Unsaturated Organosulfur Chemistry: synthesis and applications

A dissertation presented by:

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DOCTOR OF PHILOSOPHY

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Declaration

I, Mohima Begum Roomi Chowdhury, 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

The original focus of this thesis was ynol ether synthesis which was successful using simple and easy-to-prepare precursors (chloroacetylenes) but low yielding.

Attention was then diverted to the design and synthesis of a range of thioynol ethers (alkynyl sulfides) utilising chloroacetylenes. The reaction of a chloroacetylene with a thiolate salt in the presence of an amine mediator (Me_2NH or DMEDA) yielded the alkynyl sulfides in excellent yields. The alkynyl chlorides were easily prepared from the parent alkynes contrasting sharply with the cumbersome synthesis of an alkynyl sulfonamide previously required.

As well as chloroacetylenes, bromo- and iodoacetylenes have also been studied and the differences in their reactivity are highlighted.

With a successful route to thioynol ethers at hand, brief mechanistic investigations were conducted into their reactivity. Finally, preliminary studies have been carried out on the reactivity of their derivatives.

Contents

Abbreviations

Ac	Acetyl
acac	Acetylacetone
aq	Aqueous
Ar	Aryl
AIBN	Azo*bisiso*butyronitrile
BINAP	2,2'-*bis*(Diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Bz	Benzoyl
Bu	Butyl
Cy	Cyclohexyl
d	Day
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DMEDA	*N*,*N*'-Dimethylethylenediamine
DMF	*N*,*N*-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethyl sulfoxide
E^+	Electrophile
E	Entgegen (against)
EBX	Ethynyl Benziodoxolone
ee	Enantiomeric excess
EPR	Electron paramagentic resonance
er	Enantiomeric ratio
h	Hour
HAS	Homolytic Aromatic Substitution
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
LRMS	Low resolution mass spectrometry
m	*meta*
MO	Molecular orbital

NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NFSI	*N*-Fluorobenzenesulfonamide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
NTf	*bis*(Trifluoromethylsulfonyl)imide
Nu	Nucleophile
o	*ortho*
OTf	Trifluoromethanesulfonate/triflate
p	*para*
PE	Petroleum Ether
ppb	parts per billion
ppm	parts per million
Py	Pyridine
r.t.	Room temperature
sat	Saturated
SET	Single Electron Transfer
tert	Tertiary
TBAB	Tetra-*n*-butylammonium bromide
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBDMS	*Tert*-Butyldimethylsilyl
TCPOH	2,4,6-Trichlorophenol
TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Tri*iso*propylsilyl
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Tol	Tolyl
Ts	*para*-Toluenesufonyl/tosyl
UV	Ultraviolet
Z	Zusammen (together)

Acknowledgements

Firstly, I'd like to thank my supervisor, Dr. Jon Wilden, who has also been a friend over the past few years. His humour, entertainment and confidence in me has been encouraging at times when I was ready to throw the lab coat in. Special thanks must go to Dr. Vincent Gray, who was one of the main reasons I pursued a PhD in the first place. His knowledge, banter, invaluable catchphrases (you're a keeper!) and general Vincent-ness pushed me to push myself. You are my champion!

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I'd also like to acknowledge my siblings, Shooma, Shoomi and Emraj, and my brother-in-law, Hassan – they are always there, no matter our differences in views and personalities. Their endless faith in me, space when I needed it and similar idiosyncrasies have kept me going on more occasions than I care to admit.

Almost last but most certainly not least, hugest thanks to Dan, my partner in crime who has put up with me for almost a decade now. Her sense of humour, patience, encouragement, love and everything else in between happifies me no end and I could not have done this without her. Thank you for keeping me fed, relatively sane and for always being there when I need my person.

Finally, my parents: a separate thesis would need to be written to acknowledge all of the reasons I am grateful to them. Their faith in me is unconditional, as is their love. The courage they had to move 1,000's of miles away from their families to make a better life is unimaginable. Without their drive, determination and belief in us to be whatever we want to be, this PhD would not have been possible to pursue.

Thanks to my mum for always being just a phone call away, usually to ask what food I'd like cooked for my next visit, but also knowing exactly what to say to make things better. Thanks to my dad, one of my best friends, who is always there with the best advice and the proudest dad in the world (seriously). To the most knowledgeable person I know, here's a PhD to add to the four undergraduate degrees and two Masters degrees that you've accumulated so far.

"Do the best you can until you know better. Then when you know better, do better."

- Maya Angelou

“I am no longer accepting the things I cannot change. I am changing the things I cannot accept.”

- Angela Davis

"There’s an old saying in Tennessee – I know it’s in Texas, probably Tennessee – that says, fool me once, shame on – shame on you – (long pause) – fool me, you can’t get fooled again."

- George W. Bush

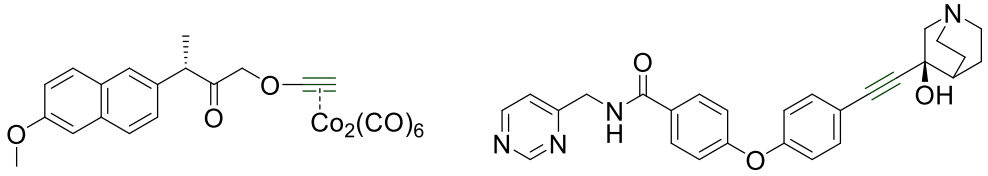
Dedicated to my dad,
Nurul Chowdhury

1. Introduction

The requirement for new and potent drugs in the treatment of a range of diseases is a constant endeavour within the scientific community. The invention of new, innovative synthetic methods is therefore a continuous goal in the field of organic chemistry.

Part of the arsenal of functional groups at hand to the organic chemist is the alkyne. These are a class of compound which are important in drug development and have found widespread applications not only in organic synthesis but also in biochemistry,[1,2] nanoscience,[3] materials science, and so on, since ethyne was first discovered in 1836 by Edmund Davy.[4–6]

The carbon-carbon triple bond is found in many classes of natural products,[4–6] including terpenes, carotenoids, amino acids and alkaloids. It can be found in useful compounds which possess medicinal properties (**Figure 1.1**) such as being antifungal, antitumour, antibacterial, antimicrobial, HIV inhibitory and so on.[7]



Acetylenehexacarbonyl dicobalt complexes with cytotoxic properties

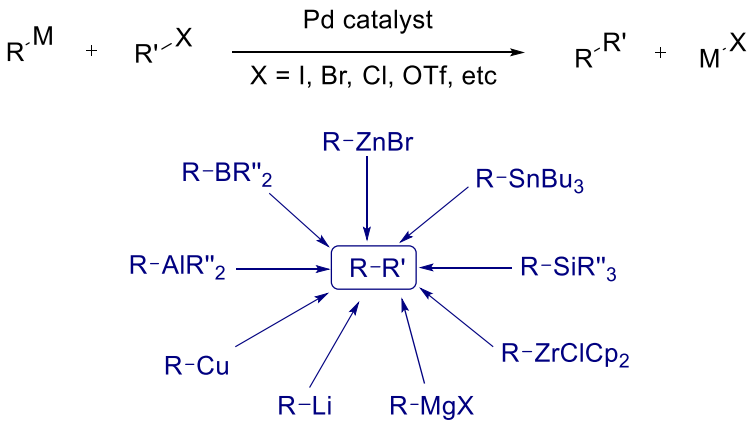
Non-zinc binding MMP13 inhibitor with anti-arthritic properties

Figure 1.1 – Examples of acetylene-containing compounds with medicinal properties

Alkynyl ethers and thioethers offer even more promise as synthetic building blocks. With the combined versatility of the carbon-carbon triple bond and a heteroatom making these classes of compounds very attractive for organic synthesis. In this thesis, a background of methodologies to ynol and thioynol ethers will be presented followed by a demonstration of new transition metal-free routes to both compound classes. Building carbon-carbon and carbon-heteroatom bonds is the basis of important organic synthesis and transition metals have found great use in assisting in this. There are drawbacks of using transition metals as catalysts, however, and therefore it has become more attractive to develop protocols in the absence of these catalysts.

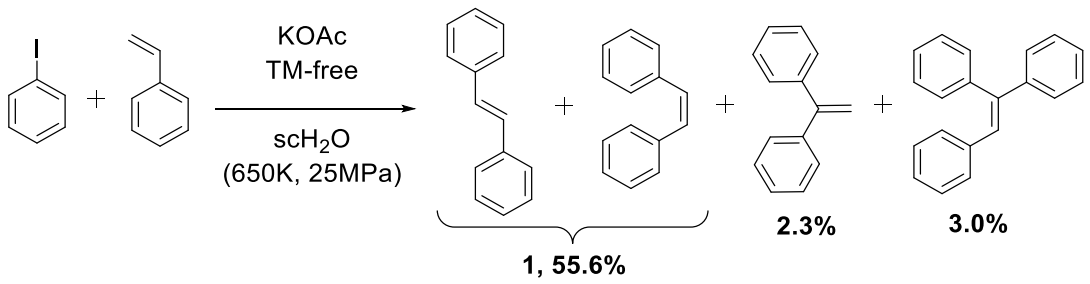
1.1 Transition metal-free organic synthesis

Transition metal-mediated coupling reactions have been one of the most important developments in chemistry over the past 50 years,[8] nevertheless, a number of drawbacks limit their practical applicability. Cost, toxicity and handling difficulties are just some of the negative factors of using transition metals. Supporting ligands can also be hard to prepare and may add extra steps in some synthetic routes making them inefficient. Palladium complexes such as $Pd(PPh_3)_4$ have found widespread use in various catalytic cross-coupling reactions along with Ni, Zn, Fe. This includes Heck[9] and Sonogashira[10] processes, C-H activations[11] and biaryl couplings (**Scheme 1.1**).[12,13]



Scheme 1.1 – Schematic summary of some cross-coupling reactions catalysed by Pd

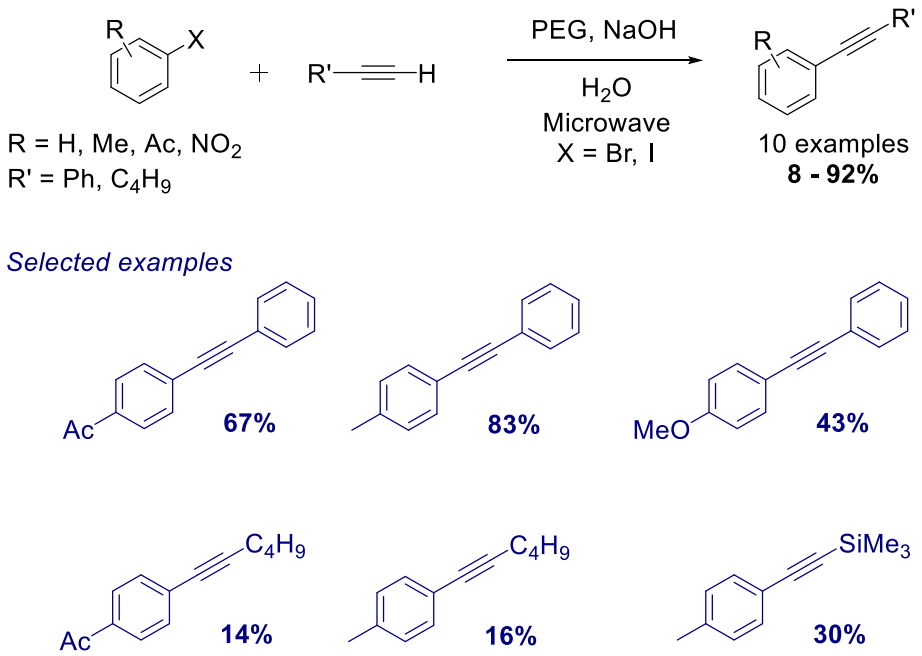
As chemists attempt to develop “greener” synthetic protocols, research has been driven towards alternative methods which do not require the use of transition metals. Interestingly, many reactions thought to be reliant on transition metal mediation, including those mentioned earlier, have proven to be possible in their absence. An example of a non-catalytic Heck-type reaction was demonstrated by Ikushima and co-workers in 2003, where they coupled iodobenzene with styrene in supercritical water using potassium acetate (KOAc) as a base.[14] As well as the absence of environmentally dangerous transition metal catalysts, Ikushima *et al*., were also interested in using more environmentally friendly solvents (**Scheme 1.2**).



Scheme 1.2 – Ikushima *et al.* noncatayltic Heck coupling of iodobenzene and styrene

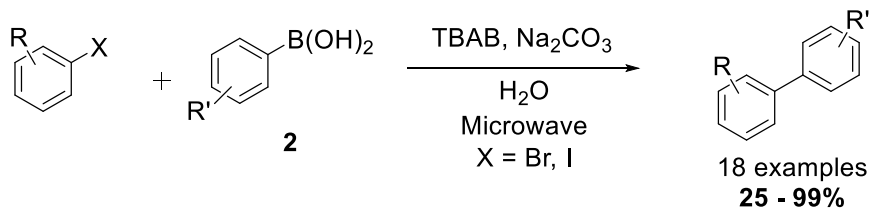
Ikushima *et al*. observed a yield of 55.6% of stilbene **1** (4:1 *trans*:*cis*) at 650 K under pressure of 25 MPa using KOAc as a base (**Scheme 1.2**). Other bases were investigated including sodium hydrogen carbonate ($NaHCO_3$), potassium carbonate (K_2CO_3) and sodium hydroxide (NaOH) with phenol being the major product formed along with diphenyl ether as a minor product. Therefore, the potassium alkoxide base proved to be the most effective in carbon-carbon bond formation.

NaOH was successfully used as a base by Leadbeater and co-workers in 2003 when they found that the Sonogashira reaction could be performed with microwave heating in the absence of transition metal catalysis. They used poly(ethylene glycol) (PEG) as a phase-transfer agent in water, without palladium and copper co-catalysis (**Scheme 1.3**).[15]



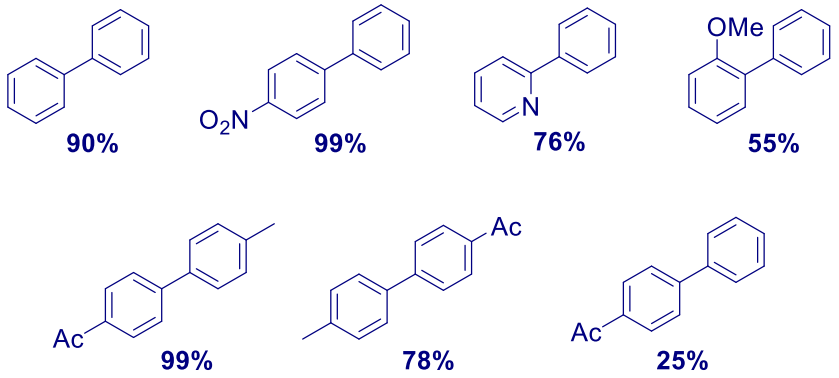
Scheme 1.3 – First example of a transition metal-free Sonogashira-type reaction

The same year saw Leadbeater and co-workers present a transition metal-free Suzuki-type coupling reaction. They used tetra-*n*-butylammonium bromide (TBAB) and sodium carbonate (Na_2CO_3) in water under microwave heating to obtain biaryl compounds from aryl halides and boronic acids **2**. They achieved good scope with yields varying to some degree but most substrates were obtained in good to excellent yields (**Scheme 1.4**).[16]



R = electron-donating, electron-withdrawing, electron neutral
R' = electron-withdrawing, electron neutral

Selected examples



Scheme 1.4 – "Transition metal-free" Suzuki coupling using TBAB and Na_2CO_3

Initially, Leadbeater and co-workers had tested for the presence of palladium, nickel, platinum, copper or ruthenium and concentrations above 1 ppm were not detected in the reaction mixture. However, after similar work by the groups of De Vries[17] and Choudary[18] showed that even trace amounts of palladium can catalyse coupling reactions, Leadbeater *et al.* reassessed their findings.[19] The presence of palladium contaminants down to a level of 20-50 ppb present in Na_2CO_3 was found to be responsible for catalysing the reaction.

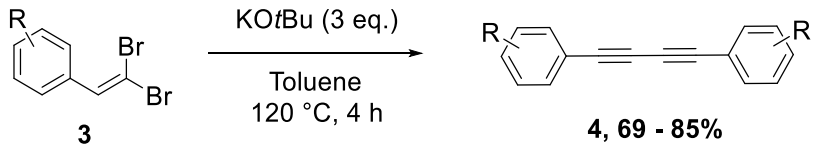
The debate on whether certain reactions can be performed under 'transition metal free' conditions is ongoing and the origin of such reactions is being probed by many. Reviews by Arancon and co-workers[20] and Leadbeater[21] highlight various publications where some reactions are claimed to be transition metal-free and other

cases where metals are used but possibly not needed. These reviews focus on the fact that there are simpler alternatives to their metal-catalysed versions offering complementary substitution patterns and better reaction conditions without the need for an exogenous transition metal catalyst.

An array of reactions described as “transition metal-free” use *tert*-butoxide bases of potassium or sodium (KO*t*Bu or NaO*t*Bu) with and without additives. Such reactions are of interest as various mechanisms, including radical mediation, have been probed and continue to intrigue the scientific community. Such reactions will be discussed in this thesis.

1.2 Transition metal-free reactions involving *tert*-butoxide

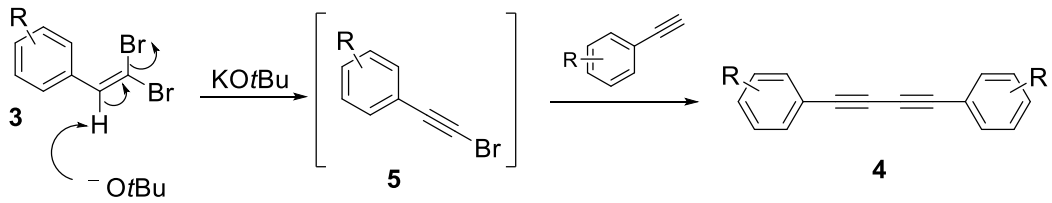
In 2005, Yan and Wang presented a base-induced Glaser-type homocoupling reaction of 1,1-dibromo-1-alkenes **3** in the absence of transition metal catalysis affording 1,3-diynes **4**.[22] A screen of various bases resulted in relatively low yields of 15-46% which was improved to 64% using NaO*t*Bu. Different solvents were also studied (DMF, THF, DMSO, acetonitrile and benzene) but yields were also relatively low (16-51%). Using KO*t*Bu in toluene resulted in the best yields (69-85%) with a variety of substituents accommodated around the ring (**Scheme 1.5**).



R = H, *p*-Me, *p*-F, *o*-Cl, *p*-OMe

Scheme 1.5 – Yan and Wang's transition metal-free Glaser-type coupling reaction

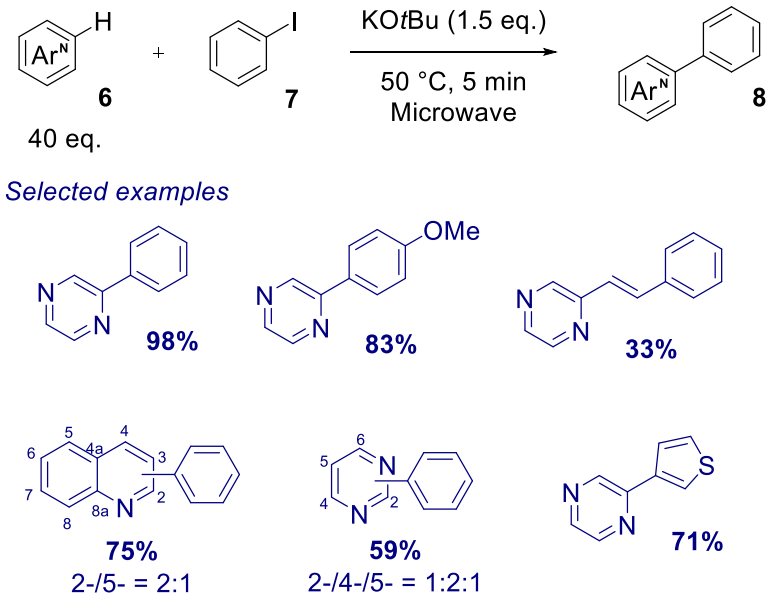
Mechanistically, the authors suggested that the reaction proceeded through the debromination of the starting dibromoalkene **3** in the presence of the base to afford an alkynyl bromide intermediate **5**. They then proposed that in a classic Glaser reaction manner,[23] homocoupling of two alkyne intermediates gave the diyne product **4** but no mechanistic studies were conducted to confirm this. The classic coupling method used a copper catalyst and an *sp*-radical intermediate was invoked in the mechanism. However, the absence of a transition metal catalyst made it difficult to elucidate the radical initiation step (**Scheme 1.6**).



Scheme 1.6 –Mechanism proposed for Yan and Wang's Glaser type homocoupling

Along with diynes, biaryls are indispensable building blocks in organic synthesis finding use in pharmaceutical compounds, agrochemicals,[24] polymers and dyes. An example of a successful biaryl coupling without the addition of an exogenous transition metal species was demonstrated in Itami *et al*. ground-breaking work in 2008.[25] They found that biaryl coupling of heteroarenes **6** and haloarenes **7** could

be promoted by KO*t*Bu alone with no transition metal catalysts or additives (**Scheme** 1.7).[26] It was a serendipitous discovery when conducting a control experiment of Fujita and co-workers' iridium-based coupling reaction. In the absence of the iridium complex, coupling of pyridine and an aryl iodide proceeded to the same degree as the original transition metal-catalysed version.[25]

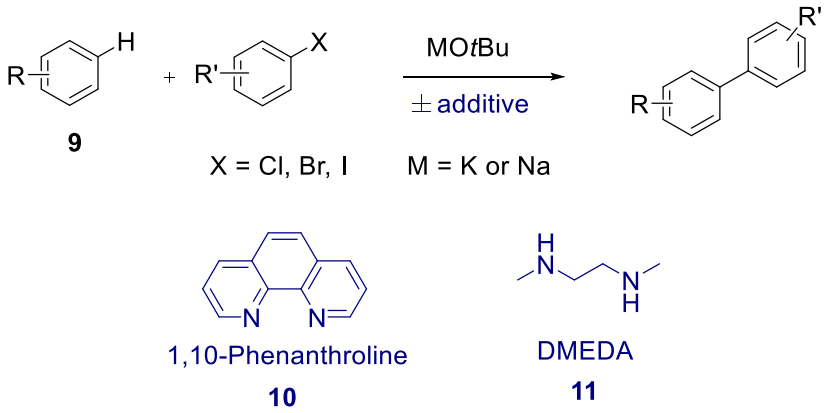


Scheme 1.7 – Itami *et al*., use of KO*t*Bu alone to promote coupling of electron-deficient nitrogen heterocycles with haloarenes

Further studies found that NaO*t*Bu and LiO*t*Bu did not furnish the biaryl products **8** under the same conditions. It is noteworthy that NaO*t*Bu was a successful reagent at higher temperatures above 80 °C. Furthermore, for the success of the reaction, a large excess of the nitrogen-based heterocycle was employed making this method somewhat unsustainable. Nonetheless, no extra solvent was required which gave this method an advantage over others.[25]

Moreover, the *tert*-butoxide moiety was found to be essential as methoxide and hydroxide anions displayed almost no reaction. Although a precise mechanism was not determined, the authors suggested the involvement of radicals. Formation of an aryl radical from iodoarene – either by homolytic aromatic substitution (HAS) or $S_{RN}1$ reaction – is proposed as addition of radical scavengers (TEMPO, galvinoxyl or acrylonitrile) shut down the reaction. Benzyne intermediates were ruled out as substitution took place exclusively at the C-I bond and no regioisomers with respect to the iodoarene were detected.[25]

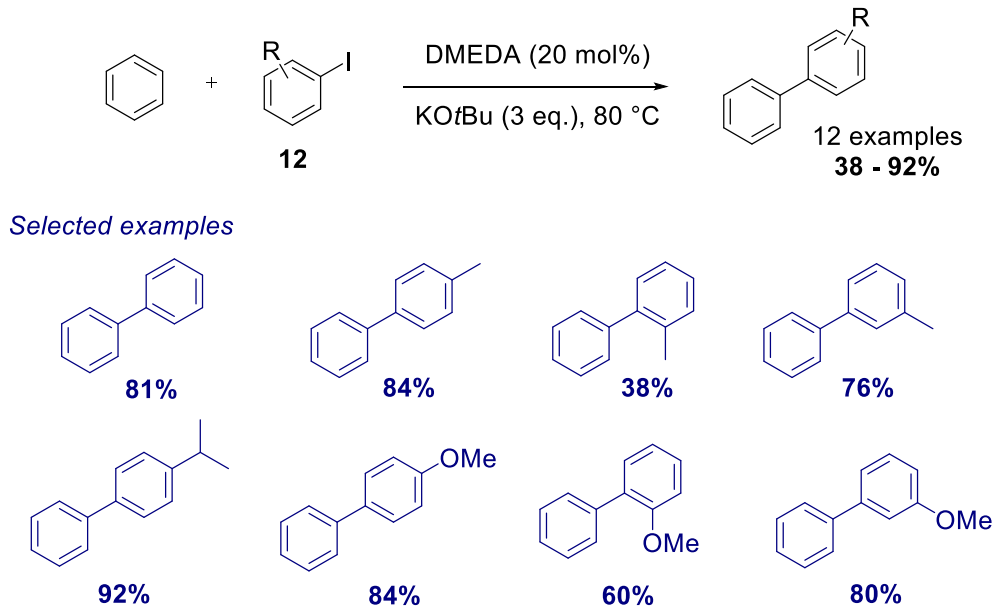
This discovery prompted an array of publications in this field where KO*t*Bu and NaO*t*Bu were used in transition metal-free coupling reactions. In 2010, the groups of Lei and Kwong,[12] Shirakawa and Hayashi,[13] and Shi[11] broadened the scope and improved efficiency of the reaction by successfully utilising unactivated aromatic substrates **9**, such as benzene, through the use of additives including 1,10-phenanthroline (1,10-phen) **10** and diamines, such as *N,N*-dimethylethylenediamine (DMEDA) **11** (**Scheme 1.8**).[27]



Scheme 1.8 – Various routes for biaryl synthesis using potassium and sodium *tert*-butoxide with and without additives

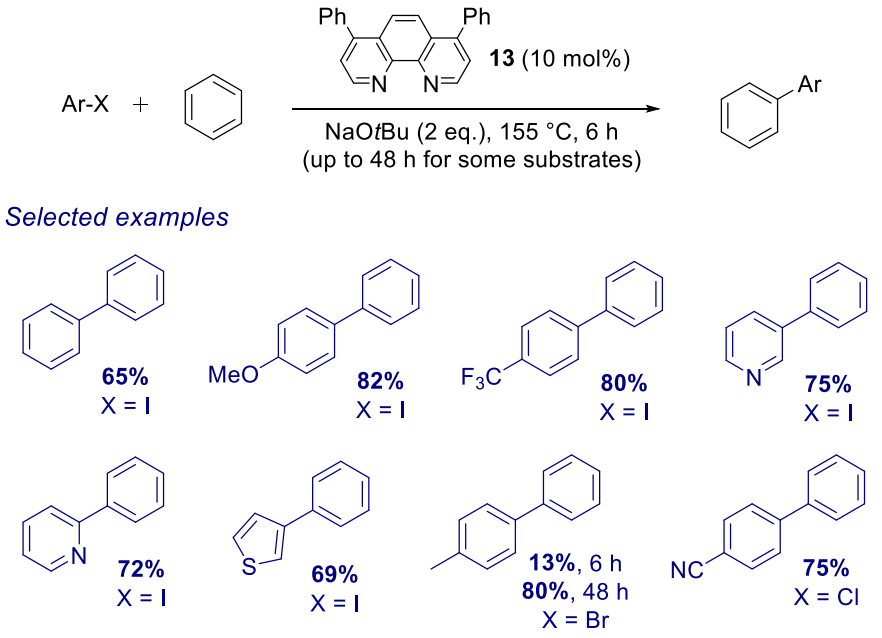
Lei and Kwong *et al.* used DMEDA **11** as an additive in the direct arylation of benzene with a variety of aryl iodides in the presence of KO*t*Bu.[12] Unfortunately, aryl bromides gave very low yields with low conversions and aryl chlorides did not work at all. A screen of other additives showed that ethylene diamine, 2-aminoethanol and *cis*-cyclohexane-1,2-diol also promoted direct arylation in good yields (67-81%). No reaction was observed in the absence of the amine additive, and free amine or hydroxyl moieties appeared to be essential. KO*t*Bu was the only base to achieve excellent conversion and high yield of the test compound, 4-methyl-1,1'-biphenyl (84%); other bases (NaH, KOH, Na_2CO_3, KOAc, NaO*t*Bu and LiO*t*Bu) were all ineffective.[12]

Addition of 18-crown-6 to trap the K^+ cation resulted in a significantly lower conversion (22%) and isolated yield (15%) of the biaryl product which suggests that K^+ plays an important role in the transformation; the fact that any transformation occurs suggests that different mechanisms may be taking place. A range of electrophilic aryl iodides **12** could be employed in this protocol with electron-rich substrates being best accommodated (**Scheme 1.9**).



Scheme 1.9 – Lei and Kwong *et al.* DMEDA-catalysed direct arylation of unactivated benzene

As with Itami's work, employment of radical scavengers by Lei and Kwong shut the reaction down, suggesting that radical intermediates were involved in the mechanism.[12,25] This was further supported by the absence of regioisomers with respect to iodoarenes as this implied that the reaction did not proceed *via* aryne intermediates. This mechanism will be discussed in more detail later. Around the same time, Shirakawa and Hayashi *et al.* reported successful arylation of arenes using NaO*t*Bu with a phenanthroline ligand (**Scheme 1.10**).[13]



Scheme 1.10 – Shirakawa and Hayashi *et al.* biaryl synthesis using NaO*t*Bu and phen ligands

Aryl iodides were most effective but the aryl bromides and chlorides were utilised as well; control experiments confirmed that both base and ligand were critical for the reaction to proceed.[13] Several heterocyclic coordinating ligands were studied and **Figure 1.2** highlights which ligands worked well, which were less effective and which ones were ineffective.

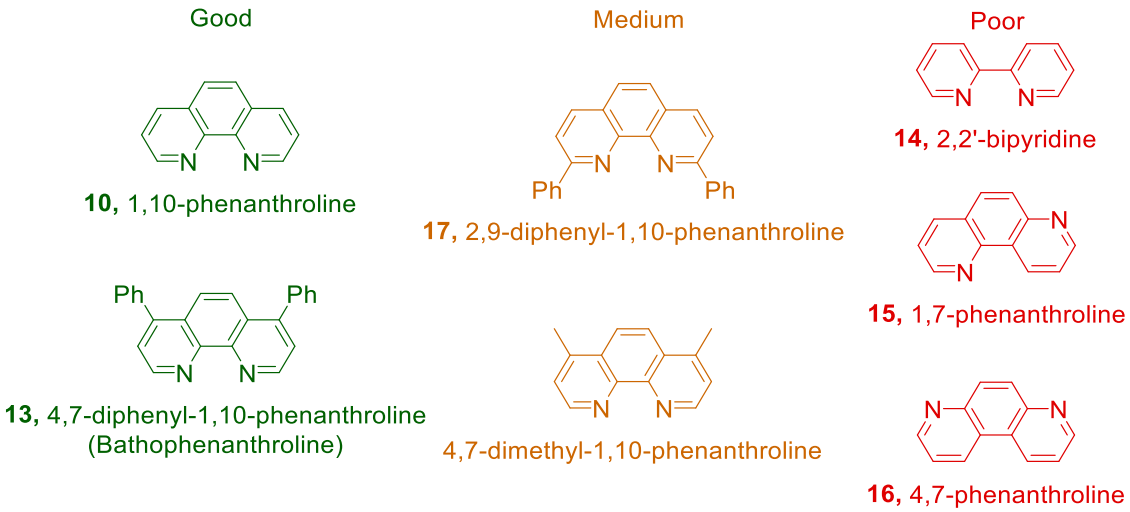


Figure 1.2 – Ligands used by Shirakawa, Hayashi and co-workers

The efficient phenanthroline ligands (**10** and **13**) were thought to act as single electron transfer (SET) mediators as they are highly conjugated with a low-lying

LUMO. This would explain why the use of 2,2'-bipyridine **14** was futile in this reaction. As well as conjugation, the chelate effect was also vital; for example, 1,7-phenanthroline **15** and 4,7-phenanthroline **16** could not coordinate with the sodium cation, and therefore did not work as additives.[13] This steric impact may result in the lowered effectiveness of the additives where phenyl groups have been introduced at the 2- and 9-positions **17** (**Figure 1.2**).

Furthermore, NaO*t*Bu and KO*t*Bu were found to be effective bases, whereas, LiO*t*Bu was not. This highlights the possible radical nature of the mechanism as a more dissociated *tert*-butoxide species (hence, with a higher electron density) is a more capable electron donor (**Figure 1.3**). Computational studies conducted by Wilden *et al.* showed shorter bond lengths (1.70-2.05 Å) for lithium and sodium *tert*-butoxide with significant covalent character between the oxygen and the alkali metal. Conversely, a longer bond length of 2.46 Å between potassium and oxygen indicate weaker binding and support the proposed formation of an ion pair and therefore dissociation.[28,29]

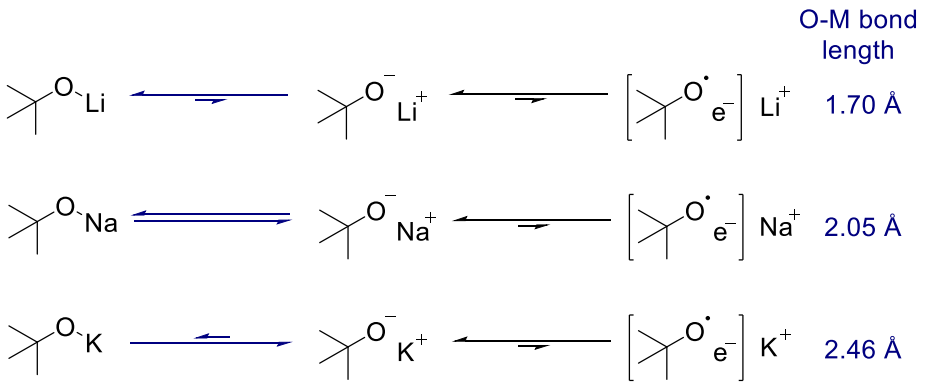
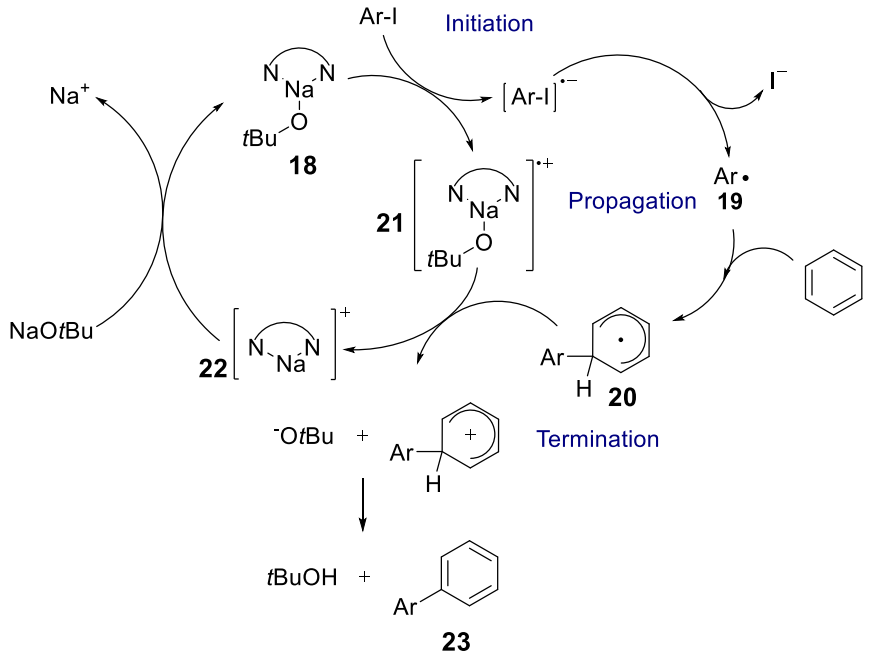


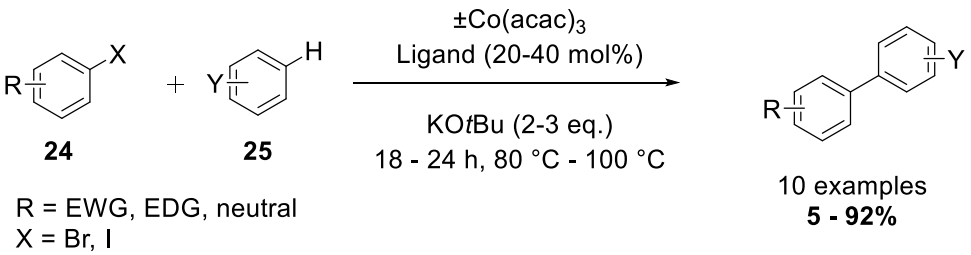
Figure 1.3 – Group 1 alkoxides with increased cationic dissociation

Shirakawa and Hayashi *et al.*, proposed mechanism[13] is shown in **Scheme 1.11**: after initial SET from an intermediate complex **18** of NaO*t*Bu and bathophenanthroline to the aryl iodide, an aryl radical **19** is formed. This is thought to couple with benzene to give a cyclohexadienyl radical **20** which is oxidised by the radical cation **21** formed in the first step. The resulting cation **22** is deprotonated by *tert*-butoxide to yield the biaryl product **23**.



Scheme 1.11 – Proposed mechanism for transition metal-free arylation of benzene by Shirakawa and Hayashi *et al.*

Similar to Itami *et al.*,[25] the reaction is thought to proceed *via* aryl radical formation from the aryl halide. The exact mechanism for radical initiation is not suggested and will be discussed in this thesis in later chapters. In the same year (2010), Shi and co-workers developed a transition metal-free protocol which originally utilised a cobalt catalyst ($Co(acac)_3$).[11] The catalyst was used to cross-couple aryl halides **24** with general arenes **25** in the presence of KO*t*Bu and a ligand (DMEDA or phenanthroline derivatives). Control experiments were conducted, and in the absence of the cobalt catalyst, the desired product was, to the authors' surprise, still formed in considerable yield (62%) (**Scheme 1.12**).

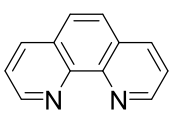


Scheme 1.12 – Shi *et al.* coupling of aryl halides with benzene promoted by cobalt catalyst or organic ligands

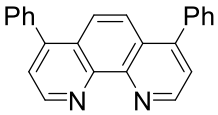
Shi *et al*. suspected that the presence of metal impurities in the ligand set and/or the base could have been responsible for catalysing the reaction. Subsequent

analysis of the base and 1,10-phen did indeed show the presence of 10 ppb – 10 ppm of palladium, copper, iron and other trace metals. However, kinetic studies of starting material consumption and product formation in the presence of varying concentrations of different transition metal catalysts showed a zero-order dependence on the catalysts. Purification of reagents, use of new apparatus and repetition of their work by other groups all resulted in the same successful results in the absence of exogenous transition metal catalysts. The authors were therefore satisfied that the reaction proceeded without transition metal catalysis or in spite of the presence of such catalysts.[11]

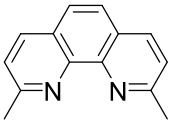
As with the work of Shirakawa *et al.*, Shi and co-workers also studied different phenanthroline ligands in addition to DMEDA. They found that DMEDA was effective only in the presence of the cobalt catalyst ($Co(acac)_3$). However, 1,10-phen **10**, bathophenanthroline **13** and neocuproine **26** were all effective (**Figure 1.4**) even without the cobalt catalyst, and achieved moderate to good yields using both the aryl bromide and iodide.



10, 1,10-phenanthroline



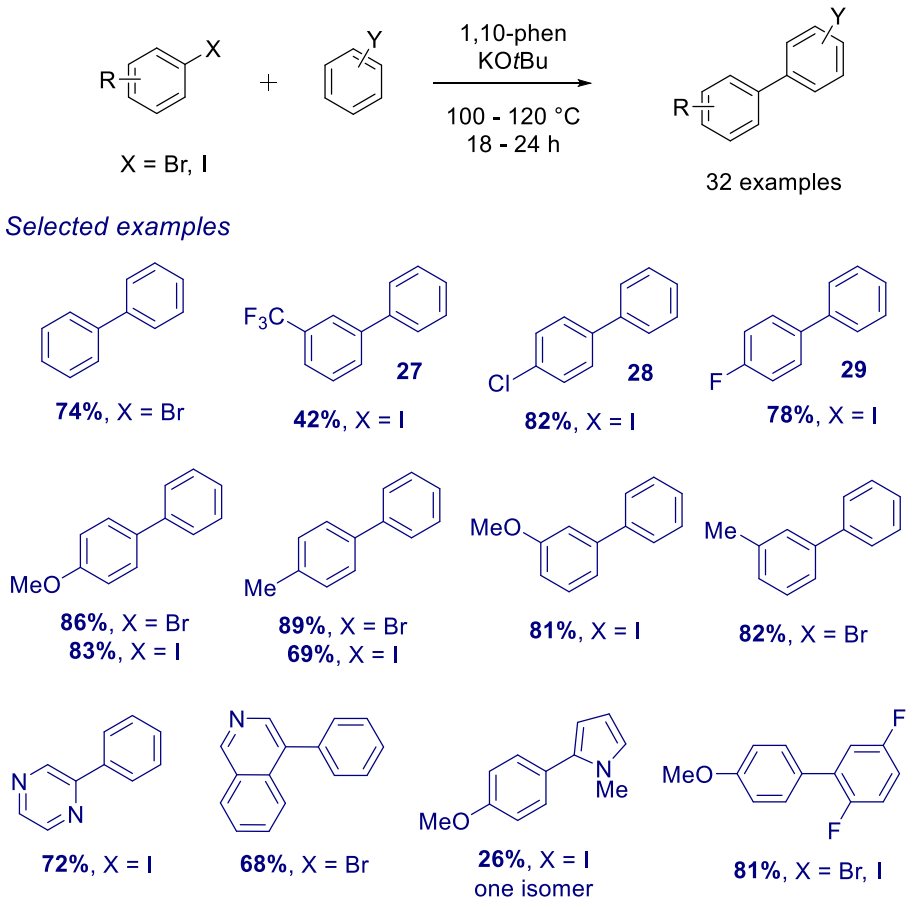
13, 4,7-diphenyl-1,10-phenanthroline (Bathophenanthroline)



26, 2,9-dimethyl-1,10-phenanthroline (Neocuproine)

Figure 1.4 – Phenanthroline ligands found to be effective in Shi *et al.* biaryl synthesis

The authors synthesised a small library of substrates using the optimised conditions shown in **Scheme 1.13**. Electron-donating substituents around the aryl halide ring gave the best results, whereas some substrates with electron-withdrawing groups showed only moderate yields (such as the 3-trifluoromethyl product **27** shown in **Scheme 1.13**). Further to this, 4-chloro- **28** and 4-fluoro- **29** substituents were also accommodated well using this protocol which would allow the products to be further functionalised.



Scheme 1.13 – Shi *et al.* biaryl synthesis using 1,10-phen and KO*t*Bu

Mechanistically, the authors suggested that radical initiation from the aryl halide was achieved by SET from KO*t*Bu assisted by the phenanthroline ligand. The proposed radical nature of the reaction was tested by using a typical radical initiator, AIBN and tributyltin hydride in the absence of the phenanthroline ligand and KO*t*Bu. Although a low yield was achieved, the cross-coupled product was still formed. This result, along with cessation of the reaction in the presence of radical scavenger, TEMPO, showed that radical intermediates could be essential for the reaction to proceed. Possible interactions between the arene, the base and the ligand in a stacked manner were originally proposed to promote the reactivity of the arene (**Figure** 1.5).[11]

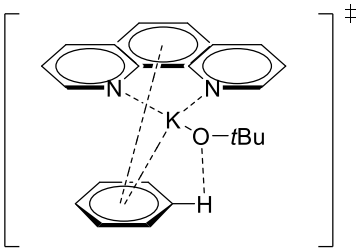
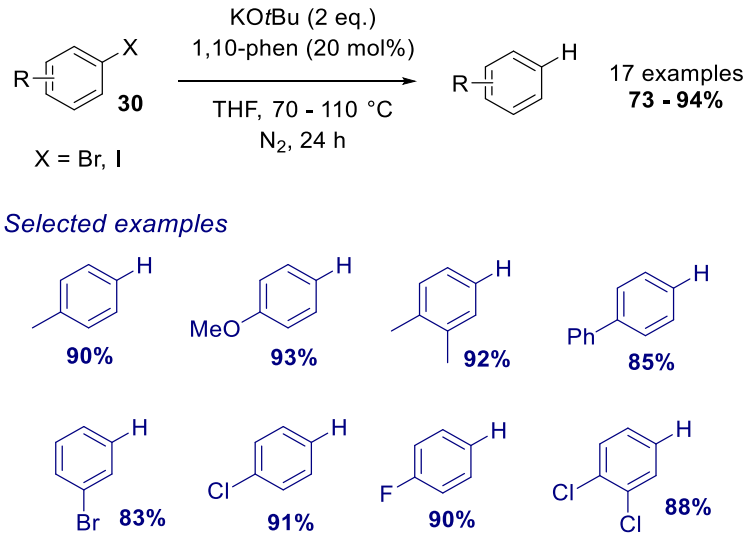


Figure 1.5 – Proposed interactions between the base, ligand and arene

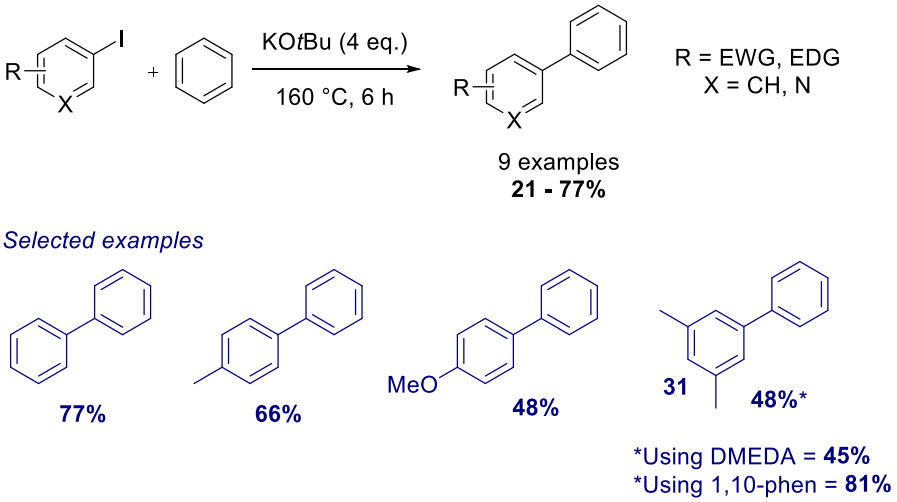
Both steric and electronic features were in agreement with this suggested *π,π*-stacking and ion-π interactions taking place. Other organic compounds, which are structurally similar to phenanthrolines, also showed good catalytic reactivity to activate arenes. However, there was no evidence to support that this stacked intermediate was formed (**Figure 1.5**).

Since these publications, there has been an explosion of research into the use of KO*t*Bu and NaO*t*Bu to initiate reactions *via* SET, either alone or in conjunction with an organic additive. More recently, KO*t*Bu has been used alongside phenanthroline to dehalogenate aryl halides **30**,[30] with proton abstraction from the solvent (THF) taking place. The authors propose a radical mechanism *via* aryl radical formation, initiated by KO*t*Bu and phenanthroline (**Scheme 1.14**).



Scheme 1.14 – Liu and Hou's recent dehalogenation method using KO*t*Bu and 1,10-phen

Another group described the use of phenanthroline ligands with KO*t*Bu to form fused polycyclic compounds which could be important for natural product synthesis.[31] In 2014, Wilden *et al.* demonstrated that transition metal-free biaryl coupling could be effected in the absence of amine additives such as DMEDA and phenanthroline derivatives; in a similar way to Itami *et al.* original finding, using KO*t*Bu alone (**Scheme 1.15**).[29]



Scheme 1.15 – Cuthbertson and Wilden *et al.* transition metal-free biaryl coupling in the absence of additives

In some cases, the group found that conducting these reactions in the absence of an amine additive was at the detriment of the rate and efficiency of the reaction. Synthesis of 3,5-dimethyl-1,1'-biphenyl **31** with and without additives showed that yield could be improved by addition of 1,10-phen, which adds to the intrigue of what role these additives play. Further to this, although using additives allowed for milder conditions, the findings were still very interesting. With continued interest in this area, inevitably, there are contradicting views on what mechanism is taking place; this will be discussed in more detail in **Section 2.4**.

1.3 Ynol ethers

1.3.1 Introduction to ynol ethers

Ynol ethers, also known as acetylenic or alkynyl ethers, remain a relatively underexploited group of synthetic intermediates. The reactive nature of the electron-rich carbon-carbon triple bond combined with the added functionality of the heteroatom means these compounds are highly efficient building blocks in organic synthesis. The polarised character of ynol ethers, which arises from the oxygen attached directly to the *sp*-hybridised carbon of the triple bond, is key to their use in accessing compounds which can be relatively difficult to make. Interestingly, they are effective as both electrophile and nucleophile (**Figure 1.6**).

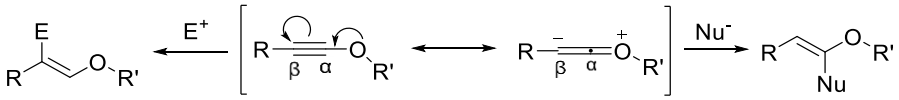


Figure 1.6 – Polarity of alkynyl ethers showing both electrophilic and nucleophilic character

Given the structure of alkynyl ethers, there are many possible paths of reactivity including:

- addition to the triple bond (electrophilic addition is likely to occur at the β-carbon and nucleophilic addition at the α-carbon as shown in **Figure 1.6**)
- substitution of the proton of terminal alkynyl ethers (i.e. R = H) such as metallation
- free radical addition
- reactions of the ether functional group
- polymerisation and associated reactions

Since Slimmer's successful isolation and characterisation of phenoxyacetylene in 1903, this class of highly functionalised compounds have been exploited by synthetic chemists.[32] However, general routes to their synthesis have been limited and only in the past 30 years has there been a steady increase in more widely applicable methods of their synthesis – these routes will be presented in more detail in this chapter as well as a discussion on earlier methods.

There are many ways to categorise these methods and three approaches will be discussed; the first category, which Slimmer's method falls into, is *β*-elimination from enol ethers. The other approaches are α-elimination *via* carbene/carbenoid rearrangement and direct functionalisation/oxidation of alkynes.[33] There are many precursors to ynol ether synthesis, some of which are outlined in **Figure 1.7**.

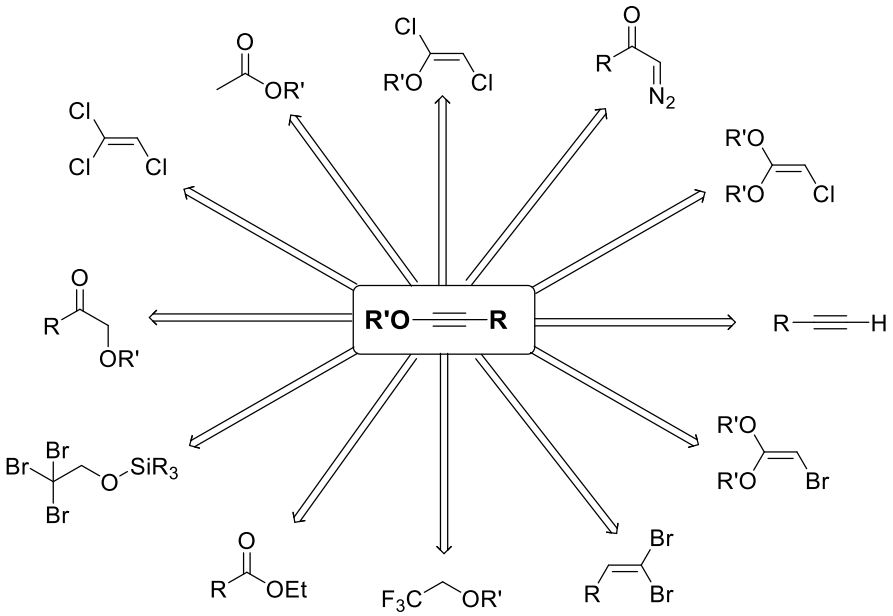
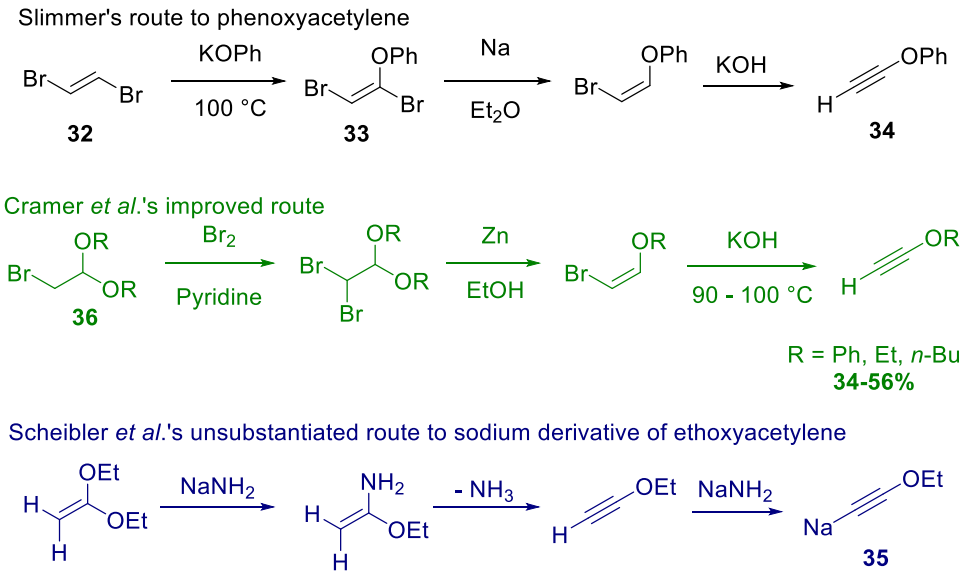


Figure 1.7 – Summary of some precursors used in ynol ether synthesis

1.3.2 Synthetic routes to ynol ethers: β-elimination

Slimmer isolated and characterised phenoxyacetylene in 1903 using a dibromoenol ether **32** and sodium metal *via* formation of 1,2-dibromo-2-phenoxyacetylene **33**.[32] Subsequent treatment with KOH gave the desired but unstable phenoxyacetylene **34** (**Scheme 1.16**). Many routes were described before 1960 involving a dehydrohalogenation step using KOH – some of these investigations involved β-halogeno- and α,β-unsaturated ethers.[34–38] Some routes utilised sodium in liquid ammonia as the base instead.[39,40]

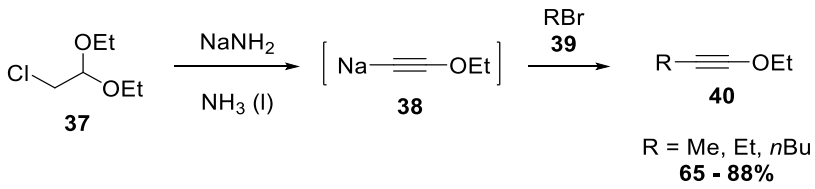


Scheme 1.16 – Slimmer's and Cramer *et al.* synthetic routes to phenoxyacetylene and others

Cramer *et al.* went on to improve Slimmer's procedure using zinc instead of sodium to induce dehydrohalogenation and reported the first preparation of ethynyl alkyl ethers (as well as phenoxyacetylene **34**)[36] which were more stable and did not polymerise at room temperature like phenoxyacetylene (**Scheme 1.16**). Previously, Scheibler *et al.* had reported what they described as the first known route to the sodium derivative of ethoxyacetylene **35** using $NaNH_2$. However, Arens describes Scheibler *et al*. synthesis of the desired alkynyl ether derivative as doubtful as the results were not substantiated with evidence to suggest otherwise.[41]

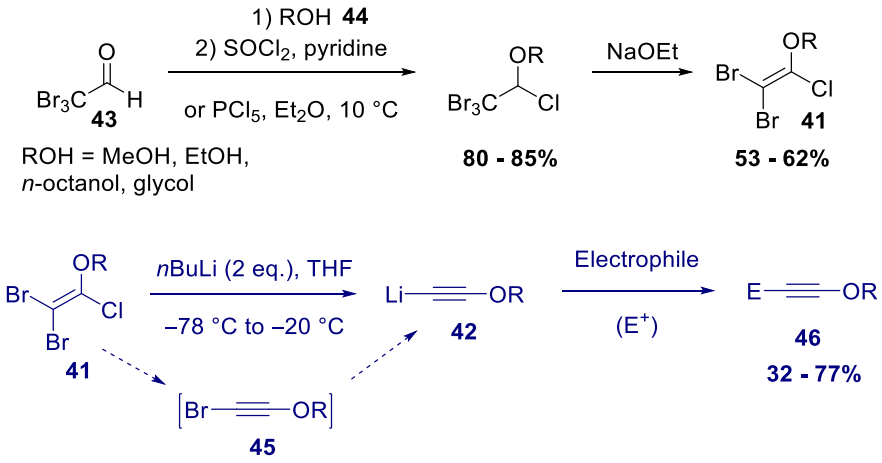
Similar to Cramer *et al*., Newman and co-workers used a haloacetal starting material – instead of the bromoacetal **36**, the chloroacetal **37** was employed with sodium amide in liquid ammonia.[42] They then treated the sodium ethoxyacetylide **38**

intermediate with various alkyl bromides **39** to furnish alkylated ynol ethers **40** (**Scheme 1.17**).



Scheme 1.17 – Newman *et al.* synthesis of ynol ethers from chloroacetaldehyde diethyl acetal

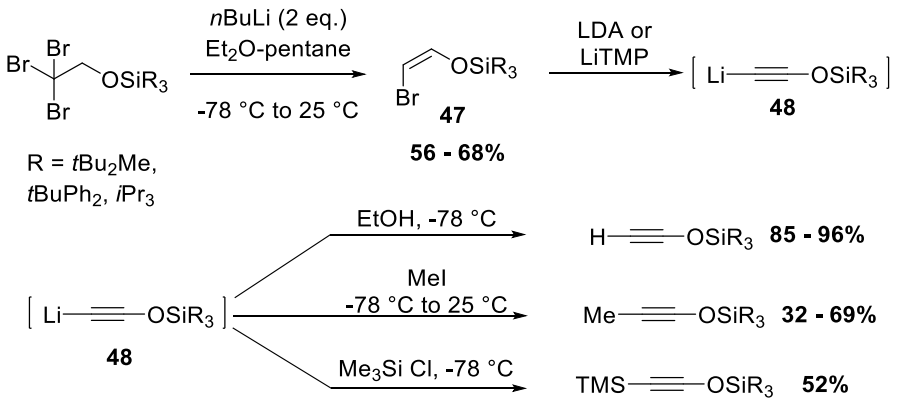
Chlorohemiacetals **41** have also been used successfully in the synthesis of ynol ethers via lithium acetylide **42** formation. Smithers used a method developed by Neher and Fleece[43] to first obtain chlorinated bromal hemiacetals **41**.[44] After initial reaction of bromaldehyde **43** and primary alcohols **44**, followed by treatment with a chlorinating agent, the intermediates were at hand. These were then subjected to sodium ethoxide to effect dehydrohalogenation and subsequent treatment with *n*-butyllithium gave the lithium acetylides **42** *via* bromoacetylene **45**. Trapping with various electrophiles such as alkyl halides and epoxides furnished the desired alkynyl ethers **46** (**Scheme 1.18**).



Scheme 1.18 – Smithers' route to alkynyl ethers using chlorohemiactecals

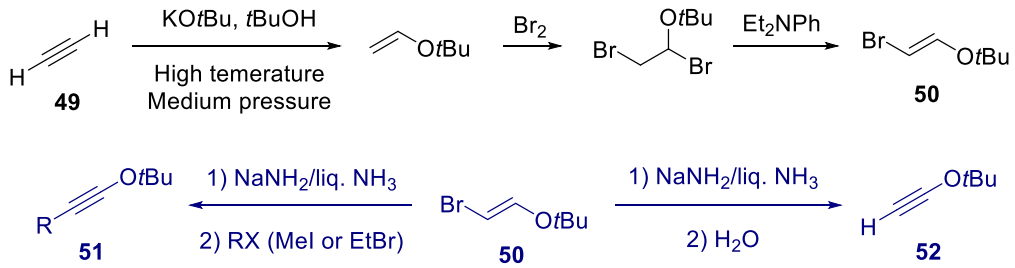
Danheiser *et al.* developed the first route to parent trialkylsilyloxyethyne derivatives during their work on aromatic annulation reactions.[45] Using a two-step method developed by Pirrung and Hwu[46] to synthesise (*Z*)-2-bromovinyl ethers **47**, three different substrates were obtained in good yields. Lithiation using LDA or LiTMP

followed by quenching of the lithium acetylides **48** with various electrophiles gave siloxyalkynes, again, in good yields (**Scheme 1.19**).



Scheme 1.19 – Danheiser *et al*. route to trialkylsilyloxyethynes

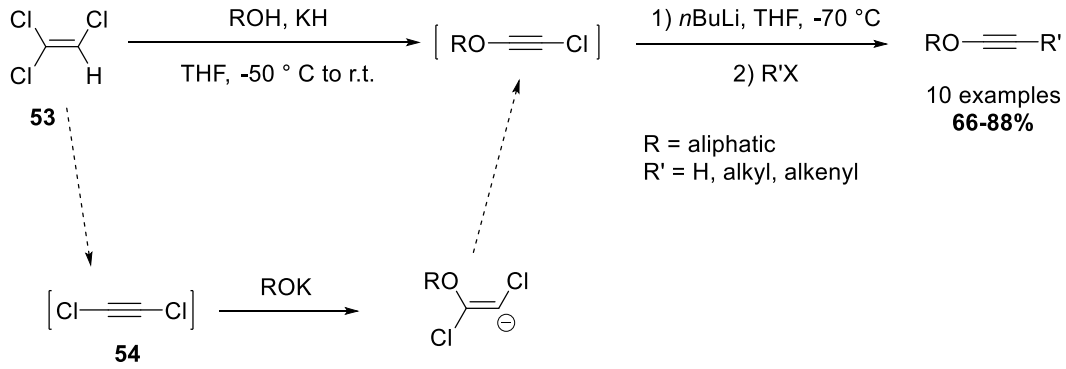
One of the earliest routes from ethyne **49** was developed by Arens and co-workers. Starting with the treatment of ethyne **49** with KO*t*Bu followed by addition of bromine, subsequent reduction steps *via* the bromoenol ether **50** gave ynol ethers **51** in good yields.[47] Terminal ynol ethers **52** could be obtained by quenching with water instead of an alkyl halide (**Scheme 1.20**).



Scheme 1.20 – An early route to ynol ethers from ethyne developed by Arens *et al.*

The drawback of this procedure was the need for relatively high temperature and pressure and the volatility of acetylene requiring special handling. Since the development of this method, a number of improved routes have been demonstrated and a recent review on ynol and thioynol ethers by Gray *et al.*[48] highlights some of the more recent methodologies towards ynol ethers. This includes a general approach by Greene *et al.* to ynol ethers from tricholoroethylene **53** using potassium alkoxides formed *in situ*.[49] This dehalogenation route developed in 1987 has been described as the most versatile synthesis in terms of scope.[33] The authors suggest the route occurs *via in situ* formation of potassium alkoxide which attacks the potentially explosive dichloroacetylene **54**. This was presumably formed after

dehydrohalogenation of trichloroethylene **53** by the alcohol or alkoxide. Following subsequent deprotonation using *n*-butyllithium, the ynol ether was formed (**Scheme** 1.21).[49] The potentially explosive nature of the intermediates in this reaction, however, leave room for improvement.



Scheme 1.21 – Greene *et al.* synthetic route to ynol ethers using trichloroethylene

The mechanism of Greene *et al*. method had been debated for years; it was unconfirmed whether the Fritsch-Buttenberg-Wiechell (FBW) rearrangement[50–52] or *β*-elimination was taking place. Poisson and Greene *et al.* conducted mechanistic studies between 2008-2011 (X-ray crystallography and ^{35}Cl-labelled isotope experiments) to elucidate the mechanism. X-ray crystallography verified that the *trans* assignment for the enol ethers was correct as shown in **Figure 1.8**. A subsequent isotope labelling experiment using a ^{35}Cl-labelled dichloroenol ether **55** was used to clarify which mechanism was taking place.[53,54] If the FBW rearrangement was taking place, the ^{35}Cl isotope would be present in the final alkyne product. However, it was the naturally abundant Cl which was present, which meant that *syn β*-elimination was taking place (**Figure 1.8**).

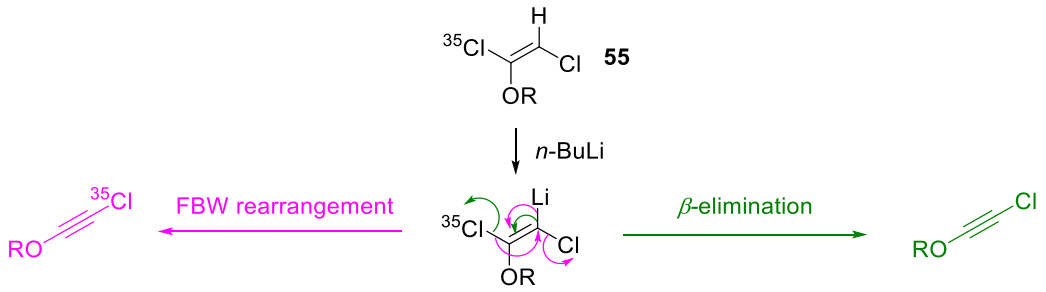
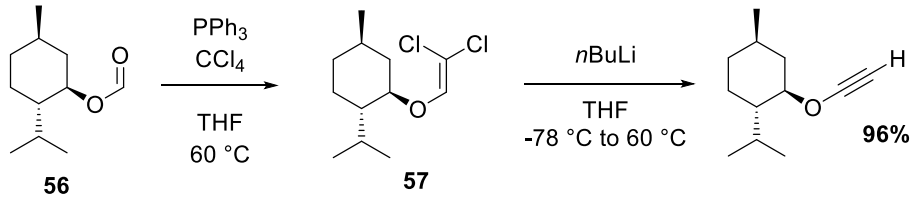


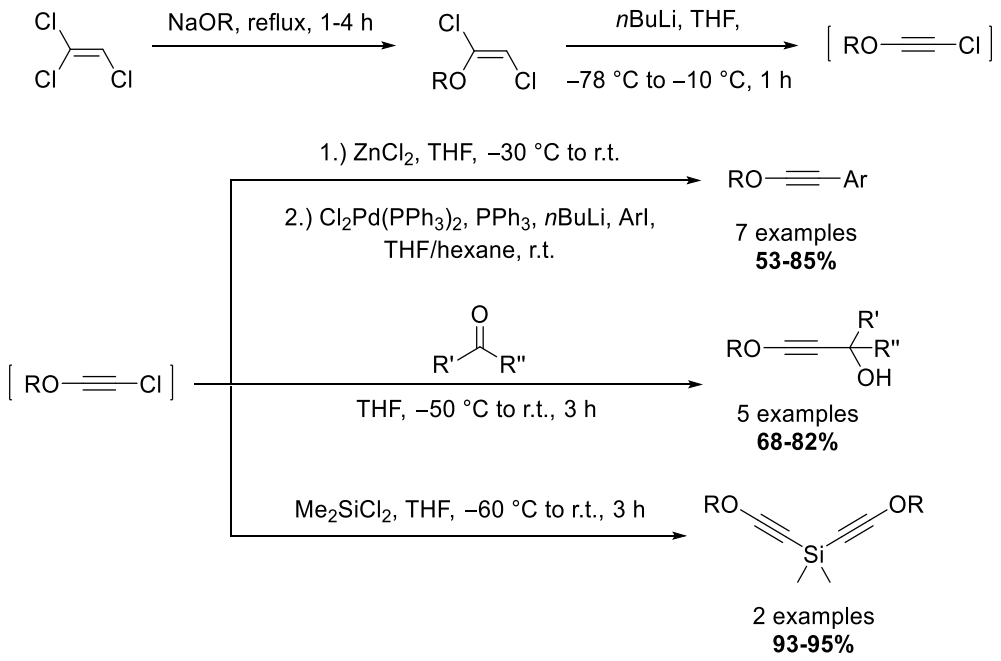
Figure 1.8 – Mechanistic studies confirming the pathway from dichloroenol ethers to ynol ethers

One advantage of this method is that chiral products can be formed relatively easily, however, some substrates required treatment with organoboranes which added an extra step to the route. Presented as an alternative to Greene *et al.* one-pot synthesis of ynol ethers, Brückner described a route to ynol ethers *via* formates in 2000.[55] After dichloromethylenation of menthyl formate **56**, subsequent dehydrohalogenation of the 2,2-dichlorovinyl ether **57** using *n*-butyllithium gave the ynol ether in excellent yield (**Scheme 1.22**).[55]



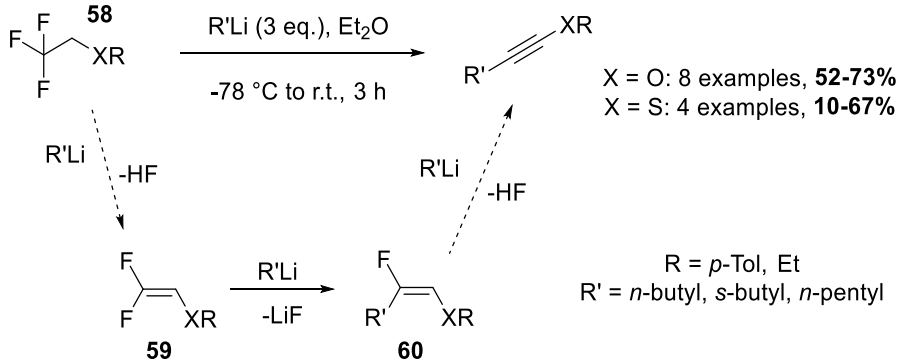
Scheme 1.22 – Brückner's route to ynol ethers *via* a formate intermediate

The use of toxic tetrachloromethane was undesirable and Brückner made no suggestion of a potential mechanism but it was possible that the dichlorovinyl ether intermediate **57** underwent a 1,2-migration. A more similar method to Greene *et al.* was developed by Himbert and co-workers using easily available non-chiral starting materials furnishing various substrates in a one-pot synthesis.[56] A wider range of substrates were offered than Greene *et al.* method. Palladium catalysis was required in this method when electron rich acetylenes or aryl iodides were used in the coupling reaction, which could be seen as a drawback (**Scheme 1.23**).[56]



Scheme 1.23 – Himbert *et al.* synthesis of alkoxyacetylenes *via* alkyl 1,2-dichlorovinyl ethers

A further example of a one-pot synthesis was Nakai *et al.* approach[57] using trifluoroethanol **58** which pre-dates the two routes already discussed. Treatment with a wide range of organolithium reagents furnishes ynol and thioynol ethers. The authors suggest that after initial formation of difluoroolefins **59**, successive elimination of lithium fluoride and hydrogen fluoride (which is highly corrosive and toxic) yielded ynol ethers in good yields (**Scheme 1.24**).[57]



Scheme 1.24 – Nakai *et al.* synthesis of ynol ethers from difluoroethanol

The authors ruled out an alternative mechanism where fluoroacetylene was formed from elimination of HF as an intermediate step as the monofluoroenol ether **60** was

detected by ^{19}F spectroscopy. Also, use of phenyllithium gave only the diphenylacetylene product **61** with no formation of the ynol ether and very low yield for the thioynol ether equivalent. This increased reactivity was attributed to the substantial stabilisation of the carbanion intermediate **62** *via* resonance effects (**Figure 1.9**).

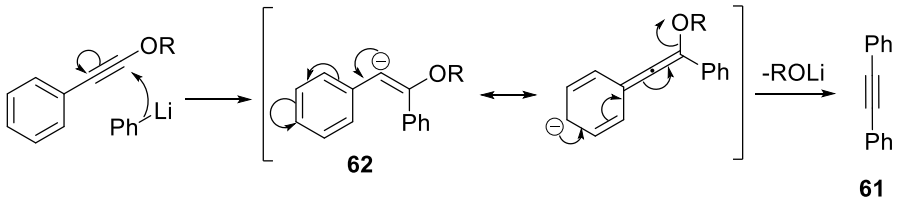
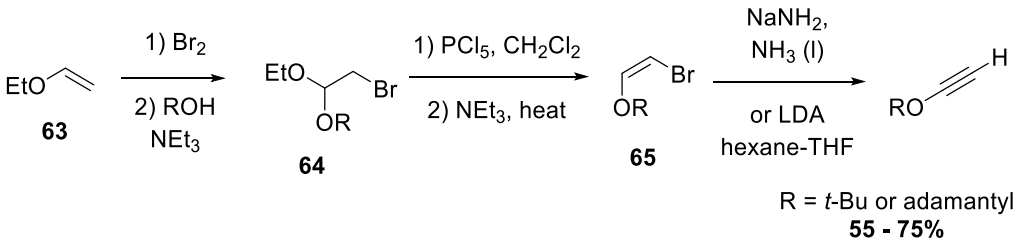


Figure 1.9 – Resonance effect stabilisation of carbanionic intermediate leading to diphenylacetylene side product when PhLi is used

Another interesting route involving halogenated intermediates was developed by Pericàs *et al* in 1987. A multi-step synthesis to form thermally unstable, but synthetically useful, terminal alkoxyacetylenes (which are prone to rearrangement to form ketenes) was demonstrated. This route has the added advantage of scalability (up to 30 g scale) which allowed for further transformations (**Scheme** 1.25).[58]

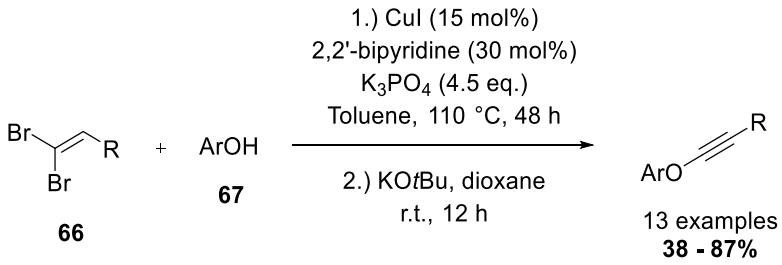


Scheme 1.25 - Pericàs *et al.* multi-step route to alkoxyacetylenes from ethyl vinyl ether

Following bromination of ethyl vinyl ether **63** (a cheap starting material), dehydrobromination was achieved using *tert*-butanol or adamantanol and triethylamine to obtain the monobrominated intermediate **64**. After subsequent cleavage of the mixed acetal using phosphorous pentachloride and then treatment with triethylamine, the vinyl bromide ether intermediate **65** was obtained. The final step depended on whether the final product was to be a terminal alkyne or an alkylated derivative. For the former, dehydrohalogenation was achieved using sodium amide in liquid ammonia to allow separation of the highly volatile product from the reaction mixture (**Scheme 1.25**). For the latter, dehydrobromination

followed by alkylation was achieved using lithium diisopropylamide (LDA) followed by an alkyl bromide in hexamethylphosphoramide (HMPA).

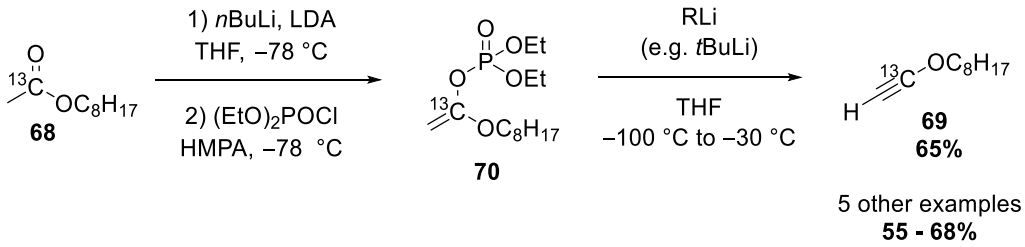
More recently, Evano *et al*., developed a copper-catalysed coupling of *gem*-dibromoalkenes **66** with phenols **67** involving dehydrohalogenation.[59] Dimerisation of the dibromoalkenes **66** was thought to take place when aliphatic alcohols were employed and therefore only aromatic alcohols **67** were found to be useful.



Scheme 1.26 – Evano's copper-catalysed cross-coupling of *gem*-dibromoalkenes and phenols

Bromo-enol ethers were obtained from initial cross-coupling and subsequent treatment with KO*t*Bu furnished alkynyl ethers in good yields (**Scheme 1.26**). There are more transition-metal catalysed routes to ynol ethers which will not be discussed in depth as the focus of the work presented is transition-metal free synthesis.[60–64]

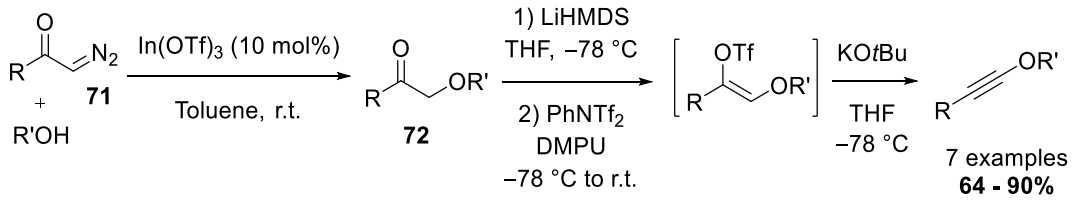
Instead of halogenated intermediates, Oehlschlager and co-workers wanted to use ^{13}C-labelled acetate **68** as starting material in order to obtain ^{13}C-labelled acetylenic ethers **69** which they required for a labelling study. Starting with the treatment of the acetate with LDA and a chlorophosphate, the enol phosphate **70** was obtained. This, in turn, underwent deprotonation and loss of the phosphate leaving group, sterically assisted by interactions between lithium and the phosphate oxygen. They succeeded in forming a ^{13}C-labelled terminal ynol ether *via* enol phosphate formation as well as a further 5 examples (**Scheme 1.27**).[65]



Scheme 1.27 – Oehlschlager *et al.* synthesis of a ^{13}C-labelled ynol ether

A range of functionalised terminal ynol ethers were synthesised by this method in good yields, however, using HMPA as solvent is undesirable due to its toxicity.

Other routes to ynol ethers utilise toxic reagents as well, such as α-diazoketones. In a similar fashion (without halogenated intermediates), Minehan and co-workers utilised α-diazoketones **71** as starting material in 2008 in their relatively mild synthesis of ynol ethers. Initial treatment with an alcohol (primary, secondary and tertiary alcohols and phenols worked well) with an indium catalyst gave α-ketoethers **72** which were subsequently enolised then turned into a good leaving group *via* treatment with a triflating agent. KO*t*Bu was then employed to induce elimination to give ynol ethers in good yields (**Scheme 1.28**).[66]

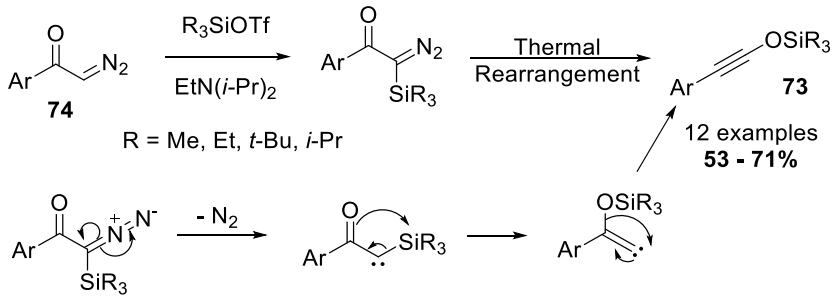


Scheme 1.28 – Minehan and coworkers' ynol ether synthesis from α-diazoketones

Although α-diazoketones are not ideal starting materials, it is interesting that both aromatic and aliphatic groups are tolerated; *t*-butyl and *n*-hexyl substrates were unsuccessful, however. This is attributed to the potential instability and decomposition of the enol triflates formed from aliphatic ketones leading to allenic compounds which then undergo unwanted side reactions.[66]

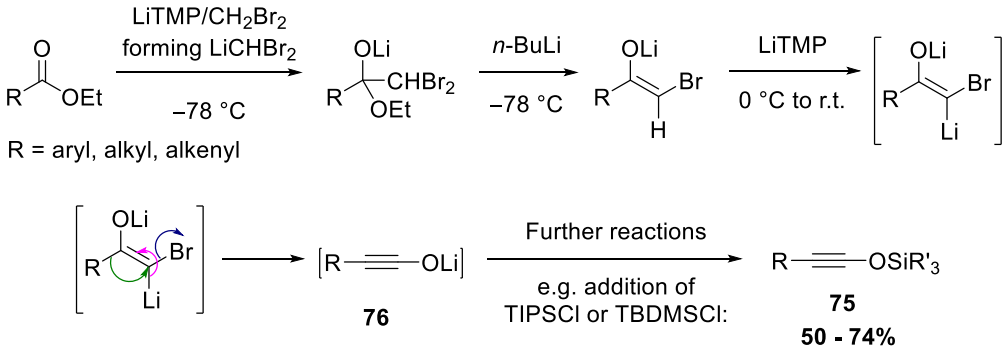
1.3.3 Synthetic routes to ynol ethers: α-elimination/carbene rearrangement

Only a few methods to ynol ethers *via* carbene rearrangement are known. Brückmann *et al.* described a route to silyloxyalkynes **73** using α-diazoketones **74** – after initial silylation adjacent to the diazo group, silyl migration and carbene formation either occurred at room temperature or was thermally induced. Finally, 1,2-migration furnished the siloxyacetylene products (**Scheme 1.29**).[67]



Scheme 1.29 – Siloxyalkyne synthesis from α-diazoketones *via* carbene rearrangement

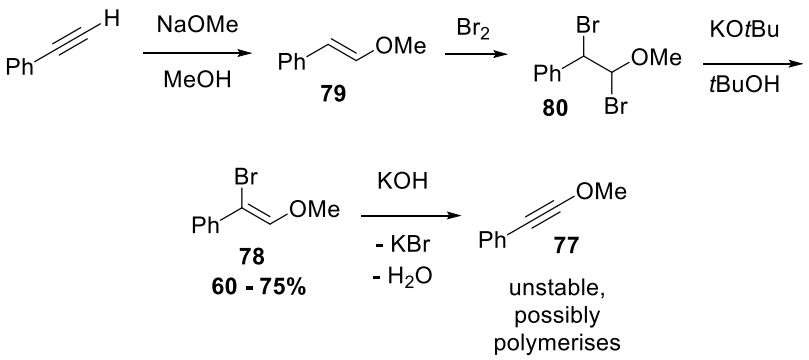
A similar route was later described by Kowalski *et al.* which effected ester homologation and could also yield silyl ynol ethers **75** *via* carbene rearrangement.[68,69] Addition of dibromo-methyllithium formed *in situ* from lithium tetramethylpiperidide (LiTMP) and methylene bromide followed by treatment with *n*-butyllithium formed a carbenoid. Through 1,2-migration, the lithiated ynol ether **76** (ynolate anion) was formed which could effectively be quenched with a chlorosilane; both chlorotri*iso*propylsilane (TIPSCl) and chloro *tert*-butyldimethylsilane (TBDMSCl) worked well (**Scheme 1.30**).[68,69]



Scheme 1.30 – Kowalski *et al.* formation of lithium ynol ether and functionalisation to silyl ynol ethers

1.3.4 Synthetic routes to ynol ethers: oxidation of alkynes

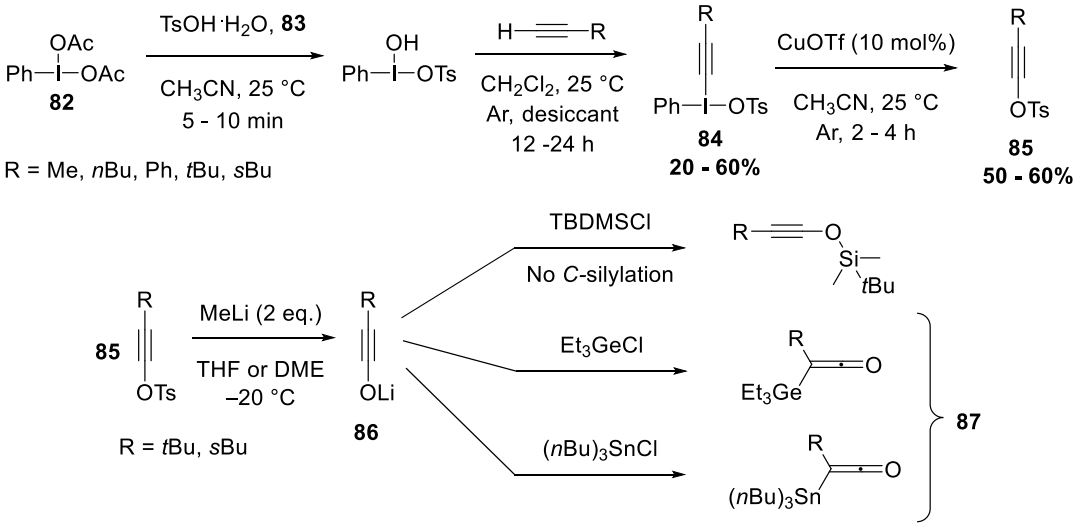
Jacobs and Scott first reported a synthetic route to phenylmethoxyacetylene **77** *via* bromomethoxystyrene **78** in 1953.[37] The authors described an initial route to these di-substituted styrenes **79** derived from phenylacetylene.[70] After initial conversion of phenylacetylene to β-alkoxystyrenes **79** using either sodium methoxide (NaOMe) in MeOH or using KOH, bromination gave the dibromoalkoxystyrene **80**. The authors faced difficulty in dehydrohalogenating these intermediates and obtained satisfactory results with the methoxystyrene substrate **79** using KO*t*Bu in *t*-butanol. A final dehydrohalogenation step using KOH was said to then furnish phenylmethoxyacetylene **77** (**Scheme 1.31**).



Scheme 1.31 – First reported route to phenylalkoxyacetylene by Jacobs and Scott in 1953

However, no evidence could be provided to show that this was successful as the methoxyacetylene **77** is thought to readily polymerise and therefore could not be isolated.[37] Nevertheless, Jacobs *et al*., series on acetylenic ethers certainly helped pave the way to understanding the reactivity of ynol ethers.[36,37,71–74]

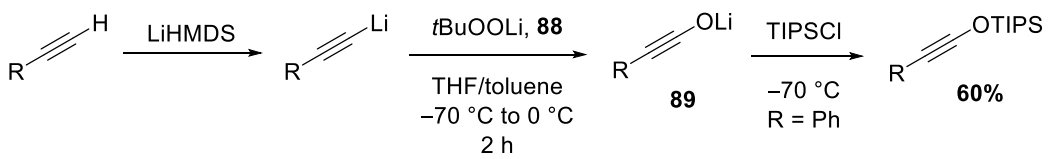
Stang *et al*. was the first to utilise a terminal alkynyl ether in the synthesis of silyloxyalkynes in 1986[75] *via* acetylenic tosylate intermediates **81** which were obtained using a method also developed within the group[76] from acetylenes (**Scheme 1.32**).



Scheme 1.32 – Stang *et al.* route to siloxyalkynes *via* acetylenic tosylate intermediates

Commercially available iodosobenzene diacetate **82** treated with toluenesulfonic acid monohydrate **83** afforded the intermediate iodonium tosylates **84** in moderate yields. Alkynyl tosylates **85** were then obtained by treating these with copper triflate and subsequent treatment with methyl lithium yielded the ynolate intermediates **86**. These could then be trapped with various electrophiles – *O*-silylation was successful with TBDMSCl but quenching with Et_3GeCl or nBu_3SnCl only yielded metallated ketenes **87** and no alkynyl products. Stang *et al*. then went on to expand this method to alkynyl carboxylates and phosphates.[77]

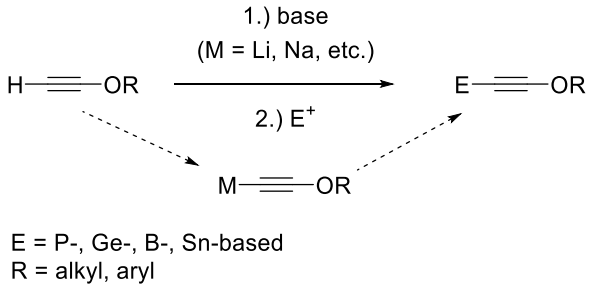
One of the major drawbacks of Stang's method was that aromatic derivatives could not be obtained due to the instability of phenylacetylenyl iodonium tosylates. Julia *et al*. went on to develop an improved route whereby aromatic ynolates could be synthesised using the lithium salt of *tert*-butyl hydrogen peroxide (TBHP) **88**. Subsequent quenching of the ynolate **89** with a silyl chloride yielded ynol ethers including aromatic derivatives in good yields (**Scheme 1.33**).[78]



Scheme 1.33 – Julia *et al*. improved route to ynol ethers including aryl derivatives

Further examples of general methods which fall into this subcategory are 1) the functionalisation of terminal alkoxyacetylenes (**Scheme 1.34**) and 2) reactions of

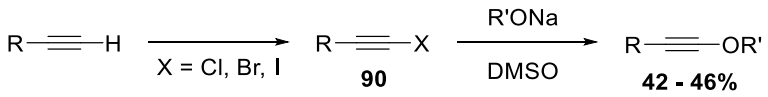
haloacetylenes with alkoxides which were discussed by Stang and Zhdankin (**Scheme 1.35**).[79]



Scheme 1.34 – General scheme for the functionalisation of terminal alkoxyacetylenes

There are several examples of substituted alkoxyacetylenes with different elements of which silicon has already been discussed. Other examples include phosphorous,[80] germanium,[81] boron[82] and tin.[81]

An example of the latter method mentioned earlier is Miller *et al.* synthesis of ynol ethers from haloacetylenes **90**.[83–86] It was found that nucleophilic attack by some alkoxides furnished ynol ethers but relatively low yields were obtained (**Scheme** 1.35).



Scheme 1.35 – Miller's route to ynol ethers form haloacetylenes and metal alkoxides

Several methods to ynol ethers have been presented in this section. The second focus of this thesis is thioynol ethers (sulfur analogues of ynol ethers) but first a brief background on organosulfur chemistry is presented.

1.4 Unsaturated organosulfur chemistry

1.4.1 Introduction to organosulfur chemistry

The abundance of sulfur in nature[87,88] and its presence in many medicinally useful compounds[89] highlights its importance in generating new drugs. Of the twenty common naturally occurring amino acids, two contain sulfur (cysteine **91** and methionine **92**); a demonstration of sulfur's importance for all living organisms. As well as amino acids, other biochemically important organosulfur compounds include vitamins thiamine **93** and biotin **94**, glutathione **95**, lipoic acid **96** and coenzyme A **97** (**Figure 1.10**).

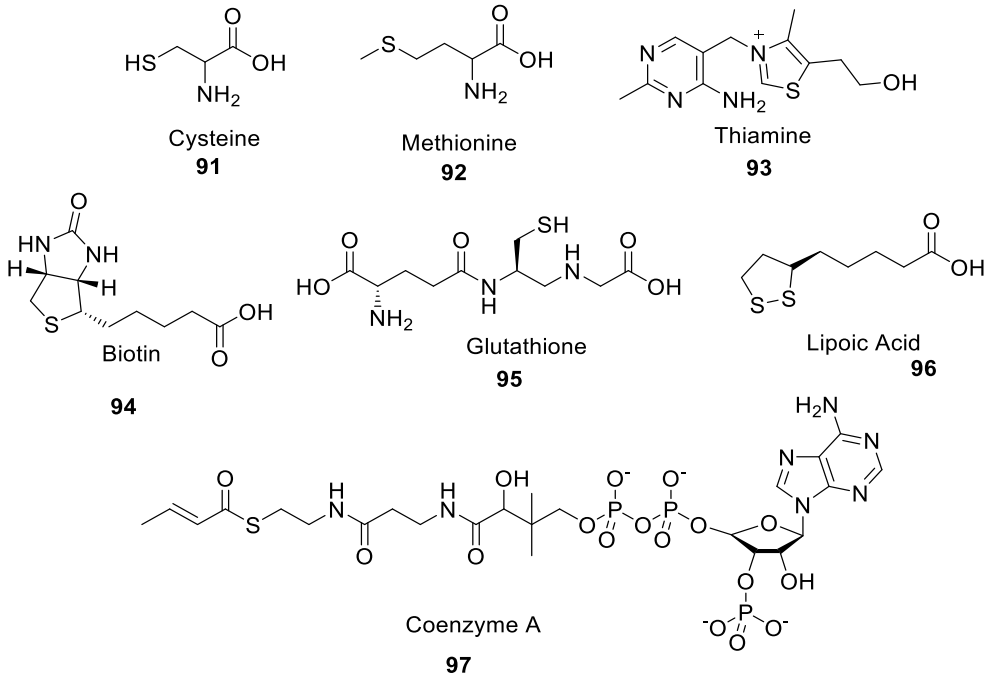


Figure 1.10 – Naturally occurring organosulfur compounds

Sulfa drugs are an example of the utility of organosulfur compounds in medicine. The first of this class of drugs was Prontosil **98** which was developed in the 1930's; sulfanilamide **99** was found to be the active agent and was widely used to fight bacterial infections (**Figure 1.11**).

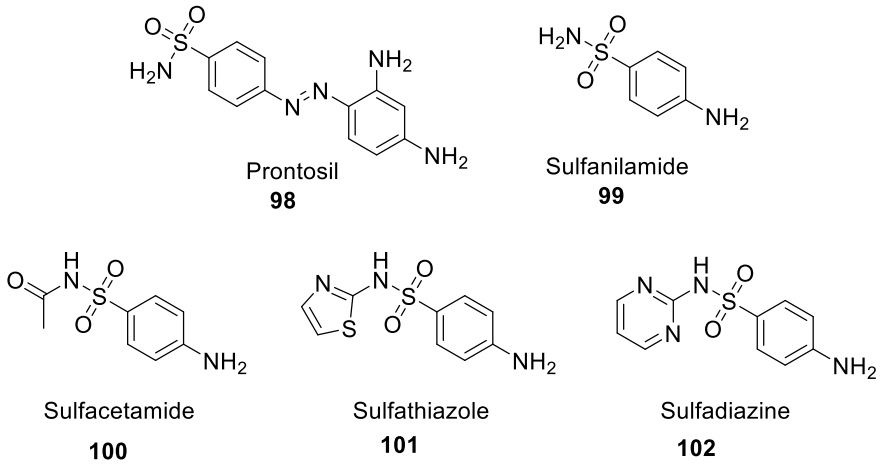


Figure 1.11 – Sulfa drugs which were used widely as antibiotics

It was found that functionalistion of the sulfonamide group of sulfanilamide **99** was one of the ways in which other useful derivatives could be formed, including sulfacetamide **100**, sulfathiazole **101** and sulfadiazine **102** (**Figure 1.11**). All of these compounds offered good antibacterial properties.

Another sulfur-containing drug soon overtook Sulfa drugs in the fight against bacterial infections, offering the advantage of fewer side effects and the ability to treat more infections including syphilis. *Penicillin* **103** (and its derivatives) remains one of the most widely used drugs today.

Figure 1.12 shows a small number of examples of useful sulfur-containing compounds including another antibiotic drug the β-lactam, *Thienamycin* **104**.[90] There are many other sulfur-containing compounds which have applications from medicine[91] and chemical biology[92] to materials science.[93]

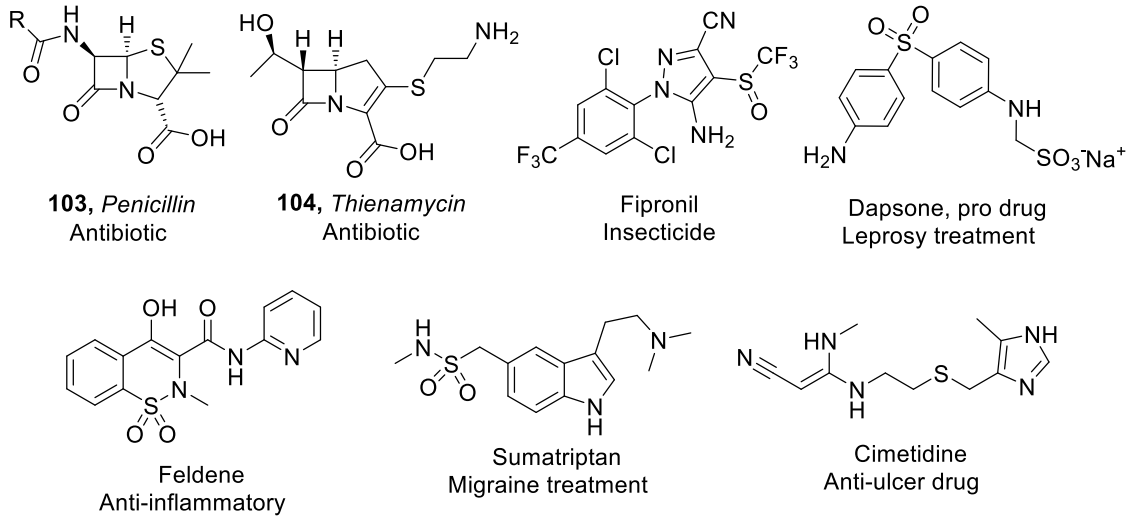


Figure 1.12 – Several examples of useful sulfur-containing compounds

Alkynyl thioethers can be used in the synthesis of *Thienamycin* intermediates; this will be discussed in more detail in **Section 1.4.3**.[94] The combined versatility of sulfur (attributed to its ability to exist in different oxidation states) and alkynyl functionality makes thioynol ethers a very attractive group of compounds with potential application in bioactive compounds and further chemical manipulation. In contrast to ynol ethers, substituting O with S adds an extra benefit as the higher valence of sulfur offers more versatility. For instance, both classes of compounds react similarly when treated with electrophiles, whereas nucleophilic attack can take place at different positions for the sulfur derivatives due to polarisation (**Figure 1.13**).

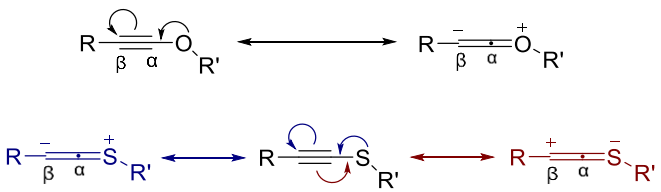


Figure 1.13 – Similarity and difference in reactivity of ynol and thioynol ethers

The alkyne unit can also undergo cycloaddition reactions and therefore complex structures can be accessed in relatively few steps. The high electron density and polarity in the bond due to the resonance structures are outlined in **Figure 1.14** demonstrating the versatility of sulfur.

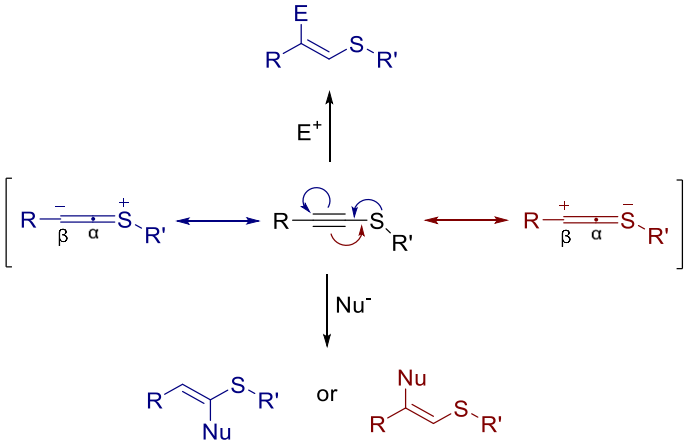
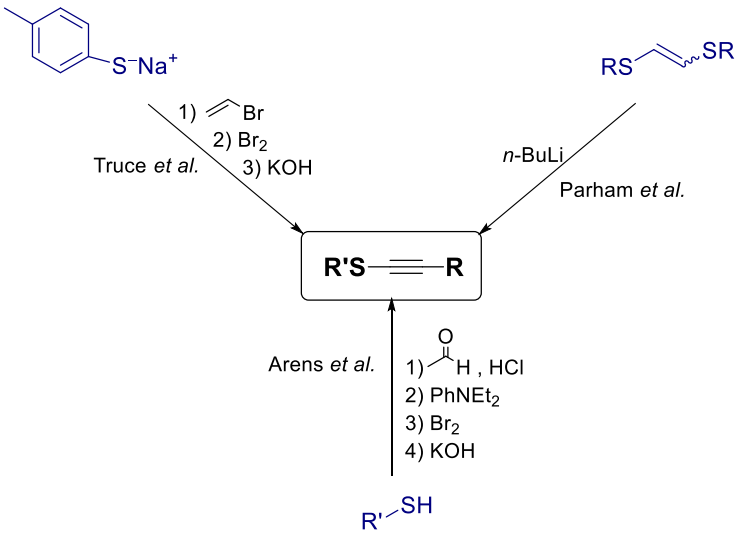


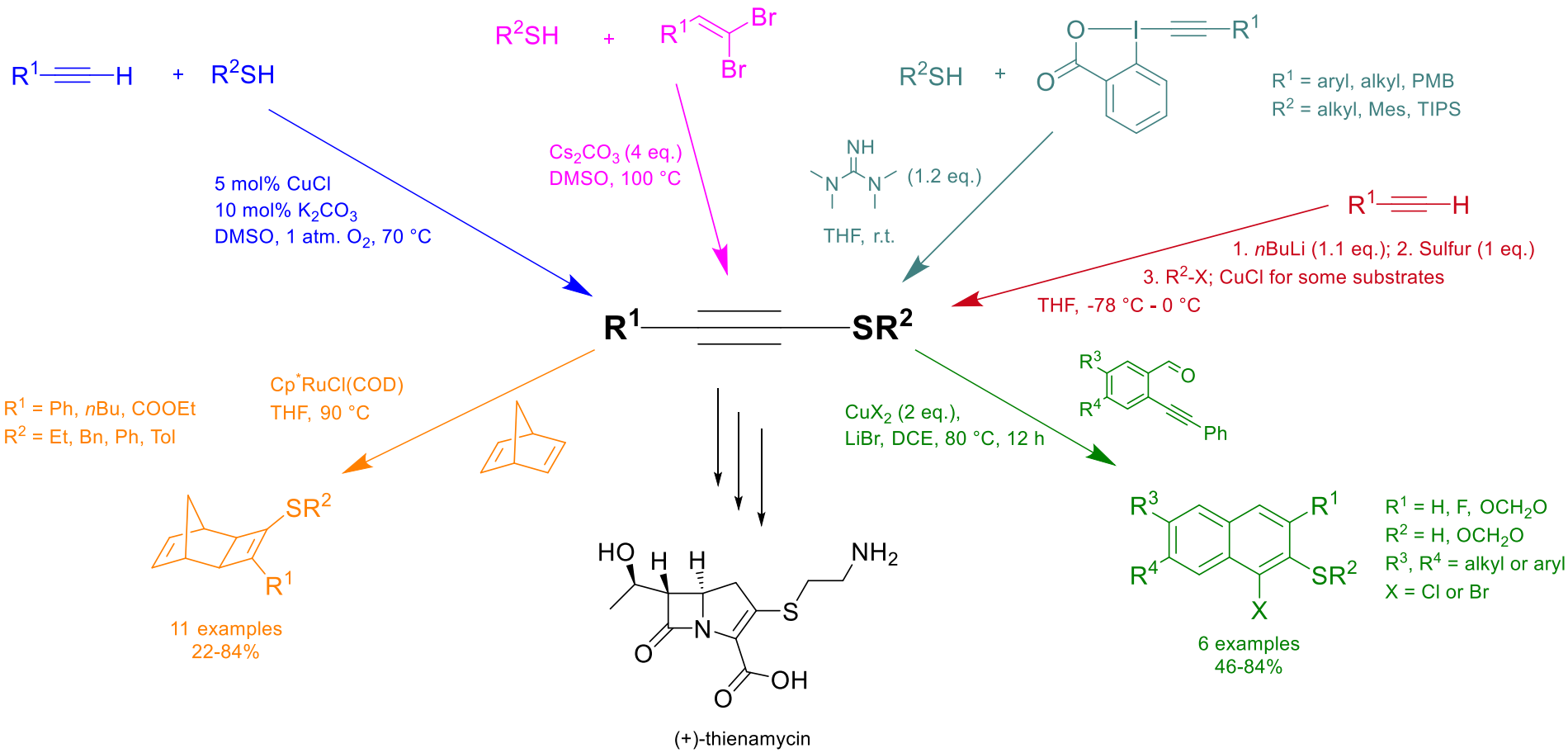
Figure 1.14 – The reactivity profile of alkynyl sulfides

Although *bis*-(arylthio)acetylenes had been known since the early 1900's, synthetic routes to thioynol ethers have only gained attention since the 1950's. Several groups simultaneously reported on their findings and these have been extensively reviewed so will not be the focus of this review but are summarised in **Scheme 1.36**.[35,95–97]



Scheme 1.36 – First routes to thioynol ethers reported simultaneously in 1956

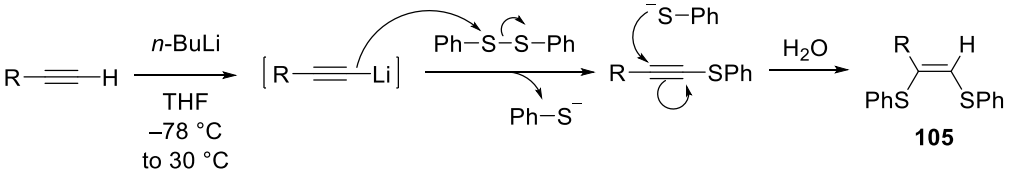
Most common routes to alkynyl sulfides involve functionalisation of terminal alkynes and use of sulfur-containing reagents. Other routes include transition metal catalysis, use of elemental sulfur and Umpolung strategies.[35,48,98]



Scheme 1.37 – Summary of routes to thioynol ethers and some uses of this class of compounds

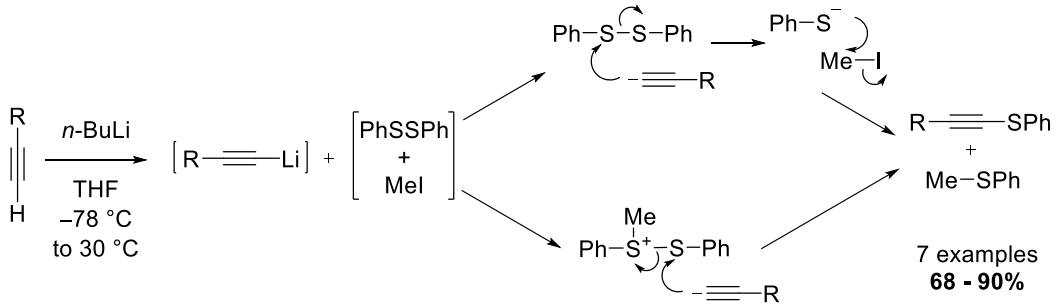
1.4.2 Synthetic routes to thioynol ethers: functionalisation of terminal alkynes

Magee and Kabanyane presented a general procedure to thioynol ethers which they described as a one-step method. After deprotonation of a parent alkyne, treatment with a pre-mixed solution of diphenyl disulfide and methyl iodide yielded alkynyl sulfides in good yields. Their initial attempt was carried out in the absence of methyl iodide and resulted in the formation of an alkenyl bis-sulfide **105** instead of an alkynyl sulfide (**Scheme 1.38**).



Scheme 1.38 – Magee *et al*. initial attempt at thioynol ether synthesis without thiolate trap

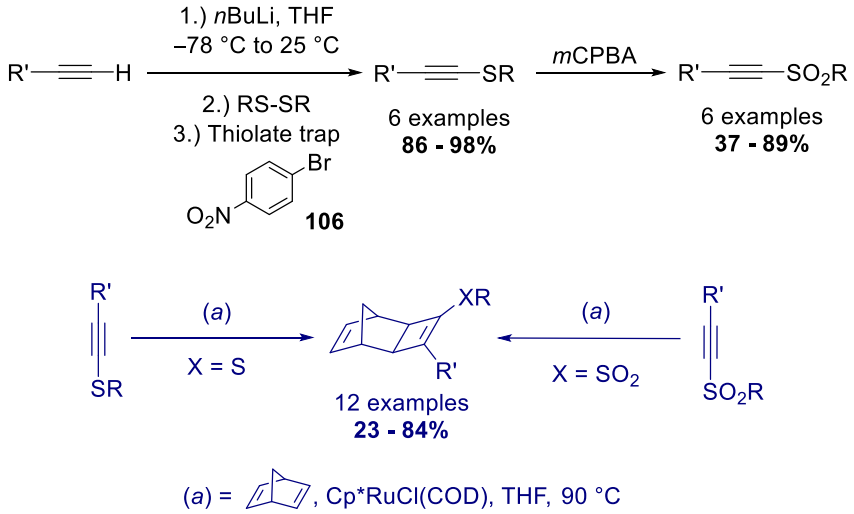
It became clear from their earlier work, that a thiophenolate trap was required to ensure the anion by-product was stopped from attacking the alkynyl sulfide after it was formed. This was mentioned in 1960 by Arens when describing Parham's early route to thioynol ethers.[35] The authors outlined the role of methyl iodide as a potential thiolate trap but suggested that an alternative role may be to activate the bis-sulfide (**Scheme 1.39**).



Scheme 1.39 – Kabanyane and Magee's route to thioynol ethers with two potential roles of MeI

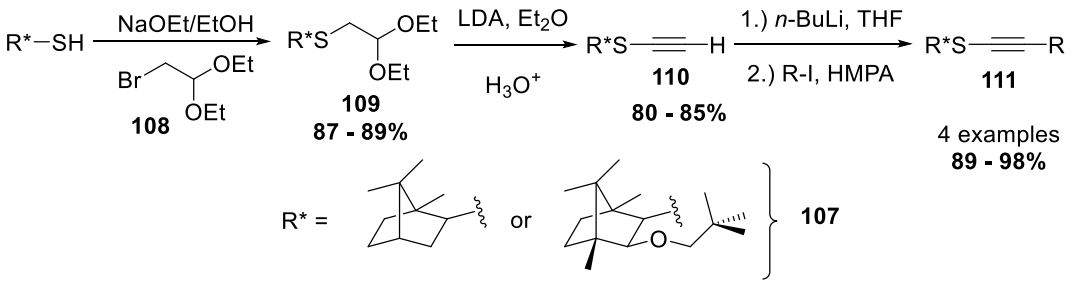
Tam *et al*. reported their challenges in the purification of the alkynyl thioethers as MeSPh had a similar R_f value and therefore developed an alternative "trap". This led to the use of *p*-nitrobenzyl bromide **106** to quench the phenylsulfide anion instead of methyl iodide. This was effective in ensuring no recombination took place and no bis-sulfide was formed. Tam *et al.* also demonstrated the compatibility of

other substituents in the disulfide; 6 substrates were obtained in excellent yields. As with many routes to thioynol ethers, these compounds were obtained as precursors to other functionalities and further transformations. The group achieved [2+2]-cycloaddition of bicyclic alkenes with the alkynyl sulfides (and sulfones, after oxidation of the sulfides using *m*-CPBA) in the presence of a ruthenium catalyst (**Scheme 1.40**).



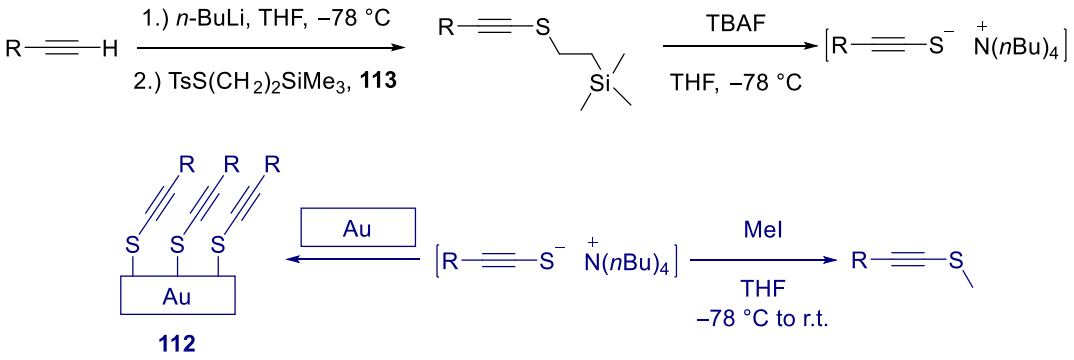
Scheme 1.40 – A different thiolate trap is used by Tam *et al*. and further transformations are shown

The use of *p*-nitrobenzyl bromide **106** poses a problem in terms of atom economy and toxicity. Therefore, routes where a thiolate trap is not required have been of interest. Pericàs *et al*. developed a method to thioynol ethers whilst looking into bicyclic, chiral compounds.[99] Using camphor-derived thiols **107** and a bromodiacetal **108**, Pericàs and co-workers obtained thiodiacetals **109** *via* sodium thiolate intermediates. Treatment with base then furnished terminal thioalkynes **110**[100] which were in turn deprotonated with *n*-butyllithium. Finally, addition of various alkyl iodides gave chiral acetylenic thioethers **111** in excellent yields (**Scheme 1.41**). Further transformations, including intramolecular and intermolecular Pauson-Khand reactions, were then carried out on these novel compounds.



Scheme 1.41 – Chiral acetylenic thioethers from camphor-derived thiols

Another interesting use of alkynyl thioethers is in composite materials with metal particles leading to potential optical properties. Matsuda *et al*. exploited this by forming self-assembled monolayers of thiolate anions on gold surfaces **112**.[93] They first obtained silyl thioynol ethers by deprotonating terminal alkynes and sulfenylating them with *S*-2-(trimethylsilyl)ethyl *p*-toluenethiosulfonate ($TsS(CH_2)_2Si(CH_3)_3$) **113**. Initial attempts with chloride as a leaving group instead of the tosyl group gave very low yields. *In situ* deprotection of the silyl group using tetrabutylammonium fluoride (TBAF) during addition to a gold surface achieved the close-packed monolayers the group was aiming for. To prove its formation, attempts were made to isolate the thiolate anion but this was unsuccessful due to its high reactivity. Instead, the group quenched the anion with methyl iodide which they presented as sound evidence of intermediate thiolate formation (**Scheme 1.42**).

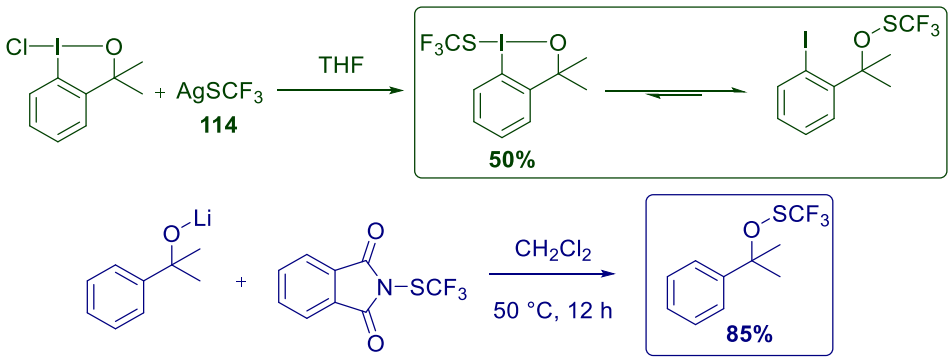


Scheme 1.42 – Synthesis of silylated alkynyl thioether and addition to Au surface

The Wilden group has also focussed their attention on the synthesis of thioynol ethers using sulfonamide precursors.[28] This is a similar synthetic approach to the ynol ether synthesis discussed earlier and will be discussed in more detail later. More applications of thioynol ethers will also be discussed later and there are many more routes to alkynyl thiothers *via* initial deprotonation which are not discussed here.[35,48,85,98,101–106]

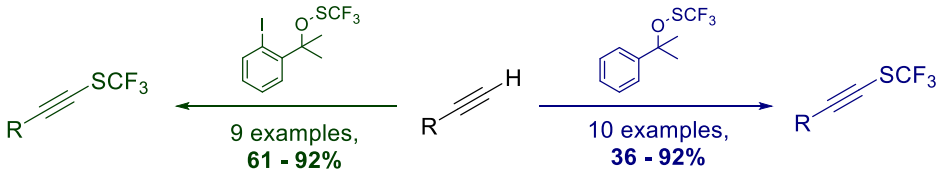
1.4.3 Synthetic routes to thioynol ethers: transition metal-catalysed routes

Trifluoromethanesulfenates **114** are utilised in a transition metal-catalysed route to thioynol ethers.[107] The lipophilic nature of the trifluoromethylthio group makes it attractive as a functional group as it is known to aid lipid membrane crossing and *in vivo* absorption rates of medicinal compounds.[92] Shen and co-workers produced a range of stable and easy-to-handle trifluoromethylthiolating reagents and over the course of two reports, using two of these reagents (**Scheme 1.43**), various alkynyl thioethers were synthesised.



Scheme 1.43 – Synthesis of trifluoromethylthiolating reagents

Both aromatic and aliphatic acetylene precursors were tolerated in the presence of a copper catalyst (**Scheme 1.44**). It is interesting to note that these reagents found use in many other transformations as well, including reactions with indoles, arylboronic acids and Grignard reagents. The advantage of using this method is direct trifluoromethylthiolation, however, the complexity of the reagents shows this is a procedure with poor atom economy.

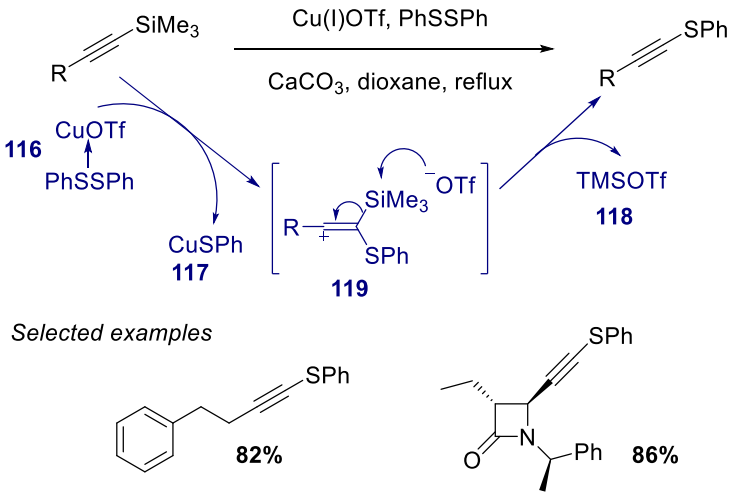


Conditions: CuBr·Me_2S (20 mol%), bpy (40 mol%), K_2CO_3 (2 eq.), DCE, 80 °C, 14 h

Scheme 1.44 – Trifluoromethylthiolation of terminal acetylenes using copper catalysis

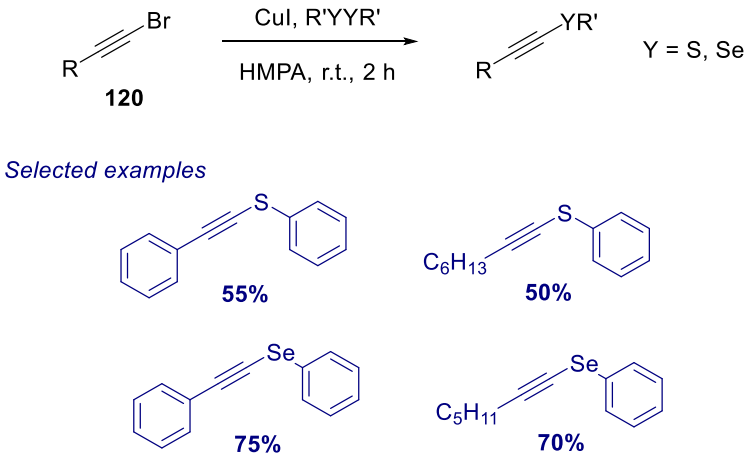
Another Cu catalyst was developed by Shibasaki *et al.* and applied in an efficient synthetic route to an intermediate of *Thienamycin* **104**.[90,94] Using diphenyl disulfide, silylated β-amino thiol esters **115** are converted to ynol thioethers in one step (**Scheme 1.45**). The PhSSPh-CuOTf species **116** is an excellent source of

PhS^+ and mechanistic studies have shown that presence of CuOTf, CuSPh and $CaCO_3$ are all vital for the desired alkynyl thiothers to be obtained. **Scheme 1.45** shows the mechanistic route *via* formation of copper thiophenolate **117** and expulsion of trimethylsilyl triflate **118**. The PhS^+ electrophile added to the triple bond and subsequent elimination of the silyl group from the vinyl cation intermediate **119** by the triflate anion furnished thioynol ethers.



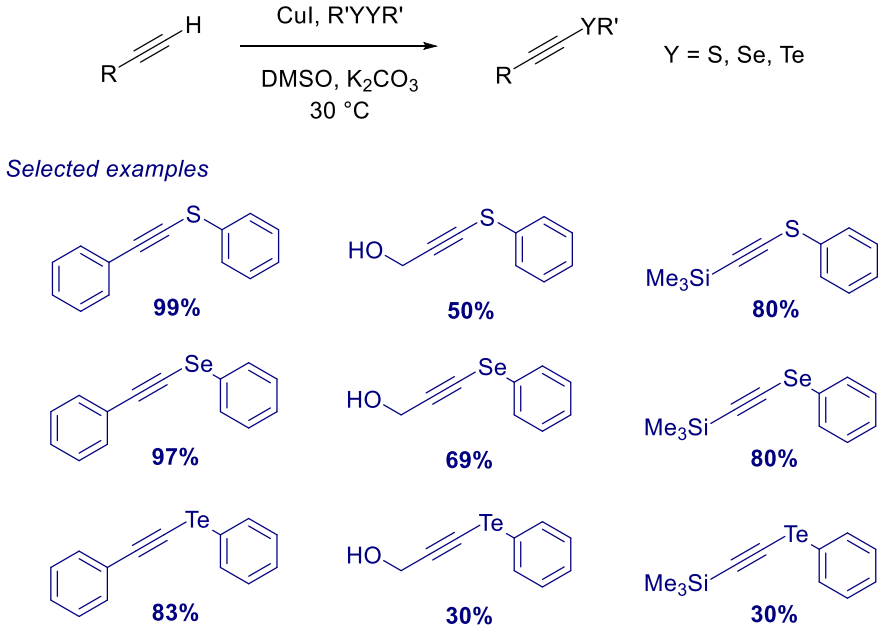
Scheme 1.45 – CuOTf and PhSSPh forming a PhS^+ complex in Shibasaki's route to thioynol ethers

Diphenyl disulfide (and other diorganoyl chalcogenides) and Cu(I) catalysis were also used by Braga *et al*. in their work to obtain alkynyl sulfides and selenides. Instead of a silylacetylene, alkynyl bromides **120** were used and it was advantageous that the reaction could be conducted at room temperature. However, the toxicity of the solvent, HMPA, was a downfall of this method (**Scheme 1.46**).



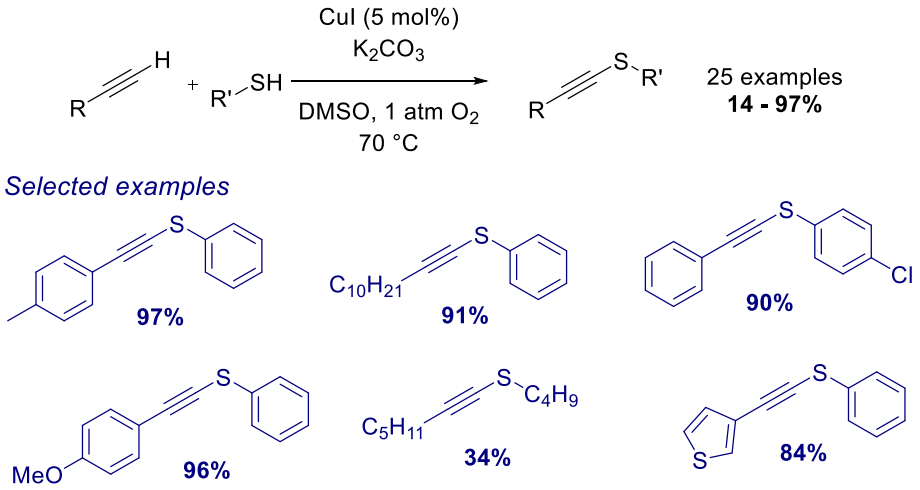
Scheme 1.46 – Braga *et al.* route to alkynyl chalcogenides from alkynyl bromides

The same group developed a different copper-catalysed route to alkynyl thioethers using terminal alkynes and phenylsulfuryl chloride but yields were relatively low (38-46%).[108] A similar route was used by Bieber *et al*. to obtain alkynyl sulfides as well as selenides and tellurides but DMSO was used instead of HMPA and a mild base was required.[109] Bieber and co-workers screened various copper catalysts, of which CuCl, CuBr, CuCN and $CuCl_2$ only gave trace amounts of alkynyl thioethers. Aromatic, aliphatic, hydroxyl and silyl groups were all tolerated (**Scheme 1.47**).



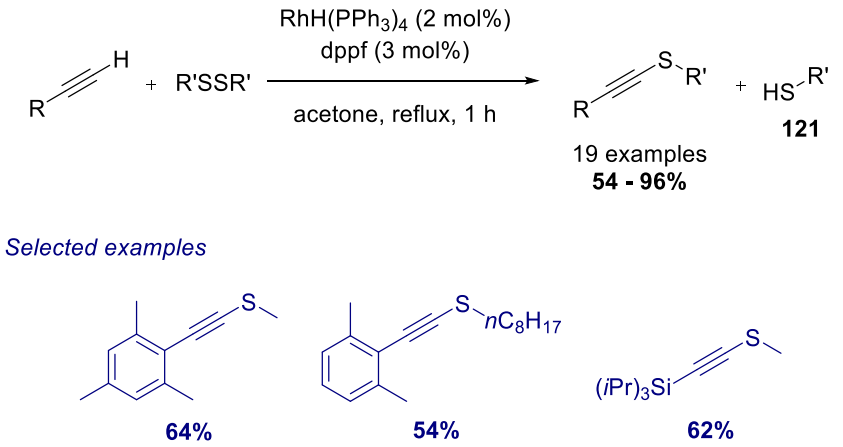
Scheme 1.47 – Bieber *et al.* route to thioynol ethers

Copper catalysts in the presence of a base have been used in the selective aerobic cross-dehydrogenative coupling reaction of terminal acetylenes and thiols by Rioux and co-workers.[110] The authors successfully overcame the common Glaser-type homocoupling side-reaction, and both aromatic and aliphatic groups were tolerated which made this route relatively attractive. After a screen of bases, the group found that K_2CO_3 gave the best yields and the lowest amounts of side products (**Scheme** 1.48)**.**



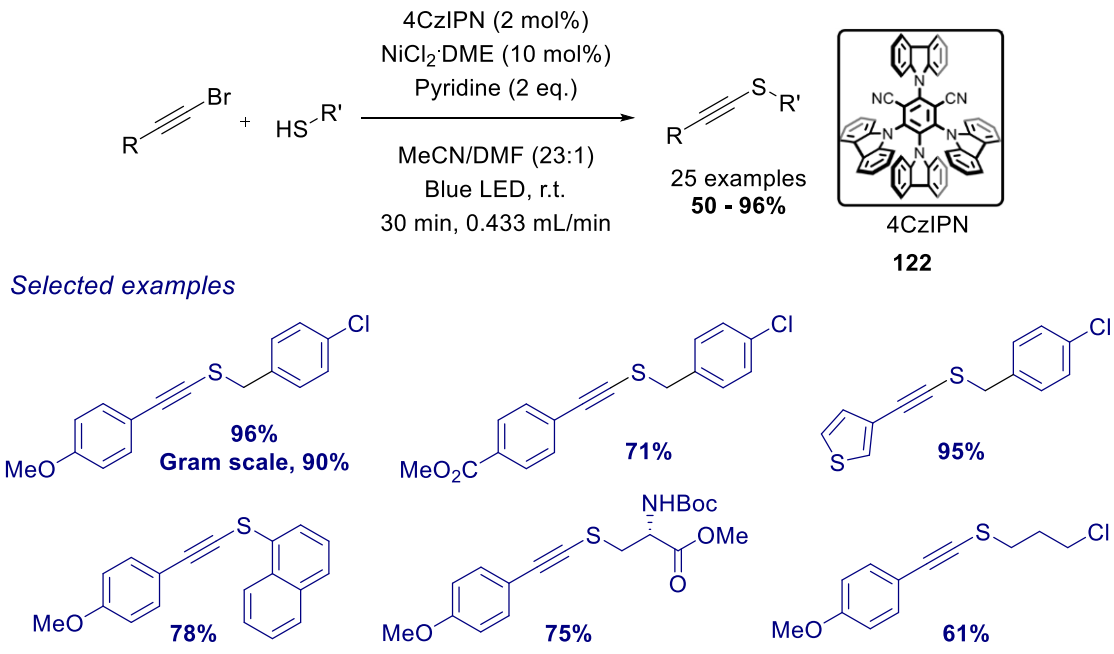
Scheme 1.48 – Rioux *et al*. Cu-catalysed aerobic dehydrogenative coupling to thioynol ethers

As well as copper catalysts, rhodium[111] and nickel[112] have also been used to promote synthesis of thioynol ethers. Yamaguchi *et al*. route to alkynyl thioethers utilised rhodium as a catalyst in the absence of stoichiometric amounts of base which yielded a range of substrates (**Scheme 1.49**).[111] The disadvantage of this route was the need for a bulky group on the starting acetylene in order to prevent dimerisation of the alkyne. Conversely, it was interesting to see that formation of free thiols **121** did not interfere with the reaction.



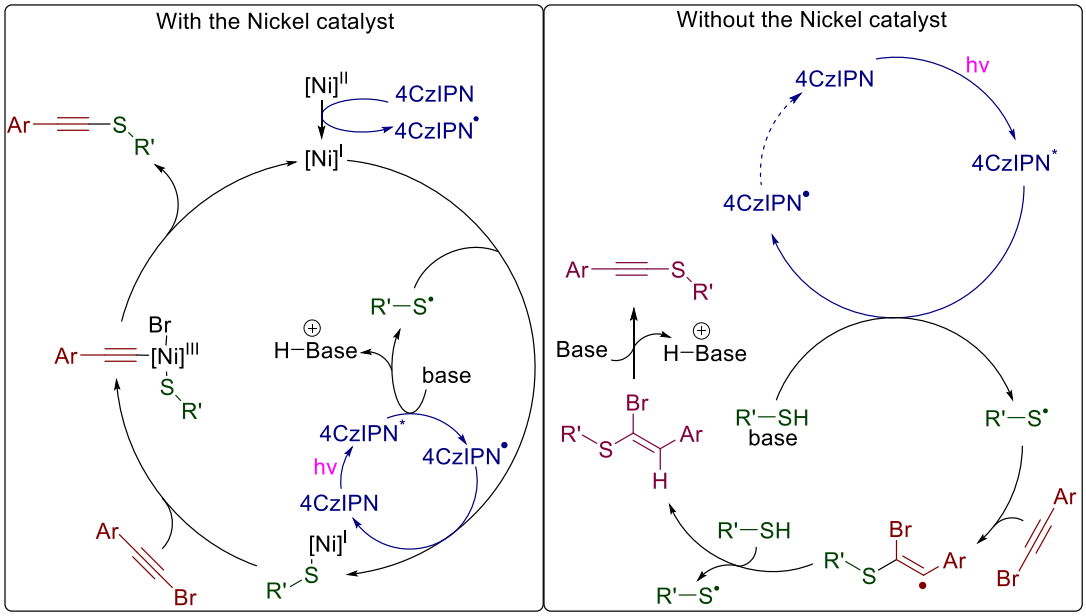
Scheme 1.49 – Yamaguchi *et al*. rhodium-catalysed route to alkynyl thioethers

A recently reported route by Collins *et al*. exploited the dual capacity of nickel catalysis and photocatalysis.[112] An intriguing continuous flow method using a nickel catalyst and 2,4,5,6-tetrakis(carbazol-9-yl)-1,3-dicyanobenzene (4CzIPN) **122** gave thioynol ethers in good yields. 4CzIPN is an example of an interpenetrating polymer network (IPN) and is part of a class of compounds known for their fluorescent behaviour.[113] The authors were able to prepare a wide range of substrates with electron-donating, neutral and electron-withdrawing groups tolerated well (**Scheme** 1.50). Furthermore, on employment of an enantiomerically pure secondary thiol, enantiopurity was fully preserved.



Scheme 1.50 – Collins *et al*. catalytic photoredox synthesis of alkynyl sulfides

Interestingly, the reaction proceeded in the absence of the nickel catalyst; two potential mechanistic routes involving radical intermediates were proposed (**Scheme 1.51**). The IPN complex acts as an electron transfer agent in both proposed mechanisms; either donating an electron to the nickel (II) catalyst to initiate the process or undergoing photolytic initiation and subsequently transferring an electron to the thiol base. In the nickel-catalysed route, the second step involves a photo-induced radical propagation cycle which gives the thiolate anion. This in turn forms a complex with the nickel (I) intermediate from the first step which oxidatively inserts in the C-Br bond of the alkynyl bromide. Finally, reductive elimination furnishes the alkynyl sulfide returning the nickel (I) complex to continue to radical cycle. Without the nickel catalyst, the mechanism is proposed to go *via* formation of an intermediate vinyl radical species followed by a dehydrobromination step to give the alkynyl thioether.

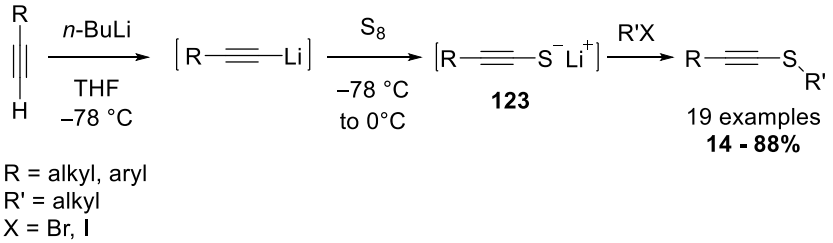


Scheme 1.51 – Collins *et al*. proposed mechanisms with and without the nickel catalyst

The fact that the reaction proceeded in the absence of the nickel catalyst is beneficial from a sustainability point of view.

1.4.4 Synthetic routes to thioynol ethers: use of elemental sulfur

One of the issues with thioynol ether synthesis is that starting materials are often more complex than products, making reactions atom inefficient.[106,114] The use of elemental sulfur in the formation of a thioynol ether unit had been demonstrated in 1977[115] and 1984[116] but more recently, Hu *et al*. presented a one-pot procedure from terminal alkynes using elemental sulfur which significantly improved atom economy (**Scheme 1.52**).[117]

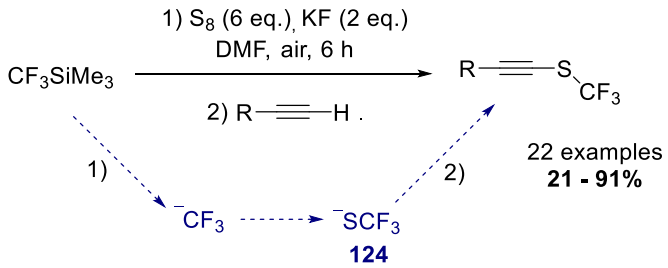


Scheme 1.52 – Hu *et al*. use of elemental sulfur in a one-pot route to thioynol ethers

After deprotonation with *n*-butyllithium, addition of elemental sulfur to the lithium acetylide intermediate was thought to give the thiolate anion **123** which can be trapped with various alkyl halides (**Scheme 1.52**). Alkyl bromides and iodides worked well whereas some substrates could not be formed using the chloride reagent; no explanation was given by the authors but this could be attributed to the relatively strong C-Cl bond. Copper (I) chloride was added to some reactions with lower yielding substrates which helped improve results. Moreover, the authors demonstrated that ethyl magnesium bromide could be used instead of *n*-butyllithium and the thiolate was formed successfully. Unfortunately, yields of alkynyl thioethers were low in these cases, due to side reactions taking place.

Another interesting route using elemental sulfur was reported by Qing and co-workers whereby oxidative trifluoromethanethiolation of terminal alkynes was achieved.[118] Previous work in the group focused on the copper-catalysed trifluoromethylation of aryl boronic acids so they continued using their copper catalysis approach, initially. A control experiment in the absence of copper iodide gave the desired thioynol ether product and the group delved deeper into the role of sulfur and the mechanism. In contrast to Hu's group, Qing *et al.* proposed that sulfur played the role of an oxidant as well as a simple precursor. This was believed to assist potassium fluoride (KF) in the generation of the trifluoromethanethiolate anion

species **124** which on addition of an acetylene, formed thioynol ethers (**Scheme** 1.53).

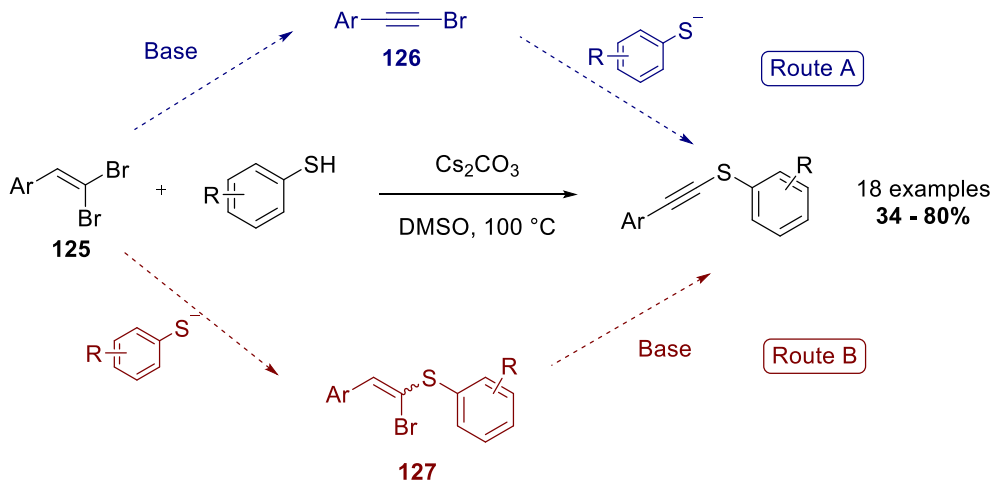


Scheme 1.53 – Proposed scheme for Qing *et al*. route to thioynol ethers using S_8

Mechanistic studies found that the active thiolating agent was more likely to be $KSCF_3$ as opposed to CF_3SCF_3 as the control experiment with just the latter present gave no thioynol ether. Both electron withdrawing and electron donating groups were accommodated, as well as aliphatic and aromatic groups, however use of excess Ruppert-Prakash reagent (CF_3SiMe_3) made this route relatively expensive.

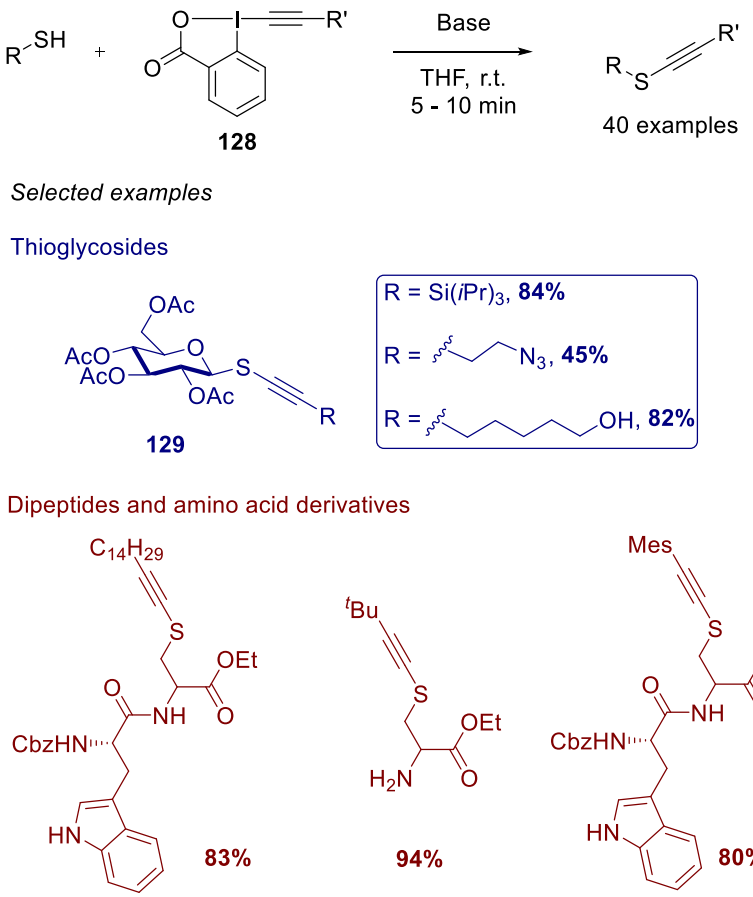
1.4.5 Synthetic routes to thioynol ethers: Umpolung strategies

As well as phenylacetylene, vinyl bromides have been used effectively in the synthesis of alkynyl sulfides. Pan *et al*. developed a transition metal-free synthesis of thioynol ethers from *gem*-dibromoalkenes **125**. In the presence of caesium carbonate (Cs_2CO_3), the reaction of vinyl dibromides and substituted thiophenols in DMSO gave thioynol ethers in reasonable yields. Two potential mechanistic routes were proposed: Route A entailed base-induced dehydrohalogenation of the dibromoalkene **125** and deprotonation of the thiophenol. Combination of the thiolate anion and the haloalkyne intermediate **126** then resulted in the formation of alkynyl thioethers. Route B involved displacement of a bromide anion with the thiolate anion and subsequent dehydrohalogenation from the intermediate mono-brominated thioalkene **127** furnished the desired products (**Scheme 1.54**).



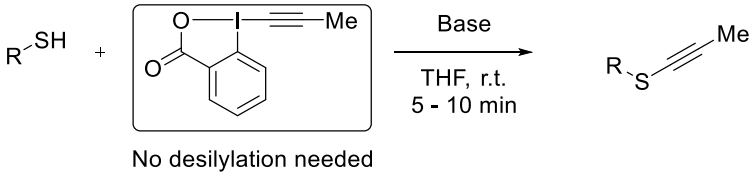
Scheme 1.54 – Pan *et al.* proposed mechanisms or TM-free thioynol ether synthesis

Although the conditions are relatively harsh, the lack of transition metals and the method's scope make this an attractive route. Waser *et al*. also presented an interesting transition metal-free method to thioynol ethers where an alkyne Umpolung strategy *via* hypervalent iodine reagents was utilised (**Scheme** 1.55).[119,120] Ethynyl benziodoxolone (EBX) reagents **128** offer a broad scope of thionyol ether products, some of which are valuable synthons in drug discovery such as thioglycosides **129**.



Scheme 1.55 – Waser *et al.* TM-free method to alkynyl thioethers using hypervalent iodine reagents

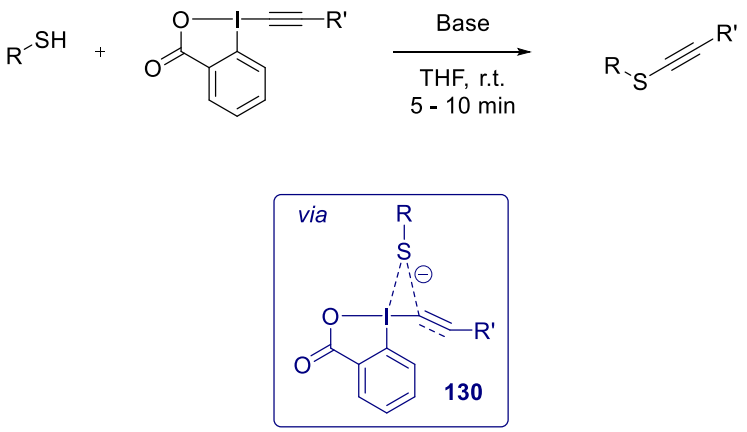
Previous work by Ochiai and co-workers led the way in using hypervalent iodine reagents in the synthesis of heteroatom-alkyne functionality but the scope was limited.[121] Waser *et al*. method accommodated for a wide range of functional groups and tweaking the starting materials allowed for further transformations to be made effectively. For instance, changing the silyl protecting group to a methyl group in the starting EBX reagent removed the sensitivity of the products to TBAF which would have to be used for desilylation (**Scheme 1.56**).



Scheme 1.56 – Waser *et al*. use of Me-EBX as an example of reagent manipulation

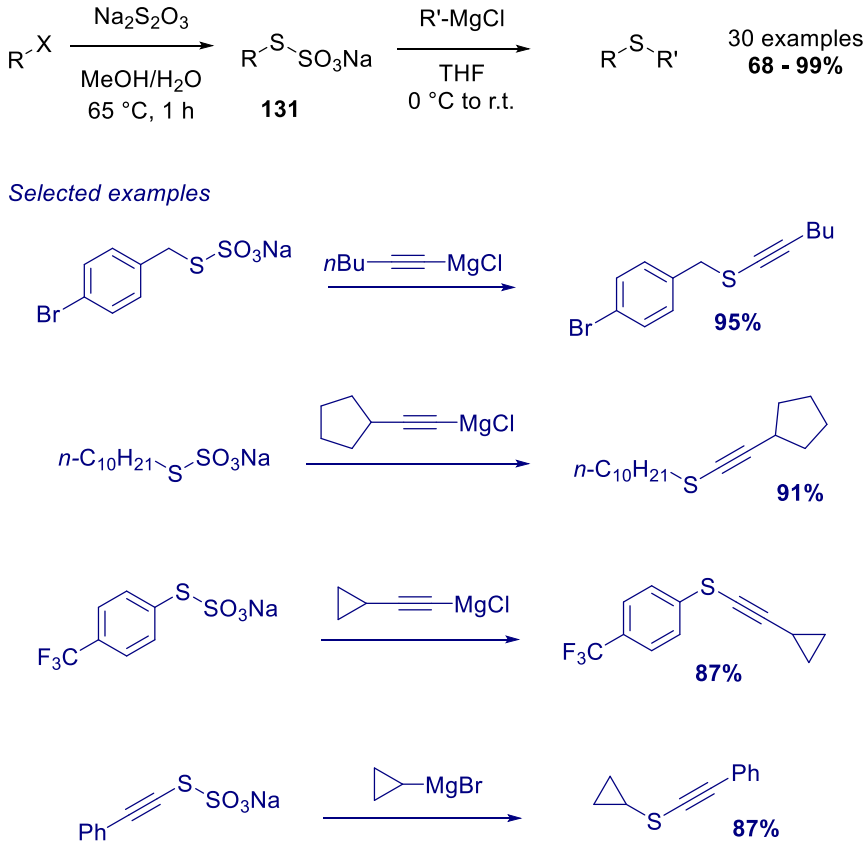
Two different bases were used depending on the reagents – 1,1,3,3-tetramethyl guanidine (TMG) and triazabicyclodecene (TBD) fully deprotonated the thiols in the

first step. Extensive mechanistic probing including computational studies unveiled a surprising three-atom quasi-triangular arrangement **130** between iodine, sulfur and carbon. This is said to result in direct α-addition of sulfur and simultaneous C-I bond cleavage (**Scheme 1.57**). This was supported by the relatively low energy barrier of just 10.8 kcal/mol.[120]



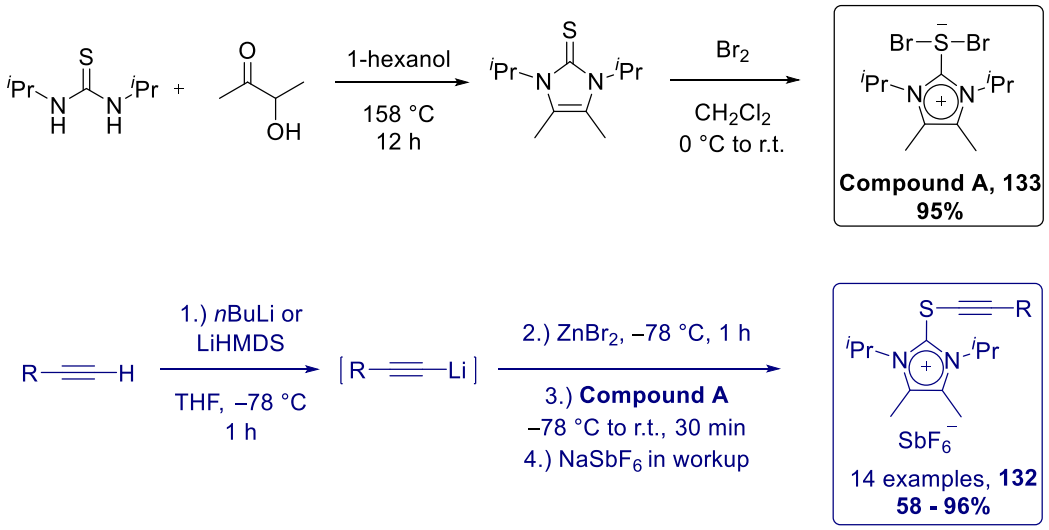
Scheme 1.57 – Proposed structure of transition state in Waser *et al*. thioynol ether synthesis

The downfall of Waser's method is the multi-step synthesis required to obtain the EBX reagents and some of the starting thiols. Additionally, the use of malodorous thiols can be seen as a negative factor. Reeves *et al*., use of thiosulfate sodium salts (Bunte salts) **131**[122] eradicated this problem in their thiol-free reaction with Grignard reagents to yield a range of sulfides including thioynol ethers (**Scheme** 1.58).[123] Interestingly, the alkyne unit could be installed from the Bunte salt or from the Grignard reagent allowing for different functionalities to be tolerated.



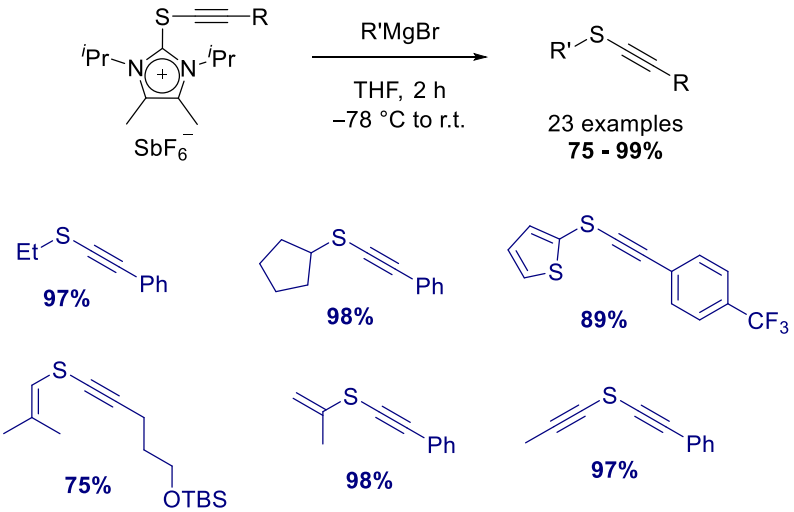
Scheme 1.58 – Reeves *et al*. thiol-free sulfide synthesis using Bunte salts

Another recent report presented the use of an air stable alkynylthioimidazolium salt **132** to obtain alkynyl thioethers. Alcarazo and co-workers described their route as the first electrophilic thioalkynylation protocol.[124] Using methods developed in their group previously,[125,126] the authors produced a range of alkynylthioimidazolium salts **132** from substituted imidazolium sulfuranes (Compound A **133** is given as an example), alkynes and zinc bromide followed by treatment with sodium hexafluoroantimonate ($NaSbF_6$) (**Scheme 1.59**).



Scheme 1.59 – Alcarazo *et al*. multi-step synthesis of starting alkynylthioimisazolium salts

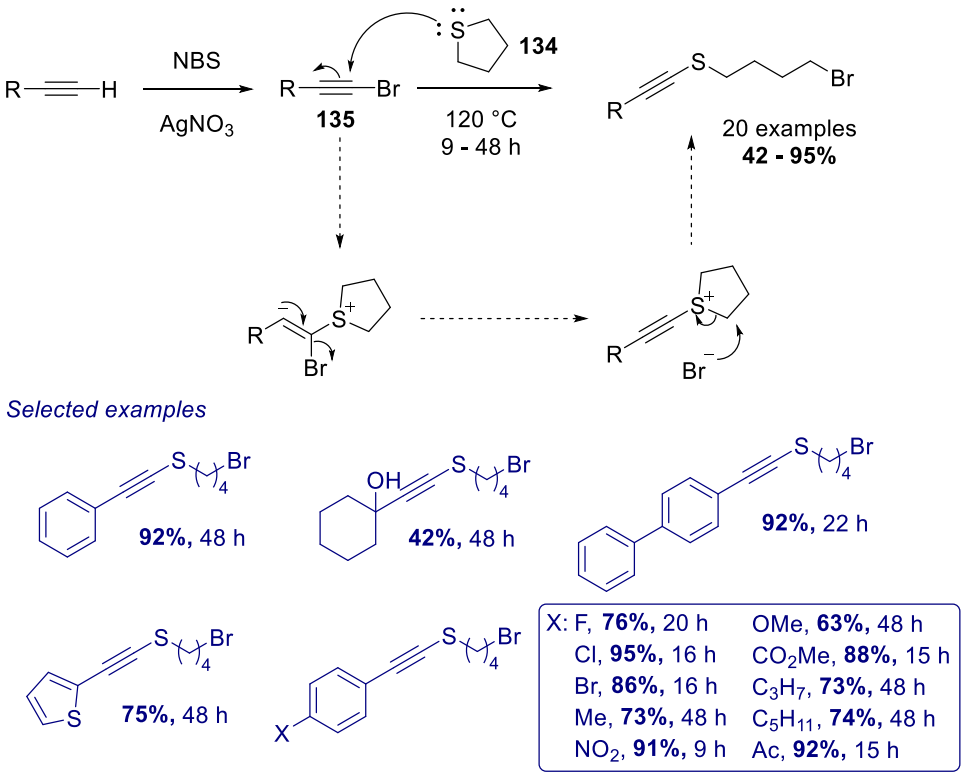
Reaction of a selection of these alkynylthioimidazolium salts with Grignard reagents yielded a small library of alkynyl thioethers (**Scheme 1.60**). Numerous substrates proved intolerant to the reaction conditions and no change in yield was observed in the presence of TEMPO. This suggests that there is no involvement of radical intermediates in this reaction but no thorough mechanistic studies have been carried out.



Scheme 1.60 – The first electrophilic thioalkynation protocol presented by Alcarazo *et al*.

Finally, an interesting method to alkynyl sulfides was demonstrated by Yang *et al*. in 2015.[127] The authors were working on extending an alkynylation method they had successfully used with tetrahydrofuran (THF)[128] to tetrahydrothiophene (THT) **134** when they found the dual role played by the alkynyl bromide unit **135**. Heating a

range of alkynyl bromides **135** in THT **134** to 120 °C furnished a library of ring-opened bromo-substituted alkynyl sulfides **136** in good to excellent yields (**Scheme** 1.61).



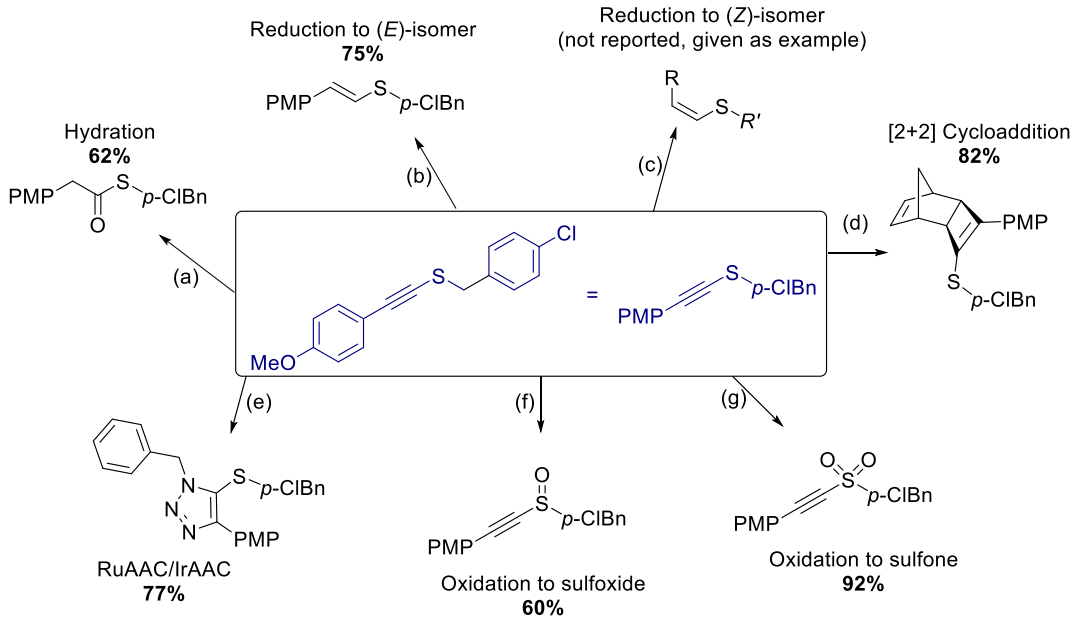
Scheme 1.61 – Yang *et al*. simple one-pot route to bromo-substituted alkynyl thioethers

The substrate scope is somewhat limited as the S-alkyl unit remains the same throughout; nonetheless, this is a simple and efficient method to obtain thioynol ethers.[127]

1.4.6 Uses of thioynol ethers

Several examples of applications of alkynyl thioethers will be presented in this section but this is by no means an exhaustive review.[35,48,85,98,129] Uses of this class of compounds are diverse including further functionalisation (hydration,[130,131] oxidation,[132–134] reduction[135] and so on), cycloaddition reactions,[136–138] cross-coupling reactions,[139,140] hydrostannation,[141] hydrohalogenation[142,143] and many others.[144–146] Intriguingly, however, there is a surprising level of stability[132] that creates difficulty in using these compounds in some reactions.

Collins *et al*. efficiently demonstrated the versatility of the thioalkyne functionality with various transformations[112] outlined in **Scheme 1.62**. Using previously reported methods, the authors subjected (4-chlorobenzyl)((4-methoxyphenyl)ethynyl)sulfane to hydration, reduction, oxidation (to a sulfoxide and a sulfone), [2+2] cycloaddition and iridium- or ruthenium-catalysed azide-alkyne cycloaddition (IrAAC/RuAAC).

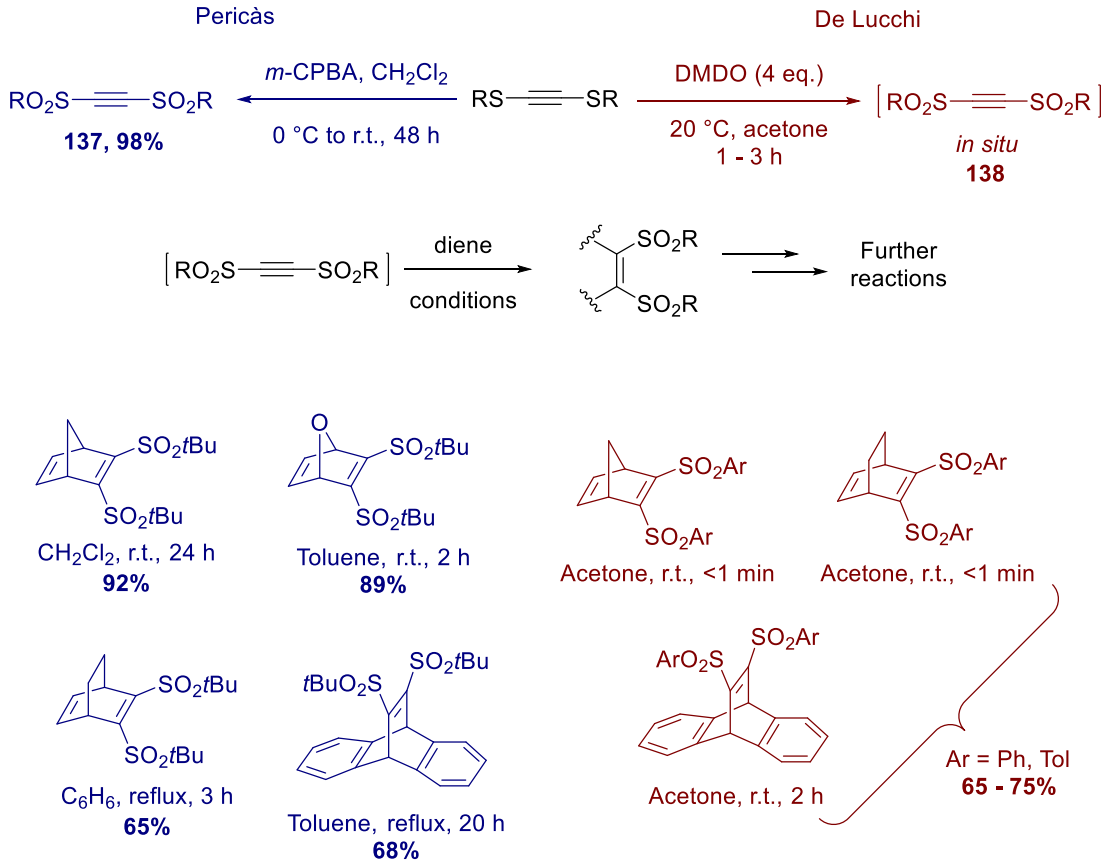


(a) TsOH or TFA, silica, CH_2Cl_2;[130,131] **(b)** $LiAlH_4$;[231,232] **(c)** RMgX, CuX, THF;[135] **(d)** Norbornadiene, Cp*RuCl(COD), THF, 90 °C;[136] **(e)** Benzyl azide, Cp*RuCl(COD) or $\{Ir(cod)Cl\}_2$, CH_2Cl_2 or benzene/toluene, r.t., 18 h;[136,162–164] **(f)** *m*-CPBA, CH_2Cl_2, 0 °C;[132,221] **(g)** Dimethyldioxirane (DMDO), acetone, 20 °C[133,221]

Scheme 1.62 – Collins *et al*. diversification of a thioynol ether

Hydration to thioesters was demonstrated by Braga *et al*. using a range of different acids with silica; *p*-toluenesulfonic acid (TsOH) or trifluoroacetic acid (TFA) were found to be the most effective.[130] The (*E*)-isomer of the vinyl sulfide was obtained

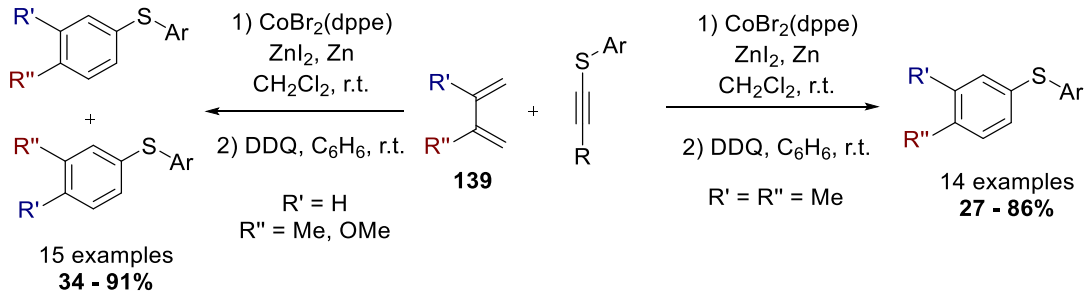
by reduction with lithium aluminium hydride ($LiAlH_4$) and the (*Z*)-isomer has been reported by Vermeer *et al*.[135] Addition of a Grignard reagent in the presence of a copper (I) halide catalyst effected *cis*-addition to give (*Z*)-vinylic sulfides. Oxidation of alkynyl sulfides can yield alkynyl sulfoxides or sulfones and a variety of oxidants can be used. Pericàs *et al*. utilised *m*-CPBA to turn alkynyl bis-sulfides into alkynyl bis-sulfones **137**.[134] Magee *et al*. showed that *m*-CPBA, oxone (monopersulfate, $KHSO_5$) and phenylsulfonyloxaziridine can be used to achieve both oxidations.[132] In addition, De Lucchi *et al*. presented an oxidation route to alkynyl bis-sulfones **138** using neutral oxidant, dimethyldioxirane (DMDO).[133] Following the oxidation step to obtain sulfones, De Lucchi *et al.* and Pericàs *et al*. carried out [4+2] cycloaddition reactions to obtain synthetically useful substituted bicyclic compounds (**Scheme 1.63**).



Scheme 1.63 – Cycloaddition reactions of alkynyl sulfones

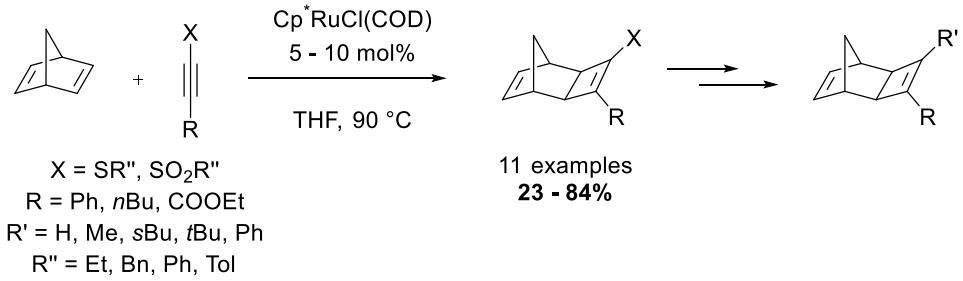
There are many examples of alkynyl sulfoxides and sulfones undergoing cycloaddition reactions[147–153] as these compounds are activated electrophiles. This can be attributed to the electron-withdrawing sulfone moiety making these compounds more prone to reaction with electron-rich dienes. There has been

relatively limited methodology for the cycloaddition of alkynyl sulfides with dienes **139**[154,155] until more recent developments of transition metal-mediated reactions. Hilt *et al*. reported the first general method to cycloadducts using alkynyl sulfides in the presence of a cobalt catalyst.[137,156] The dihydro cycloadducts were subsequently oxidised with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to re-aromatise and give diaryl sulfide products (**Scheme 1.64**).



Scheme 1.64 – Hilt *et al*. cobalt-catalysed cycloaddition method using atom thioethers

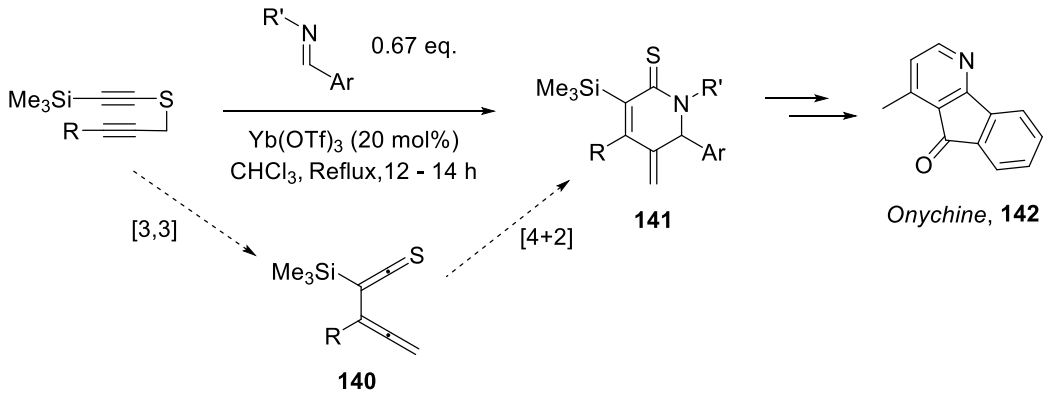
Previously, the authors used 5 mol% loading of the catalyst with alkynes but 10-50 mol% was required for reaction with alkynyl sulfides. This is rationalised by the coordination of sulfur to the catalyst centre, reducing its activity. A broad range of substrates was obtained using this Co-catalysed method. Ru-catalysed cycloaddition of alkynyl sulfides was reported in 2005 by Tam *et al*.[136] resulting in several examples of polycyclic, highly functionalised compounds. [2+2] cycloadditions of norbornadiene and other bicyclic alkenes with alkynyl sulfides gave some interesting products (**Scheme 1.65**).



Scheme 1.65 – Tam *et al*. Ru-catalysed [2+2] cycloadditions of alkynyl sulfides and sulfones

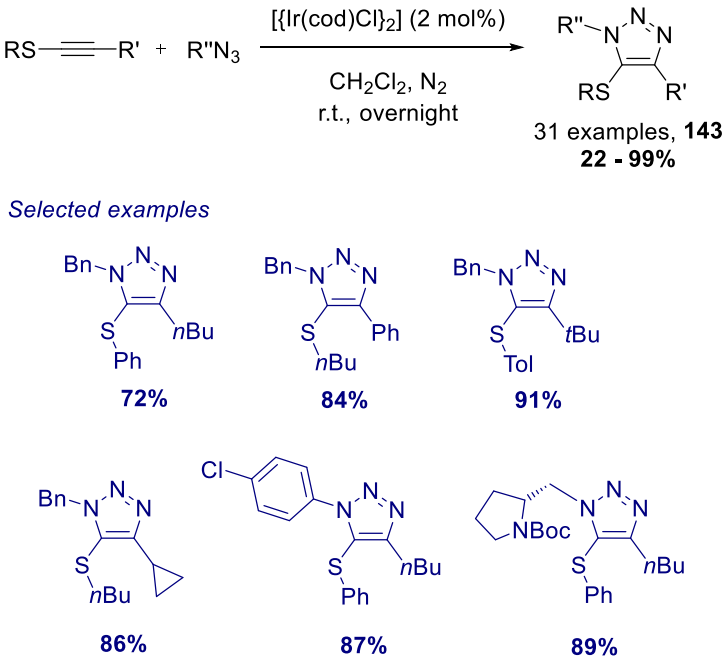
Alkynyl sulfides required prolonged reaction times (7 days) and in some cases, significant amounts of the starting alkyne were recovered. For a class of compounds with such synthetic promise, thioynol ethers can be regarded as surprisingly

unreactive under certain conditions. As with many transition metal-catalysed reactions, Tam *et al*. found that sensitivity to air and moisture resulted in the need for very careful handling. Lanthanide-based catalysts have also found use in cycloaddition reactions with alkynyl sulfides.[157] Aoyagi *et al*. demonstrated [4+2] cycloaddition reaction of allenylsilylthioketenes **140** which were formed *in situ* from alkynyl sulfides *via* [3,3]-sigmatropic rearrangement. An aza-Diels-Alder reaction with an imine in the presence of $Yb(OTf)_3$ gave the cycloadduct **141**. This was then used as a precursor to the potentially medicinally useful alkaloid, *Onychine* **142** (**Scheme 1.66**). Other natural product syntheses using alkynyl sulfides precursors *via* cycloaddition[138] have been reported.



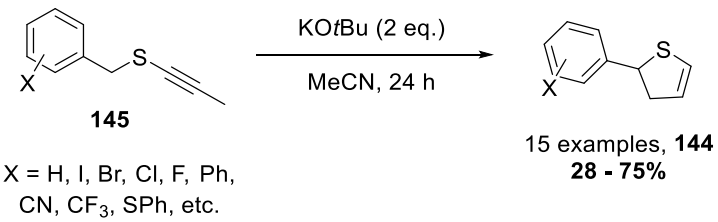
Scheme 1.66 – Aoyagi *et al.* Yb-catalysed route to natural product intermediate

1,2,3-Triazoles are a class of compounds which show potential medicinal uses[159–161] and have been formed by cycloaddition reactions using alkynyl sulfides. Transition metal-catalysed azide-alkyne cycloaddition (AAC) offers an atom economical route to 1,2,3-triazoles.[161,162] Jia *et al*. recently demonstrated an iridium-catalysed AAC reaction of thioalkynes with benzyl azide (BnN_3).[163] The authors studied a range of catalysts including ruthenium- and copper-based systems which have previously been used in reactions with other alkynes. $[\{Ir(cod)Cl\}_2]$ produced the best results with excellent regioselectivity so was utilised in obtaining a library of substrates (**Scheme 1.67**). Shen *et al*. demonstration of a similar RuAAC protocol highlighted the same difficulty of regioselectivity as a mixture of 1,2,3-triazoles **143** were obtained using $[Cp^*RuCl(cod)]$.[164] Recently, Zhang *et al*. demonstrated the same problem with a CuAAC protocol using thioalkynes[165] highlighting the superior results from the Ir-catalysed AAC method.



Scheme 1.67 – Jia *et al.* Ir-catalysed AAC reaction of thioynol ethers

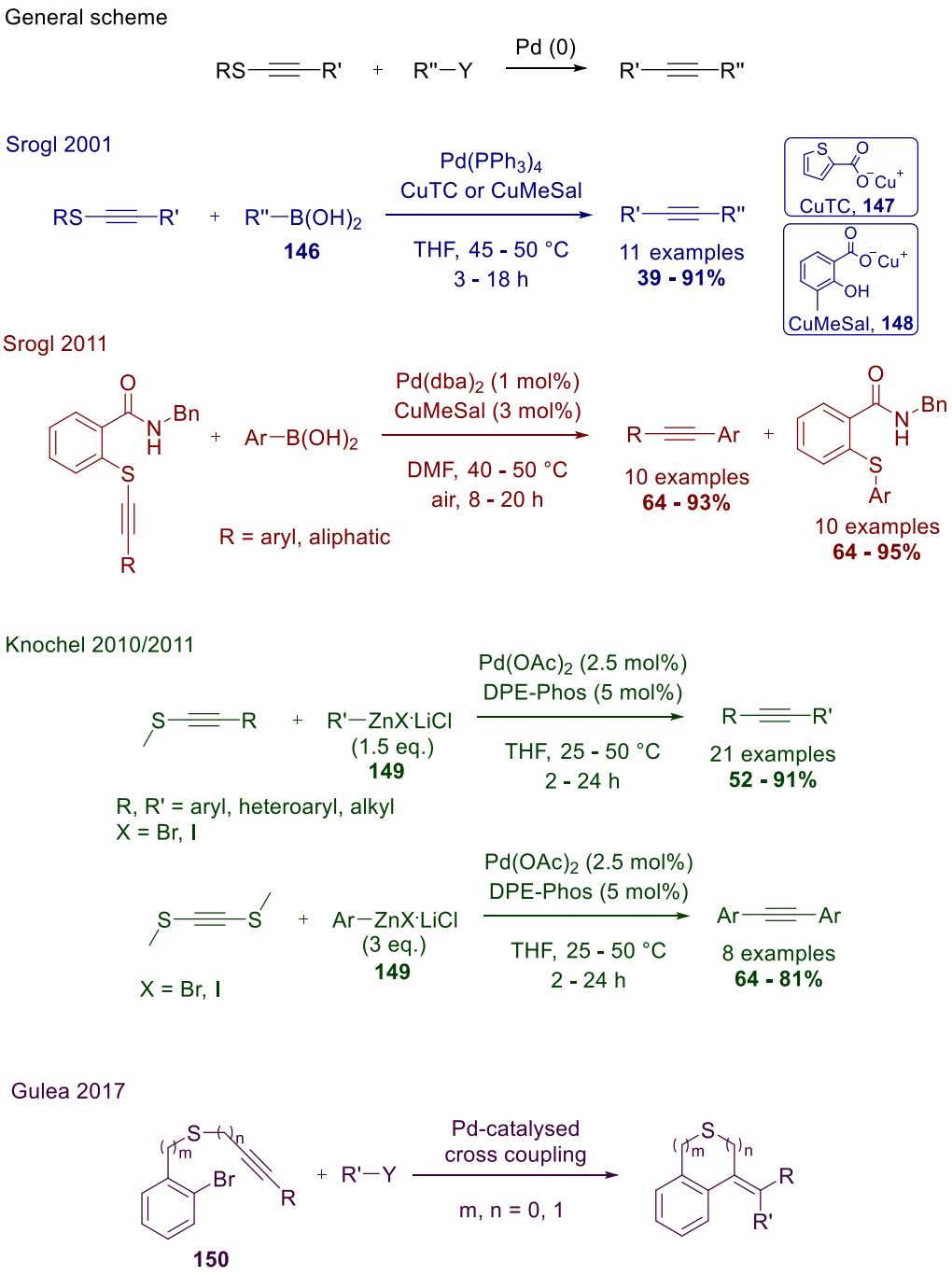
As well as cycloaddition, cyclisation methods have been used to transform alkynyl thioethers into useful cyclic products. Schwan *et al*. presented a base-induced synthesis of dihydrothiophenes **144** from alkynyl sulfides in 2000.[166] Halobenzyl-substituted thioalkynes **145** underwent cyclisation using two equivalents of KO*t*Bu; NaO*t*Bu and LiO*t*Bu were less effective. Absence of the halogen resulted in a sluggish reaction, if any; extensive mechanistic studies were reported more recently and the authors propose reasoning for the 5-*endo* cyclisation.[167] Interestingly, no extra activation is required to induce carbon-carbon bond formation. It appears that unsaturation of the 3-carbon substituent on sulfur, after deprotonation, suffices for ring closure (**Scheme 1.68**).



Scheme 1.68 – Schwan *et al.* use of thioynol ethers in dihydrothiophene synthesis

Transition metal-catalysed coupling reactions are another useful transformation of alkynyl thioethers and have been demonstrated by a number of groups.[139,140,168–170]

Scheme 1.69 shows the use of Pd, Cu, and Zn in various catalytic coupling reactions of different reagents and thioynol ethers.

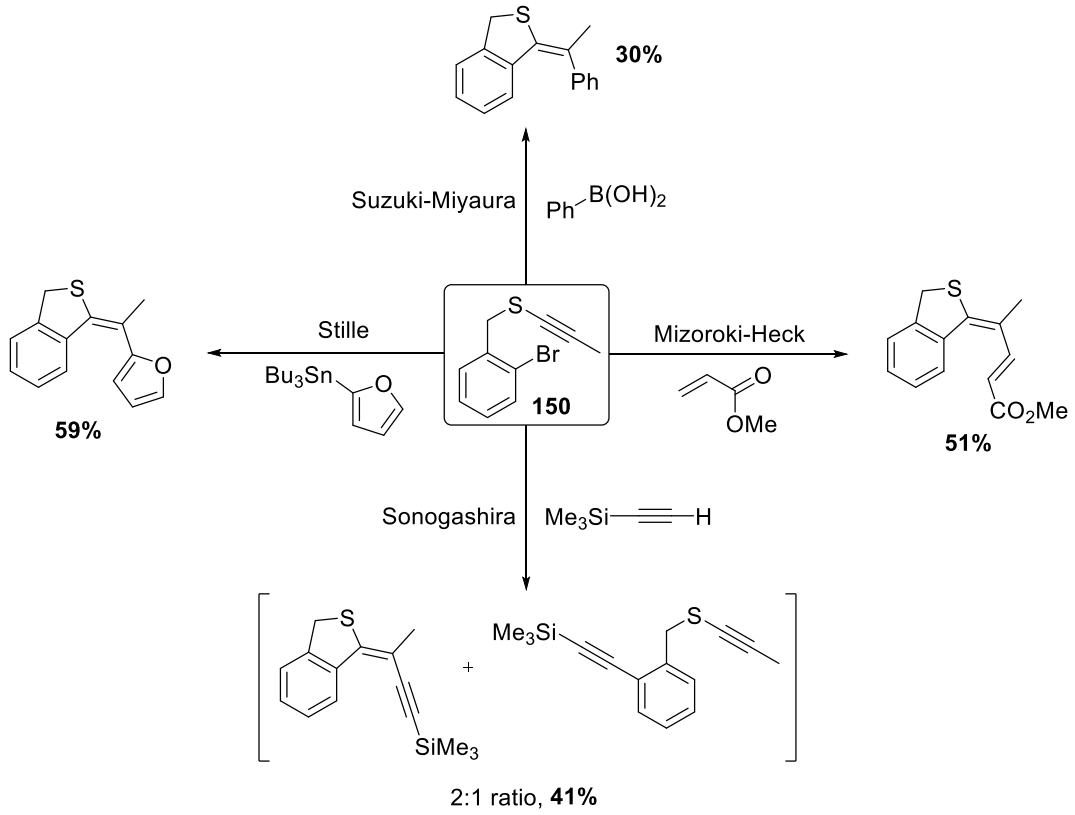


Scheme 1.69 – Transition metal-catalysed cross-coupling reactions of alkynyl sulfides

In 2001, Srogl *et al*. demonstrated a new method to obtain substituted alkynes *via* thioalkynes using boronic acids **146** in the presence of a copper salt and Pd-catalysis. Copper(I)-thiophene-2-carboxylate (CuTC) **147** and copper(I)-3-methylsalicylate (CuMeSal) **148** were effective reagents in this process.

Stoichiometric amounts of copper carboxylate were required in order to scavenge the thiolate anion and copper halide additives were found to be ineffective for this process. They then extended their Cu/Pd co-catalysed oxidative system (Umpolung complement to the Sonogashira protocol) which resulted in the formation of two synthetically useful products. Pd-catalysis was also used by Knochel *et al*. where they cross-coupled electrophilic organozinc compounds **149** rather than boronic acids **146** with thioalkynes. A good substrate scope is shown with tolerance for electron-donating and electron-withdrawing substituents. Recently, Gulea *et al*. reported a comparative study between propargylic and alkynyl sulfides with a range of cyclocarbopalladation reactions.[170]

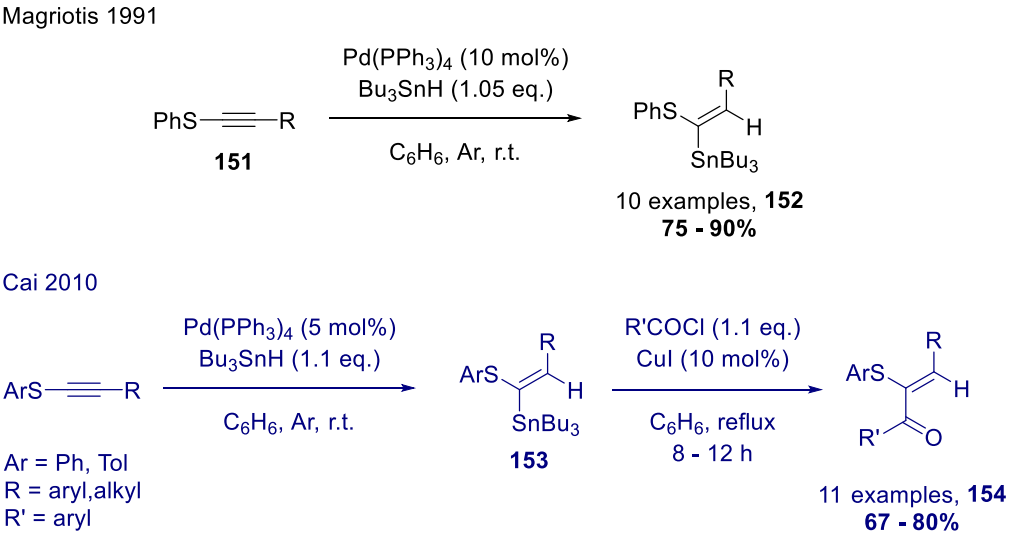
Gulea *et al*. presented successful cyclisation reactions *via* Stille, Suzuki-Miyaura, Sonogashira and Mizoroki-Heck couplings of a 2-bromobenzyl alkynyl thioether **150** (**Scheme 1.70**).[170] The authors proposed that if these coupling reactions had been carried out in the absence of Pd catalysis, halogen displacement would have occurred instead of cyclisation. The coupling products were unstable at times and resulted in relatively low yields (especially for the Suzuki-Miyaura protocol). Also, the Sonogashira reaction resulted in a 2:1 ratio of the desired cyclised product and an aryl diyne in relatively low yields. The final reaction (Mizoroki-Heck) gave 51% of the cyclised product which was lower than the propargylic thioether. The overall learning from this study was that propargylic thioethers underwent more efficient transformations. This could be due to the difference in reactivity of this class of compounds and alkynyl thioethers or it could be due to the potential favourability of 6-*exo*-dig over 5-*exo*-dig heterocycle formation.



Stille: $Pd(PPh_3)_4$ (10 mol%), PhH, 130 °C, μW, 3 h; **Suzuki-Miyaura**: $Pd(PPh_3)_4$ (10 mo%), K_3PO_4 (2.5 eq.), MeTHF/H_2O (98/2), 130 °C, μW,3 h; **Sonogashira**: $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), CuI (10 mol%), *i*Pr_2NH, 120 °C, μW, 30 min; **Mizoroki-Heck**: $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (2 eq.), Toluene, 125 °C, μW, 18 h

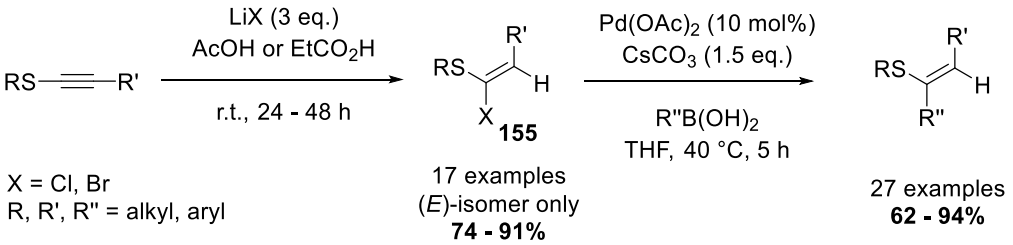
Scheme 1.70 – Gulea *et al*. cross coupling reactions with various coupling partners

Tri-substituted alkenes are another group of compounds that can be obtained from thioynol ethers. **Scheme 1.71** summarises some protocols such a hydrostannation[141,171] and hydrohalogenation[142,143] which describe relatively simple methods to obtain these synthetically useful compounds. Magriotis *et al*. developed a Pd-catalysed hydrostannation protocol converting phenylthioalkynes **151** to phenylthiol vinylstannanes **152**[141] which are useful synthetic intermediates.[172] The regioselectivity offered by the polarised nature of thioynol ethers allowed Magriotis and co-workers to achieve excellent regio- and stereocontrol. *Syn*-addition of tributyltin hydride ($SnBu_3H$) in the presence of a Pd catalyst gave a range of vinyl stannanes in good yields. An extension of this protocol was presented by Cai *et al*. treating the vinyl stannanes **153** with acyl chlorides to obtain (*Z*)-α-arylthio-α,β-unsaturated ketones **154** .[171] This tandem hydrostannation-Stille reaction was tolerant to a range of functional groups and good yields were attained but aliphatic acyl chlorides were ineffective electrophiles. The authors make no attempt to explain this but it could be attributed to delocalisation stabilising the intermediate.



Scheme 1.71 – Hydrostannation of alkynyl sulfides and further transformations

A recent method to (*E*)-α-halo vinyl sulfides **155** from alkynyl thioethers was presented by Zhu *et al*. using lithium halides in the presence on acetic or propionic acid.[143] The authors found a negative correlation between higher temperatures and stereoselectivity which suggests kinetic effects may control this reaction. Reaction optimisation found lithium chloride (LiCl) and acetic acid at room temperature to be most favourable. With a library of compounds at hand, the authors went on to further derivatise these substrates and carried out various cross-coupling reactions (**Scheme 1.72**).



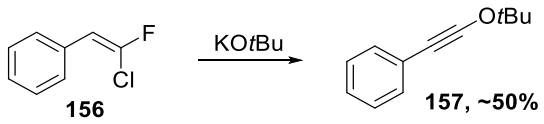
Scheme 1.72 – Zhu *et al*. hydrohalogenation of alkynyl sulfides and further functionalisation

Other than Schwan *et al*. route to dihydrothiophenes **144** (**Scheme 1.68**),[166] transition metal catalysis or activation of the sulfide is essential to transform alkynyl sulfides which demonstrates a relatively high level of stability.

1.5 Previous work in the Wilden group

1.5.1 Background

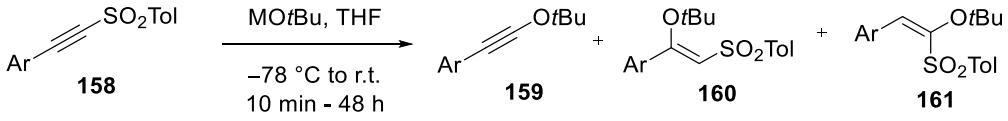
Addition of a sulfur-containing leaving group to a terminal alkyne is a more recently developed method for alkynyl ether synthesis. This has been successfully exploited by the Wilden group[173] where a sulfonamide moiety was added first to phenylacetylene and then the scope was developed to other derivatives. Treatment with alkoxides with and without amine additives furnished ynol ethers. It was Viehe who first discovered that KO*t*Bu could be utilised as a nucleophile as well as a base.[174] Addition of KO*t*Bu to a dihalogenated aryl alkene **156** furnished 50% yield of the aryl alkynyl ether **157** (**Scheme 1.73**). Viehe made no comment on how the 1-phenyl-2-chloro-2-fluoroethylene precursor **156** was synthesised and a review of the literature found the first reported method was published in 1967 (after this protocol).[175]



156 **157, ~50%**

Scheme 1.73 – Viehe's route to ynol ethers using KO*t*Bu as a nucleophile

A further progression from Wilden's sulfone-derived precursors was developed more recently by Ruano *et al*.[176] The addition of metal alkoxides to β-substituted alkynylsulfones **158** was initially found to result in formation of the desired ynol ethers **159** along with addition products **160** and **161** (**Scheme 1.74**).



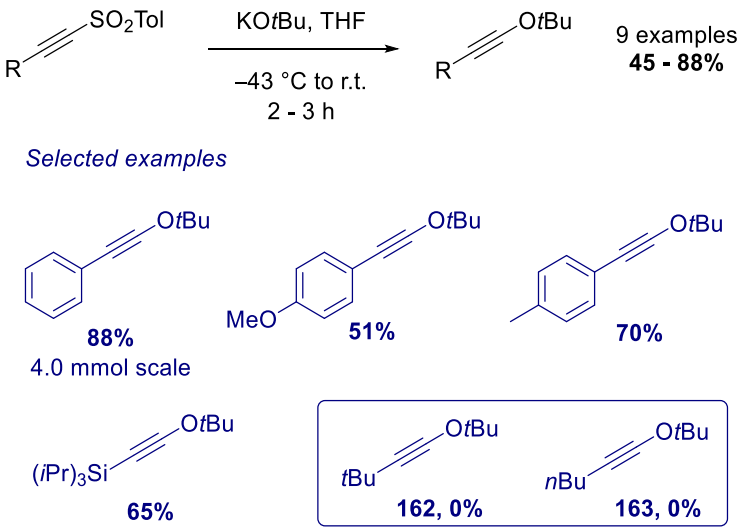
158 **159** **160** **161**

M = Li, Na, K

Scheme 1.74 – Addition of metal alkoxides to β-substituted alkynylsulfones

Interestingly, using NaO*t*Bu resulted in no reaction, regardless of temperature or proportion of the metal alkoxide. LiO*t*Bu gave a mixture of products in all instances – as well as the ynol ether product **159**, enol ether by-products **160** and **161** were also formed by Michael and *anti*-Michael addition reactions, respectively. These by-products could also be formed when using KO*t*Bu, however, Ruano *et al.* optimised

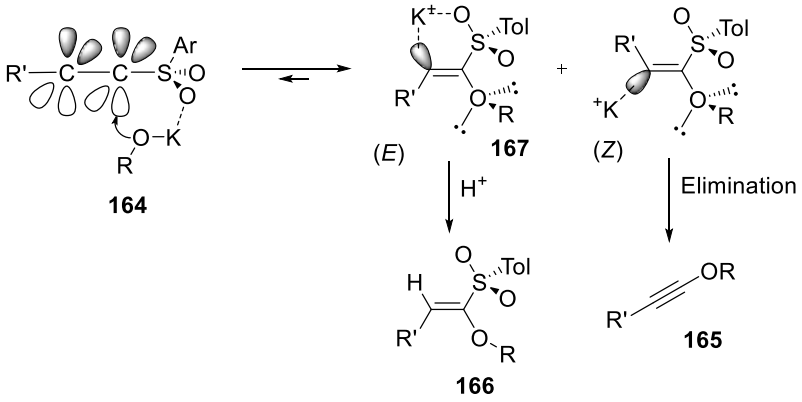
the reaction conditions to avoid this and went on to test the scope of the reaction (**Scheme 1.75**).



Scheme 1.75 – Ruano *et al*. *anti*-Michael addition of metal alkoxides to β-substituted alkynylsulfones

Both electron-donating and electron-withdrawing groups were successfully accommodated. Some aliphatic substrates proved difficult and *t*-butyl- **162** and *n*-butyl- **163** alkynyl sulfones resulted in no reaction. After optimisation, using KO*t*Bu with different sulfonylacetylenes yielded ynol ether products exclusively *via* an addition-elimination process.

The mechanism proposed for ynol ether synthesis involved *anti*-Michael addition of *tert*-butoxide at the more hindered α-carbon atom accommodated by potassium-oxygen interaction at the sulfone as shown in **164**. This was rationalised by the addition of 18-crown-6 ether inhibiting the reaction completely. Elimination of the sulfonyl leaving group from the vinyl anion intermediate then furnished the ynol ether products **165** (**Scheme 1.76**).

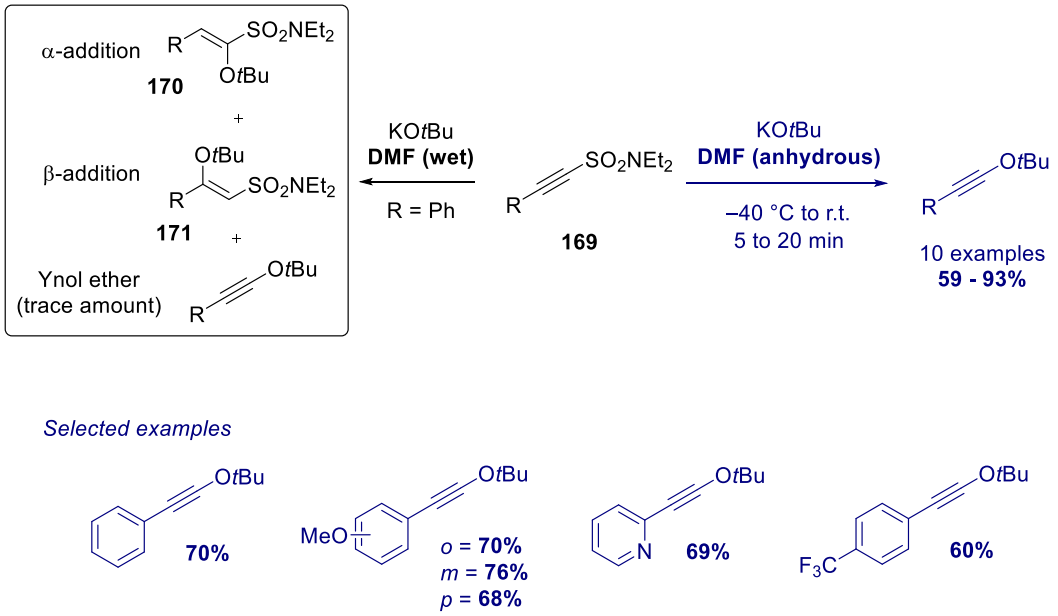


Scheme 1.76 – Proposed mechanism for Ruano *et al.* synthesis of ynol ethers from sulfones

Reasoning for the formation of the α-addition product **166** is also provided in **Scheme 1.76**. Coordination of the potassium cation with a sulfonyl oxygen in the manner shown in intermediate **167** gave the (*E*)-configuration, driving the reaction to undergo protonation to form enol sulfone **166**.

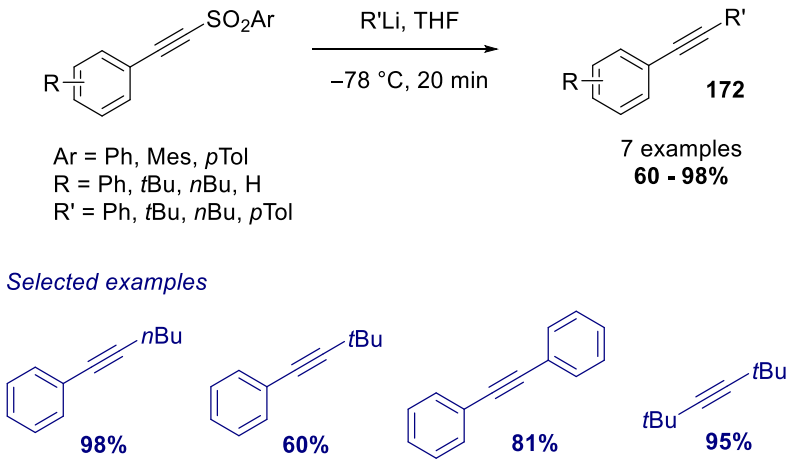
1.5.2 Previous work in the Wilden group

Ynol and thioynol ethers have been successfully synthesised in the Wilden group using sulfonamide-based precursors.[101,173,177,178] Initial observations showed that KO*t*Bu could be used to obtain trace amounts of acetylenic ethers from alkynyl sulfonamides **169** along with α- **170** and β-addition **171** products.[173] This was the result of using wet DMF as the solvent. Consequently, α- **170** and β-addition **171** products (enol ethers) could be trapped in the reaction. Swapping to anhydrous DMF resulted in exclusive formation of ynol ethers and a small library of substrates was prepared before attempting to gain a better understanding of the reaction (**Scheme 1.77**).



Scheme 1.77 – Gray and Wilden's initial observations using KO*t*Bu and alkynyl sulfonamide

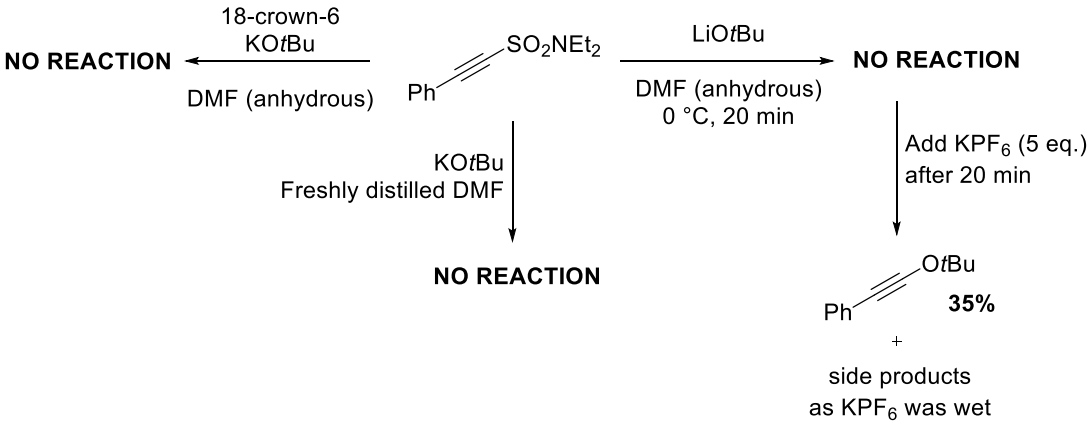
The electron-withdrawing sulfonamide group offers dual capacity as an efficient leaving group and as a radical stabiliser at the α-position.[179] The ability of sulfones and their derivatives to be readily displaced was first demonstrated by Truce and Smorada in 1979.[180] Treatment of arylsulfonyl precursors with alkyl lithium reagents gave acetylenes **172** exclusively in an *anti*-Michael addition (**Scheme 1.78**). This selectivity is attributed to an association of the sulfonyl oxygen atoms with lithium.[181]



Scheme 1.78 – Truce and Smorada's use of sulfones and sulfonamides in substituted acetylene synthesis

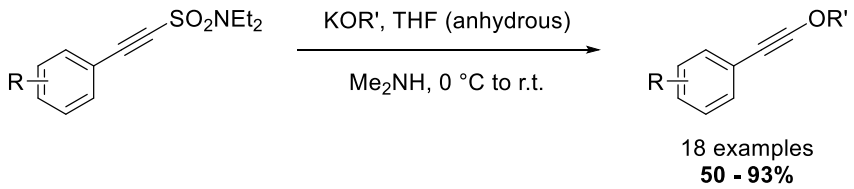
Use of sulfonamide as a leaving group remained underdeveloped until Milburn and Snieckus disclosed a reductive cleavage and cross coupling of tertiary aryl sulfonamides in 2004.[182] By utilising the electron withdrawing sulfonamide group instead of the traditional halide or triflate leaving groups, directing effects towards electrophilic aromatic substitution could be altered hence allowing functionalisation of the ring. In addition to this, Bordwell *et al.* demonstrated that sulfonyl groups have a deactivating effect on the α-position (as opposed to the activating effect of the carbonyl alternative or other electron withdrawing groups such as nitriles) and showed that this could be attributed to steric effects.[183,184]

After their initial findings, Wilden *et al*., went on to probe the mechanism by studying the role of each component. They showed that the potassium ion was vital for the formation of ynol ethers; highlighted by the addition of 18-crown-6 resulting in no reaction taking place. Additionally, lithium, sodium, aluminium, magnesium and barium counterions were all ineffective. Nevertheless, addition of potassium to these unsuccessful reactions salvaged them and ynol ethers were then formed (**Scheme** 1.79).[28,173,177]



Scheme 1.79 – Mechanistic studies on transition metal-free ynol ether synthesis

It was primarily suggested that the potassium ion may coordinate to the sulfonamide, the alkyne or the aromatic ring (or a mixture of these components), rendering the molecule susceptible to nucleophilic attack by the alkoxide anion. This was not fully explored to confirm if this is the case. Furthermore, the reaction appeared to be unique to DMF as the solvent, however, use of freshly distilled DMF gave no ynol ether. In fact, the dimethylamine (Me_2NH) impurity which developed in DMF over time was found to be essential for the success of the reaction. Repeating the reaction in a more practical solvent (hence, easier to remove from the reaction mixture), THF, with the amine additive gave ynol ethers in good yields (**Scheme** 1.80).



Scheme 1.80 – Transition metal-free synthesis of ynol ethers using a more convenient solvent

Other amine additives, such as DMEDA, diethylamine and pyrrolidine were also effective (yields of 78-83% were achieved). Amine additives which were ineffective for this transformation were 1,10-phen, *iso*propylamine, triethylamine, ammonia and pyrrolidin-1-ol (**Figure 1.15**). Due to the easy removal of Me_2NH (used as a commercially available solution in THF), this additive was employed in developing the scope of the reaction further.

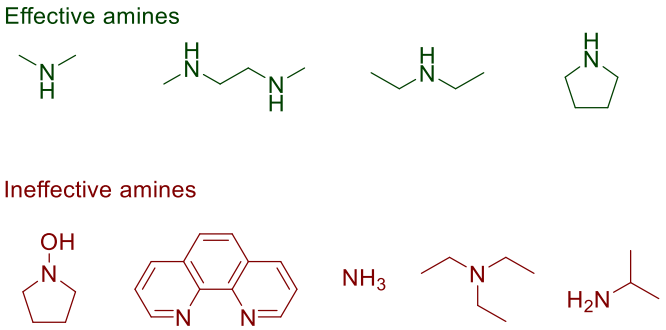


Figure 1.15 – Effective and ineffective amine additives in the formation of ynol ethers

A library of substrates was synthesised including both electron-rich and electron-deficient aromatic compounds in good yields.[177] Unfortunately, aliphatic substrates **173** proved unsuccessful; this could be due to a radical mechanism taking place which could require stabilisation by the delocalised aromatic system of the successful substrates. Also, various alkoxides (primary, secondary and tertiary) were accommodated but potassium trifluoroethoxide proved problematic. The addition of a second trifluoroethyl group is attributed to the additional electron-withdrawing capability of the trifluoroethyl group on the intermediate ynol ether; nucleophilic attack at the electron-poor carbon gave the ketene acetal **174** in 53% yield (**Figure 1.16**).

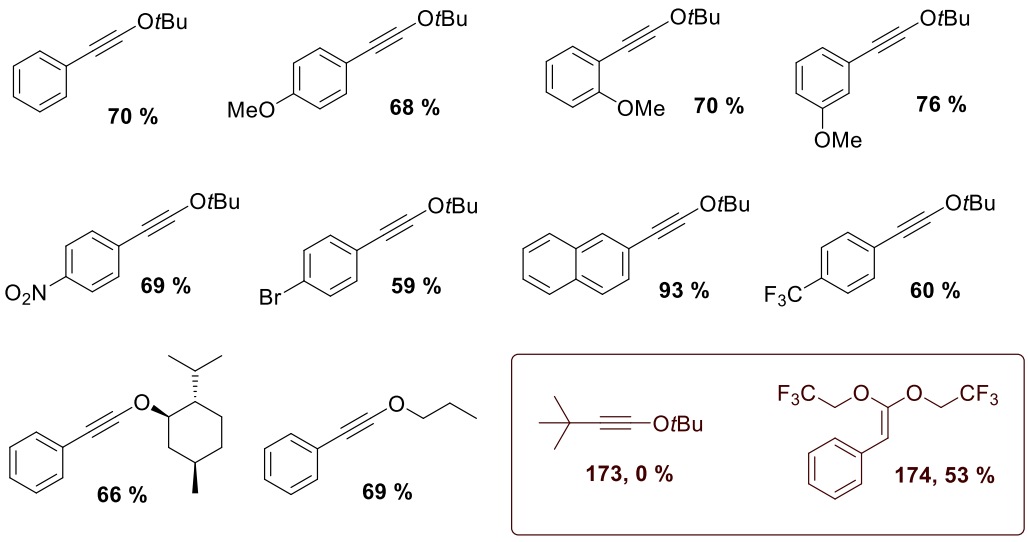
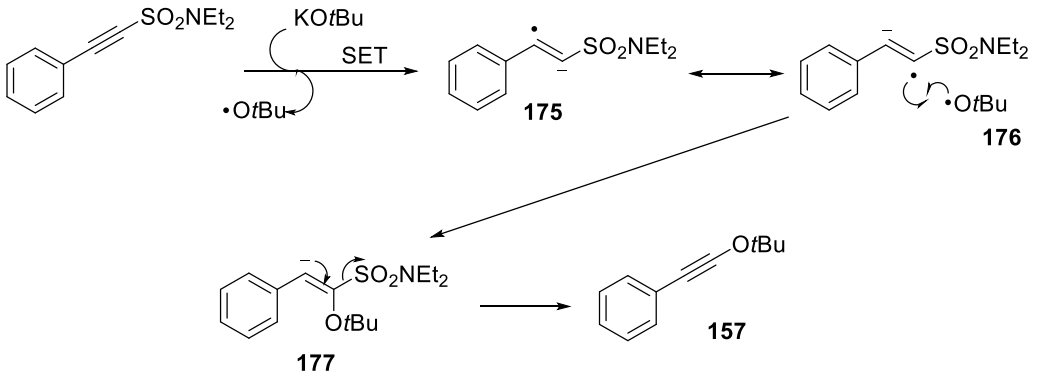


Figure 1.16 – A selection of substrates formed from Wilden *et al.* ynol ether synthesis

The protocol developed in the Wilden group was initially thought to proceed *via* an addition-elimination mechanism but further work in the group suggested a radical mechanism may be taking place. The mechanism was revised in light of more evidence suggesting a radical nature of such reactions.[185] The reaction was thought

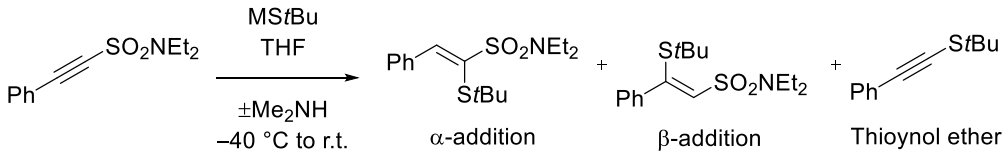
to involve an initial one-electron reduction of the starting alkyne. With the sulfonamide group facilitating the formation of the intermediate vinyl radical anion **175** and subsequent radical recombination with the alkoxide radical **176** (formed *in situ* from the parent alcohol and either KH or potassium metal) an enol anion intermediate **177** was proposed. This then collapsed and with loss of the sulfonamide leaving group, the ynol ether **157** was obtained (**Scheme 1.81**).[28]



Scheme 1.81 – Proposed mechanism for ynol ether formation *via* radical anion intermediate

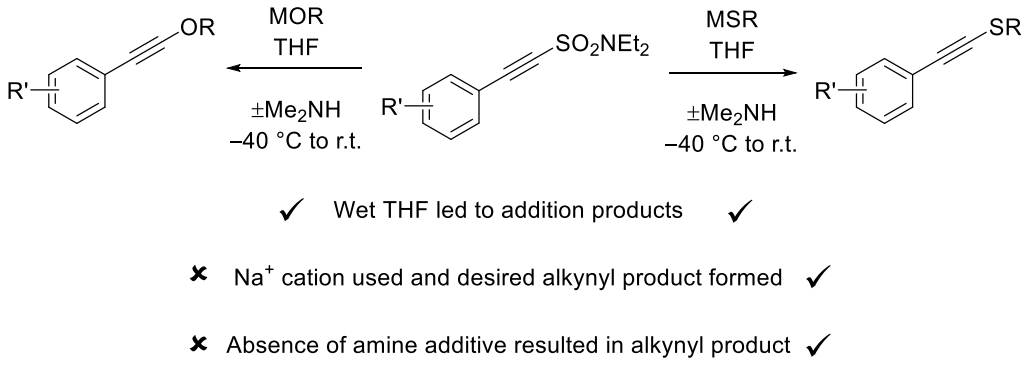
The stability of the alkoxide radical may seem unlikely to exist long enough to recombine, however, mechanistic studies show that these reactions can occur extremely fast. This could result in radical inhibitors such as TEMPO having little or no effect, as demonstrated by Wilden *et al*.[173] Furthermore, recent computational studies, to gain a better understanding of the vinyl radical anion, showed that there is more anion character on the carbon next to the ring and more radical character on the terminal carbon which justifies the addition of the *tert*-butyl radical at the terminal carbon.[186]

With this newly developed synthetic route at hand, it was recognised that *sp*-displacement could also be applied to obtain the sulfur analogues of ynol ethers. Initial studies into the impact of varying the conditions of the reaction resulted in a number of findings.[101] The reaction of a sulfonamide precursor with potassium and sodium thiolates were studied whilst varying the condition of the solvent, the temperature and the presence of an amine additive (**Scheme 1.82**).



Scheme 1.82 – Cuthbertson and Wilden's initial studies into thioynol ether formation from sulfonamides

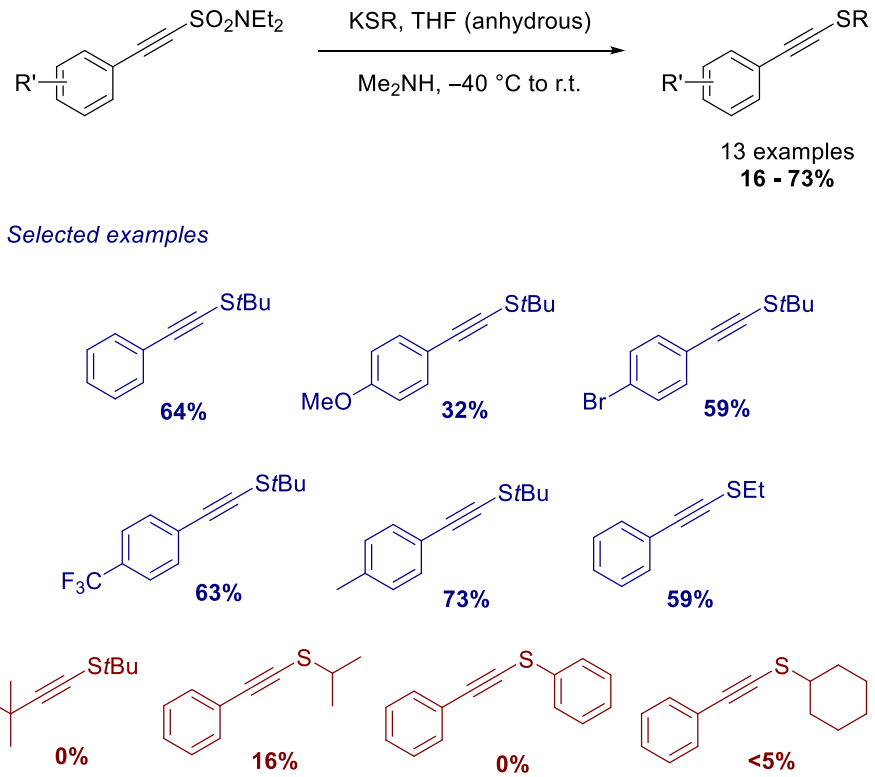
Firstly, using wet THF gave the addition products predominantly, with trace amounts of the acetylenic product. Again, this is attributed to water ingress allowing for the intermediate vinyl anion to be trapped before undergoing elimination so anhydrous THF was used going forward. An interesting difference was seen when employing the sodium cation where ynol ether synthesis was unsuccessful; the thioynol ether product was successfully obtained, albeit in a low yield (20%). The authors attribute this to the increased ability of thiolate anions to participate in SET reactions relative to alkoxide anions.[101] Another stark difference was the success of the reaction in the absence on an amine additive. This added to the mystery of the role it plays as its absence resulted in a more complex mixture of the products. **Scheme 1.83** outlines some of the similarities and differences found between ynol and thioynol ether synthesis.



Scheme 1.83 – Differences between ynol and thioynol ether syntheses from sulfonamides

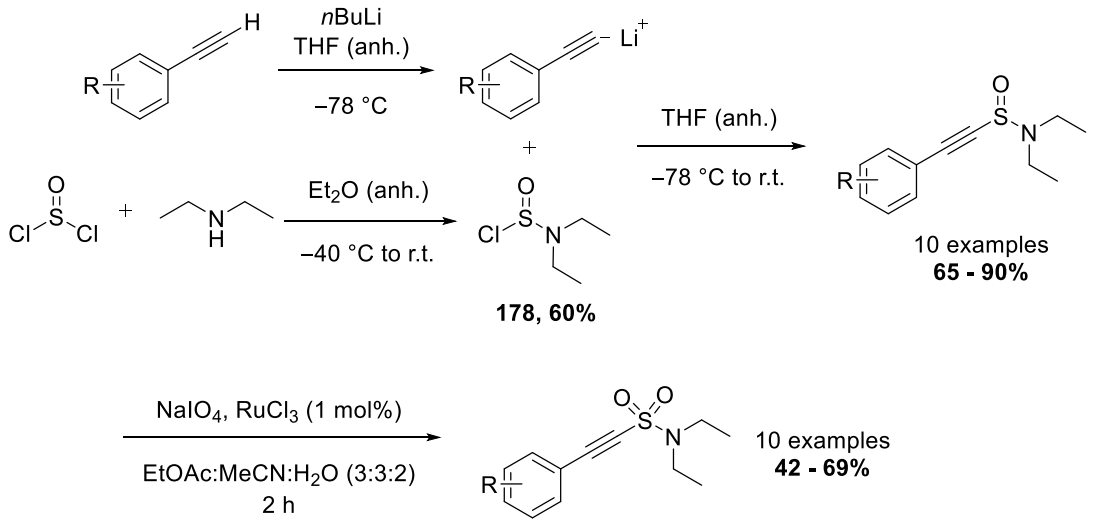
With optimised conditions identified, thioynol ethers were successfully obtained in reasonably good yields.[28,101] Various substituents were accommodated around the aryl ring along with different moieties on the sulfur atom. Regrettably, secondary thiol-derived substrates were problematic as predominantly α-addition products were formed and little or no thioynol ether. This could have been due to the presence of water in the parent thiol but this was not confirmed. Furthermore, aliphatic substituents on the alkyne continued to pose a problem. This offered potential

evidence of the proposed radical-mediated mechanism as the aryl substituent could stabilise intermediates *via* delocalisation (**Scheme 1.84**).



Scheme 1.84 – Synthesis of thioynol ethers from alkynyl sulfonamides

Synthesis of the sulfonamide precursors by a process developed by Baudin *et al.*[187] can prove difficult as the intermediate *N,N*-diethylsulfurous chloride **178** can be difficult to handle due to its volatility and when carrying out the oxidation step with sodium periodate and ruthenium(III) chloride, low yields are obtained at times (**Scheme 1.85**).

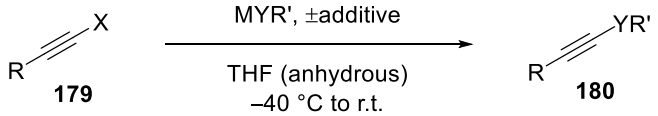


Scheme 1.85 – Four step synthesis of sulfonamide precursors used in ynol ether synthesis

2. Results and Discussion

2.1 Aims

It became clear that an improved strategy could be developed with greater atom economy where precursors were easier to prepare and handle. This led to the investigation into the use of alkynyl halides **179** in a transition metal-free *sp*-displacement method to obtain ynol and thioynol ethers in the presence of an alkali metal chalcogenide **180** with the possible addition of an amine mediator (**Scheme 2.1**).



X = Cl, Br, I
Y = O, S
M = K, Na, Li

Scheme 2.1 – General scheme for work presented in this thesis

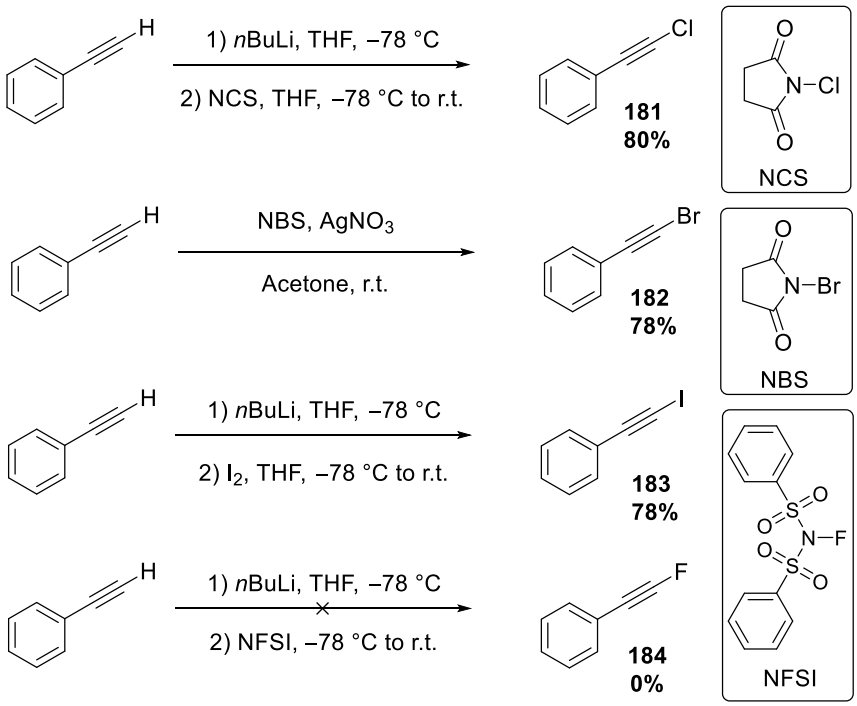
The results presented in this section will present differences in reactivity of the haloalkynes and demonstrate the steps carried out to attempt to optimise conditions for the synthesis of ynol and thioynol ethers in the absence of transition metal catalysis. The effect of various additives will be explored and mechanistic insights will be discussed.

Preliminary studies into the uses of thioynol ethers and some of their derivatives will also be disclosed with a focus on the surprisingly stable nature of aryl alkynyl thioethers.

2.2 New route to ynol ethers from acetylenic halides

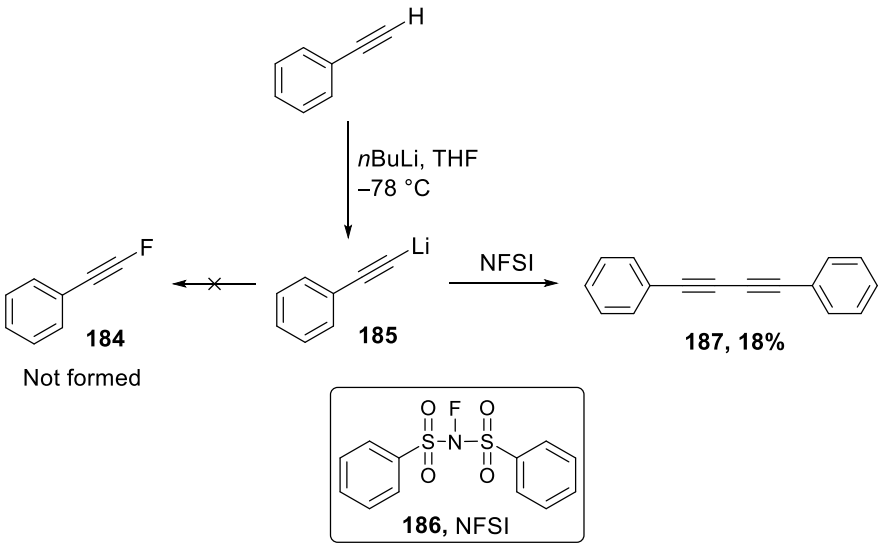
2.2.1 Precursor synthesis and preliminary studies

After recognising that non-trivial precursor synthesis could be avoided, a simpler approach to ynol ethers using a halide leaving group was attempted. The halide precursors could be prepared in a single step from the parent alkyne *via* known literature procedures,[188–192] making this more atom efficient than using other precursors such as alkynyl sulfonamides. **Scheme 2.2** outlines the literature procedures used to obtain chloro- **181**,[188,189] bromo- **182**[190,191] and iodoalkynes **183**.[192]



Scheme 2.2 – Synthesis of precursors (haloacetylenes)

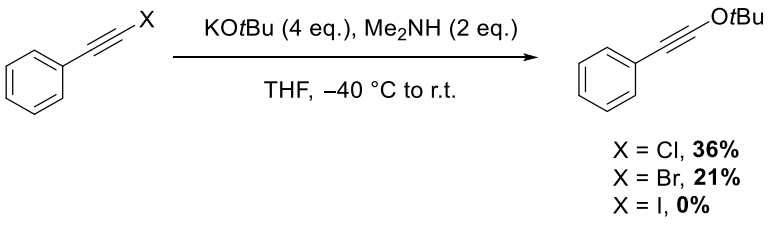
Synthesis of the fluoroacetylene analogue **184** was attempted using Ma *et al*. literature procedure[193] (**Scheme 2.3**). Deprotonation of the parent alkyne using *n*BuLi gave the lithium phenylacetylide **185** which was subsequently treated with the electrophilic fluoride source, *N*-fluorobenezenesulfonamide (NFSI) **186**. Surprisingly, these conditions did not yield the desired product **184**. NMR analysis indicated these conditions resulted in the formation of diyne **187**, contradicting Ma *et al*. fluorination protocol which has since been retracted (**Scheme 2.3**).[193]



Scheme 2.3 – Unsuccessful synthesis of fluoroalkyne using Ma *et al*. route

No further attempts were made to synthesise the fluoroalkyne **184** as literature precedent suggested that these compounds are highly reactive and tend to oligomerise, which is possibly what happened in Ma *et al.* method.[194–196]

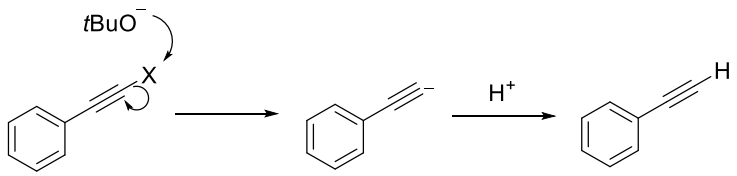
Each haloalkyne which was successfully isolated **181-183** was subjected to the transition metal-free reaction conditions previously developed in the Wilden group[173] as shown in **Scheme 2.4**. On treatment with the mixture of KO*t*Bu and Me_2NH, full consumption of chloro- **181** and bromo(ethynyl)benzene **182** was achieved after 4 h and 18 h, respectively. The desired alkynyl ether was formed in each instance, although yields were disappointing (**Scheme 2.4**). Intriguingly, treatment of iodophenylacetylene **183** with the same reaction conditions did not result in the formation of the ynol ether product **157;** only starting material was recovered, even after prolonged reaction times.



Scheme 2.4 – A route to ynol ethers using alkynyl halides

The low yields, and lack of reaction in the case of the iodoalkyne, could be attributed to a well-documented, facile X-philic reaction[197] competing with ynol ether formation, resulting in the parent alkyne reforming as a result of trace amounts of moisture in

the reaction. The trend in reactivity of the alkynyl haloacetylenes could be rationalised by the nature of the hard *tert*-butoxide anion and the relative strength of the carbon-halogen bonds. The stronger C-Cl bond was able to withstand the X-philic attack, at least to some degree; whereas, the weaker C-I bond was more susceptible to the X-philic reaction (**Scheme 2.5**).



Scheme 2.5 – X-philic reaction of *tert*-butoxide anion with halophenylacetylene

In an attempt to optimise the reaction conditions and improve the yield of ynol ether product, an extensive study was carried out on: the effect of the halide leaving group, the reaction temperature and the use of an additive (**Table 1**). The time recorded refers to the time taken for the starting haloalkyne to be fully consumed and yields refer to isolated yields.

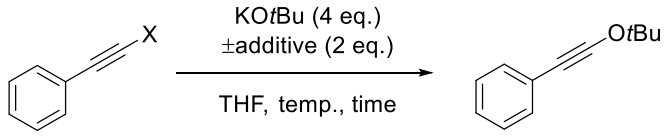
Temperatures which were studied included −78 °C, room temperature, 40 °C and 60 °C. The study looked at the effect of different amine additives: Me_2NH, DMEDA and 1,10-phen, as well as including reactions in the absence of an additive.

Making one out of the three variables constant, one at a time, allowed for a deeper understanding of the impact of altering the halide leaving group, temperature and additive on 1) the time taken for full consumption of the starting haloalkyne and 2) yield of ynol ether formation. Summaries of the trends according to the variable factors are presented here with possible rationalisations proposed alongside.

2.2.2 Observations/trends broken down for each haloacetylene

Results presented in **Table 1** show trends for the haloacetylene series, broken down into columns **A-C** for the haloalkyne used for those particular experiments (**A**=Cl, **B**=Br, **C**=I). Reactions will be referred to in the format **1A-16C**; the number referring to a row (**Entries 1-16**) which outlines the unique mixture of conditions used in each instance. In order to draw sound conclusions from observed trends, this table will be broken down to focus on certain sets of conditions at a time (**Table** 1).

Table 1 – All results for attempted ynol ether synthesis from haloalkynes

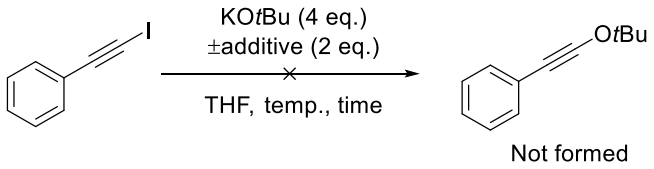


X = Cl, Br, I

Temp.	Amine	Entry	**A:** X = Cl		**B:** X = Br		**C:** X = I	
			Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
−78 °C to r.t.	Me_2NH	**1**	20	29	20	11	48	0
	DMEDA	**2**	20	24	20	13	48	0
	1,10-phen	**3**	20	22	20	10	48	0
	No amine	**4**	20	6	20	11	48	0
r.t.	Me_2NH	**5**	4	36	18	21	24	0
	DMEDA	**6**	6	29	18	0	24	0
	1,10-phen	**7**	3	27	3	0	24	0
	No amine	**8**	18	29	18	20	24	0
40 °C	Me_2NH	**9**	3	25	3	10	18	0
	DMEDA	**10**	5	13	6	0	18	0
	1,10-phen	**11**	2	24	2	0	24	0
	No amine	**12**	5	27	6	19	24	0
60 °C	Me_2NH	**13**	5 min	24	10 min	6	14	0
	DMEDA	**14**	5 min	12	10 min	0	5 min	0
	1,10-phen	**15**	<5 min	0	<5 min	0	<5 min	0
	No amine	**16**	5 min	17	10 min	4	14	0

- All yields given are isolated yields; Conditions: 1) KOtBu, additive, THF, argon, r.t., 10 min;
2) Haloalkyne (0.4 mmol), THF, argon, temp., time.
- For all entries at −78 °C to r.t., reactions were run at −78 °C for 4 h then allowed to warm to r.t.
- Iodoalkynes resulted in recovered SM; mass balance for chloro- and bromoalkynes were made up with decomposed material in addition to the product yields noted in the table

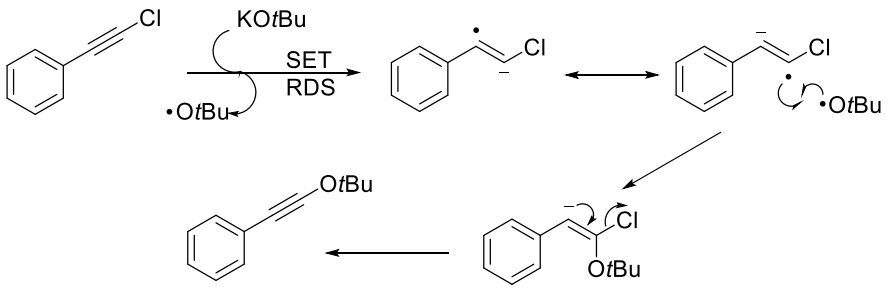
Immediately, it is clear that, iodo(phenylacetylene) **183** was not a suitable precursor in ynol ether synthesis under these conditions, regardless of the presence of an additive or temperature applied (**Column C**) (**Scheme 2.6**).



Scheme 2.6 – The unsuccessful conversion of iodoacetylene to *tert*-butyl ynol ether

Although the desired ynol ether was not isolated, there were observed differences in the rate of consumption of the starting material, iodoacetylene. Analysis indicated there was no obvious difference between additives used on the reaction outcome until the temperature was increased to 60 °C when the experiments where DMEDA and 1,10-phen were used, where full consumption of the starting alkyne was observed within minutes (**Entries 14C and 15C**). On the other hand, reactions in the absence of an amine and using Me_2NH, in turn, still took 14 h to fully consume starting material (**Entries 13C and 16C**). Use of 1,10-phen had the same effect at 60 °C on the other haloalkynes (**Entries 15A and 15B**), however, for DMEDA, this appeared to be an anomaly, therefore rationalisation of this trend was problematic.

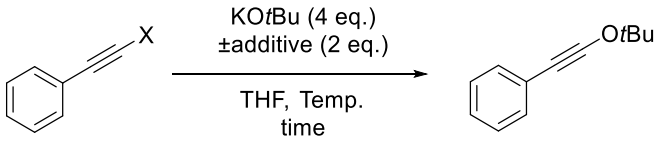
Owing to the relative strength of the C-Cl bond, chloroalkynes are often rendered the least useful of the haloalkynes, especially in reactions involving oxidative insertion, where transition metals are used for example. This reversal in reactivity seen in the transition metal-free *sp*-displacement described herein could be explained by the higher electronegativity of chlorine. Electron transfer is more likely to be the rate-determining step rather than C-X bond cleavage (**Scheme 2.7**) and therefore using a chloride precursor offers an advantage.



Scheme 2.7 – Possible mechanism for conversion of chloroacetylene to ynol ether

Chloro(phenylacetylene) **181** was the best-performing precursor under all conditions and ynol ether formation was achieved, except in the case of **Entry 15A**. At 60 °C, employment of 1,10-phen resulted in consumption of the chloroalkyne within minutes yielding only decomposed material. Another result which stands out is **Entry 4A** where a very low yield of 6% of ynol ether **157** was seen which appears to be inconsistent and difficult to rationalise.

Table 2 – Chloro- and bromo(phenylacetylene) used: effect on time and yield of ynol ether formation



X = Cl, Br

Temp.	Amine	Chloroalkyne (A)			Bromoalkyne (B)		
		Entry	Time (h)	Yield (%)	Entry	Time (h)	Yield (%)
−78 °C to r.t.	Me_2NH	**1A**	20	29	**1B**	20	11
	DMEDA	**2A**	20	24	**2B**	20	13
	1,10-phen	**3A**	20	22	**3B**	20	10
	No amine	**4A**	20	6	**4B**	20	11
r.t.	Me_2NH	**5A**	4	36	**5B**	18	21
	DMEDA	**6A**	6	29	**6B**	18	0
	1,10-phen	**7A**	3	27	**7B**	3	0
	No amine	**8A**	18	29	**8B**	18	20
40 °C	Me_2NH	**9A**	3	25	**9B**	3	10
	DMEDA	**10A**	5	13	**10B**	6	0
	1,10-phen	**11A**	2	24	**11B**	2	0
	No amine	**12A**	5	27	**12B**	6	19
60 °C	Me_2NH	**13A**	5 min	24	**13B**	10 min	6
	DMEDA	**14A**	5 min	12	**14B**	10 min	0
	1,10-phen	**15A**	<5 min	0	**15B**	<5 min	0
	No amine	**16A**	5 min	17	**16B**	10 min	4

- All yields given are isolated yields; Conditions: 1) KOtBu, additive, THF, argon, r.t., 10 min; 2) Haloalkyne (0.4 mmol), THF, argon, temp., time.
- For all entries at −78 °C to r.t., reactions were run at −78 °C for 4 h then allowed to warm to r.t.
- Mass balance for chloro- and bromoalkynes were made up with decomposed material in addition to the product yields noted in the table

The best results for both chloro- **181** and bromoalkynes **182** were achieved at room temperature using Me_2NH (**Entries 5A and 5B**). In contrast, the absence of an amine additive resulted in prolonged reaction time for the chloroalkyne (**Entry 8A**);

this suggests that the amine additive may aid the initiation step, which, as mentioned, is likely to be the rate determining step.

Looking at the results for the bromoalkyne, the most striking difference from the chloroalkyne is the complete lack of conversion using DMEDA or 1,10-phen at temperatures above −78 °C (**Entries 6-7B, 10-11B, 14-15B**). Interestingly the absence of an additive seems to have the least impact on the bromoalkyne reactions; comparing the use of Me_2NH and no amine, results are very similar (**Entries 1B vs. 4B, 5B vs. 8B)**.

In fact, at 40 °C, the absence of an amine additive resulted in almost double the yield of ynol ether (**Entry 12B**) compared to the reaction using Me_2NH at the same temperature (**Entry 9B**). This lower yield along with the lowering of the reaction time to 3 h in the presence of Me_2NH (**Entry 9B**) may suggest that in this case, the amine additive assists with side reactions which result in decomposition of the starting material, rather than conversion to the desired ynol ether product **157**.

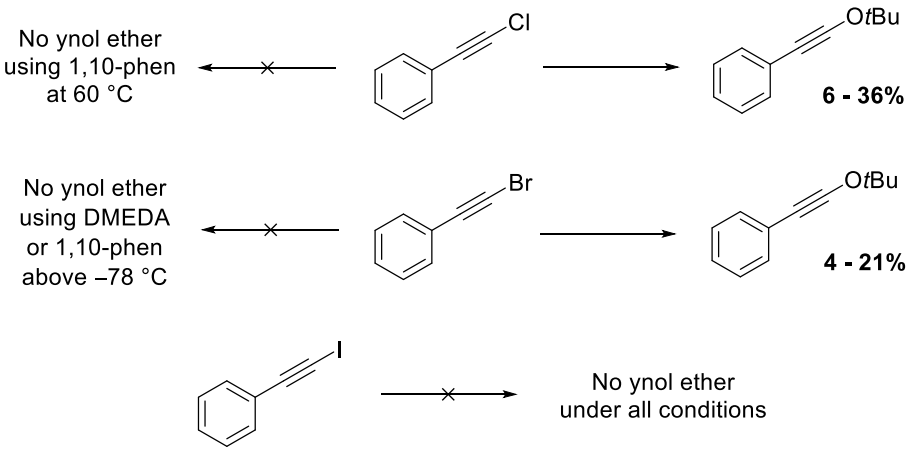
2.2.3 Summary of the effects of different temperatures

Reducing the temperature to −78 °C resulted in little or no consumption of starting material, therefore warming to room temperature was required in each case (**Rows 1-4**). The optimum temperature to achieve the highest yields in this study appeared to be room temperature (**Rows 5-8**) as yields reduced as reactions were heated to 40 and 60 °C (**Rows 9-16**). The rate of consumption of the haloacetylene precursors, on the other hand, increased alongside temperature, which is perhaps obvious as this would be expected from a thermodynamic point of view.

2.2.4 Summary of the effects of different amines

Adding Me_2NH delivered the best results in this study in terms of both comparatively high yield and relatively short reaction times. Employing DMEDA provided varies results which adds to the elusive nature of these amine additives. The relative difficulty in controlling reaction where 1,10-phen is used has been described previously;[29] however, the variations in mechanisms and modes of action of these different additives in transition metal-free reactions are yet to be confirmed.

Scheme 2.8 summarises the learnings from this study. Disappointingly, yield of ynol ether was not improved beyond 36% which was achieved using the chloroacetylene in the presence Me_2NH at room temperature.

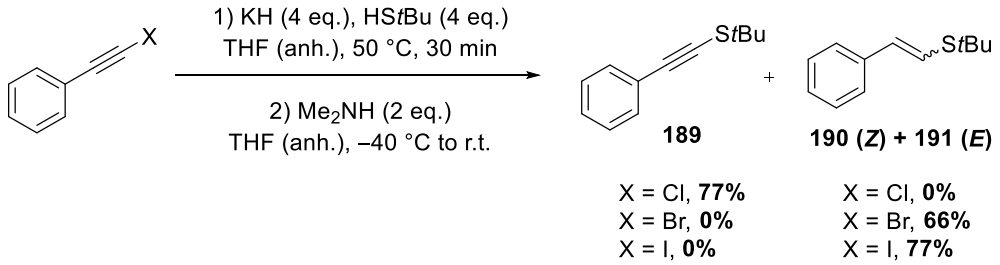


Scheme 2.8 – Summary of results for attempted ynol ether synthesis from aryl haloalkynes

Further work to improve yields of ynol ether product from halo(phenylacetylene) precursors was not attempted. In order to explore the applicability of this protocol, attention was diverted to the synthesis of thioynol ethers instead. Excellent results were obtained in preliminary studies and therefore focus was shifted to alkynyl sulfides. The applicability of the protocol resulted in published work which will be discussed in the next section.[198]

2.3 New route to thioynol ethers from acetylenic halides

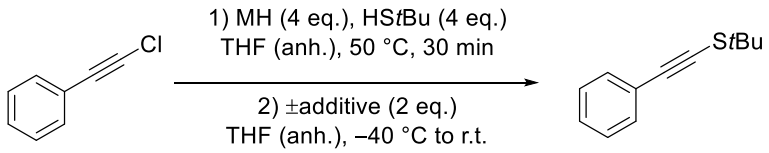
Exposure of each of these acetylenic halides to the potassium salt of *tert*-butyl thiol (formed *in situ*) under the conditions outlined in **Scheme 2.9** led to varied results depending on the alkynyl halide employed.[198] Pleasingly, chlorophenylacetylene led exclusively to the desired thioynol ether product **189** in good yield *via sp*-displacement of the chloride leaving group (77%). On the other hand, bromo- and iodophenylacetylene gave rise to alkenyl sulfides **190 and 191** and no acetylenic ether product (**Scheme 2.9**). This thioenol ether formation will be discussed in more detail later in this chapter.



Scheme 2.9 – Initial observations of KS*t*Bu addition to alkynyl halides in presence of Me_2NH

Firstly, a qualitative study was carried out with chlorophenylacetylene **181** to determine the importance of the alkali metal counterion by replacing KH with lithium hydride (LiH) and sodium hydride (NaH), in turn; the results are presented in **Table** 3.

Table 3 – Results: effect of alkali metal used with and without additive (Me_2NH or DMEDA)

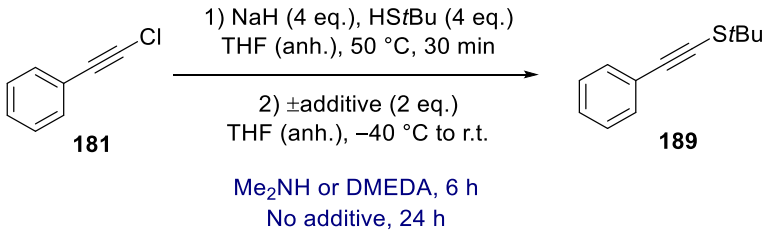


M = Li, Na, K; Additive = Me_2NH, DMEDA

M^+	**Me_2NH**		**DMEDA**		**No additive**	
	Time (h)	Yield (%)*	Time (h)	Yield (%)*	Time (h)	Yield (%)*
Li^+	>72	0	>72	0	>72	0
Na^+	6	51	6	44	24	27
K^+	1–2	77	1–2	73	4	57

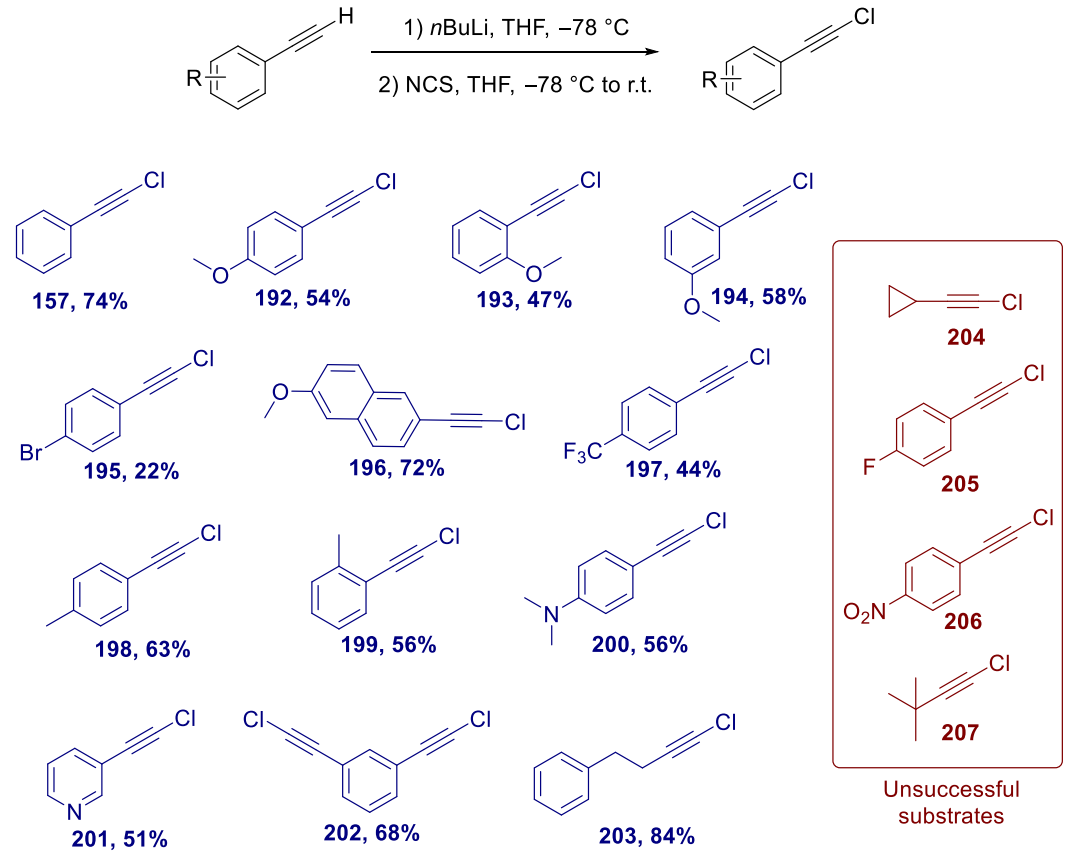
*Isolated yields of thioynol ether product formed

Employing LiH resulted in very slow consumption of starting material with no thioynol ether product formation, even after 72 h – only decomposed material and recovered starting material was present. The use of NaH was more successful, resulting in thioynol ether products, albeit in lower yields and at a slower rate of consumption than when KH was used. With Me_2NH or DMEDA, using the sodium thiolate salt took 6 h to consume the starting material completely and with no additive, the reaction took 24 h (**Scheme 2.10**).



Scheme 2.10 – Impact of using sodium thiolate salt on thioynol ether formation

Attention was then turned to investigating the reaction scope. Initially, a range of alkynyl chlorides were prepared from commercially available acetylenes by the literature procedure described earlier. Both electron-donating and electron-withdrawing groups were well-accomodated (**Scheme 2.11**).



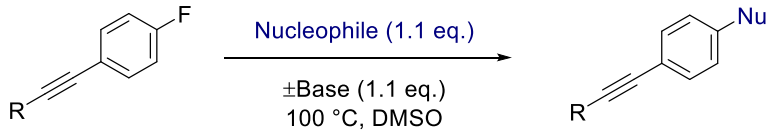
Scheme 2.11 – Substrate scope for chloroalkynes

In general, this protocol yielded the desired product in moderate to high yields (44-84%), with the exception of *p*-bromophenylchloroacetylene **195** (22%). The low yield for this substrate is most likely due to an undesired metal–halogen exchange reaction when exposed to *n*BuLi.

Remarkably, several novel compounds were prepared (**196, 201-203**) which could be used in further transformations and offer an interesting range of functionalities. Diyne **202** and the alkyl chloroacetylene **203**, for example, could provide relatively easy access to polycycle precursors which could have potential use in synthesising medicinally important compounds.

Substrates which proved difficult to prepare are highlighted in **Scheme 2.11**. Cyclopropylchloroacetylene **204** was not formed at all, possibly due to volatility of the starting material. Furthermore, due to side reactions taking place, attempts to make the *p*-nitro- **206** and *p*-fluoro- **205** substrates were also unsuccessful. This could be due to a documented side reaction taking place, whereby attack at the substituent position is predominant.[199] Due to the difference in electronegativity

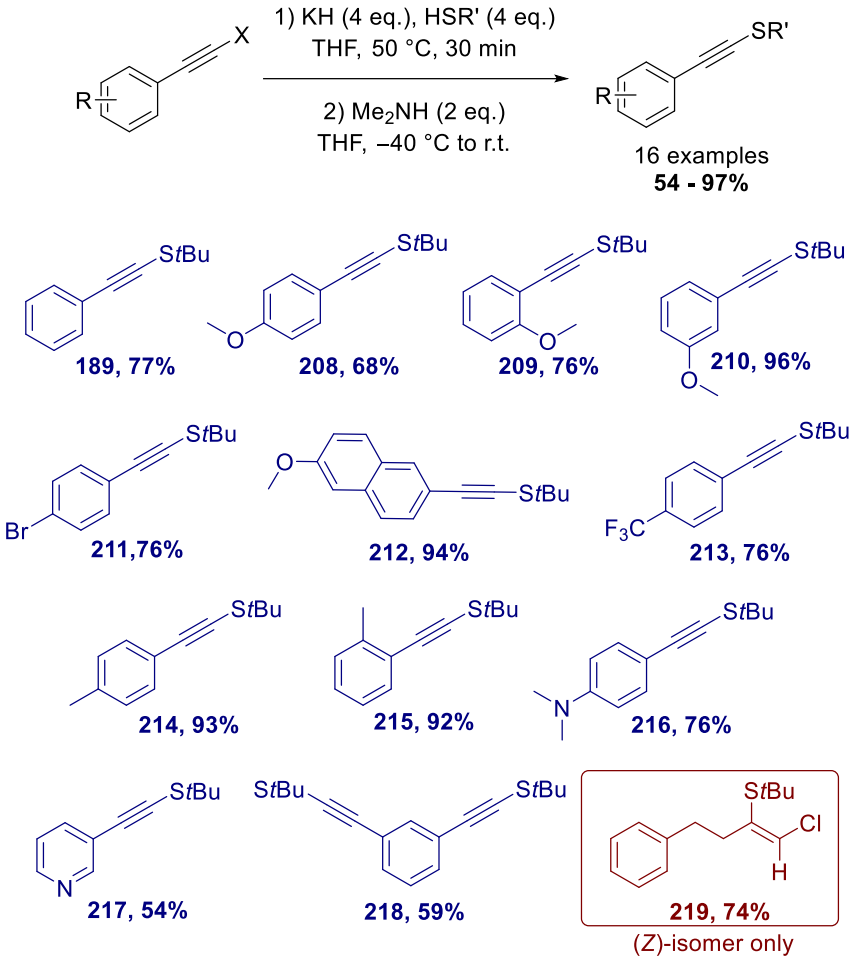
between the halides, this is not observed for the *p*-bromo- substrate **195**. Katz *et al.* demonstrated the scope of this reaction with a range of nucleophiles and bases; the authors portrayed the capacity of the alkyne group to act as an electron-withdrawing activating group. Perhaps surprisingly, alkynes have been found to be as good at promoting nucleophilic aromatic substitution as a nitro group (**Scheme 2.12**).[199]



R = H, Ph, *t*Bu
Nu = *p*-cresol, *o*-cresol, EtOH, *i*PrOH, KO*t*Bu, allyl alcohol, benzyl alcohol, *p*-toluidine, *o*-toluidine
Base = KO*t*Bu, NaH

Scheme 2.12 – Katz *et al*. demonstration of electron-withdrawing capacity of alkyne group

Exposure of the successfully formed acetylenic chlorides to the potassium salt of *tert*-butyl thiol under the conditions yielded the small library of acetylenic sulfides in good to excellent yields (**Scheme 2.13**).

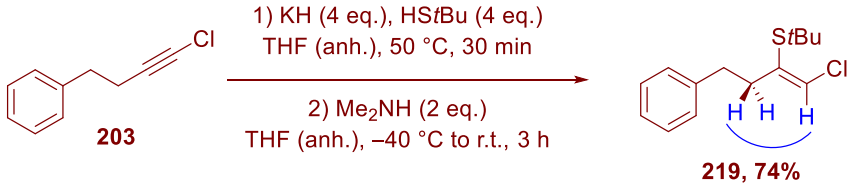


Scheme 2.13 – Substrate scope for alkynyl sulfides formed from chloroalkynes

The procedure was shown to be successful with both electron-donating and electron-withdrawing groups around the aromatic ring, however, aliphatic substrates could not be prepared. This problem has been encountered during previous work in the group and could hold importance when considering the mechanism. Delocalisation on the aromatic substituent could be essential in stabilising the aryl radical anion intermediate.

Interestingly, but perhaps unsurprisingly, the chloroalkyne **203** formed from but-3-yn-1-ylbenzene did not yield the desired thioynol ether when subjected to the reaction conditions (**Scheme 2.11**). The single geometrical isomer of the alkenyl product **219** was obtained instead of the thioynol ether; this could be attributed to the aromatic group not being directly attached to the alkyne. Analysis by NMR spectroscopy and mass spectrometry, the (*Z*)-isomer of the chloroalkenyl sulfide **219** is seen to be formed exclusively as shown in **Scheme 2.14**. A NOESY spectrum was used to determine the stereoselectivity of **219** where a cross peak

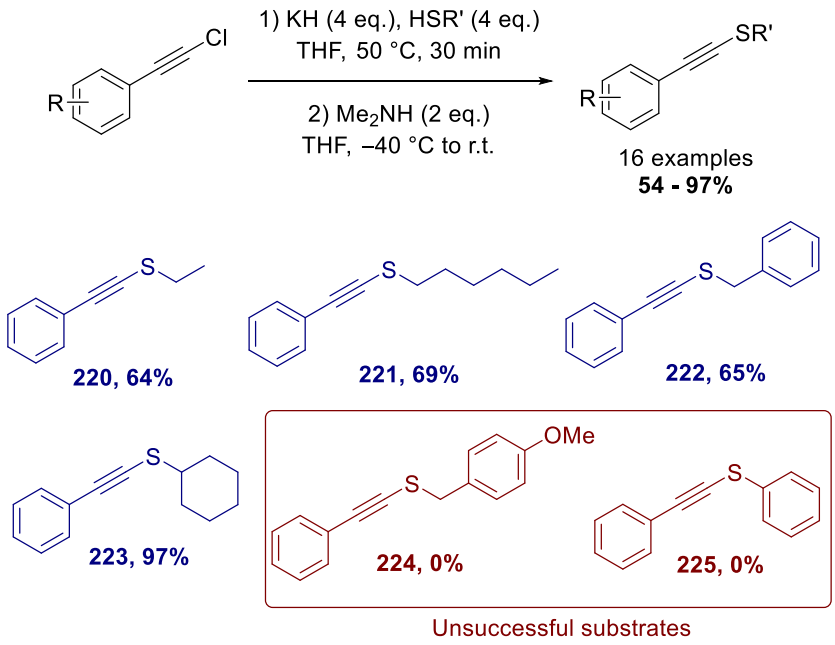
signal appears between the alkenyl proton and the protons two carbons away as shown in **Scheme 2.14.**



Scheme 2.14 – Michael addition in the absence of an aryl group directly adjacent to alkyne

Rationalising this is difficult as the steric bulk of the *tert*-butyl thiol group and the chlorine could be expected to cause hindrance. It is interesting, nonetheless that just one isomer is formed exclusively. For the successfully-transformed substrates shown in **Scheme 2.13**, in addition to varying the groups around the aromatic ring, the pyridyl derivative **217** and the diyne **218** were also successfully obtained, both of which could be potential precursors in further transformations.

Thiolate scope was also investigated: substituting *tert*-butyl thiolates with various analogues furnished the corresponding thioynol ethers in good to excellent yields (**Scheme 2.15**).



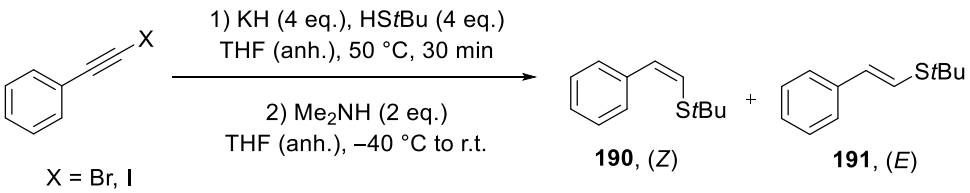
Scheme 2.15 – Further scope for alkynyl sulfides with various substituents on sulfur

Pleasingly, all of the substrates which had previously been prepared from alkynyl sulfonamide precursors[28] were obtained in higher yields from

chloro(phenylacetylene) starting materials. The most significant increase in yield was observed for the (cyclohexyl)thiol-derived substrate **223** (97%) which was only obtained in <5% yield from the sulfonamide precursor. On the other hand, an attempt to prepare novel alkynyl sulfide **224**, which could provide the means for further functional group manipulations, was unsuccessful and resulted in decomposition. Addition of the potassium salt of thiophenol to the alkynyl chloride also resulted in no thioynol ether **225** formation which was also the case in previous work in the Wilden group. This was attributed to the reduced electrophilicity of the thiophenol radical compared to alkyl variants which worked well.[101]

As introduced earlier, bromo- and iodoalkynes afforded the thioenol ether instead of the desired thioynol ether product. Use of Me_2NH or DMEDA as the additive with the bromoalkyne resulted in a similar ratio of geometrical isomers; mainly the (*Z*)-isomer **190** (~9:1 ratio). Absence of an additive resulted in around 4:1 ratio of *Z*:*E* isomers, highlighting the potential important role played by the amine additives (**Table 4**).

Table 4 – Thioenol ether formation from bromo- and iodoalkynes with different additives

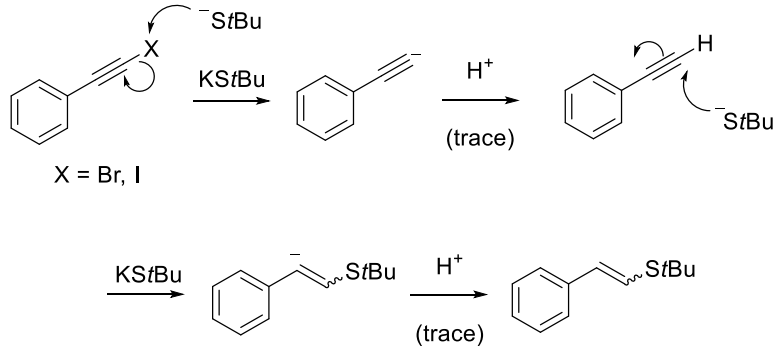


X	Me_2NH		DMEDA		No additive	
	Yield (%)*	(*Z*):(*E*)	Yield (%)*	(*Z*):(*E*)	Yield (%)*	(*Z*):(*E*)
Br	46	91:9	66	91:9	64	78:22
I	40	92:8	77	89:11	49	83:17

*Isolated yield of inseparable thioenol ether products

**Ratio of *Z* and *E* isomers of enol ethers determined by ratio of ^{1}H NMR peaks

It appears that the weaker C-I and C-Br bonds allow a (well-documented) facile competing X-philic reaction resulting in oxidation of the thiolate nucleophile.[197] Protonation by trace amounts of moisture then led to the parent alkyne that can then undergo addition reactions as previously described in the group and by others (**Scheme 2.16**). The stronger C-Cl bond is apparently able to resist the competing X-philic pathway with the soft thiolate nucleophile and leads exclusively to the thioynol ether product in good yield.



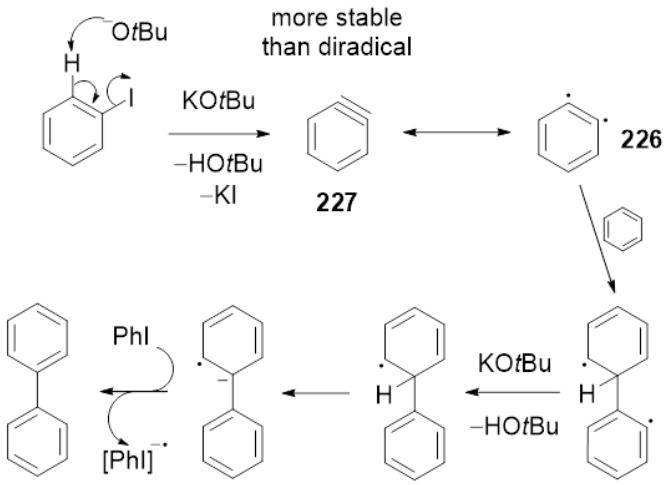
Scheme 2.16 – X-philic reaction of bromo- and iodoalkynes leading to thioenol ethers

2.4 Probing the mechanism

2.4.1 Background

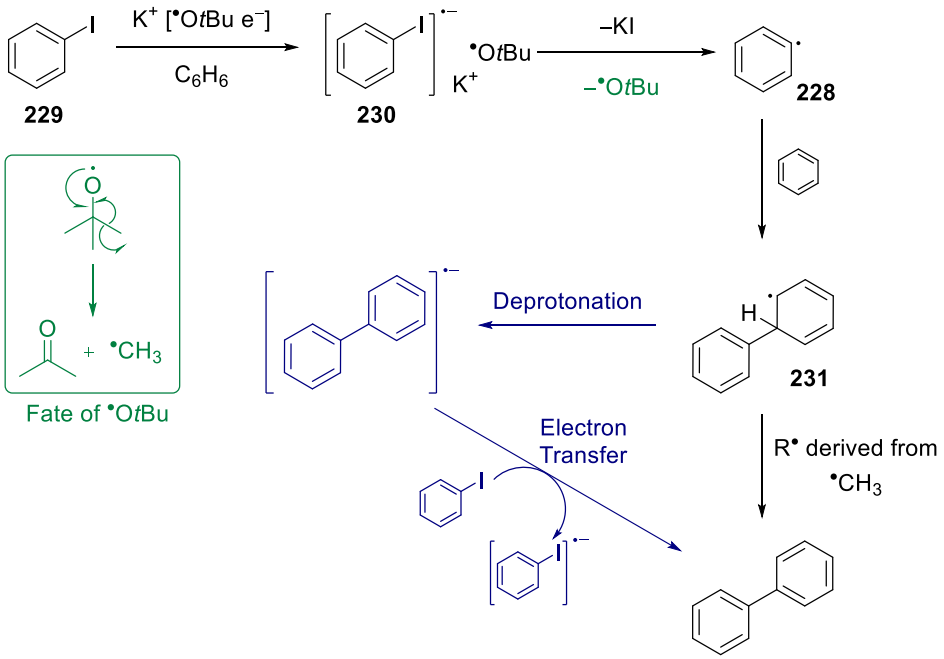
Gaining a mechanistic understanding of how *tert*-butoxide and thiolate anions facilitate transition metal-free reactions and the effect of different factors could allow for such transformations to be optimised. Following Itami *et al*. monumental discovery of the special role played by KO*t*Bu in transition metal-free coupling reactions,[25] there has been wide debate on exactly what that role is.[29,185,200–203] Although a precise mechanism was not invoked by Itami *et al.* – they simply summarised that either homolytic aromatic substitution (HAS)[201,204] or $S_{RN}1$ reaction[205,206] mechanisms were favoured.[25] Control experiments by the groups of Itami, Hayashi, Shi and Kwong all suggested that radicals were involved in these transition metal-free transformations; the question of how the initial radical is formed is still the centre of much debate.[27]

Murphy and Tuttle *et al*. proposed that a diradical resonance structure **226** of a benzyne intermediate **227** could be the initiator in the biaryl-forming reactions mentioned in **Section 1.2** (**Scheme 2.17**). However, recent studies have found that the benzyne intermediate **227** is relatively more stable than the diradical **226** therefore initiation *via* this route is relatively unlikely. The mechanistic proposals made in the early methods,[11–13] discussed in **Section 1.2**, rule out the involvement of a benzyne intermediate as no other regioisomers with respect to the aryl iodide are formed.



Scheme 2.17 – Murphy *et al*. proposed mechanism *via* benzyne intermediate

Studer and Curran described these processes as base-catalysed homolytic radical aromatic substitution (BHAS) reactions[201,204] rather than C-H activation or organocatalysis. They agreed with the four groups mentioned earlier that an aryl radical **228** was most likely formed from the aryl halide **229** in the initiation step *via* an aryl halide-based radical anion **230**. Wilden *et al.* demonstrated that the dissocation of KO*t*Bu is essential (**Scheme 2.18**).[29]



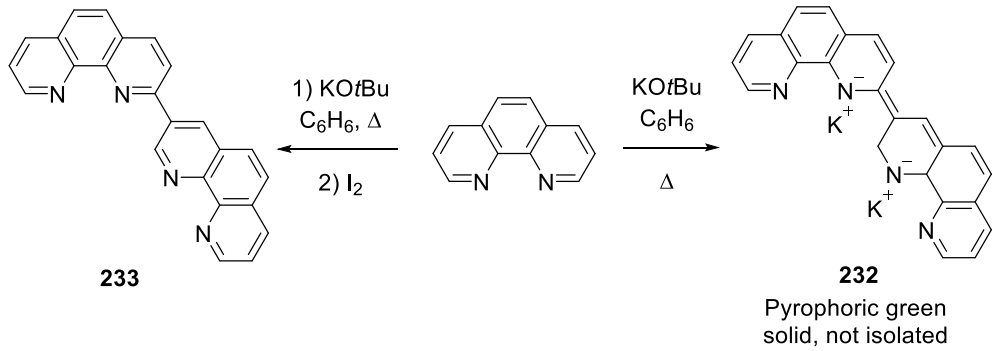
Scheme 2.18 – Proposed mechanism for biaryl synthesis by groups of Wilden and Studer

Itami *et al*. corroborate this, as in the absence of an additive, the reaction was successful. Hence, initiation can occur directly from KO*t*Bu. The fate of the biaryl radical intermediate **231** has a number of possibilities. It was initially proposed that recombination of an alkyl radical (derived from the decomposition product of the *tert*-butoxy radical) could furnish the biaryl product. Owing to the relatively low concentration of these radical intermediates, however, this pathway seemed unlikely and Studer *et al*. proposal of deprotonation followed by electron transfer is more likely (**Scheme 2.18**).[207]

Murphy and Tuttle *et al.* used Electron Paramagnetic Resonance (EPR) spectroscopy and Cyclic Voltammetry (CV) in an attempt to disprove some of the proposed mechanisms and offer alternative possibilities.[208] They outlined that these electron transfers occur either directly from the metal alkoxide or indirectly, following a reaction of the metal alkoxide with a solvent or an additive. Their theory was based

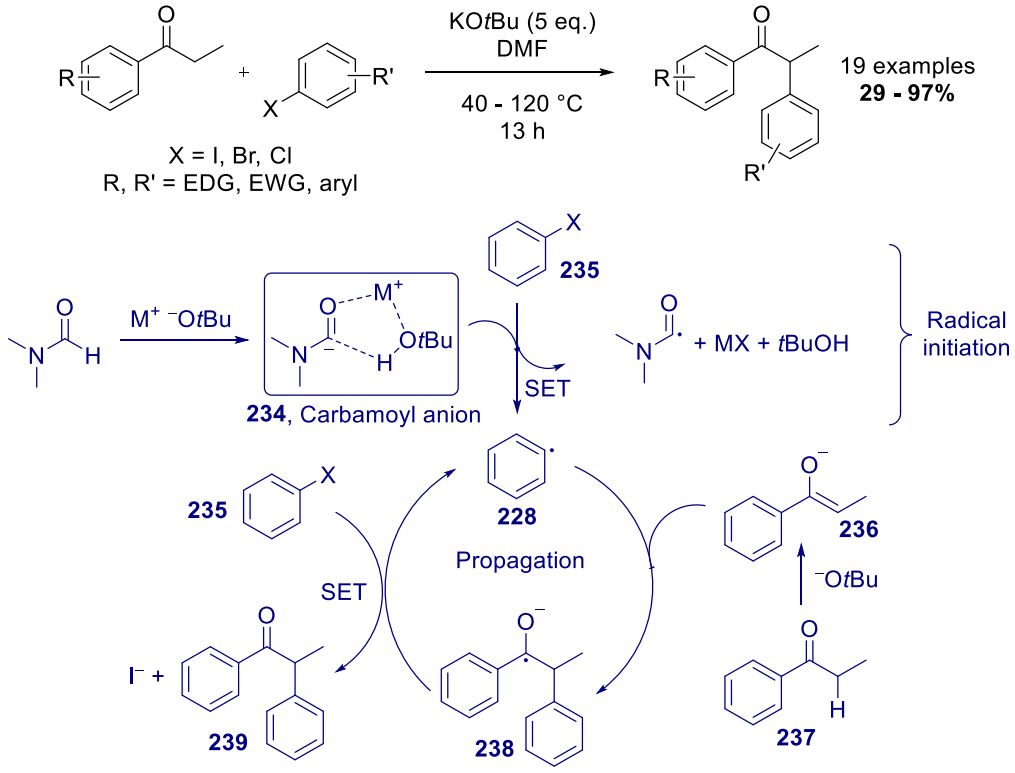
on direct electron transfer only being viable when the reduction potential of the electron acceptor was close to the oxidation potential of the metal alkoxide, which was used as grounds to disprove other theories.[208] However, they did not take into account thermal lowering of the activation barrier, for instance, as their computational studies were conducted for a standard set of conditions and therefore their theory may not be applicable to the work of other groups.

Furthermore, the role of the additive remains elusive and again, there are different theories behind their mode of action. In a similar fashion to their benzyne model, Murphy and Tuttle *et al*. have carried out extensive work and proposed the formation of organic Super Electron Donors (SEDs) from heterocyclic reagents such as 1,10-phen.[185] Again, computational studies were conducted under standard conditions and the group's attempt to isolate the example SED **232** was unsuccessful, therefore quenching with iodine was required in order to isolate the dimer **233** (**Scheme 2.19**). Although this does not fully substantiate this theory and SED formation, this is one possibility of a radical initiator.



Scheme 2.19 – Unsuccessful isolation attempt of an exemplary SED by Murphy *et al*.

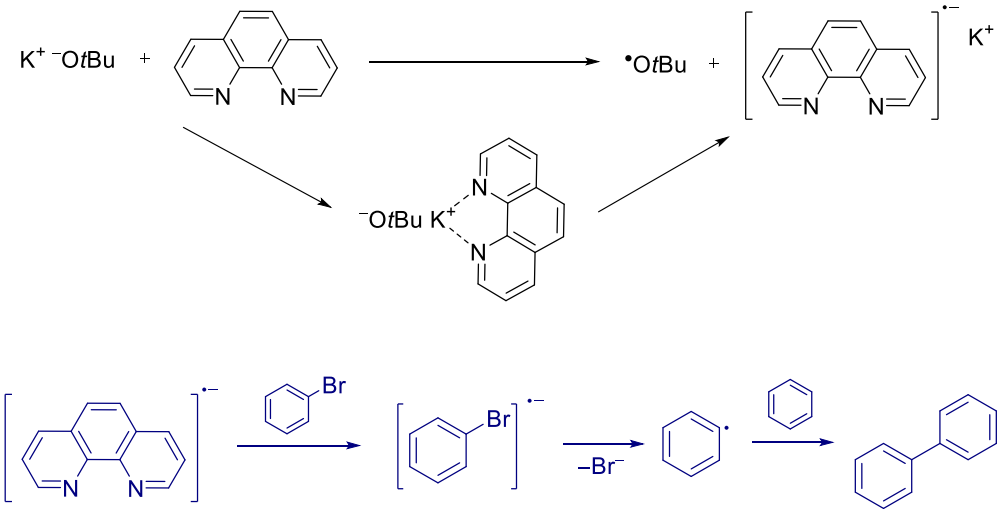
Taillefer *et al.* offered a different proposal where they described a transition metal-free α-arylation of enolisable aryl ketones promoted by KO*t*Bu and DMF.[209] The authors stated that direct electron transfer to an aryl halide would be unfavourable as calculations showed that, in DMF, there would be a shortfall in energy of 50.5 kcal mol^{-1}. Hence, Taillefer *et al*. proposed a mechanism involving a carbamoyl anion intermediate formed when KO*t*Bu abstracted a proton from DMF, where the solvent acted as an initiator (**Scheme 2.20**).



Scheme 2.20 – Taillefer *et al.* proposed mechanism for α-arylation of aryl ketones[209]

Following proton abstraction by the *tert*-butoxide anion (KO*t*Bu worked well but NaO*t*Bu did not which is possibly due to its lower solubility in DMF), the carbamoyl intermediate **234** transferred an electron to the aryl halide **235**. The aryl radical **228** then coupled with an enolate intermediate **236** (which was formed from deprotonation of the starting ketone **237** by a *tert*-butoxide anion) to give radical anion **238**. Subsequent single electron transfer (SET) with another molecule of aryl halide **235** furnished the α-aryl ketone **239** and regenerated an aryl radical **228**, propagating the radical process. The authors used density functional theory (DFT) to probe the mechanism which showed that this could be an energetically viable pathway as the computed transition state and the product were close in energy.

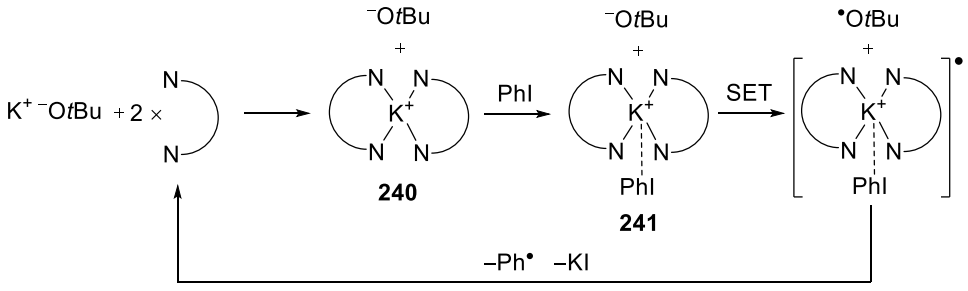
Patil also used computational tools to probe for mechanistic insights into the initiation step of base-promoted biaryl formation in the presence of an additive DMEDA and 1,10-phen.[202] Free energies of reaction (ΔG_r) were calculated to gauge the propensity of certain mechanisms. The author offered a brief review of previously proposed mechanisms including Jutand *et al*. use of CV and EPR spectroscopy to show that 1,10-phen could potentially act as an electron transfer agent from KO*t*Bu to the aryl halide (**Scheme 2.21**).



Scheme 2.21 – Jutand and Lei *et al*. proposed electron transfer role played by additive

Patil found that this process would be endergonic with DMEDA or 1,10-phen and therefore unlikely to take place.[202] Murphy *et al*. SED mechanism could also be ruled out for the same reason; although Patil explained that the presence of a strong electron acceptor could compensate for the energy deficit resulting from the release of an electron from the donor **232** (SED shown in **Scheme 2.19**). Direct electron transfer from the *tert*-butoxide anion is also improbable for this reason, however, the dissociation of the base could be invoked as a decisive factor.

The *tert*-butoxide anion completely dissociated from the potassium cation (K^+) could allow K^+ to coordinate to two additive molecules (with each acting as a bidentate ligand) forming a chelate complex **240**. Subsequent complexation of the aryl halide *via* cation-pi interactions could then lead to a second complex **241** susceptible to SET from the *tert*-butoxide anion. This could result in an aryl radical **228** and the two molecules of additive returned to propagate the system (**Scheme 2.22**).



Scheme 2.22 – Patil's proposal for an energetically viable radical initiation process

This process (**Scheme 2.22**) was found to be energetically more likely than other mechanisms and Patil justified this further as the potential activation barrier for the initial dissociation could be lowered as most of these reactions were carried out at elevated temperatures.[202] Looking back at the alkali metal alkoxide dissociation trend (**Figure 1.3**), this process could explain the viability of Wilden *et al*. transition metal-free approaches.

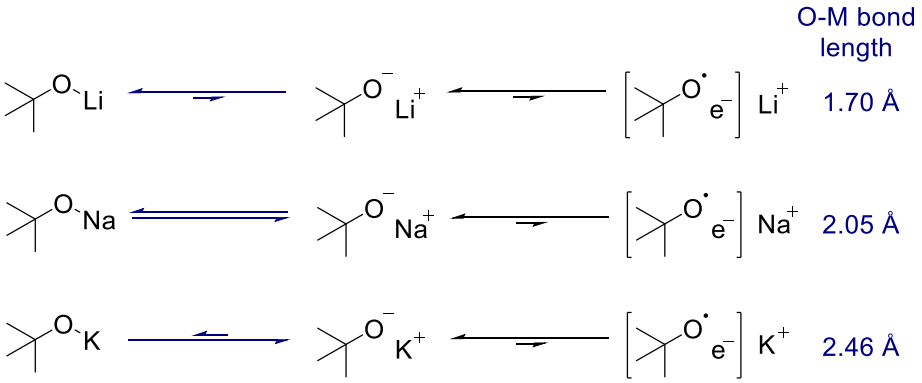
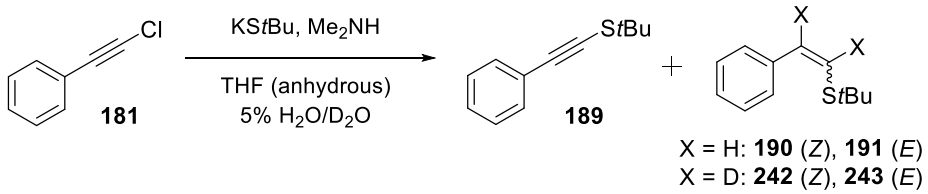


Figure 1.3 – Group 1 alkoxides with increased cationic dissociation

The use of a *tert*-butoxide anion in transition metal-free synthesis is not limited to biaryl formation[210] and similar theories could be plausible for other heteroatom-based anions (such as thiolate anions) as well.

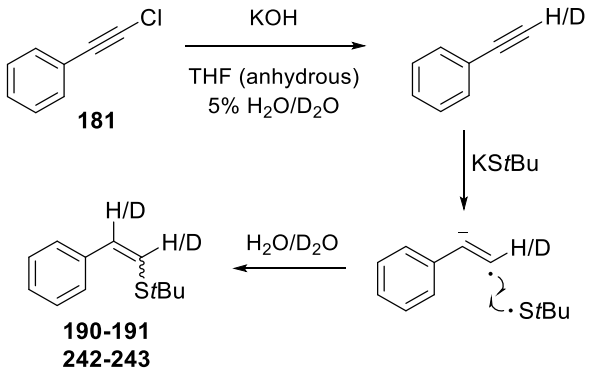
2.4.2 Mechanistic proposal for new transition metal-free synthetic route

Extensive mechanistic studies were conducted for these reaction conditions previously in the Wilden group and have been summarised in previous sections.[101,177] To gain a greater understanding of the reaction of chloroalkynes, the reaction was performed in the presence of small quantities of water (2–5%). This resulted in the formation of the enol ether by-products **190-191** along with the thioynol ether **189**, the yield of which was greatly suppressed. The (*Z*)-geometrical isomer was predominantly formed, suggesting the involvement of a radical anion intermediate (**Scheme 2.23**). When water was replaced by D_2O, deuterium incorporation was observed in both vinylic positions, evidenced by the absence of the vinyl proton peaks in the ^1H NMR spectrum.



Scheme 2.23 – Doping the reaction with H_2O or D_2O

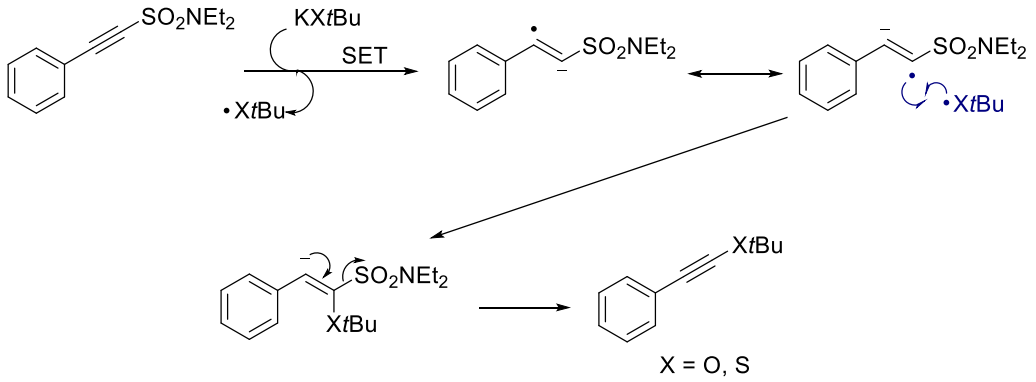
Presumably, when water was present, the hydroxide generated in the reaction medium underwent the X-philic reaction with the acetylenic chloride to yield the parent alkyne (phenylacetylene). This in turn underwent addition of a thiolate radical as outlined in **Scheme 2.24**.



Scheme 2.24 – Mechanistic pathway proposed when H_2O/D_2O is present

The Wilden group proposed a mechanism whereby a *tert*-butoxy or *tert*-butyl thiolate radical species could recombine with a vinyl radical anion intermediate leading to a

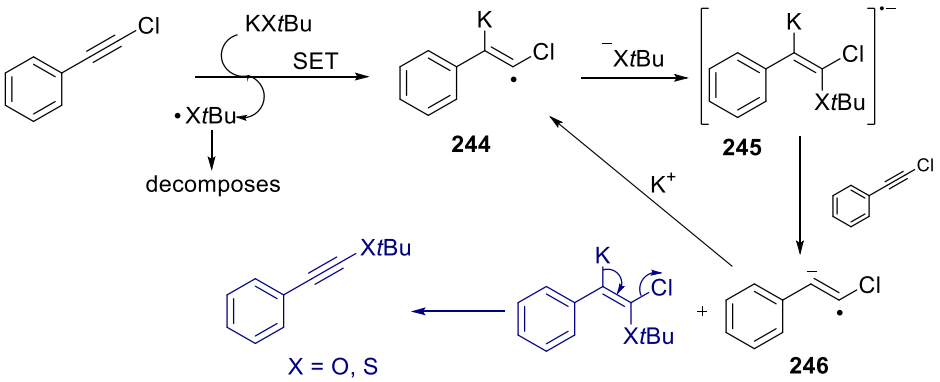
vinyl anion. The final elimination step was thought to then furnish the alkynyl ether or thioether (**Scheme 2.25**).



Scheme 2.25 – Previously proposed mechanism in Wilden group

It is possible that a solvent cage could allow for the unstable chalcogenide-based radical to come into close enough proximity to the vinyl radical anion intermediate, however, the likelihood is questionable as the radical would exist in such low concentrations.

A recent proposal could be more probable given computational findings in the Wilden group[211] of a more formal carbon-potassium bond in the intermediate vinyl radical species **244**. With the *tert*-butoxy radical more likely to decompose, another *tert*-butoxide anion could add to the vinyl radical intermediate, resulting in a radical anion species **245** stabilised by charge delocalisation; this could explain why the aryl group is vital. Although the thiolate radical is likely to be more stable, this proposed mechanism could be applicable for thioynol ether synthesis as well (**Scheme 2.26**).



Scheme 2.26 – A possible mechanistic pathway *via* radical anion intermediates

This newly-postulated mechanism is more viable as the stability of the intermediate vinyl radical anion **246** could allow for it to propagate the process. Furthermore, if the amine additive is removed from the reaction mixture the reaction still proceeds, however reaction times are significantly extended. The precise role of this additive and how it exerts its beneficial effect on the reaction remains somewhat ambiguous. Although we and others have speculated as to possible mechanistic roles for these additives, a decisive conclusion cannot yet be drawn. One possibility is that these additives play an assisting role in the initial SET process but this is yet to be confirmed.[198]

2.5 Applications of alkynyl sulfides and their derivatives

2.5.1 Introduction and aims

With a small library of thioynol ethers at hand, preliminary studies were conducted on possible applications of this understudied class of compounds and their derivatives. Heterocyclic chemistry has been of interest in the Wilden group in the past[212] as these compounds often possess highly useful properties. Five-membered ring heterocycles are important molecules that often have potential to be highly significant medicinal compounds with some 90% of all new drugs containing at least one heterocyclic ring (**Figure 2.1**).[213,214]

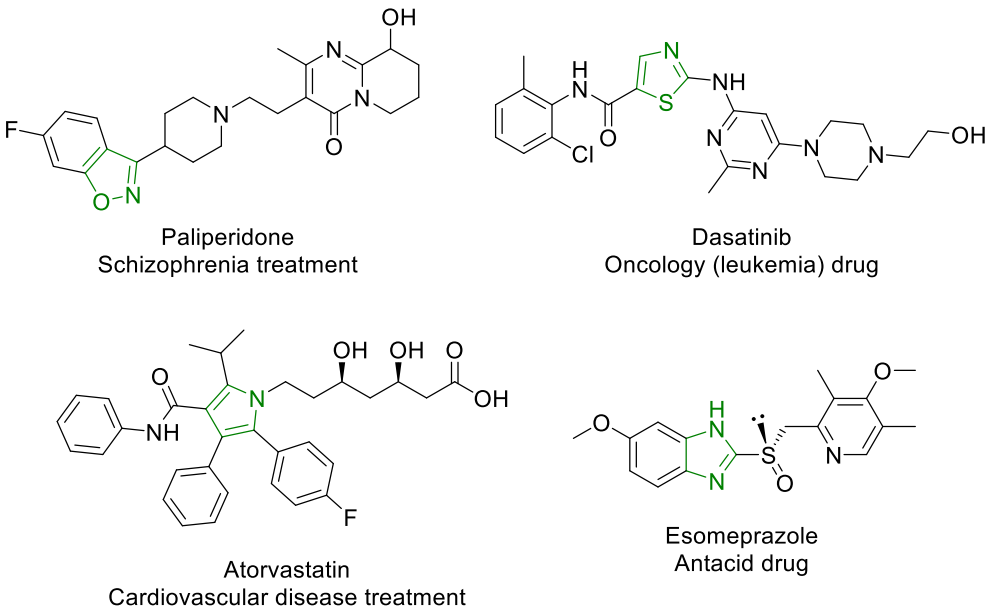


Figure 2.1 – Selected examples of drugs containing 5-membered heterocycles

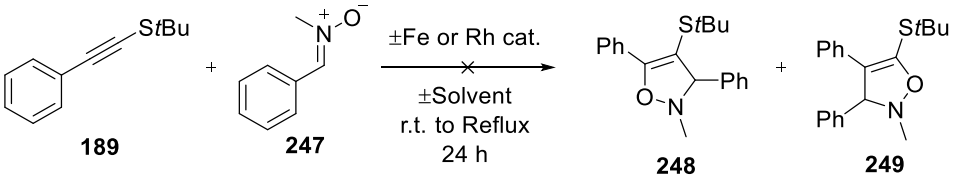
As such, new reliable routes to such heterocyclic systems are continually being sought, particularly for the preparation of compounds with more unusual substitution patterns. With an interest in nitrones within the Wilden group[215] owing to their broad range of applications,[216] they were chosen as the first reaction partner for alkynyl sulfides. Attention was then turned to the addition of acyl chlorides in order to form potential precursors for cyclisation to heterocyclic compounds.

2.5.2 Addition on nitrones to alkynyl sulfides and their derivatives

The first transformation to be tested was the addition of a nitrone to the alkynyl sulfide. The nitrone **247** was synthesised using a literature procedure[216,217] treating benzaldehyde with hydroxylamine hydrochloride under basic conditions (**Scheme** 2.27).

Scheme 2.27 – Nitrone synthesis for use in reaction with alkynyl sulfide

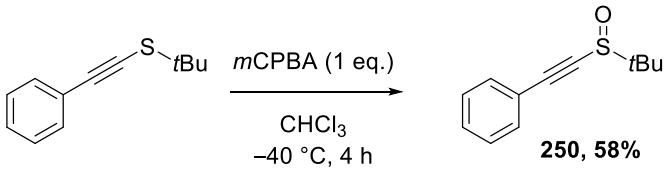
Addition of the nitrone to the *tert*-butyl thioynol ether **189** resulted in no reaction even at elevated temperatures (140 °C) and the thioynol ether was recovered. The thermal decomposition of nitrones is known,[218] therefore it is possible that the nitrone may have decomposed. **Scheme 2.28** summarises the reaction conditions used to investigate the possibility of forming highly functional heterocyclic compounds **248** and **249**.



Solvent = toluene, xylene, $(CH_2Cl)_2$

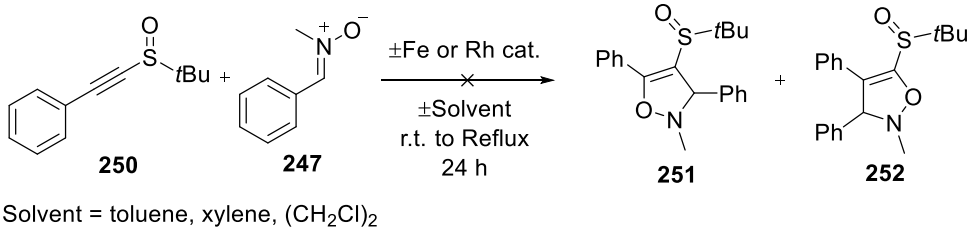
Scheme 2.28 – Schematic summary of nitrone addition reactions attempted

Catalysis by a Lewis acid or a transition metal when attempting cycloaddition with nitrones is known.[219,220] The original reaction was repeated with $FeCl_3$ and Wilkinson's catalyst $[(PPh_3)_3RhCl]$, in turn, but solely starting alkynyl sulfide was recovered. With the unreactive nature of alkynyl sulfides becoming clear, attention was diverted to the sulfoxide derivatives. Oxidation of thioynol ether with *m*CPBA furnished the desired alkynyl sulfoxide (**Scheme 2.29**).[132]



Scheme 2.29 – Oxidation of alkynyl sulfide to alkynyl sulfoxide

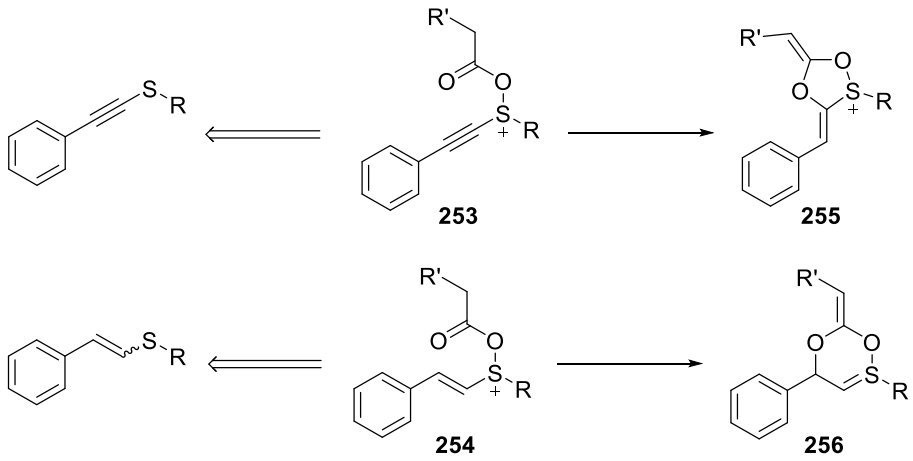
Exposure of the alkynyl sulfoxide **250** to the same reactions as the alkynyl sulfide (addition of nitrone in different solvents with and without iron and rhodium catalysis) also resulted in no formation of the desired cycloaddition products **251** and **252**. However, on heating the reaction to reflux in toluene, the starting sulfoxide was fully consumed. Disappointingly, crude NMR analysis showed no discernible products (**Scheme 2.30**).



Scheme 2.30 – Attempted addition of nitrone to alkynyl sulfoxide

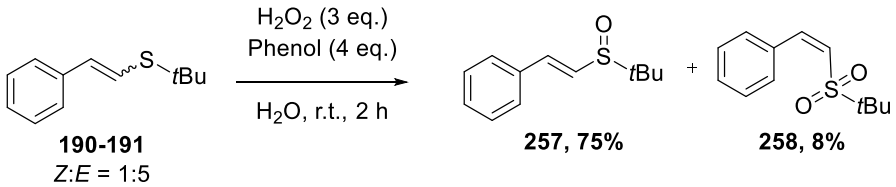
2.5.3 Addition of acyl chlorides to alkynyl sulfide derivatives

Consequently, attempts were then made to prepare compounds **253** and **254** which could potentially be cyclised to form heterocycles **255** and **256** (**Scheme 2.31**).



Scheme 2.31 – Target cyclisation precursors to lead to heterocyclic compounds

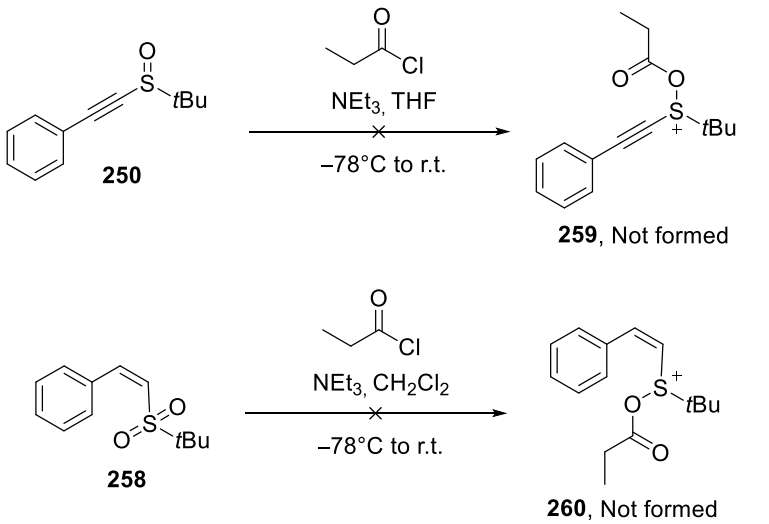
Preparation of the target cyclisation precursors **253** and **254** was pursued from the alkynyl sulfides and alkenyl sulfides, respectively, which were already at hand. Alkynyl sulfoxide preparation was outlined in **Scheme 2.29**; in the case of the alkenyl derivative **190** and **191**, hydrogen peroxide (H_2O_2) in the presence of phenol[221] was used instead of *m*-CPBA (**Scheme 2.32**). Interestingly, oxidation led to a mixture of the (*E*)-isomer of the sulfoxide **257** with no over-oxidation to the (*E*)-alkenyl sulfone, and the (*Z*)-isomer of the sulfone **258** with no (*Z*)-sulfoxide formed (**Scheme 2.32**).

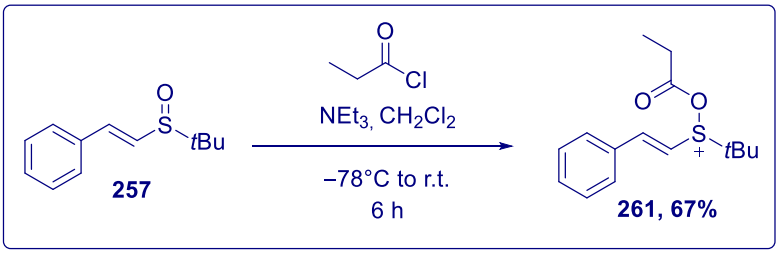


Scheme 2.32 – Oxidation of the isomeric mixture of alkenyl sulfides

With alkynyl **250** and (*E*)-alkenyl sulfoxide **257** prepared, the addition of commercially available acyl chloride was then investigated. The (*Z*)-alkenyl sulfone **258** was also included in this study.

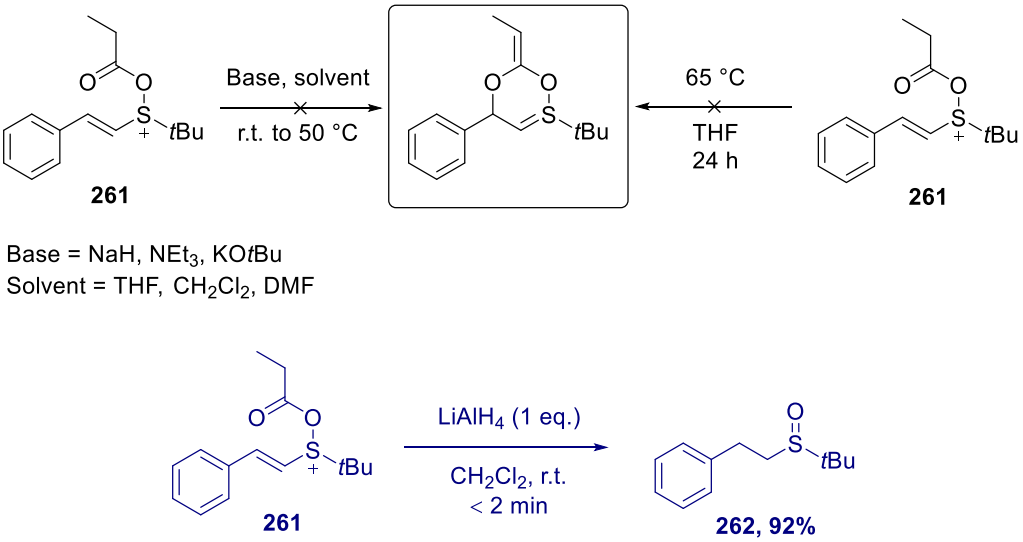
Disappointingly, alkynyl sulfoxide **250** did not undergo conversion to the desired product **259** and after 24 h at room temperature, only starting sulfoxide **250** and decomposed material were obtained (**Scheme 2.33**). When the reaction was heated up to 50 °C, full consumption of starting material was observed; unfortunately, only decomposed material resulted. Similarly, the (*Z*)-alkenyl sulfone **258** yielded no desired adduct **260** as decomposition occurred instead.





Scheme 2.33 – Treatment of unsaturated sulfoxides and sulfones with an acyl chloride

On the other hand, full consumption of the alkenyl sulfoxide **257** was achieved after 6 h of adding the sulfoxide to the mixture of propionyl chloride and triethylamine (**Scheme 2.33**). The desired adduct **261** was obtained in a good yield and was then taken through to attempt cyclisation (**Scheme 2.34**).

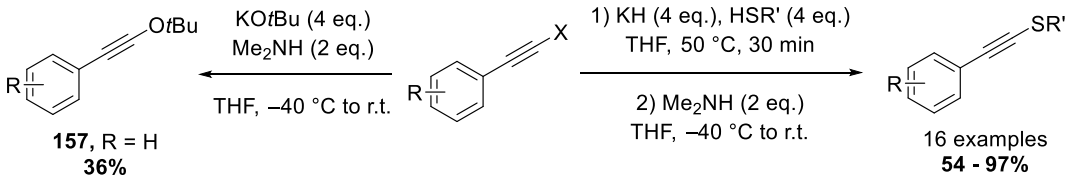


Scheme 2.34 – Schematic summary of cyclisation attempts with adduct **261**

On treatment with lithium aluminium hydride ($LiAlH_4$), the adduct **261** underwent reduction and elimination of the acyl group within two minutes and alkyl sulfoxide **262** was obtained in an excellent yield. Under all other conditions investigated, cyclisation could not be promoted; some decomposed material resulted with the majority of the somewhat stubborn starting material remaining, even after heating at 65 °C for 24 h (**Scheme 2.34**).

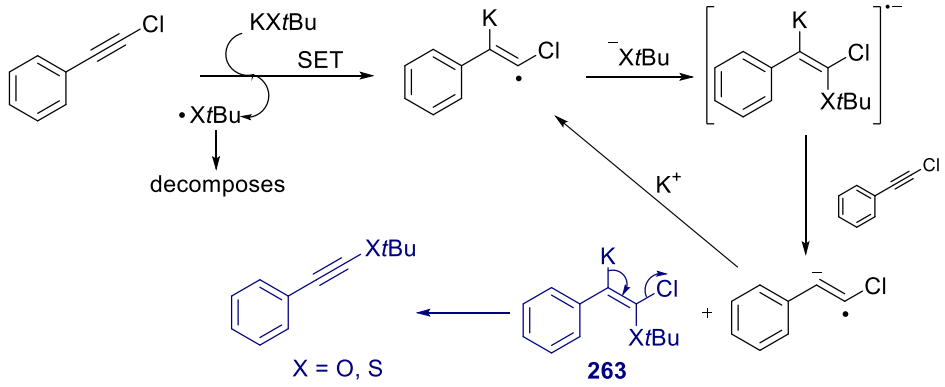
3. Conclusions and future work

A simple and efficient transition metal-free synthesis of ynol and thioynol ethers has been presented with a discussion of the possible roles played by different components (**Scheme 3.1**).



Scheme 3.1 – Summary of new transition metal-free routes developed

To investigate the likelihood of the proposed mechanism (**Scheme 2.26**), further work could involve the isolation of the uncharged vinyl potassium intermediate **263** and an in-depth study of the energetic viability of the process. Electrochemistry-based investigations are currently underway in the Wilden group.



Scheme 2.26 – A possible mechanistic pathway *via* radical anion intermediates

Further work is required in this area to gauge an understanding of how to encourage alkynyl sulfides and their derivatives to undergo transformations. Methods involving transition metal catalysis are known, however, it would be advantageous to develop routes not requiring exogenous transition metals in order to retain aspirations of more sustainable synthesis.

Although preliminary studies into some transition metal-free transformations of alkynyl sulfides were unsuccessful, further investigations could involve activation of the sulfur moiety, for instance with an amine group. The resulting sulfenamide functionality (**Figure 3.1**) has proven to be a reactive centre for further transformations.[222]

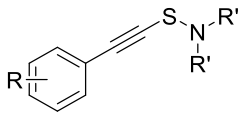


Figure 3.1 – Aryl alkynyl sulfonamides: potentially activated alkynyl sulfide derivatives

Furthermore, transition metal-free manipulation of alkenyl sulfides and sulfoxides could also be studied more extensively to gain a better understanding of these classes of unsaturated organosulfur compounds. With some of the final work presented here showing potential in providing highly functional heterocyclic compounds (**Figure 3.2**), further investigations could result in an optimised transition metal-free, and therefore sustainable, cyclisation process.

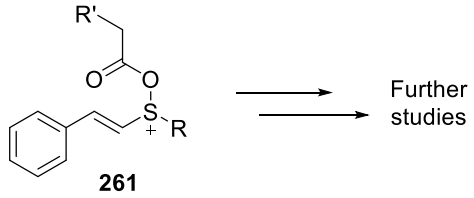


Figure 3.2 – Potential for further studies into cyclisation of adduct **261**

4. Experimental

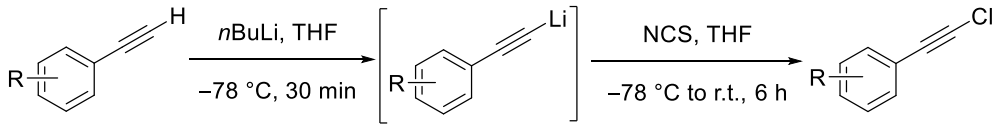
4.1 General Methods

All reactions were carried out at atmospheric pressure, in flame-dried glassware under an atmosphere of argon unless otherwise stated. Reagents and solvents were purchased from suppliers and used as received unless noted otherwise. Normal phase silica gel (Merck Kieselgel 60) 0.04/0.063 (230–400 mesh) was used for flash column chromatography. Reaction progress was monitored *via* TLC analysis, using aluminium plates pre-coated with silica gel 60 F_{254}, and visualised by combination of UV (254 nm) and potassium permanganate chemical stain with heating. Solvent removal *in vacuo* refers to rotary evaporation at 17–60 °C, using a house vacuum operating at approximately 10 mmHg. Room temperature is defined as 19–23 °C.

^{1}H NMR spectra were recorded at 500 MHz or 600 MHz using a Bruker AMX500 or AMX600 instrument, respectively, operating at ambient temperature. ^{13}C NMR spectra were recorded at 125 or 150 MHz using a Bruker AMX500 or Bruker AMX600 MHz spectrometer, respectively. For NMR experiments, $CDCl_3$ denotes deuterated (d_1) chloroform and CD_3OD denotes deuterated (d_4) methanol. Deuterated solvents were chosen according to the position of solvent peak in spectra and solubility of substrates. Chemical shifts are reported in parts per million (ppm), and are referenced to the proton impurity of deuterated solvents. Coupling constants (*J*) are reported in Hertz (Hz). The multiplicity of a given signal is reported as s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), sext. (sextet), dd (doublet of doublets) or td (triplet of doublets). In cases where complex signals make determination of the multiplicity difficult, peaks are defined as m (multiplet). *Z*:*E* assignments and ratio of alkene isomers (including deuterated products) has been determined using NOESY where appropriate and using relative ratio of alkenyl proton peaks where isomers could not be separated by purification. Infrared spectra were recorded as thin films using a FTIR Perkin Elmer Spectrum 100, operating in ATR mode. Mass spectra were measured on a Thermo Finnigan MAT900 XP operating in EI and CI mode. ESI spectra were measured on a Waters LCT premier XE LC-TOF mass spectrometer. Melting points were measured using Gallenkamp apparatus and are uncorrected.

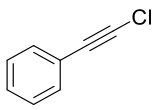
4.2 Experimental procedures

4.2.1 Synthesis of chloroalkynes



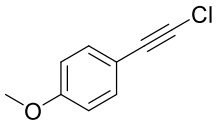
A flame-dried flask was charged with a stirring bar and the starting material acetylene (1.00 mmol, 1.0 equiv.), followed by anhydrous THF (2 mL) under argon and cooled to −78 °C. The solution was treated with *n*-butyllithium (1.6 M solution in hexanes, 0.75 mL, 1.20 mmol, 1.2 equiv.) over 5 min at −78 °C under argon. The resulting suspension was stirred at −78 °C for 30 min then a solution of recrystallised *N*-chlorosuccinimide (0.147 g, 1.10 mmol, 1.1 equiv.) in anhydrous THF (5 mL) was added in one portion. The reaction was allowed to warm to room temperature after 20 min and left to stir for 6 h under an atmosphere of argon. Then the reaction mixture was quenched with saturated NH_4Cl (15 mL), diluted with Et_2O (30 mL) and washed with brine (20 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL) and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (5% Et_2O/PE) gave desired chloroalkyne product which was stored in the freezer.

(Chloroethynyl)benzene **181**



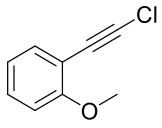
Column chromatography using PE gave colourless oil: 109 mg, 80%; IR ν_{max} (film)/cm^{-1} 3079, 2223, 1487, 751, 668; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.47−7.45 (m, 2 H, *o*-Ar*H*), 7.35−7.32 (m, 3 H, *m*- and *p*-Ar*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 132.0 (CH), 128.6 (CH), 128.4 (CH), 122.2 (C_q), 69.4 (PhC≡***C***), 68.1 (Ph***C***≡C); LRMS (EI) *m/z* (%) 138 (M^+, ^{37}Cl, 33), 136 (M^+, ^{35}Cl, 100), 101 (M^+, PhC≡C, 55). HRMS (EI) calcd for $C_8H_5{}^{35}Cl$ (M^+) 136.0074, found 136.0082. Data in agreement with literature.[189,223,224]

1-(Chloroethynyl)-4-methoxybenzene **192**



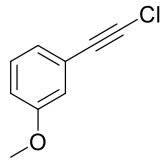
Column chromatography using 10% Et_2O/PE gave colourless oil: 90 mg, 54%; IR ν_{max} (film)/cm^{-1} 3082, 2225, 1604, 1506, 1290, 1245, 1171, 1031, 828; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.39-7.37 (d, *J* = 10.3 Hz, 2 H, O(C)CHC*H*), 6.84−6.82 (d, *J* = 10.3 Hz, 2 H, O(C)C*H*CH), 3.80 (s, 3 H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.8 (C_q), 133.4 (CH), 114.2 (CH), 114.0 (C_q), 69.3 (ArC≡***C***), 66.4 (Ar***C***≡C), 55.3 (CH_3); LRMS (EI) *m/z* (%) 168 (M^+, ^{37}Cl, 33), 166 (M^+, ^{35}Cl, 100), 150 (45), 123 (65); HRMS (EI) calcd for $C_9H_7{}^{35}ClO$ (M^+) 166.01854, found 166.018263. Data in agreement with literature.[223]

1-(Chloroethynyl)-2-methoxybenzene **193**



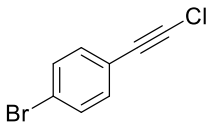
Column chromatography using 10% Et_2O/PE gave colourless oil: 79 mg, 47%; IR ν_{max} (film)/cm^{-1} 3067, 2227, 1595, 1490, 1258, 1116, 1023, 748; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.42-7.40 (dd, *J* = 7.6, 1.7 Hz, 2 H, O(C)(C)C*H*), 7.32-7.29 (td, *J* = 8.3, 1.4 Hz, 1 H, O(C)CHC*H*), 6.90 (t, *J* = 7.4 Hz, 1 H, O(C)C*H*), 6.87 (d, *J* = 8.3 Hz, 1 H, O(C)(C)CHC*H*), 3.89 (s, 3 H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 160.7 (C_q), 134.1 (CH), 130.1 (CH), 120.6 (CH), 111.4 (CH), 110.7 (C_q), 71.6 (ArC≡***C***), 66.0 (Ar***C***≡C), 55.9 (CH_3); LRMS (EI) *m/z* (%) 168 (M^+, ^{37}Cl, 33), 166 (M^+, ^{35}Cl, 100), 131 (75), 123 (85); HRMS (EI) calcd for $C_9H_7{}^{35}ClO$ (M^+) 166.01854, found 166.01833. Data in agreement with literature.[223]

1-(Chloroethynyl)-3-methoxybenzene **194**



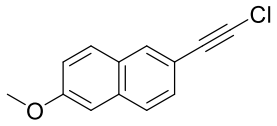
Column chromatography using 10% Et_2O/PE gave colourless oil: 97 mg, 58%; IR ν_{max} (film)/cm^{-1} 3081, 2223, 1573, 1284, 1159, 1039, 785; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.23 (t, *J* = 9.7 Hz, 1 H, O(C)CH(C)C*H*), 7.06 (dt, *J* = 9.1, 1.5 Hz, 1 H, O(C)CHC*H*), 6.99 (s, 1 H, O(C)C*H*(C)), 6.90 (dd, *J* = 10.0, 3.2 Hz, 1 H, O(C)C*H*CH), 3.80 (s, 3 H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.4 (C_q), 129.5 (CH), 124.6 (CH), 123.2 (C_q), 116.9 (CH), 115.3 (CH), 69.4 (ArC≡***C***), 68.0 (Ar***C***≡C), 55.3 (CH_3); LRMS (EI) *m/z* (%) 168 (M^+, ^{37}Cl, 15), 166 (M^+, ^{35}Cl, 45), 136 (40), 123 (100); HRMS (EI) calcd for $C_9H_7{}^{35}ClO$ (M^+) 166.01854, found 166.01891.

1-Bromo-4-(chloroethynyl)benzene **195**



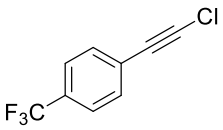
Column chromatography using PE gave white solid: 47 mg, 22%; IR ν_{max} (film)/cm^{-1} 2953, 2217, 1087, 828; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.45 (d, *J* = 8.5 Hz, 2 H, Br(C)C*H*), 7.30 (d, *J* = 8.5 Hz, 2 H, Br(C)CHC*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 133.5 (CH), 131.8 (CH), 123.0 (C_q), 121.2 (C_q), 69.5 (ArC≡***C***), 68.5 (Ar***C***≡C); LRMS (EI) *m/z* (%) 217 (M^+, ^{37}Cl+^{81}Br, 20), 215 (M^+, ^{37}Cl+^{79}Br, ^{35}Cl+^{81}Br, 100), 213 (M^+, ^{35}Cl+^{79}Br, 75), 134 (65); HRMS (EI) calcd for $C_8H_4{}^{35}Cl{}^{79}Br$ (M^+) 213.91849, found 213.91821. Data in agreement with literature.[223]

2-(Chloroethynyl)-6-methoxynaphthalene **196**



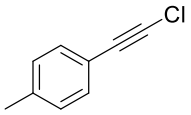
Column chromatography using 10% Et_2O/PE gave pale yellow oil: 156 mg, 72%; IR ν_{max} (film)/cm^{-1} 2956, 2224, 1620, 1029, 851; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.89 (s, 1 H, O(C)CHCH(C)C*H*), 7.69-7.65 (m, 2 H, O(C)CHC*H*(C), O(C)CH(C)CHC*H*), 7.44 (dd, *J* = 10.1, 1.9 Hz, 1 H, O(C)CH(C)C*H*CH), 7.16 (dd, *J* = 10.7, 3.1 Hz, 1 H, O(C)C*H*(C)), 7.09 (d, *J* = 2.9 Hz, 1 H, O(C)C*H*CH), 3.92 (s, 3 H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 158.5 (C_q), 134.3 (C_q), 132.0 (C_q), 129.3 (CH), 129.1 (CH), 128.4 (CH), 126.9 (CH), 119.6 (C_q), 117.1 (CH), 105.9 (CH), 69.9 (ArC≡***C***), 67.5 (Ar***C***≡C), 55.4 (CH_3); LRMS (EI) *m/z* (%) 218 (M^+, ^{37}Cl, 33), 216 (M^+, ^{35}Cl, 100), 175 (33), 173 (100); HRMS (EI) calcd for $C_{13}H_9{}^{35}ClO$ (M^+) 216.03419, found 216.03428.

1-(Chloroethynyl)-4-(trifluoromethyl)benzene **197**



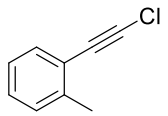
Column chromatography using 10% Et_2O/PE gave colourless oil: 90 mg, 44%; IR ν_{max} (film)/cm^{-1} 2963, 2224, 1320, 1127, 732; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.60-7.54 (m, 4 H, Ar*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 132.4 (C_q), 130.5 (q, *J* = 33.0 Hz) (C_q), 126.1 (C_q), 125.4 (q, *J* = 3.7 Hz) (CH), 123.9 (q, *J* = 272.1 Hz) (C_q), 71.0 (ArC≡***C***), 68.3 (Ar***C***≡C); LRMS (EI) *m/z* (%) 206 (M^+, ^{37}Cl, 33), 204 (M^+, ^{35}Cl, 100), 185 (20), 169 (35), 154 (20); HRMS (EI) calcd for $C_9H_4{}^{35}ClF_3$ (M^+) 203.99536, found 203.99520. Data in agreement with literature.[225]

1-(Chloroethynyl)-4-methylbenzene **198**



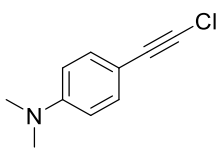
Column chromatography using 5% Et_2O/PE gave colourless oil: 63 mg, 44%; IR ν_{max} (film)/cm^{-1} 2951, 2193, 1772, 1177, 815; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.34 (d, *J* = 7.6 Hz, 2 H, $CH_3(C)CHCH$), 7.12 (d, *J* = 7.6 Hz, 2 H, $CH_3(C)CH$), 2.35 (s, 3 H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 138.9 (C_q), 132.0 (CH), 129.2 (CH), 119.1 (C_q), 69.6 (ArC≡***C***), 67.3 (Ar***C***≡C), 21.6 (CH_3); LRMS (EI) *m/z* (%) 152 (M^+, ^{37}Cl, 8), 150 (M^+, ^{35}Cl, 24), 115 (28), 32 (30), 28 (100). HRMS (EI) calcd for $C_9H_7{}^{35}Cl$ (M^+) 150.0231, found 150.0231. Data in agreement with literature.[223]

1-(Chloroethynyl)-2-methylbenzene **199**



Column chromatography using 5% Et_2O/PE gave colourless oil: 84 mg, 56%; IR ν_{max} (film)/cm^{-1} 3065, 2950, 2216, 753; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.43 (d, *J* = 7.9 Hz, 1 H, $CH_3(C)(C)CH$), 7.26 (t, *J* = 7.5 Hz, 1 H, $CH_3(C)(C)CHCH$), 7.21 (d, *J* = 7.2 Hz, 1 H, $CH_3(C)CH$), 7.15 (t, *J* = 7.7Hz, 1H, $CH_3(C)CHCH$), 2.45 (s, 3 H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 140.9 (CH), 132.4 (C_q), 129.6 (CH), 128.6 (CH), 125.7 (CH), 122.0 (C_q), 71.4 (ArC≡***C***), 68.5 (Ar***C***≡C), 20.7 (CH_3); LRMS (EI) *m/z* (%) 152 (M^+, ^{37}Cl, 17), 150 (M^+, ^{35}Cl, 51), 115 (100), 28 (64). HRMS (EI) calcd for $C_9H_7{}^{35}Cl$ (M^+) 150.0231, found 150.0231.

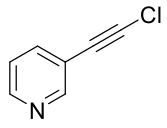
4-(Chloroethynyl)-*N*,*N*-dimethylaniline **200**



Column chromatography using 5% Et_2O/PE gave orange oil: 100 mg, 56%; IR ν_{max} (film)/cm^{-1} 3280, 2890, 2092, 1602, 1356, 1121, 741; ^1H NMR (600 MHz, $CDCl_3$) δ_H

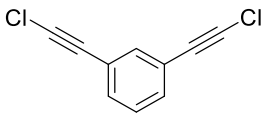
7.32 (d, *J* = 8.8 Hz, 2 H, N(C)CHC*H*), 6.61 (d, *J* = 8.8 Hz, 2 H, N(C)C*H*), 2.98 (s, 6 H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 150.3 (C_q), 133.1 (CH), 111.8 (C_q), 108.8 (CH), 70.4 (ArC≡***C***), 65.2 (Ar***C***≡C), 40.3 (CH_3); LRMS (EI) *m/z* (%) 181 (M^+, ^{37}Cl, 33), 179 (M^+, ^{35}Cl, 100), 162 (15), 110 (18), 96 (30). HRMS (EI) calcd for $C_{10}H_{10}{}^{35}ClN$ (M^+) 179.0496, found 179.0494. Data in agreement with literature.[223]

3-(Chloroethynyl)pyridine **201**



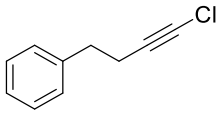
Column chromatography using 40% Et_2O/PE gave a colourless oil, 70 mg, 51%; IR ν_{max} (film)/cm^{-1} 3031, 2960, 2223, 1722, 1186, 753; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.87 (d, *J* = 1.2 Hz, 1 H, NC*H*(C)), 8.55 (dd, *J* = 1.9, 4.9 Hz, 1 H, NC*H*CH), 7.72 (dt, *J* = 1.9, 7.9 Hz, 1 H, NCH(C)C*H*), 7.26-7.23 (m, 1 H, NCHC*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 152.7 (CH), 148.9 (CH), 139.1 (CH), 123.1 (CH), 119.5 (C_q), 71.8 (ArC≡***C***), 66.3 (Ar***C***≡C); LRMS (EI) *m/z* (%) 139 (M^+, ^{37}Cl, 16), 137 (M^+, ^{35}Cl, 48), 32 (28), 28 (100). HRMS (EI) calcd for $C_7H_4{}^{35}ClN$ (M^+) 137.0027, found 137.0026. Data in agreement with literature.[226]

1,3-Bis(chloroethynyl)benzene **202**



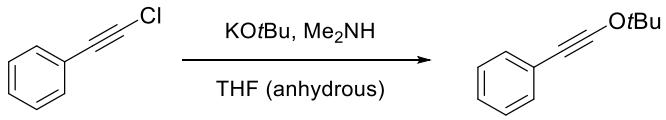
Variation from general procedure: 2.4 eq. of *n*-butyllithium and 2.2 eq. of *N*-chlorosuccinimide used. Column chromatography using PE gave a white solid: 132 mg, 68%; IR ν_{max} (film)/cm^{-1} 2987, 2901, 2213, 1054, 781; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.52 (t, *J* = 1.5 Hz, 1 H,(C)C*H*(C)), 7.40 (dd, *J* = 7.9, 1.5 Hz, 2 H, (C)C*H*CH), 7.26 (t, *J* = 7.9 Hz, 1 H, (C)CHC*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 135.4 (CH), 132.1 (CH), 128.6 (CH), 122.6 (C_q), 69.1 (ArC≡***C***), 68.4 (Ar***C***≡C); LRMS (EI) *m/z* (%) 198 (M^+, ^{37}Cl+^{37}Cl, 11), 196 (M^+, ^{35}Cl+^{37}Cl, 65), 194 (M^+, ^{35}Cl+^{35}Cl, 100), 159 (9); HRMS (EI) calcd for $C_{10}H_4{}^{35}Cl_2$ (M^+) 193.9685, found 193.9685.

(4-Chlorobut-3-yn-1-yl)benzene **203**



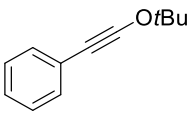
Column chromatography using PE gave colourless oil, 139 mg, 84%; IR ν_{max} (film)/cm^{-1} 3062, 2929, 2218, 1261, 747; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.38-7.33 (m, 2 H, *m*-Ar*H*), 7.30-7.24 (m, 3 H, *o*- and *p*-Ar*H*), 2.87 (t, *J* = 6 Hz, 2 H, CH_2), 2.51 (td, *J* = 6.0, 0.6 Hz, 2 H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 140.5 (C_q), 128.6 (CH), 128.5 (CH), 126.6 (CH), 69.2 (Ar***C***≡C), 58.2 (ArC≡***C***), 34.8 (CH_2), 21.1 (CH_2); LRMS (EI) *m/z* (%) 166 (M^+, ^{37}Cl, 13), 164 (M^+, ^{35}Cl, 40), 129 (30), 91 (100), 83 (10); HRMS (EI) calcd for $C_{10}H_9{}^{35}Cl$ (M^+) 164.03928, found 164.03934.

4.2.2 Synthesis of tert-butyl ynol ether



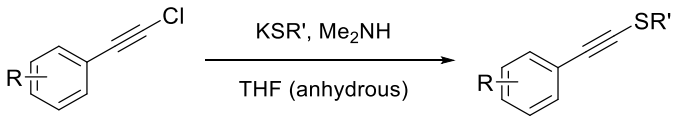
A flame-dried flask was charged with stirrer bar, followed by a solution of potassium *tert*-butoxide (4.0 equiv.) in dry THF (2 mL) and dimethylamine solution (2.0 M in THF, 0.37 mL, 0.73 mmol, 2.0 equiv.) was then added. After 5-10 min, (chloroethynyl)benzene (0.36 mmol) in dry THF (0.5 mL) was added in one burst and the solution was stirred at room temperature under argon and tracked by TLC analysis in 100% petrol. Once the reaction was complete, it was quenched with water (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (30 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography in 15% Et_2O in petrol gave the desired *tert*-butyl ynol ether product as a colourless oil.

(*Tert*-butoxyethynyl)benzene **157**



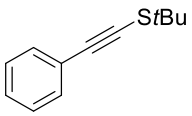
Colourless oil: 23 mg, 36%; ν_{max} (film)/cm^{-1} 2979, 2249, 1370, 1326, 1069; ^{1}H NMR (600 MHz, $CDCl_3$); δ_H 7.34 (d, *J* = 7.7 Hz, 2 H, *o*-Ar*H*, 7.25 (t, *J* = 7.7 Hz, 2 H, *m*-Ar*H*, 7.17-7.21 (m, 1 H, *p*-Ar*H*), 1.48 (s, 9 H, O(C)CH_3); ^{13}C NMR (500 MHz, $CDCl_3$) δ_C 131.4 (CH), 128.2 (CH), 126.3 (CH), 124.8 (C_q), 95.6 (ArC≡***C***), 86.8 (Ar***C***≡C), 42.9 (C_q), 27.2 (CH_3); LRMS (EI) *m/z* (%) 174 (M^+, 100), 160 (13), 159 (79); HRMS (EI) calc'd for $C_{12}H_{14}O$ (M^+) 174.1039, found 174.10426. Data in agreement with literature.[28]

4.2.3 Synthesis of acetylenic sulfides



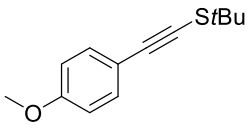
A flame-dried flask was charged with a stirring bar and thiol (0.132 g, 1.46 mmol, 4.0 equiv.), followed by anhydrous THF (2 mL) under argon and heated to 50 °C. Potassium hydride (59 mg, 1.46 mmol, 4.0 equiv., supplied as a 30% weight dispersion in mineral oil which was rinsed with PE and dried between filter paper immediately prior to use) was then added as a single portion and the mixture was stirred at 50 °C for 15 min. The mixture was allowed to cool, first to room temperature and then to −40 °C. Dimethylamine solution (2.0 M in THF, 0.37 mL, 0.73 mmol, 2.0 equiv.) was added *via* syringe, followed immediately after by alkynyl chloride (0.37 mmol, 1.0 equiv.) in anhydrous THF (1 mL). After 10 min, the solution was allowed to warm to room temperature and left to stir under an atmosphere of argon. The reaction mixture was then carefully quenched with water (20 mL), diluted with Et_2O (30 mL) and washed with brine (20 mL). The aqueous layer was extracted with Et_2O (30 mL) and the organic portions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography to yield the desired thioynol ether.

Tert-butyl(phenylethynyl)sulfane **189**



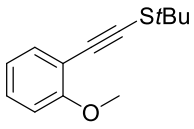
Column chromatography using PE gave a colourless oil: 54 mg, 77%; IR ν_{max} (film)/cm^{-1} 2961, 2162, 1161; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.44 (d, 2 H, (ArC)C*H*), 7.33-7.29 (m, 3 H, (ArC)CHC*H*, (ArC)CHCHC*H*), 1.49 (s, 9 H, S(C)C*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.4 (CH), 128.4 (CH), 128.0 (CH), 123.9 (C_q), 96.2 (Ar***C***≡C), 79.1 (ArC≡***C***), 48.6 (C_q), 30.5 (CH_3); LRMS (CI) *m/z* (%) 191 ($[M+H]^+$, 50), 190 (60), 135 (100); HRMS (EI) calcd for $C_{12}H_{14}S$ (M^+) 190.0811, found 190.0780. Data in agreement with literature.[28]

Tert-butyl((4-methoxyphenyl)ethynyl)sulfane **208**



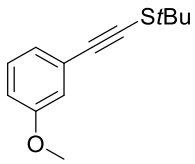
Column chromatography using PE gave an orange oil: 55 mg, 68%; IR ν_{max} (film)/cm^{-1} 2961, 2156, 1245, 1170; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.39 (d, *J* = 8.8 Hz, 2 H, O(C)CHC*H*), 6.83 (d, *J* = 8.8 Hz, 2 H, O(C)C*H*), 3.82 (s, 3 H, OCH_3), 1.47 (s, 9 H, S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.5 (C_q), 133.3 (CH), 115.9 (C_q), 113.7 (CH), 95.9 (Ar***C***≡C), 76.9 (ArC≡***C***), 55.4 (CH_3), 48.4 (C_q), 30.4 (CH_3); LRMS (EI) *m/z* (%) 220 (M^+, 15), 164 (100), 149 (40); HRMS (EI) calcd for $C_{13}H_{16}SO$ (M^+) 220.09219, found 220.09255. Data in agreement with literature.[28]

Tert-butyl((2-methoxyphenyl)ethynyl)sulfane **209**



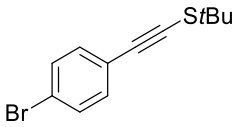
Column chromatography using 5% Et_2O/PE gave a pale yellow oil: 61 mg, 76%; IR ν_{max} (film)/cm^{-1} 2961, 2166, 1256, 749; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.38 (dd, *J* = 7.6, 1.7 Hz, 1 H, (ArC)C*H*), 7.27-7.24 (m, 1 H (ArC)CHCHC*H*), 6.89 (t, *J* = 7.5 Hz, 1 H, (ArC)CHC*H*), 6.86 (d, *J* = 8.2 Hz, 1 H, (ArC)(C)C*H*), 3.87 (s, 3 H, OCH_3), 1.50 (s, 9 H, S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.9 (C_q), 132.9 (CH), 129.2 (CH), 120.4 (CH), 113.2 (CH), 110.6 (C_q), 92.4 (Ar***C***≡C), 83.1 (ArC≡***C***), 55.8 (CH_3), 48.7 (C_q), 30.4 (CH_3); LRMS (EI) *m/z* (%) 220 (M^+, 25), 164 (100), 149 (45), 131 (35); HRMS (EI) calcd for $C_{13}H_{16}SO$ (M^+) 220.09219, found 220.09201. Data in agreement with literature.[28]

Tert-butyl((3-methoxyphenyl)ethynyl)sulfane **210**



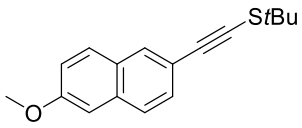
Column chromatography using PE gave a colourless oil: 77 mg, 96%; IR ν_{max} (film)/cm^{-1} 2960, 2159, 1157; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.21 (t, *J* = 7.9 Hz, 1 H, (ArC)CHC*H*), 7.04 (d, *J* = 7.5 Hz, 1 H, (ArC)C*H*CH), 6.96 (s, 1 H, (ArC)C*H*(C)), 6.85 (dd, *J* = 8.3, 2.6 Hz, 1 H, (ArC)CHCHC*H*), 3.80 (s, 3 H, OCH_3), 1.49 (s, 9 H, S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.3(C_q), 129.4 (CH), 124.8 (CH), 123.9 (C_q), 116.1 (CH), 114.5 (CH), 96.1 (Ar***C***≡C), 79.0 (ArC≡***C***), 55.3 (CH_3), 48.6 (C_q), 30.4 (CH_3); LRMS (EI) *m/z* (%) 220 (M^+, 10), 198 (10), 164 (100), 119 (18); HRMS (EI) calcd for $C_{13}H_{16}SO$ (M^+) 220.09219, found 220.09234. Data in agreement with literature.[28]

((4-bromophenyl)ethynyl)(*tert*-butyl)sulfane **211**



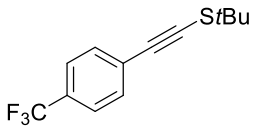
Column chromatography using PE gave a colourless oil: 75 mg, 76%; IR ν_{max} (film)/cm^{-1} 2962, 2163, 1069, 749; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.43 (d, *J* = 8.5 Hz, 2 H, Br(C)C*H*), 7.28 (d, *J* = 8.5 Hz, 2 H, Br(C)CHC*H*), 1.48 (s, 9 H, S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 132.7 (CH), 131.6 (CH), 122.8 (C_q), 122.0 (C_q), 95.2 (Ar***C***≡C), 80.6 (ArC≡***C***), 48.7 (C_q), 30.5 (CH_3); LRMS (EI) *m/z* (%) 270 (M^+, ^{81}Br, 8) 268 (M^+, ^{79}Br, 8), 216 (60), 214 (60), 85 (62), 83 (100); HRMS HRMS (EI) calcd for $C_{12}H_{13}{}^{79}BrS$ (M^+) 267.99213, found 267.99287. Data in agreement with literature.[28]

Tert-butyl((6-methoxynaphthalen-2-yl)ethynyl)sulfane **212**



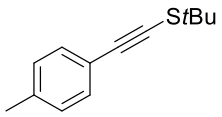
Column chromatography using PE gave a white solid: 92 mg, 94%; IR ν_{max} (solid)/cm^{-1} 2960, 2156, 1627, 1160; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.88 (s, 1 H, O(C)CHCH(C)C*H*), 7.69-7.65 (m, 2 H, O(C)CH(C)C*H*, O(C)CH(C)CHC*H*), 7.46 (dd, *J* = 8.4, 1.6 Hz, 1 H, O(C)CHC*H*), 7.15 (dd, *J* = 9.0, 2.5 Hz, 1 H, O(C)C*H*CH), 7.10 (d, *J* = 2.5 Hz, 1 H, O(C)C*H*(C)), 3.92 (s, 3 H, OCH_3), 1.49 (s, 9 H, S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 158.3 (C_q), 134.0 (C_q), 131.1 (C_q), 129.3 (CH), 129.1 (CH), 128.5 (CH), 126.8 (CH), 119.5 (C_q), 118.7 (CH), 105.9 (CH), 96.7 (Ar***C***≡C), 78.4 (ArC≡***C***), 55.4 (CH_3), 48.6 (C_q), 30.5 (CH_3); LRMS (EI) *m/z* (%) 270 (M^+, 30), 214 (100), 199 (22), 171 (20); HRMS (EI) calcd for $C_{17}H_{18}SO$ (M^+) 270.10784, found 270.10733.

Tert-butyl((4-(trifluoromethyl)phenyl)ethynyl)sulfane **213**



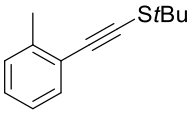
Column chromatography using PE gave a pale yellow oil: 72 mg, 76%; IR ν_{max} (film)/cm^{-1} 2964, 2161, 1613, 1320, 1122; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.55 (d, *J* = 8.2 Hz, 2 H, CF_3(C)CHC*H*), 7.50 (d, *J* = 8.2 Hz, 2 H, CF_3(C)C*H*), 1.49 (s, 9 H, S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.2 (CH), 129.4 (q, *J* = 32.8 Hz) (C_q), 127.6 (C_q), 125.3 (q, *J* = 3.5 Hz) (CH), 124.1 (q, *J* = 272.0 Hz) (C_q), 95.2 (Ar***C***≡C), 82.8 (ArC≡***C***), 49.0 (C_q), 30.5 (CH_3); LRMS (EI) *m/z* (%) 258 (M^+, 5), 236 (100), 202 (20), 57 (52); HRMS (EI) calcd for $C_{13}H_{13}F_3S$ (M^+) 258.0685, found 258.0675. Data in agreement with literature.[28]

Tert-butyl((4-tolylethynyl)sulfane **214**



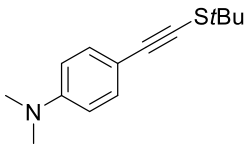
Column chromatography using PE gave a colourless oil: 70 mg, 93%; IR ν_{max} (film)/cm^{-1} 2959, 2918, 2160, 1160, 813; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.33 (d, *J* = 8.1 Hz, 2 H, $CH_3(C)CHCH$), 7.11 (d, *J* = 8.1 Hz, 2 H, $CH_3(C)CH$), 2.34 (s, 3 H, (ArC)CH_3), 1.47 (s, 9 H, S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 138.2 (C_q), 131.5 (CH), 129.1 (CH), 120.7 (C_q), 96.2 (Ar***C***≡C), 78.0 (ArC≡***C***), 48.5 (C_q), 30.5 (CH_3), 21.6 (CH_3); LRMS (EI) *m/z* (%) 204 (M^+, 20), 182 (28), 148 (100); HRMS (EI) calcd for $C_{13}H_{16}S$ (M^+) 204.0967, found 204.0962. Data in agreement with literature.[28]

Tert-butyl((2-tolylethynyl)sulfane **215**



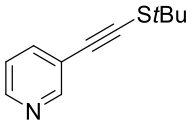
Column chromatography using PE gave a colourless oil: 69 mg, 92%; IR ν_{max} (film)/cm^{-1} 2962, 2922, 2158, 1161, 732; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40 (d, *J* = 7.5 Hz, 1 H, $CH_3(C)(C)CH$), 7.21-7.18 (m, 2 H, $CH_3(C)CH$, $CH_3(C)(C)CHCH$), 7.15-7.11 (m, 1 H, $CH_3(C)CHCH$), 2.45 (s, 3 H, (ArC)CH_3), 1.50 (s, 9 H, S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 139.9 (C_q), 131.7 (CH), 129.5 (CH), 128.0 (CH), 125.8 (CH), 123.8 (C_q), 95.2 (Ar***C***≡C), 82.7 (ArC≡***C***), 48.4 (C_q), 30.5 (CH_3), 21.1 (CH_3); LRMS (EI) *m/z* (%) 204 (M^+, 70), 148 (100), 115 (29), 57 (35), 28 (28); HRMS (EI) calcd for $C_{13}H_{16}S$ (M^+) 204.0967, found 204.0963.

4-((*tert*-butylthio)ethynyl)-N,N-dimethylaniline **216**



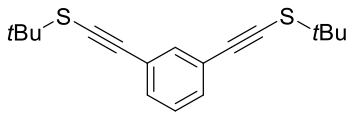
Column chromatography using 20% Et_2O/PE gave a colourless oil: 65 mg, 76%; IR ν_{max} (film)/cm^{-1} 2957, 2151, 1360, 1162; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.35 (d, *J* = 8.8 Hz, 2 H, N(C)CHC*H*), 6.62 (d, *J* = 8.8 Hz, 2 H, N(C)C*H*), 2.98 (s, 6 H, NCH_3), 1.46 (s, 9 H, S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 150.3 (C_q), 133.4 (CH), 129.0 (CH), 111.8 (C_q), 97.0 (Ar***C***≡C), 76.2 (ArC≡***C***), 48.1 (C_q), 40.4 (CH_3), 30.4 (CH_3); LRMS (EI) *m/z* (%) 233 (M^+, 33), 213 (18), 177 (100); HRMS (EI) calcd for $C_{14}H_{19}NS$ (M^+) 233.1233, found 233.1234.

3-((*tert*-butylthio)ethynyl)pyridine **217**



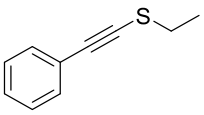
Column chromatography using 30% Et_2O/PE gave a colourless oil: 38 mg, 54%; IR ν_{max} (film)/cm^{-1} 2961, 2162, 1160, 729; ^1H NMR (600 MHz, $CDCl_3$) δ_H 8.65 (s, 1 H, NC*H*(C)), 8.49 (d, *J* = 3.4 Hz, 1 H, NC*H*CH), 7.69 (dt, *J* = 7.8, 2.1 Hz, 1 H, NCH(C)C*H*), 7.23 (dd, *J* = 7.8, 4.8 Hz, 1 H, NCHC*H*), 1.49 (s, 9 H, S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 152.1 (CH), 148.1 (CH), 138.2 (CH), 123.0 (CH), 121.0 (C_q), 92.9 (Ar***C***≡C), 83.5 (ArC≡***C***), 48.9 (C_q), 30.5 (CH_3); LRMS (EI) *m/z* (%) 191 (M^+, 10), 169 (100), 135 (47), 122 (15); HRMS (EI) calcd for $C_{11}H_{13}NS$ (M^+) 191.0763, found 191.0756.

1,3-bis((*tert*-butylthio)ethynyl)benzene **218**



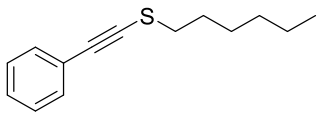
Variation from general procedure: 8.0 eq. of thiol and potassium hydride used and 4.0 eq. of dimethylamine used. Column chromatography using PE gave a white solid: 65 mg, 59%; IR ν_{max} (solid)/cm^{-1} 2957, 2918, 2897, 2860, 2154, 1158, 791; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.48 (t, *J* = 1.5 Hz, 1 H, (ArC)C*H*(ArC)), 7.33 (dd, *J* = 7.9, 1.5 Hz, 2 H, (ArC)C*H*CH), 7.24 (t, *J* = 7.9 Hz, 1 H, (ArC)CHC*H*), 1.48 (s, 18 H, S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 133.9 (CH), 130.6 (CH), 128.4 (CH), 124.1 (C_q), 95.5 (Ar***C***≡C), 80.1 (ArC≡***C***), 48.7 (C_q), 30.5 (CH_3); LRMS (EI) *m/z* (%) 302 (M^+, 20), 225 (15), 190 (100); HRMS (EI) calcd for $C_{18}H_{22}S_2$ (M^+) 302.1157, found 302.1159.

Ethyl(phenylethynyl)sulfane **220**



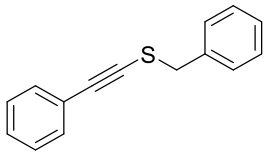
Column chromatography using 10% Et_2O/PE gave a colourless oil: 38 mg, 64%; IR ν_{max} (film)/cm^{-1} 2963, 2925, 2165, 1255, 752; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.43 (m, 2 H, *o*-Ar*H*), 7.30 (m, 3 H, *m*- and *p*-Ar*H*), 2.83 (q, *J* = 7.3 Hz, 2 H, SCH_2), 1.47 (t, *J* = 7.3 Hz, 3 H, SCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (CH), 128.4 (CH), 128.1 (CH), 123.6 (C_q), 93.5 (Ar***C***≡C), 79.5 (ArC≡***C***), 30.1 (CH_2), 14.9 (CH_3); LRMS (EI) *m/z* (%) 162 (M^+, 10), 134 (20), 86 (47), 84 (100); HRMS (EI) calcd for $C_{10}H_{10}S$ (M^+) 162.0498, found 162.0498. Data in agreement with literature.[28]

Hexyl(phenylethynyl)sulfane **221**



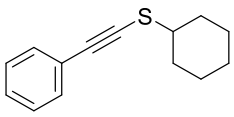
Column chromatography using PE gave a colourless oil: 55 mg, 69%; IR ν_{max} (film)/cm^{-1} 2955, 2926, 2166, 752; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.42 (m, 2 H, *o*-Ar*H*), 7.30 (m, 3 H, *m*- and *p*-Ar*H*), 2.81 (t, *J* = 7.3 Hz, 2 H, SCH_2), 1.81 (quint, *J* = 8.0 Hz, 2 H, SCH_2CH_2), 1.47-1.44 (m, 2 H, $S(CH_2)_3CH_2$), 1.35-1.32 (m, 4 H, $SCH_2)_2CH_2$ and $S(CH_2)_4CH_2$), 0.91 (t, *J* = 7.0 Hz, 3 H, $S(CH_2)_5CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (CH), 128.3 (CH), 128.0 (CH), 123.7 (C_q), 92.9 (Ar***C***≡C), 79.8 (ArC≡***C***), 35.9 (CH_2), 31.4 (CH_2) , 29.3 (CH_2), 28.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3); LRMS (EI) *m/z* (%) 218 (M^+, 60), 134 (100); HRMS (EI) calcd for $C_{14}H_{18}S$ (M^+) 218.1124, found 218.1120. Data in agreement with literature.[28]

Benzyl(phenylethynyl)sulfane **222**



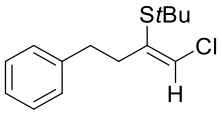
Column chromatography using PE gave a colourless oil: 53 mg, 65%; IR ν_{max} (film)/cm^{-1} 3058, 2922, 2165, 1068, 750; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.41-7.23 (m, 10 H, Ar*H*), 4.03 (s, 2 H, SCH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 136.7 (C_q), 131.4 (CH), 129.2 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 123.4 (C_q), 94.7 (Ar***C***≡C), 79.2 (ArC≡***C***), 40.5 (CH_2); LRMS (EI) *m/z* (%) 224 (M^+, 25), 191 (45), 91 (100); HRMS (EI) calcd for $C_{15}H_{12}S$ (M^+) 224.0654 found 224.0647. Data in agreement with literature.[28]

Cyclohexyl(phenylethynyl)sulfane **223**



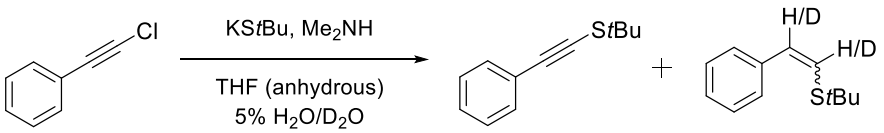
Column chromatography using PE gave a colourless oil: 77 mg, 97%; IR ν_{max} (film)/cm^{-1} 2930, 2902, 2852, 2161, 1261; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.43-7.41 (m, 2 H, *o*-Ar*H*), 7.31-7.28 (m, 3 H, *m*- and *p*-Ar*H*), 3.00 (tt, *J* = 10.9, 3.7 Hz, 1 H, SC*H*), 2.14-2.09 (m, 2 H, SCHC*H*), 1.83 (dt, *J* = 13.5, 3.7 Hz, 2 H, $SCHCH_2CH$), 1.67-1.63 (m, 1 H, $SCHCH_2CH_2CH$), 1.57 (qd, *J* = 11.7, 3.4 Hz, 2 H, SCHC*H*), 1.37 (qt, *J* = 11.7, 3.4 Hz, 2 H, $SCHCH_2CH$), 1.30-1.26 (m, 1 H, $SCHCH_2CH_2CH$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (CH), 128.4 (CH), 128.0 (CH), 123.7 (C_q), 94.5 (Ar***C***≡C), 78.7 (ArC≡***C***), 47.8 (CH), 33.1 (CH_2), 26.2 (CH_2), 25.6 (CH_2); LRMS (EI) *m/z* (%) 216 (M^+, 10), 134 (30), 89 (100), 83 (61), 62 (66); HRMS (EI) calcd for $C_{14}H_{16}S$ (M^+) 216.0967 found 216.0966. Data in agreement with literature.[28]

(*Z*)-*tert*-butyl(1-chloro-4-phenylbut-1-en-2-yl)sulfane **219**



Column chromatography using 5% Et_2O/PE gave a colourless oil: 57 mg, 74%; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.28-7.30 (t, *J* = 6.0 Hz, 2 H, *m*-Ar*H*), 7.19-7.22 (t, *J* = 9.0 Hz, 1 H, *p*-Ar*H*), 7.16-7.17 (d, *J* = 6.0 Hz, 2 H, *o*-Ar*H*), 6.42 (s, 1 H, SC=CCl*H*), 2.87-2.90 (t, *J* = 9.0 Hz, 2 H, ArCH_2), 2.66-2.68 (t, *J* = 9.0 Hz, 2 H, $ArCH_2CH_2$), 1.44 (s, 9 H, S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 141.1 (C_q), 137.0 (C_q), 128.7 (CH), 128.6 (CH), 126.2 (CH), 125.7 (C_q), 48.8 (C_q), 41.6 (CH_3), 34.9 (CH_2), 32.3 (CH_2); LRMS (ESI) *m/z* (%) 293 ($[M+K]^+$, 100), 259 (10), 277 (20), 242 (35); HRMS (ESI) calcd for $C_{14}H_{18}ClKS$ ($[M+K]^+$) 293.0533, found 293.0540.

4.2.4 Synthesis of addition products



A flame-dried flask was charged with a stirring bar and 2-methylpropane-2-thiol (0.132 g, 1.46 mmol, 4.0 equiv.), followed by anhydrous THF (2 mL) under argon and heated to 50 °C. Potassium hydride (59 mg, 1.46 mmol, 4.0 equiv., supplied as a 30% weight dispersion in mineral oil which was rinsed with PE and dried between filter paper immediately prior to use) was then added as a single portion and the mixture was stirred at 50 °C for 15 min. The mixture was allowed to cool, first to room temperature and then to –40 °C. Dimethylamine solution (2.0 M in THF, 0.37 mL, 0.73 mmol, 2.0 equiv.) was added *via* syringe, followed immediately after by (chloroethynyl)benzene (0.37 mmol, 1.0 equiv.) in THF doped with H_2O or D_2O (1 mL). After 10 min, the solution was allowed to warm to room temperature and left to stir under an atmosphere of argon. The reaction mixture was then carefully quenched with water (20 mL), diluted with Et_2O (30 mL) and washed with brine (20 mL). The aqueous layer was extracted with Et_2O (30 mL) and the organic portions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (PE) to yield desired thioynol ether and addition products in 3:2 ratio for reaction doped with water.

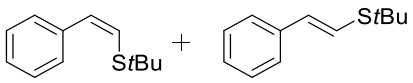
Table of results

Dopant	Ratio of products (alkyne:alkene)*	(*Z*):(*E*) ratio of minor product**
H_2O	3:2	95:5

*Ratio of ynol ether (major product) to enol ethers (minor products) calculated from ^{1}H NMR

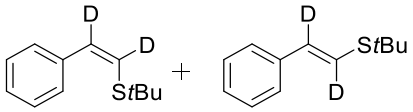
**Ratio of *Z* and *E* isomers of enol ethers (minor products) determined by ratio of ^{1}H NMR peaks

(*Z*/*E*)-*tert*-butyl(styryl)sulfane **190** and **191**



Inseparable isomers obtained as colourless oil (*Z*:*E* ratio of 95:5): 8 mg, 29%; IR ν_{max} (film)/cm^{-1} 2959, 2923, 2865, 1672, 1592; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.51 (d, *J* = 7.8 Hz, 1 H, (*Z*) isomer, *o*-Ar*H*), 7.35 (t, *J* = 18.7 Hz, 2 H, (*Z*) isomer, *m*-Ar*H*), 7.36-7.19 (m, 4 H, (*E*) isomer, *o*- and *m*-Ar*H*), 7.22-7.18 (m, 1 H, (*E*) isomer, *p*-Ar*H*) and (t, *J* = 18.1 Hz, 1 H, (*Z*) isomer, *p*-Ar*H*), 6.89 (d, *J* = 15.7 Hz, 1 H, (*E*) isomer, ArC*H*), 6.74 (d, *J* = 15.7 Hz, 1 H, (*E*) isomer, ArC=C*H*), 6.50 (d, *J* = 11.2 Hz, 1 H, (*Z*) isomer, ArC*H*), 6.46 (d, *J* = 11.2 Hz, 1 H, (*Z*) isomer, ArC=C*H*), 1.43 (s, 9 H, (*Z*) isomer, S(C)CH_3), 1.41 (s, 9 H, (*E*) isomer S(C)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (*Z*) isomer: 137.2 (CH), 128.8 (CH), 128.2 (CH), 126.6 (C_q), 125.4 (CH), 123.5 (CH), 44.6 (C_q), 30.8 (CH_3) and (*E*) isomer: 135.8 (CH), 132.1 (CH), 128.7 (CH), 126.1 (C_q), 125.6 (CH), 122.2 (CH), 44.5 (C_q), 31.1 (CH_3); LRMS (EI) *m/z* (%) 192 (M^+, 20), 136 (100), 83 (45); HRMS (EI) calcd for $C_{12}H_{16}S$ (M^+) 192.0967, found 192.0968. Data in agreement with literature.[227]

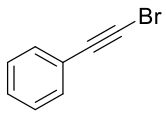
(*Z*/*E*)-*tert*-butyl(styryl)sulfane-*d*^{2} **242** and **243**



Inseparable isomers obtained as colourless oil (*Z*:*E* ratio unknown): 7 mg, 39%; IR ν_{max} (film)/cm^{-1} 2962, 2924, 2897, 2862, 1717; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.50 (d, *J* = 7.9 Hz, 1 H, (*Z*) isomer), 7.36-7.33 (t, *J* = 8.5 Hz, 2 H, (*Z*) isomer), 7.36-7.20 (m, 4 H, (*E*) isomer), 7.23-7.18 (m, 1 H, (*E*) isomer and t, *J* = 7.3 Hz, 1 H, (*Z*) isomer), 1.43 (s, 9 H, (*Z*) isomer), 1.41 (s, 9 H, (*E*) isomer); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (*Z*) isomer: 137.2, 128.8, 128.2, 126.6, 125.3, 123.5, 44.6, 30.9 and (*E*) isomer: 135.2, 131.8, 128.7, 125.4, 124.4, 123.4, 31.4, 31.1; LRMS (EI) *m/z* (%) 194 (M^+, 100), 138 (60), 124 (20); HRMS (EI) calcd for $C_{12}H_{16}S$ (M^+) 194.1093, found 194.1094.

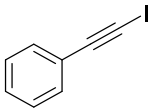
4.2.5 Synthesis of halo(phenylacetylenes)

(Bromoethynyl)benzene **182**



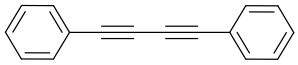
To a stirring solution of phenylacetylene (1.02 g, 10.0 mmol) in acetone (50 mL) at room temperature was added recrystallised *N*-bromosuccinimide (1.96 g, 11.0 mmol) followed by silver nitrate (170 mg, 1.00 mmol) and the mixture was stirred at room temperature for 3 h. The heterogeneous mixture was diluted with hexanes (100 mL) and the white salt was filtered off. The cloudy filtrate was concentrated *in vacuo* and purified by flash column chromatography using PE to give a colourless oil (1.41 g, 78%). Product stored in the freezer. δ_H (600 MHz, $CDCl_3$) 7.46-7.49 (m, 2 H, *m*-Ar*H*), 7.31-7.36 (m, 3 H, *o*- and *p*-Ar*H*); δ_C (150 MHz, $CDCl_3$) 132.0 (CH), 128.8 (CH), 128.5 (CH), 122.8 (C_q), 80.2 (Ar***C***≡C), 49.8 (ArC≡***C***); LRMS (CI) *m/z* (%) 183 ([M+H]$^+$, ^{81}Br, 98), 181 ([M+H]$^+$, ^{79}Br, 100), 129 (23), 102 (64). Data in agreement with literature.[190,191]

(Iodoethynyl)benzene **183**



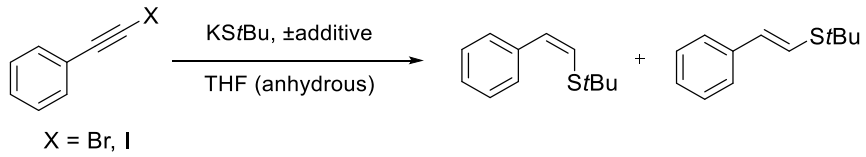
In a flame-dried flask which was backfilled with argon, a solution of phenylacetylene (1.00 g, 9.79 mmol) in dry THF (9 mL) at −78 °C was treated with *n*-butyllithium (6.7 mL, 1.6 M solution in hexanes, 10.7 mmol) over 5 min. The resulting yellow solution was stirred at −78 °C for 30 min then a solution of iodine (2.73 g, 10.7 mmol) in dry THF (9 mL) was added slowly over 5 min and the deep orange mixture was stirred at −78 °C for a further 1.5 h. The mixture was then allowed to warm to room temperature and poured into water (50 mL) and extracted with hexanes (50 mL). The aqueous layer was extracted again with hexanes (30 mL) and the organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography using PE to give the product as a colourless oil (1.74 g, 78%). Product stored in the freezer. δ_H (600 MHz, $CDCl_3$) 7.42-7.45 (m, 2 H, *m*-Ar*H*), 7.28-7.33 (m, 3 H, *o*- and *p*-Ar*H*); δ_C (150 MHz, $CDCl_3$) 132.3 (CH), 128.8 (CH), 128.2 (CH), 123.4 (C_q), 94.2 (Ar***C***≡C), 6.1 (ArC≡***C***); LRMS (CI) *m/z* (%) 229 ([M+H]$^+$, 9), 228 (100), 130 (15), 102 (91). Data in agreement with literature.[192]

1,4-Diphenylbuta-1,3-diyne **188**



In a flame-dried flask which was backfilled with argon, a solution of phenylacetylene (0.409 g, 4.00 mmol) in dry THF (20 mL) at −78 °C was treated with *n*-butyllithium (2.8 mL, 1.6 M solution in hexanes, 4.40 mmol) over 5 min. The resulting yellow solution was stirred at −78 °C for 30 min then a solution of *N*-fluorobenzenesulfonimide (97%, 1.56 g, 4.80 mmol) in dry THF (20 mL) was added slowly over 5 min and the resulting mixture was stirred at −78 °C for a further 1 h. The subsequent mixture was then allowed to warm to room temperature and stirred for a further 4 h. The orange solution was then quenched with saturated ammonium chloride (50 mL) and diluted with Et_2O (50 mL). The aqueous layer was extracted again with Et_2O (50 mL) and the organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography using PE to give the product as a colourless oil (0.148 g, 18%). δ_H (600 MHz, $CDCl_3$) 7.57-7.53 (m, 4 H), 7.39-7.33 (m, 6 H); δ_C (150 MHz, $CDCl_3$) 132.6, 129.3, 128.5, 121.9, 81.6, 74.0; LRMS (CI) *m/z* (%) 203 ($[M+H]^+$, 100), 84 (13). Data in agreement with literature.[228]

4.2.6 Addition products from bromo- and iodoalkynes



A flame-dried flask was charged with a stirring bar and 2-methylpropane-2-thiol (0.132 g, 1.46 mmol, 4.0 equiv.), followed by anhydrous THF (2 mL) under argon and heated to 50 °C. Potassium hydride (59 mg, 1.46 mmol, 4.0 equiv., supplied as a 30% weight dispersion in mineral oil which was rinsed with PE and dried between filter paper immediately prior to use) was then added as a single portion and the mixture was stirred at 50 °C for 15 min. The mixture was allowed to cool, first to room temperature and then to –40 °C. The additive (dimethylamine or *N,N*-dimethylethylenediamine) (0.73 mmol, 2.0 equiv.), if any, was added *via* syringe, followed immediately after by the alkynyl halide (0.37 mmol, 1.0 equiv.) in THF (1 mL). After 10 min, the solution was allowed to warm to room temperature and left to stir under an atmosphere of argon. The reaction mixture was then carefully quenched with water (20 mL), diluted with Et_2O (30 mL) and washed with brine (20 mL). The aqueous layer was extracted with Et_2O (30 mL) and the organic portions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using PE to yield the addition products as inseparable isomers.

Table of results

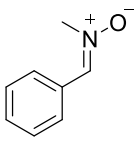
X	**Me_2NH**		**DMEDA**		**No additive**	
	Yield (%)*	(*Z*):(*E*)	Yield (%)*	(*Z*):(*E*)	Yield (%)*	(*Z*):(*E*)
Br	46	91:9	66	91:9	64	78:22
I	40	92:8	77	89:11	49	83:17

*Yield of thioenol ether product

**Ratio of *Z* and *E* isomers of enol ethers determined by ratio of ^1H NMR peaks

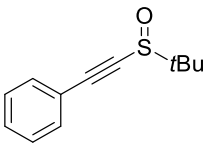
4.2.7 Applications of alkynyl sulfides and their derivatives

(*E*)-*N*-methyl-1-phenylmethanimine oxide **247**



Benzaldehyde (0.106 g, 1.00 mmol) and *N*-methyl hydroxylamine hydrochloride (84 mg, 1.00 mmol) were dissolved in CH_2Cl_2 (8 mL); anhydrous magnesium sulfate (0.200 g, 1.66 mmol) and $NaHCO_3$ (0.110 g, 1.30 mmol) were added to the mixture. The reaction flask was fitted with a reflux condenser and heated at reflux for 24 h. The reaction was allowed to cool to r.t. and the resulting white emulsion was filtered under gravity and solvent was removed *in vacuo* to give a pale yellow solid. Purification was achieved by recrystallisation from hot toluene to give white crystals (0.108 g, 80%). δ_H (600 MHz, $CDCl_3$) 8.22-8.19 (m, 2 H, *o*-Ar*H*), 7.43-7.39 (m, 3 H, *m*- and *p*-Ar*H*), 7.36 (s, 1 H, ArC*H*), 3.87 (s, 3 H, CH_3); δ_C (150 MHz, $CDCl_3$) 135.4 (CH), 130.6 (CH), 130.5 (CH), 128.6 (C_q), 128.5 (CH), 54.5 (CH_3); LRMS (EI) *m/z* (%) 135 (M^+, 82), 134 (100), 77 (24); HRMS (EI) calcd for C_8H_9NO (M^+) 135.0641, found 135.0676. Data in agreement with literature.[229]

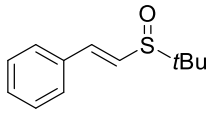
((*Tert*-butylsulfinyl)ethynyl)benzene **250**



A solution of *m*-CPBA (45 mg, 0.263 mmol) in $CHCl_3$ (1.5 mL) was slowly added over 3 min to a stirring solution of *tert*-butyl(phenylethynyl)sulfane (50 mg, 0.263 mmol) in $CHCl_3$ (1.5 mL) at −40 °C. After 2 h, the reaction was allowed to warn to −20 °C; a further 1.5 h resulted in the remaining starting material being consumed. The reaction mixture was filtered to remove the unwanted white precipitate and the filtrate was diluted with $CHCl_3$ (20 mL) and washed twice with sat. Na_2CO_3 solution (2 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$ and then filtered. The solvent was removed *in vacuo.* Purification by column chromatography using 20% Et_2O/PE gave a pale yellow oil (0.219 g,

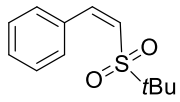
58%). δ_H (600 MHz, $CDCl_3$) 7.54-7.51 (m, 2 H, *o*-Ar*H*), 7.43 (tt, *J* = 7,5, 2.3, 1.3 Hz, 1 H, *p*-Ar*H*), 7.39-7.35 (m, 2 H, *m*-Ar*H*), 1.44 (s, 9 H, S(C)CH_3); δ_C (150 MHz, $CDCl_3$) 132.4 (CH), 130.6 (CH), 128.7 (CH), 120.1 (C_q), 102.5 (Ar***C***≡C), 83.8 (ArC≡***C***), 58.8 (C_q), 23.2 (CH_3); LRMS (CI) *m/z* (%) 413 ($[2M+H]^+$, 100), 224 ($[M+NH_3]^+$, 72), 207 ($[M+H]^+$, 27); HRMS (CI) calcd for $C_{12}H_{15}SO$ (M^+) 207.08381, found 207.08379. Data in agreement with literature.[132]

(*E*)-(2-(*tert*-butylsulfinyl)vinyl)benzene **257**



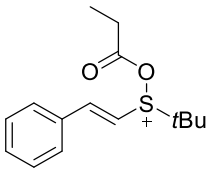
Phenol (3.76 g, 40.0 mmol) was dissolved in H_2O (30 mL) and (*E*)-*tert*-butyl(styryl)sulfane (1.92 g, 10.0 mmol) was added at r.t. To the stirring solution was added hydrogen peroxide (3.4 mL, 30.0 mmol supplied as 30 wt% in H_2O) and stirring of the reaction mixture at r.t. was continued. After 2 h, the starting material was consumed and two components were present. The reaction was slowly quenched with sat. $Na_2S_2O_3$ solution and then extracted with $CHCl_3$ (3 × 30 mL). The organic layers were combined, dried over anhydrous $MgSO_4$ and then filtered. The solvent was removed *in vacuo.* Purification by column chromatography using 20% Et_2O/PE gave the desired product as a colourless oil (1.57 g, 75%) followed by (*Z*)-(2-(*tert*-butylsulfonyl)vinyl)benzene. δ_H (600 MHz, $CDCl_3$) 7.49-7.46 (m, 2 H, *o*-Ar*H*), 7.40-7.33 (m, 3 H, *m*- and *p*-Ar*H*), 7.22 (d, *J* = 15.6 Hz, 1 H, ArC*H*), 6.79 (d, *J* = 15.6 Hz, 1 H, ArCHC*H*), 1.29 (s, 9 H, CH_3); δ_C (150 MHz, $CDCl_3$) 138.4 (CH), 129.6 (CH), 129.1 (CH), 129.0 (C_q), 127.7 (CH), 126.7 (CH), 55.8 (C_q), 23.2 (CH_3); LRMS (CI) *m/z* (%) 417 ($[2M+H]^+$, 16), 226 ($[M+NH_3]^+$, 76), 209 ($[M+H]^+$, 100); HRMS (CI) calcd for $C_{12}H_{17}SO$ ($[M+H]^+$) 209.0995, found 209.0995. Data in agreement with literature.[230]

(*Z*)-(2-(*tert*-butylsulfonyl)vinyl)benzene **258**



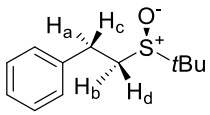
Colourless oil (172 mg, 8%). δ_H (600 MHz, $CDCl_3$) 7.54-7.51 (m, 2 H, *o*-Ar*H*), 7.38-7.31 (m, 3 H, *m*- and *p*-Ar*H*), 7.14 (d, *J* = 11.2 Hz, 1 H, ArC*H*), 6.24 (d, *J* = 11.2 Hz, 1 H, ArC=C*H*), 1.26 (s, 9 H, S(C)CH_3); δ_C (150 MHz, $CDCl_3$) 141.2 (CH), 134.3 (CH), 131.2 (CH), 130.0 (C_q), 129.4 (CH), 128.6 (CH), 55.9 (C_q), 22.9 (CH_3); LRMS (CI) *m/z* (%) 226 ([M+H]$^+$, 36), 211 (5), 210 (16), 209 (100); HRMS (CI) calcd for $C_{12}H_{17}SO_2$ ([M+H]$^+$) 226.1022, found 226.1023. Data in agreement with literature.[230]

(*E*)-*tert*-butyl(propionyloxy)(styryl)sulfonium chloride **261**



In a flame-dried flask, backfilled with argon, triethylamine (0.22 mL, 163 mg, 1.61 mmol) was added dropwise to a stirring solution of propionyl chloride (0.14 mL, 149 mg, 1.61 mmol) in CH_2Cl_2 (2 mL) at −78 °C. After 10 min, (*E*)-(2-(*tert*-butylsulfinyl)vinyl)benzene (134 mg, 0.644 mmol) in CH_2Cl_2 (2 mL) was added dropwise and the temperature was kept at −78 °C. The reaction was allowed to warm to r.t. after 1 h; following a further 4 h at r.t., the starting material was fully consumed so the reaction was quenched with H_2O and diluted with CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) and then the organic layers were combined, dried over anhydrous $MgSO_4$ and then filtered. The solvent was removed *in vacuo.* Purification by column chromatography using 10% EtOAc/PE gave a pale yellow oil (115 mg, 67%). δ_H (600 MHz, $CDCl_3$) 7.44-7.41 (m, 2 H, *o*-Ar*H*), 7.38-7.31 (m, 3 H, *m*- and *p*-Ar*H*), 6.43 (d, *J* = 7.4 Hz, 1 H,ArC*H*), 5.07 (d, *J* = 7.4 Hz, 1 H, ArC=C*H*), 2.39 (qd, *J* = 7.6, 1.7 Hz, 2 H, CH_3CH_2), 1.22 (s, 9 H, S(C)CH_3), 1.15 (t, *J* = 7.6 Hz, 3 H, CH_3CH_2); δ_C (150 MHz, $CDCl_3$) 173.4 (C_q), 137.6 (C_q), 128.9 (CH), 128.5 (CH), 128.3 (CH), 79.3 (CH), 64.9 (CH), 44.9 (C_q), 31.2 (CH_3), 28.0 (CH_2), 9.1 (CH_3); LRMS (EI) *m/z* (%) 265 (M^+, 20), 246 (36), 244 (100); HRMS (EI) calcd for $C_{15}H_{21}SO_2^+$ (M^+) 265.1257, found 265.1256.

(2-(*Tert*-butylsulfinyl)ethyl)benzene **262**



In a flame-dried flask, backfilled with argon, $LiAlH_4$ (0.38 mL, 0.380 mmol, supplied at 1 M solution in THF) was added dropwise to a stirring solution of (*E*)-*tert*-butyl(propionyloxy)(styryl)sulfonium chloride (80 mg, 0.300 mmol) in CH_2Cl_2 (2 mL) at r.t. The reaction mixture warmed up and effervesced as it turned cloudy and starting material was fully consumed within 2 min. The reaction was carefully quenched with H_2O (20 mL) and diluted with CH_2Cl_2 (20 mL); brine (20 mL) was added to aid the separation of layers. Following extractions of the aqueous layer with CH_2Cl_2 (2 × 20 mL), then the organic layers were combined, dried over anhydrous $MgSO_4$ and then filtered. The solvent was removed *in vacuo.* No purification was required as the product was formed exclusively as a colourless oil (58 mg, 92%). δ_H (600 MHz, $CDCl_3$) 7.37-7.30 (m, 4 H, *o*- and *m*-Ar*H*), 7.27-7.22 (m, 1 H, *p*-Ar*H*), 4.00-3.95 (m, 1 H, **H_a**), 3.80-3.73 (m, 1 H, **H_b**), 3.66-3.60 (m, 1 H, **H_c**), 2.27-2.23 (dd, *J* = 8.7, 4.9 Hz, 1 H, **H_d**), 1.30 (s, 9 H, S(C)CH_3); δ_C (150 MHz, $CDCl_3$) 141.9 (C_q), 128.7 (CH), 128.0 (CH), 127.3 (CH), 66.7(CH_2), 51.1 (CH_2), 44.3 (C_q), 31.6 (CH_3); LRMS (CI) *m/z* (%) 228 ($[M+NH_3]^+$, 86), 211 ($[M+H]^+$, 100), 193 (25); HRMS (CI) calcd for $C_{12}H_{19}SO$ (M^+) 211.1151, found 211.1152.

5. Appendix

Table of Schemes

Table of Figures

Organic & Biomolecular Chemistry

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An improved transition-metal-free synthesis of aryl alkynyl sulfides *via* substitution of a halide at an sp-centre†

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DOI: 10.1039/c5ob00494b

www.rsc.org/obc

A simple high-yielding preparation of aryl alkynyl sulfides is presented. The reaction of a chloroacetylene with a thiolate salt in the presence of an amine mediator (dimethylamine or *N*,*N*′-dimethylethylenediamine) yields the alkynyl sulfides in excellent yields. The alkynyl chloride is easily prepared from the parent alkyne.

Introduction

Acetylinic sulfides ('thioynol ethers') are valuable synthetic intermediates with applications in a variety of processes.[1] Their balance between stability and reactivity; being stable enough to purify and handle yet sufficiently reactive to undergo a wide variety of synthetic manipulations makes them (and their oxygen counterparts, ynol ethers) particularly versatile intermediates.[2] The high electron density and polarity in the bond due to the resonance structures are outlined in Fig. 1.

In particular, the high reactivity of the alkyne unit in cycloaddition processes is particularly valuable since complex molecules can be constructed in relatively few synthetic operations. Their reactions with electrophiles are similar to those of the related ynol ethers however the reactions of nucleophiles with these two classes of compounds are quite different. Ynol ethers tend to be attacked by nucleophiles at the α-carbon atom (bearing the oxygen substituent) whereas thioynol ethers are usually attacked at the β-carbon atom.[3] This property represents a potentially valuable 'Umpolung' strategy which has not yet been fully exploited (Scheme 1).

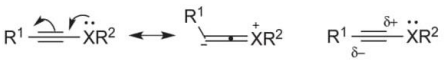

Fig. 1 Polarity exhibited by acetylinic ethers and thioethers.

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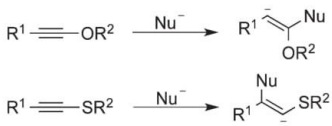
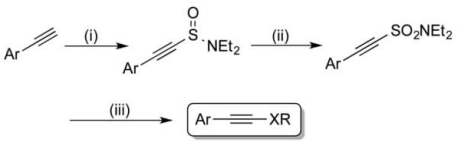
† Electronic supplementary information (ESI) available: Full experimental detail, characterization data including ^{1}H and ^{13}C NMR spectra are provided. See DOI: 10.1039/c5ob00494b



Scheme 1 Behaviour of acetylinic ethers and thioethers with nucleophiles.



Scheme 2 *Reagents and conditions*: (i) *n*BuLi then $ClSONEt_2$. (ii) $NaIO_4$, $RuCl_3$. (iii) KXR, THF, 0 °C, Me_2NH.

Our previous work had established a synthesis of ynol ethers and thioynol ethers based on the displacement of a sulfonamide leaving group at the sp-centre of an aryl acetylene.[4] Although this reaction works well, both in terms of reaction scope, rate and yield, the preparation of the alkynyl sulfonamide is non trivial and requires the preparation of the intermediate alkynyl sulfinamide followed by oxidation to the sulfonamide using $NaIO_4$ with $RuCl_3$ as a catalyst.[5] Furthermore, the sulfonamide moiety as a leaving group represents poor atom economy and conflicts with our aspirations to undertake sustainable transformations (Scheme 2).

Results and discussion

We recognized that a halide would be a more atom efficient precursor and easier to prepare than the alkynyl sulfonamides since these can be prepared in a single step from the parent alkyne. As such we prepared chloro-, bromo- and iodophenylacetylene by known literature procedures (Scheme 3).[6]

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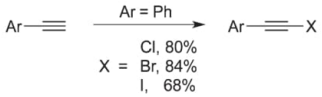
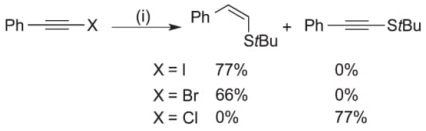


Scheme 3 *Reagents and conditions*: X = Cl: *n*BuLi then NCS. X = Br: NBS, $AgNO_3$, Me_2CO. X = I: *n*BuLi then I_2.



Scheme 4 *Reagents and conditions*: (i) KS*t*Bu, THF, RT, DMEDA.

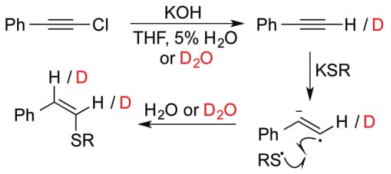
Exposure of each of these acetylinic halides to the potassium salt of *t*-butyl thiol under the conditions outlined in Scheme 2 gave the results shown in Scheme 4.

Pleasingly the chloroacetylenes yielded the thioynol ether in good yield whereas both bromo and iodoacetylenes led to the thioenol ethers as shown in Scheme 4. It appears that the weaker C–I and C–Br bonds allow a (well-documented) facile competing X-philic reaction resulting in oxidation of the thiolate nucleophile.[7] Protonation by trace amounts of moisture then lead to the parent alkyne that can then undergo addition reactions as we and others have previously described (Scheme 5).[8] The stronger C–Cl bond is apparently able to resist the competing X-philic pathway with the soft thiolate nucleophile and leads almost exclusively to the thioynol ether product in good yield.

We also noted that if the reaction was performed in the presence of small quantities of water (2–5%) then the formation of the thioynol ether was greatly suppressed and the thioenol ether was isolated instead, predominantly as the (*Z*)-geometrical isomer, suggesting the involvement of a radical anion intermediate (Scheme 6).[9] When water was replaced by D_2O, deuterium incorporation was observed in both vinylic positions. Presumably, when water is present, the hydroxide generated in the reaction medium undergoes the X-philic reaction with the acetylinic chloride to yield the parent alkyne (phenylacetylene) which can then undergo addition of thiol as outlined in Schemes 4 and 5.

The fact that alkynyl chlorides can be employed is significant since other methods of functionalizing acetylenes, particularly those that use transition metals, often rely on oxidative insertion into the weak C–X bond and almost invariably this renders alkynyl chlorides unsuitable. For example earlier preparations of thioynol ethers from thiols and alkynyl iodides and bromides employs copper or palladium catalysis.[10] The method outlined here therefore represents an alternative and potentially orthogonal method of preparing heteroatom substituted alkynes.

Scheme 5 X-philic reaction of thiolates with iodoacetylenes.



Scheme 6 Mechanistic pathway adopted when water is present.

We then turned our attention to investigating the reaction scope. Initially we prepared a range of alkynyl chlorides from commercially available acetylenes by the method outlined in Scheme 3 (**1a–l**, Fig. 2). In general this preparation is uneventful however, *p*-bromophenylchloroacetylene, **1e**, suffered a lower yield than the other examples, probably due to undesired metal–halogen exchange reactions when exposed to *n*BuLi.

Exposure of these acetylinic chlorides to the potassium salt of *t*-butyl thiol under the conditions shown in Fig. 3 yielded the small library of acetylinic sulfides in excellent yields.

If the amine additive is removed from the reaction mixture the reaction still proceeds, however reaction times are significantly extended. The precise role of this additive and how it exerts its beneficial effect on the reaction is somewhat ambiguous. Although we and others have speculated as to possible mechanistic roles for these additives, a decisive conclusion cannot yet be drawn.[9] It appears however that the additive may assist the initial electron transfer from the sulfur nucleophile to the alkyne.[11,12] Mechanistically therefore, we postulate that the reaction proceeds through a similar pathway as for the displacement of the sulfonamide group to which we have dedicated considerable effort.[5] This work has suggested that an addition-elimination mechanism is in operation but

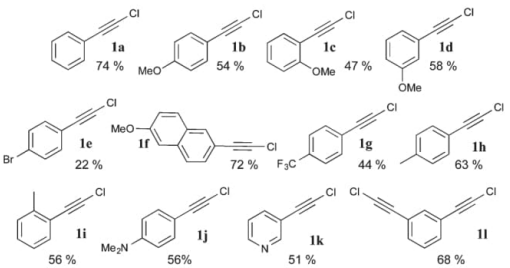


Fig. 2 Range of chloroacetylenes **1a–l** prepared.

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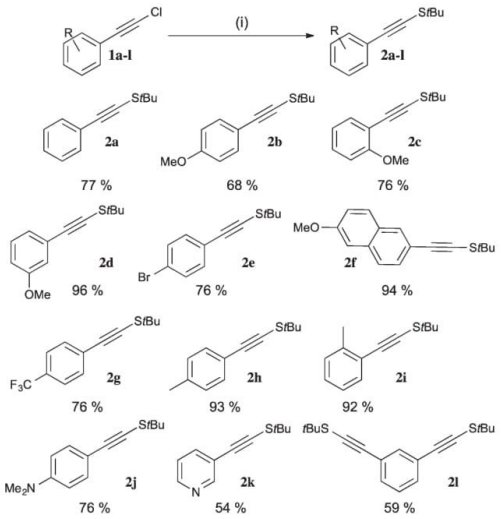
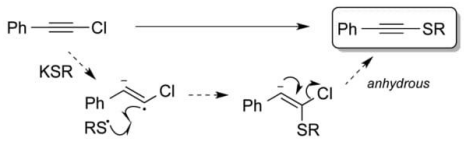


Fig. 3 *Reagents and conditions*: (i) KS*t*Bu, THF, −40 – RT, Me_2NH, 4 h.



Scheme 7 Postulated reaction mechanism.

that radical and radical anion intermediates are involved (Scheme 7).

Finally, we have demonstrated that other sulfur nucleophiles can be employed. Substituting *t*-butyl thiolates with various analogues furnishes the corresponding ynol ethers in good yields (Fig. 4).

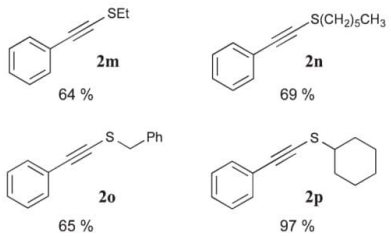


Fig. 4 Thioynol ethers **2m–2p** bearing alternative R groups.

In conclusion a short and efficient approach to aryl thioynol ethers from the acetylinic chlorides has been described. These molecules have enormous synthetic potential and are difficult to prepare by other methods. No transition metals or heavy metal mediators are required and the use of chloride as the leaving group is more atom efficient and sustainable than other alternatives. Preliminary experiments suggest that a single electron transfer mechanism is in operation, which is consistent with our previous investigations in this field.

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Data tables from ynol ether study by temperature

−78 °C to r.t					Room temperature				
Entry	Amine	Halide	Time (h)	Yield (%)	Entry	Amine	Halide	Time (h)	Yield (%)
1A	Me_2NH	Cl	20	29	**5A**	Me_2NH	Cl	4	36
2A	DMEDA	Cl	20	24	**6A**	DMEDA	Cl	6	29
3A	1,10-phen	Cl	20	22	**7A**	1,10-phen	Cl	3	27
4A	No amine	Cl	20	6	**8A**	No amine	Cl	18	29
1B	Me_2NH	Br	20	11	**5B**	Me_2NH	Br	18	21
2B	DMEDA	Br	20	13	**6B**	DMEDA	Br	18	0
3B	1,10-phen	Br	20	10	**7B**	1,10-phen	Br	3	0
4B	No amine	Br	20	11	**8B**	No amine	Br	18	20
1C	Me_2NH	I	48	0	**5C**	Me_2NH	I	24	0
2C	DMEDA	I	48	0	**6C**	DMEDA	I	24	0
3C	1,10-phen	I	48	0	**7C**	1,10-phen	I	24	0
4C	No amine	I	48	0	**8C**	No amine	I	24	0

40 °C					60 °C				
Entry	Amine	Halide	Time (h)	Yield (%)	Entry	Amine	Halide	Time (h)	Yield (%)
9A	Me_2NH	Cl	3	25	**13A**	Me_2NH	Cl	3	25
10A	DMEDA	Cl	5	13	**14A**	DMEDA	Cl	5	13
11A	1,10-phen	Cl	2	24	**15A**	1,10-phen	Cl	2	24
12A	No amine	Cl	5	27	**16A**	No amine	Cl	5	27
9B	Me_2NH	Br	3	10	**13B**	Me_2NH	Br	3	10
10B	DMEDA	Br	6	0	**14B**	DMEDA	Br	6	0
11B	1,10-phen	Br	2	0	**15B**	1,10-phen	Br	2	0
12B	No amine	Br	6	19	**16B**	No amine	Br	6	19
9C	Me_2NH	I	18	0	**13C**	Me_2NH	I	18	0
10C	DMEDA	I	18	0	**14C**	DMEDA	I	18	0
11C	1,10-phen	I	24	0	**15C**	1,10-phen	I	24	0
12C	No amine	I	24	0	**16C**	No amine	I	24	0

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