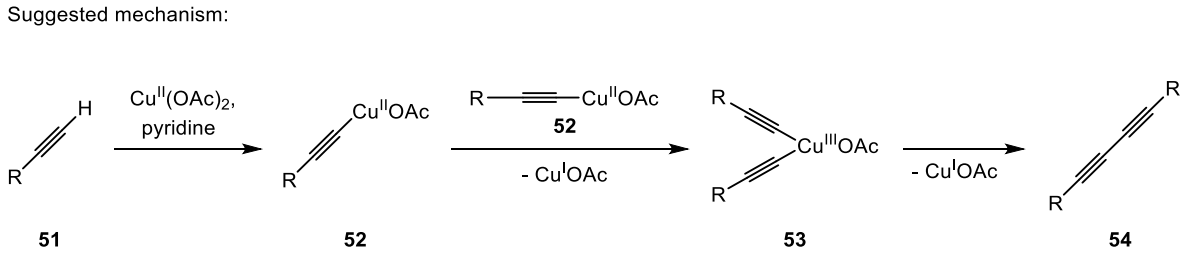
Glaser's work was refined by Eglinton & Galbraith[173] in 1956, where tetradeca-1,13-diyne **49** was treated with excess copper(II) acetate in the presence of pyridine, undergoing intramolecular coupling to give a cyclised diyne **50** (**Scheme 19**). Shortly thereafter, this

chemistry was used by Sondheimer *et al.*,[174-177] for pioneering work in the synthesis of a range of annulenes.



Scheme 19: Eglinton & Galbraith's development of diyne formation, allowing generation of the alkynyl copper species *in situ*

Under these generic conditions, it is thought that pyridine deprotonates the acetylenic starting material **51**, thereby forming the reactive alkynyl copper species **52** *in situ* (**Scheme 20**). Oxidative addition of another molecule of alkynyl copper **52**, followed by reductive elimination from the dialkynylated copper species **53** formed, generates the symmetrical diyne **54** as well as a copper(I) acetate by-product.

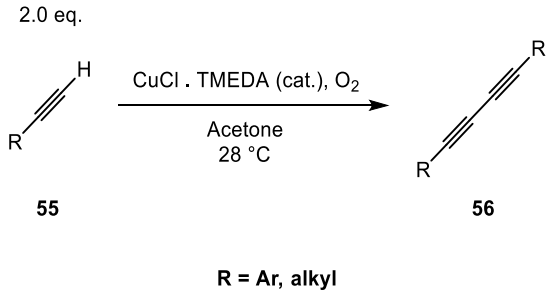


Scheme 20: The proposed mechanism for diyne formation under Eglinton & Galbraith-type conditions

Eglinton & Galbraith found that by continuously streaming oxygen through the system, the copper(I) acetate that formed could be reoxidised, and therefore only catalytic amounts of the starting copper(II) salt were required. However, for preparative simplicity, it was opted to use an excess of copper(II) species.[178] As with Glaser's work (see **Scheme 18**, **page 37**), it has also been suggested by some that the homocoupling of alkynyl species occurs *via* radicals, rather than the redox process described.[179]

In 1960, it was deduced by Hay[180] that pyridine functioned as a ligand as well as a base in Eglinton & Galbraith's work. Furthermore, Hay[181] also reported in 1962 that this role could be performed more effectively by certain amines, such as TMEDA. The use of TMEDA as both ligand and base permitted faster reaction times, and high diyne **56** yields from the alkyne

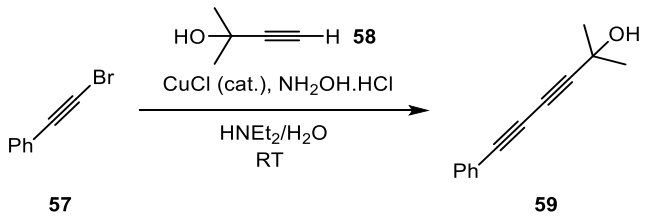
starting materials **55**. With this modification, numerous different solvents were tolerated and only catalytic amounts of copper(I) chloride were required, suggesting efficient *in situ* catalyst regeneration by atmospheric oxygen (**Scheme 21**).



Scheme 21: Hay's development of diyne formation allowing the use of only catalytic amounts of copper species, by employing a TMEDA ligand

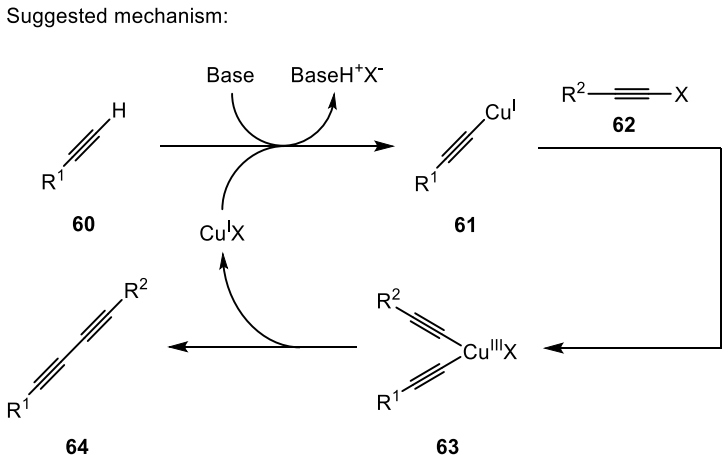
Higher solubility of the copper catalyst due to coordination by the TMEDA ligand, was thought to be the main factor responsible for the associated improvements in this reaction.[143, 172, 182] The mechanism of Hay's work is thought to be akin to that of Glaser's (see **Scheme 18**, **page 37**). The generic template for symmetrical diyne synthesis, where a terminal alkyne homocouples in the presence of a copper catalyst, has remained a standard approach to the present day.[143, 183] A base, catalyst, oxidation by oxygen, and relatively low temperatures, are features usually associated with this chemistry. Variations have nevertheless been made, and especially so since the turn of the century, such as the use of iron,[184] nickel[185] or palladium[186-191] co-catalysts, different oxidants,[186-187] and innovative solvent systems.[190, 192]

Synthesis of unsymmetrical diynes is of much greater importance than that of symmetrical ones, as the diversity of potential products is exponentially wider. Simply mixing two different terminal alkynes and subjecting them to classic "Glaser-Eglinton-Hay"-type conditions is one synthetic approach, but selectivity tends to be effectively non-existent in such reactions.[143] Traditionally, the most commonly used method has been based on the heterocoupling first reported by Cadiot & Chodkiewicz[137, 168] in 1955. This originally entailed coupling phenylacetyl bromide (**57**) with an aliphatic alkyne **58** to produce an unsymmetrical diyne **59**, catalysed by copper(I) chloride, and with hydroxylamine hydrochloride acting as a base (**Scheme 22**).



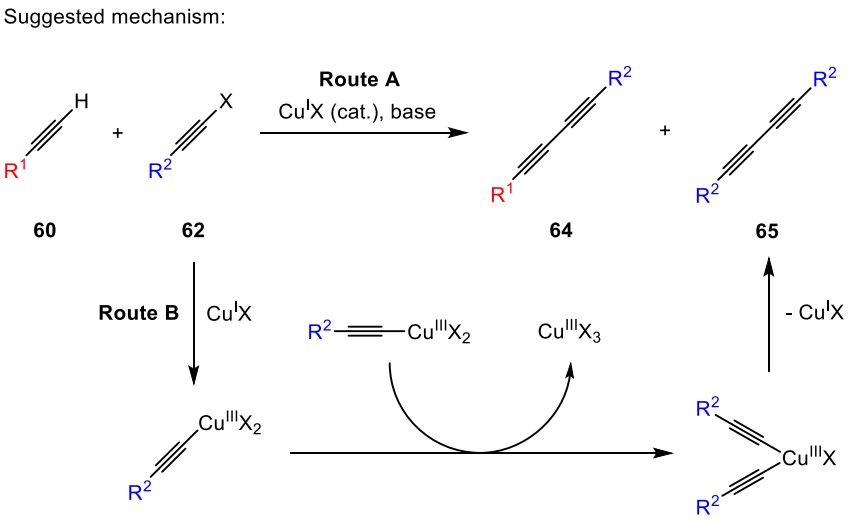
Scheme 22: The original Cadiot-Chodkiewicz-type formation of unsymmetrical diynes

The generic mechanism for this type of coupling is initiated by a copper(I) halide (often the iodide), selectively reacting with the terminal alkyne **60** as it is deprotonated by a base (**Scheme 23**). Oxidative addition of the haloalkyne **62** then occurs on the alkynyl copper **61**, producing dialkynylated copper **63**, which itself undergoes reductive elimination to yield the unsymmetrical diyne **64** and regenerate the catalyst.



Scheme 23: The proposed mechanism of the formation of unsymmetrical diynes under Cadiot-Chodkiewicz-type conditions

Cadiot-Chodkiewicz coupling normally provides relatively high yields under mild conditions, and tolerates a diverse range of alkynyl substituents.[143, 168] However, the synthesis can suffer from a significant generation of symmetrical diyne side-product **65**, particularly when substrates are bulky or possess similar electronic properties (**Scheme 24**).[193] The occurrence of such homocoupling is due to a side-reaction of the copper(I) species with the haloalkyne **62**, leading to partial implementation of "Route B" producing symmetrical diyne **65**, in addition to the unsymmetrical product **64**.

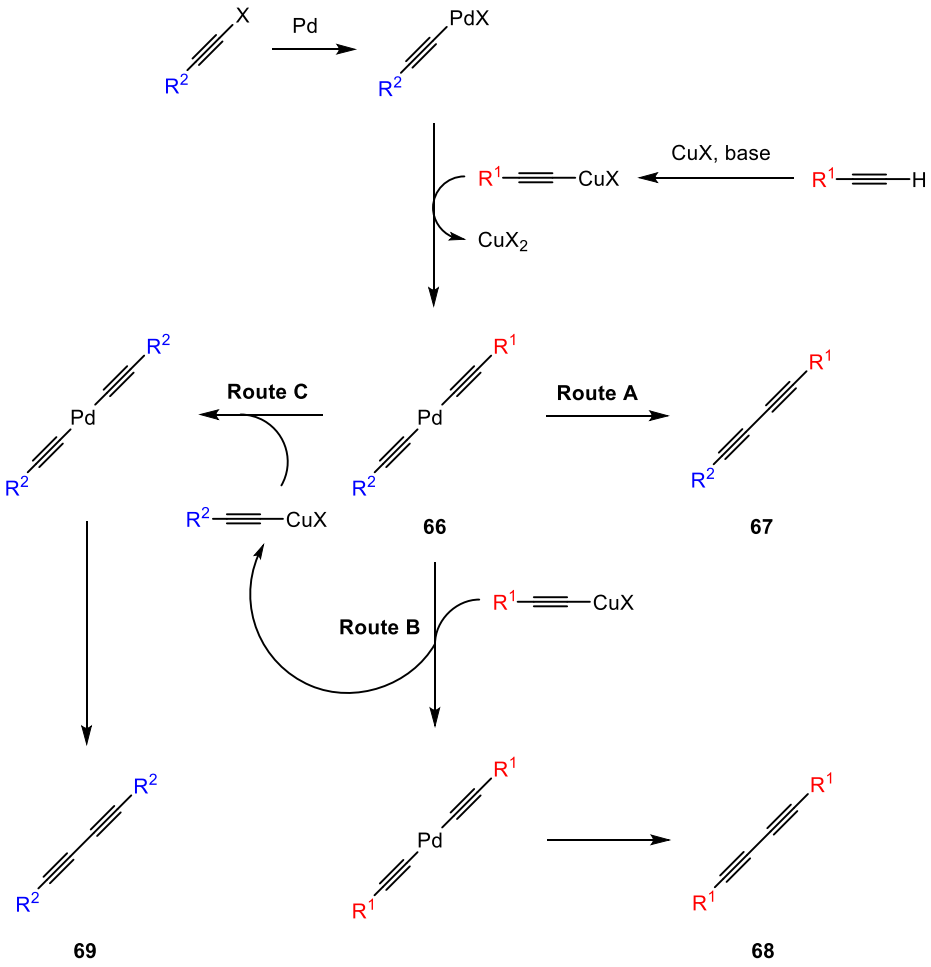


Scheme 24: The proposed formation of unwanted symmetrical diyne side-products under Cadiot-Chodkiewicz-type conditions

Excess amounts of terminal alkyne **60** are usually needed to overcome the effect of homocoupling.[137, 143] During the formation of symmetrical diyne **65**, copper(I) halide is also transformed into the copper(III) species, rendering it obsolete for further catalysis, and further impacting the efficacy of the reaction.

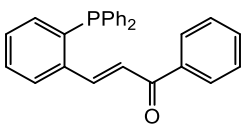
Various research groups such as those of Nye & Potts,[194] Wityak & Chan,[195] and Alami & Ferr,[196] experimented with the use of palladium co-catalysts, with the same aim of increasing unsymmetrical diyne yields and selectivities. Whilst improved yields were obtained in some instances, the use of palladium resulted in noticeable amounts of two symmetrical diyne side-products, **68** and **69** (**Scheme 25**). This is thought to be due to the intermediary species **66**, which after its formation by Sonogashira-type coupling,[197-198] may be consumed by two additional homocoupling pathways, "Route B" and "Route C". These compete with formation of the desired unsymmetrical diyne **67** from "Route A".

Suggested mechanism:



Scheme 25: The formation of unwanted symmetrical side-products under palladium catalysis

The key to improving selectivity within Cadiot-Chodkiewicz coupling therefore, lies in promotion of "Route A" and concurrent inhibition of "Route B" and "Route C". Both sterically bulky and π-acidic ligands were known to facilitate reductive elimination, and in 2008 Shi *et al.*[199] recognised a potential beneficial connection. They subsequently reported on the use of a palladium co-catalyst in partnership with a certain phosphine-olefin ligand **70** (**Figure 11**).

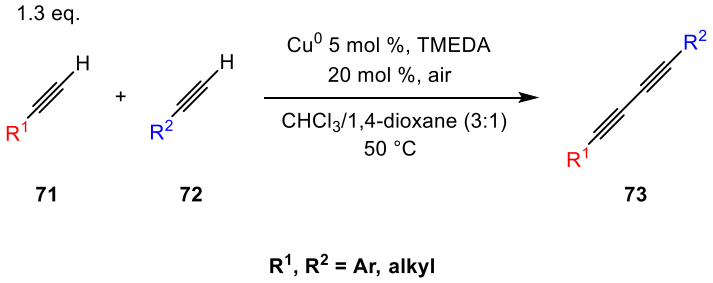


70

Figure 11: The phosphine-olefin ligand used as a co-catalyst with palladium to improve selectivity

The π-electron withdrawing, large and bidentate nature of the phosphine-olefin ligand **70**, disfavoured further oxidative addition after formation of the initial dialkynyl palladium species **66** (see **Scheme 25**, **page 42**). As a result, unsymmetrical diynes were obtained with high yields (77-99%) and selectivities (76-91%), even when the two alkynyl substituents were similar in structure.

A further development in transition metal mediated unsymmetrical diyne synthesis came in 2016, when Su *et al.*[200] designed a heteroselective coupling of two acetylene derivatives, **71** and **72** (**Scheme 26**). Under carefully tailored conditions, the copper catalyst selectively engages whichever alkynyl proton is most acidic and sterically accessible (**71** in this case), a slight excess of which is used. The alkynyl copper formed will then heterocouple with deprotonated alkyne **72**, yielding unsymmetrical diynes **73** (38-83%) with moderate selectivity (50-78% of the unsymmetrical product).



Scheme 26: Employment of tailored conditions to yield selective deprotonation of the most acidic and sterically accessible alkynyl proton

A special catalyst complex **74** is formed from copper, TMEDA and chloroform solvent, and is thought to be responsible for the interesting selectivity observed. This will only apply however, when the described reaction parameters are strictly adhered to. After isolating complex **74**, Su *et al.*[200] determined its molecular structure by single-crystal X-ray crystallography (**Figure 12**).

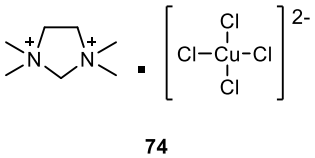
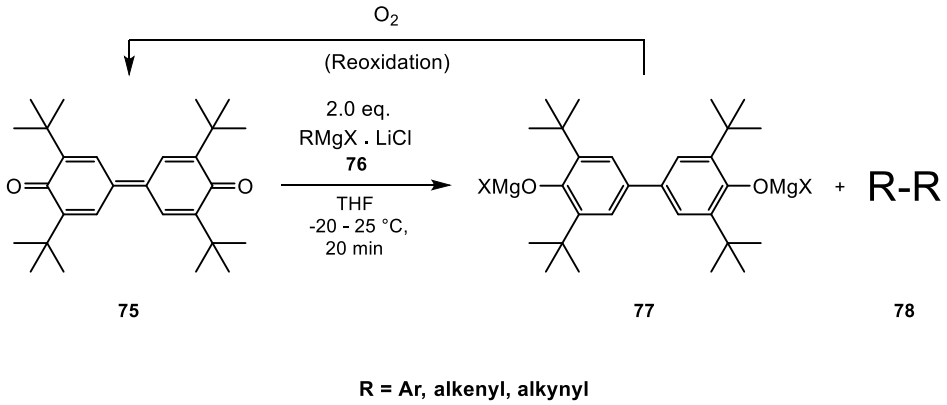


Figure 12: The copper catalyst formed *in situ* which is responsible for selectivity of the most acidic and sterically accessible alkynyl proton

Whilst the examples of transition metal mediated diyne syntheses described in this section do not present an exhaustive list of all existing routes, they are intended to give a comprehensive overview of the significant developments from 1869 to the present day.

1.2.3. Modern Transition Metal Free Routes to Diynes

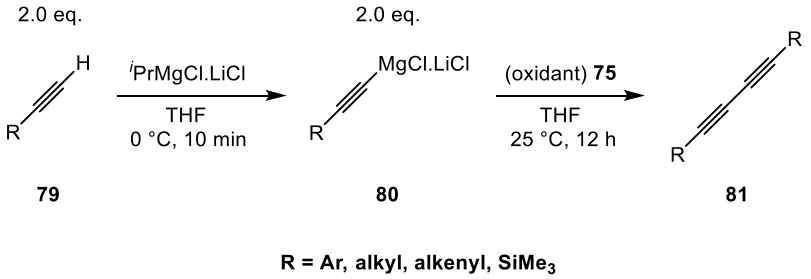
Historically, there has been very little if any research dedicated to the preparation of diynes, without some form of transition metal catalysis. More recently however, and particularly since the turn of the century, there have been a few instances of such syntheses. A relatively early example is the work of Krasovskiy *et al.*[201] in 2006, which involved the homocoupling of various organomagnesium substrates **76**, affording dimerised products **78** (**Scheme 27**).



Scheme 27: Homocoupling of organomagnesium substrates, catalysed by single electron transfer from organic oxidant 3,3',5,5'-*tetra*-*tert*-butyldiphenoquinone

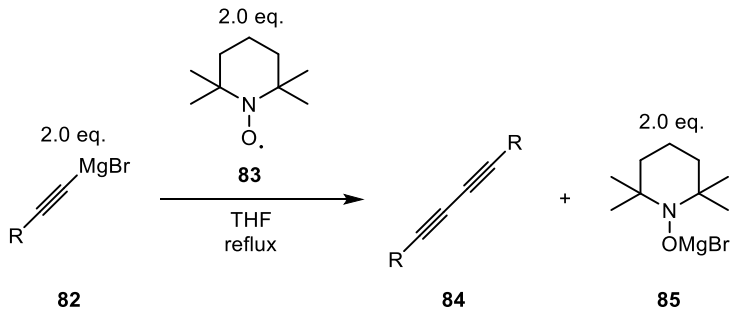
The mechanism at play was not fully understood, but thought to involve single electron transfers to the organic oxidant 3,3',5,5'-*tetra*-*tert*-butyldiphenoquinone **75**. This oxidant may be prepared from 2,6-di-tert-butylphenol, but is also commercially available (though fairly expensive).[202] It was further found that spent oxidant **75** (**77**) could be easily recovered from the product mixture, and slowly reoxidised with oxygen,[203] allowing it to be effectively recycled.

Using this chemistry, a limited number of diyne products **81** were obtained in high yields (80-90%), by employing alkynylmagnesium reactants **80** (**Scheme 28**). These were themselves prepared by treating acetylene derivatives **79**, with a solution of a isopropylmagnesium chloride-lithium chloride complex.



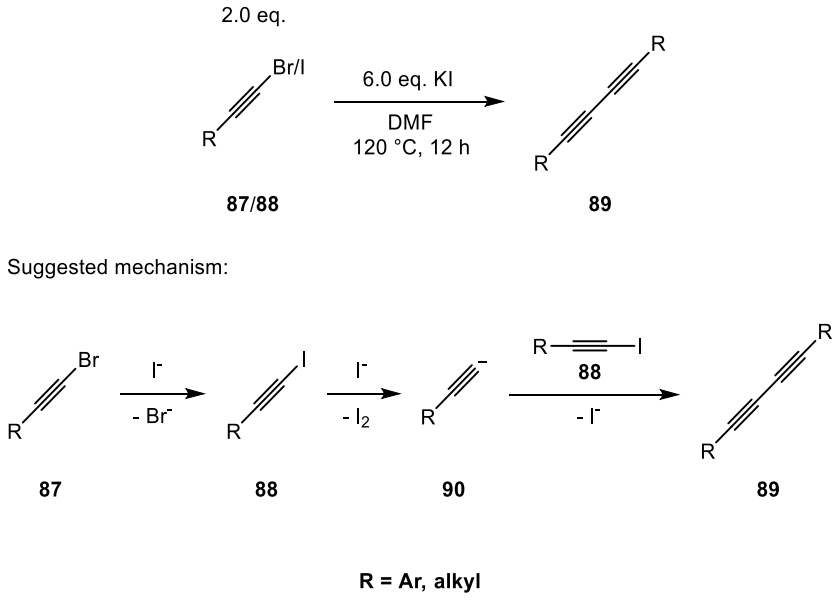
Scheme 28: The homocoupling of alkynyl magnesium substrates to form diynes

Similar work was carried out by Maji *et al.*[204] in 2008, where Grignard reagent substrates were coupled with the alternative use of TEMPO **83** (**Scheme 29**). Alkynyl Grignards **82** were employed to produce symmetrical diynes **84** in moderate to excellent yields (65-94%). Furthermore, it was found that with the use of alkynyl Grignards, simply bubbling oxygen through the solution in the absence of TEMPO **83** still produced a moderate yield of diyne (up to 62%).



Scheme 29: The homocoupling of organomagnesium substrates, catalysed by TEMPO oxidation

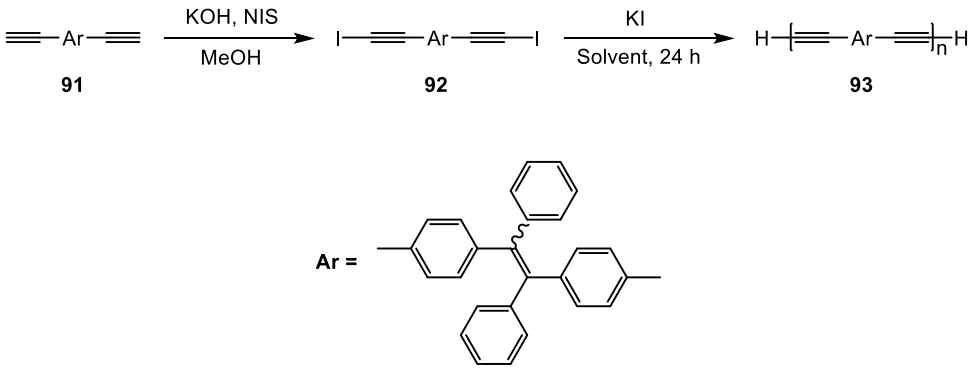
Another innovative synthesis was reported by Chen *et al.*[205] in 2010, where a reductive homocoupling of bromo/iodoalkynes **87**/**88** was carried out, without the need for any transition metals nor oxidants (**Scheme 30**). To proceed, the reaction required a reducing agent, of which potassium iodide was found to perform well, providing symmetrical diynes **89** in moderate to high yields (50-99%).



Scheme 30: The homocoupling of bromo/iodoalkynes initiated by potassium iodide reduction

A radical mechanism was proposed at first, but a more refined suggestion came from Zhang *et al.*,[206] where the iodoalkyne **88** undergoes loss of the iodine atom to give anionic species **90**, going on to attack a second molecule of **88** to produce diyne **89**. Although bromides were also employed successfully, the iodide tended to afford better yields (75-99% for iodoalkynes **88** compared to 50-94% for bromoalkynes **87**), and it was thought that the brominated starting material **87** must first undergo iodination *in situ* before reacting.

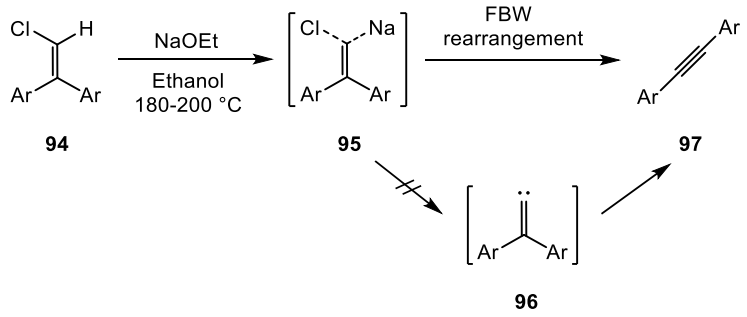
In 2016, Zhang *et al.*[206] successfully applied this chemistry to the production of functionalised polydiynes **93**, possessing excellent optical properties and thermal stabilities (**Scheme 31**). Diiodo-monomers **92** were prepared by treating the difunctionalised aromatic species (**91**) with KOH and NIS, which were then subjected to the symmetrical diyne formation, yielding the polymers **93** in low to moderate yields (18-69%).



Scheme 31: Employment of reductive homocoupling of diiodo-monomers to form functionalised polydiynes

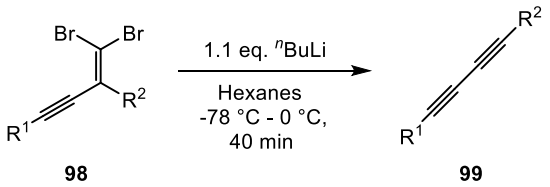
Chen *et al.* [205] also attempted to prepare unsymmetrical diynes using this synthetic route, by employing a mixture of two different haloalkyne starting materials. Unfortunately, akin to experiments mixing terminal alkynes under "Glaser-Eglinton-Hay"-type conditions (see **section 1.2.2**), selectivity was effectively non-existent. In the absence of any special modifications, a purely statistical distribution of hetero and homocoupled products will be recovered.

Interestingly however, a highly reliable approach to unsymmetrical diynes can be found in the FBW rearrangement.[207] This unique reaction was first discovered in 1895, when it was independently reported by Fritsch,[208] Buttenberg[209] and Wiechell,[210] who consecutively published their findings within the very same journal issue. These three reports all detailed the fascinating results obtained upon treating diarylvinyl chloride compounds **94** with sodium ethoxide, whereby disubstituted alkynes **97** were produced (**Scheme 32**).



Scheme 32: The rearrangement of diarylvinyl chloride compounds to form alkyne units *via* the rearrangement jointly discovered by Fritsch, Buttenberg and Wiechell

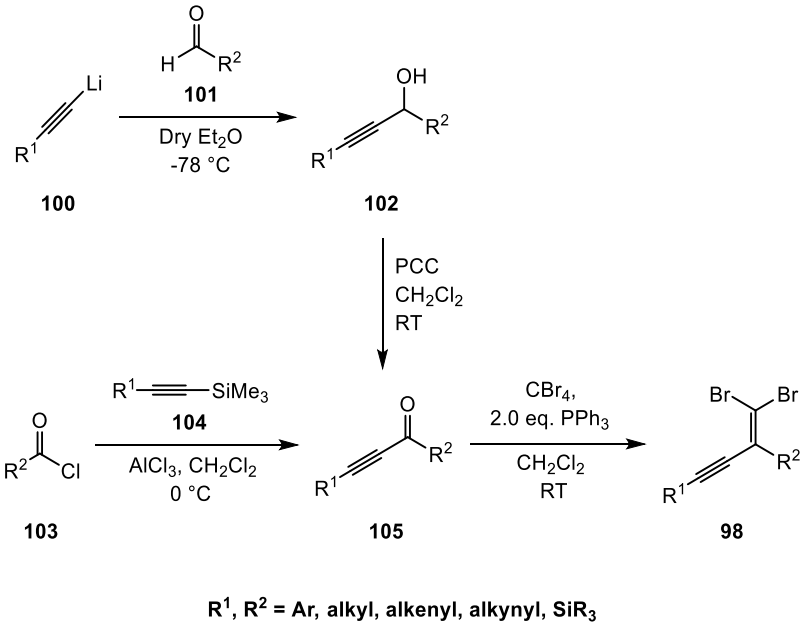
It is now known that these reactions proceed *via* formation of an intermediary organic salt **95**, which undergoes the iconic FBW rearrangement.[207] An intermediary free carbene species **96** has also often been invoked for FBW rearrangements,[211] though there does not appear to be significant evidence for this. Throughout the last century, many developments have been made to the variety of tolerated substituents and reagents,[212] and in 2000 Eisler & Tykwinski[213] first reported adaptation to produce polyynes. Later publications by Shi-Shun *et al.*[214-215] in 2003, focused on the synthesis of diynes **99** by treatment of dibromoolefins **98** with ^{n}BuLi (**Scheme 33**).



R^1, R^2 = Ar, alkyl, alkenyl, alkynyl, SiR_3

Scheme 33: Employment of the FBW rearrangement to form diynes

By choosing the alkynyl and vinyl substituents, a range of both symmetrical and unsymmetrical diynes can be obtained in moderate to excellent yield (46-95%), with no occurrence of cross-substrate products. The dibromoolefin precursors **98** are selectively acquired by treating alkynyl ketones **105** with carbon tetrabromide and triphenylphosphine (**Scheme 34**).



Scheme 34: The synthetic steps to prepare the dibromoolefin compounds used to form diynes *via* FBW rearrangement

The alkynyl ketones **105** may themselves be prepared either by reaction of acyl chlorides **103** with alkynylsilanes **104**, or by addition of lithiated alkynes **100** to aldehydes **101**, followed by oxidation of the alcohols **102**.[214-215]

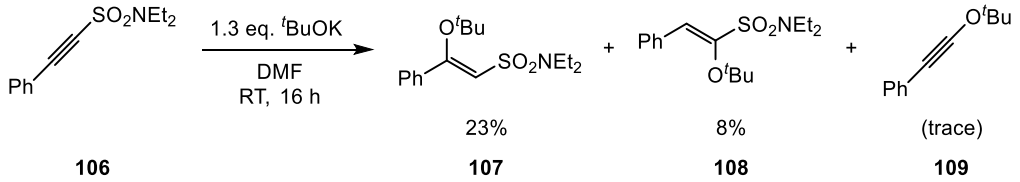
1.3. Chemistry of Alkynyl Sulfonamides

The sulfonamide moiety has historically found excellent application in the field of pharmaceuticals, making its medicinal debut in 1932 with the invention of antibiotic Prontosil.[216] More recent examples include blockbuster drugs such as Sildenafil and Celecoxib. Despite its medicinal importance, use of the sulfonamide functional group in synthesis has rarely been reported.

Whilst sharing some similarities with carbonyl based moieties such as esters and amides, and slightly more with sulfones and sulfoxides, sulfonamides exhibit unique modes of reactivity.[217] Investigations into the chemistry of sulfonamides has long been a key area of interest within the Wilden research group, and in more recent years has especially focused on that of the alkynyl sulfonamide motif.

In 2012, Gray *et al.*[218] reported upon the treatment of phenylethynyl sulfonamide **106** with ^{t}BuOK, using standard grade DMF solvent. Interestingly, in addition to a logically expected

product of Michael-type addition (**107**), an alkene resulting from the corresponding α-attack (**108**) was also obtained, in a ratio of approximately 3:1 (**Scheme 35**). Furthermore, a trace of ynol ether **109** was also isolated.



Scheme 35: The original discovery of ynol ether formation *via* substitution-elimination reaction of alkynyl sulfonamides

Nucleophilic attack on the α-carbon would be assumed generally unfavourable, due to the absence of any efficient conjugate-addition pathway. However, DFT modelling suggested that the corresponding alkenyl intermediate **110** possess an unexpected stability, possibly resulting from weak intramolecular bonding between hydrogen on the *tert*-butoxyl group, and the sulfonamidyl oxygen (**Figure 13**).

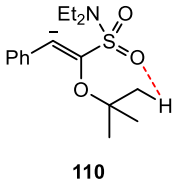
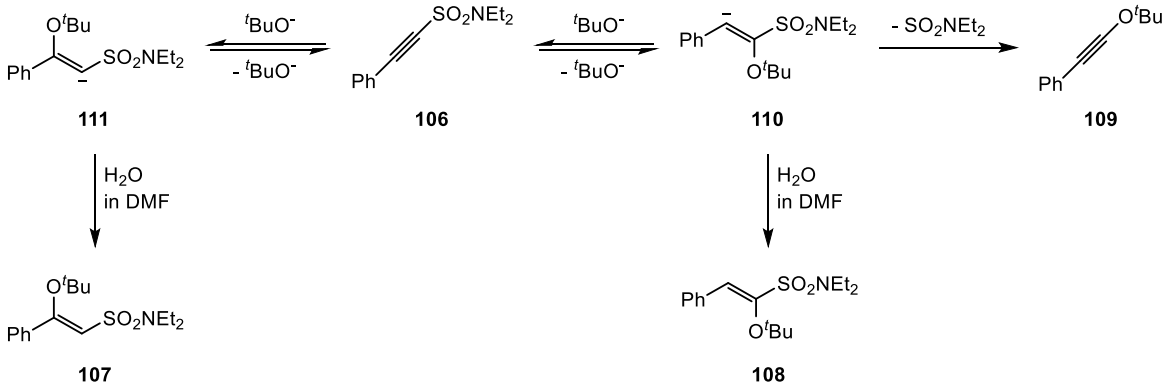


Figure 13: The stabilising intramolecular hydrogen bonding within the intermediate formed *via* initial α-addition to alkynyl sulfonamide

Consequently, the carbon framework of the molecule is pushed into a planar state, allowing facile electronic delocalisation and providing unanticipated stability. Consideration of these factors led to the proposal of a series of equilibria, accounting for the formation of the β-substituted phenylethenyl sulfonamide **107**, α-substituted phenylethenyl sulfonamide **108** and ynol ether **109** products (**Scheme 36**).



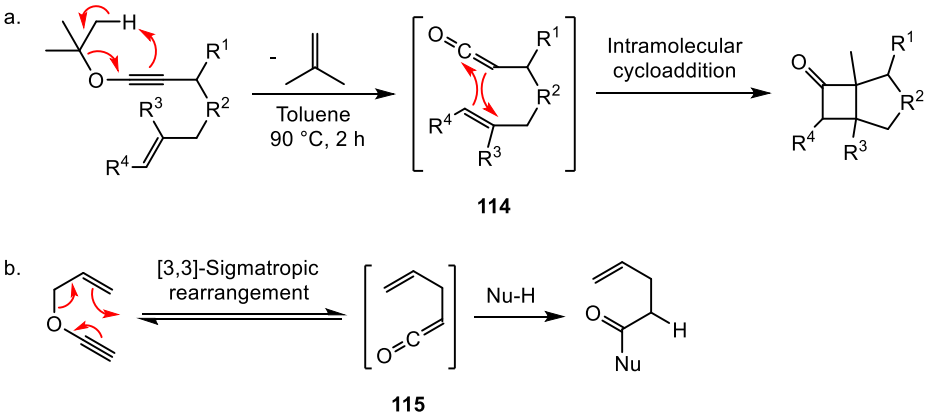
Scheme 36: The proposed equilibria responsible for the formation of β-substituted phenylethenyl sulfonamide, α-substituted phenylethenyl sulfonamide and ynol ether products from alkynyl sulfonamide

According to these mechanistic pathways, alkynyl sulfonamide **106** undergoes reversible attack by *tert*-butoxide anions to produce anionic intermediates **110** or **111**. These can then be protonated by water traces in the commercial DMF solvent, to yield alkenyl sulfonamides **108** and **107** respectively. The aforementioned stability of intermediate **110** is sufficient to allow trace amounts of ynol ether **109** to form, *via* elimination of the sulfonamide group.

It was reasoned therefore, that the use of appropriately dried DMF should increase the yield of ynol ether. Indeed, upon treating a range of arylethynyl sulfonamides **112** with ^{t}BuOK under anhydrous conditions, ynol ethers **113** were afforded as the sole products in good to excellent yields (59-93%) (**Scheme 37**). Curiously however, when an alkynyl sulfonamide with a non-aromatic substituent was employed, no reaction occurred.

Scheme 37: Treatment of various arylethynyl sulfonamides with ^{t}BuOK to form the corresponding ynol ethers

Ynol ethers are particularly useful as synthetic intermediates, due to their facile ability to form ketenes (**114** and **115**) which subsequently react, allowing access to complex molecular structures (**Scheme 38**).[219] These ketenes may be employed in intramolecular cycloaddition reactions (**Scheme 38a**),[220] or intercepted by nucleophiles (**Scheme 38b**), after their initial formation *via* low temperature sigmatropic rearrangement.[221-222]

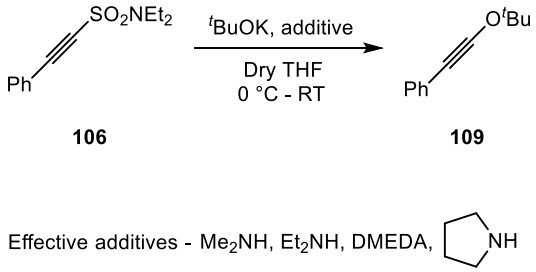


Scheme 38: Application of ynol ethers in a. intramolecular cycloaddition reactions and b. low temperature sigmatropic rearrangement reactions

Interestingly, it was found that the potassium counterion was essential for the synthesis described by Gray *et al.*[218] to proceed, as removal using 18-crown-6 rendered it inoperable. Moreover, the reaction also ceased upon substitution with other metals such as lithium, sodium, aluminium, magnesium or barium, but continued with subsequent addition of supplementary potassium cations from KPF_6.

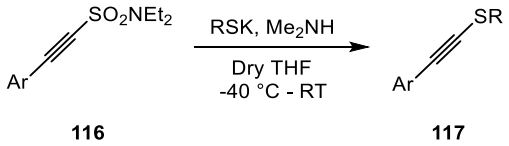
Various other studies of coupling reactions normally requiring transition metal catalysts, but instead induced by ^{t}BuOK, reported a similar dependency on potassium.[223-228] Other common features included the use of nitrogenous ligands, such as phenanthrolines and amines, and the postulation of a radical mediated mechanism. In these syntheses, as well as the work of Gray *et al.*,[218] reagents were painstakingly purified to ensure the absence of any transition metal traces, which may have covertly affected the observed reactivity.[229]

The preparation of ynol ethers *via* a radical pathway was therefore pondered, with DMF acting as the necessary amine ligand. Correspondingly, Gray *et al.*[230] repeated the previous synthetic procedure substituting the solvent for THF, along with screening of various nitrogenous ligand additives. A collection of secondary amines were found effective for the preparation of ynol ether **109** from phenylethynyl sulfonamide **106**, allowing the reaction to proceed with good yields (78-83%) under these modified conditions (**Scheme 39**).



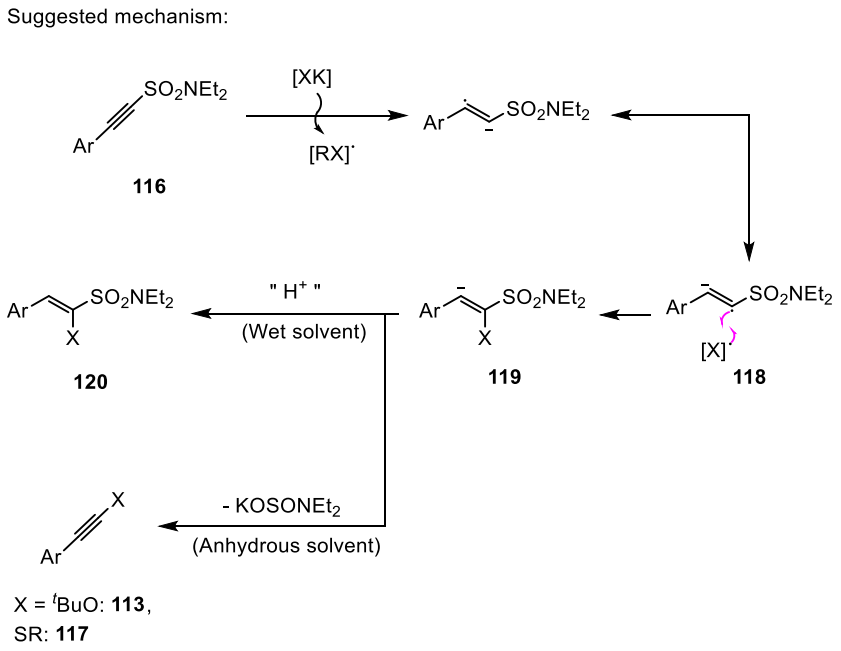
Scheme 39: Employment of various effective amine additives other than DMF as ligands in ynol ether formation

Under these reaction parameters a range of potassium alkoxide reagents were employed, with dimethylamine chosen as the standard additive, giving ynol ether products in moderate to good yields (50-71%). Further experimentation investigated application in the preparation of thioynol ethers **117** (**Scheme 40**), using potassium thiolates in place of alkoxides to afford poor to moderate yields (24-62%). Meanwhile, a range of thioynol ether samples **117** were also successfully produced in moderate to good yields (32-73%), by fixed use of the *tert*-butyl thiolate and variation of the alkynyl sulfonamide starting material **116**.



Scheme 40: Applying the ynol ether forming reaction conditions to produce thioynol ethers from alkynyl sulfonamides

Accordingly, a revised general mechanism for the formation of both ynol and thioynol ethers **113**/**117**, in addition to the quenched products of α-addition (**120**), was proposed (**Scheme 41**). This proceeded *via* a radical mechanism, initiated by single electron transfer from potassium alkoxide/thiolate to alkynyl sulfonamides **116**. It is thought that recombination of radical species **118** to the form the anion **119** is made feasible by effect of a "solvent cage".[231]



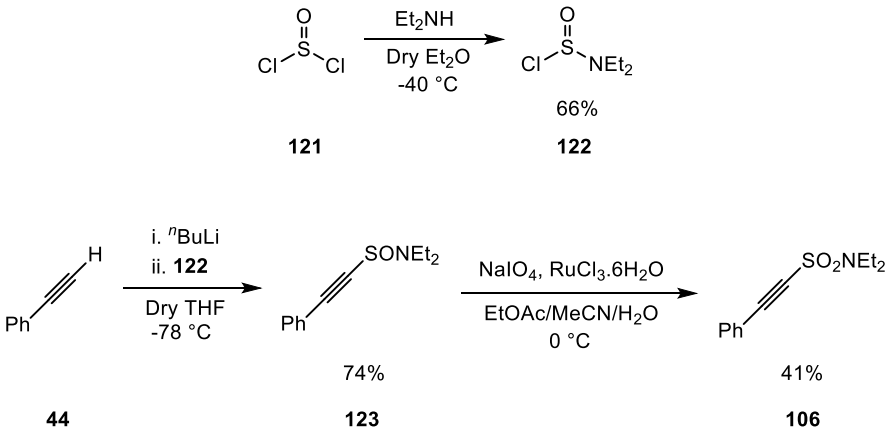
Scheme 41: Proposed radical mechanism responsible for the formation of ynol/thioynol ether products, *via* treatment of alkynyl sulfonamides with potassium alkoxides/thiolates

2. Results and Discussion

2.1. Novel Synthesis Discovery

The preparation of transition metal-free routes to diynes was of great interest, given their importance in recent literature (see **section 1.2.1**). Based on the Wilden research group's previously successful nucleophilic α-substitutions of alkynyl sulfonamides (see **section 1.3**), an analogous synthesis of diynes which employed acetylide nucleophiles was envisioned.[ii]

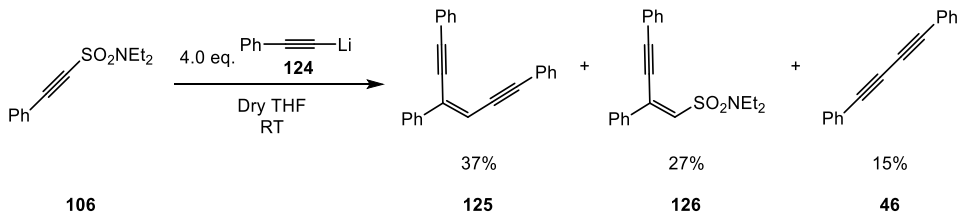
As such, the relatively simple phenylethynyl sulfonamide **106** was prepared *via* a synthetic procedure developed within the group, beginning with the formation of diethylsulfurous chloride **122**, by treating thionyl chloride **121** with diethylamine. Phenylacetylene **44** is then deprotonated and treated with the diethylsulfurous chloride **122** to produce phenylethynyl sulfinamide **123**, and finally oxidised to yield the sulfonamide **106** (**Scheme 42**).



Scheme 42: Synthetic preparation of alkynyl sulfonamide

Alkynyl sulfonamide **106** was then treated with excess lithium phenylacetylide **124** (prepared by treating phenylacetylene with an ^{n}BuLi solution), with the aim of producing the classic biphenyl diyne **46** (**Scheme 43**). In an intriguing advancement upon expected results, not only was the diyne **46** produced, but also a trisubstituted *Z*-enediyne **125**, which was obtained as the major product. Furthermore, a *Z*-alkenyl sulfonamide side-product **126** was isolated too.

[ii] From this point onwards, all experimental work was carried out by the author, unless stated otherwise.



Scheme 43: The original discovery of the enediyne, alkenyl sulfonamide and diyne forming reaction, upon treatment of alkynyl sulfonamide with lithium phenylacetylide

The *Z*-stereochemistry of both enediyne **125** and alkenyl sulfonamide **126** products was confirmed by NOESY experiments, which showed clear interaction between the alkene protons and those of the adjacent phenyl groups (**Figure 14**). As expected, alkene protons showed no through-space interaction with those on the alkynyl phenyl rings, however some was detected with the ethyl groups of the sulfonamide moiety in alkenyl sulfonamide **126**.

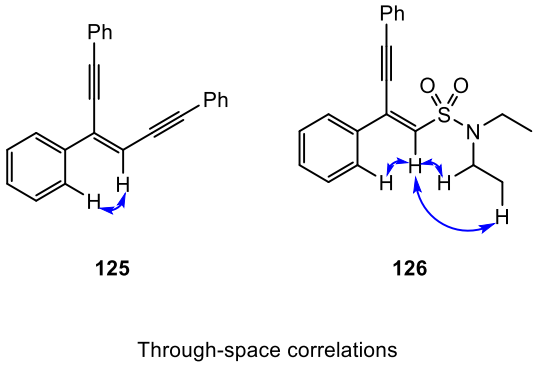


Figure 14: Confirmation of sterochemistries *via* NOESY experimentation

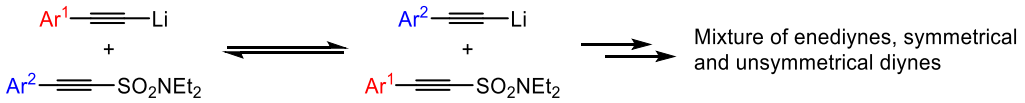
This work revealed not only a fascinating novel synthesis of medicinally important 1,3-diyne and *Z*-enediyne moieties, but also a fundamentally new mode of sulfonamide reactivity, and the previously unobserved alkenyl sulfonamide compound type.

2.2. Mechanistic Understanding

2.2.1. Early Exploration of Mechanistic Possibilities

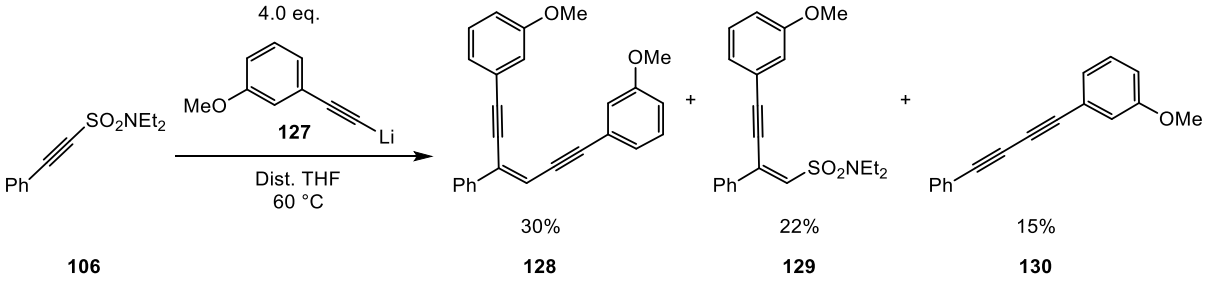
The mechanism of this curious, novel reaction was of immediate interest. The structures of the three products (see **Scheme 43**, **page 56**) implied an initial conjugate addition of lithium phenylacetylide **124** to the α or β-carbons of alkynyl sulfonamide **106**, although attack on the sulfur was not yet ruled out. The latter pathway would result in sulfonyl exchange reactions,

theoretically producing a mixture of enediynes, and both symmetrical and unsymmetrical diyne products (**Scheme 44**).



Scheme 44: Hypothetical formation of mixed enediynes and diynes if sulfonyl exchange reactions were active

Since this could not be verified when both aryl substituents were phenyl groups, the original experiment was repeated with lithium phenylacetylide **124** substituted by its *m*-methoxy analogue (**127**) (**Scheme 45**). This yielded only a single enediyne **128**, alkenyl sulfonamide **129** and diyne **130**, suggesting sulfonyl exchange does not occur.



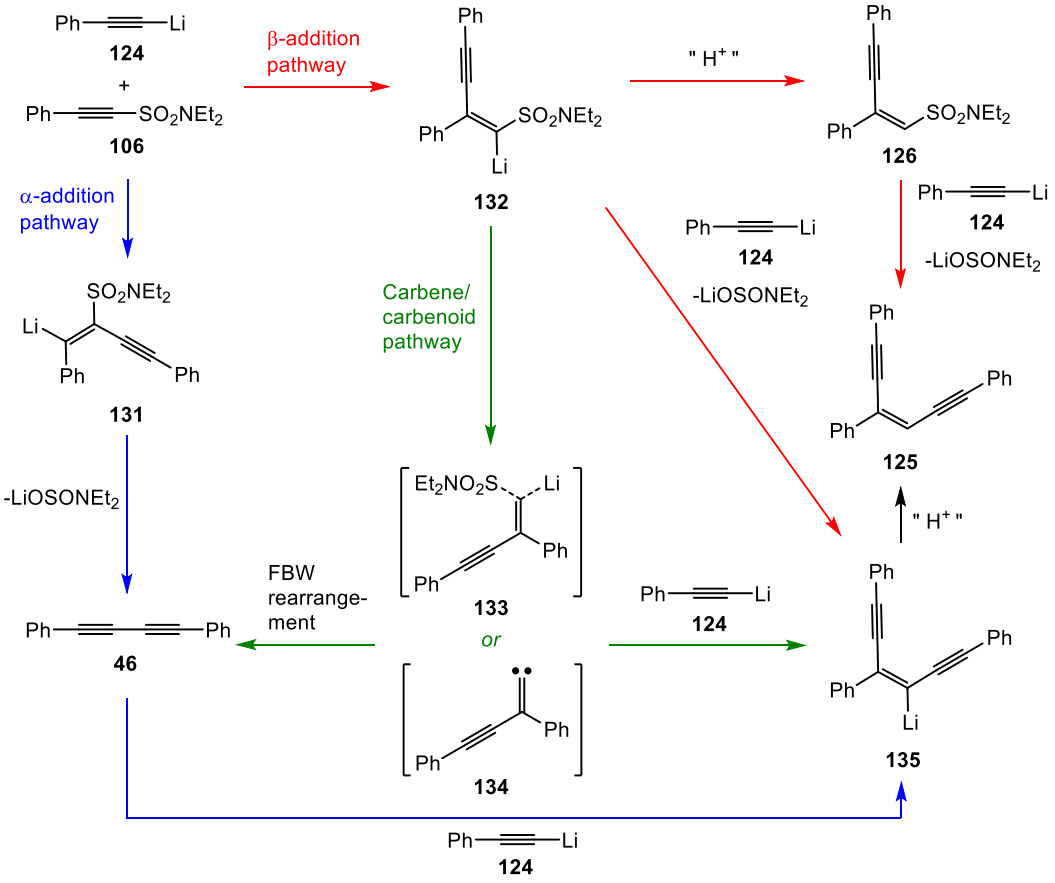
Scheme 45: Formation of single enediyne and diyne products, suggesting the absence of sulfonyl exchange reactions

These results also reinforced the assumption that the enediyne forms *via* incorporation of two molecules of acetylide into one of the alkynyl sulfonamide. Furthermore, they demonstrated that this novel synthesis has scope to produce mixed enediynes, and both symmetrical and unsymmetrical diynes, with excellent regiocontrol.

A reaction mechanism proceeding *via* radical intermediates analogous to those suggested for the formation of ynol/thioynol ethers **113**/**117** (see **Scheme 41**, **page 53**) was considered. However, upon successfully repeating the original experiment (see **Scheme 43**, **page 56**) in the presence of the radical inhibitor galvinoxyl, producing effectively unchanged results,[iii] such a

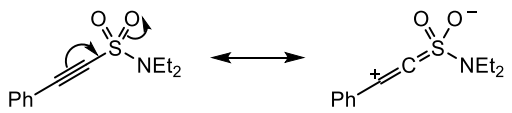
[iii] Experiment carried out by student Georgios Lefkaritis under supervision of the author, and data cited from project thesis: Lefkaritis, G., *Displacement at an sp-centre: What's the mechanism?*, MSci: University College London, **2016**.

pathway was considered unlikely. In consideration of the observations made, a limited number of potential mechanistic routes were proposed to account for the three distinct products (**Scheme 46**).



Scheme 46: Potential mechanistic routes to the enediyne, alkenyl sulfonamide and diyne products

The structure of the alkenyl sulfonamide product **126** implies an initial Michael-type addition to alkynyl sulfonamide **106**, which is favourable due to the electropositivity of the β-carbon, resulting from the mesomeric effect (**Scheme 47**). The "β-addition pathway" continues with the intermediary alkenyl sulfonamide **132** undergoing protonation to give the quenched product **126**, or attack by a second molecule of lithium phenylacetylide **124** to produce enediyne **125**. In this pathway, enediyne **125** may also form from direct alkynylation of alkenyl sulfonamide **126**.



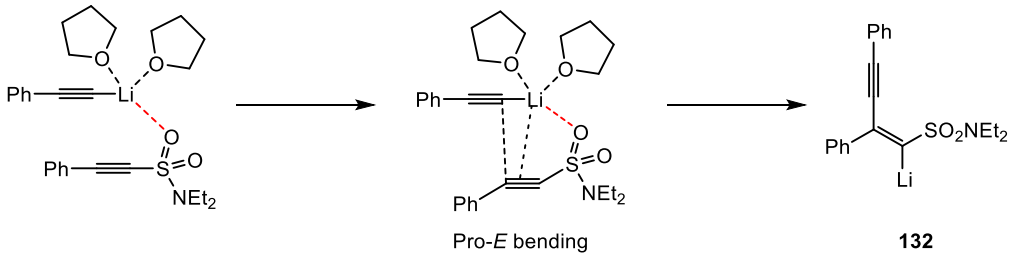
106

Scheme 47: Resonance structures promoting initial β-alkynylation

Investigations into the transition metal-free preparation of diynes *via* an FBW-type pathway, such as those reviewed by Jahnke & Tykwinski,[207] influenced the suggestion of a "carbene/carbenoid pathway". Following initial β-alkynylation, a classical vinylidene carbenoid **133** or even a free carbene species **134** (formed by elimination of the sulfonamide moiety) may be generated, followed by FBW rearrangement to yield diyne **46**. These potential carbene/carbenoid species (**133** and **134**) may even be intercepted by a second molecule of lithium phenylacetylide **124** to produce enediyne **125**.

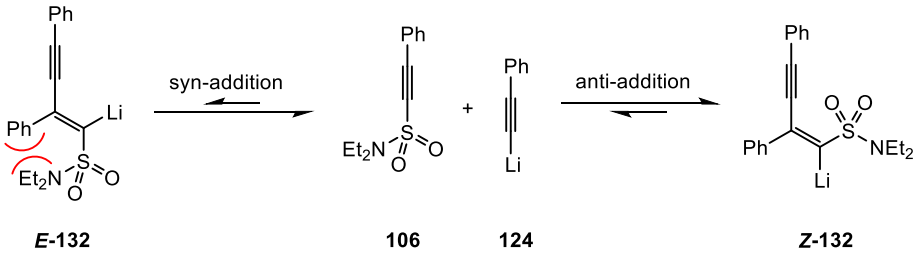
Previous work on addition-elimination reactions of alkynyl sulfonyl species, both *via* heteroatoms within the Wilden group,[218, 230] and carbon nucleophiles by Ruano *et al.*,[232] has given weight to a possible "*anti*-Michael" α-addition. An "α-addition pathway" was therefore also proposed for this novel synthesis, in which initial nucleophilic attack produces an alternative alkenyl sulfonamide species **131**. This undergoes rapid elimination of the sulfonamide moiety to generate diyne **46**, which may itself have reacted to produce enediyne **125**, *via* acetylide **124** attack. The absence of any quenched form of intermediate **131** however, suggests that if this it is passed through, it is extremely short lived.

The *anti*-addition of the β-addition pathway is in accordance with the work of Maddaluno *et. al.*,[233] which showed that carbolithiation of carbon triple bonds can proceed *via* a pro-*E* bending of the alkyne unit. Maddaluno rationalised experimental observations through a series of DFT calculations, suggesting these starting material contortions are dependent on the attacking lithium coordinating effectively to the alkynyl component. Simultaneously, lithium must also interact with the sulfonamidyl oxygen. In this novel work, interaction between lithium and oxygen occurs as the nucleophile approaches within the THF solution, enabling such pro-*E* bending (**Scheme 48**).



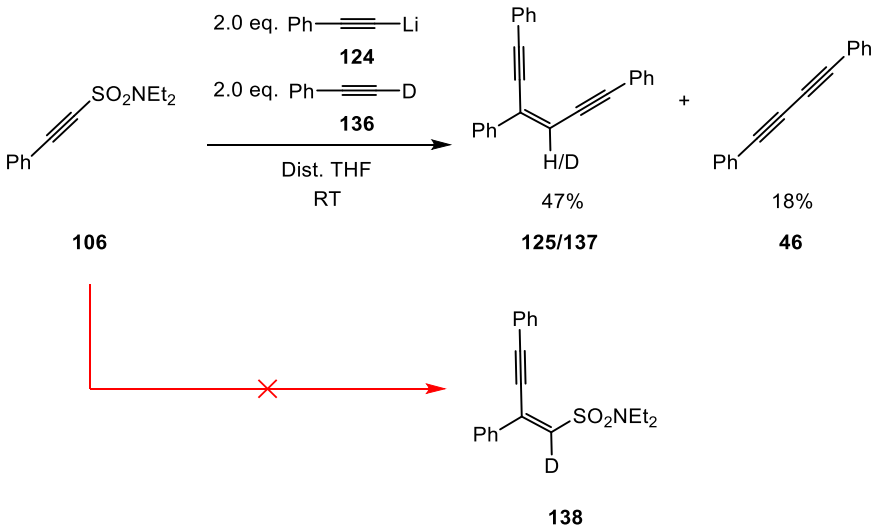
Scheme 48: Pro-*E* bending resulting from effective coordination of lithium to alkynyl carbon, whilst simultaneously interacting with sulfonamidyl oxygen

This initial *anti*-carbolithiation is further explained by comparison with similar reactions studied by Reichl & Radosevich[136] (see **Scheme 14**, **page 32**). This work suggested that *syn*-addition of nucleophilic alkynyl lithiums to alkynyl systems in which substituents are bulky, is destabilised by steric interference. It was therefore proposed that a pair of equilibria could allow interconversion of alkenyl sulfonamide isomers ***E*-132** and ***Z*-132**, selectively favouring formation of the *Z*-isomer (**Scheme 49**).



Scheme 49: Destabilisation of the *E*-intermediate, leading to sole formation of the *Z*-product

To better understand the nature of the suggested lithiated alkenyl sulfonamide (**132**) and enediyne (**135**) species, alkynyl sulfonamide **106** was treated with a mixture of lithium phenylacetylide **124** (2 eq.) and phenylacetylene-d **136** (2 eq.) (**Scheme 50**). By providing a source of labile deuterium during the reaction, a 50:50 mixture of the protonated and deuterated enediyne (**125** and **137** respectively) was isolated.



Scheme 50: Formation of only the deuterated enediyne, implying high reactivity of lithiated enediyne species and relative stability of lithiated alkenyl sulfonamide species

This was shown in ^{1}H-NMR by an approximate 50% reduction in intensity of the peak assigned to the alkene proton (peak at 6.60 ppm, **Figure 15**), relative to a purely protonated enediyne **125** sample. Meanwhile, none of the deuterated form of alkenyl sulfonamide **126** (**138**) was obtained, suggesting that lithiated alkenyl sulfonamide **132** is relatively stable in solution, whereas lithiated enediyne **135** is susceptible to weak proton donors such as acetylenes.

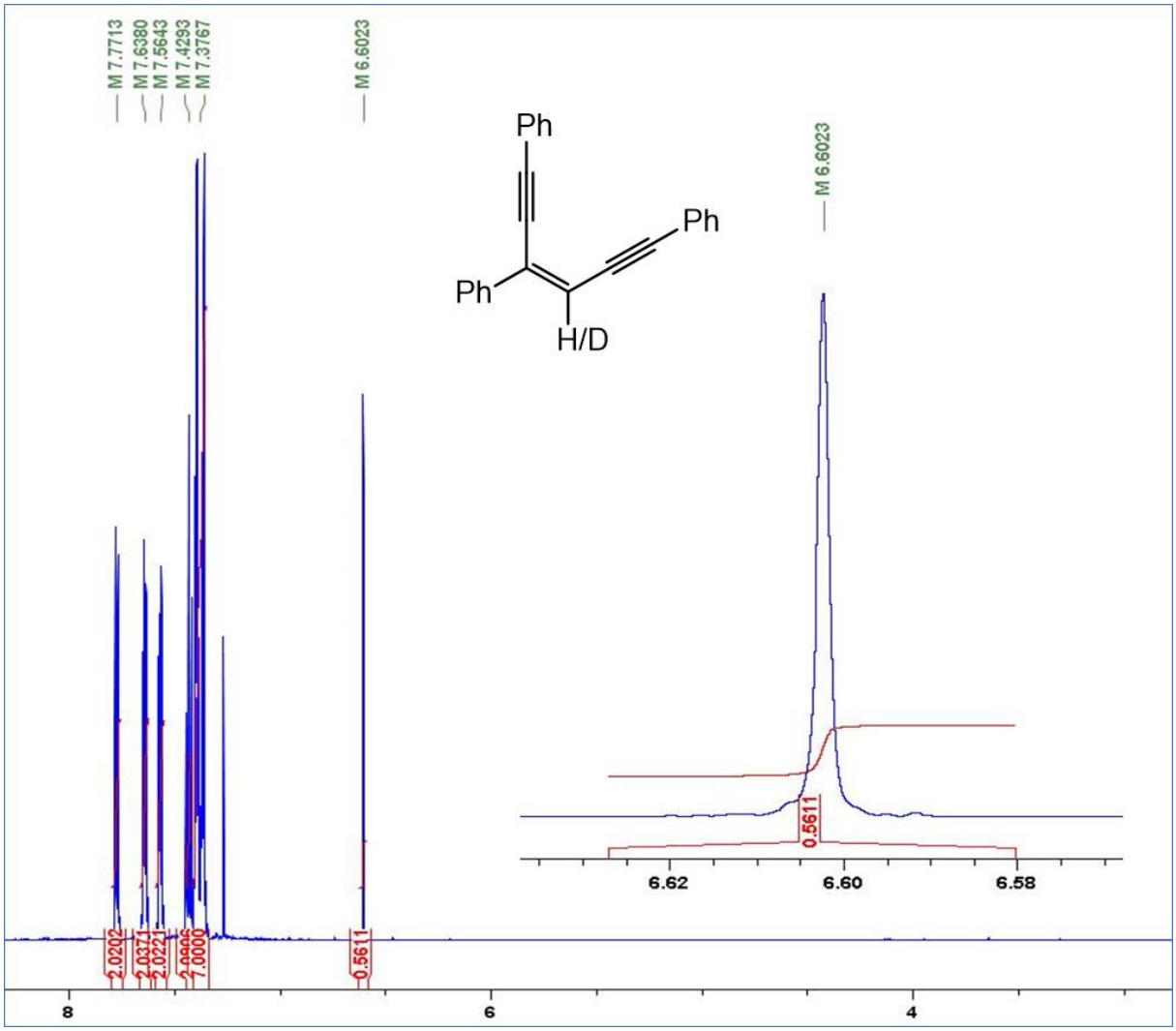


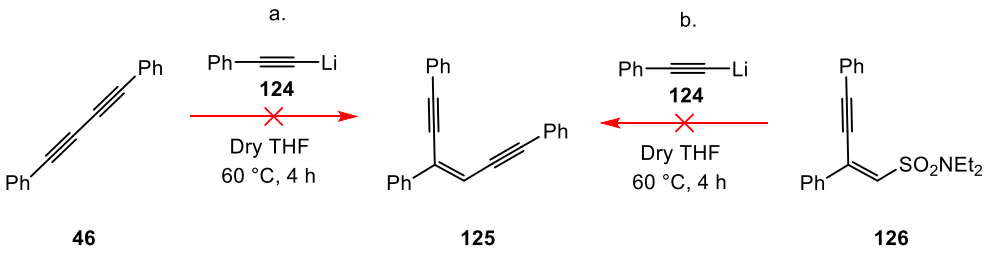
Figure 15: An approximate 50% reduction in alkene peak intensity compared to a purely protonated sample, showing effective incorporation of deuterium within enediyne

2.2.2. Discerning the Mechanism of Enediyne Formation

To better understand the exact formation of enediyne, attempts were made to produce enediyne **125** in isolation by simulating the different pathways suggested in **Scheme 46** (**Scheme 51**). It was thought unlikely that enediyne **125** formed *via* attack of a second molecule of lithiated acetylide **124** on diyne **46**, since additions to diynes tend to require harsh reaction conditions[144] and/or metal catalysts[234] (see **section 1.2.1**). This was confirmed when, upon treating a pure solution of diyne **46** with lithiated acetylide **124**, no reaction occurred (**Scheme 51a**).

Perhaps more intriguing however, when an analogous experiment was carried out with alkenyl sulfonamide product **126**, only starting material was recovered (**Scheme 51b**). In contrast with

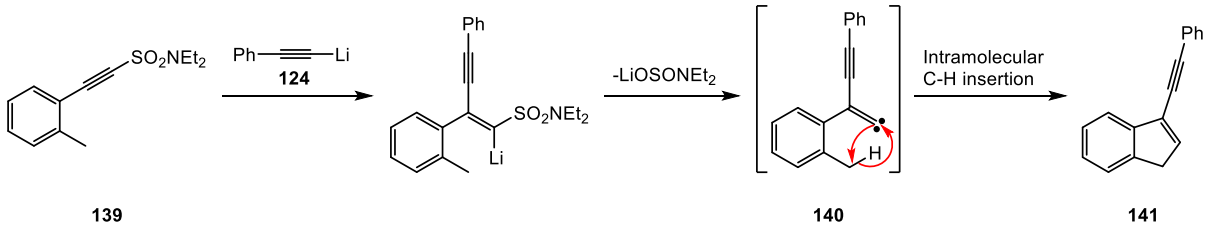
the original synthesis (see **Scheme 43**, **page 56**) which occurred rapidly at RT, neither experiment yielded any reaction even after extended periods of heating. To conclude, these two experiments ruled out formation of enediyne *via* subsequent reaction of either diyne **46** or alkenyl sulfonamide **126** products.



Scheme 51: The lithiated phenylacetylide species will not form an enediyne upon addition to either a. diyne or b. alkenyl sulfonamide compounds

Remarkably, these results suggested the lithiated centre of the alkenyl sulfonamide **132** was reactive towards nucleophiles, sparking a more in-depth consideration of a carbene/carbenoid pathway; one of the two remaining suggested routes to the enediyne (see **Scheme 46**, **page 58**). Examination of this possibility started with treating *o*-tolyl ethynyl sulfonamide **139** with lithium acetylide **124**, to test for the presence of a free carbene intermediate **140** (**Scheme 52**).

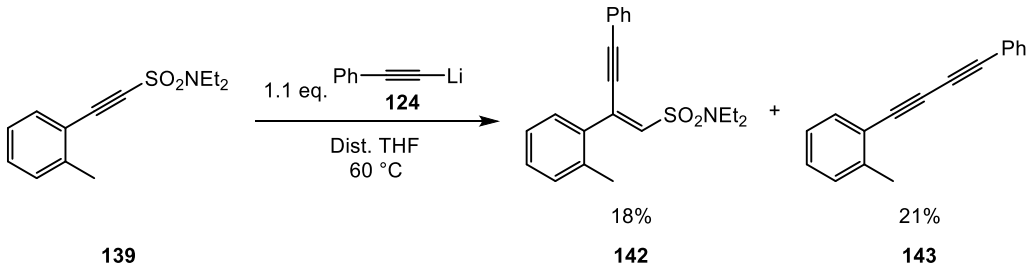
Previous work by Zhao *et al.*,[235] Doyle *et al.*,[236] and Taber *et al.*,[237] observed the facile formations of various 5-membered ring systems, *via* intramolecular C-H insertion of a carbene centre. If the free carbene species **140** was indeed generated, a degree of analogous reactivity would be expected, yielding some bicyclic product **141**.



Scheme 52: The hypothetical formation of bicyclic product if a free carbene intermediate were active

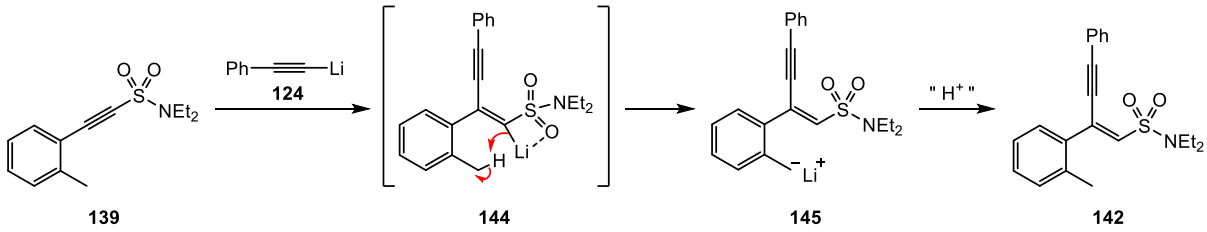
Upon carrying out the experiment however, it was in fact found that only the corresponding alkenyl sulfonamide **142** and diyne **143** were formed (**Scheme 53**). Since carbene **140** would be highly reactive and the 5-membered ring closure thermodynamically favourable, the

complete absence of any bicyclic product **141** suggests a mechanism involving a free carbene is not in effect.



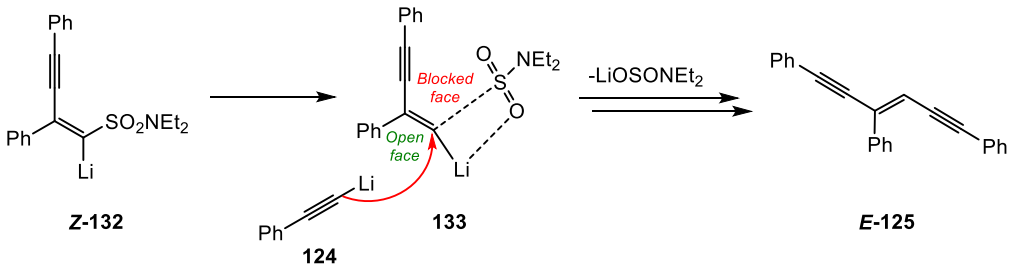
Scheme 53: Formation of only the usual alkenyl sulfonamide and diyne products, implying a free carbene species is not active

The absence of any enediyne product can be explained by intramolecular protonation of the alkenyl carbon within transition state **144**, by labile protons from the neighbouring methyl group (**Scheme 54**). The resultant anion **145** is then protonated to form the alkenyl sulfonamide product **142**.



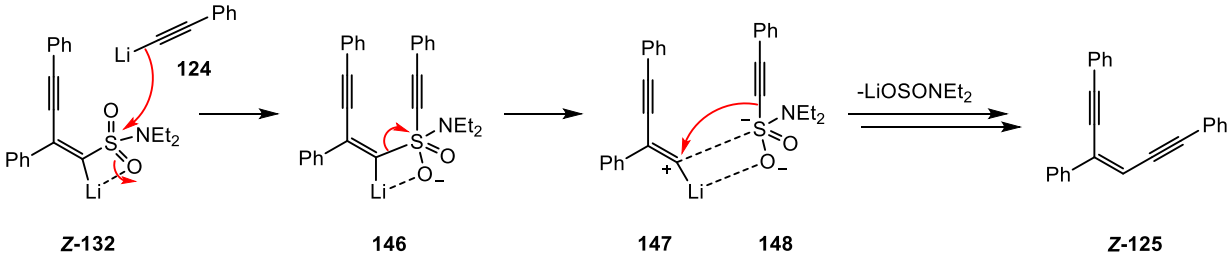
Scheme 54: Proposed explanation for the absence of enediyne product, due to intramolecular interception of reactive lithiated alkenyl sulfonamide

A classical, vinylidene carbenoid pathway was also contemplated for the formation of enediyne, similar to the models proposed by Schleyer *et al.*,[238] whereby nucleophilic attack occurs directly on the sulfonamidyl carbon (**Scheme 55**). In this mechanism however, the sulfonamide leaving group would bridge the carbon-lithium bond as it exited **133**, effectively blocking attack on the departing face, and forcing stereochemical inversion to give the *E*-enediyne product (***E*-125**).



Scheme 55: Hypothetical formation of *E*-enediyne product if a classical, vinylidene carbenoid pathway were active

Since *Z*-stereochemistry is sustained throughout the transformation of intermediary sulfonamide **132** to enediyne **125**, this route was discounted. In consideration of these observations, a novel mechanism proceeding *via* a non-classical, vinylidene carbenoid pathway was proposed (**Scheme 56**).



Scheme 56: Proposed non-classical, vinylidene carbenoid based mechanism for enediyne formation, *via* subsequent alkynylation of lithiated alkenyl sulfonamide

After initial β-carbolithiation produces the lithiated species ***Z*-132**, a second molecule of lithium phenylacetylide **124** attacks the sulfur atom, followed by cleavage of the C-S bond within dialkynylated species **146**. The alkynyl group of the sulfurous fragment **148** is then transferred to the vinylidene carbenoid **147** to form enediyne ***Z*-125**, retaining stereochemistry and releasing the sulfonamide moiety.

Addition of the second acetylide **124** to lithiated alkenyl sulfonamide ***Z*-132** is thought to be promoted by coordination of oxygen to the adjacent lithium. As this consequently increases the electrophilicity of sulfur, making it more susceptible to nucleophilic attack, it also explains why the protonated alkenyl sulfonamide (**126**) cannot form the enediyne **125** (see **Scheme 51b**, **page 63**).

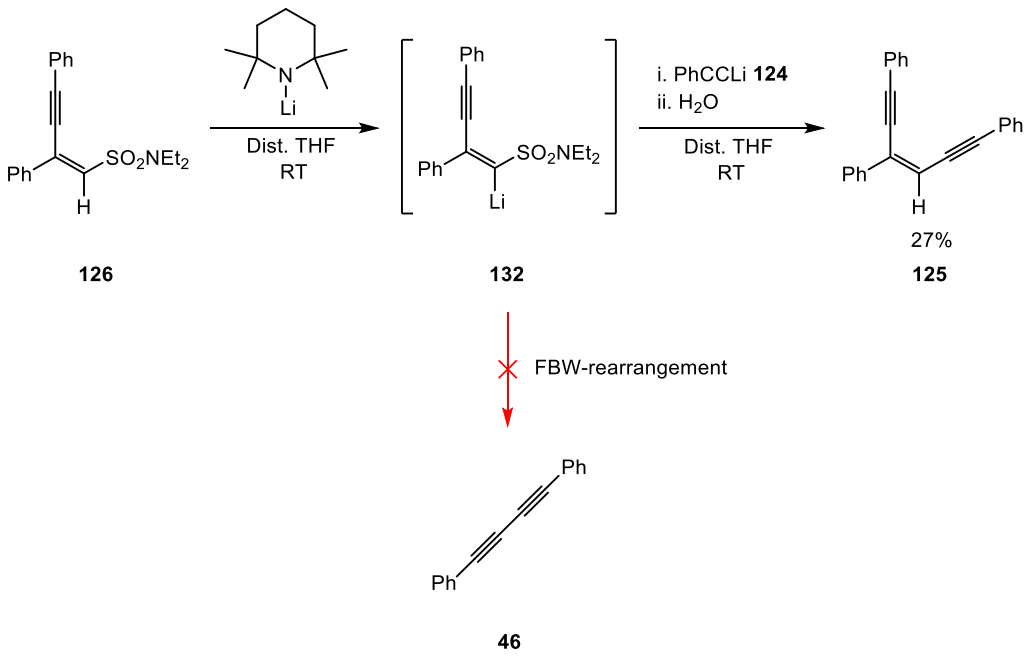
First principles molecular dynamics simulations[iv] were carried out in collaboration with Prof Ben Slater (a computational chemistry professor within the department), to reinforce this mechanistic proposal. These suggested that the C-S bond of the intermediary alkenyl sulfonamide **132** is highly robust (varying from 1.73 Å ± 0.12 Å over a 5000 fs run at 350 K),[239] and therefore unlikely to spontaneously break to form a free carbene or carbenoid species. This supports the suggested pathway in which cleavage is activated by the additional ligand interactions, detailed in **Scheme 56** on **page 65**.

This mechanism also helps to explain a marked increase in yield of **125** (8% to 21%) and accompanying decrease in alkenyl sulfonamide **126** (40% to 28%), when the reaction temperature was increased, whilst keeping all other variables constant (**Table 1**, **Entries 5-6**, **page 80**). The resultant higher energy input would be expected to further encourage cleavage of the strong C-S bond within the dialkynylated species **146**, resulting in a higher proportion of lithiated alkenyl sulfonamide **132** ultimately converting to enediyne.

As an interesting aside, these postulations may shed some light on the enediyne synthesis reported by Kimura *et al.*,[135] in that successive alkynylation of sulfinyl alkene **29** may involve an analogous non-classical vinylidene carbenoid (see **Scheme 13**, **page 31**). Likewise, such a mechanism also supports the "attack @ P" route proposed by Reichl & Radosevich,[136] for their similar reactions of alkynyl phosphonium salts **30** (see **Scheme 14**, **page 32**).

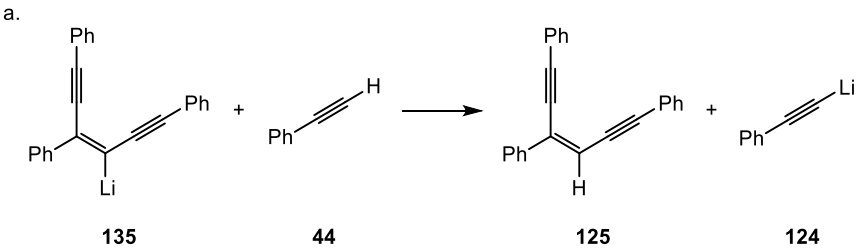
With these developments in mind, it was reasoned that **125** could theoretically be formed by adding lithium phenylacetylide **124** to an isolated solution of lithiated alkenyl sulfonamide **132** (**Scheme 57**). After ^{n}BuLi failed to deprotonate the alkenyl sulfonamide product **126**, the bulkier base LiTMP was successfully employed instead. As expected from the previous dismissal of a carbene/carbenoid pathway, no diyne **46** was produced from FBW-type rearrangement, and the lithiated species **132** remained stable in solution. Upon addition of lithiated phenylacetylide **124** however, enediyne **125** was indeed produced in moderate yield, accompanied only by unreacted starting material.

[iv] Computational simulations were carried out by Prof Ben Slater using the ORCA quantum chemistry computer program.



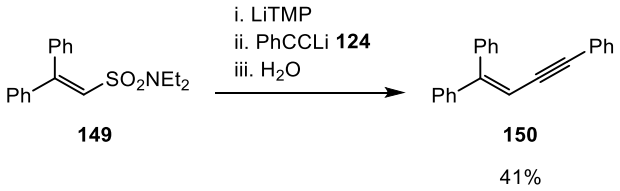
Scheme 57: Preparation of the enediyne product in isolation, supporting the proposed non-classical vinylidene carbenoid based mechansim

Interestingly, some enediyne **125** was also obtained when lithiated phenylacetylene **124** was replaced with the parent alkyne **44** (**Scheme 58**). This was possibly due to the lithiated form (**124**) being generated *in situ* by the highly basic lithiated enediyne species **135**, and/or remaining traces of LiTMP.



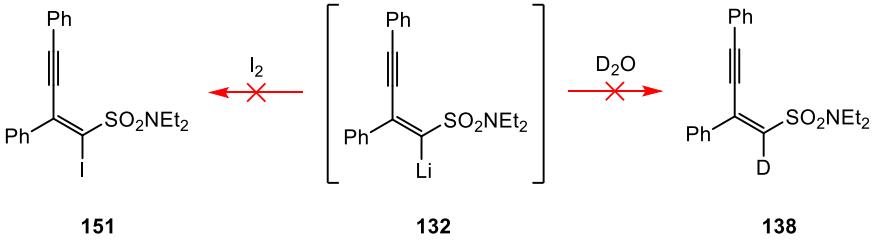
Scheme 58: Proposed *in situ* formation of lithiated phenylacetylide, responsible for enediyne formation proceeding with addition of only the parent alkyne

Furthermore, an analogous outcome was observed when a diphenylalkenyl sulfonamide **149** was treated with the same series of reagents, yielding an alkynylated product **150** (**Scheme 59**),[v] and strengthening the general mechanistic suggestion.



Scheme 59: Synthesis of alkynylated product analogous to enediyne formation

Curiously though, attempts to quench the lithiated alkenyl sulfonamide **132** with D_2O or iodine failed to produce the respective deuterated (**138**) or iodinated (**151**) products (**Scheme 60**). This suggested that the exact mechanism by which intermediate **132** is quenched is more complex than previously thought. A targeted investigation of the lithiated intermediate **132** in isolation may possibly yield a more complete understanding, but at present this has not been achieved.



Scheme 60: Failure of both deuterium oxide and iodine to quench the lithiated alkenyl sulfonamide intermediate

2.2.3. Discerning the Mechanism of Diyne Formation

Previous cases of diyne formation *via* a classical carbene/carbenoid species had been alluded to in the process of FBW rearrangement (see **section 1.2.3**).[211] However, this was deemed unlikely to be operational in this work, since such a pathway had been discounted for the enediynes (see **section 2.2.2**).

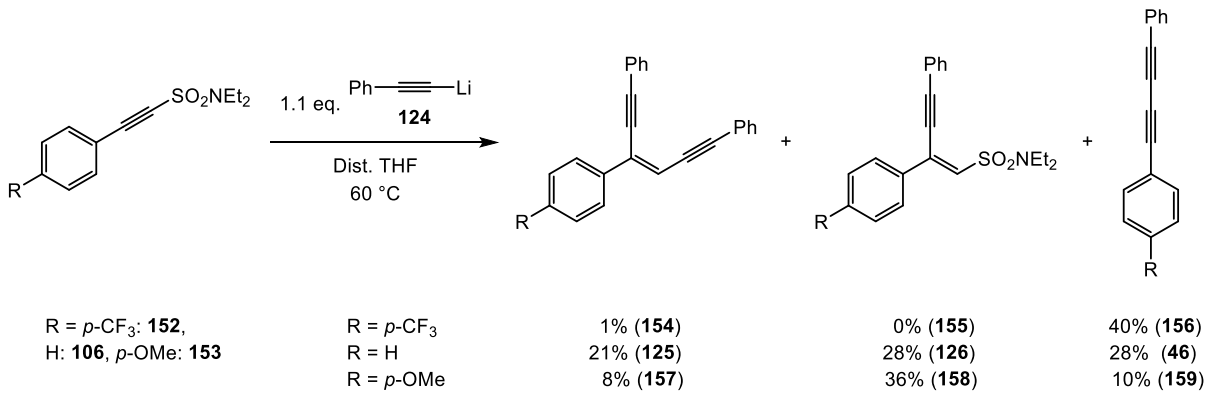
[v] Experiment carried out by student Yee Sum Joana Wong under supervision of the author, and data cited from project thesis: Wong, Y. S. J., *Easy Access to Carbenes and Carbenoids for Organic Synthesis*, MSci: University College London, **2017**.

It was decided nonetheless, to explore this mechanistic possibility by considering the work of Bichler *et al.*,[211] which had demonstrated that aryl groups tend to possess a superior migratory aptitude to alkynyl ones. As explained by Nakamura & Osamura,[240] the energy barrier to migration is inversely proportional to the stability of a substrate's corresponding cation (i.e. $aryl^+ > alkynyl^+$), since an electron deficient transition state is passed through.

With this in mind, the relative amounts of diyne, enediyne and alkenyl sulfonamide obtained, were compared when aryl *p*-substituents of varying electron donation/withdrawal were employed, whilst assuming alkynyl migration was inactive. As discussed by Waugh *et al.*,[241] an electron rich substrate will be more prone to migration, since it is better able to stabilise the electron deficient transition state. Conversely, an electron poor one will have a lower migratory aptitude.

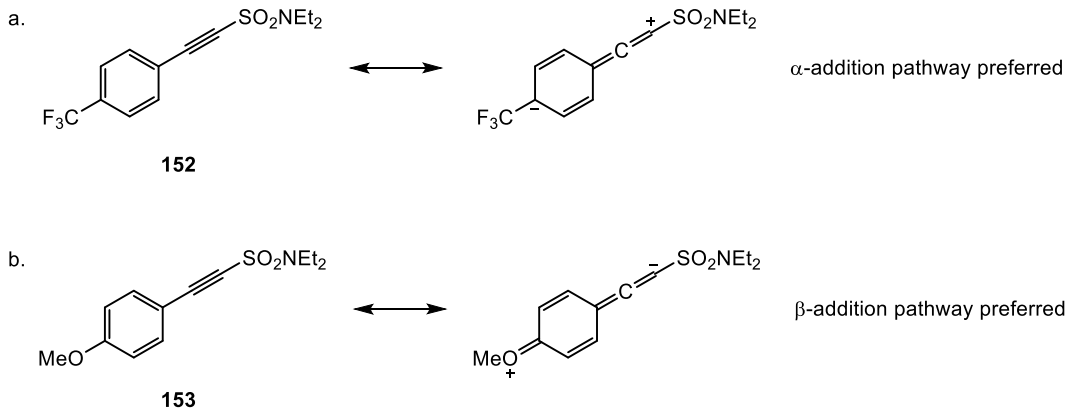
If an FBW rearrangement was operational therefore, a *p*-OMe (EDG) or *p*-CF_3 (EWG) substituent would be expected to produce higher and lower diyne yields respectively. Simultaneously, the opposite effect would be observed on the amounts of enediyne and alkenyl sulfonamide, as their production competes with that of the diyne.

Upon experimentation, results contrary to the FBW rearrangement rationale were indeed obtained, with the yield of diyne found to be inversely proportional to the electron richness of the aryl ring (**Scheme 61**). This suggested that an addition-elimination mechanism initiated by nucleophilic α-attack, was a plausible pathway to diyne production, operating in competition with attack on the β-carbon (see **Scheme 46**, **page 58**).



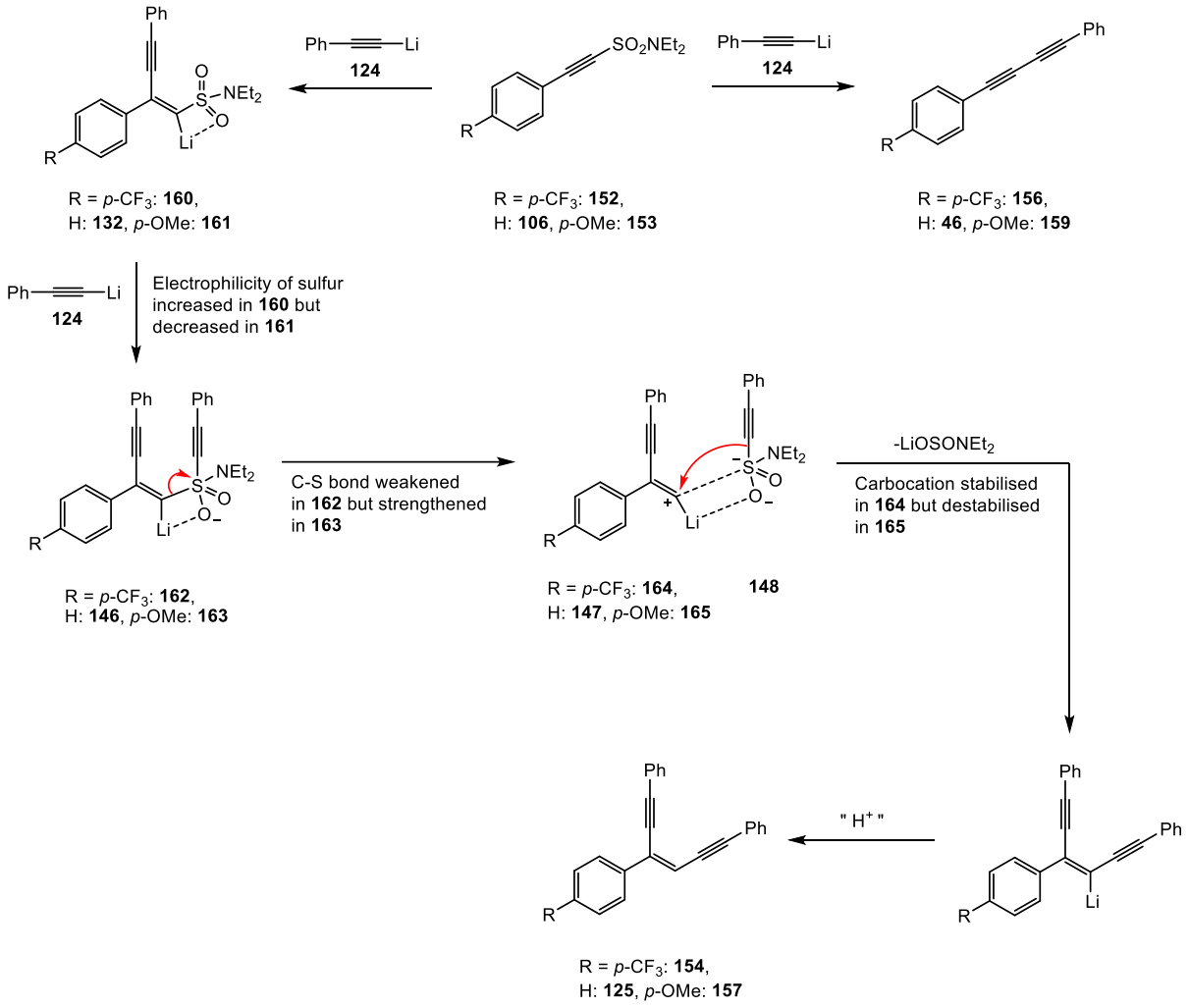
Scheme 61: Yield distribution of enediyne, alkenyl sulfonamide and diyne products when a *p*-EWG (CF_3) or a *p*-EDG (OMe) is employed, compared to an unsubstituted aryl ring

The occurrence of such a mechanistic route, may be further rationalised by considering the electrophilicities of the respective starting materials. Within the electron deficient alkynyl sulfonamide **152**, the increased electrophilicity of the α-carbon makes nucleophilic attack favourable (**Scheme 62a**), thereby yielding more *p*-CF_3 diyne **156**. The opposite effect is active in the electron rich alkynyl sulfonamide **153**, where the electron donating effect of *p*-OMe disfavours α-addition (**Scheme 62b**). This results in less *p*-OMe diyne **159**, as an increased proportion of initial nucleophilic attack occurs on the β-carbon instead.



Scheme 62: Resonance forms a. destabilise (due to the EWG) or b. stabilise (due to the EDG) initial Michael-type addition on alkynyl β-carbons

Furthermore, it can be understood that the electron withdrawal of *p*-CF_3 increases the electrophilicity of sulfur in the lithiated sulfonamide species **160**, weakens the C-S bond in the intermediate **162**, and promotes subsequent alkynylation of the cationic fragment **164** (**Scheme 63**). The combination of these effects encourages any lithiated *p*-CF_3 alkenyl sulfonamide **160** that does form *via* β-addition, to ultimately convert to enediyne **154**. This explains the absence of quenched *p*-CF_3 alkenyl sulfonamide **155**, whilst a small amount of enediyne **154** was obtained.

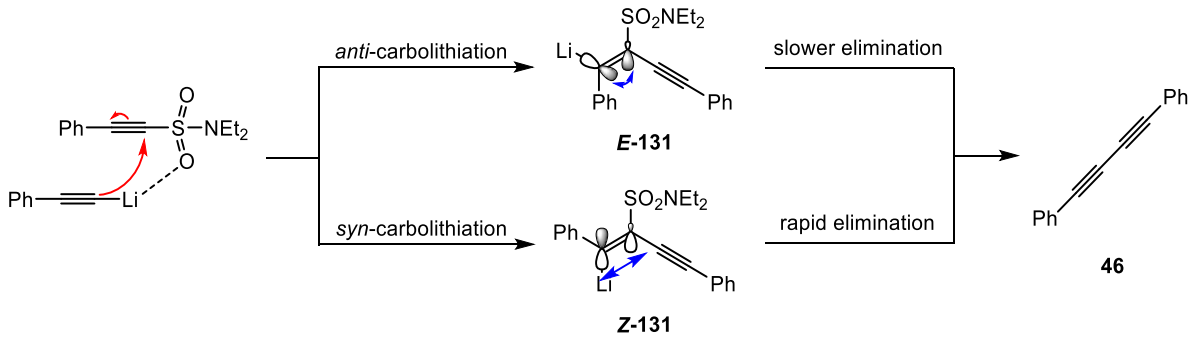


Scheme 63: The associated EWG/EDG will promote/hinder subsequent conversion of alkenyl sulfonamide to enediyne

In contrast, conversion of the *p*-OMe lithiated species **161** to the corresponding enediyne **157** is hindered by the EDG, as it affords the opposite influences to the *p*-CF_3 within intermediates **161**, **163** and **165**. As a result, a substantially greater proportion of quenched *p*-OMe alkenyl sulfonamide **158** than *p*-OMe enediyne **157** is obtained. In the case of the original alkynyl sulfonamide **106**, and the absence of any special electron withdrawing/donating effects, it follows that a moderate amount of all three products (**125**, **126** and **46**) would form.

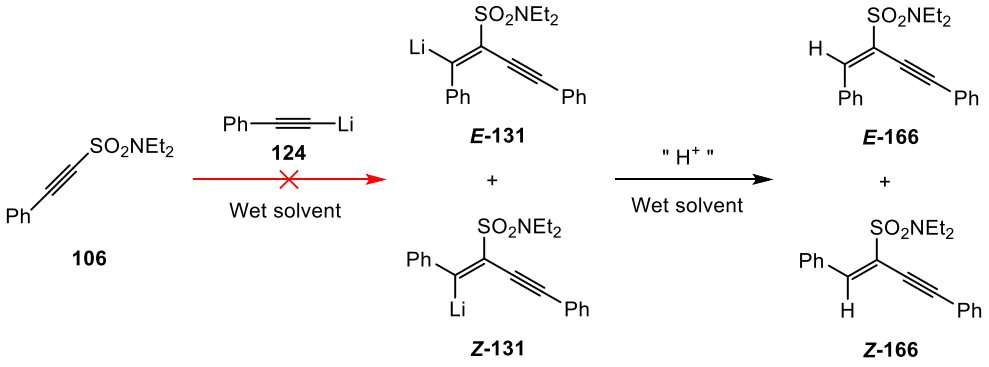
Alkynylation of the α-carbon may theoretically occur *via* either *anti* or *syn*-carbolithiation, though the products of these two pathways are identical (**Scheme 64**). Due to less favourable orbital overlap, elimination would be expected to occur much slower in the *E*-intermediate (***E*-131**) than the *Z*-intermediate (***Z*-131**), although no quenched form of either isomer was ever isolated. This absence would suggest that whichever isomer forms, both are sufficiently

reactive to decay well before the point of work-up. This is in stark contrast to the intermediary species of the β-addition pathway (**132**), which possesses no favourable elimination route, and is therefore stable in the absence of further acetylide attack.



Scheme 64: Addition-elimination pathways to the diyne, initiated by either *anti* or *syn*-carbolithiation

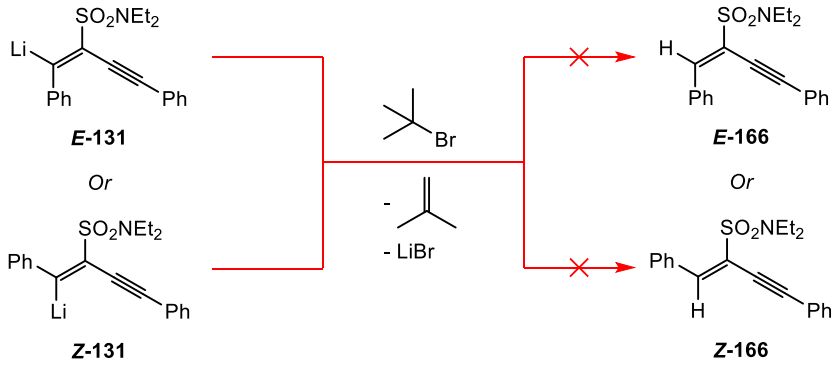
The consistent absence of any quenched intermediates from α-attack (for example ***E*/*Z*-166**) (**Scheme 65**) among reaction products was initially surprising, since previous work within the Wilden group[218, 230] had successfully isolated the protonated forms of analogous alkoxide/thiolate α-additions (**120**) (see **Scheme 41**, **page 54**). It was reasoned that since this was due to residual water in the system (whereas the quenched products **120** were absent if anhydrous solvent was used), quenched forms of intermediates ***E*/*Z*-131** (***E*/*Z*-166**) could theoretically form by using wet solvent in these experiments.



Scheme 65: Hypothetical formation of quenched intermediates is prohibited by the reaction's high sensitivity to water

Unfortunately, such an isolation attempt was not feasible with the novel syntheses of diynes described, as the reaction failed to proceed in the presence of even trace amounts of water. However, carrying out the reaction in the presence of the weaker proton donor ^{t}BuBr also failed

to isolate quenched products of α-addition (***E*/*Z*-166**) (**Scheme 66**), suggesting the preceding intermediates ***E*/*Z*-131** are extremely reactive.

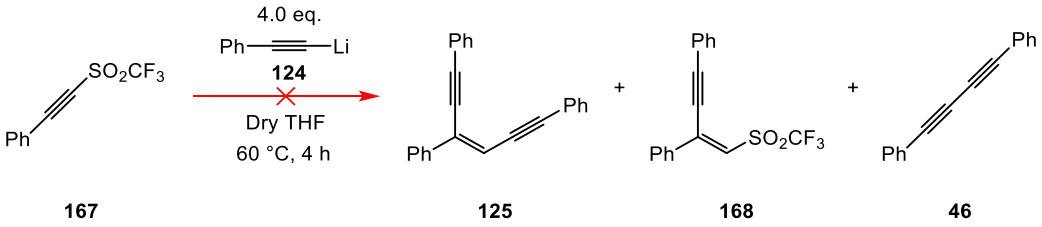


Scheme 66: Employment of ᵗBuBr as a proton source failed quench intermediates, suggesting they are highly reactively

2.3. Investigative Starting Material Modifications

2.3.1. Alternative Sulfone and Phenylacetylides

It was of great interest to explore the scope for suitable alternative starting materials, from the novel synthesis of enediynes, diynes and alkenyl sulfonamides described. In accordance with the devised mechanisms at play (see **Scheme 56**, **page 65** and **Scheme 64**, **page 72**), it was decided that the trifluoromethylsulfone analogue of alkynyl sulfonamide **106** (**167**), may present an appropriate substitute (**Scheme 67**).

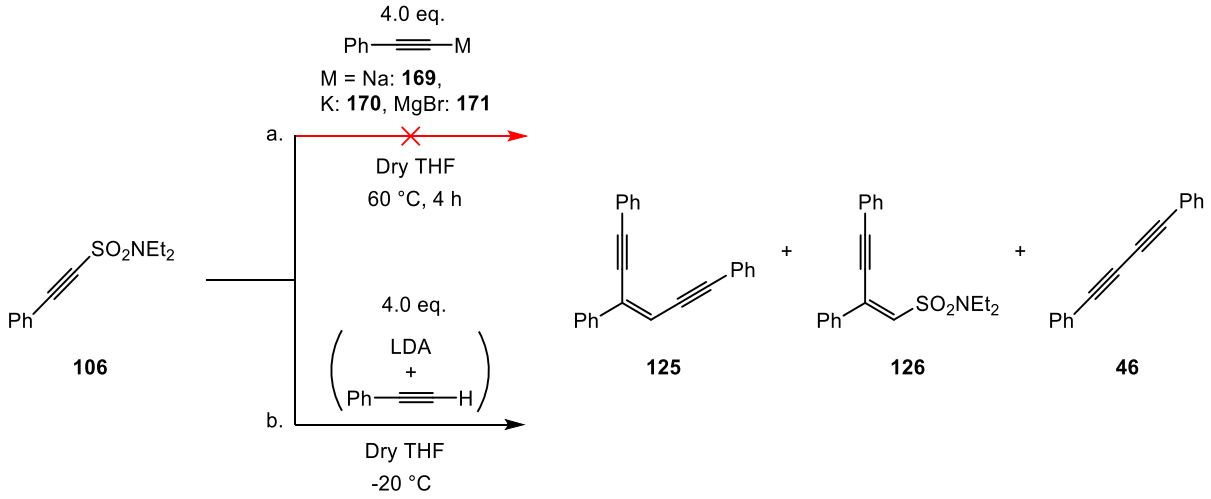


Scheme 67: Substituting the alkynyl sulfonamide for the (trifluoromethyl)sulfonyl analogue failed to react as expected

In addition to its far less cumbersome preparation, it was reasoned that the trifluoromethylsulfone **167** would exhibit superior reactivity to alkynyl sulfonamides. This was because the advanced electron withdrawing capacity of the CF_3 moiety, would be expected render the sulfonyl unit a better leaving group. In particular, a higher proportion of enediyne **125** relative to the corresponding alkenyl sulfone **168** was predicted, since the increased

electrophilicity of sulfur should promote addition of a second molecule of lithium phenylacetylide **124** (see **Scheme 56**, **page 65**). Surprisingly however, upon carrying out the experiment it was found that no reaction occurred even after long periods of heating, and only starting material was recovered.

It was also decided that a range of metal phenylacetylides should be tested as suitable replacements for the lithiated reagent **124**. Since they possess a higher ionic character (K^+ > Na^+ > Li^+),[242] it was reasoned that phenylacetylides of sodium (**169**) and potassium (**170**) should exhibit enhanced reactivity, as both would be expected to provide a more plentiful source of anionic nucleophile (**Scheme 68a**). These reagents were prepared *in situ* by treating phenylacetylene with solutions of NaHMDS and KHMDS respectively, in place of ^{n}BuLi. Given its convenient availability and stability, phenylethynylmagnesium bromide **171** was also tested.



Scheme 68: The use of a. alternative metal cations prohibited normal reactivity, whilst b. a different source of lithium still permitted it

Once again however, these modifications resulted in a complete absence of any reaction, despite extended heating times being applied. Interestingly, it was observed that substitution of ^{n}BuLi with LDA allowed the reaction to proceed normally, even at reduced temperature

(**Scheme 68b**).[vi] Together, these observations implied that the unique combination of the sulfonamide moiety and lithium cation, is essential for this novel mode of reactivity.

2.3.2. Computational Modelling Assisting Explanations

With the aid of Prof Ben Slater once more, computational modelling[vii] was employed to assist us in explaining the unique cooperation between alkynyl sulfonamides and organolithiums. It was initially suspected that within the lithiated sulfonamide intermediate **132** (**Figure 16**), the Li cation would be only loosely associated with carbon and oxygen, so much so that coordination to oxygen should break if subjected to high temperatures.

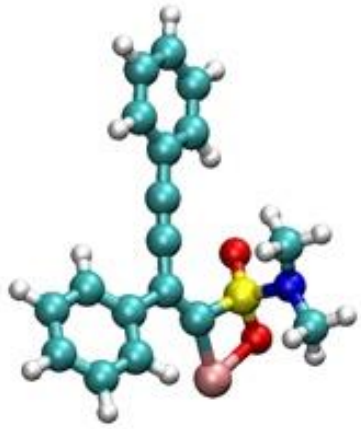


Figure 16[viii]: Visualisation of the minimum energy configuration of the lithiated alkenyl sulfonamide used for calculations

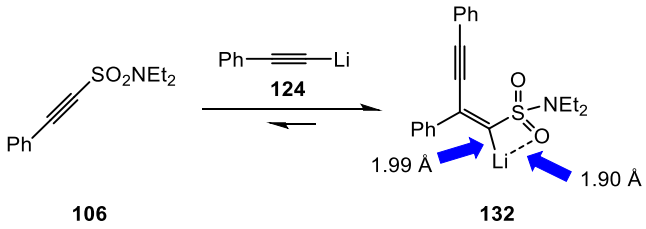
However, a quantum chemical DFT simulation of exposure to a finite temperature of 400 K, failed to disrupt bidentate coordination, which remained stable. It was further found that the metal sits in a special "cavity", where the Li-C and Li-O bonds are very similar in length (calculated to be 1.99 Å and 1.90 Å respectively).[239]

[vi] Experiment carried out by student Georgios Lefkaritis under supervision of the author, and data cited from project thesis: Lefkaritis, G., *Displacement at an sp-centre: What's the mechanism?*, MSci: University College London, **2016**.

[vii] Computational simulations were carried out by Prof Ben Slater using the ORCA quantum chemistry computer program.

[viii] The dimethyl equivalent of lithiated alkenyl sulfonamide **132** was used in calculations, due to its similar structure, and is pictured in this figure. Within the graphic, lithium is coloured pink, oxygen red, sulfur yellow, nitrogen blue, carbon cyan and hydrogen white. Figure adapted from the literature[239] and used with permission.

Similar 4-membered coordination complexes have also been described by Durst & Molin,[243] Biellmann & Vicens[244] and chasseing *et al.*[245] (though these consisted of lithiated sulfoxides for subsequent reaction with electrophiles). Based only on the generally higher stabilities of alkynyl lithium species compared to those of alkenyl analogues, the corresponding reaction equilibrium (**Scheme 69**) would be expected to lean mostly to the left. However, the stabilisation of the lithiated intermediate **132** drives the initial β-addition forward.



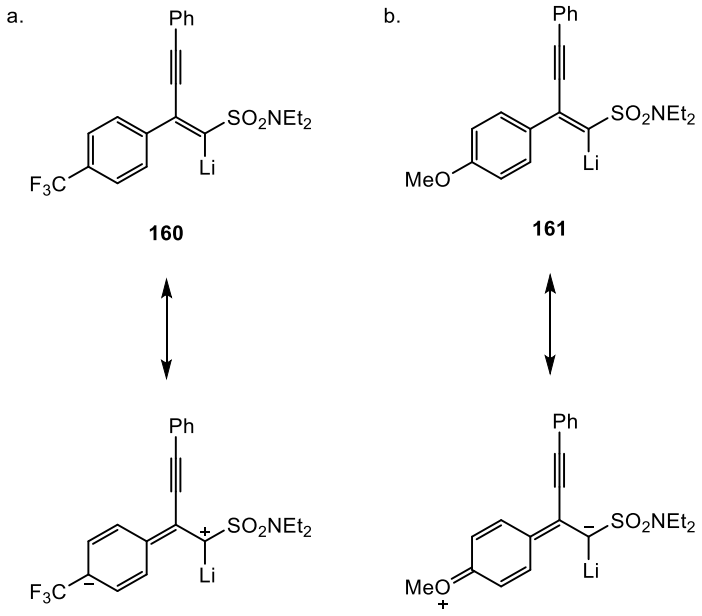
Scheme 69: The forward reaction is stabilised by the lithiated alkenyl sulfonamide structure, where the lithium cation is coordinated in a special "cavity"

Computational simulations also found that subsequent reaction of intermediate **132** with additional lithium acetylide **124**, was highly favourable, with a relatively low energy barrier of approximately 60 kJ mol^{-1} (making the forward reaction exothermic). Within the simulation based on thermodynamic considerations alone, replacing lithium metal with sodium should further facilitate the forward reaction, suggesting that the observed lack of reactivity must be due to kinetic factors.

It was therefore postulated, that the enhanced stability is due to lithium's relatively high effective charge density and small size (a 0.69 Å ionic radius accompanies a +1 charge, compared to 1.02 Å and 1.38 Å in the cases of sodium and potassium respectively).[246] Metals with larger ionic radii such as magnesium, sodium or potassium therefore, are simply too large to fit in the aforementioned intramolecular cavity. The resultant destabilisation of the hypothetical metallated alkenyl sulfonamide intermediates, explains the observed lack of reactivity with alternative metal phenylacetylides.

The molecular model also sheds light on the failure of the trifluoromethylsulfone **167** to undergo β-addition (see **Scheme 67**, **page 73**), as the powerful electron withdrawal of the CF_3 group greatly reduces electron density on the sulfonyl oxygens. This would be expected to significantly weaken the stabilising coordination to lithium, resulting in the equilibrium of **Scheme 69** lying too far to the left for subsequent reaction.

Moreover, the model is consistent with the propensities of the electron rich/deficient alkynyl sulfonamides, to respectively favour/disfavour initial β-addition (see **Scheme 61**, **page 69**). Upon attack by lithiated phenylacetylide, the electron rich sulfonamide **161** (**Scheme 70b**) is stabilised by a canonical form with substantial negative charge on the partially anionic carbon. Meanwhile, the opposite effect is at play in the electron deficient sulfonamide **160** (**Scheme 70a**). The associated stability of these intermediates or lack thereof, is therefore possibly linked to the extent of attack on alkynyl sulfonamidyl β-carbons.



Scheme 70: The partially anionic carbons of the lithiated alkenyl sulfonamides are a. destabilised by the EWG and b. stabilised by the EDG, potentially contributing to the lower and higher yields of alkenyl sulfonamide products respectively

Prohibition of the α-addition pathway with the modifications discussed in **section 2.3.1**, is less well understood at present. It may be that initial O-Li coordination is essential in activating carbometallation, hence any disruption to this would prohibit reaction. In the trifluoromethylsulfone **167**, the electron withdrawal of the CF_3 group may reduce electron density on sulfonyl oxygen to a substantially low level, that effective coordination is disallowed (**Figure 17b**). With phenylacetylides of sodium (**169**) and potassium (**170**), extensive dissociation may render the free alkynyl anions inactive (**Figure 17c**).

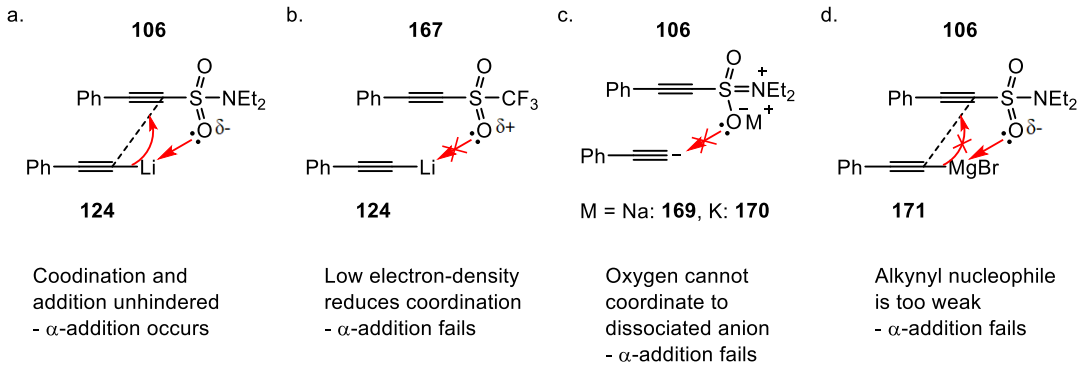


Figure 17: The dependency of α-addition on effective coordination of sulfonamidyl oxygen to lithium

As shown by Eisch,[247] Grignard reagents are far poorer sources of nucleophilic carbon compared to their organolithium equivalents, which may rationalise the failure of phenylethynylmagnesium bromide **171** to react. It is possible that this alkynyl nucleophile is simply too weak to undergo initial attack, followed by subsequent elimination of the sulfonamide, which is a relatively poor leaving group in itself (**Figure 17d**). If the described effects are indeed all active, it appears that a delicate balance of C-M bond covalency within the metal phenylacetylide must be attained, in order for α-addition to proceed. This is apparently met when lithium phenylacetylide **124** is added to alkynyl sulfonamide **106** (**Figure 17a**).

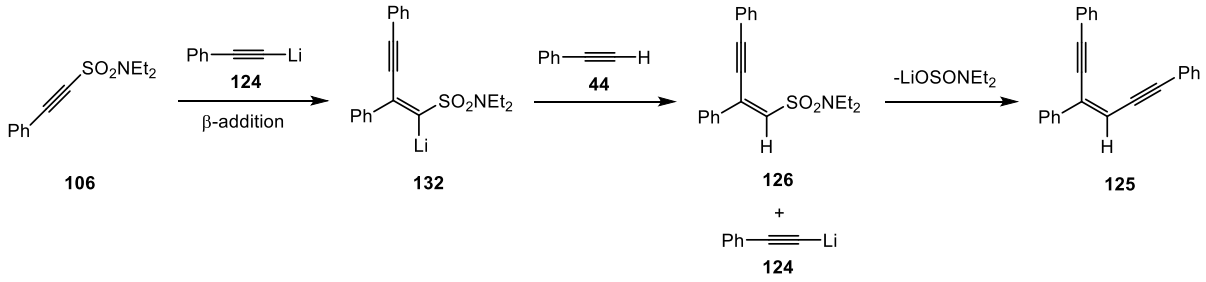
Similarly, it is also possible that the nature of O-Li coordination involves both sulfonyl oxygens simultaneously interacting, in which case lithium sits between them. This system would also be disturbed by the EWG of the trifluoromethylsulfone **167**. Additionally, in the cases of non-lithium based phenylacetylides **169**, **170** and **171**, the alternative metal cations are simply too large to fit. Further computational studies would be required to test this theory.

2.4. Reaction Optimisation

2.4.1. Initial Optimisation Experiments

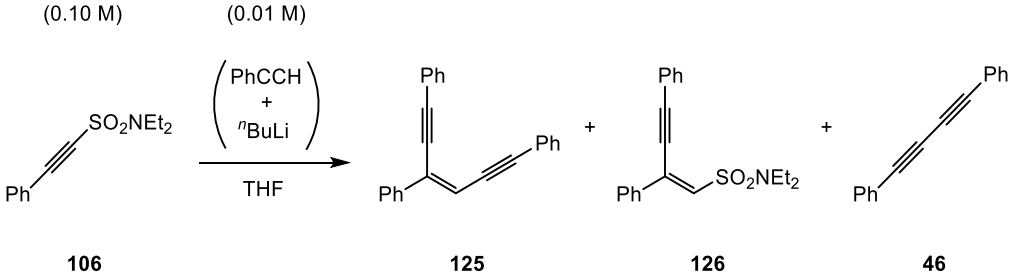
Concurrent to mechanistic studies, experiments were carried out attempting to optimise the yields of the different reaction products. With reference to similar work by Reichl & Radosevich[136] outlined in **section 1.1.6**, a direct protonation of lithiated alkenyl sulfonamide **132** by trace phenylacetylene **44**, was considered a significant sub-pathway to enediyne **125** (**Scheme 71**). This was thought to proceed *via* addition of lithium phenylacetylide **124** to the

quenched alkenyl sulfonamide **126**, for at this point it had not yet been shown that such a pathway could not happen.



Scheme 71: The hypothetical pathway for reaction of alkenyl sulfonamide with phenylacetylene to form enediyne, later found not to occur

Early on it was reasoned that if this mechanism was operating, treating alkynyl sulfonamide **106** with a 50:50 mixture of protonated and deprotonated phenylacetylene (**Table 1**, **Entry 2**), would result in an increased yield of enediyne **125**. The result however, was a substantial decrease in overall starting material conversion, presumably due to the lack of nucleophilic alkyne available to induce initial α/β-addition. The particularly low yield of enediyne **125** is also understandable, as its formation requires an additional molecule of lithium phenylacetylide **124**, relative to the alkenyl sulfonamide **126** and diyne **46** products.



Entry	PhCCH (eq.)	^{n}BuLi (eq.)	add. rate (mmol/min)	THF type	temp. (ºC)	125 (%)	126 (%)	46 (%)	SM (%)
1	4.0	4.0	0.0100	dry	RT	37	27	15	0
2	4.0	2.0	0.0100	dry	RT	3	35	10	36
3	4.0	8.0	0.0100	dry	RT	22	30	16	0
4	4.0	4.0	0.0100	dist.	RT	53	8	16	0
5	1.1	1.1	0.0025	dist.	RT	8	40	12	16
6	1.1	1.1	0.0025	dist.	60	21	28	28	6

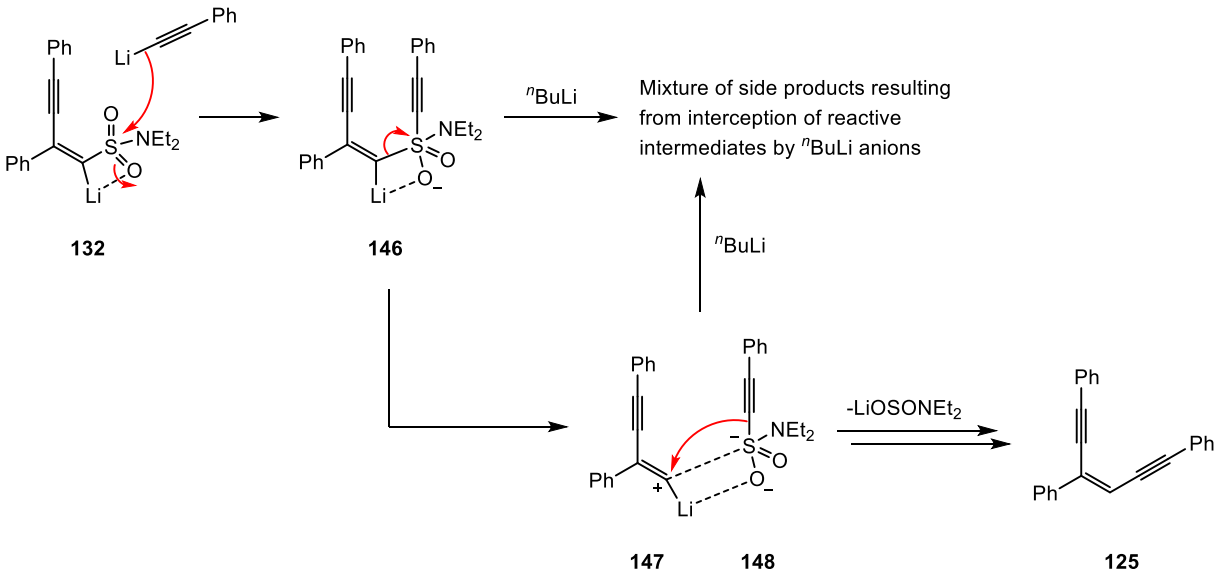
7*	1.1	1.1	0.0600	dist.	60	29	5	20	0
8	1.1	1.1	0.0025	dist.	-20	0	31	12	52

**0.1 M solution of (PhCCH + ^{n}BuLi) used.*

Table 1: The initial experimental attempts to optimise yields and tune the proportions of different products

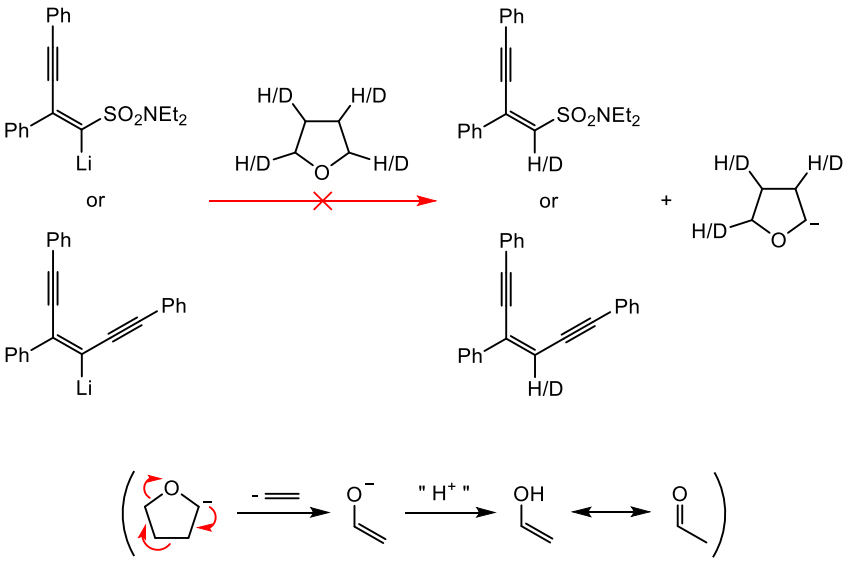
Furthermore, it was later comprehended that contrary to similar pathways proposed by Reichl & Radosevich,[136] greater quantities of any proton source would also inhibit conversion of lithiated alkenyl sulfonamide **132** to enediyne **125**. Since addition-elimination by lithium phenylacetylide **124** on alkenyl sulfonamide **126** was shown not to occur in these systems (see **Scheme 51**, **page 63**), possible protonation of the lithiated intermediate **132** by phenylacetylene **44**, would be prohibitive to further reaction.

It was decided to attempt a reduction of the influence of trace adventitious proton sources in solution, which may have been hindering conversion of the lithiated intermediate **132** to enediyne **125** product, *via* premature quenching. To do this whilst maintaining an abundant source of lithium phenylacetylide **124**, the amount of ^{n}BuLi was doubled (**Table 1**, **Entry 3**). Interestingly, this increase in base had little effect on the original results, other than to slightly reduce the yield of enediyne **125**. Whilst this decrease might not be significant, it may have been caused by a proportion of intermediary species, such as **146**, **147** and **148**, being intercepted by excess ^{n}BuLi to form side-products which were not isolated (**Scheme 72**).



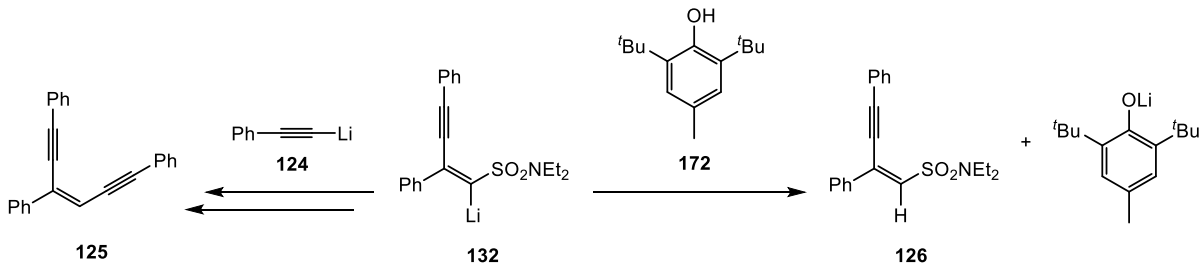
Scheme 72: Some possible pathways of reactive intermediate interception by excess ^{n}BuLi

Further contemplation of the reaction system led to the consideration that commercial solvent additives such as BHT, or even THF solvent itself, could be the key perpetrators of adventitious protons. To investigate the latter possibility, the reaction was simply repeated using THF-d_8, and after neither of the potential deuterated products were isolated, the solvent was discounted as a proton source (**Scheme 73**).



Scheme 73: The hypothetical pathway of premature protonation by THF, shown to be inactive by deuterium labelling

Testing the influence of BHT **172** (**Scheme 74**) was not so straightforward, inherently being far lower in concentration than molecules of solvent. To observe its effect on the reaction, commercial supplies of THF were distilled to remove the involatile additive (in small quantities, to reduce the associated risk of explosive peroxide formation), and the original experiment was repeated using this solvent (**Table 1**, **Entry 4**). As a result, higher yields of enediyne **125** were obtained at the expense of alkenyl sulfonamide **126**, whilst the amount of diyne **46** remained unchanged.



Scheme 74: Pathway of premature protonation by BHT, found to be probable as removal of the additive led to increased yields

This suggested that removal of BHT **172** did indeed allow greater conversion of lithiated alkenyl sulfonamide **132**, with less hindrance from premature quenching. Alternatively, it is also possible that these results were due to the freshly distilled THF simply being drier than commercial samples.

It was also of interest to observe whether the yield of diyne **46** could be optimised. In accordance with the enediyne formation mechanism (see **Scheme 56**, **page 65**), it was theorised that a lowered concentration of lithiated nucleophile **124** would reduce the amount of enediyne **125** produced, in favour of diyne **46** and alkenyl sulfonamide **126**. To test this, the effective concentration was reduced by simultaneously employing less lithium phenylacetylide **124** (1.1 eq. instead of 4.0 eq.), and slowing the addition to a quarter of the original rate (**Table 1**, **Entry 5**). Initially, a simple dilution of the lithiated alkyne solution (by a factor of ten) had been trialled, however no reaction proceeded in this case; it is suspected that such a large increase in the volume of THF permitted inhibitory amounts of water.

The observed results corroborated predictions, with a proportionally higher yield of diyne **46** relative to the enediyne **125**, and an even greater one to the alkenyl sulfonamide **126**. Furthermore, the proposed mechanistic routes to both the enediyne and diyne (see **Scheme 56**,

page 65 and **Scheme 64**, **page 72** respectively) imply an increased energy input should propagate their formation. Heating the system to 60 °C (just below THF's boiling point of 66 °C) successfully increased yields of enediyne **125** and diyne **46**, with a corresponding reduction in alkenyl sulfonamide **126**, and almost complete consumption of starting material (**Table 1**, **Entry 6**).

The increased conversion of both alkynyl sulfonamide **106** and the subsequent intermediary sulfonamide **132**, occurred despite the near 1:1 ratio of alkynyl sulfonamide **106**:lithium phenylacetylide **124**. The moderate yield of all three products obtained under these parameters led to their standardised use in various other experiments probing the reaction mechanism (see **Scheme 53**, **page 64**, **Scheme 61**, **page 69**, **Scheme 75**, **page 88**, **Scheme 77**, **page 90**, **Scheme 78**, **page 90**, **Scheme 80**, **page 91** and **Scheme 82**, **page 92**).

The consumption of both alkynyl sulfonamide **106** and intermediary sulfonamide **132**, was also relatively improved by increasing the starting material concentration, whilst simultaneously raising the addition rate (**Table 1**, **Entry 7**). This change was attributed to a decreased influence of water traces and other adventitious proton sources, resulting from the significant reductions in total solvent used and reaction time.

It was also of interest to discover the minimum temperature at which the synthesis could proceed. Preliminary experimentation, whereby the system temperature was incrementally raised, and progress monitored *via* TLC, revealed that initial α/β-addition necessary for alkenyl sulfonamide **126** and diyne **46** products, occurred as low as -20 °C. However, the subsequent incorporation of a second molecule of lithium phenylacetylide **124** required to form the enediyne **125**, could not occur below approximately 0 °C.

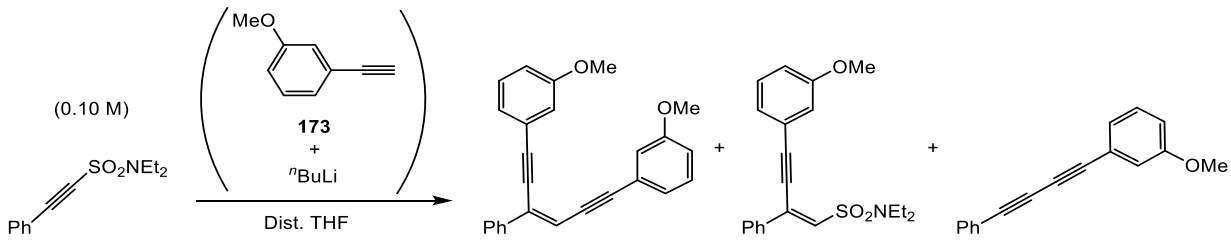
This temperature dependency was visualised when the standardised conditions were modified, carrying out the reaction at -20 °C (**Table 1**, **Entry 8**), which produced some alkenyl sulfonamide **126** and diyne **46** products, yet no enediyne **125**. The substantial amount of remaining starting material, is presumed to be due to consumption of lithium phenylacetylide **124** by side-reactions normally less active at higher temperatures.

2.4.2. Design of Experiments Study

Attempts to optimise the novel enediyne synthesis were continued by DoE methods, in collaboration with Dr Tom Sheppard (an Organic Chemist in the department with expertise in DoE). The experimental system was carefully engineered to increase efficiency, and reduce discrepancy between measured and actual results (see **section 4.2.17**); Stock solutions of reagents were prepared, fixed volumes of starting material used, reaction times were synchronised precisely, and the same apparatus was employed for each run.

It was suggested that column chromatography of individual product mixtures would introduce a significant source of relative error, since the changes to reaction conditions were so small. The highly time-consuming nature of carrying out this purification technique for each run made it further undesirable. As an alternative, it was decided to measure reaction yields *via* ^{1}H-NMR using an internal standard, by completely dissolving crudes in a $CDCl_3$ based stock solution of pentachlorobenzene. In order to provide more distinctive signals characteristic to the products, phenylacetylene was substituted with 3-methoxyphenylacetylene **173**.

Equivalents of 3-methoxyphenylacetylene **173** (1-3 eq.), equivalents of ^{n}BuLi (1-3 eq.), acetylide concentration (0.010-0.100 M), acetylide addition rate (0.0010-0.0100 mmol/min), and temperature (0-60 °C), were chosen as the parameters to be varied. Nineteen differing sets of conditions were tested, providing a full resolution of all five factors (**Table 2**).



Entry	173 (eq.)	^{n}BuLi (eq.)	add. rate (mmol/min)	conc. (M)	temp. (°C)	128 (%)	129 (%)	130 (%)	SM (%)
1	3.0	3.0	0.0010	0.010	60	25	7	49	0
2	1.0	1.0	0.0010	0.010	0	0	0	20	35
3	3.0	3.0	0.0010	0.100	0	8	0	58	0
4	1.0	1.0	0.0100	0.010	0	4	23	22	41

5	1.0	1.0	0.0010	0.010	60	0	11	30	35
6	3.0	1.0	0.0100	0.100	0	22	38	38	0
7	2.0	2.0	0.0055	0.055	30	28	15	20	0
8	1.0	1.0	0.0010	0.100	0	0	5	16	35
9	3.0	1.0	0.0010	0.010	0	0	0	21	39
10	3.0	1.0	0.0100	0.010	60	3	2	9	4
11	1.0	3.0	0.0100	0.010	60	0	0	53	24
12	2.0	2.0	0.0055	0.055	30	11	0	9	0
13	2.0	2.0	0.0055	0.055	30	23	7	4	0
14	3.0	3.0	0.0100	0.010	0	11	10	61	0
15	1.0	1.0	0.0100	0.100	60	2	0	14	0
16	3.0	3.0	0.0100	0.100	60	4	0	85	0
17	1.0	3.0	0.0010	0.100	60	0	0	0	67
18	1.0	3.0	0.0100	0.100	0	0	0	20	0
19	3.0	1.0	0.0010	0.100	60	30	24	31	0
20[*]	3.0	3.0	0.0100	0.100	60	34	0	32	0

**Experiment carried out after primary runs to test model*

Table 2: DoE experimental runs

Unfortunately, these results produced poor-quality models for the optimisation of enediyne **128** and alkenyl sulfonamide **129** production, and whilst that of the diyne **130** was better, it still possessed significant margins of error (**Figure 18**). The analysis carried out by Dr Sheppard, predicted that increases in all parameters would independently affect increased yields of diyne **130**. This was with the exception of temperature and concentration, which appeared to have little positive or negative effect.

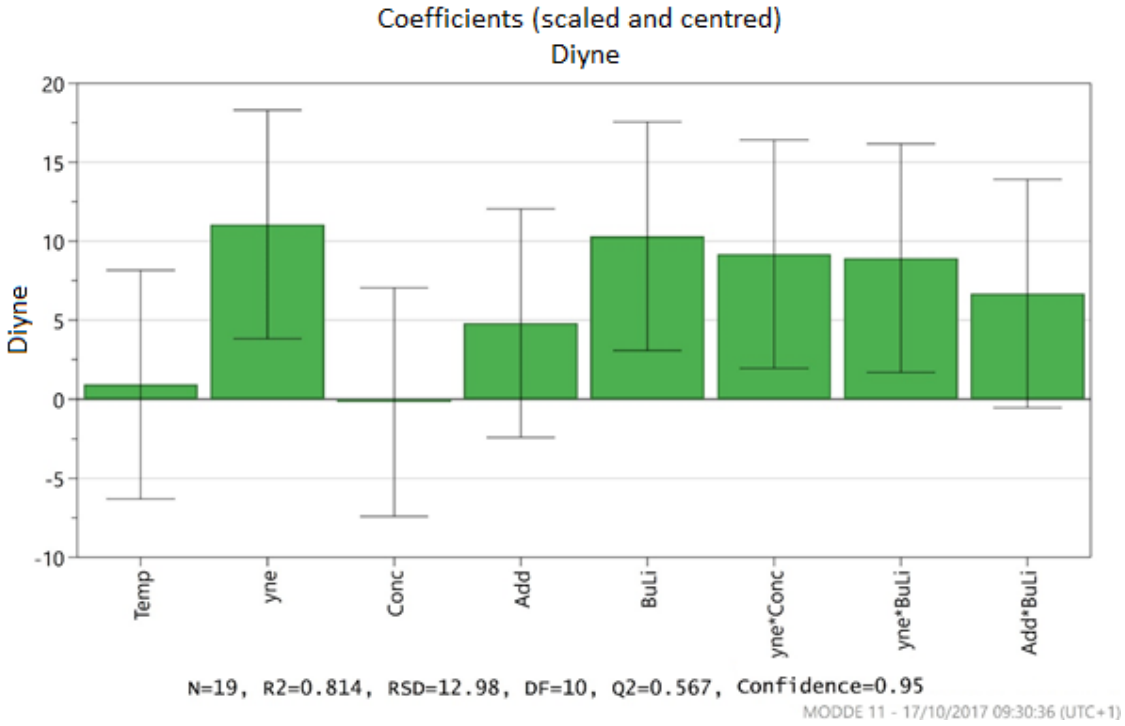


Figure 18[ix]: The effect of maximising different reaction parameters on diyne yield

Although variation of concentration alone was not predicted to bring about considerable change, the influence of 3-methoxyphenylacetylene **173** stoichiometry would be most pronounced when it was higher. Similar dependencies were also found for ^{n}BuLi on raised addition rates, and by the amount of acetylene on larger quantities of ^{n}BuLi, the latter corroborating initial optimisation experiments in **section 2.4.1** (see **Table 1**, **Entries 2-3**, **page 80**).

To test the diyne model, an experiment was carried out with all five factors maximised within their experimental ranges (**Table 2**, **Entry 20**). Surprisingly, moderate amounts of both diyne **130** and enediyne **128** were obtained, in dispute with both the predicted results, and those of an identical run (**Table 2**, **Entry 16**). In addition to the disappointing level of reproducibility

[ix] Figure produced by Dr Tom Sheppard and used with permission. Along the x axis, Temp indicates temperature, yne indicates amount of acetylene **166** starting material, Conc indicates concentration of lithiated acetylene **166** solution, Add indicates addition rate of lithiated acetylene **166** solution, BuLi indicates amount of ^{n}BuLi reagent, yne*Conc indicates the combined effect of amount and concentration of acetylene **166** starting material, yne*BuLi indicates the combined effect of amounts of acetylene **166** starting material and ^{n}BuLi reagent, and Add*BuLi indicates the combined effect of addition rate of lithiated acetylene **166** solution and amount of ^{n}BuLi reagent. The scale of the y axis indicates the expected increase in diyne yield if that variable were raised to the upper limit of the experimental range, along with the associated error.

for the centre point runs (**Table 2**, **Entries 7** and **12-13**), this outcome suggested the experimental setup possessed one or more flaws.

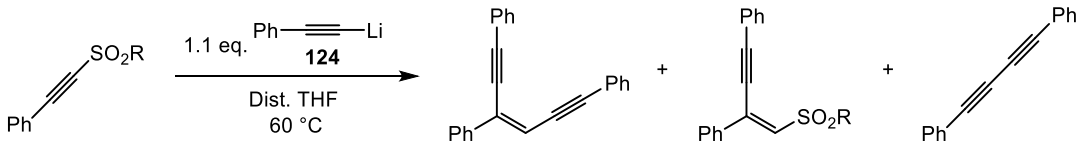
One source of experimental error may have been from runs where concentration was high, but addition rate slow (for example **Table 2**, **Entries 3**, **8**, **17** and **19**). In these cases, a stalactite on the addition needle's tip would form from the acetylide solution, eventually falling into the vortex of alkynyl sulfonamide **106** solution when it became large enough. This resulted in a sudden addition of most of the reagent, drastically altering the actual addition rate from the intended one. This issue may be resolved in future studies by raising the minimum speed within the addition rate range.

The most significant cause of discrepancy however, may be from the NMR analysis. In some instances, the pentachlorobenzene signal overlapped with product peaks, creating some uncertainty about the exact integrations. This problem might potentially be addressed by selection of a different internal standard. Methyl 3,5-dinitrobenzoate (δ_H (ppm) 9.3, 9.2 and 4.1) and benzyl benzoate (δ_H (ppm) 8.1 and 5.4), both give signals[248] more distinctive from the products of these experiments than most common internal standards would, so may be suitable alternatives to pentachlorobenzene. However, due to the complex nature of the ^{1}H-NMR spectra involved, some overlap is still predicted, and yield calculation by comparative integration may in fact be altogether unsuitable for this reactive system.

2.5. Further Starting Material Modifications

2.5.1. Alternative Amine Groups

It was proposed that increasing electron withdrawal from the starting material's amine moiety would reduce the strength of coordination detailed in **Scheme 69** on **page 76**, as well as the corresponding special stability of intermediate **132**. Additionally, this increase would also be expected to ease elimination of the sulfonamide leaving group, and improve the electrophilicity of the alkyne unit. The combination of these factors would be expected to affect a noticeable increase in enediyne and diyne yields, accompanied by a corresponding decrease in alkenyl sulfonamide. As such, the reactivities of alkynyl sulfonamides **174** and **175**, incorporating morpholine and *N*,*O*-dimethylhydroxylamine respectively, were compared with sulfonamide **106** (**Scheme 75**).



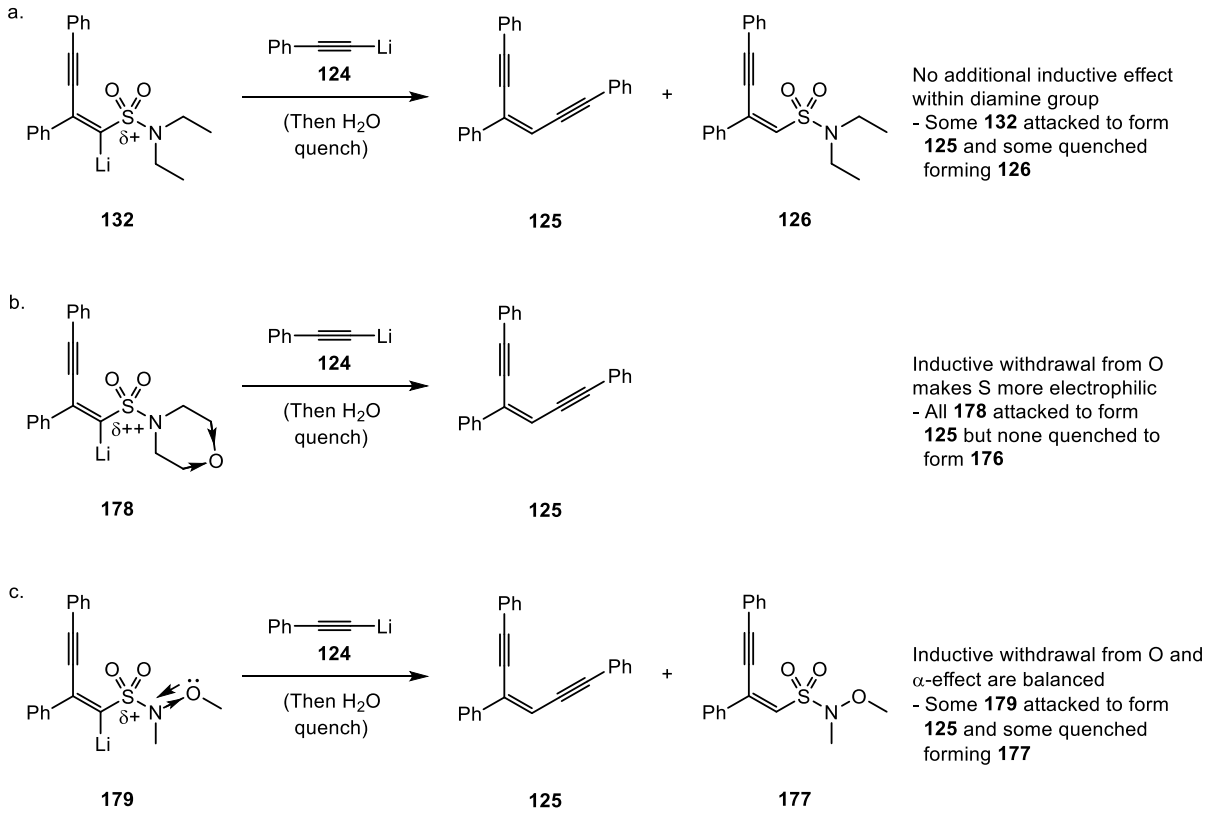
125 **46**

R = NEt_2: **106**,	R = NEt_2	21%	28% (**126**)	28%
$N(CH_2CH_2)_2O$: **174**,	R = $N(CH_2CH_2)_2O$	17%	0% (**176**)	27%
NMeOMe: **175**	R = NMeOMe	17%	29% (**177**)	21%

Scheme 75: Yield distribution of enediyne, alkenyl sulfonamide and diyne products with varying amine group

Somewhat surprisingly, these substitutions appeared to have very little effect on the outcome of the reaction. It would appear that relatively minor changes to the sulfonamide group such as these, do not significantly interfere with the coordination effects detailed in **section 2.3.2**, nor the electronics of the alkynyl sulfonamide. This may suggest that generally, only a small amount of electron donation from the amine group, is necessary to stabilise the products of an equilibrium analogous to the one in **Scheme 69** on **page 76**. Whilst these results did not achieve the desired increases in product yields, they did demonstrate a degree of flexibility in suitable starting material structures.

One noteworthy point was the absence of any alkenyl sulfonamide produced from the morpholine based starting material **174** (**176**), which was never isolated despite multiple attempts (**Scheme 76b**). Though a subtle effect, it may be due to the inductive withdrawal of oxygen increasing the electrophilicity of sulfur, making the intermediary species **178** more liable to nucleophilic attack than lithiated alkenyl sulfonamide **132** (**Scheme 76a**).

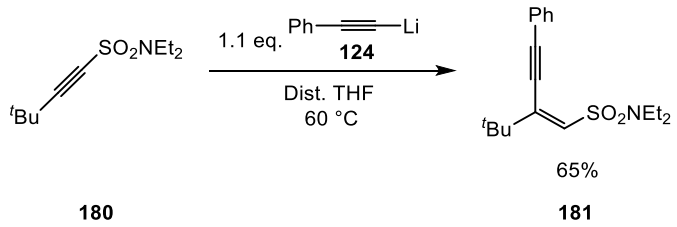


Scheme 76: Possible explanations for the formation of alkenyl sulfonamide products, when using starting materials based on a. diethylamine and c. *N,O*-dimethylhydroxylamine, but not b. morpholine

Within the intermediate preceding alkenyl sulfonamide **177** (**179**), an analogous withdrawing effect would be operational, but is thought to be balanced by the alpha effect from α-bonded oxygen, due to its lone pair electrons (**Scheme 76c**). As a result, lithiated alkenyl sulfonamides **132** and **179**, are approximately equal in their susceptibility to conversion to enediyne **125**, but much less so than the lithiated species **178**. Investigation into incorporation of other alternative amine groups, such as dimethylamine or diphenylamine, may yield further interesting results.

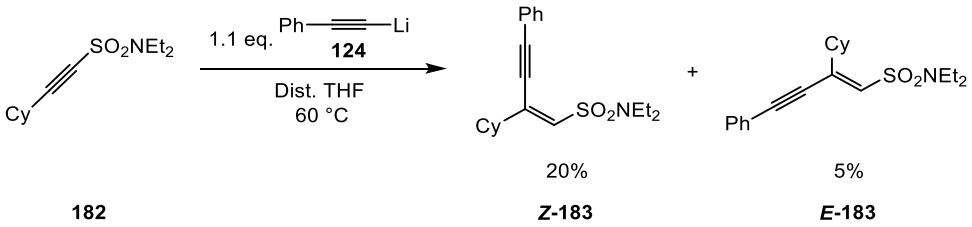
2.5.2. Non-Aromatic Alkynyl Sulfonamides

Whilst a variety of aryl-alkynyl sulfonamides had demonstrated good reactivity with lithium phenylacetylide **124**, non-aromatic examples had yet to be tested. Of particular interest was the *tert*-butyl sulfonamide **180**, as previous work within the Wilden group[218] had found its treatment with alkoxide nucleophiles failed to give any reaction. Upon carrying out the appropriate experiment, the expected alkenyl sulfonamide **181** was produced in moderate yield, however no diyne nor enediyne products were obtained (**Scheme 77**).



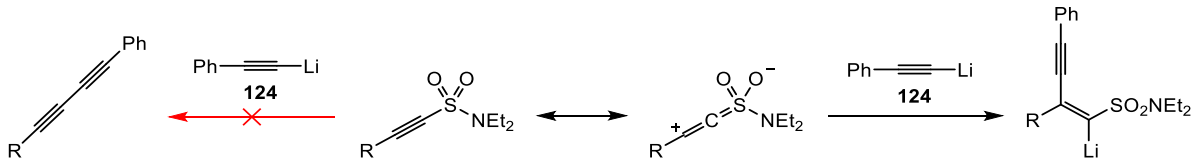
Scheme 77: The *tert*-butyl alkynyl sulfonamide produces only the alkenyl sulfonamide when treated with lithium phenylacetylide

Furthermore, substituting the alicyclic cyclohexyl alkynyl sulfonamide **182**, in place of the aliphatic *tert*-butyl analogue (**180**), also yielded only an alkenyl sulfonamide **183**, though in lower yield and of two stereoisomeric forms (**Scheme 78**). It was proposed that the products may be altered with increased heating, and so the experiment was repeated at 100 °C by employing 1,4-dioxane as the solvent. No noticeable change was observed however, suggesting the reactivity was largely temperature independent.



Scheme 78: The cyclohexyl alkynyl sulfonamide produces only alkenyl sulfonamide products when treated with lithium phenylacetylide, but unusally, both *E* and *Z* isomers are formed

It is suggested that the inability of sulfonamides **180** and **182** to produce diynes or enediynes, is directly caused by the absence of an aromatic ring on their alkynyl tail. Whilst an aryl appendage facilitates initial α-addition by providing a route for conjugate addition (see **Scheme 62**, **page 70** and **Scheme 64**, **page 72**), non-aromatic groups cannot do this. Attack by lithium phenylacetylide **124** on non-aromatic sulfonamides **180** and **182**, has therefore only been observed to occur on the β-carbon (**Scheme 79**). This is promoted by the mesomeric effect, in line with the normal expected mode of reactivity. As a result, the alkenyl sulfonamide species **184** and **185** are produced, whilst the diyne products **186** and **187** are consequently excluded .



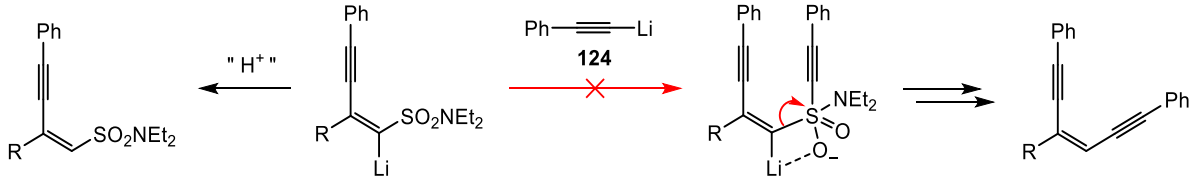
R = ^{t}Bu: **186**, Cy: **187**

R = ^{t}Bu: **180**, Cy: **182**

R = ^{t}Bu: **184**, Cy: **185**

Scheme 79: Resonance effects only promote initial β-alkynylation with these non-aromatic alkynyl sulfonamides

In the case of an aromatic R group, subsequent attack on lithiated intermediate **132** and expulsion of the sulfurous fragments from alkynylated intermediate **146**, may be aided by the extensive conjugation and charge distribution provided by an aryl ring. The absence of these effects however, prevents further reaction that might produce enediynes **190**/**191** *via* dialkynylated intermediates **188**/**189**, allowing only the alkenyl sulfonamide products **181**/**183** to form (**Scheme 80**). Meanwhile, the notably larger yield of *tert*-butyl alkenyl sulfonamide **181**, relative to the cyclohexyl equivalent **183**, may be due to the superior inductive donation from the *tert*-butyl group compared to the cyclohexyl.



R = ^{t}Bu: **181**, Cy: **183**, Ph = **126**

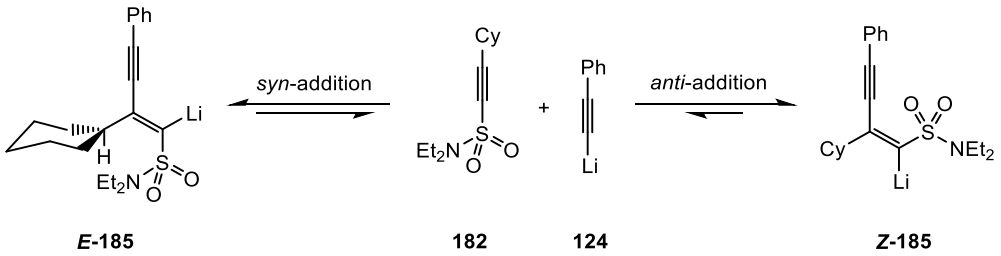
R = ^{t}Bu: **184**, Cy: **185**, Ph = **132**

R = ^{t}Bu: **188**, Cy: **189**, Ph = **146**

R = ^{t}Bu: **190**, Cy: **191**, Ph = **125**

Scheme 80: These non-aromatic lithiated alkenyl sulfonamides fail to provide the electronic conjugation required to stabilise subsequent alkynylation

The presence of a previously unobserved *E*-alkenyl sulfonamide (***E*-183**), in addition to the expected *Z*-isomer (***Z*-183**), is thought to be made feasible by stabilisation of a conformer resulting from *syn*-addition (***E*-185**) (**Scheme 81**). Whilst there is unlikely to be a significant difference in affected reactivity between the phenyl and cyclohexyl rings due to their overall size, the former is met with substantial steric interference from the sulfonamide group (see **Scheme 49**, **page 60**). Conversely, the substantially less rigid cyclohexyl group may rotate into a position that avoids this steric hindrance, circumventing such a destabilising effect and allowing *E*-intermediary alkenyl sulfonamide (***E*-185**) to form.



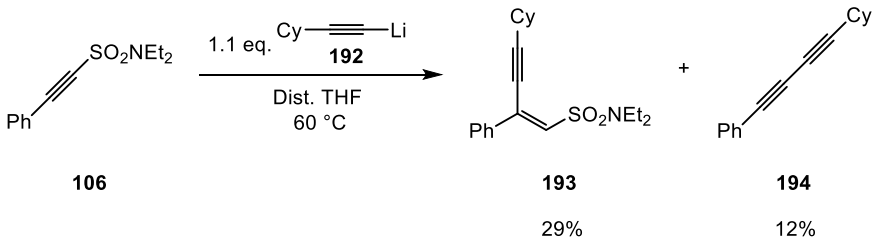
***E*-185** **182** **124** ***Z*-185**

Scheme 81: Unlike the rigid phenyl ring, the cyclohexyl group is able to rotate in order to stabilise *syn*-addition, though *anti*-addition is still preferred

Nevertheless, it appears that the more even distribution of functional groups afforded by the intermediate following *anti*-carbolithiation (***Z*-185**), is still generally favoured, as the *E*:*Z* product ratio stands at 1:4. In the case of *tert*-butyl alkynyl sulfonamide **180** however, this stabilising rotation is unable to occur due to the *tert*-butyl group's structure, and therefore only the *Z*-isomer forms.

2.5.3. Alternative Organolithium Reagents

As explained in **sections 2.3.1-2.3.2**, organometallics based on metals other than lithium fail to react with alkynyl sulfonamides, possibly due to its proposed role in stabilising the intermediary sulfonamide anion (see **Scheme 69**, **page 76**). It was therefore of interest to further explore the scope of lithiated bases that could be used in this novel reaction. Substituting lithiated phenylacetylene with the structurally similar yet non-aromatic cyclohexyl equivalent **192**, successfully produced the corresponding alkenyl sulfonamide **193** and diyne **194**. However, in this instance no enediyne was formed (**Scheme 82**).



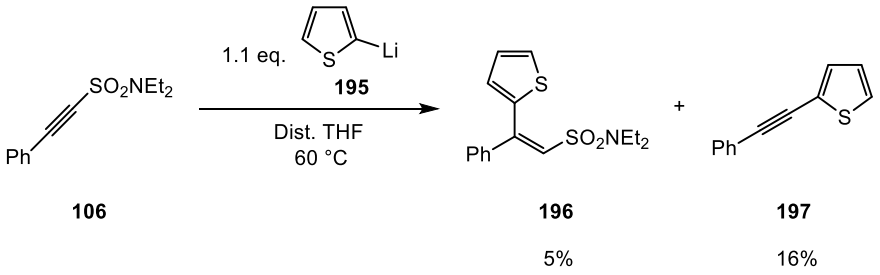
106 **193** **194**

29% 12%

Scheme 82: Addition of this non-aromatic lithiated acetylide only produces the alkenyl sulfonamide and diyne products

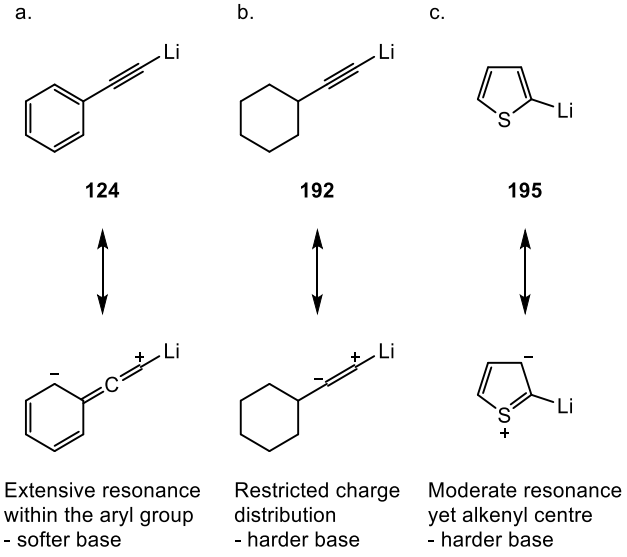
Curious to see whether this reactivity was limited to alkynyl lithiums, it was decided to test monolithiated thiophene **195** also. This too gave only an alkenyl sulfonamide **196**, and the

corresponding product of α-addition comparable to diyne formation (**197**), but none akin to an enediyne *via* sequential β then α-attack (**Scheme 83**).



Scheme 83: Addition of this alternative, non-acetylide based lithiated nucleophile, produces only the alkenyl sulfonamide and expected alkyne products

The exact cause of these peculiar occurrences was rather unclear, though one potential explanation may be found in HSAB theory. This would be based on the varying hardness or softness of the different organolithiums, and the electrophilic centres of alkynyl sulfonamide **106**. Upon formation of the lithiated reagents (**124**, **192** and **195**), distribution of electronic charge *via* resonance is fairly limited within the cyclohexylacetylide **192** (**Scheme 84b**).



Scheme 84: Possible explanations for the formation of enediyne (or equivalent) products with the addition of lithiated a. phenylacetylene, but not b. cyclohexylacetylene or c. thiophene

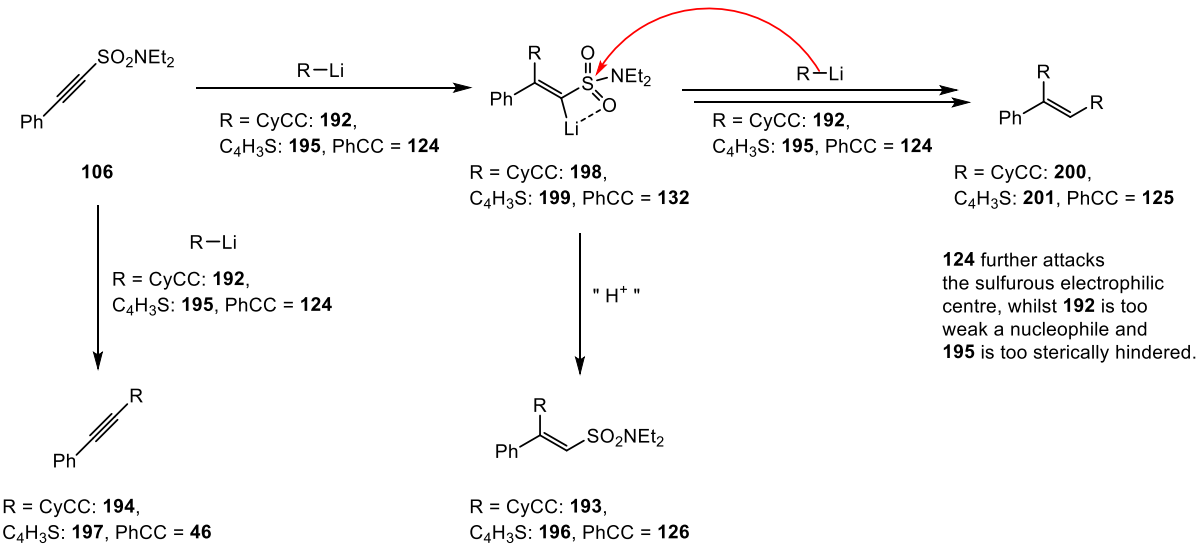
Conversely, the aryl ring of the phenylacetylide counterpart (**124**) allows extensive delocalisation of charge (**Scheme 84a**), conceivably resulting in a comparatively softer basic centre. Whilst lithiated thiophene **195** also exhibits moderate electronic distribution, the lower

polarisability of alkenes compared to alkynes[249] may possibly make it a harder base relative to lithium phenylacetylide **124** (**Scheme 84c**).

Meanwhile, the formations of alkenyl sulfonamides and diynes both involve addition to an alkynyl carbon (see **Scheme 48**, **page 60** and **64**, **page 72** respectively), whereas attack on a sulfurous centre produces enediynes or their potential analogues (see **Scheme 56**, **page 64**). Therefore, whilst the α/β-carbons of the alkyne are sufficiently hard to react with lithiated nucleophiles **192** and **195**, the sulfurous addition site is prohibitively soft. This is likely due to the atom's larger atomic radius, resulting in no enediynes/equivalent products in the cases discussed in this section.

With the use of lithium phenylacetylide **124** and other lithiated aryl-alkynes however, an adequate balance of hardness and softness is met with all three points of attack, allowing the full range of products. This theoretical explanation does however suffer from the implication of a positive charge on a formally anionic carbon, within acetylides **124** and **192**. Whilst these HSAB theory-based explanations may possibly provide an account for the absence of successive β-additions, further computational studies would be required to confirm any accuracy in this explanation.

A somewhat more plausible account for the lack of alkene products **200** and **201** (**Scheme 85**), may simply be that the nucleophilic centre in lithiated thiophene **195** is too sterically hindered. Meanwhile, in the case of lithiated cyclohexylacetylene **192**, the nucleophile may be too weakened by inductive withdrawal of the cyclohexyl group. For the sterically open and electrophilic alkynyl carbons, α/β-attack on alkynyl sulfonamide **106** to form the alkyne products (**194** and **197**) or the intermediary alkenyl sulfonamides (**198** and **199**), would be feasible. Conversely, the sulfurous centres within lithiated alkenyl sulfonamides **198** and **199**, are prohibitively inaccessible or insufficiently electrophilic, to allow successive production of alkene products **200** and **201**.

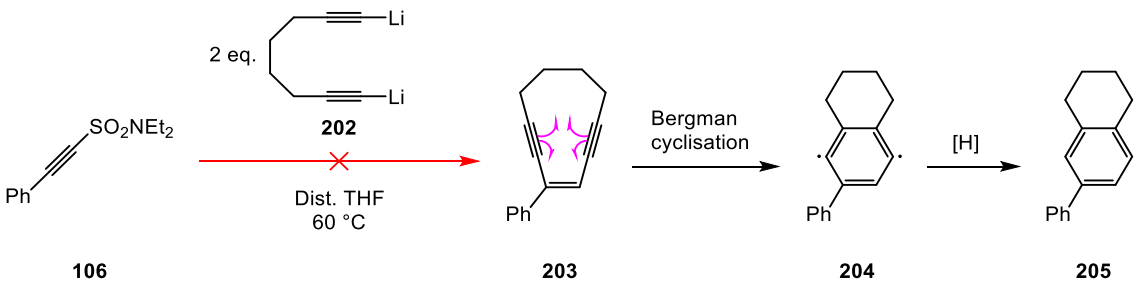


Scheme 85: A possible explanation for the failure of lithiated cyclohexylacetylene and thiophene species to yield alkene products, based on nucleophile strength and steric hinderance respectively

2.5.4. Attempted Bergman Cyclisation of Cyclic Enediyne

It was of great interest to investigate whether this novel preparation of enediynes could be used to synthesise the special class of antitumour agents described in **section 1.1.2**. As an attempted proof of concept, a 10-membered cyclic enediyne **203** was prepared by treating alkynyl sulfonamide **106** with dilithiated 1,7-octadiyne **202**. A combination of reaction conditions previously shown to produce higher enediyne yields (see **Table 1**, **Entries 4** and **6**, **page 80**) was employed.

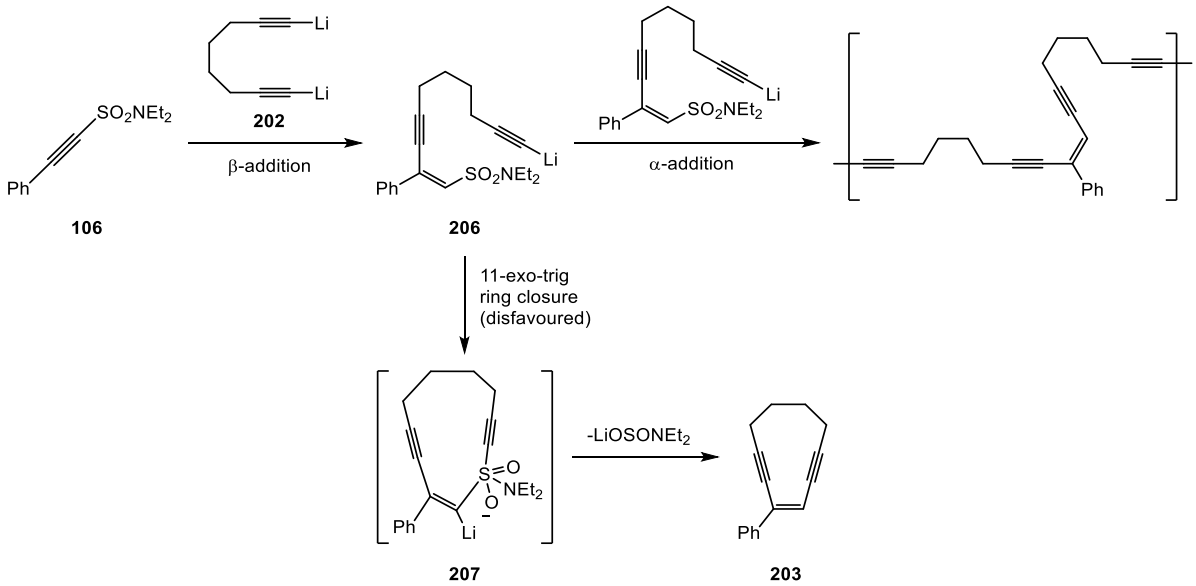
It was theorised that cyclic enediyne **203** would undergo Bergman cyclisation to produce the corresponding tricyclic compound **205** *in situ* (**Scheme 86**). The reaction was predicted to be facile at the elevated system temperature of 60 °C, given the propensity of 10-membered cyclic enediynes to undergo rearrangement at 37 °C (see **section 1.1.2**). However, upon carrying out the experiment, no product of any kind was isolated, and only a dark sparingly soluble substance (characteristic of polymerisation side reactions) was obtained.



Scheme 86: The hypothetical formation of a Bergman cyclisation precursor from alkynyl sulfonamide

It was suspected that the biradical species **204** may have successfully formed, but proceeded to engage in a runaway polymerisation similar to the kind discussed in **section 1.1.5**, preventing significant amounts of tricyclic product **205** forming. It was reasoned that carefully repeating the reaction at 0 °C could allow cyclic enediyne **203** to be isolated, however upon experimentation the same result was obtained.

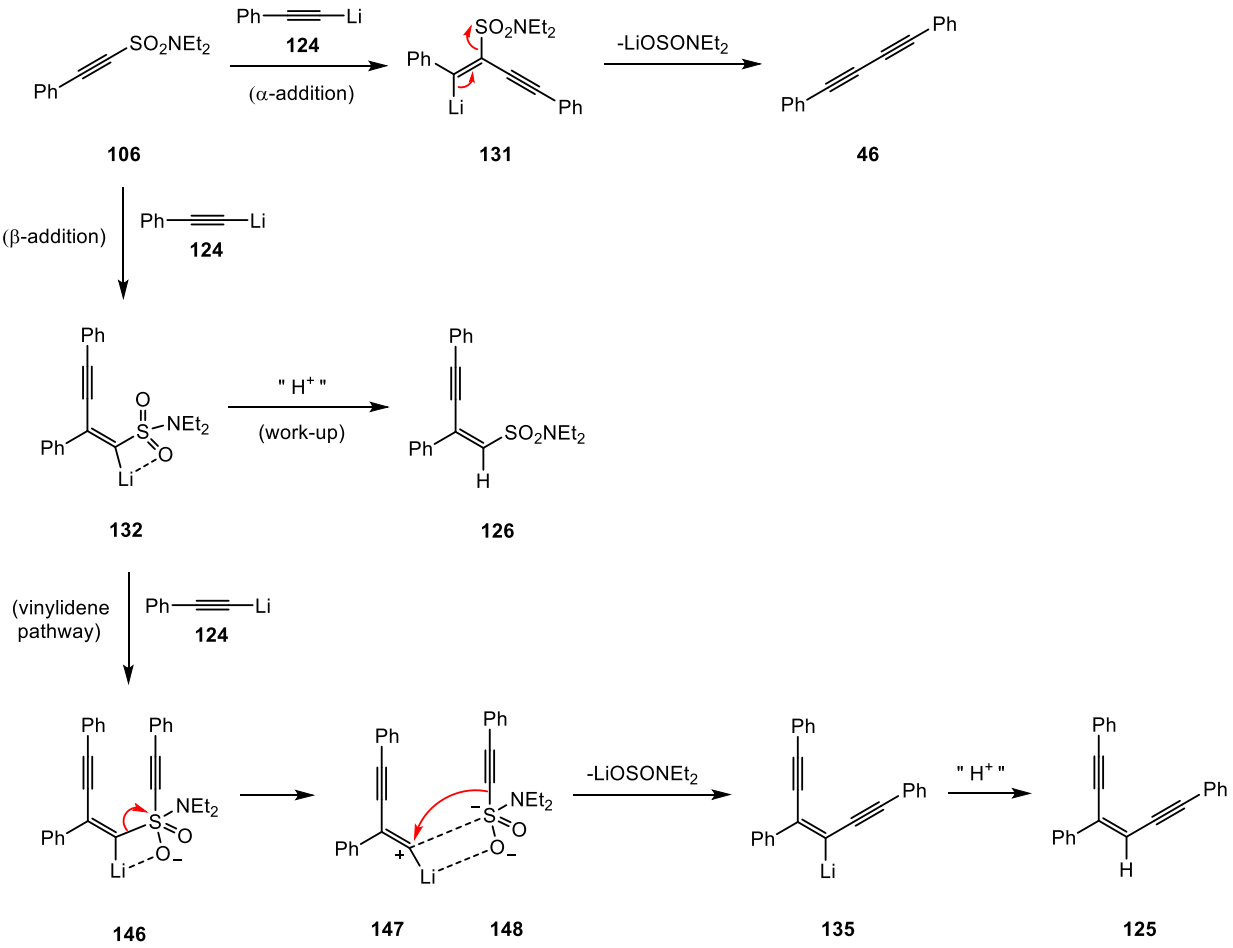
It is possible therefore, that a copolymerisation of alkynyl sulfonamide **106** and dilithiated 1,7-octadiyne **202** was in effect, with the alkenyl sulfonamide intermediate **206** acting as a comonomer (**Scheme 87**). If so, it appears this pathway is favoured over production of cyclic enediyne **203**, possibly due to its avoidance of the 11-membered ring closure that forms the consequential intermediary species **207**, and the associated entropic strain.



Scheme 87: Proposed explanation for the failed production of a Bergman cyclisation precursor, even at low temperature

3. Conclusions and Future Work

In conclusion, a novel preparation of enediynes (for example **125**) has been discovered, by treatment of alkynyl sulfonamides (for example **106**) with lithiated acetylene derivatives (for example **124**). This is accompanied by the additional formation of diyne (for example **46**) and alkenyl sulfonamide (for example **126**) products. Extensive investigations have yielded an understanding of common mechanistic routes thought to be active in these reactions (**Scheme 88**).



Scheme 88: Summary of the proposed mechanistic pathways to enediyne, alkenyl sulfonamide and diyne products

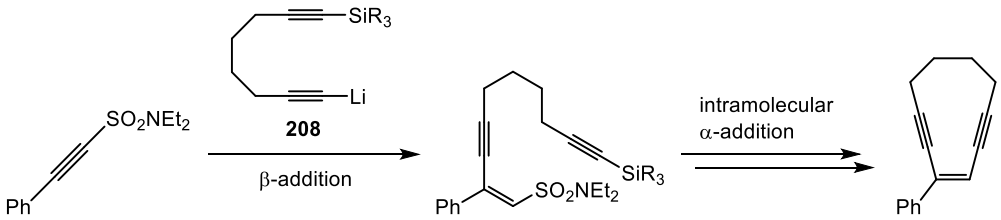
Controlled testing of *o*-substituted sulfonamide **139** suggested the mechanism did not involve a free-carbene (see **Scheme 52**, **page 63** and **Scheme 53**, **page 64**), whilst deuterium labelling implied intermediary alkenyl sulfonamide **132** remained relatively stable in solution (see **Scheme 50**, **page 61**). Computational modelling (see **sections 2.2.2** and **2.3.2**) and the controlled synthesis of the enediyne product **125** from isolated lithiated sulfonamide **132**,

strengthened the proposal of a vinylidene carbenoid pathway for the formation of enediyne (see **Scheme 57**, **page 67**). Meanwhile, experimentation with EWG and EDG substituents, aided suggestion of an α-addition pathway for the formation of diyne (see **section 2.2.3**).

These findings have contributed to the continued pursuit of synthetic routes negating the need for transition metal catalysts, where one was historically required, whilst exhibiting a significant degree of product versatility. Furthermore, this research has expanded the understanding and potential applications of alkynyl sulfonamide chemistry, which has remained largely overlooked within the literature.

Innovative incorporation of the enediyne moiety within the chemical structure of enediyne antitumour agents, may significantly improve the efficiency of their manufacture, paving the way for wider use of this powerful class of drugs. Whilst the preliminary attempts described in this thesis were unsuccessful, thought to be due to polymer forming side-reactions (see **section 2.5.4)**, there remains scope for further investigations which effectively bypass this issue.

For instance, selective formation of 10-membered cyclic enediynes from the synthesis attempted (see **Scheme 87**, **page 96**), may be promoted by lowering the reaction concentration, reducing the potential for interaction, and polymerisation of lithiated intermediates. Cyclisation may also be favoured by employing a monolithiated 1,7-octadiyne species with one silane-capped acetylene head (**208**), which could be subsequently removed to allow controlled α-addition (**Scheme 89**).



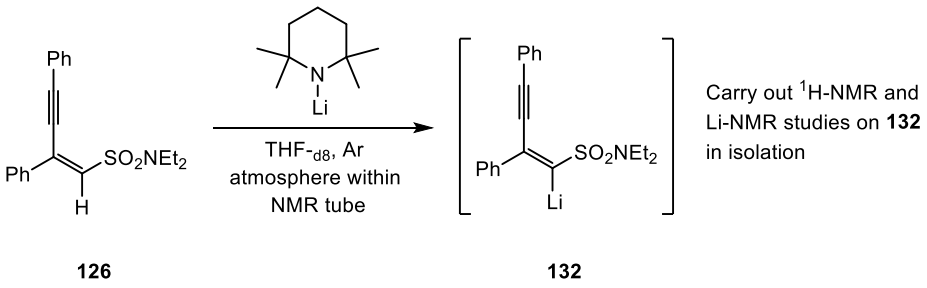
Scheme 89: A suggested alternative lithated acetylide, which may successfully produce a Bergman cyclisation precursor

Furthermore, if the alkynyl sulfonamide starting material possessed an appendage substantially larger than the simple aryl groups used, polymerisation could be discouraged due to steric hindrance. The large substrates inherent to enediyne antitumour agents, may possibly facilitate this inhibition, promoting intramolecular ring formation.

Diyne by-products were often also obtained from the enediyne synthesis, which themselves present useful chemical compounds. The proportions of different products could be tuned to an extent by altering the reaction parameters, although the DoE studies carried out did not effectively determine the factors governing product distributions. Unfortunately, the small scale of these DoE experiments rendered the determination of yields by conventional chromatography and weighing techniques inaccurate, due to the high relative errors implied. However, with larger amounts of starting material, such an approach may be suitable.

Finally, further investigation of the lithiated sulfonamide **132** is of significant interest. Although the existence of the lithiated intermediate **132** appears probable, demonstrated by its effective formation in seclusion and subsequent conversion to enediyne **125** (see **Scheme 50**, **page 61**), initial electrophilic quenching attempts using D_2O and iodine proved unsuccessful (see **Scheme 60**, **page 68**).

The exact quenching mechanism that forms the alkenyl sulfonamide **126** from intermediate **132**, therefore appears to be more complex than once thought, and attempts should be made to study it directly (**Scheme 90**). This may possibly be done by isolated formation of intermediate **132** in THF-d_8 solution, within a suitably dried vessel under an inert atmosphere, followed by targeted analysis using both ^{1}H-NMR and Li-NMR approaches.



Scheme 90: A suggested approach to directly study the lithiated alkenyl sulfonamide intermediate using NMR

4. Experimental

4.1. General

All reactions were carried out at atmospheric presure. Reagents and solvents were obtained from commercial sources and used without further modification unless stated otherwise. Distilled solvents were prepared by drying over CaH_2, distilling and storing over activated molecular sieves, 4 Å, 1-2 mm (0.04-0.08 in) beads. Stock solutions were also stored over activated molecular sieves, 4 Å, 1-2 mm (0.04-0.08 in) beads. Concentrated *in vacuo* refers to solvent removal by rotary evaporation at 20-50 ^{o}C, using the house vacuum operational at approximately 10 mmHg. RT is defined as 19-23 ^{o}C. TLC was performed using Merck Silica plates and compounds were visualised by a combination of exposure to UV (254 nm) and potassium permanganate chemical stain with heating. Flash column chromatography was carried out using Geduran® silicagel 60 (particle size 40-63 µm). Purification or separation *via* flash column chromatography was followed by concentration *in vacuo*, followed by use of a high vacuum pump operational at approximately 2.6 mmHg.

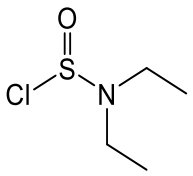
Melting points (m.p.) were measured using Gallenkamp apparatus and are uncorrected. Retardation factors (*Rf*) were measured using TLC and reported without units. (EtOAc:PE) refers to the EtOAc:PE ratio of the solvent system used to measure a specific *Rf* value. ^{1}H-NMR and ^{13}C-NMR were carried out at the stated field using Bruker AMX-300 MHz, AMX-500 MHz and AMX-600 MHz instruments. Chemical shifts (δ_H and δ_C) are reported in ppm and referenced to the proton impurity of deuterated solvents. Coupling constants (*J*) are measured in Hz. The multiplicity of specific signals are reported as: s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), dd (doublet of doublets), dt (doublet of triplets), qd (quartet of doublets), tt (triplet of triplets), qt (quartet of triplets). In incidences where complex or overlapping signals made determination of multiplicity difficult, peaks are reported as m (multiplet). Infrared spectra were recorded as thin films using a Bruker Alpha FTIR spectrometer and are reported as a list of absorption wavenumbers (ν_{max}/cm^{-1}). Mass spectra were measured on Thermo Finnigan MAT900 XE and Waters LCT Premier XE machines operating in EI, CI and ESI modes, and are reported as mass to charge ratios (*m/z*). All experimental procedures were directly implemented by the author unless stated otherwise.

4.2. Experimental Procedures

4.2.1. Procedure for the titration of nBuLi solution

A 250 mL flame-dried flask was charged with 2,2'-bipyridine (4 mg, 0.03 mmol) and dry Et_2O (15 mL) under argon to produce a yellow coloured solution. The solution was cooled to 0 °C and ^{n}BuLi was added until the mixture turned an intense red colour. In order to test the mixture, isopropanol was added until the solution turned back to yellow, ^{n}BuLi added until it had turned red again, then isopropanol added until it had just turned yellow once more. Isopropanol (1.00 ml of a 1 M solution, 1.00 mmol) was then added and titration of ^{n}BuLi was carried out, with restoration of the intense red colour marking the end-point.

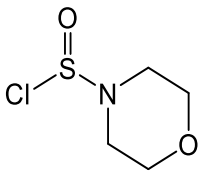
4.2.2. Procedure for the synthesis of diethylsulfuramidous chloride (122)



A 500 mL flame-dried flask was charged with thionyl chloride (9.84 g, 82.7 mmol, 1.0 eq.) and dry Et_2O (150 mL), under argon. The solution was cooled to -40 °C and a solution of diethylamine (12.0 g, 164.4 mmol, 2.0 eq.) in dry Et_2O (100 mL) was added dropwise over 2 h, whilst the mixture was allowed to stir. The reaction was then warmed to 0 °C and allowed to stir for a further 1 h. The reaction mixture was then allowed to warm to RT and quickly filtered through a pad of Celite®. The solution was **carefully**[x] concentrated *in vacuo* to yield a viscous, acrid brown crude product (19.4 g product, containing 8.53 g of the desired chloride, 66%). The crude product was quickly stored, under argon in a freezer and used without further purification. No *Rf* visualised; ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 3.03 (q, 4 H, NC*H*$_2$), 1.47 (t, *J* = 7.3 Hz, 6 H, NCH$_2$C*H*$_3$); ^{13}C-NMR (300 MHz, $CDCl_3$) δ_C 42.4 (CH_2), 12.5 (CH_3); no mass ion detected. Data in agreement with literature.[250]

[x] **HAZARD WARNING:** Previous group members have reported potential incident of vessel explosion as a result of allowing the solution to evaporate to dryness on the rotary evaporator apparatus. As essential safety measures, it is necessary to leave some solvent remaining and use the apparatus behind a safety screen.

4.2.3. Procedure for the synthesis of morpholine-4-sulfinic chloride (209)

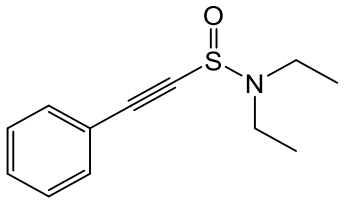


A 100 mL flame-dried flask was charged with thionyl chloride (2.38 g, 20 mmol, 1.0 eq.) and dry Et_2O (15 mL), under argon. The solution was cooled to -40 °C and a solution of morpholine (3.83 g, 44 mmol, 2.2 eq.) in dry Et_2O (20 mL) was added dropwise over 1 h, whilst the mixture was allowed to stir. The reaction was then warmed to 0 °C and allowed to stir for a further 1 h. The reaction mixture was then allowed to warm to RT and quickly filtered through a pad of Celite®. The solution was concentrated *in vacuo* to yield the crude product as a white solid (0.80 g, 24%), which was used without further purification. m.p. 165-169 ^oC; no *Rf* visualised; ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 4.00 (t, *J* = 4.9 Hz, 4 H, NC*H*$_2$CH$_2$O), 3.23-3.26 (m, 4 H, NCH$_2$C*H*$_2$O); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 63.9 (CH_2), 43.4 (CH_2); ν_{max}/cm^{-1} 2910, 2769, 2711, 2455, 1572; no mass ion detected.

4.2.4. General procedure A: synthesis of alkynyl sulfinamides

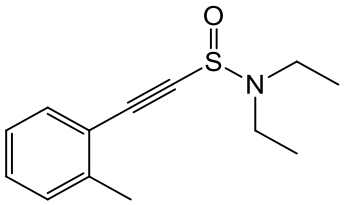
A 100 mL flame-dried flask was charged with an **acetylene derivative** (1.3-6.3 mmol, 1.1 eq.) and dry THF (0.1 M), under argon. The solution was cooled to -78 °C and ^{n}BuLi (2.5 M in hexanes, 1.1 eq.) was added dropwise, and allowed to stir for 10 min. Diethylsulfuramidous chloride **122** (1.0 eq.) was then added dropwise, and stirred for a further 20 min. The reaction mixture was allowed to warm to RT, diluted with CH_2Cl_2 (200 mL), washed with water (100 mL) then brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification *via* flash column chromatography (EtOAc/PE) was carried out to yield the alkynyl sulfinamide product.

***N*,*N*-Diethyl-2-phenylethyne-1-sulfinamide (123)**



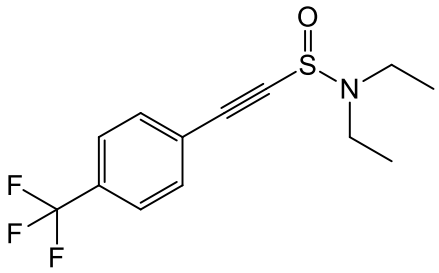
Synthesised according to general procedure A, using phenylacetylene as the acetylene derivative. Yellow oil (74%). *Rf* = 0.18 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.52 (d, *J* = 7.0 Hz, 2 H, Ar*H*), 7.43 (t, *J* = 7.6, Hz, 1 H, Ar*H*), 7.37 (t, *J* = 7.7 Hz, 2 H, Ar*H*), 3.32-3.48 (m, 4 H, NCH_2), 1.29 (t, *J* = 7.2 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 132.2 (CH), 130.3 (CH), 128.7 (CH), 120.2 (C_q), 96.4 (C_q), 86.5 (C_q), 42.7 (CH_2), 14.4 (CH_3); ν_{max}/cm^{-1} 2973, 2935, 2871, 2162, 1488; LRMS (ESI) *m/z* (%) 222 (100), 192 (8); HRMS (ESI) calc'd for $C_{12}H_{16}NOS$ $(M+H)^+$ 222.0953, found 222.0955. Data in agreement with literature.[218]

***N*,*N*-Diethyl-2-(*o*-tolyl)ethyne-1-sulfinamide (210)**



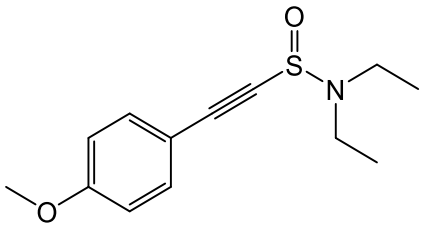
Synthesised according to general procedure A, using 2-methylphenylacetylene as the acetylene derivative. Yellow oil (93%). *Rf* = 0.17 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.48 (d, *J* = 7.6 Hz, 1 H, Ar*H*), 7.32 (t, *J* = 7.6 Hz, 1 H, Ar*H*), 7.24 (d, *J* = 7.7 Hz, 1 H, Ar*H*), 7.19 (t, *J* = 7.4 Hz, 1 H, Ar*H*), 3.35-3.47 (m, 4 H, NCH_2), 2.46 (s, 3 H, ArCH_3), 1.29 (t, *J* = 7.1 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 141.3 (C_q), 132.7 (CH), 130.4 (CH), 129.8 (CH), 125.9 (CH), 120.1 (C_q), 95.6 (C_q), 90.1 (C_q), 42.6 (CH_2), 20.8 (CH_3), 14.4 (CH_3); ν_{max}/cm^{-1} 3029, 2972, 2933, 2870, 2158, 1604, 1507; LRMS (ESI) *m/z* (%) 236 (100), 120 (12); HRMS (ESI) calc'd for $C_{13}H_{18}NOS$ $(M+H)^+$ 236.1109, found 236.1118.

***N*,*N*-Diethyl-2-(4-(trifluoromethyl)phenyl)ethyne-1-sulfinamide (211)**



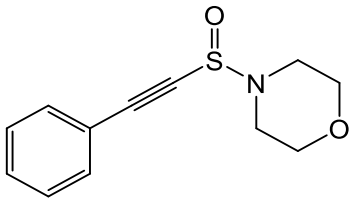
Synthesised according to general procedure A, using 4-(trifluoromethyl)phenylacetylene as the acetylene derivative. Yellow oil (20%). *Rf* = 0.21 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.62-7.65 (m, 4 H, Ar*H*), 3.35-3.48 (m, 4 H, NCH_2), 1.30 (t, *J* = 7.1 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 132.5 (CH), 131.9 (q, *J* = 32.8 Hz, C_q), 125.6 (q, *J* = 3.8 Hz, CH), 124.0 (C_q), 123.7 (q, *J* = 272.4 Hz, C_q), 94.2 (C_q), 88.8 (C_q), 42.8 (CH_2), 14.3 (CH_3); ν_{max}/cm^{-1} 2976, 2934, 2873, 2166, 1613, 1458; LRMS (ESI) *m/z* (%) 290 (100); HRMS (ESI) calc'd for $C_{13}H_{15}F_3NOS$ $(M+H)^+$ 290.0826, found 290.0810. Data in agreement with literature.[218]

***N*,*N*-Diethyl-2-(4-methoxyphenyl)ethyne-1-sulfinamide (212)**



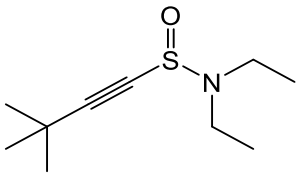
Synthesised according to general procedure A, using 4-methoxyphenylacetylene as the acetylene derivative. Yellow oil (67%). *Rf* = 0.08 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.46 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 3.84 (s, 3 H, OCH_3), 3.33-3.46 (m, 4 H, NCH_2), 1.28 (t, *J* = 7.2 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 161.2 (C_q), 134.0 (CH), 114.3 (CH), 112.1 (C_q), 97.3 (C_q), 85.3 (C_q), 55.5 (CH_3), 42.7 (CH_2), 14.4 (CH_3); ν_{max}/cm^{-1} 2972, 2934, 2870, 2839, 2155, 1602, 1569, 1507; LRMS (CI) *m/z* (%) 252 (100); HRMS (CI) calc'd for $C_{13}H_{18}NO_2S$ $(M+H)^+$ 252.10528, found 252.10534. Data in agreement with literature.[218]

4-((Phenylethynyl)sulfinyl)morpholine (213)



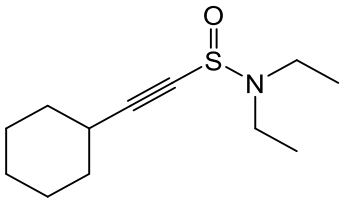
Synthesised according to general procedure A, using phenylacetylene as the acetylene derivative and morpholine-4-sulfinic chloride **209** in place of diethylsulfuramidous chloride **122**. Yellow oil (31%). *Rf* = 0.10 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.54 (d, *J* = 7.4 Hz, 2 H, Ar*H*), 7.43 (t, *J* = 7.4, Hz, 1 H, Ar*H*), 7.37 (t, *J* = 7.8 Hz, 2 H, Ar*H*), 3.83-3.86 (m, 4 H, NC*H*$_2$CH$_2$O), 3.27-3.28 (m, 4 H, NCH$_2$C*H*$_2$O); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 132.4 (CH), 130.7 (CH), 128.8 (CH), 119.6 (C_q), 98.7 (C_q), 84.3 (C_q), 66.8 (CH_2), 45.6 (CH_2); ν_{max}/cm^{-1} 3058, 2961, 2911, 2853, 2155, 1596, 1573, 1487; LRMS (ESI) *m/z* (%) 258 (100), 236 (95), 214 (25), 165 (26); HRMS (ESI) calc'd for $C_{12}H_{13}NO_2SNa$ $(M+Na)^+$ 258.0565, found 258.0557.

***N*,*N*-Diethyl-3,3-dimethylbut-1-yne-1-sulfinamide (214)**



Synthesised according to general procedure A, using *tert*-butylacetylene as the acetylene derivative. Yellow oil (65%). *Rf* = 0.24 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 3.32-3.38 (m, 4 H, NC*H*$_2$), 1.28 (s, 9 H, CC*H*$_3$), 1.23 (t, *J* = 7.2 Hz, 6 H, NCH$_2$C*H*$_3$); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 106.5 (C_q), 77.0 (C_q), 42.5 (CH_2), 30.2 (CH_3), 28.3 (C_q), 14.3 (CH_3); ν_{max}/cm^{-1} 2970, 2934, 2869, 2190, 2157, 1456; LRMS (ESI) *m/z* (%) 224 (100), 214 (77), 197 (32), 181 (60); HRMS (ESI) calc'd for $C_{10}H_{20}NOSNa$ $(M+Na)^+$ 224.1085, found 224.1088. Data in agreement with literature.[218]

2-Cyclohexyl-*N*,*N*-diethylethyne-1-sulfinamide (215)

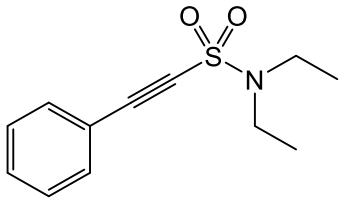


Synthesised according to general procedure A, using cyclohexylacetylene as the acetylene derivative. Yellow oil (44%). *Rf* = 0.17 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 3.23-3.39 (m, 4 H, NC*H*$_2$), 2.58 (quint., *J* = 4.4 Hz, 1 H, C*H*), 1.81-1.84 (m, 2 H, C*H*$_2$), 1.69-1.70 (m, 2 H, C*H*$_2$), 1.49-1.51 (m, 3 H, C*H*$_2$), 1.31-1.33 (m, 3 H, C*H*$_2$), 1.23 (t, *J* = 7.2 Hz, 6 H, NCH$_2$C*H*$_3$); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 103.1 (C_q), 78.3 (C_q), 42.5 (CH_2), 31.7 (CH_2), 29.6 (CH), 25.7 (CH_2), 24.7 (CH_2), 14.3 (CH_3); ν_{max}/cm^{-1} 2971, 2929, 2853, 2177, 1448; LRMS (ESI) *m/z* (%) 228 (100), 214 (70), 211 (63), 167 (28); HRMS (ESI) calc'd for $C_{12}H_{21}NOS$ $(M+H)^+$ 228.1422, found 228.1444.

4.2.5. General procedure B: synthesis of alkynyl sulfonamides

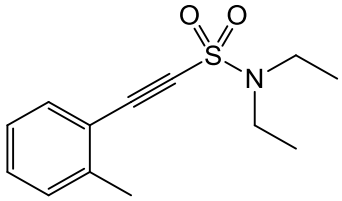
A 50 ml flask was charged with $NaIO_4$ (1.3 eq), water (12 mL) and MeCN (15 mL). The mixture was cooled to 0 °C and stirred until the solid had completely dissolved. $RuCl_3.6H_2O$ (1 mol%) was then added and the reaction mixture was stirred for a further 5 min. A solution of **alkynyl sulfinamide** (1.0-4.4 mmol, 1.0 eq.) in EtOAc (15 mL) was then added in one portion, and stirred vigorously until complete consumption of starting material had been observed *via* TLC (usually ca. 1 h). The reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with water (100 mL) then brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification *via* flash column chromatography (EtOAc/PE) was carried out to yield the alkynyl sulfonamide product.

***N*,*N*-Diethyl-2-phenylethyne-1-sulfonamide (106)**



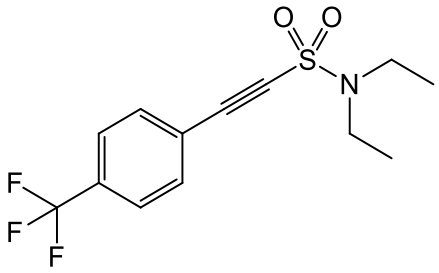
Synthesised according to general procedure B, using *N*,*N*-diethyl-2-phenylethyne-1-sulfinamide **123** as the alkynyl sulfinamide. Yellow oil (41%). *Rf* = 0.35 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.54 (d, *J* = 7.5 Hz, 2 H, Ar*H*), 7.47 (t, *J* = 7.3, Hz, 1 H, Ar*H*), 7.39 (t, *J* = 7.6 Hz, 2 H, Ar*H*), 3.39 (q, *J* = 7.2 Hz, 4 H, NCH_2), 1.30 (t, *J* = 7.2 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 132.6 (CH), 131.0 (CH), 128.8 (CH), 118.7 (C_q), 88.2 (C_q), 83.9 (C_q), 43.0 (CH_2), 13.5 (CH_3); ν_{max}/cm^{-1} 2978, 2939, 2878, 2180, 1490; LRMS (ESI) *m/z* (%) 238 (100); HRMS (ESI) calc'd for $C_{12}H_{16}NO_2S$ (M+H)+ 238.0896, found 238.0899. Data in agreement with literature.[218]

***N*,*N*-Diethyl-2-(*o*-tolyl)ethyne-1-sulfonamide (139)**



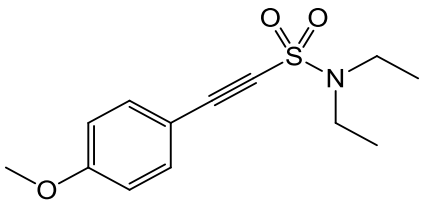
Synthesised according to general procedure B, using *N*,*N*-diethyl-2-(*o*-tolyl)ethyne-1-sulfinamide **210** as the alkynyl sulfinamide. Yellow oil (54%). *Rf* = 0.34 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.50 (d, *J* = 7.7 Hz, 1 H, Ar*H*), 7.36 (t, *J* = 7.6, Hz, 1 H, Ar*H*), 7.26 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.21 (t, *J* = 7.6 Hz, 1 H, Ar*H*), 3.39 (q, *J* = 7.2 Hz, 4 H, NCH_2), 2.47 (s, 3 H, ArCH_3), 1.31 (t, *J* = 7.2 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 141.9 (C_q), 133.1 (CH), 131.1 (CH), 130.0 (CH), 126.1 (CH), 118.6 (C_q), 87.5 (C_q), 87.4 (C_q), 43.1 (CH_2), 20.7 (CH_3), 13.5 (CH_3); ν_{max}/cm^{-1}; 2974, 2935, 2874, 2173, 1598; LRMS (ESI) *m/z* (%) 252 (100); HRMS (ESI) calc'd for $C_{13}H_{18}NO_2S$ $(M+H)^+$ 252.1058, found 252.1076.

***N*,*N*-Diethyl-2-(4-(trifluoromethyl)phenyl)ethyne-1-sulfonamide (152)**



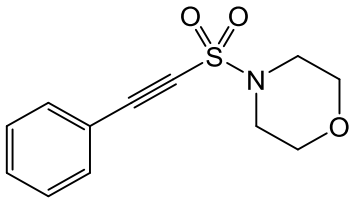
Synthesised according to general procedure B, using *N*,*N*-diethyl-2-(4-(trifluoromethyl)phenyl)ethyne-1-sulfinamide **211** as the alkynyl sulfinamide. Yellow oil (38%). *Rf* = 0.47 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.66 (s, 4 H, Ar*H*), 3.41 (q, *J* = 7.2 Hz, 4 H, NCH_2), 1.31 (t, *J* = 7.2 Hz, 6 H, NCH$_2$CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 132.9 (CH), 132.7 (q, *J* = 33.0 Hz, C_q), 125.8 (q, *J* = 3.8 Hz, CH), 123.5 (C_q), 122.6 (q, *J* = 272.7 Hz, C_q), 86.0 (C_q), 85.9 (C_q), 43.1 (CH_2), 13.5 (CH_3); ν_{max}/cm^{-1}; 2978, 2939, 2878, 2187, 1613, 1468; LRMS (ESI) *m/z* (%) 306 (100); HRMS (ESI) calc'd for $C_{13}H_{15}F_3NO_2S$ $(M+H)^+$ 306.0775, found 306.0780. Data in agreement with literature.[218]

***N*,*N*-Diethyl-2-(4-methoxyphenyl)ethyne-1-sulfonamide (153)**



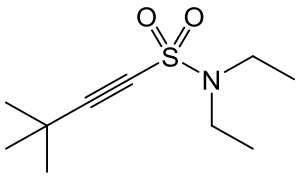
Synthesised according to general procedure B, using *N*,*N*-diethyl-2-(4-methoxyphenyl)ethyne-1-sulfinamide **212** as the alkynyl sulfinamide. Yellow oil (41%). *Rf* = 0.23 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.48 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.90 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 3.84 (s, 3 H, OCH_3), 3.37 (q, *J* = 7.2 Hz, 4 H, NCH_2), 1.29 (t, *J* = 7.2 Hz, 6 H, NCH$_2$CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 161.8 (C_q), 134.4 (CH), 114.5 (CH), 110.4 (C_q), 89.2 (C_q), 82.9 (C_q), 55.6 (CH_3), 43.0 (CH_2), 13.5 (CH_3); ν_{max}/cm^{-1}; 2976, 2937, 2174, 1602, 1570, 1508; LRMS (ESI) *m/z* (%) 536 (4), 535 (61), 519 (2), 341 (4), 269 (13), 268 (100); HRMS (ESI) calc'd for $C_{13}H_{18}NO_3S$ $(M+H)^+$ 268.1007, found 268.1006. Data in agreement with literature.[218]

4-((Phenylethynyl)sulfonyl)morpholine (174)



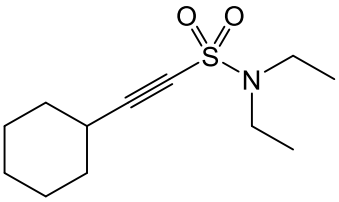
Synthesised according to general procedure B, using 4-((phenylethynyl)sulfinyl)morpholine **213** as the alkynyl sulfinamide. White solid (35%). m.p. 92-95 ^{o}C; *Rf* = 0.17 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.60 (d, *J* = 7.3 Hz, 2 H, Ar*H*), 7.52 (t, *J* = 7.6, Hz, 1 H, Ar*H*), 7.42 (t, *J* = 7.5 Hz, 2 H, Ar*H*), 3.86 (t, *J* = 4.7 Hz, 4 H, NC*H*$_2$CH$_2$O), 3.26 (t, *J* = 4.7 Hz, 4 H, NCH$_2$C*H*$_2$O); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 133.0 (CH), 131.6 (CH), 128.9 (CH), 117.9 (C_q), 91.5 (C_q), 79.4 (C_q), 65.9 (CH_2), 46.5 (CH_2); ν_{max}/cm^{-1} 3062, 2971, 2918, 2858, 2177, 1719, 1691, 1602, 1583; LRMS (ESI) *m/z* (%) 252 (100), 221 (4); HRMS (ESI) calc'd for $C_{12}H_{14}NO_3S$ $(M+H)^+$ 252.0694, found 252.0681.

***N*,*N*-Diethyl-3,3-dimethylbut-1-yne-1-sulfonamide (180)**



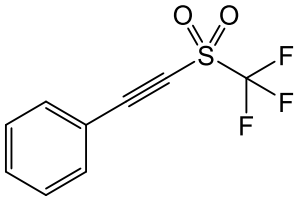
Synthesised according to general procedure B, using *N*,*N*-diethyl-3,3-dimethylbut-1-yne-1-sulfinamide **214** as the alkynyl sulfinamide. Colourless oil (51%). *Rf* = 0.46 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 3.29 (q, *J* = 7.2 Hz, 4 H, NC*H*$_2$), 1.28 (s, 9 H, CC*H*$_3$), 1.25 (t, *J* = 7.2 Hz, 6 H, NCH$_2$C*H*$_3$); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 98.6 (C_q), 75.1 (C_q), 42.8 (CH_2), 29.9 (CH_3), 27.8 (C_q), 13.2 (CH_3); ν_{max}/cm^{-1} 2973, 2935, 2903, 2874, 2209 2172; LRMS (ESI) *m/z* (%); 218 (100), 152 (2); HRMS (ESI) calc'd for $C_{10}H_{20}NO_2S$ $(M+H)^+$ 218.1215, found 218.1215. Data in agreement with literature.[218]

2-Cyclohexyl-*N*,*N*-diethylethyne-1-sulfonamide (182)



Synthesised according to general procedure B, using 2-cyclohexyl-*N*,*N*-diethylethyne-1-sulfinamide **215** as the alkynyl sulfinamide. Colourless oil (45%). *Rf* = 0.29 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 3.29 (q, *J* = 7.2 Hz, 4 H, NC*H*$_2$), 2.57 (quint., *J* = 4.6 Hz, 1 H, C*H*), 1.81-1.83 (m, 2 H, C*H*$_2$), 1.69-1.70 (m, 2 H, C*H*$_2$) 1.50-1.52 (m, 3 H, C*H*$_2$), 1.33-1.35 (m, 3 H, C*H*$_2$), 1.25 (t, *J* = 7.3 Hz, 6 H, NCH$_2$C*H*$_3$); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 95.1 (C_q), 76.2 (C_q), 42.9 (CH_2), 31.3 (CH_2), 28.9 (CH), 25.6 (CH_2), 24.6 (CH_2), 13.4 (CH_3); ν_{max}/cm^{-1} 2976, 2931, 2856, 2194, 1703; LRMS (ESI) *m/z* (%) 244 (100), 181 (78), 149 (32); HRMS (ESI) calc'd for $C_{12}H_{21}NO_2S$ $(M+H)^+$ 244.1371, found 244.1378.

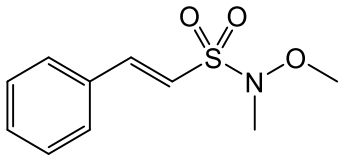
4.2.6. Procedure for the synthesis of (((trifluoromethyl)sulfonyl)ethynyl)benzene (167)



A 100 mL flame-dried flask was charged with a solution of phenylacetylene (0.11 g, 1.08 mmol, 1.0 eq.) in dry Et_2O (10 mL), under argon. The solution was cooled to -78 °C and ^{n}BuLi (0.43 mL of 2.5 M in hexanes, 1.08 mmol, 1.0 eq.) was added dropwise, and the mixture was allowed to stir for 30 min. Trifluoromethylsulfonic anhydride (0.34 g, 1.19 mmol, 1.1 eq.) was added dropwise and allowed to stir for a further 20 min. The reaction mixture was allowed to warm to RT, washed with saturated $NaHCO_3$ solution (10 mL), 1 M HCl (10 mL) then brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification *via* flash column chromatography (EtOAc/PE) was carried out to yield the product as a yellow oil (0.11 g, 53%). *Rf* = 0.44 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.71 (d, *J* = 7.5 Hz, 2 H, Ar*H*), 7.64 (t, *J* = 7.5, Hz, 1 H, Ar*H*), 7.50 (t, *J* = 7.2 Hz, 2 H, Ar*H*); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 133.9 (CH), 133.5 (CH), 129.2 (CH), 119.1 (q, *J* = 323.1 Hz, C_q), 115.9 (C_q), 100.9 (C_q), 77.4 (C_q); ν_{max}/cm^{-1} 3072, 2852, 2175, 1596, 1489; LRMS (EI) *m/z* (%) 165

(100), 89 (44); HRMS (EI) calc'd for $C_9H_5F_3O_2S$ (M^+) 233.9957, found 233.9956. Data in agreement with literature.[251]

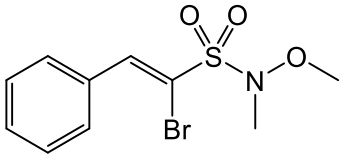
4.2.7. Procedure for the synthesis of (*E*)-*N*-methoxy-*N*-methyl-2-phenylethene-1-sulfonamide (216)



A 100 mL flask was charged with *trans*-β-styrene sulfonyl chloride (1.42 g, 7.01 mmol, 1.0 eq.) and CH_2Cl_2 (40 mL). The solution was then stirred at RT for 10 min, after which time *N*,*O*-dimethylhydroxylamine hydrochloride (0.82 g, 8.41 mmol, 1.2 eq.) was added in a single portion,[xi] then triethylamine (1.41 g, 14.0 mmol, 2.0 eq.). The reaction mixture was then stirred at RT for a further 60 min after which time it was diluted with CH_2Cl_2 (200 mL), washed with water (100 mL) then brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification *via* flash column chromatography (EtOAc/PE) was carried out to yield the product as a white solid (1.21 g, 76%). m.p. 69-72 ^oC; *Rf* = 0.32 (20:80 EtOAc:PE); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.57 (d, *J* = 15.5 Hz, 1 H, ArC*H*=CH), 7.54 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 7.41-7.48 (m, 3 H, Ar*H*), 6.85 (d, *J* = 15.7 Hz, 1 H, ArCH=C*H*), 3.83 (s, 3 H, OCH_3), 2.94 (s, 3 H, NCH_3); ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C 146.8 (CH), 132.4 (C_q), 131.5 (CH), 129.2 (CH), 128.7 (CH), 117.5 (CH), 63.9 (CH_3), 39.2 (CH_3); ν_{max}/cm^{-1} 3066, 2976, 2939, 2897, 2812, 2374, 1608; LRMS (CI) *m/z* (%) 245 (100); HRMS (CI) calc'd for $C_{10}H_{17}N_2O_3S$ $(M+NH_4)^+$ 245.0954, found 245.0955.

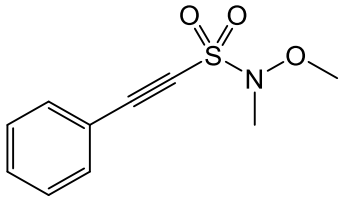
[xi] With repeated runs of this experimental procedure it is strongly advised to add *N*,*O*-dimethylhydroxylamine hydrochloride gradually in multiple portions.

4.2.8. Procedure for the synthesis of (*Z*)-1-bromo-*N*-methoxy-*N*-methyl-2-phenylethene-1-sulfonamide (217)



A 100 mL flask was charged with (*E*)-*N*-methoxy-*N*-methyl-2-phenylethene-1-sulfonamide **216** (1.20 g, 5.28 mmol, 1.0 eq.) and CH_2Cl_2 (60 mL), and stirred at RT. Excess bromine (1.36 mL, 26.4 mmol, 5.0 eq.) was then added as a single portion. The reaction mixture was stirred for 60 min after which time the mixture was washed with sodium thiosulfate solution (10% w/w, 100 mL) then brine (100 mL). Triethylamine (1.47 mL, 10.5 mmol, 2.0 eq.) was added dropwise to the organic portion and stirred for a further 30 min. The reaction mixture was washed with brine (100 mL) then 2 M HCl (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification *via* flash column chromatography (EtOAc/PE) was carried out to yield the product as a yellow oil (0.94 g, 58%). *Rf* = 0.41 (20:80 EtOAc:PE); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.12 (s, 1 H, ArC*H*=CBr), 7.86 (d, *J* = 7.7 Hz, 2 H, Ar*H*), 7.44-7.50 (m, 3 H, Ar*H*), 3.82 (s, 3 H, OCH_3), 3.18 (s, 3 H, NCH_3); ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C 143.6 (CH), 132.2 (C_q), 131.2 (CH), 130.3 (CH), 128.8 (CH), 112.1 (C_q), 63.9 (CH_3), 39.5 (CH_3); ν_{max}/cm^{-1} 3055, 3013, 2977, 2936, 2896, 2811, 1593, 1572; LRMS (ESI) *m/z* (%) 306 (100), 308 (92); HRMS (ESI) calc'd for $C_{10}H_{13}NO_3S^{79}Br$ $(M+H)^+$ 305.9799, found 305.9803.

4.2.9. Procedure for the synthesis of *N*-methoxy-*N*-methyl-2-phenylethyne-1-sulfonamide (175)



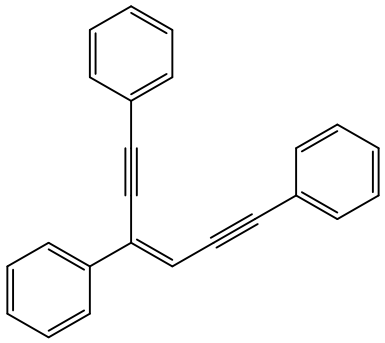
A 50 mL flame-dried flask was charged with (*Z*)-1-bromo-*N*-methoxy-*N*-methyl-2-phenylethene-1-sulfonamide **217** (0.24 g, 0.78 mmol, 1.0 eq.) and dry DMF (8 mL), under argon. NaH (0.06 g of 60 % dispersion in mineral oil, 1.50 mmol, 1.9 eq.) was added in small portions and the reaction mixture was stirred at RT for 30 min. The reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with water (100 mL) then brine (100 mL), dried over $MgSO_4$

and concentrated *in vacuo* to yield the crude product. Purification *via* flash column chromatography (EtOAc/PE) was carried out to yield the product as a yellow oil (0.13 g, 76%). *Rf* = 0.41 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.64 (d, *J* = 7.5 Hz, 2 H, Ar*H*), 7.53 (t, *J* = 7.6, Hz, 1 H, Ar*H*), 7.43 (t, *J* = 7.6 Hz, 2 H, Ar*H*), 3.88 (s, 3 H, OCH_3) 3.10 (s, 3 H, NCH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 133.2 (CH), 131.8 (CH), 128.9 (CH), 117.7 (C_q), 93.7 (C_q), 77.5 (C_q), 64.1 (CH_3), 39.6 (CH_3); ν_{max}/cm^{-1} 3062, 2986, 2941, 2901, 2818, 2178, 1488; LRMS (ESI) *m/z* (%) 226 (100), 165 (17); HRMS (ESI) calc'd for $C_{10}H_{12}NO_3S$ $(M+H)^+$ 226.0532, found 226.0531.

4.2.10. General procedure C: treatment of alkynyl sulfonamides with lithiated phenylacetylene to produce enediynes, alkenyl sulfonamides and diynes

A 100 mL flame-dried flask was charged with a solution of phenylacetylene (1.1 eq.) in dist. THF (0.01 M), under argon. The solution was cooled to 0 °C and ^{n}BuLi (2.5 M in hexanes, 1.1 eq.) was added dropwise. The mixture was allowed to warm to RT and stirred for a further 10 min. An additional, 100 mL flame-dried flask was charged with a solution of **alkynyl sulfonamide** (0.09-0.47 mmol, 1.0 eq.) in dist. THF (0.1 M), under argon. The solution was heated to 60 °C and the previously formed lithiated solution was added dropwise (add. rate 0.0025 mmol/min) with constant stirring. The reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with water (100 mL) then brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude mixture. Separation *via* flash column chromatography (EtOAc/PE) was carried out to yield the purified products.

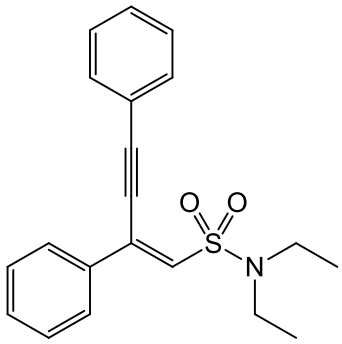
(*Z*)-1,3,6-Triphenylhex-3-ene-1,5-diyne (125)



Synthesised according to general procedure C, using *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide **106** as the alkynyl sulfonamide. Brown oil (21%). *Rf* = 0.56 (20:80 EtOAc:PE);

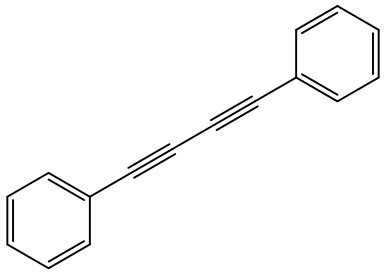
^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.75 (d, *J* = 7.5 Hz, 2 H, Ar*H*), 7.61-7.64 (m, 2 H, Ar*H*), 7.52-7.56 (m, 2 H, Ar*H*), 7.41 (t, *J* = 7.5 Hz, 2 H, Ar*H*), 7.35-7.36 (m, 7 H, Ar*H*), 6.58 (s, 1 H, C=C*H*); ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C 136.9 (C_q), 133.5 (CH), 131.9 (CH), 131.7 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 126.2 (CH), 123.5 (C_q), 123.2 (C_q), 113.7 (C_q), 98.5 (C_q), 98.4 (C_q), 89.1 (C_q), 87.7 (C_q); ν_{max}/cm^{-1} 3058, 3031, 2920, 2847, 2198, 1596; LRMS (EI) *m/z* (%) 304 (100), 226 (6); HRMS (EI) calc'd for $C_{24}H_{16}$ (M^+) 304.1247, found 304.1246. Data in agreement with literature.[136]

(*Z*)-*N*,*N*-Diethyl-2,4-diphenylbut-1-en-3-yne-1-sulfonamide (126)



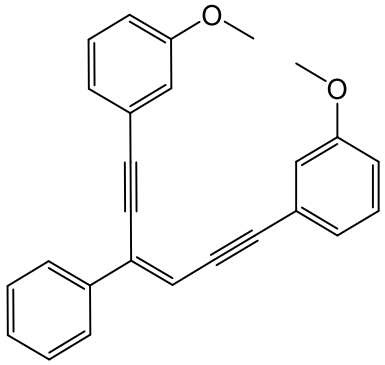
Synthesised according to general procedure C, using *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide **106** as the alkynyl sulfonamide. Yellow oil (26%). *Rf* = 0.30 (20:80 EtOAc:PE); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.72-7.73 (m, 2 H, Ar*H*), 7.61-7.63 (m, 2 H, Ar*H*), 7.43-7.45 (m, 3 H, Ar*H*), 7.38-7.41 (m, 3 H, Ar*H*), 6.88 (s, 1 H, C=C*H*), 3.43 (q, *J* = 7.2 Hz, 4 H, NCH_2), 1.24 (t, *J* = 7.6 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C 136.2 (C_q), 132.7 (CH), 132.2 (CH), 131.1 (C_q), 130.3 (CH), 129.7 (CH), 128.9 (CH), 128.6 (CH), 127.2 (CH), 122.3 (C_q), 103.6 (C_q), 84.9 (C_q), 41.9 (CH_2), 14.5 (CH_3); ν_{max}/cm^{-1} 3059, 2973, 2929, 2874, 1598; LRMS (ESI) *m/z* (%) 340 (100); HRMS (ESI) calc'd for $C_{20}H_{22}NO_2S$ $(M+H)^+$ 340.1366, found 340.1370.

1,4-Diphenylbuta-1,3-diyne (46)



Synthesised according to general procedure C, using *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide **106** as the alkynyl sulfonamide. White solid (28%). m.p. 83-87 ºC; *Rf* = 0.57 (20:80 EtOAc:PE); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.54 (d, *J* = 7.6 Hz, 4 H, Ar*H*), 7.33-7.40 (m, 6 H, Ar*H*); ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C 132.6 (CH), 129.3 (CH), 128.6 (CH), 121.9 (C_q), 81.6 (C_q), 74.0 (C_q); ν_{max}/cm^{-1} 3047, 2148, 1591, 1568; LRMS (EI) *m/z* (%) 202 (100), 101 (6); HRMS (EI) calc'd for $C_{16}H_{10}$ (M^+) 202.0777, found 202.0780. Data in agreement with literature.[252]

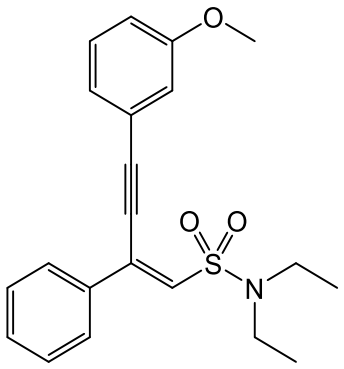
(*Z*)-3,3'-(3-Phenylhexa-3-en-1,5-diyne-1,6-diyl)bis(methoxybenzene) (128)



Synthesised according to general procedure C, using *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide **106** as the alkynyl sulfonamide and 3-methoxyphenylacetylene in place of phenylacetylene. Yellow oil (4%). *Rf* = 0.34 (20:80 EtOAc:PE); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.74 (d, *J* = 7.1 Hz, 2 H, Ar*H*), 7.35-7.43 (m, 3 H, Ar*H*), 7.20-7.29 (m, 3 H, Ar*H*), 7.12-7.15 (m, 2 H, Ar*H*), 7.05-7.06 (m, 1 H, Ar*H*), 6.88-6.93 (m, 2 H, Ar*H*), 6.57 (s, 1 H, C=C*H*), 3.79 (s, 3 H, CH_3), 3.77 (s, 3 H, CH_3); ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C 159.5 (C_q), 159.4 (C_q), 136.7 (CH), 135.1 (C_q), 133.7 (C_q), 129.6 (C_q), 129.6 (CH), 129.0 (CH), 128.7 (CH), 126.2 (CH), 124.4 (C_q), 124.3 (CH), 116.4 (CH), 116.2 (CH), 115.6 (CH), 115.5 (CH), 113.8 (CH), 113.7 (CH), 98.5 (C_q), 98.4 (C_q), 97.6 (C_q), 88.7 (C_q), 55.4 (CH_3), 55.3 (CH_3); ν_{max}/cm^{-1} 3061, 3002,

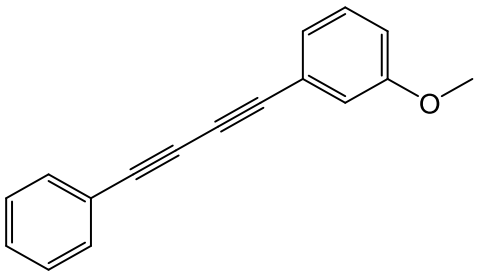
2958, 2922, 2849, 2835, 2200, 2189, 1595, 1575; LRMS (CI) *m/z* (%) 365 (100); HRMS (CI) calc'd for $C_{26}H_{21}O_2$ $(M+H)^+$ 365.1536, found 365.1537.

(*Z*)-*N*,*N*-Diethyl-4-(3-methoxyphenyl)-2-phenylbut-1-en-3-yne-1-sulfonamide (129)



Synthesised according to general procedure C, using *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide **106** as the alkynyl sulfonamide and 3-methoxyphenylacetylene in place of phenylacetylene. Yellow oil (34%). *Rf* = 0.24 (20:80 EtOAc:PE); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.70-7.72 (m, 2 H, Ar*H*), 7.43-7.45 (m, 3 H, Ar*H*), 7.29 (t, *J* = 7.8 Hz, 1 H, Ar*H*), 7.21 (d, *J* = 7.6 Hz, 1 H, Ar*H*), 7.13-7.14 (m, 1 H, Ar*H*), 6.96-6.97 (m, 1 H, Ar*H*), 6.88 (s, 1 H, C=C*H*), 3.83 (s, 3 H, CH_3), 3.42 (q, *J* = 7.2 Hz, 4 H, NCH_2) 1.23 (t, *J* = 7.1 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C 159.5 (C_q), 136.1 (C_q), 132.6 (C_q), 131.2 (CH), 130.3 (CH), 129.7 (CH), 128.9 (CH), 127.2 (CH), 124.7 (CH), 123.2 (C_q), 116.7 (CH), 116.4 (CH), 103.5 (C_q), 84.6 (C_q), 55.5 (CH_3), 41.9 (CH_2), 14.5 (CH_3); ν_{max}/cm^{-1} 3063, 2928, 2872, 2853, 2204, 1596; LRMS (ESI) *m/z* (%) 370 (100); HRMS (ESI) calc'd for $C_{21}H_{24}NO_3S$ $(M+H)^+$ 370.1477, found 370.1479.

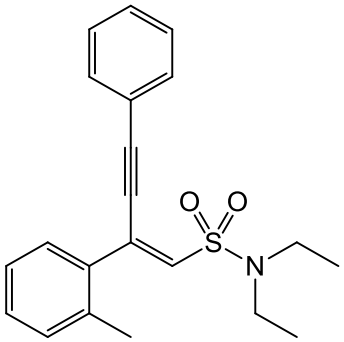
1-Methoxy-3-(phenylbuta-1,3-diyn-1-yl)benzene (130)



Synthesised according to general procedure C, using *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide **106** as the alkynyl sulfonamide and 3-methoxyphenylacetylene in place of

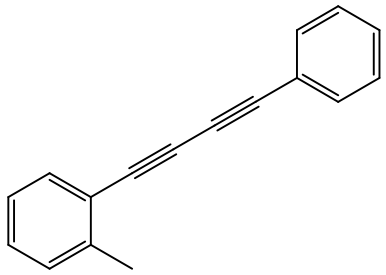
phenylacetylene. Yellow oil (13%). *Rf* = 0.50 (20:80 EtOAc:PE); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.53 (dt, *J* = 6.5, 1.7 Hz, 2 H, Ar*H*), 7.32-7.38 (m, 3 H, Ar*H*), 7.25 (t, *J* = 7.8 Hz, 1 H, Ar*H*), 7.13 (dt, *J* = 7.6, 1.1 Hz, 1 H, Ar*H*), 7.05 (s, 1 H, Ar*H*), 6.93 (d, *J* = 8.3 Hz, Ar*H*), 3.81 (s, 3 H, CH_3); ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C 159.3 (C_q), 132.6 (CH), 129.6 (CH), 129.3 (CH), 128.5 (CH), 125.2 (CH), 122.8 (C_q), 121.8 (C_q), 117.1 (CH), 116.1 (CH), 83.7 (C_q), 81.5 (C_q), 73.9 (C_q), 73.8 (C_q), 55.4 (CH_3); ν_{max}/cm^{-1} 3060, 2998, 2956, 2924, 2851, 2217, 2189, 1592, 1573; LRMS (CI) *m/z* (%) 252 (6), 250 (100), 232 (9); HRMS (CI) calc'd for $C_{17}H_{12}O$ (M^+) 232.0883, found 232.0884. Data in agreement with literature.[253]

(*E*)-*N*,*N*-Diethyl-4-phenyl-2-(*o*-tolyl)but-1-en-3-yne-1-sulfonamide (142)



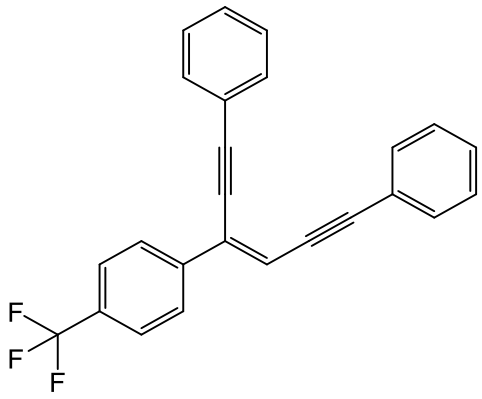
Synthesised according to general procedure C, using *N*,*N*-diethyl-2-(*o*-tolyl)ethyne-1-sulfonamide **139** as the alkynyl sulfonamide. Colourless oil (18%). *Rf* = 0.31 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.52 (d, *J* = 7.1 Hz, 2 H, Ar*H*), 7.33-7.37 (m, 3 H, Ar*H*), 7.30-7.32 (m, 1 H, Ar*H*), 7.23-7.27 (m, 3 H, Ar*H*), 6.48 (s, 1 H, C=C*H*), 3.43 (q, *J* = 7.2 Hz, 4 H, NCH_2), 2.49 (s, 3 H, ArCH_3), 1.26 (t, *J* = 7.1 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 137.6 (C_q), 135.7 (C_q), 134.6 (CH), 133.7 (C_q), 132.2 (CH), 131.0 (CH), 129.6 (CH), 129.2 (CH), 128.6 (CH), 128.5 (CH), 126.4 (CH), 122.4 (C_q), 104.1 (C_q), 85.4 (C_q), 41.9 (CH_2), 20.3 (CH_3), 14.6 (CH_3); ν_{max}/cm^{-1} 3048, 2972, 2933, 2873, 2207, 1598, 1562; LRMS (ESI) *m/z* (%) 354 (100); HRMS (ESI) calc'd for $C_{21}H_{24}NO_2S$ $(M+H)^+$ 354.1528, found 354.1507.

1-Methyl-2-(phenylbuta-1,3-diyn-1-yl)benzene (143)



Synthesised according to general procedure C, using *N*,*N*-diethyl-2-(*o*-tolyl)ethyne-1-sulfonamide **139** as the alkynyl sulfonamide. Colourless oil (21%). *Rf* = 0.54 (20:80 EtOAc:PE); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.55 (d, *J* = 7.2 Hz, 2 H, Ar*H*), 7.50 (d, *J* = 7.7 Hz, 1 H, Ar*H*), 7.34-7.39 (m, 3 H, Ar*H*), 7.27 (t, *J* = 7.6 Hz, 1 H, Ar*H*), 7.23 (d, *J* = 7.6 Hz, 1 H, Ar*H*), 7.17 (t, *J* = 7.4 Hz, 1 H, Ar*H*), 2.50 (s, 3 H, ArC*H*$_3$); ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C 141.9 (C_q), 133.1 (CH), 132.6 (CH), 129.7 (CH), 129.3 (CH), 129.3 (CH), 128.6 (CH), 125.8 (CH), 122.0 (C_q), 121.7 (C_q), 82.2 (C_q), 80.7 (C_q), 77.5 (C_q), 74.1 (C_q), 20.9 (CH_3); ν_{max}/cm^{-1} 3058, 3020, 2921, 2855, 2253, 2214, 1595, 1569; LRMS (ESI) *m/z* (%) 223 (100), 217 (49); HRMS (ESI) calc'd for $C_{17}H_{13}$ $(M+H)^+$ 217.1017, found 217.1014. Data in agreement with literature.[254]

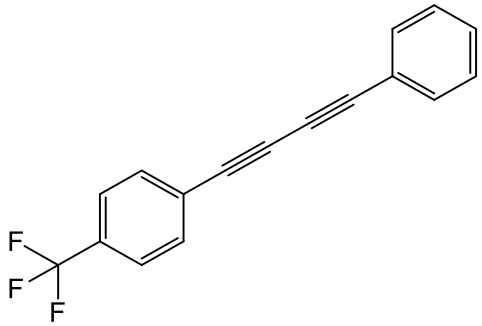
(*Z*)-(3-(4-(Trifluoromethyl)phenyl)hexa-3-en-1,5-diyne-1,6-diyl)dibenzene (155)



Synthesised according to general procedure C, using *N*,*N*-diethyl-2-(4-(trifluoromethyl)phenyl)ethyne-1-sulfonamide **152** as the alkynyl sulfonamide. Yellow oil (1%). *Rf* = 0.57 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.85 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 7.67 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 7.61-7.63 (m, 2 H, Ar*H*), 7.54-7.56 (m, 2 H, Ar*H*), 7.39-7.41 (m, 3 H, Ar*H*), 7.35-7.38 (m, 3 H, Ar*H*), 6.64 (s, 1 H, C=C*H*); ^{13}C-NMR (150 MHz,

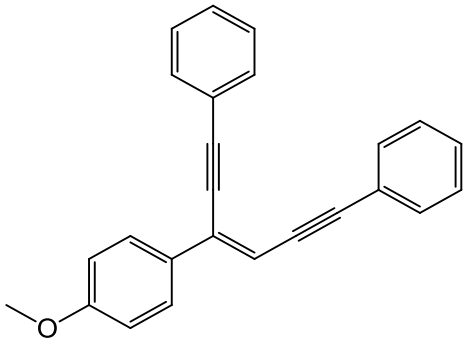
$CDCl_3$) δ_C 132.1 (C_q), 131.9 (CH), 131.8 (CH), 131.8 (CH), 131.7 (CH), 130.3 (q, *J* = 31.4 Hz, C_q), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.6 (CH), 125.7 (q, *J* = 3.4 Hz, CH), 125.0 (C_q), 124.1 (q, *J* = 273.6 Hz, C_q), 123.2 (C_q), 116.1 (C_q), 99.9 (C_q), 99.1 (C_q), 88.7 (C_q), 87.0 (C_q); ν_{max}/cm^{-1} 3079, 3060, 3023, 2954, 2923, 2853, 2183, 1616, 1597; LRMS (CI) *m/z* (%) 373 (100), 345 (26); HRMS (CI) calc'd for $C_{25}H_{16}F_3$ $(M+H)^+$ 373.1199, found 373.1199. Data in agreement with literature.[135]

1-(Phenylbuta-1,3-diyn-1-yl)-4-(trifluoromethyl)benzene (156)



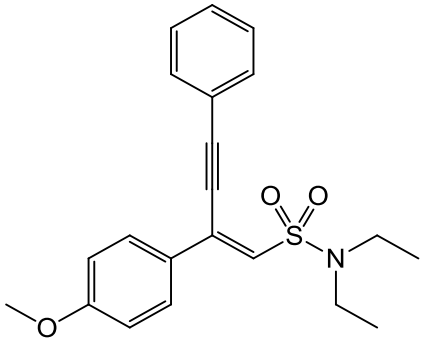
Synthesised according to general procedure C, using *N*,*N*-diethyl-2-(4-(trifluoromethyl)phenyl)ethyne-1-sulfonamide **152** as the alkynyl sulfonamide. Yellow oil (40%). *Rf* = 0.66 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.55 (d, *J* = 7.0 Hz, 2 H, Ar*H*), 7.60-7.67 (m, 7 H, Ar*H*); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 132.8 (CH), 132.7 (CH), 130.9 (q, *J* = 33.1 Hz, C_q), 129.7 (CH), 128.6 (CH), 125.8 (C_q), 125.5 (q, *J* = 3.8 Hz, CH), 123.9 (q, *J* = 272.6 Hz, C_q), 121.5 (C_q), 83.0 (C_q), 79.9 (C_q), 76.3 (C_q), 73.5 (C_q); ν_{max}/cm^{-1} 2955, 2924, 2853, 2256, 2213, 1612, 1570; LRMS (CI) *m/z* (%) 270 (100). Data in agreement with literature.[254]

(*Z*)-(3-(4-Methoxyphenyl)hexa-3-en-1,5-diyne-1,6-diyl)dibenzene (157)



Synthesised according to general procedure C, using *N*,*N*-diethyl-2-(4-methoxyphenyl)ethyne-1-sulfonamide **153** as the alkynyl sulfonamide. Brown oil (8%). *Rf* = 0.44 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.70 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.61-7.62 (m, 2 H, Ar*H*), 7.52-7.54 (m, 2 H, Ar*H*), 7.37-7.38 (m, 3 H, Ar*H*), 7.33-7.35 (m, 3 H, Ar*H*), 6.94 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.48 (s, 1 H, C=C*H*), 3.86 (s, 3 H, OCH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 160.4 (C_q), 133.0 (C_q), 131.9 (CH), 131.7 (CH), 129.5 (C_q), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 127.6 (CH), 123.7 (C_q), 123.3 (C_q), 114.1 (CH), 111.7 (CH), 98.2 (C_q), 97.9 (C_q), 89.4 (C_q), 87.8 (C_q), 55.5 (CH_3); ν_{max}/cm^{-1} 3052, 2954, 2926, 2836, 2199, 2179, 1603, 1577, 1509; LRMS (CI) *m/z* (%) 335 (100); HRMS (CI) calc'd for $C_{25}H_{19}O$ $(M+H)^+$ 335.1430, found 335.1431.

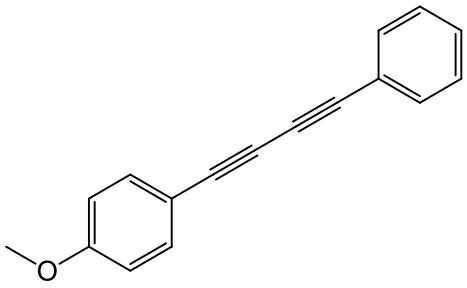
(*Z*)-*N*,*N*-Diethyl-2-(4-methoxyphenyl)-4-phenylbut-1-en-3-yne-1-sulfonamide (158)



Synthesised according to general procedure C, using *N*,*N*-diethyl-2-(4-methoxyphenyl)ethyne-1-sulfonamide **153** as the alkynyl sulfonamide. Yellow oil (36%). *Rf* = 0.20 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.69 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.62 (d, *J* = 7.6 Hz, 2 H, Ar*H*), 7.37-7.41 (m, 3 H, Ar*H*), 6.95 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.82 (s, 1 H, C=C*H*), 3.86 (s, 3 H, OCH_3), 3.42 (q, *J* = 7.2 Hz, 4 H, NCH_2), 1.23 (t, *J* = 7.1 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (150

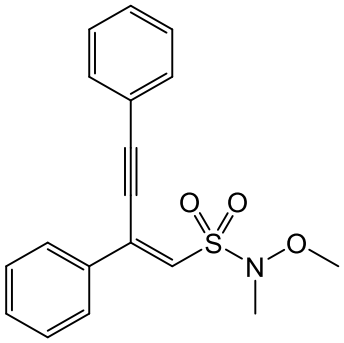
MHz, $CDCl_3$) δ_C 161.5 (C_q), 132.2 (C_q), 132.2 (CH), 129.7 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.3 (C_q), 122.4 (C_q), 114.3 (CH), 103.3 (C_q), 85.0 (C_q), 55.6 (CH_3), 41.9 (CH_2), 14.5 (CH_3); ν_{max}/cm^{-1} 3056, 2971, 2933, 2873, 2841, 2211, 1602, 1581, 1509; LRMS (ESI) *m/z* (%) 370 (100), 342 (15); HRMS (ESI) calc'd for $C_{21}H_{24}NO_3S$ $(M+H)^+$ 370.1477, found 370.1476.

1-Methoxy-4-(phenylbuta-1,3-diyn-1-yl)benzene (159)



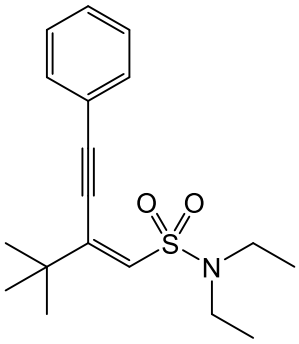
Synthesised according to general procedure C, using *N*,*N*-diethyl-2-(4-methoxyphenyl)ethyne-1-sulfonamide **153** as the alkynyl sulfonamide. Colourless oil (10%). *Rf* = 0.49 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.53 (d, *J* = 6.6 Hz, 2 H, Ar*H*), 7.48 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.32-7.38 (m, 3 H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 3.83 (s, 3 H, OCH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 160.5 (C_q), 134.3 (CH), 132.6 (CH), 129.2 (CH), 128.5 (CH), 122.1 (C_q), 114.3 (CH), 113.8 (C_q), 81.9 (C_q), 81.1 (C_q), 74.3 (C_q), 72.8 (C_q), 55.5 (CH_3); ν_{max}/cm^{-1} 3074, 2953, 2923, 2842, 2216, 1599, 1566, 1506; LRMS (CI) *m/z* (%) 251 (19), 250 (100), 234 (12), 233 (62); HRMS (CI) calc'd for $C_{17}H_{13}O$ $(M+H)^+$ 233.0961, found 233.0960. Data in agreement with literature.[254]

(*Z*)-*N*-Methoxy-*N*-methyl-2,4-diphenylbut-1-en-3-yne-1-sulfonamide (177)



Synthesised according to general procedure C, using *N*-methoxy-*N*-methyl-2-phenylethyne-1-sulfonamide **175** as the alkynyl sulfonamide. Yellow oil (29%). *Rf* = 0.39 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.80 (d, *J* = 6.6 Hz, 2 H, Ar*H*), 7.64 (d, *J* = 6.8 Hz, 2 H, Ar*H*), 7.45-7.49 (m, 3 H, Ar*H*), 7.38-7.42 (m, 3 H, Ar*H*), 6.95 (s, 1 H, C=C*H*), 3.85 (s, 3 H, OCH_3) 3.08 (s, 3 H, NCH_3); ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C 138.7 (C_q), 135.8 (C_q), 132.4 (CH), 131.0 (CH), 130.0 (CH), 129.0 (CH), 128.7 (CH), 127.5 (CH), 122.2 (CH), 122.1 (C_q), 104.3 (C_q), 84.8 (C_q), 64.0 (CH_3), 39.3 (CH_3); ν_{max}/cm^{-1} 3059, 2978, 2935, 2899, 2210, 1552; LRMS (CI) *m/z* (%) 345 (100), 328 (10); HRMS (CI) calc'd for $C_{18}H_{17}NO_3S$ $(M+H)^+$ 328.0924, found 328.0923.

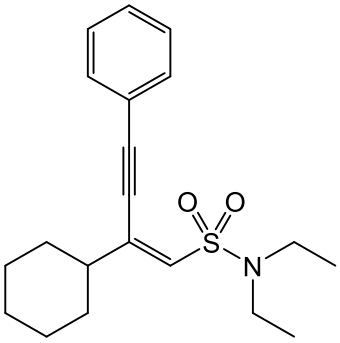
(*Z*)-2-(*tert*-Butyl)-*N*,*N*-diethyl-4-phenylbut-1-en-3-yne-1-sulfonamide (181)



Synthesised according to general procedure C, using *N*,*N*-diethyl-3,3-dimethylbut-1-yne-1-sulfonamide **180** as the alkynyl sulfonamide. Yellow oil (65%). *Rf* = 0.32 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.55 (d, *J* = 7.0 Hz, 2 H, Ar*H*), 7.34-7.37 (m, 3 H, Ar*H*), 6.40 (s, 1 H, C=C*H*), 3.36 (q, *J* = 7.2 Hz, 4 H, NCH_2), 1.26 (s, 9 H, CCH_3), 1.19 (t, *J* = 7.1 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 144.3 (C_q), 132.0 (CH), 129.7 (CH), 129.3 (CH), 128.5 (CH), 122.7 (C_q), 103.3 (C_q), 84.6 (C_q), 41.6 (CH_2), 38.2 (C_q), 29.1 (CH_3), 14.3 (CH_3);

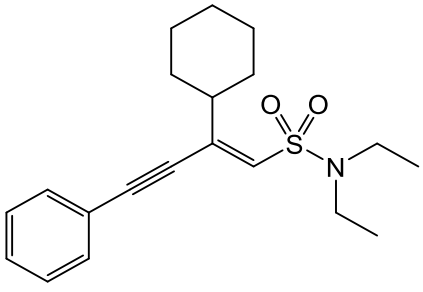
ν_{max}/cm^{-1} 3057, 3029, 2970, 2935, 2874, 2210, 1598, 1573; LRMS (ESI) *m/z* (%) 320 (100); HRMS (ESI) calc'd for $C_{18}H_{26}NO_2S$ $(M+H)^+$ 320.1684, found 320.1671.

(*Z*)-2-Cyclohexyl-*N*,*N*-diethyl-4-phenylbut-1-en-3-yne-1-sulfonamide (*Z*-183)



Synthesised according to general procedure C, using 2-cyclohexyl-*N*,*N*-diethylethyne-1-sulfonamide **182** as the alkynyl sulfonamide. Yellow oil (20%). *Rf* = 0.34 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.54 (d, *J* = 6.5 Hz, 2 H, Ar*H*), 7.34-7.37 (m, 3 H, Ar*H*), 6.35 (s, 1 H, C=C*H*), 3.34 (q, *J* = 7.1 Hz, 4 H, NCH_2), 2.23 (tt, *J* = 11.6, 3.0 Hz, 1H, C*H*), 1.81-1.88 (m, 4 H, CH_2), 1.44 (qd, *J* = 12.7, 3.2 Hz, 2 H, CH_2), 1.32 (qt, *J* = 12.9, 3.2 Hz, 2 H, CH_2), 1.22 (qt, *J* = 12.6, 3.8 Hz, 2 H, CH_2), 1.19 (t, *J* = 7.1 Hz, 6 H, NCH$_2$CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 140.4 (C_q), 132.1 (CH), 130.3 (CH), 129.4 (CH), 128.5 (CH), 122.6 (C_q), 102.6 (C_q), 84.9 (C_q), 46.8 (CH), 41.7 (CH_2), 31.8 (CH_2), 26.1 (CH_2), 25.8 (CH_2), 14.4 (CH_3); ν_{max}/cm^{-1} 3050, 2973, 2926, 2853, 2198, 1599, 1578; LRMS (ESI) *m/z* (%) 346 (100); HRMS (ESI) calc'd for $C_{20}H_{28}NO_2S$ $(M+H)^+$ 346.1841, found 346.1843.

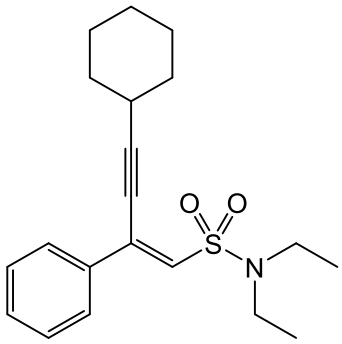
(*E*)-2-Cyclohexyl-*N*,*N*-diethyl-4-phenylbut-1-en-3-yne-1-sulfonamide (*E*-183)



Synthesised according to general procedure C, using 2-cyclohexyl-*N*,*N*-diethylethyne-1-sulfonamide **182** as the alkynyl sulfonamide. Yellow oil (5%). *Rf* = 0.34 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.48 (d, *J* = 6.5 Hz, 2 H, Ar*H*), 7.34-7.38 (m, 3 H, Ar*H*), 6.31

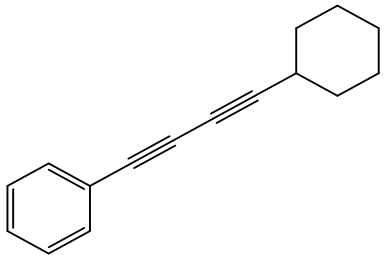
(s, 1 H, C=C*H*), 3.46 (tt, *J* = 11.7, 3.5 Hz, 1H, C*H*), 3.34 (q, *J* = 7.2 Hz, 4 H, NCH_2), 1.71-1.84 (m, 6 H, CH_2), 1.55 (qd, *J* = 12.5, 3.4 Hz, 2 H, CH_2), 1.39 (qt, *J* = 13.1, 3.4 Hz, 2 H, CH_2), 1.23 (t, *J* = 7.1 Hz, 6 H, NCH$_2$CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 143.0 (C_q), 132.0 (CH), 130.2 (CH), 129.3 (CH), 128.6 (CH), 122.3 (C_q), 95.9 (C_q), 86.9 (C_q), 43.1 (CH_2), 41.9 (CH_2), 39.0 (CH), 31.6 (CH_2), 25.8 (CH_2), 14.5 (CH_3); ν_{max}/cm^{-1} 3051, 2971, 2927, 2853, 2190, 1597, 1571, 1511; LRMS (ESI) *m/z* (%) 346 (100), 335 (30); HRMS (ESI) calc'd for $C_{20}H_{28}NO_2S$ $(M+H)^+$ 346.1841, found 346.1812.

(*Z*)-4-Cyclohexyl-*N*,*N*-diethyl-2-phenylbut-1-en-3-yne-1-sulfonamide (193)



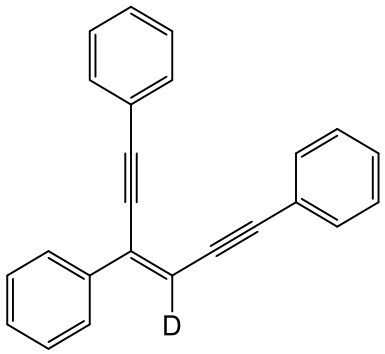
Synthesised according to general procedure C, using *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide **106** as the alkynyl sulfonamide and cyclohexylacetylene in place of phenylacetylene. Yellow oil (29%). *Rf* = 0.36 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.64 (d, *J* = 6.3 Hz, 2 H, Ar*H*), 7.37-7.41 (m, 3 H, Ar*H*), 6.78 (s, 1 H, C=C*H*), 3.39 (q, *J* = 7.1 Hz, 4 H, NCH_2), 2.73 (quint., *J* = 4.3 Hz, 1H, C*H*), 1.91-1.93 (m, 2 H, CH_2), 1.76-1.80 (m, 2 H, CH_2), 1.54-1.64 (m, 3 H, CH_2), 1.34-1.41 (m, 3 H, CH_2), 1.23 (t, *J* = 7.1 Hz, 6 H, NCH$_2$CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 136.9 (C_q), 133.6 (C_q), 130.4 (CH), 130.1 (CH), 128.8 (CH), 127.2 (CH), 110.3 (C_q), 76.4 (C_q), 41.9 (CH_2), 32.1 (CH_2), 30.4 (CH), 25.9 (CH_2), 24.9 (CH_2), 14.5 (CH_3); ν_{max}/cm^{-1} 3055, 2969, 2926, 2850, 2219, 1556; LRMS (ESI) *m/z* (%) 346 (100), 165 (16); HRMS (ESI) calc'd for $C_{20}H_{28}NOS$ $(M+H)^+$ 346.1841, found 346.1841.

(Cyclohexylbuta-1,3-diyn-1-yl)benzene (194)



Synthesised according to general procedure C, using *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide **106** as the alkynyl sulfonamide and cyclohexylacetylene in place of phenylacetylene. Colourless oil (12%). *Rf* = 0.63 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.48 (d, *J* = 7.0 Hz, 2 H, Ar*H*), 7.29-7.35 (m, 3 H, Ar*H*), 2.55 (quint., *J* = 4.4 Hz, 1 H, C*H*), 1.83-1.86 (m, 2 H, CH_2), 1.71-1.76 (m, 2 H, CH_2), 1.50-1.55 (m, 3 H, CH_2), 1.29-1.39 (m, 3 H, CH_2); ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C 132.6 (CH), 128.9 (CH), 128.4 (CH), 122.3 (C_q), 88.7 (C_q), 75.4 (C_q), 74.5 (C_q), 65.1 (C_q), 32.3 (CH_2), 29.9 (CH), 25.8 (CH_2), 24.8 (CH_2); ν_{max}/cm^{-1} 3057, 2925, 2850, 2236, 1594, 1570; LRMS (ESI) *m/z* (%) 209 (21), 197 (100); HRMS (ESI) calc'd for $C_{16}H_{17}$ $(M+H)^+$ 209.1330, found 209.1373.

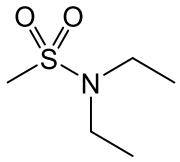
4.2.11. Procedure for deuterium labelling experiment producing (*Z*)-(hexa-3-en-1,5-diyne-1,3,6-triyl-*d*)tribenzene (137)



A 100 mL flame-dried flask was charged with a solution of phenylacetylene-d (125 mg, 1.21 mmol, 4.2 eq.) in dist. THF (12 mL), under argon. The solution was cooled to 0 °C and ^{n}BuLi (0.23 mL of 2.5 M in hexanes, 0.57 mmol, 2.0 eq.) was added dropwise. The mixture was allowed to warm to RT and stirred for a further 10 min. An additional, 100 mL flame-dried flask was charged with a solution of *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide **106** (67.9 mg, 0.29 mmol, 1.0 eq.) in dist. THF (3 mL), under argon. The previously formed lithiated solution

was added dropwise over 25 min, with constant stirring at RT. The reaction mixture was quenched with D_2O (100 mL), diluted with CH_2Cl_2 (200 mL), washed with a saturated NaCl solution in D_2O (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification *via* flash column chromatography (EtOAc/PE) was carried out to yield the product as a brown oil (40.9 mg, 47%). *Rf* = 0.56 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.77 (d, *J* = 7.6 Hz, 2 H, Ar*H*), 7.62-7.65 (m, 2 H, Ar*H*), 7.55-7.58 (m, 2 H, Ar*H*), 7.43 (t, *J* = 7.3 Hz, 2 H, Ar*H*), 7.35-7.41 (m, 7 H, Ar*H*), 6.60 (s, 0.5 H, C=C*H*); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 136.9 (C_q), 133.5 (C_q), 131.9 (CH), 131.8 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 126.3 (CH), 123.6 (C_q), 123.3 (C_q), 113.8 (CH), 113.5 (t, *J* = 25.6 Hz, C_q), 98.6 (C_q), 98.5 (C_q), 89.2 (C_q), 87.7 (C_q); ν_{max}/cm^{-1} 3056, 3023, 2955, 2923, 2852, 2208, 2181, 1595; LRMS (EI) *m/z* (%) 304 (100), 226 (7); HRMS (EI) calc'd for $C_{24}H_{15}D$ (M^+) 305.1309, found 305.1310. Data in agreement with literature.[136]

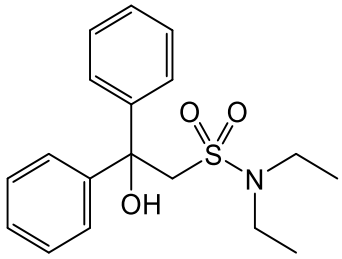
4.2.12. Procedure for the synthesis of *N*,*N*-diethylmethanesulfonamide (218)[xii]



A 250 mL flask was charged with a solution of methanesulfonyl chloride (2.20 mL, 28.4 mmol, 1.2 eq.) in CH_2Cl_2 (100 mL). The solution was cooled to 0 °C and charged with diethylamine (3.50 mL, 34.0 mmol, 1.0 eq.) and triethylamine (10.9 mL, 78.2 mmol, 2.3 eq.), then allowed to stir for 30 min. The reaction mixture was washed with 2 M HCl (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product as a colourless oil (4.20 g, 98%), which was used without further purification. *Rf* = 0.21 (20:80 EtOAc:PE); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 3.27 (q, *J* = 7.1 Hz, 4 H, NC*H*$_2$CH$_3$), 2.82 (s, 3 H, SO$_2$C*H*$_3$), 1.20 (t, J = 7.1 Hz, 6 H, NC*H*$_2$CH$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C 41.8 (CH_2), 38.9 (CH_3), 14.3 (CH_3); ν_{max}/cm^{-1} 2973, 1319; LRMS (CI) *m/z* (%) 169 (100); HRMS (CI) calc'd for $C_5H_{17}N_2O_2S$ $(M+NH_4)^+$ 169.1005, found 169.1005. Data in agreement with literature.[255-256]

[xii] Experimental procedure designed and implemented by student Yee Sum Joana Wong under supervision of the author, and data adapted from project thesis: Wong, Y. S. J., *Easy Access to Carbenes and Carbenoids for Organic Synthesis*, MSci: University College London, **2017**.

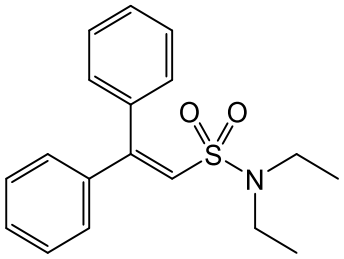
4.2.13. Procedure for the synthesis of *N*,*N*-diethyl-2-hydroxy-2,2-diphenylethane-1-sulfonamide (219)[xiii]



A 100 mL flame-dried flask was charged with a solution of *N*,*N*-diethylmethanesulfonamide **218** (0.50 g, 3.31 mmol) in dry THF (33.1 mL), under argon. The solution was cooled to -78 °C and ^{n}BuLi (1.45 mL of 2.5 M in hexanes, 3.64 mmol, 1.1 eq.) was added dropwise, the mixture was then allowed to stir for a further 10 min. A solution of benzophenone (6.02 g, 33.1 mmol, 1.0 eq.) in dry THF (7 mL) was added dropwise, and allowed to stir for a further 40 min. The reaction mixture was allowed to warm to RT and stirred for 50 min, then heated to 50 °C and stirred for a further 17 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL), washed with water (3 x 50 mL) then brine (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification *via* flash column chromatography (EtOAc/PE) was carried out to yield the product as a white solid (0.46 g, 42%). m.p. 94-96 ^{o}C; *Rf* = 0.30 (20:80 EtOAc:PE); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.48-7.50 (m, 4 H, Ar*H*), 7.32-7.35 (m, 4 H, Ar*H*), 7.23-7.27 (m, 2 H, Ar*H*), 5.18 (s, 1 H, O*H*), 3.89 (s, 2 H, SO_2CH_2), 3.12 (q, *J* = 7.1 Hz, 4 H, NCH_2CH_3), 1.16 (t, *J* = 7.1 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C 144.4 (CH), 128.4 (CH), 127.6 (CH), 126.0 (C_q), 76.5 (C_q), 61.9 (CH_2), 42.0 (CH_2), 14.7 (CH_3); ν_{max}/cm^{-1} 3471, 2981, 1490, 1449, 1299; LRMS (CI) *m/z* (%) 351 (100), 334 (20); HRMS (EI) calc'd for $C_{18}H_{24}NO_3S$ $(M+H)^+$ 334.1471, found 334.1471.

[xiii] Experimental procedure designed and implemented by student Yee Sum Joana Wong under supervision of the author, and data adapted from project thesis: Wong, Y. S. J., *Easy Access to Carbenes and Carbenoids for Organic Synthesis*, MSci: University College London, **2017**.

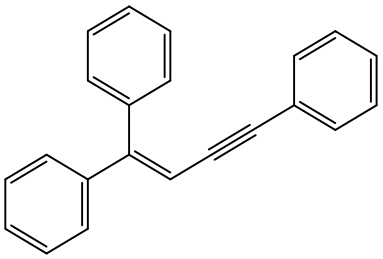
4.2.14. Procedure for the synthesis of *N*,*N*-diethyl-2,2-diphenylethene-1-sulfonamide (149)[xiv]



A 50 mL flask was cooled to 0 °C, charged with *N*,*N*-diethyl-2-hydroxy-2,2-diphenylethane-1-sulfonamide **219** (84.1 mg, 0.25 mmol, 1.0 eq.) and concentrated sulfuric acid (15 mL), then allowed to stir for 30 min. The reaction mixture was charged with ice-water (100 mL) and neutralised with saturated $NaHCO_3$ solution. The organic layer was extracted using CH_2Cl_2 (3 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product as a yellow oil (54.6 mg, 69%), which was used without further purification. *Rf* = 0.29 (20:80 EtOAc:PE); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.31-7.41 (m, 8 H, Ar*H*), 7.21-7.23 (m, 2 H, Ar*H*), 6.66 (s, 1 H, Ar_2C=C*H*), 3.13 (q, *J* = 7.1 Hz, 4 H, NCH_2CH_3), 1.15 (t, *J* = 7.2 Hz, 6 H, NCH_2CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C 152.5 (C_q), 140.1 (C_q), 136.7 (C_q), 129.8 (CH), 129.8 (CH), 128.9 (CH), 128.6 (CH), 128.3 (CH), 128.0 (CH), 126.2 (CH), 41.6 (CH_2), 14.5 (CH_3); ν_{max}/cm^{-1} 2969, 2931, 1589, 1568, 1489, 1463, 1443, 1325; LRMS (EI) *m/z* (%) 631 (96), 316 (100); HRMS (ESI) calc'd for $C_{18}H_{22}NO_2S$ $(M+H)^+$ 316.1371, found 316.1375.

[xiv] Experimental procedure designed and implemented by student Yee Sum Joana Wong under supervision of the author, and data adapted from project thesis: Wong, Y. S. J., *Easy Access to Carbenes and Carbenoids for Organic Synthesis*, MSci: University College London, **2017**.

4.2.15. Procedure for the synthesis of but-1-en-3-yne-1,1,4-triyltribenzene (150)[xv]



A 10 mL flame-dried flask (flask A) was charged with a solution of 2,2,6,6-tetramethylpiperidine (0.03 mL, 0.17 mmol, 1.0 eq.) in dry THF (1.60 mL), under argon. The solution was cooled to −78 °C and ^{n}BuLi (0.08 mL 2.5 M in hexanes, 0.19 mmol, 1.1 eq.) was added dropwise. The mixture was allowed to stir for a further 30 min. An additional, 10 mL flame-dried flask (flask B) was charged with a solution of *N*,*N*-diethyl-2,2-diphenylethene-1-sulfonamide **149** (53.6 mg, 0.17 mmol, 1.0 eq.) in dry THF (1.6 mL), under argon. The solution in flask B was added dropwise to flask A and allowed to stir for 10 min. Meanwhile a third, 10 mL flame-dried flask (flask C) was charged with a solution of phenylacetylene (0.04 mL, 0.34 mmol, 2.0 eq.) in dry THF (1.60 mL), under argon. The solution was cooled to −78 °C and ^{n}BuLi (0.08 mL 2.5 M in hexanes, 0.19 mmol, 1.1 eq.) was added dropwise. The mixture was allowed to stir for a further 30 min. The solution in flask C was added dropwise to flask A, warmed to RT and allowed to stir for a further 17 h. The reaction mixture was then warmed to 55 °C and allowed to stir for a further 17 h. The reaction was quenched with saturated $NaHCO_3$ solution (1 mL), washed with saturated $NaHCO_3$ solution (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification *via* flash column chromatography (EtOAc/PE) was carried out three times to yield the product as a yellow oil (19.3 mg, 41% and contaminated with ca. 20% of unknown compound). *Rf* = 0.53 (20:80 EtOAc:PE); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.53-7.56 (m, 5 H, Ar*H*), 7.35-7.44 (m, 5 H, Ar*H*), 7.26-7.30 (m, 5 H, Ar*H*), 6.24 (s, 1 H, Ar_2C=C*H*); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C 152.8 (C_q), 141.5 (C_q), 139.3 (C_q), 132.6 (CH), 131.5 (CH), 130.3 (CH), 129.3 (CH), 128.5 (CH), 128.4 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 127.9 (CH), 123.7 (CH), 121.9 (C_q), 107.2

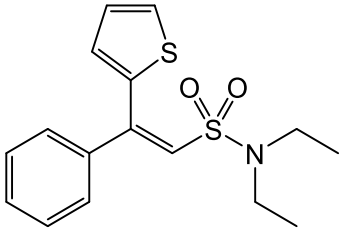
[xv] Experimental procedure designed and implemented by student Yee Sum Joana Wong under supervision of the author, and data adapted from project thesis: Wong, Y. S. J., *Easy Access to Carbenes and Carbenoids for Organic Synthesis*, MSci: University College London, **2017**.

(CH), 93.7 (C_q), 89.2 (C_q); ν_{max}/cm^{-1} 2918, 1483, 1439; LRMS (EI) *m/z* (%) 281 (100); HRMS (CI) calc'd for $C_{22}H_{17}$ $(M+H)^+$ 281.1325, found 281.1326. Data in agreement with literature.[257-258]

4.2.16. Procedure for the treatment of *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide (106) with lithiated thiophene to produce (*Z*)-*N*,*N*-diethyl-2-phenyl-2-(thiophen-2-yl)ethene-1-sulfonamide (196) and 2-(phenylethynyl)thiophene (197)

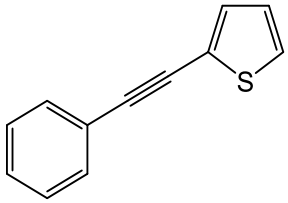
A 100 mL flame-dried flask was charged with a solution of thiophene (76.1 mg, 0.90 mmol, 4.1 eq.) in dist. THF (90 mL), under argon. The solution was cooled to 0 °C and ^{n}BuLi (0.36 mL of 2.5 M in hexanes, 0.90 mmol, 4.1 eq.) was added dropwise. The mixture was allowed to warm to RT and stirred for a further 10 min. An additional, 100 mL flame-dried flask was charged with a solution of *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide **106** (52.0 mg, 0.22 mmol, 1.0 eq.) in dist. THF (2.2 mL), under argon. The solution was heated to 60 °C and the previously formed lithiated solution was added dropwise over 1.5 h with constant stirring. The reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with water (100 mL) then brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude mixture. Separation *via* flash column chromatography (EtOAc/PE) was carried out to yield the purified products.

(*Z*)-*N*,*N*-Diethyl-2-phenyl-2-(thiophen-2-yl)ethene-1-sulfonamide (196)



Yellow oil (3.3 mg, 5%). *Rf* = 0.35 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.42-7.44 (m, 3 H, Ar*H*), 7.36-7.38 (m, 3 H, Ar*H*), 6.98 (dd, *J* = 5.0, 3.8 Hz, 1 H, Ar*H*), 6.80 (d, *J* = 3.7 Hz, 1 H, Ar*H*), 6.73 (s, 1 H, C=C*H*), 3.09 (q, *J* = 7.2 Hz, 4 H, NCH_2), 1.13 (t, *J* = 7.1 Hz, 6 H, NCH$_2$CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 145.6 (CH), 143.8 (C_q), 135.9 (C_q), 130.4 (C_q), 129.4 (CH), 129.1 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 123.4 (CH) 41.6 (CH_2), 14.5 (CH_3); ν_{max}/cm^{-1} 2953, 2913, 2869, 2846, 1700, 1579; LRMS (CI) *m/z* (%) 339 (100), 322 (49); HRMS (CI) calc'd for $C_{16}H_{19}NO_2S_2$ $(M+H)^+$ 322.0930, found 322.0930.

2-(Phenylethynyl)thiophene (197)



Colourless oil (6.6 mg, 16%). *Rf* = 0.59 (20:80 EtOAc:PE); ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.51-7.53 (m, 2 H, Ar*H*), 7.34-7.37 (m, 3 H, Ar*H*), 7.29-7.31 (m, 2 H, Ar*H*), 7.02 (dd, *J* = 5.2, 3.7 Hz, 1 H, Ar*H*); ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C 132.0 (CH), 131.5 (CH), 128.5 (CH), 128.5 (CH), 127.4 (CH), 127.2 (CH), 123.4 (C_q), 123.0 (C_q), 93.1 (C_q), 82.7 (C_q); ν_{max}/cm^{-1} 3072, 2951, 2919, 2849, 2199, 1595, 1517; LRMS (CI) *m/z* (%) 371 (6), 370 (14), 369 (46), 368 (8), 203 (15), 202 (100), 184 (51); HRMS (CI) calc'd for $C_{12}H_9S$ $(M+H)^+$ 184.0341, found 184.0342. Data in agreement with literature.[259]

4.2.17. Procedure for design of experiments

A 100 mL flame-dried flask was charged with a stock solution of 3-methoxyphenylacetylene (0.1 M in dist. THF, 1.0-3.0 eq.), and if necesarry additional dist. THF to achieve the required concentration (0.10-0.01 M), under argon. The solution was charged with ^{n}BuLi (2.5 M in hexanes, 1.0-3.0 eq.) dropwise and stirred at RT for 10 min. An additional, 100 mL flame-dried flask was charged with a stock solution of *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide **106** (0.15 mL of 0.1 M in dist. THF, 1.5 mmol, 1.0 eq.), under argon. The solution temperature was adjusted to 0-60 °C and the previously formed lithiated solution was added dropwise (add. rate 0.0010-0.0100 mmol/min) with constant stirring. After addition was completed, the reaction mixture was allowed to stir for a further 20 min then diluted with EtOAc (200 mL), washed with water (100 mL) then brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude mixture. The crude was dissolved in a pentachlorobenzene internal standard stock solution (1.00 mL of 0.10 M in $CDCl_3$, 0.1 mmol), and subsequent analysis of the ^{1}H-NMR spectrum produced was used to determine the product yields (see **Table 2**, **page 85**). Pentachlorobenzene internal standard ^{1}H-NMR (600 MHz, $CDCl_3$) δ_H 7.53 (s, 1 H, Ar*H*).

5. References

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