New Applications for Sulfur-Based Leaving Groups in Synthesis

A dissertation presented by

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Declaration

I, Vincent James Gray, confirm that the work presented in this thesis is my own. Where information is derived from other sources, I confirm that it has been indicated and acknowledged.

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Abstract

This thesis describes the discovery and development of new routes towards substituted indoles and ynol ethers based on a sulfonate and sulfonamide leaving group, respectively. Both syntheses involve the use of these electron-withdrawing moieties as α–radical stabilising groups that can be utilised in a range of mild and facile bond-forming reactions to yield useful organic compounds.

The first approach describes the synthesis of indoles utilising a water soluble, phosphorus-based chain carrier that generates a carbon-centred radical from an sp^3 α-bromo sulfonate ester. This species can consequently undergo an intramolecular cyclisation with an aromatic ring, followed by loss of the sulfonate ester to yield a range of indoles in a chemoselective fashion.

The second part of this thesis describes the synthesis of a range of ynol ethers *via* reaction of an aliphatic potassium alkoxide with an aromatic alkynyl sulfonamide. The mechanism of this process has been explored *via* a combination of synthetic chemistry and electron paramagnetic resonance spectroscopy (EPR) and the findings of these experiments will be discussed. The synthesis of *tert*-butyl ynol ethers in particular, allows for retro-*ene* decomposition to yield a ketene. This reactive intermediate can consequently undergo [2+2] cycloaddition with a ynol ether to yield tri-substituted cyclobutenones in excellent yield.

Based on these findings, a new mode of reactivity for potassium alkoxides is suggested that involves these compounds ionising at room temperature under certain conditions to form either stabilised alkoxyl or trioxyl radical complexes that are observable *via* EPR, where the latter complex is known to decompose to alkoxyl radicals and molecular oxygen. The work presented in this thesis may have implications for other areas of science such as atmospheric chemistry and transition-metal free cross-coupling chemistry.

Contents

Abbreviations

AAI	Allylic alcohol isomerisation
Ac	Acetyl
acac	Acetylacetone
aq	Aqueous
Ar	Aryl
AIBN	Azo*bisiso*butyronitrile
BINAP	2,2'-*bis*(Diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Bu	Butyl
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DMEDA	*N*,*N*'-Diethylethylenediamine
DMF	*N*, *N*-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethyl sulfoxide
E	Electrophile
EPHP	1-Ethylpiperidine hypophosphite
EPR	Electron paramagnetic resonance
er	Enantiomeric ratio
G	Gauss
HMDS	Hexamethyldisilazide
HRMS	High resolution mass spectrometry
LRMS	Low resolution mass spectrometry
m	*meta*
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NTf	*bis*(Trifluoromethylsulfonyl)imide

Nu	Nucleophile
o	*ortho*
OTf	Trifluoromethanesulfonate
p	*para*
PE	Petroleum ether
Py	Pyridine
rt	Room temperature
sat	Saturated
SET	Single electron transfer
tert	Tertiary
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBAI	Tetra-*n*-butylammonium iodide
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	Toluene
Ts	Tosyl

Acknowledgements

I'd firstly like to thank my supervisor, Dr. Jon Wilden for his support throughout the past four years. It has been great fun to be able to work on a varied range of chemistry within his group and his stress-free approach to the subject has allowed me to form many of my own ideas and not be afraid to suggest them, no matter how absurd they seem. Towards the end of my PhD, EPR spectroscopy became an invaluable tool and I'd like to thank Dr. Chris Kay and Dr. Enrico Salvadori for a fruitful collaboration. Within the Wilden group, I'd like to thank Rhian, James, Yi and Roomi for putting up with my lab tantrums and many "picture but no sound" moments when reactions didn't work as expected. To my good friends- Favaad, Lauren, Sam, Niral and Mathilde thank you for making the lab an enjoyable place to work when I first started as well as the newer members of the Baker Group. Rachel, since you showed up I have put on over a stone thanks to the countless trips to Nando's and M&S for those cosmos which almost ruined me. Thanks for that! Matt, thank you for all the great nights out we've had on many occasions. You're a great fellow and I hope you go far. I'm also thankful for the good company of Eifion, Ramiz, Vijay, Fil, Osman, Liz, Sally, Cristina, Samantha, Rosemary and Natalie over the years, especially the 'lab calming' influence of Osman. My housemate David, whom I've lived with for the past four years, also deserves my gratitude for being an excellent domestic influence, especially after a bad day at work. Going back some years, I'd like to thank my secondary school form teacher, Mrs Avril Magowan for all her support and encouragement over the years. To my A-level chemistry teacher, Dr. Marie Ferris, I am also deeply indebted for having faith and perseverance in getting me interested in the subject. To my Bristol University gang- Charlotte, Alex and Becca, I'd like to thank you for being great friends and housemates through the undergrad years and for keeping in touch since we moved our separate ways. I'd finally like to thank my family for all their support over the years. For the numerous food parcels of bacon and potato bread, with the odd tenner slipped in, I am very grateful and love you all very much.

"God grant me the serenity
to accept the things I cannot change;
courage to change the things I can;
and wisdom to know the difference."

"The Serenity Prayer"
Reinhold Niebuhr

"…The voice I hear this passing night was heard
In ancient days by emperor and clown:
Perhaps the self-same song that found a path
Through the sad heart of Ruth, when, sick for home,
She stood in tears amid the alien corn…"

From "Ode to a Nightingale"
John Keats

Dedicated to the dreams & accomplishments

of Freddie Mercury.

Preface

This thesis discusses the discovery, development and study of two reactions that utilise sulfonamide and sulfonate esters as leaving groups in synthesis. The first reaction, discussed in Section 2, is a radical-mediated synthesis of indoles that is preceeded by an introduction to a range of indole syntheses found in the literature.

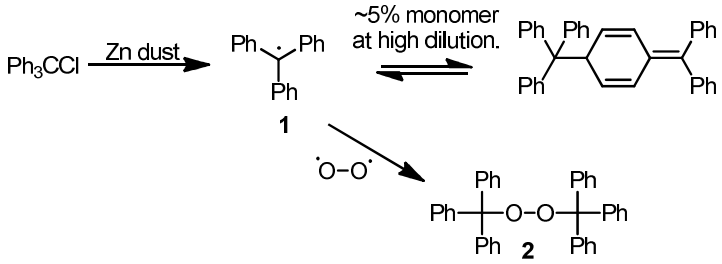
In Section 3 the synthesis of a range of ynol ethers is discussed, preceeded by an introduction to current methods towards such compounds. A mechanistic rationale is also given in an attempt to explain the unexpected reactivity and selectivity the reaction displays.

Both the indole and ynol ether syntheses discussed are thought to occur *via* radical-mediated pathways. Therefore, a brief introduction to organic radical chemistry is presented in Section 1.

1. Introduction

1.0 Organic Radical Chemistry

The use of radical-mediated processes in the field of organic chemistry has proven to be a fruitful method in the synthesis of many natural and unnatural products over the past century. Pioneering work by Moses Gomberg[1] at the turn of the twentieth century showed that preparation of the triphenylmethyl radical **1** could be achieved by treating chlorotriphenylmethane with zinc dust in the absence of oxygen. The yellow solution obtained being that of the triphenylmethyl radical **1** (**Scheme 1.0**). In the presence of triplet oxygen, the peroxide **2** is formed, indicating that a radical process is in operation.



Scheme 1.0.

Groundbreaking work by Ingold and Robinson in the 1920's laid foundations for the ionic (two electron) organic mechanism, which was successful in rationalising the outcome of many organic reactions. With this in mind, there was a lag time in the acceptance of organic radical chemistry. Studies by Koelsch on the structure of radical **3** were initially dismissed upon review on the basis that the radical was unreactive towards oxygen (**Figure 1.0**).

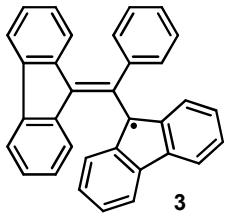
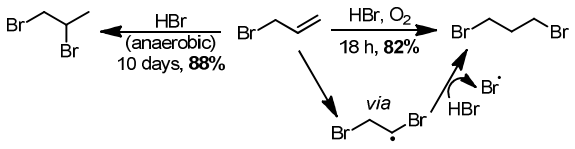


Figure 1.0

With the advent of electron paramagnetic resonance spectroscopy (EPR), it took over two decades (1957) to prove unequivocally that the structure shown in **Figure 1.0**

was indeed the radical species originally suggested. Koelsch's original sample was used for the EPR measurement and was shown to be stable under air after 23 years.[2]

It would take another three decades before the utility of organic radical chemistry was understood in greater depth. Work by Kharasch *et al.*[3] showed that treatment of olefins with hydrogen bromide in both the absence and presence of oxygen resulted in the Markovnikov and anti-Markovnikov products, respectively. For example, the reaction of allyl bromide with hydrogen bromide in the presence of oxygen was relatively more rapid than that of the anaerobic reaction and yielded the products shown in **Scheme 1.1** below.

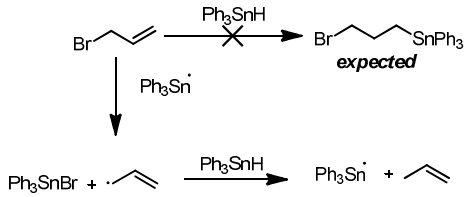


Scheme 1.1

Kharasch *et al.* therefore hypothesised that the presence of trace oxygen in the reaction mixure allowed for the formation of small amounts of allyl bromide peroxide which could undergo cleavage to yield a peroxide radical. This radical can then abstract a hydrogen atom from hydrogen bromide to form a bromine radical thus initiating a free radical chain reaction.

Important contributions to organic radical chemistry at this time were also made by Hey, who is regarded as the first person to realise that the thermal decomposition of benzoyl peroxide in solution produces peroxyl radicals.[4]

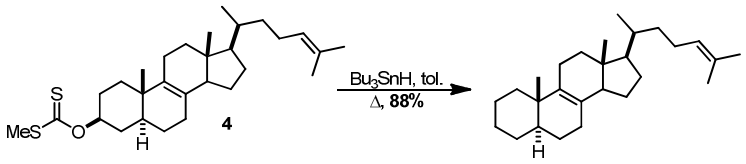
The emergence of organotin compounds as effective chain carriers soon allowed for radical chemistry began to rapidly develop and expand. Like many useful and important reactions in the modern-day chemist's armament, the reduction of alkyl halides with organotin hydrides was discovered by accident in the van der Kerk group in 1957, when expecting the hydrostannylated product shown in **Scheme 1.2**.[5]



Scheme 1.2

The formation of propene allowed for the deduction of a new radical mechanism with triphenyltin and oxygen shown to be excellent chain carriers and initiators, respectively.

Perhaps the best known use of organotin reagents in radical chemistry to-date was shown by Barton *et al.* who developed a method to deoxygenate alcohols *via* their xanthate esters.[6] The robustness of this method was proven in the deoxygenation of a range of complex substrates in high yield. For example, the radical reduction of lanosterol **4** showcases the usefulness of this method (**Scheme 1.3**).



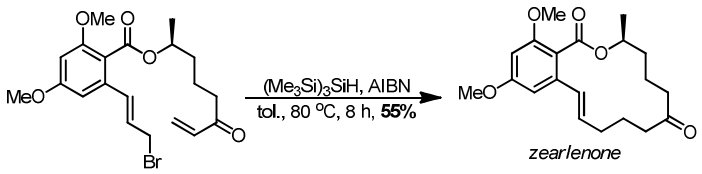
Scheme 1.3

For all the benefits of using tin-based chain carriers in synthesis, their toxicity and removal are common difficulties encountered when dealing with such reagents. To overcome these issues, the use of silicon hydrides has been developed as a relatively less-toxic alternative. One can initially assume such reagents as a poor choice for chain carriers as the Si-H bond is stronger than Sn-H. However, changing the alkyl substituents to silicon e.g. Et_3SiH to $(Me_3Si)_3SiH$ allows for the weakening of the Si-H bond.[7,8] (**Table 1.0**). It has been found more recently that this chemical property is due to the second row elements having greater radical spin delocalisation ability than the first which allows for a reduction in the Si-H bond strength.[9]

Entry	X-H	b.d.e (kcal mol^{-1})
1	$(C_2H_5)_3Si$-H	90
2	$(CH_3)_3Sn$-H	74
3	$(Me_3Si)_3Si$-H	79

Table 1.0

The key step in the synthesis of the macrolide- *zearlenone*, utilises ($(Me_3Si)_3Si$-H) to afford the product in fair yield (**Scheme 1.4**).[10] Although the use of Bu_3SnH results in a 60% yield, the time-consuming task of removing tin residues is avoided in this instance.



Scheme 1.4

In terms of radical structure and stability, both electron paramagnetic resonance and infrared spectroscopy have shown that the methyl radical is planar with the unpaired electron situated in a *p*-orbital. The repulsion between the unpaired electron and the C-H electron pairs allows for pyramidal distortion (**Scheme 1.5**).

Scheme 1.5

For the *tert*-butyl radical, a pyramidal geometry is adopted with a 1.2 kcal mol^{-1} barrier to inversion.[11,12] This pyramidal geometry is adopted due to a minimisation of torsional repulsions as well as maximisation of anti-periplanar hyperconjugative stabilisation.[13] A methyl CH bond eclipsing the half-filled p orbital will exert unsymmetrical hyperconjugative interactions on the radical centre. Hyperconjugation between a vicinal σ C-H bond and the half-filled p-orbital allows for stabilisation of the radical (**Figure 1.1**).

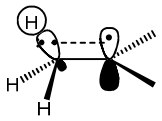


Figure 1.1

The orbital interactions shown in **Figure 1.1** result in the *tert*-butyl radical having nucleophilic character. This can be depicted in an orbital diagram (**Figure 1.2**), where the SOMO is raised and the HOMO lowered due to interaction with a β C-H bond.

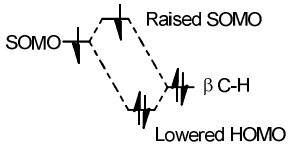


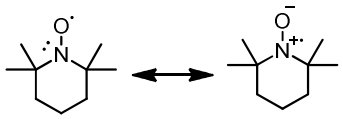
Figure 1.2

The stability of organic radicals is governed by both thermodynamic and kinetic factors. For the former, this stability is related to the bond dissociation energy of the R-X bond to give $R^{\cdot}$ and $X^{\cdot}$. The bond dissociation energy thus depends on the thermodynamic stability of $R^{\cdot}$ which is governed by conjugation, hyperconjugation, hybridisation and captodative effects. A set of stabilisation energies (E_s) for a range of radicals can be calculated given that the stabilisation of a methyl radical is considered to be zero (**Table 1.1**).[14]

R-H	**BDE (kcal mol^{-1})**	**E_s ($R^{\cdot}$) (kcal mol^{-1})**
CH_3-H	105	0
CH_3CH_2-H	101	4
$(CH_3)_3C$-H	95	10
F_3C-H	108	-3
CH_3O-H	104	1
PhH	111	-6

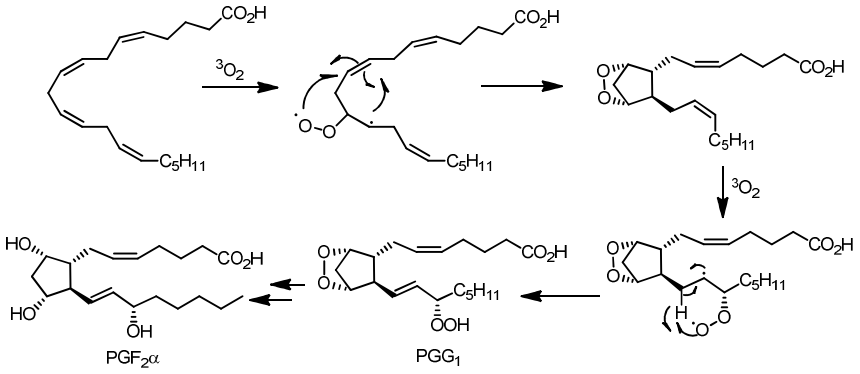
Table 1.1

The kinetic stability of a radical is generally governed by steric factors. Substrates with more sterically congested radical centres such as TEMPO are regarded as *persistent* because of their relatively long half-life. Such compounds can therefore be studied *via* IR and EPR spectroscopy to allow for greater understanding of their structure and properties. Another important factor that allows TEMPO to be a stable radical is the resonance form it can adopt due to the neighbouring nitrogen lone pair (**Scheme 1.6**).



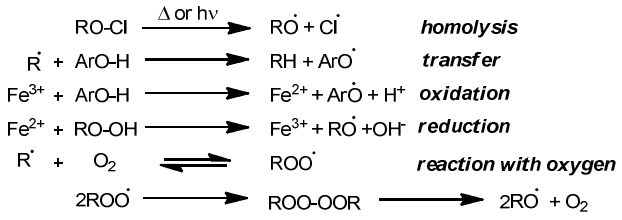
Scheme 1.6

Radical-mediated reactions can also be found in a multitude of biological processes. In particular, oxygen-centred radicals play an important role in the auto oxidation of unsaturated lipids. For example, the biosynthesis of prostaglandin $PGF_{2\alpha}$ involves the reaction of oxygen with *Arachidonic acid* followed by a cascade of cyclisation and isomerisation reactions (**Scheme 1.7**).



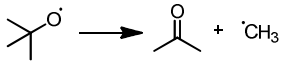
Scheme 1.7

Oxygen-centred radicals are electrophilic and the most common forms can be divided into three groups: oxyl ($RO^{\cdot}$), acyloxyl ($RC(O)O^{\cdot}$) and peroxyl ($ROO^{\cdot}$). There have been numerous methods devised to generate such radicals and these include: homoylsis, transfer, oxidation, reduction and reaction with oxygen **(Scheme 1.8**).[14]



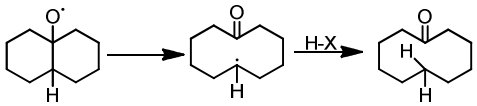
Scheme 1.8

Upon generation of an oxygen-centred radical, there are four general pathways in which the radical can react (fragmentation, addition, H-atom transfer and reaction with metals). For substituted alkoxy radicals e.g. *tert*-butoxy, β-fragmentation is the operative intramolecular reaction (**Scheme 1.9**).



Scheme 1.9

This reactivity can be harnessed in ring enlargement reactions to provide otherwise challenging synthetic targets (**Scheme 1.10**).

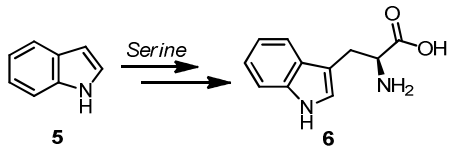


Scheme 1.10

Hydrogen transfer (H-atom abstraction by a given O-centred radical) is another reaction pathway in which oxygen radicals take part. As oxygen radicals are electrophilic, it is the enthalpy change of the reaction which governs the rate of hydrogen transfer. Given that the bond dissociation energies for RO-H and RCO_2-H are higher than that of most C-H bonds, H-atom transfer to alkoxy and acyloxyl radicals is generally a favourable process as the reactions are exothermic overall.

1.1 Indole- History and Medicinal Applications

Since the structural elucidation of Indole **5** by Baeyer and Emmerling in 1869,[15] and later the discovery by Hopkins[16] of its importance in biological systems as a group in the amino acid, tryptophan **6** (**Scheme 2.0**), there has been a constant interest in the synthesis of such compounds, in the area of natural products and pharmaceuticals.



Scheme 2.0

The presence of the indole motif in medicine is wide-ranging due to its high biological activity. Natural products such as *yohimbine* **7**[17] *reserpine* **8**[18] and *vincristine* **9**[19] have been used to treat a range of conditions such as male impotence, mental illness and cancer respectively (**Figure 2.0**).

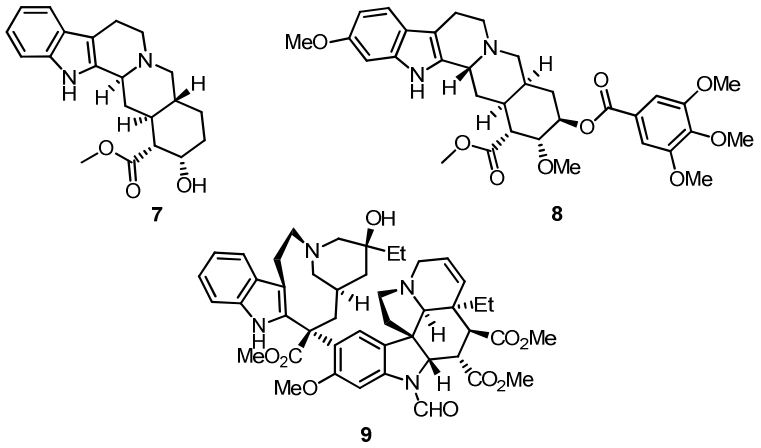
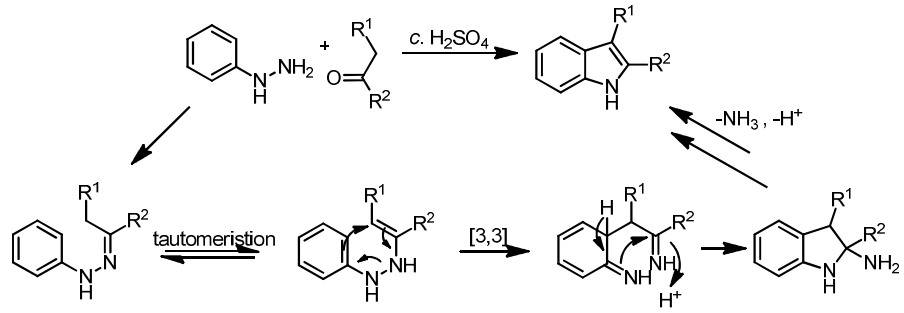


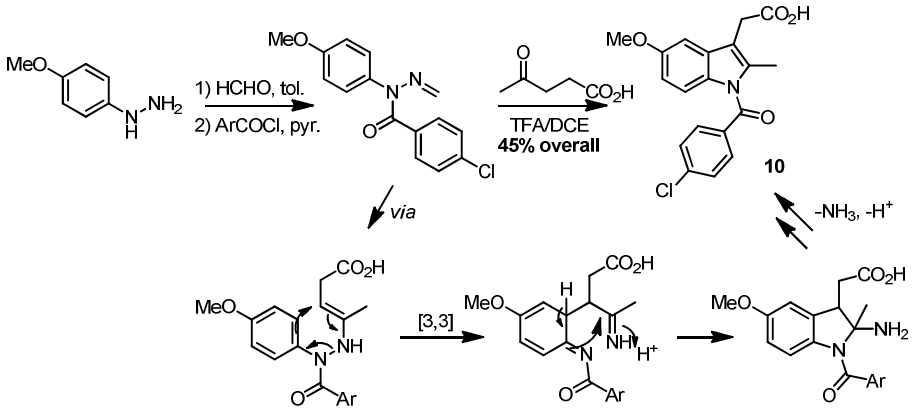
Figure 2.0

To date, there are many synthetic routes available for the preparation of indoles with varying degrees of substitution. The Fischer indole synthesis[20] is one of the earliest and, perhaps, best known methods for the synthesis of such compounds where an aryl hydrazine is reacted with a ketone under acidic conditions to form the indole *via* loss of ammonia (**Scheme 2.1**).



Scheme 2.1

Since its discovery, this reaction (and its variants) has been used in the synthesis of many important pharmaceuticals such as the nonsteroidal anti-inflammatory drug-*indomethacin* **10** (**Scheme 2.2**).[21] This compound has been used with varying degrees of success in patients suffering from arthritis[22] and Alzheimer's disease.[23] In this reaction, formaldehyde is used to protect the NH_2 group on the hydrazine as an imine. This allows selective amidation of the NH group with the acid chloride. The imine can then undergo acid hydrolysis followed by Fischer indole synthesis to yield the product.

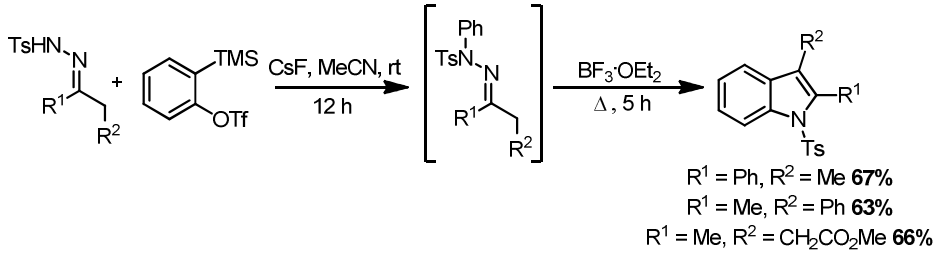


Scheme 2.2

1.2 Modern Approaches to Indoles

A contemporary approach to the Fischer indole synthesis was recently divulged by Greaney *et al.*[24] who envisaged trapping a benzyne intermediate with *N*-tosyl hydrazone to yield the arylated intermediate. With this intermediate at hand,

treatment with a Lewis acid under reflux smoothly afforded a range of substituted indoles in good to excellent yield (**Scheme 2.3**).

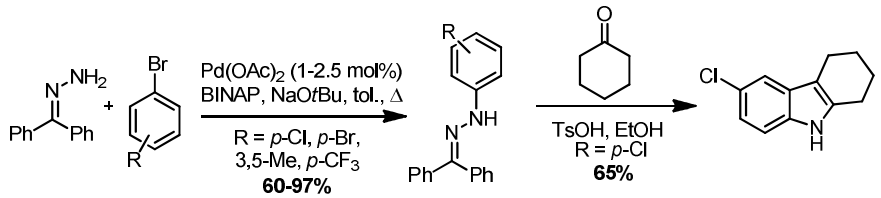


Scheme 2.3

This reaction adopts much milder conditions than the original Fischer synthesis and utilises a different set of organic building blocks in order to access the key arylhydrazone intermediate.

1.3 Pd-catalysed Indole Synthesis

The past decade has seen a surge of interest in the use of palladium as the reagent of choice for the synthesis of highly substituted indoles. Regarding the Fischer indole synthesis, many contributions have been made in designing new and easier ways to access the reaction's key intermediates. Buchwald *et al.* have presented[25] a new approach towards accessing *N*-arylhydrazones by harnessing the utility of Pd-mediated cross-coupling chemistry **(Scheme 2.4)**.

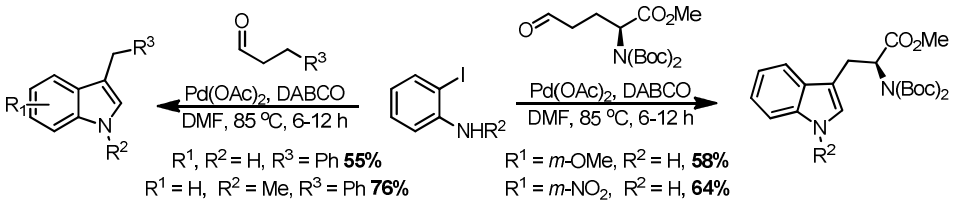


Scheme 2.4

This reaction provides advantages over the traditional Fischer indole synthesis as it avoids the initial synthesis of toxic and corrosive hydrazines, which are known for their instability. The *N*-arylhydrazone can be synthesised quickly and in good yields in the presence of catalytic palladium(II) acetate. With these compounds at hand, the

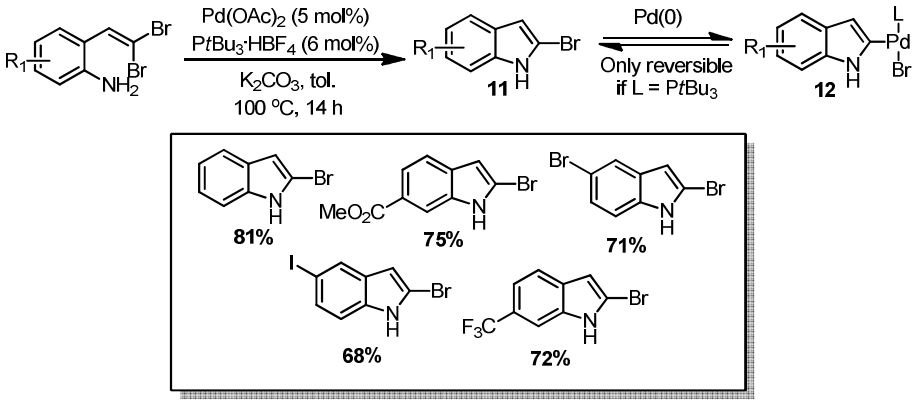
final condensation reaction can take place easily with an array of ketones to afford many structurally diverse indoles.

More recently, Zhu *et al*. have designed[26] a one-pot, Pd-catalysed synthesis of highly functionalised indoles and chiral tryptophans from *o*-haloanilines and aldehydes. This synthesis shows good substrate tolerance, with a range of electron donating and withdrawing groups giving good yields (**Scheme 2.5**).



Scheme 2.5

Selectively preserving a weaker carbon halide bond over another in a transition metal-mediated C-C bond forming process is be regarded as a difficult task to accomplish. Such a process would allow for useful functionality to be preserved in a molecule thus providing a synthetic handle for further, more elaborate transformations. In 2010, Lautens *et al.*[27] disclosed a new Pd-mediated indole synthesis that preserved both an aryl iodide and vinyl bromide bond in the coupling reaction shown below (**Scheme 2.6**).

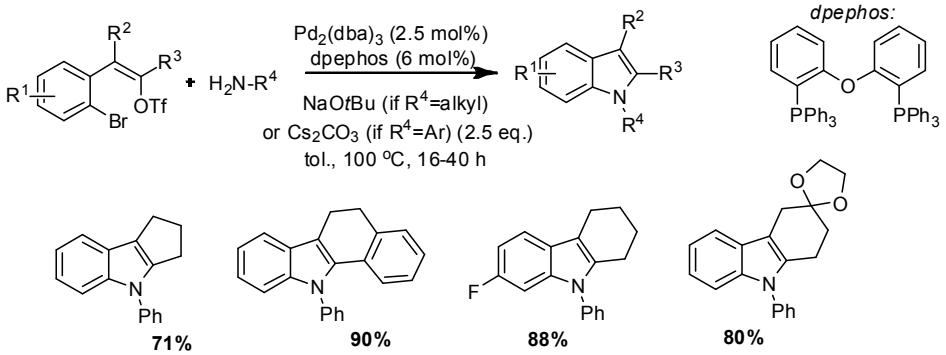


Scheme 2.6

With excellent scope and yields, this reaction provides highly useful substrates for further transition metal-mediated couplings. Lautens *et al.* state that it is the bulky

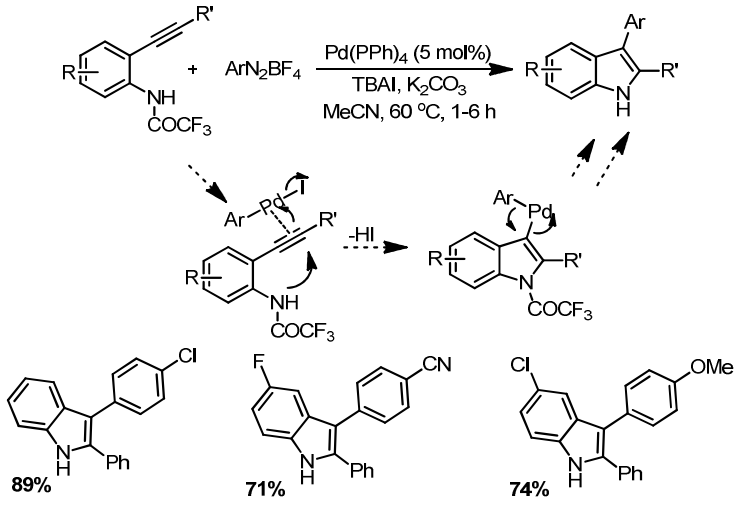
P^tBu_3 ligand that renders the oxidative addition of Pd(0) from **11** to **12** reversible, thus maintaining the catalytic cycle until the reaction is complete. Gratifyingly, the palladium is selective towards the di-bromo vinyl moiety over the aryl iodide in one of the substrates shown, presumably as the alkenyl C-Br bond is more reactive than the aryl C-I bond.

This rational design of indoles using substrates that are set up to undergo Pd-catalysed C-N bond formation has also been successfully achieved by Willis *et al*.[28] The cascade *N*-annulation they have developed provides easy access to a range of 2,3-substituted indoles with good scope and yield. In summary, the overall reaction involves an alkenyl C-N bond formation and an aryl C-N bond formation to afford the indole product (**Scheme 2.7**).



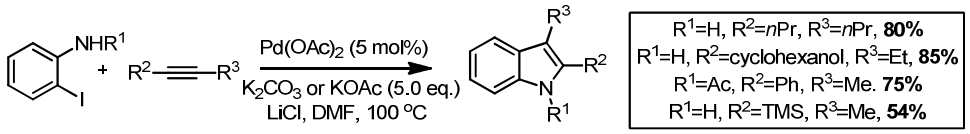
Scheme 2.7

With chemists creating new and adventurous ways to synthesise the indole motif, it is clear that Pd-catalysed cross coupling reactions have greatly expanded the methodology. In another example of rational design, Cacchi *et al.*[29] have utilised an arenediazonium salt as a useful substrate for the *in situ* generation of "ArPdI". This σ-arylpalladium iodide can consequently coordinate to an alkyne and undergo an intramolecular aminopalladation. Finally, reductive elimination and hydrolysis affords the 2,3-substituted indoles in excellent yields (**Scheme 2.8**).



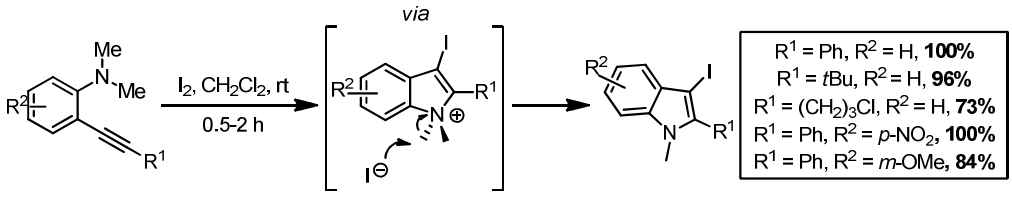
Scheme 2.8

Taking inspiration from Castro's copper acetylide coupling with *o*-iodoanilines in the 1960s,[30] work by Larock *et al.*[31] thirty years later showed that alkynes were good partners for Pd-mediated coupling with *o*-iodoanilines to yield 2,3-substituted indoles (**Scheme 2.9**). This reaction allows for further functionalisation as trimethylsilyl acetylenes can be employed. The products can therefore have a TMS group at R^2 which provides a highly useful synthetic handle for other transformations such as halogenation and the Heck reaction.



Scheme 2.9

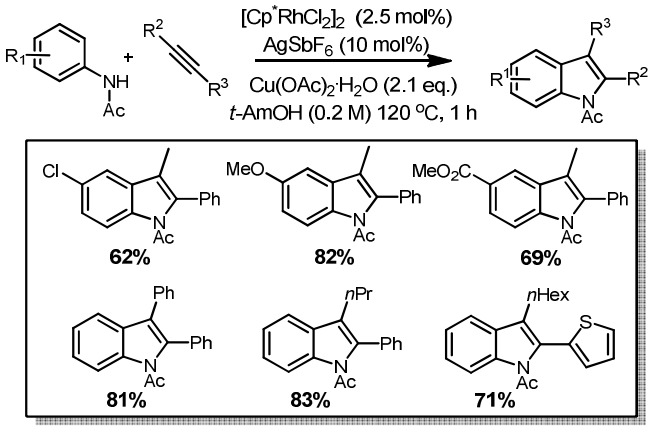
Furthering their indole campaign a few years later, Larock *et al.*[32] designed a simple and high yielding synthesis of 2-substituted 3-iodoindoles that requires only iodine to initiate the cyclisation (**Scheme 2.10**). This reaction shows excellent scope and is operationally straightforward when compared to other syntheses. Having an iodine atom at the 3-position allows, once again, for further functionalization of the indole ring.



Scheme 2.10

1.4 Rh-Mediated Indole Synthesis

Complimentary to Larock's Pd-mediated coupling, Fangou *et al.*[33] have designed a rhodium-catalysed indole synthesis, utilising *N*-acylated anilines and a range of di-substituted alkynes. Considering the advantages and disadvantages of both reactions, this synthesis allows for extra substitution on the aniline ring which are cheaper than their *o*-iodoaniline counterparts used by Larock. On the other hand, more expensive metal reagents are necessary in Fangou's synthesis (**Scheme 2.11**).

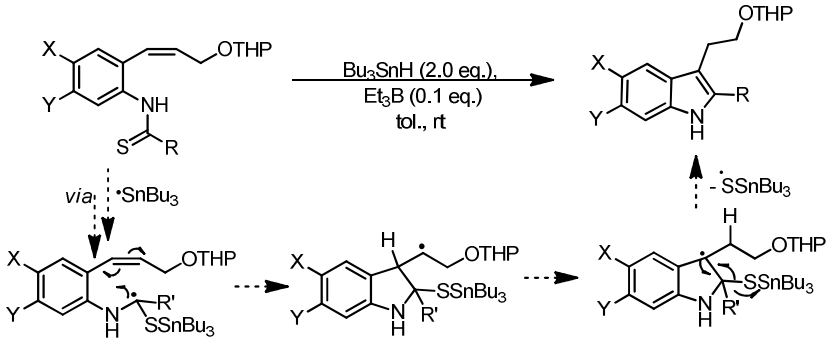


Scheme 2.11

1.5 Radical Cyclisation Approaches to Indoles

Another popular approach to indoles involves the generation of a radical on a substrate which can cyclise onto a nearby atom or ring. This process is usually followed by oxidative re-aromatization to yield the indole product. Fukuyama's

radical-based 2,3-substituted indole synthesis[34] is a good example of this route (**Scheme 2.12**).



Scheme 2.12

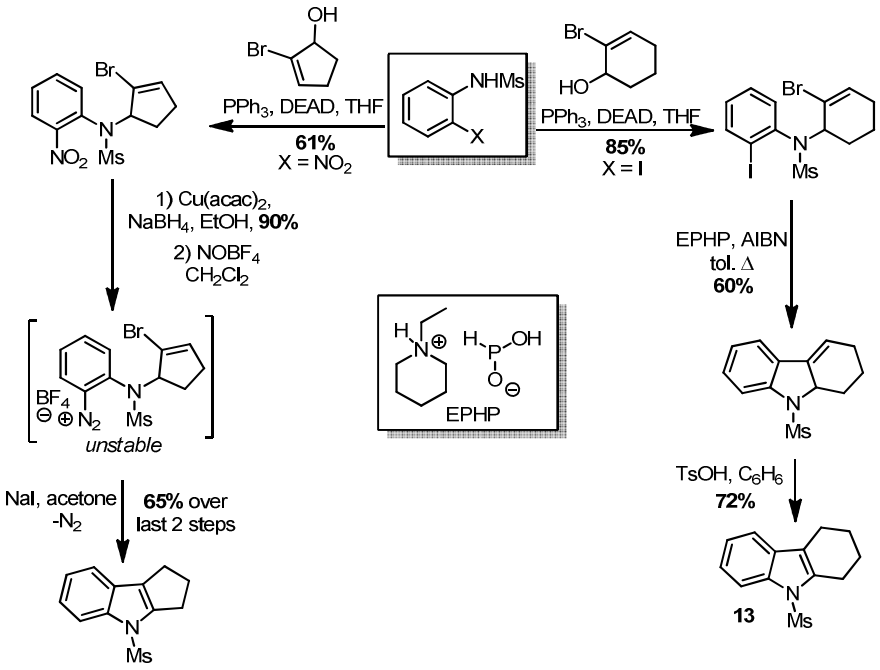
Entry	X	Y	R	Time (min)	% yield
1	OMe	H	nC_4H_9	5	79
2	OMe	H	CH_2CO_2Et	5	82
3	H	OMe	nC_4H_9	15	82
4	Br	H	nC_4H_9	5	81

Table 2.0.

Advantageously, this radical cyclisation reaction process is complete within minutes at room temperature. The Pd-mediated processes aforementioned require high temperatures and longer times to allow similar transformations. Somewhat surprisingly, an aryl bromide bond is preserved in the radical cyclisation (**Table 2.0**, **Entry 4**), with only a trace of dehalogenated product obtained. It is perhaps the mild reaction conditions, coupled with the greater reactivity of the thioamide group towards the tin radical that allows for such useful chemoselectivity. The only apparent disadvantage in this reaction is the use of stoichiometric tributyltin hydride which is known for its toxicity and difficulty in removal from organic media. Nonetheless, this method provides one of the mildest indole syntheses to date and is another entry to the 2,3-substituted indole series.

Following Fukuyama's synthesis, Murphy *et al.*[35] designed a method to prepare indoles without the use of tributyltin hydride. Although the substrate synthesis is

less elegant, the radical cyclisation step can occur at room temperature in the presence of NaI and acetone, much more benign reagents than the stannane chain carriers. The group envisaged the use of an aryldiazonium salt as a radical precursor in a reaction developed by Beckwith *et al.*[36] and this gives a decent yield of product *via* relatively mild conditions. With this result at hand, the group then pursued the use of an aryl iodide radical precursor. Treating this substrate with the phosphorus-based chain carrier, 1-ethyl piperidine hypophosphite (EPHP), cyclisation occurred smoothly to give another substituted indole product in 72% yield (after acid-induced tautomerisation). These results are summarised in **Scheme 2.13.**



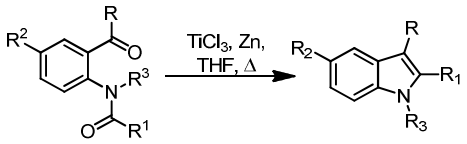
Scheme 2.13

Mechanistically, for the reaction to the bottom right in **Scheme 2.13**, *iso*butyronitrile radicals generated from AIBN can abstract a hydrogen atom from the P-H bond in EPHP to generate a phosphorus-centred radical. This can then abstract the iodide from ArI to generate an aryl radical. Cyclisation onto the alkenyl bromide moiety and consequent loss of a bromine radical will lead to product **13** (two Br radicals can undergo chain termination to form Br_2) after acid-induced tautomerisation.[37] It is also possible that a bromine radical is propagating the reaction by abstracting a hydrogen atom from the P-H bond in EPHP, thus generating another phosphorus-

centred radical which can react with another molecule of substrate until the reaction is complete.

1.6 Ti and Au-mediated indole synthesis

Another highly useful method for the preparation of substituted indoles involves the use of metals (e.g. titanium, zinc and copper) to catalyse otherwise difficult organic transformations. Fürstner *et al.*[38] have shown that aromatic acylamido carbonyl compounds are excellent precursors for cyclisation by low valent titanium compounds in the presence of zinc dust. The reaction scope is broad and yields are excellent with substitution allowed on nitrogen, C^1, C^2 and in various locations on the benzene ring (**Scheme 2.14, Table 2.1**).

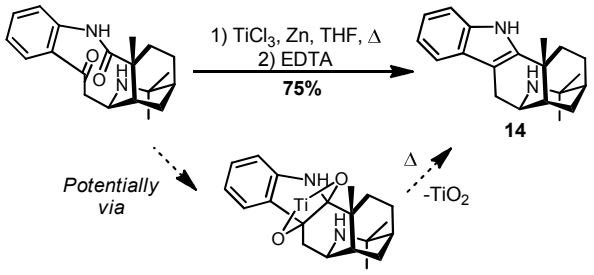


Scheme 2.14

Entry	R	R^1	R^2	R^3	% Yield
1	Ph	CO_2Et	Cl	H	**87**
2	Me	Ph	H	H	**76**
3	C_4H_9	Ph	H	Me	**70**

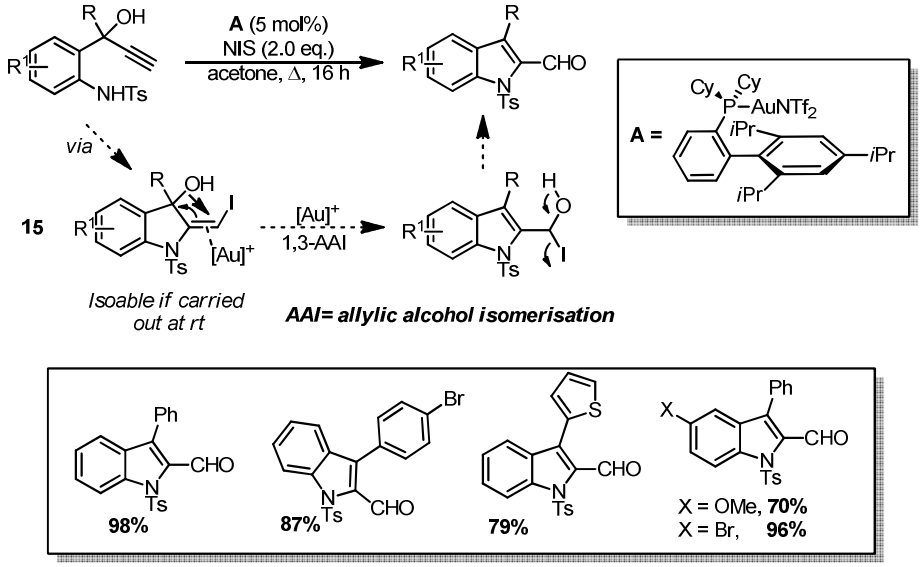
Table 2.1

This reaction also preserves any stereocentres present in the precursor compound with typical reaction times between 1-3 h. Fürstner postulates that the speed and high-yielding properties of this reaction is due to the *in situ* reduction of Ti(III) by Zn in the presence of a coordinating solvent in a synthesis similar to the McMurry reaction.[39] Fürstner has successfully utilised this reaction in the synthesis of (+)-*Aristoteline* **14** which showcases the power and efficiency of the methodology (**Scheme 2.15**).



Scheme 2.15

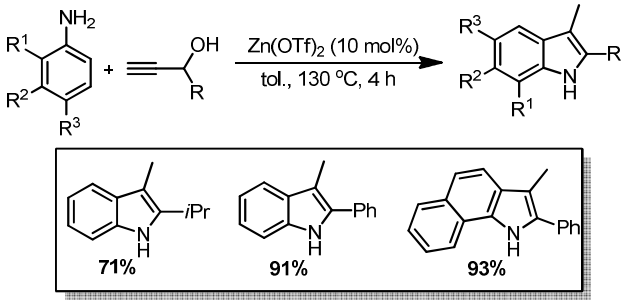
The ability to synthesise the indole core of this natural product in high yield and at such a late stage, is a testament to the carefully planned and executed use of reagents in this reaction. In this vein of thought, many gold complexes are good π-Lewis acids that can co-ordinate and activate alkynes towards nucleophilic attack. Chan *et al.*[40] have utilised the expedient properties of gold to induce an intramolecular attack of an alkyne in order to synthesise a range of 1*H*-indole-2-carbaldehydes *via* cycloisomerisation under mild conditions (**Scheme 2.16)**.



Scheme 2.16.

Iododeauration followed by formylation yields an array of substituted indole products, with aldehyde functionality installed at the C^1-position. This broadens the scope regarding substrate elaboration. The intermediate compound **15** can also be isolated in high yield (80-90%) if the reaction is carried out at ambient temperature. The aldehyde functionality at C^1 allows for further elaboration on these compounds.

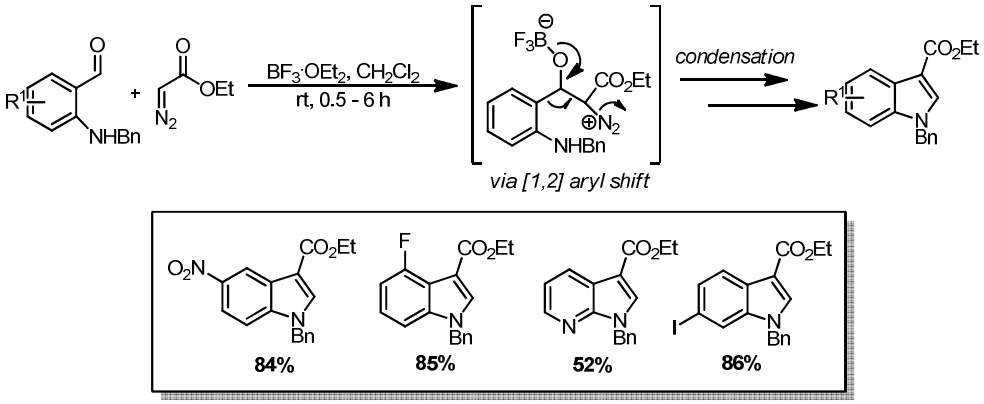
In 2006 Liu *et al.*[41] showed that propargyl alcohols and substituted anilines can be coupled in the presence of catalytic $Zn(OTf)_2$. This atom economical synthesis of highly substituted indoles possesses some advantages over other previously mentioned syntheses. The use of sub-stoichiometric $Zn(OTf)_2$ makes the reaction cleaner due to less metal waste and both the aniline and propargyl alcohol are readily accessible substrates. Previous indole syntheses mentioned tend to involve the synthesis of complex substrates for use in the final, ring closing step. The reaction can also be carried out neat hence a more environmentally-friendly reaction (**Scheme 2.17**).



Scheme 2.17.

1.7 Indole Synthesis employing N_2 as a Leaving Group

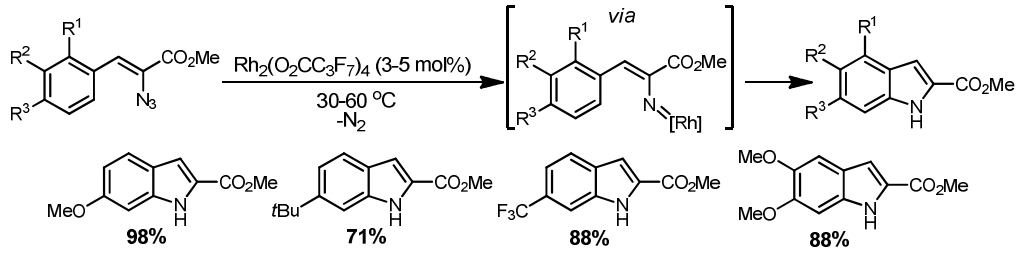
Fournier *et al.*[42] have employed a diazoacetate along with a range of aromatic aldehydes to synthesise the core indole motif (**Scheme 2.18**).



Scheme 2.18

With excellent scope and yields, a range of useful indoles can be readily synthesised in this procedure. One drawback is the necessity for five equivalents of ethyl diazoacetate to ensure high yields of product. Compared to many other indole syntheses mentioned, this reaction requires an *N*-benzyl protecting group on the starting material which adds an extra two steps if one needs to access the free NH indole at the end. Nonetheless, both iodo- and bromo functionality can be preserved in high yield; where many transition metal-mediated syntheses would fail at such a prospect.

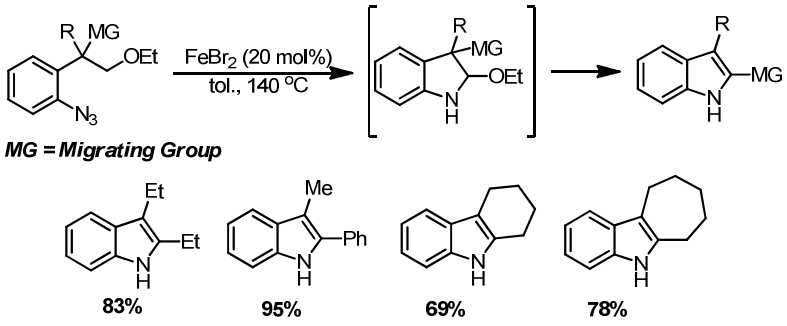
Using comparatively milder conditions to that of Liang and Glorius, Driver *et al.*[43] sought to utilise a Rh(II)-mediated process in order to synthesise a range of C^2-ester substituted indoles *via* a dirhodium(II) nitrenoid species from methodology developed by Moody *et al*.[44] This provided a range of indoles in excellent yield, complimentary to the indole products synthesised by Liang and Glorius, previously discussed (**Scheme 2.19**).



Scheme 2..19

One minor pitfall of this reaction is the time required to synthesise the azido substrates. Preparation of such compounds is possible *via* condensation of an aromatic aldehyde with methyl 2-azidoacetate, a very expensive reagent to purchase but relatively easy to synthesise *via* displacement of methyl bromoacetate with sodium azide.[45] Unlike previous syntheses discussed which allow access to the indole motif rapidly *via* cheap, commercially available substrates; extra steps are required here to access the pre-cyclised substrate. Nonetheless, this synthesis provides a milder route to the C^1-substituted indole class with good scope and excellent yields. In subsequent work, Driver *et al.* reported[46] a new route to 2,3-disubstituted indoles *via* an iron(II) bromide catalysed reaction. The authors reasonably state that the iron(II) bromide acts "as both an *N*-atom transfer catalyst

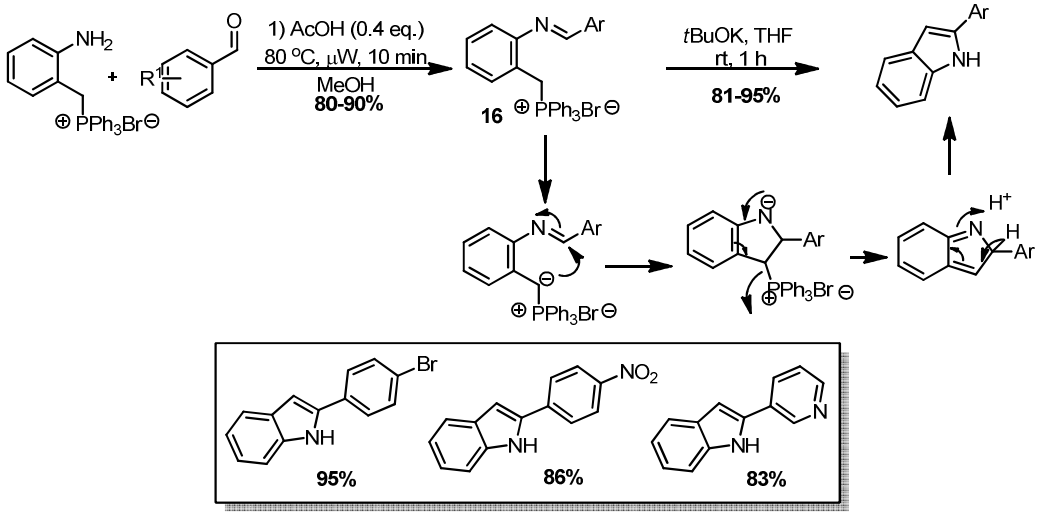
and a Lewis Acid" and this gives rise to a range of structurally diverse indoles with N_2 being a good leaving group (**Scheme 2.20**).



Scheme 2.20

1.8 Utilising a Phosphorus Ylide in Indole Synthesis

A more traditional approach towards indoles, without the use of a metal catalyst, was realised by Kraus *et al.*[47] who envisaged a Wittig-type substrate that could be successfully cyclised to an indole upon treatment with a base (**Scheme 2.21**).



Scheme 2.21

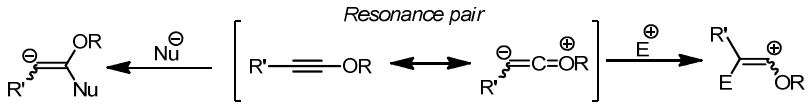
The usefulness of microwave chemistry is exemplified here as Kraus reports that conventional refluxing of the phosphorus ylide with an aldehyde in methanol led to poor yields of imine intermediate **16**. Subjecting these reagents to microwave radiation afforded excellent yields of imine which could then be easily deprotonated

with potassium *tert*-butoxide to yield the C^1-substituted indoles *via* a phosphonium ylide rearrangement. The mild conditions, high yields and fast reaction times make this an ideal synthesis towards such substituted indoles.

2. Introduction (Ynol Ethers)

2.0 Ynol Ethers- Synthesis and Applications

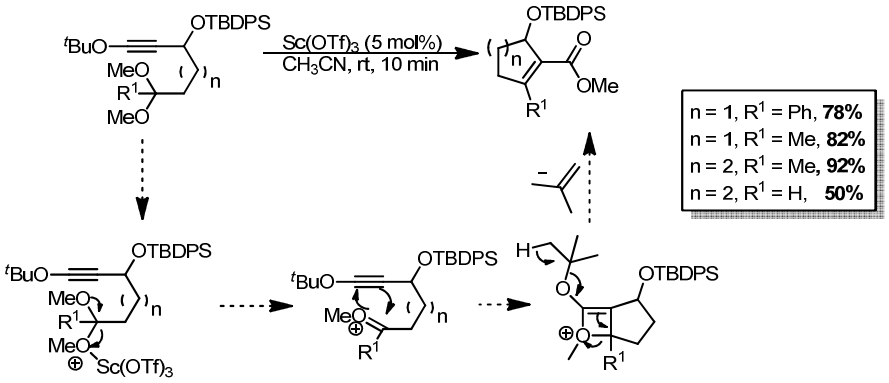
Ynol ethers serve as versatile building blocks in synthesis as they can undergo an array of further transformations to yield structures that would, otherwise, be difficult to produce. Due to the polarised nature of the triple bond, their reactivity towards both nucleophiles (at the α carbon) and electrophiles (at the β carbon) is a useful property (**Scheme 2.22**).[48]



Scheme 2.22

To date, there have been relatively few methods towards ynol ethers reported in the literature. Although the ynol ether motif is unlikely to be found in any natural products due to their reactivity, their synthesis is important as it allows access to a range of more complicated organic scaffolds.

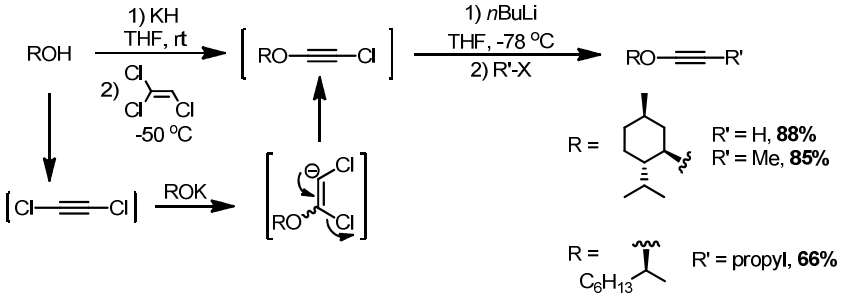
As an introductory example, Minehan *et al.*[49] have recently shown that ynol ether-tethered dialkyl acetals can undergo Lewis acid-catalysed rearrangement to afford alkoxycycloalkene carboxylates of various ring sizes (**Scheme 2.23**). This reaction showcases the potential of exploiting such functional groups in generating new ring systems, both quickly and mildly.



Scheme 2.23

2.1 Current Synthetic Routes

To date, dehalogenation of haloalkenyl ethers is one of the more popular methods for the synthesis of ynol ethers.[50] The use of trichloroethylene has been a mainstay over the past thirty years with work by Greene *et al.* exemplifying the use of such reagents in ynol ether preparation (**Scheme 2.24**).[51]

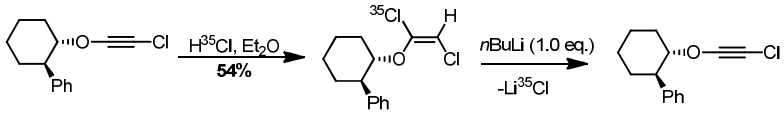


Scheme 2.24

The ability to use hindered, chiral alkoxides in this synthesis is a great advantage as these can be carefully prepared *in situ* from the alcohol and potassium hydride. Trichloroethylene is also a cheap and easy-to-handle liquid that can provide access to the dichloroacetylene intermediate under mild conditions in the presence of a potassium alkoxide which serves as both a base and nucleophile in this reaction. Quenching the lithiated acetylide with an aliphatic electrophile (i.e. MeI), yields the product ynol ethers in good yield. The entire process can also be carried out in a

single operation. On the other hand, the triple dehalogenation is not an atom-economical process and this must be balanced against the benefits of the synthesis.

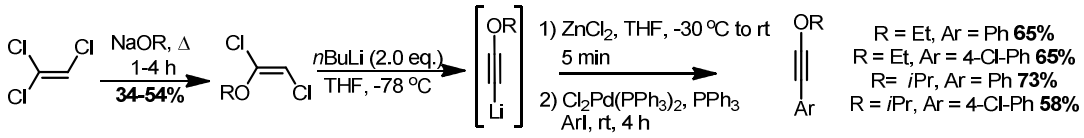
Also of interest in **Scheme 2.24** is the mechanism *via* which the dichloroenol ether eliminates to form the ynol ether. For many years it was thought that after deprotonation of the dichloroenol ether, loss of the chloride α to the lithium carbenoid would result in a carbene which could undergo a Fritsch-Buttenberg-Wichell rearrangement. Alternatively, the lithiated carbenoid could undergo *cis* β-elimination to form the corresponding chloroynol ether. To investigate this matter, Poisson *et al.* undertook a ^{35}Cl labelling experiment in order to prove which pathway was in operation (**Scheme 2.25**).[52]



Scheme 2.25

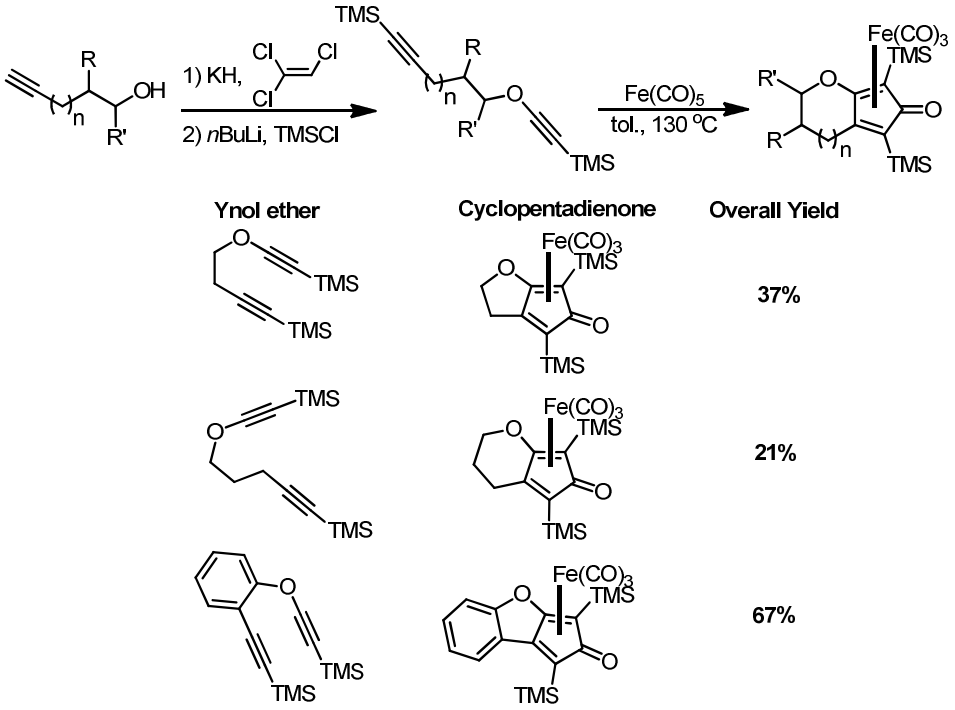
Pleasingly, the result of this labelling experiment was conclusive, and chemical ionisation mass spectroscopy analysis clearly indicated a 3:1 ratio of molecular ions at 235 and 237 $(MH)^+$ respectively for the chloroynol ether, which indicates loss of the ^{35}Cl atom. Therefore, *cis* β-elimination is the major pathway in the formation of the chloroynol ether.

Himbert *et al.*[53] have also harnessed the properties of trichloroethylene as a useful substrate in the synthesis of dichloro(alkoxy)ethenes (ynol ether precursors). Treating trichloroethylene with sodium alkoxide followed by *n*BuLi promoted elimination and lithiation of the acetylide, allows for Pd-mediated cross-coupling to yield aromatic alkynyl ethers. This reaction broadens the scope of Greene *et al.* and is a convenient method of manipulating the reactivity of the lithiated acetylide (**Scheme 2.26**).

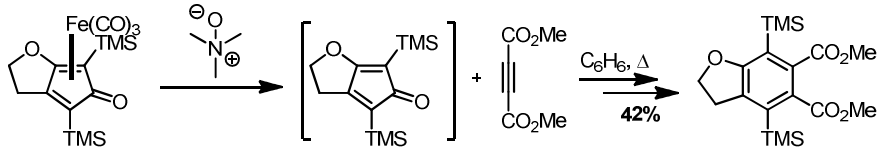


Scheme 2.26

Rainier *et al.*[54] have also incorporated a lithiated ynol ether into a substrate that is set up to undergo a [2+2+1] cycloaddition in the presence of iron pentacarbonyl. Starting from trichloroethylene, iron complexes of 3-alkoxycyclopentadienones can be synthesised in good yield. *In situ* de-metallation followed by reaction with a dieneophile yields highly functionalised heterocycles in good yield (**Scheme 2.27 & 2.28**).

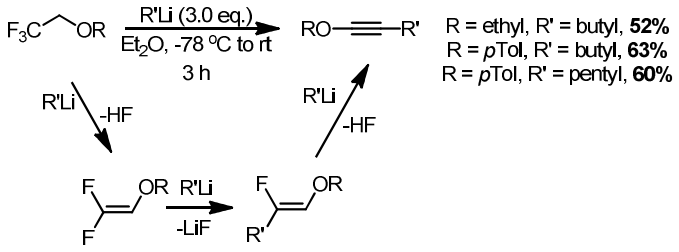


Scheme 2.27



Scheme 2.28

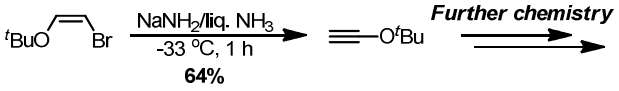
In terms of dehalogenation-based approaches, Nakai *et al.*[55] have utilised trifluoroethanol as a cheap building block in order to generate a range of ynol ethers in good yield (**Scheme 2.29**).



Scheme 2.29

This synthesis can be carried out in a single operation starting from easily-prepared trifluoroether substrates *via* successive eliminations of HF and LiF. One disadvantage is the time needed to prepare the organolithium reagents, and also, the etherification of trifluoroethanol with the necessary electrophile. The use of organolithiums as both a base and a nucleophile removes the need for other reagents in this reaction making it a more streamlined process.

Synthetic routes to terminal ynol ethers are limited due to their volatility and reactivity. One of the few syntheses that affords good yields of such compounds (e.g. *tert*-butoxyethyne) was developed by Pericàs *et al.*[56] Although a lengthy process to reach the bromo vinyl ether precursor is required; this synthesis of *tert*-butoxyethyne can be achieved on a large scale (~30 g) (**Scheme 2.30**).



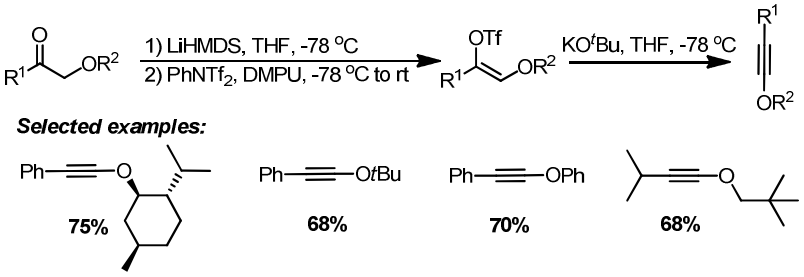
Scheme 2.30

This ynol ether is prone to rearrangement at room temperature, losing *iso*butene and generating ketene hence it must be stored below –20 °C. Nonetheless, this reactive compound may allow for an array of further modifications *via* deprotonation and nucleophilic attack, or, metal-mediated coupling reactions. The *tert*-butoxy functionality allows for the facile generation of ketene which could be trapped by a range of other compounds. Pericàs has also shown[57] that upon heating, *tert*-

butoxyethyne can undergo a [2+2] cycloaddition with a molecule of ketene to form 3-*tert*-butoxycyclobutenone, which will be discussed later.

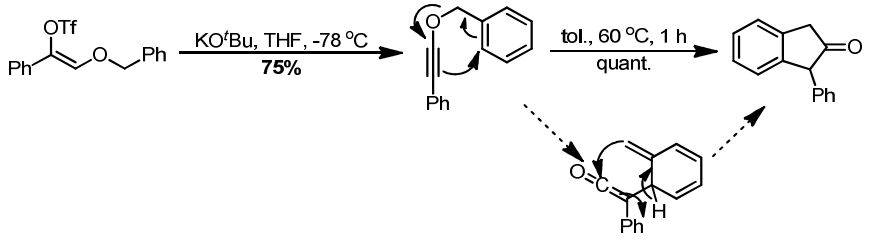
2.2 Recent Routes Towards Ynol Ethers

More recently, Minehan *et al.*[58] have developed a synthesis of alkynyl ethers starting from α-alkoxy ketones (**Scheme 2.31**).



Scheme 2.31

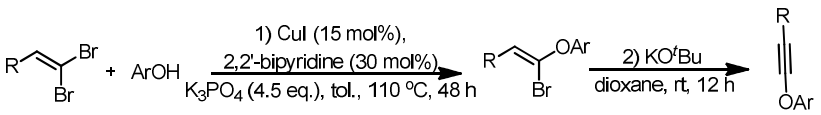
This three-step protocol for synthesising ynol ethers (α-alkoxy ketone formation,[59] enol triflate generation and elimination) provides the products in good yield with both aromatic and aliphatic groups tolerated. Primary, secondary and tertiary alcohols can be successfully employed in this synthesis to yield a range of ynol ethers. The three-step process can be simplified by taking the crude enol triflate and carrying out the elimination with an excess of KO^{t}Bu (3.0 eq.), which causes only a slight decrease in yield. When R^2 = benzyl, the ynol ether product can undergo a [3,3] sigmatropic rearrangement under mild conditions to afford a substituted indanone- another example of how ynol ethers make excellent precursors in accessing other useful organic motifs (**Scheme 2.32**).



Scheme 2.32

2.3 Cu-Mediated Ynol Ether Synthesis

Another example of rational design towards the synthesis of ynol ethers was realised and achieved by Evano *et al.*,[60,61] taking inspiration from Cook *et al.*[62] who coupled alkenyl halides with alcohols to afford enol ethers. Evano *et al.* adopted a copper-catalysed coupling between an alcohol and a *gem*-dibromoalkene to access bromo-enol ethers. These compounds could be cleanly transformed to the corresponding ynol ether in the presence of potassium *tert*-butoxide (**Scheme 2.33**).



Ynol ether yields:

Ar = *m*-Me-C_6H_4
R = ^{i}Bu, **75%**
R = Cy, **71%**
R = CH_2CH_2Ph, **84%**

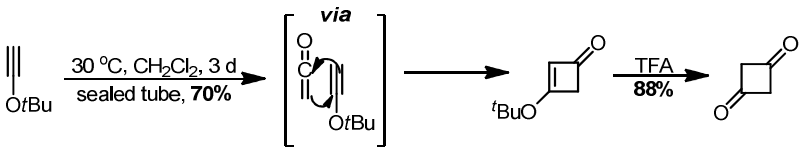
R = C_6H_{13}
Ar = *m*-Me-C_6H_4, **87%**
Ar = *p*-Cl-C_6H_4, **65%**
Ar = *p*-Br-C_6H_4, **71%**

Scheme 2.33

After careful optimisation and ligand screening, the above conditions were found most suitable in accessing the bromoenol intermediate which could then be easily converted to the ynol ether product. One disadvantage of this process is the time and temperature required for bromoenol formation. Only aromatic alcohols are tolerated in this reaction and the authors comment that dimerisation of the *gem*-dibromolefin occurs when aliphatic alcohols are employed. Overall, this synthesis furnishes a range of ynol ethers in good yield and with reasonably good scope.

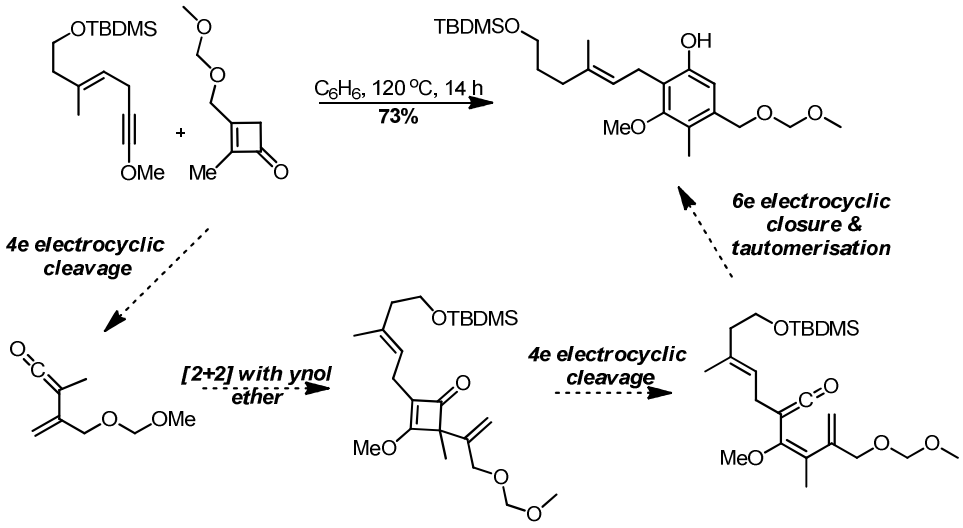
2.4 Applications of Ynol Ethers

Due to their reactivity, ynol ethers are attractive intermediates for the synthesis of compounds that would, otherwise, be difficult to access. *tert*-Butyl ynol ethers in particular provide a facile source of ketene which can undergo cycloaddition reactions with many other substrates. This fact is exemplified when *tert*-butoxyethyne is warmed to afford a cyclobutenone *via* a [2+2] cycloaddition process (**Scheme 2.34**).[57]



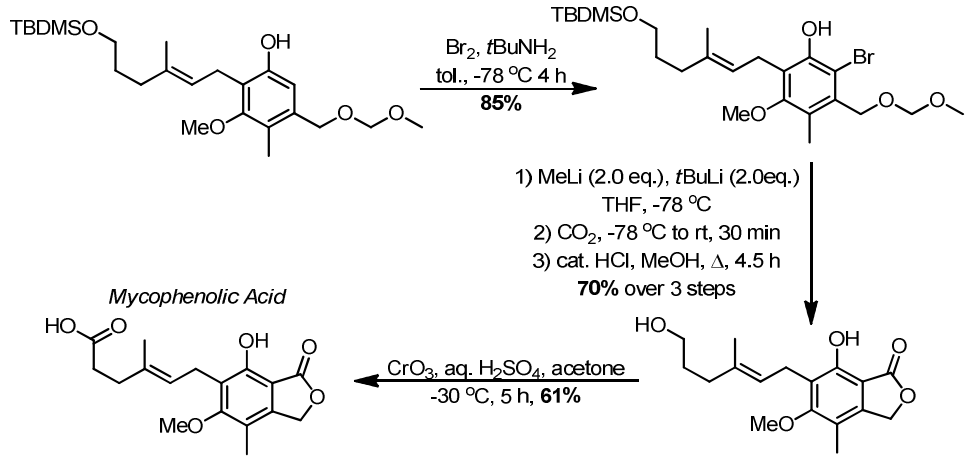
Scheme 2.34

The dimerisation product is a functionalised cyclobutenone which can be treated with TFA to give the di-ketone in good yield under mild conditions. Both these compounds are useful synthetic intermediates. Danheiser *et al.*[63] successfully harnessed the reactivity of ynol ethers along with the ability of cyclobutenones to undergo electrocyclic ring opening, in the synthesis of *Mycophenolic Acid*- a potent antiviral and antitumor agent (**Scheme 2.35**).[64]



Scheme 2.35

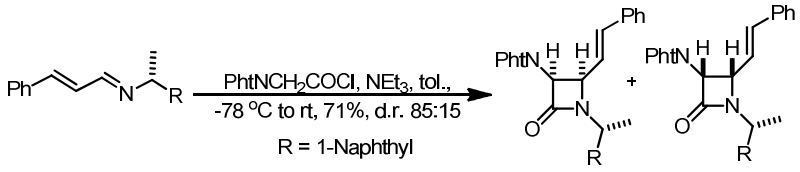
Building up such complexity in a regioselective manner is a testament to the power of this chemistry, and this allowed Danhesier *et al.* to rapidly access the endgame substrate in excellent yield. After the final steps, the product was isolated in good yield (**Scheme 2.36**).



Scheme 2.36

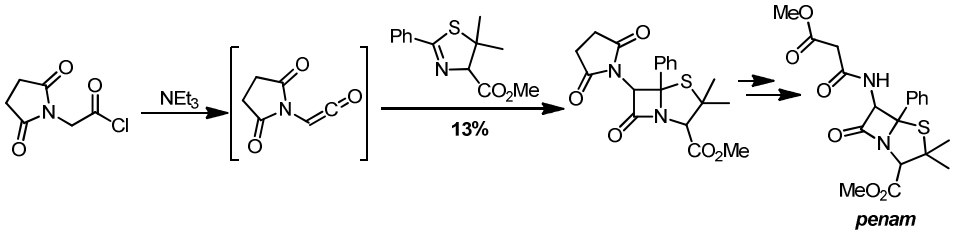
2.5 *tert*-Butyl Ynol Ethers as Ketene Sources

Classically, ketenes can be generated *in situ* from an acid chloride and a tertiary amine base and trapped *via* cycloaddition to afford useful products. The Staudinger synthesis[65] of β-lactams is a classical example of their synthetic utility (**Scheme 2.37**).[66]



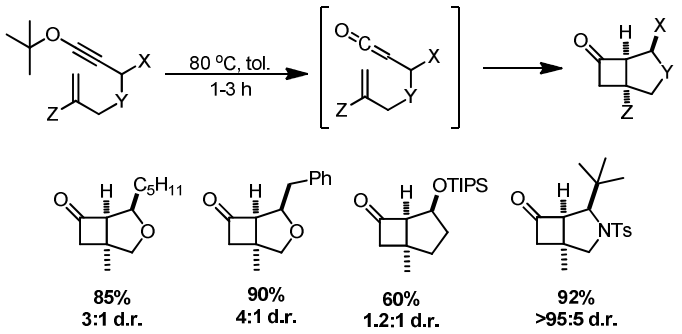
Scheme 2.37

Sheehan *et al.* utilised the reactivity of ketenes to synthesise the first synthetic penicillin (penam) and this allowed for greater study of β-lacams and their properties (**Scheme 2.38**).[67]



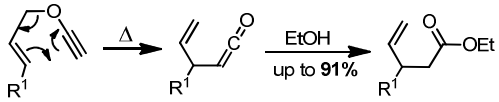
Scheme 2.38

Although difficult to control due to their high reactivity, ketenes are useful building blocks in synthesis and allow access to a range of heterocycles. A much milder method for the synthesis of ketenes can be seen upon considering the decomposition of ynol ethers. The Minehan group have shown that ketenes can be either trapped intramolecularly *via* cycloaddition[68] or, attacked by a nucleophile[69] to form structures that would be otherwise quite difficult to access (**Scheme 2.39**).



Scheme 2.39

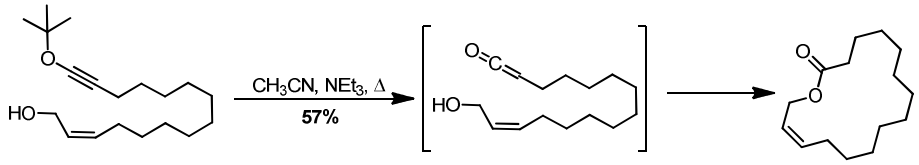
Mild thermolysis of the *tert*-butyl ynol ethers in **Scheme 2.39** allows for extrusion of *iso*butene *via* a retro-*ene* reaction, forming a ketene that can undergo a intramolecular [2+2] cycloaddition.[70] This process can be regarded as more desirable when compared to the use of air-sensitive and usually unstable acid chlorides. *tert*-Butyl ynol ethers in particular are known to undergo the retro-*ene* reaction at approximately 50 °C[71] which provides facile, controllable access to the required ketene. Minehan *et al.*[69] have also been able to access a range of γ,δ-unsaturated esters by trapping ketenes with alcohols, another example of the versatility of these reactive intermediates (**Scheme 2.40**).



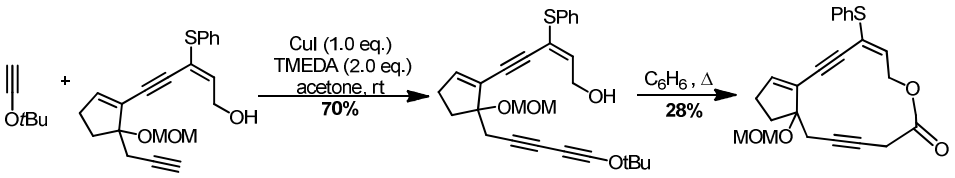
Scheme 2.40

Ynol ethers have also found useful in macrolactonisation reactions as the masked ketene can be employed as an electrophile under relatively mild conditions. Both Funk *et al.*[72] and Magriotis *et al.*[73] have shown that macrolide synthesis can easily be achieved with a *tert*-butyl ynol ether. Upon warming, the *tert*-butyl ynol ether

undergoes *iso*butene extrusion followed by intramolecular nucleophilic attack to afford the products in good yield (**Scheme 2.41 & 2.42**).



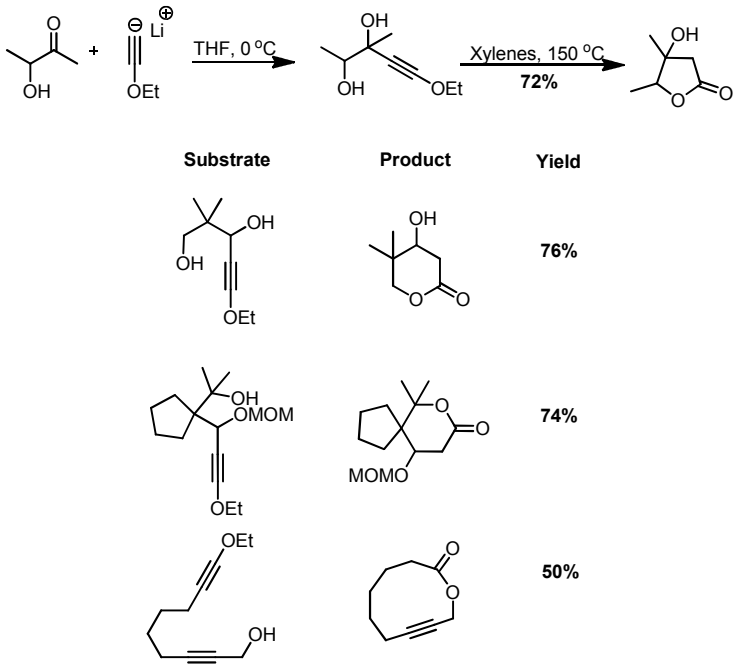
Scheme 2.41



Scheme 2.42

Pleasingly, Magriotis *et al.* have successfully coupled a terminal ynol ether with a terminal alkyne *via* Glaser coupling to give a substrate that is set up for ketene formation and ring closure. The fact that the highly reactive terminal alkyne can be manipulated in this way makes it an excellent substrate for further organic transformations. Overall, this efficient route provides a complex macrocycle that would be otherwise very difficult to make in satisfactory yield.

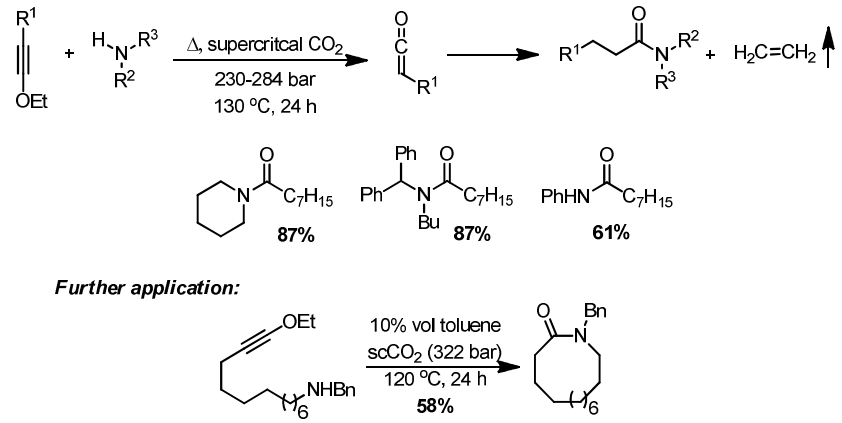
The versatility of terminal ynol ethers has also been harnessed by MaGee *et al.*[74] to give a range of functionalised medium and large rings by utilising ethoxyethyne. Reacting an α-hydroxy ketone with the lithiated ethyl ynol ether forms a substrate, which upon heating, can easily lose ethene to form a ketene that is easily trapped by an intramolecular alcohol group (**Scheme 2.43**).



Scheme 2.43

2.6 Ynol Ethers in Amide Bond Formation

Alkoxy alkynes have also seen use as masked acylating agents in amide bond formation. Danheiser *et al.* have used the masked ketene property of ethoxyacetylene in order to synthesise both macrocycle and linear amides.[75] Common acylating agents include acid chlorides and mixed anhydrides, which are less atom-economical and more toxic than ethoxyacetylene (the only leaving group being ethene in this case). Danheiser *et al.* envisioned that the use of this acylating agent would be more environmentally friendly as well as simplifying the scale-up process for industrial applications (**Scheme 2.44**).

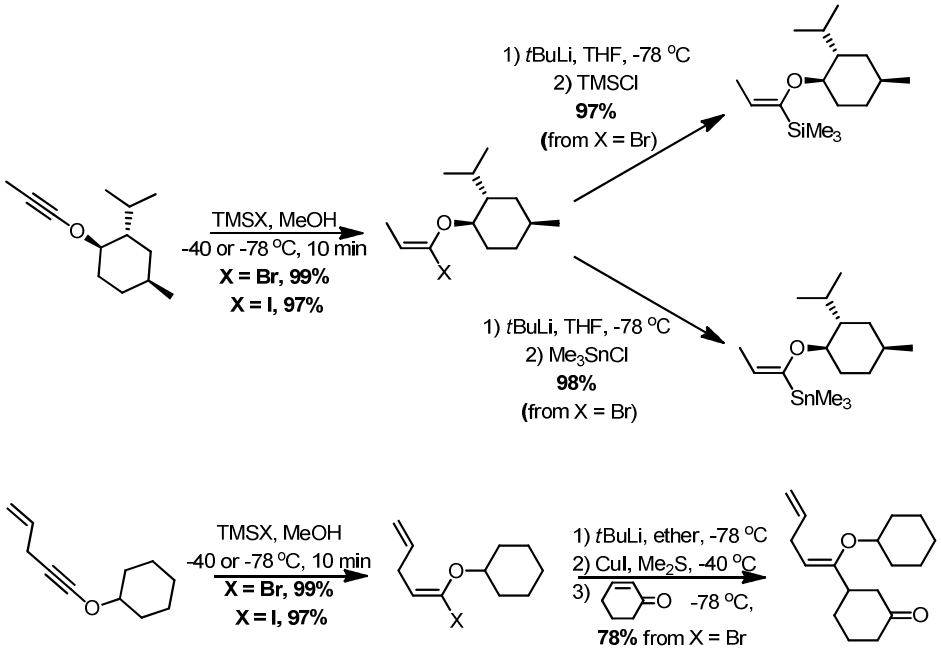


Scheme 2.44

Drawbacks of this synthesis involve the time and reagents required to make the ynol ethers as well as the use of super critical carbon dioxide which requires high pressure. Also, for a large-scale synthesis, storage of the ynol ether in question may be difficult as they readily decompose if not stored at low temperature.

2.7 Ynol Ethers as Acyl Anion Equivalents

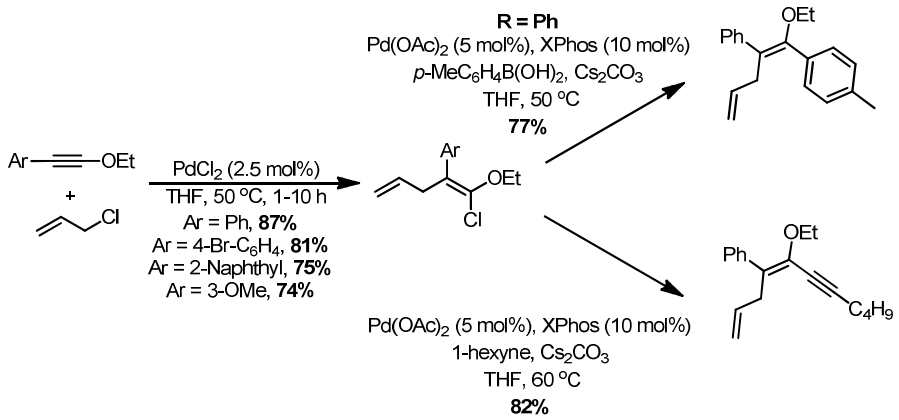
Acyl anion equivalents are useful intermediates in C-C bond forming reactions. Jin *et al.*[76] have devised a method in which ynol ethers undergo electrophilic addition with 'HX' (X = Cl, Br, I) generated *in situ* from TMSX in methanol. This mild and facile *syn* addition provides a range of α-halo vinyl ethers in excellent yield. Although the products are unstable towards chromatography and aqueous workup conditions, Jin *et al.* have demonstrated that concentrating the crude reaction mixture under vacuum to remove the methanol and MeOTMS, allows for the isolation of the product in essentially pure form which means they can be used directly in subsequent reactions (**Scheme 2.45**).



Scheme 2.45

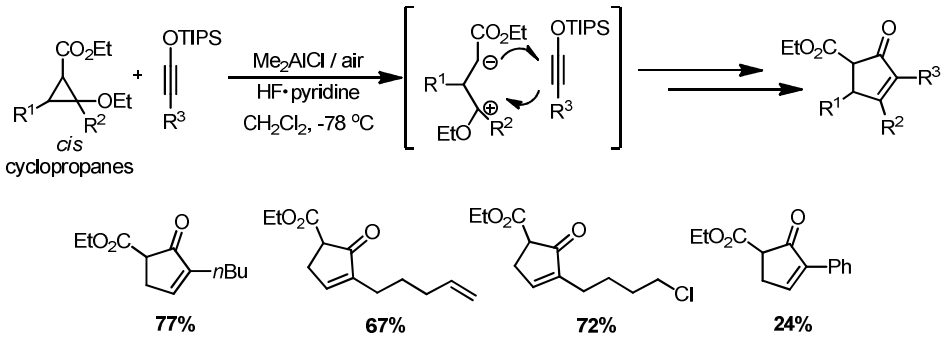
2.8 Pd-Mediated Reactions of Ynol Ethers

Zhu *et al.*[77] have also shown that ynol ethers can undergo palladium-catalysed haloallylation to yield synthetically useful α-chloro- and α-bromoenol ethers. These compounds can consequently undergo both Suzuki-Miyaura and Sonogashira coupling reactions to afford substituted enol ethers in good yield. Hydrolysis of such compounds to give the ketone can also be achieved in excellent yield (**Scheme 2.46**).



Scheme 2.46

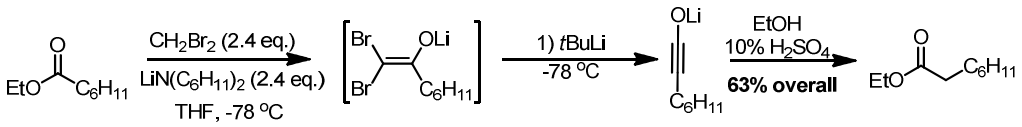
A more adventurous use of ynol ethers was realised by Ready *et al.*[78] who successfully employed these compounds in [3+2] cycloadditions with cyclopropanes. By adding a Lewis Acid, the cyclopropane can ring open to form a Zwitterion that can then undergo a cycloaddition with a ynol ether. The highly substituted cyclopentenone products are useful and this synthesis is a rapid route towards such compounds (**Scheme 2.47**).



Scheme 2.47

2.9 Synthesis and Applications of Ynolates

Analogous to ynol ethers, but with greater reactivity, ynolates are also excellent substrates in a range of organic transformations. An early example of ynolate synthesis was reported by Kowalski *et al.*[79] who designed a single-step one carbon homologation of esters that proceeded *via* a ynolate intermediate (**Scheme 2.48**).

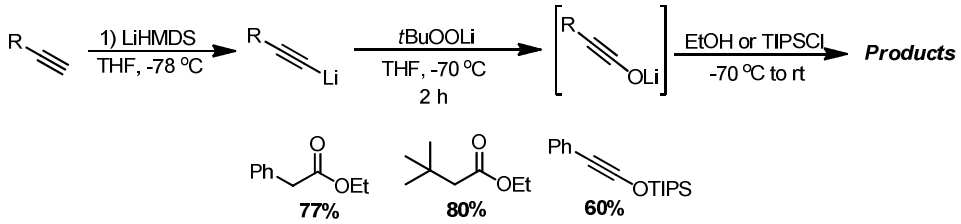


Scheme 2.48

This reaction can be regarded as the carbon analogue of the Hoffman rearrangement[80] and is a much milder alternative to the Arndt-Eistert homologation[81] which requires hazardous diazomethane.

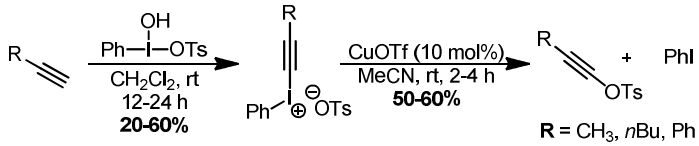
Julia *et al.*[82] have also reported a rapid route towards lithium ynolates *in situ*, *via* oxygen transfer to an acetylenic carbanion. This route allows for the synthesis of a

range of lithiated ynolates which can be isolated as the *O*-silylated derivative. Compared to other ynolate syntheses, this route is faster and much more atom economical (**Scheme 2.49**).



Scheme 2.49

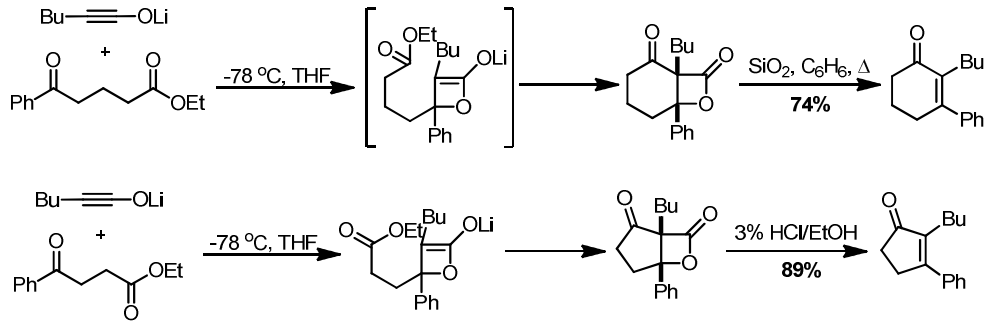
Starting from terminal acetylenes (many of which are commercially available) for ynolate synthesis is beneficial in terms of how quickly these reactive substrates can be made. Stang *et al.*[83] have shown that alkynyl tosylates can be prepared efficiently, and in reasonable yield starting from terminal acetylenes (**Scheme 2.50**).



Scheme 2.50

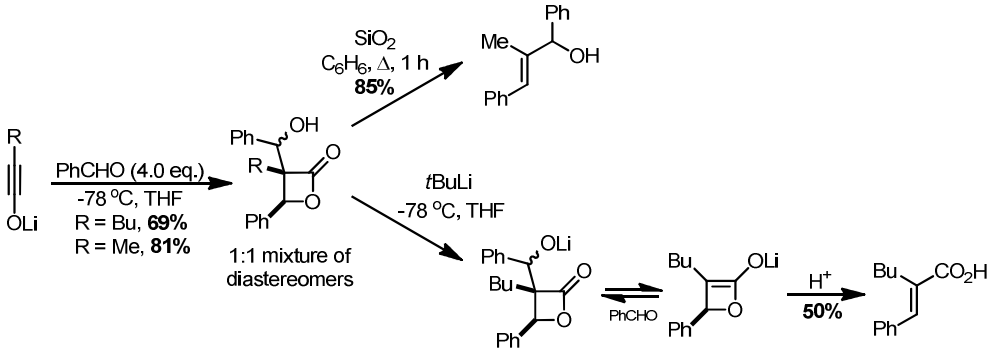
The intermediate hypervalent alkynyl aryliodinium tosylate is an understudied, interesting compound that decomposes to form the alkynyl tosylate and phenyl iodide in the presence of sub-stoichiometric copper(I) triflate. Treating this compound with methyl lithium will then lead to the ynolate, which can be *O*-silylated and isolated in acceptable yield.

Utilising the potential of ynolates in synthesis has been a focal-point for Shindo *et al.*[84] who have developed a tandem [2+2] cycloaddition-Dieckmann condensation to afford 2,3-disubstituted-2-cyclohexanones and pentanones in excellent yield (**Scheme 2.51**).



Scheme 2.51

The group also employed lithiated ynolates in [2+2] cycloadditions with aldehydes to afford *β*-lactones. Upon treatment with *tert*-BuLi, these compounds can undergo electrocyclic ring opening[85] to afford *α*-substituted cinnamic acid derivatives, as well as thermal decarboxylation[86] yielding tri-substituted allylic alcohols, thereby exemplifying the versatility of these compounds in synthesis (**Scheme 2.52**).



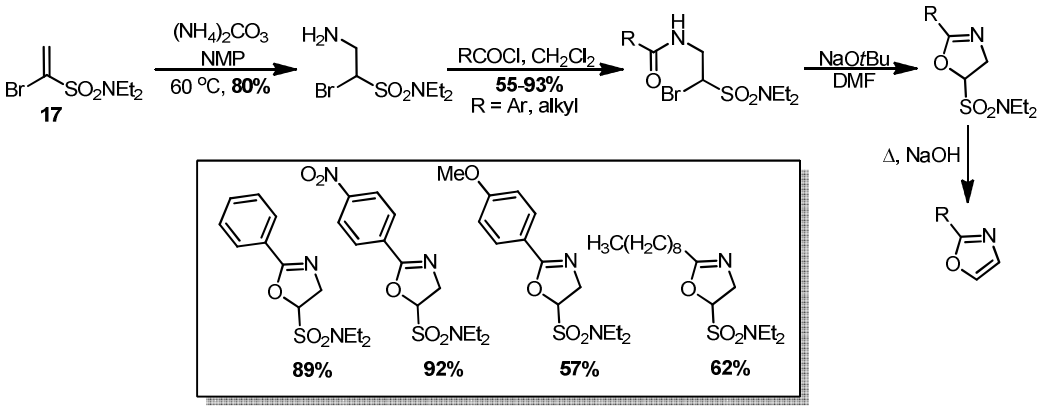
Scheme 2.52

In conclusion, a range of synthetic approaches towards substituted-indoles and ynol ethers have been presented, which consider both the advantages and disadvantages of the synthetic routes in question.

3. Results & Discussion (Indole Synthesis)

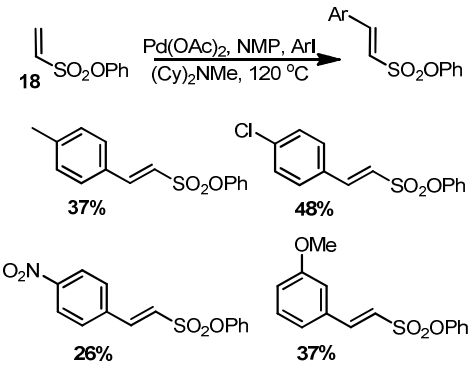
3.0 An Indole Synthesis Based on a Sulfonate Template

Previous work in the Wilden group[87] has shown that both sulfonamide and sulfonate ester groups are both useful tools for synthetic transformations. In particular, vinyl sulfonamide **17** has been shown to act as both a Michael acceptor, and consequently a leaving group to furnish a range of substituted oxazolines in good yield (**Scheme 3.0**).



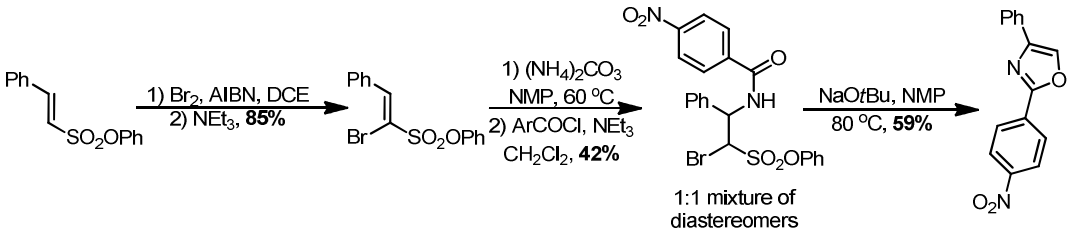
Scheme 3.0

Upon treatment with sodium hydroxide, these oxazolines can undergo base-induced elimination of the sulfonamide to afford the corresponding oxazole in good yields (50-89%). Both the vinyl sulfonamide and sulfonate esters have proven to be versatile tools in a range of reactions. For example, the Heck reaction can be carried out on vinyl sulfonate **18** in satisfactory yield (**Scheme 3.1**).



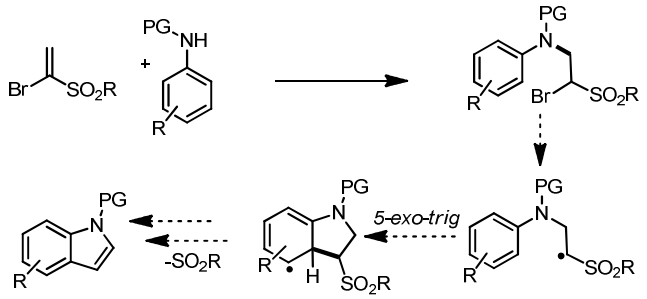
Scheme 3.1

Based on these results, bromination and elimination yields the aryl-substituted vinyl bromo-alkene sulfonate, which can be further functionalised to yield a di-substituted oxazole in good yield (**Scheme 3.2**).



Scheme 3.2

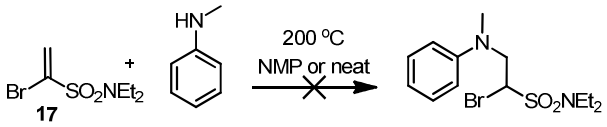
With these results at hand, it was envisaged that the intramolecular displacement of a sulfonamide could be employed to synthesise other useful compounds such as indoles. The hypothetical route considered is shown in **Scheme 3.3**.



Scheme 3.3

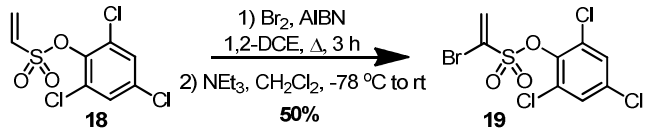
3.1 Conjugate Addition of Anilines to a Vinyl Sulfonate

With the knowledge[87] that ammonia undergoes conjugate addition to 1-bromo-*N*,*N*-diethylethenesulfonamide **17** in good yield, it was thought that adding an aromatic aniline to **17** would provide a substrate that was set up to undergo radical cyclisation under appropriate conditions to afford an indole. Unfortunately, this was not the case and *N*-methylaniline failed to add to substrate **17**, even under forcing conditions, with only starting materials recovered (**Scheme 3.4**). The unsuitability of sulfonamide **17** for conjugate addition was blamed on the relatively poorer electron withdrawing ability of the sulfonamide thus attention was turned to a vinyl sulfonate functional group. Roush *et al*.[88] have shown that vinyl sulfonates undergo 1,4 addition with thiols approximately 3000 times faster than their sulfonamide counterparts.



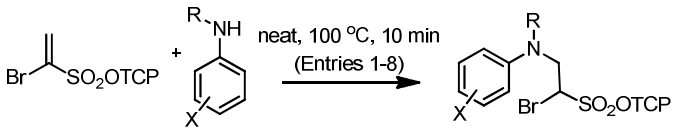
Scheme 3.4

Consequently, this approach was modified in order to introduce the more electron withdrawing vinyl sulfonate **19**, in the hope that the conjugate addition would occur more readily. Synthesis of **19** proved straightforward and yielded the target substrate in satisfactory yield over two steps as a stable white solid, starting from the known[89] vinyl sulfonate **18** (**Scheme 3.5**).



Scheme 3.5

With this substrate at hand, a range of commercially-available anilines were heated with vinyl sulfonate **19** to afford the corresponding products in good yield. For the more electron-deficient anilines (**Table 3.0**, **Entries 9 & 10**), the conjugate addition was carried out at 190 ºC for 1 h and 130 ºC for 2 h, respectively (**Scheme 3.6**, **Table 3.0**).



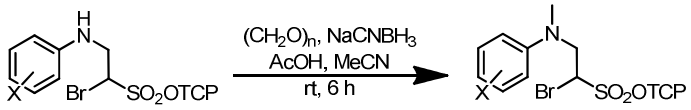
Scheme 3.6

Entry	X	R	Product	Isolated yield (%)
1	H	H	**20**	87
2	H	Me	**21**	89
3	*p*-F	H	**22**	92
4	*p*-Cl	H	**23**	71
5	*p*-Br	H	**24**	74
6	*p*-I	H	**25**	78
7	*o*-OMe	H	**26**	78
8	*m*-OMe	H	**27**	65
9	*p*-SO_2NEt_2	Me	**28**	14
10	*p*-CO_2Me	Me	**29**	70

Table 3.0[1]

3.2 *N*-Methylation of Pre-Cyclised Substrates

It was desirable for the substrates to undergo cyclisation where R=H, but disappointingly, these substrates failed to give any desired product when exposed to the radical-generating conditions discussed later. It was therefore necessary to alkylate the nitrogen atom *via* the Corey modification[90] of the Eschweiler-Clarke reaction[91,92] (**Scheme 3.7**, **Table 3.1**).



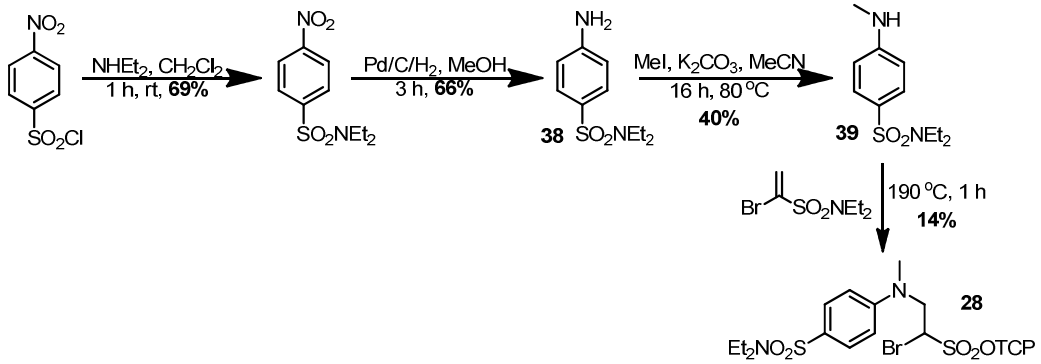
Scheme 3.7

[1] For Entries 9 and 10 (**Table 3.0**), synthesis of both methylated anilies is shown in **Scheme 3.8** overleaf.

Entry	X	Product	Isolated yield (%)
1	*p*-F	**30**	73
2	*p*-Cl	**31**	81
3	*p*-Br	**32**	56
4	*p*-I	**33**	46
5	*o*-OMe	**34**	75
6	*m*-OMe	**35**	71
7	*p*-CO_2Me	**37**	0
8	*p*-SO_2NEt_2	**39**	0

Table 3.1

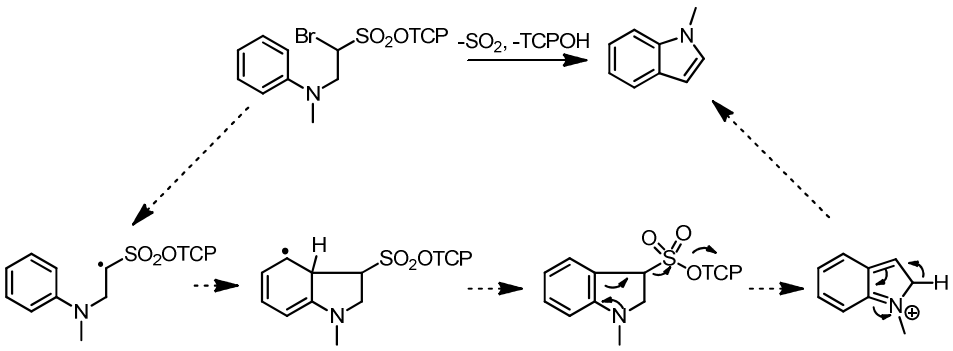
Table 3.1 shows that reductive methylation of substrates **30-35** was achieved in good yield whereas the two electron-withdrawing substrates (**Entries 7 & 8**) returned only starting materials. Due to the electron-withdrawing nature of these anilines, the nitrogen atom was regarded as less nucleophilic and thus a poor choice in this reaction. Consequently, an alternative route was devised in which the methyl group is installed in the aniline before the conjugate addition. This gave the desired product **39** in satisfactory yield, which consequently provided substrate **28** under forcing conditions (**Scheme 3.8**). A similar approach was used to synthesise **37** in 52% yield over two steps (*N*-methylation and Michael addition (130 ^oC, 2 h for the latter) starting from methyl 4-aminobenzoate (see experimental for details).



Scheme 3.8

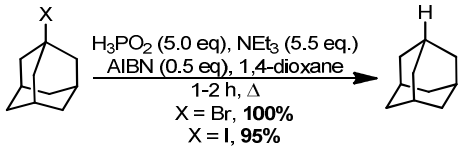
3.3 Radical Cyclisation Utilising EPHP

The initial rationale for this radical reaction came from the hypothesis that a carbon-centred radical could be easily generated from the α-bromo sulfonate, which could then undergo cyclisation onto a nearby aromatic ring. Once this key bond is formed, it was envisaged that the regeneration of aromaticity *via* loss of the sulfonate as a leaving group would yield the indole product (**Scheme 3.9**).



Scheme 3.9

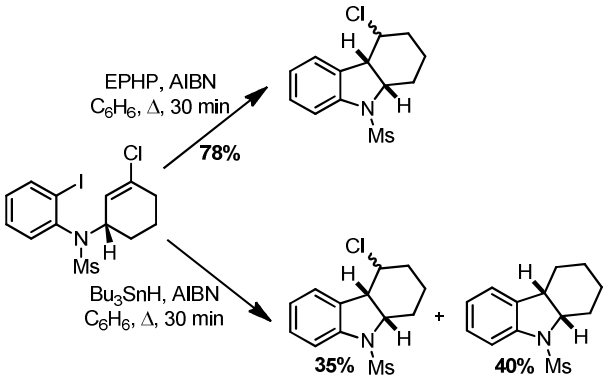
In terms of chain carriers for the cyclisation, one was keen to avoid tin-based reagents due to their difficulty in handling, toxicity and purification issues. Early studies by Barton *et al.*[93, 94] showed that the amine salts of hypophosphorous acid were good hydrogen atom sources but without the toxicity and handling issues associated with tributyltin hydride. Dehalogenation could be smoothly achieved with this reagent and the products isolated in excellent yield (**Scheme 3.10**).



Scheme 3.10

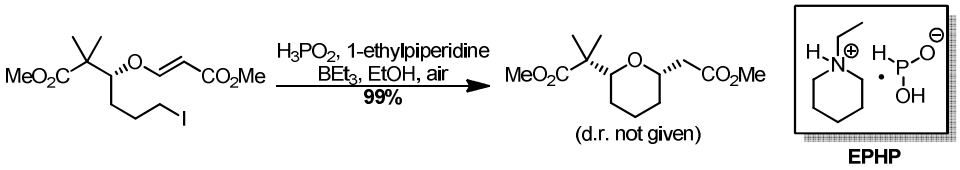
A short time after Barton's report, Murphy *et al.*[95] suggested that salts of hypophosphorous acid may not be limited to dehalogenation reactions, but may also be used in the formation of C-C bonds. The intramolecular radical cyclisation shown in **Scheme 3.11** illustrates this point, where an aryl radical is generated preferentially over an alkenyl radical to give the product in excellent yield. Attempting this

reaction with tributyltin hydride resulted in a significantly lower yield along with the formation of reduced product in 40% yield.



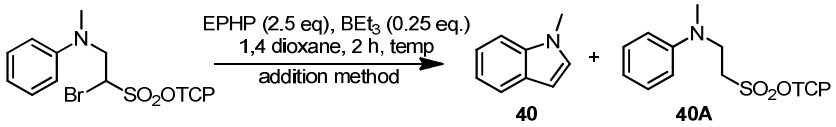
Scheme 3.11

With evidence of facilitating C-C bond formation, 1-ethylpiperidine hypophosphite (EPHP) can be seen[96] to possess many advantages over the likes of tributyltin hydride (**Scheme 3.12**).



Scheme 3.12

Firstly, the chain carrier and its products are water-soluble hence it is easily removed from the reaction mixture *via* aqueous workup. Tin-based chain carriers, on the other hand, can be difficult to remove from organic material. Secondly, the compound possesses no noticeable odour and is an easy-to-handle crystalline solid. With these benefits in mind, attempts to cyclise substrate **21** in the presence of triethylborane were carried out. Results from the initial optimisation are shown in **Scheme 3.13** and **Table 3.2**.



Scheme 3.13

Entry	Temp (^{o}C)	Addition method	Indole 40 (%)	Reduced product 40A (%)
1	21	Direct addition	36	40
2	65	Direct addition	20	38
3	21	Syringe pump	40	21
4	65	Syringe pump	54	30
5	70	Syringe pump	60	32
6	75	Syringe pump	65	33
7	90	Syringe pump	0	68

Table 3.2[2]

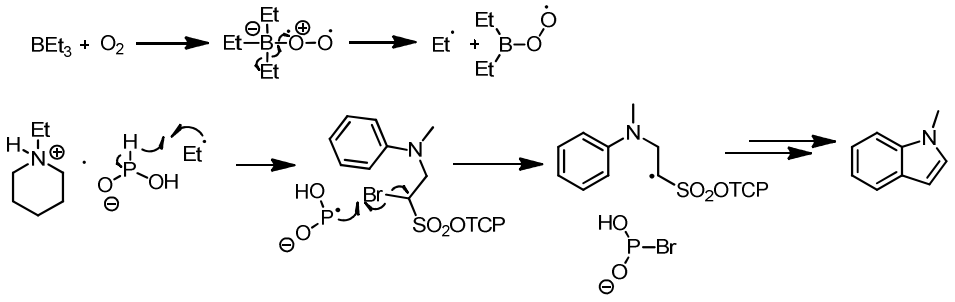
Although the overall yield of the reaction is mainly very good (>90% in some cases), isolating the desired indole over the unwanted, debrominated product involved a balance between addition time of both the chain carrier and initiator simultaneously along with careful temperature control. Initial experiments showed that using 1.0 equivalent of EPHP resulted in low starting material consumption, with only traces of indole and reduced product detected. Dioxane was adopted as an alternative to benzene in this reaction as it was removable *via* aqueous work up along with excess EPHP. Generation of ethyl radicals from the triethylborane also requires oxygen and 1,4-dioxane provides a facile source of dissolved oxygen for this initiation process. **Entry 1** shows a promising result with the indole being isolated in satisfactory yield when 2.5 equivalents of EPHP are added. It was then thought that maintaining a low concentration of EPHP in the solution would suppress the premature reduction of the radical intermediate. A 0.08 M solution of EPHP in dioxane was added dropwise via syringe pump over two hours to the substrate (also dissolved in dioxane, 0.03 molar solution initially) along with AIBN simultaneously. An improvement in these

[2] All syringe pump additions carried out over a 2 period.

results may be possible by lowering the concentration of EPHP further and increasing the addition time of this reagent.

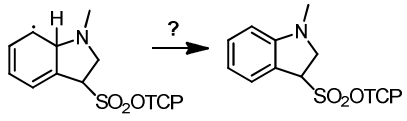
It was found that slow addition of reagents at room temperature had an adverse effect on the yield of indole and a temperature of 73 ^{o}C was found to be acceptable in giving a satisfactory yield of product. This resulted in a compromise between obtaining an acceptable yield of indole compared to debrominated product, as full consumption of the starting material could be achieved. Increasing the temperature to 90 ^{o}C resulted in no indole formation and exclusively debrominated material (**Table 3.2**, **Entry 7**). Further experiments showed that increasing the temperature over 75 ^{o}C resulted in an increase in debrominated product also.

Mechanistically, it is thought that initial generation of ethyl radicals from triethylborane and oxygen allows for H-atom abstraction from the P-H bond in EPHP. The phosphorus radical that is formed can consequently abstract the bromine atom from the substrate to form the key radical. At this stage, the radical can either cyclise onto the aromatic ring or, abstract another hydrogen atom from EPHP to give the debrominated product. A mechanism illustrating these steps is suggested in **Scheme 3.14**.



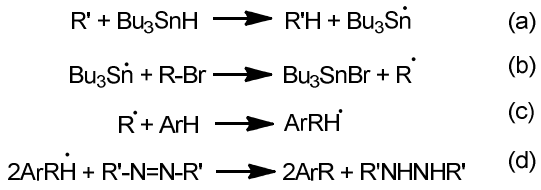
Scheme 3.14

The mechanism of re-aromatisation (oxidation) from the cyclohexadienyl radical has also been a matter of debate (**Scheme 3.15**).



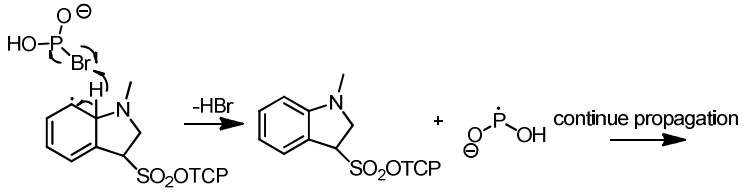
Scheme 3.15

Studies by Beckwith *et al.*[97] have indicated that the initiators AIBN and triethylborane can act as an oxidising agent in the mechanism of Bu_3SnH-mediated homolytic aromatic substitution. General equations decribing this pathway are shown below (**Scheme 3.16**)



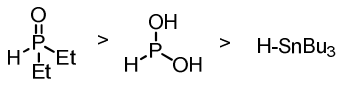
Scheme 3.16

In relation to our system, oxidation of the intermediate cyclohexadienyl radical may have occurred, to some degree, *via* ethyl radical generation from the reaction of triethylborane and oxygen. However, a sub-stoichiometic amount of the triethylborane was used in these studies and the yields of products are mainly over 50%. It would be a fair to state that the triethylborane is rapidly sequestered in the reaction in order to generate the phosphorus centered radical derived from EPHP. In order for the brominated phosphorus by-product to continue propagating the reaction, it needs to be regenerated, perhaps *via* reaction with the cyclohexadienyl radical (**Scheme 3.17**).



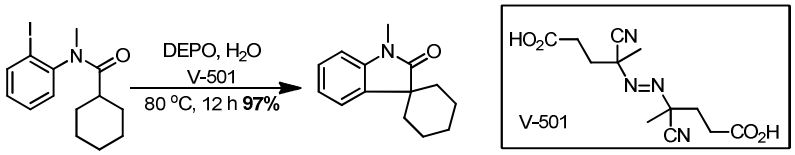
Scheme 3.17

Murphy *et al.*[98] have stated that the relative order of bond strengths progresses as shown in **Scheme 3.18**.



Scheme 3.18

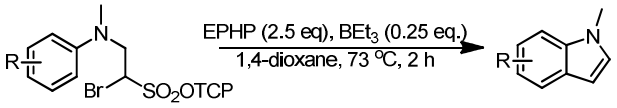
Diethylphosphine oxide (DEPO) was therefore a viable chain carrier for our radical cyclisation. Disappointingly, no reaction was observed upon its employment over EPHP. This was a discouraging result as Murphy *et al*.[99] have successfully used this reagent to carry out radical cyclisations similar to ours but under aqueous conditions (**Scheme 3.19**).

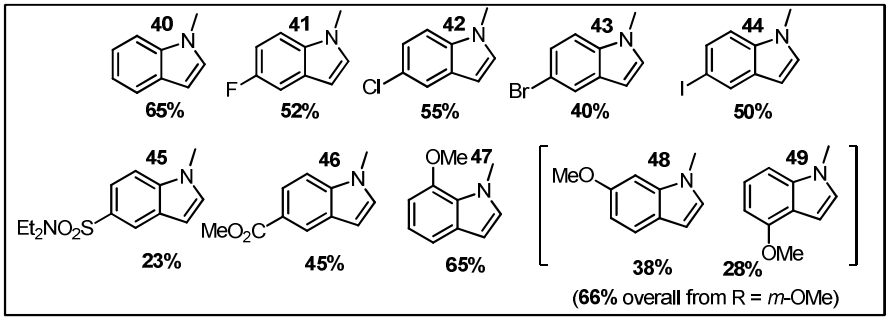


Scheme 3.19

Attempts to use tributyltin hydride were also met with failure in the indole synthesis with only debrominated product isolated. This observation would back up the relative order of bond strength suggested by Murphy *et al*.

With an acceptable optimisation at hand, a range of substituted anilines could be subjected to the cyclisation conditions and a range of indoles (**41**-**49**) were consequently isolated in fair to good yield (**Scheme 3.20**).[100]





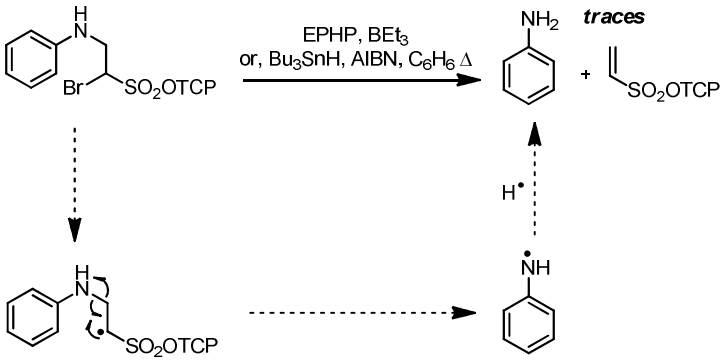
Scheme 3.20

3.4 Advantages of EPHP as a Chain Carrier

Pleasingly, this radical cyclisation also appears to be chemoselective as only the sp^3 C-Br bond appears to react, even in the presence of excess EPHP. This is notable for substrates **43** and **44** where the sp^2 aryl bromide and iodide functionality is preserved. Analysis of the crude reaction mixture by ^{1}H NMR indicated that the remaining organic material consisted of unreacted starting material and sp^3 debrominated compounds. It is therefore fair to suggest that the phosphorus-centred radical is not reactive enough to abstract an aryl bromide or iodide under these conditions, another useful advantage over tin-based reagents. Such chemoselectivity was not seen when tributyltin hydride was employed, unsurprisingly, as tin-centred radicals have a high affinity for halogens such as bromine and iodine. The preservation of the aryl iodide in this instance, contradicts the result obtained by Murphy *et al.* shown in **Scheme 3.11**. Perhaps the lower temperature and use of BEt_3 instead of AIBN were the critical differences that allowed the aryl iodide to be unreactive in this work. Indoles such as **44** are useful synthetic intermediates as the aryl iodide can be further manipulated in a range of copper and palladium-catalysed processes.

Overall, the substrate scope in this reaction was good, with another highlight being the synthesis of **46**, which is a key component in a highly active antimitotic agent, A-259745.[101] A mixture of regioisomers for substrates **48** and **49** was obtained in ~1.4:1 ratio, highlighting a major hurdle in indole synthesis- controlling regioselectivity.

As previously mentioned, it was also of interest to synthesise indoles with a free NH as these compounds would be much more useful in terms of further elaboration. Disturbed by the lack of literature precedent for radical cyclisations in the presence of unprotected nitrogen, work was carried out in the hope that the relatively mild conditions would favour product formation. Unfortunately, this was not the case with decomposition observed and traces of the starting materials shown in **Scheme 3.21.**



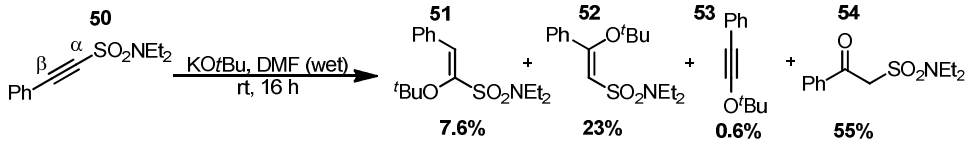
Scheme 3.21

As EPHP is acidic[102] (it is the monosalt of a dibasic acid), protonation of the nitrogen in the starting material may have deactivated the system towards cyclisation and, instead, favoured the radical intermediate to collapse *via* a similar pathway to that shown in **Scheme 3.21**. Acylating the nitrogen with acetyl chloride and subjecting it to EPHP/BEt_3 also gives rise to products analogous to those shown in **Scheme 3.21**.

Although this synthesis is performed with *N*-methylated substrates, it is rational to assume that *N*-benzylated analogues would be successfully cyclised under the given conditions. This would provide more useful indoles as the benzyl group could be removed. Although not the most atom-economical synthesis in comparison to other indole syntheses, (of which there are many), this route highlights three useful aspects of the vinyl sulfonate ester **19** as a tool in synthesis. Firstly, the electron withdrawing properties of the compound allows for facile 1,4-addition of amines under mild conditions, without the need of any solvent. Secondly, the sulfonate ester can stabilise the α radical to such a degree that allows it to cyclise onto the nearby aromatic ring. Finally, the sulfonate acts as a leaving group to yield the indole upon re-aromatisation. This final property is perhaps most important, as carrying out this reaction with a vinyl ester (i.e. methyl acrylate) instead of a sulfonate would not yield the indole due to the ester's shortcomings as a leaving group.

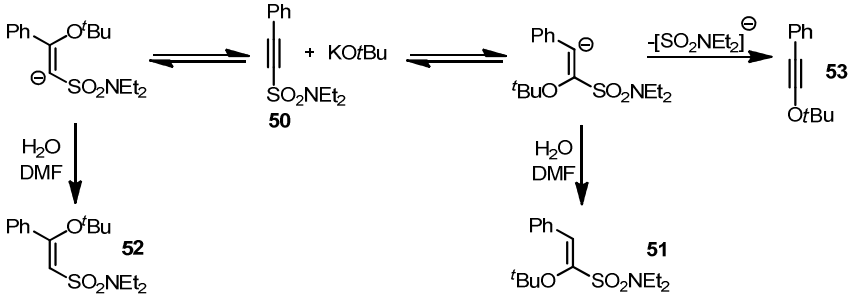
4.0 Reactions of Aryl-Substituted Alkynyl Sulfonamides

During the course of investigating the reactions of sulfonamide **50**, with a range of nucleophiles towards α and β attack, the isolation of unexpected enol ether **51** as well as ynol ether **53** in trace yield become of interest (**Scheme 4.0**).



Scheme 4.0

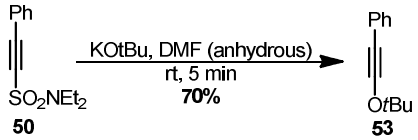
As previously mentioned, ynol ethers serve as versatile building blocks in synthesis, and routes towards such compounds are currently lacking. It was envisaged that this reaction could be optimised to afford ynol ether **53** in appreciable yield, thus making it a much more atom-economical synthesis compared to what is currently available. Protonated intermediates **51** and **52** were isolated in approximately 3:1 ratio along with the major 'hydrolysed' product- β-ketosulfonamide **54**. The initial mechanism considered for this process involved a *tert*-butoxide ion attacking the electrophilic acetylenic sulfonamide **50** under anhydrous conditions to yield ynol ether **53**. It was postulated that, in the absence of water, an equilibrium system would be established between the sulfonamide substrate and the *tert*-butoxide ion as shown in **Scheme 4.1** below.



Scheme 4.1

Consequently, it was thought that running the reaction under rigorously anhydrous conditions would suppress the formation of protonated enol ethers **51** and **52**, as well

as β-ketosulfonamide **54**. Pleasingly, the yield of ynol ether **53** increased to 70% upon employment of commercially-available anhydrous DMF (**Scheme 4.2**).

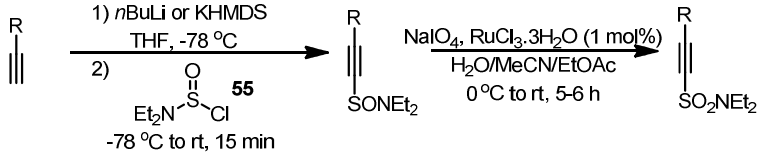


Scheme 4.2

Another advantageous property of this reaction was the speed in which the starting material was consumed. Compared to using wet DMF where the reaction proceeded slowly to give a range of products over many hours, the anhydrous solvent was complete within 5 minutes. A solvent screen showed that DMF was superior in all aspects; no reaction occurred with THF (anhydrous and wet), acetonitrile (anhydrous and wet), toluene, dichloromethane and DMSO. The scope of the reaction was therefore explored, generating a range of *tert*-butyl ynol ethers. Compared to other potassium alkoxides, *t*BuOK is relatively inexpensive and can be purchased in twice-sublimed, anhydrous form.

4.1 Substrate Synthesis

Synthesising a range of alkynyl sulfonamides (**50** & **67-76, Table 4.0**) proved a relatively fast and straight-forward process, where a route provided by Baudin *et al.*[103] was adopted, starting from commercially-available, terminal acetylenes (**Scheme 4.3**).



Scheme 4.3

The $SONEt_2$ source was easily incorporated at the terminal end of the acetylene *via* initial deprotonation and dropwise addition of $SOClNEt_2$ **55**. This substrate was prepared from $SOCl_2$ and two equivalents of diethylamine to yield the highly

reactive, malodorous product, which was stored at –20 ^{o}C under argon between use *via* a procedure developed by Baudin *et al*.[103] With the sulfinamide at hand, oxidation to the sulfonamide using sodium periodate and catalytic ruthenium(III) chloride was achieved in good yield. Although not the most efficient synthesis of such substrates in terms of overall yield and reagents required, it allows for the relatively quick synthesis of a range of alkynyl sulfonamides for subsequent transformation into the corresponding ynol ethers.

A range of substrates and corresponding yields are shown below (**Table 4.0**).

Entry	R	Sulfinamide	Yield (%) Sulfinamide	Sulfonamide	Yield (%) Sulfonamide
1	Ph	**56**	84	**50**	56
2	*p*OMe-C_6H_5	**57**	79	**67**	63
3	*m*OMe-C_6H_5	**58**	82	**68**	65
4	*o*OMe-C_6H_5	**59**	80	**69**	60
5	Pyridin-2-yl	**60**	65	**70**	50
6	*p*NO_2-C_6H_5	**61**	80	**71**	63
7	*p*F-C_6H_5	**62**	78	**72**	61
8	*p*Br-C_6H_5	**63**	72	**73**	56
9	*p*CF_3-C_6H_5	**64**	71	**74**	59
10	Naphthalen-2-yl	**65**	65	**75**	42
11	*t*-Bu	**66**	90	**76**	70

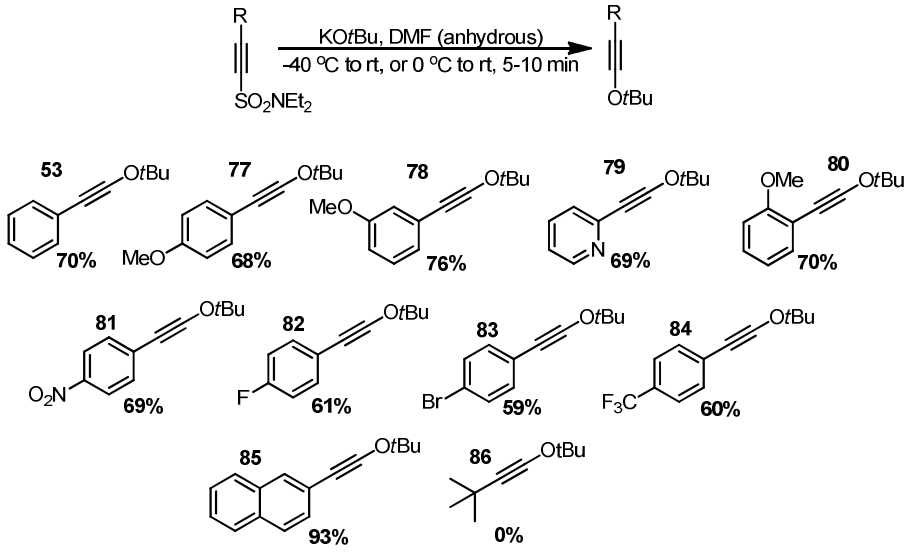
Table 4.0

4.2 Displacement of a Sulfonamide Leaving Group

With a range of substrates at hand, covering appreciable scope in terms of electron withdrawing and donating substituents, displacement of the sulfonamide leaving group was carried out to yield a range of aromatic *tert*-butyl ynol ethers in excellent

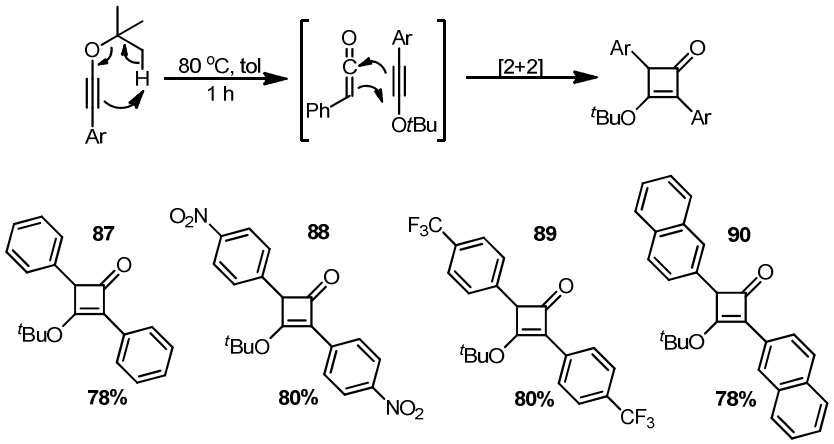
yield (**Scheme 4.4**).[104] Interestingly, the rate and efficency for both electron-donating and withdrawing examples are similar.

Aliphatic alkynyl sulfonamide **76** failed to undergo displacement with the alkoxide, resulting in *β*-attacked products (~3:2 mixture of *Z* and *E* isomers) and *β*-ketosulfonamide. A potential explanation for this behaviour will be discussed in **Section 4.6.**



Scheme 4.4

Upon heating, these ynol ethers were found to undergo a retro-ene reaction,[70] where *iso*butene was extruded to yield a ketene. This ketene could then undergo a [2+2] cycloaddition with another ynol ether molecule to afford novel, tri-substituted cyclobutenones in excellent yield. Starting from the alkynyl sulfonamide, this route provides rapid entry to a range of cyclobutenones **87**-**90** that would otherwise be much more time-consuming to synthesise (**Scheme 4.5**).

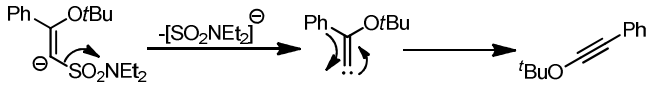


Scheme 4.5

4.3 Mechanistic Studies

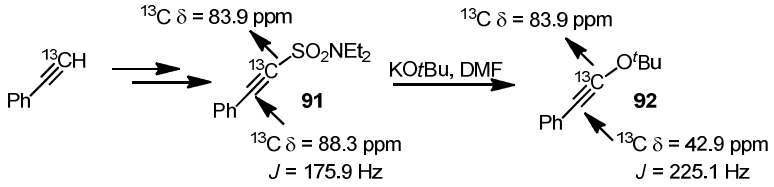
At this stage, with a range of reactive, novel ynol ethers as well as a selection of cyclobutenones, the mechanism was re-investigated in the hope of gaining more insight into this unexpected displacement.

Initially, it was important to establish whether the reaction was an addition elimination process as previously suggested, or, a Fritsch-Buttenberg-Wiechell rearrangement[105,106,107] (FBW) involving a carbene intermediate (**Scheme 4.6**).



Scheme 4.6

An experiment involving ^{13}C enriched phenylacetylene was employed to deduce whether a FBW rearrangement was in operation in this reaction. Having a much greater migratory aptitude compared to O*t*Bu, the phenyl group would be expected to undergo migration. If this mechanism is in operation, the ^{13}C would appear more upfield. The synthesis of alkynyl sulfonamide **91** was achieved uneventfully and the key step showed full retention of the ^{13}C in the *tert*-butyl ynol ether product **92**. These deductions were easily observed *via* ^{13}C NMR spectroscopy (**Scheme 4.7**).

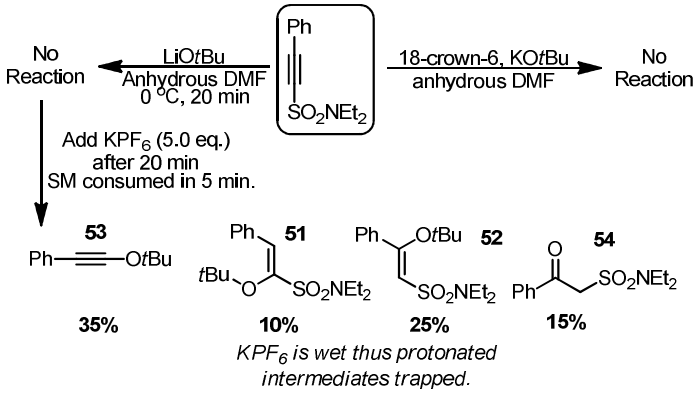


Scheme 4.7

The led us to conclude that the mechanism was an addition-elimination process.

4.4 The Importance of the Potassium Cation

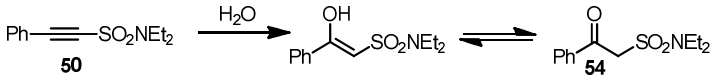
Attempting the reaction with lithium, sodium, magnesium, calcium, barium and aluminium *tert*-butoxide (and other alkoxides) yielded no product and no reaction was observed. To further demonstrate the importance of potassium ions in this reaction, an experiment involving the addition of 18-crown-6 was carried out which completely stopped the reaction, yielding only recovered starting material. Addition of a soluble potassium ion source (KPF_6) to a reaction containing Li*O*t*Bu was shown to 'activate' the reaction and the alkynyl sulfonamide was quickly consumed to give the ynol ether, albeit in lower yield. These experiments neatly demonstrated the importance of potassium cations in this reaction and are summarised in **Scheme 4.8**.



Scheme 4.8

The formation and isolation of *β*-ketosulfonamide **54** was, initially, a highly undesirable side product in this reaction as it implied the presence of water in an apparently anhydrous reaction. It was initially assumed that water was hydrating the

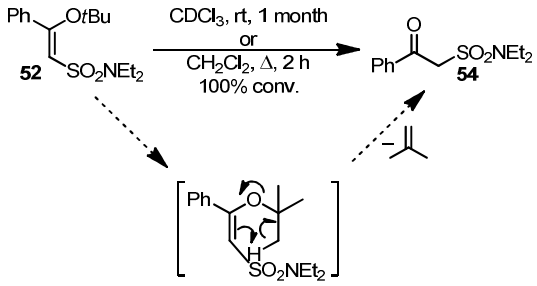
alkynyl sulfonamide *via* Michael attack at the *β*-carbon to yield an enol, which could then tautomerise to give the product (**Scheme 4.9**).



Scheme 4.9

Stirring the alkynyl sulfonamide **50** in wet DMF at room temperature showed no consumption of the starting material until the reaction was refluxed at 80 ^{o}C for 2 h. This observation led us to consider if hydroxide was present in the reaction mixture and the same reaction as above was carried out in the presence of KOH in DMF. Again, there was no consumption of the starting material to afford the *β*-ketosulfonamide **54** until the reaction mixture was refluxed for a prolonged period.

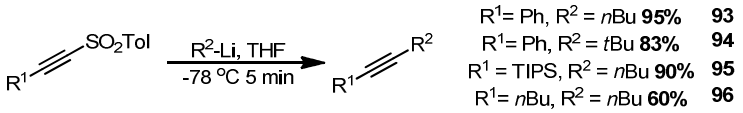
It was a serendipitous discovery that led us to understand why this 'hydrated' product was forming. A sample of enol ether **52** had been stored for a few months and upon re-running the ^{1}H NMR, it was observed that most of the enol ether had converted to the *β*-ketosulfonamide. Upon heating enol ether **52** in dichloromethane, the product ketone could be quickly obtained. It is thus apparent that this substrate can undergo a retro-*ene* reaction, extruding *iso*butene to afford the product (**Scheme 4.10**).



Scheme 4.10

With this result at hand, one can now account for the formation of this ketone in the main reaction. Therefore, to suppress this unwanted side reaction, cooling the flask to 0 ^{o}C proved to be an adequate solution and formation of this product was greatly diminished.

Reports of direct displacement of a leaving group (especially $-SO_2R$) from an alkyne are scarce in the literature. Ruano *et al.*[108] have successfully displaced sulfones from a range of alkynes with organolithium reagents to yield the corresponding to alkyne (**Scheme 4.11**).



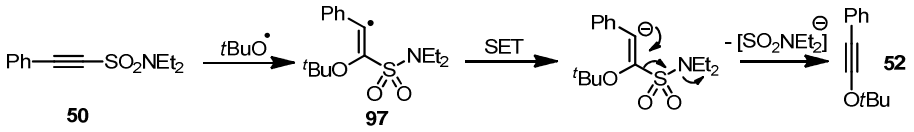
Scheme 4.11

In this case, the carbon-based alkyl lithium is much more nucleophilic in comparison to the potassium alkoxide. The group has hypothesised that Michael attack at the β carbon should be expected, but coordination of the lithium ion to a sulfonyl oxygen atom would allow for Anti-Michael attack. Computational calculations show that this lithium coordination can lower the energy barrier of the anti-Michael route enough to favour displacement products **93-96**, exclusively.

Lithium *tert*-butoxide resulted in no reaction and it was therefore important to deduce why potassium alkoxides were the only successful reagents in displacing the sulfonamide. In order to rule out the possibility of any trace-metals in the potassium *tert*-butoxide catalysing the reaction, twice-sublimed, commercially-available KO*t*Bu was used. No deterioration in yield, or speed in which the starting material was consumed, was observed.

To further investigate the role of potassium, DFT modelling was used to study the structures of LiO*t*Bu, NaO*t*Bu and KO*t*Bu. It was found that both Li-O and Na-O were relatively short bonds (1.70-2.05 Å) in comparison to K-O (2.46 Å).[104] It was hypothesised that this longer bond was the result of weaker binding and that potassium *tert*-butoxide was much more ionic in bonding character, relative to lithium and sodium *tert*-butoxide. Therefore, a facile source of *tert*-butoxide anions is available in the reaction whereas the stronger metal oxygen bond in lithium and sodium *tert*-butoxide gives rise to their relative lack of reactivity. These latter two alkoxides also exhibited poor solubility in DMF compared to KO*t*Bu.

With this data at hand, the role of the potassium cation could be re-considered. If, as the DFT modeling suggested, KO*t*Bu provided a facile source of *tert*-butoxide ions and with the knowledge that 18-crown-6 suppresses the reaction, K^+ must therefore play a discrete role in the reaction and is not merely a spectator ion in this instance. With the knowledge that organolithium reagents react rapidly with alkynyl sulfones, it seemed increasingly unlikely that an oxygen-based anion could add to such substrates with the same rapidity to afford high yields of ynol ethers without some other reactive or stabilising species being present. It was thought that another reactive species was being generated that could 'activate' the alkynyl sulfonamide towards attack by a *tert*-butoxide group. These considerations led us to investigate a mechanism where *tert*-butoxy radicals could be adding to the alkynyl sulfonamide, followed by single electron transfer and finally collapse of the intermediate to give the product. This idea is illustrated in **Scheme 4.12**, below.



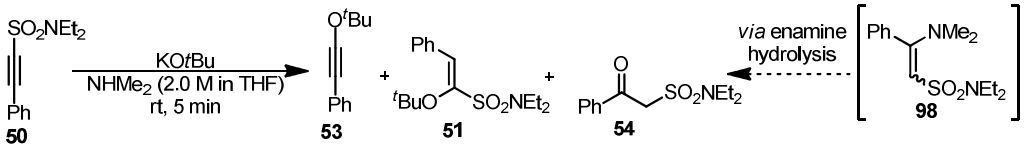
Scheme 4.12

In an attempt to trap intermediate **97** or, suppress the addition of *tert*-butoxide radicals in the reaction, a stoichiometric amount of the radical inhibitor TEMPO was employed. No deterioration in yield of ynol ether was observed and no TEMPO adducts of the substrate detected. Aware of many reports in the literature of *tert*-butoxide-promoted aryl cross-coupling reactions that employ amines,[109,110,111] it was important to deduce outright if a radical mechanism was in operation *via* other chemical or spectroscopic means, even though the radical trapping experiment did not indicate this was the case.

4.5 Understanding the Importance of DMF

With the knowledge that potassium *tert*-butoxide can increase the rate of DMF decomposition to form carbon monoxide and dimethylamine,[112] it was crucial to know if this amine was present in the reaction mixture and whether it was aiding the formation of another activated complex or substrate.

After optimisation, it was found that carrying out the reaction in dimethylamine (2.0 M anhydrous solution in THF) gave the ynol ether product rapidly and in excellent yield, indicating $NHMe_2$, derived from DMF decomposition was involved in this reaction (**Scheme 4.13** & **Table 4.1**). Conversely, using freshly distilled DMF in the reaction resulted in a suppressed reaction with only traces of product being observed.



Scheme 4.13

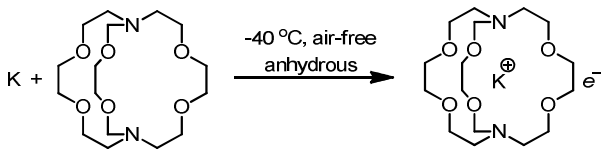
Entry	KO^{t}Bu equivalents	$NHMe_2$ equivalents	Yield (%) ynol ether 52	Yield (%) enol ether 50	Yield (%) ketone 53
1	1.3	3.0	19	29	30
2	1.3	0.1	0	0	20
3	1.7	1.0	46	38	0
4	3.0	1.0	59	20	0
5	3.0	1.5	64	16	0
6	5.0	2.5	86	0	0

Table 4.1

Superior results were obtained when an excess of both reagents was employed in a 2:1 ratio KO*t*Bu:$NHMe_2$ (**Entry 6**, **Table 4.1**) and the amount of α-attacked (enol ether) product **51** was completely suppressed, likely due to the high pH conditions favouring elimination of SO_2NEt_2 over protonation. Stirring the starting material in

$NHMe_2$ and THF led to the unstable enamine intermediate **98** after 10 min at room temperature, with complete conversion. Exposure of this enamine to column chromatography (SiO_2) or acid workup conditions, led to hydrolysis and formation of β-ketosulfonamide **54** quantitatively. It seems that a mixture of this amine and KO*t*Bu forms another reactive species/complex that can readily attack alkynyl sulfonamide **50** with complete regioselectivity for the α-position. At this point it was hypothesised that a stabilised complex of *tert*-butoxy radicals were forming when mixed with the amine solution in THF. Literature precedent demonstrated that this may be the case after considering studies and commentary by Dye on a class of compounds coined "electride salts".[113,114,115]

These complexes are prepared *via* reaction of an alkali metal with a solvent which can strongly solvate the cation as well as being resistant to reduction. The electron enters solvent "cavities" which stabilises the overall complex.[116,117] Both potassium and caesium salts can be prepared and characterised by reaction of these metals with cryptand[2.2.2] and 18-crown-6, respectively (**Scheme 4.14**).[114]



Scheme 4.14

4.6 EPR Studies of Simple Reagent/Solvent Mixtures

In order to detect any species with an unpaired electron in the reaction system, electron paramagnetic resonance spectra (EPR) of different reagent mixtures were measured. Initially, a set of control experiments were carried out with individual reagents followed by the reagent mixtures. The first reagent combination contained a 1:1 mixture of potassium *tert*-butoxide and dimethylamine (2.0 M in THF) and a triplet signal was immediately detected (**Figure 4.0**).

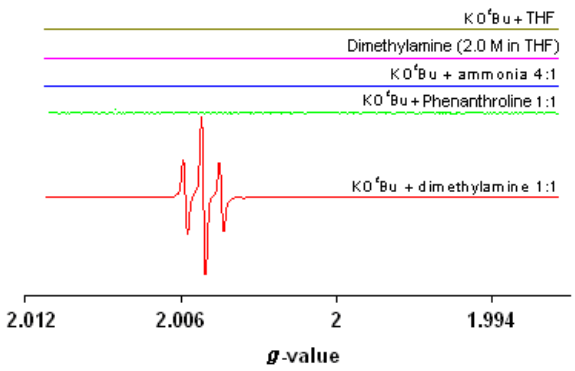


Figure 4.0

The triplet signal (1:2:1 intensity, H a_{iso} = 1.22 G or 3.64 MHz, g_{iso} = 2.0049) implies an electron coupled to two equivalent nuclei with spin ½, most likely two equivalent hydrogen atoms. At this stage *tert*-butoxy radical formation was considered, stabilised by two hydrogen-bonds from $NHMe_2$ where the free electron is solvated by the amine. A carbon-centred radical can be ruled out as the hyperfine coupling constants are too small and the g-value too high for this to be the case. The fact that this radical can be observed under ambient conditions in the presence of air is a testament to its stability and may explain why the alkynyl sulfonamide **50** is so reactive towards this reagent mixture at low temperature. No degradation in signal intensity was observed for approximately one hour. A radical concentration between 10-20 μM was calculated for a 2.0 M solution of KO*t*Bu in $NHMe_2$/THF.

To demonstrate that an electron had been dissociated from the oxygen anion, an EPR spectrum was measured in the presence of Buckminsterfullerene. Pleasingly, a singlet peak was observed in the EPR spectrum when one equivalent of C_{60} was added to a 1:1 mixture of KO*t*Bu in $NHMe_2$ (2.0 M in THF), indicating the formation of another radical species which has been assigned as $C_{60}^{\bullet -}$ (**Figure 4.1**) (H a_{iso} = 1.76 G or 4.95 MHz, g_{iso} = 2.0047. The $C_{60}^{\bullet -}$ radical anion has a g_{iso} of 2.0005 which is in line with the literature data).[118]

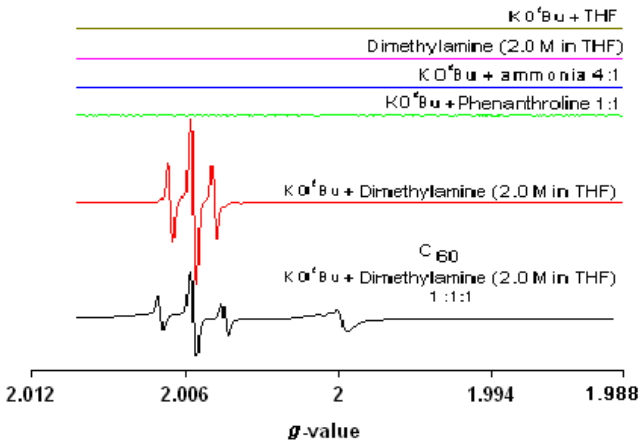


Figure 4.1

The C_{60} radical anion is a well-studied[119,120] compound that has been observed at low temperature (100 K) *via* EPR spectroscopy and it thus surprising that it can be observed under ambient, aerobic conditions. Given that only potassium alkoxides gave signals in the EPR measurements, it is clear that K^+ cations play an important role in the complex assembly. Addition of stoichiometric 18-crown-6 to a mixture of KO*t*Bu in $NHMe_2$ (2 M in THF) led to no signal. At this point, it was considered whether the potassium ion was co-ordinating the nitrogen atoms in dimethylamine, thus making them better H-bond donors for the two lone pairs on an oxygen-centered radical (**Figure 4.2**).

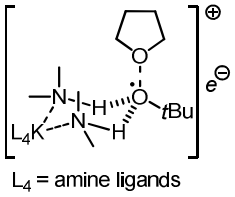


Figure 4.2

Measuring the EPR spectrum in the absence of THF gave no signal hence it was envisaged that further stabilisation of the *t*BuO$^{\cdot}$ radical with a THF molecule may be in operation. When dimethylamine is replaced with DMEDA, a triplet signal (1:2:1 intensity) is detected (H a_{iso} = 1.24 G or 3.47 MHz, g_{iso} = 2.0049) and one can thus suggest the following structure (**Figure 4.3**).

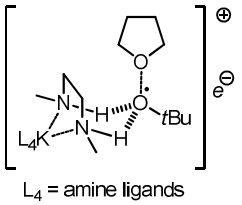


Figure 4.3

Measuring the EPR spectrum under standard conditions with LiO*t*Bu and $NHMe_2$ (2.0 M in THF) in place of KO*t*Bu gave no signal. The same can be said when a tertiary amine was employed in the reaction. Triethylamine and KO*t*Bu (THF solution) gave no signal when measured at the same concentration as previous measurements (2.0 M). After a further amine screen, it became clear that the NH moiety on the amine was critical. Furthermore, only secondary amines were effective in giving a signal. These findings are shown below (**Figure 4.4**).

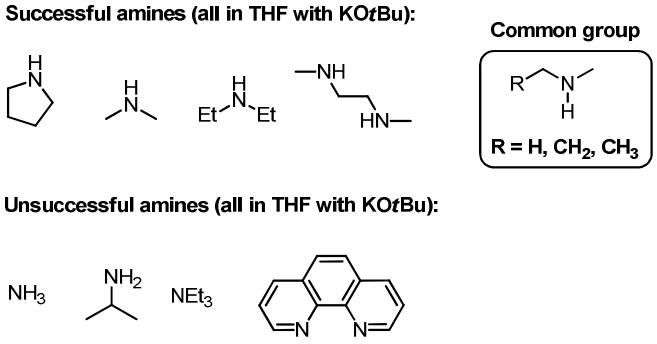


Figure 4.4

The EPR spectrum of $NHMe_2$, KOMe and KOEt in THF were also measured. For these lower member primary alkoxides (also noticeably less soluble in $NHMe_2$/THF), there was a lag time of 15-20 minutes before a signal was detected. For both these alkoxides a much less symmetrical, lower intensity signal was detected that disappeared after approximately 10 minutes. The EPR spectrum for KOMe mixed with $NHMe_2$ in THF is shown in **Figure 4.5**.

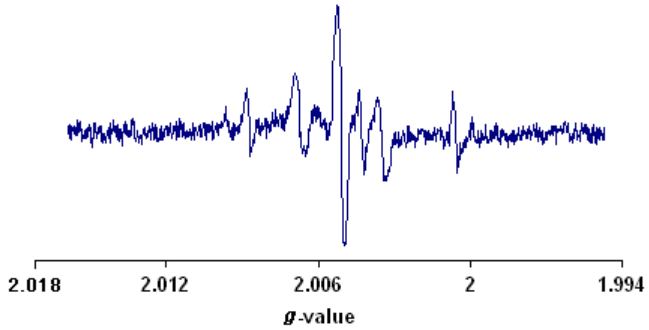
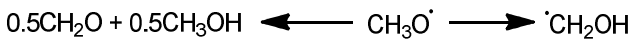


Figure 4.5

A triplet signal is discernible in **Figure 4.5** as well as other side-peaks which remain uncharacterised. Primary alkoxy radicals are known to be much less stable than their tertiary counterparts as they can more readily undergo rearrangement due to the presence of α hydrogen atoms (**Scheme 4.15**).[121] Such radicals are further destabilised by the lack of hyperconjugation which tertiary alkoxy radicals benefit from.

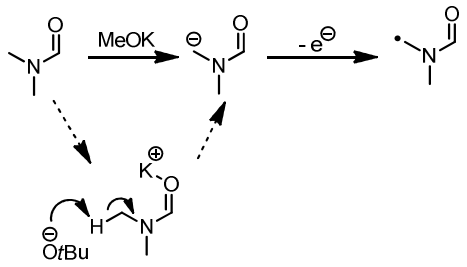


Scheme 4.15

However, these primary alkoxides successfully produced the corresponding ynol ethers in good yield and an explanation for this will be discussed later.

Taking into account the observations discussed so far, it is important to consider why certain potassium alkoxides can readily lose an electron under ambient conditions to form surprisingly stable radicals that can be detected *via* EPR spectroscopy. Studying the literature to explore this phenomenon yielded one paper[122] in which the formation of DMF and DMSO radicals are induced by potassium methoxide.

In this case, the authors suggest that MeOK can deprotonate a methyl hydrogen on DMF leading to the carbanion, which then loses an electron to form "radical adducts with solvent molecules". **Scheme 4.16** illustrates these remarks.



Scheme 4.16

The carbon-centred radical shown in **Scheme 4.16** is an unlikely candidate in our studies as the spectra do not match.

To demonstrate that the displacement of SO_2NEt_2 on alkynyl sulfonamide **50** with KO*t*Bu and DMF was due to a radical-based pathway, an EPR spectrum was recorded for a mixture of KO*t*Bu and DMF at room temperature. Pleasingly, this mixture gave a signal (triplet of triplets), indicating an unpaired electron coupled to two protons and a nitrogen centre (H a_{iso} = 1.36 G or 3.83 MHz, N a_{iso} = 12.57 G or 35.3 MHz, g_{iso} = 2.0059) (**Figure 4.6**).

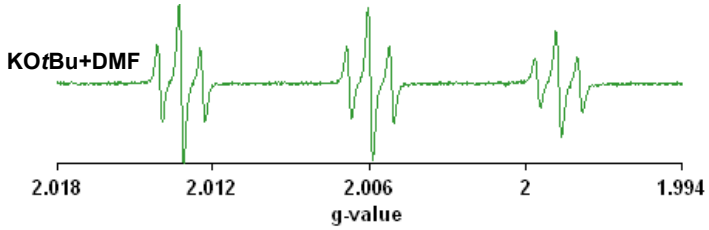


Figure 4.6

Interestingly, no signal was observed with amine-free DMF, indicating its importance in the formation of the radical complex. Traces of water in DMF (anhydrous, non-sealed bottle that had been opened for more than two weeks) appeared to have no detrimental effect on the quality of EPR spectra measured. One can envisage the slow decomposition of DMF to form dimethylamine over the course of weeks which would be of sufficient concentration to allow radical formation. When DMF was distilled from flame-dried $MgSO_4$ under vacuum and quickly used for EPR measurements, no signal was detected. The suggested structure that agrees with the EPR signal is shown below (**Figure 4.7**).

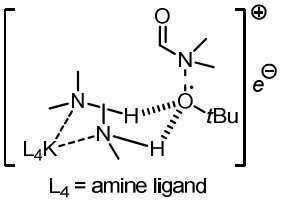


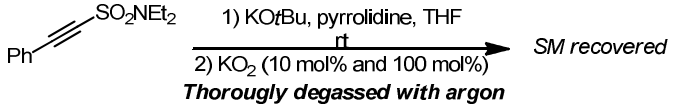
Figure 4.7

In order to ensure the radical centre was based on the alkoxy oxygen and not the solvent, both d_7-DMF and d_8-THF were employed for the EPR measurements. Unfortunately, both these solvents presented difficulties. Measuring an EPR spectrum for KO*t*Bu in d_7-DMF led to the same signal as in the un-deuterated experiment (triplet of triplets) shown in **Figure 4.6**. Confused by this result, a ^{1}H NMR spectrum of the d_7-DMF was measured and it was found that it contained up to 4% un-deuterated DMF even though the ampoule indicated 99.9% deuterium content. With this knowledge, it was clear that the EPR signal arising from KO*t*Bu and d_7-DMF was due to the un-deuterated DMF, forming the structure shown in **Figure 4.7**, making this experiment ineffective at providing the information required. Attention was then brought to employing d_8-THF along with DMEDA and KO*t*Bu, with the knowledge that DMEDA gives a triplet signal when mixed with KO*t*Bu and un-deuterated THF.

Disappointingly, it was found that KO*t*Bu was only sparingly soluble in this solvent and, along with addition of DMEDA to the mixture; it was very difficult to place this highly heterogeneous sample in the EPR tube without instant blockage, or the syringe backfiring. The EPR measurement method was therefore changed to a capillary tube and enough sample could be loaded for an EPR measurement. This led to no signal detection after longer measurement times (2 h). It was felt that this was due to the inability of the KO*t*Bu to dissociate to K^+ and $^-$O*t*Bu in this solvent.

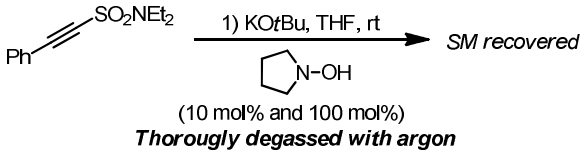
Employing d_1-pyrrolidine with KO*t*Bu in THF also appeared to greatly diminish the solubility of the alkoxide; scanning the sample for twenty minutes ultimately leads to a weak and complex multiplet signal. This suggests the importance of the NH group in un-deuterated pyrrolidine which may form H-bonds to the *tert*-butoxy radical.

Finally, it was important to deduce whether molecular oxygen was involved in the radical formation. Carrying out the displacement reaction with thoroughly degassed THF, substrates and reagents (with argon) resulted in *no* consumption of starting material. Measuring the EPR spectrum of the mixed, degassed reagents also resulted in *no* signal. Disturbed by this result, oxygen was considered as potentially playing an active role in the assembly of the radical complex. Carrying out the reaction under rigorously degassed conditions in the presence of both sub-stoichiometric and stoichiometric potassium superoxide led to no product consumption (**Scheme 4.17**).



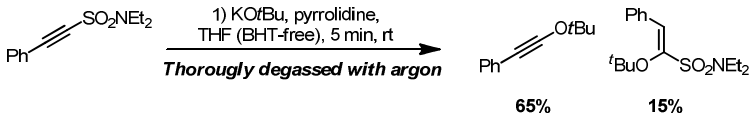
Scheme 4.17

Aware that superoxide reacts rapidly with amines,[123] *N*-hydroxylamine was considered as a potential active component in the reaction. In order to elucidate if this was the case, *N*-hydroxyl pyrrolidine was employed in the degassed reaction. Again, no starting material consumption was observed (**Scheme 4.18**)



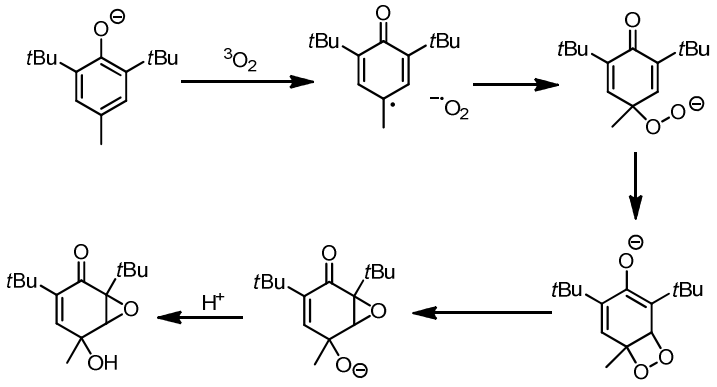
Scheme 4.18

Exasperated by the few avenues left to explain these observations, attention was turned to the solvent. THF is stabilised by ~250 ppm BHT (butylated hydroxytoluene) and it was therefore reasonable to consider this compound as a potential inhibitor in the reaction mixture. Carrying out the reaction in the presence of stoichiometric BHT without degassing the solvent and reagents showed no starting material consumption. With renewed confidence, the reaction was then conducted under thoroughly degassed conditions in the presence of BHT-free THF. Pleasingly, starting material consumption was observed within 5 minutes (**Scheme 4.19**).



Scheme 4.19

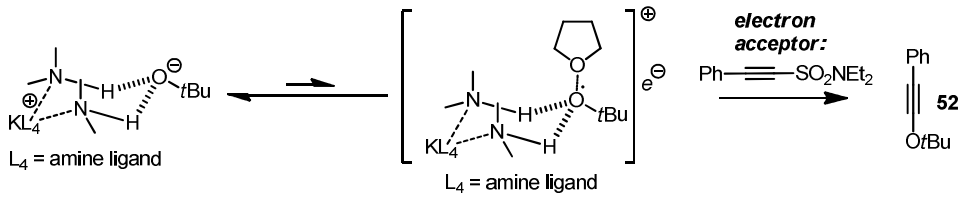
Lee *et al.* have shown that BHT reacts with triplet oxygen under basic conditions to form de-aromatised, epoxy ketones (**Scheme 4.20)**.[124]



Scheme 4.20

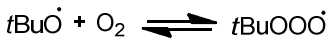
These experiments suggest that the dissolved oxygen present in THF is reacting with the BHT upon addition of KO*t*Bu and the radical complex can only be assembled once this radical inhibitor has been sequestered. It is also documented[125] that a BHT radical produces a quartet of triplets *via* EPR when generated from UV irradiated BHT thus ruling out the possibility of this compound being the cause of the EPR signal (i.e. only one triplet is observed in our measurements with THF).

However, measuring the EPR spectrum with degassed BHT-free THF, KO*t*Bu and pyrrolidine still led to no signal. At this stage, with much data at hand (some of which appears contradictory to the radical structures suggested), it was important to consider whether molecular oxygen was stabilising the radical and thus contributing to the EPR triplet signal that results when KO*t*Bu is mixed with $NHMe_2$ in THF. One suggestion is given in **Scheme 4.21**, where it is suggested that in the absence of an electron scavenger such as molecular oxygen or an alkynyl sulfonamide, the equilibrium lies to the left.



Scheme 4.21

Another explanation may arise from the reaction of the alkoxy radical with molecular oxygen to form a trioxyl radical (**Scheme 4.22**). These species have been moderately studied in the literature, especially in the field of atmospheric chemistry.[126, 127]



Scheme 4.22

It has also been shown computationally that CH_3O-OOH hydrotrioxide bond is weaker than the CH_3OO-OH bond;[128] a property which may be analogous to the trioxyl radical species. When ^{13}C-labelled potassium methoxide is mixed with $NHMe_2$ in THF, a similar asymmetric signal to that shown in **Figure 4.5** is detected via EPR after approximately twenty minutes. Both spectra are shown in parenthesis in **Figure 4.6**.

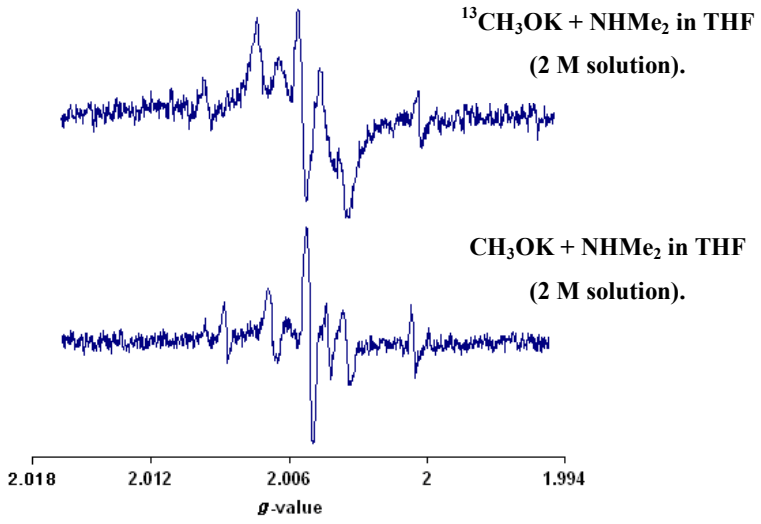


Figure 4.6

This result indicates that the radical observed *via* EPR is not that of an alkoxy as the spin ½ ^{13}C attached to the oxygen would cause additional line splitting in the spectrum. With this important detail at hand, coupled with the fact that no signal is observed under degassed conditions, another radical structure can be proposed which accommodates for these findings (**Figure 4.7**).

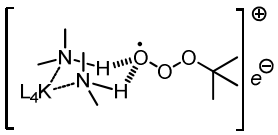
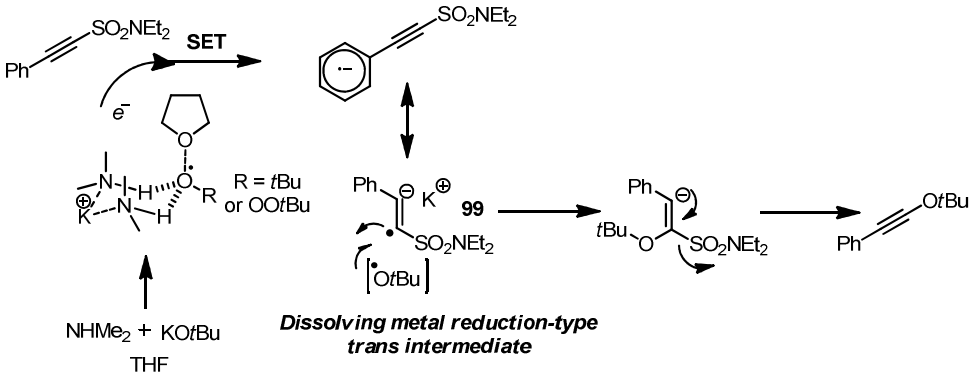


Figure 4.7

It was also noticeable that upon mixing the KO*t*Bu with $NHMe_2$ in THF, there was a short (5-6 minutes) lag time before the triplet signal abruptly appeared in the EPR spectrometer. This behaviour may be accounted for as the oxygen initially sequesters the BHT in the amine/THF solution before being able to assemble the radical complex. Trioxyl radicals are known intermediates in the decomposition of ozone in the atmosphere but, due to their lability, they are currently under-studied.[129] Suggested in **Figure 4.7** is a H-bonded trioxyl radical complex that accounts for all the spectroscopic evidence obtained thus far. This complex can thus be regarded as a source of alkoxy radicals as shown in the equilibrium in **Scheme 4.21**. To prove this structure indefinitely, switching from $^{16}O_2$ to $^{17}O_2$ (spin 5/2 nuclei) for the EPR measurement will be necessary. Synthetically, no products relating to the trioxyl radical have been isolated and if this species is present in the reaction mixture, decomposition to the more reactive alkoxyl radical would be expected. Given that the trioxyl species would be relatively more stable than the alkoxyl radical, the complex formed when KO*t*Bu and $NHMe_2$/THF are mixed may involve a stabilised trioxyl radical which decomposes to form alkoxy radicals in the presence of an electron acceptor (e.g. alkynyl sulfonamide **50**). This may explain why an EPR spectrum can be obtained of the radical species that solely results in the *alkoxy radical product* (i.e. the ynol ether) in the given synthetic transformation.

The EPR studies and the synthetic methodology should not be considered entirely dependently until more detail of the radical structure is obtained.

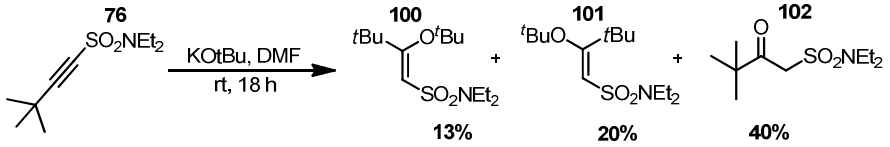
With strong evidence that stable radical complexes can be generated under ambient conditions, two potential mechanisms can be given that explain the outcome of the displacement reaction, the first of which is shown in **Scheme 4.23**.



Scheme 4.23

This pathway involves electron transfer to the aromatic ring of the alkynyl sulfonamide which then tautomerises to the captodatively-stable *trans* radical anion **99**. This intermediate is analogous to those known from sodium/ammonia type reductions of alkynes.[130]

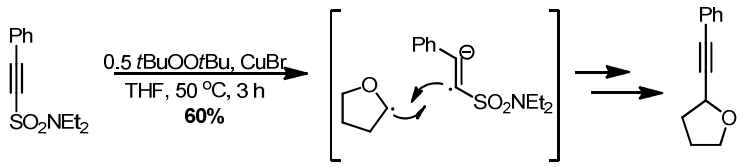
This radical anion can then react with a *tert*-butoxy radical to form a polar intermediate which collapses, eliminating $-SO_2NEt_2$ to afford the ynol ether. Evidence that this pathway may be in operation comes from three sources. Firstly, only protonated intermediates (both α and β) of the enol ether have been isolated in the *trans* configuration with respect to the phenyl group and the sulfonamide (confirmed by NOSEY experiments). Secondly, carrying out the displacement with **76** (**Scheme 4.24**) results in no α addition products. Instead, a ~3:2 ratio of *Z*/*E* isomers **100** and **101** are formed along with β-ketosulfonamide **102**, likely *via* retro-*ene* decomposition of the enol ether **100**. These products arise from Michael attack at the β-carbon by *tert*-butoxide in a non-stereoselective manner.



Scheme 4.24

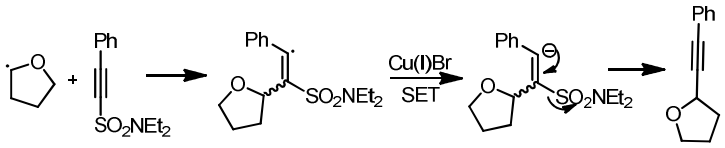
The fact that this substrate fails to give any ynol ether product would indicate that an aromatic alkynyl sulfonamide is necessary for electron transfer to the aromatic ring of the substrate initially followed by isomerisation to the *trans* radical anion. With this detail in mind, it would seem that substrate **76** undergoes relatively slow Michael addition to afford the three β-derived products **100-102**.

Thirdly, carrying out the reaction shown in **Scheme 4.25** gave no desired product. Instead the THF addition product was formed, indicating formation of THF radicals, α to the oxygen atom.[143] This result can be rationalised as the Cu(I) source is a feasible one electron donor for the alkynyl sulfonamide which will allow formation of the *trans* radical ion. This can then combine with the THF radical and collapse to yield the product.



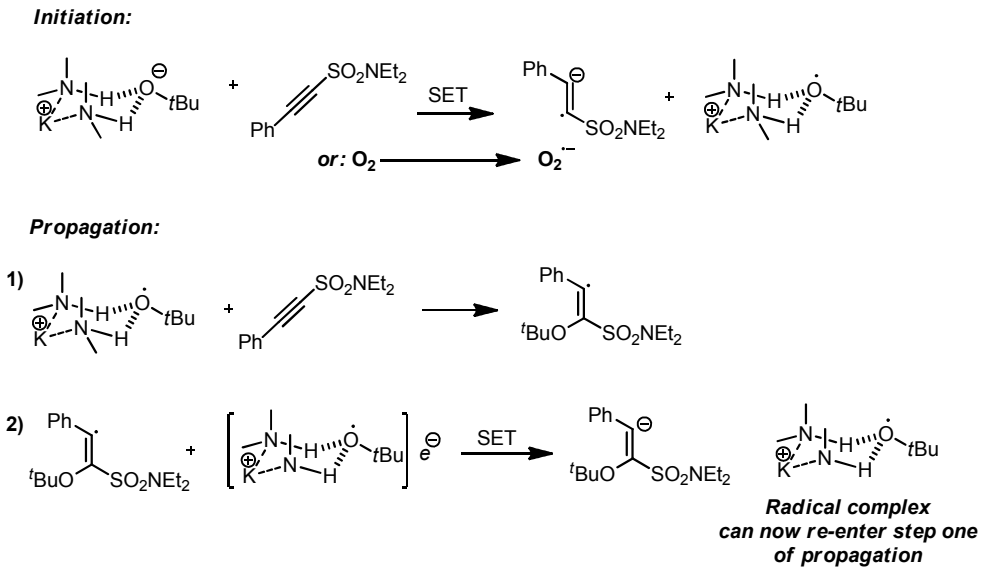
Scheme 4.25

This reaction may also proceed *via* the pathway shown in **Scheme 4.26** below. In this instance, THF radical generation occurs via hydrogen atom abstraction by a *tert*butoxy radical. This THF radical can then attack the sulfonamide, follwed by single electron transfer from the CuBr to yield the anion, which can then undergo elimination to afford the product.



Scheme 4.26

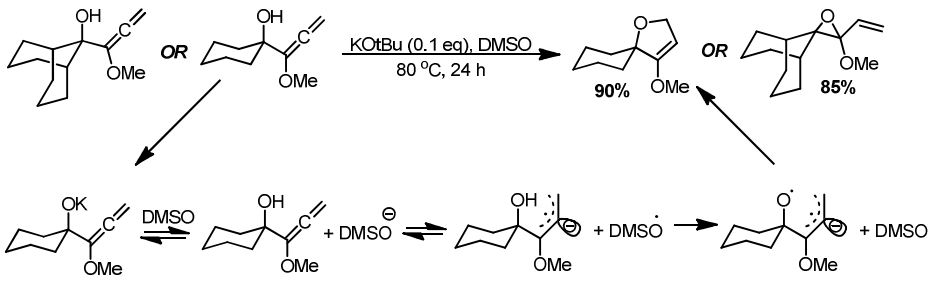
A second potential mechanism for the reaction is given in **Scheme 4.27**, which involves an electron transfer chain reaction.



Scheme 4.27

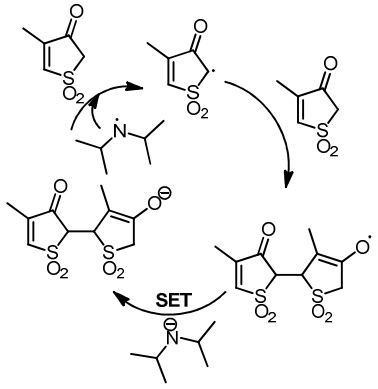
In this case, the initiation of the reaction involves the generation of a *tert*-butoxy radical *via* electron transfer to a molecule of alkynyl sulfonamide or oxygen. The *tert*-butoxy radical can then react with another molecule of alkynyl sulfonamide to generate the enol ether radical shown in propagation step one. Step two of the propagation sequence involves the electron transfer to the enol ether radical from the H-bond stabilised amine/alkoxy comples to generate the vinyl anion and another molecule of the *tert*-butoxy radical complex. This latter substrate can then re-enter step one of the propagation and the chain reaction can continue until all the alkynyl sulfonamide is consumed.

Magnus *et al*. have also studied the effect of KO*t*Bu on cyclisation reactions.[131] Treatment of the tertiary alcohols shown in **Scheme 4.28** with sub-stoichiometric KO*t*Bu in DMSO results in either a dihydrofuran or a vinyl epoxide depending on the steric environment of the starting material. The mechanism has been proven to involve a radical anion intermediate which allows for the 5-*endo-trig* (usually unfavourable) ring closure to afford the dihydrofuran in excellent yield. A 3-*exo-trig* process is in operation for the vinyl epoxide, after allyl rotation of the di-radical anion. These studies lend weight to the alkoxy radical pathways proposed for the ynol ether synthesis.



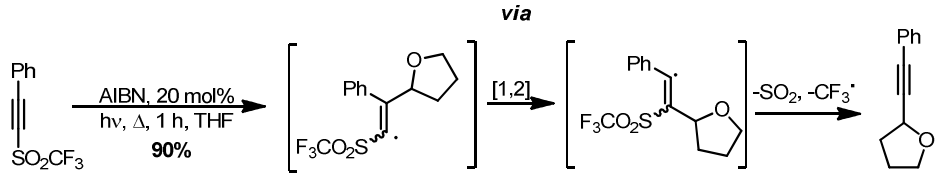
Scheme 4.28

A single electron transfer process involving lithium di-isopropylamide has also been studied by Motherwell *et al*.[132] Whilst investigating the head to tail coupling of a cyclic β-ketosulfone, it was found that the expected product was surprisingly not formed upon reaction with KO*t*Bu and NaH. Instead, employment of the strong base- lithium di-isopropylamide resulted in product formation. Carrying out the reaction in the presence of the electron scavenger- *m*-dinitrobenzene shut the reaction down thus indicating that a radical process is in operation with an aminyl radical acting as the chain carrier (**Scheme 4.29**).



Scheme 4.29

Gong and Fuchs have studied the behaviour of alkynyl triflones towards radical-inducing conditions shown in **Scheme 4.30.**[133]



Scheme 4.30

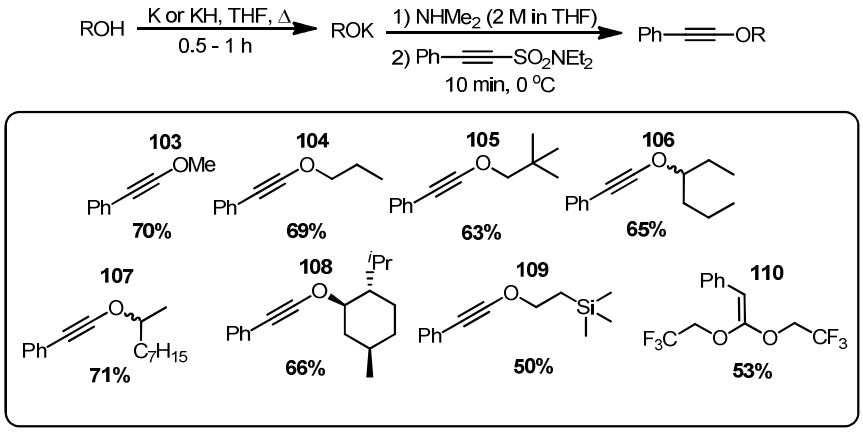
In this reaction, the authors suggest that the radical generated from AIBN decomposition, abstracts a H-atom from THF. The THF radical can then attack the alkynyl triflone at the β position followed by a [1,2] shift to give the α-intermediate. This intermediate then collapses to yield the product alkyne with loss of SO_2 and a CF_3 radical which propagates the reaction *via* H-atom abstraction from THF. The [1,2] shift of the C-C bond is highly unlikely. Initial attack of the THF radical α to the triflate followed by radical elimination to produce the product and a CF_3 radical to propagate the reaction, seems much more likely.

The authors also suggest a Fritsch-Buttenberg-Wiechell rearrangement of the first β-attacked intermediate, eliminating SO_2 and $CF_3^{\cdot}$ to give a carbene intermediate which can then under go 1,2 migration to afford the product. Based on our observations with ^{13}C-labelled phenyl alkynyl sulfonamide **91**, the latter option seems unlikely.

In the case shown in **Scheme 4.25**, thermal cleavage of the di-*tert*-butyl peroxide will produce *t*BuO$^{\cdot}$ radicals which abstract a hydrogen atom from the THF. The radical formed from this process then adds to the radical anion at the α position, followed by collapse of the anionic intermediate to yield the product.

Considering these observations, one can hypothesise why THF radicals are not formed in the presence of an alkoxyl or trioxyl radical; the presence of amines i.e. $NHMe_2$ must provide a stabilising effect *via* H-bonding to the radical. Overall, a single electron transfer from the solution of KO*t*Bu and DMF (or, KO*t*Bu $NHMe_2$, THF) to the alkynyl sulfonamide *via* the aryl group, followed by radical combination of *t*BuO$^{\cdot}$ and the α radical of the *trans* radical anion, leads to an enol anion intermediate which can collapse to yield the ynol ether product.

With a great deal learnt about the mechanism of this reaction, a range of ynol ethers could be consequently synthesised. Based on the optimisation results shown in **Table 4.1**, a range of potassium alkoxides were synthesised *in situ*, followed by addition of $NHMe_2$ (2.0 M in THF) and finally alkynyl sulfonamide **50**. This resulted in a relatively quick synthesis of a range of novel ynol ethers **103-109** (**Scheme 4.27**).



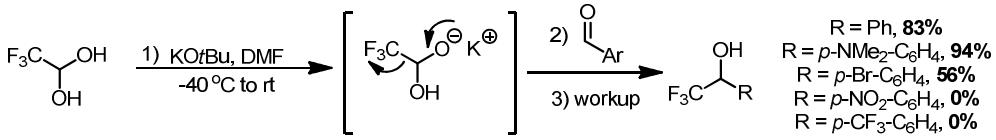
Scheme 4.27

Compounds **109** and **110** are of particular interest as the former may be deprotected to form a ynolate *in situ*, whilst the latter is a novel ketene acetal. This compound was generated from the double addition of potassium trifluroethoxide. Attempts to isolate the ynol ether were met with failure in this case, even upon reducing the equivalents of potassium trifluoroethoxide. Nonetheless, this route provides easy access to an otherwise synthetically-difficult substrate class.

4.7 Significance of the EPR Measurements

The trifluoromethyl group is an important and much-used functional group in both the pharmaceutical and agrochemical industries.[134] Ruppert's reagent[135] (trifluoromethyltrimethylsilane) and other useful trifluoromethylating adducts[136] have been used widely in organic chemistry as a souce of nucleophilic CF_3. There have been numerous reports in the literature describing the *in situ* generation of CF_3^- anions at low temperature in the presence of KO*t*Bu and DMF from both

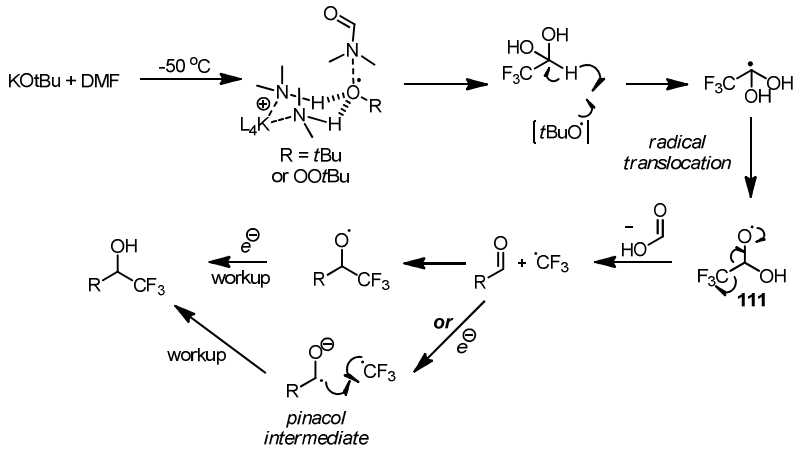
fluoroform[137,138,139] and trifluoroacetaldehyde hydrate. With the introduction of an aldehyde to this mixture, the corresponding trifluoromethylated alcohol can be isolated in good yield (**Scheme 4.28**).[140]



Scheme 4.28

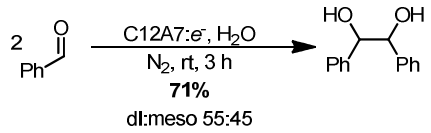
Historically, this reaction has been assumed to be ionic and, to date, there has been no study of $^{\cdot}CF_3$ radicals being potential intermediates in this transformation. Prakash *et al.*[140] state that KO*t*Bu deprotonates the trifluoroacetaldehyde hydrate to form a di-anion, which can then collapse to form a CF_3 anion. Interestingly, the reaction is only successful in DMF in combination with potassium *tert*-butoxide. Electron-withdrawing groups on the aldehyde fail to give any product which seems counter-intuitive. The authors also state that *no reaction* was observed when the KO*t*Bu was added *dropwise* to a mixture of trifluoroacetaldehyde hydrate, aldehyde and DMF, which implies a reaction/assembly forming in the KO*t*Bu/DMF mixture. With the knowledge that KO*t*Bu and DMF mixtures form stable radicals from 78 K to room temperature, an alternative mechanism was considered based on the generation of CF_3 radicals (**Scheme 4.29**).

As an alternative, one can envisage that the *tert*-butoxy radical abstracts the labile CH proton on trifluoroacetaldehyde hydrate to give a species which can undergo radical translocation, forming the oxygen-centred radical **111**. This intermediate can then collapse, releasing CF_3 radicals to the solution which rapidly react with the aldehyde. The solvated electron from the DMF/KO*t*Bu mixture can then reduce this intermediate to give the product anion.



Scheme 4.29

Alternatively, the solvated electron can attack the aldehyde first to give a radical anion, which then combines with a CF_3 radical to give the product. This latter suggestion is known in the literature with work by Buchammagari *et al.*, showing that electride salts can transfer electrons to aldehydes which can then undergo pinacol coupling to form diols in good yields under mild conditions (**Scheme 4.30**).[141]



Scheme 4.30

A radical-based mechanism would account for two important observations made by Prakash *et al*. Firstly, no reaction is observed when KO*t*Bu is added slowly to the mixture, which suggests that it deprotonates the two hydroxyl groups on the trifluoroacetaldehyde hydrate to form a relatively stable di-anionic potassium salt. In other words, the KO*t*Bu doesn't have the chance to form a radical assembly which can abstract the CH hydrogen and ultimately generate CF_3 radicals. Secondly, there is no explanation as to why electron withdrawing moieties on the aldehyde aryl groups, results in no CF_3 addition. The presence of a nitro group on the *para* position would surely enhance the electrophilicity of the aldehyde carbon atom, making it more prone to 'nucleophilic' attack by CF_3^- as the authors suggest. If a

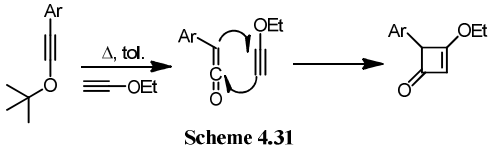
solvated electron and a *tert*-butoxy radical are involved, the deactivation of aryl group by $–NO_2$ may be enough to thwart attack of the electrophilic CF_3 radical.

5. Conclusion & Future Work

With the advent of transition-metal free cross couplings and "C-H activations" that require KO*t*Bu and amines as reagents, a wealth of new reactions have been published.[142] Realising that there was more to the reaction of KO*t*Bu and alkynyl sulfonamide **50** than was initially apparent, a potential explanation for the behaviour of KO*t*Bu in DMF has been uncovered where a loosely bound electron and a *tert*-butoxy radical can be transferred to a substrate in a step-wise fashion *via* a pre-assembled radical complex. The ability of potassium alkoxides to carry out this transformation can be accounted for as potassium can chelate to nitrogen in secondary amines, making them better H-bond donors, as well as the high solubility of these salts in THF allowing for dissociation into K^+ and $tBuO^-$ to form a complex. Both LiO*t*Bu and NaO*t*Bu have stronger metal oxygen bonds and are thus less soluble, making them poor candidates for the synthetic transformation presented in this work.

Future work in this area will involve a greater utilisation of EPR spectroscopy to study reaction mixtures- an increasingly underrated and underused tool in organic chemistry. These mixtures (KOR/DMF and KOR/$NHMe_2$/THF) will undoubtedly be successful in allowing for a range of organic transformations that yet lay undiscovered. The Wilden group[143] has already been successful in replacing alkyoxy substituents with alkyl sulfur reagents to generate a range of alkynyl sulfides *via in situ* generation of the alkyl potassium sulphide salt. The elucidation of the radical complex as either the trioxyl or alkoxyl species can only be confirmed absolutely by the use of $^{17}O_2$ which is currently being pursued, where current evidence points to the former species being present.

The *tert*-butyl ynol ether **53** is also an excellent precursor to ketenes which can be generated smoothly upon mild heating. Trapping these compounds with a range of other substrates will allow access to a range of otherwise synthetically-difficult cyclobutenones (**Scheme 4.31**).



Scheme 4.31

6. Experimental

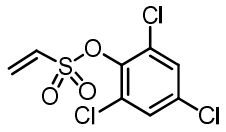
6.0 General Methods

All glassware was dried in an oven at 120 °C prior to use. All reactions were carried out at atmospheric pressure, under argon, unless otherwise stated. Solvents and reagents were purchased from suppliers and used without any further purification. Normal phase silica gel (BDH) and sand (VWR) were used for flash chromatography. All reactions monitored by TLC unless otherwise stated. TLC plates pre-coated with silica gel 60 F_{254} on aluminium (Merck KGaA) were used, detection by UV (254 nm) and chemical stain (potassium permanganate). Mass spectra were measured on a Thermo Finnigan MAT900 XP operating in EI and CI mode. Electron spray ionisation spectra were measured on a Waters LCT premier XE LC-TOF mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300, 400, 500 and 600 MHz and 75, 100, 125 and 150 MHz respectively on Bruker AMX spectrometers at ambient temperature. All chemical shifts were referenced to the residual proton impurity of the deuterated solvent. The multiplicity of the signal is indicated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (double of doublets), dt (double of triplets), m (multiplet), defined as all multipeak signals where overlap or complex coupling of signals makes definitive descriptions of peaks difficult . Coupling constants are defined as *J* and quoted in Hz to one decimal place. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FTIR Spectrometer operating in ATR mode. Melting points were measured with a Gallenkamp apparatus and are uncorrected. Room temperature is defined as between 19–22 °C. *In vacuo* is used to describe solvent removal by Büchi rotary evaporation between 17 ºC and 60 °C, at approx 10 mmHg unless otherwise stated. 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 substrate. Sublimed grade potassium *tert*-butoxide (99.99%) purchased from Aldrich, was used without further purification. Anhydrous NH_3 (0.5 M in THF, AcroSeal®) and $NHMe_2$ (2.0 M in THF, AcroSeal®) were purchased from Acros Organics and manipulated under a positive pressure of argon. Anhydrous *N*,*N*-dimethylformamide (99.8% extra dry, AcroSeal®) was purchased from Acros Organics and used without further

purification under standard Schlenk techniques. KHMDS (0.5 M solution in toluene) was purchased from Aldrich. Room temperature EPR measurements were carried out on a Bruker EMX plus spectrometer operating at 9.8 GHz (X-band) equipped with a 4122SHQE resonator. Measurements were performed with a magnetic field sweep of 0.02 T centred at g = 2, a microwave power of 0.6 mW, a modulation amplitude of 0.019 mT and a modulation frequency of 100 kHz. The samples were measured in either a flat cell (maximum volume 200 μL) or in a glass capillary (volume 50 μL) with 2 M solutions of alkoxide and amine ($NHMe_2$ 2.0 M in THF). The magnetic field offset was estimated by calibration with Bruker strong pitch standard (g = 2.0028).

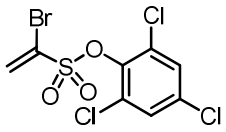
6.1 Experimental Procedures

2,4,6-Trichlorophenyl ethenesulfonate 18



2,4,6-Trichlorophenol (28.9 g, 148.2 mmol) and NEt_3 (41.3 mL, 296.4 mmol) in CH_2Cl_2 (100 mL) were added dropwise over 30 mins to a stirred solution of 2-chloroethanesulfonyl chloride (20.0 g, 123.5 mmol) in CH_2Cl_2 (200 mL) at −78 °C. The mixture was allowed to warm to rt, diluted with CH_2Cl_2 (100 mL), then washed with 2 M HCl (2 × 50 mL) and brine (2 × 50 mL). The organic layer was separated, dried over $MgSO_4$, filtered and the filtrate concentrated *in vacuo*. The crude oil was then purified *via* flash chromatography (10:2 PE/Et_2O) and allowed to crystallise overnight to give the product as a white solid (27.5 g, 96.2 mmol, 78%); m.p. 53–54 °C (CH_2Cl_2/PE); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.39 (s, 2 H, 2 × *m*-Ar*H*), 6.93 (dd, *J* = 16.6, 9.9 Hz, 1 H, CH_2CH), 6.55 (dd, *J* = 16.6, 0.9 Hz, 1 H, CH*H*CH), 6.26 (dd, *J* = 9.9, 0.9 Hz, 1 H, CH*H*CH); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 142.1 (s), 134.0 (d), 133.2 (s), 131.5 (t), 130.8 (s), 129.3 (d). Data in agreement with that reported.[c]

2,4,6-Trichlorophenyl 1-bromoethenesulfonate 19

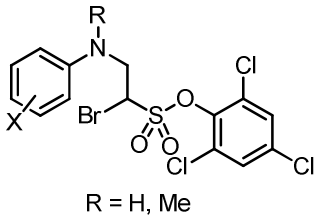


2,4,6-Trichlorophenyl ethenesulfonate **18** (20.0 g, 69.5 mmol) was dissolved in 1,2-DCE (200 mL) and Br_2 added *via* syringe (55.5 g, 17.8 mL, 347.5 mmol) followed by AIBN (0.2 g, 1.2 mmol) and the reaction heated to reflux for 3 h. The reaction mixture was then concentrated *in vacuo*, dissolved in CH_2Cl_2 (250 mL) and cooled to −78 °C. NEt_3 (10.7 mL, 6.5 mmol) was then added dropwise over 5 min and the yellow reaction mixture was allowed to warm to rt over 1 h. The reaction mixture was then concentrated *in vacuo*, dissolved in

[c] R.J. Fitzmaurice, J.M. Ahern, S. Caddick, *Org. Biomol. Chem*., **2009**, 7, 235.

Et_2O (250 mL) and washed with 2 M HCl (2 × 100 mL) and brine (2 × 50 mL). The organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude brown oil which was purified *via* flash chromatography (10:2 PE/EtOAc) to give the title compound as a colourless, viscous oil (12.6 g, 50%); ν_{max} (film)/cm^{-1} 1562, 1389, 1457, 1187, 1092; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40 (s, 2 H, 2 × *m*-Ar*H*), 7.01 (d, *J* = 3.7 Hz, 1 H, CH*H*), 6.42 (d, *J* = 3.7 Hz, 1 H, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 142.2 (s), 133.6 (s), 131.8 (s), 130.8 (s), 129.5 (d), 124.5 (t); LRMS (EI) 370 (3), 366 (4) 242 (11), 218 (15), 198 (35), 145 (36), 84 (100); HRMS (EI) calc'd for $C_8H_{14}O_3SBrCl_3$ (M^+) 363.8125, found 363.8129.

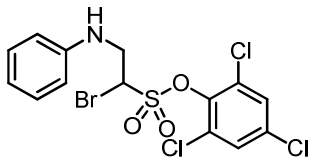
General procedure for the 1,4-addition of anilines to 2,4,6-Trichlorophenyl 1-bromoethenesulfonate



R = H, Me

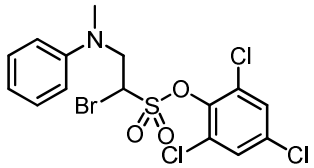
To a stirring solution of 2,4,6-trichlorophenyl-1-bromoethenesulfonate **19** (0.30-1.20 mmol, 1.0 eq.) was added the aniline (1.5-2.0 eq.) and the reaction mixture heated to 100 °C for 10 min. The reaction mixture was then dissolved in Et_2O (30 mL) and washed with 1 M HCl (2 × 20 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude addition products, which were then purified *via* flash chromatography (PE/EtOAc) to give the title compounds.

2,4,6-Trichlorophenyl 1-bromo-2-(phenylamino)ethanesulfonate 20



Colourless oil, 87%; ν_{max} (film)/cm^{-1} 3210, 1680, 1602 1563, 1391, 807; ^{1}H NMR (600 MHz, $CDCl_3$)[d] δ_H 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 7.23 (t, *J* = 7.7 Hz, 2 H, 2 × *m*-Ar*H*), 6.83 (t, *J* = 7.7 Hz, 1 H, *p*-Ar*H*), 6.72 (d, *J* = 7.7 Hz, 2 H, 2 × *o*-Ar*H*), 5.52 (dd, *J* = 7.6, 4.9 Hz, 1 H, C*H*Br), 4.40 (dd, *J* = 15.6, 4.9, 1 H, CHBrCH_2), 3.94 (dd, *J* = 15.6, 7.6, 1 H, CHBrCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 144.9 (s), 141.9 (s), 133.6 (s), 130.5 (s), 129.7 (d), 129.3 (d), 119.7 (d), 113.9 (d), 60.3 (d), 47.1 (t); LRMS (EI) 461 (7) 459 (8), 457 (6), 196 (10), 145 (40), 130 (100); HRMS (EI) calc'd for $C_{14}H_{11}NO_3SBrCl_3$ (M^+) 456.8703, found 456.8708.

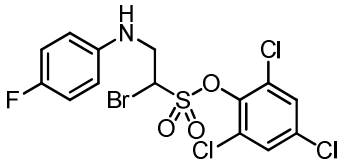
2,4,6-Trichlorophenyl 1-bromo-2 (methyl(phenyl)amino) ethanesulfonate 21



Colourless oil, 89%; ν_{max} (film)/cm^{-1} 3077, 2190, 1600, 1506, 1391, 1182; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 7.29 (t, *J* = 7.7 Hz, 2 H, 2 × *m*-Ar*H*), 6.82 (t, *J* = 7.7 Hz, 1 H, *p*-Ar*H*), 6.75 (d, *J* = 7.7 Hz, 2 H, 2 × *o*-Ar*H*), 5.61 (dd, *J* = 7.9, 4.8, 1 H, C*H*Br), 4.63 (dd, *J* = 15.8, 4.8 Hz, 1 H, CHBrCH_2), 4.10 (dd, *J* = 15.8, 7.9 Hz, 1 H, CHBrCH_2), 3.17 (s, 3 H, NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 147.0 (s), 142.0 (s), 133.6 (s), 130.6 (s), 129.7 (d), 129.3 (d), 118.0 (d), 112.2 (d), 65.9 (d), 56.3 (q), 40.5 (t); LRMS (ESI) 475 (65), 473 (100), 471 (50), 437 (20), 409 (20); HRMS (ESI) calc'd for $C_{15}H_{14}NO_3SBrCl_3$ $(M+H)^+$ 471.8943, found 471.8925.

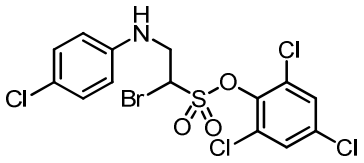
[d] N*H* not observed.

2,4,6-Trichlorophenyl 1-bromo-2-((4-fluorophenyl)amino)ethanesulfonate 22



Colourless oil, 92%; ν_{max} (film)/cm^{-1} 3430, 2151, 1506, 1390, 1226, 1179, 859; ^{1}H NMR (600 MHz, $CDCl_3$)[e] δ_H 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 6.95 (m, 2 H, 2 × *m*-Ar*H*), 6.66 (m, 2 H, 2 × *o*-Ar*H*), 5.49 (dd, *J* = 7.5, 5.2 Hz, 1 H, C*H*Br), 4.33 (dd, *J* = 15.4, 5.2 Hz, 1 H, CHBrCH_2), 3.92 (dd, *J* = 15.4, 7.5 Hz, 1 H, CHBrCH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 157.9 & 156.0 (d, $J_{C\text{-}F}$ = 238.0 Hz) (s), 141.9 (s), 141.4 (s), 133.8 (s), 130.5 (s), 129.6 (d), 116.4 & 116.2 (d, *J* = 23.0 Hz) (d), 115.1 & 115.0 (d, *J* = 7.8 Hz) (d), 60.3 (d), 47.8 (t); LRMS (EI) 479 (6), 477 (8), 474 ($M^{+\cdot}$), (4), 442 (26), 209 (36), 137 (86), 84 (100); HRMS (EI) calc'd for $C_{14}H_{10}NO_3SFBrCl_3$ 474.8609, found 474.8610.

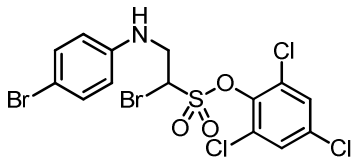
2,4,6-Trichlorophenyl 1-bromo-2-((4-chlorophenyl)amino)ethanesulfonate 23



Colourless oil, 71%; ν_{max} (film)/cm^{-1} 3433, 1738, 1500, 1387, 1179, 907, 859; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 7.16 (d, *J* = 8.8 Hz, 2 H, 2 × *m*-Ar*H*), 6.63 (d, *J* = 8.8 Hz, 2 H, 2 × *o*-Ar*H*), 5.47 (dd, *J* = 7.2, 5.2 Hz, 1 H, C*H*Br), 4.34 (br s, 1 H, N*H*), 4.32 (dd, *J* = 15.6, 5.2 Hz, 1 H, CHBrCH_2), 3.92 (dd, *J* = 15.6, 7.2, 1 H, CHBrCH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 144.0 (s), 142.0 (s), 133.8 (s), 130.8 (s), 129.9 (s), 129.5 (d), 124.2 (d), 114.8 (d), 60.1 (d), 47.1 (t); LRMS (ESI) 495 (80), 493 (100), 491 (50), 429 (20), 338 (30), 242 (33); HRMS (ESI) calc'd for $C_{14}H_{11}NO_3SBrCl_4$ $(M+H)^+$ 491.8397, found 491.8405.

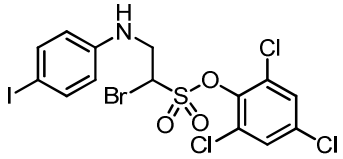
[e] N*H* not observed.

2,4,6-Trichlorophenyl 1-bromo-2-((4-bromophenyl)amino)ethanesulfonate 24



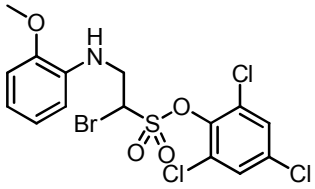
White solid, 74%; m.p. 110–111 °C (PE/Et_2O); ν_{max} (film)/cm^{-1} 3427, 1738, 1594, 1440, 1387, 879, 803; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 7.31 (d, *J* = 8.8 Hz, 2 H, 2 × *m*-Ar*H*), 6.58 (d, *J* = 8.8 Hz, 2 H, 2 × *o*-Ar*H*), 5.47 (dd, *J* = 7.4, 5.1 Hz, 1 H, C*H*Br), 4.34 (br s, 1 H, N*H*), 4.33 (dd, *J* = 15.5, 5.1 Hz, 1 H, CHBrCH_2), 3.92 (dd, *J* = 15.5, 7.4 Hz, 1 H, CHBrCH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 144.3 (s), 141.9 (s), 133.8 (s), 132.6 (d), 130.6 (s), 129.5 (d), 115.2 (d), 111.3 (s), 60.1 (d), 47.0 (t); LRMS (ESI) 539 (100), 537 (96), 535 (16), 475 (15), 338 (20), 242 (30); HRMS (ESI) calc'd for $C_{14}H_{11}NO_3SBr_2Cl_3$ $(M+H)^+$ 535.7892, found 535.7914.

2,4,6-Trichlorophenyl 1-bromo-2-((4-iodophenyl)amino)ethanesulfonate 25



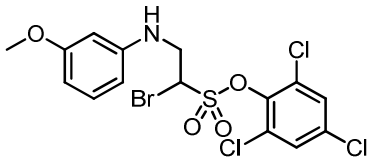
White solid, 78%; m.p. 112–113 °C (PE); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.48 (d, *J* = 9.1 Hz, 2 H, 2 × *m*-Ar*H*), 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 6.48 (d, *J* = 9.1 Hz, 2 H, 2 × *o*-Ar*H*), 5.47 (dd, *J* = 7.3, 5.2 Hz, 1 H, C*H*Br), 4.33 (br s, 1 H, N*H*), 4.32 (dd, *J* = 15.5, 5.2 Hz, 1 H, CHBrCH_2), 3.92 (dd, *J* = 15.5, 7.3 Hz, 1 H, CHBrCH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 144.9 (s), 141.8 (s), 133.4 (d), 133.8 (s), 130.5 (s), 129.5 (d), 115.7 (d), 80.5 (s), 59.9 (d), 46.8 (t); LRMS (EI) 582 (15) 326 (6), 245 (30), 232 (11), 149 (13); Elemental anal. Calculated: C- 28.72%, H- 1.72%, N- 2.39%, found- C- 28.62%, H- 1.64%, N- 2.35%.

2,4,6-Trichlorophenyl 1-bromo-2-((2-methoxyphenyl)amino)ethanesulfonate 26



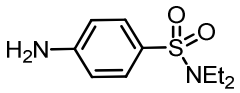
Colourless oil, 78%; ν_{max} (film)/cm^{-1} 3434, 2941, 1602, 1390, 1223, 1029, 804; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 6.90 (td, *J* = 7.7, 1.3 Hz, 1 H, NH(C)CHC*H*), 6.83 (dd, *J* = 7.7, 1.3 Hz, 1H, NH(C)C*H*CH), 6.79 (td, *J* = 7.7, 1.3 Hz, 1 H, CH_3OCCHC*H*), 6.70 (dd, *J* = 7.7, 1.3 Hz, 1 H, CH_3OCC*H*CH), 5.54 (dd, *J* = 7.9, 4.6 Hz, 1 H, C*H*Br), 4.96 (br s, 1 H, N*H*), 4.45 (dd, *J* = 15.3, 4.6 Hz, 1 H, CHBrCH_2), 3.92 (dd, *J* = 15.3, 7.9 Hz, 1 H, CHBrCH_2), 3.86 (s, 3 H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 147.6 (s), 142.0 (s), 135.2 (s), 133.7 (s), 130.7 (s), 129.4 (d), 121.4 (d), 118.8 (d), 110.4 (d), 110.3 (d), 60.6 (d), 55.8 (q), 46.6 (t); LRMS (ESI) 489 (100), 487 (50), 425 (20), 149 (15); HRMS (ESI) calc'd for $C_{15}H_{14}NO_4SBrCl_3$ $(M+H)^+$ 487.8892, found 487.8905.

2,4,6-Trichlorophenyl 1-bromo-2-((3-methoxyphenyl)amino)ethanesulfonate 27



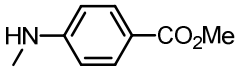
Colourless oil, 65%; ν_{max} (film)/cm^{-1} 3416, 3076, 1600, 1387, 1162, 802; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 7.13 (t, *J* = 8.2 Hz, 1 H, CH_3O(C)CHC*H*), 6.38 (dd, *J* = 8.2, 2.3 Hz, 1 H, CH_3O(C)CHCHC*H*), 6.30 (dd, *J* = 8.2, 2.3 Hz, 1 H, CH_3O(C)C*H*), 6.25 (t, *J* = 2.3 Hz, 1 H, CH_3O(C)C*H*(C)), 5.53 (dd, *J* = 7.4, 4.9 Hz, 1 H, C*H*Br), 4.37 (dd, *J* = 15.4, 4.9 Hz, 1 H, CHBrCH_2), 4.32 (br s, 1 H, N*H*), 3.92 (dd, *J* = 15.4, 7.4 Hz, 1 H, CHBrCH_2), 3.77 (s, 3 H, CH_3O); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 161.2 (s), 146.7 (s), 141.9 (s), 133.7 (s), 130.7 (d), 130.6 (s), 129.5 (d), 106.6 (d), 104.6 (d), 100.0 (d), 60.6 (d), 55.3 (q), 47.1 (t); LRMS (ESI) 491 (60), 489 (100), 487 (50), 425 (20), 208 (20), 149 (15); HRMS (ESI) calc'd for $C_{15}H_{14}NO_4SBrCl_3$ $(M+H)^+$ 487.8892, found 487.8874.

4-Amino-*N*, *N*-diethylbenzenesulfonamide 38



A vigorously stirring solution of *N*,*N*-diethyl-4-nitrobenzenesulfonamide (4.00 g, 18.1 mmol) and 5% Pd/C (0.50 g) in MeOH (40 mL) was placed under an atmosphere of H_2 for 3 h. The H_2 was then removed and placed under an atmosphere of argon and finally air. The reaction mixture was filtered through a pad of Celite® and washed with EtOAc (200 mL) and the organic contents concentrated *in vacuo* to afford the product as a pale orange solid (2.72 g, 66%); m.p. 102–103 °C (EtOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.56 (d, J = 8.7 Hz, 2 H, 2 × NH_2(C)CHC*H*), 6.65 (d, J = 8.7 Hz, 2 H, 2 × NH_2(C)C*H*), 4.11 (br s, 2 H, NH_2), 3.18 (q, J = 7.2 Hz, 4 H, 2 × NCH_2), 1.15 (t, J = 7.2 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 150.3 (s), 129.2 (d), 128.6 (s), 114.2 (d), 42.1 (t), 14.2 (q). Data in agreement with that reported.[f]

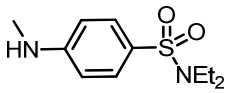
Methyl-4-(methylamino)benzoate



To a stirring solution of methyl-4-aminobenzoate (1.00 g, 6.62 mmol) in MeCN (20 mL) was added K_2CO_3 (920 mg, 6.62 mmol) followed by MeI (0.49 mL, 7.94 mmol) and the mixture refluxed at 80 °C for 16 h. The reaction mixture was then filtered, concentrated *in vacuo*, and purified *via* flash chromatography (9:1 PE/EtOAc) to give the product as a white solid (808 mg, 74%); m.p. 96–97 °C (EtOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.87 (d, J = 8.7 Hz, 2 H, 2 × MeNH(C)CHC*H*), 6.55 (d, J = 8.7 Hz, 2 H, 2 × MeNH(C)C*H*), 4.25 (br s, 1 H, N*H*), 3.85 (s, 3 H, CO_2CH_3), 2.88 (s, 3 H, NHCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 167.5 (s), 152.9 (s), 131.6 (d), 118.3 (s), 111.2 (d), 51.6 (q), 30.3 (q). Data in agreement with that reported.[g,h]

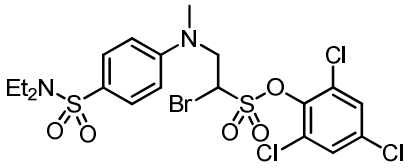
[f] K.A. Kornev, A.Y. Zheltov, *Russ. J. Gen. Chem*., **1999**, 69, 962.
[g] D. Sole, O. Serrano, *J. Org. Chem*., **2008**, 73, 2476.
[h] B. Klaus, *Chem. Ber*., **1918,** 51, 1013.

***N*, *N*-Diethyl-4-methylaminobenzenesulfonamide 39**



To a stirring solution of 4-amino-*N*, *N*-diethylbenzenesulfonamide **38** (440 mg, 1.93 mmol) in MeCN (5 mL) was added K_2CO_3 (0.32 g, 2.30 mmol) followed by MeI (0.14 mL, 2.31 mmol) at 80 °C for 16 h. The reaction mixture was concentrated *in vacuo* and purified *via* flash chromatography (7:3 PE/EtOAc) to give the product as a brown oil (187 mg, 40%); ν_{max} (film)/cm^{-1} 3398, 2936, 1598, 1142, 924, 825; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.56 (d, *J* = 8.8 Hz, 2 H, 2 × MeNH(C)CHC*H*), 6.65 (d, *J* = 8.8 Hz, 2 H, 2 × MeNH(C)C*H*), 4.34 (br s, 1 H, N*H*), 3.16 (q, *J* = 7.1 Hz, 4 H, 2 × NCH_2), 2.84 (s, 3 H, NHCH_3), 1.09 (t, *J* = 7.1 Hz, 6 H, 2 × NCH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 152.4 (s), 129.1 (d), 126.7 (s), 111.4 (d), 42.1 (t), 30.2 (q), 14.2 (q); LRMS (ESI) 243 (100), 215 (40), 213 (10), 122 (12), 118 (5); HRMS (ESI) calc'd for $C_{11}H_{19}N_2O_2S$ $(M+H)^+$ 243.1167, found 243.1162.

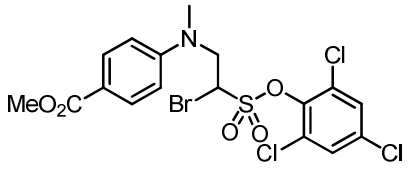
2,4,6-Trichlorophenyl 1-bromo-2-((4-(*N*,*N*-diethylsulfamoyl)phenyl)(methyl)amino)ethanesulfonate 28



2,4,6-trichlorophenyl-1-bromoethenesulfonate (260 mg, 0.71 mmol) and *N*,*N*-diethyl-4-methylaminobenzenesulfonamide (189 mg, 0.78 mmol) were heated to 190 °C for 1 h and purified directly *via* flash chromatography (PE/EtOAc) to give the product as a yellow oil (61 mg, 14%); ν_{max} (film)/cm^{-1} 2984, 1738, 1585, 1365, 1217, 804; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.70 (d, *J* = 8.9 Hz, 2 H, 2 × N(C)CHC*H*), 7.41 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 6.74 (d, *J* = 8.9 Hz, 2 H, 2 × N(C)C*H*CH), 5.56 (dd, *J* = 7.6, 5.4 Hz, 1 H, C*H*Br), 4.64 (dd, *J* = 16.2, 5.4, 1 H, CHBrCH_2), 4.18 (dd, *J* = 16.2, 7.6 Hz, 1 H, CHBrCH_2), 3.23 (s, 3 H, NCH_3), 3.20 (q, *J* = 7.1 Hz, 4 H, 2 × NCH_2CH$_3$), 1.12 (t, *J* = 7.1 Hz, 6 H, 2 × NCH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 149.8 (s), 141.9 (s), 133.9 (s), 130.5 (s), 129.5 (d), 129.3 (d), 128.6 (s), 111.5 (d), 58.2 (d), 56.0 (t), 42.0 (t), 40.7 (q), 14.3 (q); LRMS (ESI)

608 (65), 606 (30), 555 (70), 553 (100), 487 (20), 255 (20); HRMS (ESI) calc'd for $C_{19}H_{23}N_2O_5S_2BrCl_3$ $(M+H)^+$ 606.9297, found 606.9274.

Methyl-4-((2-bromo-2-((2,4,6-trichlorophenoxy)sulfonyl)ethyl)(methyl)amino)benzoate 29

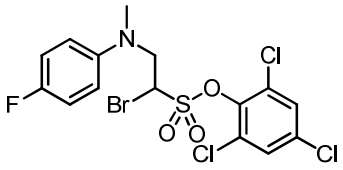


2,4,6-Trichlorophenyl-1-bromoethenesulfonate (290 mg, 0.80 mmol) and methyl-4-(methylamino)benzoate (263 mg, 1.59 mmol) were heated to 130 °C for 2 h and purified directly *via* flash chromatography (PE/EtOAc) to give the product as an off-white gum (295 mg, 70%); ν_{max} (film)/cm^{-1} 2950, 1705, 1607, 1437, 1280, 1182, 804; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.96 (d, J = 8.7 Hz, 2 H, 2 × N(C)CHC*H*), 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 6.71 (d, J = 8.7 Hz, 2 H, 2 × N(C)C*H*), 5.59 (dd, J = 7.7, 5.3 Hz, 1 H, C*H*Br), 4.65 (dd, J = 16.0, 5.3 Hz, 1 H, CHBrCH_2), 4.17 (dd, J = 16.0, 7.7 Hz, 1 H, CHBrCH_2), 3.87 (s, 3 H, CH_3CO$_2$), 3.24 (s, 3 H, NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 167.2 (s), 150.5 (s), 141.9 (s), 133.8 (s), 131.8 (d), 130.5 (s), 129.5 (d), 119.3 (s), 111.2 (d), 58.4 (d), 55.9 (t), 51.8 (q), 40.8 (q); LRMS (ESI) 531 (100) 529 (50), 467 (16), 339 (10), 273 (25); HRMS (ESI) calc'd for $C_{17}H_{16}NO_5SBrCl_3$ $(M+H)^+$ 529.8998, found 529.8986.

***N*-Methylation of intermediates 30-35**

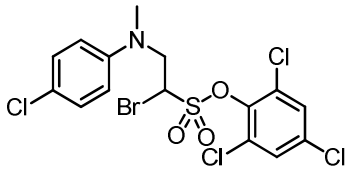
To a stirring solution of intermediate **30-35** (0.53 mmol, 1.0 eq.) in MeCN (10 mL) at 0 °C was added formalin (37% sol'n in H_2O, 3.18 mmol, 6.0 eq.), and $NaCNBH_3$ (3.18 mmol, 6.0 eq.) and the reaction mixture was stirred for 5 min. AcOH (0.11 mL, 10.6 mmol) was then added carefully and the reaction mixture stirred for 6 h at rt. The reaction mixture was then concentrated *in vacuo*, dissolved in Et_2O (50 mL), and washed with 1 M $NaHCO_3$ (2 × 20 mL). The organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product which was then purified *via* flash chromatography (9:1 PE/Et_2O) to give the products.

2,4,6-Trichlorophenyl 1-bromo-2-((4-fluorophenyl)(methyl)amino)ethanesulfonate 30



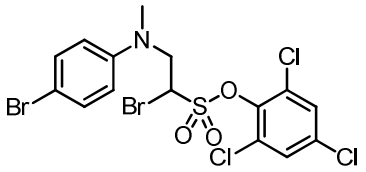
Colourless oil, 73%; ν_{max} (film)/cm^{-1} 2671, 1617, 1520, 1393, 998, 806; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 6.99 (m, 2 H, 2 × F(C)C*H*), 6.70 (m, 2 H, 2 × F(C)CHC*H*), 5.55 (dd, *J* = 7.9, 5.0 Hz, 1 H, C*H*Br), 4.56 (dd, *J* = 15.9, 5.0 Hz, 1 H, CHBrCH_2), 4.07 (dd, *J* = 15.9, 7.9 Hz, 1 H, CHBrCH_2), 3.13 (s, 3 H, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 157.2 & 155.3 (d, $J_{C\text{-}F}$ = 237.0 Hz) (s), 143.7 (s), 141.9 (s), 133.7 (s), 130.6 (s), 129.4 (d), 116.2 & 116.0 (d, *J* = 23.0 Hz) (d), 113.7 & 113.6 (d, *J* = 7.7 Hz) (d), 59.0 (d), 56.8 (t), 40.8 (q); LRMS (EI) 493 (3), 491 (6), 488 (2), 442 (3), 196 (45), 138 (22); HRMS (CI) calc'd for $C_{15}H_{12}NO_3SFBrCl_3$ 488.8765 ($M^{+\cdot}$), found 488.8758.

2,4,6-Trichlorophenyl 1-bromo-2-((4-chlorophenyl)(methyl)amino)ethanesulfonate 31



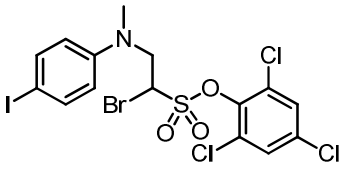
White solid, 81%; m.p. 137–138 °C (PE/CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40 (s, 2 H, 2 × *m*-Ar*H*), 7.22 (d, *J* = 9.0 Hz, 2 H, 2 × Cl(C)C*H*), 6.66 (d, *J* = 9.0 Hz, 2 H, 2 × Cl(C)C*H*CH), 5.55 (dd, *J* = 7.9, 5.1 Hz, 1 H, C*H*Br), 4.33 (dd, *J* = 16.1, 5.1 Hz, 1 H, CHBrCH_2), 4.09 (dd, *J* = 16.1, 7.9, 1 H, CHBrCH_2), 3.15 (s, 3 H, NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 145.7 (s), 141.9 (s), 133.8 (s), 130.6 (s), 129.5 (d), 129.5 (d), 123.1 (s), 113.4 (d), 58.7 (d), 56.3 (t), 40.6 (q); HRMS (ESI) calc'd for $C_{15}H_{13}NO_3SBrCl_4$ $(M+H)^+$ 505.8554, found 505.8531; Elemental anal. calculated for: C- 35.46%, H- 2.38%, N- 2.76%, found C- 35.20%, H- 2.48%, N- 2.52%.

2,4,6-Trichlorophenyl 1-bromo-2-((4-bromophenyl)(methyl)amino)ethanesulfonate 32



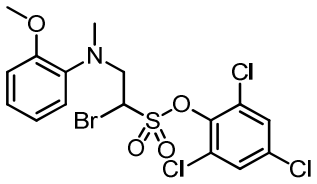
White solid, 56%; m.p. 135–136 °C (PE); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40 (s, 2 H, 2 × *m*-Ar*H*(TCP)), 7.34 (d, *J* = 9.0 Hz, 2 H, 2 × Br(C)C*H*), 6.61 (d, *J* = 9.0 Hz, 2 H, 2 × Br(C)CHC*H*), 5.55 (dd, *J* = 7.9, 5.1 Hz, 1 H, C*H*Br), 4.58 (dd, *J* = 16.1, 5.1 Hz, 1 H, CHBrCH_2), 4.09 (dd, *J* = 16.1, 7.9 Hz, 1 H, CHBrCH_2), 3.14 (s, 3 H, NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 146.1 (s), 141.9 (s), 133.7 (s), 132.4 (d), 130.6 (s), 129.4 (d), 113.9 (d), 110.3 (s), 58.7 (d), 56.2 (t), 40.5 (q); LRMS (CI) 554 (56) 553 (65), 552 (100), 550 (80), 548 (20); HRMS (CI) calc'd for $C_{15}H_{13}NO_3SBr_2Cl_3$ 549.8049 $(M+H)^+$, found 549.8053; Elemental anal. Calculated for: C- 32.61%, H- 2.19%, N- 2.54%. Found: C- 32.18%, H- 2.07%, N-2.43%

2,4,6-Trichlorophenyl-bromo-2-((4-iodophenyl)(methyl)amino)ethanesulfonate 33



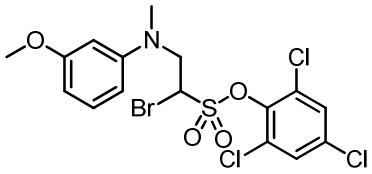
Colourless oil, 46%; ν_{max} (film)/cm^{-1} 1974, 1588, 1497, 1391, 1182, 806; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.52 (d, *J* = 8.8 Hz, 2 H, 2 × I(C)C*H*), 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 6.51 (d, *J* = 8.8 Hz, 2 H, 2 × I(C)CHC*H*), 5.55 (dd, *J* = 7.9, 5.0 Hz, 1 H, C*H*Br), 4.57 (dd, *J* = 15.9, 5.0 Hz, 1 H, CHBrCH_2), 4.08 (dd, *J* = 15.9, 7.9 Hz, 1 H, CHBrCH_2), 3.14 (s, 3 H, NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 146.7 (s), 141.9 (s), 138.3 (d), 133.8 (s), 130.6 (s), 129.5 (d), 114.4 (d), 79.5 (s), 58.6 (d), 56.1 (t), 40.5 (q); LRMS (EI) 596 (10) 445 (6), 345 (11), 246 (100), 181 (92); HRMS (EI) calc'd for $C_{15}H_{11}O_3NSBrCl_3I$ $(M-H)^+$ 595.7748, found 595.7756.

2,4,6-Trichlorophenyl-1-bromo-2-((2-methoxyphenyl)(methyl)amino)ethanesulfonate 34



Colourless oil, 75%; ν_{max} (film)/cm^{-1} 3076, 1611, 1439, 1388, 1166, 803; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 7.04 (td, *J* = 8.2, 1.5 Hz, 1 H, $CH_3O(C)CHCH$), 7.01 (dd, *J* = 8.2, 1.5 Hz, 1 H, N(C)C*H*), 6.92 (t, *J* = 8.1, 1.1 Hz, 1 H, $CH_3O(C)CHCHCH$), 6.87 (dd, *J* = 8.1, 1.1 Hz, 1 H, $CH_3O(C)CH$), 5.53 (dd, *J* = 8.8, 3.6 Hz, 1 H, C*H*Br), 4.49 (dd, *J* = 15.2, 3.6 Hz, 1 H, $CHBrCH_2$), 3.86 (dd, *J* = 15.2, 8.8 Hz, 1 H, $CHBrCH_2$), 3.83 (s, 3 H, OCH_3), 3.07 (s, 3 H, NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 152.5 (s), 142.2 (s), 138.7 (s), 133.5 (s), 130.6 (s), 129.4 (d), 123.7 (d), 121.3 (d), 121.0 (d), 110.3 (d), 61.1 (d), 57.5 (t), 55.5 (q), 42.0 (q); LRMS (EI) 503 (100) 501 (40), 441 (20), 242 (10), 162 (9); HRMS (EI) calc'd for $C_{16}H_{16}NO_4SBrCl_3$ 501.9049 $(M+H)^+$, found 501.9037.

2,4,6-Trichlorophenyl-1-bromo-2-((3-methoxyphenyl)(methyl)amino)ethanesulfonate 35

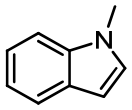


Colourless oil, 71%; ν_{max} (film)/cm^{-1} 3077, 2939, 1611, 1388, 1166, 802; δ_H (600 MHz, $CDCl_3$) 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 7.19 (t, *J* = 8.2, 1 H, $CH_3O(C)CHCH$), 6.38 (app. dd, *J* = 8.2, 2.2 Hz, 1 H, $CH_3O(C)CHCHCH$), 6.35 (app. dd, *J* = 8.2, 2.3 Hz, 1 H, $CH_3O(C)CHCHCH$), 6.28 (t, *J* = 2.3 Hz, 1 H, CH3O(C)C*H*(C)), 5.62 (dd, *J* = 7.8, 5.1 Hz, 1 H, C*H*Br), 4.62 (dd, *J* = 15.6, 5.1 Hz, 1 H, $CHBrCH_2$), 4.08 (dd, *J* = 15.6, 7.8 Hz, 1 H, $CHBrCH_2$), 3.78 (s, 3 H, CH_3O), 3.15 (s, 3 H, NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 161.2 (s), 148.5 (s), 142.0 (s), 133.7 (s), 130.7 (s), 130.5 (d), 129.4 (d), 105.1 (d), 102.8 (d), 99.1 (d), 59.1 (d), 56.3 (t), 55.6 (q), 40.7 (q); LRMS (ESI) 503 (100) 501 (40), 439 (20), 137 (30); HRMS (ESI) calc'd for $C_{16}H_{16}NO_3SBrCl_3$ $(M+H)^+$ 501.9049, found 501.9022.

General procedure for the cyclisation reactions of the *N*-methylated substrates

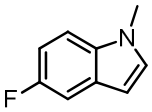
To a stirring solution of *N*-methylated substrate (0.1-0.6 mmol, 1.0 eq.) in dioxane (0.034 M) at 73 °C was added BEt_3 (1 M sol'n in hexanes, 0.25 eq.) and EPHP (2.5 eq. dissolved in dioxane [c = 0.084 M]) simultaneously *via* syringe pump over 2 h. Upon complete addition of reagents, the reaction mixture was allowed to cool to rt, dissolved in Et_2O (50 mL) and washed with 1 M K_2CO_3 (2 × 20 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil which was purified by flash chromatography to afford the indole products.

***N*-Methyl indole 40**



Yellow oil, 65%; ν_{max} (film)/cm^{-1} 3055, 2926, 1614, 1317, 1079, 740; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.76 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.42 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.35 (t, *J* = 7.8 Hz, 1 H, Ar*H*), 7.24 (t, *J* = 7.8 Hz, 1 H, Ar*H*), 7.12 (d, *J* = 2.9 Hz, 1 H, NC*H*), 6.61 (d, *J* = 2.9 Hz, 1 H, NCHC*H*), 3.84 (s, 3 H, N*CH*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 136.9 (s), 129.0 (d), 128.7 (s), 121.7 (d), 121.1 (d), 119.5 (d), 109.4 (d), 101.1 (d), 33.0 (q). Data in agreement with that reported.[i]

5-Fluoro-*N*-methyl indole 41

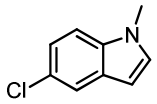


Colourless film, 52%; ν_{max} (film)/cm^{-1} 2926, 1734, 1494, 1238, 1121; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.26 (m, 1 H, Ar*H*), 7.22 (dd, *J* = 9.0, 4.3 Hz, 1 H, Ar*H*), 7.08 (d, *J* = 3.0 Hz, 1 H, NC*H*), 6.96 (td, *J* = 9.0, 2.5 Hz, 1 H, Ar*H*), 6.43 (d, *J* = 3.0 Hz, 1 H, NCHC*H*), 3.79 (s, 3 H, N*CH*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_c 158.7 & 157.2 ($J_{C\text{-}F}$ = 234.0 Hz) (s), 133.5 (s), 130.5

[i] A. Kong, X. Han, X. Lu, *Org. Lett*., **2006**, 8, 1339.

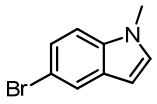
(d), 129.1 & 128.5 (d, J = 82.0 Hz) (s), 128.7 & 128.6 (d, J = 10.1 Hz) (d), 110.1 & 109.8 (d, J = 34.7 Hz) (d), 105.7 & 105.4 (d, J = 23.0 Hz) (d), 100.9 (d, J = 4.7 Hz) (d), 33.2 (q); LRMS (CI) 149 (22), 148 (100), 146 (6), 107 (6), 84 (12); HRMS (CI) calc'd for C_9H_7NF $(M-H)^+$ 148.0557, found 148.0554.

5-Chloro-*N*-methyl indole 42



Pale yellow oil, 55%; ν_{max} (film)/cm^{-1} 2925, 1726, 1476, 1278, 1062, 751; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.58 (d, J = 2.0 Hz, 1 H, Ar*H*), 7.23 (d, J = 8.7 Hz, 1 H, Ar*H*), 7.16 (dd, J = 8.7, 2.0 Hz, 1 H, Ar*H*), 7.07 (d, J = 3.0 Hz, 1 H, NC*H*), 6.42 (d, J = 3.0 Hz, 1 H, NCHC*H*), 3.78 (s, 3 H, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 135.1 (s), 130.2 (d), 129.5 (s), 125.2 (s), 121.9 (d), 120.3 (d), 110.2 (d), 100.7 (d), 33.1 (q); Data in agreement with that reported.[j]

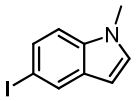
5-Bromo-*N*-methyl indole 43



White solid, 40%; m.p. 41–42 °C (PE); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.74 (d, J = 1.9 Hz, 1 H, Ar*H*), 7.29 (dd, J = 8.7, 1.9 Hz, 1 H, Ar*H*), 7.19 (d, J = 8.7 Hz, 1 H, Ar*H*), 7.05 (d, J = 3.0 Hz, 1 H, NC*H*), 6.42 (d, J = 3.0 Hz, 1 H, NCHC*H*), 3.77 (s, 3 H, NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 135.5 (s), 130.2 (s), 130.1 (d), 124.4 (d), 123.4 (d), 112.8 (s), 110.8 (d), 100.7 (d), 33.1 (q); Data in agreement with that reported.[k]

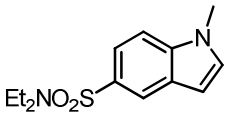
[j] L-C. Campeau, D.J. Schipper, K.J. Fagnou, *J. Am. Chem. Soc.,* **2008**, *130*, 3266.
[k] V. Diana, A. Carbone, P. Barraja, G. Kelter, H-H. Fiebig, G. Cirrincione, *Bioorg. Med. Chem*., **2010**, 18, 4524.

5-Iodo-*N*-methyl indole 44



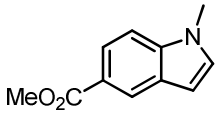
Pale yellow oil, 50%; ν_{max} (film)/cm^{-1} 2924, 1726, 1511, 1472, 1276, 1242; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.95 (d, *J* = 1.5 Hz, 1 H, Ar*H*), 7.46 (dd, *J* = 8.6, 1.5 Hz, 1 H, Ar*H*), 7.10 (d, *J* = 8.6 Hz, 1 H, Ar*H*), 7.00 (d, *J* = 3.1 Hz, 1 H, NC*H*), 6.40 (d, *J* = 3.1 Hz, 1 H, NCHC*H*), 3.77 (s, 3 H, NH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 135.9 (s), 131.1 (s), 129.9 (d), 129.7 (d), 129.7 (d), 111.4 (d), 110.4 (d), 82.9 (s), 33.1 (q); LRMS (EI) 257 (100), 256 (4), 131 (10), 103 (8); HRMS (EI) calc'd for C_9H_8NI 256.9696, found 256.9690.

***N*,*N*-Diethyl-*N*-methyl indole-5-sulfonamide 45**



Brown solid, 23%; m.p. 126–128 °C (EtOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.14 (d, *J* = 1.7 Hz, 1 H, Ar*H*), 7.65 (dd, *J* = 8.7, 1.7 Hz, 1 H, Ar*H*), 7.38 (d, *J* = 8.7 Hz, 1 H, Ar*H*), 7.17 (d, *J* = 3.0 Hz, 1 H, NC*H*), 6.60 (d, *J* = 3.0, 1 H, NCHC*H*), 3.84 (s, 3 H, NCH_3), 3.23 (q, *J* = 7.2 Hz, 4 H, 2 × NCH_2), 1.11 (t, *J* = 7.2 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 138.2 (s), 131.0 (d), 130.9 (s), 127.9 (s), 121.4 (d), 120.2 (d), 109.6 (d), 102.7 (d), 42.1 (t), 33.2 (q), 14.3 (q); LRMS (CI) 267 (100), 266 (22), 194 (65), 148 (13), 64 (22); HRMS (CI) calc'd for $C_{13}H_{19}N_2O_2SCl_3$ $(M+H)^+$ 267.1167, found 267.1162.

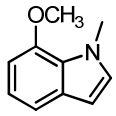
Methyl *N*-methyl indole-5-carboxylate 46



White solid, 45%; m.p. 103–105 °C (EtOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.39 (d, *J* = 1.5 Hz, 1 H, Ar*H*), 7.93 (dd, *J* = 8.7, 1.5 Hz, 1 H, Ar*H*), 7.33 (d, *J* = 8.7 Hz, 1 H, Ar*H*), 7.11 (d, *J* = 3.0 Hz, 1 H, NC*H*), 6.58 (d, *J* = 3.0 Hz, 1 H, NCHC*H*), 3.93 (s, 3 H, OCH_3), 3.82 (s, 3 H,

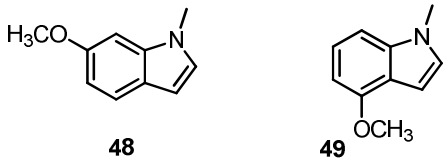
NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 168.4 (s), 139.2 (s), 130.3 (d), 128.1 (s), 124.1 (d), 123.0 (d), 121.4 (s), 109.0 (d), 102.6 (d), 52.0 (q), 31.2 (q); LRMS (EI) 189 (90), 158 (100), 194 (65), 153 (15), 130 (32); HRMS (CI) calc'd for $C_{13}H_{19}N_2O_2SCl_3$ (M^+) 189.0784, found 189.0781. Data in agreement with that reported.[n]

7-Methoxy-*N*-methyl indole 47



White solid, 65%; m.p. 53–54 °C (PE); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.19 (d, J = 8.0 Hz, 1 H, Ar*H*), 6.96 (t, J = 8.0 Hz, 1 H, Ar*H*), 6.91 (d, J = 3.0 Hz, 1 H, NC*H*), 6.60 (d, J = 8.0 Hz, 1 H, Ar*H*), 6.40 (d, J = 3.0 Hz, 1 H, NCHC*H*), 4.05 (s, 3 H, OCH_3), 3.91 (s, 3 H, NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 148.0 (s), 130.9 (s), 129.9 (d), 126.5 (s), 119.8 (d), 113.8 (d), 102.3 (d), 101.0 (d), 55.5 (q), 36.7 (q); LRMS (EI) 198 (20), 161 (100), 146 (90), 118 (35); HRMS (EI) calc'd for $C_{10}H_{11}ON$ 161.0835 ($M^{+\cdot}$), found 161.0834; Data in agreement with that reported.[l]

6-Methoxy-*N*-methyl indole (48) and 4-Methoxy-*N*-methyl indole (49)



48 **49**

Separable mixture of two isomers (66% overall yield):

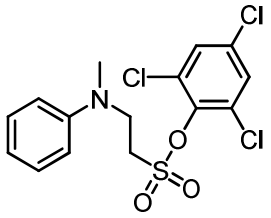
6-Methoxy-*N*-methyl indole **48**, colourless oil, 38%; ν_{max} (film)/cm^{-1} 2916, 1511, 1474, 1276, 1241, 752; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.49 (d, J = 9.2 Hz, 1 H, Ar*H*), 6.96 (d, J = 3.0 Hz, 1 H, NC*H*), 6.77-6.79 (m, 2 H, Ar*H*), 6.41 (d, J = 3.0 Hz, 1 H, NCHC*H*), 3.89 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 156.3 (s), 137.5 (s), 128.9 (d), 122.8 (s), 121.5 (d), 109.4 (d), 100.9 (d), 92.8 (d), 55.8 (q), 33.0 (q); LRMS (EI) 161 (20),

[l] J.W. Cook, J.D. Loudon, P.J. McCloskey, *Chem. Soc.*, **1952**, 3904.

146 (20), 118 (10), 88 (100); HRMS (EI) calc'd for $C_{10}H_{11}ON$ 161.0835 ($M^{+\cdot}$), found 161.0838. Data in agreement with that reported.[m]

4-Methoxy-*N*-methyl indole **49**, white solid, 28%; m.p. 88–89 °C (PE); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.15 (t, J = 8.0 Hz, 1 H, Ar*H*), 6.97-6.95 (m, 2 H, 2 ×Ar*H*), 6.58 (d, J = 3.0 Hz, 1 H, NC*H*), 6.52 (d, J = 8.0 Hz, 1 H, Ar*H*), 3.96 (s, 3 H, OCH_3), 3.77 (s, 3 H, NCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 153.5 (s), 138.3 (s), 127.4 (d), 122.4 (d), 119.0 (s), 102.8 (d), 99.2 (d), 98.2 (d), 55.4 (q), 33.2 (q); LRMS (EI) 161 (35), 146 (30), 118 (10), 88 (100); HRMS (EI) calc'd for $C_{10}H_{11}NO$ (M^+) 161.0835, found 161.0835. Data in agreement with that reported.[n,l]

2,4,6-Trichlorophenyl-2-(methyl(phenyl)amino)ethanesulfonate 40A

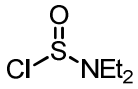


To a stirring solution of 2,4,6-trichlorophenyl-1-bromo-2-(methyl(phenyl)amino) ethanesulfonate (330 mg, 0.69 mmol, 1.0 eq.) in dioxane (5 mL) was added BEt_3 (1 M solution, 0.17 mL, 0.17 mmol, 0.25 eq.) followed by a 1 mL syringe of air. EPHP (248 mg, 1.38 mmol, 2.0 eq.) in dioxane (5 mL) was then added dropwise via a syringe pump over 2 h. The reaction mixture was stirred for a further 2 h and then dissolved in Et_2O (20 mL). The crude mixture was washed with H_2O (3 × 20 mL) and brine (3 × 20 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil which was purified by flash chromatography to give the product as a white solid (57 mg, 21%); ν_{max} (film)/cm^{-1} 3460, 3080, 1600, 1506, 1391, 1180; δ_H (500 MHz, $CDCl_3$) 7.40 (s, 2 H, 2 × *m*-Ar*H* (TCP)), 7.28 (m, 2 H, Ar*H*), 6.85 (m, 3 H, Ar*H*), 4.12 (m, 2 H, SO_2CH_2), 3.77 (m, 2 H, NCH_2), 3.04 (s, 3 H, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 147.0 (s), 141.9 (s), 133.3 (s), 130.8 (s), 129.7 (d), 129.3 (d), 128.2 (d), 112.9 (d), 50.4 (t), 47.4 (t),

[m] B.S. Lane, M. Brown, D. Sames, *J. Am. Chem. Soc*., **2007**, 129, 241.
[n] A. Kong, X. Han, X. Lu, *Org. Lett*., **2006**, 8, 1339.

38.69 (q); LRMS (ESI) 396 (100), 393 (20), 330 (15), 134 (16); HRMS (ESI) calc'd for $C_{15}H_{15}NO_3Cl_3S$ $(M+H)^+$ 393.9838, found 393.9840.

_N_,_N_-Diethylsulfurous chloride 55



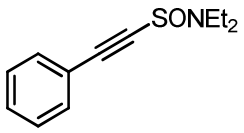
A 500 mL, flame-dried flask was placed under argon and charged with a stirring bar and thionyl chloride (9.68 g, 81.4 mmol, 1.0 eq.). Anhydrous Et_2O (150 mL) was then added and the solution cooled to –40 °C. Diethyl amine (11.9 g, 162.7 mmol, 2.0 eq.) was dissolved in anhydrous Et_2O (100 mL) and added dropwise over 2 h to the cooled solution of thionyl chloride. Upon complete addition, the reaction mixture was allowed to warm to –10 °C and stirred for a further 1 h. The reaction contents were finally warmed to rt and quickly filtered though a pad of Celite®. The ethereal contents were then *carefully* concentrated *in vacuo* to yield a viscous, acrid brown oil (7.6 g, 60%) which was immediately stored under argon at –20 °C between use. ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 3.38 (m, 4 H, 2 × NC*H*$_2$), 1.22 (m, 6 H, 2 × NCH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 39.2 (t), 12.3 (q); LRMS; no mass ion detected.

General procedure for the synthesis of alkynyl sulfinamides 56-66

A 100 mL, flame-dried flask was charged with a stirring bar and aromatic acetylene (0.5-1.5 mmol, 1.1 eq), followed by anhydrous THF (0.1 M) under argon. The flask was then cooled to –78 °C and *n*-BuLi (2.5 M in THF, 1.1 eq.) or, KHMDS (0.5 M sol'n in toluene, 1.1 eq.)[o] were added dropwise to the reaction mixture which was allowed to stir for 10 min. *N*,*N*-Diethyl sulfurous chloride (1.0 eq.) was then added *via* syringe, dropwise over 30 secs and the solution stirred at –78°C for 20 min. The reaction was allowed to warm to rt, dissolved in CH_2Cl_2 (200 mL) and washed with water (1 × 100 mL) and brine (1 × 100 mL). The organic fractions were combined, dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product which was purified *via* column chromatography (PE/EtOAc) to yield the alkynyl sulfinamides.

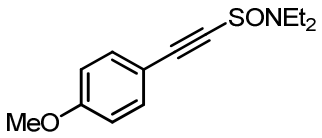
[o] KHMDS used in synthesis of sulfinamide **60** and **62**.

***N*,*N*-Diethyl-2-phenylethynesulfinamide 56**



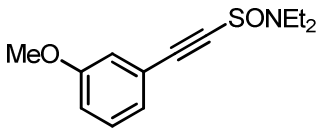
Colourless oil, 84%; ν_{max} (film)/cm^{-1} 2975, 2166, 1724, 1489, 1181, 1091; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.49 (d, J = 7.8 Hz, 2 H, 2 × *o*-Ar*H*), 7.40 (t, J = 7.8 Hz, 1 H, *p*-Ar*H*), 7.34 (t, J = 7.8 Hz, 2 H, 2 × *m*-Ar*H*), 3.41 (dq, J = 14.4, 7.2 Hz, 2 H, 2 × NC*H*), 3.35 (dq, J = 14.4, 7.2 Hz, 2 H, 2 × NC*H*), 1.26 (t, J = 7.2 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 132.2 (d), 130.3 (d), 128.7 (d), 120.2 (s), 96.7 (s), 86.9 (s), 42.7 (t), 14.4 (q); LRMS (ESI) 222 (100), 205 (30), 173 (60), 153 (35); HRMS (ESI) calc'd for $C_{12}H_{16}ONS$ $(M+H)^+$ 222.0953, found 222.0956.

***N*,*N*-Diethyl-2-(4-methoxyphenyl)ethynesulfinamide 57**



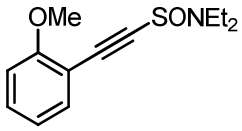
Colourless oil, 79%; ν_{max} (film)/cm^{-1} 2975, 2160, 1603, 1508, 1252, 1172; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.45 (d, J = 9.1 Hz, 2 H, 2 × $CH_3O(C)CHCH$), 6.87 (d, J = 9.1 Hz, 2 H, 2 × $CH_3O(C)CH$), 3.82 (s, 3 H, CH_3O), 3.42 (dq, J = 14.1, 7.1 Hz, 2 H, 2 × NC*H*), 3.35 (dq, J = 14.1, 7.1 Hz, 2 H, 2 × NC*H*), 1.27 (t, J = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 161.2 (s), 133.9 (d), 114.3 (d), 112.1 (s), 97.2 (s), 85.3 (s), 55.5 (q), 42.6 (t), 14.4 (q); LRMS (ESI) 252 (100), 238 (75), 222 (90), 194 (50), 164 (30); HRMS (ESI) calc'd for $C_{13}H_{18}NO_2S$ $(M+H)^+$ 252.1058, found 252.1062.

***N*,*N*-Diethyl-2-(3-methoxyphenyl)ethynesulfinamide 58**



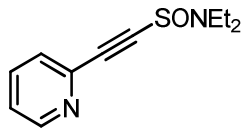
Colourless oil, 82%; ν_{max} (film)/cm^{-1} 2974, 2160, 1575, 1462, 1287, 1157, 1089; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.26 (t, *J* = 8.1 Hz, 1 H, $CH_3O(C)CHCH$), 7.10 (d, *J* = 8.1 Hz, 1 H, $CH_3O(C)CHCHCH$), 7.01 (m, 1 H, $CH_3O(C)CH(C)$), 6.95 (dd, *J* = 8.1, 2.7 Hz, 1 H, $CH_3O(C)CH$), 3.79 (s, 3 H, CH_3O), 3.41 (dq, *J* = 14.2, 7.1 Hz, 2 H, 2 × NCH), 3.35 (dq, *J* = 14.2, 7.1 Hz, 2 H, 2 × NCH), 1.27 (t, *J* = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 171.3 (s), 129.8 (d), 124.7 (d), 121.1 (s), 117.0 (d), 116.8 (d), 96.3 (s), 86.2 (s), 55.4 (q), 42.7 (t), 14.5 (q); LRMS (CI) 252 (80), 235 (20), 203 (75), 179 (100); HRMS (CI) calc'd for $C_{13}H_{18}NO_2S$ $(M+H)^+$ 252.1058, found 252.1065.

***N*,*N*-Diethyl-2-(2-methoxyphenyl)ethynesulfinamide 59**



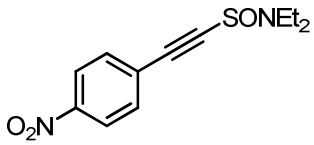
Colourless oil, 80%; ν_{max} (film)/cm^{-1} 2936, 2165, 1739, 1490, 1288, 1270, 1092; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.42 (dd, *J* = 7.8, 1.6 Hz, 1 H, $CH_3O(C)(C)CH$), 7.34 (td, *J* = 8.4, 1.6 Hz, 1 H, $CH_3O(C)CHCH$), 6.90 (t, *J* = 7.8 Hz, 1 H, $CH_3O(C)CHCHCH$), 6.86 (d, *J* = 8.4 Hz, 1 H, CH_3OCH), 3.83 (s, 3 H, CH_3O), 3.41 (dq, *J* = 14.1, 7.1 Hz, 2 H, 2 × NCH), 3.33 (dq, *J* = 14.1, 7.1 Hz, 2 H, 2 × NCH), 1.26 (t, *J* = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 160.9 (s), 134.0 (d), 132.0 (d), 120.6 (d), 110.9 (d), 109.4 (s), 93.3 (s), 90.2 (s), 55.8 9 (q), 42.6 (t), 14.4 (q); LRMS (CI) 263 (50), 252 (100), 235 (35), 203 (60); HRMS (CI) calc'd for $C_{13}H_{18}NO_2S$ $(M+H)^+$ 252.1058, found 252.1063.

***N*,*N*-Diethyl-2-(pyridin-2-yl)ethynesulfinamide 60**



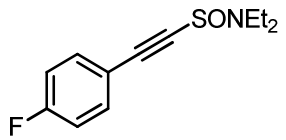
Yellow oil, 65%; ν_{max} (film)/cm^{-1} 3476, 2975, 1698, 1579, 1459, 1239, 1184, 1091, 1013; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.63 (dd, *J* = 4.9, 1.1 Hz, 1 H, ArNC*H*), 7.71 (td, *J* = 7.8, 1.1 Hz, 1 H, ArNCHCHC*H*), 7.55 (d, *J* = 7.8 Hz, 1 H, ArN(C)C*H*), 7.33 (ddd, *J* = 7.8, 4.9, 1.1 Hz, 1 H, ArNCHC*H*), 3.36 (dq, *J* = 14.7, 7.1 Hz, 4 H, 2 × NCH_2), 1.23 (t, *J* = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 150.6 (d), 141.0 (s), 136.3 (d), 128.3 (d), 124.6 (d), 94.1 (s), 85.8 (s), 42.8 (t), 14.4 (q); LRMS (CI) 223 (14), 209 (18), 193 (77), 174 (62), 122 (100); HRMS (CI) calc'd for $C_{11}H_{15}ON_2S$ $(M+H)^+$ 223.0905, found 223.0909.

***N*,*N*-Diethyl-2-(4-nitrophenyl)ethynesulfinamide 61**



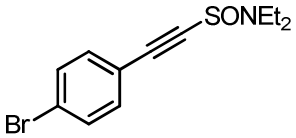
Yellow oil, 80%; ν_{max} (film)/cm^{-1} 2977, 2169, 1593, 1521, 1344, 1098; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.22 (d, *J* = 8.5 Hz, 2 H, 2 × NO_2(C)C*H*), 7.66 (d, *J* = 8.5 Hz, 2 H, 2 × NO_2(C)CHC*H*), 3.43 (dq, *J* = 14.7, 7.3 Hz, 2 H, 2 × NC*H*), 3.38 (dq, *J* = 14.7, 7.3 Hz, 2 H, 2 × NC*H*), 1.27 (t, *J* = 7.3 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 148.3 (s), 133.1 (d), 126.8 (s), 123.9 (d), 93.2 (s), 91.1 (s), 42.9 (t), 14.4 (q); LRMS (CI) 267 (85), 247 (30), 248 (95), 219 (100), 203 (20); HRMS (CI) calc'd for $C_{12}H_{15}O_3N_2S$ $(M+H)^+$ 267.0803, found 267.0798.

***N*,*N*-Diethyl-2-(4-fluorophenyl)ethynesulfinamide 62**



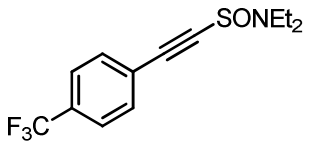
Pale yellow oil, 78%; ν_{max} (film)/cm^{-1} 2976, 2167, 1598, 1470, 1234, 1090; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.44-7.48 (m, 2 H, 2 × F(C)C*H*), 6.99-7.03 (m, 2 H, 2 × F(C)CHC*H*), 3.37 (dq, *J* = 14.1, 7.1 Hz, 2 H, 2 × NC*H*), 3.31 (dq, *J* = 14.1, 7.1 Hz, 2 H, 2 × NC*H*), 1.23 (t, *J* = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 164.6 & 162.6 (*J* = 252.4 Hz) (s), 134.3 (*J* = 8.8 Hz) (s), 116.3 (*J* = 3.2 Hz) (d), 116.1 (*J* = 22.5 Hz) (d), 95.3 (s), 86.4 (s), 42.6 (t), 14.3 (q); LRMS (CI) 240 (15), 223 (25), 191 (100), 176 (15); HRMS (CI) calc'd for $C_{12}H_{15}ONSF$ $(M+H)^+$ 240.0858, found 240.0863.

***N*,*N*-Diethyl-2-(4-bromophenyl)ethynesulfinamide 63**



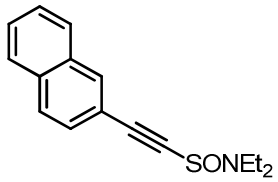
Pale yellow oil, 72%; ν_{max} (film)/cm^{-1} 2974, 2164, 1583, 1484, 1092; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.48 (d, *J* = 8.5 Hz, 2 H, 2 × Br(C)CHC*H*), 7.34 (d, *J* = 8.5 Hz, 2 H, 2 × Br(C)C*H*), 3.40 (dq, *J* = 14.1, 7.1 Hz, 2 H, 2 × NC*H*), 3.34 (dq, *J* = 14.1, 7.1 Hz, 2 H, 2 × NC*H*), 1.25 (t, *J* = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 133.5 (d), 132.0 (d), 124.9 (s), 119.0 (s), 95.0 (s), 87.5 (s), 42.6 (t), 14.25 (q); LRMS (CI) 302 (5), 300 (5), 283 (10), 253 (100), 238 (35); HRMS (CI) calc'd for $C_{12}H_{15}ONSBr$ $(M+H)^+$ 300.0058, found 300.0063.

***N*,*N*-Diethyl-2-(4-(trifluoromethyl)phenyl)ethynesulfinamide 64**



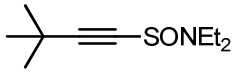
Yellow oil, 71%; ν_{max} (film)/cm^{-1} 2979, 2167, 1613, 1319, 1124, 1090; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.60 (s, 4 H, 4 ×Ar*H*), 3.41 (dq, *J* = 14.1, 7.1 Hz, 2 H, 2 × NC*H*), 3.36 (dq, *J* = 14.1, 7.1 Hz, 2 H, 2 × NC*H*), 1.26 (t, *J* = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 132.4 (d), 131.8 (q, *J* = 33.0 Hz) (s), 125.5 (q, *J* = 3.2 Hz) (s), 123.9 (d), 123.7 (q, *J* = 272.2 Hz) (s), 94.1 (s), 88.7 (s), 42.7 (t), 14.2 (q); LRMS (CI) 290 (33), 273 (45), 241 (100), 226 (80), 217 (40); HRMS (CI) calc'd for $C_{13}H_{15}ONSF_3$ $(M+H)^+$ 290.0826, found 290.0820.

***N*,*N*-Diethyl-2-(naphthalen-1-yl)ethynesulfinamide 65**



Yellow oil, 65%; ν_{max} (film)/cm^{-1} 2974, 2158, 1595, 1459, 1187, 1091; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.01 (s, 1 H, Ar*H*), 7.83 (m, 3 H, Ar*H*), 7.55 (m, 3 H, Ar*H*), 3.48 (dq, *J* = 14.7, 7.1 Hz, 2 H, 2 × NC*H*), 3.42 (dq, *J* = 14.7, 7.1 Hz, 2 H, 2 × NC*H*), 1.33 (t, *J* = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 133.6 (s), 133.0 (d), 132.6 (s), 128.4 (d), 128.1 (d), 127.9 (d), 127.7 (2C) (2d), 127.0 (d), 117.3 (s), 96.9 (s), 86.5 (s), 42.6 (t), 14.3 (q); LRMS (CI) 272 (51), 223 (100), 199 (30), 152 (11); HRMS (EI) calc'd for $C_{16}H_{18}ONS$ $(M+H)^+$ 272.1109, found 272.1114.

***N*,*N*-Diethyl-3,3-dimethylbut-1-yne-1-sulfinamide 66**

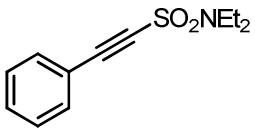


Colourless oil, 90%; ν_{max} (film)/cm^{-1} 2971, 2172, 1457, 1363, 1252, 1088; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.26 (dq, *J* = 14.1, 7.1 Hz, 2 H, 2 × NC*H*), 3.19 (dq, *J* = 14.1, 7.1 Hz, 2 H, 2 × NC*H*), 1.21 (s, 9 H, (C*H*$_3$)$_3$C), 1.17 (t, *J* = 7.1 Hz, 6 H, 2 × NCH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 106.4 (s), 77.0 (s), 42.4 (t), 30.1 (q), 28.2 (s), 14.16 (q); LRMS (CI) 202 (100), 175 (4), 120 (6); HRMS (CI) calc'd for $C_{10}H_{19}ONS$ ($M^{+\cdot}$) 202.1265, found 202.1269.

General procedure for the synthesis of alkynyl sulfonamides 50 & 67-76

A 50 mL flask was charged with $NaIO_4$ (2.0 mmol, 1.3 eq.) and the reagent dissolved in H_2O (4 mL). MeCN (5 mL) was then added and the flask cooled to 0 °C. After *complete* dissolution of the solid, EtOAc (5 mL) was added and the reaction stirred for 5 min at 0 °C. $RuCl_3.3H_2O$ (0.015 mmol, 1 mmol%) was then added in one portion and the brown reaction mixture stirred for a further 2 min. Sulfinamide **55-65** (1.54 mmol, 1.0 eq.) dissolved in EtOAc (5 mL) was then added to the reaction flask in one portion and the reaction stirred vigorously at 0 °C until complete consumption of the starting material was observed *via* TLC (usually 5-6 h). The crude reaction mixture was then dissolved in CH_2Cl_2 (200 mL) and washed with H_2O (100 mL) and brine (100 mL). The organic fractions were combined, dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude sulfonamide which was purified *via* column chromatography (EtOAc/PE) to yield the sulfonamide product.

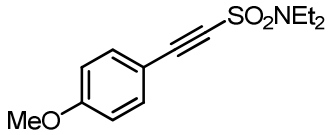
***N*,*N*-Diethyl-2-phenylethynesulfonamide 50**



Colourless oil, 56%; ν_{max} (film)/cm^{-1} 2978, 2182, 1357, 1153, 1017; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.52 (d, *J* = 7.6 Hz, 2 H, 2 × *o*-Ar*H*), 7.46 (t, *J* = 7.6 Hz, 1 H, *p*-Ar*H*), 7.38 (t, *J* = 7.6 Hz, 2 H, 2 × *m*-Ar*H*), 3.38 (q, *J* = 7.3 Hz, 4 H, 2 × NC*H*$_2$CH$_3$), 1.29 (t, *J* = 7.3 Hz, 6 H, 2

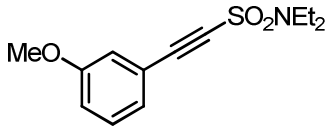
× NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 132.6 (d), 131.1 (d), 128.8 (d), 118.7 (s), 88.3 (s), 83.9 (s), 43.0 (t), 13.5 (q); LRMS (EI) 237 (20), 222 (100), 173 (37), 165 (73); HRMS (EI) calc'd for $C_{12}H_{15}O_2NS$ (M^+) 237.0818, found 237.0820.

_N_,_N_-Diethyl-2-(4-methoxyphenyl)ethynesulfonamide 67



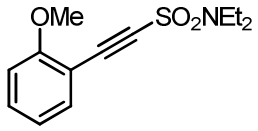
Colourless oil, 63%; ν_{max} (film)/cm^{-1} 2978, 2177, 1604, 1509, 1357, 1256, 1160; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.47 (d, J = 8.7 Hz, 2 H, 2 × $CH_3O(C)CHCH$), 6.89 (d, J = 8.7 Hz, 2 H, 2 × $CH_3O(C)CH$), 3.83 (s, 3 H, CH_3O), 3.36 (q, J = 7.1 Hz, 4 H, 2 × NCH_2CH_3), 1.28 (t, J = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 161.8 (s), 134.5 (d), 114.5 (d), 110.4 (s), 89.2 (s), 82.9 (s), 55.6 (q), 43.0 (t), 13.6 (q); LRMS (EI) 267 (15), 195 (22), 132 (100); HRMS (EI) calc'd for $C_{13}H_{17}O_3NS$ (M^+) 267.0924, found 267.0920.

_N_,_N_-Diethyl-2-(3-methoxyphenyl)ethynesulfonamide 68



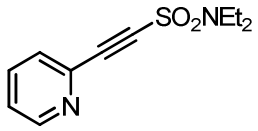
Colourless oil, 65%; ν_{max} (film)/cm^{-1} 2977, 2177, 1576, 1358, 1155; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.29 (t, J = 7.9 Hz, 1 H, $CH_3O(C)CHCH$), 7.12 (d, J = 7.9 Hz, 1 H, $CH_3O(C)CHCHCH$), 7.03 (s, 1 H, $CH_3O(C)CH(C)$), 7.01 (d, J = 7.9 Hz, 1 H, $CH_3(C)CHCH$), 3.81 (s, 3 H, CH_3O), 3.38 (q, J = 7.1 Hz, 4 H, 2 × NCH_2CH_3), 1.29 (t, J = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.6 (s), 130.0 (d), 125.1 (d), 119.6 (s), 117.7 (d), 117.2 (d), 88.2 (s), 83.6 (s), 55.6 (q), 43.0 (t), 13.5 (q); LRMS (ESI) 268 (100), 254 (11), 240 (24), 238 (5); HRMS (ESI) calc'd for $C_{13}H_{18}NO_3S$ $(M+H)^+$ 268.1007, found 268.0999.

***N*,*N*-Diethyl-2-(2-methoxyphenyl)ethynesulfonamide 69**



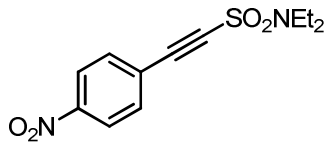
Colourless oil, 60%; ν_{max} (film)/cm^{-1} 2977, 2179, 1597, 1492, 1356, 1175; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.45 (dd, *J* = 7.7, 1.6 Hz, 1 H, $CH_3O(C)(C)CH$), 7.41 (td, *J* = 8.2, 1.6 Hz, 1 H, $CH_3O(C)CHCH$), 6.94 (t, *J* = 7.7 Hz, 1 H, $CH_3O(C)CHCHCH$), 6.89 (d, *J* = 8.2 Hz, 1 H, $CH_3O(C)CH$), 3.86 (s, 3 H, CH_3O), 3.38 (q, *J* = 7.1 Hz, 4 H, 2 × NCH_2CH_3), 1.30 (t, *J* = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 161.5 (s), 134.4 (d), 132.8 (d), 120.7 (d), 110.9 (d), 108.0 (s), 87.5 (s), 85.9 (s), 55.8 (q), 42.9 (t), 13.3 (q); LRMS (EI) 268 (90), 256 (50), 204 (100), 190 (20); HRMS (EI) calc'd for $C_{13}H_{18}NO_3S$ $(M+H)^+$ 268.1007, found 268.1012.

***N*,*N*-Diethyl-2-(pyridin-2-yl)ethynesulfonamide 70**



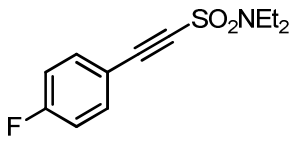
Yellow oil, 50%; ν_{max} (film)/cm^{-1} 2979, 2192, 1580, 1460, 1360, 1203, 1157; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.65 (d, *J* = 4.7 Hz, 1 H, Ar-NC*H*), 7.73 (td, *J* = 7.7, 1.7 Hz, 1 H, ArNCHCHC*H*), 7.57 (d, *J* = 7.7 Hz, 1 H, ArN(C)C*H*), 7.37 (ddd, *J* = 7.7, 4.7, 1.7 Hz, 1 H, ArNCHC*H*), 3.45 (q, *J* = 7.1 Hz, 4 H, 2 × NCH_2CH_3), 1.35 (t, *J* = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 150.8 (d), 139.9 (s), 136.6 (d), 128.8 (d), 125.2 (d), 85.8 (s), 82.7 (s), 43.3 (t), 13.8 (q); LRMS (CI) 239 (65), 223 (60), 205 (16), 166 (29), 119 (22); HRMS (CI) calc'd for $C_{11}H_{15}O_2N_2S$ $(M+H)^+$ 239.0854, found 239.0857.

***N*,*N*-Diethyl-2-(4-nitrophenyl)ethynesulfonamide 71**



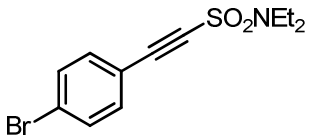
Yellow solid, 63%; m.p. 126–127 °C (CH_2Cl_2/PE); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.26 (d, *J* = 8.9 Hz, 2 H, 2 × NO_2(C)C*H*), 7.71 (d, *J* = 8.9 Hz, 2 H, 2 × NO_2(C)CHC*H*), 3.41 (q, *J* = 7.1 Hz, 4 H, 2 × NC$H_2$$CH_3$), 1.31 (t, *J* = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 148.1 (s), 133.6 (d), 125.4 (s), 124.0 (d), 88.0 (s), 84.8 (s), 43.2 (t), 13.7 (q); LRMS (CI) 311 (6), 283 (100), 219 (10), 148 (13); Elemental anal., calc'd for- C 51.05%, H 5.00%, N 9.92%, found C 51.15%, H 4.85%, N 9.84%.

***N*,*N*-Diethyl-2-(4-fluorophenyl)ethynesulfonamide 72**



Pale yellow oil, 61%; ν_{max} (film)/cm^{-1} 2980, 2183, 1600, 1506, 1358, 1202, 1170; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.51-7.54 (m, 2 H, 2 × F(C)C*H*), 7.06-7.10 (m, 2 H, 2 × F(C)CHC*H*), 3.38 (q, *J* = 7.1 Hz, 4 H, 2 × NC$H_2$$CH_3$), 1.29 (t, *J* = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 165.3 & 162.8 (*J* = 255.8 Hz) (s), 134.8 (*J* = 8.79 Hz) (s), 116.2 (*J* = 22.6 Hz) (d), 114.7 (*J* = 3.3 Hz) (d), 87.0 (s), 83.8 (s), 42.9 (t), 13.4 (q); LRMS (ESI) 298 (30), 257 (20), 256 (100), 228 (30), 212 (30); HRMS (ESI) calc'd for $C_{12}H_{15}NO_2SFNa$ $(M+Na)^+$ 256.0808, found 256.0811.

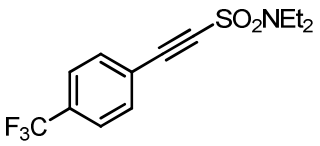
2-(4-bromophenyl)-*N*,*N*-Diethylethynesulfonamide 73



Yellow oil, 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56 (d, *J* = 8.5 Hz, 2 H, 2 × Br(C)CHC*H*), 7.41 (d, *J* = 8.5 Hz, 2 H, 2 × Br(C)C*H*), 3.40 (q, *J* = 7.1 Hz, 4 H, 2 × NC$H_2$$CH_3$), 1.32

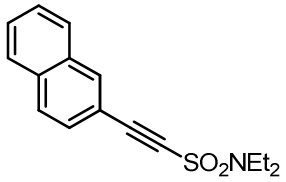
(t, J = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 133.8 (d), 132.1 (d), 125.8 (s), 117.5 (s), 86.8 (s), 84.9 (s), 42.9 (t), 13.4 (q); LRMS (EI) 317 (35), 245 (100), 193 (15), 179 (3); HRMS (EI) calc'd for $C_{12}H_{14}O_2NSBr$ (M^+) 314.9924, found 314.9931; Elemental anal., calc'd for- C 45.58%, H 4.46%, N 4.43%, found C 46.03%, H 4.54%, N 3.35%.

_N_,_N_-Diethyl-2-(4-(trifluoromethyl)phenyl)ethynesulfonamide 74



Yellow oil, 59%; ν_{max} (film)/cm^{-1} 2981, 2189, 1725, 1362, 1322, 1158; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.66 (s, 4 H, Ar*H*), 3.40 (q, J = 7.1 Hz, 4 H, 2 × NCH_2CH_3), 1.30 (t, J = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$)[p] δ_C 132.9 (d), 132.6 (q, J = 33.0 Hz) (s), 125.8 (q, J = 3.7 Hz) (d), 123.4 (q, J = 272.2 Hz) (s), 122.56 (s), 85.9 (s), 43.0 (t), 13.5 (q); LRMS (EI) 305 (10), 290 (100), 241 (30), 233 (50); HRMS (EI) calc'd for $C_{13}H_{14}O_2NSF_3$ (M^+) 305.0692, found 305.0696.

_N_,_N_-Diethyl-2-(naphthalen-1-yl)ethynesulfonamide 75

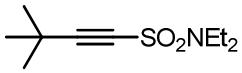


Pale yellow oil, 42%; ν_{max} (film)/cm^{-1} 2977, 2182, 1468, 1356, 1202, 1230; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.10 (s, 1 H, Ar*H*), 7.84-7.90 (m, 3 H, Ar*H*), 7.50-7.60 (m, 3 H, Ar*H*), 3.45 (q, J = 7.1 Hz, 4 H, 2 × NCH_2CH_3), 1.35 (t, J = 7.1 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 133.9 (s), 133.8 (d), 132.5 (s), 128.6 (d), 128.2 (d), 128.0 (d), 127.9 (d), 127.6 (d), 127.2 (d), 115.7 (s), 88.7 (s), 83.9 (s), 43.0 (t), 13.5 (q); LRMS (ESI) 272 (45), 223

[p] Alkynyl carbon, attached to aromatic ring not observed.

(100), 199 (22), 152 (10); HRMS (ESI) calc'd for $C_{16}H_{18}NO_2S$ $(M+H)^+$ 288.1058, found 288.1062.

_N_,_N_-Diethyl-3,3-dimethylbut-1-yne-1-sulfonamide 76

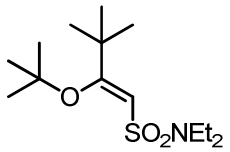


Colourless oil, 70%; ν_{max} (film)/cm^{-1} 2974, 2173, 1459, 1356, 1153; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 3.26 (q, J = 7.1 Hz, 4 H, 2 × NCH_2CH$_3$), 1.25 (s, 9 H, (CH_3)$_3$C), 1.22 (t, J = 7.1 Hz, 6 H, 2 × NCH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 98.6 (s), 75.0 (s), 42.7 (t), 29.8 (q), 27.8 (s), 13.2 (q); LRMS (EI) 217 (7), 203 (10), 202 (100), 138 (10); HRMS (EI) calc'd for $C_{10}H_{19}O_2NS$ (M^+) 217.1131, found 217.1134.

(_Z_)-2-(*tert*-Butoxy)-_N_,_N_-diethyl-3,3-dimethylbut-1-ene-1-sulfonamide, (_E_)-2-(*tert*-Butoxy)-_N_,_N_-diethyl-3,3-dimethylbut-1-ene-1-sulfonamide and _N_,_N_-diethyl-3,3-dimethyl-2-oxobutane-1-sulfonamide

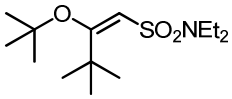
To a stirring solution of *N*,*N*-Diethyl-3,3-dimethylbut-1-yne-1-sulfonamide **76** (149 mg, 0.69 mmol, 1.0 eq.) in anhydrous DMF (1 mL) under argon, was added potassium *tert*-butoxide (108 mg, 0.96 mmol, 1.4 eq.) in one portion and the reaction stirred for 16 h. The reaction mixture was then dissolved in CH_2Cl_2 (100 mL), washed with saturated LiCl solution (2 × 100 mL) and the organic fractions combined, dried over $MgSO_4$, and concentrated *in vauco* to yield a yellow oil which was then subjected to flash chromatography (Et_2O/PE) to yield the products **100**, **101** and **102**.

(*Z*)-2-(*tert*-Butoxy)-*N*,*N*-diethyl-3,3-dimethylbut-1-ene-1-sulfonamide 100



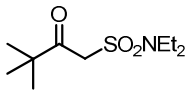
Colourless oil, (40 mg, 20%); ν_{max} (film)/cm^{-1} 2977, 1577, 1349, 1200, 1136, 1017; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 5.33 (s, 1 H, C*H*), 3.27 (q, *J* = 7.2 Hz, 4 H, 2 x CH_2CH$_3$), 1.45 (s, 9 H, ((CH_3)$_3$CO), 1.31 (s, 9 H, (CH_3)$_3$(C)(C)), 1.23 (t, *J* = 7.2 Hz, 6 H, 2 x CH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 173.4 (s), 104.2 (d), 80.0 (s), 42.6 (t), 38.9 (s), 28.8 (q), 29.4 (q), 14.3 (q); LRMS (CI) 292 (65), 236 (100), 220 (10), 178 (75); HRMS (EI) calc'd for $C_{14}H_{30}NO_3S$ $(M+H)^+$ 292.1941, found 292.1929.

(*E*)-2-(*tert*-Butoxy)-*N*,*N*-diethyl-3,3-dimethylbut-1-ene-1-sulfonamide 101



Colourless oil, (26 mg, 13%); ν_{max} (film)/cm^{-1} 2977, 1577, 1349, 1200, 1136, 1017; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 5.73 (s, 1 H, C*H*(C)), 3.22 (q, *J* = 7.2 Hz, 4 H, 2 × CH_2CH$_3$), 1.53 (s, 9 H, ((CH_3)$_3$CO), 1.17 (t, *J* = 7.2 Hz, 6 H, 2 × CH$_2$CH_3), 1.14 (s, 9 H, (CH_3)$_3$(C)(C)); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 172.5 (s), 112.7 (d), 86.1 (s), 41.8 (t), 39.1 (s), 29.7 (q), 29.5 (q), 14.4 (q); LRMS (CI) 292 (65), 236 (100), 220 (10), 178 (75); HRMS (EI) calc'd for $C_{14}H_{30}NO_3S$ $(M+H)^+$ 292.1941, found 292.1929.

***N*,*N*-Diethyl-3,3-dimethyl-2-oxobutane-1-sulfonamide 102**



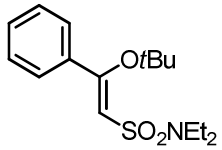
Colourless oil, (64 mg, 40%); ν_{max} (film)/cm^{-1} 2971, 1715, 1332, 1201, 1129, 1018; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 4.11 (s, 2 H, CH_2SO$_2$), 3.32 (q, *J* = 7.2 Hz, 4 H, 2 x CH_2CH$_3$), 1.21 (t, *J* = 7.2 Hz, 2 × CH$_2$CH_3), 1.21 (s, 9 H, (3 × (CH_3)$_3$); δ_C 205.0 (s), 56.5 (t), 45.6 (s), 43.0 (t),

26.0 (q), 14.9 (q); LRMS (CI) 236 (100), 218 (10), 163 (10), 154 (15); HRMS (EI) calc'd for $C_{10}H_{22}NO_3S$ $(M+H)^+$ 236.1315, found 236.1311.

(*Z*)-2-(*tert*-Butoxy)-*N*,*N*-diethyl-2-phenylethenesulfonamide 52, (*E*)-1-(*tert*-butoxy)-*N*,*N*-diethyl-2-phenylethenesulfonamide 51 and *N*,*N*-diethyl-2-oxo-2 phenylethanesulfonamide 54

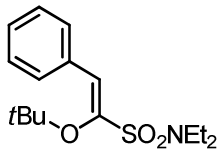
To a stirring solution of *N*,*N*-diethyl-2-phenylethynesulfonamide **50** (100 mg, 0.42 mmol, 1.0 eq.) in wet DMF (3 mL), was added potassium *tert*-butoxide (62 mg, 0.55 mmol, 1.3 eq.) in one portion and the reaction stirred for 16 h. The reaction mixture was then dissolved in CH_2Cl_2 (100 mL), washed with saturated LiCl solution (2 ×100 mL) and the organic fractions combined, dried over $MgSO_4$, and concentrated *in vauco* to yield a yellow oil which was then subjected to column chromatography (EtOAc/PE) to yield the products.

(*Z*)-2-(*tert*-Butoxy)-*N*,*N*-diethyl-2-phenylethenesulfonamide 52



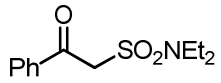
Colourless oil, (30 mg, 23%); ν_{max} (film)/cm^{-1} 2977, 1627, 1327, 1201, 1152, 1060, 1016; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.45 (d, J = 7.4 Hz, 2 H, 2 × *o*-Ar*H*), 7.40 (t, J = 7.4 Hz, 1 H, *p*-Ar*H*), 7.36 (t, J = 7.4 Hz, 1 H, 2 × *m*-Ar*H*), 5.89 (s, 1 H, *t*BuO(C)C*H*), 3.33 (q, J = 7.3 Hz, 4 H, 2 × NCH_2CH$_3$), 1.30 (s, 9 H, O(CH_3)$_3$), 1.19 (t, J = 7.3 Hz, 6 H, 2 × NCH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 163.2 (s), 137.8 (s), 130.1 (d), 128.3 (d), 128.3 (d), 116.5 (d), 84.2 (s), 41.7 (t), 29.5 (q), 14.3 (q); LRMS (CI) 312 (20), 257 (15), 256 (100), 120 (36); HRMS (CI) calc'd for $C_{16}H_{26}O_3NS$ $(M+H)^+$ 312.1633, found 312.1638.

(*E*)-1-(*tert*-Butoxy)-*N*,*N*-diethyl-2-phenylethenesulfonamide 51



Colourless oil, (10 mg, 7.6%); ν_{max} (film)/cm^{-1} 2975, 1594, 1325, 1135, 1072; ^{1}H NMR (600 MHz, $CDCl_3$); δ_H 7.57 (d, J = 7.5 Hz, 2 H, 2 × *o*-Ar*H*), 7.35 (t, J = 7.5 Hz, 2 H, 2× *m*-Ar*H*), 7.30 (t, J = 7.5 Hz, 1 H, *p*-Ar*H*), 7.14 (s, 1 H, *t*BuO(C)C*H*), 3.35 (q, J = 7.4 Hz, 4 H, 2 × NCH_2CH$_3$), 1.14 (s, 9 H, O(CH_3)$_3$), 1.22 (t, J = 7.4 Hz, 6 H, 2 × NCH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 149.3 (s), 133.4 (s), 129.8 (d), 128.8 (d), 128.5 (d), 124.4 (d), 87.2 (s), 41.9 (t), 29.4 (q), 14.3 (q); LRMS (CI) 284 (11), 257 (15), 256 (100), 220 (6); HRMS (CI) calc'd for $C_{16}H_{26}O_3NS$ $(M+H)^+$ 312.1633, found 312.1637.

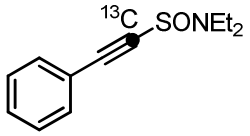
***N*,*N*-Diethyl-2-oxo-2-phenylethanesulfonamide 54**



Colourless film, (10 mg, 9.3%); ν_{max} (film)/cm^{-1} 2977, 2939, 1681, 1598, 1449, 1337, 1277, 1146, 1020; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.20 (d, J = 7.4 Hz, 2 H, 2 × *o*-Ar*H*), 7.61 (t, J = 7.4 Hz, 1 H, *p*-Ar*H*), 7.49 (t, J = 7.4 Hz, 2 H, 2 × *m*-Ar*H*), 4.54 (s, 2 H, CH_2), 3.27 (q, J = 7.2 Hz, 4 H, 2 × NCH_2CH$_3$), 1.18 (t, J = 7.2 Hz, 6 H, 2 × NCH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 189.4 (s), 135.9 (s), 134.4 (d), 129.6 (d), 128.9 (d), 59.2 (t), 43.1 (t), 14.8 (q); Data in agreement with that reported.[q]

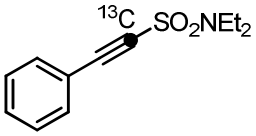
[q] L.C. Bouchez, S.R. Dubbaka, M. Turks, P. Vogel, *J. Org. Chem*., **2004**, 69, 6413.

***N*,*N*-Diethyl-2-phenylethynesulfinamide (^{13}C enriched)**



According to general procedure (pg. 104). Colourless oil, 82%; ν_{max} (film)/cm^{-1} 2973, 2129, 1488, 1181, 1091; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.45 (d, J = 7.8 Hz, 2 H, 2 × *o*-Ar*H*), 7.35 (t, J = 7.8 Hz, 1 H, *p*-Ar*H*), 7.30 (t, J = 7.8 Hz, 1 H, 2 × *m*-Ar*H*), 3.36 (dq, J = 14.4, 7.2 Hz, 2 H, 2 × NC*H*), 3.30 (dq, J = 14.4, 7.2 Hz, 2 H, 2 × NC*H*), 1.22 (t, J = 7.2, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 132.2 (d, J = 3.0 Hz) (d), 130.4 (d), 128.7 (d), 120.2 (d, J = 10.0 Hz) (s), 96.9 & 95.8 (d, J = 164.8 Hz) (s), 86.4 (s), 42.7 (t), 14.3 (q); LRMS (CI) 294 (50), 223 (15), 206 (15), 174 (100); HRMS (CI) calc'd for $C_{12}H_{16}ONS$ $(M+H)^+$ 223.0977, found 223.0978.

***N*,*N*-Diethyl-2-phenylethynesulfonamide (^{13}C enriched) 91**



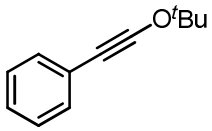
According to general procedure (pg. 109). Colourless oil, 60%; ν_{max} (film)/cm^{-1} 2976, 2145, 1357, 1202, 1152, 1017; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.52 (d, J = 7.4 Hz, 2 H, 2 × *o*-Ar*H*), 7.46 (t, J = 7.4 Hz, 1 H, *p*-Ar*H*), 7.38 (t, J = 7.4 Hz, 2 H, 2 × *m*-Ar*H*), 3.37 (q, J = 7.3 Hz, 4 H, 2 × NCH_2), 1.29 (t, J = 7.3, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 132.6 (d, J = 3.0 Hz) (d), 131.1 (d), 128.8 (d), 118.6 (d, J = 10.5 Hz) (s), 88.9 & 87.7 (d, J = 175.9 Hz) (s), 83.9 (s), 43.0 (t), 13.5 (q); LRMS (CI) 276 (15), 239 (100), 223 (15), 174 (55); HRMS (CI) calc'd for $C_{12}H_{16}ONS$ $(M+H)^+$ 239.0926, found 239.0923.

General procedure for the synthesis of ynol ethers 53, 77-85

To a 50 mL flame-dried flask, was added sulfonamide **53** or **67-75** (0.3 mmol, 1.0 eq.) followed by anhydrous DMF (2 mL) under argon. The reaction mixture was stirred for 1 min and then KO^{t}Bu (0.36 mmol, 1.2 eq.) was added over 10 secs at the temperature indicated for

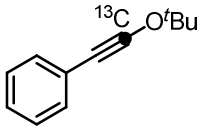
each substrate, under a flow of argon to give a brown solution which was stirred for 20 min. The reaction contents were then passed through a plug of silica (9-1 Et_2O/PE) to yield the product.

(*tert*-Butoxyethynyl)benzene 53



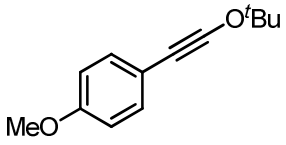
Reaction carried out at rt according to general procedure. Colourless oil, 70%; ν_{max} (film)/cm^{-1} 2981, 2246, 1371, 1327, 1064; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.34 (d, J = 7.7 Hz, 2 H, 2 × *o*-Ar*H*), 7.23 (t, J = 7.7 Hz, 2 H, 2 × *m*-Ar*H*), 7.20 (t, J = 7.7 Hz, 1 H, *p*-Ar*H*), 1.48 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (d), 128.3 (d), 126.4 (d), 124.8 (s), 95.7 (s), 86.8 (s), 42.9 (s), 27.3 (q); LRMS (EI) 174 (100), 160 (13), 159 (79); HRMS (EI) calc'd for $C_{12}H_{14}O$ (M^+) 174.1039, found 174.10426.

(*tert*-Butoxyethynyl)benzene (^{13}C enriched) 92



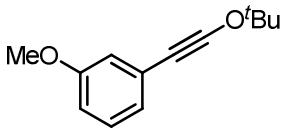
Reaction carried out at rt according to general procedure (pg. 118). Colourless oil, 73%; ν_{max} (film)/cm^{-1} 2979, 2204, 1369, 1318, 1060; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.34 (d, J = 7.7 Hz, 2 H, 2 × *o*-Ar*H*), 7.25 (t, J = 7.7 Hz, 2 H, 2 × *m*-Ar*H*), 7.20 (t, J = 7.7 Hz, 1 H, *p*-Ar*H*), 1.48 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (d, J = 2.4 Hz) (d), 128.3 (d), 126.4 (d), 124.8 (d, J = 17.3 Hz) (s), 95.7 (s), 86.8 (d, J = 3.6 Hz) (s), 43.6 & 42.1 (d, J = 225.1 Hz) (s), 27.3 (d, J = 2.0 Hz) (q); LRMS (EI) 295 (25), 239 (100), 220 (6), 175 (5); HRMS (EI) calc'd for $C_{12}H_{14}O$ (M^+) 175.1078, found 175.1042.

1-(*tert*-Butoxyethynyl)-4-methoxybenzene 77



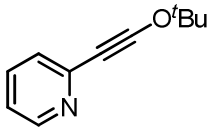
Reaction carried out at 0 °C according to general procedure (pg. 118). Colourless oil, 68%; ν_{max} (film)/cm^{-1} 2975, 2162, 1724, 1507, 1095; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.30 (d, J = 8.8 Hz, 2 H, 2 × $CH_3O(C)CHCH$), 6.82 (d, J = 8.8 Hz, 2 H, 2 × $CH_3O(C)CH$), 3.81 (s, 3 H, OCH_3), 1.49 (s, 9 H, $O(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 158.2 (s), 132.8 (d), 116.7 (d), 113.8 (s), 94.1 (s), 86.4 (s), 55.3 (q), 42.2 (s), 27.2 (q); LRMS (EI) 204 (6), 148 (100), 120 (15), 119 (12); HRMS (EI) calc'd for $C_{13}H_{16}O_2$ (M^+) 204.1145, found 204.1143.

1-(*tert*-Butoxyethynyl)-3-methoxybenzene 78



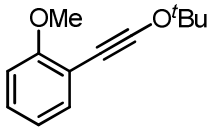
Reaction carried out at rt according to general procedure (pg. 118). Colourless oil, 76%; ν_{max} (film)/cm^{-1} 2979, 2247, 1749, 1598, 1370, 1153, 1060; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.16 (t, J = 8.0 Hz, 1 H, $CH_3O(C)CHCH$), 6.94 (d, J = 8.0 Hz, 1 H, $CH_3O(C)CHCHCH$), 6.88 (m, 1 H, $CH_3O(C)CH(C)$), 6.78 (dd, J = 8.0, 2.7 Hz, 1 H, $CH_3O(C)CH$), 3.79 (s, 3 H, CH_3O), 1.48 (s, 9 H, $O(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.4 (s), 129.2 (d), 125.9 (s), 124.1 (d), 116.5 (d), 112.8 (d), 95.6 (s), 87.1 (s), 55.3 (q), 42.9 (s), 27.3 (q); LRMS (EI) 204 (6), 148 (35), 86 (55), 84 (100); HRMS (EI) calc'd for $C_{13}H_{16}O_2$ (M^+) 204.1145 found 204.1141.

2-(*tert*-Butoxyethynyl)pyridine 79



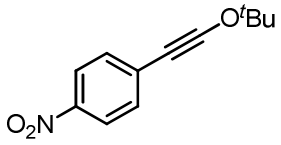
Reaction carried out at 0 °C according to general procedure (pg. 118). Yellow oil, 70%; ν_{max} (film)/cm^{-1} 2974, 1725, 1592, 1438, 1260; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.50 (d, *J* = 4.9 Hz, 1 H, Ar-NC*H*), 7.55 (td, *J* = 7.7, 1.8 Hz, 1 H, ArN(C)C*H*), 7.28 (d, *J* = 7.7, 1 H, ArN(C)C*H*), 7.09 (dd, *J* = 4.9, 1.8 Hz, 1 H, ArNCHC*H*), 1.51 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 149.8 (d), 145.2 (s), 136.0 (d), 126.7 (d), 121.1 (d), 96.0 (s), 88.5 (s), 43.8 (s), 27.4 (q); LRMS (EI) 175 (46), 164 (22), 146 (26), 121 (60), 119 (100); HRMS (EI) calc'd for $C_{11}H_{13}NO$ (M^+) 175.0992, found 175.0996.

1-(*tert*-Butoxyethynyl)-2-methoxybenzene 80



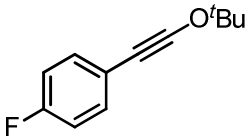
Reaction carried out at 0 °C according to general procedure (pg. 118). Colourless oil, 64%; ν_{max} (film)/cm^{-1} 2979, 2258, 1495, 1329, 1243, 1159, 1060; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.31 (dd, *J* = 7.7, 1.9 Hz, 1 H, CH_3O(C)(C)C*H*), 7.17 (td, *J* = 7.7, 1.9 Hz, 1 H, CH_3O(C)CHC*H*), 6.80-6.88 (m, 2 H, CH_3O(C)C*H* & CH_3O(C)CHCHC*H*), 3.85 (s, 3 H, CH_3O), 1.49 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 159.8 (s), 132.9 (d), 127.4 (d), 120.4 (d), 114.0 (s), 110.6 (d), 99.8 (s), 87.1 (s), 55.9 (q), 39.0 (s), 27.3 (q); LRMS (CI) 297 (40), 205 (10), 177 (60), 148 (30); HRMS (CI) calc'd for $C_{13}H_{17}O_2$ $(M+H)^+$ 205.1229, found 205.1233.

1-(*tert*-Butoxyethynyl)-4-nitrobenzene 81



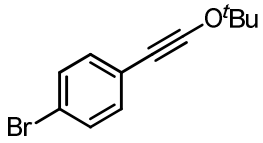
Reaction carried out at 0 °C according to general procedure ((pg. 118). Brown solid, 69%; m.p. 52–53 °C (decomposed) (CH_2Cl_2/PE); ν_{max} (film)/cm^{-1} 2982, 2244, 1749, 1596, 1517, 1343, 1152; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.14 (d, J = 8.8 Hz, 2 H, 2 × NO_2(C)C*H*), 7.43 (d, J = 8.8 Hz, 2 H, 2 × NO_2(C)CHC*H*), 1.53 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 145.5 (s), 132.7 (s), 131.5 (d), 123.5 (d), 101.5 (s), 88.9 (s), 43.0 (s), 27.3 (q); LRMS (CI) 220 (15), 205 (11), 181 (60), 167 (15), 150 (50), 136 (34); HRMS (CI) calc'd for $C_{12}H_{14}O_3N$ $(M+H)^+$ 220.0974, found 220.0969.

1-(*tert*-Butoxyethynyl)-4-fluorobenzene 82



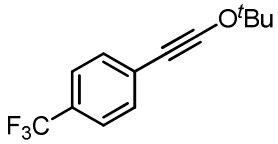
Reaction carried out at rt according to general procedure (pg. 118). Colourless oil, 51%; ν_{max} (film)/cm^{-1} 2982, 2251, 1601, 1509, 1371, 1229, 1100; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.29-7.36 (m, 2 H, 2 × F(C)C*H*), 7.92-7.00 (m, 2 H, 2 × F(C)CHC*H*), 1.50 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.2 & 162.6 (J = 246.0 Hz) (s), 133.0 (J = 8.0 Hz) (d), 120.7 (J = 3.5 Hz) (s), 115.2 (J = 21.6 Hz) (d), 95.0 (s), 86.9 (s), 41.7 (s), 27.2 (q); LRMS (EI) 192 (10), 177 (20), 149 (35), 136 (100), 123 (30); HRMS (EI) calc'd for $C_{12}H_{13}OF$ (M^+) 192.0945, found 192.0940.

1-(*tert*-Butoxyethynyl)-4-bromobenzene 83



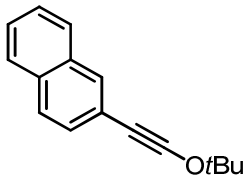
Reaction carried out at rt according to general procedure (pg. 118). Colourless oil, 59%; ν_{max} (film)/cm^{-1} 2980, 2270, 1488, 1370, 1072, 1009; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.36 (d, J = 8.0 Hz, 2 H, 2 × Br(C)CHC*H*), 7.19 (d, J = 8.0 Hz, 2 H, 2 × Br(C)C*H*CH), 1.47 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 132.8 (d), 131.3 (d), 123.8 (s), 120.0 (s), 96.6 (s), 87.3 (s), 42.0 (s), 27.2 (q); LRMS (EI) 251 (5), 237 (6), 196 (100), 170 (15); HRMS (EI) calc'd for $C_{12}H_{12}OBr$ (M-H)$^+$ 251.0072, found 251.0077.

1-(*tert*-Butoxyethynyl)-4-(trifluoromethyl)benzene 84



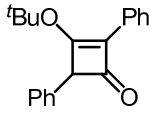
Reaction carried out at rt according to general procedure (pg. 118). Colourless oil, 60%; ν_{max} (film)/cm^{-1} 2980, 2251, 1616, 1373, 1340, 1126, 1070; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.49 (d, J = 8.2 Hz, 2 H, 2 × CF_3(C)C*H*), 7.40 (d, J = 8.2 Hz, 2 H, 2 × CF_3(C)CHC*H*), 1.49 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.4 (d), 129.0 (s), 128.0 (q, J = 32.7 Hz) (s), 125.1 (q, J = 3.6 Hz) (d), 124.7 (q, J = 271.5 Hz) (s), 98.1 (s), 88.0 (s), 42.5 (s), 27.3 (q); LRMS (CI) 243 (6), 186 (100), 159 (45), 138 (6); HRMS (CI) calc'd for $C_{13}H_{14}OF_3$ (M+H)$^+$ 243.0997, found 243.0988.

1-(*tert*-Butoxyethynyl)naphthalene 85



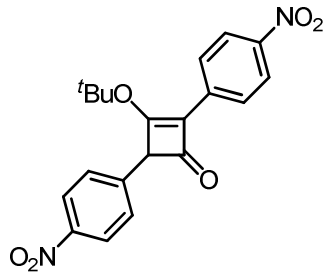
Reaction carried out at –40 °C according to general procedure (pg. 118). Yellow oil, 93%; ν_{max} (film)/cm^{-1} 2979, 2244, 1598, 1370, 1310, 1154, 1035; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.83 (s, 1 H, Ar*H*), 7.78 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.73 (t, *J* = 8.6 Hz, 2 H, Ar*H*), 7.43-7.46 (m, 2 H, Ar*H*), 7.42 (dd, J = 8.6, 1.5 Hz, 1 H, Ar*H*), 1.52 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 133.4 (s), 132.0 (s), 130.2 (d), 129.3 (d), 127.8 (2C, 2d), 127.4 (d), 126.3 (d), 125.7 (d), 122.2 (s), 96.1 (s), 87.2 (s), 43.4 (s), 27.4 (q); LRMS (EI) 224 (4), 169 (12), 168 (100), 152 (12), 140 (35); HRMS (EI) calc'd for $C_{16}H_{16}O$ $(M+H)^+$ 224.1196, found 224.1191.

3-(*tert*-Butoxy)-2,4-diphenylcyclobut-2-enone 87



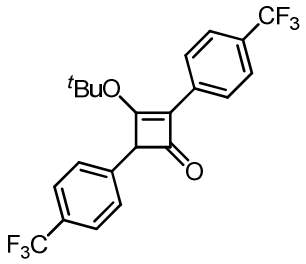
A stirring solution of **(***tert*-butoxyethynyl)benzene **53** (23 mg, 0.13 mmol) was heated to 80 °C in toluene (2 mL) for 1 h. The reaction mixture was then concentrated *in vacuo* and purified *via* chromatography (PE/EtOAc) to yield the product as a colourless oil, (15 mg, 78%); ν_{max} (film)/cm^{-1} 2981, 1747, 1621, 1594, 1493, 1371, 1155; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.86 (d, *J* = 7.5 Hz, 2 H, 2 × Ar*H*), 7.26-7.40 (m, 8 H, 8 × Ar*H*), 4.82 (s, 1 H, C*H*), 1.38 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 184.5 (s), 174.2 (s), 136.1 (s), 129.6 (s), 129.1 (d), 128.6 (d), 128.0 (d), 127.8 (d), 127.5 (d), 126.6 (d), 126.0 (s), 86.3 (s), 69.1 (d), 29.7 (q); LRMS (CI) 293 (15), 265 (13), 238 (20), 237 (100), 236 (30); HRMS (CI) calc'd for $C_{20}H_{21}O_2$ $(M+H)^+$ 293.1541, found 293.1543.

3-(*tert*-Butoxy)-2,4-*bis*(4-nitrophenyl)cyclobut-2-enone 88



A stirring solution of 1-(*tert*-butoxyethynyl)-4-nitrobenzene **81** (10 mg, 0.05 mmol) was heated to 80 °C in toluene (1 mL) for 1 h. The reaction mixture was then concentrated *in vacuo* and purified *via* chromatography (PE/EtOAc) to yield the product as a colourless oil, (7 mg, 80%); ν_{max} (film)/cm^{-1} 2981, 1749, 1619, 1517, 1370, 1152; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.26 (m, 4 H, 4 × Ar*H*), 7.97 (d, *J* = 8.7 Hz, 2 H, 2 × Ar*H*), 7.51 (d, *J* = 8.7 Hz, 2 H, 2 × Ar*H*), 5.01 (s, 1 H, C*H*), 1.44 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 181.5 (s), 175.0 (s), 165.3 (s), 147.8 (s), 146.5 (s), 142.9 (s), 134.9 (s), 128.5 (d), 127.1 (d), 124.6 (d), 124.2 (d), 88.8 (s), 69.2 (d), 29.8 (q); LRMS (ESI) 391 (40), 243 (100), 208 (30), 180 (60), 143 (20).[r]

3-(*tert*-Butoxy)-2,4-*bis*(4-(trifluoromethyl)phenyl)cyclobut-2-enone 89

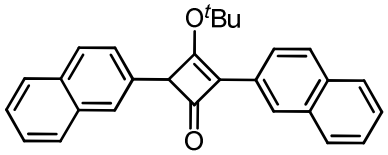


A stirring solution of 1-(*tert*-butoxyethynyl)-4-(trifluoromethyl)benzene **84** (12 mg, 0.05 mmol) was heated to 80 °C in toluene (1 mL) for 1 h. The reaction mixture was then concentrated *in vacuo* and purified *via* chromatography (PE/EtOAc) to yield the product as a colourless oil, (8.5 mg, 80%); ν_{max} (film)/cm^{-1} 2986, 1753, 1626, 1513, 1374, 1322; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.93 (d, *J* = 8.1 Hz, 2 H, 2 × Ar*H*), 7.63 (d, *J* = 8.1 Hz, 4 H, 2 × Ar*H*), 7.43 (d, *J* = 8.1 Hz, 2 H, 2 × Ar*H*), 4.92 (s, 1 H, C*H*), 1.42 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR

[r] Molecular ion not observed.

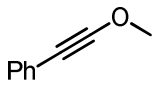
(150 MHz, $CDCl_3$) δ_C 182.8 (s), 174.6 (s), 139.9 (s), 132.4 (s), 130.5 (q, J = 32.5 Hz) (s), 129.3 (q, J = 32.5 Hz) (s), 128.0 (d), 126.7 (d), 126.2 (q, J = 3.2 Hz) (d), 125.6 (q, J = 3.2 Hz) (d), 125.1 (s), 124.2 (q, J = 272.1 Hz) (s), 124.1 (q, J =272.1 Hz) (s), 87.7 (s), 69.0 (d), 29.7 (q); LRMS (CI) 429 (60), 373 (100), 353 (65), 327 (6); HRMS (CI) calc'd for $C_{22}H_{19}O_2F_6$ $(M+H)^+$ 429.1289, found 429.1294.

3-(*tert*-Butoxy)-2,4-di(naphthalen-2-yl)cyclobut-2-enone 90



A stirring solution of 2-(*tert*-butoxyethynyl)naphthalene **85** (30 mg, 0.13 mmol) was heated to 80 °C in toluene (1 mL) for 1 h. The reaction mixture was then concentrated *in vacuo* and purified *via* chromatography (EtOAc/PE) to yield the product as a colourless film, (20 mg, 78%); ν_{max} (film)/cm^{-1} 3051, 2924, 1745, 1617, 1471, 1348, 1157, 1028; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.38 (s, 1 H, Ar*H*), 8.01 (m, 1 H, Ar*H*), 7.82-7.89 (m, 6 H, 6 × Ar*H*), 7.80 (s, 1 H, Ar*H*), 7.45-7.50 (m, 5 H, 5 × Ar*H*), 5.06 (s, 1 H, C*H*), 1.43 (s, 9 H, O(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 184.5 (s), 174.4 (s), 133.7 (s), 133.6 (s), 133.4 (s), 133.2 (s), 132.6 (s), 129.0 (d), 128.4 (d), 128.2 (d), 127.95 (d), 127.90 (d), 127.85 (d) 127.2 (d), 127.0 (s), 126.5 (d), 126.3 (d), 126.20 (s), 126.16 (d), 126.17 (d) 125.8 (d), 125.1 (d), 124.4 (d), 88.6 (s), 69.5 (d), 29.8 (q); LRMS (EI) 392 (6), 337 (25), 336 (100), 325 (10); HRMS (CI) calc'd for $C_{28}H_{24}O_2$ (M^+) 392.1771, found 392.1775.

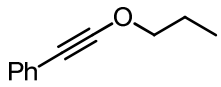
Representative Procedure: 1-Methoxy-2-phenylethyne 103



To a flame-dried, 25 mL round-bottomed flask purged with argon, was added anhydrous methanol (27.0 mg, 0.84 mmol) and anhydrous THF (0.3 mL). Freshly cut potassium metal (33.0 mg, 0.84 mmol) was then carefully added and the reaction mixture stirred at rt for 10 min, followed by reflux at 50 °C for 20 min. The reaction mixture was then allowed to cool

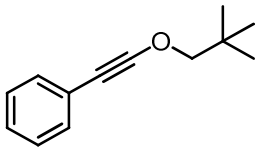
to rt and the contents concentrated *in vacuo*. The reaction flask was then cooled to 0 °C and 2 M dimethylamine in THF (0.21 mL, 0.42 mmol, 2.0 eq.) was added, followed by alkynyl sulfonamide (50.0 mg, 0.21 mmol, 1.0 eq.). The reaction mixture was then allowed to stir for 10 min whilst warming to rt, followed by *careful* addition of *i*PrOH (1.0 mL) to quench any residual potassium. The reaction mixture was then dissolved in CH_2Cl_2 (20 mL) and washed with water (10 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil, which was purified *via* flash chromatography (0-5% Et_2O/PE) to give the product as a colourless film, (17.7 mg, 70%); ν_{max} (film)/cm^{-1} 2965, 2266, 1732, 1444, 1324, 1058, 905; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.35 (m, 2 H, 2 × *o*-Ar*H*), 7.26 (m, 2 H, 2 × *m*-Ar*H*), 7.22 (m, 1 H, *p*-Ar*H*), 3.99 (s, 3 H, C*H*$_3$O); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.6 (d), 128.3 (d), 126.8 (d), 123.8 (s), 100.2 (s), 66.0 (q), 38.9 (s); LRMS (EI) 132 (98), 105 (99), 91 (36), 89 (100), 77 (81), 63 (36); HRMS (EI) calc'd for C_9H_8O (M^+) 132.0570, found 132.0571.

1-Propoxy-2-phenylethyne 104



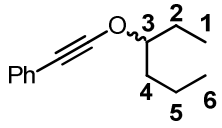
From representative procedure (pg. 126) using propan-1-ol: Colourless film, 69%; ν_{max} (film)/cm^{-1} 2968, 2261, 1724, 1323, 1064, 754; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.34 (d, *J* = 7.1 Hz, 2 H, 2 × *o*-Ar*H*), 7.26 (t, *J* = 7.1 Hz, 2 H, 2 × *m*-Ar*H*), 7.21 (t, *J* = 7.1 Hz, 1 H, *p*-Ar*H*), 4.12 (t, *J* = 6.5 Hz, 2 H, OC*H*$_2$), 1.84 (sex., *J* = 7.2 Hz, 2 H, OCH_2CH_2), 1.02 (t, *J* = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.6 (d), 128.3 (d), 126.6 (d), 124.2 (s), 99.1 (s), 80.8 (t), 39.6 (s), 22.4 (t), 10.0 (q); LRMS (EI) 160 (35), 118 (100), 117 (25), 90 (20), 90 (16); HRMS (EI) calc'd for $C_{11}H_{12}O$ (M^+) 160.0883, found 160.0886.

1-Neopentyloxy-2-phenylethyne 105



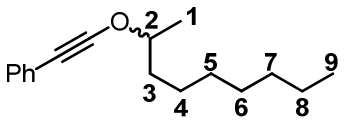
From representative procedure (pg. 126) using neopentyl alcohol: Colourless film, 63%; ν_{max} (film)/cm^{-1} 2968, 2259, 1728, 1326, 1069, 904; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.32 (d, J = 7.9 Hz, 2 H, 2 × *o*-Ar*H*), 7.25 (t, J = 7.9 Hz, 2 H, 2 × *m*-Ar*H*), 7.20 (t, J = 7.9 Hz, 1 H, *p*-Ar*H*), 3.88 (s, 2 H, OCH_2), 1.01 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (d), 128.3 (d), 126.6 (d), 124.2 (s), 100.3 (s), 89.5 (t), 38.7 (s), 32.6 (s), 26.1 (q); LRMS (EI) 188 (6), 159 (5), 119 (10), 118 (100), 90 (43); HRMS (EI) calc'd for $C_{13}H_{16}O$ (M^+) 188.1196, found 188.1193.

(Hexan-3-yloxy)ethynyl)benzene 106



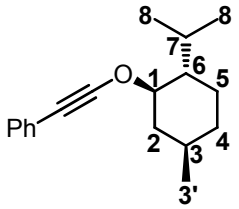
From representative procedure (pg. 126) using hexan-3-ol: Colourless oil, 65%; ν_{max} (film)/cm^{-1} 2963, 2254, 1461, 1324, 1063, 753; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.33 (d, J = 7.3 Hz, 2 H, 2 × *o*-Ar*H*), 7.24 (t, J = 7.3 Hz, 2 H, 2 × *m*-Ar*H*), 7.19 (t, J = 7.3 Hz, 1 H, *p*-Ar*H*), 4.05 (tt, J = 7.5, 4.9 Hz, 1 H, C^3*H*), 1.80-1.83 (m, 2 H, C^2*H* & C^4*H*), 1.72 (m, 1 H, C^2*H*), 1.60 (m, 1 H, C^4*H*), 1.52 (m, 1 H, C^5*H*), 1.44 (m, 1 H, C^5*H*), 1.01 (t, J = 7.4 Hz, 3 H, C^1H_3), 0.97 (t, J = 7.3 Hz, 3 H, C^6H_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (d), 128.2 (d), 126.4 (d), 124.6 (s), 97.8 (s), 91.0 (d), 40.8 (s), 35.2 (t), 26.5 (t), 18.6 (t), 14.1 (q), 9.6 (q); LRMS (EI) 202 (6), 145 (6), 119 (8), 118 (100), 86 (30); HRMS (EI) calc'd for $C_{14}H_{18}O$ (M^+) 202.1352, found 202.1349.

(Nonan-2-yloxy)ethynyl)benzene 107



From representative procedure (pg. 126) using nonan-2-ol:[s] Colourless oil, 71%; ν_{max} (film)/cm^{-1} 2928, 2253, 1724, 1264, 1063, 753; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.33 (d, J = 7.1 Hz, 2 H, 2 × *o*-Ar*H*), 7.25 (t, J = 7.1 Hz, 2 H, 2 × *m*-Ar*H*), 7.20 (t, J = 7.1 Hz, 1 H, *p*-Ar*H*), 4.25 (sex., J = 6.1 Hz, 1 H, C^2*H*), 1.82 (m, 1 H, C^3*H*), 1.58 (m, 1 H, C^3*H*), 1.42 (d, J = 6.1 Hz, 3 H, C^1*H*$_3$), 1.27-1.40 (m, 10 H, C^3*H*$_2$-C^8*H*$_2$), 0.88 (t, J = 6.2 Hz, 3 H, C^9*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.5 (d), 128.3 (d), 126.4 (d), 124.5 (s), 97.6 (s), 86.2 (d), 41.1 (s), 35.6 (t), 31.9 (t), 29.5 (t), 29.3 (t), 25.3 (t), 22.8 (t), 19.5 (q), 14.2 (q); LRMS (CI) 245 (25), 237 (37), 147 (26), 119 (100), 91 (20); HRMS (CI) calc'd for $C_{17}H_{24}O$ $(M+H)^+$ 245.1899, found 245.1892.

1-(–)-Menthoxy-2-phenylethyne 108

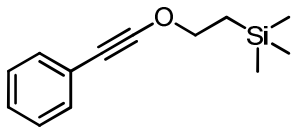


From representative procedure (pg. 126) using *(–)*-menthol:[t] Colourless oil, 66%; ν_{max} (film)/cm^{-1} 2951, 2869, 2248, 1730, 1460, 1317, 1062; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.34 (d, J = 7.3 Hz, 2 H, 2 × *o*-Ar*H*), 7.25 (t, J = 7.3 Hz, 2 H, 2 × *m*-Ar*H*), 7.20 (t, J = 7.3 Hz, 1 H, *p*-Ar*H*), 3.96 (td, J = 11.0, 4.5 Hz, 1 H, C^1*H*), 2.34 (m, 1 H, C^2*H*), 2.23 (sept. d, J = 7.0, 2.7 Hz, 1 H, C^7*H*), 1.67-1.73 (m, 2 H, C^5*H* & C^4*H*), 1.43-1.55 (m, 2 H, C^6*H* & C^3*H*), 1.27 (q, J = 11.0 Hz, 1 H, C^2*H*), 1.04 (qd, J = 13.1, 3.5 Hz, 1 H, C^5*H*), 0.98 (d, J = 6.6 Hz, 3 H, C$^{3'}$*H*$_3$), 0.96 (d, J = 6.9 Hz, 3 H, C^8*H*$_3$), 0.89 (m, 1 H, C^4*H*), 0.88 (d, J = 6.9 Hz, 3 H, C^8*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.7 (d), 128.3 (d), 126.4 (d), 124.6 (s), 97.8 (s), 88.7 (d), 47.2 (d), 40.9 (s), 40.0 (t), 34.1 (t), 31.8 (d), 26.1 (d), 23.5 (t), 22.2 (q), 20.8 (q), 16.6 (q); LRMS

[s] Alcohol and potassium refluxed for 1 h.
[t] Alcohol and potassium refluxed for 1 h.

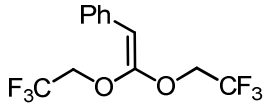
(CI) 256 (15), 237 (20), 139 (100), 118 (15), 83 (15); HRMS (CI) calc'd for $C_{18}H_{24}O$ (M^+) 256.1821, found 256.1813; $[\alpha]_D$ = –58 (c 1.1, cyclohexane) [lit.[u] $[\alpha]_D$ = –60 (c 1.5, cyclohexane)]

Trimethyl(2-((phenylethynyl)oxy)ethyl)silane 109



From representative procedure (pg. 126) using 2-(trimethylsilyl)ethanol: Colourless film, 50%; ν_{max} (film)/cm^{-1} 2948, 2256, 1724, 1639, 1316, 1062; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.34 (d, *J* = 7.0 Hz, 2 H, 2 × *o*-Ar*H*), 7.25 (t, *J* = 7.0 Hz, 2 H, 2 × *m*-Ar*H*), 7.20 (t, *J* = 7.0 Hz, 1 H, *p*-Ar*H*), 4.24 (m, 2 H, OCH_2), 1.25 (m, 2 H, OCH_2CH_2), 0.10 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 131.6 (d), 128.3 (d), 126.6 (d), 124.3 (s), 98.8 (s), 77.9 (t), 40.5 (s), 18.2 (t), −1.3 (q); LRMS (CI) 219 (66), 191 (51), 175 (33), 119 (38), 101 (30); HRMS (CI) calc'd for $C_{13}H_{19}OSi$ $(M+H)^+$ 219.1205, found 219.1209.

(2,2-*bis*(2,2,2-Trifluoroethoxy)vinyl)benzene 110



From representative procedure (pg. 126) using 2,2,2-trifluoroethanol: Yellow oil, 53%; ν_{max} (film)/cm^{-1} 2935, 1725, 1450, 1152, 1065, 1015; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.42 (d, *J* = 7.4 Hz, 2 H, 2 × *o*-Ar*H*), 7.30 (t, *J* = 7.4 Hz, 2 H, 2 × *m*-Ar*H*), 7.16 (t, *J* = 7.4 Hz, 1 H, *p*-Ar*H*), 4.87 (s, 1 H, C*H*), 4.21 (q, *J* = 8.3 Hz, 2 H, CF_3CH_2), 4.28 (q, *J* = 7.9 Hz, 2 H, CF_3CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 155.1 (s), 133.5 (s), 128.6 (d), 127.6 (d), 125.9 (d), 123.3 (q, *J* = 275.0 Hz) (s), 122.8 (q, *J* = 275.0 Hz) (s), 85.8 (d), 66.4 (q, *J* = 36.0 Hz) (t), 64.3 (q, *J* = 36.0 Hz) (t); LRMS (EI) 300 (100), 217 (38), 189 (70), 136 (20), 118 (16); HRMS (EI) calc'd for $C_{12}H_{10}O_2F_6$ (M^+) 300.0579, found 300.0577.

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7.0 References

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